BloodVoyagerS – Simulation of the work environment of medical nanobots

Regine Geyer, Marc Stelzner, Florian Büther and Sebastian Ebers
{geyer,stelzner,buether,ebers}@itm.uni-luebeck.de
University of Lübeck, Institute of Telematics, Ratzeburger Allee 160, 23562 Lübeck, Germany

ABSTRACT

The simulation of nanobots in their working environment is crucial to promote their application in the medical context. Several simulators for nanonetworks investigate new communication paradigms at nanoscale. However, the influence of the environment, namely the human body, on the movement and communication of nanobots was rarely considered so far. We propose a framework for simulating medical nanonetworks, which integrates a nanonetwork simulator with a body simulator. We derive requirements for a body model that forms the basis for our prototypical implementation of the body simulator *BloodVoyagerS* as part of the network simulator ns-3. Our evaluation shows that BloodVoyagerS successfully moves nanobots in the simulated cardiovascular system. After about 7 minutes, the nanobot distribution reaches a dynamic equilibrium. The prototype shows promise to provide a more realistic full-body simulation to investigate movement and communication of nanobots in medical applications.

CCS CONCEPTS

• **Networks** → *Network simulations*; Mobile ad hoc networks; Wireless access points, base stations and infrastructure; • **Applied computing** → *Life and medical sciences*; • **Hardware** → **Emerging simulation**;

KEYWORDS

Nanonetworks; Simulation; Medical Application; Nano medicine

ACM Reference Format:
Regine Geyer, Marc Stelzner, Florian Büther and Sebastian Ebers. 2018. BloodVoyagerS – Simulation of the work environment of medical nanobots. In *NANOCOM '18: ACM The Fifth Annual International Conference on Nanoscale Computing and Communication, September 5–7, 2018, Reykjavik, Iceland.* ACM, New York, NY, USA, 6 pages. https://doi.org/10.1145/3233188.3233196

1 INTRODUCTION

Nanobots, artificial or biological devices at nanoscale, are envisioned to be used within living bodies to be remote-controlled or autonomously detect and treat diseases, morbid cells and other medical situations. The unique circumstances of nanoscale operation as well as deployment in living tissue require new suitable devices, algorithms and applications. Before these can actually be applied in a living body, they have to be thoroughly tested. Typical testing approaches include simulations or wet-lab experiments. The latter however, are comparatively complex and expensive, as they require existing hardware and suitable labs. A simulation usually operates on a simplified model of the original system. Still, the crucial aspects of the intended investigation have to be represented adequately for the simulation to provide meaningful results about the object of investigation [17], for example, how an algorithm will perform in the original system. In addition, simulations also allow completely controllable experiment environments. The researcher can control or even intentionally ignore effects that are unavoidable in wet-lab experiments in order to deliberately pose or relax restrictions, requirements and assumptions. In combination with repeatability and cost-efficiency, these advantages make simulations valuable tools to evaluate new algorithms, especially at an early stage.

A *medical nanonetwork* [4] comprises of *nanobots* equipped with sensors, actuators and communication devices, that operate in concert within a human body. To evaluate a medical nanonetwork, a simulator has to model a communication network with communication channels and protocols usable at nanoscale. Additionally, it has to include the working environment, namely a living body, in order to correctly simulate the effect on the nanobots' movement and communication. To the best of our knowledge, a simulator including communication and a closed loop model of the cardiovascular system as the nanobots' environment does not exist. However, combining both aspects is crucial for a medical nanonetwork and, thus, their modelling for obtaining meaningful simulation results.

In this paper, we present a sketch of a simulator suitable for medical nanonetworks, which combines network and body simulation. In previous works, we found that *ns-3*[1] in conjunction with specialised modules like *Nano-Sim* [19] is a suitable nanonetwork simulator [23]. For modelling the nanobots' working environment, we develop *BloodVoyagerS*, a body simulator currently in prototypical state. It features a simplified model of a human body's cardiovascular system to simulate the nanobots' mobility. BloodVoyagerS is implemented as a ns-3 module, intended to work in concert with the rich communication models and protocols already available in ns-3.

After introducing related work in Section 2, we present the concept and architecture of our body simulator BloodVoyagerS as well as the combined simulation framework. Then we state requirements for a meaningful body simulation in Section 4. In Section 5, we describe the underlying model of our prototypical implementation. Section 6 investigates the mobility of nanobots injected into the simulated vascular system.

