# Unveiling Biological Patterns: A Mathematical and Computational Journey

The intricate beauty of the natural world is often characterized by remarkable patterns – the stripes of a zebra, the spots of a leopard, the organized arrangement of cells forming tissues and organs. Understanding how these patterns emerge from seemingly simple beginnings is a fundamental question in biology. This report delves into a mathematical and computational exploration of "pattern formation," specifically focusing on how interactions between cells and chemicals can lead to the development of organized structures. Drawing upon the principles outlined in a detailed study of such phenomena, we will explore how mathematical equations, particularly Partial Differential Equations (PDEs), serve as powerful tools to model and simulate these complex biological processes.

## Section 1: How Nature Makes Patterns: A Mathematical View

The development of organized structures in living organisms is a hallmark of life. This section introduces the concept of pattern formation within a biological context and explains why mathematical approaches, specifically using Partial Differential Equations (PDEs), are indispensable for studying these phenomena.

### 1.1 What is "Pattern Formation" in Living Things?

Pattern formation in biology refers to the processes by which cells, tissues, and organisms develop specific, organized, and often complex spatial arrangements from less ordered states. This encompasses a vast array of phenomena, from the differentiation of cells during embryonic development to the establishment of body axes, the formation of limbs, and the generation of visible markings like animal coat patterns or the venation in leaves.

The specific focus of the material under consideration is the formation of "a pattern of cells that is defined by a chemoattractant and a stimulant". This implies a system where the spatial distribution of cells is influenced by, and in turn influences, the concentrations of certain chemical substances. A chemoattractant is a substance that draws cells towards it, while a stimulant might affect cell growth, activity, or production of other substances. Understanding the dynamic interplay between these components is key to deciphering how patterns can arise.

### 1.2 Why Use Math (Specifically, Partial Differential Equations - PDEs) to Understand These Patterns?

While qualitative descriptions of biological patterns are useful, a deeper

understanding of the underlying mechanisms often requires a more quantitative approach. Partial Differential Equations (PDEs) have emerged as a particularly powerful mathematical tool for this purpose. PDEs are equations that describe how quantities change over continuous space and time. Since biological pattern formation inherently involves changes in the concentrations or densities of various components (like cells or chemicals) across a spatial domain as time progresses, PDEs provide a natural language to model these dynamics.

The use of PDE models, as demonstrated in the source material, aims to achieve several objectives:

- To illustrate "the inclusion of nonlinear terms in the PDEs," which are essential for capturing the complex feedback loops and threshold effects common in biological systems.
- To show how one might go about "adding a PDE to a model that might occur, for example, during model development," reflecting the iterative nature of scientific modeling where complexity is added incrementally.
- To enable "the calculation and display of the numerical solution of the PDE model, including an examination of the individual terms in the PDEs to provide insight into the origin of the solution properties". This means PDEs are not just descriptive but serve as an investigative tool.

The formulation of these mathematical models, especially the nonlinear terms and the specific values of parameters (like reaction rates or diffusion coefficients), is not always straightforward. It often involves "a matter of experience and judgment employed during the model formulation and most likely will require some trial and error, particularly with regard to reconciliation with experimental data". This iterative cycle of hypothesizing (formulating the PDE model), predicting (solving the PDEs), and testing (comparing with experimental observations) is fundamental to scientific progress. PDEs provide the rigorous, quantitative framework necessary for this structured inquiry. Without such a mathematical language, precisely testing hypotheses about the complex, interacting mechanisms driving pattern formation would be exceedingly difficult.

### 1.3 The Basic Ingredients of the Mathematical Recipes (Key Physical Processes in the PDEs)

The PDE models for pattern formation are built from terms that represent distinct physical or biological processes. Understanding these "ingredients" is crucial for interpreting the models. The key processes include diffusion, chemotaxis, and reaction/source terms.

