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Abstract
In this paper, we consider a flow-guided nanocommunication network deployed inside of a human vascular system. The network augments the human immune system helping with health issues related to serious bacterial infections, as well as with blood circulation and heart diseases. The network consists of nano-probes reporting medical issues, small nano-nodes working as information carriers, and nano-routers communicating with external medical systems. In order to evaluate the network performance, we propose a network architecture, discuss potential emerging medical applications and, finally, present some numerical results.

Section 1
Introduction

Nanocommunication, being one of the newest research disciplines in telecommunications, deals with exchange of information in networks of nano-machines, built on the recent enormous development of nano-technology. In this technical document, we discuss a scenario being somewhere between the nano-world and the medical in-body applications. We focus on a network composed of micrometers-in-size nodes located inside human veins and supporting the natural immune system against specific bacteria, sepsis, and blood circulation and heart diseases. The proposed network consists of the bio-sensors detecting health problems, nano-nodes carrying and passing further the health data and nano-routers being gateways between the network and external devices located outside of the human body.

The scope of the document is the following. In Section 2, we present the network architecture, describing the types of the nodes. In Section 3, we identify medical application and show how the proposed network can help in the mentioned health issues. In Section 4, we present an analytical derivation of the throughput in the network, being a function of number of the nano-nodes. Finally, we conclude the paper is Section 5.

Section 2
Network architecture

In this section the in-body nano-network architecture employed for disease detection is described. For the sake of clarity, let us first introduce its three main constituent devices.

- **Nano-probes or bio-sensors**: these devices are placed in internal parts of the body sensing a given medical parameter of interest, as will be further explained in Section 3. They are equipped with a communication module able to transmit the acquired information to the mobile nano-nodes. The longest dimension of a single bio-sensor is below 1 mm.

- **Nano-routers**: these devices receive information (contained within data frames) from nano-nodes and send it to external macro-devices (e.g. a wearable or a smartphone). They must be placed in a inner but superficial part of the body and close to a vein or an artery, following the network scheme in [1]. According to this proposal, the size of the nano-router should be in the order of 1 mm.

- **Nano-nodes**: these devices are able to transmit and receive by using electromagnetic (EM) nanocommunications, and flow through the blood circulatory system conveying the information from one or more bio-sensors to one or more nano-routers. Their size is envisaged to be in the order of a red blood cell, i.e., less than 10 μm [2] to ensure a correct circulation through veins and arteries.

Regarding the network architecture, it is mainly constrained by two factors. On the one hand, as the communication module integrated in a bio-sensor must be small enough to be implanted in an artery or vein, the frequency of the electromagnetic waves radiated will be in the order of hundreds of GHz or even reach the THz band [2,3]. On the other hand, EM waves suffer from high absorption when propagating through watery media, such as biological tissues (that are mainly composed of water). This absorption becomes higher as the frequency of the EM wave increases, thus making the communication range of this envisaged bio-sensors extremely distance-limited [4]. For this reason, the direct wireless communication between a bio-sensor implanted in a non-superficial part of the human body and a macro-device seems impractical. Hence, a flow-guided nano-network consisting of three different types of device (nano-nodes, nano-routers, and nano-probes) above described, emerges as a potential solution to sense and monitor internal parts of the body and provide accurate measurements on real-time. The general idea of the network in the vascular system is shown in Figure 1.

