Understanding regression of Hensen´s node and the caudal stem zone: a mathematical modelling approach

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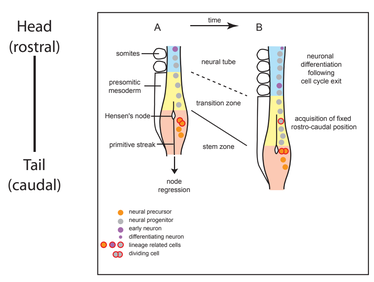
ABSTRACT

Generation of the caudal hindbrain and spinal cord as well as the adjacent mesoderm is accompanied by the regression of the node, the streak, the neighbouring caudal stem zone and caudal pre-somitic mesoderm. As this region in the embryo moves caudally, some cells are left behind and acquire a more mature state: they become notochord and floorplate in the case of the node, differentiating spinal cord in the case of the stem zone and rostral pre-somitic mesoderm in the case of the pre-somitic mesoderm. This process is regulated by several signalling pathways and in particular by FGF, retinoic acid and Wnts. We are exploring, by using a mathematical modelling approach, different gene regulatory networks involving those pathways and different mechanisms of cell behaviour (adhesion, cell movement) that could account for the maintenance of a the stem zone that moves caudally while some of its cells acquire a more mature state in a spatially and temporally controlled manner.

1. Introduction: Extension of the body axis and progressive generation of rostrocaudal structures

Growth and maturation of the developing chick spinal cord



From Diez del Corral and Storey, 2004.

Figure 1

Fgf8 maintains a stem zone state

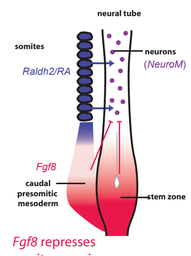


Figure 2

Fgf8 expression is maintained caudaly and progressively downregulated

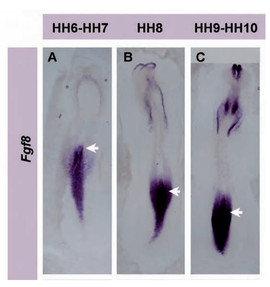


Figure 3

Active transcription domain restricted to stem zone

Fgf8 intronic probe

2. The question:

What regulates expression of Fgf8?

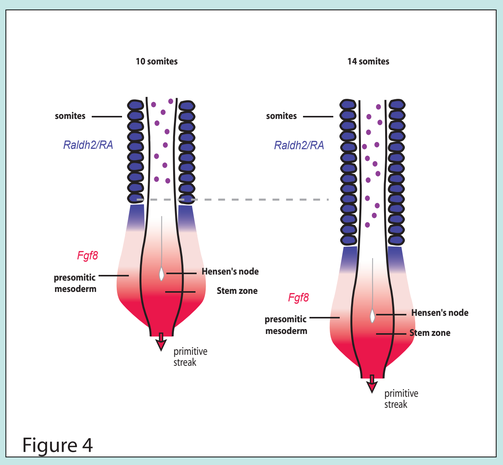


Figure 4

3. What we know about Fgf8 regulation

Retinoic acid decreases Fgf8 (1)

Fgf8 expression is expanded in Vitamine A deficient quails but progressive downregulation continues (1)

Fgf8 is not completelly downregulated in explants of stem zone (that turn on Raldh2)

Progressive downregulation of Fgf8 is restored following splitting the *Fgf8* domain

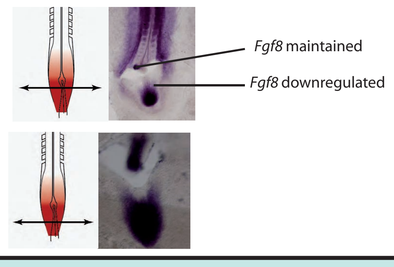


Figure 5

We are looking for simple gene regulatory mechanisms that can give rise to the progressive downregulation of Fgf8 and where the caudal movement of the stem zone cells is important .

