Modeling Clinical Decision Support based on Artificial Neural Network: Optimization of Sickle Cell Treatment

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Abstract: —Sickle cell disease (SCD) is the monogenic disease that causes complex multisystem red blood cell disorders leading sufferers to life-threatening acute dysfunctions and chronic complications. In practice, comprehensive SCD care is essential and makes it possible to limit complications and reduce early mortality. With so-called precision medicine, there are curative therapies for SDC such as hematopoietic stem cell transplants and gene therapy but which require significant financial means. Means that are not always available to ordinary people, especially in developing countries. This is where solutions for optimizing therapies based on Artificial Intelligence methods intervene. The paper present an approach of SDC treatment optimization based on Artificial Neural Network (ANN). A big data containing cases of sickle cell patients will be used for previous medical decision analysis to produce indicator performance that enables optimal drug therapy.

Key-words: — Sickle cell disease, Treatment optimization, Artificial Neural Network, Medical decision support.

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1. Introduction

THE phenomenal progress in biomedical knowledge and the increase in the number of parameters necessary for patient care pose the problem of mastering information processing.

For well over the last century, this field has been undergoing digital transformation, but often faced with the challenge of being data rich but information poor.

This is why Armoni [1] indicated that “there is a need for innovation in the healthcare organizations, and the main way of bringing innovation is using the knowledge as a driver. An important support for knowledge in the organization will be the information and communication”.

At the moment, medical information is drawn from medical record data which remains the center of interest of the healthcare organizations.

To efficiently and optimally exploit this medical data by computer, the use of artificial intelligence becomes an unconditional option.

The development of artificial intelligence in medicine is likely to offer valuable assistance in predicting a pathology, in its diagnosis, in decision-making, in the personalization of treatment as well as in more global prevention to the population.

According to [2] and in relation to AI applications, it turns out that “the key categories of applications involve diagnosis and treatment recommendations, patient engagement and adherence, and administrative activities”. And as one of the focal points of clinicians' activities is in medical decision-making. It should be noted that all major human activities involve cognitive operation that revolves around problem solving in a dynamic and unpredictable environment. Also, it is necessary to know that “decision making is one of the basic cognitive processes of human behaviors by which a preferred option or a course of actions is chosen from among a set of alternatives based on certain criteria” [3].

In this sense, we are of the opinion that “clinical decision support systems (CDSSs) using AI may provide guidance on diagnosis, treatment, maintenance/follow-up treatment, workflow(s), and patient information, and indeed may use AI or other methods to generate their outputs/advice” [4].

According to the above, we could consider AI as a problem solver. And yet today AI raises many controversies.

You will remember that “hundreds of scientists and personalities have signed an open letter calling for a six-month moratorium on the deployment of new versions of artificial intelligence like ChatGPT. [5]”

In agreement with Aurélie Jean [6], who mentions “that alongside a few actors defending an apocalyptic long-term vision of AI, a fortiori disconnected from the field, there is an overwhelming majority of scientists who agree to warn on the risks of such a posture on the sustainability of the work in progress and their future applicability". It is therefore a question of understanding the societal issues that allow us to benefit from the benefits of AI while avoiding the threats.

Indeed, it is enough to think about the impact of artificial intelligence in achieving the Sustainable Development Goals.

Our study seeks to highlight the utility side of AI technologies for medical applications. The medical field chosen to benefit from an AI-based digital intervention is sickle cell disease.

Sickle cell disease (SCD) "is a monogenetic disorder due to a single base-pair point mutation in the β-globin gene resulting in the substitution of the amino acid valine for glutamic acid in the β-globin chain" [7]. In practice, comprehensive SCD care is essential and makes it possible to limit complications and reduce early mortality.

With so-called *precision medicine*, there are curative therapies for SDC such as *hematopoietic stem cell transplants and gene therapy* [8], [9], but which require *significant financial means* [10]. Means that are not always available to ordinary people, especially in developing countries.

This is where solutions for optimizing therapies [11] based on Artificial Intelligence methods intervene.

The concern of our paper is to design an approach of SCD treatment optimization based on Artificial Neural Network.

2. Methods

The approach adopted in our study is classic insofar as it is applied research. On one side we have the area that requires digital intervention and on the other side the digital intervention itself. Our medical domain study is the sickle cell disease. The digital intervention is designed based on artificial intelligence technology, namely artificial neural networks.

2.1 Sickle Cell Disease Problem

As long as the patient's condition is known to be sickle cell disease, medical staff can quickly conduct a clinical examination. For most patients, the management of sickle cell disease revolves around prevention of complications and regular medical monitoring.

Sickle cell disease manifests itself by various signs and each person may experience symptoms differently. Symptoms and complications as stated in [12], [13] can be classified in 5 groups of manifestation of the disease: Sickle cell anemia or

Sickle cell anemia with abnormal TCDs; Vaso-occlusive complications; Frequent episodes of acute pain; Significant proteinuria; Low oxygen saturations or Hypoxemia.

