Medllecta:

Hematological preventive method (HPM)

Part 1.

[P-S Standard]

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Abstract.
Qualitatively new mechanisms for the analysis of blood cells and blood plasma proteins may open up the possibility of constructing a hematological data model (HDM) for early detection of a pathological process during the latent period of the disease. As such mechanisms, we use the algorithms of Sense Theory, a new mathematics for artificial intelligence.
In this article, we use the results of a clinical blood test as a practical example.

1. Introduction

At the current time, of the main types of medical diagnoses formed by the method of their construction, which are often used in practice, two can be distinguished: *a diagnosis by the therapeutic effect* and *a diagnosis by the result of the harmful effect of prescribed medications*.

Most of these types of diagnostics are extremely dangerous and lead to negative consequences for human health. While such, the most high-quality types of diagnostics, such as differential or synthetic diagnosis, are less and less encountered in practice by the attending physician.

This is primarily due to the large amount of information that the practitioner must know and clearly and quickly operate on it already with the patient's initial anamnesis.

“*Dysfunction of internal organs and systems of the human body is always an inflammatory process*.”

Inflammation as a typical pathological process develops according to general laws, regardless of the causes and localization caused by it. Immune, physiological and anatomical features of the human body leave an imprint on the course of the pathological process, however, its general hematological patterns remain.

The most informative medium about the state of the human body remains blood. The indicators of the blood system provide more than 70% of information about the patient's condition and are extremely reactive to any physiological and biochemical changes inside the body.

For the transition from a symptomatic method of treatment, which is widespread at the current time throughout the world, which only drowns out the pain syndrome and does not cure the disease itself, to a *hematological preventive method* (HPM) that allows to identify its etiological factors already at the stage of the latent period of the disease, it is extremely necessary to develop an innovative model of over-large volumes of medical data, as well as tools for working with such a model.

The main characteristic of this model should be the ability to construct and analyze *hematological patterns* of uniform and plasma blood components. The presence of a large number of both newly constructed patterns and historically confirmed and stored in the system will allow to quickly identify an incipient pathological process and its possible belonging to a certain disease, new or recurrent.

In our opinion, the Sense Theory [1] algorithms, which allow working in real-time mode with petabytes of data of various types, can become a very successful practical implementation in the construction of the above model.

2. Problem

The lack of a unified methodology for the dynamic construction of hematological patterns for the purpose of identifying pathological processes of diseases in the latent (incubation) period.

3. Solution

Below we will lay the foundation for the construction and practical implementation of a *hematological preventive method* (HPM) based on Sense Theory algorithms, using the example of a general clinical blood test.

Inflammation.

In the process of inflammation, the transition of plasma proteins and blood leukocytes from microcirculatory vessels to the focus of damage occurs. Damage, in turn, can be caused by various factors: biological, physical, chemical, psychogenic. The entire course of the inflammatory process is controlled mainly by endogenous chemicals [2], inflammatory mediators, which appear in the focus of inflammation.

The role of inflammatory mediators can be played by:

- lipids,
- peptides,
- proteins,
- monoamines,
- nucleosides,
- proteoglycans.

There are two main groups of inflammatory mediators. The first group of inflammatory mediators is formed before damage. The second group forms immediately after damage. One of the main inflammatory mediators of the first group is histamine. Prostaglandins can be distinguished as mediators of the second group.

Histamine.

Histamine is a decarboxylation product of the amino acid histidine. Its main source is tissue mast cells and human blood basophils. Mast cell degranulation, histamine release, can be triggered by various stimuli:

- adenosine triphosphoric acid (ATA),
- heating/cooling,

- neuropeptides,
- complement fragments,
- E immunoglobulins.

The set of stimuli forms No-Sense Set [1]:

$$\mathfrak{S}_N = \{\text{ATA, heating/cooling, neuropeptides, complement fragments, E immunoglobulins}\}, \quad (1)$$

where N =5.

Further, let us denote degranulation as the zero object $\circledcirc_D$ and obviously get the following expression:

$$S = (\circledcirc_D)\{\mathfrak{S}_5\} \quad (2)$$

where S – Sense Set.

