Modelling Formation Of The Vertebrate Embryonic Axis

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Abstract

During the early stages of embryo development we observe large scale migrations and rearrangement of cells to form the axes and body plan of the future organism. The key feature of these events is the movement of cells along the embryo's midline causing formation of the spinal cord and central nervous system (CNS). Organization of this movement is centred on a small condensation of cells known as Hensen's node. The node progresses across the epiblast of the embryo (approximately half way) stops and regresses back across the embryo and as does so lays down the CNS. The key questions we are trying to answer in this project is what mechanisms could bring about such motion and show through computer simulations how they could be achieved.

Introduction

One of the important events during embryogenesis is gastrulation when body plan of future organism is laid down. Gastrulation is associated with an extensive cell movement and cell differentiation. The key events during gastrulation is the formation, progression and regression of the primitive streak as governed by the motion of Hensen's node. Cells migrate over the surface of the embryo (epiblast) and converge on and ingress through the primitive streak into the subgerminal space as mesenchyme cells. At late stages of gastrulation, when the node moves posteriorly, cells forming the node proliferate and differentiate fuelling the extension of the CNS and the embryonic axes. In this work we check whether morphogenes produced in the node (such as FGF8) can cause the node's own motion by chemotactic mechanisms. We also check whether these morphogenes can cause differentiation of cells in Hensen's node.

Figure 1: Chick embryo at time of gastrulation.

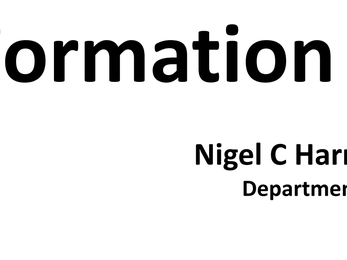

Figure2: Consecutive images of spinal cord formation: the dynamics of FGF8 and RA expression and Hensens's node migration. *(Diez del Corral & Storey 2004)*

The Models

For this study we have developed two distinct models: a caricature one-dimensional model for preliminary analysis of concentration profiles created by moving cells including analytical solutions and stability analysis and two-dimensional model for numerical investigation of the problem in more sophisticated setting which includes modelling of individual cells capable of producing morphogenes as well as growing, proliferating, differentiating and migrating.

1. In 1D the concentration of each morphogene in a frame of reference moving with the Hensen's node (speed *c*) is given by:

$$\frac{du}{dt} = D\frac{d^2u}{dx^2} + c\frac{du}{dx} + f(u)$$

2. In 2D we used the Cellular Potts Model (CPM) to study mechanisms of cell differentiation and chemotaxis. Changes guided by the "energy" of the system:

$$E = E_{adhesive} + E_{chemotaxis} + \ldots,$$

with the probability of a change:

$$P = \begin{cases} 1, & \Delta E < 0 \\ e^{-\Delta E/T}, & \Delta E > 0 \end{cases}$$

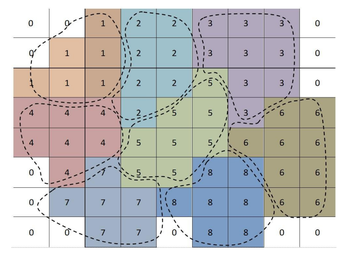

Figure 3: Section of the model medium

One Dimensional Case: three-variable system

Initially we consider the case of a three-variable system for a constant size stem domain, *S* (red hatch), moving right-wise with constant speed, *c,* in accordance with observations made in Figure 2. We assume *S* maintains a constant level of the gene FGF8 mRNA (red line) which decays exponentially outside. The production of FGF8 (green line) is proportional to the level of FGF8 mRNA. FGF8 is a diffusible agent and when its concentration falls below some threshold, T_{RA}, it activates production of extracellular RA (blue line).

The profile of FGF is asymmetric with respect to S and its maximum can be external to *S*. This apparent shift in FGF is proportional to the magnitude of *c* and can be maintained indefinitely. This gives rise to two important conclusions:

1. *regulation of the size of S can be maintained by a morphogene, possibly FGF8 (or another whose concentration profile looks similar to that of FGF8).*
2. *a posterior gradient can be maintained indicating possible chemotactic mechanisms of stem zone motility (i.e. experimental observations indicate that FGF8 is a chemorepellent)*

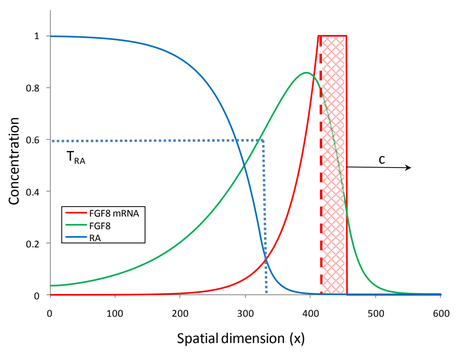

Figure 4:Concentration profiles in a frame of reference moving right-wise with speed *c*.
Stem zone is the area with high and constant mRNA level (red-hatched area).

One Dimensional Case: differentiation and chemotaxis

In the embryo the size of the stem zone is conserved while its constituent cells grow and proliferate. This indicates that some cells differentiate and leave the stem zone. The morphogene responsible for the differentiation is most likely to be produced inside the stem zone (its level correlates with the stem zone size). For example, differentiation could be regulated by FGF8 whose concentration is high on the back side of the stem zone. Also, FGF8 could be responsible for the migration of the stem zone: if cells forming the stem zone are repelled by FGF8 then the total chemotactic force exerted by them is proportional to the difference in FGF8 levels on the front and back sides of the stem zone.

