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Review Article

A Systematic Review of Mathematical and in Silico Models in Ischemic Stroke Research

Valentin V Fursov[1,2,4], Aleksandr V Ananyev[2], Daria I Zinchenko[2], Ilia V Fursov[5], Alexander A Bukhvostov[1], Pasha IO Musayev-Galbinur[6] and Dmitry A Kuznetsov[1,3]*

[1]*N.I. Pirogov Russian National Research Medical University, https://rsmu.ru, Moscow, Russia*

[2]*D.I. Mendeleev University of Chemical Technology, https://www.muctr.ru, Moscow, Russia*

[3]*N.N. Semenov Federal Research Center for Chemical Physics, https://www.chph.ras.ru, Moscow, Russia*

[4]*Peoples' Friendship University of Russia, www.rudn.ru, Moscow, Russia*

[5]*Mkhitar Gosh Russian Armenian International University, www.ariu.org, Yerevan, Armenia*

[6]*Azerbaijan Medical University, www.amu.edu.az, Baku, Republic of Azerbaijan*

***Corresponding author:** Prof. Dr. Dmitry A. Kuznetsov, Department of Medical Nanobiotechnology, N. I. Pirogov Russian National Research Medical University, Ostrovityanova str., 1, Moscow, Russia, 117997.

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Abstract

Background: Ischemic stroke and other circulatory system disorders continue to be a major global cause of mortality and long-term disability. Given the extreme sensitivity of neural tissue to oxygen deprivation and the inherent constraints of in vivo research, there is an urgent need for innovative methodologies. Among these, computer based (in silico) modeling stands out as a particularly promising alternative.

Objective: This review aims to survey contemporary mathematical and computational models employed in ischemic stroke research, assessing their role in advancing our understanding of stroke pathogenesis.

Methods: We conducted a systematic analysis of modeling approaches in stroke research, tracing their development from simple homogeneous models through phenomenological frameworks that capture core pathophysiological mechanisms, to advanced spatial models of neuroinflammation and cutting edge stochastic simulations based on cellular automata and neurovascular unit (NVU) concepts.

Findings: The trajectory of ischemic stroke modeling reveals a clear trend toward greater sophistication, with an increasing emphasis on spatial dynamics and biologically relevant constructs like the neurovascular unit. Current models go beyond qualitative descriptions, enabling quantitative alignment with empirical findings from laboratory studies.

Conclusion: Computational and mathematical modeling have emerged as essential instruments in stroke research. They facilitate the synthesis of fragmented experimental data, enable rigorous testing of pathogenic hypotheses, and pave the way for novel neuroprotective strategies.

Keywords: Ischemic Stroke; Mathematical Modeling; Computer Modeling; In Silico; Neurovascular Unit; Cellular Automata; Monte Carlo Method; Neuroinflammation

Abbreviations: NVU: Neurovascular Unit; CA: Cellular Automata; CUDA: Compute Unified Device Architecture; GPU: Graphics Processing Unit; VGCC: Voltage-Gated Calcium Channels; LBM: Load Buffer Memory

Introduction

Ischemic stroke, also known as a cerebral infarction, is a serious disease that occurs as a result of impaired blood circulation in the brain. Ischemic stroke is the death of a section of brain tissue as a result of insufficient supply of blood and oxygen to the brain due to blockage of an artery. This condition is characterized by insufficient blood supply to certain areas of the brain, which leads to the death of neurons and disruption of their functions. Ischemic stroke accounts for about 80% of all stroke cases and is one of the leading causes of disability and mortality in the world. This pathological process develops as a result of a critical disruption of normal blood flow in the vessels feeding the brain, which, in turn, leads to the death of brain cells, their subsequent damage and, as a result, to serious disorders in the brain, affecting the entire human life. To create effective therapies for ischemic stroke requires a deep understanding of its mechanisms and risk factors. Mathematical modeling is a powerful tool that allows us to study the complex processes occurring in the human body during the development of this disease. The development of mathematical models can help identify key factors influencing the development of stroke, as well as determine optimal treatment strategies. The development of a mathematical model of ischemic stroke is an urgent task in the field of medicine, as this disease continues to be one of the leading causes of disability and mortality among the population. Understanding the mechanisms of stroke development and the risk factors contributing to its occurrence is critically important for improving prevention and treatment methods.