- **Diffusion (Fick's Second Law):** This fundamental process describes the tendency of particles or substances (like cells or molecules) to spread out from regions of higher concentration to regions of lower concentration, simply due to random motion. In the context of the discussed PDEs, this is typically represented by a term like $D\nabla 2u$, where u is the concentration or density of the substance, D is its diffusivity (a measure of how quickly it spreads), and $\nabla 2$ is the Laplacian operator representing the spatial curvature of the concentration profile. For instance, D1,D2,D3 represent the diffusivities for cells (u1), chemoattractant (u2), and stimulant (u3), respectively.
- **Chemotaxis (Cell Movement Guided by Chemicals):** This refers to the directed movement of cells in response to a chemical gradient. Cells might move towards higher concentrations of an attractant (positive chemotaxis) or away from a repellent. In the models, a term like $-\nabla\cdot[(k2+u2)2k1u1\nabla u2]$ in equation (2.1a) captures this process for cells (u1) responding to a chemoattractant (u2). This term indicates that the rate of change of cell density due to chemotaxis depends on the existing cell density (u1), the strength of the chemotactic response (k1), and the gradient (spatial rate of change, $\nabla u2$) of the chemoattractant. The denominator (k2+u2)2 suggests a saturating response to the chemoattractant.
- **Reaction/Source Terms (Creation, Consumption, Interaction):** These terms account for the local production, degradation, or transformation of the substances involved. They often represent complex biological processes like cell proliferation, death, secretion of signaling molecules, or chemical reactions. These terms are frequently "nonlinear," meaning their effect is not directly proportional to the concentrations of the interacting components.
    - For cell density (u1): An example is the term $+k3u1[k9+u32k4u32-u1]$ in equation (2.1a). This can be interpreted as cell growth or production (the part involving k3u1 and the stimulant u3) being counteracted by a self-limiting factor or cell loss (the $-u1$ part within the bracket, scaled by k3u1). The term involving u3 suggests that the stimulant influences cell behavior in a concentration-dependent, nonlinear manner.
    - For chemoattractant concentration (u2): The term $+k5u3[k6+u12u12]-k7u1u2$ in equation (2.1b) represents the net rate of change of the chemoattractant. The first part suggests production of u2 influenced by the cell density (u1) and the stimulant concentration (u3), potentially with saturation effects. The second part, $-k7u1u2$, indicates a consumption or decay of the chemoattractant that depends on both cell density and its own concentration.
    - For stimulant concentration (u3): The term $-k8u1[k9+u32u32]$ in equation (2.1c) represents the consumption or degradation of the stimulant, dependent

on cell density (u1) and the stimulant's own concentration (u3).

The intricate patterns observed in biology often arise from the complex interplay of these processes. While diffusion tends to smooth out differences and promote uniformity, the nonlinear reaction and chemotaxis terms can act to create and amplify spatial variations, leading to the emergence and maintenance of structure. The document notes that "the effect and interaction of these nonlinear terms is complicated. This complexity can be elucidated by computing and examining the individual terms". This implies that simple linear relationships would be insufficient to capture the richness of biological pattern formation, such as threshold responses, saturation phenomena, and feedback mechanisms. It is within these nonlinear interactions that much of the "interesting" biological behavior is mathematically encoded. The acknowledged need for "experience and judgment" and "trial and error" in defining these terms further underscores that they are attempts to model complex biological realities that are not always easily derivable from first principles.

## Section 2: Two Mathematical Models for Pattern Formation

The document under review presents two specific mathematical models based on Partial Differential Equations (PDEs) to explore pattern formation. These models differ in their complexity, specifically in the number of interacting components they consider. They serve to illustrate how modeling can start from a simpler representation and be expanded to include more biological detail.

### 2.1 Model 1: The Two-Equation Approach (2-PDE Model)

The first model discussed is a simplified system designed as a starting point for investigation. It involves two coupled PDEs and is considered in one spatial dimension (denoted by x). A key characteristic of this initial model is its use of dimensionless variables, which can simplify mathematical analysis and highlight fundamental relationships between parameters.

The biological components represented are:

- u1(x,t): Represents the density of cells at position x and time t.
- u2(x,t): Represents the concentration of a chemoattractant at position x and time t.

The behavior of these components is governed by the following PDEs, which are variants of equations (5.20) and (5.21) from a reference work by Murray :

Equation for cell density (u1):

$$ \frac{\partial u_{1}}{\partial t}=D_{1}\frac{\partial^{2}u_{1}}{\partial x^{2}}-\alpha\frac{\partial}{\partial x}\left[\frac{u_{1}}{(1+u_{2})^{2}}\frac{\partial u_{2}}{\partial x}\right] \quad \text{(Eq. 2.2a)} $$
This equation states that the rate of change of cell density over time (∂t∂u1) is determined by two main processes:

1. D1∂x2∂2u1: The diffusion of cells, where D1 is the cell diffusion coefficient.
2. −α∂x∂[(1+u2)2u1∂x∂u2]: The movement of cells due to chemotaxis, driven by the gradient of the chemoattractant (∂x∂u2). The parameter α scales the strength of this chemotactic response. The term (1+u2)2u1 indicates that the response depends on the cell density and is modulated by the chemoattractant concentration in a nonlinear way.

Equation for chemoattractant concentration (u2):
$$ \frac{\partial u_{2}}{\partial t}=\frac{\partial^{2}u_{2}}{{\partial x}^{2}}+w\frac{u_{1}^{2}}{\mu+u_{1}^{2}} \quad \text{(Eq. 2.2b)} $$
This equation describes the rate of change of chemoattractant concentration over time (∂t∂u2) due to:

1. ∂x2∂2u2: The diffusion of the chemoattractant (its diffusion coefficient is implicitly 1 in this dimensionless form).
2. +wμ+u12u12: The production of the chemoattractant by the cells. The rate of production is scaled by w and depends on the cell density (u1) in a saturating manner, described by a Hill-type function, where μ is a constant.

To solve these PDEs, specific initial conditions (ICs) and boundary conditions (BCs) must be defined.