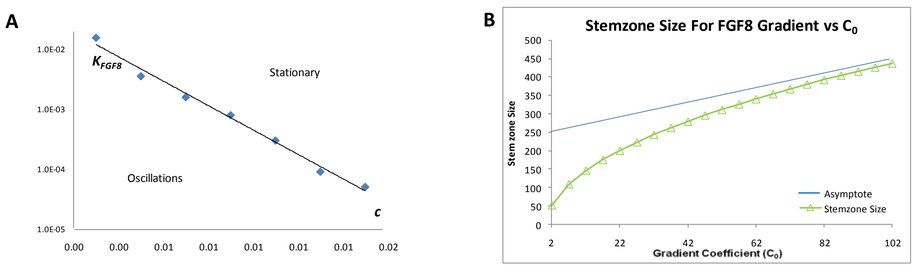

Figure 5: The differentiation of cells in the stem zone is regulated by the morphogene (FGF8).
A: Depending on the rate of morphogene kinetics (K_{FGF8}) and the speed of the stem zone (*c*) the size of stem zone is constant or oscillates. (B): The size of stem zone also depends on the strength of chemotaxis (c_0).

Motility of homogenous Ball of Cells

Informed by simulations in the 1D case we investigate how a ball of cells (generalized Hensen's node) can exhibit motility through chemorepulsion to a self-secreted chemical. As suggested by the 1D model a posterior gradient will arise when chemotaxis is strong (c is high). In the 2D case we achieve this by a transient spatial perturbation of the chemical field which initiates motion. On removal of the perturbation the gradient is maintained and the ball exhibits sustained perpetual motion.

Figure 6: Group of cells sustains uniform motion (after initial "push").
A shows initial conditions; B - moving group and its trace in course of time.

Further we have shown that such sustained motion can exist within a cell tissue.

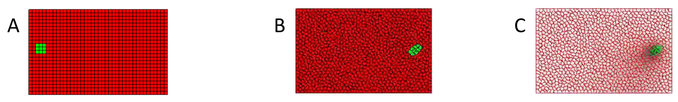

Figure 7: Migration of self-repelling group of cells in a tissue A: initial conditions; B: position of the group at t=30000; C: shows levels of repellent at t=30000.

Growth, proliferation and differentiation of cells in CPM

In these simulations we start with a group of stem zone cells (red) which are set to move right-wise. These cells produce mRNA for FGF8 and also proliferate. Differentiation takes place when the level of FGF8 achieves a threshold value and differentiated cells (green) stop FGF8 mRNA production. This differentiation mechanism allows to keep the size of the moving stem zone constant.

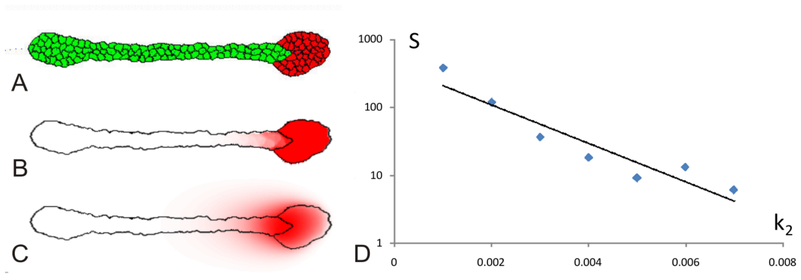

Figure 8. Migrating stem zone in Cellular Potts Model.
(A) The shape of tissue where the stem zone (red) is moving right-wise.
(B) Concentration field of FGF8 mRNA.
(C) Concentration field of FGF8.
(D) The size of stem zone versus the rate of FGF8 kinetics.

Migration of self-repelling stem zone

We assumed that the motion of stem zone is based on chemotaxis and have verified that this could be due to repulsion of cells forming stem zone by FGF8.

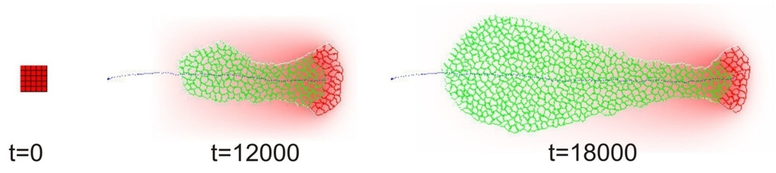

Figure 9. Snap shorts of moving stem zone (red) and the trail of daughter

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

a) Produce FGF8 mRNA .
b) Grow and proliferate.
c) Differentiate (stop producing FGF8 mRNA) in response to high level of FGF8.
d) Chemotactically sensitive (repelled) to FGF8.

If the rate of FGF8 kinetics is low (enough) there is a range for the strength of chemotactic response (not too strong or too weak) such that this group of cells start to move and keeps moving in some direction. The direction of migration can be preset by using special initial conditions.

Conclusions

1.The dynamics of concentration profiles of morphogenes (FGF8, RA) during formation of the embryonic axis can be explained by the fact that FGF8 is produced in the posteriorly moving stem zone. Therefore, there is no need to consider activator/inhibitor like interactions between chemicals and describe profiles of morphogenes as spatio-temporal patterns such as propagating waves or dissipative structures.

2.We have suggested that production of FGF8 mRNA cells in stem zone can be reduced by high level of FGF8 and confirmed in framework of both models that this mechanism allows to keep the size of migrating stem zone constant over time. This assumption is attractive from both mathematical and biological points of view: simple, in line with observations, no need to consider more morphogenes.

3.We have suggested that migration of the stem zone is due to chemotaxis: FGF8is produced by cells in the stem zone and repels the stem zone (self repellent). The assumption is simple and confirmed to be working in simulations. It also leads to an important conclusion: groups of cells in biological tissue can migrate (as a group) if they produce a chemical which acts as a chemo-repellent upon those cells themselves.

References:

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