# Some Computational Models at the Cellular Level[1]

Ray C Paton
Department of Computer Science
The University of Liverpool
Liverpool L69 3BX
U.K.

email: r.c.paton@csc.liv.ac.uk

**Summary**

A number of viewpoints on how a cell can be modelled are discussed in this paper in light of the ability it has to process information. The paper begins with a very brief summary of four general types of computation: sequential, parallel, distributed and emergent. These form the general framework from which a number of comparisons are made. Several metaphors are introduced to enable reflections to be made about cellular computational properties. The most important metaphor namely, the cell as a machine, is discussed and then a number of other ideas are introduced which complement a lot of current thinking in this area. The idea of networks or circuits in the cell is then developed as this provides a means of describing the mechanisms within a machine. Following on from this three further metaphors are applied in order to overcome certain limitations in current machine thinking, cell-as-society, cell-as-text and cell-as-field.

**Keywords**
Computational models of the cell, levels of organisation, systemic metaphors.

## 1 Introduction

The purpose of this paper is to examine a number of ways in which cells can be modelled and some general features of the computational metaphor will be considered. This includes the

[1] appears in BioSystems (1993), 29, 63-75.

notion that cells process information. We may ask what kind of computational model a cell or certain parts thereof could suggest ? There are a number of possible approaches. On one level of description the cell is decomposed into its functional compartments such as genome (program), enzymes (the program enactors), and secondary messenger systems (data buses). However, as we shall see this is extremely simplistic. From another point of view it may seem appropriate to consider certain abstract properties of the cell and model the whole as a processing unit, for example, in a cellular automaton. As the paper unfolds it will appear that a cell has many computational machines. Some correspond to existing computers within the context of certain analogies but others are far removed from many computational ideas and may require new models for their expression. In this paper we shall consider four general types of computational machine:

**SEQUENTIAL** - these machines, sometimes referred to as von Neuman machines, are the most common form. They can characterised by a single locus of control (in the central processing unit), a global memory and, as the name suggests they carry out instructions serially.

**PARALLEL** - these consist of several processors that are located close to each other. The processors get involved in the joint execution of a computational task. Communication between processors is predictable in these fixed topology systems. Two forms of parallelism may be described: coarse grained, in which programs are split up into relatively independent tasks and, fine grained, in which there is a very high degree of interaction between processors. Parallel systems can be explicitly decomposed into subunits. For the purposes of this paper we shall focus on one type of parallel computer, the multiple instruction stream, multiple data stream (MIMD) machine.

**DISTRIBUTED** - processors can be located at large distances apart in these systems and communication is unpredictable. Information that becomes available to a processor for computational purposes may only be in a partial form. The topology of such systems is variable and examples include local area networks and open systems.

**EMERGENT** - this form of computation is characteristic of cooperative self-organising systems made up of many very simple processes. The global behaviour of such systems emerges from local interactions between parts. This form of computation is typified by cellular automata and parallel distributed processing systems such as artificial neural

networks.

Computational models of the cell can utilise any of these views. The purpose of this article is not so much to say which should be used but rather, to examine the breadth of possible models and how more that one will be required. In order to do this the cell will be compared to a number of basic model-organising ideas, in particular a set of metaphors (Paton, 1992; Paton *et al*, forthcoming).

Given this kind of analysis, a cautionary note must be made even at this early stage: a potential problem with an approach to biology which transfers ideas from computing is its dependency on the latter for expression and this could lead to a "shoe-horning" effect namely, biological systems get fitted to current computational models. In many ways this would not be such a bad idea. Comprehensive conceptual frameworks for describing biological models and facilitating explanation and prediction are not so common and theoretical computer science, particularly those areas which can deal with the non-linear, highly parallel and emergent behaviour of biological systems, could be an extremely valuable asset. However, computer science is an evolving field of knowledge and a theoretical biology which is simply serviced by current or projected computational models could eventually become a stagnating narrow-minded discipline. For example, computing and electronics have greatly influenced the development of biological ideas associated with the neuron which has been variously described as a switch, transistor, multiplexer and microprocessor. However, a neuron is much more than this. Consequently a more dynamic approach to interaction between biology and computing is necessary, one in which both disciplines are enabled to co-evolve. As a result, we see the emergence of two interrelated but distinct disciplines: biologically motivated computing (using biology to inspire computing) and computationally motivated biology (using computing to inspire biology). Finally, unlike a number of reductionist writers, the present author has been very careful not to presume that a cell is necessarily a kind of machine. Hence, the metaphors for the cell which are described in the following sections are predicated by the relation "as a" rather than "is a".

## 2 The Cell as a Machine

The idea of the cell as a processor of biochemical symbols can be traced back through the work of for example, Stahl & Goheen (1963), to the notion of the cell as a Turing machine. Both

cells and their components can be modelled using the language of automata theory. For example, Hofstader (1979) describes several ways in which DNA can be described in computational terms. It may be thought of as a program written in a high level language which is subsequently interpreted in the machine language of the cell (proteins). Alternately, it is like data which is manipulated by a program (enzymes).

Kauffman (1991) describes the genome as acting like a complex parallel computer system which he models in terms of Boolean networks consisting of a large number of two-state components. This kind of model reduces the computational capacities of the genome to the simple (Boolean) behaviour of genes. On the other hand, Davidson (cited Beardsley, 1991) looks at some individual genes as operating like 'smart' agents. In this case a degree of 'knowledge' or cognitive capability is associated with the parts of the system. Keeping both of these insights in mind, we may envisage DNA, genes and the genome acting as parallel processing systems in a variety of ways for which a number of automata-based models can be described. It should also be noted that the genome is itself a highly organised parallel processing system and what used to be dismissed as 'junk DNA' is more likely to be a part of a complex integrated system (Bernardi, 1989).

