Antibody-Based Molecular Communication for Targeted Drug Delivery Systems*

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***Abstract*— Antibody-based drug delivery systems (ADDS) are established as the most promising therapeutic methods for the treatment of human cancers and other diseases. ADDS are composed of small molecules (antibodies) that selectively bind to receptors (antigens) expressed by the diseased cells. In this paper, the Molecular Communication (MC) paradigm, where the delivery of molecules is abstracted as the delivery of information, is extended to be applied to the design and engineering of ADDS. The authors have previously developed a straightforward framework for the modeling of Particulate Drug Delivery Systems (PDDS) using nano-sized molecules. Here, the specificities of antibody molecules are taken into account to provide an analytical model of ADDS transport. The inputs of the MC model of PDDS are the geometric properties of the antibodies and the topology of the blood vessels where they are propagated. Numerical results show that the analytical MC model is in good agreement with finite-element simulations, and that the anisotropy is an important factor influencing ADDS.**

I. Introduction

Antibody-based Drug Delivery Systems (ADDS) are at the forefront of targeted drug delivery research [1]. ADDS are therapeutic methods that use artificial molecules to mimic the functioning of naturally produced antibody molecules. ADDS constitute biologically available materials to build and engineer therapeutic methods. They are inspired by the naturally occurring autoimmune mechanisms that enable the human body to diagnose itself and destroy the exact source of the disease, in an adaptive and constructive fashion. ADDS are engineered and inspired by this same advanced immune system mechanism. The versatility in engineering ADDS and their attested clinical success open up the possibility to develop sophisticated therapeutic strategies to effectively target diseases [2].

We propose to use the MC paradigm to model ADDS while taking into account the unique features of antibodies and the new possibilities that are offered through them. The Molecular Communication (MC) paradigm [3], where the information is conveyed through molecules, has been previously used to model and optimize Particulate Drug Delivery Systems (PDDS) [4]. ADDS propagate in the body by advection and diffusion in the network of blood vessels and tissues.

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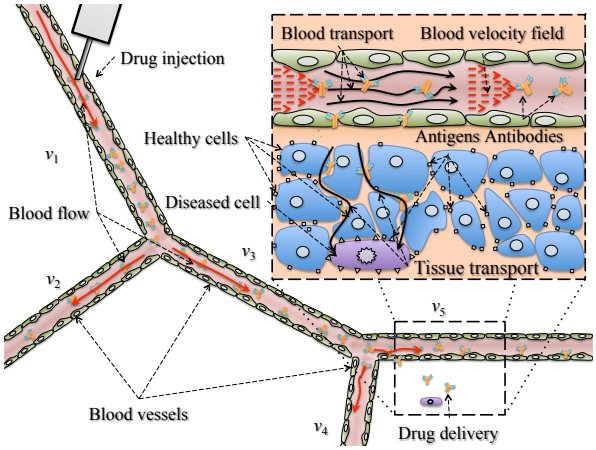

Fig. 1. Elements of an ADDS.

As shown in Fig. 1, the drug injection of antibody molecules propagates in the network of blood vessels. The antibodies are transported to the drug delivery site by blood transport and tissue transport processes. The antibodies specifically bind to the diseased cells because they express antigens that match to the antibody and do not appear in the healthy cells. They trigger their therapeutic effect to cells through a special case of the ligand-binding mechanism, called the antibody-antigen mechanism. Therefore, some aspects of the MC modeling previously developed for PDDS are readily applicable to ADDS. However, the transport and mechanism of action of ADDS is more complex and advanced than PDDS. The scope of our MC modeling of ADDS in this paper is on the extracellular-cellular transport of ADDS, by modifying the MC PDDS framework to take into account the arbitrary shape of antibody molecules. The MC ADDS modeling will provide a clearer understanding of the mode of operation of antibodies, and enable the development of innovative methods to guide the engineering of verifiable and safe antibody-based therapies.