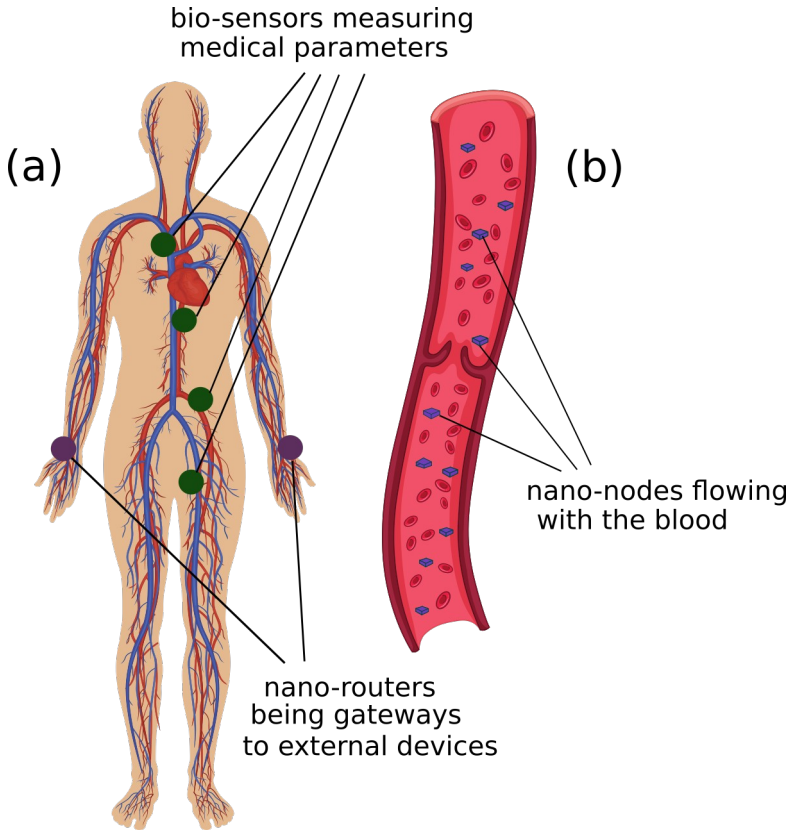

Figure 1. (a) the human vascular system with indicated some locations for bio-sensors and nano-routers. (b) a zoomed picture of a vein with red blood cells and nano-nodes circulating.

Section 3
Medical applications

The proposed network architecture is modular, thus many different bio-sensors may be used, as far as they provide signals that can be received by the mobile nano-nodes. In this paper, we propose four different bio-sensors of critical medical importance, each of them with a different architecture. The first three of them rely on antibodies detecting specific molecules in the blood. The last one is a tiny distributed sensor network composed of simple EM-based static nano-nodes.

3.1 Bacterial blood infections

While the presence of numerous bacteria types is quite common in a human body, their appearance in the vascular system is very dangerous, as they can then spread and infect multiple remote human organs. It is especially severe issue in case of patients in hospitals, because of their immune systems are already weakened. The ability of the early detection of bacteria, like *Pseudomonas*, *Escherichia coli*, *Acinetobacter*, *Staphylococcus* or *Streptococcus*, in case of a patient being already in a critical state, might be a matter of life and death, as having such knowledge early means that a specific antibiotic might be applied on time. Even a very low number of these bacteria in blood is dangerous. Thus, we would like to propose a bio-sensor consisting of antibodies for each of these bacteria types. Antibodies (immunoglobulins) are protein molecules, about 10-30 nanometers large, which recognize a specific type of different molecules, e.g. bacteria, different proteins, etc. Antibodies may signal the presence of the bacteria in many ways, but here, we focus on the technique described in [5] where the antibody is attached to an electrode. After detecting the bacteria, the electrode resistance changes. Thus, assuming a simple nano-node is connected to the electrode, the nano-node measures the resistance and starts transmitting a warning immediately after detecting its change. A single chip, not larger than a millimeter, may have antibodies detecting numerous important bacteria. We propose to have about 5-10 such chips located close to important inner body parts like lungs, urinary bladder, kidneys, in order to check the source of the bacteria.

3.2. Sepsis

Sepsis is a state of the human immunologic system, when its reaction to infections may threaten its own healthy tissues and organs, finally causing death. Sepsis is signalized by a very high density of cytokines in blood, in particular interleukin 6 (IL-6) molecules. IL-6 molecules are normally present in blood of a healthy individual as well, but in case of sepsis, their density suddenly rises from about 1.5×10^{10} / ml (a healthy person) to 3.75×10^{11} / ml and higher (for sepsis) [6]. They are produced by living cells and their lifetime may be modeled by exponential distribution with average of 45 minutes [7].

Sepsis is usually detected via blood analysis in a laboratory. However, it is quite time consuming, as the blood must be taken from the patient, delivered to the lab and analyzed. It is very often that sepsis occurrence is detected too late, as it is the matter of hours if a patient survives or not. The bio-sensor located inside the vascular system could check the patient state constantly. However, as the IL-6 density is quite high even for healthy people, sensors with antibodies cannot be used just like in the previous case with bacteria. Such a sensor would be immediately blocked with IL-6 cytokines, detecting and signaling their high density all the time. Instead, we propose to use a special small tube, about 0.25 mm long, mounted inside of a human vein. At one side, the tube has a membrane that is half-permeable, i.e. small molecules like IL-6 cytokines may flow through, but living cells cannot (living cells are quite large, about 10-20 micrometers in diameter). Other walls of the tube are not permeable. So, the IL-6 may pass through the membrane and propagate inside

the tube by diffusion, finally reaching the opposite side of the tube after about 15 minutes [8]. At this opposite side, we have a layer of antibodies matching IL-6 cytokines. When an antibody catches an IL-6, the electrical resistance of the connected electrode changes (as described in the previous subsection). The size of the half-permeable membrane and the length of the tube are carefully chosen so that only a small number of IL-6 cytokines reach the antibodies for a healthy person. However, when sepsis appears, the number of IL-6 cytokines is much larger, so the nano-node connected to the electrode receives a much higher signal and should send a warning only in such a case.

