Precise Detection and Treatment of Human Diseases Based on Nano Networking

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ABSTRACT

This paper presents an elaborate scenario to highlight and motivate interdisciplinary computer science involvement in nanotechnology for medical applications. Our scenario illustrates how nanotechnology can be employed to detect and potentially directly treat infectious diseases as a paradigm for human disorders associated with high morbidity and mortality. Thus, more precise techniques that monitor the presence and concentration of critical marker molecules (host- and pathogen-derived) may be applicable at an earlier stage of the disease. Moreover, since the concentration threshold varies from person to person, continuous and individualized monitoring of both diagnostic and therapeutic measures is required. To detect and treat diseases directly at the affected location, we propose the usage of an in-body nano network build by nano machines. To report findings and receive commands from outside of the body, the nano network is connected to a body area network via gateways. In this paper, we discuss the capabilities of nano machinery and presents the aforementioned network architecture.

CCS Concepts

•**Applied computing** → **Life and medical sciences;** Biological networks; •**Networks** → *Network protocols; Wireless access points, base stations and infrastructure;* Naming and addressing; Network simulations; Mobile networks; •**Hardware** → *Nanoelectromechanical systems;* Wireless devices; Biology-related information processing; Quantum dots and cellular automata;

Keywords

bacterial pneumonia; FCN; IoNT; molecular communication;

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1. INTRODUCTION

Diseases are an omnipresent topic in everyday life and of even greater interest in research. Scientists have analyzed new and old diseases in terms of origin, symptoms and their impact on biological—especially human—life for hundreds of years, constantly growing and updating the knowledge base. Researching diseases is of great importance, as virtually every human is confronted with different kinds of diseases throughout their life. To overcome diseases, people use traditional medicine, seek knowledge in (online) information sources, ask friends or use other resources from which they expect help. Usually only if the own or collective knowledge and treatments fail, a physician is consulted for diagnosis and treatment. Visiting a physician may not be an easy option. Often, a person needs to make an appointment, invest time for long waiting periods and eventually money.

However, time can be of the essence for some diseases that need to be diagnosed as soon as possible. For example, a tumor has to be detected before it starts metastasizing. Noticeable symptoms may appear too late or may be too indistinct to diagnose correctly right away. Different diseases have varying incubation times and progression speed. Persons with chronic diseases or conditions are even more endangered due to possible immunodeficiency. To be on the safe side, they would need constant monitoring, e.g., by daily medical appointments, which obviously is an unrealistic approach.

Therefore, it is desirable to (continuously) monitor the human body without the need for frequent examination in a hospital or clinic. To ease the load on physicians as well as potential patients, parts of the supervision and care may be outsourced to automated systems like implants. Some well-known types of implants (e.g., pace makers and insulin pumps) already function as a support for monitoring and treatment, but they are usually limited to a very specific use case.

An open research question of great interest is the reliable, local application of medical treatment, as opposed to systemic use. A systemic medicine application, e.g., an oral administration or an infusion, distributes medication within the whole body. The treatment thus not only acts on local symptoms or causes, but interacts with the non-affected, healthy body as well. For example, immunosuppressants globally inhibit the human immune system—the body's natural mechanism to maintain its own health status—which intervenes whenever necessary. Thus, the chance of new diseases to manifest themselves increases by systemic medical treatment. It is therefore desirable for a medical treatment to act as locally as possible in order to minimize any additional side effects.

We envision the use of nanotechnology, *body area networks* (BANs) and particularly nano communication as a locally deployable strategy for supervision and treatment inside the body without restricting individual mobility. BANs already offer many applications for sport, military, healthcare and more areas of interest [9,34,39]. Nanoscale devices allow these applications to be transferred to a much smaller and more accurate level. In the medical case, we expect in-body nano devices to provide continuous, precise and localized detection and possibly even treatment of diseases, while addressing the above-mentioned issues.

In the next section we explain the use of nanoscale technology based on a current medical research scenario. In Section 3, we explain the terminus and discuss the state of research in this area and define our own concept for achieving the scenario based vision in Section 4. We conclude the paper in Section 5 and pose upcoming challenges for our concept.

2. MEDICAL SCENARIO

Health care-associated bacterial pneumonias are a major cause of morbidity and mortality worldwide. Especially hospital-acquired pneumonia is associated with high mortality [6]. Currently, effective treatment of bacterial pneumonia is restricted by first, a dramatic increase of bacterial resistance to antibiotics [42] and second, by an altered patient clientele, i.e, elderly, immunosuppressed or chronically ill patients.

