The Internet of Bio-Nano Things in Blood Vessels: System Design and Prototypes

Changmin Lee, Bon-Hong Koo, Chan-Byoung Chae, and Robert Schober

Abstract—In this paper, we investigate the Internet of bio-nano things (IoBNT) which pertains to networks formed by molecular communications. By providing a means of communication through the ubiquitously connected blood vessels (arteries, veins, and capillaries), molecular communication-based IoBNT enables a host of new eHealth applications. For example, an organ monitoring sensor can transfer internal body signals through the IoBNT to health-monitoring applications. We empirically show that blood vessel channels introduce a new set of challenges in the design of molecular communication systems in comparison to free-space channels. Then, we propose cylindrical duct channel models and discuss the corresponding system designs conforming to the channel characteristics. Furthermore, based on prototype implementations, we confirm that molecular communication techniques can be utilized for composing the IoBNT. We believe that the promising results presented in this work, together with the rich research challenges that lie ahead, are strong indicators that IoBNT with molecular communications can drive novel applications for emerging eHealth systems.

Index Terms—Blood vessel, health monitoring, Internet of bio-nano things (IoBNT), molecular communications, prototypes.

I. INTRODUCTION

THE increasing global population has led to a mounting set of challenges. The resulting significant social issues may require solutions from an entirely new perspective. For example, an aging society will create a strong demand for an advanced healthcare system. While the acceleration of medical research is indispensable for overcoming diseases, bio-nano engineering can assist in preventing advanced pathogenesis. In particular, precautionary actions can play a pivotal role in ensuring the well-being of older people, who may have poorer self-healing ability. We expect that the Internet of bio-nano things (IoBNT) may allow preventative monitoring on a daily or even hourly basis, in contrast to conventional health monitoring, which is currently limited to annual or monthly examinations [1], [2]. It is worth considering the role of IoBNT in health-monitoring systems, which we refer to as eHealth.

We spotlight health-monitoring systems based on bio-nano machines, which function and communicate with each other inside a body. Such systems require substantial provisions for biocompatibility and energy efficiency. The communication function of conventional robots for eHealth mainly relies on electromagnetic (EM) waves. However, this approach poses several problems, such as the development of nanoscale actuators, antennas, and bodily absorption of tera-hertz-band frequencies. In this work, we introduce molecular communications for eHealth as an alternative technology.

Molecular communication is a bio-inspired technology wherein the system components exchange information through molecules. For example, in nature, an ant colony implements swarm intelligence using pheromone signals, and organs work in harmony by regulating each other through hormones. Studies have indicated that in certain applications, molecular communications offers several advantages over radio-frequency (RF) communication [3], [5]–[7]. The authors of [3] claimed that synthetic biology- and nanotechnology-based technologies could be used to construct bio-nano units for *in-vivo* applications. They noted that EM radiation can have negative effects on the body. Moreover, they conducted a subsequent prototype study in [5]. W. Guo *et al.* [6] compared the channel characteristics of molecular and RF communications. Numerous studies on molecular communications for general scenarios have been conducted in [4], [7].

The system exploits blood vessels as molecular communication channels. This requires a distinct channel model, whereas most existing studies on molecular communications have focused on free-space diffusive channels. Spatial limitations and the drift inherent in blood vessels are the main differences between blood vessels and free-space diffusive channels. These spatial limitations can be approximated using a cylindrical duct shape. In the studies on such cases [8]–[17], the authors of [8] introduced various channel models with varying velocity profiles and shape parameters. In particular, the channel model for a special velocity profile, Poiseuille flow, was introduced in [9], [10]. The authors of [13]–[15] suggested a channel model by considering the characteristics of a biological cylindrical environment such as molecule degradation effect and arbitrary boundary. Moreover, testbed realizations of meso- and nano-scale duct channels have been reported in [16], [17].

The remainder of this paper is organized as follows. In Section II, we introduce the IoBNT based on blood vessel networks, describe an eHealth system, and specify the channel models used in the proposed molecular communication system. In Section III, we describe the concrete design and
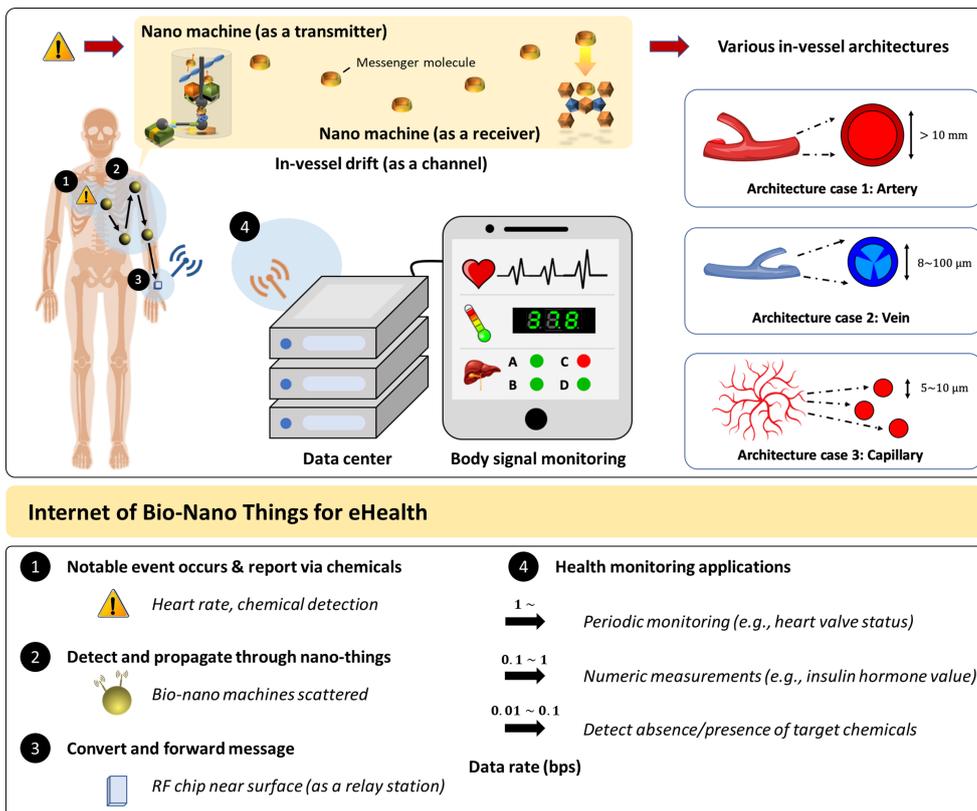
Fig. 1. A conceptual depiction of IoBNT for eHealth. In the health-monitoring scenario of interest, nano-machines that can communicate with each other through molecules are employed to improve the biocompatibility of the system relative to that of a system employing EM components. These machines are capable of adaptively transmitting and receiving target molecules in in-vessel environments by using state-of-the-art bio-nano machine technology.

