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Molecular Communication Aspects of Potassium Intracellular Signaling in Cardiomyocytes

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ABSTRACT Cardiovascular diseases continue to be a leading cause of morbidity and mortality worldwide. Cardiomyocytes, as the elementary heart components, play a crucial role in maintaining a healthy heart by coordinating contractions throughout the heart muscle that lead to a heartbeat. This study aims to characterize fine-grained ionic-level manipulation of cardiomyocytes for the controlled electrical activity that will offer new insights within the medical field. We explore the concept of Molecular Communications (MC) to analyze the propagation of potassium ions in the cardiomyocyte cytosol. By associating the number of the potassium ions in the cytosol with the membrane- and action potentials, we use metrics from the well-known Shannon's information theory to optimize the ionic injection process and manipulate cardiomyocytes electrical activity. In case ON/OFF keying modulation is adopted as the potassium ion injection method, the optimal input distribution in terms of information capacity follows the derived Bernoulli distribution. This study offers underlying concepts that can be exploited in the creation of cardiomyocyte signals either for data communication via cellular infrastructure or heart pacing. The framework presented here needs to be upgraded in the following phases and made more physiologically plausible.

INDEX TERMS Cardiomyocyte, channel capacity, intracellular communication, molecular communication, subthreshold communication.

I. INTRODUCTION

Pacemakers are permanent implants to treat patients with irregular heartbeats by injecting current to stimulate the heart in atrium and ventricle using electrodes (leads) [1]. Leads can cause infections and have led to the development of leadless pacemakers. These are small capsules-like devices containing sensors, current injectors, microcontrollers, wireless transceivers, and batteries. Due to the requirement of small physical size and lifelong operation, the researchers are now looking for solutions beyond micro- and nanotechnology fields. Interestingly, biologists, inspired by the electronic industry and device development, are designing synthetic cells, inherently biocompatible and able to function like electronic devices or chords to perform key functions like sensing, computing, actuation, and signaling [2]. The advent of synthetic biology, in turn, has inspired communications engineers to develop new models and methods for intracellular and cell-to-cell communication using information and communication theoretical approaches.

In a concept of the multi-nodal leadless pacemaker which we have recently proposed [3], communication of sensed data and commands for current injections between synthetic cells or capsules placed in atrial or ventricle can be realized utilizing cardiomyocytes, thus enabling an alternative transmission pathway and connectivity which bypass the damaged natural conduction system. Intercellular cardiomyocyte signal transmission provides interesting insights into data transmission and scheduling using the cardiomyocyte system as a transmission channel without interrupting the natural, ongoing

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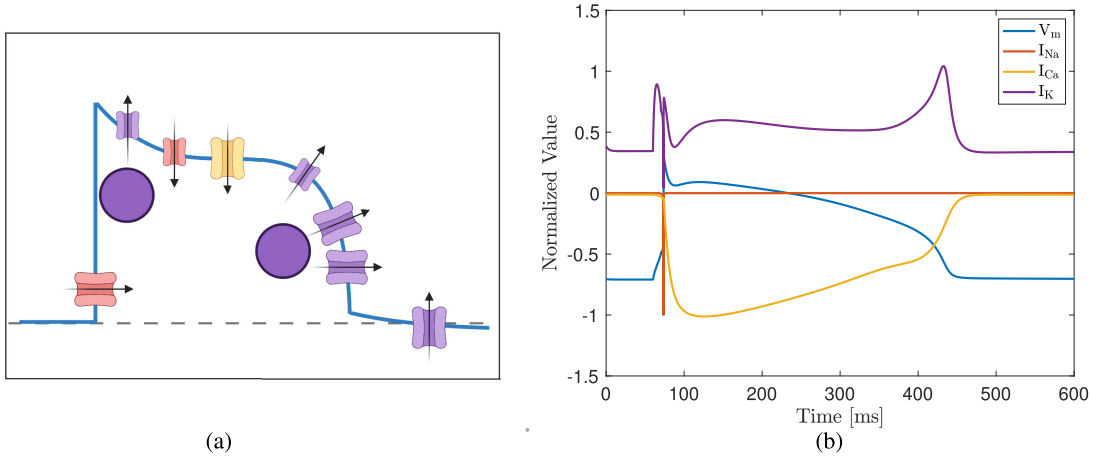

FIGURE 1. **(a) Cardiac channelopathies and (b) the normalized cardiomyocyte membrane potential, sodium current, slow inward calcium current, and potassium current change with time. The ionic currents synchronously depolarize the membrane and evoke membrane/action potentials.**

cell-to-cell communication needed for heart function [4]–[7]. In this regard, we have proposed and analyzed the resting-state (subthreshold) cardiomyocyte communication method within an intracardiac communication system [7].

In the intracardiac communication system, a cardiomyocyte is an elementary building block, where ions such as sodium (Na^+), calcium (Ca^{2+}) and potassium (K^+) ions further play a crucial role in defining electrophysiological activity. This activity is, in turn, essential for encoding data via the subthreshold membrane potential fluctuations [7]. The ions are dynamically exchanged between the intracellular and extracellular space (Figure 1a), which leads to the creation of the ionic currents (Figure 1b): *sodium current* (I_{Na}), *slow inward calcium current* (I_{Ca}), and *potassium current* (I_K), among others. The latter integrates the transient outward potassium current (I_{to}), the outward ultrarapid rectifier current (I_{Kur}), the outward rapid rectifier current (I_{Kr}) and the outward slow rectifier current (I_{Ks}), and the inward rectifying current (I_{K1}) [8]. Although the ionic currents coordinately contribute the cardiomyocyte to generate membrane and action potentials, as shown in Figure 1b, their effects can be studied independently. Thus, it is required to separately investigate the effects of ionic movements/currents and their association with cellular electrophysiological activity before conducting further relevant analysis and experimental trials in association with the proposed communication method.

Potassium ions are the first candidate whose dynamics can be analyzed in a straightforward manner. Compared to sodium and/or calcium dynamics, potassium dynamics within cardiomyocytes can be easily described. Although present in the intracellular space where they hardly propagate/diffuse longitudinally, sodium ions are predominately concentrated in the extracellular space [9]. Although exist in the cytosol where they play crucial roles, calcium ions dynamics is more complex. This is particularly valid for membrane potentials when the calcium-induced-calcium-release (CICR) mechanism in the cytosol is activated and calcium ions are released from internal stores, e.g., endoplasmic reticulum, in addition to calcium influx from the extracellular space [10].

Potassium ions in the cytosol are abundant compared to their concentration in the extracellular space and intracellular concentrations of other ions. Besides, potassium ions 1) have the potential to propagate/diffuse intracellularly in the longitudinal direction[1] either in the resting-, depolarization-, plateau-, and repolarization periods [12], and 2) are not buffered intracellularly (like calcium ions), whereas only physical barriers and local charges or components like membranes could restrict their propagation/diffusion [13], [14]. Ultimately, adequate injection of potassium ions into the intracellular space depolarizes the cardiomyocyte's membrane, which can be utilized for creation of signals for communication of sensed data and/or commands between synthetic cells or capsules.

