An Architecture of Calcium Signaling for Molecular Communication Based Nano Network

Amitava Mukherjee, Sushovan Das and Soumallya Chatterjee

1 Introduction

The Nobel laureate physicist Richard Feynman, in his famous speech in 1959 entitled "There's Plenty of Room at the Bottom", has pointed out the concepts in nanotechnology and described how the manipulation of individual atoms and molecules would give rise to more functional and powerful man-made devices. In his vision, he talked about having a billion tiny factories able to manufacture fully functional atomically precise nano-devices [1]. Several scaling issues would come up when reaching the nanoscale, which would require the engineering community to rethink totally the way in which nano- devices and nano-components are conceived. There is a need to rethink and redesign the way in which components and devices are created by taking into account the new properties of the nanoscale. A whole new range of applications can be enabled by the development of devices able to benefit from these nanoscale phenomena from the very beginning. These are the tasks at the core of the nanotechnology. Nanotechnology has been maturing since early 21st century.

A. Mukherjee (✉)
IBM India Private Limited, DLF IT Park I, Rajarhat Newtown,
Kolkata 700156, India
e-mail: amitava.mukherjee@in.ibm.com

S. Das · S. Chatterjee
Department of Electronics & Communication Engineering,
Jadavpur University, Kolkata 700032, India
e-mail: tapas1das2@gmail.com

S. Chatterjee
e-mail: sbchat13@gmail.com

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"Nanotechnology mainly consists of the processing of, separation, consolidation, and deformation of materials by one atom or by one molecule [1]." When the first simple structures on a molecular scale were obtained, the activities surrounding nanotechnology began to increase slowly and this term became more socially accepted in the early 2000s. The development of nanomachines, i.e., integrated functional devices consisting of nano-scale components which are able to perform simple tasks at the nano-level, is the aim of nanotechnology since 2000 onwards. Going one step ahead, the interconnection of nanomachines in a network or nanonetwork is proposed as the way to overcome the limitations of individual nano-devices.

2 Overview of Nanonetworks Comprising of Nanomachine (Node)

A nanonetwork is a system of interconnected or communicating nanomachines which may be conventional nanoelectronic devices, biological cells or biomimetic devices. From the term 'nano' it simply comes in our mind that one or more of the basic components of this network i.e., the transmitter, receiver, medium or message carriers are of nano-scale dimension (nano-scale refers to dimensions of 100 nm). Communication plays a very critical role in different aspects of nano-scale applications. Unlike conventional networks, nanonetworks use different physical principles than standard communication systems. These physical principles are suited to nanoscale systems, but have significantly different properties at the macroscale. In nanonetworks communication between two nano-machines can mainly takes place either using terahertz frequency electromagnetic wave or using molecular communication that are briefly discussed below.

2.1 Electromagnetic Communication

This is based on transmission and reception of classical communication principles need to undergo a change before being used in nanonetworks. Existing RF and optical transceivers suffer from several limitations that query the feasibility of EM communications among nano-devices. Few researchers have been working on the state of the art in molecular electronics of the terahertz band (0.1–10.0 THz) for EM communication among nanodevices [2]. A new propagation model for EM communications in the terahertz band is developed based on radioactive transfer theory and in light of molecular absorption [2]. This model accounts for the total path loss and the molecular electromagnetic radiations from components based on novel nano-materials. There are two ways for electromagnetic (EM) communication in the

nanoscale: (i) Receive and demodulate an electromagnetic wave by means of a nano-radio, i.e., an electromechanically resonating carbon nanotube (CNT) that decodes an amplitude or frequency modulated wave and (ii) or by graphene-based nano-antennas used as potential electromagnetic radiators in the terahertz band. The tera-hertz band waves are very much prone to absorption noise. This is major limitation during propagation of Tera-hertz band waves over short distances [2].

2.2 Molecular Communication

Molecular communication is defined as the transmission and reception of information by means of molecules. Molecular communication is a new paradigm for communication between biological nanomachines over a nano and microscale range [3]. The molecular communication provides a mechanism for a nanomachine (i.e., a sender) to communicate information by propagating molecules (i.e., information molecules) that represent the information to a nanomachine (i.e., a receiver) [3].

Molecular communication involves four basic steps:
A transmitter encodes information in terms of different types of molecules or varying the concentration of molecules or ions, the transmitter nano-machine releases those stream of molecules known as molecular wave into an aqueous environment which acts as the propagation medium, this molecular wave propagates through this aqueous environment (propagation medium), a receiver nano-machine receives this molecular wave and finally the receiver nano-machine decodes the original information from the received molecular wave. Molecular transceivers are easy to incorporate in nano-machines due to their size are of nano-scale dimensions and molecular communication is also much more compatible compared to electromagnetic communication in nano-networks. Different molecular communication techniques are based on molecule propagation like walkway-based communication, flow-based communication and diffusion-based communication. Calcium (Ca^{2+}) signaling based communication occurring as biological cellular communication is a diffusion based communication (the propagation mechanism associated here is electro-diffusion).

A biological cell uses molecular communication that involves communication of information-carrying intracellular or intercellular molecular signals to accomplish sophisticated biological functions like respiration, nerve impulse conduction, hormone secretion, etc. However, understanding the role of cellular signaling in normal cell functioning and also under pathological conditions requires systematic modeling of the network (i.e., the interconnection) of cells and incorporating proper mathematical models for quantification of the associated electrochemical phenomena. One form of cellular signaling is calcium signaling in which the concentration of a stream of calcium ions (Ca^{2+}) is modulated spatio-temporally to bring about muscle contraction, cell differentiation, hormone secretion, etc. [4].

Besides the above two communication mechanisms mentioned there are some mechanisms in nano-networks. For example acoustic communication is also possible in communication between nano-machines but it is mainly based on transmission of ultrasonic waves. This mode of communication requires the nano-machines to be integrated with ultra-sonic transducers which should be capable to sense the rapid variations of pressure produced by ultrasonic waves and to emit acoustic signals accordingly. Again, the size of these transducers is a major problem during their fabrication and integration in the nano-machines.

In nanomechanical communication, the information is transmitted through hard junctions between linked nano-devices. The main drawback of this type of communication is that a physical contact is required between the transmitter and the receiver. Moreover, this physical connections should be precise enough to ensure that the desired mechanical transceivers are aligned correctly. This communication technique is not suitable in many application scenarios where nano-machines are deployed over large areas where physical-contacts between the interconnecting nano-machines are impossible. In Sect. 3, we briefly discuss the different types of communication scenarios in nano-network and highlight the basic features of those communications.

3 Communication Among Nano-Machines

A single nanomachine can perform simple tasks and in order to assemble more computational power for performing more complex tasks, it is imperative for nanomachines to be able to communicate with each other and work cooperatively. Commutation among nano-machines can incorporate two scenarios: (a) Communication between a nano-machine and a larger system, (b) Communication between two nano-machines [2]. As we have stated earlier that communications between nano-machines can be done in mainly in two ways. (a) Molecular communication, (b) Electromagnetic wave communication using terahertz frequency range.

3.1 Molecular Communication

In molecular communication, information is encoded in the type of molecules transmitted or in the concentration changes of ions. It is most suitable for communication in biological nanonetworks due to its bio-compatibility. This communication can take place over short range (from nm to mm) using molecular motors or calcium signaling, as well as over a long range (from mm to km) using pheromonal transport or molecular neuro-spike communication [2, 5]. The different types of molecular communication are discussed below.

3.1.1 Molecular Communication Using Molecular Motors

This is an analogue of wired communication for the nano-domain is a very useful way of molecular communication over short distance (nano-scale range). Most of intra-cellular communication are based on communication using molecular motors. In this form of molecular communication, different nanomachines are connected by microtubules which are like rails along which traffic of molecular motors can move. Molecular motors are protein based carriers of molecules that use chemical energy from ATP to walk along the microtubules carrying molecules from one point to another within the aqueous intracellular space as shown in Fig. 1. Different molecular motors have different step lengths and are capable of doing a certain amount of work. For instance, kinesin is a molecular motor that uses one ATP molecule to move steps of eight nm and in each step it generates six pN of force [6]. Molecular motors support bidirectional transport as they can move either from the centre of the cell to its periphery or the opposite and are said to be positive- ended or negative-ended. Specific molecular motors are able to carry different molecules using these intracellular molecular rails. Depending on the traffic, molecular motors move at a speed up to 400 mm/day [2]. By this ability of carrying molecules molecular motors act as carriers to transport information, i.e., molecules from the transmitter to the receiver nano-machine.

Basic communication features:
Molecular communication enabled by molecular motors takes place in aqueous medium [2]. The environment should include the necessary components and the biological and chemical conditions like temperature, humidity, medium viscosity and pH should be suitable for communication. As here the information is based on the chemical nature of the molecules, the nano network is highly sensitive to these conditions and the communication process can be adversely affected by sudden variations of these environmental conditions [2]. A proper network infrastructure should be developed before the beginning of the communication process. Depending

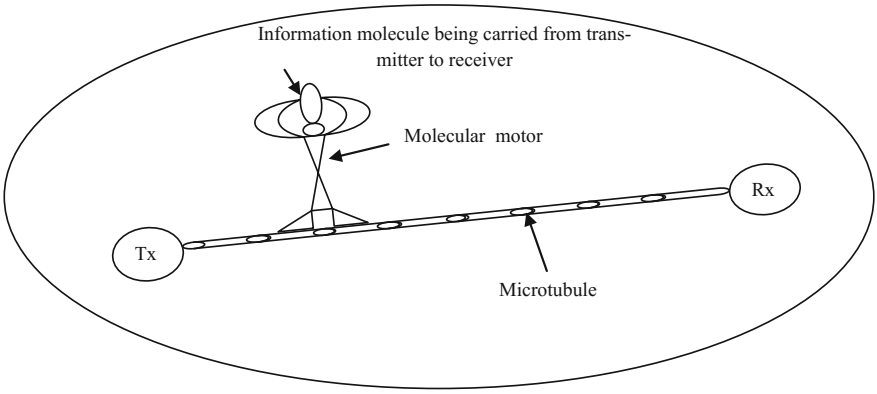


Fig. 1 Molecular communication over microtubules using molecular motors

on the nano-network infrastructure, a transmitter nano-machine will be able to support unicast or multicast communication [2]. To implement the unicast communication (i.e., communication from one single transmitter to one certain single receiver) the transmitter will have to be able to select a specific molecular rail to transmit the information molecule so that the information can reach to that particular destination receiver. To achieve a multicast communication(i.e. communication from one single transmitter to a certain group of receivers), the transmitter will have to release several molecules, each molecule containing the same data through different molecular rails so that each of these molecules reaches to different destination receivers. The propagation of molecular motors along a microtubule is unidirectional. But by indicating polarity we can also get bi-directional communication.

Communication process using molecular motors: Molecular motors carry the information molecules according to particular molecular rails from transmitter to receiver. To facilitate the reception, the transmitter uses protein tags that bind to specific receptors on receiver nano-machines [2]. The whole communication includes the following tasks:

Encoding: This is basically the generating of proper information molecule by selecting the right molecule according to the information (modulating signal). The entire process is related to the transmitter, when an external stimulus (information) is applied to the transmitter nano-machines the information molecules are generated by the transmitter. Thus it is possible to control the reaction of the reaction of the receiver according to the proper stimulus.