requirements of the health-monitoring systems. In Section IV, we present a testbed for modeling channel environments similar to the human blood vessel system. Finally, in Section V, we conclude our paper and address open challenges for advanced health monitoring.

II. IOBNT & BLOOD VESSEL ENVIRONMENTS

In this paper, we investigate the IoBNT, which utilizes molecular communications, especially in blood vessels. Blood vessels spread throughout the body and are good channels for building the IoBNT, which can gather information from various locations in the body. Fig. 1 conceptually illustrates the IoBNT-based health-monitoring system in four main steps. In the first step, various sensors measure human body signals at various locations in the body. These sensors should be harmless and be able to operate under tight energy constraints. As suggested in a few previous works [3], [5], [19], [20], nano- and bio-technology form the base for various bio-nano-based sensing systems. Second, bio-nano things are deployed inside the body to create a network through molecular communication inside blood vessels and convey the signals measured by the sensors [13], [21]–[25]. Third, the platform developed in [26] can be utilized when connecting the IoBNT network to the relay chip under the skin. The system works based on galvanic coupling and enables communication through tissue. Finally, the relay chip is connected to electronic devices outside the body through RF technology such as Bluetooth. In this manner, the collected body signals can be used in medical applications.

For example, patients with cardiac disorders may need to use a continuous monitoring system after heart surgery. In this case, a sensor near the heart measures cardiac signals, such as heartbeat rhythm. The molecular communication network forwards these cardiac signals, and eventually, users can monitor their heart function through a smartphone application. Similarly, patients with diabetes may use the system to periodically monitor their blood sugar levels. Continuous monitoring of biological signals from the body can assist doctors with diagnosis and lead to better prescription and/or treatment of previously difficult-to-capture symptoms.

From a system requirement perspective, such a communication system must be highly reliable and harmless to the patient. These systems do not necessarily require high transmission speeds because the relevant data are simple in most application scenarios. Specific components of IoBNT systems, such as transceivers and sensors, have been investigated comprehensively in previous studies [3], [5], [20], [27], [28].

Many researchers have proposed blood vessel networks as channels for IoBNT networks in the human body. Human blood vessels can play a key role in composing a communication system covering the whole body. However, thus far, researchers have mainly focused on the communication system itself without considering the effects of blood vessels [13], [21]–[25]. Therefore, we mainly address the communication method in the blood vessels.
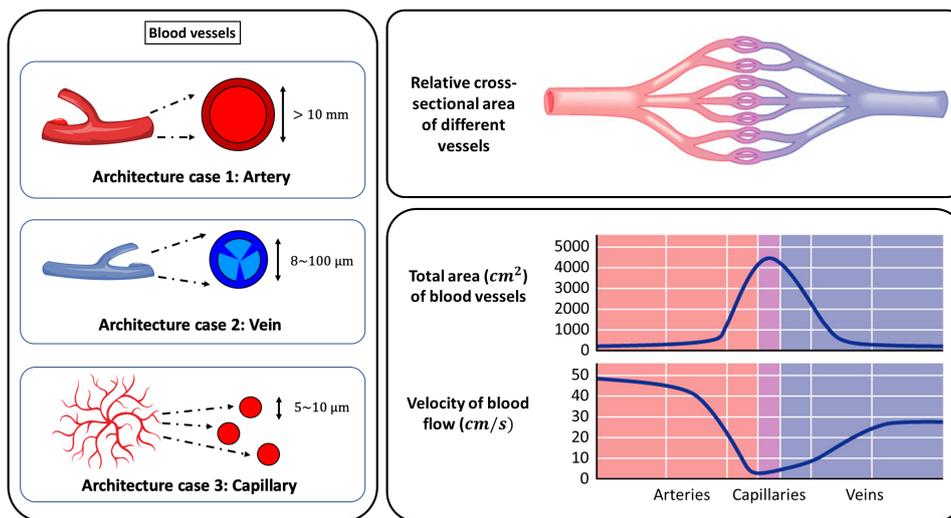
Fig. 2. Characteristics of blood vessels: Cross-sectional size, total area of blood vessels, and blood flow velocity [18].

The human blood vessel network comprises three types of vessels, namely arteries, veins, and capillaries, all of which have different channel characteristics. Therefore, we need to build an IoBNT network by considering the channel characteristics of blood vessels. Fig. 2 illustrates the characteristics of the three types of human blood vessels [18].

