Matematyka stosowana
matematyka teoretyka

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wykład o wynikach uzyskanych w Heidelbergu wspólnie z

Anną Marciniak-Czochrą i **Kanako Suzuki**

April 20, 2017

Basic model

$$
\begin{aligned}
u_t &= \left(\frac{av}{u+v} - d_c\right)u, \\
v_t &= -d_b v + u^2 w - dv, \\
w_t &= \frac{1}{\gamma} w_{xx} - d_g w - u^2 w + dv + \kappa_0
\end{aligned}
\tag{RD}
$$

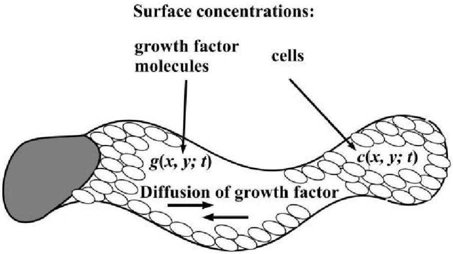
for $x \in (0,1)$, $t > 0$ with the homogeneous Neumann boundary conditions for the function $w = w(x,t)$

$$
w_x(0,t) = w_x(1,t) = 0 \quad \text{for all} \quad t > 0,
$$

and with positive initial conditions

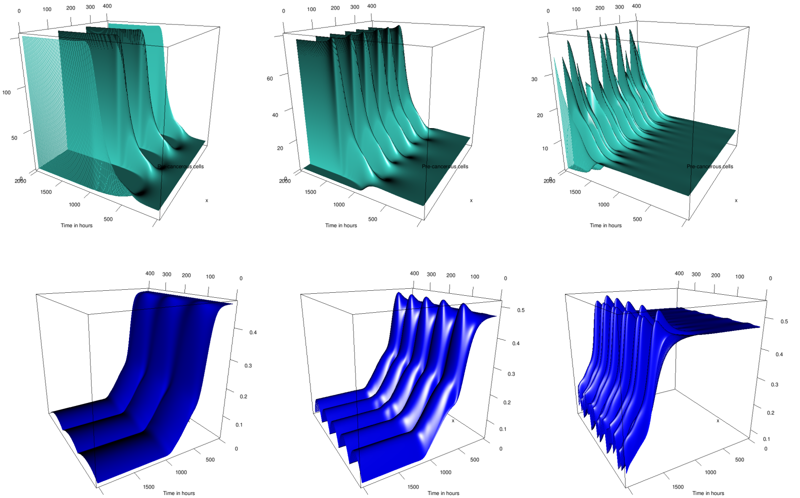
$$
u(x,0) = u_0(x), \quad v(x,0) = v_0(x), \quad w(x,0) = w_0(x).
$$

Biological system



- Cell proliferation (*e.g.* in lungs) 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
- Hypothesis: The diffusion of this growth factor may significantly influence the dynamics of the whole cell population

Spatial profiles of the solutions



Kinetic system. Boundedness of solutions

- Solutions are nonnegative and uniformly bounded (change of variables $(u, \frac{v}{u}, uw)$).
- The trivial steady state $(\overline{u}_0, \overline{v}_0, \overline{w}_0) \equiv \left(0, 0, \frac{\kappa_0}{d_g}\right)$ is locally asymptotically stable.
- Assume $a > d_c$ and $\kappa_0^2 \geq \Theta$, where $\Theta = 4 d_g d_b \dfrac{d_c^2(d_b + d)}{(a - d_c)^2}$. Then, the kinetic system has two positive constant stationary solutions $(\overline{u}_\pm, \overline{v}_\pm, \overline{w}_\pm)$, where

$$\overline{w}_\pm = \frac{\kappa_0 \pm \sqrt{\kappa_0^2 - \Theta}}{2d_g}, \quad \overline{v}_\pm = \frac{d_c^2(d_b + d)}{(a - d_c)^2} \, \frac{1}{\overline{w}_\pm}, \quad \overline{u}_\pm = \frac{a - d_c}{d_c} \, \overline{v}_\pm.$$

- $(\overline{u}_-, \overline{v}_-, \overline{w}_-)$ is stable, and $(\overline{u}_+, \overline{v}_+, \overline{w}_+)$ is unstable.

