

Article

A Three-Dimensional Cardiomyocyte-Based Sub-Threshold Cardiac Communication System

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Abstract

Diseases linked to abnormal cardiac electrical activity, such as arrhythmias and heart failure, are closely associated with impaired electrical signal conduction between cardiomyocytes. Existing research on nano-communication has primarily used simplified one-dimensional cellular models, which inadequately represent the complex structure and signal transmission dynamics of three-dimensional cardiomyocytes. This limitation hampers a comprehensive understanding of the mechanisms underlying these diseases at the microscale level. To overcome this, the present study developed a subthreshold cardiac communication system based on a three-dimensional cardiomyocyte model. By simulating signal propagation through coupled cell chains and utilizing on–off keying modulation for information encoding, the transmission performance of this system was systematically evaluated in a noisy environment. Under optimized conditions, the system achieved high-fidelity information transfer, and modulated noise levels can enhance signal quality through a random facilitation effect. This study offers a novel analytical framework for exploring the communication mechanisms of weak signals between cardiomyocytes and the pathophysiology of diseases associated with abnormal cardiac electrical activity.

Keywords: subthreshold communication; three-dimensional cardiomyocyte model; biological communication; physiological noise; channel capacity

1. Introduction

Cardiovascular diseases remain one of the leading causes of death worldwide, with a high mortality rate strongly linked to abnormal cellular signaling. The heart, as a highly coordinated organ, relies on synchronized electrical activity facilitated by a complex network of billions of cells to maintain its normal rhythm and pumping function [1,2]. Within this network, electrical coupling between cells is primarily mediated by gap junctions (GJs) formed by connexins, such as Connexin43. These nanoscale channels enable rapid diffusion of ions and small molecules between adjacent cells, ensuring efficient and smooth propagation of action potentials (APs) within the tissue [3–5]. Consequently, a comprehensive understanding of intercellular electrical signaling—particularly how signals reliably propagate and cooperate between cells—is essential for uncovering the pathophysiological mechanisms behind diseases like arrhythmias and heart failure [6,7]. However, traditional research has largely focused on APs, without systematically addressing the mechanisms underlying weak electrical signals (i.e., subthreshold membrane potentials) in intercellular communication. The low amplitude and susceptibility to interference of these signals



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present challenges for both experimental observation and theoretical analysis, creating a research bottleneck that limits our understanding of their potential role in cardiac activity and restricts deeper insights into disease processes at the microscale of electrical signals.

With the convergence of nanotechnology, biosensing, and ultra-low-power wireless communication, Body Area Networks (BANs) and their extension to the microscopic scale—Body Area Nano-networks (Nano-BANs)—are transforming life sciences research and healthcare monitoring [8–10]. Compared to macro BANs, Nano-BANs offer unique opportunities for real-time, in-situ monitoring and intervention in physiological activities at the cellular and subcellular levels. Functional nodes deployed at the nanoscale within biological tissues, even at the cellular level, enable this advanced capability. Figure 1 illustrates the structure and functional schematic of biological nano-networks, which facilitate dynamic monitoring of cells through nanoscale functional nodes within living organisms.

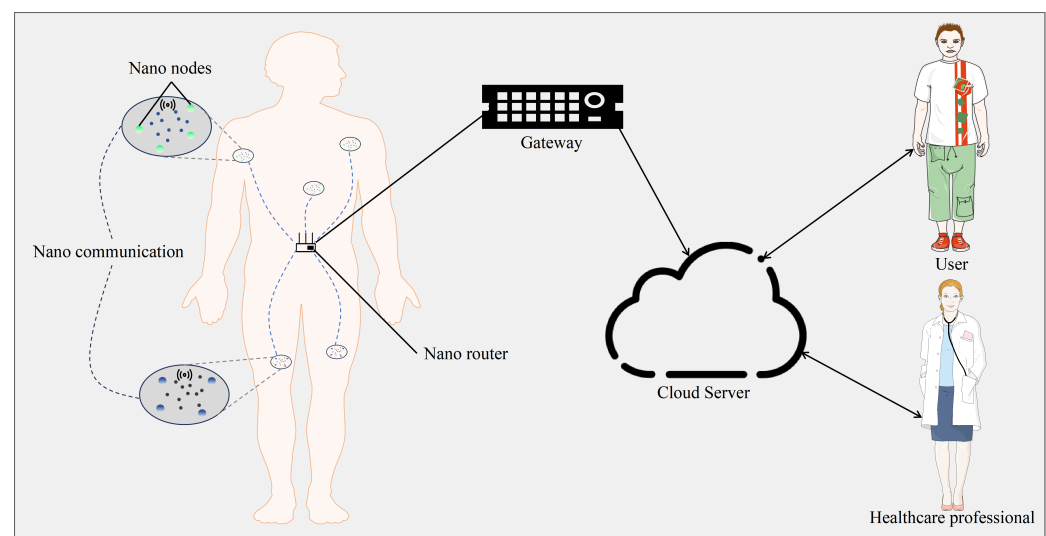


Figure 1. Schematic of the Biological Nano-Network. The figure is adapted from an existing image provided by Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

Moreover, emerging research fields such as nano-communication and molecular communication, which draw from principles of signal transmission in biological systems, aim to establish theoretical models and communication protocols for the exchange of information between nanodevices [11,12]. The central concept is to abstract processes like the diffusion of signaling molecules and electrochemical signal conduction within organisms into the components of communication systems—encoding, channeling, and decoding [13]. This engineering perspective not only offers novel ideas for designing biocompatible, low-energy implanted medical devices [14–16], but also provides researchers with a quantitative toolkit for analyzing and re-examining the inherent microscopic signaling mechanisms in biological systems from the viewpoint of information transmission.

By conceptualizing intercellular electrical signal transmission as a biological communication system and applying metrics from information theory and communication engineering for modeling and evaluation, it becomes possible to uncover patterns and anomalies in cardiac electrical activity, paving the way for a deeper understanding of cardiovascular diseases at the microscale of communication.

Despite the potential of applying nano-communication principles to the study of biological signal transmission, several critical challenges and limitations persist in researching subthreshold communication in cardiomyocytes. First, the models currently used lack sufficient complexity and dimensionality. Early studies, such as the work by Lu et al., were among the first to propose a subthreshold communication model based on resting-state

cardiomyocytes [12]. As illustrated in Figure 2, these studies demonstrated the feasibility of signal transmission between cells even without APs, highlighting its importance in cellular coordination. However, most of this research relies on one-dimensional (1D) cable theory or simplified cellular dynamic models. The heart is a complex three-dimensional (3D) organ, containing intricate subcellular structures like the T-tubule system, sarcoplasmic reticulum (SR) networks, and calcium (Ca) release units (CRUs) [17,18]. These 3D structural features significantly affect the spatial distribution of local ion concentrations and the dynamics of electrical signal generation and attenuation. While 1D models are computationally efficient, they fail to capture these 3D geometrical aspects and the resulting effects of signal propagation anisotropy and local coupling variations, potentially leading to inaccuracies in assessing the range and fidelity of subthreshold signals.

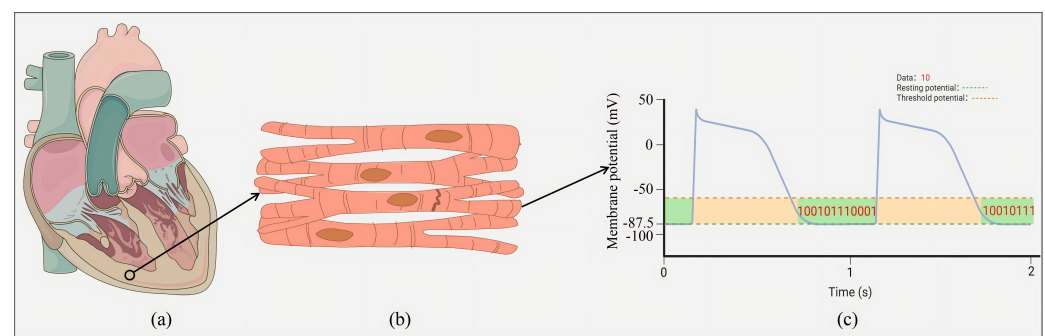


Figure 2. Hierarchical display of cardiomyocyte APs and subthreshold membrane potential communication. (a) Schematic of a longitudinal section of the heart. (b) Magnified cluster of cardiomyocytes. (c) Typical AP curve of single-cell membrane potential over time; the green dashed line represents the resting membrane potential, and the orange dashed line represents the threshold potential. Subthreshold membrane potential communication realizes signal transmission when the membrane potential lies between the two dashed lines [12]. The figure is adapted from an existing image provided by Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

Second, existing 3D model studies are often limited to single cells. Even when more complex 3D cardiomyocyte electrophysiological models are used, the focus of current research tends to remain on the simulation of single-cell electrical activity, such as Ca sparks and early afterdepolarizations [19–21]. However, systematic investigations into how subthreshold signals propagate through chains or networks of coupled 3D cardiomyocytes via GJs are still lacking. This creates a gap between detailed models of individual cells and the systemic analysis of multicellular communication, restricting a comprehensive understanding of intercellular interactions.

Third, quantitative assessments from the communication engineering perspective remain underdeveloped. The pioneering research by Kilinc and Akan, which views cardiomyocyte GJs as molecular communication channels and evaluates them using information-theoretic metrics, offers a valuable foundation for interdisciplinary research [22]. However, subsequent studies continue to face limitations in performance evaluation, often lacking a multidimensional framework for assessing communication performance. This deficiency makes it difficult to compare results across studies and limits the exploration of the efficiency and optimization potential of subthreshold communication.

Building on the current research status and existing challenges, this study proposes a novel paradigm: a subthreshold cardiac communication system based on 3D cardiomyocytes. This system conceptualizes the transmission of subthreshold signals between cardiomyocytes as a standard communication system, structured according to transmitter channels and receiver architecture. It enables the encoding and transmission of digital information within biological tissues. The framework will evaluate communication perfor-

mance through various methods to comprehensively reflect the information transmission characteristics among cardiomyocytes.

