MEHLISSA: A Medical Holistic Simulation Architecture for Nanonetworks in Humans

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ABSTRACT

In this paper, we present the concept of a complex framework, which is primarily designed to model and simulate the structures of and the processes in the human body and the interaction of nanobots with it. Medical nanobots are envisioned to perform their work in the body, for example by recognizing and destroying cancer cells. They are generally attributed an important role in a future precision medicine-based health system. It is crucial to simulate the use of nanobots in a human body before they are actually used. However, only with a comprehensive body simulation framework, like the presented medical holistic simulation architecture (MEHLISSA), it is possible to achieve meaningful results. As we model the human body as close to reality as feasible, this allows for reliable statements about the effectiveness and efficiency of the use of nanobots in vivo. To illustrate the advantages of an holistic simulation, we discuss the use case of metastasis prevention modelled in MEHLISSA.

CCS CONCEPTS

• **Networks** → **Network simulations**; • **Applied computing** → *Life and medical sciences*; • **Computing methodologies** → *Model development and analysis.*

KEYWORDS

Nanonetworks, Simulation, Medical application, Nano medicine

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1 INTRODUCTION

Metastatis is the primary cause of cancer morbidity and mortality [14]. 90% of cancer deaths are caused by systemic metastasis, however most research in cancer does not address the incidence that cancer cells disseminate through the body [14]. In the metastatic cascade, cancer cells detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade attacks of the immune system, extravasate at distant capillary beds, and invade and proliferate other organs [14]. Once the cancer cells run free in the cardiovascular system, the formation of metastatis needs to be prevented by all means. Therefor, they have to be rendered innocuous before they intrude new tissue at the latest. With the emerging field of medical nanobots, one can hypothesize a scenario where patrolling nanobots detect the freely flowing maligne cells, bind to them and force them to apoptosis by releasing proapoptotic drugs [19].

With scenarios like this in mind, we are currently developing a holistic simulation framework to model medical nanobots and their application in the cardiovascular system. Fully functional medical nanobots cannot be built yet, so that laboratory experiments, even on animal models, are not possible as of now. Thus, simulations are the driving force for new knowledge in this area. Additionally, even when nanobots become reality, it stands to reason to first simulate the application of nanobots. For example, the type and number of nanobots to be used in subsequent experiments can be determined with the simulation and thereby material and costs be saved. However, a network simulator such as ns-3[1] is not sufficient to enable realistic simulations of mobile nanobot operations in the body [21]. Rather, the structures of the body such as blood vessels and their dynamics, e.g. blood flow, must be included. These structures and dynamics of a living organism are much more complex than the processes in an electrical conductor, for example. That being said, with the necessary amendments, ns-3 is a great basis for nanonetwork simulation. As evidence of this, the THz module Terasim [7] for network simulation of nano- and macroscale scenarios has recently been added to the ns-3 main release. In addition, several other nano related modules have been developed for ns-3 in the last few years [6, 8, 13, 21].

With exception of our module BloodVoyagerS (BVS) [21], all modules address the communication layer and simulate the surrounding factors in the human body only at the channel level. We believe that it is not enough to look only at

[1] https://www.nsnam.org/

macroscopic structures such as large blood vessels; it is necessary to simulate the body as a whole complex from large vessels and organs down to the capillary and cellular level.

We therefore propose a comprehensive framework for body simulation that allows the modeling of processes and medical devices in the body at different scales and also includes the potential to model communicating nanobots and their use within the body.

