Review of Communication Mechanisms for Biological Nano and MEMS Devices

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ABSTRACT
This paper reviews the emerging area of communication for biological Nano and MEMS devices. Initially, Nano and MEMS motivation and concepts are introduced. Second, current research and related concepts are discussed under the following headings: molecular communication, nanotubes, information theory, Nano computation and biocellular signalling. Finally a novel communication platform for biological Nano and MEMS devices is proposed.

Keywords
Nano Communication, Molecular Communication, Communication protocols, Nano computation.

1. INTRODUCTION
There has been significant research activity in Biological Nano and MEMS (microelectromechanical systems) in recent times. This is in recognition of the immense potential they present in such areas as medical science and sensor networks. The research has therefore been supported by substantial resources through a broad range of government and commercial instruments. However, despite the recent flurry of research in this area, recognition of this potential is not a recent phenomenon. In 1959 Feynman challenged scientists to "think small" and investigate the enormous potential of computation on a sub-molecular scale[22], highlighting the "marvelous biological system" as a motif for new paradigms in information manipulation and computation. Much of what Feynman proposed is now being addressed through advances in research in areas such as DNA structures [20] and molecular computing[13]. However, Feynman's proposal to apply biological paradigms to information processing can also be applied to communication mechanisms. Nature has evolved numerous communication mechanisms and it is the analysis of these mechanisms that may provide the inspiration for new paradigms for nanomachine and MEMS communication.

Bionetics'07, December 10-13, 2007, Budapest, Hungary.

In this paper we review recent research and concepts in the context of biological Nano and MEMS device communication. In particular, we concentrate on research output concerning communication, signalling and computation in a biological setting and how this can be harnessed for micro and Nano based communication. The paper is constructed as follows: Section 2 presents a review of molecular communication and encoding mechanisms. Section 3 discusses biological signalling mechanisms. Section 4 introduces a novel communication platform for biological Nano and MEMS devices. Finally section 5 presents our conclusions and future work.

1.1 Nano and MEMS Concepts
Nanomachines and MEMS are tiny machines capable of accomplishing some form of work. Any machine whose constituent components are of the order of one billionth of a meter(10^{-9}) can potentially be classified as a nanomachine. As biological cells are of the order of microns(10^{-6}) so we can see that biological nanomachines operate at a sub-cellular level. Thus it is possible for nanomachines to work at a molecular level, manipulating molecules to some specific purpose. The advantages of communication at this scale are beyond doubt; the capability of Nano and MEMS devices to coordinate and cooperate, sharing both processing power and information opens up a wide variety of applications in such areas as medical science and engineering. For example, devices acting in a drug delivery capacity could deliver precise quantities of chemicals to specific cells in collaboration with other peer machines[1]. In doing so, adverse side effects inherent in conventional drug delivery mechanisms could be avoided. Machines acting as surgical assistants can find, isolate and highlight damaged or malignant cells while protecting normal tissue. Due to their size and ability to work at an atomic level, nanomachines will have applications as assemblers, accurately building atomic scale components. The feasibility of such novel applications is reliant on autonomous, programmable machines that possess the ability to communicate.

2. RELATED WORK

2.1 Molecular Communication
One approach to Nano and MEMS communication is the emerging paradigm of Molecular Communication. Inspired by biological systems, Molecular Communication enables devices to communicate through the encoding of information in Nano-scale particles i.e. molecules. The molecule becomes the information

carrier, essentially encapsulating encoded information for transmission. Fig.1 illustrates the concept of molecular communication. Hiyama et al [3] provide an insight into characteristics, applications, and challenges inherent in such an approach. The key features of this approach include the use of molecules as the information carrier and the biochemical reactions by the receiver on receipt of the molecule. The relative characteristics of molecular communications when compared to conventional communication paradigms include slow data speeds, stochastic communication, aqueous or 'wet' communication channel, low power consumption and bio-compatibility[3]. The main challenges to be addressed in molecular communication include control of molecular propagation, information encoding and decoding, and actual transmission[3]. Biological systems that can provide physical layer communication mechanism include Molecular Motors and Calcium Signalling.

