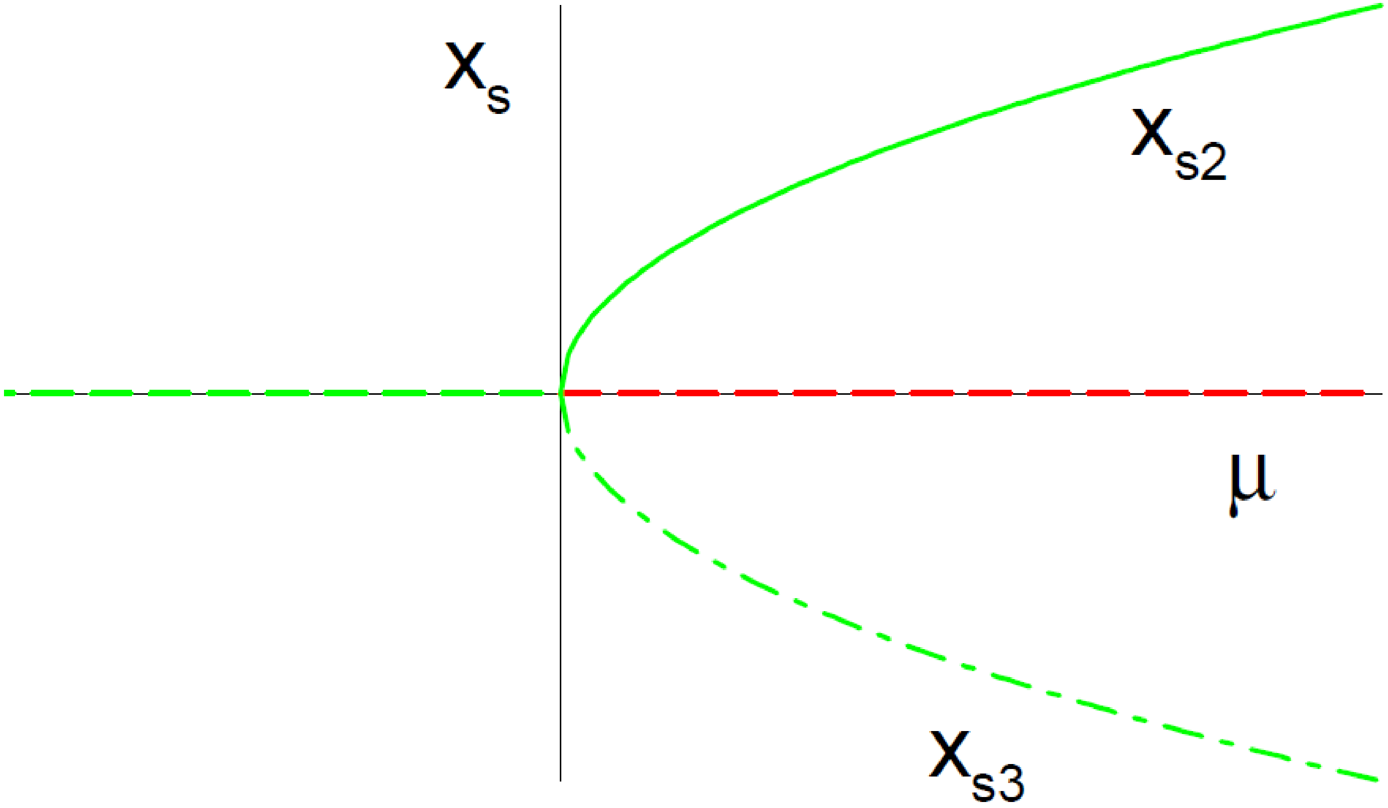
Stability analysis

Lutz Brusch, 13 August 2018



Stability analysis of ODE models

$$\frac{d}{dt}\vec{u}(t) = \vec{f}(\vec{u}(t))$$

The analysis of such models conveniently proceeds step by step from simple solutions towards related but more complex solutions via a cascade of instabilities of the respective simpler solutions.

Steady state: The simplest solution $\vec{u}^*$ has constant values $\frac{d}{dt}\vec{u}^* = 0$ and is determined from

$$0 = \vec{f}(\vec{u}^*)$$

which may yield multiple solutions if the functions $f_j(\vec{u}^*)$ are nonlinear. To determine the stability of $\vec{u}^*$ one has to consider small perturbations around $\vec{u}^*$. These allow to linearize the ODEs by means of a truncated Taylor expansion leading to a linear system written in terms of the Jacobi-matrix.

Stability analysis of ODE models

Linearization around steady state $\vec{u}^*$: Jacobi-matrix J with partial derivatives at the steady state $\left.\frac{\partial f_j}{\partial u_i}\right|_{\vec{u}^*}$ lets us write

$$\frac{d}{dt}\vec{\tilde{u}}(t) = J\vec{\tilde{u}}(t)$$

The Jacobi-matrix has eigenvalues λ_i and the linearization has solutions $\vec{u} \sim \vec{u}^* + \sum_i \vec{\epsilon} e^{\lambda_i t}$.

Linear stability of steady state $\vec{u}^*$: only if all $Re[\lambda_i] < 0$ then the solution $\vec{u}^*$ is stable towards small perturbations.

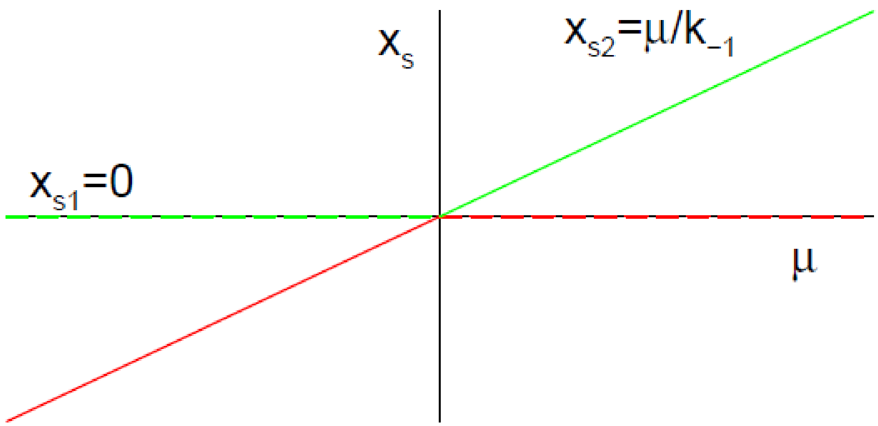
Bifurcations: If model parameters are varied then for a set of critical values the linearization may yield $Re[\lambda_i] = 0$. These critical values are called bifurcation points where the stability of the examined solution changes. Moreover, a new solution emerges from the examined one and exists for parameter values beyond the critical value [Sattinger 1972].