Moreover, all diagnostic strategies, i.e., clinical, radiologic, microbiologic, and molecular techniques have their intrinsic limitations.

Thus, antibiotic treatment is frequently performed based on clinical experience without prior detection of the specific pathogen. As an oral or intravenous application, these therapies always act systemically, thereby affecting the whole body. A systemic application of antibiotics without a defined pathogen aggravates and accelerates the problem of increasingly resistant bacteria [42]. Therefore, the development of new diagnostic and therapeutic measures is of great clinical relevance.

We envision a system to early, locally and specifically detect infections, estimate their relevance and check their severity. After consulting with an *analysis and control station* as shown in Figure 1, the proposed system responds to an infection in a suitable manner. This system comprises a (yet to be specified) number of nano machines, which act from within the human body as sensors or actuators. When equipped with communication capabilities, they form an in-body network to receive, send and forward messages. Additionally, implants or on-body microsystems form a BAN and serve as gateways between the nano machines and a control station. The control station (e.g., a smartphone) is located outside the human body, where it supplies appropriate computational power and memory to record and process the measurements taken by the nano machines and provides them to the patient or a physician. A control station with Internet access also allows to integrate external participants in the process, e.g., medical databases or physicians for additional analysis, monitoring or consultation. The whole system forms an *Internet of Nano Things* (IoNT).

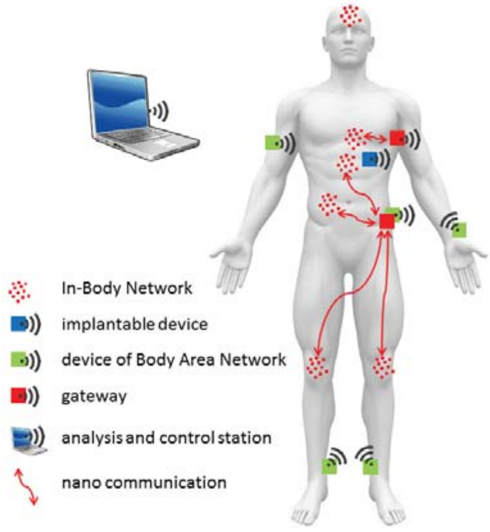

Figure 1: In-body and BAN Architecture [12]

In the presented scenario, one or more nano machines may aid in detecting a bacterial lung infection directly at the alveolar side, for example by detecting proinflammatory cytokines released by immune systems effector cells, or by detecting specific bacterial virulence factors, e.g., lipopolysaccharide, as a paradigm for the presence of Gram-negative bacteria. The machines communicate the measured concentration to the control station to decide whether the data constitutes sufficient evidence for a relevant and pathogenic infection. If appropriate, the nano machines can then be ordered to selectively release antibiotics and/or anti-inflammatory agents on spot.

3. NANOTECHNOLOGY IN MEDICINE

Nanotechnology is no new subject to medical research. It has various possible applications and promises to have a good chance of industrial and commercial success [28]. Current applications are therapeutical measures to fight cancer. For example, to remove malicious tissue, specifically designed magnetic nanoparticles may be deployed in the human body to attach themselves to a tumor. By heating these particles, the targeted tissue can be destroyed selectively [23].

While progress in nanomedicine and nanomaterials already leads to products being approved or reaching various stages of clinical studies [14], research on in-body communication between nano devices is still in a very early stage.

In this section, we explain termini as well as opportunities relevant for nano technology applied in medicine.

3.1 Characteristics of Nano Machines

Nano machines are devices with at most a few hundred nanometers in size. They aren't a mere further miniaturization of micro systems. At this magnitude, other physical laws do apply and quantum effects may disturb classical computational devices, forcing us to reconsider computation and communication at nanoscale [17]. There are currently three types of nano machines, i.e., biological, artificial and hybrid ones.

