Immunosensor Model on the Basis of Lattice Dynamic System

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Abstract: The work is devoted to construction and stability investigation of immunosensor model. From physical point of view we consider the immunosensor as a two-dimensional biopixels array. That is why the model offered is spatially discrete or lattice one. The model is based on lattice of dynamic equations. These equations are based on some biological assumptions coming from the laws of population dynamics. Each pixel is described by dynamic changes of the populations of antigenes and antibodies which play roles of preys and predators respectively. As a result of delay of immune response we need to consider in the model the delay in time. Firstly we consider the system of lattice differential equations. These continuous time equations are used in order to get lattice difference system. Stability research uses the notion of basic reproduction number. Numerical example illustrates investigation of stability of endemic steady state.

Keywords: lattice model, differential equations, difference equations, population dynamics, immunosensor.

1 Introduction

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, 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. They can be also considered as a cornerstone of Industry 4.0. Biosensors are characterized by high versatility and therefore they are widely used in food industry (Adley, 2014), environmental protection (Klos-Witkowska, 2015), the defense industry (Burnworth et al., 2007), but are most commonly used in medicine as a tool supporting making diagnoses (Mehrotra, 2016).

In whole biosensor family there are two kinds. The first one is related to the receptor layer and to the biological material used in its construction, which may be: enzyme, protein, porphyrin, antigen or antibody. The second one is bounded to the transducer layer, where the biological effect is converted on the measurable signal (electrochemical, impedance, amperometric, potentiometric optical biosensors or based on weight changed -piezoelectric biosensors).

The purpose of the work is to construct the model of immunosensor as two-dimensional immunopixels array in class of lattice differential and difference equations of population dynamics and to research its stability, including determining steady states, basic reproduction numbers.

2 Model Construction

2.1 Biological Assumptions

Let $V_{i,j}(t)$ be concentration of antigens, $F_{i,j}(t)$ be concentration of antibodies in biopixel (i,j), $i,j = \overline{1,N}$.

The model is based on the following biological assumptions for arbitrary biopixel (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:
$$\frac{dV_{i,j}(t)}{dt} = (\beta - \delta_v V_{i,j}(t-\tau))V_{i,j}(t), \tag{1}$$
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.

9. We have some diffusion of antigens from four neighboring pixels $(i-1,j)$, $(i+1,j)$, $(i,j-1)$, $(i,j+1)$ with diffusion $D > 0$. Here we consider only diffusion of antigens, because the model describes so-called "competitive" configuration of immunosensor (Cruz et al., 2002). 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 solid phase toward an immobilizated molecules) (Paek and Schramm, 1991). Moreover, there are works (Bloomfield and Prager, 1979; Berg, 1985) which assume and consider surface diffusion as an entirely independent stage.

11. We extend 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.

2.2 Continuous Time Model

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 (Marchuk et al., 1991;

Foryś, 2002; Nakonechny and Marzeniuk, 2006; Marzeniuk, 2001) and using spatial operator $\hat{S}$ offered in Prindle et al. (2011) (Supplementary information, p.10)

$$\begin{aligned}\frac{dV_{i,j}(t)}{dt} &= (\beta - \gamma F_{i,j}(t-\tau) - \delta_v V_{i,j}(t-\tau))V_{i,j}(t) + \hat{S}\{V_{i,j}\},\\ \frac{dF_{i,j}(t)}{dt} &= (-\mu_f + \eta\gamma V_{i,j}(t-\tau) - \delta_f F_{ij}(t)\Big)F_{i,j}(t)\end{aligned} \tag{2}$$

with given initial functions

$$\begin{aligned}&V_{i,j}(t) = V^0_{i,j}(t) \geq 0, \quad F_{i,j}(t) = F^0_{i,j}(t) \geq 0, \quad t \in [-\tau, 0),\\ &V_{i,j}(0), F_{i,j}(0) > 0.\end{aligned} \tag{3}$$

For a square $N \times N$ array of traps, we use the following discrete diffusion form of the spatial operator (Prindle et al., 2011)

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

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 $i, j = 0, N+1$. Further we will use the following notation of the constant

$$k(i,j) = \begin{cases} 2 & i,j = 1; \quad i = 1, j = N; \quad i = N, j = N; \quad i = N, j = 1,\\ 3 & i = 1, j \in \overline{2, N-1}; \quad i =\in \overline{2, N-1}, j = N; \quad i = N, j \in \overline{2, N-1};\\ & \quad i \in \overline{2, N-1}, j = 1\\ 4 & i,j \in \overline{2, N-1}\end{cases} \tag{5}$$

which will be used in manipulations with the spatial operator (4).

