PREDICTIVE AND PRESCRIPTIVE MODELING FOR THE CLINICAL MANAGEMENT OF DENGUE: A CASE STUDY IN COLOMBIA

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Abstract

In this research, we address the problem of clinical management of dengue, which is composed of diagnosis and treatment of the disease. Dengue is a vector-borne tropical disease that is widely distributed worldwide. The development of approaches to aid in decision-making for diseases of public health concern –such as dengue– are necessary to reduce morbidity and mortality rates. Despite the existence of clinical management guidelines, the diagnosis and treatment of dengue remains a challenge. To address this problem, our objective was to develop methodologies, models, and approaches to support decision-making regarding the clinical management of this infection. We developed several research articles to meet the proposed objectives of this thesis. The first article reviewed the latest trends in dengue modeling using machine learning (ML) techniques. The second article proposed a decision support system for the diagnosis of dengue using fuzzy cognitive maps (FCMs). The third article proposed an autonomous cycle of data analysis tasks to support both diagnosis and treatment of the disease. The fourth article presented a methodology based on FCMs and optimization algorithms to generate prescriptive models in clinical settings. The fifth article tested the previously mentioned methodology in other science domains such as, business and education. Finally, the last article proposed three federated learning approaches to guarantee the security and privacy of data related to the clinical management of dengue. In each article, we evaluated such strategies using diverse datasets with signs, symptoms, laboratory tests, and information related to the treatment of the disease. The results showed the ability of the developed methodologies and models to predict disease, classify patients according to severity, evaluate the behavior of severity-related variables, and recommend treatments based on World Health Organization (WHO) guidelines.

Keywords: Dengue, Predictive modeling, Prescriptive modeling, Artificial intelligence, Machine learning, Clinical decision-support system, Fuzzy cognitive maps, Federated learning

Resumen

En esta investigación, abordamos el problema del manejo clínico del dengue, que se compone del diagnóstico y el tratamiento de la enfermedad. El dengue es una enfermedad tropical transmitida por vectores que está ampliamente distribuida en todo el mundo. El desarrollo de enfoques que ayuden a la toma de decisiones en enfermedades de interés para la salud pública –como el dengue– es necesario para reducir las tasas de morbilidad y mortalidad. A pesar de la existencia de guías para el manejo clínico, el diagnóstico y el tratamiento del dengue siguen siendo un reto. Para abordar este problema, nuestro objetivo fue desarrollar metodologías, modelos y enfoques para apoyar la toma de decisiones en relación con el manejo clínico de esta infección. Nosotros desarrollamos varios artículos de investigación para cumplir los objetivos propuestos de esta tesis. El primer articulo revisó las últimas tendencias del modelamiento de dengue usando técnicas de aprendizaje automático. El segundo artículo propuso un sistema de apoyo a la decisión para el diagnóstico del dengue utilizando mapas cognitivos difusos. El tercer artículo propuso un ciclo autónomo de tareas de análisis de datos para apoyar tanto el diagnóstico como el tratamiento de la enfermedad. El cuarto artículo presentó una metodología basada en mapas cognitivos difusos y algoritmos de optimización para generar modelos prescriptivos en entornos clínicos. El quinto artículo puso a prueba la metodología anteriormente mencionada en otros dominios de la ciencia como, por ejemplo, los negocios y la educación. Finalmente, el último artículo propuso tres enfoques de aprendizaje federado para garantizar la seguridad y privacidad de los datos relacionados con el manejo clínico del dengue. En cada artículo evaluamos dichas estrategias utilizando diversos conjuntos de datos con signos, síntomas, pruebas de laboratorio e información relacionada con el tratamiento de la enfermedad. Los resultados mostraron la capacidad de las metodologías y modelos desarrollados para predecir la enfermedad, clasificar a los pacientes según su severidad, evaluar el comportamiento de las variables relacionadas con la severidad y recomendar tratamientos basados en las directrices de la Organización Mundial de la Salud.

Palabras Clave: Dengue, Modelamiento predictivo, Modelamiento prescriptivo, Inteligencia artificial, Aprendizaje automático, Sistema de apoyo a la decisión clínica, Mapas cognitivos difusos, Aprendizaje federado

Scientific contributions

Several scientific articles were generated and published during the development process of this research project.

Published articles:

- W. Hoyos, J. Aguilar, and M. Toro, "Dengue models based on machine learning techniques: A systematic literature review", *Artificial Intelligence in Medicine*, vol. 119. p. 102157, Aug. 2021, doi:10.1016/j.artmed.2021.102157.
- W. Hoyos, J. Aguilar, and M. Toro, "A clinical decision-support system for dengue based on fuzzy cognitive maps", *Health Care Management Science*, pp. 1-16, Aug. 2022, doi:10.1007/s10729-022-09611-6
- W. Hoyos, J. Aguilar, and M. Toro, "An autonomous cycle of data analysis tasks for the clinical management of dengue", *Heliyon*, vol. 8, no. 10, p. e10846, Oct. 2022, doi:10.1016/J.HELIYON.2022.E10846.

Articles under review in journals:

- W. Hoyos, J. Aguilar, M. Raciny, and M. Toro, "Clinical decision-making through prescriptive modeling", preprint under review in *Journal of Biomedical Informatics*, 2023.
- W. Hoyos, J. Aguilar, and M. Toro, "PRV-FCM: an extension of fuzzy cognitive maps for prescriptive modeling", preprint under review in *Expert Systems with Applications*, 2023.
- W. Hoyos, J. Aguilar, and M. Toro, "Federated learning approaches with fuzzy cognitive maps to support clinical decision-making in dengue", article accepted for publication in *Engineering Applications of Artificial Intelligence*, 2023.

Project context

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Special thanks to my aunt Marta and Raúl, who were my support during my research internship in Spain. Without them my adaptation to a country unknown to me would not have been possible.

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Contents

Chapter 1

Introduction and research context

1.1 Problem statement and motivation

Dengue is one of the most important vector-borne tropical diseases worldwide [1]. This pathology has become a public health problem in tropical and subtropical regions, with a great epidemiological, social, and economic impact [2, 3]. The disease is produced by an arbovirus (DENV) that receives the same name [4]. The infection is transmitted to humans by the bite of mosquitoes of the genus *Aedes*, mainly *A. aegypti* and *A. albopictus* [5].

In 1997, WHO classified the disease like dengue fever and dengue hemorrhagic fever [6]. A new classification was proposed in 2009, which was based on the severity level of the disease: non-severe dengue (with or without warning signs) and severe dengue (SD). This last includes the dengue shock syndrome [7]. According to the WHO, more than 350 million dengue virus infections occur annually worldwide. In addition, 20,000 deaths related to dengue in the same period of time [8]. The Pan American Health Organization annual epidemiological bulletin of arboviruses reported 1,267,151 cases of dengue in the Americas region during 2021, with a cumulative incidence of 127.72 cases per 100,000 population.

The countries in the Americas region with the highest number of cases during 2021 were Brazil, Colombia and Peru with 975,474 cases (77.0%), 53,334 cases (4.2%) and 49,274 cases (3.9%), respectively [9]. Colombia was the country with the second highest number of cases in the Americas region in 2021. According to the weekly epidemiological report by the Colombian National Institute of Health, the territorial entities with the highest number of cases were Cartagena with 7,434 cases (14.2%), Cali with 5,762 cases (11.0%) and Barranquilla with 5,178 cases (9.9%) [10].

Clinical management of dengue is the process by which health care professionals evaluate the patient to make a diagnosis based on severity and treat the patient palliatively to avoid life-threatening complications [11]. The clinical management of dengue is a major challenge for medical professionals

and health authorities worldwide [11]. The main goal of early diagnosis and timely treatment activities is to decrease morbidity and mortality rates associated with the disease [12]. Mortality rates for dengue can be high when diagnosis and treatment are not appropriate, reaching values of 20% [13]. In 2009, WHO published some guidelines for the diagnosis, treatment, prevention and control of dengue [7]. These guidelines are currently used by medical personnel for the clinical management of dengue, from diagnosis to treatment of patients. However, there are still difficulties in the diagnosis and treatment of the disease.

The processes used to diagnose and treat dengue are complex because the large amount of information that the medical staff must analyze in a short time to define the procedure to follow for each patient [14]. This information corresponds to demographic, clinical and laboratory variables such as age, signs and symptoms, among others, that a patient with dengue may present [15]. Besides, physicians' lack of experience could make the diagnosis difficult because there are not always reasonable rules to analyze a complex event such as dengue. According to experts, the appropriate clinical management of dengue patients depends on an astute interpretation of the clinical and laboratory findings to prevent or treat the life-threatening complications [14].

One way to address this type of problem is with the development of clinical decision support systems (CDSSs) based on predictive and prescriptive models to support decision-making of medical personnel caring dengue patients [16]. According to Sutton et al. [16], a CDSS is defined as a system that seeks to improve healthcare delivery by supporting medical decisions with clinical knowledge and patient information. The main objective is for the physician to combine her/his clinical knowledge with suggestions from the CDSS to make the best possible decision. Such systems use data to enhance the processes performed by a human being [17].

Advances in artificial intelligence (AI) have driven the development of CDSSs to support decision-making in clinical or hospital environments [18–21]. These systems are mainly based on predictive and prescriptive models using AI techniques. The predictive models can be used for the detection or diagnosis of diseases using prediction or classification tasks [22]; while the prescriptive models are optimization models that can be used to prescribe a suitable treatment [23].

The development of predictive models has been worked extensively for the detection of dengue and to differentiate it from other diseases with similar clinical pictures, such as Zika, chikungunya, malaria and leptospirosis [22, 24, 25]. These models are useful for the diagnosis of dengue, however, they have some disadvantages: 1) they only detect the disease, 2) they do not evaluate the behavior of variables related to severity. Thus, the diagnosis of dengue is not only a prediction or detection problem, it involves many severity-related factors that physicians must analyze to perform a correct classification of the clinical picture and a appropriate management of the patient's signs and symptoms. In this way, the development of CDSSs that not only predict an outcome, but also evaluate the behavior

of the variables involved in the process are more useful to improve the diagnostic process of dengue [26]. Therefore, it is necessary to develop CDSS based on explanatory models for the prediction and evaluation of factors related to the severity of dengue. This type of explainable techniques allows explaining the relevance of the variables involved in the system. Additionally, it is important to compare the developed models with other ML techniques proposed in the literature.

In general, the clinical management of dengue constitutes the diagnosis and treatment of the disease. Predictive models have focused on diagnosis, while prescriptive models have focused on treatment. The prescriptive models are a type of modeling to know what are the best actions to obtain a desired outcome [27]. In the case of dengue, there is no treatment or cure available; its treatment is based on palliative care and continuous assessment of signs to avoid complications leading to death. To date and to the best of our knowledge, no prescriptive model developed to support decision-making in the treatment of dengue has been reported in the literature. Therefore, it is necessary to develop prescriptive models to support decision-making so that patients with dengue have the best possible treatment within the recommendations made by WHO.

An important aspect in the development of predictive and prescriptive models for the clinical management of dengue is to ensure the privacy and security of patient data. In traditional approaches all data are collected and sent (without any security) to a single location for model training. However, potential data leaks that compromise the identity of patients constitute a serious problem for health-care institutions. To attack this problem, it is indispensable to develop different approaches such as federated learning, where predictive and prescriptive models are trained for the clinical management of diseases without data leaving their place of origin or collection.

In summary, there is a need to develop predictive and prescriptive models for the clinical management of dengue, not only to support decision-making regarding diagnosis but also treatment. Also, there is a need to ensure the privacy and security of patient data. Our expectation was to develop models to support clinical decision makers to decrease dengue mortality rates considering these aspects.

1.2 Research objectives

1.2.1 General objective

Develop predictive and prescriptive models for the clinical management of dengue

1.2.2 Specific objectives

- Develop a predictive model for classification and severity assessment of dengue.
- Develop prescriptive models to aid decision-making in the clinical management of dengue.

- Develop federated learning for FCMs to support decision-making in the clinical management of dengue.

1.3 Contributions and research scope

This research focuses on the development of models, methodologies and computational approaches to support decision-making in the clinical management of dengue. Several contributions were made to the generation of knowledge in the development of CDSS for the diagnosis and treatment of dengue.

The first contribution of the present research was a systematic literature review (SLR) to identify challenges and opportunities for dengue research. In this review, we focused on three main aspects of dengue: i) diagnostic modeling, ii) predictive modeling, and iii) prescriptive modeling. For each of these approaches, we identify challenges and opportunities for future work.

Based on the information reported in the SLR, we set out three objectives related to predictive modeling, prescriptive modeling, and federated learning. On the one hand, we applied AI techniques on datasets related to the clinical management of dengue to generate predictive models with explanatory capacity, it means, models that allow us to evaluate the behavior of included variables. In the literature there are works reported for dengue detection, however, works that dynamically evaluate dengue variables are scarce. On the other hand, we used optimization techniques such as genetic algorithms (GAs) to generate prescriptive models that prescribe treatments according to the clinical pictures of the patients. In this case, we developed a strategy called autonomous cycles of data analysis tasks (ACODAT) [28] that combines predictive and prescriptive models for dengue diagnosis and treatment, respectively.

Because prescriptive modeling is a relatively new area, and although its interest is growing, methodologies for the generation of this type of models are still scarce. For this reason, another important contribution of the present study consisted of a methodology based on an extension of FCMs for the generation of prescriptive models. This methodology uses the inference process of cognitive maps and optimization algorithms such as GAs to prescribe actions that lead to desired outcomes. It was tested in different domains such as education, business and diseases like diabetes, geohelminthiasis and dengue.

Finally, to ensure the security and privacy of dengue patient data, we developed federated learning approaches where the data used to train the models do not leave their place of origin. These approaches are useful to support decision-making in the diagnosis and treatment of dengue in different cities in Colombia. The proposed approaches present a useful alternative to centralized environments where data are gathered in one place for training.

The phases used for the development of the models corresponding to the specific objectives comprised planning, analysis, design and implementation. In the planning and analysis is important to

emphasize the support of clinical experts in dengue to extract the sources of knowledge in healthcare centers and identify the main problems related to the clinical management of dengue. Regarding the design, we defined the architectures used for the generation of AI models. Finally, the implementation consisted of the translation of the requirements and designs into functional code.

Deployment of the models in mobile, web and desktop applications is beyond the scope of this work. Difficulties in accessing clinical and hospital environments due to the COVID-19 pandemic make it difficult to evaluate and validate the results obtained at full scale. However, the results are evaluated using particular scenarios advised by experts in the clinical management of dengue.

All the contributions made in this research are represented in research articles. A total of six (6) scientific articles were generated, of which three (3) are published and the other three (3) are under review in scientific journals. The status of each of the articles is briefly explained below.

A first review article was generated to identify research opportunities in dengue modeling using ML. This article was published in the journal: *Artificial Intelligence in Medicine* (Q1 in SJR). The second research article corresponded to the predictive explainable model using FCMs for dengue diagnosis. This article was published in the journal: *Health Care Management Science* (Q1 in SJR). The third article presents an ACODAT using prediction or prescription tasks for the diagnosis and treatment of dengue, respectively. This article was published in the journal: *Heliyon* (Q1 in SJR). The fourth article generated presents a methodology based on FCMs and optimization algorithms to generate prescriptive models in clinical settings. This article is under review in the journal: *Journal of Biomedical Informatics* (Q1 in SJR). The fifth article applies this methodology to generate prescriptive models in other fields of science such as education and business. This article is under review in the journal: *Expert Systems with Applications* (Q1 in SJR). Finally, the last article presents three federated learning approaches for FCMs to support decision-making in the clinical management of dengue. This article was accepted for publication in the journal: *Engineering Applications of Artificial Intelligence* (Q1 in SJR).

1.4 Thesis organization

This thesis is presented as a collection of articles developed to fulfill each of the objectives proposed. Chapter 3, Chapter 4 and Chapter 5 correspond to the fulfillment of the first, second and third objectives, respectively. One article was generated for the first and third objectives, while three articles were generated for the second objective. The articles will be presented in each section with the title, doi (if published), abstract and full text.

Chapter 2 describes the latest trends in diagnostic, predictive and prescriptive modeling for dengue. In this chapter, we show a SLR useful to identify trends, challenges, and research opportunities in predictive and prescriptive modeling for dengue. Chapter 3 presents an article corresponding to the

fulfillment of the first objective, which consists of the development of a CDSS for dengue based on FCMs.

Chapter 4 presents three articles to meet the second objective proposed in this thesis. The first article corresponds to the development of an ACODAT for the clinical management of dengue. The second article corresponds to the development and implementation of a strategy based on FCMs and optimization algorithms to generate prescriptive models in clinical environments. Subsequently, the third article corresponds to the application of this methodology in other domains such as education and business to validate the generalizability of the developed approach.

Chapter 5 presents an article where we proposed three approaches of federated learning to support clinical decision-making in dengue and ensure privacy and security of dengue patient data. Chapter 6 presents a summary of the conclusions of all the articles presented in the previous sections. Finally, in this last chapter, we show the limitations of our research and possible future work for the development and improvement of CDSSs for the clinical management of dengue.

Chapter 2

State of the art

2.1 Motivation

In this chapter, we present an SLR that reviewed three dengue modeling approaches: diagnostic, predictive, and prescriptive. At the time of the start of the research project, there was no review in the literature that encompassed these three approaches together for dengue. The main objective of this review was to identify the main trends in these three approaches using ML techniques. In diagnostic modeling, the objective was to find the main modeling approaches to detect, diagnose or classify the disease. In predictive modeling, the objective was to find the main modeling approaches at the epidemic level, as well as modeling to study and analyze dengue morbidity and mortality rates. The prescriptive or intervention modeling was oriented to find the main developments on the analysis of the impact of interventions to mitigate epidemics and control dengue. The whole article is in Appendix A.

2.2 Identification of the article

W. Hoyos, J. Aguilar, and M. Toro, "Dengue models based on machine learning techniques: A systematic literature review", *Artificial Intelligence in Medicine*, vol. 119. p. 102157, Aug. 2021, doi:10.1016/j.artmed.2021.102157., (Q1 in SJR, H-Index = 98).

2.3 Abstract

Dengue modeling is a research topic that has increased in recent years. Early prediction and decision-making are key factors to control dengue. This SLR analyzes three modeling approaches of dengue: diagnostic, epidemic, intervention. These approaches require models of prediction, prescription, and

optimization. This SLR establishes the state-of-the-art in dengue modeling, using ma- chine learning, in the last years. Several databases were selected to search the articles. The selection was made based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. Sixty-four articles were obtained and analyzed to describe their strengths and limitations. Finally, challenges and opportunities for research on ML for dengue modeling were identified. Logistic regression was the most used modeling approach for the diagnosis of dengue (59.1%). The analysis of the epidemic approach showed that linear regression (17.4%) is the most used technique within the spatial analysis. Finally, the most used intervention modeling is General Linear Model with 70%. We conclude that cause-effect models may improve diagnosis and understanding of dengue. Models that manage uncertainty can also be helpful, because of low data-quality in healthcare. Finally, decentralization of data, using federated learning, may decrease computational costs and allow model building without compromising data security.

2.4 Link to the full article

https://doi.org/10.1016/j.artmed.2021.102157

Chapter 3

Predictive models for the clinical management of dengue

3.1 Motivation

Predictive models for dengue have been widely reported in the literature [1]. Some works have reported predictive models to detect the disease using sociodemographic and epidemiological variables. Other works have differentiated dengue from other diseases with similar clinical pictures such as leptospirosis, malaria, Zika and chikungunya. However, approaches to understand the dynamics of the variables used for diagnosis remain scarce [1]. Knowing in advance the behavior of variables related to dengue severity is crucial because complications leading to death can be avoided. For this reason, we develop a CDSS that uses FCMs both to predict the severity of dengue and to evaluate the behavior of these variables over time. Finally, we compare this approach with other ML approaches. Thus, in this chapter, we present the first paper corresponding to the fulfillment of the first objective. The whole article is in Appendix B.

3.2 Identification of the article

W. Hoyos, J. Aguilar, and M. Toro, "A clinical decision-support system for dengue based on fuzzy cognitive maps", *Health Care Management Science*, pp. 1-16, Aug. 2022, doi:10.1007/s10729-022-09611-6.

3.3 Abstract

Dengue is a viral infection widely distributed in tropical and subtropical regions of the world. Dengue is characterized by high fatality rates when the diagnosis is not made promptly and effectively. To aid in the diagnosis of dengue, we propose a clinical decision-support system that classifies the clinical picture based on its severity, and using causal relationships evaluates the behavior of the clinical and laboratory variables that describe the signs and symptoms related to dengue. The system is based on a FCM that is defined by the signs, symptoms and laboratory tests used in the conventional diagnosis of dengue. The evaluation of the model was performed on datasets of patients diagnosed with dengue to compare the model with other approaches. The developed model showed a good classification performance with 89.4% accuracy and could evaluate the behaviour of clinical and laboratory variables related to dengue severity (it is an explainable method). This model serves as a diagnostic aid for dengue that can be used by medical professionals in clinical settings.

3.4 Link to the full article

https://doi.org/10.1007/s10729-022-09611-6

Chapter 4

Prescriptive models for the clinical management of dengue

4.1 Motivation

Prescriptive models for the clinical management of dengue are essential because they support treatment decision-making. Dengue has no cure and its treatment is based on palliative care to alleviate symptoms and avoid complications. For this reason, it is necessary to develop computer-aided approaches that generate strategies capable of prescribing suitable actions to alleviate or avoid fatal complications. In addition, until 2020 there were no studies that have developed computational tools to support decisions regarding the treatment of dengue [1]. For this reason, we develop methodologies to generate prescriptive models to treat dengue based on WHO guidelines. This chapter focuses on the implementation of algorithms for the generation of prescriptive models. Particularly, it presents an ACODAT for the generation of a prescriptive model, and shows the design and implementation of an extension of FCMs for the generation of prescriptive models not only in the clinical management of dengue, but also to generate prescriptive models with high performance in several domains of science. Thus, for the fulfillment of the second objective, three papers were developed, and each subsection below shows each work.

4.2 ACODAT for the clinical management of dengue

4.2.1 Motivation

Prescriptive modeling is an area of data analytics that is gaining much interest in healthcare due to its capabilities for defining actions related to disease treatment. Until 2020, there were no prescriptive

models for prescribing actions to reduce dengue-related signs and symptoms [1]. Based on this context, we defined an ACODAT to classify dengue and prescribe treatment actions for each type of dengue. In this first prescriptive modeling article, we present the results of the implementation of ML techniques (ANNs and SVMs) for prediction and GA for prescription of a list of available treatments. The whole article is in Appendix C.

4.2.2 Identification of the article

W. Hoyos, J. Aguilar, and M. Toro, "An autonomous cycle of data analysis tasks for the clinical management of dengue", *Heliyon*, vol. 8, no. 10, p. e10846, Oct. 2022, doi: 10.1016/J.HELIYON.2022.E10846.

4.2.3 Abstract

Dengue is the most widespread vector-borne disease worldwide. Timely diagnosis and treatment of dengue is the main objective of medical professionals to decrease mortality rates. In this paper, we propose an autonomous cycle that integrates data analysis tasks to support decision-making in the clinical management of dengue. Particularly, the autonomous cycle supports dengue diagnosis and treatment. The proposed system was built using ML techniques for classification tasks (ANNs and SVMs) and evolutionary techniques (GA) for prescription tasks (treatment). The system was quantitatively evaluated using dengue-patient datasets reported by healthcare institutions. Our system was compared with previous works using qualitative criteria. The proposed system has the ability to classify a patient's clinical picture and recommend the best treatment option. In particular, the classification of dengue was done with 98% accuracy and a GA recommends treatment options for particular patients. Finally, our system is flexible and easily adaptable, which will allow the addition of new tasks for dengue analysis.

4.2.4 Link to the full article

https://doi.org/10.1016/j.heliyon.2022.e10846

4.3 Clinical decision-making through prescriptive modeling

4.3.1 Motivation

Decisions made by medical professionals in prevention, diagnosis and prognosis are difficult due to the large amount of information to be analyzed (demographic, clinical, environmental data, etc.). The lack of experience and knowledge of some health professionals makes difficult to make quickly

decisions, time that is vital in some situations to ensure the life of patients. Based on these scenarios, it is important to develop methodologies that allow the prescription of preventive actions to avoid infections that increase the costs of health systems [1]. In this work, we developed a methodology, called Prescriptive-FCM, to generate prescriptive models that define treatment actions mainly in clinical settings. The proposed approach generated prescriptive models that formulate treatments and actions for diseases. This approach is based on FCMs and optimization algorithms. This work has not yet been published; therefore, it is included in Appendix D.

4.3.2 Identification of the article

W. Hoyos, J. Aguilar, M. Raciny, and M. Toro, "Case studies of clinical decision-making through prescriptive models based on machine learning", preprint under review in *Journal of Biomedical Informatics*, 2023.

4.3.3 Abstract

Background: The development of computational methodologies to support clinical decision-making is of vital importance to reduce morbidity and mortality rates. Specifically, prescriptive analytics is a promising area to support decision-making in the monitoring, treatment and prevention of diseases. These aspects remain a challenge for medical professionals and health authorities. *Materials and Methods:* In this study, we propose a methodology for the development of prescriptive models to support decision-making in clinical settings. The prescriptive model requires a predictive model to build the prescriptions. The predictive model is developed using fuzzy cognitive maps and the particle swarm optimization algorithm, while the prescriptive model is developed with an extension of fuzzy cognitive maps that combines them with genetic algorithms. We evaluated the proposed approach in three case studies related to monitoring (warfarin dose estimation), treatment (severe dengue) and prevention (geohelminthiasis) of diseases. *Results:* The performance of the developed prescriptive models demonstrated the ability to estimate warfarin doses in coagulated patients, prescribe treatment for severe dengue and generate actions aimed at the prevention of geohelminthiasis. Additionally, the predictive models can predict coagulation indices, severe dengue mortality and soil-transmitted helminth infections. *Conclusions:* The developed models performed well to prescribe actions aimed to monitor, treat and prevent diseases. This type of strategy allows supporting decision-making in clinical settings. However, validations in health institutions are required for their implementation.

4.3.4 Link to the full article

Appendix D

4.4 PRV-FCM: an extension of FCMs for prescriptive modeling

4.4.1 Motivation

The development of methodologies to generate prescriptive models should be able to be used in any domain of science. To show the generalizability of our methodology to generate prescriptive models, we tested it in fields such as education, business and medicine. Thus, we implemented the PRV-FCM methodology developed in the previous work to generate prescriptive models in different domains. Since this article has not been published, the full text is presented in Appendix E.

4.4.2 Identification of the article

W. Hoyos, J. Aguilar, and M. Toro, "PRV-FCM: an extension of fuzzy cognitive maps for prescriptive modeling", preprint submitted to *Expert Systems with Applications*, 2023.

4.4.3 Abstract

In this paper, we present a methodology based on FCMs and metaheuristic algorithms to generate prescriptive models, called PRescriptiVe FCM (PRV-FCM). FCMs are a set of concepts interrelated that describe the behavior of a system. This kind of modeling has been extensively used to build descriptive and predictive models. We propose an extension of FCMs to develop prescriptive models and support decision-making in different domains. This adaptation characterizes FCMs, using system and prescriptive concepts. After that, it uses a metaheuristic algorithm (in this case, we use a GA) to optimize prescriptive concepts based on system concepts and the stability of the FCM. Our proposed prescriptive approach was implemented and tested in four scenarios where it demonstrated its capability to find solutions that lead to desired values for the variables of interest. Specifically, no significant differences were found between the values of the prescriptive variables in the datasets and those generated by PRV-FCM.

4.4.4 Link to the full article

Appendix E

Chapter 5

Federated learning approaches for FCMs to support clinical decision-making in dengue

5.1 Motivation

Ensuring data security and privacy when developing CDSSs remains a challenge due to the amount of data being generated today. In addition, there is interest in not sending data to a single location for model training for multiple reasons, such as vulnerability and sensitivity of healthcare data. On the other hand, the amount of lost data in healthcare continues to increase due to the increased workload faced by medical professionals that leads them to not fill in the data correctly. To date, there are no literature reports that implement federated learning to generate predictive and prescriptive models [1]. According to our literature review, this was one of the challenges identified. Based on this, there is a need to develop systems that can guarantee data privacy and security and, moreover, that combine data from different domains to transfer learning from one party to another, and thus obtain global models that can be used by all parties involved. In this chapter, we present one research where we design and implement three federated learning approaches using FCMs to support decision-making with respect to SD. Each approach is described and validated with datasets from two endemic regions of Colombia. This article has not yet been published, therefore, its full text can be found in Appendix F.

5.2 Identification of the article

W. Hoyos, J. Aguilar, and M. Toro, "Federated learning approaches with fuzzy cognitive maps to support clinical decision-making in dengue", article accepted for publication in *Engineering Applications of Artificial Intelligence*, 2023.

5.3 Abstract

Federated learning is a distributed ML approach developed to guarantee the privacy and security of data stored on local devices. In healthcare, specifically in diseases of public health interest such as dengue, it is necessary to develop strategies that guarantee such data properties. Therefore, the aim of this work was to develop three federated learning approaches with FCMs for the prediction of mortality and treatment of SD. We developed three federated learning approaches with FCMs to support decision-making regarding dengue mortality and treatment of SD. Validation of the approaches was performed on SD datasets from two dengue endemic regions in Colombia. We used accuracy to measure the performance of the models developed in each approach. The use of federated learning significantly improves the performance of models developed in centralized environments. Additionally, the use of federated learning allows guaranteeing the privacy and security of each client's data due to the local training of the models. Federated learning is a useful tool in healthcare because it guarantees the privacy and security of patient data. Our results demonstrated the ability of aggregated models to predict mortality and prescribe treatment for SD.

5.4 Link to the full article

Appendix F

Chapter 6

Conclusions

In this research, we defined predictive and prescriptive models for the clinical management of dengue, which consists of diagnosis and treatment of the disease. In this chapter, we present a summary of the conclusions of all previously presented papers. In addition, we show the limitations and research opportunities for future work.

6.1 Summary

Dengue diagnosis is a crucial component in the clinical management of the disease. To address this problem, we developed an explanatory predictive model that would allow diagnosing dengue in a more robust manner. To date, the predictive models developed for dengue diagnosis are based on early detection of the disease and differentiation of dengue from other similar diseases. Dengue diagnosis is based on severity and the models reported in the literature only make predictions, but do not evaluate the dynamics of the variables involved in the severity of dengue. This research opportunity was identified, and we proposed an explanatory model where the behavior of the variables can be evaluated as a prognostic model such that can be observed how the variables related to the diagnosis behave.

The developed CDSS allowed anticipating the presence of some key signs and symptoms to avoid complications. This type of explanatory model is useful for the diagnosis of the disease because it allows the identification of the factors that most influence severity in a particular patient. Detecting warning signs before they occur is crucial to properly manage the patient and avoid complications that lead to death. For example, shock is a defining sign of SD and is indicative of complications. Using simulations, our model was able to detect the presence of shock, even before its onset in patients. The development of this type of computational tools is fundamental to support decision-making with respect to diagnosis and thus reduce dengue mortality rates.

Another important aspect in the clinical management of dengue is treatment. This aspect is closely related to diagnosis, since treatment depends on the type of dengue present in the patient. To support decision-making regarding dengue treatment, we initially implemented ACODAT to prescribe dengue treatment based on WHO guidelines. Subsequently, we designed and implemented a methodology that generates prescriptive models to define treatment options for dengue using FCMs and optimization algorithms. This methodology was also validated on datasets from other science domains.

The prescriptive models generated with our methodology had excellent performance in prescribing and recommending actions, leading to desired outcomes of the proposed systems. The developed models had the ability to prescribe actions with respect to SD treatment, Warfarin dose estimation and geohelminthiasis prevention. With respect to other domains of science, our methodology was validated in fields such as business and education where it allowed the generation of prescriptive models to define actions that improve wine quality and increase student academic performance.

Finally, in health sciences is essential to ensure the privacy and security of patient data. In Chapter 3 and Chapter 4, the models were trained using a centralized environment. The data were collected and gathered in one place, where AI techniques were applied to obtain the trained models. This approach is known as traditional ML and does not guarantee the privacy and security of the data. To address this problem, we proposed three federated learning approaches with FCMs to support decision-making in the diagnosis and treatment of SD. The first approach, called *total federated learning,* indicates that the feature space in each site is equal. The second approach, called *target-based federated learning,* assumes that only one variable (target or decision variable) is common among all sites involved in the federation. Finally, the third approach, called *federated transfer learning*, indicates that learning can be transferred from one site to another.

The use of federated learning is a useful alternative to the traditional ML approach. Federated learning allows local training of models with local data and only shares model parameters with other parties. In all proposed approaches to support decision-making with respect to dengue diagnosis and treatment, the performance of models developed with federated approach was superior to the performance of both local models and models trained under the centralized or traditional approach. In addition, the privacy and security of dengue patient data was guaranteed because the models were trained locally with their own data and what was shared between the parties were the parameters of the trained models.

6.2 Limitations and future work

We developed strategies or approaches to support decision-making in the clinical management of dengue. With the results of the present investigation, we were able to meet the proposed objectives. However, this research has some limitations, which we summarize below.

For the generation of the predictive and prescriptive models we used data related to signs, symptoms, laboratory tests and variables related to dengue diagnosis and treatment. However, not all dengue-related variables were available. Data from dengue patients, like all data in the health care field, is difficult to collect due to the sensitivity of this type of data. The use of variables such as cytokines and complete blood count test could help to improve the performance of the developed models. Our systematic literature review showed the importance of this type of variables for the diagnosis and classification of dengue [1].

A limitation in all the works presented in this research is the number of endemic regions and the sample size used for the construction of predictive and prescriptive models for the clinical management of dengue. The availability of data depends on the frequency of the observed event, for example, SD has very low frequency when compared to non-severe dengue with and without warning signs. Increasing the sample size by adding other dengue endemic regions not only in Colombia, but also in the world, could improve performance and could yield results on the behavior of variables related to dengue severity in populations with different characteristics. Additionally, the development of methodologies that generate synthetic data with the same distribution as the original data without losing information could be helpful to address this problem.

The absence of datasets with before and after cohort did not allow evaluating the impact of predictions and prescriptions, and the analysis of factors that influence the severity of dengue. The use of longitudinal data from prospective studies and the implementation of other optimization algorithms would allow us to know the impact on patient health of the actions prescribed by the developed prescriptive models. Longitudinal data follow individuals at different time points. Knowing the real evolution of patients' severity at different time points could allow a more accurate validation of the proposed models and approaches. On the other hand, for the generation of prescriptive models, we only used GAs and particle swarm optimization algorithm, due to their simplicity to be trained and their excellent performance demonstrated in studies reported in the literature [28–30]. However, other optimization algorithms could perhaps better establish the relationships between predictor variables and decision variables.

In the last objective of the present study, federated learning approaches were developed to prevent parties involved with dengue patient data from sharing their data in violation of data privacy. Although these approaches used a federated global model, they are still centralized because the process of aggregating the local models to generate a global model is done on a federated server. A disruption to this server would disrupt the process of aggregating and updating the global model in all parties involved. It is necessary to develop new approaches where all the parties involved perform the aggregation process and all of them can access the global model at the same time.

FCMs were extensively used in this thesis to generate both prediction and prescription models.

Although research in this technique has increased considerably, there are still challenges to be taken into account. For example, there are currently enough libraries to perform the inference process with FCMs in languages such as, R [31], Python [32] and Java [33]. However, there are not enough computational tools to train FCMs with historical data. In addition, there are no libraries that implement FCMs in a federated environment. Future work could be directed towards the development of libraries that use historical data to train the FCMs, in order to obtain the map weights. Finally, the development of libraries that allow federated training with FCMs would be an interesting future work.

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Appendix A

Dengue models based on machine learning techniques: A systematic literature review

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Dengue models based on machine learning techniques: A systematic literature review

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ABSTRACT

Background: Dengue modeling is a research topic that has increased in recent years. Early prediction and decision-making are key factors to control dengue. This Systematic Literature Review (SLR) analyzes three modeling approaches of dengue: diagnostic, epidemic, intervention. These approaches require models of prediction, prescription and optimization. This SLR establishes the state-of-the-art in dengue modeling, using machine learning, in the last years.

Methods: Several databases were selected to search the articles. The selection was made based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. Sixty-four articles were obtained and analyzed to describe their strengths and limitations. Finally, challenges and opportunities for research on machine-learning for dengue modeling were identified.

Results: Logistic regression was the most used modeling approach for the diagnosis of dengue (59.1%). The analysis of the epidemic approach showed that linear regression (17.4%) is the most used technique within the spatial analysis. Finally, the most used intervention modeling is General Linear Model with 70%.

Conclusions: We conclude that cause-effect models may improve diagnosis and understanding of dengue. Models that manage uncertainty can also be helpful, because of low data-quality in healthcare. Finally, decentralization of data, using federated learning, may decrease computational costs and allow model building without compromising data security.

1. Introduction

Dengue is a vector-borne disease, with high importance in public health [1]. This disease is widely distributed worldwide; especially, in tropical and subtropical areas [2]. The disease is produced by an arbovirus (DENV) that receives the same name. To date, four virus serotypes have been identified: DENV-1, DENV-2, DENV-3 and DENV-4 [3]. The infection is transmitted to humans by the bite of mosquitoes of the genus *Aedes*, mainly *A. aegypti* and *A. albopictus* [4].

In 1997, the World Health Organization (WHO) classified the disease like dengue fever and dengue hemorrhagic fever [5]. A new classification was proposed in 2009, which was based on the severity level of the

Abbreviations: DENV, dengue virus; WHO, World Health Organization; SD, severe dengue; DSS, dengue shock syndrome; SLR, systematic literature review; PRISMA, preferred reporting items for systematic reviews and meta-analyses; LoR, logistic regression; ANN, artificial neural networks; MLP, multilayer perceptron; MCS, modified cuckoo search algorithm; PSO, particle swarm optimization; SE, structural equations; AUC, area under the curve; OR, odds ratio; CI, confidence intervals; RF, random forest; PAF, platelet activating factor; S1P, sphingosine 1-phosphate; IL-1β, interleukin 1 beta; TNFα, tumor necrosis factor alpha; IL-10, interleukin 10; FL, fuzzy logic; VEGF, vascular endothelial growth factor; SVM, support vector machines; DNA, deoxyribonucleic acid; DT, decision trees; APRI, aspartate aminotransferase/platelet count ratio index; LASSO, adaptive least absolute shrinkage and selection operator; GAM, generalized additive model; CART, classification and regression trees; GBM, gradient boosting machines; BRT, boosted regression machines; GWR, geographically weighted regression; SOM, self-organized maps; SARIMAX, seasonal autoregressive integrated moving average; MAE, mean absolute error; LiR, linear regression; BI, Breteau index; HI, house index; CoI, container index; AI, Adult index; KNN, k-nearest neighbors; MSE, mean square error; GT, Google trends; DBSI, dengue Baidu search index; RMSE, root mean square error; GLM, generalized linear model; ALT, alanine aminotransferase; BTS, bayesian time series; CRF, climate risk factor index; SS, stochastic simulation.

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disease: non-severe dengue (with or without warning signs) and *severe dengue (SD)*. This last includes the *dengue shock syndrome (DSS)* [6]. According to the WHO, more than 350 million dengue virus infections occur annually worldwide. In addition, 20,000 deaths related to dengue in the same period of time [7].

Dengue has been the subject of various studies worldwide. Its high prevalence in tropical and subtropical regions of the world has generated interest in its diagnosis, treatment and control. Different systematic literature reviews (SLRs) have been carried out of dengue. Most of them have been focused on the evaluation of molecules for the generation of vaccines, control of transmission, epidemiology and development of rapid-detection tests. In what follows, we briefly explain previous SLRs.

Several SLRs have described the epidemiology of dengue. Jing and Wang [8] showed the epidemiology of dengue according to its geographical and temporal distribution. Besides, Jing and Wang evaluated risk factors for transmission and control of dengue. Alhaeli et al. [9] conducted a review of the epidemiology of dengue in Saudi Arabia, where environmental conditions are extreme. Other reviews on the epidemiology of dengue have been carried out in different countries, such as Pakistan [10], Thailand [11], Malaysia [12], Philippines [13], Mexico [14] and Brazil [15]. Finally, Villar et al. [1] conducted a SLR of the epidemiological trends of dengue, in Colombia, for over 12 years (2000−2011).

Another group of SLRs has focused on the production of rapid-detection tests and vaccines against the virus. For instance, Lim et al. [16] and Luo et al. [17] conducted reviews and meta-analyses to assess the economic impact of rapid-screening tests. Reviews have also been conducted to identify the latest economic studies of dengue vaccination [18,19]. For the development of dengue vaccines, it has been evaluated the immunogenicity, safety and efficacy of the vaccine [20,21,22].

In recent years, with the emergence of machine learning and the increase in data generation, computational methods have been developed for the prediction and evaluation of disease-transmission dynamics. This has generated interest for SLRs on this subject, to know the latest developments and opportunities in this domain. As an example, Louis et al. [23] developed an SLR of dengue to identify the main modeling approaches of the disease risk. Another SLR on computational methods was conducted by Naish et al. [24], focusing on quantitative modeling with respect to climate change. Andraud et al. [25] conducted a review of deterministic models of dengue transmission to identify features for future models. Finally, Lourenço et al. [26] published a review of the challenges in dengue research from a computational perspective. The authors focused on real-time data collection, genetic analysis and integrative modeling approaches. Particularly, integrative-modeling approaches simulate the epidemiology and molecular evolution of the virus.

We present a review of three modeling approaches of dengue: diagnostic, epidemic and intervention. The goal is to present the development of machine learning models for these contexts. The first approach is to determine whether a patient has dengue or any of its variants. The second is to analyze the population-level dengue epidemic; in addition, to study morbidity and mortality rates. The third is to analyze the impact of interventions to mitigate epidemics of dengue. To date, there is no SLR that studies these three aspects related to the disease together. In addition, it is the first SLR to focus on models to evaluate the impact of interventions to mitigate dengue epidemics. Finally, this SLR establishes the state-of-the-art in these approaches, and, additionally, defines new challenges and opportunities for future research. The objectives of this SLR are:

- To collect and describe machine learning models for dengue.
- To visualize challenges for future work in dengue modeling.

The present document is structured as follows: Section 2 describes search and selection process of relevant articles; Section 3 describes general results of the research; Section 4 discusses the papers, as well as the challenges and opportunities for research on dengue modeling for diagnosis, epidemics and interventions to control dengue. The last section shows the conclusions, with a description of the works that would be a priority to develop in this research domain.

2. Methodology

This review was based on the PRISMA methodology [27]. The first step is to establish research questions; the second is to define a search strategy to delimit the findings; the third is to select the papers using eligibility criteria; and, finally, the last is to analyze the articles to extract strengths, limitations and challenges to overcome. To achieve the goal of this review, three research questions were proposed:

Q1. Which machine learning models have been developed for dengue diagnosis?

Q2. Which machine learning models have been developed for the analysis of dengue epidemics?

Q3. Which machine learning models have been developed for the evaluation of dengue control strategies?

2.1. Search strategy

We used several digital libraries (databases): ScienceDirect, IEEE Xplorer, Google Scholar, Emerald, Taylor & Francis and Pubmed. The inclusion criteria for the selection of publications were: i) articles from January 2015 to March 2021, in the English language, related to the development and implementation of diagnostic, epidemic and intervention models of dengue; ii) articles that match the search terms that describe the research questions. The criteria that allow discarding publications were: i) articles representing the personal opinions of individual experts, ii) conference papers, posters, abstracts, short articles and unpublished works; and iii) articles using ordinary-differential-equations models and other deterministic approaches. Table 1 shows the search strings derived from the research questions. Search strings were structured using the logical operators “OR” and “AND”.

2.2. Selection procedure

The selection procedure was carried out in three stages using inclusion and exclusion criteria above mentioned: i) We chose articles by evaluating their title and keywords to exclude any non-relevant work. We also removed duplicate papers; ii) We examined the summaries of candidate papers from Stage 1. Then, we evaluated each paper to define if it is selected to the next step; iii) We evaluated the full texts of selected papers from Stage 2 to exclude papers that did not meet the criteria. Fig. 1 shows the flowchart of the selection process.

A total of 19.327 papers were recovered from the scientific libraries. After reviewing the title and keywords, and removing duplicate elements (Stage 1), 418 papers were selected. Stage 2 consisted of abstract review, which allowed the selection of 203 papers. Finally, 64 articles met all the eligibility criteria (Stage 3), where 27 were about diagnostic modeling, 29 about epidemic models and 8 about prescriptive

Table 1
Search strings used for each research question.

Question	Approach	String search
Q1	Diagnostic	[(diagnosis OR diagnostic OR infection) AND (gender OR age OR phenotype OR race OR “clinical profile”) AND model AND dengue]
Q2	Epidemic	[(epidemic OR outbreak) AND (predictive OR predicting OR prediction) AND model AND (dengue OR aedes)]
Q3	Intervention	[(fumigation OR vaccine OR “biologic control” OR “decision making” OR intervention OR prescriptive) AND model AND (dengue OR aedes)]

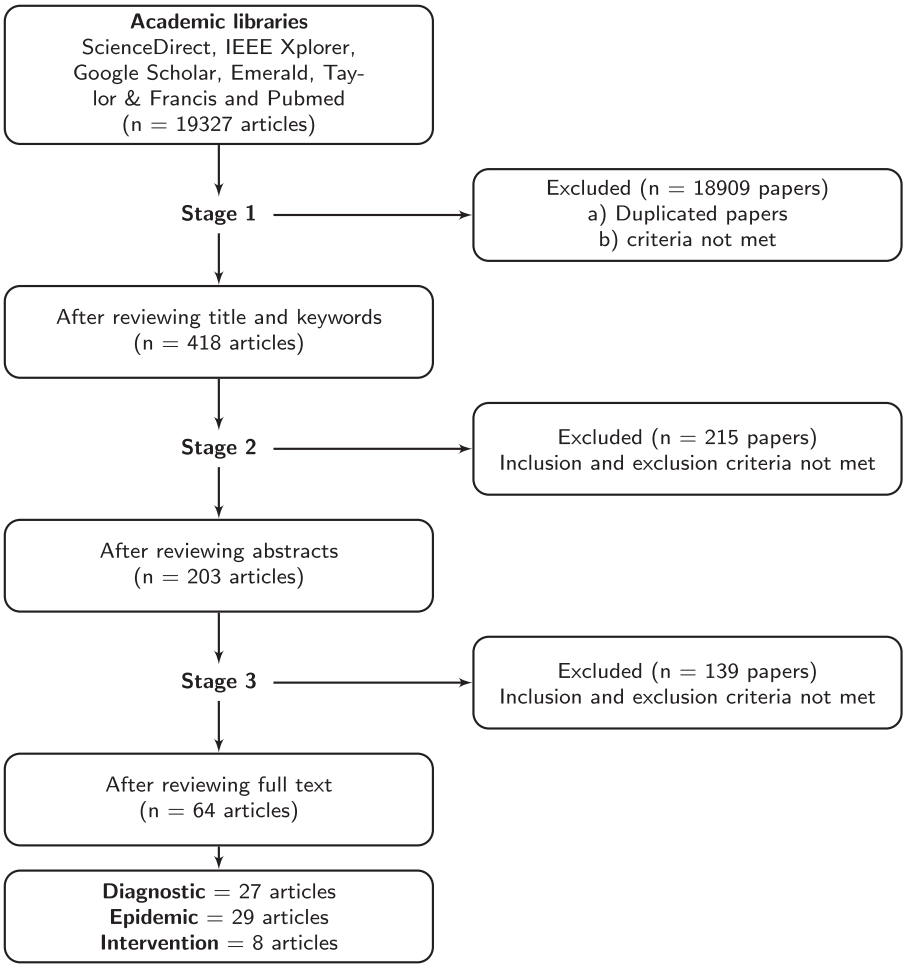

Fig. 1. Flowchart of the selection process.

(intervention) modeling.

2.3. Preliminary analysis

This subsection shows the preliminary results of selected articles. Fig. 2 shows the distribution of the reviewed articles on dengue modeling around the world. The highest number of studies were from Taiwan with 9 (14%) articles, followed by Brazil and Vietnam, with 7 (11%) articles in both countries. It was expected that Taiwan, Brazil and Vietnam would be in the top positions. First, because they are endemic countries where the amount of data available is greater. Second, because they are countries close to the equatorial axis and contain tropical and subtropical regions. In contrast, there are dengue-endemic countries with a low amount of publications on diagnostic, epidemic and

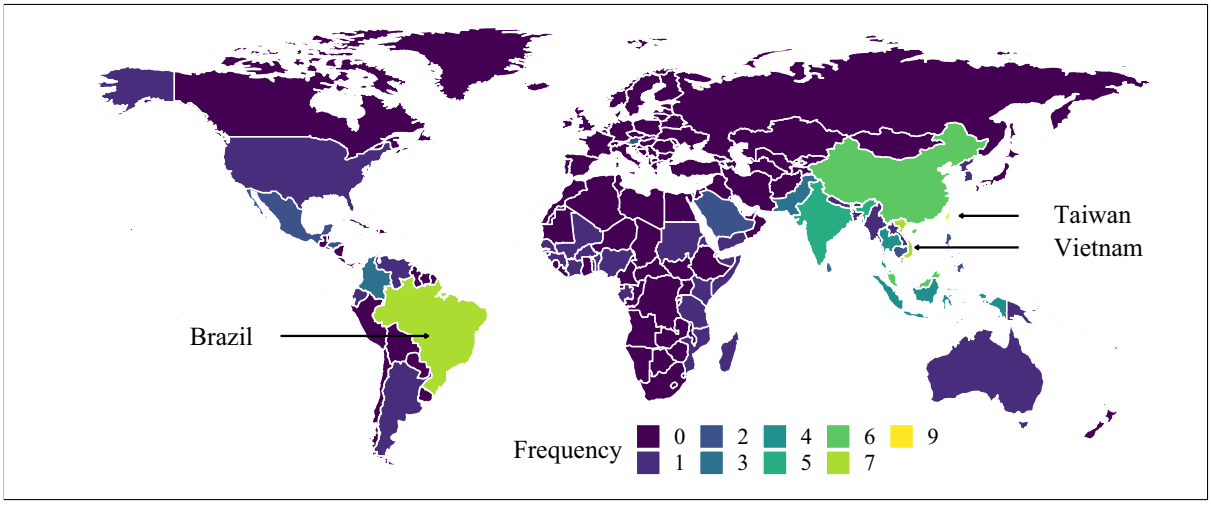

Fig. 2. Worldwide distribution of the reviewed papers on dengue modeling.

intervention modeling. Among these are Colombia, Ecuador and Venezuela. These countries may not have many publications because they invest very low in science and research [28].

Many predictors/features/variables are currently used for dengue modeling, which are classified according to their own characteristics and their method of collection. We classified them as: demographic, economic, clinical, laboratory, environmental, climatic, among others. For a better understanding, a brief description of them, with some examples, is shown in Table 2. In general, the most used variables were socio-economic and demographic data. Their easy access and availability would explain their high frequency of use. The combination of clinical and laboratory data was the most used for diagnostic modeling. The use of this data type is crucial for this approach because it allows finding relationships between the data and early detection of the disease. In terms of the epidemic approach, the most widely used predictors/variables were climatic, environmental and meteorological. These data types are widely used for the spatial-temporal analysis of dengue to map the distribution of the mosquito or disease. Finally, intervention modeling focused on the evaluation of control strategies of the mosquito. For this reason, entomological data were the most used for this purpose.

According to this review, the least used variables for dengue modeling are genomics, cellphone and thermal-imaging data. Genomics data obtained from genetic tests were not usually performed for the diagnosis of dengue. Cellphone data are not easily acquired due to user privacy issues, and thermal imaging requires specialized tools that are not available in clinical practice.

3. Analysis of reviewed papers

Sixty-four articles were reviewed and analyzed to find what has been developed on diagnostic, epidemic and intervention modeling of dengue.

Table 2
Description, examples and frequency of predictors used in dengue modeling in the reviewed papers.

Type of predictor	Definition	Examples	Articles
Demographic + Social + Economic + Population	Characteristics related to the development of a population, from a quantitative perspective.	Age, sex, population, housing type, socio-economic level.	31
Climatic + Environmental + Meteorological + Topographic	Characteristics related to climate and environment.	Temperature, rainfall, precipitation, elevation.	29
Laboratory	Analytical determinations of metabolites in the blood that may be altered in patients with dengue.	Platelet and leukocyte count, hematocrit, albumin, transaminases	25
Clinical	Signs and symptoms of patients with dengue.	Blood pressure, fever, joint pain, headache, retro-ocular pain, arthralgia, myalgia.	21
Search Index and social networks	Data from Internet	Google Trends, Baidu Search Index, Twitter.	7
Entomological	Data related to the biological vector and its propagation.	Breteau index, container index, house index, one adult index, predations rates.	7
Genomic	Genetic data	Gene-expression levels	2
Thermal Images	Images obtained from infrared cameras	Thermograms	1
Cellphone	Data obtained from cellphones	Geo-localization	1
Mobility	Air-passengers travel data	Destination country	1

3.1. Diagnostic models of dengue

This section analyzes articles related to diagnostic models of dengue. The analysis was carried out according to different aspects of the disease that are currently important: early detection, seroprevalence used to determine populations at risk to acquire the disease, use of cytokines and plasma leakage as early markers of severity, and new diagnostic methods such as Raman spectroscopy.

3.1.1. Early diagnosis of dengue

Early diagnosis of dengue could prevent complications and death. For this reason, Macedo-Hair et al. [29] presented the analysis of clinical profiles of 523 dengue patients. In this case, Macedo-Hair et al. used unsupervised learning to find natural clusters associated with clinical patterns in confirmed cases of dengue. The results showed that the model can classify dengue into four states (4 clusters): dengue without warning signs, dengue with warning signs, SD and an intermediate state. These clusters can be used as risk criteria to diagnose dengue. Fernandez et al. [30] presented a model based on *logistic regression (LoR)* to differentiate dengue from other febrile diseases. The use of laboratory, clinical and demographic data was useful to reveal the association of predictive variables with the risk of suffering dengue. The results showed that there was a strong association of dengue with the explanatory variables: male sex, petechiae, skin rashes, myalgias, retro-ocular pain, positive tourniquet test and gingival bleeding. The accuracy of the model to diagnose dengue was 69.2%.

