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SPECIAL SECTION ON BODY AREA NETWORKS

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PANACEA: An Internet of Bio-NanoThings Application for Early Detection and Mitigation of Infectious Diseases

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ABSTRACT The Internet of Bio-NanoThings (IoBNT) concept envisions the connection between biological cells and the Internet. The ultimate goal of IoBNT is to catalyze a revolution in biomedical technologies through advances in molecular communication, integrated systems, bio-nanosensors and synthetic biology to improve human health and quality of life. In this paper, an application of IoBNT called PANACEA (a solution or remedy for all difficulties or diseases in Latin) is presented as a solution for an end-to-end design towards realizing the IoBNT for the first time in the literature. The architecture of PANACEA is tailored to focus on diagnosis and therapy of infectious diseases. In PANACEA, to detect the communication within the cells of the body to deduce infection level, a submilimeter implantable bio-electronic device, a Bio-NanoThing, is proposed. BNT can transmit the detected infection data remotely to a wearable hub/gateway outside of the body. The hub can use mobile devices and the backbone network such as Internet or cellular systems to reach the healthcare providers who can remotely control the BNTs. Hence, PANACEA provides a system, where sensing, actuation and computing processes are tightly coupled to provide a reliable and responsive disease detection and infection recovery system. Incorporating molecular communication and conventional networks brings many challenges that are attacked in various fronts such as circuit and biosensor design, communications engineering, with novel solutions presented in this paper, accompanied with simulation results.

INDEX TERMS Internet of Things, internet of bio-nanothings, molecular communication, implantable medical device, biosensor, wearables.

I. INTRODUCTION

The state-of-the-art diagnostics, monitoring, and therapy in clinical settings are limited by the imprecise nature of current methods and use of devices that are either external, or when implanted, suffer from large size. A breakthrough is eminent since we are at a critical crossroad in bio-medical research in which our ability to miniaturize sensors and electronics is unprecedented, and our understanding of biological systems enables manipulation and control of behavior of cells. These technologies will be leveraged to create Internet of Bio-NanoThings (IoBNT), first introduced in [1], as a paradigm-shifting concept for communication and network engineering, which tackles challenges of developing efficient techniques for the transfer of information, communication, and networking within the biochemical domain, while enabling a connection to the electrical domain of the Internet through a bio-cyber interface.

IoBNT is envisioned to be a heterogeneous network of nanoscale bio-electronic components and engineered biological cells, so called *Bio-NanoThings (BNT)*, communicating via electromagnetic waves, and by molecular communication

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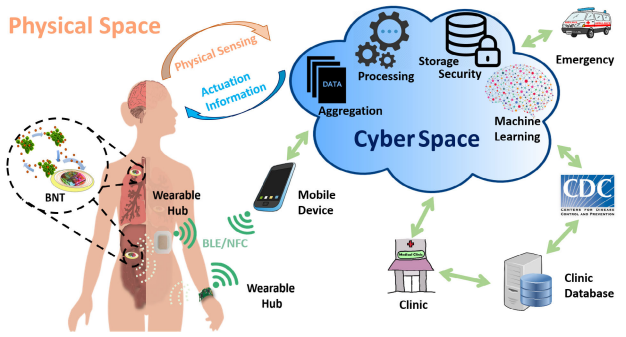

FIGURE 1. IoBNT Concept.

(MC), as illustrated in Fig.1. The objective of this concept is to directly interact with the cells enabling more accurate sensing and eventually control of complicated biological dynamics of the human body in real time. The approach taken in IoBNT requires the engineered cells to sense, process, and communicate among each other and with external devices that provide remote and minimally invasive ways of interrogation in the IoBNT concept. The realization of IoBNT starts with the design of implantable submilimeter BNTs which are capable of sensing bio-chemical information in the human body and transmitting the sensed information remotely to a wearable hub outside of the body.

In this paper, we discuss how IoBNT concept may be applied to early detection and mitigation of infectious diseases. Existing technologies for the detection of infections are usually based on the culture of microbial organisms causing the infection found in the samples collected from the patients or using polymerase chain reaction (PCR) requiring bulky devices heating and cooling the samples and reagents for enzymatic reactions to identify the molecular structure of microorganisms. IoBNT framework separates itself from these existing technologies by enabling *in vivo* continuous monitoring of infections through implanted nanoscale sensors detecting communication among infectious organisms within the body. Then, these sensors report to a wearable mobile hub which forwards the collected data to healthcare professionals. Hence, the patient does not need to visit a laboratory to get tested and also infections can be detected early, even before symptoms appear, prompting the patient to seek medical advice. This way, the risk of premature death of vulnerable patients can be reduced.

Early detection of infections is very critical especially for cancer patients who are at immuno-suppressive state after chemotherapy and vulnerable to serious infections which is a major reason for mortality. As another example, in the case of cystic fibrosis, a genetic disorder with no cure, mostly affecting lungs, infections occur wave by wave and cause the death of the patient. Thus, early detection of lung infections will improve both the quality of life of cystic fibrosis patients and increase their life expectancy. Moreover, detecting infections at an early stage in at risk patient populations will allow the timely administration of antibiotics and other drugs shortening the stay in hospital for treatment and decrease mortality [2], and both resulting in significant reduction in healthcare costs. In addition to this, with the rise of antibiotic resistance among infectious bacteria, treating infections is becoming more and more challenging for health professionals. Applying the wrong antibiotic delays the therapy and can reduce the survival rate as much as five-fold [3]. Furthermore, this IoBNT application can be used to track the efficiency of antibiotics.

This framework not only benefits individuals' health but also contributes to public health. In the case of an epidemic or pandemic, the continuous monitoring of infections provided by IoBNT systems is very valuable. Especially since they are already integrated with mobile devices and remote data analytics tools; IoBNT can be easily configured for tracking, tracing, and quarantining people.

