Numerical study of a toxin and antibody interaction inside the cell

Pranas Katauskis, Silvija Malakauskaitė

Faculty of Mathematics and Informatics, Vilnius University

Naugarduko 24, LT-03225 Vilnius

E-mail: pranas.katauskis@mif.vu.lt, silvija.malakauskaite@mif.stud.vu.lt

Abstract. A nonlinear mathematical model decribing toxin penetration into cell from the extracellular domain and its interaction with an antibody placed inside the cell is studied. The protective properties of the antibody against the toxin are investigated numerically choosing the model parameters in case of the well-mixed solution assumption.

Keywords: antibody, toxin, receptor, cell protection.

Introduction

A toxin is a poisonous substance produced by living cells, animals, microorganisms or plants. Toxins can be small molecules, peptides, or proteins that are capable to cause a disease on contact with (or absorption) by body tissues interacting with biological macromolecules such as enzymes or cellular receptors [1, 3]. Many antibodies have been generated to protect from a number of toxins. Recent progress of antibody engineering allows to produce antibodies which are used against one or several of toxins [5]. The design and production of new antibodies usually is an expensive and long process that include experimental investigation of the antibodies properties. A proper mathematical model can be used to predict the antibody properties (parameters) before experimental research [2, 4, 6]. In this paper we use the mathematical model proposed in [4] in case of the well-mixed solution assumption. The antibody is placed inside the cell where it interact with the toxin. The aim of this paper is to study the influence of the Endoplasmic Reticulum (ER) absorption rate, toxin-antibody reaction rate, initial antibody concentration on cell protection parameter and toxin concentration near the ER envelope.

1 The mathematical model

We examine the situation when the spherical cell is encircled by the toxin solution which occupies a domain between a cell membrane and an external surface. Toxin moves toward the cell and interact with receptors on the cell membrane. Some of this toxin penetrates into the cell. The other part of the toxin bounded to membrane receptors leaves them and returns into the extracellular domain. Toxin being inside the cell moves toward endoplasmic reticulum(ER) and interacts with the antibody forming the toxin-antibody complex. Part of the toxin-antibody complex splits up

again in the toxin and antibody. Toxin penetrates across the ER membrane into the cytosol, reaches ribosomes and damages the protein production mechanism.

The basic notations used in this paper are:

ρ – distance to the origin,

$S_m = \{\rho: \rho = \rho_m\}$ – the surface of the membrane of a spherical cell,

$S_e = \{\rho: \rho = \rho_e\}$, $\rho_e > \rho_m$ – the surface of the external sphere which limits domain Ω_e,

$\Omega_e = \{\rho: \rho_m < \rho < \rho_e\}$ – the domain between the cell membrane surface S_m and the sphere S_e initially occupied by the toxin,

$S_n = \{\rho: \rho = \rho_n\}$, $\rho_n < \rho_m$ – the surface of the spherical domain occupied by the endoplasmic reticulum.

$\Omega_i = \{\rho: \rho_m < \rho < \rho_e\}$ – the domain between the spheres S_n and S_m where the antibody and toxin forward and reverse reactions run,

r_0 – the concentration of receptors confined to the cell membrane,

θ – the part of the toxin-bound receptors, $1 - \theta$ – the part of the free receptors,

$r_0\theta$ – the concentration of the toxin-bound receptors,

$r_0(1 - \theta)$ – the concentration of the free receptors,

u_{T_e} – the toxin concentration in Ω_e,

$u_{T_e}^0$ – the initial toxin concentration in Ω_e,

u_T, u_A, u_C – the concentrations of the toxin, antibody and toxin-antibody complex, respectively, in the domain Ω_i,

u_A^0 – the initial antibody concentration in Ω_i,

k_1, k_{-1} – the forward and reverse constants of the toxin-antibody reaction rate,

k_2 and k_{-2} – the forward and reverse binding rate constants of the toxin and receptor confined on the membrane,

k – the toxin penetration rate constant from domain Ω_e across the membrane into the cell (into domain Ω_i),

γ – the toxin absorption rate constant describing toxin influx into ER,

$\delta(t)$ – the antibody protection function.

In [4] the advection-diffusion mathematical model was proposed where the motion and interaction of species in the extracellular and intracellular domains are described by a system of nonlinear partial differential equations. In that paper a more simple model of nonlinear ordinary differential equations was also studied assuming that the solution of the toxin, antibody and toxin-antibody complex in the intracellular domain and the toxin solution in the extracellular domain are uniformly mixed and homogeneously distributed (well-mixed solutions).