The core contributions of this study can be summarized in three key aspects:

- **Construction of a Subthreshold Communication System Framework Based on 3D Cardiomyocytes:** For the first time, complex 3D cardiomyocyte electrophysiological models are applied to the study of multicellular signal cascade propagation. A 1D coupled cell chain is established as a biological channel, and a complete communication system model is created, incorporating an on–off keying (OOK) transmitter, a noise channel, and a threshold detection receiver.
- **Development of a Multidimensional Standardized Performance Evaluation System:** This study introduces and integrates metrics such as bit error rate (BER), signal-to-noise ratio (SNR), and channel capacity to form a comprehensive framework for quantifying the quality, reliability, and theoretical limits of subthreshold communication.
- **Discovery and Analysis of Random Facilitation Effect:** For the first time, random facilitation effects are observed in subthreshold communication among cardiomyocytes. The study identifies the optimal noise window and provides a biophysical explanation for this counterintuitive phenomenon, where noise enhances signal transmission.

The remainder of this paper is organized as follows: Section 2 presents a detailed description of the communication system model based on 3D cardiomyocytes; Section 3 outlines the simulation setup and results analysis; Section 4 discusses the significance and limitations of the research findings; and Section 5 concludes the paper and suggests future research directions.

2. Model

This study establishes a subthreshold membrane potential communication system based on 3D cardiomyocytes. First, the electrophysiological characteristics of 3D cardiomyocytes are analyzed to serve as the biological medium for communication. Based on classical communication theory, a system aligned with standard communication paradigms is constructed to facilitate the encoding, transmission, and demodulation of subthreshold signals. Performance metrics—including BER, SNR, and channel capacity—are introduced to systematically evaluate the communication performance. Additionally, the impact of noise on signal transmission is investigated. This work provides a theoretical foundation for understanding the biophysical mechanisms of subthreshold cardiomyocyte communication, and highlights its potential applications in engineering disease detection.

2.1. Cardiomyocyte Electrophysiological Model

2.1.1. 3D Topological Structure

A single cardiomyocyte is modeled as a three-dimensional network of 20,000 Calcium Release Units (CRUs), as shown in Figure 3, where each CRU represents a functional dyadic unit comprising the cytosolic space, dyadic cleft, network sarcoplasmic reticulum (NSR), junctional sarcoplasmic reticulum (JSR), and associated ion channels [23]. While each cell internally features this 3D CRU architecture to capture complex intracellular Ca^{2+} dynamics, intercellular communication is achieved by coupling these 3D cell models into a one-dimensional chain via voltage diffusion through gap junctions (Section 2.2.2). This hybrid 3D/1D approach enables efficient simulation of signal propagation while preserving the physiological realism of intracellular calcium handling.

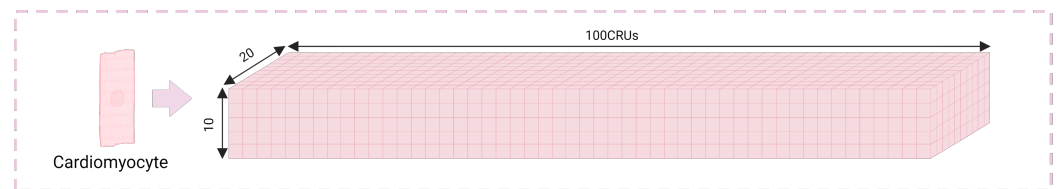


Figure 3. Geometric model of the 3D cardiomyocyte. Figure created with <https://BioRender.com>.

The CRUs are arranged according to the physiological spatial distribution of a cardiomyocyte. Specifically, the longitudinal dimension (100 CRUs) corresponds to the long axis of the cell, the transverse dimension (20 CRUs) corresponds to the cell width, and the depth dimension (10 CRUs) corresponds to the cell thickness. The CRUs are interconnected via diffusive coupling, forming a highly interconnected 3D network. This design not only aligns with the physiological characteristics of cardiomyocytes but also provides a solid physical foundation for the propagation of electrical signals.

2.1.2. Membrane Potential

The electrophysiological behavior of cardiomyocytes is simulated based on the 3D cardiomyocyte model. Operating within a reaction-diffusion framework, this model captures the bidirectional coupling between the CRU network and membrane ion currents. It includes a comprehensive set of core ion channel currents, such as the sodium (Na) channel current, L-type calcium (Ca) channel (LCC) current, and various potassium (K) channel currents (including the rapid and slow delayed rectifier K currents, fast and slow outward K currents). Additionally, the model incorporates slow inward currents and the Na-Ca exchanger (NCX) current, as well as intracellular processes like sarcoplasmic/endoplasmic reticulum Ca ATPase uptake, SR leakage, and buffering [24].

Compared to 1D models, the 3D structure better preserves micro-amplitude potential fluctuations and variations in time constants arising from channel stochasticity and spatial diffusion. This preservation prevents the attenuation of subthreshold responses, enabling a more accurate representation of the propagation characteristics of ion signals, including their attenuation and delay.

Assuming spatial uniformity of the membrane potential within each computational element (i.e., the isopotential cell assumption, where the cell length $\Delta x = 100 \mu\text{m}$ is treated as a single compartment), its temporal evolution is described by the following differential equation [23]:

$$C_m \frac{dV}{dt} = I_{ion} + I_{stim}, \quad (1)$$

where V denotes the membrane potential at time t , and C_m represents the membrane capacitance per unit area (specific values are listed in Table 1). I_{stim} is the applied external stimulus current, whereas I_{ion} represents the total current generated by various ion channels. These currents involve the transmembrane transport of Na^+ , Ca^{2+} , and K^+ , constituting the core drivers of membrane electrical activity, as expressed in the following equation:

$$I_{ion} = I_{Na} + I_{K1} + I_{Kr} + I_{Ks} + I_{to,f} + I_{to,s} + I_{NaK} + I_{Ca,L} + I_{NCX} + I_{bg}, \quad (2)$$

where I_{Na} is the Na current; I_{K1} is the inward rectifier K current; I_{Kr} and I_{Ks} are the rapid and slow components of the delayed rectifier K current, respectively; $I_{to,f}$ and $I_{to,s}$ are the fast and slow components of the transient outward K current; I_{NaK} is the Na-K pump current; $I_{Ca,L}$ is the LCC current; I_{NCX} is the NCX current; and I_{bg} is the background Ca current.

Table 1. Experimental Parameters.

Parameter	Definition	Value
D_{cell}	Diffusion coefficient	$0.0005 \text{ cm}^2/\text{ms}$
C_m	Cardiomyocyte membrane capacitance	$1 \text{ }\mu\text{F}/\text{cm}^2$
σ	Cardiomyocyte voltage noise intensity	0.0194 mV
α	Noise scaling factor	$0 - 0.5$
V_{th}	Voltage signal detection threshold	-87.4975 mV
t_{delay}	Propagation delay	5 ms
T_{bit}	Time slot	200 ms
Δx	Distance step size	$100 \text{ }\mu\text{m}$

2.2. Transformation to Communication Engineering Model

This study proposes a modeling approach for a communication system based on 3D cardiomyocytes. The overall framework consists of three components: the transmitter, the channel, and the receiver, as illustrated in Figure 4. In the context of cardiac pathology, the core information transmitted by this system involves physiological data related to myocardial conditions, such as ventricular contraction abnormalities.

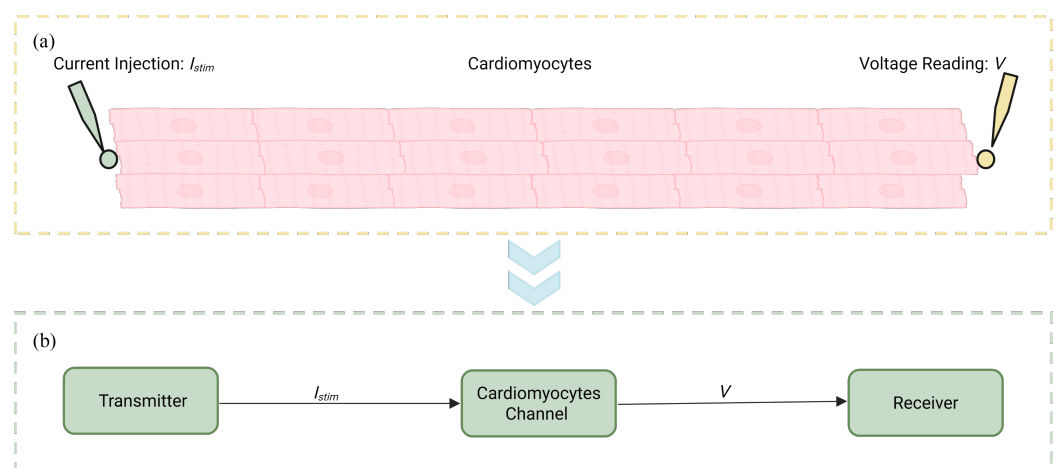


Figure 4. Overall modeling framework of the 3D cardiomyocyte-based communication system (comprising the transmitter, channel, and receiver). (a) In the 3D cardiomyocyte-based communication system, the transmitter nano-actuator injects a stimulation current (I_{stim}) via a patch attached to a specific region of the cardiomyocyte, inducing cellular depolarization. The channel is composed of 3D cardiomyocytes connected in series, and the receiver nano-actuator records the membrane potential (V) of the target cell through a corresponding patch. (b) The system is modeled as equivalent to a classical communication model, consisting of a signal transmitter, a cardiomyocyte channel, and a receiver, facilitating information transmission within biological tissues. Figure created with <https://BioRender.com>.

At the transmitter, a nano-actuator encodes the physiological data into a digital bit stream, which is then modulated into a specific current stimulation sequence. This stimulus is applied via a patch attached to a designated region of the transmitting cardiomyocyte. The stimulation intensity is carefully controlled to ensure that the peak membrane potential remains below the AP threshold. This ensures that cardiomyocyte contraction is not triggered, allowing the directional transmission of physiological information using only subthreshold membrane potential signals.