Another important source for intracellular computing is the enzymes. For example, in his discussion of biomolecular computers, Conrad (1990) notes two important cellular devices: enzymes and secondary messengers. In his scheme enzymes act as transistors or molecular switches but are far better than their electronic analogues because of their greater variety (i.e., there are many types of biomolecular transistor) and also because of the very low dissipative energy required by them to operate. What is more, the functionality of an enzyme as a parallel processing device is considerable. We may note that enzyme processing, and particularly that associated with allosteric forms and multi-enzyme complexes carries with it more that a catalytic role when its parallel processing capacities are considered. An example would be the timed and intrinsically regulatable GTPases which may contribute to a large number of cellular processes (Macara, 1991).

Marijuan (1991) seeks to model enzymes as molecular automata and argues that enzyme networks are highly parallel systems which reflect the primary computing properties of the cell. As such, networks of enzymes are a form of automata network which may be generalised as a Boolean network in a similar way to Kauffman's scheme. Quoting Kornberg, he notes that although DNA provides the script, it is the enzymes which do the acting (this type of thinking

may also be described in terms of the society and text metaphors discussed below).

Secondary messengers play the linking role in cellular information processing providing the cell with the capability to process patterns of input data. It is also worth noting that second messengers can be modelled in terms of Boolean states. For example, Lichtstein and Rothbard (1987) describe possible models for second messenger activation systems and suggest one based on the number of on/off states (i.e., $2^n$ where n is the number of messengers involved). This hypothetical scheme could be further extended if the device-behaviour of receptor molecules had some kind of processing capacity.

So far, the discussion has concentrated on three classes of molecule - DNA, enzyme and secondary messengers. However, other biomolecules and molecular complexes can also be ascribed computational capacities including protein complexes such as multi-enzyme assemblies, microtrabeculum and membrane-based channels and pumps. For example, Aizawa (1991) discusses how a photosystem can be seen as a photodiode and Lauger (1987) describes small biomolecular assemblies such as ion pumps that behave like stochastic machines. Switching (i.e., Boolean) properties can also be ascribed to ion channels and transcriptional factors (Macara, 1991).

The computational capacities of the cell are not simply restricted to particular classes of biomolecules; supramolecular systems can also be described in machine terms. One approach is that of Holcombe (1990) who provides an algebraic formalism based on Eilenberg's generalised automaton, the X-machine. In this case, intracellular biochemical organisation structured around a set of organisational layers within the cell. An X-machine is a generalisation which subsumes finite state machines, Petri nets and Turing machines. The basic thesis of Holcombe's approach is that many types of biological activity can be modelled using various types of X-machine at various levels of behavioural description. This is generalised as a hierarchy of algebraic machines that describe certain organisational and computational features to be found in the biochemical behaviour of cellular systems (Holcombe, 1992). Each hierarchical level within the model of cellular organisation has its own variety of X-machine corresponding to:

0 Energy transfers for the whole system,
1 Conformational level (the set of states)
2 Metabolic level
3 Enzyme control level

Each of these levels, of which 0 is the most general and 3 is the most specific, may be modelled as either a sequential or as a parallel machine. In this hierarchy of X-machines the enzyme control level machine (3) is used to provide inputs to the metabolic level machine (2), and so forth. The power of Holcombe's approach is its potential capacity for modelling massively parallel processes (Holcombe, 1991, 1992). We may now speculate on at least two types of parallelism which exists in the X-machine approach namely, within-level parallelism that is, the X-machine at a given level is a parallel X-machine and between-level parallelism. In this latter case, the parallelism of the models may remain implicit in the operation of the levels.

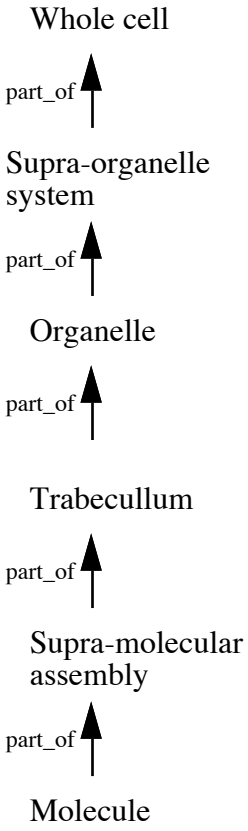



Figure 1 - Some Organisational Levels within the Cell

Welch (1977) models the cell as machine-with-slots; slots are the inputs and outputs and the machine is a transformation system. However, the functionality of the system is not restricted to a slot transfer function for Welch emphasises the spatial organisation in terms of localisation of processes (due to subcellular organelles and multi-enzyme complexes) and pooling of transformed materials due to their arrangement in space and time. These properties reflect a fractal dimension. Not only this, in their review of a model of glycolysis, Hess and Markus (1987) note that certain switching phenomena take place depending on the concentration of a

number of substrate (such as phosphoenol pyruvate and fructose 6-phosphate). This oscillatory switching may display chaotic behaviour and Hess and Markus speculate on how the pathway can then have a capacity to store information.

To summarise so far, we have seen how different molecules and supramolecular structures can exhibit computational capacities. The resulting models are often simplified to reflect these computational features for example, by abstracting state-based and/or Boolean behaviours. However, it is also important to note that a number of levels of computational organisation may be considered for example as shown in Figure 1. As we shall see, these are amenable to a variety of modelling viewpoints (see also Paton, 1992a).

Consider a way of exploring the functionality of both biological neurons and their artificial analogues in terms of organisational level. Neuroscience has influenced computing in that the nerve cell has proved to be an extremely valuable source of ideas about networks of automata. Beginning with McCulloch and Pitts (1943) and their description of a neuron as a logical processing unit there has been a steady development of neuronal analogues over the past fifty years. Simplistic models identify the functionality of the different parts of a neuron as summarised in Figure 2. In this case, the dendritic tree corresponds to the input section, the soma (cell body) to the central processor and, the axon output section.

