A few simple within-host models

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A simple simulation model

- We'll start with a very simple model, a population of entities (pathogens/immune cells/humans/animals) that grow or die.
- We'll implement the model as a discrete time equation, given by:

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

- P_t are the number of pathogens in the population at current time t, dt is some time step and P_{t+dt} is the number of pathogens in the future after that time step has been taken.
- The processes/mechanisms modeled are growth at rate g and death at rate d_P.

A simple simulation model

- If we started with 100 individuals (pathogens) at time t=0, had a growth rate of 12 and death rate of 2 (per some time unit, e.g. days or weeks or years), and took time steps of $dt = 1$, how many individual would we have after 1,2,3… time units?
- Why do we multiply by the time step, *dt*?

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

A simple simulation model - variant 1

Original:

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

Alternative:

$$P_{t+dt} = P_t + dt(g - d_P P_t)$$

What's the difference? Is this a good model?

A simple simulation model - variant 2

Original:

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

Alternative:

$$P_{t+dt} = P_t + dt(gP_t - d_P)$$

What's the difference? Is this a good model?

Discrete time models

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

- The model above is updated in discrete time steps (to be chosen by the modeler).
- Good for systems where there is a “natural”" time step. E.g. some animals always give birth in spring or some bacteria divide at specific times.
- Used in complex individual based models for computational reasons.
- For compartmental models where we track the total populations (instead of individuals), continuous-time models are more common. They are usually formulated as ordinary differential equations (ODE).
- If the time-step becomes small, a discrete-time model approaches a continuous-time model.

Continuous time models

Discrete:

$$P_{t+dt} = P_t + dt(gP_t - d_P P_t)$$

Re-write:

$$\frac{P_{t+dt} - P_t}{dt} = gP_t - d_P P_t$$

Continuous:

$$\frac{dP}{dt} = gP - d_P P$$

- If we simulate a continuous time model, the computer uses a smart discrete time-step approximation.

Some notation

The following are 3 equivalent ways of writing the differential equation:

$$\frac{dP(t)}{dt} = gP(t) - d_P P(t)$$

$$\frac{dP}{dt} = gP - d_P P$$

$$\dot{P} = gP - d_P P$$

We will use the ‘dot notation’.

Some terminology

$$\dot{P} = gP - d_P P$$

- The left side is the instantaneous change in time of the indicated variable.
- Each term on the right side represents a (often simplified/abstracted) biological process/mechanism.
- Any positive term on the right side is an inflow and leads to an increase of the indicated variable.
- Any negative term on the right side is an outflow and leads to a decrease of the indicated variable.

Extending the model

$$\dot{P} = gP - d_P P$$

For different values of the parameters g and d_P, what broad types of dynamics/outcomes can we get from this model?

Extending the model

$$\dot{P} = gP - d_P P$$

How can we extend the model to get growth that levels off as we reach some high level of *P*?

Model with saturating growth

$$\dot{P} = gP(1 - \frac{P}{P_{max}}) - d_P P$$

- We changed the birth process from exponential/unlimited growth to saturating growth. P_{max} is the level of P at which the growth term is zero.
- If $P > P_{max}$, the growth term is negative.
- The population settles down at a level where the growth balances the decay, i.e. when $gP(1 - \frac{P}{P_{max}}) = d_P P$.

Adding a second variable

- A single variable model is ‘boring’.
- The interesting stuff happens if we have multiple compartments/variables that interact.
- Let’s introduce a second variable.
- Let’s assume that *P* is a population of some bacteria (but could also be some animal), which gets attacked and consumed by some predator, e.g. the immune system or another animal. We’ll pick the letter *H* for the predator (any label is fine).

Adding a second variable

$$\dot{P} = gP(1 - \frac{P}{P_{max}}) - d_P P \pm ?$$

$$\dot{H} = ?$$

- The predator attacks/eats the prey. What process could we add to the *P*-equation to describe this?

