Molecular Communication Noise and Capacity Analysis for Particulate Drug Delivery Systems

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***Abstract*—Particulate Drug Delivery Systems (PDDS) are therapeutic methods that use nanoparticles to achieve their healing effects at the exact time, concentration level of drug nanoparticles, and location in the body, while minimizing the effects on other healthy locations. The Molecular Communication (MC) paradigm, where the transmitted message is the drug injection process, the channel is the cardiovascular system, and the received message is the drug reception process, has been investigated as a tool to study nanoscale biological and medical systems in recent years. In this paper, the various noise effects that cause uncertainty in the cardiovascular system are analyzed, modeled, and evaluated from the information theory perspective. Analytical MC noises are presented to include all end-to-end noise effects, from the drug injection, to the absorption of drug nanoparticles by the diseased cells, in the presence of a time-varying and turbulent blood flow. The PDDS capacity is derived analytically including all these noise effects and the constraints on the drug injection. The proposed MC noise is validated by using the kinetic Monte-Carlo simulation technique. Analytical expressions of the noise and the capacity are derived, and MC is presented as a framework for the optimization of particulate drug delivery systems (PDDS).**

***Index Terms*—Drug delivery systems, nanonetworks, molecular communication, time-varying channels, communication channels, intra-body communication, noise modeling, capacity, kinetic Monte-Carlo.**

I. Introduction

PARTICULATE drug delivery systems (PDDS) are therapeutic methods that use drug nanoparticles to specifically target the cause of the disease while avoiding to affect other healthy parts of the body. Drug nanoparticles are able to penetrate inside the body cells to deliver therapy, and therefore can bypass all physiological barriers that are in place inside the human body to protect it from foreign elements. The PDDS aims to engineer drug nanoparticles not only in terms of their chemical properties, size, and shape, but also in terms of the injection pattern, location, and other mechanisms that enable the optimal reception of drug nanoparticles by the diseased cells. By analyzing the PDDS, it is possible to know exactly where the drug accumulates in the body, measure the efficiency of the PDDS solution, and optimize the drug injection pattern.

The modeling of complex spatiotemporal dynamics of drug nanoparticles has been identified as one of the major challenges to develop a new generation of efficient therapies [31]. From the drug injection site, to the absorption by diseased cells, the nanoparticles undergo several biophysical processes that are noisy in nature. In this paper, an analytical noise model of the PDDS in the human body is derived, reflecting all the possible noise effects for the PDDS. First, the drug injection may suffer from imprecision due to the injection device limitations, the pressure difference between the syringe and the blood flow, and the creation of turbulences around the needle. Second, the nanoparticles are randomly dispersed by the possibly turbulent blood flow in an intricate network of irregularly shaped blood vessels, and exhibiting Brownian motion. Third, the penetration of drug nanoparticles to the tissues surrounding the blood vessels is complicated by the stochastic nature of the chemical reactions, and the time-varying mechanical forces interfering with these chemical reactions.

Our previous work in [7] uses transmission line theory to obtain the blood velocity everywhere in the cardiovascular system, and uses the theory of Taylor dispersion to obtain the deterministic drug propagation in the body from the injection to the delivery point. In this paper, the Fokker-Planck equation and the theory of inhomogeneous Poisson processes are used to mathematically derive a new stochastic and information-theoretical framework to model the random transport and binding of nanoparticles in the cardiovascular system and to quantify the effect of noise through the use of the concept of the information-theoretical capacity. This analysis uses the expressions obtained in [7] to estimate several parameters, namely the blood velocities and the PDDS drug propagation probability. The noise and capacity analysis fills an important limitation in [7] in regards to the random behavior of drug nanoparticles. An end-to-end Molecular Communication (MC) framework is proposed to analyze the noise effects in the PDDS. The novel MC paradigm [1], where the information is conveyed through molecules, instead of the conventional electromagnetic signals, is employed to enable the communication in biological environments that are governed by molecular signals, such as bacterial communication [2], [18], with the long-term aim of establishing communication networks between nanomachines inspired by intracellular signaling.

In the literature, the noise effects in the intercellular communication are shown to have both beneficial and detrimental effects in intracellular MC [32]. The noise in MC by diffusion

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is analyzed in relation to the underlying physical processes [25]. Also, the stochastic effects in the ligand-receptor binding kinetics and interference are modeled through the MC framework [26], [24]. The maximum achievable information rates in diffusion-based MC under the constraints of Brownian motion noise are derived in [23] by using a novel thermodynamic information theoretical framework. These existing models rigorously reflect the unique noise effects in MC, but they cannot be directly applied for the PDDS in the complex cardiovascular network [7], because they assume linear time-invariant channel models for the propagation medium, which is not realistic to assume in the cardiovascular system where the blood flow is highly time-varying, and they suppose diffusion in the free and isotropic space (i.e. the molecules propagate in all the Cartesian directions in the same manner and without any obstacles), while the MC in the cardiovascular system is confined to the complex topology of blood vessels. The MC reception of nanoparticles is also heavily affected by the blood flow that interferes with the chemical interactions between ligands and receptors [9].

In addition to the analysis of the noise effects in the PDDS, the use of information theory is proposed to evaluate the performance of the PDDS through the MC paradigm. The main objective of the PDDS is to engineer a system that can induce a therapeutic effect in the location where it is needed. The desired drug delivery at the location of the disease may vary from one individual to another, depending on the nature and the stage of the illness, the genomics that greatly affect the binding of drug nanoparticles to the receptors in the diseased cells [28], and the desired intensity of the treatment. Therefore, it is highly desirable that, for a given clinical setting, the PDDS can be employed effectively and reliably for the treatment of a diversity of individuals. In this paper, the PDDS is considered to be similar to a communication system, where the drug injection which corresponds to a signal transmission, induces the drug reception which corresponds to a signal reception, after being distorted by the human body which corresponds to the communication channel. Through this paradigm, the set of desired responses may be viewed as an alphabet of different responses $\mathbf{y}_A, \mathbf{y}_B, \ldots, \mathbf{y}_Z$, etc. If the PDDS can reliably deliver different kinds of responses unambiguously at the same time, this PDDS can be qualified to be very performant. The size of this alphabet can be measured in bits (1 bit for two possible different therapeutic responses, 2 bits for four possible different therapeutic responses, etc.). The existing PDDS models are mostly based on deterministic approaches, while stochastic approaches are mainly developed for the purpose of statistically estimating the required parameters of the system from experimental results. In this paper, based on the comprehensive model of the noise effects in PDDS, the capacity of the PDDS under the constraints of the noise effects is mathematically derived, and this concept is used to evaluate the performance of the PDDS. The expression of the capacity can be used as an objective function encompassing all the PDDS parameters in order to optimize its design and the drug injection rate. In classical communication theory, this optimization is solved through the water-filling algorithm which assists in designing the transmitted signal in such a way that most of the power is used in clear channel conditions, and the power is minimized in noisy channel conditions. Similarly, in the PDDS, this analysis will enable to construct a drug injection rate that transmits most of the valuable drug nanoparticles when the chances of having them absorbed are high, and a minimal amount of drug nanoparticles when the chances of their non-targeted dispersion is inevitable.

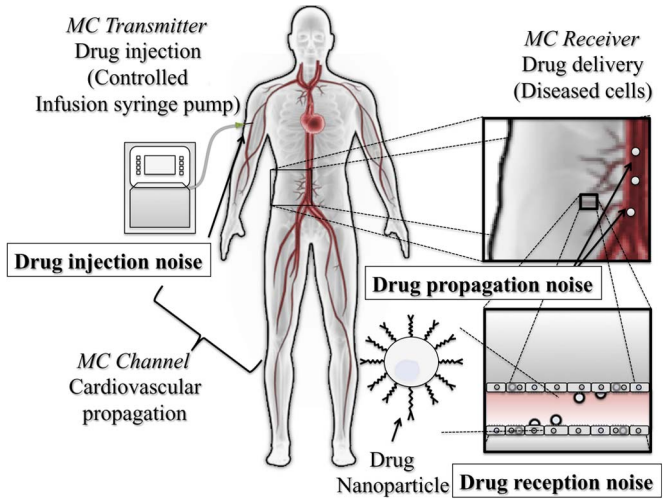

Fig. 1. MC noise effects in particulate drug delivery systems.

