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Artificial Neural Networks for Modeling the Interaction between Cytokines Inducing Lymphopenia in Patients with COVID-19

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Abstract
Objective: Cytokines induce tissue damage or inflammation due to infection, contributing to host defense through stimulation of hematopoiesis and acute phase immune reactions. The exaggerated synthesis of cytokines or cytokine storm is directly implicated in the critical cases of patients who have been affected by Corona Virus Disease 2019 (COVID-19). The cytokine storm may promote apoptosis or necrosis of T cells. Recent medical studies show T cell dramatic elimination and exhaustion in COVID-19 patients requiring Intensive Care Unit (ICU) care. However, no consensus on whether there is a negative correlation between cytokine concentration and lymphopenia exists. There is not even agreement on which are all the cytokines involved in this process. *How do the involved cytokines interact with each other and how do they affect the number of lymphocytes in patients affected by COVID-19?* Our objective has been to design a computational simulation of these interactions for predicting the lymphopenia in patients with COVID-19. *Methods:* Taking the data from a meta-analytic study of 10 medical articles carried out with laboratory findings of samples of patients (our dataset contains 10 samples with 261 complete data and 2,224 instances) affected by COVID-19, we have designed an artificial neural network (ANN) for modeling the process. *Results:* The learning algorithm has been cascade-correlation using backpropagation. Learning rate (η) has been 0.25 and target net error has been 0.01. The artificial neural network has predicted with a relative error less than 0.01 the influence of the biochemical cascade originated by cytokines in the lymphopenia of the patients affected by COVID-19. The prediction accuracy achieved has been 94%. *Conclusion:* This study has supported computationally the hypothesis that a higher level of serological concentration of cytokines can lead to a significant decrease in the lymphocite count of patients affected by COVID-19.

Keywords: Cytokines; Lymphopenia; Corona Virus Disease 2019 (COVID-19); Artificial Neural Networks (ANN); Cascade-Correlation Algorithm

Introduction

The Corona Virus Disease 2019 (COVID-19) epidemic caused by coronavirus 2 (SARS-Cov-2) has spread over more than 150 countries [1]. Patients infected with COVID-19 show abnormal respiratory findings, lymphopenia [2], and high levels of pro-inflammatory cytokines [3]. Additionally, and in the cases of severe patients and deceased, a value of blood C-reactive protein (CRP) above the normal range (0.3 to 1.0 mg/dL) [4] and high values of D-dimer, ferritin, fibrinogen and lactate dehydrogenase -5 (LDH-5) [5].

The cytokine storm syndrome (CSS) is a clinical process suggestive of massive inflammation progressing to multiple organ dysfunction syndrome and eventually death [6]. One of the primary

mechanisms for acute respiratory distress syndrome (ARDS), the common immunopathological event for SARS-Cov-2, is the cytokine storm [7]. CSS yields hemodynamic instability [8] represented by clinical features of circulatory shock. Also, this syndrome can produce abnormal hematological parameters, such as leukocytosis [9].

Cytokines are proteins that help cell proliferation and differentiation and communication between cells [10-12] in the inflammatory reaction. They regulate the immune response and activate signal transduction mechanisms in target cells [13]. The production of pro-inflammatory cytokines is a prerequisite to start the anti-infectious process. Pro-inflammatory stimuli may include antigens, superantigens, adjuvants (such as toll-like receptor-TLR-ligands), and allergens, in addition to the cytokines themselves [14]. When an infectious process initiates inflammation, the presence of microorganisms and their derived products are potent activators of cytokines production. Macrophages are one of the largest sources of cytokines.

All the studies considered in this article present laboratory findings of inflammatory markers and lymphocyte count in patients infected with SARS-Cov-2 [15-24], but there is only total coincidence in the influence of interleukin-6 (IL-6) in the process of severe lymphopenia [25] or lymphocytopenia that occurs in severe patients with COVID-19. Interleukin-6 (IL-6) is a prototypical cytokine featuring redundant and pleiotropic activity [26-28]**.** Il-6 was originally identified as B cell stimulating factor 2 (BSF-2), which induced immunoglobulin by producing plasma cells [29].