The listed properties prompt us to deploy Molecular Communication (MC) paradigm and the Shannon's information theory to

- analyze the potassium-based signaling (sub)-system, and
- propose a novel way of associating the intracellularly transmitted ions with the membrane potential fluctuations relevant for encoding data via the resting-state cardiomyocyte communication method [7], [15]–[19].

The diffusion-based MC framework has been previously used to study the leadless pacemaker communications in the heart chambers [20]. In that scenario, the communication is based on pheromone transmission using unspecified molecules which diffuse through the blood medium, where

[1]Potassium ion diffusion in the longitudinal direction is about 5000 times greater than the permeability of the surface membrane to outward movement [11].

the propagation distance is larger than the length of a single cell [20], [21]. We describe the potassium ion propagation within the cardiomyocyte cytosol with the diffusion-based MC models [22]–[25] and ground this study on the system model presented in [23]. We assume that 1) **the potassium ion transmitter** is a point source which integrates the ions transmitted via gap junctions from the neighboring cells and/or externally injected ions (e.g., via electrophoresis), 2) the potassium ions movement in the intracellular space can be characterized by the diffusion law, and 3) **the potassium ion receiver** absorbs or accumulates the ions. Finally, we use the information theory metrics such as the channel capacity to characterize the performance of the potassium-based intracellular signaling (sub)-system. Unlike in the existing works, e.g., [26]–[28], here we associate the concept of Shannon's information capacity with the cardiomyocyte intracellular potassium, with the objective to optimize the ionic injection process and manipulate cardiomyocytes electrical activity. The concept of information theory can further be used to derive measures to investigate, diagnose, or treat cardiac diseases in nanomedicine [5], [6].

The rest of the paper is organized as follows. Section II introduces the potassium-based intracellular signaling model. Section III characterizes the channel capacity of the proposed system. Section IV presents the numerical simulations and results. Finally, Section V discusses and concludes the study.

II. POTASSIUM-BASED INTRACELLULAR SIGNALING (SUB)-SYSTEM

Weidmann's use of multiple compartment methods showed that potassium ions could diffuse through multiple cardiac cells in the longitudinal direction [11], [29]. Besides, the diffusion process is divided into two steps: 1) diffusion through the intracellular space, and 2) diffusion across the gap junctions between two cells. Potassium ions diffusion in the intracellular space could be considered as a source-sink communication [30] where the ions move from one selected compartment to another. Due to the similarities of the ionic movement and molecular diffusion, we adapt the existing basic MC concepts developed by the communications engineering community to model the potassium-based intracellular signaling in cardiomyocytes.

A. BASIC MC MODEL

The conventional MC system uses molecules/ions to transmit information between its peers. Figure 2 shows a general diffusion-based MC model which consists of source encoding, sending (emission), propagation (diffusion), reception (absorption), and source decoding [31], [32]:

- Encoding: the transmitter encodes the signal related data into the specific number of molecules/ions,
- Sending: the transmitter emits information molecules/ions into the channel,
- Propagation: the emitted molecules/ions roam in the communication channel between the transmitter and receiver,

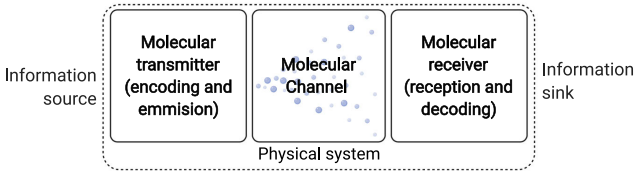

FIGURE 2. Basic diffusion-based MC system.

- Reception: the receiver absorbs the information molecules/ions from the communication channel,
- Decoding: the receiver reacts to the molecules/ions.

B. POTASSIUM-BASED INTRACELLULAR SIGNALING (SUB)-SYSTEM MODEL

Since the flow of potassium ions in cardiomyocytes can be considered as propagation from the source/emission point to the sink/receiver point, we conceptualize the potassium-based intracellular signaling (sub)-system model as shown in Figure 3. While establishing a potassium-based intracellular signaling system, we:

- consider the potassium ions diffusion in a three-dimensional space with a point source and a three-dimensional receiving sphere with the radius r that equals the cardiomyocyte's radius; it is reasonable to count the received ions in a sphere as adult cardiomyocytes exhibit a rod shape which could be taken as a curve surface in a three-dimensional space [33],
- assume the homogeneous cytosolic milieu where organelles do not interrupt the propagation of ions, and
- neglect the impact of other ions.

The corresponding system thus consists of three main compartments: the **transmitter**, the **channel**, and the **receiver**.

- The transmitter emits potassium ions. The ions source presumably comes either from 1) neighboring cells or ionic exchange between the intracellular and extracellular space, or 2) the external (coordinated) electrophoretic injection [34]. The transmitter ''occupies'' the area close to the cell membrane, as shown in Figure 3. In this study, the transmitter is abstracted as a point source to simplify the analysis.
- The channel allows for the emitted ions to propagate in the intracellular space following the diffusion law. The channel ''occupies'' the cytoplasm of the communicating cell.
- The receiver abstracts as a sphere receptor/nanosensor which detects the ions. According to the received ions, we quantify the encoding membrane potential which helps us decide whether we should stimulate the cell with potassium injection or electrical stimulation and how strong the stimulus should be to successfully propagate information signals to other cells/nodes via gap junctions. The receiver ''occupies'' the distal segment of the cell in the longitudinal direction, as shown Figure 3.

The conceptual division in compartments helps us abstract and understand the intracellular communication system.

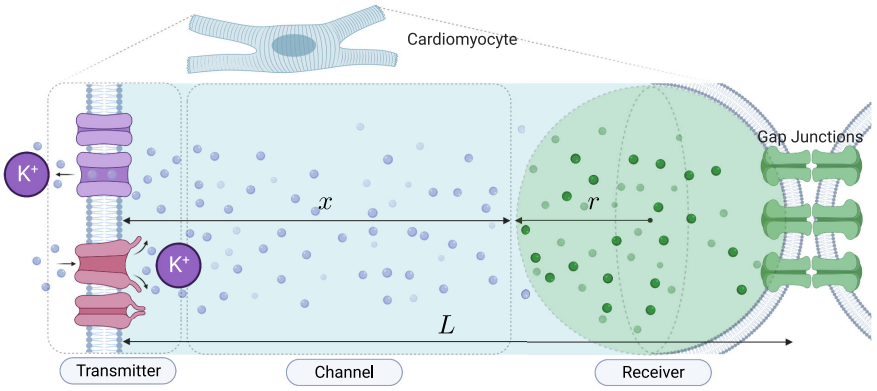

FIGURE 3. Potassium-based intracellular signaling (sub)-system model.

