Molecular communication Model Of Nanoparticle-Body Interactions In Particulate Drug Delivery Systems

Youssef Chahibi
Broadband Wireless Networking Laboratory
School of Electrical and Computer Engineering
Georgia Institute of Technology
Atlanta, Georgia 30332, USA
E-mail: youssef@ece.gatech.edu

Massimiliano Pierobon
Department of Computer Science and Engineering
University of Nebraska-Lincoln
Lincoln, NE, 68508, USA
E-mail: pierobon@cse.unl.edu

Sang Ok Song
Bio Research Center
Samsung Advanced Institute of Technology
Gyeonggi-Do 449-712, Korea
E-mail: so4057.song@samsung.com

***Abstract*—Existing work in pharmacokinetics, the study of the movement of drugs in the body, has largely focused on multicompartmental models, based on ordinary first-order equations with constant flow. Nano-scale Particulate Drug Delivery Systems (PDDS) require better computational models. PDDS has been previously abstracted by the same authors as Molecular Communication (MC) systems, by solving the advection-diffusion problem with time-varying flow. In this paper, this framework is extended to solve the nanoparticle-body interactions problem. The delay and path loss of the system are expressed analytically. The results are validated by finite-element simulations. This model will enable more thorough pharmacokinetics than multicompartmental models.**

I. Introduction

Particulate Drug Delivery Systems (PDDS) [11] are therapeutic methods at the cutting-edge of nanomedicine, and they aim at providing a localized drug presence where the medication is needed while minimizing the effects of the drug on healthy parts of the body. The physicochemical interactions of a PDDS with the biological medium are important to capture due to their considerable implications on the distribution of the PDDS nanoparticles in the body [7][9]. These physicochemical interactions can be accurately measured *in vitro*, but, *in vivo* measurements are often not performed due to the ethical and financial constraints they pose [2].

For classical drug delivery methods, the drug propagation is computationally modeled using the multi-compartmental approach [13], where large sections of the human body are viewed as homogeneous compartments described by first-order different equations, and the drug evolution is studied in a large time scale, in the order of hours. Multi-compartmental models are not sufficiently accurate to study advanced drug delivery systems. Nanomedicine-enabled methods such as PDDS require new computational models where the drug interactions with the body are described with great precision at a much smaller time and space resolution.

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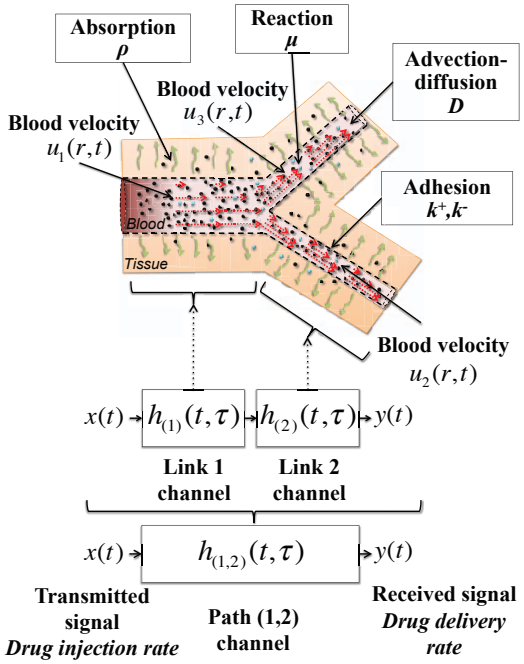

Figure 1. Scheme of the MC model of the physicochemical interactions of PDDS with the body.

We propose to model the physicochemical interactions of nanoparticles with the body at the level of each blood vessel using the Molecular Communication (MC) model [1], which is a communication paradigm where the information is conveyed through the transport of molecules. By modeling the reaction of nanoparticles in the blood, their adhesion and absorption by tissues and biological fluids, separately for each blood vessel in the body, we provide greater accuracy than classical multi-compartmental methods. Also, in contrast to the constant blood

flow approximation at the basis of the multi-compartmental models, we model here the time-varying characteristics of the blood flow, which significantly affects the drug propagation.