The paper is organized as follows: First, in Section II, all the noise effects that exist in the PDDS are presented, which are going to be modeled by using the MC paradigm. Second, in Section III, the elements of the MC abstraction of the PDDS noise effects are presented, and the notion of capacity in the PDDS is defined and justified. Third, the MC end-to-end drug reception noise is derived in Section IV. Fourth, in Section V, the MC capacity of the PDDS is derived within an information theoretical framework, and is expressed as a function of all parameters of the noise effects from the drug injection to the drug reception by diseased cells. Fifth, a kinetic Monte-Carlo scheme of the PDDS in the cardiovascular system is described in Section VI, and the numerical results from this scheme are compared with the analytical MC noise. Finally, Section VII concludes the paper by discussing the key outcomes of the MC noise modeling for the PDDS, the PDDS capacity, and its application to the design and optimization of the PDDS.

II. PDDS Noise Scheme

The **PDDS noise scheme** consists of all the noise effects that affect the injection, propagation, and reception of drug nanoparticles. As illustrated in Fig. 1, the following noise effects are identified in the PDDS:

- The **drug injection noise** is caused by the mechanical limitations of the drug injection device. The drug injection device is a computer-controlled infusion syringe pump that allows the control of the drug injection rate in the drug injection site. This device is likely to suffer from imperfections that cause an inaccurate drug injection rate. Also, the drug injection device cannot be controlled arbitrarily fast, because of the mechanical friction and compression phenomena occurring in the pump. In addition, the drug injection rate is limited by the toxicity level. All these

effects will be considered for the MC noise and capacity modeling of the PDDS.

- The **drug propagation noise** is due to the stochastic nature of the motion of drug nanoparticles in a possibly turbulent blood flow. After being injected, drug nanoparticles are lost randomly at the level of blood vessel bifurcations, towards organs and tissues where their effect is not desired. Especially at high concentration levels, drug nanoparticles become more agitated, causing a noticeable Brownian noise effect, since drug nanoparticles try to move from the regions with high concentration to the regions with low concentration.
- The **drug reception noise** affects the reception of drug nanoparticles by the diseased cells. In fact, the ligand-binding interactions by which drug nanoparticles bind to the surface of diseased cells is very stochastic. The diseased cells surface is a site where different kinds of energies interact, such as the kinetic energy due to the blood flow, the chemical energy of reaction between the ligands and the receptor, characterized by a chemical potential, and the thermal energy related to the Brownian motion in the blood medium. The small surface of interaction, irregularities in the cells, the weakness of the chemical affinity between ligands and receptor, and the negative effect of blood flow, which impede the drug delivery to the diseased cells.

These noise effects are numerous, complex, and interdependent, making their modeling tedious and challenging. However, the MC paradigm is well suited to address these issues. In fact, it provides a comprehensive PDDS noise from the drug injection to the drug reception, and enables the performance evaluation of the PDDS through the concept of the capacity.

III. MC Noise and Capacity Abstraction for the PDDS

The **MC Noise And Capacity Abstraction for the PDDS** provides the model of the noise effects in the PDDS, how the aggregate consequences of the noise effects are evaluated by using the concept of the capacity, and how the noise is validated by using kinetic Monte-Carlo simulations. As illustrated in Fig. 2, the PDDS is modeled as an MC channel with the following components:

- The **MC Transmitter** represents the drug injection device, which applies a *drug injection rate* $x(t)$ at the *drug injection site*, where the drug injection device syringe is inserted.
- The **MC Channel** reflects the effect of the blood flow on the propagation of drug nanoparticles in a complex network of interconnected blood vessels. As presented in our previous work [7], the PDDS channel is characterized by a *time-varying drug propagation probability* $h(t,\tau)$, and by cross-sectional blood velocities in every blood vessel l, denoted by $\{u_l(t); l \in CV\}$.
- The **MC Receiver** is the set of the diseased cells that require the PDDS therapeutic effect. The MC receiver, located in the *drug reception rate* $y(t)$, receives drug nanoparticles through the ligand-binding mechanism. This mechanism allows ligand-coated drug nanoparticles to have a high affinity to receptors located in the surface of the diseased cells. The MC reception is complicated due to the fact that the influence of the blood flow on the affinity between ligand and receptors varies periodically with time.

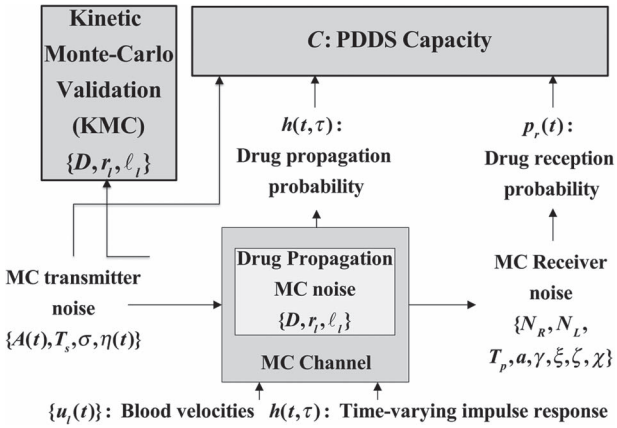

Fig. 2. Elements of the MC abstraction of the noise effects in the PDDS, and their relationship with the PDDS capacity.

MC noises for all the components of the PDDS system are provided. These noises are derived individually and then combined to obtain the aggregate effect of the end-to-end drug reception noise in the PDDS, as follows:

- The **drug injection noise** describes the noise limitations of the drug injection device. This model depends on the maximum injection rate $A(t)$, the sampling period T_s, the average drug injection constraint, and the drug leakage rate $\eta(t)$. In Section IV-A, these noise limitations are formulated depending on the pump injection syringe.
- The **drug propagation noise** depends on the drug diffusivity D and the topology of the cardiovascular system. In Section IV-B, a detailed probabilistic derivation of the drug propagation noise is provided, which gives the *drug propagation probability* $h(t,\tau)$, where t and τ are time variables.
- The **drug reception noise** gives the probability that drug nanoparticles located in the drug reception site are received by the diseased cells through the ligand-binding mechanism. This model depends on the number of ligands in a drug nanoparticle N_L, the number of receptors in the diseased cells N_R, the temperature T_p, the drug nanoparticle spheroid dimensions, with a radius a and an aspect-ratio γ, the maximum attraction distance ξ, the bond equilibrium length ζ, the characteristic length χ, and the cross-sectional average blood velocity at the drug reception site $u_l(t)$. In Section IV-C, these parameters are explained in detail, and are related to the *drug reception probability* $p_r(t)$.

These noise effects are aggregated to obtain an end-to-end model of the MC noise effects for the PDDS. In this paper, it is found that the drug reception rate $y(t)$ is an inhomogeneous

Poisson process related to the drug injection rate $x(t)$ through the following relationship:

$$y(t) \sim Pois\left(p_r(t)\eta(t) + \int_{-\infty}^{+\infty} h(t,\tau)p_r(t)x(\tau)d\tau\right), \quad (1)$$

where $Pois(.)$ denotes the Poisson distribution.

Based on the result in (1), the MC capacity of the system is presented which is a measure derived from information theory quantifying how much the drug injection rate $x(t)$ can reliably affect the drug reception rate $y(t)$ under the constraints of the various aforementioned noise effects. The capacity is found to be expressed as:

$$C_N = T_s \sum_{m=1}^{M} \psi_m \left(\sum_{n=1}^{N} \alpha_{n,m} A_n p_m\right), \quad (2)$$

where $\alpha_{n,m}$ is an expression of the drug propagation probability and the drug reception probability at the drug injection time sample n and the drug reception time sample m, A_n is the maximum non-toxic number of drug nanoparticles at the time nT_s, p_m is a coefficient depending on the maximum drug reception rate and the drug reception noise, m is the drug injection time sample, n is the drug reception time sample, M is the length of the discretized MC channel memory, N is the length of the drug injection rate $x(t)$, $\psi_m(\cdot)$ is a function depending on the drug injection noise parameters, the drug leakage rate, and the drug injection time sample m. The MC channel for the PDDS is unique in many senses. First, it is not Gaussian, as it is often assumed to derive the capacity in molecular and electromagnetic communications. Second, all its parameters are time-varying. Third, the PDDS channel has important memory effects due to the spread by diffusion.

