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CURRENT DRUG TARGETS, 2018, Volume 1

Nanonetworks in Biomedical Applications

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Abstract. By interconnecting nanomachines and forming nanonetworks, the capacities of single nanomachines are expected to be enhanced as the ensuing information exchange will allow them to cooperate towards a common goal. Nowadays, systems normally use electromagnetic signals to encode, send and receive information, however, in a novel communication paradigm, molecular transceivers, channel models or protocols use molecules. This article presents the current developments in nanomachines along with their future architecture to better understand nanonetwork scenarios in biomedical applications. Furthermore, to highlight the communication needs between nanomachines, two applications for nanonetworks are also presented: i) a new networking paradigm, called the Internet of NanoThings, that allows nanoscale devices to interconnect with existing communication networks, and ii) Molecular Communication, where the propagation of chemical compounds like drug particles, carry out the information exchange.

Keywords: Nanonetworks, nanocommunication, nanothings, bionanothings, molecular communication, targeted drug delivery.

1. INTRODUCTION

Nanotechnology provides a new set of tools to control matter on an atomic and molecular scale. With such tools, we are able, on the one hand, to create atomically precise materials and structures with revolutionary electrical, optical and mechanical features. On the other hand, for the first time ever, we can interact with living systems on the same scale as they *naturally* interact, i.e., the molecular scale. Ultimately, at the intersection of these two paths, human-made nanostructures can be engineered to engage with living systems on the nanoscale level. In fact, nanosensors and nanoactuators, able to both monitor and control biological processes at (sub) cellular level, have already been developed. For example, researchers have successfully employed surface plasmon resonance (SPR) particle-based nanosensors to analyze biomarkers circulating in body fluids to diagnose deadly diseases, ranging from different cardiovascular and neuronal diseases [1, 2, 3, 4] to, more recently, different types of cancer [5, 6, 7, 8].

Similarly, in addition to nanosensors, nanoactuators that leverage electrical, optical and chemical principles have also been developed. Among others, targeted drug delivery systems (DDSs) are being intensively studied nowadays, as they are at the cutting edge of modern medical therapies [9, 10, 11, 12]. The goal of a DDS is to deliver a drug only to where it is required, thus avoiding any healthy tissue from being affected. Recently, drugs composed of nanoparticles have been diffused into the blood stream for this very purpose.

For the time being, however, nanoparticle applications need external macro-sized equipment to operate them, which drastically limits the applications in which they can be utilized. In the future, *smart nanoparticles* or nanomachines able to collect, process and share information, will enable transformative applications of nanotechnology in diverse fields [13, 14]. Nanomachines are devices up to a few hundred cubic nanometers in size and possess computing, data storing, sensing and actuation capabilities.

Interconnecting nanomachines in a network, or nanonetwork, overcomes the limitations individual nanodevices may have. Nanonetworks are expected to expand the capabilities of single nanomachines, in terms of both complexity and range of operation, by allowing them to coordinate, share and fuse information. Nanonetworks will allow new nanotechnology applications in environmental research, biomedical scenarios, and industrial use [15], among others, to be developed. Ultimately, integrating nanonetworks with macronetworks and the Internet, will result in cyberphysical systems such as the Internet of NanoThings [16] and the Internet of Bio-Nano Things [17].

In this article, we focus on the biomedical applications of nanonetworks; a truly interdisciplinary and novel field. First, we discuss the technologies that enable the devices that will eventually form the nanomachines to be created (Sec. 2), and then present the communication alternatives for nanonetworks, including nano-electromagnetic communications for nanomaterial-based nanomachines (Sec. 3) and molecular communications for biologically-defined nanomachines (Sec. 4). While having a fully-operational nanomachine available is still a future objective, in the meantime bio-device-oriented research and

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communication-focused investigations will benefit from the resulting research into nanonetworks.

2 NANOTECHNOLOGY: A TOOLBOX FOR CREATING NANOMACHINES

In 1959, the Nobel Laureate physicist Richard Feynman described how the manipulation of individual atoms and molecules would allow more functional and powerful human-made devices [18]. In his vision, Feynman talked about having fully-functional atomically precise nanodevices. During that same talk, he noted that, upon reaching the nanoscale, several scaling issues would arise and require the engineering community to totally rethink the way in which nanodevices and nanocomponents were conceived.

More than a half-century later, current technological trends, which are still mainly based on the miniaturization of existing manufacturing techniques, are facing the very limitations he predicted. Consequently, as these new nanoscale properties are taken into consideration, the way in which components and devices are created needs to be rethought and redesigned. Moreover, from the very beginning a whole new range of applications can be enabled through the development of devices able to benefit from these nanoscale phenomena. Such are the challenges to be found at the core of nanotechnology.

Among the many other applications, nanotechnology can be used to build miniature functional nanomachines. As first discussed in [13, 15, 16], there are different approaches not only to designing and manufacturing nanomachines (Figure 1), but also to classifying them. On the one hand, we can distinguish between top-down and bottom-up approaches. In a *top-down approach*, the focus is on miniaturizing existing devices (e.g., sensors, actuators, processors, memories) with or without loss of functionality. Improvements in photolithography (i.e., the use of light and photomask processes to build electronic and optical circuits) and electron or ion beam lithography are examples of top-down designs in which the starting point was a macro-structure (e.g., a silicon wafer) from which the nanodevices were then defined. In a *bottom-up approach*, the objective is to create essentially new devices starting from the most fundamental of elements: atoms. Controlled biochemical reactions and atomic force microscopy are examples of two tools that nanotechnology provides the community with to create nanomachines in a bottom-up approach.