Furthermore the different categories of treatment of sikle cell diseases are the following: "Medicine to prevent the sickling of red blood cells, Medicine to reduce vaso-occlusive and pain crises, Medicine to reduce or prevent multiple complications, Medicine to treat pain, Medicine to reduce risk of infection, Transfusions and Potential genetic therapy treatments" [14].

According to [15], "there are no standard treatments that cure sickle cell disease. However, there are treatments that help people manage and live with the disease".

2.2 Artificial Neural Network: Problem Solver

In accordance with [16], "clinical decision-support systems (DSSs) aim to enhance healthcare decision-making, with the final objective to improve the quality of care provided by healthcare organizations".

Also, Ramesh et al. [17] note that "artificial intelligence is a branch of computer science capable of analyzing complex medical data. Their potential to exploit meaningful relationship with in a data set can be used in the diagnosis, treatment and predicting outcome in many clinical scenarios."

Furthermore, a recent systematic review, in [18], investigated the use of AI/ML-based approaches towards clinical decision support (CDS) for monitoring cardiovascular patients in intensive care units (ICUs). The study identified 21 studies that used AI/ML models for CDS. The most common input modalities were clinical time series and electronic health records (EHR) data. Methods such as gradient boosting, recurrent neural networks (RNNs), and reinforcement learning (RL) were mostly used for the analysis.

Artificial neural networks (ANNs) are a popular choice for medical decision support systems. ANNs are a type of machine learning algorithm that can learn from data and make predictions based on that data.

Artificial neural networks (ANNs) have been used in healthcare to improve decision-making and optimize treatment for various diseases. In the context of sickle cell disease,

ANN contains a set of interconnected neurons to do all needed operation. A neuron is a processing element. The input information arrive at the neuron through connections and connecting weights. Neuron has memory to store information. ANN has an ability to learn, recall and generalize from the given data by suitable assignment and adjustment of weights. The power of problem solving is possible through the association and collective behavior of neurons.

3. Results

3.1 An Approach of Treatment Optimization of SCD

Optimizing therapies for SCD with Artificial Neural Network is the problem of predicting treatment response.

Our ANN is designed to explore different combinations of drugs, doses and treatment durations in order to find the best approach depending of course on the historical data of the case concerned. Also, once a treatment is administered, our ANN can help monitor the patient's response and adjust the treatment in real time in case of unwanted side effects [19].

In the following, we describe basic stage of our model.

1) *Referential Domain*

The domain of study is sickle cell disease. The SCD's model of disease can be based on protocols of management [20], [21]: Pathophysiologic knowledge, clinical diagnosis, Laboratory and complementary examination diagnosis, Medical decision and Treatment protocols.

Based on the SCD's model of disease and the protocols of management, let formalize the application definition domain as follows:

$$P= \{p_1, p_2, \ldots, p_n\},\ p_k \in K$$

where p_k are knowledge to manage SCD according to protocols.

2) Data Set

The referential domain is a collection of necessary information on SCD management. Besides, we are exploring another domain, the medical records.

Let the data set of a case's patient be a multi-dimensional vector where each dimension corresponds to a distinct vector. The elements of the vectors are taken from the multi-dimensional set X; and each subset of X contains variables to which one or more values may be associated.

$X= \{x_1, x_2, \ldots, x_m\},\ X_m \in I$

where X_m is a multidimensional set define on the domain I (medical record information).

1° Patient profile vector: X_1 = [PatientId: $x_{1,1}$; Sex: $x_{1,2}$; AverageAge: $x_{1,3}$; AverageWeight: $x_{1,4}$; …];
2° Conditions/Diseases vector: X_2 = [Status: $x_{2,1}$; PastMedications: $x_{2,2}$; Allergies: $x_{2,3}$; ..]
3° Symptoms/signs vector: X_3 = [$x_{3,k}$]
4° Complementary examens/Tests vector: X_4 = [$x_{4,l}$]
5° Therapies vector: X_5 = [$x_{5,m}$]

Within the limits of our study, let us presented, in table 1, a set of illustrative and non-exhaustive features on the management of sickle cell disease.

