Pattern Formation with Reaction-Diffusion Systems

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Physics in Biology Seminar

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Introduction

- Morphogenesis: development of pattern and form in biological organisms
- How does a homogeneous mass of cells spatially organize? How is genetic information physically translated?
- Cells possibly react to a chemical morphogen concentration → concept of positional information
- A. Turing (1952): reaction-diffusion theory of morphogenesis
- Self-organization of adult stem cells

Part I

Turing Instabilities in Reaction-Diffusion Systems

Reaction-Diffusion Systems

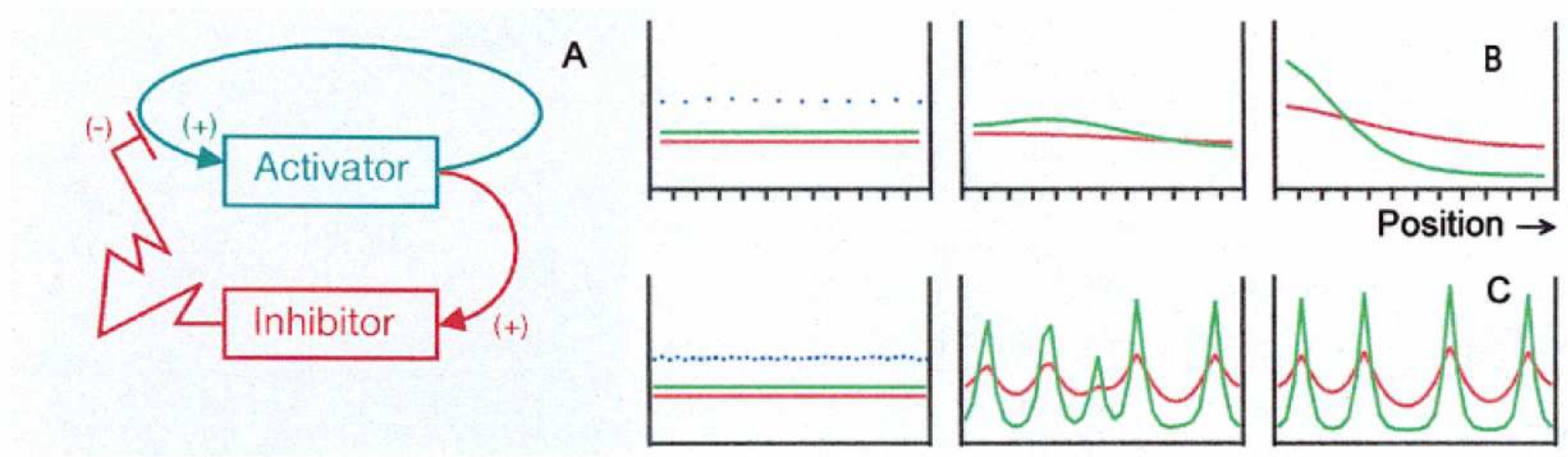
- Spatially distributed chemicals/species can react and diffuse (RD):

$$\begin{aligned} \partial_t A &= F(A,B) + D_A \Delta A \\ \partial_t B &= G(A,B) + D_B \Delta B \end{aligned}$$

- Turing´s idea: if, in the absence of diffusion, a linearly stable homogeneous steady state exists, then spatially inhomogeneous patterns can evolve in a diffusion driven instability induced by different diffusion velocities

Activator-Inhibitor Mechanism

- Gierer and Meinhardt (1972): Theory of biological pattern formation based on short-range activation and long-range inhibition

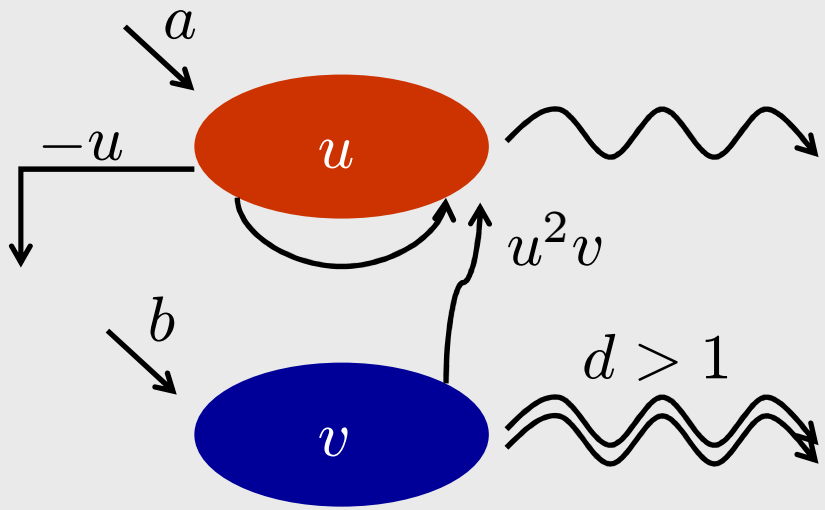


Simple RD System

- Autocatalytic creation of one species consuming the other [Schnakenberg (1979)]:

$$\partial_t u = \gamma \left(a - u + u^2 v\right) + \Delta u =: \gamma f(u,v) + \Delta u$$
$$\partial_t v = \gamma \left(b - u^2 v\right) + d\Delta v =: \gamma g(u,v) + d\Delta v$$

