CHALMERS, GÖTEBORGS UNIVERSITET

EXAM for
COMPUTATIONAL BIOLOGY

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

Time:	August 23, 2023, 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: 50 points (need 20 points to pass).
Maximum score for homework problems: 50 points (need 20 points to pass).
CTH $\geq$40 grade 3; $\geq$60 grade 4; $\geq$80 grade 5,
GU $\geq$40 grade G; $\geq$70 grade VG.

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1. Short questions [12 points] For each of the following questions give a concise answer within a few lines per question.

a) Give two examples of biological systems, one where a time delay model is a suitable model and one where a discrete growth model is suitable.

Solution
Delay example: house flies (delay due to time spent as egg). Discrete example: Synchronised growth of cells.

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

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

c) Enzyme reactions involving substrate S, enzyme E, and product P can be simplified using the Michaelis-Menten approximation. Describe the Michaelis-Menten approximation and its core assumption.

Solution
Lecture notes 4.1

d) Consider a system in one spatial dimension that has a homogeneous stable steady state. Explain how the analysis of a small spatio-temporal perturbation can explain pattern formation in this system.

Solution
Lecture notes 7.3.2

e) Give two examples of systems that show spiral wave patterns that can be modeled using reaction-diffusion models.

Solution
Lecture notes 8.2

f) The SIR model for the number of susceptibles S, infectives I and recovered R was introduced in the lectures

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

State two shortcomings of this model, and propose how you would improve the model to overcome these shortcomings.

Solution
Bernhard's lecture notes 6.1

g) What is meant by the hypothesis of neutral evolution in the context of population genetics?

Solution
It assumes that most of the variation of genome in a population can be explained with mutations and genetic drift, rather than referring to natural selection.

h) In the lectures the following equation for population homozygosity was derived in the infinite alleles model

$$F_2^{(t+1)} = (1-\mu)^2 \left[\frac{1}{N} + \left(1 - \frac{1}{N}\right) F_2^{(t)}\right] .$$

Here N is the population size and μ is the mutation rate per individual and generation. Explain what is meant by homozygosity and explain the different factors in this equation.

Solution
Bernhard's lecture notes 8.3

2. Prevention of insect outbreaks [10 points] A model for the population growth of insects subject to predation by birds is given by

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) - \frac{BN}{A+N} . \tag{1}$$

Here N is the population size of insects and r, K, A, and B are positive parameters.

a) Explain the last term in the model and give plausible interpretations of the parameters A and B.

Solution

The term describes reduction in growth due to predation. It models predation with a saturation. When N is small, predation occurs proportional to N, for example modeling a feeding rate proportional to encounters between birds and insects for a constant bird population. When N is large, predation saturates due to limited bird appetite. A is the population scale for this saturation, and B is a constant death rate (not per capita) of insects in the saturation limit.

In what follows, consider $K = 2A$.

b) Convert to dimensionless units to express Eq. (1) using a single dimensionless parameter ρ (possible because $K = 2A$). Explicitly state ρ in terms of the original dimensional parameters.

Solution

Let $u = N/N_0$ and $\tau = t/t_0$

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = \frac{t_0}{N_0}\frac{\mathrm{d}N}{\mathrm{d}t} = \frac{t_0}{N_0}[rN_0u\left(1 - \frac{N_0u}{2A}\right) - \frac{BN_0u}{A + N_0u}]$$

Choose, for example, $N_0 = A$ and $t_0 = A/B$ to obtain

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = \rho u\left(1 - \frac{u}{2}\right) - \frac{u}{1+u}$$

with $\rho = Ar/B$.

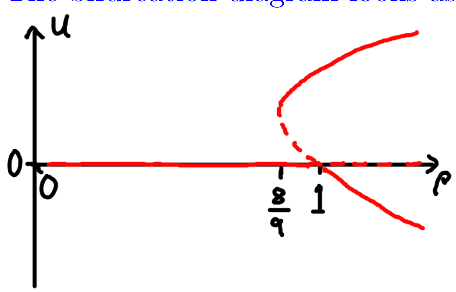
An alternative is $t_0 = 1/r$ and $N_0 = A$, giving

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = u\left(1 - \frac{u}{2}\right) - \frac{1}{\rho}\frac{u}{1+u}$$

c) Find all fixed points of the system in subtask b) and find a condition on the dimensionless parameter such that there are two positive steady states, with one being stable and the other unstable. If you did not solve subtask b), find a condition on the dimensional parameters instead.

