

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 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

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

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

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

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

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

- The discrete-time version of the model is:

$$P_{t+dt} = P_t + dt \left(g_P P_t \left(1 - \frac{P_t}{P_{max}}\right) - d_P P_t - k P_t H_t \right)$$

$$H_{t+dt} = H_t + dt (g_H P_t H_t - d_H H_t)$$

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.

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

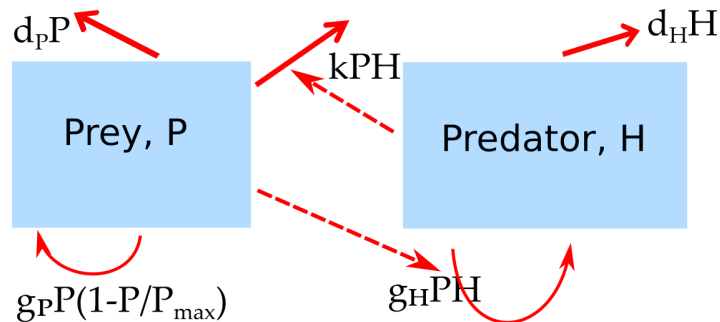
$$\dot{I} = rBI - d_I I$$

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

$$I_{t+dt} = I_t + dt(rB_t I_t - d_I I_t)$$

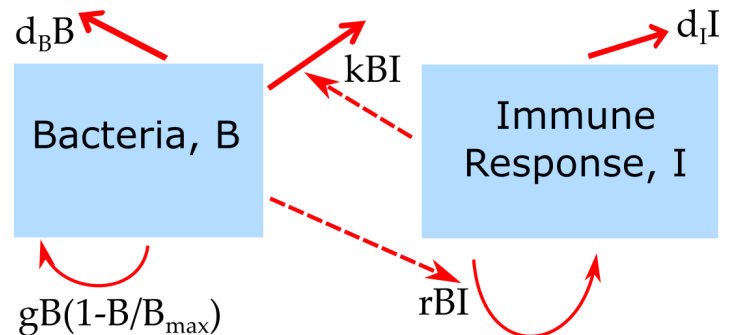
Graphical model representation

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



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

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



$$\dot{B} = g_B B \left(1 - \frac{B}{B_{max}}\right) - d_B B - kBI$$

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

Model exploration

- We could mathematically 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 and values for all model parameters.

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

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

$$\dot{B} = g_B \left(1 - \frac{B}{B_{max}}\right) - d_B B - kBI$$

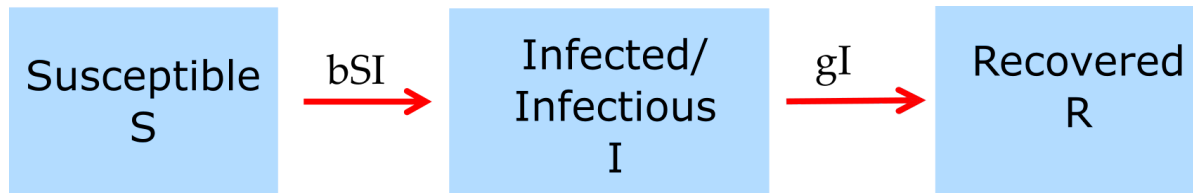
$$\dot{I} = rBI - d_I I$$

- The *Basic Bacteria Model* app in DSAIRM allows you to analyze this model graphically.

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.



$$\dot{S} = -bSI$$

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

$$\dot{R} = gI$$

- 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?

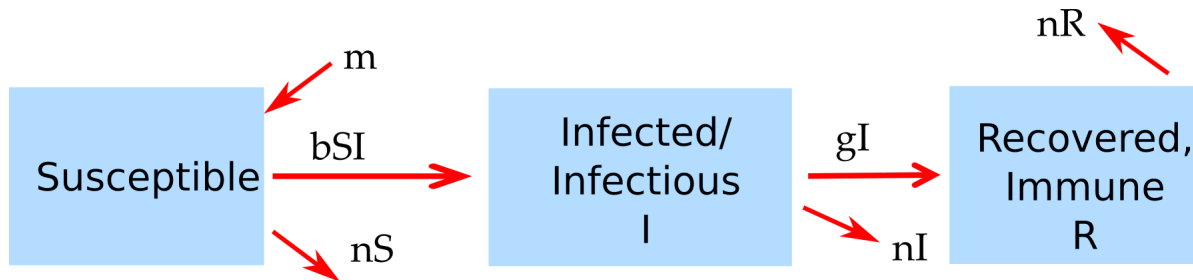
$$\dot{S} = -bSI$$

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

$$\dot{R} = gI$$

SIR model with births and deaths

One possible variant



$$\dot{S} = m - bSI - nS$$

$$\dot{I} = bSI - gI - nI$$

$$\dot{R} = gI - nR$$

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!

