Turing Instabilities in Reaction-Diffusion Equations

A Model for the Formation of Mammalian Coat Patterns

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Biological Motivation

Have you ever wondered how a zebra gets its stripes?

Photo taken from whozoo.org

Melanocytes and Pigment

- Melanocytes (pigment cells) are located in the innermost layer of skin and produce melanin (pigment).
- As the hair moves through the skin, the melanin passes through and colors the hair.
- Mammalian coat patterns are determined by the distribution of the melanocytes and the type of melanin produced.

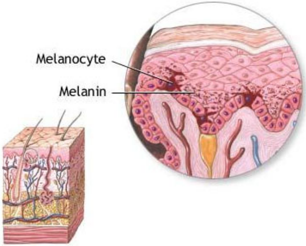


Photo from wikipedia.org

Morphogenesis

Definition

Morphogenesis is the biological process by which form and structure is created during embryonic development.

- Upon fertilization of the egg, cell division begins.
- After a certain point, cells begin to differentiate. This differentiation is determined by location within the cell cluster.
- Once melanocytes are formed, what determines the type of melanin they will produce?
- Some biologists believe that this is determined by the presence of certain activator and inhibitor chemicals, called *morphogens*.

Patterns in the concentrations of these morphogens are the key to the actual patterns found in mammalian coats.

Mathematical Motivation

Alan Turing (1912-1954)

Photo from wikipedia.org

- In 1952, Turing put forth a model for spatial pattern formulation of chemicals reacting and diffusing throughout tissue.
- The model is a system of partial differential equations known as the *Reaction-Diffusion Model*.
- Such spatial patterns in the chemicals are thought to play a role in the determination of the type of melanin is produced by the melanocytes, and thus impact the formation of patterns in the mammalian coats.

Outline

The Model

We use a continuum mechanics approach to the derivation of the model.

1. $\Omega \subset \mathbb{R}^n$ is the domain. Biological considerations dictate $n \leq 3$.
2. $\mathbf{c}(\mathbf{x}, t)$ is the concentration of morphogens.
3. $\mathbf{Q}(\mathbf{x}, t)$ is the net creation rate of morphogens.
4. $\mathbf{J}(\mathbf{x}, t)$ is the flux density. We assume $\mathbf{J}$ is smooth.

Let $B \subset \Omega$ be closed and integrable. Then

$$\begin{aligned} \int_B \mathbf{c}_t \, dV &= \frac{d}{dt} \int_B \mathbf{c} \, dV \\ &= \int_{\partial B} \mathbf{J} \cdot \mathbf{n} \, dA + \int_B \mathbf{Q} \, dV \\ &= \int_B (-\nabla \cdot \mathbf{J} + \mathbf{Q}) \, dV. \end{aligned}$$

The Model (continued)

Thus we arrive at a conservation law

$$\mathbf{c}_t = -\nabla \cdot \mathbf{J} + \mathbf{Q}.$$

By Fick's law, we have

$$\mathbf{c}_t = D\Delta\mathbf{c} + \mathbf{Q}(\mathbf{c}),$$

where D is a $n \times n$ matrix with positive entries called the *diffusivity* and $\mathbf{Q}$ is called the *reaction kinetics*.

Our model is a two morphogen system with

$$\mathbf{c}(\mathbf{x}, t) = \begin{pmatrix} u(\mathbf{x}, t) \\ v(\mathbf{x}, t) \end{pmatrix},$$

$$D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix},$$

$$\mathbf{Q}(u, v) = \gamma \begin{pmatrix} f(u, v) \\ g(u, v) \end{pmatrix}.$$

The Model (continued)

By putting all of this together we arrive at the Reaction-Diffusion model

$$\begin{aligned} u_t &= \quad \Delta u + \gamma \cdot f(u,v) \\ v_t &= \ d\Delta v + \gamma \cdot g(u,v). \end{aligned}$$

We will assume that no external influences are present, and thus impose homogeneous Neumann boundary conditions on the system.

