Software Complex in the Study of the Mathematical Model of Cyber-Physical Systems

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Abstract

The paper describes the mathematical description of the discrete population dynamics in combination with the dynamic logic of the studied models. The lattice difference equations with delay are proposed to simulate antigen-antibody interaction within rectangular biopixels. The article deals with the analysis of the results of numerical modeling of mathematical models of cyber-physical biosensor systems on rectangular lattices using lattice difference equations with delay. Based on the developed models and methods of compartmental mathematical modeling of cyber-physical systems of medical and biological processes, a set of computer programs for studying their stability has been created, which can be used both separately and as additional specialized software for cyber-physical biosensor systems. The paper presents the results of numerical simulations in the form of phase plane images and lattice images of the probability of antigen to antibody binding in the biopixels of cyber-physical biosensor systems for antibody populations relative to antigen populations. The results of numerical modeling of the developed mathematical models of cyber-physical Systems of medical and biological processes in the form of bifurcation and phase diagrams of antigen populations against antibodies are obtained, using the software package for the study of phase diagrams of cyber-physical biosensor systems.

Keywords

cyber-physical model, biosensor system, stability of the model, difference equations, rectangular lattice

1. Introduction

The development and implementation of sensor with different functions in practical use are one of the priority areas of modern electronics. Development of biosensors requires integration of knowledge in different subjects such as molecular biology, genetic and protein engineering, analytical chemistry, materials science, microelectronics, and nanotechnology. Biosensors are analytical devices that use biochemical reactions to detect a wide range of chemical compounds: metabolites, medications, environmental pollutants, etc.

At present, the integration between computing and physical resources leads to the creation of complex computing systems with distributed parameters. Such systems are managed or controlled by computing resources that are integrated into the Internet [1, 2]. Such systems are called cyber-physical systems (CPS) – these are systems consisting of various natural objects, artificial subsystems, and control computers that allow such an education to be represented as a single entity. CPS ensures close communication and coordination between computational and physical resources. Computers monitor

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and control physical processes using such a feedback loop, where what happens in physical systems affects computations and vice versa [3–5].

Mathematical models of biosensors for cyber-physical biosensor system (CPBSS) on rectangular and hexagonal lattices using lattice differential and difference equations with delay have been developed [6, 7]. This takes into account the presence of antigen colonies and antibodies localized in pixels, as well as the diffusion of antigens between pixels. A detailed description of the mathematical model of the immunosensor on a rectangular lattice using differential equations with delay is presented in [8, 9].

Static mathematical models of biosensors in CPS of medical and biological processes are considered on the examples of mathematical models of optical biosensors based on surface plasmon resonance [10] and multilayer model. The method of the transfer matrix for studying various performance parameters of the proposed structure for p-polarized incident light is considered [11, 12]. In [13] the dynamic model of the second order was developed to predict the change in the efficiency of the biosensor over time during the measurement. In [14] a biosensor model was considered, which contains three areas: the enzyme layer (enzyme membrane), where the enzymatic reaction takes place; mass transfer layer by diffusion of both substances (substrate and product) through a semipermeable membrane; convective region, where the analyte concentration is kept constant. In first-order dynamic models that use the Arrhenius equation, the temperature dependence of the rate of change is used to estimate the stability of biosensors [15, 16]. In [16] a mathematical model from a set of laboratory experiments based on accelerated aging due to elevated temperatures on glucose oxidase modified screen printed electrodes as a model electrochemical biosensor was proposed. In [17] a model of an electrochemical cell that is integrated with viable bacterial cells that express an intracellular enzyme that responds to the added substrate, and the generated product is secreted and oxidized on the electrode surface is considered. A mathematical model of an amperometric biosensor response for substrate and inhibitor detection has been developed in the [18]. The model is based on system of reaction–diffusion equations containing a non-linear term related to Michaelis–Menten kinetics of the enzymatic reaction[19].

To obtain complete information about the stability of CPS biomedical processes are not enough only to use mathematical model, the appropriate ratios for local, global asymptotic stability, permanence and persistence. It is necessary to develop CPBSS software for numerical modeling of phase planes, bifurcation diagrams, lattice images of antigen-antibody bonds, fluorescence images of developed models, electrical signal from the converter, which characterizes the number of fluorescent pixels of the studied systems.

2. Cyber-physical Biosensor System

2.1. Discrete Dynamics CPBSS on rectangular lattice using lattice differencial equations with delay.

A model of a biosensor on a rectangular lattice with the use of lattice differential equations with delay is developed, using a number of assumptions. In particular, it is assumed that $V_{i,j}(t)$ is the concentration of antigen populations, $F_{i,j}(t)$ – respectively, the concentration of antibody populations in the biopixel (i, j), $i, j = \overline{1, N}$.

