Modelling in Biology, Part I: Key Concepts and Learning Outcomes

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        3. Deterministic vs stochastic
        4. Linear vs nonlinear
        5. Autonomous vs non-autonomous
    2. Identify the order of the model you are dealing with
    3. Identify the approach you need to use to analyse an ODE model of a given type and order
    4. Draw functions, i.e. f(x) vs x
    5. Linearise ODEs
        1. Know how to obtain the Jacobian matrix of a nonlinear ODE by linearising it around its fixed points
    6. Non-dimensionalise ODEs
    7. Compute the fixed points of ODEs
        1. Solve sets of algebraic equations of the form f(x)=0 where f() is a function
        2. Extract the roots of second and third order polynomials analytically and graphically
        3. ODEs of order 1: Find graphically the fixed points on the phase line
        4. ODEs of order 2: Find graphically the intersection of nullclines in the phase plane
    8. Perform graphical stability analysis for models of order 1 and 2
        1. ODEs of order 1: draw the flow on the phase line
        2. ODEs of order 2: Draw the vector field on the nullclines and in the regions of the state space delimited by the nullclines in the phase plane
    9. Perform analytical stability analysis for linear ODE models of any order
        1. Compute the eigenvalues and corresponding eigenvectors of matrices
        2. Write the analytical solution of linear ODEs of any order
    10. Perform bifurcation analysis
        1. Identify the type of bifurcation that can happen when a bifurcation parameter is varied in a given ODE model
        2. Find the critical bifurcation value analytically and graphically
        3. Draw bifurcation diagrams

1 Types of models considered in the first part of Modelling in Biology

- In this first part of the Modelling in Biology course, we will focus on continuous-time, deterministic, linear and nonlinear, autonomous Ordinary Differential Equation models

2 Ordinary Differential Equation (ODE) models

- *Ordinary Differential Equations (ODEs)* are used to describe models which depend on *1 independent variable*, typically time

2.1 Order of an ODE model

- Number of (dependent) variables used in the ODE model
- In practice: the dimension of (the vector) x in ODE models, e.g. if the model is given by $\dot{x} = \frac{dx}{dt} = f(x)$ with $x \in \mathbb{R}^2$, then the model is of order 2

2.2 State variable

- The (time-)dependent variables of an ODE are typically called its *state variables*, e.g. in $\dot{x} = f(x)$, x is called the state variable

2.3 Parameter

- Component of a model that can be varied, but which does not depend on the state variable, e.g. in $\dot{x} = f(x, k)$, where the values of k can be varied, k is called a parameter

2.4 Analytical solution of an ODE

- Solution that can be written down in "closed form"

- This course is specifically about methods allowing to determine the dynamical "behaviour" of the state variables without having to write their analytical solution down

2.5 Numerical integration of an ODE

- Algorithm used to *iteratively* compute a *numerical approximation* (also called numerical solution) to the solution of an ODE

3 Linear ODE models

- Example: $\dot{x} = kx$, where $x \in \mathbb{R}_{\geq 0}$ is the state variable and $k \in \mathbb{R}$ is a parameter
- This ODE model is:
  - Linear as the right-hand side of the ODE is a linear function of the state variable
  - Order 1 as the ODE is defined using only 1 state variable
- **We can always write down the analytical solution of *linear* ODE models of any order** as a linear combination of exponential terms whose arguments are the eigenvalues of the Jacobian matrix of the linear ODE.

4 Time evolution of the state variables of an ODE model, also called time trajectory or time trace

- Graph of the time evolution of the variables, i.e. the trace $x(t)$ in a graph of $x(t)$ vs t

4.1 Asymptotic behaviour

- *Asymptotic* = "when time goes to infinity", also called long-term behaviour
- *Asymptotic value*: The value the state variables end up with when time goes to infinity

4.2 Attractor

- *Set of points* in the phase space (also called state space) to which the state variables of the ODE *asymptotically converge*

4.3 Basin of attraction of a given attractor

- *Set of all points in the state space* such that if the state variables *start* on these points the corresponding trajectories end up on the considered attractor

4.4 Initial condition, also called initial value

- The *initial value* of the state variables at the initial time

4.5 Fixed point, also called steady state value of the state variables

- Value such that if the state variables start at this value they stay at that value for all times
- The fixed points can be found by considering the left-hand sides of all the equations describing the ODE to be zero, i.e. by finding the solution to the *set of algebraic equations* $\dot{x} = 0 = f(x)$, for $x \in \mathbb{R}^n$

5 Phase portrait, also called phase space

- Graph for which the *axes are the state variables*
- The space subtended by the axes of the phase portrait is called the *state space* (since each axis is a *state* variable) or phase space
- Time is thus not one of the axes in a phase portrait

