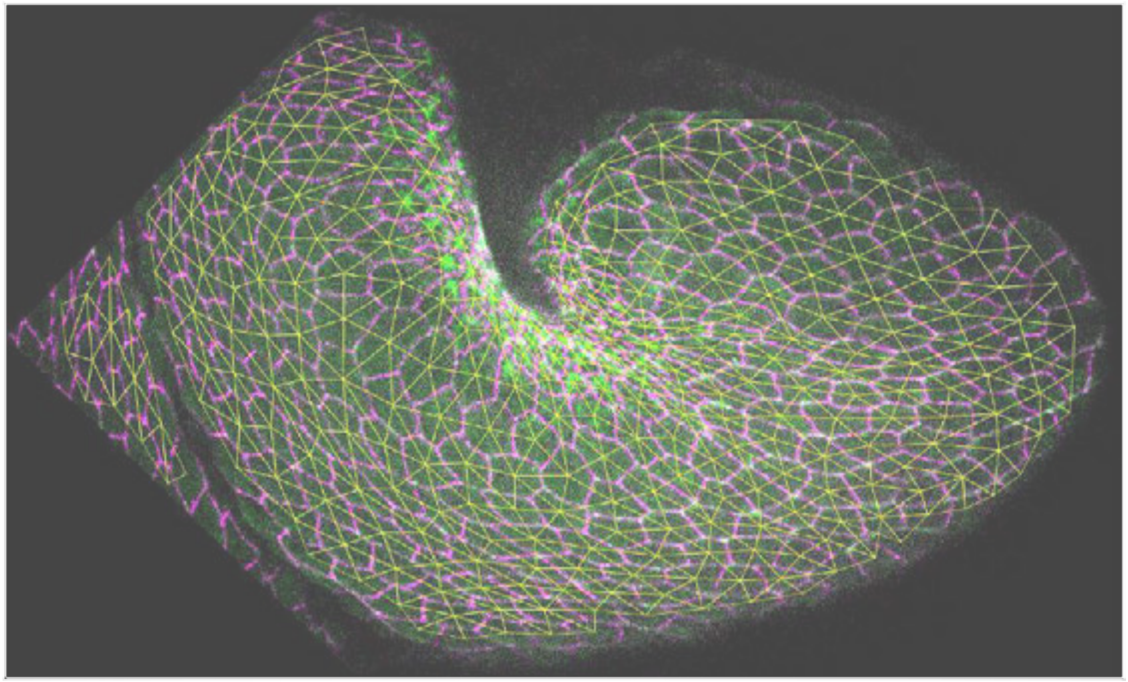
Morphogenesis: space, time, information



Course 2: Spatial and temporal instabilities

Thomas Lecuit
chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

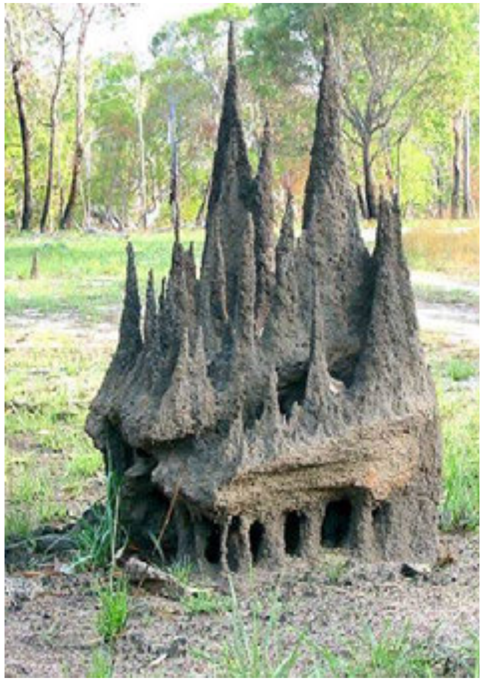
Biological organisation in space and time

- Two modalities of information flow during morphogenesis

Program

- hierarchical, indirect interactions
- modular
- long and short range interactions
- high-wired
- multiple parameters

Self-organization



- local and direct interactions
- few rules and parameters

Mechano-chemical information

Biochemistry ⇄ Mechanics

Biochemistry

- Sets mechanical parameters (stiffness: actin crosslinkers, viscosity: turnover)
- Regulates stresses (eg. activation of motors)

Mechanics

- affects transport of molecules: advection by flow
- elicits mechanotransduction: stress/strain dependent effect
- affects geometry of environment: polarity

Time scale
Length scale

- **diffusion:** $\lambda = (D.\tau)^{1/2}$
- **transport:** $\ell = v.\tau$

D: diffusion coefficient
v: velocity of motor + processivity

- **propagation of deformation:** $\tau = \eta / E$
- **hydrodynamic length:** $\ell = (\eta / \gamma)^{1/2}$

E: stiffness
η : viscosity
γ : friction

Information
(genetics/biochemistry)
↓
Mechanics

Information
(mechano-chemistry)

Self-organisation with mechano-chemical information

Information
(genetics/biochemistry)

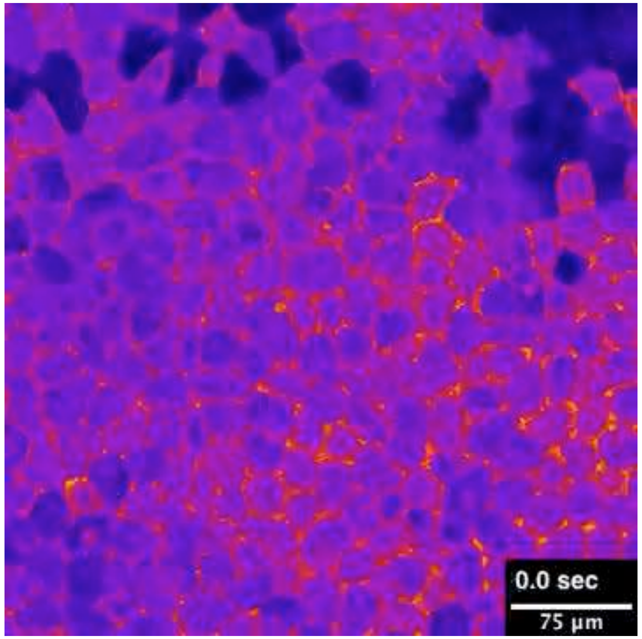
↓

Mechanics

Information
(mechano-chemistry)

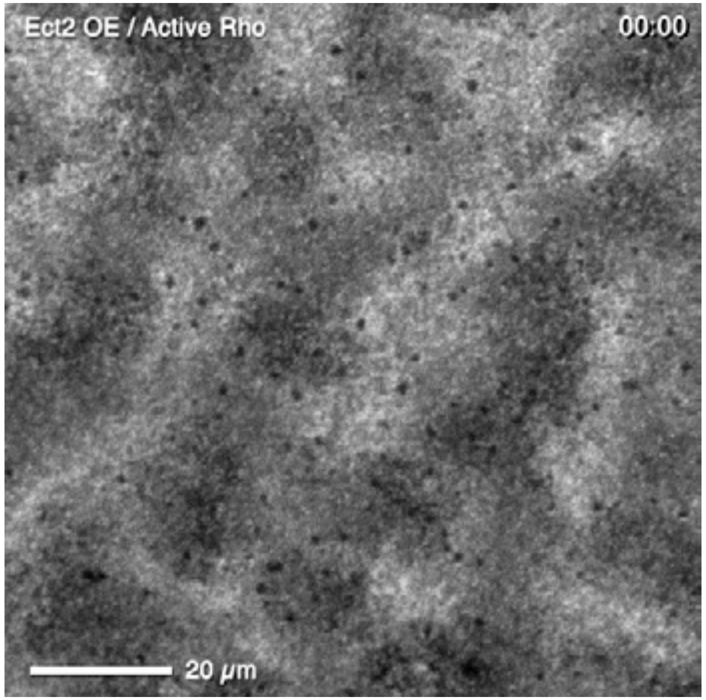
What underlies the spatial and temporal organisation of cellular activity ?

Xenopus



Calcium imaging
• Image by Nicholas Davenport, Graduate Student, Cellular and Molecular Biology | Confocal Microscope

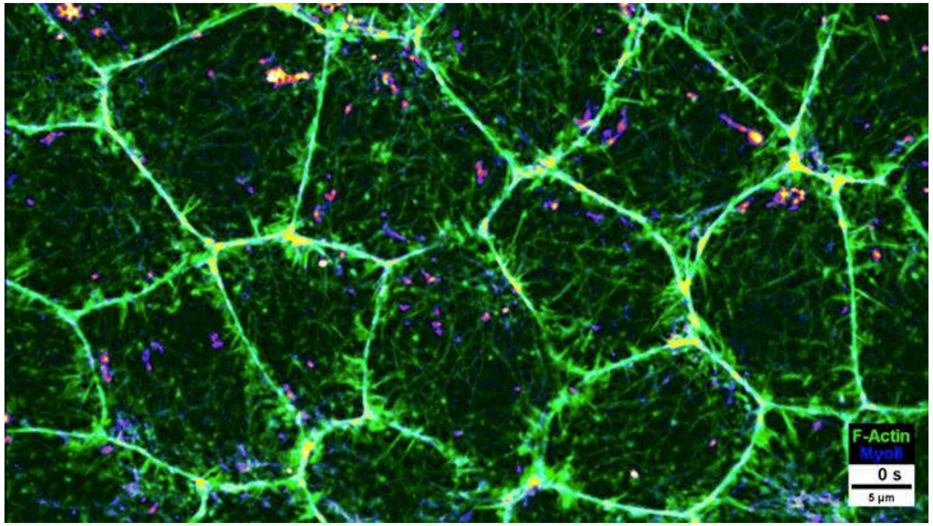
Sea Urchin/Starfish



W. Bement et al *Nature Cell Biology* 2015

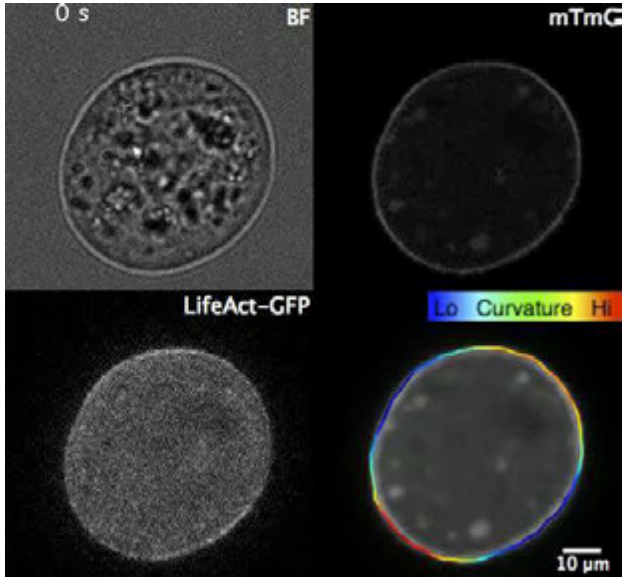
What underlies the spatial and temporal organisation of cellular activity ?

Drosophila



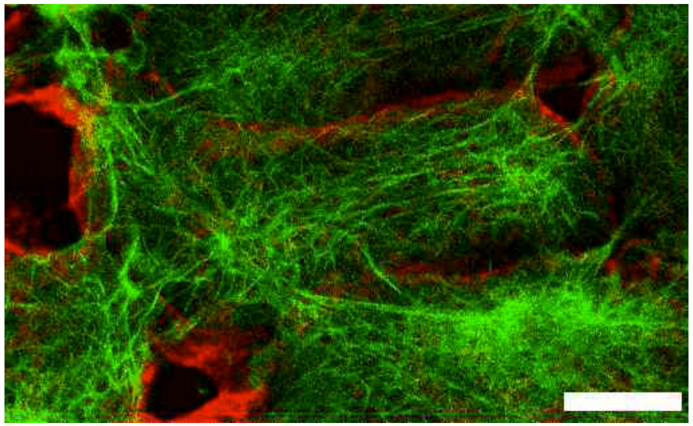
B. Dehapiot and T. Lecuit, *unpublished*

Mouse



JL Maître, R. Niwayama, H. Turlier F. Nédélec and T. Hiragii. *Nature Cell Biology* (2015) 17:849-855

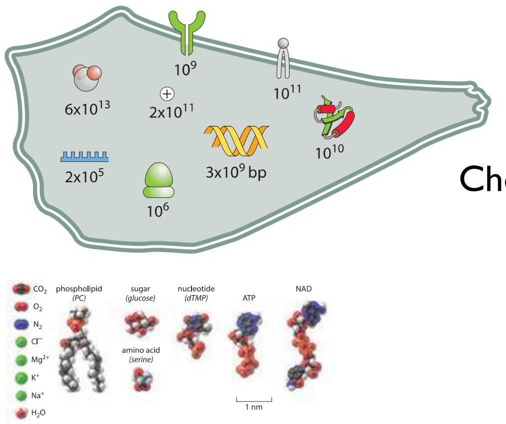
Xenopus



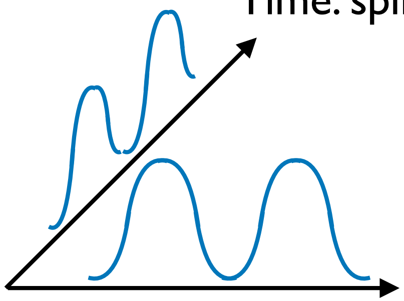
HY. Kim and LA. Davidson, *Journal of Cell Science (*2011) 124:635-646

Self-organisation of biological patterns: Time and Space

Chemical and Mechanical Information



Chemistry

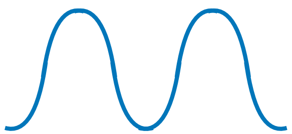


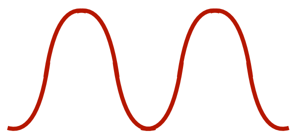
Time: spikes, oscillations

Space: Turing instabilities

self-organization in nonequilibrium chemical systems

Chemistry → Mechanics





self-organization in nonequilibrium mechano-chemical systems

Chemistry → Mechanics (Mechanics → Chemistry)

1. Introduction - Program and Self-Organisation

2. Chemical Instabilities
    21. Spatial instabilities - Turing patterns
    22. Temporal instabilities - Excitability
    23. Spatial-temporal instabilities: waves

3. Mechanical instabilities
    31. Cellular aggregates: viscoelastic model
    32. Active gel: hydrodynamic and viscoelastic models

4. Mechano-chemical Instabilities
    41. Mechano-chemical coupling: actomyosin dynamics
    42. Actin based trigger waves

5. Developmental significance: impact on cellular and tissue morphogenesis

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Self-organisation of biological patterns: chemistry and mechanics.

