Introduction to R and Modeling

The 2016 Summer Institute in Statistics and Modeling of Infectious Diseases
Module 6: Infectious Diseases, Immunology and Within-Host Models
Author: Andreas Handel, Department of Epidemiology and Biostatistics, University of Georgia
ahandel@uga.edu

Introduction to R

Software needed for this Module

- R, some additional R packages.
- An editor for R scripts, such as RStudio.
- All programs are cross-platform and freely available online.
- Install R first, then Rstudio.

About R

- R is a “high level” programming language, relatively easy to learn (compared to Fortran, C, etc.)
- R comes with many integrated functions
- R has very good for statistical methods
- R is pretty good for other things (ODEs, data fitting)
- R is Open Source & FREE
- Stable, lots of state-of-the-art packages, pretty good documentation
- Slower than compiled languages (Fortran, C, etc.)

Adding packages to R

- Start Rstudio (which also loads R).
- Click on the “packages” tab in the lower right corner window. Click on “install packages” and enter the names of the packages you want to install.
- For now, we need the package **deSolve.** Other packages we will use are: **lhs, sensitivity, nloptr, boot, GillespieSSA, adaptivetau.** You can install them sometime between now and just before we need them.
- You can see which packages are already installed by typing **library()** at the R prompt (the window to the left).

Learning R

- I wrote the scripts for the hands-on examples we will be doing. You will only need to do minor modifications, so you will not need to know much R.
- **But by knowing/understanding some R, you will get more out of the course!**
- R has many help files included, but those usually assume some level of general R familiarity.
- The R website has manuals/tutorials. You can also search the web, many good ones exist.
- “A beginner’s guide to R” by Zuur et al (2009), Springer.

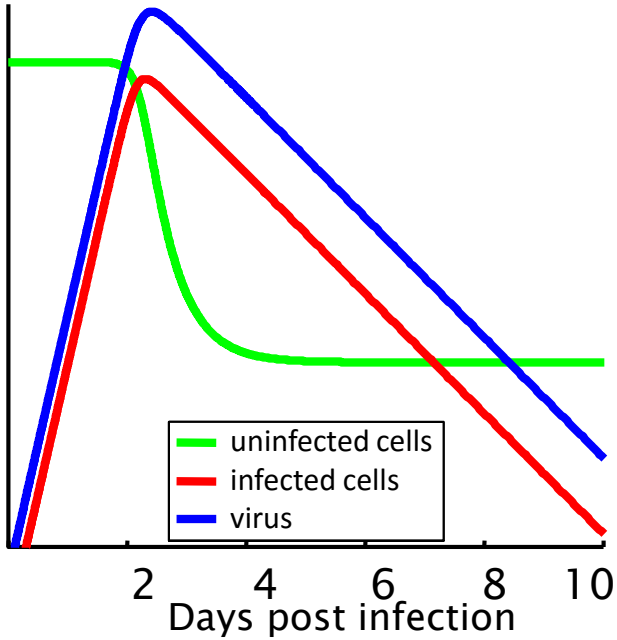
Learning R - YaRI

- I compiled a short R tutorial (called YaRI) : http://handelgroup.uga.edu/resources.htm
- If you know R at the level of what's covered in YaRI, you should be able to understand the code in most scripts.
- If you are less familiar with R, you will still be able to run the examples but you might not quite understand what's going on in the code.

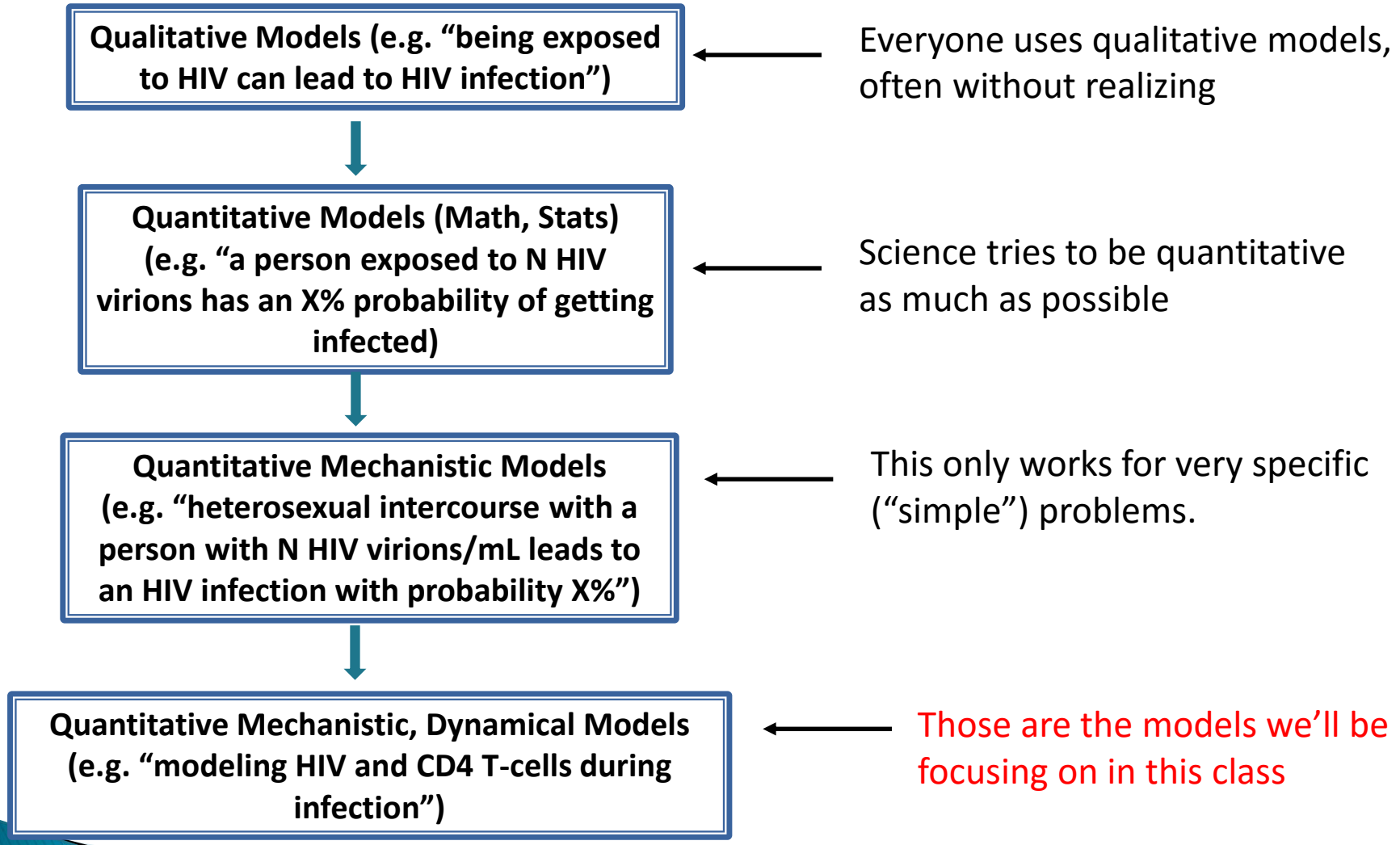
Introduction to Modeling

Modeling – what are we talking about

- For this module, we will consider a specific class of mathematical/computational models:
  - We will look at the dynamics (= changes in time) of a system
  - We will try to model mechanisms that lead to dynamical patterns
  - We will take a system/population perspective



