Delta-Notch Lateral Inhibition within the Organ of Corti

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Abstract. Lateral inhibition is described as an emergent property of the Delta-Notch signalling network. Two separate model representations of lateral inhibition are proposed for different purposes. One provides information about bioenergetics while the other has the capability to produce a physical representation. It is proposed that both can be used in further studies of the sensory pathways in the human connectome model of brain function.

1. Introduction

Over the last 60 or so years there have been many advances in the understanding of life at the level of scale at which microbiology provides the underpinning science. These advances have allowed several streams of thought to be intertwined to what might conveniently be termed here, 'systems biology'. In the study of systems biology: the gene provides the basis of heredity; biological physics and chemistry gives the details of cellular bioenergetics that drives the various cellular functions; the cell itself can be considered as the basic functional unit of life; and evolution is via natural selection. Each of these four processes operate at different spatial and temporal scales simultaneously, from which a multi-scale approach to functional analysis might provide an enhanced systemic understanding of behaviour.

For microbiology to advance further it may require further thinking in 'informatics and systems', where here there is a subtle difference in the meaning of the term 'system' than used in the previous term introduced – 'systems biology'. 'Systems science' [1] and more latterly 'systems engineering' [2] are themselves distinct disciplines that concern the study of organisational entities and the relations between them. From this simple definition it is possible to conduct numerous types of intervention that link functions to other functions, or functions to behaviour. So, using appropriate methods it is possible, for example, to study complex adaptive systems and their information flows which together may represent a regulatory system (including positive and negative feedback), an oscillatory system, and a network system. Clearly such systems occur in finance and economics, industry and commerce etc., but it is their use and interpretation in biological systems that are of concern in this paper. However, whatever the application, there are some systems-based terms that can be used to describe systemic behaviour that is of wider interest. Such a term is 'emergence' that leads to a need to define an 'emergent property' of a system. For the purposes of this paper an emergent property can be defined as behaviour or function that is exhibited at one level of scale that can not be determined from behaviour or function at a lower level of scale. Thus, the behaviour of a group of cells will not be deducible from the behaviour of individual cells.

Previous work by the research team at Loughborough University has investigated the link between multi-scale functions and behaviour in the development of heart tissue using an ontological approach [3] and more specifically epithelial to mesenchymal transition in cardiac cushion growth in the development of heart valves [4, 5]. In the latter studies, the role of the trans-membrane protein Delta-

Notch cell signalling network is particularly important. Further studies of the Delta-Notch protein network reveal examples of emergent properties of the system – in the patterns of activity at a cellular level obtained as a consequence of lateral inhibition and lateral induction of the Delta-Notch protein signals. This paper investigates an occurrence of Delta-Notch lateral inhibition by producing two model representations of the process applied to the development of hair cells within the sensory end-organ of hearing – the Organ of Corti.

2. Biological Context

The Delta-Notch protein signalling network is an example of juxtacrine signalling, meaning that the cell-cell signals are restricted to neighbouring cells in physical contact with one another. Both Delta and Notch are trans-membrane proteins. Juxtacrine signalling occurs when a Delta-type ligand binds to a Notch receptor (see Figure 1a, b). Binding causes a conformational change in the Notch protein which has the effect of breaking off the intra-cellular portion of the protein – termed the 'Notch Intra-cellular Domain' (NICD) component. The NICD component passes through the intra-cellular boundary to the nucleus of the cell where it interacts with a DNA-binding protein called CSL. The resultant change caused by the reception of this NICD 'signal' depends on a second intra-cellular Notch protein component termed Notch^{intra}. When Notch^{intra} is absent the target cell is repressed which leads to lateral inhibition (Figure 1a); but in its presence the target cell is activated which leads to lateral induction (Figure 1b).

