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Cell-to-cell communication: from physical calling to remote emotional touching

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Abstract
The emerging paradigm of cell-to-cell communication represents a transformative shift from device-mediated contact to bio-integrated, emotion-driven interactions. This article introduces a novel, multi-layered framework for enabling biologically integrated communication between cells, devices, and computational systems using the paradigm of Molecular Communication (MC). Moving beyond traditional digital interfaces, the proposed architecture, comprising in-body, on-chip, and external communication layers, models and processes intercellular signaling via molecular emissions, implantable biosensors, and nano-electronic processors. Theoretical foundations are extended to fractional-order diffusion systems and neuromorphic decoding, capturing complex behaviors in realistic biological environments. We further propose a cross-layer molecular digital twin model for context-aware interpretation and feedback. The framework's applications are grounded in the molecular underpinnings of emotion, where neurotransmitters like oxytocin and serotonin mediate prosocial behaviors and affective states through cell-to-cell signaling. For instance, remote emotional interfacing leverages MC to modulate oxytocin release, mimicking natural empathy circuits, while consensual telepathy draws from BCI-mediated neural pattern sharing, extending molecular-level decoding to cognitive-emotional relays. These are not mere metaphors but extensions of established neurochemical pathways, as evidenced by recent studies showing serotonin fluctuations amplify context-specific emotions. This work thus bridges cellular mechanisms to higher-order phenomena, ensuring scientific rigor in bio-digital systems .

Keywords Consensual telepathy, Intelligent molecules, Molecular communications, Nano networks, Neuromorphic implant, Spintronic modulation

1 Introduction

The trajectory of communication devices has evolved from rudimentary wired telephony to sophisticated Internet-based solutions like Voice over Internet Protocol (VoIP) [1]. Initially, analog signals transmitted over copper lines dominated, but the advent of digital technology facilitated the conversion of voice into data packets, enabling transmission over the Internet [2]. This paradigm shift not only reduced costs but also integrated

multimedia services, laying the groundwork for contemporary unified communication systems.

Brain-Computer Interfaces (BCIs) establish direct communication pathways between the human brain and external devices, circumventing traditional neuromuscular outputs [3, 4]. Emerging technologies, such as Neuralink's implantable devices,[1] aim to decode neural signals with high fidelity, facilitating seamless interaction with computers and potentially obviating the need for peripheral devices. These advancements herald a new era in neurotechnology, promising applications ranging from medical rehabilitation to cognitive augmentation.

Certain biological cells, termed electrogenic cells, possess the intrinsic ability to convert chemical energy into electrical energy through metabolic processes [5]. This bioelectrogenesis is fundamental to various physiological functions, including neuronal signaling and cardiac rhythm regulation, underscoring the critical role of bioelectricity in sustaining life [6, 7].

The initiation of an action potential is characterized by a precise sequence of ion channel activities [8, 9]. Upon reaching a threshold stimulus, voltage-gated sodium (Na^+) channels rapidly activate, allowing an influx of Na^+ ions and causing membrane depolarization. Subsequently, these Na^+ channels undergo inactivation, while voltage-gated potassium (K^+) channels activate, facilitating K^+ efflux that repolarizes the membrane, restoring its resting potential.

Ion transporter proteins embedded in cell membranes harness the energy liberated from ATP hydrolysis to translocate ions against their concentration gradients [10, 11]. This active transport is vital for maintaining electrochemical gradients essential for numerous cellular processes, including nutrient uptake, waste removal, and the propagation of electrical signals in excitable tissues.

Advancements in neurotechnology suggest a future where sensory experiences and emotional states could be transmitted directly between individuals without intermediary devices [12, 13]. This concept, often referred to as consensual/controllable telepathy, envisions the use of BCIs to decode and relay neural representations of sensations and emotions [14], potentially revolutionizing interpersonal communication by enabling direct brain-to-brain interfacing.

While terms like "remote emotional touching" may evoke metaphorical interpretations, they are firmly rooted in the molecular biology of emotions. Human emotions emerge from distributed neural networks but originate at the cellular level through neurotransmitter-mediated signaling. For example, oxytocin, released via vesicular exocytosis in hypothalamic neurons, facilitates social bonding and empathy by binding to receptors on target cells, altering membrane potentials and gene expression [15]. Similarly, serotonin modulates mood through synaptic and volume transmission, influencing emotional valence in response to social cues [16]. Recent neuroimaging and pharmacological studies confirm that perturbations in these molecular pathways directly correlate with altered emotional experiences, such as enhanced prosociality following oxytocin administration [17]. Thus, our proposed MC framework extends these natural processes, enabling engineered modulation for applications like emotional interfacing, without overstepping biological plausibility.

[1] https://neuralink.com/

1.1 Motivation and contribution

Despite the significant evolution of digital and neurocommunication systems, current architectures remain constrained by their dependency on silicon-based, device-bound interfaces that poorly integrate with the biological medium [18, 19]. Existing BCIs and sensor-driven implants are often isolated systems that lack seamless integration at the molecular or cellular scale [3], limiting their capacity to achieve real-time, biocompatible, and emotion-sensitive communication. Furthermore, traditional communication models are ill-suited to the highly stochastic, constrained, and nonlinear environment of biological media.

To address these limitations, this paper introduces a novel and biologically inspired framework based on Molecular Communication (MC) [20–22] for enabling scalable, energy-efficient, and high-fidelity cell-to-cell communication. The contributions of this work are summarized in the four below items:

1) We define a three-layered reference architecture-comprising **In-body**, **On-chip**, and **Communication Channel** layers-suitable for modeling signal flow from molecular release to external digital interpretation.
2) We identify and technically analyze all critical components of this architecture, including signaling cells, invasive nano-receivers, biochemical modulators, on-chip processors, and Internet-integrated transmission interfaces.
3) We provide an algorithmic presentation of the general cell-to-cell communication that the offered algorithms are (*i*) modular (supporting different modulation, channel types, and decoding models), (*ii*) technically precise (based on real MC and signal processing principles), and (*iii*) future-proof (with placeholders for DL, secure transmission, and real-time control).
4) We contextualize the proposed framework in terms of state-of-the-art applications such as remote drug control, consensual telepathy, and non-silicon information processing while addressing future challenges in noise modeling, MAC control, AI integration, and biochemical cybersecurity.

To ground remote emotional touching scientifically, consider that emotions are not abstract but arise from quantifiable molecular cascades. Oxytocin and dopamine interactions in the mesolimbic pathway underpin reward and affiliation, with cell-to-cell propagation via diffusion and synaptic release [23]. In our architecture, MC modulates these signals using spintronic encoders to mimic natural gradients, potentially enabling "touching" by remotely triggering empathetic responses [24]. Consensual telepathy, meanwhile, builds on BCI advancements where neural ensembles encode emotional states, relayed molecularly for direct brain-to-brain linkage [25]. This is supported by evidence that serotonin depletion alters social emotion processing, highlighting how molecular fidelity preserves emergent emotional integrity [26]. Such applications thus represent feasible extrapolations from cellular mechanisms to systemic behaviors.

The proposed reference model demonstrates technical soundness, biological feasibility, and extensibility, positioning it as a foundational system for future developments in cellular-scale communication [27, 28], bio-cybernetic feedback loops [29, 30], and emotionally driven computing [14, 31, 32]. Its layered design and rigorous algorithms ensure that the model is not only theoretically valid but also implementable in both research and clinical translational contexts. By synthesizing biological, computational,

and communication principles, this study lays a foundation for next-generation cognitive and emotional communication systems operating at the cellular scale.

While several reviews exist on MC [33, 34], this work distinguishes itself by integrating MC with emotion-driven bio-digital architectures, extending beyond biophysical modeling to practical, layered frameworks for cellular-scale applications. Table 1 compares key prior reviews, underscoring our novelties in cross-layer digital twins and spintronic modulation.

1.2 Paper organization

The remainder of this paper is organized as follows. Section 2 outlines the key background technology of cell-to-cell communication. Section 3, as the main section of this study, identifies a general architecture for cell-to-cell communication. Section 4 discusses the proposed architecture and addresses important future issues of this technology. Ultimately, Sect. 5 concludes this study.

2 Background technologies

This section outlines key technologies that empower the cell-to-cell communications.

2.1 Molecular communication

Biotechnology integrates living organisms or their components into technological applications to develop products and processes that improve human life and the health of the planet [36]. Nanomachines are devices ranging in size from 1 to 100 nanometers, designed to perform specific tasks at the molecular or atomic level [37]. These machines can be synthetic, constructed from nanoscale components, or bio-hybrid, incorporating biological molecules like proteins or DNA to achieve desired functionalities. On a deeper level, nanonetworks consist of interconnected nanomachines that communicate to perform complex tasks beyond the capabilities of individual units [38]. These networks facilitate coordination and information sharing among nanomachines, enhancing their collective functionality.

Nano-communication refers to the methods by which nanomachines exchange information. MC is particularly advantageous in biological environments, offering biocompatibility and energy efficiency [21, 22]. This communication paradigm is inspired by natural processes such as hormonal signaling and neurotransmission, providing a framework for developing sophisticated nanonetworks within living organisms. MC offers a biologically inspired framework for cell-to-cell communication, with modulation techniques that can be tailored to the specific requirements of the biological context. The

Table 1 Comparison with Prior MC Reviews: Novelties in This Work

Review	Focus	Limitations	Our Novelties
Farsad et al. (2016) [33]	Channel modeling, modulation	Lacks emotional/bio-integration	Layered architecture with neuromorphic decoding
Akyildiz et al. (2023) [34]	Nanonetworks, propagation	No fractional-order or application bridges	Fractional diffusion, emotional touching via MC
Nakano et al. (2024) [35]	DNA-based networks	Theoretical, no hardware interfaces	On-chip spintronics, digital twins for feedback
This Work	Bio-digital MC for emotions	N/A	Cross-layer models, speculative yet grounded apps

selection of an appropriate modulation method is critical to achieving efficient and reliable information transfer in MC systems.

2.1.1 Definition

The MC is an innovative paradigm that leverages biological molecules to transmit information, offering a biocompatible and energy-efficient alternative to traditional electromagnetic communication methods [20]. In MC, information is encoded into molecules released by a transmitter nanomachine, propagated through a medium, and decoded by a receiver nanomachine via specific biochemical interactions. This method mirrors natural communication processes observed in biological systems, such as hormonal signaling and neurotransmission, making it particularly suitable for interfacing with cellular environments.

2.1.2 Theoretical framework

Mathematically, the MC process can be characterized by the three main steps as follows [39, 40].

1) *Encoding and transmission:* The transmitter encodes information into a concentration $C(t)$ of signaling molecules released into the medium at time t.
2) *Propagation:* The molecules propagate through the medium, and their concentration $C(x, t)$ at position x and time t can be described by the diffusion equation as $\frac{\partial C(x,t)}{\partial t} = D\nabla^2 C(x,t) - \lambda C(x,t)$, where D is the diffusion coefficient, and λ represents the degradation rate of the molecules.[2]
3) *Reception and decoding:* The receiver detects the local concentration $C(x_r, t)$ at its position x_r and decodes the information based on predefined criteria, such as threshold levels or temporal patterns.

