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Computation Model of Cyber-Physical Immunosensor System

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ABSTRACT This paper initiates a study toward developing and applying computation models of cyber-physical immunosensor systems (CPISS). The focus is on the mathematical description of continuous population dynamics combined with dynamic logic used for discrete events. First, we introduce a class of lattice differential equations with time delay simulating antigen-antibody interactions within immunopixels. The spatial operator is modeling diffusion-like interaction between immunopixels. We then use the syntax of dynamic logic to describe discrete states of the immunopixel as a result of fluorescencing. An electrical signal which is simulated as a number of immunopixels' fluorescencing is important from the viewpoint of CPISS design. Stability research is focused on the notion of practical stability. For this purpose, we constructed a specific randomized multivariate algorithm, which provides a probabilistic estimate of the practical stability of the immunosensor system. In particular, we use the Monte Carlo technique. It analyzes both initial conditions and time delay and rate parameters. The experimental results obtained provide a complete analysis of immunosensor model stability with respect to changes of time delay, namely, as the time delay was increased, the stable endemic solution changed at a critical value to a stable limit cycle. Furthermore, when increasing the time delay, the behavior changed from convergence to simple limit cycle to convergence to complicated limit cycles with an increasing number of local maxima and minima per cycle until, at sufficiently high time delay, the behavior became chaotic. Such behavior can be seen using both phase portraits, tile plots, and simulated electrical signal. Mathematical models and algorithms, which are developed in this paper, may be considered as additional skills of CPISS. There is shown their software implementation as methods in language R.

INDEX TERMS Cyber-physical system, immunosensor, population dynamics, dynamic logic, practical stability.

I. INTRODUCTION

Cyber-physical system (CPS) implements integration of the computation layer and physical processes. They occur most often in the form of embedded systems and networks for monitoring and controlling physical processes operating in the feedback loop, where physical processes are a source of data for calculating the object control signal [1].

Cyber-physical systems are identified with the manifestation of the fourth industrial revolution that takes place in modern times [2]. Thus, there is also the physical possibility of using the Internet of Things technology, where it is necessary to use signals from sensors and measuring devices. Thus, in the literature [3] there is a growing number of publications that draws attention to these concepts and proposes new innovative solutions.

A. Platzer offered approach based on ''dynamic logic'' to describe and analyze cyber-physical systems [4], [5]. The cornerstone of these works are hybrid programs (HPs), which capture relevant dynamical aspects of CPSs in a simple programming language with a simple semantics. HPs allow the programmer to refer directly to real valued variables representing real quantities and specify their dynamics.

A. IMMUNOSENSOR SYSTEMS

With the growing pace of life and the need for more and more accurate detection methods, interest in biosensors is rising among science and industry as well. Biosensors are an alternative to commonly used measurement methods, which are characterized by: poor selectivity, high cost, poor stability,

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slow response and often can be performed only by highly trained personnel. They are a new generation of sensors, which use in their construction a biological material that provides a very high selectivity, also allow very quick and simple measurement [6], [7].

Cell biosensors can be applied for the quantitative assessment of infectiousness of organism with help of certain electrochemichal or optical phenomena. For example, in the work [8] there is described a cell biosensor which uses electrochemical impedance spectroscopy. Its aim is to count human CD4+ cells. The sensing area of this biosensor includes electrode pixels, each of which is comparable with CD4+ cell in size. CD4+ cells are captured by electrode pixels. They are detected by observing imperdance changes on the pixel. The ''on'' or ''off'' states of electrode pixel indicates about the detection of a single CD4+ cell. Thus, in order to count the CD4+ cells, we need to summarize the electrode pixels in the ''on'' state.

This general approach for quantitative detection of cells will be used here for modeling immunosensor system which is based on the phenomenon of fluorescence.

Due to [9], [10], [11] immunosensors are affinity ligand-based biosensor solid-state devices in which the immunochemical reaction is coupled to a transducer. The fundamental basis of all immunosensors is the specificity of the molecular recognition of antigens by antibodies to form a stable complex.

Firstly the term cyber-physical sensor system (CPSS) was defined in [12]. This definition was introduced in case of industrial applications of sensors. The first step is a general definition of cyber-physical sensor systems. This definition for CPSS implies ''the higher degree of crosslinking, distributed systems, possibilities of embedded systems in the field of automation and respects the current standards'' [12]. The second step means a characterization of skills of sensors. This approach will be used for characterizing CPISS (see Fig.1) allowing us to perform its computation modeling.

The paper is organized as follows. In Section II, we present the general flowchart of cyber-physical immunosensor system (CPISS). A continuous dynamics of CPISS, which is based on mathematical description with help of delay differential equations is given in Section III. In Section IV, we give a description of discrete dynamics of CPISS using syntaxis of dynamic logic. In Section V, a notion of practical stability for CPISS is introduced and an algorithm for stability research is offered. Numerical results are presented for stability of CPISS in Section VI. Conclusions are then provided in Section VII.

Within this paper we use the following notation:

- $\mathbf{R}$, $\mathbf{N}$ be the sets of real and natural numbers respectively;
- the symbol $i = \overline{m,n}$ for some integer i, m, n, $m < n$ means $i = m, m+1, ..., n$;
- Euclidean norm $\|x\|$ for vector $x \in \mathbf{R}^n$;
- the norm of a vector-function $|\phi(\bullet)|^\tau = \sup_{\theta\in[-\tau,0],i=\overline{1,n}} |\phi_i(\theta)|$, where functions $\phi \in \mathbf{C}^1[-\tau, 0]$;
- let the space $C[-\tau, 0] = C([-\tau, 0], \mathbf{R}^n)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbf{R}^n$ with the topology of uniform convergence;
- the space $\mathbf{C}^1[-\tau, 0]$ of continuously differentiable functions $\phi : [-\tau, 0] \to \mathbf{R}^n$, with the norm $|\phi(\bullet)|^\tau$.

II. CHARACTERIZATION OF CYBER-PHYSICAL IMMUNOSENSOR SYSTEM (CPISS)

Referring to the definitions of cyber-physical sensor system (CPSS) in [12] this leads to the definition and figures for a cyber-physical immunosensor system (CPISS).

Let $\mathcal{Q} \subset \mathbf{R}$, $q \in \mathbf{N}$ be the subspace of immunological quantity values (e.g., describing amount of cells in certain immunological state), K be the dimension of output digital information, $\mathcal{A}$ be the space of CPISS skills. Given instant of time $t \in \mathbf{R}_+$ cyber-physical immunosensor system $\sum$ converts a physically measured immunological quantity $q(t) \in \mathcal{Q}$ into digital information $d(t) \in \mathbf{R}^K$, i.e. $\sum : \mathcal{Q} \to \mathbf{R}^K$, allowing a signal process under the influence of external time-variable information and by means of an algorithm.

In addition, there is a communication of one's own abilities, requirements, internal data and internal tasks in terms of dissemination to the same or higher levels of the hierarchy.

The CPISS (outer rectangle in Figure 1) is based on the concept of CPS as well as on the immunosensory and continued development of smart immunosensors. With the added skills $A \in \mathcal{A}$ (dashed line in Figure 1), a sensor is extended to a CPISS. This process signals $s(t) \in \mathbf{R}$ and converts it into information $I(t) \in \mathbf{R}_+$.

Thus CPISS $\sum$ can be described as $\sum = \Big(q(t), d(t), s(t), I(t), A\Big)$.

The general immunopixel design, which uses the approach, which was offered in [9] is depicted in Fig. 2 in case of fluorescence . There are four types of immunosensor detection devices: electrochemical (potentiometric, amperometric or conductometric/capacitative), optical, microgravimetric, and thermometric [9]. The latter detection mode are neglected in this discourse due to a lack of considerable applications. All types can either be run as direct (nonlabeled) or as indirect (labeled) immunosensors. The direct sensors are able to detect the physical changes during the immune complex formation, whereas the latter sensors use signal-generating labels which allow more sensitive and versatile detection modes when incorporated into the complex.

