Patterns in systems of a single reaction-diffusion equation coupled with ODE equations

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Joint work with Anna Marciniak-Czochra (University of Heidelberg) and Grzegorz Karch (University of Wroclaw)

Cortona, 21 June 2011

Mathematical model

System of three ordinary/partial differential equations:

$$
\begin{aligned}
u_t &= \Big(\frac{av}{u+v} - d_c\Big)u, \quad 0 < x < 1,\ t > 0, \\
v_t &= -d_b v + u^2 w - dv, \quad 0 < x < 1,\ t > 0, \\
w_t &= \frac{1}{\gamma} w_{xx} - d_g w - u^2 w + dv + \kappa_0, \quad 0 < x < 1,\ t > 0,
\end{aligned}
\tag{RD}
$$

with Neumann boundary conditions for the function $w = w(x,t)$

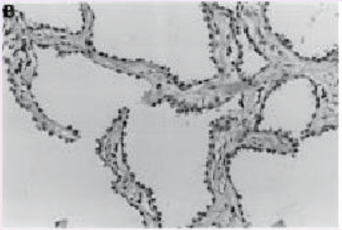
$$
w_x(0,t) = w_x(1,t) = 0 \quad \text{for all} \quad t > 0.
$$

- This is a model of early carcinogenesis proposed by A. Marciniak-Czochra and M. Kimmel (2006, 2007, 2008).
- This is called *Receptor-based model*.

Idea 2: Diffusion-driven instability

We need an idea to understand the invasion of tumor cells into tissue.

Example: Bronchoalveolar Carcinoma (BAC)



In a very early stage of BAC, lumps appear along the walls of alveoli.

To explain how tumor cells can generate patterns observed at the macroscopic scale,

Receptor-based model + Diffusion-driven instability

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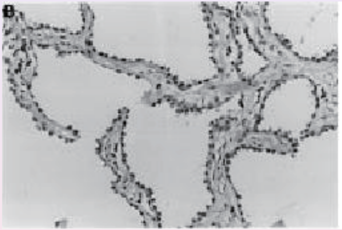

In a very early stage of BAC, lumps appear along the walls of alveoli.

To explain how tumor cells can generate patterns observed at the macroscopic scale,

Receptor-based model + Diffusion-driven instability

Mathematical problem

System of three ordinary/partial differential equations which exhibits the diffusion-driven instability:

$$
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u_t &= \Big(\frac{av}{u+v} - d_c\Big)u, \quad 0 < x < 1,\ t > 0,\\
v_t &= -d_b v + u^2 w - dv, \quad 0 < x < 1,\ t > 0, \\
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\qquad \text{(RD)}
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Study the existence of spatial patterns and its stability

Preliminaries

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w_t &= \frac{1}{\gamma} w_{xx} - d_g w - u^2 w + dv + \kappa_0, \quad 0<x<1,\ t>0,
\end{aligned}
$$

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 corresponding (RD) has two positive constant stationary solutions, one is stable and another is unstable.

Diffusion-driven instability: stable constant steady state becomes unstable in (RD).

Preliminaries

Let A be the Jacobian matrix at a positive spatially homogeneous steady state.

Diffusion-driven instabilities in the model with one-diffusion operator (A. Marciniak-Czochra and M. Kimmel)

- the kinetics system is asymptotically stable:

$$-tr(A) > 0, \quad -tr(A) \sum_{i<j} |A_{ij}| + |A| > 0, \quad -|A| > 0,$$

- the complete system is unstable for spatially non-homogeneous perturbations:

$$|A_{12}| < 0,$$

where A_{ij} is a submatrix of A consisting of the i-th and j-th column and i-th and j-th row, and $|\cdot|$ denotes the determinants.

Results

Study the existence of spatial patterns and its stability

Assume $a > d_c$ and $\kappa_0^2 > \Theta$.

- Existence of spatial patterns
  - for all $\gamma \in (0, \gamma_0]$, the system has only constant stationary solutions,
  - for all $\gamma > \gamma_0$, we describe all positive nonconstant stationary solutions.
- Stability for nonconstant stationary solutions
  - they appear to be unstable solution of the reaction-diffusion equations (RD).

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Existence of spatial patterns of (RD)

Construction of patterns

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

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

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

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

- We interested only in $U(x) > 0$ and $V(x) > 0$,
- Let $a > d_c$, $\kappa_0^2 > \Theta$.