Model Types


Qualitative Models (e.g. "being exposed to HIV can lead to HIV infection")
Everyone uses qualitative models, often without realizing
Quantitative Models (Math, Stats) (e.g. "a person exposed to N HIV virions has an X% probability of getting infected)
Science tries to be quantitative as much as possible
Quantitative Mechanistic Models (e.g. "heterosexual intercourse with a person with N HIV virions/mL leads to an HIV infection with probability X%")
This only works for very specific ("simple") problems.
Quantitative Mechanistic, Dynamical Models (e.g. "modeling HIV and CD4 T-cells during infection")
Those are the models we'll be focusing on in this class

Types of ID models - overview

- The models we will focus on are **dynamical mechanistic models.**
- **Dynamical:** Tracking how things change in time
- **Mechanistic:** Having equations or computer rules that explicitly describe how things happen

Statistical/phenomenological models

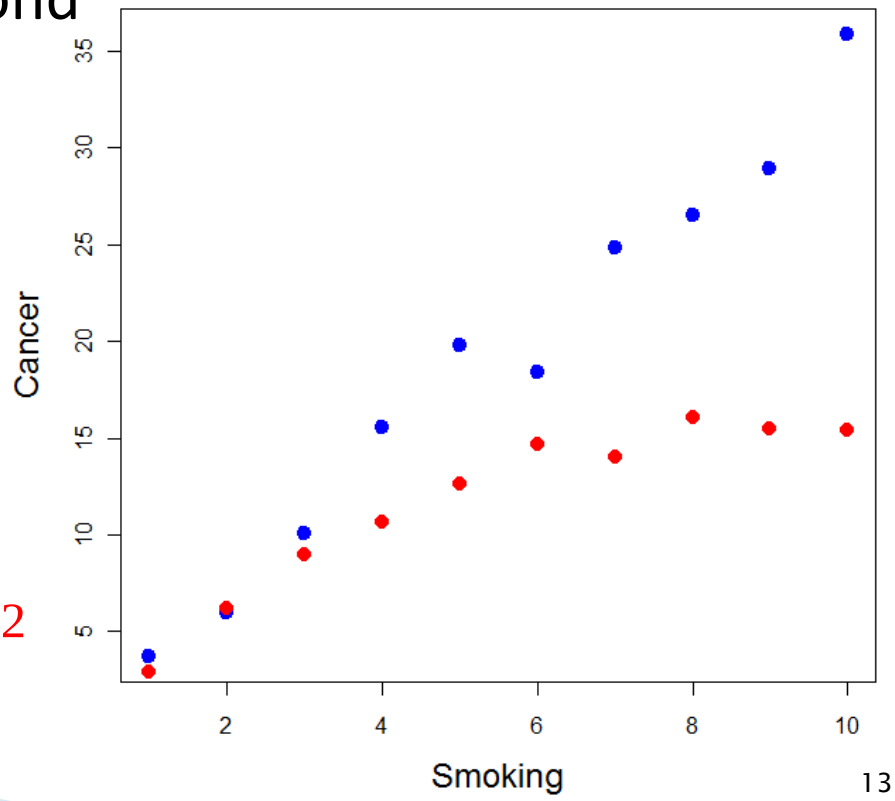
- You might be familiar with statistical models.
- Most of those models are phenomenological/non-mechanistic (and static).
- Those models are used extensively in epidemiology, social sciences, finance, –omics disciplines, etc.
- The main goal of these models is to “understand data” (and make predictions)

Non-mechanistic models

- You are probably familiar with models that are used to analyze data
- Most of those models are phenomenological/non-mechanistic (and static).
- Those models are used extensively in many areas of biomedical sciences and beyond
- We use those models to understand **patterns** in the data and possibly predict.
- **Most statistical models are *non-mechanistic.***

$$C = b_0 + b_1 S$$

$$C = b_0 + b_1 S + b_2 S^2$$

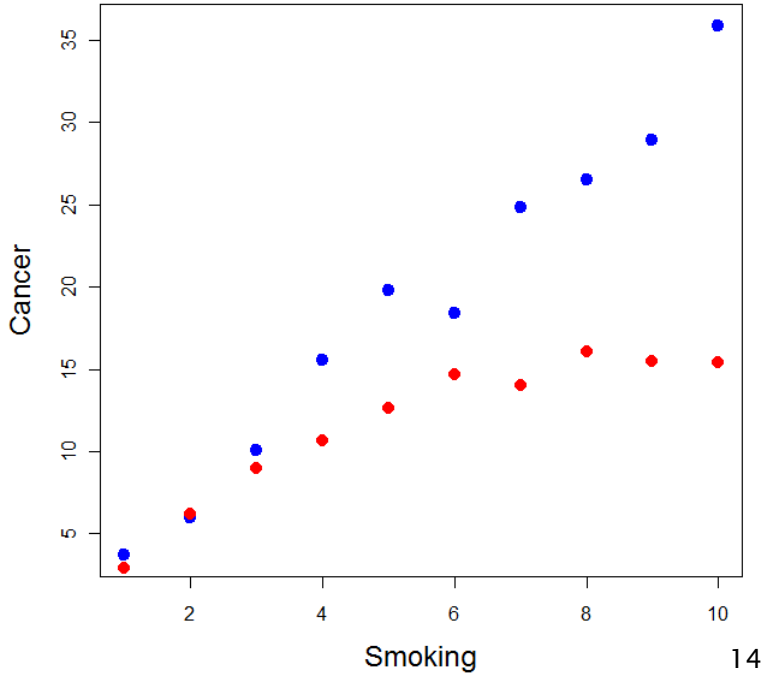


Non-mechanistic models - Advantages

- Finding correlations/patterns is (relatively) simple.
- Sometimes we can go from correlation to causation.
- We don't need to understand the underlying mechanisms. We can determine that input is correlated with (causes) output (e.g. smoking causes cancer) without having to understand ***how.***