Self-awareness is distinguishing feature of CPISS. From viewpoint of service-oriented approach it means availability of set of methods (interfaces) enabling the knowledge about the status and internal data of the system. These data should be accessable to other CPSs. According to [12], a self-description system needs a comprehensive knowledge about the own dynamic structure and the infrastructure of the total system. It requires the definition of classes of immunosensing devices based on their functional target, e. g. sensing levels of CK-MB to assess heart disease, sensing insulin to assess

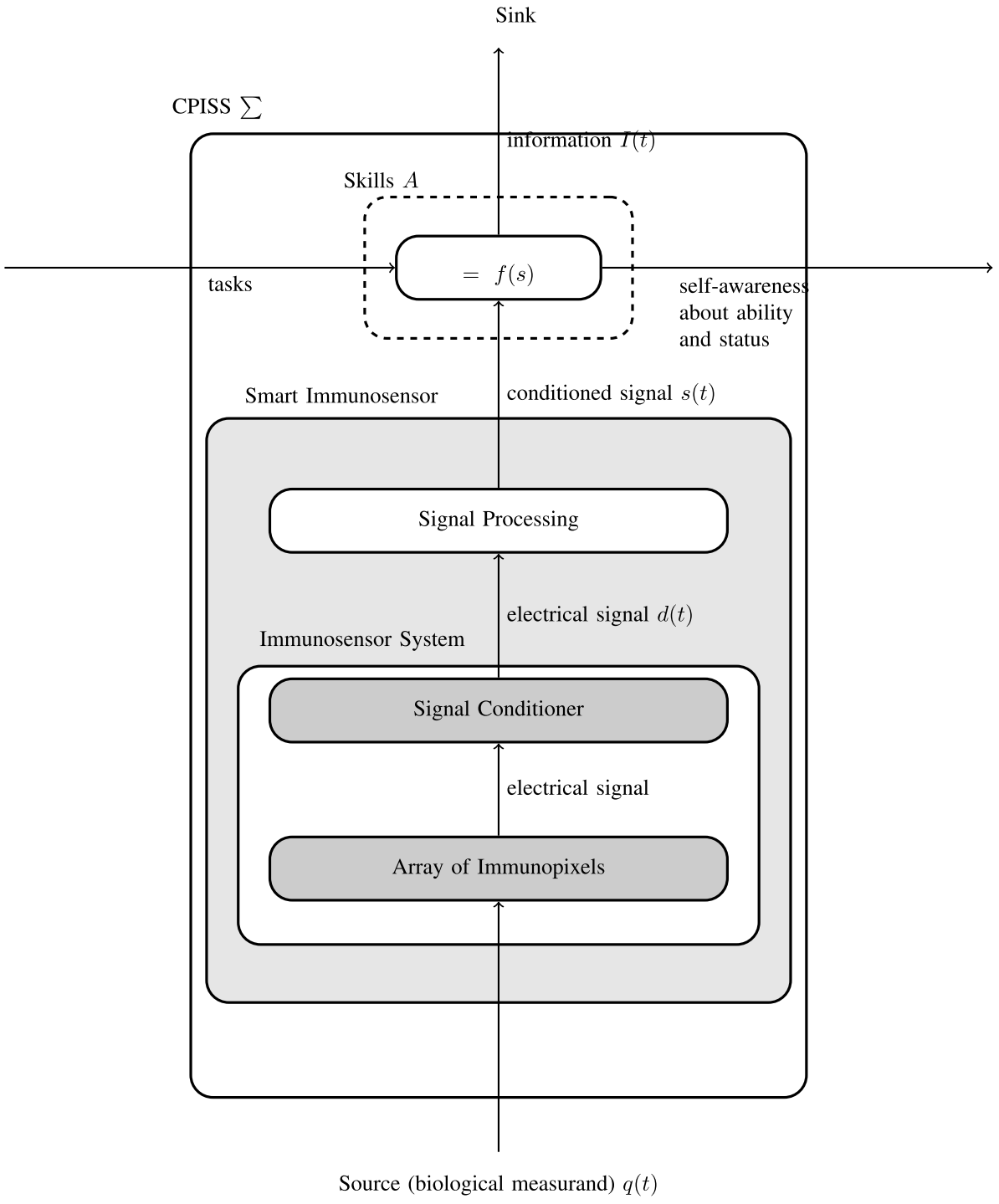


FIGURE 1. Cyber-physical immunosensor system (adapted from [12] for CPISS).

hypoglycemia, and the detection and/or quantitative measurement of some pharmaceutical compounds.

In work [12] there was offered the structure of the self-description of a general CPSS. When applying this scheme in case of immunosensors, we get the three kinds of activities, dealing with basic information about immunosensor, measuring immunological measurand and skills concerning with unit conversions, calibration and interactions with other immunosensors. The activity includes certain methods allowing us to describe the immunosensor. Here we show

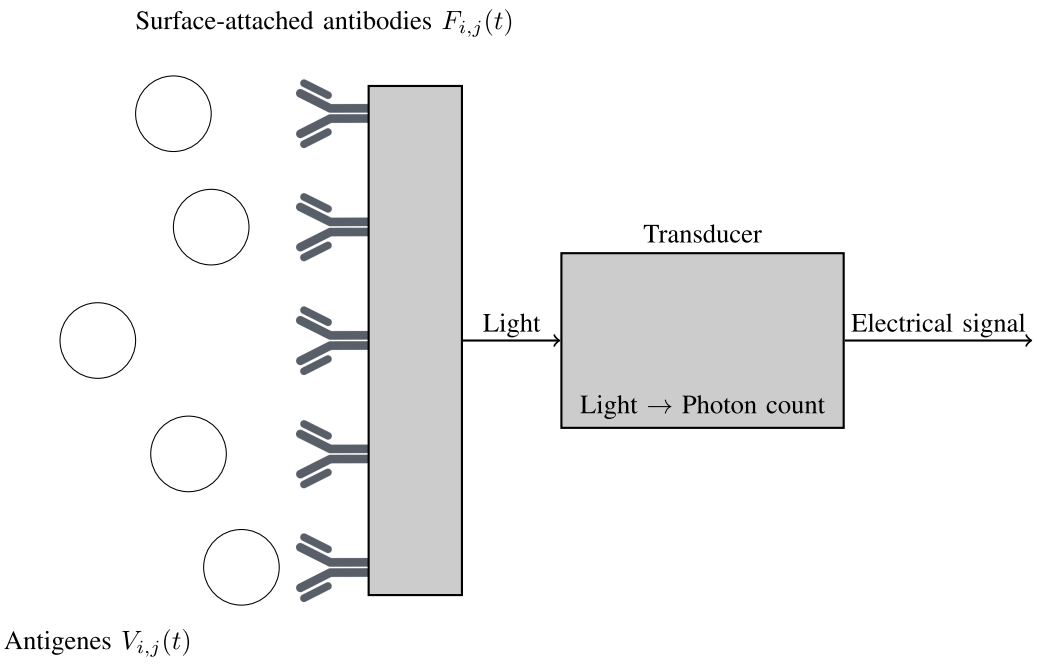


FIGURE 2. Scheme of the fluorescencing immunopixel design depicting the intimate integration of immunological recognition at the solid-state surface and the signal transduction (adapted from [9] in case of fluorescence).

implementation of the methods with help of language R. We note that there are a variety of languages, which are used in CPS design, e.g. Assembly, C, C++, D, Java, JavaScript, Python, Ada etc (see review in [13]. The language R is widely used currently in a lot of branches dealing with machine learning and data visualization. Its semantics may be applied also for CPISS modeling. Packages rootSolve and deSolve enable us solving algebraic and differential equations (with time delay). Package ggplot2 supporting grammar of graphics can be easily used for displaying graphs including tiles.