We have developed in [5] an MC model to calculate the time-varying blood velocity everywhere in the cardiovascular system and to predict the propagation of the drug due to advection-diffusion in the blood flow. In this paper, building upon our previous work, we include in the model the physicochemical interactions of nanoparticles with the human body, such as absorption, reaction, and adhesion, through the molecular communication paradigm. In this paper, we consider several physicochemical interaction processes, namely:

- The **advection-diffusion process**, which is the combination of two physical processes [10] [5]. First, the *advection process*, which is the transport of nanoparticles thanks to the blood velocity $u_i(r,t)$ in each blood vessel i, where r is the radial coordinate and t is a time variable. Second, the *diffusion process*, which is the movement of nanoparticles by Brownian motion, characterized by the diffusion coefficient D.
- The **absorption process**, characterized by the absorption rate ρ, which measures the absorption of nanoparticles by the tissues surrounding the blood vessels [8].
- The **reaction process**, characterized by the reaction rate μ, which is caused by the degradation of nanoparticles in the blood [3].
- The **adhesion process**, characterized by the adsorption process with rate k^+ and the desorption process with rate k^-, which are the phenomena of having other biomolecules stick to the nanoparticles. The adhesion of biomolecules on nanoparticles can severely affect the performance of the PDDS [14].

We focus on two important molecular communication metrics to evaluate the temporal and spatial distribution of the nanoparticles, namely:

- The **channel delay**, which is the time required for the injected nanoparticles to reach their maximal concentration at the delivery site.
- The **channel path loss**, which is the ratio between the number of nanoparticles that arrive at the delivery site over the number of nanoparticles that were initially emitted at the injection site.

The paper is organized is follows. In Sec. II, we describe the **MC model** that takes into account all the physicochemical interaction processes, namely, advection-diffusion, absorption, reaction, and adhesion, and enables the prediction of the delivery rate of the nanoparticles. In Sec. III, we provide a **performance analysis** of a PDDS through the MC paradigm by defining and expressing the *channel delay* and the *channel path loss*. In Sec. IV, we explain the validation with multiphysics finite element simulation of the MC model for PDDS. In Sec. V, the **numerical results** are presented for the performance analysis and the validation of the model. Finally, Sec. VI concludes the paper with comments about the validity of the model and the effect of the parameters of the physicochemical interaction processes on the performance of a PDDS.

II. Molecular Communication System Model

In this section, we describe the molecular communication channel model of a PDDS which takes into account all the physicochemical interactions that occur to the nanoparticles from the injection site to the delivery site. We first describe how one blood vessel is modeled as a molecular communication link in Sec. II-A. Second, in Sec. II-B, we describe how the physicochemical interactions along the path from the injection site to the delivery site can be modeled by combining the molecular communication links.

The interconnection of blood vessels is here abstracted as a blood network. Fig. 1 illustrates the physicochemical interactions in a blood network consisting of three blood vessels. The blood velocity in a blood vessel i is denoted as $u_i(r,t)$, where r is the radial coordinate, and t is the time variable. The drug propagates in this blood network subject to an absorption with rate ρ, reaction with rate μ, adhesion with adsorption rate k^+ and desorption rate k^-, diffusion with coefficient D, and advection due to the blood velocity. The drug propagation is viewed as an MC link channel, and completely describes the relationship between the drug injection rate, which is the MC transmitted signal, at the inlet of the blood vessel and the drug delivery rate, which is the MC received signal, at the outlet of the blood vessel with a time-varying impulse response $h_{(i)}(t,\tau)$, according to the time variable τ, for every blood vessel i ($i = 1, 2, 3$). The MC link channels i are cascaded to form an MC path, which relates the drug injection rate $x(t)$ to the drug delivery rate $y(t)$ thanks to the time-varying impulse response for the path channel, denoted, e.g. , by $h_{(1,2)}(t,\tau)$ for the cascade of the MC link 1 and the MC link 2.