Solution

The system has fixed points $u_1^* = 0$, $u_2^* = (1 + \sqrt{9 - 8/\rho})/2$, and $u_3^* = (1 - \sqrt{9 - 8/\rho})/2$. The two latter fixed points exist if $\rho \geq 8/9$. The bifurcation diagram looks as follows:



The stability was determined by geometrical inspection of the flow. For small u, the flow reads $\frac{\mathrm{d}u}{\mathrm{d}\tau} \approx \rho u - u$, i.e. u_1^* goes from stable to unstable as ρ passes 1 (in a transcritical bifurcation with u_2^*). For large positive u, the flow $\frac{\mathrm{d}u}{\mathrm{d}\tau} \approx -\rho \frac{u^2}{2}$ is negative, making u_2^* stable. The intermediate fixed point u_3^* is unstable when it is positive. In conclusion, the flow has two positive steady states of opposite stability if $8/9 < \rho < 1$.

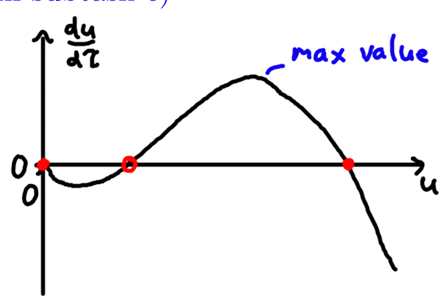
d) In the past, insecticides were heavily employed as a reaction to insect outbreaks. Model these insecticides by adding a constant negative term, $-I$, into Eq. (1). Assume that the condition in subtask c) is satisfied. Describe how you would estimate the minimal value I_c needed to remove the insects permanently. No explicit solution is necessary.

Solution

Adding $-I$ to Eq. (1), the dimensionless dynamics reads

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = \rho u \left(1 - \frac{u}{2}\right) - \frac{u}{1+u} - \frac{I}{B}$$

When $I = 0$, the flow has three intersections with zero for the condition in subtask c)



At an outbreak, the population lies at the large stable steady state. If $I > 0$, this curve is lowered. To permanently remove the insects, it must be lowered below the maximal value of the flow without insecticides. The value can be estimated by solving $\frac{\partial}{\partial u} \frac{\mathrm{d}u}{\mathrm{d}\tau}_{I=0} = 0$ for u and inserting the resulting value into $I_\mathrm{c} = B \frac{\mathrm{d}u}{\mathrm{d}\tau}_{I=0}$.

e) Modern pest control strategies use early intervention by identifying hotspots where the population is slightly above the unstable fixed point in subtask c). Countermeasures are then implemented in these areas. Estimate the value of I_c needed to remove the insects permanently in this case. Compare to the value of I_c in subtask d).

Solution

In a hotspot, the initial population size u_0 lies to the right of the unstable steady state. It is enough with a comparatively small value of I_c, $I_\mathrm{c} = B \frac{\mathrm{d}u}{\mathrm{d}\tau}(u_0)|_{I=0}$, to move the unstable steady state to the right of the hotspot population. Since $\frac{\mathrm{d}u}{\mathrm{d}\tau}(u_0)|_{I=0}$ is smaller than the maximal value for any u_0, this strategy always lead to a smaller I_c compared to the strategy in subtask d).

3. Paradox of pesticides [8 points] Assume that a pest with population size N interacts with a predator of population size P. A simple model for their dynamics is given by 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) For this subtask, let $a = b = c = d = 1$ 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 pest and predator sizes should be clear. Briefly explain the dynamics.

   Solution
   Lecture notes 3.1.1

c) Analytically show that the average populations satisfy $\overline{N} = d/c$ and $\overline{P} = a/b$ independent of their initial sizes.
   Hint: Start by averaging the per capita growth of N in Eq. (2).