In addition to B cells, IL-6 also affects T cells by inducing the specific differentiation of naïve CD4+ T cells into effector T cell subsets. IL-6 also inhibits the induction of regulatory T cells.

IL-6 is produced by various cell types, such as monocytes, macrophages, T and B lymphocytes, glial cells, etc. [30]. The main stimuli for its synthesis and release are infections by certain microorganisms such as viruses and bacteria and the action of other cytokines such as IL-1 and TNF-α (Tumor Necrosis Factor-α). Several studies link IL-6 with exacerbation of the viral disease. Besides, experimental evidence supports the observation that overexpression of IL-6 during the viral immune response might induce viral persistence through different mechanisms, leading to chronic infections. As consequence of the constant antigen stimulation, CD8+ T cells become unresponsive, a situation that limits viral clearance [31-33]. Persistent IL-6 production may also contribute substantially to COVID-19 pathogenesis. Deceased patients or who stayed in ICU, presented high levels of IL-6. Specifically, in SARS-Cov-2 infection, the studies that provide the data collected in this article all agree that patients who were critically ill or who died had severe depletion of lymphocytes (see also [34-35]) and high IL-6 levels.

Common cytokines that mediate COVID-19, according to the studies analyzed in this article, are IL-1β, IL-2, IL-4, IL-10, IL-17, IFN-γ (Interferon-γ), TNF-α and, especially, IL -6.

Table 1 briefly describes the cytokines mentioned that are not IL-6.

Lymphopenia or lymphocytopenia is defined as a peripheral blood lymphocyte count < 1500/μL in adults. Strong lymphopenia is a very distinctive feature of severe and seriously ill patients with COVID-19 [40]. It accompanies severe systemic bacterial infections and many viral infections. Lymphocytes are immune cells made in the bone marrow. They are found in blood and lymphatic tissue. The two types of lymphocytes are B lymphocytes and T lymphocytes. B lymphocytes make antibodies, and T lymphocytes help control immune responses, among other functions. In COVID-19 it appears that T lymphocyte subsets (CD4+ helper cells and CD8+ cells) are highly affected by SARS-Cov-2. CD4+ T lymphocytes are involved in the activation and targeting of other immune cells. They are essential in the subsequent formation of antibodies by B lymphocytes and in the activation and growth of CD8+ lymphocytes or cytotoxic T lymphocytes. They are generated in the thymus and are key elements for immune defense against intracellular pathogens, including viruses and bacteria. When a CD8+ T cell recognizes its antigen and becomes activated, secrets TNF-α and IFN-γ cytokines with anti-viral and anti-tumor effects. CD8+ T cells can also contribute to an excessive immune response that leads to immune-mediated damage [41-42].

How does the action of cytokines influence lymphopenia that SARS-Cov-2 produces? There is **a** disagreement between those who defend the existence of a negative correlation between cytokine concentration and T cell numbers [21] and those who do not find a significant linear correlation between lymphocytes and cytokines [18].

Table 1. Brief description of common cytokines that mediate COVID-19

Cytokine	Description
IL-1	Interleukin-1 (IL-1), is a pro-inflammatory cytokine that promotes the acute response in the inflammatory phase. Reducing the ability of infected cells to generate the active form IL-1β has a significant effect on inflammation at the site of infection.
IL-2	Interleukin-2 (IL-2) is a glycoprotein produced by T cells and stimulates the proliferation of activated CD4+ and CD8+ subsets of T cells.
IL-4	Interleukin-4 (IL-4) was identified for its capacity to induce lipopolysaccharide (LPS) activated B cells [36]. T cells constitute a major source of IL-4 and IL-4 displays potent T cell growth factor activity.
IL-10	Interleukin-10 (IL-10) is a protein produced by several cell types including CD4+ and CD8+ T cells, natural killer (NK) cells and B cells. IL-10 is a major endogenous anti-inflammatory mediator [37]. IL-10 acts by inhibiting the synthesis of proinflammatory cytokines (i.e. TNF, IL-1, IL-6 and IL-8).
IL-17	Interleukin-17 (IL-17) was cloned in humans either from a CD4+ T clone or from activated peripheral blood mononuclear cells (PBMC). IL-17 may play a significant role in T cell-dependent inflammatory responses.
IFN-γ	Interferon-γ (IFN-γ) is a protein produced, even by non-lymphocytic cells such as macrophages, neutrophils and neurons [38]. Larger quantities are produced only under pathologic circumstances (trauma, infection, cancer, autoimmunity) by activated NK cells and T cells.
TNF-α	Tumor necrosis factor (TNF) designates a family of polypeptides. Many of the TNF receptor family members seem to play a relevant role in the regulation of the immune response and in the generation of cells involved in these responses. The ability to directly induce cell death is a feature of this family. One major function of the TNF family is to control T cell mediated immunity [39]. TNF-α is a member of the family and is very important for resistance to infection and cancers.