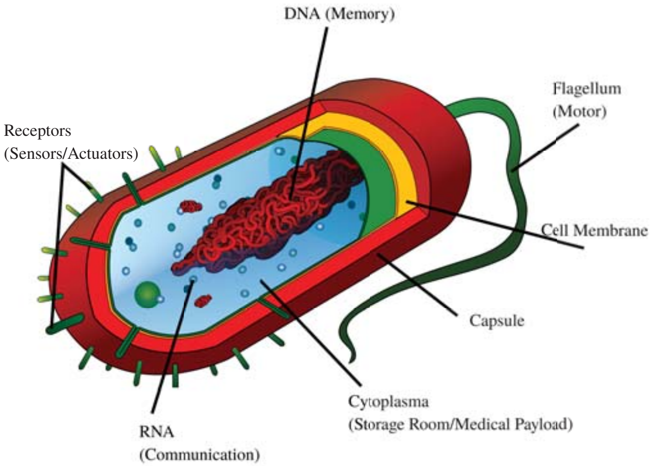

Figure 2: Structure and components of a prokaryote cell functioning as a nano machine.

As for the artificial nano machines, they can be seen as extremely resource constrained variants of micro system-devices known from the *Internet of Things* (IoT). Thus, we have to deal with constrained energy, memory and computation power. Solutions for the former involve zinc oxide high-density nano-wires as nano-sized batteries and piezoelectric energy harvesting techniques [24, 26] as well as heat engines the size of a single atom [37] as well as energy harvesting techniques. To solve the latter problem, many new concepts have been proposed, mostly involving carbon nanotubes (CNT), formed by one atom-thick sheets of graphene. The structural stability and conductivity of CNTs allow the construction of nanoscale field effect transistors (FET), but accurate manufacturing and placement are still open problems [21]. The physical integrity of a nano machine in the human body is another issue to be considered. Nano machines might be destroyed by chemical atom-sized reactions or carried away accidentally.

One key problem with the construction of nano machinery is the strictly limited size of the used components. Current CMOS-technology appears to malfunction due to quantum-effects at the nanoscale [17]. One approach to cope with the size-restrictions are alternative transistor-implementations that are robust to quantum-effects. CNTs have been suggested as a building block for future components.

Alternatively, nano machines can be biologically inspired constructs, for example cells (see Figure 2). All the challenges listed above do also apply here in a similar manner. The environment for a biological nano machine is the same and so are the problems. A cell may die or be destroyed and monitoring single cells is a difficult task. A cell requires cellular respiration to refill its ATP energy reserves that may be used for computational processes. Therefore, energy management facilities are required to regulate a modified cell's energy consumption. Otherwise, vital functionality may experience a lack of energy if other processes deplete the energy storage [25].

Additionally, bottom-up approaches may be used for the construction of nano machinery. In [43], Winfree suggests exploiting the process of DNA-self-assembly to construct arbitrary shapes out of artificially designed DNA-tiles. He also shows that his model is Turing-complete, while requiring vast amounts of space for those computations/constructions. DNA has also been suggested as a template for the construction of nano-electronics [8]. In this case, a self-assembled sheet of DNA is used to harbor a network of nanoscale computational- or memory-nodes. Depending on the implementation, this solution may be completely bio-inspired or a hybrid of DNA-scaffolding and artificially constructed nanoscale components.

3.2 Communication Types

Traditional means of communication use electromagnetic waves or wires. Radio communication in the range of megahertz radio waves using nanoscale antennas hasn't been possible yet [1]. CNT antennas [22] provide extremely good conductivity, while offering good stability. Given nanoscale size, the resulting wavelength of these antennas is in the terahertz band. At these high frequencies, atmospheric disturbances make communication distances exceeding 10 mm very susceptible to interferences [1].

Bio-inspired molecular communication is a completely alternative approach to traditional communication. It offers a range of different communication principles with varying properties in speed, accuracy, range, reliability and data capacity. For example, *pheromones* [33] can be used as a chemical long range communication option either through a fluid or aerial medium. The pheromones spread out via diffusion, a passive transportation process, where the direction of particle movement is not directly influenced by the source or messenger, but dependent on the surrounding environment. Although it provides a long range for organisms to communicate, the provided concentration for the diffused molecules has to be high enough to provide a sensible concentration at the target location. This may require a more potent source than a single nano machine can provide.

Furthermore, several new approaches exist: *calcium cell signaling* is a process of diffusion through calcium waves [31], the *optoacoustic effect* passes messages through optical excitation [38], *ultrasonic waves* feature a low frequency for reduced attenuation, i.e., increased range [15] and *neuronal communication* can make use of nerve tracts to transmit information by using electric surges [4].

3.3 Movement

It cannot be assumed that the position of a nano machine is static. As mentioned before, at least the environment has an impact on the position. Considering that nano machines in the human body are most likely be located in a fluid medium, this leads to different phenomena. In the bloodstream for example, the machines are driven by the flow velocity and direction, which is influenced by the proximity to the heart, general blood pressure, muscle contractions and gravitational acceleration. The devices are also exposed to effects that only exist at the nanoscale, like collisions with other moving atoms or molecules through Brownian motion. This constantly affects the direction of movement and thereby the relative position.

