A comparison of stochastic and analytical models for cell migration

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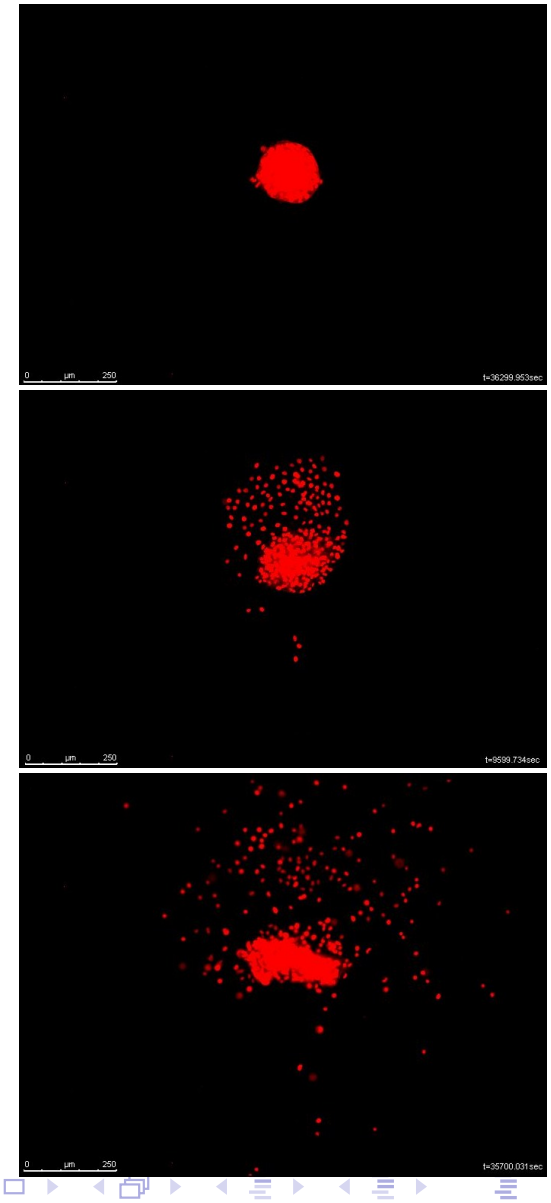
Introduction

Introduction

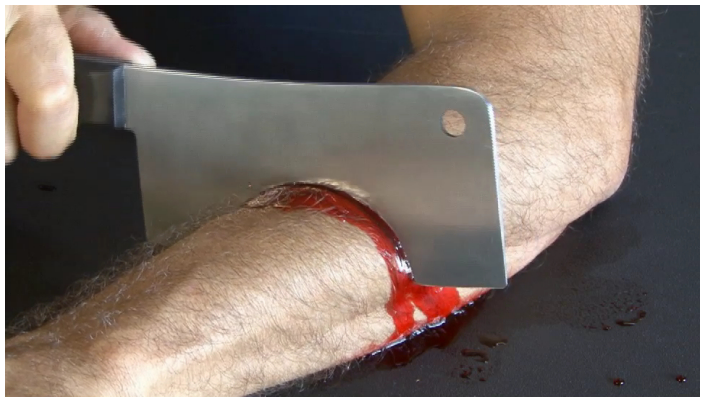
Outline

- What is cell migration?
- Why do we want to model it?
- Application areas.
- Modelling approaches for cell migration: stochastic vs continuum.
- Equivalence between the two approaches on the non-growing domain: theory and simulation.
- Equivalence on the growing domain: simulation and theory.
- Special types of domain growth.
- Where next?



What is cell migration

- The directed movement of cells.
- A central process in the development and maintenance of multicellular organisms.
- Applications in many areas of development from conception to death:
  - Embryogenesis
  - Nervous system formation and repair.
  - Vasculature formation and repair.
  - Limb formation.
  - Repair (e.g wound healing).
  - Immune responses.



Wound healing, immune responses and limb (de)formation!

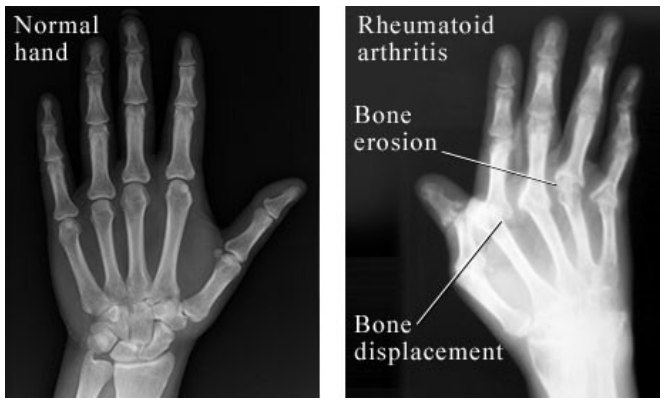
What happens when cell migration goes wrong?