   Solution
   Average the per capita growth rate $\dot{N}/N$ in Eq. (2) over one period time T

$$\frac{1}{T}\int_0^T \mathrm{d}t \frac{\dot{N}}{N} = \frac{1}{T}\int_0^T \mathrm{d}t[a - bP] \quad \Rightarrow \quad \frac{1}{T}\int_0^T \mathrm{d}t \frac{\mathrm{d}}{\mathrm{d}t}\ln N = a - b\overline{P}$$

   Since the integral on the left-hand side is zero over one period, it follows that $\overline{P} = a/b$.

   Similarly for the $\dot{P}$-equation

$$\frac{1}{T}\int_0^T \mathrm{d}t \frac{\mathrm{d}}{\mathrm{d}t}\ln P = c\overline{N} - d$$

   giving $\overline{N} = d/c$.

d) Now, assume that pesticides are introduced to the system, leading to a reduction of the per capita growth rate by a constant for both populations. Discuss, using the averages in subtask c), the impact of pesticides on the populations. Do they result in an unintended behavior?

   Solution
   Applying the pesticide effectively reduces a and increases d (the growth rate of predators become more negative). From subtask c), this implies

that the average pest population $\overline{N}$ becomes larger and the predator population $\overline{P}$ becomes smaller.

This is unwanted and paradoxial, because pesticides are added to reduce the pest population, but here it instead increases it on average. This behavior has been observed multiple times when applying pesticides to pests in nature, and is known as the paradox of pesticides.

4. Propagation of nerve signals [10 points] The following is a dedimensionalized model for the propagation of nerve signals through an axon

$$\begin{aligned}\frac{\partial V}{\partial t} &= V^2 - V^3 - R + \frac{\partial^2 V}{\partial x^2}\\ \frac{\partial R}{\partial t} &= V - \frac{9}{2}R\end{aligned} \tag{3}$$

Here $V(x,t)$ is the plasma membrane potential. It describes the signal strength at location x along an axon, where $V = 0$ means no signal. Moreover, $R(x,t)$ models recovery from large outbursts.

a) Find all homogeneous steady-state solutions of the system (3).

Solution
The homogeneous steady states are

$$(V_1^*, R_1^*) = (0,0)\,,\ (V_2^*, R_2^*) = \frac{1}{3}\left(1, \frac{2}{9}\right)\,,\ (V_3^*, R_3^*) = \frac{2}{3}\left(1, \frac{2}{9}\right)$$

b) Assume that V and R depend on x and t only through $z = x - ct$, with a positive constant c. Introduce $u(z) = V(x,t)$, $v(z) = \frac{\mathrm{d}u}{\mathrm{d}z}$, and $w(z) = R(x,t)$ to rewrite Eq. (3) as a dynamical system for u, v, w.

Solution
The system (3) becomes (replacing $\frac{\partial}{\partial t} = -c\frac{\mathrm{d}}{\mathrm{d}z}$ and $\frac{\partial}{\partial x} = \frac{\mathrm{d}}{\mathrm{d}z}$) Introducing $u(z) = V(x,t)$, $v(z) = \frac{\mathrm{d}u}{\mathrm{d}z}$ and $w(z) = R(x,t)$, the system becomes (replacing $\frac{\partial V}{\partial t} = -c\frac{\mathrm{d}u}{\mathrm{d}z} = -cv$, $\frac{\partial^2 V}{\partial x^2} = \ddot{u} = \frac{\mathrm{d}v}{\mathrm{d}z}$ and $\frac{\partial R}{\partial t} = -c\frac{\mathrm{d}w}{\mathrm{d}z}$)

$$\begin{aligned}\frac{\mathrm{d}u}{\mathrm{d}z} &= v\\ \frac{\mathrm{d}v}{\mathrm{d}z} &= -cv - u^2 + u^3 + w\\ \frac{\mathrm{d}w}{\mathrm{d}z} &= \frac{1}{c}\left[\frac{9}{2}w - u\right]\end{aligned}$$

c) Assume that c is very small, so that the change in one of the variables is fast. Use this assumption to reduce the dynamical system you derived in subtask b) to a system of dimensionality 2.

Solution
In the proposed limit, w relaxes quickly to its equilibrium $w = 2u/9$. The dimensionality two system becomes

$$\frac{\mathrm{d}u}{\mathrm{d}z} = v$$
$$\frac{\mathrm{d}v}{\mathrm{d}z} = -cv - u^2 + u^3 + \frac{2}{9}u$$

d) Sketch the phase-plane dynamics of the system in subtask c) and sketch the wave profiles of allowed travelling wave solutions $V(x,t)$ and $R(x,t)$.