4. One dimensional continous modelling approach movement of the domain of cells producing FGF

4.1. Looking at the FGF8 protein profile derived from a group of cells producing Fgf8 mRNA and moving caudally

- We consider concentration profiles of biochemicals in a frame of reference moving with a constant speed c (as we would move with the stem zone)

$$\frac{du_i}{dt} = D_i \frac{d^2 u_i}{dx^2} + c\frac{du_i}{dx} + f_i(\mathbf{u})$$

- We consider the dynamics of 2 reagents
  - *i=1:* Fgf8 mRNA (fibroblast growth factor messanger RNA)
  - *i=2:* FGF8 (fibroblast growth factor, protein that diffuses)
- Initially, we set a region (stem zone) where production of *Fgf8* mRNA level is constant :

$f_1(\mathbf{u}) = k_1(1-u_1)$ in the stem zone and
$f_1(\mathbf{u}) = -k\,u_1$ everywhere else.

- Production of FGF8 protein is proportional to the level of Fgf8 mRNA

$$f_2(\mathbf{u}) = k_2(u_1 - u_2)$$

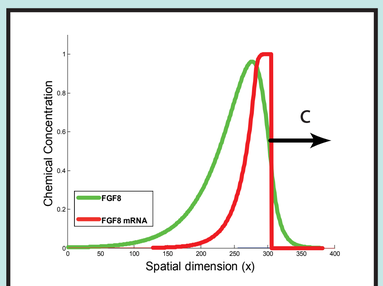


Figure 6

Previously, Baker and Maini (2005) have developed a model where a travelling wave bahaviour of FGF8 expression can be observed by FGF self-activation. However this model does not consider the caudal movement of cells (3).

4.2. Control of Stem Zone (Fgf8 mRNA producing) Size by FGF8 self-regulation

We assume that the size of stem zone is regulated by the level of FGF8

For example: $f_1(\mathbf{u}) = k_1(1-u_1)$ if $u_2 < T_{mRNA}$ and $\frac{\partial u_2}{dx} < 0$

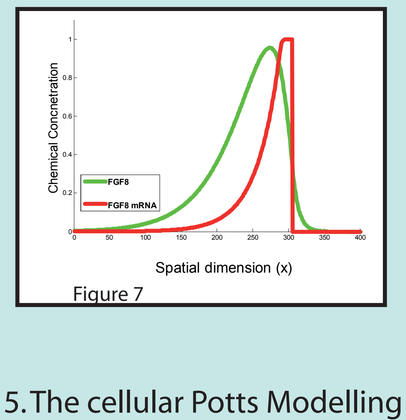


Figure 7

4.3. Control of Stem zone (Fgf8 mRNA producing) by activation of a repressor (Wnt8?)

The rate of Repressor (WNT?) production is proportional to the level of FGF: $f_4(\mathbf{u}) = k_4(u_2 - u_4)$

The size of stem zone is regulated by both WNT and FGF, for example:

$f_1(\mathbf{u}) = k_1(1-u_1)$ if $u_4 - u_2 < T_{mRNA}$ ($\alpha,\beta>0$) and $\frac{u_2}{dx} < 0$

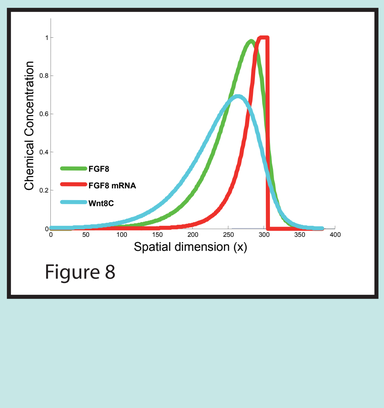


Figure 8

5. The cellular Potts Modelling approach

We are using the Cellular Potts Model (CPM) to test different possible mechanisms of cell differentiation and chemotaxis (4).

Cells in this model are represented by number of lattice nodes in the regular lattice. Cells can exchange their lattice nodes and this results to changes in the shape of cells and their movement. The central element of the CPM is an energy minimization formalism. The energy of system, E, is defined as:

$$E = E_{adhesive} + E_{cell\_size} + E_{chemotaxis} + \ldots$$

Probability of change:

P=1 if $\Delta E<1$

P=exp(-ΔE/T)

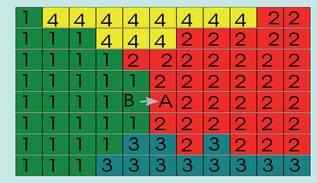


Figure 9

5.1. Exploring proliferation and cell movement: FGF involved in cell motility.

According to 5 downregulation of FGF signalling decreases the caudal movement of cells

For this model, we start with a group of stem zone cells (red) which are set to move right-wise.
These cells produce Fgf8 mRNA and give rise to blue cells that stop Fgf8 production
(we continue here with the 4.2 hypothesis where high FGF8 turns off production of Fgf8 mRNA) and continue to move caudally.
When FGF8 decreases, cells stop moving (green).