The validity of this expression is confirmed by the fulfillment of the following equality:

$$\lim_S \mathfrak{S}_5 = \circledcirc_D \quad (3)$$

From the general definition of a sense sequence, we have:

$$\mathfrak{S} = \{\{genetic\}, \{common\}\} \quad (4)$$

where

{genetic} – genetic properties (for its zero object),

{common} – common properties (for its zero object),

and, the expression (2) can be written in the following form:

$$S_H = (\circledcirc_D)\{G_2, \mathfrak{S}_5\} \quad (5)$$

where G_2 = {mast cells, blood basophils}.

Histamine, $\circledcirc_H$, as a derivative of the degranulation process can be expressed by the following expression:

$$\lim_{S} S_{O(H)} = ◎_{H} \tag{6}$$

where $S_{O(H)} = (◎_{H})\{S_H\}$.

The action of histamine on target cells in the focus of inflammation is realized through special receptors: H_1 and H_2.

H_1 agonists (AgH_1):

- 2-ethylamine,
- 2-methylhistamine

H_2 agonists (AgH_2):

- dimaprit
- 4-methylhistamine

H_1 antagonists (AnH_1):

- levocetirizine
- desloratadine
- chlorpheniramine
- mericamine
- diphenhydramine
- clemastine

H_2 antagonists (AnH_2):

- ranitidine
- nizatidine
- roxatidine
- cimetidine
- famotidine

Consequences of H_1 activation ($ConH_1$):

- an increase in the content of cGMP in target cells
- increased vascular permeability
- smooth muscle contraction

Consequences of H_2 activation ($ConH_2$):

- muscle contraction of the esophagus

- secretion of hydrochloric acid
- an increase in the content of cAMP in target cells

In terms of Sense Theory, the consequences $ConH_1$ of activating AgH_1 can be written as follows:

$$S_1 = (ConH_1)\{AgH_1\}, \tag{7}$$

where

$ConH_1$ - zero object (Z_0) of the above three values,

AgH_1 – sense sequence of the above two values,

as well as for the consequences $ConH_2$ of activating AgH_2:

$$S_2 = (ConH_2)\{AgH_2\}, \tag{8}$$

where

$ConH_2$ - zero object (Z_0) of the above three values,

AgH_1 – sense sequence of the above two values.

In practice, having received blood test data, for example, an increased norm of the content of complement fragments (C3a, C5a):

$$\mathfrak{S}_2 = \{\mathrm{C3a}, \mathrm{C5a}\}, \tag{9}$$

we get the expression:

$$(\circledcirc_D)\{\mathfrak{S}_2\} = S \tag{10}$$

which assumes the presence of a process of degranulation of mast cells.

Further, for more information about the incipient inflammatory process, we can take the semantic derivative on p_i-properties on union [3]:

$$S_f^{diff}(p_i)(\mathfrak{S}_2) = [S_f(\mathfrak{S}_2) \cup S_f(\mathfrak{S}_1)] = S_f(\mathfrak{S}_3) \tag{11}$$

where

$\mathfrak{S}_1$ - {ATP}

,

$\mathfrak{S}_3$ - {C3a, C5a, ATP},

p_i - i-property of $\mathfrak{S}_2$,

$\mathfrak{S}_1$ - $\underset{S}{PN}(\mathfrak{S}_1(p_i))$, where $\underset{S}{PN}$ – sense punctured neighborhood.

$S_f(\mathfrak{S}_3)$ is a sense function [4] defined on the set $\mathfrak{S}_3$. This set is a sense sequence because the following equality holds:

$$\circledcirc_D \subset \mathfrak{S}_3 = S \tag{12}$$

To obtain a *complete* picture of the inflammation process, the calculation of the semantic derivative can be performed until the following equality is satisfied:

$$S_f(\mathfrak{S}_3) \overset{S}{=} S_f(\mathfrak{S}_N) \text{ [5]}, \tag{13}$$

or, for example:

$$S_f(\mathfrak{S}_3) \overset{S}{=} S_f(\mathfrak{S}_5) \text{ (see (2))} \tag{14}$$

In other words, the semantic derivative makes it possible to find all possible stimuli causing degranulation of mast cells and, as a consequence, the presence of an inflammatory process at the earliest stages of its manifestation.