The proposed system will continuously monitor the tissues at risk of serious infection to detect it earlier than conventional methods which requires culturing the bacteria in a laboratory to increase its quantity to detectable levels, which typically takes 48-72 hours [4]. While alternative molecular methods such as enzyme-linked immunoabsorbent assay (ELISA) and polymerase chain reaction (PCR) provide higher sensitivity and specificity within a shorter assay time, they require complex instrumentation and skilled operators limiting their use to clinical laboratories. As such, these methods are not suitable for continuous *in vivo* monitoring for early detection of infections.

The approach considered in this paper is based on the proposed system eavesdropping on the quorum sensing (QS) communication among infectious bacteria in the tissue by distributed BNTs which host electronic devices and highly miniaturized bio-sensors. QS is a method of communication where bacteria coordinate their behavior by exchange of molecules. By listening in to QS via BNTs, the spatio-temporal distribution of abnormally growing bacteria in tissue can be obtained to detect an infection even before the patient shows symptoms. QS signals are transformed into electrical signals measured and converted into raw data relayed through the coil/antenna to the wearable hub, which may come in the form of a patch, bandage, or smartwatch. The wearable hub forwards the raw data via access networks such as wi-fi or cellular systems to the Internet where it is processed and delivered to interested parties such as healthcare institutes and emergency services, and send an actuator information if required. Fig. 2 summarizes the overview of a design of IoBNT for infection detection application.

Besides the early detection of infections, we can use IoBNT framework to help us with the mitigation of infections by incorporating active and passive drug delivery systems. For passive drug delivery, external devices can be configured to release the pre-programmed drug recipe or send a message to patients to take the personalized medicine. For active drug delivery, a mechanism can be incorporated in the implantable devices to release drugs.

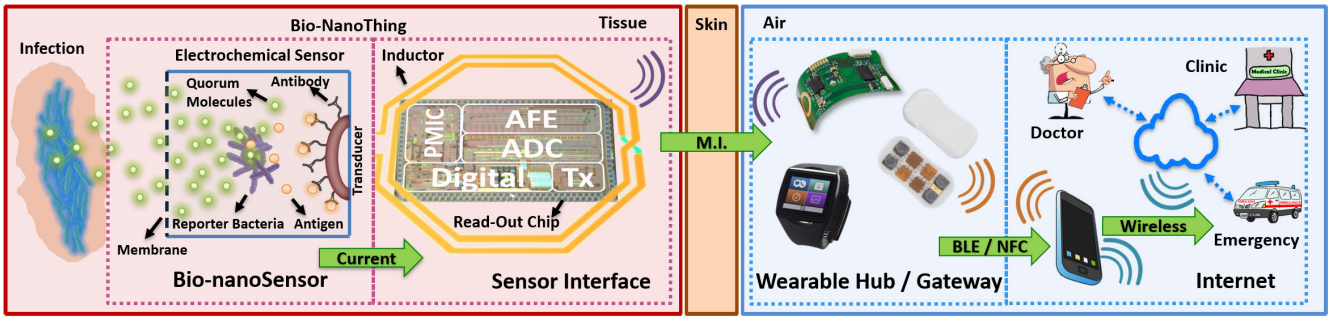

FIGURE 2. Overview of PANACEA System.

Although numerous studies have been conducted in IoBNT paradigm focusing on the communication and networking aspects, there is a lack of validation platforms. Implementing devices that can receive and process biochemical domain signals, i.e., the building blocks of IoBNT is not a trivial task. A broad expertise from various fields, such as genetic engineering of bacteria, bio-nano molecular sensing, and implantable and wearable bio-interface designs is needed. Hardship of bringing a multi-disciplinary expertise makes it a daunting task for researchers. As a firs step of creating validation platforms for IoBNT, we introduce a novel design for a device serving as a BNT, capable of working in biological environment.

The research on IoBNTs will make contributions in many broad directions discussed in the following sections of this paper which we divide into two, namely, development of BNTs depicted in light of the advancements in synthetic biology and nanotechnology discussed in Section II, and development of communication channels and networks among BNTs and the Internet discussed in Section III. Finally, we conclude the paper by future research directions and challenges.

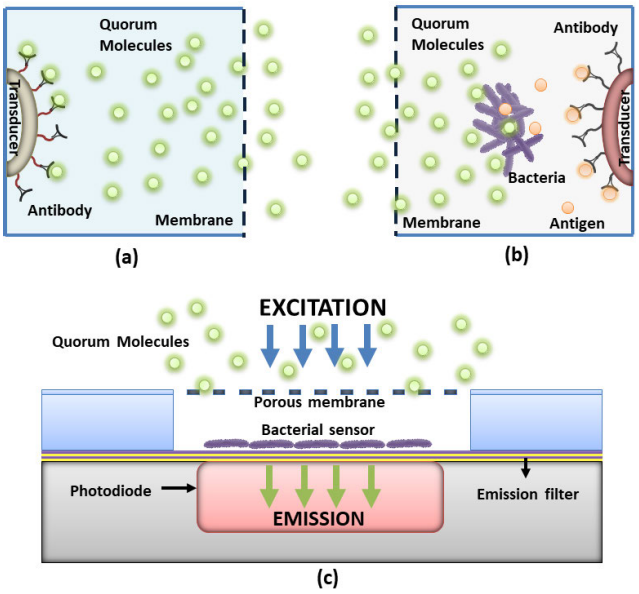

FIGURE 3. Bio-sensor with a) direct electro-chemical, b) bacterial sensor, c) optical measurement.

II. DEVELOPMENT OF BIO-NanoThings

The first aspect of the framework described in this paper is the development of BNTs which are main devices of IoBNTs. In this section, a realistic design solution for a hybrid Bio-NanoThing is described for the first time in literature and required features of BNTs for infection detection application are discussed. A BNT device, consists of mainly three parts: a bio-nanosensor, a sensor-interface chip, and a coil/antenna. BNTs can be utilized for detecting the quorum sensing signals of infectious bacteria and for wirelessly transferring the sensed data of infection to a wearable hub outside of the body as depicted in Fig. 2. The miniature BNT can be deployed both as implantable and wearable device in the body.