Arteries have considerably larger cross-sections than the other two types of blood vessels, as well as the fastest rate of blood flow. Therefore, the blood flow through arteries is generally turbulent. In particular, the arteries close to the heart exhibit strong turbulent flow owing to heartbeat-induced fluctuations in blood pressure. Naturally, the pressure is more stable in the arteries located farther away from the heart.

Veins have various cross-sectional sizes and flow speeds. Accordingly, their flow characteristics vary according to their specific environment. The Reynolds number of a flow in a blood vessel, expressed in terms of the radius of the vessel and flow speed, is an appropriate criterion for determining whether the flow in a vessel is turbulent or laminar. However, the blood pressure in veins is often negative because they are located far from the heart. Therefore, biological valves assist with blood flow in veins.

Capillaries have the smallest cross-sectional sizes and flow speeds. Therefore, they usually exhibit laminar flow characteristics. Unusually, the capillary surface is permeable, to ensure that nutrients can be conveyed to adjacent cells. The channel model of capillaries differs from those of the other two types of blood vessels in this regard.

The three aforementioned types of blood vessels exhibit different schemes owing to their different characteristics. Therefore, we should consider the optimal communication system for each environment. However, the results of molecular communication channel studies conducted in free space channels are difficult to apply to this system. Physical boundaries, such as blood vessel walls, lead to differences in the movement of molecules. In addition, the various characteristics of blood vessels influence the communication channel. Therefore, we introduce a method for addressing each of these factors to

build a communication system and suggest system designs for IoBNT in the following section.

III. SYSTEM DESIGN

In this section, we investigate the system design of molecular communication in blood vessels for eHealth applications, as depicted in Fig. 3.

The types of messenger molecules, flow speed, cross-sectional size, and degradation influence the development of channel models. Moreover, the positions of the transmitter and receiver influence the channel model. We expect the transmitter and receiver to be located at the surface because extra energy is required when the transceiver is located in inner blood vessels to keep the position in a realistic application view. Finally, we discuss the optimal system composed of modulation, detection, coding, error correction, and relay system based on each type of blood vessel channel model.

A. Channel

Although they exhibit different characteristics, all types of blood vessels can be modeled as cylindrical ducts [8]–[12]. Fig. 4 illustrates the three different channel models considered in the previous studies: The free-space channel, cylindrical duct channel with uniform flow, and cylindrical duct with Poiseuille flow. We consider only communication systems in blood vessels that exhibit laminar flow, such as uniform flow and Poiseuille flow, because it is difficult to model communication systems in turbulent flows.

We assume that the point transmitter emits the messenger molecules as carriers, and the spherical receiver absorbs them. The number of molecules absorbed by the receiver constitutes the channel response of molecular communications. In the cylindrical duct channel models, the transmitter is located at one end of the duct and adheres to the surface, while the receiver is located at the other end of the duct on the surface. The channel responses illustrated in Fig. 4 were obtained through
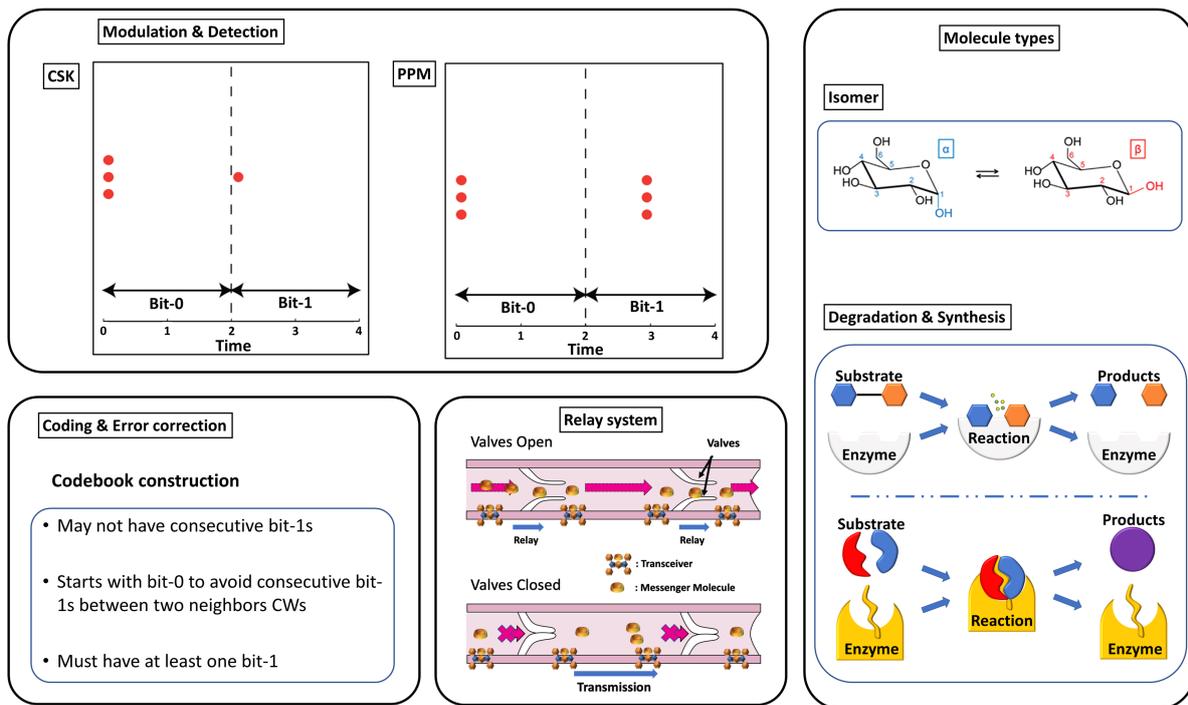
Fig. 3. Proposed system design for molecular communication in blood vessels.

computer simulations by applying the channel parameters of veins.[1]

Fig. 4 illustrates the differences between the channel responses of the cylindrical duct channel and the free-space channel. The cylindrical duct channel yields a higher signal amplitude than the free-space channel, which indicates that the channel is more directional. However, the tail, which increases the inter-symbol interference (ISI), is elevated. As the duct radius increases, the response of the cylindrical duct channel becomes similar to that of the free-space channel.