The reaction kinetics we use were proposed by Thomas.

$$\begin{aligned} f(u,v) &= a - u - h(u,v), \\ g(u,v) &= \alpha(b - v) - h(u,v), \\ h(u,v) &= \frac{\rho \cdot u \cdot v}{1 + u + Ku^2}, \\ a = 150, b = 100,& \alpha = 1.5, \rho = 13, K = 0.05. \end{aligned}$$

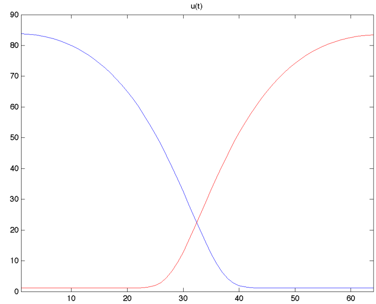
Turing Instabilities

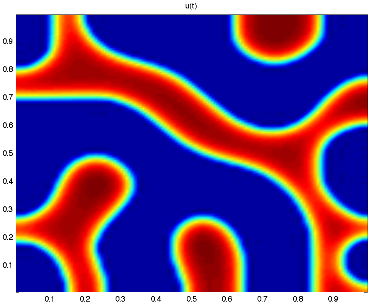
Turing concluded that the Reaction-Diffusion model may exhibit spatial patterns under the following two conditions:

1. the equilibrium solution is linearly stable in the absence of diffusion,
2. the equilibrium solution is linearly unstable in the presence of diffusion.

Such an instability is called a *Turing instability* or *diffusion-driven instability*.

Example Patterns





Images generated by Richard Tatum.

Equilibrium Solution

The equilibrium solution of

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

in the absence of diffusion is precisely the solution to

$$\begin{aligned} f(u,v) = 0 \\ g(u,v) = 0. \end{aligned}$$

By Newton's Method for systems of nonlinear equations, the equilibrium solution is

$$\begin{pmatrix} u_0 \\ v_0 \end{pmatrix} \approx \begin{pmatrix} 37.73821081921373 \\ 25.15880721280914 \end{pmatrix}.$$

Linear Stability without Diffusion

We can linearize f and g about the equilibrium solution (u_0, v_0) as

$$f(u,v) \approx \cancelto{0}{f(u_0,v_0)} + (u-u_0)f_u(u_0,v_0) + (v-v_0)f_v(u_0,v_0),$$
$$g(u,v) \approx \cancelto{0}{g(u_0,v_0)} + (u-u_0)g_u(u_0,v_0) + (v-v_0)g_v(u_0,v_0).$$

The linearized Reaction-Diffusion model (without diffusion) can be written as

$$\mathbf{w}_t = \gamma A \mathbf{w}$$

with

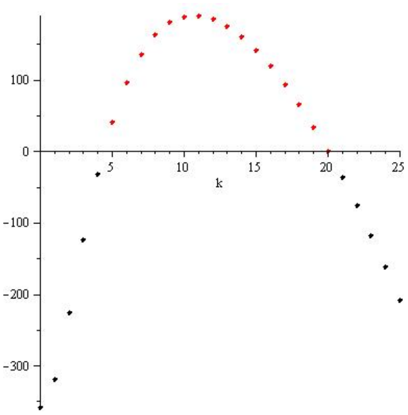
$$A = \begin{pmatrix} f_u(u_0,v_0) & f_v(u_0,v_0) \\ g_u(u_0,v_0) & g_v(u_0,v_0) \end{pmatrix}, \quad \mathbf{w} = \begin{pmatrix} u-u_0 \\ v-v_0 \end{pmatrix}.$$

So (u_0, v_0) is linearly stable if and only if

$$\mathrm{tr}\, A < 0$$
$$\det A > 0.$$

Solution Stability

For a given d and γ value, we can explicitly determine the eigenvalues of the linear system.