In this section, we focus on the design and fabrication of a novel sub-millimeter sized bio-nanosensor, its interface chip, and a coil/antenna as the components of BNT as illustrated in Fig. 2. First, we introduce various sensing modules and explain the methods of implementing the bio-nanosensor. Then, we move on to the design of ultra-low power interface circuits with wide range of sensing capabilities and high-efficiency wireless power transfer circuits along associated coil/antenna.

A. BIO-NANOSENSOR

An infection is the invasion of various healthy human tissues by pathogenic bacteria that are multiplying and disrupting tissues' operation, causing diseases. To detect it with IoBNT, we design BNTs exploiting quorum sensing communication of bacteria infecting human body detected by bio-nanosensors. Quorum sensing is the major cell-to-cell communication mechanism where bacteria produce and release chemical signal molecules whose external concentration increases as a function of increasing cell-population density [5]. Therefore, by sensing the concentration of its quorum sensing molecules, it is possible to estimate the density of the infectious bacteria population.

There are many alternative ways to design the biosensor of BNT. An alternative method can be the direct detection of QS molecules of the bacteria of interest via antibodies [6] attached to a transducer, depicted in Fig. 3.a. Other methods

include utilizing another species of bacteria as a detector in the sensor. The engineered bacteria of the bio-nanosensor sense MC signals generated by the infectious bacteria and catalyze a chemical process to produce an electro-active product [7], as depicted in Fig. 3.b or produce light detected by the transducer which converts light into electrical current, depicted in Fig. 3.c.

Researchers widely utilize bacterial sensors with engineered synthetic pathways for molecular sensing [8]. The main advantage of bacterial sensors is that they are equipped with membrane receptors evolved to interact with the target of interest with high sensitivity and specificity. In the bacterial sensor, a genetically engineered *E. coli* K12 strain, which is harmless to human, can be employed to bind to QS molecules and produce an optical signal as bioluminescence/fluorescence or molecular signals easy to be detected by electrochemical sensors. An *E. coli* strain either expresses the lux genes (light output) or catalyzes a chemical process to produce an electroactive product (chemical output). For physical transduction, electrochemical, mass-based, magnetic, or optical approaches can be evaluated and compared for the highest achievable specificity and sensitivity.

In this paper, we elaborate on bacterial sensors for QS with light output and optical transducers, both already having established design processes. The design of bio-nanosensor has two steps. First step is designing a microfluidic reservoir that harbors the bacterial sensor colony. The reservoir should be sealed with a porous membrane with pores small enough to entrap the bacteria while allowing diffusion of QS molecules. Second step is designing an optical transducer that consists of light emitting diodes for excitation and a photo-diode array placed in close proximity of the colony to detect low levels of fluorescence emission from the bacterial sensor colony. Over the photo-diode array, a distributed Bragg reflector that specifically blocks the excitation wavelength to maximize the sensitivity, can be constructed. Finally, the bacterial sensors needs to be introduced into the chamber and immobilized on the functionalized surface.

From micro-electro-mechanical systems' perspective, to develop the proposed bio-nanosensor architecture, there are many challenges to be tackled: (i) *Bacterial sensor growth:* Ideally, we would like to have a constant number of live bacterial sensors that only as act chemical transducers. Live bacteria however replicate. Hence, keeping the bacterial sensor population steady within the reservoir is a major challenge. (ii) *Bacterial noise:* Live bacteria interact with the environment and adapt. Therefore, the effect of stochastic behavior of bacteria on the sensor performance should be analyzed. There are approaches to address these challenges, namely, physical and chemical means for population control. Physical approaches include use of confinement of bacteria mechanically [9], thermally [10] or optically [11]. Mechanical confinement makes use of membranes to force a monolayer of bacteria. Thermal control is based on joule heating through integrated heaters on the perimeter of the colony. Likewise, structured UV illumination is used to inactivate bacteria in the perimeter regions. For chemical control, bacteriostatic antibiotics such as tetracycline as well as selectively patterned antibacterial coatings such as silver nanoparticles [59] are other alternatives to balance the death and reproduction rate within the bacterial colony. (iii) *High sensitivity:* The overall sensitivity of the system will depend on the efficiency of individual transduction steps and their integration. To optimize device sensitivity, the bacteria strains that produce more fluorescent molecules per sensed quorum sensing molecule through evolution should be identified. Photodiodes, and the filter can be designed to help minimize cross-talk. An array of photodiodes under the colony as well as use of lenses to focus light from large area bacteria population onto the photodiodes might also help to solve this challenge. (iv) *Specificity:* It should be confirmed that the detection is specific to the molecule of interest. Bacteria species have diverse quorum sensing molecules ranging from N-acyl homoserine lacton (AHL) molecules for Gram-negative bacteria to modified oligopeptides (autoinducer peptides, AIP) for Gram-positive bacteria. Bacterial sensors are genetically engineered to only respond specifically to the quorum sensing molecule of interest unique to the infectious bacteria that is being detected. Hence, many bacterial sensors developed for biological studies of quorum sensing can be incorporated in the bio-nanosensor alleviating the specificity challenge.

B. SENSOR-INTERFACE CHIP

To increase the reliability of the infection detection system in the decision making mechanism, we consider to have more than one modality. Therefore, a multimodal-sensing paradigm, incorporating both optical (florescence/bioluminescence) and electro-chemical sensing mechanisms, that maximizes both sensitivity and specificity of BNTs should be adopted. Even though florescence/bioluminescence has been studied extensively and used in various biomedical applications [12]–[16], detection of low light is still a key challenge. Similar to low light detection, in electrochemical sensing, it is required to detect ultra-low current levels on the order of picoamperes to nanoamperes [17], which should be considered in conjunction with ultra low power requirement in an implementable medical device (IMD). In an effort to minimize the heat generated in the wireless power delivery and management blocks, and prevent possible tissue damage in compliance with regulatory requirements, such as specific electromagnetic power absorption limits [18], [19] a low μW-level sensor-interface chip is necessary. Considering these requirements, the sensor-interface chip has mainly four parts:

1) ANALOG FRONT-END (AFE)

AFE circuit, which interacts with bio-nanosensors, requires a current and/or impedance detection circuit with wide range sensing capability and high linearity performance preferably at various frequencies [20]. Another important issue for the AFE circuit is the adaptation of the electronic system to

biological systems. The timing between two appearances of a biological event may take a very long time, *i.e.*, minutes or even hours range. Furthermore, this may happen very slowly. Therefore, the electronic system should be capable of long integration time [13]. At the same time, aggressive duty cycling that significantly reduces the average power consumption of the circuit down to low μW level should be deployed. Beside low power sensing and long integration capability, to minimize the effect of in-body noise to the sensed data, the AFE circuit should be very low noise.