- **Initial Conditions (ICs):** These specify the state of the system at the beginning of the simulation (t=0). They are given by u1(x,t=0)=f1(x) and u2(x,t=0)=f2(x) (Eqs. 2.3a,b) , where f1(x) and f2(x) are functions defining the initial spatial distributions of cells and chemoattractant.
- **Boundary Conditions (BCs):** These define how the system behaves at its spatial boundaries (e.g., at x=0 and x=L, where L is the length of the system). The model uses zero-flux (or homogeneous Neumann) boundary conditions, such as ∂x∂u1(x=0,t)=0 and ∂x∂u1(x=L,t)=0 (Eqs. 2.4a,b). These conditions mean that no cells or chemoattractant can enter or leave the defined spatial domain through its boundaries. Similar conditions apply to u2 (Eqs. 2.4c,d).

### 2.2 Model 2: Adding More Detail (3-PDE Model)

The second model represents an extension of the modeling approach, increasing complexity by incorporating a third PDE and using dimensional variables. Dimensional

variables (e.g., concentration in Molar, time in seconds) allow for more direct comparison of model predictions with experimental measurements. This model is based on equations (5.11), (5.12), and (5.13) from Murray.

The biological components represented in this more comprehensive model are :

- u1(x,t): Density of cells.
- u2(x,t): Concentration of the chemoattractant.
- u3(x,t): Concentration of a stimulant.

The governing equations for these three components are:

Equation for cell density (u1):
$$ \frac{\partial u_{1}}{\partial t}=D_{1}\nabla^{2}u_{1}-\nabla\cdot\left[\frac{k_{1}u_{1}}{(k_{2}+u_{2})^{2}}\nabla u_{2}\right]+k_{3}u_{1}\left[\frac{k_{4}u_{3}^{2}}{k_{9}+u_{3}^{2}}-u_{1}\right] \quad \text{(Eq. 2.1a)} $$
Meaning: The change in cell density over time is due to:

1. D1∇2u1: Diffusion of cells.
2. −∇·[(k2+u2)2k1u1∇u2]: Chemotaxis towards u2.
3. +k3u1[k9+u32k4u32−u1]: A net growth term, where cell proliferation is promoted by the stimulant u3 (the k9+u32k4u32 part) and limited by a density-dependent factor (the −u1 part). The constants k1,k2,k3,k4,k9 are rate constants or parameters characterizing these processes.

Equation for chemoattractant concentration (u2):
$$ \frac{\partial u_{2}}{\partial t}=D_{2}\nabla^{2}u_{2}+k_{5}u_{3}\left[\frac{u_{1}^{2}}{k_{6}+u_{1}^{2}}\right]-k_{7}u_{1}u_{2} \quad \text{(Eq. 2.1b)} $$
Meaning: The change in chemoattractant concentration over time is due to:

1. D2∇2u2: Diffusion of the chemoattractant.
2. +k5u3[k6+u12u12]: Production of chemoattractant, influenced by cells (u1) and the stimulant (u3).
3. −k7u1u2: Degradation or consumption of the chemoattractant, dependent on both cells and its own concentration. k5,k6,k7 are relevant parameters.

Equation for stimulant concentration (u3):
$$ \frac{\partial u_{3}}{\partial t}=D_{3}\nabla^{2}u_{3}-k_{8}u_{1}\left[\frac{u_{3}^{2}}{k_{9}+u_{3}^{2}}\right] \quad \text{(Eq. 2.1c)} $$
Meaning: The change in stimulant concentration over time is due to:

1. D3∇2u3: Diffusion of the stimulant.
2. −k8u1[k9+u32u32]: Consumption or degradation of the stimulant by cells (u1), with the rate influenced by the stimulant's own concentration (u3). k8 and k9 are parameters.

For this 3-PDE model:

- **Initial Conditions (ICs):** The simulations typically start with Gaussian (bell-shaped) distributions for all three variables. For example, the initial cell density is u1(x,t=0)=u10e−λx2, and similar forms apply for u2 and u3 (Eqs. 2.7a,b,c). The constants u10,u20,u30 define the initial peak amplitudes, and λ determines the width of the Gaussian.
- **Boundary Conditions (BCs):** Similar to the 2-PDE model, zero-flux boundary conditions are applied for all three variables, ensuring no substance flows in or out of the system boundaries (Eqs. 2.8a-f).
- **Parameter Estimation:** An important practical aspect highlighted is that some parameters for this 3-PDE model (specifically u20,k5,k6,k7, and k8) were not directly available from the original source literature (Murray). These were therefore estimated using "order-of-magnitude analysis and assumed values of the LHS [left-hand side] derivatives," possibly followed by adjustments, rather than being derived from direct physical or chemical measurements. This practice underscores a common challenge in biological modeling: not all parameters are always precisely known or easily measurable, sometimes necessitating reasoned estimations to proceed with simulations.

