Molecular Communication Modeling of Antibody-Mediated Drug Delivery Systems

Youssef Chahibi*, *Student Member, IEEE*, Ian F. Akyildiz, *Fellow, IEEE*,
Sasitharan Balasubramaniam, *Senior Member, IEEE*, and Yevgeni Koucheryavy, *Senior Member, IEEE*

***Abstract*—Antibody-mediated Drug Delivery Systems (ADDS) are emerging as one of the most encouraging therapeutic solutions for treating several diseases such as human cancers. ADDS use small molecules (antibodies) that propagate in the body and bind selectively to their corresponding receptors (antigens) expressed at the surface of the diseased cells. In this paper, the Molecular Communication (MC) paradigm, where information is conveyed through the concentration of molecules, is advocated for the engineering of ADDS and modeling their complex behavior, to provide a realistic model without the over-complication of system biology models, and the limitations of experimental approaches. The peculiarities of antibodies, including their anisotropic transport and complex electrochemical structure, are taken into account to develop an analytical model of the ADDS transport and antigen-binding kinetics. The end-to-end response of ADDS, from the drug injection to the drug absorption, is mathematically derived based on the geometry of the antibody molecule, the electrochemical structure of the antibody-antigen complex, and the physiology of the patient. The accuracy of the MC model is validated by finite-element (COMSOL) simulations. The implications of the complex interplay between the transport and kinetics parameters on the performance of ADDS are effectively captured by the proposed MC model. The MC model of ADDS will enable the discovery and optimization of drugs in a versatile, cost-efficient, and reliable manner.**

***Index Terms*—Molecular communication, pharmacokinetics, protein-protein interactions, targeted drug delivery systems.**

I. Introduction

ANTIBODY-MEDIATED Drug Delivery Systems (ADDS) are at the forefront of current therapeutic research [29]. The system uses artificial molecules that are constructed from biological materials to build and engineer drug delivery systems. They are inspired by the naturally occurring immune mechanisms that enable the human body to diagnose itself and destroy the exact source of the disease, in an adaptive and constructive fashion. The versatility in engineering ADDS and their attested clinical success open up the possibility to develop sophisticated therapeutic strategies to effectively target diseases [35]. Fig. 1 illustrates the elements of the ADDS. The drug injection occurs in the blood vessels, and the drug delivery occurs in the extracellular matrix. The drug injection introduces antibodies which are transported by the blood flow and diffused through the tissues. The blood velocity field transports the antibodies and some of them diffuse through the vascular walls into the tissues. Upon arriving at the diseased cell, the antibodies bind with the antigens located on the surface of the diseased cell at the antigen-antibody binding site promote the selective targeting of the diseased cells without affecting the healthy cells.

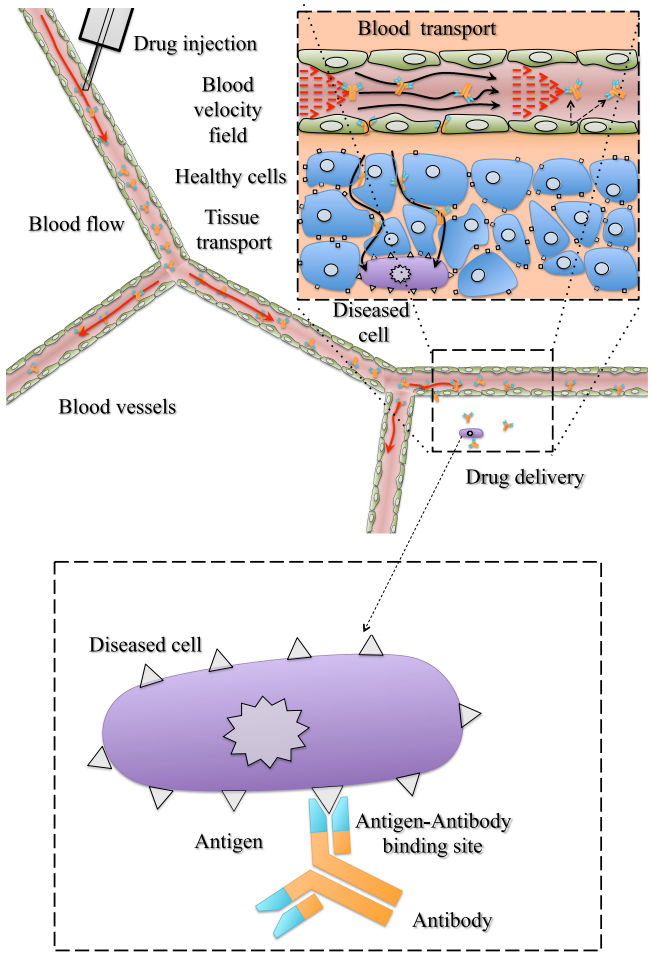

Fig. 1. Elements of ADDS.

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*Y. Chahibi is with the Broadband Wireless Networking Laboratory, School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA (e-mail: youssef,ian@ece.gatech.edu).

I. F. Akyildiz is with the Nano Communication Centre (NC2), Department of Electronics and Communication Engineering, Tampere University of Technology and also with the Broadband Wireless Networking Laboratory, School of Electrical and Computer Engineering, Georgia Institute of Technology.

S. Balasubramaniam and Y. Koucheryavy are with the Nano Communication Centre (NC2), Department of Electronics and Communication Engineering, Tampere University of Technology.

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The interplay of these different transport and kinetic processes contributes to the performance of the ADDS in maximizing the delivery of the antibodies to the diseased cells.

In this paper, Molecular Communication (MC) paradigm [1], where the information is conveyed through molecules, is proposed to model the ADDS while considering the unique properties of antibodies and the possibilities that they offer. This new model will address the short comings of *Physiologically-based Pharmacokinetics* (PB/PK) models that have been proposed for ADDS propagation in the literature. PB/PK methods suffer from many limitations that make them inapplicable to helping the current state-of-the-art in nanomedicine [14],[12]. The issue with the PB/PK model is that the diseases that are meant to be targeted with ADDS, such as tumors, are highly localized and grow quickly, and this model does not provide enough spatial and temporal accuracy to assess the efficiency of the ADDS. Also, by modeling complex molecules for the first time in the area of MC, this work addresses the limitations in the existing MC modeling works [23], [24].

By using the MC-ADDS paradigm, a bottom-up approach of modeling the propagation of antibodies is proposed where the appropriate structure of the antibody is determined, and from that, propagation around the body is predicted. The MC-ADDS model solves this problem by providing mechanistic models, based on the laws of biophysics instead of empirical observations, and minimizing the need for parameters estimation. This will provide higher spatial and temporal resolution tracking of the drug propagation in the micro and millisecond scale, while being scalable to lower and higher resolutions with small changes to the system model. In MC-ADDS, the human body is modeled as a complex network of blood vessels and tissues where the transmitted signal is modulated by the antibody concentration at the injection location, which is the location of the body where the injection is administered, and the propagation in the body is represented with simple analytical models, directly derived from the physiology of the patient and the chemical and electrical structure of the antibody molecule. Section VII will show that the MC-ADDS modeling allows the calculation of the end-to-end impulse response of the system, and evaluating which kinetic processes are impeding the drug delivery.

In particular, the main contributions of this work are as follows:

1) *Modeling an end-to-end abstraction of ADDS as an MC channel:* The abstracted MC channels divide the ADDS into three different channels corresponding to different parts of the body. These three different channels include the vascular, extracellular, and antigen binding channels. Numerical evaluations are conducted for each channel to determine the influence on the delivery of the antibodies.
2) *Determining an optimized shape for the antibody molecular structure:* The movement of the antibodies with the blood flows is modeled based on their 3-D structure. The optimized geometrical structure for the antibodies is determined based on the diffusion behavior, as well as their successful binding process to the diseased cells. The model considers the chemical components within the blood that affect the antibody, as well as the electrochemical properties of the antibody-antigen complex.
3) *Validation of the end-to-end ADDS MC channel:* Validations of the ADDS are conducted using both analytical MC modeling and comparison to the COMSOL,[1] finite-element simulations. The comparison showed strong agreement between the MC models and the COMSOL simulations.