With such a tube, the sensor with antibodies detecting IL-6 cytokines may work for a long time. Most of the IL-6 cytokines die when propagating through the tube, only a small amount of them reach the opposite side of the tube. After matching an IL-6, an antibody is not active during a certain period of time, but recovers after that and may work again. Moreover, as the membrane is half-permeable, not letting living cells inside, the IL-6 cytokines cannot be produced inside the tube. A single tube is a vein is enough, because with sepsis, the density of IL-6 cytokines quickly rises in the whole vascular system. We consider second such a device, as a back-up.

3.3. Heart attacks

The discussed nano-network and bio-sensors may be also critically helpful in cardiac issues, e.g. in case of people endangered with heart attacks (myocardial infarctions). A marker, helping to detect the danger of a heart attack very early, is a so called Heart-type Fatty Acid Binding protein (H-FABP). If the H-FABP density exceeds 1.8×10^{11} / ml, it is considered as a serious warning that may suggest a myocardial infarction [9]. Here, we also propose a bio-sensor being a layer of specific antibodies attached to an electrode, but the layer is not in a tube, instead it is covered with a shutter opening just for the time to make a measurement. The shutter is normally closed, so the H-FABP present in the blood do not block the bio-sensor completely. The shutter opens periodically, once per e.g. 15 minutes, in order to measure the H-FABP density. If the density is high, the warning signal is transmitted by the bio-sensor. The bio-sensor may be also activated externally, i.e. a request is sent from the external device through the gateway and the nano-network, in order to make the H-FABP measurement on demand. This procedure may be initiated if a person feels bad, e.g. has some clinical symptoms like a pain in its chest, dyspnea (shortness of breath), or low physical effort tolerance. Clinical symptoms correlated with high H-FABP level is a clear indication of a myocardial infarction [9].

3.4. Restenosis

One more application is related to stenosis, i.e. the process of narrowing of blood arteries, usually caused by atherosclerosis. A popular solution is putting a stent into such an artery, in order to keep the artery patent. However, stents frequently get blocked after some time, as some thrombus (solidfied blood) may gather on it and, in consequence, the artery is blocked again, which may cause a heart attack [10].

In order to control the state of a stent, nano-nodes may be mounted on it. The nodes on the stent should then periodically transmit signals to mobile nano-nodes flowing through the artery. When the process of restenosis becomes serious, which usually means the lumen of an artery is closed in more than 90%, i.e., the stent is covered with 1-1,5 millimeters of thrombus [10], the signals from nodes on the stent will be much weaker. Thus, the network can detect this situation and pass the information to the gateway and further to the external medical devices. About 20-30 of nano-nodes may be mounted on a single stent, in order to have a clear information about its state.

Section 4
Network performance analysis

The analytical model for the proposed flow-guided nano-network is based on the following reasonable assumptions:

- There are n nano-nodes uniformly distributed along the flow (blood stream), $n \geq 1$, $n \in \mathrm{N}$. They continuously move through the blood circulatory system, that can be modeled as a closed circuit. In average, nano-nodes take T time units to complete a round through it.
- Depending on the zone of the circulatory system in which nano-nodes flow, their speed will be variable, being v_R the speed when passing through the nano-router coverage zone (A_R) and v_P when passing through the bio-sensor/nano-probe coverage zone (A_P).
- A nano-node battery is charged every $1/f$ time units using a piezoelectric nano-generator, as thoroughly described in [11]. Due to energy constraints, a nano-node can only transmit or receive one data frame per battery charge.
- Nano-nodes cannot perform more than one transmission when crossing the coverage area, since the time to recharge the battery is much longer than the time to cross the transmission coverage zone, that is, $A_R/v_R << 1/f$.
- The time between two battery charges, $1/f$, is divided into σ slots ($\sigma \geq 1$, $\sigma \in \mathrm{N}$). Provided that a frame has been successfully received, a nano-node transmits a frame randomly, with a probability $1/\sigma$, in one of these slots. The maximum number of slots is limited by the frame size. Thus, if t_f is the time required to transmit a frame, $t_f \leq (f\,\sigma)^{-1}$.
- A successful transmission can only be achieved when a nano-node starts and ends the transmission of a data frame within the nano-router coverage area and no other nano-node starts a transmission while the data frame is still being sent (i.e. no collision occurs). Thus, the probability of a nano-node being in the transmission zone (p_{tx}) can be modeled as:
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$$p_{tx} = \frac{A_R - v_R t_f}{v_R T},\ v_R t_f < A_R \tag{1}$$