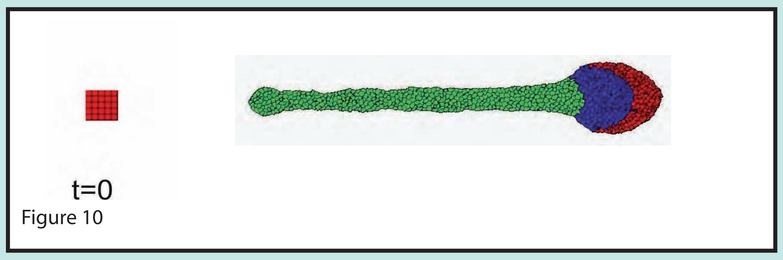


Figure 10

5.2. FGF involved in chemotaxis: a chemotactically repulsive activity has been attributed to FGF8 in several contexts (6)

Different behaviours can be observed depending on chemotactic force vs FGF production kinetics

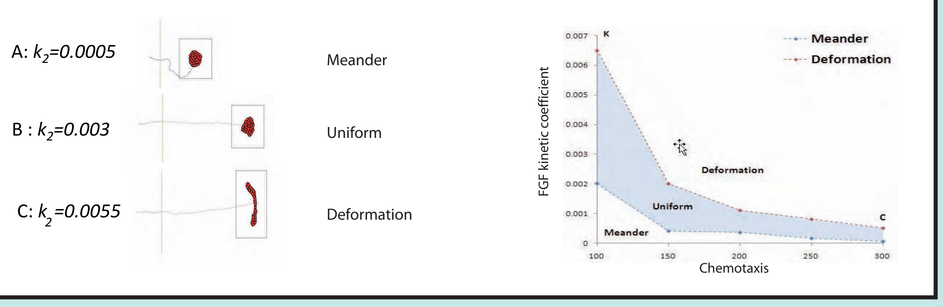


Figure 11

5.2. Integration of proliferation, chemotaxis and a gene regulatory network

We start with a small group of cells (25 cells, red) which:

Produce FGF m-RNA.
Proliferate.
Stop producing FGF mRNA in response to high level of FGF.
Chemotactically sensitive (repelled) to FGF.

If the rate of FGF kinetics is low (enough) there is a range for the strength of chemotactic response (not too strong or too week) such that this group of cells start to move and keeps moving in some direction.

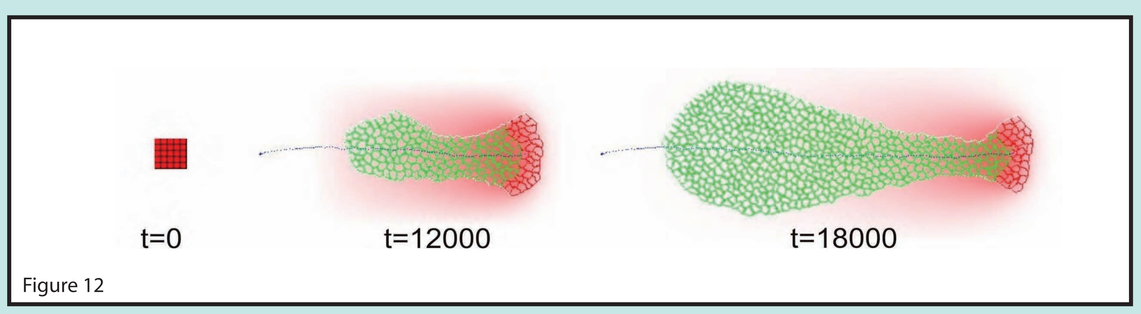


Figure 12

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Acknowledgements

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