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

NANOCOM '18, September 5–7, 2018, Reykjavik, Iceland

ACM ISBN 978-1-4503-5711-1/18/09…$15.00
https://doi.org/10.1145/3233188.3233196

2 RELATED WORK

There are several ways to subdivide existing simulators of the cardiovascular system (SCS), e.g., by simulation of standard versus pathological conditions. In the early 60's one of the first SCS was developed to examine the hemodynamics of the arterial system by means of an analog computer [15]. Another standard condition simulator, which is used in teaching, is a real-time simulator that helps to get a deeper understanding of the relation between blood pressure, volume and flow [8]. In the first approach BloodVoyagerS will aim to simulate standard conditions to get a better understanding of the movement of nanobots in a healthy body. However, in the further course of development the simulation of pathological conditions and medical scenarios is desired, just as the majority of the SCS are used to model pathological conditions.

In this area simulations have the advantage that system damaging states can be simulated without consequences and variations of the parameters can be tested well due to their reproducibility [11]. This way animal experiments can be reduced and newly developed medical products can be tested without ethical limitations [11]. One of the early SCS describes the arterial system and was used to investigate hemodynamics under pathological conditions (e.g., arterial sclerosis, stenosis) [2]. Furthermore, many SCS are used to test and analyze cardiac support systems [7], e.g., heart-lung machines [21] or mechanical cardiovascular devices in general [9].

All SCS have in common, that the underlying model is mostly contingent upon the medical problem or question that should be examined. One can subdivide the SCS again in groups according to their model. There are simulators that model only the arterial tree [2, 15], the systemic circulation [7]. Other model both, the pulmonary and systemic circulation [3, 8, 9, 21]. However, they all have in common that their model consists of simplistic compartments. Depending on the field of application the compartments differ in complexity, scope and level of detail. The need for different levels of abstraction results from the high complexity of the human body. In the context of medical nanobots, the focus is on simulating the cardiovascular system as a transport system. Therefore, the large and the small blood circulation must be simulated with the same level of detail. Furthermore, in contrast to all existing simulators the limbs and body parts have to be included explicitly in the model as well.

Another interesting SCS simulator is SimVascular, a free simulator that takes a different approach. It is a grand open source project, that offers a complete system from the segmentation of medical image data to patient specific blood flow simulation and analysis [25]. SimVascular contains the boundary conditions to represent physiological levels of pressure and fluid interactions and builds a vessel model from image data. It is used to examine the blood flow in the heart, brain or lungs, for different disease scenarios or for operational planning. Basically, SimVascular is designed to output a complete file which summarizes the models and results after completing a simulation. SimVascular then visualizes the hemodynamic results in graphics and images. That said, it would require an unpredictable programming effort to output the data at run-time. The data on the different bloodstreams, for example, position and speed and the basic information about the vessels such as diameter and shape would be of interest for the nanonetwork. For this purpose, SimVascular crucially lacks a model that maps the entire human body or its vessels. There is a repository for models, but they always show only small parts of the whole system, such as the aorta or the bronchi. In addition, the repository is not available for free.

For the purpose of examining the movement of nanobots in the complete cardiovascular system one would therefore first need whole-body scans that SimVascular then needs to translate into an overall model. Problematically, images of whole-body scans in the necessary resolution are not publicly available. Because of the unpredictable programming effort and the lack of a suitable model or suitable medical images for the creation of such a model, the use of SimVascular as a body simulator for the movement of nanobots currently appears to make little sense.

In the nano community relevant work has already been done to incorporate the physical environment in nano network simulations. In [10] a software platform called BiNS2 was introduced that simulates molecular communication with drift inside bloodvessels. This marks an important step towards a realistic simulation. However, the effects that are included are limited to one up to a few blood vessels. This is also the case for a novel communication scheme which is mapped into the 1906.1 framework [12] by [27]. Another limitation of most existing models is that nodes are assumed to be fixed [1, 18], which is rather unrealistic since the medium, i.e., the fluid in the human body, is in constant movement and exchange. A first approach for a more holistic blood vessel model was made in [6] where they combined a cardiovascular model and a drug propagation network. The model analytically calculates the drug delivery rate based on the injection rate. Unfortunately, the model is restricted to arteries so the result of the distribution over more than a few heartbeats is not realistic. Furthermore, drugs are almost always injected into the venous system since arterial drug injection leads to major complications [20]. Therefore, the simulation should start in the venous system which is not possible in [6]. Accordingly, in [5] the need for a simulator with a closed circulation loop is discussed. To the best of our knowledge no such simulator exists to date and we intend to close the gap with BloodVoyagerS.