- A collision occurs when a nano-node enters the nano-router coverage zone transmitting a frame while another transmission is still active. Thus, the probability of a nano-node being in the collision zone (p_{cx}) is modeled as:

$$p_{cx} = \frac{A_R + v_R t_f}{v_R T},\ v_R t_f < A_R \tag{2}$$

- When there is not a frame stored in memory, nano-nodes listen to the channel each $1/f$ seconds. Thus, the probability of a nano-node receiving a frame from a bio-sensor/nano-probe in each round (p_{rx}) is:

$$p_{rx} = \left(\frac{A_P - v_P t_f}{v_P} \right) f,\ v_P t_f < A_P \tag{3}$$

- Nano-nodes discard a received frame before completing a round and after crossing all nano-routers (before T time units). Under this assumption, we ensure that the information received by a nano-router is up-to-date.

A nano-router communicating with nano-nodes is depicted in Fig. 2. In case of a bio-sensor, the scenario is very similar.

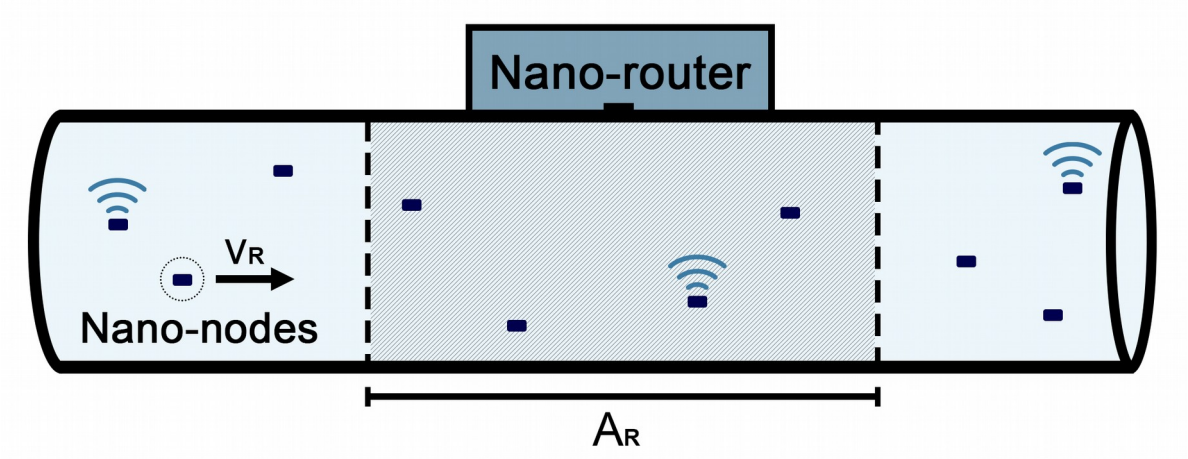

Figure 2. Flowing nano-nodes communicating with a nano-router attached to the vein.

Based on these assumptions, the throughput achieved by the proposed nano-network is modeled by this expression:

$$Th\left(n, A_R, A_P, \sigma, t_f\right) = nf\ p_{tx}\, p_{rx}\left(1 - \frac{p_{cx}\, p_{tx}}{\sigma}\right)^{n-1} \tag{4}$$

Equation (4) represents the frames per time unit that can successfully reach the nano-router. In order to achieve a correct transmission, nano-nodes must receive an updated frame, store it in their memories, and then transmit it to the nano-router without collisions.

As can be seen in Fig. 3, the achieved throughput increases with the number of nano-nodes until it reaches a maximum. From that point, collisions prevail and the throughput sharply decreases as the number of nano-nodes grows. Therefore, the results reveal that there is an optimum number of nano-nodes (around $3.5 \cdot 10^6$) that produces the maximum nano-network throughput (21 frames per minute). Note that this number of nano-nodes might be certainly excessively high to be injected in a human body, making the nano-network deployment unfeasible.