Artificial neural networks (ANN) are machine learning algorithms that describe functional dependencies between input and output variables. One drawback of ANN is their optimization functions. ANN is set-up as a non-convex optimization problem where there could be a local minimum that is not a global minimum. To overcome this, Chatterjee et al. [31] used an ANN (*multilayer perceptron (MLP)*) with a Cukoo search algorithm (ANN-MCS), to classify healthy people, patients with dengue and SD. The results showed that ANN-MCS improves the model accuracy (95.65%), compared to the use of unmodified ANN (87.5%). Gambhir et al. [32] also used an ANN (MLP) to early predict dengue. The authors supplemented ANN with the *particle swarm-optimization (PSO)* algorithm. The results of the combined model showed an accuracy of 87%, higher than the accuracy of ANN without PSO (79%). A *deep neural network (DNN)* is an ANN with several hidden layers between the input and output layers. This kind of ANN can model more complex nonlinear relationships [33]. Ho et al. [34] used a DNN to identify laboratory-confirmed dengue cases using only four input variables (age, body temperature, leukocyte count and platelets). The developed model by Ho et al. was compared to LoR and DT. The *area under the curve* (AUC) was used to evaluate the performance. The results showed similar performance in the developed models (DNN = 0.86 Vs. DT = 0.85 Vs. LoR = 0.84), with DNN being slightly better.

Park et al. [35] developed models to classify dengue, SD and DSS using *structural equation (SE)* modeling. Park et al. used clinical and laboratory data for this purpose, and their models showed good performance for each disease variety (dengue: AUC = 0.84, SD: AUC = 0.67, DSS: AUC = 0.70). Finally, Khosavanna et al. [36] developed two diagnostic algorithms (LoR and DT) based on clinical symptoms of dengue patients. The models performed similarly in specificity (LoR = 0.63 Vs. DT = 0.67) and sensitivity (LoR = 0.78 Vs. DT = 0.77).

3.1.2. Seroprevalence of dengue

Dengue seroprevalence studies allow knowing past or current circulation of the virus in a specific area. This allows, among other things, to determine the populations at risk for a disease, and to evaluate the mechanisms of transmission [37]. Al-Raddadi et al. [38] developed the first multivariate model using LoR to estimate dengue seroprevalence in

four endemic cities in Saudi Arabia. The authors analyzed the association of risk factors (demographic, clinical, and environmental) with the disease using a multivariate LoR. They used the *odds ratio (OR)* with a 95% *confidence interval (CI)* to present the results. The predictors associated with the highest seroprevalence rate were: age over 30 years (OR [95% CI] = 3.91[2.78, 5.50]), housing type (OR [95% CI] = 1.93[1.62, 2.31]), absence of pest-control activities (OR [95% CI] = 1.39 [1.13, 1.72]) and presence of mosquitoes at home (OR [95% CI] = 1.39 [1.14, 1.70]). Aguas et al. [39] used *random forest (RF)*, on laboratory data (antibody titration), to estimate the proportion of asymptomatic dengue in children. The algorithm presented an accuracy of 99.45%, correctly classifying 361 cases out of 363.

3.1.3. Cytokines

Cytokines are molecules that increase their levels in the blood after a severe infection. Jayasundara et al. [40] presented a study describing the role of cytokines in SD: *platelet activating factor (PAF)*, *sphingosine 1-phosphate* (*S1P*), *interleukin-1 beta* (*IL-1β*), *tumor necrosis factor-alpha (TNFα)* and *interleukin-10 (IL-10)*. They used *fuzzy-logic (FL)* to diagnose SD. The patients were analyzed 96, 108 and 120 h from onset of fever, using blood levels of cytokines for each time point. The developed model showed the best accuracy after 108 h from the onset of fever (85%). Low et al. [41] evaluated *vascular endothelial growth factor (VEGF)* and pentraxin-3 to classify the disease into severe and non-severe. The proposed diagnostic model using LoR showed 76.2% and 73.6% of sensitivity and specificity, respectively. According to the results, pentraxin-3 is not useful to differentiate SD from non-severe dengue. There was no significant difference between the two groups for this cytokine's blood levels.

3.1.4. Raman spectroscopy

In recent years, Raman spectroscopy has been used for medical diagnoses, such as cancer [42,43], liver diseases [44,45], and infectious diseases, such as tuberculosis [46] and Chagas disease [47]. Khan et al. [48] proposed the extraction of the Raman spectrum, in serum samples, from healthy people and dengue patients. The goal was to classify the samples into normal and pathological using RF. The model had a good performance (accuracy = 91%). The same authors published another paper [49], but this time, they used a *support vector machine (SVM)* for the classification task. Different kernels were used: linear, polynomial and radial. The best kernel was the grade one polynomial; however, the performance with SVM was lower (85%) compared to RF (91%).

3.1.5. Plasma leakage and severity

Plasma extravasation is a warning sign for SD and should be detected early to avoid complications and death. This sign is characterized by serous effusions at the level of various cavities, such as pleura, pericardium and peritoneum. For this reason, Suwarto et al. [50] developed a scoring system to detect pleural and/or ascitic effusion. Suwarto et al. implemented a LoR using laboratory data. To each factor, a score is assigned to determine the risk of plasma leakage. The higher score is assigned to a patient, the more likely the patient is to leak plasma. The developed model detected plasma leakage or ascites, with an accuracy of 77.4%. Another study by da Silva et al. [51], used the same regression technique (LoR) to evaluate risk factors for hospitalization after dengue infection. The explanatory variables used were demographic, clinical and laboratory. The authors found that multi-organ failures are the most influential factors in hospitalization (OR[95% CI] = 5.75[3.53, 9.37]). Fernandez et al. [52] used a multivariate logistic model, in Honduran patients, using demographic, clinical and laboratory data. Fernandez et al. used plasma leakage as the target variable since this is the main warning sign of SD. The developed model achieved an accuracy of 70.9%, with a sensitivity of 76.4% and a specificity of 70.3%. The same modeling technique was used by Phuong et al. [53], with the addition of free plasma *deoxyribonucleic acid (DNA)* as a predictor variable. The model achieved a sensitivity of 87.5%, and a specificity of 54.7%.

Davi et al. [54] used gene expression data to diagnose SD. The authors used an MLP model with an average accuracy of 86%. Another study conducted by Tuan et al. [55], in Vietnam, applied multivariate LoR models to demographic, clinical and laboratory data. The AUC results were 0.95, with a sensitivity of 87% and specificity of 88%. Another model, using the same data and technique, was developed by Ahmad et al. [56]. The authors evaluated the main warning signs for SD. The best results showed that the model had a sensitivity of 91% when at least one warning sign was present, and a specificity of 99% when there were more than 5 warning signs. The study of Phakhounthong et al. [57] presented the use of *decision trees (DT)* for SD in children. The model was based on clinical and socio-demographic data of dengue patients. The sensitivity, specificity, and accuracy of the model were 60.5%, 65% and 64.1%, respectively. Finally, Huang et al. [58] developed several models to diagnose severe dengue using demographic information and laboratory-test results. Huang et al. applied several machine learning techniques, such as LoR, RF, GBM, SVM and ANN. The best model was ANN with an accuracy of 75% and an AUC of 0.83.

Zhang et al. [59], in their study, showed a new variable to diagnose SD: the *aspartate aminotransferase/platelet count ratio index (APRI)*. The authors developed an LoR to evaluate the performance of APRI, in conjunction with other laboratory variables, such as prothrombin time and leukocyte count. The model performed well, reporting an AUC of 0.87. Another work carried out by Lin et al., [60] also used LoR, but using hyaluronic acid as a feature or variable. The developed model by these authors had a moderate performance, with an AUC of 0.69, specificity of 55%, and sensitivity of 76%. Lee et al. [61] implemented LoR models for the development of a clinical-risk score for early diagnosis of SD. The researchers proposed that the coefficients in the model can be used as a risk score. The best developed model obtained an AUC of 0.92. The sensitivity and specificity of the model were 80.3% and 85.8%, respectively.

DSS is a potentially life-threatening complication of the disease. Lam et al. [62] proposed a diagnostic model to detect DSS in children. The authors developed LoR models to determine the relationships between clinical and laboratory variables with the presence of DSS. In addition, alternative techniques, such as *adaptive least absolute shrinkage and selection operator (LASSO)*, *generalized additive model (GAM)*, *classification and regression trees (CART)* and *gradient boosting machine (GBM)*, were compared. The logistic model performed favorably (AUC = 0.74), compared to the alternative modeling strategies (LASSO = 0.73, CART = 0.61, GAM = 0.69, GBM = 0.72). Another research work using LoR was carried out by Lam et al. [63], in Vietnam, where they evaluated the platelet count for the diagnosis of DSS. The model was better with the use of platelet count than without it (AUC = 0.73 Vs. AUC = 0.66).

In summary, most of the modeling approaches for dengue diagnosis were based on LoR (see Fig. 3). Logistic models are widely used in the health field because of their simplicity to perform and interpret the results. These models were developed primarily to assess the factors associated with the risk of dengue infection, and to determine the association of predictive factors with disease severity. The categories of variables most frequently used to construct these models were demographic, clinical and laboratory parameters (see Fig. 3). This result is possibly due to the fact that these types of features are the most available in all countries with mandatory surveillance systems. GBM, FL and SE models are possibly the least used because of their mathematical complexity and difficulty to implement. Finally, the reviewed models for diagnosis were implemented as classification tasks: They only determined whether the patient had the disease or not. Diagnostic models should go further, and evaluate causal relationships among predictors and dengue.

3.2. Epidemic models of dengue

This section analyzes epidemic modeling approaches of dengue. This section was divided into subsections according to key aspects, such as

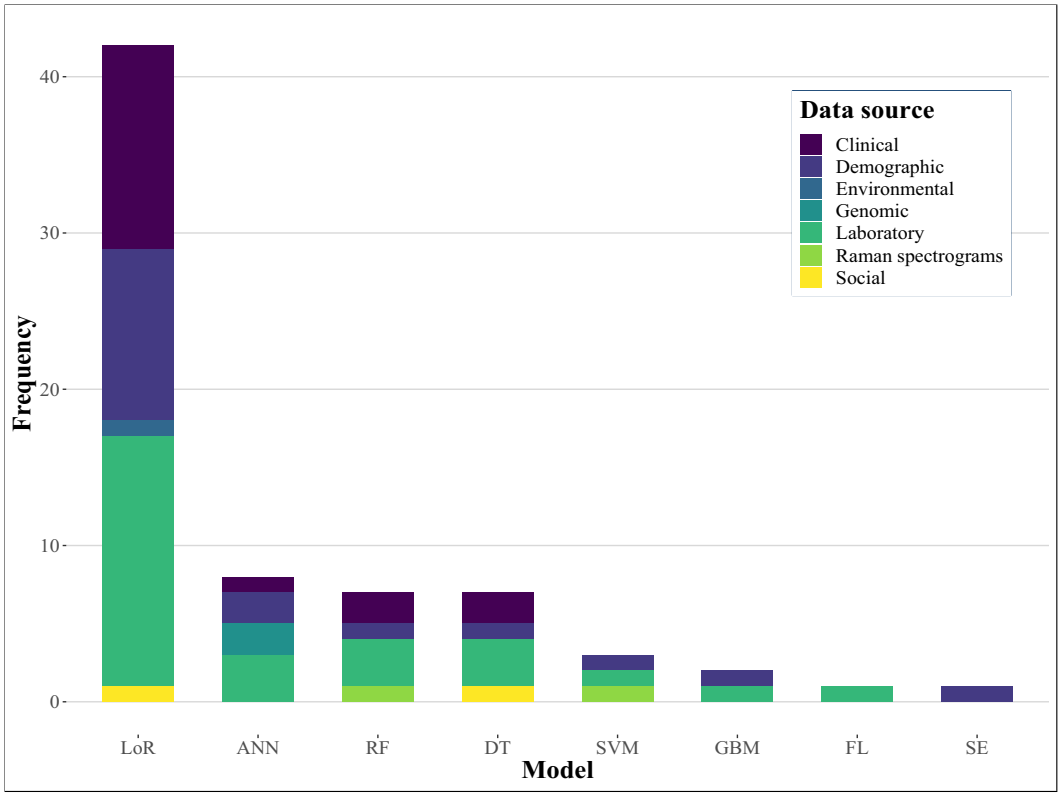

Fig. 3. Types of models vs. type of data sources for diagnostic models. The frequency indicates the number of times the technique was implemented in the studies. Abbreviations: LoR = Logistic Regression, ANN = Artificial Neural Networks, RF = Random Forest, DT = Decision Trees, SVM = Support Vector Machines, GBM = Gradient Boosting Machines, FL = Fuzzy Logic, SE = Structural Equations.

the type of analysis performed (e.g., spatial-temporal analysis), the types of data used (e.g., the Internet data from the social networks and search indexes). Finally, there is an important section dealing with the prediction of mortality, a latent problem that should be addressed with predictive modeling.

3.2.1. *Spatial-temporal analysis of dengue*

The spatial-temporal analysis of dengue is the most studied field of the disease, among the reviewed articles. There are many studies that use machine learning to evaluate the spread of vectors and diseases. Rossi et al. [64] used *boosted regression-trees (BRT)* to conduct a spatial-temporal analysis of dengue with data from 76 countries. BRT is a modeling technique used primarily in ecology to explain or predict a phenomenon. The data collected were temperature, rainfall, migration and population density. The study showed that higher population density and shorter distances between countries with dengue outbreaks are relevant factors that characterize the disease. *Geographically weighted regression (GWR)* was used by Delmelle et al. [65], to evaluate the role of environmental and socioeconomic determinants of dengue in Cali, Colombia. The authors found that socioeconomic status, population density, proximity to both tire shops and plant nurseries; and the presence of sewage systems, are related to the disease. Mao et al. [66] used RF to predict the presence of dengue cases in a given area using topographic, climatic and population data. Since people are more likely to become ill when they travel to other locations, an important contribution of this work is the use of cellphone tracking data. Based on this, the authors reported an accuracy of 95%. Finally, Mutheneni et al. [67] mapped the levels of dengue endemicity in some districts of India, to identify groups at risk. The authors used *self-organizing maps (SOM)*, with environmental data, for this purpose. The results indicated that the districts of Warangal, Karimnagar, Khammam and Vizianagaram are hot spot regions.

A study by Akter et al. [68] used *linear regression* (LiR), with ecological and socio-demographic factors, to observe the spatial-temporal trend of dengue in Australia. The results of regression analysis showed an increased trend of dengue incidence with some factors, such as housing types and households with rainwater tanks. Yue et al. [69] and Reyes-Castro et al. [70] used the same technique in five districts of China and two arid cities of Mexico, respectively. The two studies used environmental and spatial data to build the models. Besides, socioeconomic data were aggregated for model improvement. On one hand, Yue et al. indicated the factors and dengue outbreak were significantly positively correlated. On the other hand, Reyes-Castro et al. showed that transmission foci started in neighborhoods with high-population density and low access to health services.

In Brazil, according to the Ministry of Public Health, a year is epidemic, in a city, if the incidence is greater than 100 cases per 100,000 inhabitants [71]. In this regard, Stolerman et al. [72] developed an SVM to predict whether a year will be epidemic or not. The data used by Stolerman et al. were climatic and epidemiological of 16 years. The SVM predicted the epidemicity of a year at 91% accuracy.

Several studies have compared the performance of different machine learning models to predict dengue burden, outbreaks and importation of dengue into Europe. Carvajal et al. [73] compared machine learning models, using weather factors, in the Philippines. The objective was to find out which meteorological factors were the best predictors of dengue in that country. The techniques used were GAM, *seasonal autoregressive integrated moving average with exogenous variables (SARIMAX)*, RF and GBM. They reported that relative humidity is the most important meteorological factor in the model. The highest performance, in terms of *mean absolute error (MAE)*, was RF (0.23), followed by GBM (0.24). Zhao et al. [74] compared RF and ANN to predict dengue burden, in Colombia, at national and local scales. The comparison between the models was performed using MAE, and the results showed that RF (0.86)

performs slightly better than ANN (0.95). According to the level of prediction, the results showed that RF performs better at the national level than the sub-national level, demonstrated by lower MAE values in 12-week forecasts (national = 0.86 Vs. local = 0.97). Salim et al. [75] used various machine learning techniques (SVM, DT, ANN, Bayes Network) to predict epidemics in Malaysia. Climatic variables were used as a predictor to build the models. According to the results reported by Salim et al., linear SVM performed the best, with an accuracy of 70%, specificity of 95% and sensitivity of 14%, when using the original data. On the other hand, class balancing improved the sensitivity to 64%. Finally, Salami et al. [76] developed and compared machine learning models to predict dengue importation into Europe. Salami et al. used air-passenger data to create connectivity indices between a source and destination country. The techniques implemented were RF, GLM, GBM and partial least squares. GBM had the best performance, with an AUC of 0.94, a sensitivity of 0.94 and a specificity of 0.93.

3.2.2. Distribution of the vector

Simulation of vector distribution that transmits dengue is important to establish control strategies by health authorities. For this type of modeling, entomological data, such as the *Breteau index (BI)*, *house index (HI)*, *container index (CoI)* and *adult index (AI)*, are commonly used. BI is the number of positive containers per 100 houses inspected. HI is the percentage of houses infested with mosquito larvae or pupae. CoI is the percentage of water containers infested with mosquito larvae or pupae. Finally, AI is the number of female mosquitoes captured divided by the number of houses inspected [77,78].

Parra et al. [79] developed a GAM using BI and mosquito genetic data. Meteorological data were also used to build the model. The proposed model required 71.5% fewer human and operational resources than the BI measurement. Similarly, Chang et al. [77] used entomological indices as a tool for early prediction of a dengue epidemic. The implemented regression models obtained accuracies of 83.8, 87.8, 88.3 and 88.4%, for BI, HI, CoI and AI, respectively. Ding et al. [80] simulated the distribution of *A. aegypti* and *A. albopictus* using environmental, climatic, social data and three machine learning methods (SVM, GBM and RF). Models with RF performed better followed by GBM; however, there were no significant differences between the results of AUC (*A. aegypti*: 0.973 Vs. 0.974 and *A. albopictus*: 0.971 Vs. 0.972). Jacome et al. [81] used LiR to identify the most important risk factors for the distribution of *A. aegypti* in a coastal zone in Ecuador. Environmental and spatial data were used for this purpose. Temperature and population density were the factors most likely to predict the number of cases.

Modeling of mosquito breeding sites, using remote sensing, is gaining interest in the scientific community. Scavuzzo et al. [78] implemented several machine learning techniques to model the oviposition activity of *A. aegypti*, using time series obtained from satellite image data. The use of these techniques allowed finding non-linear relationships between environmental variables and the oviposition of *A. aegypti*. The techniques used were: SVM, MLP, *k-nearest neighbors (KNN)* and DT. The evaluation of the models was done with *mean square error (MSE)*. The results showed that the best model was KNN (MSE = 0.49), followed by MLP (MSE = 0.52), SVM (MSE = 0.61) and DT (MSE = 0.77).

3.2.3. Search-index data

The use of Internet searches has become a useful tool to predict disease outbreaks, where *Google trends (GT)* is the reference in this field. GT is a tool from Google that displays the most popular search terms in a fixed time and location. Data associated with these searches is used for prediction.

The research conducted by Wu et al. [82] used climatic data from Taiwan combined with GT data. The model was built with DT and the findings revealed that temperature and humidity were the most relevant factors, with the greatest power of classification, while age and gender were the least relevant. Wu et al. [82] found that the use of GT data decreases the accuracy of the model (96% Vs. 94%). Strauss et al. [83] compared the accuracy of GT with conventional surveillance systems, in Venezuela, for 10 years. The authors used LiR to predict the cases, reported officially by the Ministry of Health, based on GT data. The overall coefficient of determination (R^2) was 0.75.

In countries such as China, GT is not available to users, but there are alternatives, such as Baidu Search, a search engine that stores the searches made by users. Li et al. [84] used the data from Baidu index database and calculated the *Dengue Baidu search index* (DBSI) to improve the prediction of local dengue epidemics in Guangzhou. Climatic data also were used by Li et al. to train a GAM. The model performance was evaluated with the *root mean square error (RMSE)*. The results showed that the model with DBSI was better than without DBSI (RMSE = 59.9 Vs. RMSE = 203.3). Another study, conducted in China, by Liu et al. [85], used regression trees on DBSI data. The results demonstrated a strong association between DBSI and dengue incidences. The accuracy of the models was above 90%.

3.2.4. Social networks

Social networks provide information on the mobility of individuals in a population because a large percentage of social-network data is geo-tagged. According to this review, Twitter is the most used social network to predict dengue. Marques-Toledo et al. [86] used tweets to predict dengue, at local and national levels, in Brazil. Social network data were supplemented with demographic and incidence variables. The model had the ability to predict an outbreak up to 8 weeks in advance, with an MAE of 0.35. Another similar work was carried out by Ramadona et al. [87], who used geo-tagged data from Twitter and a *generalized linear model (GLM)*. The main objective of this research was to predict the risk of dengue in Yogyakarta, Indonesia. The model yielded an RMSE value of 0.78 when including Twitter data with the dynamic index of incidence weighted by mobility. Finally, Souza et al. [88] used Twitter data to create unsupervised models that detect spatial clusters to characterize high-risk regions of dengue.

3.2.5. Prediction of morbidity and mortality

The mortality rate in patients with SD is too high, mainly in children and geriatric patients [89,90]. For this reason, it has been important to develop models to predict morbidity and mortality. Kesorn et al. [91] applied various machine learning techniques to predict the morbidity rate of SD. DT, KNN, SVM (with linear, polynomial and radial kernels) and ANN were applied to climatic and demographic data. *A. aegypti* infection rates were also used to improve model performance. The results showed that SVM with radial kernel had better accuracy, with 88.4%, when the infection rate in the mosquito was added. Md-Sani et al. [92] developed an LoR model in Malaysia. The goal was to identify risk factors that would allow the prediction of mortality. The best developed model was with age, serum bicarbonate, serum lactate and *alanine aminotransferase (ALT)*, with an AUC of 0.84.

Huang et al. [89] used demographic, clinical and laboratory data of patients over 65 years of age (N = 627). They used an LoR model to estimate the mortality of dengue. The model predicted a mortality of 57.1% when at least two predictors were present in dengue patients. Huang et al. [90] conducted another study with a larger sample (N = 2358). Huang et al. developed a similar model to the one developed in [89] to assign a score to each patient, to know its probability of death. The results showed that the model had an AUC of 0.85.

3.2.6. Thermal images

Nagori et al. [93] used thermal imaging for the prediction of DSS. The authors used images of pediatric patients to train a GLM. The developed model demonstrated the usefulness of thermal imaging to predict DSS, with an AUC of 0.76.

In summary, compared to diagnostic models, where LoR was most commonly used (see Fig. 3), in epidemic models, there is a variability in the frequency of the modeling approaches used. Although LiR was the most used approach for prediction, other techniques, with a high

frequency, such as RF, SVM, LoR and GAM/GLM, were also implemented. Spatial-temporal analyses were used for the case of prediction using regression approaches. The most used technique for this task was LiR, where several studies used 16 times this type of modeling. As we see in Fig. 4, there is a relationship between the use of data types and modeling types. The LiR models used socioeconomic, demographic and environmental data. This type of data has been widely used for LiR because it allows mapping the distribution of the mosquito and the disease. These types of data were used in almost all the epidemic modeling approaches (see Fig. 4), except with LoR, which did not use environmental data. Clinical and laboratory data were mainly used with LoR, a technique widely used by medical personnel and epidemiologists to predict the presence or absence of a disease (classification task, 9 papers). ANN have been little used, probably because of the low-quality and availability of data for dengue. It has been demonstrated that the performance of ANN is directly proportional to the quantity and quality of data [94]. Cellphone data have been little used to map dengue risk. The limited availability of data and the problem of data privacy could be the reason for this inconvenience. Finally, the use of GAM/GLM has increased with data extracted from the Internet (search indexes and social networks). These non-parametric models are increasing their use because they can capture features of a non-linear nature from unstructured data, such as trend data or tweets.

3.3. Strategy evaluation models to control dengue

Few intervention models have been developed for the evaluation of dengue control strategies. In this subsection, we analyze the articles according to different approaches, such as biological control using copepods, entomopathogenic fungi, *Wolbachia* strains, vaccination and fumigation.

3.3.1. Copepods

In recent years, biological control of the vector *A. aegypti* and *A. albopictus* has emerged using biological predators called copepods. These are crustaceans with the ability to systematically devour young mosquito larvae [95]. Kalimuthu et al. [95] used a GLM to evaluate the predation efficiency of *Mesocyclops formosanus* on young larval populations. The developed model showed the effectiveness of using copepods to control the vector, and thus the disease. Another study, by Udayanga et al. [96], also used a GLM to compare the predation efficiency rates of five copepods on *Aedes* larvae. According to the model, the highest predation efficiency rates were higher with *Mesocyclops leuckarti*, with 17.45% and 16.75% for *A. aegypti* and *A. albopictus*, respectively.

3.3.2. Entomopathogenic fungi

Entomopathogenic fungi produces diseases and cause the death of insects and arthropods. These types of fungi are a useful alternative to control the mosquito that transmits dengue. Lee et al. [97] built a GLM to evaluate the pathogenic activity of six species of fungi (*Beauveria, Cordyceps, Metarhizium, Paecilomyces, Purpureocillium*, and *Verticillium*) on *A. albopictus*. The model showed that *Metarhizium anisopliae* had the highest activity to eliminate *A. albopictus*, with a mortality rate of 73% after two days, and 90% after 5 days.

3.3.3. Wolbachia strains

Wolbachia is a bacterium that naturally infects insects. Infection of males with this bacterium produces a generation with unviable offspring when mated with an uninfected female [98]. This approach has been

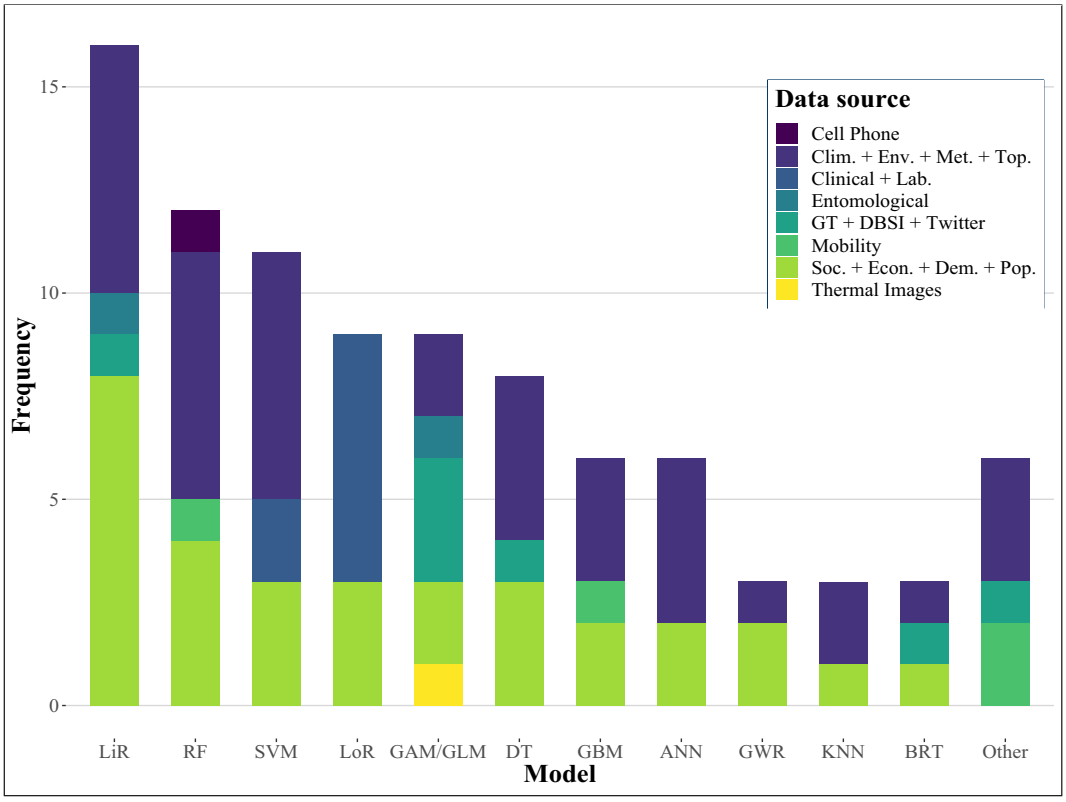

Fig. 4. Types of models vs. type of data sources for epidemic models. The frequency indicates the number of times the technique was implemented by the studies. Abbreviations: Clim = Climatic, Env = Environmental, Met: Metrological, Top = Topographic, Lab = Laboratory, GT = Google Trends, DBSI = Dengue Baidu Search Index, Soc = Social, Econ = Economic, Dem = Demographic, Pop = Population, LiR = Linear Regression, RF = Random Forest, SVM = Support Vector Machines, LoR = Logistic Regression, GAM = Generalized Additive Model, GLM = Generalized Linear Model, DT = Decision Trees, GBM = Gradient Boosting Machine, ANN = Artificial Neural Networks, GWR = Geographically Weighted Regression, KNN = K-Nearest Neighbors, BRT = Boosted Regression Trees.

developed as a method to control the spread of *Aedes*. Nazni et al. [99] used a Bayesian model (*Bayesian time series* (BTS)) to estimate the reduction of dengue cases in Malaysia after infecting mosquitoes with *Wolbachia w*AlbB strain. The model estimated dengue case reduction of 40.3% in intervention sites. Other authors have also developed models to evaluate the impact of *Wolbachia* against *Aedes;* for instance, Indriani et al. [100] used a GLM model to estimate the effect of *Wolbachia* (*w*Mel strain) over the reduction of dengue incidence in Indonesia. The developed model was able to reduce dengue incidence by 73% (95% CI: 49%–86%). Finally, Ryan et al. [101] used the same model and the same *Wolbachia* strain, and achieved a 96% (95% CI: 84%–99%) reduction of dengue incidence in Australia.

3.3.4. Vaccination

Another option for dengue control is vaccination. Lee et al. [102] implemented a GLM for validation between the *climatic risk factor index (CRF)* and dengue incidence, to estimate the vaccination coverage rate and the number of doses required. CFR index was created using 12-month moving averages of climatic and non-climatic factors. The climatic factors were temperature, precipitation and humidity. The non-climatic factors were population, density and elevation. The study was conducted in Colombia, Thailand and Vietnam, and the estimated vaccination coverage rates were 63%, 90% and 91%, respectively.

3.3.5. Fumigation

Fumigation has been widely used worldwide to reduce the burden of dengue virus-infected mosquitoes. Thus, Hladish et al. [103] constructed a *stochastic simulation (SS)* model to predict the effectiveness of spraying in Yucatán, Mexico. The results of the model indicate that the proactive application of this control method could reduce symptomatic infections by up to 89.7% in the first year, and 78.2% in the five cumulative years.

In summary, GLM was the most applied technique for intervention modeling. GLM was implemented with entomological, climatic and population data, where entomological data were the most used. A stochastic simulation was only used in one work, with entomological and population data. Finally, BTS was implemented in one work with entomological data. Entomological data is very frequent because dengue control is based mainly on the control of the mosquito, the vector of dengue transmission. Fig. 5 shows the types of data used for each intervention modeling approach.

3.4. A general analysis of data types and machine-learning techniques for dengue modeling

The types of data and techniques considered in the reviewed studies were analyzed by question (see previous sub-sections); however, it is important to analyze them globally. Fig. 6 shows the intersection between the types of data and techniques used in all the reviewed studies. In this figure, we may see that the predominant technique used was LoR, and, as we comment in the section of diagnostic models, this technique was frequently used with clinical data and laboratory results. LoR models are often used by medical personnel to diagnose dengue. According to Fig. 6, the second is RF, with different data sources used by this technique, such as climatic, clinical and sociodemographic variables. This variability in the use of predictors/variables is explained because RF is a technique that was found in diagnostic models and epidemic models, and can be used for both regression (spatio-temporal analysis) and classification (dengue diagnosis) tasks. Also, Fig. 6 shows that LiR is used in spatio-temporal analysis where logically the utilization of climatic and sociodemographic variables to map the distribution of the disease or vector was predominant. Finally, another of the most used techniques was GAM/GLM, a technique mainly used in epidemic models and intervention models. For the first case, the objective was to determine relationships between predictors and dengue incidence, and for the second case, the objective was to evaluate the impact of dengue

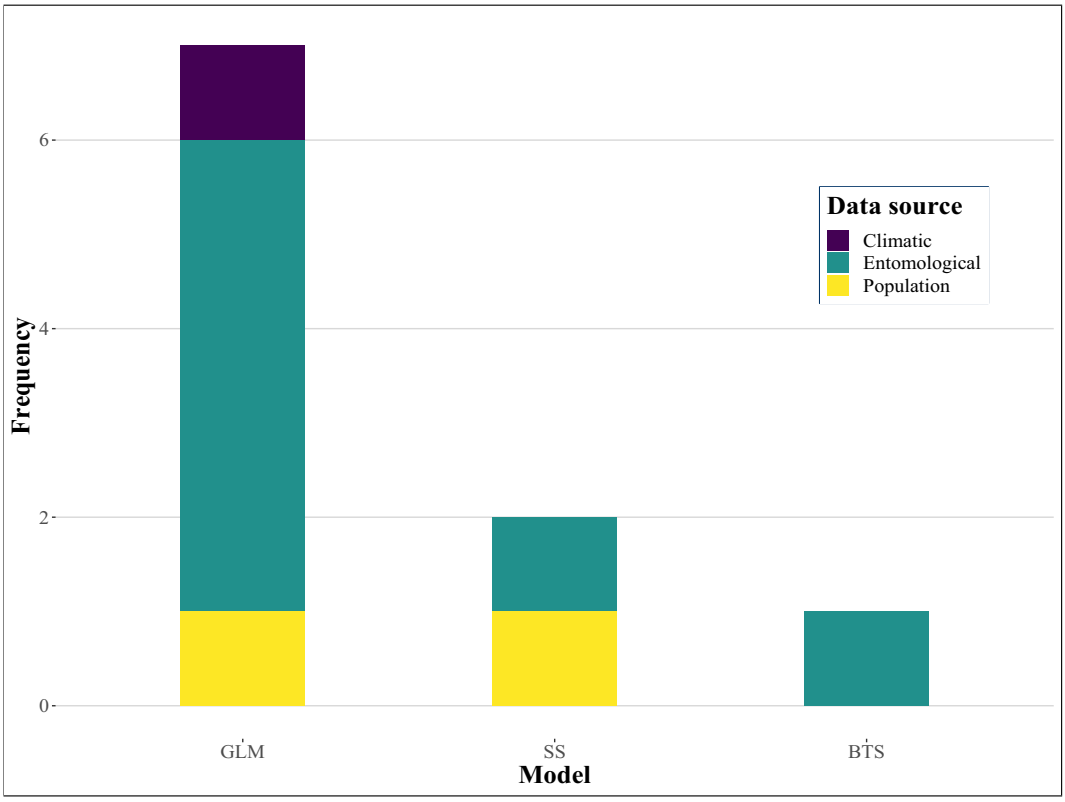

Fig. 5. Types of models vs. type of data sources for intervention models. The frequency indicates the number of times the technique was implemented by the studies. Abbreviations: GLM = Generalized Linear Model, SS = Stochastic Simulation, BTS = Bayesian Time Series.

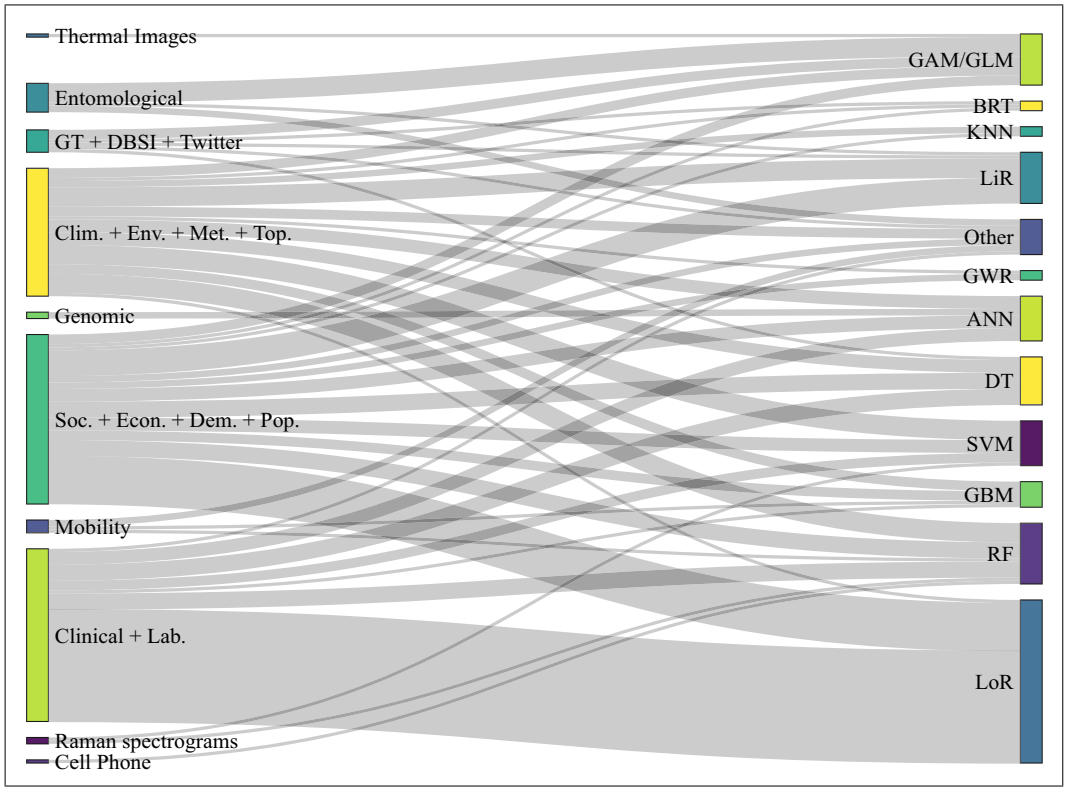

Fig. 6. Types of models vs. type of data sources for all models. The thickness of the links indicates the number of times the technique and data type was implemented by the studies. Abbreviations: GT = Google Trends, DBSI = Dengue Baidu Search, Clim = Climatic, Env = Environmental, Met: Metrological, Top = Topographic, Soc = Social, Econ = Economic, Dem = Demographic, Pop = Population, LoR = Logistic Regression, RF = Random Forest, LiR = Linear Regression, GAM = Generalized Additive Model, GLM = Generalized Linear Model, DT = Decision Trees, SVM = Support Vector Machines, ANN = Artificial Neural Networks, GBM = Gradient Boosting Machine, KNN = K-Nearest Neighbors, GWR = Geographically Weighted Regression, BRT = Boosted Regression Trees.

control strategies.

4. Discussion

Dengue modeling is a key tool for early detection of dengue, evaluation of risk factors for SD, and may also be useful to control vectors that transmit the disease. Although extensive works have been done on these issues, it is important to know what aspects of dengue modeling have not been worked on, to develop future works that will allow a significant decrease in disease morbidity rates. The main objective of this work was to give an overview of diagnostic, epidemic and intervention modeling, in addition, to determine important challenges for future works.

4.1. Limitations of the studies and challenges

This section is focused on the limitations of the reviewed studies. Based on those limitations, we describe some research challenges or opportunities for each of the approaches presented: diagnostic, epidemic and intervention.

4.1.1. Diagnostic models

The diagnostic models reported in the reviewed articles focused on the detection of dengue or the differentiation between other diseases, such as zika, chikungunya and malaria [29,30,35,39,51,59]. This is useful because the characteristics presented in these diseases, as signs and symptoms, are also present in dengue. However, it is necessary to go further and develop cause-effect models that allow a deeper understanding of the main causes that lead to high morbidity and mortality rates of dengue. It is fundamental to develop cause-effect models of dengue to know the importance of the factors that contribute to the disease. Specifically, there is a need to understand both the interrelationship among the characteristics present in the disease, and the influence on the variants of dengue. For example, the comorbidities are basic diseases that can occur jointly with dengue, being the most common chronic-renal disease and chronic-hepatic disease. In these diseases, the blood levels of some parameters are elevated, which also increases in dengue. This aspect must be taken into account to develop future models of dengue.

According to the reviewed articles, there are many predictors/features used for the diagnostic, epidemic and intervention models of dengue (see Table 2). However, other predictors could be used and evaluated for this purpose. Raman spectroscopy data would be useful because the technique has the ability to diagnose the disease early [48]. Another type of predictor that could be used for modeling would be genomic data. According to this review, only two papers [31,54] have used this type of data to look for relationships with the disease. Techniques to measure genetic data are expensive and are not usually performed in clinical practice, making it difficult to obtain such data. The wide collection of genetic data would allow a better understanding of the dynamics of dengue at the population level, providing key insights into genetic factors that are difficult to track with clinical records alone.

The use of a large number of variables could be useful to model dengue; however, a disadvantage of this approach is that the use of too many descriptors could cause the problem of the curse of dimensionality. This is characterized by the high dimensionality of the feature space where patterns cannot be easily recognized [104]. In addition, this phenomenon can sometimes hinder the optimization and speed of execution of the models. To solve this problem, different preprocessing techniques have been developed. However, in the reviewed papers, very little use of these techniques was reported (see Fig. 8). The most-reported preprocessing technique was normalization with 9.4%, followed by PCA with 6.3%. This shows that it is necessary to increase the

use of preprocessing techniques (feature engineering processes [105,106]) that allow, among other things, analysis between all the predictors available, to find the most influential features on the disease, weighting their influence.

4.1.2. Epidemic models

Epidemic models of dengue are the most published modeling approach at present, according to this literature review. The largest percentage of reviewed studies use environmental and climatic data to analyze the distribution of the mosquito and the disease.

In recent years, there has been an increasing interest to map the distribution of mosquitoes (*A. aegypti* and *A. albopictus*). Knowledge of the distribution of these vectors can help prevent the disease [99]. For this task, *geographic information systems (GIS)* have been used to analyze the relationship between climatic conditions and the distribution of the vector [64,79,97,102]. However, this type of information, collected and used for the models generation, has not a high resolution [80]. For this reason, a deep-learning approach and high-resolution Google images could be considered, using significant features (shrubs, urban areas, roads and puddles) identified from the images. The goal is to predict regions suitable for mosquitoes on a finer scale.

Data quality is an important aspect for some machine learning algorithms because their performances depend on this feature [107]. The management of dengue data quality is one of the most important challenges at present. Most of the databases, with clinical and epidemiological data, reported by surveillance systems, have some problems, such as incorrect data or missing data [51]. The high demand for healthcare, in some places, may cause that medical personnel do not correctly fill out the epidemiological forms provided for this purpose. This was one of the most common limitations found in the reviewed studies [35,38,40,53,57,59,93]. When this type of data needs to be analyzed, this inconvenience sometimes forces the elimination of complete records, which reduces the size of the database. According to the reviewed articles, none of the papers used models to manage uncertainty related to data quality. To solve this problem in dengue, several machine learning alternatives could be used, such as Bayesian models and fuzzy approaches, which have been used in other domains [108,109,110,111]. Besides, approaches that use robust estimators to deal with the problem of missing values and outliers have been developed [112]. Another option could be to generate complementary data to the existing ones. This consists of creating new data that have similar characteristics (e.g., distribution) to the available data. In recent years, also, the generation of synthetic data has allowed the construction of more robust models in other areas of knowledge, such as environmental sciences [113,114]. This could also be explored in this domain.

4.1.3. Intervention models

Of the three approaches described in this article, this is the most promising for future works, because the use of these models, in decision-making for dengue, is very limited [102]. Below, we show some fields that have not been much explored on dengue modeling.

Prescriptive models have uncertainty, and being probabilistic, can lead to incorrect decision-making [115]. Particularly, the uncertainty of prescriptive models is one of the main challenges in dengue. The key components of this aspect are the lack of certainty of the model, the uncertainty in the quality of data, and the subjectivity of the human being to build the prescriptive model [116]. There is a need to generate prescriptive models based on data and less based on expert knowledge of the domain. Additionally, real-time data processing has not been explored. The developed models are static, and the priority is to use strategies that have the capacity to process time-varying data. Automation of prescriptive processes is needed, where the model is always adjusted in case any inconvenience occurs. In this way, higher-quality decisions can be made in the shortest possible time to overcome the problem presented.

Standard machine-learning approaches require the centralization of training data in one device or data center. This could be a problem if the data are in different locations. According to this review, all articles used the centralized machine-learning approach. Most dengue information systems, in many countries, do not collect their data in one place. To overcome this drawback, one of the most secure and robust cloud infrastructures to process this data, developed by Google, could be used. The approach, called federated learning, is a kind of collaborative machine-learning without centralized training data and works as follows (see Fig. 7): the device downloads the current model, improves it by learning from the phone data, and then summarizes the changes as a small focused update. Only this updated model is sent to the cloud, using encrypted communication, where it is immediately averaged with the global model to improve the shared model. All training data remains on the device, and no individual update is stored in the cloud [117].

Finally, no studies were found that have considered implementing combined models for diagnosis, prediction and prescription. An important challenge of dengue modeling is the development of these types of hybrid models. Diagnostic, epidemic and intervention models combined could be superior in performance to the three models separately developed. Additionally, real-time updating for diagnostic and epidemic models, with the automation of prescriptive model decision-making, would considerably decrease the uncertainty present in these types of problems.

4.2. General summary

This section shows a brief summary of the challenges found that could be used to develop future works. Fig. 8 represents and summarizes the aspects evaluated in this article. In the upper part, we can note the aspects evaluated: i) the most used preprocessing techniques, ii) the applied machine learning tasks, iii) the type of modeling approach, iv) the technique used and, v) the varieties of dengue that were studied. Fig. 8 shows the characteristics most and least used to model dengue. The width of the nodes and links is proportional to the number of reviewed articles that fall into each of the categories. Different colors were used in the links, to facilitate the visualization of the connections. Fig. 8 clearly shows the little use of preprocessing techniques (feature engineering) in the reviewed articles (45 of 64 articles do not report preprocessing techniques). Perhaps, the authors assume preprocessing as an implicit stage within modeling. Also, we can observe that almost all articles on diagnostic modeling used the classification task to detect the presence of the disease. The regression task was closely related to epidemic and intervention models. As mentioned above, intervention modeling was the least frequent approach in the reviewed articles. Finally, it can be observed that SSD is the least worked variation of the disease, mainly because of the low frequency and low quality of the data related to this syndrome.

For the diagnostic modeling approach, three challenges could be identified. As we could see in this work, models to detect the disease and differentiate it from similar ones are quite implemented. Now, it is fundamental to develop cause-effect models of dengue because they are necessary to know the importance of the factors that can contribute to the disease. As can be seen in Fig. 3, several types of features have been used for the diagnosis of dengue. Adding new predictors for diagnosis could facilitate and improve detection time for treatment and avoidance of death. Although the use of many predictors for diagnosis could be beneficial, it could also cause difficulties with respect to the dimension of the data. One opportunity is the creation or improvement of preprocessing techniques that will enable the identification of key characteristics that are most related to dengue.

Although dengue epidemic modeling is the most reported in the literature, data available for dengue has quality problems. The uncertainty of models based on this type of data is high. One of the main challenges of epidemic approaches is the development of models that address and clearly express the associated uncertainty and measure the reliability of the predictions. It is crucial that improvements are

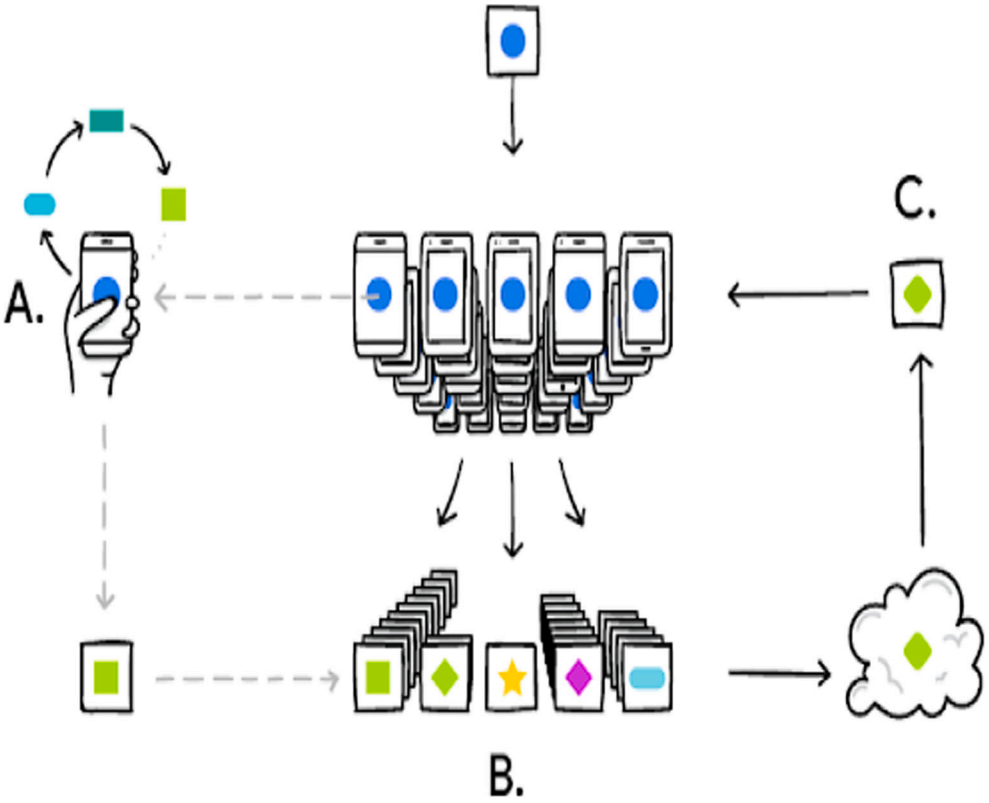

Fig. 7. Description of federated learning. The device personalizes the model locally, based on the usage (A). Many users' updates are aggregated (B) to form a consensus change (C) to the shared model, after which the procedure is repeated. Source: https://tinyurl.com/y9ykdbve

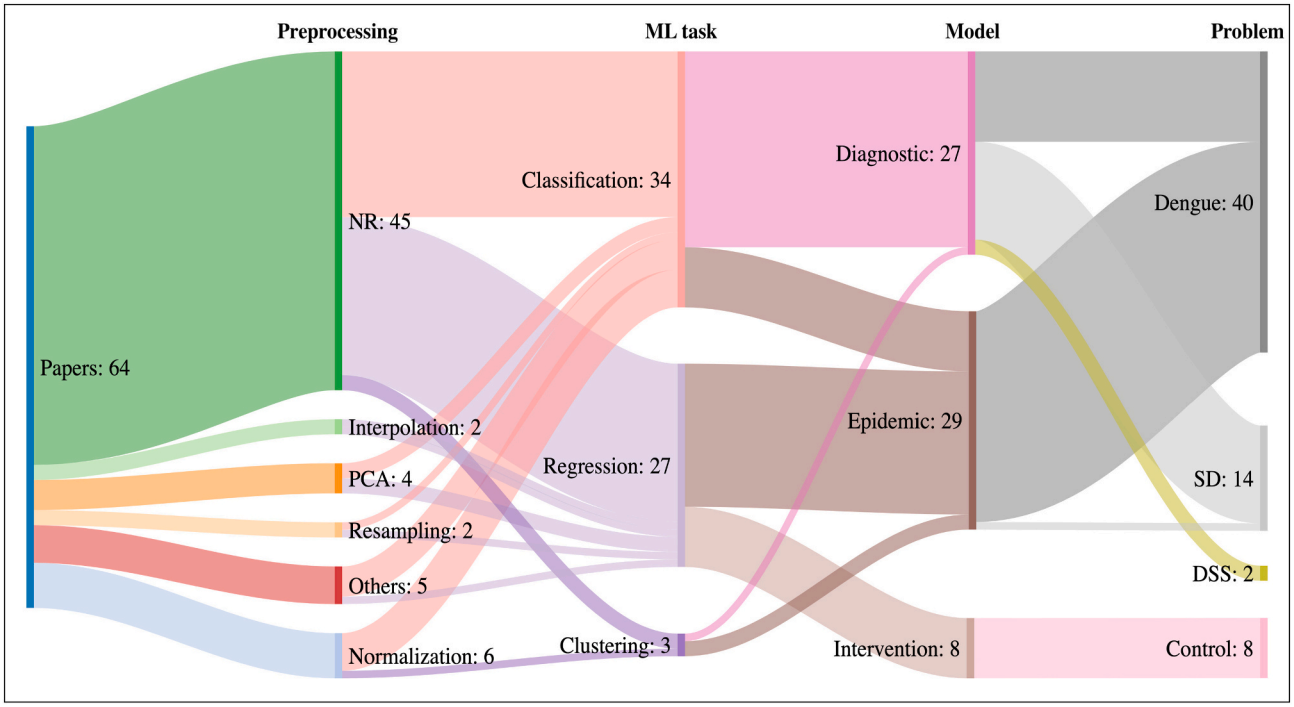

Fig. 8. Trends of reviewed papers for dengue modeling. Abbreviations: ML = Machine Learning, NR = Not reported, PCA = Principal Component Analysis, SD: Severe Dengue, DSS = Dengue Shock Syndrome.

developed, or new techniques are created, to generate more accurate results.

The frequency of articles on intervention modeling of dengue is low. Decision-making for treatment and control of the disease depends on this modeling approach. Prescriptive analysis, in general, presents challenges that must be taken into account. One of these is the low

number of automatic prescriptive models for data-based decision-making systems. The subjectivity of the domain expert could affect the quality of the decision made, and static models can not handle the changes that occur. Data-based and up-to-date prescriptions would be a valuable tool for the treatment and/or control of dengue.

