CHALMERS, GÖTEBORGS UNIVERSITET

EXAM for
COMPUTATIONAL BIOLOGY A

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

Time:	March 21, 2019, at $14^{00} - 18^{00}$
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) Give an example of a biological system which is suitable to model using a time delay model.

Solution

b) What do we typically mean when we say a population size is 'small' or 'large'?

Solution
It does not make sense to relate the population size to unity because the number of individuals are usually much larger, and cannot be smaller unless the population has gone extinct. Small and large instead refer to reference scales in the system, for example the carrying capacity or a threshold for the Allee effect. The population size is small if it is much smaller than the reference scales, and large if it is much larger than the reference scales.

c) Assume a one-dimensional map $x_{n+1} = F(x_n)$ with a single stable fixed point x^* for $r < r_c$, where r is a system parameter. At $r = r_c$, the system undergoes a period-doubling bifurcation. Show that the eigenvalue of the second iterate of the map evaluated at the fixed point, $F(F(x^*))$, is equal to $+1$ at $r = r_c$.

Solution

Since x^* is a fixed point, we have $F(x^*) = x^*$. At the period-doubling bifurcation $\Lambda = F'(x^*) = -1$. Evaluating the eigenvalue Λ_2 of the second iterate at the fixed point we have

$$\Lambda_2 = \frac{\mathrm{d}}{\mathrm{d}x} F(F(x))|_{x=x^*} = F'(F(x^*))F'(x^*) = F'(x^*)^2 = (-1)^2 = +1$$

d) In the first problem set you analyzed a time-delayed model with an Allee effect. Explain what the Allee effect is and give an example of a biological system where it may be important.

Solution

In systems where the population has a reduced reproduction or survival capacity for small population sizes, the population may go extinct if the population density becomes too small. This is the Allee effect. It may for example be important in systems where anti-predator strategies becomes inefficient in small groups.

e) Consider the following chemical reaction

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{SE} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}\,,$$

where k_{-1}, k_1, and k_2 are rate constants. Using the law of mass action, write down a dynamical system model for the change in concentrations of the chemicals.

Solution

Introducing concentrations $s = [S]$, $e = [E]$, $c = [SE]$, $p = [P]$ the law of mass action states that the reaction rate is proportional to the product of concentrations of the reactants. We get:

$$\begin{aligned}
\dot{s} &= -k_1 es + k_{-1}c \\
\dot{e} &= -k_1 es + (k_{-1} + k_2)c \\
\dot{c} &= k_1 es - (k_{-1} + k_2)c \\
\dot{p} &= k_2 c\,.
\end{aligned}$$

f) Describe a possible mechanism that may explain morphogenesis such as patterns in animal coating.

Solution

g) Explain the difference between a quasi-steady state and a regular steady state. Give an example of a system with a quasi-steady state.

Solution

A quasi-steady state is a state for which the dynamics approximately does not change for a long time, but where, in the long run, the dynamics will move to a different state. For example in a stochastic model, the distribution of individuals is approximately constant for a long time, but since there is a finite probability that the population goes extinct, the distribution must drift towards a Dirac delta function at zero population as time goes to infinity.

h) The Kuramoto model for N coupled oscillators with phases $\theta_1, \theta_2, \ldots \theta_N$ has the following time evolution

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

Here ω_i are random angular frequencies with a symmetric and unimodal (single peak) distribution $g(\omega)$. Discuss what is meant by drifting and phase-locked modes in a mean-field analysis of this model.

Solution
Bernhard's lecture notes 2.6

2. Interaction model with mutualism [2 points] A simple model for mutualistic interactions (symbiosis) between two species of sizes N_1 and N_2 is given by

$$\frac{\mathrm{d}N_1}{\mathrm{d}t} = r_1 N_1 \left(1 - \frac{N_1}{K} + \alpha\frac{N_2}{K}\right)$$
$$\frac{\mathrm{d}N_2}{\mathrm{d}t} = r_2 N_2 \left(1 - \frac{N_2}{K} + \alpha\frac{N_1}{K}\right)$$

where r_1, r_2, K, and α are positive constants.

a) For the upper equation governing N_1, explain the role and meaning of the parameters r_1, K and α

Solution
r_1 is the growth rate of N_1 for small population sizes. K is the carrying capacity of N_1 in absence of N_2. α models the mutualistic benefit from the second species on the first one by assuming that interactions between the species reduce competition within species 1, allowing for a larger population.

b) Introduce dimensionless variables to reduce the number of parameters to a minimum. Write out your resulting dimensionless parameters in terms of the original parameters.

