multilevel modeling of morphogenesis: cell based morphodynamics
Cell-based morphodynamics

cell shape, cell movement and multicellular development

- \textit{stripes again!} morphodynamics of segmentation
  shape changes by cell differential adhesion
- \textit{single cells}
  Mutual interaction cell shape and internal dynamics
  keratocyte chemotactic movement
  amoeboid movement (Dictyostelium).
- \textit{“what about the horse part” \textquotesingle; “from single cells to multicellular organism”}
  through signaling, chemotaxis and differential adhesion

(from data intensive to beaviour intensice models)
segmentation, differential adhesion and convergent extension

Previous models:
- segmentation without cells
- segmentation without shape-changes (morphogenesis ss)

During or after segmentation: convergent extension (CE)
elongation of tissue by intercalating cells
(movement of cells towards center)

Hypotheses on mechanisms of CE based on experiments on different animals:
- graded adhesion (> in center) sensed through morphogen
- axial adhesion (elongated cells, > adhesion on elongated side; polarity preset or alignment)

how do these mechanisms interact with segmentation?
Models: graded adhesion, axial adhesion, persistent motion, CPM

A

B

C

D

strength of adhesion

upper side
lower side

high adhesion
low adhesion

anterior
lateral (left)
lateral (right)
posterior

x-axis of field
y-axis of field
Convergent extension scramble segmentation UNLESS differential adhesion

A. Convergent extension (CE) with and without segment-specific adhesion.
B. Graphs showing the long axis length (grid points) over the number of steps (10^5 MCS) for different conditions.

C. Graphs showing the long axis length (grid points) for different conditions.

D. Graphs showing the long axis length (grid points) for different conditions.

E. Graphs showing the long axis length (grid points) for different conditions.

F. Graphs showing the long axis length (grid points) for different conditions.

G. Graphs showing the long axis length (grid points) for different conditions.

H. Graphs showing the long axis length (grid points) for different conditions.

I. Graphs showing the long axis length (grid points) for different conditions.
Differential adhesion ALONE sufficient for convergent extension
Persistent motion enhances CE in large and/or stiff tissues
segmentation and elongation from randomly scrambles cells

2 opposing gradients and graded differential adhesion
conclusions

A priori hypotheses often:

less minimal
less robust
then potential selforganizing process.
chemotaxis: modeling internal dynamics at different levels of detail

In CPM model chemotaxis can be implemented as 'extend phylloposia 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

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

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

Concentrations:
- \( R(x_1, y) \)
- \( R_1(x_1, y) \)
- \( C(x_1, y) \)
- \( C_1(x_1, y) \)
- \( P(x_1, y) \)
- \( Q(x_1, y) \)
- \( A(x_1, y) \)

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

Densities of actin at the angle \( \Theta_{m=5} \) at a site at cell edge:

Extension

Retraction
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>µMs$^{-1}$</td>
</tr>
<tr>
<td>$I_R$</td>
<td>Rac activation input rate</td>
<td>0.5</td>
<td>µMs$^{-1}$</td>
</tr>
<tr>
<td>$I_\rho$</td>
<td>Rho activation input rate</td>
<td>3.3</td>
<td>µMs$^{-1}$</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>$\mu$M</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>$n_0$</td>
<td>Arp2/3 nucleation rate</td>
<td>60</td>
<td>$\mu$M nm s$^{-1}$</td>
</tr>
<tr>
<td>$K_m$</td>
<td>saturation constant for Arp2/3 nucleation</td>
<td>2</td>
<td>$\mu$M</td>
</tr>
<tr>
<td>$l$</td>
<td>scale factor converting units of $F$ to concentration</td>
<td>255</td>
<td>$\mu$M 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$^{-2}$ $\mu$M</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>$\mu$M</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

polarisation 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

PIP network inhibits reorientation in static round cell

BUT speeds up response to cell shape
AND reorientation in flexible cell
AND Maintains cell integrity
Amoeboid cell movement, e.g. lymphocytes, Dictyostelium

Dictyostelium
two-dimensional excitable waves
govern self-organized morphodynamics
of amoeboid cells
Taniguchi,1, .. Sawai, PNAS 2013

visualised

modeled (excitable medium)
elastic cell

1. Inhibition of actin polymerization or PI3Kinase activity reduces the wave nucleation and simplifies the wave patterns. (A) PIP3 (PHcrac-
Very simple model for Keratocyte
AND Amoeboid movement
duration of local, directional memory
(== actin network persistance)
Ioanna Niculescu and Rob de Boer Plos comp biol 2015

Simple extension of CPM model with periphery constraint
No representation of internal dynamics.
Only memory of previous movement
builds up from spontaneous
membrane fluctuations

2 params: strenght $\lambda$
and duration Max
method
\[
\Delta \mathcal{H}_{\text{Act}}(u \rightarrow v) = \frac{\lambda_{\text{Act}}}{\lambda_{\text{Max}_{\text{Act}}}} \left( \text{GM}_{\text{Act}}(u) - \text{GM}_{\text{Act}}(v) \right)
\]

\[
\text{GM}_{\text{Act}}(u) = \sqrt[5]{15 \times 17 \times 15 \times 18 \times 20}
\]

\[
\text{GM}_{\text{Act}}(v) = \sqrt[4]{17 \times 16 \times 19 \times 11}
\]
Duration 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)

Why?