The communication channel is constructed as a 1D chain structure composed of multiple 3D cardiomyocyte model units, simulating the cascade conduction characteristics of signals within myocardial tissue. Adjacent cardiomyocyte units are electrically coupled

via physiologically driven GJs, ensuring efficient and directional transfer of intercellular voltage signals.

At the receiver, a nano-actuator is placed at the end of the cellular chain. By attaching to a specific region of the receiving cardiomyocyte, it performs real-time acquisition and demodulation of the membrane potential signals. A threshold detection mechanism is employed: if the detected membrane potential exceeds a preset threshold, it is interpreted as information bit 1; otherwise, it is interpreted as bit 0. Finally, the demodulated bit stream is reconstructed into the original physiological information, providing critical data for the precise detection and analysis of diseases.

2.2.1. Transmitter

In the subthreshold cardiomyocyte communication system, the transmitter node's core function is to encode, modulate, and initiate the communication signal. Specifically, physiological information related to myocardial pathology is first encoded into a binary bit stream, which is then modulated into a sequence of stimulation currents. These currents are applied via a patch attached to a designated region of the first cardiomyocyte. The stimulation induces a minor depolarization response, generating a subthreshold membrane potential that enables the subsequent cascade propagation of electrical signals between cardiomyocytes.

The transmitter's functionality is enabled by a nano-actuator within a multi-node nano-actuator pacemaker network [12]. While these nano-actuators offer various clinical capabilities, including pacing, communication, and collaborative regulation, this study focuses their role in communication. The device incorporates three core functional modules: a microelectrode module, a signal processing module, and an energy module. These modules comprehensively address the three essential components required by the transmitter—electrical signal encoding/modulation, stimulation signal generation/control, and central processing—forming a closed functional loop.

The microelectrode module serves as the physical interface between the transmitter and the cardiomyocyte, acting as the unit responsible for electrical signal generation and transmission. Designed with a direct-attachment structure, it forms a tight interface with specific regions of the cardiomyocyte membrane, minimizing energy loss during current transmission and ensuring precise injection of stimulation currents for communication. When the current is injected through the microelectrode, it moderately activates the corresponding ion channels within the cardiomyocyte, converting the current signal into membrane potential fluctuations. These fluctuations, as the information carriers in the system, complete the signal conversion process from the artificial device to the biological channel.

The signal processing module functions both as the stimulation signal generation control unit and the central processing unit. For signal generation, the module employs a preset encoding scheme to convert the physiological information into a specific sequence of stimulation currents, effectively mapping the information onto the signal carrier and providing a standardized source for output. In terms of central processing, the module regulates the amplitude, duration, and timing of the stimulation current. Precise control of these parameters ensures that the current injected into the cardiomyocyte stays strictly within the subthreshold range, preventing signal distortion due to superposition, and thereby ensuring the precision and stability of information transmission.

The energy module supports the continuous operation of the transmitter, with core functions including energy storage and on-demand output. Featuring a low-power design, the module dynamically provides power matched to the injection requirements of the microelectrode module and the encoding regulation needs of the signal processing module. This approach not only meets the energy consumption demands of the communication

process but also protects cardiomyocytes from potential damage due to excessive power. Moreover, it aligns with the core requirement for low energy consumption in implantable medical devices, ensuring sustained energy security for long-term stable operation.

In this study, OOK modulation is employed at the transmitter [25]. To transmit a binary bit 1, the nano-actuator generates a stimulation current; to transmit a binary bit 0, no current stimulation is applied. The corresponding current expression is as follows:

$$I_{stim} = \begin{cases} I_{exist}, & \text{if bit is 1,} \\ I_{none}, & \text{if bit is 0,} \end{cases} \quad (3)$$

where I_{exist} denotes the presence of stimulation current, and I_{none} denotes the absence of stimulation current.

2.2.2. Channel

As the transmission medium connecting the transmitter and receiver in the subthreshold communication system, the channel's core function is to enable the cascade transmission of electrical signals between cardiomyocytes. In this study, a 1D cell chain is constructed by coupling multiple 3D cardiomyocyte models to simulate the spatial propagation characteristics of signals within real myocardial tissue. Each 3D cardiomyocyte model acts as a node, connected to its neighboring cells via physiological GJs. Intercellular coupling is mediated exclusively through voltage diffusion; calcium dynamics remain confined within each individual cell. In functional cardiomyocytes (e.g., ventricular myocytes), these GJs are primarily composed of Connexin43 [26]. These protein-formed nanoscale channels provide the structural foundation for the efficient transfer of intercellular electrical signals, ensuring the propagation of membrane potential signals across cells through ionic coupling.

During signal transmission within the channel, the cardiomyocyte serves as the biological medium where internal ion chemical reactions and diffusion mechanisms jointly drive signal transfer. When the stimulation current injected at the transmitter activates the cardiomyocyte's ion channels, transmembrane fluxes of Na^+ , Ca^{2+} , and K^+ generate ionic currents. These ions are transferred to neighboring cells via diffusive action through GJs, progressively propagating the electrical signal from the transmitter side to the receiver side, completing the spatial conduction of the signal within the channel.

To quantitatively describe the spatiotemporal evolution of electrical signals in the channel, a reaction–diffusion equation is used to model signal propagation. This equation incorporates both the reaction process (changes in membrane potential due to transmembrane ion currents and external stimulation currents) and the diffusion process (the spatial propagation of electrical signals via intercellular coupling).

Considering factors such as stochastic ion channel openings, cell membrane noise, and the uncertainty of external stimuli in actual cardiomyocytes, a stochastic noise term, $\alpha\sigma\eta(x, t)$, is introduced into the reaction–diffusion framework to account for membrane potential fluctuations caused by microscopic stochasticity. Here, $\eta(x, t)$ represents Gaussian white noise with a mean of 0 and a variance of 1, reflecting the statistical characteristics of ion channel stochastic switching events. σ denotes the noise intensity, determined from empirical measurements of voltage noise during cardiomyocyte APs, as reported by Tanskanen et al. [27]. α serves as a scaling factor to adjust the noise intensity based on different physiological states. The choice of the Gaussian white noise model assumes that ion channel stochastic switching events approximate a Poisson process, with their superposition approximating a Gaussian distribution under the Central Limit Theorem. This ensures statistical validity while enhancing the computational feasibility and theoretical consistency of the model.

Incorporating these factors, the specific form of the equation is as follows:

$$\frac{\partial V}{\partial t} = D_{\text{cell}} \frac{\partial^2 V}{\partial x^2} + \frac{1}{C_m} (I_{\text{ion}} + I_{\text{stim}}) + \alpha \sigma \eta(x, t), \quad (4)$$

where V denotes the membrane potential at position x and time t , D_{cell} represents the effective diffusion coefficient of electrical signals between cardiomyocytes. This coefficient characterizes the strength of intercellular electrical coupling and is proportional to the conductance of the GJs. The value of this coefficient is based on the research results of Liu et al. (Table 1) [28].

During the cardiomyocyte resting phase, the majority of Na channels and LCCs are in an inactivated or closed state, significantly attenuating ion channel activity. Thus, the endogenous noise level during the resting phase is lower compared to the AP phase. This noise modeling approach provides a parametric foundation for further investigation into how noise modulation affects subthreshold signal transmission performance.

To facilitate subsequent numerical simulation and result reproduction, the finite difference method is employed to discretize the continuous reaction-diffusion equation. This transforms continuous changes in time and space into iterative updates of discrete nodes. In the discretization process, the time dimension is divided into n time steps, and the space dimension is divided into i position nodes (each node corresponding to a 3D cardiomyocyte). The resulting discrete update formula for membrane potential is:

$$V_i^{n+1} = V_i^n + \Delta t \left[D_{\text{cell}} \frac{V_{i+1}^n - 2V_i^n + V_{i-1}^n}{\Delta x^2} + \frac{1}{C_m} (I_{\text{ion},i}^n + I_{\text{stim},i}^n) \right] + \alpha \sigma \sqrt{\Delta t} N(0, 1), \quad (5)$$

where Δt is the time step, and Δx represents the distance step, corresponding to the length of the cardiomyocyte [23] (specific values are listed in Table 1). $N(0, 1)$ is a standard normal distribution random variable (corresponding to $\eta(x, t)$ in the continuous model), and $\sqrt{\Delta t}$ serves as the time discretization coefficient for the noise term, ensuring that the statistical characteristics of the noise after discretization remain consistent with the continuous model. This discretized model can be directly applied to simulate and calculate membrane potential changes at various positions in the cell chain under different conditions, providing a quantitative basis for evaluating subsequent communication performance.

2.2.3. Receiver

In the subthreshold cardiomyocyte communication system, the receiver is designed to detect bio-electrical signals and restore the transmitted information. Its core function involves capturing membrane potential signals at the end of the channel using a high-sensitivity microelectrode array, followed by precise detection and decoding via a threshold detection algorithm to reconstruct the originally transmitted physiological information related to myocardial pathology.

The realization of the receiver's functions relies on the nano-actuator within the multi-node nano-actuator pacemaker network [12]. In accordance with the receiver's communication requirements, its core components are divided into two units: the subthreshold membrane potential signal detection unit and the signal demodulation and physiological information restoration unit. These components are supported by an energy module to ensure continuous operation, forming a functional closed loop from signal capture to the output of physiological information.

The signal detection module, as the subthreshold membrane potential signal detection unit, captures subthreshold signals at the channel's terminus. It employs high-sensitivity,

attachable microelectrodes as the detection interface to acquire minute fluctuations in cardiomyocyte membrane potential in real time. The cardiomyocyte at the end of the channel receives upstream subthreshold signals via GJs, triggering mild ion channel activation and generating membrane potential perturbations. The microelectrode converts these perturbations into quantifiable electrical signal data, providing clear raw input for subsequent demodulation.