Results of modeling (2) are presented in Appendix A. It can be seen that qualitative behavior of the system is determined mostly by the time of immune response τ (or time delay), diffusion D and constant n.

2.3 Discrete Time Model

We approximate system (2) without diffusion by differential equations with piecewise constant arguments of the form

$$\begin{aligned}\frac{dV_{i,j}}{dt} &= \big(\beta - \gamma F_{i,j}([t/h]h - [\tau/h]h) - \delta_v V_{i,j}([t/h]h - [\tau/h]h)\big)V_{i,j}(t),\\ \frac{dF_{i,j}(t)}{dt} &= \big(- \mu_f + \eta\gamma V_{i,j}([t/h]h - [\tau/h]h) - \delta_f F_{i,j}([t/h]h)\big)F_{i,j}(t)\end{aligned} \tag{6}$$

for $t \in [nh, (n+1)h)$, $n \in \mathbb{Z}^+$.

Noting that $[t/h] = n$, $[\tau/h] = r \in \mathbb{Z}^+$, we integrate (6) over $[nh, t)$, where $t < (n+1)h$, then (6) can be reformulated as

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

Denoting $V_{i,j}(n) = V_{i,j}(nh)$, $F_{i,j}(n) = F_{i,j}(nh)$, then we have

$$\begin{aligned}V_{i,j}(t) &= V_{i,j}(n)\exp\big\{\beta - \gamma F_{i,j}(n-r) - \delta_v V_{i,j}(n-r)\big\},\\ F_{i,j}(t) &= F_{i,j}(n)\exp\big\{-\mu_f + \eta\gamma V_{i,j}(n-r) - \delta_f F_{i,j}(n)\big\}.\end{aligned} \tag{7}$$

Setting $t \to (n+1)h$ in (7) and simplifying, adding diffusion to the first equation, we get a discrete analogue of continuous time system (2) with the form

$$\begin{aligned}V_{i,j}(n+1) &= V_{i,j}(n)\exp\big\{\beta - \gamma F_{i,j}(n-r) - \delta_v V_{i,j}(n-r)\big\} + \hat{S}\Big\{V_{i,j}(n)\Big\},\\ F_{i,j}(n+1) &= F_{i,j}(n)\exp\big\{-\mu_f + \eta\gamma V_{i,j}(n-r) - \delta_f F_{i,j}(n)\big\},\end{aligned} \tag{8}$$

Definition 1. It is said that system (8) is **permanent** if there exist positive constants $m_{v,i,j}$, $M_{v,i,j}$, $m_{f,i,j}$, $M_{f,i,j}$, $i,j = \overline{1,N}$ that only positive solution $\big\{\big(V_{i,j}(n), F_{i,j}(n)\big)\big\}$, $i,j = \overline{1,N}$ of system (8) satisfies

$$\begin{aligned}m_{v,i,j} \le \lim\inf_{n\to\infty} V_{i,j}(n) \le \lim\sup_{n\to\infty} V_{i,j}(n) \le M_{v,i,j},\\ m_{f,i,j} \le \lim\inf_{n\to\infty} F_{i,j}(n) \le \lim\sup_{n\to\infty} F_{i,j}(n) \le M_{f,i,j}.\end{aligned}$$

Definition 2. A positive solution $\Big\{\big(V^\star_{i,j}(n), F^\star_{i,j}(n)\big)\Big\}$, $i,j = \overline{1,N}$ of system (8) is **global attractive** if each other positive solution $\big\{\big(V_{i,j}(n), F_{i,j}(n)\big)\big\}$, $i,j = \overline{1,N}$ of system (8) satisfies

$$\lim_{n\to\infty}|V_{i,j}(n) - V^\star_{i,j}(n)| = 0, \quad \lim_{n\to\infty}|F_{i,j}(n) - F^\star_{i,j}(n)| = 0, \quad i,j = \overline{1,N}.$$