For example, method fluorescencingPixels(time) (see Listing 1) allows us to get dataframe presenting pixels fluorescencing at some instant of time. Here we use method simulate(t) for getting pixels with all their values concerning populations of antigens and antibodies.

```
[Listing 1]
fluorescencingPixels <- function(time){
pixels <- simulate(time)
# we get lattice of fluorescencing pixels
fluorescence_tile
<-ifelse(k_fl*pixels$V*pixels$F
  >fluorescence_intensity_threshold,1,0)
list(fluorescence_tile)
}
```

Method plotLattice() displays fluorescencing pixels in tile plot (see Listing 2). The results of calling this method are shown on Tables 4, 5, 6, 7.

```
[Listing 2]
plotLattice<-function(fluorescence_tile){
# plotting tiles with help of ggplot
colors <- c("white","red")
fluorescence_tile.data <-
data.frame(fluorescence_tile,
            index_i,index_j)
fluorescence_tile <-
ggplot(fluorescence_tile.data,
aes(x=index_i,y=index_j))
+ ggtitle(paste("Fluorescencing pixels,
time=",time,sep=""))
fluorescence_tile <-
factor(fluorescence_tile,levels = c("0","1"))
fluorescence_tile <- fluorescence_tile
+geom_tile(aes(fill=factor(fluorescence_tile)))
+scale_fill_manual(values=colors,guide=FALSE)
biosensor_matrix_fluorescence_tile
<- biosensor_matrix_fluorescence_tile
+ theme_set(theme_bw(base_size=28))
print(biosensor_matrix_fluorescence_tile)
dev.off()
}
```

Another example (Listing 3) presents the method for getting electrical signal as the number of pixels fluorescencing.

```
[Listing 3]
getElectricalSignal(time){
pixels <- simulate(time)
# we get lattice of fluorescencing pixels
fluorescence_tile<-fluorescencingPixels(time)
# for electrical signal
fluorescence_sum <- rbind(fluorescence_sum,
list(time=time,
fluorescence_tile_sum=sum(fluorescence_tile)))
list(fluorescence_sum)
}
```

In order to plot electrical signal within time interval we can use method plotElectricalSignal(time1, time2) (Listing 4). The results of calling this method are shown on Figures 4, 5, 6.

```
[Listing 4]
plotElectricalSignal(time1, time2){
# get electrical signal within
# interval [time1,time2]
fluorescence_sum
 <- getElectricalSignal(time1, time2)
# plot graph
electricalSignal
<- ggplot(data=fluorescence_sum,
aes(x=time, y=fluorescence_tile_sum))
+ ylab("fluorescencing pixels")
+ geom_line(color="blue")+geom_point()
list(electricalSignal)
}
```

III. CONTINUOUS DYNAMICS OF CPISS

For continuous dynamics we use mathematical description with help of nonlinear delay differential equations. Let $V_{i,j}(t)$ be concentration of antigens, $F_{i,j}(t)$ be concentration of antibodies in immunopixel (i, j), $i, j = \overline{1, N}$.

The model is based on the following biological assumptions for arbitrary immunopixel (i, j).

1) We have some constant birthrate $\beta > 0$ for antigen population.
2) Antigens are detected, binded and finally neutralized by antibodies with some probability rate $\gamma > 0$.
3) We have some constant death rate of antibodies $\mu_f > 0$.
4) We assume that when the antibody colonies are absent, the antigen colonies are governed by the well-known delay logistic equation:

$$\frac{dV_{i,j}(t)}{dt} = (\beta - \delta_v V_{i,j}(t-\tau))V_{i,j}(t), \qquad (1)$$

where β and δ_v are positive numbers and $\tau \geq 0$ denotes delay in the negative feedback of the antigen colonies.
5) The antibody decreases the average growth rate of antigen linearly with a certain time delay τ; this assumption corresponds to the fact that antibodies cannot detect and bind antigen instantly; antibodies have to spend τ units of time before they are capable of decreasing the average growth rate of the antigen colonies; these aspects are incorporated in the antigen dynamics by the inclusion of the term $-\gamma F_{i,j}(t-\tau)$ where γ is a positive constant which can vary depending on the specific colonies of antibodies and antigens.
6) In the absence of antigen colonies, the average growth rate of the antibody colonies decreases exponentially due to the presence of $-\mu_f$ in the antibody dynamics and so as to incorporate the negative effects of antibody crowding we have included the term $-\delta_f F_{i,j}(t)$ in the antibody dynamics.
7) The positive feedback $\eta\gamma V_{i,j}(t-\tau)$ in the average growth rate of the antibody has a delay since mature adult antibodies can only contribute to the production of antibody biomass; one can consider the delay τ in $\eta\gamma V_{i,j}(t-\tau)$ as a delay in antibody maturation.
8) While the last delay need not be the same as the delay in the hunting term and in the term governing antigen colonies, we have retained this for simplicity. We remark that the delays in the antibody term, antibody replacement term and antigen negative feedback term can be made different and a similar analysis can be followed.

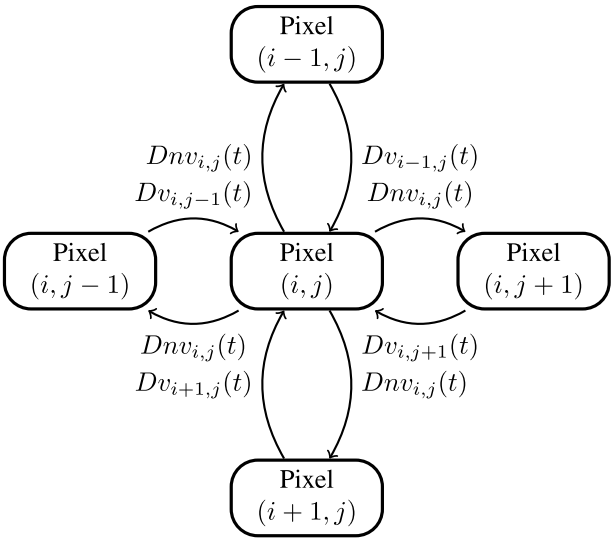


FIGURE 3. Linear lattice interconnected four neighboring pixels model, $n > 0$ is disbalance constant.

9) We have some diffusion of antigens from four neighboring pixels $(i-1, j)$, $(i+1, j)$, $(i, j-1)$, $(i, j+1)$ (see Fig. 3) with diffusion $D > 0$. Here we consider only diffusion of antigens, because the model describes so-called "competitive" configuration of immunosensor [14]. When considering competitive configuration of immunosensor, the factors immobilized on the biosensor matrix are antigens, while the antibodies play the role of analytes or particles to be detected.
10) We consider surface lateral diffusion (movement of molecules on the surface on the solid phase toward immobilized molecules) [15]. Moreover, there are works [16], [17] which assume and consider surface diffusion as an entirely independent stage.
11) We extend the definition of usual diffusion operator in case of surface diffusion in the following way. Let $n \in (0, 1]$ be a factor of diffusion disbalance. It means that only nth portion of antigens of the pixel (i, j) may be included into diffusion process to any neighboring pixel as a result of surface diffusion.
12) As a result of binding antigens with pixel antibodies, pixel is fluorescencing. We assume that fluorescence intensity is proportional to amount of contacts between antigens and antibodies, i.e., $k_{fl} V_{i,j}(t) F_{i,j}(t)$. We let that the pixel (i, j) is in the fluorescencing state if

$$k_{fl} V_{i,j}(t) F_{i,j}(t) \geq \Theta_{fl}, \qquad (2)$$

where $\Theta_{fl} > 0$ is some threshold value of binds enabling fluorescence.
13) Output signal $s(t)$ is proportional to amount of pixels in fluorescencing state.

14) Information about quantity of biological measurand is calculated based on output signal.