The signal processing module is responsible for signal demodulation and the restoration of physiological information. In line with the OOK modulation scheme used at the transmitter, this module demodulates the signal via threshold decision. The receiver nano-actuator compares the sampled membrane potential (V_{recv}) with a preset threshold (V_{th}) to demodulate the signal:

$$\text{bit} = \begin{cases} 0, & \text{if } V_{\text{recv}} < V_{\text{th}}, \\ 1, & \text{if } V_{\text{recv}} \geq V_{\text{th}}. \end{cases} \quad (6)$$

In this equation, the predefined threshold V_{th} is established based on the difference between the defined resting membrane potential and the signal levels capturable by current high-sensitivity electrophysiological instruments. Notably, state-of-the-art high-performance microelectrodes are capable of measuring potentials as small as 0.0025 mV [29] (specific values are listed in Table 1).

For the j -th bit, the sampling time is defined as:

$$t_j = j \cdot T_{\text{bit}} + t_{\text{delay}}, \quad (7)$$

where T_{bit} is the bit period and t_{delay} is the propagation delay (specific values are listed in Table 1). By combining the membrane potential at the sampling time with the threshold definition, the receiver nano-actuator can effectively distinguish whether the received signal corresponds to a bit 1 or bit 0.

2.2.4. Maximum Transmission Distance

The maximum transmission distance (MTD) serves as the core theoretical metric for the spatial performance of the cardiomyocyte communication system. It is defined as the farthest cellular position along the 1D cardiomyocyte chain where the signal can be reliably distinguished. Essentially, it reflects the limiting distance at which the subthreshold membrane potential signal, due to attenuation during propagation, becomes insufficient for reliable detection. This metric provides a theoretical foundation for designing the system's spatial coverage and optimizing parameters.

From a theoretical standpoint, deriving the MTD requires combining the signal attenuation laws of the channel model with the decision criteria of the receiver. In the channel model based on the reaction–diffusion equation (Equation (4)), the subthreshold membrane potential signal progressively attenuates as the propagation distance increases. The rate of attenuation is determined by the intercellular diffusion coefficient, membrane capacitance, and ionic currents: a larger D_{cell} indicates stronger intercellular electrical coupling and slower signal attenuation; whereas components within I_{ion} , such as I_{K1} , accelerate the restoration of membrane potential to the resting state, exacerbating signal decay at distal ends. When the signal propagates to a specific cell, if its membrane potential V_i (the potential of the i -th cell) falls below the receiver's preset detection threshold, that cell cannot perform a reliable decision. The position of this cell marks the boundary of the MTD.

To quantitatively characterize signal detectability at each cellular position, a characteristic function a_i is introduced to represent the response characteristics of the i -th cell within a bit period. This function reflects the coupling properties of the signal in both time and space domains: when the membrane potential of the cell at the sampling instant satisfies

$V_i^n \geq V_{th}$, a_i is defined as 1, indicating that a valid threshold response is detected within the bit period; if the potential remains below V_{th} at the sampling instant, a_i is 0, indicating the cell cannot effectively determine the presence of the signal.

Based on this, the MTD S can be defined as follows:

$$S = \max \left(\sum_{i=0}^X a_i \begin{cases} 1, & V_i^n \geq V_{th} \\ 0, & V_i^n < V_{th} \end{cases} \right), \quad (8)$$

where X is the total length of the cell chain. The term $\sum_{i=0}^X a_i$ represents the total sum of cells capable of detecting the signal starting from the transmitter (the 0-th cell), and $\max(\cdot)$ takes the maximum value of this sum, indicating the index of the furthest cell that the system can cover. The calculation process for the MTD is illustrated in Figure 5.

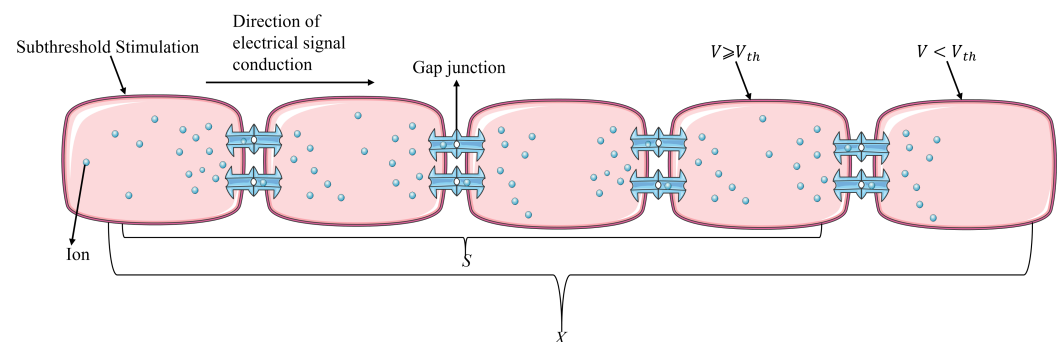


Figure 5. Schematic illustration of the maximum transmission distance calculation process. S denotes the maximum transmission distance, and X represents the total length of the cell chain. The figure is adapted from an existing image provided by Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

Based on the reaction-diffusion channel model, the dependence of the MTD S on the stimulation current I_{stim} can be theoretically analyzed as follows. First, from Equation (1) ($C_m dV/dt = I_{ion} + I_{stim}$), a larger I_{stim} produces a proportionally larger initial depolarization amplitude $\Delta V_0 \propto I_{stim}/g_{eff}$ at the first cell, where g_{eff} is the effective membrane conductance near the resting potential. This larger initial depolarization translates into a stronger signal at downstream cells after spatial attenuation, thereby increasing the number of cells i for which the sampled membrane potential V_i^n exceeds the detection threshold V_{th} . Consequently, S is expected to increase monotonically with I_{stim} .

Second, the saturation behavior can be understood from the interplay between intercellular coupling and membrane currents. The spatial attenuation of the signal is governed by the effective electrotonic length constant $\lambda \propto \sqrt{D_{cell}/g_{eff}}$, which depends on both the intercellular diffusion coefficient D_{cell} and the membrane conductance g_{eff} . As I_{stim} increases, the signal reaches more distant cells, but the background inward rectifier potassium current I_{K1} acts as a strong restorative force that rapidly drives the membrane potential back toward V_{rest} , limiting further propagation regardless of how large I_{stim} becomes. This physical ceiling imposed by the finite λ predicts that $S(I_{stim})$ exhibits nonlinear monotonic growth with asymptotic saturation rather than unbounded increase. The experimental results in Section 3.1.1 confirm this prediction.

2.3. Performance Evaluation

To evaluate the information transmission efficiency of our proposed 3D cardiomyocyte-based communication system under subthreshold membrane potential communication, this paper primarily adopts three typical engineering communication metrics: channel capacity (characterized by mutual information $I(X;Y)$), SNR, and BER. These metrics

comprehensively reflect signal amplitude attenuation, decision errors, and theoretical throughput capabilities under given noise conditions. In the simulation experiments, the BER was calculated by determining the ratio of decision errors at each bit decision point, distinguishing between the false positive rate (FPR) and the false negative rate (FNR). The SNR was evaluated using the root mean square (RMS) deviation method, defined as the ratio of the signal deviation from the resting potential to the noise. Channel capacity was computed by maximizing the system's mutual information $I(X; Y)$, employing a grid search with 1000 input probability points for precise numerical optimization.

2.3.1. Mutual Information and Channel Capacity

Channel capacity is the core theoretical limit of a communication system [30], defining the maximum amount of information that can be reliably transmitted per unit of time under specific noise conditions. For a binary asymmetric channel [31], let the input random variable be $X \in \{0, 1\}$ and the output random variable be $Y \in \{0, 1\}$. The transition probability matrix is given by:

$$P(Y|X) = \begin{pmatrix} 1-a & a \\ b & 1-b \end{pmatrix}, \quad (9)$$

where $a = P(Y = 1|X = 0)$ represents the probability of transmitting a 0 but detecting a 1 (false positive), and $b = P(Y = 0|X = 1)$ represents the probability of transmitting a 1 but detecting a 0 (false negative).

Mutual information $I(X; Y)$ is defined as:

$$I(X; Y) = H(Y) - H(Y|X). \quad (10)$$

where the entropy function $H(Y)$ is:

$$H(Y) = - \sum_y P(y) \log_2 P(y). \quad (11)$$

The conditional entropy $H(Y|X)$ is:

$$H(Y|X) = - \sum_{x,y} P(x, y) \log_2 P(y|x). \quad (12)$$

For this communication system, assuming the input probability $P(X = 0) = p$, then:

$$P(Y = 0) = p(1-a) + (1-p)b, \quad (13)$$

$$P(Y = 1) = pa + (1-p)(1-b). \quad (14)$$

The conditional entropy can be expressed as:

$$H(Y|X) = pH_{bin}(a) + (1-p)H_{bin}(b). \quad (15)$$

where the binary entropy function $H_{bin}(x)$ is:

$$H_{bin}(x) = -x \log_2(x) - (1-x) \log_2(1-x). \quad (16)$$

Channel capacity C is defined as the maximum value of mutual information:

$$C = \max_p I(X; Y). \quad (17)$$

In the experiments, the transition probabilities a and b are estimated via the Monte Carlo method. The optimal input distribution is searched within the range $p \in [0, 1]$ to calculate the channel capacity under varying noise intensities. Specifically, for the channel capacity experiments, a grid search with 1000 uniformly distributed values of p is employed to ensure the identification of the global optimal solution.

2.3.2. Signal-to-Noise Ratio

SNR is a key metric for evaluating signal quality, reflecting the intensity of the useful signal relative to the noise. For the subthreshold membrane potential communication system, we define SNR based on the RMS value.

For the i -th cell, the membrane potential deviation within the time window $[t_1, t_2]$ is defined as:

$$\Delta V_i(t) = V_i(t) - V_{rest}, \quad (18)$$

where V_{rest} is the resting membrane potential of the cardiomyocyte.

The signal component (characterized by the RMS value) when transmitting a bit 1 is defined as:

$$V_{signal,i} = \sqrt{\frac{1}{N_1} \sum_{k=1}^{N_1} \left(\frac{1}{T} \int_{t_1}^{t_2} \Delta V_i^{(k)}(t)^2 dt \right)}. \quad (19)$$

The noise component (characterized by the RMS value) when transmitting a bit 0 is defined as:

$$V_{noise,i} = \sqrt{\frac{1}{N_0} \sum_{k=1}^{N_0} \left(\frac{1}{T} \int_{t_1}^{t_2} \Delta V_i^{(k)}(t)^2 dt \right)}, \quad (20)$$

where N_1 and N_0 represent the number of transmitted 1 and 0 bits, respectively, and $T = t_2 - t_1$ is the length of the sampling window.

