AN APPROACH TO EVOLVING ARTIFICIAL CELL SIGNALING NETWORKS

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GOAL OF WORK PRESENTED IN THIS POSTER

We are investigating the use of artificial Cell Signaling Networks to implement computation, signal processing and (or) control functionality. In the following sections we review a number of the research issues which this raises.

INTRODUCTION

• We distinguish CSNs as being networks made up of more than one distinct cell signaling pathway, which interact with each other. An example of a simple chemotaxis signaling pathway is shown in Figure 1.

• Viewed as signal processing systems, Cell Signaling Networks (CSNs) can be regarded as special purpose computers [4]. In contrast to conventional silicon-based computers, the computation in CSNs is not realized by electronic circuits, but by chemically reacting molecules in the cell.

• Lauffenburger [13] presents an approach where cell signaling pathways could be thought of and modelled as control modules in living systems.

• Yi et al. [19] demonstrated that CSNs may have some of the essential properties of an integral feedback control.

• Artificial CSNs (ACSNs) may therefore be used to implement computation and signal processing.

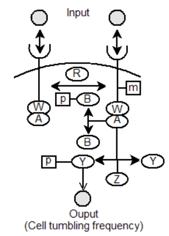


Figure 1: Schematic representation of bacterial chemotaxis signaling pathway, adapted from [1]. The output is designated by the tumbling frequency which is determined from the input, the concentration level of ligand bound to the membrane receptors. This signal transduction is carried out by the reaction cascade depicted by the proteins A, B, R, W, X and Z. Details on chemical reactions can be found in [16].

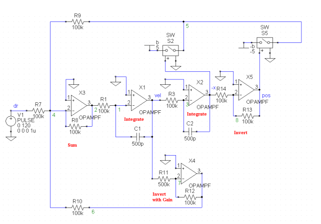


Figure 2: Schematic for the analog computer simulation of the driven constant-force magnitude oscilator. http://physics.mercer.edu/petepag/yoyo.html

COMPUTATION

CSNs and ANALOG COMPUTERS:

As a "computational" device, CSNs can be compared to analog computers:

• CSNs can be modelled with systems of continuous differential equations

• Analog computers are precisely designed to model the operation of a target dynamical system by creating an "analogous" system which shares the same dynamics.

ADVANTAGES OF USING CSNs AS MOLECULAR ANALOG COMPUTERS:

• Electronic analog computers have long been displaced by digital computers due to their much greater ease of programming and stability.

• Nonetheless, there may be applications where a molecular level analog computer, in the form of a CSN, may have distinct **advantages**:
  - CSNs may offer capabilities of high speed and small size that cannot be realised with solid state electronic technology.
  - More critically, where it is required to interface computation with chemical interaction, a CSN may bypass difficult stages of signal transduction that would otherwise be required. This could have direct application in so-called **"smart drugs"** and other bio-medical interventions.

CHEMICAL COMPUTING

CSNs are typically treated in an aggregate manner, where the signal or information is carried by molecular concentration. An alternative approach is to consider the finer grained behaviours of individual molecules as **computational units**.

A single enzyme molecule can be regarded as carrying out **pattern matching** to identify and bind target substrates, and then executing a discrete computational operation in transforming these into the product molecule(s).

This has clear parallels with a wide variety of so-called **rewriting systems** in computational theory.

However, it differs in important ways, such as:

• Operation is **stochastic** rather than deterministic.
• Operation is intrinsically **reflexive** in that all molecules can, in principle, function as both "rules" (enzymes) and "strings" (substrates/products).

Dittrich [6] provides a more extended discussion of the potential of such "chemical computing".

EVOLUTION

Evolutionary Algorithms (EAs) are non-deterministic search and optimisation algorithms inspired by the principles of neo-Darwinism. They have been applied successfully in a variety of fields (business, engineering, optimization based problems, etc) [7, 10, 11].

Generally based on genetic operations such as **crossover** and **mutation**, EAs initially generate a wide range of candidate solutions. Over time, through selection, this can be reduced to an optimized set. Evolutionary computation can deliver useful results without requiring a priori knowledge of the entire search space [7, 11].

Such techniques are relevant to the study of Artificial CSNs because:

• The complex, and unpredictable, interactions between different components of CSNs, make it very difficult to design them "by hand" to meet specific performance objectives.

• Natural evolution shows that in suitable circumstances, effective CSNs functionality can be achieved through evolutionary processes.

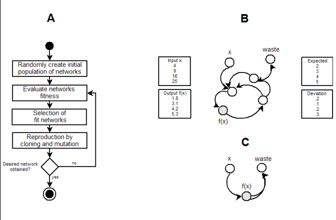


Figure 3: A: Flowchart of the Lakhesis evolutionary algorithm adapted from [5], the initial population of networks is randomly generated referring to genetic diversity. Fitness computation is obtained by: solving ODEs which allows one to compute steady states of the network, then the deviation of each node is calculated according to the mathematical computation we want the network to perform. Selection implies removal of unfit networks and reproduction correspond to asexual reproduction where mutation operators are applied. This process is repeated until we get a correct network performing the desired mathematical function. B: Deviation calculation is performed via a series of different inputs. C: An evolved network performing exact square-root computation.