Means of targeted movement also exist in nature. Options inside the human body include *molecular motors* riding along rails like microfilaments or microtubules [3, 7]. Molecular motor proteins like Myosin and Kinesin harness ATP as chemical energy to power the movement process. They can also form a binding with other molecules and transport them along the rails. For railless locomotion some cells possess flagella [19]. A flagellum is a tentacle-like structure used to sense and to guide the cells movement process. These forms of biological movement can also be utilized as inter- and intracellular messages and therefore, as a means of communication.

Wang [41] provides a survey of recently developed ways of micro- and nanoscale locomotion advances, featuring Self-electrophoretic-, Bubble-, Electrical-, Magnetic- and Ultrasound Propulsion. For example, the hydrogen-bubble-propelled engine is a cone-shaped hollow rocket on the microscale [16]. It produces hydrogen from spontaneous chemical reaction at the inner zinc-coated inner layer. The resulting hydrogen is expelled through the wide end of the cone working as a bubble-propulsion. The engine does not need to carry additional fuel for movement, but requires an acidic environment.

The choice of locomotion closely relates to the structure of the nano machine and several self-directed motors have specific demands on the environment.

3.4 EHS and ELSI

When discussing nano machine deployment in human lifeforms, we cannot ignore the existence of environmental health and safety (EHS) risks as well as ethical, legal and social issues (ELSI).

When estimating the risks and safety issues of new technologies, the first approach often features an evolutionary analysis [11]. Substances (including particles) a species often experiences or interacts with are typically harmless [2]. Species adapt to the natural occurrence of particles and sometimes use them in their organisms as building blocks when suitable (food) while some of them become essential (vitamins/essential fats). Particles that are less common or less common in high quantities often impose a significant risk to a person's health or may at least trigger unpredictable consequences.

A suitable example are metal particles in the organism that might lead to metal intoxication once a certain threshold is met. Small quantities of iron are essential in the building process of red blood cells and zinc is required to build testosterone—too much might be lethal though. The filter-organs—liver, kidneys or spleen—never adapted to large quantities of rare or unknown particles and they naturally accumulate somewhere in the organism where it might be impossible to dispose of them.

Under these circumstances possible materials for in-body nano machines are harshly restricted—DNA appears to be a suitable building block tough. Even with DNA, safety issues might occur nevertheless. Chances are better that the liver or kidneys might be able to filter the resulting waste.

A precise estimation of the risks isn't possible for the above reasons, but a general direction may be derived. Clinical tests or animal studies are necessary to determine the true risk.

Environmental consequences are much harder to predict. For example, agricultural practices have shown that we aren't able to predict the effect pesticides like glyphosate have on the population of certain insects [18]. The effects of nano machinery in high quantities on the environment seems completely unpredictable[1] and thus are subject to laboratory tests. The advantages and possible future challenges render laboratory tests worthwhile, even despite risks.

Assuming that the proposed system may successfully complete the stages of simulation and in vitro testing from a scientific perspective, the ELSI still remain to place it on the market. International and national laws are still adapting to the upcoming nanotechnologies. In Germany, the system and its devices most likely are objective to the German *Medical Devices Act* [10] as it is a medical system to provide measurements, diagnosis and treatment. The Medical Devices Act is a legislation derived and implemented from the EU directives 93/42/EEC, 98/79/EEC and 90/385/EEC. In the process, an ethics commission and a federal authority need to approve the device before a clinical investigation is initiated for performance evaluation and exhibition. The devices will receive a classification to reflect its level of risk according to Annex IX from Directive 93/42/EEC. As nano machines are very invasive, may be long-living and may bear not yet completely investigated risks of impairing human health, the highest risk classification Class III is to be expected.

However, the ethics commission should not be the first group to think about ethical and social implications of new technologies for society. Public reception on the topic of invasive medical nanotechnology for monitoring and treatment has to be assessed and evaluated. If the technology is rejected by the society, it is less attractive to the market and more likely to be delayed. There has always been a co-influencing relationship between technology and society. New technology has the potential to heavily influence everyday life after integration, e.g. smartphones. Through change of society, new demands on technology arise, e.g. free high bandwidth access. The proposed system may change the frequency of how often medical examinations are applied or may change the job of a physician to be more remotely involved. But what are the consequences of continuous monitoring and maintenance of body functions? Will the personal freedom and range of possibilities increase, if medical treatment can be performed more independently from location and physician? To cope with this topic, Hunt and Mehta [20] investigated how nanotechnology is introduced, how it is perceived, which actors are involved—including governments—and how related sciences influence the framing.