Solution
Change to dimensionless variables $t = A\tau$, $N_1 = Bu$, $N_2 = Cv$

$$\frac{B}{A}\frac{\mathrm{d}}{\mathrm{d}\tau}u = Br_1 u\left(1 - \frac{Bu}{K} + \alpha\frac{Cv}{K}\right)$$
$$\frac{C}{A}\frac{\mathrm{d}}{\mathrm{d}\tau}v = Cr_2 v\left(1 - \frac{Cv}{K} + \alpha\frac{Bu}{K}\right)\,,$$

Choose $A = 1/r_1$, $B = K$, $C = K/\alpha$ to get the dimensionless equations

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}\tau}u &= u\left(1-u+v\right)\\ \frac{\mathrm{d}}{\mathrm{d}\tau}v &= \rho v\left(1-\frac{v}{\alpha}+\alpha u\right),\end{aligned},$$

where we defined $\rho = r_2/r_1$.

The dimensionless parameters are $\rho = r_2/r_1$ and α

c) Consider the special case $\alpha = 1/2$ in this subtask. Locate the fixed point for which both population sizes are positive and investigate its stability. Discuss how the dimensional population sizes N_1^* and N_2^* at this fixed point compares to the positive steady state without interactions ($\alpha = 0$).

Solution
The dimensionless dynamics has one non-zero fixed point at $(u^*, v^*) = (1,\alpha)/(1-\alpha) = (2,1)$. The stability matrix evaluated becomes

$$\mathbb{J} = \begin{pmatrix}1-u+v-u & u\\ \frac{\rho v}{2} & \rho\left(1-2v+\frac{u}{2}\right)-2\rho v\end{pmatrix}\Bigg|_{(u,v)=(u^*,v^*)} = \begin{pmatrix}-2 & 2\\ \frac{\rho}{2} & -2\rho\end{pmatrix}$$

$$\mathrm{tr}\mathbb{J} = -2(1+\rho) < 0$$

$$\det\mathbb{J} = 3\rho > 0$$

The fixed point is stable (node).

In the steady state the fixed point $(u^*, v^*) = (2,1)$ is reached. In the original units, we have $N_1^* = u^*K = 2K$, $N_2^* = K/\alpha v^* = 2K$. Both population sizes are doubled in the steady state compared to the case without interactions (where $N_1^* = K$ and $N_2^* = K$).

d) Investigate the long-term dynamics for the case $\alpha = 1$ and $r_1 = r_2$. Discuss what consequences your result has for the model.
Hint: It may be simpler to analyze the model by considering the coordinates $w_\pm = u_1 \pm u_2$, where u_1 and u_2 are the dimensionless population sizes.

Solution
Let $\rho = \alpha = 1$ and evaluate

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}\tau}w_+ &= u\left(1-u+v\right)+v\left(1-v+u\right) = w_+ - w_-^2\\ \frac{\mathrm{d}}{\mathrm{d}\tau}w_- &= u\left(1-u+v\right)-v\left(1-v+u\right) = w_-\left(1-w_+\right),\end{aligned},$$

If the initial w_- is chosen small enough, then the sum of populations w_+ will grow without bounds while w_- will remain small (in fact any initial condition with $u > 0$ and $v > 0$ will grow without bound).

Since the population grows to infinity the model is not realistic for the case $\rho = \alpha = 1$ (in fact it is unrealistic for all $\alpha \geq 1$).

3. Stochastic population model [2 points]

a) Write down an equation for how the probability $Q_N(t)$ to have a population of size N at time t changes in small time steps δt. Assume stochastic dynamics. At each time step δt any individual has the probability $b_1 \delta t$ to give birth to one offspring and the probability $b_2 \delta t$ to give birth to two offsprings.

Solution
The change in probability $Q_N(t)$ during one time step is given by one-step transitions due to births or deaths from or to N individuals. These are

- $N - 1 \to N$ due to birth with one offspring
- $N \to N + 1$ due to birth with one offspring
- $N - 2 \to N$ due to birth with two offsprings
- $N \to N + 2$ due to birth with two offsprings

The change in probability taking all of these transitions into account is

$$\begin{aligned} Q_N(t + \delta t) - Q_N(t) &= b_1 \delta t (N - 1) Q_{N-1}(t) - b_1 \delta t N Q_N(t) \\ &\quad + b_2 \delta t (N - 2) Q_{N-2}(t) - b_2 \delta t N Q_N(t) \end{aligned}$$

b) By taking the limit $\delta t \to 0$, derive a differential equation in time (Master equation) for the probability in subtask a).