3 CONCEPT

Similar to vehicular networking simulations we model communication and the environment in separate bidirectionally coupled modules. The characteristics of the cardiovascular system need to be appropriately modelled, since the nanobots will most likely move almost permanently in the bloodstream. A suitable and well established discrete-event network simulator is ns-3 [16].

It is implemented in C++, its construction is modular and therefore free and easy to extend. Hence we implement our prototype BloodVoyagerS as a module in the ns-3 simulator. In its prototypical design and implementation, BloodVoyagerS is a self-contained ns-3 module. Nanobots currently resemble plain ns-3 nodes, are instantiated directly in BloodVoyagerS and do not communicate with each other. We conceptualize the framework for simulating medical nanonetworks consisting of the ns-3 simulator, including the BloodVoyagerS module and a nanonetwork-module, e.g., *Nano-Sim* [19], as sketched in Figure 1.

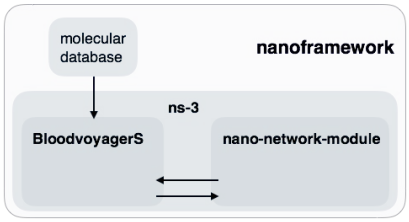

Figure 1: Components of our conceptualized medical nanonetwork simulator based on ns-3.

In addition there is need for a molecular database, that should be connected with BloodVoyagerS to feed realistic data about the molecular conditions in the cardiovascular system.

A full medical nanonetwork covering the complete human circulatory system requires a high number of nanobots, which directly influences simulation performance. The overall blood volume in a human body is about 4900 cm^3 [22]. Assuming a communication distance of 2 mm [26], a medical network thus requires at least 2.45×10^6 nanobots. Alternatively, the length of all vessels in the vascular system is estimated at 120 000 km [24]. With the same communication distance, the system requires 60×10^9 nanobots to cover the full length. While these estimations provide an orientation for expected nanobot counts, a simulation should be able to deliver more precise estimations.

4 REQUIREMENTS

BloodVoyagerS aims to provide a simulation environment to study the behavior of nanobots within the human vascular system. It focuses on simulating the environmental influence on communication, as well as detection and actuation of medical parameters. A set of requirements makes these goals explicit:

(1) The simulator must model a complete human circulatory system. It should include all major vessels, and simulate abstractions for arterioles, venules and capillaries to a suitable level of detail. The model for each vessel should include its diameter and length, as well as its relative position, including the connectivity to other vessels.

(2) The simulator must provide a spatial model of the cardiovascular system. As discussed in Section 2, to date no model exists that congruently describes the entire circulatory system at a uniform depth. The limbs or body regions are particularly neglected, as they contain no vital organs. However, in the context of medical nanobots, the precise localization of nanobots is important to correctly correlate data. Therefore, the model needs to represent the locality as precisely as possible.

(3) The simulator must represent the medium inside the circulatory system, that is, the blood. The composition of blood has a strong influence on electromagnetic communication [26]. A high amount of water as well as moving cells within the blood interfere with or outright block communication. Additionally, the blood may react chemically or mechanically with the nanodevices, damaging or displacing them. A special case of this are the cells of the immune system, which may react to the nanobots, in the worst case specifically attacking them.