The aim of this study was to simulate computationally (using a cascade-correlation algorithm) the influence of cytokines on lymphopenia in patients with COVID-19, checking whether the statistical data provided by a meta-analytic study including the serological results obtained by 10 medical and laboratory analysis support the following hypothesis formulated in [21]: *higher concentration of cytokines in the serum of severe patients affected by COVID-19 results in a greater decrease in the number of lymphocytes*.

Material and Method

Dataset

Articles were identified through a computerized literature search using PubMed and The Lancet databases to find relevant studies with the search terms "Lymphopenia" OR "Cytokines" AND "Covid-19". The search was limited to English articles published between January 2020 and April 2020 that presented laboratory findings (at Hospital admission and ICU) of serum cytokine concentration and lymphocyte count appearing in patients diagnosed by COVID-19 (from mild to severe and critically ill patients). Additionally, a manual review of articles was performed using cross-references from subsequent original articles.

Method

It has been carried out a meta-analytic study on the clinical analysis of patients affected by COVID-19 that present laboratory findings of lymphocyte count and concentration of cytokines. The *hypothesis* to be tested has been the following: a higher concentration of cytokines, especially IL-6, produces a greater decrease in lymphocytes in severe patients affected by SARS Cov-2. For it, a computational simulation of the process has been created through a cascade backpropagation ANN (Artificial Neural Network).

The cascade-correlation architecture adds hidden neurons one by one in the network. In the process of adding new neurons to the network, each neuron receives a synaptic connection from each of the input neurons and from the hidden neurons that precede it. After adding each new hidden neuron, the synaptic weights of its inputs are frozen, while the weights of its outputs are repeatedly trained. This process continues until the execution desired is achieved. The cascade architecture allows adding a new hidden neuron each time and the new weights are updated. For each new hidden unit, the algorithm maximizes the magnitude of the correlation between the new hidden unit and the residual network error, that is, hidden neurons are added to try to reduce network error.

The computational architecture designed has consisted of 10 neurons, of which one is input and the other is output. As input, the first neuron (CYTOK) represents the total concentration of cytokines. From here, the neurons representative of the cytokines whose laboratory findings have detected a high presence in patients are added: first, interleukin-6 (IL-6), the interleukin in which all the articles consulted have agreed that it is always present and that it makes the greatest contribution to the cytokine storm that is triggered in severe patients affected by COVID-19. Then IL-10, TNF-α, IL-1β, IFN-γ, IL-4, IL-2, IL-17, respectively. The output neuron (LYMPH) represents the number of lymphocytes obtained from the interactions between cytokines. Figure 1 shows the structure of the ANN (all neurons are activated and the blue lines express inhibitory connections between neurons).

