Modelling Collective Cell Motion in Biology

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Outline

Epithelial sheets (rosettes)

Cranial neural crest cell invasion

Acid-mediated invasion hypothesis (cancer)
ROSETTES
Egg-cylinder stage mouse embryo: AVE cells migrate in a typical way to correctly orientate A-P axis.
Shankar Srinivas
Bradley Joyce
Abigail Moore
Tristan Rodriguez
Jacintha Sughnaseelan
Georgios Trichas
Natalia White
Vivienne Wilkins
Aaron Smith
David Kay
Ruth Baker
During AVE migration, multi-cellular rosettes form (discovered by Shankar Srinivas). Why?
Questions

• What causes the cells to move – pushing or pulling?
• How do rosettes form ????
• Are rosettes an inevitable consequence of coherent cell movement?
• What happens if rosettes do not form?
Vertex Model (Oster and Weliky, Honda, Julicher, etc etc)
\[ P = \left| C_A \frac{|a_t - a|^{n_1 + 1}}{(a_t - a)} \right| + C_H H + C_D \frac{|\phi - \theta|^{n_2 + 1}}{(\phi - \theta)} \hat{P}, \]

\[ T = C_L \left( l_c \hat{T}_c + l_a \hat{T}_a \right) + C_P \left( \hat{T}_c + \hat{T}_a \right) p, \]

\[ \frac{dx_i}{\mu_i} = F_i. \]
Junctional rearrangements

- We allow vertices closer than a certain threshold distance to join together.

Vertex rearrangement known as a T1 swap
Cell growth and mitosis

- Cells are assigned a certain volume and which grows over time.
- Cells can divide when they reach a certain volume.
Migration with or without rosettes
Comparison with experiment: I

- Reduction in mean polygon number in the Epi-VE (pre- and post-migration) agreeing with observations:

![Diagram with images and bar chart comparing average polygon number between ExE-VE and Epi-VE in early and late simulation stages.]
Comparison with experiment: II

- Similar trends observed – 6-sided cells relatively less frequent in Epi-VE, while 4-sided cells more frequent there.
Migration with or without rosettes
A. Bar graphs showing the mean number of rosettes/embryo and mean number of VE cells/embryo across different stages.

B. Images of wild type embryo profiles and anterior views.

C. Images of ROSA26 embryo profiles and anterior views.

D. Bar graphs comparing mean polygon number for different conditions.

E. Diagrams illustrating the distribution of Epi-VE and Ex-E-VE in different regions of the embryo.

Significance levels indicated: *p < 0.05, **p < 0.01.
Conclusions

- Our simple model qualitatively captures a lot of features observed in AVE migration
- Rosettes are not essential for successful AVE migration
- Rosettes are essential for ordered migration observed in vivo

- Trichas, Smith, White, Wilkins, Watanabe, Moore, Joyce, Sugnaseelan, Rodriguez, Kay, Baker, Maini, Srinivas, Multi-cellular rosettes in the mouse visceral endoderm facilitate the ordered migration of anterior visceral endoderm cells, PLoS Biology, 2012, 10(2), e1001256
MODELLING EPITHELIAL SHEETS
Cell-based modelling approaches

- Cell-centred
- Vertex Models (Oster, Honda, Davidson et etc)
- Potts Models (Glazier, Graner, Hogeweg)

• WHICH IS CORRECT??
\[ m_i \frac{d^2 \mathbf{r}_i}{dt^2} = \sum_{j \neq i} F_{ij}^{\text{int}} + F_{ij}^{\text{Visc}}, \]

\[ F_{ij}^{\text{int}} = -k(|\mathbf{r}_i - \mathbf{r}_j| - a) \frac{\mathbf{r}_i - \mathbf{r}_j}{|\mathbf{r}_i - \mathbf{r}_j|}. \]

\[ \frac{d \mathbf{r}_i(t)}{dt} = \alpha[\mathbf{r}_{i-1}(t) - 2\mathbf{r}_i(t) + \mathbf{r}_{i+1}(t)], \quad i = 2, \ldots, N-1, \]

- Need to then take limits (cf polymer chains – Rouse, J. Chem. Phys. 21, 1272, 1953) and then transform to cell density.
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From a discrete to a continuum model of cell dynamics in one dimension

Philip J. Murray,1 Carina M. Edwards,2 Marcus J. Tindall,3 and Philip K. Maini1,4

\[
\frac{\partial q}{\partial \tau} = \frac{\partial}{\partial r} \left( \frac{k}{\eta q^2} \frac{\partial q}{\partial r} \right),
\]

where \(k\) is the spring constant, \(\eta\) is the cell viscosity, \(\tau\) is time, and \(r\) is the spatial coordinate. We define the nonlinear diffusion coefficient \(D(q) = k/\eta q^2\).
Individual cell movement at the **discrete scale** modelled using **nonlinear force laws** can be described by nonlinear diffusion coefficients on the continuum scale.

