Mathematical Models of Biological Systems

CH924

November 25, 2012
Course outline

Syllabus:

▶ Week 6: Stability of first-order autonomous differential equation, genetic switch/clock, introduction to enzyme kinetics.

▶ Week 7: Continuation of enzyme kinetics, method of separation of variables/variation of constants.

▶ Week 8: Stability of systems of linear differential equations, introduction to non-linear systems.

▶ Week 9: Stability of non-linear systems, applications in infection and immunity.

Course web-site: http://www2.warwick.ac.uk/fac/sci/sbdtc/msc/ch924/

Morning/afternoon tutors: Barbara, Vinicio, Siren, Chris, James
For the essay:

▶ you need to form groups of 3-4 people with diverse academic backgrounds
▶ you will choose a published paper from a selection, discuss it in your groups and then each individual will write an essay that should address the following points:
  ▶ what is the biological question being tackled?
  ▶ which mathematical techniques have been employed to do so?
  ▶ critique the paper: e.g. Are the methods employed sensible? Are there any other improvements that could be made? What are the achievements/ failings of the paper?
▶ aim to write 2-3 pages double-spaced (printed, not handwritten) per point
▶ additional 2-3 pages for references and figures are acceptable
▶ one student from each group should email the title of the paper chosen and the names of the group members to b.szomolay@warwick.ac.uk
Bibliography

This course covers selected sections from chapters 2 and 7 and all of chapter 3 from *Mathematical Models of Biological Systems* by H. A. van den Berg.

Other books are on the web-site.
The modeling process

- what is mathematical modeling
- the five stages of modeling
- *ordinary differential equations* (ODEs) - to study time-dependent phenomena (e.g., exponential growth/decay processes)

*Lisette de Pillis, 2005*
The Malthusian growth model

- a population grows when birth rate > death rate
- T. Malthus, *An Essay on the Principle of Population* (1798), the population of his parish doubled every 30 years
- consider the population balance equation

\[
\frac{dN}{dt} = bN - dN, \quad (1)
\]

where \( N(t) \) - number of individuals in a population at time \( t \), \( b, d \)-average *per capita* birth and death rates. What are the units of \( b, d \)? What is the probabilistic interpretation of \( d \)?

- *initial state/condition* of population: \( N(0) = N_0 \)
- rewrite (1) as

\[
\frac{dN}{dt} = rN, \quad N(0) = N_0, \quad (2)
\]

where \( r = b - d \) is the *Malthusian parameter*

- Show that the solution of (2) is \( N(t) = N_0 e^{rt} \). What happens for \( r > 0, r = 0, r < 0 \)?
Estimate $r$ based on Malthus’ observation. How does it compare to the current growth rate of the human population 2% a year?

Predicting human population growth is problematic.

- Human population grows exponentially (or faster) over long time period.
- Most biological populations are regulated by competition for limiting resources (logistic equations).
Logistic equation

- P. F. Verhulst (1838): \( \frac{dN}{dt} = \alpha N - \beta N^2 \)
- Assume that the per capita birth rate in (1) decays linearly with \( N \) to reach a value of 0 at some population density \( \Gamma \):
  \[
  \frac{dN}{dt} = b \left( 1 - \frac{N}{\Gamma} \right) N - dN = r \left( 1 - \frac{N}{K} \right) N, \tag{3}
  \]
  where \( r = b - d \) and \( K = b \frac{b - d}{b} \Gamma \).
- (3) is an example of a nonlinear ODE with constant coefficients that can be solved explicitly:
  \[
  N(t) = \frac{N_0}{N_0/K + \left( 1 - N_0/K \right) e^{-rt}}
  \]
- Coupled systems of nonlinear ODEs are virtually never possible to solve explicitly.
- Sketch the graph of \( N(t) \) for different values of \( N_0 \).
Qualitative behavior of ODEs

- only a limited number of ODEs can be solved explicitly
- *numerical integration methods* - only a particular set of parameters and initial conditions is used
- (2) shows drastically different types of behavior w.r.t. $r$
- *model uncertainty* - value of the parameters and *conceptualization of the system*
- *qualitative behavior* of the model:
  what different types of dynamics the model can exhibit?
  what are the ranges of parameter values and initial conditions for the different types of dynamics?
Analyzing flow patterns

- consider the first-order autonomous ODE

$$\frac{dN}{dt} = f(N) \quad (4)$$

- Sketch the flow patterns for (2) and (3).