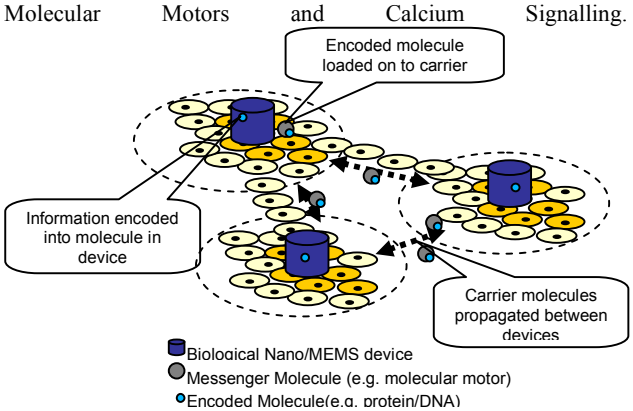

Figure 1. Molecular communication in a biological medium.

2.1.1 Molecular Motors

Hiyama proposes molecular motors and rail molecules[3] as a means to propagate encoded molecules. Molecular motors are naturally occurring biological nanomachines observed in cells that can move molecules or materials along cytoskeletal filaments or rail molecules. Most protein based molecular motors can transform energy in the form of ATP molecules into movement. Enomoto at al[2] suggests that this naturally occurring mechanism could be exploited to develop a molecular communication network using molecular motors to transport information carrying molecules. The system proposed is analogous to conventional communication systems containing both encoding and decoding of information at sender and receiver nanodevices. Signal propagation is performed using molecular motors that transport encoded information molecules from sender to receiver interconnected by a network of rail molecules.

The effect of environmental noise on the encoding/decoding process is seen as an unknown factor that may be addressed using 3D protein and DNA strand techniques that have noise resistant characteristics. Indeed the characterisation of noise in the aqueous environment is a recurring issue in related literature and will be addressed later in this paper. However, molecular communication mechanisms can provide for both inter and intra nanomachine communication analogous to observed inter and intra biocellular molecular communication.

2.1.2 Calcium signalling

Calcium signalling occurs through stimulation of calcium ions (Ca^{2+}) from intracellular stores. Signalling frequently occurs as repetitive increases in Ca^{2+} concentration or “calcium waves” and has been observed to exhibit periodic behaviour. Much of the basic research into calcium signalling has been accompanied by mathematical modelling(often applying bifurcation techniques) and simulation resulting in various models for both intra and inter cellular signalling[4][5]. While research has centred predominantly on intracellular calcium signalling, significant research has also focused on the mechanics and function of intercellular calcium signalling where calcium waves are transmitted across a multi-cellular system or tissue[6][9]. Cells with homogeneous gap junction permeability will broadcast waves uniformly in all directions. However, cells exhibiting gap junction heterogeneity result in preferential wave propagation in certain directions or channels due to the permeability profile of the cell itself. The dynamic control of gap junction permeability can be accomplished through the external signalling to selectively activate and deactivate certain kinases that in turn control the permeability of gap junctions. In [19], Nakano illustrates examples of signal switching and aggregation using dynamic gap junction permeability control. Similar to techniques referred to by Nakano, Thordmann[5] demonstrates calcium wave directionality using a decreasing gradient of calcium inducing agonist receptors(Vasopressin in this case). Such a technique could be applied by bio-nanomachines to direct a carrier signal which could be modulated through the mechanical manipulation of IP3 concentration in the signal originating cell. Of particular interest is the spatial range and attenuation/decay of intercellular calcium waves. Hofer et al[6] highlight that the predominant method of wave propagation is through gap junctions and that attenuation at gap junctions is the main restricting factor in wave propagation. The restriction on diffusion of IP3 from one cell to another is represented by a diffusion coefficient in several intercellular models[4][9]. However what is required is the accurate characterisation of calcium channels in accordance with Shannon's theorems, particularly the modelling and quantification of noise and attenuation in the calcium propagating channel.