Transmission: This is basically the releasing of information molecules to the medium. We have stated earlier that molecular motors act as carrier for transmission of information from transmitter to receiver, so for successful transmission there will have to remain a high affinity between the information molecules and the molecular motors. Encapsulation techniques can be used to increase the affinity between the information molecules and molecular motors.

Propagation: This basically involves the movements of carriers (molecular motors) with information molecules. Here the micro-tubules or molecular rails controls the propagation direction restriction from diffusion of random movement of information molecules through the whole medium.

Reception: This is basically the receiving the information molecules by the receiver after arrival of the information molecules to the receiver nano-machine. In this step the molecular motors containing information molecules reach to the receiver nano-machine then the information molecules are detached or extracted from the molecular motors in the receiver by different mechanisms like fusion, pore-formation etc.

3.1.2 Molecular Communication Using Calcium Signaling

Like molecular motor based communication calcium signaling is one of the most convenient way of molecular communication over short distances. This calcium signaling is the basic mechanism of intercellular communication occurring in

biological cells. In calcium signaling, a stimulus applied to the cell generates second messengers, inositol 1, 4, 5 triphosphate (IP_3), that bind to IP_3 receptors and trigger Ca^{2+} ion release from intracellular stores [4]. These Ca^{2+} diffuse through the aqueous medium in the cell. Their concentration, $[Ca^{2+}]$, is modulated by cellular components (that act as a calcium signaling "toolkit") so as to produce different amplitudes or frequencies (spike rate) of the $[Ca^{2+}]$. This modulated $[Ca^{2+}]$ is called the Ca^{2+} signal. According to the amplitude or frequency of the Ca^{2+} signal, cellular processes such as contraction, hormone secretion, differentiation, etc. are induced depending on the type of cell in which Ca^{2+} signaling is taking place [7]. This is short range communication [2] which can be both intracellular and intercellular. The entire framework of calcium signaling based network is discussed in Sect. 6. Figure 2 shows the steps in which calcium signaling takes place.

Communication features:
As stated earlier that calcium signaling is an approach of short distance molecular communication so naturally it implies that the transmitter and receiver nano-machines should be near each other. The propagation of information is also performed in two different ways:

Direct access: When the transmitter and receiver nano-machines are physically connected Ca^{2+} can flow from the transmitter to receivers through these connections (gates). These gates simply work as gap junctions allowing the flux of ions flowing from one nano-machine (transmitter) to another nano-machine (receiver) [2].

Indirect access: If there is not any physical connection between the transmitter and receiver then to transmitter will have to release the information based Ca^{2+} signal to the medium. Then the Calcium signal can flow through the medium by diffusion mechanism (more properly electro-diffusion) and ultimately received by the receiver.

From these two propagation schemes, it is clear that the main communication mechanism is diffusion and there are no pre-defined communication paths like molecular rails. These are discussed in Sect. 1.3.1.1. So this type of communication mainly supports braoadcast or multicast not unicast.

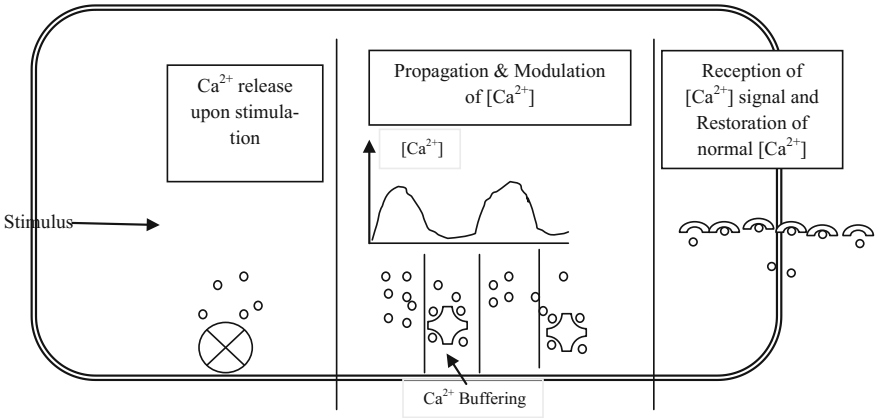


Fig. 2 Molecular communication using calcium signaling

Communication process using Calcium signaling: As discussed above that there two scenarios of information propagation in calcium signaling based nano-networks. In direct access the nano-machines are physically located one next to each other. The receiver can be any of these nano-machines members of these network. In indirect access method, the signals are directly released in the propagation medium (normally aqueous cytosol) by the transmitters and signals propagate through the medium and ultimately reaches to receiver. In both scenarios, the communication process contains following basic steps:

Encoding: This is the step involving generating information molecules. In calcium signaling based system when an external stimulus is applied the transmitter nano-machine encodes the information using Ca^{2+} concentration. The information is precisely encoded in amplitude and frequency of the function (modulating signal) describing the concentration of Ca^{2+} signal. An external stimulus is required to initiate the encoding process. It has been found that external stimulus applied to the cell cause the generation of IP_3 substance inside the cell. This presence of IP_3 unleashes the release of Ca^{2+} ions to the medium of Ca^{2+}.

Transmission: This involves the initiation of signalling. In direct access scheme, transmitter nano-machines stimulate neighbouring cells and consequently the signalling process starts. The signalling generates the initiation of propagation of Ca^{2+} waves [2]. Due to stimulus IP_3 is generated in the neighbouring cells. Now this presence of IP_3 cause more generation of Ca^{2+} ions by the neighbouring nano-machines. In the indirect access technique, transmitters may initiate signalling by releasing substances to the environment. Similar processes to cell fission or pore formation could be used by nano-machines to release the information molecules [2].

Propagation: In direct access when IP_3 is transmitted to neighbouring cells or nano-machines Ca^{2+} is released from the IP_3-sensitive Ca^{2+} stores. Then IP_3 is diffused to new neighbouring nano-machines and Ca^{2+} is released from these nano-machines. This chain reaction causes an increase of the Ca^{2+} concentration on the nano-machines which needs to be communicated and as a result, the Ca^{2+} wave propagates across the networked nodes (nano-machines) affected by IP_3. This propagation can be controlled varying the permeability of the gates or gap junctions [2]. When nano-machines use indirect access, the information molecules are propagated through diffusion (more specifically electro-diffusion) or Brownian motion. When these information molecules bind to the receptors of the receiver nanomachines, they are translated into Ca^{2+} internal signals [2]. In indirect access the medium participates more actively during propagation of Calcium signals than direct access. The medium has components like mitochondria, buffer, ER, SOC (source operated channel), VOC (voltage operated channel), ROC (receptor operated channel) etc., which can affect the Ca^{2+} concentration during propagation in many ways. So we can say that the propagation of Ca^{2+} from transmitter to receiver is very much medium controlled unlike other communication systems. So during propagation transmitter nano-machines should consider the medium conditions such as flow, temperature, pH etc. to ensure that the information molecules will arrive to the intended receiver.

Reception: In direct reception receiver nano-machine establishes gap-junctions with the neighbouring cells and perceives the Ca^{2+} concentration from inside of these cells [2]. After the message is received the receiver nano-machine closes the gates or gap junctions connecting with other nano-machines to stop further signal propagation. In the case of indirect reception receiver converts the information molecules to internal Ca^{2+} signals. A nano-machine can be equipped with different receptors to detect different information molecules [2]. This technique can be used to make parallel communication channels with different nano-machines.

Decoding: As we have stated earlier that an internal Ca^{2+} signal is generated according to the received information molecules. This Ca^{2+} signal can be encoded in amplitude and frequency to enable the activation of besides molecular motors and calcium signaling pheromones also act as a mode of molecular communication using nano-machines. Pheromones are nothing but chemicals released by organisms into the surrounding medium in order to convey messages to other members of the same species. The major difference of pheromone based communication over molecular motor based communication or Ca^{2+} signaling based communication is that as pheromones can diffuse through the surrounding medium over long distances so in this case the distance between two nano-machine are very much larger compared to the dimensions of the nano-machines whereas the distance between two nano-machines must be of nano-scale range for the other two cases. So we can say that pheromones can support communication from a transmitter nano-machine to a receiver nano-machine located at long distance apart from the transmitter [2].

3.1.3 Molecular Communication Using Pheromones

Different types of pheromones are capable of producing specific reactions in the receiving organism. Thus information is encoded in the type of pheromone used. The variety in the type of pheromones can be utilized for molecular division multiple access whereby, pheromones of different types can be released into the surrounding medium simultaneously without any interference [8]. Since the pheromones released by an organism can be sensed only by organisms of the same species, the information is secured from organisms of other species. The control and communication of nano-machines over long distances by this mechanism can be useful in many applications such as military field or environmental monitoring. Figure 3 shows pheromonal transport when there are two types of pheromones.

Communication features:

The communication is same as short distance communication implemented by molecular motors or calcium signaling but as the distance between the transmitter and receiver is very much so the channel is not deterministic here. The communication is also dependent on medium conditions like medium flow, temperature, humidity etc. Like all other molecular communication systems the message here is also encoded in terms of molecules. Since messages consist of molecules, there must be a huge number of possible combinations of molecules to encode messages.

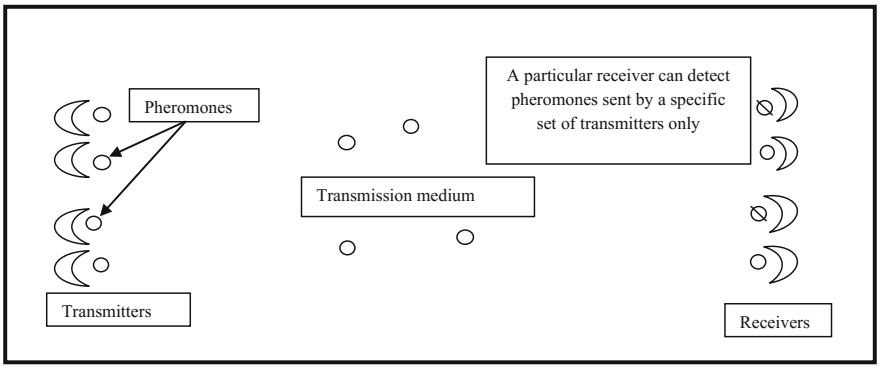


Fig. 3 Molecular communication using pheromones

Moreover, messages can be compounded by several different molecules allowing even more combinations to encode the information [2]. This reception of signals is basically ligand-receptor binding process same as in the case of calcium signalling. A ligand is a molecule that interacts and bind with a specific information molecule. In molecular communication using pheromones, the receptor proteins can be considered as the receiver nano-machine which converts the information contained in the message into a reaction at the receiver.

Communication process using pheromones: As other molecular communication processes the communication using pheromones can consists of five similar five taks which are discussed below briefly:

Encoding: Normally in a pheromone based communication a specific pheromone or appropriate molecule is used as a particular message. Encoding basically refers to the selection of proper molecules (pheromones) according to proper massages.

Transmission: This is basically the releasing of selected pheromones in the medium after the encoding process is over. The molecular messages are normally released in liquids or gases.

