INTRODUCTION TO BIOMATHEMATICS

also MATHEMATICAL BIOLOGY

The subject is not as hierarchical as many areas of mathematics and there is some flexibility over what is included. It is an interdisciplinary science.

Classical areas:

- population biology
- epidemiology
- population interactions of several species
- population genetics
- [ ] mathematical physiology
- [ ] DNA modelling

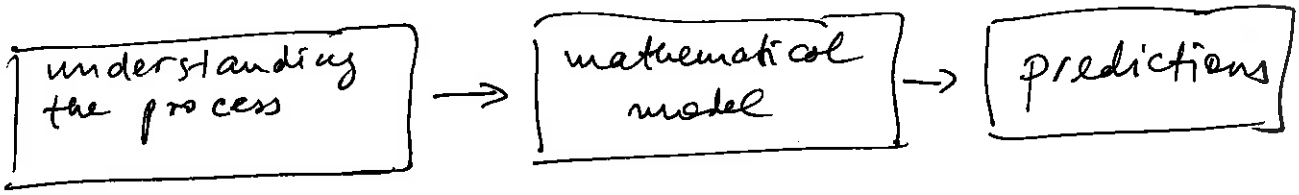
Mathematical background

- linear algebra
- ODE & PDE
- difference equations
- [ ] vector calculus
- [ ] probabilities & statistics.

Biomathematics as a mathematics discipline

- comparatively new - last 20 & 30 years.
- increased number of advertised positions in academia, medicine and industry around the world
- new subareas emerge as subject becomes so large, such as
  - biofluid mechanics
  - theoretical ecology
  - cancer ~~models~~ growth models
  - cardiomathematics

- The mathematical descriptions of biological phenomena are not biological explanations
- The principal use of any theory is its predictions, this is why mathematical models are important. However only experiments can confirm how closely the model relates to the real biology.



- The model can not take into account every single process - it captures the essence of the process that dominates the interations. With more data available, more sophisticated models are possible. From mathematical point of view the art of good modeling relies on

(i) sound understanding and appreciation of the biological problem
(ii) a realistic mathematical representation of the important biological phenomena
(iii) finding useful solutions, preferably quantitative
(iv) biological interpretation of the mathematical results in terms of insights & predictions.

The mathematics is dictated by the biology and not vice-versa.

We will be using Dynamic Models

- Dynamic models are simplified representations of some real-world entity, in equations or computer code
- They mimic some essential features of the study system while leaving out inessentials.
  - The models are called dynamic because they describe how system properties change over time; e.g.
    - gene expression level
    - abundance of an endangered species
    - mercury level in different organs within an individual, ...
  - Allow for making forecasts that can not be made strictly by extrapolating from data

The modeling process:

1. Conceptual model - represents our ideas about how the system works
2. Diagram with boxes or arrows
3. Equations are developed for the rates of each process and are combined to form a mathematical model consisting of dynamic equations for each state variable.

Compartment models – based on conservation of mass:

Example: Enzyme Kinetics

Enzyme mediated biochemical reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE$$

$$SE \xrightarrow{k_2} P + E$$

S = substrate (sucrose) $C_{12}H_{22}O_{11}$ table sugar

E = enzyme (invertase)

P = reaction product $C_6H_{12}O_6$

(Hydrolysis of sucrose into glucose & fructose)

Only assumption: Law of Mass Action – the rate of chemical reaction is proportional to the product of concentration of reactants

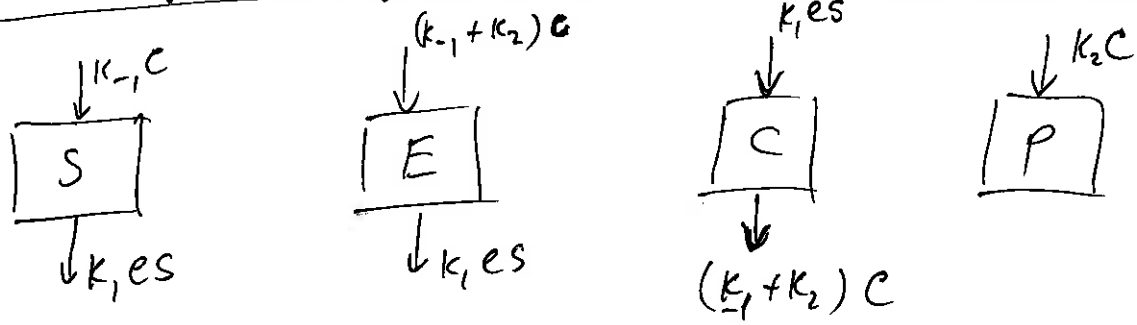
k_1, k_{-1} – constants of proportionality

s, e, c, p → concentrations of S, E, SE, P

- S and E combine to form SE at rate $k_1 se$
- SE separate to S + E at rate $k_{-1} c$
  SE —"— S + P —"— $k_2 c$

we have 4 state variables s, e, c, p

rate of change = inflow rate – outflow rate



We can write now equations

$$\frac{ds}{dt} = k_{-1}c - k_1 es$$

$$\frac{de}{dt} = (k_{-1} + k_2)c - k_1 es$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2)c$$

$$\frac{dp}{dt} = k_2 c$$

Nonlinear system of 4 ODE s.

