CHALMERS, GÖTEBORGS UNIVERSITET

EXAM for
COMPUTATIONAL BIOLOGY A

COURSE CODES: **FFR 110, FIM740GU, PhD**

Time:	June 8, 2018, at $08^{30} - 12^{30}$
Place:	Johanneberg
Teachers:	Kristian Gustafsson, 070-050 2211 (mobile), visits once around 10^{00}
Allowed material:	Mathematics Handbook for Science and Engineering
Not allowed:	any other written material, calculator

Maximum score on this exam: 12 points (need 5 points to pass).
Maximum score for homework problems: 18 points (need 7 points to pass).
CTH $\geq$15 grade 3; $\geq$20 grade 4; $\geq$25 grade 5,
GU $\geq$15 grade G; $\geq$ 23 grade VG.

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1. Short questions [3 points] For each of the following questions give a concise answer within a few lines per question.

a) Explain what a period-doubling bifurcation is. In what kind of biological models do you find them?

Solution
Found in discrete dynamical systems models. Bifurcations where eigenvalue of map passes through -1 (fixed point with stable oscillations becomes unstable and periodic orbit forms).

b) The Lotka-Volterra model is given by

$$\dot{N} = N(a - bP)$$
$$\dot{P} = P(cN - d)$$

where a, b, c, and d are positive constants. Discuss the limitations of this model and how it can be improved.

Solution
Lecture notes 3.1

c) Explain the difference between stochastic and deterministic growth models. Under which circumstances is it better to use a stochastic model?

Solution
Lecture notes 5.1

d) In the law of diffusion for Brownian motion the mean-square displacement is given by $\langle (x - x_0)^2 \rangle = 2Dt$. Discuss whether the diffusion constant D increases, decreases, or remains unchanged upon an increase of the system temperature, or upon an increase of the particle size.

Solution
D increases with temperature and decreases with particle size

e) Explain what a travelling wave is.

Solution
Solution to reaction diffusion equations that travels with constant speed and shape.

f) A simple model for disease spreading is the SIR model

$$\begin{aligned}\dot{S} &= -rSI \\ \dot{I} &= rSI - \alpha I \\ \dot{R} &= \alpha I\end{aligned}$$

Explain what it means to have an epidemic in this model.

Solution
Bernhard's Lecture notes p. 4

g) Can the SIR model describe an endemic disease, i.e. a disease with a non-zero number of infectives in the long run? If not, suggest a model that may describe an endemic.

Solution
In the SIR model the number of infectives eventually go to zero, so it cannot describe an endemic disease. A simple modification that may describe an endemic disease is the SIS model, where infectives becomes susceptible after recovery. For example:

$$\begin{aligned}\dot{S} &= -rSI + \alpha I \\ \dot{I} &= rSI - \alpha I\end{aligned}$$

Has $N = S + I = \text{const.}$ and

$$\dot{I} = r(N - I)I - \alpha I$$

has a stable positive fixed point if $\alpha/r < N$.

h) This problem is not part of the course material this year.
Explain how one can use linear filters to remove linear trends in a time series.

Solution
Lecture notes 14.4.2

2. Discrete model for harvesting [2.5 points] Consider the following discrete model for a population of density u_τ at discrete times $\tau = 0, 1, 2, \ldots$

$$u_{\tau+1} = \frac{bu_\tau^2}{1+u_\tau^2} - Eu_\tau\,,$$

with $b > 2$ and $E > 0$.

a) Interpret the two terms on the right-hand side from the viewpoint of a model that describes regular harvesting of the population. Does the population show a linear growth rate? What is the stability of the steady state $u = 0$?

Solution
The first term describes the growth rate of individuals. It interpolates u^2 for small population sizes to a constant b (carrying capacity when $E = 0$) due to finite system resources for large population sizes. The second term describes harvesting at regular periods, proportional to the population size with effort E.

Since the first term does not have a linear contribution for small population sizes, the stability for small population sizes is determined by $u_{\tau+1} = -Eu_\tau$, i.e. the fixed point $u = 0$ has stable oscillations if $E < 1$ and shows growing oscillations if $E > 1$ (model is only relevant until population first becomes negative though).

We could interpret the second term as the combination of linear growth rate minus an actual harvest rate that is larger than the growth rate, forcing the population extinct if it becomes too small.

b) Show that there exists a threshold E_m such that when $E > E_\mathrm{m}$ no harvest can be obtained in the long run.