Propagation: The basic propagation mechanism of pheromones from transmitter to receiver is diffusion or Brownian motion. Environmental conditions like temperature, pressure, humidity etc., affect the propagation of pheromone molecules very much. Besides this, antagonist molecules present in the atmosphere may negatively the communication by modifying the information molecules before they reach the destination.

Reception: We have stated earlier that the reception of messages is a ligand-receptor binding process. Some receptor proteins do the work of this reception. When the pheromonal message reaches the receiver these receptor proteins detach the information molecules from the carrier. Generally receptor proteins are such molecules which have high affinity to the information molecules and help to detach the information molecules from the carrier.

Decoding: This is basically the extraction of information from the received message and this work is done is also done by the receptor. For example, the

antennae and the maxillary palps of a fruit fly include 1300 olfactory receptor neurons (ORN) which can 40 different odours according to their information. The decoding system is embedded in the receptor organs and can be expressed as spatial-temporal activation pattern of the receiver.

3.1.4 Molecular Neuro-Spike Communication

This type of communication may be used when nanomachines are mobile. When an information-carrying nanomachine collides with another nanomachine, they adhere to each other. After adhesion, they establish a synapse which forms the communication medium between the nanomachines. The information is transferred in the form of an action potential which is an electrical pulse of about 80 mV. These action potentials are 'spikes' that are electrochemically transmitted from one neuron to other. The signal is transmitted by means of chemical messengers called neuro-transmitters [5]. This type of communication is inspired from neural communication in the nervous system. Thus, it is referred to as 'neuro-spike' communication [5].

Communication features and processes: Similar to other communication mechanisms, the communication involves four basic steps:

Encoding: Similar to other traditional digital communication systems, two bit levels are used: spike bit 1 and spike bit 0 corresponding to logic 0 and 1 respectively. Like calcium signaling, the information is encoded in terms of molecular concentration [5].

Transmission: This process involves initialization of electrochemical signalling. When a transmitter wants to send to a spike bit 1, it activates the release of vesicles containing neuro-transmitters [5].

Propagation: As stated above the released neuro-transmitters propagate through the synaptic channel formed between the adjacent nano-machines.

Reception: The neuro-transmitters propagating through the synaptic channels reach to the receiver and bind to the receptors on the receiver membrane. The binding of neuro-transmitters to receptors cause to the opening of the ligand gated channels. So ions flow into or out of the receiver. This flow of ions changes the membrane voltage.

Decoding: Receiver nano-machine monitors the plasma membrane voltage for certain time periods [5]. When a rapid change of the membrane voltage occurs the receiver nano-machine decides the received bit as spike bit 1, when no change occurs, it is decided as spike bit 0.

3.2 Nano-Electromagnetic Communication

This type of communication is suitable for nanomachines that are developed using nanoelectronic devices. This technology is very much similar to conventional

networks using EM waves, only exception is that the device needs to be fabricated in nano-scale. A graphene based nano-antenna, carbon nanotubes (CNTs) or graphene nanoribbons (GNRs), have been shown to operate in the terahertz band (0.1–10.1 THz) [2, 9].

Communication features: Like the conventional electromagnetic communication systems here also a transmitter transmits a signal, the signal propagates through a medium (normally wire-less medium) and finally received by the receiver and the information is decoded. As the novel nano-antennas used in these cases can operate at Terahertz range frequencies the nano-transmitters and nano-receivers work in Terahertz frequency band unlike transmitters and receivers used in conventional communication systems which normally in Megahertz and Gigahertz frequency band. Though some electromechanical nano-trans-receivers are there which are able to operate at the upper range of Megahertz band but these are rarely used as their efficiency are very much low. Nano-machines may communicate using a binary stream where logic '1' is a femto-second long pulse as its frequency components are mainly in the THz band and for logic '0', non-transmission can be used. For nano-electromagnetic communication, it is also essential to develop nano-transceivers that are capable of receiving THz frequency.

Communication process:

Similar to other communication technologies this communication also includes five basic steps. The steps are discussed below:

Encoding: Encoding is the generating of proper signals corresponding to proper information. Different nano-sensors perform this work. Nano-sensors can be broadly classified in two classes: (i) Physical nano-sensors (Senses different physical quantities like mass, pressure, force etc. Working principal is based on the fact that the electronic properties of both CNTs and GNRs change with deformation). (ii) Chemical nano-sensors (Senses different chemical conditions like presence of certain molecule etc. Working principal is based on the change of number of electrons able to move through the carbon lattice of CNTs and GNRs when different molecules are adsorbed on their surface. When the information either in physical or in chemical form is sensed by the nano-sensors, they change their electronic property and generates signal in electromagnetic domain according to the information. Then the information is encoded.

Transmission: Several nano-trans-receivers (i.e., the work as both transmitters and receivers) do this job. For this job the EM trans-receiver should support baseband processing, frequency conversion, filtering, power amplification, modulation of the signals that have to be transmitted. Various graphene based FET nano-transistors are able to these works. After that the modulated signal is transmitted to the medium by nano-antennas. But all of the devices mentioned above should operate at Terahertz frequency range to incorporate them at nano-networks. For example, envisioned nano-antenna working at terahertz band frequency, RF FET transistors able to operate at these very high frequencies are necessary.

Propagation: Like other wireless communication systems, the signal propagation is the propagation of electromagnetic waves through the wireless media. We

have stated that 0.1-10 THz frequency band can be used in nano-network applications. Some other factors come during propagation of these high frequency waves. For example:

(i) ***Path loss***: This is the addition of spreading loss and molecular absorption loss. First loss occurs due to spreading of EM waves during propagation and it depends on signal frequency and transmission distance and increases with both distance and frequency independently. Molecular absorption loss is the loss caused by absorption of energy by the molecules present in the medium and converting that energy into kinetic energy of those molecules. This is basically dependent on the molecular composition of the medium.

(ii) ***Noise***: In Terahertz frequency wave propagation the noise is basically the molecular noise generated by the molecules present in the medium. This noise is neither white nor Gaussian and the power spectral density of this noise is not flat but has peaks at certain frequencies.

(iii) ***Bandwidth and channel capacity***: Molecular absorption also determines the usable bandwidth. As molecular absorption is dependent on the molecular composition of the medium tho Bandwidth capacity is also medium sensitive.

(iv) ***Multi-path fading***: Depending on the scenario in which nano-sensor devices are deployed multiple replicas of the transmitted signal will be generated at the receiver. The combination of these replicas will cause oscillations of power detected in reception and cause degradation of the received signal.

(v) ***Particle scattering***: This occurs due to scattering of EM waves by the medium particles. As high frequency are more prone to scattering, so Terahertz frequency EM wave used here is also very much affected by scattering.

Reception: Like transmission this job is also done by nano-antennas and nano-trans-receivers. The work is basically the reverse of transmission. The electromagnetic wave propagated through the medium is received by a suitable nano-antenna and then demodulated to get the modulating signal.

Decoding: Finally the signal is decoded to get the original information by a suitable decoder. This information is used to do different operations or used for stored in nano-memories for future use.

Recent advancements in molecular and carbon electronics have opened a new age of generation of various nano-electronic devices like nano-batteries, nano-memories, nano-scale logical-circuitry including logic gates and even nano-antennas. From a communication point of view, the unique properties observed in novel nano-materials characterizes the specific bandwidths of electromagnetic radiation used, the time-lag of the emission of electromagnetic waves, time-delay produced due to propagation of these waves or the magnitude of the emitted power for a given input energy for a particular nano-network. All these advancements enhance a broad change in the present state of the art of analytical channel models, network architectures or communication protocols [10].

Table 1 Differences between electromagnetic communication and molecular communication

Communication	Electromagnetic communication	Molecular communication
Carrier	Electromagnetic waves	Molecules
Signal type	Electrical signal	Chemical signal
Propagation speed	As all are EM waves so propagation speed is very high	As the propagation is basically the diffusion of information molecules though the medium so speed is very low
Medium activity	Here medium is basically passive. It can only produce noise during propagation	Medium actively participates during propagation
Noise	External electromagnetic fields	Particles and molecules present in the medium

After discussing all the communication techniques we get some main differences between electromagnetic communication and molecular communication which are listed below in Table 1.

The next section, i.e., in Sect. 4, discusses a comparative study in between molecular and electromagnetic communication.

4 Advantages of Molecular Communication Over Electromagnetic Communication in Nano-Networks

We have discussed basic two techniques of communication in nano-networks. But molecular communication is more advantageous than electromagnetic communication during connection of nano-machines due to some reasons. The reasons are discussed below:

(i) ***Easy to integrate***: Molecular transmitters and receivers are much more easy to integrate than electromagnetic transmitters and receivers or trans-receivers in nano-machines.

(ii) ***Power consumption***: The molecular communications are entirely based on some chemical processes and reactions which consume very less amount of power compared to electromagnetic nano-devices. This is the main drawback of electromagnetic communication as more power consumption means high energetic power supply will be required which will more difficult to integrate in nano-machines.

(iii) ***Affection by noise***: As we have discussed above Terahertz frequency band used in electromagnetic communication in nano-networks is very sensitive to noise wheras molecular waves are very less sensitive to external molecular noise present in the medium.

(iv) ***Limitation of distance***: In electromagnetic communication the minimum distance between transmitter and receiver will be 1 m otherwise cross-talks

and other negative effects will occur which will degrade the quality of the received signal. But in molecular communication as the information is encoded in terms of molecules so there is no limitation of distance between transmitter and receiver.

(v) ***Medium activity***: As the medium plays an active role in molecular signal propagation so signal propagation can be controlled with the help of the medium. But in electromagnetic communication the medium is passive so it cannot be used for controlling the signals.

(vi) ***Biocompatibility***: Most of the nano-networks used till nowadays are used for mainly biochemical and biological applications. Molecular communication is more compatible to biological processes, so most biological application based nano-networks are implemented by molecular communications.

Due to these reasons most of the nano-networks are implemented using molecular communication technologies. In the next section i.e. Sect. 4, we concentrate our discussion about the architecture of nano-networks using molecular communication with Calcium signaling.

5 Proposed Architecture for Nanonetwork Using Molecular Communication with Calcium Signaling

Presently, the standard architecture for nano-communication network is being studied for the development of a comprehensive framework which would address the unique features of communication in the nano-domain [11]. We propose an architecture for nanonetworks that uses molecular communication by means of calcium signals [12, 13, 14]. In nanonetworks, the channel plays a central role in signal processing unlike conventional networks where the channel is passive and ideally acts only as a transmission medium. The calcium signaling process involves: (i) generation of stimuli; (ii) modulation (encoding) of the amplitude or frequency of Ca^{2+} concentration [Ca^{2+}] during propagation; (iii) transmission of the Ca^{2+} signal by diffusion through the intracellular space and over to the adjacent cells through the cell membrane or gap junctions; (iv) decoding of the Ca^{2+} signal [5]. In Ca^{2+} signaling, modulation of signals takes place along the channel rather than at the transmitter end. The components in the channel that take part in the modulation process may be regarded as active nodes within a passive diffusion channel. So, modelling of the overall nanonetwork as well as to model its different components is an important part. In this context, first we highlight the related works on different types of models for implementation of a nanonetwork and then we discuss our (authors of this chapter) proposed network architecture. And the protocol stack component model of the physical channel layer has been discussed in detail in the following sub sections.