Initial data:

$s(0) = s_0$
$e(0) = e_0$
$c(0) = p(0) = 0$

- Our interest is in the rate of product formation, we do not need the eqn. for p: the rate of product formation is $\boxed{k_2 c(t)}$

- We can further simplify by nothing that

$$\frac{de}{dt} + \frac{dc}{dt} = 0 \Rightarrow c(t) + e(t) = c(0) + e(0) = e_0$$

$$\Rightarrow \boxed{e(t) = e_0 - c(t)}$$

This makes sence because e and c are the unbound and bound forms of the enzyme which is not created or destroyed in this reaction scheme, whereas substrate is irreversibly converted to product.

- We can substitute $e_0 - c$ for e into the equations for s and c, leaving us with a system of only two equations

$$\begin{cases} \dfrac{ds}{dt} = k_{-1} c - k_1 (e_0 - c) s \\ \dfrac{dc}{dt} = k_1 (e_0 - c) s - (k_{-1} + k_2) c \end{cases}$$

we can not solve these (except numerically using computer) but we can get the information that we want by a simple approximation

Enzymes are in a very low concentration, e_0 is small $\quad e(t) = e_0 - c(t) \geq 0 \Rightarrow \quad c(t) \leq e_0$

$\Rightarrow c(t)$ is also small.

We introduce new variable:

$$v = \frac{c}{e_0} \quad \Rightarrow c = e_0 v$$

$$\frac{dv}{dt} = \frac{1}{e_0} \frac{dc}{dt} = k_1 \left(\frac{e_0}{e_0} - \frac{c}{e_0} \right) s - (k_{-1} + k_2) \frac{c}{e_0}$$

$$\boxed{\frac{dv}{dt} = k_1 (1 - v) s - (k_{-1} + k_2) v}$$

The other equation becomes

$$\frac{ds}{dt} = k_{-1} e_0 v - k_1 (e_0 - e_0 v) s = \underbrace{e_0}_{\text{small.}} \left[k_{-1} v - k_1 (1 - v) s \right]$$

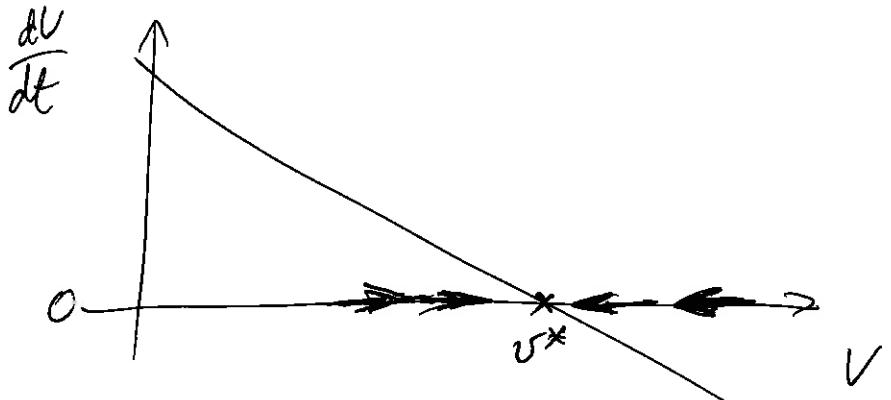
$\Rightarrow s$ changes much more slowly because e_0 is small $\Rightarrow$ we can proceed as if s were constant $\quad \boxed{s \approx \text{const.}}$

This brings us down to the single eqn:

$$\frac{dv}{dt} = k_1 S - (k_{-1} + k_2 + k_1 S) v$$

Observations:

$$\frac{dv}{dt} > 0 \quad \text{at} \quad v = 0$$



$v(t)$ approaches value v^* at which $\frac{dv}{dt} = 0$

$$k_1 S = (k_1 S + k_{-1} + k_2) v^* = (k_1 S + k_{-1} + k_2) \frac{c^*}{e_0}$$

$$c^* = \frac{k_1 e_0 S}{k_1 S + k_{-1} + k_2} = \frac{e_0 S}{K + S} \quad ; \quad K = \frac{k_{-1} + k_2}{k_1}$$

c^* is called stable equilibricum point: the system tends towards it and then stays there.