The model is based on the following biological assumptions for an arbitrary biopixel (i, j):

1. The value $\beta > 0$ was used for the fertility population constant of the antigen population.
2. Antigens are neutralized by antibodies with some probabilistic rate $\gamma > 0$.
3. The population of antigens tends to some extent of saturation at the rate $\delta_\upsilon > 0$.
4. It is assumed that the diffusion of antigens from four adjacent pixels $(i-1, j)$, $(i+1, j)$, $(i, j-1)$, $(i, j+1)$ (Fig. 1) occurs at the diffusion rate $D\Delta^{-2}$, where $D > 0$ and $\Delta > 0$ is the distance between the pixels.
5. Antibody mortality constant $\mu_f > 0$.

6. As a result of the immune response, the density of antibodies increases with a probabilistic rate $\eta\gamma$.

7. The antibody population tends to some level of saturation at epy rate $\delta_f > 0$.

8. The immune response comes with some delay in time $\tau > 0$.

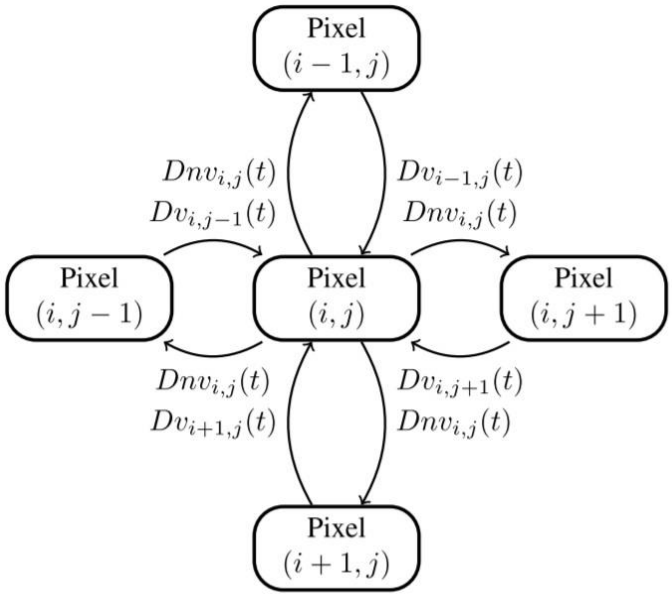


Figure 1: A rectangular grid that connects four adjacent pixels in the biosensor model using a Cartesian coordinate system

Based on the above assumptions, the design of a biosensor model on a rectangular lattice of the "antigen-antibody" type with a delay for a two-dimensional array of biopixels, which is based on the known Marchuk model and uses a spatial operator $\hat{S}$, is considered.

$$\begin{aligned}\frac{dV_{i,j}(t)}{dt} &= (\beta - \gamma F_{i,j}(t-\tau) - \delta_v V_{i,j}(t-\tau))V_{i,j}(t) + \hat{S}\{V_{i,j}\},\\ \frac{dF_{i,j}(t)}{dt} &= (-\mu_f + \eta\gamma V_{i,j}(t-\tau) - \delta_f F_{i,j}(t))F_{i,j}(t), \quad t > 0.\end{aligned} \tag{1}$$

Model (1) is given by initial functions (2)

$$\begin{aligned}&V_{i,j}(t) = V_{i,j}^0(t) \geq 0, \quad F_{i,j}(t) = F_{i,j}^0(t) \geq 0,\\ &t \in [-\tau, 0), \quad V_{i,j}(0), F_{i,j}(0) > 0.\end{aligned} \tag{2}$$

For a square array $N \times N$, discrete diffusion is used for the spatial operator, taking into account the imbalance constant n_{dsbn}