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 mediated therapies. This includes the design and engineering of the drug structure [9], [26], mode of administration, and dosage optimization [33]. This opens up the possibility to optimize the properties of the ADDS to achieve a desired therapeutic effect, by determining the drug injection rate in terms of drug dosage concentration, the timing of the dosage, and the location of injection, thus maximizing the safety and success of ADDS and minimizing the costs [18]. The second motivation behind the use of MC-ADDS modeling, is to understand the physicochemical interactions between ADDS and the body, which are more complex than in PDDS. For example, ADDS undergo electrostatic forces within the *Extracellular Matrix* (ECM) due to negatively charged proteins [3]. These electric forces significantly affect the intercellular transport, antigen binding, and the absorption of the ADDS by the cells.

The rest of the paper is organized as follows: in Section II, we explain the abstraction of the ADDS through the MC paradigm, the objectives, and principles of this approach. Section III presents the *MC-ADDS Vascular Channel Model*, which describes the MC analytical model of ADDS transport through the blood vessels, taking into account the roles of tissue absorption, and the plasma binding. Section IV introduces the *MC-ADDS Extracellular Channel Model*, which is the MC analytical model of ADDS transport through the extracellular matrix (ECM), taking into account the role of ECM protein binding. Section V presents the *MC-ADDS Antigen Binding Channel Model* which is developed through the MC paradigm, by incorporating the electrochemical structure of the antibody molecule. Section VI defines the realistic COMSOL Multiphysics model that was simulated to validate the MC-ADDS model. Section VII presents numerical results that were evaluated using the MC-ADDS model and the COMSOL Multiphysics simulation model. Section VIII concludes the paper with the main outcomes of the MC-ADDS model and its prospective use for the design and engineering of optimal ADDS.

II. MC Abstraction of ADDS

In this section, we present the MC-ADDS framework which abstracts the kinetics processes that the antibody undergoes in different parts of the body as MC channels. In the context of communication theory, a channel is a communication medium characterized by an input-output relationship. The combination

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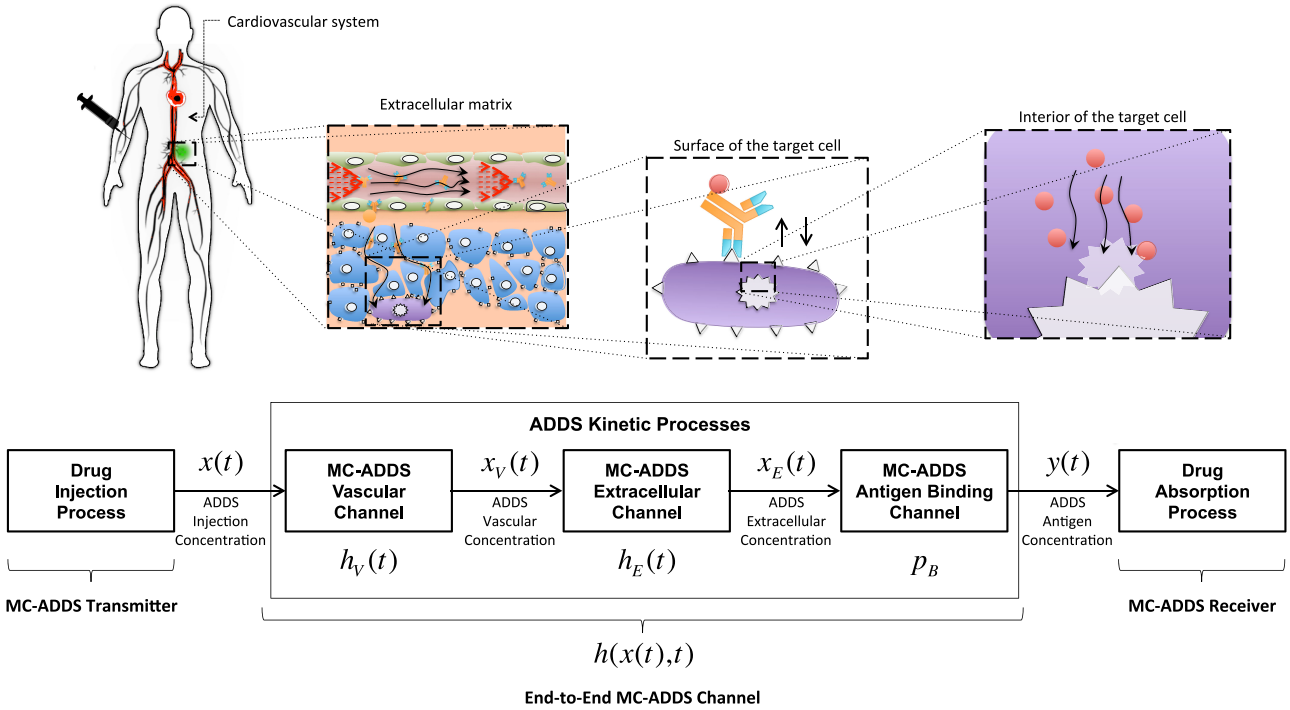

Fig. 2. MC abstraction of the ADDS.

of several channels together enables establishing a network between several transmitters and receivers. The concept of channels is useful for modeling, analyzing the performance, and optimizing a system regardless of the initial conditions and input signals. As illustrated in Fig. 2, cascading the MC-ADDS channels for each of these processes provides the *end-to-end MC-ADDS channel* from the location where the antibodies are injected to the location where they are absorbed by the cells. The drug injection is abstracted as a *MC-ADDS transmitter* and the drug absorption process is abstracted as a *MC-ADDS receiver*. The antibody concentrations at different phases of their propagation in the body are considered as MC signals, which are the inputs and outputs of the following MC-ADDS channels:

1) *The MC-ADDS Vascular Channel* models the propagation of the antibodies by advection-diffusion through the force of the blood flow, the Brownian motion of the antibodies in the blood, and the chemical binding with the molecules present in the blood. The MC-ADDS vascular channel is characterized by a function $h_V(t)$. The input signal to the MC-ADDS Vascular Channel is the *ADDS Injection Concentration* $x(t)$, defined as the concentration of antibodies in the injection location, which is represented as follows:

$$x(t) = Ab(t)|_{\text{Injection location}}. \tag{1}$$

$Ab(t)$ denotes the antibody concentration at the location of the injection at the time t. The output from the MC-ADDS Vascular Channel is the *Vascular ADDS Concentration* $x_V(t)$, which is defined as the concentration of antibodies in the blood as a function of time t, as follows:

$$x_V(t) = Ab(t)|_{\text{Blood}} = h_V(t) * x(t) \tag{2}$$

where $*$ denotes the application of the impulse response $h_V(t)$ to the signal $x(t)$.

2) *The MC-ADDS Extracellular Channel* models the transport of the antibodies through the ECM. This channel is located between the vascular tissues and the surface of the target cells, and is driven by the interstitial pressure between the blood vessel walls and the target cells, the lymphatic flow, and the binding with the molecules of the ECM. The MC-ADDS extracellular channel is characterized by a function $h_E(t)$. The output signal of the MC-ADDS extracellular channel is the *ADDS Extracellular Concentration* $x_E(t)$, which is the concentration of antibodies in the ECM as a function of the time t as follows:

$$x_E(t) = Ab(t)|_{\text{ECM}} = h_E(t) * x_V(t). \tag{3}$$

3) *The MC-ADDS Antigen Binding Channel* models the antigen-antibody binding occurring at the surface of the target cell. The antigen-antibody binding is influenced by the chemical affinity between the antigens expressed by the cell and the antibody, as well as the physical forces exerted by the flow in the ECM. The MC-ADDS Antigen Binding Channel is characterized by a function p_B, which provides the output of the MC-ADDS Antigen Binding Channel as the *ADDS-Antigen Concentration* $y(t)$, which is the concentration of antibodies bound to the antigens as a function of the time t, given the ADDS extracellular concentration $x_E(t)$ as follows:

