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M-ary Modulation Signalling for Intercellular Communication: an Electrical Engineering Point of View

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Abstract

Biologists engineer complex artificial biological systems either to investigate natural phenomena, or to make them perform new tasks such as digital and analog computation, but also intercellular communication. A similarity with computer engineering is often suggested to foster the design of such synthetic biological systems. However, in an electronic communication system, each source generates symbols from a source-alphabet, the size of which may range from 2 (that is two symbols only, 0 and 1) to a few tens of symbols. In practice, for alphabet sizes greater than 2, a binary number composed of bits (0 and 1), or code word, is assigned to each symbol. These code words, or frames, are classically used to transmit information over a digital network. Considering biology, it seems difficult to devise a communication protocol based on the same scheme. In this presentation we will demonstrate that, while an extended-size alphabet is very valuable for intercellular communication, a reference to binary symbols and frames is to be avoided.

Key words: intercellular communication, information, modulation, network

1 Introduction and purpose of work

Today, since the pioneering work of Leonard Adleman (Adleman, 1994) synthetic biologists engineer complex artificial biological systems either to investigate natural phenomena, or to make them perform new tasks (Adrianantoandro *et al.*, 2006). More precisely, the task of these biologists is "to enable cells to perform sophisticated digital and analog computation, both as individual entities and as part of larger communities" (Weiss *et al.*, 2003). In this context, a hierarchy inspired by computer engineering is often suggested (Baker *et al.*, 2006): proteins and genes correspond to basic electrical components, either

passive (resistors, capacitors, inductors, or diodes) or active, such as transistors. Biological reactions correspond to logic gates and functions, and finally cells correspond to computers. Such an approach of biotechnology modeled on electronics engineering may even be considered as very efficient and therefore desirable (Baker *et al.*, 2006).

Nevertheless, a cell has a limited interest isolated from a population of cells and it is also considered as essential to study multicellular systems to reliably perform complex tasks. There, intercellular communication is cardinal to coordinate cell behavior: "the ability to engineer (...) communication systems using cell-cell interaction capabilities will be central to the future engineering of multi-cellular structures" (Weiss *et al.*, 2003). Also worth to be quoted, "we need to replicate the ability of a cell to process a great many converging inputs and to produce output that influence a great many other cells. The organization of the network of chemical interactions in microbiology may one day serve as inspiration to create complex artificial computing networks" (Sarpeshkar, 2006). Considering again the analogy with electronics and computers, there is an obvious similarity between the concept of communicating cells and that of computer networks. However, to transport information, instead of electrical signals, chemical signals, i.e. chemical concentrations of specific molecules, are used: intercellular communication is controlled by inducing cells to synthesize molecules and diffuse them outside their membrane to enter the cytoplasm of neighbor cells (Weiss, 2003). However, cell-to-cell communication may alternatively require direct contact that connects cytoplasms.

On another scale, our work originates in the area of silicon-based Micro Electro Mechanical Systems (MEMS) (Dilhac and Dragomirescu, 2002): cubic-millimeter MEMS are there considered for deploying a massively distributed sensor network (i.e. hundreds to thousands dust motes), taking advantage of advances in microelectronics providing increasing functionalities in smaller sizes, considering sensing, signal processing, communications and energy management. For this kind of implementation, we have devised low-complexity protocols for percolating information through such a network of densely deployed communication nodes. But due to the tremendous progress being accomplished in microelectronics, implementation of adapted versions of already-existing more complex protocols seems, at least for a while, more efficient. However, non-silicon technologies (nano, molecular, polymers) together with biological systems are out of reach of this top-down approach, where protocols devised for wireless ad-hoc networks are simply adapted to the energy and reliability limitations of the MEMS nodes: new concepts are needed. In the following, considering artificial biological systems, we will demonstrate how it is possible to efficiently achieve communication tasks without employing neither frames of symbols, nor the associated signal memorization and processing steps.

This paper is organized as follows. In section two, communication processes

in the fields of microbiology and electrical engineering are compared, while in section three the context of the design of M-ary protocols for intercellular communication is detailed. Finally, section four considers two basic illustrating examples.

