CHALMERS, GÖTEBORGS UNIVERSITET

EXAM for
COMPUTATIONAL BIOLOGY A

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

Time:	June 12, 2019, at $08^{30} - 12^{30}$
Place:	Johanneberg
Teachers:	Kristian Gustafsson, 070-050 2211 (mobile), visits once around 15^{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) Consider the logistic equation for a population of size $N(t)$ with a time delay T:

$$\frac{\mathrm{d}N}{\mathrm{d}t}(t) = rN(t)\left(1 - \frac{N(t-T)}{K}\right).$$

Without doing any calculations, discuss the nature of the possible solutions to this equation i) without delay ($T = 0$), ii) with a small delay ($T \ll r^{-1}$), and iii) with a large delay ($T \gg r^{-1}$).

Solution
Without the delay, starting from a non-zero N the system monotonously approaches the stable fixed point $N^* = K$. With a small delay, solutions may show oscillations, but will still decay towards $N^* = K$. For the large delay, $N^* = K$ is no longer stable and the dynamics approaches a limit cycle.

b) Consider a process where a substrate forms a product. How is this process different in a spontaneous reaction compared to an enzyme reaction?

Solution
In the spontaneous reaction the substrate is transformed directly into

the product with some reaction rate k, $\mathrm{S} \xrightarrow{\mathrm{k}} \mathrm{P}$. In an enzyme reaction this reaction is catalyzed by an enzyme, typically

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{SE} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E}\,,$$

with rate constants k_{-1}, k_1, and k_2, where k_1 and k_2 both are much smaller than k.

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

d) Explain what is meant by a Turing (diffusion driven) instability.

Solution
Lecture notes 8.2

e) Why is it common to treat the total population size N as constant in the SIR model for disease spreading? For which types of diseases do you think a constant N is relevant?

Solution
We can neglect the population dynamics (births, deaths, ...) if it is much slower than the dynamics of the disease and therefore treat the total population as constant on these the time scale if the disease. This is the case for many endemics, for example the seasonal flu among humans which spreads quickly through the population.

f) What is meant by the 'order parameters' in the Kuramoto model? What do they quantify?

Solution
Bernhard's lecture notes 2.4.

For subtasks g) and h), consider a concentration $n(x,t)$ in a bounded domain $0 \le x \le L$. At $t = 0$, $n(x,0)$ is unity at $x = 0$, decreases linearly to zero for small x, and stays at zero up to $x = L$, as illustrated below:

Assume that the concentration is governed by Fisher's equation:

$$\frac{\partial n}{\partial t}(x,t) = rn(x,t)(1 - n(x,t)) + D\frac{\partial^2 n}{\partial x^2}(x,t)\,,$$

with constant boundary condition at $x = 0$ and no-flux condition at $x = L$:

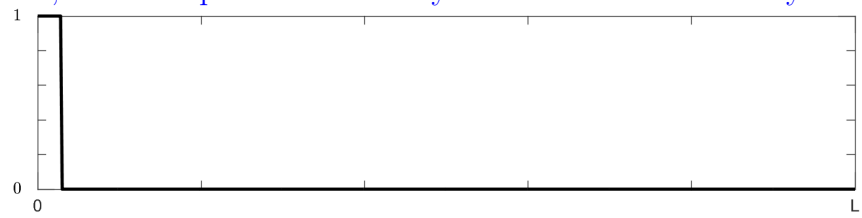
$$n(0,t) = 1\,, \qquad \frac{\partial n}{\partial x}(L,t) = 0\,.$$

Consider the following three cases for the parameters r and D:
i) $D = 0$ and $r = 1$; ii) $D = 1$ and $r = 0$; iii) $D = 1$ and $r = 1$.