Solution
The fixed points are obtained by solving $u_{\tau+1} = u_\tau$:

$$u_1^* = 0$$
$$u_2^* = \frac{b - \sqrt{b^2 - 4(1+E)^2}}{2(1+E)}$$
$$u_3^* = \frac{b + \sqrt{b^2 - 4(1+E)^2}}{2(1+E)}$$

The latter two fixed points only exist if they are real, i.e. if

$$b^2 - 4(1+E)^2 > 0 \quad \Rightarrow \quad E < (b-2)/2 \equiv E_\mathrm{m}\,.$$

Thus, when $E > E_\mathrm{m}$ the only fixed point is the origin and it is stable as discussed in subtask a).

c) Determine the bifurcation that is obtained when E passes E_m, for example by sketching a cobweb plot.

Solution
From the cobweb plot, the bifurcation is a saddle-node bifurcation.

d) For $0 < E < E_{\rm m}$, the model only has positive stable steady states u between two positive values $u_- < u^* < u_+$. Find analytical expressions for u_- and u_+. Hint: To simplify the calculation, it may be useful to sketch a cobweb plot.

Solution

Sketching the function $F(u) = bu^2/(1+u^2) - Eu$ shows that u_3^* is the only stable positive steady state. When E is increased monotonically, u_3^* moves from its maximal value when $E = 0$ to its minimal value when $E = E_{\rm m}$ (this can also be seen from the derivative ${\rm d}u_3^*/{\rm d}E$ which becomes smaller than zero in the range $0 < E < E_{\rm m}$). We obtain the limits

$$u_1 = u_3^*|_{E=E_{\rm m}} = 1$$
$$u_2 = u_3^*|_{E=0} = \frac{b+\sqrt{b^2-4}}{2}$$

3. Hypercycles [2.5 points] One example of a so called *hypercycle* for n molecules with concentrations $x_i(t)$, with $i = 1, 2, \ldots, n$ is given by

$$\dot{x}_i = x_i \left(x_{i-1} - \sum_{j=1}^{n} x_j x_{j-1} \right) . \tag{1}$$

Assume periodic indices so that $x_0(t) = x_n(t)$ and assume $x_i(t) > 0$ for all i.

a) Consider the case $n = 2$ in Eq. (1). Derive the explicit equations for $\dot{x}_1$ and $\dot{x}_2$ in terms of x_1 and x_2.

Solution

$$\begin{aligned}
\dot{x}_1 &= x_1 (x_2 - 2x_1x_2) = x_1x_2 (1 - 2x_1) \\
\dot{x}_2 &= x_2 (x_1 - 2x_1x_2) = x_1x_2 (1 - 2x_2)
\end{aligned}$$

b) Determine all relevant fixed points and their stability for $n = 2$.

Solution

The system has a single isolated fixed point at $(x_1^*, x_2^*) = (1/2, 1/2)$

Jacobian

$$\begin{aligned}
\mathbb{J}(x_1^*, x_2^*) &= \begin{pmatrix} x_2(1-4x_1) & (1-2x_1)x_1 \\ (1-2x_2)x_2 & x_1(1-4x_2) \end{pmatrix} = \begin{pmatrix} -1/2 & 0 \\ 0 & -1/2 \end{pmatrix} \\
\mathrm{tr}\mathbb{J} &= -1 \\
\det \mathbb{J} &= 1/4
\end{aligned}$$

The fixed point is stable (star).

c) Determine the long-term fate for all relevant initial conditions when $n = 2$. Hint: To come to a definite conclusion, it may simplify to change to the coordinates $x_\pm = x_1 \pm x_2$.

Solution

In terms of the coordinates $x_\pm$ the dynamics becomes

$$\dot{x}_\pm = \dot{x}_1 \pm \dot{x}_2 = x_1x_2 (1 \pm 1 - 2(x_1 \pm x_2)) = \frac{1}{4}(x_+^2 - x_-^2)(1 \pm 1 - 2x_\pm)$$

In conclusion we have

$$\begin{aligned}
\dot{x}_- &= -\frac{1}{2}(x_+^2 - x_-^2)x_- \\
\dot{x}_+ &= \frac{1}{2}(x_+^2 - x_-^2)(1 - x_+)
\end{aligned}$$

In the region of validity $x_1 \geq 0$ and $x_2 \geq 0$, meaning that $x_+ > x_-$. The first equation therefore implies that x_- approaches zero in the long run and that the second equation implies that x_+ approaches 1. In conclusion, all relevant initial conditions approach the fixed point $x_1^* = x_2^* = 1/2$.

d) Now consider a general value of n. What is the long-term fate of the sum $N = \sum_{i=1}^{n} x_i$?

Solution

Using Eq. (1) we obtain

$$\dot{N} = \sum_{i=1}^{n} x_i x_{i-1} - \sum_{i=1}^{n} x_i \sum_{j=1}^{n} x_j x_{j-1} = \underbrace{\sum_{i=1}^{n} x_i x_{i-1}}_{A(t)}(1 - N)$$

Since we assume all $x_i > 0$, the prefactor $A(t)$ is positive and the long-term fate is $N \to 1$, similar to the case of x_+ in subtask c).

e) Explain the effect of the two terms $x_i x_{i-1}$ and $-x_i \sum_{j=1}^{n} x_j x_{j-1}$ in Eq. (1). Explain how the hypercycle may model molecules that are connected in a cyclic, autocatalytic manner.

