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Simulating an in vitro experiment on nanoscale communications by using BiNS2

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ABSTRACT

Nanoscale communications is an emergent research topic with potential applications in many fields. In order to design nanomachines able to exploit the communication potentials of nanoscale environments, it is necessary to identify the basic communication mechanisms and the relevant parameters. In this paper, we show how system parameters can be derived by suitably matching the results of in vitro experiments with those obtained via simulations by using the BiNS2 simulator. In order to scale the simulation from micrometric settings, with timescale in the order of seconds, to real experiments lasting tens of minutes with millimetric size, we enhanced the BiNS2 simulator by introducing a space partition algorithm based on the octree. In this way, the simulator can exploit the high level of parallelism of modern multicore computer architectures. We have used this technique for simulating an experiment focused on the communication between platelets and endothelium through the diffusion of nanoparticles. Simulation results match experimental data, thus allowing us to infer useful information on the receiver operation.

1. Introduction

Nanoscale communications is an emergent research topic, with potential applications in many fields [1], such as military usage, environmental monitoring, food control and, above all, healthcare [3,21]. In particular, nanomedicine has achieved a lot of important results in the design of nanomachines in last decades [11]. However, the capability of coordinating the behavior of a number of nanomachines is still missing. Thus, the need of modeling information transfer at the nanoscales, especially for biological systems, requires a study able to identify the basic components of a communication system in the new environment, such as an information encoder, a transmitter, a communication medium, a receiver, and an information decoder [22,6].

Due to the heterogeneity of different environments at nanoscales, it is unfeasible to identify general models, valid for most of nano-communication systems [1], which span from terahertz communications [25] to neuronal communications [12] to communications via diffusion of information molecules [13]. Hence, their analysis requires different models, strictly related to their environmental features. For this reason, through the combination of interdisciplinary expertise, for each area that could be involved in the research at nanoscales, it is necessary to plan and execute experiments for achieving a deep knowledge of the nanoscale environment of interest.

In this regard, simulation platforms are useful tools for gaining insight on nanoscale communications. In fact, a simulator can allow predicting the evolution of the system without having to implement it, trigger a response to an external stimulus, and observe the outcomes, thus reducing time spent and saving money [6]. Clearly, parameters

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and algorithms in simulators have to be accurately calibrated by matching the outcomes of real experiments with simulation results, in order to produce reliable estimates.

In this paper, we compare the experimental data of a real biological, in vitro experiment with the results of the relevant simulations obtained through the BiNS2 simulator, a Java software platform for simulating biological, nanoscale, molecular communications [10]. The experiment aims to investigate the molecular communication mechanisms between platelets and endothelium, which is of recognized importance in the study of the early stages of atherosclerosis, known as atherogenesis. The resulting communication system is composed of mobile transmitters (the platelets) which communicates through the release of specific molecules (sCD40L) with fixed receivers (the endothelial cells). The communication channel is represented by the aqueous solution (in the experiment) or by the blood in which the molecules diffuse from the transmitter to the receiver. Understanding these communication mechanisms, and in particular the minimum stimulus intensity able to activate the endothelium, is preparatory to more accurate studies involving communications inside blood vessels [9]. To simulate this experiment, the BiNS2 simulator has been enhanced with a space partition algorithm based on the octree structure [27]. This algorithm allows both exploiting the increased level of parallelism offered by modern multicore computer architectures, and scaling the simulated environment from micrometric to millimetric size, with a timescale in the order of tens of minutes.

The goal of this comparison is twofold. First, we assess the correctness of the simulation results obtained through BiNS2. Second, by matching the results of the simulations with those of the real experiment, we derive the values of some system parameters which cannot be easily obtained by means of measurements. In particular, we succeeded in estimating the numbers of receptors on the surface of endothelial cells, the receiver sensitivity, and the minimum level of the received stimulus on the endothelium able to trigger the decoding of the received signal.

In Section 2 we illustrate the background relevant to the platelet–endothelium interaction and the related works on simulating communications at the nanoscale. Section 3 presents a detailed description of the experiment, whereas Section 4 shows the relevant simulation along with numerical results. Finally, concluding remarks are sketched in Section 5.

2. Background and related works

2.1. Biological background

It is well known that the interaction between activated platelets and endothelium triggers the formation of atherosclerotic plaques below endothelial cells [17,2]. When these plaques are released into the blood vessel due to a rupture of the endothelium, there is the formation of a thrombus. Activated platelets expose on their surface the CD40L cytokines [26]. The CD40L is a trimeric, transmembrane protein of the tumor necrosis factor family. Resting platelets store the CD40L inside the cytoplasm, and expose them on their surface only when activated, that is upon receiving an external stimulus, such as the thrombin. If the stimulus persists for a given time, these proteins are cleaved from the platelet surface and shed in the blood flow as soluble CD40L (sCD40L). Endothelial cells expose on their surface the CD40L receptor, known as CD40 [26]. When (s)CD40L ligand binds with its receptor on the endothelium surface, the complex is internalized, and a new receptor is exposed (or the old one is recycled) through a process named trafficking [18]. If this stimulus persists for a given time, the CD40L-based signaling triggers the activation of endothelial cells [14,16,5,20], that is the production of adhesion molecules (vascular adhesion molecules, VCAM-1) on their surface. When monocytes, a special type of white blood cells, get in contact with VCAM-1, they stick to them and penetrate below the endothelium by passing through the gaps between endothelial cells (diapedesis process).

In normal conditions, the diapedesis is useful, since it allows platelets to both aggregate and repair damaged vessels, and to trigger the exposure of adhesion molecules, so that monocytes can move towards the site of tissue damage or infection. However, in pathological conditions, this process allows monocytes to penetrate below the endothelium, where they transform into macrophages and initiate the process which leads to the formation of atherosclerotic plaques (fatty streak).

Since, as explained above, this communication process is extremely important in both normal and pathological conditions, a study able to derive system parameters can be extremely useful to design sensing or actuator nanoscale devices.

2.2. Simulation platforms for nanoscale communications

A number of software simulators of communications at the nanoscale exist. Some of them are aimed to simulate communications in biological nanonetworks by using diffusion of carriers/ions. In [15] the authors present a simulator based on NS-2, which uses the Brownian diffusion on a tridimensional environment, and implement three types of reaction models, i.e. NoReaction (pure contact with receiver surface triggers the assimilation of a carrier), Berg, and Gillespie. In [13], another software platform is presented for simulating Brownian diffusion channels, which implemented in Java and it is able to work in a two dimensional space, with an ongoing effort for the tridimensional extension under specific scenarios. Finally, it is worth citing the BiNS simulator, which is the platform used in this work. The basic functions of it have been illustrated in [8]. BiNS has been recently upgraded to BiNS2, which offers new functions to simulate bounded environments (cubes, cylinder, and spheres) by making use of the concept of simulation domains. The interested reader can find additional details in [10]. We used this simulator in this work thanks to its capability of simulating bounded spaces.

Finally, there are also simulators which model nanoscale electromagnetic communications (e.g., see [25]).

3. Experiment set up

With reference to the communication between platelets and endothelium illustrated in Section 2.1, since 95% of