

multilevel modeling of morphogenesis: cell based morphodynamics

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Cell-based morphodynamics

cell shape, cell movement and multicellur development

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

(from data intesive to behaviour intensice models)

segmentation, differential adhesion and convergent extension

Previous models:

- segmentation without cells
- segmentation without shape-changes (morphogenesis ss)

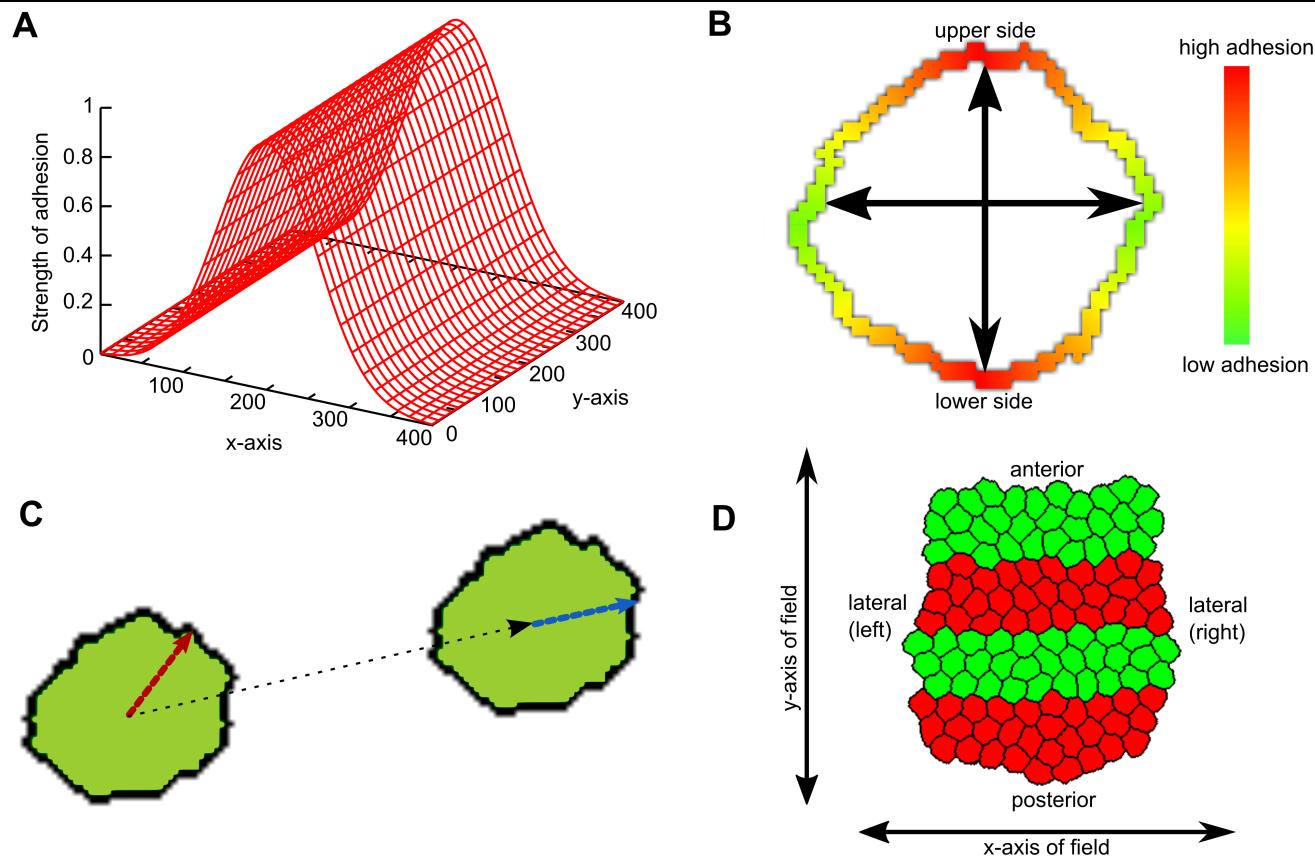
During or after segmentation: convergent extention (CE)
elongation of tissue by intercalating cells
(movement of cells towards center)

Hypotheses on mechanisms of CE based on experiments on different animals:

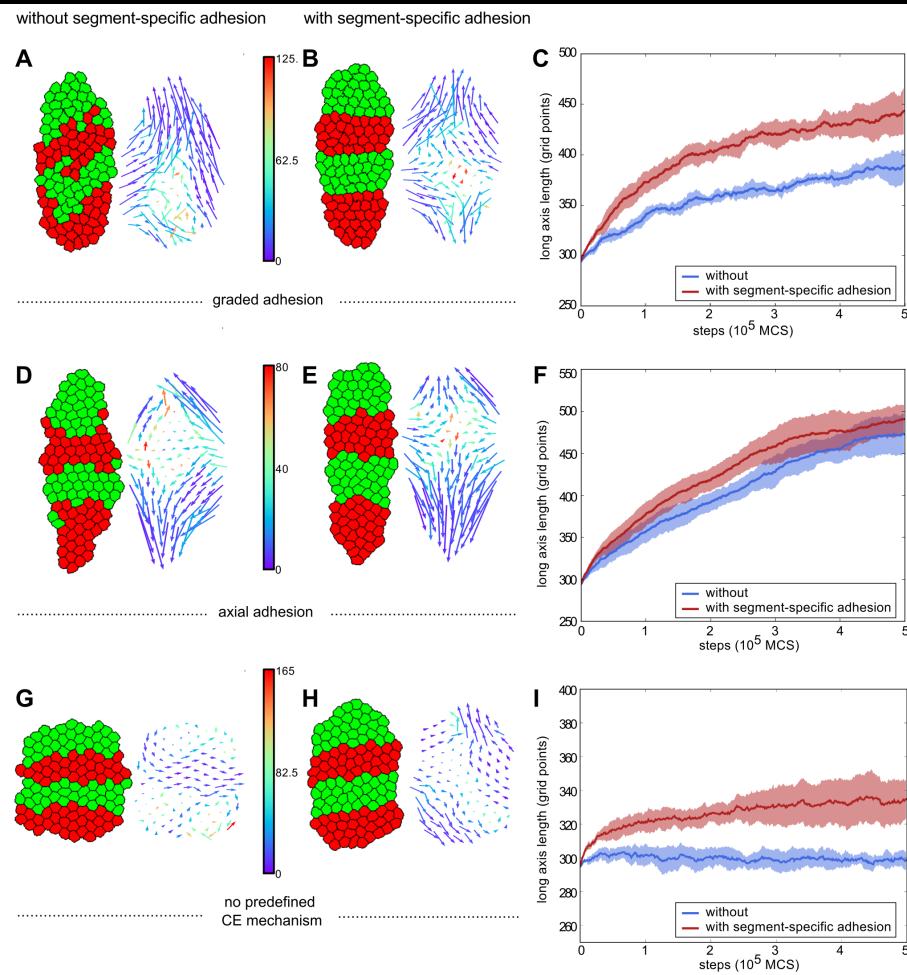
- graded adhesion (> in center) sensed through morphogen
- axial adhesion (elongated cells, > adhesion on elongated side; polarity preset or alignment)

how do these mechanisms interact with segmentation?

Models: graded adhesion, axial adhesion, persistent motion, CPM

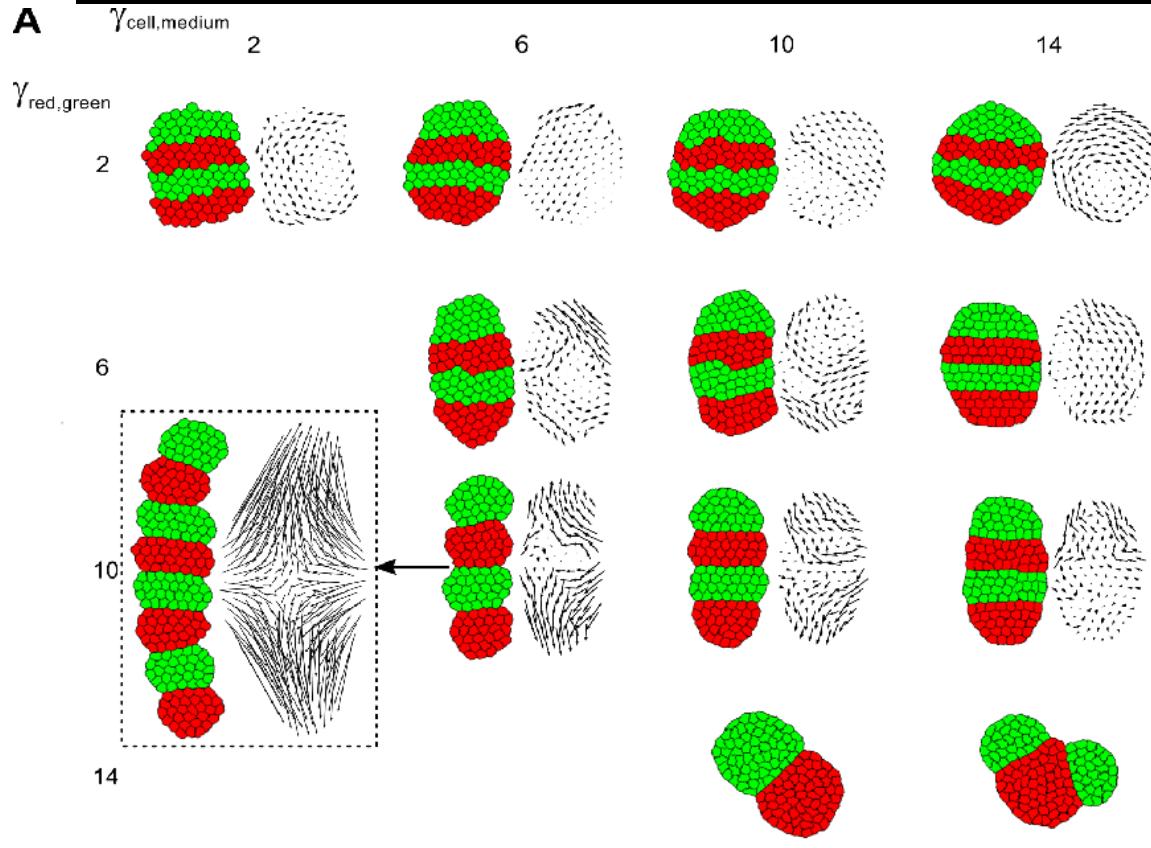


Convergent extension scramble segmentation UNLESS differential adhesion

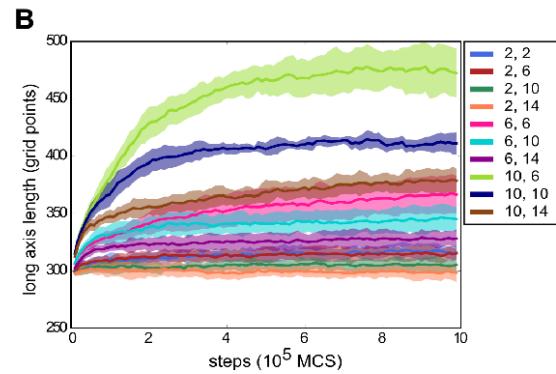


Differential adhesion ALONE sufficient for convergent extension

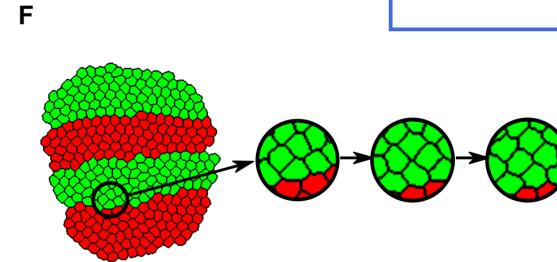
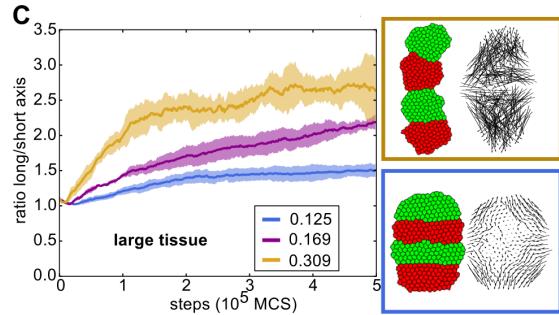
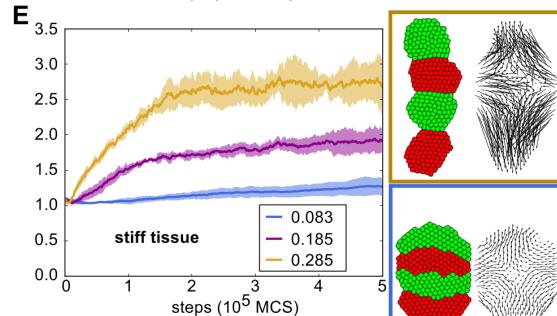
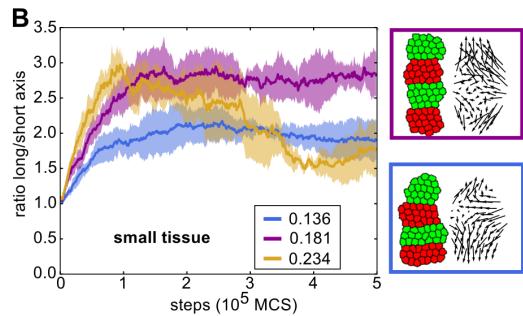
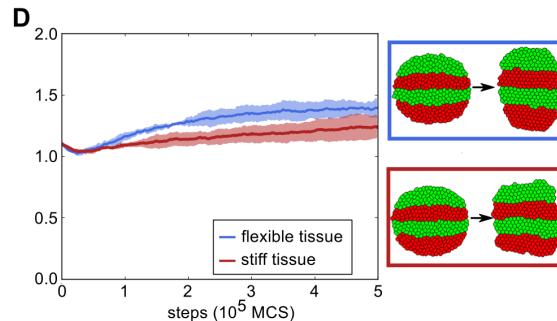
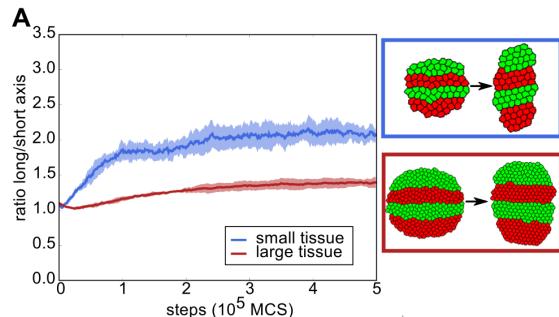
A



