EAI Endorsed Transactions
on Bioengineering and Bioinformatics
Research Article EAI.EU

Modelling COVID-19 using Fuzzy Cognitive Maps (FCM)

Peter P. Groumpos[1,*]

[1]Emeritus Professor, Department of Electrical and Computer Engineering,
University of Patras, Greece

Abstract

INTRODUCTION: The outbreak of COVID-19 has gained ground in many countries, leading towards a global health emergency. Research efforts have been intensified all around the humankind.

OBJECTIVE: The main objective of this paper is to study the new pandemic COVID-19 using for the first-time theories of Fuzzy Cognitive Maps (FCM).

METHODS: All known studies for COVID-19 are done based on statistical models. These statistical approaches depend solely on correlation factors. The factor of causality has not been considered due to the luck of sufficient mathematical models based on causality. *Correlation does not imply causality while causality always implies correlation.* The approach of Fuzzy Cognitive Maps (FCM) that is considering the causality factors is proposed, to investigate the whole spectrum of COVID-19.

RESULTS: Early theoretical simulation studies using a COVID-19 FCM model have been conducted. Simulations with real patient data give excellent results. The state space Advanced Fuzzy Cognitive Maps (AFCM) is the natural sequence of the classical FCM theories.

CONCLUSIONS: This study gives strong evidence that the "generic FCM theories" are probably the only ones that explore the causality between the variables of medical problems in a sound mathematical and scientific foundation.

Keywords: COVID-19, medical diagnosis, modelling, fuzzy cognitive maps (FCM), artificial intelligence, advanced fuzzy cognitive maps (AFCM).

Received on 01 September 2020, accepted on 17 February 2021, published on 24 February 2021

doi: 10.4108/eai.24-2-2021.168728

*Corresponding author. Email: groumpos@ece.upatras.gr

1. Introduction

The main purpose of this paper is to address the modelling problem of COVID-19. In late 2019 a virus apparently closely related to SARS coronavirus emerged in Wuhan, China. The rapid spread of the epidemic worldwide has aroused serious concerns in the international community. The virus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Today everybody is referred to it as COVID-19. By early 2020, it had spread throughout regions of China and had reached many countries around the world. Most probably been carried by travelers from affected regions. In March 11 of 2020, the World Health Organization (WHO), after many hesitations, declared the outbreak a pandemic. The recent news from Italy, Spain, France, USA, United Kingdom, Germany, Russia, Brazil and other countries are scaring the whole humankind. The placing of entire cities and/or countries in 'lockdown'

directly affects urban economies on a multi-lateral level, including from social and economic standpoints. This is being emphasized as the outbreak gains ground in most countries of the world, leading towards a global health emergency, and as global collaboration is sought in numerous quarters. Recent events have shown us (again) how rapidly a new disease can take root and spread. Such events are accompanied by an explosion of clinical and epidemiological information and research.
Reported illnesses have ranged from mild symptoms to severe illness and death for confirmed coronavirus disease 2019 (COVID-19) cases. As of today, more than 840 ,000 of people worldwide have died of COVID-19. The number of people who have tested positive for COVID-19 has exceeded 25,1 million people and over 16,5 million people have recovered from the disease, according to official data. All these in less than six (6) months, since March. There is no dough that these numbers will continue to rise within the next few months. However, these health data have provided us with a big database of the Coronavirus pandemic. Therefore, these data will be very useful in studying all aspects of COVID-19. The early data have been used in this study.
The COVID-19 pandemic has sparked an unprecedented wave of research, data sharing and open science as the scientific world seeks to understand the disease, track its spread and analyze the SARS virus that causes COVID-19 or called more medically correct, SARS-CoV-2. Existing Medical Decision Support Systems (MDSS) methods are complex, difficult and insufficient to address the new emerged pandemic. The science of complex dynamical systems is a multidisciplinary field aiming at understanding the complex real world that surrounds us [1]. The problem of Decision Support Systems (DSS) has also attracted considerable research [2-3]. A good number of Clinical Decision Support Systems (CDSS) have also been developed the last 30-35 years based on different methodologies. They can be found on many references. No one can deny that most of them served to a certain extent many of the medical problems. The majority of them are based on statistical approaches. Indeed, all mathematical models used in confronting the recent pandemic of COVID-19 also are using statistical models. However, all medical problems are non-linear and statistical models are based on the assumption that variables have linear correlation between them. It is an undeniable fact that all medical problems are dynamic and non-linear. At present, many discussions are held regarding the decision mechanisms relating the inputs and the desired outputs of medical systems using non-statistical methods. A new approach, the Fuzzy Cognitive Map (FCM) methodology [4], has been proposed as not a statistical method to study and analyze such systems. Fuzzy Cognitive Maps (FCMs) constitute a simple computational and graphical methodology to represent complex problems. FCMs' decision-making mechanism is a useful method of handling the parameters of a desired Medical Decision Support Systems (MDSS) for complex medical problems. In this paper, the recent COVID-19 pandemic is considered and the classical Fuzzy Cognitive Maps (FCM) methodology is proposed as a first step to model the new disease.
So far, many mathematical models have been used when a number of medical problems are investigated. This is the case with the COVIC-19 pandemic. Despite the wide application and success of mathematical models, a more careful analysis of the presented medical results and facts show that all if not most mathematical models use statistical and probability theories. However, there are several problems and pitfalls in using statistics in complex dynamic systems involving experimental design, data collection, analysis and their interpretation. These may include ignoring the sample size and data distribution, incorrect summarization measurement, wrong statistical test methods especially for repeated measures, ignoring the assumption for t-test or other similar tests, failing to perform the adjustment for multiple comparison. Utilization of statistical analysis in biomedical and biological research is common and an early discussion of results is given in [5]. However, there is still a lot of misunderstanding and misinterpretation of statistical concepts when it comes to correlation and causation. In theory, these are easy to be distinguished but not in practice. An occurrence can cause another (such as smoking causes lung or stomach cancer), or it can correlate with another (such as heavy smoking is correlated with high levels of drinking alcoholics). This scientific relationship is defined as correlation. But, sometimes it is confused with another important scientific relationship that of causality or causation. Therefore, just because two things occur together does not mean that one caused the other, even if it seems to make sense. Methods that use correlation as the basis for hypothesis tests for causality, including the Granger causality test and convergent cross mapping have been used extensively in the past [36]. However, the results are not satisfactory since it uses statistical methods. This brings up the serious problem of confusing statistical correlation and causal relationship between variables and especially in the case of medical problems. Correlation does not imply causation; even though the research question at hand involves causality. This issue will be addressed in more details in section 4. A mathematical model that provides information on the causality of a dynamic complex system is the Fuzzy Cognitive Map (FCM) [4], [15]. Thus, FCM is proposed in this study to model the COVID-19 without using statistical models or probability density function.
This perspective paper, written only FOUR (4) months after detection and during the outbreak, surveys the virus outbreak from an urban standpoint and advances how smart city networks should work towards enhancing standardization protocols for increased data sharing in the event of outbreaks or disasters, leading to better global understanding and management of the possible usefulness of the new FCM methodologies. Providing a complete FCM mathematical model for COVID-19 based on real data is not possible in the present study as enough medical data are not yet available. A simple but sufficient COVID-19 FCM model is proposed based only on data acquired from reviewing the limited COVID-19 literature and the statistics been collected by different National Health Centers. For