Finally, a challenge common to all three approaches reviewed in this article is the development of combined models (diagnostic, epidemic and intervention), to automate the prescription. Autonomous cycles of data analysis tasks (see [118,119] for more details about this concept), which integrate the previous models, can assist in decision-making as quickly as possible. For dengue, this is crucial, due to the high morbidity and mortality of the disease.

5. Conclusions

We conducted an SLR on dengue modeling based on machine learning. The main objective was to know about diagnostic, epidemic and intervention models that have been developed for the disease. Sixty-four articles were selected and analyzed from several scientific libraries, to find out the state-of-the-art in the three approaches mentioned above. The results show that dengue modeling is constantly growing.

The most frequent diagnostic models were based on LoR. LoR is one of the most used modeling techniques because of its ease of realization and interpretation of results. Although other techniques, such as decision trees, can be easily interpreted, they consist of a large number of nodes, which can require a significant amount of mental effort to understand a particular prediction. In contrast, an LoR model is simply a list of coefficients, which is attractive to know the influence of characteristics on the target variable. In addition, regression does not require that the continuous independent variables follow a normal distribution, and continuous and discrete predictors can be used together. With respect to the category of features, the most used for these models were demographic, clinical and laboratory data. Data are readily available from local health authorities in each country.

In general, the most frequent epidemic models were based on LiR, RF and SVM, with socioeconomic, demographic, climatic and environmental data. From this category, the most explored approach is the spatial-temporal analysis of dengue and its transmission vector. These techniques are commonly implemented to map disease risk in endemic areas, and establish relationships between risk factors and dengue incidence.

Studies on intervention systems for dengue are quite limited. In this review, we found only eight studies with developed models for disease control. The techniques used were GLM, SS y BTS. The main data used were entomological. The morbidity and mortality of the disease clearly depend on the decisions made by health authorities, therefore, more studies are needed in this field to support the decisions. Finally, an important general remark is that the diagnostic, epidemic and intervention models of dengue are normally machine learning models of predictive, diagnostic or prescriptive type.

Several limitations were found in the reviewed papers, among which we have: the absence of reporting of preprocessing techniques used, and small sample sizes for disease variations, such as SD and DSS. Reviewing the strengths and limitations of the articles allowed the identification of future works for research: i) cause-effect models for dengue diagnosis, ii) use of new features, such as genetic data and Raman spectroscopy, for disease diagnosis, iii) a preprocessing phase based on feature engineering processes, iv) implementation of Bayesian or fuzzy models that adequately manage data uncertainty, v) automatic prescriptive models for data-based decision-making systems, and vi) models combining the three approaches discussed in this article using autonomous cycles of data analysis.

Based on these future works, prioritization should focus on cause-effect models for disease diagnosis. Not only the detection of the disease is critical, but also, the assessment of factors that most influence the infection. A better understanding of dengue-related causes with more robust diagnostic models, would help considerably in prevention and reducing complications and deaths. Likewise, modeling for the management of data uncertainty is urgent. The low quality of epidemiological data on dengue is one of the main obstacles for the improvement of existing models. The use of other types of predictors, such as genetic data and spectrograms, could be useful, but their high cost of determination and collection could be a limitation. Finally, the use of autonomous cycles of data analysis tasks would automate decisions for disease control.

This study has a few limitations. The first limitation is that some online databases (ScienceDirect, IEEE Xplorer, Google Scholar, Emerald, Taylor & Francis and PubMed) were used, and interesting articles from other digital libraries could have been ignored. Second, the language chosen was English because most of the latest advances in dengue modeling are written and published in this language. The absence of articles in other languages, such as Spanish and Portuguese, limits the scope of the results of this study.

CRediT authorship contribution statement

All authors have participated in the design of the original study, data analysis, interpretation of results. They also participated in the writing, review and approval of the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix B

A clinical decision-support system for dengue based on fuzzy cognitive maps

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A clinical decision-support system for dengue based on fuzzy cognitive maps

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Abstract
Dengue is a viral infection widely distributed in tropical and subtropical regions of the world. Dengue is characterized by high fatality rates when the diagnosis is not made promptly and effectively. To aid in the diagnosis of dengue, we propose a clinical decision-support system that classifies the clinical picture based on its severity, and using causal relationships evaluates the behavior of the clinical and laboratory variables that describe the signs and symptoms related to dengue. The system is based on a fuzzy cognitive map that is defined by the signs, symptoms and laboratory tests used in the conventional diagnosis of dengue. The evaluation of the model was performed on datasets of patients diagnosed with dengue to compare the model with other approaches. The developed model showed a good classification performance with 89.4% accuracy and could evaluate the behaviour of clinical and laboratory variables related to dengue severity (it is an explainable method). This model serves as a diagnostic aid for dengue that can be used by medical professionals in clinical settings.

Keywords Machine learning · Dengue · Artificial intelligence · Diagnosis · Fuzzy cognitive maps · Clinical decision-support system

Highlights

- Availability of dengue data about signs, symptoms, and laboratory tests provides opportunities to explore new dengue diagnosis tools.
- Precise dengue diagnosis models greatly assist physicians in detecting and treating dengue severity.
- We developed a clinical decision-support system for dengue diagnosis using fuzzy cognitive maps.
- The proposed explanatory model can be used to identify the main dengue variables that determine its severity.

1 Introduction

Dengue is a globally distributed disease spread –mainly– in tropical and subtropical regions [1]. The infection is transmitted by the bite of *Aedes* female mosquitoes [2]. According to the *World Health Organization* (WHO), dengue cases around the world have increased eight times in the last 20 years. In 2000, 505,430 cases were reported; while, in 2019, the number of cases raised to 4.2 million [3]. Currently, dengue diagnosis is a challenge due to its complexity. The process used to diagnose the disease is complex because the amount of information involved is high and some physician's lack of experience could make the diagnosis difficult [4]. According to clinical experts, the diagnosis of dengue depends on an astute interpretation of the clinical and laboratory findings, mainly in severe cases [5]. According to Sutton et al. [6], these problems could be addressed with the use of *clinical decision-support systems* (CDSS) based on

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artificial intelligence (AI) techniques. Sutton et al. define a CDSS as a system that seeks to improve healthcare delivery by supporting medical decisions with clinical knowledge and patient information. The main objective is for the physician to combine her/his clinical knowledge with suggestions from the CDSS to make the best possible decision.

Diagnosis of dengue has two approaches: 1) to detect the disease and differentiate it from other diseases with similar signs and symptoms like malaria, Zika, chikungunya and leptospirosis; 2) to classify the patient according to its severity. In recent years, the development of CDSS based on AI techniques for the early detection of dengue has been increasing (see [7], for more details). As an example, Fernandez et al. [8] developed a logistic-regression-based system to detect dengue and differentiate it from other febrile diseases. The system used demographic and clinical predictors to fit the model and achieved an accuracy of 69.2%. Gambhir et al. [9] developed a hybrid approach based on an *artificial neural network* (ANN) to predict dengue, and a *particle swarm optimization* (PSO) to optimize the model parameters. The results showed that ANN-PSO performed better (accuracy = 87.2%) than when the ANN alone is used (accuracy = 79.1%).

Dengue is classified based on its severity into three types: dengue without warning signs, dengue with warning signs and severe dengue (SD). Early classification is crucial to avoid complications and death. Previous studies have attempted to develop systems to deal with this aspect of dengue. For example, Khan et al. [10] developed a system based on *support vector machines* (SVM) to classify dengue patients. The main contribution of Khan et al.'s work is the development of a system with Raman spectroscopy data. The diagnostic accuracy of the developed system was 85%. Davi et al. [11] proposed a decision system using gene expression data together with *machine learning* (ML) techniques, such as ANN and SVM. Davi et al. justified the use of this type of data because dengue phenotypes based on clinical and laboratory data are not very accurate. The work proposed by Davi et al. used SVM to find an optimal subset of features and an ANN to classify patients. The accuracy of the best model presented was 86%.

As we have seen previously, several works have been developed for the prediction of dengue, for the differentiation with other diseases with similar clinical pictures, and for the classification of dengue patients based on severity. However, the previous works did not evaluate the behavior of the clinical and laboratory features/variables that describe the signs, symptoms, and severity of dengue. Understanding the impact and behavior of these features over time is a useful strategy for the diagnosis and clinical management of dengue. Anticipating the appearance of signs and symptoms, in dengue, is crucial to avoid complications. Based on the above, the main contribution of this work is a CDSS based on *fuzzy cognitive maps* (FCMs), which aids in the decision making for the clinical management of dengue. FCMs have been used to build CDSS in medicine for other diseases such as autism [12], meningitis [13] and pulmonary infections [14]. However, to date, no CDSS based on FCMs has been developed for the clinical management of dengue. Besides, our approach not only classifies the type of dengue but also allows analyzing over time the behavior of the clinical and laboratory variables that physicians use for the conventional diagnosis of dengue. Thus, we propose an explainable method that maintains a competitive predictive accuracy of the severity of dengue, which is a "glass box" approach that describes the way that it comes to decisions. These combined properties make this system more robust and solve the result interpretability problem of the machine learning systems very important in sensitive yet critical domains such as healthcare, which other reported systems in the literature do not do.

This article is organized as follows. Section 2 introduces the medical background of dengue and a conceptualization of FCMs. Section 3 describes the methodology implemented for the development of the proposed FCM. Section 4 shows computational experiments and model evaluation. Finally, the last section describes conclusions and future works.

2 Theoretical background

This section introduces background on dengue and its conventional diagnosis. In addition, this section provides the basic concepts of FCMs used in this research.

2.1 Medical background

In this section, the main aspects of dengue are presented: its causes, symptoms and clinical course of the disease. In addition, the conventional diagnosis of dengue is introduced.

2.1.1 Introduction to dengue

Dengue is a mosquito-borne viral disease of more rapid spread in the world. Dengue virus is transmitted by female mosquitoes of *Aedes aegypti* and *Aedes albopictus* [3]. The clinical picture of dengue varies from patient to patient. Typically, the individuals infected by dengue are asymptomatic (80%). Dengue has an incubation period of 3 to 14 days. After this period, a viral picture appears characterized by a fever of more than 38°C, headache, retro-ocular pain, intense pain in the joints (arthralgia) and muscles (myalgia), nausea/vomiting and inflammation of lymphatic nodes [15].

2.1.2 Clinical course of dengue

The clinical presentation of dengue is divided into three phases: febrile, critical and recovery [16]. Figure 1 shows the three dengue phases.

The first phase lasts from two to seven days and it is characterized by a sudden increase in body temperature, headache, generalized body pain, myalgia, arthralgia and rash [16]. In this febrile phase, it can be difficult to distinguish –clinically– dengue from other febrile diseases, such as malaria and leptospirosis.

At the beginning of the critical stage (second stage), the fever decreases or disappears [17]. This is the phase of complications and usually lasts 24 to 48 hours. A predominant feature is plasma extravasation with an increase in the values of the hematocrit [18, 19]. At this time, the patients who do not present increased capillary permeability, improve; while, those with increased capillary permeability, can worsen as a result of the loss of plasma volume. When there is a critical loss of plasma volume, shock may occur and the patient may die [19].

In the third stage, called the recovery phase, the plasma extravasation decreases and the patient enters in a convalescent phase. The patient's well-being improves due to a balance of the hemodynamic state by gradual reabsorption of the extravasated fluid [16, 20]. Other characteristics of the third phase are that appetite returns, gastrointestinal symptoms decrease, hemodynamic status stabilizes, and diuresis occurs. This last phase can last between three to five days [21, 22].

2.1.3 Conventional diagnosis of dengue

Efficient and accurate diagnosis of dengue is of fundamental importance for clinical care: early detection of severe cases, confirmation of cases and a differential diagnosis with respect to other infectious diseases. Diagnosis of dengue can be difficult because the signs and symptoms can be –easily– confused with those of other diseases, such as malaria, leptospirosis and typhoid fever.

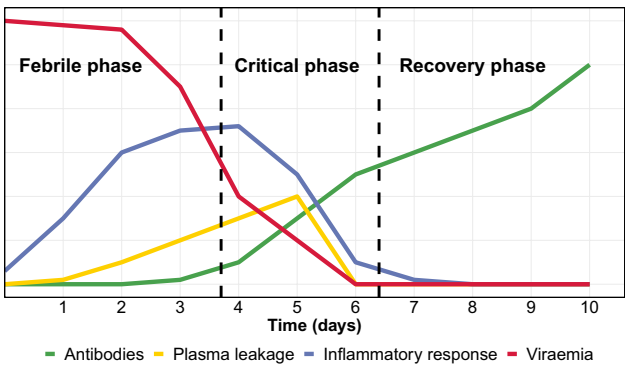

Fig. 1 Clinical course of dengue. Adapted from [17]

In 2009, the WHO set out guidelines for the clinical management of dengue [21]. This guide serves as a standard diagnostic criterion for dengue. In addition, the guide provides a global approach to the classification of dengue [23]. Figure 2 shows the progression of dengue, with signs, symptoms and laboratory tests, for each variant of the disease. These parameters are used as criteria for the diagnosis of dengue.

Laboratory tests to confirm dengue infection can be: isolation of the virus, detection of viral nucleic acid, antigens, antibodies or a combination of these techniques. During the first stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of the infection, serology is the method of choice for diagnosis (see Fig. 1) [3].

2.2 Fundamentals of FCMs

In this section, the fundamentals of FCMs are shown. First, a conceptualization of FCMs is described, and, finally, the learning process used in this work is briefly explained.

2.2.1 Introduction to FCMs

FCMs were introduced by Kosko, in 1986, [24] from the cognitive maps created by Axelrod, in 1976 [25]. FCMs are used to model complex systems due to their ease of construction and interpretation. FCMs are directed graphs composed of concepts and relationships. Concepts represent the variables involved in a system, while relationships represent the influence among these concepts [26].

Figure 3 shows a simple example of an FCM with eight concepts (from C_1 to C_8). Each concept represents a variable, entity or factor of the system, such as severity, disease's symptoms and laboratory tests. A relationship, represented by a weight on a directed edge, shows the influence of one concept over another [27]. There are several ways to assign these relationships to FCMs. Aguilar in [27] describes three approaches to assign this type of relationship in FCMs: i) assignment of causal relationships using fuzzy rules, ii) assignment of relationships using generic logic rules and iii) assignment of relationships using mathematical models describing the system to be evaluated. In some of these approaches can be used experts to assign the weights (e.g., in the first two approaches), but also, data can be used to infer causal relationships in these approaches. The strength of a relationship depends on the value assigned, which varies from -1 to +1. A value of +1 represents an excitatory effect from the C_i concept to the C_j concept, a value of -1 represents an inhibitory effect between C_i and C_j, and a value of 0 indicates that no causal relationship exists between the two concepts. Other values in the interval [-1, +1], represent different degrees of causality. For instance, if the antecedent concept C_i has a very low value and the consequent concept C_j has a high

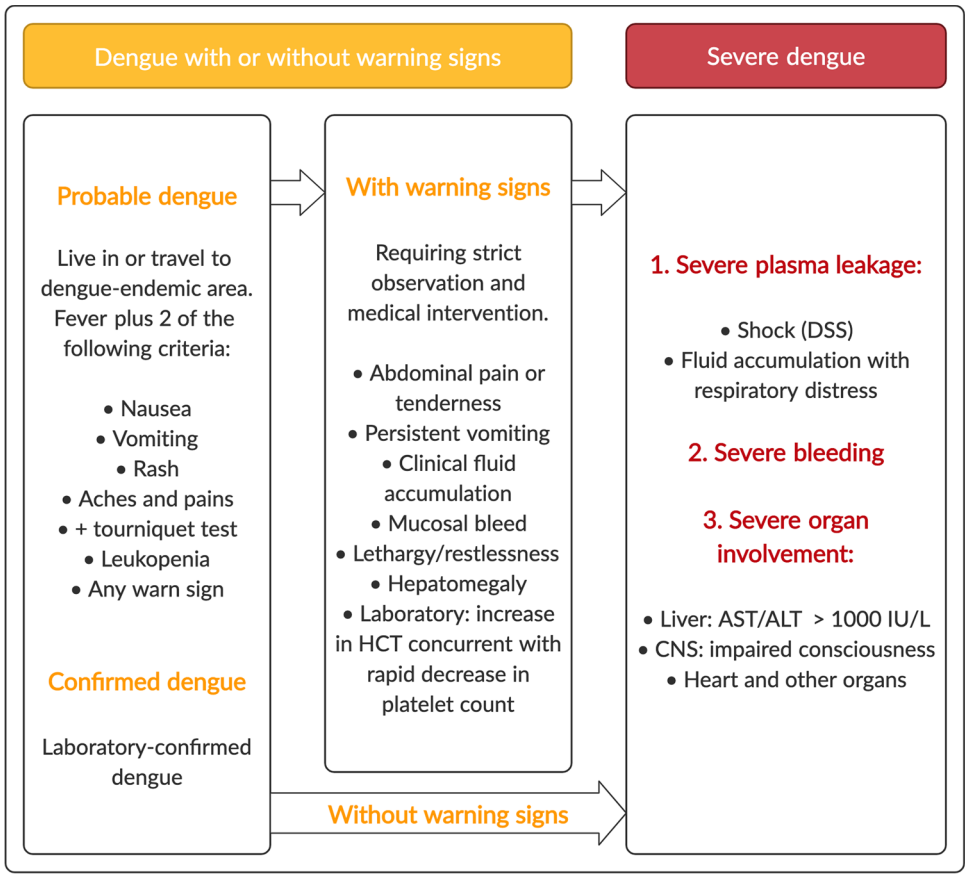

Fig. 2 Criteria for diagnosis of dengue. Adapted from WHO guidelines [21]. (Abbreviations: HCT = hematocrit, DSS = dengue shock syndrome, AST = aspartate aminotransferase, ALT = alanine aminotransferase, CNS = central nervous system)

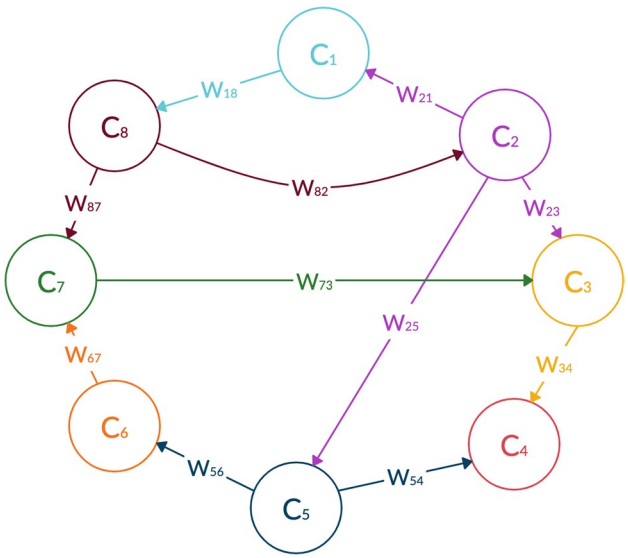

Fig. 3 Simple graphical representation of an FCM model with eight concepts

value, then the causal relationship between concepts could be determined as *Negative high*. Table 1 shows an example of causality degrees, with their respective linguistic terms. This table can be used to facilitate the assignation of the relationships by the domain experts according to their knowledge.

Table 1 Type of causal relationships using some generic logic rules based on concepts' values

Linguistic term	Numerical value	Generic logic rule	
		Antecedent C_i	Consequent C_i
Positive complete	1	Very high	Very high
Positive high	0.75	High	High
Positive moderate	0.5	Medium	Medium
Positive low	0.25	Low	Low
Null	0	NA	NA
Negative low	−0.25	Very low	Low
Negative moderate	−0.5	Low	High
Negative high	−0.75	Very low	High
Negative complete	−1	Very low	Very high

Each linguistic term represents the causality degree between antecedent and consequent concepts. NA = Not applicable

Mathematically, an FCM is represented as a tuple of four elements:

$$\Phi = \langle n, f(\cdot), r, W \rangle \tag{1}$$

where $n \in \mathbb{R}^m$ is the set of concepts $(n_1, \ldots, n_m)$, and $f(\cdot)$ is the activation function that holds concept values in determined range r. For example, the sigmoid function holds concepts values between 0 and 1, where 0 indicates absence and 1 indicates the complete presence of the concept. This function allows assigning and expressing semantically a categorical state to each concept in each iteration [28]. Table 2 shows several functional forms used for this goal. The choice of an activation function to model FCMs will depend on the problem to be solved. For example, if we want to model the symptoms of a disease, then it would be more useful to use the sigmoid function because the values of the concepts to be modeled will be between values of 0 (absence of the symptom) and 1 (presence of the symptom). For this case, it does not make sense to have negative values, thus, it would not be necessary to choose the hyperbolic tangent function that has a range between -1 and 1. Finally, $W \in \mathbb{R}^{m \times m}$, is the adjacency matrix to represent the interactions among concepts. The adjacency matrices are square matrices that allow storing the influences among concepts of an FCM. As an example, the adjacency matrix for the FCM in Fig. 3 is:

$$\mathbf{W} = \begin{array}{c} \\ \boldsymbol{C_1} \\ \boldsymbol{C_2} \\ \boldsymbol{C_3} \\ \boldsymbol{C_4} \\ \boldsymbol{C_5} \\ \boldsymbol{C_6} \\ \boldsymbol{C_7} \\ \boldsymbol{C_8} \end{array} \begin{array}{c} \begin{array}{cccccccc} \boldsymbol{C_1} & \boldsymbol{C_2} & \boldsymbol{C_3} & \boldsymbol{C_4} & \boldsymbol{C_5} & \boldsymbol{C_6} & \boldsymbol{C_7} & \boldsymbol{C_8} \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & w_{18} \\ w_{21} & 0 & w_{23} & 0 & w_{25} & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{34} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & w_{54} & 0 & w_{56} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & w_{67} & 0 \\ 0 & 0 & w_{73} & 0 & 0 & 0 & 0 & 0 \\ 0 & w_{82} & 0 & 0 & 0 & 0 & w_{87} & 0 \end{pmatrix} \end{array} \tag{2}$$

2.2.2 Reasoning of FCMs

The inference process in an FCM, can be defined –mathematically– using three components: a weight matrix, $W \in \mathbb{R}^{m \times m}$, which defines the interaction among concepts, an activation function that holds concepts values between a range, and, a state vector, $a \in \mathbb{R}^m$, that represents the degree of activation of the concepts. The activation degree of a concept indicates the value of that concept in a determined iteration. We refer to the term *activation of a concept* when the value of a concept at iteration t is 0 $(a_i(t) = 0)$ and at iteration $t+1$ greater than 0 $(a_i(t+1) > 0)$. In simple words, it is when an absent concept becomes present in the system.

The inference procedure consists of calculating the state vector a through iterations with successive multiplications of the state vector by the weight matrix, until the system finds a steady state. Equation 3 summarizes this process [24]:

$$a_j(t+1) = f\left(\sum_{i=1, i \neg j}^{m} W_{ij} a_i(t) \right) \tag{3}$$

where $a_j(t+1)$ is the value of concept C_j at iteration $t+1$, m is the number of concepts, W_{ij} is the value for relationship from concept C_i to concept C_j, and $a_j(t)$ is the value of concept C_j at iteration t. The point of equilibrium (steady state) is reached when $a(t) = a(t-1)$ or $a(t) - a(t-1) \leq 0.001$.

The use of FCMs is essential in simulation scenarios, because it allows experts to study the system behavior for different initial conditions. This initial condition is defined by $a(0)$ and is denoted as:

$$a(0) = \left[a_1(0), a_2(0), \ldots, a_m(0) \right] \tag{4}$$

where $a_1(0)$ is the value of concept C_1 at iteration = 0.

Table 2 Activation functions used in FCMs

Activation function	Equation	Range
Bivalent	$f(x) = \begin{cases} 1 & x > 0 \\ 0 & x \leq 0 \end{cases}$	$f(x) \in \{0, 1\}$
Trivalent	$f(x) = \begin{cases} 1 & x > 0 \\ 0 & x = 0 \\ -1 & x < 0 \end{cases}$	$f(x) \in \{-1, 0, 1\}$
Sigmoid	$f(x) = \frac{1}{1+e^{-\lambda x}}$	$f(x) \in [0, 1]$
Hyperbolic tangent	$f(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}}$	$f(x) \in [-1, 1]$

3 Methodology

In this section, we describe the methodology used to develop an CDSS for dengue using FCMs. Figure 4 shows the six-step methodological framework. Each of the steps is briefly explained below.

3.1 Selection of experts

Three clinical experts in dengue were selected. The medical professionals agreed to participate in this research. The selected experts have a wide experience in physiopathology of dengue. All of them add up to more than 70 years of experience in the clinical management of the disease.

3.2 Concepts and relationships

This stage is developed by the clinical experts of dengue. First, the concepts were defined according to the diagnostic

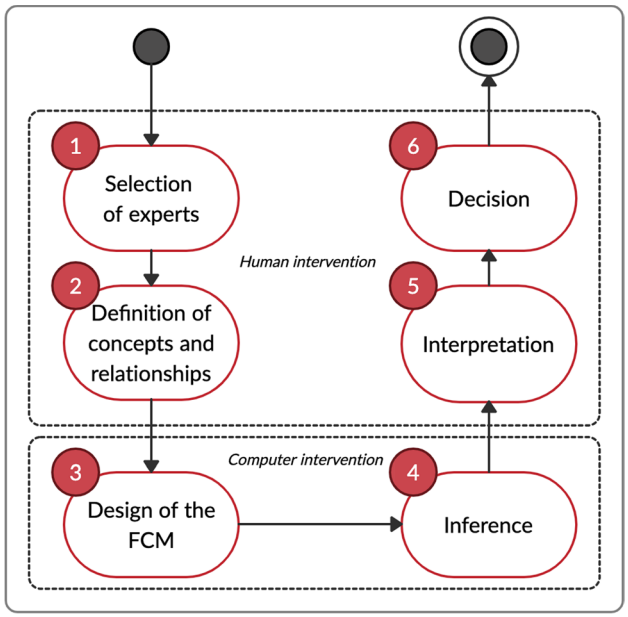

Fig. 4 Flowchart of the CDSS for dengue

criteria developed by WHO [21]. Table 3 shows a brief description of the concepts. These concepts are classified into five types: i) demographic: variables related to population, ii) signs: clinical manifestations that the physician detects in the medical consultation, iii) symptoms: clinical manifestations that the patient experiences and refers to the physician in the medical consultation, iv) laboratory tests: tests performed in the clinic or hospital to know the status of some parameters such as platelet levels, plasma volume and cell-content ratio. v) target, which indicates the final classification.

After the definition of concepts, each expert generated a matrix of weights with values between -1 and 1, corresponding to the influences among the previously defined concepts. This assignment process was performed according to the protocols and clinical algorithms for the diagnosis of dengue published by WHO [21]. Each expert combined their experience and knowledge extracted from WHO guidelines, to establish how each concept influences the other. To facilitate this procedure, the experts used Table 1 to choose the linguistic term for each causal relationship, and then, the associated numerical value was used to construct the weight matrix.

Table 3 Concepts used to build an FCM for dengue based on [21]

Concept node	Concept name	Type of variable	Description
C1	Age	Demographic	Time elapsed since the birth of an individual
C2	Fever	Sign/symptom	Increase in body temperature
C3	Cefalea	Symptom	Pain and discomfort located in any part of the head
C4	Pain BE	Symptom	Pain behind eyes
C5	Myalgias	Symptom	Muscle aches
C6	Arthralgias	Symptom	Joint pain
C7	Rash	Sign/symptom	Skin exanthema
C8	Abdominal pain	Sing/symptom	Intense pain, located in the epigastrium and/or right hypochondrium
C9	Vomit	Symptom	Violent expulsion by the mouth of what is contained in the stomach.
C10	Lethargy	Sign/symptom	State of tiredness and deep and prolonged sleep
C11	Hypotension	Sign	Excessively low-blood pressure on the artery wall
C12	Hepatomegaly	Sign	Condition of having an enlarged liver
C13	Mucosal bleeding	Sign/symptom	Manifestations of mild to severe bleeding in the nasal mucosa, gums, skin, female genital tract, brain, lungs, digestive tract and hematuria
C14	Hypothermia	Sign/symptom	Decrease of body temperature
C15	High hematocrit	Lab. test	Indirect increase in hematocrit test
C16	Low platelets	Lab. test	Decrease of platelet levels in the blood
C17	Edema	Sign/symptom	Swelling caused by excess fluid trapped in body tissues.
C18	Extravasation	Sign	It is characterized by serous spills at the level of various cavities
C19	Bleeding	Sign/symptom	Blood leaks from the arteries, veins or capillaries through which it circulates, especially when it is produced in very large quantities
C20	Shock	Sign/symptom	Manifestation of severity evidenced by cold skin, thready pulse, tachycardia and hypotension
C21	Organ failure	Sign	Affectation of several organs due to the extravasation of liquids
S1	Severity	Target	Dengue severity

3.3 Design of the model

This stage summarizes the FCMs developed by the experts in a general map. The procedure to create a single global map is defined by the following equation [29]:

$$E_{ij}^{G} = \sum_{e=1}^{NE} \frac{E_{ij}^{e}}{NE} \tag{5}$$

where E_{ij}^{G} is the global weight for the general FCM, E_{ij}^{e} is the opinion of each expert on the causal relationship between the concept C_i and C_j, and NE is the number of experts. Finally, the general FCM is built using the *igraph* package [30] in R Software (version 4.0.1) [31]. Figure 5 shows the final FCM. The construction of FCMs with experts has an implicit bias due to the subjectivity of the experts in assigning causal relationships [32]. Addressing bias in FCMs is beyond the scope of our study.

3.4 Inference

Step 4 of the methodology shown in Fig. 4 consisted of implementing the FCM previously defined in the FCM tool used in this work [33], and then, performing the inference processes for each case study. The inference is performed with the reasoning process defined in Section 2.2.2, and we used the sigmoid function as the activation function. Configuration of the experiments and the results of this stage are shown in Section 4.2.

3.5 Interpretation

This step consisted of the interpretation of the inference results by the FCM in each case study. Configuration of the experiments and the discussion of the results of this stage are shown in Section 4.3

3.6 Decision

The final step of CDSS for dengue is the decision that the medical professional makes to improve the diagnosis of dengue.

4 Computational experiments

In this section, we analyze the diagnostic capability of our FCM. For that, validation and scenario-based simulations were executed. First, a dataset is preprocessed. Then, the global FCM is used to classify dengue patients. Because the result of the analysis of factors related to dengue severity is qualitative, we chose three scenarios (one for each dengue type) to show the capability of our model in interpreting the results. The diagnostic capability of our FCM is compared with ML techniques, such as ANN and SVM. Finally, a qualitative comparison with other previous works is performed.

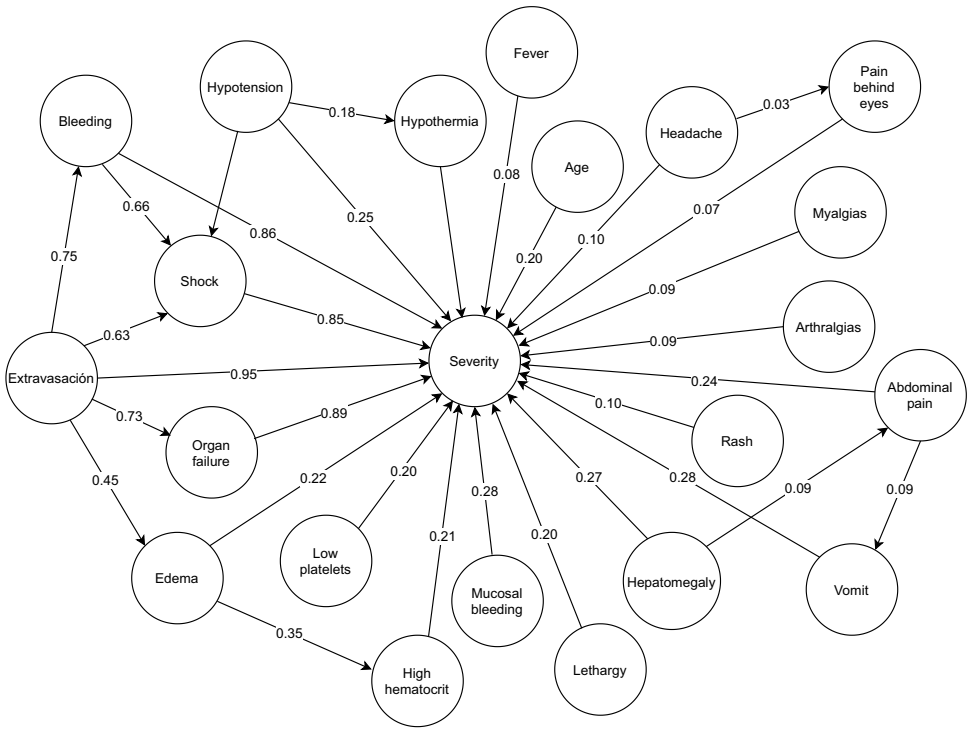

Fig. 5 General FCM to support the diagnosis of dengue

4.1 Dataset

The dataset used for the computational simulations is described below. The dataset corresponded to 52,051 patients who attended the Health-Service Providers Institutions with a diagnosis of dengue reported to the National System of Surveillance of Colombia [34], from 2008 to 2018, in Medellin, Colombia.

We selected from the dataset the 22 variables that the experts defined as concepts in the FCM (see Table 3). These variables are signs, symptoms, laboratory tests and the final classification of dengue, which was used as the target to compare with the target predicted by the ML models. Other variables such as address, first names, last names and zip codes were eliminated because they did not contribute to the objective proposed in this study. Missing data are very common in this type of dataset, therefore, the records with more than 50% of missing values, for the variables, are eliminated. This process was performed because missing data in datasets can increase the bias and decrease the performance of the models [35]. In this dataset, it is difficult to know the cause of missing data, because it is not known if the physician did not enter the information by mistake or because of the absence of any symptom in the patients.

Categories of the input variables were binary (presence = 1, absence = 0), except age. We re-coded age as follows: patients younger than 5 years and older than 60 years were assigned values of 1, patients with other ages were assigned a value of 0. This modification is justified by the input variables having the same categories, the prevalence of SD is higher in patients under 5 years of age [36], older patients are more likely to develop SD [37]. At the end, the dataset consisted of 10,210 patients with DWS-negative, 11,123 patients with DWS-positive, and 123 patients with SD. For this last class, *oversampling* [38] was used to balance the classes. Finally, the number of patients for the latter class was 11,186 records.

4.2 Classification of dengue based on the severity

The diagnosis of dengue is based on severity. This aspect in dengue is important because it allows medical professionals to make an early diagnosis and avoid complications and death. In what follows, we show three cases of dengue to classify them with the FCM. To validate the capability of the FCM model developed, we used the dataset described in the previous section. To show how our model performs the classification, we tested three cases (one for each type of dengue) corresponding to patients randomly extracted from the dataset.

For this classification model, an initial vector with the age, symptoms and laboratory tests of the patients was used. After the inference process, a final vector was obtained when the system found a steady state (see Section 2.2.2). The steady state in this case can be interpreted as a state in which the signs/symptoms/laboratory tests do not evolve further. In general, real-life problems such as dengue are dynamic problems that constantly evolve over time through the interaction of related factors. In this work, iterations are understood as evolutions over time of disease. For example, if in the initial iteration there is no shock but there is extravasation, the presence of the latter may lead to the presence of the former after some time. It is important to remember that the weight matrix is never modified during iterations because it reflects the causal relationships between the concepts and these were defined by the experts. Thus, causal relationships are static and variables or concepts are dynamic

The decision concept $S1$, in the final vector, was used to quantify the percentage degree of severity (PDS) in the patients. This was done to bring the values of the decision concept $S1$ to a range of diagnostic values and make the results more interpretable by the medical staff. The conversion of the final decision concept $S1$ to PDS was performed using the following rule from [39]:

$$PDS\ (S1) = \begin{cases} 0, & S1 \leq 0.5 \\ \frac{S1-0.5}{0.5} \times 100\%, & S1 > 0.5 \end{cases} \tag{6}$$

The values of PDS will be between 0 and 1. On one hand, when $PDS = 0$ means that the characteristic that the concept represents is not present (0%). In this case, since the concept of decision represents severity, then it is not present. On the other hand, 1 means that the characteristic that the concept represents is 100% present [39]. Specifically, values between 0 and 1 will indicate different degrees of severity in terms of percentage. We used the functional form in Eq. 6 because of its simplicity and its good performance in other medical studies [14, 39]. PDS was discretized into three ranges to evaluate the classification made by the model. Patients with a PDS less than 20% are classified as DWS-negative, patients with PDS between 20% and 60% are classified as DWS-positive, and patients with PDS greater than 60% were classified as SD. All these criteria and thresholds were adjusted according to the experts' opinions and application of our FCM over the dataset.

In order not to make this section longer, here we only focus on the prediction and interpretation of the target concept. The interpretation of the values of the other concepts (signs/symptoms/laboratory tests) in the final vector is described in Section 4.3, where we describe the behavior of the variables through the iterations simulated with the FCM.

4.2.1 Case 1: A patient with DWS-negative

A 65 years-old patient with the following symptoms: fever, headache and myalgias. The vector of concepts

corresponding to the patient's signs, symptoms and laboratory tests (the initial vector) is passed to the inference rule (Eq. 3), and the final vector was obtained when the system reached a steady state (in iteration 73). The initial and the final vector of this patient can be seen in Table 4, and each iteration is the dynamic evolution of concepts. In the vector final, the decision concept $S1$ reached a value of 0.54 (blue number), which was converted to an PDS of 8.2% (red number), using Eq. 6. Based on this result, and using the rule defined by dengue clinical experts in Section 4.2, we may classify this patient as DWS-negative.

4.2.2 Case 2: A patient with DWS-positive

A 64 years-old patient with the following symptoms: fever, headache, myalgias, pain behind the eyes, vomit and hypothermia. The final vector was obtained when the system reached a steady state (in iteration 82). The initial and final vectors of this patient can be seen in Table 5. When the system reached a steady state, the decision concept $S1$ reached a value of 0.67 (blue number), which was converted to an PDS of 35.2% (red number). Based on this result, and using the rule defined by dengue clinical experts, we may classify this patient as DWS-positive.

4.2.3 Case 3: A patient with SD

A 71 years-old patient with the following symptoms: fever, headache, arthralgias, vomit, shock and organ failure. The final vector was obtained when the system reached a steady state (in iteration 84). The initial and final vectors of this patient are shown in Table 6. When the system reached the steady state, the decision concept $S1$ reached a value of 0.82, which means an PDS of 64%. Thus, we may classify this patient as SD.

4.3 Analysis of risk factors

Diagnosis of dengue involves several factors related to severity. It is of great importance to analyze these factors to know their behavior over time to avoid complications and death. In this section, we evaluate the behavior of the variables used for the classification of dengue in three scenarios (one for each type of dengue).

4.3.1 Scenario 1: A patient with DWS-negative

The patient to be evaluated is 75 years old and presents: fever, headache, retro-ocular pain, myalgias, arthralgias and skin rash. Plot A, in Fig. 6, shows the simulation results of this patient, using the FCM. In this patient, we find that the value of the concepts activated at iteration 1 (factors present in the patient) –initially– decreases as the model achieves a

Table 4 Concept values at the first and final iterations of the FCM for a patient with DWS-negative (*Case 1*)

Vector	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	S1	PDS (%)
Initial	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Final	0.14	0.14	0.14	0.21	0.14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0.54**	**8.2**

S1 and an PDS are the concepts inferred by the FCM

Table 5 Concept values at the first and final iterations of the FCM for a patient with DWS-positive (*Case 2*)

Vector	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	S1	PDS (%)
Initial	1	1	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Final	0.13	0.13	0.13	0.20	0	0	0	0	0.13	0	0	0	0	0.13	0	0	0	0	0	0	0	**0.67**	**35.2**

S1 and an PDS are the concepts inferred by the FCM

steady state; furthermore, the concepts reach the same value (blue curve). This could be explained by the fact that WHO guidelines [21] show that DWS-negative can be diagnosed by having fever plus two of the following: headache, retro-ocular pain, myalgias, arthralgias or rash. Another aspect to show is that the presence of headaches increases the value of retro-ocular pain (green curve). This could be explained because the headache produced by the disease would have a causal effect on the back of the eye. The patient's severity concept (red curve) remains at a moderate value (0.585); however, this value must be converted to severity percentage to establish the severity in terms of diagnosis. Performing this conversion, the patient's severity is 17%. Finally, we note that the concepts –initially set to 0– remain disabled during inference (black curve).

4.3.2 Scenario 2: A patient with DWS-positive

In this scenario, we have a 3-year-old patient with abdominal pain, lethargy, hypotension, hepatomegaly, mucosal bleeding, hypothermia, high hematocrit, low platelets and edema. Plot B, in Fig. 6, shows the simulation results for this particular patient.

The first thing we may observe in this plot is that the initial signs/symptoms of dengue are not present from the beginning of the simulation (i.e., fever, headache, retro-ocular pain, myalgias, arthralgias and erythema). The concepts associated with these signs/symptoms are deactivated during all iterations of the simulation; this can be seen in the black curve in the plot. According to the WHO [21], the critical phase of dengue can begin when the fever decreases or has disappeared, and, in this patient, the fever is not present, indicating that the patient is likely to develop this phase [18].

With respect to the activated concepts, corresponding to the patient's signs and symptoms, we may note that age, lethargy, hypotension, hepatomegaly, mucosal bleeding, low platelets and edema, have the same behavior (yellow curve) and reach the same values at the end of the simulation. Some concepts that are deactivated (i.e., signs or symptoms that the patient does not refer to in the consultation or that the physician does not detect) are activated at the beginning of the simulation.

The vomiting concept (green curve) is activated from the first iteration, indicating that this patient is likely to vomit for different related causes. For example, hepatomegaly, edema and abdominal pain (blue curve) could be likely causes of this activation; liver enlargement can displace other organs such as the stomach and fluid accumulation in that area, which could increase the likelihood of persistent vomiting [23].

Another concept activated from the first iteration of the simulation, is shock (pink curve). The shock concept achieves higher values of 0.8 after the fourth iteration;

Table 6 Concept values at the first and final iterations of the FCM for a patient with SD (*Case 3*)

Vector	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	S1	PDS (%)
Initial	1	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	1	1	0	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
Final	0.15	0.15	0	0	0.15	0	0	0	0.15	0	0	0	0	0.13	0	0	0	0	0	0.15	0.15	**0.82**	**64.0**

S1 and an PDS are the concepts inferred by the FCM

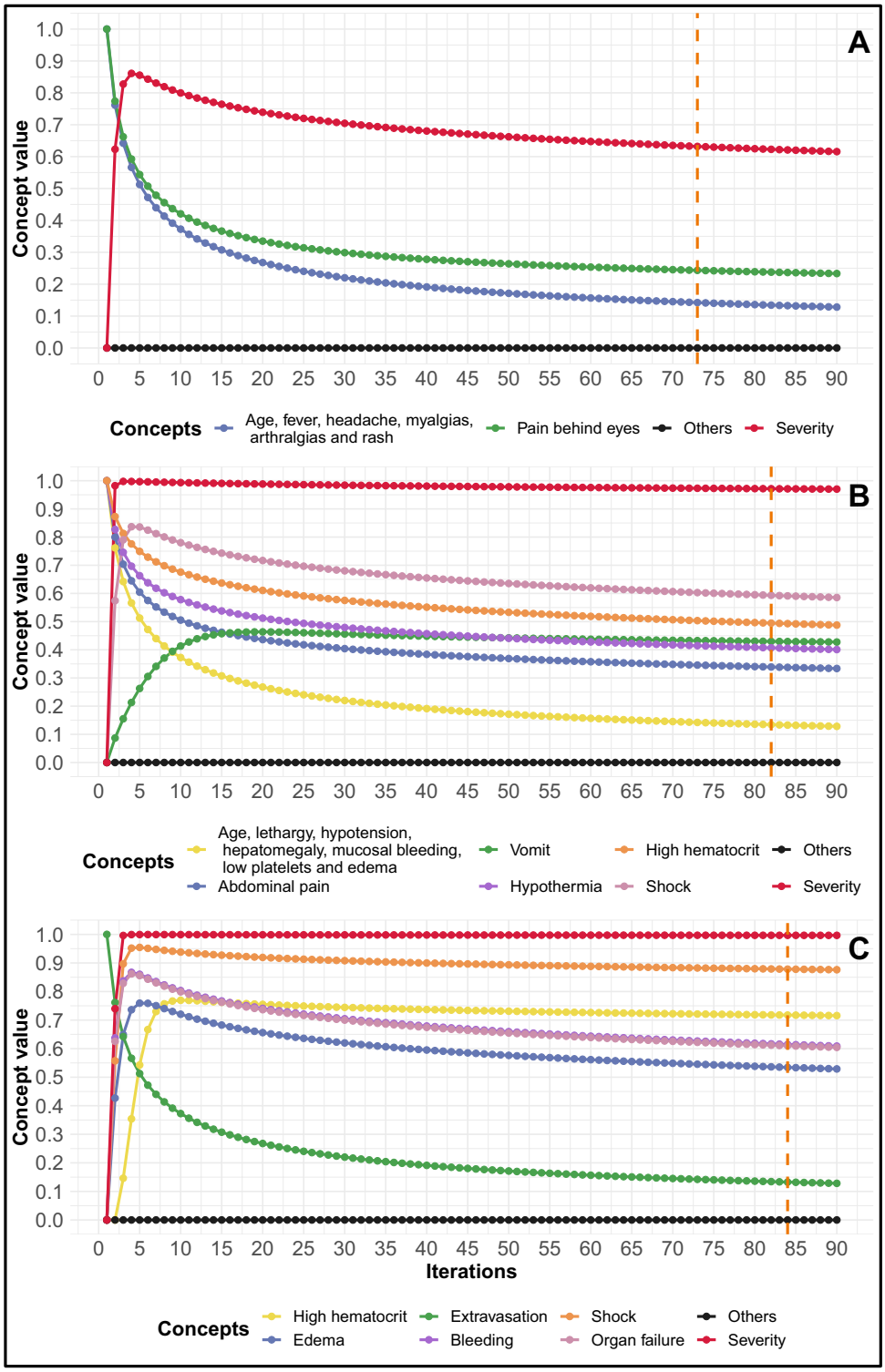

Fig. 6 Concept values of a patients with **(A)** = DWS-negative, **(B)** = DWS-positive, and **(C)** = SD. Dashed orange line indicates when the system reached equilibrium

however, when the model reaches a steady state, the values are approximately 0.6. With the exception of the concept of severity, the concept with the highest value is the concept of shock, which indicates that this patient could be complicated and life-threatening. Although this patient does not present any WHO criteria to define it within SD (see Fig. 2), the activation of the shock concept (appearance of this sign in the simulation) with a high value alerts the physician of possible complications in the patient. The performed simulation allowed the detection of this sign that was not present in the patient. Early detection of these signs or symptoms is crucial to reduce complications and mortality in patients with dengue.

With respect to severity (red curve), this concept is activated from the first iteration, achieving values above 0.95, maintaining high values throughout the simulation.

Other concepts –present throughout the simulation– maintain their values activated and with moderate values; for example, high hematocrit (orange curve), which measures the relationship between the plasma volume and the cellular package in the blood. This concept is directly influenced by edema, which is characterized by the loss of plasma fluid from the blood to the tissues. Another activated concept is hypothermia (purple curve), which is mainly caused by a decrease in blood pressure (hypotension). One of WHO criteria to define hypotension is the presence of cold extremities with a recharged capillary refill, which is closely related to hypothermia [21].

In summary, if WHO guidelines are used, the signs, symptoms and laboratory tests show that this patient can be diagnosed as DWS-positive. However, the FCM goes further and may indicate that the patient could present a shock immediately and compromise the patient's life.

4.3.3 Scenario 3: A patient with severe extravasation

The last scenario is a 28-year-old patient with severe blood plasma extravasation. Plot C, in Fig. 6, shows the behavior of the concepts during the iterations of the simulation. The presence of extravasation (green curve) leads to a chain of activations of other important concepts and severity markers. One of these concepts is: elevated hematocrit (yellow curve) –as a consequence of fluid loss from the blood into the tissues (this concept reaches values of 0.7 after the fifth iteration). The increase in this laboratory parameter is relatively due to fluid loss and not to cellular increase.

Another concept that is activated after the presence of extravasation is edema (blue curve), which reaches values above 0.5. The presence of this concept is due to the fact that plasma leakage in dengue causes fluid accumulation in the tissues.

The concepts that define SD are all activated: shock (orange curve) caused by the loss of blood plasma to the tissues. This concept reaches values between 0.85 and 0.95 from iteration 5 onwards. Hemorrhages (purple curve) are caused by the loss of plasma proteins essential for coagulation. In this case, the values of the concept hemorrhages reach moderate values between 0.6 and 0.8 after the fifth iteration. Another common finding in SD, is multi-organ failure (pink curve). This concept is possibly triggered by plasma leakage, causing hypotension, and leading to decrease blood supply to the organs. Another probable cause is that extravasation causes fluid accumulation in the organs and hinders their regular functioning. The concept of a multi-organ failure follows a similar behavior to that of hemorrhage, with similar concept values after iteration 5.

As we observed in this scenario, all the previously analyzed concepts are activated –from the first iteration– and remain with high values after the fifth iteration of the inference process. Finally, the severity concept is activated in the first iteration, and it is maintained with a high value (0.99) during all iterations. This indicates that the severity of the patient is high and should be adequately treated to avoid death.

In the three scenarios presented above, we see some concepts keep their same values during all iterations (see Fig. 6). This occurs when a concept is not activated from the beginning and has no concepts influencing it. For example, if the patient to be evaluated does not have fever (non-activated concept), this concept will have the same value during all iterations because it has no influential concepts that modify its value.

4.4 Comparisons with other ML techniques

In this section, we evaluate the predictive capability of the FCM and compare it with other ML techniques, such as ANN and SVM (see Table 7). We use these two ML techniques for two reasons: 1) they are techniques that have shown good performance on structured data, and, 2) according to the literature review [7], they are the most widely used techniques for the development of CDSS for dengue (see Section 1).

The dataset, described in Section 4.1, was divided into 70% for training and 30% for testing. We used 10-fold cross-validation to choose the best model. The metrics used for model evaluation were accuracy and F1-measure. *Receiving operating characteristic (ROC)* curves also were implemented to calculate the *area under the curve* (AUC) of ROC.

Table 7 Results of the FCM classification approach and comparison with other ML techniques

Model	Accuracy	F1-Score
FCM	0.894	0.921
ANN	0.979	0.978
SVM	0.981	0.981

4.4.1 Results for ANN

We used a single hidden-layer ANN (multilayer perceptron). We implemented different network configurations: i) number of units in the hidden layer (16, 32, 64, 128, 256); ii) two activation functions (tanh, relu); iii) two optimization algorithms (gradient descent, Adam); iv) learning-rate values (0.0001, 0.001, 0.01, 0.05, 0.1, 0.5). The optimal parameters of the final model were: a learning rate of 0.01, 256 units in the hidden layer, a relu-activation function, and Adam as the optimization algorithm. After training and testing, it was found that the ANN correctly classifies the dengue severity class with an accuracy of 97.9%.

4.4.2 Results for SVM

The SVM model was built using mutiple configurations to find the best one for the dengue-severity classification problem. The configurations were: i) three types of kernel (linear, radial and sigmoid); ii) C values (0.0001, 0.001, 0.01, 0.1, 1.0, 10.0, 100.0, 1000.0); iii) gamma values (0.0001, 0.001, 0.01, 0.1, 1.0, 10.0, 100.0, 1000.0). The best configuration was the radial kernel with values of 10 for both gamma and C. Evaluation on the test set yielded an accuracy of 98.1%.

The results shown in Table 7 and Fig. 7 indicate that accuracy, AUC and F1 score values are lower for FCM than for ANN and SVM. ANN and SVM are excellent models to classify structured data; this capability is related to the discovery of functional dependencies in ANN hidden layers and the use of support vectors to find separation hyperplanes in SVMs. Furthermore, they are data-driven techniques, where model parameters are extracted directly from the data, unlike FCMs where parameters are assigned by human experts with some bias. Nevertheless, a disadvantage of ANN and SVM is that they are poorly explanatory models [40], which indicates that they are excellent for classification and not so good to evaluate among behaviour of concepts or variables. The FCM performed well, and it is able to correctly classifies dengue in 89.4% of the cases. The added value of the FCM is that it allows medical staff to evaluate the behavior of the concepts involved in the process. It is an explainable method that solves the result interpretability problem of the ML approaches, very important in sensitive critical domains such as healthcare. For example, in several scenarios –such as the one presented in Section 4.3.3– it was shown the ability of the FCM to analyze the relationships between extravasation and other concepts, such as shock, hemorrhage, organ failure, among others. The diagnosis of dengue is not only a classification problem, as there are many factors related to the severity and classification of the disease that physicians must analyze to make a correct treatment decision.

Taking into account the accuracy and F1-score values of the FCM compared to the other ML models (see Table 7), we decided to use ROC curves to evaluate the behavior of each of the classes of dengue. One of the problems encountered is that class 2 (DWS-positive) has lower AUC values than the other two classes (see Fig. 8). One of the reasons why the low AUC value in class 2 may be occurring is that patients with DWS-positive are being diagnosed as SD; this may be due to the difficulty that –still– exists in differentiating between these two classes. There is a gray area between these two classes that does not allow a very accurate classification to diagnose dengue. Another reason for the low AUC value in class 2 is that many patients with DWS-positive are being classified as SD because of the high number of alarm signs present in dengue. A patient with all warning signs could be classified as SD due to high scores calculated by the inference rule.