Table 1. Treatment Protocol

Symptoms & Signs	Clinical Examination	Complementary Examination	Patient Groups	Treatment
Anemia, Episodes of Pain, Swelling of Hands and Feet, Frequent Infections, Delayed Growth or Puberty, Vision Problems	Medical History; Past medication, Assessing Stroke risk	Hemoglobin, Electrophoresis, Complete Blood Count, Sickle Solubility Test, Abnormal Transcranial Doppler	Sickle cell anemia	Penicillin V, Hydroxyurea, Voxelotor, Regular blood transfusions
Pain, Swelling, Fever, Fatigue and Weakness	Medical History; Past medication	Hemoglobin, Electrophoresis, Complete Blood Count	Vaso-occlusive complications	Penicillin V, Opioid Analgesics, Crizanlizumab
Sickle Cell Pain Crises, Acute Inflammatory Arthritis, Septic Arthritis	Medical History; Past medication, Assessing: localized tenderness, swelling, rednesa, spinal range of motion, muscle strength, neurological function, wound healing; Evaluation of sensory deficits, nerve function, and reflexes	Inflammatory markers (C-reactive protein or erythrocyte sedimentation rate), Blood glucose levels, Urinalysis, Complete Blood Count , Electrocardiogram, X-rays, MRI or CT scans	Frequent episodes of acute pain	Penicillin V, Nonsteroidal, Anti-Inflammatory Drugs (NSAIDs), L-glutamine, Acetaminophen (Tylenol),
Swelling (Edema), More Frequent Urination, Shortness of Breath, Tiredness, Nausea and Vomiting, Lack of Appetite, Muscle Cramping at Night, Puffiness Around the Eyes	Medical History; Past medication; Assess for signs of kidney disease, fluid retention (swelling)	Blood Tests (Serum Protein Levels, Kidney Function Tests), Urine Tests (Urine Dipstick Test, 24-Hour Urine Protein Excretion Test); CT Scans, Ultrasounds	Significant proteinuria	Penicillin V, Angiotensin-Converting-Enzyme, Inhibitors, Dietary Changes
Headache, Difficulty breathing, Rapid heart rate, Coughing, Wheezing, Confusion, Bluish color	Medical History; Past medication; Listen to the heart and lungs; Checking for bluish skin, lips, or fingernails	Arterial Blood Gas Test, Pulse Oximetry, Normal Oxygen Saturation Levels	Low oxygen saturations or Hyponemia	Penicillin V, Overnight oxygen

3) Processing Units and Functions

Initially, the basic functions are respondents of the vectors as defined above.

The diagnosis and therapy aids of SCD are carried out using mainly heuristics and rules-based reasoning.

Our approach at this stage is to combine knowledge, in all its forms, with a reasoning model to take advantage. Note that medical semiological reasoning is partly based on the cause and effect relationship [22], being able to combine deductive reasoning, abductive and inductive reasoning.

a) The General Form of Rules

- Type of rule: Rn
- Rule syntax:

1° Deductive reasoning
If <conditions> Then <conclusion1> Else <conclusion2>
Conditions: <condition1> [operator] <condition2> …
Conclusion: Conclusion1 (satisfaction), conclusion2 (alternative)

2° Abductive reasoning
Simple form A ⇒ B: "A produces, or explains";
(Or) If A⇒ C and B ⇒ C, then A ∨ B ⇒ C.

3° Inductive Reasoning
There are several equivalent forms of the induction principle. The most common, simple induction, proceeds in two stages:

* A base case (also called initialization):
M is an atom or a variable, its only subterm (*ST*) is itself;
If M is an atom Then ST(M) = { M };

* A recursive case (or inductive step):
M is an application of (*P Q*), the subterms of *M* are *M*, the subterms of *P* and the subterms of *Q*

If M ≡ (P Q) Then ST(M) = {M} ∪ ST(P) ∪ ST(Q).
- Some criteria of condition and primitive symbols: ⇒, ¬, ⊢, ∧, ∨, ~,<, >, <>, = .

b) Production Rules-Based System

Initially our system based on production rules relies on deductive reasoning. We present some basic rules.

(1) Clinical Diagnosis Rules (CDR):

It reasons on the association of patient's profile, a set of cooccuring symptoms and status or condition, following protocol to produce clinical decision:

CDR: If <profile> and <symptoms> and <status-condition> Then <clinical-diagnosis>

(2) Examination Rules (TR)

It reasons on the association of specific clinical diagnosis and exams following protocol to produce an exam results:

TR: If <clinical-diagnosis > and <exam > Then <exam-result>

(3) Medical Decision Rules (MDR)

It reasons on the exam results following protocol to produce a decision:

MDR: If <examen-result> Then <decision>

(4) Therapy Rules (ThR)

It reasons on the decision taken following protocol to produce prescription:

ThR: If <decision> and <performance-indicator> Then <drug-therapy>

3.2 Smart SDC Treatment

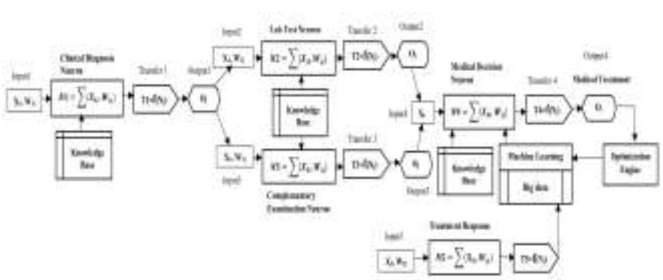

Fig 2 architecture of the artificial neural network system

Fig. 2, below, represents the architecture of our artificial neural network system called Smart SDC Treatment.

