Pattern formation in reaction-diffusion-ode models

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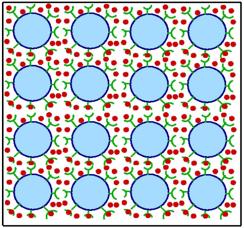
Reaction-diffusion-ode models of biological processes

Receptor-based models

Models of biological tissues

Macroscopic receptor-based models



$$\partial_t u = D\Delta u + f(u,v)$$
$$\partial_t v = g(u,v)$$

+ zero-flux boundary conditions
+ initial conditions
$x \in \Omega \subset \mathbb{R}^N, \; t \in \mathbb{R}^+$

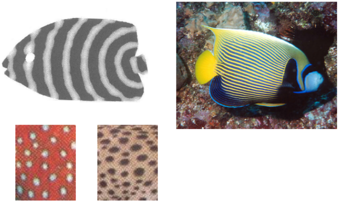
homogenisation

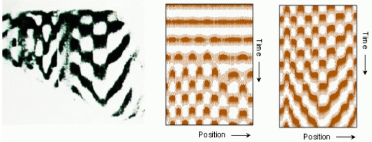
(rigorous)

Mechanisms of pattern formation

- What is the role of non-diffusing components ?
- Can models with only one diffusion exhibit patterns?

Classical concept of pattern formation





Turing idea

Diffusion-driven instabilities (DDI) $\rightarrow$ Turing-type patterns

- DDI takes place when
  - the kinetics system is asymptotically stable
  - the complete system unstable for spatially non-homogeneous perturbations
- Linear stability analysis

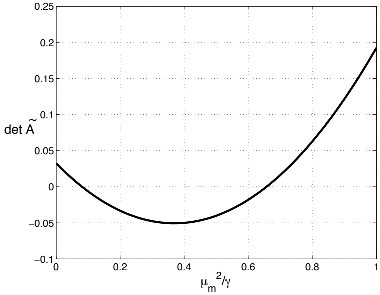
$$\tilde{A}(\mu_m) = A - \frac{1}{\gamma} D {\mu_m}^2.$$

A is Jacobian matrix at a steady state and ${\mu_m}^2$ is a wavenumber obtained from the Laplacian's eigenproblem:

$$\begin{aligned} \triangle_x \phi_m &= -{\mu_m}^2 \phi_m \quad in \ \Omega, \\ \partial_n \phi_m &= 0 \end{aligned}$$

Dispersion relation

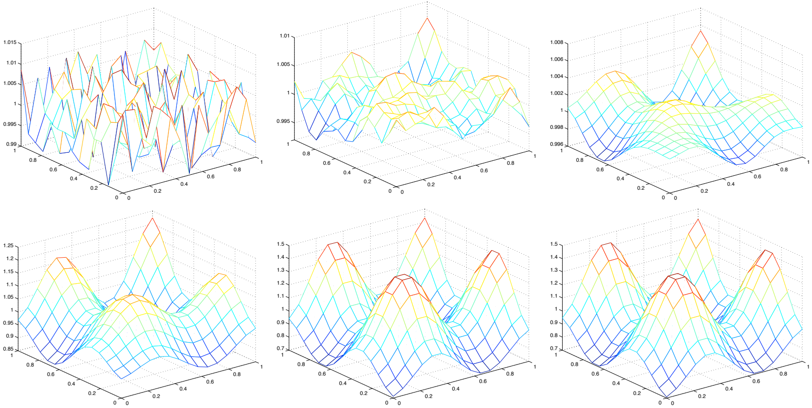
- Eigenvalues λ of $\tilde{A}$ depend on the model parameters and the wave number ${\mu_m}^2$.
- DDI condition for a 2-equation model $\det \tilde{A}(\mu_m) > 0$.



- The dependence $\lambda({\mu_m}^2)$ is called the dispersion relation.

How do patterns grow?

Examples in two-dimensional domain



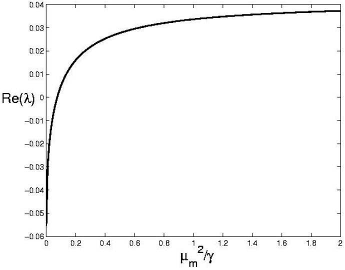
Turing patterns

Definition

By Turing patterns we call the solutions of reaction-diffusion equations that are

- stable,
- stationary,
- continuous,
- spatially heterogenous and
- arise due to the Turing instability (DDI) of a constant steady state.