$$y(t) = AbAg(t)|_{\text{Cell surface}} = p_B x_E(t). \tag{4}$$

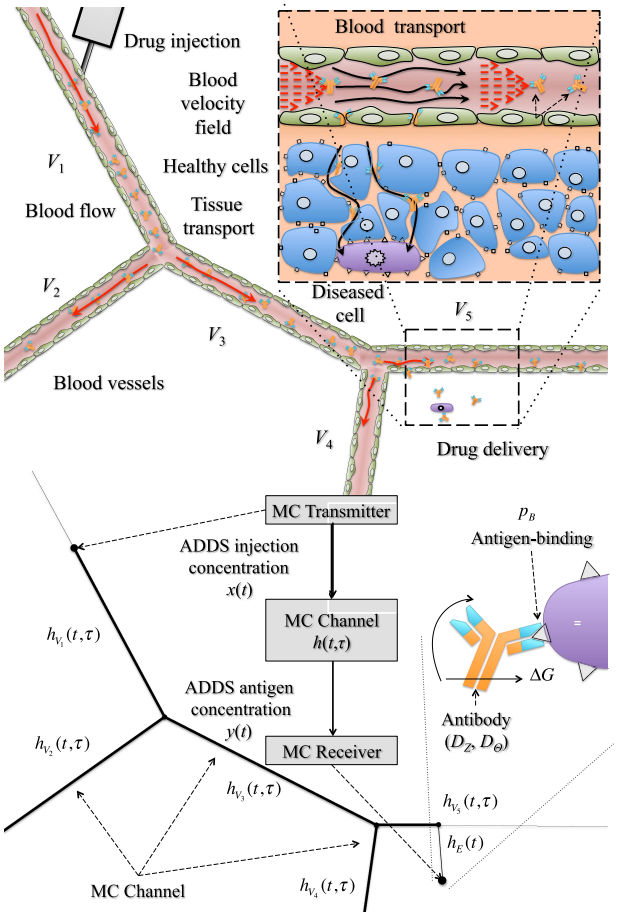

Fig. 3. MC Abstraction of the ADDS

$AbAg(t)$ denotes the concentration of drug antibodies that are bound to antigens at the location of the injection at the time t. p_B is not time-varying because there is a scalar relationship between the antibodies around the diseased cells and the antibodies that bind to the antigens, in a steady state. $y(t)$ is determined from the number of antibodies that arrive around the surface of the diseased cells and the thermochemical properties of the antibody-antigen binding.

This study will allow the optimization of MC-ADDS systems by appropriately designing the antibody structure, shape, and chemical characteristics to maximize its ability to deliver its therapeutic effect where it is needed in a timely and efficient way.

III. MC-ADDS Vascular Channel Model

In this section, we derive an analytical model of ADDS vascular transport using the MC paradigm. As illustrated in Fig. 3, the blood velocity field drives the transport of antibodies in the vascular region, and also the antibodies diffuse randomly by Brownian motion. The antibody molecule is characterized by two diffusion parameters, namely: the *translational diffusion coefficient* D_Z, and the *radial diffusion coefficient* D_R. D_Z is the parameter that characterizes the diffusion of antibodies along the axis of the blood vessels. It is formally defined as follows:

$$< z^2(t) >= 2D_Z t \tag{5}$$

where the variable z is the translational coordinate of the antibody at the time t along the axis of the blood vessels. The rotational diffusion coefficient D_Θ is the parameter that characterizes the diffusion of antibodies around their center. It is formally defined as follows:

$$< \theta^2(t) >= 2D_\Theta t \tag{6}$$

where the variable θ is the angle of rotation of the antibody around its center.

A. MC-ADDS Vascular Channel Impulse Response

In classical MC, only one parameter, namely the diffusion coefficient D, is involved in the transport of the molecules according to Ficks law by Brownian motion, but in the case of ADDS, we will consider two parameters, namely the *translational diffusion coefficient* D_Z, which depends on the shape of the molecule, and the *radial diffusion coefficient* D_R, which depends also on the structure of the diffusion medium. Based on the general theory of diffusion developed by Brenner [4], the irregular shape of molecules has an important effect on their transport. In fact, the irregularity causes coupling between the rotational and the translational diffusion parameters of complex molecules [5]. In addition, to the translational-rotational anisotropy due to molecule shape, there is a translational-radial anisotropy owed to the nonhomogeneity of cells matrices where one direction is more conducive to diffusion than the perpendicular direction. Examples of translational-radial anisotropy include the transport of molecules in blood vessels, where the nonuniform distribution of red blood cells affects the diffusion in the radial direction [10], and the anisotropy in the ECM, where the cells are organized in a preferential direction, due to the direction of mechanical forces, especially the ones involving connective tissues [28].

An MC-ADDS transport model is developed, enabling the prediction of the propagation of antibodies in the vascular channel. This model is deterministic, but it should be noted that there are many fluctuations in drug delivery systems in general owing to blood turbulence, Brownian motion, and ligand-binding noise. These noise effects are explained in a previous work [6], and can be applied to ADDS with little modifications. The impulse response $h_V(t,\tau)$ is obtained by cascading the impulse responses of each channel between the drug injection site and the drug delivery site, which can be expressed as follows:

$$h_V(t,\tau) = h_{V_1}(t,\tau) \otimes \ldots h_{V_i}(t,\tau) \ldots \otimes h_{V_L}(t,\tau) \tag{7}$$

where $\otimes$ denotes the operator for cascading the periodically time-varying impulse responses of two systems as described in [7], $h_{V_i}(t,\tau)$ is the impulse response of the ith MC vascular channel, and L is the number of blood vessels located between the drug injection site and the drug delivery site.

The transport process in the ECM is dominated by diffusion, although there is an advective transport due to the plasma exudating drug particles from blood vessels to the lymphatic

system in a directed way. However, the flow rate is so slow that the dispersion due to advection is negligible. This coincides with clinical observation of antibody transport [19]. The impulse response $h_{V_i}(t,\tau)$ is expressed for each MC vascular channel based on the generalized anisotropic Taylor dispersion equation with absorption [2], with the assumption of diffusion-dominated transport around the blood vessels, as follows:

$$h_{V_i}(t,\tau) = \frac{1}{\sqrt{2\pi\sigma_i^2(t,\tau)}} \exp\left(-\frac{(l-m_i(t,\tau))^2}{2\sigma_i^2(t,\tau)}\right) \quad (8)$$

where:

1) The mean antibody velocity varies with time and is expressed as follows:

$$m_i(t,\tau) = \int_\tau^t v_i(r,t)dt', \quad (9)$$

2) The variance of the antibody concentration increases with time and is expressed as follows:

$$\sigma_i^2(t,\tau) = 2\int_\tau^t D_i(t')\,dt', \quad (10)$$

where t and t' are time parameters, The effective diffusion coefficient of the antibodies $D_i(t)$ is expressed as follows [2]:

$$D_i(t) = D_Z P_f + D_E P_w + P_f^3 v_i^2(t)\left(\frac{K_V}{K_E} + \frac{r_i^2}{48D_R}\right) \quad (11)$$

where D_Z is the translational diffusion coefficient of the ADDS in the blood expressed in (14), D_E is the diffusion coefficient in the ECM, which is defined in Section IV, D_R is the radial diffusion coefficient due to anisotropy [10], r_i is the radius of the vessel i, K_V is the nonspecific binding equilibrium constant in the vascular channel, K_E is the nonspecific binding equilibrium constant in the ECM, $P_f = \frac{1}{1+K_V}$ is a kinetic ratio, and the effective blood velocity $v_i(t)$ is expressed as follows:

$$v_i(t) = P_f u_i(t). \quad (12)$$

The nonspecific binding equilibrium constant in the vascular channel can be calculated from the nonspecific binding energy ΔG_V. This is calculated between the antibody and the proteins contained in the blood in a similar way to the calculation of the specific binding energy ΔG between the antibody and the antigens in (24) (see Section V), and is represented as follows:

$$K_V = \exp\left[-\frac{\Delta G_V}{RT}\right] \quad (13)$$

where ΔG_V is the nonspecific binding free energy between the antibody and the proteins in the vascular channel, and R is the ideal gas constant. Finally, from (7) and (8), we obtain the MC end-to-end impulse response of the ADDS.

B. MC-ADDS Vascular Channel Diffusion Coefficients

Here, we introduce the model of the structure of the antibody which provides the reference geometrical and electrochemical properties of the ADDS. These properties will be used to derive the transport diffusion coefficients. The structural information is obtained from the *Protein Data Bank* (PDB) [16], which hosts the tridimensional structural data of a large number of biological molecules, including antibodies and their antigens. A visualization of such a structure is presented in Fig. 4 which represents the atomic structure of the antibodies as an assortment of balls occupying the volume of the atoms and their bonds with other atoms. The PDB also includes the constituting chemical elements of the antibodies and their electric charges. Among all the information provided by the PDB, in this paper we focus on the geometry of a molecule and its charges. Each element of the antibody is denoted as n, and the total number of elements constituting the antibody as N. An element n possesses the following information:

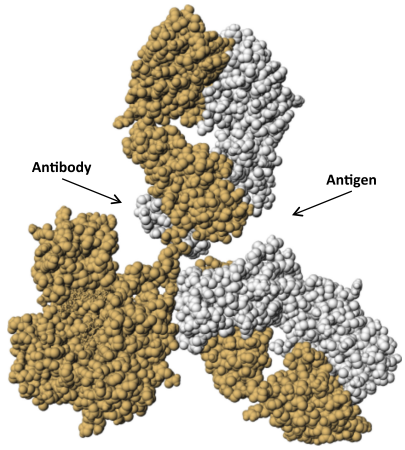

Fig. 4. 3-D structure of the antibody-antigen complex from the Protein Data Bank.