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

- Mature fruiting body
- Spores
- Free-living amoebae
- Cell division
- Aggregation induced by starvation
- Slug formation
- Migrating slug
- Germination
Goldbeter-Martel model of cAMP signalling

equations

\[
\begin{align*}
\frac{d\rho}{dt} &= -f_1(\gamma)\rho + f_2(\gamma)(1 - \rho), \\
\frac{d\beta}{dt} &= s_1 \Phi(\rho, \gamma) - \beta, \\
\frac{d\gamma}{dt} &= s_2 \beta - \gamma.
\end{align*}
\]

where

- \( \rho \) = fraction of receptor in active state,
- \( \beta = \frac{[cAMP]_{intracellular}}{K_R} \),
- \( \gamma = \frac{[cAMP]_{extracellular}}{K_R} \),
- \( t = k_1 \times \text{time} \),
- \( f_1(\gamma) = \frac{1 + k_1 \gamma}{1 + \gamma} \),
- \( f_2(\gamma) = \frac{L_1 + \kappa L_2 \gamma}{1 + c \gamma} \),
- \( \Phi(\rho, \gamma) = \frac{\lambda_1 + \gamma^2}{\lambda_2 + \gamma^2} \),
- \( Y = \frac{\rho \gamma}{1 + \gamma} \).

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)**

\[
\begin{align*}
R & \xrightleftharpoons[k_{-1}]{k_1} D \\
R + P & \xrightleftharpoons[d_1]{a_1} RP \\
D + P & \xrightleftharpoons[d_2]{a_2} DP \\
RP & \xrightleftharpoons[k_{-2}]{k_2} DP \\
2RP + C & \xrightleftharpoons[d_3]{a_3} E \\
E + S & \xrightleftharpoons[d_4]{a_4} ES \xrightarrow[k_4]{k_4} E + P_i \\
C + S & \xrightleftharpoons[d_5]{a_5} CS \xrightarrow[k_5]{k_5} C + P_i \\
P_i & \xrightarrow[k_i]{k_i} \\
P_i & \xrightarrow[k_e]{k_e} \\
S & \xrightarrow[k']{k'} 
\end{align*}
\]
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Set A</td>
</tr>
<tr>
<td>(L_1)</td>
<td>(k_{1-1}/k_1)</td>
<td>10</td>
</tr>
<tr>
<td>(L_2)</td>
<td>(k_{1-1}/k_2)</td>
<td>0.005</td>
</tr>
<tr>
<td>x</td>
<td>(k_{2-2}/k_5)</td>
<td>18.5</td>
</tr>
<tr>
<td>c</td>
<td>(K_E/K_D)</td>
<td>10</td>
</tr>
<tr>
<td>(a)</td>
<td>(ATP)/(K_m)</td>
<td>3</td>
</tr>
<tr>
<td>(k_1)</td>
<td>(K_{1-1}/K_{1-2})</td>
<td>(10^{-4})</td>
</tr>
<tr>
<td>(k_2)</td>
<td>(1 + \alpha K_E/K_m)</td>
<td>(K_E)</td>
</tr>
<tr>
<td>(s_1)</td>
<td>(V_m/K_m)</td>
<td>(a)</td>
</tr>
<tr>
<td>(s_2)</td>
<td>(k_{2-2}/k_5)</td>
<td>0.033</td>
</tr>
<tr>
<td>t</td>
<td>(t'/t_2)</td>
<td>23</td>
</tr>
<tr>
<td>(r')</td>
<td>(k_2/k_5)</td>
<td>0.014</td>
</tr>
<tr>
<td>(t)</td>
<td>(k_1/k_{2-2})</td>
<td>0.0067</td>
</tr>
<tr>
<td>Time-scale</td>
<td>(1/k_1)</td>
<td>28</td>
</tr>
<tr>
<td>Space-scale</td>
<td>((K_d D)^{1/2}/k_1)</td>
<td>10</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>Set A</th>
<th>Set B</th>
<th>Set C</th>
<th>Set D</th>
<th>Set E</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^{-9})</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(K_B)</td>
<td>Dissoc. const.</td>
<td>(10^{-7}) to (10^{-9})M</td>
<td>(10^{-7})</td>
<td>(10^{-7})</td>
<td>(10^{-7})</td>
<td>(10^{-7})</td>
<td>(9 \times 10^{-8})</td>
</tr>
<tr>
<td>(K_D)</td>
<td>Dissoc. const.</td>
<td>(3 \times 10^{-6}) to (9 \times 10^{-8})M</td>
<td>(3 \times 10^{-8})</td>
<td>(10^{-8})</td>
<td>(10^{-8})</td>
<td>(10^{-9})</td>
<td>(2 \times 10^{-9})</td>
</tr>
<tr>
<td>(k_1)</td>
<td>Rate const.</td>
<td>0.012 min^{-1}</td>
<td>0.036</td>
<td>0.036</td>
<td>0.12</td>
<td>0.036</td>
<td>0.06</td>
</tr>
<tr>
<td>(k_{1-1})</td>
<td>Rate const.</td>
<td>0.104 min^{-1}</td>
<td>0.36</td>
<td>0.36</td>
<td>1.2</td>
<td>0.36</td>
<td>0.6</td>
</tr>
<tr>
<td>(k_{1-2})</td>
<td>Rate const.</td>
<td>0.22 min^{-1}</td>
<td>0.666</td>
<td>0.666</td>
<td>2.22</td>
<td>0.666</td>
<td>1.1</td>
</tr>
<tr>
<td>(K_{1-1})</td>
<td>Rate const.</td>
<td>0.055 min^{-1}</td>
<td>0.0033</td>
<td>0.0033</td>
<td>0.011</td>
<td>0.0033</td>
<td>(5 \times 10^{-4})</td>
</tr>
<tr>
<td>(K_{1-2})</td>
<td>Dissoc. const.</td>
<td>(NA, M^2)</td>
<td>(9 \times 10^{-16})</td>
<td>(9 \times 10^{-15})</td>
<td>(9 \times 10^{-15})</td>
<td>(9 \times 10^{-15})</td>
<td>(3.6 \times 10^{-15})</td>
</tr>
<tr>
<td>(K_m)</td>
<td>Michaelis const.</td>
<td>(2 \times 10^{-7}) to (5 \times 10^{-6})M</td>
<td>(4 \times 10^{-8})</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(V_m/K_m)</td>
<td>Apparent</td>
<td>rate const.</td>
<td>0.05-1.4 min^{-1}</td>
<td>0.6</td>
<td>0.57</td>
<td>2</td>
<td>0.86</td>
</tr>
<tr>
<td>(K_{1-1})</td>
<td>Michalis const.</td>
<td>(NA, M)</td>
<td>(4 \times 10^{-7})</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(K_{1-2})</td>
<td>Dissoc. const.</td>
<td>(NA, min^{-1})</td>
<td>(6 \times 10^{-5})</td>
<td>(6 \times 10^{-5})</td>
<td>(2.1 \times 10^{-4})</td>
<td>(8.6 \times 10^{-5})</td>
<td>(2.7 \times 10^{-5})</td>
</tr>
<tr>
<td>(k_{1-1})</td>
<td>Rate const.</td>
<td>1.7 min^{-1}</td>
<td>1.7</td>
<td>1.0</td>
<td>3.3</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>(k_{1-2})</td>
<td>Rate const.</td>
<td>0.3-0.9 min^{-1}</td>
<td>0.9</td>
<td>0.9</td>
<td>3.0</td>
<td>5.5</td>
<td>4.2</td>
</tr>
<tr>
<td>(k_{1-3})</td>
<td>Rate const.</td>
<td>2.5-12 min^{-1}</td>
<td>5.4</td>
<td>3.6</td>
<td>12</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>(h)</td>
<td>Ratio of extracellular to intracellular volumes</td>
<td>5 - 100</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(D)</td>
<td>Diffusion coeff.***</td>
<td>(0.024) mm^2 min^{-1}</td>
<td>(0.024)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*From Martiel 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 Martiel and Goldbeter to model cAMP oscillations in well-stirred cell suspensions.
Set B: used by Martiel 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.
Sets D and E: used in this paper to calculate spiral waves in the two-component model.