B

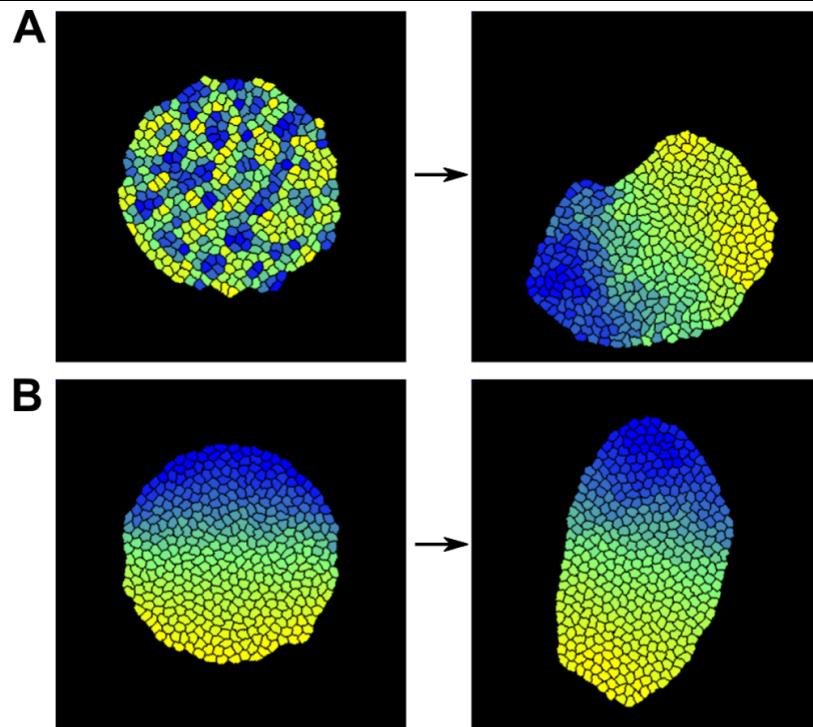


Persistent motion enhances CE in large and/or stiff tissues



**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 phalloposia preferentially in direction of gradient'

How does the cell do this?

Interaction of small g proteins and actin network

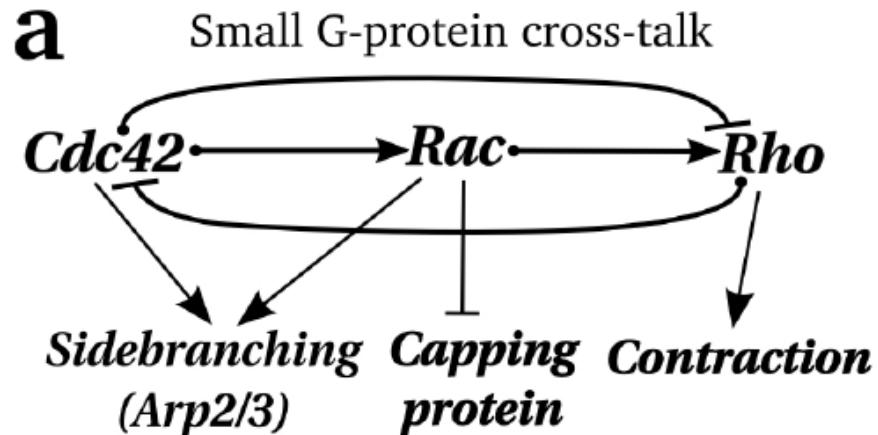
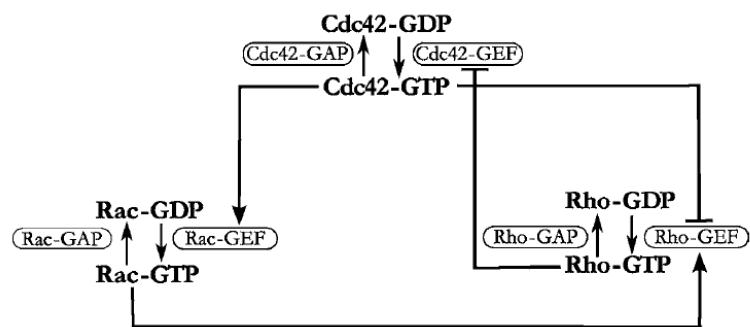
Well studied in Keratocytes

Modelled by Stan Maree et al (Bull Math Biol 2007 and Plos comp biol 2012)

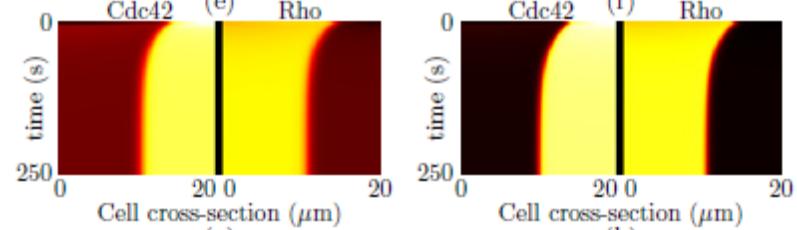
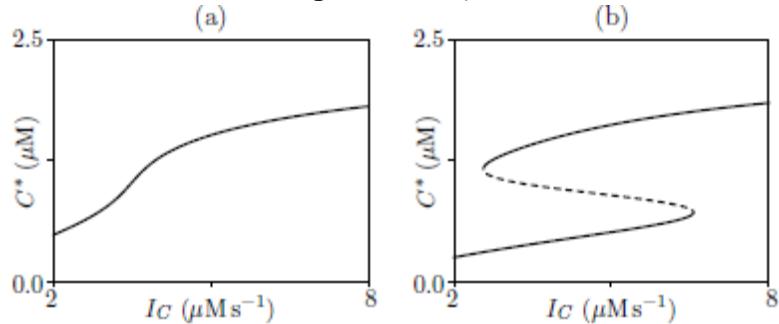
importance of mutual feedback between cell shape and gene regulation

importance of biochemical detail ONLY apparent through this interaction

relevant small g protein interactions

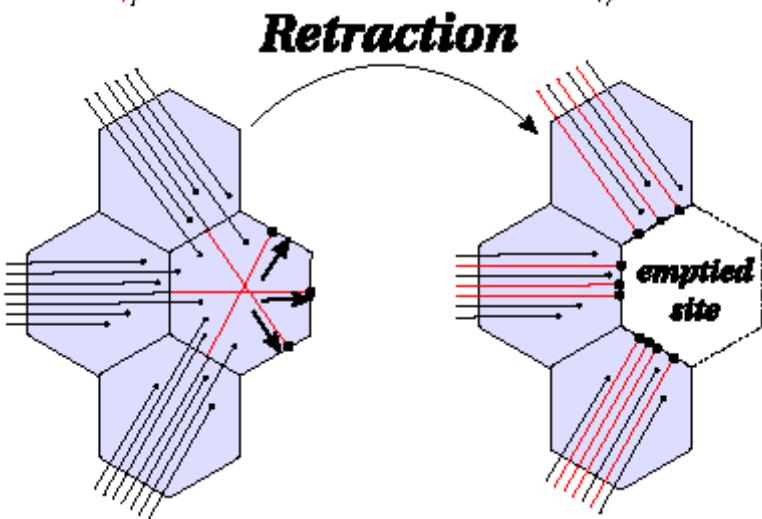
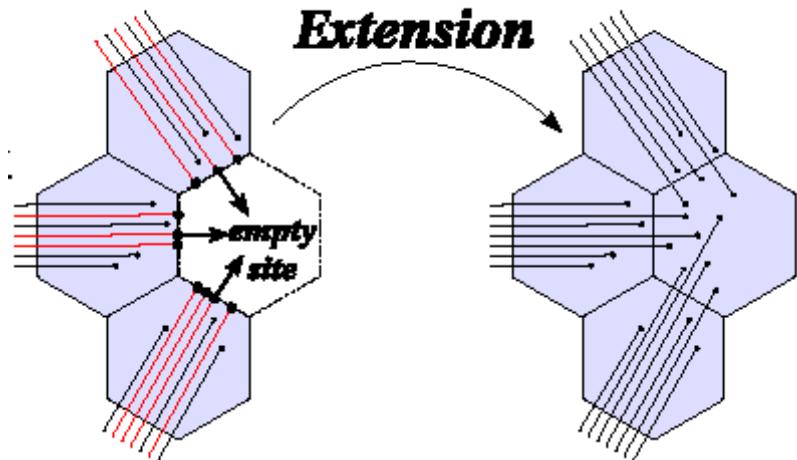
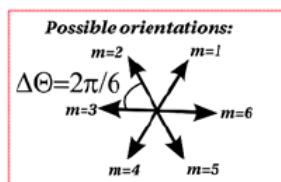
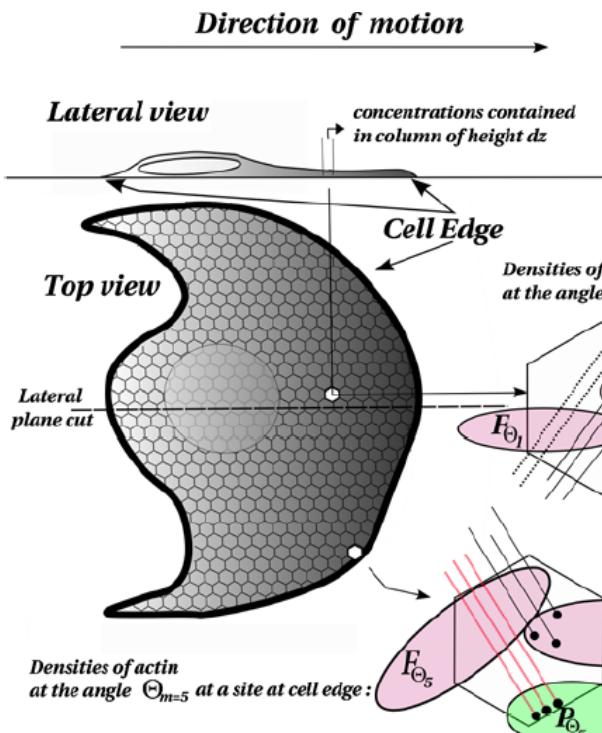


bistability in space due to fast diffusion inactive form



actin dynamics and cell wall dynamics

17



fully parametrized

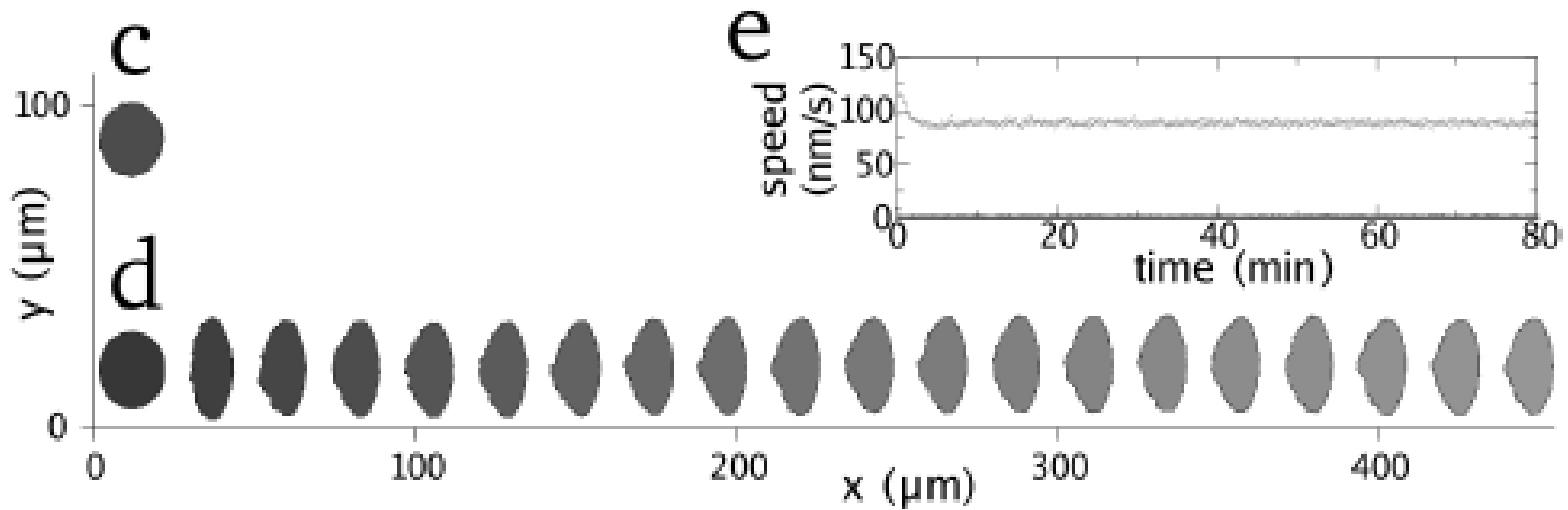
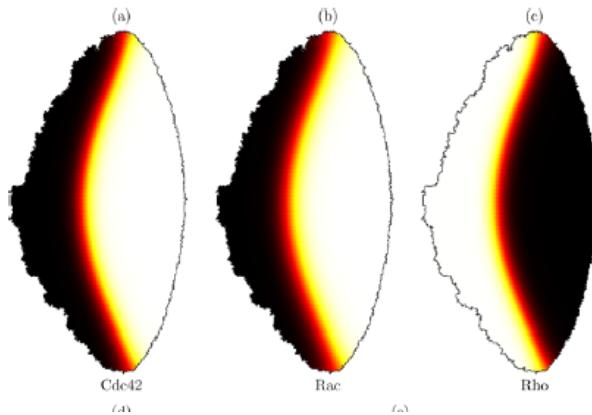
Table 1 Parameter estimates relevant to the small G-proteins and their interactions

