Morphogenesis: pattern formation, growth, and cell movement
Morphogenesis: pattern formation, growth, and cell movement

“what about the horse part”

LAST TIME

Clasical models of (pre)pattern formation

*Themes:* Hypothesis vs Search image; supervised modeling; evolutionary drift in mechanism/trajectory but conserved/converged outcome and at multiple levels

TODAY

Include tissue growth, cell movement/ Tissue (de)formation

- Limbbud morphogenesis by differential cell growth rate possible/compatible with measurements?
- consequences of segmentations -Elongation by segmentation
- single cell movement models
  - detailed model of keratocytes
  - mini model: keratocytes and amoeboids
- Multicellularity “by coming together”
  “from single cells to multicellular organism” through signaling, chemotaxis and differential adhesion
  *(from data intensive to behavior intensive models)*
Making and fitting shape measuring and modeling shape
limb bud development

Question: can limb bud MORPHOGENESIS be explained by gradient based differential cell proliferation?

The Role of Spatially Controlled Cell Proliferation in Limb Bud Morphogenesis Bernd Boehm1, Henrik Westerberg1, Gaja Lesnicar-Pucko1, Sahdia Raja1,2, Michael Rautschka1, James Cotterell1,2, Jim Swoger1, James Sharpe1,3* PLOS BIOL 2010
Measurement

Of 3D shape at 2 developmental stages

Of mitotic frequencies in different regions of the bud

colour cell cycle specific proteins
calculated cycle frequencies

DO these 2 measurement FIT?

(Is differential proliferation sufficient to explain growth/morphogenesis?)

NO...
Finite element simulation of measured growth rates
Failure due to mistakes in growthrates measurements? Do growth rates exist such that shape emerges?
Yes differential growth CAN generate bud morphogenesis
BUT only for VERY different proliferation patterns (+ shrinkage)
conclusions

- Nice (because negative result!)
- Their hypothesis: directed cell movement plays a role

Use measured growth + fitted outward force (representing cell movement)
convergent extension, morphogenetic cell movement common to insects, fish, frogs, (mammals)

Elongation by intercalation but by different mechanisms, eg

- (Drosophila intercalation by contraction of those parts of the membrane that have a dorsal-ventral orientation)
- Xenopus: dorsal mesodermal cells polarize and change their adhesive properties; cells then crawl between each other in a zipper-like process (intercalation) *axial adhesion*
- Zebrafish: directed migration to the dorsal axis and intercalation follow a gradient in cadherin activity towards the central axis *graded adhesion*
- Xenopus and Drosophila: anterior-posterior patterning / segmentation crucial for convergent extension

*how is tissue patterning maintained during extensive cell movement?*
adhesion based models; superimposed axis

Segment-Specific Adhesion as a Driver of Convergent Extension Renske M. A. Vroomans et al 2015
Convergent extension (CE) (often) after segmentation; How is segmentation conserved? Segment specific adhesion (here minimal)
Segmentation by itself sufficient for CE (AND needed for CE (xenopus, drosophila))

\[ \gamma_{\text{cell, medium}} \]

\[ \gamma_{\text{rod, green}} \]

2

6

10

14
more “realistic”: extension to posterior only
same results
Xenopus after mixing of cells: sorting AND CE

For sorting strong persistence is needed;
Weak persistence is sufficient in sorted tissue (WT)
chemotaxis: modeling internal dynamics at different levels of detail

In CPM model chemotaxis can be implemented as ‘extend phyllopodia preferentially in direction of gradient’

How does the cell do this?