2.2 Nanotubes

The use of nanotubes in the creation of a nanoscale network could provide a solution to propagation directionality and specificity lacking in other forms of biological communication, i.e. calcium signalling, molecular diffusion). A nanotube is a wire like structure on a Nano scale that can be used to propagate materials or signals. Onfelt et al[29] demonstrated in vitro the use of membrane nanotubes to transport organelles between immune cells. Onfelt mechanically induced a small network of cells interconnected by membrane nanotubes and demonstrated the successful transport of protein molecules between cells. This offers a model for intercellular communication that could provide a physical mechanism for Nano and MEMS device communication. It is believed that such mechanisms also occur in vivo although this has yet to be confirmed[24]. Also, accurate addressing or routing of information molecules in nanotube networks of more than two nodes is an outstanding issue. Bush et al[30] demonstrated a routing model though complex networks of carbon nanotubes by superimposing a matrix of gates on the nanotubes network. Routing is controlled by switching various

combinations of gates to manipulate nanotube conductivity in various regions, thus routing electrical signals across the network.

2.3 Information Theory and Channel Capacity

Nano and MEMS devices are limited by their processing power, size and materials. Peer to peer communication between various devices will enhance the cooperative capabilities of Nano and MEMS devices. The accurate characterisation of channel and machine capacity is required and has been highlighted as one of the current challenges in communication in Nano and MEMS devices[7]. Shannon et al[16] rigourously defines the concept of information theory that has become fundamental in conventional communication networks design. The maximum rate of information transfer across a channel is given by Shannon's formula:

$$C = B \log_2 (1 + S / N), \qquad (1)$$

where B is the bandwidth and S/N is the signal to noise ratio. As with most communication systems, the signal to noise ratio is key to channel characterisation. While Shannon's theory is routinely applied in conventional communication networks, it is difficult to quantify the signal to noise ratio in aqueous channels used in biological Nano and MEMS communication. Phenomena such as temperature change, thermal noise, interaction with enzymes, PH fluctuations are all potential contributors to environmental noise in MEMs and Nano communication [3]. For example, molecular communication at a Nano scale in biological medium more often involves the movement of molecules via diffusion. Distance travelled by a set of molecules in time t is approximately given by[23]:

$$L = (2Dt)^{1/2}, \qquad (2)$$

where D is the diffusion coefficient. D is constant for a particular molecule in a given fluid and temperature. As D is a function of time, the length travelled by a messenger molecule in a given time is dependant on the temperature. Furthermore, as the distance is proportional to the square root of time, it is evident that diffusion will be fast for very short distances(up to 5μm) but very slow for larger distances(>1cm)[23]. A potential approach towards channel characterisation for molecular communication is to investigate if bandwidth can be related to distance travelled by messenger molecules.

In [17], Schneider characterises the machine capacity of molecular machines, thus giving an indication of the capacity that must be approached by the channel. The basis of Schneider's proof is the development of the lock and key model used in molecular biology to describe enzyme specificity and interactions. The state of a molecule is defined by the positions and motion of its constituent atoms. Based on Schneider's proof, molecular machines can operate precisely in the presence of thermal noise with sufficiently complex encoding algorithms. This formula can potentially be applied to calculate the capacity of molecular machines or automata that produce the encoded molecules illustrated in fig 1. Schneider proposes that the maximum possible information gain of a molecular machine is a function of the energy that the machine dissipates into the environment, the thermal noise that disturbs the machine, and the number of independently moving parts involved in the operation. Nano and MEMs machines must be initially 'primed' with energy so that they can perform work(as is the case with any machine). The processing of information requires that work is performed and energy(heat) is dissipated. In this case, information is gained in exchange for lost energy. Thermal noise is caused by collisions with other molecules and the associated disturbances, while the number of moving parts refers to the parts of the molecule involved in the operation that are subject to disturbances. The example used by Schneider is a ribosome bonding to messenger RNA(mRNA). The capacity of a molecular machine derived by Schneider is as follows:

$$C = d_{space} \log_2 (1 + P_y / N_y), \qquad (3)$$

where d_{space} is the number of free moving part or "pins", P_y is the energy the machine has to dissipate, and N_y is the thermal noise. The similarities to Shannon's formula for channel capacity are striking and suggests that Shannon's theorems also apply to machines that work on a molecular scale. Thus the error rate can be negligible where the transmission rate is less than the channel capacity and the message encoding is sufficiently complex. It must be made clear that Schneider addresses machine capacity of a molecular machine, i.e. the rate at which the machine can process information.

