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Pattern formation in discrete cell tissues under long range filopodia-based direct cell to cell contact

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ABSTRACT

Pattern formation via direct cell to cell contact has received considerable attention over the years. In particular the lateral-inhibition mechanism observed in the Notch signalling pathway can generate a regular periodic pattern of differential cell activity, and has been proposed to explain the emergence of patterns in various tissues and organs. The majority of models of this system have focussed on short-range contacts: a cell signals only to its nearest neighbours and the resulting patterns tend to be of fine-scale "salt and pepper" nature. The capacity of certain cells to extend signalling filopodia (cytonemes) over multiple cell lengths, however, inserts a long-range or non-local component into this process. Here we explore how long range signalling can impact on pattern formation. Specifically, we extend a standard model for Notch-like lateral inhibition to include cytoneme-mediated signalling, and investigate how pattern formation depends on the spatial distribution of signal from the signalling cell. We show that a variety of patterns can be obtained, ranging from a sparse pattern of single isolated cells to larger clusters or stripes.

1. Introduction

Determining the communication channels through which a cell population patterns and differentiates itself is central to understanding the development, homoeostasis, repair and pathogenesis of the tissues and organs of our bodies. Many early theories invoked the concept of *morphogens*, chemical signalling molecules capable of directing the behaviour and differentiation of cells: for example, the seminal model of Turing [30] proposed that a system of reacting and diffusing molecules could form a spatially periodic pattern, and that this information offered a patterning blueprint; the French-flag model of Wolpert [34] posited that a non-uniform distribution of a morphogen could pattern a tissue via distinct differentiation paths being followed by cells according to the morphogen level. Numerous morphogens have been discovered, and their various modes of operation have been the source of considerable theory and speculation (e.g. see the review in [23]).

In many models, morphogen transport is explicitly or implicitly assumed to result from simple diffusion in the extracellular space: for example, in Turing's model diffusion is (surprisingly) the critical factor that breaks initial symmetry to create pattern; Crick [6] calculated that small(ish) molecules were (theoretically) capable of diffusing through tissues in timescales relevant for early embryonic processes. In recent years, a combination of theoretical modelling and experimental data have supported molecular diffusion as a potential morphogen transport mechanism (e.g. [14,35]).

In certain signalling systems, however, the intercellular communication required for pattern formation can be achieved without extracellular diffusion, a particular well known example being the Notch system. This crucial signalling pathway is widely conserved throughout the animal kingdom and found to control/regulate a diverse range of processes in both developing and adult tissues [1,10]. The Notch receptor and its ligands, the Delta/Serrate/Lag2 (DSL) family, are transmembrane proteins that require cell to cell contact due to their membrane-tethered nature: while diffusible forms of ligand exist, they do not appear to trigger signalling [12]. In other words, cell to cell signalling is achieved through a *direct and one-to-one* contact between a signaller cell and receiver cell, providing *juxtacrine signalling*. Diffusion, on the other hand, allows *paracrine* signalling: a secreting cell could signal many or all other cells in a population. Such direct signalling is by no means confined to the Notch signalling system, or receptor/ligand modes of communication: for example, cadherin adhesion molecules create cell-to-cell adhesive bonds that also provide signalling [33]; information can also pass directly from cell to cell via "gap-junction" tunnels between two membranes [16], allowing small molecules to pass directly from cytoplasm to cytoplasm.

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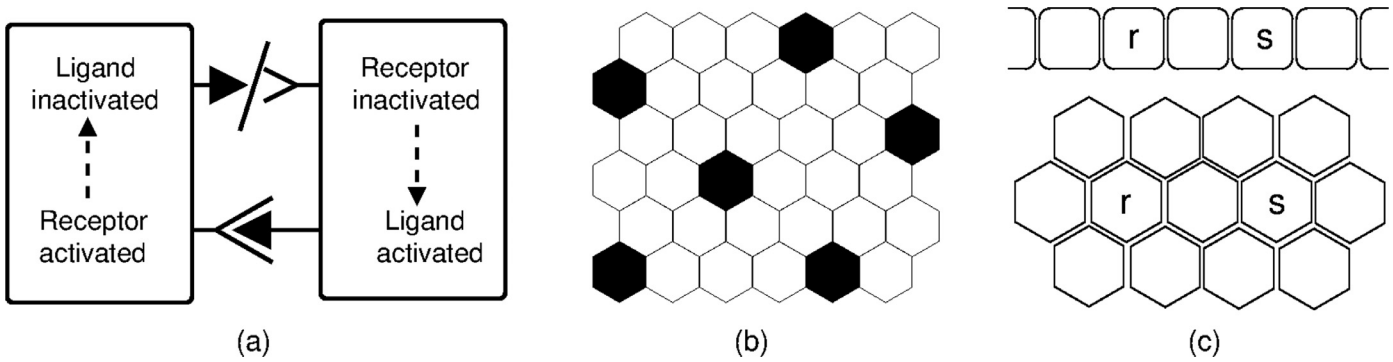

Fig. 1. (a) Illustration of the Delta–Notch lateral inhibition mechanism, adapted from [5]. (b) Lateral-inhibition operating in a juxtacrine signalling process is capable of creating a finely grained pattern of alternate cell fates. (c) The 1D and 2D geometries considered for the modelling. We note that for the two cells r and s we have $d_{r,s} = 2$.