$$\dot{S} = m - bSI - nS$$

$$\dot{I} = bSI - gI - nI$$

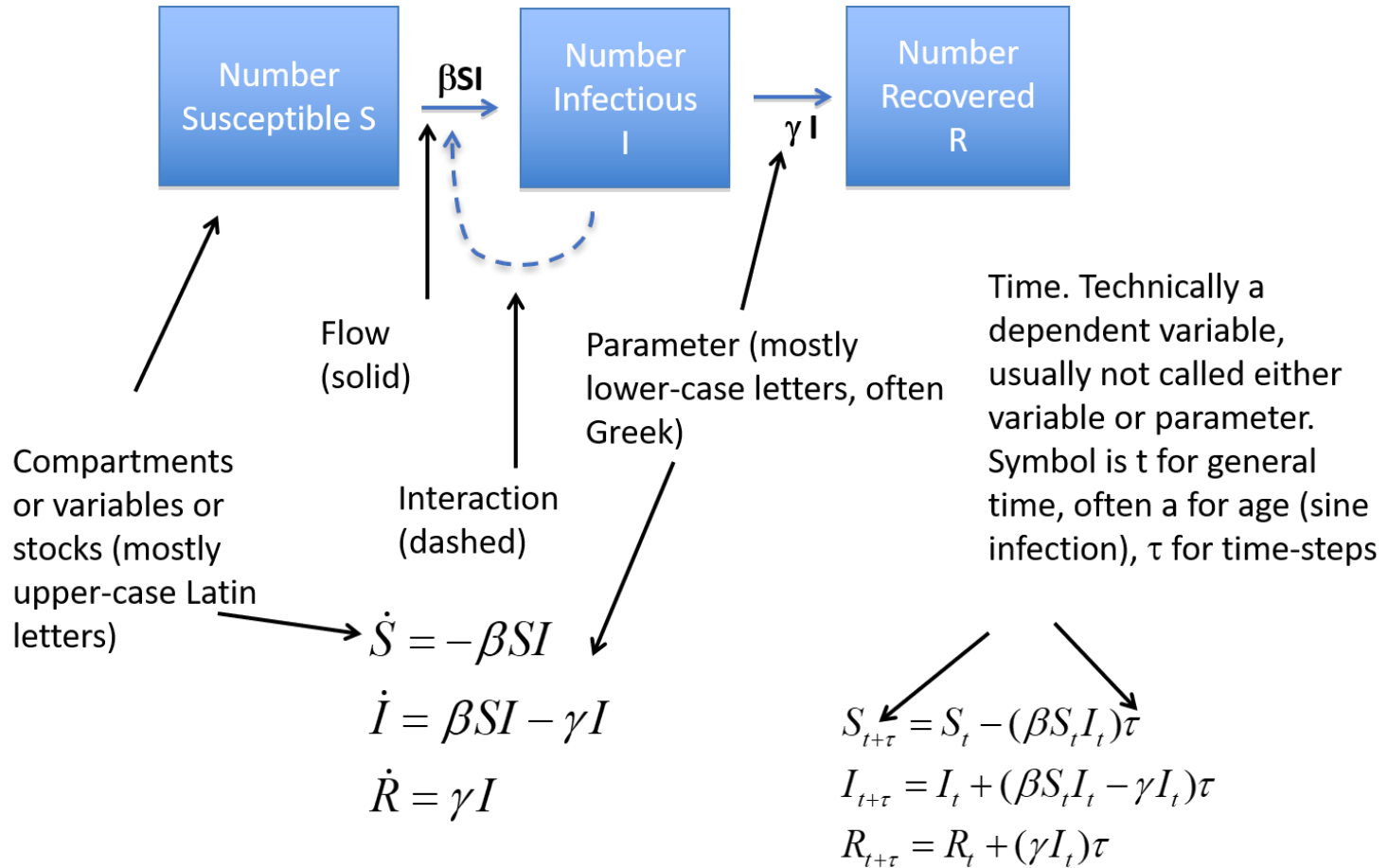
$$\dot{R} = gI - nR$$

$$\dot{x} = \lambda - bx - \beta xz$$

$$\dot{y} = -by - \kappa y + \beta xz$$

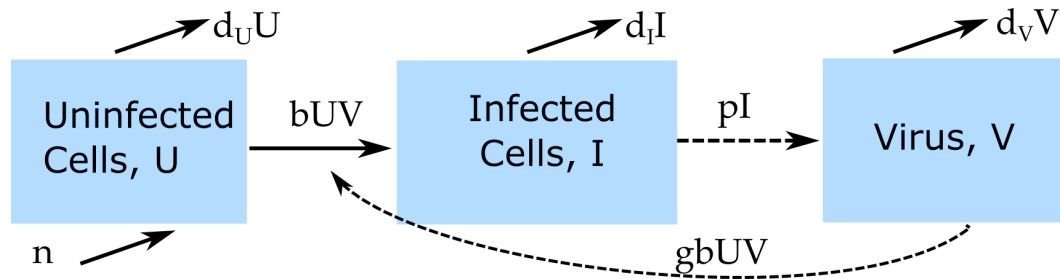
$$\dot{z} = \kappa y - bz$$

Terminology again



A simple virus infection model

A simple virus infection model

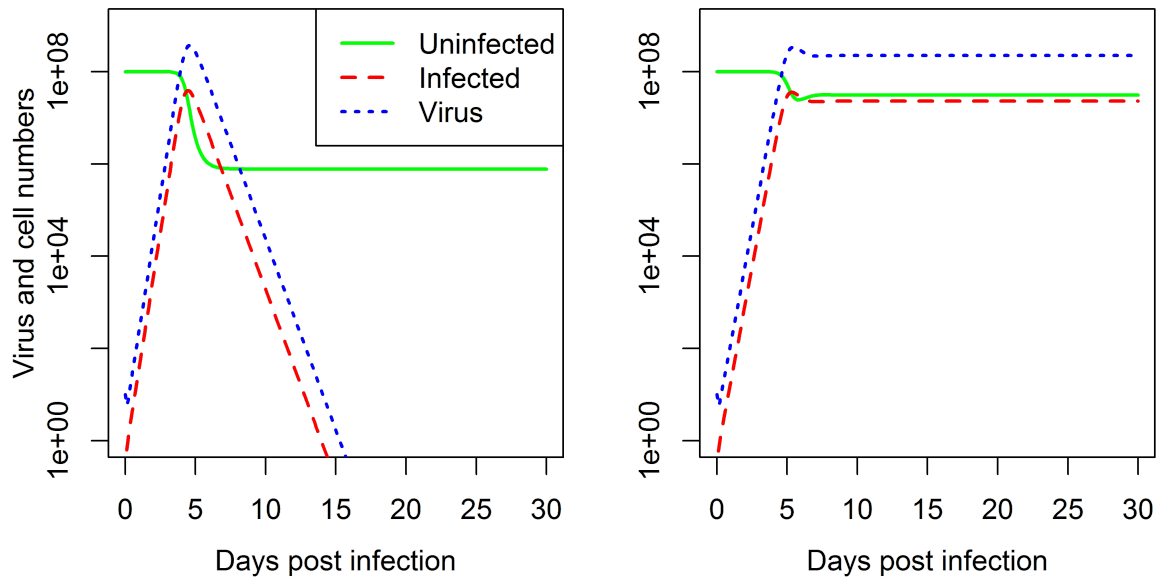


Uninfected Cells $\dot{U} = n - d_U U - bUV$

Infected Cells $\dot{I} = bUV - d_I I$

Virus $\dot{V} = pI - d_V V - gbUV$

A simple virus infection model



Dynamics of simple viral infection models. A) acute infection. B) chronic infection.

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!

$$\dot{T} = s - kT - \beta TV$$

.

$$T^* = \beta TV - dT^*$$

$$\dot{V} = nT^* - cV - \beta gTV$$

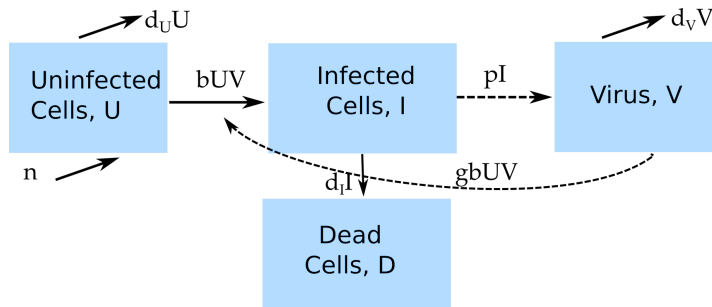
$$\dot{x} = \lambda - dx - \beta xv$$

$$\dot{y} = \beta xv - ay$$

$$\dot{v} = \kappa y - uv - \beta gxv$$

Matching models

Can you spot the differences?

