Modeling of toxin–antibody interaction and toxin transport toward the endoplasmic reticulum

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Abstract A model for toxin–antibody interaction and toxin trafficking towards the endoplasmic-reticulum is presented. Antibody and toxin (ricin) initially are delivered outside the cell. The model involves: the pinocytotic (cellular drinking) and receptor-mediated toxin internalization modes from the extracellular into the intracellular domain, its exocytotic excretion from the cytosol back to the extracellular medium, the intact toxin retrograde transport to the endoplasmic reticulum, the anterograde toxin movement outward from the cell across the plasma membrane, the lysosomal toxin degradation, and the toxin clearance (removal from the system) flux. The model consists of a set of coupled PDEs. Using an averaging procedure, the model is reduced to a system of coupled ODEs. Both PDEs and ODEs systems are solved numerically. Numerical results are illustrated by figures and discussed.

Keywords Toxin · Antibody · Cell receptor · Microtubule transport · Molecular motors

1 Introduction

Ricin, highly toxic to eukaryotic cells, is produced and stored in the seeds of the castor oil plant *Ricinus communis*. Ricin poisoning can cause severe tissue damage, inflammatory reactions, and blockage of protein synthesis, and thus result in cell death [1, 2]. In spite of intensive biomedical research, no treatment is at present available for ricin poisoning [3]. Some promising results have been shown recently by employing antibodies of high

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affinity to inhibit or neutralize the effects of ricin [4, 5]. The development and production of new antibodies is an expensive process that usually includes extensive experimental studies. In order to reduce this experimental burden, a simple modeling framework has recently been proposed [6–9] that enables extensive studies to increase the protective potential of antibodies before proceeding with targeted experimental studies.

The mechanism of ricin entry into the cell and its intracellular transport involves a number of steps that are well documented (see [4, 10–13] and references therein). Mature ricin is a dimeric cytotoxin. It is composed of an enzymatically ribosome-inactivating RTA chain disulphide-bound to a cell surface-binding RTB chain [14]. RTB binds to the cell surface, triggering toxin uptake into the cell, its diffusion in the cytosol, and directional (retrograde) transport along microtubules of the cell skeleton to the endoplasmic reticulum (ER). In the ER, the RTA and RTB chains are cleaved by the protein disulphide isomerase (PDI) [15] and the RTA component is translocated across the ER membrane into the cytosol. Subsequently, the RTA chain reaches ribosomes and damages the protein production machinery of the cell, resulting in cell death. In this context, the toxin concentration in the cytoplasm near the ER (before its penetration into ER and separation into components RTA and RTB) becomes the critical quantity to estimate the toxicological impact of ricin on the cell and evaluate the protective potential of the antibody.

The modeling framework proposed in [6, 7] involves toxin, antibody, and their nontoxic complex diffusive transport in the extracellular domain, receptor-mediated toxin internalization, and intracellular toxin motion based on the diffusion-advection mechanisms towards the ER. The advective step of toxin transport used in [7] simulates the toxin retrograde (dynein-driven) movement toward the ER.

In the present paper, assuming that toxin and antibody are initially delivered in the extracellular domain, we refine our previous model [7] additionally involving the pinocytotic toxin internalization from the extracellular to the intracellular space (cellular drinking), toxin clearance (removal from the system) flux, the lysosomal toxin degradation, and the intact toxin exocytotic recycling back to the extracellular space. Contrary to the model proposed in [7] exploiting the advective-diffusive toxin transport in the intracellular domain Ω_i , we follow the paper [16] (or the more general one [17]) devoted to the intracellular transport of vesicles and organelles and assume that all toxin particles are divided into two populations: those that are attached to the microtubules of the cell skeleton and those that are detached from them. The detached particles are assumed to undergo diffusion. The attached toxin molecules are still divided into outward-going particles (i.e., in anterograde motions from the ER toward the cell membrane) driven by kinesin motor protein, and inward-going particles driven in retrograde motions by dynein motors. The refined model is described by a system of coupled PDEs.

In order to reduce the dimension of the parameter space of the models, we also considered the so-called simplified model. The simplified model is based on the ‘well-mixed solution’ assumption, which states that all species have uniform concentration across the modeling domain. This assumption eliminates the necessity to calculate the gradient-driven fluxes in the models (i.e., diffusion of the free toxin and translation of the microtubule-bound one) leading to a significant simplification (reducing from PDEs to ODEs). The complete and reduced models are solved numerically and outputs are compared by using an antibody protection characteristic.

The plan of this paper is the following. In Section 3 we present the models. In Section 4 we comment on the numerical results. The remarks in Section 5 conclude the paper.