Parameter	Meaning	Values	Units
C^*	typical level of active Cdc42	1	μM
R^*	typical level of active Rac	3	μM
ρ^*	typical level of active Rho	1.25	μM
C_{tot}	total level of Cdc42	2.4	μM
R_{tot}	total level of Rac	7.5	μM
ρ_{tot}	total level of Rho	3.1	μM
I_C	Cdc42 activation input rate	3.4	$\mu\text{M s}^{-1}$
I_R	Rac activation input rate	0.5	$\mu\text{M s}^{-1}$
I_ρ	Rho activation input rate	3.3	$\mu\text{M s}^{-1}$
β_p	Rho level for half-max inhibition of Cdc42	1.25	μM
β_C	Cdc42 level for half-max inhibition of Rho	1	μM
n	Hill coefficient of Cdc42-Rho mutual inhibition response	3	—
a_C	Cdc42-dependent Rac activation rate	4.5	s^{-1}
a_R	Rac-dependent Rho activation rate	0.3	s^{-1}
d_C, d_R, d_ρ	decay rates of activated small G-proteins	1	s^{-1}
D_m	diffusion coefficient of active small G-proteins	1×10^5	$\text{nm}^2 \text{s}^{-1}$
$D_{m\text{c}}$	diffusion coefficient of inactive small G-proteins	1×10^7	$\text{nm}^2 \text{s}^{-1}$

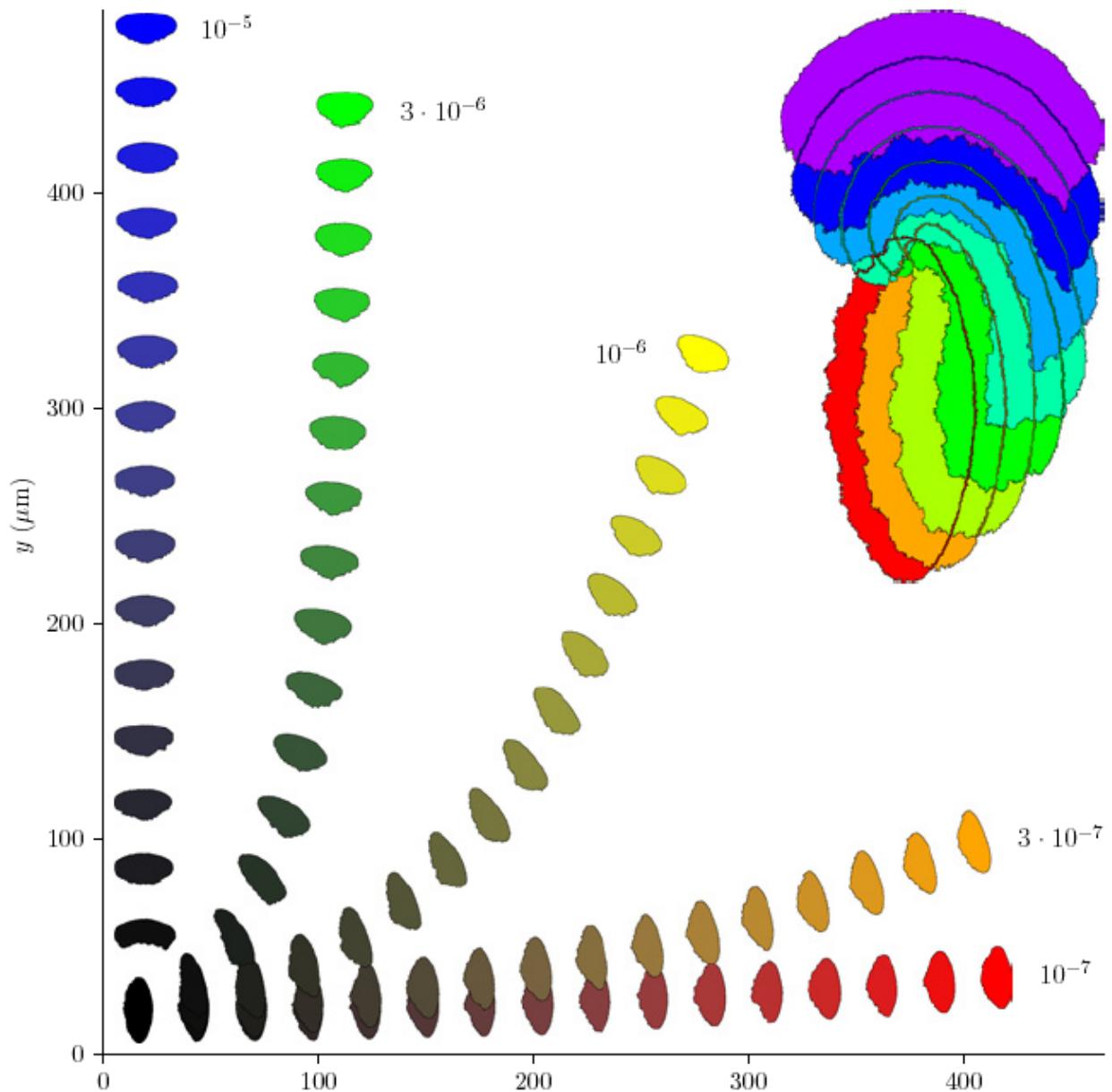
Table 2 Parameter estimates relevant to actin dynamics

Parameter	Meaning	Values	Units
A^*	typical Arp2/3 concentration	2	μM
F^*	typical filament density	0.278	nm^{-1}
B^*	typical barbed end density	1.7×10^{-5}	nm^{-2}
P^*	typical edge density of barbed ends	0.05	nm^{-1}
μ_C, μ_R	Cdc42 and Rac-dependent Arp2/3 activation	0.16	s^{-1}
d_A	activated Arp2/3 decay rate	0.1	s^{-1}
D_A	diffusion coefficient of Arp2/3	1×10^6	$\text{nm}^2 \text{s}^{-1}$
η_0	Arp2/3 nucleation rate	60	$\mu\text{M nm s}^{-1}$
K_m	saturation constant for Arp2/3 nucleation	2	μM
l	scale factor converting units of F to concentration	255	$\mu\text{M nm}$
k	scale factor converting concentration to units of B	1.06×10^{-4}	$\text{nm}^{-2} \mu\text{M}$
v_0	actin filament growth rate (free polymerization)	500	nm s^{-1}
d_F	actin filament turnover rate	0.03	s^{-1}
κ_{\max}	barbed end capping rate	2.8	s^{-1}
κ_{Rac}	max reduction of capping by Rac	2.1	s^{-1}
K_R	Rac level for half-max reduction of capping	3	μM
r	reduction of capping close to the edge	0.14	-

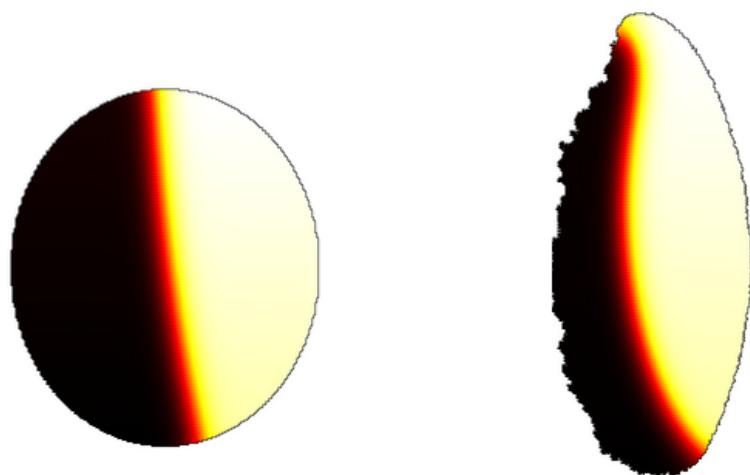
Shapes itself into a walking keratocyte and Walks! (and at the correct speed)



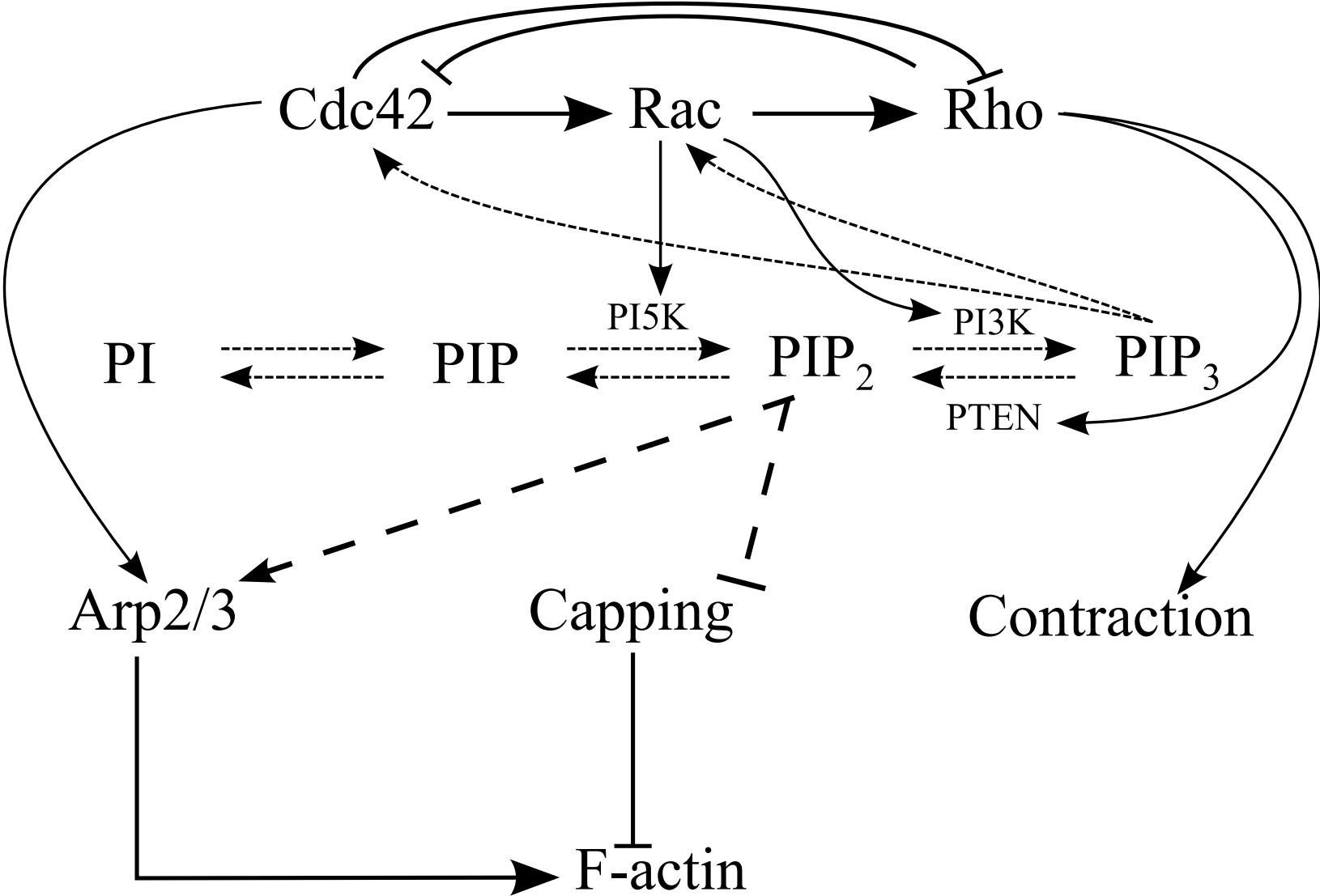
**Can reorient itself:
polarity and/vs rotation and/vs shape**