example, for Greece from the National Health Organization [https://eody.gov.gr/epidimiologika-statistika-dedomena/imerisies-ektheseis-covid-19/]. The application of FCM in modelling COVID-19 is supported mathematically and is illustrated in the following sections of this paper. In section two (2), the basics of the new FCM approach which takes into consideration the causality are covered. In the same section the problem of confusion of correlation with causation is considered. This leads to consider the FCM approach as a new and appropriate mathematical approach to address medical problems. However, the early FCM methods have had some drawbacks and specific limitations. These theories are referred as the “Classical FCM theories”. Thus, a new FCM model is proposed. The new model, which overcomes these drawbacks and limitations is referred to as the Advanced Fuzzy Cognitive Maps (AFCM). In section three (3), some real medical problems modeled with the FCMs methodologies are presented. In the same section the obtained scientific research results for a number of medical applications using real data are given. In section four (4) for the first time an FCM model for COVID-19 is proposed. The model is purely mathematical using data based from existing literature for COVID-19 and some simulations are performed. In section five (5) simulations are performed using real data from the local University Hospital and discussion of obtained promising results are provided. Finally, in section six (6), conclusions and future research directions are provided and discussed.

2. Methods

2.1. Basics of Fuzzy Cognitive Maps (FCM)

Fuzzy Cognitive Maps came as a combination of methods of fuzzy logic and neural networks [4]. FCMs were first, introduced by Kosko in 1986, [4], in order to represent the causal relationship between concepts and analyze inference patterns. They take advantage of the knowledge and the experience of experts, offering them an alternative way of addressing the problems, yet in the same way a human mind does. This is achieved by using a conceptual procedure, which can include ambiguous of fuzzy descriptions [4] [15-17]. Late in 1999s and early in 2000s, Fuzzy Cognitive Maps were employed for the first time to describe and solve medical problems [6-9] by the research team been supervised by the author of this paper.

The FCM theories embody the accumulated knowledge and experience from experts who know how the medical system behaves in different circumstances. This is one of the strongest points of the FCM approach that rely mainly on the experience of the experts. This knowledge is extracted using linguistic variables which then are transformed to numeric values using a defuzzification method. In other words, they recommend a modeling process consisting of an array of interconnected and interdependent nodes Ci (variables), as well as the relationships between them W (weights). Concepts take values in the interval [0,1] and weights belong in the interval [-1,1]. Figure 1 shows a representative diagram of a FCM.

The full procedure of the development of a FCM is provided in [15]. During the simulation the value of each concept is calculated using the following rule:

$$A_i(k+1) = f(k_2 A_i(k) + k_1 \sum_{j=1, j\neq i}^{N} A_j(k) W_{ji}) \qquad (1)$$

where N is the number of concepts, Ai(k + 1) is the value of the concept Ci at the iteration step k+1, Aj(k) is the value of the concept Cj at the iteration step k, Wji is the weight of interconnection from concept Cj to concept Ci. The constant “k1” expresses the influence of all the other interconnected concepts on the configuration of the new value of the concept Ai and “k2” represents the proportion of the contribution of the previous value of the concept in computing the new value. Their values usually are set equal to 1, unless the experts of a particular dynamic system can determine these influences and contributions to the behavior of the system. This could be an interest future research topic for certain medical problems, such as COVID-19. Meanwhile function f, is the sigmoid function:

$$f = 1/(1+e^{(-\lambda x)}) \qquad (2)$$

where λ>0 determines the steepness of function f. The FCM’s concepts are given some initial values which are then changed depending on the weights Wij and the way the concepts affect each other. The calculations stop when a steady state is achieved, the concepts’ values become stable.

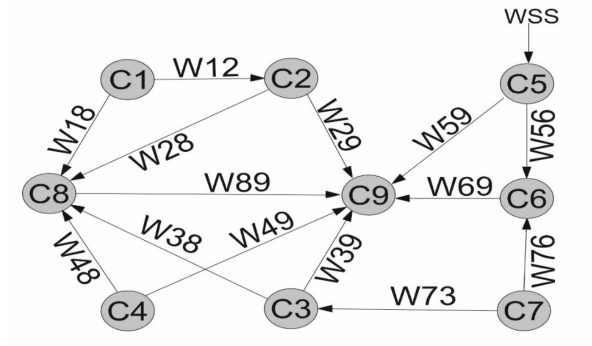


Figure 1. A simple Fuzzy Cognitive Map (FCM)

The FCM approach is based on expert’s knowledge for the construction of matrix Wij. This experience is not always reliable though. That is the reason why the weights need to be trained by a learning algorithm [16]. Several learning principles originally developed for ANNs have been applied to FCM modelling. These approaches were based on the concept of Hebbian learning. The full mathematical approach and comprehensive results describing FCM theories and their application in medical problems can be found in [6-9] [11] [15-17] [20-21] [27] [30] [32-35].

2.1. Why model medical complex dynamic systems with FCM methods?

Correlation vs Causation or Causality

In the introduction, a question was raised: how the FCM method adds anything to the many multivariate statistical approaches and tools available in analyzing and studying the behavior of Complex Dynamic Systems. This is the case of most Health problems, one of them just arrived in our front steps, Coronavirus COVID-19. This can be explained, only if we stress and prove the fact that the FCM method is not one more statistical method. Another important issue is if Correlation and Causation-Causality are the same scientific principles. It must become clear that while causality always implies correlation the reverse is not true. This is the reason that this paper claims that the new approach, the Fuzzy Cognitive Maps (FCMs) in modelling many medical, physical and human made processes, is not another statistical method. An FCM describes the cause and effect relations between variables or concepts, thus giving us the opportunity to describe the dynamic behavior of a system in a simple and symbolic way. FCM models are unique and the only one so far that address the causation-causality problem of any physical or human made system. FCMs do not calculate statistical values for the variables of a complex system. FCM have membership functions and not probability density functions. In order to better appreciate the usefulness of the new FCM methodology, in medical problems, there is a need to clarify the difference between correlation and causality or also known as causation, Rohrer (2018), [18].