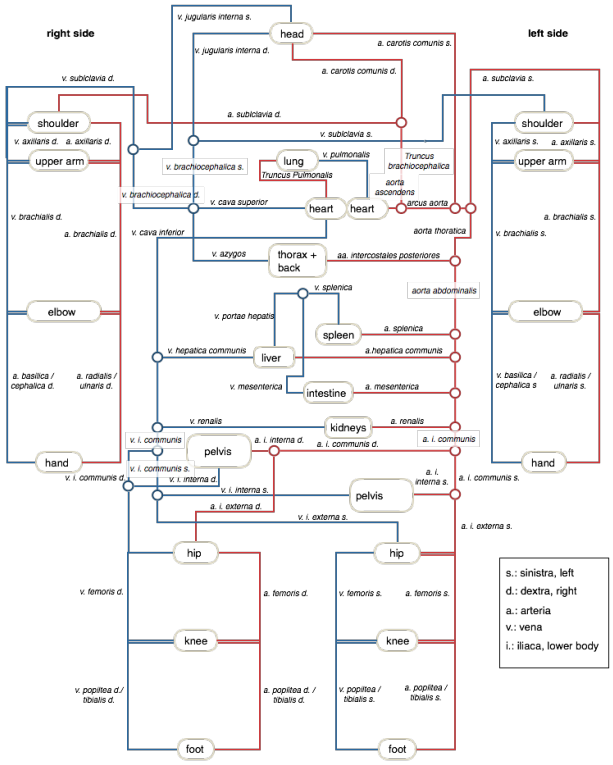

Figure 2: Representation of the most important vessels of the human body.

(4) The circulatory system pushes floating particles around with its flow, moving nanobots through the body. This movement is of great importance for continuous or long time tasks for nanobots, especially if the whole body must be observed. The simulator must consequently simulate the movement of nanobots within the blood as accurately as possible. In the context of Requirement 1, the simulator needs to route nanobots at branches in the circulatory system. Nanobots should be distributed according to the blood distribution ratio. For example, if a small vessel forks from a larger, it should be more likely that the nanobot stays within the larger vessel.

5 MODEL

To meet Requirement 1, the relevant vessels must first be determined. Figure 2 shows the main vessels that provide local coverage and contain large organs and limbs. Overall there are 94 vessels and organs covered. Since there are no databases or collections on the vessel length, for rough orientation, a 1.72 m woman, weighing 69 kg was measured on the skin surface.

With the aid of anatomical drawings [14], the correct course of the vessels and the organ positions were derived as realistically as possible. For simplicity, only the chest and back are summarized and positioned in the left half of the body, as it is difficult to visualize in its spread. Coordinates are derived from the measured distances. The origin of the resulting xy–coordinate system is placed in the left half of the heart.

Since the human body is three-dimensional, the spatial direction from the front (anterior) to the back (posterior), the z-coordinate, is still lacking. The measurement of the organs from anterior to posterior on the skin is not possible and again there is no record of all relevant dimensions. Therefore, in our prototype, the spatial depth of all organs is equated. As a guideline, the thickness of the kidney is used, which is between 3 and 5 cm. Accordingly, all z distances are set at 4 cm. The z–axis should run in the middle, resulting in z–coordinates between 2 and -2. As a further simplification, it is assumed that arteries are set anterior and veins posterior. This corresponds to anatomical reality in many places. Transitions from arteries to veins exist not only at organs but also, for example, on the limbs such as hands, head or knees. Here is the depth set to 4 cm as well. Thus, the z-coordinates are from 2 to -2, since the flow direction is always from arteries (z = 2) to veins (z = -2). Only the heart transitions blood from the venous system to the arterial system and therefore pumps the blood in the model from posterior to anterior. In Figure 5 the xyz–coordinates of the organs and body regions relevant to the simulation are shown with nanobots added.

In addition to coordinates, length and angle, the vessels have other important properties. Requirement 1 as well requires the determination of vessel diameter, flow and flow rate. For most vessels, there are no exact details about their diameter. The vessels to be explicitly simulated are the aorta, arteries, and veins. Arterioli and venules are not among the most important vessels and often have no names of their own. There are about 400 million arterioles and similar numbers of venules. The inclusion of so many vessels in the body model with reasonable effort is not feasible at the moment. It is important to determine exactly what level of detail is required to perform or simulate a rough localization of the nanobots while keeping the computational effort within a certain time frame.

For arteries the average diameter is 4 mm and for veins 5 mm [13, 22]. The flow rate depends on the relationship between pressure difference and flow resistance. The smaller the vessel, the greater its resistance and the slower the blood will flow. In the aorta the blood has an average velocity of 20 cm/s, in the arteries 10 cm/s and in the veins 2–4 cm/s. This can be transferred directly to the large vessels. The transitions between arteries and veins are greatly simplified and no arterioles, venules or capillaries are explicitly modeled. In the arterioles there is a velocity of 2 cm/s and in the capillaries 0.02 cm/s. These velocities cannot be transmitted directly, but are approximated by 1 cm/s in the transitions.

In a healthy cardiovascular system, the flow in the bloodstream is laminar except in the aorta and pulmonary artery, meaning that the flow consists of ordered layers that slide past each other.