Interaction of small g proteins and actin network

Well studied in Keratocytes

importance of mutual feedback between cell shape and gene regulation

importance of biochemical detail ONLY apparent through this interaction
relevant small g protein interactions

Small G-protein cross-talk

\[ \frac{\partial G}{\partial t} = k^{+}_G \text{GEF}_G G_t - k^{-}_G \text{GAP}_G G + D_m \Delta G \quad \text{with } G = C, R, \rho, \]

bistability in space due to fast diffusion inactive form
actin dynamics and cell wall dynamics

Possible orientations:
\[ \Delta \Theta = \frac{2\pi}{6} \]

Densities of actin at the angle \( \Theta_{m=1} \) at site \((x,y)\):

Concentrations:
- \( R(x,y) \)
- \( C(x,y) \)
- \( G(x,y) \)
- \( F(x,y) \)
- \( A(x,y) \)

Direction of motion

Extension

Retraction

Lateral view

Top view
Table 1  Parameter estimates relevant to the small G-proteins and their interactions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Values</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C^*$</td>
<td>typical level of active Cdc42</td>
<td>1</td>
<td>μM</td>
</tr>
<tr>
<td>$R^*$</td>
<td>typical level of active Rac</td>
<td>3</td>
<td>μM</td>
</tr>
<tr>
<td>$\rho^*$</td>
<td>typical level of active Rho</td>
<td>1.25</td>
<td>μM</td>
</tr>
<tr>
<td>$C_{tot}$</td>
<td>total level of Cdc42</td>
<td>2.4</td>
<td>μM</td>
</tr>
<tr>
<td>$R_{tot}$</td>
<td>total level of Rac</td>
<td>7.5</td>
<td>μM</td>
</tr>
<tr>
<td>$\rho_{tot}$</td>
<td>total level of Rho</td>
<td>3.1</td>
<td>μM</td>
</tr>
<tr>
<td>$I_C$</td>
<td>Cdc42 activation input rate</td>
<td>3.4</td>
<td>μM s$^{-1}$</td>
</tr>
<tr>
<td>$I_R$</td>
<td>Rac activation input rate</td>
<td>0.5</td>
<td>μM s$^{-1}$</td>
</tr>
<tr>
<td>$I_\rho$</td>
<td>Rho activation input rate</td>
<td>3.3</td>
<td>μM s$^{-1}$</td>
</tr>
<tr>
<td>$\beta_\rho$</td>
<td>Rho level for half-max inhibition of Cdc42</td>
<td>1.25</td>
<td>μM</td>
</tr>
<tr>
<td>$\beta_C$</td>
<td>Cdc42 level for half-max inhibition of Rho</td>
<td>1</td>
<td>μM</td>
</tr>
<tr>
<td>$n$</td>
<td>Hill coefficient of Cdc42-Rho mutual inhibition response</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>$\alpha_C$</td>
<td>Cdc42-dependent Rac activation rate</td>
<td>4.5</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$\alpha_R$</td>
<td>Rac-dependent Rho activation rate</td>
<td>0.3</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$d_C$, $d_R$, $d_\rho$</td>
<td>decay rates of activated small G-proteins</td>
<td>1</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$D_m$</td>
<td>diffusion coefficient of active small G-proteins</td>
<td>$1 \times 10^5$</td>
<td>nm$^2$ s$^{-1}$</td>
</tr>
<tr>
<td>$D_{mc}$</td>
<td>diffusion coefficient of inactive small G-proteins</td>
<td>$1 \times 10^7$</td>
<td>nm$^2$ s$^{-1}$</td>
</tr>
<tr>
<td>Parameter</td>
<td>Meaning</td>
<td>Values</td>
<td>Units</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>$A^*$</td>
<td>typical Arp2/3 concentration</td>
<td>2</td>
<td>μM</td>
</tr>
<tr>
<td>$F^*$</td>
<td>typical filament density</td>
<td>0.278</td>
<td>nm$^{-1}$</td>
</tr>
<tr>
<td>$B^*$</td>
<td>typical barbed end density</td>
<td>$1.7 \times 10^{-5}$</td>
<td>nm$^{-2}$</td>
</tr>
<tr>
<td>$P^*$</td>
<td>typical edge density of barbed ends</td>
<td>0.05</td>
<td>nm$^{-1}$</td>
</tr>
<tr>
<td>$\mu_C$, $\mu_R$</td>
<td>Cdc42 and Rac-dependent Arp2/3 activation</td>
<td>0.16</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$d_A$</td>
<td>activated Arp2/3 decay rate</td>
<td>0.1</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$D_A$</td>
<td>diffusion coefficient of Arp2/3</td>
<td>$1 \times 10^6$</td>
<td>nm$^2$ s$^{-1}$</td>
</tr>
<tr>
<td>$\eta_0$</td>
<td>Arp2/3 nucleation rate</td>
<td>60</td>
<td>μM nm s$^{-1}$</td>
</tr>
<tr>
<td>$K_m$</td>
<td>saturation constant for Arp2/3 nucleation</td>
<td>2</td>
<td>μM</td>
</tr>
<tr>
<td>$l$</td>
<td>scale factor converting units of $F$ to concentration</td>
<td>255</td>
<td>μM nm</td>
</tr>
<tr>
<td>$k$</td>
<td>scale factor converting concentration to units of $B$</td>
<td>$1.06 \times 10^{-4}$</td>
<td>nm$^{-2}$ μM</td>
</tr>
<tr>
<td>$v_0$</td>
<td>actin filament growth rate (free polymerization)</td>
<td>500</td>
<td>nm s$^{-1}$</td>
</tr>
<tr>
<td>$d_F$</td>
<td>actin filament turnover rate</td>
<td>0.03</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$\kappa_{\text{max}}$</td>
<td>barbed end capping rate</td>
<td>2.8</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$\kappa_{\text{Rac}}$</td>
<td>max reduction of capping by Rac</td>
<td>2.1</td>
<td>s$^{-1}$</td>
</tr>
<tr>
<td>$K_R$</td>
<td>Rac level for half-max reduction of capping</td>
<td>3</td>
<td>μM</td>
</tr>
<tr>
<td>$r$</td>
<td>reduction of capping close to the edge</td>
<td>0.14</td>
<td>-</td>
</tr>
</tbody>
</table>
Shapes itself into a walking keratocyte and Walks! (and at the correct speed)
Can reorient itself:
polarity and/vs rotation and/vs shape
feedback internal dynamics and cell shape faster internal polarity change because of cell shape changes (which are caused by internal polarity change)
HOWEVER, internal dynamics more complex WHY?
Feedback through PIP network smoothes out gradient
Feedback through PIP network causes faster adaptation