The principle of or relationship between cause and effect is referred as causality. Another definition (Marriam Webster Dict. https://www.merriam-webster.com/): "the relation between a cause and its effect or between regularly correlated events or phenomena". Causality is also referred as causation. The main theories of causation and the surrounding debates, as well as considering the integral and very important role causation plays in medicine, physics, technology, geology, economics, business, sociology and law have never been well understood and be comprehended. Causality is universal. No one can deny that any phenomena in the whole world do not give rise to specific consequences and have not been caused by other phenomena. Medicine could not be an exception. Ours is a world of cause and effect. Causal factors are part of any process. Most importantly they all lie on the past of any process. Furthermore. all causes are part of a process. An effect can in turn be a cause of, or causal factor for, many other effects, which all lie in its future. Thus, the connection between cause and effect takes place over time. But how well is this understood by most scientists today? There is no drought that cause always precedes effect. There is always a certain interval between the time when the cause begins to act and the time the effect appears. Thus cause and effect coexist for some time, then the cause dies out and the consequence ultimately becomes the cause of something else. This is also true in medicine since many medical problems are studied and treated over some period. Some serious diseases especially epidemics need to be treated over long periods of time even for years!

Correlation is the process of establishing a relationship or connection between two or more things. It is a term that is a measure of the strength of a linear relationship between two quantitative variables (e.g., temperature, humidity). In Statistics the degree to which two or more attributes or measurements, between two random variables on the same group of elements show a tendency to vary together. For example, excessive tobacco and alcohol alone each increase the risk of several cancers. Combined, these two habits significantly increase the risk of cancers in the aero-digestive tract—the lips, mouth, larynx, pharynx, throat, esophagus and colon, [39].

Limitations and Drawbacks of FCM Theories

However, despite the many theoretical developments of FCMs based on the material presented on the previous section 2 and their success to many medical applications (and not only), FCMs still have a number of limitations and drawbacks [17] and [34]. All theories are essentially based on the material of section 2 which will be referred from now on as the "classical FCM theories". They do not go into the depth of the dynamic behavior of complex systems especially the medical ones. In addition, the initial system structure described by experts and the learning principles-algorithms cannot follow the evolution of the medical complex dynamic system. The natural-human world evolves and the human-made systems progress by applying knowledge derived from observations of and familiarity with repeatable human events and phenomena of nature. Our perceptions, understanding and ability to model medical problems, enable us to develop policies, processes and products that are invented and required in solving them. This requires new advanced interdisciplinary theories and technologies [17].

Generally speaking, our goal is either to model and control if possible optimally (and exploit) the natural phenomena, or to create human-made systems and processes with the desired properties. However, this is not possible using the "classical FCM theories".

The main problem stems from the existing approach that all concepts, C, (say N) are grouped as one vector A. The values A of all N concepts at all instant of times, k, are calculating using equations 1-2. Similarly, the learning - training algorithms for upgrading the causality coefficients Wij, is performed for all N concepts and for all instant of times, k [11] and [15-17]. Equations been used for Hebbian learning are using all N concepts. This is not mathematically correct since from the total number N of concepts, there is a number of concepts, whose values remain constant for long period of time when other concepts are changing slowly or fast. There are also exogenous variables that are not easily identified in the first place and thus cannot be part of the classical learning algorithms. In the "classical FCM theories", another problem has been that no matter what initial conditions were used, the algorithm was always converted to the same final values. Sometimes, "classical FCM theories" have a convergence problem of the algorithms. This in return forces us to increase the number of simulations consulting the behavior of the changes of the weights Wij through their changes based learning algorithms [11] [17].

Another drawback has to do with the NHL learning method [11-13] [15-18]. While running several simulations we have observed that due to the way weights are being calculated if the number of iterations of the algorithm is increased, in order to reach a steady state, the causality sometimes reverses all or some of the Wij values. This is a very serious drawback as it changes the causality between concepts [37] and in several occasions instead of having a lower we are going to have a larger result which can cause serious problems not only in the interpretation of the obtained results but also on stability issues to a number of real life systems. This is very crucial to medical problems and especially for COVID-19.

All the above drawbacks and some other ones were addressed by the research team of the Laboratory for Automation and Robotics (LAR) of the University of Patras under the supervision of the author. We are proud to be the first ones to present our results in International journals as well in many international conferences with full paper review evaluation. The new approached addressing these drawbacks and deficiencies of FCMs is called the state space Advanced Fuzzy Cognitive Maps (AFCM) approach. The basic mathematical approach is to separate the total number of concepts N to: 1) N1-State Concepts 2) N2-Input Concepts 3) N3-Output Concepts and 4) N4-Exogenous Concepts.

The Advanced Fuzzy Cognitive Maps (AFCM) approach is an evolution of the classic methodology, which promises more accurate results for a large variety of complex medical systems. This methodology, which is thoroughly analyzed in [17], and it overcomes some issues of the classic FCMs. Those issues are: (a) the presence of concepts of different nature is ignored in the traditional approach and, (b) the utilization of the classic sigmoid normalization function was fuzzing the system, especially in cases of the existence of several concepts. The AFCM approach was used in two medical applications with excellent results [19-22]. However due to the fact that we have not enough information and the required scientific knowledge for COVID-19 the AFCM approach cannot be used in this study. It is under consideration to use it within the next 3-4 months.

3. Medical applications of Fuzzy Cognitive Maps

Despite the above discussion of section 2 the “classical FCM theories” approach was used by the research team of this author to study many problems as early on late 1990s. It was the first one to use FCM in medical problems and applications obtaining very useful and interesting results. We provide here only a small number of these applications. It was first used on the human pregnant problem by this author [6]. The pregnancy of a woman was modeled with FCM and the health of the pregnant woman as well as the health of the fetus were carefully followed until the delivery of the baby. The study was conducted in cooperation with the Gynecology clinic of the University Hospital of Patras. The total number of pregnant women was 80. The health of the pregnant woman and of the embryo were monitored every week at the same day and time. It was decided to collect the data every Friday around 11am in the morning. The expected mothers were not restricted to any specific diet prior to their health monitoring. For the last week were monitored every day at the same time usually around 2pm. A health parameter (among many others) was calculated, the case of natural birth vs a cesarean of the baby been delivered. An amazing 95 per cent correct answers for the FCM model was observed regarding the determined number of natural birth vs cesarean baby delivery. The physicians were very happy and enthusiastic but when an EE grant was obtained due to administrative changes on the medical school of the University of Patras, the research team was forced to withdraw from the project.