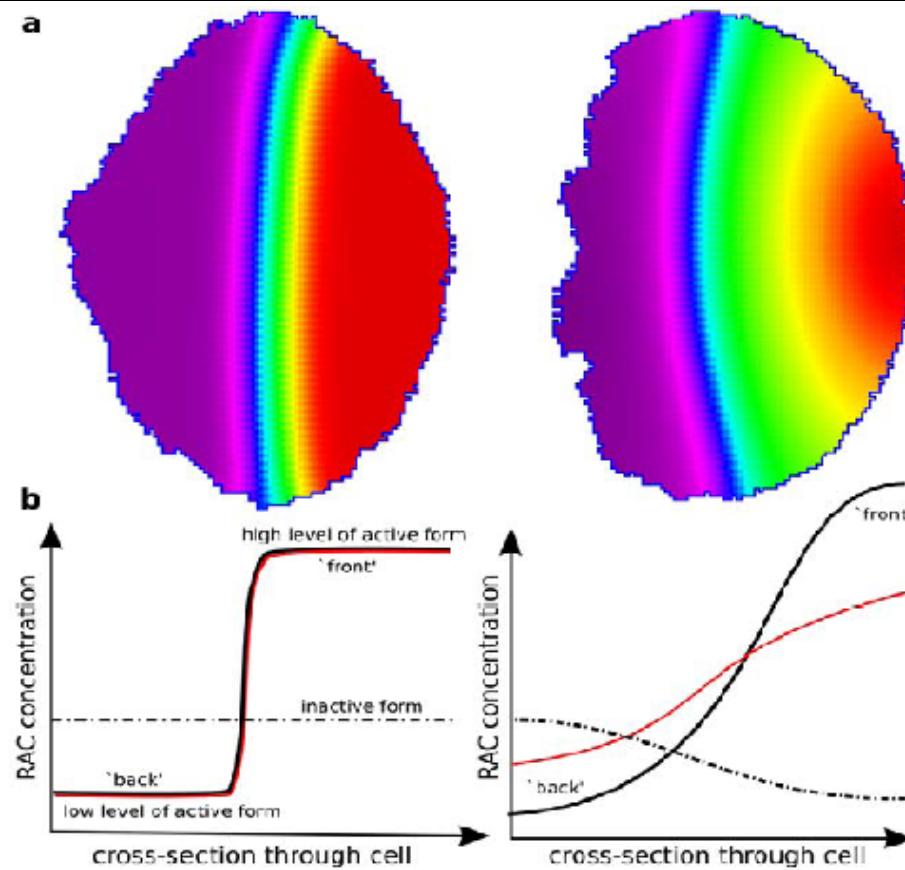
**feedback internal dynamics and cell shape
faster internal polarity change because of cell shape
changes (which are caused by internal polarity
change)**



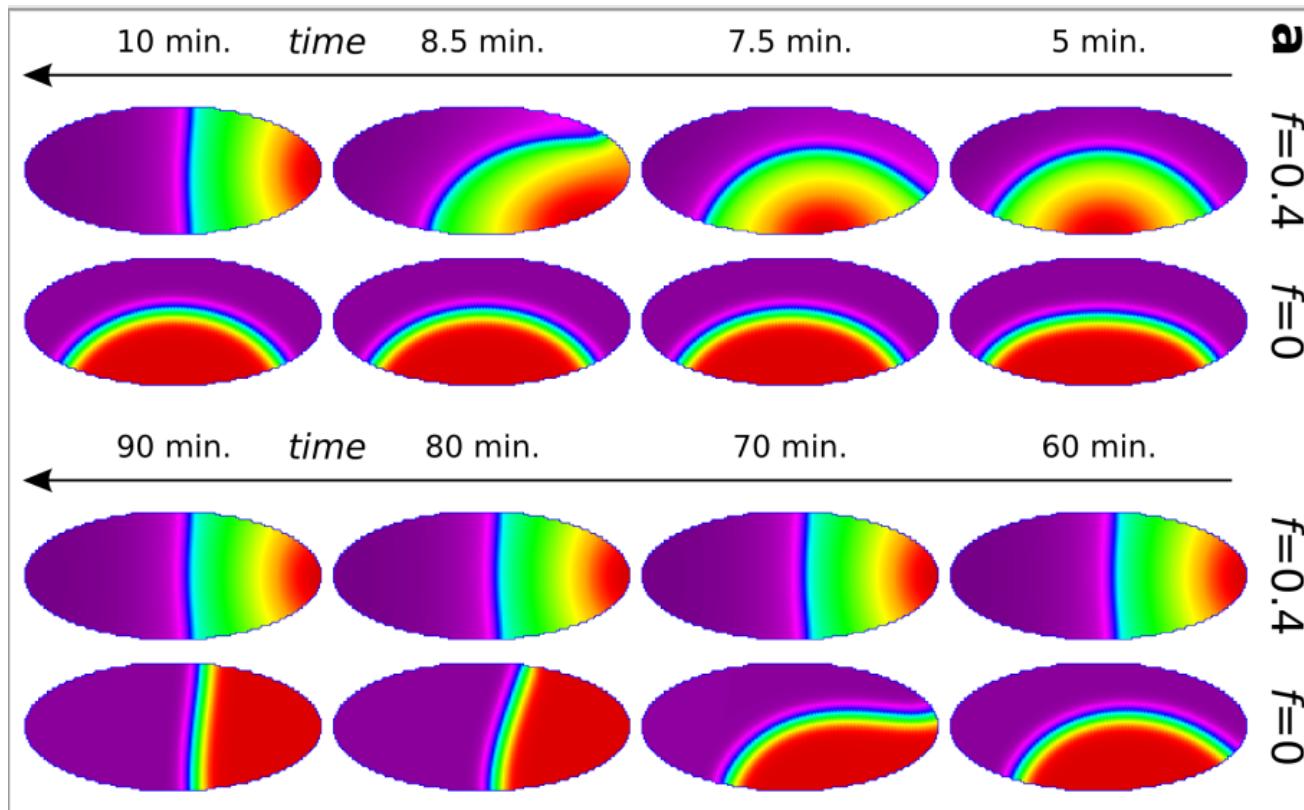
HOWEVER, internal dynamics more complex WHY?



Feedback through PIP network smoothes out gradient

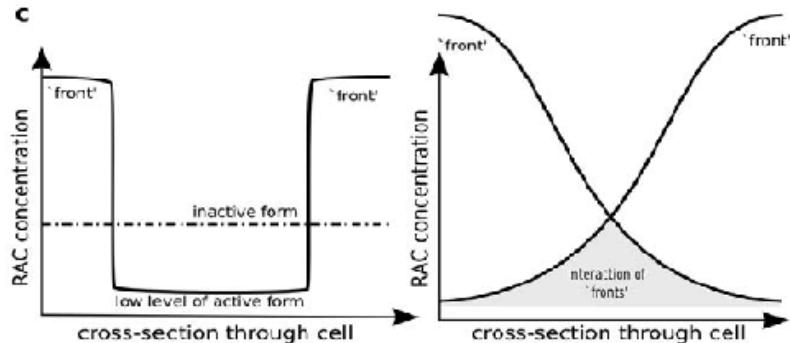


Feedback through PIP network causes faster adaptation

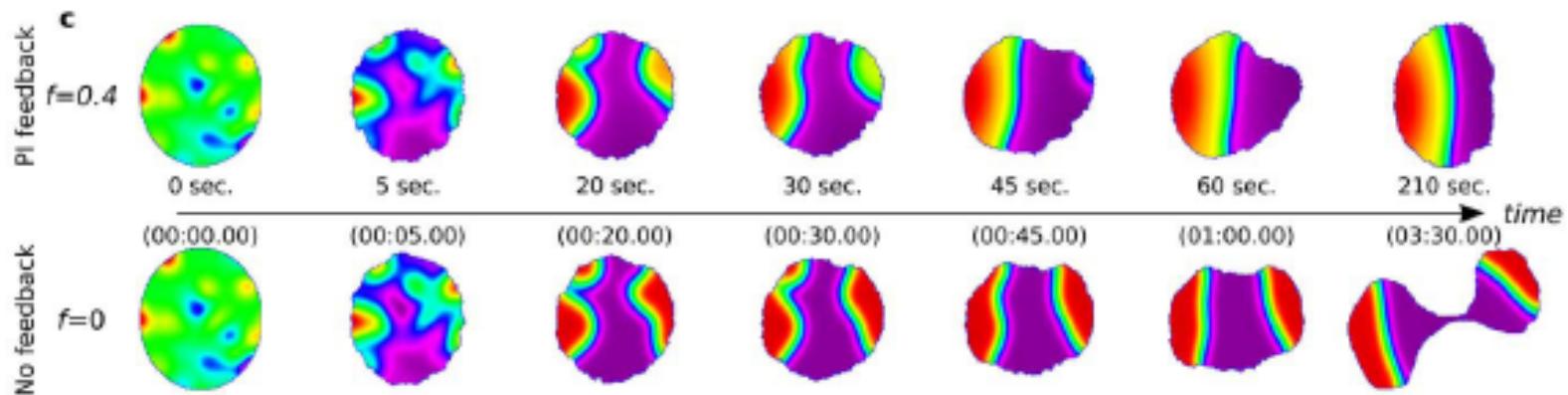


(HOWEVER: in round cell SLOWER reorientation to external signal!)

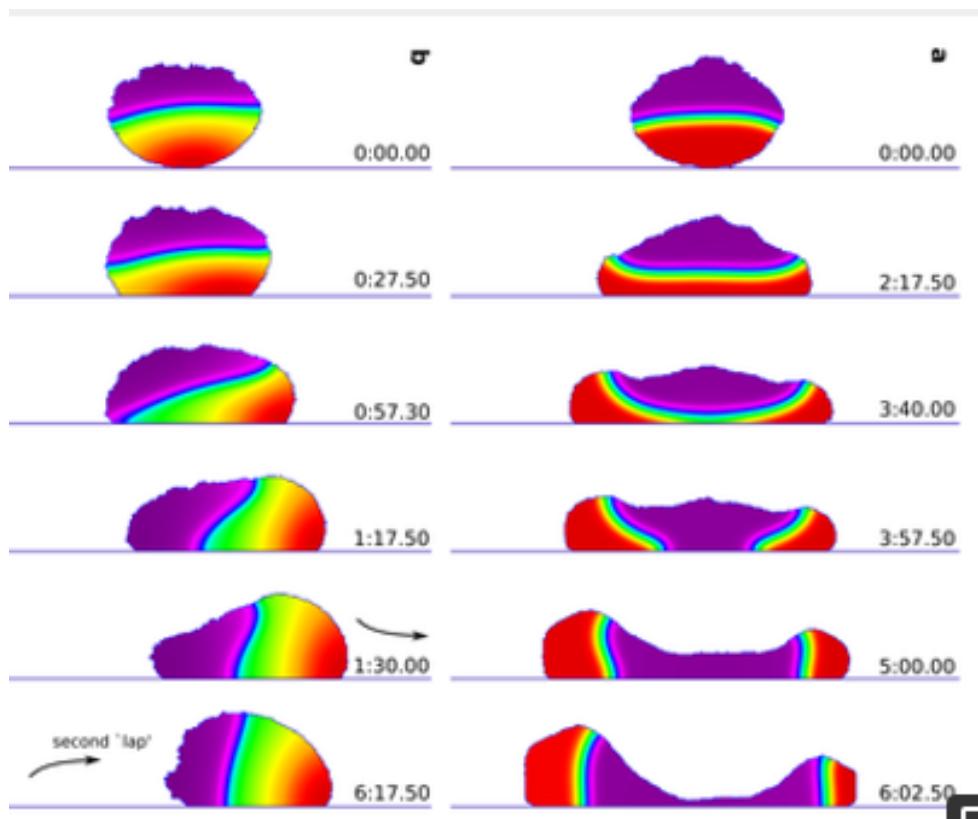
Feedback through PIP network enable resolving conflicting signals