This effect is implemented in the model by separate streams in each vessel. In the area of the arteries and veins, these currents do not mix. In order to indicate the high degree of branching of the smaller vessels in the organs, the nanobots can change the currents here. This turns each stream into a pseudo-vessel that communicates with its neighbors.

6 EVALUATION

This section assesses the established body model and its implementation in BloodVoyagerS. BloodVoyagerS provides a first implementation of the requirements outlined in Section 4. First, the simulation parameters of BloodVoyagerS are analyzed and some simulation results are discussed. For the analysis of the position data MATLAB (2014b) was used. Thereafter, the fulfilment of the individual requirements is checked concretely. If requirements have not yet been met satisfactorily, a potential implementation is discussed.

The representative scenario investigates nanobot distribution speed. At the start of simulation, all nanobots are injected at the same location. The simulation investigates the duration required to achieve a stable equilibrium, that is, until the number of nanobots in each vessel is constant.

Analysis of simulation parameters

Section 3 mentions the number of nanobots as an important simulation parameter, and establishes an upper bound of 60×10^9 nanobots based on the full system length. Our simulation includes a total length of 12.717 m of blood vessels, which results in an estimate of 6359 nanobots to achieve full connectivity, so that a message can be sent from any point and, through forwarding by other nanobots, reaches all nanobots existing in the body.

A suitable simulation duration is achieved if the average distribution of the nanobots no longer changes. It has then reached a dynamic equilibrium, where in each time step just as many nanobots leave a vessel as nanobots enter. As an upper limit, a simulation duration of 2 h was proposed.

The central injection site was the *aorta ascendens* and the results of the distribution were later compared with other injection sites. By visual comparison of the distribution of nanobots after 1 min, 15 min and 2 h (not shown), it becomes clear that the distribution after 1 min differs from that after 2 h. There are apparently fewer nanobots in the arterial vessel area than after 2 h, and the nanobots are more clustered. The distribution after 15 min is already similar to 2 h. In the heart area, the nanobots are very close to each other and more scattered in the limbs (see Figure 5). The similarity or deviation is clearly visible in Figure 3. While there are deviations of up to 255 nanobots per vessel after 1 min (bar), the largest deviation after 15 min is 4.1 nanobots per Vessel (line). The numbers always compare to the average number of nanobots in the respective vessel over the last minute, for example, the distribution after 15 min compares to the average over 14 min to 15 min.

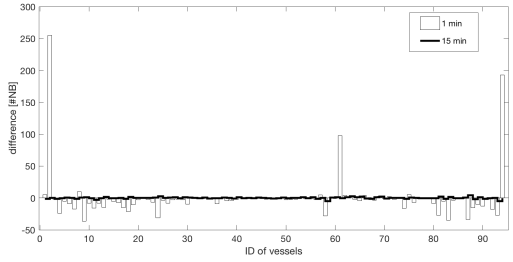

Figure 3: The x-axis shows the 94 simulated vessels (see Figure 2), the y-axis shows the difference in number of nanobots (#NB) relative to the previous minute.

To determine the point in time at which the nanobots are sufficiently distributed, the simulation measured the number of nanobots in each vessel each minute for the first 40 min. The results are compared with the distribution after 2 h by the standard deviation between the distribution after each minute and that after 2 h per vessel. The results were summed up and divided by the number of vessels. Figure 4 shows the resulting mean standard deviations.

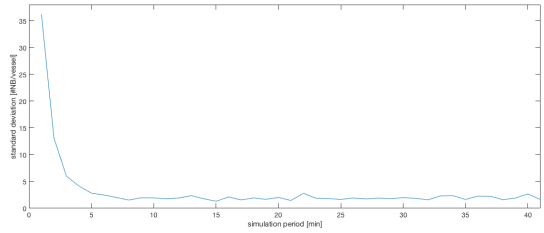

Figure 4: Standard deviation between different distributions.

The deviation quickly decreases within the first 5 min, after which it undergoes only slight fluctuations. Thus, even after a simulation time longer than 2 h, without external influences no major fluctuations in the distribution can be expected.

The mean standard deviation in Figure 4 is 2.11 NB per vessel (excluding values after 1 to 2 min due to large deviation). Thus on average, there is a variation of 2–3 nanobots per vessel compared to the distribution after 2 h. This corresponds to a total deviation of 3.11 %, and is therefore low enough to be considered a dynamic equilibrium. The standard deviation falls below the mean value for the first time after 7 min, where it reaches a value of 2.03 NB per vessel. The distribution of nanobots after 7 min is shown in Figure 5. Therefore, a simulation duration of 7 min is sufficient to compare the simulation results of different injection sites below.