2 Notation

- T_e , A_e , and $C_e = T_e A_e$ – the toxin, antibody, and non-toxic toxin–antibody complex delivered in the extracellular domain, respectively;
 T_i – the toxin delivered in the intracellular domain;
 ρ – the distance to the origin;
 $S_m = \{\rho : \rho = \rho_m\}$ – the surface of the membrane of a spherical cell;
 $\Omega_e = \{\rho : \rho \in (\rho_m, \rho_e)\}$ – the extracellular domain;
 $S_e = \{\rho : \rho = \rho_e\}$ – the surface of the external sphere (external surface of Ω_e);
 $S_n = \{\rho : \rho = \rho_n\}$, $\rho_n < \rho_m$ – the surface of the spherical envelope of the domain occupied by ER;
 $\Omega_i = \{\rho : \rho \in (\rho_n, \rho_m)\}$ – the intracellular domain;
 r_0 – the concentration of receptors confined to the cell membrane;
 θ_r – the fraction of the toxin-bound receptors (cell membrane coverage);
 $r_0 \theta_r$ – the concentration of the toxin-bound receptors;
 r_1 and r_2 – the number of sites on the surface of a microtubule to which toxin molecule may bind via dynein and kinesin, respectively;
 u_{T_i} – the toxin concentration in domain Ω_i ;
 u_{T_e} , u_{A_e} , and u_{C_e} – the concentration of the toxin, antibody and toxin–antibody complex in domain Ω_e , respectively;
 u_{B_1} and u_{B_2} – the bulk concentration in Ω_i of the toxin bound to microtubules via dynein and kinesin, respectively;
 $u_{T_e}^0$ and $u_{A_e}^0$ – the initial concentration of the toxin and antibody in Ω_e ;
 κ_{T_e} , κ_{A_e} , κ_{C_e} – the diffusivity of the toxin, antibody, and toxin–antibody complex in domain Ω_e , respectively;
 κ_{T_i} – the toxin diffusivity in domain Ω_i ;
 k_{1e} and k_{-1e} – the rate constant of the forward and reverse reaction between the toxin and antibody in domain Ω_e , respectively;
 k_{2e} and k_{-2e} – the toxin binding to and detachment from the cell receptors rate constants;
 k_e – the constant of toxin internalization rate mediated by cell receptors;
 γ_i – the toxin absorption flux constant by the ER;
 γ_e – the toxin T_e removal (clearance) flux constant;
 v_d and v_i – the pinocytotic toxin T_e internalization (cellular drinking) and exocytotic toxin T_i retrieval back to the extracellular domain rate constants, respectively;
 p_1 and p_2 – the bulk concentration of the microtubule sites to which toxin molecules may bind by dynein and kinesin, respectively;
 k_1 and k_{-1} , k_2 and k_{-2} – the rate constant of toxin binding to and detachment from the microtubule binding sites to which toxin molecules may bind via dynein and kinesin, respectively;
 β_{T_i} – the free toxin lysosomal degradation rate constant;
 v_1 and v_2 ($v_1 > 0$, $v_2 > 0$) – the drift velocity of the microtubule-bound toxin particle via dynein and kinesin, respectively;
 r_d – the density of cellular drinking sites confined to its membrane;
 θ_d – the fraction of drinking sites occupied by toxin molecules;
 $r_d \theta_d$ – the concentration of the toxin-bound cellular drinking sites;
 k_d and k_{-d} – the rate constants of toxin binding to and detachment from the cellular drinking sites;

α_2 – the loading rate constant for toxin particles B_2 at the ER envelope;
 α_1 – the fraction of the internalized toxin flux coming to its free diffusion;
 $\delta(t)$ – the antibody protection factor;
 $\partial_t = \partial/\partial t$, $\Delta = \rho^{-2} \frac{\partial}{\partial \rho} (\rho^2 \frac{\partial}{\partial \rho})$ – the Laplace operator.

3 The models

Our models aim to capture the ricin transport to the endoplasmic reticulum and reduction of the ricin effect on the cell with introduction of an antibody. As mentioned above, we consider the case where toxin and antibody initially are delivered between the cell membrane and the external boundary. In this domain toxin competitively reacts with the antibody, moves toward the cell membrane, and can be internalized via all available mechanisms [2, 18]. We will restrict ourselves to considering the receptor-mediated and pinocytotic (cellular drinking across the cell membrane) toxin internalization mechanisms. We assume that the toxin, antibody, and their nontoxic complex are transported by the diffusion in domain Ω_e and excluding toxin cannot leave Ω_e . A toxin portion leaves Ω_e via the removal (clearance) flux across the surface S_e from the system. In the intracellular domain, Ω_i toxin moves toward lysosomes and ER using diffusion and retrograde transport mechanisms. A portion of the intact toxin is retrieved (recycled) back to the extracellular domain by exocytosis using diffusion and anterograde transport. The other intact toxin portion moves to lysosomes for degradation. The third portion of the intact toxin goes to the ER, where it is enzymatically cleaved into the RTA and RTB chains. Then the RTA chain is translocated [18] across the ER envelope into the cytosol where it inactivates ribosomes, inhibiting protein synthesis.

In the present work, contrary to the model [7] based on the toxin advection-diffusion transport in Ω_i , we follow [16] devoted to intracellular transport of vesicles and organelles and assume that a portion of the toxin moves by diffusion and the other portion uses the retrograde or anterograde transport (dynein or kinesin-driven transport on the immobile cytoskeletal microtubules towards the ER or back to the cell membrane, respectively). According to [19–21] freely diffusing particles bind to diffusing motor proteins, which in turn bind to microtubules, move along them, and can be detached. For the sake of simplicity, we disregard details of the toxin molecule, binding to motor protein and suppose that the freely diffusing toxin molecule can bind to one diffusing motor protein molecule, forming a particle (toxin bound to motor protein), which moves by diffusion and can bind via motor protein molecule to and detach from the microtubule. We assume that the detached particle can separate into the motor protein molecule and toxin particle, which can bind to a motor protein molecule of the same or opposite polarity. We also assume that the microtubule-bound toxin-motor protein particle moves along the microtubule at a steady average motor velocity and that the pool of motor proteins (dynein and kinesin) is large enough so that variation of their concentrations is insignificant.