For the reasonings given we consider a very simple delayed antibody-antigen competition model for biopixels two-dimensional array which is based on well-known Marchuk model [18], [19], [20] and using spatial operator $\hat{S}$ offered in [21] (Supplementary information, p.10)

$$\frac{dV_{i,j}(t)}{dt} = (\beta - \gamma F_{i,j}(t-\tau) - \delta_v V_{i,j}(t-\tau))V_{i,j}(t) + \hat{S}\{V_{i,j}\}, \quad (3)$$

$$\frac{dF_{i,j}(t)}{dt} = (-\mu_f + \eta\gamma V_{i,j}(t-\tau) - \delta_f F_{ij}(t))F_{i,j}(t) \quad (4)$$

with given initial functions

$$V_{i,j}(t) = V^0_{i,j}(t) \geq 0, \quad F_{i,j}(t) = F^0_{i,j}(t) \geq 0, \quad t \in [-\tau, 0], \quad V_{i,j}(0), F_{i,j}(0) > 0. \quad (5)$$

For a square $N \times N$ array of traps, we use the following discrete diffusion form of the spatial operator [21]

$$\hat{S}\{V_{i,j}\} = \begin{cases} D\Big[V_{1,2} + V_{2,1} - 2nV_{1,1}\Big] & i,j = 1, \\ D\Big[V_{2,j} + V_{1,j-1} + V_{1,j+1} - 3nV_{i,j}\Big] & \\ i = 1, j \in \overline{2, N-1}, & \\ D\Big[V_{1,N-1} + V_{2,N} - 2nV_{1,N}\Big] & i = 1, j = N, \\ D\Big[V_{i-1,N} + V_{i+1,N} + V_{i,N-1} - 3nV_{i,N}\Big] & \\ i = \in \overline{2, N-1}, j = N, & \\ D\Big[V_{N-1,N} + V_{N,N-1} - 2nV_{N,N}\Big] & i = N, j = N, \\ D\Big[V_{N-1,j} + V_{N,j-1} + V_{N,j+1} - 3nV_{N,j}\Big] & \\ i = N, j \in \overline{2, N-1}, & \\ D\Big[V_{N-1,1} + V_{N,2} - 2nV_{N,1}\Big] & i = N, j = 1, \\ D\Big[V_{i-1,1} + V_{i+1,1} + V_{i,2} - 3nV_{i,1}\Big] & \\ i \in \overline{2, N-1}, j = 1, & \\ D\Big[V_{i-1,j} + V_{i+1,j} + V_{i,j-1} + V_{i,j+1} - 4nV_{i,j}\Big] & \\ i, j \in \overline{2, N-1} & \end{cases} \quad (6)$$

Each colony is affected by the antigen produced in four neighboring colonies, two in each dimension of the array, separated by the equal distance Δ. We use the boundary condition $V_{i,j} = 0$ for the edges of the array $i, j = 0, N+1$.

We define the phase space C of system (3) as follows, C is the Banach space of continuous functions $\phi(t) : [-\tau, 0] \to \mathbf{R}^{2N^2}$ with the norm $\|\phi\|^\tau = \sup_{t\in[-\tau,0]} \|\phi(t)\|$.

Let

$$C_+ = \{\phi = \{(\xi_{i,j}, \eta_{i,j})\}_{i,j=\overline{1,N}} \in C : \xi_{i,j}, \eta_{i,j} (i,j = \overline{1,N}) \text{ are nonnegative and bounded on } [-\tau, 0] \text{ and } \xi_{i,j}(0) > 0, \eta_{i,j}(0) > 0\}$$

Motivated by the biological background of system (3), (5), we see that solutions initial condition satisfy $\{(V^0_{i,j}, F^0_{i,j})\}_{i,j=\overline{1,N}} \in C_+$.

We can easily prove that the functional of the right side of system (3) is continuous and satisfies the local Lipschitz condition with respect to $\{(V_{i,j}, F_{i,j})\}_{i,j=\overline{1,N}}$ in the space C. Therefore, by the fundamental theory of functional differential equations with finite delay [22], for any $\phi = \{(V^0_{i,j}, F^0_{i,j})\}_{i,j=\overline{1,N}} \in C_+$ system (3) has a unique solution $\mathcal{E}(t,\phi) = \{(V_{i,j}(t,\phi), F_{i,j}(t,\phi))\}_{i,j=\overline{1,N}}$ satisfying the initial condition (5). In addition, we also can easily prove that, when $\phi \in C_+$, the solution $\mathcal{E}(t,\phi)$ is positive, that is $V_{i,j}(t,\phi) > 0, F_{i,j}(t,\phi)) > 0, i,j = \overline{1,N}$ on the interval of the existence.

Numerical solution of lattice system (3), (5) is of special interest. Here we only refer to the work [23] reviewing Runge-Kutta methods, particularly to the methods specially tuned to integrate problems with ''oscillatory character'' solutions. In the numerical simulation we use package `deSolve`[1] for the numerical solution of initial value problems for ordinary differential equations with delay.

IV. DYNAMIC LOGIC-BASED MODELING OF CPISS

With purpose of modeling dynamic logic of CPISS here we use syntax offered by A.Platzer for general cyber-physical systems [4].

We begin from continuous program. After preparations for understanding differential equations and domains for immunosensor system in Section III, we start implementing a programming language for cyber-physical systems. This programming language of hybrid programs contains more features than just differential equations.

The first layer of hybrid programs (HP) are purely continuous programs. These are defined by the following grammar

$$\alpha ::= \frac{dV_{i,j}(t)}{dt} = (\beta - \gamma F_{i,j}(t-\tau) - \delta_v V_{i,j}(t-\tau))V_{i,j}(t) + \hat{S}\{V_{i,j}\}, \quad \frac{dF_{i,j}(t)}{dt} = (-\mu_f + \eta\gamma V_{i,j}(t-\tau) - \delta_f F_{ij}(t))F_{i,j}(t) \quad \&\Phi_t, \quad (7)$$

where Φ_t is evolution domain constraint in the form of a formula of first-order logic of real arithmetic

$$\Phi_t \overset{def}{\equiv} V^{\min} \leq V_{i,j}(t) \leq V^{\max} \wedge F^{\min} \leq F_{i,j}(t) \leq F^{\max} \wedge i,j = \overline{1,N} \wedge t > 0. \quad (8)$$

The functioning of immunopixel (i,j) is determined by two states with respect to fluorescence. Namely, s_{fl} is fluorescencing state and s_{nonfl} is nonfluorescencing one. Using first-order logic semantics and satisfaction relation $s \models L$ for a first-order formula L of real arithmetic and state s, we can define for some pixel (i,j), $i,j \in \overline{1,N}$ the states s_{fl} and s_{nonfl} as

$$s_{fl} \models k_{fl} V_{i,j}(t) F_{i,j}(t) \geq \Theta_{fl}, \quad s_{nonfl} \models k_{fl} V_{i,j}(t) F_{i,j}(t) < \Theta_{fl} \quad (9)$$

[1] See https://cran.r-project.org/web/packages/deSolve/index.html

Discrete change happens in computer programs when they assign a new value to a variable. Such a situation takes place if fluorescence in the pixel (i, j) occurs. The statement $s_{fl,i,j} := 1$ assigns the value 1 to variable $s_{fl,i,j}$. It leads to a discrete, discontinuous change, because the value of $s_{fl,i,j}$ does not vary smoothly but radically when suddenly assigning 1 to $s_{fl,i,j}$, which causes a discrete jump in the value of $s_{fl,i,j}$.

This gives us a discrete model of change, $s_{fl,i,j} := 1$, in addition to the continuous model of change (7). Now, we can model pixel that is either discrete or continuous. So, we need to model proper CPS that combine cyber and physics with one another and that, thus, simultaneously combine discrete and continuous dynamics. We need such hybrid behavior every time a pixel has both continuous dynamics (such as the continuous dynamics of populations in real world) and discrete dynamics (such as starting measurement). One way how cyber and physics can interact is if a computer provides input to physics. Physics may mention variables like $F_{i,j}(0)$ for initial antibody density and a computer program sets their values depending on whether the computer program wants to measure or not. That is, cyber could set the values of actuators that affect physics.

V. ALGORITHM OF STABILITY INVESTIGATION

In the context of biosensors two types of stability can be distinguished: self stability and operational stability.