- Parameters
  - Kinetics: a and b
  - $d = D_B \,/\, D_A$
  - Spatial domain size: γ



Linear Stability Analysis

- Linearization of the homogeneous steady state (u_o,v_o):

$$\dot{w} = \gamma A w \quad \text{with} \quad A = \begin{pmatrix} \partial_u f & \partial_v f \\ \partial_u g & \partial_v g \end{pmatrix} (u_0, v_0)$$

- Steady state (u_o,v_o) is stable, if (Hurwitz theorem)

i. $\mathrm{tr}(A) = f_u + g_v < 0$

ii. $\det(A) = f_u\, g_v - f_v\, g_u > 0$

Boundary Conditions

- Spatial domain of the RD system:

$$B \subset \mathbb{R}^n \, , \; n = 1, 2, 3$$

- Zero flux (Neumann) boundary conditions (BCs):

$$\vec{n} \cdot \vec{\nabla} \begin{pmatrix} u \\ v \end{pmatrix} = 0 \quad \text{on } \partial B$$

- These BCs mean no external input, otherwise spatial patterns could be a consequence of the BCs

Solution of the Linearized System

- Linearized RD system:

$$\dot{w} = \gamma A w + D \Delta w \,, \quad D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix}$$

- Eigenvalue problem for the spatial RD domain:

$$\begin{aligned} -\Delta w - k^2 w &= 0 \quad \text{in} \, \mathrm{B} \,, \\ \vec{n} \cdot \vec{\nabla} w &= 0 \quad \text{on} \, \partial \mathrm{B} \end{aligned}$$

- Set of spatial eigenfunctions $W_k(x)$ with wavenumber k

Solution of the Linearized System

- Initial conditions (ICs) can be expanded using the spatial eigenfunctions:

$$w(x,0) = \sum_k c_k W_k(x)$$

- The ansatz $w(x,t) = \sum_k c_k W_k(x) \exp(\lambda t)$ yields

$$\left(\lambda I - \gamma A + D k^2\right) W_k = 0$$

- Dispersion relation:

$$\det\left(\lambda I - \gamma A + D k^2\right) = 0 \quad \Rightarrow \quad \lambda = \lambda_{\pm}(k^2)$$

Turing Instability

- The homogeneous steady state (u_o, v_o) becomes unstable if for some wavenumber k

$$\mathrm{Re}(\lambda_{\pm}(k^2)) > 0$$

- With random pertubations as ICs the unstable solution emerges as

$$w(x,t) \approx \sum_{\gamma L < k^2 < \gamma M} c_k W_k(x) \exp(\lambda(k^2)t)$$

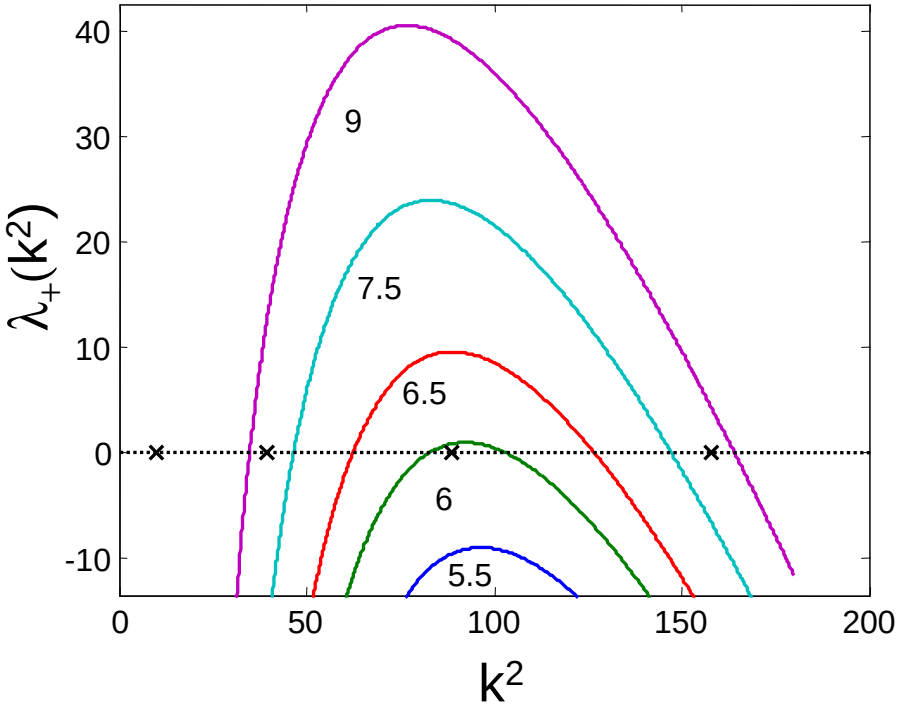
- Idea: Exponentially growing modes become bounded by nonlinear terms and a spatially inhomogeneous steady state emerges

Dispersion Relation

- For suitable parameters the system exhibits a bifurcation with increasing d
- Eigenfunctions and -values for the 1-d domain $B = [0,1]$:

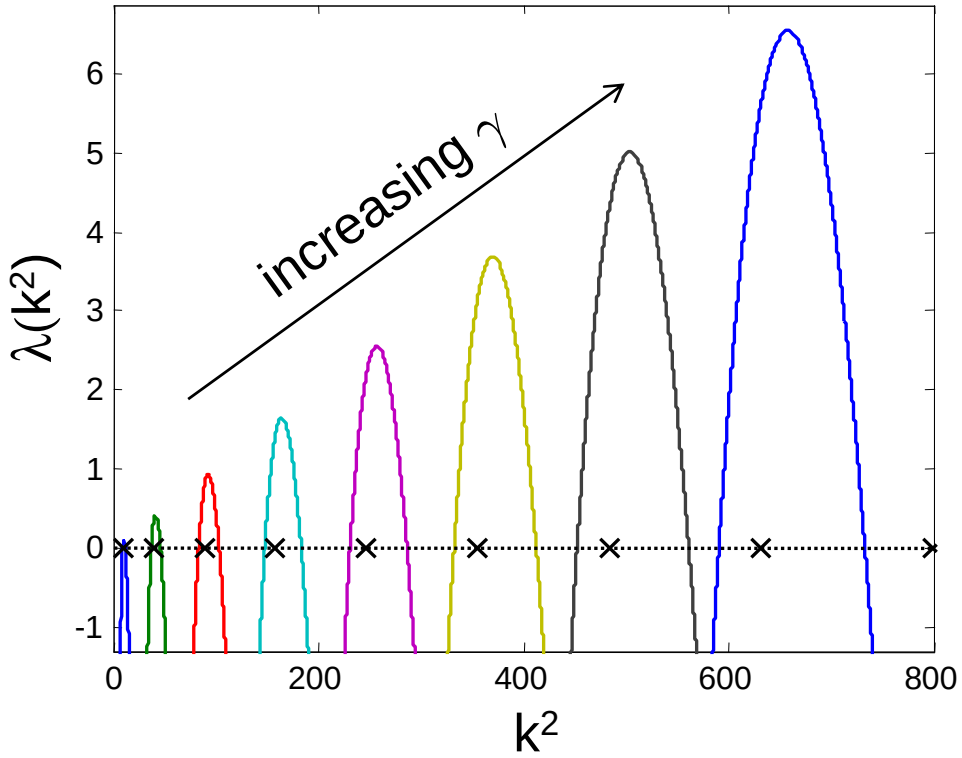
$$W_k(x) = A_n \cos(n\pi x)\,,$$
$$n = 1, 2, \ldots\,,\; k = n\pi$$

- Maximum growing mode is expected to determine the system's behavior

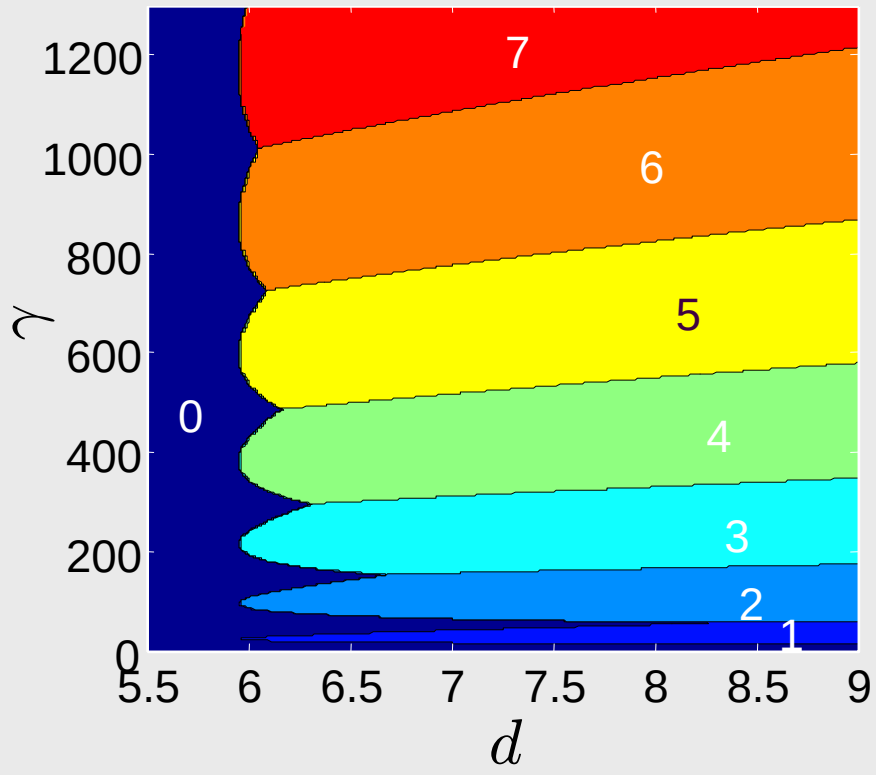


Mode Selection

- For $d > d_c$ different modes become unstable when varying γ



Maximum Growing Mode



Numerical solution for (d,γ) = (7.5,100), (9,40), (5.5,100), (7.5,1200)

Summary of Part I

- Simple RD systems can generate spatially inhomogeneous patterns through a Turing instability
- Good prediction by linear stability analysis in 1D
- Higher dimensions: Are the dispersion relation and the eigenfunctions sufficient?
- Morphogenesis: Chemical prepatterns of morphogens could be generated by RD systems

Part II

Pattern Formation by Vascular Mesenchymal Cells

Garfinkel et al.