2.4 Encoding and Decoding

The transmission of messages between a sender and receiver across a communication channel involves encoding and decoding. This requires some form of computational component or machine in both the sender and receiver device. Similar to modularisation in silicon chip design, a modularised and layered approach predominates data communication protocols prevalent in modern data and telecommunication systems[21]. In the case of Calcium signalling discussed in section 2.1.2 the accepted hypothesis is that information is encoded in the amplitude and frequency of calcium spikes thus eliciting a specific response. In [19], Nakano et al proposes this mechanism to facilitate encoding of information in intercellular calcium waves. This can be achieved by the nanomachine attaching to a neighbouring cell and stimulating the release of calcium ions through IP_3 stimulation or through the controlled release of agonists into the local intercellular environment. The receiving nanomachine can establish a connection to a neighbouring cell through a gap junction and detect calcium waves directly. Alternatively, indeirect detection is achieved though the observation of calcium induced reaction in the local environment such as light emission or chemical release.

The use of biomolecular machines can act as automata for encoding and decoding of information into DNA strands. For example, Benenson et al[8] describe several biomolecular computing techniques, one of which involves DNA , ribosomes and recombinases to perform an automaton function. Such a biololecular machine could be incorporated into biological Nano devices to encode DNA strands, essentially creating encoded molecules for information transmission between peer devices.

2.5 Nano Computation

2.5.1 Synthetic Biology

A common approach in Synthetic Biology is to view biological systems and sub-components (e.g. cells) as devices which can be

programmed in much the same way as conventional computers and is comprehensively reviewed in [28]. Notably, in [25] Reiss experimentally demonstrated the creation of digital logic operations by optimising genetic regulatory networks. This technique is applied successfully to create the digital logic functions necessary to facilitate cell-cell communication via chemical diffusion of message molecules. Specifically, a chemical concentration gradient produced in a sender cell is recieved and activates a remote gene transcription response in a receiver cell, thus creating a controlled genetic circuit. Both constant and controlled cell-cell signalling is experimentally demonstrated and has obvious applications for nano and micro scale device communication.

Modularised functions and components have expedited the design of complex integrated circuits and electronic devices. Similarly, modularisation is a fundamental aspect in synthetic biology. Collaborative efforts to produce components have evolved into a research community with several similarities to the Open Source community prevalent in computer software development [27]. For example, the BioBricks Foundation [26] (BBF) aims to create a registry of standard 'parts' that can be used to create biological functions. Such resources provide the modularisation required to create complex functions that can be used to construct bio-compatible Nano and MEMS communication mechanisms.

2.5.2 Enzymatic Computation

Stetter et al[11] developed a enzyme based model for logical Nano computation by manipulating the concentration of biological enzymes. Stetter uses the bistable nature of biological enzymatic reactions to develop a reusable architecture to construct basic logic operations such as AND/OR/NOT. The use of a bistable chemical reaction to construct logic operations is similar to that used in Hjelmfelts neuron in his chemical based finite state machine[13]. In both cases, the proposed architectures are modelled using systems of ordinary differential equations. Markevich et al [10] also exploit this biological mechanism to create a bistable switch using a MAPK signalling cascade. As we approach the physical limitations of current silicon based electronics at the Nano scale[20], enzyme based computation mechanisms are a viable solution for biological Nano scale computation. Additionally, such mechanisms can provide the necessary computational functions to support Communication Mechanisms for Biological Nano and MEMS Devices.

3. BIOCELLULAR SIGNALLING

The term signalling is interpreted based on the discipline or context to which it is applied (e.g. Economics, Evolutionary Theory etc.). We adopt the interpretation of signalling as applied to information theory as proposed by Shannon[16]. This involves a sender that encodes information in a message, which is transmitted over a channel and is finally received and then decoded by the receiver to reveal the underlying information.