Alan Turing
(1912-1954)

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

In the continuous form of the theory the concentrations and diffusibilities of each substance have to be given at each point. In determining the changes of state one should take into account

(i) The changes of position and velocity as given by Newton's laws of motion.
(ii) The stresses as given by the elasticities and motions, also taking into account the osmotic pressures as given from the chemical data.
(iii) The chemical reactions.
(iv) The diffusion of the chemical substances. The region in which this diffusion is possible is given from the mechanical data.

One cannot at present hope to make any progress with the understanding of such systems except in very simplified cases. The interdependence of the chemical and mechanical data adds enormously to the difficulty, and attention will therefore be confined, so far as is possible, to cases where these can be separated. The mathematics of elastic solids is a well-developed subject, and has often been applied to biological systems. In this paper it is proposed to give attention rather to cases where the mechanical aspect can be ignored and the chemical aspect is the most significant. These cases promise greater interest, for the characteristic action of the genes themselves is presumably chemical.

II. Chemical Instabilities

1. Reaction — Diffusion (chemical) systems

self-organization in nonequilibrium chemical systems

$$\partial_t u = D\partial_x^2 u + R(u)$$

Diffusion Reaction

1-component

$$\begin{pmatrix} \partial_t u \\ \partial_t v \end{pmatrix} = \begin{pmatrix} D_u & 0 \\ 0 & D_v \end{pmatrix} \begin{pmatrix} \partial_{xx} u \\ \partial_{xx} v \end{pmatrix} + \begin{pmatrix} F(u,v) \\ G(u,v) \end{pmatrix}$$

Diffusion Reaction

2-components

⋮

n-components

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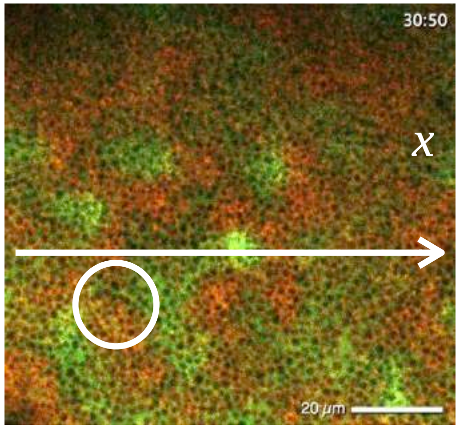
II. Chemical Instabilities

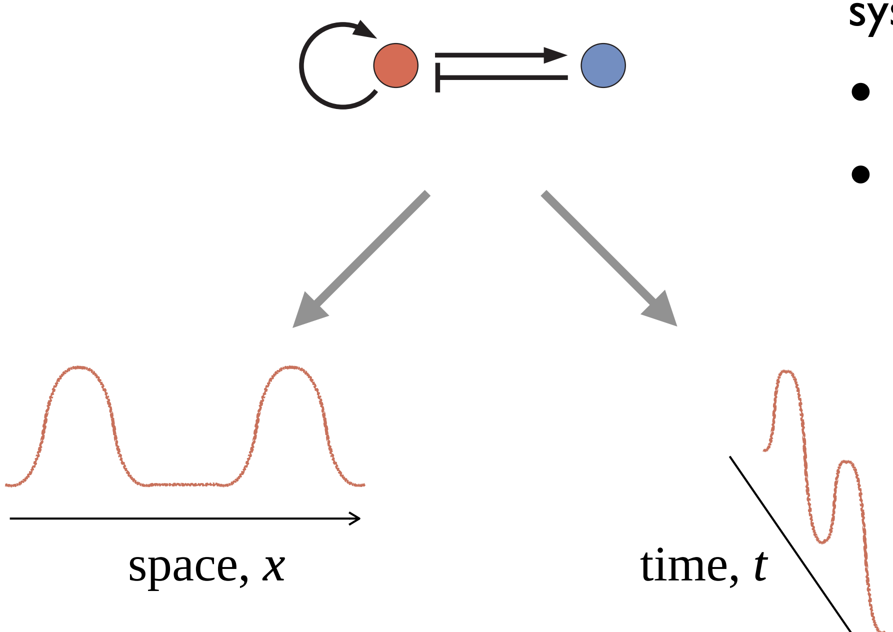
1. Reaction — Diffusion systems
Self-organisation of spatial and temporal patterns

self-organization in nonequilibrium chemical systems:

- activator auto-activation
- inhibitor induction



W. Bement, et al and George von Dassow. *Nature Cell Biology.* 2015

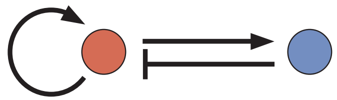


✓ Diffusion

✓ Reaction speed

21. Spatial patterns: Turing instabilities

self-organization in nonequilibrium chemical systems



$$\begin{pmatrix} \partial_t u \\ \partial_t v \end{pmatrix} = \begin{pmatrix} D_u & 0 \\ 0 & D_v \end{pmatrix} \begin{pmatrix} \partial_{xx} u \\ \partial_{xx} v \end{pmatrix} + \begin{pmatrix} F(u,v) \\ G(u,v) \end{pmatrix}$$

2-component

Diffusion   Reaction

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✓ Turing Instabilities (role of diffusion)

$$Du << Dv$$

21. Spatial patterns: Turing instabilities

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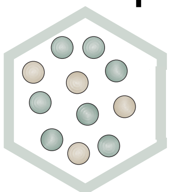
1 Cell - 2 species (activator and inhibitor)



X stimulates X and Y
Y inhibits both

$$\frac{dX}{dt} = 5X - 6Y + 1$$
$$\frac{dY}{dt} = 6X - 7Y + 1$$

$X = Y = 1$
unique steady state

linear stability analysis: deviation from steady state $X = 1 + x$ and $Y = 1 + y$

$$\frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 5 & -6 \\ 6 & -7 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}$$

solutions $x(t) = x_0 e^{\lambda t}$, $y(t) = y_0 e^{\lambda t}$

Condition on stability: λ negative

λ is solution of $\det\begin{pmatrix} 5-\lambda & -6 \\ 6 & -7-\lambda \end{pmatrix} = \lambda^2 + 2\lambda + 1 = 0$ so $\lambda = -1$

Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
Physical Biological of the Cell (Garland Science)

21. Spatial patterns: Turing instabilities — Diffusion!

THE CHEMICAL BASIS OF MORPHOGENESIS

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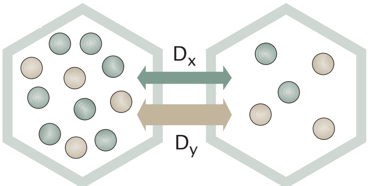
2 Cells - 2 species + diffusion



$$\begin{aligned}\frac{dX_1}{dt} &= 5X_1 - 6Y_1 + 1 + D_X(X_2 - X_1)\\ \frac{dY_1}{dt} &= 6X_1 - 7Y_1 + 1 + D_Y(Y_2 - Y_1)\\ \frac{dX_2}{dt} &= 5X_2 - 6Y_2 + 1 + D_X(X_1 - X_2)\\ \frac{dY_2}{dt} &= 6X_2 - 7Y_2 + 1 + D_Y(Y_1 - Y_2)\,,\end{aligned}$$

$X_1 = Y_1 = X_2 = Y_2 = 1$

unique steady state

but: Diffusion makes the system potentially UNSTABLE if $D_y >> D_x$

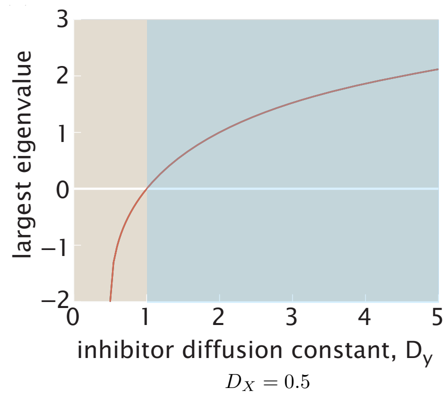
linear stability analysis:

$$\frac{d}{dt}\begin{pmatrix} x_1\\ y_1\\ x_2\\ y_2\end{pmatrix} = \begin{pmatrix} 5-D_X & -6 & D_X & 0\\ 6 & -7-D_Y & 0 & D_Y\\ D_X & 0 & 5-D_X & -6\\ 0 & D_Y & 6 & -7-D_Y\end{pmatrix}\begin{pmatrix} x_1\\ y_1\\ x_2\\ y_2\end{pmatrix}$$

$$x(t) = x_0 e^{\lambda t}$$
$$y(t) = y_0 e^{\lambda t}$$

and λ is eigenvalue of rate matrix

hence: stability depends on D_y relative to D_x



21. Spatial patterns: Turing instabilities — Diffusion!

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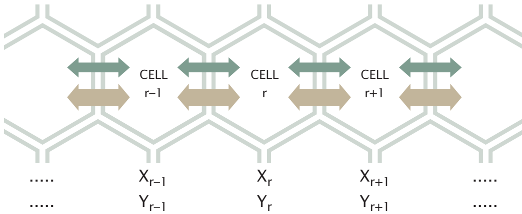
N Cells - 2 species + diffusion



linear stability analysis:

$$(X_r, Y_r) = (h + x_r, k + y_r)$$

$$\frac{dx_r}{dt} = A_1 x_r + B_1 y_r + D_X(x_{r+1} + x_{r-1} - 2x_r)$$
$$\frac{dy_r}{dt} = A_2 x_r + B_2 y_r + D_Y(y_{r+1} + y_{r-1} - 2y_r)\ .$$

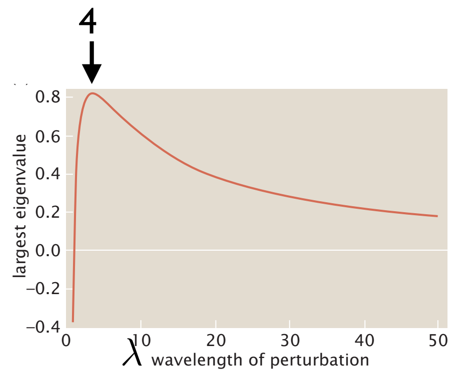
(equation of deviation from steady state)

$$x_r(t) = x(t)\exp\left(i\frac{2\pi r}{\lambda}\right)$$
$$y_r(t) = y(t)\exp\left(i\frac{2\pi r}{\lambda}\right)\ ,$$

λ is wavelength of perturbation

rate matrix (approximation with λ >>1)

$$\mathcal{R} = \begin{pmatrix} A_1 - D_X(2\pi/\lambda)^2 & B_1 \\ A_2 & B_2 - D_Y(2\pi/\lambda)^2 \end{pmatrix}$$



Of all possible perturbations with periodic waves, some will dominate and give rise to spatial patterns

(will have a value of λ with largest eigenvalue of rate matrix)

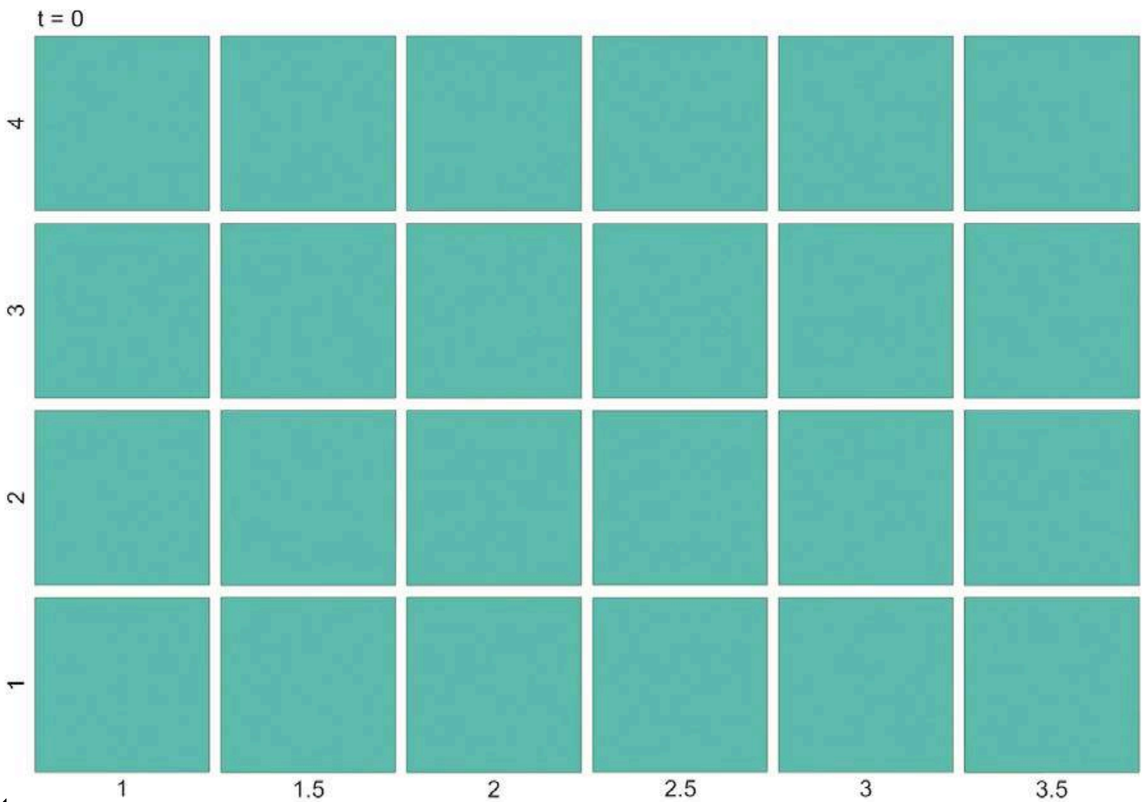
Solutions depend of respective values of Diffusion coefficients

