Tummy Troubles

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Motivation

Schematic–neural crest cell invasion

Abnormal cell invasion can result in Hirschsprung’s Disease

Oro-anal NC migration

- vagal level
- neural tube
- foregut
- midgut
- hindgut
Mathematical models

- Cell invasion = Motility + Proliferation + Gut growth
- Continuum invasion model–Cell population properties

\[
\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} + C(1 - C) - \frac{\partial (vC)}{\partial x} \tag{1}
\]

- Discrete cellular automata algorithm–Individual cell properties

<table>
<thead>
<tr>
<th>CA RULES</th>
<th>MOTILITY RULE</th>
<th>PROLIFERATION RULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current configuration</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Potential new configuration</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
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</tbody>
</table>

Neural crest cell rules, Simpson et al. 2007
Gut from E11.5 *Ednrb-kik* mouse photoconverted and cultured for 24 h

T = 0 + 24 h

T. Manabe, H. Young, H. Enomoto
Non-growing tissue, \( \nu = 0 \)

- Non-growing gut tissue cells (yellow), NCCs (red, blue, green)
- Simulation, single cells swamped by sub-population
- Simulation, single cells do okay in sub-population
- Simulation, single cell swamps the sub-population
Growing tissue, $v \neq 0$

Image of an E6 quail embryo illustrating the landmarks along the gut
Consider a single growing region \( 0 < x < L(t) \)

Can be shown that rate of elongation is

\[
\frac{dL}{dt} = \int_0^{L(t)} \frac{\partial v}{\partial x} dx
\]  

(2)

Growth rate

\[
\frac{\partial v}{\partial x} = \alpha(t) = \alpha
\]  

(3)

Solving eqns. (2)-(3) with \( L(0) = L_0 \) gives

\[
L(t) = L_0 e^{\alpha t}
\]  

(4)

Also time evolution of the path of a general point \( x_0 \) is

\[
x(t) = x_0 e^{\alpha t}
\]  

(5)
In a single region $N \approx L(t)(e^\alpha - 1)$ gut cells (yellow) are inserted randomly on each row of lattice.
Nonuniform versus uniform growth model comparison with observational data

Observational data (triangles), Nonuniform CA model (circles), Nonuniform continuum model (solid), Uniform continuum model (broken)

- Nonuniform model necessary to determine position of umbilicus and cecum
CA statistical analysis

Mean

$$\bar{x}(x_0, t) = \frac{1}{MY} \sum_{j=1}^{M} \sum_{y_0=1}^{Y} x_j(x_0, y_0, t)$$

Standard deviation

$$s(x_0, t) = \sqrt{\frac{1}{MY - 1} \sum_{j=1}^{M} \sum_{y_0=1}^{Y} (x_j(x_0, y_0, t) - \bar{x})^2}$$

Skewness

$$k(x_0, t) = \frac{1}{s(x_0, t)^3 MY} \sum_{j=1}^{M} \sum_{y_0=1}^{Y} (x_j(x_0, y_0, t) - \bar{x})^3$$

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Consider initially a total number of $L_0$ cells in a single row of the CA lattice. We mark one of the cells and note it is initial position in the row by $x_0$. We then randomly insert $N$ new cells one at a time into the row.

What is the probability that $I$ insertions are made to the left of the marked cell $x_0$?
Sketch of problem

Initial position of marked cell

\[ p = \frac{x}{L} \quad q = \frac{L-x}{L} \]

Insertion not successful

\[ p = \frac{x}{L+1} \quad q = \frac{L-x+1}{L+1} \]

Insertion successful

\[ p = \frac{x+1}{L+1} \quad q = \frac{L-x}{L+1} \]
Probability tree after two insertions

\[ p = \frac{x}{L} \]
\[ q = \frac{L-x}{L} \]
\[ p = \frac{x}{L+1} \]
\[ q = \frac{L-x+1}{L+1} \]
\[ q = \frac{L-x}{L+1} \]
\[ p = \frac{x+1}{L+1} \]

\[ x(x+1) \]
\[ L(L+1) \]

\[ pp = \frac{x(x+1)}{L(L+1)} \]
\[ pq = \frac{x(L-x)}{L(L+1)} \]
\[ qp = \frac{(L-x)x}{L(L+1)} \]
\[ qq = \frac{(L-x)(L-x+1)}{L(L+1)} \]

\[ P(I=2,N=2) = pp \]
\[ P(I=1,N=2) = pq + qp = 2pq \]
\[ P(I=0,N=2) = qq \]
Spotted the pattern after four insertions

\[ P(I, N) = \binom{N}{I} \frac{x(x+r)\cdots(x+(I-1)r)(L-x)(L-x+r)\cdots(L-x+(N-I-1)r)}{L(L+r)\cdots(L+(I-1)r)(L+Ir)(L+(I+1)r)\cdots(L+(N-1)r)} \]

where \( \binom{N}{I} = \frac{N!}{I!(N-I)!} \) and \( r = 1 \) in our example

Let \( p_i = \frac{x + (i - 1)r}{L + (i - 1)r} \) and \( q_i = \frac{L - x + (i - 1)r}{L + (I + i - 1)r} \)

\[ P(I, N) = \binom{N}{I} \prod_{i=1}^{I} p_i \prod_{i=1}^{N-I} q_i \]