Main Body

Modeling of ischemic stroke. Approaches and results

Ischemic stroke is an acute cerebrovascular accident that occurs due to blockage of cerebral vessels. As a result, brain cells do not receive enough oxygen and nutrients, which leads to their death. Ischemic strokes can occur for various reasons, including atherosclerosis, hypertension, diabetes mellitus, atrial fibrillation, and other diseases. Risk factors are also smoking, obesity, sedentary lifestyle, and old age. The symptoms of an ischemic stroke depend on which area of the brain is affected. These may include weakness or paralysis on one side of the body, speech, vision, coordination, loss of sensitivity, and problems with memory and thinking. Research on ischemic stroke is of critical importance because of its significant impact on human health, as well as because of the need to develop more effective methods of treatment and prevention.

The absolute incidence of various forms of stroke increased by 70% in just 30 years of follow-up, and the prevalence increased by 85%. At the same time, mortality rates also increased (by 43%). In Russia, 445,959 cases of stroke were registered in 2019, mortality – 327,885 cases, prevalence – 3,020,719 [1]. The importance of research on the topic of brain stroke is also evidenced by the special attention paid to this topic by the national Healthcare project [2]. Ischemic stroke, which is one of the main causes of death and disability among the world's population, is a serious problem for the healthcare system. According to experts, by 2030, the number of deaths caused by this disease may increase to 4.9 million people, which is a very significant figure and requires close attention [3]. These statistics highlight the need to improve preventive measures and treatment approaches that aim to reduce the risk of developing ischemic stroke and increase the effectiveness of therapy for those who are already ill.

In recent decades, modeling of physical, chemical, and biological processes has gained importance not only as a tool for understanding the world around us, but also as a basis for decision-making in high-tech companies [4]. Despite decades of research, there are still no widely recognized neuroprotective or neuro-therapeutic drugs, which makes research in this area extremely necessary [5]. Research in this area opens up new horizons in understanding the mechanisms of the brain and provides hope for the development of innovative therapeutic approaches. Modeling of ischemic stroke is the creation of mathematical or computer models that help to understand the mechanisms of disease development and evaluate the effectiveness of various treatment methods. There are several basic methods for modeling ischemic stroke:

Physical and mathematical modeling. This method is based on the use of the laws of physics and mathematics to describe the processes occurring in the human body during the development of ischemic stroke. Physical and mathematical models can be used to study parameters such as blood flow, pressure, temperature, and others.

Computer simulation. This is a method that uses computer programs to create virtual models of the human body. Computer models can be more complex and realistic than physical and mathematical models, and they allow us to study processes occurring at the cellular level.

Experimental modeling. This method involves conducting experiments on animals or human brain tissues. Experimental models provide more accurate data on the mechanisms of ischemic stroke development, but their use is limited by ethical considerations.

Each of these methods has its advantages and disadvantages, and the choice of method depends on the goals and objectives of the study. For example, physical and mathematical modeling can be used to quickly obtain preliminary results, and computer modeling can be used to study the mechanisms of disease development in more detail. Experimental modeling provides the most accurate results, but its use is limited by ethical and practical considerations.

The improvement of preclinical models and research methods contributes to a more successful translation into clinical settings [6]. These models are aimed at providing a more accurate and predictable reproduction of biological processes, which, in turn, contributes to a more efficient transfer of research results from the laboratory directly into clinical practice. Improving these models and methods allows not only to improve the quality of scientific research, but also to significantly increase the likelihood of successful development and implementation of new therapeutic approaches and medicines that will meet modern requirements and expectations in the field of healthcare.

The development of a mathematical model of ischemic stroke is crucial for understanding its complex mechanisms and improving patient outcomes. These models facilitate the integration of biological data at various scales, allowing researchers to model disease development and treatment response. Using computational systems biology, doctors can predict outcomes and optimize therapeutic strategies, ultimately improving the decision-making process in an emergency setting.

Cellular automata (CA) are a discrete dynamical system. It develops in discrete time steps, while the next state of the lattice of a cellular automaton depends on its previous state. Most models of physical phenomena, including Conway's "game of life," use a two-dimensional grid governed by complex rules. The general definition of a cellular automaton includes the following parameters: A grid is defined together with its boundary conditions. Many implementations use periodic boundary conditions.; Therefore, a two-dimensional (2D) grid represents the surface of a torus.

One of the main applications of cellular automata in biology is the study of tumor growth. There are a number of characteristics of the tumor environment that are difficult to model in discrete terms, such as nutrient levels, toxin levels, and pH levels of the cell's extracellular environment. However, it is possible to determine the rules of the cellular automaton based on the following characteristics associated with tumor growth.

Despite the fact that modeling methods have significantly advanced the study and treatment of ischemic stroke, problems remain due to the fact that these models do not always accurately reflect the complexities of human physiology and pathology. Further improvement and verification of these systems are necessary for the implementation of research results in clinical practice.