21. Spatial patterns: Turing instabilities — Diffusion!

Standing waves in 2D form spots and stripes

Of all possible perturbations with periodic waves, some will dominate and give rise to spatial patterns

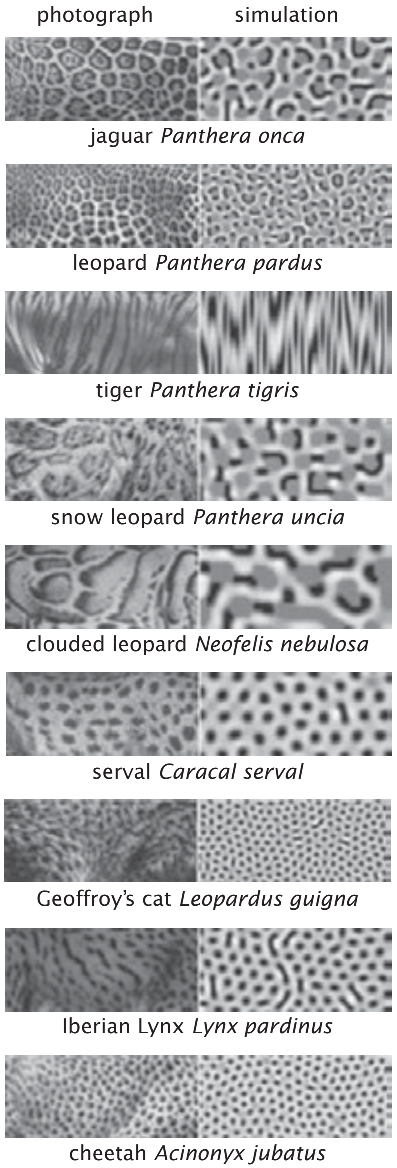
low activator



high activator

21. Spatial patterns: Turing instabilities — Diffusion!

Standing waves in 2D form spots and stripes



Allen WL et al
Proc. R. Soc. B (2011) **278**, 1373–1380

21. Spatial patterns: Local self-enhancement - Global inhibition

A Theory of Biological Pattern Formation

A. Gierer and H. Meinhardt
Max-Planck-Institut für Virusforschung, Tübingen, Germany

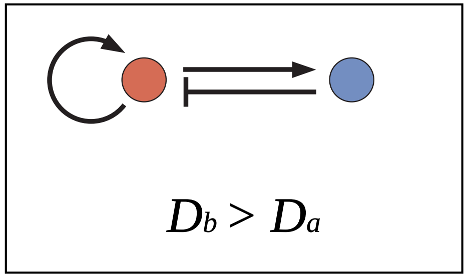
Kybernetik 12, 30—39 (1972)

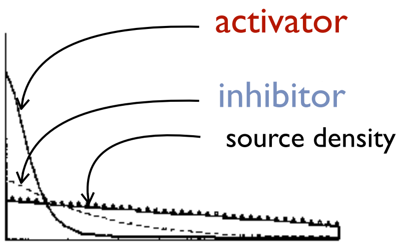
Hans Meinhardt
(1938-2016)

Local Excitation - Global Inhibition model
(activator-inhbitor scheme)

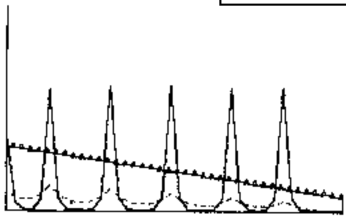
$$\frac{\partial a}{\partial t} = s\left(\frac{a^2}{b} + b_a\right) - r_a a + D_a \frac{\partial^2 a}{\partial x^2}$$

$$\frac{\partial b}{\partial t} = s a^2 - r_b b + D_b \frac{\partial^2 b}{\partial x^2} + b_b$$



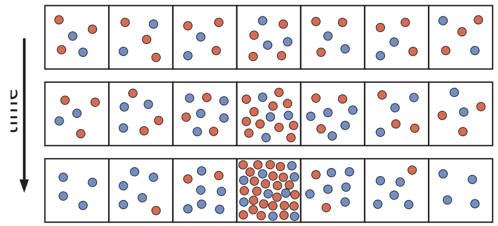


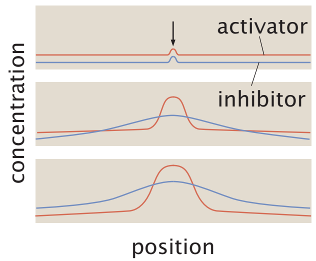
High Diffusion of Inhibitor
✔ Gradient



Lower Diffusion of Inhibitor
(smaller than field size)

✔ Periodic patterns





Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
illustration: Nigel Orme
Physical Biological of the Cell (Garland Science)

21. Spatial patterns: Local self-enhancement - Global inhibition

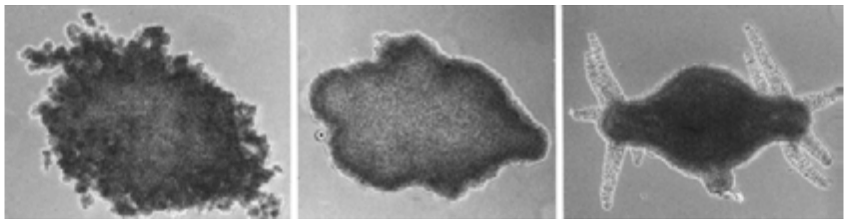
Local Excitation - Global Inhibition model
(activator-inhbitor scheme)

(*i.e.* local instability and global stabilisation)

Hans Meinhardt
(1938-2016)

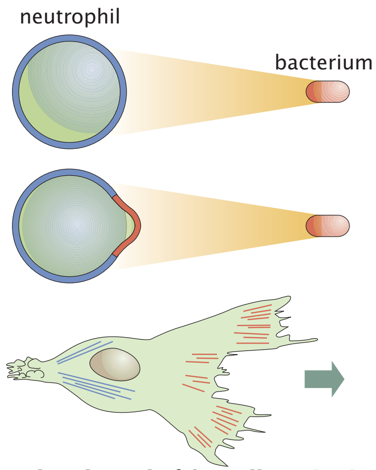
The theory was proposed to explain symmetry breaking at tissue level (morphogenesis) and at cellular level (cell polarisation)

Hydra morphogenesis/regeneration



https://www.eb.tuebingen.mpg.de/emeriti/hans-meinhardt/

Cell polarisation/motility



Physical Biological of the Cell (Garland Science)

21. Spatial patterns: Local self-enhancement - Global inhibition

Local Excitation - Global Inhibition model

(activator - substrate depletion scheme)

Hans Meinhardt
(1938-2016)

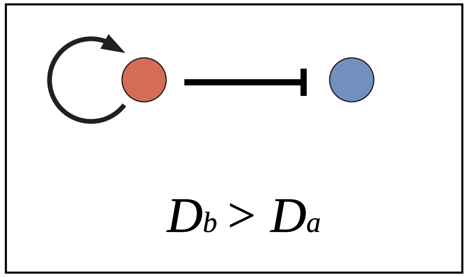
- The activator A needs a substrate B and depletes it.
- The Global inhibition/Negative Feedback is due to depletion of the substrate

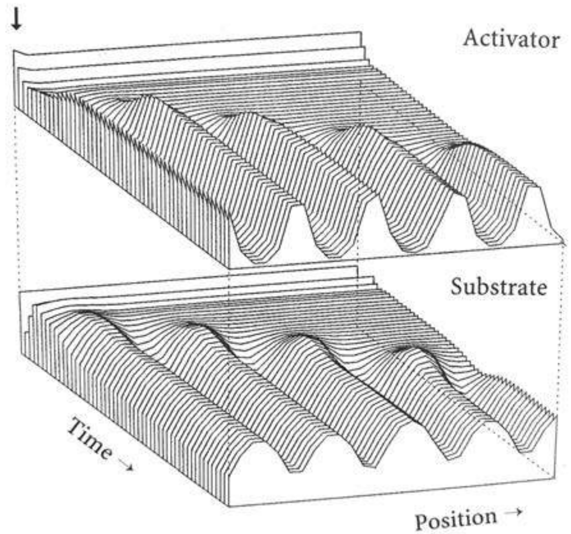
$$\frac{\partial a}{\partial t} = sba^{*2} - r_a a + D_a \frac{\partial^2 a}{\partial x^2}$$

$$\frac{\partial b}{\partial t} = b_b(x) - sba^{*2} - r_b b + D_b \frac{\partial^2 b}{\partial x^2}$$

$$a^{*2} = \frac{a^2}{1 + s_a a^2} + b_a$$

saturation term s_a





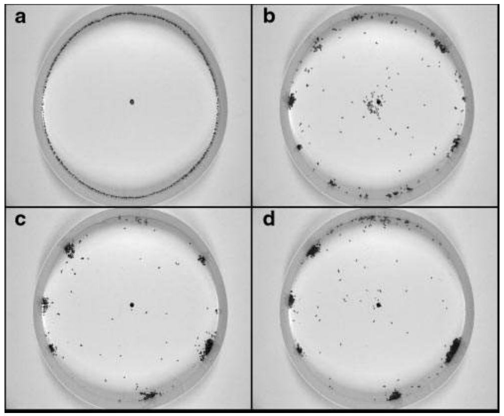
Hans Meinhardt
The algorithmic beauty of seashells (Springer)

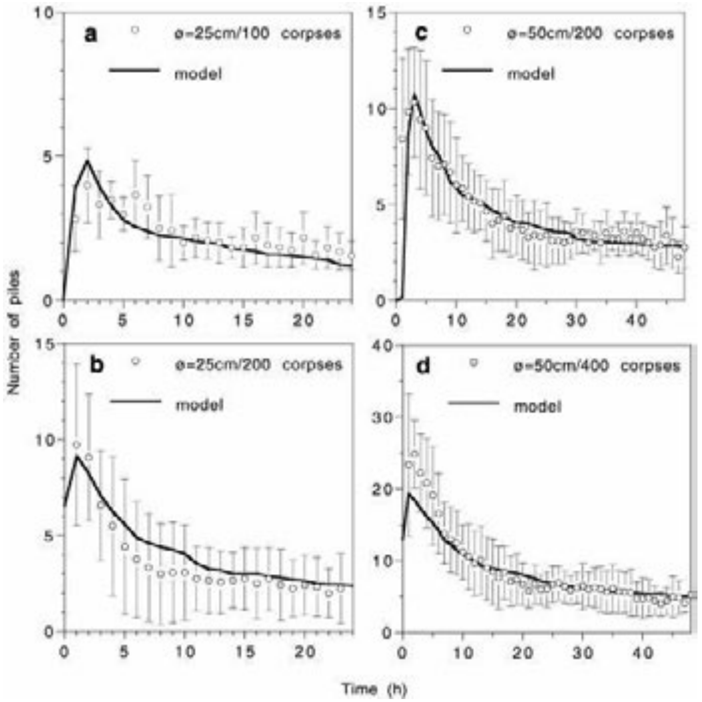
21. Spatial patterns: Local self-enhancement - Global inhibition

Local Excitation - Global Inhibition model

(activator - substrate depletion scheme)

- Example: Ant cemetery construction
  Ants carry dead corpses and deposit them to forme piles
  Local + Feedback (ants deposit on piles)
  Global negative feedback: depletion of corpses that arrest growth of piles





c corpses

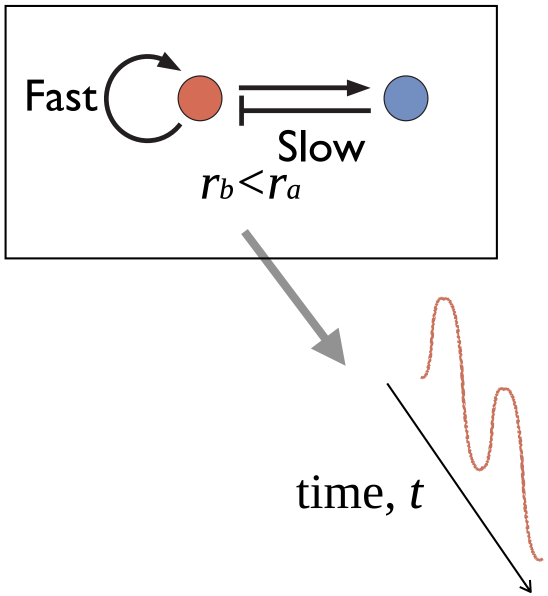
a corpse-carrying ant

$$\frac{\partial c}{\partial t} = \Omega(c, a)$$

$$\frac{\partial a}{\partial t} = -\Omega(c, a) + D\frac{\partial^2 a}{\partial x^2},$$

Guy Theraulaz et al, and J-L. Deneubourg. *PNAS* 99:9645-9649 (2002)

22. Temporal patterns: Bistability, Excitability and Oscillations.



$$\frac{\partial a}{\partial t} = s\left(\frac{a^2}{b} + b_a\right) - r_a a + D_a \frac{\partial^2 a}{\partial x^2}$$
$$\frac{\partial b}{\partial t} = s a^2 - r_b b + D_b \frac{\partial^2 b}{\partial x^2} + b_b$$

self-organization in nonequilibrium chemical systems:

- activator auto-activation
- inhibitor induction

✓ Inhibition with a delay: slow action of inhibitor compared to activator

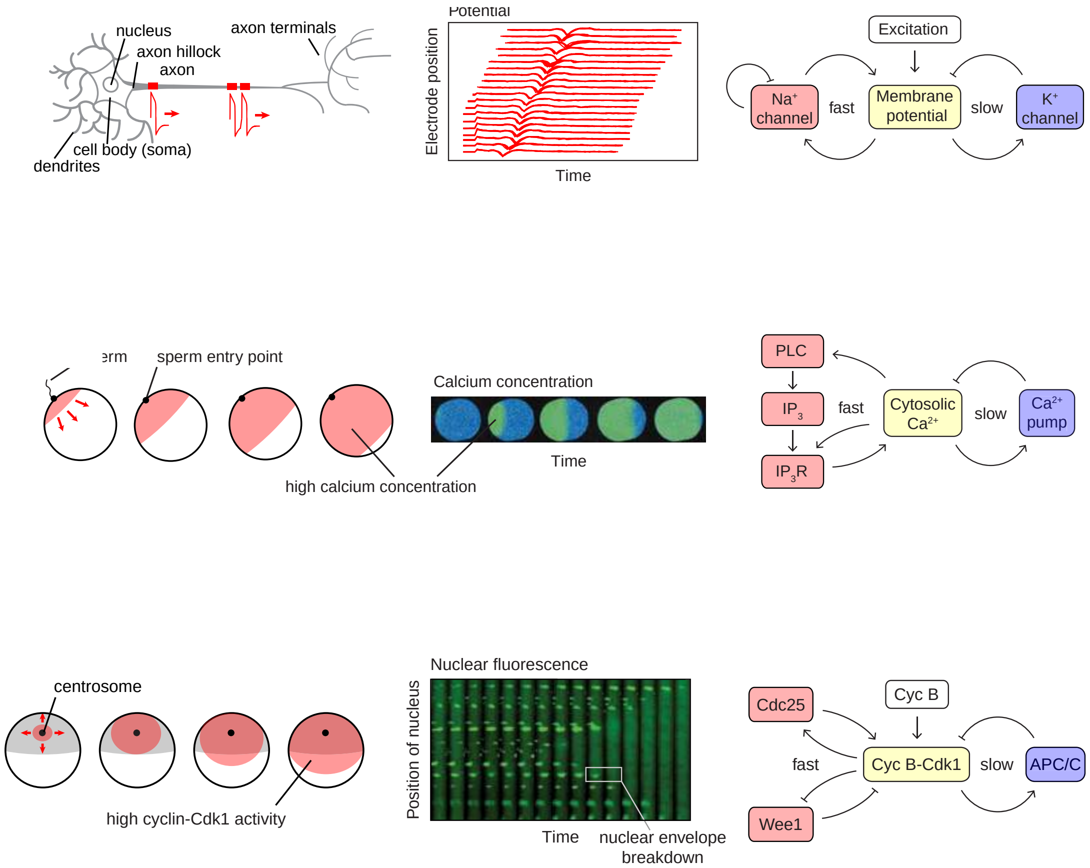
✓ Decay rate:

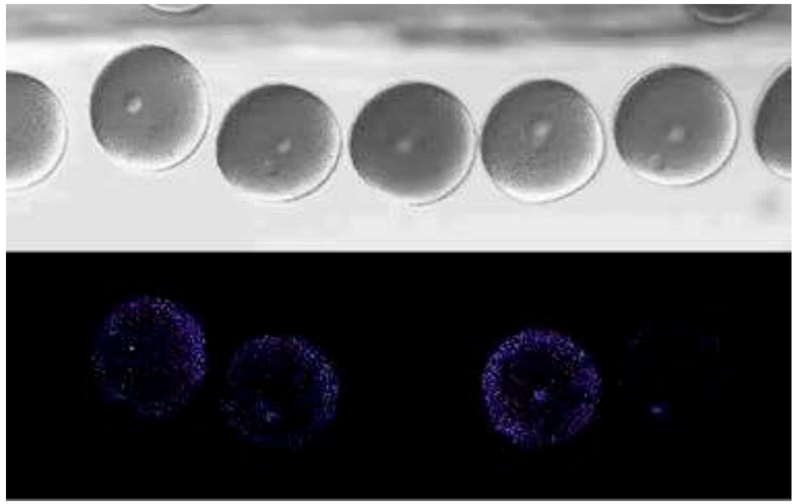
the decay rate of inhibitor must be lower than that other activator ($r_b < r_a$)

Existence of refractory period: time needed to clear inhibitor (or to re-synthesise depleted substrate)

II. Chemical Instabilities

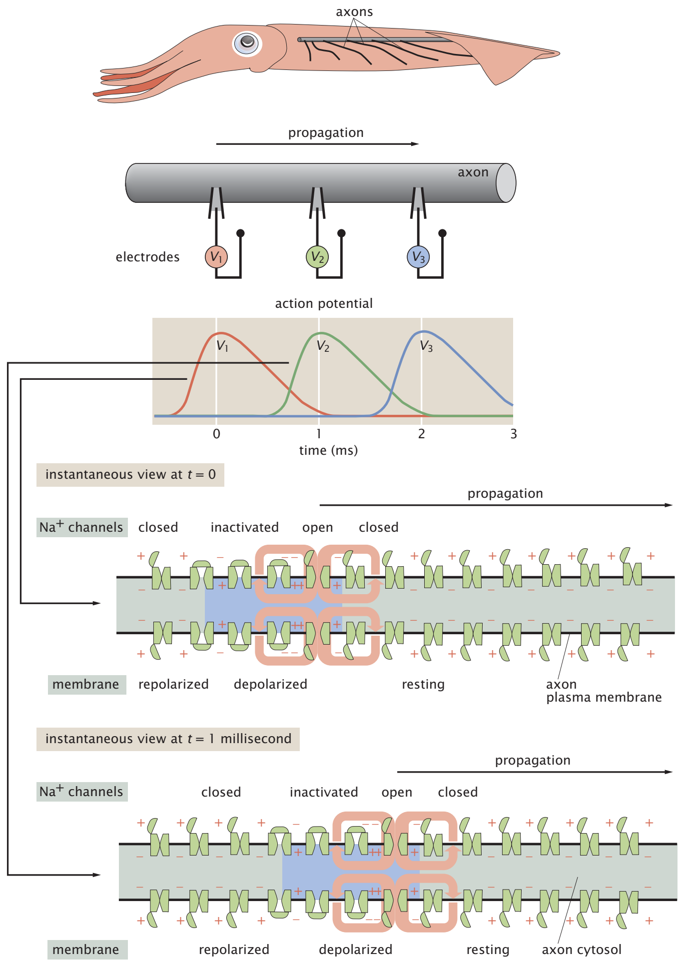
22. Temporal patterns: Bistability, Excitability and Oscillations.





L. Gelens, G.A. Anderson and James Ferrel. *MBoC* 25:3486-3493. 2014

22. Temporal patterns: Bistability, Excitability and Oscillations.



Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
illustration: Nigel Orme
Physical Biological of the Cell (Garland Science)

22. Temporal patterns: Bistability, Excitability and Oscillations.

- FitzHugh-Nagumo Model :

(heuristic model adapted for study of action potential)

$$\frac{du}{dt} = u - u^3 - v \qquad \textbf{Fast reaction}$$

$$\frac{dv}{dt} = \varepsilon(u - bv + a) \qquad \textbf{Slow reaction}$$

$(\varepsilon \ll 1)$

$du/dt \propto u$, positive feedback

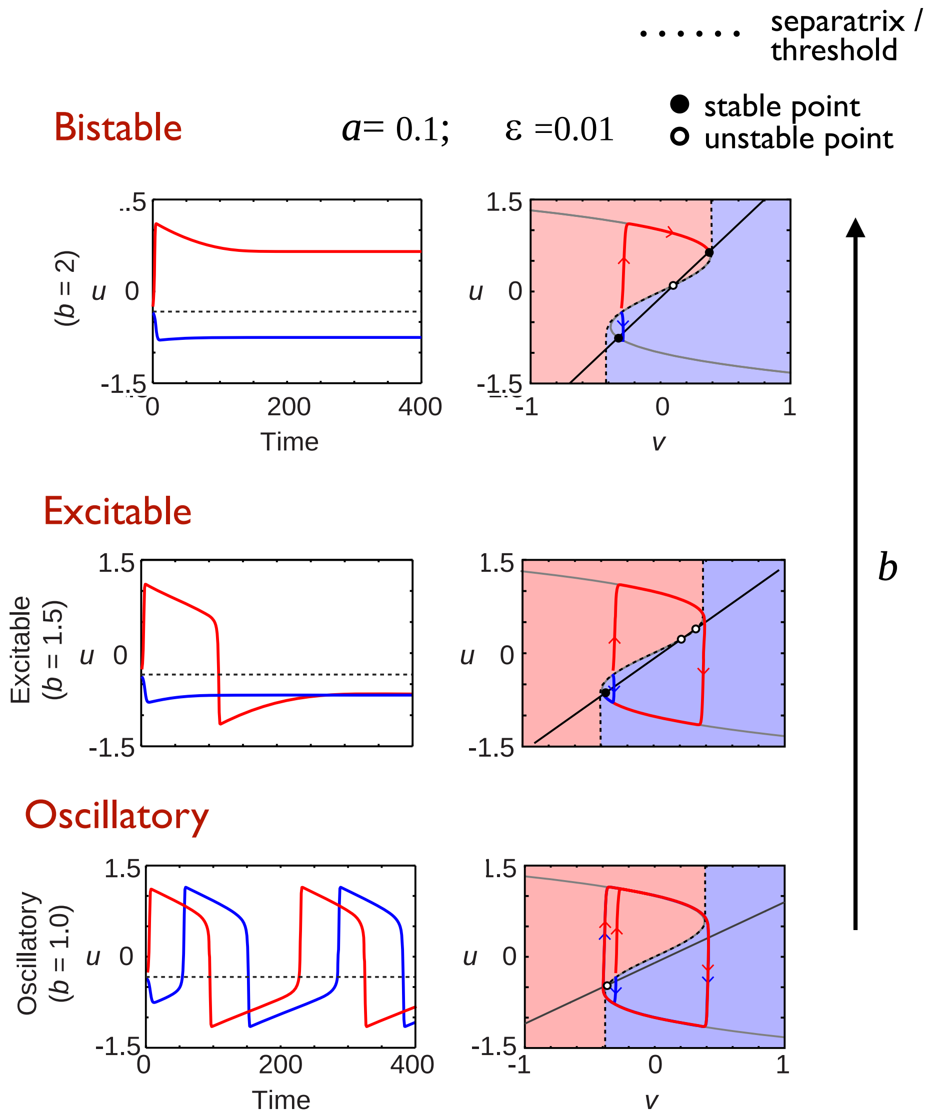
$du/dt \propto -u^3$ fast negative feedback

- Conditions on steady state

$$u - u^3 - v = 0$$

$$\varepsilon(u - bv + a) = 0$$

(nullclines in uv plane: steady state response of u to v and of v to u)



L. Gelens, G.A. Anderson and James Ferrel. *MBoC* 25:3486-3493. 2014

23. Spatial Temporal patterns: Trigger waves

Belousov-Zhabotinsky reaction

$$
\begin{aligned}
\mathrm{A} + \mathrm{Y} &\xrightarrow{k_3} \mathrm{X} + \mathrm{P} \\
\mathrm{X} + \mathrm{Y} &\xrightarrow{k_2} 2\mathrm{P} \\
\mathrm{A} + \mathrm{X} &\xrightarrow{k_5} 2\mathrm{X} + 2\mathrm{Z} \\
2\mathrm{X} &\xrightarrow{k_4} \mathrm{A} + \mathrm{P} \\
\mathrm{B} + \mathrm{Z} &\xrightarrow{k_c} \frac{1}{2} f\mathrm{Y}.
\end{aligned}
$$

$$
\begin{aligned}
\frac{dX}{dt} &= k_3 AY - k_2 XY + k_5 AX - 2k_4 X^2 \\
\frac{dY}{dt} &= -k_3 AY - k_2 XY + \frac{1}{2} f k_c BZ \\
\frac{dZ}{dt} &= 2k_5 AX - k_c BZ.
\end{aligned}
$$

23. Spatial Temporal patterns: Trigger waves

- Spatial coupling by diffusion — Synchronization

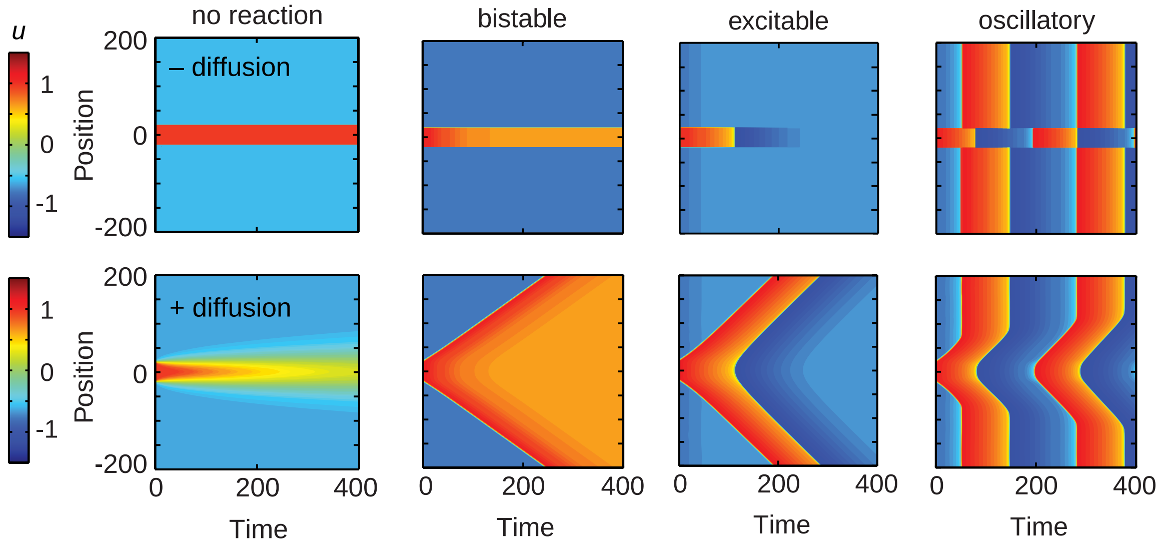
FitzHugh-Nagumo Model :

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + u - u^3 - v$$

$$\frac{\partial v}{\partial t} = D\frac{\partial^2 v}{\partial x^2} + \varepsilon(u - bv + a)$$