The SNR is defined as the squared ratio of the signal component to the noise component (equivalent to the power ratio):

$$\text{SNR}_i = \left(\frac{V_{signal,i}}{V_{noise,i}} \right)^2. \quad (21)$$

Expressed in decibels (dB):

$$\text{SNR}_{dB,i} = 10 \log_{10}(\text{SNR}_i). \quad (22)$$

2.3.3. Bit Error Rate

BER serves as a direct metric for the reliability of a communication system, defined as the ratio of the number of erroneously received bits to the total number of transmitted bits:

$$\text{BER} = \frac{N_{error}}{N_{total}} = \frac{N_a + N_b}{N_{total}}, \quad (23)$$

where N_a denotes the number of $0 \rightarrow 1$ errors, N_b denotes the number of $1 \rightarrow 0$ errors, and N_{total} represents the total number of transmitted bits.

3. Simulation Experiments and Result Analysis

All simulations were performed using a custom CUDA C++ implementation [23,24,28] executed on an NVIDIA GPU. The numerical integration of the stochastic reaction–diffusion equation (Equation (5)) employed the explicit forward Euler method with operator splitting between the deterministic reaction–diffusion terms and the stochastic noise term [32].

Data analysis and figure generation were conducted using Python (version 3.10.9, NumPy version 1.23.5, Pandas version 1.5.3, Matplotlib version 3.7.0).

In the simulation experiments, the initial membrane potential was set to the resting potential V_{rest} , specifically -87.5 mV, providing a larger dynamic range for current stimulation during data transmission. With the AP threshold of -60 mV, the effective range of membrane potential fluctuation induced by the stimulation current reaches 27.5 mV [12]. Considering the propagation characteristics of subthreshold membrane potentials, a bit rate of 5 bit/s was selected [12] to prevent signal distortion due to superposition at higher rates while avoiding time resource waste at excessively low rates, all within the available time window of ventricular diastole. Additionally, a propagation delay parameter, t_{delay} , was introduced to the bit decision timing to account for the time required for the subthreshold membrane potential to propagate along the cell chain. Under the 1D cell chain and stimulation intensity conditions established in this study, this delay ensures that the signal waveform reaches the receiver and achieves a steady-state response, thus avoiding decision errors from premature sampling.

The core parameter configuration for the simulation experiments was systematically tuned and verified to ensure the stability and reproducibility of the model within the subthreshold communication environment. The specific parameter settings are presented in Table 1. The experimental design employed a rigorous randomization strategy within a Monte Carlo framework. The Mersenne Twister pseudo-random number generator was used to produce high-quality random bit sequences, ensuring an equiprobable occurrence of binary 0 and 1. To minimize the impact of stochastic effects on the results, the experiment generated random information sequences containing 1000 bits.

3.1. Evaluation of Signal Propagation Characteristics

3.1.1. Analysis of Maximum Transmission Distance

To validate the theoretical predictions presented in Section 2, we systematically evaluated the maximum reliable transmission distance of the signal under varying stimulation intensities to characterize the spatial propagation limits of the subthreshold membrane potential communication system. The experimental results, shown in Figure 6, align closely with the theoretical predictions: as the stimulation current increases from $5 \mu\text{A}/\text{cm}^2$ to $35 \mu\text{A}/\text{cm}^2$, the MTD increases monotonically from 11 cells to 18 cells; as the current further increases from $35 \mu\text{A}/\text{cm}^2$ to $75 \mu\text{A}/\text{cm}^2$, the MTD increases monotonically from 18 to 22 cells. These results highlight distinct propagation threshold effects and saturation characteristics within the system: when the stimulation intensity is below $10 \mu\text{A}/\text{cm}^2$, the signal propagation distance is severely restricted, while stimulation intensities exceeding $35 \mu\text{A}/\text{cm}^2$ lead to a saturation in the propagation distance, which ultimately reaches a limit of approximately 22 cells. This saturation behavior confirms the theoretical analysis, reflecting intrinsic limitations imposed by intercellular coupling strength (D_{cell}) and membrane ionic current dynamics (I_{ion}). These findings delineate the boundaries of the system's spatial propagation capabilities, providing critical parameters for power consumption and layout design in implantable devices.

To further characterize the factors governing the spatial propagation limits, we conducted a two-dimensional parameter sweep of the MTD across the $(I_{\text{stim}}, D_{\text{cell}})$ parameter space. Under the same noise-free conditions as Figure 6, I_{stim} was varied from 5 to $75 \mu\text{A}/\text{cm}^2$ and D_{cell} from 0.0001 to $0.005 \text{ cm}^2/\text{ms}$. The resulting MTD map, presented as a heatmap in Figure 7, reveals two distinct propagation regimes. At low I_{stim} (5 – $20 \mu\text{A}/\text{cm}^2$), the MTD increases monotonically with both I_{stim} and D_{cell} , consistent with passive cable-like attenuation. At high I_{stim} ($\geq 45 \mu\text{A}/\text{cm}^2$), for $D_{\text{cell}} \geq 0.0005 \text{ cm}^2/\text{ms}$ the signal saturates the 20-cell chain at moderate stimulation, whereas at very weak cou-

pling ($D_{\text{cell}} = 0.0001 \text{ cm}^2/\text{ms}$) the MTD exhibits an abrupt jump from 10 to 20 cells between $I_{\text{stim}} = 45$ and $55 \mu\text{A}/\text{cm}^2$, suggesting a nonlinear threshold-crossing phenomenon. Notably, at intermediate coupling strengths ($D_{\text{cell}} = 0.0002 \text{ cm}^2/\text{ms}$), the MTD at high I_{stim} is lower than at the weakest coupling—the coupling is strong enough to suppress the regenerative threshold effect but still too weak for efficient passive propagation to the chain terminus. This non-monotonic transition highlights the complex interplay between local depolarization dynamics and intercellular coupling in determining the effective communication range.

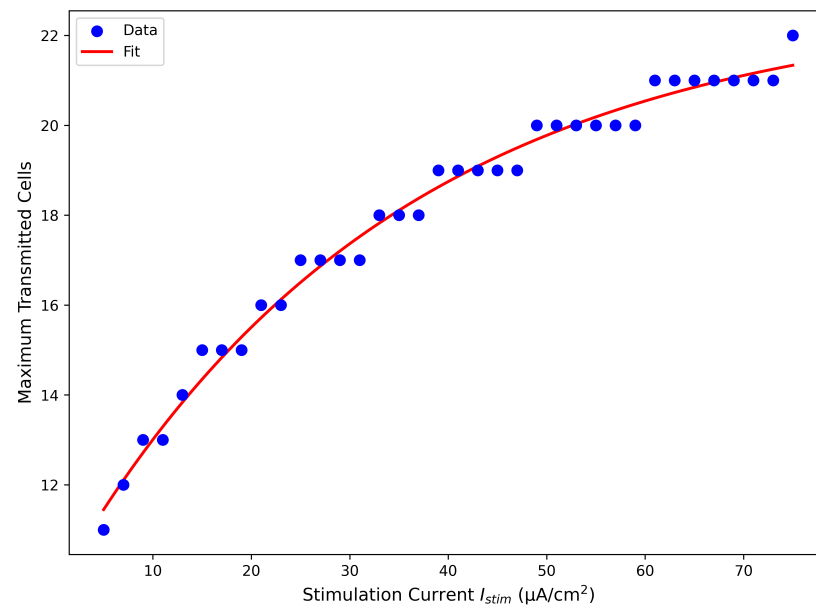


Figure 6. Relationship between the maximum transmissible cell number and stimulation current intensity.

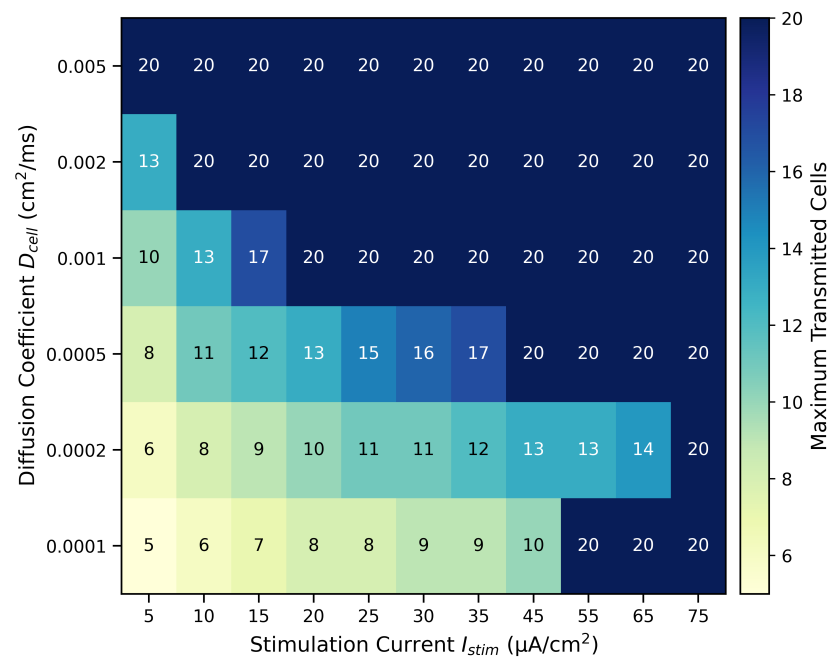


Figure 7. Two-dimensional heatmap of the MTD as a function of stimulation current I_{stim} and intercellular diffusion coefficient D_{cell} . Values in each grid cell represent the number of cells reached by the subthreshold signal.