Around the same time, the FCM approach was used to study the radiation therapy for breast cancer [7]. Radiation therapy decision-making is a complex problem. Fuzzy factors must be considered in the calculation of the appropriate dose to be given to the patient. This increases the complexity of the medical decision-making process. Addressing this problem, a new and novel approach has been introduced and is the Fuzzy Cognitive Maps (FCMs) [7-8]. The FCM methods tackle the complexity and allow the analysis and simulation of the clinical radiation procedure. This FCM approach was used to determine the success of radiation therapy process estimating the final dose delivered to the target volume [8]. Furthermore, a two-level integrated hierarchical structure was proposed to supervise and evaluate the radiotherapy process prior to treatment execution [9]. The supervisor, was also modeled using the FCM approach, determines the treatment variables of cancer therapy and the acceptance level of final radiation dose to the target volume. Two clinical case studies were used to test the proposed methodology and evaluate the simulation results. The FCM model had 33 concepts and 198 interconnections. The physicians collaborating with us were very happy with the obtained results and believed that the proposed FCM model would help the radiotherapist to simulate the treatment procedure, decide if the treatment execution will or not be successful, keeping the prescribed dose between the accepted limits. This decision-making system was developed to improve planning efficiency and consistency for treatment cases, selecting the related factors and treatment variables, and describing and determining the causal relationships among them. Furthermore, in [8], a Fuzzy Cognitive Map (FCM) model was used for the supervision and monitoring of the radiotherapy process, and is optimized through the minimization of an objective function, using the Differential Evolution algorithm.

The research team continued around the same time, and in cooperation with physicians from the University Hospital of Patras, to study the cancer of the human urinary system [10-11]. The application of Fuzzy Cognitive Maps (FCM) as a modeling and classification tool, for assessing tumors grade for urinary bladder, is examined in this research work. One hundred twenty-nine cases were classified according to the World Health Organization (WHO) grading system in two classes, by experienced pathologists: a) Low Grade and b) High Grade. Eight significant histopathological features that histopathologists selected for each case were used to reach this classification [12]. This research work incorporates doctor's knowledge in developing the FCM model for tumor grading and utilizes the Nonlinear Hebbian Learning algorithm to further train the FCM and thus to achieve tumor malignancy classification [11]. The classification is based on the histopathological characteristics of tissue that features are the concepts of the Fuzzy Cognitive Map model that was trained using the unsupervised learning algorithm [8]. The classification accuracy was 93.18% for High Grade tumor cases and 90.59%, for tumors of Low Grade [10]. Since 2003 FCM methodologies have been used extensively in a wide range of Medical problems: knee meniscus injury [13-14], mathematical modeling of Parkinson's [27-28]. Some other studies use also FCM methods for medical problems [24-25] or other medical applications [30-35].

The classical FCM methods have some drawbacks that have been raised and addressed in ref. [17]. The State space Advanced Fuzzy Cognitive Maps (AFCM) [17], is a new innovative approach. It uses the basic theory of FCM with the difference that, not all variables-concepts of the system are treated in the same way as in the “classical FCM theories”. The procedure of constructing the AFCM is remaining the same [36-37]. First, experts should define all basic system’s variables-concepts. Then the main change and innovation is that after this procedure, variables-concepts should be divided into three categories:

- Fuzzy Concept States
- Fuzzy Concept Inputs
- Fuzzy Concept Outputs

The fuzzy concept states of a dynamic system refer to a minimum set of variables, known as fuzzy state variables, which fully describe the system and its response to any given set of fuzzy inputs. The fuzzy concept inputs concern signals that stimulate the system. The fuzzy output variables constitute those that we should examine their behavior. In that way we take into consideration what exactly each concept does. We no more treat outputs in the same way as inputs and inputs are separated from states. We do not use equations (1) and (2) for calculating the dynamic behavior of the system. The mathematical description of the system and the combination of initial states and inputs are sufficient to provide information about both the future states and outputs. Mathematically the standard form of the new AFCM model is described by the system general equations [17].

To the best of my knowledge, State Space AFCMs have been applied and evaluated only to two medical problems [19-20] and [21-22]. In the first application [19-20] the new AFCM approach is being tested for its accuracy in Decision Support Systems in medicine, trying to model knee injuries by using 17 real cases of patients. The new AFCM proposed model is able to diagnose meniscus injuries and to distinguish between acute and degenerative injury. Subsequently we observe the evolution of the injury by administering a proposed treatment by the physician. Results of this new method, were very satisfactory for both two levels and treatment stage, and in total agreement with Magnetic Resonance Imaging outcomes having excellent results for all 17 patients. The whole methodology was the outcome of a close collaboration between engineers of LAR of the University of Patras and medical doctors of the Patras University Hospital.

In the second case [21-22] we employed the newly emerged State Space AFCM approach for the automatic and non-invasive prediction of Coronary Artery Disease (CAD). The Coronary Artery Disease is caused when the atherosclerotic plaques load, namely fill, in the lumen of the blood vessels of the heart, which are named coronary arteries, and they obstruct the blood flow to the heart. According to the World Health Organization, 50% of deaths in European Union is caused by Cardiovascular Diseases (CV), while 80% of the premature heart diseases and strokes can be prevented [23]. Diagnosing CAD in a non-invasive way is an open challenge, despite the massive number of researches been made so far [24-25]. More specifically, in this work [21-22], we designed two new models and proposed some alterations in order to address the problem. Designing AFCM models requires the collaboration between health experts and engineers. The health experts suggest and aid for the design of the FCM, for it to be user-friendly, scientifically acceptable, and interpretable. In this work, the Nuclear Medicine staff suggested that the casual relationships between concepts were unable to explain some unique and complex connections. Hence, the proposed models were designed to function with the aid of some universal rules. Rule-Embedded State AFCM, which is proposed in this work, was evaluated on a real patient-candidate database from the Laboratory of Nuclear Medicine of the University of Patras. Aiming to improve and evaluate AFCM’s performance, we experimented with the new and traditional FCM equations, as well as with different activation functions, and architectures. The optimal parameters were defined through the experiments and correspond to an improvement in the accuracy by +7%, over the traditional approach [22]. The results demonstrated the effectiveness of the newly emerged State Space AFCM approach which can be applied to other medical problems, with the appropriate modifications and with respect to the nature of the inputs. Thus, the state space AFCM approach is proposed for future research studies in investigated COVID-19.

4. Modelling COVID-19 with FCM methodologies

The pandemic COVID-19 is an acute resolved disease, but it can also be deadly, with a not easily determined case fatality rate. Severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure or due to other chronic diseases of the patient that are been further deteriorating from COVID-19. First, the early and automatic diagnosis of COVID-19 would be extremely beneficial to the patient and his/her relatives. It will also be beneficial to any state and private health system. In addition, it would be beneficial for countries for timely referral of the patient to quarantine, rapid intubation of serious cases in specialized hospitals, and monitoring of the spread of the disease. Although the diagnosis has become a relatively fast process, the financial issues arising from the cost of diagnostic tests concern both states and patients, especially in countries with private health systems, or restricted access health systems due to prohibitive prices.