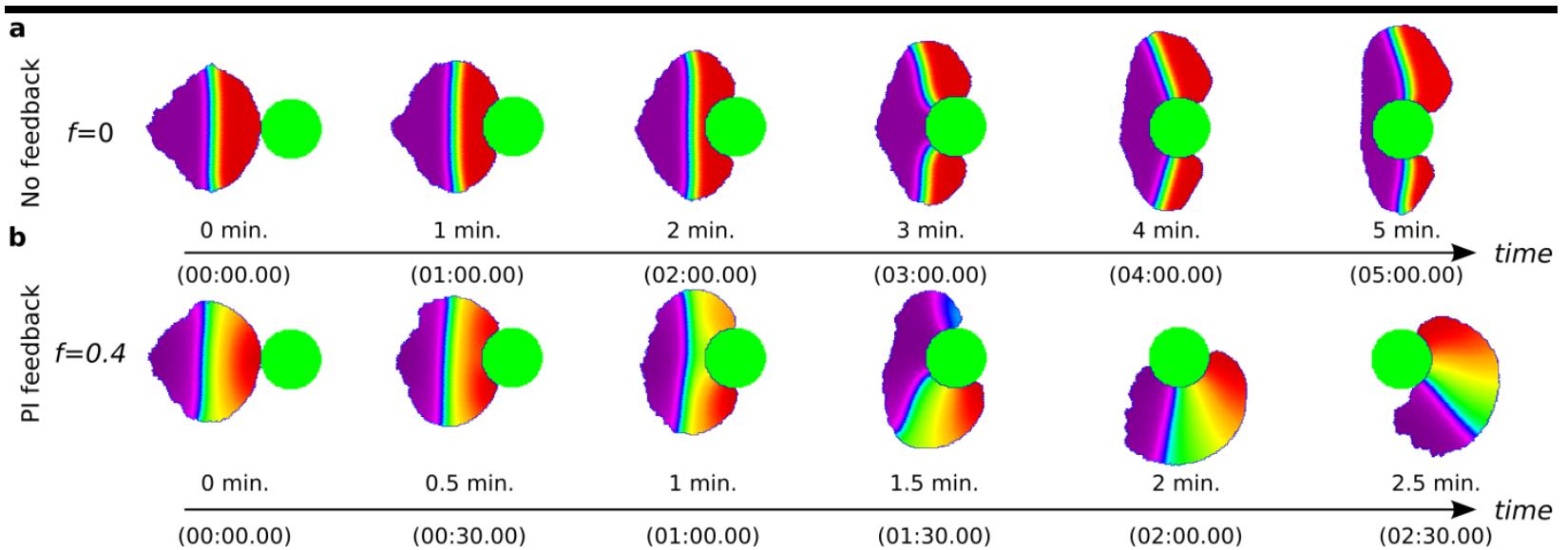
polarisation through noise instead of gradient



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

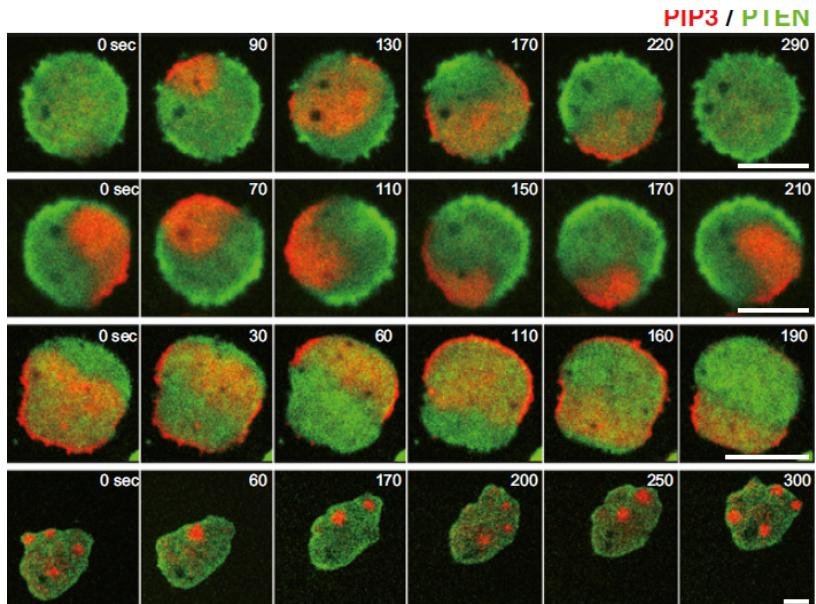
Dictyostelium

two-dimensional excitable waves
govern self-organized morphodynamics
of amoeboid cells

Taniguchia,1, .. Sawai, PNAS 2013

visualised

modeled (excitable medium)
elastic cell



1. Inhibition of actin polymerization or PI3Kinase activity reduces the of 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

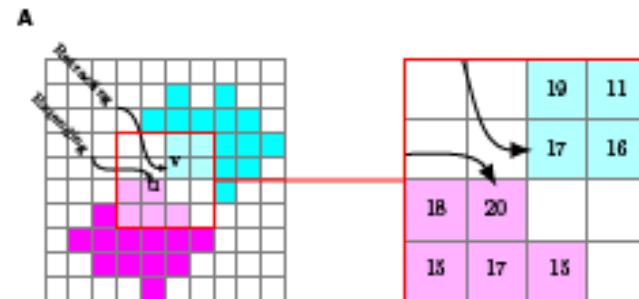
Simple extension of CPM model with periphery constraint

No representation of internal dynamics.

Only memory of previous movement

builds up from spontaneous
membrane fluctuations

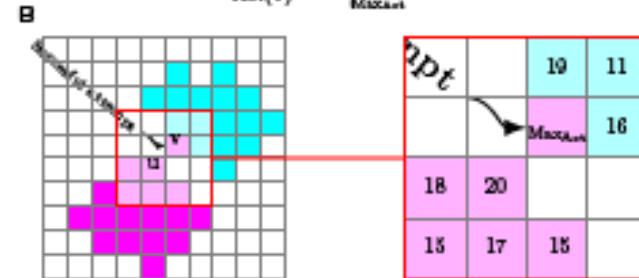
2 params: strength λ
and duration Max



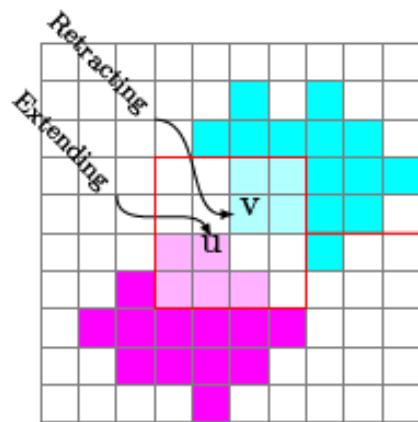
$$\Delta H_{Act}(u \rightarrow v) = \lambda_{Act} (\text{Act}(u) - \text{Act}(v))$$

$$\text{Act}(u) = \frac{\sqrt{15+17+15+18+10}}{\text{Max}_{Act}}$$

$$\text{Act}(v) = \frac{\sqrt{19+16+14+9+1}}{\text{Max}_{Act}}$$



method

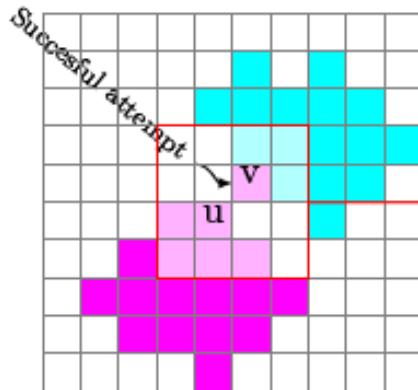
A

		19	11
		17	16
18	20		
15	17	15	

$$\Delta \mathcal{H}_{\text{Act}}(u \rightarrow v) = \frac{\lambda_{\text{Act}}}{\text{Max}_{\text{Act}}} (\text{GM}_{\text{Act}}(u) - \text{GM}_{\text{Act}}(v))$$

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

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

B

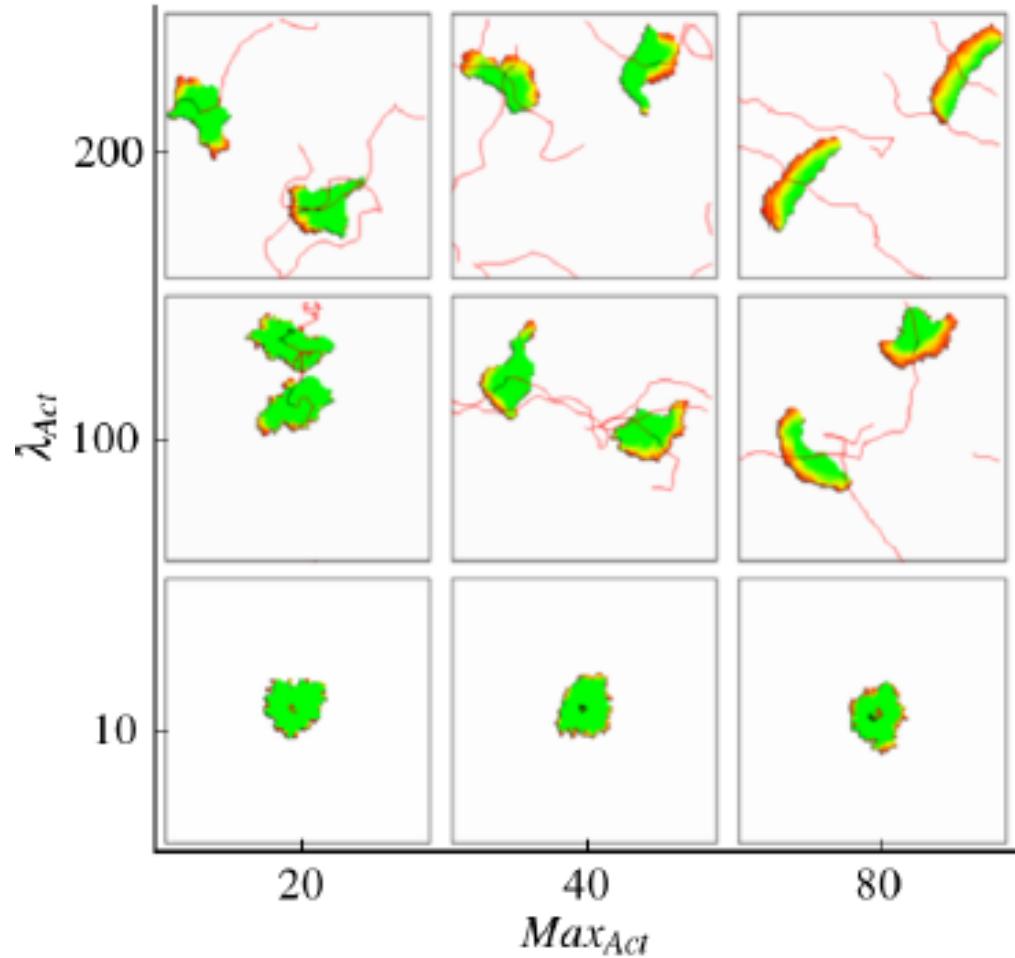
<i>pt</i>		19	11
		20	16
18	20		
15	17	15	