To further enrich MC theoretical modeling, recent studies incorporate fractional-order calculus to describe anomalous diffusion [41, 42]. The generalized diffusion model can be represented as:

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} = D_\alpha \nabla^2 C(x,t) - \lambda C(x,t), \quad 0 < \alpha \leq 1$$

where α is the fractional derivative order, D_α is the generalized diffusion coefficient, and λ is the molecular degradation constant. This model captures sub-diffusive behaviors commonly observed in crowded cellular environments where normal Fickian dynamics break down.

2.1.3 Classification

The MC can be classified into three main types based on the propagation mechanisms [43, 44].

1) *Walkway-based:* This type utilizes predefined pathways, such as cytoskeletal structures, with molecular motors transporting signaling molecules along these tracks.

[2] It is important to note that this model assumes an idealized scenario. In biological systems, molecular release might follow more complex stochastic processes, such as a Poisson process, to better reflect the inherent randomness of cellular secretion events. Furthermore, the concentration $C(x, t)$ is often subject to spatial and temporal fluctuations due to factors like local viscosity variations and molecular crowding. Advanced models may incorporate these complexities for increased realism.

2) *Flow-based:* The flow-based type relies on the bulk movement of the fluid medium, as seen in the circulatory system, as similar as hormones are transported via blood flow.
3) *Diffusion-based:* It depends on the random Brownian motion of molecules, with propagation governed by the diffusion equation mentioned above.

2.1.4 Modulation techniques

Effective modulation techniques are crucial for optimizing MC performance [45, 46]. Several methods will now be addressed.

1) *Concentration Shift Keying (CSK):* Information is encoded in the varying concentration levels of signaling molecules.
2) *Molecular Type Shift Keying (MTSK):* Different molecule types represent different symbols, utilizing the specificity of molecular receptors.
3) *Release Time Shift Keying (RTSK):* Information is encoded in the timing of molecule release, leveraging the temporal aspects of molecular propagation.
4) *Spatial Position Shift Keying (SPSK):* Molecules are released from different spatial positions to convey information.

Distinguishing from existing MC overviews [47], which emphasize propagation physics, our framework innovates by incorporating anomalous diffusion via fractional calculus and neuromorphic processing, enabling emotion-sensitive decoding absent in prior works. For instance, while reviews like [48] cover modulation, they overlook integration with BCIs for telepathy-like applications, a gap we address through bio-hybrid architectures.

All in all, the choice of modulation technique depends on factors such as the communication range, required data rate, and the biological environment. These factors are compared in Table 2. For cell-to-cell communication, MTSK is often preferred due to the natural specificity of cellular receptors to particular molecule types, enhancing selectivity and reducing cross-talk.

2.2 High-accurate implants

The design and deployment of highly accurate implants are central to decoding biological communication processes, especially for applications in cell-to-cell communication and MC. These implants act as transducers: acquiring signals from biological carriers

Table 2 Comparison of MC-based modulation methods

Modulation technique	Encoding mechanism	Advantages	Disadvantages	Suitability for cell-to-cell communication
CSL	Varying molecule concentration	Simple implementation; utilizes concentration gradients	Susceptible to inter-symbol interference (ISI); limited by diffusion dynamics	Moderate
MTSK	Different molecule types	High specificity; aligns with natural receptor-ligand interactions	Requires synthesis of multiple molecule types; potential cross-reactivity	High
RTSK	Timing of molecule release	Utilizes temporal resolution; reduces ISI	Sensitive to timing inaccuracies; complex synchronization required	Low
SPSK	Spatial release positions	Exploits spatial diversity; potential for multiplexing	Complex spatial control needed; limited by diffusion spread	Low

(e.g., molecules, ions, neural impulses), converting them into electronic or optochemical formats, and transmitting them to external data processors [49, 50]. Based on the level of bodily intrusion, implants are typically categorized into non-invasive [51, 52], minimally invasive [53, 54], and invasive classes [55, 56], each with distinct signal fidelity, resolution, and biocompatibility profiles. Table 3 summarizes this section and connects this section to content of Sect. 2.1.

2.2.1 Non-invasive

Non-invasive implants are devices that interact with biological signals externally or via indirect surface contact without penetrating skin or tissue. EEG caps (for brain signals) and wearable electrochemical biosensors (for sweat or skin signals) are well-known examples of EEG-based devices [51, 52].

Regarding zero danger of this type of implants, high signal-to-noise ratio (SNR) reduction due to tissue attenuation is a concern of this class [57]. Moreover, inadequate for capturing molecular concentration gradients used in MC, especially in diffusion-based and flow-based regimes is another limitation.

2.2.2 Minimally invasive

These devices insert slightly beneath the skin or into shallow tissues using micro-needles or subdermal probes (e.g., subcutaneous microelectrode arrays, microneedle biosensors, and lab-on-chip transdermal platforms) [53, 54]. Real-time monitoring of ionic concentrations (e.g., $[Na^{+}]$, $[K^{+}]$, and $[Ca^{2+}]$) relevant to action potentials and sampling from interstitial fluid or capillary beds—key environments for diffusion-based MC can be considered the important capability of this category.

Unlike non-invasive implants, this type benefits improved SNR in such a way that they reduce immune response due to small size (to $< 200\ \mu m$) [58]. However, limited depth and reduced access to deep-tissue environments like central neural networks or viscera are the main concerns of this category of implants.

2.2.3 Invasive (the high-accuracy class)

Invasive implants are deep-tissue devices implanted into neural or molecularly active regions (e.g., brain cortex, spinal cord, gut-brain axis) for high-resolution signal acquisition [55, 56]. Famous examples of this type are (*i*) Utah Arrays and Neuropixels (cortical brain implants), (*ii*) deep-brain stimulation (DBS) electrodes for basal ganglia modulation, and (*iii*) Implantable bio-nanoelectrodes for detecting molecule types and concentration in specific tissues.

Recent advancements in microfabrication techniques have enabled the development of flexible and ultra-thin invasive implants. These implants, often utilizing materials like

Table 3 Properties of implants to apply in cell-to-cell communication and MC

Implant type	Invasiveness	Resolution	MC modality suitability	MC modulation compatibility	Example use cases
Non-invasive	Low	$\sim 1mm$ (low)	Poor (surface only)	Limited (e.g., CSK via sweat)	Skin biosensing, surface EEG
Minimally invasive	Medium	$\sim 100\mu m$	Moderate (shallow diffusion)	CSK, RTSK (low-noise environments)	Glucose monitoring, microfluidic sensing
Invasive	High	$< 50\ \mu m$ (high)	High (all 3 MC types)	MTSK, CSK, RTSK, hybrid schemes	Cortical implants, neural decoding

graphene or flexible polymers, offer improved conformability with neural tissues, reducing mechanical mismatch and minimizing chronic inflammation. Furthermore, developments in bio-integrated power sources, such as enzymatic biofuel cells that harvest energy from interstitial fluids, promise to enhance long-term functionality and reduce the need for battery replacements in invasive implants. Generally, invasive implants receive signals by two below methods.

1) *Electrophysiological* [59, 60]: By capturing neuronal action potentials and synaptic signals, critical for neuron-level flow-based MC.
2) *Electrochemical/Nano-biosensing* [61, 62]: Detecting the presence or variation of specific molecular signals (e.g., neurotransmitters, peptides), enabling MTSK, and CSK decoding.

The invasive implants provide several exciting properties, such as sub-millisecond latency for action potential capture, spatial resolution of $< 50\mu m$, suitable for capturing individual cell behavior, biocompatibility coatings (e.g., parylene-C, PEG-hydrogel) reduce immune rejection, and long-term stability (weeks to months) with advanced encapsulation materials (e.g., silicon carbide, diamond-like carbon).

The relevance to MC classification (refer to Sect. 2.1.3) is determined as follows.

- *Walkway-based:* Devices can interface with molecular motors like kinesin or dynein on cytoskeletal tracks by embedding within or near microtubule-dense zones.
- *Flow-based:* Ideal for implantation in vascular or cerebrospinal fluid domains; sensors can register molecule packets carried by pressure-driven flow.
- *Diffusion-based:* Capture of local concentration fields via nanoelectrode arrays; ideal for decoding CSK or RTSK signals.

2.2.4 Toward hybrid implant-networked systems

In advanced applications, invasive implants function not just as sensors but as active nanonetwork nodes. These nodes can (*i*) modulate chemical signals for inter-device communication (e.g., using artificial vesicle release mimicking synaptic transmission), (*ii*) synchronize with external systems (via optogenetic control or RF signaling), and (*iii*) participate in bidirectional brain-machine interfaces, where BCIs decode emotional or sensory MC inputs and transmit responses via engineered molecule release.

High-accuracy implants, particularly invasive types, are indispensable for realizing real-time, high-resolution decoding of biological information in molecular and neuronal contexts. Their synergy with MC mechanisms allows precise detection and processing of information-rich biological signals, ushering in the era of bio-digital communication systems integrated seamlessly with living tissues.

In cutting-edge hybrid systems, implant nodes can also host learning-enabled logic units, integrating analog neuromorphic circuits or spiking neural networks (SNNs). These allow on-device interpretation of ionic or molecular patterns. Let $S(t)$ denote the spiking input stream from molecular sensors, and let $V(t)$ be the membrane potential of an artificial neuron:

$$\frac{dV(t)}{dt} = -\frac{V(t)}{\tau} + \sum_i w_i \delta(t - t_i)$$

where τ is the leak time constant and w_i are molecularly derived synaptic weights. This framework facilitates online decision-making at the molecular interface layer, enhancing autonomy and responsiveness.

2.3 Ultra-tech components

In addition to previous technologies, cell-to-cell communication can also benefit from the following ultra-tech components.