2 FRAMEWORK

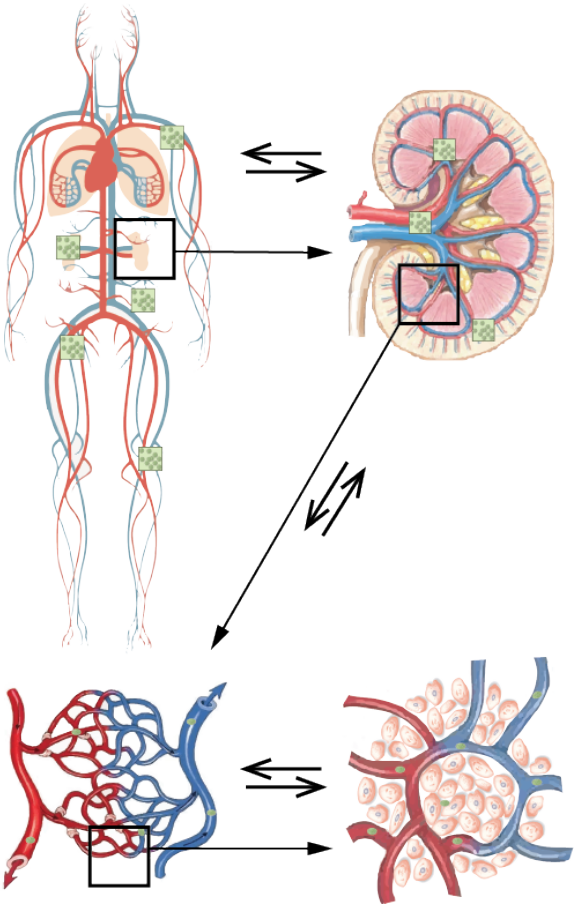

Figure 1: MEHLISSA: body-, organ- capillary- and cell-layer (from left to right, from top to bottom).

MEHLISSA consists of four connected but independent modules that represent distinct layers, namely the body-, organ-, capillary- and cell-layer. The layers differ in their temporal and spatial resolution and are linked through the exchange of parameters like mobility or state. The body-layer has already been implemented as BVS[2] in the established network simulator ns-3 [21]. BVS models the movement of a fixed number of nanobots through a simplified closed-loop cardiovascular system over time. The vessels are implemented as major arteries, veins and organs. In MEHLISSA the vesseltype organ is going to be the new module organ-layer that takes into account the significant differences like the vessel structure or the blood flow rate of organs. The structure and connection of the smaller vessels, i.e. arterioles, venules and capillaries also differs greatly depending on the region. This is going to be reflected in the capillary-layer. All three aforementioned layers mainly model the global and local movement of the nanobots. The fourth layer, cell-layer, models the inter- and intracellular communication, respectively the communication within cells and between cells or nanobots.

MEHLISSA enables the simultaneous simulation of most commonly discussed nanonetwork components with the four layer approach. Akyildiz and Jornet [1] introduced a network architecture for the internet of nano-things for intrabody applications. In [2] we discussed the challenges of such networks and the connection of in-body nano communication with body area networks (BANs). We presented our envisioned Nano Internet of Things (IoT) Network architecture which includes four major components. Firstly an analysis and control station is necessary, that communicates with BAN devices. Then those BAN devices are linkend with the in-body network via a gateway. The gateway can either be an implantable or an on-body device and needs to be able to use both micro- and nanocommunication. One main advantage of MEHLISSA is, that we can test and simulate the interaction of all four components in a setting, designed as holistic as possible.

In the following sections we take a closer look at every layer, which components of the Nano IoT Network are represented in it, and the important characteristics we need to model for a realisitic representation of the aforementioned layers. On the basis of our envisioned scenario of metastasis prevention, Section 7 additionally addresses how these layers can be interconnected and what kind of knowledge we can get from it for real life applications.

3 BODY-LAYER

The body-layer already exists in a basic version in BVS. BVS simulates the global movement of nanobots through the human body. We recently introduced BVS-Vis [20], a web-based visualizer for BVS result files, that enables rough visual analysis of the simulated nanobot distribution.

The BloodVoyagerS module has been released on github[2] with increased performance and in an extended version, which we present in the following subsection. Furthermore, a complete docker setup of BVS and BVS-Vis is available, which facilitates the execution of the project.[3]

3.1 BVS Update

BVS is constantly being refined and three major features have been added since introduction. Firstly, the vessels are now implemented in 3D with an adjustable number of virtual

[2]https://github.com/RegineWendt/blood-voyager-s

[3]https://github.com/RegineWendt/BVS-Vis

streams (see Figure 2). Secondly, this enables the implementation of different stream speeds to represent the characteristics of laminar flow. Thirdly, it is possible to load a vascular system model into the simulator dynamically.