Regarding inter-individual variations, one of the main advantages of the MC approach is that all system parameters are directly related to the physiology of the patient and the chemical properties and shape of drug nanoparticles (cf. Fig. 2). This allows the design of personalized medicine that is specific to each individual. The existing pharmacokinetic models use statistical methods to estimate the parameters of the system, which are valid only for one individual. The MC model allows the incorporation of individual variabilities mathematically.

Finally, the PDDS end-to-end noise is validated by comparing the results with simulation obtained by a kinetic Monte-Carlo scheme presented in Section VI.

IV. Drug Delivery Noise

The **drug reception noise** allows to probabilistically describe the noise effects from the drug injection to the drug reception. Here it is shown that the drug reception rate $y(t)$ is an inhomogeneous Poisson process related to the drug injection rate $x(t)$ as expressed in (1).

A. Drug Injection Noise

The **drug injection noise** is composed of all limitations and noise effects that are caused by the imperfections of the drug injection device, as illustrated in Fig. 3. Our PDDS scheme

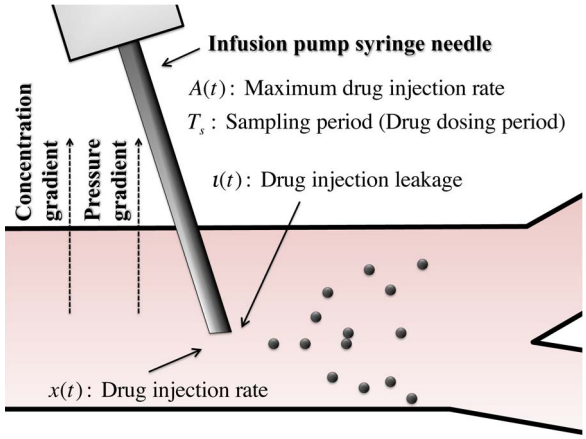

Fig. 3. Elements of the drug injection noise.

requires that the drug injection rate is controllable. Here the drug injection rate is assumed to be modulated by an infusion pump syringe, which is connected to a computer system. The computer system is programmed to induce a desired drug injection rate by changing the pressure of the infusion pump. The drug injection device creates the following limiting factors:

- The **injection leakage**, which is the uncontrolled leaking of drug nanoparticles from the tip of the needle. The pump infusion syringe can leak drug nanoparticles because of the concentration gradient between the drug solution, and the pressure difference between the needle and the blood flow. The leakage is independent of the drug injection rate $x(t)$. Since the blood flow is periodic, the drug leakage rate varies periodically, and creates additional drug nanoparticles in the drug reception site. The the drug reception rate is expressed as follows:

$$y(t) = g\left(x(t)\right) + \eta(t), \quad (3)$$

  where $g(x(t))$ represents the part of the drug reception rate that is dependent on the drug injection rate $x(t)$. Since the drug propagation is linear, the drug delivery rate $\eta(t)$ depends on the *drug syringe spill rate* $\iota(t)$ as follows:

$$\eta(t) = g\left(\iota(t)\right). \quad (4)$$

  The leakage is supposed to be slower than the drug injection. Therefore, the drug leakage rate $\eta(t)$ is also sampling rate limited by the sampling period T_s.
- The **maximum injection rate** is limited, because the drug injection rate should not create a drug concentration of drug nanoparticles that is toxic to the location where the drug is injected. This constraint is expressed as follows:

$$x(t) \leq A(t), \quad (5)$$

  where $A(t)$ is a periodic function $(A(t) = A(t+T))$, which specifies the maximum drug injection rate during a heartbeat period, and T is the blood velocity period. The maximum drug injection rate will vary with time due to the periodic blood flow.
- The **sampling rate** is the maximum rate at which the drug injection can be changed in time. This rate is limited by the mechanical deficiencies of the pump infusion syringe,

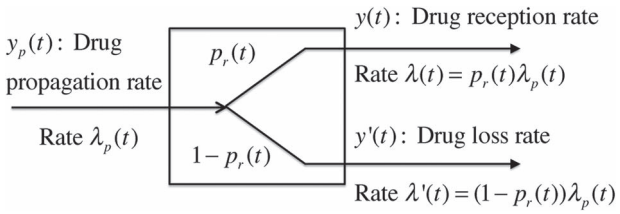

Fig. 4. Drug nanoparticle reception as the time-varying splitting of an inhomogeneous Poisson process.

such as the friction of the syringe rubber piston, or the presence of small compressible gas bubbles in the solution. Therefore, the drug injection cannot be arbitrarily fast. The maximum sampling rate limitations is expressed as follows:

$$|f| \geq \frac{1}{T_s} \Longrightarrow X(f) = 0, \tag{6}$$

where f is the frequency and $X(f)$ is the frequency transform of the drug injection rate $x(t)$.

B. Drug Propagation Noise

The **drug propagation noise** gives a probabilistic description of the presence of drug particles in the delivery site. The drug propagation along the cardiovascular system is noisy because of the Brownian motion of drug nanoparticles, which are randomly dispersed in the blood vessels, and lost at vessel bifurcations to regions of the body where the drug is not needed. Here it is shown that drug nanoparticles that propagate to reach the drug reception site, given a drug injection rate, is expressed as follows:

$$y_p(t) \sim Pois\left(\eta(t) + \int_{-\infty}^{+\infty} h(t,\tau)x(\tau)d\tau\right), \tag{7}$$

where $y_p(t)$ is the drug propagation rate which denotes the number of drug nanoparticles that reach the drug reception site at the time t as shown in Fig. 4.

1) Drug Propagation Poisson Binomial Noise: This gives the drug propagation rate $y_p(t)$ at the drug reception site, given a drug injection rate $x(t)$, as a function of the probability that one single drug nanoparticle injected at the time τ in the drug injection site is located at the drug reception site at the time t, which is denoted by $p_s(t,\tau)$, which is the *single drug nanoparticle propagation probability* developed in Section IV-B2. The drug propagation Poisson binomial model expresses the drug propagation rate $y_p(t)$ as a function of the drug injection rate $x(t)$ as follows [16]:

$$P\left[y_p(t) = k\right] = \frac{1}{K}\sum_{n=0}^{K-1} e^{\frac{-2ink\pi}{K}} \times \prod_{m=1}^{K-1}\left(1 + (e^{\frac{2ik\pi}{K}} - 1)p_s(t, mT_s)\right), \tag{8}$$

where k is the number of nanoparticles that reach the drug reception site after propagation in the cardiovascular system, $p_s(t, mT_s)$ is the probability that one single nanoparticle injected at a time τ at the drug injection site is delivered at the time mT_s at the drug reception site, the number of trials K is the total of injected nanoparticles expressed as:

$$K = \sum_{n=0}^{N-1} x(nT_s), \tag{9}$$

with N the number of time samples drug injection rate $x(t)$, such as the drug injection rate $x(t)$ is written as a sequence of Dirac impulses with different weights, as follows:

$$x(t) = \sum_{n=0}^{N-1} x(nT_s)\delta(t - nT_s). \tag{10}$$

The aforementioned relationship is proved by considering the probability that k nanoparticles among a batch of $x(nT_s)$ nanoparticles, all injected at the time nT_s, reach the drug reception site at the time t. The probability that exactly k nanoparticles among the ones enveloped in the drug injection rate $x(t)$ be delivered at the time t is the probability that the total number of nanoparticles among the N different batches that are successfully delivered is equal to k. In other words, the number of successful nanoparticle receptions is a sum of independent Binomial trials each with different probabilities of success. Therefore, $y_p(t)$ follows a *Poisson binomial distribution* [15], where the number of trials is the total number of nanoparticles enveloped by the drug injection rate $x(t)$, and the success rates are the probabilities of the drug delivery for each nanoparticle m, with $m = 0, \ldots, N-1$, as expressed by (8).