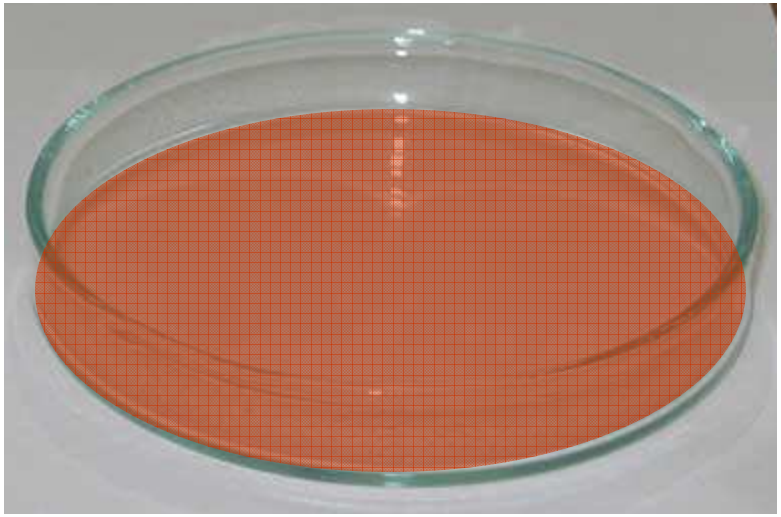
Proc. Nat. Acad. Sci. 101, 9247 (2004)

Mesenchymal Stem Cells

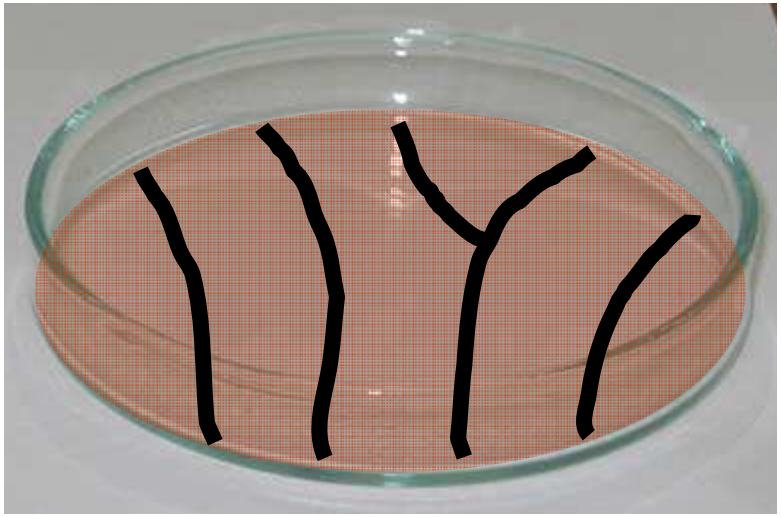
- Embryo: Mesenchymal stem cells develop into patterned tissues
- Adult diseases (atherosclerosis, aortic valvular stenosis): Multipotential vascular mesenchymal cells (VMCs) differentiate and form bone-like tissue within the artery wall → patterns
- Pattern formation mechanisms in these cells