Duration determines mode of movement

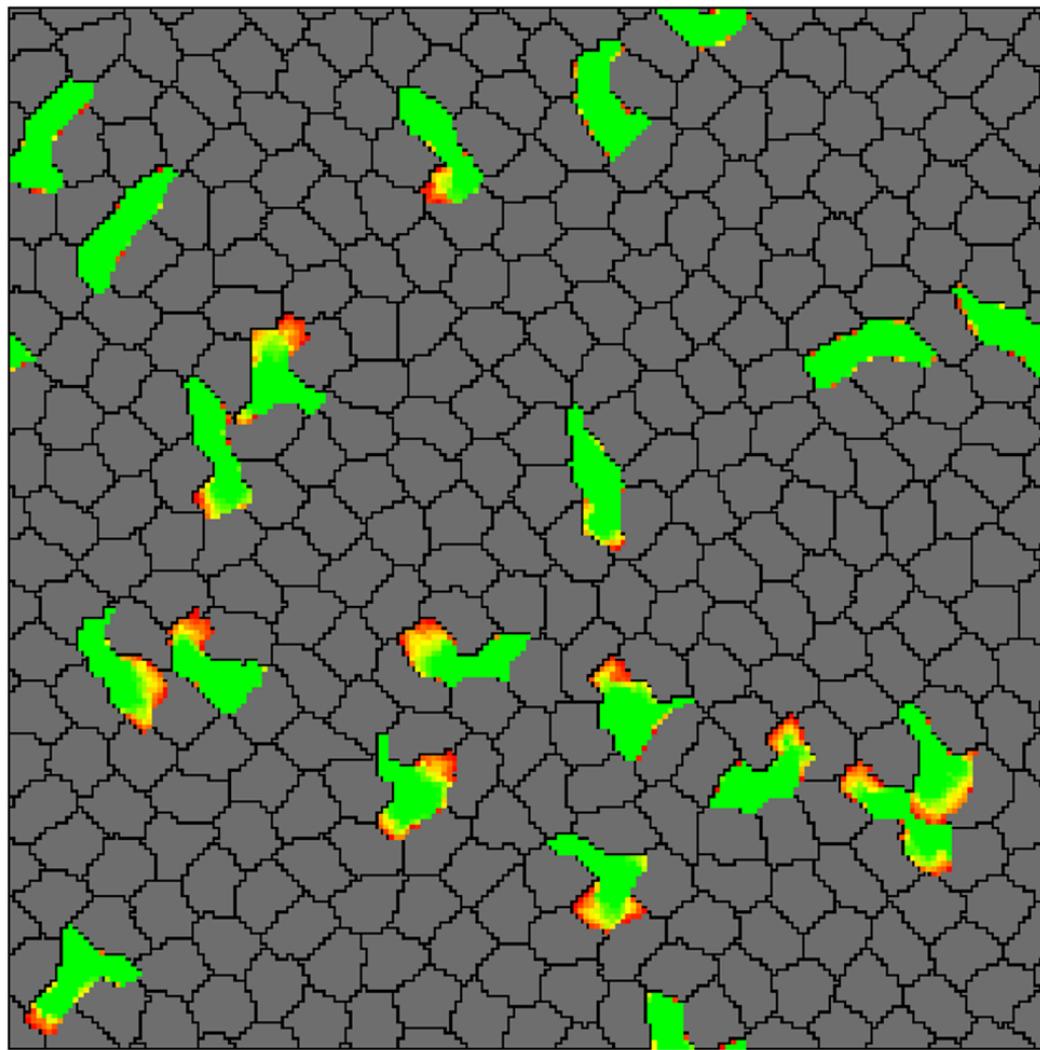
limited duration

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

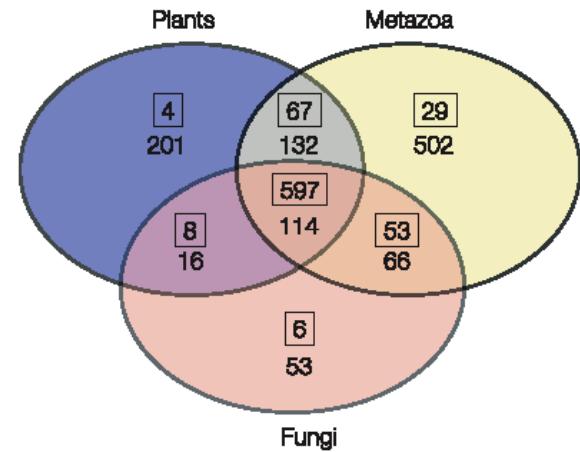
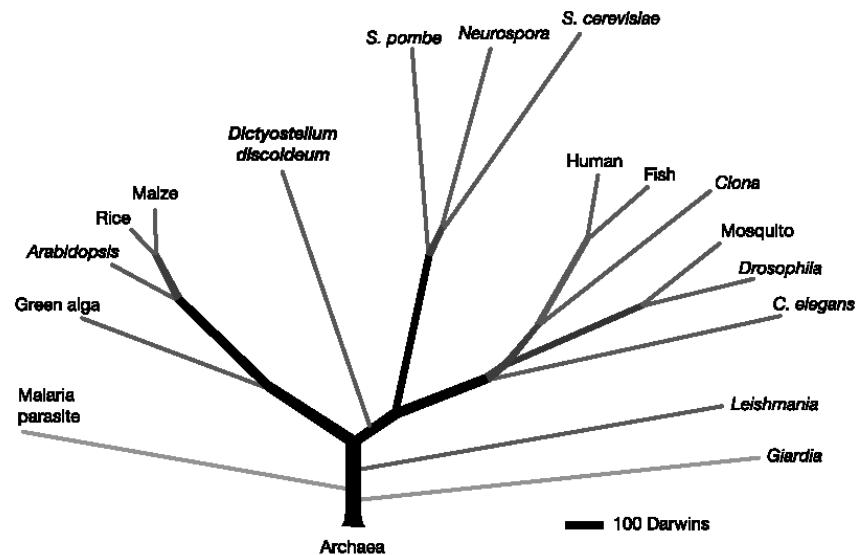
explicit 2-level model for implicit multilevel behavior

Dd morphodynamics:

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

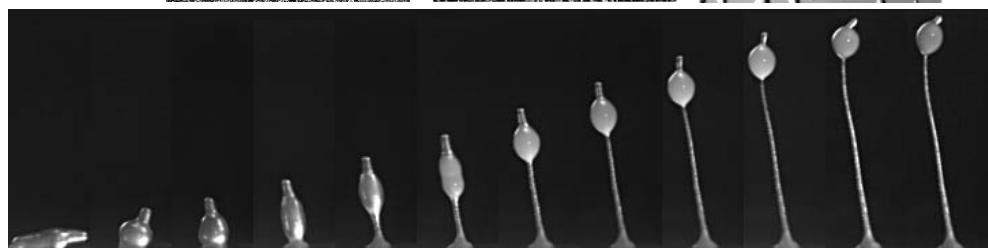
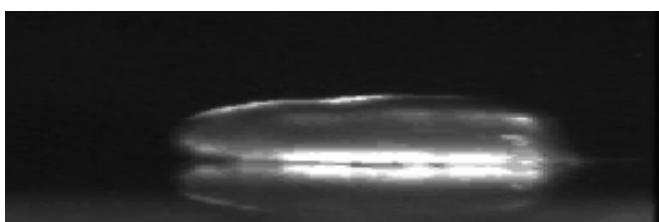
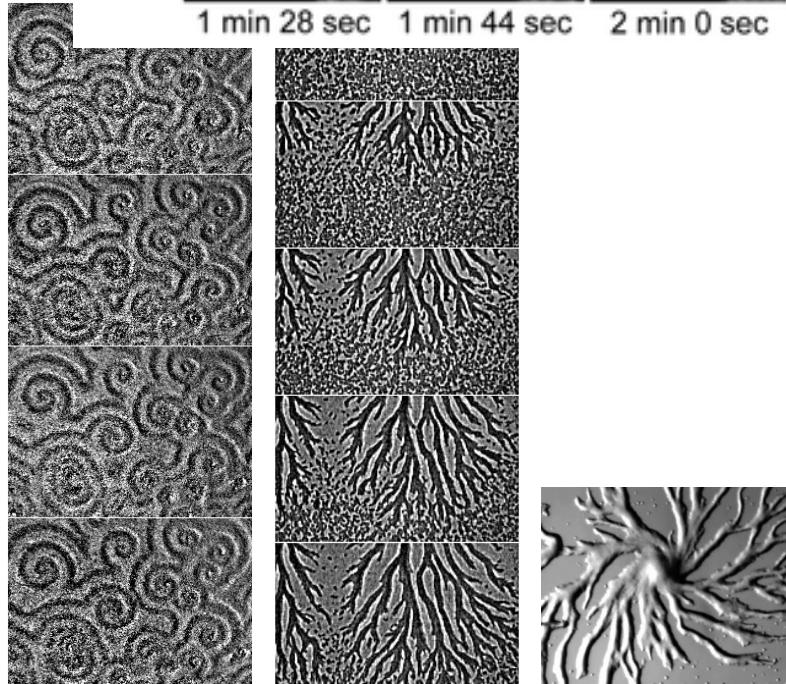
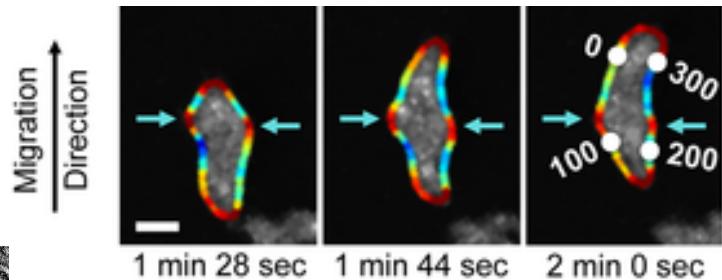
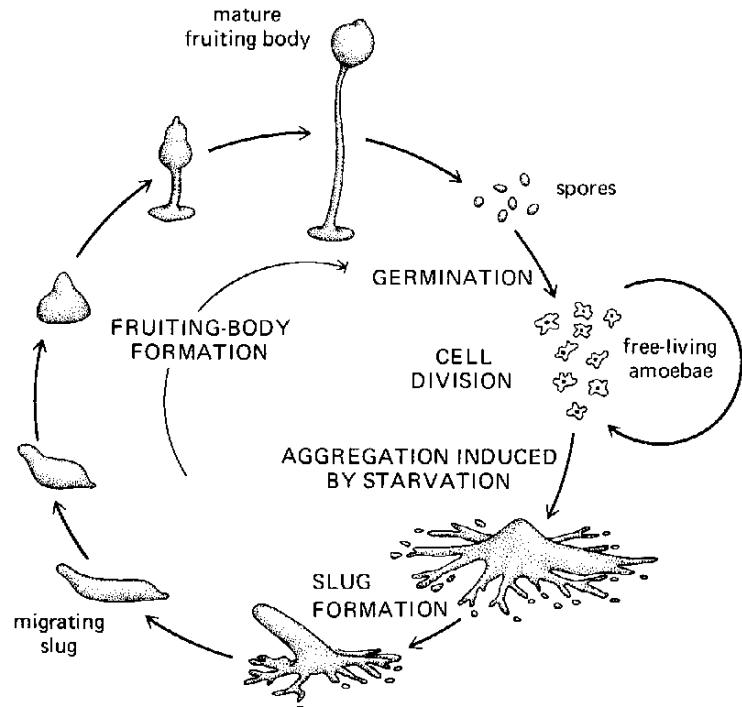
Savill et al 1997, Marée et al 1999a,b, 2001,2002

Dictyostelium phylogeny



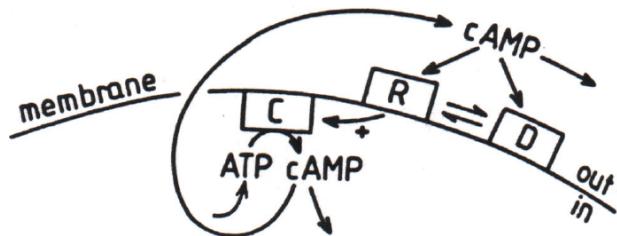
Early offshoot:
shares protein domains otherwise exclusive for
plants, fungi, and animals

Lifecycle *Dictyostelium*



Goldbeter-Martel model of cAMP signalling

Models for cAMP signalling in Dictyostelium



equations

$$\frac{d\rho}{dt} = -f_1(\gamma)\rho + f_2(\gamma)(1-\rho), \quad (1)$$

$$\epsilon' \frac{d\beta}{dt} = s_1 \Phi(\rho, \gamma) - \beta, \quad (2)$$

$$\epsilon \frac{d\gamma}{dt} = s_2 \beta - \gamma, \quad (3)$$

and

$$f_1(\gamma) = \frac{1 + \kappa\gamma}{1 + \gamma}, \quad f_2(\gamma) = \frac{L_1 + \kappa L_2 c\gamma}{1 + c\gamma},$$

$$\Phi(\rho, \gamma) = \frac{\lambda_1 + Y^2}{\lambda_2 + Y^2}, \quad Y = \frac{\rho\gamma}{1 + \gamma}.$$

where

ρ = fraction of receptor in active state,

β = [cAMP]_{intracellular}/ K_R ,

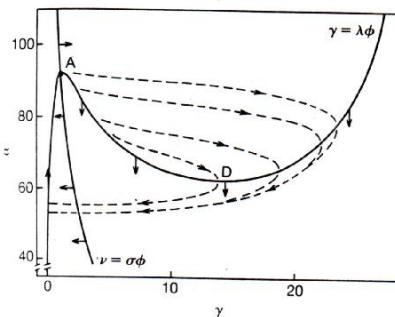
γ = [cAMP]_{extracellular}/ K_R ,

$t = k_1 \times$ time,

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

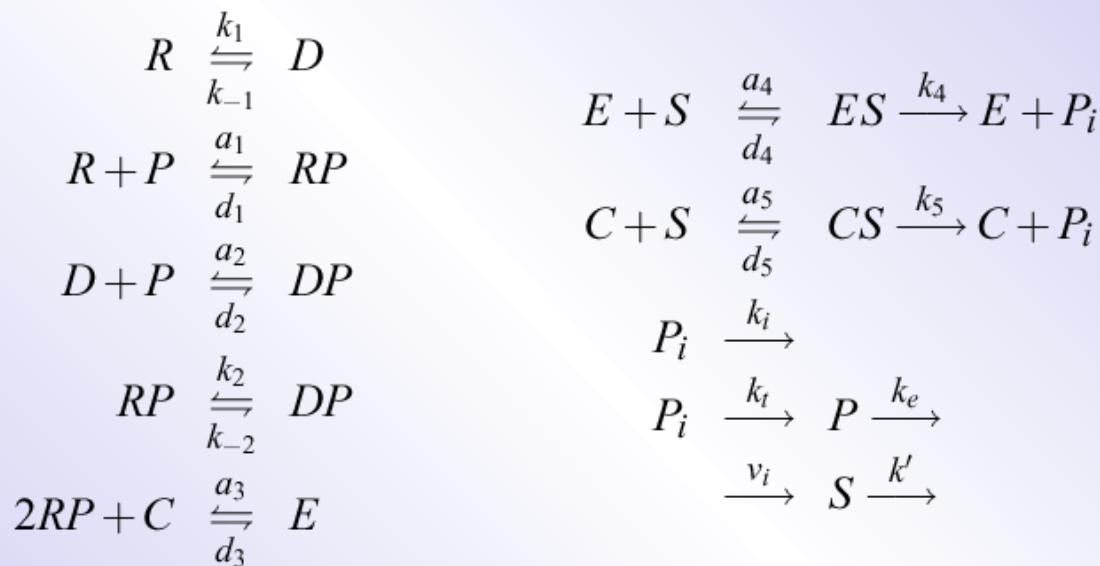
Parameter set A in table II was used by Martiel and Goldbeter [16] to model autonomous oscillations of cAMP in stirred suspensions of *Dictyostelium* cells. The numerical solution of the

5.3 Relay and oscillations



chemical reactions Goldbeter model

MARTIEL & GOLDBETER, 1987 (cont'd)



Parameter estimates of Goldbeter-model (Tyson 1989)

J.J. Tyson et al./Spiral waves of cyclic AMP

Table II
Model parameters.