2) Single Nanoparticle Propagation Noise: This provides a description of the random movement of one nanoparticle injected in the cardiovascular system. In this section, an expression of the probability that one single nanoparticle injected at a time τ at the drug injection site is delivered at the time t close to the drug reception site is provided for this model. The probability that one single drug nanoparticle is delivered at the drug reception site at the time t if it is injected at the time τ is denoted as $p_s(t,\tau)$. A single drug nanoparticle delivery is found to follow a Bernoulli distribution with probability $p_s(t,\tau)$ that is equal to $h(t,\tau)$. This is proved based on the analogy between the advection-diffusion equation and the Fokker-Planck equation, which is the basis of the random motion of drug nanoparticles. A deterministic model of the movement of drug nanoparticles in the cardiovascular system is proposed in [7]. The deterministic model was based on the generalized Taylor dispersion equation that governs the cross-sectional concentration of drug nanoparticles $c(z,t)$ under the effect of advection by a fluid with cross-average velocity $u(z,t)$ and effective diffusivity $D_{eff}(t)$, as follows:

$$\frac{\partial c(z,t)}{\partial t} = -u(t)\frac{\partial u(z,t)}{\partial z} + D_{eff}(t)\frac{\partial^2 c(z,t)}{\partial z^2}, \tag{11}$$

where ∂ is the symbol for the partial derivative. Since the advection-diffusion equation does not capture the micro-scale

variations in the propagation of nanoparticles, the deterministic model that solves it is only adequate for describing the average space and time evolution of the movement of drug nanoparticles. Therefore, a stochastic model is needed to reflect both the macro-scale and micro-scale variations in the movement of drug nanoparticles.

The stochastic nature of drug nanoparticles is described by the Fokker-Planck equation [22]. The Fokker-Planck equation is the basis of dynamic techniques for obtaining the random path of a drug nanoparticle subject to Brownian motion [6]. The one-dimensional form of the Fokker-Planck equation states that the position $z(t)$ of the drug nanoparticles at the time t has a probability density function $p(z,t)$ governed by the following equation:

$$\frac{\partial p(z,t)}{\partial t} = -\frac{\partial \mu(z,t)p(z,t)}{\partial z} + \frac{\partial^2 D(z,t)p(z,t)}{\partial z^2}, \tag{12}$$

where $\mu(z,t)$ is the nanoparticle drift related to the advection process and $D(z,t)$ is a function related to the diffusion process, such as, in the micro-scale, the position $z(t)$ of the nanoparticle is incremented by the random process $dz(t)$ obeying the following stochastic differential equation:

$$dz(t) = \mu\left(z(t),t\right)dt + \sqrt{2D\left(z(t),t\right)}dw(t), \tag{13}$$

where $dw(t)$ is called a Wiener process, with the following probability density function:

$$f_{w(t)}(z) = \frac{1}{\sqrt{2\pi t}} e^{-\frac{z^2}{2t}}. \tag{14}$$

The generalized Taylor dispersion (11) and the Fokker-Planck (12) have the same form, and therefore, by assuming spatially uniform drift and diffusivity, and by taking the drift term $\mu(z,t)$ to be equal to the cross-sectional average velocity $u(t)$, the equations become identical. Given that these equations are linear, it is possible to conclude that the deterministic solution of the advection-diffusion equation $c(z,t)$ and the probability density function of the movement of a drug nanoparticle $p(z,t)$ are equal to each other up to a multiplicative constant, i.e.:

$$p(z,t) = \frac{1}{c_0} c(z,t), \tag{15}$$

where c_0 is the multiplicative constant, which is obtained from the fact that the integral of the probability density function over the entire space and time is equal to one, i.e.:

$$c_0 = \int\limits_{z \in CV} \int_{-\infty}^{+\infty} c(z,t) dz dt, \tag{16}$$

where CV denotes the spatial domain in the cardiovascular system, z is the space coordinate, and t is the time coordinate. From the results above, the probability density function that describes the drug propagation rate $y_p(t)$ close to a drug reception site by interpreting the time-varying impulse response $h(t,\tau)$ at a drug reception site for an input at drug injection site can be expressed as a probability density function. The time-varying drug propagation probability of the PDDS $h(t,\tau)$ is equal to the drug propagation rate $c(z,t)$ at the longitudinal coordinate $z = \ell_l$ with a drug injection rate $x(t)$ equal to an impulse $\delta(t-\tau)$ centered around the time τ, as expressed in the following:

$$c(z,t)|_{x(t)=\delta(t-\tau), z=\ell_l} = p(z,t)|_{z=\ell_l}. \tag{17}$$

It follows by definition that:

$$h(t,\tau) = p_s(t,\tau). \tag{18}$$

Therefore, the probability that k nanoparticles ($k \in \{0,1\}$), injected at the time $t-\tau$ at the drug injection site, are delivered at the time t at the drug reception site is expressed by the following:

$$P\left[y_s(t) = k\right] = h^k(t,\tau)(1-h(t,\tau))^{1-k}, \tag{19}$$

where $y_s(t)$ denotes the number of drug nanoparticle located at the drug reception site.

3) Drug Propagation Poisson Noise: This provides an approximation of the drug propagation Poisson binomial noise described in Section IV-B1. By using Le Cam's theorem [20], a Poisson binomial distribution can be approximated by a Poisson process with a rate equal to the sum of the probabilities of the Poisson binomial distribution. Therefore:

$$y(t) \sim Pois\left(\lambda(t)\right), \tag{20}$$

where $Pois(\lambda(t))$ denotes an inhomogeneous Poisson process with rate $\lambda(t)$. The rate $\lambda(t)$ is equal to the following:

$$\lambda(t) = \int_{-\infty}^{+\infty} x(\tau)h(t,\tau)d\tau. \tag{21}$$

C. Drug Reception Noise

The **drug reception noise** provides the probability that particles that reach the drug reception site after propagating in the cardiovascular system will be received by the diseased cells, which are here modeled as an MC receiver, through the adhesion to the cells and absorption into the interior of the cell. This reception process is characterized by a **drug reception probability** $p_r(t)$. The time-variance is due to the periodic blood flow, which affects the ligand-binding mechanism by which drug nanoparticles are received by the diseased cells.

The study of MC stochastic receiver models is proposed in [26] in a diffusion-based environment, which allows simulating the random behavior of the chemical reactions of an MC receiver. Such diffusion-only MC models would not accurately describe the ligand-binding reception in a flow-dominated environment. In fact, several qualitative and experimental studies [9], [30] have shown that flow creates a shear stress along the blood vessel walls, which significantly affects the deposition and the reception of the drug nanoparticles.

The MC receiver proposed here is based on the mathematical modeling of receptor-mediated endocytosis of nanoparticles under shear stress, which means the absorption of drug

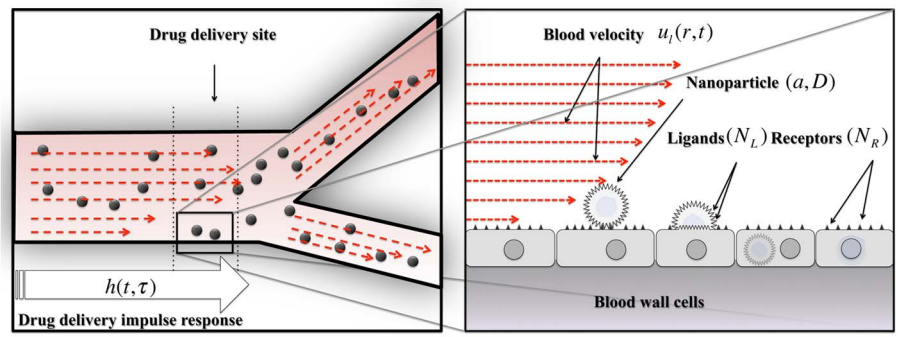

Fig. 5. Ligand-binding reception scheme.

