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Review article

Ca^{2+}-signaling-based molecular communication systems: Design and future research directions

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ABSTRACT

Nanomedicine is revolutionizing current methods for diagnosing, treatment and prevention of diseases with the integration of molecular biology, biotechnology as well as nanotechnology for sensing and actuation capabilities at the molecular scale using nanoscale devices, namely nanomachines. While numerous examples of these applications have been tested *in vivo*, the real deployments are far from reality. Limitations in controlling, monitoring, miniaturization, and computing inhibit access and manipulation of information at the nano-scale. Integrating communication and networking functionalities provide new opportunities for such challenges with the newly introduced Molecular Communications. These natural communication systems are found with plurality inside the human body. The current challenge is to utilize these natural systems to create artificial biocompatible communication networks that can interconnect multiple nanomachines in multiple parts of the body and connected to the cloud, is defined as the *Internet of Bio-Nano Things* (*IoBNT*). Nanonetworks inside cellular tissues perform communication using a signaling process such as Ca^{2+}. This specifically signaling process is very important for many regulatory functions in tissues and its control and communication is crucial to allow nanomedicine capabilities towards diagnosis and treatments of diseases at the nano-scale. This paper presents a review of techniques that enable the design of the Ca^{2+}-signaling-based molecular communication system for cellular tissues, essential tools for its deployment, application and, lastly, the research future direction in this field. In the end, one must acquire the sufficient knowledge to understand both biological and telecommunication concepts that encompass this technology to bring it further.

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1. Introduction

Molecular communications systems is an essential mechanism that enables cellular evolution through molecular diffusion across multi-cellular organisms. Biologists have development mathematical and statistical models for analyzing such system towards manipulating biological systems, e.g., living organisms or derivatives thereof, to create a wide range of innovative products [1]. This approach termed biotechnology runs in parallel with other interdisciplinary fields, such as bioengineering, biomedical engineering, and nanotechnology for revolutionizing medical science with high-level precision and accuracy even at the nano-scale, which collectively composes *Nanomedicine*. Limitations in diagnosis, treatment, and prevention of diseases are being eliminated by the usage of nanomaterials and nanoparticles [2–4]. As an example, *Co-polymer poly(lactic-co-glycolic acid)* (PLGA) nanotechnology has been developed for many years and has been approved by the *US Food and Drug Administration* (FDA) for the use in drug delivery, diagnostics and other clinical applications including cardiovascular disease and cancer treatment, as well as vaccine and tissue engineering.

The **Internet of Bio-Nano Things** is an intra-body nanonetwork that provides nanomedicine functionalities such as real-time monitoring, fast actuation at the molecular level, fast disease treatment, intelligent drug delivery, tissue engineering and many others. This envisioned scenario is presented in Fig. 1, and illustrates the many networks within the human body that can monitor neurodegenerative diseases, heart, cancer, and glucose, as an example. Based on this IoBNT can bring along new forms of real-time health monitoring and response that dramatically increases life quality and expectancy. Healthcare is a major industry for the modern society, and evidently, any research in that topic has the potential impact to affect millions of people and generate large revenue for a number of industries.

Currently, such technology is only at the early stage of development, and many challenges are being investigated by the community. Two major challenges are classified: IoBNT theory development and IoBNT realization. The plurality of intra-body molecular communication systems are not yet fully understood or modeled, and those which are modeled have limited analysis on their behavior. The IoBNT theory needs a lot more development on its foundation to pave the way for IoBNT realization. This issue concentrate on the development of nanomachines and its interoperability within the human body. At the same time, the capabilities of engineering information transfer between these nanomachines to suit various applications remain to be investigated before a full IoBNT solution can be realized. To summarize, the short term vision of IoBNT is to allow future nanomachines that have communication capabilities to perform more complex tasks cooperatively as well as providing connections between different types of *nanonetworks*. And the long-term vision of IoBNT is to have nanonetworks inside the human body working cooperatively using the envisioned communication platform, and connect to the cloud to provide a new form of fine granular personal health monitoring solution [5–7].

Among the nanonetworks that were classified, three main backbone networks were defined: nervous nanonetwork, cardiovascular molecular nanonetwork and also endocrine nanonetwork [8]. These networks were identified as long range molecular communication systems within the human body. Although the modeling of these nanonetworks has been studied extensively, they are not sufficient for the deployment of IoBNT. The current challenge is integrating short-range nanonetworks that connect with long range nanonetworks. This requires intense research work, both theoretically and experimentally, due to their complex behavior at the molecular scale.

Ca^{2+} signaling is the most important natural signaling mechanism that is involved in cell–cell communication. Ca^{2+}, in addition, is responsible for many regulatory functions of in-body cellular tissue, and therefore, can be a robust choice for short-range molecular communication systems for empowering the development of nanomedicine solutions [9]. A Ca^{2+}-signaling-based molecular communication system comprises of a transmitter nanomachine that releases information into levels of Ca^{2+} that are propagated across the tissue towards a receiver nanomachine. The complexity is on the stochastic behavior of inter/intra Ca^{2+} signaling, which has an intense flow of molecules all across the cellular tissue creating new types of noise and interference [9–11]. This communication system can, thus, cooperatively perform simple tasks inside the cellular tissue, which has already been demonstrated in [12]. However, novel methods for further developing theoretically such technology needs to be done for both understanding better this biological system as well as creating engineering mechanisms for its control.

This paper presents a review of techniques that enable **design of Ca^{2+}-signaling-based molecular communication systems**. The encoding, modulation, propagation, demodulation and decoding techniques are presented. The **experimentation** tools for either theoretical and in-vitro analysis are presented, highlighting also the mathematical and simulation models. **Essential tools** such as synthetic biology and control systems are the needed building blocks for the realization of this molecular communication and is also presented. **Relevant applications** are also discussed, including nanomedicine, bio-computing and the Internet of Bio-Nano Things. Lastly, the **future research directions** in this field is also highlighted. In the end, one must acquire the sufficient knowledge to understand both biological and telecommunication concepts that encompass this technology.