Name	Definition	Values used in calculations*				
		Set A	Set B	Set C	Set D	Set E
L_1	k_{-1}/k_1	10	=	=	=	=
L_2	k_{-2}/k_2	0.005	0.005	0.005	0.005	0.0005
κ	k_2/k_1	18.5	=	=	=	=
c	K_R/K_D	10	10	10	10	45
α	$[ATP]/K_m$	3	=	=	=	=
λ_1	$\left(\frac{V_m/K_m}{V_m/K_m} \right) \left(\frac{K_E}{R_T^2} \right)$	10^{-4}	10^{-3}	10^{-3}	10^{-3}	6.7×10^{-4}
λ_2	$\left(\frac{1 + \alpha K_m/K_m}{1 + \alpha} \right) \left(\frac{K_E}{R_T^2} \right)$	0.26	2.4	2.4	2.4	1.0
s_1	$\left(\frac{V_m/K_R}{k_1 + k_1} \right) \left(\frac{\alpha}{1 + \alpha} \right)$	690	950	950	360	80
s_2	$k_1/k_e h$	0.033	0.05	0.05	0.13	0.35
s	$s_1 s_2$	23	47	47	47	28
ϵ'	$k_1/(k_1 + k_1)$	0.014	0.019	0.019	0.005	0.01
ϵ	k_1/k_e	0.0067	0.01	0.01	0.01	0.024
Time-scale	$1/k_1$	28	28	8.3	28	17
Space-scale	$(k_e D)^{1/2}/k_1$	10	8.2	4.5	8.2	4.1

*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).

Name	Description	Experimental range*	Values used in calculations**				
			Set A	Set B	Set C	Set D	Set E
R_T	Total receptor concentration	1.5×10^{-9} - 3×10^{-9} M	3×10^{-8}	=	=	=	=
K_R	Dissoc. const.	10^{-7} - 10^{-9} M	10^{-7}	10^{-7}	10^{-7}	10^{-7}	9×10^{-8}
K_D	Dissoc. const.	3×10^{-9} - 9×10^{-9} M	10^{-8}	10^{-8}	10^{-8}	10^{-8}	2×10^{-9}
k_1	Rate const.	0.012 min^{-1}	0.036	0.036	0.12	0.036	0.06
k_{-1}	Rate const.	0.104 min^{-1}	0.36	0.36	1.2	0.36	0.6
k_2	Rate const.	0.22 min^{-1}	0.666	0.666	2.22	0.666	1.1
k_{-2}	Rate const.	0.055 min^{-1}	0.0033	0.0033	0.011	0.0033	5×10^{-4}
K_E	Dissoc. const.	(NA, M^2)	9×10^{-16}	9×10^{-15}	9×10^{-15}	9×10^{-15}	3.6×10^{-15}
K_m	Michaelis const.	2×10^{-5} - 5×10^{-6} M	4×10^{-6}	=	=	=	=
V_m/K_m	Apparent rate const.	0.05 - 1.4 min^{-1}	0.6	0.57	2	0.86	0.16
K_m'	Michaelis const.	(NA, M)	4×10^{-2}	=	=	=	=
V_m/K_m'	Apparent rate const.	(NA, min^{-1})	6×10^{-5}	6×10^{-5}	2.1×10^{-4}	8.6×10^{-5}	2.7×10^{-5}
k_1	Rate const.	1.7 min^{-1}	1.7	1.0	3.3	1.7	1.7
k_1	Transport coeff.	0.3 - 0.9 min^{-1}	0.9	0.9	3.0	5.5	4.3
k_c	Rate const.	2.5 - 12.5 min^{-1}	5.4	3.6	12	3.6	2.5
h	Ratio of extracellular to intracellular volumes.	5-100	5	=	=	=	=
D	Diffusion coeff.***	$0.024 \text{ mm}^2 \text{ min}^{-1}$	0.024	=	=	=	=

*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.

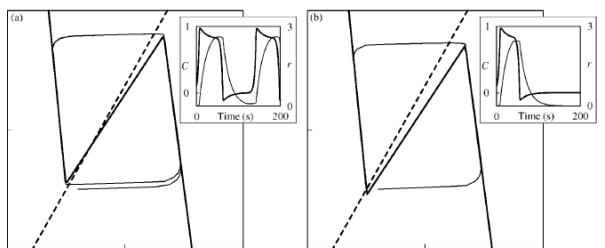
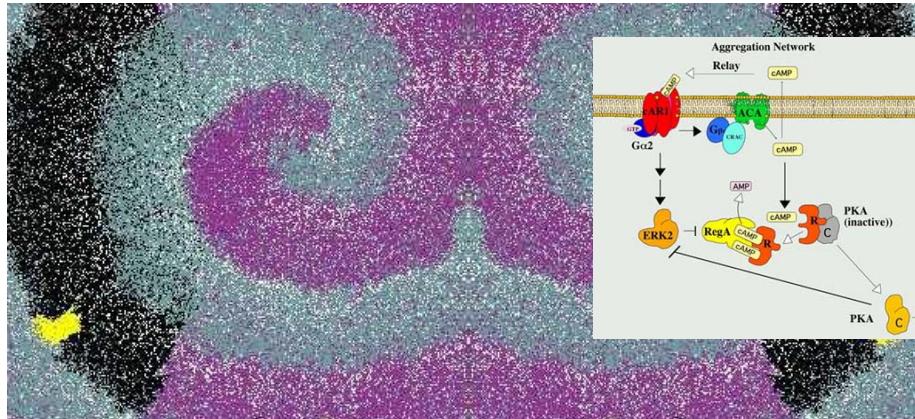
Set C: used in this paper to calculate spiral waves in the full three-component model.

Sets D and E: used in this paper to calculate spiral waves in the two-component model.

***Dworkin and Keller [6].

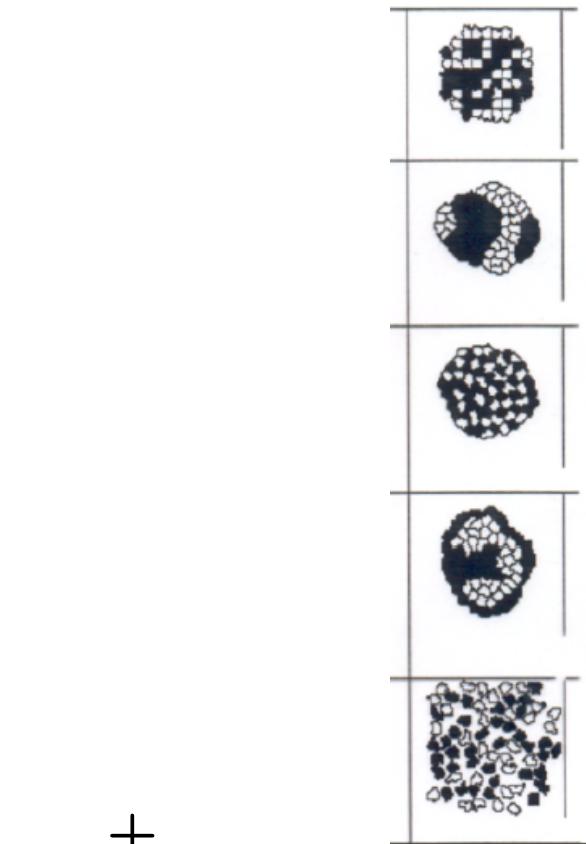
simplify dynamics - add cells:

Dd life cycle by excitable medium and differential adhesion



$$\left. \begin{aligned} \frac{\partial c}{\partial t} &= D_c \Delta c - f(c) - r \\ \frac{\partial r}{\partial t} &= v(c)(kc - r) \end{aligned} \right\} \text{inside the amoebae}$$

$$\left. \begin{aligned} \frac{\partial c}{\partial t} &= D_c \Delta c - d_c(c - c_0) \end{aligned} \right\} \text{outside the amoebae}$$

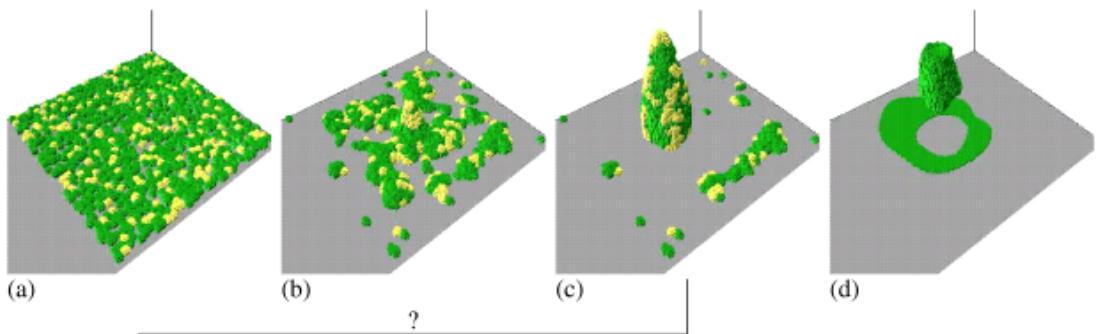


excitable medium

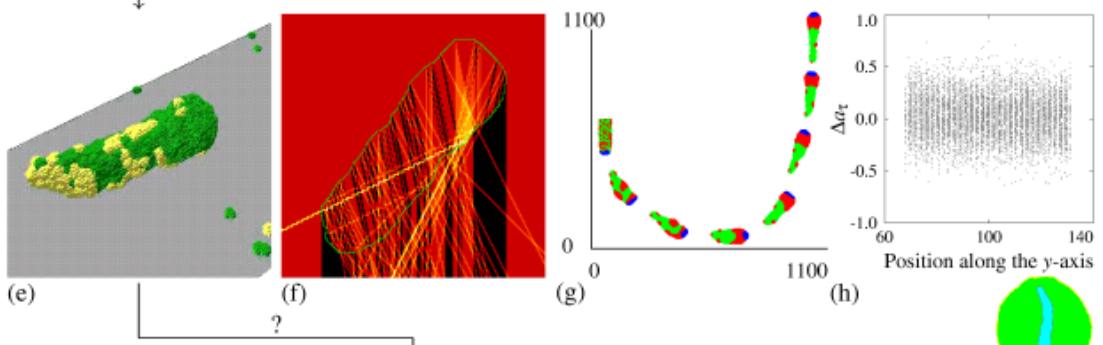
differential adhesion

Lifecycle of Dd by chemotaxis and adhesion

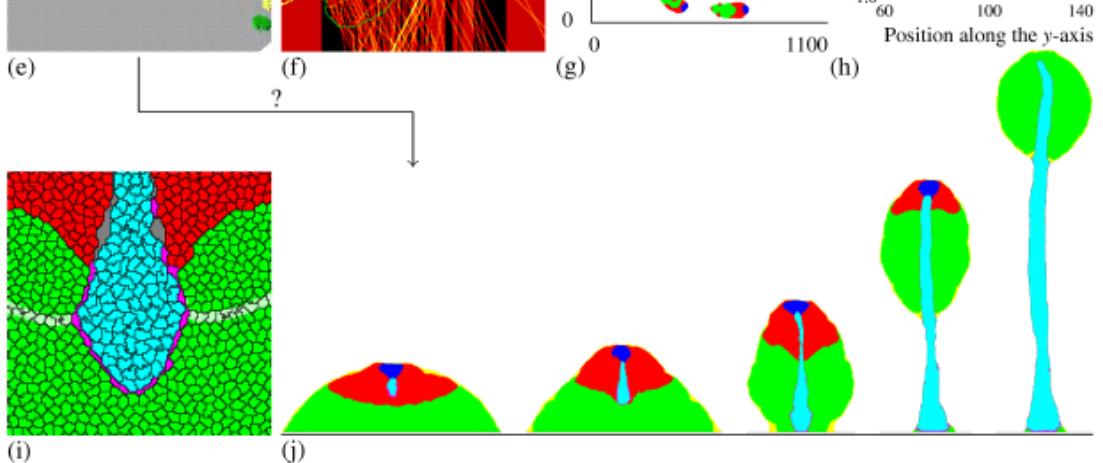
aggregation streams



orientation



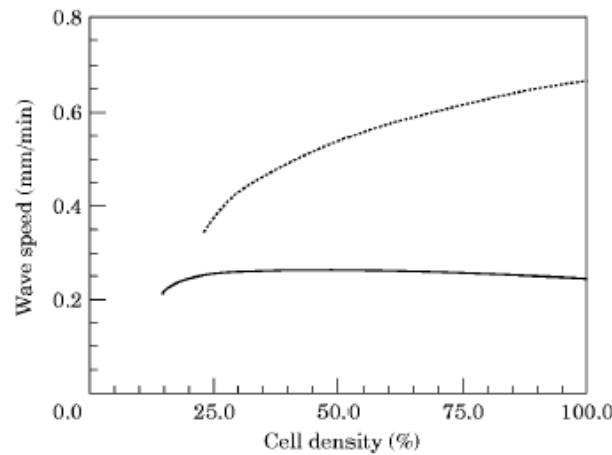
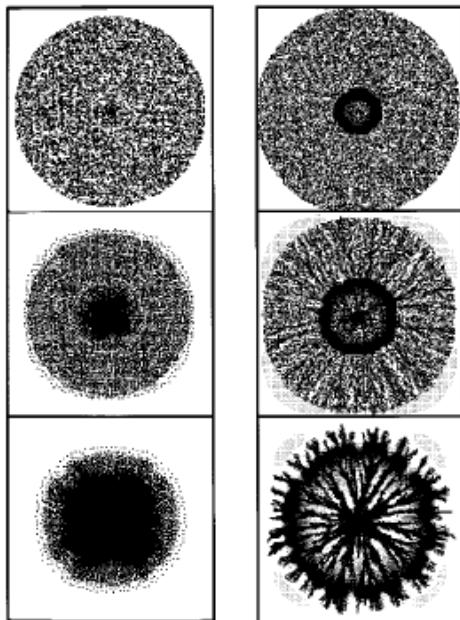
culmination



Dd morphodynamics: multiple causes and multiple effects

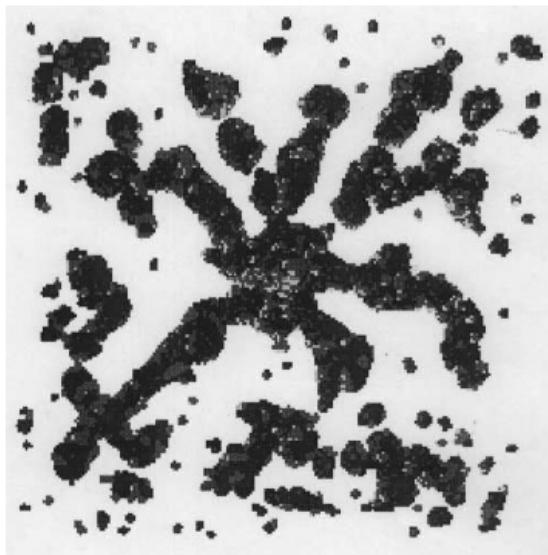
Aggregation	streams if wavepropagation dep on density faster movement in streams
Mount/slug slug	cell sorting by differential adhesion AND chemotaxis slug shape attractor of energy minimisation vs inward movement (wave shape) taxis (thermo- photo-taxis) via NH3 effect on excitability slug shape and wave 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)



Van Oss, C., Panfilov, A.V., Hogeweg, P., Siegert, F. and C.J. Weijer (1996) JTB
181:203-213

Why streams?