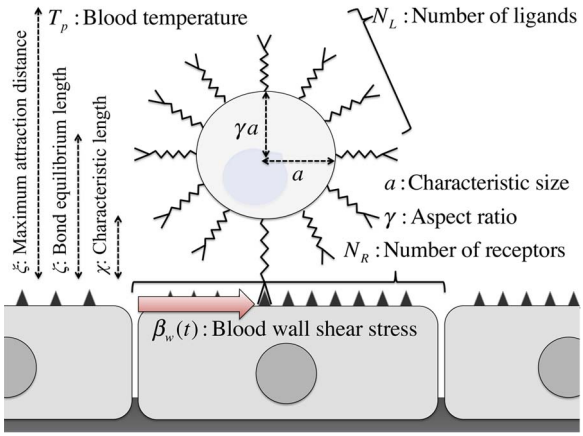

Fig. 6. Elements of the drug reception noise.

nanoparticles inside blood vessel wall cells under the effect of the blood velocity [14]. As shown in Fig. 5, this model is extended by taking into account the blood velocity $u_l(r,t)$ in the drug reception site, the size of the diseased region, and the parameters of the drug nanoparticle coating. The MC receiver model scheme is pictured in Fig. 6. The MC receiver is affected by the following elements and parameters:

- The **nanoparticle characteristic size** a, which is equal to the radius for a sphere.
- The **nanoparticle aspect ratio** γ, which is equal to the ratio between the polar diameter and the equatorial diameter of a spheroid-shaped nanoparticle. It is equal to one for a sphere.
- The **number of ligands** N_L is the total number of ligands that cover the nanoparticle surface. The ligands are supposed to be uniformly distributed on the surface of the nanoparticle. The density of the ligands is assumed to be the same for all nanoparticles.
- The **number of receptors** N_R is the total number of receptors that are available in the drug reception site. It is supposed that there are more receptors than ligands (i.e. $N_R \gg N_L$).
- The **ligand-receptor bond characteristic length** χ, which is the distance between the ligand and the receptor when they are bound together without any external force affecting the bond, and which is approximately equal to 0.1 nm.
- The **ligand-receptor bond equilibrium** ζ, which is the distance between the ligand and the receptor when they are bound together in equilibrium under the effect of shear stress.
- The **ligand-receptor maximum attraction length** ξ, which is the maximum distance between the ligand and the receptor at which the bonding is possible.

It is supposed that a drug nanoparticle is delivered when at least one stable bond is established between the nanoparticle and the drug reception site. This work is based on classical results from [13] and [27]. In this paper, the relationship between the drug reception probability and the time-varying blood velocity is derived. The resulting drug reception probability $p_r(t)$ can be expressed as:

$$p_r(t) = \pi r_0^2 m_R m_L e^{-\frac{\chi a \beta_w(t)}{k_B T_p r_0 m_R}\left(\left(\frac{a}{\gamma}+\zeta\right)F_s + \frac{a^2}{r_0}R_s\right)}, \tag{22}$$

where:

- r_0 is the radius of the section of the nanoparticle located at a ligand-receptor maximum attraction length ξ from the blood vessel wall cells, and is expressed as follows:

$$r_0 = a\sqrt{1-\left(1-\frac{\xi-\zeta}{a}\gamma\right)^2}. \tag{23}$$

- m_R is the receptor surface density, defined as follows:

$$m_R = \frac{\gamma N_R}{\frac{4}{3}\pi a^3}. \tag{24}$$

- m_L is the ligand surface density, defined as follows:

$$m_L = \frac{\gamma N_L}{\frac{4}{3}\pi a^3}. \tag{25}$$

- k_B is the Boltzmann constant, which is approximately equal to the following:

$$k_B = 1.4806488 \times 10^{-23}\ \mathrm{m^2 kg\ s^{-2}\ K^{-1}}. \tag{26}$$

- T_p is the blood temperature, which is approximately equal to 310 K.
- F_s is a coefficient that is proportional to the drag force due to the blood flow, and is equal to $F_s = 6 + (10.416 - 0.8280\gamma + 0.768\gamma^2 + 0.54\gamma^3)e^{-\gamma}$, with γ the nanoparticle aspect ratio.

- R_s is a coefficient that is proportional to the rotational moment of force due to the blood flow, and is equal to $R_s = 8 + (-164 - 372\gamma - 280\gamma^2 + 71.6\gamma^3)e^{-\gamma}$ with γ the nanoparticle aspect ratio.
- $\beta_w(t)$ is the wall shear stress, which is derived below. Supposing the approximation of blood flow as a Newtonian fluid, by definition, the shear stress $\beta_w(t)$ at the wall is expressed as $\tau = \mu\beta_w(t)$, where μ is the blood dynamic viscosity, which is approximately equal to $\mu = 4.88 \times 10^{-3}$ Pa.s, and $\beta_w(t)$ is the wall shear rate, defined as:

$$\beta_w(t) = \left.\frac{\partial u(r,t)}{\partial r}\right|_{r=r_l}, \tag{27}$$

where r_l is the radius of the blood vessel located in the drug reception site. Based on a result from [29], the shear rate is time-varying, and can be expressed as follows:

$$\beta_w(t) = \frac{1}{2i\pi r_l}\int_{-\infty}^{+\infty}\frac{\alpha^2(\omega)W(\omega)}{1-W(\omega)}U_l(\omega)e^{i\omega t}d\omega, \tag{28}$$

where i is the imaginary unit number, ω is the radial frequency, and $\alpha(\omega)$ is the Womersley number, defined as $\alpha(\omega) = r_l\sqrt{\frac{\omega}{\nu}}$. $W(\omega)$ is the Womersley function, defined as:

$$W(\omega) = \frac{2J_1\left(\alpha(\omega)\, i^{\frac{3}{2}}\right)}{\alpha(\omega)i^{\frac{3}{2}}J_0\left(\alpha(\omega)i^{\frac{3}{2}}\right)}, \tag{29}$$

which is expressed as a function of the Bessel function of the first kind, and, respectively, of the zero and first order, $J_0(\cdot)$ and $J_1(\cdot)$ [3]. $U_l(\omega)$ is the Fourier transform of the cross-sectional average blood velocity $u_l(t)$ in the drug reception site, which is expressed as follows:

$$U_l(\omega) = \int_{-\infty}^{+\infty} u_l(t)e^{-i\omega t}dt. \tag{30}$$

Biologically plausible numerical values are used for the parameters for the PDDS. For the numerical evaluation, it is considered that the nanoparticle size to be $a = 20$ μm, the maximum attraction length $\xi = 10^{-8}$ m, the bond characteristic length $\zeta = 5 \cdot 10^{-9}$ m, the receptor density $m_R = 5 \cdot 10^{13}$ m^{-2}, the ligand density $m_L = 3 \cdot 10^{-3}$ m^{-2}, the blood density $\rho = 1.06 \cdot 10^3$ kg $\cdot$ m^{-3}, the blood kinematic viscosity $\nu = 4.603 \cdot 10^{-6}$ m$^2 \cdot$ s^{-1}, and a spherical nanoparticle shape with $\gamma = 1$. The dimensions and topology of the considered portion of the arterial network are presented in Fig. 9. The blood velocity network is calculated by using the same numerical values as in [7]. These numerical values can be used to extrapolate for individuals of different ages by using empirical laws such as the Preece-Baines model, which conforms to the human growth curve [5]. Fig. 7 shows how the drug reception probability changes with respect to time during one heartbeat period. The numerical evaluations show that properly designing the time pattern of the drug reception rate $y(t)$ can highly affect the efficiency of the PDDS.

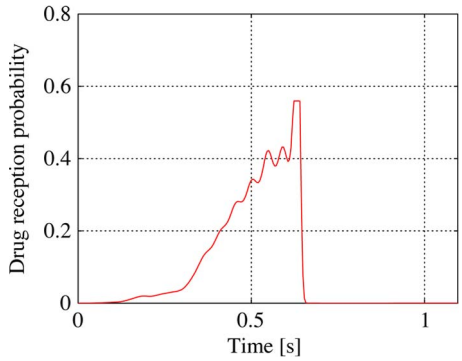

Fig. 7. Drug reception probability in the drug reception site as a function of time.