Thus, the urgency of creating new discrete mathematical models of biological processes and, in particular, models of brain stroke is extremely high.

The vascular network of the brain

The goal of all interconnected processes of blood supply to the brain is the sufficient functioning of the nervous tissue, according to the needs of the body [7]. Two closely related subsystems of the cerebral vascular system can be distinguished:

Microcirculation - provides blood to the brain substance and thus forms the local cerebral circulation;

Macrocirculation forms a pool of general blood supply on the surface of the brain [8].

In the microcirculation subsystem, a morphofunctional unit is distinguished in the form of a set of microvessels that allow blood to be supplied to individual specialized cell populations. This is the so-called vascular module. This scheme is most pronounced at the level of the cerebral cortex in its projection areas [9]. The selectivity of the transport of components from the blood to the brain tissue is provided by the blood-brain barrier. This barrier is formed due to the spatial and functional structure of filling the intercellular space with astrocytes [10]. Vascular epithelial cells are layered on top of each other in such a way that the vessels become almost impermeable [11].

Due to this circulatory system, the internal chemical environment of the brain is an isolated system consisting of many isolated subsystems. Only in some areas of the brain, such as the suture nucleus, hypothalamus, and others, is the permeability to a number of chemicals, such as acids, increased. This is necessary for the needs of the chemoreceptors grouped there [10]. At the same time, the penetration of water, carbon dioxide and oxygen through the capillary wall occurs almost unhindered. Multiple contacts between tightly fitting endotheliocytes form the intima layer of the cerebral arterioles. In addition, the subendothelial zone contains so-called myoendothelial junctions [12]. In this way, due to the ability to secrete vasoactive substances – factors of contraction and relaxation of smooth muscle muscles, endotheliocytes independently control the contractile activity of arterioles. The nexuses and plasma outgrowths of the muscle layer, due to their numerous contacts, are the structure of electrotonic conduction. This allows you to quickly excite the entire smooth muscle layer.

Review of Existing Mathematical Models of Brain Stroke

Most mathematical models of tissue ischemia described in the literature consider cardiac ischemia. This is due to the fact that processes in the electromechanical system of automatism and heart contraction are easier to systematize than processes in brain tissue, where the density of elements is higher. In addition, effective technologies exist for conducting experiments on a working heart. However, there are also models of brain stroke that deserve attention and will be considered in this context.

The Model by Duval et al.

Duval's model was one of the firsts among mathematical and computer stroke models. It was designed in 2002 and represented a description of a brain region as a fragment of a lattice of order x×y [13]. Each of the lattice's cells had a certain set of parameters with non-focal and local blood circulation characteristics, as well as the water diffusion coefficient, alongside them.

The model allowed to form a one-time state of the considered cell in the result of solving a system of equations based on the cell's parameters 7×7. Moreover, adjacent cells' interactions were taken into account according to empirically derived rules. It was not possible to get a dynamic picture, using that model, besides, the set of parameters was virtually inadequate for an ischemia development process description. Nevertheless, on the qualitative plane, it proved quite well in comparison to apoplectic focus pictures acquired during instrumental researches. In the figure below, the model's matrix structure, determined on a matrix of order 7×7, is presented (Figure 1).

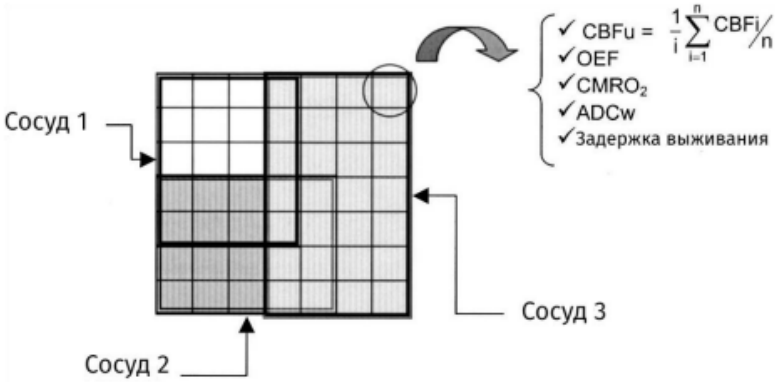

Figure 1: The matrix structure of Duval's model.

The model by Dronne V. et al.

This model was being designed during the period of 2004 to 2006 years [14]. The researchers' attention was concentrated on temporal and spatial mechanisms of a penumbra appearing after an ischemic insult.