Solution
The fixed points have $v^* = 0$, and u^* was calculated in subtask a)

$$(u_1^*, v_1^*) = (0,0)\,,\ (u_2^*, v_2^*) = \left(\frac{1}{3}, 0\right)\,,\ (u_3^*, v_3^*) = \left(\frac{2}{3}, 0\right).$$

The stability matrix is

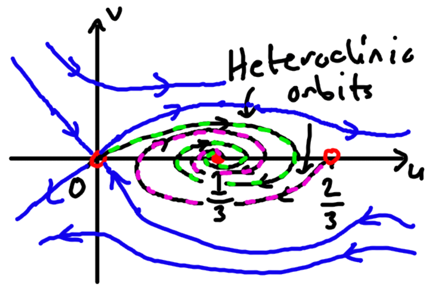
$$J = \begin{pmatrix} 0 & 1 \\ \frac{2}{9} - 2u + 3u^2 & -c \end{pmatrix} \Rightarrow \mathrm{tr}\mathbb{J} = -c < 0 \text{ and } \det\mathbb{J} = -\frac{2}{9} + 2u - 3u^2\,.$$

The determinant evaluated at the fixed points becomes

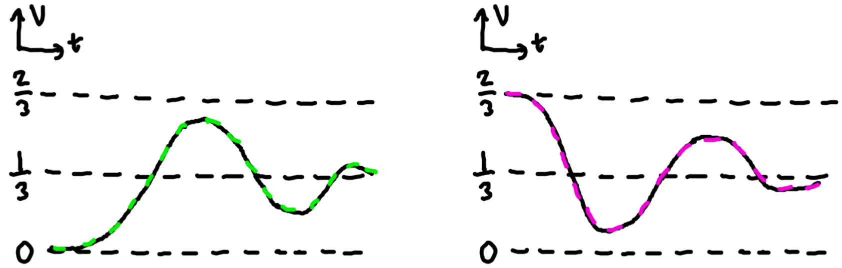
$$\det\mathbb{J}(u_1^*, v_1^*) = -\frac{2}{9}\,, \quad \det\mathbb{J}(u_2^*, v_2^*) = \frac{1}{9}\,, \quad \det\mathbb{J}(u_3^*, v_3^*) = -\frac{2}{9}\,.$$

The first and third fixed points are saddle points. Since c is small, $\mathrm{tr}\mathbb{J}$ is small and negative, implying that the second fixed point is a stable spiral.

Using that $\frac{\mathrm{d}u}{\mathrm{d}z} > 0$ for $v > 0$ and $\frac{\mathrm{d}u}{\mathrm{d}z} < 0$ for $v < 0$, the phase portrait becomes



with corresponding allowed travelling wave solutions



5. The Kuramoto model [10 points] Consider a number N of coupled oscillators with phases $\theta_1, \theta_2, \dots \theta_N$ with the following time evolution

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

Here ω_i are constant natural angular velocities of the oscillators and $K > 0$ is constant. Define the complex order parameter as

$$r(t)e^{\mathrm{i}\,\psi(t)} = \frac{1}{N}\sum_{j=1}^{N} e^{\mathrm{i}\,\theta_j(t)}\,, \tag{5}$$

where r and ψ are real.

a) Commonly, oscillators are described using a second order differential equation for θ. The oscillators in Eq. (4) have only the first time derivative of θ. Why are there no second order time derivatives in Eq. (4)?