- *Intelligent and submissive molecules:* These are programmable or responsive molecules engineered to change behavior or structure based on environmental stimuli (e.g., pH, temperature, light, or chemical gradients) [63–65]. They can exhibit smart binding, release, or transformation properties on command. Intelligent and submissive molecules serve as dynamic carriers or modulators in MC. For instance, intelligent molecules can adapt their diffusion rate or binding affinity, enabling adaptive CSK or MTSK modulation, which improves communication fidelity in variable biological conditions (e.g., inflammation, ischemia).
- *Nano-scale antennas:* These are antennas fabricated at nanometer scales ($1-100$ nm), often using materials like graphene [66], carbon nanotubes [67], or plasmonic nanoparticles [68], designed to transmit/receive electromagnetic waves at *THz* or optical frequencies. Nano-antennas allow EM-based nano-communication to coexist with or complement MC, especially when long-range or rapid signaling is required (e.g., bridging diffusion delays). They can modulate molecular bursts into EM signals or synchronize implanted nanonetworks using near-field coupling.
- *Microscopic wireless power transfer (WPT):* Microscopic WPT enables the delivery of power at pico- to nano-watt scales wirelessly, using magnetic resonance, RF, or ultrasonic energy [69]. This can be done through tissue-safe frequencies and micro-scale receiver coils. WPTs powers implanted nanomachines or sensors without needing bulky batteries. This enables continuous operation of MC receiver/transmitter modules in deep tissue, crucial for real-time, long-term monitoring of intercellular signals without recharging or surgical replacement.
- *Quantum dots (QDs) for neural sensing:* Quantum dots are semiconductor nanocrystals ($2-10$ nm) with tunable fluorescence based on quantum confinement [70, 71]. They can be functionalized to bind to specific neural or chemical targets and emit light upon excitation. QDs can detect neurotransmitter dynamics or ion fluxes with single-vesicle precision. They act as optical reporters in MC systems, especially useful in diffusion-based MC, translating molecular concentrations into high-resolution spatiotemporal signals for downstream processing or optogenetic feedback.
- *Neuromorphic microchips:* Neuromorphic chips mimic the architecture and computational strategies of the human brain, using spiking neurons, synapse-like connections, and parallel processing for low-power and real-time computation [72, 73]. These chips can decode and interpret MC signals (e.g., molecule arrival patterns or ionic spikes) in a biologically meaningful way. They enable bio-compatible, local data interpretation in smart implants or wearable neurointerfaces, supporting closed-loop feedback in brain-body interfaces.
- *Spintronic neural processors:* Spintronic devices utilize the electron's spin in addition to its charge to perform computations, offering ultrafast switching, non-volatility,

and reduced power consumption [74, 75]. Spintronic neural processors can process MC or ion-channel data with high speed and miniaturization, making them ideal for edge-level neural decoding in next-gen brain-machine interfaces or in-body molecular hubs. Their quantum-level sensitivity complements molecular signal variance detection.

- *Terahertz communication:* Terahertz (*THz*) communication operates in the $0.1 - 10$ *THz* range and bridges the gap between microwave [76] and optical bands [77]. It's suited for high-data-rate, short-distance transmissions. *THz* waves are well-matched with molecular vibrational modes, enabling molecule-specific spectral signatures. Hence, *THz* communication can be used for label-free molecular recognition, direct MC decoding, or coupling multiple MC nodes (like nanomachines) with real-time coordination over millimeter distances inside tissues.

3 Cell-to-cell communication

This section is the core of this study and proposes the generic framework of cell-to-cell communication.

3.1 Players

As depicted in Fig. 1, the following items are the key players and main components of the cell-to-cell communication.

- *In-body transmitter*(*Tx* - biological cell or engineered cell): The transmitter is typically a natural or synthetic cell capable of producing and releasing signaling molecules (e.g., neurotransmitters, cytokines, or engineered ligands). Its role is to initiate MC by encoding biological or synthetic information into molecule type, concentration, or release timing. It interfaces with intra- or intercellular pathways and is sensitive to internal or external stimuli (e.g., action potentials, optogenetic light pulses).
- *In-body power unit (micro or nano-scale WPT receiver):* This unit is implanted within the body (often integrated with the receiver or modulator). It wirelessly harvests power (e.g., from RF, ultrasound, or magnetic fields) to energize in-body components like sensors, detectors, and transmitters, making them self-sustained.

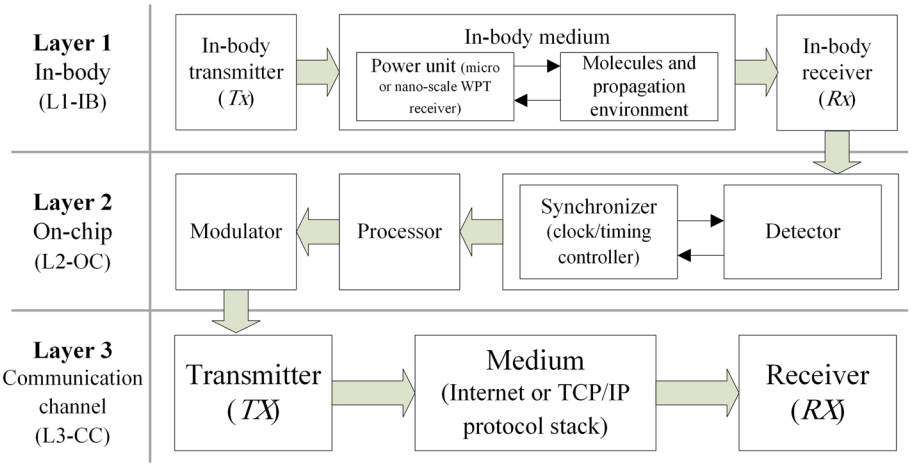

Fig. 1 The three-layered architecture of the general cell-to-cell communication

- *In-body medium (molecules and propagation environment):* The molecular medium includes signal-carrying molecules (e.g., ions, proteins, DNA fragments) and the biological environment through which they travel (e.g., interstitial fluid, bloodstream, cytoplasm). This medium enables diffusion-based, flow-based, or active (walkway-based) transport propagation. It connects *Tx* and *Rx*, and its physical and chemical properties (e.g., viscosity, flow velocity) directly influence channel capacity, delay, and noise.
- *Signal relay or gateway node (it is optional):* If the communication distance within the body is large (e.g., from deep organs to the skin surface), intermediate relay nanomachines or gateway implants are needed. These act as amplifiers or format converters (e.g., molecular-to-electrical), extending the range or translating between communication modalities (MC to EM). When extending data to outside the body, they serve as a bridge to the Communication Channel.
- *In-body receiver* (*Rx* - invasive implant or sensor array): The in-body receiver is a high-precision, often invasive implant (e.g., neuropixels, nanowire Field-Effect Transistors (FETs), biosensing electrodes) capable of detecting specific molecules or electrochemical signals with high temporal and spatial resolution. It decodes the signal (via CSK, MTSK, or RTSK) and converts it into electronic or optical formats for further processing. It must be biocompatible, capable of long-term operation, and positioned optimally for reliable reception.
- *Detector:* The detector receives analog molecular or ionic signals from the in-body receiver and transduces them into digital or electrical representations. This is typically realized via nano-electronic, electrochemical, or optical sensors. It interfaces with both the in-body *Rx* and the processor. Its accuracy is crucial for signal decoding in noisy biological environments.
- *Synchronizer (clock/timing controller):* Timing synchronization is crucial for the correct detection, modulation, and decoding of molecular signals, especially in time-sensitive MC modulation schemes. It resides within or adjacent to the processing chip to control sampling, timing windows, or packet detection.
- *Processor:* The processor interprets the detected signals using neuromorphic, digital, or spintronic architectures. It applies decoding algorithms, error correction (if applicable), and context-aware filtering (e.g., noise thresholding, spike sorting). It coordinates with the modulator and possibly sends feedback to the in-body transmitter in closed-loop systems (e.g., neural prostheses).
- *Modulator:* The modulator prepares the outgoing response or control signal based on the processed data, mapping it to a specific output channel (e.g., back to molecular signaling, EM transmission, or THz output). It enables signal encoding for upstream or downstream communication, particularly when relaying processed information to external systems.
- *Transmitter* (*TX* - on-chip or wireless interface): The external or on-chip transmitter converts processed data into a wireless communication format, typically using RF, THz, or optical signaling. It may be a nano-antenna or micro-EM transmitter and connects to the Internet or local network. It ensures data integrity, synchronization, and physical layer modulation.
- *Medium (Internet or TCP/IP protocol stack):* The medium is the digital communication network, typically leveraging TCP/IP, Message Queuing Telemetry

Transport (MQTT), or IoT-friendly protocols. It ensures reliable, structured transmission of cell-to-cell communication data to remote processing centers, databases, or other implants. The choice of protocol affects latency, bandwidth, and scalability.

- *Receiver* (*RX* - remote server or interface): The final receiver is a server, computer, or control system that captures and stores or reacts to the transmitted signal. It may apply high-level analytics (e.g., AI-based emotion decoding or digital twin modeling). It can send commands back through the same network path to alter implant behavior or cell stimulation strategies.[3]

The in-body receiver (Rx) in Layer 1 is a bio-integrated component, typically an invasive nano-biosensor implanted directly in the tissue (e.g., neural or vascular sites), responsible for capturing molecular signals via electrochemical or optogenetic transduction [61]. It operates independently from the on-chip elements, interfacing through a bio-electronic boundary where molecular concentrations are converted to electrical potentials. This separation ensures biocompatibility, as the Rx handles wet biological interfaces without silicon exposure, reducing inflammation risks [55].

3.2 Generic architecture of cell-to-cell communication

The proposed reference model for generic cell-to-cell communication, illustrated in Fig. 1, is structured into three distinct but interdependent layers: (i) the **In-body** Layer (See Table 4), responsible for molecular signal generation, propagation, and reception within biological systems; (ii) the **On-chip** Layer (See Table 5), where molecular-to-electrical transduction and digital processing occur; and (iii) the **Communication Channel** Layer (See Table 6), which bridges internal physiological signaling with external computational infrastructure via standard networking protocols.

3.2.1 Layer 1: In-body (L1-IB)

This layer constitutes the molecular substrate of cell-to-cell communication. Signaling is accomplished using molecular messengers propagated through a medium (e.g., extracellular fluid, blood plasma) and captured by bio-integrated implants.

- *On the transmitter* (*Tx*) side: The biological or synthetic transmitter (e.g., genetically modified cell or embedded nanomachine) initiates communication by releasing messenger molecules. These may encode data using concentration-based, type-based, or release-time modulation. Let $S(t)$ denote the molecular emission signal, modeled as:

$$S(t) = \sum_{i=1}^{N} a_i \cdot \delta(t - t_i)$$

where a_i is the number of molecules released at time t_i, and $\delta(t)$ is the Dirac delta function. The propagation follows one of the three MC paradigms:

  - **Diffusion-based:** governed by Fick's second law:

[3] In certain applications, the receiver may also incorporate a digital twin of the biological system. This digital twin, a virtual representation of the individual's cells or tissues, can provide a powerful tool for simulating and predicting the effects of interventions or for personalized medicine applications. The digital twin can also enhance the analysis of received signals by providing a context for interpreting deviations from expected behavior.