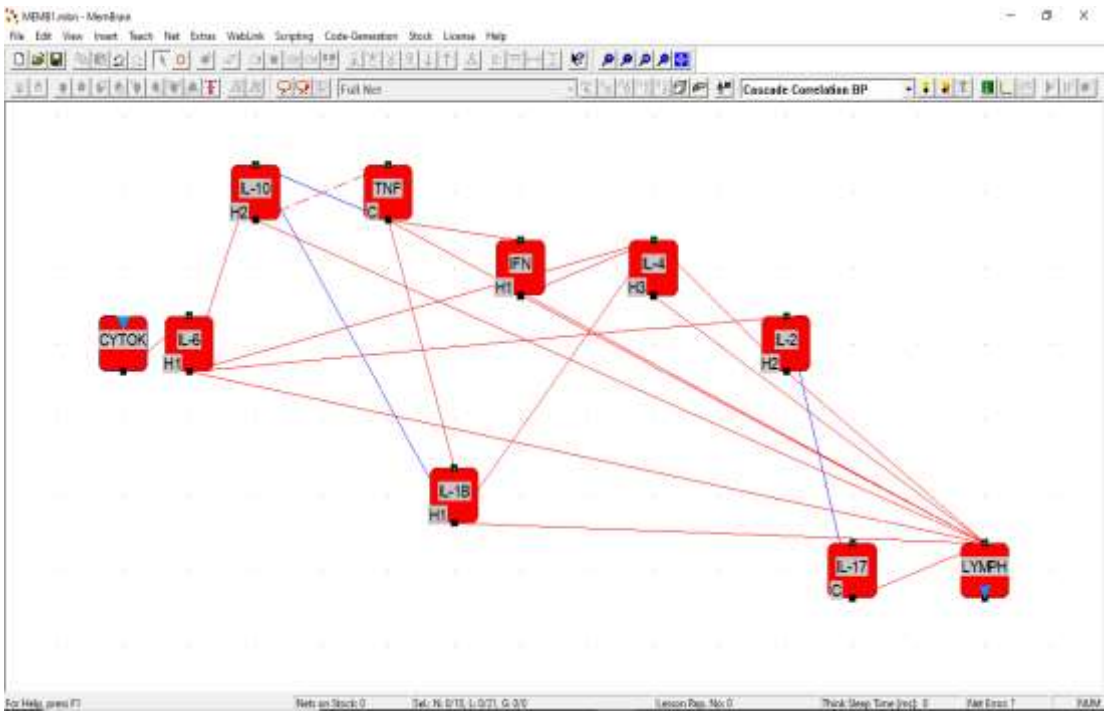

Figure 1. Structure of the used Artificial Neural Network

The learning algorithm has been cascade-correlation using backpropagation. Sigmoid (logistic) function has been used as a transfer function with values between -0.5 and 0.5. The activation function value has been 0.1. The learning rule has been applied to minimize the Mean Squared Error (MSE), which is calculated with the average difference between the observations and the expected values, obtaining the result with the iterations produced with the help of the learning algorithm.

Technical Information

MemBrain© (version V03.08.01.00) software has been used for the design of the ANN. It contains an implementation for some of the major learning algorithms, including cascade-correlation using backpropagation [43-47].

The learning algorithm has been cascade-correlation using backpropagation. Learning rate (η) has been 0.25, and the target net error has been 0.01, as can be seen in Figure 2.

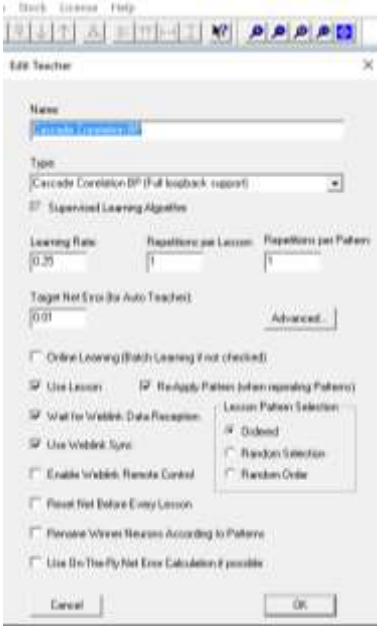

Figure 2. Edit Teacher showing learning algorithm, learning rate, and target net error

There are essentially two classes of parameters used in the cascade-correlation algorithm-those that are used to specify the weight modification, and those that control the generation of new nodes (candidate pool size and patience). We have performed a sequence of exploratory runs (lessons) sampling the weight parameter space. Maximum growth factor (μ) implies that no weight change can be allowed to be greater in magnitude. Maximum growth factor has been varied from 1.5 to 2.5 in steps of 0.25. Weight range specifies the range of values for randomly generated initial weights and has been varied from 0.5 to 1.5 in steps of 0.5. Weight decay (γ) ensures that the weights do not grow excessively, avoiding any possible floating-point overflow in changing of weights and has been 0.0.