Model with diffusion. Boundedness of mass

Theorem

Let $\kappa_0 \geq 0$*. The solution* (u, v, w) *of (RD) satisfies*

$$\limsup_{t\to\infty} \int_0^1 u(x,t)\,dx \leq \frac{\kappa_0}{\mu d_c},$$

$$\limsup_{t\to\infty} \int_0^1 v(x,t)\,dx \leq \frac{\kappa_0}{\mu},$$

$$\limsup_{t\to\infty} \|w(t)\|_\infty \leq \kappa_0 \left(\frac{Cd}{\mu d_g^{1/2}} + \frac{1}{d_g} \right).$$

Here $\mu = \min\{d_g, d_b\} > 0$*.*

Stationary problem

$$\left(\frac{aV}{U+V} - d_c\right) U = 0, \tag{1}$$

$$-d_b V + U^2 W - dV = 0, \tag{2}$$

$$\frac{1}{\gamma} W_{xx} - d_g W - U^2 W + dV + \kappa_0 = 0 \tag{3}$$

and the boundary condition $W_x(0) = W_x(1) = 0$.

- We are interested only in $U(x) > 0$ and $V(x) > 0$,
- Let $a > d_c$,
- We obtain

$$U(x) = \frac{a - d_c}{d_c} V(x) \quad \text{and} \quad V(x) = \frac{d_c^2(d_b + d)}{(a - d_c)^2} \frac{1}{W(x)}. \tag{4}$$

Two-point boundary value problem

The boundary value problem for $W(x)$

$$\frac{1}{\gamma}W'' - d_g W - d_b \frac{d_c^2(d_b+d)}{(a-d_c)^2}\ \frac{1}{W} + \kappa_0 = 0,$$
$$W_x(0) = W_x(1) = 0.$$

We find explicit γ_0 such that

- for all $\gamma \in (0, \gamma_0]$, the above problem has only constant solutions,
- for all $\gamma > \gamma_0$, we describe all positive solutions of the problem.

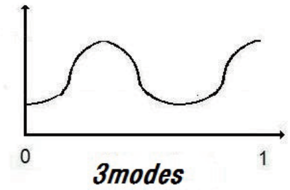
Construction of patterns

Definition

Let $k \in \mathbb{N}$ and $k \geq 2$. We call a function $W \in C([0,1])$ a periodic function on $[0,1]$ with k modes if $W = W(x)$ is monotone on $\left[0, \frac{1}{k}\right]$ and if

$$W(x) = \begin{cases} W\left(x - \frac{2j}{k}\right) & \text{for} \quad x \in \left[\frac{2j}{k}, \frac{2j+1}{k}\right] \\ W\left(\frac{2j+2}{k} - x\right) & \text{for} \quad x \in \left[\frac{2j+1}{k}, \frac{2j+2}{k}\right] \end{cases}$$

for every $j \in \{0, 1, 2, 3, ...\}$ such that $2j + 2 \leq k$.



Instability of patterns

Let $W(x)$ be one of the functions from the previous theorem, and $(U(x), V(x), W(x))$ be a stationary solution of our system, where

$$U(x) = \frac{a - d_c}{d_c}\ V(x) \quad \text{and} \quad V(x) = \frac{d_c^2(d_b + d)}{(a - d_c)^2}\ \frac{1}{W(x)}.$$

This stationary solution appears to be unstable solution of the reaction-diffusion equations (RD).

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Let us be more precise.

Instability of patterns

Linearized operator

The linearization of system (RD) at the steady state (U, V, W)

$$\mathcal{L} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\gamma}\partial_x^2 \end{pmatrix} + \mathcal{A}(x).$$

We consider $\mathcal{L}$ as an operator in the Hilbert space

$$\mathcal{H} = L^2(0,1) \oplus L^2(0,1) \oplus L^2(0,1)$$

with the domain

$$D(\mathcal{L}) = L^2(0,1) \oplus L^2(0,1) \oplus W^{2,2}(0,1).$$

$\mathcal{L}$ has infinitely many positive eigenvalues.

Instability of patterns

Spectrum of $\mathcal{L}$

Together with the matrix

$$\mathcal{A}(x) = (a_{ij})_{i,j=1,2,3} = \begin{pmatrix} d_c\left(\frac{d_c}{a} - 1\right) & \frac{(a-d_c)^2}{a} & 0 \\ 2K & -d_b - d & \frac{K^2}{W^2(x)} \\ -2K & d & -d_g - \frac{K^2}{W^2(x)} \end{pmatrix},$$

we consider its sub-matrix

$$\mathcal{A}_{12} \equiv \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}.$$

Lemma

Let λ be an eigenvalue of the matrix $\mathcal{A}_{12}$. Then λ belongs to the continuous spectrum of the operator $\mathcal{L}$.