C. DIFFUSION EQUATION

The diffusion equation is applied to characterize any substance diffusing in intracellular space (e.g., ions or small molecules [35]). In general, the diffusion could be complex and anisotropic, and is affected by the cytosolic milieu. We model the potassium ions diffusion in cardiomyocytes with a point emitter and a sphere receiver [23], as shown in Figure 3, and assume that 1) the cardiomyocyte is cylindrically rod shaped, 2) the potassium ions propagate in the longitudinal direction since the length of a cardiomyocyte is usually about ten times bigger than the radius [36], and 3) the potassium diffusion coefficient in the longitudinal- is higher than in the radial-direction [12].

The transmembrane efflux of the potassium ions affects the concentration of the potassium ions movement in the longitudinal direction. Thereby, by taking into account the potassium efflux, the potassium ions concentration variation ($C(x,t)$) is described as [37]

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} - kC(x,t), \tag{1}$$

where x is the propagation distance, t is the propagation time, D is the diffusion coefficient of the potassium ions, and k is the rate constant of transmembrane efflux in ms^{-1} ($k = 0$ denotes that none of the ions move out of the intracellular space, and the permeability of the cell membrane is very low, whereas k>0 denotes that some of the ions move from the intracellular- to the extracellular space). The rate constant k is described as [37]

$$k = -\frac{M_{\mathrm{out}}}{C(x,t)}\frac{A_{\mathrm{cell}}}{V_{\mathrm{cell}}}, \tag{2}$$

where M_{out} is the efflux in mmol/($\mu\mathrm{m}^2$·ms), and $A_{\mathrm{cell}}/V_{\mathrm{cell}}$ is the surface-to-volume ratio of the considered cardiomyocytes in cm^{-1}. As the efflux is hardly measured, we use the half-life cycle ($t_{1/2}$) of the potassium ions to calculate the efflux rate [38], [39], which is written as

$$k = \frac{\ln(2)}{t_{1/2}}. \tag{3}$$

To solve (1), we need to set the initial- and the boundary condition. When considering that the propagation channel is infinite, and the potassium ions are emitted at $x = 0$ with an initial number Q_0, we yield

$$C(x,t) = Q_0(4\pi Dt)^{-3/2}\exp\left[-\frac{x^2}{4Dt} - kt\right]. \tag{4}$$

Of note, Q_0 is the initial value of the potassium ions in the system and is changed depending on the setup.

D. RELATION BETWEEN THE IONIC INJECTION AND THE MEMBRANE POTENTIAL CHANGE

The lipid bilayer of the cardiomyocyte membrane forms a capacitor that isolates the intracellular- and extracellular space. In the resting state, ions accumulate on both sides of the layer and keep the balance. The balance is disrupted when an external stimulation or physiological environment changes. Injecting cations into the intracellular space depolarizes the membrane and creates a potential difference. The membrane potential difference caused by the number of injected ions is described as [40]

$$V_{\mathrm{d}} = \frac{eQ_0}{C_{\mathrm{m}}A_{\mathrm{cap}}}, \tag{5}$$

where e denotes the elementary charge, C_{m} denotes the specific capacitance of the cardiomyocyte membrane in the unit area, and A_{cap} denotes the capacitive membrane area.

With the membrane potential difference, the actual membrane potential V_{m} is then calculated as

$$V_{\mathrm{m}} = V_{\mathrm{d}} + V_{\mathrm{rest}}, \tag{6}$$

where V_{rest} is the membrane potential in the resting state.

When cations are continuously injected into the intracellular space, the membrane continuously depolarizes while the membrane potential increases reaching the membrane potential threshold value (V_{th}) and, ultimately, the maximum membrane potential value (V_{max}). Therefore, we derive the threshold (Q_{th}) and the maximum (Q_{max}) as of the number of

injected cations according to (5) and (6), respectively, as

$$Q_{\text{th}} = \frac{C_{\text{m}} A_{\text{Cap}}}{e}(V_{\text{th}} - V_{\text{rest}})$$
$$Q_{\max} = \frac{C_{\text{m}} A_{\text{Cap}}}{e}(V_{\max} - V_{\text{rest}}). \quad (7)$$

III. CHANNEL CAPACITY

The channel capacity is one of the most-frequently-used metrics to characterize the communication channel's data transmission. We use the channel capacity in this study to evaluate the potassium-based intracellular signaling [41].

We analyze the ionic transmission within time slots. The transmitter emits a certain number of potassium ions in each time slot. However, in the diffusion-based MC system, the inter-symbol interference (ISI) is generated at the receiver point due to residual molecules/ions originating from the previous time slots. The ISI can be eliminated unless the signal propagation duration is infinite. One approach is to use a dynamic threshold detection technique [42]. We consider the ISI by taking into account the impact of the previously emitted ions, but simplify the detection procedure with a predefined threshold detection to avoid the computational burden.

A. CHANNEL MODEL

In a time-slotted system, the ionic diffusion happens within time $T = nT_d$, where n denotes the number of time slots and T_d the duration of each time slot. We consider the ON/OFF keying modulation method. The transmitter emits M potassium ions when sending bit 1, and none when sending bit 0.

The probability $P(x, t)$ of the ion at distance x and time t is given as [43]

$$P(x,t) = \int_0^t f(x,t') \int_{t'}^{\infty} g(u)\mathrm{d}u\mathrm{d}t', \quad (8)$$

where $f(x, t')$ denotes the probability density function (PDF) of one ion arriving at the receiver at distance x and time t', $g(u)$ denotes the PDF that characterizes the transmembrane efflux of ions, and is an exponential distribution function ($g(u) = k \exp[-ku]$). In our scenario, we define $f(x, t')$ as [19], [43]

$$f(x,t') = \begin{cases} 0 & t' = 0 \\ \frac{r}{r_0}\frac{x}{\sqrt{4\pi D t'^3}} \exp\left[-\frac{x^2}{4Dt'}\right] & t' > 0, \end{cases} \quad (9)$$

where x is the distance from the transmitter to the surface of the receiver, r is the radius of the receiver sphere, and $r_0 = x + r$ is the distance from the transmitter to the center of the receiver (Figure 3).

B. ISI ANALYSIS

At the start of each time slot $i \in [1, n]$, the transmitter sends bit 1 by emitting M ions with the transmission probability p_i. The transmitter thus sends bit 0 by emitting no ions with probability (1-p_i). All the ions diffuse independently, with the binary state when reaching the receiver. Therefore, to decode bit 1, the receiver successfully receives the ions with the probability $p_i P(x, T_d)$, where $P(x, T_d)$ stems from (8). The receiver fails to receive the ions with the probability $p_i(1 - P(x, T_d))$.