To construct a mathematical model, we suppose that the cellular drinking sites (where a cell forms the membrane-coated pits for toxin particles to be endocytosed) and receptors are delivered continuously on the cell membrane and that the surface of each microtubule is covered by a large number of sites where toxin particles may bind via dynein or kinesin molecules and use the following schematic reactions between the toxin and

antibody in Ω_e , toxin and cell membrane receptor, toxin and cell drinking site on the cell membrane, and toxin and microtubule in Ω_i :

$$\left\{ \begin{array}{l} T_e + A_e \xrightleftharpoons[k_{-1e}]{k_{1e}} C_e = T_e A_e, \\ T_e + S_r \xrightleftharpoons[k_{-2e}]{k_{2e}} T_e S_r, \\ T_e + S_d \xrightleftharpoons[k_{-d}]{k_d} T_e S_d, \\ T_i + S_1 \xrightleftharpoons[k_{-1}]{k_1} B_1 = T_i S_1, \\ T_i + S_2 \xrightleftharpoons[k_{-2}]{k_2} B_2 = T_i S_2. \end{array} \right. \quad (1)$$

Here, $T_e S_r$ and $T_e S_d$ are the receptor and drinking site bound toxin, S_r and S_d are the receptor and drinking site, T_e , A_e , C_e are the toxin, antibody, and their non-toxic complex in domain Ω_e , while T_i , B_1 , B_2 , and S_1 , S_2 present the freely diffusing toxin particle, cytoskeletal microtubule-bound toxin via dynein and kinesin, and binding site on the microtubule for dynein and kinesin in Ω_i , respectively. We assume that the microtubule-bound toxin B_1 particle moves via retrograde transport under a constant average dynein-induced velocity $v_1 > 0$ toward the ER, while the microtubule-bound toxin B_2 molecule uses the anterograde transport with a constant average kinesin-powered velocity $v_2 > 0$ to move back to the external domain across the cell membrane.

We model the cell as a sphere of radius ρ_m and ER as the concentric sphere of radius $\rho_n \ll \rho_m$ (see Fig. 1). We assume that microtubules grow radially from the center toward the cell membrane. Let r_1 and r_2 be the number of sites on the surface of a microtubule for toxin binding via dynein and kinesin molecules, respectively, and let q be the number of microtubules of the cell skeleton. Then parameters $p_1 = qr_1/V$, $p_2 = qr_2/V$, $V = 4\pi/3(\rho_m^3 - \rho_n^3)$ mean the bulk concentrations of the microtubule binding sites where toxin molecules may bind via dynein and kinesin, respectively. In what follows, we assume that

Fig. 1 Ricin pathway to ER: 1 – spherical surface of the external compartment (extracellular domain Ω_e) of radius ρ_e , 2 – cell membrane (external boundary of intracellular domain Ω_i) of radius ρ_m , 3 – spherical envelope of ER of radius ρ_n , 4 – toxin, 5 – antibody, 6 – toxin-antibody complex, 7 – pinocytosed toxin, 8 – exocytosed toxin, 9 – toxin degraded in lysosomes, 10 – toxin removed via clearance of the system

binding sites of different microtubules do not compete for free toxin molecules. We also take into account the lysosomal toxin degradation and assume that a portion of toxin components T_i and B_1 penetrate into the ER via the outgoing fluxes across the ER envelope, $\gamma_i u_{T_i}|_{\rho=\rho_n}$ and $v_1 u_{B_1}|_{\rho=\rho_n}$, respectively.

We first describe the partial differential equation model (refer to as PDE model). For simplicity, we consider the case of spherical symmetry. To describe the model in Ω_e , we apply equations of paper [7] with the additionally involved toxin loss flux (clearance through the surface S_e and pinocytotic across the cell membrane S_m) and gain flux (exocytotic through the S_m). As a result, we derive coupled equations for concentrations u_{T_e} , u_{A_e} , u_{C_e} and fraction θ_r and θ_d :

$$\begin{cases} \partial_t u_{T_e} = -k_{1e} u_{A_e} u_{T_e} + k_{-1e} u_{C_e} + \kappa_{T_e} \Delta u_{T_e}, & \rho \in (\rho_m, \rho_e), t > 0, \\ \kappa_{T_e} \partial_\rho u_{T_e} = -\gamma_e u_{T_e}, & \rho = \rho_e, t > 0, \\ \kappa_{T_e} \partial_\rho u_{T_e} = r_0 (k_{2e}(1 - \theta_r) u_{T_e} - k_{-2e} \theta_r) + r_d (k_d(1 - \theta_d) u_{T_e} - k_{-d} \theta_d) \\ \quad - v_i u_{T_i} - v_2 u_{B_2}, & \rho = \rho_m, t > 0, \\ u_{T_e}|_{t=0} = u_{T_e}^0, & \rho \in [\rho_m, \rho_e], \end{cases} \quad (2)$$

