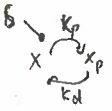
D-BSSE Spatio-Temporal Modeling in Biology 2019/20
Prof. D. Iber

Summary



1. Reaction Modeling.

a) What is the "Law of mass action"? What are the limitations in using it in systems biology?

b) Write down the scheme for the Michaelis-Menten and the Goldbeter-Koshland approximation. What are the underlying assumptions? When do they apply and when do they fail?

c) When can we observe ultrasensitivity?

d) What do we mean by negative and positive cooperativity? What is the Hill equation?

e) What are the standard assumptions in simplifying mathematical models of signalling networks? How can activating and inhibitory links be modelled?

f) What does positive and what does negative feedback stand for?

2. Phase Plane analysis.

a) What is a phase plane?

b) In a system with two components explain how you can draw the plane and the phase vectors.

3. Linear stability analysis.

a) Describe the steps of linear stability analysis of a nonlinear system around a steady state. Why is it useful?

b) How can one evaluate the stability of steady states of a 2D system based on the eigenvalues of the Jacobian?

4. Diffusion Equation

a) Derive the diffusion equation.

b) Solve the diffusion equation using separation of variables. How do you deal with inhomogeneous boundary conditions?

c) Solve the reaction-diffusion equation with linear and non-linear decay term. How do the size of the domain, the diffusion coefficient and the decay term affect the time to reach steady state?

5. Morphogen Gradients

a) What are morphogens? What are morphogen gradients? How do they arise?

b) Discuss possible transport mechanisms for morphogens.

c) Provide possible mathematical descriptions of morphogen gradients.

d) How are morphogen gradients interpreted by cells? What is the French Flag model?

e) What limits the precision of morphogen read-out?

f) Discuss how self-enhanced degradation affects the precision of morphogen read-out in the face of a noisy morphogen source.

g) How to model patterning on growing domains? Derive the advection and dilution terms. What is advection? What is dilution? Derive the reaction-diffusion equation in case of uniform growth.

h) What is the problem of pattern scaling? Discuss conditions and mechanisms for pattern scaling.

6. **Travelling Waves**

a) What are Travelling Waves?
b) Derive the conditions for travelling waves.
c) What are kinematic waves?
d) How does the shape of the wave influence its speed of propagation?
e) Explain the observed Travelling Waves in fertilized oocytes and during somitogenesis.
f) What is wave pinning?

7. **Turing Patterns**

a) What are Turing patterns?
b) Derive the conditions for Turing patterns using the linear stability analysis.
c) What is the wave number? What does it say about the pattern?
d) How do the reaction parameters and the diffusion coefficients affect the pattern?
d) What role do the initial and boundary conditions play?
e) What biological properties do Turing systems have?
f) Do Turing patterns scale with domain size? What happens on a growing domain?
g) How does the speed of patterning compare to Travelling Waves?

8. **Chemotaxis**

a) What is chemotaxis?
b) How can we describe chemotaxis in continuum models?
c) Derive the conditions for chemotaxis using the linear stability analysis.
d) Under what conditions do we obtain aggregation? Under which conditions do travelling waves emerge?
e) How can bacteria sense gradients?
f) The problem of gain: how can bacteria sense the occupancy of a single receptor. Explain the Ising and the MWC Model.
g) What is adaptation? What is perfect adaptation? What role does it play in chemotaxis?
h) Provide two different examples of 3-node network topologies that can exhibit adaptation.
i)* Derive these two network topologies mathematically from the requirements for perfect adaptation.
j) Define proportional* and integral control. Relate them to the two network topologies and their phase planes.

9. **Cell-based Modelling**

a) What cell-based modelling approaches do you know?
b) What is the difference between on-lattice and off-lattice approaches?
c) What are agent-based models?
d) What is the spheroid model? What is the subcellular element model?
e) What is the vertex model?
f) What are Cellular Potts Models?
g) Describe Notch-Delta-Jagged signalling. What kind of patterns can emerge?

10. **Tissue Mechanics**

a) What are epithelia? How is the apical side organised?

b) Discuss models for the apical organisation of epithelia, i.e. topological models based on cell division and vertex models based on energy minimisation.

c) How can tension be inferred from images of epithelia?

d)* How is the Navier-Stokes equation used in modelling tissue? What are the limitations?

11. **Growth Control**

a) Describe the limitations of current models of Growth Control.