2 Intercellular chemical communication vs. electronic communication

Let us first specifically consider intercellular communication. This spatial aspect of the behavior of biological systems has already been explored through receiver cells producing a response depending upon a given molecule concentration. This is a capability obviously needed to induce a localized response to a diffusible signal. More precisely, when cell-cell communication takes place, living cells react to a chemical specie, provided its concentration is above a certain threshold. It has already been demonstrated (You *et al.*, 2004), both theoretically and experimentally that receiving cells could be engineered to respond to cell-cell communication signals from senders, but only if the signal concentrations fall within pre-specified ranges corresponding to different detection thresholds. In that way, engineered cells use a binary modulation scheme, like transistors do in a numerical circuit by exchanging 0s and 1s.

However, for functions more sophisticated than Boolean expressions such as NOT, AND and OR, or even slightly more complex ones such as ring oscillators, and more generally for any communication application mimicking digital electronics by employing its two-element (binary) alphabet, direct implementation to artificial biological systems may be costly in terms of processing time and complexity. The difficulty of fast and complex signal processing based on biological structures may jeopardize long range communication targeted at a given cell population. This is also true because insulation between multiple bidirectional communication channels is required for complex applications, even if genetic circuits able to respond simultaneously to two input signals have already been engineered (Adrianantoandro *et al.*, 2006). Fortunately, it has already been experimentally demonstrated for biological systems that complex global emergent behavior may arise from the interaction of cells through simple local rules (Prehofer and Bettstetter, 2005).

Let us now briefly summarize how a computer network operates. In the context of electrical engineering, conveying a message over a distance is often realized by modulating one or many electrical parameters, such as amplitude, phase or frequency, of a carrier signal. If these parameters are varied discretely, that is in the case of digital modulation, a digital bit stream is transmitted. The various parameter values are chosen from a finite number of alternative symbols forming the modulation alphabet. In the simplest case, the alphabet

comprises only two symbols, 0 and 1: in the case of digital amplitude modulation, only two amplitude values are then used, each amplitude encoding one bit, and the modulation is said to be binary.

To increase the bit rate B_R (in bits per second), for a given symbol rate S_R (also known as the baud rate, in baud or symbols per second) which is usually limited by the communication channel frequency performances, the size of the alphabet is often increased. If the alphabet consists of $M = 2^N$ symbols (M and N being positive integers), each symbol may be labeled by N bits, and the bit rate is N times the symbol rate:

$$B_R = NS_R \quad (1)$$

The modulation is said to be M-ary. The bit rate could therefore be considered as limitless. Unfortunately, electrical noise together with interferences and signal corruption due to hardware limit the number of symbols likely to be used. In the case of amplitude modulation, for a given maximum value (i.e. for a given maximum power of the transmitter) the received value may be moved by noise closer to a possible level than the one actually transmitted. This phenomenon is one of the practical limits of the bit rate increase.

From another point of view, let us consider the information content carried by a random variable as defined by the information theory founded by Claude Shannon (Shannon, 1948). This information content is related to the amount of uncertainty: if the future values are known ahead of transmission, no information at all is transmitted. On the contrary, if the variable is totally random, the transmitted information is maximum. More precisely, the mean information content, called the entropy H (in unit of information or shannon), of a discrete source using a M-symbol alphabet, is maximum when the transmission of these symbols is equally likely. Then

$$H = \log_2 M \quad (2)$$

In other words, the largest the alphabet size, the highest the amount of information possibly carried by each symbol. This latter point is strongly in favor of large size alphabets, but back to intercellular communication, the propagation of the chemical signals is usually driven by the isotropic liquid phase diffusion of the molecules synthesized by the sender cells. In this context, a M-ary alphabet based on concentration (amplitude of signal) may be considered as difficult because of the cross-dependence between concentration and distance. But it could be appropriate to base such an alphabet not on concentrations, but on the nature of molecules. As already stated, this may be practically possible because genetic circuits able to respond simultaneously at least to two input signals have already been engineered. Using different chemical species

to carry information is a way to deal with large propagation latency by not mimicking too closely electronic hardware, and by increasing the amount of information carried by a symbol.

3 Implementation of M-ary signaling for intercellular communication

In the following we consider an interconnection network composed of cells. The network may be of any size, but without isolated island (i.e. group of cells out of reach of signals) or voids. In other words, cell density (i.e. amount of cells per unit volume) is supposed to be uniform. The traffic will propagate through the network via a hopping mechanism involving little intermediate processing.

As already stated, many cell signals for intercellular communication are carried by molecules that are released by transmitting cells and move to make contact with receiving cells; in some cases, the receiver may respond differently depending upon the amount of molecules received. In the following, we consider that the receiver cell reacts only if the concentration reaches a unique threshold.