We need rate of product formation

$$\left(\frac{dP}{dt}\right)_* = k_2 c^* = \frac{k_2 e_0 S}{K + S} = \frac{V_{max} S}{K + S} \quad \text{where } \underline{k_2 e_0 \equiv V_{max}}$$

Michaelis - Menten equation.

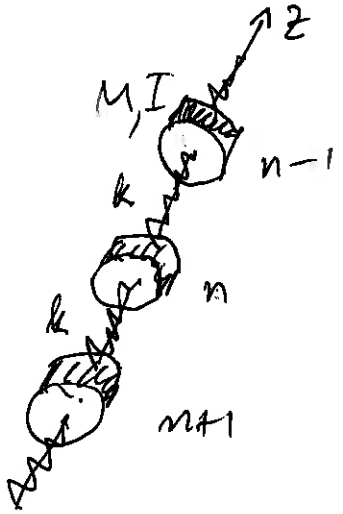
We have some additional information: the c - equation describes how enzyme moves between bound and unbound states — it reaches equilibrium value, that depends on S (the ammount of substrate)

Physics Models

Based on the physical laws of Mechanics
The variables are normally positions and velocities, accelerations, forces, etc.
Equations come from Newton's laws of motion.

Example: DNA molecule

Simple model: A chain of coupled disks



u_n and φ_n are longitudinal and angular displacements of the n-th disk
M and I are the mass and the moment of inertia of the disk, ~~k and K~~
k - elasticity constant of spring
K - torsional rigidity of the chain

$$M\ddot{u}_n = K(u_{n+1} - 2u_n + u_{n-1})$$ linear approx.

$\ddot{u}_n$: acceleration of n^{th} node

$K(u_{n+1} - 2u_n + u_{n-1})$: Force acting on n-th disk due to (elasticity)

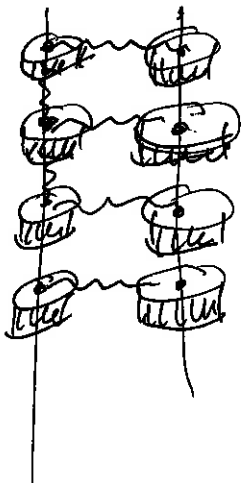
~~This is a linear approximation~~

$$I\ddot{\varphi}_n = K(\varphi_{n+1} - 2\varphi_n + \varphi_{n-1})$$

$\ddot{\varphi}_n$: angular acceleration

$K(\varphi_{n+1} - 2\varphi_n + \varphi_{n-1})$: torque

These two equations give the linear approximation of <u>one</u> of the DNA strands. But DNA has two strands, which have a planar representation — in the next approximation:



Each Disk represents a base of DNA

Actually the real DNA molecule is by far more complex. It is a double ~~coil~~ helix with a turn of about 36° per base.