$$\hat{S}\{V_{i,j}\} = \begin{cases} D\Delta^{-2}\left[V_{1,2} + V_{2,1} + V_{i,j-1} - 2n_{dsbn}V_{1,1}\right], & i, j = 1\\ D\Delta^{-2}\left[V_{2,j} + V_{1,j-1} + V_{1,j+1} + V_{i,j+1} - 3n_{dsbn}V_{i,j}\right], & i = 1,\ j \in \overline{2, N-1}\\ D\Delta^{-2}\left[V_{1,N-1} + V_{2,N} - 2n_{dsbn}V_{1,N}\right], & i,\ j \in \overline{2, N-1}\\ D\Delta^{-2}\left[V_{i-1,N} + V_{i+1,N} + V_{i,N-1} - 3n_{dsbn}V_{i,N}\right], & i \in \overline{2, N-1},\ j = N\\ D\Delta^{-2}\left[V_{N-1,N} + V_{N,N-1} - 2n_{dsbn}V_{N,N}\right], & i = N,\ j = N\\ D\Delta^{-2}\left[V_{N-1,j} + V_{N,j-1} + V_{N,j+1} + V_{i,j+1} - 3n_{dsbn}V_{N,j}\right], & i = N,\ j \in \overline{2, N-1}\\ D\Delta^{-2}\left[V_{N-1,1} + V_{N,2} - 2n_{dsbn}V_{N,1}\right], & i = N,\ j = 1\\ D\Delta^{-2}\left[V_{i-1,1} + V_{i+1,1} + V_{i,2} - 3n_{dsbn}V_{i,1}\right], & i \in \overline{2, N-1}, \quad j = 1\\ D\Delta^{-2}\left[V_{i-1,j} + V_{i+1,j} + V_{i,j-1} + V_{i,j+1} - 4n_{dsbn}V_{i,j}\right], & i, j \in \overline{2, N-1}. \end{cases} \tag{3}$$

Each pixel is exposed to antigens from four adjacent pixels that are separated by equal distances Δ.

The boundary condition $V_{i,j}=0$ for the edges of the array $i,j=0,N+1$ is used.

2.2. Discrete Dynamics CPBSS on rectangular lattice using lattice difference equations with delay.

A biosensor model on a rectangular lattice using lattice difference equations with delay is used, using additional assumptions:

1. It is assumed that when the antibody colonies are absent, the antigen colonies are regulated by a known logistic equation with a delay

$$V_{i,j}(n+1)=(1+\beta-\delta_{\upsilon}V_{i,j}(n-r))V_{i,j}(n),$$

where n is the discrete moment of time, $r\geq 0$ is the discrete time of delay of the negative response of antigen colonies.

2. Antibodies cannot instantly detect and bind antigens because they need to spend r units of time before they can reduce the average growth rate of antigen colonies. The above assumptions are included in the dynamics of antigens in the expression $-\gamma F_{i,j}(n-r)$, where γ – is a positive constant, which may vary depending on the specific colonies of antibodies and antigens.

3. In the absence of antigen colonies, the average growth rate of antibody colonies decreases exponentially due to the magnitude $-\mu_f$. In order to take into account the negative effects of antibody accumulation, the value $-\delta_f F_{i,j}(n)$ in the dynamics of antibodies is introduced.

4. A characteristic of the growth rate of antibodies is an expression $\eta\gamma V_{i,j}(n-r)$ that is delayed until the maturation of adult antibodies and characterizes the production of antibody biomass. The value r in $\eta\gamma V_{i,j}(n-r)$ is considered as a delay in the maturation of antibodies.

5. Surface diffusion (motion of molecules on a solid surface for immobilized molecules) with diffusion coefficient $D>0$ is considered. In this case, the factors immobilized on the biosensor matrix are antigens, while the antibodies play the role of analytes or detected particles.

6. The definition of a conventional diffusion operator in the case of surface diffusion is used by introducing a diffusion imbalance coefficient $n_{dsbn}\in(0,1]$, which means that only n part of the pixel antigens (i,j) can be included in the diffusion process relative to neighboring pixels as a result of surface diffusion.

The system (1) without diffusion is approximated by differential equations with partially constant arguments

$$\begin{aligned}\frac{dV_{i,j}(t)}{dt}&=\big(\beta-\gamma F_{i,j}([t/h]h-[t/h]h)-\delta_{\upsilon}V_{i,j}([t/h]h-[t/h])\big)V_{i,j}(t),\\ \frac{dF_{i,j}(t)}{dt}&=\big(-\mu_f+\eta\gamma V_{i,j}([t/h]h-[t/h]h)-\delta_f F_{i,j}([t/h]h)\big)F_{i,j}(t)\end{aligned}\tag{4}$$

for $t\in[nh,(n+1)h],\ n\in\mathrm{N}$.

