On the Affection of the Human Immune System on a Nanoparticulate Nanomedicine System

Valeria Loscrí
INRIA
FUN Research Lab.
Lille Nord-Europe, France
Email:valeria.loscri@inria.fr

Anna Maria Vegni
Department of Engineering
Roma Tre University, Italy
Rome, Italy
Email:annamaria.vegni@uniroma3.it

ABSTRACT

In this paper, a nanoparticulate system model for nanomedicine applications, based on the molecular communication paradigm, is presented. The biological environment, comprised by the presence of the human immune system, is object of study, since it can affect the optimal behavior of nanoparticles, aiming to locally deliver drug inside the human body. Indeed, when a flow of nanoparticles is injected in the blood, the interference due to the immune system can provide a strong decrease of the nanoparticle concentration, by means of phagocytosis process. As a consequence, the correct drug delivery will occur with a lower probability. It is well-known that the mechanism behind the biological immune system is very complicated. In this paper a simplistic model is derived, by assuming nanoparticles similar in the shape and the size to B-cells. This assumption is realistic, since scientists that design and implement nanodevices try to build them in a way that the immune response is minimal. These remarks make possible the application of diffusion laws to the global system, constituted by the nanoparticles and the cells of the immune system. Finally, the end-to-end physical model of a nanoparticulate nanomedicine system with the presence of the human immune system is derived. It will be analyzed from the perspective of the errors that can occur in such an environment, and how these errors can affect the performance of the system, in terms of nanoparticle survival probability.

Keywords

Nanonetworks, Human Immune System, Fault Probability, Drug Delivery

1. INTRODUCTION

In the past few years, nanotechnology has emerged as an evolution of technology enabling the design of miniaturized nanoscale devices (*i.e.*, nanorobots and nanoparticles). At this scale, the behaviors and characteristics of nanodevices need more comprehension and a deep knowledge with respect to well-known features of devices at the macroscale level [3]. A nanodevice is the most basic functional unit, which is allowed performing very easy tasks, like sensing or actuation, due to the passive nature of these devices. However, a nanosensor is not just a device with reduced size, but has unique properties of nanomaterials and nanoparticles. For instance, through the functionalization process of nanosensors, it is possible to detect chemical compounds in concentrations, or the presence of different infectious agents, such as virus or bacteria [19, 2].

A set of nanodevices, sharing the same medium (*e.g.*, the human blood flow) and collaborating for a common task (*e.g.*, to deliver a drug concentration to a receptor), forms a nanonetwork [4]. Nanonetworks are expected to expand the capabilities of single nanodevices, and then to enable new nanotechnology applications in several fields.

Communication and signal transmission techniques occurring in nanonetworks are challenging topics, due to the limited computation skill of nanodevices [10]. Molecular Communication paradigm is largely exploited for nanonetworks [4, 5, 11], under the assumption that molecules (*i.e.*, nanoscale particles) are transmitted by nanomachines (*i.e.*, artificial devices), propagate in the medium following a diffusion process, and then arrive at the receiver, where ligand-receptor bindings eventually occur.

By assuming that a nanoparticle is as small as a molecule [1], we can consider the same principles of molecular communications, so that nanoparticles are transmitted by nanomachines, propagate in the medium following a diffusion process, until reaching the receiver. Since the nanoparticles are accordingly functionalized, they can form bindings with specific receptors, whenever available.

In real scenarios, the emission, diffusion and reception processes can show different behaviours. For example, many biomedical applications require a multi-source emission of nanoparticles, where each source (*i.e.*, each nanomachine) can emit a nanoparticle flow. Moreover, in biological environments, the presence of the *immune system* could affect the behavior of the diffusion and reception of nanoparticle

[1]Molecules have a dimension of a few angstroms, [8]. The largest molecule is the mesoporous silica that has been produced with a diameter of 1000 *angstrom* (*i.e.*, 100 nm).

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flows. Indeed, the immune system plays a vital role in beings' health, since it is generally thought to protect against external invaders, such as bacteria, viruses, and other pathogens, while ignoring itself. This task is accomplished by means of the phagocytosis process (*i.e.*, a major mechanism used to remove pathogens).