Related works on different network models:

All over the world, group of researchers have been working with the different types of models for nano networks. Some of them are discussed below in brief.

(i) Based on the basic concepts of nano-networks a fast parallel multi-scale stochastic modelling based platform can be designed which will help to investigate the dynamics of large scale bacteria-based nano-networks. If the chemical signaling pathway inside each bacterium and the chemical gradients created by the receiver node can be accurately modelled the dynamics of a targeted drug-delivery system can be characterized [15].

(ii) A non-equilibrium statistical model can be developed for the dynamics of dense networks of bacteria. Secondly the chemotactic response of bacteria and their intercellular communication can be characterized for this purpose. A kinetic Monte Carlo method derived from standard Gillespie's algorithm can be used to generate realizations of the stochastic models [16].

(iii) The effect of Additive Inverse Gaussian Noise (AIGN) noise channel can be adopted in molecular communication based networks to know the corruption of information by molecular noise in the fluid medium. From this it can also be shown that use of multiple molecules leads to reduced error rate [17].

Our Proposed Architecture:

As we have pointed out, at the introduction of Sect. 5, Various processes such as Ca^{2+} release, Ca^{2+} buffering, spike generation, Ca^{2+} sequestration, sensing of Ca^{2+} signal, etc. are segregated and grouped into the four layers: Environmental Impact Control layer, Interface Control layer, Information Density Control layer and Physical Channel. This group of layers is the driver to propose this architecture of the network that is essentially channel-centric [18]. The environmental impact control layer has been proposed as the topmost layer of the architecture although it encloses the physical channel layer as it deals with all the secondary phenomena of the physical channel which affect calcium signaling but do not play a direct role in the communication process.

The different layers are discussed in detail as follows:

Physical channel

The physical channel for Ca^{2+} signaling is an aqueous medium through which Ca^{2+} ions diffuse from one region to another within a cell or among cells. Thus, it is possible to achieve intracellular as well as intercellular communication using Ca^{2+} signals. The cytosol acts as a passive, aqueous diffusion medium for Ca^{2+} signals. However, the channel, as a whole, is in no way passive since there are fixed and mobile active components within the cytosol that actively modulate the amplitude of Ca^{2+} signal during propagation. These active components are Ca^{2+} binding proteins present in the cytosolic channel, that act as Ca^{2+} buffers. Also, there are potential Ca^{2+} release sites like single membrane bound compartments like endosomes, Golgi vesicles, lysosomes, secretory granules and melanosomes which reside within the physical channel [18]. Thus, the physical channel is characterized by the distribution of active components in it. Cell organelles like mitochondria,

endoplasmic reticulum (ER), inositol 1, 4, 5 triphosphate (IP_3) receptors and various Ca^{2+} pumps form feedback loops that regulate Ca^{2+} signal frequency locally. The resultant amplitude or frequency modulated Ca^{2+} signal propagates by electro-diffusion through the cytosol. The role of this layer is to model calcium dynamics in the channel and to mathematically model electro-diffusion.

Information density control layer

A Ca^{2+} signaling network uses a broadcast scheme of information transmission. Ca^{2+} signals from a stimulated cell is transmitted to adjacent cells through different channels such as connexin channels or ionic channels like NMDA, nicotinic, purinergic ionotropic channels. Ca^{2+} permeant channels like nicotinic receptors, NMDA receptors on adjacent cell membranes are gated by ATP, acetylcholine or small amino acids like glutamate [19]. Upon application of stimulus, Ca^{2+} release into the cytosol may be initiated through mainly three different types of channels: voltage-operated channels (VOCs), receptor-operated channels (ROCs), and store-operated channels (SOCs). These channels have different mechanism of activation [20]. The VOCs are activated when the membrane potential exceeds a threshold, i.e., by membrane depolarization [21]. The ROCs may be activated by Ca^{2+} itself or by messengers like IP_3 which bind to their respective receptors to initiate release of Ca^{2+} into the cytosol. The SOCs can release Ca^{2+} ions into the cytosol only until the store is depleted to a certain threshold, depletion below which causes Ca^{2+} uptake to replenish the store [Ca^{2+}].The endoplasmic reticulum (ER) is a SOC that leaks Ca^{2+} into the cytosol all the time while Sarco-endoplasmic Reticulum Ca^{2+} ATPase (SERCA) pumps continuously restore Ca^{2+} into the ER. Ca^{2+} release is also activated by Ca^{2+} itself [18]. This is known as calcium induced calcium release.

Thus, Ca^{2+} signals may propagate using the ROCs or take the VOC route that are activated when the plasma membrane of adjacent cells are depolarized [21]. The information density control layer deals with the broadcast range control by determining the effect of multiplexing Ca^{2+} signals from different channels on the spatio-temporal propagation of the Ca^{2+} signals.

When signaling is over, the cytosolic [Ca^{2+}] must be brought down to the resting level and global Ca^{2+} homeostasis is to be established. This is done by sequestering Ca^{2+} into the mitochondria or by the action of Plasma Membrane Ca^{2+} ATPase (PMCA) pumps, Na^+/Ca^{2+} exchanger, Na^+/Ca^{2+}-K^+ exchangers which remove Ca^{2+} from the cytosol and restore resting levels of [Ca^{2+}] to around 100 nM [18]. This may lead to activation of Ca^{2+} channels of the adjacent cells and thereby facilitate propagation of Ca^{2+} signals from the stimulated cell to the surrounding cells in a broadcast fashion.

In addition, Ca^{2+} sequestration by mitochondria plays an important role in maintaining global Ca^{2+} homeostasis [22]. The PMCA help to maintain low cytosolic [Ca^{2+}] in the long run. An estimation of the pump rate and the overall rate at which Ca^{2+} homeostasis can be achieved within the cell, determines the controllability of the information density. There are also parameters that increase the effectiveness of the information density control mechanisms. For instance, the

presence of calmodulin increases the Ca^{2+} affinity of PMCA pumps as well as the pumping rate of ATPases [18].

Interface Control Layer

The amplitude or spike rate of the Ca^{2+} signal is sensed by Ca^{2+} sensors which initiate Ca^{2+} sensitive cellular processes based on the amplitude or spike frequency detected and the duration for which the signal persists in the cytosol [20]. The quantification of different types of stimuli and their relationship with the Ca^{2+} release pattern over time into the cytosol are to be determined in the interface control layer. The stimulus may be molecules of chemicals called ligands for activating the ROCs or voltage or a small triggering Ca^{2+} current. Each type of stimulus may activate Ca^{2+} release to different levels. At the receiving ends of the broadcast system, the role of this layer is to map various Ca^{2+} sensitive cellular processes with different amplitude and frequency of the Ca^{2+} signal.

The transduction of Ca^{2+} signals into cellular response in terms of stress (for contraction), volume of chemical release (for secretion), gene transcription, etc., requires modeling the associated cellular components. For instance, in cardiac cells Ca^{2+} signals bind to troponin-tropomyosin molecules followed by actin-myosin cross-bridge formation, thereby, resulting in contraction. For such a case, the role of this layer is to model the excitation-contraction (EC) coupling mechanism involving actin myosin proteins. Another task of this layer is to determine the sensitivity of different Ca^{2+} sensors (troponin C for cardiac cells) to the signal level, spike frequency and signal duration.

Environmental impact control layer

The investigation and analysis of the impact of different environmental parameters such as temperature, pH, etc. on the signaling rate or on the efficiency of information transfer is an important role of the environmental impact control layer. For instance, the transient receptor potential (TRP) channels get activated by environmental changes in temperature, pH, volatile chemicals, etc. [18]. The Ca^{2+} signals also interact with other signaling pathways such as mitogen-activated protein kinase, nitric oxide (NO), cyclic AMP, phosphatidylinositol-3-OH kinase, etc. [20]. The understanding of such interactions is crucial for determination of secondary effects that arise due to cross-talk between calcium and other channels.

We summarize the functionalities of four different layers for molecular communication based nanonetwork in Table 2.

5.1 Protocol Stack Components in Physical Channel Layer

The physical channel layer of the above mentioned four layered nano-network can be defined using the protocol stack components [11]. This stack is made up of the components (i) message carrier, (ii) perturbation, (iii) motion, (iv) field and (v) specificity. The physical channel for Ca^{2+} signaling is the cell cytosol through which Ca^{2+} ions diffuse from one region to another within the cell (intracellular) or

Table 2 Functionalities of four different layers for molecular communication

Nanonetwork reference model (Architecture)			
	Layer	Function	
5	Environmental impact control	Ability to control the channel's impact on the environment	Upper layer
4	Interface control	Ability to control the "injection" of information from the channel into the target node	
3	Information density control	Ability to control the channel signaling rate (corresponds to bandwidth)	
2	Direction control	Ability to control the direction of channel "flow" (corresponds to LINK/ROUTING)	Lower layer
1	Physical channel	The material comprising the nanonetwork channel that facilitates the flow of information	

from cell to cell (intercellular). There are also different active components like buffers, mitochondria, endoplasmic reticulum (ER), and receptors those help in the processing of the Ca^{2+} signal during propagation. The resultant modulated Ca^{2+} signal propagates by electro-diffusion through the cytosol. In other words, the physical channel layer deals with modeling of the physical processes involved in the communication of Ca^{2+} signals like binding of ligands with receptors, e.g., the binding of first messengers, IP_3, to IP_3 receptors, ensuring *specificity*; amplitude and frequency modulation of the [Ca^{2+}] by different cell components e.g. mitochondria, ER, ER pumps, buffers etc. ensuring *perturbation;* propagation of Ca^{2+} through the cells by electro-diffusion (controlled by both drift and diffusion of ions) signifying *field* and *motion* respectively. And, most importantly this modulated Ca^{2+} is the *message carrier* in this communication process. So, to model the complete physical channel we have to model the components required as well as the dynamics of the Ca^{2+} propagation (electro-diffusion).

5.2 Detail Discussion on Protocol Stack Components

Specificity: The Ca^{2+} signaling toolkit includes receptors such as IP_3 receptors and ryanodine receptors; Ca^{2+} binding proteins such as parvalbumin, calbindin, calretinin, etc., that act as Ca^{2+} buffer; intracellular Ca^{2+} stores formed by sarco-endoplasmic reticulum, cell organelle like mitochondria and Ca^{2+} sensors such as troponin C, synaptotagmin, protein kinase C, Ca^{2+}/calmodulin dependent protein kinase II (CAMKII), etc. These components specifically interact with Ca^{2+}.

Perturbation: When a cell is stimulated, Ca^{2+} released into the cytosol through a single or through multiple channels, increases the cytosolic [Ca^{2+}] from 50-100 nM to 500-1000 nM. A part of the cytosolic Ca^{2+} is bound by Ca^{2+} buffers, thereby, lowering the amplitude of the cytosolic Ca^{2+} signal. The amplitude of the Ca^{2+} signal depends on the concentration of buffers in the cell. Also, the duration of the Ca^{2+} signal varies with the concentration of fixed and mobile buffers [18].