$$C = b_0 + b_1 S$$

$$C = b_0 + b_1 S + b_2 S^2$$

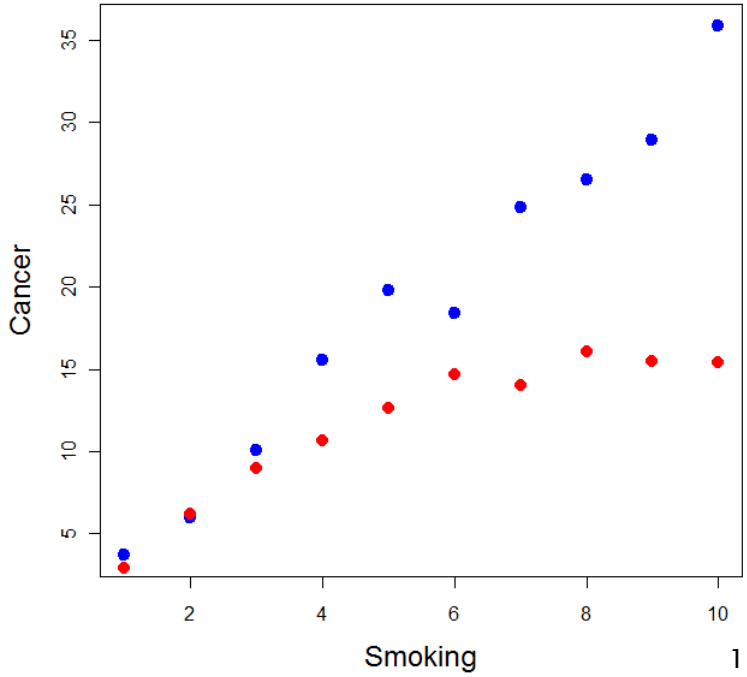


Non-mechanistic models - Disadvantages

- The jump from correlation to causation is always tricky since so many things can go wrong (bias/confounding/systematic errors).
- Even if we can assume a causal relation, we do not gain any mechanistic insights (e.g. we don't know **how** smoking causes cancer).

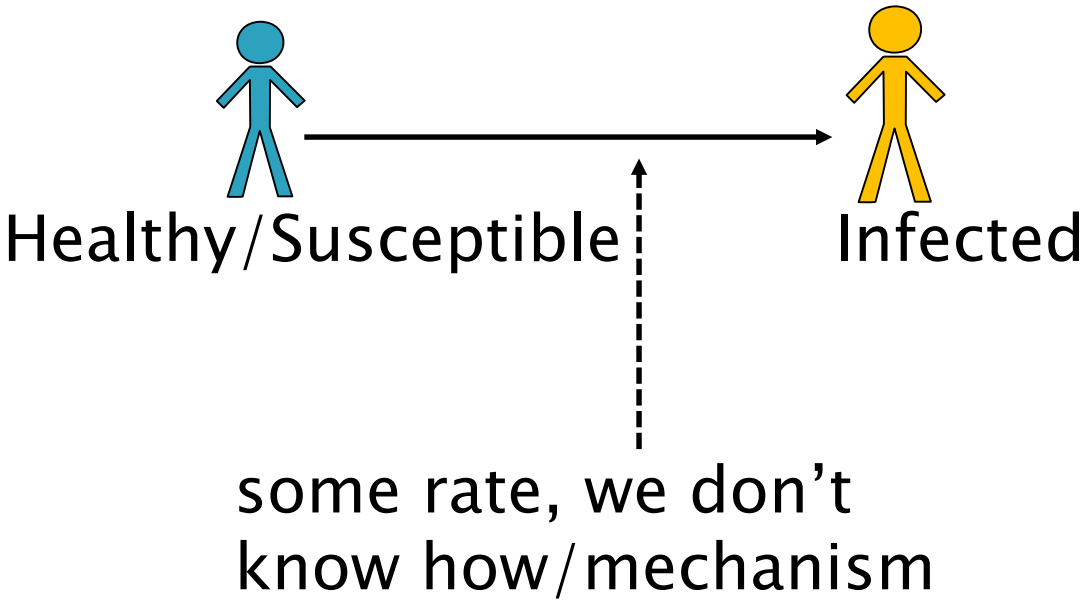
$$C = b_0 + b_1 S$$

$$C = b_0 + b_1 S + b_2 S^2$$



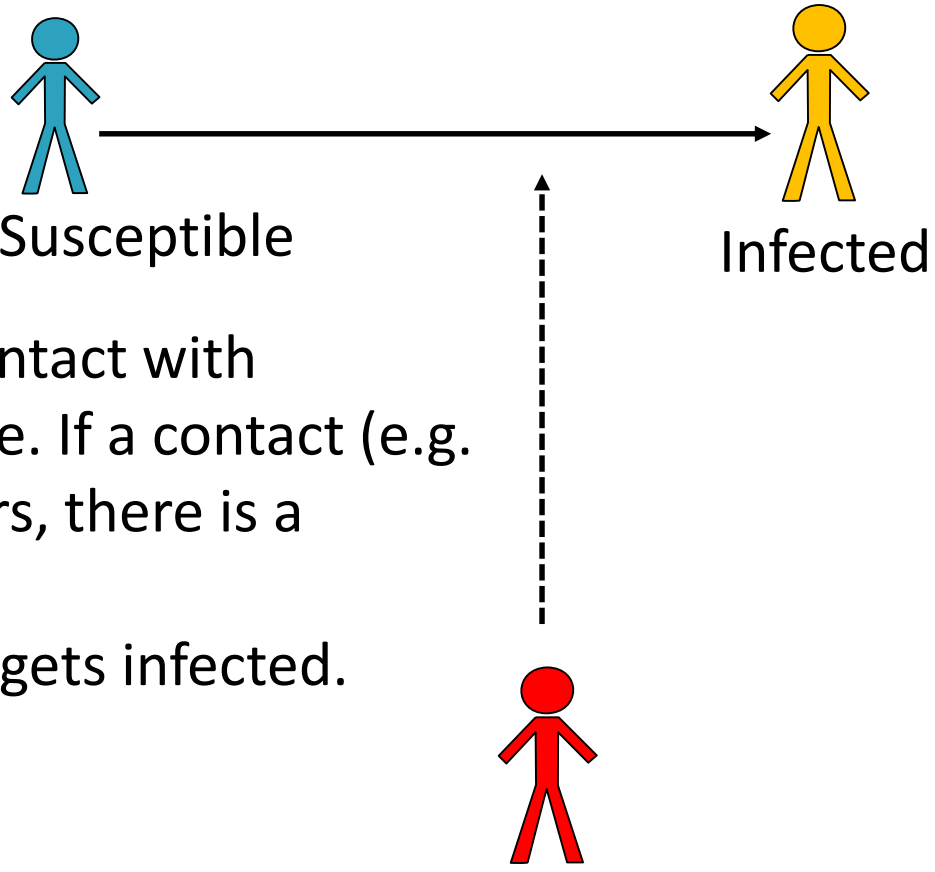
Non-mechanistic ID model

- Assume we are interested in the spread of some ID. In a non-mechanistic model, we say that new cases occur at a given rate, and maybe use our data to estimate that rate



Mechanistic ID model

- In a mechanistic model, we describe and mathematically model the mechanism of getting infected



Healthy person comes in contact with infected person at some rate. If a contact (e.g. sneezing, intercourse) occurs, there is a chance/probability that the healthy/susceptible person gets infected.