In this paper, we investigate the role of the immune system in a biological environment, where one or more flows of nanoparticles are emitted for nanomedicine purpose (*i.e.*, drug delivery application). Under the assumption that the main cells comprising the immune system (*i.e.*, the B-cells) are comparable –in terms of size– to the flows of nanoparticles emitted in the organism, we consider a very simple model for the immune system. Then, we can assess how the immune system affects the diffusion and reception of nanoparticles. The characterization of the end-to-end physical model permits to perform a detailed analysis of errors that can occur during the diffusion process, and that impact on the performance of the system, expressed in terms of *nanoparticle survival probability*.

The remainder of this paper is organized as follows. The modeling of the human immune system as a network with active molecules (*i.e.*, the B-cells) is deeply described in Section 2. A very simple model for the immune system has been assumed in this paper, so that we can observe the interactions that occur among nanoparticles and the B-cells. More in detail, in Section 3 we discuss the physical end-to-end model for one nanoparticle flow emitted by a nanomachine, toward a receiver. We describe how nanoparticles diffuse in the biological environment, where the presence of B-cells can cause interferences, and then a reduction of the nanoparticle flow reaching the receiver. Other errors occurring along the biological channel are investigated in Section 4, where we assume that our nanoparticles can be affected by two main types of errors (*i.e.*, lost, and interfering nanoparticles). A model describing the nanoparticle errors is then presented. Finally, conclusions are drawn at the end of the paper.

2. MODELING OF THE HUMAN IMMUNE SYSTEM

The immune system aims to protect the biological environment, against external invaders (*i.e.* pathogens). It is organized as a network of lymphocytes, and antibody molecules, that interact via specific processes (*e.g.*, phagocytosis).

The role of idiotypic networks [1] in the operation of the immune system has been investigated by a number of mathematical models [13, 14, 18, 6]. The immune system operates as an interconnected network, really complex and difficult to be realized through experiments. Sometimes, scientists perform experiments with a few of cell types, in order to obtain some useful information about isolated interactions. It is clear that this kind of experiments can be useful in some ways, but it isolates the immune cells from the natural context of a very large biological network, and this can lead to a non-physiological behavior.

On the other side, *in-vivo* experiments allow considering and observing the phenomena in their physiological context. However, by neglecting the several difficulties related with this kind of experiments, the results derive from a global behavior, and it is difficult to fix the individual components. This represents a very relevant gap in terms of immune systems knowledge, but it can be bridged by a mathematical modeling.

Based on the taxonomy presented in [9], we can classify the modeling of immune systems in the following five categories:

- Ordinary Differential Equations (ODE): this type of model is the most common and has been used for cancer immunology;
- Delay Differential Equations (DDE): they are infinite-dimensional dynamical systems, and then require more computational capabilities and more complexity, from an analytical point of view, than the finite dimensional based modeling, like ODE;
- Partial Different Equations (PDE): able to capture more complex features than ODE and DDE. This category is usually applied as age-structured models, that consider the progression of individual cells via a scheduled development process. It can also be applied as spatio-temporal models. Based on this approach, in [12] the authors represented the simulation of two chemical signals that interact as antagonist by allowing neuthrophyls to self-orient based on the chemical gradient. Their PDE model is represented as a diffusion system with chemotaxis equations in one-dimension;
- Stochastic Differential Equations (SDE): they are written in a similar way like ODE, but their variables can assume random values. Through SDE it is possible to take into consideration the noise and other sporadic events modeled as Poisson process;
- Agent-Based Models (ABM): these models refer to a totally different way of characterization with respect to differential equation systems. In ABMs there are distinguishable agents (*i.e.*, molecules or cells), while the differential equations based models deal with a collective population (*i.e.*, cell densities). ABMs allow taking into account the probabilistic uncertainty related to the biological interactions.

Leveraging on this classification, a spontaneous question related to all the possible models available is how to select the most appropriate and suitable. The models present different levels of complexity and this could be a selection criterion, then justifying the enormous success of ODE models, which are adopted to represent also complex biologic systems without requiring too much computational complexity. On the other hand, ODE models are not effective whenever it is necessary to include spatial distribution of molecules.

In any case, a right way to select the most appropriate model is based on the analysis of the requirements related to the specific application and context considered. This is exactly what we realized in this work. Specifically, we started from the consideration that a certain amount –density– of nanoparticles is injected in the blood, and we need to model the immune system by considering both spatial-temporal dynamics and progression of individual nanoparticles. In

this way, we take into account (*i*) the evolution process [2] of nanoparticles, and (*ii*) the associated desired functionality of death, in order to be absorbed through the normal biological process.