For example, an expression describing the entire inflammatory process from the moment of its inception to the moment of the consequences of AgH_1 activation can be written as follows:

$$ConH_1\{(AgH_1)\{(\circledcirc_H)\{\circledcirc_D\}\}\} = S_N \tag{15}$$

where $S_N = \underset{S}{\text{grad}}\, S_f$ [5].

The expression (15) exists if and only if there is a sense limit for each of the expressions:

$$\lim_{S} AgH_1 = ConH_1 \tag{16}$$

$$\lim_{S} ⓪_{H} = AgH_1 \tag{17}$$

$$\lim_{S} ⓪_{D} = ⓪_{H} \tag{18}$$

It is worth noting that the process of degranulation itself stimulates the synthesis of new inflammatory mediators, the source of which is the lipids of the membranes of activated mast cells and basophils. Among those mediators are prostaglandin D_2, which leads to an increase in vascular permeability.

The most important element of the inflammatory process is also *complement*, which is a system of proteins interacting with each other, present in an inactive form in blood plasma and other body fluids. When inflammation occurs, complement proteins form new inflammatory mediators (C2a, C3a, C4a, C5a, etc.) and, also form protein complexes that are involved in the lysis of alien cells. Protein complexes, in turn, synthesize the C3-convertase enzyme, which breaks down component C3. The C3-cleavage process marks *the beginning of a common component activation pathway*.

So if we denote the immunoglobulins G and M for $⊘_{I}$ and the component C1 of the complement for $⓪_{C1}$, then the existing sense limit,

$$\lim_{S} ⊘_{I} = ⓪_{C1} \tag{19}$$

,

where $⓪_{C1}$ - zero object of C1,

will mean the activation of the C1 component. Which, in turn, guarantees the existence of two other sense limits,

$$C2 = \lim_{S} \{⓪_{C1}\} \tag{20}$$

where $\{⓪_{C1}\}$ - sense sequence consisting of one element,

or

$$◎_{C2} = \lim_{S} \{◎_{C1}\} \tag{21}$$

and,

$$C4 = \lim_{S} \{◎_{C1}\} \tag{22}$$

or

$$◎_{C4} = \lim_{S} \{◎_{C1}\} \tag{23}$$

The existence of the sense limits (20), (21), (22) and (23) means the activation of the C2 and C3 components. In turn, the existence of these limits guarantees the existence of the following sense limit:

$$\lim_{S} \{◎_{C2}, ◎_{C4}\} = ◎_{C3\text{-}Con}, \tag{24}$$

where $◎_{C3\text{-}Con}$ - C3-convertase.

Unlike the semantic derivative discussed above, which allows us to determine each subsequent step of the inflammation process, the Sense Theory also has a mechanism for obtaining information about the previous stages of the inflammatory process. This mechanism is called the semantic integral [6]:

$$\oint\oint\oint [S_f(◎_{C3\text{-}Con})] = S_F^{\circ}''' = S_f(\mathcal{S}_I), \tag{25}$$

where $\mathcal{S}_I$ - set of immunoglobulins.

The most important mediators of inflammation, products of complement activation, are fragments C3a, C4a and C5a. These fragments are called anaphylatoxins. Anaphylotoxins trigger critical cellular responses, including:

- release of histamine
- PAF
- interleukin-1 activation
- release of serotonin
- activation of arachidonic acid metabolism
- chemotaxis of leukocytes
- etc.

One of the important cellular responses is the activation of the metabolism of arachidonic acid. One of the derivatives of arachidonic acid is *prostaglandins*. The full cycle from the moment of complement activation to the receipt of certain inflammatory mediators at a certain stage of the inflammatory process can also be expressed through the mechanisms of the Sense Theory.

As a rule, the process of inflammation is divided into three phases:

1. *Alteration*. The stage of the onset of the inflammatory process when a pathogenic irritant affects the tissues of the human body and leads to their destruction.
2. *Exudation*. Migration of blood cells from blood vessels to human tissues and organs.
3. *Proliferation*. Reproduction of new cells to replace dead ones.