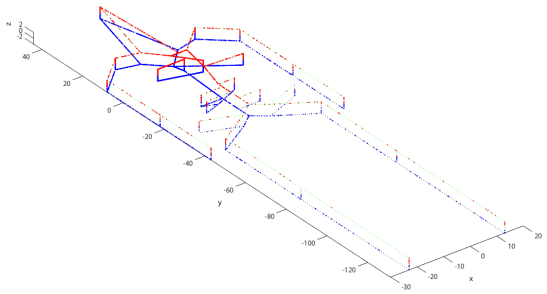

Figure 5: Distribution of 6359 nanobots after 7 min simulation period with injection in the *aorta ascendens*.

In order to inspect injection point dependence, a second simulation investigates the *vena poplitea tibialis*, which is the vessel furthest away from the *aorta ascendens*. Again, the simulation injects 6359 nanobots into this vessel and observes the distribution after 7 min. This distribution has a mean standard deviation of 4.0 % from the previous simulation's reference, the distribution from injection into the *aorta ascendens* after 2 h. Direct comparison of the two distributions after 7 min yields a deviation of 3.95 %.

The distribution 7 min after injection in *vena poplitea tibialis* is close to the distribution after injection in *aorta ascendens*, with 4 % deviation compared to 3.11 % deviation on average. In simulation, the injection site of the nanobots thus becomes irrelevant after a duration of a few minutes. Further experiments therefore always inject the nanobots into the *aorta ascendens*.

Lastly, a third evaluation inspects the last simulation parameter, the number of nanobots. In the results from previous simulations, there are clearly parts of the body that are not covered by nanobots, as can be seen in Figures 5. These gaps interrupt communication, which in turn limits overall connectivity. As other parts receive good coverage, the nanobots are apparently not uniformly distributed.

It is unclear if the non-uniform distribution stems from an insufficient simulation or if it might occur similarly in a real deployment. A further simulation inspects the results with the tenfold amount of 63 590 nanobots. Figure 6 shows the distribution result after a simulation of 7 min. Gaps in coverage are smaller, but still occur, mainly in the limbs. Large enough numbers of nanobots might be able to eventually reach full connectivity, however, the number of nanobots does not resolve the phenomenon of non-uniform distribution. In order to validate the obtained results and verify the BloodVoyagerS prototype, the next section provides a qualitative comparison of BloodVoyagerS with the requirements defined in Section 4.

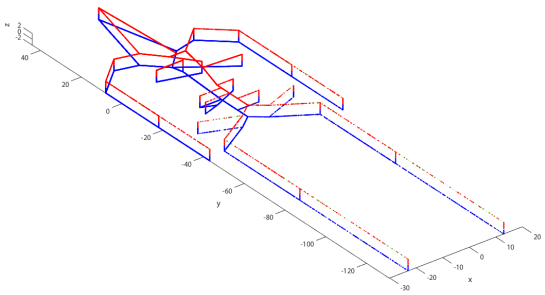

Figure 6: Distribution of 63590 nanobots after 7 min simulation period.

Review of requirements

Next to the previous quantitative evaluation, we can evaluate how successfully the requirements from Section 4 are met in the prototype version of the simulator.

As requested by Requirements 1 and 2, BloodVoyagerS provides a representation of the circulatory system as a complete closed network including all major organs, arteries and veins, as seen in Figure 2. This does include correct relative positioning and length of the vessel in two of the three dimensions as well as the branches between the components, the variation in diameter is not included. The integration of the third dimension proved to be very difficult, as the literature is vague here, mostly oriented at 2D models. Nevertheless our implementation does allow the simulation to track the position of each individual nanobot in the bloodstream, as per Requirement 4. The millions of smaller arteries and veins are not directly represented in BloodVoyagerS, as they are not explicitly

defined and therefore require a different implementation approach. In order to indicate a high branching degree, parallel streams of the same vessel are introduced. We envision to add procedurally generated smaller blood vessels to the body model using the explicitly defined major blood vessels as junctions and roots.

Requirement 3, the simulation of the circulatory medium, is not yet met with BloodVoyagerS. The representation of the medium and its properties is an additional and complex topic of its own. The future integration of a molecular database is essential for a realistic illustration of the biological and chemical processes in the medium.