Pattern Formation of Cultured VMCs

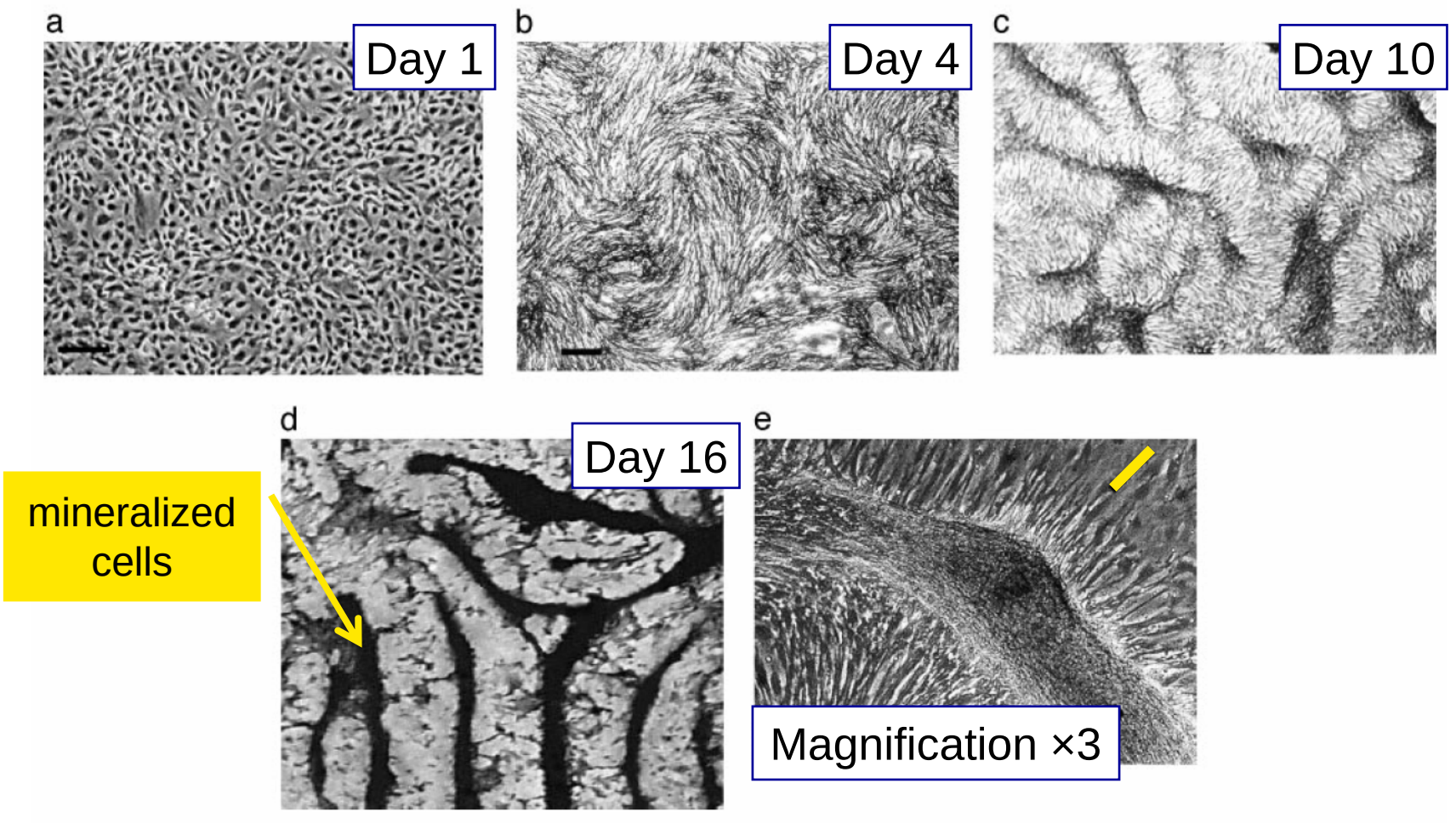
Day 1



≈ 20 days



Pattern Formation of Cultured VMCs



Pattern Formation of Cultured VMCs

- Can pattern formation be described by a reaction-diffusion model exhibiting a Turing instability?
- Identification of the specific morphogens
- Experimental testing of the model

Activator and Inhibitor

- Pattern formation by local activation and lateral inhibition
- Activator-inhibitor systems in 2D are able to generate stripe-like patterns [Koch and Meinhardt (1994)]
- Requirements for the activator:
  i. known chemoattractant
  ii. known morphogen
  iii. It has a known inhibitor
  iv. It diffuses more slowly than its inhibitor

Activator and Inhibitor

- Activator: bone morphogenetic protein 2 (BMP-2)
  - powerful morphogen expressed by VMCs
  - known chemoattractant
- Inhibitor: matrix carboxyglutamic acid protein (MGP)
  - inhibits BMP-2 effects
  - unusually small → fast diffusion
- This protein pair satisfies all four requirements

Reaction-Diffusion Model

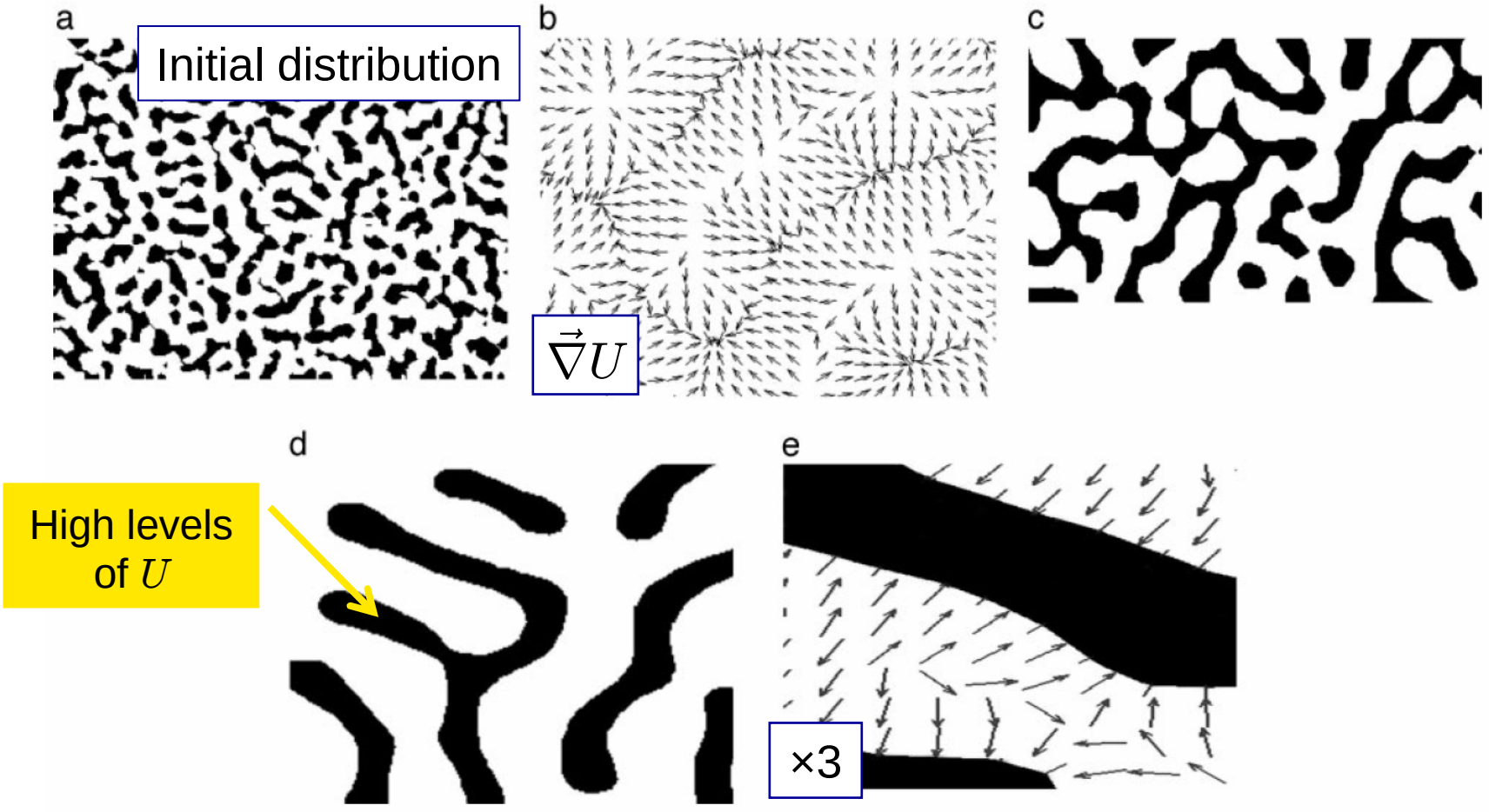
$$\begin{aligned} \partial_t U &= \gamma \left(\frac{U^2}{(1 + kU^2)V} - cU \right) + D\Delta U \\ \partial_t V &= \gamma \left(U^2 - eV + S \right) + \Delta V \end{aligned}$$