A. Molecular Communication Link Model

We found that the input-output expression in a blood vessel i between the injection rate $x_i(t)$ and the delivery rate $y_i(t)$ is governed by the following expression [5]:

$$y_i(t) = \int_{-\infty}^{+\infty} x_i(\tau) h_{(i)}(t,\tau) d\tau \,, \tag{1}$$

where $h_{(i)}(t,\tau)$ is the time-varying impulse response of the blood link i, and is a function of the time variables t and τ. It should be noted that the equation in (1) is not a convolution, since $h_{(i)}(t,\tau) \neq h_{(i)}(t-\tau)$ because of the time-variance. We derived an analytical expression of the time-varying impulse response of the blood link i which is a function of all the physicochemical interaction process parameters and the dimensions of the blood vessel i, as follows:

$$h_{(i)}(t,\tau) = \frac{\exp\left(-\frac{(l_i - m_i(t,\tau))^2}{2\sigma_i^2(t,\tau)} - \mu(t-\tau)\right)}{\sqrt{2\pi\sigma_i^2(t,\tau)}} \,, \tag{2}$$

where:

- $m_i(t,\tau)$ depends on the *apparent velocity* $\bar{v}_i^{p_i}(t)$, which is the observed average velocity of an ensemble of drug particles, in the link i as follows:

$$m_i(t,\tau) = \int_\tau^t \bar{v}_i^{p_i}(t')dt' \,, \tag{3}$$

where p_i is the physicochemical interaction process in the blood vessel i, which can be either $p_i = reaction$, $p_i = absorption$, $p_i = adhesion$, or $p_i = none$, and t and τ are time variables. We did not consider the case where both absorption and adhesion are present at the same time, because absorption is a special asymptotic case of adhesion where the desorption rate is close zero.
- $\sigma_i^2(t,\tau)$ depends on the *effective diffusivity* $D_i^{p_i}(t)$ as follows:

$$\sigma_i^2(t,\tau) = 2\int_\tau^t D_i^{p_i}(t')dt' \,, \tag{4}$$

where p_i is defined above.
- μ characterizes the *reaction process*, and represents the reaction rate of the nanoparticles with the blood.

In the following, we express the apparent velocity $\bar{v}_i^{p_i}(t)$ and the effective diffusivity $D_i^{p_i}(t)$ for the cases of advection-diffusion (Sec. II-A1), absorption (Sec. II-A3), and adhesion (Sec. II-A3).

1) No Reaction Case: When there is no reaction, and only the advection-diffusion is considered, the *apparent velocity* $\bar{v}_i^{none}(t)$ and the *effective diffusivity* $D_i^{none}(t)$ are

$$\begin{cases} \bar{v}_i^{none}(t) = \bar{u}_i(t) \\ D_i^{none}(t) = D + \frac{\bar{u}_i^2(t) r_i^2}{192D} \,, \end{cases} \tag{5}$$

which is a result we derived in [5].

2) Absorption Case: When there is absorption by the tissues surrounding the blood vessels, the *apparent velocity* $\bar{v}_i^{absorption}(t)$ and the *effective diffusivity* $D_i^{absorption}(t)$ are [4]

$$\begin{cases} \bar{v}_i^{absorption}(t) = \left(1 + \frac{2}{15}\rho_i\right) \bar{u}_i(t) \\ D_i^{absorption}(t) = D + \frac{\bar{u}_i^2(t) r_i^2}{192D} \left(1 - \frac{4}{15}\rho_i\right) \,, \end{cases} \tag{6}$$

where ρ_i is the blood absorption rate in the blood vessel i. This is derive (7), we used a method similar to the work in [4] by stochastic methods, with the difference that we considered circular instead of parallel plates geometry.

3) Adhesion Case: When there is adhesion to the proteins in the blood plasma or to the blood vessel walls, the *apparent velocity* $\bar{v}_i^{adhesion}(t)$ and the *effective diffusivity* $D_i^{adhesion}(t)$ are [12]

$$\begin{cases} \bar{v}_i^{adhesion}(t) = \frac{1}{1+\frac{k_i^+}{k_i^-}} \bar{u}_i(t) \\ D_i^{adhesion}(t) = \frac{r_i^2 \bar{u}_i^2(t)}{48D} \frac{44 r_i^2 \left(\frac{k_i^+}{k_i^-}\right)^2 + 12 r_i^2 \frac{k_i^+}{k_i^-} + r_i^3}{\left(r_i + 2\frac{k_i^+}{k_i^-}\right)^3} \\ \quad + \frac{2\bar{u}_i^2(t) r_i^2 \frac{k_i^+}{k_i^-}}{k^- \left(r_i + 2\frac{k_i^+}{k_i^-}\right)^3} \end{cases} , \tag{7}$$

where $\bar{u}_i(t)$ is the cross-sectional average blood velocity and k_i^+ and k_i^- are the adsorption and the desorption coefficients in the blood vessel i, respectively. The derivation is based on expressing the mean and variance of the particle positions, starting from the differential equation of the particle movement, and the boundary conditions at the blood vessel wall.