Let

$$\begin{aligned}\Delta_{1,i,j} &= -\mu_f + \eta\gamma M_{1,i,j}\frac{\exp(\beta - 1)}{\delta_v}\\ \Delta_{2,i,j} &= \beta - \gamma\frac{\exp(\Delta_{1,i,j} - 1)}{\delta_f\Delta_{1,i,j}}\\ \Delta_{3,i,j} &= -\mu_f + \frac{\eta\gamma}{\delta_v}\exp(\Delta_{2,i,j}(1 - \delta_v M_{1,i,j})).\end{aligned} \tag{9}$$

Theorem 1. If the conditions

$$\min\big\{\Delta_{k,i,j}, k = \overline{1,3}, i,j = \overline{1,N}\big\} > 0 \tag{10}$$

hold, then (8) is permanent.

3 Stability problem for immunosensors

In the context of biosensors two types of stability can be distinguished (from viewpoint of engineering!): 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 (Gibson, 1999). 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).

3.1 Steady states

The steady states of the model (2) are the intersection of the null-clines $dV_{i,j}(t)/dt = 0$ and $dF_{i,j}(t)/dt = 0$, $i, j = \overline{1, N}$.

Antigen-free steady state. If $V_{i,j}(t) \equiv 0$, the free antigen equilibrium is at $\mathcal{E}^0_{i,j} \equiv \Big(0, 0\Big)$, $i, j = \overline{1, N}$ or $\mathcal{E}^0_{i,j} \equiv \Big(0, -\frac{\mu_f}{\delta_f}\Big)$, $i, j = \overline{1, N}$. The last solution does not have biological sense and can not be reached for nonnegative initial conditions (3).

When considering endemic steady state $\mathcal{E}^*_{i,j} \equiv \Big(V^*_{i,j}, F^*_{i,j}\Big)$, $i, j = \overline{1, N}$ for (2) we get algebraic system:

$$\begin{aligned} &\Big(\beta - \gamma F^*_{i,j} - \delta_v V^*_{i,j}\Big) V^*_{i,j} + \hat{S}\left\{V^*_{i,j}\right\} = 0, \\ &\Big(- \mu_f + \eta\gamma V^*_{i,j} - \delta_f F^*_{i,j}\Big) F^*_{i,j} = 0, \quad i, j = \overline{1, N}. \end{aligned} \tag{11}$$

The solutions $\Big(V^*_{i,j}, F^*_{i,j}\Big)$ of (11) can be found as a result of solving lattice equation with respect to $V^*_{i,j}$, and using relation $F^*_{i,j} = \frac{-\mu_f + \eta\gamma V^*_{i,j}}{\delta_f}$

Then we have to differ two cases.

Identical endemic state for all pixels. Let's assume there is the solution of (11) $V^*_{i,j} \equiv V^*$, $F^*_{i,j} \equiv F^*$, $i, j = \overline{1, N}$, i.e., $\hat{S}\left\{V^*_{i,j}\right\} \equiv 0$. Then $\mathcal{E}^*_{i,j} = \Big(V^*, F^*\Big)$, $i, j = \overline{1, N}$ can be calculated as

$$V^* = \frac{-\beta\delta_f - \gamma\mu_f}{\delta_v\delta_f - \eta\gamma^2}, \quad F^* = \frac{\delta_v\mu_f - \eta\gamma\beta}{\delta_v\delta_f - \eta\gamma^2}. \tag{12}$$

provided that $\delta_v\delta_f - \eta\gamma^2 < 0$.

Nonidentical endemic state for pixels. In general case we have endemic steady state which is different from (12). It is shown numerically in Appendix B that it appears as a result of diffusion between pixels D.

At absence of diffusion, i.e. $D = 0$, we have only identical endemic state for pixels of external layer. At presence of diffusion $D > 0$ nonidentical endemic states tends to identical one (12) at internal pixels, which can be observed at numerical simulation. This phenomenon is clearly appeared at bigger ammount of pixels.