In this sense, a considerable amount of works has arisen around a model, namely the *B-cell* model [13, 14, 18]. It includes only B-cells, and attempts to describe the population dynamics of a set of n distinguishable B-cell clones that interact in a network. The B-cell model has been thoroughly studied for the case of two B-cell clones ($n = 2$) [17]; however, when a large number of clones are present, the model relies on the replicator equation model. In order to capture all the key features that characterize our system, we consider a PDE model and, more specifically, we make reference to the B-cell model.

Let y_k denote the concentration of k-th B-cell clone (*i.e.*, with $k = \{1, \ldots, n\}$), and be c the total concentration of clones *i.e.*,

$$c = \sum_{k=1}^{n} y_k, \tag{1}$$

from which, the relative concentrations of the clones will be derived as $x_k = y_k/c$. When stimulated by interactions with other clones, a clone will proliferate. It is possible to summarize the effects of all other clones by a variable, called as *field*. Then, the field of clone k is given by [17]

$$h_k(y) = \sum_{j=1}^{n} \tilde{b}_{kj} y_j = c \sum_{j=1}^{n} \tilde{b}_{kj} x_j = c \cdot h_k(x), \tag{2}$$

where the coefficients $\tilde{b}_{kj}$ describe the topology of the B-cell network.

In the B-cell model [17], the population dynamics of B-cell clones are described by

$$\dot{y}_k = y_k \left[p\tilde{f}(h_k(y)) - \tilde{d}_k \right] + \tilde{s}_k, \tag{3}$$

where p is the proliferation rate, $\tilde{f}$ is a response function determining the fraction of cells proliferating, $\tilde{d}_k$ is the death-rate of k-th clone, and $\tilde{s}_k$ is the (constant) influx of the k-th clone from the bone marrow. Notice that the influx rates are typically small (*i.e.*, assumed as zero), and they can be reintroduced as perturbations of the simplified dynamical system with $\tilde{s}_k = 0$. Further, we assume that the death-rates for all clones are equal, *i.e.*, $\tilde{d}_k = d$. Thus, from (3) we can obtain the following differential equation

$$\dot{y}_k = y_k \left[p\tilde{f}(h_k(y)) - \tilde{d} \right]. \tag{4}$$

The rate of proliferation of B-cells in response to the field that they experience is determined by the response function $\tilde{f}(h)$. The response of B-cells to a ligand (*i.e.*, an antigen that interacts in a specific manner with the receptors on the cell's surface) is typically unimodal [7], and then small concentrations of ligands give little or no response and there is an optimal concentration that gives a maximal response.

[2]Nanoparticles diffuse and interact with B-cells.

3. END-TO-END PHYSICAL MODEL

In this section, we present the end-to-end physical model of the emission, diffusion and reception of nanoparticles, assumed to be introduced in the human body (*e.g.*, via injection). In this model, we relay on well-known Fick's laws of diffusion, and the assumption that a nanoparticle can be captured and form a binding with a receptor. We also exploit the B-cell model by assuming one B-cell flux interacting with a concentration of nanoparticles.

Similarly to [15], we consider a single nanoparticle as an indivisible object, released to (during the emission process), or collected from (during the reception process), a position in the space S, by means of chemical reactions. In the diffusion process, nanoparticles are free to move into the space following the laws of diffusion of particles in a flow. Fig. 2 depicts the schematic of the end-to-end model in a biological environment, where a transmitting nanomachine emits a flux of nanoparticles toward a receiver [3].

The nanomachine is provided with several apertures from where the nanoparticles exit, when emitted. The overall nanoparticle concentration flux emitted by the nanomachine is stimulated by a concentration gradient between c_{out} and c_{in}, which represent the nanoparticle concentration value outside, and inside the nanomachine, respectively. Notice that we assumed only a positive nanoparticle rate modulation *i.e.*, $c_{in} < c_{out}$, [16].

A single nanoparticle is functionalized to be captured by a receptor, by means of chemical reactions. When captured, the reception process allows decoding the information within the nanoparticle (*e.g.*, the drug concentration).

In the space S within the biological environment, we assume the presence of B-cells, which can recognize neighboring nanoparticles as antigens, and then will try to defeat (*i.e.*, interference nanoparticle/B-cell). Finally, along the biological channel we consider the presence of errors, expressed in terms of lost, and interfering nanoparticles.