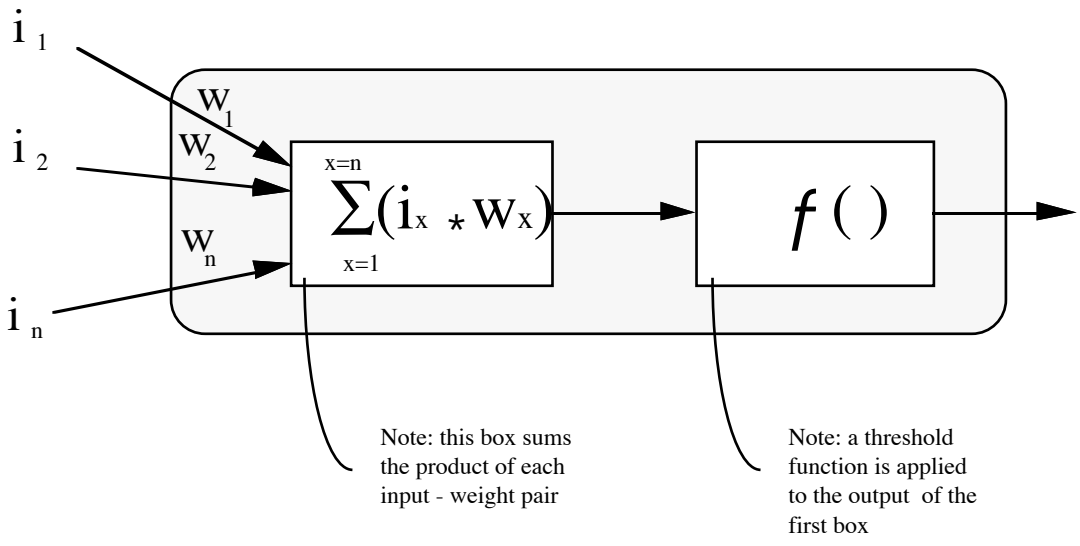
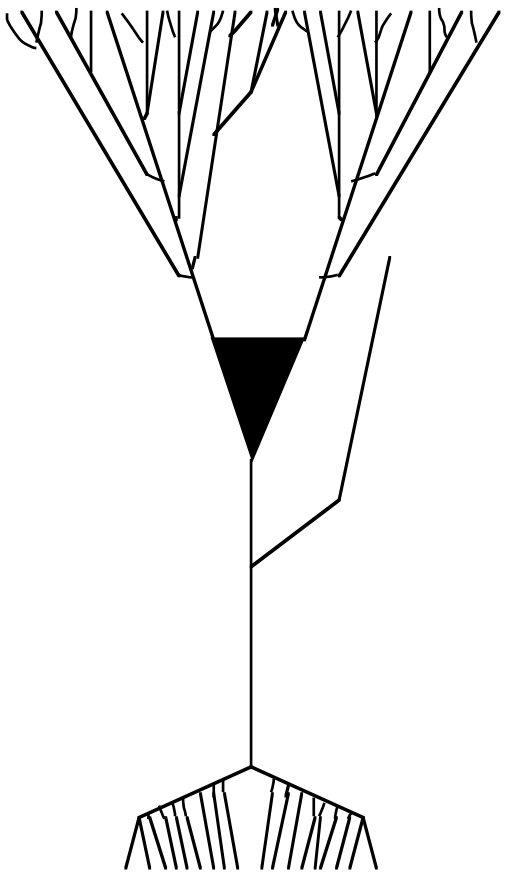



Figure 2 - Diagrammatic Representation of an ANN Processing Unit

In this kind of architecture the processing unit, rather than say the dendritic tree and axon, does the computation. This is far removed from the computational power of a biological neuron in which considerable information processing takes place in dendrites and axons as well. Interest in the cell (rather than the network) as a source for modelling adaptive computational systems is related to its non-linear behaviour and should not be underestimated (Shepherd, 1992). Shepherd (1990) argues that the synapse should be considered to be the basic unit of computation in the nervous system rather than the neuron. Indeed, he describes a number of organisational levels of computation between synapse and cell:

synapse -> microcircuit -> dendritic tree -> neuron-> local circuit -> module -> column.

Shepherd and Brayton (1987) describe how excitable dendritic spines may compute AND, OR and NAND functions. As a consequence of this a single dendritic tree could be considered as computing a very complicated function. It is therefore important to acknowledge that there are considerable biological sources for the development of novel artificial neurons. Indeed, the



**DENDRITIC TREE**

Pre-processing of weights in relation to:

- Spine distribution
- Affect of neuromodulators
- Intracellular messengers
- Dendro-dendritic synapses
- Analog processing
- Tree toplogy

**SOMA**

Cell-dependent firing frequency - input relationships

**AXON**

A number of features of axon functionality can be used to account for changes to ANN units including:

- frequency-dependent multiplexin
- recurrent effects

**TERMINAL ARBORIZATION**

Some key features here include:

- learning in termini
- effect of neuromodulators
- axo-axonic communicatio

Figure 3 - Some Ways of Exploring Computational Features of Neurons

limited capacities of the McCulloch-Pitts neuron require extension. What is more, the artificial neuron remains very much a serial processor (in a parallel network) whereas a biological neuron is a parallel processor in a parallel network.

To be fair, a number of researchers are seeking to apply more biological detail to ANNs in order to increase their functionality and improve their performance. Consider a very important example from Carpenter and Grossberg (1990) who describe a neural network architecture which is greatly influenced by the chemical processing properties of the synapse. In this case, they transfer ideas associated with the mechanism of synaptic release such as transmitter accumulation, release, inactivation and neuromodulation within a particular kind of architecture based upon an Adaptive Resonance Theory (ART). This architecture (called ART 3) is able to establish a stable self-organisation of recognition codes for arbitrary sequences of input patterns. A mechanism for parallel search of learned pattern recognition codes is based on synaptic processes associated with transmitter release rate and post-synaptic activation. Some of the complex processing capabilities of neurons which could enhance their artificial homologues are summarised in Figure 3.