The methods proposed in related works [5] are unable to differentiate drugs reaching the target site from the other drugs. The path takes by drugs remains unknown in existing models. The system parameters are statistical estimated, and, generally, the most complex compartmental models consist of two of three compartments assuming constant blood flow perfusion. The MC-ADDS model solves this problem by providing mechanistic models, based on law of biophysics instead of empirical observations, without the need of parameters estimation, and by giving higher spatial

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and temporal resolution tracking of the drug propagation in the micro-scale and millisecond scale, and being scalable to lower and higher resolutions with small changes to the system model.

The remainder of the paper is organized as follows: in Sec. II, the analytical MC model of ADDS and the method to obtain the diffusion parameters of antibody molecules from their 3D geometry are presented. Second, in Sec. III, finite-element simulations results and numerical evaluations of the analytical model are shown to validate the MC model of ADDS. Finally, Sec. IV concludes the paper with the outcomes of this work.

II. MC ADDS Model

In this section, we derive an analytical model of ADDS extracellular transport using the MC paradigm. As illustrated in Fig. 2, the drug injection is regarded as an *MC Transmitter*, the body is regarded as an *MC Channel*, and the drug delivery is regarded as an *MC Receiver*. The signals of the MC system are the concentrations of the antibody molecules. The antibody molecule is characterized by two diffusion parameters, namely: the *translational diffusion coefficient* D_t, and the *radial diffusion coefficient* D_r. The MC model provides a time-varying impulse response $h(t,\tau)$ which relates the transmitted signal $x(t)$, which is the drug injection concentration, to the received signal $y(t)$, which is the drug delivery concentration at the diseased cell. The MC model consists of two parts. First, the transport model is presented in Sec. II-A. Second, the calculation of the diffusion parameters on which the MC ADDS transport model depends in presented in Sec. II-B.

A. MC ADDS Transport Model

We develop here the MC ADDS transport model that enables the prediction of the propagation of antibodies in the blood vessels and tissue segments. The impulse response $h(t,\tau)$ is obtained by cascading the impulse responses of each segment between the drug injection site and the drug delivery site, which can be expressed as follows:

$$h(t,\tau) = h_{i_1}(t,\tau) \otimes \dots h_{i_n}(t,\tau) \cdots \otimes h_{i_L}(t,\tau)\,, \qquad (1)$$

where $\otimes$ denotes the cascading operation of two linear periodically time-varying systems as presented in [4], $h_{i_n}(t,\tau)$ is the impulse response of the k-th blood vessel or segment. , k is the index of the blood vessel or tissue segment, and L is the number of blood vessels and/or tissue segments from the drug injection to the drug delivery.

The transport process in the tissue compartment is diffusion-dominated since the hydrodynamic dispersion is so small that it can be neglected. Based on that, we derive the impulse response $h_{i_n}(t,\tau)$ for each segment from the generalized anisotropic Taylor dispersion equation with absorption [6] as follows:

$$h_{i_n}(t,\tau) = \frac{1}{\sqrt{2\pi\sigma^2_{i_n}(t,\tau)}} \exp\left(-\frac{(l - m_{i_n}(t,\tau))^2}{2\sigma^2_{i_n}(t,\tau)}\right)\,, \qquad (2)$$

where:

- The mean antibody velocity is time-varying and expressed as:

$$m_{i_n}(t,\tau) = \int_\tau^t u^{eff}_{i_n}(r,t)\,dt'\,, \qquad (3)$$

- The variance of the antibody is time-varying and is equal to:

$$\sigma^2_{i_n}(t,\tau) = 2\int_\tau^t D^{eff}_{i_n}(t')\,dt'\,, \qquad (4)$$

where t and t' are time parameters, The effective diffusion coefficient of antibodies $D^{eff}_{i_n}(t)$ is expressed as follows [6] :

$$D^{eff}_{i_n}(t) = D_t P_{f_{i_n}} + D_{w_{i_n}} P_{w_{i_n}} + \Delta D^{eff}_{i_n}(t)\,, \qquad (5)$$

where D_t is the translational diffusion coefficient of the ADDS in the blood expressed in (8), $D_{w_{i_n}}$ is the diffusion coefficient in the vessel or cell walls in i, and $\Delta D^{eff}_{i_n}$ is the diffusion coefficient increment of antibodies due to anisotropy, the effective blood velocity $u^{eff}_{i_n}(t)$ is expressed as follows:

$$u^{eff}_{i_n}(t) = P_{f_{i_n}} u_{i_n}(t)\,, \qquad (6)$$

where $P_{f_{i_n}} = \frac{1}{1+K_{i_n}}$ and $P_{f_{i_n}} = \frac{K_{i_n}}{1+K_{i_n}}$ are kinetic ratios, $K_{i_n} = \frac{k^+}{k^-}$ is the equilibrium constant, $u_{i_n}(t)$ is the real blood velocity, $k^+_{i_n}$ and $k^-_{i_n}$ are, respectively, the association and disassociation kinetic coefficients of antibodies with the walls of the vessel i_n. The diffusion coefficient increment of antibodies due to anisotropy, $\Delta D^{eff}_{i_n}$, is expressed as follows:

$$\begin{aligned}\Delta D^{eff}_{i_n}(t) = P^3_{f_{i_n}}\Big((v_{f_{i_n}}(t) - v_{w_{i_n}})\frac{K_{i_n}}{k^{-\,2}_{i_n}} \\ + \frac{K_{i_n}}{k^-_{i_n}}\frac{r^2_{i_n}}{48D_r}(1 + 6K_{i_n} + 11K^2_{i_n})v^2_{f_{i_n}} \\ - 4K_{i_n}(K_{i_n}+1)v_{f_{i_n}}(t)v_{w_{i_n}} + 6K^2_{i_n} + v^2_{w_{i_n}}\Big)\,,\end{aligned} \qquad (7)$$

where D_r is the radial diffusion coefficient of the ADDS in the blood expressed in (8) r_{i_n} is the radius of the vessel i_n, $v_{w_{i_n}}$ is the blood velocity on the wall.

Finally, from (1) and (2), we obtain the MC end-to-end impulse response of the ADDS.

B. MC ADDS Diffusion Parameters

This section presents a method to obtain the ADDS diffusion parameters that are used by the MC ADDS transport model presented in Sec. II-A, namely the *translational diffusion coefficient* D_t and the *radial diffusion coefficient* D_r.

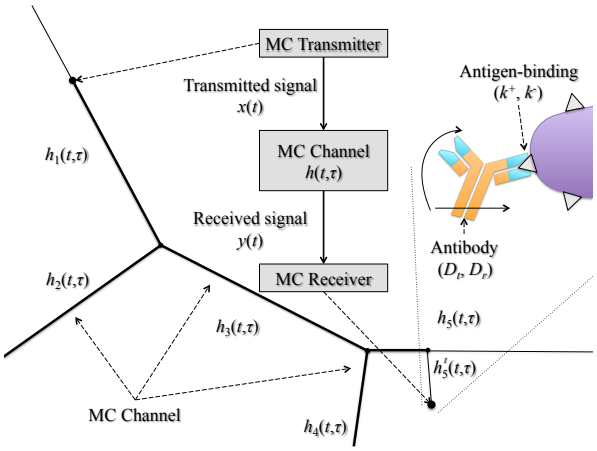

Fig. 2. MC Abstraction of an ADDS

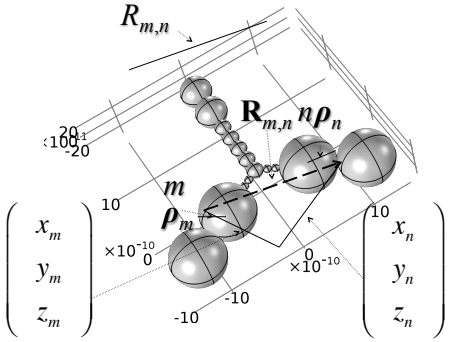

Fig. 3. Bead model of an antibody.