(a)

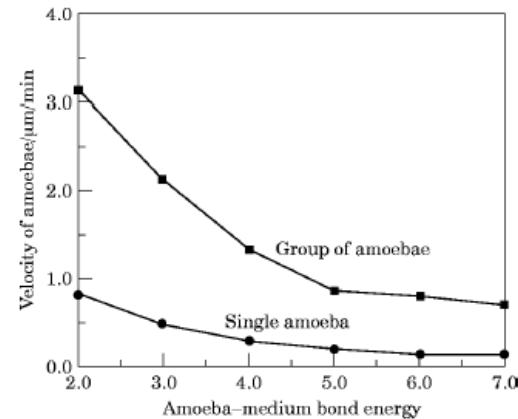
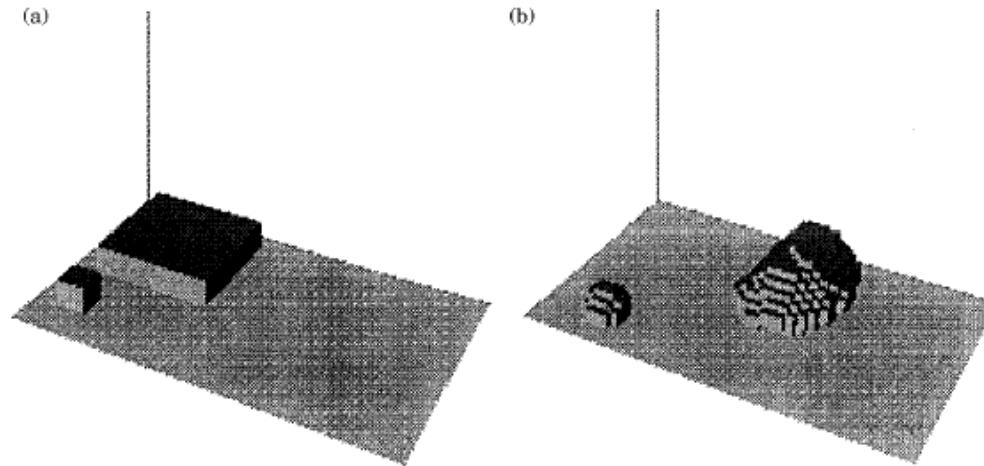
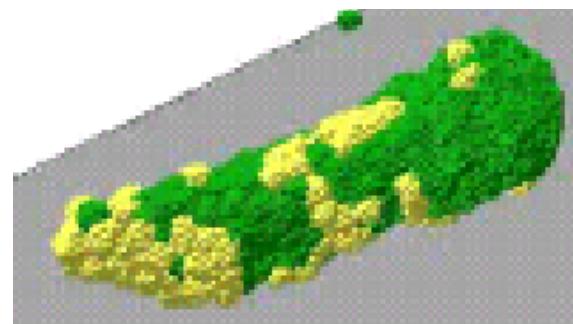
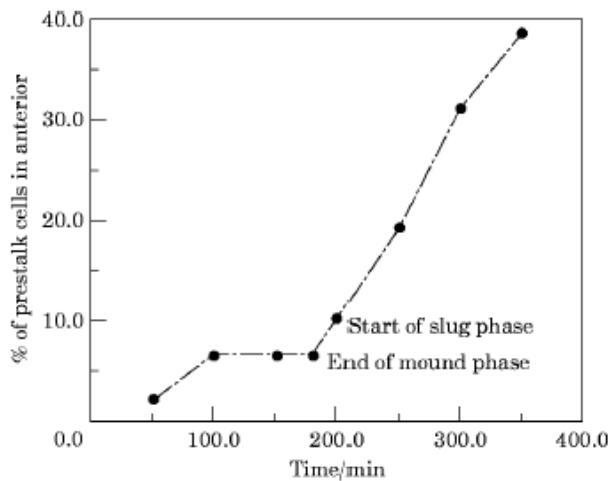
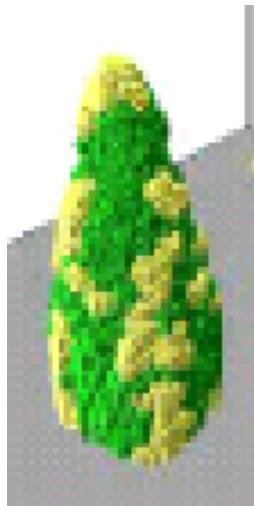


FIG. 4. Plot of velocity (each point averaged over 10 simulations) against the cell–medium bond energy for prespore amoebae. Given that the amoebae adhere to each other the group will always move faster than a single amoeba. Parameters are as described in the legend to Fig. 1. ■, Group of amoebae; ●,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

Cell Sorting much faster in moving slug than in fixed mount WHY?

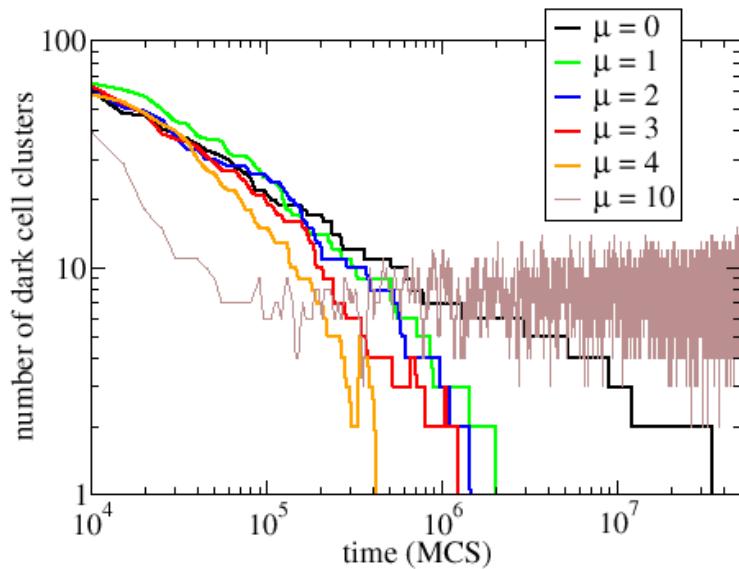


Prestalk cells (Yellow) stronger adhesion Prespore cells (Green)
 $J_{yy} < J_{gg} < J_{yg}$

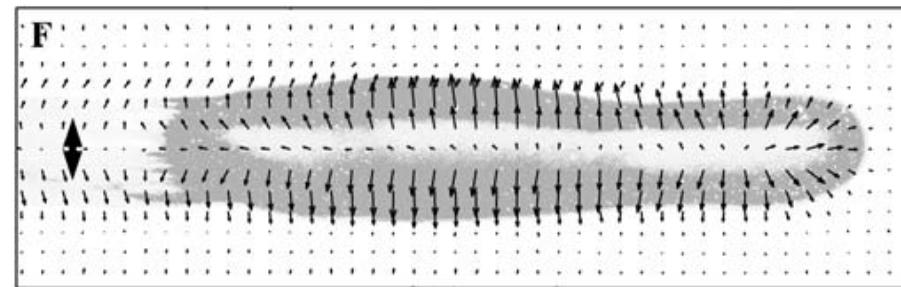
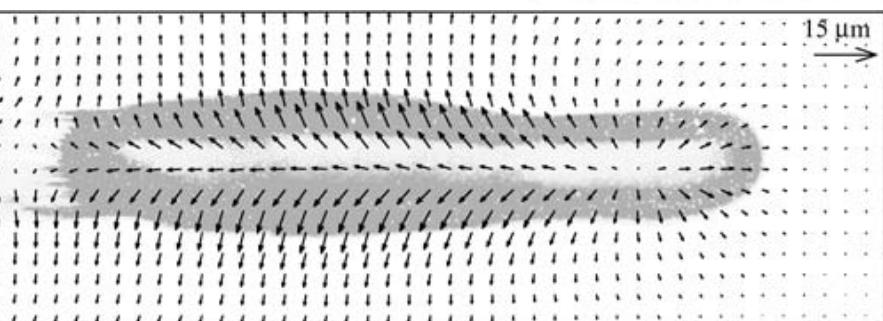
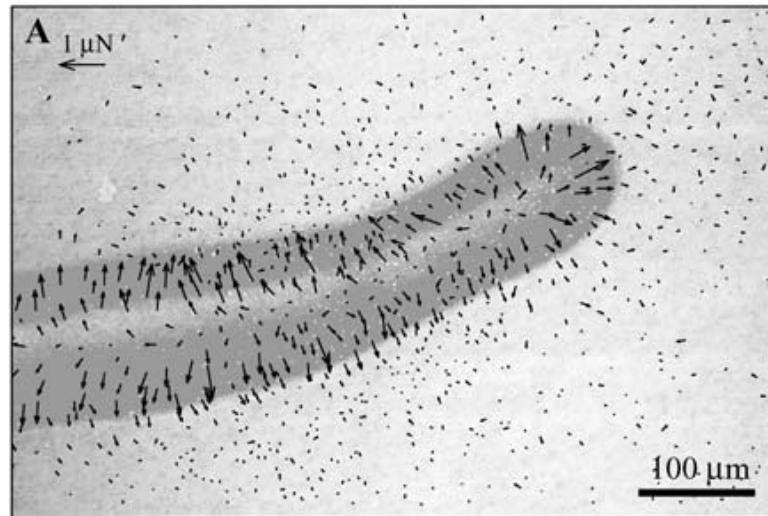
Same chemotactic response

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?

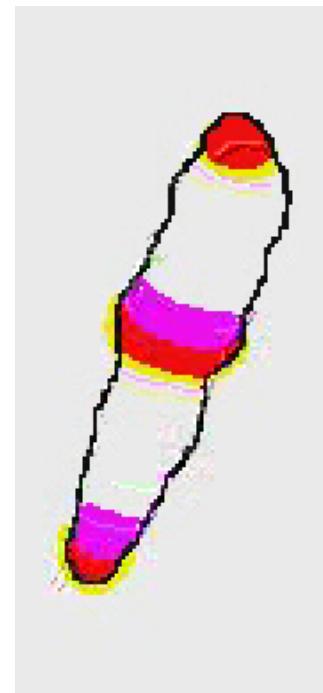
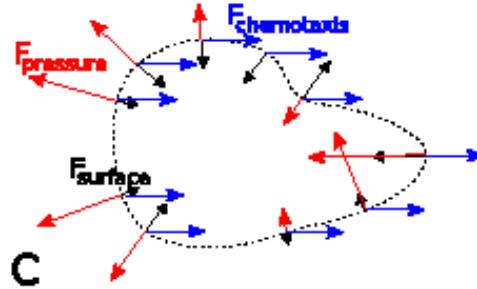
Note:

forces are (emergent) observables
instead of model ingredients!

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

Perpendicular forces expected because:

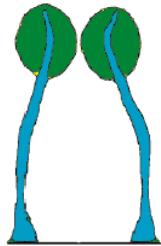
- wave shape (most concave in middle of slug)
- sideward push because of pressure gradient



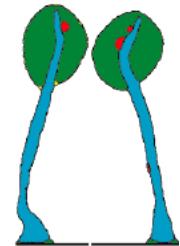
b

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?

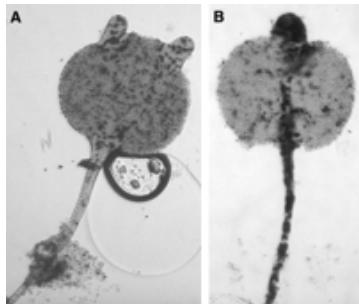
Evolution of cooperation and why cheaters do not take over single gene greenbeard effect

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



Queller et al. Science 299:105-106 (2003)

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)