Diffusion Reaction

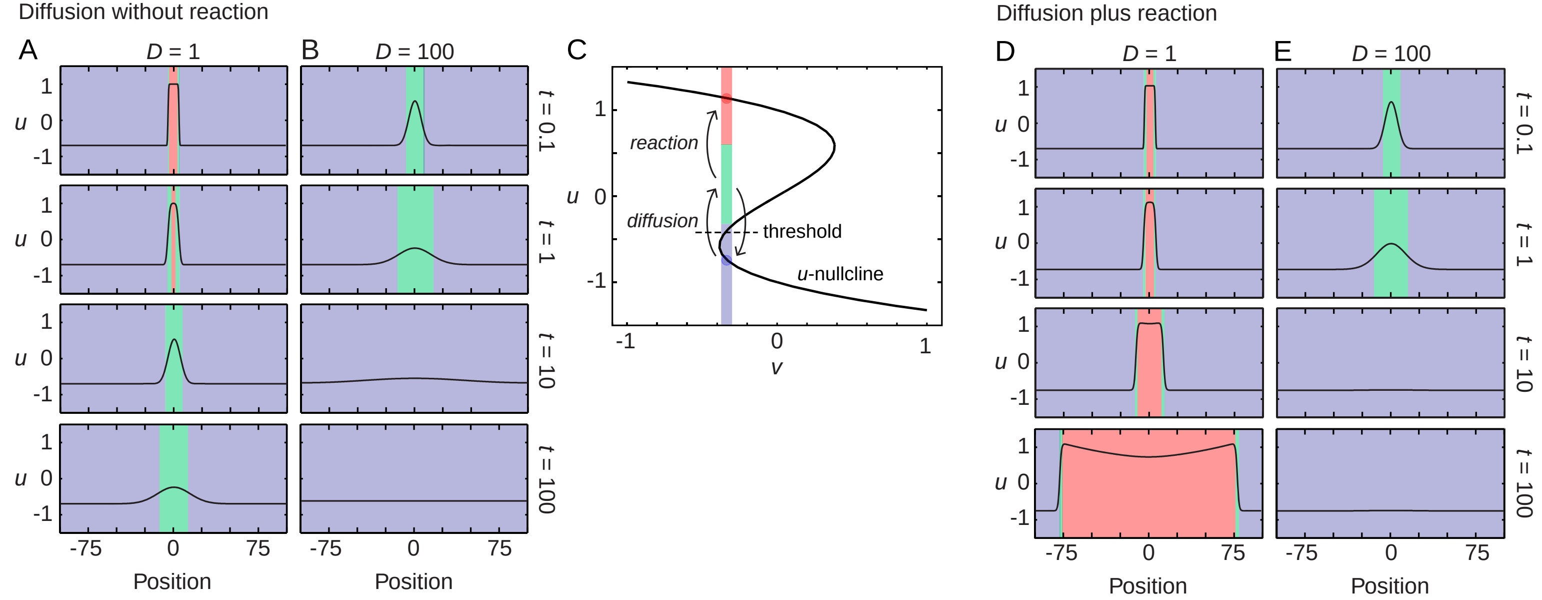
Kymographs (x, t):



L. Gelens, G.A. Anderson and James Ferrel. *MBoC* 25:3486-3493. 2014

23. Spatial Temporal patterns: Trigger waves

- Diffusion is a mechanism for crossing the threshold in space



- a low u value state will increase its u concentration due to diffusion of nearby high u state

but will relax back

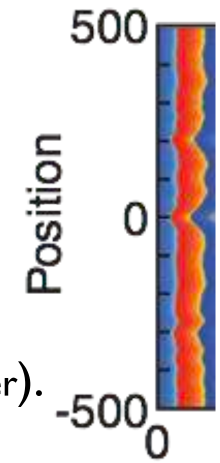
- Higher diffusion increases rate of local propagation but makes it more transient

- The presence of a reaction captures supra-threshold state and move to high u state
- This depends on the relative time scale of diffusion and reaction

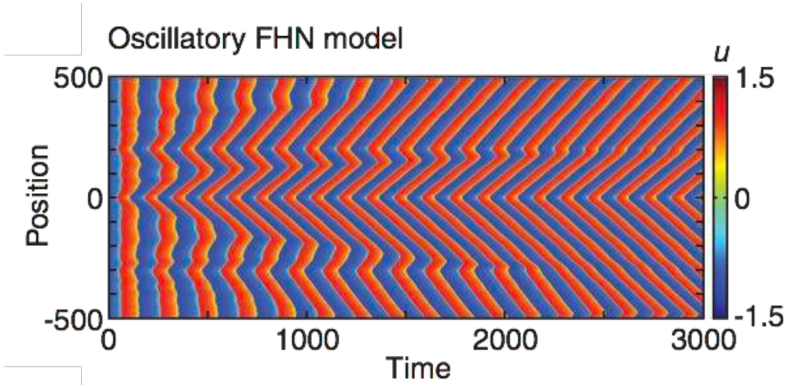
- Speed: $s = 2\sqrt{\frac{D}{\tau}}$ ← doubling time of + feedback

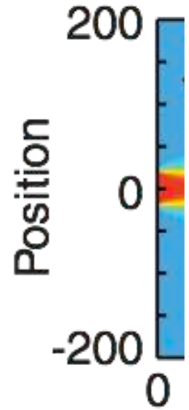
L. Gelens, G.A. Anderson and James Ferrel. *MBoC* 25:3486-3493. 2014

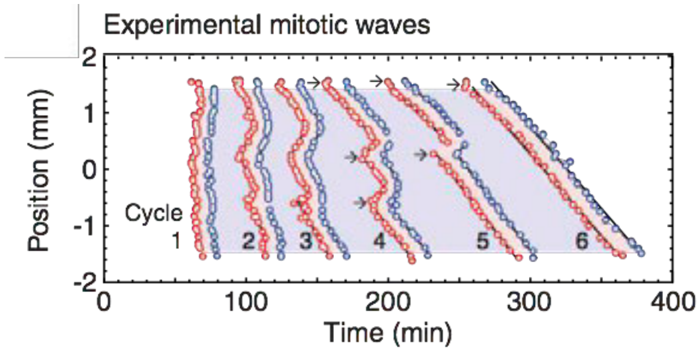
23. Spatial Temporal patterns: Trigger waves



- Initiation of waves: self-organisation
  1. Stochastic processes in homogeneous medium
  2. Pacemaker: spatial bias (heterogeneous medium) set up by pre-pattern (e.g. frequency modulation: higher frequency region will become pacemaker).







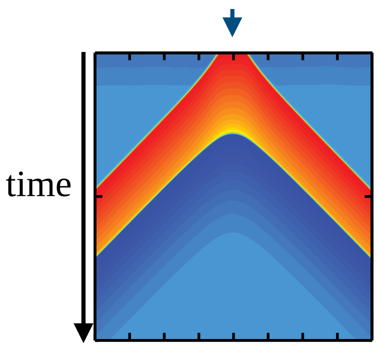
L. Gelens, G.A. Anderson and James Ferrel. *MBoC* 25:3486-3493. 2014

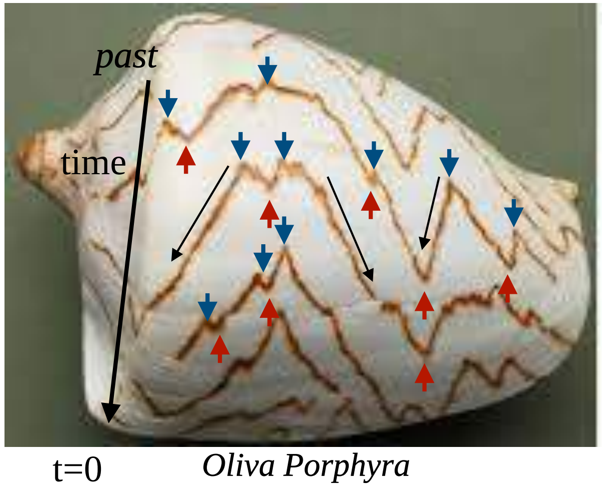
23. Spatio-temporal patterns: seashell patterns

Summary: Properties of **excitable** systems

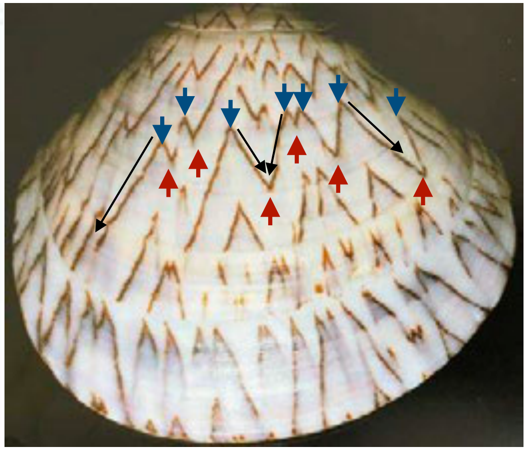
- Initiation beyond a ***threshold*** for activation
- Self-organisation of ***trigger** waves*
- *Refractory period*: clearance of excess inhibitor or new synthesis of depleted substrate
- ***Colliding waves annihilation:*** due to wave entering refractory zone.

✓ Seashells patterns as developmental kymographs





Oliva Porphyra



Lioconcha lorenziana

Hans Meinhardt
The algorithmic beauty of seashells (Springer)

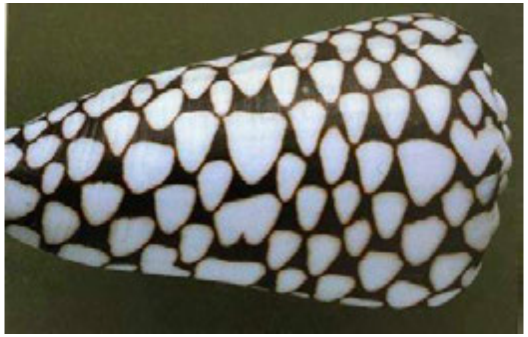
23. Spatio-temporal patterns: seashell patterns

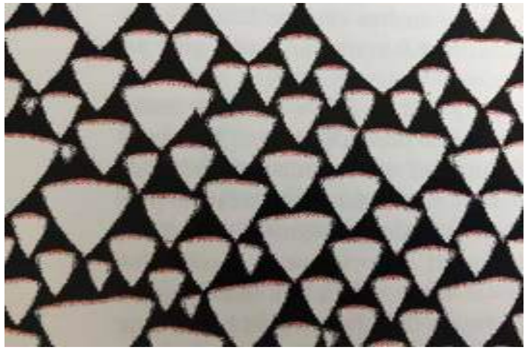
- **Excitability**

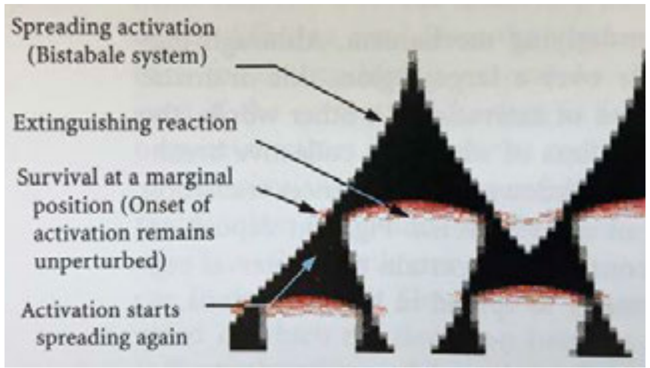
- **Bistability**

Lioconcha hieroglyphica

Conus marmoreus





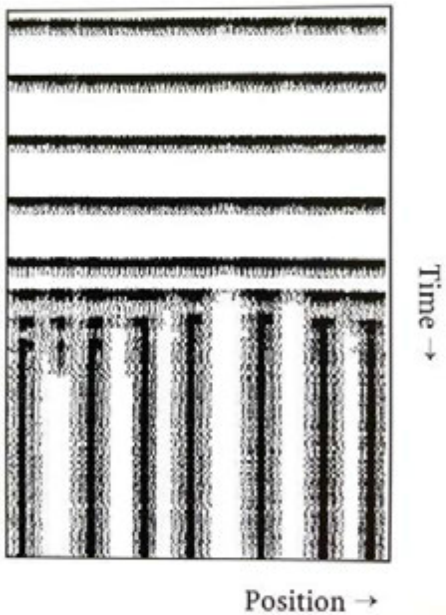


Hans Meinhardt
The algorithmic beauty of seashells (Springer)

23. Spatio-temporal patterns: seashell patterns

- Temporal instability: **Oscillations**

- Spatial instability: Turing patterns



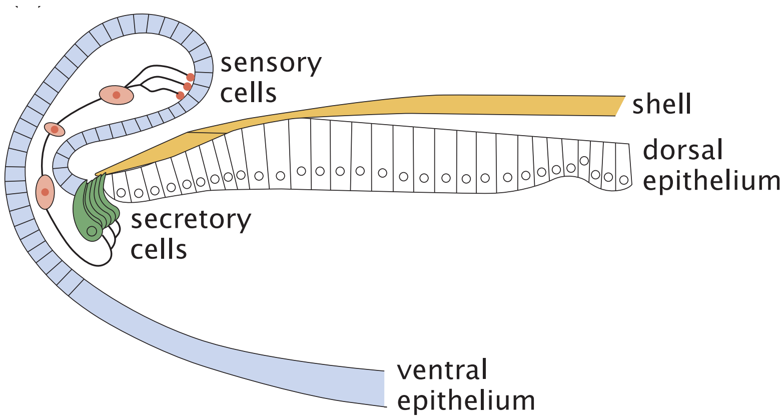
Synchronous oscillations:
(diffusion mediated coupling)

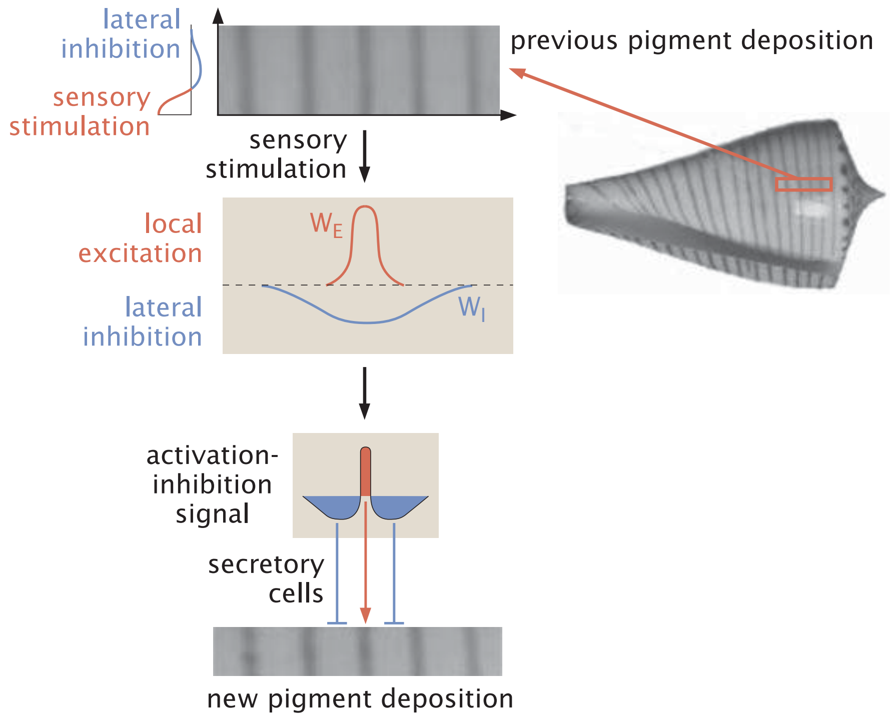
Spatial patterns:
Reduced inhibitor lifetime