Ca^{2+} spikes are generated by a feedback loop formed by the mitochondria, ER, IP_3 receptors and SERCA pumps. IP_3 generated upon externally stimulating the cell, binds to IP_3 receptors. This disables the SERCA pumps. Thus the ER releases Ca^{2+} into the cytosol due to its continuous leakage and is not replenished by the SERCA pump. This reduces the ER [Ca^{2+}]. The released ER Ca^{2+} increases the cytosolic [Ca^{2+}] but it is taken up by mitochondria which again reduce the cytosolic [Ca^{2+}] and cause further Ca^{2+} release from the ER [22]. However, when the ER [Ca^{2+}] falls below a threshold the SERCA pumps are again activated, net Ca^{2+} release is reduced as the depleted store is replenished by the pumps. After replenishment of the store, if IP_3 is still present in the cytosol then the process is repeated. This gives rise to regenerative local Ca^{2+} spike generation. The algorithm for Ca^{2+} spike generation is explained with the help of a flowchart in Fig. 4 and the corresponding changes in [Ca^{2+}] in the cytosol, ER and within the mitochondria are shown in Fig. 5 given below.

Discussion about the flow chart shown in Fig. 4:
When the external stimulus comes into the cell, IP_3 is started to be released and IP_3 is bounded with the IP_3 receptors. At that time, ER pumps are disabled and ER is started to release the Ca^{2+} into the cytosol. So, the [Ca^{2+}] in the cytosol is increased. Now, while this process is going on, when the cytosolic [Ca^{2+}] is crossed the threshold of Mitochondria, it is activated and starts to uptake Ca^{2+} from its surroundings. So gradually, the rate of increase of the cytosolic [Ca^{2+}] is somehow gets lowered. After some time, the Ca^{2+} concentration in the ER will be lower than the its threshold, then ER pumps are become activated and the cytosolic Ca^{2+} gets pumped into the ER. On the other side Mitochondria is still up taking the Ca^{2+} from the cytosol. So, now, due to these cooperative effects, the cytosolic [Ca^{2+}] is decreased. Thus the Ca^{2+} spike is generated and if there is more IP_3 still present in the cell, this process will be repeated again.

There are three phases of cytosolic Ca^{2+} concentration shown in Fig. 5:

(i) At first, only ER is activated and releasing Ca^{2+} into cytosol, ER pumps are disabled, so cytosolic [Ca^{2+}] is increased at that phase.
(ii) At the next phase, the cytosolic [Ca^{2+}] is crossed the threshold of Mitochondria, so Mitochondria is starting to uptake Ca^{2+} but till then ER is also releasing Ca^{2+} into cytosol, so effectively cytosolic [Ca^{2+}] comes to the peak value.
(iii) At the 3rd phase, as [Ca^{2+}] in ER is got lower than its corresponding threshold, ER pumps are enabled and ER stops leaking. So, now both mitochondria and ER pumps are taking Ca^{2+} from the cytosol. So, from the peak, the cytosolic [Ca^{2+}] is become lowered.

Due to this overall process, the nature of the variation of cytosolic [Ca^{2+}] w.r.t time will be like a sine wave and as the frequency of this wave is very high, so it will be looked like a SPIKE. This is called the spike generation process. This qualitative analysis will be cleared from the figure given below:

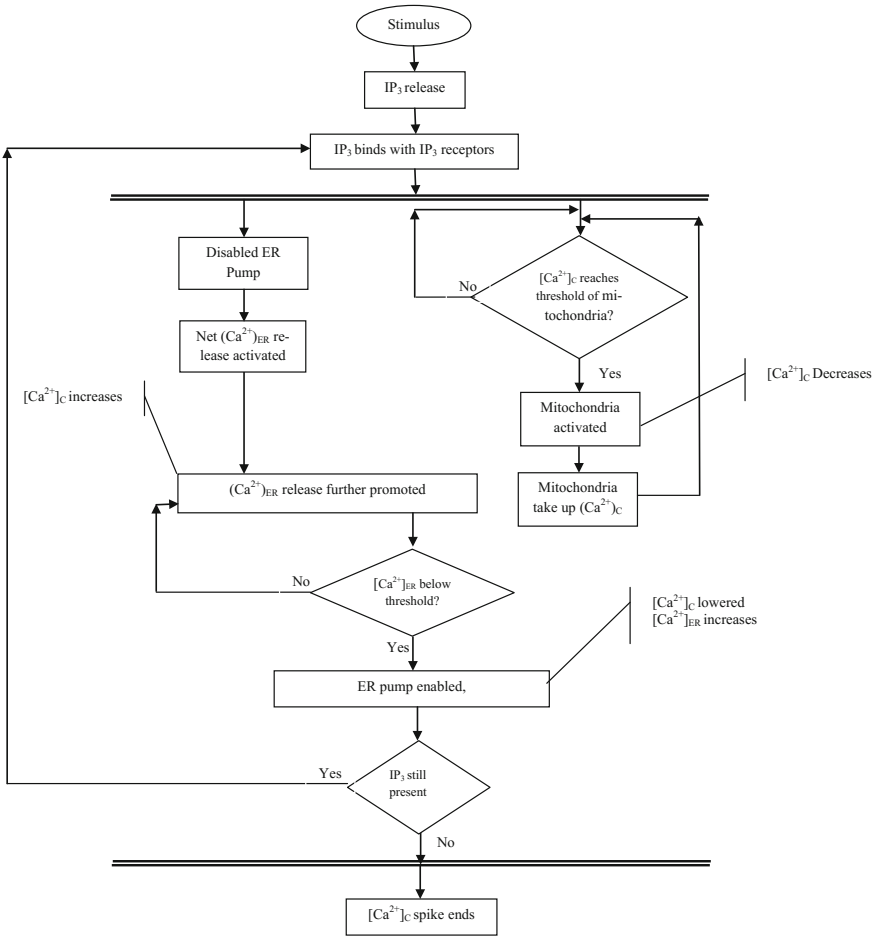


Fig. 4 Flow chart for the algorithm of Ca^{2+} spike generation

Figure 5 Calcium concentration in ER, $[Ca^{2+}]_{ER}$, mitochondria, $[Ca^{2+}]_{M}$, and spike generation in cytosolic concentration, $[Ca^{2+}]_{C.}$

Field and Motion: Ca^{2+} signals propagate within the intracellular space by electro-diffusion. Thus propagation is driven by field created by differences in potential in different regions of the cell. Also, the motion of Ca^{2+} takes place by diffusion which is governed by the concentration gradient of Ca^{2+}.

Message Carrier: The modulated concentration of Ca^{2+} constitutes the Ca^{2+} signal which carries the information regarding the cellular process to be triggered at the receiver. Hence, the Ca^{2+} ion is the message carrier propagating in the physical channel [11].

The functionalities of the protocol stack components is summarized in Table 3:

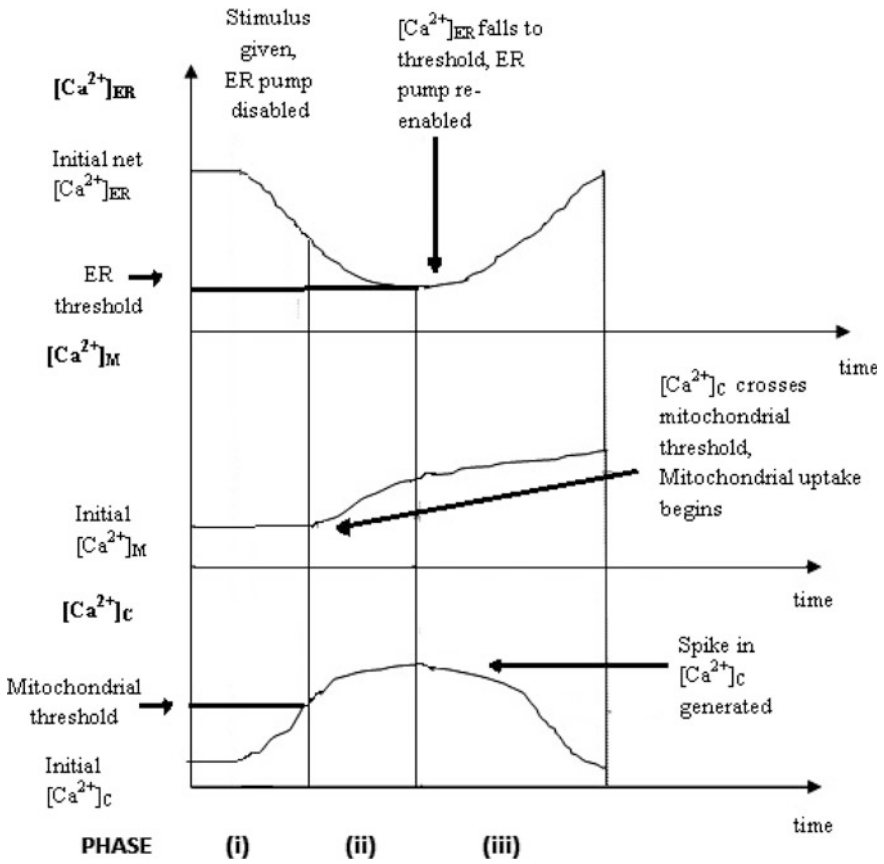


Fig. 5 Variation of Ca^{2+} concentration in cytosol, ER and Mitchodria

Figure 6 is the simplified outlook of the protocol stack components establishing the communication in the cell.

5.3 Channel Modeling and Solution Scheme

Physical channel modeling constitutes modeling components like receptors for specificity; signaling components like buffers, mitochondria, ER, ER pumps, etc. which modulate the amplitude or frequency of Ca^{2+} signals; and modeling of electro-diffusion which governs the motion of the message carrier, Ca^{2+} ions. We subdivide this task in two steps, namely, mathematical modeling of electro-diffusion and component modeling.

Table 3 Functionalities of the protocol stack components

Component level	Protocol stack component	Functionalities of protocol stack components
Component 0:	Mass or Energy [Message Carrier]	Fundamental Component: Message Carrier encodes the message. Molecular structure encodes information
Component 1:	Motion or Flow or Thrust (Force)	Builds upon Component 0. Flow rate (in any direction) caused by force/thrust of message carrier. This is the potential to form a channel Examples: Molecules diffusing through liquid, etc.
Component 2:	Field	Builds upon Component 1. This component provides organized flow. It may be thought of as routing or a virtual waveguide Examples: Fluid flow, applied EM field, etc.
Component 3:	Perturbation	Builds upon Component 2. Ability to vary message carriers as needed to represent a signal. This may be thought of as modulation (signal impression) Example: Controlled dense vs. sparse concentrations of molecules, etc.
Component 4:	Specificity	Builds upon Component 3. Ability to control sensing or attachment of message carrier to a target. This may be thought of as addressing Examples: The shape or affinity of a molecule to a particular target, etc.