Continuing the work of Duval et al., the model united the fundamental tissular, cellular and molecular mechanisms participating in an ischemic insult development to model the penumbral zone evolution, both temporal and spatial, in case of a therapeutic intervention or its absence. Such an approach to numerical simulation had been used earlier in cardiology for in silico experiments imitating drugs' effect on a pathology-affected heart. For that, a formal model was developed. Based on gathering and classification of data taken from animal models and observation of patients, ten submodels, which could be simulated and tested irrespective of each other, had been formed: i. e., submodels of tissural reactions, ionic transfers, edema development, glutamate excitotoxicity, depression spreading, NO synthesis, inflammation, necrosis, apoptosis and reperfusion. The models itself poses as a system of equations presented lower (Figure 2).

$$
\begin{cases}
\frac{d}{dt}(f_n[S]_n) = -k_{s,n} I_{s,n}([Ca^{2+}]_n, [K^+]_n, [Na^+]_n, [Cl^-]_n, [glu]_n, V_n), \\
\frac{d}{dt}(f_a[S]_a) = -k_{s,a} I_{s,a}([Ca^{2+}]_a, [K^+]_a, [Na^+]_a, [Cl^-]_a, [glu]_a, V_a), \\
\frac{d}{dt}((1-f_n-f_a)[S]_e) = k_{s,n} I_{s,n}([Ca^{2+}]_n, [K^+]_n, [Na^+]_n, [Cl^-]_n, [glu]_n, V_n) \\
\qquad + k_{s,a} I_{s,a}([Ca^{2+}]_a, [K^+]_a, [Na^+]_a, [Cl^-]_a, [glu]_a, V_a), \\
\frac{df_n}{dt} = \frac{1}{S_{0,n}} \frac{d}{dt}\left(f_n\left(\sum_s [S]_n + [A_0]_n\right)\right), \\
\frac{df_a}{dt} = \frac{1}{S_{0,a}} \frac{d}{dt}\left(f_a\left(\sum_s [S]_a + [A_0]_a\right)\right), \\
\sum_s (z_s[S]_n) + z_A[A_0]_n = 0, \\
\sum_s (z_s[S]_a) + z_A[A_0]_a = 0,
\end{cases}
$$

Figure 2: The equations set in Duval's model.

This particular model demonstrates a qualitatively similar picture based on the data of ion transport across a membrane and intracellular liquid volume during a stroke development. However, the latter's spatial picture and process dynamics were not described. Furthermore, the processes were considered in one cell interacting with a single astrocyte only, both located in a conventional intercellular space.

The model by S.S. Makarov et al.

The essence of the model is the Makarov S.S. et al. model [15]: computer simulation of the development of ischemic stroke using CUDA technology (to accelerate calculations on the GPU).

The object of the simulation was a system of brain cells (neurons and astrocytes) + an intercellular space. The model is discrete — each cell is described separately.

The key parameters for each cell are: membrane potential; intracellular concentrations of ions: $Ca2^+$, K^+, Na^+, Cl^-, as well as ionized forms of glutamate.

The following spatiotemporal dynamics of concentrations of the same ions (K^+, Na^+, $Ca2^+$, Cl-, and glutamate) are modeled in the intercellular space.

The basic components of the model are: the operation of ion channels on the cell membrane; calcium signaling between astrocytes; synaptic connections between neurons; diffusion of substances in the intercellular space.

The mathematical basis is represented by a system of equations, including:

partial differential equations (of the type of rection-diffusion); ordinary differential equations; nonlinear algebraic equations.

Ischemic stroke is modeled as a local lack of blood supply, leading to:

¬ disruption of ion channels (requiring energy consumption);

¬ a sharp increase in intracellular concentrations of $Ca2^+$, Na^+, Cl^-;

¬ increase in intercellular concentrations of K^+ and glutamate;

¬ growth of the membrane potential of cells.

The pathology spreads due to the diffusion of K^+ and glutamate, synaptic connections and calcium signaling, and the lesion spreads to areas with normal blood flow.

The model was initially developed for a 1D system (3 neurons + 3 astrocytes), then generalized to a three-dimensional environment with a large number of cells.

The authors indicate modeling of the depolarization wave of neuronal membranes as key results; profiles of changes in substance concentrations are consistent with empirical data; analysis of the role of synapses and calcium signaling in the development of the affected area.

The model by Bikulov D.A. et al.

The authors of [16] apply the Lattice Boltzmann Method (LBM) to numerically simulate the spread of ischemia in brain tissue. The key feature is the implementation of the algorithm on a GPU cluster to significantly speed up calculations.

The process of the spread of ischemic damage in the brain is modeled, including: the diffusion of substances in the intercellular space; changes in concentrations of ions and metabolites; the formation of a zone of infarction and penumbra (areas of "threatened" cells).