Adding a second variable

$$\dot{P} = gP(1 - \frac{P}{P_{max}}) - d_P P - kPH$$

$$\dot{H} = ?$$

- The more *P* there is, the more the predator will grow, e.g. by eating *P* or by receiving growth signals.
- What term could we write down for the growth dynamics of *H*?
- Finally, *H* individuals have some life-span after which they die. How can we model this?

Predator-prey model

The model we just built is a version of the well-studied predator-prey model from ecology.

$$\dot{P} = g_P P(1 - \frac{P}{P_{max}}) - d_P P - kPH$$
$$\dot{H} = g_H PH - d_H H$$

The discrete-time version of the model is:

$$P_{t+dt} = P_t + dt(g_P P_t(1 - \frac{P_t}{P_{max}}) - d_P P_t - kP_t H_t)$$
$$H_{t+dt} = H_t + dt(g_H P_t H_t - d_H H_t)$$

Bacteria and immune response model

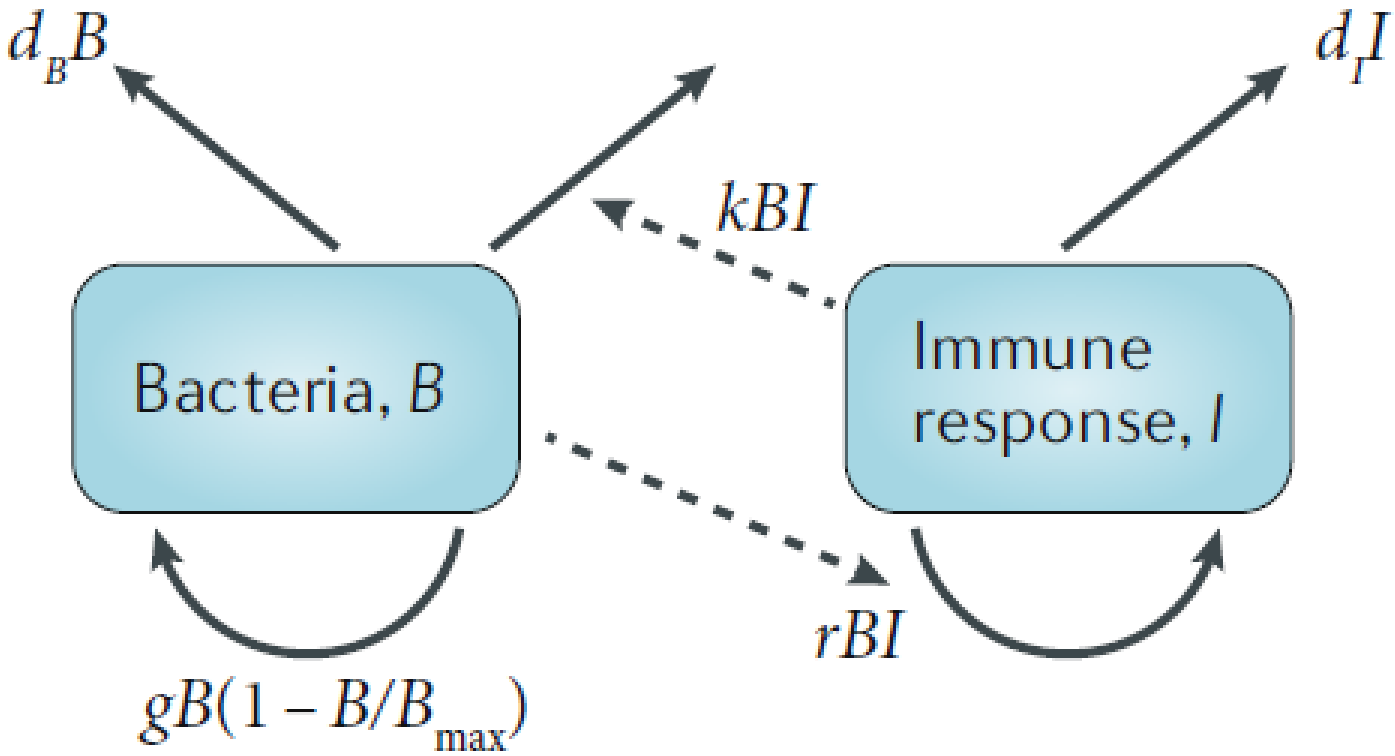
The names of the variables and parameters are arbitrary. If we think of bacteria and the immune response, we might name them *B* and *I* instead.