Furthermore, the effects of different flow velocity profiles along the radial axis are depicted in Fig. 4(b). Poiseuille flow has a non-uniform velocity profile that depends on the characteristics of the flowing liquid, its flow speed, and the cross-sectional size of the duct. The friction force between the tube surface and the liquid in the duct leads to a non-uniform velocity profile. Typically, in small ducts such as blood vessels, this friction force cannot be ignored. The Péclet number, defined as the ratio of the rate of advection of a physical quantity due to the flow to the rate of diffusion of the same quantity driven by an appropriate gradient (i.e., $Pe = Rv/D$, where R is the radius of the tube, v is the flow velocity, and D is the diffusion coefficient) can be used to describe the relative importance of flow and diffusion. A flow acts as a Poiseuille flow when its dispersion factor, α_d ($\alpha_d = L/PeR$), is smaller than one. This is because there is insufficient time to achieve uniform flow by radial diffusion when the dispersion factor is smaller than one. The first arrival

of molecules is faster in the Poiseuille flow, and the tail of the channel response is longer in some cases.

Unlike prior works that have focused on free-space channels, in this work, we utilize cylindrical duct channels to model molecular communications in blood vessels. Generally, large blood vessels exhibit uniform flow [8], [11], [12], while blood vessels of other sizes exhibit Poiseuille flow, which leads to a more complex channel response [9], [10]. However, the characteristics of the other types of blood vessels influence the flow conditions as well. Therefore, it is important to select a proper flow channel model based on the Péclet number and dispersion factor calculated using the given blood vessel parameters.

B. Boundary Condition

Blood vessels have different types of vessel walls based on their role and location. Furthermore, veins are equipped with special valves. Arteries generally have thick walls that make them durable against high pressure and prevent leakage. Therefore, arteries without wall malfunctions can be modeled using a cylindrical duct with a full reflection boundary.

By contrast, capillaries have extremely thin walls that facilitate the exchange of various nutrients. A permeable boundary can cause leakage of messenger molecules. The leakage rate varies depending on the size of the molecules and their interaction with the walls. Fig. 5(a) shows the capillary and channel responses influenced by surface leakage. The authors of [15] introduced a cylindrical duct channel model with arbitrary boundary conditions. Based on a previous study, we can model a capillary channel if we know the leakage rate of messenger molecules through its walls.

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[1]The diffusion coefficient and the uniform flow velocity are 670 $\mu m^2/s$ and 0.5 cm/s, respectively, and the length of the cylindrical duct, the radius of the duct, and the receiver size are 2000 μm, 30 μm, and 5 μm, respectively.
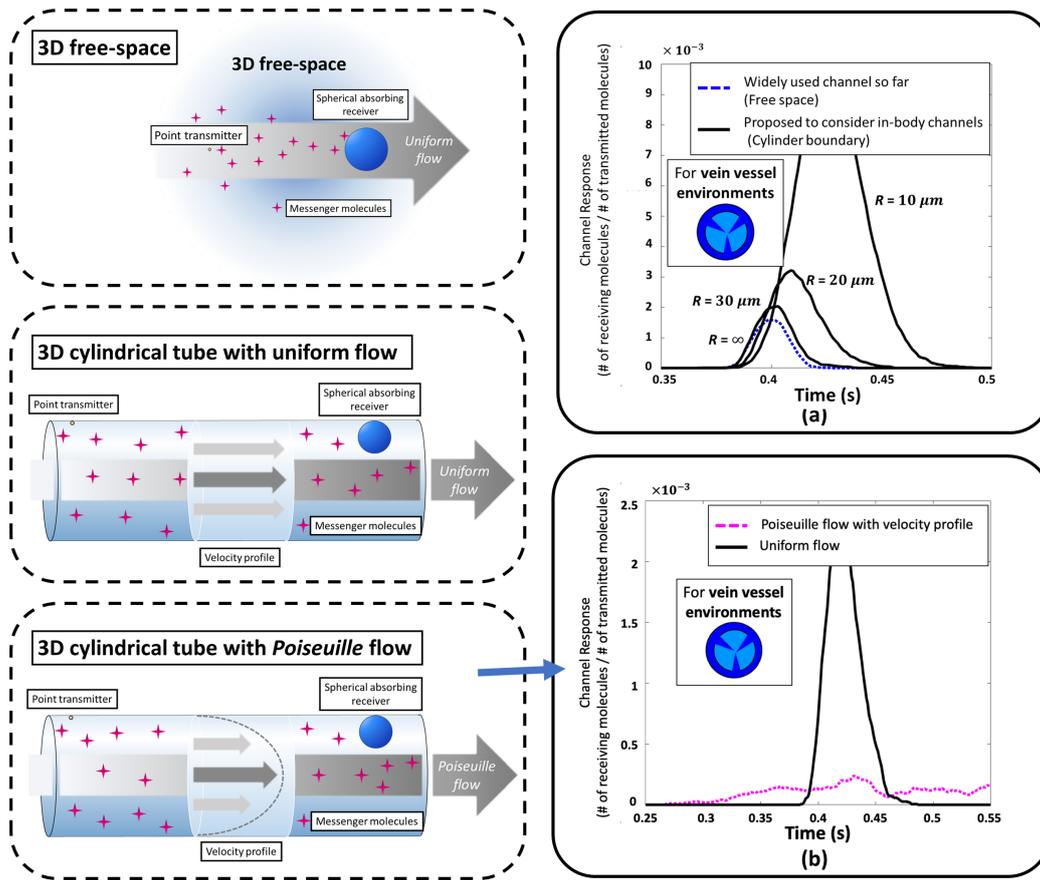
Fig. 4. Illustration of channel environments (left) and channel responses in a vein (right). In each channel environment (left), a point transmitter emits molecules and a spherical absorbing receiver counts the received molecules. The transmitter and receiver are assumed to adhere to the surface of the 3D cylindrical tube. Each environment under consideration has different flow phenomena based on its velocity profile. For the channel responses (right), we propose adopting the cylindrical tube channel as the in-body network channel model.