The number (N_c) of the received ions emitted by the transmitter within time slot n follows the Binomial distribution

$$N_c \sim \mathcal{B}(M, P(x, T_d)). \quad (10)$$

A binomial distribution $\mathcal{B}(n, p)$ can be approximated with a normal distribution $\mathcal{N}(np, np(1 - p))$, when n is greater than 50 [25], [44]. Since in the considered scenario n is significantly higher than 50, as shown in Figure 8a, eq. (10) is approximated as

$$N_c \sim \mathcal{N}(\mu, \delta^2), \quad (11)$$

where

$$\mu = MP(x, T_d),$$
$$\delta^2 = MP(x, T_d)(1 - P(x, T_d)).$$

Further, we denote with $P_{i,n}(1 \le i \le n)$ the probability of a single ion to be received in time slot n when emitting M ions in time slot i, and define as

$$P_{i,n} = p_i \left[P(x, (n - i + 1)T_d) - P(x, (n - i)T_d)\right]. \quad (12)$$

From (10) to (12), we denote the residual ions from the previous $(n - 1)$ time slots in the current time slot with the following distribution

$$N_{\text{ISI}} \sim \sum_{i=1}^{n-1} p_i (\mathcal{B}(M, P(x, (n - i + 1)T_d)) - \mathcal{B}(M, P(x, (n - i)T_d))). \quad (13)$$

Since all the ions independently propagate in the channel, eq. (13) is approximated from (10) and (11) as a normal distribution

$$\begin{aligned} N_{\text{ISI}} &\sim \sum_{i=1}^{n-1} p_i \left(\mathcal{N}(\mu_a, {\delta_a}^2) - \mathcal{N}(\mu_b, {\delta_b}^2)\right) \\ &= \sum_{i=1}^{n-1} p_i \left(\mathcal{N}(\mu_a - \mu_b, {\delta_a}^2 + {\delta_b}^2)\right) \\ &= \mathcal{N}\left(\sum_{i=1}^{n-1} p_i(\mu_a - \mu_b), \sum_{i=1}^{n-1} {p_i}^2({\delta_a}^2 + {\delta_b}^2)\right), \end{aligned} \quad (14)$$

where

$$\mu_a = MP(x, (n - i + 1)T_d),$$
$${\delta_a}^2 = MP(x, (n - i + 1)T_d)(1 - P(x, (n - i + 1)T_d)),$$
$$\mu_b = MP(x, (n - i)T_d),$$
$${\delta_b}^2 = MP(x, (n - i)T_d)(1 - P(x, (n - i)T_d)).$$

C. DETECTION

With the hypotheses H_0 and H_1 (Figure 4), we denote the numbers of the received ions N_0 when the transmitter sends 0 and N_1 when the transmitter sends 1 in the time slot n, respectively. N_0 and N_1 follow the normal distribution, respectively,

$$\begin{aligned} N_0 = N_{\text{ISI}} &\sim \sum_{i=1}^{n-1} p_i(\mathcal{N}(\mu_a - \mu_b, \delta_a^2 + \delta_b^2)) \\ &\sim \mathcal{N}(\mu_0, \delta_0^2), \end{aligned} \tag{15}$$

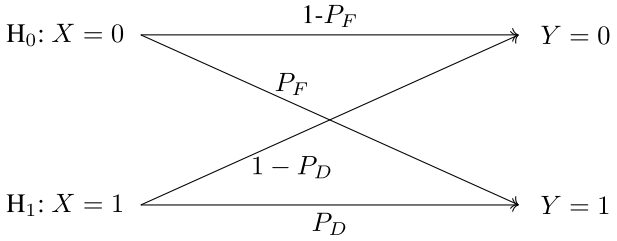

FIGURE 4. Binary test channel of the potassium-based intracellular signaling model.

where

$$\mu_0 = \sum_{i=1}^{n-1} p_i(\mu_a - \mu_b),$$
$$\delta_0^2 = \sum_{i=1}^{n-1} p_i^2(\delta_a^2 + \delta_b^2),$$

and

$$\begin{aligned} N_1 &\sim \mathcal{N}(\mu, \delta^2) + \sum_{i=1}^{n-1} p_i(\mathcal{N}(\mu_a, \delta_a^2) - \mathcal{N}(\mu_b, \delta_b^2)) \\ &\sim \mathcal{N}(\mu_1, \delta_1^2), \end{aligned} \tag{16}$$

where

$$\mu_1 = \mu + \sum_{i=1}^{n-1} p_i(\mu_a - \mu_b),$$
$$\delta_1 = \delta^2 + \sum_{i=1}^{n-1} p_i^2(\delta_a^2 + \delta_b^2).$$

To reduce the ISI, we set the threshold θ to a predefined value. The probability ($P(\theta|H_1)$) that the hypothesis H_1 happens and the probability ($P(\theta|H_0)$) that the hypothesis H_0 happens can then be calculated from the cumulative distribution function of the normal distribution, $F(\theta, \mu_1, \delta_1^2)$ and $F(\theta, \mu_0, \delta_0^2)$, respectively. Therefore, the false alarm probability P_F and the detection probability P_D are given as

$$\begin{aligned} P_F &= Pr(N \geq \theta | X = 0) = 1 - F(\theta; \mu_0, \delta_0^2), \\ P_D &= Pr(N \geq \theta | X = 1) = 1 - F(\theta; \mu_1, \delta_1^2), \\ Pr(Y = 1|X = 0) &= P_F, \\ Pr(Y = 1|X = 1) &= P_D, \\ Pr(Y = 0|X = 0) &= 1 - P_F, \\ Pr(Y = 0|X = 1) &= 1 - P_D. \end{aligned} \tag{17}$$

Ultimately, we resort to the error probability to find the proper detecting threshold θ using numerical methods (Section IV). The error probability of transmitting the random bit 0/1 in the current time slot n is written as

$$P_e = p_c(1 - P_D) + (1 - p_c)P_F, \tag{18}$$

where p_c is the probability of transmitting bit 1. As shown in Figure 5, the error probability highly depends on the detecting threshold θ.

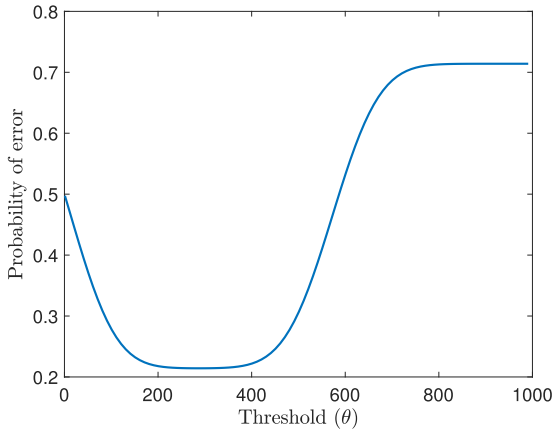

FIGURE 5. The error probability P_e versus threshold values with $T_d = 0.8$ s, $k = 0.005\text{ms}^{-1}$ and $Q_0 = 3 \times 10^5$.

D. CHANNEL CAPACITY

From the binary communication channel (Figure 4), the mutual information can be expressed as [45]

$$\begin{aligned} I(X; Y) &= H(Y) - H(Y|X) \\ &= \sum_{X=0}^{1} \sum_{Y=0}^{1} P(Y|X)P(X) \log_2 \frac{P(Y|X)}{P(Y)} \\ &= H(p_c(1 - P_D) + (1 - p_c)(1 - P_F)) \\ &\quad -(1 - p_c)H(P_F) - p_c H(1 - P_D), \end{aligned} \tag{19}$$

where $H(x)$ is the entropy of x, and it is given as $H(x) = -x \log_2(x) - (1 - x) \log_2(1 - x)$.