In this paper the mathematical model proposed in [4] for case of the well-mixed solution assumption is used. The change in time of the toxin concentration in the extracellular domain Ω_e and the number of toxin-bound receptors is described by the system of nonlinear ordinary differential equations:

$$\begin{cases} \dfrac{du_{T_e}}{dt} = -k_3 r_0\big(k_2(1-\theta)u_{T_e} - k_{-2}\theta\big), & t > 0, \\ u_{T_e}|_{t=0} = u_{T_e}^0, \\ \dfrac{d\theta}{dt} = k_2(1-\theta)u_{T_e} - k_{-2}\theta - k\theta, & t > 0, \\ \theta|_{t=0} = 0. \end{cases} \tag{1}$$

Concentrations of the toxin, antibody and toxin-antibody complex in the intracellular domain Ω_i are calculated from the system of the nonlinear differential equations:

$$
\begin{cases}
\dfrac{du_T}{dt} = -k_1 u_T u_A + k_{-1} u_C + k k_4 r_0 \theta - k_5 \gamma u_T, & t > 0, \\
u_T|_{t=0} = 0, \\
\dfrac{du_A}{dt} = -k_1 u_T u_A + k_{-1} u_C, & t > 0, \\
u_A|_{t=0} = u_A^0, \\
\dfrac{du_C}{dt} = k_1 u_T u_A - k_{-1} u_C, & t > 0, \\
u_C|_{t=0} = 0,
\end{cases}
\tag{2}
$$

where $k_3 = 3\rho_m^2/(\rho_e^3 - \rho_m^3)$, $k_4 = 3\rho_m^2/(\rho_m^3 - \rho_n^3)$, $k_5 = 3\rho_n^2/(\rho_m^3 - \rho_n^3)$. The systems (1) and (2) are coupled by function θ. The term $k k_4 r_0 \theta$ determines an amount of the toxin internalized from domain Ω_e across the membrane into the cell.

In the case where no antibody is used in domain Ω_i only the equation describing the toxin concentration is solved instead of system (2):

$$
\begin{cases}
\dfrac{du_T}{dt} = k k_4 r_0 \theta - k_5 \gamma u_T, & t > 0, \\
u_T|_{t=0} = 0.
\end{cases}
\tag{3}
$$

The effectiveness of antibody treatment is measured by comparison of the toxin concentrations near ER in the case where antibody is used ($u_A^0 > 0$) and in the case where antibody is absent ($u_A^0 = 0$). The dimensionless parameter (antibody protection factor) is defined by the expression

$$
\delta(t) = \frac{u_T(t, u_A^0)}{u_T(t, 0)}.
\tag{4}
$$

The numerator is determined by solving systems (1) and (2), denominator is solution of problem (1) and (3). By definition, $0 \leqslant \delta(t) \leqslant 1$ with the lower values corresponding to the better therapeutic effect of the antibody treatment. Values of δ close to unity inform that the influence of the antibody treatment is negligible – the difference of concentrations of internalized toxin near ER in cases $u_A^0 > 0$ and $u_A^0 = 0$ is small.

Using characteristic dimensional time, length and concentration units τ_*, l, u_*, respectively, Egs. (1)–(3) can be rewritten in a dimensionless form. By substituting new variables, $\rho = l\bar{\rho}$, $t = \tau_* \bar{t}$, $r_0 = l u_* \bar{r}_0$, $u_{T_e} = u_* \bar{u}_{T_e}$, $u_T = u_* \bar{u}_T$, $u_A = u_* \bar{u}_A$, $u_C = u_* \bar{u}_C$, $u_{T_e}^0 = u_* \bar{u}_{T_e}^0$, $u_T^0 = u_* \bar{u}_T^0$, $u_A^0 = u_* \bar{u}_A^0$, $u_C^0 = u_* \bar{u}_C^0$, $\bar{k}_1 = \tau_* u_* k_1$, $\bar{k}_2 = \tau_* u_* k_2$, $\bar{k} = \tau_* k$, $\bar{k}_{-1} = \tau_* k_{-1}$, $\bar{k}_{-2} = \tau_* k_{-2}$, $\bar{k}_3 = l k_3$, $\bar{k}_4 = l k_4$, $\bar{k}_5 = l k_5$, we deduce the same problem (1)–(3) but in the dimensionless form. In what follows all variables are non-dimensional.