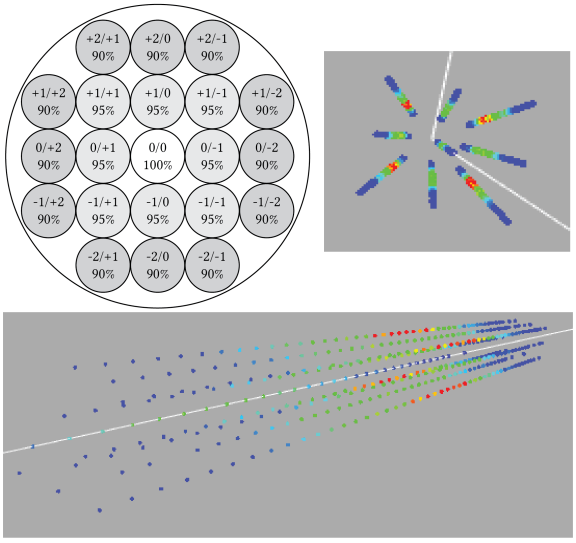

Figure 2: 3D representation of one vessel with several streams. At the top, the vessel cross section is shown with the offset from the origin and the proportional flow speed. At the bottom, the side view is illustrated.

So far, the implementation of the BVS vascular system has been realized with a fixed number of streams for all vessels. In the new version the class `Bloodstream` has been developed to map several streams in a blood vessel. `Bloodstream` has an ID, a size, a base speed and a speed factor. Aside from that, the coordinates of the stream are given to indicate the deviation from the center of the vessel, if necessary. The streams coordinates are calculated automatically from the number of streams and the vessel size.

`Bloodvessel` now manages a list of `Bloodstream` objects on which it calls operations to move the nanobots. Additionally, `Bloodvessel` contains the definition of the stream size. This stream definition consists of a constant that specifies the number of streams and a two-dimensional integer array that defines a velocity factor in percent and an offset for the coordinates for each stream, followed by an indication of the displacement of the coordinates on the two coordinates that do not correspond to the direction of flow. The stream definition is shown in Figure 2 on the top left.

The 3D vessel representation is the basis for the implementation of lower layers as it enables the subsequent splitting of particular streams from one big vessel into new and smaller vessel structures like needed at the organ or capillary level. In addition, the introduction of the velocity distribution in a vessel with laminar flow is an important step towards a more realistic representation of the vessel system, as it is the foundation of many characteristics of the blood supply. For example, the slower speed at vessel walls due to the increased friction, allows for the exchange of substances between the bloodstream and adjacent cells.

The third new feature enables the use of any cardiovascular models if they fit the CSV format: ID, $vesseltype$, $startcoordinate\ x$, y, z, $stopcoordinate\ x$, y, z. The CSV file must be named `vasculature.csv` and must be located in the ns-3 root directory so that it is recognized and loaded by the BVS module. The file is converted into an internal two-dimensional array. The array is used to instantiate the required vessels in the software. Afterwards the vessels are linked to each other by the start- and end-coordinates to create a vessel system, which is then used in the simulation.

This enables the simulation of different body models and scenarios in an automated way. The next step, we are currently working on, is to generate body models from CT images of real patients and to feed them into our simulator. For the model generation we utilize SimVascular [18] which enables medical image data segmentation and patient-specific blood flow simulation.

Open Questions: The body-layer is used to model the BAN-to-gateway and the gateway-to-nanonetwork communication level. Open questions are for example, where the stationary BAN devices and gateways can be positioned and how this will influence the spreading of messages. How many gateways are needed to read out the nanobots, trigger a program change, reliably communicate with enough nanobots or to localize specific nanobots. Stelzner and Traupe [15] introduced an FCNN algorithm for localization and used BVS to analyze triangulation of nanobots via gateways. They have shown that the positioning and amount of gateways have an impact on the precision of the estimated location of nanobots [15]. Other questions are if microsized gateways or smart probes are needed for stable communication on this layer and if the nanobots can be read out reliably as they flow past a gateway, without being stationary or slowed down while being read out.

