A few simple simulation models

on the population and within-host levels

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A simple process/simulation model

- We'll start with a very simple model, a population of individuals (humans or animals or pathogens) 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 people/pathogens in the population at time t, dt is some time step, g is the growth/birth rate and d_P is the death rate.

- What processes exactly does this model describe 'translated into words'?

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- Why do we multiply by the time step, dt?

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- If we started with 100 people/pathogens at time t=0, had a growth rate of 12 and death rate of 2 (per year or day), and took time steps of 1 year (or day), how many individual would we have after 1,2,3… years/days?

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 instantanous 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.

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 animal or some bacteria, which gets attacked and consumed by some predator, e.g. another animal or the immune system. 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?
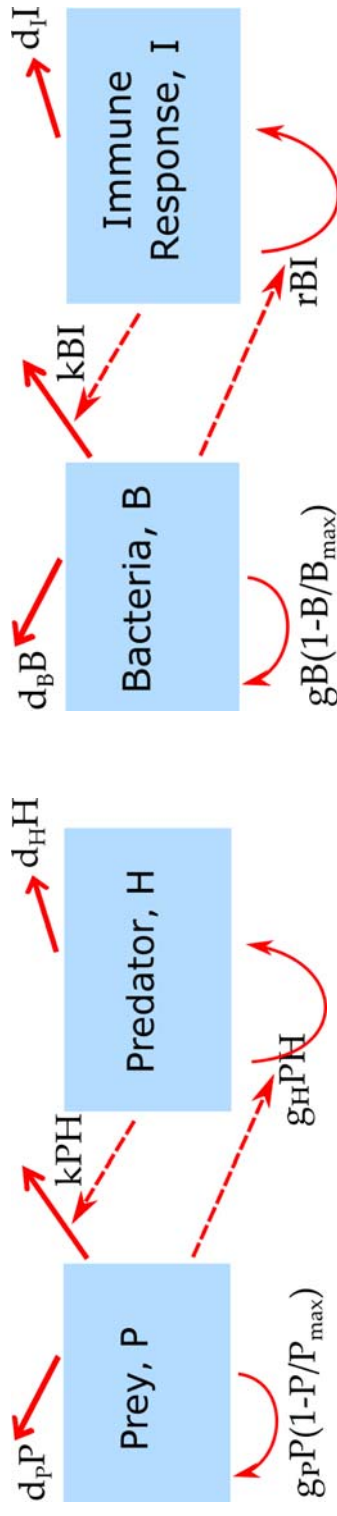
Predator-prey model

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

$$\dot{H} = g_H PH - d_H H$$

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

- 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.

- 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.

Graphical model representation

- It is important to go back and forth between words, diagrams, equations.

- Diagrams specify a model somewhat, but not completely. The diagrams below could be implemented as ODEs (shown) or discrete time or stochastic models.

$d_P P$

$g_P P(1\text{-}P/P_{max})$

Prey, P

kPH

$g_H PH$

$d_H H$

Predator, H

$d_B B$

$gB(1\text{-}B/B_{max})$

Bacteria, B

kBI

rBI

$d_I I$

Immune Response, I

$$\dot{P} = g_P P\left(1 - \frac{P}{P_{max}}\right) - d_P P - kPH \qquad \dot{B} = gB\left(1 - \frac{B}{B_{max}}\right) - d_B B - kBI$$

$$\dot{H} = g_H PH - d_H H \qquad \dot{I} = rBI - d_I I$$

Model exploration

- We could analyze the model behavior with 'pencil and paper' (or some software, e.g. Mathematica/Maple/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 (here P and H) and values for all model parameters.

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

$$\dot{H} = g_H PH - d_H H$$

- We won't do that now but will explore these kinds of models later using the DSAIDE/DSAIRM R packages.

The basic SIR model

The basic SIR model

- We'll now look at the most fundamental/basic model for population level infectious disease modeling.

- This model tracks individuals (humans or animals) in 3 states, susceptible, infected/infectious and recovered/removed. It is called the SIR model.

| Susceptible S | $\xrightarrow{bSI}$ | Infected/ Infectious I | $\xrightarrow{gI}$ | Recovered R |

$$\dot{S} = -bSI$$
$$\dot{I} = bSI - gI$$
$$\dot{R} = gI$$

- Only 2 processes are modeled, what are they?