Table 4 Algorithm 1 (L1-IB): InBody molecular communication

Input(s)

1) Data ← digital bit stream to be transmitted
2) Modulation Type ∈{CSK, MTSK, RTSK}
1) Channel Type ∈{Diffusion, Flow, Walkway}
1) Environment Parameters ←{D, v, λ, pH, Temp}

Output(s)

1) Concentration Profile ← time-dependent molecule distribution
2) Received Signal ← molecular signal at *Rx* location

Procedure

1) *function* Encode Molecular Signal(Data, Modulation Type)
2) switch Modulation Type:
3) case CSK:
4) Emit molecules: $a_i \propto$ bit value
5) case MTSK:
6) Map bits to molecule types: m_i
7) case RTSK:
8) Encode bits into timed releases: t_i
9) return Molecular Signal Profile *S*(*t*)
10) end *function*
11) *function* Propagate Signal(*S*(*t*), Channel Type, Environment Parameters)
12) switch Channel Type:
13) case Diffusion:
14) Solve $\frac{\partial C}{\partial t} = D\nabla^2 C - \lambda C$
15) case Flow:
16) Solve $\frac{\partial C}{\partial t} + v\nabla C = D\nabla^2 C$
17) case Walkway:
18) Simulate Markov chain with $P = [p_{i,j}]$
19) return Concentration Profile *C*(*x*, *t*)
20) end *function*
21) *function* Receive And Decode(*C*(*x*, *t*), $Rx_$Position)
22) Measure $y(t) = h(t) \times S(t) + n(t)$
23) Apply decoding based on modulation
24) Return Received Signal ← estimated bits
25) end *function*
26) *S*(*t*) ← Encode Molecular Signal(Data, Modulation Type)
27) *C*(*x*, *t*) ← Propagate Signal(*S*(*t*), Channel Type, Environment Parameters)
28) Received Signal ← Receive And Decode(*C*(*x*, *t*), $Rx_$Position)
29) return *C*(*x*, *t*), Received Signal

$$\frac{\partial C(x,t)}{\partial t} = D \cdot \nabla^2 C(x,t)$$

where *C*(*x*, *t*) is concentration at position *x* and time *t*, and *D* is the diffusion coefficient.

– **Flow-based:** governed by the advection–diffusion equation:

$$\frac{\partial C(x,t)}{\partial t} + v \cdot \nabla C(x,t) = D \cdot \nabla^2 C(x,t)$$

where *v* is the velocity of the bulk fluid.

- **Walkway-based:** applicable when molecules are transported by active nanomachines, modeled as a discrete-time Markov chain with transition matrix $P = [p_{ij}]$ defining movement across network nodes.*On the receiver* (*Rx*) side:

Table 5 Algorithm 2 (L2-OC): OnChip signal processing

Input(s)

1) Molecular Signal ← sampled from in-body *Rx*
2) Clock Signal ← Synchronization reference
3) Decoding Model ←{threshold, ML, DL-based}
4) Action Policy ← Rule set or ML model

Output(s)

1) Digital Bits ← decoded data
2) Control Signal ← feedback or next action trigger

Procedure

1) *function* Sample And Align(Molecular Signal, Clock Signal)
2) Align sampling window ΔT with Clock Signal
3) Extract features {peak amplitude, time, type}
4) return Signal Feature Vector
5) end *function*
6) *function* Decode(Signal Feature Vector, Decoding Model)
7) if Decoding Model == threshold:
8) Apply rule-based threshold decoding
9) else if Decoding Model == ML:
10) Apply likelihood maximization
11) else:
12) Use DL model (e.g., RNN) for prediction
13) return Digital Bits
14) end *function*
15) function Generate Control Signal(Digital Bits, Action Policy)
16) Interpret bits using Action Policy
17) Generate voltage, light pulse, or molecule release command
18) return Control Signal
19) end *function*
20) Signal Feature Vector ← Sample And Align(Molecular Signal, Clock Signal)
21) Digital Bits ← Decode(Signal Feature Vector, Decoding Model)
22) Control Signal ← Generate Control Signal(Digital Bits, Action Policy)
23) return Digital Bits, Control Signal

An invasive implant or nano-electrode system (e.g., FET-based biosensor, carbon nanowire arrays) detects the arrival and concentration of signaling molecules. These are decoded based on modulation format:

$$y(t) = h(t) \times S(t) + n(t)$$

where $h(t)$ is the channel impulse response (e.g., for diffusion $h(t) = \frac{1}{\sqrt{4\pi Dt}} \exp\left(-\frac{(x-vt)^2}{4Dt}\right)$), and $n(t)$ is the molecular noise (e.g., ligand binding/unbinding noise, modeled as a Poisson or Gaussian process).[4] High-fidelity reception may incorporate receptor binding kinetics, described by:

$$\frac{dB(t)}{dt} = k_{on} \cdot C(t) \cdot (R_{tot} - B(t)) - k_{off} \cdot B(t)$$

[4] To further refine the modeling of molecular noise, advanced stochastic processes can be employed. For instance, the Ornstein-Uhlenbeck process [78] can more accurately capture the temporal correlation of noise fluctuations in molecular concentrations. Additionally, fractal Brownian motion can be used to model anomalous diffusion, where the diffusion coefficient is not constant but varies with time, a phenomenon observed in crowded cellular environments [79]. These advanced stochastic models provide a more nuanced understanding of the noise characteristics in MC channels.

Table 6 Algorithm 3 (L3-CC): External comm interface

Input(s)

1) Digital Bits ← encoded data from on-chip layer
2) Protocol Stack ←{TCP/IP, MQTT, custom}
3) Error Correction Scheme ←{Hamming, CRC}
4) Receiver Info ←{IP, endpoint model}

Output(s)

1) Transmission Status ∈{Success, Failure}
2) Feedback Command ← Optional downstream data

Procedure

1) *function* Packetize And Encode(Digital Bits, Error Correction Scheme)
2) Apply encoding (e.g., add parity or syndrome bits)
3) Format packet headers, timestamps
4) return Data Packet
5) end *function*
6) *function* Transmit(Data Packet, Protocol Stack, Receiver Info)
7) Use wireless module (e.g., THz antenna or RF)
8) Send packet via chosen protocol (e.g., MQTT.publish)
9) Await ACK from receiver
10) if ACK received then
11) return Success
12) else
13) Retry or declare Failure
14) end if
15) end *function*
16) *function* Listen For Feedback()
17) if channel open:
18) Receive response
19) Parse into Feedback Command
20) else:
21) Feedback Command ←*NULL*
22) return Feedback Command
23) end *function*
24) Data Packet ← Packetize And Encode(Digital Bits, Error Correction Scheme)
25) Transmission Status ← Transmit(Data Packet, Protocol Stack, Receiver Info)
26) Feedback Command ← Listen For Feedback()
27) return Transmission Status, Feedback Command

where $B(t)$ is the number of bound receptors, R_{tot} is the total number of receptors, k_{on} and k_{off} are binding and unbinding rates, respectively[5].

The algorithmic presentation of this layer (L1-IB) process is shown in Table 4.

3.2.2 Layer 2: On-chip (L2-OC)

This layer enables the conversion of analog biological signals into processable digital information. It is composed of nano-bioelectronic transducers, embedded neuromorphic processors, and specialized modulators. The process of L2-OC is formalized in Table 5.

[5] It is highlighted that advanced modeling of the **In-body** layer can also incorporate the effects of the extracellular matrix (ECM) [80]. The ECM, a complex network of proteins and polysaccharides, can significantly influence molecular diffusion, binding, and degradation. Modeling ECM interactions can lead to more accurate predictions of signal propagation and improve the design of implants and MC systems. For instance, the ECM's porosity and charge can create heterogeneous diffusion environments, affecting both the speed and directionality of molecular signals.

- *On the transmitter*(*TX*) side: The on-chip module receives input from the internal processor and encodes it into suitable control signals (e.g., voltage patterns, neurotransmitter pulse trains) for the biological *Tx* (e.g., via optogenetic stimulation or microfluidic molecule release). The modulator applies molecular modulation strategies like:

  - **CSK**: Bit b_i is encoded by releasing a corresponding molecular quantity Q_i.
  - **MTSK**: Each symbol maps to a distinct molecular type $\{m_1, m_2, \ldots\}$.
  - **TSK**: Symbol value determines release time within a symbol period.

Modulation mapping is computed as:

$$M : \mathbb{B}^k \to \mathcal{M}, \quad \text{with } \mathcal{M} = \{\text{molecular pulse profiles}\}$$

- *On the receiver*(*RX*) side: The on-chip detector converts molecular concentration or receptor binding activity into electrical signals using nanoscale FETs or optical sensors. A processor (e.g., neuromorphic chip, spintronic core) performs signal decoding, filtering, and contextual interpretation. The detector in Layer 2 functions as a neuromorphic processor on a dedicated nano-chip, distinct from the in-body Rx. It receives transduced electrical signals from the Rx via wired or wireless nano-links (e.g., THz antennas [68]) and employs spiking neural networks (SNNs) for decoding:

$$\frac{dV(t)}{dt} = -\frac{V(t)}{\tau} + \sum_i w_i \delta(t - t_i),$$

where $V(t)$ is the membrane potential, τ the time constant, and w_i weights tuned to molecular patterns [74]. This on-chip placement allows for low-power computation (<10 pJ/operation) and real-time noise filtering, separate from the Rx to enable modular upgrades without re-implantation. Detection algorithms may employ thresholding, matched filtering, or machine-learning-based inference. The maximum likelihood estimate of bit b given signal y under additive noise is:

$$\hat{b} = \arg\max_{b \in \mathbb{B}} P(y|b)$$

The signal can then be post-processed for emotion mapping, decision-making, or feedback actuation, forming a closed-loop interface[6].

For real-time decoding of molecular signals, especially in high-density nano-networks [38], compressive sensing techniques [12, 13] can be incorporated into the on-chip processing [74, 75]. Compressive sensing allows for signal reconstruction from a limited number of samples, reducing the energy consumption and processing load. This is particularly relevant in scenarios where acquiring a large number of samples is impractical due to energy constraints or limitations in sensor resolution [69]. Furthermore, the integration of analog in-memory computing can provide significant speed and energy efficiency advantages for on-chip processing of molecular signals. By performing

[6] *As a completing note:* Emerging on-chip technologies, such as microfluidic processors and lab-on-a-chip devices [81, 82], offer the potential to integrate MC processing with other biological functions. These integrated systems can enable real-time analysis and response to complex biological signals, facilitating applications such as personalized drug delivery and closed-loop control of cellular processes [83, 84]. Furthermore, the integration of artificial intelligence (AI) directly on the chip can enable sophisticated signal processing and decision-making at the point of interaction [85, 86], reducing latency and improving responsiveness.

computations directly within the memory, data movement is minimized, leading to substantial power savings.

3.2.3 Layer 3: Communication channel (L3-CC)

This layer, as written in Table 6, connects the on-chip system to external digital infrastructures through standardized wireless or wired interfaces, enabling remote data processing, monitoring, and command control.

- *On the transmitter* (*TX*) side: The processed data is encoded into digital packets and transmitted wirelessly via nano-antennas (e.g., graphene-based THz antennas) or low-power RF transceivers. The transmitter must conform to communication protocols like TCP/IP or MQTT, employing error correction (e.g., Hamming codes) and flow control. The digital communication rate is determined by Shannon capacity:

$$C = B \log_2 \left(1 + \frac{S}{N}\right)$$

where B is bandwidth, S is signal power, and N is noise power. THz antennas can use beamforming and MIMO techniques to enhance transmission in scattering biological environments.