1) *Cartesian coordinates*, denoted by the vector (x_n, y_n, z_n) with a given Cartesian center O.
2) *Radius*, denoted by the scalar value ρ_n, which measures half the distance between one atom and its closest element.
3) *Charge*, denoted by the value q_n, which is the electric charge born by the element n.

These three types of information are sufficient to describe the kinetic parameters of the antibody. In the following, we explain how these parameters are derived directly from the PDB information.

In the literature [8], [15], [34] all MC and pharmacokinetic models contain information on the basic shapes for the molecules such as spheres, and rarely ellipsoids and rods, to capture the 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. The antibodies come in different arbitrary shapes and structures as can be seen in X-Ray structure analysis of this type of molecules [13]. As illustrated in Fig. 5, the antibody-antigen is composed of several beads. In general, the antibodies are roughly Y-shaped molecules and consist of different heterogeneous regions (light chain and heavy chain). The geometry of the antibody has an important effect on its motion in the blood and tissues. The irregular shape can create arbitrary motions and fluctuations that are different from the case of spherical nanoparticles that were considered in PDDS.

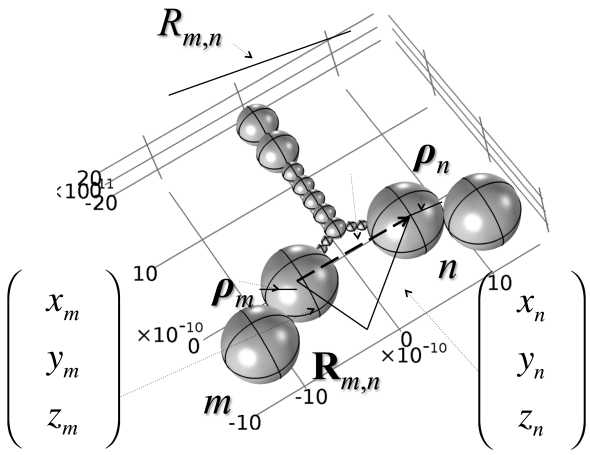

Fig. 5. Bead model of an antibody.

The translational diffusion coefficient D_Z and the rotational diffusion coefficient D_Θ are calculated as follows [31]:

$$\begin{cases} D_Z = \frac{k_B T}{3\eta} tr(A_Z) \\ D_\Theta = \frac{k_B T}{3\eta} tr(A_\Theta) \end{cases} \tag{14}$$

where k_B is Boltzmann coefficient, T is the temperature of the blood, η is the fluid viscosity, $tr(\cdot)$ is the trace function of the matrices A_Z and A_Θ, which represent the *translational mobility tensor matrix* and the *rotational mobility tensor matrix* [5]. These matrices A_Z and A_Θ are expressed as follows [11]:

$$\begin{cases} A_Z = \sum_{m=1}^{N} \sum_{n=1}^{N} \left[\frac{\delta_{m,n}\mathbf{I}}{6\pi\eta R_{m,n}} + (1-\delta_{m,n})\,\mathbf{T}_{m,n} \right]^{-1} \\ A_\Theta = -\sum_{m=1}^{N} \sum_{n=1}^{N} U_m \left[\frac{\delta_{m,n}\mathbf{I}}{6\pi\eta R_{m,n}} + (1-\delta_{m,n})\,\mathbf{T}_{m,n} \right]^{-1} U_n \\ \qquad + 8\pi\eta \left(\sum_{n=1}^{N} \rho_n^3 \right) \mathbf{I} \end{cases} \tag{15}$$

where m and n are the indices of two beads m and n in the molecular compound, as illustrated in Fig. 5, N is the total number of beads in the molecular compound, η is the fluid viscosity, $R_{m,n}$ is the center-to-center distance between two beads m and n, ρ_n is the radius of the bead n, $\delta_{m,n}$ is the Kronecker delta function, $\mathbf{T}_{m,n}$ is the hydrodynamic tensor of the antibody calculated as follows from the geometric parameters of the antibody molecule:

$$\mathbf{T}_{m,n} = \frac{1}{8\pi\eta R_{m,n}} \left[\left(\mathbf{I} + \frac{\mathbf{R}_{m,n}\mathbf{R}_{m,n}^\dagger}{R_{m,n}^2} \right) + \frac{\rho_m^2 + \rho_n^2}{R_{m,n}^2} \left(\frac{\mathbf{I}}{3} - \frac{\mathbf{R}_{m,n}\mathbf{R}_{m,n}^\dagger}{R_{m,n}^2} \right) \right] \tag{16}$$

where $\mathbf{R}_{m,n}$ is the distance vector between the beads m and n, $\{\cdot\}^\dagger$ is the transpose function of the vector $\mathbf{R}_{m,n}$, $R_{m,n}$ is the center-to-center distance between two beads m and n, ρ_n is the radius of the bead n, ρ_m is the radius of the bead m, and $\mathbf{U}_m$ is the skew matrix of the bead m and is expressed as follows:

$$\mathbf{U}_m = \begin{pmatrix} 0 & -z_m & y_m \\ z_m & 0 & -x_m \\ -y_m & x_m & 0 \end{pmatrix} \tag{17}$$

where (x_m, y_m, z_m) are the Cartesian coordinates of the bead with index m from an arbitrary origin O. Similarly, $\mathbf{U}_n$ is the skew matrix of the bead n expressed as follows:

$$\mathbf{U}_n = \begin{pmatrix} 0 & -z_n & y_n \\ z_n & 0 & -x_n \\ -y_n & x_n & 0 \end{pmatrix} \tag{18}$$

where (x_n, y_n, z_n) are the Cartesian coordinates of the bead with index n from the origin O.

IV. MC-ADDS Extracellular Channel Model

In this section, we present how the transport of ADDS in the ECM is modeled. Due the differences between tissues in the body in terms of geometry, arrangement, tortuosity, and density, the transport of ADDS is going to vary greatly in different parts of the body. The parameter D_E denotes the diffusion coefficient in a tissue surrounding a blood vessel. The structure of the ECM is similar to foam. The antibodies will perform random motions and collide with the membranes of the cells, thus affecting the distribution of their concentration. Using the theory of transport in porous media [21][27], it is possible to derive an expression for D_E based on the characteristics of the tissue. In practice, it has been observed that the transport in the ECM is largely dominated by the diffusion, therefore, we neglect the transport due to interstitial pressure differences.

The MC-ADDS model of extracellular transport becomes a diffusion MC channel [23] with a diffusion coefficient D_E and a nonspecific binding equilibrium constant K_E in the ECM, as follows:

$$h_E(t) = \frac{1}{\sqrt{2\pi D_E t}} \exp\left[\frac{-z^2}{(4D_E + K_E)\,t} \right] \tag{19}$$

where z is the coordinate towards the target cell, K_E is the nonspecific binding equilibrium constant in the ECM, and D_E is the diffusion coefficient in the ECM. The nonspecific binding equilibrium constant is a value that characterizes the rate of the first-order linear reaction between two reactants such as the antibody and other molecules

$$D_E = \frac{\phi}{\kappa} D_Z \,. \tag{20}$$

As shown in Fig. 6, the diffusion coefficient D_E is a function of following parameters which can be estimated from the shape of the ECM:

1) *The porosity* ϕ measures the propensity of the tissue components to allow the antibodies to pass.
2) *The tortuosity* κ is the arc length of the path over the geometric distance between the input and the output locations of the channel. Typical values for the tortuosity are measured experimentally from cellular imaging. The

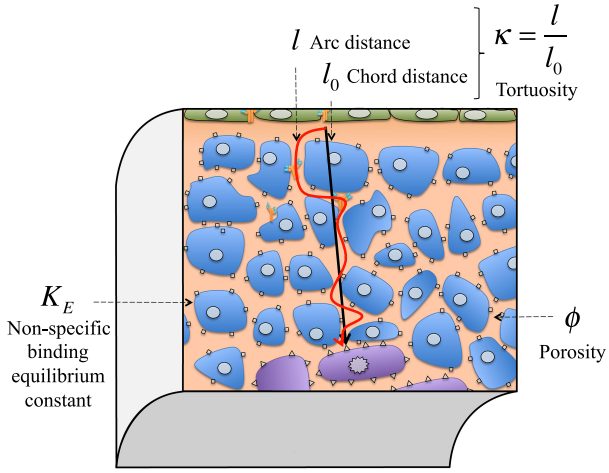

Fig. 6. Parameters of the MC-ADDS extrallelular transport model.

work in [32] cites values between $\kappa = 1.55$ and $\kappa = 1.65$ in the human adult brain. The work in [36] cites values between $\kappa = 2$ and $\kappa = 3$, and the work in [36], mentions that the tortuosity can be as high as $\kappa = 9$ in crowded protein-loaded environments.