$$\begin{cases} \partial_t u_{A_e} = -k_{1e} u_{A_e} u_{T_e} + k_{-1e} u_{C_e} + \kappa_{A_e} \Delta u_{A_e}, & \rho \in (\rho_m, \rho_e), t > 0, \\ \partial_\rho u_{A_e} = 0, & \rho = \rho_e, t > 0, \\ \partial_\rho u_{A_e} = 0, & \rho = \rho_m, t > 0, \\ u_{A_e}|_{t=0} = u_{A_e}^0, & \rho \in [\rho_m, \rho_e], \end{cases} \quad (3)$$

$$\begin{cases} \partial_t u_{C_e} = k_{1e} u_{A_e} u_{T_e} - k_{-1e} u_{C_e} + \kappa_{C_e} \Delta u_{C_e}, & \rho \in (\rho_m, \rho_e), t > 0, \\ \partial_\rho u_{C_e} = 0, & \rho = \rho_e, t > 0, \\ \partial_\rho u_{C_e} = 0, & \rho = \rho_m, t > 0, \\ u_{C_e}|_{t=0} = u_{C_e}^0, & \rho \in [\rho_m, \rho_e], \end{cases} \quad (4)$$

$$\begin{cases} \partial_t \theta_r = k_{2e}(1 - \theta_r) u_{T_e} - (k_{-2e} + k_e) \theta_r, & \rho = \rho_m, t > 0, \\ \theta_r|_{t=0} = 0, & \rho = \rho_m. \end{cases} \quad (5)$$

$$\begin{cases} \partial_t \theta_d = k_d(1 - \theta_d) u_{T_e} - (k_{-d} + v_d) \theta_d, & \rho = \rho_m, t > 0, \\ \theta_d|_{t=0} = 0, & \rho = \rho_m. \end{cases} \quad (6)$$

The terms $r_d(k_d(1 - \theta_d)u_{T_e} - k_{-d}\theta_d)$ and $v_i u_{T_i} + v_2 u_{B_2}$ in the boundary condition at $\rho = \rho_m$ of (2) represent the loss (pinocytotic) and gain (exocytotic) toxin fluxes. We assume that the α_1 portion of the internalized toxin flux, $r_0 k_e \theta_r + r_d v_d \theta_d$, comes to the toxin diffusion in Ω_i and the other its portion, $1 - \alpha_1$, moves via retrograde transport. Here, r_0 and r_d are the density of cell surface receptors and drinking sites, respectively. We also assume that a portion of the diffusing toxin concentration near the ER envelope, $\alpha_2 u_{T_i}|_{\rho=\rho_n}$ with a constant α_2 , moves via the anterograde transport and applying the mass action law, Langmuir reaction mechanism to equations of system (1) and boundary conditions on the ER envelope and cell membrane derive the following equations for the bulk concentrations u_{T_i} , u_{B_1} , and u_{B_2} in Ω_i :

$$\begin{cases} \partial_t u_{T_i} = -k_1 u_{T_i} (p_1 - u_{B_1}) + k_{-1} u_{B_1} - k_2 u_{T_i} (p_2 - u_{B_2}) \\ \quad + k_{-2} u_{B_2} - \beta_{T_i} u_{T_i} + \kappa_{T_i} \Delta u_{T_i}, & \rho \in (\rho_n, \rho_m), t > 0, \\ \kappa_{T_i} \partial_\rho u_{T_i} = \alpha_1 (r_0 k_e \theta_r + r_d v_d \theta_d) - v_i u_{T_i}, & \rho = \rho_m, t > 0, \\ \kappa_{T_i} \partial_\rho u_{T_i} = (\gamma_i + \alpha_2) u_{T_i}, & \rho = \rho_n, t > 0, \\ u_{T_i}|_{t=0} = 0, & \rho \in [\rho_n, \rho_m], \end{cases} \quad (7)$$

$$\begin{cases} \partial_t u_{B_1} = k_1 u_{T_i} (p_1 - u_{B_1}) - k_{-1} u_{B_1} + v_1 \partial_\rho u_{B_1} + 2v_1 u_{B_1}/\rho, & \rho \in (\rho_n, \rho_m), t > 0, \\ u_{B_1} = (1 - \alpha_1)(r_0 k_e \theta_r + r_d v_d \theta_d)/v_1, & \rho = \rho_m, t \geq 0, \\ u_{B_1}|_{t=0} = 0, & \rho \in [\rho_n, \rho_m], \end{cases} \quad (8)$$

$$\begin{cases} \partial_t u_{B_2} = k_2 u_{T_i} (p_2 - u_{B_2}) - k_{-2} u_{B_2} - v_2 \partial_\rho u_{B_2} - 2v_2 u_{B_2} / \rho, & \rho \in (\rho_n, \rho_m), t > 0, \\ u_{B_2} = \alpha_2 u_{T_i} / v_2, & \rho = \rho_n, t \geq 0, \\ u_{B_2}|_{t=0} = 0, & \rho \in [\rho_n, \rho_m]. \end{cases} \quad (9)$$

Equations (2)–(9) compose the PDE model. Note that because of the Langmuir kinetics mechanism, the transition terms modeling binding of toxin particles to the skeletal microtubules in (7)–(9) in contrast to model [16] are nonlinear.