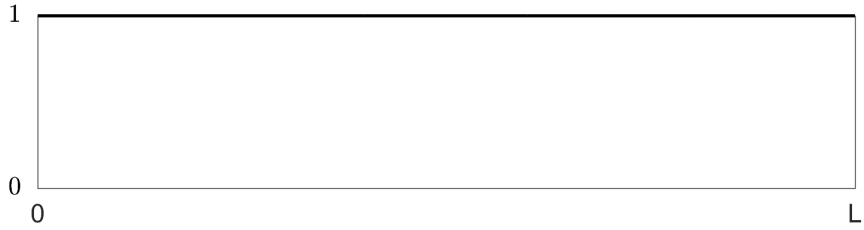
g) Without doing any calculations, sketch the concentrations as $t \to \infty$ for the three cases i), ii) and iii).

Solution

For case 1 there is no spatial flux and all parts of the domain that initially had non-zero concentration approach the stable fixed point at $n = 1$, while the parts that initially had zero distribution stay at $n = 0$:



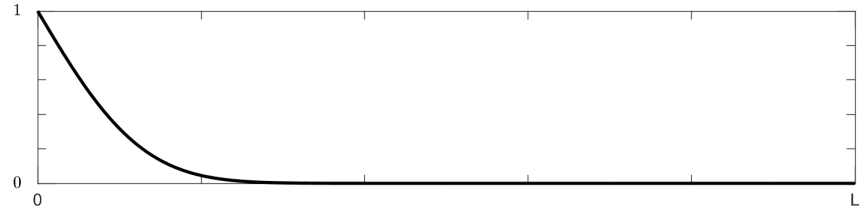
For cases ii) and iii) the diffusion makes the concentration spread uniformly in the domain (the constant boundary condition at $x = 0$ allows for an influx of concentration, $\partial_x n \neq 0$ until distribution becomes uniform):



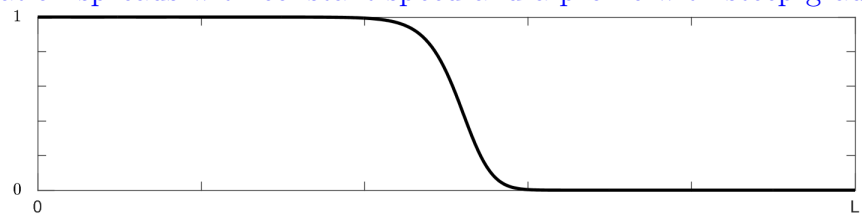
h) Without doing any calculations, explain the difference in the dynamics for the cases with $D = 1$, i.e. cases ii) and iii).

Solution

When $r = 0$ we have regular diffusion, the initial concentration very slowly spreads through the system. Since sharp gradients are smoothed by diffusion, we expect that the concentration gradient successively becomes more gentle:



For case iii) on the other hand, we expect a travelling wave, the concentration spreads with constant speed and a profile with steep gradient:



2. Discrete and continuous logistic growth model [2 points] The discrete logistic growth model is given by

$$N_{\tau+1} = aN_\tau \left(1 - \frac{N_\tau}{C}\right) \tag{1}$$

where a, C are positive parameters and $\tau = 0, 1, 2, \ldots$ denotes discrete time.

a) Discuss how the model above is related to a time discretisation of a continuous logistic growth equation. How is a and C related to the growth rate r, carrying capacity K and the discretisation time step δt of the continuous model?

Solution
Discretising the continuous growth equation

$$\dot{N} = \frac{N(t+\delta t) - N(t)}{\delta t} = rN(t)\left(1 - \frac{N(t)}{K}\right)$$

gives

$$N(t+\delta t) = N(t) + r\delta t N(t)\left(1 - \frac{N(t)}{K}\right)$$

Rescaling time $\tau = t/\delta t$ gives

$$N_{\tau+1} = N_\tau + r\delta t N_\tau \left(1 - \frac{N_\tau}{K}\right) = (1 + r\delta t)N_\tau - r\delta t \frac{N_\tau^2}{K}$$

Comparison with the discrete model gives

$$a = 1 + r\delta t$$
$$\frac{a}{C} = \frac{r\delta t}{K} \;\Rightarrow\; C = \frac{aK}{r\delta t} = K\left(1 + \frac{1}{r\delta t}\right)$$

b) For which values of a and C is the discretised model a good approximation of the continuous model?