Hans Meinhardt
The algorithmic beauty of seashells (Springer)

23. Spatio-temporal patterns: seashell patterns

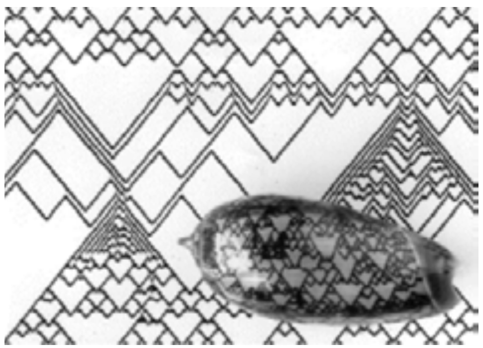
- Seashell patterns are not mediated by diffusing chemical activators/inhibitors
- They reflect the spatial-temporal activity patterns of neural nets
- Sensory cells « read » past activity and induce secretory cells





A. Boettiger, B. Ermentrout and G. Oster. *P.N.A.S* 106:6837-6842. 2009

Seashell patterns as EEGs…

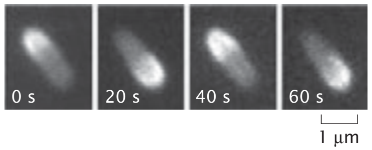


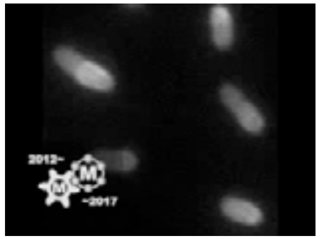
https://www.eb.tuebingen.mpg.de/emeriti/hans-meinhardt/

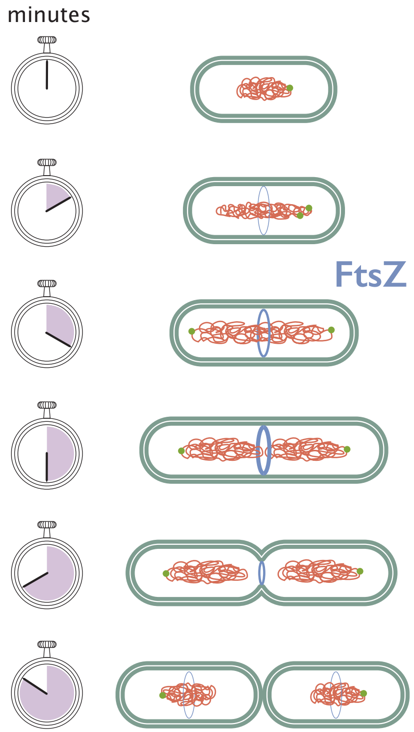
Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
illustration: Nigel Orme
Physical Biological of the Cell (Garland Science)

23. Spatio-temporal patterns: defining the middle of a cell

MinD standing wave results from opposing moving waves







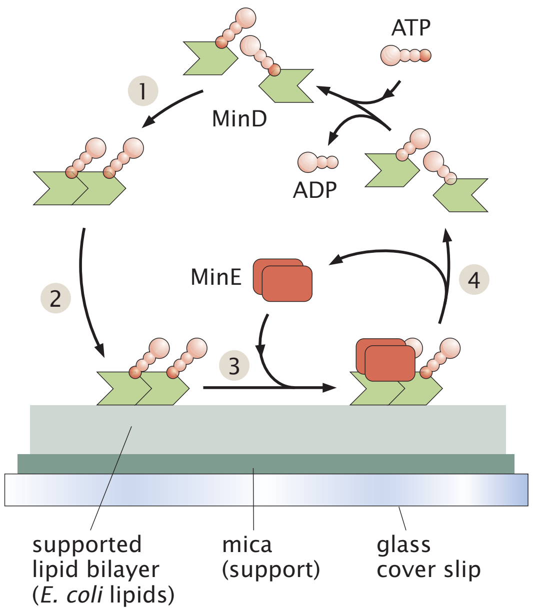
Oscillations of MinD
MinC recruited by MinD
>mean MinC concentration is lowest in middle

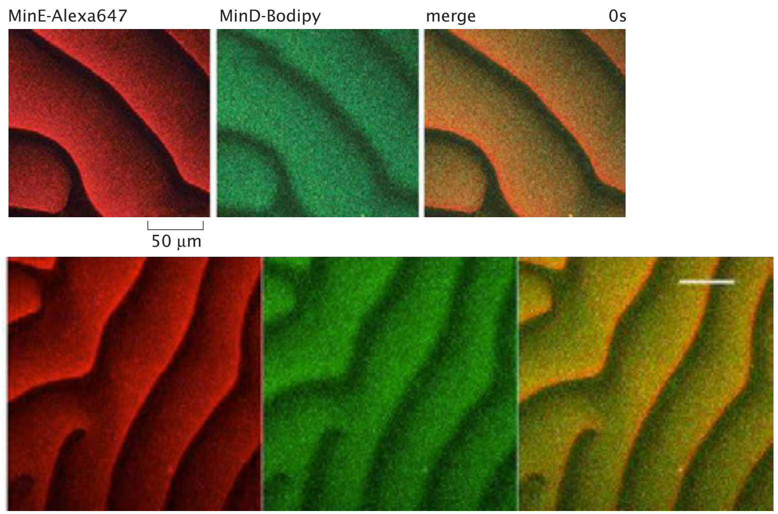
MinC inhibits FtsZ (tubulin homolog in Bacteria)

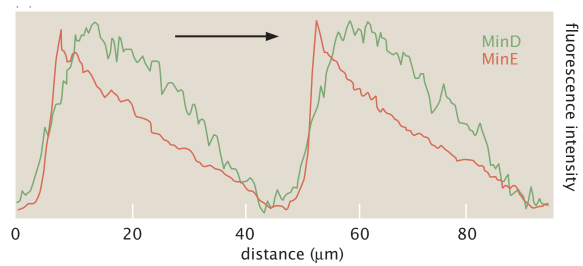
Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
illustration: Nigel Orme
Physical Biological of the Cell (Garland Science)

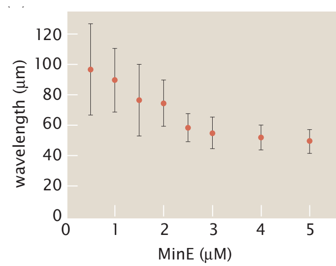
23. Spatio-temporal patterns: defining the middle of a cell

Turing instabilities: travelling waves in 2D









MinD is an autocatalytic activator
MinD recruits its own inhibitor MinE
MinE induces its dissociation via MinD dissociation

Loose M, Fischer-Friedrich E., Ries J. Kruse Karsten and Schwille Petra. *Science*, 320:789-792 (2008)

Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
illustration: Nigel Orme
Physical Biological of the Cell (Garland Science)

23. Spatio-temporal patterns: defining the middle of a cell

stable length scale requires that k_{on} = k_{off}, which can be achieved if MinE promotes MinD dissociation.

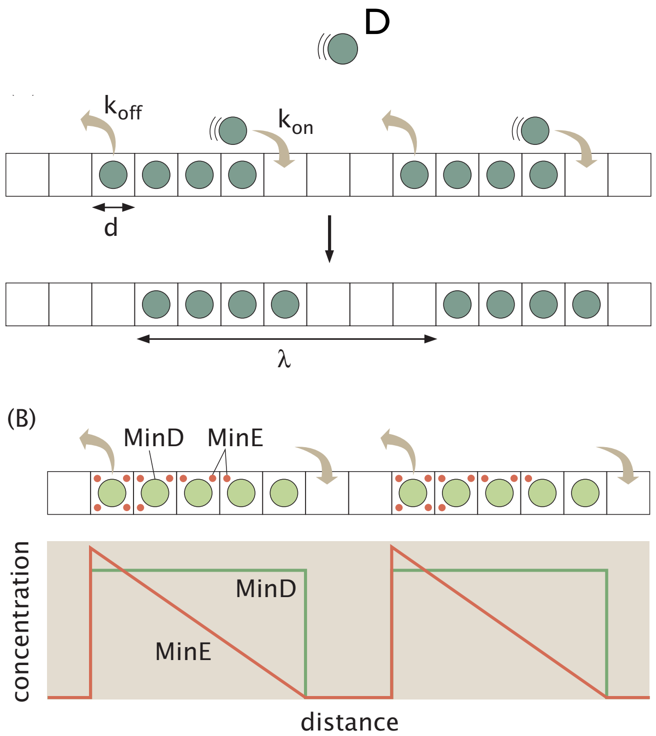
dissociation of MinD above threshold of MinE recruitment

$$v = k_{on} d \qquad d = 5 \text{ nm}$$

$$k_{on} = Ddc \qquad D = 60 \ \mu\text{m}^2/\text{s} \qquad c = 1 \ \mu\text{M}$$

$$v \approx 0.7 \ \mu\text{m/s}$$

Experiments: $v = 0.3 - 0.8 \ \mu\text{m/s}$



Rob Philipps, Jane Kondev, Julie Theriot, Hernan G. Garcia.
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Physical Biological of the Cell (Garland Science)

Loose M, Fischer-Friedrich E., Ries J. Kruse Karsten and Schwille Petra. *Science*, 320:789-792 (2008)

1. Introduction - Program and Self-Organisation

2. Chemical Instabilities
    21. Spatial instabilities - Turing patterns
    22. Temporal instabilities - Excitability
    23. Spatial-temporal instabilities: waves

3. Mechanical instabilities
    31. Cellular aggregates: viscoelastic model
    32. Active gel: hydrodynamic and viscoelastic models

4. Mechano-chemical Instabilities
    41. Mechano-chemical coupling: actomyosin dynamics
    42. Actin based trigger waves

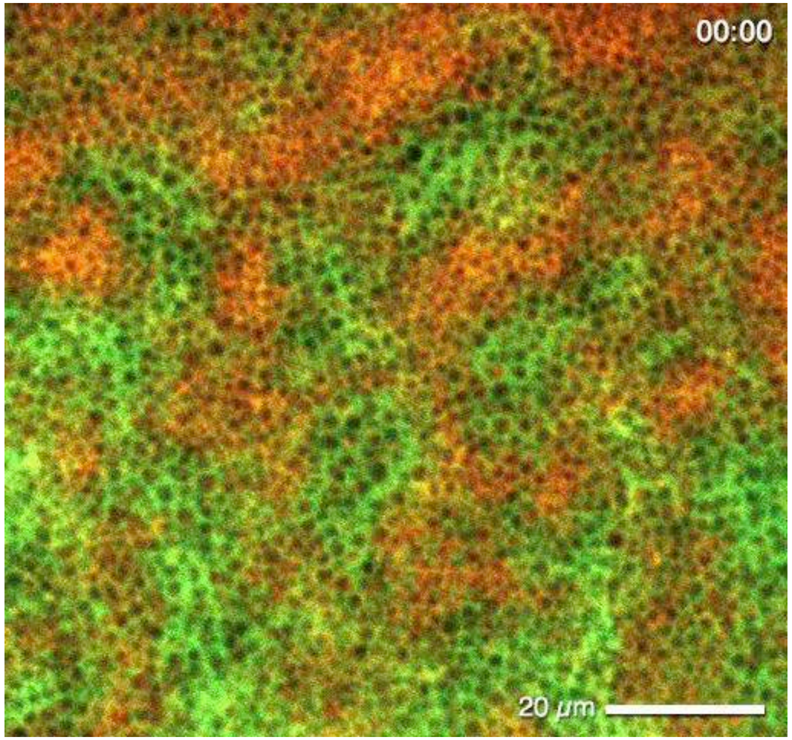
5. Developmental significance: impact on cellular and tissue morphogenesis

III - Mechanical Instabilities

One cannot at present hope to make any progress with the understanding of such systems except in very simplified cases. The interdependence of the chemical and mechanical data adds enormously to the difficulty, and attention will therefore be confined, so far as is possible, to cases where these can be separated. The mathematics of elastic solids is a well-developed subject, and has often been applied to biological systems. In this paper it is proposed to give attention rather to cases where the mechanical aspect can be ignored and the chemical aspect is the most significant. These cases promise greater interest, for the characteristic action of the genes themselves is presumably chemical.

The difficulties are, however, such that one cannot hope to have any very embracing *theory* of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis. It might even be possible to take the mechanical aspects of the problem into account as well as the chemical, when applying this type of method.