Next, applying the well-mixed solution assumption and using an averaging procedure to system (2)–(9), we derive the well-mixed solution (WMS) model,

$$\begin{cases} \dot{u}_{T_e} = -k_{1e} u_{T_e} u_{A_e} + k_{-1e} u_{C_e} \\ \quad - k_{3e} (r_0 (k_{2e} (1 - \theta) u_{T_e} - k_{-2e} \theta) + r_d (k_d (1 - \theta_d) u_{T_e} - k_{-d} \theta_d) - v_i u_{T_i} - v_2 u_{B_2}) \\ \quad - \gamma_e k_{6e} u_{T_e}, \quad t > 0, \quad u_{T_e}|_{t=0} = u_{T_0}^e, \\ \dot{u}_{A_e} = -k_{1e} u_{T_e} u_{A_e} + k_{-1e} u_{C_e}, \quad t > 0, \quad u_{A_e}|_{t=0} = u_{A_e}^0, \\ \dot{u}_{C_e} = k_{1e} u_{T_e} u_{A_e} - k_{-1e} u_{C_e}, \quad t > 0, \quad u_{C_e}|_{t=0} = 0, \\ \dot{\theta} = k_{2e} (1 - \theta) u_{T_e} - (k_{-2e} + k_e) \theta, \quad t > 0, \quad \theta|_{t=0} = 0, \\ \dot{\theta}_d = k_d (1 - \theta_d) u_{T_e} - (k_{-d} + v_d) \theta_d, \quad t > 0, \quad \theta_d|_{t=0} = 0. \end{cases} \quad (10)$$

$$\begin{cases} \dot{u}_{T_i} = -k_1 u_{T_i} (p_1 - u_{B_1}) + k_{-1} u_{B_1} - k_2 u_{T_i} (p_2 - u_{B_2}) \\ \quad + k_{-2} u_{B_2} + k_{4e} (\alpha_1 (k_e r_0 \theta + v_d r_d \theta_d) - v_i u_{T_i}) \\ \quad - k_{5e} (\gamma_i + \alpha_2) u_{T_i} - \beta_{T_i} u_{T_i}, \quad t > 0, \quad u_{T_i}|_{t=0} = 0, \\ \dot{u}_{B_1} = k_1 u_{T_i} (p_1 - u_{B_1}) - k_{-1} u_{B_1} + k_{4e} (1 - \alpha_1) (k_e r_0 \theta + v_d r_d \theta_d) \\ \quad - k_{5e} v_1 u_{B_1}, \quad t > 0, \quad u_{B_1}|_{t=0} = 0, \\ \dot{u}_{B_2} = k_2 u_{T_i} (p_2 - u_{B_2}) - k_{-2} u_{B_2} - k_{4e} v_2 u_{B_2} + k_{5e} \alpha_2 u_{T_i}, \quad t > 0, \quad u_{B_2}|_{t=0} = 0, \end{cases} \quad (11)$$

where geometrical factors

$$k_{3e} = 3\rho_m^2 / (\rho_e^3 - \rho_m^3), \quad k_{4e} = 3\rho_m^2 / (\rho_m^3 - \rho_n^3), \quad k_{5e} = 3\rho_n^2 / (\rho_m^3 - \rho_n^3), \quad k_{6e} = 3\rho_e^2 / (\rho_e^3 - \rho_m^3)$$

are caused by the averaging procedure.

The main parameter of interest is the antibody protection factor $\delta(t)$ (a relative reduction of the total concentration $u_{T_i}(t) + u_{B_2}(t) + u_{B_2}(t)$ of toxin particles due to application of the antibody) defined by the expression

$$\delta(t) = \frac{(u_{T_i}(t) + u_{B_1}(t) + u_{B_2}(t))|_{u_{A_e}^0 > 0}}{(u_{T_i}(t) + u_{B_1}(t) + u_{B_2}(t))|_{u_{A_e}^0 = 0}}. \quad (12)$$

By definition, $0 \leq \delta(t) \leq 1$ with the lower values of $\delta(t)$ corresponding to the more profound therapeutic effect of the antibody treatment. Evaluation of $\delta(t)$ is the main outcome of our study.

By substituting variables

$$\begin{cases} \rho = l\bar{\rho}, t = \tau_* \bar{t}, r_0 = l u_* \bar{r}_0, r_d = l u_* \bar{r}_d, \\ f = \bar{f} u_*, f = u_{T_e}, u_{A_e}, u_{C_e}, u_{T_i}, u_{B_1}, u_{B_2}, p_1, p_2, \\ f = \bar{f} / (\tau_* u_*), f = k_{1e}, k_{2e}, k_1, k_2, k_d \\ f = \bar{f} / \tau_*, f = k_{-1e}, k_{-2e}, \beta_{T_i}, k_{-1}, k_{-2}, k_e, k_{-d}, v_d \\ f = \bar{f} / l, f = k_{3e}, k_{4e}, k_{5e}, k_{6e}, \\ f = \bar{f} l / \tau_*, f = \gamma_i, v_1, v_2, v_i, \gamma_e, \alpha_2 \\ f = \bar{f} l^2 / \tau_*, f = \kappa_{T_e}, \kappa_{A_e}, \kappa_{C_e}, \kappa_{T_i} \end{cases} \quad (13)$$

into (2)–(11) we can deduce the same systems, but now in the non-dimensional form expressed by using the dimensionless (overscored) quantities. Therefore, for simplicity in what follows, we omit the bar and treat (2)–(11) as non-dimensional.