SIR model with births and deaths

- If we wanted to include births and deaths in our model, how could we do that?

$$\dot{S} = -bSI$$
$$\dot{I} = bSI - gI$$
$$\dot{R} = gI$$

SIR model with births and deaths

One possible variant

$$\dot{S} = m - bSI - nS$$
$$\dot{I} = bSI - gI - nI$$
$$\dot{R} = gI - dR - nR$$

A notation example

These 2 models are the same!
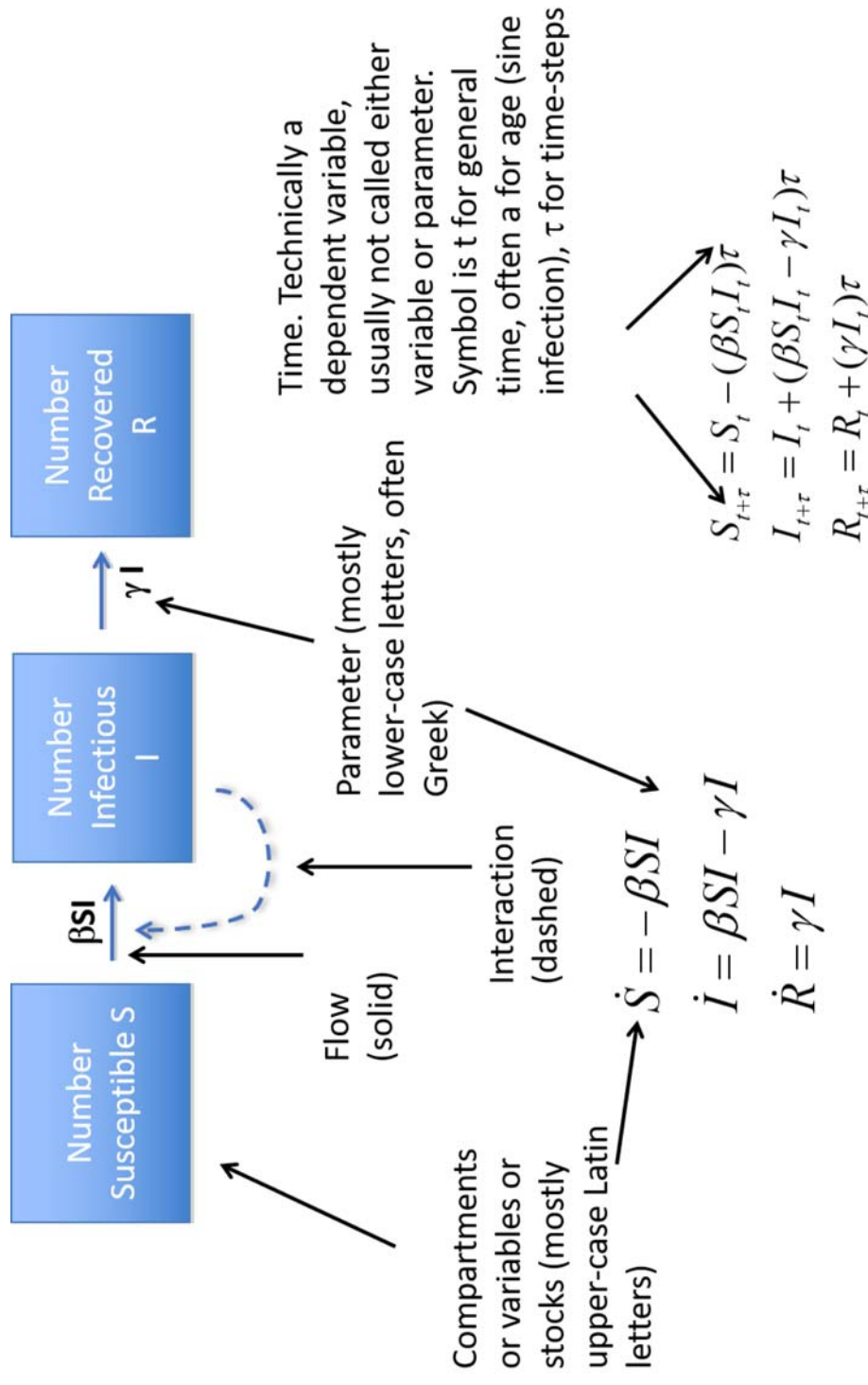
$$\dot{S} = m - bSI - nS$$
$$\dot{I} = bSI - gI - nI$$
$$\dot{R} = gI - nR$$

$$\dot{x} = \lambda - bx - \beta xz$$
$$\dot{y} = -by - \kappa y + \beta xz$$
$$\dot{z} = \kappa y - bz$$