3) *The free fluid coefficient* D_Z is the translational diffusion coefficient of the antibodies in the fluid, which is calculated using the result in (14).

It is noted that extracellular transport may also be subject to protein binding [22], in which case, the model of the following section could supplement the binding of antibodies with gels and ECM proteins. In fact, the nonspecific binding equilibrium constant in the ECM K_E can be calculated from the nonspecific binding energy ΔG_E, which is calculated between the antibody and the proteins of the ECM (such as collagens) in a similar way to the computation of the specific binding energy ΔG between the antibody and the antigens in (24) (see Section V), as is represented in the following:

$$K_E = \exp\left[-\frac{\Delta G_E}{RT}\right] \tag{21}$$

where ΔG_E is the nonspecific binding free energy between the antibody and the ECM proteins. For simplicity, we assume that the environment around the blood vessel is homogeneous, but, technically, the different heterogeneous layers of cell types around the blood vessels could be accounted for by cascading the impulse response for each layer from the plasma to the target diseased cells, based on their own tortuosity and porosity.

V. ADDS Antigen Binding Channel Model

In this section, we derive the characteristic function p_B of the MC-ADDS Antigen Binding Channel, as a function of the geometry and charge of the antibody, and the number of antigens in the surface of the diseased cells. This function allows to obtain the distribution of the ADDS antigen-antibody density at the surface of the cell $y(t)$ as a function of the ADDS extracellular concentration $x_E(t)$ as follows:

$$y(t) = p_B x_E(t)\,. \tag{22}$$

The antigen binding probability p_B is found to be expressed as [25]:

$$p_B = \frac{C_{ag}}{RT}\exp\left[-\frac{\Delta G}{RT}\right] \tag{23}$$

where C_{ag} is the concentration of antigens on the surface of the diseased cells, and T is the temperature. In the following, we derive the expression for the antigen-antibody binding free energy ΔG, the binding probability, and the kinetic rates of the antibodies in reaction with other proteins including extracellular matrix proteins and antigens. The antigen-antibody binding free energy ΔG is calculated as follows [20]:

$$\Delta G = G^+ - G^- \tag{24}$$

where G^- is the unbound free energy defined as:

$$G^- = \sum_{\substack{m,n=1\\ n\neq m}}^{N} (S_{m,n} + V_{m,n} + E_{m,n}) + \sum_{\substack{m,n=N+1\\ n\neq m}}^{M+N} (S_{m,n} + V_{m,n} + E_{m,n}) \tag{25}$$

where M is the total number of beads in the antigen, N is the total number of beads in the antibody, m and n are the indices of the beads, $S_{m,n}$ is the *pair solvent free energy* for two beads m and n, $V_{m,n}$ is the *pair van der Waals energy* for two beads m and n, $E_{m,n}$ is the *pair electrostatic potential* for the two beads m and n. The equation in (25) consists of the addition of the total energies for the antibody and the antigen, each taken individually, where the first sum is the free energy for the individual antibody, and the second sum is the free energy for the individual antigen. G^+ is the bound free energy defined as:

$$G^+ = \sum_{\substack{m,n=1\\ n\neq m}}^{M+N} (S_{m,n} + V_{m,n} + E_{m,n}) \tag{26}$$

where $S_{m,n}$ is the *pair solvent free energy* for two beads m and n, $V_{m,n}$ is the *pair van der Waals energy* for two beads m and n, $E_{m,n}$ is the *pair electrostatic potential* for two beads m and n. The equation in (26) consists of the free energy of the antigen-antibody compound joined together. The PDB database provides the antigen-antibody bead coordinates in their joined state, therefore the bound free energy is directly computable from the database.

The pair energies used in the expressions of the unbound and bound free energies, in (25) and (26), respectively are expressed as follows:

1) The *pair solvent energy* $S_{m,n}$ for the beads m and n is expressed as follows [30]:

$$S_{m,n} = \frac{1}{8\pi}\left(\frac{1}{\epsilon_0} - \frac{1}{\epsilon}\right)\frac{q_m q_n}{f_{m,n}}\,, \tag{27}$$

where q_m is the charge on the bead m, q_n is the charge on the bead n, ϵ_0 is the free space permittivity, ϵ is the dielectric constant of interstitial fluid, and $f_{m,n}$ is given by

$$f_{m,n} = \sqrt{R_{m,n}^2 + \rho_m \rho_n e^{-g_{m,n}}} \tag{28}$$

where $R_{m,n}$ is the distance between two elements m and n, ρ_n and ρ_m are, respectively, the radii of the two elements m and n, and $g_{m,n}$ is a ratio defined as follows:

$$g_{m,n} = \frac{R_{m,n}}{4\rho_m \rho_n}. \tag{29}$$

This model is based on the generalized Born salvation free energy [30] which is an approximation of the solution to the Poisson-Boltzmann equation.

2) The *pair van der Waals energy* $V_{m,n}$ for the beads m and n is calculated as follows [17]:

$$V_{m,n} = -\frac{A}{6}\left(\frac{2\rho_m\rho_n}{R_{m,n}^2 - (\rho_m + \rho_n)^2} + \frac{2\rho_m\rho_n}{R_{m,n}^2 - (\rho_m - \rho_n)^2} + \ln\left[\frac{R_{m,n}^2 - (\rho_m + \rho_n)^2}{R_{m,n}^2 - (\rho_m - \rho_n)^2}\right]\right) \tag{30}$$

where A is the Hamaker coefficient [17] which depends on the properties of the material, and $R_{m,n}$ is the center-to-center distance between two beads m and n.

3) The *pair electrostatic potential* $E_{m,n}$ for the beads m and n is calculated as follows:

$$E_{m,n} = \frac{q_m q_n}{8\pi\epsilon R_{m,n}}, \tag{31}$$

where q_m is the charge on the bead m, q_n is the charge on the bead n, and ϵ is the dielectric constant of interstitial fluid.

Finally, based on the structure data of the antigen and antibody from the PDB, namely the charges $\{q_n; n = 1 \ldots M+N\}$, the radii $\{\rho_n; n = 1 \ldots M+N\}$, the beads center-to-center distances $\{R_{m,n}; m, n = 1 \ldots M+N\}$, the medium parameters $\{A, \epsilon\}$ we have derived the relationship between the ADDS antigen-antibody density at the surface of the cell $y(t)$ and the ADDS extracellular concentration $x_E(t)$ as expressed in (22) and (23).

VI. COMSOL Multiphysics Simulation

In this section, we present the simulation scheme used to validate the MC-ADDS model in a realistic 3-D environment. COMSOL Multiphysics is a finite-element modeling (FEM) software package which helps to set up complex 3-D simulations involving different physical laws and models. In the interest to accurately capture the complexity of MC-ADDS systems, COMSOL is used here to simulate two important physical laws involved in the propagation of antibodies. First, the *fluid dynamics* (see Section VI-A) provide the time-varying blood velocity field in the blood vessels. Second, the *advection-diffusion* physics (see Section VI-B) provide the time-varying concentration of the antibodies transported in an anisotropic manner through the blood vessels and their surrounding tissues. By combining these two physical laws, COMSOL provides a realistic reference model for the spatio-temporal evolution of the antibody through the body.