Non-mechanistic versus Mechanistic Models

- Non-mechanistic models are useful to see if we can find patterns in our data and possibly predict, without necessarily trying to understand the mechanisms.
- Mechanistic models are useful if we want to study the mechanism(s) by which observed patterns arise.

Mechanistic modeling – why?

- Understanding
  - We can build and analyze models to gain insights into the complex dynamics of infectious diseases
- Prediction & What-if scenarios
  - We can make specific testable predictions
  - We can perform virtual experiments that would be unfeasible to do (costly, lengthy, unethical)
- Hypothesis testing & Parameter Estimation
  - We can use mechanistic models together with data to test different mechanisms/hypotheses
  - We can estimate parameters that are not directly measurable

Types of mechanistic models

Quantitative Mechanistic, Dynamical Models

Many types of quantitative, mechanistic, Dynamical Models exist

Compartmental ↔ Agent-based
Discrete time ↔ continuous time
Deterministic ↔ Stochastic
Space-less (homogeneous) ↔ Spatial
Memory-less (Markov) ↔ with memory
Small ↔ Big
Data-free ↔ With data

Those are the models we'll be focusing on, formulated as Ordinary Differential Equations

Comparison of between and within host

Between-host	Within-host
Spread on the population level (ecology, epidemiology)	Spread inside a host (virology, microbiology, immunology)
Populations of hosts (humans, animals)	Populations of cells & pathogens
Epidemic/Endemic (e.g. Flu/TB)	Acute/Persistent (e.g. Flu/TB)
Often no explicit modeling of pathogen	Usually (but not always) explicit modeling of pathogen

Within-host ID modeling – Brief History

- More recent than between-host modeling.
- HIV garnered a lot of attention starting in the late 80s, some influential work happened in the early 90s (Perelson, Nowak).
- Since then, a fair amount of work on HIV, HCV, HBV (Perelson & Nelson 1999 SIAM Reviews, Perelson 2002 Nat Rev Imm, Nowak and May 2001 Oxford University Press).
- Recently, interest in acute viral infections (flu) (Beauchemin & Handel 2011 BMC Public Health, Smith & Perelson 2011 WIRE)
- A fair amount of work on other major diseases, e.g. TB (Kirschner group), Malaria (Read, others).
- Also since the late 70s, models have been used to study the immune response, mainly T-cells (Antia 2003 Nat Rev Imm, Wodarz 2007 Springer).
- Overall much less work has been done compared to between-host modeling, but it's rapidly growing.

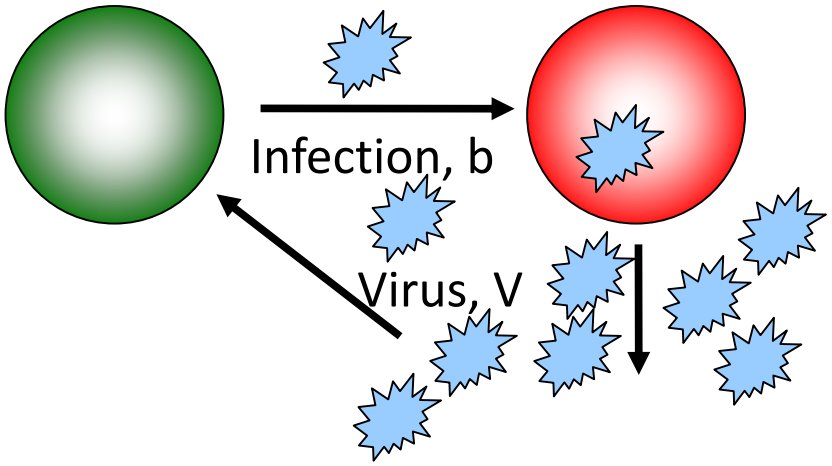
Population Dynamics Perspective

The “systems” of interest

- We will look at the dynamics (= changes in time) of an infection
- We will try to model mechanisms that lead to dynamical patterns
- We will take a system/population perspective
- We need a few main ingredients:
  - The agents/players/entities (e.g. pathogen, immune components)
  - The behavior/characteristics of each agent/entity by itself (e.g. doubling time of cells, rate of clearance of pathogen)
  - The interactions between agents (e.g. infection of a cell by a virus)
  - Characteristics of the “system” (e.g. drug interventions)

The agents/players/entities

- We often do not track individuals but instead describe the behavior of the “average” agent.
- Of course somewhat crude, but often a good starting point.