The candidate pool size controls the space of possible cascading neurons, which is searched for the next hidden unit to recruit. Runs or lessons have been made with a size of candidate set (12) and a maximum number of candidates to add (8).

Patience is calculated from the change in error required over a period to continue training. The patience period is measured through epochs. The number of epochs is the number of complete passes through the training dataset. When the maximum number of epochs has been reached or no progress has been made in the training of the candidate neurons, the best candidate is placed into the network and the output layer is retrained; the algorithm cycles through installing hidden neurons.

The output value of the patience percentage has been 1% and the patience period has been 50 epochs since the learning error no longer decreased its value by performing more iterations, indicating that the network had been trained. The epoch limit has been 200.

Statistics

Confidence scores values provided by the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) protein-protein PPI database [48] have been employed. These confidence scores indicate the degree of biochemical interaction between cytokines from 0 to 1, taking into account factors such as co-occurrence, co-expression, genetic fusion, experimental evidence, and the number of databases that document the interaction ("0" denotes null interaction and "1" denotes total interaction). These values have served to calculate the weights of the connections between neurons in the proposed ANN. Besides, a graph on interactions between cytokines formulated by [49, p. 179]

has been employed to inspire the design of the ANN (the types of interaction selected have been activation, binding and inhibition).

Results

The search procedure yielded 24 articles. Of the original 24 articles found, 14 were excluded due to overlap between samples. Finally, 10 articles were included in the final analysis (Table 2). The overall sample size was 2,224 instances with serological findings including average cytokine concentration and average lymphocyte count. Lymphocyte count percentages were included in all cases. The dataset contained 10 samples with 261 complete data corresponding to the 9 attributes measuring cytokine concentration (8 attributes) and lymphocyte count (1 attribute).

Table 2. Reviewed articles included in the analysis

Ref	Cytokine concentration (CC)	Lymphocyte count (LC)*	Sample size
Chen, Wu et al. [15]	IL-1β (5 pg/ml) IL-6 (26.6 pg/ml) IL-10 (6.1 pg/ml) TNF-α (8.8 pg/ml)	900/μL	21
Wang, Lu et al. [16]	IL-2 (8.1 pg/ml) IL-6 (27.2 pg/ml) IL-10 (9.5 pg/ml) TNF-α (9.5 pg/ml)	900/μL (all patients in ICU)	344
Chen, Zhou et al. [17]	IL-6 (7.9 pg/ml)	900/μL	99
Wan et al. [18]	IL-4 (1.7 pg/ml) IL-6 (25.6 pg/ml) IL-10(3.6 pg/ml) IL-17 (1.1 pg/ml) TNF-α (3.5 pg/ml) IFN-γ (6 pg/ml)	1590/μL	123 63 123 123 123 118
Wang, Nie et al. [19]	IL-6 (13 pg/ml)	800/μL	60
Zeng et al. [20]	IL-6 (11.1 pg/ml)	1050/μL	752
Diao et al. [21]	IL-6 (45 pg/ml) IL-10 (9.5 pg/ml) TNF-α (12.5 pg/ml)	456.5/μL (critically ill patients)	522
Peng et al. [22]	IL-2 (2.3 pg/ml) IL-4 (1.9 pg/ml) IL-6 (9.1 pg/ml) IL-10 (4.6 pg/ml) IFN-γ (2.8 pg/ml)	1100/μL	32
Liu et al. [23]	IL-2 (2.3 pg/ml) IL-6 (30 pg/ml) IL-10 (6.1 pg/ml)	1100/μL	80
Zhou et al. [24]	IL-6 (7.4 pg/ml)	1000/μL	191

* below normal values: <1500/μL

The main interactions between the cytokines are presented in Table 3 and shows whether the interactions are positive (excitation) or negative (inhibition). In the left column the cytokines that influence other cytokines (in the right column).