4. CONCEPT

This section covers the concepts we envision as part of solutions for the medical scenario described in Section 2.

4.1 Function Centric Networking

In order to communicate in a network, message content needs to be delivered from one position to another. Since the possibilities of communication and machine types change drastically in the nanoscale environment, the protocols used in the Internet and IoT have to be analyzed for suitability.

Standard for traditional networks is the packet-switched Internet Protocol (IPv4/IPv6). This protocol requires at least addresses from sender and receiver. For resource constrained networks in the IoT lightweight solutions like 6LoWPAN [29], Zigbee or IEEE 802.15.4 [5] have been established to remove less relevant header information and therefore reduce communication overhead. These protocols may be viable approaches for an even more resource constrained WSN.

Nevertheless, even in conventional networks the IP-standard is questioned. IP is a host-centric architecture to connect

[1]Even *Grey Goo* apocalyptical scenarios seem possible.

endpoints with one another, while applications are typically focused on obtaining specific data and not on where the data is exactly located. E.g., *Named Data Networking* (NDN) [44] is a mature project for a data-centric architecture. Instead of addressing hosts, data is directly addressed in the NDN concept. An *Interest Packet*, carrying the name to identify the desired data, is emitted by the receiver to indicate interest. To match the interest a corresponding *Data Packet* has to be found. Routers in the network forward the interest by a lookup in the *Forward Interest Table* and leave a remark in a *Pending Interest Table* to remember interest and receiver. If the content is found at a host or router, it gets delivered backwards to the receiver and stored at *Content Stores* along the way.

A data-centric network is a useful approach in the medical IoNT as applications are not focused on communication with a specific nano machine itself but on receiving measurements and issuing treatments in defined body locations. We even have to reconsider the possibility or usefulness of addressing each nano machine individually. As depicted in Section 3.1, nano machines themselves are hard to monitor and may have a very short lifespan. Research is aimed at the production of self-assembling nano machines consisting of replaceable parts [7]. Additionally, a strong resource limit has to be expected, therefore stores and tables for routing and distribution—as used in NDN—will either have a very limited size or need to be discarded. On the other hand, information that is vital for the monitoring and treatment process for patients can be used in return. A nano machine needs to be aware of its sensory functions to provide semantically meaningful measurement data and its actor capabilities to correctly carry out requested actions. Hence we proposed the concept of *Function Centric Networking* (FCN) [40] to use the location[2] of a nano machine and its functional capabilities as part of the addressing scheme. This scheme does not allow to address a specific nano machine, but a group of nano machines fulfilling the same purpose in same position. For example, a message including the part 'Alice/LeftThumb/Sensor' addresses all nano machines in Alice's left thumb capable of any sensory action. Leaving function and/or location blank can be used like a broadcast, e.g., 'Alice/Leg/-' would address all nano machines in Alice's legs. Consequently, a nano machine can easily be replaced by another and multiple devices can handle requests. Applying this concept to a constantly mobile network of nano machines means that devices, which circle around in the human body irregularly, change their location and therefore their address. These machines only accept messages matching their current position. By this means, localized and precise treatment can be performed, e.g., releasing antibiotics on spot.

4.2 Nano Computation and Construction

Two key problems directly emerge from the presented vision. The first is the actual construction of nanoscale shapes, pattern or devices, while the second focuses on possible computer realizations that tolerate interfering quantum-effects. Various computational models haven been proposed to cope with the expected difficulties at the nanoscale. Nanoscale devices for in-body application have to fulfill special requirements in terms of bio-compatibility (see Subsection 3.4).

[2]Moore and Nakano [30] propose location-addressing using particle releasing beacons and chemotaxis navigation as some kind of biological triangulation.

The discipline of DNA-computing features alternative models of computation on a biological basis. The process of self-assembly is often exploited to perform computations or grow arbitrary shapes using bottom-up principles.

Especially the DNA-self-assembly process is currently tested as a candidate for nanoscale circuit templates. Nano-electronics are often too small for conventional top-down construction. Self-assembly processes offer an alternative bottom-up approach. While DNA-self-assembly is capable of universal computation, it potentially requires vast amounts of space and differs fundamentally from elaborate approaches. The process seems to be better suited for the construction of scaffoldings or templates than computations.