Bifurcation analysis

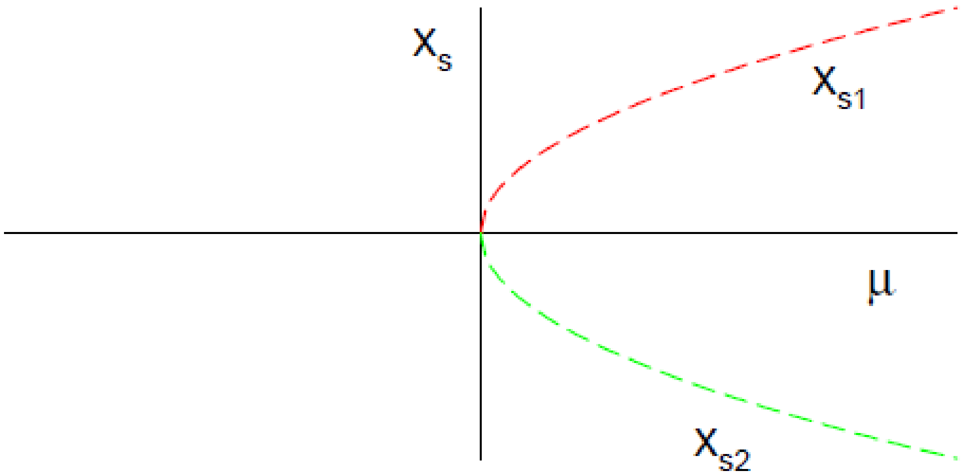
Exactly 4 types of local codimension-1 bifurcations

Multiple solution branches are shown as curves with different line-styles to distinguish individual solutions. Their linear stability is indicated by color: stable=green, unstable=red.

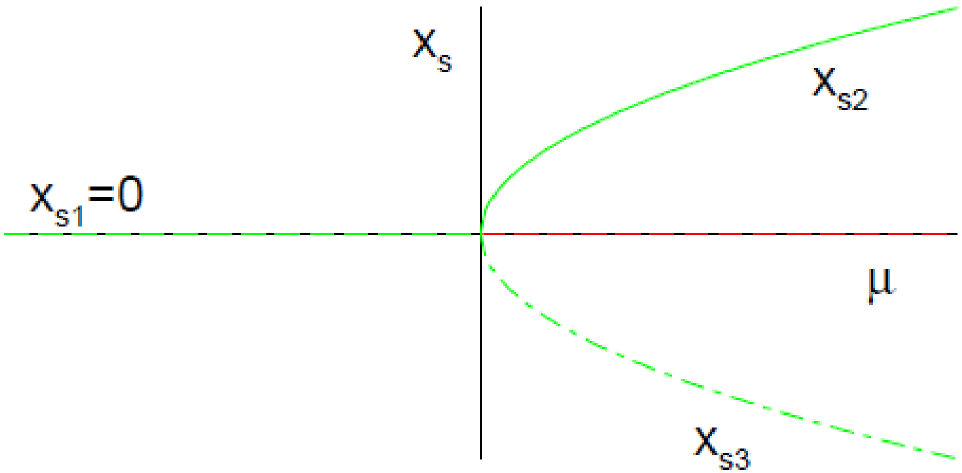
1. **Transcritical bif.** is possible in systems with the normal form $\frac{dx}{dt} = \mu x - x^2$
   Two solution branches intersect and exchange stability properties.



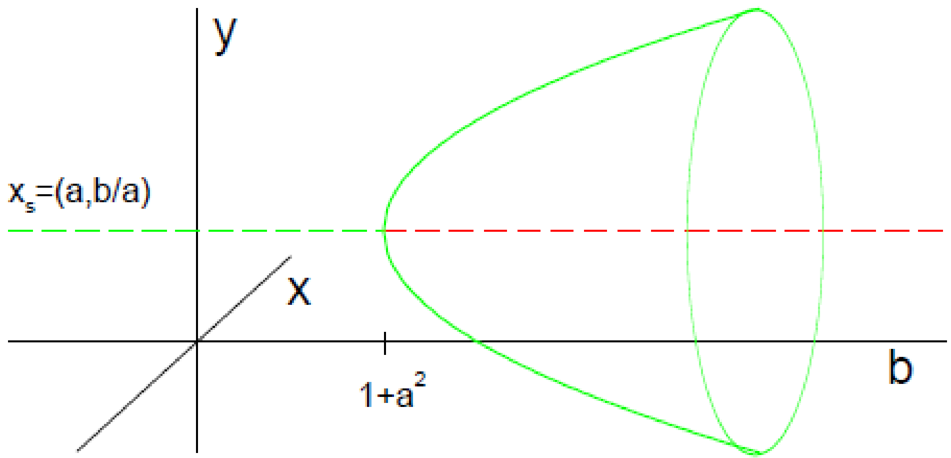
2. **Saddle-node bif.** has the normal form $\frac{dx}{dt} = \mu - x^2$.



3. **Pitchfork bif.** has the normal form $\frac{dx}{dt} = \mu x - x^3$.



4. **Hopf bif.** occurs in the Brusselator model $\frac{dx}{dt} = a - (b+1)x + x^2y$, $\frac{dy}{dt} = bx - x^2y$
which in polar coordinates $x = R\cos\varphi$, $y = R\sin\varphi$, $R \geq 0$
yields the normal form of the Hopf bif. $\frac{dR}{dt} = R(\mu - R^2)$, $\frac{d\varphi}{dt} = 1$.



Oscillations: If eigenvalues λ_i possess imaginary parts then they come in pairs of complex conjugates and the solution oscillates in time around the examined $\vec{u}^*$. If $Re[\lambda_i]$ crosses zero (the pair has purely imaginary values) then one speaks of a Hopf-bifurcation and oscillatory solutions exist on one side of the critical parameter value.