3.1.2. Signal Spatial Attenuation Characteristics

Upon establishing the propagation limits, we further analyzed the attenuation characteristics governing signal strength along the propagation path. To investigate the spatial evolution of the signal in a noise-free environment, Figure 8 illustrates the variation of the peak membrane potential amplitude with respect to cell position under a constant stimulation intensity. In this setup, noise interference was eliminated, and stimulation was applied over multiple bit periods to accurately quantify the attenuation characteristics of the pure signal. Using a channel consisting of 20 cells with a stimulation current of $15 \mu\text{A}/\text{cm}^2$, the peak membrane potential following stimulation was measured at each cell. The results show that the signal amplitude decreases asymptotically as the conduction distance increases. Notably, signal attenuation within the channel exhibits dual dependence: it is regulated by D_{cell} (where lower coupling strength results in faster attenuation) and decays asymptotically as the propagation distance x increases; specifically, as the signal propagates to distal cells, the amplitude of the membrane potential perturbation gradually diminishes. Consequently, the amplitudes of certain downstream cells eventually approach the detection threshold V_{th} . Specifically, starting from the 17th cell, the peak amplitude of the membrane potential falls below the detection threshold; once the signal decays below this level, downstream cells can no longer reliably detect the signal. These findings demonstrate that the spatial coverage of the communication system depends not only on stimulation parameters but is also constrained by signal attenuation laws governed by the dual regulation of coupling strength and propagation distance. These attenuation characteristics establish the boundary conditions for subsequent system optimization and the design of multi-bit signal links.

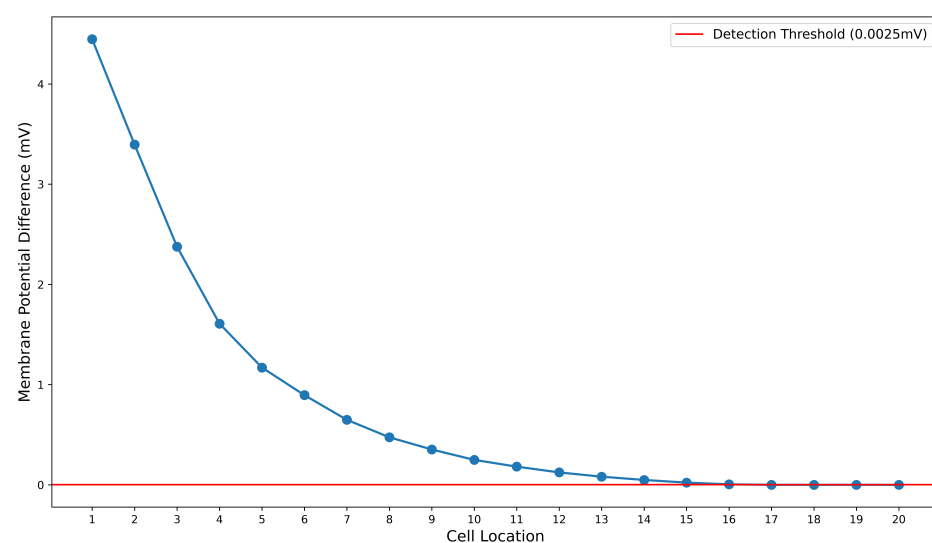


Figure 8. Signal attenuation curve. The blue dots and line represent the peak membrane potential amplitude at each cell.

3.2. Communication Performance in Noisy Environments

3.2.1. Relationship Between BER and Noise Intensity

To systematically evaluate the impact of noisy environments on the communication performance of subthreshold cardiomyocytes, this study modulated noise conditions of varying intensities by adjusting the noise scaling factor α . For this set of BER–noise experiments, the stimulation current was held constant at $8 \mu\text{A}/\text{cm}^2$. The experiment focused on quantifying how noise intensity affects communication reliability.

As shown in Figure 9, the variation of BER with the scaling factor α exhibits three distinct regions:

- Low-Noise Region ($\alpha < 0.1$): The BER remains close to 0, indicating that bit errors are rare. The system demonstrates robust noise immunity under these conditions.
- Medium-Noise Region ($0.1 < \alpha < 0.2$): The BER increases gradually, rising from 0.01% to 10.1%, highlighting a significant impact of noise on communication quality.
- High-Noise Region ($\alpha > 0.2$): The BER rises more rapidly, reaching 23.8% when α is 0.3, indicating a substantial degradation in the system's decision-making performance.

Further analysis shows that under low-noise conditions, FPR, which represents the erroneous identification of a 0 as a 1, accounts for approximately 80–90% of errors. This suggests that false alarms are the predominant error mode in this regime. In contrast, under high-noise conditions, the proportion of FPR decreases to around 60%. Although this might indicate a relative shift in error types, the overall BER of the system increases sharply in high-noise environments, reflecting a significant deterioration in communication quality. These results suggest that in high-noise environments, the decision-making performance of the system is severely constrained.

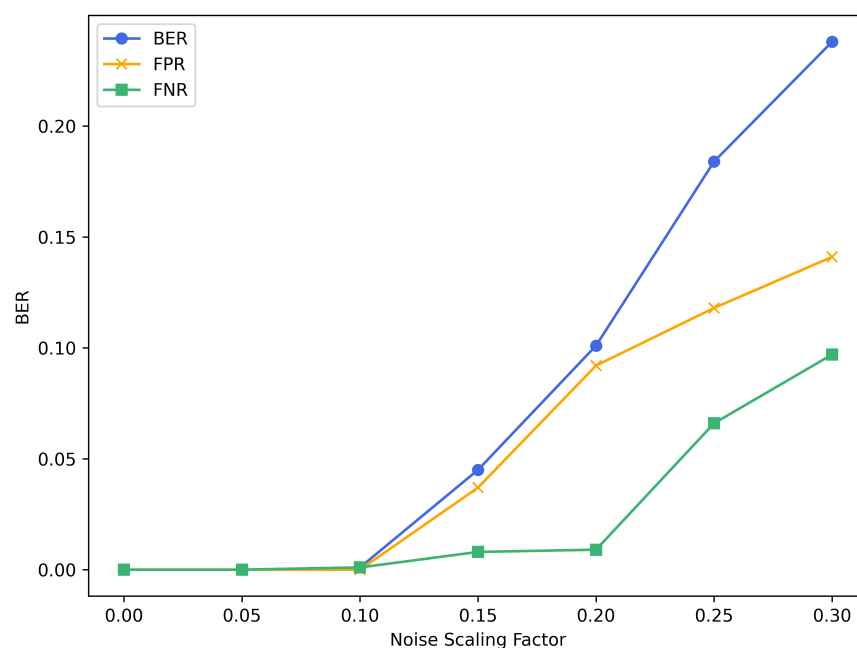


Figure 9. Relationship between BER and noise intensity.

3.2.2. Relationship Between BER and Stimulation Intensity

Under fixed noise conditions ($\alpha = 0.2$), the impact of stimulation intensity on the BER was investigated. Experimental results show that as the stimulation current increases, the BER decreases significantly, as illustrated in Figure 10. Specifically, when the stimulation current rises from $7 \mu\text{A}/\text{cm}^2$ to $9 \mu\text{A}/\text{cm}^2$, the BER drops from 16% to 10%. This indicates that stimulation intensity directly influences signal recognition, allowing the system to maintain a lower BER at appropriate stimulation currents.

Further analysis of FPR and FNR reveals that the FPR is relatively high at low stimulation currents. Notably, the FPR reaches a significant level when the stimulation current is $8 \mu\text{A}/\text{cm}^2$. As the current increases, the FPR decreases, suggesting that the system's signal identification accuracy improves with higher stimulation currents. Conversely, the FNR is high when the stimulation current is $7 \mu\text{A}/\text{cm}^2$ and remains low and relatively constant as the current increases. This suggests that at higher stimulation intensities, the system experiences fewer instances of misidentifying signals as 0. This indicates that appropriate stimulation currents enhance cell membrane depolarization, both improving the efficiency and stability of signal transmission.

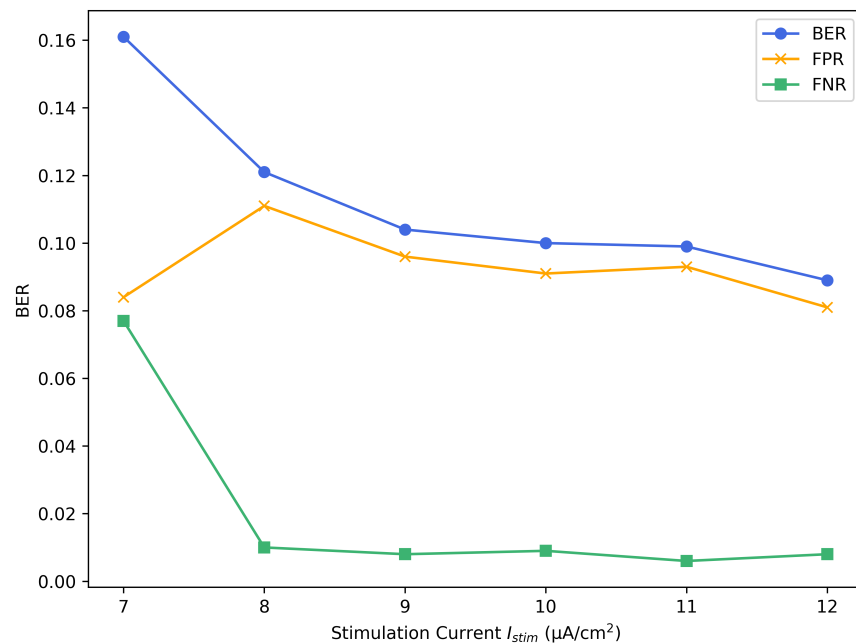


Figure 10. Relationship between BER and stimulation current.

Overall, as the stimulation current increases, signal transmission quality improves, and the BER gradually decreases. This can be attributed to the enhanced membrane depolarization effect at higher stimulation intensities, which increases signal transmission efficiency. However, it should be noted that this trend is influenced by the intercellular coupling strength D_{cell} and the specific ionic model employed [24]; generalization to other cell types or coupling configurations requires further validation.