Alan Turing. The chemical basis of morphogenesis.
Journal of Theoretical Biology. 1952



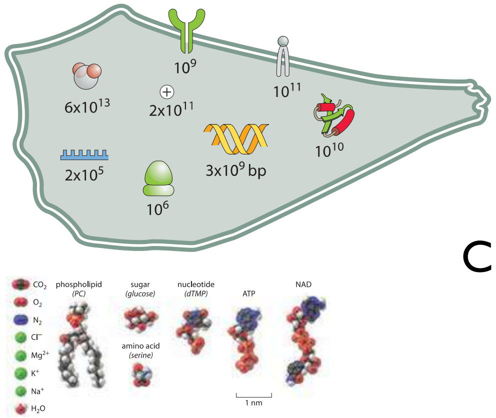
Actin filaments
Active Rho1

Xenopus Egg

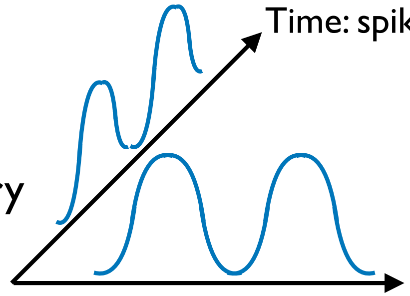
William Bement et al and George von Dassow. *Nature Cell Biology* 17(11):1471-83 (2015)

III - Mechanical Instabilities

Chemical and Mechanical Information

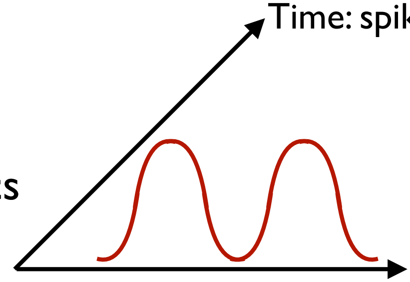


Chemistry



self-organization in nonequilibrium chemical systems

Mechanics



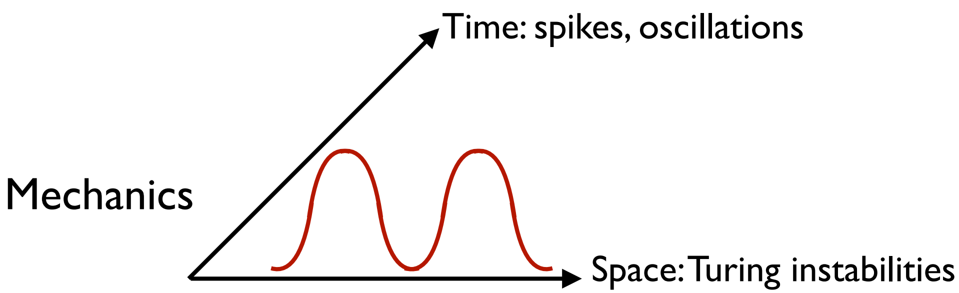
self-organization in nonequilibrium mechanical systems

Chemistry → Mechanics

self-organization in nonequilibrium mechano-chemical systems

Chemistry ⇄ Mechanics

Spatial and temporal Mechanical instabilities



self-organization in nonequilibrium mechanical systems

- Viscoelastic model: cell motility and active gel
- Hydrodynamic model: active gel

III - Mechanical Instabilities

Mechanically driven self-organisation of cellular patterns

J. Embryol. exp. Morph. 80, 1–20 (1984) 1

Generation of spatially periodic patterns by a mechanical instability: a mechanical alternative to the Turing model

By ALBERT K. HARRIS[1], DAVID STOPAK[2] AND PATRICIA WARNER[1]

[1] *Department of Biology, Wilson Hall (046A), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514, U.S.A.*

[2] *Department of Biological Sciences, Stanford University, Stanford, Carolina 94305-2493, U.S.A.*

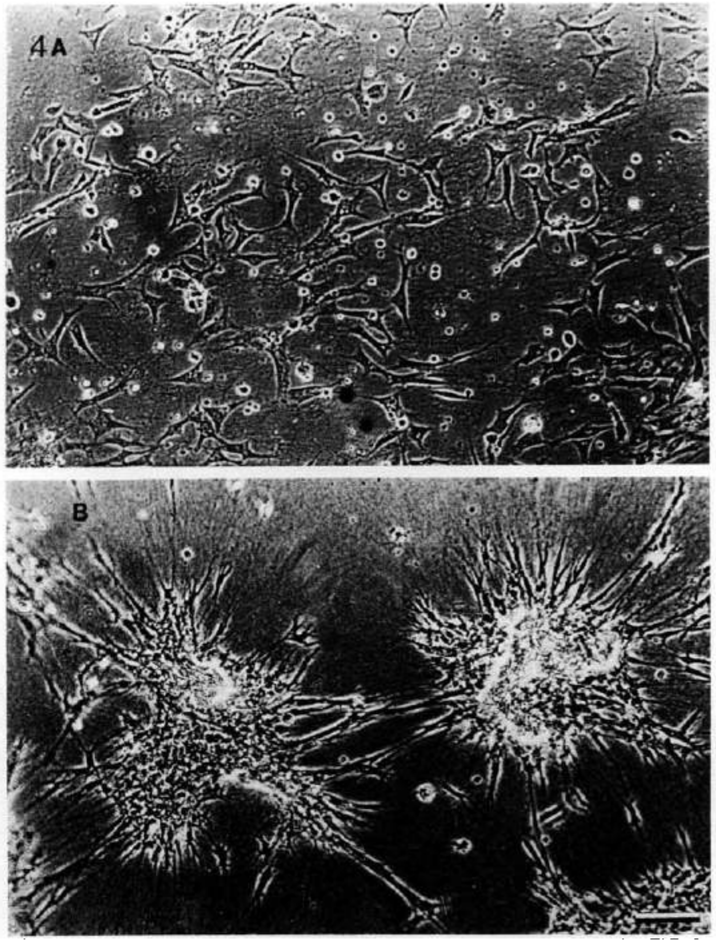


Fig 4. Time sequence of pattern development. A. 24 h after plating, fibroblasts are still evenly distributed. B. After 6 days, the formation of periodic condensations is complete. The scale bar equals 100 μm.

A.K Harris, D. Stopak and P. Warner. *J. Embryol exp. Morph.* 1984. 80:1-20

III - Mechanical Instabilities

Mechanically driven self-organisation of cellular patterns

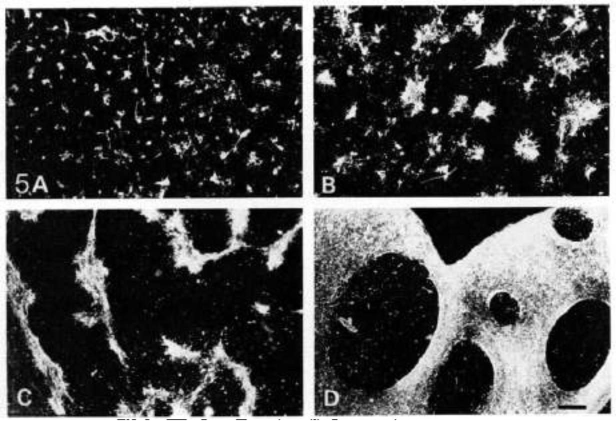
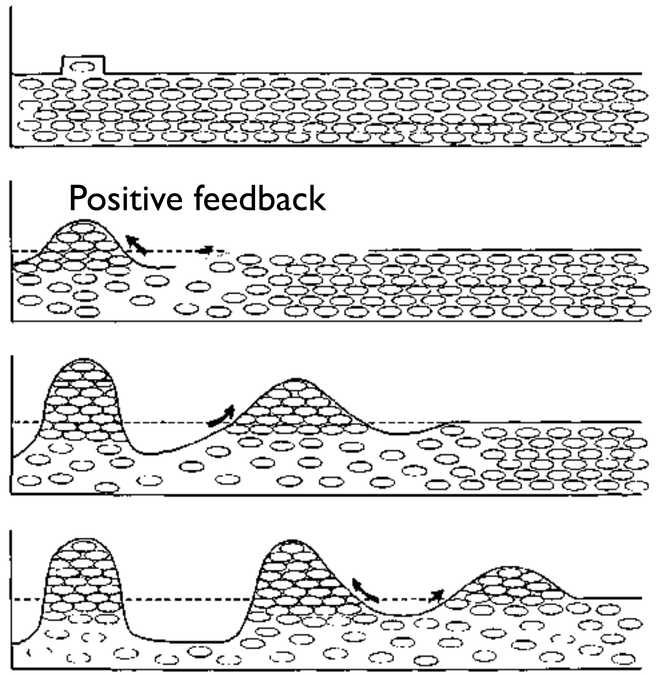


Fig. 5. Effects of differing initial population densities of fibroblasts on the resulting spatial pattern. Scale bar equals 400 μm. A. 2×10^4 cells/cm^2. B. 4×10^4 cells/cm^2. C. 7×10^4 cells/cm^2 D. 9×10^4 cells/cm^2.

Higher density of initial cell population affects aggregate pattern



A.K Harris, D. Stopak and P. Warner. *J. Embryol exp. Morph.* 1984. 80:1-20

III - Mechanical Instabilities

Mechanically driven self-organisation of cellular patterns

- Modelling cell motility on viscoelastic matrix

flux $\mathbf{J}$ mitosis $\mathbf{M}$

$$\frac{\partial n}{\partial t} = -\nabla \cdot \left\{ [D_2(\mathbf{e})\nabla(\nabla^2 n) - D_1(\mathbf{e})\nabla n] + [\alpha n \nabla \rho] + \left[n \frac{\partial \mathbf{u}}{\partial t} \right] \right\} + rn(N-n) \quad (1)$$

Autocatalytic aggregation

diffusion (non-local interactions) — diffusion (local interactions) — haptotaxis — advection

random motion with strain guidance — directed motion

$n(t, \mathbf{x})$ cell density

$\rho(t, \mathbf{x})$ matrix density

$\mathbf{u}(t, \mathbf{x})$ displacement vector of matrix

$$\frac{\partial \rho}{\partial t} = -\nabla \cdot \left(\rho \frac{\partial \mathbf{u}}{\partial t} \right). \quad (2)$$

Conservation law

- **Random motion:** harmonic (Fickian, short-range) diffusion and biharmonic (long-range) diffusion
- **Directed motility:** passive cell dragging (advection), migration up adhesion gradient (haptotaxis), contact guidance (mediated via anisotropic mechanical strain of matrix by cell tractions)

G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125

J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129

Donald Cohen and J.D. Murray *J. Math. Biology* 1981. 12:237-249

III - Mechanical Instabilities

Mechanically driven self-organisation of cellular patterns

- Feedback mechanism between cells and the matrix: traction forces due to cell motility causes matrix deformation which steers cell motility

$n(t, \mathbf{x})$ cell density

$\rho(t, \mathbf{x})$ ECM matrix density

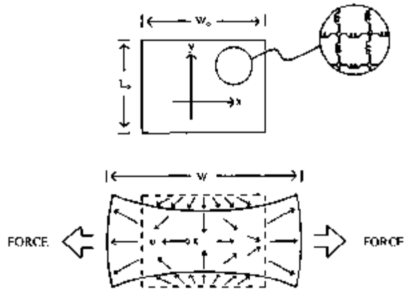
$\mathbf{u}(t, \mathbf{x})$ displacement vector of ECM

$\theta = \nabla \cdot u$ dilatation of ECM matrix

$\mathbf{e}$ strain matrix

E Young's modulus

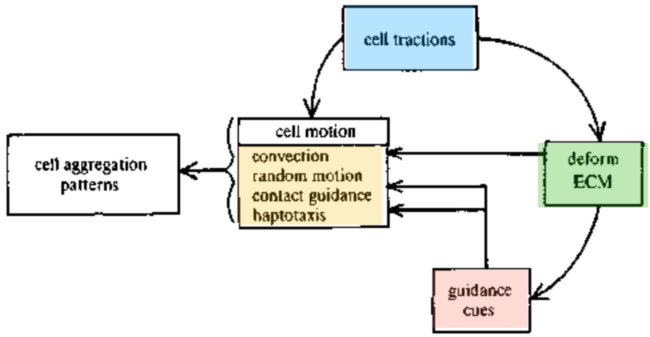
ν Poisson ratio



$$\nabla \cdot \left\{ \left[\mu \frac{\partial \mathbf{e}}{\partial t} + \lambda \frac{\partial \theta}{\partial t} \mathbf{I} \right] + \left[\frac{E}{2(1+\nu)} \left(\mathbf{e} + \frac{\nu}{1-2\nu} \theta \mathbf{I} \right) + \tau \rho n \mathbf{I} \right] \right\} = 0. \quad (3)$$

viscous force — elastic force — traction force | Force balance

$$\frac{\partial n}{\partial t} = -\nabla \cdot \left\{ [D_2(\mathbf{e}) \nabla (\nabla^2 n) - D_1(\mathbf{e}) \nabla n] + [\alpha n \nabla \rho] + \left[n \frac{\partial \mathbf{u}}{\partial t} \right] \right\} + rn(N - n)$$



$$\frac{\partial \rho}{\partial t} = -\nabla \cdot \left(\rho \frac{\partial \mathbf{u}}{\partial t} \right).$$

G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125

J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129

III - Mechanical Instabilities

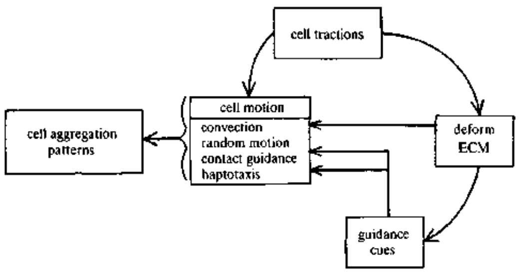
Mechanically driven self-organisation of cellular patterns

- Feedback mechanism between cells and the matrix: traction forces due to cell motility causes matrix deformation which steers cell motility

- dimensionless traction parameter (cell traction, matrix density and Poisson ratio play equivalent roles)

$$\tau^* = \tau\rho_0 N(1+\nu)/E$$

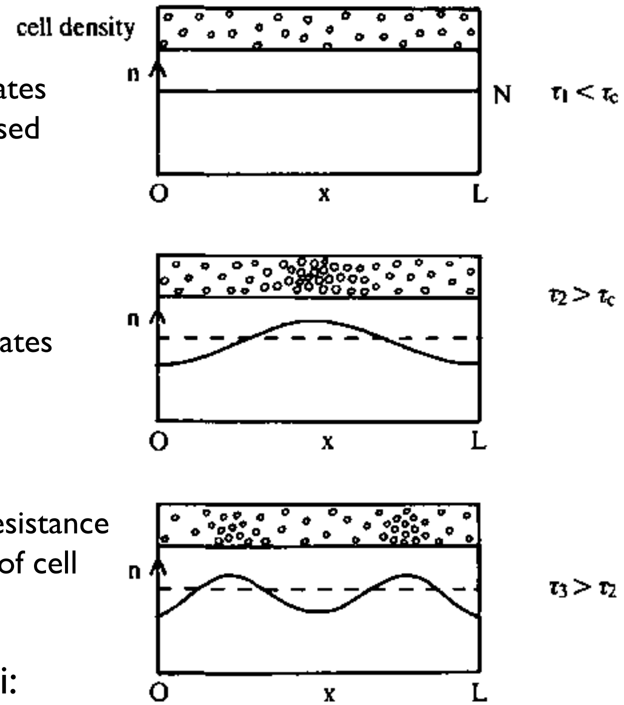
- Bifurcation point: when cell traction induced strain guidance, haptotaxis and advection overcome diffusion
- Multiple foci can emerge: elastic resistance limits the range of local contraction
- Elasticity as a Turing like « long range inhibitor » and cell traction as « local activator» with autocatalysis (guidance effects)