4.5 Comparison of this model with other works

In this section, we compare our model with other works developed for dengue diagnosis. The comparison was performed based on the two most commonly used metrics in

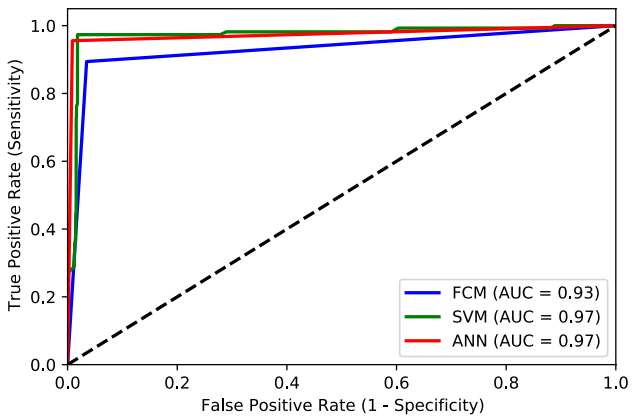

Fig. 7 ROC curves for the FCM model

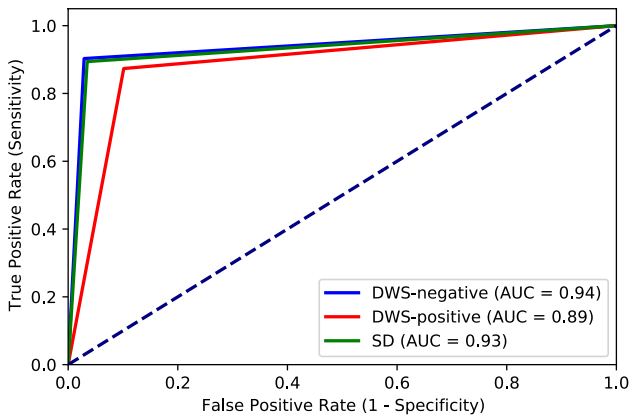

Fig. 8 ROC curves for the FCM model

classification tasks (accuracy and AUC). Table 8 shows the results of this comparison.

The implementation of dengue models with new types of data has been increasing [7, 10, 11]. As an example, Khan et al. [10] developed an SVM-based classification model using Raman-spectroscopy data obtained from the serum of dengue patients. Davi et al. [11] proposed a hybrid approach with SVM (for feature engineering) and ANN to classify dengue using gene expression data.

Our model performed better than these previously presented works, probably because the utilization of clinical and laboratory data allows establishing stronger functional dependencies with disease severity. Studies have shown that the use of clinical and laboratory data has a higher performance with respect to other types of data [7, 41, 42]. For instance, Park et al. [41] and Ho et al. [42] used structural equations and deep learning -respectively- to classify dengue using clinical and laboratory data. Although the works by Park et al. and Ho et al. used clinical and laboratory data, Table 8 shows that the result of our model is superior. This is probably due to the fact that the works implemented by Park et al. and Ho et al. used a smaller sample size than the one we used. It has been shown that the larger the size of the database, the better performance is obtained in the models [43, 44].

The global results of our FCM model show an excellent performance for classification, even outperforming many models previously developed for the same purpose, and our model has an additional feature: It allows evaluating the presence or absence of some features/variables related to the severity of dengue (it is an explainable method). Additionally, our model had the ability to detect signs or symptoms before they appear, in order for physicians to take preventive actions that reduce complications and decrease mortality rates.

5 Conclusions

The use of computational methodologies to analyze dengue risk factors and classify dengue based on severity are useful to support the diagnosis and clinical management of the disease. In this study, we propose a computational tool to analyze the main variables involved in the clinical course of dengue (signs, symptoms and laboratory tests). In addition, the model allows the diagnosis of dengue based on its severity. This is the first work that proposes an FCM for dengue using the signs, symptoms and laboratory tests established by WHO for the diagnosis of the disease.

Table 8 Results of the FCM model and comparison with other works

Study	Model	Accuracy	AUC
Khan et al. [10]	SVM	85%	–
Davi et al. [11]	ANN	86%	–
Park et al. [41]	SE	–	0.85
Ho et al. [42]	ANN	–	0.86
Our work	FCM	89%	0.92

The developed model achieved 89.4% accuracy to diagnose dengue. The accuracy was lower than other ML models, such as ANN and SVM (ANN = 97.9%, SVM = 98.1%). However, the FCM allowed the analysis of the behavior of factors associated with dengue. The model allowed the analysis of the relationships among these factors. ANN and SVM are less explanatory models because they do not assess the behavior of the variables involved in the process. Particularly, our approach is an explainable method that allows the result interpretation, very important for the clinical management of dengue. This approach is very useful because it allows detecting signs and symptoms before they appear to generate preventive actions to reduce their presence. This ensures that complications and mortality rates are reduced. For this reason, FCMs are more integral methodologies that not only classify an outcome but also evaluate the behavior of the factors. Finally, the developed model is flexible and easily adaptable to add more concepts and relationships. In this case, only a reconfiguration of the initial vector and weight matrix is necessary.

The severity of dengue should be evaluated early to avoid complications that lead to the death of patients. In this study, we found that the factor that most influences severity is extravasation. The extravasation of plasma fluids to the tissues produces the loss of substances necessary for the proper functioning of the body. Extravasation leads to the failure of many organs and the patient may become complicated and die. The model developed made it possible to evaluate the presence or activation of extravasation on the severity of dengue.

The developed FCM in this work has four limitations. First, the FCM did not take into account other laboratory tests that physicians might have available when treating a patient with dengue such as liver enzymes and white blood cells. The use of demographic variables, such as origin, could also improve the performance of the system. Second, FCM-based models based on human knowledge could lead to a biased assessment of the accuracy of these models because the weights were based on a predefined topology [45]. Automatically constructed FCMs perform better in dynamic analysis than in static analysis [28]. According to this, algorithms, such as *particle swarm optimization*, can be useful because they allow constructing FCMs –automatically– from the dataset. Thus, the use of techniques that extract causal relationships –directly– from the dengue data is an opportunity to improve the work presented.

Third, there is still some uncertainty between the DWS-positive class and the SD class. Future work could be aimed at decreasing the uncertainty between these dengue classes. The last limitation of this work is that the dataset used is from a single city, in Colombia, and it only evaluates the behavior of the concepts in that population. It would be useful to develop distributed strategies –such as federated learning [46] – to achieve a global model of different cities.

For a medical professional, the interpretation and analysis of the signs, symptoms, laboratory tests and severity of dengue are more valuable than a classification of the dengue severity. There is no cure for dengue and treatment is aimed at palliating the signs and symptoms. Preventing the patient from developing complications is the primary goal of the physician when treating a patient with dengue. For this reason, an analysis of the patient's signs/symptoms is more useful to a medical professional than just a classification of dengue severity.

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Author Contributions **William Hoyos:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Validation, Visualization & Writing - original draft. **Jose Aguilar:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Supervision, Writing – reviewing & editing. **Mauricio Toro:** Conceptualization, Resources, Supervision, Writing - reviewing & editing.

Declarations

Conflicts of interest The authors declare no conflict of interest.

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Appendix C

An autonomous cycle of data analysis tasks for the clinical management of dengue

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Research article

An autonomous cycle of data analysis tasks for the clinical management of dengue

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ABSTRACT

Dengue is the most widespread vector-borne disease worldwide. Timely diagnosis and treatment of dengue is the main objective of medical professionals to decrease mortality rates. In this paper, we propose an autonomous cycle that integrates data analysis tasks to support decision-making in the clinical management of dengue. Particularly, the autonomous cycle supports dengue diagnosis and treatment. The proposed system was built using machine learning techniques for classification tasks (artificial neural networks and support vector machines) and evolutionary techniques (a genetic algorithm) for prescription tasks (treatment). The system was quantitatively evaluated using dengue-patient datasets reported by healthcare institutions. Our system was compared with previous works using qualitative criteria. The proposed system has the ability to classify a patient's clinical picture and recommend the best treatment option. In particular, the classification of dengue was done with 98% accuracy and a genetic algorithm recommends treatment options for particular patients. Finally, our system is flexible and easily adaptable, which will allow the addition of new tasks for dengue analysis.

1. Introduction

Dengue is an arthropod-borne viral disease transmitted by *Aedes* mosquitoes, mainly *Aedes aegypti* and *Aedes albopictus* [1]. Currently, this infection is considered the most important arbovirosis worldwide in terms of morbidity, mortality and economic impact [2]. Between epidemiological weeks 1 and 49 of 2021, 1,173,674 dengue cases in the Americas region were reported, with a cumulative incidence rate of 118 cases per 100,000 inhabitants. In this period, the most affected subregions were the Southern Cone with a cumulative incidence of 323 cases/100,000 inhabitants, and the Andean subregion with 89 cases/100,000 inhabitants. Within the Andean subregion, Colombia is in third place with an incidence of 95 cases per 100,000 inhabitants, surpassed by Peru and Ecuador with 140 and 108 cases per 100,000 inhabitants, respectively [3]. Mortality rates for dengue can be high when diagnosis and treatment are not appropriate, reaching values of 20% [4].

In 2009, World Health Organization (WHO) published guidelines for diagnosis, treatment, prevention and control of dengue [5]. These guidelines are, currently, used by medical personnel for the clinical management of dengue, from diagnosis to treatment of patients, and, used to avoid complications leading to death. However, there are still difficulties in the diagnosis and treatment of the disease. The main difficulty in these two aspects of dengue lies –mainly– in the large amount of information that the medical staff must analyze in a short time to define the procedure to follow for each particular patient. This information corresponds to demographic, clinical and laboratory variables such as age, signs and symptoms that a patient with dengue may present [6]. One way to address this problem is to use decision support systems (DSS) to support the decision-making of medical personnel caring for dengue patients. Such systems can use data to enhance the processes performed by a human being [7].

With respect to the previously presented background, the contribution of this paper is a clinical DSS using an autonomous cycle of data analysis tasks (ACODAT) to aid decision-making in clinical settings. In particular, ACODAT uses the interaction of different successive tasks to extract the necessary knowledge to recommend improvements in a given process [8]. The use of ACODAT in different fields such as educa-

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tion, telecommunications and industry 4.0, have been reported [9, 10, 11]. For example, in the educational field, ACODAT has been used to determine learning styles in smart classrooms. Aguilar et al. [9] used ACODAT to analyze web and social network data to build knowledge models about students. These models are used to permanently monitor the learning process. The results showed the capacity of ACODAT for the generation of useful knowledge to improve the learning process. In the field of telecommunications, Morales et al. [10] developed ACODAT for quality of service management in Internet of Things (IoT) platforms. The implemented ACODAT allowed analyzing the quality of IoT platforms using classification and clustering tasks. In Industry 4.0, ACODAT has been developed and implemented to improve the efficiency of production processes. For example, Sanchez et al. [11] presented a framework that helps to solve the problems of integration and heterogeneity of the actors involved in manufacturing processes. The results show that ACODAT allowed to these actors (people, data, things and services) to interact for the creation of a self-configuration and self-optimization plan. Finally, it also has been used in smart cities, to control and supervise heating, ventilation, and air conditioning systems [12, 13].

The ACODAT concept has not been applied in the field of medicine. Particularly, ACODAT has not been used for clinical disease management to date. Based on the problem of dengue, a disease that generates high mortality rates if not diagnosed or treated in time, and its economic impact on health systems, it is necessary to develop clinical DSS for the clinical management of dengue. For this reason, the objective of this work is to develop an ACODAT to support decision-making for the clinical management of dengue. Currently, there are different clinical DSS for dengue [14]; however, the studies reported in the literature use predictive and prescriptive approaches separately, and to date, there are no models that integrate these two approaches, which are closely related to each other. Especially, prediction alone is not very useful when there is no prescriptive model to recommend the best options for solving the problem. The main contribution of this work is the development and implementation of an ACODAT that verifies and corrects clinical data, classifies dengue patients and recommends the best treatment options to avoid complications and death of patients.

The remainder of this paper is structured as follows: Section 2 presents a brief literature review about dengue modeling for the clinical management of dengue. Section 3 introduces the generalities of dengue and the conceptualization of ACODAT. Section 4 describes the ACODAT proposed in this article, and the methodology used for its definition and implementation. Section 5 shows the results of ACODAT's implementation in two dengue datasets. Section 6 discusses the results and compares them with previous studies. Finally, Section 7 concludes the paper.

2. Related work

In this section, we show a brief literature review on dengue modeling for the clinical management of dengue. To date, many machine learning (ML) models have been developed to support dengue diagnosis (see [14] for more information). Here, we present the most recent ones related to early detection, classification of the disease and prescription of the treatment.

2.1. Early detection of dengue

Early detection of dengue is difficult and challenging due to the lack of specificity in the clinical presentation of the disease. However, in recent years, computer-aided strategies have been developed to support medical professionals in these difficult tasks. [15, 16]. For example, Khosavanna et al. [15] used two techniques, logistic regression (LR) and decision trees (DT), to develop predictive models for the assessment of possible early dengue infections. The authors used self-reported clinical manifestations from patients in non-endemic regions. The best performance was from the DT model with an area under the curve (AUC) of 0.75. Ho et al. [16] compared several ML techniques to identify confirmed dengue cases using only age, body temperature, white blood cell count and platelet count. Models were built with deep learning, DT and LR, where deep learning performed best with an AUC of 0.86.

2.2. Dengue classification

Dengue is classified into three types according to WHO: non-severe dengue (with or without warning signs) and severe dengue (SD). Differentiation of these stages can be difficult in some cases due to the variability of the signs and symptoms of dengue. Different studies have attempted to model this type of problem to support diagnostic decision-making [17, 18, 19]. For instance, Huang et al. [17] used demographic data and laboratory test results to classify dengue patients based on its severity. Several ML methods such as LR, random forest (RF), support vector machines (SVM) and artificial neural networks (ANN) were used to train the models. The best model was ANN with an accuracy of 0.75.

Chatterjee et al. [18] proposed a hybrid ANN model with a modified cuckoo optimization algorithm. The model proposed by Chatterjee et al. had an accuracy of 0.957 using gene expression data. However, the classification performed was based on that recommended by WHO in 1997 (dengue fever, dengue hemorrhagic fever and dengue shock syndrome) [20].

Hoyos et al. [19] developed a DSS for dengue using fuzzy cognitive maps (FCM). They implemented diagnostic models using FCM to classify patients according to the type of dengue, with an accuracy of 0.89. Also, they analyzed the behavior of signs, symptoms, laboratory tests and disease severity. This study goes further, and not only classifies the patient, but also evaluates the behavior of the signs and symptoms of dengue over time, giving recommendations as to what factors might influence and appear in the course of the disease.

2.3. Dengue treatment

Treatment of dengue consists of palliating symptoms and avoiding complications leading to death. The complexity of the treatment is represented by the high variability of the clinical manifestations presented. Despite WHO recommendations, the treatment of dengue remains a challenge for medical professionals. Unfortunately, to date, no computational models have been developed to support decision making regarding the treatment of dengue.

In summary, the approaches proposed for the diagnosis of dengue based on severity are few. The models developed by [15] and [16] have the limitation of only detecting the disease without classifying it. On the other hand, the approaches developed for the classification of dengue have limitations such as the low classification performance in the work of [17], or the use of genetic data by [18], which is not useful in clinical practice because this type of data is not easy available for the clinician. Finally, there are no prescribing approaches that recommend treatment options for dengue.

The clinical management of dengue comprises both diagnosis and treatment. Thus, there is a need for the development of prescriptive models (treatment) integrated with classification models (diagnosis) to support decision making. The use of clinical data such as signs, symptoms and routine laboratory tests for the development of these models is important because of the availability and ease of collection in regular clinical settings.

3. Theoretical background

3.1. Clinical management of dengue

In this section, we describe the principal aspects of dengue, including generalities, diagnosis and recommendations for treatment.

Table 1. Summary of clinical management of dengue by treatment group recommended by WHO [5].

Treatment group	Characteristics	Management
A	No warning signs	Paracetamol
	Tolerate adequate volumes of oral fluids	Drink water
	Adequate diuresis	Oral intake of rehydration solutions
	Normal hemogram	Daily monitoring
B	Warning signs	Hospitalization
	Comorbidities	Isotonic solutions
	Social conditions	Hematocrit and platelets monitoring
C	Severe extravasation	Hospitalization
	Severe bleeding	Isotonic solutions 5-7 ml/kg/hour
	Shock	Colloid solutions 10-20 ml/kg/hour
	Organ failure	Vital signs monitoring

3.1.1. Generalities of dengue

Dengue is an acute infection caused by a virus of the flavivirus group. To date, there are four (4) serotypes of the virus (DENV-1, DENV-2, DENV-3 & DENV-4). The infection is transmitted from person to person by the bite of an *Aedes* mosquito [21]. Dengue can be classified according to the severity of the disease into: 1) non-severe dengue without warning signs (NoWS-Dengue), 2) non-severe dengue with warning signs (YesWS-Dengue) and, 3) SD. This classification was recommended by a WHO expert group in 2009 [5]. Dengue has various forms of clinical expression: undifferentiated fever, headache, general malaise, osteomyoarticular pain, with or without exanthema and leukopenia. Severe forms of the disease are characterized mainly by hypovolemic shock caused by plasma extravasation, with moderate or severe thrombocytopenia and major bleeding in the gastrointestinal tract and other locations [22]. Dengue is also capable of expressing itself through the so-called "atypical" forms, which are relatively infrequent and result from particularly intense involvement of an organ or system: encephalopathy, cardiomyopathy or hepatopathy, among others [23].

3.1.2. Diagnosis of dengue

The definitive and confirmatory diagnosis of dengue is made using direct methods such as virus isolation, detection of viral nucleic acid or antigens; and indirect methods such as detection of antibodies produced against the virus [2]. However, these laboratory tests can take a long time, which could cause the patient with dengue to develop complications and die. To solve this problem, there are dengue diagnosis guidelines published by WHO [5]. These guidelines state that the first step in the diagnosis of dengue is the general evaluation of the patient by the physician to classify the patient into a group: NoWS-Dengue, YesWS-Dengue & SD. The physical examination, analysis of the medical history, and laboratory tests such as a complete blood count, allow the identification of warning signs and evaluation of the patient's hydration status. Classification of the patient into a group constitutes the second stage in the clinical management of dengue. The use of this guide is crucial to provide adequate management of the disease due to the wide spectrum of clinical manifestations of dengue.

3.1.3. Recommendations for treatment

The third step in the clinical management of dengue is treatment. The information obtained in the previous two steps is vital to provide an adequate and timely treatment for the patient with dengue. Table 1 summarizes the clinical management of dengue, by treatment group, based on the WHO guidelines. The treatment routes for dengue are categorized into three groups (A, B & C). In group A, we have patients who do not present warning signs or comorbidities and who tolerate oral water volumes. In addition, this group includes patients with adequate diuresis. In group B, we have patients with warning signs or pre-existing conditions such as diabetes mellitus, obesity, renal failure, pregnancy, among others. Patients with some social conditions, such as living alone or living far from a health institution, are also classified in this group. Finally, group C constitutes all patients with any of the following complications: severe plasma extravasation, severe bleeding, shock, and severe organ deterioration.

3.2. ACODAT

The high amount of data generated today continues to increase considerably. For this reason, it is necessary to develop new tools for data manipulation to extract meaningful knowledge. ACODAT is one of these strategies, which consists of a set of data analysis tasks that must be performed together to achieve an objective in a given system or situation [24]. This set of tasks interacts, and has different roles in the cycle [25, 26]: observing the process, analyzing and interpreting what happens in it, and making decisions to achieve the objective for what the cycle was designed.

The performance of successive tasks connected allows solving complex problems that require a lot of knowledge for the solution [8]. The tasks in an ACODAT can be classified into three types [27]: observation, analysis and decision making. Observation tasks are those in charge of collecting data and information about the system or environment. The analysis tasks are in charge of interpreting or diagnosing the system using data. This function is performed by building knowledge models about the behavior of the cycle. Finally, the decision-making tasks are those in charge of performing decision-making activities to improve the process.

4. Methodology

In this section, we describe the methodology to create an ACODAT for the clinical management of dengue. Then, we specify each of ACODAT's tasks. Finally, we show the implementation of these tasks on specific datasets to support decision-making related to clinical management of dengue.

MIDANO is a *methodology for data analytic based on organizational characterization* that has been defined for the development of applications based on data analysis, and especially, ACODAT [28]. In this paper, we use the MIDANO methodology with a little modification for the development of this work. The MIDANO methodology consists of three main phases (see Fig. 1). The objective of phase 1 is to know everything related to the organization to define the objective of the data analysis application. This stage focuses on identifying and conceptualizing the solution to a problem, from the perspective of developing applications based on data analysis. Phase 2 is in charge of data preparation and treatment. This process is based on the ETL paradigm (E = Extraction of data from its sources, T = Transformation of data, and L = Loading of data). The main objective of this stage is to generate quality data in order to create knowledge models, and define the multidimensional data model of ACODAT. The objective of phase 3 is the implementation of the data analysis tasks in the ACODAT to generate knowledge models (descriptive, predictive, classification, prescriptive, among others) [29]. In our work, the first phase was used to characterize the problem. In addition, we included data preparation and

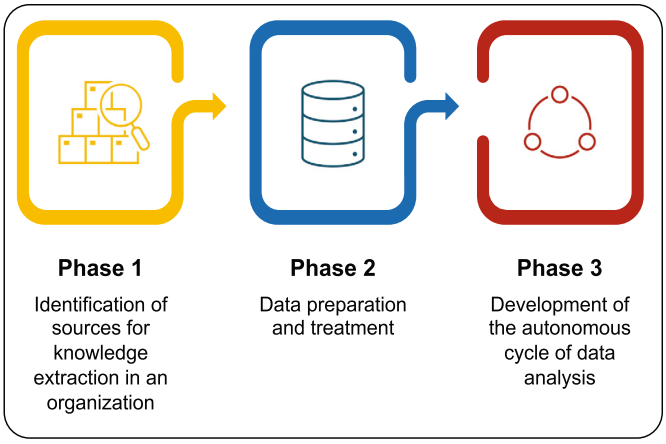

Fig. 1. MIDANO methodology. Adapted from [29].

treatment (second phase) inside the ACODAT, such a way that the data is processed online (real-time) by the cycle to make the process more autonomous. Also, the second phase was responsible to identify the data sources needed to build the ACODAT. Next, we explain –in detail– each of the MIDANO phases applied to the clinical management of dengue.

4.1. Characterization of the dengue context

The first phase of the MIDANO methodology is to identify sources to extract knowledge in an organization [29]. In this case, we met with dengue clinical experts to identify those knowledge sources. The clinical experts in dengue expressed the difficulties presented in the hospital environment: 1) problems with the labeling of patients with each type of dengue due to unintentional errors in the database entry, 2) difficulties in the classification of patients with dengue due to the high number of variables to analyze in a short time, added to this, the lack of experience of some physicians for a correct classification of the patient with dengue, and, 3) difficulties in the palliative treatment of dengue for the same reasons expressed above.

4.2. Identification and analysis of data sources

The second phase of MIDANO corresponds to the identification of data sources that can help develop clinical DSS for dengue. In this case, the most suitable option is the use of open databases published by the Colombian government through the National Institute of Health (INS in Spanish). The data that health institutions report to the Colombian national health institute were identified. These data correspond to demographic variables such as age, clinical variables such as signs and symptoms, and finally, results of laboratory tests. In MIDANO methodology, this phase also considers the preparation and treatment of the data; however, to make the process more dynamic, we included the processing of the data within the ACODAT.

4.3. Specification of the ACODAT for the clinical management of dengue

The last phase of MIDANO corresponds to the specification of ACODAT. This paper proposes an ACODAT for the clinical management of dengue. Fig. 2 shows the architecture of ACODAT for clinical management of dengue. This ACODAT is composed of three steps with interconnected tasks for the improvement of dengue decision-making at the hospital level. Step 1, called *monitoring*, comprises the tasks of data verification and correction. Step 2, called *disease analysis*, consists of the task of classifying patients based on their signs, symptoms and laboratory tests. Finally, step 3, called *treatment decision making*, comprises the prescription task, which consists of recommending the best treatment option for a given patient. The data analysis tasks used techniques that belong to different fields of artificial intelligence (AI), such as ANN and genetic algorithm (GA) which belong to the field of computational intelligence; and SVM which belongs to the ML field.

4.3.1. Task 1: data verification and correction

The results obtained in modeling depend largely on the quality of the data [30]. The first task of our ACODAT is to detect and correct possible errors to perform the next tasks in the best way. Missing data is very common in this kind of data; for this reason, rows with missing data are removed from the dataset. Another problem with dengue datasets is the imbalance of their classes, because one of the classes (SD) is always in lower proportion to the other two classes (NoWS-Dengue & YesWS-Dengue). For this reason, an oversampling technique was used.

4.3.2. Task 2: classification

After data are prepared and verified, they are passed to the second ACODAT task. This task uses classification techniques to determine the type of dengue in patients. For this task, we used ANN and SVM. The main characteristics of this task are shown in Table 2.

4.3.3. Task 3: prescription

This task uses a list of prescriptions for dengue –described in the WHO guidelines– for the clinical management of dengue. Based on the results of the previous task, a GA optimizes the best treatment option for a particular patient. Table 2 shows the characteristics of this task.

4.4. Implementation of ACODAT for the clinical management of dengue

In this section, we implemented ACODAT for the clinical management of dengue using datasets from two regions of Colombia.

4.4.1. Datasets

The Data used for this implementation are those stored in the database of the Colombian epidemiological surveillance system (SIVIGILA in Spanish), which correspond to records of dengue patients reported by health institutions to the Colombian National Health Institute, the entity in charge of managing this type of information in Colombia. For the experiments, we used data from the city of Medellin (2008-2018) and the department of Córdoba (2010-2021) [31]. We chose these regions because they are endemic for dengue. According to epidemiological reports, the annual incidences reported are 161-745 and 51-503 per 100,000 inhabitants for Medellín and Córdoba, respectively [32].

Medellín and Córdoba datasets were composed of 52,051 and 16,670 patients, respectively. Both datasets had 36 variables, of which 14 were eliminated because they did not contribute to our study or were not related to the clinical management of dengue, for example: address, type of social security, city and department codes, among others. Finally, 22 variables were selected corresponding to the signs, symptoms and laboratory tests that the medical professional observes or detects in each patient suspected of dengue. Table 3 shows each of the variables included in the datasets, their type and a brief description. All predictor variables in the datasets are binary (except age, which was numerical), where 1 represents the presence of the sign or symptom and 0 represents the absence. The target variable is categorical with 3 classes corresponding to the WHO classification of dengue (No WS-Dengue, Yes WS-Dengue & SD).

4.4.2. Implementation of task 1: data verification

In general, health data have some very common particularities, such as low quality [30]. In the case of dengue data, there are many errors for different reasons. One of the reasons is the speed of the medical professionals in entering the dengue notification forms to the health authorities. Also, the high demand for hospital care causes medical professionals to enter unintentional errors into the datasets. For example,

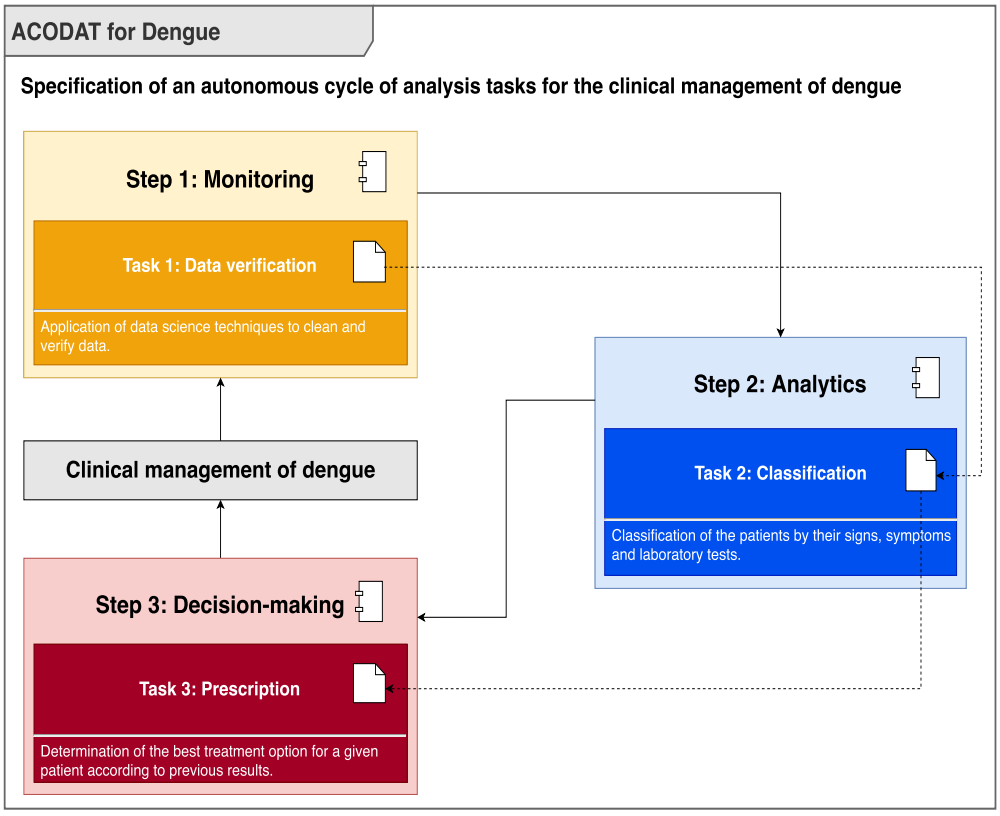

Fig. 2. Architecture of ACODAT for clinical management of dengue.

Table 2. Description of the ACODAT's tasks for clinical management of dengue.

Task name	Characteristics of the task				
	Description	Data source	Analytics type	Technique	Knowledge model
Data verification	Verification of data and correction of errors	Datasets of National Institutes of Health about dengue	Description	Verification Oversampling	Descriptive
Classification	Classification of a patient by their variables	Previous task	Classification Prediction	ANN SVM	Predictive
Prescription	Determination of the best treatment option for dengue	Previous task	Optimization	Genetic algorithm	Prescriptive

a very common error in the databases is to find patients with NoWS-Dengue classified as having SD.

Missing data treatment was carried out using the listwise method, which consists of eliminating all the data of an observation if there is at least one missing data. For class balancing, we used the Synthetic Minority Oversampling Technique (SMOTE) due to the low frequency of the SD category. Table 4 shows the distribution of dengue type in the datasets after applying preprocessing techniques.

For this first task, a Python 3.5 program was written to verify and correct the data. We used libraries such as *Pandas* [33] to extract and process the structured data. The *Imbalanced-learn* library [34] was used to correct the imbalance of the classes. The steps to follow in this task are the following: 1) extract the structured database of patients with the three types of dengue, 2) verify if there are errors in the patient labels; for example, if there are patients without warning signs classified as SD, reassign the label as NoWS-Dengue, 3) eliminate rows with missing data because the value of the variable for that patient cannot be established, 4) Balance the classes using the oversampling technique that consists of increasing the number of samples of lower frequency in the dataset [35]. In this case, the records for the SD class. Fig. 3 represents the activities or subtasks performed in this task.

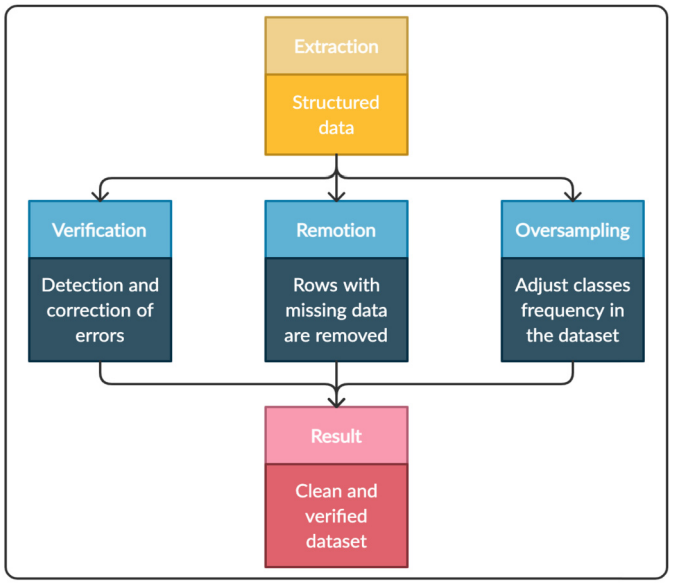

Fig. 3. Activities or sub-tasks related to task 1 (data verification and correction).

Table 3. Variables used to build the ACODAT for clinical management of dengue.

Code	Variable	Type of variable	Description
V1	Age	Demographic	Time elapsed since the birth of an individual
V2	Fever	Sign/symptom	Increase in body temperature
V3	Cefalea	Symptom	Pain and discomfort located in any part of the head
V4	Pain BE	Symptom	Pain behind eyes
V5	Myalgias	Symptom	Muscle aches
V6	Arthralgias	Symptom	Joint pain
V7	Rash	Sign/symptom	Skin exanthema
V8	Abd. pain	Sign/symptom	Intense pain, located in the epigastrium and/or right hypochondrium
V9	Vomit	Symptom	Violent expulsion by the mouth of what is contained in the stomach
V10	Lethargy	Sign/symptom	State of tiredness and deep and prolonged sleep
V11	Hypotens.	Sign	Excessively low-blood pressure on the artery wall
V12	Hepat.	Sign	Condition of having an enlarged liver
V13	Muc. hemo.	Sign/symptom	Manifestations of mild to severe bleeding in the nasal mucosa, gums, skin, female genital tract, brain, lungs, digestive tract and hematuria
V14	Hypoterm.	Sign/symptom	Decrease of body temperature
V15	High hem.	Lab. test	Indirect increase in hematocrit test
V16	Low plat.	Lab. test	Decrease of platelet levels in the blood
V17	Edema	Sign/symptom	Swelling caused by excess fluid trapped in body tissues
V18	Extrav.	Sign	It is characterized by serous spills at the level of various cavities
V19	Bleeding	Sign/symptom	Blood leaks from the arteries, veins or capillaries through which it circulates, especially when it is produced in very large quantities
V20	Shock	Sign	Manifestation of severity evidenced by cold skin, thready pulse, tachycardia and hypotension
V21	Org. fail.	Sign	Affectation of several organs due to the extravasation of liquids
V22	Dengue category	Target	Type of dengue based on the severity

Table 4. Distribution of dengue categories in the datasets.

Dataset	Dengue category	Original	After listwise deletion	After balancing
Medellín	No WS-Dengue	27,230	10,210	10,210
	Yes WS-Dengue	12,669	11,123	11,123
	SD	437	123	11,186
	Total	52,051	21,456	32,519
Córdoba	No WS-Dengue	9,905	4,563	4,563
	Yes WS-Dengue	6,179	5,134	5,134
	SD	586	231	5,623
	Total	16,670	9,928	15,320

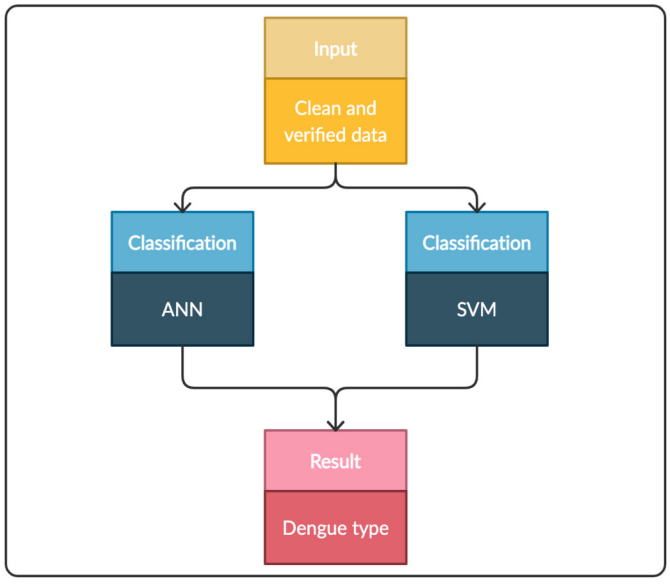

Fig. 4. Steps related to task 2 (classification).

4.4.3. Implementation of task 2: classification

The second task of the ACODAT classified the patients in the three labels of the dataset. Fig. 4 shows the activities in this task. The labels were NoWS-Dengue, Yes-WS-Dengue & SD. This task was performed using ANN and SVM techniques, which were chosen for their high performance for classification with clinical datasets [19].

This task had as input the clean and verified dataset product of the previous task (data verification and correction). We divide the dataset in 70% for training and validation, and 30% for testing. We used 10-fold cross-validation to find the best combination of hyperparameters and used different configurations for both ANN and SVM. In the case of ANN, we used a multi-layer perceptron with a single layer, and for SVM, we used SVM in its classifier version. Table 5 shows the different configurations of hyperparameters for each implemented technique.

The implementation of this task was performed in Python 3.5 using the *Scikit-learn* library [36] for modeling and the *Numpy* library [37] for matrix and vector processing.

4.4.4. Implementation of task 3: prescription

Task 3 was focused on decision-making. In this case, it was focused on determining the best treatment option for a patient with a particular type of dengue. Fig. 5 shows the steps of this task. The implementation of this task was performed using a GA to find an optimal solution to the problem. The first step of this task was to identify some prescriptions recommended by WHO in the guidelines for the treatment of dengue. We identified six prescriptions: paracetamol (P), drinking water (W), oral rehydration solutions (ORS), isotonic solutions 5-7 ml/kg/hour (IS), colloid solutions 10-20 ml/kg/hour (CS) and hospitalization (H). These are the main prescriptions recommended by WHO for the treatment of dengue (see Table 1 and [5] for more information).

Fig. 6 summarizes the methodological framework for the creation of a prescriptive model using a GA. The prescriptions were binary coded to feed the GA. The steps to find the optimal solution were: 1) generation of random binary chromosomes representing different solutions (alternative prescriptions). The number of generations depended on having individuals with prescriptions greater than or equal to 95% as-

Table 5. Hyperparameter settings used to build the ANN and SVM models.

Technique	Hyperparameter	Options
ANN	Number of hidden units	16, 32, 64, 128, 256
	Learning rate	0.0001, 0.001, 0.01, 0.05, 0.1, 0.5
	Activation function	tanh, ReLU
	Optimizer	Gradient descent, Adam
SVM	Kernel	Linear, radial, sigmoid
	C	0.0001, 0.001, 0.01, 0.1, 1.0, 10.0, 100.0, 1000.0
	gamma	0.0001, 0.001, 0.01, 0.1, 1.0, 10.0, 100.0, 1000.0

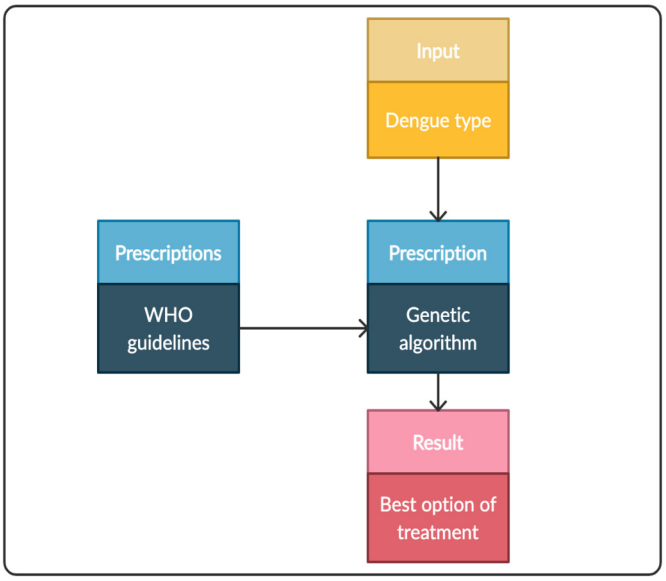

Fig. 5. Steps related to task 3 (prescription).

sertiveness. 2) estimation of the fitness of each chromosome using a function, 3) creation of new individuals using genetic operators. In this step, two parent chromosomes with the best fitness are selected, and crossover and mutation operators are used in them. 4) generation of a new population for a new iteration/generation. Fig. 7 shows a graphical representation of the chromosomes, crossover and mutation processes. The crossover and mutation probabilities were set to 0.5, respectively.

Several studies have shown that these probability values generate the best performance results on similar problems [38, 39, 40]. The crossover operator takes two selected parents and cuts the chromosomes at a randomly chosen position to produce two initial and two final gene subsets. The final subsets are then swapped, producing two new complete chromosomes. The mutation operator is applied to each offspring individually, and consists of the random alteration of each component gene of the chromosome. Regarding the fitness functions to evaluate the possible solutions, these were established based on the type of dengue. All the fitness equations proposed have as output a value between 0 and 100 that corresponds to the fitness of a solution (chromosome) to solve the problem, being 0 not suitable at all and 100 very suitable. The variables involved in these functions are: the list of prescriptions described above (P, W, ORS, IS, CS, H), $WP_i, \{i = 1, 2, 3\}$, which corresponds to the penalty when unsuitable treatment options are recommended for the type of dengue, F_i which corresponds to the result of the fitness function for each type of dengue. The ith value corresponds to the dengue type. Finally, the r value is a random number to increase the searching space.

$$WP_1 = IS \times 2 + CS \times 2 \tag{1}$$

$$F_1 = (r(30,40) \times P + r(50,60) \times W) \times 0.8^{WP_1} \times 0.1^{H} \tag{2}$$

$$WP_2 = P + CS \times 2 \tag{3}$$

$$F_2 = (r(65,75) \times IS + r(15,25) \times ORS) \times 0.8^{WP_2} \times 0.1^{1-H} \tag{4}$$

$$WP_3 = P + W \times 2 \tag{5}$$

$$F_3 = (r(65,75) \times CS + r(15,25) \times IS) \times 0.8^{WP_3} \times 0.08^{1-H} \tag{6}$$

All fitness equations were constructed with the help of dengue clinical experts, who assigned the coefficients for each variable or treatment option depending on its importance in the clinical management of the disease for each type of dengue. Eq. (2) is the fitness function for NoWS-Dengue. In this type of dengue, the use of recommendations such as the application of IS and CS is not recommended, so the fitness function penalizes the use or the presence of this recommendation in a chromosome during the optimization process (see Eq. (1)). For this case, the clinical experts in dengue assigned a coefficient of 0.8 to penalize the use of these strategies in this type of patient. In addition, the fact of being hospitalized (H) is penalized, because a patient with no warning signs does not need to be hospitalized [5]. For this case, the experts assigned a coefficient of 0.1 for this variable, because it is not so serious for the patient to be hospitalized. Random intervals are included to simulate the fact that prescriptions are not absolute and a prescription will not work the same for all patients. In these random intervals, a little more weight is given to W since hydration is key to keeping the patient from getting worse [5]. In Eq. (4) corresponding to YesWS-Dengue, the use of CS is penalized because they are patients who are not in severity and do not require this type of treatment (see Eq. (3)). Besides, there is a severe penalty if the patient is not hospitalized, since patients with warning signs need to be closely monitored given the high risk of worsening [5]. In the same way as in Eq. (2), experts assigned coefficients for each treatment variable. Finally, Eq. (6) represents the fitness function for SD. In this function, the use of P and W is penalized (see Eq. (5)) because these patients are in a state of severity and do not tolerate the use of oral solutions or medications. Finally, it is penalized if the patient is not hospitalized, since patients with SD need to be treated on an emergency basis [5]. In the same way as in Eq. (2) and Eq. (4), experts assigned coefficients for each treatment variable to build fitness functions.

Due to the lack of datasets with dengue treatment results, we implemented this prescriptive task in some specific scenarios. We use a binary vector to represent the patient's age, clinical and laboratory variables, where 0 means the absence of the variable and 1 means the presence of the variable. For the type of dengue, we used 1 = NoWS-Dengue, 2 = YesWS-Dengue and 3 = SD. With respect to treatment options, 1 means that this treatment option is recommended for that patient, while 0 represents that this treatment option is not recommended. The implementation of this task was done using the Python 3.5 *Pandas* and *Numpy* libraries [33, 37].

5. Results

In this section, we show the results of each of the tasks implemented in ACODAT. First, we show the main characteristics of the cleaned and corrected datasets. Second, the results of the classification model and, finally, the results of the prescription in specific scenarios.

5.1. Clean and corrected dataset

The first task aims to detect and correct errors in the dataset. Table 4 shows the results of the dataset after applying different data science

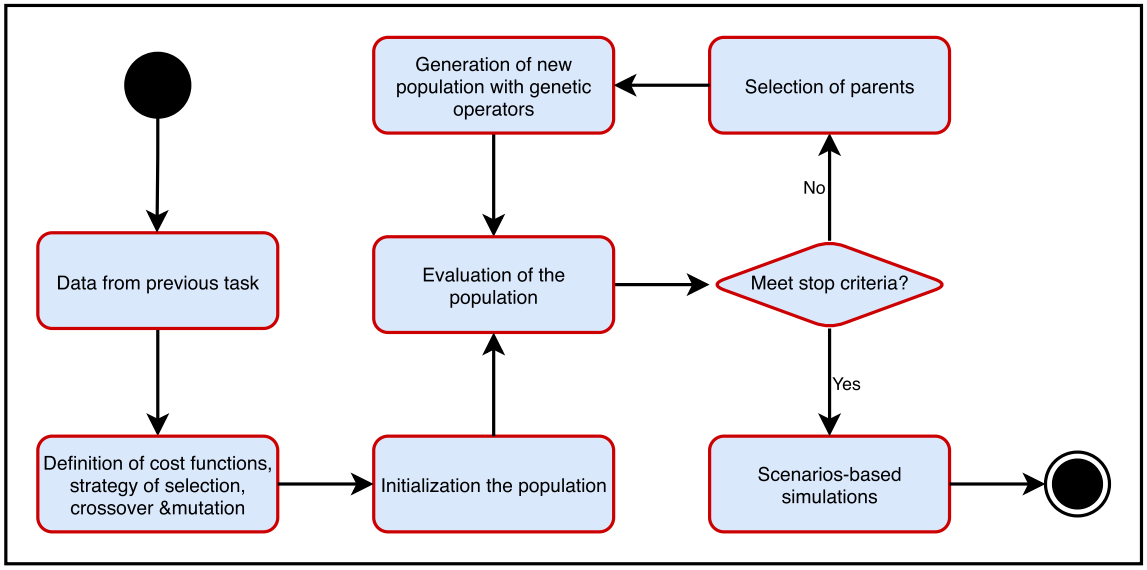

Fig. 6. Methodological flowchart to create a prescriptive model using a GA.

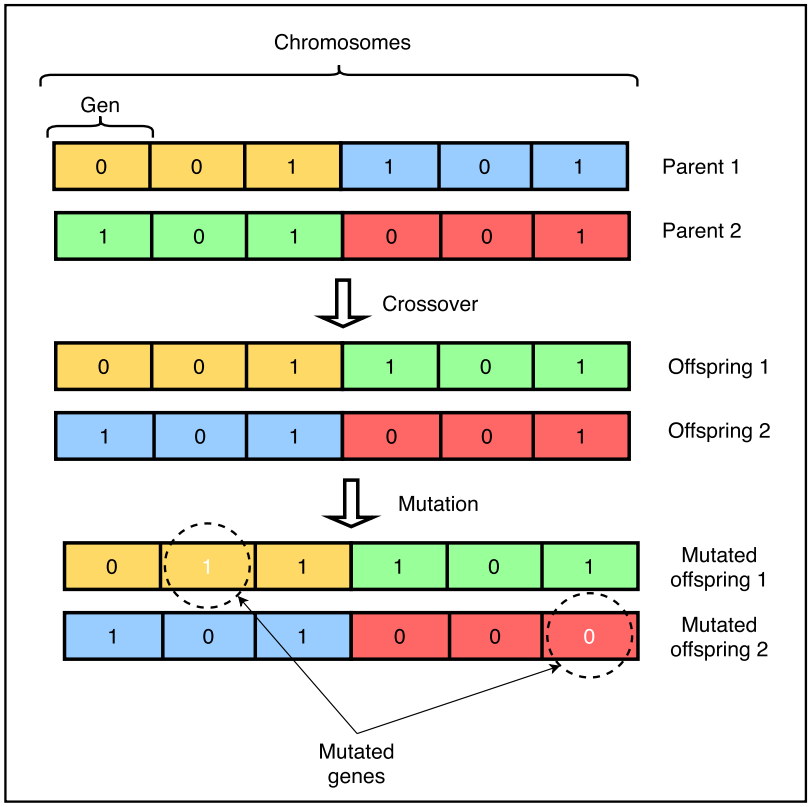

Fig. 7. Example of chromosomes, crossover and mutation processes in a GA.

techniques for data correction. Finally, we used 32,519 and 15,320 records to generate the classification models for Medellín and Córdoba, respectively.

The description of the categorical variables in the dataset was done in the previous section. The only quantitative variable was age, and its distribution is shown in Fig. 8. Plots A, B and C in Fig. 8 represent the age distribution in the Medellín dataset, while plots D, E and F represent the age distribution in the Córdoba dataset. The distribution of age, in the three dengue categories, showed similar results for both the Medellín and Córdoba datasets. The Kolmogorov-Smirnoff test was performed to test the normality of this variable. The results showed that they do not follow a normal distribution ($p < 0.001$ for the three categories). The right-skewed density curves in Fig. 8 confirm the results, where the average age is greater than the median.

5.2. Classification models

Table 6 and Fig. 9 show the performance results of this task, and the optimal values of the hyperparameters for each technique. Plot A in Fig. 9 corresponds to the performance of the classification model on

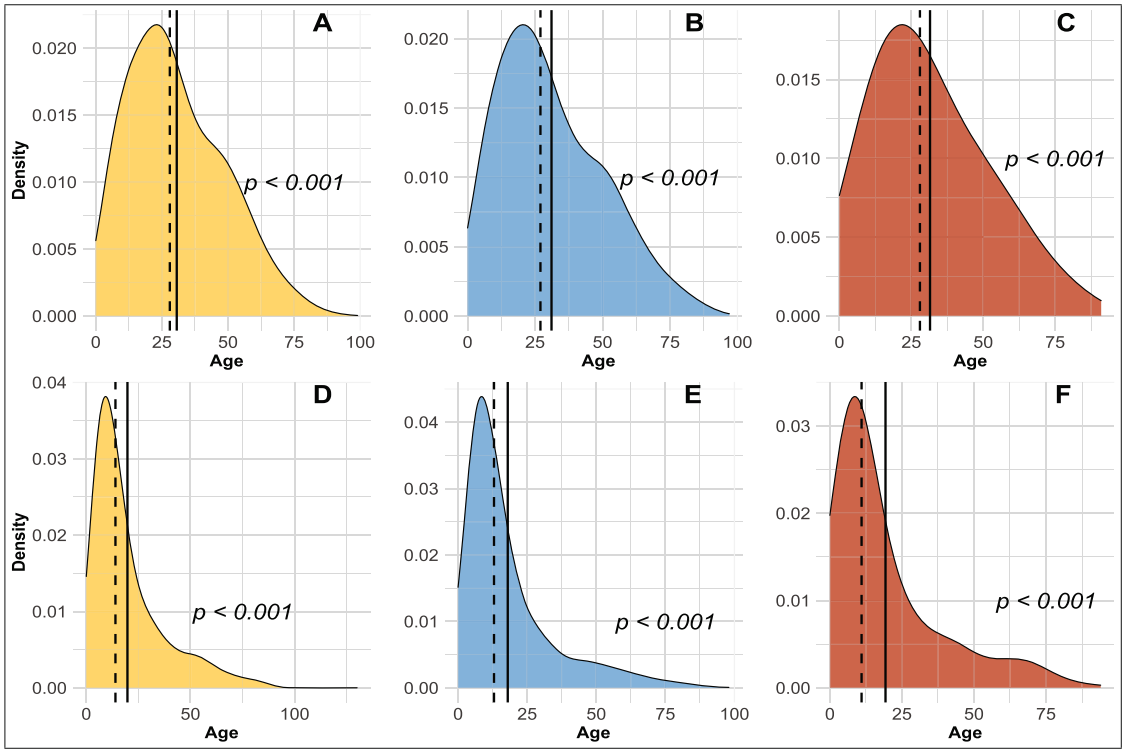

Fig. 8. Age distribution in the datasets according to the dengue category (yellow = NoWS-Dengue, blue = YesWS-Dengue, red = SD). **A**, **B** and **C** correspond to the Medellín dataset, while **D**, **E** and **F** correspond to the Córdoba dataset. The solid and dash lines indicate the mean and the median, respectively. The p-values are the result of normality test for each class.

Table 6. Quality of developed models used to classify dengue patients.

Model	Hyperparameters	Dataset			
		Medellín		Córdoba	
		Accuracy	F1-Score	Accuracy	F1-Score
ANN	• 256 hidden units	0.979	0.978	0.977	0.977
	• ReLU				
	• Adam				
	• $\alpha = 0.01$				
SVM	• Radial kernel	0.981	0.981	0.972	0.971
	• C = 10				
	• $\gamma = 10$				

the Medellin dataset, while Plot B represents the performance on the Córdoba dataset. The implemented models showed an excellent performance to classify patients based on severity. The best performing model was the one developed with the Medellin dataset, with an accuracy of 0.981 and AUC of 0.98. However, all models had a high performance with accuracies above 0.97.

5.3. Prescriptive model

In this section, we show the results of the prescriptive model in specific scenarios. We chose three scenarios (one for each type of dengue) to show the ability of the model to prescribe treatment for dengue in each disease variant.

5.3.1. Scenario 1

Patient 65 years old with following symptoms: fever, headache, myalgias. The previous task (classification) classifies this patient as NoWS-Dengue. This information is received by the prescriptive task, and based on the fitness function assigned for this type of dengue (Eq. (2)), it optimizes the solution that corresponds to the best treatment option for this patient. Table 7 shows the vectors corresponding to the patient variables, the result of the classifying task, and the result of the prescriptive task showing the options that are recommended for this particular patient. In this case, the output of the predictive model is used by the prescriptive model to optimize the optimal treatment for this patient.

The results show that the prescriptive model recommends the use of P, W and ORS. This result is correct because, in this patient, it is only important to rehydrate to maintain plasma volume and P to relieve symptoms such as fever, headache and muscle aches. Regarding the other decision variables, it is not necessary to apply IS or CS because there are no signs indicating fluid accumulation in the patient's body. Furthermore, this type of patient does not need to be hospitalized, so the prescriptive model does not recommend this treatment option. In summary, the prescriptive model makes a correct recommendation with respect to the WHO recommendations.