Terminology again

| Number Susceptible S | | Number Infectious I | | Number Recovered R |

βSI

γI

Flow (solid)

Interaction (dashed)

Compartments or variables or stocks (mostly upper-case Latin letters)

Parameter (mostly lower-case letters, often Greek)

Time. Technically a dependent variable, usually not called either variable or parameter. Symbol is t for general time, often a for age (sine infection), τ for time-steps

$$\dot{S} = -\beta SI$$
$$\dot{I} = \beta SI - \gamma I$$
$$\dot{R} = \gamma I$$

$$S_{t+\tau} = S_t - (\beta S_t I_t)\tau$$
$$I_{t+\tau} = I_t + (\beta S_t I_t - \gamma I_t)\tau$$
$$R_{t+\tau} = R_t + (\gamma I_t)\tau$$

A simple virus infection model

A simple virus infection model
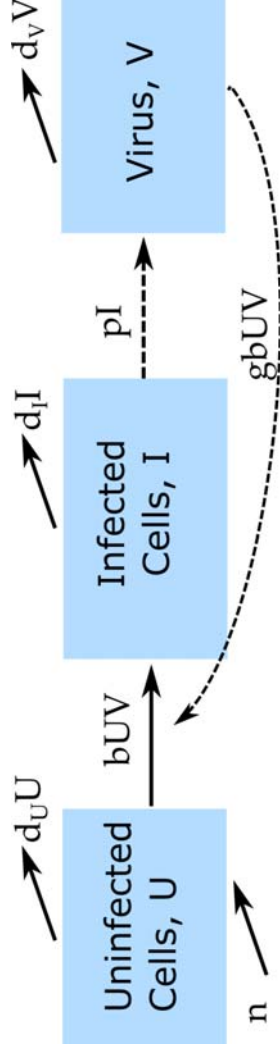
$$\dot{U} = n - d_U U - bUV$$
$$\dot{I} = bUV - d_I I$$
$$\dot{V} = pI - d_V V - bgUV$$

Uninfected Cells

Infected Cells

Virus

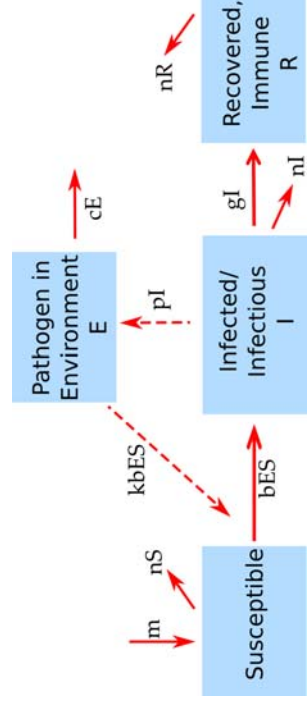# Matching models

Can you spot the differences?
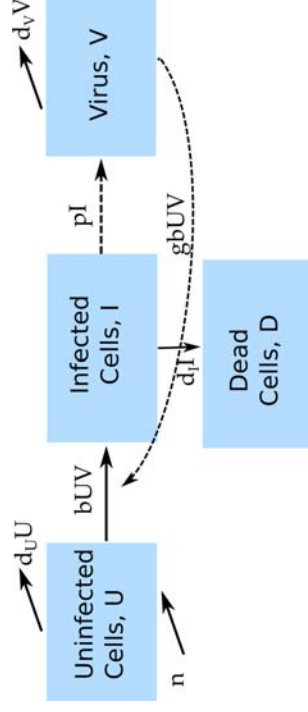
$$\dot{U} = m - d_U U - bUV$$
$$\dot{I} = bUV - d_I I - nI$$
$$\dot{D} = d_I I$$
$$\dot{V} = pI - d_V V - gbUV$$