The mathematical basis is LBM, an alternative approach to solving equations of hydrodynamics and diffusion. Unlike classical methods (finite differences/elements), LBM: operates with "particles" on a discrete lattice; simulates their collisions and transport; effectively reproduces diffusion processes at the microlevel.

The key components of the model include:

The presence of a spatial grid is a discrete grid where each cell corresponds to an element of brain tissue.

Particle distribution — virtual particle distribution functions are defined in each cell, reflecting the flows of substances.

Collision rules — simulate the exchange of substances between neighboring cells.

Boundary conditions — take into account blood vessels, ischemic zones and healthy tissues.

Features of the model implementation: GPU parallelization — calculations are distributed between GPU cores, which allows processing large three—dimensional grids and reducing simulation time tenfold compared to the CPU; scalability - the algorithm is adapted for cluster systems with multiple GPUs.

Advantages of LBM in this context:

- Natural processing of complex geometries (sinuous vessels, heterogeneous tissue).
- High accuracy in microlevel diffusion modeling.
- Convenient parallelization — each grid node is processed independently.

The model makes it possible to visualize the dynamics of the spread of ischemia in real time, makes it possible to test hypothetical scenarios (for example, the effect of reperfusion on the size of the infarction zone), and can serve as a tool for predicting stroke outcomes, planning thrombolytic therapy, and studying the mechanisms of penumbra formation.

The limitations of the model include the fact that it requires significant computing resources (GPU cluster).

The model provides a simplified description of biochemical processes (emphasis on diffusion rather than ion channels/metabolism).

Nevertheless, the work demonstrates the potential of LBM in neuromodeling, combining the physical adequacy of the description of diffusion processes; computational efficiency due to GPU acceleration.

All this opens up opportunities for detailed modeling of ischemia on large-scale three-dimensional models of the brain.

The model by Shapiro B. E.

This presented model qualitatively differed from its precursor in terms of describing a depression spreading wave and gap junctions, cytosolic voltage gradients and osmotic volume changes [17]. The author successfully united 29 parameters in the set of equations and bound the wave's form and speed to particular biophysical substrates (e.g., to the influence of particular ionic channels). The new models allowed for the movement of ions and substrates through the cytosolic continuum of neurons connected by gap junctions. Extracellular diffuse movement was also allowed, but, as the simulations showed, this movement was less innovative than other components of the model. However, it should be noted that the model was one-dimensional, although it adequately described wave deflections when analyzed with experimental data. The same characteristics of nerve cells were averaged, without separating cell types, and the influence of neurotransmitters and mediators on ionic chains was not considered (Figure 3).

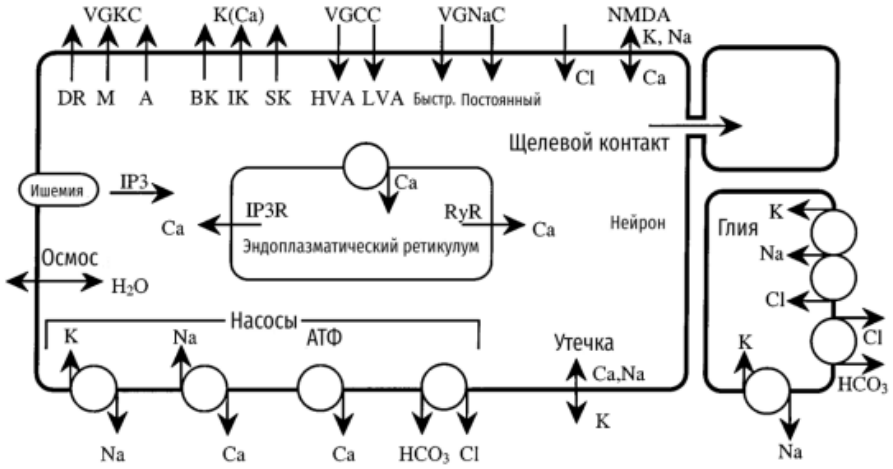

Figure 3: Ion flows included in the Shapiro model.

$$\partial tN = pNDH - \varepsilon N,$$
$$\partial tAs = pADH - pAD(\cdot - tA)H(\cdot - tA),$$
$$\partial tAe = pAD(\cdot - tA)H(\cdot - tA) - \varepsilon Ae,$$
$$\partial tH = -DH,$$
$$\partial tMa = (cAAe + cNN)Mi - TM,1Ma,$$
$$\partial tMi = -(cAAe + cNN)Mi + TM,1Ma + cMiMi(1 - Mi)1t > TM,2,$$
$$\partial tMadh = [pMadh,[cy](1 - Madh)[cy] - eMadhMadh]1\text{blood vessels}.$$

Figure 4: The system of regular differential equations (Russo et al. model).