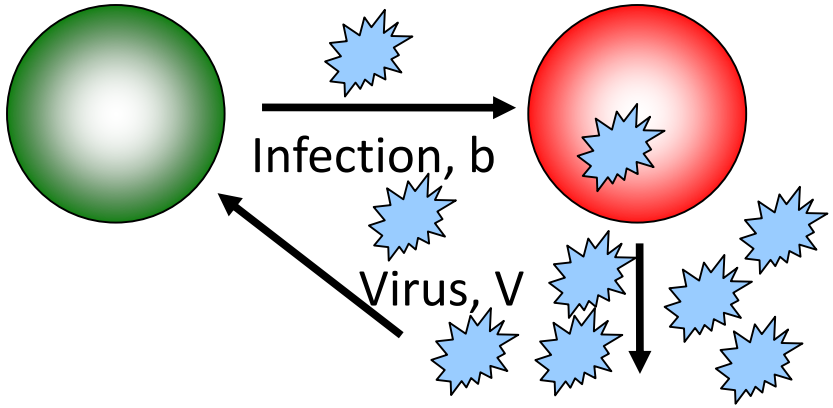


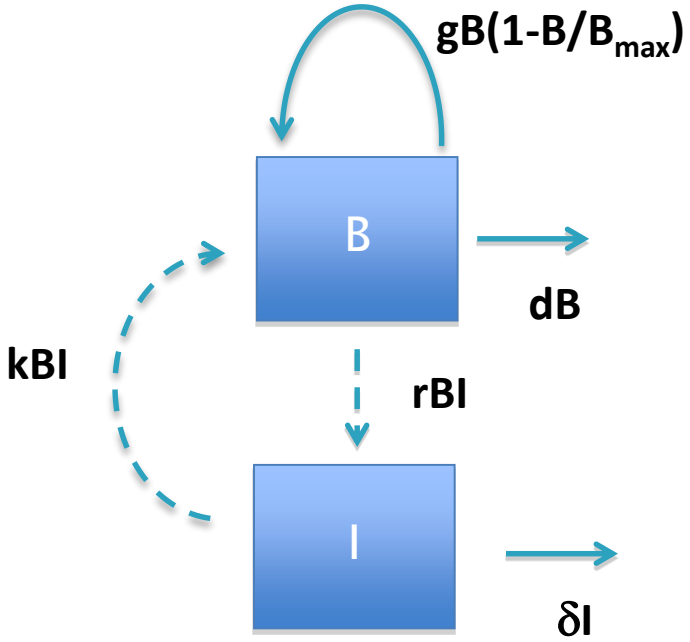
Agent characteristics

- Anything that's intrinsic to each agent and doesn't interact with other agents in the system
- Often these characteristics are considered constant for the purpose of the modeling study
- Examples:
  - Lifespan of a bacteria
  - Rate of cell division
  - Half-life of some cytokine
  - Number of virus particles a cell produces (but: immune response)

Interactions

- What makes our system and models both interesting and complicated is that agents/players interact.
- Host, pathogen and immune response interact in complicated ways. So do different components of the immune response.





System characteristics/behavior

- Anything that's not something the hosts/agents do on their own or through interactions
  - Interventions campaigns (vaccination, drug treatment…)
  - External influences (weather, change in sanitation,…)
- The simplest assumption is that nothing of this sort happens or matters.
- Again, of course not right, but can often be assumed as a first step.

Simple Examples of models

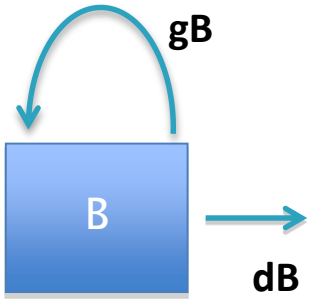
A simple discrete-time model

- Bacteria dynamics (within-host or between-host, e.g. environment)

birth/growth/inflow

death/decay/outflow

$$B_{t+\tau} = B_t + (gB_t - dB_t)\tau$$



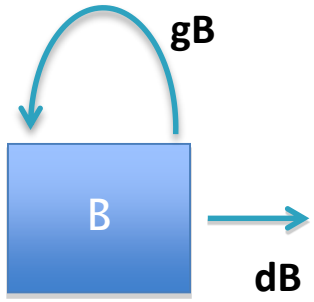
Total number of bacteria at next time step

Total number of bacteria right now

RHS describes how change happens (the mechanisms)

Need to multiply by time step since a larger time step means more events can happen

Discrete time model – worked example



$$B_{t+\tau} = B_t + (gB_t - dB_t)\tau$$

- Assume g=12/hour, d=2/hour, τ=1 hour.
- B at start (t=0) = 100
- What do we get after 1,2,3,4,… hours?

Discrete time models

- The system is updated in discrete time-steps.
- Good for systems where there is a “natural” time step
  - Example: Some pathogens have a more-or-less fixed replication cycle (e.g. ≈24h for Plasmodium falciparum).
  - Example: For some animals, births occur during a small period in spring. Modeling the long-term dynamics of an ID in such a population might lend itself to a model that is updated annually.
- Complex models, such as Agent-based simulations are almost always discrete-time (for computational reasons).
- For simple models where we track the total populations (instead of individuals), discrete-time models are not that commonly used. Continuous-time models, usually formulated as ordinary differential equations (ODE), are more common.
- If the time-step becomes small, a discrete-time model approaches a continuous-time model.

Ordinary Differential Equations (ODE)

- ODEs can be derived as the continuum limit of discrete models:

$$B_{t+\tau} = B_t + (gB - dB)\tau \xrightarrow[\text{rewrite}]{} \frac{B_{t+\tau} - B_t}{\tau} = (gB - dB)$$

$$\frac{B_{t+\tau} - B_t}{\tau} = (gB - dB) \xrightarrow[\tau \to 0]{} \frac{dB(t)}{dt} = gB(t) - dB(t)$$

or

$$\dot{B} = gB - dB$$

Ordinary Differential Equations (ODE)

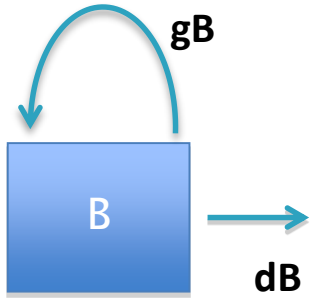
- Often, ODEs are derived as the continuum limit of discrete models:

The computer uses this

$$B_{t+\tau} = B_t + (gB - dB)\tau$$

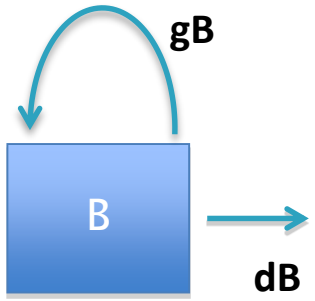
We often can/could do math with this

$$\dot{B} = gB - dB$$



Same flow diagram for both models

Continuous time models - Notation



$$\frac{dB(t)}{dt} = gB(t) - dB(t)$$

$$\frac{dB}{dt} = gB - dB$$

$$\dot{B} = gB - dB$$

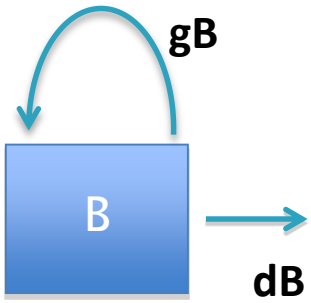
A simple model

- Bacteria dynamics

birth/growth/inflow

death/decay/outflow

$$\dot{B} = gB - dB$$



LHS is the change in a variable/compartment

RHS describes how change happens (the mechanisms)

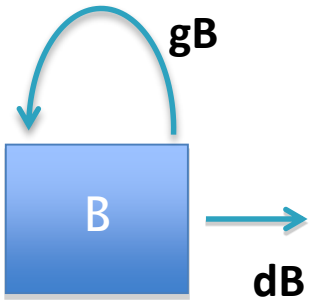
A simple model

- Bacteria dynamics

birth/growth/inflow

death/decay/outflow

$$\dot{B} = gB - dB$$



LHS is the change in a variable/compartment

RHS describes how change happens (the mechanisms)

- How could we implement saturating growth?