The hepatocyte is another highly parallel computational system with a capacity to contribute to over five hundred hepatic functions. A cell may have upwards of two thousand mitochondria, with seven percent of the cell volume rough endoplasmic reticulum and twelve percent smooth endoplasmic reticulum/Golgi bodies. Its computational capacities are very high and a variety of levels of intracellular organisation involved ranging from amplification of genes and gene regulation of enzyme levels through localisation of membrane receptors, pathway regulation and intracellular signalling systems dynamics to the organisation of the microtrabeculum, compartmentation and pooling. The resulting computational system is highly complex. Figure 4 summarises some of the functional relations between non-nuclear systems which are involved in cellular information processing.

The hepatocyte as a parallel distributed processing source can be contrasted with the neuron and both cell types exhibit considerable computational capabilities. It should be clear to the reader that non-linear behaviour of neurons it related to their architectural complexity as reflected in dendritic trees and axonal arborizations. However, hepatocytes are biochemically very complex as reflected in the very large numbers of organelles and active chemical processes. Both of these complexities have their parallel distributed processing analogues represented by processing units and connecting weights and the challenge to a better

understanding of PDP at this level would be to attempt to import greater biological detail at the mechanistic level. In computational terms, the hepatocyte approximates to a MIMD machine handling large amounts of various types of data through the integrated workings of its metabolism and data driven processing. The pattern recognition capabilities of these metabolic MIMDs are vast given that input patterns must take account of hormones, nerve impulses, metabolic products, oxygen and gap junctional signals.

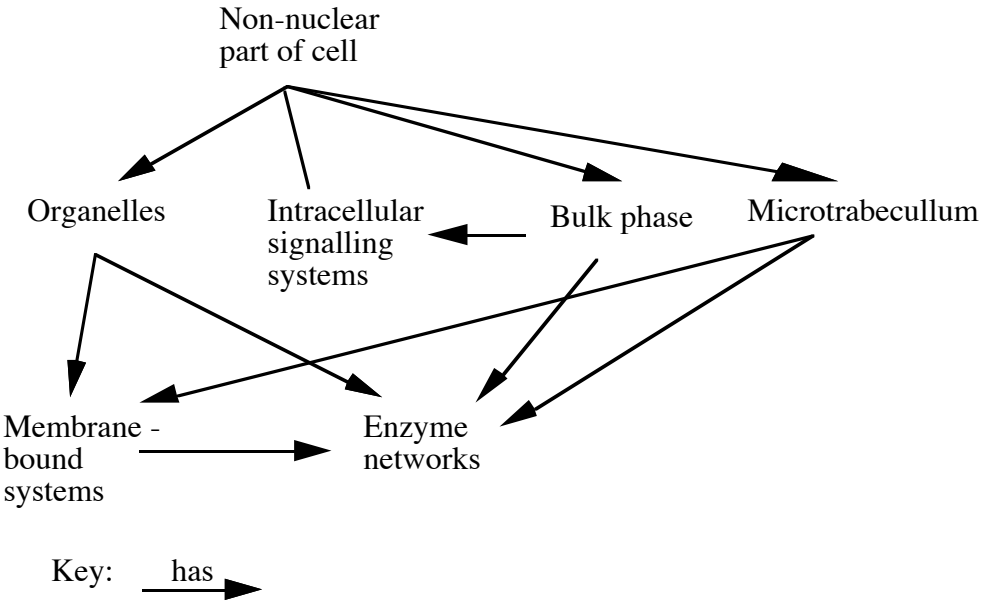



Figure 4 - Some Decompositions of the Computational Hepatocyte

In concluding this section we note that part of the value of machine thinking is that it can supply a mathematical formalism for specifying complex devices. However, as we shall see machine thinking on its own cannot fully accommodate all pertinent features of cellular systems - whether they be somewhat concrete models such as cells as electrical circuits (Sen, 1990) to abstract models based on sophisticated mathematics (Rosen, 1985). The rest of this paper seeks to consider some alternate metaphors.

## 3 Circuits in the Cell

Network models of the cell depend on the idea of flow of information which involves some form of computational activity. Indeed, the circuit metaphor is often an ideal companion to the

machine metaphor with the former providing the mechanistic details by which the latter may be articulated. Thus, a Boolean network, Petri Net or X-machine represent abstract automata structures which are specified in algebraic terms but visualised as graphs. Circuits in the cell can also be expressed in abstract terms for example, Smith and Welch (1991) present a model of cell metabolism in which enzymes represent the organisational *conduit* facilitating the transport of matter-energy *flux*.

The circuit metaphor is very important to the life sciences for a number of reasons. Cycles are highly pervasive models ranging from the blood circulation to biogeochemical cycles to biochemical cycles such as Krebs' TCA cycle (Paton, 1992a)). Given that a cycle such as TCA can be modelled as an algebraic machine (X-machine). It does not seem unfeasible to speculate that X-machine models of all biosystems that display cyclical behaviour could be subjected to the same treatment. However, the machine approach tends to emphasise input-output (transformation) relations whereas focus on networks and cycles allows for a greater understanding of the mechanisms within the machine and of its history of state transitions. This kind of approach can be seen in relation to switching circuit networks (e.g., Glass, 1975), metabolic networks (Kohn & Lemieux, 1991; Marijuan, 1991) and networks of automata (Weisbuch, 1986). Kampis and Csanyi (1991) describe biological systems as organised networks of self-reproducing processes at various levels. Rather than discussing the range of approaches, we now focus on a couple of specific examples, intracellular signalling and membrane-based electron transfer.