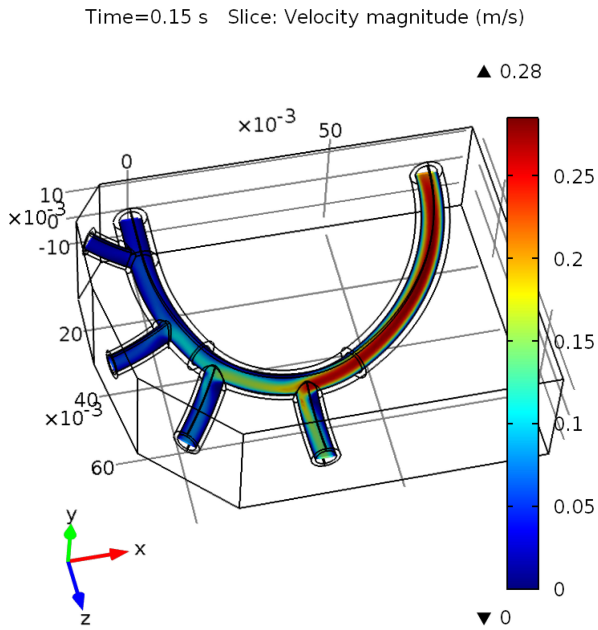

Fig. 7. COMSOL simulation of ADDS propagation in the vascular channel.

A. COMSOL Fluid Dynamics

The blood flow is simulated by COMSOL fluid dynamics simulations to predict the blood velocity field in the tridimensional coordinates inside the blood vessels. The blood flow is important since it is the main driving force transporting antibodies throughout the body. This realistic simulation is utilized to demonstrate that the assumption of uniform blood velocity in each blood vessel is valid for the analytical model. The uniform blood velocity allowed us to derive the simple expressions of time-varying impulse responses.

The COMSOL fluid dynamics is based on the Navier-Stokes equation. Blood is supposed to be an incompressible fluid in laminar flow with a density $\rho = 1060\ \mathrm{kg \cdot m^{-3}}$ and a fluid viscosity $\eta = 0.005\ \mathrm{Pa \cdot s}$. The Navier-Stokes equation is written as follows:

$$\rho\left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v}\right) = -\nabla p + f \tag{32}$$

where p is the blood pressure, v is the blood velocity, ρ denotes the blood density, ∇ is the vector differential operator, η is the fluid viscosity, and f represents forces applies by the blood vessel walls.

The geometry of the blood vessels network is presented in Fig. 7. The networks consists of 9 curved blood vessels. The 3-D data was obtained from the COMSOL simulation library and scaled down by a 100 factor to have the typical size of

TABLE I
NUMERICAL VALUES OF THE BLOOD PRESSURE AT THE INLETS AND OUTLETS OF THE BLOOD VESSELS NETWORK

i	0	1	2	3	4	5
$p_{i,0}$	11 208	11 148	11 148	11 148	11 148	11 148

TABLE II
PHYSIOLOGICAL LENGTHS AND RADII OF THE BLOOD VESSELS

Vessels	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8	V_9
Length [mm]	81	17	16	18	11	14	17	11	6
Radius [mm]	2.8	2.5	2.8	2.5	2.8	2.5	2.8	2.5	2.8

arterioles. The dimensions of the blood vessels are given in Table II. The blood vessels are surrounded by elastic vascular walls and muscles that apply stress on the surface of the blood vessels. The outlets and inlets of the blood vessel network are assumed to be open with a predefined blood pressure. The objective of the simulation is to verify that the MC analytical model properly predicts the diffusion through the walls and the diffusion along the radial dimension by comparing the end-to-end impulse response with the concentration at the output of the COMSOL simulated network given an initial concentration at the inlet of the network. The surrounding tissue is simulated as a thin diffusion layer in COMSOL with a porosity of 1.6.

The boundary conditions for COMSOLfluid dynamics consist of the time-varying pressure applied at the inlets and outlets of the blood vessel network. The pressure at a vessel i is denoted by $p_i(t)$ where t is the time-variable. The heartbeat period is supposed to be constant and equal to $1s$. The function $p_i(t)$ is expressed as follows:

$$\begin{cases} p_i(t) = p_{i,0}\sin(\pi t) & 0 \le t \le 0.5\,\mathrm{s} \\ p_i(t) = p_{i,0}\left(1.5 - 0.5\cos(-2\pi(0.5-t))\right) & 0.5 \le t \le 1\,\mathrm{s} \end{cases} \tag{33}$$

where $p_{i,0}$ are pressure constants in (Pa) for which the numerical values are available in Table I.

B. COMSOL Advection-Diffusion

The COMSOL advection-diffusion physics are modeled using the time-varying advection-diffusion equation in different domains of the simulated geometry. The geometry consists of two domains, namely the blood vessels and the ECM that surrounds it. Each domain is denoted by the index i. The advection-diffusion equation is expressed as follows:

$$\frac{\partial c}{\partial t} = \nabla\cdot(D\nabla c) - \nabla\cdot(\vec{v}c) + K_V\, c \tag{34}$$

where c_i is the antibody concentration in the domain i, D_i is the diffusion coefficient or matrix in the domain i and v is the blood velocity calculated from the COMSOL fluid dynamics physics, K_V is the nonspecific binding equilibrium constant between the antibody and the blood.

Between two domains, there is a molecular flux discontinuity, expressed by the following equation:

$$\begin{cases} -\mathbf{n}\cdot D_i = \frac{D_i}{D_j}(c_i - c_j) \\ -\mathbf{n}\cdot D_j = \frac{D_i}{D_j}(c_j - c_i) \end{cases} \tag{35}$$

where D_i and D_j are the diffusion coefficients or matrices for the domains i and j, respectively, c_i and c_i are the antibody concentrations in the domains i and j, respectively, and $\mathbf{n}$ is the unit vector normal to the surface boundary delimiting the two domains i and j.

The following equation describes the initial concentration antibodies at the time $t = 0$:

$$\begin{cases} c_0(x,y,z) = \frac{e^{-\frac{z^2}{2\sigma_0^2}}}{\sqrt{2\pi\sigma_0^2}}C_0 & x \ge x_0 \text{ and } z \le z_0 \\ c_0(x,y,z) = 0 & \text{otherwise} \end{cases} \tag{36}$$

where $\sigma_0 = 0.25\,\mathrm{mm}$, $C_0 = 1\,\mathrm{mol}\cdot\mathrm{L}^{-1}$, and $\sigma_0 = 0.35\,\mathrm{mm}$, $x_0 = 50\,\mathrm{mm}$, and z is the third Cartesian axis as shown in Fig. 7. A Gaussian function is used to have a smooth impulse, which helps to avoid numerical problems.

The inlets and outlets of the blood vessel network are assumed as open extremities, which is expressed by the following equation:

$$\mathbf{n}\cdot D\nabla c = 0\,. \tag{37}$$

The anisotropic diffusion matrix is defined in the curvilinear coordinates along the axis of the blood vessels.

Finally, the equations in (34), (35), (36), and (37) are applied to the geometry of the vascular channel in Fig. 7. COMSOL calculates the concentration $c(x,y,z,t)$ of the antibodies in the Cartesian coordinates $(x,y,z,)$ and time t.

VII. NUMERICAL RESULTS

In this section, we show numerical results which compare the MC-ADDS analytical model with a finite-element methods simulation model in a realistic 3-D geometry and show the significance of anisotropy. COMSOL- was used to simulate the propagation of antibodies using the complete advection-diffusion equation in a 3-D setting, and the effect of anisotropy on the impulse response of the system was evaluated.

Fig. 8 compares the mathematical model, derived in (7) and (8) from Section III, from the MC-ADDS paradigm incorporating the effect of anisotropy and the complete 3-D simulation with COMSOL on one blood artery. The translational and radial diffusion coefficients, calculated based on the bead model, have been used in both COMSOL and the MC-ADDS model. An excellent agreement between the two results is shown in the figure. This is to our knowledge the first work to validate through FEM the anisotropic transport of molecules undergoing advection and diffusion. The anisotropic diffusion coefficient was specified in COMSOL in matrix form in the cartesian coordinates, where the x and y represented the radial diffusion, and z represents the translational diffusion. The results show that MC anisotropic model will allow taking into account realistic diffusion environments that occur in biology.