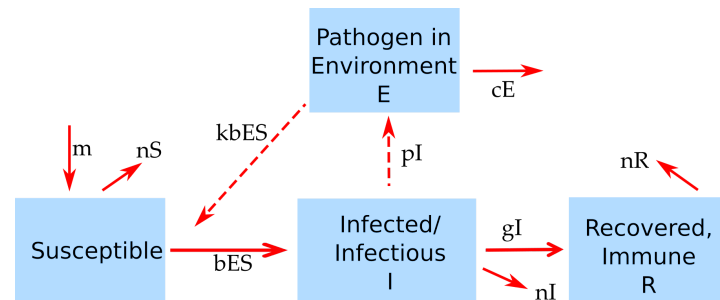


$$\dot{U} = m - d_U U - bUV$$

$$\dot{I} = bUV - d_I I - nI$$

$$\dot{D} = d_I I$$

$$\dot{V} = pI - d_V V - gbUV$$



$$\dot{S} = m - nS - bSE$$

$$\dot{I} = bSE - gI - nI$$

$$\dot{R} = gI - nR$$

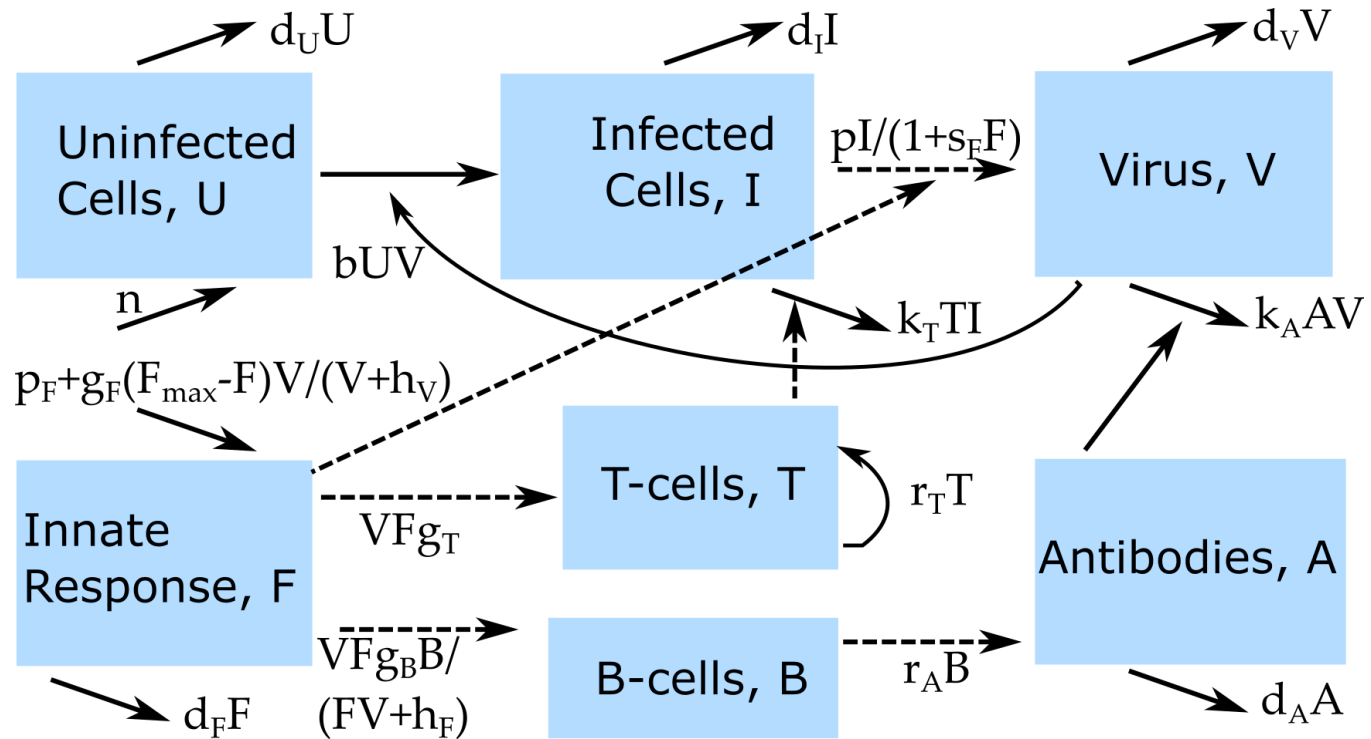
$$\dot{E} = pI - cE - kbSE$$

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



Model Equations

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

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

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

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

$$\dot{T} = FVg_T + r_T T$$

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

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

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.