In the context of developmental pattern formation Delta–Notch signalling is capable of operating a lateral-inhibition scheme [1,10], where high receptor (Notch) activity in a receiving cell down-regulates its own ligand (Delta) activity, and hence its capacity to signal other cells (see Fig. 1(a)). Between two quasi-identical cells, stochastic fluctuations in their initial ligand and receptor activities will be steadily amplified, with one cell's ligand activity progressively downregulated to the extent that it cannot induce a similar response in the other: one cell "wins" and the other "loses", distinct signalling activities are displayed and the cells take alternate fates. In an array of cells, this juxtacrine-based mechanism of lateral inhibition can generate a fine-scale "salt and pepper" pattern of signalling activity (see Fig. 1(b)), and hence provide a potential mechanism for certain types of tissue patterning. Notch-based pattern formation has received intense scrutiny during many development processes, such as sensory bristle formation in the fruit-fly thorax [1,10,27]. These mechanosensory bristles develop from single sensory organ precursor (SOP) cells, which form at regular spaced intervals in an epithelial field through a Notch–Delta lateral inhibition process [27].

A number of mathematical models have been developed to explore juxtacrine-based signalling in patterning. Collier et al. [5] devised a model for juxtacrine-based lateral inhibition that consisted of a network of coupled equations for the signalling activities of Delta and Notch in each cell. Juxtacrine signalling was incorporated via a cell's receptor activity depending on the ligand activity of its nearest neighbours, and the model was shown to reproduce the fine-grained patterning of a cell sheet. This framework has subsequently been adapted and extended in various directions, from more detailed analytical explorations to refined representation of the molecular interactions, or specific modelling of particular instances of pattern formation: as examples, we refer to [2,3,8,13,17–21,26,28,29,31,32].

On initial reading, the "juxtacrine" labelling of Delta–Notch interactions suggests strictly local communication, such that a cell can only signal to its nearest neighbours. Consequently, the length scales of any developing patterns is somewhat uncertain. For example, in the lateral-inhibition based model of [5], each cell signals only to its nearest neighbours and the corresponding pattern tends to a fine-scale form: a more-or-less alternating pattern of distinct signalling states (e.g. see an example in Fig. 9(a)). In contrast, the spacing between SOPs during bristle formation is somewhat larger, raising the question as to what coarsening factors could contribute to the process.

Many cells, even in highly packed epithelial layers, have a dynamic form that allows the extension of long membrane protrusions such as filopodia. In particular, much attention has focussed on the capacity of certain cells to extend long, oriented "signalling filopodia" – often referred to as cytonemes [22] – that can contact and directly signal to more distant cells, possibly up to 200 μm (10s of cell lengths) away (e.g. see the reviews in [9,11,25]). Consequently, the directly-contactable neighbourhood of a cell may extend considerably beyond its nearest neighbours. In the context of Notch–Delta based SOP patterning, de Joussineau et al. [7] found Delta expressed along filopodia puncta and, speculating that this may increase the range of lateral inhibition, showed that disrupting the protrusions resulted in a shorter spacing and over-expressed SOPs. More recently, Cohen et al. [3] used a combined experimental/theoretical approach to show that the length and lifetime of the dynamic filopodia extended by bristle precursors correlated with the pattern and density of bristles. Beyond this role in lateral-inhibition based pattern formation, cytoneme- or filopodia-mediated cell to cell signalling has been associated to numerous processes in development: most frequently in drosophila, such as Dpp-regulated anterior/posterior border specification and hedgehog (Hh) delivery in the wing-disc, but also vertebrates (for example sonic hedgehog signalling in chick limb buds); we refer to [9,11,25] for reviews.

1.1. Outline

In this paper we consider the impact of long-range, direct contact signalling on the patterning of cellular tissues. We use the classic system of Delta–Notch signalling as a case study, extending the analytically convenient model of [5] to account for non-local interactions. Specifically, we construct a general form in which each cell creates a signalling net, contacting other cells in some non-local neighbourhood. In its general form the equations can be adapted to include a variety of precise modes of non-local signalling, such as dynamically changing according to the concentration of specific components. For the more general purposes here we subsequently restrict to the specific and analytically convenient case in which each cell creates an equivalent and fixed signalling net. Yet, even within this simplification a wide variety of distinct forms of non-local signalling can still be considered, including uniform, tip-based and polarised scenarios. A combination of linear stability analysis and numerical simulation is used to unravel the complexities of pattern formation and determine how the spatial distribution of signal through the net impacts on the pattern form.

2. Model derivation

2.1. Collier et al. model

We suppose the tissue to be formed from a set of identically-sized discrete cells, $\mathcal{C}$, arranged into either a 1-dimensional chain or 2-dimensional regular hexagonal lattice (Fig. 1(c)) and of total cell number $|\mathcal{C}|$. Each cell operates as both a *signaller* and