Diseases caused by erroneous cell migration:

- ⋆ Jarcho-Levin syndrome.
- ⋆ Congenital scoliosis.
- ⋆ Tumour invasion and metastasis.
- ⋆ **Rheumatoid arthritis.**

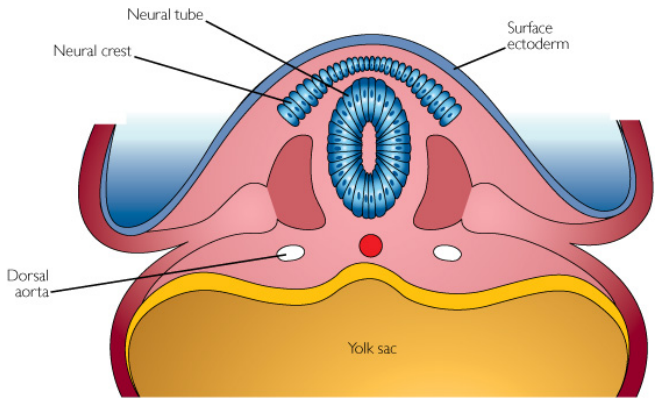
Rheumatoid arthritis:

- ⋆ Inflammatory cells migrate to joints.
- ⋆ Joint tissue constantly destroyed.

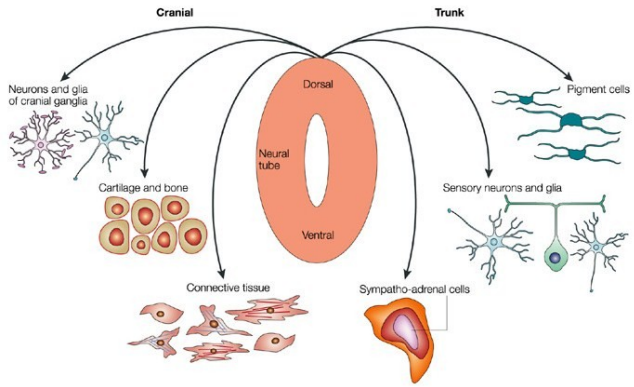


Neural crest cell migration

- Neural crest located between neural tube and epidermis.
- Neural crest cells migrate quickly to different locations giving rise to various adult tissues (nerve cells, chromaffin cells, melanocytes, Schwann cells).



The neural crest in an embryo cross-section.



Schematic of the various specialisations of neural crest cells.

- Migrational pathway determines specialisation.
- Contact inhibition of locomotion has been seen to be crucial to migration.

Neural crest cell migration: Some example movies

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Disperal of an initial cluster of neural crest cells expressing cytoplasmic GFP.

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Disperal of the same cluster of neural crest cells expressing nuclear RFP.

Modelling Approaches

Modelling Approaches

Two Contrasting Modelling Approaches

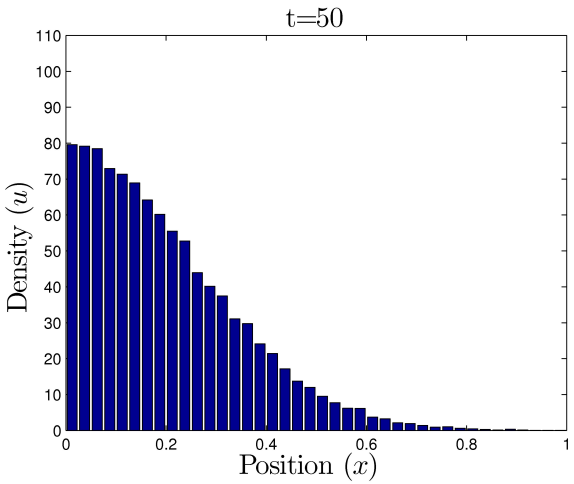
Given initial cell density across the domain and boundary conditions how do we find cell density at later times?