- The eigenvalues of the linear system are related to the eigenvalues of $-\Delta$.
- The eigenvalues are indexed by k, which correspondes to the eigenvalues of $-\Delta$, which are $n^2\pi^2$ for $n \in \mathbb{Z}$.

Strategy for Finding Patterns

- We want to see where along the equilibrium solution Turing instabilities occur. To do this, we vary the parameters d and γ to find bifurcations along the equilibrium solutions.
- We can determine where these bifurcations occur along the trivial solution by finding the non-trivial equilibrium solutions of the Linear system

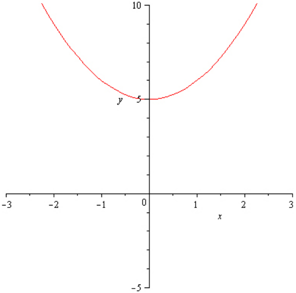
$$\mathbf{w}_t = (\gamma A - D\lambda_n)\mathbf{w},$$

where λ_n is the n^{th} eigenvalue of $-\Delta$.
- We turn the system of PDEs into a system of ODEs and utilize AUTO to continue along these bifurcations off the equilibrium solution.

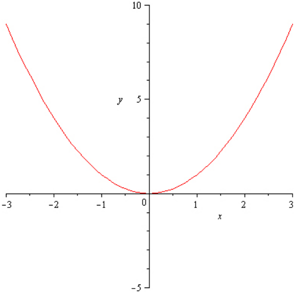
A bifurcation is a qualitative change in a family as a parameter is varied.

What does this mean?

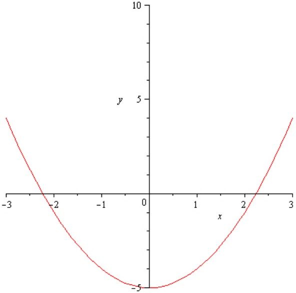
Consider the family of functions $f_\alpha(x) = x^2 - \alpha$.



$\alpha < 0$
0 real roots

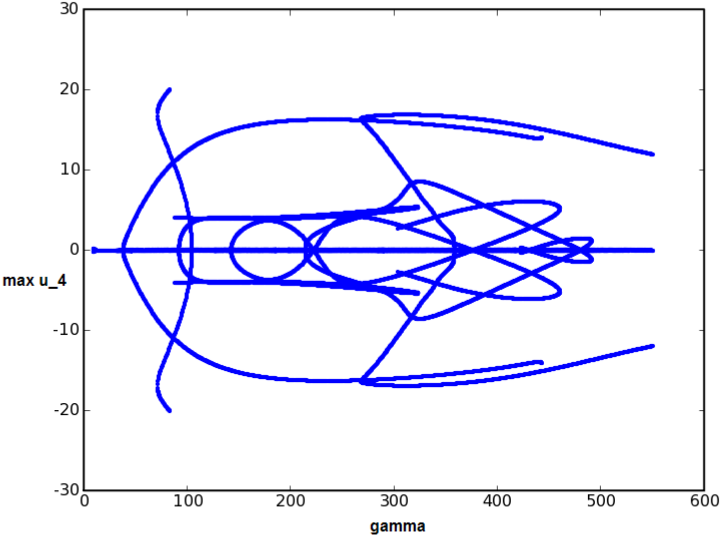


$\alpha = 0$
1 real root



$\alpha > 0$
2 real roots

Example Bifurcation Structure



Our Spectral Method

For the computation of the solution, we employ a spectral method

- We approximate the solution by a Fourier series. Instead of discretizing in space, we solve for the coefficients in the Fourier series.
- The homogeneous Neumann boundary conditions force the solution to be a cosine series.
- We use an inverse cosine transform to map into the spatial variable, where we compute the non-linear term. Then we map back into Fourier space to compute the coefficients.

Benefits of using this method

- Uses the structure of the problem to solve it.
- Able to solve a stiff problem.