From (1) and (2),

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

Construction of patterns

The boundary value problem for $W(x)$

$$\frac{1}{\gamma}W'' - d_g W - d_b \frac{d_c^2(d_b + d)}{(a - d_c)^2} \frac{1}{W} + \kappa_0 = 0, \quad (5)$$

$$W_x(0) = W_x(1) = 0. \quad (6)$$

By the change of variables

$$x \mapsto Tx, \qquad \text{where} \qquad T = \sqrt{\gamma},$$

the boundary value problem becomes

$$W'' + h(W) = 0 \qquad x \in (0, T), \quad (7)$$

$$W'(0) = W'(T) = 0. \quad (8)$$

A solution $W = W(x)$ to problem (7)–(8) satisfies the differential equation:

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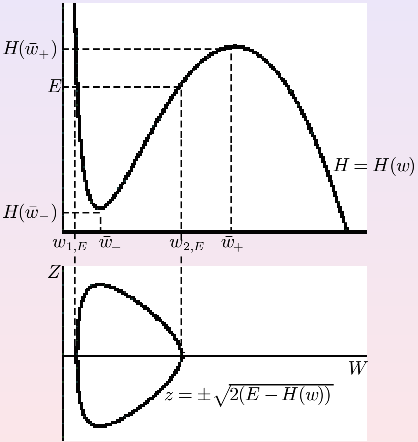
Construction of patterns

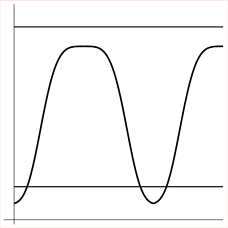
Idea



$$W'(x) = \pm\sqrt{2(E - H(W(x)))}$$

for $E \in \mathbb{R}$. Here $H' = h$.

All patterns are constructed by using the well-known method from the classical mechanics. E is called the *total energy*, H corresponds to the *potential energy*.



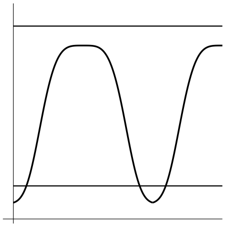
Construction of patterns

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 $2j + 2 \leq k$.



Construction of patterns

Theorem

Assume that $a > d_c$ *and* $\kappa_0 > \Theta$. *Fix* $\gamma > \gamma_0$ *and consider the biggest* $n \in \mathbb{N}$ *such that* $\gamma > n^2\gamma_0$. *Then, problem (5)–(6) has the following solutions:*

- *a unique strictly increasing solution and a unique strictly decreasing solution,*
- *for each* $k \in \{2, ..., n\}$, *a unique periodic solution* W_k *with* k *modes that is increasing on* $[0, \frac{1}{k}]$ *as well as its symmetric counterpart:* $\widetilde{W}_k(x) \equiv W_k(1 - x)$,
- *the constant steady states* $\overline{w}_{\pm}$.

There are no other positive solutions of problem (5)–(6).

Stability of spatial patterns

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).

Let us be more precise.

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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) contains the linear operator

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

where

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

with the constant $K = U(x)W(x) = \frac{d_c(d_b+d)}{a-d_c}$.

Instability of patterns

Linearized operator

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

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

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

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Instability of patterns

Spectrum of $\mathcal{L}$

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

Together the matrix above, we consider its sub-matrix

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

Assumption: $|\mathcal{A}_{12}| < 0 \quad \Rightarrow \quad \mathcal{A}_{12}$ has a positive eigenvalue λ_0.

Lemma

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

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Instability of patterns

Spectrum of $\mathcal{L}$ - the crucial lemma

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:*

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

Proof. Study the system

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

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Instability of patterns

Spectrum of $\mathcal{L}$ - main result

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

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

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Conclusion

We consider a system of two ordinary differential equations and one nonlinear parabolic equation with non-flux boundary conditions.

- all possible nonhomogeneous stationary solutions were described,
- those stationary solutions are unstable,

What are the patterns which we see in numerical simulations?

There are singular patterns which cannot be handled by a classical theory.

Works in progress.

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Works in progress.

Numerical simulations

Spike-type spatially patterns obtained by A. Marciniak-Czochra and M. Kimmel (2006, 2007, 2008).