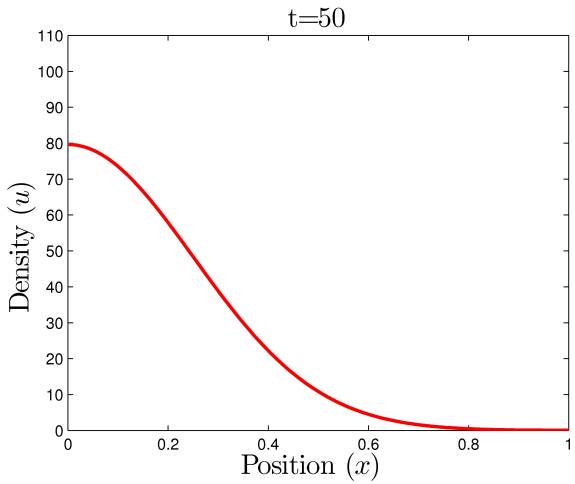
Stochastic/Discrete Approach

- ⋆ Gillespie Algorithm
- ⋆ $\alpha_0 = \sum_{i=1}^{k} \alpha_i^+ + \sum_{i=1}^{k} \alpha_i^-$
- ⋆ $\tau = \frac{1}{\alpha_0} \ln\left(\frac{1}{rand_1}\right)$

Deterministic/Continuum Approach

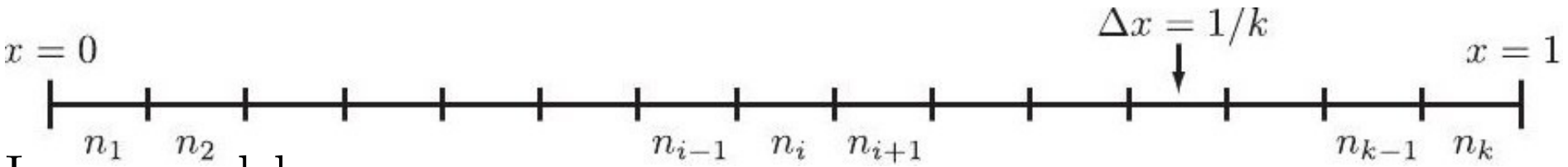
- ⋆ Partial Differential Equations
- ⋆ $\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2},$
- ⋆ $(x,t) \in [0,1] \times [0,\infty)$





Aside - What is a Gillespie Algorithm? - Background

- ⋆ Assume $k \geq 1$ (chemical) species $\{N_1 \dots N_k\}$.
- ⋆ Classify a set of $M \geq 1$ reactions (chemical or otherwise) $\{R_1 \dots R_M\}$.
- ⋆ Associate with each reaction, R_j, a 'propensity function', $\alpha_j(\boldsymbol{N})$, which describes the probability one R_j reaction will happen in the next small time interval dt.



In our model:

- ⋆ k is the number of boxes we split the domain into.
- ⋆ $\{N_1 \dots N_k\}$ represents the number of cells in each box.
- ⋆ $\{R_1 \dots R_M\}$ are the reactions of a cell moving left or right out of the box.
- ⋆ Hence $M = 2k$.
- ⋆ The propensity of each reaction is proportional to the number of cells in the corresponding box.

Aside - What is a Gillespie Algorithm? - The Algorithm

The Algorithm

1. Initialize (i.e., set initial numbers of species, set t=0).
2. Calculate the propensity functions, α_j, for $j = 1 \dots M$.
3. Generate a uniform random number, r_1, and choose a time τ for the next reaction (using formula $\tau = \frac{1}{\sum_{j=1}^{N} \alpha_j} \log(\frac{1}{r_1})$).
4. Generate a second uniform random number, r_2, and choose which of the reactions will happen (with probability proportional to their propensity functions). i.e. find i s.t. $\sum_{j=1}^{i-1} \alpha_j \leq r_2 \leq \sum_{j=1}^{i} \alpha_j$.
5. Change the number of species to reflect execution of the chosen reaction.
6. update $t \leftarrow t + \tau$.
7. Go to step 2.

Model Comparison

Advantages and Disadvantages

Stochastic/Discrete Approach

- ⋆ Statistically accurate with low numbers of cells.
- ⋆ Allows for the incorporation of noise.

BUT

- ⋆ Slow.
- ⋆ Different results each time.

Deterministic/Continuum Approach

- ⋆ Fast.
- ⋆ Consistent results.
- ⋆ Good results with large cell numbers.