The overall nanoparticle concentration flux $J_T(x,t)$ is given by the sum of the N nanoparticle concentration gradients *i.e.*, with N as the number of apertures of the nanomachine, at time t and position x through the Fick's first law, as follows

$$J_T(x,t) = -D \sum_{i=1}^{N} \nabla C_{i,NP}(x,t), \tag{5}$$

and at the transmitter side (*i.e.*, at position $x = x_T$ [nm], and time instant $t = t_0$ [ns]) it becomes

$$J_T(x_T,t_0) = -D \sum_{i=1}^{N} \nabla C_{i,NP}(x_T,t_0), \tag{6}$$

where $C_{i,NP}(x,t)$ [mol/cm^3] is the i-th nanoparticle concentration with $i = \{1, 2, \ldots, N\}$, and D [cm^2/s] is the diffusion coefficient, assumed as a constant value for a given fluidic

[3]Notice that the receiver modeling is not addressed in this paper, since the aim is the modeling of the human immune system, and how it affects the nanoparticulate drug delivery system.

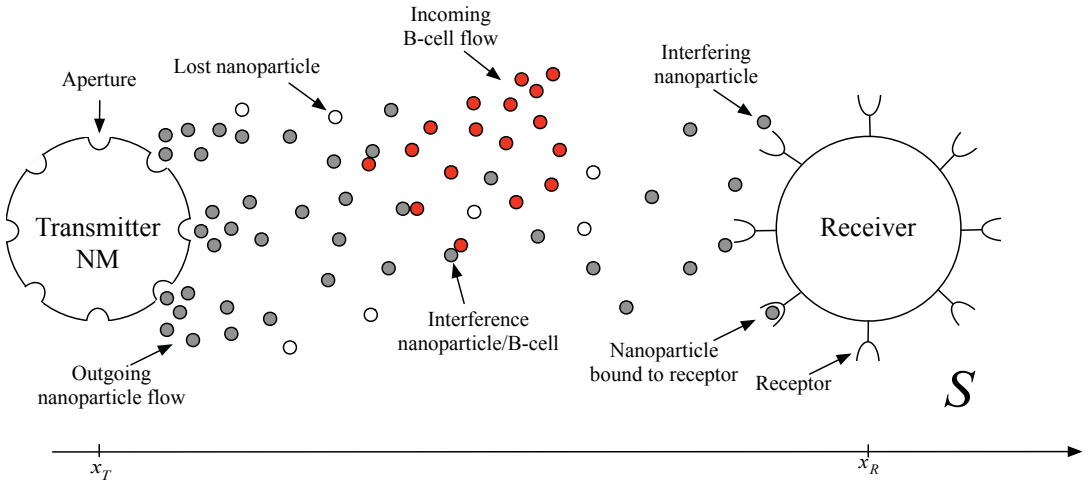

Figure 1: End-to-end physical model in the biological space S, linking a transmitting nanomachine to a receiver. One or more fluxes of nanoparticles are emitted by the transmitter, and diffuse along the propagation channel. The presence of B-cells causes a reduction of nanoparticle concentration able to reach the receiver. Moreover, lost and interfering nanoparticles can provide errors during the reception process (*i.e.*, no reception, and wrong reception, respectively).

medium, and depending on the size and shape of nanoparticles, as well as the interaction with the solvent and viscosity of the solvent.

Unfortunately, the Fick's first law works when applied to steady state systems, namely the concentration will keep constant both along the space and in time. However, since nanoparticles diffuse along the space, the concentration changes during the time, and they determine different levels of concentrations. Then, we can rely on Fick's second law, *i.e.*

$$\frac{\delta C_{NP}(x,t)}{\delta t} = D\frac{\delta^2 C_{NP}(x,t)}{\delta x^2}, \tag{7}$$

where C_{NP} is the nanoparticle concentration as emitted by the transmitter.