Current Users of This Method

Simulation Systems

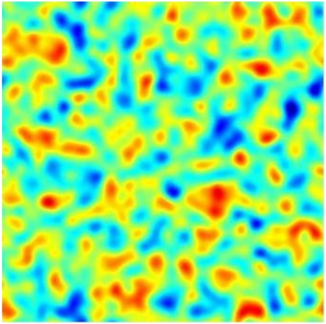


Image from Hartley [4].

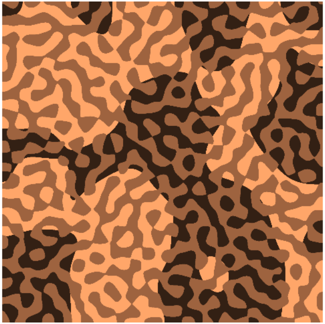
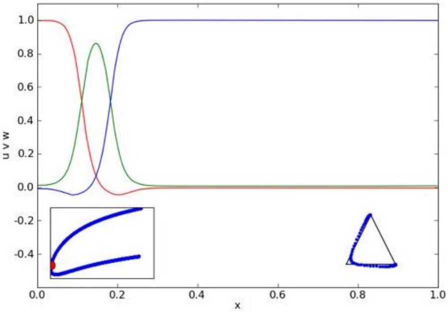
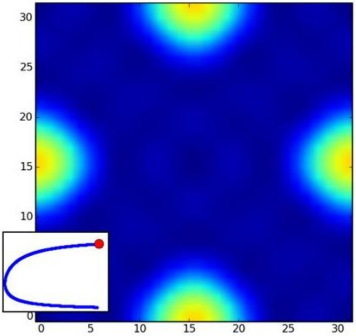


Image generated by Andrew Corrigan.

Bifurcation Analysis





Images produced by Hanein Edrees and John Price as part of the URCM program 2007-2008.

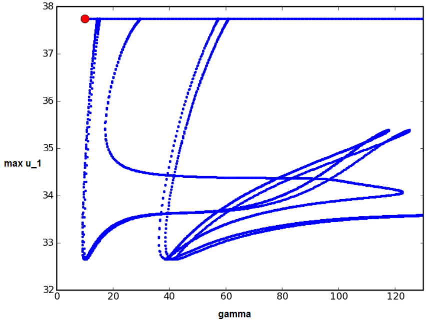
Visualization Framework

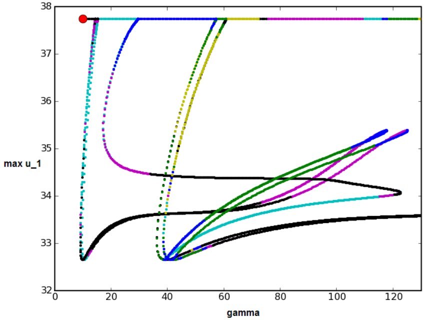
- AUTO includes a visualization utility. However, other than bifurcation diagrams, visualization is specific to the system.
- What AUTO is not able to do is visualize solutions of our Thomas system, or any generic system. An external visualization tool is needed.

Our Immediate Visualization Needs:

- Visualize bifurcation diagrams with stability information.
- Visualize solutions of the One and Two Dimensions.
- Produce document-ready images.
- Produce movies.

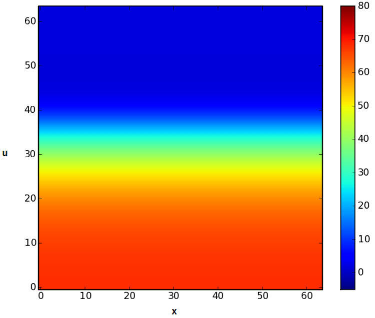
- Although AUTO is capable of displaying Bifurcation diagrams, we found the need to manipulate the images to make them document-ready.
- AUTO records stability information, but does not provide a means by which to view.