4 ORGAN-LAYER

Stelzner and Traupe [15] have shown that it is possible to correlate the nanobots location with the proximity to an organ via triangulation. This enables the assignment of measured values of one nanobot to an individual organ, which is a key point for meaningful analysis of detected anomalies. Firstly, since the composition of metabolic products differs from body region to region. Secondly, for a specific treatment after the detection it is important to know the site of action. So, if nanobots measured markers of inflammation in the lungs, the drug release should also be restricted to this area.

On the organ-layer we model the organs as introduced in BVS, but in greater detail. Each organ is a group of at least two tissues that are arranged in such a way that they fulfill a specific function. In that sense, skin, muscle, bone and blood are organs as well and are added as individual classes

in the organ-layer. Each class models the peculiarities of the respective organ, such as the tissue and vascular structure. The goal is also to represent the realistic size and extent of individual organs. Figure 3 shows the size of the colon and kidney in relation as an example. While the kidney measures $11 \cdot 5.5 \cdot 3.5$ cm on average, the colon 120 to $135 \cdot 7$ cm and the small intestine is even 3 to 6 m long. This has a significant influence on the vascular structure of the supplying blood vessels. Apart from this, organs differ greatly in their perfusion in general and depending on the activity. The blood volume flow changes according to the oxygen consumption of the individual organs in the current situation. While exercising, for example, the demand for bloodflow by the heart is more than doubled and the demand of muscles is up to tenfold [9]. This is going to be reflected in different scenarios within the simulator.

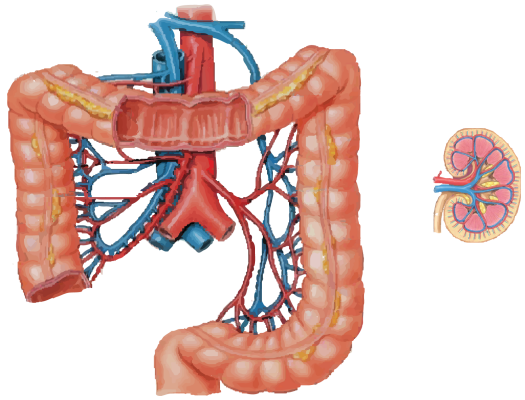

Figure 3: Size of the colon and kidney in approximated relation.

Open Questions: The organ-layer is used to model the organ-wide communication of nanobots. The key question is, whether a mapping of organs is possible so that a nanobot has an organ awareness. Every nanobot should record in which location substances or events were detected for meaningful interpretation. Building on that, the question arises whether more powerful devices like nanorouters, microinterfaces or gateways are necessary in specific locations or even at every organ to ensure this organ awareness of simple nanobots. Apart from this, the impact of different scenarios on the blood flow and therefore nanobot distribution is simulated. This is the basis to analyze and compare the performance of communication strategies in more depth and under more realistic conditions.

5 CAPILLARY-LAYER

The human vascular system consists of arteries, capillaries and veins, through which the heart pumps blood continuously. Large, elastic arteries conduct the blood away from the heart and are divided into medium-sized, muscular arteries. This level is reflected in the body-layer. The arteries are broken down into smaller arteries and then into even smaller arterioles, which is modelled in the organ-layer. The arterioles penetrate the tissue and split there into tiny, innumerable capillaries, which are the smallest vessels in the body. The exchange of substances between the blood, tissues and organs takes place in the capillaries. Oxygen, nutrients and other metabolites diffuse from the blood through the capillaries into the interstitial fluid, from there into the cells and back the other way round. The interstitial fluid fills the narrow space between organs, tissues or cells.