$$\dot{B} = gB(1 - \frac{B}{B_{max}}) - d_B B - kBI$$
$$\dot{I} = rBI - d_I I$$

$$B_{t+dt} = B_t + dt(gB_t(1 - \frac{B_t}{B_{max}}) - d_B B_t - kB_t I_t)$$
$$I_{t+dt} = I_t + dt(rB_t I_t - d_I I_t)$$

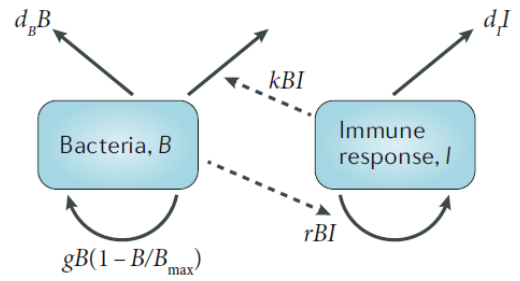
Graphical model representation

- It is important to go back and forth between words, diagrams, equations.
- Diagrams specify a model somewhat, but not completely. The diagram below could be implemented as ODEs or discrete time or stochastic models.



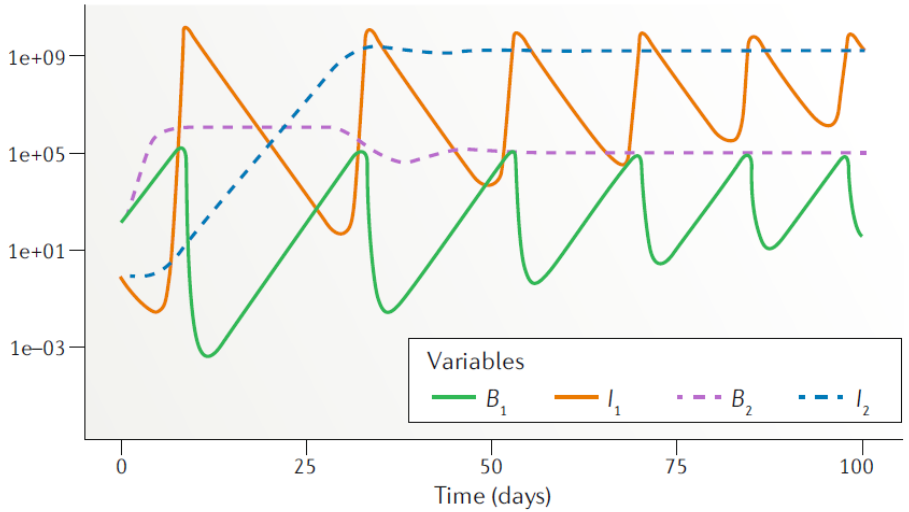
Model exploration

- We could analyze the model behavior with ‘pencil and paper’ (or some software, e.g. Mathematica/Maxima). This only works for simple models.
- We could analyze the model behavior by simulating it.
- To simulate, we need to implement the model on a computer, specify starting (initial) conditions for all variables and values for all model parameters.