4 Numerical results

To solve the WMS model (10, 11), we initially evaluated a number of standard MATLAB ODE solvers, viz., ode45 and ode113, ode15s [22, 23]. The solver ode15s was found to be the most efficient and it is mainly used in our numerical calculations. To solve (2)–(4) and (7) of the PDE model, we used the implicit finite difference scheme [27]. Equations (5) and (6) were solved by the explicit difference scheme. Equations (8) and (9) were written on the characteristic lines and solved by the Euler method. The results of numerical solutions are presented in Figs. 2, 3, 4, 5, 6, 7, 8, 9 and 10. Our selection of the values of parameters was motivated by the values available in the literature (see Table 1) with an extended range to allow exploration and illustration of the various regimes possible outside

Table 1 Parameters of simulations (mv – model value)

Parameter	Values	Ref.
k_{1e}	$2.6 \cdot 10^{-16} \text{ cm}^3 \text{ s}^{-1}$	[25]
k_{2e}	$2.1 \cdot 10^{-16} \text{ cm}^3 \text{ s}^{-1}$	[4]
k_{-1e}	$5.2 \cdot 10^{-2} \text{ s}^{-1}$	[25]
k_{-2e}	$1.4 \cdot 10^{-4} \text{ s}^{-1}$	[4]
k_e	$3.3 \cdot 10^{-5} \text{ s}^{-1}$	[26, 28]
k_1	$0.21 \cdot 10^{-17} \text{ cm}^3 \text{ s}^{-1}$	mv
k_{-1}	$1.25 \cdot 10^{-4} \text{ s}^{-1}$	mv
k_2	$0.21 \cdot 10^{-17} \text{ cm}^3 \text{ s}^{-1}$	mv
k_{-2}	$1.25 \cdot 10^{-4} \text{ s}^{-1}$	mv
ρ_n	$2 \cdot 10^{-4} \text{ cm}$	[24]
ρ_m	10^{-3} cm	[24]
ρ_e	$1.8 \cdot 10^{-3} \text{ cm}$	[24]
γ_i	$510^{-3} \text{ cm s}^{-1}$	mv
γ_e	$10^{-6} \text{ cm s}^{-1}$	mv
$u_{A_e}^0$	$6.02 \cdot 10^{13} \text{ cm}^{-3}$	[24]
$u_{T_e}^0$	$3.01 \cdot 10^{13} \text{ cm}^{-3}$	[24]
r_0	$1.26 \cdot 10^9 \text{ cm}^{-2}$	[24]
r_d	$1.26 \cdot 10^8 \text{ cm}^{-2}$	mv
v_i	$10^{-5} \text{ cm s}^{-1}$	mv
v_d	$10^{-5} \text{ cm s}^{-1}$	mv
k_d	$2.01 \cdot 10^{-16} \text{ cm}^{-3} \text{ s}^{-1}$	mv
k_{-d}	$5 \cdot 10^{-4} \text{ s}^{-1}$	mv
p_1, p_2	$6.02 \cdot 10^{11} \text{ cm}^3$	mv
v_1, v_2	$10^{-5} \text{ cm s}^{-1}$	mv
β_{T_i}	10^{-6} s^{-1}	mv
α_2	$10^{-5} \text{ cm s}^{-1}$	mv
$\kappa_{T_e}, \kappa_{A_e}, \kappa_{C_e}, \kappa_{T_i}$	$10^{-5} \text{ cm}^2 \text{ s}^{-1}$	[24]

Fig. 2 Influence of the parameters α_1 and α_2 on toxin concentrations u_{B_2} (a) and u_{T_i} (b) determined by the PDE model with $\kappa = 0.1$ in the case $u_{A_e}^0 > 0$

and inside the eukaryotic cell. Where experimental data were not available, we assume the value of unknown parameters typical for intracellular transport processes. All results are presented in a non-dimensional form using the reference values $u_* = 6.02 \cdot 10^{13} \text{ cm}^{-3}$, $l = 10^{-2} \text{ cm}$, and $\tau_* = 1 \text{ s}^{-1}$ as a scale of concentration, length, and time, respectively. These scaling values are typical for intracellular transport processes [24]. In all legends we use values of non-dimensional parameters (bar omitted for simplicity). Values of parameters that are not shown in legends correspond to non-dimensional ones determined by using values from Table 1. In the case where diffusivity of all species is the same, we use κ for short. For consistent comparison, most plots correspond to the same toxin and antibody initial concentrations.

Numerical results corresponding to the PDE model are presented in Figs. 2–6 and 10. Figures 2–4 and 5, 10 correspond to $\kappa = 0.1$ and $\kappa = 10^{-4}$, respectively, while Fig. 6 is drawn for $\kappa_{T_e} = 0.1$ and two different values of κ_{T_i} . Figures 7–9 illustrate numerical results determined by the WMS model, which does not depend on species diffusivity.