During the diffusion process, we consider that the nanoparticles encounter the B-cells. Due to comparable sizes, we can model the B-cells by means of Fick's first and second laws, as well as considered for the nanoparticles. Under this assumption, the interactions among B-cells and the nanoparticles can occur, thus providing affections to nanoparticles flows. Indeed, analogously to (6), we can model the B-cell concentration flux $J_B(x,t)$ as an unique contribution, which is expressed as

$$J_B(x,t) = -D_B \nabla C_B(x,t), \tag{8}$$

where $C_B(x,t)$ is the B-cell concentration in position x, and at time t, and D_B [cm^2/s] is the diffusion constant for the B-cells (*i.e.*, with $D_B \neq D$). Also, from (9) we can derive the B-cell diffusion along the space x, and at time t, as

$$\frac{\delta C_B(x,t)}{\delta t} = D_B\frac{\delta^2 C_B(x,t)}{\delta x^2}. \tag{9}$$

Due to the phagocytosis process of the immune system, the B-cell flux interacts with the nanoparticles, thus providing a reduction of nanoparticle concentration flux. The interaction among B-cells and nanoparticles allows writing the following

$$J_{[T+B]}(x,t) = \frac{J_T(x,t) + J_B(x,t)}{2}, \tag{10}$$

where we assumed

$$J_T(x,t) = \frac{Q_{NP}}{\sqrt{(4\pi D t)^3}} e^{-\frac{x^2}{4Dt}}, \tag{11}$$

and

$$J_B(x,t) = \frac{Q_B}{\sqrt{(4\pi D_B t)^3}} e^{-\frac{x^2}{4D_B t}}, \tag{12}$$

with $Q_{NP/B}$ as the initial concentration of nanoparticles and B-cells, respectively. Eq. (10) represents the nanoparticle concentration flux after the phagocytosis process, and it can be rewritten as

$$J_{[T+B]}(x,t) = \frac{1}{2\sqrt{(4\pi t)^3}}\left[\frac{Q_{NP}}{D\sqrt{D}} e^{-\frac{x^2}{4Dt}} + \frac{Q_B}{D_B\sqrt{D_B}} e^{-\frac{x^2}{4D_B t}}\right]. \tag{13}$$

Fig. 2 depicts the concentrations of nanoparticles and B-cells, occurring along the space, by assuming the nanoparticles are emitted in position $x_T = 0$ [nm], while the B-cells in position $x_B = 99$ [nm]. The flows diffuse in opposite direction *i.e.*, from left to right for the nanoparticles, and from right to left for the B-cells. Different curves are for different values of $Q_{NP/B}$, specifically for $Q_{NP/B} = 300$ [mol] (solid lines), and $Q_{NP/B} = 1000$ [mol] (dotted lines). Numerical values are chosen as a practical example.

The interaction among nanoparticles and B-cell vs. space is shown in Fig. 3 (a), where we observe how the flow of nanoparticles decreases due to the response of the immune system that recognizes the nanoparticles as invaders. As a result, after the phagocytosis process, the percentage of

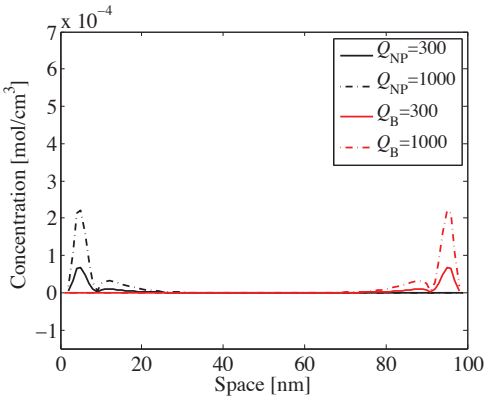

Figure 2: Variation of nanoparticle and B-cell concentrations, vs. space and for different values of initial concentration $Q_{NP/B}$.

nanoparticles able to reach the receiver (*i.e.*, NP + B-cell flow) will be lower than that in case of no response of the immune system (*i.e.*, NP flow). Indeed, if in the space the concentration of B-cells is low (*i.e.*, approximable to zero), there will be no response of the immune system, and then no decrease of the nanoparticle concentration. Finally, Fig. 3 (*b*) depicts the dynamic behavior of the nanoparticle flow vs. space, when affected by the B-cell concentration (*i.e.*, after the phagocytosis process). We observe a decrease of nanoparticle concentration flow due to the response of the immune system. This shows that in a real scenario, during the diffusion process the nanoparticle concentration flow does not follow an ideal behavior, but is affected by other molecules (*i.e.*, the B-cells), which destroy the nanoparticles, since they are recognized as pathogens.

4. NANOPARTICLE ERRORS

Apart the presence of B-cells that can cause a reduction of nanoparticle concentration, we can distinguish other errors occurring in our nanoparticulate system, during the diffusion process, namely (*i*) the interfering nanoparticles *i.e.*, nanoparticles that can approach the receiver but are not able to form bindings, and cause interference, and (*ii*) the lost nanoparticles *i.e.*, nanoparticles that are not able to reach the receiver, since they are lost during the diffusion process.