Self stability is defined as the enhancement or improvement of activity retention of an enzyme, protein, diagnostic or device when stored under specific condition. Operational stability is the retention of activity when in use [24]. The stability of the sensible element located in the biosensor receptor layer and the stability associated with the activity of the biosensor matrix components during use, determine the usefulness of the device

Qualitative results which are obtained hereinafter can be applied for both types of stability. Namely, simulation of different types of stability problems can be implemented through different initial conditions for pixels (especially for boundary pixels).

There are a lot of definitions of stability which are used for dynamic systems. They are stability, asymptotic stability, uniform asymptotic stability, exponential stability, robust stability etc. The most reasonable for CPSs is usage of the notion of practical stability [25].

For the problems of practical stability it is characteristic feature that they are investigated on finite time interval, certain initial conditions and dynamic restrictions are given. So, we consider model of CPISS at $t \in [0, T]$. Let $G_0 \subset \mathbf{R}_+^{2N}$ be set of initial vector-functions at $t \in [-\tau, 0]$, $\Phi_t \subset \mathbf{R}_+^{2N}$ be sets of admissible values of $V_{i,j}(t)$, $F_{i,j}(t)$, $i, j = \overline{1, N}$. We introduce the following definition.

The solution $\mathcal{E}(t) = \{(V_{i,j}(t), F_{i,j}(t))\}_{i,j=\overline{1,N}}$ of the model (3) is called $\{G_0, \Phi_t, T\}$-*stable* if $(\mathcal{E}(t) \in \Phi_t \wedge t \in [0, T]) \wedge (\mathcal{E}(t) \in G_0 \wedge t \in [-\tau, 0])$.

The model (3), (5) is a system of nonlinear differential equations. Application of differential equations for mathematical modeling does not mean obtaining analytical representation for their solutions (or approximations). Moreover these clear formulas don't exist in most cases. A formula for clear or approximate analytic solution is very often so complex that nothing can be said of nature of the solution until the graph is constructed. That is why in practice, graphs of solutions (at least their general form), are generated without getting the solutions in the form of formulas first.

Traditional approach of stability investigation is based on method of Lyapunov functionals. It combines general approach to construction of Lyapunov functionals of the predator-prey models with lattice differential equations.

Earlier in the work [6] we have used Lyapunov functional for the entire system (3) of the following form [2]

$$W(t) = \sum_{i,j=1}^{N} \left\{ \frac{1}{\gamma V_{i,j}^*} W_{i,j,1}(t) + \frac{1}{\eta\gamma F_{i,j}^*} W_{i,j,2}(t) \right\},$$

where $V_{i,j}^*$ and $F_{i,j}^*$ are endemic steady states. $W(t)$ summarizes Lyapunov functionals for all pixels $i, j = \overline{1, N}$. Lyapunov functionals $W_{i,j,1}(t)$ were constructed basing on the first equation from (3), $W_{i,j,2}(t)$ used the second ones.

As a rule Lyapunov functional approach are used for local or global asymptotic stability research of continuous dynamics systems only. It is not applicable for CPSs, which take into account discrete dynamics also. Moreover, our purpose is $\{G_0, \Phi_t, T\}$-stability investigation, which is practical generalization of the notion of stability allowing us to study more complex dynamic behavior of CPSs as compared with Lyapunov stability.

In order to overcome these shortcomings of traditional approach, when applied for stability investigation of CPISS, we use a nontraditional approach for qualitative analysis of biological systems, resulting in decision tree induction, which was offered in [26]. The basic idea of such a method is using Monte-Carlo method to gather learning tuples that are further used in data mining algorithm. They only considered initial conditions for a dynamic system. Here we try to extend this technique to rate constants and time delay also with purpose of practical stability investigation.

It is assumed the existence of solutions of the model (3), (5) at initial values, time delay and rate parameters determined by first-order logic:

Parameters

$$P \stackrel{def}{\equiv} \left\{ \beta^{\min} \le \beta \le \beta^{\max} \wedge \gamma^{\min} \le \gamma \le \gamma^{\max} \wedge \delta_v^{\min} \le \delta_v \le \delta_v^{\max} \wedge \mu_f^{\min} \le \mu_f \le \mu_f^{\max} \wedge \eta^{\min} \le \eta \le \eta^{\max} \wedge \delta_f^{\min} \le \delta_f \le \delta_f^{\max} \wedge \tau^{\min} \le \tau \le \tau^{\max} \right\},$$

[2]Here we denote the value of functional $W : \mathbb{C}[-\tau, 0) \to \mathbf{R}_+$, which is calculated at vector-interval $x(t + s)$, $s \in [\tau, 0]$, by $W(t)$.

initial conditions

$$G_0 \stackrel{def}{\equiv} \left\{ V_{i,j}^{\min} \le V_{i,j}(t) \le V_{i,j}^{\max} \wedge \right.$$
$$\left. F_{i,j}^{\min} \le F_{i,j}(t) \le F_{i,j}^{\max} \wedge i,j = \overline{1,N} \wedge t \in [-\tau, 0] \right\}$$

The basic idea of the method is that we will generate initial values, time delay and rate constants randomly, that they belonged to the given range. For each set of parameters we integrate system (3), (5) and obtain corresponding trajectories. Decision tree induction algorithm will then be applied to the results obtained in order to discover some knowledge structure for practical stability.

The algorithm includes the following five steps.

1) Determining the trajectory classes of the system. We will use classes corresponding to $\{G_0, \Phi_t, T\}$-stability and -unstability. To denote class of trajectory we introduce class attribute C which accepts one of 2 binary values $C \in \{0, 1\}$.
2) Generation of matrix of random initial values, time delay and rate parameters. Here we assume that initial values, time delay and rate parameters are uniformly distributed at intervals. Each column corresponds to the set of values of one parameter - either initial value, time delay or rate constant. Each line is a set of initial values and rate constants for one running the model based on (3), (5).

$$M = \left\{ \begin{array}{cccc} \beta^1 & \gamma^1 & \dots & F_{N,N}^1 \\ \beta^2 & \gamma^2 & \dots & F_{N,N}^2 \\ \dots & \dots & \dots & \dots \\ \beta^M & \gamma^M & \dots & F_{N,N}^M \end{array} \right\} \in \mathbf{R}^{N \times N+7}$$

3) Running the model and classification of input data. Each set of initial values, time delay and rate parameters generated in the second step are used as input for immunosensor model. Output trajectories are classified on the basis of the criteria proposed in the first step. Based on the results of classification the appropriate class attribute values (0 or 1) are assigned to initial values, time delay and rate parameters
4) Building a matrix of relationships between initial values, time delay and between rate parameters. The method assumes that for the system trajectories shape correlation between initial values, time delay and rate constants is more important than their absolute values. So the matrix containing information in the categorized coded form on the relationship between initial values, time delay and rate parameters generated in step 2 is constructed:

$$D = \left\{ \begin{array}{cccc} \beta \otimes \gamma & \beta \otimes \delta_v & \dots & C \\ p(\beta^1, \gamma^1) & p(\beta^1, \delta_v^1) & \dots & C_1 \\ p(\beta^2, \gamma^2) & p(\beta^2, \delta_v^2) & \dots & C_2 \\ \dots & \dots & \dots & \dots \\ p(\beta^M, \gamma^M) & p(\beta^M, \delta_v^M) & \dots & C_M \end{array} \right\}$$

Here

$$p(u, v) = \left\{ \begin{array}{l} 0, \text{ if } v < v \\ 1, \text{ if } u = v \\ 2, \text{ if } u > v \end{array} \right.$$

$C_l \in \{0, 1\}$ is class attribute value associated with the form of corresponding trajectories. Thus, at this step, the numerical values of initial values, time delay and rate parameters are transformed into categorized attribute values for training datasets. Since the probability of random value equals zero, the matrix is a sort of "binarization" of relationship between initial values, time delay and rate parameters. That is matrix includes only the values 0 and 2.