( HOWEVER: in round cell SLOWER reorientation to external signal!)
Feedback through PIP network enable resolving conflicting signals

polarization through noise instead of gradient
Feedback through PIP network maintains cell integrity when bumping in wall
Feedback through PIP network maintains cell integrity when bumping in obstacle
conclusions

Multilevel modeling makes things simpler!

Understanding of complexity at one level needs understanding of multilevel interactions

**BUT** speeds up response to cell shape

AND reorientation in flexible cell

AND Maintains cell integrity
Very simple model for Keratocyte AND Amoeboid movement duration of local, directional memory (== actin network persistence)

Ioanna Niculescu and Rob de Boer Plos comp biol 2015

Simple extension of CPM model wit
No representation of internal dynam
Only memory of previous movement builds up from spontaneous membrane fluctuations

2 parameters: strength $\lambda$
and duration $\text{Max}$
\[ \Delta \mathcal{H}_{\text{Act}}(u \rightarrow v) = \frac{\lambda_{\text{Act}}}{\text{Max}_{\text{Act}}} \times (\text{GM}_{\text{Act}}(u) - \text{GM}_{\text{Act}}(v)) \]

\[ \text{GM}_{\text{Act}}(u) = \frac{\sqrt{15 \times 17 \times 15 \times 18 \times 20}}{} \]

\[ \text{GM}_{\text{Act}}(v) = \frac{\sqrt{17 \times 16 \times 19 \times 11}}{} \]
Duration (MAX) determines mode of movement

**limited duration**

**long duration**

**sensitive to chemotaxis**
lymphocyte movement through skin
conclusions

Duration of local memory of protrusion sufficient to model difference between keratocyte and amoeboid movement

Keratocytes very robust (like extended model with PIP network)

Efficient Movement within tight tissue by small cell shape fluctuations
“How to compute an organism
Multilevel modeling of Morphogenesis
bridging levels of organization

Model premises

- Target morphogenesis ss (not only pattern formation)
- Cell basic unit (growth, division, movement, ...)
- Cell is NOT point, bead, homunculus
- Cells are deformable highly viscous objects
- Genes act through cells 'with a dynamics of their own’