Solution

In light of the result in subtask d), x_i denotes fraction of molecules of type i. The first term $x_i x_{i-1}$ increases this fraction. The second term $-x_i A(t)$ limits the fraction of molecule x_i such that the total sum $\sum_{i=1}^{n} x_i$ is constrained to 1 (in the long run). The growth for each x_i is catalysed by x_{i-1}, forming a closed feedback loop with one molecule serving as catalyst for the next.

4. Turing instability [2 points] Consider the following reaction-diffusion equation in one spatial dimension for two reactants $N_1(x, t)$ and $N_2(x, t)$:

$$\begin{aligned} \frac{\partial N_1}{\partial t} &= k_1 - k_2 + k_4 \frac{N_1}{N_2} + D_1 \frac{\partial^2 N_1}{\partial x^2} \\ \frac{\partial N_2}{\partial t} &= k_4 N_1^2 - k_3 N_2 + D_2 \frac{\partial^2 N_2}{\partial x^2} \end{aligned} . \tag{2}$$

a) Discuss a mechanism which may cause the reaction-diffusion system in Eq. (2) to form spatial patterns if $D_2 > D_1$.

Solution

See lecture 8. Activator-inhibitor system with N_1 activator and N_2 inhibitor.

b) Make Eq. (2) dimensionless by introduction of suitable dimensionless variables u, v, x', t' such that the dimensionless reaction-diffusion system becomes

$$\begin{aligned} \frac{\partial u}{\partial t'} &= \alpha + \frac{u}{v} + d \frac{\partial^2 u}{\partial x'^2} \\ \frac{\partial v}{\partial t'} &= u^2 - v + \frac{\partial^2 v}{\partial x'^2} \end{aligned} . \tag{3}$$

What are the expressions for α and d?

Solution

Let $N_1 = Au$, $N_2 = Bv$, $t = Ct'$, $x = Dx'$ to get

$$\frac{\partial u}{\partial t'} = \frac{C}{A}\left[k_1 - k_2 + \frac{k_4 A}{B}\frac{u}{v} + \frac{AD_1}{D^2}\frac{\partial^2 u}{\partial x'^2}\right]$$
$$\frac{\partial v}{\partial t'} = \frac{C}{B}\left[k_4 A^2 u^2 - k_3 B v + \frac{BD_2}{D^2}\frac{\partial^2 v}{\partial x^2}\right]$$

Choose $C = 1/k_3$, $D = \sqrt{D_2/k_3}$, $B = k_4/k_3$ and $A = 1$

$$\frac{\partial u}{\partial t'} = \underbrace{\frac{k_1 - k_2}{k_3}}_{\alpha} + \frac{u^2}{v} + \underbrace{\frac{D_1}{D_2}}_{d}\frac{\partial^2 u}{\partial x'^2}$$
$$\frac{\partial v}{\partial t'} = u^2 - v + \frac{\partial^2 v}{\partial x^2}$$

c) Find the condition on α for which the homogeneous steady state of Eq. (3) is stable.

Solution

The homogeneous steady state is obtained by solving Eq. (3) with $u(x', t')$ and $v(x', t')$ constant:

$$\begin{aligned} 0 &= \alpha + \frac{u}{v} \\ 0 &= u^2 - v \end{aligned} \Rightarrow (u^*, v^*) = (-\frac{1}{\alpha}, \frac{1}{\alpha^2}) \,.$$

Jacobian at the steady state

$$\mathbb{J}(u^*, v^*) = \begin{pmatrix} \alpha^2 & \alpha^3 \\ -2\alpha^{-1} & -1 \end{pmatrix}$$
$$\mathrm{tr}\mathbb{J} = \alpha^2 - 1$$
$$\det\mathbb{J} = \alpha^2$$

The steady state is stable if $|\alpha| < 1$.