Veins have moderate wall thicknesses. Moreover, they are equipped with natural valves at intervals of several centimeters to help with blood circulation. However, this makes it difficult to analyze the channel model when molecules pass through multiple valves. The transmission signal may be degraded by these valves, which open and close periodically. To the best of our knowledge, there is no proper boundary condition to help model a channel with natural valves. Fig. 5(b) illustrates that the presence and operation of valves in veins influence the channel response of veins.

C. Molecule Types

The transformation of molecules should be considered in channel modeling to ensure safety. In other words, appropriate molecules should be utilized as messengers to make sure that the resulting health-monitoring system is safe. Also, the receiver may not detect the transformed molecules, thus influencing the channel model.

Many natural molecules, other than messengers, are present in blood vessels. Therefore, messenger molecules may be transformed through chemical reactions with other molecules. We describe the three main types of such transformations: Isomerization, degradation, and synthesis.

First, isomer molecules have different shapes but identical molecular formulas. Isomers have different chemical characteristics that may be used to indicate different information. In [29], the authors proposed modulation by using the isomer group of glucose. If each isomer has similar physical characteristics, such as the diffusion coefficient, the channel model can be developed conveniently.

Second, the degradation and synthesis of molecules influence the molecular communication channel model. The chemical reactions that occur in blood vessels may disassemble or assemble messenger molecules while they convey information. The transmitted signal is lost if the receiver cannot detect the byproducts of degradation and synthesis. Subsequently, the channel impulse tail becomes shorter [8]. These characteristics can be used to mitigate the ISI and increase the reliability of communication if the byproducts are safe for the human body. The authors of [14] analyzed a cylindrical duct channel model by applying a first-order chemical reaction. A channel model can be built when the communication system utilizes changeable molecules by selecting the proper effect. The machine-learning method can be used when intractable chemical reactions occur in the channel environment.

From the safety perspective, the utilization of molecules that do not undergo any chemical reaction in the body and
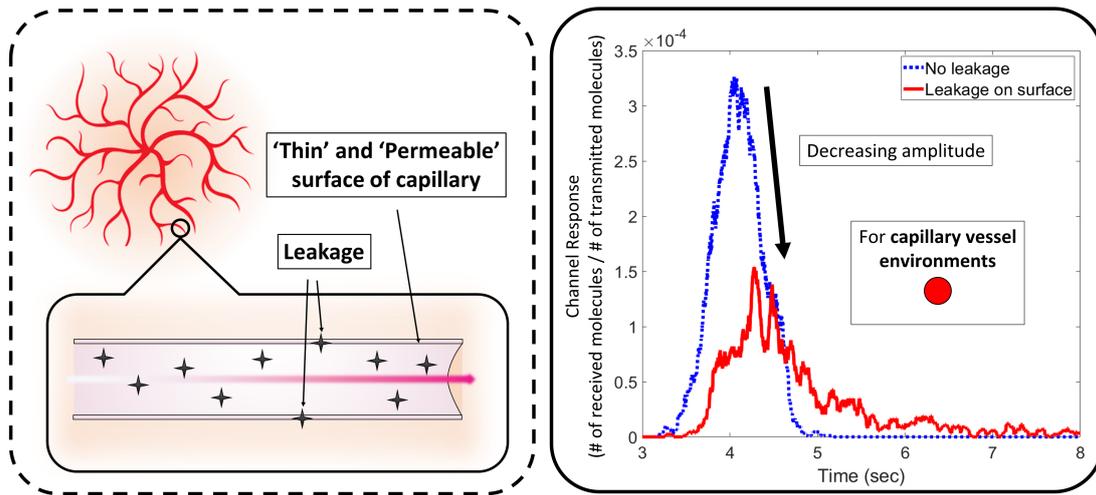
(a) Illustration of capillary blood vessels (left) and channel responses with/without leakage (right)
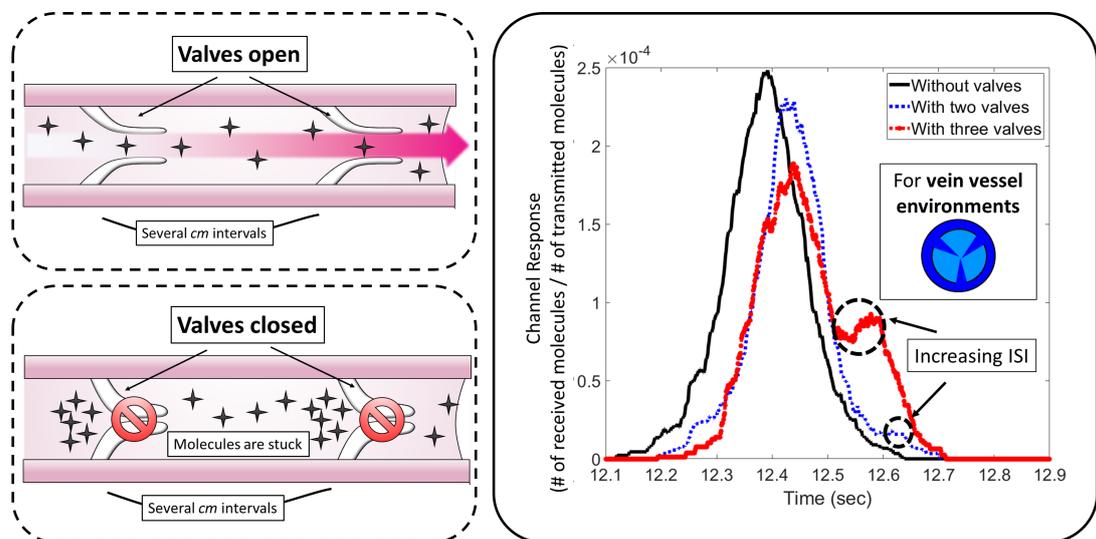
(b) Illustration of valves operation in veins (left) and channel responses with/without valves (right)