Table 3. Main interactions between the most prominent cytokines that mediate in COVID-19

Cytokines	Interactions and confidence scores	Cytokines
IL-1β	Positive (excitation) (0.989)	TNF
IL-2	Negative (inhibition) (0.982)	IL-17
IL-4	Positive (excitation) (0.991) Positive (excitation) (0.996) Positive (excitation) (0.996) Positive (excitation) (0.992)	IL-1β IL-2 IL-6 TNF
IL-6	Positive (excitation) (0.997)	Il-10
IL-10	Negative (inhibition) (0.996) Negative (inhibition) (0.997)	IL-1β TNF
IL-17	Inhibited by IL-2	
IFN-γ	Positive (excitation) (0.975)	TNF
TNF	Positive (excitation) (0.997)	IL-10

The following Table 4 summarizes the results concerning to the main analyzed parameters for candidate and output layer training parameters.

Table 4. Main parameter settings for the cascade-correlation algorithm

Parameter	Candidate value	Output value
η	1.0	0.25
μ	1.75	1.75
γ	0.0	0.0
Patience percentage	3%	1%
Patience period (epochs)	50	50
Epoch limit	200	200
Activation function offset	0.0	0.1

As Figure 3 of the Net Error Graph shows, training results have averaged 10 runs or lessons and the Net Error has been 0.00941378550857168.

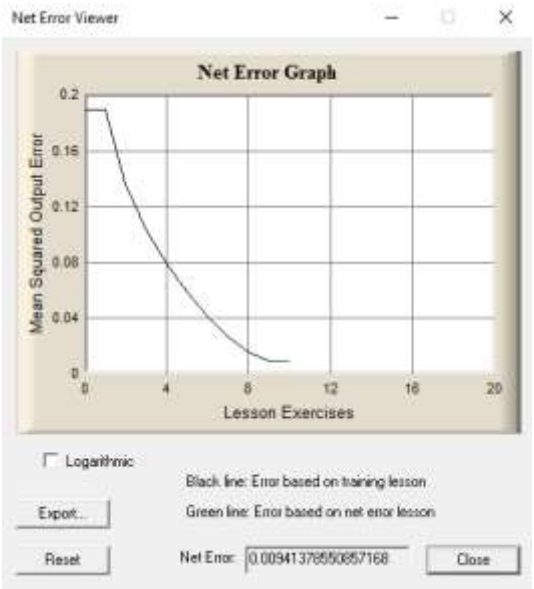

Figure 3. Net Error Graph

The accuracy achieved has been 94.1% with 8 hidden layers (1 neuron in each layer). Networks were defeated if they had failed to converge after recruiting 12 hidden units. Table 5 shows the results of training averaged over 10 lessons (the numbers in parentheses in both the average hidden units and average epochs columns indicate the minimum and maximum values).

Table 5. Results of training averaged over 10 lessons

Epochs	Average Hiddens	Average Epochs
200	4.5 (4/5)	132 (96/168)
100	5.5 (3/8)	147 (101/193)
50	8.0 (4/12)	109 (85/133)
20	7.0 (4/10)	87 (66/108)
10	defeated	defeated

Discussion

This is the first study, as far as the author is aware, in which the technique of artificial neural networks has been used to validate a hypothesis about the influence of high concentration of cytokines on the destruction and exhaustion of lymphocytes in severe patients affected by COVID-19. The main result has been the computational confirmation of the following hypothesis formulated by Diao et al. [21]: lymphocyte count is negatively correlated to serum cytokine concentration, specially IL-6, IL-10 and TNF-α concentration in severe patients affected by COVID-19. Based on the findings made so far, there seems to be a consensus on the influence of high concentrations of interleukin-6 (IL-6) in the serum of patients as a first-order factor of the disease severity. Less consensus seems to exist regarding the relevance of the intervention of other cytokines, which, however, also appear elevated above normal levels in this type of patient. On the other hand, in the recent medical literature related to the mechanisms of action of SARS-Cov-2, there also seems to be no unanimity regarding the hypothesis that this study has supported using a computational technique. And so, Wan et al. [18] indicates that there is no significant linear correlation between the lymphocyte subsets and cytokines. Only low levels of CD4 + and CD8 + T cells, as well as higher levels in IL-6 and IL-10, are common in severe patients but the authors insist that "large number of samples are still needed to confirm the warning value of CD4 + T, CD8 + T, IL-6 and IL-10 ".