D. End-to-End Drug Reception Noise

The **end-to-end drug reception noise** provides a model of the noise effects from the injection to the reception of drug nanoparticles by the diseased cells. This model is based on the drug injection noise (Section IV-A), the drug propagation noise (Section IV-B), and the drug reception noise (Section IV-C). The following relationship between the drug reception $y(t)$, and the drug injection rate $x(t)$, is obtained through this model as expressed in (1). To prove the expression in (1), the property of splitting inhomogeneous Poisson processes [17] is used. In fact, based on the Poisson approximation of the drug propagation model presented in Section IV-B3, the drug propagation rate $y_p(t)$ is an inhomogeneous Poisson process with rate $\lambda_p(t)$ expressed as follows:

$$\lambda_p(t) = \eta(t) + \int_{-\infty}^{+\infty} h(t,\tau)x(\tau)d\tau. \tag{31}$$

The delivered drug nanoparticles are received by the diseased cells according to the drug reception probability $p_r(t)$ presented in Section IV-C. By using a property of the splitting inhomogeneous Poisson processes [17] illustrated in Fig. 4, the drug reception rate is also an inhomogeneous Poisson process with rate $\lambda(t)$ expressed as follows:

$$\lambda(t) = p_r(t)\lambda_p(t). \tag{32}$$

V. Capacity Analysis of the PDDS

Here the capacity of the PDDS expressed in (2) is derived based on the drug delivery noise developed in Section IV. The **average mutual information** I of the PDDS is defined as:

$$I = \lim_{N\to\infty}\frac{1}{N}I(\mathbf{x}_N;\mathbf{y}_N), \tag{33}$$

where lim is the limit symbol, the **drug injection sequence** $\mathbf{x}_N$ represents the drug injection rate, and is defined by $\mathbf{x}_N = [x_1,\ldots,x_n,\ldots,x_{N-1}]$, where **the n-th drug injection sample** x_n is the number of drug nanoparticles injected at the time nT_s and N is the length of the drug injection sequence $\mathbf{x}_N$, the **drug reception sequence** $\mathbf{y}_N$ represents the drug reception rate, and is defined by $\mathbf{y}_N = [y_1,\ldots,y_m,\ldots,y_{N+L-2}]$ where **the m-th drug reception sample** y_m is the number of drug nanoparticles

delivered during the time interval $[mT_s, (m+1)T_s[$, and L is the channel memory. $M = N + L - 1$ is the length of the drug reception sequence. The channel memory is defined as the number of time samples for which any drug injected at the time τ is no longer observed at any time t larger than $\tau + LT_s$. The memory is here considered finite, such as $\forall\, t, \tau \in \mathbb{R}\ t \leq \tau + LT_s \Longrightarrow h(t,\tau) = 0$, and $I(\mathbf{x}_N; \mathbf{y}_N)$ is the **mutual information** between the random drug injection sequence $\mathbf{x}_N$ and the random drug reception sequence $\mathbf{y}_N$.

A. Drug Injection Sequence

The drug injection sequence consists of N time samples of the drug injection rate, such as it is possible to write the drug injection sequence as $\mathbf{x}_N = [x(nT_s)|n = 0, \ldots, N-1]$. By using the Dirac function, the drug injection rate $x(t)$ can be expressed as a function of the drug injection sequence $\mathbf{x}_N$ as follows:

$$x(t) = \sum_{n=0}^{N-1} x_n \delta(t - nT_s), \tag{34}$$

where N is the length of the drug injection sequence $\mathbf{x}_N$. The drug injection rate is composed of N Dirac functions, each delayed by n time samples, and weighted by the number of injected nanoparticles at the time nT_s. The drug injection sequence $\mathbf{x}_N$ is subjected to the two following constraints:

- the **toxicity constraint**, which limits the number of injected nanoparticle to a maximum allowed toxicity level. Beyond the toxicity level, the drug injection has an adverse effect on the body. This constraint is written as follows:

$$\forall n \in \{0, \ldots, N-1\}\ x_n \leq A_n. \tag{35}$$

- the **average number of injected nanoparticles** σ, which can be written as follows:

$$\frac{1}{N} \sum_{n=0}^{N-1} x_n = \sigma. \tag{36}$$

B. Drug Reception Sequence

The drug reception sequence is a sequence of M random variables $[y_m|m = 0, \ldots, M-1]$, which represent the number of delivered nanoparticles during each the T_s-long m-th time duration. It is shown here that the number of nanoparticles delivered during the time interval $[mT_s, (m+1)T_s[y_m$, which is called the m-th drug reception sample, follows a Poisson distribution with rate λ_m expressed as $y_m \sim Pois(\lambda_m)$, where the rate λ_m is expressed as:

$$\lambda_m = \eta_m T_s + \sum_{n=0}^{N-1} x_n \alpha_{n,m}, \tag{37}$$

with η_m the discrete drug leakage rate in the drug reception site at the m-th time sample (i.e. $\eta_m = \eta(mT_s)$), and:

$$\alpha_{n,m} = \int_{mT_s}^{(m+1)T_s} h(t, t - nT_s) p_r(t) dt. \tag{38}$$

where $h(t, t - nT_s)$ denotes the time-varying drug propagation probability with injection time $t - nT_s$ and observation time t. In the following part of this section, the derivation of the result in (37) is presented. The result is obtained in (37) by moving from the continuous domain of Poisson processes to the discrete domain of Poisson distribution. This is performed by building the Poisson distribution y_m from the Poisson process $y(t)$ as the expected number of drug nanoparticle deliveries in the interval $[mT_s, (m+1)T_s[$. The rate of y_m is the integrated continuous rate of the inhomogeneous Poisson process $y(t)$ in the interval $[mT_s, (m+1)T_s[$ [21]. According to the expressions (21) and (39), this is expressed as follows:

$$\begin{aligned}\lambda_m &= \int_{mT_s}^{(m+1)T_s} \lambda(t) dt \\ &= \int_{mT_s}^{(m+1)T_s} \left(\eta_m + \int_{-\infty}^{+\infty} x(t-\tau) p_r(t) h(t,\tau) d\tau\right) dt,\end{aligned} \tag{39}$$

which can be simplified as follows with a discrete drug injection rate.

$$\lambda_m = \sum_{n=0}^{N-1} x_n \left(\eta_m T_s + \int_{mT_s}^{(m+1)T_s} p_r(t) h(t, t - nT_s) dt\right). \tag{40}$$

Finally, by using the definition of the coefficients $\alpha_{n,m}$ in (38), the following expression of the rate λ_m is obtained:

$$\lambda_m = \eta_m T_s + \sum_{n=0}^{N-1} x_n \alpha_{n,m}. \tag{41}$$

1) Capacity Expression: The mutual information between the drug injection sequence $\mathbf{x}_N$ and the drug reception sequence $\mathbf{y}_N$ used in (33) is as follows [11]:

$$I(\mathbf{x}_N; \mathbf{y}_N) = H(\mathbf{y}_N) - H(\mathbf{y}_N \mid \mathbf{x}_N), \tag{42}$$

where $H(\mathbf{y}_N|\mathbf{x}_N)$ is the conditional entropy of the drug reception sequence defined as:

$$H(\mathbf{y}_N \mid \mathbf{x}_N) = -E\left[\log\left(p_{\mathbf{y}_N|\mathbf{x}_N}\right)\right], \tag{43}$$

where $p_{\mathbf{y}_N|\mathbf{x}_N}$ is the conditional probability mass function of the discrete random variables $y_1, y_2, \ldots, y_{M-1}$ of the drug reception sequence given the occurence of the discrete random variables $x_1, x_2, \ldots, x_{M-1}$, and $H(\mathbf{y}_N)$ is the marginal entropy of the drug reception sequence:

$$H(\mathbf{y}_n) = -E\left[\log(p_{\mathbf{y}_n})\right], \tag{44}$$

where $p_{\mathbf{y}_N}$ is the joint conditional probability mass function of the discrete random variables $y_1, y_2, \ldots, y_{M-1}$ of the drug reception sequence. In the following, the derivation of the conditional and marginal entropies of the drug reception sequence is presented.