5) Application of decision tree induction algorithm C5.0 to the relationship between initial values and between rate parameters. Matrix of binary relations built in step 4 contains a set of training data for decision tree induction algorithm. Decision tree built includes verification of relations between initial values, time delay and rate parameters in their nodes. Classes of model trajectories $C \in \{0, 1\}$ are as tree leaves.

VI. EXPERIMENTAL RESULTS

We consider model (3) at $N = 32$, $\beta = 2\ min^{-1}$, $\gamma = 2\frac{mL}{min \cdot \mu g}$, $\mu_f = 1\ min^{-1}$, $\eta = 0.8/\gamma$, $\delta_v = 0.5\frac{mL}{min \cdot \mu g}$, $\delta_f = 0.5\frac{mL}{min \cdot \mu g}$, $D = 0.2\frac{nm^2}{min}$, $\Delta = 0.3\ nm$. The values of parameters come from the work [18], where they were applied for modeling simplified immune response.

The numerical simulations were implemented at different values of $n \in (0, 1]$. For example, at $n = 0.9$ corresponding simulations for $\tau > 0$(min) are presented (See Tables 1, 2). Here we can see that when changing the value of τ we have changes of qualitative behavior of pixels and entire immunosensor (when analyzing the form of electrical signal).

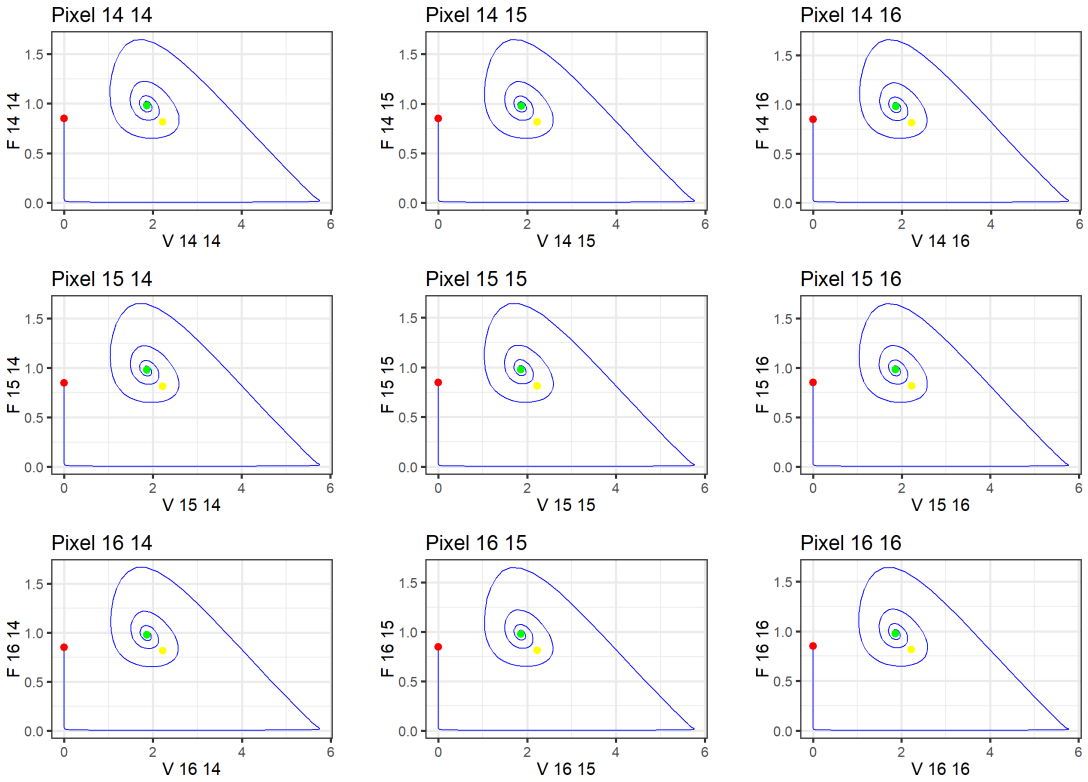
These changes with respect to τ can be explained from biological point of view also. Namely, taking into account the facts that the antibody decreases the average growth rate of antigen linearly with the time delay τ and that antibodies cannot detect and bind antigen instantly but spending τ units of time before they are capable of decreasing the average growth rate of the antigen colonies.

We considered the parameter value set given above and computed the long-time behavior of the model (3) for $\tau = 0.2, 0.28$. The phase diagrams of the antibody vs. antigen populations for the pixels around pixel (15, 15) for these values of τ are shown in Tables 1, 2.

For example, at $\tau \in [0, 0.22]$ we can see trajectories corresponding to stable focus for all pixels (see Table 1). Biologically it means that for antibody colonies with some small values of τ(i.e. antibodies spend a little of time before they are capable to bind antigens and to effect on growth rate of the antigen colonies) concentrations of antigens and antibodies tend to the certain constant values.

At values τ near 0.2223min Hopf bifurcation occurs [6] and further trajectories correspond to stable limit cycles of

TABLE 1. The phase plane plots of the system (3) for antibody populations $F_{i,j}$ versus antigen populations $V_{i,j}$, $i, j = \overline{14, 16}$. Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.2$. Here ● indicates identical steady state, ● indicates nonidentical steady state. Trajectories are constructed for $t \in [0, 100]$. The solution converges to the nonidentical steady state which is stable focus.



ellipsoidal form for all pixels. We note that in order that the numerical solutions regarding Hopf bifurcation were in agreement with the theoretical results, we should look for a complex conjugate pair of purely imaginary solutions of the corresponding characteristic equation of the linearized system.

Biologically it means that antibody spends too much time τ before it is capable of binding the antigens. As a result antibodies as well as antigens are not able to reach some constant levels of their concentrations but oscillate. We have oscillating population dynamics of antigens and antibodies.

In [6] the model (3) was investigated using phase diagrams at $N = 4$. For $\tau = 0.23$, the phase diagrams show that the solution is a limit cycle with two local extrema (one local maximum and one local minimum) per cycle. Then for $\tau = 0.2825$ the solution is a limit cycle with four local extrema per cycle, and, for $\tau = 0.2868, 0.2869, 0.28695$ the solutions are limit cycles with 8, 16 and 32 local extrema per cycle, respectively.

Finally, for $\tau = 0.28725$, the behavior shown in Figs. 4.8 is obtained which looks like chaotic behavior. We have regarded behavior as ''chaotic'' if no periodic behavior could be found in the long-time behavior of the solutions. As a check that the solution is chaotic for $\tau = 0.28725$, we perturbed the initial conditions to test the sensitivity of the system. A comparison

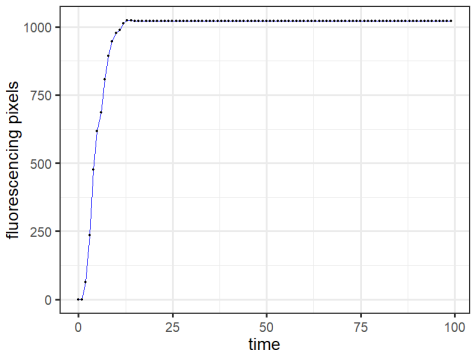


FIGURE 4. Electrical signal from transducer characterizing the number of fluorescencing pixels at $\tau = 0.05$.

of the solutions for the antigen population $V_{1,3}$ with initial conditions $V_{1,3}(t) = 1$ and $V_{1,3}(t) = 1.001$, $t \in [\hat{a}\acute{L}'\tau, 0]$, and identical all the rest ones shows chaotic behavior. Near the initial time the two solutions appear to be the same, but as time increases there is a marked difference between the solutions supporting the conclusion that the system behavior is chaotic at $\tau = 0.28725$. We have also checked numerically that the solutions for the limit cycles are periodic and computed the periods for each of the local maxima and minima in the cycles.

TABLE 2. The phase plane plots of the system (3) for antibody populations $F_{i,j}$ versus antigen populations $V_{i,j}$, $i, j = \overline{14, 16}$. Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.28$. Here ● indicates identical steady state, ● indicates nonidentical steady state. Trajectories are constructed for $t \in [0, 100]$. The solution converges to a stable limit cycle with local extremas per cycle.