DDI in the model with 1 diffusion operator



- DDI condition: $(-1)^k \det \tilde{A} < 0$, where $\det \tilde{A} = \det A - \frac{\mu_m^2}{\gamma} \det A_{ODE}$
- Destabilisation of the constant stationary solution is caused by the ODE subsystem

How does it work for two equations?

$$
\begin{aligned}
u_t &= f(u, v), \\
v_t &= D_v \Delta v + g(u, v) \\
\partial_n v &= 0 \qquad x \in \partial\Omega, \ t > 0 \\
u(x, 0) &= u_0(x), \\
v(x, 0) &= v_0(x).
\end{aligned}
$$

Theorem

Assume that the constant vector $(\bar{u}, \bar{v})$ is a (stationary) solution of the initial-boundary value problem for this reaction-diffusion-ode system. If

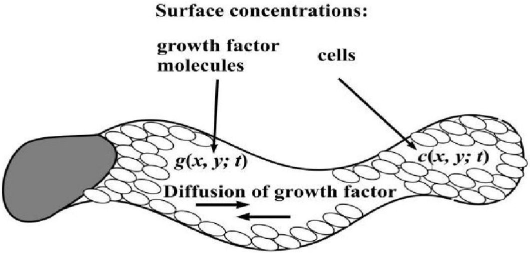
$$f_u(\bar{u}, \bar{v}) > 0,$$

then $(\bar{u}, \bar{v})$ is an **unstable** *solution of this problem.*

Autocatalysis leads to DDI.

Reaction-diffusion-ode system with DDI leading to unbounded growth of solutions

Inspiring example: Model of early cancerogenesis



- Cell proliferation is influenced by growth factor
- Growth factor is externally supplied or produced by the cells
- Growth factor diffuses along the structure formed by the cells and binds to cell membrane receptors

A.M-C and M.Kimmel, Math. Meth. Mod. Appl. Sci, 2007,
A.M-C and M.Kimmel, Math. Mod. Natural Phenomena, 2008, ...

Basic model

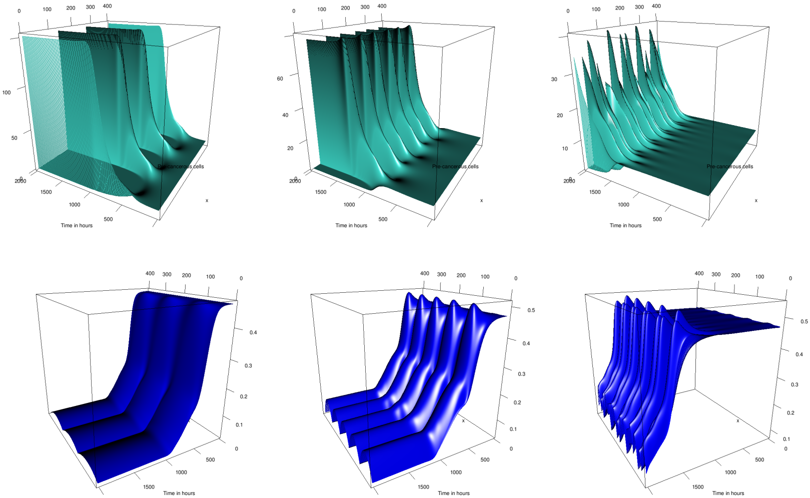
$$u_t = \left(\frac{a\frac{v}{u}}{1+\frac{v}{u}} - d_c\right)u,$$
$$v_t = -d_b v + u^2 w - dv,$$
$$w_t = \frac{1}{\gamma} w_{xx} - d_g w - u^2 w + dv + \kappa_0$$

for $x \in (0,1)$, $t > 0$ with the homogeneous Neumann boundary conditions for the function $w = w(x,t)$.