Fig. 5. Characteristics of blood vessels (capillaries and veins).

are eliminated naturally is better if their reliability and energy efficiency meet the requirements of health-monitoring systems. The molecules used in medical checkups are candidates for stable messenger molecules.

D. Modulation & Detection

In the literature on molecular communication, several modulation methods have been proposed such as pulse position modulation (PPM), concentration shift keying (CSK), and molecule-type shift keying (MoSK). Under the condition that the receiver can detect any type of molecule, MoSK modulation can be considered suitable in terms of reliability [30], [31]. However, the receiver required to support MoSK is too complex to be implanted in the inner body, which is not desirable for health-monitoring systems. Thus, alternatives such as PPM and CSK can be considered more suitable for eHealth applications. Although these schemes have been studied extensively for free-space channels, their characteristics for blood vessel channels need to be elucidated.

In [7], many versions of both modulations were introduced. PPM modulates information by transmitting a signal at a specific time according to the modulation policy. This modulation scheme offers advantages in terms of energy consumption because it uses the same quantity of molecules for all signals. Furthermore, sending a small number of molecules in a single shot is adequate to realize decent reception performance. However, a long symbol duration is required for higher modulation levels, leading to lower transmission speeds. Nevertheless, PPM is an acceptable candidate for our proposed system, because it prioritizes energy efficiency over transmission speed.

By contrast, CSK modulates information by emitting varying quantities of molecules with respect to the designated levels. This method is analogous to amplitude modulation in RF communications. CSK modulation is extremely simple at the transmitter end. However, it may lead to a high ISI if the proper molecule count is not configured. The molecular com-

munication channel impulse generated by counting molecules generally has a long tail and causes a high ISI. Flow assistance in such an environment mitigates the longtail characteristic, but the use of coding and error correction can improve it to a greater extent. Thus, CSK modulation offers practical advantages owing to its low complexity.

The above modulation schemes have generally been studied using free-space channel models. Therefore, channel characteristics such as leakage on the surface of the capillary should be considered. In simulations conducted in capillary environments, surface leakage decreases the amplitude of the desired signal, but the receiving time is not affected to the same extent as the amplitude. Accordingly, appropriate techniques should be developed utilizing the previous method. Moreover, we can consider utilizing the hybrid modulation method described in [32] for this purpose.

Optimal detection was developed to pair each modulation scheme. The use of maximum likelihood (ML) and maximum a-posteriori (MAP) has been proposed to achieve the best performance. However, it is difficult to adopt the above detection methods directly because of their complexity. Realistically, a nanomachine may utilize various thresholding methods because it merely detects the transmitting sequence based on whether the sequence exceeds the threshold. Channel characteristics are typically used to set the threshold. For example, the adaptive thresholding method reflects the ISI and interlink interference (ILI) in the set threshold [33]. The system may require a threshold that differs according to the type of blood vessel in which it is installed.

Notably, a vein channel requires the incorporation of ISI mitigation methods owing to the existence of valves. These valves help facilitate efficient blood travel, even at low blood pressure. However, they can disturb molecular communications inside veins by causing ISI. Therefore, we should consider a detection method to mitigate such ISI. For example, a threshold can be configured to address the ISI caused by the tail part of the channel response. The channel response can be modeled using different schemes by changing the period and intervals of valves closing and opening. Considering these valve operations, the vein channel model may be too complex to be developed properly. Therefore, the use of machine-learning techniques for this purpose is a plausible option in the development of an integrated vein channel model.

E. Coding & Error Correction

Coding and error correction techniques are necessary to achieve high reliability. However, nano-machines in the body may lack sufficient energy to execute the complex methods used in traditional RF communications. Coding and error correction for molecular communication was introduced in [7], [34]. Coding methods based on hamming and convolution codes have been proposed, such as RF communication. These coding methods offer satisfactory performance. However, an ISI-free or mitigating code is required to increase system reliability.

In [35], ISI-mitigating channel codes were proposed for molecular communication. These codes use channel information and exhibit a lower bit error rate (BER). In the

binary concentration shift keying (BCSK) modulation scheme, successive bit-1s cause severe ISI. Therefore, the rule of the codebook was set to avoid consecutive bit-1s. A free-space diffusion channel was assumed in that study, but we can utilize it by replacing it with our system channel. Furthermore, the coding method may perform better because flow-assistance channels generally have a lower ISI.

F. Relay System

Although blood vessels provide flow assistance, the molecular communication system requires a relay system [36]. With only one transceiver pair, it is difficult to convey data from the sensors that measure biological signals to a machine outside the body. Therefore, a reliable and energy-efficient relay system should be used in the health-monitoring system.

The neural system has a relay for transmitting the signal to the entire body. Furthermore, messenger molecules are reused at the synapses, which represent intervals between front and back neurons. From the molecular communication perspective, a relay with a system for reusing molecules was introduced in [37].