For example, Deckard and Saura [5] used such evolutionary techniques to construct (simulated) biochemical networks capable of certain simple forms of signal-processing, see Fig 3.

1 2
3 4

CROSSTALK

"Crosstalk" phenomena happen when signals from different pathways become mixed together. An example is shown in Fig 4. In traditional communications and signal processing engineering, crosstalk is regarded as a defect—an unintended or undesigned interaction between signals, that therefore has the potential to cause system malfunction. This can also clearly be the case of crosstalk in CSNs. However, in the specific case of CSN's, crosstalk also has additional potential functionality, which may actually be constructive:

• Even where an interfering signal is, in effect, adding uncorrelated "noise" to a functional signal, this may sometimes improve overall system behaviour. This is well known in conventional control systems engineering in the form of so-called "dither". Compare also, [2, 17] on constructive biological roles of noise.

• The crosstalk mechanism provides a very generic way of creating a large space of possible modifications or interactions between signaling pathways. Thus, although many cases of crosstalk may be immediately negative in their impact, crosstalk may still be a key mechanism in enabling incremental evolutionary search for more elaborate or complex cell signaling networks.

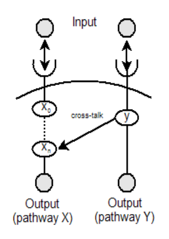


Figure 4: Schematic illustration of a CSN composed from two distinct cell signaling pathways with unique input and output, an interaction between pathways occurs as molecule y interacts with xn, this modulates the output ofpathway X.

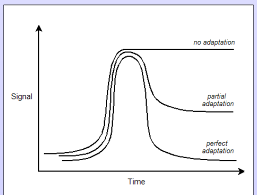


Figure 5: Representation of dynamic responses of a system to a stimuli taken from [13]. No adaptation is observedwhen the system response attains a new steady state following the change in input. Partial adaptation describe a partial recovery, the difference between the initial state and the new state is lower than the one observed in the previous case. Perfect adaptation is met when the system is able to come back to its initial state

ROBUSTNESS

• It is argued that key properties in biochemical networks are to be **robust**, this is so as to ensure their correct functioning [3]. Similar works include research carried out at the Santa Fe institute in studying Cytokine signaling networks to design distributed autonomous networks, that are robust to small perturbations and responsive to larger ones [14], see Fig 5. **Potential applications** are distributed intelligent systems such as large fleets of robots working together, for automated response in computer security, for mobile computing networks, etc.

• Alon et al. have demonstrated from studying Escherichia coli chemotaxis that molecular interactions can exhibit robustness [1, 13]. In this case it means that after a change in the stimulus concentration (input), the tumbling frequency (output) managed to reach a steady state that is equivalent to the pre-stimulus level. Such properties are highly desirable in dynamic engineered systems when subjected to internal and external uncertainty and perturbation.

FUTURE WORK

We want to address a number of questions:

• How to evolve systems of ACSNs that control each other?
• How to investigate the ability of those systems to create and sustain specific internal conditions (homeostasis)?
• How to investigate and quantify the robustness of such systems to external shocks and changes of conditions?
• How to transfer insights from this work to build more resilient "self-repairing" and adaptive control-systems?

THE ESIGNET PROJECT

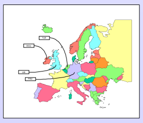
The ESIGNET project (Evolving Cell Signaling Networks in Silico) is a Specific Targeted Research Project funded by the European Commission under the Sixth Framework Programme.

The overall goal of this project is to study the computational properties of CSNs by evolving them using methods from evolutionary computation, and to re-apply this understanding in developing new ways to model and predict real CSNs. The project is highly interdisciplinary. Its completion requires insight into the subject from many points of views. The research will be at the interface of (at least) Biology, Computer Science, and Control Engineering.

It also utilises a plethora of approaches and methods. The high potential of the proposal is largely due to the co-ordinated and concerted multi-disciplinary and methodological approaches. This is reflected in the composition of the consortium. All researchers in this consortium have previously been involved in research at the interface between Computer Science and Biology and have a strong ability to integrate insights from those fields.

PARTNERS:

• UNIVERSITY OF BIRMINGHAM, SCHOOL OF COMPUTER SCIENCE
• TECHNICAL UNIVERSITY EINDHOVEN, BIOMODELING AND BIOFORMATICS GROUP
• FRIEDRICH SCHILLER UNIVERSITY, JENA, BIO SYSTEMS ANALYSIS GROUP
• DUBLIN CITY UNIVERSITY, ARTIFICIAL LIFE LAB, RINCE



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