BUT

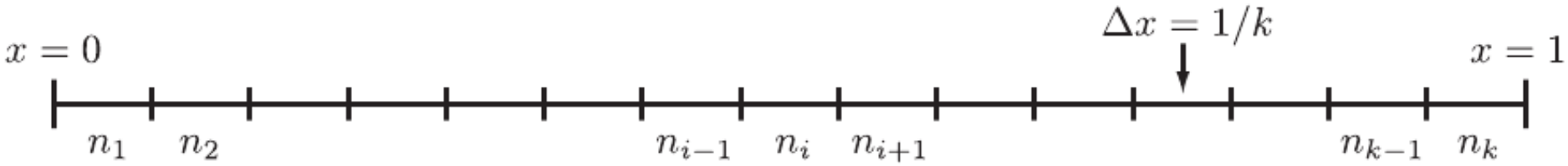
- ⋆ Statistically innaccurate for low cell numbers.
- ⋆ Unrealistic as no noise effects.




Non-growing domain - Stochastic Individual Model... (1)

$\boldsymbol{N}(t) = [N_1(t), N_2(t) \dots N_i(t) \dots N_k(t)]$.

$P(\boldsymbol{n}, t) = P(\boldsymbol{N} = \boldsymbol{n}, t)$.



Define the operators $J_i^+ : \mathbb{R}^k \to \mathbb{R}^k$, for $i = 1, 2, \dots, k-1$ and $J_i^- : \mathbb{R}^k \to \mathbb{R}^k$, for $i = 2, \dots, k$, by

$$J_i^+ : [n_1, \dots, n_i, \dots, n_k] \to [n_1, \dots, n_{i-2}, n_{i-1}, n_i + 1, n_{i+1} - 1, n_{i+2} \dots,$$
$$J_i^- : [n_1, \dots, n_i, \dots, n_k] \to [n_1, \dots, n_{i-2}, n_{i-1} - 1, n_i + 1, n_{i+1}, n_{i+2} \dots,$$

J_i^+ moves a cell from interval $i+1$ to interval i and J_i^- moves a cell from interval $i-1$ to interval i.

Non-growing domain - Stochastic Individual Model... (2)

Master Equation

$$
\begin{aligned}
P(\boldsymbol{n}, t+\delta t) &= \sum_{i=1}^{k-1} T_i^+(n_i+1)P(J_i^+\boldsymbol{n}, t)\delta t \\
&+ \sum_{i=2}^{k} T_i^-(n_i+1)P(J_i^-\boldsymbol{n}, t)\delta t \\
&+ P(\boldsymbol{n}, t)\left(1 - \sum_{i=1}^{k-1} T_i^+ n_i \delta t - \sum_{i=2}^{k} T_i^- n_i \delta t\right).
\end{aligned}
$$

... To continuous population model

Define $\langle \boldsymbol{n} \rangle = [\langle n_1 \rangle, \ldots, \langle n_k \rangle] = \sum_{\boldsymbol{n}} \boldsymbol{n} P(\boldsymbol{n}, t)$ to be the vector of stochastic means. Then we can show

$$\begin{aligned}
\frac{\partial \langle n_1 \rangle}{\partial t} &= d\langle n_2 \rangle - d\langle n_1 \rangle, \\
\frac{\partial \langle n_i \rangle}{\partial t} &= d\langle n_{i-1} \rangle - 2d\langle n_i \rangle + d\langle n_{i+1} \rangle, \quad i = 2 \ldots k-1 \\
\frac{\partial \langle n_k \rangle}{\partial t} &= d\langle n_{k-1} \rangle - d\langle n_k \rangle.
\end{aligned}$$

This is clearly a discretisation of $\frac{\partial \langle \boldsymbol{n} \rangle}{\partial t} = D \frac{\partial^2 \langle \boldsymbol{n} \rangle}{\partial x^2}, \quad D = d(\Delta x)^2$

A numerical comparison of the two models of diffusion

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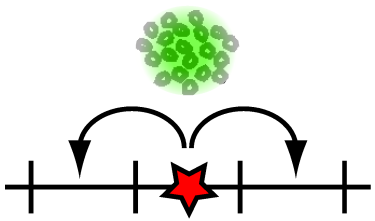
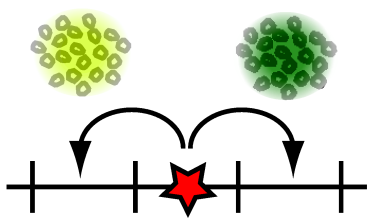
Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