Each phase can be described by a Neuro-Amorphic Function [7] that allows one to approximate the dynamics of inflammation changes within the human body. For example, *the primary alteration* caused by the action of the damaging factor, phlogogen, can be expressed by the following neuro-amorphic function:

$$m_1 = \alpha e^{(\beta \sqrt[3]{x} - e^{\frac{x^2}{\gamma}})}, \quad (26)$$

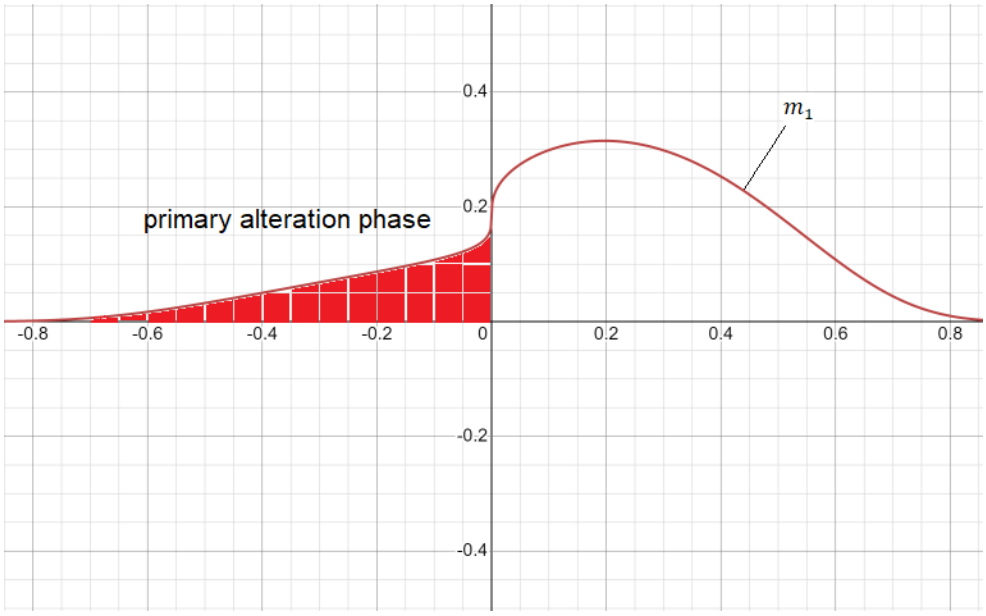
where

$\alpha = 0.5,$

$\beta = 1.1,$

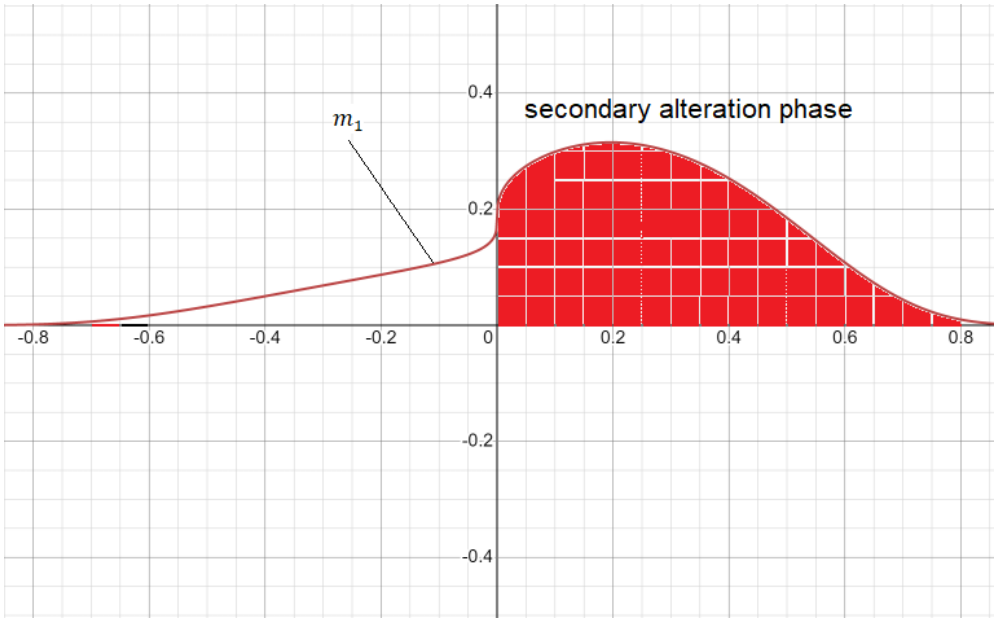
$\gamma = 0.4,$

$x \in \{-\infty; 0\}.$



pic.1. Primary alteration