The notations $[t/h]=n$, $[t/h]=r\in\mathrm{N}$ are entered. We integrate system (4) on $[nh,t)$, where $t<(n+1)h$, then we receive system (5):

$$\begin{aligned}\frac{dV_{i,j}(t)}{dt}&=\big(\beta-\gamma F_{i,j}(nh-rh)-\delta_{\upsilon}V_{i,j}(nh-rh)\big)V_{i,j}(t),\\ \frac{dF_{i,j}(t)}{dt}&=\big(-\mu_f+\eta\gamma V_{i,j}(nh-rh)-\delta_f F_{i,j}(nh)\big)F_{i,j}(t)\end{aligned}\tag{5}$$

In the system (5) the notation $V_{i,j}(n)=V_{i,j}(nh)$, $F_{i,j}(n)=F_{i,j}(nh)$, is entered, and we receive next result

$$\begin{aligned}V_{i,j}(t)&=V_{i,j}(n)\exp\{\beta-\gamma F_{i,j}(n-r)-\delta_{\upsilon}V_{i,j}(n-r)\},\\ F_{i,j}(t)&=F_{i,j}(n)\exp\{-\mu_f+\eta\gamma V_{i,j}(n-r)-\delta_f F_{i,j}(n)\}\end{aligned}\tag{6}$$

Given $t \to (n+1)h$, the system (6) is simplified by adding diffusion to the first equation. The result is a discrete analog time-continuous system

$$\begin{aligned} V_{i,j}(n+1) &= V_{i,j}(n)\exp\left\{\beta - \gamma F_{i,j}(n-r) - \delta_\upsilon V_{i,j}(n-r)\right\} + \hat{S}\left\{V_{i,j}(n)\right\}, \\ F_{i,j}(n+1) &= F_{i,j}(n)\exp\left\{-\mu_f + \eta\gamma V_{i,j}(n-r) - \delta_f F_{i,j}(n)\right\}, \quad n > 0 \end{aligned} \tag{7}$$

The model (7) is given by initial functions (8)

$$\begin{aligned} &V_{i,j}(n) = V_{i,j}^0(n) \geq 0, \quad F_{i,j}(n) = F_{i,j}^0(n) \geq 0, \\ &n \in [-r,0), \quad V_{i,j}(0), F_{i,j}(0) > 0. \end{aligned} \tag{8}$$

The mathematical model of the biosensor on a rectangular lattice using the difference equations with delay is presented by system (7).

3. Numerical Simulation of Cyber-physical Biosensor System

3.1. Parameters of mathematical model of CFBSS on rectangular lattice using lattice difference equations with delay.

In order to obtain the results of numerical simulation of the immunosensor on a rectangular lattice using differential equations with delay, the values of the parameters of the immunosensor model on a rectangular lattice using differential equations with delay are introduced. The names of the model parameters, their numerical values, as well as the representation of parameters and their numerical values in the package R are determinants in the computer program "Investigation of the phase planes of the immunosensor model on a rectangular lattice using differential equations with delay".

Fig. 2 shows the result of the introduction of a mathematical model of the immunosensor on a rectangular lattice using differential equations, which has the form of

$$\begin{aligned} \frac{dV_{i,j}(t)}{dt} &= (\beta - \gamma F_{i,j}(t-\tau) - \delta_\upsilon V_{i,j}(t-\tau))V_{i,j}(t) + \hat{S}\left\{V_{i,j}\right\}, \\ \frac{dF_{i,j}(t)}{dt} &= (-\mu_f + \eta\gamma V_{i,j}(t-\tau) - \delta_f F_{i,j}(t))F_{i,j}(t) \end{aligned} \tag{9}$$

where $V_{i,j}(t)$ – is the concentration of antigens in the immunopixel; $F_{i,j}(t)$ – the concentration of antibodies in the immunopixel; β – the fertility constant for antigen population; γ – the probabilistic rate of neutralization of antigens by antibodies; τ – the constant of delay in time, when the immune response comes; δ_f – the rate at which the population of antibodies tends to a certain limit saturation; δ_υ – the rate at which the population of antigens tends to a certain limit saturation; $\hat{S}$ – spatial diffusion operator between adjacent pixels; $\eta\gamma$ – probabilistic rate of immune response to increasing antigen density; μ_f – antibody mortality constant.

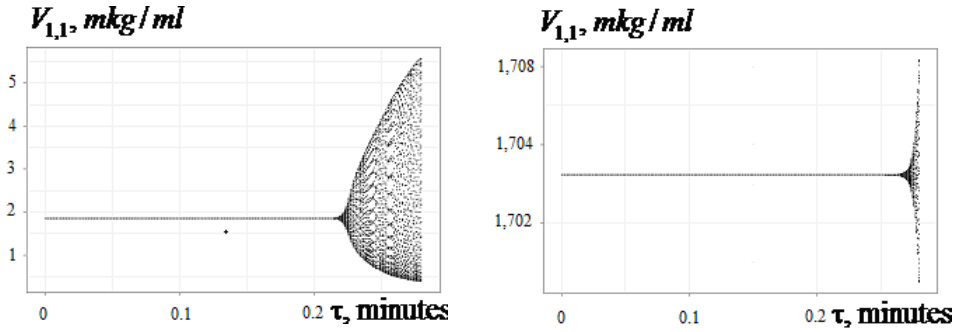
3.2. Results of numerical simulation of mathematical model of CFBSS on rectangular lattice using lattice difference equations with delay.