An alternative computational model that theoretically enables computation at the nanoscale are quantum-dot cellular automata (QCA). QCA are a model of computation that exploits field-polarization to perform computations. Since it uses quantum-effects and electron-repulsion it is expected to function at the nanoscale and thereby offers an alternative to CMOS-technology. The automaton behavior may be exploited to form logical gates and compute boolean functions.

A combined approach of self-assembly systems and QCA may enable the construction of functioning nano machinery and thereby solve the most fundamental nanotechnology problem—from a computer science centric point of view. Once nano devices with capabilities comparable to current microchips are available, they may be applied to various medical problems.

We plan to explore the possibilities of the mentioned approach and establish a suitable mathematical model for simulations or general behavior prediction [27, 35].

4.3 Nano Networking Simulation

Since we currently lack physical nano machines, we will investigate our previously presented concepts using simulations. For simulations, a model and simplified version of the original system, respectively, has to be created. However, aspects important for the investigation have to identified be modeled sufficiently precise to obtain accurate and useful results [32]. Thus, a simulation tool has to support domain-specific and up-to-date communication protocols as well as communication and mobility models. To find a suitable simulation tool, we investigated the current state of research in this field. We found, that *Nano-Sim* [36] is currently the most promising approach since it comes with models and protocol suites, especially developed to meet the complexity of communication at nanoscale. It supports communication based on electromagnetic waves and provides us a starting point for research in more advanced and efficient nano communication strategies. As a module of the ns-3 simulator[3], Nano-Sim can exploit models and protocols already available in ns-3. Also it lowers the hurdles for the research community to get in touch with nano communication as ns-3 is one of the most used network simulator. However, Nano-Sim does not cover all aspects needed for our evaluations like, e.g., a communication model for molecular communication in human bodies. The human body comprised many different types of fluids and tissues featuring their own characteristics which react differently on the various substances also present in the human body (cf. Section 2). These characteristics of the human body will influence the movement, communication

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

means and physical integrity of our nano machines. Thus, these aspects have to be modeled sufficiently precisely to get accurate results.

To the best of our knowledge, there is no simulation framework for nano networks providing appropriate communication models and protocols combined with means to model the human body's characteristics. Thus, we are currently developing a modular framework for simulating nano networks covering both aspects. The framework will comprise two modules, one will simulate communication, the other one human body characteristics. For simulating communication, we will build upon Nano-Sim and extend it where necessary. The architecture of our framework compares to the one used by *Veins*[4] which simulates vehicular networks by connecting a network simulator with a traffic simulator.

5. CONCLUSION AND FUTURE WORK

Nanotechnology on the described scale is still far from realizable, but also far from impossible and several scientific disciplines are currently creating the theoretical foundations—sometimes proving them in wet-lab experiments.

In this paper, we presented a medical scenario showing the benefit of employing nano technology for detecting and treating infectious diseases. However, the scenario can easily be adjusted to either detect or treat other diseases by modifying the sensors or actors to detect/treat accordingly.

We further presented an architecture comprising a combination of in-body nano network and body area network (BAN). The former consists of nano machines responsible serving as in-body sensors and actors. The sensed data is transmitted via gateways into the BAN to be analyzed by devices providing far more resources than the nano machines. If necessary, commands are issued from the BAN into the nano network, e.g., to directly and locally treat the detected diseases. We further presented concepts for addressing nano machines based on their location and functionality and discussed approaches for constructing nano machines and their computation capabilities. Additionally, we presented our requirements for a nano networking simulator and proposed elements of a suitable architecture based on the ns-3 simulator and its module Nano-Sim.

The FCN concept needs to be deployed as a protocol and defined in more detail. In this regard, safety and security [13] as well as routing of FCN messages will be explored as a next step.

Another goal of our research group it the design and evaluation of potential nano machine architectures. We aim at deriving a design template for possibly scalable, universal nano machines that fulfills the requirements of in-body environments. We currently research the limitations and possibilities of self-assembly processes at the nanoscale for the construction of nano machinery and explore if DNA-based self-assembly processes may be combined with quantum-dot cellular automata to form fully functional nano machinery with computational power comparable to current computers.

Furthermore, we are currently developing a simulation framework to be published in conjunction with the previously mentioned evaluation of current simulation tools.

[4]http://veins.car2x.org/

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