There are a number of intracellular signalling pathways which transduce extracellular signals such as hormones and neuromodulators into cellular behaviour. The two major forms are the cyclic AMP (cAMP) pathway and the $Ca^{2+}$/phosphatidylinositol pathway. These and other intracellular signalling systems cooperate and interact as parallel processes for example, both systems stimulate the release of glucose from hepatocytes). As such, they provide valuable sources (as separate and integrated systems) for parallel distributed processing models at this level of organisation displaying a number of important source properties such as distributed memory, fault tolerance, partial computation and non-linear behaviour. Bray (1990) models the cAMP signalling system as a parallel distributed process (PDP) in which different molecular types act as processing units in a network. In this case, the PDP network is not bounded and is unlayered and contains such processing elements as adenyl cyclase (the enzyme involved in cAMP synthesis). Bray's application is of the glucagon-processing behaviour of hepatocytes

and was developed to simulate the pattern recognition capabilities of these cells.

A more detailed application of network relations can now be considered in relation to a possible biological mechanism for learning. In this case we shall see how a network in the cell can exhibit learning capacities and is but one of many examples of the capacity of cells and parts of cells to demonstrate a capacity for cognition. Gingrich & Byrne (1987) propose activity-dependent neuromodulation as a mechanism for associative learning in certain sensory neurons in *Aplysia*. The mechanism they describe applies to events taking place in the axon terminals of neurons in circuits concerned with gill and tail withdrawal reflexes.

The associative learning system can be modelled as a network which is under the joint influence of both cAMP and $Ca^{2+}$/phosphatidylinositol signalling pathways (see Figure 5).

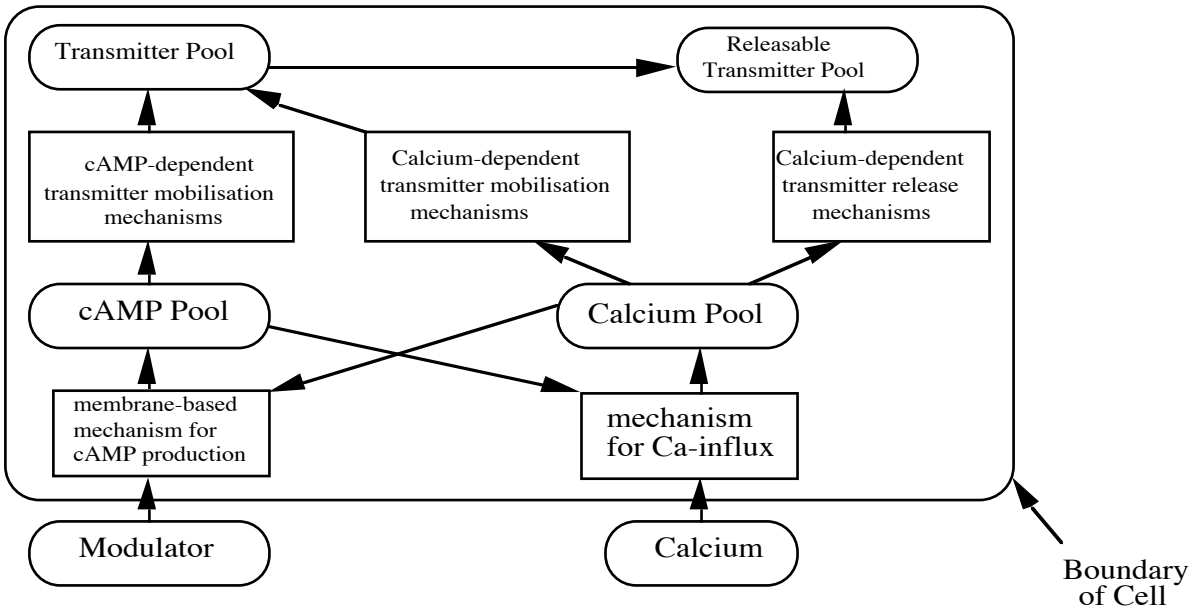



Figure 5 - Activity-dependent Neuromodulation Model of Synaptic Associative Learning (adapted from Gingrich & Byrne (1987))

In this case, the neuromodulator acts as the unconditioned stimulus (US) and the conditioned stimulus (CS) is the spike activity near the axon terminal. The CS elevates $Ca^{2+}$ influx into the cell which primes the cAMP production system.This amplifies modulator (US) - mediated cAMP synthesis. As the cAMP pool increases so the mechanism for $Ca^{2+}$ influx is enhanced. The joint increase in $Ca^{2+}$ and cAMP mobilises transmitter into a releasable form for which its subsequent release is governed by $Ca^{2+}$ - dependent release mechanisms. This rather detailed

example is intended to show how a circuit appreciation of certain computational aspects of a system permits a fuller understanding of the underlying mechanisms. We may also note how the importance of a number of properties associated with circuit emerge in particular the importance of pooling to the computational economy of the cell.

## 4 The Cell as a Society

Parallel, distributed and emergent computer systems can be modelled from an ecological point of view and a computational ecosystem is one in which local interactions determine global behaviour as for example in a network of computers and associated peripheral devices. There is a high degree of information exchange in these systems, albeit often in partial form and they can be characterised by their non-linear behaviour.

Cells can be described in this way, as open systems (Huberman and Hogg, 1988) which contain collections of autonomous computational agents interacting with each other. These open systems exhibit parallel distributed processing in that different parts of the cell do different things and the adaptive capabilities of the system are reflected in its data driven capacities, considerable degree of lack of global control, fault tolerance, high degree of communication and ability of multiple parts to carry out partial computations.