*use CPM as simple but basically correct representation of a cell*
Finding Sufficient Conditions for complex behavior using only (subset of) known processes allowing many (open set) different observations

explicit 2-level model for implicit multilevel behavior

Dd morphodynamics:

From single cells (amoebae) to multicellular 'individuals' with 'new' ways of sensing and metamorphosis to groups of those

Dictyostelium phylogeny

Early offshoot:
shares protein domains otherwise exclusive for plants, fungi, and animals
Lifecycle Dictyostelium discoideum

Question

Can the morphodynamics of Dd emerge by selforganization from the behavior of the 2scale CA "cells" when (a minimum of) known properties of Dd are added?

YES...(almost)
Goldbeter-Martel model of cAMP signaling

\[ \frac{dp}{dt} = -f_1(\gamma)p + f_2(\gamma)(1 - p), \]

\[ \frac{d\beta}{dt} = s_1 \Phi(\rho, \gamma) - \beta, \]

\[ \frac{d\gamma}{dt} = s_2 \beta - \gamma. \]

where

\[ \rho \] = fraction of receptor in active state,

\[ \beta = \frac{[\text{cAMP}]_{\text{intra cellular}}}{K_R}, \]

\[ \gamma = \frac{[\text{cAMP}]_{\text{extracellular}}}{K_R}, \]

\[ t = k_1 \times \text{time}, \]

and

\[ f_1(\gamma) = \frac{1 + \kappa \gamma}{1 + \gamma}, \]

\[ f_2(\gamma) = \frac{L_1 + \kappa L_2 \gamma}{1 + c\gamma}, \]

\[ \Phi(\rho, \gamma) = \frac{\lambda_1 + \gamma^2}{\lambda_2 + \gamma^2}, \]

\[ Y = \frac{\rho \gamma}{1 + \gamma}. \]

The parameters appearing in system (1)–(3) are explained and estimated in tables I and II; refer also to fig. 2.

Parameter set A in table II was used by Martiel and Goldbeter [16] to model autonomous oscillations of cAMP in stirred suspensions of Dictyostelium cells. The numerical solution of the
chemical reactions Goldbeter model

Martiel & Goldbeter, 1987 (cont’d)

\[
\begin{align*}
R & \xrightleftharpoons[k_{-1}]{k_1} D \\
R + P & \xrightleftharpoons[a_1]{d_1} RP \\
D + P & \xrightleftharpoons[a_2]{d_2} DP \\
RP & \xrightleftharpoons[k_{-2}]{k_2} DP \\
2RP + C & \xrightleftharpoons[a_3]{d_3} E \\
E + S & \xrightleftharpoons[a_4]{d_4} ES \xrightarrow{k_4} E + P_i \\
C + S & \xrightleftharpoons[a_5]{d_5} CS \xrightarrow{k_5} C + P_i \\
P_i & \xrightarrow{k_i} \\
P_i & \xrightarrow{k_e} P \\
S & \xrightarrow{k'}
\end{align*}
\]
Parameter estimates of Goldbeter-model (Tyson 1989)

Table II
Model parameters.