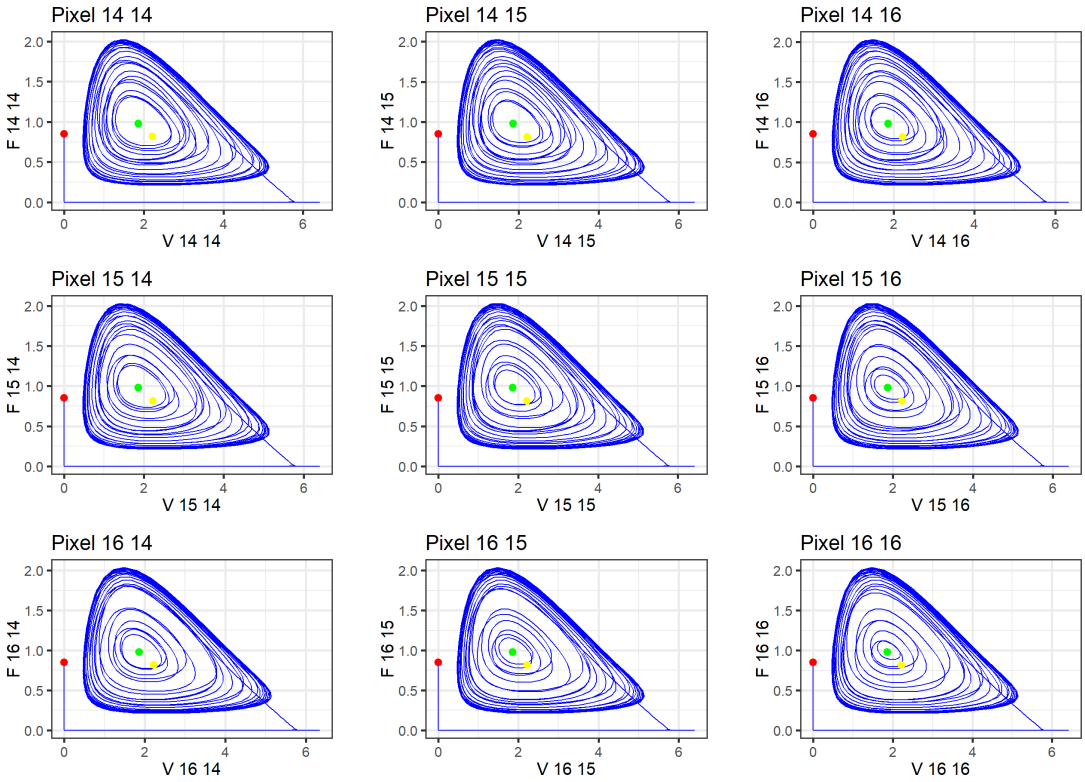
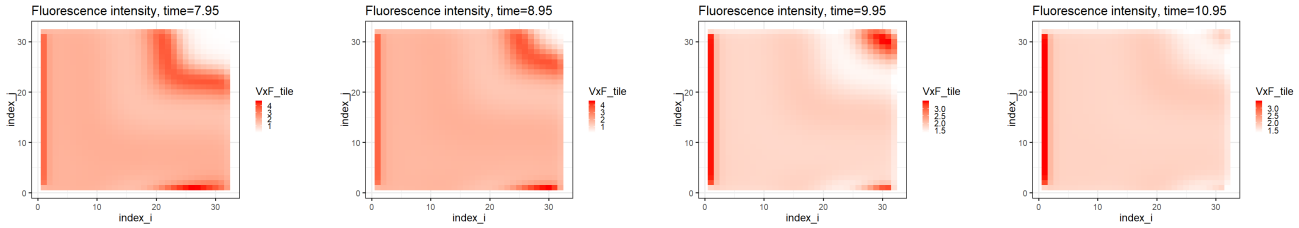


TABLE 3. Tile plots of binds of antigenes with antibodies within pixels for the system (3) at $n = 0.9$, $\tau = 0.05$.



This route to chaos can be explained with help of biological reasons as it was done in [27]. They describe it as a result of "a desynchronization of the predator and prey adaptation that comprises a form of the "Red Queen" effect" [28]. That is the value of time of "immune response" is too large in order to synchronize evolution of antibody over timescale comparable to the antigen evolution.

In case of $N = 32$ we have analyzed immunosensor model with help of tile plot displaying fluorescencing pixels. When analyzing simulation of fluorescence due to condition (2) we let $\Theta_{fl} = 1.5$. Firstly we get tile plots indicating the number of binds of antigenes with antibodies within pixels (see Table 3). Then, comparing it with threshold value Θ_{fl}, we have fluorescencing pixels to investigate.

So, in case $\tau = 0.05$ we have self stability. Namely, at about $t = 11$ we get all pixels fluorescencing (see Table 4 and Fig. 4 for amount of fluorescencing pixels).

Further, when increasing time delay we observe Hopf bifurcation, which was mentioned above, and corresponding one-periodic limit circle (see Table 5 and Fig.5 for $\tau = 0.24$).

In case $\tau = 0.28$ we see chaotic behavior, starting from wave-like changes in fluorescencing pixels (Fig. 6) and transiting to chaotic ones (Table 7). Electric signal, which is characterized by the number of fluorescencing pixels, evidences this undeterministic effect (see Table 6).

Note, that these investigations of fluorescencing pixels and output signal as their number corresponds entirely our previous stability research of two-dimensional immunopixels array.

TABLE 4. Fluorescence plots of the system (3). Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.05$, threshold value for fluorescence $\Theta_{fl} = 1.5$. The case is corresponding to stable focus. Traveling wave of "nonfluorescencing" pixels can be seen.

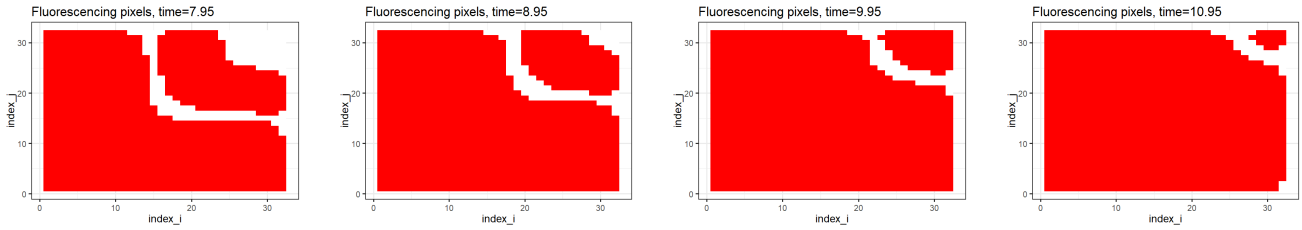


TABLE 5. Fluorescence plots of the system (3). Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.24$, corresponding tending to limit circle. Traveling wave of fluorescencing pixels can be seen.

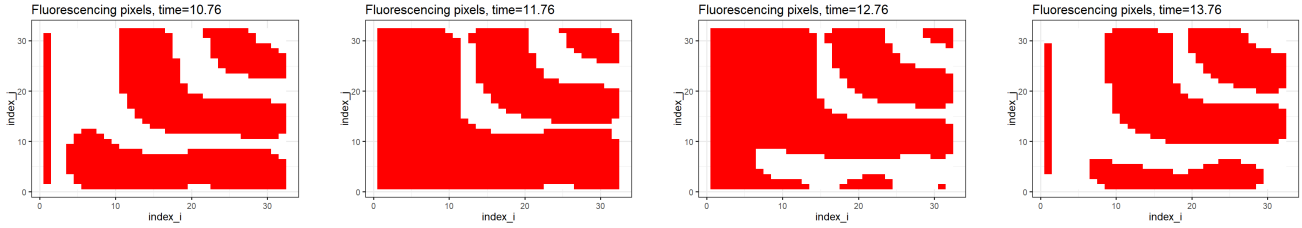


TABLE 6. Fluorescence plots of the system (3). Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.28$. Traveling wave of fluorescencing pixels can be seen.