We provide numerical values for the cross-sectional average blood velocities of three blood vessels in Sec. IV-B, which are used for the simulation in Sec. IV, and were obtained using the transmission line method described in [5].

B. Molecular Communication Path Model

The molecular communication channel model of a path $(i_1, ...i_n, ..., i_N)$ where i_n is the index of a link i, which gives the input-output relationship between the drug injection rate $x(t)$ at the inlet of the link i_1 and the drug delivery rate $y(t)$ at the outlet of the link i_N, is obtained by using the *Harmonic Transfer Matrix* function $HTM\{\cdot\}$ and its inverse $HTM^{-1}\{\cdot\}$ [5]

$$y(t) = \int_{-\infty}^{+\infty} x(\tau) h_{(i_1,...i_n,...,i_N)}(t,\tau)d\tau \,, \tag{8}$$

where the time-varying impulse response of the path $h_{(i_1,...i_n,...,i_N)}$ is calculated as follows:

$$h_{(i_1,...i_n,...,i_N)} = HTM^{-1}\left\{ \prod_{k=N}^{k=1} HTM\left\{h_{(i)}(t,\tau)\right\} \right\} \,, \tag{9}$$

where $h_{(i)}(t,\tau)$ is the time-varying impulse response of the blood link i, defined in Sec. II-A, and it is a function of the time variables t and τ.

III. Performance Analysis

In this section, we analyze the performance of a PDDS by using the MC paradigm through the definition of the channel delay and the channel path loss. The channel delay is the time required by nanoparticles at the injection site to reach their maximal concentration at the delivery site. The channel path loss measures how many of the nanoparticles are lost due to the vessels branching, reaction, adhesion, and absorption.

A. Channel Delay

The channel delay t_{delay} for the path $(i_1, ..., i_n, ..., i_N)$ is defined as

$$t_{delay} = \frac{1}{T}\int_0^T \arg\max_{t>\tau} h_{(i_1,..,i_N)}(t+\tau,\tau)d\tau \tag{10}$$

where $h_{(i_1,...,i_n,...,i_N)}(t,0)$ is the time-varying impulse response of the path $(i_1, ..., i_n, ..., i_N)$, defined in II-B with injection starting at the time τ, and T is the heartbeat period.

The channel delay t_{delay} is defined in (10) as the average time required for the drug concentration to reach its maximum level at the delivery site. Since the channel is time-varying, because of the periodic blood flow changes, an injected drug nanoparticle will arrive with a different delay at the delivery site depending on the blood velocity that was in the body at the time of the injection. We take into account the ambiguity

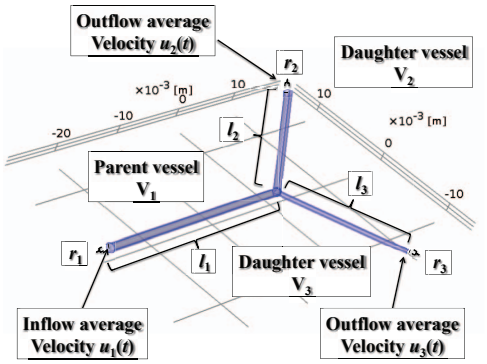

Figure 2. Topology of the blood vessel network considered for the multiphysics finite-element simulation validation.

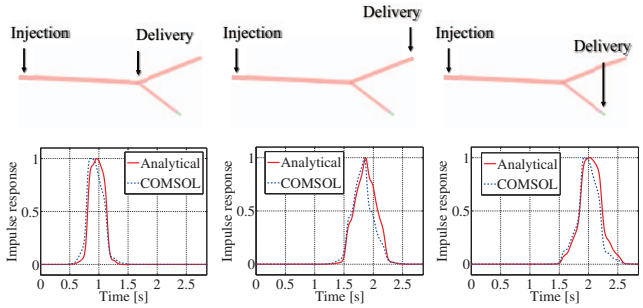

Figure 3. Comparison between the impulse responses obtained by the molecular communication model and the impulse responses obtained by the multiphysics finite-element simulation technique for different delivery sites at the outlet of the blood vessels V_1, V_2, and V_3, respectively.

in knowing the blood velocity at the time of injection by averaging over the delay for all possible blood velocity states.