The relay system plays an important role in vein and capillary channels. First, the vein communication system requires a relay because of the valves present in veins. However, it is difficult to analyze the channel model when the molecules pass through many valves. The transmission signal may be degraded by these valves, which open and close periodically, as shown in Fig. 5(b). We propose that the transceiver pairs should be distributed considering the distribution of valves to possibly increase the reliability of communication, and we expect to achieve superior performance if the relay period matches the period of the valves.

The capillary channel requires the relay system for another reason. The capillaries have the lowest flow speed, and leakage may occur at the capillary surface, as shown in Fig. 5(a). Moreover, capillaries have the smallest duct cross-sections, which limits the energy that can be carried by nano-machines. The abovementioned characteristics complicate the transmission of molecular signals over long distances, which can be mitigated by the relay system.

IV. PROTOTYPE DESIGN

Several studies have introduced testbeds for molecular communications to demonstrate practical possibilities. All of these testbeds were developed for free-space, vast water, and tube environments. Moreover, they use different forces such as compressed air [33], [38]–[40], liquid flow [16], [17], [41]–[43], magnetic force [44], [45], and gravity [46] to transmit molecules. Here, we introduce meso- and nano-scale testbeds to verify the feasibility of molecular communication in vessels.

A. Vessel MIMO Prototype

In [16], we introduced a meso-scale in-vessel molecular MIMO communication testbed, as shown in Fig. 6(a). The transmitter was composed of four pumps that facilitate flow
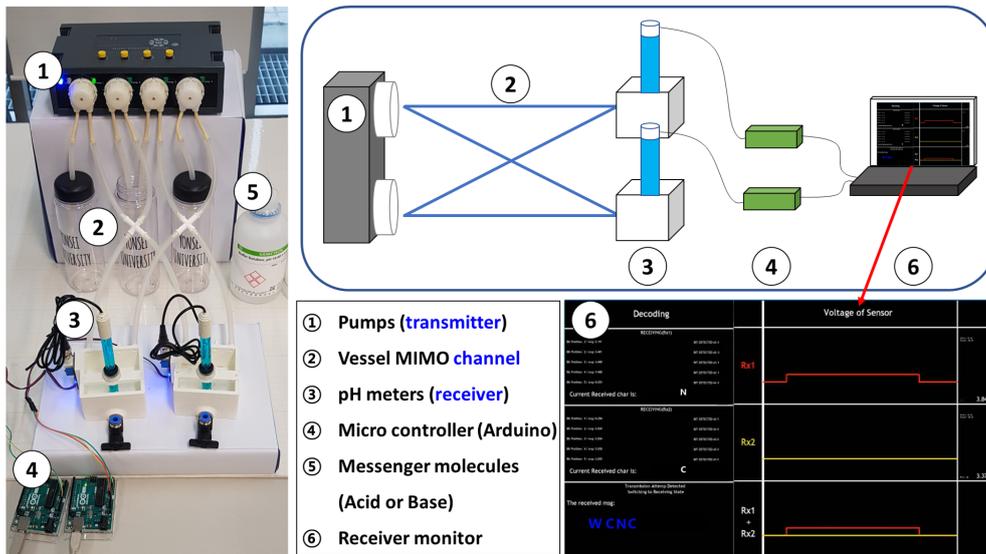
(a) Meso-scale vessel MIMO prototype
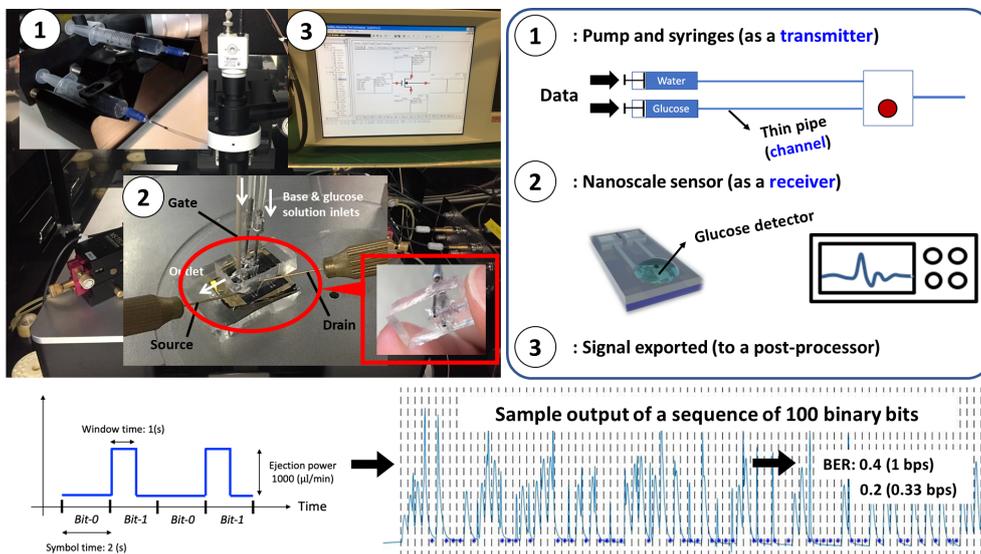
(b) Nano-scale human implantable vessel prototype

Fig. 6. Prototypes of blood vessel networks.

in the tube channel and emit messenger molecules. The system utilizes bases and acids as messenger molecules, and each pump can indeed use different types of molecules. The emitted molecules pass through a 2×2 MIMO channel composed of junction parts and silicon tubes. The receiver measures the change in pH value in the receiver tank and converts it to an electrical signal. Finally, the computer displays the detection results on the screen by using the conveyed electrical signal. The system is operated by CSK modulation, international telegraph alphabet no. 2 (ITA2) coding, adaptive threshold detection, and spatial multiplexing. An Arduino microcontroller is used to control both the transmitter and the receiver. Therefore, the testbed can utilize various modulation schemes, coding methods, and detection methods. Furthermore, the testbed can be composed of various multiple-branches channels by using

junction parts fabricated with a 3D printer.