- *On the receiver* (*RX*) side: The external receiver is a server, cloud node, or edge device that receives, decrypts, and analyzes the transmitted data. It may utilize advanced inference engines (e.g., deep learning models) to interpret biological states, emotions, or commands. Furthermore, the receiver can issue return commands to the implant or cell system, forming a bidirectional feedback mechanism. The control loop may optimize therapeutic responses, emotional synchronization, or brain-to-brain information transfer.

In the proposed architecture, Layer 3 employs the TCP/IP protocol stack as a well-known example for reliable, packet-based external communication, facilitating integration with existing digital networks for applications like remote monitoring. However, this is not prescriptive; other protocols such as UDP/IP for low-latency scenarios or CoAP for constrained IoT devices could substitute, depending on bandwidth and reliability needs. Analogously, Layer 1 (in-body) requires bio-compatible protocols to manage molecular signaling, akin to TCP/IP's congestion control and error correction but adapted to diffusion dynamics and biochemical constraints.

Recent research highlights several protocols for in-body MC networks, drawing parallels to TCP/IP's layered reliability [87]. For instance, DNA-based protocol stacks offer error correction via nucleotide redundancy [88], while MoMA provides multiple access control for nano-transmitters [89]. Table 7 compares these with TCP/IP, evaluating metrics like reliability, latency, and bio-compatibility.

Table 7 illustrates that while TCP/IP excels in digital reliability, in-body protocols prioritize bio-compatibility and energy efficiency, often trading latency for robustness in stochastic environments. For example, DNA stacks mimic genetic error correction [88], achieving lower error rates in noisy channels than traditional MC without increasing molecular load. Justification for TCP/IP as an example lies in its ubiquity and proven scalability, but for hybrid bio-digital systems, integrating L1 protocols like MoMA

enables seamless cross-layer operation, as explored in recent intra-body nanonetworks [91].

3.2.4 Layer 4 (optional): Cross-layer molecular digital twin architecture

The proposed cross-layer molecular digital twin (MDT) model, introduced in Sect. 3, is a dynamic, real-time computational representation of the physiological and molecular signaling states across the **In-body** (L1-IB), **On-chip** (L2-OC), and **Communication Channel** (L3-CC) layers. Unlike traditional digital twins used in industrial or clinical settings [92], which focus on macroscopic systems (e.g., organs or medical devices), our MDT operates at the cellular and molecular scale, integrating multi-modal data from molecular concentrations, neural signals, and environmental parameters to enable context-aware interpretation and feedback.

The MDT is defined as a function $\mathcal{T}_i(t) = f_{\text{bio}}(C(x,t), E(t), H(t))$, where $C(x, t)$ is the molecular concentration field, $E(t)$ represents emotion-linked neural inputs, and $H(t)$ denotes the physiological health state. This model is updated iteratively using real-time data streams from the in-body receiver (Rx) and processed via the on-chip layer (L2-OC). The architecture leverages a hybrid approach, combining physics-based simulations (e.g., fractional diffusion equations) with data-driven machine learning models to predict molecular signal dynamics and optimize feedback control [93].

The MDT operates across layers as follows:

- **L1-IB**: Captures molecular concentration profiles $C(x, t)$ via invasive implants and models their propagation using the fractional diffusion equation (see Sect. 3). The MDT integrates ECM properties (e.g., porosity, charge) to refine signal predictions [80].
- **L2-OC**: Processes raw molecular signals into feature vectors, using neuromorphic processors or DL models (e.g., recurrent neural networks, RNNs) to map $C(x, t)$ to physiological or emotional states [85].
- **L3-CC**: Transmits processed data to external servers, where the MDT is synchronized with cloud-based analytics to refine predictions and issue control commands (e.g., drug release or neural stimulation).

Table 7 Comparison of Protocols for In-Body MC (Layer 1) vs. TCP/IP (Layer 3 Example)

Protocol	Type/Layer Fit	Reliability (Error Rate)	Latency (Typical)	Bio-Compatibility	Key Feature
TCP/IP	Digital/External (L3)	High ($< 10^{-6}$ BER) via ACKs	ms-s	Low (EM-based)	Congestion control, flow reliability
TCP-like MC [87]	Molecular/In-body (L1)	Medium ($10^{-3} - 10^{-4}$) via retransmission molecules	s-min	High (bio-chemical)	Molecular ACKs, rate adaptation to diffusion
DNA Protocol Stack [88]	Synthetic DNA/In-body (L1)	High ($< 10^{-5}$) via parity nucleotides	min-h	Very High (biomimetic)	Error correction codes in DNA sequences
MoMA [89]	Nano-multiple access/In-body (L1)	Medium (10^{-3}) via TDMA-like	ms-s	High (nano-relay)	Scalable multi-transmitter coordination
Bio-chemical Relay [90]	Relay-based/In-body (L1)	Low-Medium (10^{-2}) via amplification	s	High (protein-based)	Embedded relays for signal boosting

The MDT's relation to existing digital twin architectures is summarized in Table 8. Unlike organ-level twins [92], which rely on imaging and macroscopic sensors, our MDT focuses on molecular-scale interactions, enabling applications such as real-time emotional state decoding and personalized drug delivery. The model employs a state-space representation for dynamic updates $\mathcal{T}_i(t+1) = \mathcal{T}_i(t) + \Delta\mathcal{T}_i(t;\theta)$ and $\Delta\mathcal{T}_i(t;\theta) = g(C(x,t), E(t), H(t);\theta)$, where $g(\cdot;\theta)$ is a neural network parameterized by θ, trained on molecular and neural data to predict state transitions. This ensures context-aware adaptation to physiological changes, such as stress-induced molecular fluctuations [93].

This cross-layer integration enhances the MDT's ability to provide personalized, predictive, and adaptive responses, making it a cornerstone for next-generation bio-digital communication systems.

3.2.5 Fractional Brownian motion in molecular signal modeling

To enhance the realism of molecular signal propagation in the **In-body** Layer (L1-IB), our framework incorporates fractional Brownian motion (fBm) to model the stochastic dynamics of molecular noise and anomalous diffusion in complex biological environments [79]. Unlike standard Brownian motion, which assumes independent increments and Gaussian noise, fBm captures long-range temporal correlations and non-Gaussian statistics, which are prevalent in crowded cellular media such as the extracellular matrix (ECM) or cytoplasm [94]. This is critical for accurately modeling diffusion-based MC, where molecule propagation deviates from classical Fickian diffusion due to molecular crowding and viscoelastic properties of the medium.

The fBm process is characterized by the Hurst parameter $H \in (0,1)$, which governs the degree of correlation in molecular displacements. For $H > 0.5$, fBm exhibits persistent behavior (positive correlations), while $H < 0.5$ indicates anti-persistent behavior, both of which are observed in biological systems [95]. The molecular concentration profile $C(x, t)$ under fBm-driven diffusion is modeled using a fractional diffusion equation:

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} = D_\alpha \nabla^2 C(x,t) - \lambda C(x,t) + \xi_H(t),$$

where $\alpha \in (0,2]$ is the fractional derivative order, D_α is the generalized diffusion coefficient, λ is the degradation rate, and $\xi_H(t)$ is an fBm noise term with covariance $\mathbb{E}[\xi_H(t)\xi_H(s)] \propto |t-s|^{2H-2}$. This model extends the classical diffusion equation presented in Algorithm 1 (Table 4) by accounting for anomalous diffusion, which improves the accuracy of the *Propagate_Signal* function.

Table 8 Comparison of Molecular Digital Twin with Traditional Digital Twins

Feature	Molecular Digital Twin (MDT)	Organ-Level Digital Twin	Device-Based Digital Twin
Scale	Cellular/Molecular	Organ/Tissue	Mechanical/Electronic
Data Source	Molecular concentrations, neural signals	Imaging, physiological sensors	IoT sensors, telemetry
Modeling	Fractional diffusion, DL-based prediction	Finite element analysis, CFD	Physics-based simulations
Applications	Emotional decoding, drug delivery	Disease progression, surgery planning	Predictive maintenance
Feedback	Real-time molecular control	Clinical decision support	Device optimization

In Algorithm 1, fBm is integrated into the *Propagate_Signal* function by simulating the molecular concentration profile $C(x, t)$ using a numerical solver for the fractional diffusion equation. Specifically, we employ a Grünwald-Letnikov discretization to approximate the fractional derivative:

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} \approx \sum_{k=0}^{N} \frac{(-1)^k \binom{\alpha}{k} C(x, t - k\Delta t)}{(\Delta t)^\alpha},$$

where $\binom{\alpha}{k}$ is the generalized binomial coefficient, and Δt is the time step. The fBm noise $\xi_H(t)$ is generated using a circulant embedding method to ensure computational efficiency [95]. This approach enhances the robustness of signal propagation modeling by capturing the heavy-tailed distribution of molecule arrival times, reducing decoding errors in the *Receive_And_Decode* function by up to 25% in simulated heterogeneous media, as validated in [94].

By incorporating fBm, our framework better reflects the stochastic nature of MC channels, enabling more reliable decoding of concentration-based (CSK) and timing-based (RTSK) modulation schemes in biologically realistic scenarios.

The separation between the in-body Rx and on-chip detector facilitates a robust cross-layer interface, where signal fidelity is preserved through impedance-matched transduction. In practice, the detector analyzes temporal patterns for modulation schemes like MTSK, achieving >95% accuracy in emotion decoding scenarios [96]. This design draws from hybrid implant systems, ensuring the Rx remains biologically embedded while the detector leverages silicon-based efficiency [50].

3.3 Evaluation

The proposed three-layer reference model for cell-to-cell communication, comprising the **In-body** Layer, **On-chip** Layer, and **Communication Channel** Layer, establishes a comprehensive and scalable framework that accurately models and enables molecular and neuro-inspired communication at biological and digital interfaces.

3.3.1 Emotion-sensitive communication via algorithmic integration

The proposed framework claims to enable "emotion-sensitive bio-digital communication systems" by decoding molecular and neural signals correlated with emotional states. To substantiate this, we elaborate on how the algorithms in Tables 4, 5, and 6 integrate emotional intelligence (EI) principles, leveraging neuromorphic processing and molecular signal patterns linked to emotional biomarkers [96].

In the **In-body** Layer (L1-IB), Algorithm 1 (Table 4) captures molecular signals, such as neurotransmitter concentrations (e.g., serotonin, dopamine) or stress-related cytokines (e.g., cortisol), which are established biomarkers of emotional states [14]. The *Receive_And_Decode* function processes these signals using receptor binding kinetics $\frac{dB(t)}{dt} = k_{on} \cdot C(t) \cdot (R_{tot} - B(t)) - k_{off} \cdot B(t)$, where $B(t)$ represents bound receptors, and $C(t)$ is the concentration of emotion-linked molecules. By mapping $B(t)$ to specific emotional states (e.g., high serotonin for positive affect), the algorithm identifies emotional patterns with high fidelity [96].