***Dworkin and Keller [6].
simplify dynamics - add cells:
Dd life cycle by excitable medium and differential adhesion

excitable medium

+ differential adhesion
Lifecycle of Dd by chemotaxis and adhesion

aggregation
streams

orientation

culmination
# Dd morphodynamics:
## multiple causes and multiple effects

| Aggregation | streams if wavepropagation dep on density faster movement in streams |
| Mount(slug) slug | cell sorting by differential adhesion AND chemotaxis slug shape attractor of energy minimisation 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 |
stream formation requires

density dependent speed of cAMP wave propagation

(i.e. fast internal cAMP dynamics)

181:203-213
Why streams?

Fig. 4. Plot of velocity (each point averaged over 10 simulations) against the cell-medium bond energy for prespore amoebae. Given that the amoebae adhere to each other the group will always move faster than a single amoeba. Parameters are as described in the legend to Fig. 1. ■, Group of amoebae; ●, single amoeba.
Cell Sorting much faster in moving slug than in fixed mount
WHY?

Prestalk cells (Yellow) stronger adhesion
Prespore cells (Green)

\[ J_{yy} < J_{gg} < J_{yg} \]

Same chemotactic response

Savill and Hogeweg 1997
EQUAL chemotaxis speeds up sorting
(moving slug instead of fixed mount also faster sorting
(cf Kafer, “go against the flow” (binf4))
Movement Dd slugs:
measured bead displacement and calculated force fields

cf Rieu, Baranth, Maeda and Sawada 2005

outward directed forces!
similar forces in model Dd slugs?

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

Can be measured (like in experiments)
cf Marée and Grieneisen (in prep)

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

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

continuous redifferentiation prestalk-stalk sidebranches (polyshondinimum)