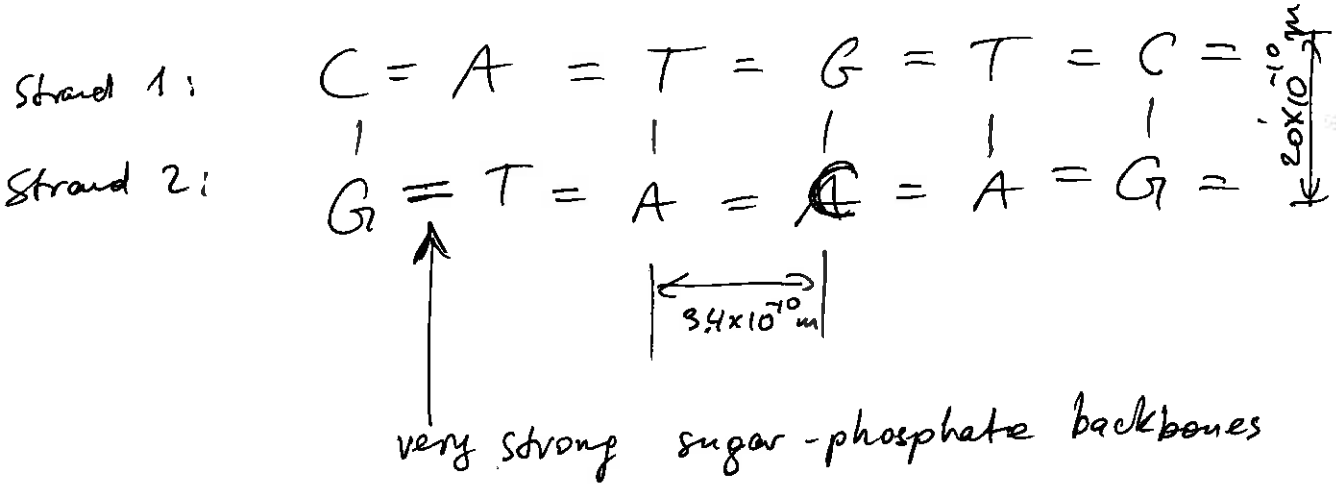
The Watson - Crick Model of DNA

1953

DNA composed of 4 bases (or nucleotides) A, T, C, G which pair according to the rules

A - T C - G

Two complementary strands



Each cell contains 10^{10} base pairs $\simeq 3.4$ m of DNA in each cell of our body! Actually it is between 1 - 2 meters and not in one piece.

The total volume however of DNA is still rather small and can be packed in individual cells with plenty of space left over

One gene encodes one entire protein and a typical lenth of a gene is 500 - 600 bp (basic pairs)

One bp ⇒ 60 atoms.

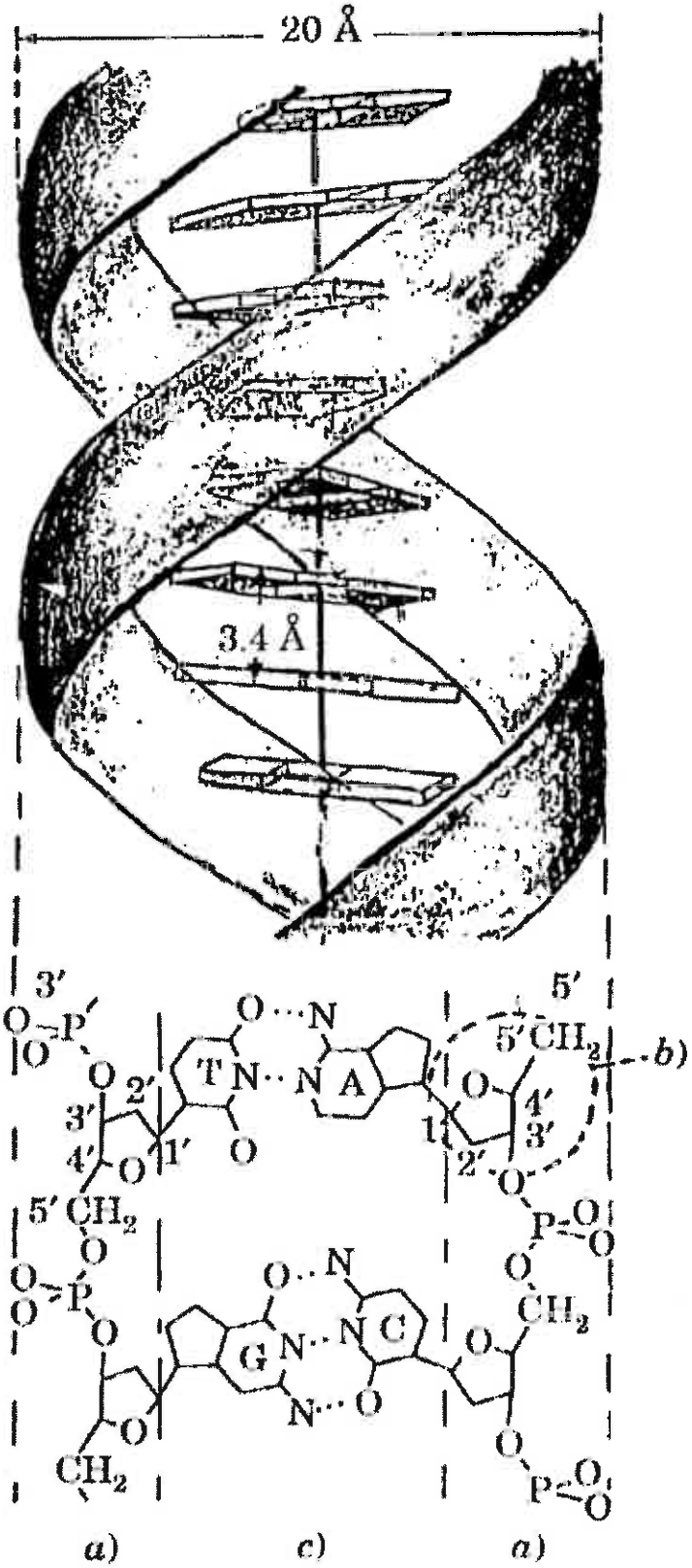


Fig. 1. – Schematic drawing of the double helix (B form), the sugar-phosphate backl represented as a ribbon, with detailed chemical structure shown in *a*) and *b*) (sugar n The bases are sketched as rectangular plates, with detailed chemical structures shown