3.2 Basic reproduction numbers

Here we define the basic reproduction number for antigen colony which is localized in pixel (i, j).

When considering epidemic models, the basic reproduction number, $\mathcal{R}_0$, is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population. It is important to note that $\mathcal{R}_0$ is a dimensionless number (Jones, 2007). When applying this definition to the pixel (i, j), which is described by the equation (2), we get

$$\mathcal{R}_{0,i,j} = \mathcal{T}_{i,j}\bar{c}_{i,j}, d_{i,j}$$

where $\mathcal{T}_{i,j}$ is the transmissibility (i.e., probability of binding given constant between an antigen and antibody), $\overline{c}_{i,j}$ is the average rate of contact between antigens and antibodies, and $d_{i,j}$ is the duration of binding of antigen by antibody till deactivation.

Unfortunately, the lattice system (2) doesn't include all parameters, which allow to calculate the basic reproduction numbers in a clear form. Firstly, let's consider pixel $(i^\star, j^\star)$ without diffusion, i.e., $\hat{S}\left\{V_{i^\star,j^\star}\right\} \equiv 0$. In this case the non-negative equilibria of (2) are

$$\mathcal{E}^0_{i^\star,j^\star} = \left(V^0, 0\right) := \left(\frac{\beta}{\delta_v}, 0\right), \quad \mathcal{E}^\star_{i^\star,j^\star} = \left(V^\star, F^\star\right).$$

Due to the approach which was offered in (Yang et al., 2008) (in pages 4 for ordinary differential equations, 5 for delay model), we introduce the basic reproduction number for pixel $(i^\star, j^\star)$ without diffusion, which is given by expression

$$\mathcal{R}_{0,i^\star,j^\star} := \frac{V^0}{V^\star} = \frac{\beta}{\delta_v V^\star} = \frac{\beta(\eta\gamma^2 - \delta_v\delta_f)}{\delta_v(\beta\delta_f + \gamma\mu_f)}.$$

Its biological meaning is given as being the average number of offsprings produced by a mature antibody in its lifetime when introduced in a antigen-only environment with antigen at carrying capacity.

According to the common theory it can be shown that antibody-free equilibrium $\mathcal{E}^0_{i^\star,j^\star}$ is locally asymptotically stable if $\mathcal{R}_{0,i^\star,j^\star} < 1$ and it is unstable if $\mathcal{R}_{0,i^\star,j^\star} > 1$. It can be done with help of analysis of the roots of characteristic equation (similarly to (Yang et al., 2008), p.5). Thus, $\mathcal{R}_{0,i^\star,j^\star} > 1$ is sufficient condition for existence of the endemic equilibrium $\mathcal{E}^\star_{i^\star,j^\star}$.

We can consider the expression mentioned above for the general case of the lattice system (2), i.e., when considering diffusion. In this case we have the "lattice" of the basic reproduction numbers $\mathcal{R}_{0,i,j}$, $i,j = \overline{1,N}$ satisfying to

$$\mathcal{R}_{0,i,j} := \frac{V^0_{i,j}}{V^\star_{i,j}}, \quad i,j = \overline{1,N}, \tag{13}$$

where $\mathcal{E}^0_{i,j}$, $i,j = \overline{1,N}$ are nonidentical steady states, which are found as a result of solution of the algebraic system

$$\left(\beta - \delta_v V^0_{i,j}\right)V^0_{i,j} + \hat{S}\left\{V^0_{i,j}\right\} = 0, \quad i,j = \overline{1,N}, \tag{14}$$

endemic states $\mathcal{E}^\star_{i,j} = \left(V^\star_{i,j}, F^\star_{i,j}\right)$, $i,j = \overline{1,N}$ are found using (11).

It is worth to say that due to the common theory the conditions $\mathcal{R}_{0,i,j} > 1$, $i,j = \overline{1,N}$ are sufficient for the existence of endemic state $\mathcal{E}^\star_{i,j}$. We will check it only in the Section 4 with help of numerical simulations.