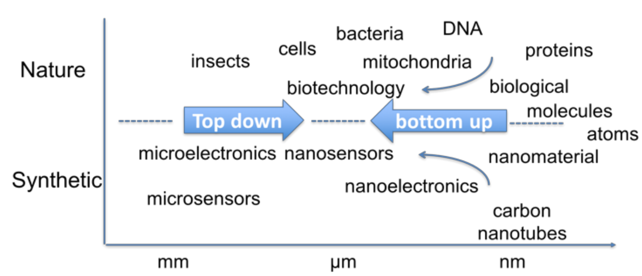


Figure 1: Nanomachine design approaches.

On the other hand, a separation can be made in terms of *human-made processes* and *biological* or *naturally occurring* processes. The objective of the latter is to take millions of years of evolution and exploit what Nature has provided us with. Bio-molecular processes and living cells are perhaps the most sophisticated nanomachines we see today. Nevertheless, while it would be easy to claim that Nature provides us with the *best way* to create nanomachines, capabilities beyond the natural ones can be obtained in a *hybrid approach* that combines the best of both worlds.

The way in which nanomachines are built ultimately determines the way in which they can communicate. For the time being, there are two main approaches to nanomachine design and, thus, to the way they communicate. In other words, there are nanomaterial-based nanomachines that communicate through nano-electromagnetic communication at Terahertz (THz) and optical frequencies, and biological nanomachines that communicate via molecular signals.

3 NANOMATERIAL-BASED NANONETWORKS

3.1 From Nanomaterials to Nanomachines

Nanomaterials either have a nanoscale external dimension (sizes range from approximately 1 to 100 nm) or a nanoscale internal or surface structure. A popular nanomaterial is graphene [19], which is a one-atom-thick planar sheet of bonded carbon atoms in a honeycomb crystal lattice. Despite having been theoretically investigated since 1859, it was not until 2004 that Andre Geim and Konstantin Novoselov successfully produced it experimentally. For this and their pioneering experimental studies into graphene, they were awarded the Nobel Prize in Physics in 2010. Graphene comes in different forms, including *graphene nanoribbons (GNRs)*, *i.e.*, thin (≤ 50 nm) strips of graphene, *carbon nanotubes (CNTs)*, i.e., rolled GNRs, and *buckyballs*, i.e., graphene spheres.

Graphene is one of the world's lightest and thinnest materials. As it is stronger than diamond and has very high electron mobility, it is a very good conductor and can absorb light effectively. Although graphene is the first of its kind, it is not the only two-dimensional material that exists. As of today, more than one hundred 2D nanomaterials have been reported, including Molybdenum Disulfide (MoS_2) [20] and Hexagonal Boron Nitride (hBN) [21], all with different electronic properties. Moreover, by combining different nanomaterials, new nanostructures with novel properties can be produced [22].

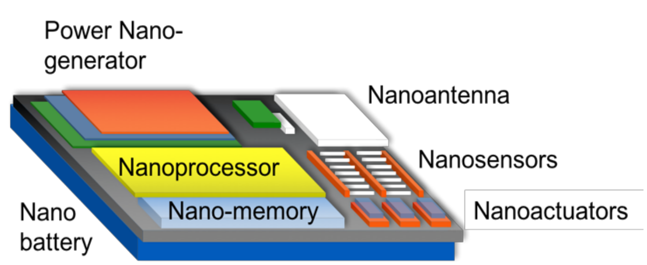


Figure 2: Conceptual architecture of a nanomachine.

By utilizing nanomaterials and the tools provided by nanotechnology, the different components that compose a nanomachine can be produced. Figure 2 depicts the conceptual architecture of such a nanomachine (adapted from [14]). The nanoprocessor interprets commands and processes data. From a physics perspective, a processor is a collection of (up to millions of) transistors. To be able to produce nanoprocessors, smaller transistors must be developed, i.e., with a shorter channel length. Current commercially-available processors are based on 32 nm, 22 nm and 14 nm transistor technology. To date, the smallest transistor built is on a graphene strip of just 10 by 1 carbon atoms, *i.e.*, less than 1 nm long [23]. This technology allows not only for very small transistors to be produced, but they are also able to be operated at higher clock frequencies.

Nanomemory is responsible for storing both the instruction set to be executed and the data collected; both of which are ultimately represented as a collection of bits ("0"s and "1"s). To decrease memory size, the number of atoms required to store a bit must also be reduced. Ultimately, single-atom memories are the basis for ultra-compact data storing in nanomachines. For the time being, different single-atom memories based on different physical principles have been demonstrated, including electronic [24] and optical memories [25].

Furthermore, in addition to the nanobatteries required to store energy [26], and because it is impossible to manually recharge individual nanobatteries, nanogenerators are needed to power the nanomachines so they can operate continuously. To date, different energy harvesting systems have been demonstrated, including mechanical energy harvesting through piezoelectric devices (i.e., devices able to convert vibration and mechanical deformations into electrical currents) [27], and electromagnetic energy harvesting at optical (photovoltaic) and RF frequencies (rectennas) [28].

Nanosensors and nanoactuators have been developed by using graphene and other nanomaterials that are able to detect and measure the presence of biological agents such as viruses or cancerous cells [7].

For communication purposes, nanomachines also require miniature transceivers and antennas. On the one hand, noble metals, such as gold and silver, can be employed to produce plasmonic nanoantennas which are just hundreds of nanometers in length and can efficiently operate at infra-red and visible optical frequencies [29]. These require similarly small nanolasers [30] and nanophotodetectors [31] to operate. Graphene can be employed to build miniature nanotransceivers [32] and nanoantennas [33,34] that operate at frequencies much lower than their metallic counterparts. Such devices open up many opportunities for communication in nanonetworks; as we explain next.