### 2.3 Key Table: Comparing the Two Models

| Feature | 2-PDE Model | 3-PDE Model |
|---|---|---|
| **Biological Agents** | Cells (u1), Chemoattractant (u2) | Cells (u1), Chemoattractant (u2), Stimulant (u3) |
| **Primary Focus** | Basic cell-chemoattractant dynamics | More complex interactions involving a stimulant |
| **Variable Type** | Dimensionless | Dimensional (allows direct comparison with experimental units) |

| | | |
|---|---|---|
| **Number of Equations** | Two PDEs | Three PDEs |
| **Source Reference** | | |
| **Key Distinction** | Simpler model, focuses on core interactions | Includes an additional biological factor (stimulant), aims for more detail |

To clarify the distinctions and the progression in model complexity, the following table provides a side-by-side comparison of the 2-PDE and 3-PDE models:The progression from a 2-PDE model (often using dimensionless variables for theoretical exploration and identifying key parameter groupings) to a 3-PDE model (using dimensional variables for more direct comparison to experiments) reflects a common and effective strategy in scientific modeling. One often starts with a simplified system to understand fundamental dynamics and then incrementally adds complexity to capture more specific or nuanced biological features. The document explicitly states one of its intents is to demonstrate "Adding a PDE to a model that might occur, for example, during model development".

This iterative approach allows researchers to isolate the effects of newly introduced components. For instance, if the simpler 2-PDE model fails to reproduce certain experimental observations, the more complex 3-PDE model can be used to test whether the inclusion of the stimulant (u3) and its associated interactions can account for these discrepancies. This structured way of building and testing models is crucial for advancing understanding.

## Section 3: Using Computers to See Patterns Emerge: The Computational Approach

The mathematical models described by Partial Differential Equations (PDEs), especially those involving nonlinear terms as seen in biological pattern formation, are typically too complex to be solved analytically (i.e., with pen and paper to find an exact formula for the solution). Therefore, computational methods are essential to simulate these models and observe how patterns might emerge and evolve over time.

### 3.1 The Challenge: Why Computers are Needed

The coupled, nonlinear nature of the PDEs in both the 2-PDE and 3-PDE models makes finding exact analytical solutions generally intractable. Computers allow for numerical approximation of these solutions, providing valuable insights into the

system's behavior under various conditions.

### 3.2 The "Method of Lines" (MOL): Turning a Hard Problem into Many Simpler Ones

A central computational technique employed in the document is the Method of Lines (MOL). The MOL is a numerical strategy for solving PDEs that works by discretizing the spatial dimensions of the problem while leaving the time dimension continuous.
Imagine the spatial domain (e.g., the length L along the x-axis) is divided into a finite number of discrete points or grid cells. At each of these spatial points, the spatial derivatives in the PDEs (like ∂x2∂2u1) are approximated using finite difference formulas. This transformation effectively converts the original PDE (or system of PDEs) into a large system of coupled Ordinary Differential Equations (ODEs). Each ODE in this system describes how a variable (like cell density u1) changes at a specific spatial grid point over time.
For example, if the 2-PDE model is discretized using nx=51 spatial points, the MOL converts it into a system of 2×51=102 ODEs. Similarly, for the 3-PDE model with nx=51 points, it results in 3×51=153 ODEs. This system of ODEs, though potentially large, can then be solved using well-established numerical integrators designed for ODEs.

### 3.3 The Toolkit: R Programming Language and deSolve Package

The implementation of these computational models is carried out using the R programming language. R is a versatile environment widely used for statistical computing and graphics, but it also possesses powerful capabilities for numerical computation.
Within R, the deSolve package is specifically utilized. This package provides a suite of functions for solving various types of differential equations. The particular ODE integrator mentioned and used in the provided code is lsodes , which is suitable for solving stiff or non-stiff systems of ODEs, such as those arising from the MOL.

### 3.4 Anatomy of the Code: Key R Functions

The computational solution is orchestrated through several R functions and scripts, each playing a specific role:

- ODE Routines (p_form_1 and p_form_2): Defining the "Rules of Change"
  These functions are the heart of the MOL implementation, as they define the system of ODEs that lsodes will solve.
  - p_form_1 (Listing 2.1 for the 2-PDE model) :
    This function is called repeatedly by the lsodes solver. At each call, it receives the current values of u1 and u2 at all spatial grid points (passed as a single vector u) and the current time t as input.
    Its tasks include:
    1. Separating the input vector u into two distinct vectors, u1 and u2, each representing the spatial profile of one variable. This is done to facilitate more problem-oriented programming.

2. Calculating the necessary spatial derivatives (e.g., ∂x∂u1, ∂x2∂2u1, ∂x∂u2, ∂x2∂2u2) at each grid point. This is achieved using library differentiation routines like dss004 (for first-order derivatives) and dss044 (for second-order derivatives), which implement finite difference approximations.
3. Applying the boundary conditions. For the zero-flux conditions, this means setting the calculated derivatives at the boundary points to zero (e.g., u1x=0, u1x[nx]=0).
4. Using these derivatives and current variable values, it computes the right-hand side (RHS) of each PDE (equations 2.2a and 2.2b from the 2-PDE model) at every spatial grid point. This RHS effectively represents the time derivatives ∂t∂u1 and ∂t∂u2 at each point.
5. Finally, it combines these computed time derivatives (u1t and u2t) into a single output vector ut and returns it (as a list, as required by lsodes) to the solver. The solver then uses these derivatives to advance the solution of u1 and u2 to the next small time step.