Therefore, we can **(a)** relate different discrete models of cell behaviour; **(b)** derive discrete, inter-cell force laws from previously posed diffusion coefficients.


- **Comparing vertex-based models** (Fletcher, Osborne, PKM, Gavaghan, Implementing vertex dynamics models of cell populations in biology within a consistent computational framework, Prog. Biophys. Mol. Bio., 113, 299-326, (2013) )
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NEURAL CREST CELL MIGRATION
Migration of Cranial Neural Crest Cells

- Paul Kulesa, Rebecca McLennan, Katherine Prather, Jason Morrison
  [Stowers Institute, Kansas]

- Louise Dyson, Ruth Baker
Fig. 1. NC cell direction is acquired after cells exit the neural tube and cells move faster than non-linear tissue growth. (A) Orientation angle measurements. (B-D) Typical confocal images from 3D confocal stacks of transverse sections through the NC cell migratory stream at 8h, 16h and 24h hours after electroporation. (E) Average nuclear orientation angle with respect to distance along the migratory route from 8h: (n=318 cells, 29 embryos), 16h: (n=346 cells, 15 embryos) and 24h: (n=240 cells, 25 embryos) hour data. (F) Representative images of migratory NC cells. (G) Average cell body orientation angle with respect to distance along the migratory route for 8h: (n=89 cells, 10 embryos), 16h: (n=254 cells, 27 embryos) and 24h: (n=248 cells, 11 embryos) hour data. (H) Gap43-EGRF membrane-labeled NC cells. (I) Average length of the NC cell migratory domain at increasing developmental times. (B) Focal injection (arrowhead) of Dil into the lateral mesoderm prior to NC cell emigration. (K) Twenty-four hours after injection in I. Arrowhead indicates site of injection. (L) Average spread of Dil-labeled tissue. Scale bar: 100 μm. NC, neural crest; NT, neural tube.
Model and manipulation

- Can a chemoattractant (VEGF) produced by the overlying ectoderm be sufficient for robust invasion?
Cell invasion with “leaders” and “followers”
Model Prediction and Validation

- A single chemotactic gradient with a single cell type is not a feasible mechanism. There must be at least 2 cell types – one chemotactic, one not chemotactic.

- By FACS (flow cytometry analysis) and by LCM (laser capture microdissection) show significant differences in expression of 19 out of 84 genes.

- Leading NC cells have upregulated expression of cell guidance and navigation genes (cell guidance factor receptors [EphA4]; integrins [Itgb5]; MMPs [MMP2]). Trailing cells have upregulated expression of cadherins distinct from leading NC cells in particular cadherin 11 upregulated at the front, cadherin 7 upregulated at the back.
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Loss of Trailing Cells

- Disrupts migration (maybe the effects of pushing are lost)
- No change – leaders forge ahead
- Affects movement of leaders through a global change in chemoattractant profile
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Cells move more slowly due to a less directed VEGF gradient.

Figure 3.3: Experimental results for an ablated migratory stream (see Section 3.2.3): (a) Representative images 24 hours into migration; (b) Cell orientation angles profiled at varying distances along the migratory pathway.
2D is NOT 3D!!

Fig. 4. Behavior and molecular profile of trailing NC cells transplanted to the leading position of the migratory mouse. A-C: Experimental schematic. (E) Transversal sections after transplantation. (F) Average number orientation angles with respect to distance along the migratory wave (72 host cells blue), 128 donor cells (pink), 12 embryonic). (F) Schematic representation of cell migration after transplantation. (G) Heat map of qPCR molecular profiles of LCM-isolated NC cells. (H) Model simulation. Leaders (yellow), trails that are following others (white), trails that are not following others (red). (I) Model simulation. Tissue transplant is half the width of the domain. Trailing cells given the ability to become leading cells. Scale bar: 50 μm. NC, neural crest cells; NT, neural tube; h, hours.
Lead Cells Transplanted Proximally