As illustrated in Fig. 3, the antibody-antigen has a unique shape. In fact, antibodies are generally Y-shaped molecules that consist of different heterogeneous regions (light chain and heavy chain). Antibodies come in different arbitrary shapes and structures as can be seen in X-Ray structure analysis of this type of molecules [7]. The geometry of the antibody necessarily affects its motion. The irregular shape can create arbitrary motions and fluctuations that are different from the case of spherical nanoparticles that were considered in PDDS. In the literature, all MC and pharmacokinetic models have supposed spherical or, at best, ellipsoid particles, for the modeling of antibody propagation. Therefore, there is a need for a model that takes into account the antibody shape and structure to predict the diffusion parameters of this small molecule without any empirical choices.

According to Brenner's general theory of diffusion [8], the transport of irregularly shaped molecules leads to the anisotropic coupling of radial and translational diffusion parameters of the molecules [9]. In classical MC, such motion is governed through Fick's law, with one parameter D, called the diffusion coefficient, but in the case of ADDS, we will consider two parameters, namely the *translational diffusion coefficient* D_t, and the *radial diffusion coefficient* D_r.

As illustrated in Fig. 3, we approximate the antibody molecule as a set of N beads B_n. A bead B_n is characterized by a radius ρ_n, and is located at the Cartesian coordinates (x_n, y_n, z_n) from an arbitrary origin O. Two beads B_m and B_n are located at the distance $R_{m,n}$ from each other. $\mathbf{R}_{m,n}$ denotes the distance vector between the beads B_m and B_n.

The *translational diffusion coefficient* D_t is calculated as follows [10]:

$$D_t = \frac{k_B T}{\mu} \frac{1}{3} tr(A_t)\,, \tag{8}$$

where k_B is Boltzmann coefficient, T is the temperature of the blood, supposed constant, and A_t is the top-left component of the mobility tensor [9] of the antibody molecule. The *radial diffusion coefficient* D_r is expressed by a similar expression as follows [10]:

$$D_r = \frac{k_B T}{\mu} \frac{1}{3} tr(A_r)\,, \tag{9}$$

where A_r is the top-left component of the mobility tensor [9] of the antibody molecule.

The top-left component of the mobility tensor A_t of the antibody molecule is expressed as follows:

$$A_t = \sum_{m=1}^{N} \sum_{n=1}^{N} \left[\frac{\delta_{m,n} \mathbf{I}}{6\pi\eta R_{m,n}} + (1 - \delta_{m,n})\, \mathbf{T}_{m,n} \right]^{-1}, \tag{10}$$

Similarly, the bottom-right component of the mobility tensor A_r of the antibody molecule is expressed as:

$$A_r = -\sum_{m=1}^{N} \sum_{n=1}^{N} U_m \left[\frac{\delta_{m,n} \mathbf{I}}{6\pi\eta R_{m,n}} + (1 - \delta_{m,n})\, \mathbf{T}_{m,n} \right]^{-1} U_n + 6\eta \left(\frac{4\pi}{3} \sum_{n=1}^{N} \rho_n^3 \right) \mathbf{I}\,, \tag{11}$$

where $\mathbf{T}_{m,n}$ is the hydrodynamic tensor of the antibody calculated as follows from the geometric parameters of the antibody molecule:

$$\mathbf{T}_{m,n} = \frac{1}{8\pi\eta R_{m,n}} \left[\left(\mathbf{I} + \frac{\mathbf{R}_{m,n} \mathbf{R}_{m,n}^T}{R_{m,n}^2} \right) + \frac{\rho_m^2 + \rho_n^2}{R_{m,n}^2} \left(\frac{\mathbf{I}}{3} - \frac{\mathbf{R}_{m,n} \mathbf{R}_{m,n}^T}{R_{m,n}^2} \right) \right], \tag{12}$$

and $\mathbf{U}_n$ is the skew matrix of the bead n, expressed as follows:

$$\mathbf{U}_n = \begin{pmatrix} 0 & -z_n & y_n \\ z_n & 0 & -x_n \\ -y_n & x_n & 0 \end{pmatrix}. \tag{13}$$

Finally, from (8) and (9), we have the analytical expression of the diffusion parameters of an antibody molecule based solely on its geometric arrangement and diameters.