To study the occurrence of bifurcation and deterministic chaos in compartmental mathematical models of lattice type on a rectangular lattice using differential equations, model (1) at $N = 4$ and values of parameters $\beta = 2\min^{-1}$, $\gamma = 2\frac{ml}{min \cdot mkg}$, $\mu_f = 1\min^{-1}$, $\eta = 0.8/\gamma$, $\delta_\upsilon = 0.5\frac{ml}{min \quad mkg}$, $\delta_f = 0.5\frac{ml}{min \quad mkg}$, $D = 0.2\frac{nm^2}{\min}$, $\Delta = 0.3nm$ are considered. The concentrations of antigens populations $V_{i,j}(t)$, $V_{i,j,k}(t)$ and antibodies populations $F_{i,j}(t)$, $F_{i,j,k}(t)$ are measured in $\frac{mkg}{ml}$.

This set of parameters ensured the fulfillment of sufficient conditions of local asymptotic stability. In Fig. 2 (a, b) presents bifurcation diagrams for changing the parameter τ for different values n_{dsbn}. Solid lines for certain values τ indicate boundary cycles, areas of "scattered" values require additional research on deterministic chaos. The influence of the time delay value as well as the imbalance index n_{dsbn} on the qualitative behavior of the model is numerically shown.

As these numerical studies show, the above set of parameters that satisfies the conditions of local asymptotic stability, allows to obtain a rather complex qualitative behavior of the model.

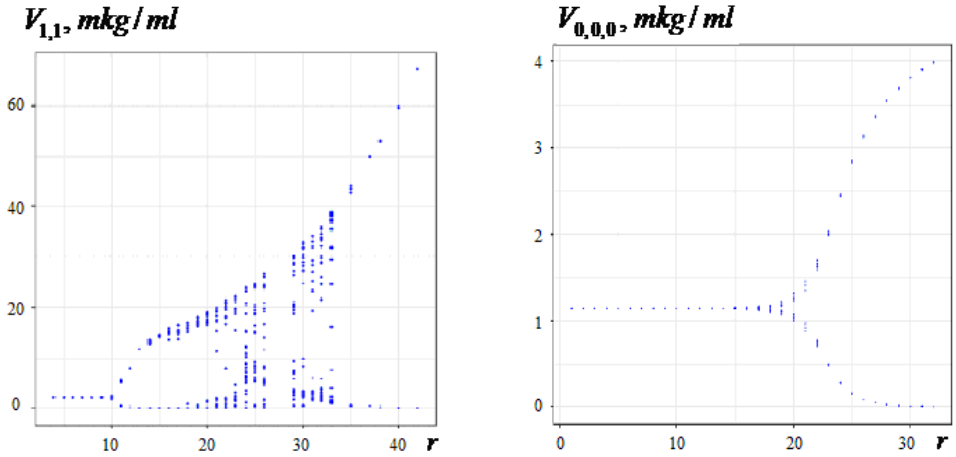
Basic reproduction numbers $\Re_{0,v} = 1.125 > 1, \Re_{0,f} = 1.333 > 1$ are obtained, which indicate that the endemic state without antigens or antibodies is unstable and there is an endemic state of equilibrium $\mathrm{E}^*_{i,j} = (V^*_{i,j}, F^*_{i,j}), \quad i, j = \overline{1,N}$.



a) b)

Figure 2: Bifurcation diagrams of the mathematical model of CPBSS using lattice differential equations with delay on a rectangular lattice at $n_{dsbn} = 0.9$ (a) and $n_{dsbn} = 1$ (b)

The investigation of bifurcation and deterministic chaos in a mathematical model of a biosensor based on difference equations was done. The bifurcation diagram of the mathematical model of CPBSS based on the difference equations on a rectangular (Fig. 3 (a)) and hexagonal (Fig. 3 (b)) lattices at $D = 0$ shows the maximum and minimum points for the boundary cycles of the antigen population.