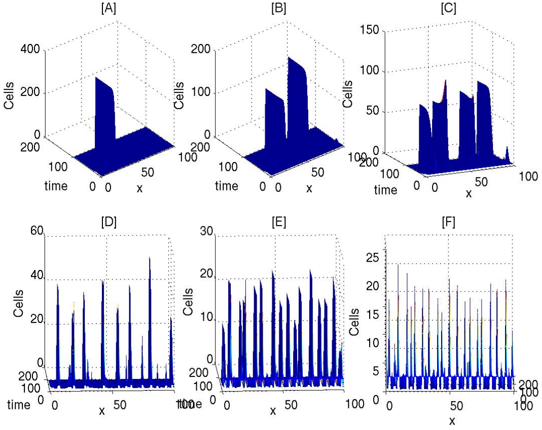
- The model has a positive spatially constant stationary solution exhibiting DDI (the autocatalysis condition is fulfiled)

A.M-C, G.Karch, K.Suzuki, J.Math.Pures et Appl., 2013

Spatial profiles of the solutions



Random initial perturbation



Goal: Understand what we see in simulations

Do we observe Turing patterns?

- Spatially homogeneous solutions are uniformly bounded
- The model has a positive spatially constant stationary solution exhibiting DDI (the autocatalysis condition is fulfiled)
- We show that all Turing patterns are unstable.

Generic reaction-diffusion-ode system

$$
\begin{aligned}
u_t &= f(u, v), && \text{for} \quad x \in \overline{\Omega},\ t > 0 \\
v_t &= D\Delta v + g(u, v) && \text{for} \quad x \in \Omega,\ t > 0
\end{aligned}
$$

in a bounded domain $\Omega \subset \mathbb{R}^n$.

- Homogeneous Neumann boundary condition:

$$\partial_n v = 0 \qquad \text{for} \quad x \in \partial\Omega,\ t > 0$$

- Initial data:

$$u(x, 0) = u_0(x), \qquad v(x, 0) = v_0(x).$$

- $D > 0$
- Arbitrary C^1-nonlinearities $f = f(u, v)$ and $g = g(u, v)$.

Regular stationary solutions

Assume that we can solve the equation

$$f(U(x), V(x)) = 0$$

to have

$$U(x) = k(V(x))$$

for a C^1-function $k = k(V)$.
Regular stationary solutions of

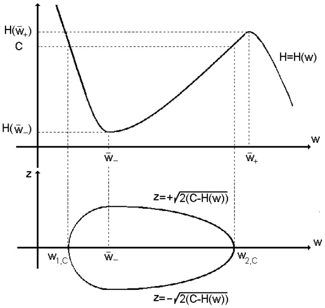
$$\begin{aligned} &f(U, V) = 0, \\ &D\Delta V + g(U, V) = 0 \\ &\partial_n V = 0 \qquad x \in \partial\Omega \end{aligned}$$

satisfy the boundary value problem

$$\begin{aligned} &D\Delta V + h(V) = 0, \\ &\partial_n V = 0 \quad \text{on} \quad \partial\Omega, \end{aligned}$$

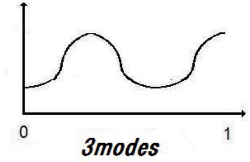
where $h(V) = g(k(V), V)$.

Construction of patterns in one-dimensional domain



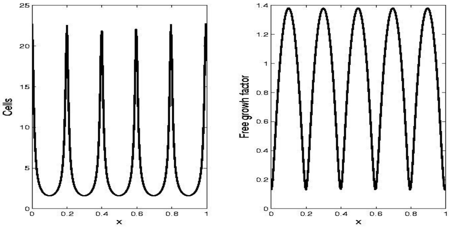
- Energy equation $\frac{1}{2}z^2 + H(V) = C$, where $V' = z$.
- All trajectories are symmetric with respect to V-axis.
- The condition $z(0) = z(T)$ is satisfied for a certain $T < 0$ if energy describes a close curve for a certain $C \in \mathbb{R}$.
- Such closed curves exist only if the potential energy $H(V)$ has a local minimum.

We construct regular periodic patterns:



Which solutions are stable?

- Several nonconstant solutions for sufficiently small D
- As long as $D > m^2 D_0$ there exists a solution with m peaks.



Instability of stationary solutions

Theorem
Let (U, V) be a regular stationary solution satisfying the autocatalysis assumption

$$f_u(U(x), V(x)) > 0 \quad \text{for all } x \in \overline{\Omega}.$$

Then, (U, V) is an unstable solution.

The same mechanism which destabilizes constant solutions of such models, destabilizes also non-constant stationary solutions.