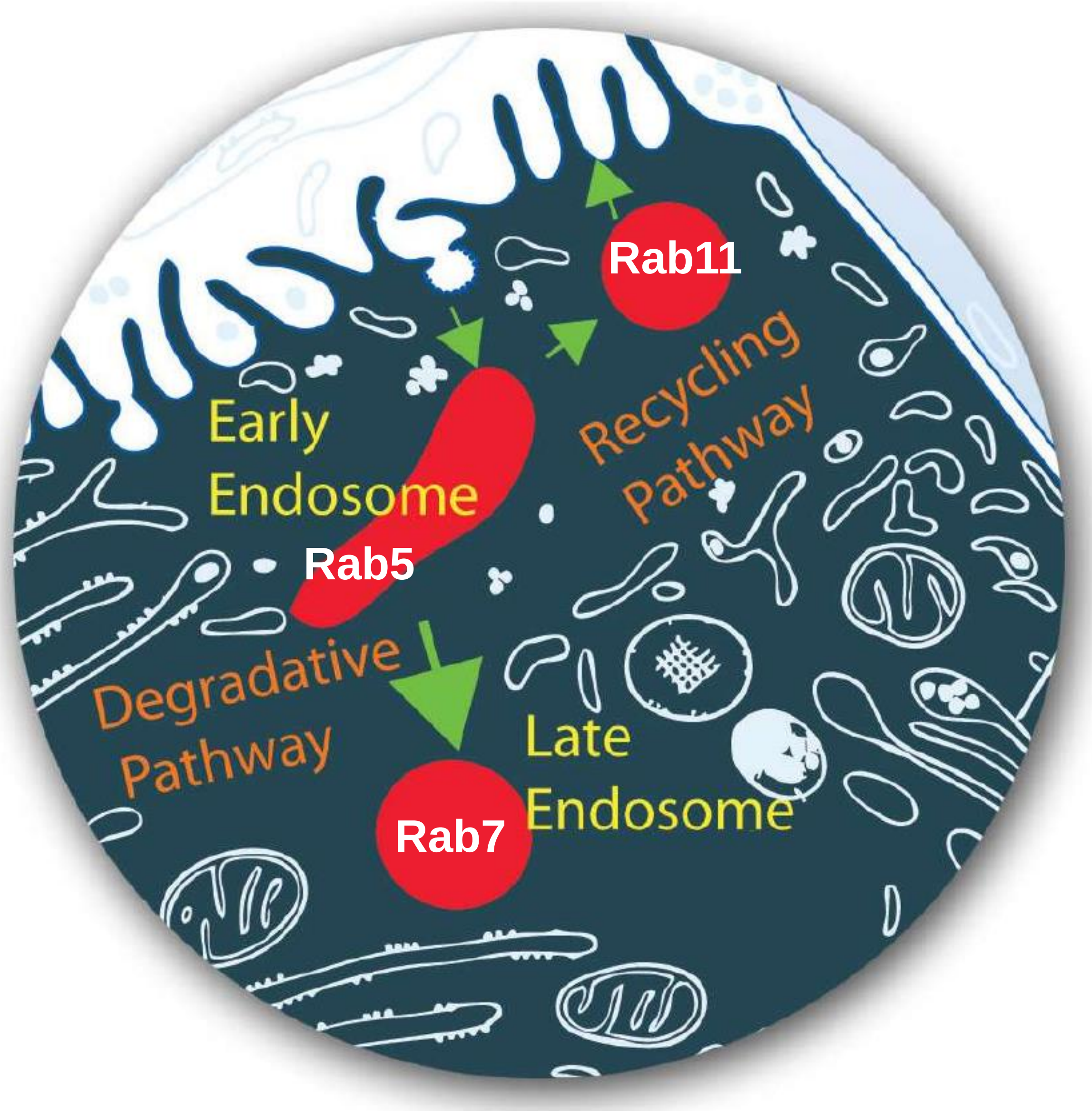
Numerical tools for linear stability and bifurcation analysis

AUTO: http://indy.cs.concordia.ca/auto/

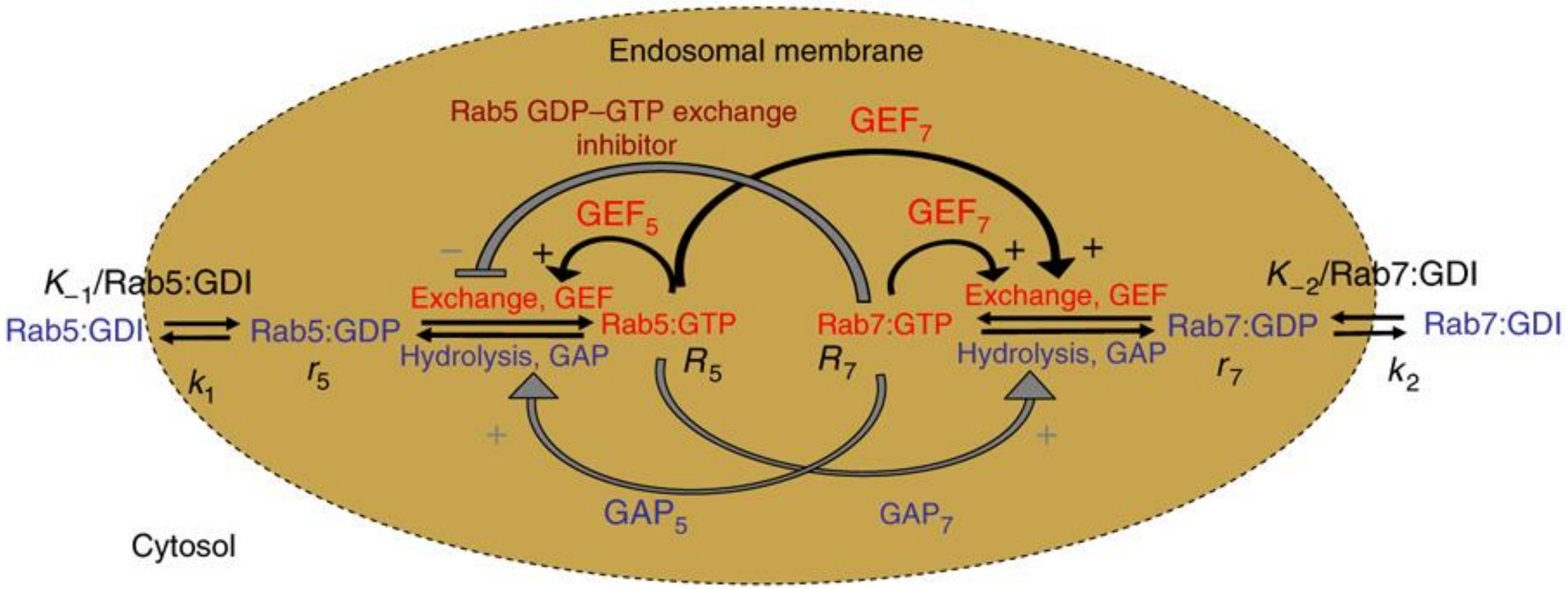
XPP: http://www.math.pitt.edu/~bard/xpp/xpp.html

MATCONT: http://sourceforge.net/projects/matcont/

Example: Intracellular membrane identities



Rab GTPases interact via GEFs and GAPs



$$\frac{dr_5}{dt} = K_{-1} - (k_1 + GEF_5(R_5, R_7))r_5(t) + GAP_5(R_5, R_7)R_5(t)$$