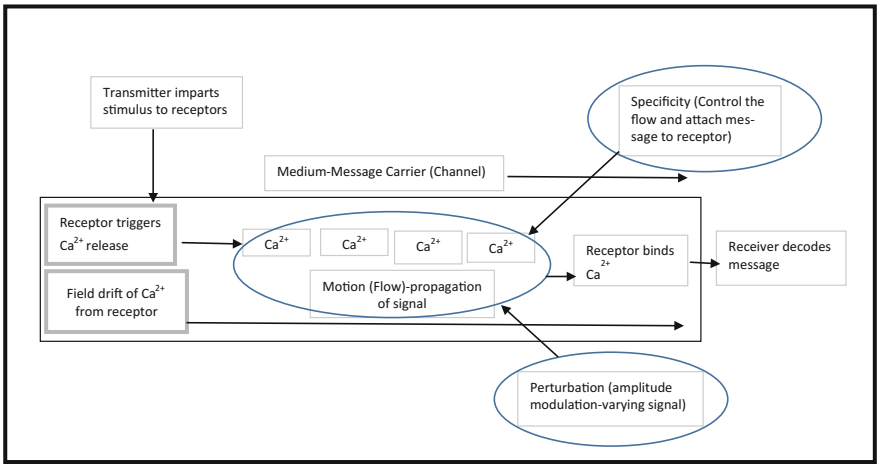


Fig. 6 Protocol stack components for calcium signaling

(i) *Mathematical model for electro-diffusion through physical channel*

The intracellular space forms the physical channel for propagation of signals. We mathematically model the propagation of Ca^{2+} in the intracellular space by electro-diffusion using electro neutral model [23]. We model a cylindrical cell as a

three-dimensional space with a cylindrical membrane. Upon reaching the membrane, these ions either add to the surface charge on the membrane or enter the extracellular space by flow of transmembrane current through the membrane ion channels. The membrane acts as a capacitor and maintains a membrane potential across it. In the electro neutral model, the ionic concentration follows ion conservation, drift-diffusion flux equation and electro neutrality condition given below:

$$\frac{\partial c}{\partial t} = -\nabla.\mathbf{f} \ldots \tag{1}$$

$$\mathbf{f} = -D\left(\nabla c + \frac{qzc}{k_B T}\nabla \mathbf{\Phi}\right) \ldots \tag{2}$$

$$0 = \rho_0 + qzc \ldots \tag{3}$$

Here, **f** denotes the flux, D is the diffusion coefficient, qz is the amount of charge of Ca^{2+}, where q is the elementary charge, i.e., the charge on a proton. qD (= $k_B T$) is the mobility of Ca^{2+} (Einstein relation) where k_B is the Boltzmann constant, and T the absolute temperature. ρ_0 is the background charge density.

Solution Scheme:
To solve the coupled P.D.Es the numerical scheme is adopted stated in [23], where a finite-volume method (FVM) is used to solve the partial differential equations (PDEs). FVM is a method for representing and evaluating PDEs in the form of algebraic equations. A cylindrical boundary is incorporated to the computational domain that represents the cytosol or physical channel within a single cell. The cell membrane is considered as a transparent boundary at present and the Ca^{2+} concentration is calculated in the intracellular region only. A three dimensional Cartesian mesh has been laid within this domain such that finite volumes (FVs) are formed. Each FV (p) has a characteristic point ($\mathbf{x}_c$) where the properties of that FV are defined. The divergence theorem is used to convert the volume integrals in a partial differential equation that contain a divergence term to surface integrals. The flux through each face common to a pair of FVs, (p, p') is then calculated. The flux entering a FV (p') is identical to that leaving the adjacent FV (p).

$$\text{At } x = \mathbf{x}_c,$$
$$\frac{\partial c}{\partial t} \approx \frac{1}{V}\int_{\text{finitevolume}} \frac{\partial c}{\partial t} dV = -\frac{1}{V}\int_{\text{finitevolume}} \mathbf{f}.\mathbf{n} d\mathbf{A} \approx -\frac{1}{V}\sum_l e_l F^l \ldots \tag{4}$$

where $F^{(p,p')}$ is the flux density approximation from FV p to p′ as. The ionic concentration is conserved when

$$F^{(p,p')} = -F^{(p',p)} \ldots \tag{5}$$

$$\frac{\partial c^p}{\partial t} = -\frac{1}{V}\sum_{p \neq p'} \left[hF^{(p,p')} + \gamma^{p,p'} G^{(p,p')}\right] \ldots \tag{6}$$

where h is the area of the face common to finite volumes p and p' and $G^{(p,p')}$ is the flux from a finite volume p to another finite volume p' that share a membrane of area $\gamma^{p,p'}$, so $G^{(p,p')}$ is termed as the membrane flux will make an effect only for the boundary FVs of the cell. For ordinary FVs in the intracellular space, $\gamma^{p,p'} = 0$, so the second term is zero. The ordinary flux $F^{(p,p')}$ is calculated using the equation

$$F = D\left[\frac{c^p - c^{p'}}{h} + \frac{qz(c^p + c^{p'})}{2K_B T}\frac{\varphi^p - \varphi^{p'}}{h}\right] \ldots \quad (7)$$

where D is the diffusion coefficient. $\varphi^p - \varphi^{p'}$ gives the potential difference between the representative points $\mathbf{x}_c$ for the finite volumes p and p'. $z = 2$ for Ca^{2+} as it is divalent. To calculate the concentration in the (n + 1)th instant from that in the nth instant of time we use the relation:

$$\frac{c^{p,n+1} - c^{p,n}}{\Delta t} = -\frac{1}{V}\sum_{p \neq p'}\left[hF^{(p,p',n)}\right] \ldots \quad (8)$$

where Δt should have a value long enough for the ions to move over from one FV to an adjacent FV in this time period. However it should not be so long that ions can move over more than one FV.

(ii) ***Behavioral modeling for components of toolkit***

(a) ***Emitters***: The emitters are randomly oriented in the cellular space acting as basic transmitters. They emit Ca^{2+} to the medium, in order to modify the concentration in its environment. The emission patterns can be of different types like square wave, sine wave, random pattern etc. The emission pattern has been configured using different mathematical functions and in later section, the corresponding emission pattern has also been observed.

(b) ***Buffers***: The buffers are modelled as a storage component which has a predefined absorption capacity. It actually takes the Ca^{2+} ions from the background near to its surroundings until it reaches the absorption capacity and then it becomes inactive. So, due to the presence of buffers, the amplitude of Ca^{2+} is lowered and by increasing the number of buffers, naturally the amplitude is reduced further. The buffers may be positioned anywhere within the space provided it doesn't coincide with any other component. They may be modelled as static or mobile.

(c) ***Mitochondria***: The mitochondrion is modelled as a transceiver with a configurable absorption capacity and threshold. It accumulates Ca^{2+} ions from the background near to its surroundings when the background concentration exceeds the threshold and absorb until it reaches the absorption capacity and when the background concentration falls to the resting level it starts releasing the accumulated ions at a slow rate.

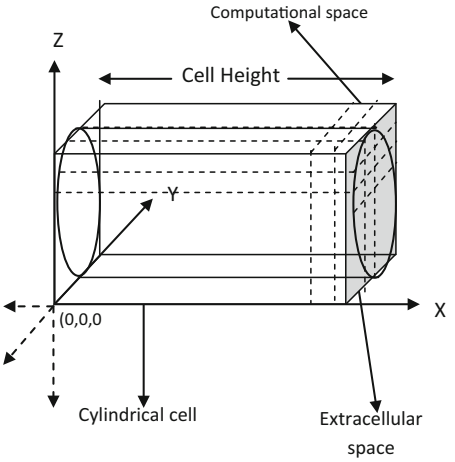
(d) ***Receptors***: The receptors are also modelled and placed randomly at different points in the cellular space. They accumulate and measure the concentration of particles within a predefined radius in their environment.
(e) ***ER and ER pumps***: The ER is modeled as a leaky store that releases Ca^{2+} continuously at a given leak rate until the store content falls to a threshold value, below which the leakage stops. During leakage, ER pumps restore the ER with Ca^{2+} at a given pumping rate.

5.4 Evaluation and Observations

Presently, we are trying to evaluate the above equations for modelling the physical channel layer of the architecture described in the previous sections and for testing the performance of the protocol stack components discussed before. A 3D cellular space is considered with a cylindrical transparent boundary in a cuboidal computational space as shown in Fig. 7i. A uniform initial background concentration has been introduced and Ca^{2+} ions have been modelled as divalent particles. The components are also being configured within the intracellular space with their respective parameters are given in Table 4 below and their different characteristics are implemented individually according to its nature and function in the signaling process. Each FV has been identified as inner, outer or boundary types on the basis of their position in the mesh. Each FV has been assigned a characteristic point, given by the geometric Centre of the FV, where the properties (potential, concentration, etc.) of the space within that FV are defined and used for calculations. The whole system should run for a certain time frame and all the components including the background concentration are updated to find the overall state of the cell in the next time frame. Figure 7ii shows the 2D cross-sectional view of the cell as a sum of finite volumes.

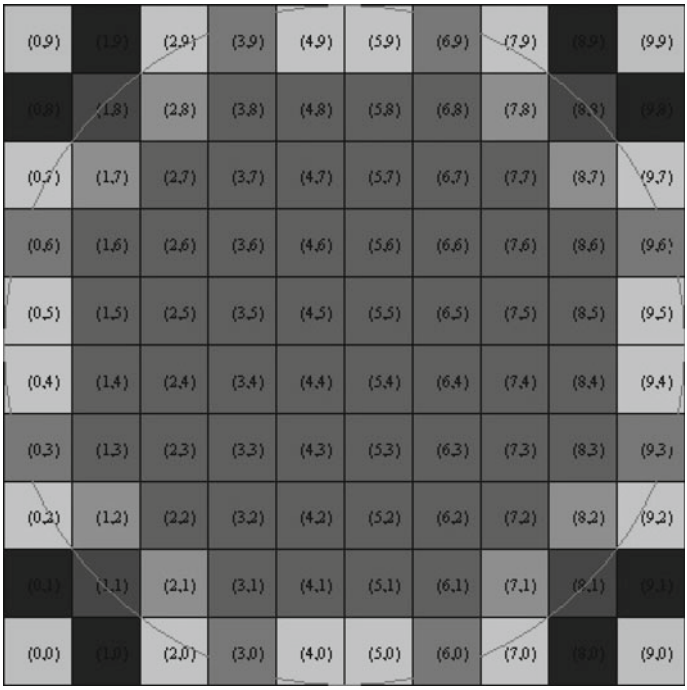
The different types of emission pattern observed after the evaluation are also given in Fig. 8. The different types of emission pattern observed after evaluation are shown in Fig. 8a, b, c.

Another important part is to model the membrane to implement the intercellular communication. To model the membrane we have to model the different type of ionic channels (e.g., ROC, SOC etc.) and then by spreading them on the membrane, the intercellular calcium signaling flow can be observed. There are another components like pumps (SERCA pump, PMCA pump etc.) and exchangers on the membrane controlling the intercellular Calcium signaling flow which are also to be modeled. So, our future work is to model the membrane by modeling the ion channels and the membrane components like pumps, exchangers etc.