- p_form_2 (Listing 2.3 for the 3-PDE model) :
  This function operates analogously to p_form_1 but is tailored for the 3-PDE model. It handles three dependent variables (u1,u2,u3) and computes the RHS terms for the three corresponding PDEs (equations 2.1a, 2.1b, 2.1c). If nx=51 grid points are used, this function defines a system of 153 ODEs.

- Main Programs (Listings 2.2 and 2.4): Orchestrating the Simulation
  These are R scripts that set up and run the entire simulation.
  - **Listing 2.2 (for the 2-PDE model)** and **Listing 2.4 (for the 3-PDE model)**.
  - Their responsibilities include:
    1. Loading necessary R libraries (like deSolve) and sourcing the custom-written functions (like p_form_1 or p_form_2, and the dss differentiation routines).
    2. Defining global simulation parameters: the number of spatial grid points (nx), the spatial domain boundaries (xl, xu), and the time points at which output is desired (tout).
    3. Setting the specific model parameters: diffusion coefficients (D1, etc.), reaction rate constants (k1, etc.), and any dimensionless constants (α, etc.) pertinent to the model being solved [, p11, p14 (for 2-PDE); p37-38 (for 3-PDE)].
    4. Specifying the Initial Conditions (ICs) for the simulation.
       - For the 2-PDE model, a parameter ncase is used to select from different predefined ICs, such as a spatially uniform distribution (ncase=1), a Gaussian (bell-shaped) distribution (ncase=2), or a

step-function distribution (ncase=3).
        - For the 3-PDE model, Gaussian ICs are typically used for u1,u2, and u3.
    5. Invoking the lsodes ODE integrator, passing it the vector of initial conditions (u0), the vector of output time points (tout), and the name of the relevant ODE routine (p_form_1 or p_form_2).
    6. Receiving the solution array (named out) back from lsodes. This array contains the values of the dependent variables at each grid point for each specified output time.
    7. Processing and reshaping this output data into formats suitable for plotting (e.g., into matrices like u1_plot, u2_plot) and for display in numerical tables [, p12, p16 (for 2-PDE); p39-40, p44 (for 3-PDE)].
    8. Generating graphical plots of the solutions and, if specified, printing numerical tables of the results.
- Supplemental Routine (pde_terms in Listing 2.5 for the 3-PDE model) :
  This specialized function is used in conjunction with the 3-PDE model, particularly when ncase=6 is selected in its main program (Listing 2.4).
  Its purpose is to calculate and make accessible the values of the individual terms that make up the right-hand side of each PDE (e.g., the diffusion term separately, the chemotaxis term separately, each component of the reaction term separately). These calculations are performed at each point in space and for each output time.
  This detailed breakdown allows for a deeper analysis of the model's dynamics, helping to understand which specific sub-processes are the dominant contributors to the observed changes in u1,u2, and u3 at different stages of the simulation.

The overall computational framework is designed with a high degree of modularity. Specialized functions handle distinct tasks (e.g., dss004 for differentiation, p_form_1 for defining the ODE system, lsodes for numerical integration). This separation of concerns is a hallmark of good software engineering practice in scientific computing, making the complex process more manageable, easier to debug, and simpler to modify or extend. The use of the ncase parameter to switch between different initial conditions or parameter sets effectively transforms the code into a flexible experimental tool. Researchers can readily test various hypotheses about the influence of initial states or the relative importance of different terms in the PDEs by changing a single parameter and re-running the simulation, thereby exploring the model's behavior comprehensively.

## Section 4: What the Computer Simulations Revealed: Observing

## Patterns in Motion

The computational solution of the PDE models provides a window into how initial spatial arrangements of cells and chemicals evolve over time. This section details the outcomes of simulations for both the 2-PDE and 3-PDE models, highlighting the behavior observed under different starting conditions, as illustrated by figures and tables in the source material.

### 4.1 Insights from the 2-PDE Model: Cells and an Attractant

The 2-PDE model, representing cell density (u1) and chemoattractant concentration (u2), was simulated with three distinct initial conditions:

- **Scenario 1: Spatially Uniform Start (ncase=1)**
  - **Observation:** When starting with a uniform distribution of cells (u1(x,t=0)=1) and no chemoattractant (u2(x,t=0)=0), the cell density u1 remained constant and spatially uniform throughout the simulation. The chemoattractant u2 also remained spatially uniform, but its concentration increased steadily over time.
  - **Graphical Evidence:** Figure 2.1, plotting u1(x,t), shows a single flat line, indicating no change in space or time. Figure 2.2, plotting u2(x,t), displays multiple flat lines, each successive line at a later time point being higher, representing the uniform increase in concentration.
  - **Explanation:** With no initial spatial variations in u1, the diffusion term (D1∂x2∂2u1) and the chemotaxis term in its PDE (Eq. 2.2a) are both zero. Consequently, ∂t∂u1=0, so u1 does not change. The chemoattractant u2 is produced by cells (according to Eq. 2.2b); since u1 is constant and uniform, u2 is produced uniformly and its overall concentration rises.
- **Scenario 2: Gaussian (Bell-Curve) Start (ncase=2)**
  - **Observation:** When u1 started as a Gaussian-shaped peak (and u2=0), this initial peak of cells gradually spread out and flattened over time. The concentration of u2, produced by u1, showed a similar trend of spreading and flattening, influenced by the evolving distribution of u1.
  - **Graphical Evidence:** Figure 2.3 (u1(x,t)) clearly shows the initial bell-shaped curve for u1 diffusing, becoming broader and shorter with time. Figure 2.4 (u2(x,t)) illustrates how the attractant, starting from zero, develops a spatial profile driven by u1 and also diffuses over time.
  - **Key Behavior:** The document notes, "Through the effect of diffusion... u1(x,t) moves toward a uniform value with increasing t". An interesting numerical detail is that even if the initial Gaussian function does not perfectly match the zero-flux boundary conditions at the edges of the domain (i.e., its slope might not be zero at the boundaries), "This discontinuity could be accommodated

numerically because of the smoothing effect of the diffusion," which is a general property of parabolic PDEs like the diffusion equation.

- **Scenario 3: Step (Sharp Boundary) Start (ncase=3)**
  - **Observation:** Starting u1 as a step function (a sharp boundary between a region of high cell density and low cell density, with u2=0), the sharp edge in u1 was observed to smooth out progressively over time. The system again moved towards a more uniform distribution of cells. The chemoattractant u2 mirrored this smoothing behavior.
  - **Graphical Evidence:** Figure 2.5 (u1(x,t)) shows the initial sharp step becoming progressively less steep and more spread out. Figure 2.6 (u2(x,t)) shows the corresponding evolution of the attractant profile.
  - **Key Behavior:** Similar to the Gaussian case, diffusion is the dominant process driving the change in the spatial pattern, effectively smoothing out the initial sharp discontinuity.
- **Overall Finding for 2-PDE Model:** In these simulations of the 2-PDE model, diffusion plays a very significant role. It consistently acts to dissipate initial spatial heterogeneities, whether they are smooth peaks (Gaussian) or sharp boundaries (step), leading the system towards more uniform distributions of both cells and chemoattractant over the simulated time.

### 4.2 Insights from the 3-PDE Model: Adding a Stimulant

The 3-PDE model, which includes cell density (u1), chemoattractant (u2), and a stimulant (u3), was simulated using dimensional variables and more complex interaction terms. For these simulations, all three variables typically started with Gaussian spatial distributions.

- **General Evolution:**
  - **Observation:** The initial Gaussian profiles of u1,u2, and u3 were all observed to evolve over time. Generally, the peaks of these distributions spread out and decreased in height, indicating a movement towards more spatially uniform values, though not necessarily towards zero concentration.
  - **Graphical Evidence:** Figures 2.7 (u1(x,t)), 2.8 (u2(x,t)), and 2.9 (u3(x,t)) visually demonstrate these trends, showing the initial sharp Gaussian peaks broadening and flattening as time progresses.
  - **Noteworthy Feature:** The model and the numerical solver (lsodes) successfully handled simulations where the initial magnitudes of the variables differed by many orders of magnitude. For example, initial cell density u10 was around 1.0×108 cells/ml, while initial chemoattractant concentration u20 was around 5.0×10−6 M. Simulating such "stiff" systems, where different

components might change on vastly different scales or at very different rates, can be numerically challenging. The successful computation implies that the chosen numerical methods and solver parameters were robust.

- Peeking "Under the Hood" (Analysis of Individual PDE Terms via ncase=6 and pde_terms)
  A powerful feature of the computational approach is the ability to dissect the contributions of individual terms within the PDEs. This was done for the 3-PDE model (when ncase=6) using the pde_terms routine.
  - **Purpose:** This analysis helps to understand *why* the solutions for u1,u2, and u3 behave as they do, by quantifying how much of the change is attributable to diffusion, how much to chemotaxis, and how much to each part of the reaction/source terms at any given point in space and time.
  - **Example 1: Diffusion term for u1 (D1∂x2∂2u1):** This term, plotted as chemo1 in Figure 2.10, shows a complex spatial and temporal profile. Initially, it can be large where the curvature of the u1 profile is significant (e.g., at the peak and flanks of the Gaussian). As u1 becomes more uniform due to diffusion, this term generally diminishes and approaches zero.
  - **Example 2: Time derivatives (∂t∂u1,∂t∂u2,∂t∂u3):** These terms (plotted as chemo8, chemo9, and chemo10 in Figures 2.11-2.13, respectively) directly show the net rate of change of each variable. They indicate where and when the system is changing most rapidly. These derivatives also tend towards zero as the system approaches a steady state or equilibrium.
  - The document emphasizes that "this analysis demonstrates how PDEs can be studied in detail to understand the origin and properties of the solutions".