To better understand the architecture, we briefly describe the basic neurons (processing units).

4) Input data

The data source is the input data *X* that is a multidimensional set containing medical record information. The input data is define as a pair:

(X_1, W_{1j})

where X_1 a set of input values, W_{1j}, the weight associated to each input value, *I* a unit number of input values, *j* a unit number of weight values.

5) Clinical Diagnosis Neuron

It is formalized by the function below:

$$N_1 = \sum(X_{1i}.W_{ij}) \qquad (1)$$

where N_1 is a neuron, X_1 a set of input values, W_{ij}, the weight associated to each input value, *I* a unit number of input values, *j* a unit number of weight values.

6) Lab Test Neuron

It is formalized by the function below:

$$N_2 = \sum(X_{2i}.W_{ij}) \qquad (2)$$

where N_2 is a neuron, X_2 a set of input values, W_{ij}, the weight associated to each input value, *I* a unit number of input values, *j* a unit number of weight values.

7) Complementary Examination Neuron

It is formalized by the function below:

$$N_3 = \sum(X_{3i}.W_{ij}) \qquad (3)$$

where N_3 is a neuron, X_3 a set of input values, W_{ij}, the weight associated to each input value, *I* a unit number of input values, *j* a unit number of weight values.

8) Medical Decision Neuron

It is formalized by the function below:

$$N_4 = \sum(X_{4i}.W_{ij}) \qquad (4)$$

where N_4 is a neuron, X_4 a set of input values, W_{ij}, the weight associated to each input value, *I* a unit number of input values, *j* a unit number of weight values.

9) Optimal Therapy

The optimal therapy in our artificial neural network is obtained by recursive calculations of neurons from the input data. It is formalized by the functional equation below:

$$O_m = O(\sum_{1}^{j} F(N_{jm}, f(X_{4i}, W_{ij}))) \qquad (5)$$

where O_m, the optimized output; *F*, the transfer function of the output; N_{jm}, the parameter of the transfer function; X_4, set of input values; W_{ij}, the weight associated to each input value; *m*, unit number of output values; *i*, unit number of input values; *j*, unit number of weight values.

4. Discussion and Conclusion

The goal of smart SDC treatment is to find an optimal drug therapy based on an indicator of performance. To do this it is necessary to organize the information in big data as indicated in [23]. The organization of big data containing cases of sickle cell patients will be used for previous medical decision analysis to produce indicator performance [24].

Pointing out the medical decision *neuron N4*, the variable X_4 contains output of both clinical diagnosis and all necessary exams.

Let X_4 be an input value that implicitly contains the following: *PROFIL_SCD={Male} and STATUS={Sickle cell Patient}* and *SYMPTOM_SDC={Anemia, Episodes of Pain, Swelling of Hands and Feet}* associated to *EXAMN-RES_SCD={ Hemoglobin < 13.5 gm/dl; Hb-S is present}* produce *TYPE_SCD={Sickle cell anemia}* with the threshold transfer function *T4* produces *TREATMENT_SDC={Penicillin V, Hydroxyurea, Voxelotor}*.

We can construct the following model from this specification:

Neuron1: *If (Sex="Male" and Status="Sickle cell Patient" and Symptom="Anemia, Episodes of Pain, Swelling of Hands and Feet")*
Then Type-exam is"Hemoglobin, sickle cell solubility test"

Neuron2: *If (Examn-Result="Hemoglobin < 13.5 gm/dl; Hb-S is Present")*
Then Group_Pt is "Sickle cell anemia"

Neuron4: *If (Group_Pt="Sickle cell anemia" and Indicator_Performance is "Good")*
Then Drug_Therapy is "Penicillin V, Hydroxyurea, Voxelotor"

In itself, neuron 4 is a consequent of a composition and an association of different neurons. It has the ability to infer and acquire other information (unseen input) logically necessary and recursively for a better result (output).

Like any machine learning-based system, it requires learning. Our medical decision analysis system already mentioned is one of the foundation for learning. And it is the ultimate way to optimize the outcome.

Furthermore, sickle cell disease is a very surprising illness. It is clear that monitoring and improving data on drug interactions is crucial, especially in low-income countries.

This is where pharmacovigilance, supported by neuron 5 of our system, intervenes. It involves identifying patients' therapeutic responses and preventing morbidity.

It is turn out that the evaluation of the SDC smart treatment system is beyond the scope of this article. Certainly, this will be the subject of our next study and article which will focus on the experimentation and simulation of the system with a set of data.

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