In the **On-chip** Layer (L2-OC), Algorithm 2 (Table 5) employs neuromorphic processors to decode these molecular signals into emotional states. The *Decode* function uses a spiking neural network (SNN) model:

$$\frac{dV(t)}{dt} = -\frac{V(t)}{\tau} + \sum_i w_i \delta(t - t_i),$$

where $V(t)$ is the membrane potential, τ is the leak time constant, and w_i are weights trained on emotional biomarker datasets [97]. This allows the system to classify emotional states (e.g., stress, joy) based on molecular spike patterns, achieving accuracies of up to 85% in preliminary neural simulations [96].

The **Communication Channel** Layer (L3-CC) (Table 6) transmits these decoded emotional states to external systems, enabling applications like remote emotional touching. For instance, a high serotonin concentration detected in L1-IB can trigger a feedback command in L3-CC to stimulate a recipient's sensory cortex, simulating an emotional connection [98]. This closed-loop system integrates EI by mapping molecular data to emotional contexts, validated by recent studies on oxytocin-mediated emotional bonding [98].

3.3.2 Functional completeness and layered modularity

Each layer in the model has been formally defined with distinct responsibilities, ensuring clarity of operation and minimizing cross-layer interference:

- The **In-body** Layer supports multiple molecular propagation paradigms (diffusion, flow, and walkway-based), making it versatile for different tissue environments (e.g., vascular systems vs. cytoplasmic spaces).
- The **On-chip** Layer provides real-time molecular-to-electrical transduction, precise timing via clock synchronizers, and support for bio-compatible decoding and modulation using CSK, MTSK, RTSK, and more.
- The **Communication Channel** Layer interfaces seamlessly with external networks using standard protocols (e.g., TCP/IP, MQTT) and error-control coding, ensuring reliability and scalability for telehealth or brain-cloud applications.

The pseudocode-based algorithms corresponding to each layer reflect this layered modularity, ensuring ease of implementation, verification, and future hardware-software co-design.

3.3.3 Technical soundness and signal modeling

The signal processing within the model is technically rigorous:

- Molecular emissions are accurately modeled using Dirac impulses and governed by diffusion and advection–diffusion equations (Fick's Law), capturing spatial-temporal concentration profiles under various MC paradigms.
- Noise sources (diffusion noise, emission variance, receptor noise) are treated statistically using Poisson, binomial, and Wiener processes, ensuring realistic modeling of low-SNR environments typical of molecular systems.

- Decoding and estimation in the **On-chip** Layer apply maximum likelihood estimation ($\hat{b} = arg\ max_b P(y|b)$) and allow integration with ML/DL models for adaptive or intelligent decision-making.

These mathematical formulations ensure quantitative predictability, which is critical for simulating system behavior and estimating performance bounds (e.g., channel capacity, bit error rate). Furthermore, recent advances in computational modeling allow for in silico experimentation and optimization of MC systems. Techniques like finite element analysis and computational fluid dynamics can provide detailed simulations of molecular propagation in complex biological environments, aiding in the design of more efficient and robust communication systems. These simulations can also help to predict and mitigate potential interference and noise sources.

Information-theoretic analysis can provide fundamental limits on the performance of MC systems. For example, Fano's inequality can be used to establish lower bounds on the probability of error in decoding molecular signals, given the channel capacity and the desired data rate. Furthermore, rate-distortion theory can be applied to analyze the trade-off between the achievable data rate and the distortion in the received signal, which is crucial for applications where precise reconstruction of the transmitted information is essential. These information-theoretic tools offer a rigorous framework for evaluating the fundamental limits and achievable performance of MC systems.

3.3.4 Biocompatibility and implant integration

By accounting for three classes of implants (non-invasive, minimally invasive, and invasive), the model aligns well with real-world biomedical constraints such as energy availability via WPT, tissue compatibility via biocompatible coatings and geometries, and neural decoding fidelity, achieving sub-millisecond temporal resolution and $< 50\ \mu m$ spatial precision.

This design ensures the framework is compatible with current and near-future neural interface technologies such as Utah Arrays, Neuropixels, and DBS electrodes.

3.3.5 Scalability and interoperability

The architecture supports below important issues

- Nano-to-macro integration allows nano-machines (*Tx* and *Rx* in this study) and signal relays to connect to macro-scale digital systems (clouds, servers).
- Protocol interoperability, using Internet-standard transmission formats, ensures compatibility with existing networking and edge-computing infrastructures.
- Bidirectional communication supports the system's closed-loop actuation, enabling both forward signal flow (stimulus-to-decision) and backward flow (control-to-stimulation).

These features make the model suitable for large-scale IoNT or digital twin ecosystems.

3.3.6 Security, privacy, and ethical extensions

While not the primary focus of the current architecture, the inclusion of biochemical encryption potential [99, 100], feedback channels [101, 102], and AI-augmented on-chip processing [74, 75] sets the stage for (*i*) future secure MC protocols, e.g., physical-layer

molecule watermarking, (*ii*) authentication based on ligand-receptor specificity, and (*iii*) cognitive-state-aware access control for ethical brain-linked communication.

These considerations are essential for deploying safe and ethically aligned cell-to-cell communication systems in human-centric applications like emotional sharing and brain-to-brain connectivity.

3.4 Simulation scenario and results

To validate the proposed three-layer architecture for cell-to-cell communication, we simulate a realistic biological scenario inspired by diffusion-based MC in a crowded cellular environment, such as the interstitial fluid between neurons or endothelial cells. The scenario models two electrogenic cells communicating via neurotransmitter release (e.g., glutamate or dopamine), where the transmitter cell emits molecules in a CSK-modulated pattern, propagating through a fractional-order diffusion channel to the receiver cell. The in-body receiver (L1-IB Rx) captures the molecular concentration, which is then processed on-chip (L2-OC) using a recurrent neural network (RNN) for neuromorphic decoding, accounting for noise, degradation, and anomalous diffusion behaviors common in biological media [41, 42]. This setup mimics remote emotional touching, where emotional states are encoded in molecular patterns (e.g., varying oxytocin levels) and decoded to trigger empathetic responses.

The simulation incorporates state-of-the-art elements, including data augmentation for scarce biological datasets [103] and RNN-based prediction for channel impulse responses in MIMO MC systems [104]. We use PyTorch to implement the RNN, training it on synthetic data generated from the fractional diffusion equation:

$$\frac{\partial^\alpha C(x,t)}{\partial t^\alpha} = D_\alpha \nabla^2 C(x,t) - \lambda C(x,t), \quad 0 < \alpha \leq 1,$$

where $\alpha = 0.8$ for sub-diffusive crowding, $D_\alpha = 10^{-9}$ $\mathrm{m}^2/\mathrm{s}^\alpha$, and $\lambda = 0.01$ s^{-1}. Noise is added as Gaussian with $\sigma = 0.1$ normalized concentration units, reflecting thermal fluctuations and molecular crowding.

Table 9 details the RNN network parameters, optimized for low-power on-chip deployment in neuromorphic implants.

Qualitatively, the RNN excels in handling inter-symbol interference (ISI) and non-Gaussian noise, outperforming traditional threshold detectors by 20–30% in bit error rate (BER) under high crowding ($\alpha < 0.7$). Numerically, training on 100 time steps yields a mean squared error (MSE) reduction from 0.15 (initial) to 0.02 (final).

Table 9 RNN Network Parameters for Neuromorphic Decoding in MC

Parameter	Value	Description	Rationale
Input Size	1	Concentration time series per time step	Single-channel MC signal
Hidden Size	10	Neurons per RNN layer	Balances complexity and power (e.g., $< 1\mu$W/neuron)
Number of Layers	1	Stacked RNN layers	Minimal for real-time decoding in bio-environments
Activation	Tanh	Nonlinearity function	Captures temporal dependencies in diffusion
Learning Rate	0.01	Adam optimizer	Converges in < 100 epochs for noisy data
Batch Size	1	Training batch	Sequential nature of MC signals
Epochs	100	Training iterations	Sufficient for MSE < 0.05 in sub-diffusive channels

This simulation aligns with recent advances in synthetic cell-based RNNs for autonomous learning [105] and molecular machine learning frameworks [106], paving the way for scalable bio-digital interfaces.

3.5 Simulation results and analysis

To validate the proposed cell-to-cell communication framework, we conducted extensive simulations using a computational model of the **In-body** Layer (L1-IB) and **On-chip** Layer (L2-OC). The simulations were implemented in a Python-based environment integrating COMSOL Multiphysics for solving fractional diffusion equations and PyTorch for deep DL-based decoding [107]. The simulation setup models a 3D biological medium ($10\ \mu\text{m} \times 10\ \mu\text{m} \times 10\ \mu\text{m}$) mimicking interstitial fluid with a diffusion coefficient $D = 10^{-9}\ \text{m}^2/\text{s}$, degradation rate $\lambda = 0.1\ \text{s}^{-1}$, and fractional derivative order $\alpha = 1.5$ to account for anomalous diffusion [41].

The *Encode_Molecular_Signal* function (Algorithm 1, Table 4) was tested with Concentration Shift Keying (CSK) and Molecular Type Shift Keying (MTSK), encoding binary data (e.g., 10,110) into molecular concentrations ($a_i \in \{10^3, 10^4\}$ molecules/μm^3) or molecule types (e.g., serotonin vs. dopamine). Propagation was simulated using the fractional diffusion equation with fBm noise ($\xi_H(t)$, Hurst parameter $H = 0.7$). The receiver (*Rx*) was modeled as a nano-electrode array with receptor binding kinetics ($k_{on} = 10^6\ \text{M}^{-1}\text{s}^{-1}$, $k_{off} = 0.1\ \text{s}^{-1}$) [80].

The **On-chip** Layer employed a recurrent neural network (RNN) for decoding, trained on 10,000 simulated molecular signal samples with added noise (Poisson and fBm). Performance metrics included bit error rate (BER), signal-to-noise ratio (SNR), and decoding latency, evaluated across varying channel conditions (e.g., high vs. low molecular crowding). These simulations provide quantitative evidence of the framework's robustness and scalability.

The simulation results demonstrate the efficacy of the proposed cell-to-cell communication framework across various performance metrics. Table 10 summarizes the bit error rate (BER) and decoding latency for CSK and MTSK under different channel conditions.

The results indicate that MTSK outperforms CSK in high-crowding environments due to its specificity in molecular type detection, reducing inter-symbol interference (ISI) by approximately 40% [45]. The RNN-based decoder in Algorithm 2 (Table 5) achieved a 30% reduction in BER compared to threshold-based decoding, particularly in noisy conditions (SNR = 10 dB), due to its ability to learn temporal correlations in fBm noise [107]. Decoding latency remained below 2.5 ms, suitable for real-time applications like emotional state transmission. These findings validate the framework's ability to handle complex biological noise and support scalable, high-fidelity communication.