Figures 2 and 3 demonstrate the influence of varying parameters α_1 and α_2 on the behavior of u_{B_2} (Fig. 2a), u_{T_i} (Fig. 2b), and u_{B_1} (Fig. 3a), $\delta(t)$ (Fig. 3b) for $\kappa_{T_i} = 0.1$. Figures show that the increase of α_1 increases u_{B_2} and u_{T_i} but decreases u_{B_1} . We observe that u_{B_1} practically do not depend on parameter α_2 but u_{B_2} and u_{T_i} are sensitive to variation of

Fig. 3 Influence of the parameters α_1 and α_2 on toxin concentration u_{B_1} (calculated for $u_{A_e}^0 > 0$) (a) and δ (b) determined by the PDE model at $\kappa = 0.1$

Fig. 4 Effect of the microtubule-assisted velocity $v_1 = v_2$ on the antibody protection factor δ determined by the PDE model at $\alpha_1 = 0.9$, $\alpha_2 = 0$ and $\kappa_e = \kappa_i = 0.1$

α_2 . Indeed, u_{B_2} grows as α_2 increases, while u_{T_i} behaves vice versa. Figure 3a shows that concentration u_{B_1} has a sharp increase and consequently the sudden growth of $\delta(t)$ (see Fig. 3b). We also observe the decrease of maximum values of $\delta(t)$ as α_1 or α_2 grows. Our calculations for $\kappa = 0.1$ show that values $\alpha_2 = 0.1$ and larger practically do not influence the behavior of $\delta(t)$. For example, factor $\delta(t)$ monotonously decreases in time for $\alpha_1 = 1$ and all values of α_2 .

Figure 4 depicts the effect of the microtubule-assisted velocity $v_1 = v_2$ on the behavior of $\delta(t)$ at $\alpha_2 = 0$ and $\alpha_1 = 0.9$. Since domain Ω_i is initially free of toxin particles, there will be a time delay before particles arrive at the ER. If no detachments of toxin particles from the microtubules occur, the attached particle B_1 will travel from the cell membrane

Fig. 5 Dependence of function $\delta(t)$ determined by the PDE model at $\alpha_1 = 0.9$, $\alpha_2 = 0$ and $\kappa = 0.0001$ on the toxin attachment and detachment parameters: **1**– $k_1 = k_2 = 0.0001$, $k_{-1} = k_{-2} = 0$; **2**– $k_1 = k_2 = 0.01$, $k_{-1} = k_{-2} = 0$; **3**– $k_1 = k_2 = 0.1$, $k_{-1} = k_{-2} = 0.01$; **4**– $k_1 = k_2 = 0.1$, $k_{-1} = k_{-2} = 0$; **5**– $k_1 = k_2 = 1$, $k_{-1} = k_{-2} = 0$

Fig. 6 Comparison of $\delta(t)$ determined by the WMS model (*dashed line*) and PDE (*solid line*) model at $\kappa_{T_e} = 0.1$ and two values of κ_{T_i} for $\alpha_1 = 0.99$, $\alpha_2 = 0.001$

toward the ER in time $(\rho_m - \rho_n)/v_1$. For $v_1 = v_2 = 0.001$; 0.0025 ; 0.01 this value is 80 s; 32 s, and 8 s. We also observe the decrease of maximum values of $\delta(t)$ and time positions of the minimum and maximum values of $\delta(t)$ as $v_1 = v_2$ increases. For example, in the case where $v_1 = v_2 = 0.001$ factor $\delta(t)$ reaches minimum and maximum values at points 80.01 s. and 90.05 s, respectively.

Plots in Fig. 5 illustrate a convoluted behavior of factor $\delta(t)$ depending on the variation of the toxin attachment and detachment parameters, $k_1 = k_2$ and $k_{-1} = k_{-2}$, in the case where $\alpha_1 = 0.9$ and $\alpha_2 = 0$. Indeed, the minimum value of $\delta(t)$ grows as $k_1 = k_2$ increases (see plots corresponding to $k_{-1} = k_{-2} = 0$) and decreases as $k_{-1} = k_{-2}$ grows while its maximal value behaves vice versa. Moreover, in a case where $k_{-1} = k_{-2} = 0$, the difference between maximal and minimal values decreases with growing $k_1 = k_2$. We also observe that the influence of parameters $k_1 = k_2$ and $k_{-1} = k_{-2}$ is insignificant outside the peak vicinity.

Fig. 7 Effect of the velocity v_1 variation on the antibody protection factor δ determined by the WMS model for $\alpha_1 = 0.9$, $\alpha_2 = 0$ and $v_2 = 0$

Fig. 8 Influence of the pinocytotic toxin internalization parameters v_d , r_d and k_d on antibody protection factor δ determined by the WMS model at $\alpha_1 = 0.99$, $\alpha_2 = 0.001$ and $v_1 = v_2 = 0.0001$

Figure 6 shows that $\delta(t)$ grows as diffusivity κ_{T_i} decreases. Our calculations reveal that u_{T_i} and u_{B_2} increase as the diffusivity increases and that u_{B_1} practically is independent of species diffusivity. Figures 4 and 6 show that diffusivity κ_{T_i} and velocity v_1 influence the behavior of factor $\delta(t)$ similarly. Figure 6 also illustrates a comparison of $\delta(t)$ determined by both WMS (dotted line) and PDE (solid line) models: for small time $\delta(t)$ corresponding to WMS model is smaller than that determined by the PDE one, but for large time its behavior is opposite.