2 Numerical results

To solve the nonlinear problems (1), (2) and (1), (3) we apply the Runge–Kutta fourth order method using a uniform discrete grid. The following non-dimensional
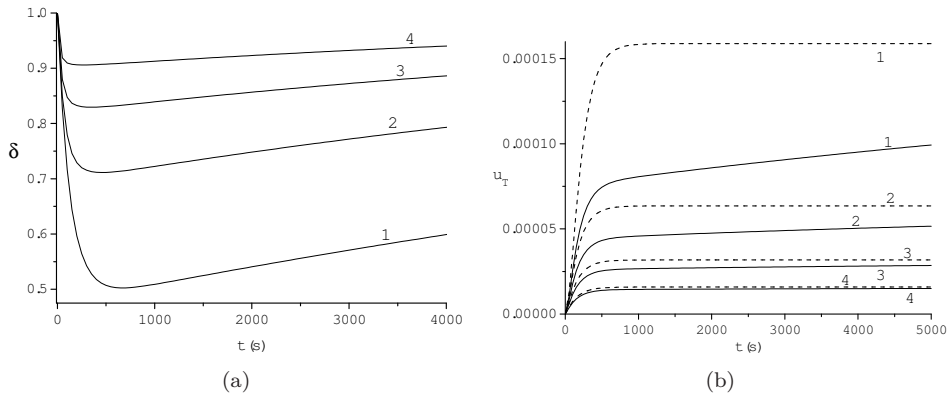
(a)

(b)

Fig. 1. Dependence of antibody protection factor δ (a) and toxin concentration u_T (b) on toxin absorption rate constant γ: 0.01 (1), 0.025 (2), 0.05 (3), 0.1 (4). — $u_A^0 = 1$, - - - $u_A^0 = 0$.
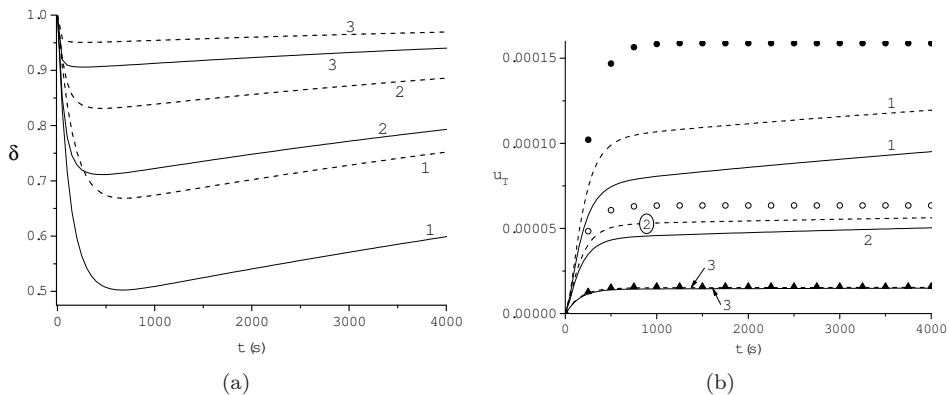

(a)

(b)

Fig. 2. Dependence of antibody protection factor δ (a) and toxin concentration u_T (b) on the initial antibody concentration u_A^0: 1 (—), 0.5 (- - -) and toxin absorption rate constant γ: 0.01 (1), 0.025 (2), 0.1 (3). In case $u_A^0 = 0$, absorption rate constant γ: $0.01 - \bullet$, $0.025 - \circ$, $0.1 - \blacktriangle$.

values were used in calculations [4, 6]: $\rho_n = 0.02$, $\rho_m = 0.1$, $\rho_e = 0.18$, $k_1 = 1.3 \cdot 10^{-2}$, $k_{-1} = 1.4 \cdot 10^{-4}$, $k_2 = 1.25 \cdot 10^{-2}$, $k_{-2} = 5.2 \cdot 10^{-4}$, $k = 3.3 \cdot 10^{-5}$, $r_0 = 2.115 \cdot 10^{-3}$, $\rho_c = 10^{-1}$, $\rho_e = 1$, $u_A^0 = 1$, $u_{T_e}^0 = 0.5$. If value of parameter differ from indicated then it is specified in the text or in the legends of plots.