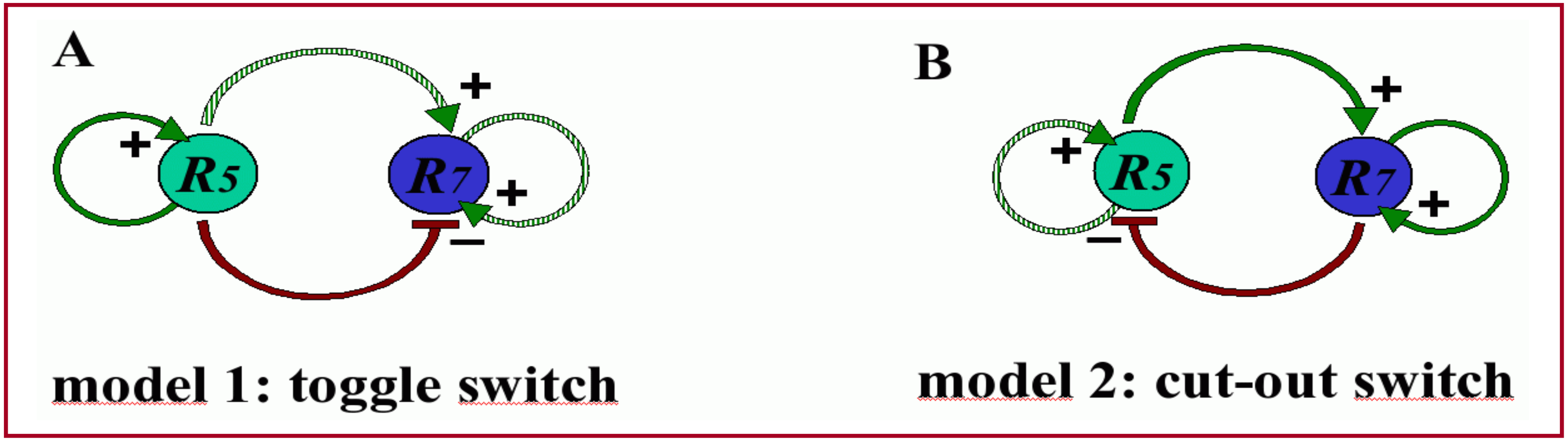
$$\frac{dR_5}{dt} = GEF_5(R_5, R_7)r_5(t) - GAP_5(R_5, R_7)R_5(t)$$

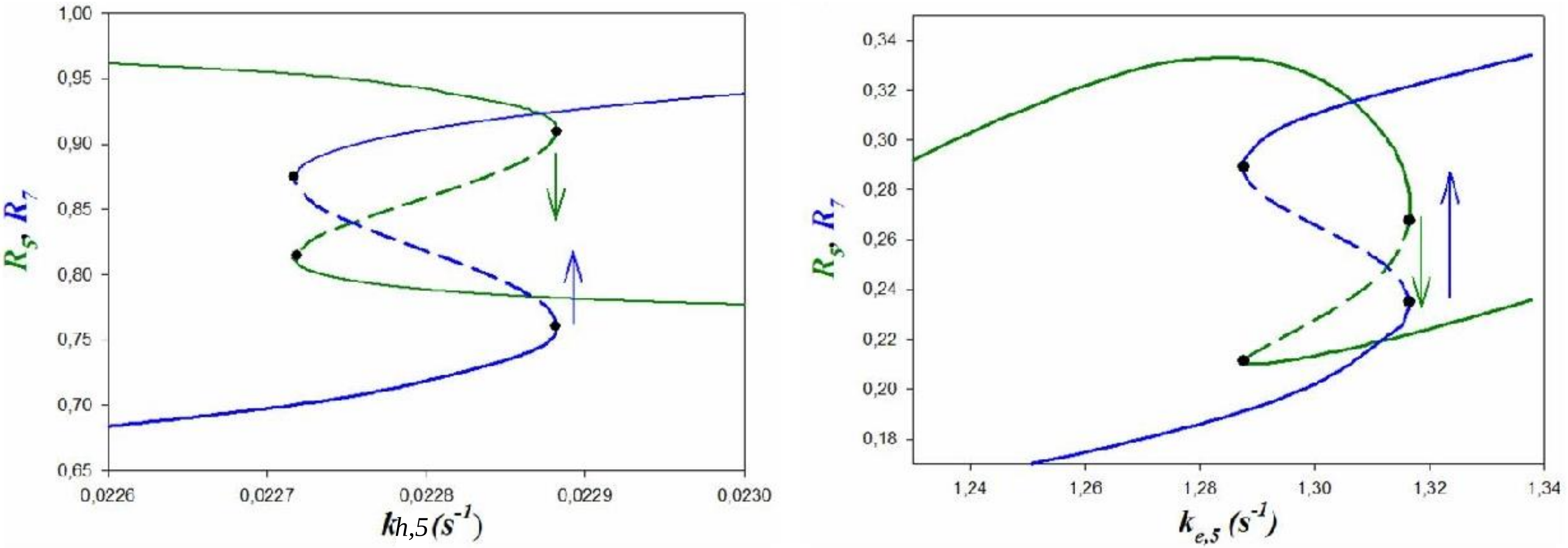
$$\frac{dr_7}{dt} = K_{-2} - (k_2 + GEF_7(R_5, R_7))r_7(t) + GAP_7(R_5, R_7)R_7(t)$$

$$\frac{dR_7}{dt} = GEF_7(R_5, R_7)r_7(t) - GAP_7(R_5, R_7)R_7(t)$$

Del Conte-Zerial et al., Mol Syst Biol, 4, 206, 2008.

Rab GTPases interact via GEFs and GAPs





Del Conte-Zerial et al., Mol Syst Biol, 4, 206, 2008.

Linear stability analysis of reaction-diffusion PDEs

Linear stability of reaction-diffusion PDEs

$$\frac{\mathrm{d}u}{\mathrm{d}t} = f(u,v) + D_u \frac{\partial^2 u}{\partial x^2}$$
$$\frac{\mathrm{d}v}{\mathrm{d}t} = g(u,v) + D_v \frac{\partial^2 v}{\partial x^2}$$

Instability of homogeneous steady state towards spatially periodic modulation:

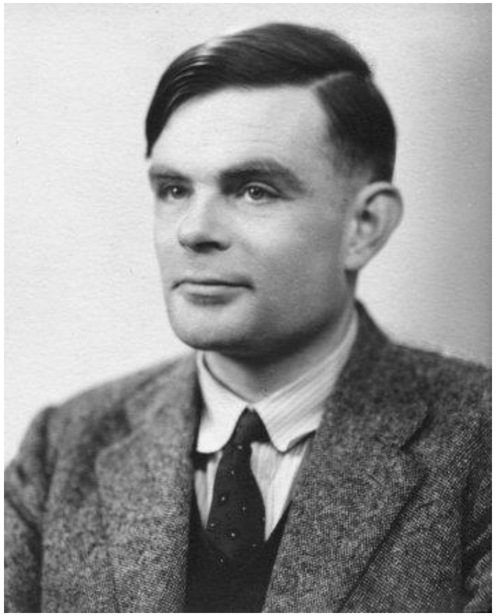
$$\frac{D_v}{D_u} > \frac{\left(\sqrt{f_u g_v - f_v g_u} + \sqrt{-f_v g_u}\right)^2}{(f_u)^2}$$

with a wavelength l of the spatial modulation:

$$l = 2\pi \left(\frac{f_u}{2D_u} + \frac{g_v}{2D_v} \right)^{-1/2}$$

Chara et al., Curr. Top. Dev. Biol., 108, 283-317, 2014.