- Reaction kinetics are based on known interactions between BMP-2 and MGP → activator-inhibitor system
- Spatial domain size γ
- Ratio of diffusion coefficients $D = D_U / D_V$
- External source of the inhibitor S

Numerical Simulation

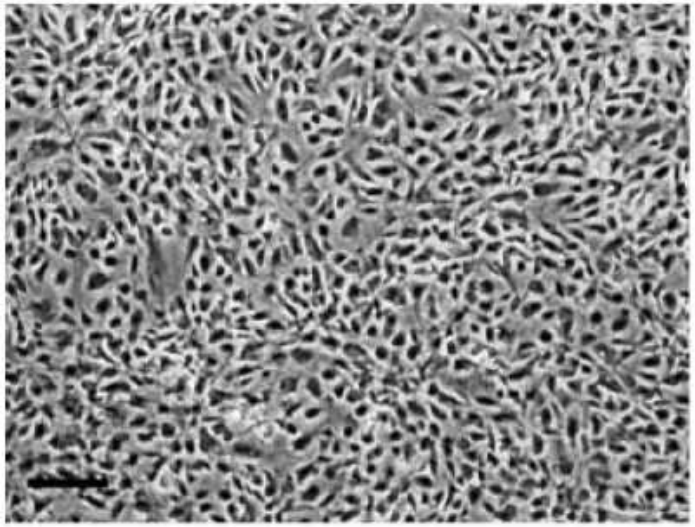
- 2D spatial domain with zero-flux boundary conditions
- Initial conditions: small (2%) random pertubations about the steady state values U_{o} and V_{o}