To reflect *the secondary alteration*, when biologically active substances are activated and the immune mechanisms of the human body are triggered, the neuro-amorphic function can be used in the interval $\{0, +\infty\}$.



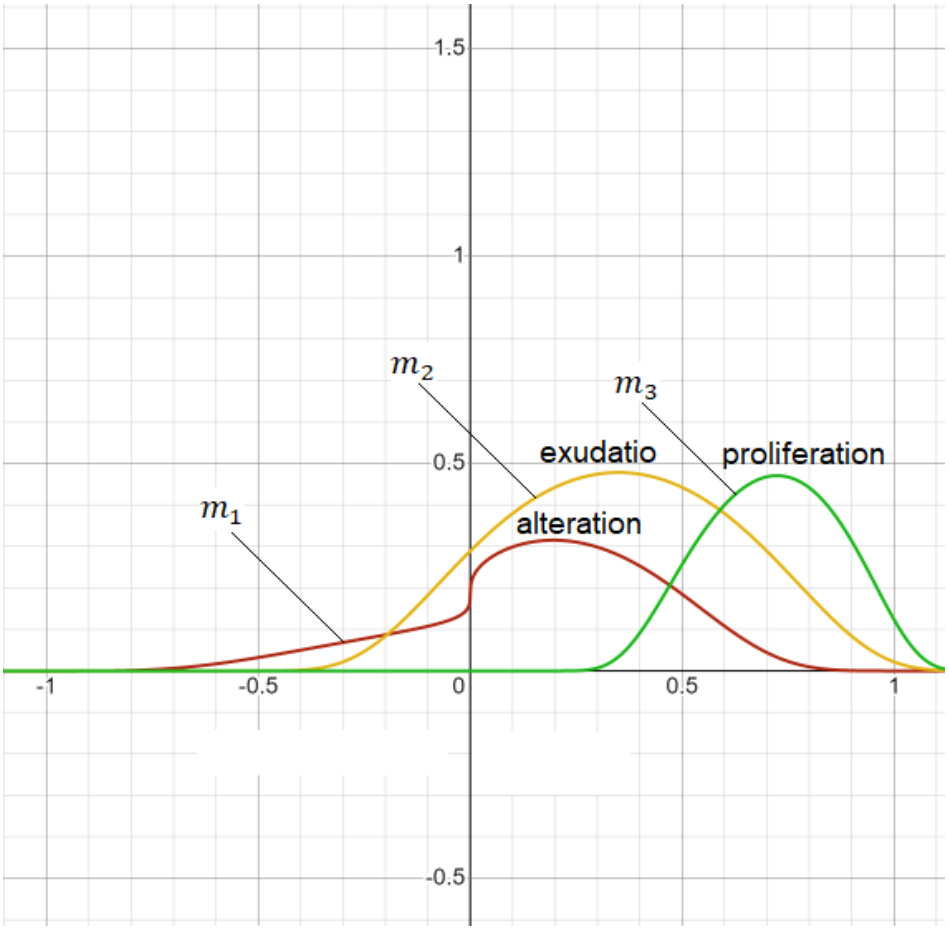
pic.2. Secondary alteration

All three phases of the inflammation process can be expressed by three neuro-amorphic functions:

$$m_1 = 0.5e^{(1.1\sqrt[3]{x} - e^{\frac{x^2}{0.4}})}, \text{ (alteration)} \quad (27)$$

$$m_2 = 1.3e^{(-e^{\frac{(x-0.3)^2}{0.3}})}, \text{ (exudation)} \quad (28)$$

$$m_3 = 0.4e^{(1.1\sqrt[3]{x} - e^{\frac{(x-0.7)^2}{0.1}})}, \text{ (proliferation)} \quad (29)$$



pic.3. Inflammation phases

General clinical blood test.