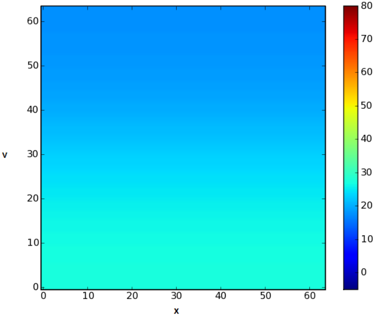




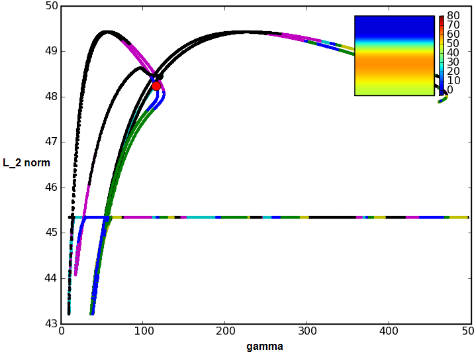
Solution Visualization

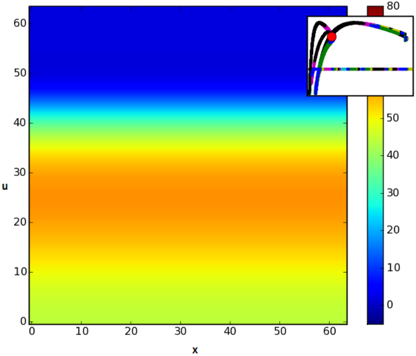
Because we are having AUTO solve for the coefficients in a Fourier series, having AUTO visualize the solution to our system would not be meaningful.





Merging Bifurcation & Solution Visualization





Testimonial Usage

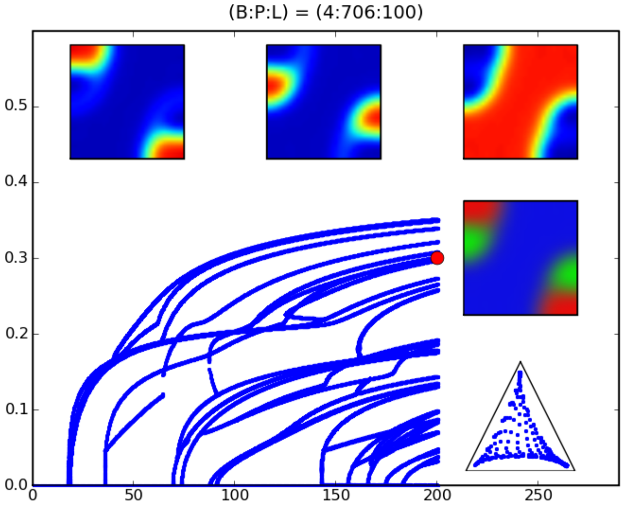
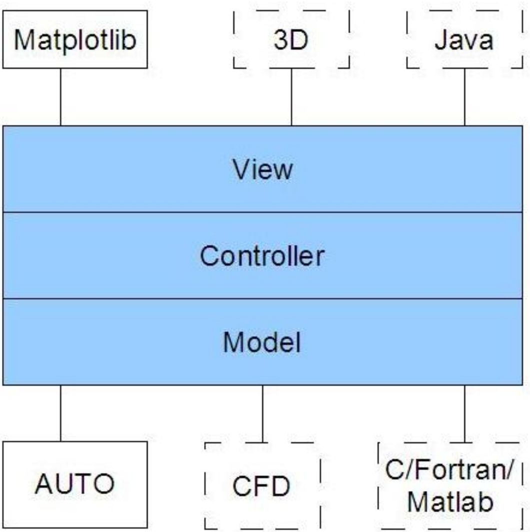


Image generated by Evelyn Sander.