Let $\delta u(x, t) \equiv u(x, t) - u^*$ and $\delta v(x, t) \equiv v(x, t) - v^*$ be small perturbations from the homogeneous steady state. In the lectures we showed that the ansatz

$$\begin{pmatrix} \delta u \\ \delta v \end{pmatrix} = e^{\lambda t + \mathrm{i}k_x} \begin{pmatrix} \delta u_0 \\ \delta v_0 \end{pmatrix}$$

in Eq. (3) with small δu and δv gives rise to the following equation:

$$0 = [\lambda - \mathbb{K}] \begin{pmatrix} \delta u_0 \\ \delta v_0 \end{pmatrix} \,, \text{ where } \mathbb{K} = \mathbb{J}(u^*, v^*) - k^2 \begin{pmatrix} d & 0 \\ 0 & 1 \end{pmatrix} \,.$$

Here $\mathbb{J}$ is the Jacobian of the homogeneous system.

d) Assume that $\alpha = 1/2$. Analytically find the bifurcation point $d_c(k_c)$ for which space-dependent perturbations first become unstable, i.e. for $d > d_c$ all space-dependent perturbations are stable and for $d < d_c$ at least one wave number k_c corresponds to unstable perturbations.

Solution

The matrix $\mathbb{K}$ takes the form

$$\mathbb{K} = \begin{pmatrix} \alpha^2 - k^2 d & \alpha^3 \\ -2\alpha^{-1} & -1 - k^2 \end{pmatrix} = \begin{pmatrix} 1/4 - k^2 d & 1/8 \\ -4 & -1 - k^2 \end{pmatrix}$$

$$\mathrm{tr}\mathbb{K} < 0$$

$$\det \mathbb{K} = 1/4 + (d - 1/4)k^2 + dk^4\,.$$

Perturbations are unstable if $\det \mathbb{K}(k^2) < 0$. First, solve $\det \mathbb{K} = 0$ in terms of k^2 to get

$$k^2 = \frac{1}{8d}(1 - 4d \pm \sqrt{1 - 24d + 16d^2})\,.$$

At the bifurcation we have a double root, i.e. solve $1 - 24d + 16d^2 = 0$ to get $d_c = (3 \pm \sqrt{8})/4$. But only the smaller of these gives a positive $k^2 \Rightarrow$ the bifurcation point is $d_c = (3 - \sqrt{8})/4$

5. Kuramoto model [2 points] Consider a large number N of coupled oscillators with phases $\theta_1, \theta_2, \ldots \theta_N$ with the following time evolution

$$\dot{\theta}_i = \omega_i + \frac{K}{N}\sum_{j=1}^{N} \sin(\theta_j - \theta_i)\,. \tag{4}$$

a) Introduce the order parameters $r(t)$ and $\psi(t)$

$$re^{\mathrm{i}\psi} = \frac{1}{N}\sum_{j=1}^{N} e^{\mathrm{i}\theta_j} \tag{5}$$

and show that Eq. (4) can be written on the following form

$$\dot{\theta}_i = \omega_i + Kr\sin(\psi - \theta_i)\,.$$

Solution

Multiplication of Eq. (5) with $e^{-\mathrm{i}\theta_i}$ and evaluation of the imaginary part gives

$$\mathcal{I}m[re^{\mathrm{i}(\psi-\theta_i)}] = \mathcal{I}m\left[\frac{1}{N}\sum_{j=1}^{N} e^{\mathrm{i}(\theta_j-\theta_i)}\right]$$

$$\Rightarrow r\sin(\psi - \theta_i) = \frac{1}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i)\,.$$

Inserting this relation into Eq. (4) gives the sought form:

$$\begin{aligned}\dot{\theta}_i &= \omega_i + \frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i) \\ &= \omega_i + Kr\sin(\psi - \theta_i)\,.\end{aligned}$$

b) Give interpretations of the order parameters r and ψ in subtask a). Illustrate the distribution of oscillators when $r \approx 0$ and $r \approx 1$.

Solution

We note that the right-hand side of Eq. (5) is the arithmetic mean, $\overline{e^{i\theta}}$, over all oscillators. $\psi = \text{atan}(\overline{\sin\theta}/\overline{\cos\theta})$ is therefore the circular mean (obtained by mean of cosines and sines of each angle and calculating arctan) of θ (this gives a more reasonable value of an average phase, since simply averaging angles arithmetically is unreliable because the angles 0 and 2π should be considered equal).

r quantifies phase coherence: it will be unity if all phases are equal and zero if phases are uniformly distributed.

c) Consider the limit where $K \to \infty$ and assume that $0 < r < 1$ initially. What is the long term fate of the Kuramoto model in this limit? Which value does r approach?

Solution

When $K \to \infty$ we can neglect ω_i and the dynamics of oscillator i becomes

$$\dot{\theta}_i = Kr\sin(\psi - \theta_i)\,.$$

The flow on the right-hand side shows that the dynamics rapidly approaches $\theta_i = \psi$ for all oscillators (except for the special case $\theta_i(0) = \psi + \pi$ and $\omega_i = 0$). The oscillators therefore end up in phase and $r \to 1$.

d) What does it mean to do a mean field analysis of the Kuramoto model? What can the results of the mean-field analysis be used for?

Solution

Bernhard's lecture notes, 7.4-7.6