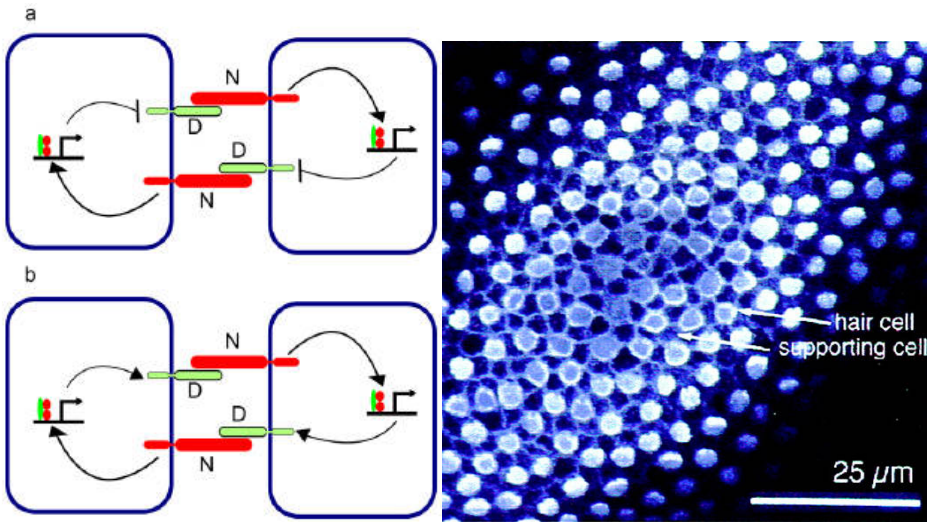


Figure 1: a) schematic diagram of lateral inhibition [6]; b) schematic diagram of lateral induction [6]; c) Sensory hair patches in a chick's inner ear [7].

Whereas the emergent pattern behaviour of lateral induction can take many forms, the behaviour of cells that exhibit lateral inhibition has a typical chequer-board pattern where each activated cell is surrounded by repressed cells. The sensory end-organs are examples of where lateral inhibition of neighbouring cells can be found, which can also contribute towards physiological function. In the eye, lateral inhibition of the rod cells yield a greater visual acuity between shades of grey; and in the organ of Corti in the inner ear, each hair cell is surrounded by a so-called 'supporting' cell (Figure 1c refers). The model representations below are sufficiently rich to demonstrate the tell-tale chequer-board patterns found in lateral inhibition. They can therefore be used in simulations to test hypotheses in behaviour of the model that maps to behaviour that may be found in the development of hair cells within the organ of Corti.

3. Outline Methods

3.1. Cellular Potts Models

Cellular Potts models (CPMs) provide simulations in which biological cells are represented by multiple sites on a pixelated lattice. The simulation is driven by updating the lattice one pixel at a time based on rules that reduce the entropy of the system as a whole. Finding the lowest energy configuration can be achieved in CPMs by using the Metropolis Monte Carlo algorithm. For this, a Hamiltonian Energy, H, is defined as a measure of entropy for the whole lattice. In each simulation step a random copy attempt is made at each lattice site that represents a cell surface. The resulting change in energy, ΔH, is calculated and accepted with a probability of $min(1, e^{\Delta H/T})$, where the T parameter is an intrinsic measure of cell motility.

Though CPMs can model cell behaviours such as adhesion, surface area, chemotaxis, and apoptosis, in this study cell-cell signalling is highlighted.

3.2. Biological Circuits

To represent Delta-Notch lateral inhibition as a biological circuit takes the programming environment used – National Instruments LabVIEW ® (LabVIEW) - into a novel domain and thereby stretches the use cases available to users across the globe. In essence, LabVIEW is a graphical programming environment for hardware and software integration to design and deploy measurement and control systems. It is employed as the program of choice here, as juxtacrine signalling can be considered as a biological measurement and control system, exhibiting regulatory cycles that are composed primarily of negative feedback control loops. The LabVIEW program component at the heart of the 'develop-and-test cycle' is termed the VI (for Virtual Instrument). The VI comprises three components: the block diagram, the front panel (user interface); and the connector panel (for sub-system integration).