- **Steady states (equilibrium or stationary points)** of (4) are defined as the values of $N$ for which $\frac{dN}{dt} = 0$. What happens to the solution if $N(0)$ is a steady state? How does small perturbations of the steady-states in (2) and (3) affect the solution behavior?

- A steady state is **stable** if a small perturbation from it decays to zero, so that the solution returns to the steady state. A steady state **unstable** if a small perturbation grows exponentially, so that the solution moves away from it.

- **small** perturbations (**local** stability)
Linear stability analysis

- consider (4) and let $N^*$ be an equilibrium point, i.e., $f(N^*) = 0$
- to determine analytically if $N^*$ is stable/unstable, we perturb the solution $N(t) = N^* + \epsilon(t)$, where $\epsilon(0) \neq 0$
- derive the **stability condition**: $N^*$ is stable, if $f'(N^*) < 0$ and unstable, if $f'(N^*) > 0$
- $\lambda = f'(N^*)$ is called the **characteristic equation** and $\lambda$ is called the **eigenvalue**
- when is the stability condition inconclusive?
- use the stability condition for (3)
- for systems of ODEs the characteristic equation is a matrix equation, all eigenvalues need to have a negative real part for a steady state to be stable
Determine the stability of equilibrium points of the following ODE:

\[ \frac{dy}{dt} = (y^2 - 4)(y + 1)^2 \]
Autonomous planar ODE systems

- consider
  \[
  \frac{dR}{dt} = f(R, N), \quad \frac{dN}{dt} = g(R, N)
  \]

- to graphically analyze (5) without actually solving it
- \(f(R, N) = 0\) and \(g(R, N) = 0\) are called the \(R\)- and \(N\)-nullclines (null isoclines)
Genetic switch

- the genetic information from DNA is copied into mRNA, which moves out of the nucleus and uses ribosomes to form a polypeptide
- transcription factors - regulate transcription by turning genes on and off
consider the simplest gene regulatory network (GRN)

\[
\frac{du}{dt} = \frac{\phi_1 u}{1 + \alpha u + \beta v} - \lambda_1 u, \quad (6)
\]

\[
\frac{dv}{dt} = \frac{\phi_2 v}{1 + \alpha u + \beta v} - \lambda_2 v, \quad (7)
\]

where \( u, v \) are the concentrations of transcription factors

Sketch the *phase portrait* of this two-dimensional nonlinear dynamic system if \( \frac{a}{d} < \frac{\rho}{\mu} < \frac{b}{c} \) (specified later).
Why does (6)-(7) have the same phase curves as

\[
\frac{du}{dt} = \rho u - au^2 - buv, \quad (8)
\]
\[
\frac{dv}{dt} = \mu v - cv^2 - duv, \quad (9)
\]

where \( \rho = \phi_1 - \lambda_1, \mu = \phi_2 - \lambda_2, a = \alpha \lambda_1, c = \alpha \lambda_2, b = \beta \lambda_1, d = \beta \lambda_2 \)?

- find the equilibria, sketch the \( u - \) and \( v - \) nullclines and the vector field, explain the stability of equilibria
Genetic clock

- GRN can have periodic (oscillatory) dynamics - to adjust the timing of adaptive responses
- coupling of two switch networks:

\[
\begin{align*}
\frac{du}{dt} &= \frac{\phi_1 u}{1 + \alpha_1 u + \beta_1 yv} - \lambda_1 u, \\
\frac{dv}{dt} &= \frac{\phi_2 v}{1 + \alpha_2 xu + \beta_2 v} - \lambda_2 v, \\
\frac{dx}{dt} &= \frac{\phi_3 x}{1 + \alpha_3 x + \beta_3 uv} - \lambda_3 x, \\
\frac{dy}{dt} &= \frac{\phi_4 y}{1 + \alpha_4 vx + \beta_4 y} - \lambda_4 y,
\end{align*}
\]

- consider the \((u, v)\)-plane as a slice of the \((u, v, x, y)\) phase space
the phase portrait is shown for the case $y \ll 1, x \gg 1$

'big' $x$ favors $u$ over $v$, 'big' $y$ favors $v$ over $u$, 'big' $u$ favors $y$ over $x$, 'big' $v$ favors $x$ over $y$ (cycle of inhibitory influences)