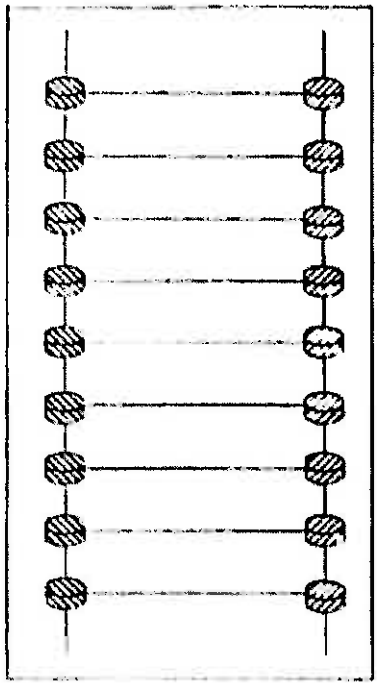


Fig. 9.

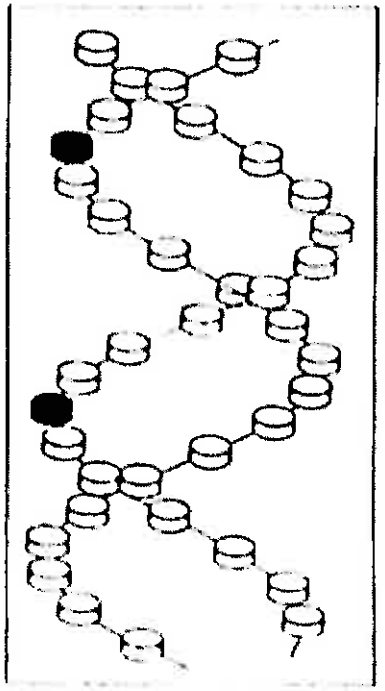


Fig. 10.

Fig. 9. – Abstract representation of planar models of DNA. Each base is consider interact only with first neighbours on its chain (stacking interactions, modell harmonic potential), and on the pairing base at the same site on the other chain (p forces due to H-bonds, modelled by non harmonic potentials). The abstract model c considered planar, which explains the name; in actual DNA, the geometry of the bac is at the origin of the double-helix structure, with a turn of about 36° per base

Fig. 10. – Abstract representation of helicoidal models of DNA. In addition to stackin pairing interactions indicated in fig. 9, these consider also interaction between bas opposite chains which are half-pitch of the helix away in the sequence, and the nearby in three-space due to helical geometry; two bases connected by such an «helic interaction are indicated. In real DNA, these interaction are mediated by water filar joining the concerned bases.

Another mechanical model: DNA is smoothed or averaged to yield a model as an elastic line.

- DNA is big enough to be seen with various microscopy techniques
- DNA quite often occurs into closed loops (150 bp or less), mini-circles, as well as thousands of bp
- DNA is rather stiff; it has a well-defined shape.

Optimization Models

Biologists also use optimization models, in which the modeler assumes that the study organisms are trying to achieve some particular goal.

- For example; an animal will gather food in the habitat that gives it the best chance of getting enough food to survive, without itself being eaten by predators
- Optimization of drug usage: effect/damage.

Usage of dynamical models

Why do we need dynamical models?

1. Scientific understanding of the underlying process or phenomenon

2. Using scientific understanding to manage the world

- Forecasting disease or pest outbreaks
- Designing man-made systems, for example biological pest control, bioingeneering
- Managing existing systems such as agriculture or fisheries
- Optimizing medical treatments or improving athletic performances

3. There are experiments that you would rather not do:

- Endangered species management by trial & error
- Clinical experiments on humans
- Experiments with toxic substances, radiological experiments, dosymetry and radiation protection.

Theoretical versus Practical Models

Practical	Theoretical
• Main goals are management, design & prediction	• Main goals are theoretical understanding and theory development
• Numerical accuracy is desirable even at the expense of simplicity	• Numerical accuracy is not essential; the model should be as simple as possible.
• Processes and details can be ignored only if they are numerically unimportant	• Processes and details can be ignored if they are conceptually irrelevant to the theoretical issues
• Assumptions are quantitative representations of system processes	• Assumptions may be qualitative representations of hypotheses about the system, adopted conditionally in order to work out their consequences
• System and question specific	• Applies to a range of similar systems

Outline of the modelling process