Linearisation and Spectral Mapping Theorem

Lemma

Consider the linear operator $\mathcal{L}$ given by

$$\mathcal{L}\begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix} \equiv \begin{pmatrix} 0 \\ \Delta\tilde{v} \end{pmatrix} + \begin{pmatrix} f_u(U,V) & f_v(U,V) \\ g_u(U,V) & g_v(U,V) \end{pmatrix}\begin{pmatrix} \tilde{u} \\ \tilde{v} \end{pmatrix}$$

with homogeneous Neumann boundary condition $\partial_\nu \tilde{v} = 0$. Then, the operator $\mathcal{L}$ with $D(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$ generates an analytic semigroup $\{e^{t\mathcal{L}}\}_{t\geq 0}$ of linear operators on $L^2(\Omega) \times L^2(\Omega)$, which satisfies

$$\sigma(e^{t\mathcal{L}}) \setminus \{0\} = e^{t\sigma(\mathcal{L})} \qquad \text{for every} \quad t \geq 0.$$

Spectrum of $\mathcal{L}$

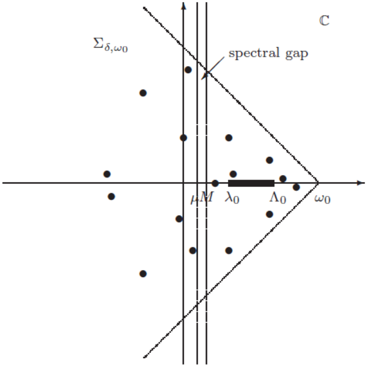
Define the constants

$$\lambda_0 = \inf_{x\in\overline{\Omega}} f_u\big(U(x),V(x)\big) > 0 \qquad \text{and} \qquad \Lambda_0 = \sup_{x\in\overline{\Omega}} f_u\big(U(x),V(x)\big) > 0,$$

The spectrum $\sigma(\mathcal{L})$ of the linear operator

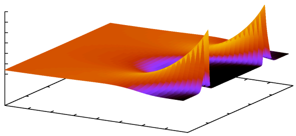
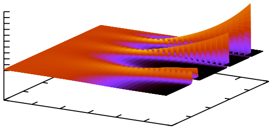
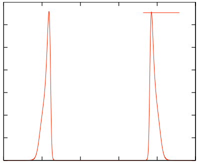
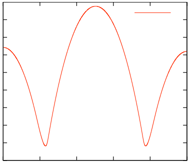
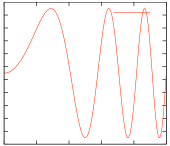
$$\mathcal{L}\begin{pmatrix}\tilde{u}\\ \tilde{v}\end{pmatrix} \equiv \begin{pmatrix}0\\ \Delta\tilde{v}\end{pmatrix} + \begin{pmatrix} f_u(U,V) & f_v(U,V)\\ g_u(U,V) & g_v(U,V)\end{pmatrix}\begin{pmatrix}\tilde{u}\\ \tilde{v}\end{pmatrix}$$

with the domain $D(\mathcal{L}) = L^2(\Omega)\times W^{2,2}(\Omega)$ looks as on the picture.



Numerical simulations

What are the patterns, which we see in numerical simulations?

Our conjecture: there are singular patterns.

Shadow system

Shadow problem

The solutions $(u^D, v^D) = (u^D(x,t), v^D(x,t))$ of

$$\begin{aligned} u_t &= f(u,v), \\ v_t &= D\Delta v + g(u,v) \end{aligned}$$

converge as $D \to \infty$ towards a solution

$$(u,\xi) = (u(x,t), \xi(t))$$

of the following **shadow system**

$$\begin{aligned} u_t &= f(u,\xi), && \text{for} \quad x \in \overline{\Omega}, \ t > 0 \\ \xi_t &= \int_\Omega g\big(u(x,t), \xi(t)\big)\, dx && \text{for} \quad t > 0 \end{aligned}$$

in a bounded domain $\Omega \subset \mathbb{R}^n$ supplemented with initial data

$$u(x,0) = u_0(x), \qquad \xi(0) = \xi_0.$$

Instability of steady states

Theorem

Assume that a constant vector $(\bar{u}, \bar{\xi})$ is a solution of the initial-boundary value problem of the system

$$\begin{aligned} u_t &= f(u, \xi), \\ \xi_t &= \int_\Omega g\big(u(x,t), \xi(t)\big)\, dx, \end{aligned}$$

which means that $f(\bar{u}, \bar{\xi}) = 0$ and $g(\bar{u}, \bar{\xi}) = 0$.
If

$$f_u(\bar{u}, \bar{\xi}) > 0,$$

then $(\bar{u}, \bar{\xi})$ is an unstable solution of this initial-boundary value problem.