Different sorts of signal sensing

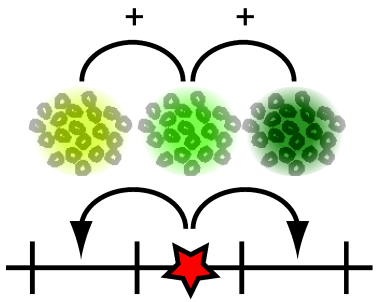
- ⋆ Introduce a signal molecule concentration across the domain (i.e. s(x)=exp(-x).
- ⋆ Local - constrain cells to sense the strength of the signalling chemical only at their current site, $T^- = T^+ = f(s_i)$.
- ⋆ Non-local - cells sense the strength of the signalling profile over a wider region, but must disregard information at the current site, i, $T^\pm = f(s_{i\pm1})$.
- ⋆ Average - cells use information from the current position and adjacent positions, $T^\pm = f^l(s_i) + f^n(s_{i\pm1})$.



Local sensing



Non-local sensing



Average sensing

A numerical comparison of the two models of local signal sensing

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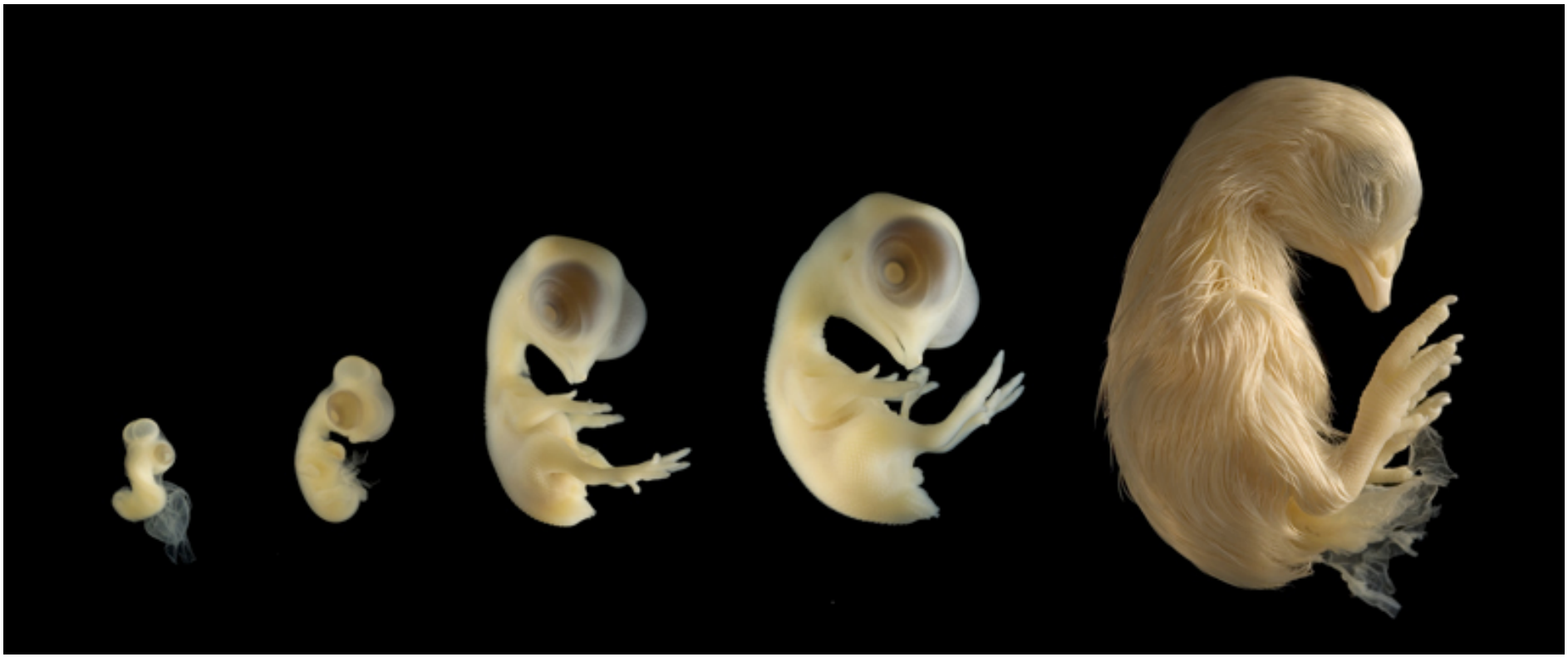
Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

Domain Growth

Incorporating domain growth

In reality, during embryogenesis cell migration occurs on a growing domain.