Solution
The oscillators can be understood as overdamped and driven by the other oscillators. A driven damped oscillator will oscillate (described using a second-order differential equation) but eventually damping will stabilize the dynamics to a steady state given by the driving. If the time scale of the damping is short compared to the other time scales in the system, we can neglect this transient behavior and only consider the stabilized behavior. In this limit it is enough to consider a first-order equation to describe a system with a stable steady state.

b) Show that Eq. (4) can be rewritten using the order parameter as

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

Solution
Rewrite Eq. (4) using the definition of the order parameter

$$\begin{aligned}\dot{\theta}_i &= \omega_i + \frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i) = \omega_i + \mathrm{Im}\left[\frac{K}{N}\sum_{j=1}^{N} e^{\mathrm{i}\,\theta_j - \mathrm{i}\,\theta_i}\right] \\ &= \omega_i + \mathrm{Im}\left[Kre^{\mathrm{i}\,\psi}e^{-\mathrm{i}\,\theta_i}\right] = \omega_i + Kr\sin(\psi - \theta_i)\end{aligned}$$

c) Assume that for large times $r(t) = \text{const.}$ and $\psi(t) = \Omega t$, with constant Ω. Show that the dynamics in subtask b) takes the following form in a frame rotating with angular velocity Ω:

$$\dot{\theta}'_i = \omega'_i - Kr\sin(\theta'_i)\,,$$

where $\theta'_i(t)$ is the phase in the rotating frame. What is the form of ω'_i?

Solution

Changing coordinates to the rotating frame, $\theta'_i = \theta_i - \Omega t$, gives the dynamics

$$\dot{\theta}'_i = \dot{\theta}_i - \Omega = \underbrace{\omega_i - \Omega}_{\omega'_i} - Kr\sin(\theta'_i)\,.$$

d) Consider the case where the natural angular velocities of all oscillators in the rotating frame have the same magnitude, $|\omega_i| = \omega$, but half are positive, $\omega'_i = +\omega$ for $i = 1, \dots, N/2$ and half are negative, $\omega'_i = -\omega$ for $i = N/2+1, \dots, N$ (assume N even). What is the long-term dynamics in this case? Does it depend on the parameters?

Solution

Using $\omega_i = \pm\omega$ in the equation above, we have

$$\dot{\theta}'_i = \pm\omega - Kr\sin(\theta'_i)\,,$$

In the steady state $r(t)$ is constant, meaning that all equations for θ'_i decouples. If $\omega/(Kr) < 1$, this system has two fixed points obtained by solving $\dot{\theta}'_i = 0$ for θ'_i: $\theta'^*_i = \pm\mathrm{asin}[\omega/(Kr)]$ (stable) and $\theta'^*_i = \pi - \pm\mathrm{asin}[\omega/(Kr)]$ (unstable), where the stability follows by a geometrical analysis of the plot $\dot{\theta}'_i$ against θ'_i. If $\omega/(Kr) > 1$, the system has no fixed points, meaning θ_i increases/decreases indefinitely.

e) For the case in subtask d), use the definition (5) to find an expression of the order parameter r in the steady state in terms of the parameters K and ω_0. Does at least one solution exist for all parameter values? If not, explain what happens.

Solution

For the case $\omega/(Kr) < 1$, evaluation of Eq. (5) with half oscillators with $\theta_j = \mathrm{asin}[\omega/(Kr)]$, the other half with $\theta_j = -\mathrm{asin}[\omega/(Kr)]$ and $\psi(t) = 0$ in the rotating frame gives

$$\begin{aligned} r &= \frac{1}{N}\sum_{j=1}^{N} e^{\mathrm{i}\,\theta^*_j} = \frac{1}{2}e^{\mathrm{i}\,\mathrm{asin}[\omega/(Kr)]} + \frac{1}{2}e^{-\mathrm{i}\,\mathrm{asin}[\omega/(Kr)]} = \cos(\mathrm{asin}[\omega/(Kr)]) \\ &= \sqrt{1 - \omega^2/(Kr)^2} \end{aligned}$$

Square this equation, multiply by r^2 and solve for r to obtain:

$$r^4 - r^2 + \omega^2/K^2 = 0 \quad \Rightarrow \quad r = \frac{1}{\sqrt{2}}\sqrt{1 \pm \sqrt{1 - (2\omega/K)^2}}$$

For $\omega/K < 1/2$ two solutions exist (the correct one turns out to be the larger one according to numerical simulations). For $\omega/K > 1/2$ no solution exist to the self-consistency condition $r = \sqrt{1 - \omega^2/(Kr)^2}$. This is a contradiction to the assumption that r takes a constant value in the steady state. As a consequence the order parameter r will change indefinitely, and consequently so must the phases since $\theta'^* = \pm\mathrm{asin}[\omega/(Kr)]$ depends on r.