Instability of patterns

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Lemma

Let λ be an eigenvalue of the matrix $\mathcal{A}_{12}$. Then λ belongs to the continuous spectrum of the operator $\mathcal{L}$.

The matrix $\mathcal{A}_{12}$ has a positive eigenvalue λ_0.

Lemma

A complex number λ is an eigenvalue of the operator $\mathcal{L}$ if and only if the following two conditions are satisfied

- *λ is not an eigenvalue of the matrix $\mathcal{A}_{12}$,*
- *the boundary value problem has a nontrivial solution:*

$$\begin{aligned} &\frac{1}{\gamma}\eta'' + \frac{\det(\mathcal{A} - \lambda I)}{\det(\mathcal{A}_{12} - \lambda I)}\eta = 0, \quad x \in (0,1) \\ &\eta'(0) = \eta'(1) = 0. \end{aligned}$$

Proof. Study the system

$$\begin{array}{ccccccccc} & & (a_{11}-\lambda)\varphi & + & a_{12}\psi & & & = & 0 \\ & & a_{21}\varphi & + & (a_{22}-\lambda)\psi & + & a_{23}\eta & = & 0 \\ \frac{1}{\gamma}\partial_x^2\eta & + & a_{31}\varphi & + & a_{32}\psi & + & (a_{33}-\lambda)\eta & = & 0, \end{array}$$

supplemented with the boundary condition $\eta_x(0) = \eta_x(1) = 0$ $\square$

Theorem

Denote by λ_0 the positive eigenvalue of the matrix $\mathcal{A}_{12}$. There exists a sequence $\{\lambda_n\}_{n\in\mathbb{N}}$ of positive eigenvalues of the operator $\mathcal{L}$ that satisfy $\lambda_n \to \lambda_0$ as $n \to \infty$.

Recall that λ_0 belongs to the continuous spectrum of the operator $\mathcal{L}$.

Idea of the proof. Analysis of solutions of the generalized Sturm-Liouville problem

$$\frac{1}{\gamma}\eta'' + q(x,\lambda)\eta = 0, \quad x \in (0,1)$$
$$\eta'(0) = \eta'(1) = 0,$$

where

$$q(x,\lambda) = \frac{\det(\mathcal{A}(x) - \lambda I)}{\det(\mathcal{A}_{12} - \lambda I)}.$$

□

Existence of discontinuous patterns

$$\left(\frac{aV}{U+V} - d_c\right) U = 0, \tag{5}$$

$$-d_b V + U^2 W - dV = 0, \tag{6}$$

$$\frac{1}{\gamma} W_{xx} - d_g W - U^2 W + dV + \kappa_0 = 0 \tag{7}$$

Theorem

Assume that $a > d_c$ and $\kappa_0^2 > \Theta$. There exists a continuum of weak solutions of the stationary system with some $\gamma > 0$. Each such solution $(U, V, W) \in L^\infty(0,1) \times L^\infty(0,1) \times C^1([0,1])$ has the following property: there exists a sequence $0 = x_0 < x_1 < x_2 < ... < x_N = 1$ such that for each $k \in \{0, N-1\}$ either

- *for all $x \in (x_k, x_{k+1})$, $U(x) = V(x) = 0$ and $W(x)$ satisfies $\frac{1}{\gamma} W'' - d_g W + \kappa_0 = 0$,*

or

- *for all $x \in (x_k, x_{k+1})$, $U(x) > 0$, $V(x) > 0$ and W are solutions of the stationary equation.*

Instability of discontinuous stationary solutions

Theorem

Every discontinuous weak stationary solution $(U_{\mathcal{I}}, V_{\mathcal{I}}, W_{\mathcal{I}})$ with a null set $\mathcal{I} \subset [0,1]$, is an unstable solution of the nonlinear system considered in the Hilbert space $\mathcal{H}_{\mathcal{I}}$.

- For a null set $\mathcal{I}$, we define the associate L^2-space

$$L^2_{\mathcal{I}}(0,1) = \{v \in L^2(0,1) \,:\, v(x) = 0 \quad \text{on} \quad \mathcal{I}\},$$

  supplemented with the usual L^2-scalar product, which is a Hilbert space as the closed subspace of $L^2(0,1)$.