The cylindrical cell arranged on 3D axis with intersection (partial)

(i) Overall cellular space



(ii) 2Dcross-section of cellular space with mesh

Fig. 7 **i** Overall cellular space. **ii** 2D cross-section of cellular space with mesh

Table 4 Component model parameters

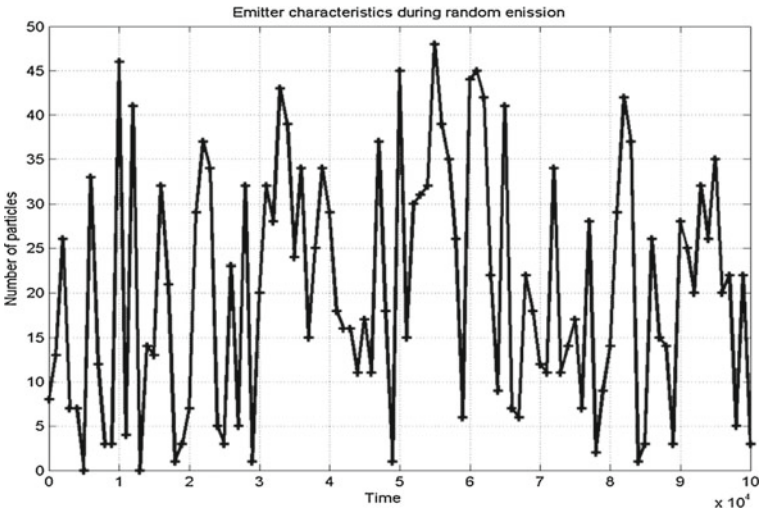
Component	Simulation parameters
Emitter	Emitter_radius (nm); x location (nm); y location (nm); z location (nm); start time (ns); end time (ns); initial speed (m/s); punctual; concentration emitter; Scale Factor
Buffer	x location (nm); y location (nm); z location (nm); absorb particles; accumulated counting; receiver radius (nm); Absorption Capacity
Mitochondria	x location (nm); y location (nm); z location (nm); threshold; absorb particles; Absorption Capacity; accumulated counting; receiver radius (nm); Signal Threshold
Receptor	x location (nm);y location (nm); z location (nm);absorb particles; accumulated counting; receiver radius (nm)
Endoplasmic reticulum	x location (nm); y location (nm); z location (nm); absorb particles; accumulated counting; receiver radius (nm); Signal Threshold; Leak Rate
ER Pumps	Pumping rate

6 Discussion of Simultion Study for Communication Principles in Simulators

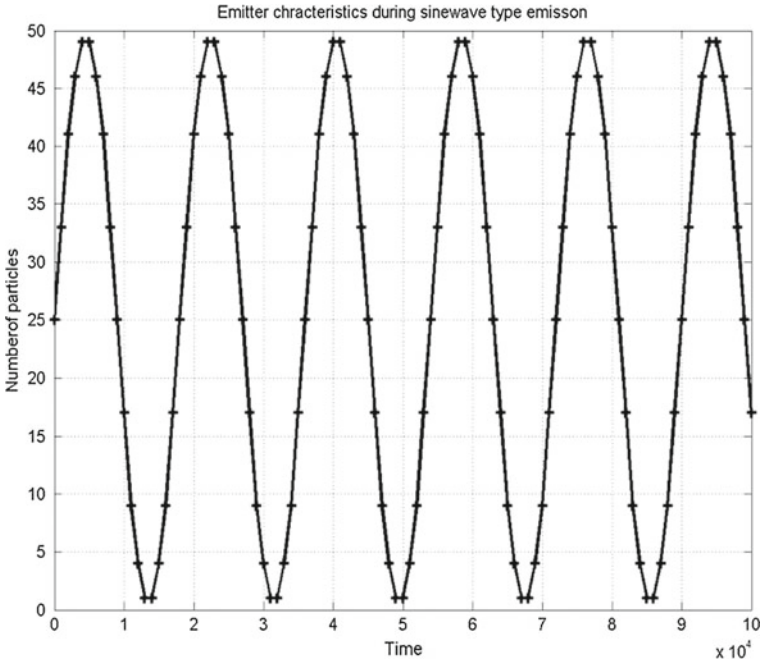
Computer simulation is used to model and analyze the physical systems. Applications of simulators into nano networking to study the behavior of its different components are relatively new. The principal idea is that if a system can be modeled, then features of the model can be modified and the corresponding results can be analyzed. As the process of model modification is relatively simpler than the complete real implementation, a wide variety of scenarios can be analyzed at the low cost relatively than to making similar changes to a real network.

Nano/molecular communication involves transmission of information at the nano-scale. This type of communication can be achieved by using terahertz frequency, transport of molecular motors, calcium signaling, pheromonal transport, etc. In order to explore the potential of nano/molecular communication for nano-networks, it is essential to study the mechanism of each of these modes of communication taking into account their unique features. A simulation framework has to be developed in order to extract the parameters that affect communication in the nano-network. However, the simulation models that take into account the unique features of nano/molecular communication are not easy to obtain. The simulation model may be based on mathematical formulation for terahertz frequency and laboratory based data for molecular communication. However, as the technology is still in the nascent stages obtaining real data may not always be possible for all forms of molecular communication. In such cases, the parameters affecting the communication are identified and the data input is made configurable by the user.

This section contains two sub-sections. In Sect. 6.1 we discuss about a number of simulators available in nano-communication research domain to use and in sub

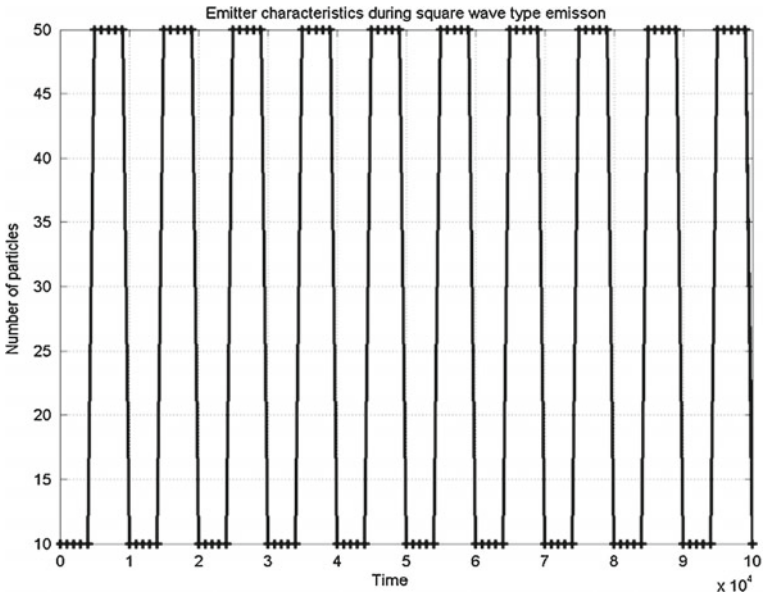


(a) Random emission



(b) Sinusoidal emission

Fig. 8 **a** Random emission. **b**. Sinusoidal emission. **c**. Square waveform emission



(c) Square waveform emission

Fig. 8 (continued)

Sect. 6.2, we have briefly introduce our (authors of this chapter) simulation framework based on *cell tool kit sim*, the work on which is going on.

6.1 Available Simulators

6.1.1 Molecular Motor Based Simulator [24]

A molecular motor based communication system uses molecular motors (such as kinesin) to actively transport along micro-tubules. The micro-tubules together may form a topology of multiple asters randomly affixed onto a surface [24]. The aster is nothing but a topology that self-organizes the microtubules and can be produced artificially from growing microtubules. The model of the molecular motor system contains simplified components for each step of a molecular communication process so that simulations run in a reasonable time for the length scale of the network (∼10–1000 μm) and the time scale of communication (∼1–100 s) [24]. The communication sender is abstracted as a component that generates a single kinesin molecule (representing the encoded information) on the molecular communication network. The communication receiver is assumed to receive and decode information molecule from nearby information molecules [24]. So one can easily design a

simulator which can support the molecular motor based communication as discussed in [24].

6.1.2 3D Brownian Motion Simulator [25]

One important work in this aspect is the modelling of the three dimensional Brownian motion of the nanoparticles. The reliable modelling of this fast distribution is needed in the high sensitivity applications in molecular recognition [25]. In this model, the nanoparticles are placed uniformly random in the 3D container and they start to walk randomly until they find the target spot. The approach for this simulation model is that if the nano particle is far from the target point, it will be simulated in larger time step and when it reaches very near to the target point, the time step is taken smaller. This is called dual time-step approach. There is a possibility of collision for those particles if they hit the rough boundary of the container. This collision is modelled with equal probability to bind the particles.

6.1.3 N3 Sim [26]

For the analysis of diffusion based molecular communication, N3Sim is one of the most well-known simulation framework [26] available in nano-network research. In this framework, the nano machines communicating in the fluid media through molecular diffusion can be easily simulated. At the transmitter nanomachine, the information is modulated at first and then this modulated information propagates through the medium to the receiver. The receiver estimates the concentration of the particles and decodes the information [26].

To run this simulator, the user has to specify the different parameters like distribution of transmitters, receivers, size of emitted particles, diffusion coefficient of the medium etc. in a configuration file. Then the diffusion takes place by the help of diffusion simulator and the outputs are stored in the receiver files containing the concentration of nanoparticles measured by the receivers as a function of time. The variation can be visualized by graphically represent the results into a single plot. Figure 9 describes the N3 Sim architecture [26].

6.1.4 Simulator Based on Java [27]

Another simulator has been made in JAVA for simulating different communication types in nanoscale. It consists of a JAVA package able to provide a set of tools for simulating different nanoscale environments [27]. This framework is quite generic in the sense that it can be customized to analyze different scenarios with different modelling schemes for types of nanomachines, communication channel etc.

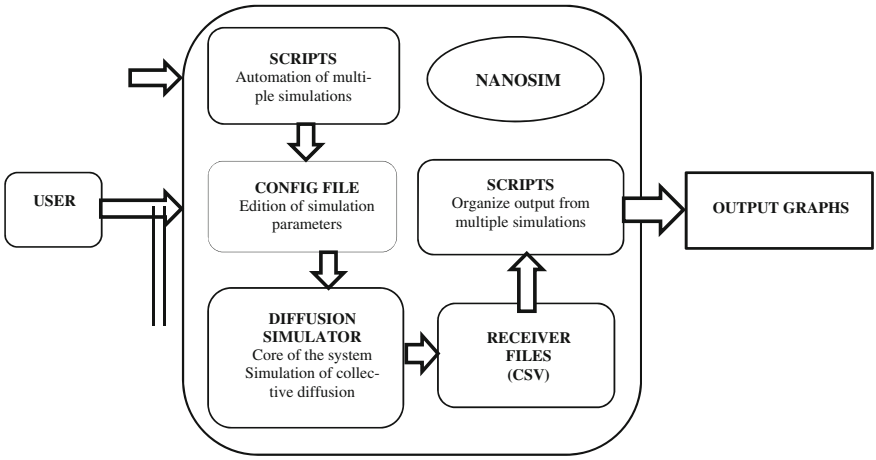


Fig. 9 N3 Sim architecture

(i) **Software architecture**:

The software package consists of different classes some of which are representing different network elements and the others are handling different operations. The software architecture has a multi-thread structure in order to optimize the performance of the computationally expensive operations, such as nano-object propagation and collision management [27]. The propagation of the nano particles are based on Brownian molecular diffusion process and there position and velocity are measured at each and every time step. Some of the classes are described as follows:

Manager class is the main class of the program. It learns from two XML files the configuration parameters that are necessary to setup the simulation environment. This class manages the three dimensional computational space (through the domain class)and controls the proper sequence of operation. The propagation phase and everything related to the simulated environment is managed by the **Mobility Model class** [27]. **Motion strategy class** determines the nature of movement of the nano-objects in the space. Carriers can be received by nodes only through specific receptors located on the outer surface of the node. The relevant code is implemented in the **Receptor abstract class** [27]. The specificity i.e. the compatibility in between the carrier and receptor is handled and taken care by **Carrier Observer Class.** Apart from them, there are **Living object observer class**, **Engine 3D class**, **Output strategy class**, **Nano object class** etc. Figure 10 represents the different classes implemented in this Java simulator.