Numerical Simulation

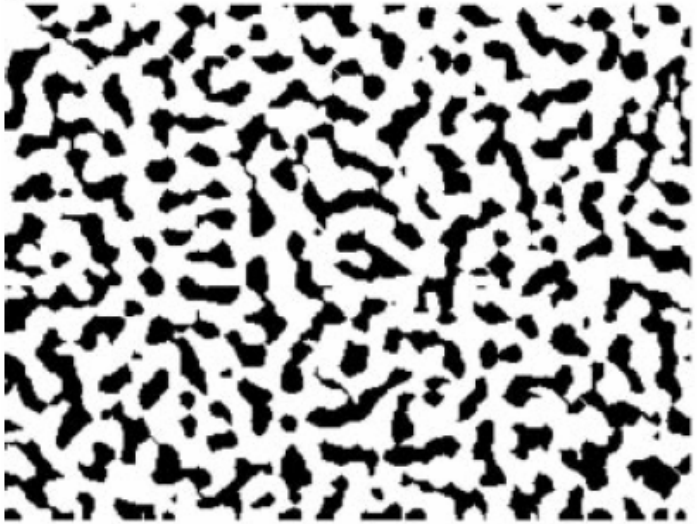


Comparison with Experiments

Cultured cells



Simulation



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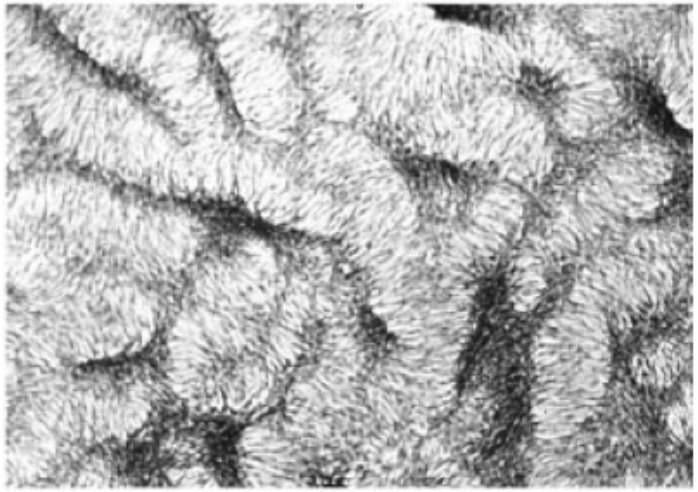
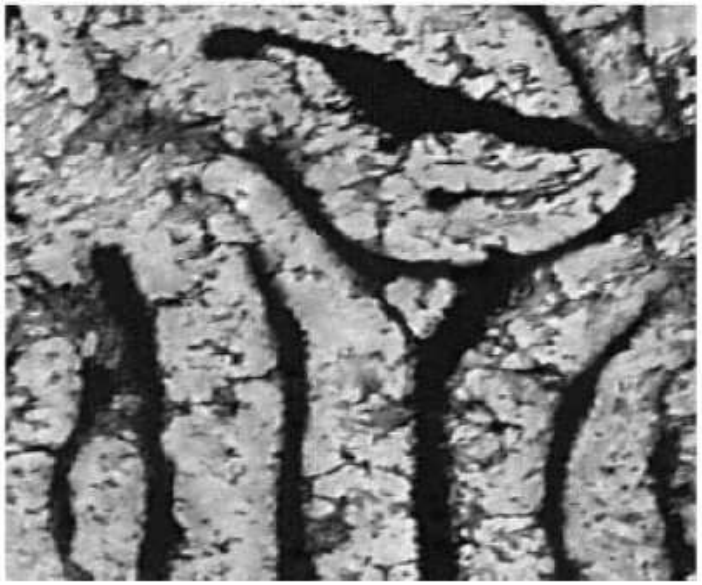