2) Conditional Entropy: The conditional entropy is expressed in (43). Conditioned on the drug injection sequence, the drug reception samples $\{y_m; m = 0, \ldots, M-1\}$ are independent and have the probability mass function $p_{y_m|\mathbf{x}_N}$. It is then possible to write:

$$H(\mathbf{y}_n \mid \mathbf{x}_n) = \sum_{m=0}^{M-1} H(y_m \mid \mathbf{x}_N), \tag{45}$$

where $H(y_m|\mathbf{x}_N)$ is the conditional entropy of the m-th drug reception sample given the occurrence of the drug injection sequence $\mathbf{x}_N$. $H(y_m|\mathbf{x}_N)$ is by definition equal to the following [11]:

$$H(y_m \mid \mathbf{x}_n) = -\log\left(E\left[p_{y_m|\mathbf{x}_n}\right]\right), \tag{46}$$

where $E[\cdot]$ is the expectation operator, $p_{y_m|\mathbf{x}_n}$ denotes the conditional probability mass function of the m-th drug reception sample given the occurrence of the drug injection sequence $\mathbf{x}_N$. By identification with the Lemma 1 obtained in [19], the conditional entropy $H(\mathbf{y}_n|\mathbf{x}_n)$ can be expressed as follows:

$$H(\mathbf{y}_N \mid \mathbf{x}_N) = -\sum_{m=0}^{M-1} E\left[\lambda_m T_s \log(\lambda_m)\right] + \sum_{m=0}^{M-1} E[\lambda_m T_s]. \tag{47}$$

3) Marginal Entropy: The marginal entropy in (44) of the drug reception sequence is derived. The drug reception samples $\{y_m; m = 0, \ldots, M-1\}$ are independent and have the probability mass function $p_{y_m|\mathbf{x}_N}$. Therefore, the marginal entropy is $H(\mathbf{y}_N) = \sum_{m=0}^{M-1} H(y_m)$, where $H(y_m)$ is the marginal entropy of the m-th drug reception sample. $H(y_m|\mathbf{x}_N)$ is by definition equal to $H(y_m) = -\log(E[p_{y_m}])$ where p_{y_m} is the probability mass function of the m-th drug reception sequence.

By identification with the expression of the least-square estimator of Poisson-distributed random variables performed in [19] by using semimartingale methods, and supposing that the channel does not vary in time during T_s, the marginal entropy of the drug reception sequence $H(\mathbf{y}_N|\mathbf{x}_N)$ can be expressed as follows:

$$H(\mathbf{y}_N) = -\sum_{m=0}^{M-1} E\left[\hat{\lambda}_m T_s \log(\hat{\lambda}_m)\right] + \sum_{m=0}^{M-1} E[\lambda_m T_s], \tag{48}$$

where $\hat{\lambda}_m$ is the least-squares estimator of λ_m given the occurrence of the drug reception sequence $\mathbf{y}_N$, i.e. $\hat{\lambda}_m = E[\lambda_m|\mathbf{y}_N]$. The least-squares estimator $\hat{\lambda}_m$ of the rates λ_m can be expressed as a function of the least-squares estimator $\hat{x}_n$ of the drug injection samples x_n, as follows:

$$\hat{\lambda}_m = \sum_{n=0}^{N-1} \hat{x}_n \alpha_{n,m} + \eta_m T_s, \tag{49}$$

where the least-squares estimator $\hat{x}_n$ of the drug injection samples x_n is equal to the following:

$$\hat{x}_n = E\left[x_n|\mathbf{y}_N\right]. \tag{50}$$

The expression of the mutual information $I(\mathbf{x}_N; \mathbf{y}_N)$ is obtained by substituting in (42) the drug injection sequence conditional and marginal entropies by their expressions (47) and (48), respectively, as follows:

$$I(\mathbf{x}_N; \mathbf{y}_N) = T_s \sum_{m=0}^{M-1} E\left[\lambda_m \log(\lambda_m)\right] - E\left[\hat{\lambda}_m \log(\hat{\lambda}_m)\right], \tag{51}$$

where $\hat{\lambda}_m$ is the least-squares estimator of the rate λ_m given the drug reception sequence $\mathbf{y}_N$.

By using the notation proposed in [12] for the treatment of the single-input single-output Poisson channel, the mutual information in (51) can be rewritten as the difference between two quantities, where the first is larger than the second, as follows:

$$\begin{aligned} &I(\mathbf{x}_N; \mathbf{y}_N) = \\ &T_s \sum_{m=0}^{M-1} \psi_m\left(\sum_{n=0}^{N-1} x_n \alpha_{n,m}\right) - E\left[\psi_m\left(\sum_{n=0}^{N-1} x_n \alpha_{n,m}\right)\right] \\ &- T_s \sum_{m=0}^{M-1} \psi_m\left(\sum_{n=0}^{N-1} x_n \alpha_{n,m}\right) - E\left[\psi_m\left(\sum_{n=0}^{N-1} \hat{x}_n \alpha_{n,m}\right)\right], \end{aligned} \tag{52}$$

where the functions $\psi_m(\cdot)$ $(m = 0, \ldots, M-1)$ are defined as follows:

$$\begin{aligned} \psi_m(x) = \frac{x}{B_m} &\left[(\eta_m + B_m)\log(\eta_m + B_m) - \eta_m \log \eta_m\right] \\ &- (\eta_m + x)\log(\eta_m + x) - \eta_m \log \eta_m, \end{aligned} \tag{53}$$

where x is a variable of η_m, and $B_m = \sum_{n=0}^{N-1} A_n \alpha_{n,m}$ is the m-th drug reception sample given the occurrence of a drug injection sequence at the maximum levels A_n (35) that constrain it, and $\alpha_{n,m}$ are the channel coefficients defined in (38). By identification with the derivation in [12], the capacity is found to be closely bounded by the expression in (2) where the coefficients p_m are equal to $p_m = \min(\frac{(1+s_m)^{(1+s_m)}}{e s_m^{s_m}} - s_m, \sigma)$, where s_m is the ratio between the reception noise and the average received number of drugs in the m-th sample, which can be written as $s_m = \frac{\eta_m}{B_m}$. Finally, the capacity of the delivery system is obtained as:

$$C_\infty = \lim_{N \to +\infty} \frac{1}{T_s} C_N. \tag{54}$$

C. Spatial Capacity Numerical Results

1) Effect of Blood Vessel Dimensions: Fig. 8(a) shows how the length of the blood vessel affects the performance of the PDDS capacity. The longer the vessel is, the more dispersive the channel becomes, and therefore the capacity of the channel is negatively affected. Fig. 8(c), shows how the radius of the blood vessel affects the performance of the system capacity. When the length of the vessels is long, the variance of the drug propagation probability increases, which creates a more severe memory effect, and reduces the capacity of the channel. Similarly, when the radius of the vessels increase, the mixing along the radial coordinate is reduced, which makes the drug propagation probability more dispersive.

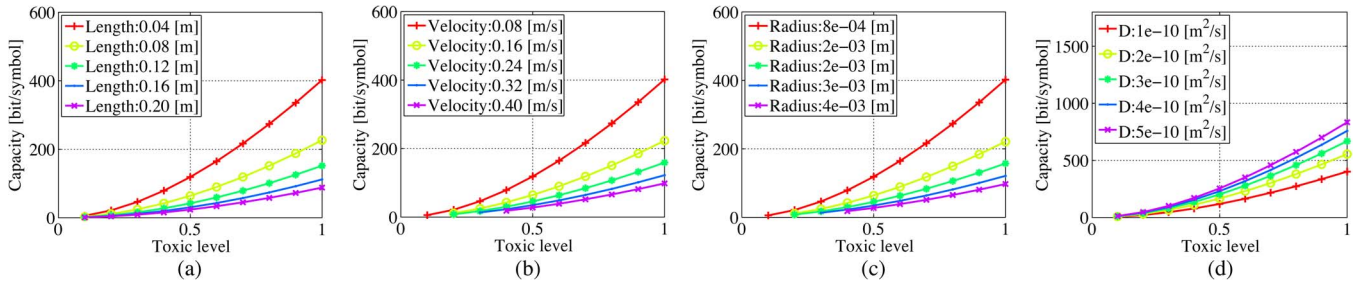

Fig. 8. The effect of the drug parameters, the vessel dimensions, and the toxic level on the capacity of the PDDS channel. (a) Effect of the link length on the capacity. (b) Effect of the blood velocity on the capacity. (c) Effect of the link radius on the capacity. (d) Effect of the diffusion coefficient on the capacity.

2) Effect of Blood Velocity: Fig. 8(b) shows how the length of the blood vessel affects the performance of the system capacity. At this regime, when the blood velocity becomes high, the channel becomes more dispersive, and therefore the capacity of the channel is affected. However, due to the Taylor dispersion effect, the blood velocity can actually reduce the dispersion in the channel, and produce the opposite observation in some conditions.