Solution
Dividing the equation in subtask a) by δt and taking the limit $\delta t \to 0$ we obtain the following differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t} Q_N(t) = b_1 (N - 1) Q_{N-1}(t) + b_2 (N - 2) Q_{N-2}(t) - (b_1 + b_2) N Q_N(t) \,.$$

c) Show that in the limit of large N the average population size approaches a deterministic dynamics. What is the growth rate of the deterministic dynamics?

Solution

Multiply the Master equation by N and sum over N

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{N=0}^{\infty} NQ_N = b_1 \sum_{N=0}^{\infty} N(N-1)Q_{N-1} + b_2 \sum_{N=0}^{\infty} N(N-2)Q_{N-2} - (b_1+b_2)\sum_{N=0}^{\infty} N^2 Q_N$$

[Change of variables $N = N'+1$ in the first sum, $N = N'+2$ in the second sum]

$$= b_1 \sum_{N'=-1}^{\infty}(N'+1)N'Q_{N'} + b_2 \sum_{N'=-2}^{\infty}(N'+2)N'Q_{N'} - (b_1+b_2)\sum_{N=0}^{\infty} N^2 Q_N$$

[The probability to have a negative population must be zero.]

$$= b_1 \sum_{N'=0}^{\infty}(N'+1)N'Q_{N'} + b_2 \sum_{N'=0}^{\infty}(N'+2)N'Q_{N'} - (b_1+b_2)\sum_{N=0}^{\infty} N^2 Q_N$$

$$= \sum_{N=0}^{\infty}\left[b_1 NQ_N + 2b_2 NQ_N\right]$$

$$= \sum_{N=0}^{\infty}\left[b_1 + 2b_2\right] NQ_N\,.$$

The average population size N at time t is

$$\langle N(t)\rangle = \sum_{N=0}^{\infty} NQ_N(t)$$

which gives the deterministic dynamics

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle N(t)\rangle = (b_1+2b_2)\langle N(t)\rangle\,.$$

This is a Malthus growth with birth rate $b_1 + 2b_2$.

d) Explain the form of the growth rate you obtained in subtask c) in relation to the assumptions in subtask a).

Solution

It seems reasonable that the total growth rate is the sum of the two birth rates. The second birth rate is weighted by a factor 2 because each birth event give rise to two offsprings.

e) Without doing any calculations, write down the growth rate in a model where, in addition to the conditions in subtask a), there are birth events with probability $b_3\delta t$ that result in three offsprings.

Solution

The growth rate if births with three offsprings are taken into account becomes $r = b_1 + 2b_2 + 3b_3$.

4. Reaction diffusion with density-dependent diffusion [2.5 points]

In spatial diffusion of insects, the diffusion sometimes depends on the density of the population. One example of a model taking this into account is

$$\frac{\partial n}{\partial t}(x,t) = rn(x,t)\left(1-\frac{n(x,t)}{K}\right) + \frac{\partial}{\partial x}\left[D(n(x,t))\frac{\partial}{\partial x}n(x,t)\right]. \qquad (1)$$

Here $n(x,t)$ is the population density at position x and time t, r is a positive growth rate, K is the carrying capacity and $D(n(x,t))$ is a density-dependent diffusion coefficient. In what follows, assume $D(n(x,t)) = D_0 n(x,t)$, where D_0 is a positive constant.

a) What is the dimensionality of D_0?

Solution
In terms of a time scale T, length scale L and population density scale N, the equation has dimensionality N/T, the term involving D_0 has dimensionality $[D_0]N^2/X^2$, meaning that $[D_0] = X^2/(NT)$.

b) Introduce dimensionless units such that Eq. (1) can be written without any parameters.

Solution
Let $t = At'$, $n = Bn'$ and $x = Cx'$ to get (drop primes to simplify notation)

$$\frac{\partial n}{\partial t}(x,t) = \frac{A}{B} rBn(x,t)\left(1 - \frac{B}{K}n(x,t)\right) + \frac{A}{B}\frac{B^2}{C^2}D_0\frac{\partial}{\partial x}\left[n(x,t)\frac{\partial}{\partial x}n(x,t)\right] \tag{2}$$

$$= n(x,t)\left(1 - n(x,t)\right) + \frac{\partial}{\partial x}\left[n(x,t)\frac{\partial}{\partial x}n(x,t)\right]. \tag{3}$$

where we used $A = 1/r$, $B = K$ and $C = \sqrt{KD_0/r}$ to remove all dimensional parameters.

c) Assume that n, x, t are the new dimensionless coordinates and that $n(x,t) = u(z)$ only depends on the combination $z = x - ct$. Starting from your dimensionless version of Eq. (1) derive an ordinary differential equation for $u(z)$.