5.3.2. Scenario 2

Patient 35 years old with: headache, myalgias, arthralgias, vomiting, abdominal pain. Using the result of the previous task, this patient is classified as *YesWS-Dengue*. The GA uses the fitness function of Eq. (4) to choose the best solutions for this particular patient. A chromosome with the best fitness is obtained. In Table 8, we can observe the age, signs, symptoms and laboratory tests of this patient represented in a vector. In addition, we can observe the type of dengue classified by the previous task, and, finally, we observe the best treatment options for this patient. In this scenario, the most important finding is that the patient presents two warning signs, such as vomiting and abdominal pain. Based on these findings, the prescriptive model recommends P, W, ORS, application of IS and H.

The presence of fever and pain in the patient confirms the recommendation of analgesics such as P. The use of ORS and W is recommended in this type of patient, since hydration is an important aspect to prevent dengue complications. However, as this patient presents some warning signs, such as vomiting and abdominal pain, the application of IS is necessary to help with the patient's hydration. Regarding hos-

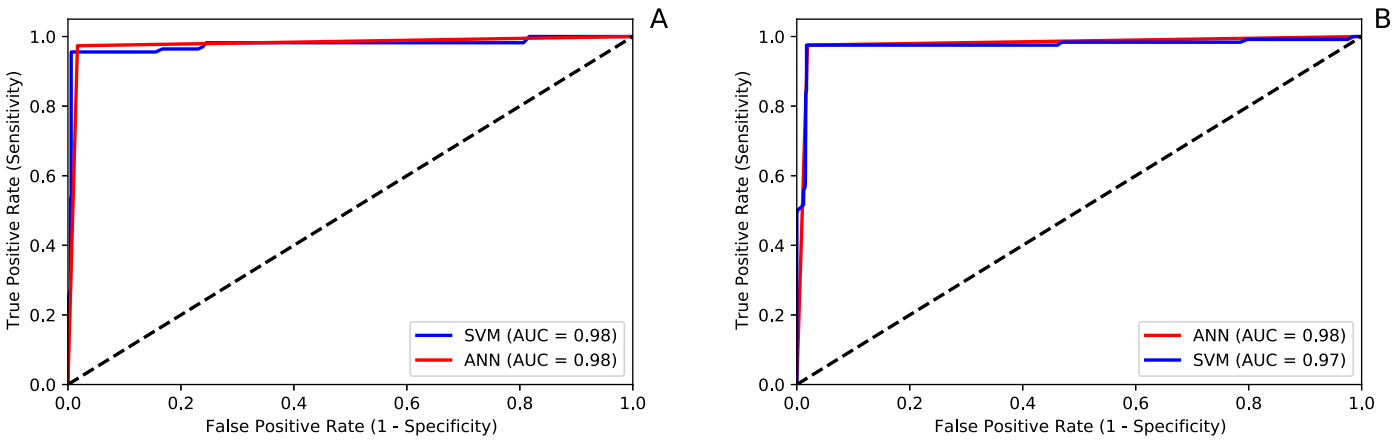

Fig. 9. ROC curves to evaluate the quality of the models used to classify dengue patients. **A** = Medellín dataset, **B** = Córdoba dataset.

pitalization, the model prescribes that it is one of the best treatment options, due to the patient's warning signs. This type of patient must be constantly monitored and assessed to avoid complications and death. In summary, the prescriptive model developed makes a correct recommendation with respect to the clinical management guidelines for dengue published by WHO.

5.3.3. Scenario 3

Case 3: Patient 49 years old with: fever, myalgias, arthralgias, shock. Using the result of the previous task, this patient is classified as having SD. The GA uses the fitness function of Eq. (6) to choose the best solutions for this particular patient. In Table 9, we can observe the age, signs, symptoms and laboratory tests of this patient represented in a vector. In addition, we can observe the type of dengue classified by the previous task, and, finally, we observe the best treatment options for this patient. In this case, the most important manifestation of the patient is shocked.

The use of P, W and ORS are not the best options. The prescriptive model does not recommend any of these options because it does not find them feasible for this patient. Instead, the prescriptive model recommends the application of IS and CS to restore the patient's plasma volume. In addition, the prescriptive model recommends hospitalization, since this patient should be hospitalized immediately for adequate treatment and follow-up. In summary, the prescriptive model recommends optimal and feasible treatment options for patients with SD. The recommendations made by the prescriptive model are in accordance with the recommendations published by the WHO.

6. Discussion

The clinical management of dengue is of vital importance to reduce mortality rates from the disease. Diagnosis and treatment must be optimal and prompt to avoid complications leading to death. We set out to develop an ACODAT to support decision-making in the clinical management of dengue.

Our proposal monitored data quality and corrected possible errors related to missing data, misclassification of dengue patients, and balancing of dengue categories. The quality of the models depends to a large extent on the quality of the data. The excellent quality of the classification models obtained in ACODAT's task 2 indicates the quality of the data used to train these models. Although in recent years data-driven strategies continue to increase, this aspect remains a challenge for modeling in medicine.

Dengue classification was performed using two ML techniques widely used in the medical field. ANN and SVM are excellent techniques for finding linear and nonlinear variable relationships in medical datasets. Few works have been developed using SIVIGILA datasets for dengue classification. The work of Hoyos et al. [19] developed a classification model using FCM. The results of this work showed an accuracy of 0.89. The results of our model showed a higher performance (see Table 6 and Fig. 9), perhaps because the relationships were extracted from the data and not assigned by experts, as occurs with FCM.

On the other hand, to date, there is no specific treatment for dengue. However, WHO has published treatment guidelines to alleviate symptoms and avoid complications. The non-specificity of signs and symptoms makes it difficult to choose the appropriate treatment in specific scenarios. The development of computer-aided strategies could support decision-making in clinical settings. In this sense, our work is the first study to report a prescriptive model to generate treatment recommendations based on WHO guidelines. The prescriptive model developed has the capacity to prescribe suitable actions for the palliative treatment of dengue.

We qualitatively compare our work with other similar works using some criteria listed below: A) The proposed approach uses AI techniques for the classification of dengue. B) The proposed approach uses a technique of AI to recommend the best option for the treatment of dengue. C) The proposed approach automates the clinical management of dengue (diagnosis and treatment). D) The proposed approach is intuitive, extensible y easily adaptable (e.g., if it can become a multi-agent clinical decision-making system [41]).

Table 10 shows the comparison between previous works and our research. The study by Chatterje et al. [18] implemented a hybrid approach to dengue classification using gene expression data. The authors used an ANN enhanced with the Cucko search optimization algorithm. The type of ANN used was the multi-layer perceptron with a single hidden layer in its structure. The aim of this work was to classify patients into different dengue classes; however, 2009 WHO dengue classification was not used. The authors used 1997 WHO dengue classification, which proposed to classify dengue into classic dengue, dengue hemorrhagic fever and dengue shock syndrome. Additionally, the data used were genetic, which is not easy or inexpensive to collect in routine clinical practice. Finally, this work does not present treatment options for the disease.

Macedo-Hair et al. [42] analyzed the clinical profiles of dengue patients to identify clusters of patients, and thus classify them into the three types of dengue suggested by WHO. The authors used self-organizing maps and RF with clinical and laboratory data to identify characteristics that could be used as risk criteria for dengue severity. The results of this work are interesting because they show the characteristics of each disease group; however, it only focused on the diagnosis or classification of the disease and the recommendation of the best treatment option was not addressed.

Park et al. [43] implemented predictive models to classify patients with dengue. The authors used clinical and laboratory variables that fed into structural equation models. This was the first work that imple-

Table 7. Results of classification and prescription tasks for a patient with NoWS-Dengue.

Variables (age, signs, symptoms and laboratory tests)																					Dengue type	Treatment options					
V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	P	W	ORS	IS	CS	H
1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-	-	-	-	-
↓																											
Classification task																											
↓																											
1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-	-	-	-	-	-
↓																											
Prescription task																											
↓																											
1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0

Table 8. Results of classification and prescription tasks for a patient with YesWS-Dengue.

Variables (age, signs, symptoms and laboratory tests)																					Dengue type	Treatment options					
V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	P	W	ORS	IS	CS	H
0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	-	-	-	-	-	-	-
↓																											
Classification task																											
↓																											
0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	2	-	-	-	-	-	-
↓																											
Prescription task																											
↓																											
0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	1	1	0	1

Table 9. Results of classification and prescription tasks for a patient with SD.

Variables (age, signs, symptoms and laboratory tests)																					Dengue type	Treatment options					
V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	P	W	ORS	IS	CS	H
0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	-	-	-	-	-	-	-
↓																											
Classification task																											
↓																											
0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	-	-	-	-	-	-
↓																											
Prescription task																											
↓																											
0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	1	1	1

Table 10. Criteria for evaluation of our work with previous works.

Research	Evaluation criteria			
	A	B	C	D
[18]	✓	✗	✗	✓
[42]	✓	✗	✗	✓
[43]	✓	✗	✗	✓
Our work	✓	✓	✓	✓

mented structural equations applied to clinical data to develop predictive models; however, their work only used children and a small sample size to develop the models. It is difficult to generalize these results to patients of all ages. Additionally, the work was only focused on diagnosis and did not take into account the treatment of the disease.

The approaches and models previously developed and reported in the literature only meet two criteria corresponding to the use of ML techniques to generate the models, and the intuitiveness, extensibility and adaptability to increase their capabilities. It is important to remember that the clinical management of dengue involves not only diagnosis, but also treatment. The prediction or classification of dengue is insufficient if it does not support decision-making regarding treatment.

With this problem in mind, we proposed an ACODAT for the clinical management of dengue. The proposed approach considers data processing, classification and diagnosis of the patient into one of the three categories recommended by the WHO. Besides, our approach also provides an additional feature, which consists of the recommendation of the best treatment option (within a range of initially defined prescriptions) for a patient according to the type of dengue presented. The integration of different tasks that use AI techniques in the ACODAT was effective and allowed a more efficient clinical management of dengue patients, knowing that time is a critical factor for this type of patient. The proposed ACODAT was evaluated in different types of dengue. The results shown in previous sections demonstrate the diagnostic and prescriptive capability of the proposed approach.

In summary, our model is the only one that meets the four criteria defined in Table 10. Our approach uses AI techniques, not only for the classification of dengue, but also for prescribing the best treatment options (criteria A and B). To the best of our knowledge, there are no reports of automated systems for classifying dengue and recommending treatment (criteria C). Using only the variables used in conventional dengue diagnosis, our system can classify the clinical picture and recommend automatically treatment options. According to criteria D, our system is intuitive and easy to use, because the clinician only must enter age, signs, symptoms and laboratory tests. With this information, the system will automatically classify the patient and then recommend the best treatment options for that particular patient. Finally, our system is flexible and easily adaptable because it is possible to add new tasks to the cycle to consider other important aspects of dengue.

7. Conclusions

This paper proposed a clinical DSS for dengue using ACODAT. The objective was to develop a system that allows the processing of data, classification of the patient according to the type of dengue, and based on this last characteristic, recommendation of the best treatment option from a list of available treatments. The ACODAT developed has the ability to prepare the data and process them so that they are ready for the next task of the cycle. The AI techniques used, ANN and SVM, have the ability to correctly classify patients with high performance. The GA used in the last task of the cycle has the potential to recommend (prescribe) the best treatment option according to symptoms, signs and laboratory tests. The joint use of data analysis tasks in a cycle had key advantages over separate approaches. One of them is time to diagnose. With the proposed approach, it is possible to diagnose and recommend automatically patient treatment. This is very important because the time to diagnose and treat dengue is crucial to avoid complications and death of patients. To the best of our knowledge, this is the first work that uses an autonomic approach to support the clinical management of dengue. In addition, it is the first work to propose a prescriptive model for the clinical management of this disease.

This study has several limitations. First, some variables involved in the overall assessment process by the medical professional were not available to be included in the implementation of the models. Second, the unavailability of cohort datasets (before/after) to verify whether the recommended treatment had a positive impact on patients' health. For this latter, it is necessary to validate the results of this study in real hospital environments.

Future work should be aimed at improving the models implemented using routine laboratory tests such as white blood cell counts, blood levels of liver enzymes and cytokines. In addition, the inclusion of comorbidities such as diabetes and arterial hypertension could improve the performance of the models due to the influence of these diseases on the severity of dengue. Finally, the creation of available datasets with prescriptive or treatment variables would be useful to validate the results of prescriptive models.

Declarations

Author contribution statement

William Hoyos: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Jose Aguilar and Mauricio Toro: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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Appendix D

Clinical decision-making through prescriptive modeling

Case studies of clinical decision-making through prescriptive models based on machine learning

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Abstract

Background: The development of computational methodologies to support clinical decision-making is of vital importance to reduce morbidity and mortality rates. Specifically, prescriptive analytic is a promising area to support decision-making in the monitoring, treatment and prevention of diseases. These aspects remain a challenge for medical professionals and health authorities.

Materials and Methods: In this study, we propose a methodology for the development of prescriptive models to support decision-making in clinical settings. The prescriptive model requires a predictive model to build the prescriptions. The predictive model is developed using fuzzy cognitive maps and the particle swarm optimization algorithm, while the prescriptive model is developed with an extension of fuzzy cognitive maps that combines them with genetic algorithms. We evaluated the proposed approach in three case studies related to monitoring (warfarin dose estimation), treatment (severe dengue) and prevention (geohelminthiasis) of diseases.

Results: The performance of the developed prescriptive models demonstrated the ability to estimate warfarin doses in coagulated patients, prescribe treatment for severe dengue and generate actions aimed at the prevention of geohelminthiasis. Additionally, the predictive models can predict coagulation indices, severe dengue mortality and soil-transmitted helminth infections.

Conclusions: The developed models performed well to prescribe actions aimed to monitor, treat and prevent diseases. This type of strategy allows supporting decision-making in clinical settings. However, validations in health institutions are required for their implementation.

Keywords: Prescriptive model, Clinical decision-making, Predictive model, Artificial intelligence

1. Introduction

Prescriptive analytic is an area of data analytic that is concerned with generating actions that lead to desired outcomes in modeled systems [1]. In healthcare, prescriptive modeling has established itself as a promising area for the improvement of healthcare systems. With the development and implementation of prescriptive modeling, it is expected to achieve greater speed and accuracy in the monitoring, treatment and prevention of disease, as well as an improvement in the quality of health care.

In this work, we are interested in developing methodologies to generate prescriptive models to support decision-making focused on treatment, follow-up and prevention of diseases. The development of methodologies for clinical decision-making has generated much interest in recent years. Machine learning, computational intelligence and clinical decision analysis have been widely used for this purpose. However, there are some limitations or disadvantages associated with the use of such approaches. The complexity of the models for medical professionals to understand is a disadvantage, because they consider machine learning and computational intelligence models as a "black box"[2]. With respect to clinical decision models, specifically, decision trees do not take into account recurrent events and require individuals with similar characteristics. Markov models have been developed to overcome the problems presented by decision trees. However, Markov models ignore the interaction between individuals and consider few health states. Another important problem is the computational complexity; probability evaluations in Markov decision processes can increase with the complexity of the problem or system to be modeled [3, 4]. Finally, another limitation is that clinical decision analysis requires more data than other stochastic modeling techniques due to variations in transition probabilities at each decision stage [5]. Based on these problems, it is necessary to develop methodologies that generate prescriptive models that are explainable to medical professionals, that are computationally efficient regardless of the complexity of the problem, and that have a minimally acceptable performance with small datasets.

In this study, we propose an approach for generating prescriptive models to support decision-making in clinical settings. Our approach is capable of generating prescriptive models that suggest

prescribing actions for treatment, follow-up and prevention of diseases. The combination of fuzzy cognitive maps (FCMs) –explainable method– and genetic algorithms (GAs) allowed the development of a methodology for the generation of prescriptive models. The ease of construction and interpretation of FCMs brings an added value different from the models reported in the literature. Our approach starts with FCM creation and subsequent characterization of the FCM using the nature of the concepts. Each concept is discriminated in two layers: *system and action*. In the first case, they are all those variables measurable in patients such as demographic variables, signs, symptoms and laboratory tests. While the action variables are all those related to actions aimed at the treatment, follow-up and prevention of diseases. The second stage of our approach consists of the initial instantiation of the system, where the medical user sets the desired state for the system variables. Finally, an optimization algorithm (GAs) is used to find the optimal action values that through the FCM inference system leads to the desired state of the variables related to the system. The proposed approach is tested in three case studies and the results obtained in this research demonstrate the capability of the designed prescriptive models to generate prescriptions with high accuracy and low error.

The remainder of this paper is organized as follows: Section 2 shows a literature review about the last trends in prescriptive modeling in medical settings. Section 3 describes the methodology used to generate the prescriptive models. The next section presents three case studies with the datasets for each case study, and the configuration of experiments. Section 5 shows the results based on case studies. Section 6 discusses the results and shows a comparison with previous works. Finally, Section 7 concludes the paper.

2. Related work

Prescriptive analytic is responsible for the generation of prescriptive models that support decision-making [1]. In this context, the prescription is a set of actions that the decision-maker executes to achieve a given outcome [6]. Prescriptive models can be categorized into three main areas: i) prescriptive modeling using machine learning, ii) prescriptive modeling using computational intelligence, and iii) prescriptive modeling using clinical decision analytics. Below, we show some studies related to each of these categories.

2.1. *Prescriptive modeling using machine learning*

Prescriptive analytic has attracted much interest due to its potential application in medical environments. The use of machine learning has been widely extended for the development of prescriptive models to support decision-making in clinical or medical settings [7–9]. For example, Bertsimas et al [7] proposed and implemented two machine learning methods (prescriptive optimal tree and prescriptive support vector machines) to generate prescriptive models that generate recommendations to reduce the risk of readmission after surgery. The authors used red blood cell transfusion as an actionable feature. The models developed by Bertsitmas et al. have the ability to reduce the risk of readmission by 12% and the results are interpretable because the models allow the identification of variables that influence the prescription made. Harikumar et al. [8] developed a prescriptive analytic solution that uses machine learning approaches to recommend actions in diabetes, heart attack, and stroke. The goal was to find the smallest change within the actionable characteristics to achieve the change from an undesirable to a desirable class. The capability of the developed models was tested on Center for Disease Control and Prevention (CDC) datasets using logistic regression, k-nearest-neighbor (KNN) and random forest (RF). The most favorable results were for KNN on the stroke dataset (88% accuracy), and for the other datasets the results are very similar. Hosseini et al [9] proposed an algorithm to optimize decision variables with respect to a variable of interest. The developed algorithm used Bayesian networks to reduce diabetes mortality rates, by prescribing the optimal combination of drugs for disease control. The algorithm was tested on a dataset of patients with diabetes and had the particularity of generating interpretable prescriptive models because the variables influencing the prescription could be identified. The models generated by Hosseini et al, obtained an accuracy of 88.75% and an area under the curve of 71.15%.

2.2. *Prescriptive modeling using computational intelligence*

Computational intelligence is a subarea of artificial intelligence where fuzzy logic, artificial neural networks and evolutionary algorithms are combined. Such approaches have been used for the development of prescriptive models in clinical settings [10, 11]. For example, Hoyos et al. [10] implemented an autonomous cycle of data analysis tasks where they combined artificial neu-

ral networks and GAs to optimize decision-making in the clinical management of dengue. Dengue is a disease that has no cure and its treatment is based on alleviating symptoms and avoiding complications. The models created had the ability to classify dengue and follow the recommendations given by the WHO for the treatment of each type of dengue. Chalmers et al. [11] proposed a prescription approach to optimize the treatment of adolescent idiopathic scoliosis. The goal was to identify optimal orthotic corrections that would reduce disease progression using fuzzy logic. The developed model had the ability to recommend actions that adjust the orthosis and reduce disease progression by 26%.

2.3. Prescriptive modeling using clinical decision analysis

Clinical decision analysis is a quantitative approach widely used to optimize decision-making in healthcare settings [12]. This approach has been extensively implemented to establish or determine the optimal expected utility of treatments or interventions as healthcare strategies to reduce costs, morbidity, or mortality rates [13, 14]. The main techniques within decision analysis comprise decision trees, Markov decision processes and partially observable Markov decision processes.

Clinical decision trees allow the optimization of strategies aimed at screening and treatment of diseases. This approach has been used to quantify the utility of treatments or strategies based on transition probabilities. For example, Kurisu et al. [13] developed a clinical decision analysis with decision trees to quantify the utility of various antipsychotic treatment options (risperidone, haloperidol, olanzapine, amisulpride, ziprasidone and quetiapine) in patients with delirium. Sensitivity analysis showed that quetiapine is the best antipsychotic treatment option for patients with delirium. Keikes et al [14] implemented decision trees to convert colorectal cancer diagnosis and treatment recommendation guidelines into a computational tool for clinical decision support. The decision trees developed and implemented generated recommendations for the diagnosis, follow-up and treatment of colorectal cancer with a concordance of 81% when compared to recommendations suggested by an interdisciplinary team of experts.

Markov chains are a stochastic approach that allows sequential processes to be modeled [15]. Due to the complexity present in clinical decision-making, Markov models are a useful tool to

compare the effectiveness and utility of available treatment combinations, optimize screening policies, and prevent disease-related complications [16–20]. For example, Habu [16] conducted a clinical decision analysis using Markov modeling to evaluate the efficacy of two treatment strategies (proton pump inhibitor vs. potassium-competitive acid blocker) for gastroesophageal reflux. The results of the analysis yielded a superiority of the competitive acid blocker with respect to cost-effectiveness and the number of days required to treat the disease. These findings were confirmed by the sensitivity analysis implemented in the study. Similarly, Shen et al [17] compared the efficacy of various combinations of interventions for stroke patients in the convalescent stage. The main strategies used for modeling were rehabilitation therapy, use of traditional Chinese medicine, and acupuncture treatment. The Markov decision model had the ability to recommend the best possible combination of treatments for stroke patients in different stages of recovery. Eghbali-Zarch et al [18] modeled the drug treatment of type 2 diabetes to determine the optimal treatment policy to decrease adverse medication reactions that increase the economic burden of the disease and decrease quality-adjusted life years. The Markov model could recommend treatment options that involve a minimum amount of medication with acceptable expected quality of life.

Dunlu et al [19] proposed a partially observable Markov decision model to establish the optimal screening policy in the preclinical stages of Alzheimer's disease. The model aims to maximize the quality-adjusted life years and recommends the time when the patient should be screened. The results of the cost-effectiveness analysis show that implementing the optimal policies recommended by the model reduced costs. Prayogo et al [20] formulated models based on partially observable Markov sequential processes for the evaluation of screening policies for early diagnosis of lung cancer. Early detection of this type of disease through screening is crucial to decrease mortality rates. The research results demonstrated the ability of the proposed model to recommend an optimal screening policy that guarantees higher quality-adjusted life years.

3. Methodology

In this section, we present the methodology to generate prescriptive models. First, we briefly explain the approach used to generate the prescriptive model, which includes the construction of a predictive model. Then, we present three case studies with their datasets and their preprocessing

prior to model creation. Fig. 1 shows a schematic representation of the general methodology to achieve the objective of this study. According to the methodology, the first step is data preparation and analysis (cleaning, normalization and balancing). Next, a classical FCM is built to predict using particle swarm optimization (PSO), which is then used by our prescriptive-FCM to assess the actions it could prescribe, in such a way as to find the most appropriate ones.

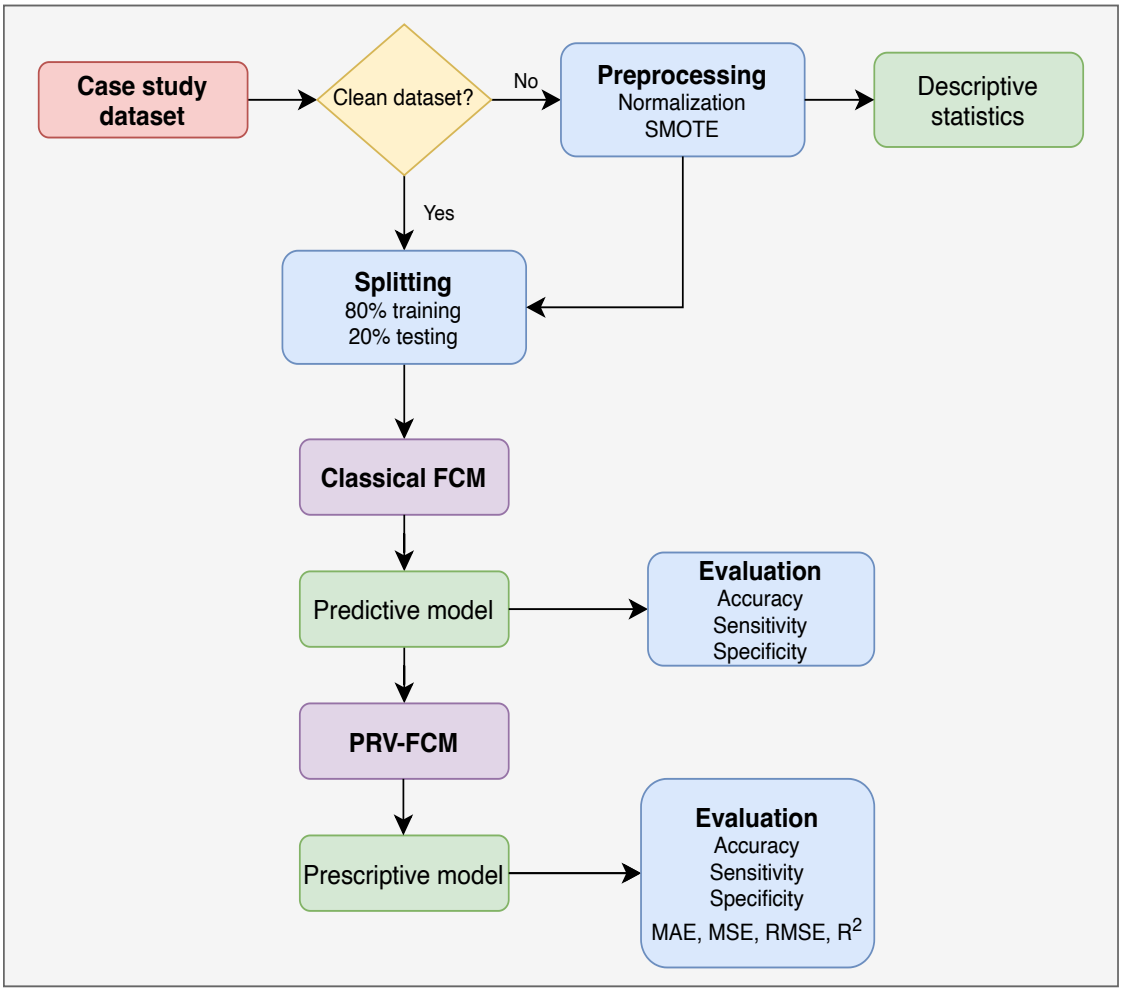

Fig. 1. Methodological general used in this study (PRV-FCM=Prescriptive-FCM).

3.1. Descriptive analysis

The descriptive analysis consists of examining data to interpret past behavior and learn about data distribution, such that we can describe things like, for example, that the classes of a label

are unbalanced, and if there are variables with a lot of noise. In this case, we use descriptive statistics to extract information from the datasets in each case study. We used measures of central tendency and dispersion to understand the behavior of quantitative data. For qualitative data, we used frequency distribution.

3.2. Generation of the predictive models

The predictive models were generated using a data-driven PSO-FCM approach. The predictive model is used by the prescriptive-FCM to propose several sets of actions (each one is a different prescription), and requires a model/function that determines the quality of the proposed prescriptions. The predictive model was used for these tasks.

3.2.1. Data-driven PSO-FCM

FCM is a technique of computational intelligence that allows modeling systems using concepts and relationships. The concepts correspond to the variables of the system to be modeled and the relationships correspond to the influence that exists between them [21–24]. FCMs are composed of a 5-element tuple (Ψ) where n is the number of concepts or variables to be modeled, v is an initial or activation vector, W is the weight matrix, and $f()$ is an activation function to keep the concept values in a desired range r. Eq. 1 shows the main elements of an FCM. The most commonly used activation functions for FCMs are shown in Table 1.

$$\Psi = \langle n, v, W, f() \tag{1}$$

Table 1

Most commonly used activation functions in FCMs.

Activation function	**Equation**	**Range**
Sigmoid	$f(x) = \frac{1}{1+e^{-\lambda \times x}}$	$f(x) \in [0, 1]$
Hyperbolic tangent	$f(x) = \frac{e^{x}-e^{-x}}{e^{x}+e^{-x}}$	$f(x) \in [-1, 1]$

FCMs can be built by experts using their knowledge and experience. They can also be built with algorithms that extract the relationships from historical data. The relationships are stored in square matrices to be used in the inference process. Eq. 2 shows an example of an extracted matrix and Fig. 2 shows the FCM constructed with this matrix. In this study, FCMs were constructed using the PSO algorithm due to its superior performance when extracting relationships from the data [25–27]. In addition, the lack of experts in each domain limited the creation of FCMs using expert knowledge and experience.

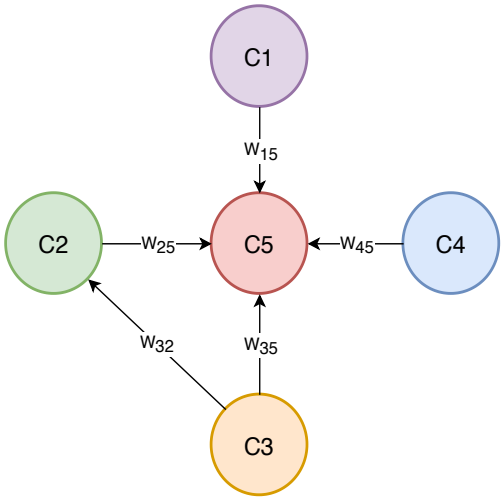

Fig. 2. Example of FCM with five concepts and five relationships.

$$\mathbf{W} = \begin{array}{c} \\ \boldsymbol{C_1} \\ \boldsymbol{C_2} \\ \boldsymbol{C_3} \\ \boldsymbol{C_4} \\ \boldsymbol{C_5} \end{array} \begin{array}{c} \begin{array}{ccccc} \boldsymbol{C_1} & \boldsymbol{C_2} & \boldsymbol{C_3} & \boldsymbol{C_4} & \boldsymbol{C_5} \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & w_{15} \\ 0 & 0 & 0 & 0 & w_{25} \\ 0 & w_{32} & 0 & 0 & w_{35} \\ 0 & 0 & 0 & 0 & w_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array} \tag{2}$$

PSO is an optimization technique that simulates the behavior of particles in nature [28]. This technique can be used for the construction of FCMs and optimization of their weight matrices (PSO-FCM) [27]. In this way, an optimized FCM is obtained that can be used to predict a response variable. In this case, each FCM is a particle i and the weight matrix (W_i) is its position.

Table 2

Inference functions used for inference in FCMs.

Inference function	Equation	Main characteristics
Kosko [21]	$v_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} W_{ij}v_i(t)\right)$	The FCM has no memory capacity because it does not take into account the previous iteration ($v_j(t)$) during inference.
Modified Kosko [29]	$v_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} v_j(t) + W_{ij}v_i(t)\right)$	The FCM has memory capacity because it takes into account the previous iteration ($v_j(t)$) during inference.
Rescaled [30]	$v_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} (2\times v_j(t)-1) + W_{ij}(2\times v_i(t)-1)\right)$	It disables null initial values ($v_j = 0$) that are activated when passed by the activation function.

The algorithm first updates the particle velocity and then its position. Eq. 3 and Eq. 4 show the optimization process with PSO.

$$v_i(t+1) = v_i(t) + r_1 \cdot (W_i^{best} - W_i(t)) + r_2 \cdot (W_i^{gbest} - W_i(t)) \tag{3}$$

$$W_i(t+1) = W_i(t) + v_i(t) \tag{4}$$

where v_i is the particle velocity, r_1 and r_2 are random values with uniform distribution; W_i^{best} is the best position obtained by a specific particle, while W_i^{gbest} is the best position obtained by any particle in the swarm.

After the construction of the FCM and the optimization of its weight matrix, the FCM was ready to make predictions using inference rules or functions. To date, several inference functions have been reported in the literature, which are used depending on the problem to be solved. Table 2 shows the most commonly used inference functions reported in the literature.

3.3. Generation of the prescriptive models

To generate prescriptive models, we developed a methodology, called prescriptive-FCM. This methodology is an extension of FCMs for prescriptive modeling. In the following, we will explain the proposed approach. Prescriptive-FCM is a prescriptive modeling approach that uses FCMs and GA to generate prescriptions or optimal actions that achieve a desired outcome in the modeled system. Before explaining our approach, we will explain the elements that compose Prescriptive-

FCM. FCMs were briefly explained in the previous subsection, and a brief explanation of GAs follows.

3.3.1. GA

A GA is an optimization technique inspired by the general theory of biological evolution. This technique reflects natural selection where the fittest individuals are selected to reproduce and generate new offspring [31]. Fig. 3 shows the methodological framework for a GA. The first steps in the development of GAs are problem definition and fitness functions. GAs start with a random initial population, whose fitness is calculated using functions that depend on the proposed objective (minimization or maximization). Subsequently, this initial population is subjected to selection, crossover and mutation processes. These procedures are carried out to vary the composition of each of the individuals of the initial population. The individuals with the best fitness are selected and the process is repeated until a certain stop condition is reached.

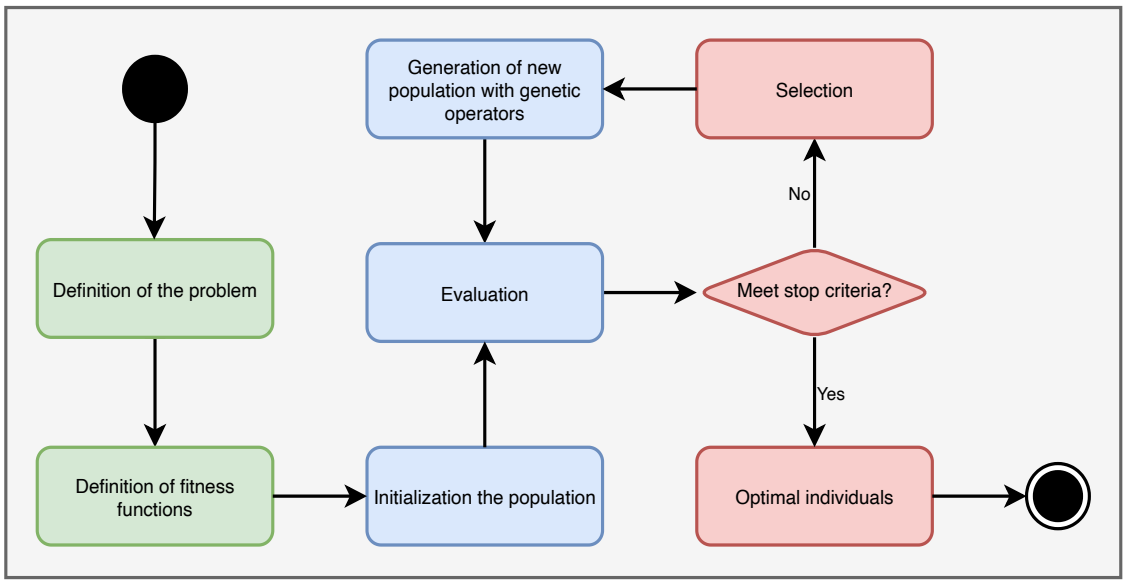

Fig. 3. Methodological framework for a GA.

3.3.2. Prescriptive-FCM

In this study, we propose a methodology called Prescriptive-FCM to generate prescriptive models. Prescriptive-FCM uses three stages for the generation of prescriptive models (see its ar-

chitecture in Fig. 4). The first stage consists of the characterization of the concepts of the problem to be solved. With these concepts is built the FCM with two layers, according to the nature of the concepts. Thus, these two layers constitute the system concepts and the action concepts. The former is related to the system to be modeled. For example, in a disease, the concepts related to the system could be the symptoms present in the patients. The action concepts, also called prescriptive concepts, are actions that, when executed, modify the system concepts. For example, in a medical problem, an analgesic could be an action concept. Changes in this variable will generate changes in the system variables, in this case, the patient's symptoms. Particularly, the first layer is defined by the previously built predictive model.

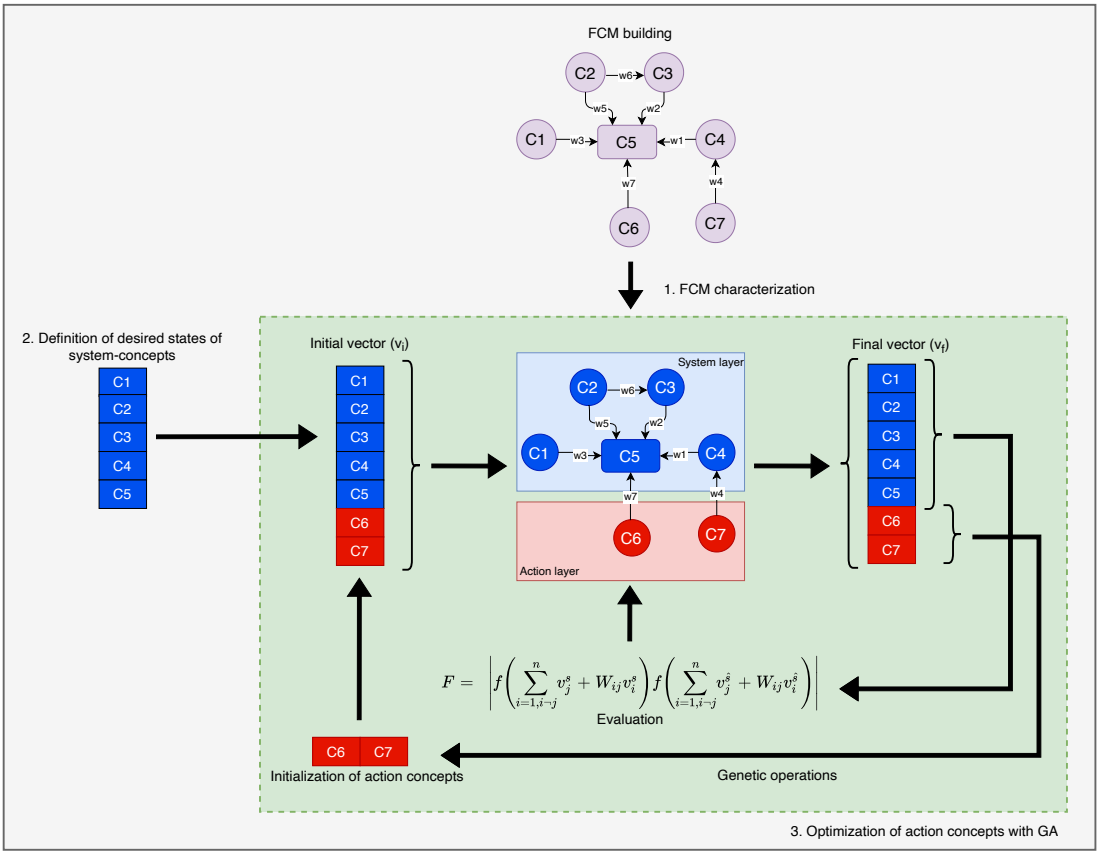

Fig. 4. Architecture of Prescriptive-FCM approach.

The second stage of Prescriptive-FCM consists of the definition of the desired state. In this stage, the decision maker defines the desired values of the system concepts. For example, if the physician wants to lower the fever, then she/he will set this concept to a value of 0 because the

goal is to minimize the fever as much as possible. The final stage consists of the optimization of the action concepts such that using the inference process of the FCMs leads to the desired system concepts. For this last stage, a GA is used that selects, crosses and mutates the values of the action concepts. The FCM inference process generates a vector corresponding to system concepts and action concepts. The former is used for evaluation with a fitness function (see Eq. 5), while the latter are the prescribed variables. The latter is the ones generated by our proposed methodology.

$$F = \left| f\left(\sum_{i=1, i\neg j}^{n} v_j^s + W_{ij} v_i^s \right) - f\left(\sum_{i=1, i\neg j}^{n} v_j^{\hat{s}} + W_{ij} v_i^{\hat{s}} \right) \right| \tag{5}$$

where v^s is the vector representing the value of the desired concepts, $v^{\hat{s}}$ is the vector representing the values generated by Prescriptive-FCM, W_{ij} is the weight matrix of the characterized FCM. Finally, f is a function that holds the values in the desired range.

4. Experiments

4.1. Data preparation

For the validation of our approach, we used three case studies related to the monitoring, treatment and prevention of diseases in public health. Specifically, they correspond to the estimation of Warfarin dose in anticoagulated patients, treatment of severe dengue (SD) and prevention of soil-transmitted helminth infections. Each case study contained a dataset, which was preprocessed using data cleaning technique. First, rows with missing data were removed to decrease bias. The normalization process of the variables was performed to scale the variables within the same range and thus improve the speed of model training. In electronic health records, it is very common to find class imbalance in the objective variables. For this reason, we used synthetic minority oversampling technique (SMOTE) to balance the classes before feeding the predictive and prescriptive algorithms. The characteristics of the variables in each of the datasets are described in each case study. For the internal validation process of the models, each dataset was divided into 80% for training and validation and 20% for testing. We used 10-replicate cross-validation to find the optimal hyperparameters of the best model.

4.2. *Configuration of hyperparameters*

In the development of machine learning models, it is common to use a combination of hyperparameters, and thus find the optimal values that represent the best model to be used in the test set. We used a 10-fold cross-validation technique to find the best hyperparameters in each model. For this study, we used different hyperparameter values from similar studies reported in the literature depending on the nature of the data in each case study.

For the optimization of FCM matrices with PSO, we use a grid of random values for initial population and iteration steps. For the first case, we use values between 10 and 200, for the second hyperparameter, values between 10 and 800. The inference process of FCMs involves activation functions and their slope, and inference functions. We established a combination of these hyperparameters to find the best model. We implemented the activation functions and inference algorithms described in Table 1 and Table 2, respectively. Finally, the slope of the activation functions was established with a grid of random values between 0.1 and 1000.

The search method used in Prescriptive-FCM was a GA. For this case, we used different combinations of initial population size, crossover and mutation probabilities. The hyperparameter grid for the initial population contained random values between 10 and 400 individuals. For the probabilities, we used a grid of random values between 0 and 1.

4.3. *Evaluation metrics*

We evaluated the quality of the developed models using several metrics. We use accuracy, sensibility and specificity to measure the quality of classification-type predictive models. We also use classification metrics to assess the quality of prescriptive models when the prescriptive variables are qualitative in nature. When the prescriptive variables are quantitative in nature, we use mean absolute error (MAE), mean squared error (MSE), root mean squared error (RMSE) and R^2 metrics. The following is a brief description of each of the metrics used to evaluate the performance of the models developed.

- *Accuracy*: percentage of correctly classified examples among the total number of classified examples. Greater accuracy means a greater performance of the model.

$$Accuracy = \frac{TP + TN}{TP + FN + FP + TN} \tag{6}$$

where TP are the true positives, TN are true negatives, FN are false negatives, and TN are true negatives.

- *Sensitivity*: measures the ability of the classifier to predict positive cases to those actually positive.

$$Sensitivity : \frac{TP}{TP + FN} \tag{7}$$

- *Specificity*: measures the ability of the classifier to predict negative cases to those actually negative.

$$Specificity : \frac{TN}{TN + FP} \tag{8}$$

- *MAE*: calculated as an average of absolute differences between the correct prescriptive concepts values and prescriptions.

$$MAE = \frac{1}{m} \sum_{i=1}^{m} \left| v_i^a - \hat{v}_i^a \right| \tag{9}$$

where m is the number of records in testing set, v_i^a is the actual prescriptive value and $\hat{v}_i^a$ is the prescribed value.

- *MSE*: measures the average square error of our prescriptions. For each point, it calculates the square difference between the prescriptions and the prescriptive concepts, and then, averages those values.

$$MSE = \frac{1}{m} \sum_{i=1}^{m} (v_i^a - \hat{v}_i^a)^2 \tag{10}$$

- *RMSE*: is the squared root of the error described above.

$$RMSE = \sqrt{\frac{1}{m} \sum_{i=1}^{m} (v_i^a - \hat{v}_i^a)^2} = \sqrt{MSE} \tag{11}$$

- R^2: Coefficient of determination.

$$R^2 = \frac{\sum_{i=1}^{m}(\hat{v}_i^a - \bar{v}_i^a)^2}{\sum_{i=1}^{m}(v_i^a - \bar{v}_i^a)^2} \tag{12}$$

where $\bar{v}_i^a$ is the mean of actual prescriptive values.

4.4. Case study 1: warfarin dose estimation

Warfarin is the most frequently used anticoagulant worldwide to prevent thromboembolism and thrombosis. Establishing the dose of Warfarin is important because a higher dose than necessary may increase the risk of bleeding and a lower dose may decrease protection against thrombotic processes [32]. For coagulation monitoring, physicians use a laboratory test known as the international normalized ratio (INR). The INR value in normal patients is usually 1; however, in patients on anticoagulant therapy, INR levels may be between 2 and 3, a range that generally indicates appropriate anticoagulation for most cases. For patients with values above 3, they present a high risk of bleeding or hemorrhage, while values below 2 represent a risk of thrombosis or thromboembolism [33]. To test our proposed approach, we used a dataset published by *The International Warfarin Pharmacogenetics Consortium (2009)* [34]. Table 3 and Table 4 show the variables used in this dataset. For this case, we used sociodemographic variables such as age and race; anthropometric variables such as height and weight; and the next genetic variables: cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9), and vitamin K epoxide reductase complex, subunit 1 (VKORC1). Additionally, we used INR as a target variable and Warfarin dose as an action variable. The INR variable was categorized due to the importance of establishing Warfarin doses that maintain INR values between 2 and 3. For this reason, INR was established as *controlled INR* (between 2 and 3) and *altered INR* (lower than 2 or higher than 3). After the data preprocessing described in subsection 4.1, the dataset had 3385 records corresponding to 2085 patients with *controlled INR* and 1800 patients with *altered INR*.

4.5. Case study 2: Treatment of SD

Dengue is a disease caused by a virus and transmitted by the bite of a mosquito of the genus *Aedes spp*. The most severe phase of the disease is known as severe dengue, and represents the

Table 3

Descriptive statistics of numerical variables of case study 1.

Concept	Concept type	Variable name	Median (Interquartile range)
C1	System	Age (years)	65.0[55.0-75.0]
C2	System	Height (m)	1.70[1.61-1.78]
C3	System	Weight (Kg)	78[65.30-92.30]
C8	Prescriptive	Warfarin	31.25[22.50-42.0]

Table 4

Descriptive statistics of categorical variables of case study 1.

Concept	Concept type	Variable name	Category	N	Percentage (%)	CI 95%
C4	System	Race				
			White	1207	49.37	47.39-51.35
			Asian	424	17.34	15.84-18.84
			Black	328	13.42	12.07-14.77
			Other	486	19.87	18.29-21.45
C5	System	Amiodarone				
			No	2286	93.50	92.52-94.48
			Yes	159	6.50	5.52-7.48
C6	System	Vkorc1				
			A/A	587	24.01	22.32-25.70
			A/G	937	38.32	36.39-40.25
			G/G	921	37.67	35.75-39.59
C7	System	Cyp2c9				
			*1/*1	1780	72.80	71.04-74.56
			*1/*2	379	15.50	14.07-16.93
			*1/*3	215	8.79	7.67-9.91
			Other	71	2.90	2.23-3.57
C9	Target	INR				
			Controlled INR	2085	53.70	52.12-55.26
			Altered INR	1800	46.30	44.73-47.86

main cause of death from dengue [35]. Studies have reported a mortality rate of over 20% when treatment is inadequate or delayed [36]. Currently, dengue has no definitive cure and its treatment is based on the relief of signs and symptoms. In addition, treatment is aimed at considerably reduc-

ing the complications that the virus causes during its stay in the patient's body [37]. Establishing the optimal treatment policy for severe dengue is important to avoid complications and reduce mortality rates associated with the disease. To test the proposed methodology, we used a dataset of mortality data from patients with dengue. The data correspond to 398 patients from Córdoba, Colombia. The variables used for the generation of the models are shown in Table 5. In this case, we used 4 variables related to severe dengue such as, extravasation, shock, hemorrhage and organ failure. While 4 treatment related variables were used to find the optimal values to minimize mortality. In this dataset, all variables used had values of 0 for absence and 1 for presence. For the target variable, surviving patients were coded to 0 while deceased patients were coded to 1. After preprocessing of the data, defined in subsection 4.1, there were 210 surviving patients and 188 deceased patients.

Table 5

Descriptive statistics of variables in case study 2.

Concept	Concept type	Variable name	Category	N	Percentage (%)	CI 95%
C1	System	Extravasation	0	277	69.60	65.08-74.12
			1	121	30.40	25.88-34.92
C2	System	Shock	0	276	69.35	64.82-73.88
			1	122	30.65	26.12-35.18
C3	System	Bleeding	0	161	40.45	35.63-45.27
			1	237	59.55	54.73-64.37
C4	System	Organ failure	0	268	67.34	62.73-71.95
			1	130	32.66	28.05-37.27
C5	Prescriptive	Transfusion	0	276	69.35	64.82-73.88
			1	122	30.65	26.12-35.18
C6	Prescriptive	Cristalloid solutions	0	277	69.60	65.08-74.12
			1	121	30.40	25.88-34.92
C7	Prescriptive	Colloid solutions	0	161	40.45	35.63-45.27
			1	237	59.55	54.73-64.37
C8	Prescriptive	ICU	0	107	26.88	22.52-31.24
			1	291	73.12	68.76-77.48
C9	Target	mortality	Survivor	210	52.76	51.19-54.33
			Dead	188	47.24	45.67-48.81

Table 6

Descriptive statistics of variables in case study 3.

Concept	Concept type	Variable name	Category	N	Percentage (%)	CI 95%
C1	System	Sex				
			F	397	52.1	48.55-55.65
			M	365	47.9	44.35-51.45
C2	System	Weight				
			<20	71	9.32	7.26-11.38
			20-40	552	72.44	69.27-75.61
			40-60	137	17.98	15.25-20.71
			>60	2	0.26	-0.1-0.62
C3	System	Indigenous				
			No	576	75.59	72.54-78.64
			Yes	186	24.41	21.36-27.46
C4	System	Source of drinking water				
			1	22	2.89	1.7-4.08
			2	4	0.52	0.01-1.03
			4	185	24.28	21.24-27.32
			5	514	67.45	64.12-70.78
			6	37	4.86	3.33-6.39
C5	System	Floor of the house				
			1	675	88.58	86.32-90.84
			2	26	3.41	2.12-4.7
			3	60	7.87	5.96-9.78
			5	1	0.13	-0.13-0.39
C6	System	Disposal of human excreta				
			1	280	36.75	33.33-40.17
			2	187	24.54	21.48-27.6
			3	295	38.71	35.25-42.17
C7	Prescriptive	Child wears closed shoes				
			1	203	26.64	23.5-29.78
			2	240	31.5	28.2-34.8
			3	319	41.86	38.36-45.36
C8	System	Child washes his hands after defecating				
			1	234	30.71	27.43-33.99
			2	209	27.43	24.26-30.6
			3	319	41.86	38.36-45.36
C9	Prescriptive	Child washes his hands before eating				
			1	317	41.6	38.1-45.1
			2	191	25.07	21.99-28.15
			3	254	33.33	29.98-36.68
C10	Target	Geohelminthiasis				
			Negative	429	56.29	54.73-57.85
			Positive	333	43.71	42.15-45.27

4.6. Case study 3: Prevention of geohelminthiasis

Soil-transmitted helminth infection or geohelminthiasis is a disease characterized by the ingestion of embryonated eggs of parasites or by penetration through the skin of their infective larvae present in humid and warm soils [38]. These infections are facilitated by poverty, illiteracy, lack of drinking water and hygienic habits [39]. Prevention of this type of infection is important due to the high morbidity that impacts human health leading to stunting, vitamin deficiencies and poor cognitive function [40]. It is necessary to establish prevention strategies to reduce the morbidity rates associated with these types of infections. Based on these issues, we tested our prescriptive approach to generate a model with optimal recommendations that will lead to disease prevention and thus minimize the occurrence of parasite infections. The dataset used to test the prescriptive approach corresponded to demographic and epidemiological data of 130 school-aged children in a rural area of the department of Córdoba, Colombia. The variables used for model generation are shown in Table 6. Seven variables are classified as variables directly related to the disease, while two variables related to prevention were considered action variables. The target variable indicated the clinical condition of the children with respect to the presence or absence of geohelminths. After preprocessing of the data, the cleaned and sorted dataset contains 64 healthy or uninfected children and 66 infected children.

5. Results

In this section, we show the results of the models generated. Each subsection describes the results of the descriptive statistics, prescriptive model (and its underlying predictive model) for each case study.

5.1. Case study 1: warfarin dose estimation

5.1.1. Descriptive statistics

Descriptive statistics for this case study are summarized in Table 3 and Table 4. For the statistical description of the data, measures of central tendency such as median with interquartile ranges were used for variables C1, C2 and C3, which had median with interquartile ranges of 65.0[55.0-75.0], 1.70[1.61-1.78] and 78[65.30-92.30], respectively. For categorical variables, the

relative frequency with 95% confidence intervals (95% CI) was used. In this study, the majority of individuals were white, with a relative frequency of 49.37% (95% CI = 39-51.35), and 93% (95% CI = 92.52-94.48) of patients reported not taking the antiarrhythmic agent amiodarone. The variables related to the genotypic conditions of the patients, such as C6 - Vkorc1 with category A/G was the most frequent with 38.32% (95% CI = 36.39-40.25) and C7 - Cyp2C9 in category *1/*1 showed higher relative frequency than the other categories 72.8% (95% CI = 71.04-74.56).

5.1.2. Predictive model

We developed a predictive model using INR as the target variable. This model based on FCM has the ability to predict INR, and is built by adjusting the weights of the FCM using PSO (initial population = 80 individuals, iterations = 120). This FCM is used by Prescriptive-FCM to evaluate the quality of a prescription.

Table 7

Performance and optimal hyperparameters of the predictive models developed in this work for all case studies.