The virus is mainly transmitted via respiratory droplets and contact, and the population is generally susceptible. The basic productive number (R0) at the beginning of the epidemic was 2.2, with an average incubation period of 5.2 days. The proportion of critically ill patients was 23.4%, the mortality rate was lower than those of SARS and MERS, and 96.5% of deaths occurred in Hubei Province, where the outbreak occurred first. Elderly human beings with underlying diseases and affected by COCID-19 had a higher mortality rate. Younger ages and especially children are not easily affected by the disease. For some reasons males are more susceptible to the disease. Since the pandemic has caught the whole world by surprise, no one was ready to deal with it. Very few studies have been conducted and all research article are either on SARS and MERS [40] or on COVID-19 the3-4 months [41-46]. Again, most of them use statistical methods and probability theories. New theories are needed to address the many challenging questions for COVID-19.

There are many questions related to this pandemic. What causes a coronavirus infection? Do humans first get a coronavirus from contact with animals? Then, how can it spread from human to human? How can we predict the spread of the Coronavirus? Do health officials comprehend and understand the COVID-19 pandemic? How is diagnosed? What are its symptoms? Which patients require an Intensive Care Unit? How is treated from medical point? Which of today's drugs are most effective? Do we have mathematical models that can follow the patient for 24 hours a day? On a broader sense questions such how is spread throughout the populations? What are the consequences of all restricted measures imposed by governments on the economic and social life of the societies? On the financial markets? On specific industries such as: tourism, agriculture, auto, manufacture, energy, environment and so many other areas?

Certainly, it spreads from human to human through contact with certain bodily fluids, such as droplets in a cough. It might, also be caused by bringing our hands to our face (especially: mouth, nose, and eyes) after touching something an infected person has touched. Thus, the advice for following good hygiene practices.

The symptoms reported have been growing since the first detection of VOVID-19. These symptoms may appear 3-14 days after exposure. In order to develop an FCM model following the methodology been outlined in section 2 the first step is to determine the number and the kind of concepts Ci that constitute the Fuzzy Cognitive Map (FCM). Not been a physician but an engineer and from today's available literature, Talking to MD doctors of the Patras University hospital and other relevant data by official organizations, the following seventeen (17) concepts have been selected, see table 1.

Table 1. Concepts of COVID-19

Concepts and Symptom description
C1: Fever-body temperature
C2: Cough
C3: Shortness of breath-breathing problems
C4: Headache
C5: Persistent pain or pressure in the chest
C6: Bluish lips or face
C7: New confusion or inability to arouse
C8: Diarrhea
C9: Feeling weak
C10: heart rate
C11: loosing sense of smell
C12: Contact with confirmed case
C13: inability to communicate with doctor
C14: Swelling in the legs
C15: Hemodynamic instability
C16: Shivering-cold
C17: outcome of test: positive or negative

The next steps are:

- Each expert defines the relationship between the concepts:
- 1) as "positive" or "negative" or "zero"
  2) their degree of influence using a linguistic variable, such as "very low", "low", "medium", "high", "very high".
- The FCM schematic diagram is developed
- The table of weights Wij is determined
- Run simulations with equation 1
- Report the obtained results.

A hypothetical case of COVID-19 and simulation tests can be performed using reasonable assumptions. This was the method we followed back in late 1999s when addresing medical problems [6-12]. The concept C17 would be in the center with all other 16 concepts to be interconnected and finally feed Concept C17. Thus figure 2 is created.

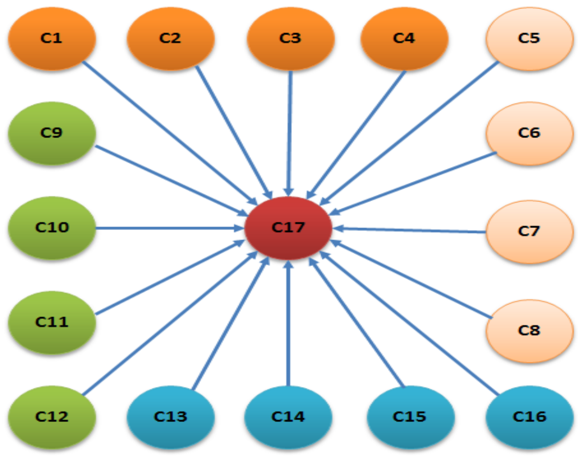


Figure 2. A simple Fuzzy Cognitive Map (FCM) for COVID-19

5. Simulations and discussion of Results

Using the Fuzzy Cognitive Map (FCM) methodologies a number of simulations were conducted. Two examples are given here using the following basic assumption for the COVID-19 of figure 2.

NP: Not present=0.0
VL: Very low=0.1
L: Low =0.3
M: Medium=0.5
H: High=0.7
VH: Very High=0.9

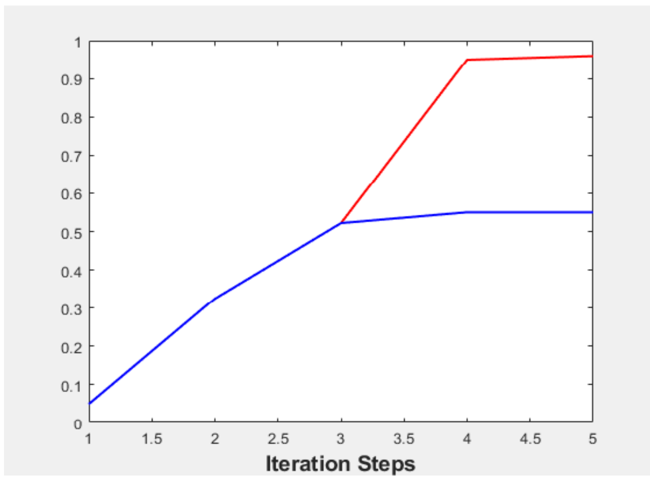
EXAMPLE A

Using above values for the 16 concepts for two hypothetical cases Table 2 is developed. Then using Fuzzification and defuzzification methods, the weight matrix Wij for the COVID-19 FCM model is developed. Using FCM theories simulations were conducted.[15], [30]. The results in figure 3.

Table 2. Linguistic variables for the concepts of COVID-19

Concepts	**Case 1**	**Case 2**
C1: Fever-body temperature	VH	L
C2: Cough	VH	L
C3: Shortness of breath-breathing problems	VH	VL
C4: Headache	M	M
C5: Persistent pain or pressure in the chest	VH	M
C6: Bluish lips or face	VL	NP
C7: New confusion or inability to arouse	NP	NP
C8: Diarrhea	NP	NP
C9: Feeling Weak	VH	M
C10: heart rate	H	M
C11: Loosing sense of smell	M	NP
C12: Contact with confirmed case	VH	M
C13: Inability to communicate with doctor	H	NP
C14: Swelling in the legs	NP	NP
C15: Hemodynamic instability	M	NP
C16: Shivering-cold	H	NP

The simulation results of figure 3 confirm the validity of the FCM methodology that provides satisfactory results. The iteration steps are equal to one full day (24 hours). If we want this can be changed and become an iteration step of one hour. This provides us with the capability to attend the health progress of a patient on a continuous basis. The red line is for a patient having COVID-19 while the blue line is for a patient without COVID-19. Please note that the blue line starts with same initial conditions for both cases and rises for the first 3 days to a value slightly above 0.5. In other words, both hypothetical patients are tested for having or not the COVID-19 disease. After three days, the C17 output concept continues to rise, red line with a steep slope and in less than a day reaches a value close to 1 (0.98). This result is considered as a positive result and thus the patient (case 1) is affected with COVID-19. On the other hand, the blue line after the third day, rises slightly but after the fourth day remains constant and below a threshold 0.6 (that.medical doctors would have set). Therefore, the patient that continues to have a steady output concept C17, blue line, is not affected by COVID-19



.