Diffusion dominates over traction based guidance

Guidance dominates diffusion

Matrix elastic resistance shortens range of cell aggregation



Spacing between foci:

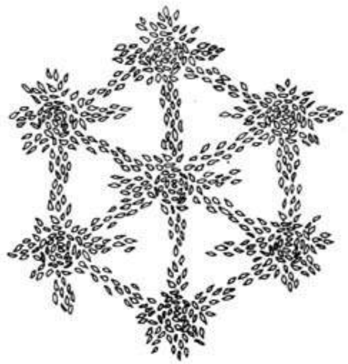
$$W_c \sim \left(\frac{D_2}{rN}\right)^{1/4}.$$

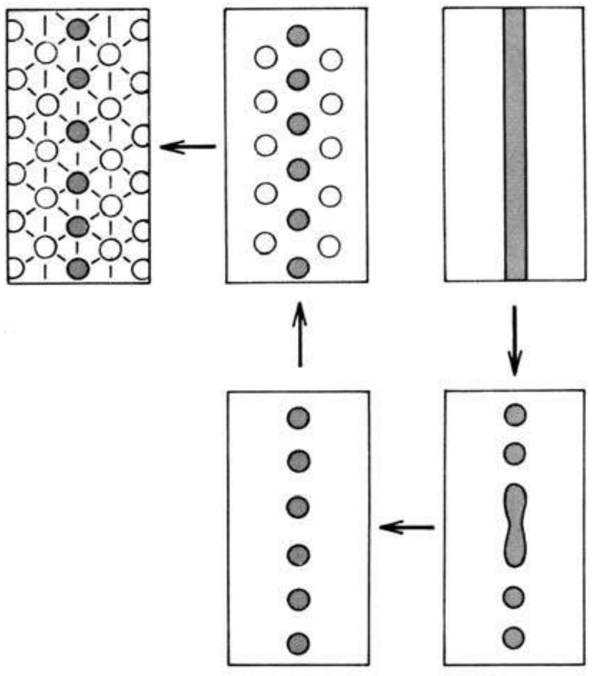
G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125

J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129

Mechanically driven self-organisation of cellular patterns

- Feedback mechanism between cells and the matrix: traction forces due to cell motility causes matrix deformation which steers cell motility
- Emergence of cellular patterns





G.F. Oster, J.D. Murray, and A.K. Harris. *J. Embryol. esp. Morph.* 1983. 78:83-125

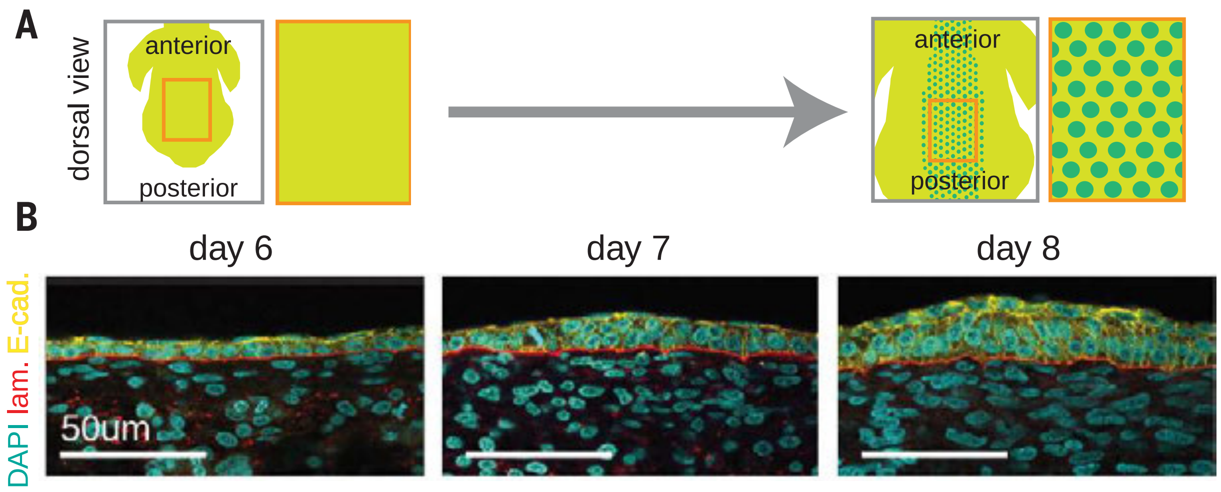
J.D. Murray, G.F. Oster and A.K. Harris. *J. Math. Biology* 1983. 17:125-129

III - Mechanical Instabilities

Mechanically driven self-organisation of cellular patterns

Emergent cellular self-organization and mechanosensation initiate follicle pattern in the avian skin

Amy E. Shyer,[1*†] Alan R. Rodrigues,[1,2*] Grant G. Schroeder,[1] Elena Kassianidou,[3] Sanjay Kumar,[3] Richard M. Harland[1]



Shyer *et al.*, *Science* **357**, 811–815 (2017) 25 August 2017

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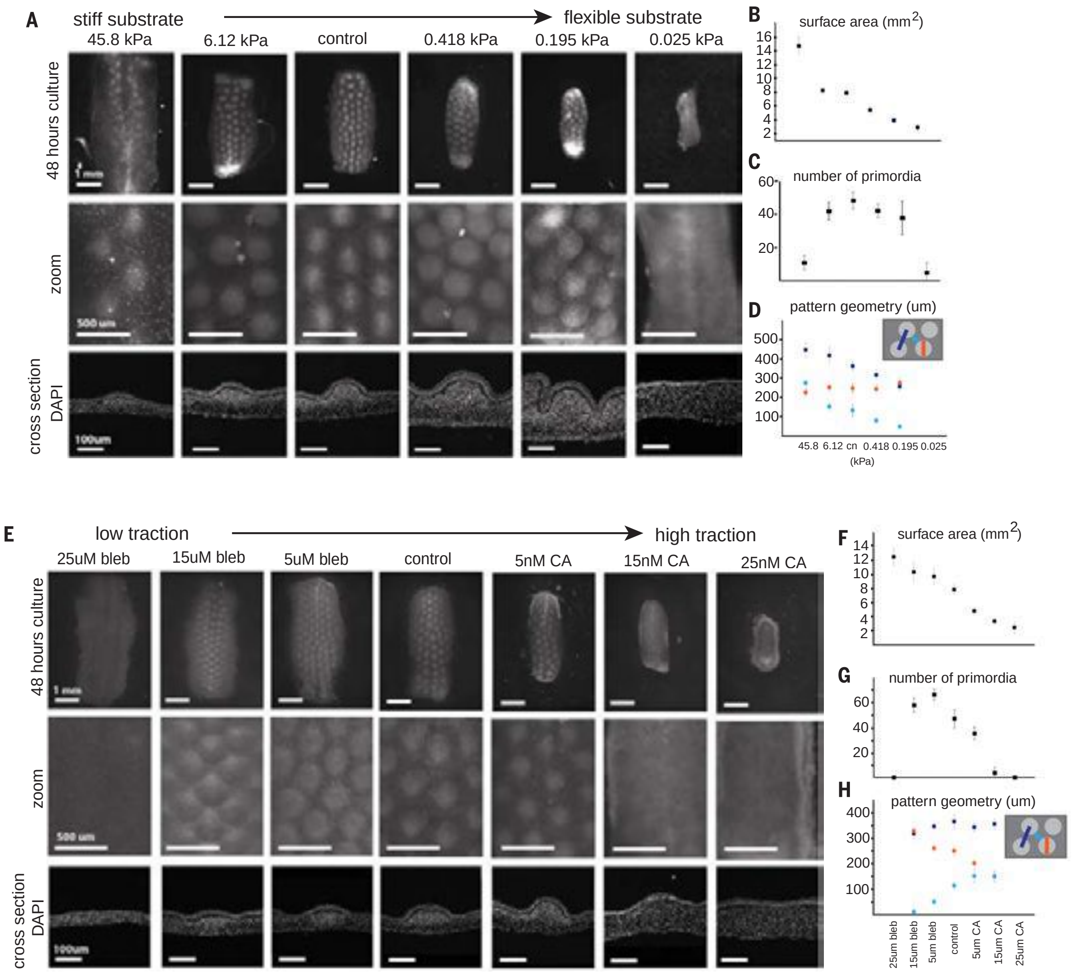
- Spatial patterns require mechanical resistance of substrate

- Spatial patterns require cellular contractility



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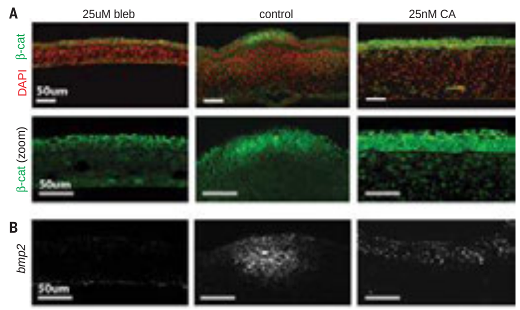
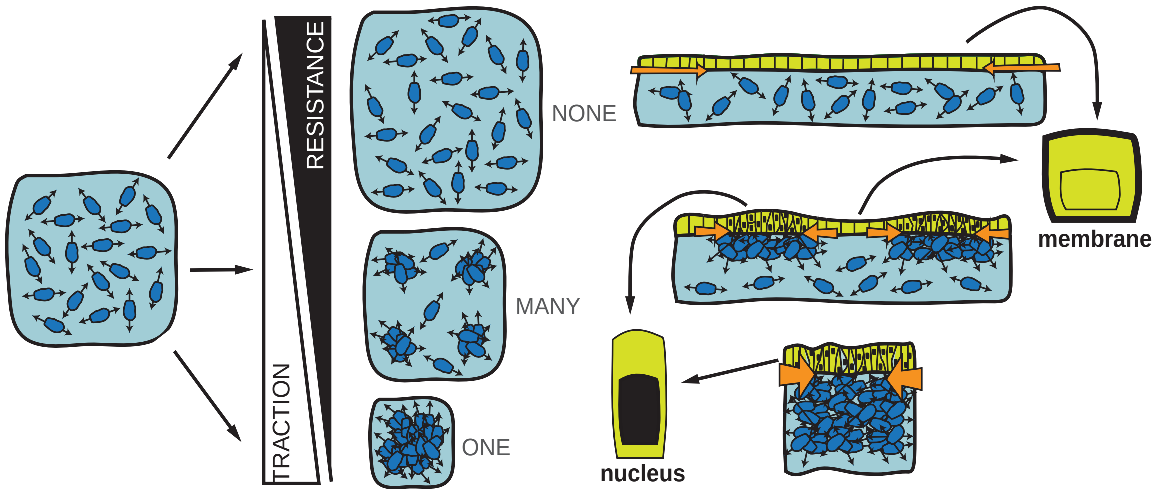


Uniform traction when adequately resisted leads to an array of aggregates
[field of dermal cells from above]

Dermis COMPRESSES epidermis
force causes translocation of β-catenin
[cross-section of tissue bilayer]



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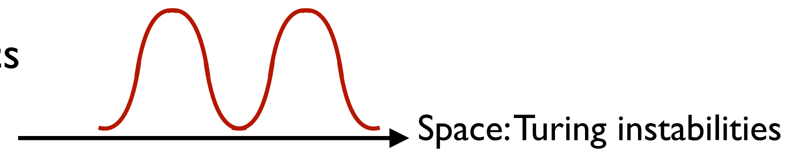
III - Mechanical Instabilities

Spatial Mechanical instabilities

Mechanics



self-organization in nonequilibrium mechanical systems

- <u>Turing like pattern</u>: Contraction must overcome Inhibitory effect of substrate stiffness
- Cell traction as « local activator» with autocatalysis (guidance effects) and Elasticity as« long range inhibitor ».

Conclusions

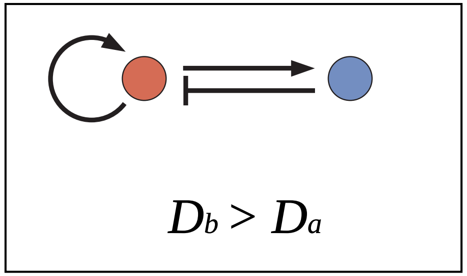
Spatial Instabilities

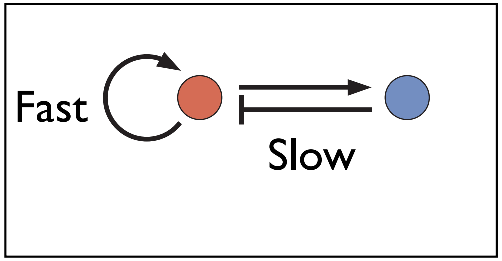
- Local positive feedback
- Long range inhibition

Temporal Instabilities

- Local positive feedback
- Negative feedback with a delay

Chemical





Mechanical

Contractility driven positive feedback
Elasticity: negative feedback

Next Course: 4 December

1. Introduction - Program and Self-Organisation
2. Chemical Instabilities
   21. Spatial instabilities - Turing patterns
   22. Temporal instabilities - Excitability
   23. Spatial-temporal instabilities: waves

3. Mechanical instabilities
   31. Cellular aggregates: viscoelastic model
   32. Active gel: hydrodynamic and viscoelastic models

4. Mechano-chemical Instabilities
   41. Mechano-chemical coupling: actomyosin dynamics
   42. Actin based trigger waves

5. Developmental significance: impact on cellular and tissue morphogenesis