Across both models, a recurring theme is the powerful homogenizing effect of diffusion. It consistently acts to smooth out initial patterns. For *de novo* pattern formation – where complex, stable patterns emerge from near-uniform or random initial conditions (which is the broader goal of many pattern formation models, though not the primary focus of the specific simulations shown evolving from defined ICs here) – the nonlinear reaction and chemotaxis terms would need to actively work *against* diffusion. These terms would have to create and maintain spatial heterogeneity in the face of diffusion's tendency to eliminate it. The simulations presented in the document primarily illustrate how given initial non-uniform patterns *evolve*, often towards greater homogeneity due to the influence of diffusion over the time scales observed. The capacity to "examine the individual terms" is therefore crucial for understanding this dynamic balance between homogenizing forces like diffusion and potentially pattern-generating nonlinearities.

## Section 5: Are the Computer's Answers Reliable? Checking the Accuracy of Simulations

Numerical simulations provide approximate solutions to the mathematical models. It is therefore essential to perform checks to ensure that these approximations are sufficiently accurate and reliable representations of the true (but often unknown) solutions to the Partial Differential Equations (PDEs). The document discusses two such verification methods: h-refinement and p-refinement.

### 5.1 The Need for Verification

Because numerical methods involve discretizations and approximations, they introduce errors. The goal of verification is to estimate and control these errors to ensure that the computed solution is a faithful representation of the behavior described by the PDE model. As stated in the text, this type of "error analysis should be a standard procedure for new PDE applications".

### 5.2 Method 1: h-refinement (Changing Spatial Resolution)

In numerical methods like the Method of Lines, the spatial domain is divided into a discrete grid. The letter "h" is often used in numerical analysis literature to denote the size of the spatial step (i.e., the distance between grid points). **h-refinement** involves changing this spatial resolution, typically by varying the number of grid points (nx) used to discretize the domain.

- **Procedure:** The simulation is run multiple times with different values of nx. For instance, the 3-PDE model was run with nx=41 and then with nx=51 grid points.
- **Interpretation:** The solutions obtained from these different runs are then compared. If increasing the number of grid points (i.e., making the spatial mesh finer) leads to a significant change in the solution, it suggests that the coarser grid was not providing enough spatial detail to accurately capture the solution's features. Conversely, if the solution remains "essentially identical" as the grid is refined (as was reported for nx=41 versus nx=51 in Table 2.8 for the 3-PDE model), it indicates that the solution has likely converged with respect to spatial discretization. This suggests that the chosen grid (nx=51 in this case) was adequate for achieving an acceptable level of accuracy.

### 5.3 Method 2: p-refinement (Changing Approximation Order)

The letter "p" in numerical analysis often refers to the polynomial order of the approximation method used, which relates to its accuracy. **p-refinement** involves changing the order (and thus, the theoretical accuracy) of the formulas used to

approximate the spatial derivatives in the PDEs. For example, finite difference approximations can be second-order accurate, fourth-order accurate, etc., with higher orders generally providing better accuracy for a given step size, especially for smooth solutions.

- **Procedure:** The document describes replacing the fourth-order accurate spatial differentiation routines (dss004 for first derivatives, dss044 for second derivatives) with sixth-order accurate routines (dss006, dss046). This involves changing the function calls in the ODE routine (e.g., p_form_2) and ensuring the main program sources these higher-order routines.
- **Interpretation:** If using higher-order (more mathematically precise) formulas for the derivatives results in a noticeably different solution, it might imply that the lower-order approximations were introducing significant error. In the case presented, switching from fourth-order to sixth-order approximations led to "no perceptible change in the solution". This outcome suggests that the fourth-order approximations were already providing a level of accuracy sufficient for this particular problem and its characteristics.

### 5.4 Context Matters: Smooth Problems, Smooth Solutions

It is important to recognize that the ease of achieving numerical accuracy can depend on the nature of the problem itself. The document notes that the "apparent accuracy of the numerical solution is due in part to a relatively smooth problem". This smoothness arises from two factors:

1. The PDEs themselves contain diffusion terms (e.g., D1∇2u1), which inherently tend to smooth out sharp variations in the solution.
2. The Initial Conditions (ICs) used, particularly the Gaussian functions for the 3-PDE model, are also smooth functions.

For problems that are "more stringent"—for example, those involving the formation and movement of sharp fronts, shock waves, or other types of discontinuities—achieving a similar level of numerical accuracy might be more challenging and could require more sophisticated numerical techniques or significantly finer grids and higher-order approximations.