Figure 3. The response for concept C17 of the COVID-19 FCM model Red Line = Case 1 Blue line = Case 2

EXAMPLE B

In this example, based on real data from the local Patras University Hospital for three patients-cases simulations were also conducted. In this example using the same values for the linguistic variables, table 3 provides us the necessary information to conduct simulations. The results are shown in figure 4. In the same table, 3, the data of the hypothetical initial conditions for Example A are also provided (the last two columns). This is done so the results can be discussed under these two examples.

Table 3. Linguistic variables for the concepts of COVID-19

Concepts	**Case 1 Ex. B**	**Case 2 Ex. B**	**Case 3 Ex. B**	**Case 1 Ex. A**	**Case2 Ex.A**
C1: Fever-body temperature	VH	M	M	VH	L
C2: Cough	VH	H	L	VH	L
C3: Shortness of breath-breathing problems	VH	H	VL	VH	VL
C4: Headache	VH	M	L	M	M
C5: Persistent pain or pressure in the chest	VH	H	M	VH	M
C6: Bluish lips or face	NP	NP	NP	VL	NP
C7: New confusion or inability to arouse	NP	NP	VL	NP	NP
C8: Diarrhea	M	NP	L	NP	NP
C9: Feeling Weak	VH	M	M	VH	M
C10: heart rate	VH	H	M	H	M
C11: Loosing sense of smell	NP	L	NP	M	NP
C12: Contact with confirmed case	VH	H	L	VH	M
C13: Inability to communicate with doctor	H	NP	NP	H	NP
C14: Swelling in the legs	NP	NP	NP	NP	NP
C15: Hemodynamic instability	VH	M	NP	M	NP
C16: Shivering-cold	H	NP	L	H	NP

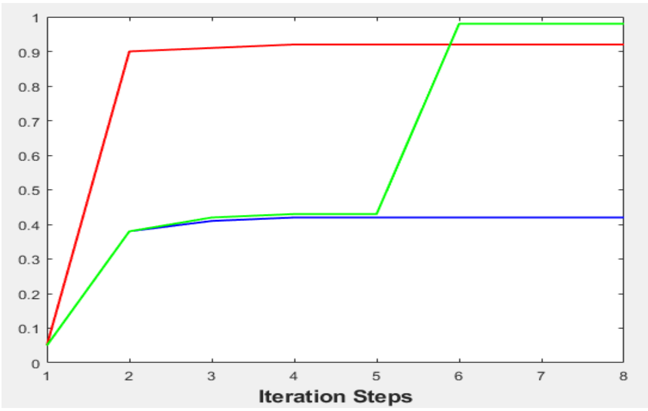


Figure 4. Simulation results concept C17, using real data of the COVID-19 FCM model Red line = Case 1 Green line = Case 2 Blue line = Case 3

The simulation results of figure 4 clearly confirm the validity and usefulness of the FCM methodology in studying COVID-19. The iteration steps as in example A, are equal to one full day (24 hours). Again, if we want this can be changed and become an iteration step of one hour. This provides us with the capability to attend the health progress of a patient on a continuous basis. The results of this second example with real data are extremely informative. The two cases been confirmed having COVID-19 are with the read and green line. The patient not been confirmed with COVID-19 is with the blue line. The patient case 1 show the positive result with the first day (red line-figure 4). The second patient case 2-Example B (table 3) show the positive outcome (green line) after five full days. Observing closer the table 3 this is also clear by comparing the initial conditions of the symptoms. We see that a good number of concepts, C of Case 1 (example B) are in a worst position than corresponding concepts, C of case 2 (Example B). This is shown better in Table 4.

Table 4. Linguistic variables for the concepts of COVID-19 for Cases 1 and 2 of example B

Concepts	**Case 1 Example B**	**Case 2 Example B**
C1: Fever-body temperature	VH	M
C2: Cough	VH	H
C3: Shortness of breath-breathing problems	VH	H
C4: Headache	VH	M
C5: Persistent pain or pressure in the chest	VH	H
C6: Bluish lips or face	NP	NP
C7: New confusion or inability to arouse	NP	NP
C8: Diarrhea	M	NP
C9: Feeling Weak	VH	M
C10: heart rate	VH	H
C11: Loosing sense of smell	M	NP
C12: Contact with confirmed case	VH	M
C13: Inability to communicate with doctor	H	NP
C14: Swelling in the legs	NP	NP
C15: Hemodynamic instability	VH	NP
C16: Shivering-cold	H	NP

This explains why patient one Case 1, shows positive COVID-19 immediately after day 1 (red line-figure 4) while the second patient with positive COVID-19 (green line figure 4) appears after the fifth day and reaches even higher values (very close to 1, than the red line which reaches the value of 0.9 and stays constant). Please note that the FCM model shows that for the examples under study in both cases of COVID-19 the positive results seem to be reached with one day. On the other hand, in the case of the negative results for patients been affected by COVID-19 (blue line of figures 3 and 4) show that after a small rise very soon stay below a base line been set by the medical doctors and stay constant. In both examples this happens after the third day (blue line figures 3 and 4).

Another important remark is due: Table 3 shows that the hypothetical initial example A (cases 1 and 2) are not far from real data of the hospital data. The same for Example B with the three cases the hypothetical data are not far from the real data, figure 3 for all cases. Simulations were run for 40 real cases with data from hospitals and the results been obtained using the FCM methodologies were 96 per cent in agreement with the final medical outcome of the COVID-19's positive results. These are very encouraging results. Already new studies are under way in close cooperation with the medical doctors of three Greek University Hospital to study further many aspects of the COVID-19 Pandemic and not only. Future research directions are given on the next section.

VERY IMPORTANT REMARK In both examples A and B the simulations using the FCM methodologies, the initial conditions tables 2 and 3 were the ONLY data been fed to equation 1. The simulations give us the value of concepts every day without any additional information. Therefore, there is a lot of room for improvements of the FCM methods for studying the COVID-19 pandemic. However even the results of this study show that the FCMs can be a very useful tool in fighting COVID-19.