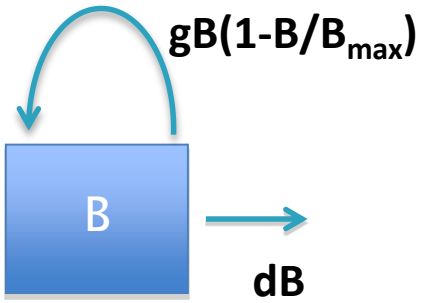
A simple model

- Bacteria dynamics

Saturating
birth/growth/inflow

death/decay/outflow

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



LHS is the change in a variable/compartment

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A simple model

- Bacteria dynamics

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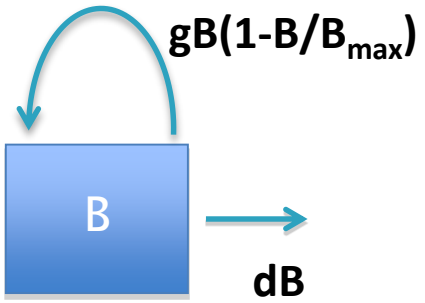


LHS is the change in a variable/compartment

RHS describes how change happens (the mechanisms)

- What equation could we add to describe some (abstract) immune response?

A simple model

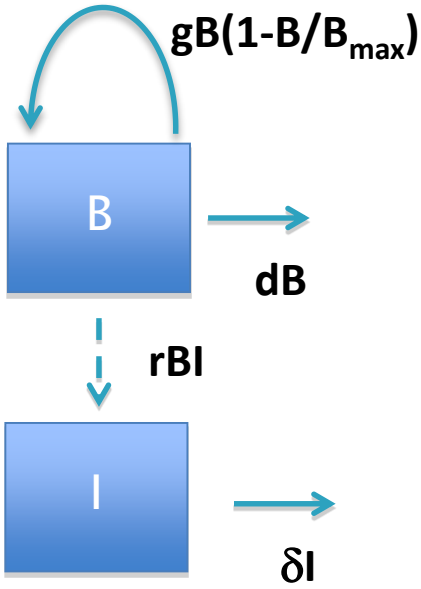
- Bacteria dynamics with immune response (IR)

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

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

Immune response (IR)

Mechanisms of IR dynamics



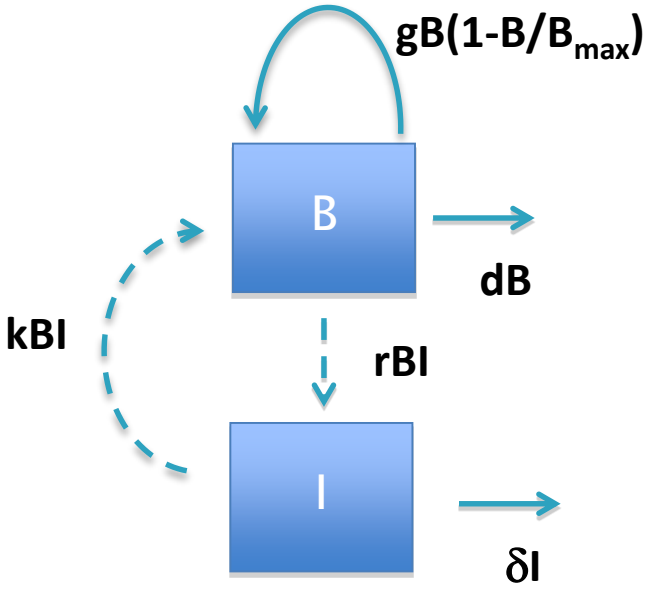
- What's missing?

A simple model

- Bacteria dynamics with immune response (IR)

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

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



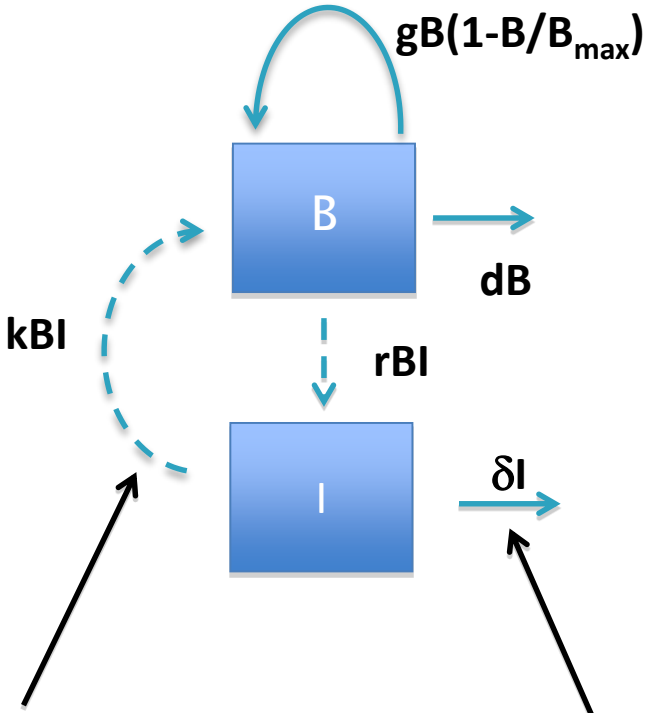
- (Predator-prey model)

A simple model

- Bacteria dynamics with immune response (IR)