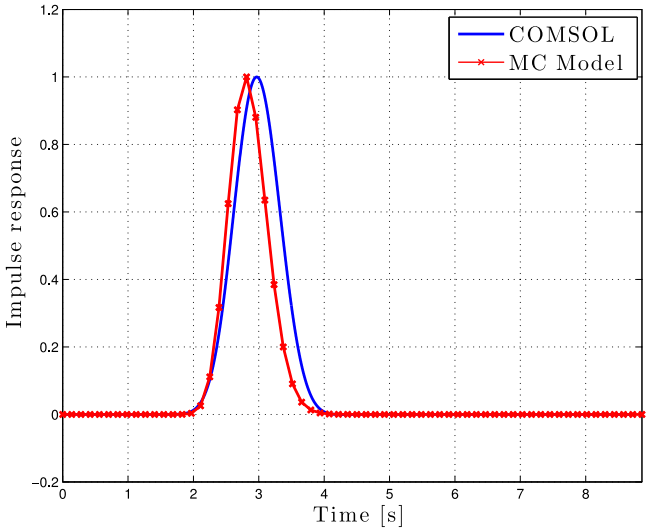

Fig. 8. Validation of the analytical impulse response with COMSOL simulation results.

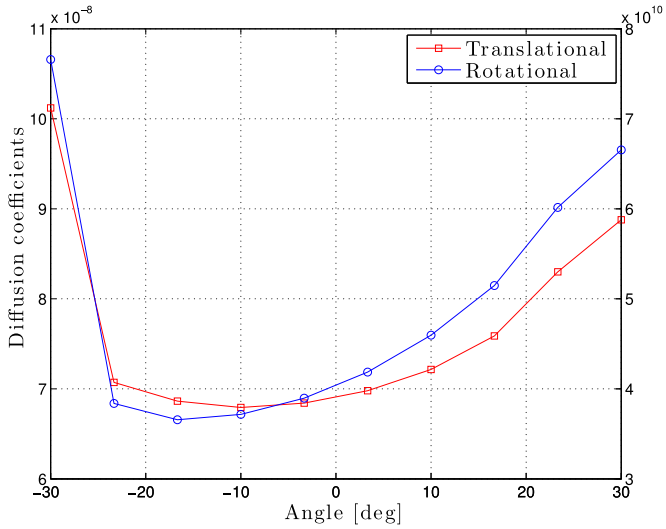

Fig. 10. Translational diffusion coefficient and rotational diffusion coefficients as functions of the angle between antibody arms.

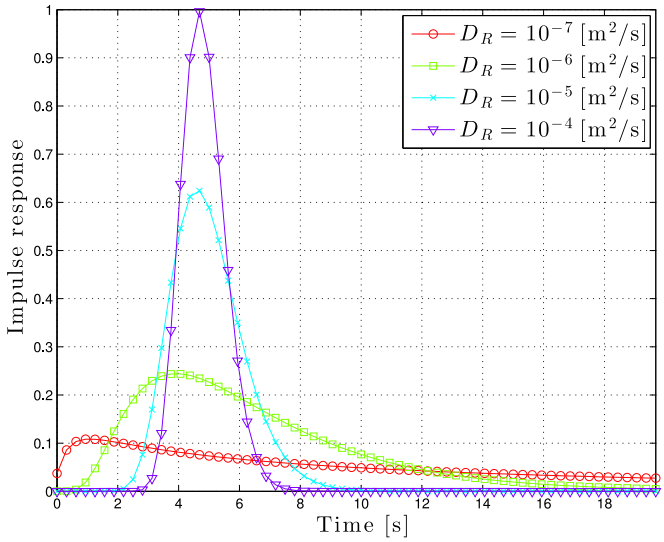

Fig. 9. MC Vascular Channel impulse responses for different radial diffusion coefficient D_R.

Fig. 9 illustrates how the normalized impulse response from (8) presented in Section III, varies highly depending on the radial diffusion coefficient. For a fixed translational diffusion coefficient, the radial diffusion coefficient was varied from $D_R = 10^{-7}\mathrm{m}^2/\mathrm{s}$ to $D_R = 10^{-4}\mathrm{m}^2/\mathrm{s}$. The numerical evaluations of the MC-ADDS extracellular impulse response for these different values show that the anisotropic transport due to a radial diffusion that is different from translational diffusion can have an important effect on the transport of antibodies. It can be seen that the impulse response is attenuated exponentially as a function of the radial diffusion coefficient. Therefore, radial diffusion coefficient is a critical parameter for the computational and numerical evaluation of MC-ADDS systems.

Fig. 10 shows the dependence of the anisotropic diffusion parameters on the angle between the arms of the antibody given by (14). from Section III-B. In this figure, our objective is to quantify the effect of changing the shape of the antibody on the diffusion parameters. The bead model of the antibody illustrated in Fig. 5 at Section V has been considered, and we have varied the angle between the two long arms of the antibody from -30° to 30°, and we have plotted the rotational diffusion coefficient D_Θ and the translational diffusion coefficient D_Z for these different shapes. Note that the change in shape can have a considerable effect on these two diffusion coefficient in a similar way. The more the molecule resembles a rectangular shape the higher the diffusion coefficient is, and the more the molecule resembles a spherical shape, the lower is the diffusion coefficient. This can be explained by the fact that a spherical shape maximizes the contact surface area of the antibodies, which causes more collisions, and therefore a higher diffusion coefficient due to Brownian motion.

Fig. 11 shows the effect of the different kinetic processes on the MC-ADDS end-to-end response by cascading the impulse responses of the different transport and kinetic processes through (7). The end-to-end impulse response is calculated for three different sets of parameters, each corresponding to either the color red, green, or blue, i.e. the end-to-end impulse response $h_1(t)$ is for $D_Z = 10^{-8}\,\mathrm{m}^2/\mathrm{s}$, $D_E = 10^{-9}\,\mathrm{m}^2/\mathrm{s}$, $C_{ag} = 0.01\,\mathrm{mol}/\mathrm{m}^2$, and $\Delta G = 5\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}$, the end-to-end impulse response $h_2(t)$ is for $D_Z = 5\cdot 10^{-8}\,\mathrm{m}^2/\mathrm{s}$, $D_E = 0.5\cdot 10^{-9}\,\mathrm{m}^2/\mathrm{s}$, $C_{ag} = 0.05\,\mathrm{mol}/\mathrm{m}^2$, and $\Delta G = 5\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}$, and the end-to-end impulse response $h_3(t)$ is for $D_Z = 10^{-7}\mathrm{m}^2/\mathrm{s}$, $D_E = 10^{-8}\,\mathrm{m}^2/\mathrm{s}$, $C_{ag} = 0.1\,\mathrm{mol}/\mathrm{m}^2$, and the antigen-antibody binding free energy $\Delta G = 5\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}$ obtained through (24) in Section V. For the vascular impulse response, we observe that increasing the translation diffusion coefficient of the antibodies increases the delay and the dispersion of the impulse response. The figures for the vascular and extracellular impulse response are normalized with regard to the maximum value of the impulse responses. The vascular impulse response

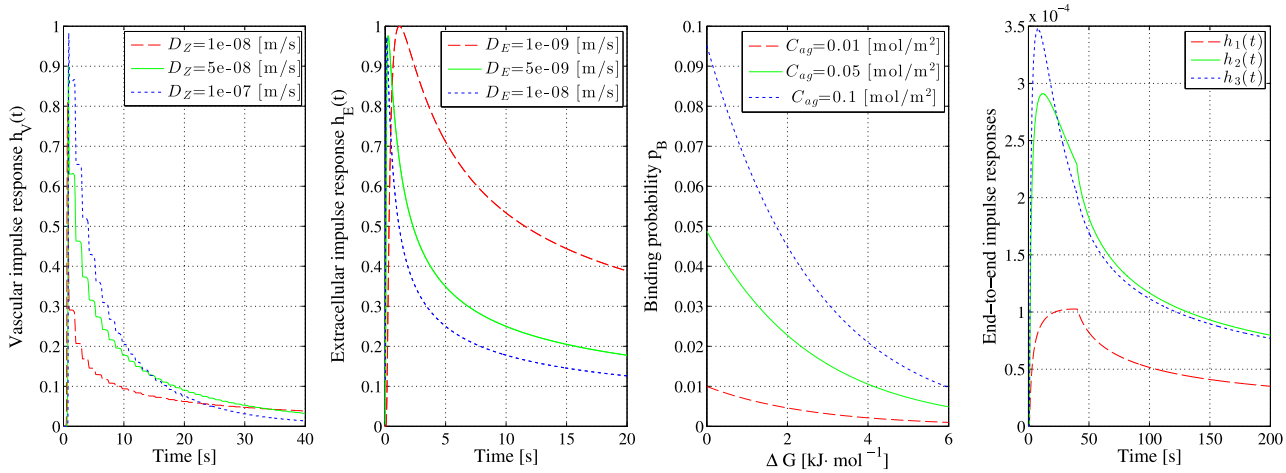

Fig. 11. Numerical evaluation of the MC-ADDS end-to-end response.