Subsequently, we define the information capacity C_K as [45]

$$\begin{aligned} C_{\text{K}} &= \max_{p_c}(I(X; Y)) \\ &= \log_2(1 + z) - \frac{P_F}{P_F - P_D} H(1 - P_D) \\ &\quad + \frac{P_D}{P_F - P_D} H(P_F), \end{aligned} \tag{20}$$

where $z = 2^{\frac{H(1-P_D)-H(P_F)}{P_F-P_D}}$. Note that the input distribution at the transmitter follows the Bernoulli distribution, owing to the pre-selected ON/OFF keying modulation method.

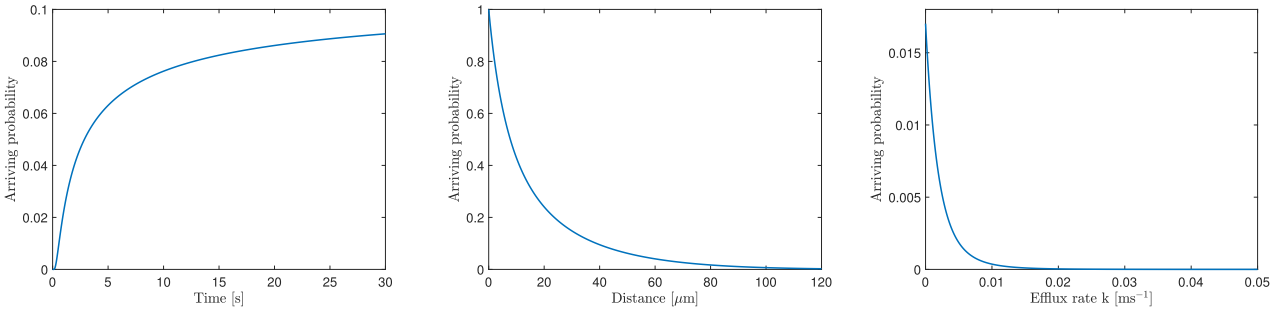

FIGURE 6. The arriving probabilities for potassium ions change with the time slot duration and efflux rate k: a) the arriving probabilities increase with T_d for $x = 80$ μm and $k = 0$; b) the arriving probabilities decrease with x for $T_d = 0.8$ s and $k = 0$; c) the arriving probabilities decrease with k for $T_d = 0.8$ s and $x = 80$ μm.

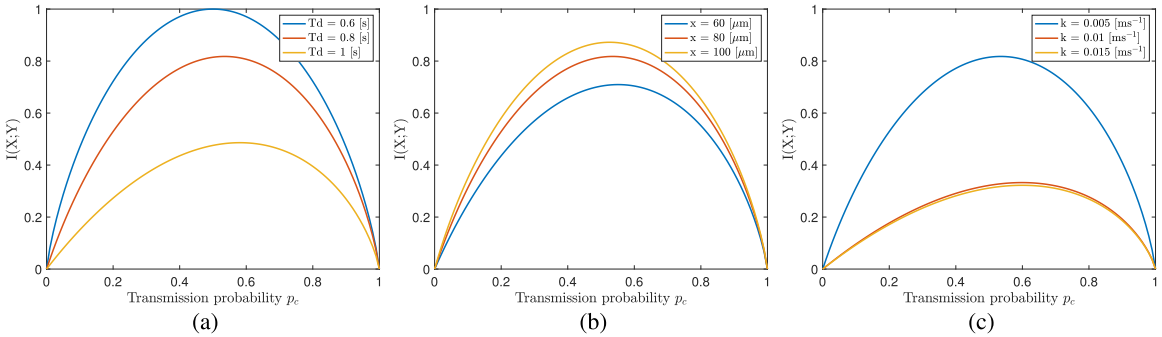

FIGURE 7. When the emitted potassium ions is 2×10^7, the channel mutual information changes with (a) the time slot duration ($k = 0.005$ ms^{-1} and $x = 80$ μm), (b) the propagation distance ($T_d = 0.8$ s and $k = 0.005$ ms^{-1}) and (c) the efflux rate ($T_d = 0.8$ s and $x = 80$ μm).

IV. NUMERICAL SIMULATION RESULTS

In this section, we present the numerical results from the computational simulations performed to characterize the potassium-based intracellular signaling in cardiomyocytes. Table 1 gives the primary parameters used in the simulation framework. The potential difference between the resting potential and the threshold potential is set to 24 mV. The potential difference between the resting potential and the maximum membrane potential is set to 124 mV. Therefore, according to (7), the threshold number of the injected potassium ions is $Q_{\text{th}} = 2.30100 \times 10^7$, and the maximum number of the injected potassium ions is $Q_{\text{max}} = 1.18885 \times 10^8$.

The time slot duration, propagation distance and efflux rate influence whether the potassium ions are successfully transmitted to the receiver at the observation points. The time slot duration could be set to reflect the cardiac cycle length. The propagation distance reflects the cell length. The efflux rate reflects the properties of the membrane, which is affected by the pathology of potassium channels and pumps on the membrane. The ions arriving probability thus changes with time slot duration, propagation distance and efflux rate, as shown in Figure 6. We infer that the ions arriving probability increases for higher values of the time slot duration, shorter propagation distance and smaller values of the efflux rate. Concerning the efflux rate, the arriving probabilities reach maximum when $k = 0$, which indicates a very low permeability of the cell membrane when no ions move out of the intracellular space. However, the arriving probability is still small even when $k = 0$, which indicates that only a few ions reach the receiver.

The time slot duration, propagation distance and efflux rate change the ions arriving probability and, therefore, impact the mutual information, as shown in Figure 7. The mutual

TABLE 1. Parameters used in the simulation framework.

Parameter	Meaning	Value
D	Diffusion coefficient of potassium ions	1.96 μm^2/ms
T_d	Time slot duration	0.8 s
n	Number of time slots	20
e	Elementary charge	1.60×10^{-19} C
$t_{1/2}$	Half-life cycle	130 ms
x	Propagation distance	80 μm
L	Length of the cardiomyocyte	100 μm
r	Radius of the cardiomyocyte	10 μm
C_{m}	Specific capacitance of the cardiomyocyte membrane	1 μm/cm^2
A_{cap}	Capacitive membrane area	1.534×10^4 cm^2
V_{rest}	Resting membrane potential	-84 mV
V_{th}	Threshold membrane potential	-60 mV
V_{max}	Maximum value of the membrane potential	~40 mV