The biochemist's view of the cell developed by Welch not only makes use of a highly organised machine-with-slots, but also indicates the need to model enzyme societies. Welch describes two kinds of society, a molecular democracy and a supramolecular socialism (Welch & Keleti, 1987). In the former case, each enzyme is modelled as an autonomous agent and the model of cellular organisation is characterised as a bulk aqueous phase in which enzymes and metabolites are homogeneously dispersed. However, this view of a democratic society of enzymes is not supported by empirical and theoretical findings for a lot of cellular metabolism is spatially organised. This includes membrane adsorbed enzyme clusters, multienzyme complexes and enzyme arrays along the cellular microtrabeculum. Hence, the society is partitioned and the individual molecules lose their autonomy giving rise to a supramolecular socialism. Furthermore, some enzyme systems can reversibly partition between organised states and the bulk aqueous phase depending on metabolic conditions. This emphasis on organisation in Welch's model shifts the focus from a homogeneous bulk reaction-diffusion system to a heterogeneous system which is structured according to the topographical

segregation of individual processes.

It is also important to be aware that an appreciation of a cell as a society can bring with it new ideas about organisation and the internal mechanisms of the system (Paton, 1992). This is particularly important when current thinking suggests that models are unsatisfactory. For example, a cell can be seen as an ecological society in which there is microzonation of structures and resources as seen in compartmentation and pooling, niche structure of the cell as defined for example by role and the integrative effects and symbolic and cognitive significance of communication. Ideas about the cell as an economy have some degree of support for example, the notion of ATP as the energy currency of the cell would fall into this category.

It should also be borne in mind that tissues and organs in multicellular organisms could be described as societies of cells. For example, Albrecht-Buehler (1990) seeks to provide a non-reductive account of the cell by comparing much-idealised simple organisms with biomolecules. For example, he describes the emergence of colonies of the green alga, *Chlamydomonas* in which the individual organisms, which in the context of the general cell-as-society metaphor represent molecules, are treated as chaotically-active goal-driven units, subtly interacting with each other and their environment. The emergent properties of this system are described in cognitive terms and include the colony being able to self-structure itself into vertical columns, solve problems about circulation of oxygen and carbon dioxide, exchange information and actively cooperate. A more exciting source of emergent computation is that of the slime mould *Dictyostelium* which has a remarkable life history (see Alberts, Bray et al, 1989). Under normal conditions they exist as individual motile cells. However, when starved of food they aggregate to form 1-2mm multicellular wormlike slugs each of about 100,000 cells. These 'super-organisms' aggregate through inter-cellular cAMP signalling and display an elaborate collective colonial behaviour. For the purposes of the current discussion the models and language that could be used to describe the collective behaviour of the slug can be applied to certain aspects of the high degree of collective behaviour within a cell, particularly at the level of multi-molecular complexes and membrane-based systems.

## 5 The Cell as Text

It has been noted elsewhere that important ideas can be displaced between system-as-society and system-as-text such as the need for interpretation of context-dependent relations across

organisational levels (Paton, 1992a; Paton *et al*, 1991). The text metaphor carries with it important ideas related such concepts as context and interpretation and to emergent properties associated with structure such as the word -> sentence -> paragraph -> chapter -> etc hierarchy. In this case if a cell is like a book then we may begin to speculate on the nature of its parts and how they may be described. Indeed, it may well be that the cell is a library.

The reasons for this are related to complexity for example, the large intracellular compartments such as mitochondria contain very large numbers of interacting molecules for which a full account cannot be made at the cellular level. Furthermore, the variety of component molecules is very high although most of the thousands of molecular species present are in very low concentrations. In one sense it is possible to say that the cell is like a text, containing many different kinds of molecules (words). Albrecht-Buehler (1990) goes further and defines cellular information as the "glue" which holds the cell together. The more a cell is decomposed into molecular letters, the more its meaning is destroyed. In a similar manner, Kincaid (1990) argues that the intracellular signalling hypothesis cannot be completely describe from a reductive point of view. Consequently, cellular information is not only context-dependent, it is an emergent property.

The work of Varela (e.g., 1979) is of crucial importance to any comprehensive understanding of biological information. Biological systems are described as autonomous devices because their emergent behaviours and internal self-organising processes define what counts as relevant interactions. This autopoietic description provides a contrast with machine thinking associated with control and the transformation of inputs into outputs. Indeed, Varela draws the important distinction between a heteronomous device which are defined according to a set of instructions and the related control mechanisms acting on it and an autonomous device which is defined according to its internal self-organising processes, emergent behaviours and operational closure. Although it is not possible to review his work here (see Bourgine and Varela, 1992 for a brief summary), it is worth noting the distinction he makes between two kinds of information namely, instruction and representation. Varela points out that information in biological systems is not simply related to the way behaviour can be adequately represented independent of the systems structure (what he calls the representational view of information), it is also about the way in which the system constructs information namely, the instructional view. As such, many biological systems exhibit cognitive capacities (Manderick, 1992).

This can also be seen in the analysis of Emmeche and Hoffmeyer (1991) who examined

several ways in which biological information can be described using a basic metaphorical assumption of nature-as-language. For them, information as articulated within the mathematical theory of information is a category which is much less comprehensive than information exchanged between people. They argue that biological information must be understood as embracing the semantic openness that is characteristic of information exchange in human communication. Consequently, information is inseparable from a subject to whom the information makes sense. Thus, when Barwise (1984) notes how verbs are like the 'glue' which holds together the nouns and other parts of speech, we find a way in which the organisational structure of a whole - in this case discourse - can be made.

It can be argued that the simple relational properties of verbs-as-glue can be seen as a starting point for looking at certain general properties of biosystems particularly with respect to categories and functors (Rosen, 1973). There are inadequacies with the concept of cellular information based solely on thermodynamic models, which talks in terms of negative entropy and physical constraints (see also, Kampis & Csanyi, 1991). It can be described in a number of ways and from a number of viewpoints. The metaphor of text can be important when discussing the organisational level of description; hence, cells have meaning from one point of view.