3.2 Electromagnetic Nanoscale Communication

The very small size of nanoantennas obliges the use of very high frequencies for electromagnetic wireless communication between the nanomachines. This ranges from the THz band to the infrared and visible optical frequency bands and presents many challenges as well as new opportunities for electromagnetic nanonetworks [35].

The first step involves understanding how THz and optical signals propagate within and across the human body. Electromagnetic waves propagated at THz-band and optical frequencies suffer from spreading, absorption and scattering. Moreover, the expansion of the wave front also attenuates the electromagnetic waves; something which is a common drawback to any wireless communication system.

The *molecular absorption loss* is the attenuation due to the conversion of electromagnetic energy into kinetic energy inside vibrating molecules. In fact, at THz and optical frequencies, electromagnetic waves can induce internal vibrations into molecules (but cannot break molecules because they are not ionizing). The *scattering loss* refers to signal misplacement resulting from the diffusion and reflection of electromagnetic waves as they propagate through a non-perfect medium. The amount of loss depends on the obstruction size in terms of wavelength. At THz frequencies, molecular absorption poses the greatest problem [36, 37], whereas at optical frequencies scattering is the main challenge to overcome [38].

The second step to electromagnetic nanonetworks involves defining the waveforms or types of signals to be transmitted and able to encapsulate the capabilities of nanomachines and the peculiarities of the channel. In this direction, the transmission of very short pulses, just one-hundred-femtosecond long, has been proposed for efficient communication in nanonetworks [39]. These pulses, whose main frequency components are in the THz band (between 0.5 and 4 THz), can be generated with nanotransceivers and are already widely used in THz (nano-bio) sensing applications. Similarly, optical sources can commonly be operated in pulsed or continuous wave modes. In addition, because of the challenging propagation environment and the expectedly very weak signals that can be transmitted in the body, ways to prevent or recover from signal errors and increase the reliability of the system are needed [40]. Independent of the modulation and coding process, synchronization, because of the very low power and very short duration of the symbols, is an important issue that must be resolved.

In the applications envisioned in Section 5, large assemblies of nanomachines will need to be orchestrated to work towards the same goal. In communication jargon, this involves defining networking protocols. The very large bandwidth at THz and optical frequencies allows for parallel simultaneous links between nanomachines. On the other hand, the very large number of nanomachines in nanonetworks requires the development of new *addressing* schemes, which can help to uniquely identify nanomachines in the network. In addition, due to the limited transmission range of nanomachines, *multi-hop relaying and routing* strategies need to be developed [41].

4 BIO-MOLECULAR COMMUNICATION NETWORKS

4.1 Bio-Nanomachines

The concept of the bio-nanomachine comes as an abstraction of the tools available today to program, control, and interact with computational structures in the biological environment. In particular, a bio-nanomachine is identified with a programmable cell [17], made possible by the latest developments in synthetic biology and nanotechnology. While the former provides tools to tap into the genetic code of biological cells, enabling the manipulation of cell behavior and functionalities [43], the latter opens the way to developing artificial cells from the ground up [44].

The primary components of a bio-nanomachine are the basic functional units utilized by cells, *i.e.*, organic molecules (nucleic acids, proteins, *etc.*). These are organized together to form structures and interact through chemical reactions. In particular, as shown in Fig. 3, thanks to the aforementioned technologies, we can compare the molecular elements of a cell to the elements of a nanomachine, as defined in Sec. 3.1 [17]. In other words, the nanomachine's processor is the molecules, chemical reactions, and molecular structures (*e.g.*, ribosomes) that allow the information from DNA to be expressed into proteins or cell behaviors. The nanomemory, meanwhile, corresponds to the molecular content of the entire cell and the nanobattery is the reservoir of the Adenosine Triphosphate (ATP) molecule managed by other molecular structures, the mitochondria. The nanosensors and nanoactuators correspond to the molecules and molecular structure able to react to or interact with the external environment and finally, the cells communicate with each other and the environment primarily by exchanging molecules on the nanoscale; a paradigm which has been investigated in communication theory in the past decade and is explained next.

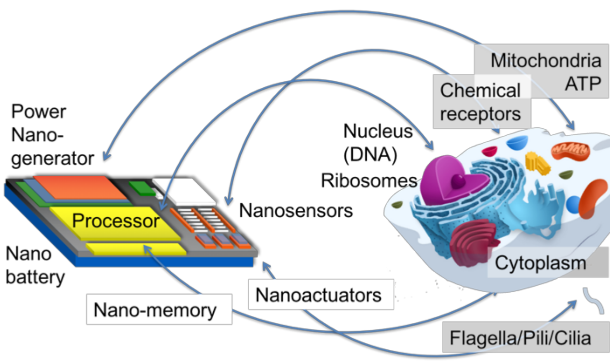


Figure 3: Functional relationship between the elements of a nanomachine and a biological cell.

4.2 Bio-Molecular Communications

In a biological environment, molecules are basic information exchange units as their structure and concentration convey information between cells. How the molecules propagate between biological cells has been a defining concept in the studies undertaken by the communication theory community [15], in their attempt to control or re-engineer the components using the aforementioned engineering technologies [45]. For example, the study of molecule diffusion as a communication channel has resulted in transformative models and theories [46, 48] which have found direct applications in biomedicine [52]. To date, several other molecule-based information-exchange processes have been studied by this discipline, known as Molecular Communication (MC) theory. The exchange processes range from intracellular molecular motors [49] and cell chemotaxis [51], to gap junction between cells [50], including the whole cardiovascular system [51].