(ii) **The software library**:

The software library of this simulator, which has been made in JAVA, provides a toolkit for simulating different types of nanonetworks and supports the possibility of simulating different types of nano-communications. The library provides also the

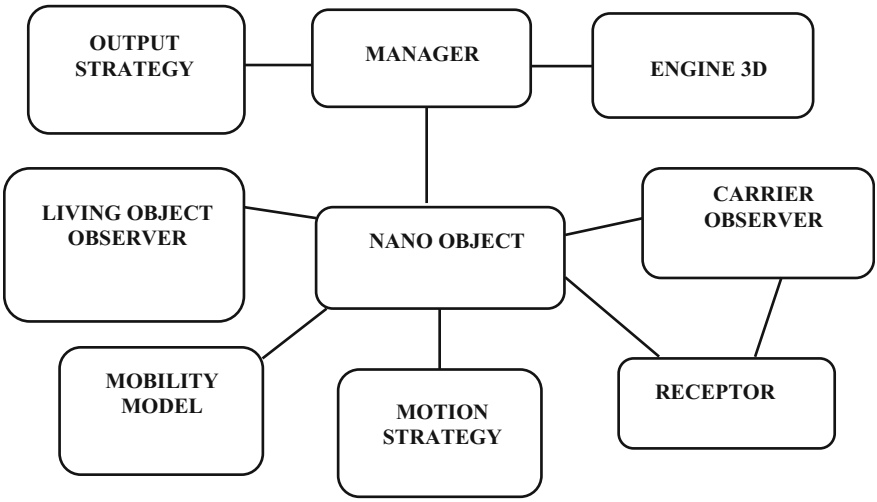


Fig. 10 A simplified picture of the class diagram

general rules for the specific interactions between nanomachines and carriers, carriers and carriers, nanomachines and nanomachines. These interactions realize a generalized behavior and do not limit the development of complex or custom scenarios [27].

Moreover, due to large number of simulated objects, the simulation can be done parallel by using multi-thread approach. Using this simulator, different case studies are also made e.g. in molecular communication, immune systems (Lymphocytes, Antibody response etc.).

6.1.5 NanoNS [28]

This simulator has been designed based on diffusion communication model. Diffusive molecular communication can be modelled according to ligand-receptor binding mechanism as it has been stated earlier that in diffusion based molecular communication system a transmitter releases ligand molecules to the medium. The released molecules diffuse in the environment and some of them bind to the receptor of a receiver. The binding event is a chemical reaction between ligand and receptor molecules and allows the receiver entity to capture the ligand molecules. After the receiver entity captures the molecules from the molecular channel, receiver decodes the information encoded in terms of molecules to fire an action potential [28]. Molecular diffusion is basically Brownian motion i.e., the random movement of molecules in a gas or liquid medium [28]. This diffusion process is formulated by using and solving the well-known Fick's law of diffusion. The reaction can be modelled by two approaches: deterministic approach (where the molecular reactions are continuous and predictable), stochastic approach (here the

reaction is modelled by stochastic methods such as Gillespie's method). However, a reaction is not a continuous process and the number of molecules change discretely with time. So it is not possible to predict a reaction.

During designing the simulator it may be assumed that diffusion and reaction are distinct events. The model the basic diffusion process the medium is divided into several lattice sides. So the inhomogeneity of the system is reduced to the lattice volume [28]. Each lattice site contains a discrete number of molecules which are assumed to be uniformly distributed throughout the lattice site. Molecules randomly moves through the lattices and are distributed to six neighbor lattices randomly. If a small number of molecules exist in the lattice, molecules move individually to neighbor lattices. If the number of molecules is larger than 60, it may be assumed that the molecules move in bulk to a lattice according to a Gaussian distribution. However, the utility of the process is that the positions of the molecules are not required, only the lattice position of the molecule is required during designing. Thus, lattice coordinate system is utilized in the simulator. The diffusion time-step, τ_{D_S}, of each species is calculated as follows:

$$\tau_{D_S} = \frac{1}{2d}\frac{\lambda^2}{D_S}$$

where D_S is the diffusion coefficient of the species, λ is the length of each lattice, d is the dimension of the simulation medium [28].

To design a simulator with above characteristics any simulation environment can be chosen but *Network Simulator (ns-2)* is most advantageous because first of all ns-2 is an open source discrete event-driven network simulator providing the simulation of several networking layers like transport, routing, and multicast, protocols over wired and wireless networks. Secondly it supports development to model promising networks which are different from traditional communications. NS-2 is an object-oriented simulator which is written in C++ and an object-Tcl (OTcl) interpreter. To develop the simulator to support molecular communication one has to make some modifications on ns-2. First of all, a new library has to be developed. A new node structure supporting molecular communication requires to be designed which will be plumped in this library file, besides, new network components, parameters and methods for molecular communication are to be defined in this file. A separate class is required to model trans-receiver nano-nodes and another class to incorporate the features of carrier molecules such as proteins, ions or DNA. Subsequently a new class must be created to model the diffusion proposed above. Besides these a separate class also needs to be created to relocate every object position to lattices. The trans-receiver nano-nodes may be created in the lattice space by volume occupation facility. Nano-nodes are normally assumed to be static. For design purpose the shapes of the nano-nodes may be considered as spheres.

In the simulator each nano-node object contains a position object that points to the center of itself, a ligand and receptor molecule pointers [28]. The radius of the

nano-node and the number of receptor molecules of the nano-node should remain constant. Likewise, there are some pointers which point to the network components in nano-node. The diffusion and molecular reactions can be modelled by adopting proper and suitable numerical methods. The ligand molecules in the simulator are considered as spheres. Thus Diffusion coefficient for the ligand molecules can be derived from the Stokes-Einstein formula

$$D = \frac{kT}{6\pi r\eta}$$

where k is Boltzmann constant, T is the absolute of the medium, r is the radius of the sphere of the ligand molecules, η is the viscosity of the aqueous medium.

6.2 Cell Tool Kit Sim

To understand the behavior of cell mechanism in molecular communication, laboratory based techniques offer a good insight but the development of required infrastructures and the availability of equipment are difficult in many cases. Although these methods are accurate, but they are expensive, time consuming, labor intensive and less feasible in real time scenario. The ***Cell Toolkit Sim*** is being designed as a simulator for researchers where one can simulate the proposed architecture model discussed in Sect. 5 so that the behavior of calcium signaling mechanism performed in cell can be simulated and analyzed. In the 3D cellular space described in Sect. 5.4, all the cell toolkit components (e.g., Emitter, Buffer, Mitochondrion, ER, ER pumps etc.) described in Sect. 5.3 are being programmed individually in accordance with their corresponding modelling parameters and the dynamics of Ca^{2+} flow through the channel can be programmed using the electro-diffusion equation described in that section.

It is being written in Java to take the advantages of object oriented programming (OOP) and multi-threading. Most of the characteristics of all the components can be configured individually to analyze the performance of the cell architecture mechanism. The way to configure the mechanism is by providing the values from the real experiments.

Software architecture:
This software architecture has three basic components:

(a) input configuration file
(b) architecture space and
(c) trace file (see Fig. 11).

These three components are briefly describes below and Fig. 11 represents the simplified block diagram of this software architecture.

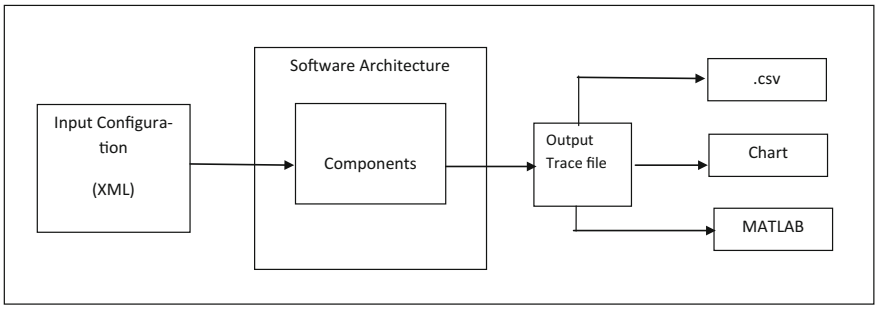


Fig. 11 Block diagram of CELL TOOL KIT SIM

(a) ***Input configuration file***:
In input configuration files, whole configuration of the cell (number of components along with their attributes) is given. In this file, mitochondria, buffer, ER, ER pumps, background, cell dimensions and their individual characteristics can be represented in XML format. Thus, this file describes the environment of the cell to the simulator.

(b) ***Architecture space***:
The second component is the core part of the simulator called as architecture space. This space is to coordinate and control the behavior of each component. In the component part of the space, all the components can be defined with their own activities. Their activities will be affected and completely managed by the architecture space.

(c) ***Trace file***:
Finally, the architecture space generates trace files where behavior of each component at every instant of time can be stored. They may be in CSV format or they may be presented in graphical chart or in appropriate format for MATLAB. If they are saved as CSV (**comma separated value**) file, each column is created by each comma and each row is created by each new line. Therefore, if the file is opened in a spreadsheet program such as Microsoft Excel, it would create a table that would help to make the graphs.

7 Conclusion

In this chapter, we have discussed in Sect. 3 about the various communication techniques those take place among nano machines. Among these techniques, molecular communication is considered as the practically suitable for its bio compatibility and other related reasons discussed in Sect. 4. Thereafter we have focused on molecular communication through calcium signaling and proposed the four architectural layers for nano networks in Sect. 5. Our goal is to model all these layers and virtually realize the overall architecture. Initially we have dealt with the

realization of the physical layer by implementing the different cell components according to their modelling discussed in the later subsections of Sect. 5. The further work is to implement the dynamics of Ca^{2+} flow through the physical channel using electro-diffusion model equations as described before and then to observe the intracellular concentration at different points in the cell at each and every timing instances. The observation of the background concentration by varying the parameters of different cell components e.g. for different emission pattern of emitters; for different absorption capacity, position, size and density of buffers, ER, for different threshold, release rate etc., of Mitochondrion may also be an important study. The measurement of received signal power by varying the characteristics of receptors e.g. their sensing capacity, distance from the emitter etc. can give some important information about the quality of the communication and also validation of the discussed model. Furthermore, by using the real laboratory data as the input to the simulator, the obtained result can be compared with the practical one which may help the different branches of medical science. In near future, the readers may also try to implement the whole process by modelling all the necessary components in the proper simulation environment. They can make their own simulator for this and can view the overall process virtually by taking the help of the simulation frameworks discussed above and that would be beneficial for the mankind.

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