Interfering nanoparticles provide an increase of noise level in the channel, causing a *false reception*, since they can lay very close to the receiver, and then obstructing other nanoparticles from the correct capture at the receptor. In this context, a false reception means that a nanoparticle lays very close to the receptor, but is not bound.On the other side, lost nanoparticles will never reach the receiver, and then will provide a *missing reception*, since no correct nanoparticle capture will occur. In this context, a missing reception means that a nanoparticle will never form a binding, since it will be reach the receiver.

Based on such errors, we can distinguish two kinds of events such as (*i*) the individual and correlated simultaneous nanoparticle faults, and (*ii*) the interference-based nanoparticle faults. In the case of individual nanoparticle faults, at least one

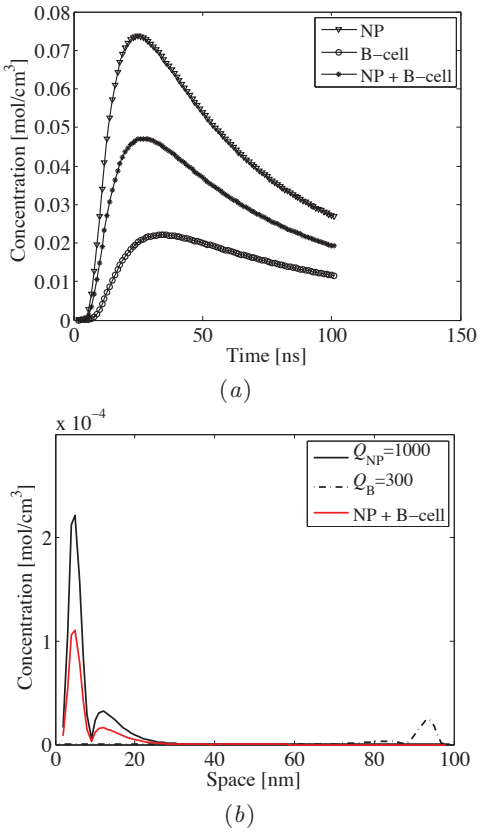

Figure 3: Variation of nanoparticle and B-cell concentrations, vs. (*a*) time, and (*b*) space, for different values of initial concentrations *i.e.*, $Q_{NP} = 1000$ [mol], and $Q_B = 300$ [mol]. The superposition effect provides the average concentration due to the interaction among nanoparticles and B-cells (*i.e.*, NP + B-cell).

nanoparticle out of a nanoparticle flow is affected by noise, and then the nanoparticle reception at the receiver can be corrupted. Finally, the case of correlated simultaneous nanoparticle faults represents the extension of individual faults, since it assumes errors correlated among multiple nanoparticle flows.

4.1 Individual and Correlated Simultaneous Nanoparticle Errors

We can define p as the probability of having one failed nanoparticle *i.e.*, $NP_f = 1$ (specifically, one lost nanoparticle), out of N_{NP} nanoparticles, whose expression is:

$$p[NP_f = 1] \cong N_{NP} \cdot P_{NPf}, \quad \text{with} \quad P_{NPf} \ll 1, \qquad (14)$$

where P_{NPf} is the rate of nanoparticle faults. It follows that the probability p of having 2 failures out of N_{NP} nanoparticles is

$$p[NP_f = 2] = \begin{pmatrix} N_{NP} \\ 2 \end{pmatrix} P_{NPf}^2 \cdot (1 - P_{NPf})^{N_{NP}-2}, \qquad (15)$$

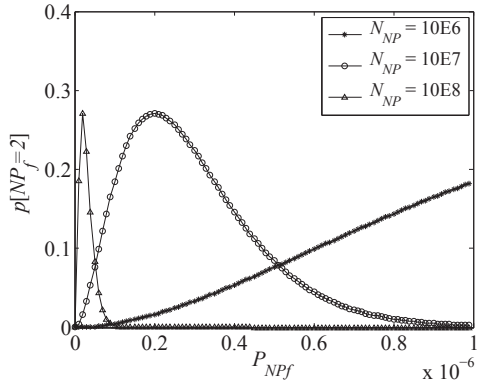

Figure 4: Probability of having two failed nanoparticles out of a flow of $N_{NP} = 10^6$ (asterisk marker), $N_{NP} = 10^7$ (circle marker), and $N_{NP} = 10^8$ (upward-pointing triangle marker).