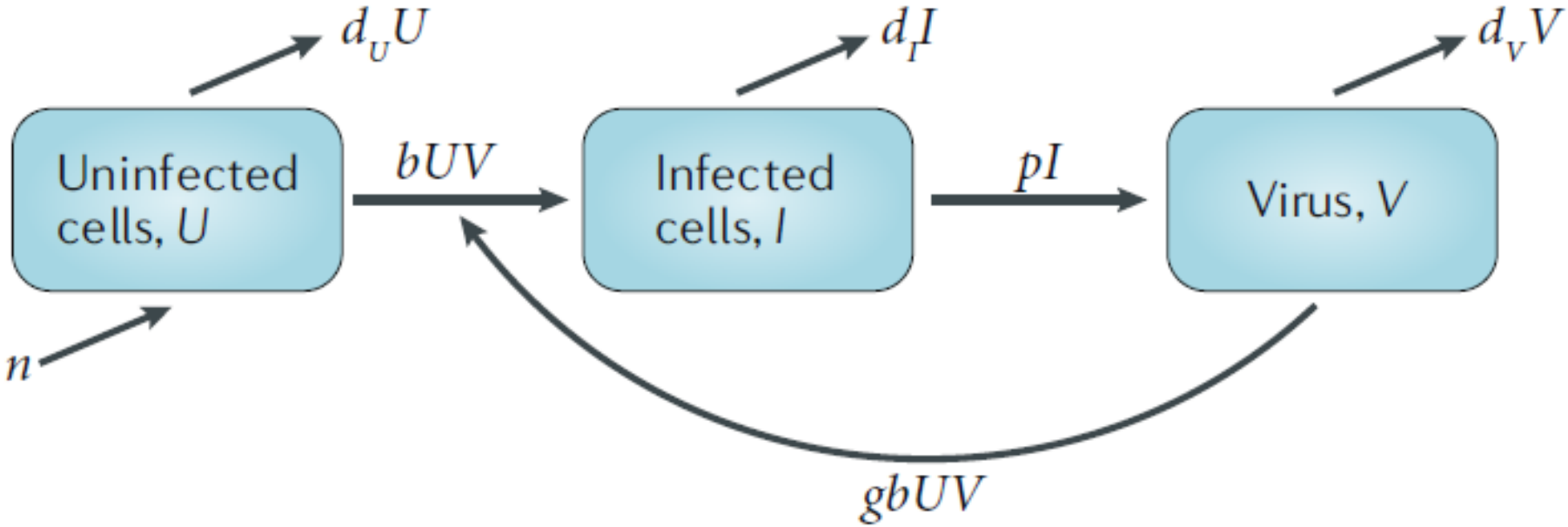
Bacteria $\dot{B} = gB(1 - \frac{B}{B_{max}}) - d_B B - kBI$

Immune response $\dot{I} = rBI - d_I I$



A simple virus infection model

A simple virus infection model



Uninfected cells	$\dot{U} = n - bUV - d_U U$
Infected cells	$\dot{I} = bUV - d_I I$
Virus	$\dot{V} = pI - gbUV - d_V V$

A simple virus infection model

Notation comment

- If you read the literature, you'll see all kinds of letters used for variables and parameters. That can be confusing but unfortunately unavoidable.
- Look carefully at models and see how variables/parameters are defined. A model that looks new might in fact be one that you know, just using different notation.
- These 2 models are the same as the model we just saw!

$$\dot{T} = s - kT - \beta TV$$
$$\dot{T^*} = \beta TV - dT^*$$
$$\dot{V} = nT^* - cV - \beta gTV$$