However, for the proposed medical applications there is no need for this high number of readings per minute, since the variation over time of the measurements takes a few minutes. Taking a reference time of a measurement every five minutes (i.e. 0.2 frames per minute), we can see in Fig. 3b that the required number of nano-nodes to attain this throughput is more realistic and thus feasible, around 12,000 nano-nodes. Keeping in mind the ultra-small size of these nano-nodes, this number of devices, in-body deployed, should not entail any health problem. It should be noted, that this result for the number of nano-nodes satisfying the appropriate network throughput has been obtained for the simplest network configuration, namely, one nano-probe, one nano-router, and only one single transmission slot. Therefore, with a fine-tune of the nano-network parameters the number of nano-nodes needed can be further reduced.

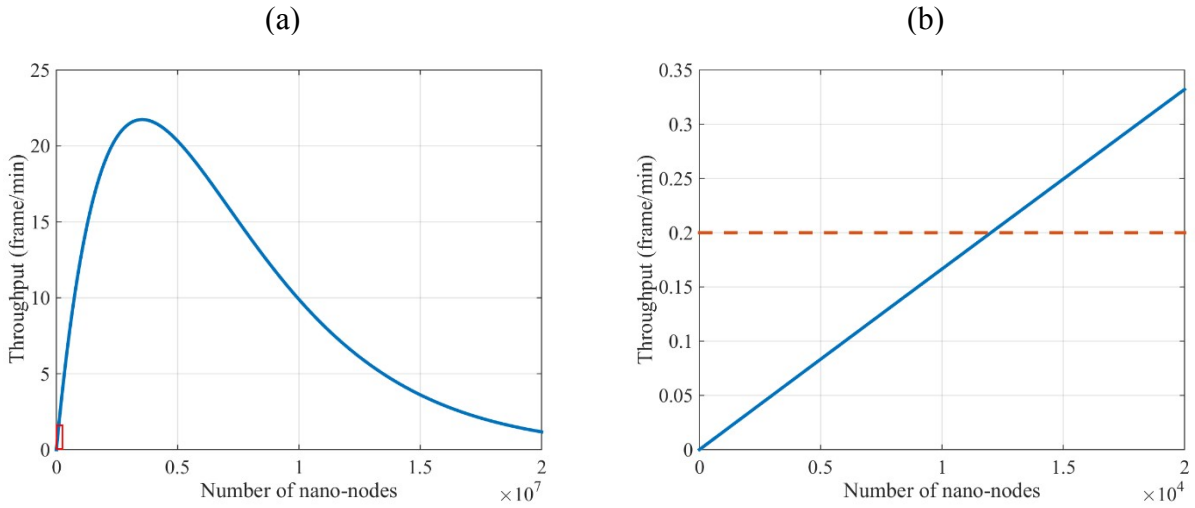

Figure 3. (a) Throughput achieved (in frames per second) as a function of the number of nano-nodes for f = 1 Hz, v_R = 24 cm/s, A_R = 2 mm, v_P = 48 cm/s, A_P = 1 mm, T = 60 s, σ = 1. All these values are based on real measurements of the human circulatory system from the related literature. (b) Zoom of the red rectangle depicted in (a). Red dashed line shows the objective throughput (0.2 frames/second).

Section 5
Conclusions

In this paper, we have presented a concept of a nano-network serving specific medical purposes, i.e., augmenting the human immune system. The network is located in the veins and arteries and is composed of three segments: (a) bio-sensors measuring medical parameters, (b) nano-nodes circulating with the blood and working as data carriers and (c) nano-routers performing as gateways, and forwarding medical information from the nano-network to some medical devices located outside of the body. The network may aid in severe medical situations when patients in critical conditions are hospitalized and bacterial infections may cause sepsis and, in consequence, death. The network allows to detect bacteria and sepsis in a very early state, when medical staff still can react using specific antibiotics. Another considered application is related to people endangered with heart attacks and cardial problems like restenosis. Again, the proposed nano-network is able to send a warning signal early, so that a medical doctor have time for a suitable reaction.

We have assessed a throughput required for the network to perform properly. Then, we derived analytical formulas and calculated the number of the required nano-nodes. The results can be easily scaled up or down, depending on the medical application and demanded functional parameters of the nano-network.

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