Applying communication theory to the biological environment when studying MC, has brought about a novel approach to exploring biochemistry and the information therein. The study of how information is distorted in the channel [46], as well as the effect noise sources have [47], and the mathematical modeling of the amount of information that can be theoretically conveyed [48], are bringing an information-centric forward-engineering approach to the development of systems based on these processes, where mathematical models are utilized in advance of experimental testing and clinical trials. As an example, MC theory has been applied to study the information that is propagated through cells [61]. A specific example of this is in cancer biology, where information losses during propagation are correlated to the initiation and progression of cancer cells [62]. A further example is studying the potential for designing MC systems through synthetic biology [63] and, inspired by their electronic counterparts, the engineering of novel communication functionalities in cells [54, 55].

While achieving a complete communication engineering framework based on MC, able to bring to biology the lessons learned in classical communication systems and networks, *e.g.*, the Internet, is looking increasingly promising, the research community is constantly being faced with new challenges as well. One of the most prominent of which is the inherent complexity of biochemistry with respect to human-made circuits and systems, and which often results in dealing with communication channels that are not analytically tractable, mostly because of non-linear behavior and cross-talk from shared media and environments. The ultimate frontier in this field will be to build heterogeneous interfaces where MC-based systems could interact with electronic, or even nanomaterial-based systems[17].

5 APPLICATIONS

In this section, two key applications, namely, i) the Internet of Bio-Nano Things and ii) an example of a molecular communication system model for particulate drug delivery systems, are described as examples of target scenarios where nanonetworks can play a crucial role.

5.1 The Internet of Bio-Nano Things

For more than twenty years, but particularly over the last decade, the Internet of Things (IoT) has become a key topic for fundamental and applied research. In the IoT, physical objects embedded with sensors, electronics, software and network connectivity, can both collect and exchange data as well as receive control commands and act accordingly. The IoT, which is the best example of a cyber (Internet) and physical (Things) system, is at the basis of many applications in medical, environmental, commercial, and military and defense fields.

One of the fundamental challenges facing the IoT is how to sense or collect data without altering the process being monitored. To this end, major research efforts have been focused on developing tiny, concealable and non-intrusive Things. Along these lines, the concept of the Internet of Nano-Things (IoNT) was defined almost ten years ago [16]. The objective of the IoNT is not only to make smaller devices or Nano-Things, but to utilize them in sensing processes or collecting data on nano- and micro- scales. For example, using nanosensors, chemical components with a single molecule resolution can be detected. Of course, the development of such nanosensors is only one step towards the overall development of the IoNT, as this also requires developing new communication solutions for nanomachines (Sections 3 and 4 in this paper), interfaces between nanomachines and micro/macro-devices, and new communication protocols to glue all the elements together.

Obviously, one of the immediate applications for such sensor technology is in the biomedical domain. While the majority of existing nano-bio-sensing strategies rely on using nanomaterial-based nanomachines (e.g., engineered nanoparticles, magnetic nano-rods), it is easy to imagine that the biological Nano-Things are much better suited for the intra-body/medical domain. As such, the Internet of Bio-Nano-Things (IoBNT) [43] was introduced five years ago. The fundamental idea underpinning the IoBNT is to, instead of utilizing nanomaterial-based nanomachines (Section 3), leverage bio-nanomachines (Section 4). As we discussed earlier, such bio-nanomachines can be programmed using synthetic biology and can communicate via molecular signals. Below are some of the applications envisioned for this truly cyber-physical system aimed at interconnecting biological processes in the human body with the Internet:

- **Intra-body sensing and actuation:** In this application, Bio-Nano-Things operate inside the human body and collaboratively collect health-related information, transmit it to an external healthcare provider through the Internet, who, in turn, then sends control commands to trigger different processes such as the synthesis and release of drugs, see Figure 4.
- **Intra-body connectivity control:** In this scenario, Bio-Nano-Things are utilized to recover lost functionalities in the body (such as those resulting from neurodegenerative diseases) by re-establishing the communication between dysfunctional and disconnected areas.

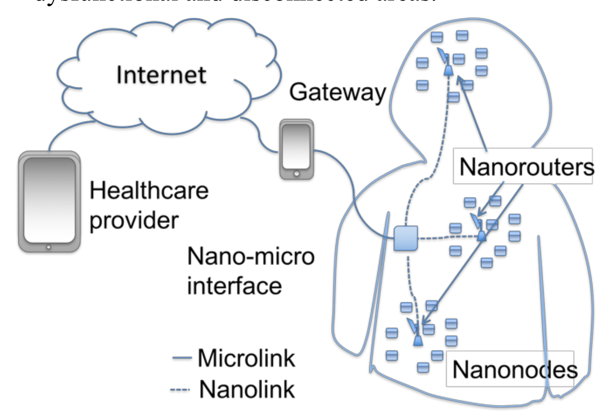


Figure 4: Network architecture for the Internet of NanoThings.