Alan Turing
1912 - 1954



Philos Trans R Soc Lond B 237, 3772 (1952):

THE CHEMICAL BASIS OF MORPHOGENESIS

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

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

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by

Periodic Turing patterns

$$
\begin{aligned}
X_t &= 5X - 6Y + 1 \quad + 0.5X_{xx} \\
Y_t &= 6X - 7Y + 1 \quad + 4.5X_{xx}
\end{aligned}
$$

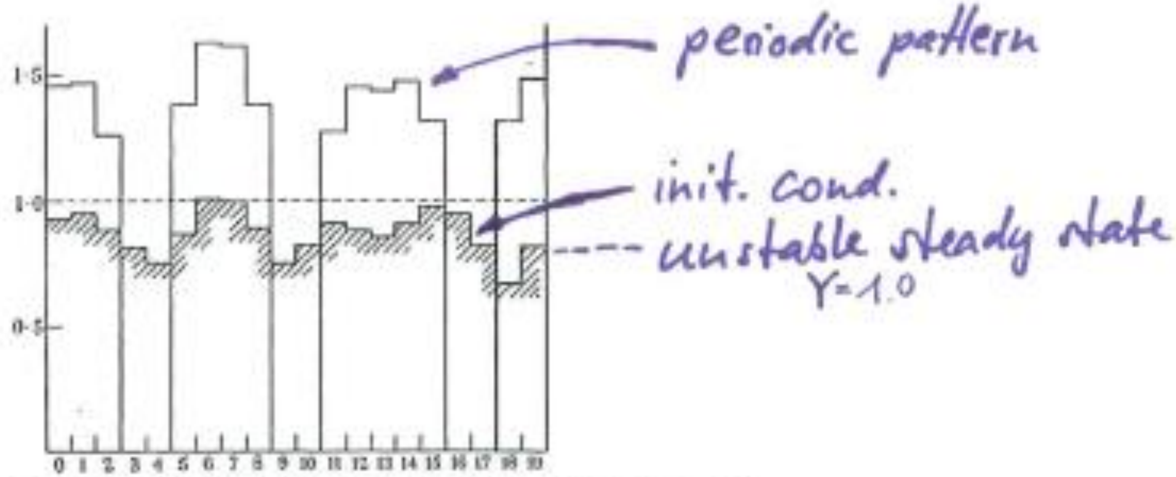
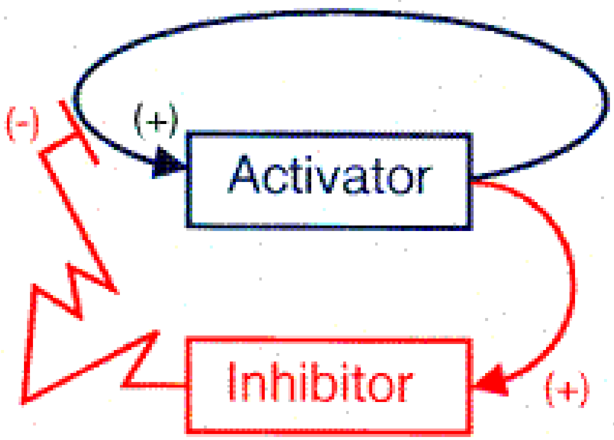


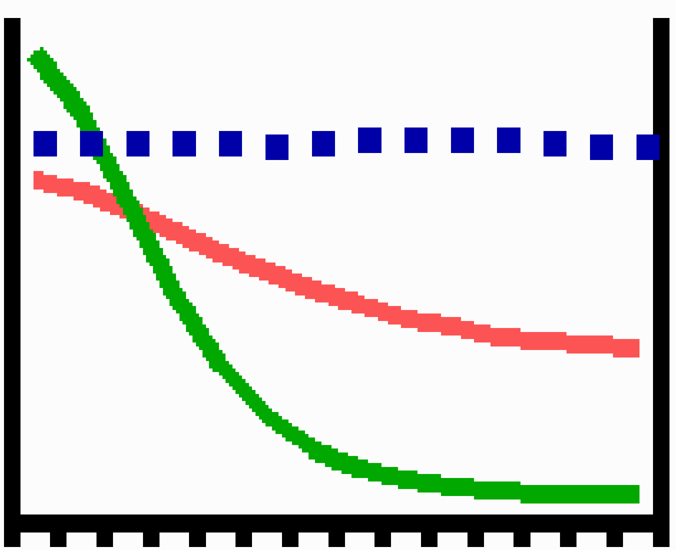
FIGURE 3. Concentrations of Y in the development of the first specimen (taken from table 1). ------- original homogeneous equilibrium; ////// incipient pattern; ——— final equilibrium.

Gierer-Meinhardt principle: local activation, lateral inhibition

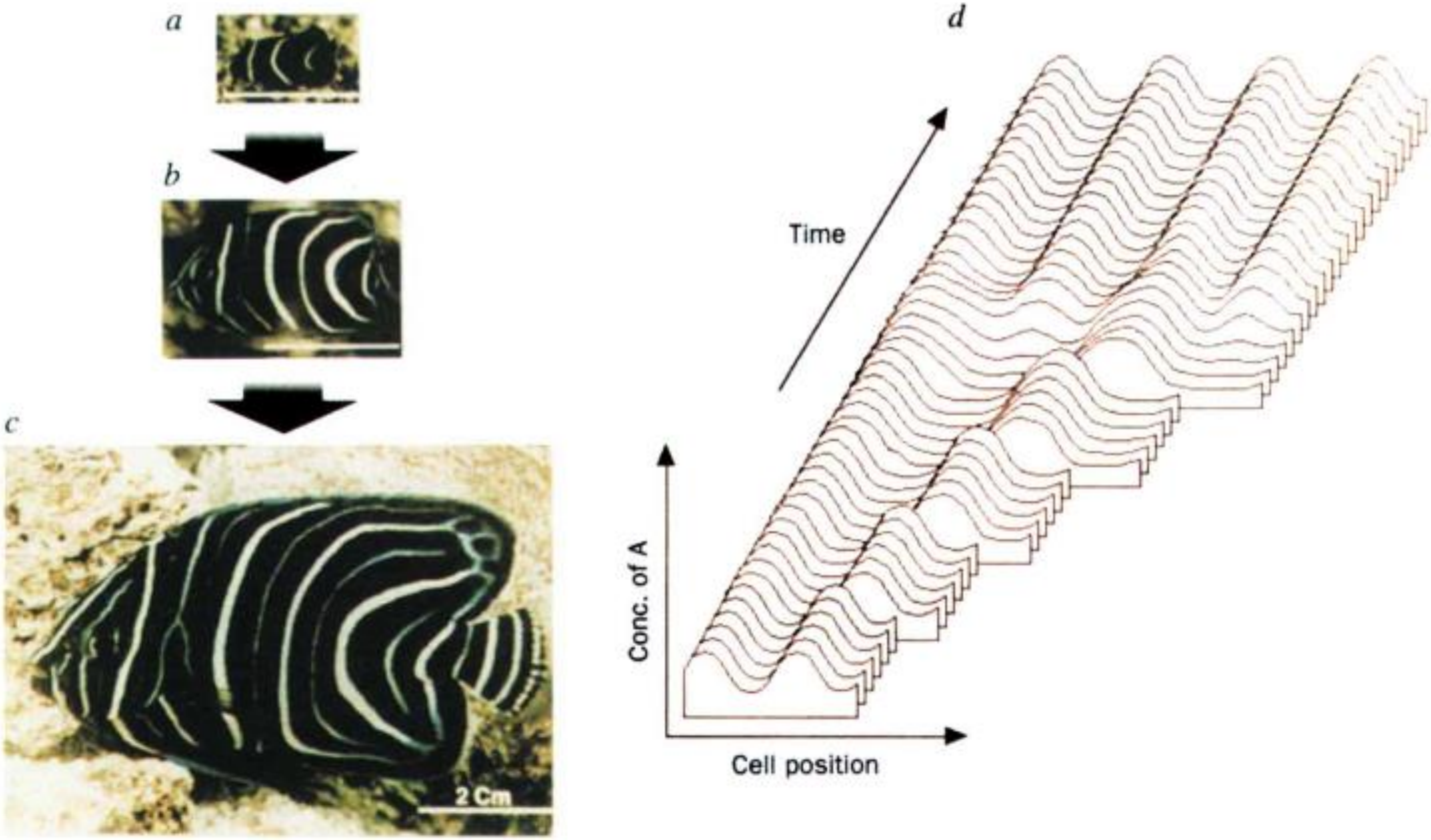
Gierer, A. and Meinhardt, H. (1972).