12. **Image-based Modelling - *In Silico* Organogenesis**

a) How can microscopy images be used in modelling?

b) How can one obtain growth fields?

c) How to infer parameter values? (see below)

d) How to select the best model? (see below)

13. **Parameter Estimation.**

a) What is the purpose of parameter estimation?

b) Describe the Bayesian approach for parameter estimation.

c) What is the maximum-likelihood estimate?

d) What is the objective function?

e) Why do we need an optimization algorithm? Derive the Newton-Raphson algorithm. How does the Levenberg-Marquardt algorithm differ? Why does this help? What other local and global optimization algorithms do you know? What are their advantages and disadvantages?

f)* How can prior information be incorporated in the parameter estimation process?

g)* What are pre-regression diagnostics and post-regression diagnostics? Why do we need them?

h) How can we evaluate the quality of the fit? What is a co-variance matrix? How does it relate to the log-likelihood and the confidence intervals of the estimate?

i)* What is the Fisher Information Matrix? What is the Cramer-Rao bound?

j) Summarize the main steps of parameter estimation.

k) If we have several competing models, how can we select the most appropriate model? What are BIC and AIC? When do they work? How can models be compared when BIC and AIC fail to work?

Questions marked with * were not covered in this year's course and will not appear in the exam.

u, v 2-component system

$u_t = f(u,v) + D_1 \Delta u$

$v_t = g(u,v) + D_2 \Delta v$

we would like to do linear stability analysis.

$J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}$ $w = (u - u^*, v - v^*)^T$

$w \to 0$ as $t \to \infty$ then we have a stable.

BC Zero flux $(\vec{n} \cdot \nabla)\begin{pmatrix} u \\ v \end{pmatrix} = 0$ on $\partial\Omega$.

w/o Diffusion

$\dot{\vec{w}} = J\vec{w} + D\Delta\vec{w}$

without

$\dot{\vec{w}} = J\vec{w}$

eigenvalue decomp

Begin with separation of var.

$w(x,t) = \psi(x)\phi(t)$

$\Rightarrow \begin{cases} \dot{\phi} = J\phi \Rightarrow \phi = \sum \alpha_i \vec{v}_i \exp(\lambda_i t) \\ 0 = JW + D\Delta W \quad W = \sum \alpha_i \vec{v}_i \exp(ik_i x) \end{cases}$

λ_i 是 eigenvalue.

$w(x,t) = \sum \alpha_i \vec{v}_i \exp(\lambda_i t + ikx)$

代换到这个可得

$\lambda W = JW + D\Delta W$

$\lambda\vec{w} = J\vec{w} + k^2 D\vec{w} \Rightarrow$ -

$(H - \lambda I)w = 0 \qquad H = J - k^2 D$

$\det(H) = 0 \Rightarrow$ stable solute

等一个等式 $\det(H) = \det(J - k^2 D) \quad D = \begin{bmatrix} D_1 & \\ & D_2 \end{bmatrix}$

$= D_1 D_2 k^4 - (D_2 f_u + D_1 g_v) k^2 + \det(J)$ < 0 要求 Diffusion

-driven instability.

$D_2 f_u + D_1 g_v > D_1 D_2 k^2 + \det(J)/k^2 > 0$

$\Rightarrow$

$D_2 \neq D_1$ 且 g_v f_u 不同符号

$\mathrm{tr}(J) < 0 \quad \det(J) > 0$

求 k wave number.

要 < 0 :

$\det(H) = h(k^2) = D_1 D_2 k^4 - (D_1 f_u + D_2 g_v) k^2 + \det(J)$

要使得 $h_{min} < 0$ 二元二次方程

等于 BC $\vec{n} \nabla \vec{w} = 0$ on $\partial\Omega$

If $\Omega = [0, L]$

$\Rightarrow w(x) = \sum \alpha_n \cos\left(\frac{n\pi x}{L}\right)$ 因为 $\sin\left(\frac{n\pi x}{L}\right) = 0$

$\Rightarrow \vec{w}(x,t) = \sum \alpha_n \vec{v}_n \exp(\lambda(k^2) t) \cos\left(\frac{n\pi x}{L}\right)$

$k^2 = \frac{n^2\pi^2}{L^2}$.

$(D_1 f_u + D_2 g_v)^2 - 4\det(J) \cdot D_1 D_2 > 0$

What is the concept of Turing space?

$\mathrm{tr}(J) < 0$

$\det J > 0$

Example

$u(x,t) \sim u_0 + C_{1,0} \exp\left(\lambda \frac{\pi^2}{p^2} t\right) \cos\left(\frac{n\pi x}{p}\right)$

General Form of models After non-dimension

$u_t = \gamma f(u,v) + \Delta u$

$v_t = \gamma g(u,v) + d\Delta v$

o Wave number. 是 $\cos\left(\frac{n\pi x}{L}\right)$

$n = \pm 1, \pm 2$.