2) ANALOG-TO-DIGITAL CONVERTER (ADC)

Specific absorption rate (SAR) ADCs are among the lowest power consuming architectures with amazingly low 0.88 pJ per conversion levels reported in [21]. However, to achieve both low power and high resolution, they occupy a large area on chip. Delta-sigma ADCs can achieve high resolution at relatively low power levels and very small foot-prints [22]. However, they need high clock frequency and generate large data volume those need to be decimated in the digital domain. Existing ADC circuits need a trade off between large-area occupation and low-power consumption. In [23], on the other hand, researchers sensed fluorescence produced by bacteria through a simplified discrete-time comparator-based ADC, which quantifies with threshold crossing. A solution for BNT might be a new hybrid ADC architecture by combining the ultra-low power highly popular SAR architecture for most significant bits (MSB), with high resolution and and small foot-print delta-sigma modulation for the least significant bits (LSB) [24].

3) POWER MANAGEMENT IC

In this proposed system, the wireless reading range of BNTs is projected to be more than 15 cm, so that the physicians are able to eventually implant BNTs at a desired location within the body. Therefore, the anticipated amount of delivered power even after optimization of the multi-coil wireless power transmission (WPT) link [25], [26] would be around several tens of μW. This is a major challenge but not a major concern, because the operating frequency in bacterial sensing systems is in Hz range. Thus, in an adaptive heavily duty-cycled architecture, it is possible to build an extremely efficient charging mechanism to harvest the low incoming electromagnetic energy from the wireless power link, store it in high charge density, yet very small off-chip capacitors - boosting the voltage level [27], [28] - and use it over a short period of time when the bio-nanosensors are activated, the AFE conditions/pre-processes the acquired signals, the ADC samples and digitizes them, and the back telemetry link send the resulting data to the wireless/wearable hub outside the host body.

4) WIRELESS DATA TRANSMITTER

Following ADC, digitized optical and biochemical signals are compressed, packetized, and wirelessly transmitted from inside the host body to the external wearable Internet hub. Since the available power to the BNTs will be limited to μW level, load shift keying (LSK) or passive back telemetry can be incorporated. Beside the back telemetry switch, the data communication block includes forward data modulation, encoding, and encryption (if necessary) to improve data integrity and security. Since the optimal power carrier frequency might be in the range of hundreds of MHz range, the L and C values are much smaller; therefore, the back telemetry link can offer a much higher bandwidth than what has been demonstrated in the traditional 13.56 MHz RFID links. In this system, a high bandwidth is not desired because of transmitting high volume of data. Instead, it is desired to apply aggressive duty cycling and the need to send small amount of collected data in a very short period of time. Using impulse-radio based transmission, which eliminates carrier signal to save power, is an alternative mean of data transmission which can be incorporated in this IoBNT application.

C. COIL/ANTENNA

WPT plays an increasingly important role in energizing IMDs that are either too small or inefficient for primary batteries to power [29]. Although researchers have considered powering smaller IMDs via ultrasound, laser, and ultra-high frequency (UHF) fields [30], WPT to IMDs is still considered the safest and most reliable technique to establish power/data link between one or more transmitter (Tx) and one or more receiver (Rx) coils that are electromagnetically coupled in the near field [31]–[33]. Since these IMDs are small and arbitrarily placed, the design of an electromagnetically coupled WPT link poses a great challenge. The link should deliver enough power to the load (PDL) while ensuring that the temperature and human body exposure to electromagnetic (EM) field remain within safe limits. EM exposure is defined by the SAR that should not exceed 1.6 W/kg for safe operation within 3 kHz – 300 GHz band [19]. The essential components of WPT are coil and antenna. Hence the design of coil/antenna needs special concentration. The operating frequency, f, and the EM field intensity strongly impact the Tx-Rx coil/antenna geometry design, power source characteristics, power transfer efficiency (PTE), and PDL. In an effort to increase the received power on a small mm-sized in-body coil, the optimization of the coil design and the choice of f are key aspects of the overall design.

Power efficient and reliable energy harvesting and wireless communication links based on magnetic induction requires a precisely designed miniaturized coil to connect BNTs to the wearable hub, which is a key challenge.

III. COMMUNICATION NETWORKS AMONG BIO-NanoThings

Since the severity of infection is directly related to the amount of infectious bacteria, it is the target to be detected using BNTs, described in Section II. To this end, we consider quorum sensing (QS) of bacteria as an indicator of infection. QS is a cell-to-cell communication mechanism where bacteria produce and release chemical signaling molecules whose

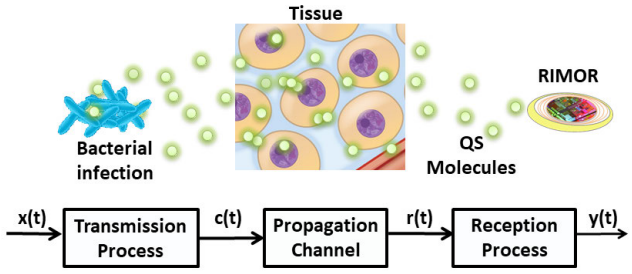

FIGURE 4. End-to-end model for MC Channel for infection.

concentration reflects bacterial cell density [5] as explained in Section II. By measuring the spatio-temporal concentration of QS molecules unique to target bacteria by a network of sub-milimeter sized BNTs deployed in tissues in large numbers, we can estimate the amount of infectious bacteria and learn about the progress of the infection.