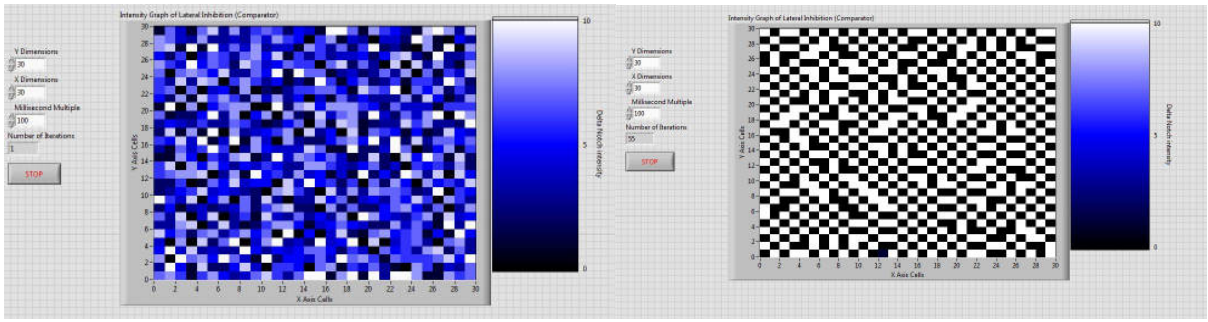
4. Outline Results

4.1 Cellular Potts Models

Multi-scale cellular Potts models have been used to represent Delta-Notch lateral inhibition and lateral induction. This was achieved by assigning a SBML model to each cell in a simulation which had previously been solved dynamically. Cell level parameters were set as a function of sub-cellular variables, and the sub-cellular models took input values calculated from neighbouring cells in the Potts simulation environment. This multi-scale implementation gives the freedom to investigate developmental processes that involve both pattern formation through signalling, and changes in the physical shape, architecture and arrangement of cells in tissue. The development of the organ of Corti is an excellent candidate for this kind of modelling and simulation. It has been investigated thoroughly via experimental means, and involves juxtacrine signalling, growth and remodelling simultaneously.

4.2 Biological Circuits

A holistic systems approach was adopted to generate requirements for a simulation model to represent cell-cell communication. A 2-D array of cells (30 x 30 array in Figure 2a, b) was constructed with each cell possessing a random value between zero and 10. If the value of the cell was greater than 5, Delta is said to be expressed; otherwise the fate of the cell is Notch-expressed. The simulation was driven by averaging a 4-neighbour cell configuration; should this average exceed 5, then 0.5 is subtracted from the value of the target cell, otherwise 0.5 is added. Clearly, this may alter the fate of cell expression. This process is repeated for each cell in the array, and when all the cells in one iteration have been compared they adopt their new values. Figure 2a shows a typical simulation start state. After 55 whole array iterations, the tell-tale chequer-board pattern of lateral inhibition can be determined (Figure 2b refers).



a) b)

Figure 2 A LabVIEW VI front panel for a simulation of lateral inhibition a) at the start of a simulation, b) at the end of a simulation.

To improve the verification and validation of the simulation, the simple arithmetic comparison rule that drives the simulation will be replaced by linked differential equations. A 6-neighbour configuration will also be adopted where each cell has a hexagonal representation.

5. Conclusions

It is hoped that model-based representations and simulations of sensory systems will provide deep insights into the study of the neuronal wiring of the brain. Though results thus far from mapping the connectome have produced stunning visualisations, it would be interesting to map the effect of lateral inhibition of the Delta-Notch signalling network of one of the sense end-organs to their locations in either the visual or auditory cortex. A multi-scale understanding of the signalling pathway, helped via further model-based interventions of cell signal transmission other than juxtacrine (e.g. by the use of neuristors that comprise a new electrical circuit component termed a 'memrister' [8] that can mimic the spikes seen in neurone models) might then yield new kinds of therapeutic interventions for blindness and deafness.

References

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