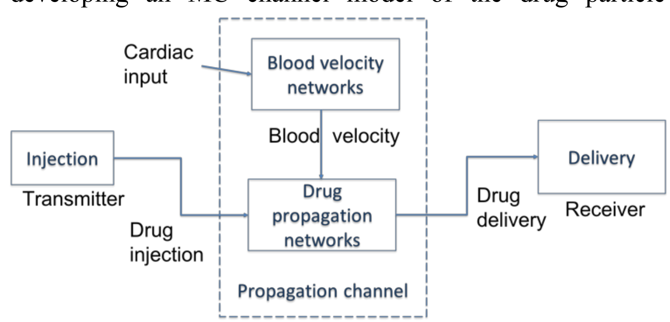
- **Environmental control and cleaning:** As an example of an application outside the human body, Bio-Nano-Things can also be utilized to monitor an ecosystem and check for toxic and pollutant agents and then collaboratively transform these agents. An example of this is the bacteria that can clean up oil spills.

5.2 A molecular communication model for particulate Drug Delivery

As we briefly discussed in the Introduction, one of the very first applications of nanotechnology developed nanoparticles for nano-bio-sensing. A quick scholarly search returns more than 70,000 published papers in the broad field of *nanosensing*, with the vast majority relating to the use of photonic and magnetic metallic and plasmonic nano-structures. As important as sensing biological processes with nanoscale resolution is, being able to actuate on such biological processes with nano-accuracy is a fundamental challenge. Along these lines, major research efforts have been focused on developing innovative particulate Drug Delivery Systems (DDSs).

In targeted DDSs, the fundamental idea is to engineer release, control propagation and selectively activate drug-carrying particles in the human body. Therefore, a DDS can be considered an MC system, where the information conveyed by the particles is the therapeutic action [10, 52]. A particulate DDS takes advantage of the blood circulation in the cardiovascular system to propagate drug particles from the location where they have been injected into the blood flow, to the targeted site. Here, as shown in Figure 5, we describe a particulate DDS as three-fold process: injection, propagation, and delivery.

Two processes govern their propagation, namely, advection and diffusion. Advection is the process by which the particles suspended in the blood follow the heart-imposed flow and pass through areas at different velocities. Diffusion refers to the process by which individual particles are subject to Brownian motion and so move within the blood from a region of higher concentration to one of lower concentration. In this application example (Figure 5), the molecular communication abstraction of a particulate DDS is accomplished by developing an MC channel model of the drug particle



propagation through the cardiovascular system. For this, two separate contributions are identified within the model: the cardiovascular network model and the drug propagation network model.

Figure 5: Scheme of the MC channel model of a particulate DDS.

Thanks to MC theory, we can now precisely control the release, propagation and activation of drug particles, following an analytical approach instead of an empirically-driven methodology.

6 AUTHORS' INSIGHT INTO THE TOPIC

Up to this point, we have described the enabling technologies, communication alternatives and potential applications of nanonetworks in biomedical paradigms. Nevertheless, there are several knowledge gaps, and thus, research opportunities and challenges that need to be grasped and resolved for this vision to be made real.

In terms of nanomaterial-based nanomachines, one of the major challenges relates to the biocompatibility of the materials and the resulting nanodevices and nanomachines. As with any foreign body entering the human body, the immune system will react to it and try to isolate, if not eliminate, it from the system. To avoid this, biocompatible coatings that protect the nanomachine, while still ensuring its working conditions, will need to be developed.

Similarly, the use of electromagnetic signals inside the human body could raise some issues. As discussed in Section 3.2, optical, and especially THz-band signals, are absorbed by the different types of molecules in the body; in particular water content in the blood plasma and hemoglobin in the red blood cells. While this radiation cannot break molecules, it does induce internal vibrations and, as bodies belonging to a liquid or solid entity cannot freely vibrate, friction occurs. This friction eventually leads to heat, and so the resulting photothermal effects need to be studied. Ultimately, the use of biocompatible modulations is needed. For example, while it might not be needed from the application perspective, transmitting at very high data-rates can lead to very short transmissions and, thus, minimal photothermal effects. Once again, a joint design of device, channel model and communication system is needed.

The same consideration can be made for biomolecular communications, where molecular signals coming from engineered devices may interfere with natural body processes, such as the aforementioned immune system, or even pollute body tissue with the presence of unwanted chemical compounds. The example of the MC modeling applied to the DDS mentioned in Section 5.2, demonstrates the potential cross-disciplinary investigation has, where a communication systems approach is applied to solve physiological biodistribution problems.

In terms of bionanomachines, one of the most promising lines comes from the latest gene editing tools, such as CRISPR-Cas9, derived from synthetic biology, and which are enabling a direct reprogramming of the very same cells that compose our body [60]. While this could potentially solve biocompatibility problems in the development of an IoBNT for biomedical applications, (as described in Section 5.1), safety and ethical concerns need to be addressed before such systems can become part of clinical reality. On the one hand, questions such as the predictability of the effects that a functioning and living IoBNT can have inside the human body currently clash with the complexity and (many) unknowns of the biology underlying our organism. On the other hand, the risks in utilizing IoBNTs for non-medical goals, i.e., to create a perfected organism, or "superhuman", need to be discussed, together with realistic mitigation strategies.

We believe that the solution to all the aforementioned research challenges, as well as its concerns, will come from a collaboration between computer engineers and the biomedical community that is based on a common interface and understanding. Several of the concepts presented in this paper, especially those comparing biological processes to interconnected computing systems, are efforts heading in this direction.

7 CONCLUSIONS

Nanonetworks are expected to impact almost every field of our society, including health care. To enable communication among nanomachines, new communication alternatives that contemplate the nature of nanoscale need to be designed. As nanotechnologies are expected to grow considerably and, likewise, their potential to detect and diagnose numerous health related issues, the challenges for research are to further enhance their current capabilities and ensure applicability not only in the biomedical domain, but also across a broader range of deployments as well.