A theory of biological pattern formation. Kybernetik **12**, 30-39.



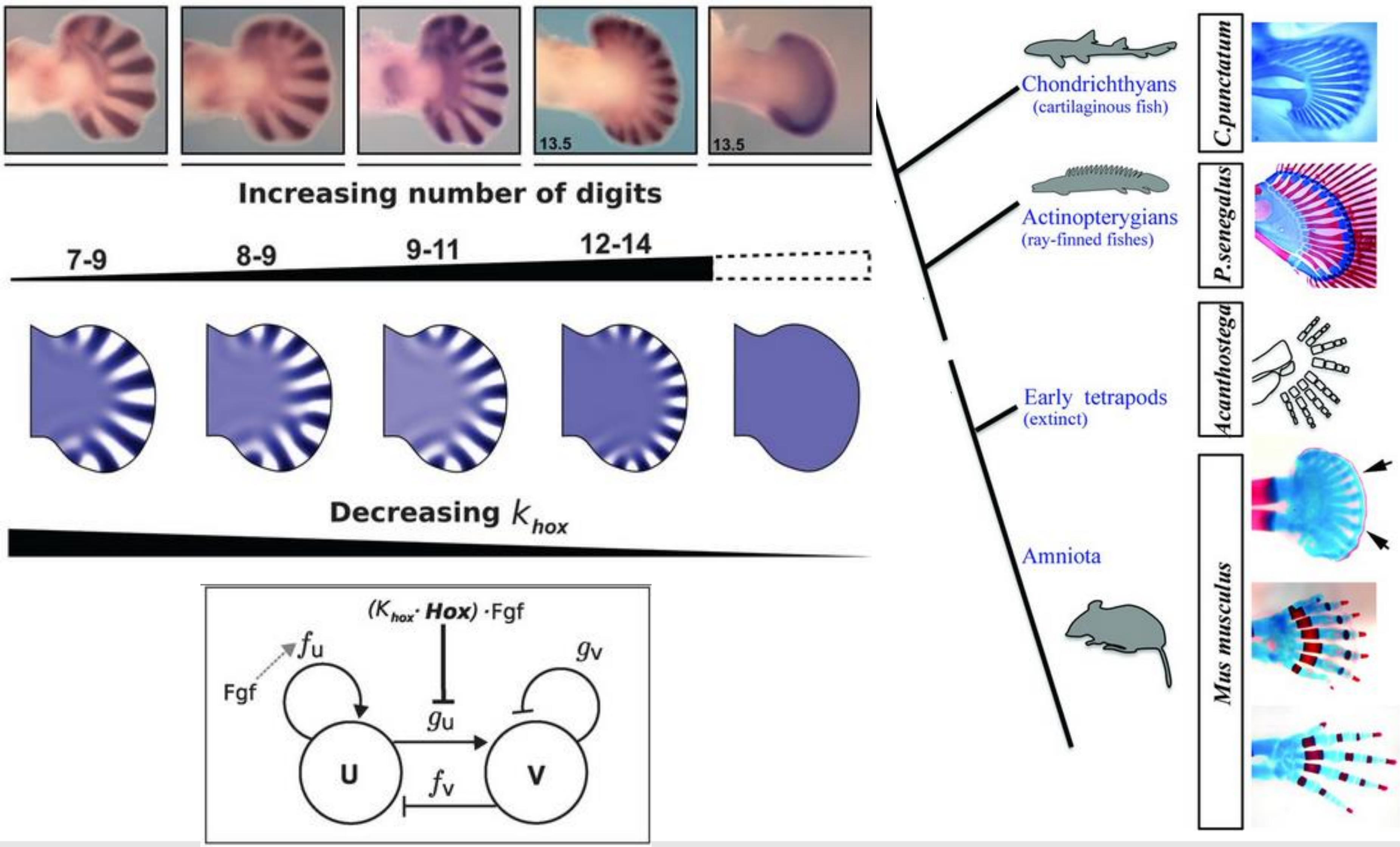


Turing pattern: pigment stripes



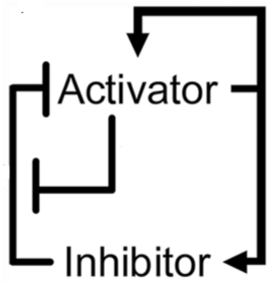
Kondo et al., Nature 376, 765 (2002)

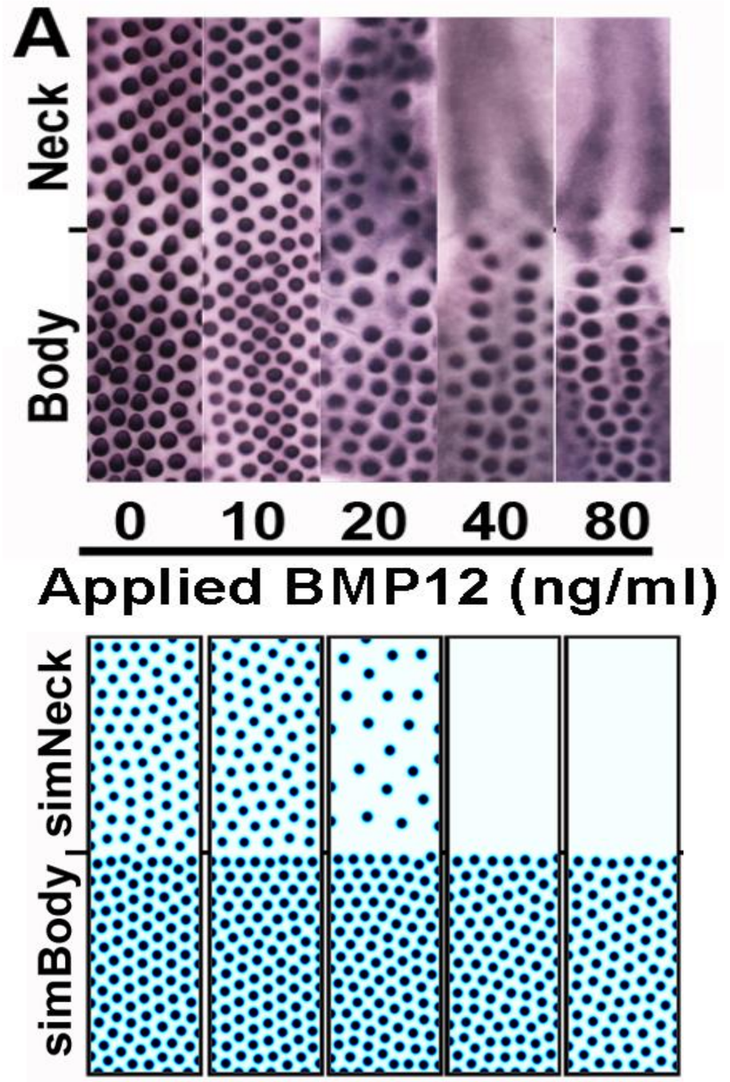
Turing pattern: fingers



Sheth et al., Science 338, 1476 (2012)