### 5.5 Key Table: Understanding Accuracy Checks

To provide a clearer, non-technical summary of these two important validation techniques, their purpose and methodology can be understood as follows:

| Method | What it Changes | What it Tests | Analogy for Understanding |
|---|---|---|---|
| **h-refinement** | Number of spatial grid points (nx) used to represent the system | Whether the solution is stable and consistent when using finer or coarser spatial detail (i.e., resolution). | Zooming in on a digital photograph: does adding more pixels (a finer grid) reveal significant new details, or does the overall image stay largely the same? |
| **p-refinement** | Mathematical precision (order) of the formulas used to calculate derivatives | Whether employing a more "sophisticated" or higher-accuracy calculation method yields a different result. | Using a more precise measuring instrument (e.g., a ruler with finer markings): does it give a significantly different measurement than a less precise one? |

These refinement techniques are crucial for building confidence in the *numerical solution* of the model equations. They address the critical question: "Is the computer solving the given mathematical equations correctly, to a sufficient degree of accuracy?" This is a distinct question from whether the *mathematical model itself* is an accurate representation of the biological reality. The latter requires comparison with experimental data and biological validation. The analysis in the document primarily focuses on the numerical validation for the specific examples shown. This systematic approach to verifying numerical results is a cornerstone of reliable computational science.

## Section 6: The Big Picture: Why This Mathematical Exploration Matters

The detailed examination of pattern formation through Partial Differential Equations (PDEs) and computational simulations, as presented, offers significant insights not only into the specific biological models studied but also into the broader value of such approaches in biomedical research. This concluding section synthesizes the main takeaways, emphasizing the power and versatility of numerical simulations for understanding complex biological systems.

### 6.1 The Power of Computational Experiments

A central conclusion is that numerical simulations are an invaluable, if not indispensable, tool for investigating complex biological models that are described by PDEs. Many such systems, especially those involving multiple interacting components and nonlinear dynamics, are analytically intractable, meaning their behavior cannot be predicted by deriving exact mathematical solutions with pen and paper. Computational methods bridge this gap, allowing scientists to perform "in silico" experiments—simulations run on a computer—to explore the model's behavior.

### 6.2 What These Tools Allow Scientists To Do

The computational framework demonstrated provides scientists with a powerful and flexible toolkit to:

- **Explore Diverse Scenarios:** Researchers can easily study the impact of different initial conditions (ICs) on how patterns evolve. For example, the simulations showed how uniform, Gaussian, or step-function initial distributions for cell density led to different transient dynamics, even if diffusion tended to homogenize them over time. This allows for testing the system's response to various starting states.
- **Test Sensitivity to Parameters:** The influence of various model parameters (such as diffusion rates, chemical reaction constants, or chemotactic sensitivity) on the system's behavior can be systematically investigated. The use of ncase in the provided code to switch between different parameter sets or active terms in the PDEs exemplifies this capability, allowing for a form of sensitivity analysis.
- **Iteratively Develop Models:** The process of scientific modeling is often iterative. Models can be adapted and extended based on new hypotheses or experimental data. The document illustrates this by showing how a 2-PDE model can be expanded to a 3-PDE model by "adding a PDE" to incorporate more biological detail, such as the role of a stimulant. This modularity is crucial for refining models as understanding grows.
- **Gain Deeper Mechanistic Insight:** Computational simulations allow researchers to go beyond merely observing the final patterns or overall changes in concentrations. By calculating and examining the individual terms within the PDEs (as done with the pde_terms routine), scientists can pinpoint which specific processes—diffusion, chemotaxis, or particular reaction pathways—are the dominant drivers of the observed behaviors at different times and locations within the system. This provides a much deeper, mechanistic understanding of how the system functions.
- **Ensure Numerical Reliability:** As discussed, methods like h-refinement and

p-refinement are integral to the computational workflow. They allow scientists to assess and build confidence in the accuracy of the computed solutions, ensuring that the observed behaviors are genuine properties of the model rather than artifacts of the numerical approximation.

### 6.3 The Ultimate Goal: Bridging Models and Reality

The detailed insights obtained from numerical simulations—understanding the "origin and properties of the solutions" —are not just academic exercises. They are critically important for "model development, revision, and interpretation," and, most significantly, for the "reconciliation of the solutions with experimental data". This highlights the essential synergy between computational modeling and experimental biology. Models can generate testable predictions, help interpret complex experimental results, and guide the design of new experiments.

### 6.4 Concluding Thought

The exploration of pattern formation models effectively demonstrates that the numerical simulation of PDE-based models is a versatile, robust, and powerful approach in biomedical science and engineering. It provides a dynamic laboratory where complex biological interactions can be dissected, hypotheses can be rigorously tested, and a deeper understanding of how patterns and organized structures emerge in living systems can be achieved. This computational methodology serves as a vital partner to traditional experimental research, accelerating discovery and providing a framework for integrating diverse biological knowledge. The ability to systematically vary parameters, initial conditions, and even the model structure itself, coupled with detailed term analysis and rigorous accuracy checks, makes numerical simulation an indispensable tool for tackling the complexities of biological pattern formation.

### Works cited

1. Pattern Formation.pdf