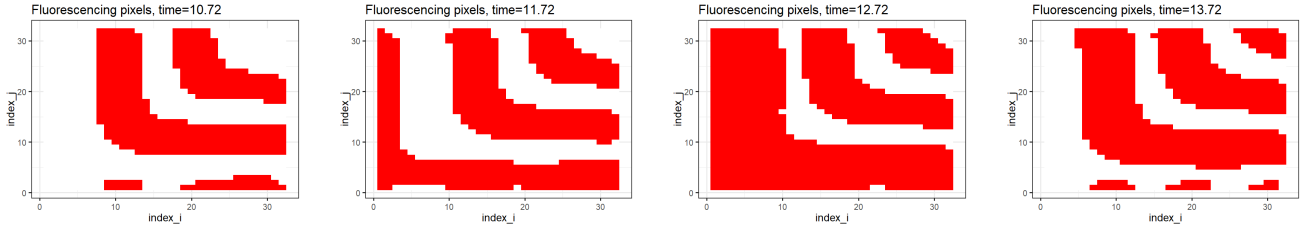
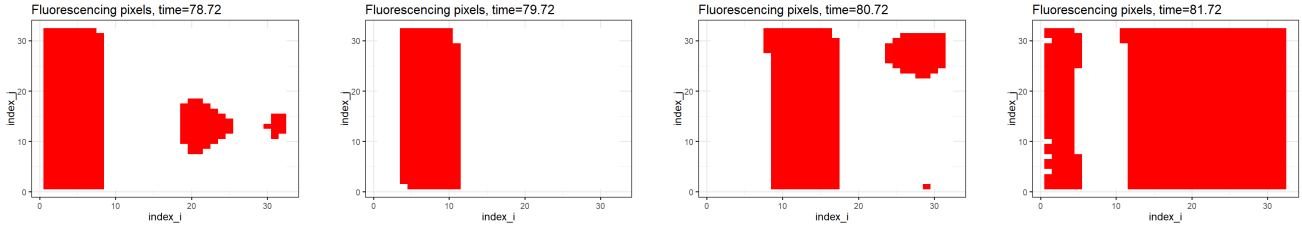


TABLE 7. Fluorescence plots of the system (3). Numerical simulation of the system (3) at $n = 0.9$, $\tau = 0.28$. Chaotic distribution of fluorescencing pixels can be seen.



As comparison study we use the work [21], where they engineered the synchronization of thousands of oscillating colony 'biopixels' over centimetre-length scales. Quorum sensing as the ability to detect and to respond to cell population density by gene regulation was used. The simulation is also based on predator-prey model of lattice delay-differential equations, where they consider colonies of H_2O_2 as 'prey' and LuxI as 'predator'. The work was focused primarily on studying oscillations of concentrations of colonies and their synchronization for neighboring biopixels. Experimentally they obtained upper bound of spacing between pixels Δ where synchronization of oscillations were lost. The model used Holling type I and II functional responses. Following from the results of modeling (3) we think that chaotic behavior for the model from [21] is also possible but it needs to be studied. Moreover, here also the algorithm of practical stability investigation, which was offered in Section V, can be applied.

Another approach to compare is based on application of Navier-Stokes partial differential equation system (see e.g. [15]). However it is more appropriate for microfluidic-based immunoassays. When we have immunosensor consisting from pixels, lattice differential equations describe discrete spatially structure better.

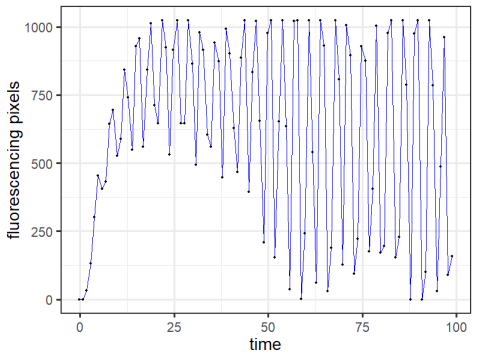


FIGURE 5. Electrical signal from transducer characterizing the number of fluorescencing pixels at $\tau = 0.24$.

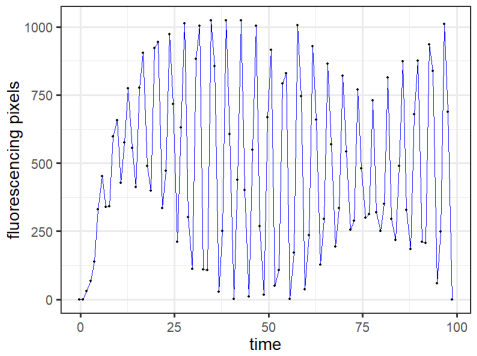


FIGURE 6. Electrical signal from transducer characterizing the number of fluorescencing pixels at $\tau = 0.28$.

At last when comparing our model of immunosensor with models mentioned above, we note that they don't consider cyber-physical systems, so they don't give tools for dynamic logic-based modeling.

VII. CONCLUSION

In this paper, we have constructed and investigated the computation model of CPISS. For this purpose general scheme of CPSS offered in [12] was used. It was modified taking into account particularities of immunosensors. Namely, we consider immunosensor as two-dimensional array of immunopixels. We pay attention that each immunopixel may be considered as CPS as well. Namely, it includes continuous dynamics of immunological response. Additionally, fluorescencing states change due to discrete dynamics laws. Moreover immunopixels communicate each other with help of diffusion of antigens.

Mathematical description of CPISS includes the continuous population dynamics combined with dynamic logic used for discrete events. So, here we study a class of lattice differential equations with time delay simulating antigen-antibody interactions within immunopixels. Spatial operator is modeling diffusion-like interaction between immunopixels. Continuous mathematical modeling is insufficient in order to simulate discrete dynamics of immunosensor. Hence, we use the syntax of dynamic logic which was offered for CPS by A.Platzer to describe discrete states of the immunopixel as a result of fluorescencing.

Electrical signal which is simulated as a number of immunopixels fluorescencing is important from viewpoint of CPISS design. Namely, stability research can be performed using its form. Stable focus, limit cycle and chaotic behavior are characterized with corresponding shape of immunosensor electrical signal. Also decision on immunosensor stability may be made basing on the tile plot displaying fluorescencing pixels.

Stability research is focused on a notion of practical stability. For this purpose we constructed specific randomized multivariate algorithm which provides a probabilistic estimate of the practical stability of the immunosensor system. In particular, we use Monte Carlo technique. It analyses both initial conditions and time delay and rate parameters.

The experimental results obtained provide a complete analysis of immunosensor model stability with respect to changes of time delay. Namely, as the time delay was increased, the stable endemic solution changed at a critical value to a stable limit cycle. Further, when increasing the time delay, the behavior changed from convergence to simple limit cycle to convergence to complicated limit cycles with an increasing number of local maxima and minima per cycle until at sufficiently high time delay the behavior became chaotic. Such behavior can be seen using both phase portraits, tile plots and simulated electrical signal. Mathematical models and algorithms, which are developed in the paper, may be considered as additional skills of CPISS. There is shown their software implementation as methods in language R.

We realize that a lot of mathematical problems dealing with evidencing positivity of solutions, persistence, and extinction of antigen-antibody populations have left to be open. Namely, we need some conditions enabling us positivity of the model solutions.

Practical experiments show us that the diffusion D should be small enough, that the values of $V_{i,j}(t)$ be positive. On the other hand, when considering the problem of extinction of antigene population, we get experimentally that the number N should be big enough that the values of $V_{i,j}(t)$ be not tending to zero.

Clear conditions of positivity, persistence, and extinction of the computation model of CPISS are of special interest.

Another very important problem to be solved is dealing with the synchronization of populations through biopixels. Such a problem was studied experimentally in [21]. We believe that the modification of the algorithm of stability investigation offered above, allow us to get corresponding conditions for the CPISS model parameters.

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