Reduced model of early carcinogenesis

$$u_t = \Big(\frac{au\xi}{1+u\xi} - 1\Big)u$$

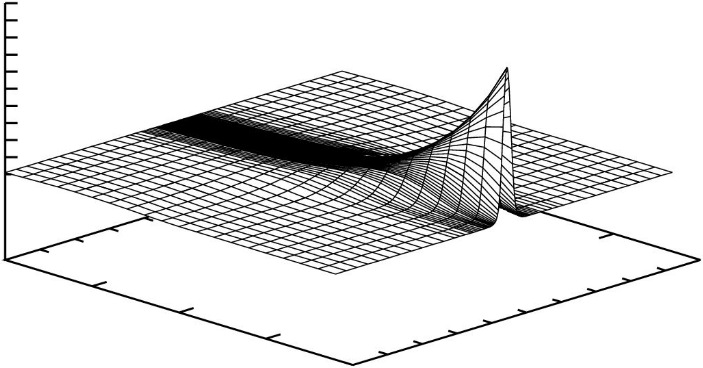
$$\xi_t = -\xi - k\xi \int_\Omega u^2 \, dx + B$$

in a bounded set $\Omega \subset \mathbb{R}^n$. We complete this system with nonnegative initial conditions

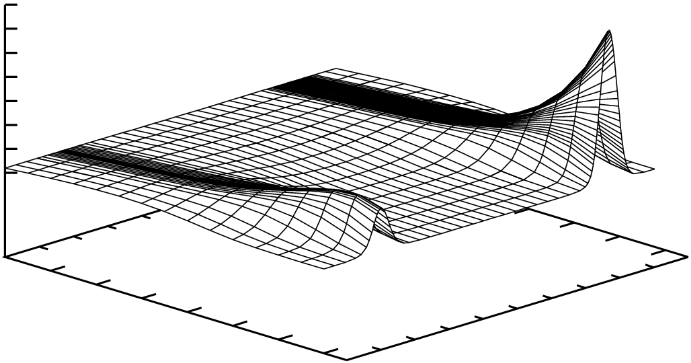
$$u(0,x) = u_0(x), \qquad \xi(0) = \xi_0.$$

- All nonnegative solutions are global-in-time.
- Space **homogeneous** solutions are uniformly bounded
- Blowup of some space **inhomogeneous** solutions appears when $t \to \infty$.

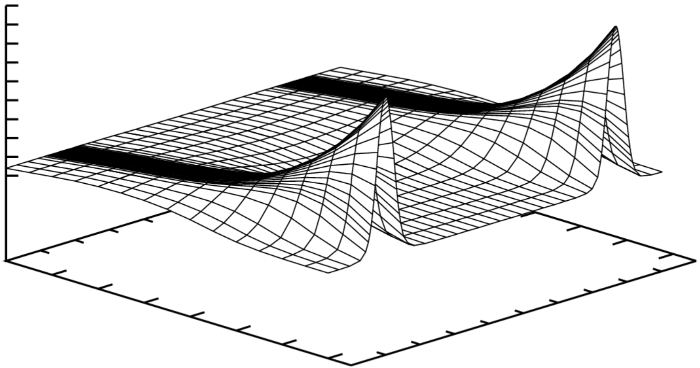
Emergence of a single spike



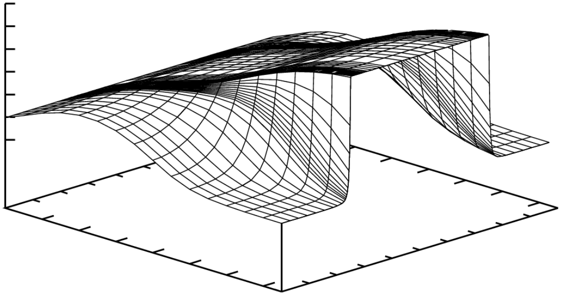
Competition of spikes



Coexistence of spikes



Plateau



- If $u_0(x_1) = u_0(x_2)$ for some $x_1 \neq x_2$, then $u(x_1, t) = u(x_2, t)$ for all $t \geq 0$, because both quantities $u(x_1, t)$ and $u(x_2, t)$ as functions of t satisfy the same Cauchy problem.
- Consequently, if the measure of Ω_* is positive, the function $u(x, t)$ cannot escape to $+\infty$ for all $x \in \Omega_*$ due to the boundedness of the mass.