## 6 Spatial Metaphors and Cellular Organisation

The cell as text is related to ideas that information equals form (e.g., Thom, 1972) and to the development of spatial metaphors associated with cell models. Spatial metaphors, as the name indicates, convey ideas about space ranging from dimension, form and surface through generalised 'spaces' such as adaptive landscapes to the very heart of this paper namely, perspectives or viewpoints on the cell. Reflecting on the text metaphor, we may consider for example how Thompson (1942) notes that "the form of an object is a 'diagram of forces'" (p16) and that the living organism "represents or occupies a field of force" (p30). The 'diagrams' can be generalised in number of ways and often point to mathematical interpretation.

Savageau (1991) argues that modelling a biochemical system in terms of parts alone (i.e., from the bottom-up) is insufficient to describe its complexity and he proposes an integrative or synthetic phase of modelling as well as a reductive or analytical phase. The synthetic phase accounts for the global behaviour of biochemical systems and the mathematical relation between

the whole and its parts is achieved by the use of a Power Law (in which enzyme catalysed reactions are accounted for in terms of self-similar scaling). Savageau shows that when a reaction is modelled within a three dimensional homogeneous space, the kinetic order (the mathematical relationship between the number of molecules participating in a reaction and the reaction rate) is identical to the number of molecules involved in the reaction. However, if the reaction takes place on a two dimensional surface such as a membrane, the kinetic order is higher than the number of participating molecules. Smith and Welch (1991) and Welch (1992) seek to develop a spatial approach to cell metabolism by an analogical description of a metabolic space. This involves the application of the mathematical notion of a field.

The fractal dynamics of the cell can in part be attributed to the spatial organisation of molecules and cytomatrix surfaces and their associated flow processes. It is suggested that the field concept can be applied to models of cells with respect to spatial complexity (i.e., the abstraction of biological form) and to temporal relations (i.e., the abstraction of dynamical behaviours). How does this apply to an appreciation of biocomputation at the cellular level ? Several proposals are now made:

- self-similar scaling can be applied to intracellular organisational hierarchies in that levels are characterised by a fractal dimensionality,
- computational comparisons between different cells can be made with respect to their their fractal organisation for example, between the architectural complexity of a neuron and the metabolic complexity of a hepatocyte,
- certain modelling principles may emerge with respect to relational invariance concerned with intracellular, intra-organismal and inter-organismal systems.

**Concluding Remark**

The cell is a complex biological object. It displays a variety of computational activities and can in different ways be described as a parallel distributed computer with emergent properties. The computational metaphor is very useful to biology but in how to model certain features. An awareness of the existence and nature of these gaps may lead to a greater understanding not only of cell biology but also of the emergence of new computational models.

**Acknowledgements**

The writer is very grateful for advice and comments from Professors Mike Holcombe, Gordon Shepherd and Rick Welch.

**References**

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J.D., 1989, Molecular Biology of the Cell (Garland Publishing, New York).

Albrecht-Buehler, G., 1990, In Defense of 'Nonmolecular' Biology, International Review of Cytology 120, 191-241.

Beardsley, T., 1991, Smart Genes. Scientific American, 265, 2, 72-81.

Bernardi, G. 1989, The Isochore Organisation of the Human Genome. Ann. Rev. Genetics, 23, 637-671.

Bourgine, P. & Varela, F.J. 1992, Towards a Practice of Autonomous Systems. in Varela, F.J. & Bourgine, P. (eds), Towards a Practice of Autonomous Systems. (MIT/Bradford, Cambridge, MA), pp xi-xvii.

Bray, D. 1990, Intracellular Signalling as a Parallel Distributed Process. Journal of Theoretical Biology, 143, 215-231.

Emmeche, C. & Hoffmeyer, J. 1991, From Language to Nature: The Semiotic Metaphor in Biology. Semiotica, 84, 1/2, 1-42.

Forrest, S. 1990, Emergent Computation: Self-Organizing, Collective and Cooperative Phenomena in Natural and Artificial Computing Systems. Physica D, 42, 1-11.

Glass, L. 1975, Classification of Biological Networks by their Qualitative Dynamics. Journal of Theoretical Biology, 54, 85-107.

Hess, B. & Markus, M. 1987, Order and Chaos in Biochemistry. TIBS, 12, 45-48.

Hesse, M.B. 1963, Models and Analogies in Science. (Sheed & Ward, London).

Hinkle, P.C. & McCarty, R.E. 1978, How Cells make ATP. Scientific American, 238, 3, 104-123.

Hofstader, D.R. 1979, Godel, Escher, Bach: An Eternal Gold Braid. (Harvester Press, Brighton ).

Holcombe, W.M.L. 1990, Towards a Description of Intracellular Biochemical Organisation. Computers Math. Applications, 20, 4-6, 107-115.

Holcombe, W.M.L. 1991, Mathematical Models of Cell Biochemistry. In Ji, S. (ed),

Molecular Theories of Cell Life and Death. (Rutgers University Press, New Brunswick) Chapter 4.

Holcombe, W.M.L. 1992, Abstract Machine Models of Cell Metabolism. ACM SIGBIO Newsletter, 12, 2, 14-17.

Huberman, B.A. & Hogg, T. 1988, The Behaviour of Computational Ecologies, in: Huberman, B.A. (ed), The Ecology of Computation. (Elsevier, New York), pp 77-115.

Kagawa, Y. 1991, Bioenergetics and Biodevices, in: Kaminuma, T. & Matsumoto, G. (eds), Biocomputers: The Next Generation from Japan. (Chapman and Hall: London), pp. 51-68.

Kampis, G. & Csanyi, V. 1991, Life, Self-reproduction and Information: Beyond the Machine Metaphor. Journal of Theoretical Biology, 148, 17-32.