$$\dot{S} = m - nS - bSE$$
$$\dot{I} = bSE - gI - nI$$
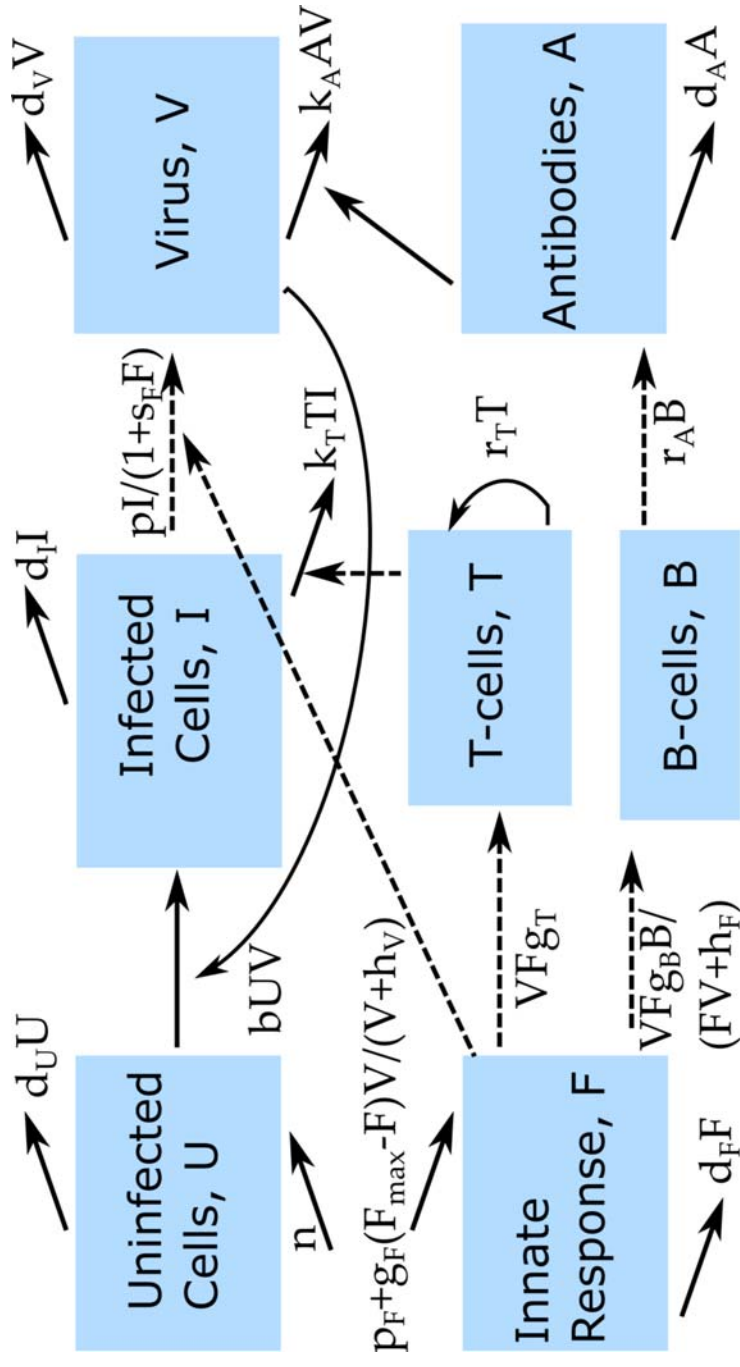$$\dot{R} = gI - nR$$
$$\dot{E} = pI - cE - kbSE$$

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.

- We'll consider a virus infection model that includes the following components/variables:

- **U** - uninfected cells

- **I** - infected cells

- **V** - (free) virus

- **F** - innate immune response

- **T** - CD8 T-cells

- **B** - B-cells

- **A** - Antibodies

Model Diagram

Uninfected Cells, U — $d_U U$

n

bUV → Infected Cells, I — $d_I I$

$pI/(1+s_F F)$

Virus, V — $d_V V$

$p_F + g_F(F_{max}-F)V/(V+h_V)$

Innate Response, F — $d_F F$

VFg_T

$k_T TI$

$k_A AV$

T-cells, T — $r_T T$

$VFg_B B/(FV+h_F)$

$r_A B$

B-cells, B

Antibodies, A — $d_A A$

Model Equations

$$\dot{U} = n - d_U U - bUV$$

$$\dot{I} = bUV - d_I I - k_T TI$$

$$\dot{V} = \frac{pI}{1 + s_F F} - d_V V - bUV - k_A AV$$

$$\dot{F} = p_F - d_F F + \frac{V}{V + h_V} g_F (F_{max} - F)$$

$$\dot{T} = FV g_T + r_T T$$

$$\dot{B} = \frac{FV}{FV + h_F} g_B B$$

$$\dot{A} = r_A B - d_A A - k_A AV$$

Learn more

DSAIDE package:

- *Basic SIR Model app.*
- *Characteristics of ID app.*
- *ID Patterns app.*
- *Environmental Transmission app.*

DSAIRM package:

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