Solution
The discretised model is a good approximation if δt is much smaller than all other time scales, i.e. if $\delta t \ll r^{-1}$. From subtask a) we find that a should be close to unity and $C \approx K/(r\delta t)$.

c) Find the positive fixed point of the discrete logistic map (1) and determine for which range of a the fixed point is stable.

Solution
Solving the logistic map for $N_{\tau+1} = N_\tau = N^*$ gives

$$N^* = C\left(1 - \frac{1}{a}\right)$$

Stability

$$\Lambda = \left.\frac{\mathrm{d}N_{\tau+1}}{\mathrm{d}N_\tau}\right|_{N_\tau=N^*} = a\left(1-2\frac{N^*}{C}\right) = 2-a$$

The system is stable for $-1 < 2-a < 1 \Rightarrow 1 < a < 3$.

d) Make a cobweb plot illustrating the dynamics of Eq. (1) for $2 < a < 3$.

Solution
The map is an inverted parabola that is positive between $0 < N < C$ with maximum at $C/2$. For $2 < a < 3$ we have that $-1 < \Lambda < 0$ and the system shows stable oscillations around the fixed point (located between $C/2$ and $2C/3$).

3. Lotka-Volterra model [2 points] A simple model for predator prey interaction between two species of sizes N and P is the Lotka-Volterra model:

$$\begin{aligned} \dot{N} &= aN - bNP \\ \dot{P} &= cNP - dP \end{aligned}, \tag{2}$$

where a, b, c and d are positive parameters.

a) Explain the forms of the different terms in the Lotka-Volterra model (2).

Solution
Lecture notes 3.1.1

b) Consider $a = b = c = d = 1$ in Eq. (2) and sketch the solution starting from $N(0) = 2$ and $P(0) = 1$ in the N-P plane. Also plot the solutions $N(t)$ and $P(t)$ against time t in a separate plot. You do not need to find an analytical solution, but the qualitative behavior of prey and predator sizes should be clear. Briefly explain the dynamics.

Solution
Lecture notes 3.1.1

c) Identify one weakness of the Lotka-Volterra model in modelling a biological system.

Solution
On weakness is that solutions of the Lotka-Volterra model are not structurally stable, adding a small perturbation (which will always be present in the real world) destroys the periodic motion and the dynamics become a spiral.
Another weakness is that for many initial conditions the periodic motion reaches very small values where the description as a continuous deterministic system can be questionable.

d) One way to improve the Lotka-Volterra model is to modify the growth rate $\dot{N}$ in Eq. (2) to

$$\dot{N} = aN\left(1-\frac{N}{K}\right) - \frac{bNP}{1+N/B},$$

where K and B are positive parameters. Explain the form of these modifications. What are the significance of K and B?

Solution
Lecture notes 3.1.2

4. Model with spatially regulated fishing [2.5 points] Assume that fishing is regulated in a zone of width H from a country's shore (taken to be a straight line) and that outside of this zone over-fishing makes the population vanish. Consider the following model for the fish concentration $n(x,t)$:

$$\frac{\partial n}{\partial t} = rn\left(1-\frac{n}{K}\right) - En + D\frac{\partial^2 n}{\partial x^2}\,, \tag{3}$$

where r,K and D are positive parameters, $0 < E < r$, and with boundary conditions

$$n(x=H,t) = 0\,, \qquad \frac{\partial n}{\partial x}(x=0,t) = 0\,.$$

a) Briefly explain the different terms and parameters in this model. In particular explain the significance of the boundary conditions.