Solution
For this coordinate change partial derivatives transform as

$$\frac{\partial n}{\partial t} = -c\frac{\mathrm{d}u}{\mathrm{d}z}$$
$$\frac{\partial n}{\partial x} = \frac{\mathrm{d}u}{\mathrm{d}z}$$

and Eq. (1) gives the ordinary differential equation

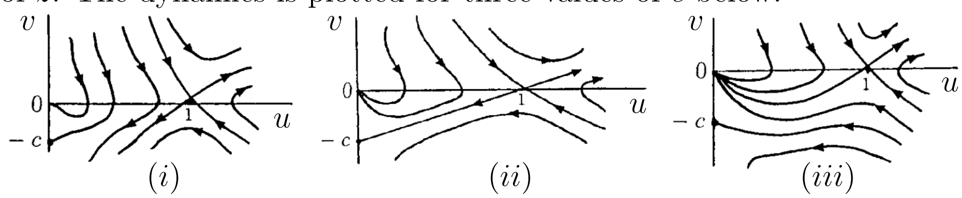
$$-c\frac{\mathrm{d}}{\mathrm{d}z}u(z) = u(z)(1-u(z)) + \frac{\mathrm{d}}{\mathrm{d}z}\left[u(z)\frac{\mathrm{d}}{\mathrm{d}z}u(z)\right],$$

d) Rewrite the ordinary differential equation for $u(z)$ obtained in subtask c) in terms of a first order system for $u(z)$ and $v(z) = u'(z)$.

Solution

$$
\begin{aligned}
\frac{\mathrm{d}u}{\mathrm{d}z} &= v(z) \\
\frac{\mathrm{d}v}{\mathrm{d}z} &= u(z) - 1 - \frac{v(z)}{u(z)}(c + v(z))
\end{aligned}
$$

e) The equations you derived in subtask d) should have a singularity at $u = 0$. This singularity can be regularized (you do not need to show nor consider this). The regularized dynamics has three fixed points at $(u^*, v^*) = (0, 0)$ (saddle point), $(u^*, v^*) = (1, 0)$ (saddle point) and $(u^*, v^*) = (0, -c)$ (stable non-linear node). Note that due to the singularity, trajectories reach the node $(u^*, v^*) = (0, -c)$ for finite values of z. The dynamics is plotted for three values of c below:



Discuss in which of the three cases travelling wave solutions are possible and sketch the wave profiles (as functions of z) for these cases.

Solution

Travelling waves are solutions connecting steady states (heteroclinic orbits) of the phase-plane dynamics. The cases (ii) and (iii) have such solutions and may therefore have travelling wave solutions.

For the case (iii) the heteroclinic trajectory connects the steady states $(u^*, v^*) = (1, 0)$ and $(u^*, v^*) = (0, 0)$. The wave profile is similar to that of Fisher's equation with constant diffusion. The curve decrease monotonously from $u = 1$ at $z \to -\infty$ to $u = 0$ at $z \to \infty$.

For the case (ii) the heteroclinic trajectory connects the steady states $(u^*, v^*) = (1, 0)$ and $(u^*, v^*) = (0, -c)$. Also in this case the trajectory decreases monotonously, but it will have an ever-increasing slope, intersecting the line $u = 0$ with non-zero slope at some value z_{c} (as stated in the problem formulation, the node is reached at a finite z) and the profile is zero for $z > z_{\mathrm{c}}$.

5. Disease spreading with vaccination [2.5 points] A simple model for disease spreading is the following modified SIR model with the dynamics

$$
\begin{aligned}
\dot{S} &= (1-p)b(S + I + R) - \beta SI - dS \\
\dot{I} &= \beta SI - \alpha I - dI \\
\dot{R} &= pb(S + I + R) + \alpha I - dR\,.
\end{aligned}
\tag{4}
$$

Here S is the number of susceptibles, I is the number of infectives, and R is the number of immune individuals (recovered or vaccinated individuals).

The parameters b, d, β, α are positive, and p is the ratio of individuals that are vaccinated at birth, $0 \leq p \leq 1$.

a) Give brief explanations of the different terms in Eq. (4). Does the model apply to a disease that is likely to be transmitted from the mother to the baby upon birth? Does the model apply to a deadly disease?