Fig. 1 demonstrates the influence of the endoplasmic reticulum (ER) absorption rate γ on antibody protection factor $\delta(t)$ and toxin concentration $u_T(t)$. Since all other parameters are fixed, the amount of toxin which penetrates into the cell, $k_4 k r_0 \theta$, and amount of the toxin neutralized by the antibody is the same for all values of γ. The toxin concentration near the ER decreases as the absorption rate increases since more toxin crosses the ER envelope (Fig. 1(b)). The toxin concentration is monotonically increasing time function and rapidly reaches a saturation value excluding the case where γ is small and the antibody is used (Fig. 1(b), solid curves 1 and 2). The antibody protection factor $\delta(t)$ is monotonically increasing γ function, but non-monotonic time function: decreases, reaches the minimum, tends increasing to a steady-state value. There is a time interval for which the application
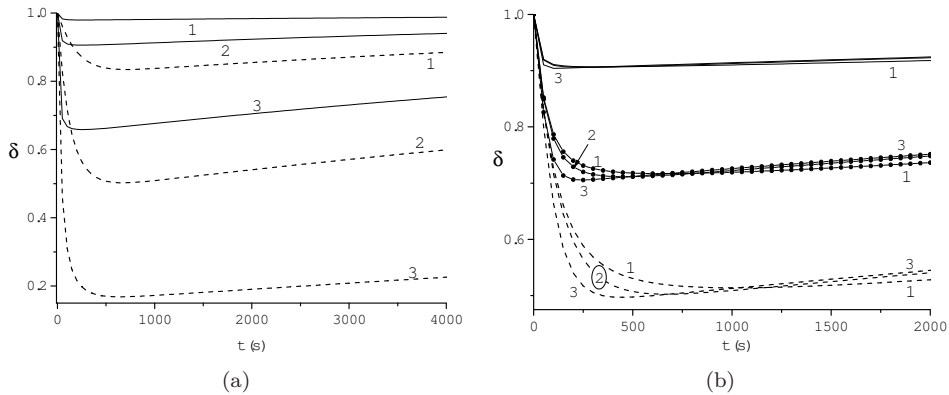
Fig. 3. (a) Effect of the toxin-antibody reaction rate constant k_1: 0.0026 (1), 0.013 (2), 0.065 (3) and (b) toxin and receptor binding rate constant k_2: 0.00125 (1), 0.0125 (2), 0.125 (3) on antibody protection factor δ for γ: 0.01 (—), 0.025 ($\bullet$), 0.1 (- - -).

of the antibody is the most effective. The plots in Fig. 1 show that the efficiency of the antibody application is low if absorption rate constant is large – the reduction of the internalized toxin due to application of antibody is negligible (Figs. 1(a) and 1(b), curves 4).

Fig. 2 shows the dependence of antibody protection factor and toxin concentration on the initial antibody concentration u_A^0 for different values of the ER absorption rate γ. In Fig. 2(b) we see that the higher initial antibody concentration reduces the toxin concentration at the ER since the amount of the toxin-antibody complex grows. The difference between toxin concentrations grows as γ decreases. For $\gamma = 1$ the influence of u_A^0 on the toxin concentration is negligible – in cases $u_A^0 = 1$, 0.5, and 0 the toxin concentrations are almost the same (Fig. 2(b), curves 3). For small and larger values of γ the cell protection increases as u_A^0 grows (Fig. (2a)).

The plots in Fig. 3(a) illustrate the effect of the forward toxin-antibody reaction rate constant k_1 for two values of the absorption rate $\gamma = 0.01$ and 0.1. The cell protection grows as k_1 increases. Constant k_1 more influence function $\delta(t)$ at lower values of the ER absorption rate. Fig. 3(b) demonstrates the behavior of function $\delta(t)$ for three values of the toxin and receptors binding rate constant k_2 and for three values of γ. $\delta(t)$ is non-monotonic function with respect to time and k_2. Calculations show that $\delta(t)$ weakly depends on k_2 for large γ (Fig. 3(b), solid lines).

3 Conclusions

The toxin, antibody, and receptors interaction was studied numerically by using a model proposed in [4] in the case of the well-mixed solution assumption. The results of numerical investigation are the following:

1. The efficiency of the antibody placed inside the cell is low when the ER absorption rate is large.
2. The efficiency of the antibody grows as the ER absorption rate decreases, the toxin-antibody reaction rate and initial antibody concentration increase.

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REZIUMĖ

Antikūno ir toksino sąveikos ląstelėje skaitinis tyrimas
P. Katauskis, S. Malakauskaitė

Nagrinėjamas netiesinis modelis, aprašantis toksino, patenkančio į ląstelę iš ją supančio tirpalo, sąveiką su į ląstelę įleistu antikūnu. Skaitiniais metodais, keičiant modelio parametrus, tiriamas antikūno panaudojimo efektyvumas, tariant, kad toksinas ir antikūnas yra gerai išmaišytame tirpale.

Raktiniai žodžiai: antikūnas, toksinas, receptorius, ląstelės apsauga.