3.3 Global Attractivity of Difference Model

Theorem 2. Assume that there exists a positive constant ξ such that

$$\begin{aligned} &\exp\left\{\gamma m_f + \delta_v m_v - \beta\right\} - \delta_v - \frac{1}{m_v} - \eta\gamma \geq \xi, \\ &\min\left\{\delta_f, \frac{2}{M_f} - \delta_f\right\} - \gamma \geq \xi \end{aligned} \tag{15}$$

hold.

Then any positive solution $\left\{\left(V^\star_{i,j}(n), F^\star_{i,j}(n)\right), i,j = \overline{1,N}\right\}$ of system (8) is global attractive

Proof: Denote $\left\{\left(V_{i,j}(n), F_{i,j}(n)\right), i,j = \overline{1,N}\right\}$ be any other positive solution of system (8). Let

$$W_{1,1,i,j}(n) = |\ln\left(V_{i,j}(n) - \hat{S}\left\{V_{i,j}(n-1)\right\}\right) - \ln\left(V^{\star}_{i,j}(n) - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}\right)|$$

Then it follows from the first equation of (8) that

$$\begin{aligned} W_{1,1,,i,j} \leq & |\ln V_{i,j}(n) - \ln V^{\star}_{i,j}(n)| + \gamma |F_{i,j}(n-r) - F^{\star}_{i,j}(n-r)| \\ & + \delta_v |V_{i,j}(n-r) - V^{\star}_{i,j}(n-r)|. \end{aligned} \tag{16}$$

By the Mean Value theorem, we get

$$\ln V_{i,j}(n) - \ln V^{\star}_{i,j}(n) = \frac{1}{\theta_1(n)}(V_{i,j}(n) - V^{\star}_{i,j}(n)),$$

where $\theta_1(n)$ lies between $V_{i,j}(n)$ and $V^{\star}_{i,j}(n)$,

$$\begin{aligned} & \ln(V_{i,j}(n) - \hat{S}\left\{V_{i,j}(n-1)\right\}) - \ln(V^{\star}_{i,j}(n) - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}) \\ = & \frac{1}{\theta_2(n)}((V_{i,j}(n) - V^{\star}_{i,j}(n)) - (\hat{S}\left\{V_{i,j}(n-1)\right\} - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\})), \end{aligned}$$

where $\theta_2(n)$ lies between $V_{i,j}(n) - \hat{S}\left\{V_{i,j}(n-1)\right\}$ and $V^{\star}_{i,j}(n) - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}$. Consider

$$\begin{aligned} & |\ln V_{i,j}(n) - \ln V^{\star}_{i,j}(n)| \\ & = |\ln(V_{i,j}(n) - \hat{S}\left\{V_{i,j}(n-1)\right\}) - \ln(V^{\star}_{i,j}(n) - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\})| \\ & - |\ln(V_{i,j}(n) - \hat{S}\left\{V_{i,j}(n-1)\right\}) - \ln(V^{\star}_{i,j}(n) - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\})| \\ & + |\ln V_{i,j}(n) - \ln V^{\star}_{i,j}(n)| \\ & \geq W_{1,1,i,j}(n) - \left(\frac{1}{\theta_2(n)} - \frac{1}{\theta_1(n)}\right)|V_{i,j}(n) - V^{\star}_{i,j}(n)| \\ & - \frac{1}{\theta_2(n)}\left(\hat{S}\left\{V_{i,j}(n-1)\right\} - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}\right). \end{aligned} \tag{17}$$

Combining (16) and (17), we have

$$\begin{aligned} \Delta W_{1,1,i,j}(n) &= W_{1,1,i,j}(n+1) - W_{1,1,i,j}(n) \\ &\leq -\left(\frac{1}{\theta_2(n)} - \frac{1}{\theta_1(n)}\right)|V_{i,j}(n) - V^{\star}_{i,j}(n)| \\ &+ \gamma |F_{i,j}(n-r) - F^{\star}_{i,j}(n-r)| \\ &+ \delta_v |V_{i,j}(n-r) - V^{\star}_{i,j}(n-r)| \\ &- \frac{1}{\theta_2(n)}\left(\hat{S}\left\{V_{i,j}(n-1)\right\} - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}\right). \end{aligned} \tag{18}$$