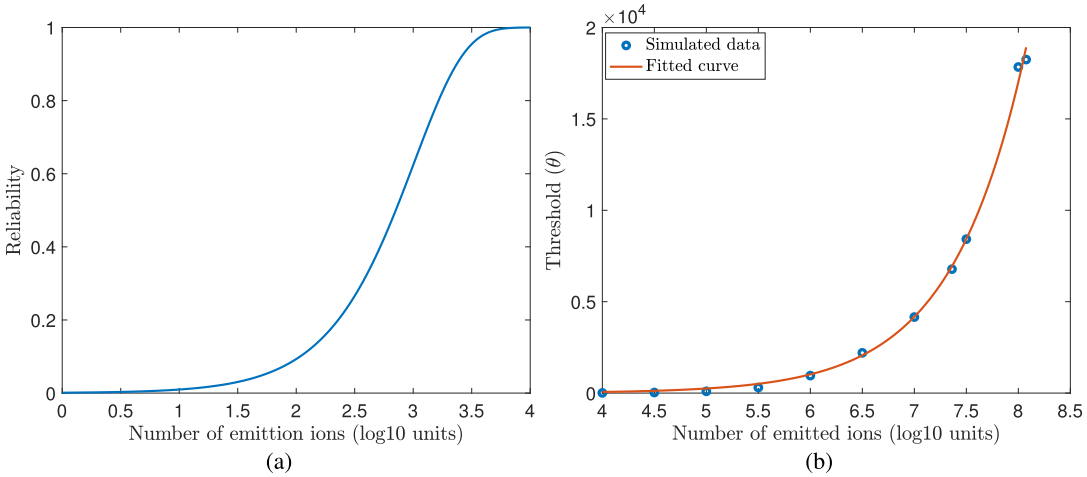

FIGURE 8. a) The reliability of at least one potassium ion to reach the receiver. b) The relation between the number of emitted ions and the detection threshold.

information, in turn, reflects how much information in transmitted, on average, through the potassium-based signaling (sub)-system. Although the arriving probabilities increase, the mutual information decreases when the time slot duration increases (Figure 7a) and the propagation distance decreases (Figure 7b). One explanation is that more error bits are received when the time slot is longer and propagation distance is shorter because of the ISI. Intuitively, the mutual information decreases when the efflux rate increases (Figure 7c) because less ions are received.

Further, we show the reliability of at least one of the emitted M ions to reach the receiver in Figure 8a. We observe that the reliability increases with the number of emitted ions without considering the efflux. The reliability almost reaches 1 when the transmitter emits more than 10^4 potassium ions.

However, the error probability could be very high when the transmitter emits 10^4 ions. In such scenarios, a dynamic detecting threshold should be deployed at the receiver. An inappropriate detecting threshold causes erroneous detections. For example, if the threshold is too high, the receiver may decode bit 0 when the transmitter sends bit 1 because the accumulated ions in the current time slot do not reach the threshold; conversely, if the threshold is too low, the receiver may decode bit 1 when the transmitter sends bit 0 because the accumulated ions from the previous time slots reach the threshold. We restrict the time slot duration $T_d = 0.8$ s, propagation distance $x = 80$ μm and efflux rate $k = 0.005$ ms^{-1} to find the relationship between the number of emitted ions and the optimal detecting threshold. This relation is shown in Figure 8b. We then vary the number of emitted potassium ions to test the error probabilities of the system, and select the detecting thresholds when the error probability has the lowest value. By using the fitting method, we yield the following expression

$$\theta = 0.2223 \exp\left[1.406 \log_{10} Q_0\right], \tag{21}$$

where Q_0 denotes the number of the emitted potassium ions from the transmitter, and θ denotes the corresponding optimal detecting threshold.

Regarding (21), we experimented with different curves to fit the simulated data. Only the exponential curve and the power curve have a reasonably good fit. We have, however, selected the exponential curve due to the following two reasons: 1) The exponential curve is commonly used in the literature. With the exponential curve fitting, the confidence bound was 95%, R-square (coefficient of determination) was 0.9974, and adjusted R-square was 0.9971. Both R-square and adjusted R-square normally take values less than or equal to 1, with a value closer to 1 indicating a better fit. 2) The exponential curve is a natural fit for the considered phenomenon. When there is a large number of transmitted potassium ions, the distribution of the received ions at the receiver can be approximated as a Poisson distribution [42]. This distribution belongs to the class of exponential families of distributions.

Finally, the number of emitted potassium ions affects the detecting threshold θ, which then impacts the mutual information and channel capacity. We infer how the channel capacity changes with the number of injected potassium ions according to (20). As shown in Figure 9, we observe that both the channel capacity at different propagation distances and the membrane potential increase when the number of emitted potassium ions increases.[2] The capacity reaches nearly 1 bit/s when the number of emitted ions is $Q_{\max} = 1.18885 \times 10^8$. The membrane potential then reaches nearly 40 mV. Practically though, the cell membrane reaches 40 mV with significantly less number of the emitted ions (i.e., Q_{th}) sufficient to bring the cell membrane to the threshold potential. When the number of injected ions is lower than Q_{th}, the cell membrane generates membrane potentials in the subthreshold range

[2]Here we assume that the capacitive membrane area A_{cap} in (5) does not change when the propagation distance changes.

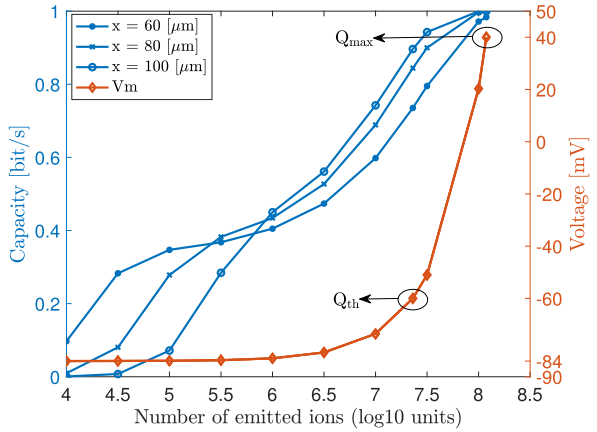

FIGURE 9. The potassium channel capacity at different propagation distances and the membrane potential as functions of the number of emitted potassium ions.

relevant for data transmission [7]. Within the subthreshold range, the maximum channel capacity is about 0.84 bit/s when the propagation distance $x = 80$ μm.

V. DISCUSSION AND CONCLUSION

In the presented study, we have explored the concept of Shannon's information capacity to analyze the propagation of potassium ions in the cardiomyocyte cytosol. The capacity is given by the maximum of the mutual information between the cellular compartment where potassium ions are injected and the cellular compartment where the potassium ions are counted. The maximization is taken with respect to the input distribution of the injected potassium ions. Since the potassium ions are theoretically injected either 1) for the creation of signals for communication of sensed data and/or commands between synthetic cells or capsules or 2) for the creation of missed action potentials, i.e., cardiomyocyte pacing, the concept of the information capacity helps in optimizing the ionic injection process.