Solution

The model has two birth terms: a contribution $(1-p)b(S+I+R)$ to S and a contribution $pb(S+I+R)$. Since the latter is proportional to the vaccination rate, all newborns that are vaccinated contribute to growth of R, while newborns not vaccinated contribute to growth of S. The proportionality to the total population size $S+R+I$ indicates that all individuals can give birth at equal rate. Since no births contribute to I it is assumed that the disease is unlikely to be transmitted upon birth, and the model would not apply to that case.

The model has three death terms, all proportional to the number of individuals in respective category. Thus, the model does not assume increased death rate for infectives and the model does therefore not apply to a deadly disease.

The terms βSI is the infection term, proportional to the interaction rate between susceptibles and infectives. The terms αI is the removal rate of infectives due to recovery.

b) Find a condition on the model parameters such that the total population size $N = S + I + R$ is constant.

Solution

The total population size evolves as

$$\dot{N} = \dot{S} + \dot{I} + \dot{R} = (b-d)(S+I+R)$$

Thus, the total population size does not change if $d = b$.

c) In what follows, consider the special case $b = d = 1$ and $\alpha = 99$, leaving two model parameters β and p. Consider first the case of full vaccination, $p = 1$, and investigate the long-term behaviour of the system (4). Give an explanation of the result.

Solution

Since $d = b$ the total population size is constant and it is enough to consider the equations for S and I since the equation for R decouples. We have

$$\begin{aligned}
\dot{S} &= (1-p)N - \beta SI - S \\
\dot{I} &= \beta SI - 100I
\end{aligned}$$

When $p = 1$, this system has a single biologically relevant steady state $(S_1^*, I_1^*) = (0, 0)$. The Jacobian at this steady state becomes

$$\mathbb{J} = \begin{pmatrix} -\beta I - 1 & -\beta S \\ \beta I & \beta S - 100 \end{pmatrix}\Bigg|_{(S,I)=(S_1^*,I_1^*)} = \begin{pmatrix} -1 & 0 \\ 0 & -100 \end{pmatrix}$$

This matrix has $\mathrm{tr}\mathbb{J} = -101 < 0$ and $\det \mathbb{J} = 100 > 0$, i.e. the steady state is stable.

In conclusion, since all newborns are vaccinated, all initial susceptibles will either become infected or die in the long run. As a consequence also all infectives will die out and in the steady state the entire population will belong to the recovered+vaccinated group with size $R = N$.

d) Use the parameters of subtask c) (with general p) to find a condition on the vaccination ratio p below which the disease may become endemic (non-zero number of infectives in the long run).

Solution

For the disease to be endemic, the system must sustain a finite number of infectives, i.e. the system must have a stable steady state (S^*, I^*) with $I^* > 0$. The system

$$\begin{aligned} \dot{S} &= (1-p)N - \beta SI - S \\ \dot{I} &= \beta SI - 100I \end{aligned}$$

has a steady state with $I^* > 0$, $(S_2^*, I_2^*) = (\frac{100}{\beta}, (1-p)\frac{N}{100} - \frac{1}{\beta})$, if $0 \le p < 1 - \frac{100}{N\beta} \equiv p_c$ and $\beta > 100/N$.

Examining the stability of this steady state, we have

$$\mathbb{J} = \begin{pmatrix} -\beta I - 1 & -\beta S \\ \beta I & \beta S - 100 \end{pmatrix}\Bigg|_{(S,I)=(S_2^*,I_2^*)} = \begin{pmatrix} -(1-p)\beta\frac{N}{100} & -100 \\ (1-p)\beta\frac{N}{100} - 1 & 0 \end{pmatrix}$$
$$= \begin{pmatrix} -\frac{1-p}{1-p_c} & -100 \\ \frac{1-p}{1-p_c} - 1 & 0 \end{pmatrix}$$

Since $p < p_c$, we have $\frac{1-p}{1-p_c} > 1$, i.e. $\mathrm{tr}\mathbb{J} = -\frac{1-p}{1-p_c} < 0$ and $\det \mathbb{J} = 100(\frac{1-p}{1-p_c} - 1) > 0$, i.e. the fixed point is stable.

In conclusion, the condition is $0 \le p < 1 - \frac{100}{N\beta} \equiv p_c$ and $\beta > 100/N$.

Alternative solution: Since $N = S + I + R \ge R$ we have

$$\dot{R} = N - R + \alpha I \ge 0$$

i.e. R stops increasing only when $S = I = 0$, i.e. the steady state of the system.