III. Numerical Results

In this section, we present numerical results to validate the anisotropic transport with a realistic 3D model and to show the significance of anisotropy. We used COMSOL®to

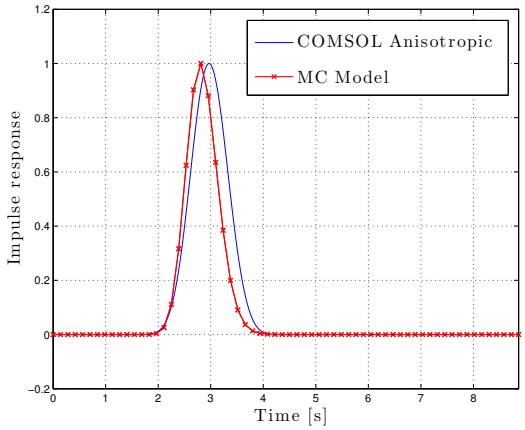

Fig. 4. Validation of the analytical impulse response with COMSOL simulation results.

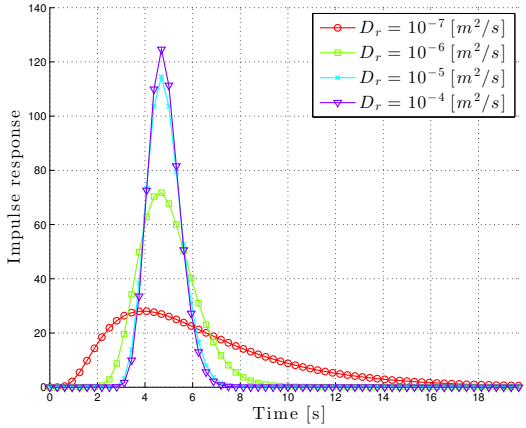

Fig. 5. Impulse responses for different values of the radial diffusion coefficients.

simulate antibody propagation based on the full advection-diffusion equation in a 3D geometry, and we evaluated the effect on anisotropy on the impulse response of the system. Fig. 4 shows the comparison between the mathematical model stemming from the MC paradigm incorporating the anisotropy effect and the full 3D simulation with COMSOL®. We have used the translational and radial diffusion coefficients calculated from the bead model in both COMSOL®and the MC models. The figure shows and excellent agreement between the two results. Fig. 5 illustrates how the impulse response varies highly depending on the radial diffusion coefficient. Fig. 6 shows the dependence of the anisotropic diffusion parameters on the angle between the hands of the antibody.

IV. Conclusion

The Molecular Communication (MC) framework was used as an abstraction of Antibody-based Drug Delivery Systems (ADDS) which is at the forefront of drug delivery system research. The proposed MC model is based on the biophysical laws of antibody transport in the human body. An analytical expression of the impulse response characterizing ADDS propagation was given, and the distribution of ADDS

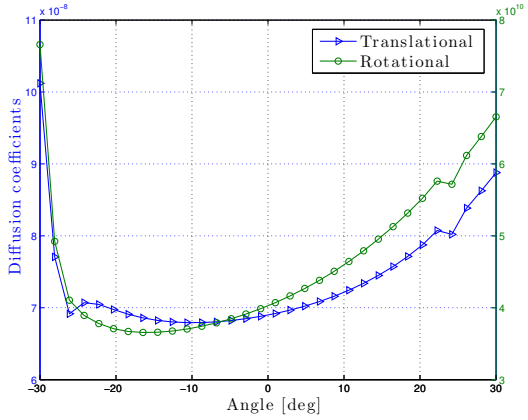

Fig. 6. Dependence of the translational and rotational diffusion coefficients on the antibody angle.

molecules is predicted through the generalized Fick's law where the diffusion parameters of the ADDS are anisotropic and expressed as a function the geometric structure of the molecule. The results show good agreement with finite-element simulations, and numerical evaluations show the significant of anisotropy in ADDS systemic distribution. The finite-element simulations requires hours to complete while the MC model requires a few seconds to provide the impulse response of the system. We propose to study as future work non-specific binding of antibodies in the blood serum and extra-cellular matrix, and the variability of tortuosity of the paths separating cells. This work can be used to create versatile, scalable, low-computational cost, and precise pharmacokinetic and pharmacodynamic models of antibody-based therapies.

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