QS communication of bacteria can be abstracted using molecular communication theory which studies the information exchange through emission, propagation, and reception of molecules [34]. MC theory focuses on the biological communication mechanisms based on transport of molecules for the information flow among biological cells, tissues, and organisms spontaneously evolved in nature. According to the transport media, different channel models can ve devised such as diffusion-based, flow-based, and molecular motors [35]–[38]. Our prior works on bacteria-based molecular communication specifically on how to use bacteria as biotransceiver device for MC [39] and as active message carriers [40], [41]. MC paradigm helps with modeling the principles of multi-scale molecular and biological phenomena realistically without the over-complication of system biology models, and the limitations of experimental approaches. MC abstraction of QS helps us to model and analyze the propagation of QS molecules from the infection site to BNTs providing us a tool to estimate the original location and amount of bacteria at the infection site.

A. MC CHANNEL FOR INFECTION

The amount of infectious bacteria can be considered as the message transmitted by the concentration of QS molecules diffusing through tissue reaching BNTs. This channel can be represented with an end-to-end model similar to [35] as shown in Fig. 4.

The first process in this MC channel is the transmission process, i.e., production and release of QS molecules by infectious bacteria. This QS mechanism can be modeled by one of the many QS models [42] considering a population of bacteria as a single entity and abstracting all the intermediate biochemical reactions to reduce the system to a set of coupled nonlinear differential equations. In the transmission process, the differences among individual bacterium in a population and the random spatial distribution of bacteria can be introduced as noise sources.

The next step is the propagation process, i.e., the transport of QS molecules through the tissue where they diffuse through the cells and in fluid between the cells. As a starting point, only local infections where infectious bacteria is yet to reach bloodstream are considered. The movement of small molecules such as QS molecules in the interstitial space (small spaces between biological structures) occurs by diffusion and convection modeled by the general mass transport balance depending on the flow velocity of the interstitial fluid, the diffusion coefficient, and the reaction rates that account for consumption, degradation and binding to the cells. The values of the transport coefficients are determined by the structure of the interstitial space and the physicochemical properties of QS molecules.

Unlike the previous studies on diffusion-based MC model [35], which is analogous to free-space channel model in wireless communication, the transport in interstitial space is more complex where QS molecules should navigate around the cells, diffuse inside and outside of cells that is analogous to channel models with multipath, shadowing, reflection and refraction in a crowded environment. The noise for the propagation process arises from the random nature of diffusion and the dynamic properties of interstitial fluid such as flow rate and pressure.

The last step is the reception process where QS molecules arrive to the vicinity of BNTs and may be detected by the bio-nanosensors. As decribed in Section II bacterial bio-nanosensors which sense the concentration of QS molecules by the receptors of bacteria coupled to generation of bioluminescence and/or fluorescence detected by photodiodes constitute the MC receivers. The speed of this signal transduction is limited by the time required to produce bioluminescence, fluorescence or electroactive proteins (reporter). The delay arising from this phenomena can be compensated by a very sensitive photodiode that can even detect one reporter protein.

To estimate the number of bacteria from the concentration measured by BNTs, we need to fully understand all these three processes, and analyze the delay, the attenuation and the noise of each process. The delay and attenuation models dictate the sensor and receiver design to maximize the infection detection. The capacity of this MC channel derived using the models describing these processes and the respective noises represent the accuracy of the estimation of infection.

In a more realistic infection scenario, multiple tissues in an organ might be infected simultaneously creating multiple transmitters at different locations. However, BNTs can sense a limited area around themselves. Hence, multiple BNTs can be deployed to monitor multiple transmitters in a larger area. This resembles a MIMO MC system with multiple transmitters and multiple receivers. QS molecules follow different paths while arriving to different BNTs located far from each other. Hence, the received QS concentrations experience different delay and attenuation profiles. By combining the data sensed by all BNTs, it is possible to more accurately detect the level of infection and generate a map of probable

infection locations. By exploiting these multiple channels, novel localization techniques can be developed for MC that will indicate the infection sites in this scenario. This MIMO model is also useful to determine the locations and the amount of BNTs that is needed to implant in the body for an efficient detection and whole coverage of organs at risk.

B. MC CHANNEL FOR DRUG DELIVERY

To create a closed loop system, the proposed IoBNT application can include an actuator mechanism implemented in a passive or an active drug delivery form. For passive drug delivery, humans in the decision loop can be incorporated by including healthcare providers' opinions into the delivery logic. According to that, an external device that releases the pre-programmed drug recipe or sends a message to patients to take the personalized medicine might be configured. For active drug delivery, a drug can be released directly from BNTs or the wearable hub. As an extension of QS eavesdropping concept, another alternative actuator mechanism is quorum quenching, i.e., prevention of quorum sensing by disrupting the signaling. By interrupting their quorum sensing communication and preventing quorum sensing controlled virulence mechanisms, infectious bacteria may be prevented from infecting healthy tissues [43].

Besides modeling bacterial infection, MC paradigm has also been used for modeling drug delivery systems (DDS) as an abstraction of the propagation of drug particles in the body [44], [45] which can be used for the mitigation of infection by administering antibiotics. By bringing abstractions traditionally used to characterize the functions of networking and computing systems, MC can formulate DDS problems in a way to be tackled with the mathematical tools used in communications, such as stochastic analysis, information theory and control theory. The biodistribution of drugs through the blood vessels is modeled with particle advection and diffusion combined with other physicochemical processes such as absorption, reaction, and adhesion. However, this model studies only the drug injected in blood vessels. Other passive drug delivery methods such as orally administered antibiotics requires the abstraction of absorption of drugs through gastro-intestinal system and mixing in the blood from MC perspective. For active drug delivery systems such as implanted and dressing/patch drug delivery, the controlled drug release should be incorporated into MC paradigm.

IV. COMMUNICATION OF BNT NETWORKS WITH INTERNET

BNT networks are composed of mixed types of devices such as electronic and cell-based, as well as various types of communication such as MC and near field communication as shown in Fig. 2. In order to enable IoBNT operation, the realization of the interfaces between different domains is essential. This will provide the seamless interconnection of cyberspace and the biological environment towards the ultimate goal of "cell-connected-to-Internet."