Solution
Within the zone the fish population grows logistically with growth rate r and carrying capacity K. The population is harvested with effort E, giving a yield proportional to the local population size. Since the shore is a straight line and since 'a country' assumes a long coastal line, the spatial dynamics can to lowest order be treated as one-dimensional. The fish spreads diffusively within $0 < x < H$ and is zero at the outer boundary (where overfishing starts), and there is no flux over the inner boundary (fishes do not spread up on land).

b) Introduce dimensionless variables $\tau = t/t_0$, $u = n/n_0$, $\xi = x/x_0$ and determine t_0, n_0 and x_0 such that Eq. (3) does not depend on any parameters in the dimensionless variables. What are the boundary conditions in these units?

Solution
Let $t = \tau t_0$, $n = un_0$, $x = \xi x_0$ and choose $t_0 = 1/(r-E)$, $n_0 = K/(t_0 r) = K - EK/r$, and $x0 = \sqrt{t_0 D} = \sqrt{D/(r-E)}$ to obtain

$$\frac{\partial u}{\partial \tau} = u(1-u) + \frac{\partial^2 u}{\partial \xi^2}\,.$$

The boundary conditions become

$$u(\xi = H/x_0, \tau) = u(\xi = H\sqrt{(r-E)/D}, \tau) = 0\,, \qquad \frac{\partial u}{\partial \xi}(\xi = 0, \tau) = 0\,.$$

c) Investigate the linear stability of the homogeneous steady state $u^* = 0$ by making a small perturbation $u(\xi, \tau) \approx 0 + \delta u(\xi, \tau)$ and keeping only first-order terms in δu. Using the ansatz $\delta u(\xi, \tau) = A\cos(k\xi)e^{\lambda\tau}$ with real parameters A, k and λ, find a condition on k such that the boundary conditions are satisfied.

Solution
Inserting $u(\xi, \tau) \approx \delta u(\xi, \tau)$ into the dimensionless version of Eq. (3) gives to first order in δu

$$\frac{\partial \delta u}{\partial \tau} = \delta u + \frac{\partial^2 \delta u}{\partial \xi^2}$$

using the ansatz $\delta u(\xi, \tau) = A\cos(k\xi)e^{\lambda\tau}$ gives

$$\begin{aligned} &\lambda A\cos(k\xi)e^{\lambda\tau} = A\cos(k\xi)e^{\lambda\tau} - Ak^2\cos(k\xi)e^{\lambda\tau} \\ &\Rightarrow \lambda = 1 - k^2\,. \end{aligned}$$

i.e. the equation is satisfied if $\lambda = 1 - k^2$. The boundary condition $\frac{\partial \delta u}{\partial \xi}(\xi = 0, \tau) = 0$ is automatically satisfied for the ansatz because $\cos(k\xi)$ has zero slope at $\xi = 0$. Implementing the second boundary condition $\delta u(\xi = H\sqrt{(r-E)/D}, \tau) = Ae^{(1-k^2)\tau}\cos(kH\sqrt{(r-E)/D}) = 0$ gives $kH\sqrt{(r-E)/D} = \pi/2 + n\pi$ with integer n, i.e.

$$k = \left[\frac{\pi}{2} + n\pi\right]\frac{1}{H}\sqrt{\frac{D}{r-E}}$$

is a condition on k for the boundary conditions to be satisfied.

d) Show that if $H < H_c = \frac{\pi}{2}\sqrt{\frac{D}{r-E}}$ the fishing zone is not sustainable, i.e. $u(\xi, \tau) = 0$ is stable.

Solution
If $H < H_c$ the condition on k from subtask c) implies that $k > 1$ and consequently $\lambda = 1 - k^2$ is smaller than zero and small perturbations around $u = 0$ decay to zero.

5. Disease spreading in large but finite populations [2.5 points]
Assume that a population consists of N (constant in time) individuals. Each individual is either infected by, or susceptible to a disease. Assume that recovered individuals once again become susceptible (SIS model).

a) In the lecture notes and the hand-ins a Master equation was derived that describes the probability ρ to observe n infected individuals. Discuss what it means that this Master equation has a 'quasi-steady state'.