5.1 Phase portrait analysis

- Graphical method used to understand the behaviour of a given ODE using a phase portrait

5.2 Phase line and phase plane

- For ODE models of order 1, the phase portrait is also called the *phase line*
- For ODE models of order 2, the phase portrait is also called the *phase plane*

6 State space trajectory

- The trace in the state space, e.g. the trace in a graph of $x_1(t)$ vs $x_2(t)$ for a second order ODE

6.1 Property of state space trajectories for ODEs for which the right-hand side does not depend explicitly on time

- For ODEs described by $\dot{x} = f(x)$ where $f(x)$ is a *function* that does *not depend explicitly on time*, **state space trajectories cannot cross**
- This property is particularly useful for the graphical analysis of ODEs of order 2

7 Flow or vector field

- The *flow* (also called *vector field*) describes the direction of motion of trajectories in the state space
- At every point in the state space, the *flow* (also called *vector field*) is tangential to state space trajectories
- Appendix A in the lecture notes provides an explanation for the direction of the flow based on the sign of the components of the vector $\dot{x}$

8 Bifurcation

- A bifurcation occurs when a change in the parameter(s) of the model produces a qualitative (i.e. large) change in the asymptotic behaviour of the attractors, e.g.
  - change in the number of attractors
  - change in the type of attractors
  - change in the stability of the attractors
- There are different types of bifurcations
  - *Saddle-node*, a.k.a *blue sky* bifurcation
  - *Transcritical* bifurcation
  - *Pitchfork* bifurcation
  - *Hopf* bifurcation
  - …

8.1 Critical bifurcation value

- The specific value at which the bifurcation occurs

8.2 Bifurcation diagram

- Graph where some of the axes are the state variables of the ODE and the other axes are the parameters of the ODE

8.3 Bifurcation analysis

- Graphical method used to understand how the dynamic behaviour of an ODE model changes (or "bifurcates") when its parameter(s) are varied

9 Nonlinear ODE models

- ODE for which the right-hand side is a nonlinear function of the state variable(s)

10 Linearisation around a fixed point

- The process of obtaining a *linear ODE approximation* to a nonlinear ODE around a fixed point
- The linear approximation is typically only valid when staying in *close vicinity* to the fixed point around which the linearisation was performed
- Mathematically, the linearisation is performed via a *Taylor series expansion* of the right-hand side of the ODE

10.1 The Hartman-Grobman Theorem, also called the linearisation theorem

- Theorem providing the conditions under which the dynamic behaviour of the linearised ODE is a *valid approximation* to the dynamic behaviour of the original nonlinear ODE in the vicinity of the fixed point around which the linearisation was performed
- The condition states that the linearistaion provides a valid approximation if and only if the Jacobian matrix of the linearised system *does not have any eigenvalue with zero real part*, i.e. if the fixed point is *not a centre* for the linearised model

10.2 Jacobian matrix

- The matrix appearing in the right-hand side of the linearised ODE is called the *Jacobian matrix*
- The Jacobian matrix is typically noted J, e.g. in $\dot{x} = Jx$ where $x \in \mathbb{R}^n$ and $J \in \mathbb{R}^{n \times n}$, J is called the Jacobian matrix

10.3 Eigenvalues of the Jacobian matrix

- The real part of the eigenvalues of the Jacobian matrix gives information in terms of the "*magnitude*" of the state space solutions/trajectories
- The imaginary part of the eigenvalues of the Jacobian matrix gives information in terms of the "*rotation*" of the state space solutions/trajectories
- If the imaginary part of the eigenvalues of the Jacobian matrix is zero, the corresponding fixed point is called a *node*
- If the imaginary part of the eigenvalues of the Jacobian matrix is non-zero, the corresponding fixed point is called a *spiral*
- If the real part of the eigenvalues of the Jacobian matrix is zero, the corresponding fixed point is called a *centre*

11 Diagonalisation

- The process of "*decoupling*" ODE equations via "*diagonalisation*" of the Jacobian matrix
- The Jacobian matrix is always diagonalisable if all its eigenvalues are distinct
- Diagonalisation relies on a *change of coordinates* allowing to rewrite a set of coupled ODEs of order n into an equivalent set of n decoupled ODEs of order 1
- The change of coordinates requires to obtain the eigenvalues and the corresponding eigenvectors of the Jacobian matrix

12 Stability

12.1 Global asymptotic stability

- An attractor is said to be *globally asymptotically stable* if trajectories end up on the attractor wherever they start in the state space
- In this case, the basin of attraction of the attractor is the whole state space
- Global asymptotic stability analysis is typically performed using graphical methods