and then the probability of having 3 or more failures is

$$p\left[NP_f > 2\right] = \sum_{l=3}^{N_{NP}} P_{NPf}^{l} \cdot \left(1 - P_{NPf}\right)^{N_{NP}-l}. \quad (16)$$

As an example, for $P_{NPf} = 10^{-6}$, we obtain $p\left[NP_f = 2\right] = 0.183$ in the case of $N_{NP} = 10^6$, while the probability decreases (*i.e.*, $p\left[NP_f = 2\right] = 0.0023$) in the case of $N_{NP} = 10^7$. Fig. 4 depicts the nanoparticle fault probability for different values of fault probability of a single nanoparticle out of N_{NP}, for $N_{NP} = [10^6, 10^7, 10^8]$.

Notice that it is realistic to assume that the probability of correlated simultaneous nanoparticle faults (*i.e.*, P_{cNPf}) can exceed the individual fault probability (*i.e.*, P_{sNPf}). On the other hand, when m nanoparticle flows are considered, the probability that at least one flow is not affected by a correlated failure (*i.e.*, $m_{healthy} \geq 1$) is:

$$\Pr\left\{m_{healthy} \geq 1\right\} = 1 - P_{cNPf}^{m}. \quad (17)$$

Thus, for $P_{cNPf} = 10^{-6}$ with $m = 3$ nanoparticle flows, the probability that at least one flow is not affected by correlated faults is less than $\left(1 - 10^{-18}\right)$.

4.2 Interference-based Nanoparticle Faults

This case occurs due to interference errors along the channel from the transmitter to the receiver. When the nanoparticles diffuse, an additional delay can happen, mainly due to the presence of obstacles in a lattice *i.e.*, a three-dimensional space. This corresponds to the nanoparticle to "surf" in a pepertuum way until this will be eliminated by the human body. In this case, a wrong reception can still arise due to large random errors produced during the reception process (*i.e.*, interfering nanoparticles that are laying near the receptors, but are not bound). However, besides their small probability of occurrence, interfering nanoparticles can cause a false reception, due to the very short proximity of these nanoparticles to the receptors.

Let us denote with P_{sNPf} the probability of fault of a single nanoparticle, and with N_{NP} the number of nanoparticles available at the end of the diffusion process. The probability p that none of them is affected by a fault (*i.e.*, the nanoparticles can form bindings, and are not interferers) is bounded by the probability that none of them is affected by an independent fault, *i.e.*:

$$p \leq \left(1 - P_{sNPf}\right)^{N_{NP}}. \quad (18)$$

In practice, for $P_{sNPf} \ll 1$, the following approximation holds

$$p \leq 1 - N_{NP} \cdot P_{sNPf}. \quad (19)$$

We need to compute the conditions under which this approximation is true. In order to do that, we will derive a free boundary problem for the associate Fokker-Planck partial differential equation, that is derived from the calibration of the *barrier function*.

Let us define the function $P_{sNPf}(t)$ as the probability that a single nanoparticle has faulted by time t, and $P'_{sNPf}(t)$ as the fault probability density. Then, the probability of fault between t and $(t + \Delta t)$ can be represented as $P'_{sNPf}(t)\Delta t$, as seen at time $t = 0$.

By considering $W(t)$ as a standard Wiener process, we can associate the nanoparticle concentration process as an Ito process $X = \{X_t, t \geq 0\}(t)$, with $X_{t=0} = X_0$. The reasons for which we associate an Ito process to our system is that an Ito process is a stochastic process that can be expressed as the sum of an integral with respect to Brownian motion, and an integral with respect to time, as shown in:

$$X_t = X_0 + \int_0^t a\left(X_s, s\right) ds + \int_0^t b\left(X_s, s\right) dW_s, \quad t \geq 0, \quad (20)$$

where X_0 is a scalar starting point, $\{a\left(X_t, t : t \geq 0\right)\}$ and $\{b\left(X_t, t : t \geq 0\right)\}$ are stochastic processes satisfying certain regularity conditions. A solution of Eq. (20) is

$$dX_t = a_t dt + b_t dW_t, \quad (21)$$

where $a_t = a\left(X_t, t\right)$, and $b_t = b\left(X_t, t\right)$. Eq. 21 represents the expression of Brownian motion with an instantaneous drift a_t, and an instantaneous variance b_t^2 of diffusion. The faults of the nanoparticles at time t are expressed through:

$$X\left(t\right) = b\left(t\right), \quad (22)$$

with the assumption that $X\left(t-1\right) > b\left(t-1\right)$, where $b(t)$ represents the *barrier function* related with the density of nanoparticles present in the solution.