Let's consider a brief implementation of the Sense Theory mechanisms using the example of such a common disease as *anemia*. As an informational basis, we will take laboratory tests that evaluate the functions of erythrocytes:

- Erythrocytes count
- Hemoglobin
- Hematocrit
- Mean cell volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC, color index)
- Red cell distribution width (RDW)

All the results of the above laboratory tests can be combined into one No-Sense Set, $\mathfrak{S}_E$. This set becomes a Sense Set only when the following equality is fulfilled:

$$\lim_{S} \mathfrak{S}_E = ⓪_A \tag{30}$$

where $⓪_A$ - zero object of Anemia.

In other words, when one or several indicators of laboratory tests included in $\mathfrak{S}_E$ deviate from their normal values, then they indicate the possible presence of anemia. The anemia group is determined by $⓪_E$ value, that is, those values of $\mathfrak{S}_E$ elements that deviated from their norm. In turn, such erythrocyte indices as *the mean cell volume* and *color index* also help to determine the causes of anemia.

The underlying causes of anemia are:

1. blood loss (trauma, surgery)
2. chronic inflammation (infection, malignancy)
3. iron deficiency
4. erythropoietin deficiency (chronic renal failure)
5. vitamin B_{12} deficiency (pernicious anemia)
6. bone marrow stem cell deficiency (aplastic anemia)
7. increased rate of destruction of erythrocytes, <120 days (hemolytic anemia)

Since the above causes lead to specific consequences, types of anemia, they can be combined into one sense sequence $\mathfrak{S}_{O(C)}$ which will satisfy the following expression:

$$S_f(\mathfrak{S}_{O(C)}) = \{◎\}_i \quad (31)$$

where $i - number\ of\ types\ of\ anemia$, $\mathfrak{S}_E \in \mathfrak{S}_{O(C)}$.

The value of the sense function $S_f(\mathfrak{S}_{O(C)})$ is determined by the activated values of the elements of the semantic sequence $\mathfrak{S}_{O(C)}$. Which, in turn, leads to a specific $◎_i$ value. For example, when constructing a *differential diagnosis*, the doctor must determine the main symptom in the primary anamnesis. This symptom, in turn, can be caused by one or several reasons (different etiology). Further, moving from symptomatology to analyzing the results of a general clinical blood test, the doctor either confirms or refutes the primary diagnosis based on the main symptom.

Let's consider a practical example.

Let's say we received the results of a general clinical blood test of a male patient:

Erythrocytes count: $3.6x10^{12}/l$,
Hemoglobin: $9.8\ g/dl$,
Hematocrit: 37%,
Mean cell volume (MCV): $70\ fL$,
Mean corpuscular hemoglobin concentration (MCHC, color index): $20\ g/dL$,
Red cell distribution width (RDW): 18%.

Let us denote them by $\mathfrak{S}_6$ .The first indicator, the number of red blood cells is reduced. A moderate decrease in red blood cells leads to the activation of elements 4, 5, 6 and 7 of $\mathfrak{S}_{O(C)}$ (31). This, in turn, leads to the existence of the following four equations:

$$S_f(\mathfrak{S}_{O(1)}) = ◎_{CRF} \quad (32)$$

where $◎_{CRF}$ - zero object of chronic renal failure,

$$S_f(\mathfrak{S}_{O(1)}) = ◎_{PA} \quad (33)$$

where $\circledcirc_{PA}$ - zero object of pernicious anemia,

$$S_f(\not{S}_{O(1)}) = \circledcirc_{AA}, \quad (34)$$

where $\circledcirc_{AA}$ - zero object of aplastic anemia,

$$S_f(\not{S}_{O(1)}) = \circledcirc_{HA}, \quad (35)$$

where $\circledcirc_{HA}$ - zero object of hemolytic anemia.

Hemoglobin is significantly reduced from the norm for male patient. This, in turn, immediately activates and adds more weight to element 3 (iron deficiency) of $\not{S}_{O(C)}$ and determines the following equation:

$$S_f(\not{S}_{O(C)})_3 = \circledcirc_{IDA}, \quad (36)$$

where $\circledcirc_{IDA}$ - zero object of iron deficiency anemia.