The model by Chapuisat G. et al.

In their work, the authors developed the ideas expressed in Shapiro's model and, for the first time among all models of brain stroke, used the so-called membrane potential depression wave [18]. This was not the authors' only contribution to the development of their predecessors' ideas. The model was built on the following list of key phenomena:

1. The starting point of an ischemic stroke is a sudden reduction in blood flow to a region of the brain.

2. In response, oxygen consumption from the blood increases to compensate for the tissue's lack of oxygen.

3. If available energy is insufficient, it becomes impossible to maintain cellular homeostasis. Consequently, potassium concentration in the extracellular space increases.

4. Potassium diffuses into the extracellular space

5. Increased extracellular potassium concentration promotes cell depolarization and, in particular, opens voltage-gated calcium channels (VGCC), allowing calcium to enter neurons and astrocytes.

6. Excess calcium spreads throughout astrocytes via gap junctions.

7. Finally, increased calcium concentration in neurons promotes the opening of certain channels, such as calcium-gated potassium channels, which cause even more potassium to exit the cells.

8. Recovery from a depression wave requires energy. Both neurons and astrocytes will replenish their energy reserves to recover from the ionic disturbances caused by the depression wave.

9. The only damage to a cell is an increase in calcium ions.

10. If a cell is severely damaged but has sufficient energy, it will die by apoptosis. If it lacks energy, it will die by necrosis. Moreover, the necrotic pathway is the most likely, accounting for more than half of all dead cells [19].

Therefore, in this model, depression waves are not artificially introduced. In fact, the only way to detect them is by measuring the membrane potential of cells, which is related to calcium and potassium concentrations, as in in vivo or in vitro experiments. The spatial scale of this model is the entire brain. However, due to complexity and time constraints, the authors' calculations are performed on a specific brain region. Thus, the model space has only two dimensions. Sometimes, calculations are even performed in one-dimensional space.

In addition, the authors considered only the square area of the cerebral cortex and were not interested in the evolution of stroke in the white matter. Three different subsystems in gray matter were considered: extracellular space, neurons, and astrocytes. These three subsystems were considered homogeneous, and due to the scale of space, it is impossible to distinguish different cellular networks; therefore, each subsystem is assumed to be continuous. At the same time, the size of the subsystem was not taken into account. The authors focused on two ions: potassium (K+) and calcium (Ca2+). More precisely, the model includes only extracellular potassium concentration (|K+|e), astrocytic calcium concentration (|Ca2+|a) and neural calcium concentration (|Ca2+|n). An important assumption of the model was that the wave of depression eventually spreads throughout the brain, so it is important to study the above concentrations as a function of time and coordinate space. In fact, all the values of the model depend on the time variable t and on the spatial variable x, which is a vector with the same number of coordinates as the space under consideration. For example, |Ca2+|n(t, x) denotes the concentration of calcium in neurons near point x at time t, and |K+|e(t, x) denotes the concentration of potassium in the extracellular space near x at time t. The authors of the work really managed to fit the propagating wave of depression well into the model. stroke as the most important factor in the enlargement of the affected area.

The model by Di Russo C. et al.

Di Russo et al. in their research focused their attention on the inflammatory process in the ischemic stroke [20]. The function of the inflammation in the ischemic stroke is the dead cells lysis, yet it also may cause the normal cells destruction. The authors of the model performed in silico experiment to explore the inflammation influence in the stroke. The developed model created a basis for possible therapeutic approaches.

The pathophysiological processes, which are important for research, are described below:

1) As a result of the ischemic stroke, neurons and glial cells are dying as a consequence of necrosis and apoptosis.

2) The dead cells induce the microglia activation and other cells' death due to the toxic substances being expelled during the cells' disintegration.

3) The activated microglia cells are able to perform phagocytosis of the dead cells and to produce cytokines (causing the adhesion molecules accumulation) and chemokines (causing the leucocytes migration).

4) After that, macrophages and neutrophils, which are able to perform phagocytosis as well, are penetrating the ischemic brain tissue. The side effect of those cells' function is a destruction of the healthy cells.

The model is based on the following facts:

- Cells are being damaged primarily by the neutrophils-produced cytokines and other substances, and the toxic substances released by the necrotic cells (the diffusion of the mentioned toxic substances is omitted from the Russo's model)
- In the case of significant damage sustained, cells are dying. Some of them die due to necrosis and others due to apoptosis.
- The apoptosis requires the time delay tA.
- Microglial cells, macrophages and neutrophils perform phagocytosis of the dead cells and delete them from the tissue.
- Neurons and astrocytes are static.
- Apoptotic and/or necrotic cells in the tissues cause the microglia activation.
- In the case of the lack of the stimuli microglia inactivates.
- During the stroke, inactivated microglial cells are reproducing via mitosis. This process requires a long time (around 24 hours).