- If $u_0(x) = v_0(x) = 0$ for some $x \in [0,1]$ then $u(x,t) = v(x,t) = 0$ for all $t \geq 0$. Hence, the space $\mathcal{H}_{\mathcal{I}} = L^2_{\mathcal{I}}(0,1) \times L^2_{\mathcal{I}}(0,1) \times L^2(0,1)$ is invariant for the flow generated by the system.

Main result:
instability of ALL stationary solutions

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

Reaction-diffusion-ODE system

(A. Marciniak-Czochra, G.K., K. Suzuki)

The point of departure:
a general system of reaction-diffusion (reaction-diffusion-ODE) equations:

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

in a bounded domain $\Omega \subset \mathbb{R}^n$.
The Neumann boundary condition:

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

Initial data:

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

- $D > 0$ – a constant diffusion coefficient. (We can set $D = 1$.)
- arbitrary C^1-nonlinearities $f = f(u,v)$ and $g = g(u,v)$.

Constant stationary solutions – Turing instability

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

Theorem

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

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

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

Remark.
Autocatalysis leads to the instability of stationary solutions.

Regular stationary solutions – standing assumption

We consider only **regular stationary solutions**, namely, we 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 $k = k(V)$.

Under this assumption, regular stationary solutions of

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

satify the boundary value problem

$$\begin{aligned} & \Delta V + h(V) = 0, \qquad \text{where} \quad h(V) = g(k(V), V), \\ & \partial_n V = 0 \quad \text{on} \quad \partial\Omega. \end{aligned}$$

Non-constant stationary solutions

Theorem (Instability of solutions)

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

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

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

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

`A.M-C, G.K., K.S., J. Math. Biology., 2017`

Example:
The Gray-Scott model

We consider positive solutions of the system

$$\begin{aligned} u_t &= -u + u^2 v, \\ v_t &= \Delta v - v - u^2 v + 2, \\ \partial_n v &= 0. \end{aligned}$$

Regular stationary solutions satisfy

$$U = 1/V.$$

Autocatalysis assumption:

$$f_u(U, V) = -1 + 2UV = 1 > 0.$$

Example:
Activator-inhibitor system with no diffusion of activator

We consider positive solutions of the system

$$u_t = -u + \frac{u^p}{v^q},$$
$$\tau v_t = \Delta v - v + \frac{u^r}{v^s},$$
$$\partial_n v = 0,$$

where $p > 1$.
Regular stationary solutions satisfy

$$U = V^{q/(p-1)}.$$

Autocatalysis assumption:

$$f_u(U, V) = -1 + p\frac{U^{p-1}}{V^q} = -1 + p > 0.$$

Example: Model of an early carcinogenesis

We consider positive solutions of the system

$$\begin{aligned} u_t &= \left(\frac{av}{u+v} - d_c\right) u, \\ w_t &= \Delta w - d_g w - u^2 w + dv + \kappa_0, \\ \partial_n w &= 0, \end{aligned}$$

where

$$-d_b v + u^2 w - dv = 0.$$

Here, the autocatalysis assumption is satisfied, by a simple calculation.

Linearization of reaction-diffusion-ODE problems.

Let (U, V) be a stationary solution of the system

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

Substituting

$$u = U + \widetilde{u} \qquad \text{and} \qquad v = V + \widetilde{v}$$

into the equations we obtain the problem for $(\widetilde{u}, \widetilde{v})$ of the form

$$\frac{\partial}{\partial t}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} = \mathcal{L}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} + \mathcal{N}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix},$$

with the Neumann boundary condition, $\partial_\nu \widetilde{v} = 0$.

Lemma

We consider the following linear system

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

with the Neumann boundary condition $\partial_\nu \widetilde{v} = 0$.

Then, the operator $\mathcal{L}$ *with the domain* $D(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$ *generates an analytic semigroup* $\{e^{t\mathcal{L}}\}_{t \geq 0}$ *of linear operators on* $L^2(\Omega) \times L^2(\Omega)$.