While the Internet of Things is enabling the pervasive connectivity of real-world physical elements between themselves and the Internet, the Internet of NanoThings proposes to push the limits of this concept to nanotechnology-enabled nanoscale devices. Synthetic biology and nanotechnology can be combined to develop new nanothings based on the control, reuse, modification, and reengineering of biological cells. A relevant challenge is to facilitate their ability to communicate and network. For instance, the goal of a DDS is to provide a localized drug presence where the medication is needed, all the while preventing the drug from affecting other healthy parts of the body. The Molecular Communications paradigm condenses the propagation of information between a sender and a receiver and executed through the molecules that must physically cover the distance from one location to the other.

Beyond nanomaterial-based nanomachines or synthetically engineered living cells, hybrid nano-bioengineered nanomachines and nanonetworks will enable unique applications and capabilities; some of which are yet to be envisioned. The Internet of Bio-Nano Things technologies presented here, could pose serious security threats if handled with malicious intent. For instance, Bio-Nano Things could be used to access the human body and steal personal health-related information, or even create new diseases. These problems should be addressed by combining the existing security methods with the original security mechanisms evolved by Nature, such as the human immune system.

LIST OF ABBREVIATIONS

- **ATP** Adenosine Triphosphate
- **DDSs** Drug Delivery Systems
- **IoBNT** Internet of Bio-Nano Things
- **IoNT** Internet of NanoThings
- **IoT** Internet of Things
- **IP** Internet Protocol
- **MAC** Medium Access Control
- **MC** Molecular Communication

CONFLICT OF INTEREST

The authors declare that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work is partially supported by the Spanish Ministry of Science and Innovation project GIROS TEC2015-66412-R and by the *Generalitat de Catalunya* research support program SGR-1469. This work was also partially supported by the National Science Foundation under Awards IIP-1718177, CBET-1706050, and CCF-1816969.

REFERENCES

[1] Wong and M. Olivo, “Surface plasmon resonance imaging sensors: a review,” Plasmonics, vol. 9, no. 4, pp. 809–824, 2014.

[2] H. H. Nguyen, J. Park, S. Kang, and M. Kim, “Surface plasmon resonance: a versatile technique for biosensor applications,” Sensors, vol. 15, no. 5, pp. 10 481–10 510, 2015.

[3] A. Qureshi, Y. Gurbuz, and J. H. Niazi, “Biosensors for cardiac biomarkers detection: A review,” Sensors and Actuators B: Chemical, vol. 171, pp. 62–76, 2012.

[4] M. Yang, X. Yi, J. Wang, and F. Zhou, “Electroanalytical and surface plasmon resonance sensors for detection of breast cancer and Alzheimer’s disease biomarkers in cells and body fluids,” Analyst, vol. 139, no. 8, pp. 1814–1825, 2014.

[5] M. Vendrell, K. K. Maiti, K. Dhaliwal, and Y.-T. Chang, “Surface-enhanced Raman scattering in cancer detection and imaging,” Trends in biotechnology, vol. 31, no. 4, pp. 249–257, 2013.

[5] M. Vendrell, K. K. Maiti, K. Dhaliwal, and Y.-T. Chang, “Surface-enhanced Raman scattering in cancer detection and imaging,” Trends in biotechnology, vol. 31, no. 4, pp. 249–257, 2013.

[6] S. D. Hudson and G. Chumanov, “Bioanalytical applications of sers (surface-enhanced Raman spectroscopy),” Analytical and bioanalytical chemistry, vol. 394, no. 3, pp. 679–686, 2009.

[7] L. Wu and X. Qu, “Cancer biomarker detection: recent achievements and challenges,” Chemical Society Reviews, vol. 44, no. 10, pp. 2963–2997, 2015.

[8] P. H. Aoki, L. N. Furini, P. Alessio, A. E. Aliaga, and C. J. Constantino, “Surface-enhanced Raman scattering (SERS) applied to cancer diagnosis and detection of pesticides, explosives, and drugs,” Reviews in Analytical Chemistry, vol. 32, no. 1, pp. 55–76, 2013.

[9] M. Kumar, Handbook of Particulate Drug Delivery: Applications. plus 0.5em minus 0.4emAmerican Scientific Publishers, 2008.

[10] Y. Chahibi, “Molecular communication for drug delivery systems: A survey,” Nano Communication Networks, vol. 11, pp. 90–102, 2017.

[11] R. K. K. Sharma, Anil K and R. K. Kesharwani, Nanobiomaterials: Applications in Drug Delivery. plus 0.5em minus 0.4emApple Academic Press, Internet resource, 2017.

[12] W. Zhang, J. Pei, and L. Lai, “Computational multitarget drug design,” Journal of Chemical Information and Modeling, vol. 57, no. 3, pp. 403–412, 2017.

[13] I. F. Akyildiz, F. Brunetti, and C. Blazquez, “Nanonetworks: a new communication paradigm,” Computer Networks (Elsevier) Journal, vol. 52, no. 12, pp. 2260–2279, Aug. 2008.

[14] I. F. Akyildiz and J. M. Jornet, “Electromagnetic wireless nanosensor networks,” Nano Communication Networks (Elsevier) Journal, vol. 1, no. 1, pp. 3–19, Mar. 2010.

[15] I. F. Akyildiz, J. M. Jornet, and M. Pierobon, “Nanonetworks: a new frontier in communications,” Communications of the ACM, vol. 54, no. 11, pp. 84–89, Nov. 2011.

[16] I. F. Akyildiz and J. M. Jornet, “The internet of nano-things,” IEEE Wireless Communications Magazine, vol. 17, no. 6, pp. 58–63, Dec. 2010.