6. Conclusion and Future Research

This study gives strong evidence that the FCM theories are probably the only ones that explore the causality between the variables of medical problem in a sound mathematical and scientific foundation. The outbreak of coronavirus disease (COVID-19) that began in China and spread rapidly has now made its way to a large part of the world worldwide and will stay with us for some considerable time. The current source of the disease is mainly patients infected with COVID-19. Patients in the incubation period may also become sources of infection. So far, all studies of COVID-19 (as well as for SARS-COV-2) are based on statistical methods and/or precise models using either static equations or ordinary differential equations. However, all of them have a number of drawbacks. In addition, all medical problems are non-linear and statistical models are based on the assumption that variables are simply correlated. All medical problems are dynamic and non-linear. Moreover, physicians are requested to handle information of different nature, e.g. patient's history, clinical diagnostic tests, medical images, personal health problems and demographic characteristics. The interpretation of these results involves ambiguity, fuzziness and uncertainty, which plays a critical role for the decision-making to a wide and diverse set of medical problems. The COVID-19 pandemic has all these characteristics. Although these approaches provide us with answers that are needed and used to study the medical problems, there are still not sufficient and adequate to provide us with acceptable and convincing solutions. Therefore, new advanced scientific approaches and new mathematical models are urgently needed. This paper provides a different mathematical approach based on fuzzy logic and theories of Fuzzy Cognitive Maps (FCM).

The COVID-19 is reviewed with today's existing knowledge. The Fuzzy Cognitive Maps (FCM) approach is briefly presented. A historical overview for the use of FCM theories to a number of medical problems with the useful and promising results are given. The excellent results been obtained using real data from clinical studies and having satisfying very much medical doctors have powered this author to dare to address the pandemic COVID-19. A first effort to model COVID-19 with FCM theories is provided. Two hypothetical cases for COVID-19 is considered and results are obtained. The results identified which patient was positive and who was negative to COVID-19. It is clearly stated that this is basically a theoretical study. However, with very promising results. Recognizing that present theories of FCM have a number of drawbacks and deficiencies an effort to overcome them has been undertaken by the author. The difference between correlation (statistical) and causality is analyzed. Medical problems affecting humans and the involvement heavily of human intervention makes the problem of causality more acute. Solutions cannot rely on classical methods. Even present FCM theories are called "classical FCM theories". A new state space Advanced Fuzzy Cognitive Map (AFCM) methodology is proposed. An algorithm for modelling COVID-19 based on the AFCM approach is briefly outlined and references to two medical applications are provided.

The future research directions are numerous, challenging and very difficult. Difficult because we know very little for this new and unexpected Coronavirus. The fundamental difference between correlation and causality for the medical problem of COVID-19 must be carefully addressed. A systematic and careful survey must be performed for the virus outbreak from an urban standpoint and advances how smart city networks should work towards enhancing standardization protocols for increased data sharing in the event of outbreaks or disasters. The classical statistical models needs to be modified and take into consideration other methods and techniques such as: co-integration analysis, Granger causality, "volatile correlation" as it was first known as "nonsense-correlation". Methods of Artificial Intelligence (AI) such as: machine learning, deep learning, probabilistic methods for uncertain reasoning, should be used to study COVID-19.

However, I personally believe that the new proposed FCM and AFCM approaches hold the most promising ways to better understand the COVID-19. Both need to be improved and use real data. New concepts that the medical doctors can make new AFCM models. A close cooperation with medical doctors is needed. New FCM and AFCM need to be developed. Models must be developed for different COVID-19 affected people (age, sex, underlying medical diseases, geographical regions, health condition of the considered patient, hereditary history, close contact with suspected COVID-19 case etc). One immediate research direction: categorize and analyzed all so far collected data according to the FCM and AFCM methodologies. New learning methods for new proposed methods. Use the new proposed methods to predict the progress of COVID-19 after the patient is tested positive and has started receiving medication. For each different patient a specified AFCM model with the sick history of the patient. It can be seen clearly now, that the proposed AFCM is unique for modelling COVID-19. Concepts can be added and/or deleted from a basic original AFCM. Medical experts can be consulted in an easy and flexible way. An AFCM to predict the spread of the Coronavirus can also be developed. New software tools need to be developed. More research directions can be proposed by medical doctors' as well biomedical engineers.

Acknowledgments

I would like to express my deep gratitude and very great appreciation to my wife Alexandra for her valuable and constructive suggestions during the planning and development of this research work. I am grateful to her for teaching me how Ancient Greek Philosophy is always an inspiring source providing insights to face wisely all kinds of challenges.

References

1. Levin S (2003) Complex adaptive systems: exploring the known, the unknown and the unknowable. Bulletin of the American Mathematical Society 40:3–19
2. Keen PG (1978) Decisión support systems; an organizational perspective
3. Scott Morton MS (1971) Management decision systems: Computer based support for decision making. Boston: Harvard University
4. Kosko B, others (1986) Fuzzy cognitive maps. International journal of man-machine studies 24:65–75
5. Yan F, Robert M, Li Y (2017) Statistical methods and common problems in medical or biomedical science research. International journal of physiology, pathophysiology and pharmacology 9:157
6. Groumpos PP , Stylios CD, Tzigounis V, (1999) A new mathematical model for human pregnancy using Fuzzy cognitive Maps. International Conference Proc. CIST 1999, May 23-26, Ufa, Russia
7. Papageorgiou E, Stylios CD, Groumpos P (2002) Decision making in external beam radiation therapy based on fuzzy cognitive maps. In: Proceedings First International IEEE Symposium Intelligent Systems. IEEE, pp 320–325
8. Papageorgiou EI, Groumpos PP (2003) Optimization of fuzzy cognitive map model in clinical radiotherapy through differential evolution algorithm. International Journal of Biomedical Soft Computing and Human