Solution
Bernhard's lecture notes, Section 4

An approximate solution for the quasi-steady state that is valid for large N can be found by an ansatz

$$\rho(I) = \exp\left[-NS_0(I) - S_1(I) - 1/NS_2(I) - \dots\right],$$

where $I = n/N$ is the ratio of infected individuals. To lowest order in N^{-1}, the dynamics of $I(t)$ and $p(t) = S_0'(I)$ was shown to follow Hamilton's equations

$$\begin{aligned} \dot{I} &= \beta I(1-I)e^p - \gamma I e^{-p} \\ \dot{p} &= -\beta(1-2I)(e^p - 1) - \gamma(e^{-p} - 1)\,. \end{aligned} \tag{4}$$

Here β and γ are positive parameters.

b) A disease is said to be endemic if it can sustain a finite number of infected individuals in the long run. Find a condition on the parameters β and γ for which the disease described by Eq. (4) is endemic in the limit $N \to \infty$ (corresponding to $p \to 0$).

Solution
When $p = 0$, we have the dynamics

$$\dot{I} = I[\beta - \gamma - I\beta]$$

This reaches a positive steady state $I^* = 1 - \gamma/\beta$ if $\beta > \gamma$. For $\beta > \gamma$ this steady state is stable ($\partial\dot{I}/\partial I|_{I_*} = \gamma - \beta$) and the disease is therefore endemic when $\beta > \gamma$.

c) In the endemic limit found in subtask b), find all biologically relevant fixed points of Eq. (4) that lies on either of the axes $I = 0$ or $p = 0$ and determine their stability. To speed up this calculation, it may be helpful to first evaluate the trace of the stability matrix (Jacobian) for general points (I, p) and to think about how the flow behaves along the axes $I = 0$ and $p = 0$.

Solution
For $p = 0$ we have the fixed points:
$(I_1^*, p_1^*) = (0, 0)$
$(I_2^*, p_2^*) = (1 - \gamma/\beta, 0)$
When $I = 0$ we get

$$\begin{aligned} &\beta e^p + \gamma e^{-p} = +\gamma + \beta \\ &e^{2p} - \frac{\gamma+\beta}{\beta} e^p + \frac{\gamma}{\beta} = 0 \\ &\Rightarrow e^p = 1 \text{ (case } p = 0 \text{ already treated) or } e^p = \frac{\gamma}{\beta} \end{aligned}$$

We have the fixed point:
$(I_1^*, p_1^*) = (0, \log(\frac{\gamma}{\beta}))$

Either by explicit evaluation, or by using that the dynamics is Hamiltonian and hence volume preserving, the trace of the stability matrix is zero. The eigenvalues becomes

$$\lambda_{\pm} = \pm\sqrt{-4 \det \mathbb{J}}\,.$$

Assuming $\det \mathbb{J} \neq 0$, we either have a saddle point or a center. Since $\dot{p} = 0$ when $p = 0$, and since $\dot{I} = 0$ when $I = 0$, the flow moves along the axes and therefore centers are ruled out. All the fixed points must therefore be saddle points. It can be noted that for the case $\det \mathbb{J} = 0$ both eigenvalues are zero, but this is not consistent with a sketch of the flow along the axes $I = 0$ or $p = 0$ in the endemic limit ($\beta > \gamma$).

d) In the endemic limit found in subtask b), the dynamics (4) has one additional biologically relevant fixed point (I^*,p^*) with $I^* > 0$ and $p^* < 0$. You can assume that this fixed point is a center.

Contrast the case $p = 0$ (corresponding to $N \to \infty$) and $p \neq 0$ (corresponding to large but finite N). In particular, discuss the implications of a finite population size for endemic diseases. It could be helpful to sketch the phase portrait for the dynamics in Eq. (4) for non-negative values of I.

Solution

Bernhard's lecture notes, p. 36