Analysis of spike formation

Theorem

Let (u, ξ) be a nonnegative solution of the shadow problem with

- *large a:* $2(a-d) \geq 1$
- *large constant* κ_0*:* $\kappa_0 \geq 4a$.

Let $\frac{1}{2} \leq \lambda \leq 1 - \frac{2a}{\kappa_0}$*. Assume that* $u_0 \in C(\Omega) \cap L^\infty(\Omega)$ *and* $\xi_0 \in \mathbb{R}$ *satisfy*

$$\xi_0 \int_\Omega u_0^2(x)\, dx > \lambda \kappa_0 \qquad \text{and} \qquad 0 < \xi_0 \leq (1-\lambda)\kappa_0$$

and $\Omega_* = \{x_* \in \Omega \,:\, u_0(x_*) = \max_{x \in \Omega} u_0(x)\}$ *has measure zero. Then*

$$\sup_{t>0} u(x_*, t) = +\infty \qquad \text{if} \quad x_* \in \Omega_*,$$

$$\sup_{t>0} u(x, t) < +\infty \qquad \text{if} \quad x \in \Omega \setminus \Omega_*$$

Main ideas of the proof

Lemma

Under the assumptions of the above Theorem, it holds

$$\xi(t) \int_\Omega u^2(x,t)\,dx > \lambda\kappa_0 \qquad \text{and} \qquad 0 < \xi(t) \le (1-\lambda)\kappa_0$$

for all $t \ge 0$.

Lemma

Let the assumptions of the Theorem hold true. Assume that $x_* \in \Omega_*$ *and suppose that* $u_*(t) \equiv u(x_*, t) = \max_{x\in\Omega} u(x,t)$ *is a bounded function for* $t \ge 0$. *Then, for each* $x \in \Omega$ *such that* $u_0(x) < u_0(x_*)$ *it holds* $u(x,t) \to 0$ *exponentially as* $t \to \infty$.

Proof using equation for $\frac{u(x,t)}{u_*(x,t)}$.

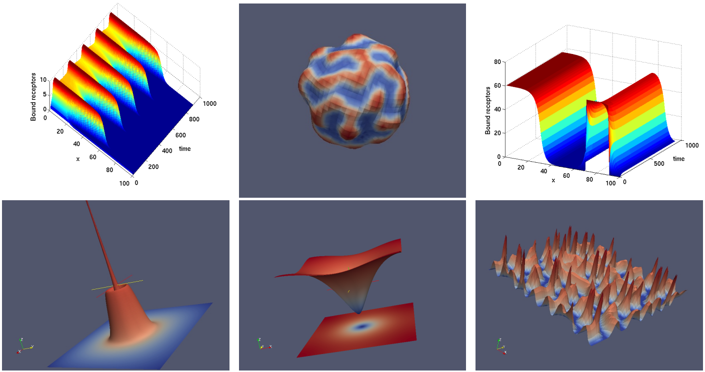
- Open Question: How to show positivity of mass?

Conclusions and challenges

- Coupling a scalar reaction-diffusion equation to ODEs may lead to emergence of spatial patterns.
- Autocatalysis is a necessary and sufficient condition for Turing instability in such models; however it leads to instability of all Turing patterns.
- The solutions may exhibit dynamical patterns tending asymptotically to Dirac measures (diffusion-driven mass concentration).
- Models with DDI may also lead to bounded patterns with jump-discontinuity (due to the hysteresis effect)

Open questions and perspective:

- Mass concentration in the reaction-diffusion-ode model.
- Pattern selection.
- Identification of key players in real biological systems.


Bound receptors
10
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time
Bound receptors
80
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40
20
0
0
20
40
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80
100
x
0
500
1000
time

Thank you!

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