Sciences: the official journal of the Biomedical Fuzzy Systems Association 9:25–31
9. Papageorgiou EI, Stylios CD, Groumpos PP (2003) An integrated two-level hierarchical system for decision making in radiation therapy based on fuzzy cognitive maps. IEEE Transactions on Biomedical Engineering 50:1326–1339
10. Papageorgiou EI, Spyridonos P, Stylios CD, et al (2003) A Fuzzy Cognitive Map model for grading urinary bladder tumors. In: 5th Int. Conf. in Neural Networks & Experts Systems in Medicine & Healthcare 1st Int. Conf. in Computational Intelligence in Medicine & Healthcare, NNESMED/CIMED Conference. p 2003
11. Papageorgiou EI, Spyridonos P, Stylios CD, et al (2003) Grading urinary bladder tumors using unsupervised Hebbian algorithm for fuzzy cognitive maps. International Journal of Biomedical Soft Computing and Human Sciences: the official journal of the Biomedical Fuzzy Systems Association 9:33–39
12. Parsopoulos KE, Papageorgiou EI, Groumpos PP, Vrahatis MN (2004) Evolutionary computation techniques for optimizing fuzzy cognitive maps in radiation therapy systems. In: Genetic and Evolutionary Computation Conference. Springer, pp 402–413
13. Antigoni AP, Panagiotis P, Groumpos PP, Ioannis G (2016) A new meniscus injury diagnostic model using fuzzy cognitive maps. In: 2016 24th Mediterranean Conference on Control and Automation (MED). IEEE, pp 7–12
14. Anninou AP, Groumpos PP, Poulios P, Gkliatis I (2017) A New Approach of Dynamic Fuzzy Cognitive Knowledge Networks in Modelling Diagnosing Process of Meniscus Injury. IFAC-PapersOnLine 50:5861–5866
15. Groumpos PP (2010) Fuzzy cognitive maps: Basic theories and their application to complex systems. In: Fuzzy cognitive maps. Springer, pp 1–22
16. Groumpos PP (2011) Fuzzy cognitive maps: basic theories and their applications in medical problems. In: 2011 19th Mediterranean Conference on Control & Automation (MED). IEEE, pp 1490–1497
17. Groumpos PP (2018) Intelligence and fuzzy cognitive maps: scientific issues, challenges and opportunities. Studies in Informatics and Control 27:247–264
18. Rohrer JM (2018) Thinking clearly about correlations and causation: Graphical causal models for observational data. Advances in Methods and Practices in Psychological Science 1:27–42
19. Anninou AP, Groumpos PP, Poulios P, Gkliatis I (2017) A New Approach of Dynamic Fuzzy Cognitive Knowledge Networks in Modelling Diagnosing Process of Meniscus Injury. IFAC-PapersOnLine 50:5861–5866
20. Anninou A, Poulios P, Groumpos PP, Gliatis I (2018) A Novel Software Tool for Detection of Meniscus Injury using Dynamic Fuzzy Cognitive Networks. Physiother Rehabil 3:2573–0312
21. Apostolopoulos ID, Groumpos PP, Apostolopoulos DI (2017) A Medical Decision Support System for the Prediction of the Coronary Artery Disease Using Fuzzy Cognitive Maps. In: Conference on Creativity in Intelligent Technologies and Data Science. Springer, pp 269–283
22. Apostolopoulos ID, Groumpos PP, Apostolopoulos DI (2020) State Space Advanced Fuzzy Cognitive Map approach for automatic and non Invasive diagnosis of Coronary Artery Disease. arXiv preprint arXiv:200403372
23. Organization W.H. (2014) Global status report on no communicable diseases 2014. World Health Organization
24. Dilsizian SE, Siegel EL (2014) Artificial intelligence in medicine and cardiac imaging: harnessing big data and advanced computing to provide personalized medical diagnosis and treatment. Current cardiology reports 16:441
25. Soni J, Ansari U, Sharma D, Soni S (2011) Predictive data mining for medical diagnosis: An overview of heart disease prediction. International Journal of Computer Applications 17:43–48
26. Chen T-M, Rui J, Wang Q-P, et al (2020) A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. Infectious diseases of poverty 9:1–8
27. Groumpos PP, Anninou AP (2012) A theoretical mathematical modeling of Parkinson's disease using Fuzzy Cognitive Maps. In: 2012 IEEE 12th International Conference on Bioinformatics & Bioengineering (BIBE). IEEE, pp 677–682
28. Zhang W, Zhang X, Sun Y (2017) A new fuzzy cognitive map learning algorithm for speech emotion recognition. Mathematical Problems in Engineering 2017:
29. Amirkhani A, Papageorgiou EI, Mohseni A, Mosavi MR (2017) A review of fuzzy cognitive maps in medicine: Taxonomy, methods, and applications. Computer methods and programs in biomedicine 142:129–145
30. Groumpos PP (2012) The challenge of modeling decision support systems for medical problems using fuzzy cognitive maps: An overview. In: 2012 IEEE 12th International Conference on Bioinformatics & Bioengineering (BIBE). IEEE, pp 132–138
31. Bourgani E, Stylios CD, Manis G, Georgopoulos VC (2014) Time dependent fuzzy cognitive maps for medical diagnosis. In: Hellenic conference on artificial intelligence. Springer, pp 544–554
32. Iakovidis DK, Papageorgiou EI (2010) Intuitionistic fuzzy cognitive maps for medical decision making. IEEE Transactions on Information Technology in Biomedicine 15:100–107
33. Papageorgiou EI, Papandrianos NI, Karagianni G, et al (2009) A Fuzzy Cognitive Map based tool for prediction of infectious diseases. In: 2009 IEEE International Conference on Fuzzy Systems. IEEE, pp 2094–2099
34. Papageorgiou EI (2011) A new methodology for decisions in medical informatics using fuzzy cognitive maps based on fuzzy rule-extraction techniques. Applied Soft Computing 11:500–513
35. Papageorgiou EI, Spyridonos P, Glotsos DT, et al (2008) Brain tumor characterization using the soft computing technique of fuzzy cognitive maps. Applied Soft Computing 8:820–828
36. Granger CWJ (1969) Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica 37:424. https://doi.org/10.2307/1912791

37. Mpelogianni V, Groumpos PP (2018) Re-approaching fuzzy cognitive maps to increase the knowledge of a system. Ai & Society 33:175–188
38. Mpelogianni V, Groumpos PP (2016) A revised approach in modeling fuzzy cognitive maps. In: 2016 24th Mediterranean Conference on Control and Automation (MED). IEEE, pp 350–354
39. World Health Statistics 2019 (2019). Geneva: World Health Organization
40. de Wit E, van Doremalen N, Falzarano D, Munster VJ (2016) SARS and MERS: recent insights into emerging coronaviruses. Nature Reviews Microbiology 14:523
41. Toğaçar M, Ergen B, Cömert Z (2020) COVID-19 detection using deep learning models to exploit Social Mimic Optimization and structured chest X-ray images using fuzzy color and stacking approaches. Computers in Biology and Medicine 121:103805. https://doi.org/10.1016/j.compbiomed.2020.103805
42. Hijikata A, Shionyu-Mitsuyama C, Nakae S, et al (2020) Knowledge-based structural models of SARS-CoV-2 proteins and their complexes with potential drugs. FEBS Lett 1873-3468.13806. https://doi.org/10.1002/1873-3468.13806
43. Gralinski LE, Menachery VD (2020) Return of the Coronavirus: 2019-nCoV. Viruses 12:135
44. Wrapp D, Wang N, Corbett KS, et al (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260–1263
45. Li G, De Clercq E (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature Publishing Group
46. Ling C (2020) Traditional Chinese medicine is a resource for drug discovery against 2019 novel coronavirus (SARS-CoV-2). Journal of Integrative Medicine