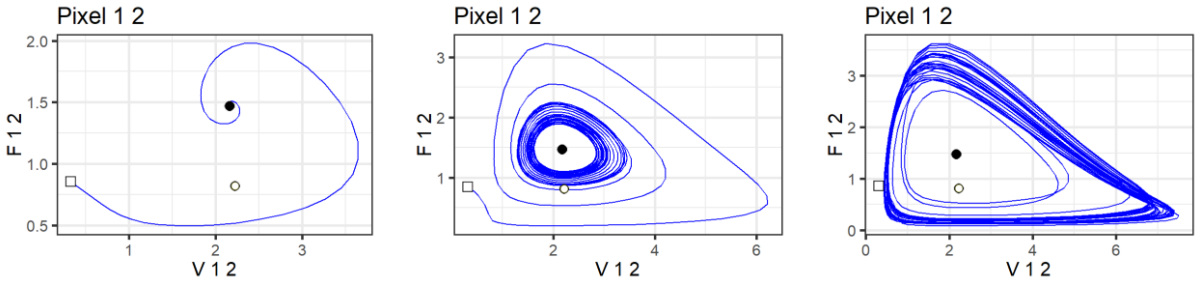


a) b)

Figure 3: Bifurcation diagrams of the mathematical model of CPBSS using difference equations on rectangular (a) and hexagonal (b) lattices

Analyzing the dynamic changes in the bifurcation diagrams (Fig. 2 (a, b), Fig. 3 (a, b)), we can conclude that the qualitative behavior of model (1) varies from a stable focus through the Hopf bifurcation to the limit cycle and deterministic chaos.

The behavior of model (1) in the form of phase diagrams at $\tau = 0.05$, $\tau = 0.23$, $\tau = 0.2865$, at the values of the parameters presented above (Fig. 4 (a - c)) is analyzed.



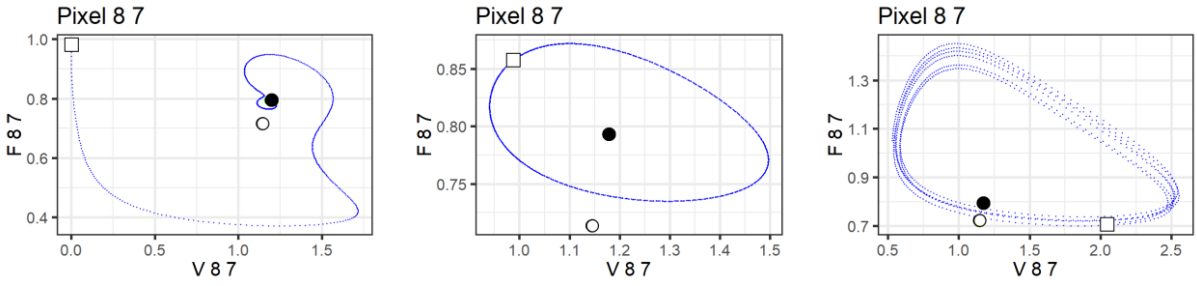
a) b) c)

Figure 4: Phase diagrams of system (1) for antibody populations $F_{i,j}$ relative to antigen populations $V_{i,j}$ at $\tau = 0.05$ (a), $\tau = 0.23$ (b), $\tau = 0.2865$ (c): □ – initial state; ○ – identical steady state; ● – non-identical steady state

Analyzing the phase diagrams of antigen populations relative to antibodies (Fig. 4 (a)), we can conclude that for $\tau = 0.05$ the solution of system (1) tends to a non-identical endemic state, which in this case is a stable focus. For $\tau \in [0, 0.22]$ trajectories corresponding to a stable node (Fig. 4 (a)) are observed. At values τ close to 0.23 min Hopf's bifurcation occurs (Fig. 4 (b)). For values τ greater than 0.2865 min we observe chaotic behavior (Fig. 5 (c)).

The long-term behavior of the mathematical model of the biosensor using the difference equations on the rectangular lattice (7) at $r = 8$ (a), $r = 12$ (b), $r = 16$ (c) is analyzed by scaling the corresponding parameters, which depend on the sampling step $h = 0.01^2$; $\beta = 2h$; $\gamma = 2h$; $\mu_f = h$; $\eta = 0.01184/\gamma$; $\delta_\upsilon = 0.5h$; $\delta_f = 0.5h$; $D/\Delta^2 = 2.22\sqrt{h}$; $N = 4$.

The results of numerical simulations are shown in Fig. 6 (a - c). In fig. 6 (a), when $r \in [0, 11]$, it is seen the trajectories that correspond to a stable focus for all pixels. For values $r = 12$ (Fig. 5 (b)) there is a Hopf bifurcation and the following trajectories correspond to stable boundary cycles of elliptical shape for all pixels.



a) b) c)

Figure 5: Representation of the phase planes of the system (7) for $r = 8$ (a), $r = 12$ (b), $r = 16$ (c) (⌐- initial state, ○ - identical steady state, ● - non-identical steady state)

For $r = 12$ the phase diagrams shows that the solution is a boundary cycle with two local extrema (one local maximum and one local minimum per cycle). For $r = 14$ the solutions is a boundary cycle with twelve local extrema per cycle. For $r = 16$ (Fig. 5 (c)) there is chaotic behavior, ie the absence of periodic behavior over a long period of time.