The need for realistic movement described in Requirement 4 is implemented in a more abstract first version, and depends only on the type of vessel the nanobot is in. Of course, the bloodstream in the human body is not of constant velocity. In the further process of development we first consider to integrate the distance to the heart and the heartbeat frequency as velocity modifiers. Second we look at additional options such as the posture of the human as well as the human's level of arousal.

7 CONCLUSION

This paper presented BloodVoyagerS, a prototype of a body simulation module for ns-3 as part of a simulation framework for medical nanonetworks. To obtain meaningful results form a simulative evaluation, the key aspects of a medical nanonetwork—namely suitable communication protocols and models as well as a suitable working environment—have to be modelled. For communication, our framework will utilize functionality already provided in ns-3 and available third-party modules. Since – to the best of our knowledge – no ns-3 module for simulating the whole cardiovascular system exists, we designed and implemented BloodVoyagerS. The prototype models a simplified human vascular system to realize the movement of nanobots within the human body. The simulation shows that BloodVoyagerS moves injected nanobots as expected, and that the nanobots achieve a dynamic equilibrium after about 7 min.

So far, BloodVoyagerS only models major blood vessels, but neither specifics of organs and smaller vessels nor the chemical and physical properties of blood. Since a lot of these local effects can affect the system-level distribution and communication of nanobots we plan to incorporate these aspects into the simulator in future work. Similarly, the blood flow model can be refined to for example, include the pulsing nature of heart pumping motion. By now, the simulated nanobots were moved but did not communicate. Further work must evaluate the behavior of cooperating medical nanobots, thus testing the combination of communication and body simulation.

REFERENCES

[1] Baris Atakan, Ozgur B. Akan, and Sasitharan Balasubramaniam. 2010. Body area nanonetworks with molecular communications in nanomedicine. *IEEE Communications Magazine* 50, 1 (2010). https://doi.org/10.1109/MCOM.2012.6122529

[2] A. P. Avolio. 1980. Multi-branched model of the human arterial system. *Medical and Biological Engineering and Computing* 18, 6 (1980). https://doi.org/10.1007/bf02441895

[3] Michael Broomé, Elira Maksuti, Anna Bjällmark, Björn Frenckner, and Birgitta Janerot-sjöberg. 2013. Closed-loop real-time simulation model of hemodynamics and oxygen transport in the cardiovascular system. *BioMedical Engineering OnLine* 12, 69 (2013). https://doi.org/10.1186/1475-925X-12-69

[4] Florian Büther, Florian-Lennert Lau, Marc Stelzner, and Sebastian Ebers. 2017. A Formal Definition for Nanorobots and Nanonetworks. In *Proceedings of the 4th ACM International Conference on Nanoscale Computing and Communication - NANOCOM'17*. Washington DC, USA.

[5] Youssef Chahibi. 2017. Molecular communication for drug delivery systems: A survey. *Nano Communication Networks* 11 (2017). https://doi.org/10.1016/j.nancom.2017.01.003

[6] Youssef Chahibi, Massimiliano Pierobon, Sang Ok Song, and Ian F. Akyildiz. 2013. A molecular communication system model for particulate drug delivery systems. *IEEE Transactions on Biomedical Engineering* 60, 12 (2013). https://doi.org/10.1109/TBME.2013.2271503

[7] Martin J. Conlon, Donald L. Russell, and Tofy Mussivand. 2006. Development of a mathematical model of the human circulatory system. *Annals of Biomedical Engineering* 34, 9 (2006). https://doi.org/10.1007/s10439-006-9164-y

[8] T.L. Davis and R.G. Mark. 1990. Teaching physiology through simulation of hemodynamics. *Proceedings Computers in Cardiology* (1990). https://doi.org/10.1109/CIC.1990.144303

[9] Bartomiej Fajdek and Alicja Golnik. 2010. Modelling and simulation of human circulatory system. *15th International Conference on Methods and Models in Automation and Robotics* (2010). https://doi.org/10.1109/MMAR.2010.5587199

[10] Luca Felicetti, Mauro Femminella, and Gianluca Reali. 2013. Simulation of molecular signaling in blood vessels: Software design and application to atherogenesis. *Nano Communication Networks* 4, 3 (2013). https://doi.org/10.1016/j.nancom.2013.06.002

[11] a C Guyton, T G Coleman, and H J Granger. 1972. Circulation: overall regulation. *Annual review of physiology* 34 (1972). https://doi.org/10.1146/annurev.ph.34.030172.000305

[12] IEEE P1906.1 working group. [n. d.]. P1906.1 Simulation Framework. http://standards.ieee.org/downloads/1906/1906.1/P1906.1/ieee-p1906-1-reference-code-release-1_4/README, abgerufen am 24.10.17. ([n. d.]).