Simulation

Comparison with Experiments

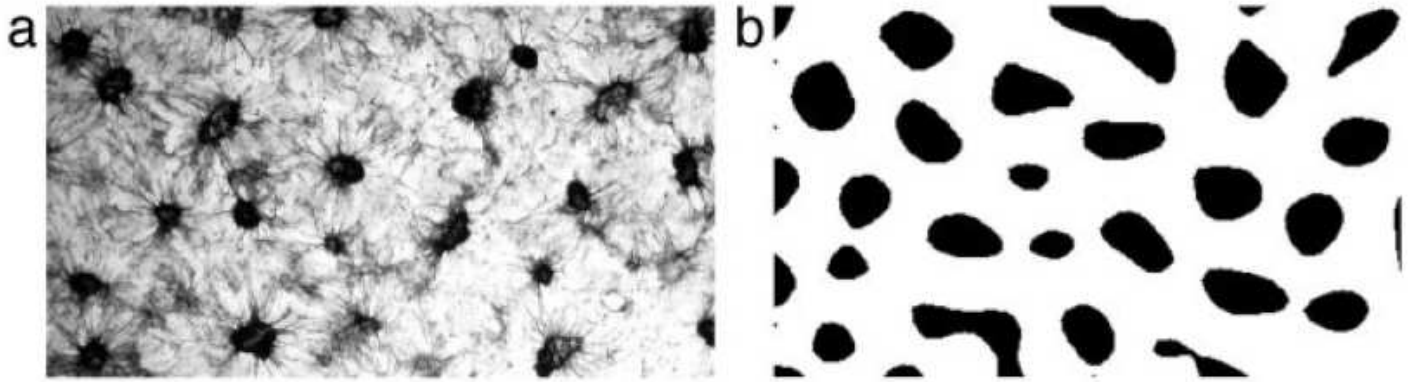
Cultured cells



Simulation

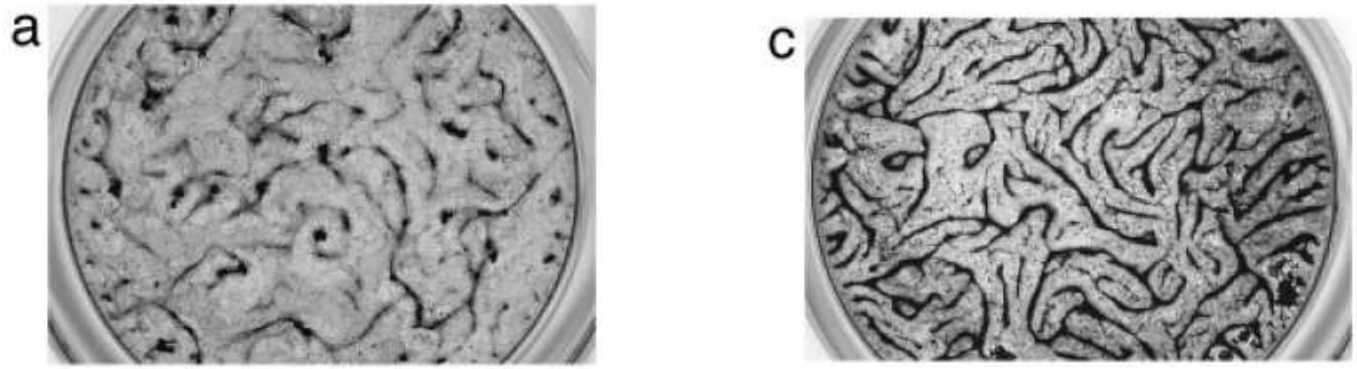
From Stripes to Spots

- Model prediction: external source S of inhibitor changes stripe to spot patterns (Movie)
- Addition of MGP → Cells organize into spot-like patterns



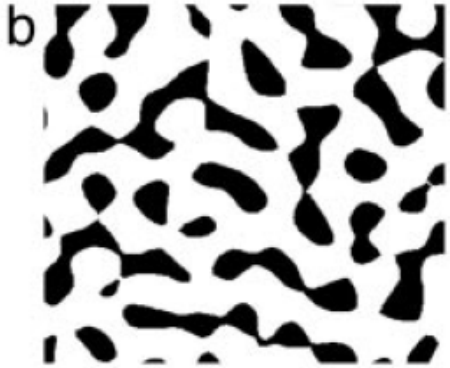
Stripe Doubling

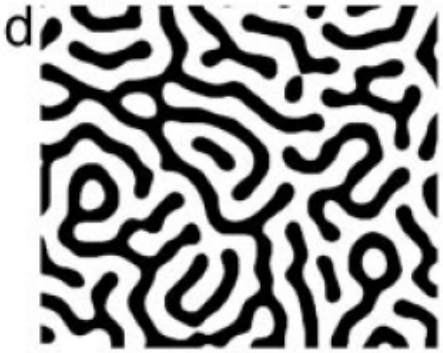
- The drug warfarin partially blocks MGP → expected change of patterns
- Cultured VMCs: refinement of stripe patterns



Stripe Doubling

- Reaction-diffusion models can show mode doubling by increasing the spatial domain size (parameter γ)
- Simulation: doubling of γ causes stripe doubling (Movie)

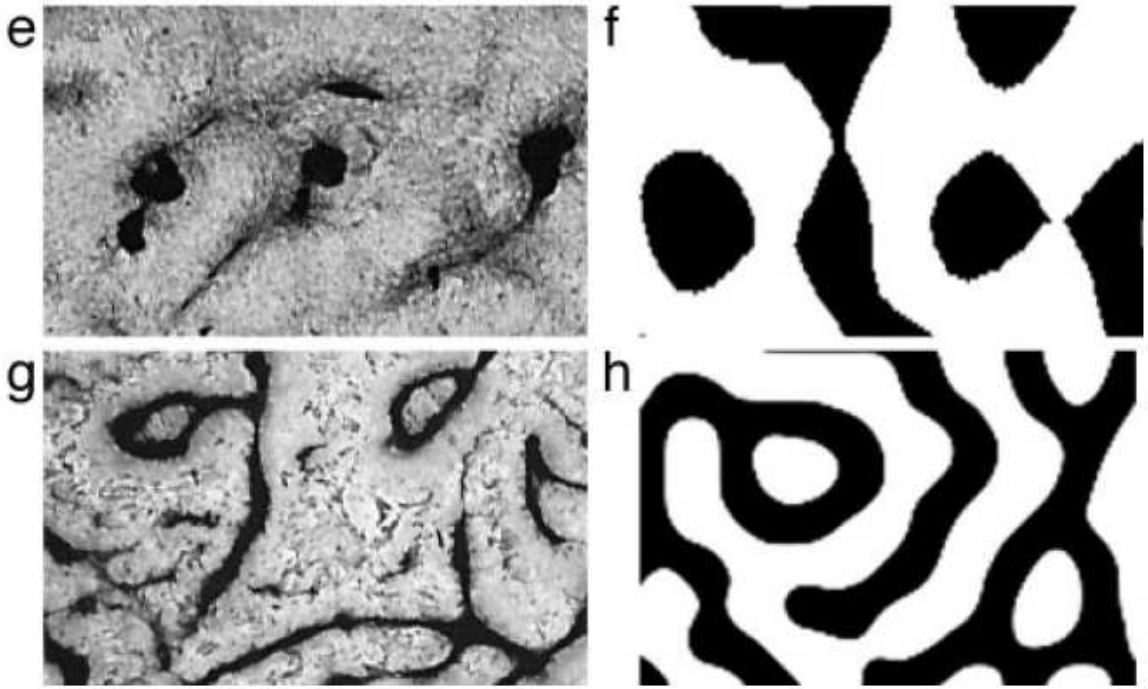




Comparison with Experiments

Cultured cells

Simulation



Summary

- Self-organization of multipotential vascular mesenchymal cells (VMCs) is predicted by a reaction-diffusion model
- Successful identification of the specific morphogens
- Model describes chemical prepattern
- Cells aggregate and differentiate according to this prepattern
- Pattern formation of mineralized cells may play a role in atherosclerotic vascular calcification