4. Software complex in the study of stability of mathematical models of Cyber-physical systems of medical and biological processes

The software package for the study of phase diagrams of Cyber-Physical Biosensor Systems (CPBSS) consists of the following main software modules and units: input and identification of input parameters of CPBSS models, the decision-making unit on the stability of CPBSS and the

visualization unit. A software package for the study of CPBSS phase diagrams using the R package (http://www.r-project.org/) has been developed. The block diagram of the software package for the study of the stability of CPBSS is shown in Fig. 6. The software module for studying of the dynamic behavior of CPBSS consists of blocks for obtaining bifurcation and phase diagrams.

The software module for studying the dynamic behavior of CPBSS consists of blocks for obtaining bifurcation and phase diagrams.

Using software to study the stability of CPBBS obtained the results of numerical modeling of the developed mathematical models of CPS of medical and biological processes in the form of bifurcation and phase diagrams of antigen populations relative to antibodies.

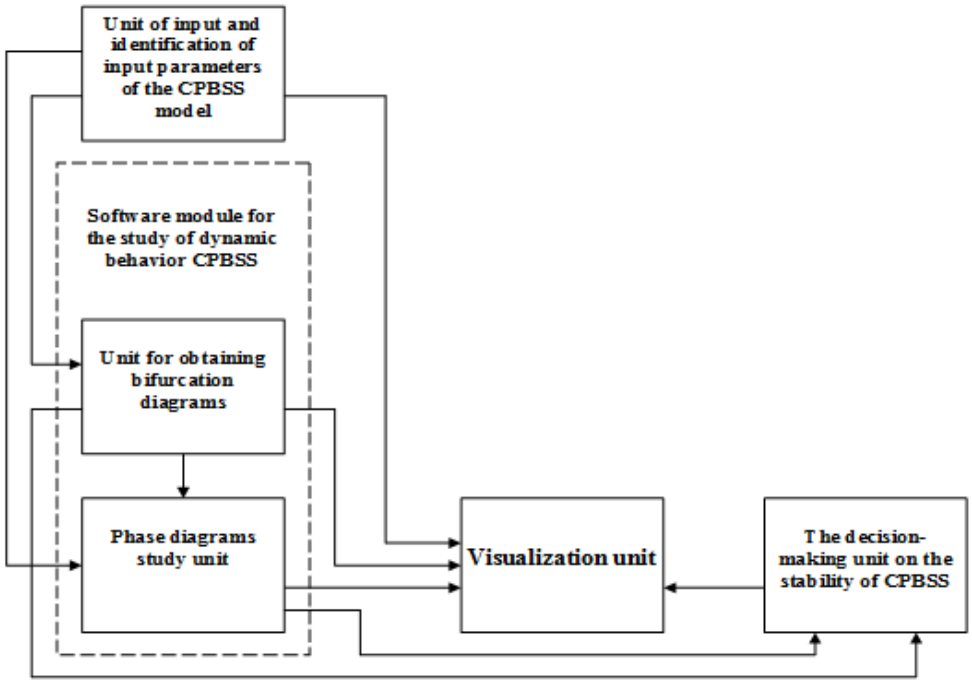


Figure 6: Block diagram of the software package for the study of phase diagrams CPBSS

Fig.7 shows the interfaces of the software package for studying the stability of CPBSS in the form of the input window of the program (Fig. 7 (a)) and the window of selection of program blocks (Fig. 7 (b)).