Biological systems, have evolved numerous mechanisms for communication. Signals are often in the form of molecules that are released by one cell and received by another. In this review, as we are discussing devices that operate at a molecular level we will focus on methods and modes of communication at a micro and sub-micro scale. Analysis of highly evolved biological mechanisms for signalling and communication can provide motifs for communication between Nano devices. It is worth noting that cell signalling is a broad research area in its own right. However, the resulting cell signalling models and frameworks can form the basis of biological Nano and MEMS communication solutions.

3.1 Cell Signalling Networks

Cells and organisms have evolved sophisticated signalling networks to handle a multitude of signals and stimuli that regulate their behaviour. Processing of both external and internal signals often takes place in parallel. A common type of signalling found in biological cellular systems involves phosphorylation and dephosphorylation of structural and regulatory proteins (known as kinase and phosphatase). Mitogen-Activated Protein Kinase (MAPK) is an example of such signalling pathways that can transduce several external signals, leading to a variety of cellular responses, including growth, inflammation and apoptosis[14]. This is the main mechanism for signalling pathways in biocellular networks. Often, these pathways are composed of layers or cascades of kinase and phosphatase signals. The same chemical species are often involved in several pathways and often cross link with each other, known as crosstalk. Frequently crosstalk can be an integral part of the signalling process as part of a complex network of interlinked paths. However crosstalk can also adversely affect the specificity and fidelity of a signal[15]. As a result, natural compartmentalisation techniques have evolved to insulate cell signalling pathways and minimise the effects of crosstalk. For example, spatial separation isolates pathways in different locations of the cell. Protein scaffolds provide templates for specific signal cascades to occur thus isolating them from other pathways. What is noticeable is the analogy of biological signalling crosstalk to electromagnetic crosstalk present in electronic equipment. Just as engineers have developed techniques to minimise eletromagnetic crosstalk in electrical systems, nature has evolved comparable methods to achieve the same in cell signalling networks.

Sauro et al[12] postulates the idea that modularization also occurs in cell signalling networks. Sauro's expectation is that biological networks have also evolved modularising mechanisms to address complex signalling systems. This is borne out in [18] through the integration of several logic operations into one complex operation using molecular and enzymatic reactions. Furthermore, the compartmentalisation techniques in MAPK cascades proposed in [15] together with logic operations detailed by Stetter et al in [11] and the logic function integration demonstrated in [18] potentially could be combined in the creation of natural biological computational components. These components could then be orchestrated to perform complex computational functions. Such complex functions can contribute to computation required to implement protocols of Nano communication.

4. PROPOSED SOLUTION

We propose a biological Nano and MEMS communication platform to support a Nano scale communication network. The primary aim is to create a general platform that will interface Nano and MEMS biochip devices to biological cells thus supporting communication between peer devices. A key aspect of our approach is the mapping of current telecommunication and data protocols to biological systems and processes such as those discussed in previous sections. One of the novel aspects of this solution is the ability of Nano and MEMS devices to perform logic computation by exploiting existing biological cell signalling

processes such as the solutions describe in [10],[11],[18]. Fig. 2 illustrates our proposed architecture. The biochip, which is part of the Nano/MEMS device, interacts with the biological cell through a microfluid interface to perform the necessary computation to support communication. The biochip can also communicate with an external computing device through an external interface. The biochip affects communication through the monitoring and control of logic computation via existing cell signalling mechanisms.