Next, we let

$$W_{1,2,i,j}(n) = \sum_{s=n-r}^{n-1} \delta_v |V_{i,j}(s) - V^{\star}_{i,j}(s)| + \sum_{s=n-r}^{n-1} \gamma |F_{i,j}(s) - F^{\star}_{i,j}(s)|$$

Then we have

$$\begin{aligned} \Delta W_{1,2,i,j}(n) &= W_{1,2,i,j}(n+1) - W_{1,2,i,j}(n) \\ &= \sum_{s=n+1-r}^{n} \delta_v |V_{i,j}(s) - V^{\star}_{i,j}(s)| + \sum_{s=n+1-r}^{n} \gamma |F_{i,j}(s) - F^{\star}_{i,j}(s)| \\ &- \sum_{s=n-r}^{n-1} \delta_v |V_{i,j}(s) - V^{\star}_{i,j}(s)| - \sum_{s=n-r}^{n-1} \gamma |F_{i,j}(s) - F^{\star}_{i,j}(s)| \\ &= \delta_v |V_{i,j}(n) - V^{\star}_{i,j}(n)| - \delta_v |V_{i,j}(n-r) - V^{\star}_{i,j}(n-r)| \\ &+ \gamma |F_{i,j}(n) - F^{\star}_{i,j}(n)| - \gamma |F_{i,j}(n-r) - F^{\star}_{i,j}(n-r)|. \end{aligned} \tag{19}$$

We set $W_{1,i,j} = W_{1,1,i,j}(n) + W_{1,2,i,j}(n)$. Then it follows from (18) and (19) that

$$\begin{aligned}\Delta W_{1,i,j}(n) &= \Delta W_{1,1,i,j}(n) + \Delta W_{1,2,i,j}(n) \\ &\leq \left(\delta_v - \frac{1}{\theta_2(n)} + \frac{1}{\theta_1(n)}\right)|V_{i,j}(n) - V^{\star}_{i,j}(n)| \\ &+ \gamma|F_{i,j}(n) - F^{\star}_{i,j}(n)| \\ &- \frac{1}{\theta_2(n)}\left(\hat{S}\left\{V_{i,j}(n-1)\right\} - \hat{S}\left\{V^{\star}_{i,j}(n-1)\right\}\right)\end{aligned} \tag{20}$$

4 Numerical Example

First of all we calculate the basic reproductive numbers $\mathcal{R}_{0,i,j}$, $i,j = \overline{1,4}$. Solving (14) we have the values of equilibrium without antibodies $V^0_{i,j}$, $i,j = \overline{1,4}$ (see Table 1).

$V^0_{i,j}$	1	2	3	4
1	5.951989	7.420163	7.659892	5.966077
2	5.907517	6.180657	6.183041	5.718244
3	5.703791	5.772168	5.737166	5.500841
4	5.322284	5.459773	5.440191	5.254434

Table 1: The values of $V^0_{i,j}$, $i,j = \overline{1,4}$

The values of $V^{\star}_{i,j}$, $i,j = \overline{1,4}$ for the endemic steady state are presented in the Table 2.

$V^{\star}_{i,j}$	1	2	3	4
1	1.8491747	2.1662985	2.2047148	1.8500473
2	1.8628235	1.9105332	1.9105342	1.8289965
3	1.8445217	1.8573021	1.8527207	1.8092236
4	1.7757109	1.8073319	1.8056241	1.7683109

Table 2: The values of $V^{\star}_{i,j}$, $i,j = \overline{1,4}$

Hence, the basic reproductive numbers which are calculated due to (13) are shown in the Table 3.

$R^{\star}_{0,i,j}$	1	2	3	4
1	3.218727	3.425273	3.474323	3.224824
2	3.171270	3.235043	3.236289	3.126438
3	3.092287	3.107824	3.096617	3.040443
4	2.997269	3.020902	3.012915	2.971442

Table 3: The values of $R_{0,i,j}$, $i,j = \overline{1,4}$

We see that the conditions for basic reproductive numbers hold. Thus, equilibrium without antibodies $\mathcal{E}^0_{i,j}$, $i,j = \overline{1,4}$ is unstable and there exists endemic equilibrium $\mathcal{E}^{\star}_{i,j}$, $i,j = \overline{1,4}$.