3) Effect of Diffusion Coefficient: Fig. 8(a), shows how the diffusion coefficient affects the performance of the system capacity. The higher the diffusion coefficient is, the more dispersive the channel becomes, and therefore the capacity of the channel is affected. When the diffusion coefficient is high, the drug disperses faster in the blood, causing a longer delay and higher memory effect.

VI. Monte-Carlo Simulation of the PDDS

In this section, a simulation method to study the propagation of a drug nanoparticle in the cardiovascular system with unsteady flow by introducing a Monte-Carlo simulation method of the PDDS is presented. The deterministic impulse response model developed in [7] has been validated by using finite-element simulation on COMSOL in [8]. For the noise analysis of the PDDS, the kinetic Monte-Carlo technique [4] is used to observe the random path of nanoparticles caused by random Brownian motion and validate it against the developed stochastic model. The random Brownian motion is generated by the model described in Section IV. In the kinetic Monte-Carlo technique, the path of nanoparticles is simulated by assuming that every nanoparticle is a random walker affected by Brownian motion (diffusion) and by a randomly fluctuating velocity field (convection). A model is proposed where parameters of the Brownian are directly related to the diffusion coefficient of the nanoparticles, and the random velocity field is generated by assuming that the radial and transversal components of the blood velocity field are correlated Gaussian random variables. The objective of the simulation is to study the effect of the blood turbulence on the movement of drug nanoparticles, and to compare these results with the analytical model of drug propagation.

A. Monte-Carlo Nanoparticle Random Walk

The stochastic differential equation governing the displacements of the nanoparticles according to the Langevin equations [10] describing the movement of a drug nanoparticle in a fluid are $dz(t) = Re\{u_z(z,r,t)\}dt + G_z\sqrt{2Ddt}$ and $dr(t) = Im\{u_r(z,r,t)\}dt + G_R\sqrt{2Ddt}$, where D is the nanoparticle diffusion coefficient defined, $u_z(z,r,t)$ and $u_r(z,r,t)$ are the axial and the radial components of the random blood velocity process at time t in the point with coordinates (z,r) respectively, $Re\{\cdot\}$ is the operator giving the real part, $Im\{\cdot\}$ is the operator giving the imaginary part, G_z and G_r are independent standard normal random variables.

B. Monte-Carlo Simulation Results

Fig. 9(a)–(c) compare the drug propagation probability obtained by using the analytical for the PDDS and the drug propagation probability obtained by kinetic Monte-Carlo simulation. The results are obtained by placing nanoparticles in the injection point of the blood vessel network, and the nanoparticles that arrive to the drug delivery site of the blood vessel network are counted as the simulation time advances. Fig. 9(a)–(c). show the topologies of the corresponding networks. A good agreement between the analytical model and the kinetic Monte-Carlo results is observed. The drug propagation probability obtained by kinetic Monte-Carlo simulation is noisy because of the discrete number of nanoparticles and their Brownian motion.

VII. Conclusion

Particulate drug delivery systems (PDDS) aim to delivery a drug load to the parts of the body where it is needed, at the right time and the right concentration levels drug nanoparticles, through the use of drug nanoparticles that are able to penetrate inside the cells and unleash their drug load. The analysis of the PDDS is crucial for the development of optimal drug delivery formulations and techniques. The modeling of the PDDS allows the prediction of the locations where drug nanoparticles propagate, their number, and the noisiness in their movement. It has been shown in this paper that the MC communication paradigm where the information is conveyed through molecules enables a thorough analysis of the PDDS in the human body. In fact, an MC model of the PDDS is developed, taking into account all the possible physiological parameters of the system, such as the drug injection device, the propagation in the intricate network of blood vessels, the time-variance and turbulence of the blood flow, as well as the absorption of drug nanoparticles by the diseases cells through the ligand-binding mechanisms.

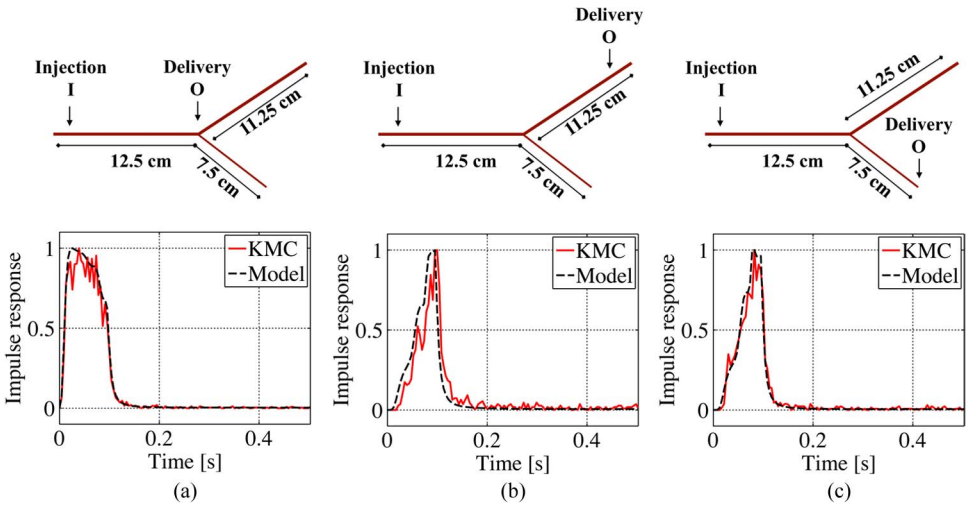

Fig. 9. Comparison between the drug propagation probabilities obtained by the MC model and the drug propagation probabilities obtained by the Monte-Carlo simulation for different delivery locations.

Drug nanoparticles undergo many noise effects such as the injection noise, the blood velocity turbulence, the ligand-binding noise, and the Brownian motion of nanoparticles. In this paper, these noise effects have been modeled through the MC paradigm where information is conveyed through the propagation of nanoparticles. These noise effects have been modeled as interference in an MC system. The use of information theory was advocated for the design of the PDDS. The analogy between the number of possible therapeutic responses deliverable by the PDDS and the size of the alphabet in a communication system was used. The PDDS was assessed as an efficient system if it is able to reliably deliver a diverse set of therapeutic responses, depending on the stage and nature of the disease and the individual specificities.

To our knowledge, this is the first work to propose the use of information theory in the PDDS design. Other works were mainly based on deterministic and probabilistic analysis of the long-term drug distribution throughout the body. Our information-theoretical approach can be applied to put into use high precision nanomedicine delivery, in contrast with traditional medicine where the drug injection is not optimized with respect to the body variabilities such as the blood flow, the ligand-binding kinetics, and their interaction.

The noise effects in the propagation of drug nanoparticles in the cardiovascular system have been simulated by using kinetic Monte-Carlo simulations. The simulations show a good agreement between the analytical model and the kinetic Monte-Carlo simulation results. This study confirms that the MC paradigm can be conveniently used for the analysis and optimization of the PDDS.

We suggest as future work to experimentally measure the distribution of drug nanoparticles in the cardiovascular system at an accurate time and space scale. These experimental results would be beneficial to validate the MC model. The existing experimental work on the distribution of nanoparticles is constrained to study their space and time evolution on a very large scale, in the order of hours and on the level of organs as a whole. We believe that the advent of nanomedicine allows to control the drug injection at a much more accurate resolution, and that therefore the distribution of nanoparticles should be studied in the order of millimeters and seconds to develop a highly targeted PDDS.

The PDDS model makes it possible to engineer therapeutic solutions that are inspired by the naturally-occurring defense mechanisms that the body deploys to combat diseases and anomalies in its functioning. The noise modeling is particularly important to the field of cancer therapy, where the choice of low concentration of drug nanoparticles is made to avoid toxic effect of the drugs, at the expense of the accuracy of the drug delivery. The PDDS model provides quantitative models to find trade-offs between toxicity and drug efficiency to facilitate cancer therapy. Ultimately, the MC paradigm can be used to create bio-inspired molecular nanonetworks for the advanced nano-scale monitoring and healing of the human body.

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