B. Human Implantable Nano Prototype

We also implemented a nano-scale system that can communicate using molecules, as shown in Fig. 6(b) [17]. While the entire communication model requires enhancements so that it can be applied in practice, the remarkable point of this model is that the nano-scale sensor designed in that study is specialized for molecular communication tasks. The sensor is adequately small such that it can be implanted near the human skin without causing any harm. Thus, it is suitable for use as a molecular communication receiver. It can notice a sensitive amount of glucose molecules by using indium gallium zinc oxide (IGZO) enzymes and report variations in the detected concentrations so that the information can be converted and

conveyed to users. Moreover, the manufacturing costs of this sensor are low. Therefore, it can be replaced easily, which compensates for its short lifetime. Our results indicate that a data rate of 0.33 bps can be achieved with a reliable error rate. Therefore, we conclude that the performance bottleneck of this system is not the channel uncertainty but the mechanical units used, and in the future, the performance of this nano-molecular communication system can be improved.

V. OPEN CHALLENGES AND CONCLUDING REMARKS

In this work, we investigated the system design and reported prototypes of the IoBNT that can be utilized in eHealth applications. Bio-nano things are connected through molecular communications in blood vessels. We demonstrated that various types of blood vessel channels differ considerably from the free-space channel, and the use of cylindrical duct channel models is appropriate for realizing molecular communications. Moreover, we proposed molecular communication system designs that guarantee high reliability and low energy consumption by building architectures tailored for the types of blood vessels. We empirically demonstrated that the channel environments of blood vessels introduce a novel set of challenges compared to free-space channels and suggested the utilization of cylindrical duct channel models for realizing molecular communication. Furthermore, we confirmed the feasibility of the proposed IoBNT systems by developing and implementing nanoscale molecular communication prototype.

Although the proposed system is in its preliminary stages, we see a number of interesting research challenges that can be addressed, including obtaining a deeper understanding of biological channel environments, new components, and system architectures for supporting effective modulation, detection, and coding. The results of this study are expected to lead to new applications and prototype implementations that can further enhance the practical applicability of IoBNT systems. We expect that this work will provide insights into the system design of IoBNT with molecular communication.

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Changmin Lee (S'15) received the B.S. degree from the School of Integrated Technology, Yonsei University, Seoul, South Korea, in 2015. He is currently pursuing the Ph.D. degree at the School of Integrated Technology, Yonsei University. He was the recipient of the Best Demo Award at IEEE WCNC (2020) and the Best Demo Award at IEEE INFOCOM (2015). His research interests include emerging communication technologies.

Bon-Hong Koo received his B.S. degree in the School of Integrated Technology from Yonsei University, Korea, in 2014. He is now with the School of Integrated Technology, at the same university and is working toward the Ph.D. degree. He was the co-recipient of the best demo awards at IEEE WCNC (2020) and IEEE INFOCOM (2015). His research interest includes emerging communication technologies.

Chan-Byoung Chae (S'06-M'09-SM'12-F'21) is an Underwood Distinguished Professor in the School of Integrated Technology, Yonsei University, Korea. Before joining Yonsei University, he was with Bell Labs, Alcatel-Lucent, Murray Hill, NJ, USA from 2009 to 2011, as a Member of Technical Staff, and Harvard University, Cambridge, MA, USA from 2008 to 2009, as a Postdoctoral Research Fellow. He received his Ph.D. degree in Electrical & Computer Engineering from The University of Texas at Austin in 2008. Prior to joining UT, he was a Research Engineer at the Telecommunications R&D Center, Samsung Electronics, Suwon, Korea, from 2001 to 2005.

He is now an Editor-in-Chief of the IEEE Trans. Molecular, Biological, and Multi-scale Communications and a Senior Editor of the IEEE Wireless Communications Letters. He has served/serves as an Editor for the IEEE Communications Magazine (2016-present), the IEEE Trans. on Wireless Communications (2012-2017), and the IEEE Wireless Communications Letters (2016-present). He is an IEEE ComSoc Distinguished Lecturer for the term 2020-2021 and 2022-2023.

He was the recipient/co-recipient of the CES Innovation Award in 2023, the IEEE ICC Best Demo Award in 2022, the IEEE WCNC Best Demo Award in 2020, the Best Young Engineer Award from the National Academy of Engineering of Korea (NAEK) in 2019, the IEEE DySPAN Best Demo Award in 2018, the IEEE/KICS Journal of Communications and Networks Best Paper Award in 2018, the IEEE INFOCOM Best Demo Award in 2015, the IEIE/IEEE Joint Award for Young IT Engineer of the Year in 2014, the KICS Haedong Young Scholar Award in 2013, the IEEE Signal Processing Magazine Best Paper Award in 2013, the IEEE ComSoc AP Outstanding Young Researcher Award in 2012, the IEEE VTS Dan. E. Noble Fellowship Award in 2008.

Robert Schober (S'98 - M'01 - SM'08 - F'10) received the Diplom (Univ.) and the Ph.D. degrees in Electrical Engineering from Friedrich-Alexander University of Erlangen-Nuremberg (FAU), Germany, in 1997 and 2000, respectively. From 2002 to 2011, he was a Professor and Canada Research Chair at the University of British Columbia (UBC), Vancouver, Canada. Since January 2012 he is an Alexander von Humboldt Professor and the Chair for Digital Communication at FAU. His research interests fall into the broad areas of communication theory, wireless communications, and statistical signal processing.