Case study	Optimal hyperparameters	Accuracy	Sensitivity	Specificity
Warfarin dose	Activation function = sigmoid	0.65	0.51	0.77
Treatment of SD	Slope = 10	0.74	0.79	0.68
Prevention of geohelmintiasis	Inference function = Modified Kosko	0.74	0.76	0.73

Table 7 shows the performance of the developed predictive models and the optimal hyperparameters of the best model for each case study. Regarding the case study of the warfarin dose estimation, the performance of the model developed with the classical FCM approach obtained values of 0.65, 0.51 and 0.77 for accuracy, sensitivity and specificity, respectively.

5.1.3. Prescriptive model

We developed a prescriptive model that formulated the dose of warfarin for anti-coagulated patients. The GA using Prescriptive-FCM optimized the action concept, which in this case is the warfarin dose. Because warfarin dose was a numerical variable, the performance of the model generated with Prescriptive-FCM was evaluated using MAE, MSE, RMSE, obtaining values of 2.76, 14.8 and 3.8, respectively. We used R^2 as a measure of agreement between the actual data and

that prescribed by the generated model. Fig. 5 shows a plot with the corresponding R^2 value and the significance value of the analysis. For this case study, the R^2 value expressed as a percentage was 96%.The optimal hyperparameters for this model were initial population of 50 individuals, crossover and mutation probabilities of 0.1 and 0.3, respectively.

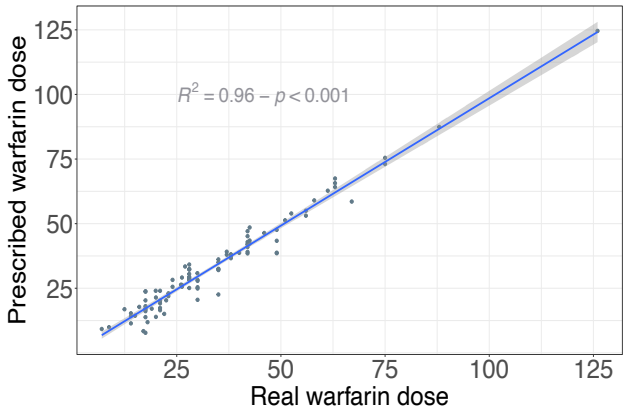

Fig. 5. Relationship between the warfarin values prescribed in the dataset and the warfarin values prescribed by our approach.

5.2. Case study 2: treatment of SD

5.2.1. Descriptive statistics

Descriptive statistics for this case study are summarized in Table 5. In this dataset, all variables were qualitative. The frequency distribution shows that variable C8 was the most frequent variable in the group of patients who presented SD. The least frequent variables in this category were C1 - extravasation and C6 - use of crystalloid solutions, both with frequencies of 30.40% (95% CI = 25.88-34.9). The opposite case occurred in the group of patients who did not present SD, these two variables C1 and C6 were the most frequent with respect to the others, in both cases the relative frequency was 69.60% (95% CI = 65.08- 74.12). ICU stays within this group only occurred in 26.88% (95% CI = 22.52 - 31.24).

5.2.2. Predictive model

The mortality rate for SD can reach 20% if the clinical management of the disease is not done in an ideal way [36]. For this case study, we developed a model to predict mortality by SD. As

in the previous case study, this procedure was performed by adjusting the weights of the FCM constructed by PSO (initial population = 70 individuals, iterations = 140). Table 7 shows the performance of the model developed to predict mortality by SD. The developed model had the ability to predict whether the patient dies or not with an accuracy of 0.74, sensitivity of 0.79 and specificity of 0.68.

5.2.3. Prescriptive model

Prescribing treatment in SD is of vital importance to prevent patient death. We developed a model for prescribing treatment actions aimed at preventing patient death by SD. Four treatment options were used to generate the prescriptive model (see Table 5). Due to the binary nature of these actions, we used accuracy as a metric to evaluate the performance of the developed model. Table 8 shows that the prescriptive model generated with Prescriptive-FCM for the formulation of treatment actions for SD has an accuracy greater than 0.81. The best performance of this model was for the prescription of colloid solutions with an accuracy, sensitivity and specificity of 1. The optimal hyperparameters for this model were initial population of 100 individuals, and crossover and mutation probabilities of 0.5 and 0.5, respectively.

Table 8

Performance of the prescriptive model for the treatment of SD.

Case study	Prescriptive concept	Variable name	Accuracy	Sensitivity	Specificity
Treatment of SD	C5	Red blood cells transfusion	0.81	0.64	1.00
	C6	Crystalloid solutions	0.87	0.80	0.93
	C7	Colloid solutions	1.00	1.00	1.00
	C8	Intensive care unit	0.84	0.87	0.83

5.3. Case study 3: Prevention of geohelminthiasis

5.3.1. Descriptive statistics

The results of the nine categorical variables that make up this dataset allowed describing it statistically using relative frequencies with 95% CI. 52.1% (95% CI = 48.55-55.65) of the individuals in the dataset were women with weights between 20-40 kg in 72.4% (95% CI = 69.27-75.61) and between 40-60 kg in 17.9% (95% CI = 15.25-20.71). Only 24.4% (95% CI = 21.6-27.46)

of the participants reported belonging to an indigenous ethnicity. Variables C4, C5, C6 and C8, all of them from the system and related to epidemiological aspects, showed that the origin of the water for cooking is mainly from wells in 67.4% (95% CI = 64.12-70.78) or from a river or stream in 24.2% (95% CI = 21.24-27.32). Dirt floors predominate in 88.5% (95% CI = 86.32-90.84) of the dwellings of these subjects, and excreta disposal is done in toilets without connection in 38.7% (95% CI = 35.25-42.17) or connected to a septic tank in 36.7% (95% CI = 33.33-40.17) mainly. After defecation few participating subjects washed their hands, 30.7% (95% CI = 27.43-33.99) said they always washed their hands, while 41.8% (95% CI = 38.36-45.36) said they never washed their hands. The two prescriptive variables of the dataset (C7 and C9) showed as results that the use of closed footwear is not a common practice among the study subjects, 41.8% (95% CI = 38.36-45.36) reported never using this type of footwear, likewise, a similar percentage of subjects, 41.6% (95% CI = 38.1-45.1) stated that they washed food before consumption.

5.3.2. Predictive model

We developed a predictive model with PSO-FCM (initial population = 50 individuals, iterations = 150) to predict the presence of geohelminths infections using demographic and epidemiological variables. The performance of this model can be seen in Table 7. The model predicted the parasitosis with an accuracy of 0.74, sensitivity of 0.76 and specificity of 0.73.

5.3.3. Prescriptive model

The prevention of geohelminthiasis is important to avoid the spread of parasites in communities. We developed a model to prescribe two crucial actions in the prevention of geohelminthiasis. The results show the model's ability to prescribe these actions with accuracies between 0.67 and 0.74. The developed model had greater sensitivity than specificity for the two prescriptive variables used (see Table 9). The optimal hyperparameters for this model were initial population of 50 individuals, and crossover and mutation probabilities of 0.5 and 0.5, respectively.

6. Discussion

In this study, we developed prescriptive models (and its underlying predictive model) to support decision-making in clinical settings. We used three case studies: the first, related to the

Table 9

Performance of the prescriptive model for the prevention of geohelminthiasis.

Case study	Prescriptive concept	Variable name	Accuracy	Sensitivity	Specificity
Prevention of	C12	Child wears closed shoes	0.74	0.80	0.74
geohelminthiasis	C14	Child washes hands before eating	0.67	0.78	0.55

estimation of warfarin doses for anticoagulated patients. The second case study related to the treatment of dengue fever to reduce mortality rates. Finally, the third case was focused on the prevention of soil-transmitted parasitic infections.

6.1. Warfarin dosing

The estimation of the warfarin dose is crucial to avoid both bleeding and the presence of clots in patients with coagulation disorders. The developed predictive model used demographic and genetic variables to obtain an acceptable performance (see Table 7). The results are expected due to the lack of clinical and laboratory variables necessary for careful monitoring since there is a wide variation in dose response explained by baseline clinical conditions, lifestyles and food consumption. Including variables such as comorbidities (diabetes and arterial hypertension), would be useful because these types of diseases have been reported as risk factors for hemorrhagic complications in patients receiving warfarin. Aggregation of these types of variables will possibly allow better prediction of the INR. Another variable to take into account when considering the dose of warfarin is the intake of vitamin K, since it actively participates in the blood coagulation process. To prescribe the appropriate dose of warfarin to maintain a well-controlled INR, it is necessary to consider the measurement of vitamin K in the meals eaten by anticoagulated patients, since any variation in this may change the amount of warfarin to be taken. [41]. Other variables such as lifestyle changes, discontinuation of warfarin, falls or serious injuries, consumption of two or more alcoholic beverages per day, becoming pregnant or breastfeeding may affect the INR [33]. Therefore, it is important to consider some of these changes as variables within the predictive models developed.

Regarding the prescriptive model for estimation of warfarin dose, the results were satisfactory due to very low error values such as MAE below 2.8, exceeding the performance of previous

Table 10

Comparison of models developed to estimate warfarin doses.

Reference	Model	MAE	R^2
[34]	Clinical	9.9	0.26
[34]	Pharmacogenetic	8.5	0.43
[42]	Predictive	-	0.36
Our work	Prescriptive	2.7	0.96

works. Table 10 shows a comparison of the models developed to estimate warfarin dose with the dataset used in the present work. The International warfarin Pharmacogenetics Consortium developed two models using a clinical and pharmacogenetic algorithm, obtaining values of MAE 9.9 and 8.5, respectively [34]. Considering the R2 that measures the degree of agreement between the actual warfarin values in the dataset and the value prescribed in the developed model, our model had a superior performance with values of 0.96. The models developed by this consortium obtained maximum values of 0.43. Another work developed by Chen et al [42], proposed a weighted learning method to estimate warfarin dose on the same dataset used in this study. The results of the model generated with the methodology proposed by Chen obtained an R2 of 0.36. Our model performed better than the models developed and reported in the literature.

6.2. SD treatment

In the second case study, the results demonstrated a good capacity both to predict mortality by SD and prescribe treatment options to prevent the patient's death. The predictive model performed well with accuracy values above 74%. The variables defining SD have functional dependencies with mortality. Several studies have demonstrated the influence of shock, extravasation, bleeding and multiorgan failure on dengue death [43–45]. However, other variables considered as warning signs of dengue may be more influential in the prediction. Among these variables are abdominal pain, hepatomegaly, which consists of an increase in liver size due to fluid accumulation in the abdominal region; small mucosal hemorrhages and edema, which consists of fluid accumulation in the tissues underlying organs.

The prescriptive model for the treatment of SD consisted of prescribing treatment options

according to WHO indications. The results showed a good performance of the developed models reaching values between 81% and 100% accuracy. Our model has the capacity to prescribe actions aimed at reducing the dengue mortality rate. The scarcity of works on prescriptive modeling makes it difficult to compare our work with previous studies. To date, there is no prescriptive model for the treatment of SD. An important work to highlight in the palliative treatment of dengue is the one performed by Hoyos et al [10] In this work, a prescriptive model was developed using autonomous cycles of data analysis tasks based in GAs; however, the work was focused on the three types of dengue. In addition, the model developed was validated in specific scenarios and not in a complete dataset.

6.3. Geohelminthiasis prevention

The prevention of soil-transmitted helminth infections is of public health importance. The predictive model generated performed well only using demographic and epidemiological data. However, other epidemiological, clinical and laboratory variables could improve the prediction performance. These variables could be, for example, maternal or caregiver schooling. In the prevention of geohelminthiasis, it is important that those responsible for the care of children have adequate levels of education since it is possible that people with more schooling are more aware of the importance of adopting healthy practices, such as boiling water or washing hands before handling food; in addition, these people are more capable of transmitting this knowledge to their families. Clinically, geohelminthiases are polymorphic and do not present pathognomonic signs and symptoms, many of them are asymptomatic, so the measurement of clinical variables is related to the presence of a particular parasitic agent; however, among the general symptoms and/or signs are anemia, weight loss and growth retardation. When these symptoms become evident, the parasitic infection is in progress, being useful these clinical variables in the prevention of the course of the intensity of the infection towards severity [39]. In endemic areas for these parasitic infections, the necessary diagnostic tools are often not available and the local epidemiology is unknown, overlooking the performance of laboratory tests that yield diagnostics. Often the results of a blood count, which shows laboratory variables such as hemoglobin and eosinophil count useful in the prediction of geohelminthiasis, are available. These parasites affect nutritional status by

various mechanisms by feeding on host tissues, particularly blood, which causes a loss of iron and protein. Likewise, by activating TH2 lymphocytes (T helper type 2), they stimulate the secretion of IgE, producing an increase in the levels of eosinophils in blood, becoming the main cause of eosinophilia in pediatric age [46].

The prescriptive model generated to prescribe geohelminthiasis prevention actions performed acceptably with average accuracy values of 70.5%, perhaps for the reasons mentioned above. Additionally, a small sample size in categorical variables does not allow finding functional dependencies between these variables and the target variable. Despite having used SMOTE to generate new training examples of prescriptive variables, the variability of the data is very low and does not allow finding the necessary patterns to make a prescription with greater accuracy. According to our literature review, to date, no predictive models have been proposed to detect at individual-level geohelminthiasis. Previous work has focused mainly on estimating prevalence over a 5-year period during a disease control program [47]. Another work has been developed to determine the status and distribution of geohelminths in specific regions [48]. In addition, several studies have focused on determining the factors that most influence the disease to develop control strategies [49, 50]. To the best of our knowledge, this is the first work to report a predictive model to detect geohelminthiasis using only demographic and epidemiological variables.

7. Conclusions

In recent years, the development of computer-aided strategies to support decision-making in clinical settings has increased. The objective of this work was to develop prescriptive models to support decision-making in scenarios related to the treatment, follow-up and prevention of diseases of public health interest. We used the Prescriptive-FCM methodology which consists of characterizing a problem into concepts defined as system concepts and action concepts, by using predictive and prescriptive models. The goal is to optimize the action concepts leading to desired outcomes of the system concepts. The results demonstrate the ability of the developed models to predict INR values and estimate warfarin dosage in patients on anticoagulation therapy. In addition, we proved the ability to generate models that predict mortality from SD and prescribe treatment actions to

avoid fatalities. Finally, we were able to demonstrate that prescriptive models generate actions aimed at the prevention of geohelminth infection.

Our study demonstrated the ability of our Prescriptive-FCM methodology to generate prescriptive models that can be applied to any medical problem, whether for treatment, follow-up or prevention of public health events. Finally, the generated models were validated on real datasets to know their performance.

This work has some limitations. First, we did the characterization of FCM's concepts manually. The characterization of these variables could be done automatically, speeding up the creation of the models. Second, we only use one algorithm (GA) for the optimization of the action concepts of each case study. Other optimization algorithms could improve the quality of the developed models. Third, we used the data that was available, so variables of interest in the diagnosis, treatment, and prevention of the diseases related to each case study were not taken into account. Examples of these variables are shown in the Discussion section. Finally, another limitation was that the learning of the FCMs (for prediction and prescription) was done in a single stage, using the system concepts and the action concepts together, and also, using the PSO technique, being able to use other techniques that may improve the learning process.

Future work should be aimed at improving the models developed and their implementation in clinical settings. The predictive models for each case study can be improved using other techniques such as XGBoost and RF, which have shown better performance on structured data. Prescriptive modeling could be improved with a two-stage learning for FCMs: initial learning with system concepts (prediction) and then, learning with action concepts (prescription). Discriminating learning by concept type could generate knowledge that could be extracted with the techniques used.

Finally, the implementation of this type of approach in health institutions would provide useful information for both health professionals and governmental authorities to reduce morbidity and mortality rates of diseases of public health concern.

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Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

William Hoyos: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Validation, Visualization & Writing – original draft. **Jose Aguilar:** Conceptualization, Formal analysis, Resources, Supervision, Writing – reviewing & editing. **Mayra Raciny:** Conceptualization, Formal analysis, Investigation, Resources, Writing – reviewing & editing. **Mauricio Toro:** Conceptualization, Resources, Supervision, Writing – reviewing & editing.

8. Summary table

What was already known on the topic?

- Prescriptive models are a promising area with only initial results for the improvement of health systems, which have been developed into the next main areas: i) prescriptive modeling using machine learning and computational intelligence techniques, and ii) prescriptive modeling using clinical decision analytics

What does this study add to our knowledge?

- The paper proposes a methodology for the development of prescriptive models to support decision-making in clinical settings in the context of disease monitoring, treatment and prevention.

- The proposed hybrid approach is based on a predictive model developed using fuzzy cognitive maps and the particle swarm optimization algorithm, and a prescriptive model developed with an extension of fuzzy cognitive maps that combines genetic algorithms.

- Our approach allows an explainability analysis to detail the prescriptions that are reached, tested in the different case studies.

- We evaluated the proposed approach in three medical case studies related to monitoring (warfarin dose estimation), treatment (severe dengue) and prevention (geohelminthiasis) of diseases.

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Appendix E

PRV-FCM: an extension of FCMs for prescriptive modeling

PRV-FCM: an extension of fuzzy cognitive maps for prescriptive modeling

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Abstract

In this paper, we present a methodology based on fuzzy cognitive maps (FCMs) and metaheuristic algorithms to generate prescriptive models, called PRescriptiVe FCM (PRV-FCM). FCMs are a set of concepts interrelated that describe the behavior of a system. This kind of modeling has been extensively used to build descriptive and predictive models. We propose an extension of FCMs to develop prescriptive models and support decision-making in different domains. This adaptation characterizes FCMs, using system and prescriptive concepts. After that, it uses a metaheuristic algorithm (in this case, we use a genetic algorithm) to optimize prescriptive concepts based on system concepts and the stability of the FCM. Our proposed prescriptive approach was implemented and tested in four scenarios where it demonstrated its capability to find solutions that lead to desired values for the variables of interest. Specifically, no significant differences were found between the values of the prescriptive variables in the datasets and those generated by PRV-FCM.

Keywords: Fuzzy cognitive maps, Prescriptive models, Metaheuristics, Modeling, Genetic algorithm

1. Introduction

Prescriptive modeling is a domain of business analytics, which aims to recommend actions within a system to reach the desired objective (Poornima and Pushpalatha, 2020). It is one of the

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areas that has attracted the most interest in recent years because it provides valuable support for decision-makers (Lepenioti et al., 2020). In this paper, we propose a methodology to generate prescriptive models using fuzzy cognitive maps (FCMs) and metaheuristic algorithms. FCMs are a set of nodes, also called concepts, which represent variables within a system; and arrows directed between them that indicate the influence of one concept on another (Kosko, 1986). Metaheuristic algorithms are techniques used to search solutions in an n-dimensional space, imitating eventually the behavior of individuals in nature (Sharma and Tripathi, 2022). These types of algorithms are commonly used to solve optimization problems.

The use of FCMs is interesting because of their ease of construction, reasoning and interpretation (Pelaez, 2019; Aguilar, 2001). FCMs have been widely used in descriptive (Stylios and Groumpos, 2004; Sánchez et al., 2019), diagnostic (Hoyos et al., 2022) and predictive modeling (Puerto et al., 2019; Mago et al., 2012; Papageorgiou et al., 2009); however, it has not been sufficiently used for prescriptive modeling. Despite the increase in the development of frameworks to generate prescriptive models (see Section 2), a common finding in all of them is that the prescriptive model uses as input the output of a predictive model. That is, the framework contains a predictive model that generates an output, and based on this output, the prescriptive model generates recommendations.

In previous works, we have presented the development of prescriptive models for healthcare environments. For example, in Hoyos et al. (2022), we presented a prescriptive model for dengue treatment using a genetic algorithm (GA) and prior predictions with artificial neural networks (ANNs) and support vector machines (SVMs). However, it was only the application of an existing algorithm on a dataset. Additionally, the prescriptive part could not be validated due to the lack of datasets with prescriptive variables.

Unlike our previously published work, in this case, we present a new technique that combines FCMs with optimization algorithms for the generation of prescriptive models. Our methodology has the particularity of generating prescriptive models with excellent performance in a variety of domains such as business, health and education. Our methodology uses an initial desired instance of the system, the FCM inference process, and an optimization algorithm to find the optimal values of the action or decision options. Furthermore, because it uses the FCM inference process, it

allows generating prescriptive models that can be explained using previously defined relationships between concepts. This methodology is validated in different datasets with system and prescriptive variables.

The main contribution of this work is a methodology to generate prescriptive models using FCMs and metaheuristic algorithms. Our methodology consists, first, in the characterization of the FCM where a division of the map into two layers is established: system concepts and prescriptive concepts. System concepts are the set of variables that describe/define the system to be modeled. Prescriptive concepts are action variables that the decision-maker executes to obtain a desired result in the system.

The discrimination of the concepts in two layers allows using a metaheuristic algorithm to optimize the prescriptive concepts, and thus obtain the desired result in the concepts related to the system. The metaheuristic algorithm optimizes the concepts of the prescriptive layer using as fitness function only the concepts that by the business logic can be modified. At the end, we obtain the values of the prescriptive variables that lead to desired results for the system concepts, depending on the proposed problem.

Our framework, which is called PRescriptiVe FCM (PRV-FCM), is validated in four case studies to demonstrate its ability to prescribe actions within a system. We use one synthetic and three real datasets in the experiments. The real datasets correspond to business, medical and education domains. Based on the results obtained, our methodology can be used in any application domain and has the potential to generate prescriptive models that support decision-making in organizations.

The remainder of this paper is organized as follows: Section 2 shows a literature review of the last trends in prescriptive modeling and optimization approaches. Section 3 describes an overview of FCMs (learning and inference process). Section 4 shows our proposed prescriptive approach with its stages. Section 5 shows the specification of the case studies. Section 6 shows the experiments and results. Section 7 discusses the results and shows a comparison with previous works. Finally, Section 8 concludes the paper.

2. State-of-the-art

In this section, we show a brief literature review on prescriptive modeling and the current status of optimization approaches and models in different fields of science.

2.1. Prescriptive analytics

Business analytics is a discipline that uses data to find patterns and extract knowledge (Lopes et al., 2020). In this discipline can be defined different models, for example: i) descriptive modeling, ii) predictive modeling and iii) prescriptive modeling, among others. In descriptive modeling, the objective is to investigate what has occurred using the data (Lopes et al., 2020). Predictive modeling is concerned with predicting what is going to happen, and prescriptive modeling is concerned with suggesting or prescribing the best decision options. In some cases, the latter type of modeling uses the output of predictive modeling and artificial intelligence (AI) techniques to optimize and provide automated decisions (Lepenioti et al., 2020). While descriptive and predictive modelings are the most studied domains in business analytics (Lepenioti et al., 2020; Hoyos et al., 2021); prescriptive modeling is a less studied area, and its research interest is increasing due to its importance for decision making.

Over the last years, the number of papers focused on the proposal of frameworks for the generation of prescriptive models in different application domains is increasing Lepenioti et al. (2020). Lepenioti et al. (2020) reviewed the main approaches to generate prescriptive models. These approaches depend on the category of methods used to build them, e.g., mathematical programming (Berk et al., 2019; Dey et al., 2019), logic-based rules (Ramannavar and Sidnal, 2018; Srinivas and Ravindran, 2018), simulation (Jank et al., 2019), and machine learning (ML) (Hoyos et al., 2022; Revathy and Mukesh, 2020). In what follows, we explain some recent works in the previous categories.

2.1.1. Mathematical programming

Berk et al. (2019) used a robust and adaptive optimization approach to improve human resource planning by modeling uncertainty in hiring requests in a corporation. The methodology proposed by Berk et al. allowed to prescribe hiring actions to maximize their benefits and reduce negative

scenarios. Dey et al. (2019) proposed a hybrid approach implementing computational intelligence techniques such as, ANNs and GAs to optimize the combination of steel properties in the industry. The goal of the Dey et al's approach was to find the combination of composition and processing parameters for steel to meet desired conditions. The models developed by Dey et al. demonstrated their ability to recommend actions to improve the quality of the steel produced.

2.1.2. Rules-based on logic

Ramannavar and Sidnal (2018) proposed a context model for the analysis of resumes to recommend or prescribe the best job for a particular candidate. The goal was to map a job offer to a resume. To achieve the goal, they used logic-based models, discovering hierarchical correlations between concepts extracted from resumes. Srinivas and Ravindran (2018) developed a generic framework for optimizing an appointment system in hospital environments. The developed framework first predicts an outcome based on patient data, and then prescribes the best decision with logical rules. The proposed framework outperforms benchmark rules reported in the literature.

2.1.3. Simulation

Jank et al. (2019) used prescriptive modeling to improve product portfolio designs in the industry. The proposed model supported product managers in designing product portfolios to align them with company objectives. Jank et al. used ANNs to quantify the correlations between product portfolio metrics and the company's strategic objectives to maximize success.

2.1.4. Machine learning

Revathy and Mukesh (2020) used prescriptive models to assure the privacy of information in Hadoop (a distributed processing platform). The goal was to generate a prescriptive model to distribute the data on nodes to avoid data leaks. The developed model recommends strategies to protect data from misuse by classifying the nodes in the system based on the information sensitivity. This model was based on unsupervised learning and suggest the node where the information must be placed. Finally, Hoyos et al. (2022) developed an autonomous cycle of data analysis tasks to predict severity with ANNs and SVMs; and prescribe the best treatment options for dengue fever with a GA. The application developed by Hoyos et al. could predict severity with high ac-

curacy (98%), and based on that result, it prescribed the best actions for every patient based on World Health Organization guidelines for diagnosis and treatment of dengue.

2.2. Optimization approaches

The development of optimization approaches and models has increased in recent years. Here, we present some interesting works that have generated important results in several areas of knowledge.

Singh and Shukla (2022) developed a hybrid precoding multiple optimization algorithm for both minimizing the bit error rate in Mm-wave massive MIMO system and maximizing the energy and spectral efficiency of millimeter-wave wireless communications. Simulations performed during the research showed improved efficiency and cost when compared to other conventional algorithms reported in the literature. Pozna et al. (2022) combined the particle filter algorithm and the particle swarm optimization algorithm to minimize the energy consumption of integral servo systems. The coupling of these two techniques allows particle generation and a broadening of the search field to avoid local minima. The proposed approach allowed significant energy reduction in the fuzzy control system used in the experiments. The comparative results with other metaheuristics reinforce the capabilities of the proposed hybrid approach for energy reduction in the studied systems. Zamfirache et al. (2022) proposed an optimization approach that integrates the gray wolf optimization algorithm, reinforcement learning and iteration policies. The objective of the proposed approach was to train ANNs to optimize servo motor tracking control. The proposed approach was compared with approaches based on reinforcement learning and iteration policies that implement PSO and down gradient for optimization. However, the use of the gray wolf optimizer generates better results for the defined problem.

3. Fuzzy cognitive maps (FCMs)

In this section, we present an overview of FCMs, and their learning and inference processes.

3.1. Mathematical notation

In this subsection, the mathematical notation used in this article is briefly described. Vectors will be represented in lowercase letters ($\mathbf{v}$) and matrices with capital letters ($\mathbf{W}$). Both with bold

letters. Vectors are by default represented as columns. We used the notation $a \in \mathbb{R}$ to indicate that an element is a scalar, the notation $\mathbf{v} \in \mathbb{R}^n$ to indicate a vector of length n. To indicate that an element is a matrix, we use the convention $\mathbf{W} \in \mathbb{R}^{n \times n}$. Superscripts are used to indicate the type of1 variable, while subscripts indicate a specific element in a vector (the i-th element) or matrix (the i-th and j-th element).

3.2. Overview of FCMs

FCMs are directed graphs that were introduced by Kosko (1986), taking as an initial idea the development of cognitive maps developed by Axelrod (1976). The map consists of nodes representing concepts and arrows representing relationships or influences between them. Nodes are causally related variables within a system, where one variable can cause some kind of effect on another. This type of relationship is represented with arrows directed from a source node to a destination node. Fig. 1 shows an example of FCM with five nodes or concepts and five relationships. The subindex in the edge value indicates the direction of that relationship, i.e. W_{15} indicates that the relationship goes from concept 1 (C_1) to concept 5 (C_5).

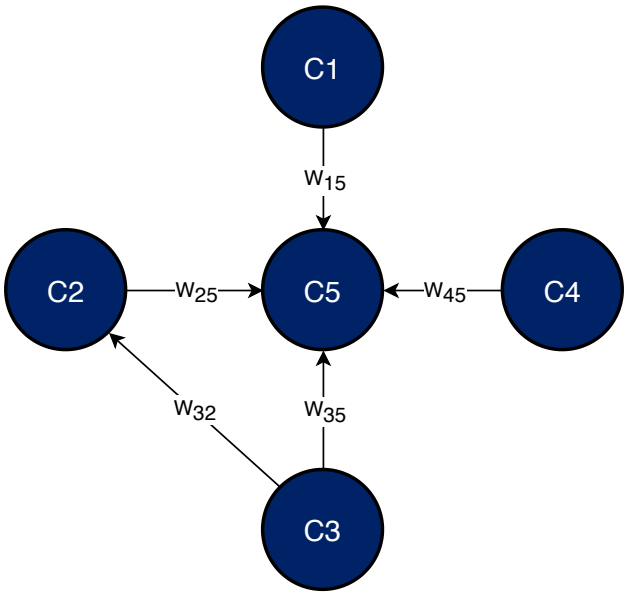

Fig. 1. Example of an FCM with five concepts and five relationships.

An FCM is composed of five main elements, summarized by the following expression (Hoyos et al., 2022):

$$\Omega = \langle n, \mathbf{v}, \mathbf{W}, f(\cdots), \mathbf{r} \rangle \tag{1}$$

Where Ω represents the tuple that contains all the elements of an FCM; n is the number of nodes or variables, $\mathbf{v}$ is an activation or initial vector —$\mathbf{v} \in \mathbb{R}^n$— that stores the value of the concepts or nodes at time $t = 0$ (see Eq. 2); $\mathbf{W}$ is a matrix that stores the causal relationships between the concepts, —$\mathbf{W} \in \mathbb{R}^{n \times n}$— (an example of a weight matrix for the FCM of Fig. 1 is shown in Eq. 3); finally, $f(\cdots)$ is a nonlinear activation function that keeps the values within a given range determined by $\mathbf{r}$. This range of $\mathbf{r}$ depends on the activation function used.

$$\mathbf{v}(0) = (\mathbf{v}_1(0), \mathbf{v}_2(0), \ldots, \mathbf{v}_n(0)) \tag{2}$$

$$\mathbf{W} = \begin{array}{c} \\ \boldsymbol{C_1} \\ \boldsymbol{C_2} \\ \boldsymbol{C_3} \\ \boldsymbol{C_4} \\ \boldsymbol{C_5} \end{array} \begin{array}{c} \begin{array}{ccccc} \boldsymbol{C_1} & \boldsymbol{C_2} & \boldsymbol{C_3} & \boldsymbol{C_4} & \boldsymbol{C_5} \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & w_{15} \\ 0 & 0 & 0 & 0 & w_{25} \\ 0 & w_{32} & 0 & 0 & w_{35} \\ 0 & 0 & 0 & 0 & w_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array} \tag{3}$$

Different activation functions can be used such as sigmoid and hyperbolic tangent. The use of each of them depends on the system to be simulated, i.e. the sigmoid function keeps the concept values between 0 and 1, while the hyperbolic tangent keeps them between -1 and 1. Table 1 shows the equations for some of the activation functions used in FCMs.

3.3. Learning of FCMs

The construction and optimization of FCMs can be carried out by two main approaches (Aguilar, 2013; Aguilar and Contreras, 2010): i) definition of concepts and assignment of relationships by domain experts, and ii) optimization of the matrix that stores relationships between concepts. In the latter approach, ML algorithms are used to compute the matrix using historical data to fit specific patterns. It is worth mentioning that in the latter approach, human intervention is not necessary.

Table 1

Example of activation functions used in FCMs.

Activation function	Equation	Range
Bivalent	$f(x) = \begin{cases} 1 & x > 0 \\ 0 & x \leq 0 \end{cases}$	$f(x) \in \{0, 1\}$
Trivalent	$f(x) = \begin{cases} 1 & x > 0 \\ 0 & x = 0 \\ -1 & x < 0 \end{cases}$	$f(x) \in \{-1, 0, 1\}$
Sigmoid	$f(x) = \frac{1}{1+e^{-\lambda \times x}}$	$f(x) \in [0, 1]$
Hyperbolic tangent	$f(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}}$	$f(x) \in [-1, 1]$

One of the most widely used algorithms for the construction of FCMs is Particle Swarm Optimization (PSO). PSO is a search algorithm described by Kennedy and Eberhart (1995), which is inspired by the behavior of insect swarms in nature. It can be used to train the weights matrix of an FCM where each particle i is an FCM and its position is a candidate weight matrix ($\mathbf{W}_i$). The process consists of two stages to move the particle to a new position: i) update the particle velocity, ii) update the particle position (Salmeron et al., 2017). Formally, the PSO algorithm can be described by two equations. First, the update of the velocities:

$$\mathbf{v}_i(t+1) = \mathbf{v}_i(t) + r_1 \cdot (\mathbf{W}_i^{best} - \mathbf{W}_i(t)) + r_2 \cdot (\mathbf{W}_i^{gbest} - \mathbf{W}_i(t)) \tag{4}$$

Where $\mathbf{v}_i(t)$ is the velocity of particle i at instant t, r_1 and r_2 are two random values generated during the search process; $\mathbf{W}_i^{best}$ is the best position the particle has passed through throughout the search process and $\mathbf{W}_i^{gbest}$ is the best global position of the whole swarm.

After the particle velocities are updated, the positions are updated using the following equation:

$$\mathbf{W}_i(t+1) = \mathbf{W}_i(t) + \mathbf{v}_i(t) \tag{5}$$

Finally, the algorithm generates the best weight matrix ($\mathbf{W}_i$) using previous updates. We used this algorithm to create and train FCMs (the predictive models) using synthetic and real datasets, due to the lack of domain experts and avoid bias introduced by humans.

3.4. *Inference of FCMs*

The reasoning or inference process of FCMs is carried out by successive multiplication of an activation vector $\mathbf{v}$ with a square matrix $\mathbf{W}$ corresponding to the influences between those concepts. One of the goals of this process is to predict an outcome. The inference procedure is iterative through time t and ends when the steady-state is reached. The equilibrium point is achieved when the difference between the value of the concept at time $t+1$ and the value of the concept at time t is less than or equal to 0.0001. As an example, the following expression represents the calculation of the vector values in the first iteration of the inference process using the Kosko function (Kosko, 1986):

$$\mathbf{v}(1) = \begin{bmatrix} — & \mathbf{W}_1^T & — \\ — & \mathbf{W}_2^T & — \\ — & \vdots & — \\ — & \mathbf{W}_4^T & — \end{bmatrix} \begin{bmatrix} \mathbf{v}_1(0) \\ \mathbf{v}_2(0) \\ \vdots \\ \mathbf{v}_n(0) \end{bmatrix} \tag{6}$$

For simulation with FCMs, different inference functions have been developed such as the one developed by Kosko (Kosko, 1986), the modified Kosko (Stylios and Groumpos, 2004), and the rescaled one (Papageorgiou, 2011). Table 2 shows the equations of each of the inference functions and their main characteristics.

4. Our proposed prescriptive approach: PRV-FCM

In this work, we propose a methodology to generate prescriptive models with FCMs and meta-heuristic algorithms, called PRV-FCM. Prior to the generation of the prescriptive model, an FCM must be built for each specific problem. In this research, we used data-driven PSO-FCM for the construction of the predictive models with FCMs. In this case, FCMs were not built based on expert knowledge and experience but based on historical data, due to better model performance when this approach is used.

The generation of a prescriptive model with PRV-FCM requires three steps: i) Characterization of the FCM, ii) Initial instantiation of the FCM, and, iii) Inference and optimization processes. Fig. 2 represents the methodological framework to generate prescriptive models using PRV-FCM. In the following, we describe briefly the stages of our approach.

Table 2

Main properties of inference functions used for reasoning in FCMs.

Inference function	Equation	Main characteristics
Kosko (Kosko, 1986)	$\mathbf{v}_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} \mathbf{W}_{ij}\mathbf{v}_i(t)\right)$	It does not include the values of the concepts in the previous iteration. The FCM has no memory capacity and the change between iterations tends to be abrupt.
Modified Kosko (Stylios and Groumpos, 2004)	$\mathbf{v}_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} \mathbf{v}_j(t) + \mathbf{W}_{ij}\mathbf{v}_i(t)\right)$	It includes the value of the concept in the previous iteration; therefore, the FCM has memory capacity and the change after each iteration is done in a smoother way.
Rescaled (Papageorgiou, 2011)	$\mathbf{v}_j(t+1) = f\left(\sum_{i=1,i\neg j}^{n} (2\times\mathbf{v}_j(t)-1) + \mathbf{W}_{ij}(2\times\mathbf{v}_i(t)-1)\right)$	Solve the problem with initial concept values of 0, which when passed to the activation function take values of 0.5 in the second iteration.

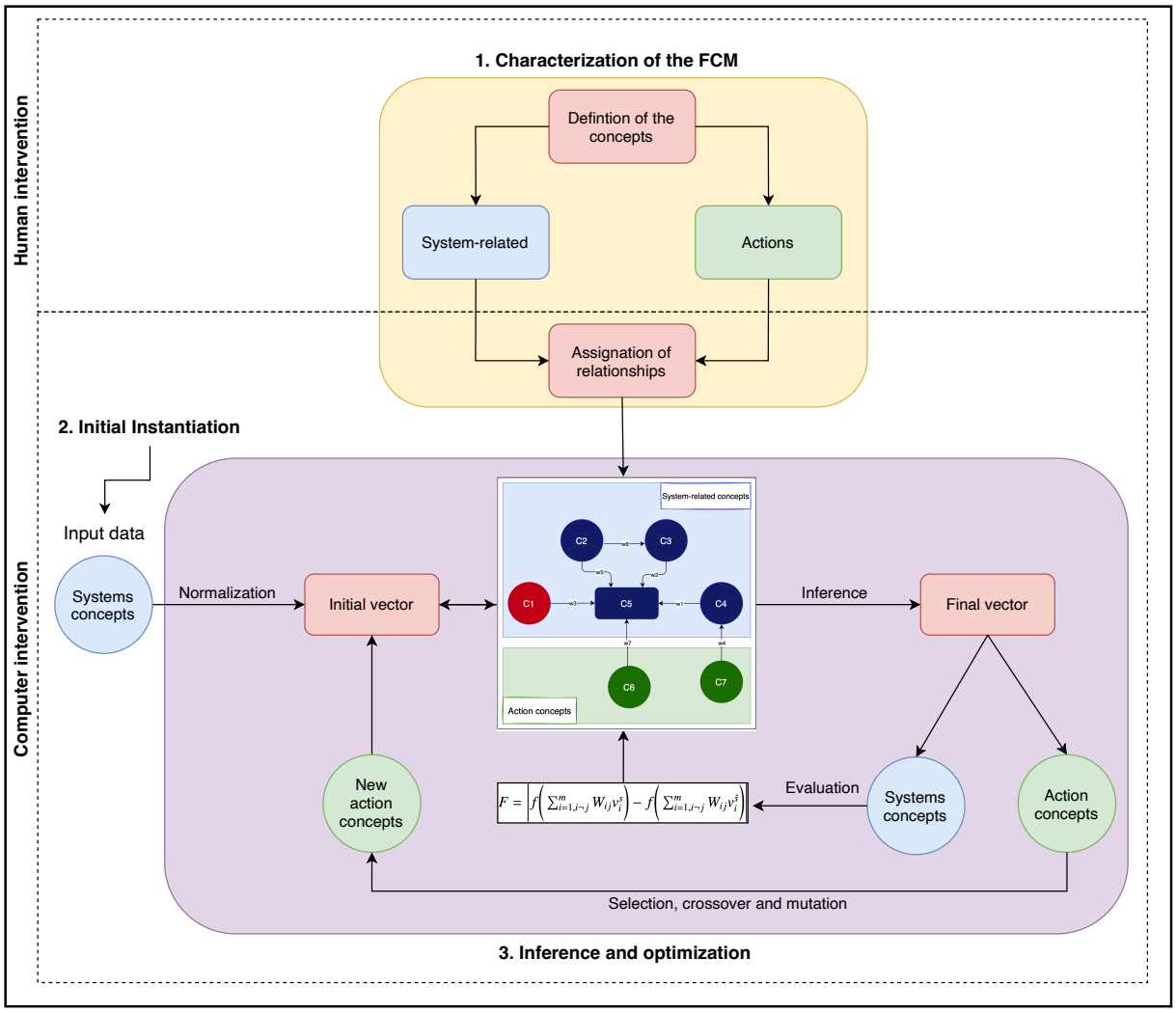

Fig. 2. Methodological framework to generate prescriptive models using PRV-FCM.

4.1. Characterization of the FCM

The first step consists of characterizing the FCM by classifying its concepts into two main layers: the system layer (blue area in Fig. 3) and the action layer (green area in Fig. 3). The first layer contains the concepts that are related to the system, which describe it. In the action layer, there are the prescriptive or action concepts that wish to be found for the system to reach the desired state. In the following, we define each of the concepts involved in the prescriptive model:

1. system-related concepts ($\mathbf{v}^s$): are those that belong to the system to be studied. System concepts are the variables that describe a system that relate to each other to achieve an objective.

For example, a disease is a biological system where the system concepts correspond to signs, symptoms and alterations in the body of the sick person. This kind of concept is classified into changeable and non-changeable:

- Non-changeable concepts ($\mathbf{v}^{nc}$): are those that cannot be modified in the logic of the system. For example: in a biological system, biological sex is a non-changeable concept in real-time.
- Changeable concepts ($\mathbf{v}^{c}$): are those that can change during the simulation of the system. For example: in a biological system, changeable concepts could be those that can be minimized or maximized for a particular objective. Some examples of minimization could be symptoms of a patient with a disease. These concepts are the ones to be optimized following decision guidelines that are represented by the action concepts.

2. Action concepts ($\mathbf{v}^{a}$): are those that act on the changeable concepts of the system to optimize them to achieve a desired result in the system. These concepts have a causal effect on some changeable concepts related to the system. Moreover, these variables are the ones that make up the prescriptive model. An example of this type of concept could be a treatment (i.e. analgesic), which has an effect on reducing a patient's symptom (i.e. headache).

Fig. 3 shows a general example of an FCM to define a prescriptive model. In this figure, we can see the types of concepts for this problem: system-related and action concepts. Thus, to use an FCM as a prescriptive model, three types of concepts and causal relationships to the changeable concepts are defined.

4.2. Initial instantiation of the system-related concepts

The system's initial vector – $\mathbf{v}^{s}(0)$ – corresponds to the values of the system concepts desired by the decision maker. This vector serves as input to PRV-FCM to find the values of the action concepts leading to that initially defined system state.

$$\mathbf{v}^{s}(0) = \begin{bmatrix} \mathbf{v}_i^{s}(0) \\ \vdots \\ \mathbf{v}_o^{s}(0) \end{bmatrix} = \begin{bmatrix} \mathbf{v}_i^{nc}(0) \\ \vdots \\ \mathbf{v}_p^{nc}(0) \end{bmatrix} \cup \begin{bmatrix} \mathbf{v}_i^{c}(0) \\ \vdots \\ \mathbf{v}_q^{c}(0) \end{bmatrix} \tag{7}$$

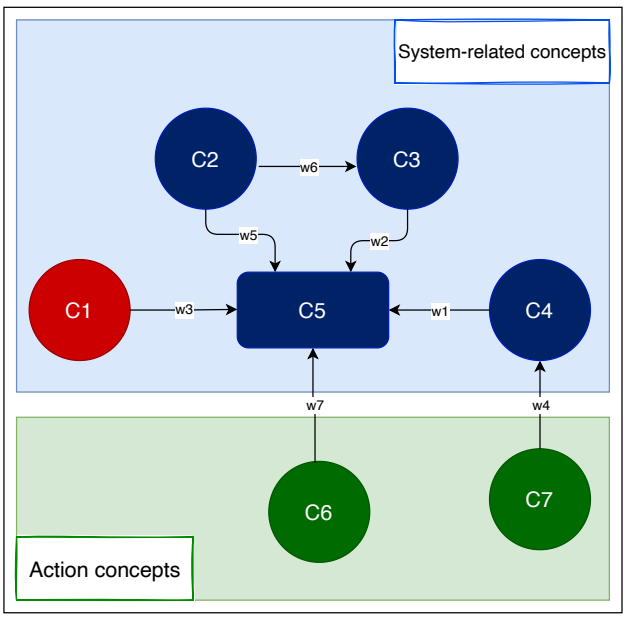

Fig. 3. Example of an FCM used as a prescriptive model. The non-changeable concepts are represented in red, while the changeable in dark blue.

where, $\mathbf{v}^{nc}(0)$ is a vector with non-changeable concepts and p is the number of them, and the vector $\mathbf{v}^{c}(0)$ stores the changeable system-related concepts and q is the number of them.

4.3. Optimization process

In this section, we describe the process for finding the optimal action values that lead to the desired values of the system concepts. The optimization mechanism internally uses the PRV-FCM inference process to generate solutions and, once evaluated, they are discarded or selected. A more in-depth explanation of this process is described below.

Algorithm 1 describes the steps of the optimization process, which are carried out to obtain the optimal values of action concepts that generate the desired values of the system concepts. In our case, we used a GA for the optimization process, however, any metaheuristic can be used to obtain these values. GA is a probabilistic search technique used to find the optimal subset of features for a specific problem. This algorithm is an ideal choice for the optimization of prescriptive concepts with FCMs due to several reasons: 1) its ease of implementation and versatility; the general structure of a GA is the same regardless of the problem to be solved. 2) the ability to operate

simultaneously with several solutions, instead of working sequentially like other techniques. 3) They use the information provided by the objective function and do not require other methods or auxiliary knowledge. These features make it more easily adaptable to different problems.

The input parameters of the algorithm are the initial vector of desired system concepts $\mathbf{v}^s(0)$. The algorithm must initially know the desired values of the system, a matrix of weights $\mathbf{W}$ that corresponds to the relationships that exist between all the concepts, a stop condition of the algorithm to avoid an infinite loop, the dimensions of the action vector, and the fitness function F to evaluate the individuals generated in the process.

To start the optimization process with the GA (Step 1), the generation counter is set to 0 (Step 2). Step 3 is the random generation of a population of individuals or vectors $\mathbf{v}^a(0)$ with dimension s corresponding to the action concepts. A solution (individual) is a set of possible values for each of the action concepts. The vector $\mathbf{v}^a(0)$ is defined as follows:

$$\mathbf{v}^a(0) = \begin{bmatrix} \mathbf{v}_i^a(0) \\ \vdots \\ \mathbf{v}_s^a(0) \end{bmatrix} \tag{8}$$

where $\mathbf{v}^a(0)$ stores the prescriptive concepts and s is the number of them.

For the inference process, an initial vector $\mathbf{v}(0)$ is required. This vector is constituted by an initial vector of the system $\mathbf{v}^s(0)$ corresponding to the desired state of the system that was defined in the previous stage. The other component of the initial vector is an initial action vector $\mathbf{v}^a(0)$, which was randomly generated at the beginning of the process and is the objective vector to optimize. These two vectors are combined to form the initial vector (Step 4). This step is important, so that the dimensions of the weight matrix should match the dimensions of the initial vector and thus the dot product is performed correctly (see Eq. 6). The initial vector is defined as:

$$\mathbf{v}(0) = \mathbf{v}^s(0) \cup \mathbf{v}^a(0) = \begin{bmatrix} \mathbf{v}_i^s(0) \\ \vdots \\ \mathbf{v}_o^s(0) \end{bmatrix} \cup \begin{bmatrix} \mathbf{v}_i^a(0) \\ \vdots \\ \mathbf{v}_s^a(0) \end{bmatrix} \tag{9}$$

Subsequently, with the constructed initial vector $\mathbf{v}(0)$, the inference process is performed (Step 7). Unlike a classical FCM that consists of a five-element tuple (see Eq. 1), PRV-FCM is repre-

Algorithm 1: Optimization algorithm to generate optimal values of action concepts

Input : $\mathbf{v}^s(0)$ = desired system vector, $\mathbf{W}$ = weigh matrix, F = fitness function, sc = stop condition

Output: Optimal $\mathbf{v}^a$

begin

  Set the generations counter $g = 0$

  Generate randomly one population $P(0)$ of individuals $\mathbf{v}^a$

  Generate initial vector $\mathbf{v}(g)$ with the combination of $\mathbf{v}^s(0)$ and $\mathbf{v}^a$

  while *sc is not met* **do**

    for *each initial vector* $\boldsymbol{v}(g)$ **do**

$$\mathbf{v}_{final} = f\left(\sum_{i=1}^{n} \mathbf{W}\mathbf{v}(g)\right)$$

      for *each final vector* $\boldsymbol{v}_{final} \in P(g)$ **do**

        Split final vector $\mathbf{v}_{final}$ in $\mathbf{v}^{\hat{a}}$ and $\mathbf{v}^{\hat{s}}$

        Evaluation of fitness:

$$F = \left| f\left(\sum_{i=1,i\neg j}^{n} \mathbf{W}_{ij}\mathbf{v}_i^s\right) - f\left(\sum_{i=1,i\neg j}^{n} \mathbf{W}_{ij}\mathbf{v}_i^{\hat{s}}\right)\right|$$

      end

    end

    Selection of best individuals $\mathbf{v}^{\hat{a}}$ by genetic operators

    Generation of a new population $P(g+1)$

    $g = g + 1$

  end

  return optimal $\mathbf{v}^a$

end

sented as a twelve-element tuple. Eq. 10 represents mathematically all the PRV-FCM elements and Table 3 shows a comparison between classical FCM and PRV-FCM elements.

$$\Psi = \langle n, \mathbf{W}, f(\cdots), \mathbf{r}, \mathbf{v}^s, o, \mathbf{v}^{nc}, p, \mathbf{v}^c, q, \mathbf{v}^a, s \rangle \tag{10}$$

Table 3

Comparison of elements used in classical FCMs and our proposed prescriptive approach (PRV-FCM).

Element	Definition	
	Classical FCM	**PRV-FCM**
n	Total number of variables	total number of variables
$\mathbf{W}$	Weight matrix for the FCM	Weight matrix for PRV-FCM
$f(\cdots)$	Threshold function	Threshold function
$\mathbf{r}$	Range of concept values	Range of concept values
$\mathbf{v}^s$	–	System concepts
o	–	Number of system concepts
$\mathbf{v}^{nc}$	–	Non-changeable concepts
p	–	Number of non-changeable concepts
$\mathbf{v}^c$	–	Changeable concepts
q	–	Number of changeable concepts
$\mathbf{v}^a$	–	Action concepts
s	–	Number of action concepts

The inference process consists of the iterative computation (t iterations) of initial vector $\mathbf{v}(0)$ with the weight matrix $\mathbf{W}$ to obtain a final stable vector. This process is defined by the equations described in Table 2. However, for the practical case, we will use a modification of the inference function proposed by Kosko (1986):

$$\mathbf{v}_{final} = f\left(\sum_{i=1}^{m} \mathbf{W}\mathbf{v}(t) \right) \tag{11}$$

The result of the inference process is a final vector that corresponds to the steady state of PRV-FCM (Step 8). This final vector is divided again into action vector $\mathbf{v}^{\hat{a}}$ and system vector $\mathbf{v}^{\hat{s}}$ (Step 9). The fitness of the action vector is evaluated using the $\mathbf{v}^s(0)$, $\mathbf{v}^{\hat{s}}$ and a fitness function (Steps

10 and 11). We proposed several fitness functions (see Table 4). For this explanation, we use the following function:

$$\min \left| f\left(\sum_{i=1, i\neg j}^{m} \mathbf{W}_{ij}\mathbf{v}_i^s \right) - f\left(\sum_{i=1, i\neg j}^{m} \mathbf{W}_{ij}\mathbf{v}_i^{\hat{s}} \right) \right| \tag{12}$$

$$\text{s.t.} \quad l_l < \mathbf{v}^{\hat{s}} < l_u \tag{13}$$

where $\mathbf{v}_i^s$ indicates the desired state of the system concepts, $\mathbf{v}_i^{\hat{s}}$ indicates the vector of systems concepts as a result of inference with the PRV-FCM; l_l and l_u are lower and upper limits ([0, 1] or [-1, 1], depending on the inference function used), respectively.

Table 4

Fitness functions used to generate prescriptive models with PRV-FCM.

Fitness function	**Equation**
Prescriptive Kosko	$F = \left\| f\left(\sum_{i=1,i\neg j}^{n} \mathbf{W}_{ij}\mathbf{v}_i^s \right) - f\left(\sum_{i=1,i\neg j}^{n} \mathbf{W}_{ij}\mathbf{v}_i^{\hat{s}} \right) \right\|$
Prescriptive Modified Kosko	$F = \left\| f\left(\sum_{i=1,i\neg j}^{n} \mathbf{v}_j^s + \mathbf{W}_{ij}\mathbf{v}_i^s \right) - f\left(\sum_{i=1,i\neg j}^{n} \mathbf{v}_j^{\hat{s}} + \mathbf{W}_{ij}\mathbf{v}_i^{\hat{s}} \right) \right\|$
Prescriptive rescaled	$F = \left\| f\left(\sum_{i=1,i\neg j}^{n} (2 \times \mathbf{v}_j^s - 1) + \mathbf{W}_{ij}\mathbf{v}_i^{\hat{s}} \right) - f\left(\sum_{i=1,i\neg j}^{n} (2 \times \mathbf{v}_j^{\hat{s}} - 1) + \mathbf{W}_{ij}v_i^{\hat{s}} \right) \right\|$

Subsequently, crossover and mutation genetic operators are applied to the action vector to select the best individuals (Step 14) and create a new population with the best individuals (Step 15). The main objective of this stage is to find the values of the action concepts that when used in the inference process minimize the difference between the initial values of system concepts and the values of system concepts generated during the inference process. Finally, when the stop condition is reached, the optimal values for the action concepts are obtained (Step 18), and thus, they constitute the optimal prescriptive variables that lead to the desired state of the system.