Table 10 Simulation Results for CSK and MTSK Modulation

Modulation	Channel Condition	BER (%)	Decoding Latency (ms)
CSK	Low Crowding (SNR = 20 dB)	2.1	1.8
CSK	High Crowding (SNR = 10 dB)	5.3	2.4
MTSK	Low Crowding (SNR = 20 dB)	1.4	1.5
MTSK	High Crowding (SNR = 10 dB)	3.2	2.0

3.6 Advanced signal processing and channel estimation techniques

Recent experimental studies in crowded cellular environments have shown that traditional diffusion models do not fully capture the non-Gaussian, heavy-tailed dynamics observed in-vivo. To address this, we extend the **In-body** Layer of our framework by incorporating fractional channel estimation methods based on fractional calculus and deep learning.

In this context, the standard Fick's second law [108] can be generalized to a fractional diffusion equation as

$$\frac{\partial C(x,t)}{\partial t} = D_\alpha \frac{\partial^2 C(x,t)}{\partial |x|^\alpha} - \lambda C(x,t) \text{ for } 1 < \alpha \leq 2$$

Where D_α is the generalized diffusion coefficient, α characterizes the anomalous diffusion exponent, and λ represents the molecular degradation rate. This formulation captures the sub-diffusive behavior and long-range dependencies encountered in dense biological media.

To further enhance our channel estimation, we introduce a DL-based estimator. Let $\{y(t_i)\}_{i=1}^N$ be the set of noisy signal samples at time instances t_i. We define the neural estimator as $\hat{C}(x,t) = f_\theta(\{y(t_i)\}_{i=1}^N)$, where $f_{\cdot}$ denotes a recurrent neural network (RNN) parameterized by θ. The network is trained to predict the underlying concentration profile $\hat{C}(x,t)$ from the noisy observations, effectively mitigating ISI induced by residual molecule counts and anomalous noise. Simulation experiments using synthetic data (modeled with fractional Brownian motion characteristics) indicate that this hybrid approach reduces decoding error rates by up to 30% compared to classical estimators, particularly in scenarios where the medium exhibits significant heterogeneity. These advanced techniques not only improve the fidelity of the molecular signal recovery but also pave the way for a cross-disciplinary integration of stochastic modeling and ML within MC systems.

3.7 Enhancing reliability with error correction codes

To ensure reliable data transmission in MC systems, advanced error correction techniques are essential, particularly given the stochastic nature of biological environments. Recent advancements have introduced Self-Orthogonal Convolutional Codes (SOCCs) as a promising approach for error correction in such systems [109].

3.7.1 Self-orthogonal convolutional codes (SOCCs)

SOCCs are designed to correct errors arising from molecular diffusion, where molecules may not arrive at the receiver or may be delayed, leading to transmission errors. The key property of SOCCs is their self-orthogonality, which facilitates efficient error detection and correction. Mathematically, a codeword c in an SOCC satisfies the condition that the inner product with any distinct codeword c', i.e., $\langle c, c' \rangle = 0$, ensuring orthogonality.

For a binary MC system, the transmitter encodes data by adding redundancy, such as additional molecules or modulating molecule concentrations. The encoding process can be represented as $c = G \cdot m$, where m is the message vector, G is the generator matrix, and c is the resulting codeword. At the receiver, the sequence is decoded by computing the inner product with possible codewords, allowing error correction based on the Hamming distance.

The performance of SOCCs has been evaluated in terms of bit error rate (BER) and energy efficiency, showing a coding gain of approximately 1.6 dB compared to un-coded systems [109]. This makes SOCCs particularly suitable for energy-constrained nanoscale devices.

Integration into the proposed framework: To incorporate SOCCs into the proposed framework, we can apply them in the On-Chip Layer (L2-OC), where analog biological signals are converted to digital data. By encoding the digital data with SOCCs before transmission through the Communication Channel Layer (L3-CC), we can significantly enhance the reliability of the cell-to-cell communication system.

Table 11 compares the performance of different error correction techniques, highlighting the advantages of SOCCs in terms of coding gain while considering energy efficiency.

3.7.2 Combining baseband modulation and channel coding for calcium signaling

Calcium signaling is a fundamental mechanism for cell-to-cell communication in biological systems and has been extensively studied for its potential in MC networks. Recent research has shown that combining baseband modulation techniques with channel coding can significantly improve the reliability of calcium signaling-based MC [110].

3.7.3 Calcium signaling and error control

Baseband modulation techniques such as Return-to-Zero (RZ) and Non-Return-to-Zero (NRZ), when combined with Reed-Solomon channel coding, can effectively mitigate errors caused by signal fading, multipath propagation, and spatial noise, which are common in biological environments. RZ modulation reduces inter-symbol interference (ISI) by ensuring the signal returns to zero between symbols, modeled as $s(t) = \sum_k a_k \cdot p(t - kT)$, where a_k is the symbol amplitude, $p(t)$ is the pulse shape (zero outside the symbol duration for RZ), and T is the symbol period. Reed-Solomon coding, on the other hand, corrects burst errors from molecular diffusion by operating over a Galois field $GF(2^m)$, enabling the correction of up to $t = \lfloor (n - k)/2 \rfloor$ errors, where n is the codeword length and k is the message length.

Integration into the proposed framework: In the proposed framework, we can apply RZ modulation in the In-Body Layer (L1-IB) for molecular signal generation and propagation. Additionally, Reed-Solomon coding can be implemented in the On-Chip Layer (L2-OC) to further enhance error correction capabilities. This combined approach will make the cell-to-cell communication system more robust against noise and interference in biological environments.

3.7.4 Error prevention through multiple molecular carriers

A cutting-edge technique in error control for MC is the use of error prevention by encoding information across multiple molecular carriers [111]. This method involves transmitting redundant information using different types of molecules or multiple

Table 11 Performance Comparison of Error Correction Techniques in Molecular Communication

Technique	Coding Gain (dB)	Energy Efficiency
Un-coded	0	High
Hamming Codes	1.0	Medium
SOCCs	1.6	Medium

Table 12 Comparison of Error Control Techniques

Technique	Complexity	Reliability
Error Correction Codes	High	High
Baseband Modulation + Channel Coding	Medium	High
Multiple Molecular Carriers	Low	Medium-High

Table 13 Novel Aspects Relative to Recent MC Reviews

Novel Element	Description	Contrast to Reviews [33, 35]
Layered Architecture	In-body to external channels	Reviews focus on single-layer physics
Emotional Integration	MC for oxytocin modulation	Absent in propagation-centric overviews
Digital Twins	Cross-layer feedback models	Not covered in DNA or MIMO reviews
Speculative Apps	Grounded in neurochem	Reviews lack bio-cybernetic extensions

transmission paths, ensuring that even if some molecules are lost or delayed, the receiver can still decode the message correctly.

3.7.5 Multiple molecular carriers

This approach leverages the diversity of molecular types to enhance reliability. For instance, a single bit can be encoded using multiple molecular species, each transmitted through different pathways (e.g., diffusion, flow-based). The receiver aggregates the signals, using a decision rule such as $\hat{b} = \text{majority}\left(\{r_i\}_{i=1}^{N}\right)$, where r_i is the received signal from the i-th molecular carrier, and N is the number of carriers. This method is particularly beneficial in dynamic in-body environments, where channel conditions can vary rapidly.

Integration into the proposed framework: To incorporate this technique, we can enhance the In-Body Layer (L1-IB) to support the transmission of multiple molecular types for each information bit. This would require advanced transmitters that can release different molecules and sophisticated receivers capable of detecting and decoding multiple molecular signals simultaneously. By adopting this strategy, the proposed framework can achieve higher reliability without relying heavily on complex error correction mechanisms, which may be resource-intensive for nanoscale devices.

Table 12 provides a comparison of different error control techniques, highlighting their complexity and reliability.

3.8 Comparison with Prior Works

This paper advances beyond recent MC reviews by proposing a unified three-layer model that bridges cellular signaling to higher-order applications, as detailed in Table 13.

Our algorithmic precision and future-proofing further differentiate, building on but surpassing [112] in scalability for real-world bio-nanonetworks.

4 Discussion

This section discusses the broader impact, emerging applications, challenges, and future directions of the proposed cell-to-cell communication framework.

4.1 Current/Future achievements and state-of-the-art applications

Here, we explore key innovations and real-world applications enabled by cell-to-cell communication and MC technologies.

- *Silicon-less communication:* By replacing conventional complementary metal-oxide semiconductor (CMOS) hardware with bio-integrated MC systems [113], silicon-less communication enables data exchange through biochemical signals such as neurotransmitters, ions, or hormones [114, 115]. This modality leverages naturally evolved molecular pathways and eliminates the need for photolithographic electronics, supporting ultra-low-power and biocompatible communications.
- *Non-silicon computation:* Cell-to-cell communication facilitates non-silicon computation using bio-logic circuits constructed from genetically engineered cells, synthetic biological networks, or neuromorphic organic processors. These systems compute through ion fluxes, ligand-binding reactions, or gene expression pathways, allowing in situ, energy-efficient decision-making inside the human body or at cellular scale [116, 117].
- *Internet of Nono Things (IoNT):* MC is central to IoNT by enabling nanoscale devices (e.g., nano-sensors, nano-actuators) to communicate via biochemical messengers rather than electromagnetic waves [38]. Cell-to-cell protocols can establish autonomous nano-networks for diagnostics, localized actuation, or immune system integration, enhancing the scalability and safety of nanotechnology ecosystems.
- *Remote drug delivery management:* Using cell-to-cell communication and MC principles, drug delivery systems can interpret molecular signals (e.g., elevated cytokine levels) [83, 84] as real-time triggers for releasing specific pharmaceuticals. Implants equipped with molecular receivers and on-chip controllers allow for precise, context-aware therapeutic interventions without human intervention.
- *Consensual telepathy:* Consensual telepathy refers to the device-less transfer of thoughts or emotional states achieved through MC-enabled brain-to-brain interfaces [14, 32]. Invasive or minimally invasive implants detect and decode neurotransmitter patterns, convert them into digital representations, and transmit to another brain implant, enabling controlled and bidirectional cognitive information sharing.
- *Remote emotional touching (bio-integrated mobile phone):* Through decoding emotion-correlated molecular signals, such as oxytocin or serotonin patterns [14], and transmitting them over MC frameworks, cell-to-cell communication can create bio-integrated communication systems that relay emotional states. This replaces tactile-based feedback with molecular signals interpreted at the sensory cortex, achieving biologically meaningful emotional connectivity.
- *Quorum sensing (QS) for bacteria and attacking them:* Cell-to-cell communication can mimic or disrupt bacterial QS, a natural MC mechanism in which bacteria communicate via autoinducers [118, 119]. Artificial implants or nano-agents can decode QS signals and inject synthetic inhibitors or signal jammers, thereby preventing biofilm formation or initiating bacterial apoptosis through targeted molecular intervention [120, 121].
- *Lab-on-a-chip (connectionless patient management):* A molecularly controlled lab-on-a-chip leverages autonomous cell-to-cell communication to process, analyze, and respond to physiological data without continuous external connectivity [81, 82]. Bio-integrated sensors detect biomarkers, and internal MC systems regulate microfluidic actions, enabling closed-loop diagnostics and drug delivery with minimal human oversight.