We have taken a large sample of serological findings of 2,224 patients, of whom lymphocyte count and cytokine concentration were made during the hospitalization process. This sample has come from a meta-analytic study carried out from the serological tests of cytokines and the lymphocyte count found in 10 articles (see Table 2) published and available from internet between the months of January and April of 2020. All of them agreed that they were the only ones found at that time in which the cytokine and lymphocyte serological parameters were quantified and in which there was no overlap of samples from larger review studies. All the samples came from Hospitals in China. We would have liked to find studies that met the above requirements and that came from Hospitals in other nations but either did not present cytokine and lymphocyte counts or were studies of a few cases. These data have served us to train a neural network using the cascade-correlation algorithm.

A cascade-correlation algorithm can model very well the cascade interaction process that occurs in a cytokine storm like the one that takes place in severe COVID-19 patients and its influence on the level of lymphocytes. A cytokine storm is a phenomenon of signaling in a cascade of biochemical elements and the dynamic and constructive topology of a cascade neuronal architecture allows us to account for this process of complex biochemical interaction by progressively adding units that compete and interact with each other. Some cytokines inhibit others and others activate or reinforce them. The activation (excitation) and inhibition interactions between the cytokines that seem to mediate COVID-19 [49] have been instrumental in the design of our neural network. Thanks to the quantification of these interactions that we have found in the protein-protein interaction (PPI) database from STRING [48] (see Table 3), we have been able to carry out the task that has been most difficult for learning our neural network: adjusting the connection weights.

We can say that the results support the hypothesis established by Diao et al. [21]. With a very small margin of error (prediction efficiency has been as high as 94%), we have verified how a cascade-

correlation artificial neural network seems to fit very well with the prediction of the mentioned hypothesis.

The limitations of this study are precisely two: (a) it supports an inverse correlation hypothesis between parameters and not a causation hypothesis; (b) does not consider what may be the direct influence of cytokines on various lymphocyte subsets, such as CD4 + and CD8 + T cells. Otherwise, much more ambitious studies would be necessary, such as an extensive computational simulation of the cytokine storm triggered by COVID-19.

The medical implications of the computationally validated hypothesis are important in clarifying the disease and in the search for effective treatments. Almost 85% of patients with severe COVID-19 have lymphopenia [15] and the persistence of lymphopenia is a poor prognostic sign in terms of survival. The lymphopenia correlated with hypercytokinemia induced by COVID-19, would emerge as a biomarker that could be very useful in quickly predicting which COVID-19 patients will progress to critical cases and could be one of the keys to seek and develop effective pharmacological strategies against the new coronavirus. Drugs targeting lymphocyte proliferation or apoptosis, as suggested by Bermejo-Martín et al. [2] could help to prevent lymphopenia or restore lymphocyte count in severe patients suffering COVID-19. On the other hand, neutralizing key inflammatory mediators, are being used to cope with cytokine storm in COVID-19. And so, antibodies blocking the IL-6 receptor (tocilizumab and sarilumab) and TNF-blocking antibodies (e.g., adalimumab and golimumab) have been recommended for the hospitalized COVID-19 patients [49].

Conclusions

The neural network has been successfully possible to train for proving the hypothesis. Furthermore, the developed ANN has been the suitability of a computational architecture based on a cascade-correlation algorithm to simulate complex phenomena involving cascades of biochemical signaling such as the interaction between cytokines and their effects on cells of the immune system.

List of abbreviations

COVID = Corona Virus Disease
ICU = Intensive Care Unit
ANN = Artificial Neural Network
SARS-Cov-2 = Severe Acute Respiratory Syndrome Coronavirus-2
CRP = C-reactive protein
LDH = Lactate Dehydrogenase
CSS = Cytokine Storm Syndrome
ARDS = Acute Respiratory Disease Syndrome
TLR = Toll-Like Receptor
IL = Interleukin
BSF = B Cell Stimulating Factor
TNF = Tumor Necrosis Factor
IFN = Interferon
LPS = Lipopolysaccharide
NK = Natural killer
PBMC = Peripheral Blood Mononuclear Cells
CC = Cytokine Concentration
LC = Lymphocyte Count
MSE = Mean Squared Error
STRING = Search Tool for the Retrieval of Interacting Genes/Proteins
PPI = Protein-Protein Interaction

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