The number of capillaries depends on the metabolic activity of the tissues, that surround them. Therefore, in the muscles, brain, liver, kidneys and nervous system many capillaries are to be found. If a tissue is passive, the blood only flows through a small proportion of its capillaries. Precapillary sphincters (ring muscles), which are located at the end of the arterioles, control the inflow. Most sphincters are closed in a passive tissue. When the tissue is active, such as a contracting muscle, the sphincters relax and the entire capillary network is flowed through. Such a capillary network, also called capillary bed, is shown in Figure 4. Depending on the communication range of the respective simulated method, it is likely that communication from one end of the capillary bed to the other requires multiple hops. Hence, the communication is between several nanobots which form a cluster.

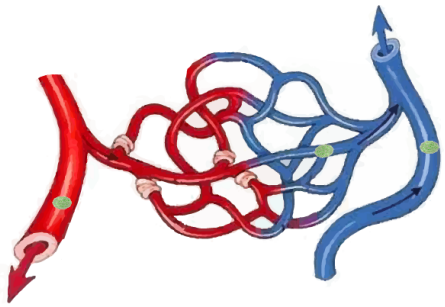

Figure 4: Capillary bed with four closed sphincters. Nanobots indicated in green.

Open Questions: The capillary-layer is the level where different communication strategies among nanobots are implemented and the actual communication channel is modeled. As there is extensive research available on channel models, we are going to incorporate those findings into our model and focus on the comparison of different approaches. Open questions, that are going to be answered on this layer are for example, how many nanobots are needed to cover communication over a capillary bed. This knowledge is going to be useful to simplify the simulation on higher layers, so that the communication over a capillary bed can be abstracted with a distance and duration constant if the necessary number of nanobots is present. Subsequently it is also of interest how long a nanobot holds its position on the micrometer or millimeter scale of the capillaries and if it can be assumed to be partly stationary over a short period of time.

6 CELL-LAYER

The cell-layer focuses on the actual communication of nanobots with cells mainly via molecules, while on the capillary-layer the communication of nanobots among each other is addressed. The cell-layer plays an important role as it is the level of initiation and progression of disease and the target site of pharmacological intervention. Targeted drug delivery is a key component to improve cancer treatment and to minimize the serious side-effects of chemotherapy, where healthy cells get killed as collateral damage. To model the identification of biomarkers or cells and the subsequent treatment via targeted drug delivery we take a look at the cell-to-cell communication.

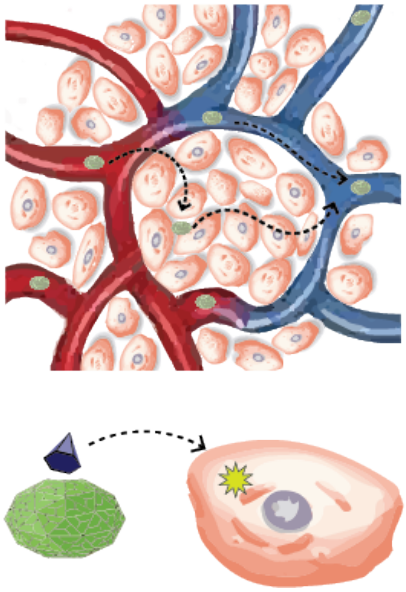

Figure 5: Cell-layer: On the top, capillaries holding nanobots and surrounding cells. On the bottom, a nanobot releasing a drug, which diffuses to a cell, where a subsequent reaction occurs.

Cells have several signaling mechanisms to exchange important biological information. In the scope of nanobots and their interaction with those techniques cell-cell contact mediated strategies like gap-junctions, autocrine and paracrine signaling are of no ostensible interest. The key paradigm for nanobot-to-cell communication is the endocrine signaling, where signaling molecules travel from transceiver cells to target cells via the bloodstream. The signaling molecules are either released directly, like Insulin, into the bloodstream or within secretory vesicles [11]. The distribution of those molecules and vesicles through the cardiovascular system is simulated on the higher layers.