B. Channel Path Loss

The channel path loss for the path $(i_1, ..., i_n, ..., i_N)$ is defined as

$$L = -10\log_{10}\left(\int_0^{+\infty} h_{(i_1,..,i_N)}(t,0)dt\right) + 20\log_{10}\left(\frac{r_{i_1}}{r_{i_N}}\right) \quad (11)$$

where $h_{(i_1,...,i_n,...,i_N)}(t,0)$ is the time-varying impulse response of the path $(i_1, ..., i_n, ..., i_N)$, defined in Sec. II-B with injection starting at the time $\tau = 0$, r_{i_1} is the radius of the first blood vessel in the path, and r_{i_N} is the radius of the last blood vessel in the path. This relationship comes from expressing the ratio between the number of nanoparticles at the injection site and the number of nanoparticles at the delivery site. We use the log-scale because about $30\% - 60\%$ of the nanoparticles are lost at every blood vessel bifurcation, making the particle loss follow a geometric trend, therefore obtaining the expression in (11).

IV. Validation with Multiphysics Finite-Element Simulation

The validation is carried out using COMSOL Multiphysics ® [6], a finite element simulation software package, which enables combining several physical phenomena together. In the following we define a topology, boundary conditions for computing the blood velocity, and initial conditions for computing the drug propagation impulse response.

A. Topology

In the scope of the paper, we defined a blood network as the interconnection of three blood vessels V_i, where i is the blood vessel index ($i = 1...3$). The *parent blood vessel* V_1 bifurcates into two blood vessels, the *daughter blood vessel* V_2 and the *daughter blood vessel* V_3. The blood vessel V_i has a radius r_i and a length l_i, for $i = 1...3$. We take $r_1 = 0.5\ mm$, $r_2 = 0.45\ mm$, $r_3 = 0.3\ mm$, $l_1 = 25\ mm$, $l_2 = 22.5\ mm$, $l_3 = 15\ mm$.

Table I
Blood network boundary conditions numerical values

k	$p_{k,1}$	$q_{k,1}$	$p_{k,2}$	$q_{k,2}$	$p_{k,3}$	$q_{k,3}$
1	116.457	116.457	104.699	104.699	87.918	87.9180
2	-0.002	0.322	0.005	0.293	-0.021	0.2369
3	-0.202	0.079	-0.185	0.081	-0.146	0.0351
4	-0.106	-0.097	-0.105	-0.089	-0.057	-0.0714
5	0.028	-0.073	0.025	-0.072	0.021	-0.0407
6	0.016	-0.023	0.016	-0.023	0.009	-0.0124
7	0.036	-0.020	0.036	-0.020	0.019	-0.0119
8	0.027	0.022	0.026	0.023	0.016	0.0104
9	0.003	0.016	0.002	0.016	0.003	0.0088
10	0.001	0.013	0.000	0.013	0.002	0.0079

B. Blood Velocity Boundary Conditions

The multiphysics finite-element simulation allows to define boundary conditions, which are values defined at the surfaces of the blood network, and then searches for numerical solutions that obey the physical equations. The boundary conditions used are the blood velocities in the surface boundaries of the network $(\bar{u}_i(t); i = 1, 2, 3)$. Since the boundary conditions $\{\bar{u}_i(t); i = 1...3\}$ are time-varying and periodic, we express them in terms of their Fourier series decomposition as follows:

$$\bar{u}_i(t) = \sum_{k=-N}^{k=N} p_{k,i} sin(k\omega_0 t) + q_{k,i} sin(k\omega_0 t)\,, \quad (12)$$

where $\omega_0 = 2\pi/T$ is the radial sampling frequency, T is the heartbeat period, N is the number of Fourier components, $\{p_{k,i}; k = -N, -N+1, ..., N-1, N\}$ and $\{q_{k,i}; k = -N, -N+1, ..., N-1, N\}$ are the even and odd Fourier coefficients, respectively, and t is the time variable.