This semigroup satisfies "the spectral mapping theorem":

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

Spectrum of $\mathcal{L}$

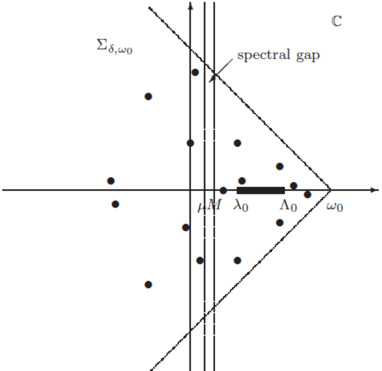
Define the constants

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

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

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

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



Turing mechanism in reaction-diffusion-ODE problems not only destabilizes **all** steady states, but it may induces a **blowup of solutions**.

Model problem

$$
\begin{aligned}
u_t &= d\Delta u - au + u^p f(v), \\
v_t &= D\Delta v - bv - u^p f(v) + \kappa
\end{aligned}
$$

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

- $f \in C^1([0,\infty))$ is an arbitrary function satisfying $f(v) > 0$ for $v > 0$.
- Fixed parameters:

$$
d \geq 0, \quad D > 0, \quad p > 1, \qquad a, b \in [0,\infty), \quad \kappa \in [0,\infty).
$$

- The homogeneous Neumann boundary conditions:

$$
\frac{\partial u}{\partial n} = 0 \text{ (if } d > 0) \quad \text{and} \quad \frac{\partial v}{\partial n} = 0 \qquad \text{for} \quad x \in \partial\Omega, \quad t > 0, \quad (8)
$$

- Bounded, nonnegative, and continuous initial data

$$
u(x,0) = u_0(x), \qquad v(x,0) = v_0(x) \qquad \text{for} \quad x \in \Omega.
$$

Main results

$$u_t = d\Delta u - au + u^p f(v),$$
$$v_t = D\Delta v - bv - u^p f(v) + \kappa$$

- For $d > 0$ and $D > 0$,
  all nonnegative solutions to the problem are **global-in-time**.

Main results

$$u_t = d\Delta u - au + u^p f(v),$$
$$v_t = D\Delta v - bv - u^p f(v) + \kappa$$

- For $d > 0$ and $D > 0$,
  all nonnegative solutions to the problem are **global-in-time**.

- If $d = 0$ and $D > 0$,
  there are solutions to this problem which **blowup** in a finite time and at one point only.

Theorem

There exist numbers $\alpha \in (0,1)$, $\quad \varepsilon > 0$, $\quad R_0 > 0$ *such that if*

$$0 < u_0(x) < \left(u_0(0)^{1-p} + 2\varepsilon^{-(p-1)}|x|^{\alpha}\right)^{-\frac{1}{p-1}} \quad \textit{for all} \quad x \in \Omega$$

$$u_0(0) \geq \left(\frac{a}{(1-e^{(1-p)a})F_0}\right)^{\frac{1}{p-1}}, \qquad \textit{where} \quad F_0 = \inf_{v \geq R_0} f(v),$$

$$v_0(x) \equiv \bar{v}_0 > R_0 > 0 \qquad \textit{for all} \quad x \in \Omega,$$

then the corresponding solution to the initial-boundary problem for system

$$u_t = -au + u^p f(v), \quad v_t = D\Delta v - bv - u^p f(v) + \kappa$$

blows up at certain time $T_{max} \leq 1$.

Moreover,

$$0 < u(x,t) < \varepsilon|x|^{-\frac{\alpha}{p-1}} \quad \textit{and} \quad v(x,t) \geq R_0 \qquad \textit{for all} \quad (x,t) \in \Omega \times [0, T_{max}).$$

Diffusion induced blowup

Solutions to the following system of ordinary differential equations:

$$\frac{d}{dt}\bar{u} = -a\bar{u} + \bar{u}^p f(\bar{v}), \qquad \frac{d}{dt}\bar{v} = -b\bar{v} - \bar{u}^p f(\bar{v}) + \kappa,$$
$$\bar{u}(0) = \bar{u}_0 \geq 0, \qquad \bar{v}(0) = \bar{v}_0 \geq 0.$$

are global-in-time and bounded on $[0, \infty)$.

By our theorem, there are nonconstant initial conditions such that solutions to

$$u_t = -au + u^p f(v), \quad v_t = D\Delta v - bv - u^p f(v) + \kappa$$

blows up at one point in a finite time.