Hematocrit is reduced but not below the critical values (<20%).

MCV is significantly reduced, which leads to confirmation of the existence of the following expression:

$$S_f(\not{S}_{O(C)})_3 = \{\circledcirc\}_i, \quad (37)$$

where $i = \{1,2\}, 1 - IDA, 2 - thalassemia$,

or

$$S_f(\not{S}_{O(C)})_3 = \circledcirc_M, \quad (38)$$

where $\circledcirc_M$ - microcytic anemia.

Index 3 in the expressions (37) and (38) means that iron deficiency cause has more weight than thalassemia one in the world medical practice.

RDW is increased which confirms the choice of the iron deficiency cause (36, 38).

Further, having made a preliminary diagnosis of *iron deficiency anemia*, we look at the sense sequence $\mathfrak{S}_F$ for which the following condition is satisfied:

$$\circledcirc_M \subset \mathfrak{S}_F = S_{IDA}, \tag{39}$$

$where\ \mathfrak{S}_F = \{serum\ iron, serum\ ferritin\}$, $S_{IDA} = Sense\ Set\ of\ IDA$.

The fulfillment of the condition (39) does not mean the final diagnosis, since iron deficiency can be caused by several more reasons, that is, the element $\circledcirc_1$ *of the set of zero objects* $\{\circledcirc\}_i$ *in expression (37) can also be an element of another sense sequence tending to a zero object (cause) of a higher order.*

Thus, the construction of a *hematological preventive method (HPM)* consists in the construction of a sense, synapse-to-synapse (S2S) network, where the activation of one or millions of elements of any sense sequence leads to the activation of one or more zero objects (causes, diagnoses) at a certain point in time.

The weights for each activated element of the sense sequence are calculated based on its deviation from its normal value accepted in medical practice, as well as the hematological pattern of the values of blood corpuscles at a certain stage of the inflammatory process.

4. Conclusion

In this article, we have described the primary mechanisms of the Sense Theory for the problems of diagnosing medical diseases at the early stages of the pathological process.

We hope that our decent work will help other researchers in their life endeavors.

To be continued.

References

[1] E. Mielberg, “Sense Theory. Part 1”, 2018, https://vixra.org/pdf/1905.0105v1.pdf

[2] Y. Sverdlov, “Inflammation mediators”, 2006, https://rsmu.ru/fileadmin/templates/DOC/Faculties/LF/pathophysiology/mediatory_vospaleniya.pdf

[3] E. Mielberg, “Sense Theory. Derivative, Part 3”, 2019,

https://vixra.org/abs/2003.0116

[4] E. Mielberg, “Sense Theory. Sense Function. Part 2”, 2018, https://vixra.org/abs/1907.0527

[5] E. Mielberg, “Arllecta: A Decentralized Sense-To-Sense Network”, 2019, https://vixra.org/abs/2002.0314

[6] E. Mielberg, “Sense Theory. Antiderivative, Part 4”, 2020,

https://www.researchgate.net/publication/344876386_Sense_Antiderivative

[7] E. Mielberg, “Neuro-Amorphic Function (NAF)”, 2018,

https://www.researchgate.net/publication/344903625_Neuro-Amorphic_Function_NAF

[8] L. Abdulkhaleq, M. Assi, R. Abdullah, M. Zamri-Saad, Y. Taufiq-Yap, M. Hezmee, “The crucial roles of inflammatory mediators in inflammation: A review”, 2018, https://www.semanticscholar.org/paper/The-crucial-roles-of-inflammatory-mediators-in-A-Abdulkhaleq-Assi/64580c0ce4a0ba820559d75b58ff49e03deaa74e

[9] G. Larsen, P. Henson, “Mediators of Inflammation”, 1983, https://www.annualreviews.org/doi/abs/10.1146/annurev.iy.01.040183.002003?journalCode=immunol

[10] C. Higgins, “Understanding Laboratory Investigations: A Guide for Nurses, Midwives and Health Professionals”, 2013

[11] M. Ingerleib, “Laboratory tests. Complete reference”, 2011