We need to incorporate domain growth into out model of cell migration in both the analytical and stochastic models.

Analytical derivation of domain growth PDE

How to solve a PDE on a growing domain

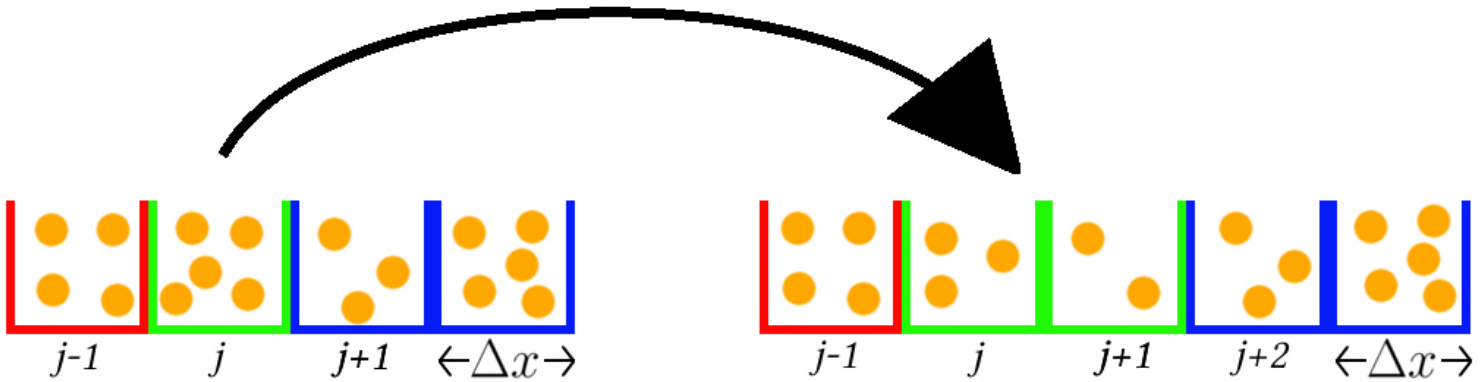
- Apply Reynolds transport theorem:
  $\frac{\partial u}{\partial t} + \nabla \cdot (\boldsymbol{v}u) = D\nabla^2 u + R(u)$, $\boldsymbol{x} \in \Omega(t)$, $\quad t \in [0, \infty)$, where $\Omega(t)$ is the now time-dependent growing domain.

- In one dimension determine the flow, v:
  $v = \frac{dx}{dt} = S(u)x$,
  where S is the (possibly density dependent) strain.

- Convert to Lagrangian (normalised) coordinates to solve the PDE.

- Transform the solution back to the growing domain.

Stochastic growth through interval splitting



Stochastic interval splitting mechanism

- j^{th} interval (green) splits.
- Cells are redistributed into the two new intervals using a symmetric probability distribution, π.
- New intervals are renumbered j and $j+1$.
- Subsequent intervals have their index increased by 1.

Domain growth master equation

'Inverse growth' operators G_i: $\mathbb{R}^{k(t)} \to \mathbb{R}^{k(t)-1}$

$$G_i : [n_1, \ldots, n_{i-1}, n_i, n_{i+1}, \ldots, n_k] \to [n_1, \ldots, n_{i-1}, n_i + n_{i+1}, \ldots, n_k].$$

G_i concatenates intervals i and $i+1$ adding their cell numbers together. r is the constant stochastic rate of box splitting.

Master Equation

$$\begin{aligned} P^{k(t)}(\boldsymbol{n}, t+\delta t) &= r \sum_{i=1}^{k(t)-1} \pi(n_i, n_{i+1} | n_i + n_{i+1}) \times P^{k(t)-1}(G_i \boldsymbol{n}, t)\delta t \\ &+ P^{k(t)}(\boldsymbol{n}, t) - r \sum_{i=1}^{k(t)} P^{k(t)}(\boldsymbol{n}, t)\delta t. \end{aligned}$$

A numerical comparison of the two models of average sensing on a domain with exponential domain growth

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Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