From an electrical engineering point of view, we consider that cells make up a network of simple nodes, with very little processing and memory capabilities. We assume that each node at least basically operates as a repeater processing symbols from a source-alphabet. Consequently, protocols below keep minimum node functionality and processing overhead.

More precisely, our goal is to introduce communication protocols by defining simple local interactions that achieve complex global functionality (Prehofer and Bettstetter, 2005): in the considered communication networks, the nodes do not require any central coordination and only react to their closest environment. Such self-organizing systems are adaptive, failure-robust and scalable (Prehofer and Bettstetter, 2005).

Finally, it is worth mentioning that this concept of transmission protocols comply with the general principles for building self-organizing systems such as the four design paradigms detailed in [9]:

- design local behavior rules that achieve global properties
- do not aim for perfect coordination, but exploit implicit coordination
- minimize long-lived state information
- design protocols that adapt to changes

Whatever the implementation, the nodes/cells have neither physical nor logical address. There is neither central supervising entity updating a location register as in cellular networks for mobile telephony, nor routing tables as in cable networks exhibiting a static topology.

In addition, entities potentially but not necessarily more sophisticated than nodes/cells, called "terminals" may exist. They may act as the primary sources of information. They may be implanted anywhere within the network. Like cells, terminals ignore both their own positions within the network, and the location of the other terminal(s). Therefore, messages cannot be addressed by location or directed diffusion, if the task is to exchange data between terminals. In the following, we will consider only one terminal and we will describe examples of protocols, which can perform either broadcasting, or broadcasting over a limited area.

4 Examples of communication protocols

Below are given two examples of protocols, which are meant to be illustrations of the previous considerations, rather than a final "how-to" manual. Actual applications should be tailored for a given application environment.

Let us first consider the action of broadcasting: that is the distribution of a signal (i.e. symbol) to a number of recipients (i.e. nodes). We will here consider a distribution to all cells/nodes of the network. The process we suggest is that a terminal transmits a specific symbol (i.e. a symbol dedicated to broadcast) to all cells within its connectivity range, and then that each cell/node executes locally the following elementary algorithm: it simply reemits this symbol only once.

There, the nano-node acts as a simple 'one-shot' repeater. Nevertheless, this elementary local behavior leads to a global effect: the symbol (i.e. a synthesized molecule) is transmitted to all cells, as it diffuses across the network through multiple hops from the emitting cell/terminal and finally propagates right to the network limits. Without this multi-hop effect, it is very likely that a single cell/terminal would not have the resource to flood the entire network with a given molecule.

However, in many circumstances, a cell/terminal may have to broadcast symbols (to diffuse a chemical signal) over a limited distance only, without reaching all cells/nodes. For this purpose, we again suggest a straightforward protocol using for this task a new and specific symbol from the source-alphabet. The procedure is as follows. First, a terminal transmits a stream of identical symbols to all cells/nodes it is connected with. Then, a cell/node transmits a

symbol from this new set only if it previously received an identical symbol. In other words, the first symbol of a stream of identical symbols is not reemitted.

The global property achieved by this local behavior results in this new set of symbols propagating from a source/terminal over a limited distance only. This distance depends upon the length of the stream of symbols initially emitted by the source; a stream of i symbols will propagate over i hops. However, this procedure may seem well adapted to electrical engineering, but out of reach of chemical communication. Easy implementation to diffusing molecules is nevertheless possible provided that in this case a symbol should be associated with two chemical species diffusing one after the other, and alternatively reacting to make locally the respective concentrations oscillating between zero and a maximum. There again, without the multi-hop effect, it is very likely that a single cell/terminal would not have the resource to flood the network with a given molecule, even over a limited distance. This second protocol additionally gives the possibility to set this distance to a relatively precise value.

5 Conclusion

It is worth to be noted that this paper is not meant to be all-encompassing, and that each issue presented above could be discussed in much more details provided that a specific environment and application are given, for instance details about the medium channel over which the message is to be sent. Conversely, it is meant to be an initial guide considering the issue of performing efficient information transfer within an intercellular communication environment. The main conclusion of this work is that too largely mimicking digital electronics by employing its two-element (binary) alphabet for cell-cell communication in artificial biological systems may be costly in terms of processing time and complexity. Alternatively, taking advantage of the availability of different molecules synthesized by the sender cells, the usage of a M -ary alphabet could be advantageous for reducing the physical size of messages while retaining their meaning.

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