The most challenging interface in IoBNT is the transduction of MC signals into electrical signals, which can be realized by BNTs, where the sensor bacteria receive MC signals in the form of QS molecules and generate bioluminescence and/or fluorescence that is captured by photodiodes creating a current. Since this interface is dependent on the sensor bacteria, it is acquiring the inherent noisy behavior of biological systems. Furthermore, since sensor bacteria need time to produce bioluminescence and/or fluorescence proteins, this interface adds delay on top of the already large propagation delays in MC.

Another challenge is that MC networks require their own protocols due to peculiarities of MC channels and the limited computation capability of MC devices. The networking protocols for MC are extensively studied such as the TEC-SMART MAC protocol, amplitude source addressing. The next challenge for heterogeneous IoBNT networks is to find a solution to integrate these protocols with conventional network protocols on cyber side of IoBNTs. It is critical to develop novel protocols for IoBNT networks satisfying the requirements of both the molecular world and electrical world of networks.

After being converted into electrical signals, the data coming from MC channels is forwarded to outside of the body by BNTs to a wearable hub using near-field communication techniques. Magnetic-induction, ultrasound or radio frequency can be used to ensure both the data and power delivery to the implanted BNTs. This wireless and wearable controller hub is responsible to transmit data received from BNTs to the Internet. Standard protocols such as BLE or NFC can be used for data transmission. A compact flexible printed circuit board (Flex-PCB), which can be easily attached to the body in the abdominal area, e.g. in the form of a patch, close to where BNTs are implanted, or a device similar to a smart watch can form the wearable hub.

V. SIMULATION RESULTS

In this section, we quantitatively illustrate the feasibility of the IoBNT framework described in the previous sections targeting specifically infections caused by *Pseudomonas aeruginosa (P. aeruginosa)* bacterial species, a leading cause of hospital-acquired infections.

P. aeruginosa is resistant to a large spectrum of antibiotics and can infect various organs such as lungs, urinary tract, kidney, and skin [46] which can even lead to death [47]. *P. aeruginosa* infections affect the most the patients who are struggling with other diseases such as cancer, cystic fibrosis and burns, thus with weak immune system. Infection in cancer patients is associated with 8.5% of all cancer deaths at a cost of $3.4 billion per year [48]. Most of cystic fibrosis patients are infected by *P. aeruginosa* which by the time they reach the age 7 and after that they suffer chronical lung infections increasing the rate of mortality [49].

In clinical laboratories, plate culturing is used to determine the presence of *P. aeruginosa* in the samples collected from the patients. Plate culturing is the gold standard for

bacteria detection which is the method of multiplying bacteria inoculated in Petri dishes with predetermined culture mediums for identification of the species. Typically, it takes *P. aeruginosa* 16-24 hours to grow from streaking onto plates in rich medium [50]. The aim of our simulations is to show that in case of an infection, the IoBNT framework discussed in this paper can detect the presence of the bacteria earlier than 16-24 hours time period to be considered as an early detection.

For the simulation scenario, we consider a wound infection where bacteria first attach to damaged skin and colonize the wound which is pretty common in burns [51]. During the growth of bacteria in the wound, quorum sensing is fundamental to the initiation, propagation, and maintenance of acute *P. aeruginosa* infection. Quorum sensing molecules for *P. aeruginosa* are the autoinducers 3-oxo-C12-homoserine lactone (3-oxo-C12-HSL) and N-butyryl homoserine lactone (C4-HSL) [52]. These QS molecules are produced proportional to the bacterial density, i.e., the strength of the infection.

We simulate the diffusion of quorum sensing molecules (QS molecules) in soft tissues near damaged skin as the MC channel described in Section III to determine the amount of QS molecules reaching the BNTs. Then, we calculate the time it takes for the BNTs to detect alarming amount of QS molecules indicating the start of an infection to demonstrate that the proposed IoBNT framework in this paper has potential for early detection of infections.

A. BACTERIAL GROWTH AND QUORUM SENSING

During infection, *P. aeruginosa* adheres to the epithelium of the skin and starts to reproduce and release toxins penetrating into the body through the cells of the skin or through the gaps in between the damaged cells of the wound [51]. With the activation of quorum sensing which encourages the accumulation of *P. aeruginosa*, the destruction of the epithelium begins which will no longer act as a barrier against the entry of bacteria in the tissues and later into the bloodstream.

The growth of infectious bacteria in a wound follow the logistic equation [53] expressed as

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{1}$$

where $N(t)$ represents the bacterial population density, r is the bacterial growth rate, and K is the carrying capacity [54].

Assuming quorum sensing is already activated in the initial colony of bacteria, the QS molecule production can be expressed as

$$\frac{dA}{dt} = D_w \nabla^2 A + kN - \beta A, \tag{2}$$

where $A(t)$ represents the QS molecule concentration, D_w corresponds to the diffusion of QS molecules in the wound, k is the production rate of QS molecules, and β is the degradation rate of QS molecules [53]. Since we are considering a small wound on surface, we will assume that bacteria is homogeneously distributed in the wound and QS molecules do not diffuse within the wound, hence we assume the first term in (2) is 0.

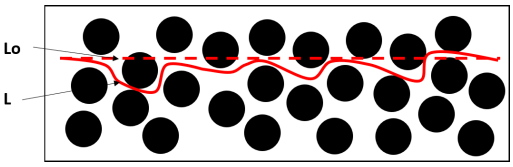

FIGURE 5. Diffusion in porous medium.

B. MOLECULE TRANSPORT IN TISSUES

Cells receive nutrients and oxygen from blood and emit waste, metabolites, and carbon dioxide into the extracellular space, i.e., the volume outside cells in tissues filled with interstitial fluid into which cells and blood vessels are embedded. In some tissues, the extracellular space also contain extracellular matrix composed of materials such as collagen and fibers providing a structure for cells to adhere. This complex structure impedes the transport of molecules through the tissues.