Other types of domain growth

Other more complicated types of growth

- ⋆ Density-dependent domain growth:
  - ⋆ Linear dependence
    $S(u) = r \times u.$
  - ⋆ Quadratic dependence
    $S(u) = r \times u^2$
  - ⋆ Inverse dependence
    $S(u) = \frac{r}{r+u}$
  - ⋆ Many more to explore
    $S(u) =$???
- ⋆ Linear domain growth
- ⋆ Logistic domain growth

A numerical comparison of the two models of non-local sensing on a domain with linearly density dependent domain growth

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Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

A numerical comparison of the two models of diffusion on a domain with logisitc domain growth

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Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

Conclusions

Conclusions

Summary

- ⋆ Introduction to cell migration.
- ⋆ Comparison of stochastic and continuum models for cell migration.
- ⋆ Equivalence of stochastic and continuum models on a non-growing domain.
- ⋆ Different types of signal sensing.
- ⋆ Equivalence of the two model types on growing domians.
- ⋆ Different types domain growth.
- ⋆ Lots of simulations.

A numerical comparison of the two models of diffusion on a domain with quadratically density dependent domain growth

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Histogram represents the average over 40 stochastic simulations and the red curve represnts the solution of the corresponding PDE.

Further work

Where Next

- ⋆ Sort out quadratic density dependent domain growth.
- ⋆ Acceleration of stochastic algorithms.
- ⋆ Different boundary conditions i.e. non-zero flux.
- ⋆ Cell death/birth*.
- ⋆ Alternate signalling gradients*.
- ⋆ Density dependent cell movement*.
- ⋆ Extension to 2 and 3 dimensions.
- ⋆ Model validation with experimental evidence e.g. Neural crest cell migration.

*These extensions have been implemented in R. E. Baker, C. A. Yates, and R. Erban. **From microscopic to macroscopic descriptions of cell migration on growing domains**.*Bull Math Biol*, Accepted.

Acknowledgements

- ⋆ Dr Ruth Baker
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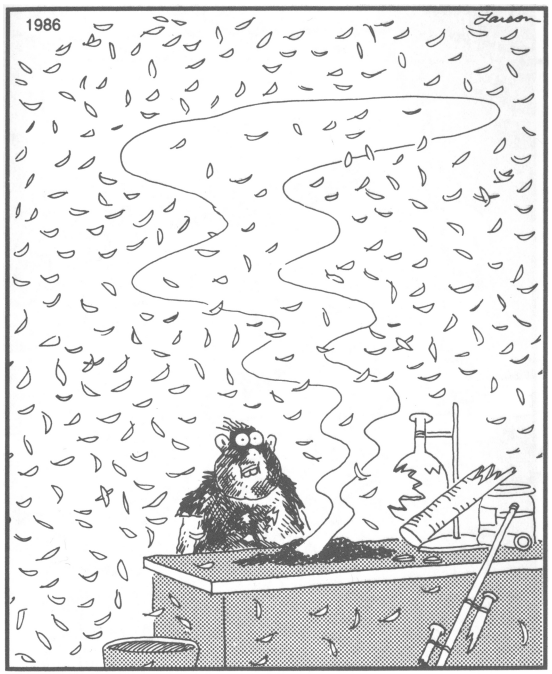
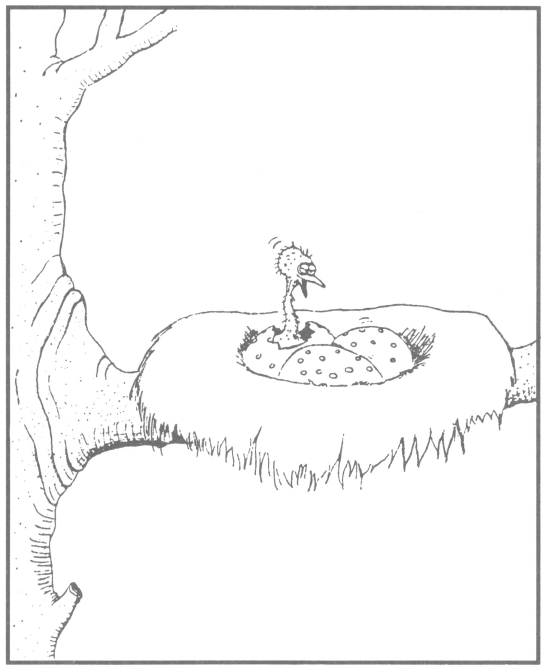


God as a kid tries to make a chicken in his room.



"Last one out's a rotten egg!"

- ⋆ And Gary Larson for these.