3.2.3. Spatial Distribution Characteristics of Signal-to-Noise Ratio

The SNR is a critical indicator for evaluating communication system performance. In this study, the SNR distribution characteristics among cardiomyocytes under varying noise conditions were systematically analyzed, revealing an unexpected phenomenon that challenges traditional intuition. Experimental results demonstrate two primary characteristics of the SNR spatial distribution: a general attenuation trend as cell position increases, and a non-monotonic influence of noise intensity on SNR, as shown in Figure 11. Specifically, under all noise conditions, the SNR exhibits a decaying trend with increasing cell index, consistent with the fundamental physical principle of energy loss during signal propagation. However, the impact of noise intensity on SNR is more complex.

Under ideal noise-free conditions ($\alpha = 0$), the system's SNR remains relatively low; the SNR of the first cell is approximately 11 dB, decreasing to nearly 0 dB by the tenth cell. When a moderate noise ($\alpha = 0.1$ – 0.3) is introduced, the SNR improves to varying degrees. Notably, under conditions of $\alpha = 0.1$ and $\alpha = 0.2$, the SNR of the first cell increases to approximately 11.5 dB, surpassing the noise-free condition's transmission performance. This improvement is particularly pronounced in distal cells (Cells 6–10), where the SNR increase is approximately 2.0 dB. As noise intensity increases further, the SNR begins to decline when α reaches 0.4 and 0.5. At $\alpha = 0.5$, the SNR of the first cell drops to approximately 7.5 dB, while the tenth cell's SNR is only about 1 dB, indicating that excessive noise severely degrades signal transmission quality.

The non-monotonic influence of noise intensity on SNR observed in this study suggests the presence of a noise-assisted signal enhancement mechanism in subthreshold cardiomyocyte communication. A detailed biophysical interpretation of this phenomenon is provided in Section 4.

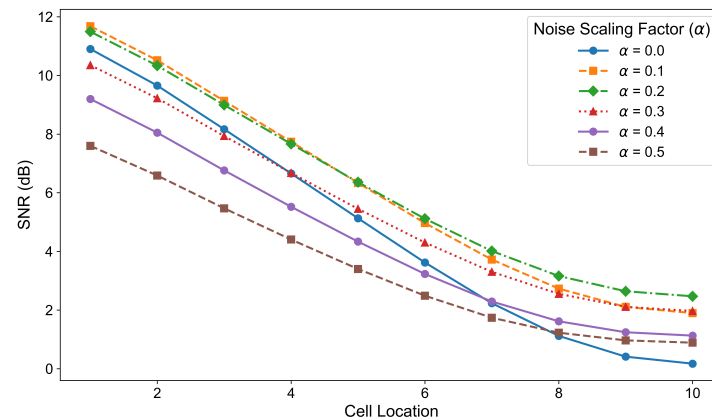


Figure 11. Relationship between SNR and cell distance.

In summary, the experimental results reveal that moderate noise levels ($\alpha = 0.1$ – 0.2) produce a systematic enhancement of SNR across all cell positions, with the most pronounced improvement in distal cells. However, excessive noise ($\alpha > 0.3$) leads to SNR degradation, indicating the existence of an optimal noise window for signal transmission. Additionally, analysis of the spatial attenuation characteristics reveals an important finding: noise modulates the attenuation rate of the signal. In the presence of noise, the spatial attenuation rate is slower, enabling distal cells to maintain a relatively higher SNR. In contrast, under noise-free conditions, the attenuation rate accelerates significantly, limiting the performance of the communication system.

Defining 2 dB as the SNR threshold, the maximum effective communication distance under different noise conditions can be determined. Under optimal noise conditions ($\alpha = 0.1$ – 0.2), effective communication can extend to the 10th cell. Under noise-free or high-noise conditions ($\alpha = 0.5$), the effective communication distance is reduced to the 7th and 6th cells, respectively.

3.2.4. Channel Capacity and Mutual Information Characteristics

We further explored the information transmission capability of the communication system under various conditions by analyzing the channel capacity of cardiomyocytes. Channel capacity refers to the maximum rate at which information can be reliably transmitted under specific channel conditions. Through simulation experiments, we calculated how channel capacity varies with environmental noise and stimulation intensity.

Using the Monte Carlo method, we analyzed the relationship between mutual information $I(X;Y)$ and the input probability distribution $p = P(X = 0)$ under different noise conditions. As shown in Figure 12, under noise-free conditions with a scaling factor $\alpha = 0.05$, the mutual information reaches a maximum value of 1.0 bit, indicating perfect information transmission. However, as noise increases, the maximum mutual information gradually decreases. Specifically, when $\alpha = 0.1$, the maximum mutual information shows a slight decline, reflecting the negative impact of increased noise on information transmission. With further increases in noise intensity ($\alpha = 0.2$ and $\alpha = 0.3$), the maximum mutual information drops to approximately 0.5 bit and 0.2 bit, respectively, indicating significant degradation of the channel's information transmission capability under high-noise conditions. Notably, as noise intensity rises, the mutual information curve flattens, revealing that the optimal range for the input signal gradually narrows. This suggests that achieving efficient transmission becomes increasingly difficult in high-noise environments.

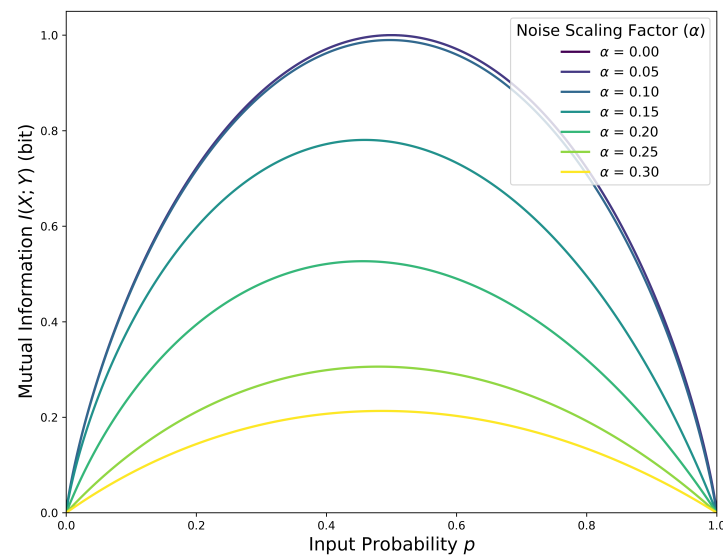


Figure 12. Relationship between mutual information and noise intensity.

In analyzing variations in channel capacity C under different conditions, its dependence on noise intensity and stimulation current was systematically explored. The experimental results reveal a significant non-linear relationship between channel capacity and noise intensity. Specifically, as noise intensity increases, channel capacity gradually declines.

The influence of stimulation current on channel capacity is also notable. As shown in Figure 13, with a scaling factor of $\alpha = 0.2$, the channel capacity demonstrates a trend of initially increases and then approaches saturation as the stimulation current rises. When the stimulation current reaches $12 \mu\text{A}/\text{cm}^2$, the channel capacity stabilizes at approximately 0.64 bit/use. Further analysis indicates that higher stimulation currents facilitate more effective intercellular communication, thereby enhancing the efficiency of bio-electrical signal transmission.

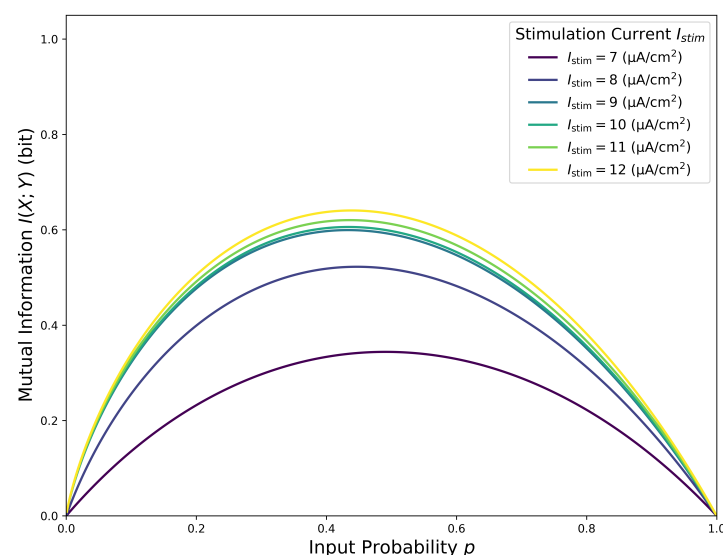


Figure 13. Relationship between mutual information and stimulation current.

This study uses three categories of performance metrics to comprehensively evaluate the system: BER, which directly reflects the reliability of the communication system, approaches 0 under optimal parameter combinations ($\alpha < 0.1$, stimulation current $> 8 \mu\text{A}/\text{cm}^2$), indicating highly reliable communication under appropriate conditions. SNR

is a key indicator for measuring signal quality, and is higher under optimal noise levels ($\alpha = 0.1\text{--}0.2$) compared to noise-free conditions and exhibits a stochastic facilitation enhancement effect, challenging the conventional view that “noise is always detrimental”. Channel capacity, representing the theoretical limit of information transmission, reaches 0.64–1.0 bit/use under optimized conditions, demonstrating the system’s potential for efficient communication.

The comprehensive analysis of these metrics highlights several key trends: the relationship between propagation distance and stimulation intensity exhibits non-linear growth that tends toward saturation, reflecting intrinsic limitations in cell membrane electrodynamics. The performance-noise relationship reveals an optimal noise window, highlighting the significant role of stochastic facilitation in biological communication. The capacity-stimulation relationship suggests that while increased stimulation enhances capacity, it tends toward saturation, indicating the existence of a theoretical limit. These trends provide valuable insights for both academic value study and practical system design, guiding the determination of optimal operating points and parameter combinations.

4. Discussion

This study developed a communication system based on a 3D cardiomyocyte model and systematically analyzed the information transmission characteristics of cardiomyocytes below the AP-threshold through simulation. While previous research [12] has explored the theoretical feasibility of subthreshold membrane potential communication using simplified 1D models, and Kilinc and Akan [22] provided an information-theoretic analysis of gap junction channels between cardiomyocytes, this study advances the field by integrating a 3D intracellular Ca^{2+} handling network into the communication framework, enabling the discovery of phenomena (such as the stochastic facilitation effect) that arise from the coupling between intracellular dynamics and intercellular signal propagation.