Scalable Architecture



Murray's Characterization of Stable Patterns in One Dimension

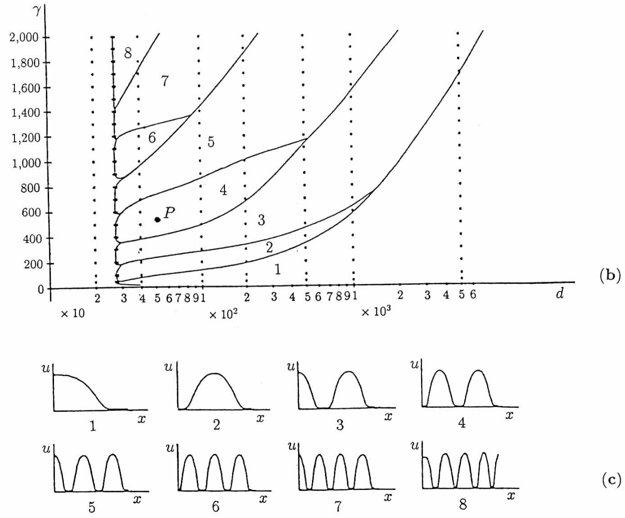
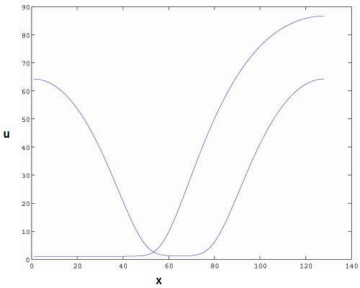


Image taken from Murray [2].

Unexpected Stable Solutions

d	γ	Murray	Calculated
200	100	1	1, 1S, 2S
	200	2	1, 1S, 2S
	300	2	2S
500	50	1	1, 1S
	100	1	1, 1S
	200	1	1, 1S
	300	1	1, 1S
	400	2	1, 1S
1000	50	1	1S, 2S
	100	1	1, 1S, 2S
	200	1	1, 1S
	300	1	1, 1S
	400	1	1, 1S
5000	50	1	1S, 2S
	100	1	1S, 2S



Unanticipated Symmetric Stable Solutions

Simulation generated by Richard Tatum.

Pattern Formation in Two Dimensions

Further Developments

One Dimension

1. Further develop the bifurcation structure.
2. Determine any stable patterns not predicted by Murray.

Two Dimensions

1. Further develop the bifurcation structure.
2. Investigate the "convergence point" further.
3. Determine the stability of solutions.

Visualization Framework

1. Move from prototype to production system.
2. Include package for 3-D visualization of data.

References

- R. Allen, *Turing Instabilities and Spatial Pattern Formation in One-Dimension*, Undergraduate Thesis, George Mason University, 2003.
- J. Deering, *Computation of the Bifurcation Structure of the Cahn-Hilliard Equation*, Master's thesis, University of Maryland Baltimore County, May 2002.
- E. Doedel, A. Champneys, T. Fairgrieve, Y. Juznetsov, B. Oldeman, R. Paffenroth, B. Sandstede, X. Wang and C. Zhang, *AUTO 07-p: Continuation and Bifurcation Software for Ordinary Differential Equations*, 2006.
- T. Hartley, *An Analysis of Phase Separation Processes for Stochastic and Nonlocal Extensions of the Classical Phase-Field Model*, Ph.D. dissertation, George Mason University, 2008.

References

- S. Kim, J. Kim & H. Park, *Spatial Structures Evolving from Homogeneous Media in Immobilized Enzyme Systems*, Korean J. Chem. Eng. **18**, 2001, 14-20.
- J. Murray, *Mathematical Biology*, Springer-Verlag, 2^{nd} corrected edition, 1993.
- E. Sander & T. Wanner, *Pattern Formation in a Nonlinear Model for Animal Coats*, J. of Diff. Eq. **191**, 143-174, 2003.
- A. Turing, *The Chemical Basis of Morphogenesis*, Phil. Trans. R. Soc. **237**, 1952, 37-72.