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

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



Dashed: System interactions, not necessarily flows

"actual/physical" flows

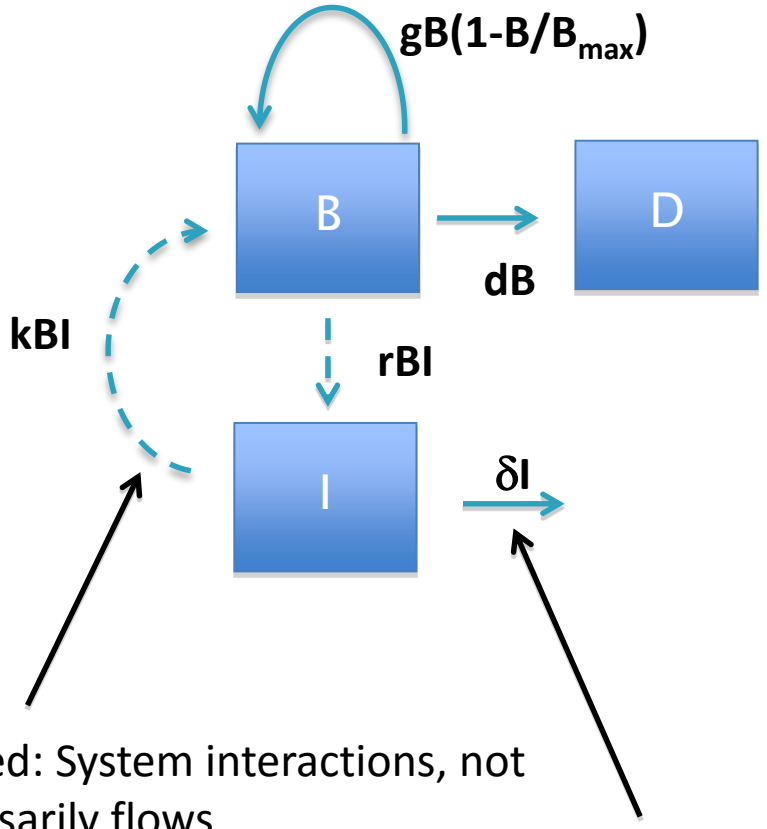
A simple model

- Bacteria dynamics with immune response (IR)

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

$$\dot{D} = dB + kBI$$

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



Dashed: System interactions, not necessarily flows

"actual/physical" flows

Defining parameters

- To fully specify a model, we need to pick values for the parameters.
- Parameter values are chosen based on what we know about the biology of the infection.
- We can choose our unit of time (hours, days, weeks,…), we just have to be careful that our parameters are in agreement.
- Good practice: Pick a unit of time that makes sense for the disease, e.g. days or weeks for flu, measles, months or years for TB, HIV.

Parameter	Value [Units]	Comment
g	1 [1/day]	bacteria growth rate
B_{max}	1E6 [Bacteria units]	max bacteria load
d	0.1 [1/day]	bacteria death rate
k	1E-7 [1/(day*IR units)]	bacteria killing rate
r	1e-3 [1/(day*Bacteria units)]	IR activation/growth rate
δ	1 [1/day]	IR death/decay rate

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

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

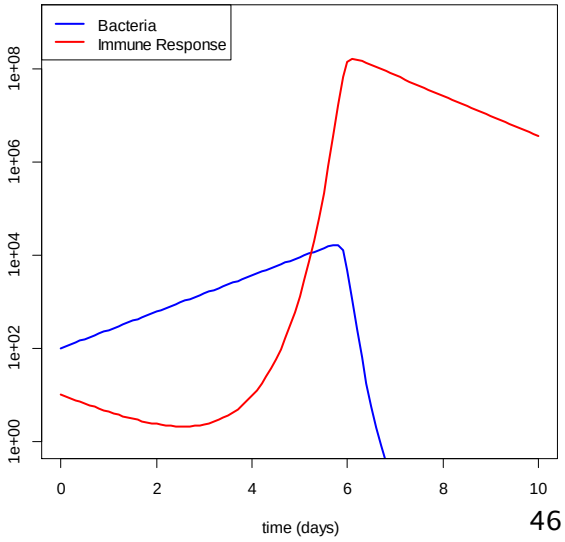
Choosing initial conditions

- Once we have defined parameters, we also need to set initial conditions for the variables to be able to run the model.
- Start time: Arbitrary, using t=0 at the beginning makes sense.

Compartment	Initial condition symbol	Initial condition value
Bacteria	$B(t=0)=B(0)=B0=B_0$	100
Immune Response	I0	10

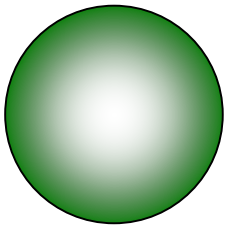
Simple bacteria model - R Example

- Open the file **SISMID-U2-bacteria.r** in RStudio.
- Read through the program and try to understand it.
- Run the script by pressing the "Source" button.
- Change some of the parameter values *(g, B_{max}, d, k, r, δ)*, save the file. Then run the program again with the **source** button. Do that a few times to see how different parameter values affect your results.