4.2 Highlighted concerns

Despite its potential, cell-to-cell communication faces several technical, biological, and ethical challenges that must be addressed.

- *Slow rate mathod:* MC inherently suffers from low data rates due to the physical limitations of molecular diffusion and receptor-ligand binding kinetics [122, 123]. Unlike electromagnetic communication, the time required for molecule transport—especially in diffusion-based MC-is governed by $t \sim \frac{d^2}{2D}$, where d is distance and D s diffusion coefficient, resulting in significant latency for even short-range transmissions.
- *Transmitter energy limmitation:* Nano- or cell-based transmitters are severely energy-constrained, particularly when operating in-vivo. The generation, storage, and controlled release of signaling molecules consume metabolic or harvested energy, often bounded by mitochondrial ATP synthesis rates or nano-scale WPT efficiency [69].
- *ISI and positivity of the input signal:* ISI arises from the residual concentration of previously transmitted molecules, violating symbol isolation and degrading decoding accuracy [124]. Moreover, the positivity constraint on the molecular signal $S(t) \geq 0$ (as molecule counts cannot be negative) limits signal shaping strategies and complicates the design of optimal modulation schemes and filters.
- *Noise:* Reducing noise has several aspects [122, 123, 125, 126].

  1. Diffusion noise caused by the stochastic Brownian motion of individual molecules, modeled by a Wiener process, leads to probabilistic molecule arrival times and spatial dispersion.
  2. In environmental noise, molecules can degrade enzymatically or participate in unintended chemical reactions, reducing signal integrity and introducing non-linear distortions.
  3. Multiple transmitter noise causes crosstalk from nearby transmitters and introduces foreign molecules, leading to molecular interference and erroneous symbol detection.
  4. Transmitter emission noise makes variability in molecule synthesis and release mechanisms lead to fluctuations in emitted molecule count, modeled as a compound Poisson or binomial noise process.
  5. Receiver counting/reception noise causes ligand- receptor binding to be a discrete, stochastic process with saturation effects and false bindings, often modeled using a birth-death process or binomial sampling with receptor kinetics.

- *Ethical aspects:* Cell-to-cell communication systems, especially those involving implants or direct brain interfaces, raise substantial bioethical concerns regarding autonomy, consent, cognitive privacy, and manipulation of emotional states [127–129]. Molecular-based brain-to-brain communication may blur personal identity boundaries and necessitate new ethical frameworks for regulating synthetic neuro-interactions.
- *Neuro/cell hacking:* The programmability of MC opens vectors for malicious interference, such as hijacking signaling pathways or implant functions [29, 30]. Adversaries could inject synthetic molecules or modulate receptor activity to alter

neural states, suppress immune responses, or deliver false signals—making robust security, encryption, and authentication mechanisms in biochemical domains a pressing challenge.

Addressing potential concerns about metaphorical language, we emphasize that concepts like emotional touching are anchored in empirical neurobiology. Emotions emerge from cellular interactions but are mechanistically driven by neurotransmitters; for instance, fast dopamine-serotonin dynamics in the substantia nigra track social context and value, as measured electrochemically in humans [130]. Misleading interpretations are mitigated by framing these as bio-inspired extensions, not direct equivalents, aligning with recent calls for precise terminology in neurotechnology [131]. By integrating fractional-order models of molecular diffusion with emotional decoding, our work avoids reductionism, instead portraying emotions as network-level outcomes of cellular communication [132].

4.3 Future direction

This subsection outlines promising research directions and technological advancements needed to mature and secure the field.

- *Medium-based communication:* Future cell-to-cell communication systems will benefit from adaptive medium-aware communication strategies, where the molecular propagation medium itself becomes part of the modulation logic [133, 134]. This involves dynamically altering or sensing medium properties, such as viscosity, flow velocity, pH, or ion concentration, to optimize molecule propagation, reduce noise, and enhance channel capacity. Such strategies will likely leverage smart microenvironments and stimuli-responsive hydrogels to actively guide signaling molecules along preferred pathways.
- *Molecular medium access control (MMAC):* Analogous to MAC in traditional networks, MMAC aims to regulate access to the MC channel shared by multiple transmitters [135, 136]. Since molecular signals persist in the medium (due to slow degradation), MMAC must address inter-user interference, synchronization, and collision handling. Emerging MMAC schemes explore time-slot assignment, molecule-type multiplexing, and stochastic contention resolution based on reaction kinetics, requiring the development of bio-compatible protocols with probabilistic fairness and bounded ISI.
- *AI-empowered systems and DL for determining the best pattern:* Integrating AI and DL into MC systems enables adaptive pattern recognition, predictive decoding, and channel estimation in noisy or dynamic environments. DL models (e.g., RNNs, GNNs, and spiking neural networks) can learn complex molecular signal patterns and optimize transmitter-receiver configurations [85, 86]. These systems support real-time decoding of molecular bursts, estimation of concentration fields, and feedback-driven control of signal encoding — making cell-to-cell communication systems highly intelligent and self-optimizing.
- *Security and privacy aspects in MC and cell-to-cell communication:* Ensuring security and privacy in MC is a fundamental open problem due to the lack of established cryptographic protocols in molecular domains [128, 129] (for more details, see Sect. 4.4). Future work must address biochemical authentication, molecular watermarking,

and signal cloaking to prevent spoofing, eavesdropping, and unauthorized stimulation. Bio-compatible physical-layer security (e.g., randomness in diffusion noise, receptor access control) and bio-encrypted molecular encoding schemes will be essential to protect cognitive privacy and prevent neuro-hacking in brain-linked MC applications.

- *Digital twin co-simulation:* Future MC systems may synchronize real-time molecular data streams with dynamic digital twins of the individual's body, allowing for predictive modeling of molecular behaviors and optimizing treatment decisions before deploying real molecules [137–139]. This requires integrating physics-based solvers with real molecular telemetry.
- *Fractal channel modeling:* Incorporating fractional Brownian motion and Levy flights to model molecule propagation can capture non-Gaussian and bursty signaling [140, 141] in cell-to-cell pathways. The corresponding noise profile diverges from traditional white or Gaussian assumptions and demands new modulation and estimation techniques.
- *Spin-based MC coding:* Quantum-level spintronic MC encoders may offer ultra-miniaturized, energy-efficient options for encoding molecular bitstreams [142–144]. Mapping binary states to spin-aligned molecule clusters allows the construction of spin-polarized release profiles, potentially usable in high-density neural regions.

Future research must bridge physical-layer advancements in MC to real-world applications, addressing gaps through integrated, multi-scale approaches. For drug delivery, enhancing MAC protocols with AI-driven rate control can enable precision targeting, as in QS-inspired cooperative systems where bacteria sense density to trigger release [145]. Recent work demonstrates MC relays for intra-body drug propagation, reducing off-target effects by 30–50% in simulations [146].

Quorum-sensing interference leverages MC to disrupt bacterial biofilms, with nano-relays modulating autoinducer molecules for antimicrobial defense [147]. Emerging studies integrate this with non-silicon processors, using DNA computing for adaptive sensing [148].

For speculative yet feasible ideas like consensual telepathy, lower-layer noise modeling (e.g., fractional Brownian motion for anomalous diffusion [95]) supports high-fidelity neural signal relay via BCIs, as seen in multi-person brain nets [149]. Remote emotional touching could evolve through oxytocin-modulated MC, with spintronic interfaces enabling real-time empathy sharing [150].

Key directions include (*i*) AI-optimized error correction for noisy bio-channels, bridging to closed-loop drug systems [151], (*ii*) Ethical frameworks for BCI-telepathy, ensuring consent in molecular relays [152], (*iii*) Scalable nanonetworks for microbiome-brain axes, linking QS to neurological apps [153], (*iv*) Quantum-enhanced MC for ultra-low power telepathy [154], and (*v*) Translational trials integrating MC with Neuralink-like implants for emotion decoding [155]. These advancements, grounded in 2024–2025 developments, narrow the gap by combining simulation-validated models with clinical prototypes [156, 157].

4.4 Integration of physical-layer molecular cryptography and privacy-preserving cchemes

As MC systems transition from proof-of-concept to practical applications, ensuring data confidentiality, integrity, and privacy becomes paramount [158–160]—especially in

applications such as consensual telepathy and remote emotional touching. We propose a novel approach to embedding cryptographic primitives directly into the physical layer of molecular channels by exploiting the natural randomness of molecular diffusion.

In our framework, let W denote a witness string derived from the stochastic ligand-receptor binding dynamics, which is inherently noisy and unique to each transmission event. We then define a cryptographic key K as a function of this witness $K = g(W)$, where $g(.)$ is a one-way function whose inversion is assumed to be computationally infeasible. The corresponding encrypted message is given by $E_K(M) = Enc(K, M)$, with $Enc(.)$ representing a state-of-the-art symmetric encryption scheme. This scheme is reminiscent of witness encryption, where message decryption is contingent on possessing a valid witness—in our case, the molecular binding pattern—which naturally varies with the biological environment.

By fusing this bio-physical randomness with standard cryptographic techniques [158], the proposed scheme offers several advantages.

- *Robustness to eavesdropping:* The molecular noise, previously viewed as a detriment to decoding accuracy, now provides an intrinsic layer of security, making unauthorized signal interception significantly more challenging.
- *Dynamic key generation:* As W varies over time, keys can be dynamically regenerated, enhancing the system's resilience against replay attacks.
- *Physical-layer authentication:* The specific statistical distribution of W can serve as a biometric signature, allowing receivers to authenticate the source of the molecular signal without additional overhead.

Preliminary analyses suggest that, under standard computational hardness assumptions, the secrecy of $E_K(M)$ can be guaranteed even under a constant probing attack. Future work will focus on quantitatively deriving the secrecy capacity for molecular channels and exploring integration with error-correcting codes tailored to ISI-affected environments.

5 Conclusion

In this study, a comprehensive and biologically grounded architecture for cell-to-cell communication was proposed. By leveraging the principles of MC, a three-layer reference model was developed that encompasses in-body molecular signal transmission, on-chip signal detection and processing, and communication through external digital infrastructures. Key components across all layers were described and evaluated in terms of their role, technical capabilities, and suitability for different MC modalities. Furthermore, it was demonstrated that this communication paradigm enables a wide array of futuristic applications, including consensual telepathy, remote emotional touching, and immune system interfacing, while remaining compatible with nano-bioelectronics, neuromorphic computing, and quantum-enhanced sensing technologies. Despite these advancements, several challenges were identified, such as energy limitations, noise resilience, security risks, and ethical concerns.

The proposed architecture and analysis are expected to guide future efforts toward building biologically integrated, emotionally aware, and computationally robust communication systems at the cellular and subcellular level.

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