In terms of biophysical mechanisms, using the communication system based on the 3D cardiomyocyte model, we systematically analyzed the relationship between signal propagation distance and stimulation intensity, revealing saturation characteristics distinct from those observed in previous 1D cable theory-based studies [12]. It is important to note that a direct quantitative comparison between the present 3D cardiomyocyte model and a standard passive cable equation is methodologically challenging. The cable equation treats the cell membrane as a linear resistive element with a fixed time constant, whereas our 3D model incorporates complex voltage- and Ca^{2+} -dependent ionic currents (Equation (2)), stochastic gating of individual ion channels, and spatially resolved intracellular Ca^{2+} dynamics within the CRU network. These active membrane properties fundamentally alter the signal transmission characteristics in ways that a passive cable model cannot capture. Rather than a simple comparison of propagation distances, the key contribution of the 3D model lies in its ability to reveal phenomena that are invisible to simplified frameworks—such as the noise-assisted stochastic facilitation effect and the Ca^{2+} -dependent modulation of membrane excitability—which emerge from the interplay between 3D intracellular dynamics and intercellular voltage coupling. When stimulation intensity exceeds $35 \mu\text{A}/\text{cm}^2$, the propagation distance growth tends toward saturation, reflecting the physical limits of ion channel conductance and electrochemical driving forces. Unlike simplified analyses based on 1D cable theory, the 3D cell model adopted in this study more accurately captures the regulatory role of complex cellular geometry and the spatiotemporal distribution of CRUs in membrane potential fluctuations. Under subthreshold conditions, even though the stimulation intensity is insufficient to trigger a full AP, local depolarization can still activate a portion of voltage-gated ion channels, thereby maintaining signal propagation across cells. This mechanism closely mirrors the electrical

activity of cardiomyocytes in real physiological environments, offering a new perspective on signal conduction in myocardial tissue under weak stimulation.

Notably, the noise-dependent signal enhancement effect discovered in this study should be classified as stochastic facilitation, as defined by McDonnell and Ward, rather than classical stochastic resonance [33]. Unlike traditional stochastic resonance studies, which typically focus on periodic signal detection using sinusoidal or other periodic stimuli, the input in this system is an aperiodic digital bit stream, aimed at achieving reliable transmission of complex information. To further validate this classification, future studies could test the system with modulated sinusoidal stimuli (e.g., I_{stim} at varying frequencies) to determine whether a frequency-dependent stochastic resonance peak also exists in this biological communication context.

From a biophysical perspective, additive Gaussian white noise (with zero mean and controllable variance, adjusted via the scaling factor α) is used to simulate endogenous noise, as its statistical properties align with the Poisson stochastic activity of ion channels. Under completely noise-free conditions ($\alpha = 0$), weak subthreshold signals fail to effectively activate voltage-gated ion channels, leading to insufficient downstream cell response. When a moderate noise ($\alpha = 0.1\text{--}0.2$) is introduced, noise fluctuations provide additional energy to the signal, helping it overcome the activation thresholds of Na^+ channels and LCCs. This significantly enhances the depolarization response of distal cells by modulating the channel opening probability, resulting in an SNR improvement of approximately 2.0 dB. This range forms a distinct “noise window”. However, as noise intensity increases further ($\alpha > 0.3$), its masking effect dominates the system dynamics, leading to disordered stochastic activation of ion channels and a subsequent decline in communication performance, consistent with the stochastic facilitation theoretical framework. Simulation data reveal that under moderate noise levels ($\alpha = 0.1\text{--}0.2$), the system’s SNR is significantly better than under noise-free conditions. Although this is based on an artificially encoded communication model, the mechanism uncovered offers a novel physical perspective on physiological phenomena: the inherent ion channel noise within cardiomyocytes may not merely be interference to suppress, but rather an auxiliary resource to maintain robust transmission of subthreshold weak signals. This finding supports the “noise-exploitable” viewpoint, suggesting that in specific physiological noise environments, nonlinear systems can enhance the robustness of signal propagation through stochastic facilitation mechanisms.

In terms of engineering applications, research on subthreshold membrane potential communication systems provides a key theoretical foundation and technical support for implantable medical devices. Compared to traditional cardiac pacemakers based on supra-threshold APs, the subthreshold membrane potential communication framework established in this study can significantly reduce energy consumption, opening new avenues for the design of miniaturized implantable devices. Simulation results demonstrate that under optimized stimulation parameters, high channel capacity can be achieved while maintaining an extremely low BER, offering key insights for the design of low-power cardiac implants. Nanotechnology-based subthreshold cardiac communication systems hold the potential to revolutionize treatment strategies for cardiac arrhythmias. By precisely regulating local subthreshold stimulation parameters, abnormal heart rhythms can be gently corrected, avoiding the tissue damage and high energy consumption associated with traditional electric shock therapies. This low-energy regulation approach offers substantial advantages, particularly for arrhythmias requiring long-term management, such as atrial fibrillation. Additionally, the stochastic facilitation phenomenon discovered in this study can be applied to the design of adaptive regulatory nanodevices. By intelligently adjusting noise levels to optimize signal transmission efficiency, stable communication performance can be maintained even in physiologically noisy environments.

Despite the significant progress made in theoretical modeling and simulation analysis in this study, several limitations remain that require further refinement. First, the limitations of the model assumptions are apparent. The current noise model adjusts noise intensity derived during the AP phase using a scaling factor. This simplified approach struggles to accurately represent the actual noise characteristics in the subthreshold state. The randomness of subthreshold membrane potential fluctuations may differ fundamentally from that during APs, and this oversimplification could lead to inaccurate performance assessments.

Second, the restrictions arising from parameter simplifications cannot be overlooked. While a 3D cellular model is used, simplified structural assumptions are still employed when analyzing signal cascade propagation, failing to fully capture the true 3D anisotropic characteristics of cardiac tissue. The orientation of myocardial fibers, the layered arrangement of cells, and the complex spatial distribution of GJs significantly influence signal conduction pathways; yet these factors have been simplified in the current model. Notably, the current implementation employs a 3D intracellular Ca^{2+} handling network (the CRU model of Nivala et al. [23]) within each individual cell, while intercellular signal propagation is restricted to a 1D chain structure. This means that tissue-level 3D anisotropy—including the distinction between longitudinal and transverse propagation—has not yet been incorporated. Additionally, the assumption of a constant resting membrane potential may affect the accuracy of the results. During rest, cardiomyocytes may exhibit hyperpolarization, lowering the membrane potential below -87.5 mV, which is particularly important for subthreshold communication. Given the low amplitude of the stimulating current, a more negative membrane potential could further inhibit effective signal transmission.

Third, the sensitivity to the intercellular diffusion coefficient was evaluated through a two-dimensional ($I_{\text{stim}}, D_{\text{cell}}$) parameter sweep (Figure 7). The default value $D_{\text{cell}} = 0.0005 \text{ cm}^2/\text{ms}$, adopted from Liu et al. [28] and verified against cardiac bidomain conductivity measurements [34], lies at the boundary of the observed threshold transition, indicating that the baseline configuration operates near a critical coupling regime where pathological gap junction remodeling could significantly compromise the communication range.

Fourth, the present 2D parameter sweep (Figure 7) covers a regular grid of six D_{cell} values and eleven I_{stim} values. A higher-resolution exploration with finer parameter spacing and an extended chain length (beyond 20 cells to avoid boundary saturation) would further refine the characterization of the MTD landscape.

Fifth, due to the significant computational demands of the 3D CRU-based simulation, it is computationally prohibitive to perform the large number of independent trials ($N \geq 20$) that would be necessary to report meaningful standard deviations for every data point in Figures 9 and 10. For this reason, the BER values reported in this study represent single-run results that demonstrate the qualitative trends. We acknowledge that the inclusion of standard deviation error bars would strengthen the statistical rigor of these results, and we plan to address this in future work leveraging high-performance computing resources for massively parallel parameter sweeps.

5. Conclusions

This study established and systematically verified, for the first time, a subthreshold membrane potential communication system based on a 3D cardiomyocyte model, demonstrating that high-fidelity information transmission can still be achieved below the AP threshold. A complete communication architecture encompassing the transmitter, channel, and receiver was constructed, and a standardized evaluation methodology centered on BER, channel capacity, and SNR was developed. A two-dimensional parameter sweep

(Figure 7) further revealed that the MTD depends jointly on I_{stim} and D_{cell} , with a non-monotonic transition regime at intermediate coupling strengths. Under conditions with endogenous physiological noise, it was found that moderate noise ($\alpha = 0.1\text{--}0.2$) could stabilize and significantly enhance end-to-end communication performance through stochastic facilitation. These results provide both theoretical and methodological support for low-power, reliable in vivo biological communication between implantable nano-devices. Rather than replacing conventional supra-threshold cardiac pacemakers, this subthreshold communication framework is proposed as a complementary modality that enables distributed sensing and data exchange between nano-actuators at energy levels below the action potential threshold [12]. This work also lays the foundation for the engineering of “noise-exploitable” intelligent healthcare systems and in vivo networked monitoring.

Based on the findings of this study, future work will primarily focus on two key directions. First, in terms of model expansion and validation, the existing 1D cell chain model will be extended to 2D and 3D networks to more accurately capture the structure and signal propagation characteristics of cardiac tissue. Additionally, cell culture experiments will be designed to validate the theoretical predictions of subthreshold signal communication, particularly the random facilitation phenomenon, thereby enhancing the physiological realism of the model and further exploring the synergistic mechanisms of electrical, chemical, and mechanical signaling. Second, in the area of technical applications and protocol development, communication protocols that adaptively adjust based on noise and channel conditions will be developed to improve the robustness and efficiency of the system. This technological advancement will provide experimental support for the theoretical model and facilitate the translation of subthreshold membrane potential communication theory into practical medical and engineering applications.

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