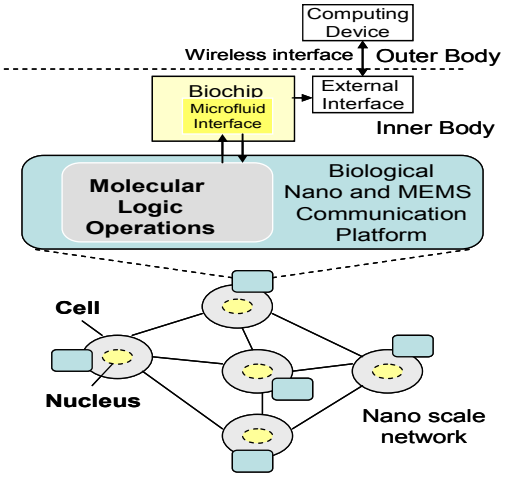

Figure 2. Biological Nano and MEMS Communication Platform

Each biochip is designed to interface with a specific cell type and operate in a specific biological multi-cellular environment or tissue. A number of steps are required to define the required biochip functionality at design time: a full definition of the destination cell type that specifies all cell signalling systems; mapping of communication logic computation to relevant signalling processes; integration with physical layer communication mechanism such as calcium signalling or nanotubes as illustrated in fig.3. First, the cell type definition will specify all cell signalling mechanisms that can be used for computational purposes. For example, bistable MAPK cascades such as those described in section 2.5.2 and [10] can be used to perform logic computations and cell compartmentalisation can facilitate parallel processing. Secondly, mapping of logic functions to cell signalling mechanisms provides a means of offloading computational processes to biological cells. Conceptually, this modularises cell signalling processes into a set of useable components to construct computational functions. This modularisation is fundamental to complex computational design as described in section 3. Thirdly, our solution is intended to support and control various physical molecular communication mechanisms that provide physical layer connectivity for the Nano or MEMS network such as solutions provided by Enomoto[2] and Nakano[19]. Key to this is the successful integration of communication protocol computation to transmission and reception of molecular communication and will be the subject of future work.

4.1 Communication Protocol

Communication is controlled by mapping the logic circuit required to perform a particular biological protocol(e.g. Bio-TCP, Bio-UDP) to corresponding cell signalling. The selection of the correct encoding algorithm can be achieved based on the information capacity of the encoding mechanism or automaton as described by Schneider[17]. Similarly, the application and configuration of a suitable communication protocol can be achieved by accurate characterisation of the physical communication channel. The selection of a suitable communication protocol is reliant on the channel capacity and noise of the physical layer signalling mechanism. Also, for example, configuration properties such as window size and window scaling in a biological implementation of TCP can also be influenced by channel capacity. Therefore a link exists between the physical layer channel capacity and the computation design required to implement the communication protocol as illustrated in fig. 3.

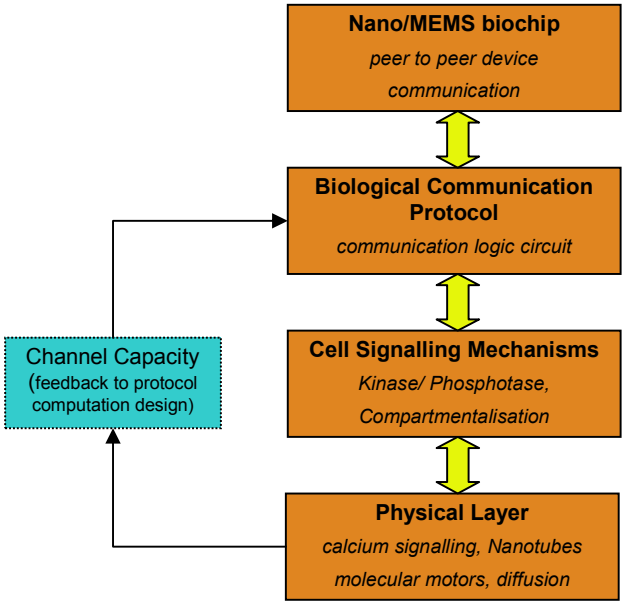

Figure 3. Biological Nano and MEM Communication for Nano scale network.

Each logic gate or function in the particular logic circuit is matched to a suitable cell signalling component. For example, a logic AND gate could be mapped to a MAPK signalling process similar to [10]. Biocellular based compartmentalisation techniques such as those modelled by Komovara et al[15] are utilised to support parallel logic operations. The biochip controls communication logic by detecting and identifying residual proteins resulting from each cell signalling operation. This removes the need for complex bio-engineered circuits to control communication and allows the bio device the flexibility to interface with any cell when communication is required.

5. CONCLUSION

This paper gave a review of communication mechanisms and related research for biological Nano and MEMS devices. The diverse approaches in the literature reviewed for this paper highlight the truly interdisciplinary nature of this emerging research area. The proposed communication platform emphasises the capacity for novel solutions through the successful collaboration of disparate research areas.

ACKNOWLEDGEMENT

This work has received support from Science Foundation Ireland via the Autonomic Management of Communication Networks and Service programme (grant no. 04/IN3/I4040C).

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