$h_V(t)$ shows some periodic sharp drops due to the periodicity of the heartbeat. For the extracellular impulse response $h_E(t)$, at a fixed association and dissociation kinetic set of parameters, the extracellular impulse response shows increased delay but decreased dispersion, due to the interplay of kinetic and diffusion parameters in the ECM. For the binding probability function p_B, we see that the concentration of antigens in the surface of the cells is a determining factor for the binding rate, and the higher the binding energy, the lower is the binding probability. This is explained by the fact that a high binding probability is more likely if the required energy for the antibody-antigen binding is low. The end-to-end impulse responses use the average values for the binding probability. The figure shows that the binding probability for these specific numerical values is the most significant factor in the end-to-end impulse response, and that although the vascular and extracellular parameters are very dissimilar for the green and blue end-to-end impulse response, the difference in the binding probability makes the two end-to-end impulse responses mostly the same.

MC-ADDS systems are remarkably complex due to the interplay of different kinetic and transport processes. The MC modeling approach allows capturing all the important kinetic parameters in a simple analytical expression and combining them together. The MC-ADDS approach makes it possible to evaluate numerically the effect of each of these kinetic parameters as well as the geometry of the disease and the physiology of the patient. Fig. 11 has shown that diffusion in the vascular space can exhibit a trend that is opposite to the one in the extracellular space. This means that values for the diffusion coefficient that are beneficial for the transport in the vascular channel may be detrimental in the extracellular channel. Therefore, there is a tradeoff value for the diffusion coefficient that improves transport in the vascular channel without sacrificing the transport in the extracellular transport. This is important for appropriate engineering the diffusion properties of the antibodies. The figure also shows the importance of the binding parameters, which remain the most critical barrier for the efficiency of ADDS. The numerical evaluation of these impulse responses and functions does not require important computational resources, which makes the optimization of MC-ADDS for a specific clinical scenario very tractable using this approach.

VIII. Conclusion

The Molecular Communication (MC) framework was used as an abstraction of antibody-mediated Drug Delivery Systems (ADDS), which is one of the therapeutic methods at the forefront of pharmacological research. The proposed MC model is based on the biophysical equations which govern antibody transport and kinetics in the human body. Analytical expressions of the impulse responses and drug delivery probabilities for the vascular transport, propagation in the ECM, and antigen binding were derived to mathematically capture ADDS. The transport and antigen-binding kinetics of ADDS are predicted based on the geometry of the human body, and the shape and electrochemical structure of the antibody-antigen compound.

The aim is to provide a novel model for ADDS based directly on the chemical and structural information about the antibody molecule. Based on the geometry and the charge of the ADDS constituting elements, we have derived the transport and binding parameters of the ADDS based on the theory of anisotropic diffusion and the thermodynamics of antibody-antigen interactions.

The derived MC model is based on the recent advances in mass transport theory to provide an analytical solution to the problem of ADDS transport. In the frame of the current, often over-complicated models of system biology, the proposed MC approach models the complex behavior of ADDS with a straightforward model. Using the MC paradigm, the ADDS transport from the point of injection to the interior of a cell has been abstracted as a cascade of MC channels, each characterized by an analytical impulse response. The MC-ADDS model studies the ADDS transport in the blood vessels, in the ECM, and through the ligand binding. Compared with existing models, the majority of the systems parameters are directly related to the physiology, instead of using empirical values that involve statistical estimations from experiments.

There are several important issues that remain to be investigated on the modeling of ADDS systems. First, an optimization framework should be devised to take advantage of the possibilities offered by the MC approach. Second, the interference from the immune system and the endocrine system should be added to the model as a feedback process to improve the targeting of the disease. Finally, the toxicity of ADDS should be quantified mathematically in this framework.

The MC-ADDS model allowed determining the parts of the human body which influence the efficiency of the drug delivery, and the ADDS molecule parameters that are critical to overcome the obstacles posed by these limiting parts. Moreover, the MC model showed how the shape and electrochemical structure simultaneously affects the transport and antigen-binding kinetics of the ADDS. Finally, the validation of the MC-ADDS model against finite-element simulations in a realistic 3D geometry has shown that the model is a good approximation for the anisotropic advection-diffusion in the complex geometry of the body. This analytical model can be readily used to predict, design, and optimize advanced drug delivery systems in a versatile and accurate manner, and to simulate sophisticated therapeutic scenarios.

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Youssef Chahibi (S'13) received the M.S. degree from the Georgia Institute of Technology, Atlanta, GA, USA, in 2012, and the Diplôme d'Ingénieur in Telecommunications and Networks from the Institut National Polytechnique de Toulouse, France, in 2011. He has been working toward the Ph. D. degree at the BWN Lab of the School of Electrical and Computer Engineering, Georgia Institute of Technology, since January 2012.

During 2011, he was a physical-layer Engineer at Alcatel-Lucent, Antwerp, Belgium. In Summer 2014, he was a guest research scholar at the Nano Communication Center (NCC) at Tampere University of Technology, and during 2015, he was a fellow of the Research Council of Norway at the Norwegian University of Science and Technology (NTNU) in Trondheim, Norway. His research interests include nanoscale biologically-inspired communications, and drug delivery systems.

Ian F. Akyildiz (M'86-SM'89-F'96) received the B.S., M.S., and Ph.D. degrees in Computer Engineering from the University of Erlangen-Nurnberg, Germany, in 1978, 1981, and 1984, respectively.

He is currently the Ken Byers Chair Professor in Telecommunications with the School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, USA, the Director of the Broadband Wireless Networking Laboratory, and Chair of the Telecommunication Group at Georgia Tech. He is an honorary Professor with the School of Electrical Engineering, Universitat Politecnica de Catalunya, Barcelona, Catalunya, Spain, and the Founder of N3Cat (NaNoNetworking Center in Catalunya). He is also an honorary Professor with the Department of Electrical, Electronic, and Computer Engineering, University of Pretoria, South Africa, and the Founder of the Advanced Sensor Networks Lab. Since 2011, he is a Consulting Chair Professor at the Department of Information Technology, King Abdulaziz University, Jeddah, Saudi Arabia. Since January 2013, he is also a Finland Distinguished Professor Program (FiDiPro) Professor supported by the Academy of Finland at the Department of Communications Engineering, Tampere University of Technology, , Finland. His current research interests include nanonetworks, and Long Term Evolution advanced.

Dr. Akyildiz is the Editor-in-Chief of *Computer Networks* (Elsevier) Journal, and the founding Editor-in-Chief of the *Ad Hoc Networks* (Elsevier) Journal, the *Physical Communication* (Elsevier) Journal, and the *Nano Communication Networks* (Elsevier) Journal. He is an ACM Fellow (1997). He received numerous awards from the IEEE and the ACM. According to Google Scholar as of October 2014, his h-index is 83 and the total number of citations he has received is 64 211.

Sasitharan Balasubramaniam (SM'14) received the Bachelor's degree in Electrical and Electronic Engineering from the University of Queensland, Qld., Australia, in 1998, the Master's degree in Computer and Communication Engineering from the Queensland University of Technology, Qld., Australia, in 1999, and the Ph.D. degree from the University of Queensland, in 2005.

He is currently an Academy of Finland Research Fellow at the Nano Communication Centre, Department of Electronic and Communication Engineering, Tampere University of Technology, Finland.

Dr. Sasitharan has published more than 70 papers and actively participates in a number of technical programme committee for various conferences. He is the General Co-Chair for ACM NANOCOM 2015 and was the TPC Co-Chair for ACM NANOCOM 2014 and IEEE MoNaCom 2011, both conferences which he co-founded. He is currently an Editor for the IEEE INTERNET OF THINGS journal and Elsevier *Nano Communication Networks*. His current research interests include bio-inspired communication networks, as well as molecular communications.

Yevgeni Koucheryavy (SM'09) received the Ph.D. degree from the Tampere University of Technology (TUT), Tampere, Finland, in 2004.

Prior joining TUT, he spent five years in the industry with R&D LONIIS, St. Petersburg, Russia, where he held various technical and managerial positions. He is an invited Expert for ITU-T and the Skolkovo Foundation (Russia) and acts as an External Reviewer for the state funding agencies of several European countries. He is currently a Professor with the Department of Communications Engineering, TUT. His current research interests include heterogeneous wireless communications and systems, network and services performance evaluation, Internet of Things, and machine-to-machine communications.