C. Drug Propagation Initial Conditions

The drug propagation initial conditions describe the initial values of the drug concentration in the blood network at the time $t = \tau$. We express the initial drug concentration $c_1(x, y, z, t = \tau)$ in the blood vessel V_i as a function of the Cartesian coordinates, with the origin at the center of the inlet of the blood vessel i, and the $\vec{x}_i$ axis along the longitude of the blood vessel. We approximate the drug injection impulse [5] with a Gaussian function with a low variance.

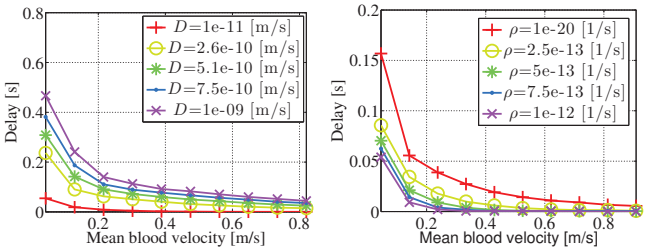

Figure 4. Effect of the diffusion coefficient D and the absorption rate ρ on the channel delay.

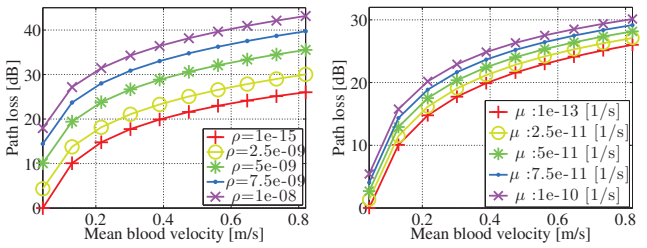

Figure 5. Effect of the absorption rate (ρ) and the reaction rate (μ) on the path loss.

D. Impulse Response Evaluation

The impulse responses $h_{(i)}(t,\tau)$ are evaluated at the outlets of the blood vessels V_i where $i = 1...3$. We evaluate the impulse response $h_{(i)}(t,\tau)$ as:

$$h_{(i)}(t,\tau) = \frac{1}{S_{O_i}} \int_{M(x,y,z)\in O_i} c_i(x,y,z,t)dxdydz \qquad (13)$$

where O_i designates the surface at the outlet of the blood vessel i, S_{O_i} is the surface area of O_i, $M(x_i,y_i,z_i)$ is a point in O_i, and $c_i(x,y,z,t)$ is the concentration at the time instant t and the point with the coordinates (x_i,y_i,z_i).

V. Numerical Results

A. Molecular Communication Channel Delay and Path Loss

In Fig. 4, we observe the effect of the blood velocity, the drug diffusion coefficient and the reaction rate on the delay of the channel. In our evaluated scenario, the drug diffusion coefficient increases the delay of the channel, while the effect of the absorption rate is to reduce the delay. In Fig. 5. We notice that reaction or absorption have almost similar effects in terms of path loss. For the absorption, we notice that an increased absorption rate reduces the delay, which may seem counterintuitive. The reduction in delay for increased absorption can be explained by the fact that the absorption reduces the number of particles in the flow that are in proximity to the walls, which are the slowest moving particles, which increases the average velocity of all the particles.

B. Multiphysics Finite-Element Simulation Results

In Fig. 3, we compare the impulse responses obtained by multiphysics finite-element simulation, as described in Sec. IV-D, with the analytical results obtained using the molecular communication model described in Sec. II. We used $D = 10^{-8}\ m^2/s$ and $\rho = 1e-5$. We compare the results for all three blood vessels V_1, V_2, and V_3, and we notice in the three cases that there is good agreement between the values generated through the simulation and the model.

VI. Conclusion

In this paper, we have extended the molecular communication model for particulate drug delivery systems to take into account different physicochemical interaction processes such as reaction, absorption, adhesion, in addition to the advection-diffusion. The performance of the particulate drug delivery systems has been evaluated in terms of communication metrics such as delay and path loss, which are important criteria to evaluate the performance of the PDDS. We computed the performance metrics of the PDDS with the molecular communication model, and we evaluated them through the molecular communication model using the multiphysics finite-element simulation. The molecular communication paradigm has proven to be a well-adapted, accurate, and flexible paradigm to model and analyze complex particulate drug delivery systems.

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