Turing pattern: feathers





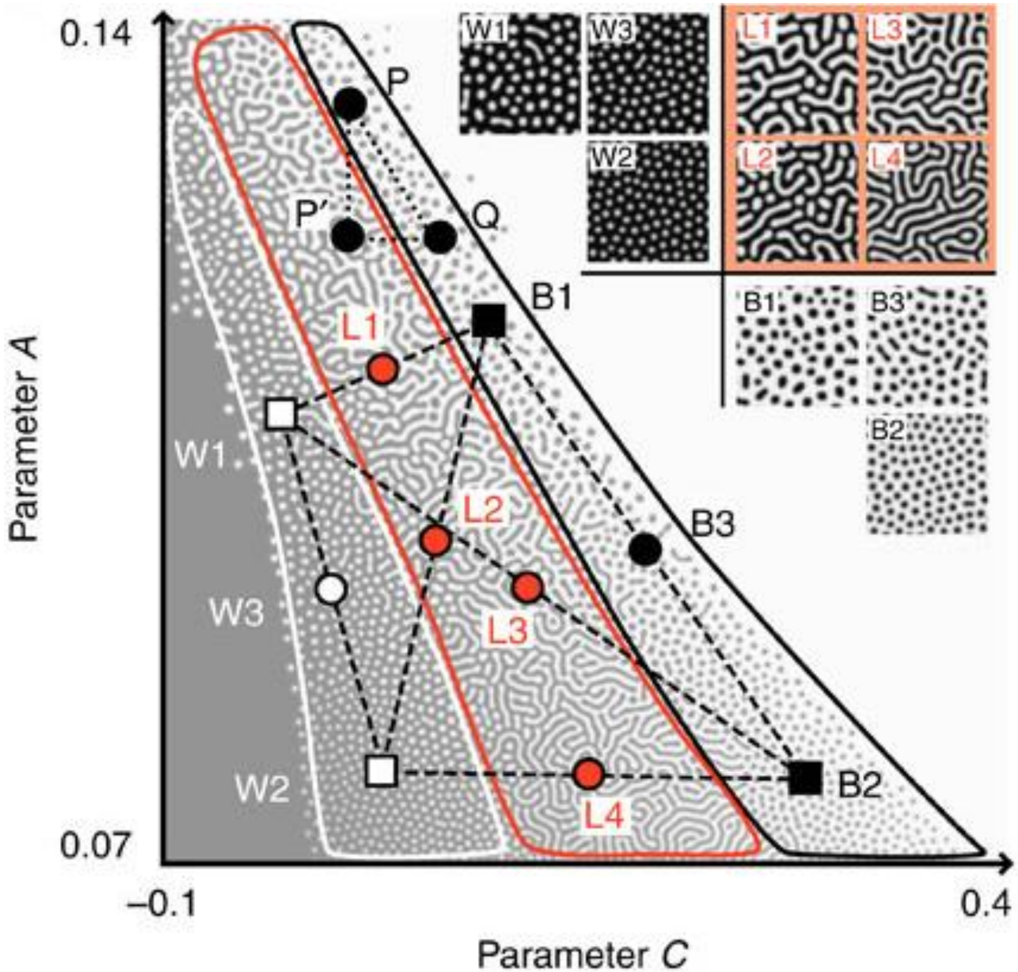
Mou et al., PLoS Biol 9, e10010282 (201

Pattern hybridization

white spots + dark spots = ?

Miyazawa et al., Nature Comm.1, 66

Pattern hybridization



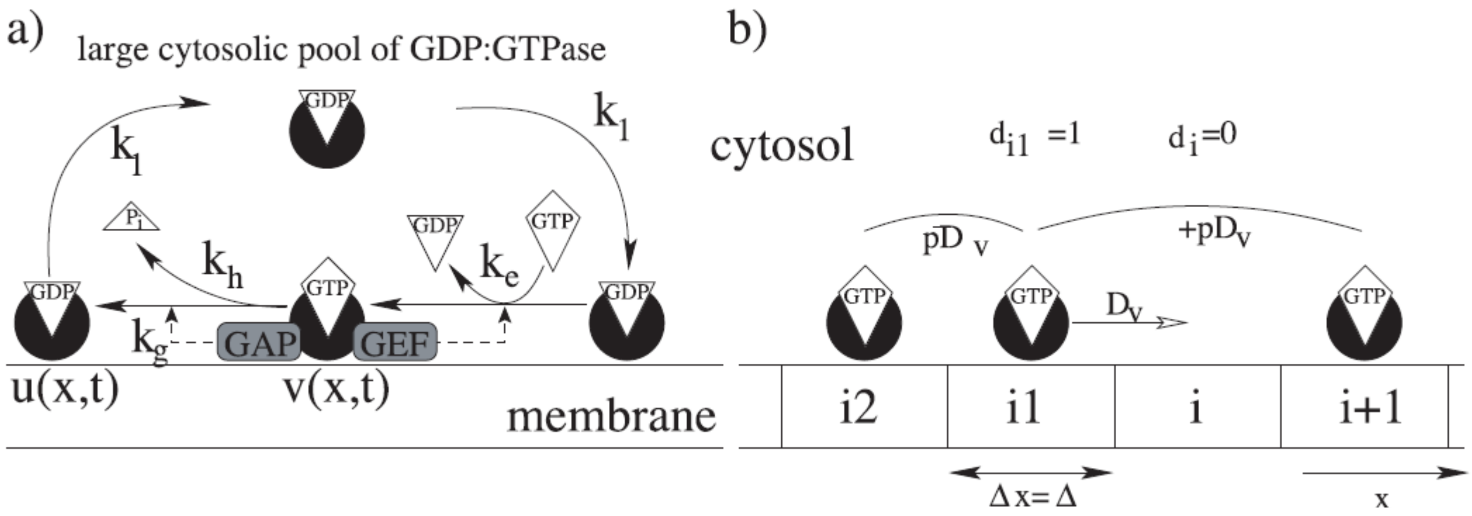
Miyazawa et al., Nature Comm.1, 66

Pattern hybridization

white spots + dark spots = labyrinth

Miyazawa et al., Nature Comm.1, 66

Beyond reaction-advection-diffusion: GTPase domains on membranes



$$\frac{\Delta d_i}{\Delta t} = \frac{D_v}{\Delta^2}\left[1 + p d_{i+1} - \bar{p} d_{i-2}\right](1-d_i)d_{i-1} \qquad \text{jump } i-1 \rightarrow i$$