- They maintain their ordering and migrate
- May overtake the host cells as, after all, they are the leaders
Model Prediction – nothing happens
Let $C_i(x,t)$ be the probability density function (pdf) for the $i$th cell center position at time $t$. For $\Delta t \ll 1$,

$$
C_j(x, t + \Delta t) = C_i(x, t) \left\{ 1 - \alpha \Delta t + \frac{\alpha \Delta t}{2} \left[ P^L_i(x, t) + P^R_i(x, t) \right] \right\} + C_i(x - d, t) \frac{\alpha \Delta t}{2} \left[ 1 - P^R_i(x - d, t) \right] + C_i(x + d, t) \frac{\alpha \Delta t}{2} \left[ 1 - P^L_i(x + d, t) \right] + O(\Delta t^2), \quad (1)
$$

$$
P^R_i(x, t) = \sum_{j \neq i} \int_{2R}^{-2R} C_j(x + \bar{x}, t) d\bar{x}; \quad (2)
$$

$$
P^L_i(x, t) = \sum_{j \neq i} \int_{-2R - d}^{2R + d} C_j(x + \bar{x}, t) d\bar{x}. \quad (3)
$$

$$
\frac{\partial C}{\partial t} = \hat{a} \frac{\partial}{\partial x} \left\{ \left[ 1 + 4R \frac{(N - 1)}{N} C \right] \frac{\partial C}{\partial x} \right\} + \frac{(N - 1)}{N} O(R^2), \quad (8)
$$

$$
\frac{\partial C}{\partial t} = \frac{\alpha \sigma^2}{2} \frac{\partial^2 C}{\partial x^2} + \frac{\alpha \sigma^2}{4} \frac{N - 1}{N} \left( 4R - 2\sqrt{2} \frac{\sigma}{\sqrt{\pi}} \right) \frac{\partial}{\partial x} \left( C \frac{\partial C}{\partial x} \right). \quad (11)
$$

Extending to normally distributed distance moved.
References

- McLennan, Dyson, Prather, Morrison, Baker, Maini, Kulesa, Multiscale mechanisms of cell migration during development: theory and experiment, Development, 139, 2935-2944 (2012)

ACID-MEDIATED INVASION HYPOTHESIS
Acid-Mediated Invasion Hypothesis

- A bi-product of the glycolytic pathway is lactic acid – this lowers the extracellular pH so that it favours tumour cell proliferation AND it is toxic to normal cells.

$N_1$ is normal cell density
$N_2$ is tumour cell density
$L$ is lactic acid concentration.

\[
\frac{\partial N_1}{\partial t} = r_1 N_1(1 - N_1/K_1) - d_1 LN_1
\]

\[
\frac{\partial N_2}{\partial t} = r_2 N_2(1 - N_2/K_2) + \frac{\partial}{\partial x} [D_2(1 - N_1/K_1) \frac{\partial N_2}{\partial x}]
\]

\[
\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + \frac{\partial^2 L}{\partial x^2}
\]
Travelling waves of invasion
Experimental results
(Gatenby et al, Cancer Research, 66, 5216-5223, 2006)
Therapeutics

- Add bicarbonate to neutralise the acid
Metastatic Lesions (Robey et al, Cancer Res, 69(6), 2260-2268)
For a more realistic model:

- In the asymptotic limit (small parameter is tumour cell diffusion divided by lactic acid diffusion) this is Fisher’s eqn.
- Using asymptotics (some subtilities arise) -- determine parameter space in which gaps occur.
- Is it consistent for a continuum model to predict a gap of a few cells?

McGillen, Martin, Gaffney, PKM (J. Math. Biol. online)
Travelling waves of invasion
FROM MOUSE TO HUMAN
Equivalent dose less effective in humans (Du Bois height-weight formula)
Results

- Previously unseen potentially dangerous elevation in blood pH resulting from bicarbonate therapy in mice – confirmed by our in vivo expts
- Limited efficacy of bicarbonate in humans

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Martin, Robey, Gaffney, Gillies, Gatenby, PKM, Predicting the safety and efficacy of buffer therapy to raise tumour pHe: An intergrative modelling study, Brit. J. Cancer, 106, 1280-1287 (2012)
Buffer therapy most effective

(a) in elderly patients with renal impairments

(b) in combination with proton production inhibitors (such as DCA), renal glomular filtration rate inhibitors (eg non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors) or

(c) with an alternative buffer reagent possessing an optimal pK of 7.1 - 7.2 (pK = -log(dissociation constant)) – does not elevate (to dangerous levels) blood pH in the same way that bicarbonate can!!
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(a) Used a vertex-based model for AVE migration on the mouse ectoderm to investigate the role of rosettes

(b) Used a hybrid model to study neural crest cell invasion

(c) Used a PDE model to study tumour cell invasion

(d) Showed how many of these approaches lead to novel nonlinear diffusion type systems
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