[17] I. F. Akyildiz, M. Pierobon, S. Balasubramaniam, and Y. Koucheryavy, “The internet of bio-nano things,” IEEE Communications Magazine, vol. 53, no. 3, pp. 32–40, 2015.

[18] R. Feynman “There’s Plenty of Room at the Bottom”. Talk, American Physical Society at the California Institute of Technology (Caltech) Pasadena, 29 December 1959). http://www.zyvex.com/nanotech/feynman.html

[19] A. C. Ferrari, F. Bonaccorso, V. Fal’Ko, K. S. Novoselov, S. Roche, P. Bøggild, S. Borini, F. H. Koppens, V. Palermo, N. Pugno et al., “Science and technology roadmap for graphene, related two-dimensional crystals, and hybrid systems,” Nanoscale, vol. 7, no. 11, pp. 4598–4810, 2015.

[20] A. Splendiani, L. Sun, Y. Zhang, T. Li, J. Kim, C.-Y. Chim, G. Galli, and F. Wang, “Emerging photoluminescence in monolayer mos2,” Nano letters, vol. 10, no. 4, pp. 1271–1275, 2010.

[21] G. Giovannetti, P. A. Khomyakov, G. Brocks, P. J. Kelly, and J. Van Den Brink, “Substrate-induced band gap in graphene on hexagonal boron nitride: Ab initio density functional calculations,” Physical Review B, vol. 76, no. 7, p. 073103, 2007.

[22] A. K. Geim and I. V. Grigorieva, “Van der waals heterostructures,” Nature, vol. 499, no. 7459, p. 419, 2013.

[23] L. A. Ponomarenko, F. Schedin, M. I. Katsnelson, R. Yang, E. W. Hill, K. S. Novoselov, and A. K. Geim, “Chaotic Dirac billiard in graphene quantum dots,” Science, vol. 320, no. 5874, pp. 356–358, Apr. 2008.

[24] J. J. Pla, K. Y. Tan, J. P. Dehollain, W. H. Lim, J. J. Morton, D. N. Jamieson, A. S. Dzurak, and A. Morello, “A single-atom electron spin qubit in silicon,” Nature, vol. 489, no. 7417, p. 541, 2012.

[25] H. P. Specht, C. Nölleke, A. Reiserer, M. Uphoff, E. Figueroa, S. Ritter, and G. Rempe, “A single-atom quantum memory,” Nature, vol. 473, no. 7346, p. 190, 2011.

[26] A. Brazier, L. Dupont, L. Dantras-Laffont, N. Kuwata, J. Kawamura, and J.-M. Tarascon, “First cross-section observation of an all solid-state lithium-ion "nanobattery" by transmission electron microscopy,” Chemistry of Materials, vol. 20, no. 6, pp. 2352–2359, 2008.

[27] Z. L. Wang, T. Jiang, and L. Xu, “Toward the blue energy dream by triboelectric nanogenerator networks,” Nano Energy, vol. 39, pp. 9–23, 2017.

[28] M. Gadalla, M. Abdel-Rahman, and A. Shamim, “Design, optimization and fabrication of a 28.3 thz nano-rectenna for infrared detection and rectification,” Scientific reports, vol. 4, p. 4270, 2014.

[29] M. Nafari and J. M. Jornet, “Modeling and performance analysis of metallic plasmonic nano-antennas for wireless optical communication in nanonetworks,” IEEE Access, vol. 5, pp. 6389–6398, 2017.

[30] L. Feng, Z. J. Wong, R.-M. Ma, Y. Wang, and X. Zhang, “Single-mode laser by parity-time symmetry breaking,” Science, vol. 346, no. 6212, pp. 972–975, 2014.

[31] L.-B. Luo, Y.-F. Zou, C.-W. Ge, K. Zheng, D.-D. Wang, R. Lu, T.-F. Zhang, Y.-Q. Yu, and Z.-Y. Guo, “A surface plasmon enhanced near-infrared nanophotodetector,” Advanced Optical Materials, vol. 4, pp. 763–771, 2016.

[32] J. M. Jornet and I. F. Akyildiz, “Graphene-based plasmonic nano-transceiver for terahertz band communication,” in Proc. of European Conference on Antennas and Propagation (EuCAP), 2014.

[33] J. M. Jornet and I. F. Akyildiz, “Graphene-based plasmonic nano-antenna for terahertz band communication in nanonetworks,” IEEE JSAC, Special Issue on Emerging Technologies for Communications, vol. 12, no. 12, pp. 685–694, Dec. 2013.

[34] H. T. Maune, S.-p. Han, R. D. Barish, M. Bockrath, W. A. Goddard III, P. W. Rothemund, and E. Winfree, “Self-assembly of carbon nanotubes into two-dimensional geometries using dna origami templates,” Nature nanotechnology, vol. 5, no. 1, p. 61, 2010.

[35] Ian F. Akyildiz, Josep M. Jornet, Massimiliano Pierobon. Chapter 215-1, Nanonetworks, Springer Nature America, Inc, 2018.

[36] J. M. Jornet and I. F. Akyildiz, “Channel modeling and capacity analysis of electromagnetic wireless nanonetworks in the terahertz band,” IEEE Transactions on Wireless Communications, vol. 10, pp. 3211–3221, 2011.

[37] C. Han, A. O. Bicen, and I. Akyildiz, “Multi-ray channel modeling and wideband characterization for wireless communications in the terahertz

band," IEEE Transactions on Wireless Communications, vol. 14, pp. 2402–2412, 2015.