$$+ \frac{D_v}{\Delta^2}\left[1 + p d_{i-1} - \bar{p} d_{i+2}\right](1-d_i)d_{i+1} \qquad \text{jump } \quad i \leftarrow i+1$$

$$- \frac{D_v}{\Delta^2}\left[1 + p d_{i-2} - \bar{p} d_{i+1}\right](1-d_{i-1})d_i \qquad \text{jump } i-1 \leftarrow i$$

$$- \frac{D_v}{\Delta^2}\left[1 + p d_{i+2} - \bar{p} d_{i-1}\right](1-d_{i+1})d_i \qquad \text{jump } \quad i \rightarrow i+1$$

Brusch et al. in Mathematical Modeling of Biological Systems, Birkhauser, 33-46, 2008.

Beyond reaction-advection-diffusion: GTPase domains on membranes

$$u_t = k_1(1-u-v) - \left(k_{-1} + k_e \frac{v}{k_M + v}\right) u + k_h \left(1 + k_g \frac{v}{k_M + v}\right) v + D_u u_{xx}$$

$$v_t = k_e \frac{v}{k_M + v} u - k_h \left(1 + k_g \frac{v}{k_M + v}\right) v + D_v v_{xx}$$

Turing

$$+ D_v p \Big[(-2v + 3v^2) v_{xx} + (-2 + 6v) v_x^2$$

extended Swift-Hohenberg

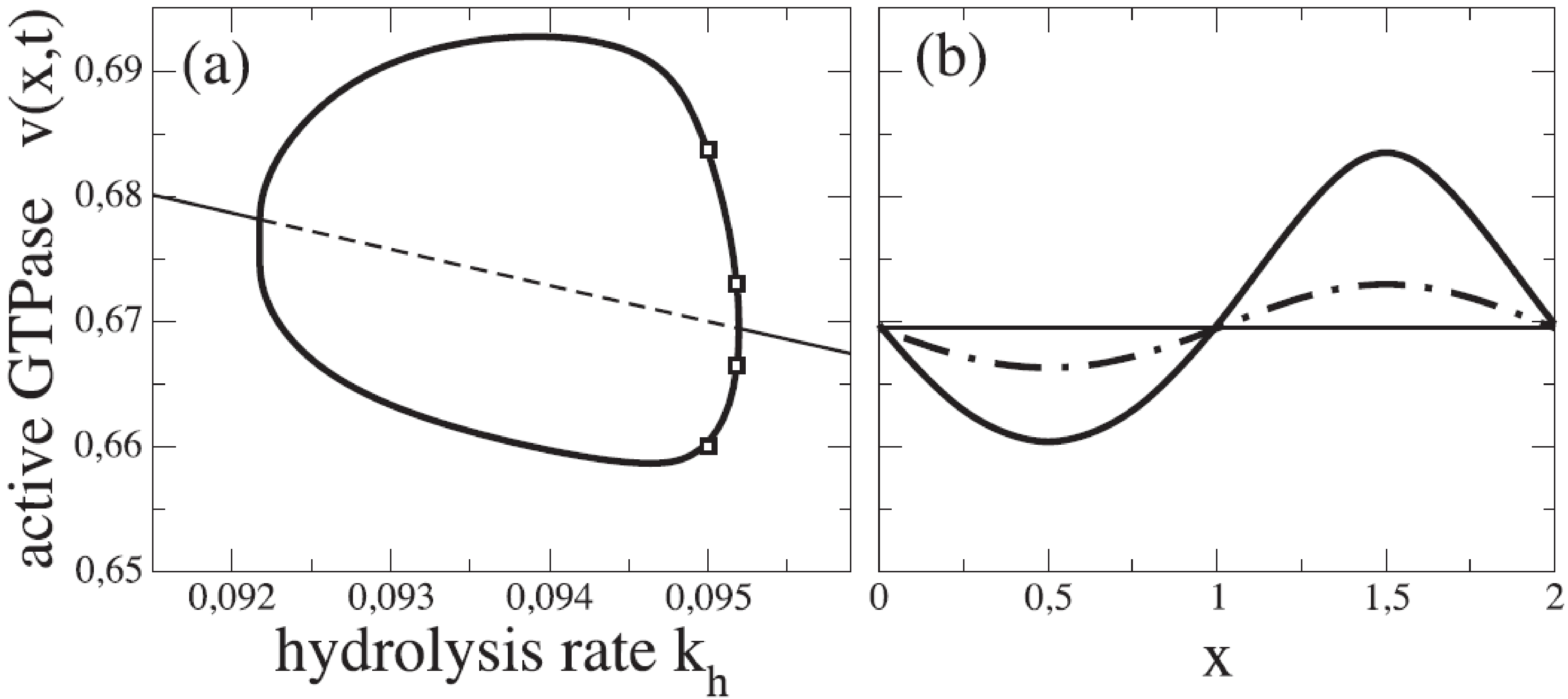
$$+ \Delta^2 \left\{ \left(-\frac{7}{6} v + \frac{5}{4} v^2\right) v_{xxxx} + \left(-\frac{2}{3} + 4v\right) v_x v_{xxx} + \left(\frac{1}{2} + \frac{3}{2} v\right) v_{xx}^2 \right\} \Big]$$

$$- D_v \bar{p} \Big[(4v - 3v^2) v_{xx} + (4 - 6v) v_x^2$$

$$+ \Delta^2 \left\{ \left(\frac{4}{3} v - \frac{5}{4} v^2\right) v_{xxxx} + \left(\frac{10}{3} - 4v\right) v_x v_{xxx} + \left(2 - \frac{3}{2} v\right) v_{xx}^2 \right\} \Big].$$

Brusch et al. in Mathematical Modeling of Biological Systems, Birkhauser, 33-46, 2008.

Beyond reaction-advection-diffusion: GTPase domains on membranes



Brusch et al. in Mathematical Modeling of Biological Systems, Birkhauser, 33-46, 2008.

Literature

- A. Turing (1952) The Chemical Basis of Morphogenesis. Phil. Trans. R. Soc. Lond. B 237, 37-72.
- A. Gierer and H. Meinhardt (1972) A theory of biological pattern formation. Kybernetik 12, 30-39.
- H. Meinhardt (1982) Models of Biological Pattern Formation. Academic Press and http://www.eb.tuebingen.mpg.de/de/forschung/emeriti/hans-meinhardt/home.html
- J. D. Murray (2007, 3rd ed.) Mathematical Biology. Springer
- S. Kondo and T. Miura (2010) Reaction-Diffusion Models as a Framework for Understanding Biological Pattern Formation. Science 329, 1616-1620.