5. Specification of the case studies

In this section, we specify case studies to validate the proposed approach. We used several case studies from different domains. We tested our methodology in a synthetic dataset, and after in three real datasets. Although work on prescriptive modeling continues to increase, there are still challenges that need to be addressed. For example, there is currently a low availability of datasets with prescriptive variables included. Of the selected case studies, only one dataset had variables considered prescriptive. We reviewed hundreds of datasets that were hosted in different repositories and could be downloaded to determine the nature of the features present in each of them and used this criterion for the selection of case studies. Finally, we selected datasets where system-related variables could be assumed to be prescriptive variables (see Section 7 for more details).

5.1. Synthetic case study

To carry out this first case study, we generated a balanced synthetic dataset for classification with 1000 records, 10 features and a binary class.

Table 5

Features included in the synthetic dataset.

Concept	Concept type
C1	System
C2	Prescriptive
C3	System
C4	System
C5	System
C6	System
C7	System
C8	System
C9	Prescriptive
C10	System

5.2. *Wine case study*

For this case study, we use the *red wine quality dataset* available in UCI ML datasets (Cortez et al., 2009). This dataset comprises 1599 records, 11 physicochemical variables, and the class (wine quality). Table 6 shows the 11 variables used in this case.

Table 6

Features included in the red wine dataset.

Feature	Concept	Concept type
Fixed acidity (g(tartaric acid)/dm^3)	C1	System
Volatile acidity (g(acetic acid)/dm^3)	C2	System
Citric acid (g/dm^3)	C3	System
Residual sugar (g/dm^3)	C4	System
Chlorides (g(sodium chloride)/dm^3)	C5	System
Free sulfur dioxide (mg/dm^3)	C6	Prescriptive
Total sulfur dioxide (mg/dm^3)	C7	System
Density (g/cm^3)	C8	Prescriptive
pH	C9	System
Sulphates (g(potassium sulphate)/dm^3)	C10	System
Alcohol (vol.%)	C11	System

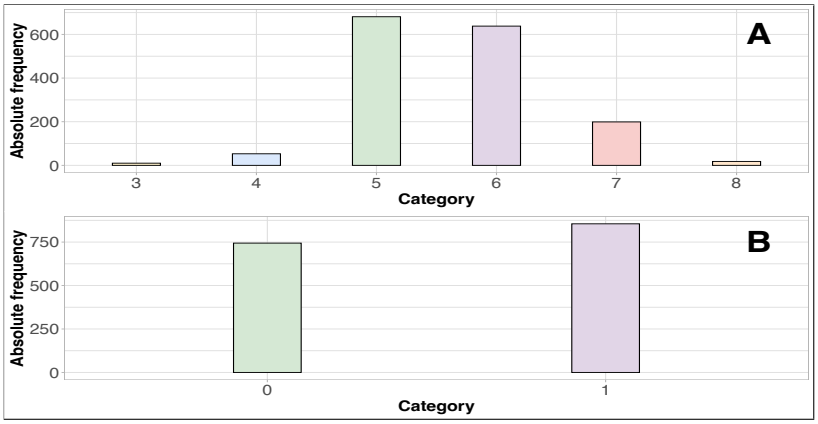

Fig. 4. Frequency distribution of the classes in the red wine dataset (Plot A corresponds to the frequency distribution of the classes in the original dataset. Plot B corresponds to the frequency distribution after reducing the classes to two categories).

The wine quality is defined by an expert team by assigning a score between 0 and 10 (Cortez et al., 2009). This score is considered the class within the red wine dataset. Although the score can be assigned from 0 to 10, in the dataset, there were no wines with class categories below 3 or above 8. In addition, some categories were unbalanced, and there were categories with few instances (see Plot A in Fig. 4). To overcome this problem and avoid using oversampling techniques for each minority class, we reduced the categories to two categories: *low quality*, when wine quality is lower and equal to 5 (class = 0); and *high quality*, when wine quality is greater than 5 (class = 1). At the end, we obtained a balanced dataset with 744 records for class 0 and 855 for class 1 (see Plot B in Fig. 4).

Table 7

Features included in the diabetes dataset.

Feature	**Concept**	**Concept type**
Number of times pregnant	C1	System
Plasma glucose concentration a 2 hours in an oral glucose tolerance test	C2	Prescriptive
Diastolic blood pressure (mm Hg)	C3	Prescriptive
Triceps skin fold thickness (mm)	C4	System
2-Hour serum insulin (mu U/ml)	C5	System
Body mass index (weight in kg/(height in m)^2)	C6	System
Diabetes pedigree function (familiar and genetic antecedents)	C7	System
Age (years)	C8	System

5.3. Diabetes case study

Our third case study corresponds to diabetes, which is a disease characterized by high levels of glucose in the blood and complications related to this blood alteration (Pangaribuan and Suharjito, 2014). In this case, we used the *Pima Indians Diabetes Database* from the National Institute of Diabetes and Digestive and Kidney Diseases (Smith et al., 1988). The dataset is composed by 768 patients and 9 features, including the class (500 patients for class 0 = negative for diabetes, and 268 patients for 1 = positive for diabetes). Table 7 shows the variables included in this dataset. We used Synthetic Minority Oversampling Technique (SMOTE) (Chawla et al., 2002) to balance the classes, and at the end, we obtained 1000 records, 500 for each class.

Table 8

System-related categorical features included in the student academic performance dataset.

Feature	Feature type	Concept	Concept type	Categories
Gender	Demographic	C1	System	Male, female
Nationality	Demographic	C2	System	Kuwait, Lebanon, Egypt, Saudi Arabia, USA, Jordan, Venezuela, Iran, Tunis, Morocco, Syria, Palestine, Iraq, Lybia
Educational stages	Academic	C3	System	Lowerlevel, Middle School, High School
Grade levels	Academic	C4	System	01, 02, 03, 04, 05, 06, 07, 08, 09, 10, 11, 12
Classroom	Academic	C5	System	A, B, C
Topic	Academic	C6	System	English, Spanish, French, Arabic, IT, Math, Chemistry, Biology, Science, History, Quran, Geology
Semester	Academic	C7	System	First, Second
Responsible parent	Academic	C8	System	Mother, Father
Parent answering survey	Behavioral	C13	System	Yes, No
Parent school satisfaction	Behavioral	C14	System	Yes, No
Student absence days	Behavioral	C15	System	Above-7, Under-7

5.4. Student performance case study

Student academic performance is conceived as a construct that depends not only on student motivation, but also on other factors such as student-student relationships, demographic, socio-economic and psychological variables (Kumar and Pal, 2011). To test our approach, we used an educational dataset, called *Student Academic Performance*, with 480 students and 16 features (academic, demographics and behavioral) (Amrieh et al., 2016). This dataset has information collected from a Learning Management System called K360, which allows students access to online educational resources. Table 8 shows the categorical variables, and Table 9 shows the numeric features included in this dataset. These last variables will be the prescriptive concepts. For this experiment, we drop the variable *place of birth* because of its high correlation with the

variable *nationality* (0.95). With respect to the class, we created two classes based on students' grade: class 0 when the grade is lower than 70, and class 1 when the grade is greater or equal to 70. We used SMOTE to balance the classes (353 records for each class).

Table 9

Action numerical features included in the student academic performance dataset.

Feature	Feature type	Concept	Concept type
Raised hand	Behavioral	C9	Prescriptive
Visited resources	Behavioral	C10	Prescriptive
Viewing announcements	Behavioral	C11	Prescriptive
Discussion groups	Behavioral	C12	Prescriptive

6. Experiments and results

In this section, we present the experiments set up to test the proposed approach. Additionally, we present the results of the generated models. First, we give an overview of the data preparation; then, we present the metrics to evaluate the performance of the models and finally, we present the results of the prescriptive models and their corresponding predictive model.

6.1. Data preparation

Normalization process was implemented to convert values in the range from 0 and 1 before feeding the FCMs (see Eq. 14). Specific processes of modification of variables in datasets are described in each case study's subsection. For all experiments, datasets were divided in training and testing in a proportion 70%/30%, respectively, and we use 10-fold cross-validation to find out the best configuration of hyperparameters (see Fig. 5).

$$x_{norm} = \frac{x_i - x_{min}}{x_{max} - x_{min}} \tag{14}$$

6.2. Evaluation metrics

We used accuracy as a metric for classification; mean absolute error (MAE), mean squared error (MSE), and root-mean-square error (RMSE) as error metrics to evaluate the prescriptive

models; and prescriptive success rate (PSR) to determine the quality of the prescription. It's important to mention that we used accuracy as a metric because all datasets were balanced at the moment of developing the models, and error metrics because the prescriptive variables in datasets were numerical. In the following, we describe briefly each of these metrics.

- *Accuracy*: percentage of correctly classified examples among the total number of classified examples. Greater accuracy means a greater performance of the model.

$$Accuracy = \frac{TP + TN}{TP + FN + FP + TN} \tag{15}$$

  where TP are the true positives, TN are true negatives, FN are false negatives and TN are true negatives.

- *MAE*: calculated as an average of absolute differences between prescriptive concepts values and prescriptions.

$$MAE = \frac{1}{m} \sum_{i=1}^{m} \left| v_i^a - \hat{v}_i^a \right| \tag{16}$$

  where m is the number of records in the testing set, v_i^a is the actual prescriptive value and $\hat{v}_i^a$ is the prescribed value.

- *MSE*: measures the average square error of our prescriptions. For each point, it calculates the square difference between the prescriptions and the prescriptive concepts, and then averages those values.

$$MSE = \frac{1}{m} \sum_{i=1}^{m} (v_i^a - \hat{v}_i^a)^2 \tag{17}$$

- *RMSE*: is the squared root of the error described above.

$$RMSE = \sqrt{\frac{1}{m} \sum_{i=1}^{m} (v_i^a - \hat{v}_i^a)^2} = \sqrt{MSE} \tag{18}$$

- *PSR*: calculated as a ratio between prescribed values by PRV-FCM and actual values in the dataset. The numerator should be lower than the denominator to assure values between 0 and 1.

$$PSR = \frac{\sum_{i=1}^{s} \sum_{j=1}^{m} \hat{v}_i^a}{\sum_{i=1}^{s} \sum_{j=1}^{m} v_i^a} \tag{19}$$

6.3. Training, validation and testing

After data preparation, the model development process consisted of three stages: i) training, ii) validation and iii) testing. Seventy percent of the data from each case study was used for training and validation, while 30% was used for testing in cases not seen by the model. We used the 10-fold cross-validation technique to determine the best model and its hyperparameters. The 10-fold cross-validation process can be seen in Fig. 5. Specifically, this process divides the training dataset into ten subsets, taking nine for training and one for validation. Subsequently, it repeats the process by taking one subset different from the previous one for validation and the remaining nine for training. After ten training and validation processes, the best performing model and associated hyperparameters are selected. The best selected model is applied to the test data set to evaluate its performance on previously unseen models.

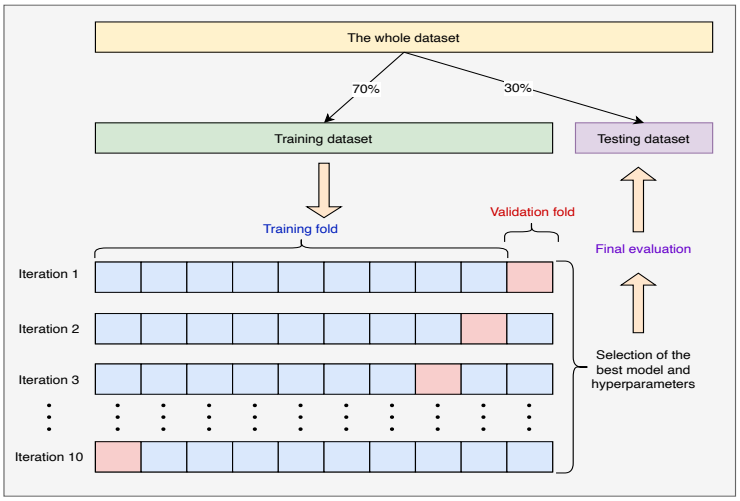

Fig. 5. Schematic representation of 10-fold cross-validation.

For the case of predictive models, we use a grid of hyperparameters for tuning. We used the sigmoid and hyperbolic tangent activation functions with random values of slopes. We also use the

Kosko, modified Kosko and Rescaled inference functions for the reasoning process with the FCM. For the case of prescriptive models, we used a random grid of values for the hyperparameters of the GA such as initial population, number of generations, crossover probability and mutation probability.

6.4. Synthetic dataset

6.4.1. Predictive model

Before prescription with PRV-FCM, we generated an FCM using PSO. For that, using the training set from the previous dataset, we adjust the weights of FCM, and test using the testing set. The generated FCM was able to classify with 96% accuracy. Table 10 shows the results of the evaluation on the testing set, including the optimal hyperparameters. The results of this case study show an excellent performance of the model for prediction, and this result was expected because the dataset was built with well-differentiated clusters that allowed classifying the classes with high accuracy.

6.4.2. Prescriptive model

We selected two concepts from previously developed FCM as prescriptive variables: C_2 and C_9 (see Table 5). This decision was made because these two variables had no incoming influences on them, and in this way, we ensured that the value of them is not altered by other variables in the system. The idea is to find the optimal values of these prescriptive concepts that achieve a desired result in the system concepts. To find out these values, the PRV-FCM used a GA with different hyperparameters such as population, number of generations, crossover and mutation probabilities. The best configuration were: population = 50, number of generations = 20, crossover = 0.3 and mutation = 0.4. Table 11 shows the evaluation of PRV-FCM with respect to MAE, MSE and RMSE. The prescription results show an excellent performance of the model generated with PRV-FCM, such that it prescribes actions to achieve desired results of the system concepts in the dataset. The different levels of error measured between the values of the prescriptive variables in the dataset and the prescriptive values generated by PRV-FCM are very low (MAE < 0.014, MSE < 0.0004 and RMSE < 0.019) and demonstrate that our approach is useful for generating prescriptive models that optimize actions to achieve desired outcomes.

6.5. Wine quality dataset

6.5.1. Predictive model

To test the inference process, we generated an FCM using PSO. For that, using the training set generated from the previous dataset, we adjust the weights of generated FCM, and test in the testing set. The developed FCM was able to predict wine quality with 71% accuracy. Table 10 shows the results of the evaluation on the testing set, including the optimal hyperparameters.

Several predictive models have been developed with the previously described dataset in this case study. Our predictive model performed slightly better than that reported by Kumar et al. (2020), who developed a predictive model obtaining the best model with SVMs and an accuracy of 68%. On the other hand, our model had a similar performance to the one developed by Laughter and Omari (2020) where with Random Forest they obtained a performance of 72% accuracy. This comparison shows the competitive capacity of our model to predict wine quality using physicochemical characteristics as predictor variables. The performance of the predictive model was good, however, it could be improved by using other variables related to wine quality. For example, a high concentration of metals such as iron, aluminum and copper can alter the organoleptic properties of wine, and thus, its quality. In addition, these molecules have the ability to modify the turbidity and color of wine due to the formation of complexes with molecules present in wine such as tannins and anthocyanins (Frank and Kowalski, 1984).

6.5.2. Prescriptive model

In the wine dataset, there were no action concepts per se, but some concepts that can be modified by the decision-maker to achieve the desired result. We assume these variables as prescriptive concepts. For this case, we selected two of the FCM concepts as prescriptive variables: C_6 and C_8 (see Table 6). This decision was made because these two variables had no incoming influences on them, and in this way, we ensured that the value of them is not altered by other variables in the system. The idea is to find the optimal values of these prescriptive concepts that achieve a desired result in the system concepts. To find out these values, the PRV-FCM used a GA with different hyperparameters. The best configuration was population = 50, number of generations = 20, crossover = 0.5 and mutation = 0.5. Table 11 shows the evaluation of PRV-FCM with respect to

MAE, MSE and RMSE. As in the synthetic case study, the prescriptive results for this case study were excellent, finding MAE, MSE and RMSE values below 0.02, 0.0007 and 0.03, respectively. The prescriptive model generated with PRV-FCM has the ability to generate recommendations on prescriptive variables that lead to improved wine quality. Finally, because this dataset has not been used in any prescriptive model previously, unfortunately, we cannot compare it quantitatively with previous studies.

6.6. Diabetes dataset

6.6.1. Predictive model

The inference process was tested using an FCM built with PSO (with it was adjusted the FCM weights). Then, the FCM was tested in a testing set. The developed FCM model was able to predict diabetes with 70% accuracy. Table 10 shows the results of the evaluation in the testing set, including the optimal hyperparameters. Our model performed inferior to studies reported in the literature. For example, Olisah et al. (2022) and Hasan et al. (2020) developed predictive models for diabetes using feature selection techniques to improve model performance. The two studies presented performances above 90% using SVMs and correlation-based techniques, respectively. Despite the superiority of these models, our model has the advantage of being interpretable, where the inference process could be used to evaluate the behavior of variables over time.

The diagnosis or detection of diabetes is composed of the analysis of blood glucose levels, symptoms and risk factors present in the patient (Elliott and Pfotenhauer, 2022). The performance of predictive models for diabetes can be improved by using all the risk factors or symptoms used in the diagnosis of the disease. The acceptable performance of our predictive model could also be explained by the fact that many known symptoms of diabetes such as polydipsia, polyuria, polyphagia, abdominal girth, or risk factors such as physical exercise and obesity, were not available within the dataset. In addition, the small size of the dataset could influence the performance of the developed model. Several studies have shown that increasing the dataset size improves the performance of predictive models (Rácz et al., 2021; Barbedo, 2018; Quintero et al., 2021).

6.7. Prescriptive model

In the diabetes dataset there were no action concepts per se, but some concepts that can be modified by the decision-maker to achieve the desired result. We assume these variables as prescriptive concepts. For this case, we selected two of the FCM concepts as prescriptive variables: C_2 and C_3 (see Table 7). This decision was made because these two variables had no incoming influences on them, and in this way, we ensured that the value of them is not altered by other variables in the system. The algorithm finds the optimal values of these prescriptive concepts to achieve a desired result in the system concepts. To find out these values, the PRV-FCM used a GA with different hyperparameters, and the best configuration was population = 150, number of generations = 30, crossover = 0.5 and mutation = 0.3. Table 11 shows the evaluation of PRV-FCM with respect to MAE, MSE and RMSE. The very low values of MAE < 0.02, MSE < 0.0002 and RMSE < 0.015 of the prescriptive model generated with PRV-FCM demonstrate the ability of the model to generate recommendations that decrease the risk of diabetes. Like the wine quality dataset, the diabetes dataset has not been used in the literature to generate prescriptive models that generate recommendations or prescriptions to reduce the risk of diabetes.

6.8. Student performance dataset

6.8.1. Predictive model

To test the inference process, we generated an FCM using PSO and the training set from the previous dataset. Then, the FCM is tested in the testing set. Table 10 shows the results of the evaluation in the testing set, including the optimal hyperparameters. The FCM model can predict student academic performance with an accuracy of 85%. The performance of our predictive model was good and outperforms the results reported in the literature. Two studies reported by Amrieh et al. (2016, 2015) used this dataset to predict academic performance. The best performance of all experiments performed in the two studies was 80% accuracy using ANNs. Another work applied in the educational field was developed by Tan et al. (2014), who implemented a hybrid prediction approach composed of ANNs and structural equations to create a framework that identifies the factors that influence the adoption of mobile learning based on the technology acceptance model and psychological constructs. The results of applying the approach to academic datasets show that

the technology acceptance model, social influence variables and academic qualifications significantly influence the intention to adopt mobile learning. According to these results, our model is superior because it better represents the functional dependencies between the predictor variables and student academic performance. Additionally, our model can be used to evaluate the behavior of student-performance-related variables in different scenarios.

6.8.2. Prescriptive model

In the student academic performance dataset, there were action concepts per se, such as C_9, C_{10}, C_{11} and C_{12} (see Table 9). These variables are behavioral, and the decision-maker decides if execute them or not. In other words, they are the actual actions that the student can take to achieve the desired result, in this case, to improve academic performance. The algorithm finds the optimal values of these prescriptive concepts that achieve a desired result in the system concepts. To find out these values, the PRV-FCM used a GA with the next configuration: population = 200, number of generations = 50, crossover = 0.2 and mutation = 0.3. Table 11 shows the evaluation of PRV-FCM with respect to MAE, MSE and RMSE. The results showed that the model generated with PRV-FCM generates prescriptions with very low error rates (MAE < 0.04, MSE < 0.0023 and RMSE < 0.048), which demonstrates that PRV-FCM is a useful methodology for the generation of prescriptions in the educational field.

Table 10

Performance and optimal hyperparameters of predictive models generated by classical FCMs for each dataset.

Case study	**Hyperparameters**			**Accuracy (%)**
	Activation function	**Slope**	**Inference function**	
Synthetic	Sigmoid	1	Modified Kosko	96.67
Wine	Sigmoid	10	Modified Kosko	70.62
Diabetes	Sigmoid	1	Modified Kosko	69.86
Student academic performance	Sigmoid	10	Modified Kosko	84.91

Table 11

Performance of prescriptive models developed with PRV-FCM. NA = not applicable.

Case study	FCM concept	Variable name	MAE	MSE	RMSE
Synthetic	C2	NA	0.01146	0.00024	0.01559
	C9	NA	0.01341	0.00035	0.01872
Wine	C6	Free sulfur dioxide	0.01761	0.00066	0.02583
	C8	Density	0.01991	0.00069	0.02644
Diabetes	C2	Plasma glucose concentration a 2 hours in an oral glucose tolerance test	0.01112	0.00020	0.01429
	C3	Diastolic blood pressure	0.00743	0.00010	0.01000
Student academic performance	C9	Raised hands	0.02674	0.00120	0.03466
	C10	Visited resources	0.03358	0.00188	0.04337
	C11	Viewing announcements	0.03560	0.00222	0.04717
	C12	Discussion groups	0.00999	0.00018	0.01349

6.9. Comparison of means

We performed a mean comparison test between the values of the variables in the dataset and the values of the variables prescribed by our approach. This is another way to test if our approach can generate prescriptive models with excellent performance because this comparison uses a hypothesis test to determine significant differences between two sets of data. Before comparing means, we tested the normality of the data using the Lilliefors test (Lilliefors, 1967). We used Student's t-test and Wilcoxon signed-rank test to compare the means between the two groups. The student's t-test was used when the two groups to be compared followed a normal distribution, while the Wilcoxon test was used when at least one comparison group did not follow a normal distribution. These tests use the following hypothesis to test:

- $H_0 : \bar{X}_{actual} = \bar{X}_{prescribed}$
- $H_1 : \bar{X}_{actual} \neq \bar{X}_{prescribed}$

Where H_0 is the null hypothesis stating that there are no significant differences between the prescriptive values of the dataset and the prescriptive values generated by our PRV-FCM approach. H_1 is the alternative hypothesis that states that there are significant differences between the pre-

scriptive values of the dataset and the prescriptive values generated by our PRV-FCM approach. A significance value of 0.05 was established. If $p < 0.05$, the null hypothesis is rejected.

The results of this test are shown in Table 12. For all prescriptive variables in all case studies, $p > 0.05$ were found, indicating that there are no significant differences between the prescriptive values in the dataset with the prescriptive values generated with our approach. The p-value indicates the probability that the prescriptive values could have occurred under the previously defined null hypothesis (H_0). The higher the p-value, the closer the values prescribed by PRV-FCM are to the values included in the dataset. With respect to this comparison, the best performance was for the prescriptive models generated for diabetes and student academic performance case studies, which yielded p-values above 0.934 for all prescriptive variables. This result is possible because variables in these two datasets follow a normal distribution. For this reason, the parametric Student's t-test was used. It has been shown that this type of parametric test has greater statistical power than non-parametric tests such as the Wilcoxon test (Amandeep and Robin, 2015; Grech and Calleja, 2018). With respect to the variables C2 and C9 of the synthetic dataset and C8 for the wine dataset, they did not follow a normal distribution, a test with statistical power lower was used; therefore, the p-value is lower because a higher variability of the data influences the comparison test. Despite of these results, we can confirm the excellent performance of our approach to generate prescriptive models. To ensure full transparency of the results obtained with our approach, the synthetic data, those used for statistical comparison and the architecture of the FCM models are available in (Hoyos, 2023). Links to the datasets of the other case studies are cited in Section 5.

In summary, the prescriptive models generated with PRV-FCM in all case studies presented excellent performance with very low error rates and without significant differences between the actual and prescribed values. This demonstrates the general capacity of our approach for generating prescriptive models with excellent performance in any domain. A broader discussion of the results obtained with respect to prescriptive models is made in the next section.

7. Discussion

In this paper, we propose a methodology to generate prescriptive models. The main objective of this type of model is to find ideal actions that lead to the desired outcome. To test our approach,

Table 12

Mean comparisons between the values in the dataset and prescribed values using PRV-FCM. NA = not applicable († indicates the Wilcoxon test was performed because the corresponding variable did not follow a normal distribution, ⋆ indicates the Student's t-test was performed because the corresponding variable follows a normal distribution).

Case study	Prescriptive concept	Variable name	Mean±SD		p
			Actual	Prescribed	
Synthetic	C2	NA	0.448±0.305	0.432±0.315	0.844†
	C9	NA	0.523±0.313	0.500±0.317	0.776†
Wine	C6	Free sulfur dioxide	0.216±0.128	0.216±0.127	0.966⋆
	C8	Density	0.522±0.101	0.528±0.101	0.672†
Diabetes	C2	Plasma glucose concentration a 2 hours in an oral glucose tolerance test	0.547±0.130	0.547±0.129	0.973⋆
	C3	Diastolic blood pressure	0.557±0.172	0.558±0.169	0.970⋆
Student academic performance	C9	Raised hands	0.568±0.250	0.570±0.247	0.961⋆
	C10	Visited resources	0.697±0.263	0.694±0.257	0.934⋆
	C11	Viewing announcements	0.449±0.239	0.449±0.250	0.999⋆
	C12	Discussion groups	0.462 + 0.256	0.462±0.257	0.987⋆

we use four case studies in different domains. The results shown in the previous section demonstrate the capabilities of our approach to generate prescriptive models with excellent performance. In this section, we first analyze the results of the prescriptive models developed. Subsequently, we made a quantitative comparison with papers that used the same datasets that we used in the present study. Then, in the qualitative comparison, we focused on comparing computational intelligence models that had a similar architecture to the ones we used to develop our approach. In this case, we specifically refer to FCM and GAs.

7.1. Analysis of results of the prescriptive models

The generation of prescriptive models is increasing; however, the availability of data with prescriptive variables or actions is low. Therefore, in two case studies (wine and diabetes), we assumed some system variables to be "prescriptive". In those cases, the generated "prescriptive" model would behave as a recommender, let's see why. Fig. 6 represents the difference between actions variables and system variables defined as prescriptives:

- A variable is *prescriptive* when it is considered an action within the system (see side A in

Fig. 6). That is, this variable acts on the other concepts in the system, but there is no variable acting on it. For example, if we have a patient with a febrile illness, then the symptom *fever* is the system concept, while taking paracetamol is considered the prescriptive variable that will decrease the fever. Additionally, there is no variable within the logic that acts on the paracetamol.

- On the other hand, we have system variables that can be modified, but by actions that are not within the initial system or dataset. In these cases, the variable can behave as prescriptive, and a system could recommend modifications on this variable but not the action to modify it (see side B in Fig. 6). For example, *body temperature* is a system variable that can be used as a prescriptive variable. In this case, A prescriptive system might recommend raising or lowering the temperature, but does not specify the action to change the *body temperature* values.

It is crucial to keep this aspect in mind to explain the results of each case study.

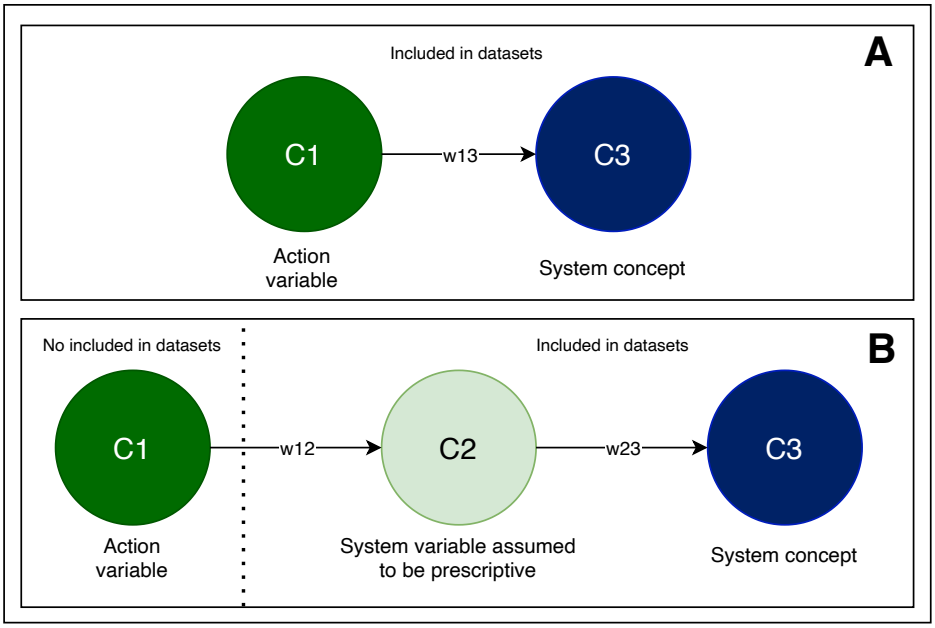

Fig. 6. Difference between using a system variable as "prescriptive" **(A)** and action or prescriptive variable **(B)**. In case A, a system concept is used as a prescriptive, but this concept is not an action. In case B, the system has action variables or prescriptive variables per se.

For the synthetic case study, prescriptive variables were assumed, due to the lack of context within the dataset. We assumed variables C_2 and C_9 because they were variables that did not have the influence of other variables in the FCM. These variables are considered actions or prescriptive because the decision-maker uses them to generate the desired outcome in the simulated system. According to the results of the prescriptive model, with our approach, it is possible to find the optimal values of decision-driven actions to obtain desired results with excellent performance (see Table 11).

Wine quality is a characteristic of wine obtained through the process where experts assign a quality score to different types of wine with different physicochemical characteristics (Cortez et al., 2009) (see Table 6). According to the prescriptive model, we identified prescriptive variables such as sulfur dioxide free and density. It is important to remember that these variables (sulfur dioxide and density) are not actions per se. They are system variables that we assign them the role of prescriptive to test our approach due to the lack of datasets with actions or prescriptions. For this particular case, what the prescriptive model does is to recommend what should be done with these two variables. For example, if the decision-maker wants to improve the quality of the wine, the model, in this case, will recommend that he/she adjusts the density values, but it will not specifically give him/her the action to change the density values to improve the quality of the wine. The decision-maker will be able to modify the wine density using different actions that were not initially included in the system, as they were not present in the dataset.

Diabetes is a disease that has high morbidity rates due to its associated complications. Our third case study consisted of generating both a predictive model to classify patients and a prescriptive model to recommend values for blood glucose concentrations and diastolic blood pressure. Similar to the previous case study, we assumed these variables as prescriptive, due to the lack of datasets with actions aimed at treating the disease. The performance of the model in prescribing is very outstanding, with very low errors when comparing what was prescribed with what was stored in the dataset (see Table 11). Our approach allows generating prescriptive models with high performance, even if the variables being prescribed are not prescriptive or actions themselves (in these last two cases, recommendations).

Student academic performance is a fundamental aspect in education and different strategies

Table 13

Behavior of prescriptive models generated with PRV-FCM according to types of prescriptive variables in the case studies' datasets.

Case study	Prescriptive	Recommender
Synthetic	✓	✓
Wine	✗	✓
Diabetes	✗	✓
Student academic performance	✓	✓

have been developed to maximize it in schools and universities. Unlike the case studies on wine and diabetes, in this dataset, there are prescriptive variables or actions (see Table 13), i.e., the decision-maker (in this case, the student) performs them directly to obtain the desired results. For this case study, it was not necessary to assume system variables as prescriptive because they are behavioral variables collected in the dataset. Clear examples are the variables *raised hands* and *Visited Resources* that correspond to the number of times the student raises his/her hand and the number of times he/she visits the academic resources available on the online education platform, respectively.

Thus, of the real datasets used in this work, only the student academic performance dataset has been used for prescriptive modeling. Harikumar et al. (2022) proposed an approach for prescriptive models. They used two classifiers (logistic regression and SVMs) and the student academic performance dataset, to demonstrate the applicability of their approach. The action variables selected by Harikumar et al. corresponded to the same variables that we selected to test our approach (see Table 9). For a quantitative comparison, we calculated the PSR defined in Eq. 19. Harikumar et al reported a PSR of 66% with logistic regression and 98% with SVMs. The PSR of our approach was 96%, a higher value than the logistic regression and a slightly lower than SVMs reported by Harikumar et al.

Although our approach was slightly inferior to the approach developed with SVMs by Harikumar et al., our approach has two advantages over this work: 1) usability: our approach proved to be excellent for prescribing in different fields or domains; Harikumar's approach is limited to preserving data privacy. 2) interpretability: our approach uses FCMs, which are interpretable and

allow knowing the behavior of the variables over time (iterations); Harikumar et al's work used SVMs, known as a black box technique where it is difficult to know the behavior of the variables involved in the prescription.

7.2. Qualitative comparison with previous works

In this section, we compare our approach with previous work using qualitative criteria. Table 14 shows the criteria used and the evaluation.

He et al. He (2008) implemented a decision-oriented immune algorithm with FCMs. The results showed its capability for goal-oriented decision-making; however, there was no validation of the approach using synthetic or real data sets. In addition, the case study used does not allow for the real prescription because there were no prescriptive variables or actions per se. Thus, the model developed by He yue et al. is a recommender system that recommends what to do, but not how to do it.

Dey et al. (2019) implemented evolutionary and ML techniques such as GA and ANNs to recommend actions. The approach proposed by Dey et al. used a desirability function to improve the quality of steel in the industry, with the ability to recommend the properties that steel should have to be of the desired quality. Thus, the model recommends the properties but not the actions that lead to those properties. An advantage of this model is that it does not need a prior predictive model to recommend the desired characteristics.

Hoyos et al. (2022) implemented data analysis tasks to prescribe dengue treatment. The authors used a GA to find the optimal values of disease treatment options as reported by WHO. The prescriptive model developed had the ability to prescribe actions that reduce the severity of dengue. The only disadvantage of this model is the dependence on the output of a previous predictive model. The prescriptive model uses as input the outcome of the dengue severity prediction, and based on that outcome, it prescribes the best possible actions that minimize the severity of the disease.

Chalmers et al. (2015) proposed a prescriptive analysis approach to identify optimal orthotic corrections for adolescent idiopathic scoliosis. The authors implemented fuzzy logic to predict whether changes in bracing would improve or worsen the patient's deformity. This study was able

to obtain good results to recommend actions to reduce the progression of the disease. The disadvantage of this study is the dependence on a previous predictive model. The prescriptive model developed needs to know the outcome of the prediction to generate an appropriate prescription. Another disadvantage of this model is its application. The model recommends adjusting variables to obtain the desired outcome but does not prescribe the action itself.

In summary, we propose a prescriptive approach using FCMs and metaheuristic algorithms, called PRV-FCM. The prescriptive and recommender capability of our approach has been validated on synthetic and real datasets. PRV-FCM has the ability to either recommend, prescribe, or perform both tasks with high performance. Regarding this last aspect, overfitting is one of the concerns that arise when models have excellent performance. Overfitting is a problem characterized by the inability of the model to generalize on unseen data. In our case, we use data partitioning into training and validation (70%) and testing (30%) to reduce overfitting. The random selection of subsets in the 10-run cross-validation process reduces the overfitting, considering that, if the solution performs consistently on several subsets of the population, its performance is likely to be consistent on unseen data. The results shown in this paper are the product of the application of the models on previously unseen data.

The convergence of the proposed algorithm is not affected by the metaheuristic because it uses the values of the final state of the FCM, which is a numerical vector and represents the stability of the system after successive multiplications with the weight matrix. Particularly, although our algorithm uses the combination of the metaheuristic algorithm and the FCM inference process, these processes are not combined within the learning process. The result of the inference process is a final numerical vector, which is used as the fitness function, while the metaheuristic searches the prescriptive values in the search space.

Finally, PRV-FCM only requires instantiating an FCM to obtain optimal prescriptions. Finally, our approach is intuitive because it is only necessary to define the variables involved in the system; it is extensible and easily adaptable to any domain in which it can be used.

Table 14

Results of qualitative comparison among our work and previous prescriptive approaches.

Qualitative criteria	Work				
	He (2008)	Dey et al. (2019)	Hoyos et al. (2022)	Chalmers et al. (2015)	Our work
Prescriptive capability	✗	✗	✓	✗	✓
Recommender capability	✓	✓	✓	✓	✓
Validated on datasets	✗	✓	✗	✓	✓
Intuitive, extensible and easily adaptable	✓	✓	✓	✓	✓

8. Conclusions

In this paper, we proposed a methodology to generate prescriptive models using FCMs and metaheuristic algorithms. First, we define a discriminated FCM with system concepts and action concepts. Subsequently, we implemented a GA to find the optimal values of action variables that lead to the desired outcome of the system variables using FCM inference. The results showed the ability of our approach to be used in different fields. We tested it on several datasets, one synthetic and others in the fields of business, health and education, with excellent performance.

The main goal of the proposed methodological framework was not to improve the performance of current FCM approaches but to introduce a useful methodology for the generation of prescriptive models. The particularity of our approach is the ability to recommend or prescribe actions, its good behavior with scarce datasets, and finally, its ease of use and adaptability to any area of knowledge.

This work has some limitations, such as: i) the use of experts at the beginning of the methodological framework to select the variables of interest, both system and action variables. Furthermore, in datasets where no action variables are stored, the human must select which system variables behave as prescriptive to generate the prescriptive models. ii) Other metaheuristic algorithms were not used to optimize the action concepts.

Future work should be aimed at using other metaheuristic techniques to improve the optimization process of our approach. In addition, automate the process so that the algorithm automatically selects prescriptive variables, for example, detecting those variables of interest that have no influence of other variables on them, differentiating them from variables that can be modified within the logic of the system. Also, testing other optimization algorithms or experts to build the FCMs could

improve the performance of the developed models. Finally, a two-stage learning (first with the system concepts and then with the action concepts) could be useful to generate better-performing prescriptive models.

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CRediT authorship contribution statement

William Hoyos: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Validation, Visualization & Writing – original draft. **Jose Aguilar:** Conceptualization, Methodology, Formal analysis, Validation, Supervision, Writing – reviewing & editing. **Mauricio Toro:** Conceptualization, Resources, Supervision, Writing – reviewing & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix F

Federated learning approaches for FCMs to support clinical decision-making in dengue

Federated learning approaches for fuzzy cognitive maps to support clinical decision-making in dengue

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Abstract

Federated learning is a distributed machine learning approach developed to guarantee the privacy and security of data stored on local devices. In healthcare, specifically in diseases of public health interest such as dengue, it is necessary to develop strategies that guarantee such data properties. Therefore, the aim of this work was to develop three federated learning approaches for fuzzy cognitive maps for the prediction of mortality and the prescription of treatment of severe dengue. The validation of the approaches was performed on severe dengue datasets from two dengue endemic regions in Colombia. According to the results, the use of federated learning significantly improves the performance of models developed in centralized environments. Additionally, the use of federated learning allows guaranteeing the privacy and security of each client's data due to the local training of the models. Federated learning is a useful tool in healthcare because it guarantees the privacy and security of patient data. Our results demonstrated the ability of aggregated models to predict mortality and prescribe treatment for severe dengue.

Keywords: Fuzzy cognitive maps, Federated learning, Clinical decision-making, Predictive modeling, Prescriptive modeling

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1. Introduction

Dengue is a febrile disease caused by a virus of the *Flaviviridae* family, and is transmitted by the bite of female *Aedes* mosquitoes [1]. It causes a clinical picture ranging from asymptomatic processes to severe disease; with a wide spectrum of clinical manifestations such as fever, headache, retro-ocular pain to severe signs such as shock, severe bleeding, multi-organ failure and death [2]. Based on severity, World Health Organization (WHO) categorized the disease into three: i) dengue without alarm signs, ii) dengue with alarm signs, and iii) severe dengue (SD), which includes dengue shock syndrome [3]. The latter category is an important cause of mortality and has reached a rate of 44% [4]. Dengue infection has spread globally, being endemic in more than 120 countries worldwide, mainly in Africa, Western Pacific, Southeast Asia and the Americas, generating a high epidemiological, economic and social impact [5]. According to the WHO, more than 3.8 billion people are at risk of infection and approximately 100 to 400 million infections occur annually worldwide, with approximately 25% of them showing some type of symptom [6].

Diagnosis and treatment of dengue are the main components of the clinical management of the disease. Diagnosis is made by interpreting signs and symptoms to classify the patient according to the severity of the clinical picture, which can be challenging for health personnel due to the variability of clinical manifestations present in infected patients. Additionally, dengue presents similar clinical manifestations to other febrile diseases such as Zika, chikungunya and leptospirosis, with which a differential diagnosis should be made [7]. On the other hand, laboratory tests such as detection of dengue antigens, antibodies against the virus and viral isolates, allow confirmation of the disease, but may cause delays in areas that do not have all the health services [8]. There is currently no specific antiretroviral treatment for dengue available in developing countries. Therefore, available treatment focuses on alleviating signs and symptoms and avoiding complications leading to death, and clinical management of dengue remains a challenge for health professionals [9].

One way to address the problem of clinical management is through the development of computer-aided approaches that use predictive modeling for diagnosis and prescriptive modeling for treatment. The development of such methods can support medical decision-making in relation to the course of disease, which could have an impact on reducing mortality rates due to timely classifi-

cation and appropriate treatment [10].

The validation of models, approaches and methodologies for the diagnosis and treatment of dengue is quite widespread. However, the works reported in the literature present some limitations. First, the published studies focus on developing complex models that are not very understandable for the medical professional, who is interested in knowing how the model classifies patients according to their severity. Moreover, they maximize predictive performance by compromising the interpretability of predictor variables in different situations or scenarios. Second, there are few studies focused on the clinical management of dengue in a comprehensive manner. Most of the studies only emphasize one of the two components: diagnosis or treatment; however, it is crucial to integrate both processes to optimize medical decision-making aimed at improving health care. Third, the reported works use the traditional machine learning (ML) approach, which gathers dengue data in one place for training. This may raise issues with respect to the privacy and security of the data used. Transporting and sending the data from one place to another can cause loss, damage and violate laws related to personal data protection.

Therefore, it would be of great clinical utility to generate decision support approaches for the diagnosis and treatment of dengue that provide understandable and explainable results for clinicians. It would also be of clinical interest to develop systems that, in addition to predicting an outcome, also allow treatment to be prescribed according to the specific patient scenario. Finally, the use of distributed learning approaches such as federated learning that guarantee data security and privacy would be a great added value.

In this sense, the main contributions of our work are the definition of three approaches as medical support tools for the diagnosis and treatment of dengue, specifically SD. These approaches are characterized by using federated learning with fuzzy cognitive maps (FCMs) and optimization algorithms for the generation of predictive and prescriptive models. The first approach implemented is based on the similarity of the feature space among the participating clients or sites where the signs and treatment options of SD are identical. The second is based on the objective, where the only feature in common among all clients or parties is a decision variable (for our application domain, it was SD mortality). Each client or party has different characteristics related to mortality and treatment of SD. Finally, the third approach uses parameter learning transfer to send informa-

tion from one site/party to another. Specifically, the implemented approach transmits the learned parameters from SD treatment to mortality prediction. The novelties proposed in the present study are focused on several aspects: i) the generation of federated learning approaches with a different architecture (approaches 1 and 2) from that reported in the literature; ii) the application domain, since to date there are no reports on the implementation of federated learning with FCMs for the diagnosis and treatment of dengue; iii) the combination of predictive and prescriptive models in a single architecture that allows integrated support for decision-making with respect to the diagnosis and treatment of dengue.

This paper is organized as follows: Section 2 shows the related works about the last trends in FCMs for prediction and prescription. Also, it presents the main studies about federated learning for medical environments. Section 3 describes the methodology used to develop the federated learning approaches, and Section 4 describes the experiments to validate them. Section 5 shows the results for each approach and discusses them. Finally, Section 6 concludes the paper.

2. Related work

In this section, we present the main works related to the use of FCMs for prediction and prescription. Additionally, we present the main studies about federated learning for healthcare.

2.1. FCMs

FCMs are computational intelligence algorithms that allow modeling complex systems using concepts and relationships between them [11]. In the following, we present a literature review on the implementation of this type of algorithm for prediction and prescription.

2.1.1. FCMs for prediction

FCMs use inference functions to make predictions based on the interconnection among the concepts [12]. The development of clinical decision support systems for prediction with FCMs has increased in recent years due to the simplicity of construction and ease of interpretation of results. In previous work, we developed a clinical decision support system for dengue diagnosis based on FCMs [13]. We used the knowledge and experience of clinical experts in dengue to

construct the FCM with signs, symptoms, and laboratory test results. The constructed FCM model had the ability to classify dengue severity (dengue with and without warning signs, and SD) with 89% accuracy and the additional ability to assess the behavior of severity-related variables. In addition, we developed another previous work with SD prediction models using FCMs trained with the particle swarm optimization algorithm [14]. The models were trained using historical data from two endemic cities in Colombia and their peak performance reached 74% accuracy due to small sample sizes.

FCMs have also been widely used for predicting the risk of outbreaks or epidemics of viral diseases such as dengue [15, 16]. For example, Pelaez [15] proposed a model based on FCMs to predict the risk of presenting tropical viral diseases such as dengue. The authors trained FCMs with unsupervised learning to represent causal relationships and knowledge related to environmental conditions, symptoms, and historical data related to tropical viral diseases. The historical data for training the FCMs corresponded to seasonal outbreaks and epidemics in Ecuador. The proposed model had the potential to improve the chances of early forecasting of seasonal diseases related to tropical regions. Jayashree et al [16] used FCMs using expert knowledge to build a system that classified the risk of dengue outbreak in tropical regions of Southern India. The results showed that the performance of FCM was superior when compared to other techniques such as Bayesian classifier, decision tree, support vector machines, and multilayer perceptron. The classification of risk into low, moderate and high allows health authorities to establish prevention strategies in the regions to prevent the spread of the disease.

2.1.2. FCMs for prescription

FCMs have now started to be used to prescribe actions leading to desired outcomes in complex modeled systems. Reported work in the literature using FCMs to support decision-making related to dengue treatment is scarce. However, they have been used for the treatment of other diseases such as urinary tract infections and cancer. Papageorgiou [17] developed a computational tool based on FCMs for treatment management of urinary tract infections. The results of the evaluation of the software on a small sample of diseased patients demonstrated its capability for classification and recommendation of suggested treatments.

For cancer treatment, several studies have been performed for treatment management using radiotherapy [18, 19]. Papageorgiou [18] used FCMs for computational modeling of the complexity of the clinical radiation procedure to calculate the final dose that should be administered in cancer patients. The model was built with a combination of expert knowledge and fuzzy rule extraction from the data. The system was able to handle uncertainty, is simple, and is less complex than other previously reported models. Papageorgiou and Stylios [19] determined the success of the radiation therapy process by implementing FCMs as a modeling technique. The proposed system had a hierarchical structure to simulate and evaluate the radiation therapy process. The developed model was evaluated in point scenarios to demonstrate its performance with prior determination of treatment variables by the medical professional.

According to our literature review, only one work has used FCMs for dengue treatment prescription. Hoyos et al [14] developed an extension of FCMs with optimization algorithms for the generation of prescriptive models. The proposed algorithm uses a genetic algorithm to optimize prescriptive variables leading to desired system values. The methodology was tested in the treatment of SD. The evaluation of the generated model showed a good performance yielding accuracies between 81% and 100% accuracy for recommending treatment options for SD, which constitutes an excellent tool to support decision-making for the treatment of SD and reduce mortality rates.

2.2. Federated learning in medical environments

Federated learning is a distributed ML approach developed by Google [20]. This approach allows training models with distributed data anywhere in the world, such that local models are trained with their data and its parameters are shared in a federated server to build a global model. The main feature of this approach is that the data never leave their original location. This type of methodology is useful to attack the problem of guaranteeing data security and privacy, mainly, in clinical environments [21]. Federated learning in recent years has attracted the attention of the scientific community due to its interesting ability to generate global models avoiding data sharing between involved parties [22]. This distributed ML approach has been widely used in healthcare due to the security and privacy of data in this domain. Additionally, this approach can be used to

transfer learning from one healthcare institution to another [23].

Several surveys and literature reviews have provided comprehensive reviews of the work reported in the literature on architectures, approaches, use, and application of federated learning for healthcare [24–27]. For example, Antunes et al [24] present a systematic literature review where they discuss the main problems of federated learning, possible solutions and the most frequently used ML methods. Additionally, they propose an architecture based on the results of the systematic review. A survey by Nguyen et al [25] presents the main advances and requirements for a correct implementation of federated learning with the internet of medical things. The authors review several current researches and analyze different aspects such as medical imaging, remote health monitoring and data management. Prayitno et al [26] provide a systematic review of current advances in federated learning for healthcare applications with a data-centric perspective. The review evaluates the use of reference datasets, data protection strategies, data partitioning and distribution properties. Finally, Xu et al [27] conducted a survey presenting a general review on federated learning, specifically, issues related to data privacy, system challenges, and possible solutions to statistical challenges in implementing federated learning in medical environments.

According to our literature review, there are no papers that have implemented federated learning for dengue analysis. However, different works on federated learning have been reported for other events of interest in public health. This type of work can be classified into two main groups based on the types of data used: i) federated training for unstructured data, mainly the use of biomedical images; and ii) federated training for structured data. In the following, we will show some relevant works developed in each group.

2.2.1. Federated learning for unstructured data

Unstructured data are those that do not have a defined structure. Within this group, we find images, text and audio. In clinical environments, the most commonly used data type to implement federated learning approaches are medical images such as X-ray images, CT scans, nuclear magnetic resonance and histopathological images. Thus, several works have been developed to detect COVID from chest X-ray images [28], brain tumor detection [29], and histopathological image analysis [30]. Feki et al [28] proposed a federated collaborative learning approach with deep

learning for COVID-19 screening in several healthcare institutions without sharing data among them. The authors used two pre-trained convolutional neural network architectures, VGG16 and ResNet50. The accuracy of the models in the federated approach was similar for both VGG16 and ResNet50 when compared to the centralized approach. Sheller et al [29] compared a federated learning approach with collaborative data sharing learning. The study was conducted across several institutions storing brain tumor images. The models developed with federated learning were able to achieve superior performance to the data sharing approach with the additional value of ensuring privacy and confidentiality of the data used. Adnan et al [30] proposed a differentially private federated learning approach for medical image analysis, specifically, histopathological images across multiple healthcare institutions. Although models with federated learning performed well, learning with centralized data obtained better accuracy values.

2.2.2. Federated learning for structured data

Structured data are those composed of data frames where the columns correspond to patient variables or characteristics and the rows represent the records of each patient. This type of data has been widely used in building federated learning approaches and models [31–35]. For example, Brisimi et al [31] developed an algorithm to generate federated predictive models with sparse Support Vector Machine to predict hospitalizations due to cardiac diseases. The results showed the ability of federation to generate a global model with local models trained on several hospitals, however, the global model did not perform superior to the local models. Dang et al [32] implemented mortality prediction models in intensive care units of several hospitals in a federated environment using two aggregation algorithms (FedAvg and FedProx) and two training approaches (local and centralized). Of all the approaches implemented, FedProx performed the best, however, there was no significant difference between centralized training and federated training. Rahman et al [33] developed regression models in a federated environment to predict the length of hospital stay of patients in ten hospitals. The models were evaluated and the results showed that the performance of the models increases when the number of aggregated clients in the federated server increases. Kerkouche et al [34] proposed a federated learning approach that preserves data privacy for the prediction of in-hospital mortality. The authors found a relationship between model per-

formance and patient-level privacy. Increasing the level of privacy decreases prediction accuracy. Finally, Salmeron & Arevalo [35] developed an approach based on FCMs for breast cancer diagnosis, and additionally, preserve data privacy. The development of this approach allowed obtaining performance of federated global models superior to the local models and the model trained with centralized data.

3. Methodology

In this section, we describe the general methodology of the present study. First, we show a global workflow where we schematically represent the activities performed in our research for the development of models under the federated approach and the traditional ML approach. Then, we present the techniques used to build the predictive models (data-driven PSO-FCM) and prescriptive models (PRV-FCM). Finally, we describe the federated learning approaches reported in the literature and the proposed approaches. Fig. 1 shows a schematic representing the workflow of this research. Initially, 80% of the data is used for training and validation of the models. We use 5-fold cross-validation to tune hyperparameters and select the best predictive and prescriptive models. The evaluation of these models was done with the remaining 20% of the data. Specifically, for the proposed federated approaches, predictive and prescriptive models are trained and tested on local datasets. The parameters of these models are aggregated to build a global model. For the traditional approach, the data were pooled to obtain a single dataset to perform training and testing on the corresponding data. At the end, we performed a comparison of all the predictive and prescriptive models obtained.