The ions, such as potassium, sodium, chloride, calcium, etc., are dynamically exchanged between the intracellular- and extracellular space through specific ion channels [46]. The ions themselves do not interact with each other directly. However, their concentrations in the intracellular- and extracellular spaces affect the cellular activity which, in turn, affects the ionic concentration levels. Regarding potassium concentration relevant factors, we note that hydrogen potassium ATPase (H^+/K^+ ATPase) can cause a decrease or increase of potassium ions in cytosol depending on whether the hydrogen ion concentration increases or decreases extracellularly, respectively [47]. Moreover, sodium potassium ATPase (Na^+/K^+ ATPase) can extrude three sodium ions from the intracellular- to the extracellular- space and import two potassium ions from the extracellular space [48]. From this evidence, the probability of error of the considered binary channel seems to depend on both potassium ion dynamics and the impact of other ions at the receiver. However, since we restrict the cellular activity to the subthreshold regime, the membrane potential activity in a form of action potential has a limited impact on opening and closing of voltage-gated channels. As a consequence, action potentials will not activate voltage-gated potassium channels for exporting potassium ions from- or importing to the intracellular space [49], [50]. This reduces the modeling constraints.

Manipulating potassium ions is, from the practical perspective, one of the critical issues in the proposed concept, where highly specialized tools (e.g., for electrophoresis) should be designed. This problem has been out of the scope of the presented study. Besides, the simplified homogeneous channel for the propagation of potassium ions has been analytically described, unlike the heterogeneous channel in a form of complex cytosol where temperature and/or acid-base conditions, inter-organelle communication (including the endoplasmic reticulum and the microtubules network [51], [52]) and other ions complicate intracellular ionic diffusion. However, as an initial step in analyzing cellular excitation at the ionic level, we believe that this study offers underlying concepts which could be upgraded in the following phases.

As the additional future work, the results from the proposed potassium-based intracellular signaling model should be verified by in-vitro experiments. To this end, new and ultra-sensitive detection methods should be developed to track the movement and concentration of ions in various cellular compartments. Ultimately, noise sources from other obstacles in the cytosol should be thoroughly investigated.

REFERENCES

[1] E. Cingolani, J. I. Goldhaber, and E. Marbán, "Next-generation pacemakers: From small devices to biological pacemakers," *Nature Rev. Cardiol.*, vol. 15, no. 3, p. 139, 2018.

[2] A. Deplazes and M. Huppenbauer, "Synthetic organisms and living machines," *Syst. Synth. Biol.*, vol. 3, nos. 1–4, p. 55, 2009.

[3] P. Lu, M. Veletić, M. Laasmaa, M. Vendelin, W. E. Louch, P. S. Halvorsen, J. Bergsland, and I. Balasingham, "Multi-nodal nano-actuator pacemaker for energy-efficient stimulation of cardiomyocytes," *Nano Commun. Netw.*, vol. 22, Dec. 2019, Art. no. 100270.

[4] N. A. Ruhi and P. Bogdan, "Multiscale modeling of biological communication," in *Proc. IEEE Int. Conf. Commun. (ICC)*, Jun. 2015, pp. 1140–1145.

[5] D. Kilinc and O. B. Akan, "An information theoretical analysis of nanoscale molecular gap junction communication channel between cardiomyocytes," *IEEE Trans. Nanotechnol.*, vol. 12, no. 2, pp. 129–136, Mar. 2013.

[6] H. Ashikaga, J. Aguilar-Rodríguez, S. Gorsky, E. Lusczek, F. M. D. Marquitti, B. Thompson, D. Wu, and J. Garland, "Modelling the heart as a communication system," *J. Roy. Soc. Interface*, vol. 12, no. 105, 2015, Art. no. 20141201.

[7] P. Lu, M. Veletić, J. Bergsland, and I. Balasingham, "Theoretical aspects of resting-state cardiomyocyte communication for multi-nodal nano-actuator pacemakers," *Sensors*, vol. 20, no. 10, p. 2792, May 2020.

[8] E. Marbán, "Cardiac channelopathies," *Nature*, vol. 415, no. 6868, pp. 213–218, Jan. 2002.

[9] C. H. Luo and Y. Rudy, "A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction.," *Circulat. Res.*, vol. 68, no. 6, pp. 1501–1526, Jun. 1991.

[10] J. G. Restrepo and A. Karma, "Spatiotemporal intracellular calcium dynamics during cardiac alternans," *Chaos, Interdiscipl. J. Nonlinear Sci.*, vol. 19, no. 3, Sep. 2009, Art. no. 037115.

[11] R. L. DeHaan and H. G. Sachs, "Cell coupling in developing systems: The heart-cell paradigm," in *Current Topics in Developmental Biology*, vol. 7. Amsterdam, The Netherlands: Elsevier, 1972, pp. 193–228.

[12] S. Weidmann and A. L. Hodgkin, "The diffusion of radiopotassium across intercalated disks of mammalian cardiac muscle," *J. Physiol.*, vol. 187, no. 2, pp. 323–342, Nov. 1966.

[13] H. Haljamäe, B. Johansson, O. Jonsson, and H. Röcker, "The distribution of sodium, potassium and chloride in the smooth muscle of the rat portal vein," *Acta Physiologica Scandinavica*, vol. 78, no. 2, pp. 255–268, Feb. 1970.

[14] M. M. Civan, "Intracellular activities of sodium and potassium," *Amer. J. Physiol.-Renal Physiol.*, vol. 234, no. 4, pp. F261–F269, Apr. 1978.

[15] T. Nakano, T. Suda, M. Moore, R. Egashira, A. Enomoto, and K. Arima, "Molecular communication for nanomachines using intercellular calcium signaling," in *Proc. 5th IEEE Conf. Nanotechnol.*, 2005, pp. 478–481.

[16] I. Llatser, A. Cabellos-Aparicio, and E. Alarcon, "Networking challenges and principles in diffusion-based molecular communication," *IEEE Wireless Commun.*, vol. 19, no. 5, pp. 36–41, Oct. 2012.

[17] M. Kuran, T. Tugcu, and B. Edis, "Calcium signaling: Overview and research directions of a molecular communication paradigm," *IEEE Wireless Commun.*, vol. 19, no. 5, pp. 20–27, Oct. 2012.

[18] N. Farsad and A. Goldsmith, "A molecular communication system using acids, bases and hydrogen ions," in *Proc. IEEE 17th Int. Workshop Signal Process. Adv. Wireless Commun. (SPAWC)*, Jul. 2016, pp. 1–6.

[19] N. Farsad, H. B. Yilmaz, A. Eckford, C.-B. Chae, and W. Guo, "A comprehensive survey of recent advancements in molecular communication," *IEEE Commun. Surveys Tuts.*, vol. 18, no. 3, pp. 1887–1919, 3rd Quart., 2016.

[20] E. U. Thodesen, "Diffusion-based molecular communications in wireless pacemakers," M.S. thesis, NTNU, Trondheim, Norway, 2016.

[21] B. D. Unluturk and I. F. Akyildiz, "An End-to-End model of plant pheromone channel for long range molecular communication," *IEEE Trans. Nanobiosci.*, vol. 16, no. 1, pp. 11–20, Jan. 2017.

[22] I. Llatser, A. Cabellos-Aparicio, M. Pierobon, and E. Alarcon, "Detection techniques for diffusion-based molecular communication," *IEEE J. Sel. Areas Commun.*, vol. 31, no. 12, pp. 726–734, Dec. 2013.