12.2 Local/Linear asymptotic stability

- An attractor is said to be *locally asymptotically stable* if trajectories end up on the attractor whenever they start close to it (whenever they start in the basin of attraction of the attractor)
- Local/linear asymptotic stability analysis is typically performed via computation of the eigenvalues of the Jacobian matrix

12.3 Asymptotic stability as a sign property

- Graphically, asymptotic stability is a *sign property for the flow vector*
  - If the flow vector points towards an attractor from all directions then this attractor is asymptotically stable
- Algebraically, asymptotic stability is a *sign property of the real part of the eigenvalues of the Jacobian matrix*
  - If all the eigenvalues of the Jacobian matrix have a strictly negative real part, then the fixed point around which the Jacobian matrix was calculated is asymptotically stable

13 Nullcline

- Set of points (also called locus of points) in the state space for which the right-hand side of *individual* ODE equations is zero
- Example: for an ODE or order 2, there are 2 nullclines, one for $\dot{x}_1 = 0 = f_1(x_1, x_2)$ and another one for $\dot{x}_2 = 0 = f_2(x_1, x_2)$

13.1 Properties of nullclines

- Fixed points are found at the intersection of nullclines
- The flow (or vector field) on nullclines always has one component equal to zero by definition
  - For an ODE of order 2, the flow on any given nullcline is either vertical or horizontal
  - The direction of the flow (upwards or downwards if it is vertical, or left or right if it is horizontal) depends on the sign of the non-zero component(s) of the flow

14 Limit cycle and periodic solutions of ODEs

- *Limit cycles* are closed trajectory in the state space
- Such closed trajectories correspond to periodic time solutions of the ODE
- Limit cycles are only possible for ODEs of order 2 and above (this is a consequence of the non-crossing property of trajectories)

14.1 Stable limit cycle

- A stable limit cycle is a closed trajectory in the state space that **attracts other (nearby) trajectories to it**
- The basin of attraction of a stable limit cycle is the set of all points in the state space such that trajectories starting at these points asymptotically converge to the limit cycle
- Stable limit cycles are only possible for *nonlinear* ODEs of order 2 and above (this is a consequence of the fact that periodic solutions of linear ODEs can only be produced via centre points for which each initial condition defines a new closed trajectory returning to that same initial condition)

14.2 Hopf bifurcation

- Limit cycles often emerge via a *Hopf bifurcation* when a bifurcation parameter is varied
- The *signature of a Hopf bifurcation* when a bifurcation parameter is varied is 2 complex conjugate eigenvalues of the Jacobian matrix crossing the imaginary axis (at non zero speed), i.e. two complex conjugate eigenvalues such that their real part goes from negative to zero to positive values when the value of a bifurcation parameter is varied

14.3 Poincaré-Bendixson theorem

- Theorem allowing to assert the existence of at least 1 stable limit cycle
- Requires the definition of a “doughnut (toroidal)” region that trajectories cannot escape once entered and that does not contain any fixed point

15 Law of mass action

- A law (i.e. a rule or a method) to deduce ODEs for the concentrations of the species involved in chemical or biochemical reactions

- Law of mass action: *when two or more reactants are involved in a reaction, their reaction rates (at constant temperature) are proportional to the product of their concentrations.*

16 Leaning outcomes and things you need to be able to do

16.1 Identify the type of model you are dealing with

16.1.1 Continuous-time vs discrete-time

16.1.2 Continuous-values vs discrete-values

16.1.3 Deterministic vs stochastic

16.1.4 Linear vs nonlinear

16.1.5 Autonomous vs non-autonomous

16.2 Identify the order of the model you are dealing with

16.3 Identify the approach you need to use to analyse an ODE model of a given type and order

16.4 Draw functions, i.e. f(x) vs x

16.5 Linearise ODEs

16.5.1 Know how to obtain the Jacobian matrix of a nonlinear ODE by linearising it around its fixed points

16.6 Non-dimensionalise ODEs

16.7 Compute the fixed points of ODEs

16.7.1 Solve sets of algebraic equations of the form f(x)=0 where f() is a function

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16.7.3 ODEs of order 1: Find graphically the fixed points on the phase line

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16.8 Perform graphical stability analysis for models of order 1 and 2

16.8.1 ODEs of order 1: draw the flow on the phase line

16.8.2 ODEs of order 2: Draw the vector field on the nullclines and in the regions of the state space delimited by the nullclines in the phase plane

16.9 Perform analytical stability analysis for linear ODE models of any order

16.9.1 Compute the eigenvalues and corresponding eigenvectors of matrices

16.9.2 Write the analytical solution of linear ODEs of any order

16.10 Perform bifurcation analysis

16.10.1 Identify the type of bifurcation that can happen when a bifurcation parameter is varied in a given ODE model

16.10.2 Find the critical bifurcation value analytically and graphically

16.10.3 Draw bifurcation diagrams