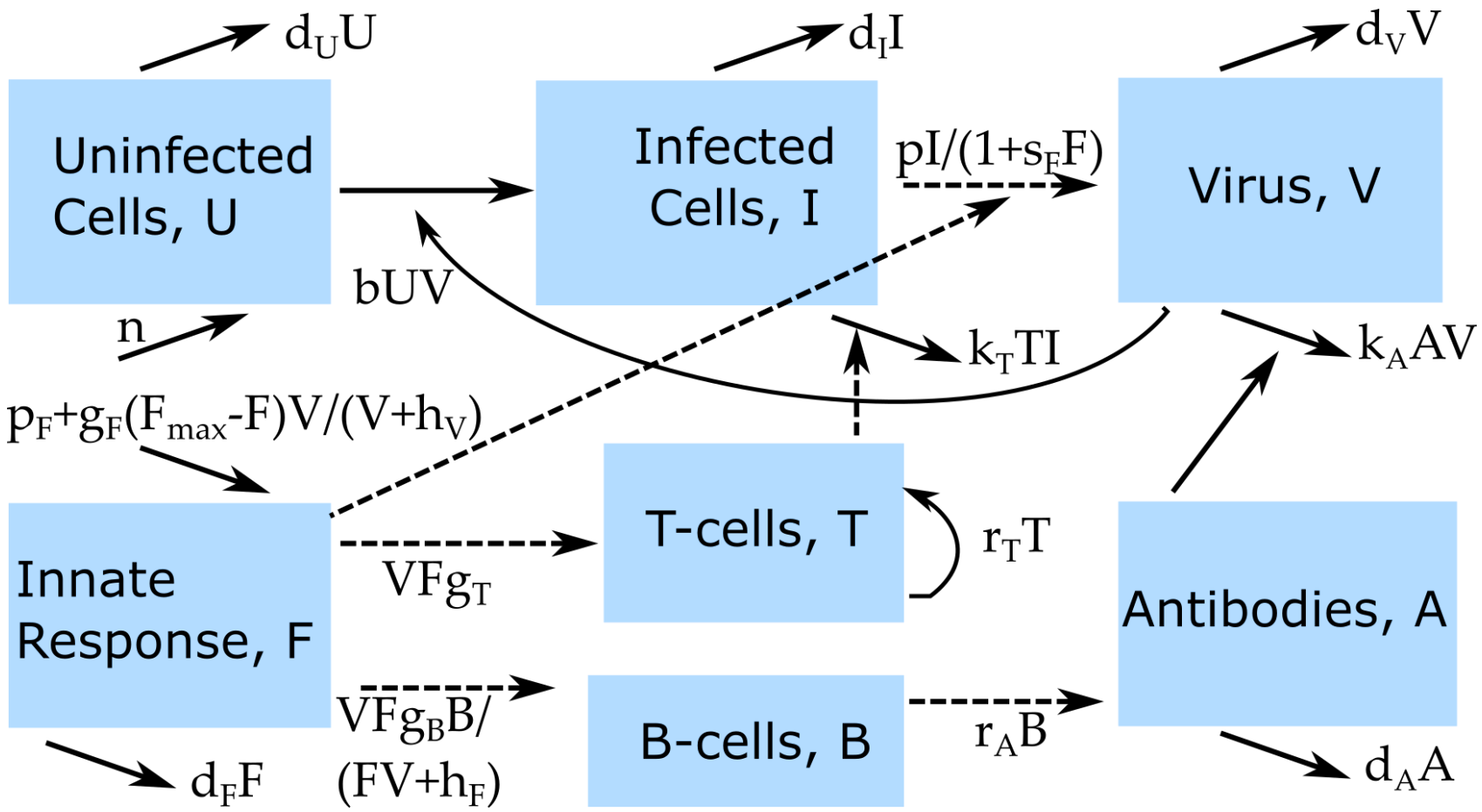
$$\dot{x} = \lambda - dx - \beta xv$$
$$\dot{y} = \beta xv - ay$$
$$\dot{v} = \kappa y - uv - \beta gxv$$

A larger virus infection model

Virus and Immune Response Model

- The immune response is incredibly complex, we still don't know how to model it in much detail.
- We can nevertheless build and explore models that are a (hopefully) good balance between realism and abstraction.
- Let's look at a virus model that contains uninfected cells (**U**), infected cells (**I**), virus (**V**), an innate immune response (**F**), CD8 T-cells (**T**), B-cells (**B**) and Antibodies (**A**).

Model Diagram



Model Equations

$$
\begin{aligned}
\dot{U} &= n - d_U U - bUV \\
\dot{I} &= bUV - d_I I - k_T T I \\
\dot{V} &= \frac{pI}{1 + s_F F} - d_V V - bUV - k_A A V \\
\dot{F} &= p_F - d_F F + \frac{V}{V + h_V} g_F (F_{max} - F) \\
\dot{T} &= FV g_T + r_T T \\
\dot{B} &= \frac{FV}{FV + h_F} g_B B \\
\dot{A} &= r_A B - d_A A - k_A A V
\end{aligned}
$$

Learn more

DSAIRM package:

- *Basic Bacteria Model* app.
- *Basic Virus Model* app.
- *Virus and Immune Response* app.