[13] Bruce M Koeppen, Bruce A Stanton, and Robert M Berne. 2010. *Berne and Levy physiology* (6. ed.). Philadelphia, PA : Mosby/Elsevier.

[14] Herbert Lippert. 2000. *Lehrbuch Anatomie* (5. völlig überarbeitete ed.). München ; Baltimore : Urban und Schwarzenberg, c1993.

[15] Abraham Noordergraaf, Pieter D. Verdouw, and Herman B.K. Boom. 1963. The use of an analog computer in a circulation model. *Progress in Cardiovascular Diseases* 5, 5 (1963). https://doi.org/10.1016/S0033-0620(63)80009-2

[16] ns-3 Consortium. [n. d.]. ns-3 overview, releases and documentation. Retrieved 24/10/17 from https://www.nsnam.org. ([n. d.]).

[17] B. Page, H. Liebert, A. Heymann, L. Hilty, and A. Häuslein. 1991. *Diskrete Simulation: Eine Einführung mit Modula-2.* Springer Berlin Heidelberg.

[18] Massimiliano Pierobon and Ian Akyildiz. 2010. A physical end-to-end model for molecular communication in nanonetworks. *IEEE Journal on Selected Areas in Communications* 28, 4 (may 2010). https://doi.org/10.1109/JSAC.2010.100509

[19] Giuseppe Piro, Luigi Alfredo Grieco, Gennaro Boggia, and Pietro Camarda. 2013. Nano-Sim: Simulating Electromagnetic-based Nanonetworks in the Network Simulator 3. In *Proceedings of the 6th International ICST Conference on Simulation Tools and Techniques (SimuTools '13)*. ICST, Brussels, Belgium, Belgium. http://dl.acm.org/citation.cfm?id=2512734.2512762

[20] K M Rai and K S Raoand K K Maudar. 1942. Accidental intra-arterial drug injection (A Case Report). *Medical Journal Armed Forces India* 53, 2 (1942). https://doi.org/10.1016/S0377-1237(17)30686-X

[21] A Schwarzhaupt. 1998. Simulation metabolischer Vorgänge im menschlichen Kreislauf : Betrachtung von pH-Wert und CO2. *Biomedizinische Technik* 43, 10 (1998).

[22] Dee Unglaub Silverthorn, Bruce R Johnson, William C Ober, Claire W Garrison, and Andrew C Silverthorn. 2016. *Human physiology : an integrated approach* (5. ed.). [San Francisco] : Pearson, c2010.

[23] Marc Stelzner, Florian-Lennert Lau, Katja Freundt, Florian Büther, Mai Linh Nguyen, Cordula Stamme, and Sebastian Ebers. 2016. Precise Detection and Treatment of Human Diseases Based on Nano Networking. In *11th International Conference on Body Area Networks (BODYNETS 2016)*. EAI, Turin, Italy.

[24] Gerard J Tortora and Bryan Derrickson. 2014. *Principles of anatomy and physiology* (14. ed.). Danvers, MA : Wiley, c2000.

[25] Adam Updegrove, Nathan M. Wilson, Jameson Merkow, Hongzhi Lan, Alison L. Marsden, and Shawn C. Shadden. 2016. SimVascular: An Open Source Pipeline for Cardiovascular Simulation. *Annals of Biomedical Engineering* 45, 3 (2016). https://doi.org/10.1007/s10439-016-1762-8

[26] Rui Zhang, Ke Yang, Qammer H. Abbasi, Khalid A. Qaraqe, and Akram Alomainy. 2017. Analytical modelling of the effect of noise on the terahertz in-vivo communication channel for body-centric nano-networks. *Nano Communication Networks* (2017). https://doi.org/10.1016/j.nancom.2017.04.001

[27] Yu Zhou, Yifan Chen, and Ross D. Murch. 2017. Simulation framework for touchable communication on NS3Sim. *2017 IEEE 17th International Conference on Nanotechnology, NANO 2017* (2017). https://doi.org/10.1109/NANO.2017.8117480