<table>
<thead>
<tr>
<th>Name</th>
<th>Definition</th>
<th>Values used in calculations*</th>
<th>Set A</th>
<th>Set B</th>
<th>Set C</th>
<th>Set D</th>
<th>Set E</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_1$</td>
<td>$k_{-1}/k_1$</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>$L_2$</td>
<td>$k_{-2}/k_2$</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>$k_1$</td>
<td>$k_2/k_0$</td>
<td>18.5</td>
<td>18.5</td>
<td>18.5</td>
<td>18.5</td>
<td>18.5</td>
<td>18.5</td>
</tr>
<tr>
<td>$a$</td>
<td>$[ATP]/K_a$</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>$(V_m/K_m)(K_E)/R_E$</td>
<td>$10^{-4}$</td>
<td>$10^{-4}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
<td>$6.7 \times 10^{-4}$</td>
</tr>
<tr>
<td>$\lambda_2$</td>
<td>$(1+\alpha K_m/K_m)(K_E)/R_E$</td>
<td>0.26</td>
<td>2.4</td>
<td>2.4</td>
<td>2.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>$r_1$</td>
<td>$(V_m/K_m)(a)/(1+a)$</td>
<td>690</td>
<td>950</td>
<td>950</td>
<td>360</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>$r_2$</td>
<td>$k_m/k_h$</td>
<td>0.033</td>
<td>0.05</td>
<td>0.05</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>$s$</td>
<td>$s_0/s_2$</td>
<td>23</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>$\varepsilon'$</td>
<td>$k_0/(k_0 + k_1)$</td>
<td>0.014</td>
<td>0.019</td>
<td>0.019</td>
<td>0.005</td>
<td>0.005</td>
<td></td>
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<tr>
<td>$t$</td>
<td>$k_0/k_h$</td>
<td>0.0067</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>Time-scale</td>
<td>$1/k_h$</td>
<td>28</td>
<td>28</td>
<td>8.3</td>
<td>28</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Space-scale</td>
<td>$(k_a D)^{1/2}/k_h$</td>
<td>10</td>
<td>8.2</td>
<td>4.5</td>
<td>8.2</td>
<td>4.1</td>
<td></td>
</tr>
</tbody>
</table>

*All parameters (except the last two) are dimensionless. The time-scales are given in min, the space-scales in mm. When all four sets have the same value of a parameter, the symbol = is used.

Table I
Kinetic constants (refer to fig. 2).

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Experimental range*</th>
<th>Values used in calculations**</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_T$</td>
<td>Total receptor concentration</td>
<td>$1.5 \times 10^{-9}$ to $3 \times 10^{-9}$ M</td>
<td>$3 \times 10^{-8}$</td>
</tr>
<tr>
<td>$K_R$</td>
<td>Dissoc. const.</td>
<td>$10^{-8}$ to $10^{-8}$ M</td>
<td>$10^{-8}$ to $10^{-8}$</td>
</tr>
<tr>
<td>$K_D$</td>
<td>Dissoc. const.</td>
<td>$3 \times 10^{-8}$ to $9 \times 10^{-8}$ M</td>
<td>$10^{-8}$ to $10^{-8}$</td>
</tr>
<tr>
<td>$k_1$</td>
<td>Rate const.</td>
<td>0.012 min$^{-1}$</td>
<td>0.036 0.036 0.12 0.036 0.06</td>
</tr>
<tr>
<td>$k_2$</td>
<td>Rate const.</td>
<td>0.014 min$^{-1}$</td>
<td>0.36 0.36 1.2 0.36 0.6</td>
</tr>
<tr>
<td>$k_3$</td>
<td>Rate const.</td>
<td>0.22 min$^{-1}$</td>
<td>0.666 0.666 2.22 0.666 1.1</td>
</tr>
<tr>
<td>$k_4$</td>
<td>Rate const.</td>
<td>0.055 min$^{-1}$</td>
<td>0.0033 0.0033 0.011 0.0033 0.0033</td>
</tr>
<tr>
<td>$K_E$</td>
<td>Dissoc. const.</td>
<td>(NA, M$^2$)</td>
<td>$9 \times 10^{-16}$ $9 \times 10^{-15}$ $9 \times 10^{-15}$ $9 \times 10^{-15}$ $3.6 \times 10^{-15}$</td>
</tr>
<tr>
<td>$K_m$</td>
<td>Michaelis const.</td>
<td>$2 \times 10^{-3}$ to $5 \times 10^{-3}$ M</td>
<td>$4 \times 10^{-9}$</td>
</tr>
<tr>
<td>$V_m/K_m$</td>
<td>Rate const.</td>
<td>Apparent</td>
<td>0.05 to 1.4 min$^{-1}$</td>
</tr>
<tr>
<td>$K_m'$</td>
<td>Michaelis const.</td>
<td>(NA, M)</td>
<td>$4 \times 10^{-2}$</td>
</tr>
<tr>
<td>$V_m/K_m'$</td>
<td>Rate const.</td>
<td>Apparent</td>
<td>(NA, min$^{-1}$)</td>
</tr>
<tr>
<td>$k_1$</td>
<td>Rate const.</td>
<td>1.7 min$^{-1}$</td>
<td>1.7 1.0 3.3 1.7 1.7</td>
</tr>
<tr>
<td>$k_2$</td>
<td>Transport coeff.</td>
<td>0.3 to 0.9 min$^{-1}$</td>
<td>0.9 0.9 3.0 5.5 4.3</td>
</tr>
<tr>
<td>$k_3$</td>
<td>Rate const.</td>
<td>2.5 to 12.5 min$^{-1}$</td>
<td>5.4 3.6 12 3.6 2.5</td>
</tr>
<tr>
<td>$k$</td>
<td>Ratio of extracellular to intracellular volumes.</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>$D$</td>
<td>Diffusion coeff.</td>
<td>$0.024$ mm$^2$ min$^{-1}$</td>
<td>$0.024$</td>
</tr>
</tbody>
</table>