As a result of the study the self-enclosed system of the 13 equations were derived. For the static types of cells modelling there are 7 regular differential equations: (Figure 4)

The other 4 equations of diffusion reactions are used to describe the movement of the mobile types of the cells: (Figure 5)

$$\partial L_m/\partial t - D_{lm} \cdot \Delta L_m = -\mu_{lm} \cdot \nabla \cdot (L_m(1-L_m) \cdot \nabla[ch]) + c_{lm} \cdot M_a DH \cdot (-T_{lmin}) \cdot \hat{H}(LM) - L_m/T_{lm}$$

$$\partial L_n/\partial t - D_{ln} \cdot \Delta L_n = -\mu_{ln} \cdot \nabla \cdot (L_n(1-L_n) \cdot \nabla[ch]) + c_{ln} \cdot M_a DH \cdot (-T_{lnin}) \cdot \hat{H}(LM) - L_n/T_{ln}$$

$$\partial[cy]/\partial t - D^{cy} \cdot \Delta[cy] = p^{cy} \cdot (M_a + L_m) \cdot (N + A_e) - e^{cy} \cdot [cy]$$

$$\partial[ch]/\partial t - D^{c}H \cdot \Delta[ch] = p^{c}H \cdot (M_a + L_m) \cdot (N + A_e) - e^{c}H \cdot [ch]$$

Figure 5: The equations of the diffusion reactions (the Russo et al. model).

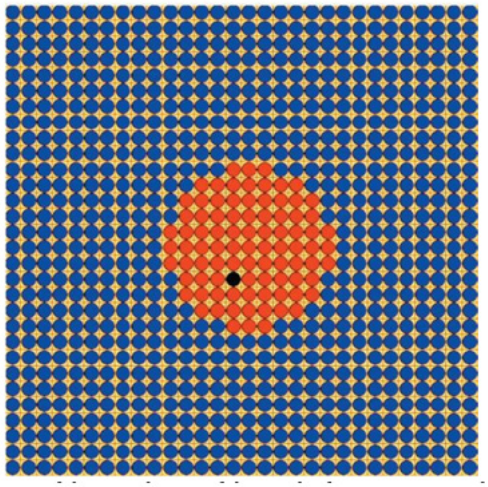

Figure 6: Visualization of the initial state of the stroke focus using a modeling program. Dead cells are marked in black, ischemic cells in red, healthy tissue cells in blue.

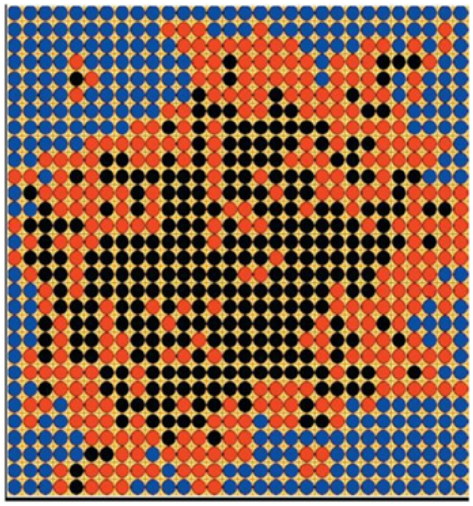

Figure 7: Visualization of the spread of the infarct zone and the formation of the penumbra by the modeling program. Dead cells are indicated in black, ischemic cells in red, and healthy tissue cells in blue. Penumbra is the zone between blue and black density.

In this study the model was constructed based on the set of the regular on diffusion differential equations for the inflammatory processes modelling during the ischemic stroke. The model reflects the different types of cells and chemical substances interactions. As a result of the study the behavior of the healthy, necrotic, apoptotic and immune cells, such as microglia, neutrophils and macrophages was simulated. Besides the cells, the cytokines, chemokines, adhesion molecules are included into the model. The most important part of the model is the dimensional measurement simulation, which allows for the simulation of the protein diffusion and the leucocytes chemotaxis.

We should note that Russo's model has its up- and downsides. The upside of the model is the integration of the damage mechanism as a complex process, which can be described via the "universal" functions, which are describing the inflammatory and decay products intoxicating role in the ischemic stroke, as well as the dead cells phagocytosis. Some authors are pointing out that experimental data and Russo's model predictions are not in line and that the model is good enough only for the qualitative description of the process.