In molecular communication theory, the most used transport equation is free diffusion of molecules in a semi-infinite space [55]. The channel models, inter-symbol interference expressions, noise models, and detection algorithms are mostly based on unrestricted movement of molecules. However, in biological environments, especially for *in vivo* applications, molecules are always found in a confined environment surrounded by biological cells hindering their diffusion by acting as obstacles. Therefore, in this paper, we consider the more realistic diffusion in porous medium which can account for the diffusion of molecules in tissues through the interstitial fluid in between the cells constituting that tissue [56].

As seen in Fig. 5, cells in the extracellular space can be very dense leaving very small space for the interstitial fluid flow which is often modeled with Darcy's Law describing fluid flow through a porous medium. In that case, the transport of molecules in extracellular space is due to both diffusion and convection of molecules.

The propagation of quorum sensing molecule concentration in tissues is described by mass transport equation in porous media as

$$\frac{\partial C}{\partial t} = \frac{D}{\lambda^2} \cdot \nabla^2 C + \frac{Q}{\alpha} - \frac{f(C)}{\alpha} - v \cdot \nabla C, \tag{3}$$

where C corresponds to the concentration of the quorum sensing molecule, D is the diffusion coefficient, λ is the tortuosity, and α is the volume fraction. The term $f(C)$ represents the clearance, loss, and uptake [57].

The structure of the tissue is represented in the transport equation (3) through two non-dimensional parameters, namely, the volume fraction α, and the tortuosity λ. Volume fraction is defined as

$$\alpha = \frac{\text{volume of ECS}}{\text{volume of tissue}}, \tag{4}$$

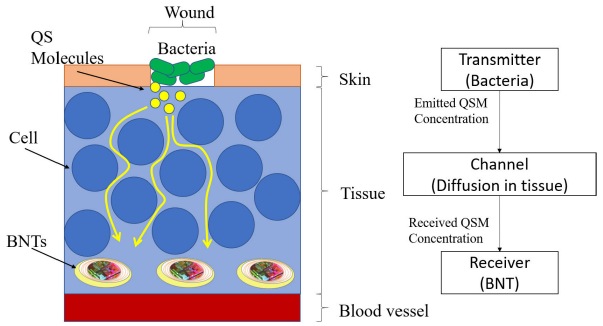

FIGURE 6. MC channel for infection detection.

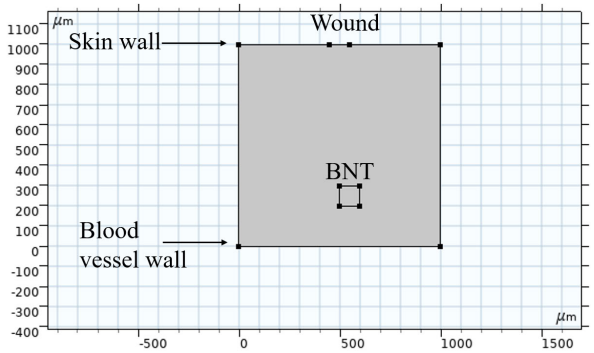

FIGURE 7. COMSOL simulation domain.

which describes the geometry of the ECS as a diffusion medium. Tortuosity is a complex measure of how cellular obstructions are hindering the diffusion incorporating several geometric effects and the interstitial fluid viscosity. Often, tortuosity is determined empirically using

$$\lambda = (D/D^*)^{1/2}, \tag{5}$$

comparing the diffusion coefficients in free solution to that in obstructed medium determined with experiments [58].

Using the above-mentioned porous diffusion theory, we are considering the molecular communication channel for infection described in Sec. III, where the transmitter is the infectious bacteria emitting QS molecules and BNTs are receivers in a wound environment as shown in Fig. 6. We consider a cross-section of soft tissue with a wound on the skin hosting bacteria. As the bacterial population increases, the concentration of QS molecules also increases and these molecules diffuse through the tissue arriving the BNTs where they are captured by ligand-binding. Upon capturing QS molecules, BNTs measure the concentration of QS molecules and report to the wearable hub if a critical threshold is reached.

C. COMSOL SIMULATIONS

To simulate this MC channel, we use COMSOL which is finite element based multiphysics simulator capable of both simulating the growth of the bacteria and the propagation of QS molecules in the given simulation geometry. The physics interface of Transport of Diluted Species is used for the diffusion of QS Molecules in 2D. The simulation domain implemented in COMSOL is shown in Fig. 7 for a 1 mm × 1mm soft tissue.

The initial bacteria population in the wound is modeled to be contained in the skin and the BNT of 0.1 mm × 0.1 mm is placed at (500 μm,200 μm) in the middle of the domain towards the blood vessel. To be able to evaluate the porous diffusion equation given in (3) in this domain, the boundary conditions should be set. The first boundary condition is at the interface of skin with tissue at y= 1 mm. Since QS molecules are only diffusing through the tissue and not towards outside of the body, we set a no flux boundary condition expressed as

$$\frac{\partial C}{\partial t} = 0, \quad \text{at y= 1 mm.} \tag{6}$$

The second boundary condition is for the tissue/blood vessel interface at y= 0 mm. Here, we assume that all the QS molecules reaching this interface are washed away by bloodstream. Hence, we set a zero concentration boundary condition expressed as

$$C = 0, \quad \text{at y= 0 mm.} \tag{7}$$

Also, we have assumed that initially there is no QS molecules in the tissue which corresponds to a zero concentration initial value in the domain expressed as

$$C(x, y) = 0, \quad \text{at t=0 sec.} \tag{8}$$

The simulation parameters are the diffusion coefficient of the QS molecule for *P. aeruginosa*, $D = 4.3 \times 10^{-11}\ m^2/s$, the bacterial growth rate, carrying capacity, $K = 3 \times 10^9\ cells/ml^{-1}$, $r = 0.6\ h^{-1}$, QS production rate, $k = 74000\ h^{-1}$, QS degradation rate, $\beta = 600\ h^{-1}$ [53].

Furthermore, we assumed that $f(C) = 0$ since the loss of QS molecules in the tissue is negligible when there is a high production during the infection. Also, the velocity of the interstitial fluid, v, is assumed to be 0 since interstitial fluid flow rates are very small and the transport is mainly dominated by the diffusion and not the convection [56].