Kauffman, S.A. 1991, Antichaos and Adaptation. Scientific American, 265, 2, 64- .

Kincaid, H. 1990, Molecular Biology and the Unity of Science. Philosophy of Science, 575-593.

Kohn, M.C. & Lemieux, D.R. 1991, Identification of Regulatory Properties of Metabolic Networks by Graph Theoretical Modelling. Journal of Theoretical Biology, 150, 3-25.

Lauger, P. 1987, Dynamics of Ion Transport Systems. Physiological Review, 67, 4, 1296-1331.

Lichtstein, D. & Rodbard, D. 1987, A Second Look at the Second Messenger Hypothesis. Life Sciences, 40, 2041-2051.

Macara, I.G. 1991, The RAS Superfamily of Molecular Switches. Cellular Signalling, 3, 3, 179-187.

Manderick, B. (1992), Selectionist Systems as Cognitive Systems, in: Varela, F.J. & Bourgine, P. (eds), Towards a Practice of Autonomous Systems, (MIT/Bradford, Cambridge), pp. 441-447.

Marijuan, P.C. 1991, Enzymes and Theoretical Biology: Sketch of an Informational Perspetive of the Cell. BioSystems, 25, 259-273.

Marijuan, P.C. & Westley, J. 1992, Enzymes as Molecular Automata: A Reflection on some Numerical and Philosophical Aspects of the Hypothesis. BioSystems (in press).

Miwa, J., Tabuse, Y. & Kaminuma, T. 1991, Information Processing in Biological Organisms, in: Kaminuma, T. & Matsumoto, G. (eds), Biocomputers: The Next Generation from Japan. (Chapman and Hall, London), pp. 69-79.

Paton, R.C. 1992a, Towards a Metaphorical Biology. Biology and Philosophy, 7, 279-294.

Paton, R.C. 1992b, Perspectives on Adaptation and Environment. submitted for publication.

Paton, R.C., Nwana, H.S., Shave, M.J.R., Bench-Capon, T.J.M.& Hughes, S. 1991,Transfer of Natural Metaphors to Parallel Problem Solving Applications, in: Schwefel, H-P. & Maenner, R. (eds), Parallel Problem Solving from Nature, Lecture Notes in Computer Science. (Berlin, Springer), pp. 363-372.

Paton, R.C., Nwana, H.S., Shave, M.J.R. & Bench-Capon, T.J.M. 1992, Computing at the Tissue/Organ Level (with particular reference to the liver), in: Varela, F.J. & Bourgine, P. (eds), Towards a Practice of Autonomous Systems, (MIT/Bradford, Cambridge), pp.411-420.

Paton, R.C., Nwana, H.S., Shave, M.J.R. & Bench-Capon, T.J.M. forthcoming, An Examination of Some Metaphorical Contexts for Biologically Motivated Computing. accepted for publication in the British Journal for the Philosophy of Science.

Rosen, R.1973, Is there a Unified Mathematical Biology ?, in Rosen, R. (ed), Foundations of Mathematical Biology Volume III Supercellular Systems, New York: Academic Press, 361-393.

Rosen, R. 1985 , Anticipatory Systems. (Pergamon Press, Oxford).

Savageau, M.A. 1991, Reconstructionist Molecular Biology. The New Biologist, 3, 2, 190-197.

Sen, A.K. 1990, Application of Electrical Analogues to Control Analysis of Simple Metabolic Pathway. Biochemical Journal, 272, 65-70.

Sernetz, M., Gélleri, B. & Hoffmann, J. 1985, The Organism as Bioreactor. Interpretation of the Reduction Law of Metabolism in Terms of Heterogeneous Catalysis and Fractal Structure. Journal of Theoretical Biology, 117, 209-230.

Shepherd, G.M. 1990, The Significance of Real Neural Architectures for Neural Network Simulations, in Schwartz, E.L. (ed), Computational Neuroscience, Cambridge: MIT/Bradford, 82-96.

Shepherd, G.E. 1992, Canonical Neurons and their Computational Organisation. In ... (eds), Single Neuron Computation, New York: Academic Press.

Shepherd, G.M. & Brayton, R.K. 1987, Logic Operations are Properties of Computer-Simulated Interactions between Excitable Dendritic Spines. Neuroscience, 21, 1, 151-165.

Smith, H.A. & Welch, G.R. 1991, Cytosociology: A Field-Theoretic View of Cell Metabolism. in Ji, S. (ed), Molecular Theories of Cell Life and Death. (Rutgers University

Press, New Brunswick), Chapter 6.

Stahl, W.R. & Goheen, H.E. 1963, Molecular Algorithms. Journal of Theoretical Biology, 5, 266-287.

Thompson, D'Arcy W. 1942, On Growth and Form A New Edition. (University Press, Cambridge).

Varela, F.J. 1979, Principles of Biological Autonomy. (NorthHolland, New York).

Weisbuch,G. 1986, Networks of Automata and Biological Organisation. Journal of Theoretical Biology, 121, 255-267.

Welch, G.R. 1987, The Living Cell as an Ecosystem: Hierarchical Analogy and Symmetry. Trends in Ecology and Evolution, 2, 10, 305-309.

Welch, G.R. 1992, An Analogical "Field Construct in Cellular Biophysics: History and Present Status. Prog. Biophys. molec. Biol., 57, 71-128.

Welch, G.R. & Kell, D.B. 1986, Not just Catalysts - Molecular Machines in Bioenergetics, in Welch, G.R. (ed), The Fluctuating Enzyme, (John Wiley, New York) pp451-492.

Welch, G.R. & Keleti, T. 1987, Is Cell Metabolism Controlled by a 'Molecular Democracy' or by a 'Supramolecular Socialism' ? Trends Biochem. Sci., 12, 216-217.