The model by O.F. Voropayeva et al.

The goal of the Voropaeva's et al. research is to create the mathematical model of the brain cells ceasing functions, which allows for the quantity analysis of the experimental data on the basis of the Russo model [21]. The primary novelty of Voropaeva's model is change of the approximation in the Russo equations. Also the model omitted the chemotaxis of the stroke development.

The change of the cell density dynamic of the beginner-apoptotic (As, red ones), apoptotic (Ae, black ones), alive (H, black ones), necrotic (N, red lines) brain cells in dependence of the function pN = {0.1, 0.3, 0.6, 0.9} (lines 1 to 4 respectively). The model's predictions were consistent with the experimental results on the cell cultures both qualitatively and quantitatively, based on which authors claim the validity of the developed model.

We should note that all of the models mentioned in the chapter show good results, which are getting close to the experimental data, yet aforementioned models don't claim the precise quantitative description of the process. The closest to the experimental data is O. F. Varapayeva's et al. model, in which Russo's model was improved, though even their model doesn't account for the spatial structure of the stroke centre.

CA-NVE Stroke Model (V.V. Fursov et al.)

This model is a discrete stochastic model of the development of ischemic stroke based on the concept of a cellular automaton and the Monte Carlo method [22-26].

The basic idea is that the minimal unit to be modeled is not a single cell or molecule, but a neurovascular unit (NVE). This is a functional unit of the brain, including microvessels (capillaries, pericytes) and surrounding nerve cells

(neurons, astrocytes). It is the defeat of the NVE that is considered the key event in stroke.

In this model, the brain is represented as a two-dimensional lattice (mesh), where each cell is one NVE. Each NVE can be in one of four states:

- Health (H): Normal functioning.
- Ischemia (I): Blood supply is impaired, but the condition is reversible. Death (D): Irreversible death of the unit (necrosis or apoptosis).
- PAS accumulation (F): A condition where a pharmacologically active substance is present in a unit.

Transitions between states (for example, Health → Ischemia or Ischemia → Death) occur according to stochastic (probabilistic) rules, which are specified by rate constants. These transitions can depend on the state of neighboring NVEs, which makes it possible to simulate the propagation of damage in space. The evolution of the system over time is calculated using the Monte Carlo algorithm. Figures 10, 11 show visualization of the spread of the stroke focus: (Figure 6,7)

The use of a neurovascular unit as an elementary unit is a major advantage. This allows us to abstract from the excessive complexity of modeling individual cells, but at the same time adequately reflect the pathophysiology, since stroke is a vascular event that immediately affects the entire functional unit.

This model also takes into account spatial dynamics. It clearly shows how a small focus of ischemia forms an infarct zone and the surrounding penumbra (the zone of "stunned" but still viable cells), which is critical for understanding the "therapeutic window."

The model was purposefully developed as simple for numerical implementation and containing relatively few parameters. This makes it less cumbersome than PDE-based models while still maintaining key functionality.

The use of the Monte Carlo method allows one to take into account the random nature of biological processes. This provides a more realistic picture of stroke progression, which may vary from run to run, as opposed to deterministic models.

The authors empirically selected the rate constants so that the model reproduces the known time frame for the development of infarction (for example, 50% of the volume in 90 minutes, 80% in 6 hours), which confirms its adequacy.

Conclusions

The examination of contemporary mathematical and computational models of ischemic stroke yields several key insights:

Mathematical modeling has firmly established itself as a vital methodology for exploring cerebral ischemia. It enables scientists to probe pathogenetic mechanisms that remain inaccessible or extremely challenging to investigate via conventional biological experiments.

The field has witnessed a clear trajectory of advancement — moving from basic phenomenological frameworks toward sophisticated multicomponent systems. These advanced models can now

capture both the spatiotemporal progression of the pathological process and the inherent stochasticity of biological systems.

Current modeling approaches have transcended mere qualitative description, achieving the capability to generate quantitative predictions. This development lays the groundwork for potential clinical applications and practical medical implementation in the near future.

A particularly promising avenue involves the creation of unified models that synthesize diverse datasets — including cerebral hemodynamics, cellular metabolism, neuroinflammatory responses, and tissue repair mechanisms. Such integrated frameworks hold significant potential for advancing personalized stroke treatment strategies.

In summary, computational modeling has emerged as a transformative approach in stroke research. It not only deepens our understanding of ischemic stroke pathogenesis but also opens new pathways for developing effective therapies against this major public health challenge.

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Conflicts of interests

No conflicts of interests of any sort beyond.

Informed Consent

None to declare.

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