In Fig. 8, the QS molecule concentration distribution in the field after 8000 sec is shown. This illustrates how QS molecules are propagating towards BNTs. To understand the impact of the porous diffusion and the tissue structure, we have plotted the concentration at the BNT with respect to time for varying volume fraction and tortuosity parameters.

In Fig. 9, the concentration of QS molecules with respect to time is plotted for a constant tortuosity, $\lambda = 1.45$, and for two values of volume fraction $\alpha = 0.25, 0.5$. It is observed that the higher the volume fraction, the lower the QS concentration at the receiver. Since the total tissue volume considered is fixed, the higher volume fraction corresponds to a larger volume of extracellular space as defined in (4) creating more possibilities for QS molecule to diffuse which in turn results in lower number of molecules reaching the receiver.

In Fig. 10, the concentration of QS molecules with respect to time is plotted for a constant volume fraction, $\alpha = 0.25$, and for two values of tortuosity, $\lambda = 1.45, 1.75$. It is observed that the higher the tortuosity, the lower the QS concentration

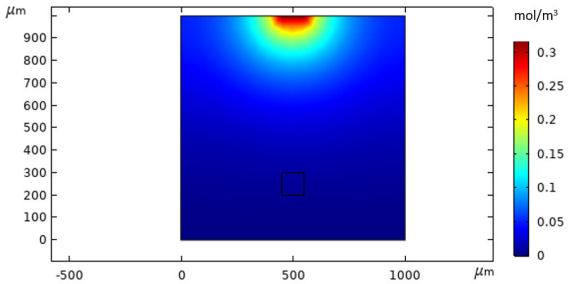

FIGURE 8. Concentration of QS molecules at time t=3 hours.

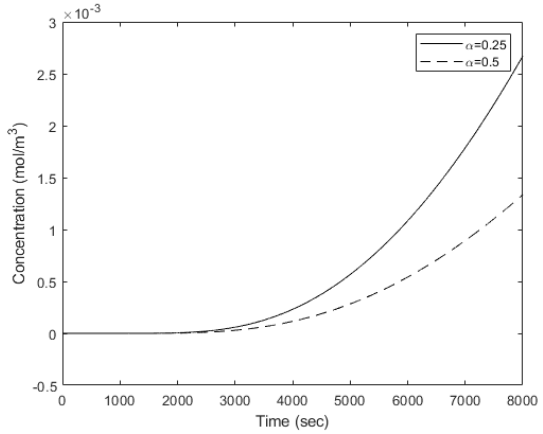

FIGURE 9. QS Concentration at BNT for varying volume fraction.

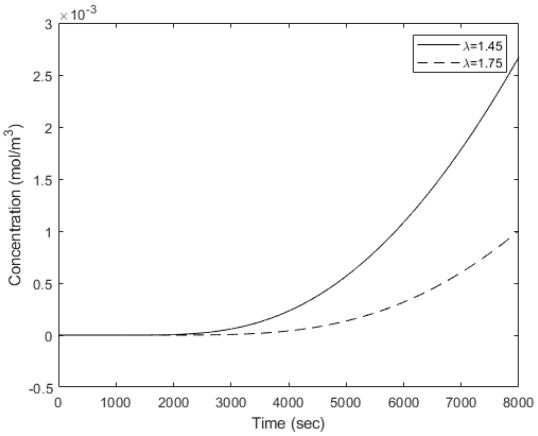

FIGURE 10. QS Concentration at BNT for varying tortuosity.

at the receiver. The tortuosity depends both on geometry and viscosity of the diffusion medium. A higher value for tortuosity corresponds to a lower effective diffusion coefficient. Hence, in Fig. 10, it is observed that a higher tortuosity value corresponds to a lower QS concentration at the receiver.

D. INFECTION DETECTION TIME

In previous sections, we have simulated the QS molecule concentration at the receiver, i.e., BNTs in a tissue environment. As described in Section II, BNTs are equipped with QS sensors. In the literature, there are sensors specific for the QS molecules of *P. aeruginosa* reporting minimum detectable concentrations around 100 nanomolars which corresponds to $10^{-3}\ mol/m^3$ [59]. Therefore, a concentration above this level is deemed measurable by BNTs.

Even though we have bacteria in and on our body, not all of them are causing infections. However, a continuous logistic growth with concentration exceeding 10^5 CFU/ml is considered as abnormal growth leading to infection for *P. aeruginosa*. During the simulations, we observed that this critical threshold corresponds to approximately a $2 \times 10^{-3}\ mol/m^3$ for the given BNT distance to the wound.

In both Fig. 9 and 10, it is observed that the threshold $2 \times 10^{-3}\ mol/m^3$ is reached in a time interval of [6000,7000] sec. Therefore, BNTs can detect the infection of *P. aeruginosa* in 1.5-2 hours after the start of infection. Compared to 16-24 hours required for the culture of *P. aeruginosa* for lab test. Our proposed framework can detect infections earlier than lab tests.

The detection time of 1.5-2 hours found for this scenario may vary according to infected tissue structure, the distance of BNTs to the infection site, and diffusion properties of QS molecules, and may be higher or lower for different systems. However, by utilizing the various detection techniques devised for molecular communication in the literature, it is possible to improve the detection times. Another improvement might come from the compensation of interpersonal variations since every patients body is unique. Hence, a calibration of the sensors at the time of deployment can be also used to improve the detection efficiency and speed paving the way for personalized medicine.

VI. SUMMARY AND CONCLUDING REMARKS

A compelling and critical stage in the realization of IoBNT concept is developing the proper BNT, able to detect the communication with molecules among biological cells, so that the ''cell-to-Internet'' connection will be put into practice. In this paper, we carry further the discussion of IoT, IoNT, and IoBNT theory to practice by introducing a logical implementation flow for a BNT devoted to detect the communication among the infectious bacteria. As showing an example in this specific PANACEA application, the outcomes of IoBNT research will be the proof of its game-changer position in the communication society and catalyze a revolution in biomedical technologies.

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