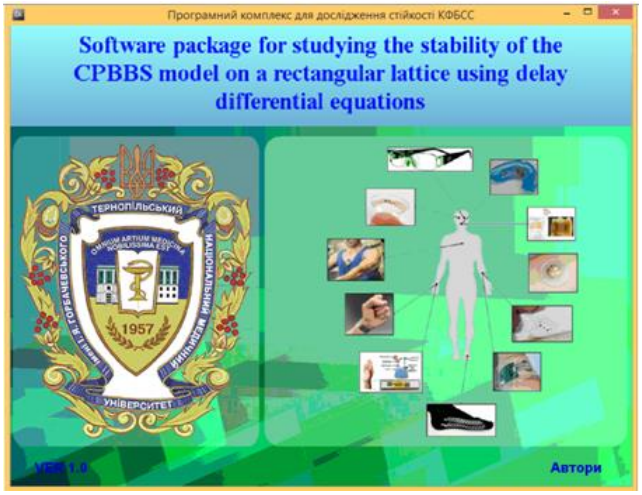
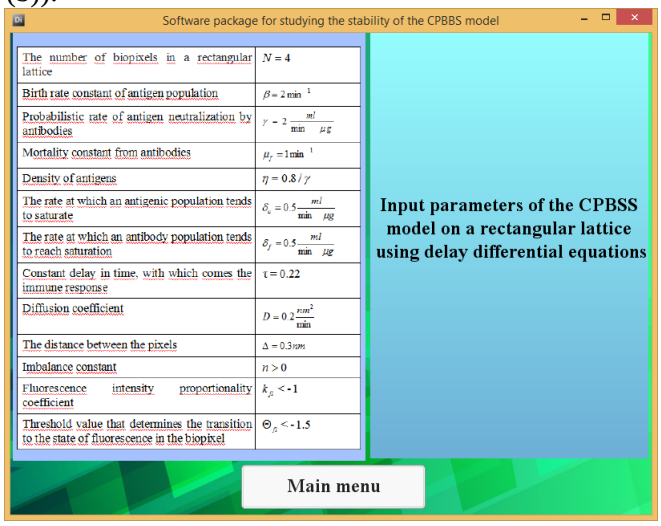
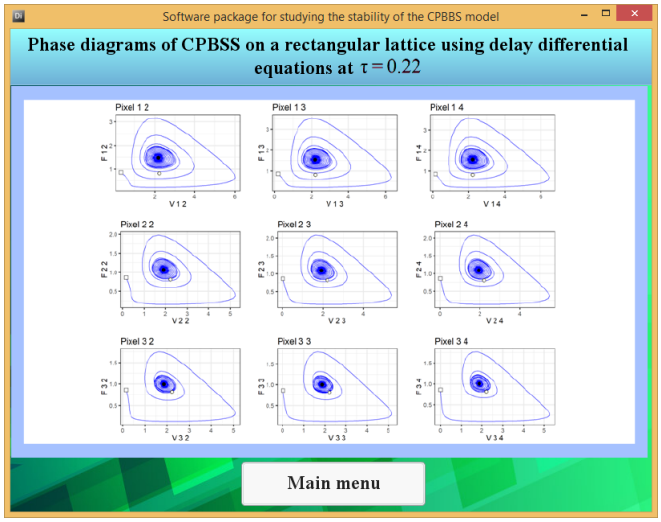


Figure 7: Interfaces of the software complex for research of stability of CPBSS (an input window of the program)

In fig. 8 presents the interfaces of the developed software package in the form of program windows for input of input parameters of the model (Fig. 8 (a)) and windows for modeling lattice images of antigens (Fig. 8 (b)).



a)



b)

Figure 8: Interfaces of the software package for the study of the stability of CPBSS: the introduction of the input parameters of model (a), modeling of phase diagrams (b)

When working with a software package to study the stability of CPBSS, the input parameters of the model are first introduced (Fig. 8 (a)), then bifurcation and phase diagrams of antigen populations relative to antibodies (Fig. 8 (b)).

5. Conclusion

In the work the general scheme of the cyber-physical sensor system proposed in [20] was used. The basic model has been modified to take into account the features of biosensors. Lattice images in biopixels are modified according to the laws of discrete dynamics. The developed models take into account the interaction of biopixels with each other by antigen diffusion.

The mathematical description of the CPBSS contains discrete population dynamics, which is combined with the dynamic logic used for discrete events. The paper uses a class of time-lattice difference equations that model the interaction of antigens and antibodies in biopixels. Spatial operators model the interaction of diffusion type between biopixels.

In the paper represents the results of numerical simulations in the form of phase plane images and lattice images of the probability of antigen to antibody binding in the biopixels of cyber-physical biosensor systems for antibody populations relative to antigen populations. The obtained experimental results make it possible to carry out a comparative analysis of the stability of mathematical models of cyber-physical biosensor systems on hexagonal and rectangular lattice. We can conclude that for r=12 Hopf bifurcation occurs and all sub-sequent trajectories correspond to stable boundary cycles for all pixels.

The numerical simulation results obtained in the paper make it possible to carry out stability analysis and comparisons of the studied models, taking into account the time delay.

A set of computer programs for the study of phase diagrams has been created, which can be used both separately and as additional specialized software for CPBSS, which makes it possible to study the phase planes of the model of the immunosensory system on a rectangular lattice using differential equations using the R package. This also takes into account the presence of antigen and antibodies colonies, that are localized in pixels, as well as the diffusion of antigen colonies between pixels.

The developed computer programs for the study of phase diagrams should be used in research, design organizations, medical and laboratory centers in the development and testing of cyber-physical systems of medical and biological processes.

6. References

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