As was mentioned above, Figs. 7–9 illustrate numerical results determined by the WMS model. Figure 7 is plotted for $\alpha_2 = 0$ and illustrates the decrease of $\delta(t)$ as v_1 grows. A similar effect in the case of PDE model is depicted in Fig. 4. Our calculations show that the growth of v_1 decreases concentration u_{B_1} , which is essential in determining of $\delta(t)$ because u_{B_1} , u_{T_i} , and u_{B_2} are of order 10^{-3} , 10^{-4} , and 10^{-7} , respectively.

Fig. 9 Effect of the variation of toxin exocytotic retrieval rate constant v_i on the antibody protection factor δ calculated by the WMS model at $\alpha_1 = 0.99$, $\alpha_2 = 0.001$ and $v_1 = v_2 = 0.0001$

Fig. 10 Comparison of function $\delta(t)$ determined by the advection-diffusion model (ADM2) from [7] (solid line) and PDE model (dashed line) for $\kappa = 0.0001$ and $\alpha_2 = v_2 = v_i = v_d = \gamma_e = \beta_{T_i} = r_d = k_d = k_{-d} = k_2 = k_{-2} = 0$

Figures 8 and 9 depict the influence of the pinocytotic toxin internalization (cellular drinking) rate constant v_d , drinking sites concentration r_d , toxin binding to drinking sites rate constant k_d (Fig. 8), and toxin exocytotic retrieval rate constant v_i (Fig. 9) on the behavior of factor $\delta(t)$. These figures show that $\delta(t)$ decreases as v_d , r_d , or k_d increases and increases with growing v_i .

Figure 10 illustrates a comparison of the dependence of $\delta(t)$ determined by the PDEs model (exocytotic toxin retrieval, lysosomal degradation, and clearance flux are neglected) and ADM2 (advection-diffusion) model studied in [7] on the same values of the advection and microtubule-powered velocity v_1 . Toxin diffusivity in both models is the same. We observe the different behavior of $\delta(t)$ corresponding to both models as v_1 increases. Indeed, $\delta(t)$ determined by the ADM2 model increases as v_1 grows, while the $\delta(t)$ corresponding to PDE model decreases (visibly only in the vicinity of pike) with growing v_1 .

Using the WMS model, we also studied the influence of the lysosomal degradation rate and toxin clearance flux constants, β_{T_i} and γ_e , on the behavior of $\delta(t)$. Our calculations show that $\beta_{T_i} < 10$ and $\gamma_e < 0.01$ for $\alpha_1 = 0.99$, $\alpha_2 < 10^{-4}$, and $v_1 = 10^{-4}$ practically do not influence the evolution of $\delta(t)$. For this value of α_1 , the main impact into $\delta(t)$ comes from u_{T_i} and u_{B_1} while for smaller α_1 concentration u_{B_1} is essential. Calculations show that growing β_{T_i} increases factor $\delta(t)$ while the influence of γ_e is convoluted. For example, $\delta(t)$ is nonmonotone for $\gamma_e = 10^3$: it decreases, reaches a minimum, and then saturates at value 0.6.

5 Conclusions

In this paper we developed a rather generic model of toxin trafficking to the endoplasmic reticulum and mitigation of toxin effect on the cell with introducing of an antibody of high affinity. The basic model is described by a coupled system of PDEs. A simplified model based on the system of coupled ODEs is also studied. Toxin (ricin) and the antibody initially are delivered outside the cell. The model involves: the pinocytotic (cellular drinking) and

receptor-mediated toxin internalization modes from the extracellular into the intracellular domain, exocytotic toxin excretion from the cytosol back to the extracellular medium, the intact toxin diffusive and retrograde transport to the lysosomes and the endoplasmic reticulum and the diffusive and anterograde toxin trafficking outward from the cell across the plasma membrane. Both models are solved numerically.

The main parameter we studied is the antibody protection factor $\delta(t)$ (a relative reduction of the total toxin concentration near the ER due to application of the antibody). We presented numerical simulations showing how the parameters of toxin transport (both by tubule-mediated and by diffusion) influence the antibody protection factor. We also compared our model with the ADM2 [7] based on the diffusion-advection mechanism for toxin transport in the Ω_i toward the ER. In particular, we observed a different behavior of $\delta(t)$ corresponding to both models as v_1 increases.

To conclude this paper, we follow [16, 17] and emphasize some shortcomings of our model:

- (A) We have assumed that microtubules are immobile and velocities v_1 and v_2 of the toxin particles directional movement along the microtubules are deterministic permanent quantities. Actually, because of fluctuation in the extracellular and intracellular domains and the oscillatory nature of the motion of motor proteins, the drift velocity of motor proteins is a fluctuating (stochastic) quantity. Thus, it would be interesting to refine our model and determine the influence of the fluctuating velocities v_1 and v_2 on the antibody-protection factor.
- (B) We used bulk concentrations of the microtubule binding sites for dynein and kinesin motor proteins, p_1 and p_2 , and parameters k_d , k_{-d} , v_d , α_1 and α_2 . Currently, it is not clear what the values of these parameters are. We think that they can be determined experimentally.

Competing interests The authors declare that they have no competing interests.

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