Blowup and control of mass

Total mass

$$\int_\Omega \big(u(x,t)+v(x,t)\big)\,dx$$

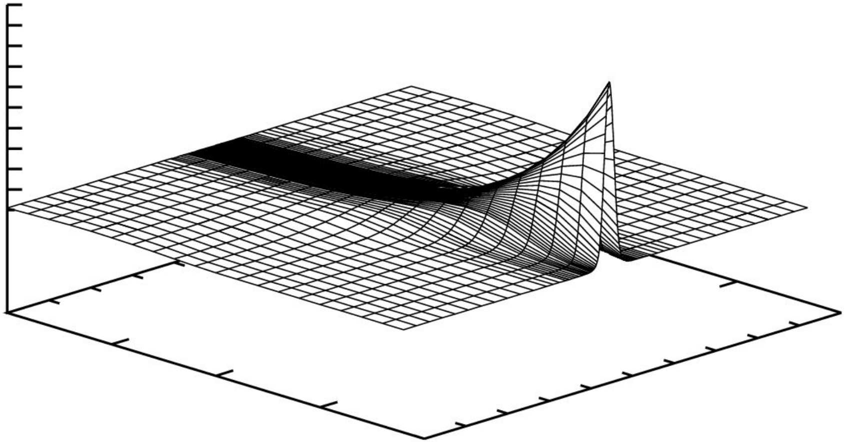
of any nonnegative solution to

$$u_t=-au+u^p f(v),\quad v_t=D\Delta v-bv-u^p f(v)+\kappa$$

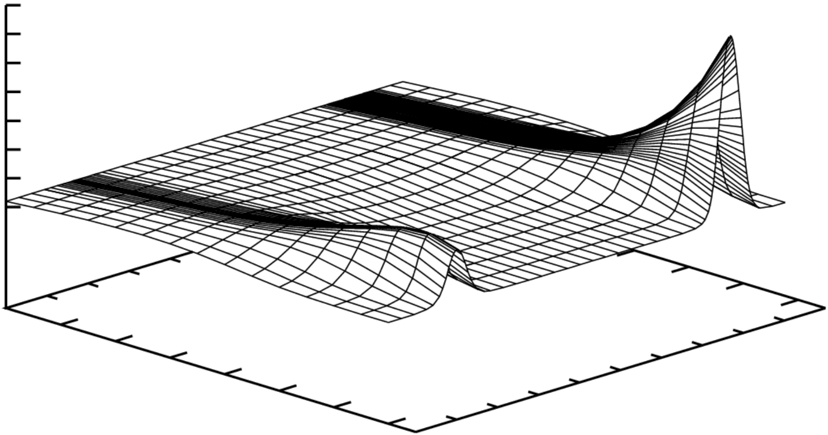
does not blow up and $u(t)$, $v(t)$ stay bounded in $L^1(\Omega)$ uniformly in time.

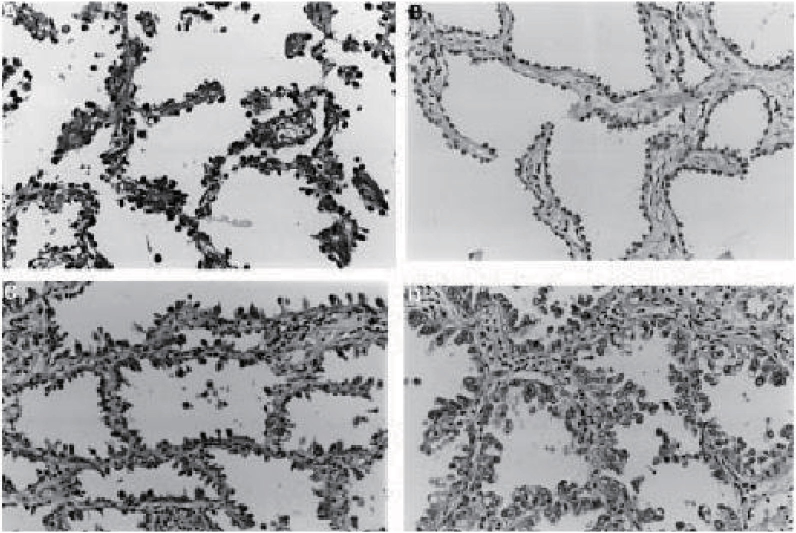
We showed this *a priori* estimate is not sufficient to prevent the blowup of solutions in a finite time.

One point blowup



Two point blowup

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