3.1. Data-driven PSO-FCM

Predictive models were generated using FCMs due to their simplicity of construction, and inference and interpretability skills. An FCM is a computational intelligence technique that simulates human reasoning with concepts and relationships [11, 36]. Concepts correspond to variables within a system and relationships are the influence between those concepts. An FCM can be represented by a matrix that shows the relationships among the concepts. For example, Eq. 1 shows a

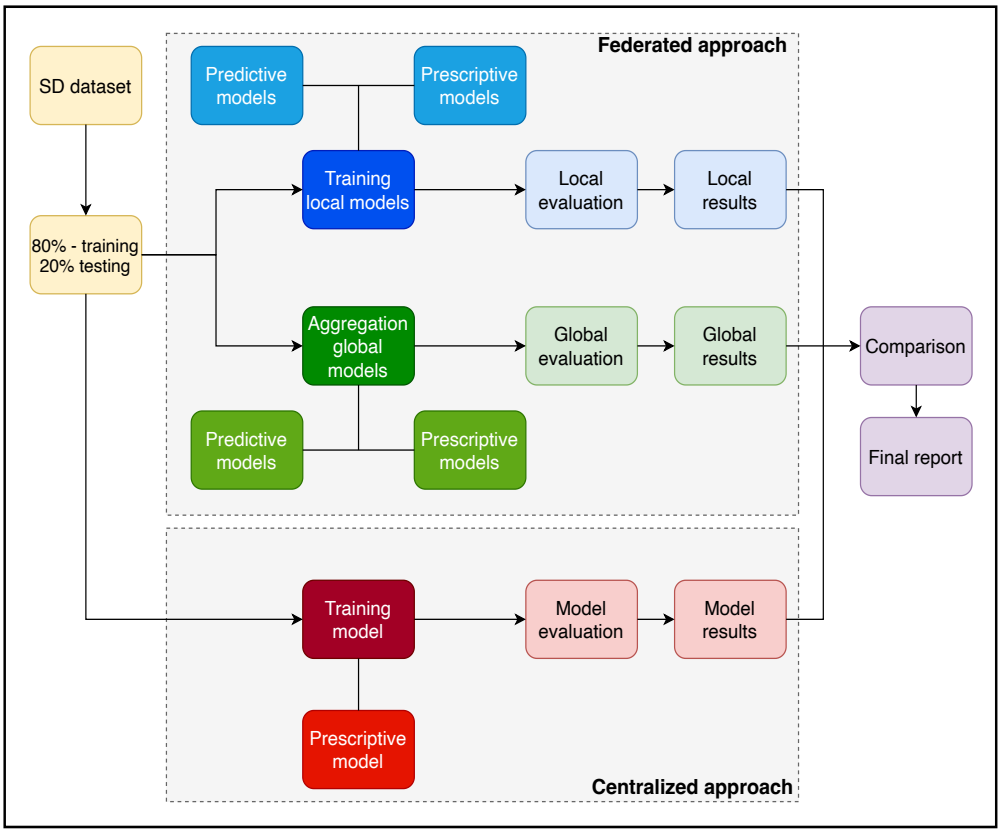

Fig. 1. Flowchart representing the main activities performed in this research.

matrix for five concepts and five relationships among them, represented by the values of w_{ij}. Fig. 2 shows a schematic representation of the FCM defined in the matrix of Eq. 1.

$$\mathbf{W} = \begin{array}{c} \\ C_1 \\ C_2 \\ C_3 \\ C_4 \\ C_5 \end{array} \begin{array}{c} \begin{array}{ccccc} C_1 & C_2 & C_3 & C_4 & C_5 \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & w_{15} \\ 0 & 0 & 0 & 0 & w_{25} \\ 0 & w_{32} & 0 & 0 & w_{35} \\ 0 & 0 & 0 & 0 & w_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array} \tag{1}$$

FCMs have been mainly used for description, prediction, and lately, they have been used for prescription. These three aspects are developed using inference rules that allow an initial state vector to reach a stable state. For the construction of the predictive models, we used the data-driven PSO-FCM technique. This technique uses the particle swarm optimization algorithm on

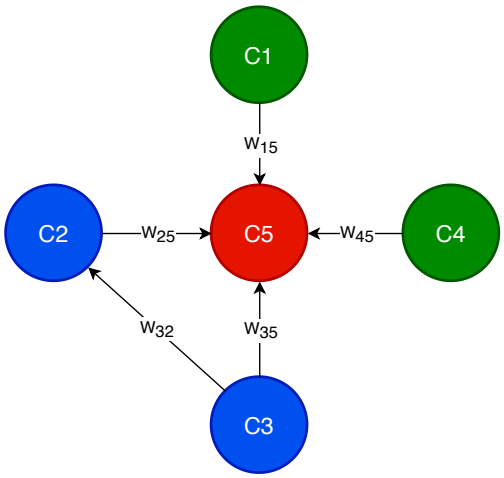

Fig. 2. Example of an FCM with five variables and five relationships.

datasets to find an FCM that describes relationships between the variables. The data-driven PSO-FCM algorithm is defined by:

$$v_i(t+1) = v_i(t) + s_1 r_1 \cdot (W_i^{best} - W_i(t)) + s_2 r_2 \cdot (W_i^{gbest} - W_i(t)) \tag{2}$$

$$W_i(t+1) = W_i(t) + v_i(t) \tag{3}$$

where v_i is the particle velocity; r_1 and r_2 are random values with uniform distribution; s_1 is the cognitive coefficient, responsible for the particle tending to move towards the position where it has obtained the best results so far; s_2 is the social component, also known as collective behavior, it is responsible for the particle tending to move towards the best position found by the swarm so far; W_i^{best} is the best position obtained by a specific particle, while W_i^{gbest} is the best position obtained by any particle in the swarm. For this case, each particle i is an FCM, while the position is a candidate matrix to build each FCM.

3.2. Prescriptive-FCM

The generation of prescriptive models was developed with the PRV-FCM methodology [37]. This methodology uses the inference process of FCMs and optimization algorithms to find optimal

values of prescriptive variables that lead to the desired results to the concepts of the system. PRV-FCM first characterizes variables depending on their nature into prescriptive or action variables and system variables. Prescriptive variables are actions that a decision maker can perform to solve a problem, while system variables are those related to the system to be modeled. After initializing the system with desired values, an optimization algorithm is used to find the values of the prescriptive variables that lead to the desired values to the system variables.

3.3. Federated learning

Federated learning is a distributed ML approach developed in 2017 [20]. Federated learning allows to collaboratively generate a shared ML model by keeping all training data at its place of origin or collection, decoupling the ability to do ML from the need to store the data in the cloud. Federated learning works like this: one party downloads the current model, improves it by learning from local data, and then summarizes the changes as a small update. Only this model update is sent to the cloud, via encrypted communication, where it is immediately averaged with updates from other parties to improve the shared model. All training data remains in its original location, and no individual updates are stored in the cloud.

To date, three main approaches have been developed, known as horizontal federated learning, vertical federated learning, and federated learning with transfer learning. Fig. 3 shows a schematic representation of each. A brief explanation of each follows.

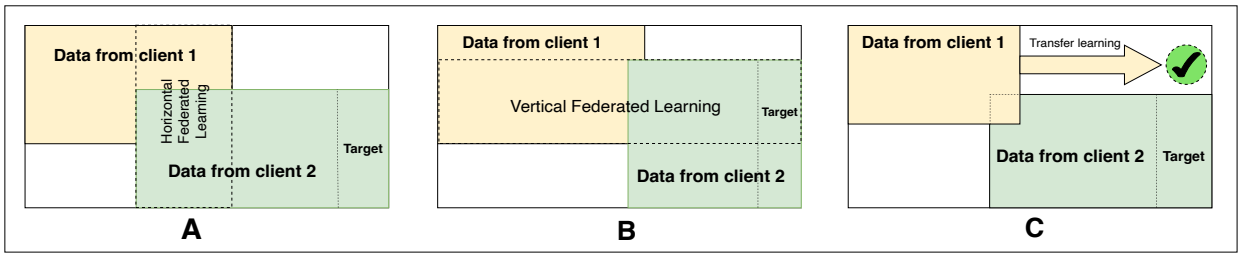

Fig. 3. Schematic representation of federated learning approaches reported in the literature. **A** y **B** represents horizontal and vertical federated learning, respectively, while **C** represents federated learning with transfer learning.

3.3.1. *Horizontal federated learning*

Scheme A in Fig. 3 shows horizontal federated learning. This type of federated learning is suitable in the case where the features/variables of the two datasets overlap a lot, but the records/data overlap little. Horizontal federated learning consists of splitting the datasets horizontally (by the dimension of the records), and then, extracting the part of the data where the features/variables are the same but the records are not exactly the same [38].

3.3.2. *Vertical federated learning*

Vertical federated learning is shown in Scheme B in Fig. 3. Vertical federated learning is suitable in the case where the features/variables of the two datasets overlap little, but the records/data overlap a lot. Vertical federated learning consists of splitting the datasets vertically (by the dimension of the features/variables), and then, extracting the part of the records that are the same, but the features or variables are not exactly the same [39].

3.3.3. *Federated transfer learning*

A representation of federated learning with transfer learning is shown in Scheme C in Fig. 3. In the case where the records and variables in the two datasets rarely overlap, the data is not segmented, but transfer learning is used to overcome the missing data or labels. In this approach, models are trained on one dataset and applied to another dataset from another related domain. [40].

3.4. *Our proposed approaches*

In this section, we describe each of our federated learning approaches. Fig. 4 shows schematic representations of each of the approaches.

3.4.1. *Total federated FCM*

Scheme A in Fig. 4 shows this approach. We call this approach *total federated learning* because all the variables in client 1 have the same characteristics/features as those in client 2. A clear example is all the signs, symptoms, laboratory tests and classification of dengue in different cities in Colombia.

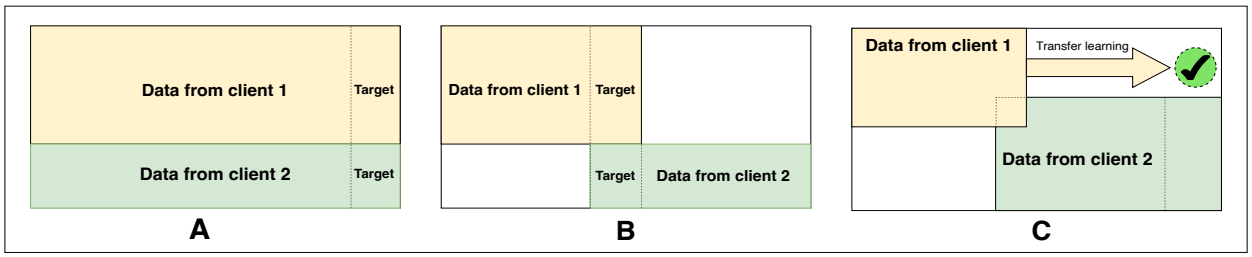

Fig. 4. Schematic representation of our federated learning approaches. **A** represents total federated learning; **B** represents target-based federated learning; and **C** represents federated learning with transfer learning.

For this case, the local models are trained by generating a weight matrix W_i^l, where i is the model number and l indicates that the model is local. Each local model sends the parameters to the server and this calculates an updated matrix by aggregating the information using the arithmetic average. Subsequently, the updated matrix W_{ij}^G is sent to each of the parties so that the updated model is used everywhere. The aggregation of the parts is performed with the average using the following equation:

$$W_{ij}^G = \frac{1}{n} \sum_{c=1}^{n} W_{ij}^c \tag{4}$$

Where W_{ij}^G is the global matrix aggregated with the two local model matrices, n is the number of clients used, and c is the client/site number.

3.5. Federated target-based FCM

In target-based federated learning, only one characteristic is common among the parties involved, and it corresponds to the target (see Scheme B in Fig. 4). This case is focused on predictive models. For example, one city has signs, another city symptoms, and finally, another city laboratory tests. In our problem, the only common variable is the label or target for the diagnosis or prediction of mortality due to SD. From that, a global model is constructed that includes all the variables from all the cities. Since in this case, there are no common concepts, simply the weights corresponding to the concepts of the different parts of the architecture are added. At the end, each city has a global model with all the characteristics to be used. The aggregation process is done

according to the following equation:

$$W^G = \begin{bmatrix} 0 & W_{ij} \\ W_{kl} & 0 \end{bmatrix} \tag{5}$$

Where W^G is the global matrix, W_{ij} is the local matrix of local model 1, and W_{kl} is the local matrix of local model 2.

3.6. Federated FCM with transfer learning

The federated FCM with learning transfer is useful for the development of prescriptive models. Scheme C in Fig. 4 shows the design of this approach. For this variant, the concepts are divided into system and action. In one part are the action concepts that act on the system concepts. For example, treatment concepts that influence signs or symptoms. In another part are the system concepts that influence the prediction. The aggregation process is done using Eq. 5. In that particular case, the predictive model of the second party is previously trained/built, and then, it is transferred for the second party to use to build the predictive model.

4. Experiments

In this section, we describe the experiments to validate the proposed approaches. First, we describe the datasets used. Then, we show the statistical validation process using 5-fold cross-validation. Subsequently, we present the evaluation metrics, and finally, we present a brief description of the experimental setup for the generation of local and global models in each proposed approach.

4.1. Datasets

For the validation of our approaches, we used two datasets from two dengue endemic regions in Colombia: Medellín and Córdoba. According to data from the National Institute of Health, this municipality and department are endemic because of the dengue incidence rates they show annually of 161-745 and 51-503 per 100,000 inhabitants for Medellín and Córdoba, respectively [41]. The selected datasets correspond to dengue mortality. Dataset 1 corresponds to the city of Medellín with 400 records collected between January 2008 and December 2019. Dataset 2

corresponds to the department of Córdoba and contained 398 records collected between January 2010 and December 2021. Table 1 shows the variables included in the datasets. The first variables define SD and were selected according to WHO guidelines for the diagnosis of this type of dengue. The variables related to SD and its mortality are: extravasation, shock, bleeding and organ failure. The variables related to the treatment of this type of dengue are: blood transfusion, crystalloid solutions, colloid solutions and access to intensive care units. Finally, the decision/target variable was mortality due to SD, where 0 means that the patient recovered while 1 indicates that the patient died. The preprocessing of these datasets is described in [42].

Table 1

Brief description of the variables included in the datasets used for the experiments.

Concept	Variable type	Variable name	Description
C1	Sign	Extravasation	It is characterized by serous spills at the level of various cavities.
C2	Sign	Shock	Manifestation of severity evidenced by cold skin, thready pulse, tachycardia and hypotension.
C3	Sign	Bleeding	Blood leaks from the arteries, veins or capillaries through which it circulates, especially when it is produced in very large quantities
C4	Sign	Organ failure	Affectation of several organs due to the extravasation of liquids.
C5	Prescriptive	Blood transfusion	Routine medical procedure in which the patient receives donated blood in a vein in the arm.
C6	Prescriptive	Crystalloid solutions	Solutions containing water, electrolytes and/or sugars in different proportions.
C7	Prescriptive	Colloid solutions	Solutions with high molecular weight particles capable of increasing plasma oncotic pressure and retaining water in the intravascular space.
C8	Prescriptive	ICU	Intensive care unit
C9	Target	Mortality	Dengue mortality

4.2. Statistical validation

Eighty percent of the data was used for training and validation. During this process, the hyperparameters were tuned to select the best model with 5-fold cross-validation. The best model was evaluated on the testing set corresponding to the remaining 20% of the data. The evaluation process on the test set was repeated 100 times to perform a mean or median comparison test to determine if there were significant differences between the performances of the developed models. Before performing the comparison test between models of the same approach, the distribution

of the data was determined using the Lilliefors test [43]. For this statistical test, we defined the following hypotheses:

- H_0: the data come from a normal distribution.
- H_1: the data do not come from a normal distribution.

According to the result of the Lilliefors test, we use Student's t-test because the data follows a normal distribution. The hypotheses for the comparison between two groups can be defined as follows:

- $H_0 : \bar{\mu}_{local} = \bar{\mu}_{global}$
- $H_1 : \bar{\mu}_{local} \neq \bar{\mu}_{global}$

In this way, it was possible to test the ability of the models to predict and prescribe on previously unseen data. Additionally, it was possible to test whether the difference in model performance was statistically significant. For all experiments, we defined the significance level at 0.05.

4.3. Evaluation of the models

We evaluated the models developed using classification metrics due to the categorical nature of the variables included in the datasets. In the following, we present the three metrics used with a brief description and their corresponding equation.

- *Accuracy:* percentage of correctly classified examples among the total number of classified examples.

$$Accuracy = \frac{TP + TN}{TP + FN + FP + TN} \tag{6}$$

  where TP are the true positives, TN are true negatives, FN are false negatives, and TN are true negatives.

- *Sensitivity*: it measures the ability of the classifier to predict positive cases to those actually positive.

$$Sensitivity: \frac{TP}{TP+FN} \tag{7}$$

- *Specificity*: it measures the ability of the classifier to predict negative cases to those actually negative.

$$Specificity: \frac{TN}{TN+FP} \tag{8}$$

4.4. Total federated FCM

Fig. 5 shows the architecture for this approach. In this first approach, the variables are exactly the same in all clients/sites. Here, we see that both the local models and the global model present the same variables (blue = concepts related to prediction, green = concepts related to prescription, red = target). In the following, we explain the local and global training of the models; as well as their evaluation.

4.4.1. Local training on clients

For this first case, the local training was carried out with all the variables related to the prescription to avoid mortality in patients with SD. The training was performed on each dataset of each client/site, separately. The training of the FCMs was carried out with the data-driven PSO-FCM technique, which has demonstrated its excellent performance for the optimization of matrices that generate FCMs. Subsequently, the prescriptive modeling technique PRV-FCM was used to find the optimal values of prescriptive variables. Each of these clients/sites shares the parameters, in this case, the weights matrix corresponding to the relationships between the modeled variables.

4.4.2. Global training on the federated server

After all the clients, in our case cities, train their models, the FCM construction parameters are shared to a global server, where a global model is created using the aggregation method defined in Eq. 4. One of the advantages of this approach is that the sample size of the training is increased because the patients in one client are different from those in the other clients. In this way, we increase the sample size for training. This global model is then sent to all clients, and the trained model is updated so that it can be used by each client.

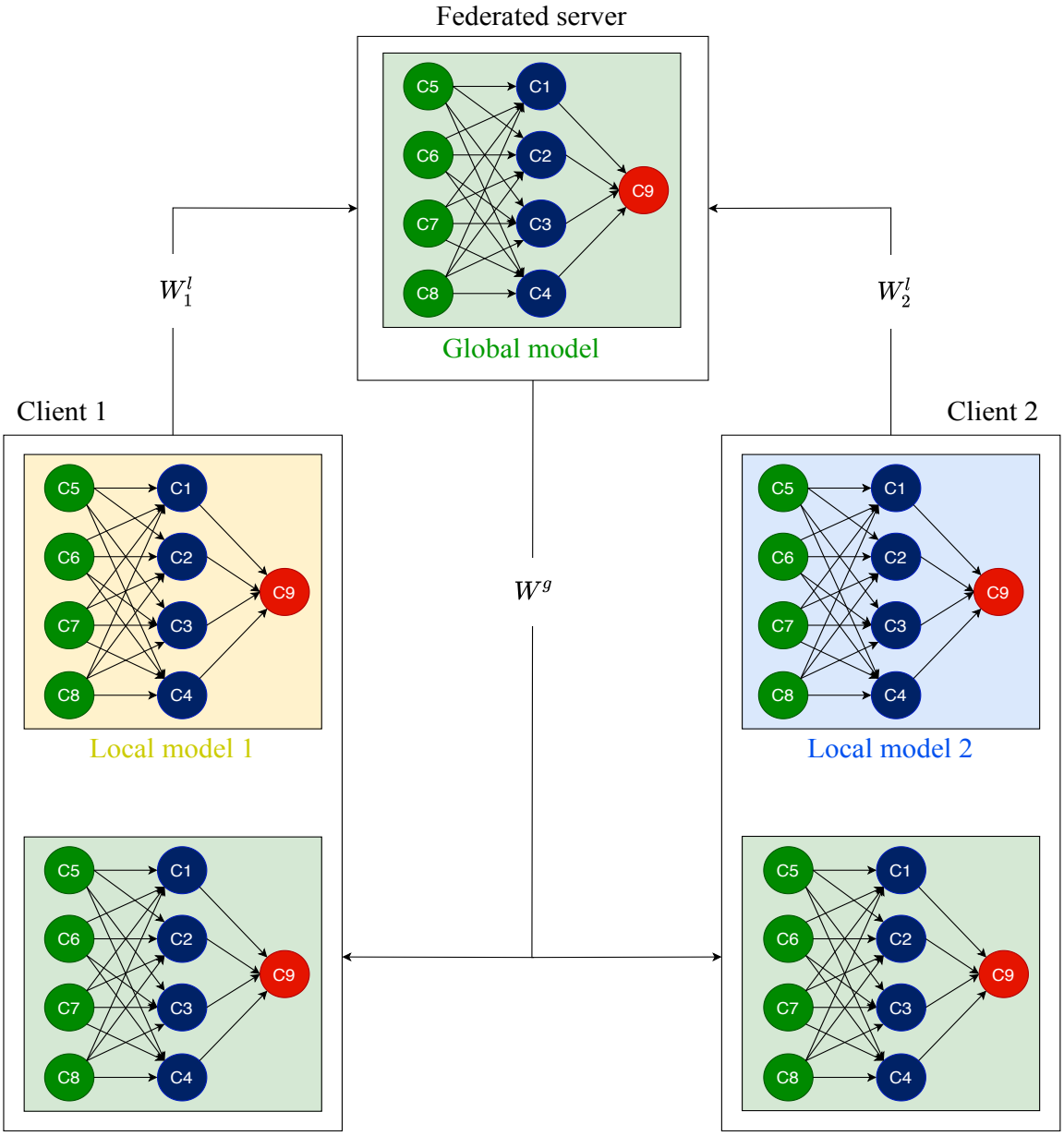

Fig. 5. Architecture of total federated FCM (the blue and green concepts are related to prediction and prescription, respectively. The red concept corresponds to the target).

4.5. *Federated FCM based on the target*

Fig. 6 shows the architecture for this approach. In this approach, only the target (this variable is represented in red color in Fig. 6) is common across all client data. In the following, we briefly explain the configuration of local and global training.

4.5.1. *Local training on clients*

In this case, the common variable is the prediction class or target. To simulate this case, we eliminate variables in the Medellin and Cordoba dataset. In each client/site, we leave two different variables so that only the target is repeated. In this way, a different predictive model of SD mortality is created for each client. The training is developed using the PSO algorithm to find the optimal weight matrix to build the FCM.

4.5.2. *Global training on the federated server*

The aggregation process on the federated server is a little different from the first approach. In this case, we do not use averaging to aggregate the models because the relationships between the concepts and the target are not repeated. Therefore, it is only sufficient to aggregate the two matrices into one, adding the weights of each of the clients. This process is done using Eq. 5 to create the global model. At the end, a global model is obtained that represents the information of all clients/sites. This model is updated for each of the clients so that it can be used to predict mortality from SD.

4.6. *Federated FCM with transfer learning*

Fig. 7 shows the architecture of the federated FCM with transfer learning. In the latter approach, learning will be transferred from one client to another because the target is located at a single client/site (see Fig. 4). For this approach, we used parameter-based transfer learning because the sample size in the two clients was approximately similar. In addition, the sign/symptom-related variables were common across the participating clients in the federation. We were interested in transfer learning because of the possibility of learning in one domain and making predictions or prescriptions in a different but related test domain. In healthcare, it is common to find healthcare institutions with treatment-related data and other institutions that collect only diagnosis-related

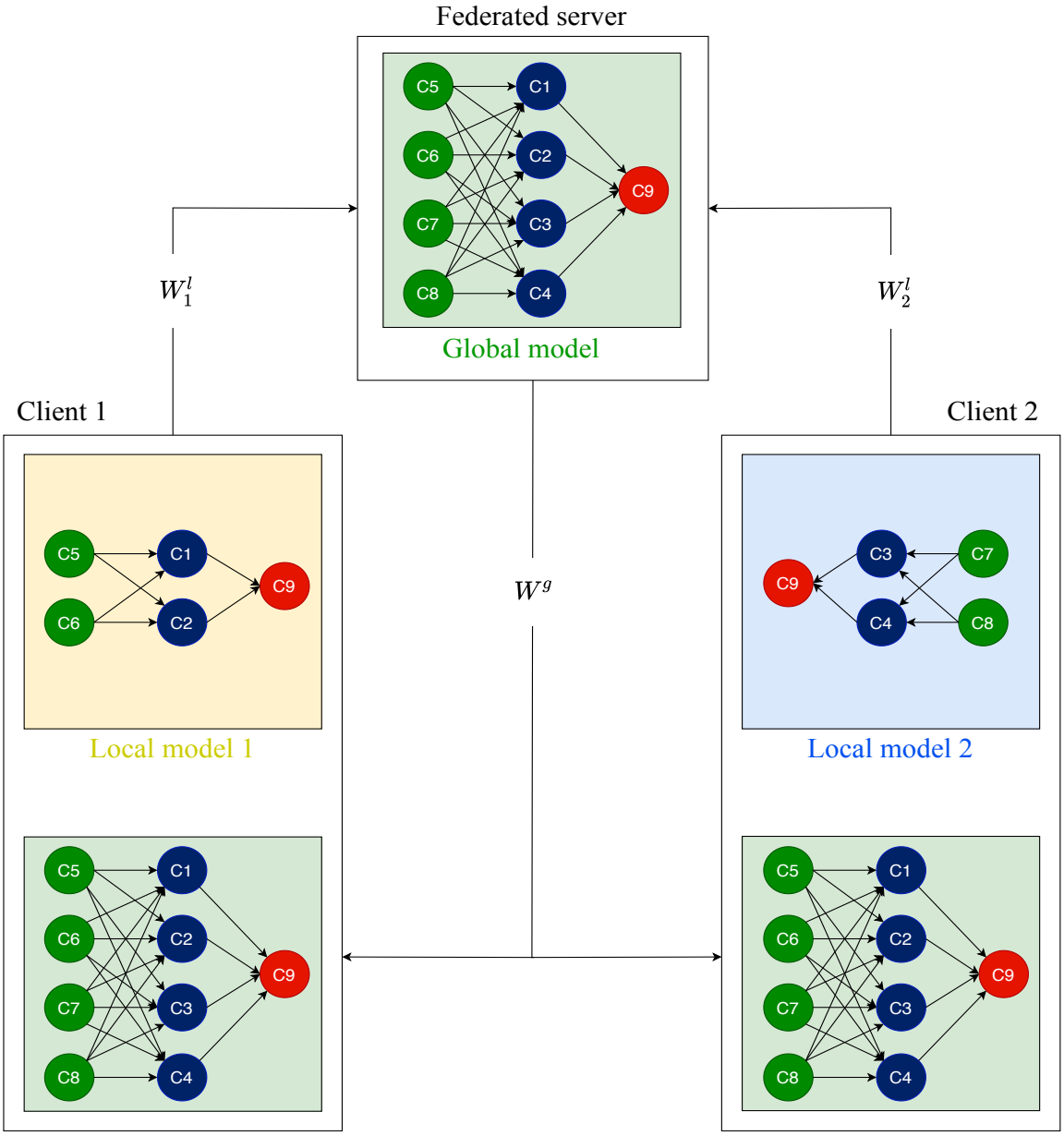

Fig. 6. Architecture of target-based federated FCM (the blue and green concepts are related to prediction and prescription, respectively. The red concept corresponds to the target).

data. Specifically, training local models with data that represent the therapeutic process of dengue, and that the extracted knowledge can be transferred to other settings, which would be of great utility to support clinical decision-making. To achieve this goal, two processes were performed: i) a local training of the prescription model (see local model 1 in Fig. 7) and its subsequent evaluation; ii) the second step consisted of a retraining of the predictive model (see local model 2 in Fig. 7) leaving constant the parameter values of the initial prescriptive model. Next, we explain the training of the variables at the local level and their update in the global model.

4.6.1. Local training on clients

The local training of each client will be different due to the presence of different variables. For example, client 1 has the prescriptive variables acting on the diagnostic variables, while client 2 has only the diagnostic variables with the target variable. For the first case (client 1), the PRV-FCM algorithm was used to build the prescriptive models (local model 1), while for the second step (client 2) the data-driven PSO-FCM algorithm was used to train the predictive model and generate local model 2.

4.6.2. Global training on the federated server

The creation of the global model was performed using the aggregation process defined in Eq. 5. This process is responsible for integrating the prediction and prescription FCMs to generate a federated global model.

5. Results and discussion

In this article, we aimed to develop and implement three federated learning approaches for FCMs to support clinical decision-making in dengue, specifically SD. In this section, we show the results obtained from the implementation of each of the proposed approaches on the described datasets. Then, we will discuss each of the results obtained in each approach. Finally, we compare our work with previous studies.

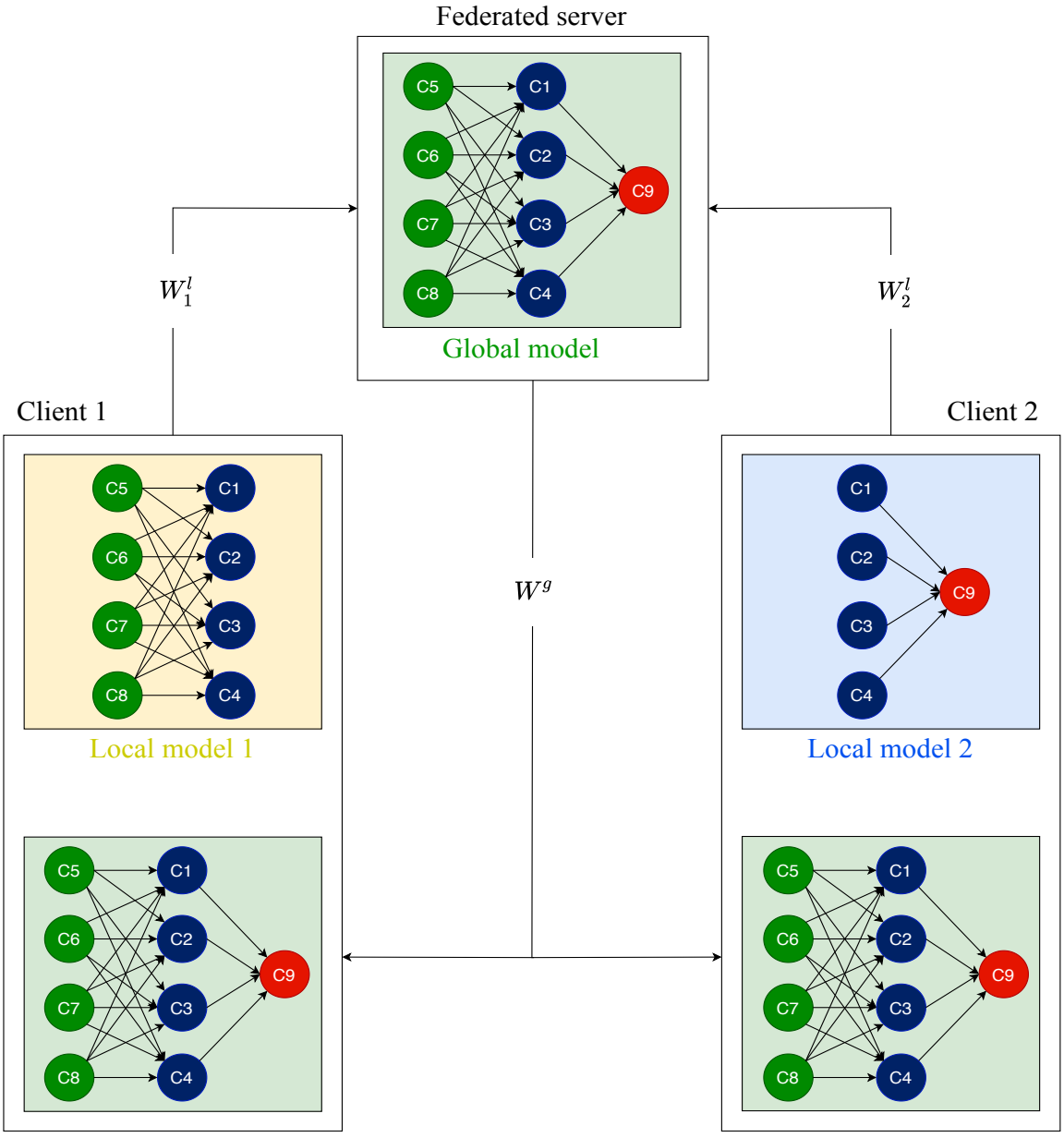

Fig. 7. Architecture of transfer learning federated FCM (the blue and green concepts are related to prediction and prescription, respectively. The red concept corresponds to the target).

Table 2

Performance of the models developed with the total federated FCM approach. * indicates the average for all prescriptive variables. NA = not applicable.

Data type	Model	Data configuration	Task	Accuracy	Sensitivity	Specificity
Signs, treatment options and target	Local 1	Local data from Medellín	Prediction	0.68	0.68	0.50
			Prescription	0.87*	0.75*	1.00*
	Local 2	Local data from Córdoba	Prediction	0.74	0.77	0.51
			Prescription	0.86*	0.89*	0.81*
	Global federated	NA	Prediction	0.76	0.85	0.67
			Prescription	0.96*	0.92*	0.97*
	Global non-federated	Centralized data	Prescription	0.88*	0.83*	0.94*

5.1. Total federated FCM

Table 2 shows the results of the local models and the global models applied to the previously described datasets. Fig. 8 shows the result of 100 simulations performed during the evaluation process of the models with a total federated learning approach. Additionally, it shows the statistical comparison of the performance of the predictive and prescriptive models. Both Local 1 and Local 2 models obtained good results for prescription with accuracy values of 0.87 and 0.86, respectively. However, it can be seen that the global federated predictive and prescriptive models were superior to all the local models, including the model with centralized data. Regarding sensitivity and specificity, the results showed the same trend of accuracy where federated global models performed better than local and centralized models.

Total federated learning consisted of a federated learning approach where all client variables are common. In this way, local models can be trained with different data and the sample size can be increased to improve prediction or prescription performance. The results of the local predictive models showed the ability to predict SD mortality. The results were acceptable, with accuracies between 0.68 and 0.74. Federated learning improved these results with 0.76. This demonstrates the ability to increase the sample size with federated learning. The same was true for the prescriptive models. The federated global model performed better than local models perhaps because the sample size was larger.

Although this accuracy is good, we only used a few variables for SD. The use of only 4 system variables and 4 prescriptive variables is too few to develop more robust models. Additionally, the

Table 3

Performance of the models developed with the target-based approach. * indicates the average for all prescriptive variables. NA = not applicable.

Model	Data configuration	Data type	Task	Accuracy	Sensitivity	Specificity
Local 1	Local data from Medellín	Two signs, two treatment options and target	Prediction	0.71	0.76	0.48
			Prescription	0.75*	0.67*	0.80*
Local 2	Local data from Córdoba	Two signs, two treatment options and target	Prediction	0.69	0.66	0.61
			Prescription	0.85*	0.78*	0.85*
Global federated	NA	All signs, treatment options and target	Prediction	0.76	0.90	0.66
			Prescription	0.95*	0.91*	0.96*
Global non-federated	All data centralized	All signs, treatment options and target	Prescription	0.88*	0.83*	0.94*

sample size is small, which is a limitation of the models to generalize. It is necessary to increase the sample size by adding other cities in Colombia and integrating new variables to explain their influence on mortality from SD.

5.2. Target-based federated FCM

Table 3 shows the accuracy, sensitivity and specificity of the models based on target-based federated FCM. Fig. 9 shows the result of 100 simulations performed during the evaluation process of the models with a total federated learning approach. Additionally, it shows the statistical comparison of the performance of the predictive and prescriptive models. In this approach, the target is the only variable in common between the clients. As in the first approach, the results showed that the federated global model performs better than the local models and the centralized model. One of the methodological novelties of the present work is the federated FCM approach based on the target variable. On many occasions, we have data in different locations and their only common feature is the target. This approach allows building global models where features are not repeated between datasets in different locations.

The results show the ability of our approach to predict in local environments with few variables. Local models 1 and 2 use two prescriptive variables and two diagnostic variables. Despite the small number of variables, the performance of the models is satisfactory. Additionally, the federated global model has the ability to predict and prescribe better than a model with centralized data. The sensitivity and specificity of the federated global models developed in this approach had higher performance, however, the predictive models are better able to classify positive cases than negative

Table 4

Performance of the models developed with the transfer learning federated approach. * indicates the average for all prescriptive variables. NA = not applicable.

Model	Data configuration	Data type	Task	Accuracy	Sensitivity	Specificity
Local 1	Local data from Medellín	Signs and treatment options	Prescription	0.95*	0.94*	0.93*
Local 2	Local data from Córdoba	Signs and target	Prediction	0.69	0.71	0.50
Global federated	NA	Signs, treatment options and target	Prediction	0.73	0.86	0.61
			Prescription	0.98*	0.96*	0.99*
Global non-federated	All data centralized	Signs, treatment options and target	Prescription	0.88*	0.83*	0.94*

cases (see Table 3). It is clear that the performance could be improved, either by increasing the size of the data used or by adding variables that explain the influence on dengue severity and mortality. The results of applying this approach to the data demonstrated that the use of clinical and treatment data are useful for predicting mortality and prescribing treatment to prevent death. The presence of warning signs established by the WHO has been shown to influence the severity and can be used as predictors of mortality from SD. Adding these types of variables to the models could improve their performance to obtain more robust models.

5.3. Federated FCM with transfer learning

Table 4 shows the accuracy, sensitivity and specificity of the models based on target-based federated FCM. Fig. 10 shows the result of 100 simulations performed during the evaluation process of the models with a total federated learning approach. Additionally, it shows the statistical comparison of the performance of the predictive and prescriptive models. In this latter learning approach, we can observe the ability of the federated global model to predict and prescribe with excellent performance outperforming the local models and the non-federated centralized model. In this case, as in the two previous approaches, the accuracy, sensitivity and specificity of the models were superior in the federated global model. The implementation of federated learning to transfer learning from prescription to prediction allows the integration of diagnosis and treatment of SD.

The federated FCM approach with transfer learning is an approach, which can be used to transfer learning from one domain to another. In our case, we were able to transfer learning from SD treatment to the mortality prediction domain.

Of the three approaches, this was the one that gave the best results for the prescription. It is

true that the division of the data in this approach allowed separating the domains, and only left the important variables in each part of the architecture. In the client with prescriptive variables and clinical manifestations, the relationship between treatment and the defining signs of SD is evident. Predicting SD mortality with only the defining variables remains a challenge. Using only four variables to predict mortality from this type of dengue is not enough to have models with excellent performance.

Finally, the statistical tests performed, whose significance values (p-values) are inserted in Fig. 8, Fig. 9 and Fig. 10 for the three approaches show that there are significant differences between the models developed.

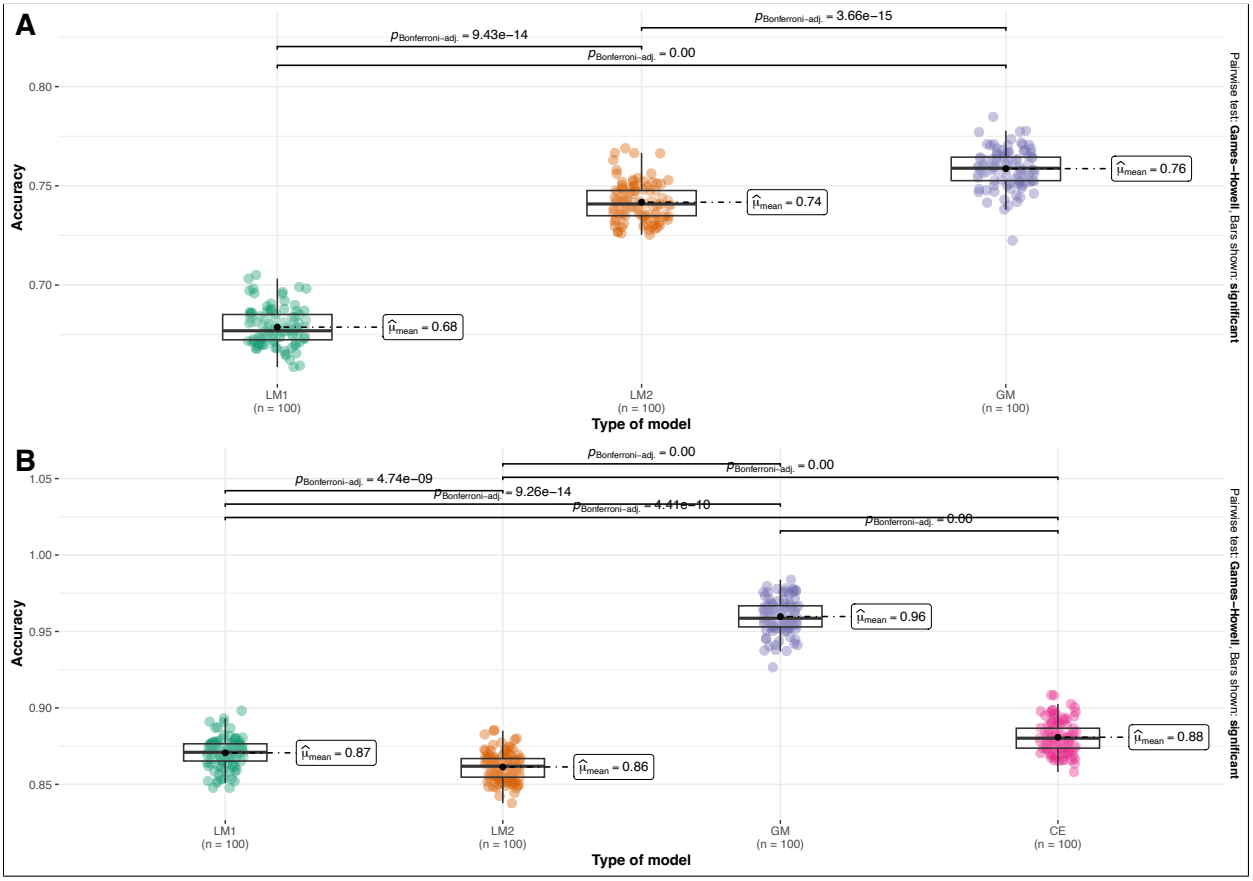

Fig. 8. Boxplots to compare the models' performance in a total federated learning approach. A and B correspond to the predictive and prescriptive models, respectively. Abbreviations: LM1 = local model 1, LM2 = Local model 2, GM = global model, CE = centralized approach.

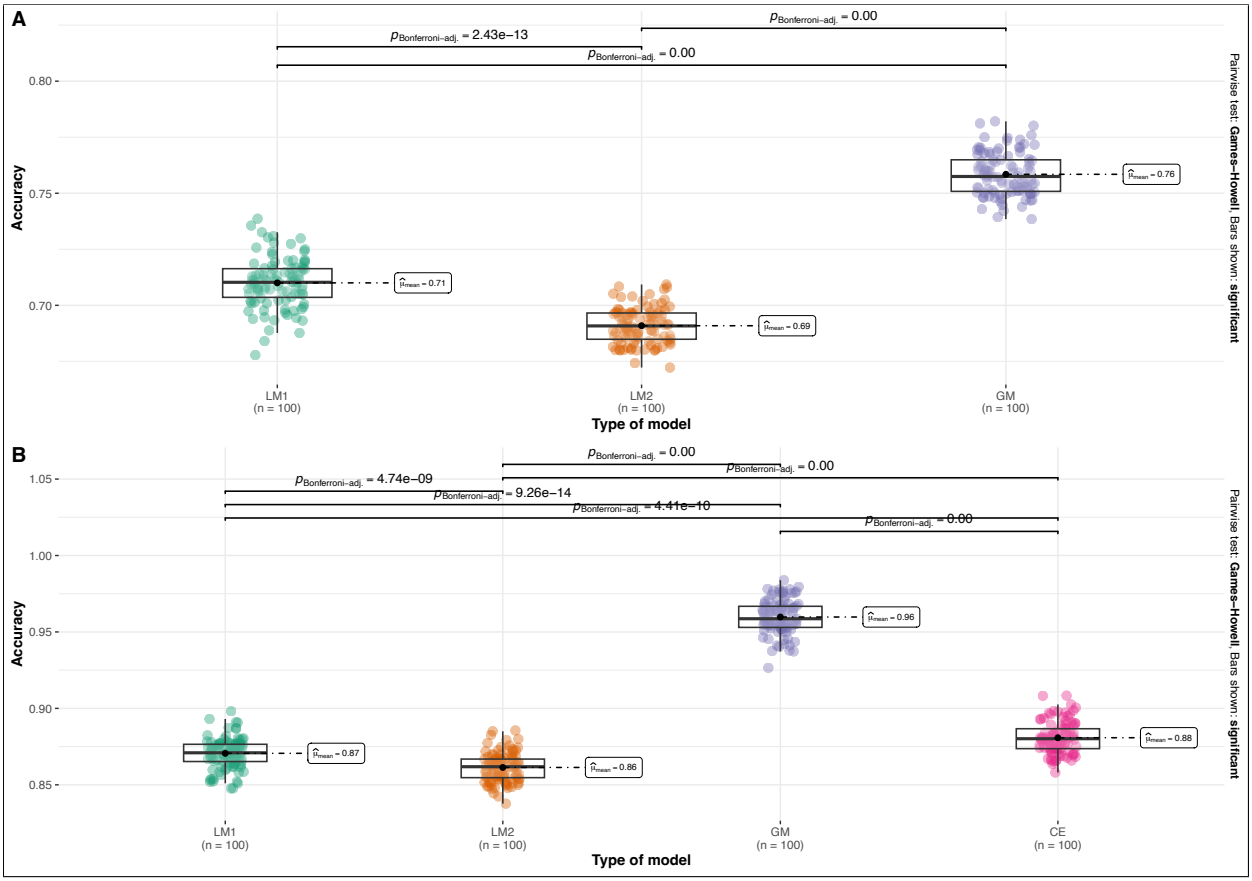

Fig. 9. Boxplots to compare the models' performance in a target-based federated learning approach. A and B correspond to the predictive and prescriptive models, respectively. Abbreviations: LM1 = local model 1, LM2 = Local model 2, GM = global model, CE = centralized approach.

5.4. Comparison with previous work

In this section, we compared the results of the present work with previously developed approaches published in the literature. Initially, we performed a qualitative comparison with other federated learning approaches that have been implemented in medical settings. On the other hand, since this is the first paper to propose federated learning approaches for FCMs for the clinical management of SD, we compared our results with prediction and prescription models for the clinical management of SD with centralized approaches.

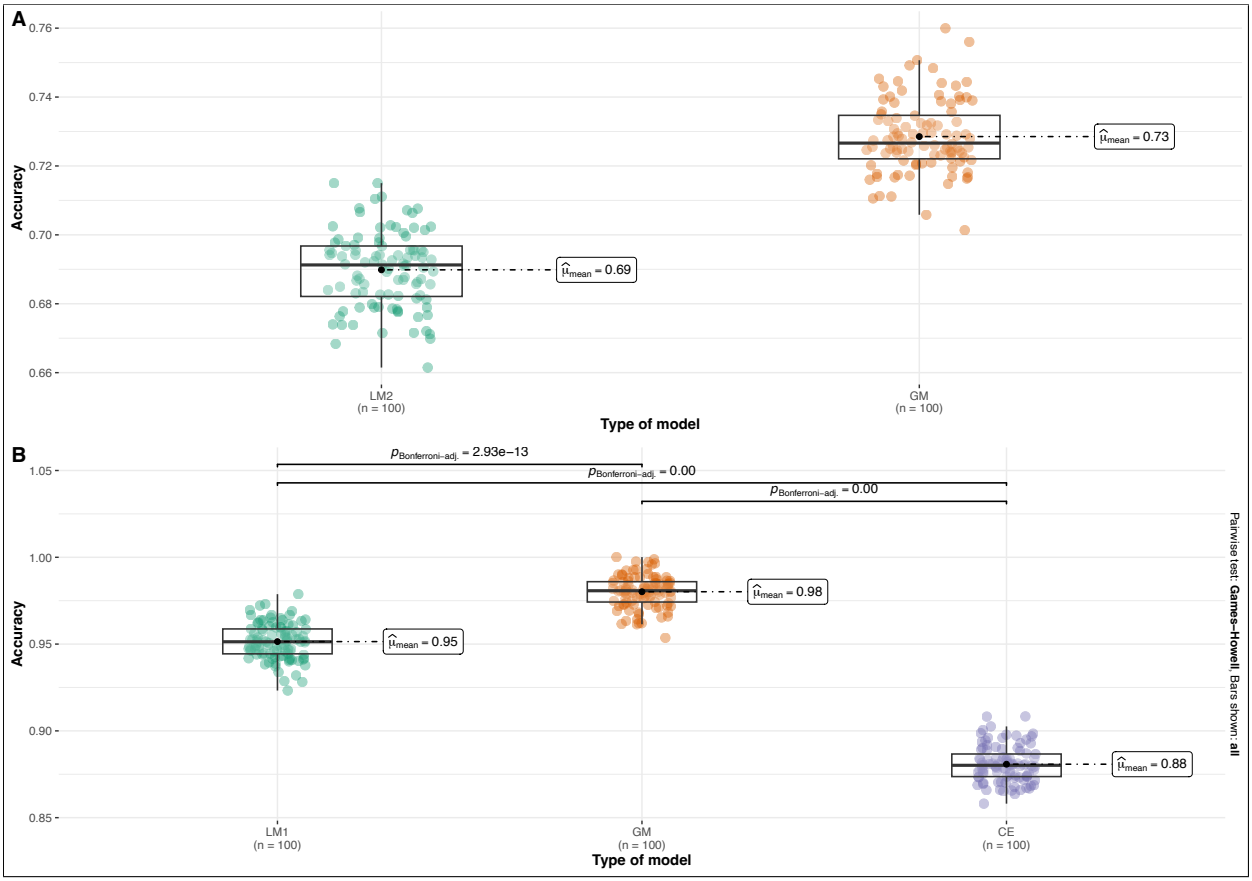

Fig. 10. Boxplots to compare the models' performance in federated transfer learning. A and B correspond to prescriptive and predictive models, respectively. Abbreviations: LM1 = local model 1, LM2 = Local model 2, GM = global model, CE = centralized approach.

5.5. Qualitative comparison

We performed a qualitative comparison of our work with other studies due to the lack of research implementing federated learning for SD. We used qualitative criteria defined in Table 5 for comparison with other approaches reported in the literature. The first criterion is related to the use and implementation of artificial intelligence techniques for the generation of predictive models for diagnosis. The second criterion evaluates the use and implementation of prescriptive models for disease treatment. The third criterion evaluates the ability of proposed systems to have an integration of predictive and prescriptive models in the federated learning environment. Finally, the last criterion indicates the ability of the approach to be intuitive and easily adaptable.

Table 5

Qualitative comparison between previous studies and our work.

Qualitative criteria	Work				
	[35]	[44]	[45]	[46]	Our work
AI models with FL for diagnosis	✓	✓	✗	✓	✓
AI models with FL for treatment	✗	✗	✓	✗	✓
Integration of AI models with FL for diagnosis and treatment	✗	✗	✗	✗	✓
Ease of use and adaptability	✓	✓	✓	✓	✓

Federated learning has been widely implemented in different fields of medical application [35, 44–46]. For example, Salmeron and Arevalo [35] developed a federated learning approach using computational intelligence techniques such as PSO and FCM for cancer diagnosis. The authors implemented an identical structure of FCMs across all clients or federation participants and demonstrated the ability of the federated approach to generate models with higher performance than local models. However, this work does not integrate prescriptive models with federated learning, nor does it integrate disease diagnosis and treatment. The proposed system is intuitive and easily adaptable. Another work developed by Li et al [44] supports decision-making in colorectal cancer prognosis by using random forests to build multi-center predictive models. The approach proposed by Li et al is easy to use, adaptable to any medical institution and is aimed at supporting decision-making with respect to diagnosis, guarantees the privacy of patient data, but does not generated treatment-oriented actions. Liu and Yang [45] trained a robot with deep learning to support physicians with the treatment of patients with depression. The work developed by Liu and Yang is novel and ensures privacy of patient data with federated learning. However, this approach only focuses on treatment and does not support decision-making for a depression diagnosis. Finally, a work developed by Li et al [46] preserved data privacy using a federated learning approach for Alzheimer's disease detection. The developed system used classification models and performed well in diagnosing the disease. Moreover, it can be adapted for the aggregation of new features to increase prediction performance.

In contrast to the previously presented work, we implemented three federated learning approaches with different architectures for predictive and prescriptive model generation. These ap-

proaches use different configurations to support decision-making in the diagnosis and treatment of SD using AI techniques. The integration of predictive and prescriptive models for diagnosis and treatment could be more useful than generating models only for diagnosis or only for treatment. The systems generated in each of our proposed approaches are also intuitive and their easy adaptation would allow the addition of other important variables for the analysis of SD.

5.6. Quantitative comparison

Although the availability of data regarding SD mortality remains scarce, which has led to the development of models based on the expertise of experts [13], our models performed well for both predicting and prescribing when compared to previous work based on data reported in the literature. For example, Hoyos et al [42] developed prediction models for SD mortality using the same dataset used in the present study. The authors developed the models with FCMs with average accuracies of 0.74. Another similar work is developed by Chattopadhyay et al. [47] where they developed classification models to predict dengue death with a maximum performance of 0.72 of accuracy in a smaller sample size (100 patients). Regarding prescriptive models, the PRV-FCM methodology yielded excellent results due to its ability to find optimal values using the FCM inference process and optimization algorithms. Our results confirm the results reported by several previous studies where the prescriptive capability of PRV-FCM in medical settings has been demonstrated.

6. Conclusions

We set out to develop three federated learning approaches for FCMs to support clinical decision-making in dengue, specifically SD. Each approach consisted of clients/sites with different/equal data depending on their settings. For each approach, predictive and prescriptive models were built using FCMs and optimization algorithms. The results showed that the three federated learning approaches with FCMs outperform local models trained on private data. Additionally, the federated approach outperforms models trained with centralized data. Finally, it is shown that federated learning approaches are useful for fields of science where data security and privacy must be guaranteed.

This work has some limitations. For example, the approaches are distributed but centralized, because a single federated server does the aggregation process. If this server has problems or is unavailable due to some circumstances, then the global model cannot be updated. For this reason, it is necessary to develop decentralized federated models. For example, an aggregation process can be performed in all the nodes of the system, so that if one node stops working, the others have a backup of the information and the aggregation information is not lost.

Another limitation of the present study is the number of clients used for the simulations. In this case, we only used two clients due to data availability. It is recommended to apply these approaches on larger clients to analyze the predictive and prescriptive capabilities of both local and global models. Finally, the approaches were not validated in licensed clinical institutions. Strict validation of these approaches in hospitals or clinics in Colombia would be useful to understand its usefulness in decision-making in clinical settings.

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Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

William Hoyos: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Validation, Visualization & Writing – original draft. **Jose Aguilar:** Conceptualization, Formal analysis, Resources, Supervision, Writing – reviewing & editing. **Mauricio Toro:** Resources, Supervision, Writing – reviewing & editing.

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