*From Martiol and Goldbeter [16]. NA = not available, in which case units of the quantity are given with no numerical value.

**Units are the same as in column giving experimental range. When all four parameter sets assume the same value of a parameter, the symbol = is used.

Set A: used by Martioli and Goldbeter to model cAMP oscillations in well-stirred cell suspensions.
Set B: used by Martioli and Goldbeter to model cAMP signal-relaying in well-stirred cell suspensions.
Set C: used in this paper to calculate spiral waves in the full three-component model.
Set D: used in this paper to calculate spiral waves in the two-component model.

***Dworkin and Keller [6].

--- > spirals
from single cell to moving slug

GG 2scale CA (CPM) + excitable medium (PDE) + chemotaxis

\[ J_{y,y} < J_{y,g} = J_{g,g} < J_{*,M} \]

cAMP dynamics towards cAMP refractory period

aggregation and SLUG: behaviour ++

- Faster movement in streams & larger slug move faster than smaller ones

- Slug keeps elongated shape because of cAMP diffusion: curved wavefront

- Cell sorting during slug-phase: differential adhesion + equal chemotaxis + movement

Marée & al 1999, Savill & Hogeweg 1997
Emergent sensing of environment in slug
Thermotaxis (and phototaxis)

cAMP dynamics depends on temperature
skews shape of wave front
cell chemotaxis up gradient
pushes slug towards higher temperatures
noise reduction!

Marée & al 1999
The culmination (fruiting body formation)

++ Cell differentiation:

- prespore-cells (green) → prestalk-cells (red) →
- autocycling cells (blue) → scenecent-cells (light-blue):

which do not produce or react to cAMP; produce stiff slime

Marée & Hogeweg PNAS 2001
CPM mechanics of culmination
how does the stalk move down?
why does it stop when bottom is reached?

Pressure waves in prespore cells push
the non-responding scenecent cells downwards
This stops when no prespore cells surround them
(i.e. when the prespore cells moved upwards toward the cAMP waves)

Marée & Hogeweg PNAS 2001
Lifecycle of Dd by chemotaxis and adhesion

- **aggregation streams**

- **orientation**

- **culmination**
Dd morphodynamics: multiple causes and multiple effects

| Aggregation | streams if wave propagation dep on density faster movement in streams |
| Mount/slug slug | cell sorting by differential adhesion AND chemotaxis slug shape attractor of energy minimization vs inward movement (wave shape) taxis (thermo- photo-taxis) via NH3 effect on excitability) slug shape and wave shape bi-directional mutant direction of movement vs momentum |
| culmination | needs dynamic cell differentiation downward movement of stalk cells caused by peristalsis caused by upward movement of spore cells pressure waves and wave shape self-correcting and self-terminating |
Movement Dd slugs: measured bead displacement and calculated force fields cf Rieu, Baranth, Maeda and Sawada 2005

outward directed forces!

displacement field

stress field
similar forces in model Dd slugs?

Note:
forces are (emergent) observables instead of model ingredients!