5 Conclusions

So, we offered in the work the construction and stability investigation of immunosensor model. From physical point of view the immunosensor can be imagined as a two-dimensional biopixels array. That is why the model offered is spatially discrete or lattice one. The model is based on lattice of dynamic equations. These equations are based on some biological assumptions coming from the laws of population dynamics.

Each pixel was described by dynamic changes of the populations of antigenes and antibodies which play roles of preys and predators respectively. As a result of delay of immune response we need to consider im the model delay in time. Other very important physical phenomenon is related with diffusion of antigenes within biopixels. Firstly we considered the system of lattice differential equations. Then these continuous time equations were used in order to get lattice difference system.

Stability research used the notion of basic reproduction number. Numerical example illustrated the investigation of stability of endemic steady state.

Further research should be dealt with qualitative analysis of immunosensor model taking into account changes in model parameters.

Other important research have to consider different biopixel array configurations, e.g. hexagonal lattice allowing us to simulate three-dimensional arrays of biopixels.

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Rational Solutions in an Optimization Problem with a Fuzzy Set of Constraint Indices

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Abstract: The present paper investigates a mathematical programming problem with a fuzzy set of constraints indices. It is shown that the set of feasible solutions is a type-2 fuzzy set (a fuzzy set whose membership function takes fuzzy values). Furthermore, the corresponding membership function is given. It is also proved that solutions are characterized by the degree of their feasibility and infeasibility simultaneously. The notion of a general rational solution is proposed in the form of a type-2 fuzzy set, too. The support of this set is defined as the set of Slater's optimal alternatives for a three-criteria optimization problem. In this problem the degree of the solution feasibility is maximized together with the objective function and the degree of its unfeasibility is minimized. Finally, a procedure is pointed out of constructing elements of the support of the general rational solution with the maximal degree of their feasibility and the degree of unfeasibility not exceeding a given threshold.

Keywords: fuzzy set, type-2 fuzzy set, fuzzy mathematical programming, decision-making.

1 Introduction

Mathematical programming (MP) is a classical area which is in high demand for many disciplines. Engineering, management, politics, operations research and many other fields are, in one way or another, concerned with optimization of solutions, structures or processes. Many specific problems that may be formulated in an optimization setting are full of fuzziness sources. Models and methods of Fuzzy mathematical programming (FMP) are sufficiently well developed. For a more detailed picture of FMP's achievements, see Carlsson and Fuller (2002), Lodwik (2010), Sakawa (2001). Also, there are nice surveys of the area (Delgado et al., 1990; Inuiguchi and Ramik, 2000; Inuiguchi et al., 1990; Luhandjula, 2015; Rommelfanger, 1996).

In most of the previously known formulations of FMP problems fuzziness manifested in both the description of the objective function and the description of the set of feasible solutions. However, it did not concern the set of constraints indices. But as will be shown below, using known FMP approaches leads to paradoxical results. The reason behind this paradox is the fact that the set of feasible solutions of a mathematical programming problem with a fuzzy set of constraints indices is a type-2 fuzzy set (T2FS) with a special structure, rather than a standard fuzzy set. For the first time, the set of feasible solutions to such problems was analyzed in (Mashchenko, 2013). However, the solution selection problem only received partial attention. The present paper focuses on the notion of a rational solution to a mathematical programming problem with a fuzzy set of constraints indices with a special emphasis on the solution selection problem.

We note that MP problems with fuzzy sets of constraints indices often arise in practice. Examples of such formulations include the transportation problem with fuzzy sets of suppliers, consumers and routes, the assignment problem with fuzzy sets of employees and employers, and many others.

2 Formulation of the problem

Consider the MP problem

$$g(x) \to \max; \tag{1}$$

$$s.t. \quad f_i(x) \le 0, i \in M; \tag{2}$$

$$x \in X; \tag{3}$$