[23] H. B. Yilmaz, A. C. Heren, T. Tugcu, and C.-B. Chae, "Three-dimensional channel characteristics for molecular communications with an absorbing receiver," *IEEE Commun. Lett.*, vol. 18, no. 6, pp. 929–932, Jun. 2014.

[24] A. Zare and A. Jamshidi, "Receiver design and performance analysis for pulse position modulation technique in diffusion-based molecular communication," *Nano Commun. Netw.*, vol. 21, Sep. 2019, Art. no. 100256.

[25] A. O. Kislal, H. B. Yilmaz, A. E. Pusane, and T. Tugcu, "ISI-aware channel code design for molecular communication via diffusion," *IEEE Trans. Nanobiosci.*, vol. 18, no. 2, pp. 205–213, Apr. 2019.

[26] A. Gohari, M. Mirmohseni, and M. Nasiri-Kenari, "Information theory of molecular communication: Directions and challenges," *IEEE Trans. Mol., Biol. Multi-Scale Commun.*, vol. 2, no. 2, pp. 120–142, Dec. 2016.

[27] H. Awan and C. T. Chou, "Molecular communications with molecular circuit-based transmitters and receivers," *IEEE Trans. Nanobiosci.*, vol. 18, no. 2, pp. 146–155, Apr. 2019.

[28] N. Abadi, A. A. Gohari, M. Mirmohseni, and M. Nasiri-Kenari, "Zero-error codes for multi-type molecular communication in random delay channel," in *Proc. Iran Workshop Commun. Inf. Theory (IWCIT)*, Apr. 2018, pp. 1–6.

[29] L. Cleemann and M. J. Gaughan, "Measurement of intracellular 42K diffusion in frog ventricular strips," *Pflügers Archiv Eur. J. Physiol.*, vol. 401, no. 1, pp. 101–103, May 1984.

[30] S.-M. Yu, S.-F. Lo, and T.-H.-D. Ho, "Source–sink communication: Regulated by hormone, nutrient, and stress cross-signaling," *Trends Plant Sci.*, vol. 20, no. 12, pp. 844–857, Dec. 2015.

[31] T. Nakano, A. W. Eckford, and T. Haraguchi, *Molecular Communication*. Cambridge, U.K.: Cambridge Univ. Press, 2013.

[32] P. Lu, Z. Wu, and B. Liu, "A vertical channel model of molecular communication and its test-bed," *EAI Endorsed Trans. Pervas. Health Technol.*, vol. 3, no. 9, Mar. 2017, Art. no. 152390.

[33] Y. Guo and W. T. Pu, "Cardiomyocyte maturation," *Circulat. Res.*, vol. 126, no. 8, pp. 1086–1106, Apr. 2020.

[34] W. DeMello, *Intercellular Communication*. Cham, Switzerland: Springer, 2013.

[35] C. Koch, *Biophysics of Computation: Information Processing in Single Neurons*. Oxford, U.K.: Oxford Univ. Press, 2004.

[36] C. H. Luo and Y. Rudy, "A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes.," *Circulat. Res.*, vol. 74, no. 6, pp. 1071–1096, Jun. 1994.

[37] R. Weingart, "The permeability to tetraethylammonium ions of the surface membrane and the intercalated disks of sheep and calf myocardium," *J. Physiol.*, vol. 240, no. 3, pp. 741–762, Aug. 1974.

[38] J. F. Lamb and J. A. S. McGuigan, "The efflux of potassium, sodium, chloride, calcium and sulphate ions and of sorbitol and glycerol during the cardiac cycle in frog's ventricle," *J. Physiol.*, vol. 195, no. 2, pp. 283–315, Mar. 1968.

[39] A. C. Heren, H. B. Yilmaz, C.-B. Chae, and T. Tugcu, "Effect of degradation in molecular communication: Impairment or enhancement?" *IEEE Trans. Mol., Biol. Multi-Scale Commun.*, vol. 1, no. 2, pp. 217–229, Jun. 2015.

[40] A. Moorhouse, "Membrane potential: Concepts," in *Encyclopedia of Cell Biology*, R. A. Bradshaw and P. D. Stahl, Eds. Waltham, MA, USA: Academic, 2016, pp. 218–236.

[41] T. Nakano, M. J. Moore, F. Wei, A. V. Vasilakos, and J. Shuai, "Molecular communication and networking: Opportunities and challenges," *IEEE Trans. Nanobiosci.*, vol. 11, no. 2, pp. 135–148, Jun. 2012.

[42] Z. Cheng, Y. Zhu, K. Chi, Y. Li, and M. Xia, "Capacity analysis for diffusive molecular communication with ISI channel," *Nano Commun. Netw.*, vol. 13, pp. 43–50, Sep. 2017.

[43] T. Nakano, Y. Okaie, and J.-Q. Liu, "Channel model and capacity analysis of molecular communication with brownian motion," *IEEE Commun. Lett.*, vol. 16, no. 6, pp. 797–800, Jun. 2012.

[44] H. B. Yilmaz, C.-B. Chae, B. Tepekule, and A. E. Pusane, "Arrival modeling and error analysis for molecular communication via diffusion with drift," in *Proc. 2nd Annu. Int. Conf. Nanosc. Comput. Commun. (NANOCOM)*, 2015, pp. 1–6.

[45] R. W. Yeung, *A First Course in Information Theory*. Cham, Switzerland: Springer, 2012.

[46] B. Arnold, C. A. Kaiser, H. Lodish, A. Amon, H. Ploegh, A. Bretscher, M. Krieger, and K. C. Martin, *Molecular Cell Biology*. San Francisco, CA, USA: Freeman, 2008.

[47] I. R. Driel and J. M. Callaghan, "Proton and potassium transport by H+/K+-ATPases," *Clin. Experim. Pharmacol. Physiol.*, vol. 22, no. 12, pp. 952–960, Dec. 1995.

[48] Z. Xie and A. Askari, "Na+ /K+ -ATPase as a signal transducer," *Eur. J. Biochem.*, vol. 269, no. 10, pp. 2434–2439, May 2002.

[49] F. Bezanilla, "Voltage-gated ion channels," in *Biological Membrane Ion Channels*. Cham, Switzerland: Springer, 2007, pp. 81–118.

[50] M. P. Mahaut-Smith, T. J. Rink, S. C. Collins, and S. O. Sage, "Voltage-gated potassium channels and the control of membrane potential in human platelets.," *J. Physiol.*, vol. 428, no. 1, pp. 723–735, Sep. 1990.

[51] N. Panayotis, A. Karpova, M. R. Kreutz, and M. Fainzilber, "Macromolecular transport in synapse to nucleus communication," *Trends Neurosciences*, vol. 38, no. 2, pp. 108–116, Feb. 2015.

[52] A. Enomoto, M. J. Moore, T. Suda, and K. Oiwa, "Design of self-organizing microtubule networks for molecular communication," *Nano Commun. Netw.*, vol. 2, no. 1, pp. 16–24, Mar. 2011.

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