Can be measured (like in experiments)
cf From energy to cellular forces in the Cellular Potts Model: An algorithmic approach EG Rens, L Edelstein-Keshet - PLoS Computational Biology, 2019

Perpendicular forces expected because:
- wave shape (most concave in middle of slug)
- sideward push because of pressure gradient
conclusions

- Using simplifications which allows multilevel modeling we “can go for the horse part”
- Development as trajectory of dynamical system model minimizes regulation within cells
- Assumption of CPM seem very suitable to describe biological cells
- Relatively few parameters need to be specified; large set of ’new’ observables
- Treating forces as observables rather than model assumption allow close comparison with experimental measurements

BUT WHAT ABOUT THE GENES?
Evolutionary “testing” of the model

who wants to be a stalk?, cf Queller
how to come become another dictyosteloid?

*multiple levels needed to understand complexity*
Who want to become a stalk?
Evolution of cooperation and why cheaters do not take over
single gene greenbeard effect

Who depends on phase in cell cycle
Cell adhesion gene csA binds to csA
on agar csA knockouts become spores because wildtype cells
have more adhesion – > go to front - become stalk
BUT
in soil csA knockouts are left behind during aggreg. phase
– > fruiting body 85% wildtype

Conclusion: who wants to become a stalk

Simple optimality reasoning often flawed

Important role of non-inheritable behaviour

Stochasticity

Environmental heterogeneity

Selforganization
from Dictyostelium to other discyosteliids
Polysphondinium

Polysphondylium violaceum

A.R. Swanson, A Guide to the Common Dictyostelid Slime Molds of Great Smoky Mountains National Park

continuous redifferentiation prestalk-stalk sidebranches (polyshondinium)
....so far - so good BUT
mostly unidirectional micro→macro level causation
cell property changes only externally imposed
within CPM one can do better!
(include macro→micro level causation)

Multilevel modeling of multilevel behaviour
Morphogenesis as side effect of
cell differentiation and differential adhesion

combining
within cell dynamics (gene regulation)
between cell dynamics (signalling and adhesion)
cell growth and division
evolutionary dynamics (fitness cell differentiation)

physical processes + inherited information

Hogeweg 2000a,b
Modelling Morphogenesis: Interplay between Gene regulation, Differential adhesion and Evolution

DEVELOPMENT

2 scale CA model (Glazier and Graner 1993)
1 biotic cell represented as many CA cells
   cell surface energy minimisation

\[ H = \sum \frac{J_{ij}}{2} + \sum J_{im} + \sum \lambda(v - V)^2 \]

\[ \text{cell migration} \]
\[ \text{cell death (} v = 0 \text{)} \]
\[ \text{cell growth/division (} v > V + \tau \rightarrow V + + \text{)} \]

\[ \text{cell (re-)} \text{differentiation} \]

GENE-REGULATION

boolean network:< 32 nodes
   2 nodes define cell signalling
   2 nodes define maternal factors
   10 nodes define \( J_{ij} \)

\[ \text{cell differentiation} \]

EVOLUTION

GA : population size 32
   genetic operators: point mutations + gene duplication/loss
   selection fitness\(^3\), random\text{death}

\[ \text{fitness: sum of distance between cell types} \]
Morphogenesis by differential adhesion and cell differentiation
## modes of cell differentiation and morphogenesis

<table>
<thead>
<tr>
<th>cell differentiation</th>
<th>evolved morphogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>alternative attractors of gene regulation network = <em>stable memory</em></td>
<td>many morphemes by few mechanisms</td>
</tr>
<tr>
<td></td>
<td>- engulfing</td>
</tr>
<tr>
<td></td>
<td>- intercalation</td>
</tr>
<tr>
<td>signal dependent cell differentiation <em>re-differentiation</em></td>
<td>- convergence extension</td>
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<tr>
<td></td>
<td>- meristematic growth</td>
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<tr>
<td></td>
<td>- budding</td>
</tr>
<tr>
<td></td>
<td>automatic orchestration of adhesion,migration,differentiation cell growth - division and - death “pseudo-isomorphic outgrowth”</td>
</tr>
</tbody>
</table>

Morphogenesis as sustained transient of energy minimization intrinsic conflict maintained by cell growth cell division and cell differentiation.
Evolutionary history: after cell differentiation diversity of shapes
Simplicity

easily extendable

"natural" flexible interface between levels

dynamic micro-macro and macro-micro interactions

emergence at multiple space and time scales

(and .... models "real" biological cells pretty well)