Mean \( \mu = \frac{Nx}{L} = Np_1 \) \hspace{1cm} variance \( \sigma^2 = \frac{(L+Nr)Np_1q_1}{(L+r)} \) and

skewness \( k = \frac{A(N,L,r)(1-2p_1)}{\sigma} \) \hspace{1cm} where \( A(N, L, 0) = 1 \)
Pólya-Eggenberger distribution, 1923

- Random drawings of coloured balls from an urn
- Initially $x$ white balls and $L - x$ black balls
- One ball is drawn at random, and then replaced along with $r$ balls of identical colour
- Repeat $N$ times, and $I$ represents the total number of times a white ball is drawn, then the distribution of $I$ is the Pólya distribution, parameters $N, x, L - x$ and $r$
Scaled standard deviation and skewness

Average position

\[ \bar{x} = x_0 + \mu = x_0 + \frac{N x_0}{L_0} = x_0 e^{\alpha t} \]
CA rule changes and $r$

- Values of $r > 1$ correspond to multiple cells being inserted into a row.
- If only the initial cells allowed to proliferate, then this corresponds to $r = 0$, giving the Binomial distribution.
- Change proliferation mechanism to only allow the mitotic division of cells that are generated at previous time steps, then CA statistics match those of the Pólya distribution for $0 < r < 1$.
- The case $r < 0$, provided $L_0 + r(N - 1) > 0$, gives a valid Pólya distribution that corresponds to cell death.
Biaxial (2D) growth

Logistic in $x$ and linear in $y$ direction
NCC invasion on growing and non-growing gut tissue

More NCCs on growing tissue but invasion is more advanced on non-growing tissue

Gut tissue (yellow), NCCs (blue)
NCC invasion on growing and non-growing gut tissue

Gut tissue (yellow), NCCs (blue)
Simulations of NCC invasion on growing tissue

- Growing gut tissue cells (yellow)
- NCCs (black, blue, green, red)
- Simulation of unsuccessful invasion
- Simulation of successful invasion
- Simulation of tissue growing in width as well as length
Back to equation (1)–excluding NCC proliferation, $\lambda = 0$

On $0 < x(t) < L(t)$

$$\frac{\partial C}{\partial t} = D_C \frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 (D_L C)}{\partial x^2} - \frac{\partial (vC)}{\partial x}, \quad (6)$$

From Pólya distribution

$$v(x, t) = \frac{dL}{dt} \frac{x}{L}, \quad (7)$$

and

$$D_L(x, t) = \frac{dL}{dt} \frac{L}{2(L+1)} \frac{x}{L} \left(1 - \frac{x}{L}\right). \quad (8)$$

and Simpson et al. 2007

$$D_C = \frac{P_m}{4} \quad (9)$$
Diffusion of NCCs on growing tissue

Gut (yellow), NCCs (green), $\alpha = 0.69$, $P_m = 1$

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NCC proliferation and multi-species

\[
\frac{\partial R}{\partial t} = D_R \frac{\partial}{\partial x} \left[ (1 - R - G) \frac{\partial R}{\partial x} \right] + D_R \frac{\partial}{\partial x} \left[ R \frac{\partial (R + G)}{\partial x} \right] \\
+ \lambda_R R(1 - R - G) + \frac{\partial^2 (D_L R)}{\partial x^2} - \frac{\partial (vR)}{\partial x}, \quad (10)
\]

\[
\frac{\partial G}{\partial t} = D_G \frac{\partial}{\partial x} \left[ (1 - R - G) \frac{\partial G}{\partial x} \right] + D_G \frac{\partial}{\partial x} \left[ G \frac{\partial (R + G)}{\partial x} \right] \\
+ \lambda_G G(1 - G - R) + \frac{\partial^2 (D_L G)}{\partial x^2} - \frac{\partial (vG)}{\partial x}. \quad (11)
\]

- With \( D_R = \frac{P^R_m}{4} \) and \( D_G = \frac{P^G_m}{4} \)
- With \( \lambda_R = P^R_p \) and \( \lambda_G = P^G_p \)
- If \( \frac{\lambda_R}{D_R} \ll 1 \) and \( \frac{\lambda_G}{D_G} \ll 1 \) then agreement good
Multi-species

\[ D_R = 0.125, \quad D_G = 0.25. \quad (b) \quad \lambda_R = \lambda_G = 0.01 \quad (c) \quad \lambda_R = \lambda_G = 0.1 \]
Conclusion

- Mathematical models parameterised by experimental data
- Averaging individual cell properties (CA) – gives cell population properties (Continnum)
- Other geometries – CA rules, time dependent
- Include other mechanisms – differentiation, chemotaxis

‘A great discovery solves a great problem but there is a grain of discovery in the solution of any problem. Your problem maybe modest; but if it challenges your curiosity and brings into play your inventive faculties, and if you solve it by you own means, you may experience the tension and enjoy the triumph of discovery.’ (Polya, preface in Stewart)