For the cell-layer, we plan to model the drug release from nanobots and the effects on a specific target cell (see Figure 5). To get an understanding of the time bounds of such a drug release, we are going to use the cell-to-cell communication network of Thurley et. al. [17]. They developed a model where intracellular signal transduction networks are treated as black boxes and can predict communication network structures. The simulation runs in Matlab R2015a[4] and we plan to use the resulting response time distribution as input parameter for our simulations at the cellular level.

Open Questions: The cell-layer is the level of inter- and intra-cellular communication. One key goal is to incorporate results of in vitro and in vivo experiments to get realistic abstractions for the modeling of higher levels. In addition to the simulation of molecule detection, drug release and its consequences, an important question is whether nanobots are able to communicate through cells with specific methods as indicated in Figure 5. This is going to be tested for different communication strategies like acoustic, electromagnetic molecular and ultrasonic communication.

7 METASTASIS PREVENTION IN MEHLISSA

For our envisioned scenario, the prevention of metastasis formation, every layer of our framework plays an important role. In summary, the nanobots run in the bloodstream where they detect a maligne cell. This detection triggers the release of a proapoptotic drug which diffuses to the maligne cell. The formation of a metastasis can be averted that way.

The starting point of our scenario is the modeling of nanobots patrolling the body. No communication is taking place, so the nanobots are just being distributed by the body-, organ-, and capillary-layer. When a nanobot arrives at an organ, it is handed over to the respective organ and then to one of its capillary beds and back in the same way.

Quite similar, a cancer cell gets detached from a primary tumor, e.g. at a capillary-layer of the lungs and then handed to the organ- and then the body-layer.

Now, the maligne cell and nanobots run free through the cardiovascular system. Next steps are the modeling of the nanobots detection of the maligne cell and the release of the death ligand till the binding. The release of the drug and the subsequent binding to the maligne cell are a classic transmitter-receiver relation. In this area, a lot of research has been done in the past years on molecular communication. As one of the first Pierobon and Akyildiz [12] introduced a physical end-to-end model for the diffusion of particles in a fluidic medium. In general, basic diffusion channels have been studied and described with Brownian motion in Fick's law [16]. Up to date, there are several simulators for molecular communication [4, 6, 10, 22]. When comparing the four simulators, BiNS2 [4] has the most features and is the only simulator that is continuously expanded and adapted to new technologies. Felicetta, Femminella and Reali [4] built the software platform BiNS2 that simulates diffusion-based molecular communications with drift inside blood vessels. It allows the simulation of a variety of different scenarios, including pure diffusion and specific medical scenarios. There

[4]https://www.mathworks.com/

is already a scenario implemented, that simulates the detection of circulating tumor cells in the bloodstream so we plan to carry out the simulation in BiNS2 and use the data the simulator outputs to a database as input for our simulation framework at the capillary-layer [5].

In addition to the modeling of the signal molecule transmission with BiNS2 we plan to incorporate another model that simulates the secretion of molecules within a vesicle. Sun et. al. [16] developed a model of blood capillary systems which considers the vesicle release and propagation process in capillaries and the positive drift due to the bloodstream pressure. We think it is important to have both options for our simulation, as it is not clear, if the free release of apoptotic factors into the bloodstream won't have any side effects that means the release within vesicels could be a promising alternative.

On the cellular-layer we model the induced apoptosis after the drug was received at the maligne cell, as simulated in the capillary-layer. We are going to model the caspase activation and execution pathway to get a response time distribution for the time it takes from death ligand binding to the actual cell death, like described in [3]. The holistic simulation of this exemplary scenario in MEHLISSA is going to generate a realistic timeframe on how long it actually takes to intercept a maligne cell, starting from the detachment from the primary tumor and distribution through the body, till the cell is killed.

8 FUTURE DIRECTIONS

The combination of differently scaled and specialized layers in MEHLISSA enables a realistic simulation of the global distribution of nanobots and cells in concert with the simulation of nanobot-to-cell communication. With this approach we aim to model the detection of biomarkers, the subsequent release of drugs and the effect of those drugs on the targeted cells. The simulation results will be more realistically compared to simulations where only stationary positions are assumed, as they are deployed into a living and breathing body.

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