[38] P. Johari and J. M. Jornet, "Nanoscale optical wireless channel model for intra-body communications: Geometrical, time, and frequency domain analyses," IEEE Transactions on Communications, vol. 66, 1579 1593, 2018.

[39] J. M. Jornet and I. F. Akyildiz, "Femtosecond-long pulse-based modulation for terahertz band communication in nanonetworks," IEEE Transactions on Communications, vol. 62, no. 5, pp. 1742–1754, May 2014.

[40] J. M. Jornet, "Low-weight error-prevention codes for electromagnetic nanonetworks in the terahertz band," Nano Communication Networks (Elsevier) Journal, vol. 5, no. 1-2, pp. 35–44, Mar. 2014.

[41] M. Pierobon, J. M. Jornet, N. Akkari, S. Almasri, and I. F. Akyildiz, "A routing framework for energy harvesting wireless nanosensor networks in the terahertz band," Wireless Networks, pp. 1–15, 2013.

[42] A. Tsioliaridou, C. Liaskos, S. Ioannidis, and A. Pitsillides, "Corona: A coordinate and routing system for nanonetworks," in Proceedings of the Second Annual International Conference on Nanoscale Computing and Communication. plus 0.5em minus 0.4emACM, 2015, p. 18.

[43] L. J. Kahl and D. Endy, "A survey of enabling technologies in synthetic biology," Journal of Biol. Eng., vol. 7, no. 1, p. 13, May 2013.

[44] F. Wu and C. Tan, "The engineering of artificial cellular nanosystems using synthetic biology approaches," WIREs Nanomedicine and Nanobiotech, vol. 6, no. 4, July/August 2014.

[45] S. Payne and L. You, "Engineered cell-cell communication and its applications," Adv Biochem Eng Biotechnol, vol. 146, pp. 97–121, 2014.

[46] M. Pierobon and I. F. Akyildiz, "A physical end-to-end model for molecular communication in nanonetworks," IEEE Journal on Selected Areas in Communications (JSAC), vol. 28, no. 4, pp. 602–611, May 2010.

[47] M. Pierobon and I. F. Akyildiz, "Diffusion-based noise analysis for molecular communication in nanonetworks," IEEE Transactions on Signal Processing, vol. 59, no. 6, pp. 2532–2547, June 2011.

[48] M. Pierobon and I. F. Akyildiz, "Capacity of a diffusion-based molecular communication system with channel memory and molecular noise," IEEE Transactions on Information Theory, vol. 59, pp. 942–954, February 2013.

[49] M. Moore, A. Enomoto, T. Nakano, R. Egashira, T. Suda, A. Kayasuga, H. Kojima, H. Sakakibara, and K. Oiwa, "A design of a molecular communication system for nanomachines using molecular motors," Fourth Annual IEEE International Conference on Pervasive Computing and Communications Workshops, pp. 6–12, Mar. 2006.

[50] T. Nakano, T. Suda, T. Koujin, T. Haraguchi, and Y. Hiraoka, "Molecular communication through gap junction channels: system design, experiments and modeling," in Proc. of 2nd Intl. Conf. on Bio-Inspired Models of Network, Information and Computing Systems (Bionetics), Dec. 2007, pp. 139–146.

[51] M. Gregori and I. F. Akyildiz, "A new nanonetwork architecture using flagellated bacteria and catalytic nanomotors," IEEE Journal of Selected Areas in Communications (JSAC), vol. 28, no. 4, pp. 612–619, May 2010.

[52] Y. Chahibi, M. Pierobon, S. O. Song, and I. Akyildiz, "A molecular communication system model for particulate drug delivery systems," IEEE Transactions on Biomedical Engineering, vol. 60, no. 12, pp. 3468–3483, June 2013.

[53] M. Pierobon, "A systems-theoretic model of a biological circuit for molecular communication in nanonetworks," Nano Communication Networks (Elsevier), vol. 5, no. 1-2, pp. 25–34, March-June 2014.

[54] B. Unluturk, A. Bicen, and I. Akyildiz, "Genetically engineered bacteria-based biotransceivers for molecular communication," IEEE Transactions on Communications, vol. 63, no. 4, pp. 1271–1281, 2015.

[55] A. Marcone, M. Pierobon, and M. Magarini, "Parity-check Coding Based on Genetic Circuits for Engineered Molecular Communication Between Biological Cells," IEEE Transactions on Communications, July 2018. (https://doi.org/10.1109/TCOMM.2018.2859308)

[56] D. L. Nelson and M. M. Cox, Lehninger Principles of Biochemistry. 1em plus 0.5em minus 0.4emW. H. Freeman Company, May 2008.

[57] L. Parcerisa and I. F. Akyildiz, "Molecular communication options for long range nanonetworks," Computer Networks (Elsevier) Journal, vol. 53, no. 16, pp. 2753–2766, Nov. 2009.

[58] M. Pierobon and I. F. Akyildiz, "Diffusion-based noise analysis for molecular communication in nanonetworks," IEEE Transactions on Signal Processing, vol. 59, no. 6, pp. 2532–2547, 2011.

[59] L. L. M. Heaton, E. López, P. K. Maini, M. D. Fricker, and N. S. Jones, "Advection, diffusion, and delivery over a network," Phys. Rev. E, vol. 86, p. 021905, Aug 2012.

[60] J. Weltner, D. Balboa, S. Katayama, M. Bespalov, K. Krjutškov, E. M. Jouhilahti, R. Trokovic, J. Kere, and T. Otonkoski,"Human pluripotent reprogramming with CRISPR activators," *Nat Commun*. vol. 9, no. 1, p. 2643, Jul 2018.