Let us call τ as the first time that $X(t)$ hits its barrier, then:

$$\tau = \inf\left\{t \geq 0 : X\left(t\right) \leq b\left(t\right)\right\}. \quad (23)$$

By calling $P_S(x,t)$ as the survival probability density function of $X(t)$, we have:

$$P_S\left(x,t\right) dx = \Pr\left[x < X\left(t\right) < x + dx, \tau \geq t\right], \quad (24)$$

for $x \geq b(t)$. Then, by applying results known in the theory of probability, the function $P_S(x,t)$ in (24) satisfies the Fokker-Planck equation, such as:

$$\frac{\partial P_S\left(x,t\right)}{\partial t} = \frac{\sigma^2}{2\gamma^2}\Delta P_S\left(x,t\right) + \frac{F\left(x\right)}{\gamma}\nabla P_S\left(x,t\right), \quad (25)$$

where $\frac{\sigma^2}{2\gamma^2} = D$ is the diffusion coefficient, γ is a viscosity coefficient, and $F(x)$ is a strength field. From (18), we can

define the *survival probability* up to time t corresponding to $(1 - P_{sNPf}(t))$, and calculated by integration as:

$$1 - P_{sNPf}(t) = \int_{b(t)}^{\infty} P_S(x,t)\,dx, \tag{26}$$

so that the fault probability $P_{sNPf}(t)$ is related to the survival probability density function $P_S(x,t)$, and the barrier $b(t)$, through the following equation:

$$P_{sNPf}(t) = 1 - \int_{b(t)}^{\infty} P_S(x,t)\,dx. \tag{27}$$

Since the pair $\{P_S(x,t), b(t)\}$ has to be consistent with the fault probability $\{P_{sNPf}(t); t > 0\}$, the barrier $b(t)$ has to be chosen in an appropriate fashion. This is clear by differentiating the fault probability with respect to time in (27):

$$\begin{aligned} P_{sNPf}(t) &= -\int_{b(t)}^{\infty} \frac{\delta P_S}{\delta t}\,dx + P_S[b(t),t]\,b'(t) = \\ &= \tfrac{1}{2}\frac{\delta}{\delta x}\left(\sigma^2 P_S\right)\big|_{x=b(t)}. \end{aligned} \tag{28}$$

In practice, the survival density function has to satisfy both the condition (26), and a boundary condition at the barrier $x = b(t)$. This implies a free boundary problem for the forward Fokker-Plank equation, since the boundary $b(t)$ is not known, and the choice of its value has to be consistent with the boundary conditions (26) and (28). Notice that the derived model is invariant in respect of transformation as scaling. Indeed, by introducing s_0 as a positive number, and transforming $\tilde{x} = x/s_0$, $\tilde{b}(t) = b/s_0$, and $\tilde{a}(\tilde{x},t) = a(x,t)/s_0$, then the new function can be written as

$$\tilde{P}_S(\tilde{x},t) = s_0 P_S(x,t), \tag{29}$$

that satisfies equations from (25) to (28). Finally, if s_0 is a constant value *i.e.*, $(s_0 = 1)$, the fault index is taken to be a standard Brownian motion. On the other side, if s_0 is not constant, we can also take into account index as the time.

5. CONCLUSIONS

In this paper we investigated the errors (*i.e.*, lost and interfering nanoparticles), occurring in a nanoparticulate system for nanomedicine applications. In order to provide the analysis of the errors as much real as possible, we also considered the presence of B-cells of the immune system. This latter has been represented through a simplified mathematical model, based on differential equations, since it allows representing the spatio-temporal characteristics of the immune response and the maturation process of the B-cells that compete with the nanoparticles to share the biological environment. This specific analysis allows us to treat the cells deriving from an immune response as a kind of interferent. Finally, we derived the probability analysis for the cases of false and missing reception, on the basis of the presence of nanoparticle errors (*i.e.*, lost and interfering nanoparticles).

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