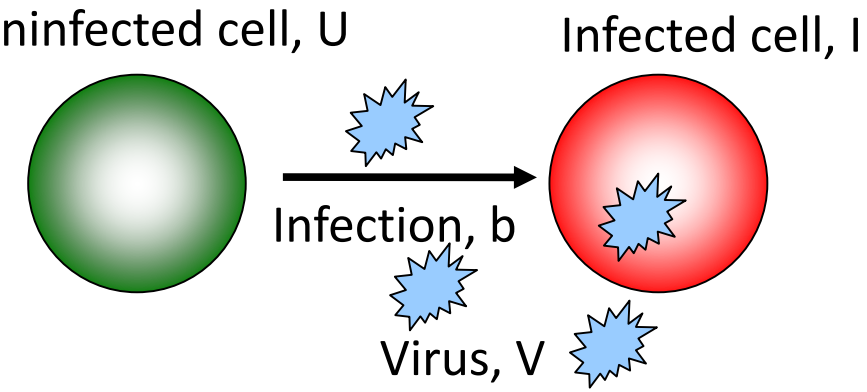


Simple model for acute virus infection

Uninfected cell, U



Simple model for acute virus infection

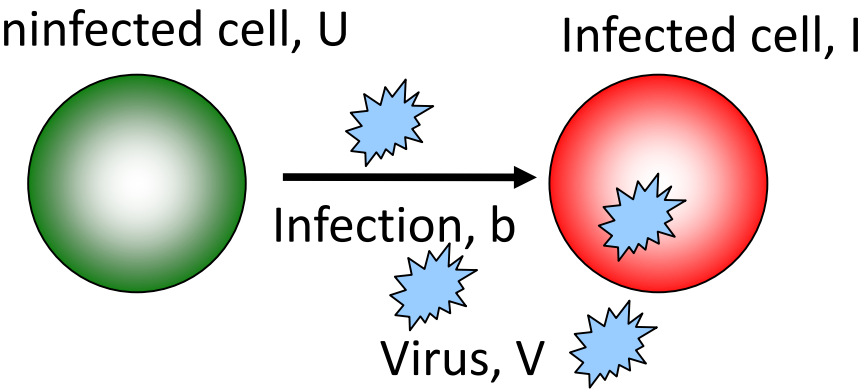


$$\frac{dU}{dt} = -bUV \qquad \text{(uninfected cells)}$$

$$\frac{dI}{dt} = bUV \qquad \text{(infected cells)}$$

$$\frac{dV}{dt} = -bUV \qquad \text{(free virus)}$$

Simple model for acute virus infection

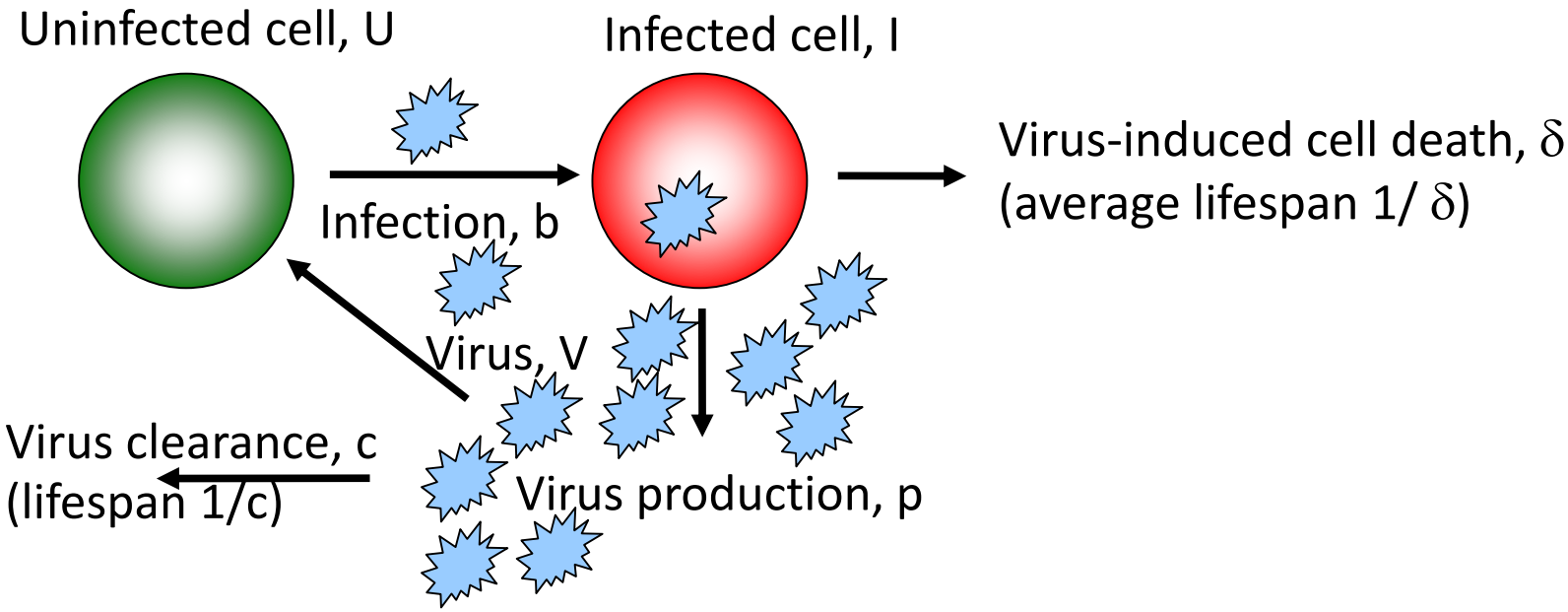


$$\dot{U} = -bUV \quad \text{(uninfected cells)}$$

$$\dot{I} = bUV \quad \text{(infected cells)}$$

$$\dot{V} = -bUV \quad \text{(free virus)}$$

Simple model for acute virus infection

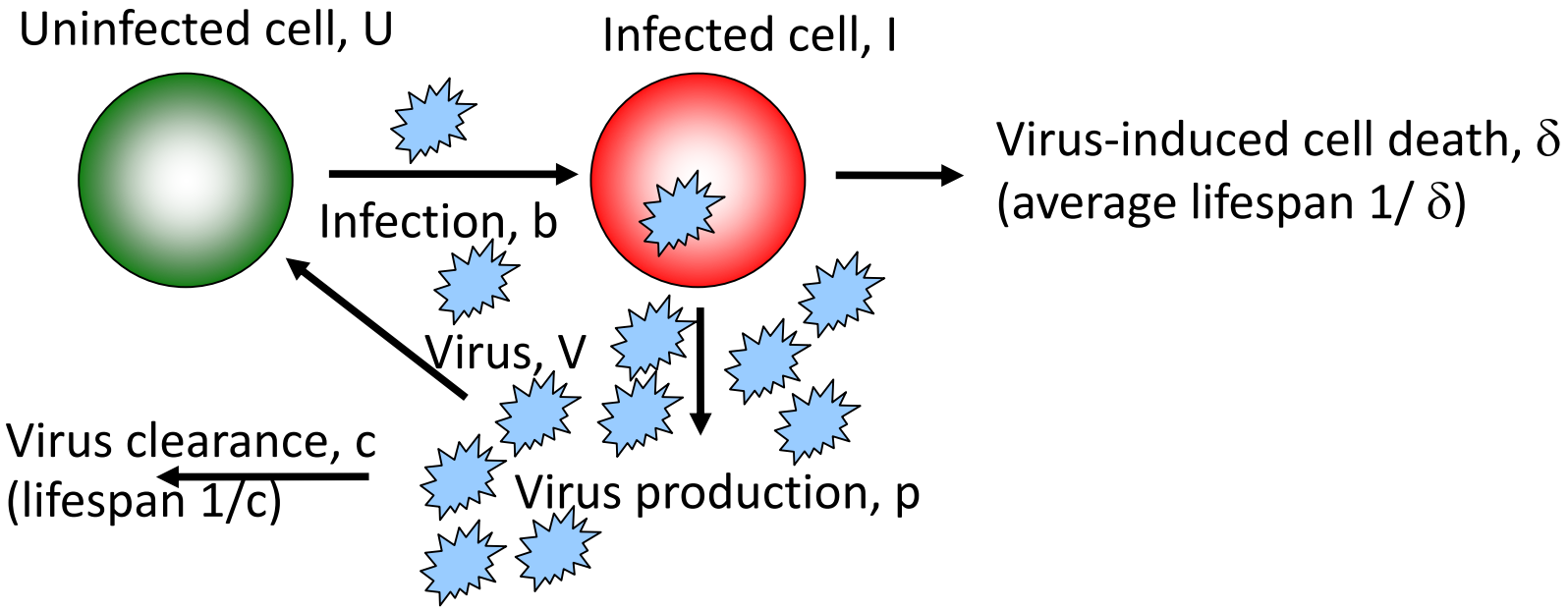


$$\dot{U} = -bUV \qquad \text{(uninfected cells)}$$

$$\dot{I} = bUV - \delta I \qquad \text{(infected cells)}$$

$$\dot{V} = pI - cV - bUV \qquad \text{(free virus)}$$

Simple model for acute virus infection



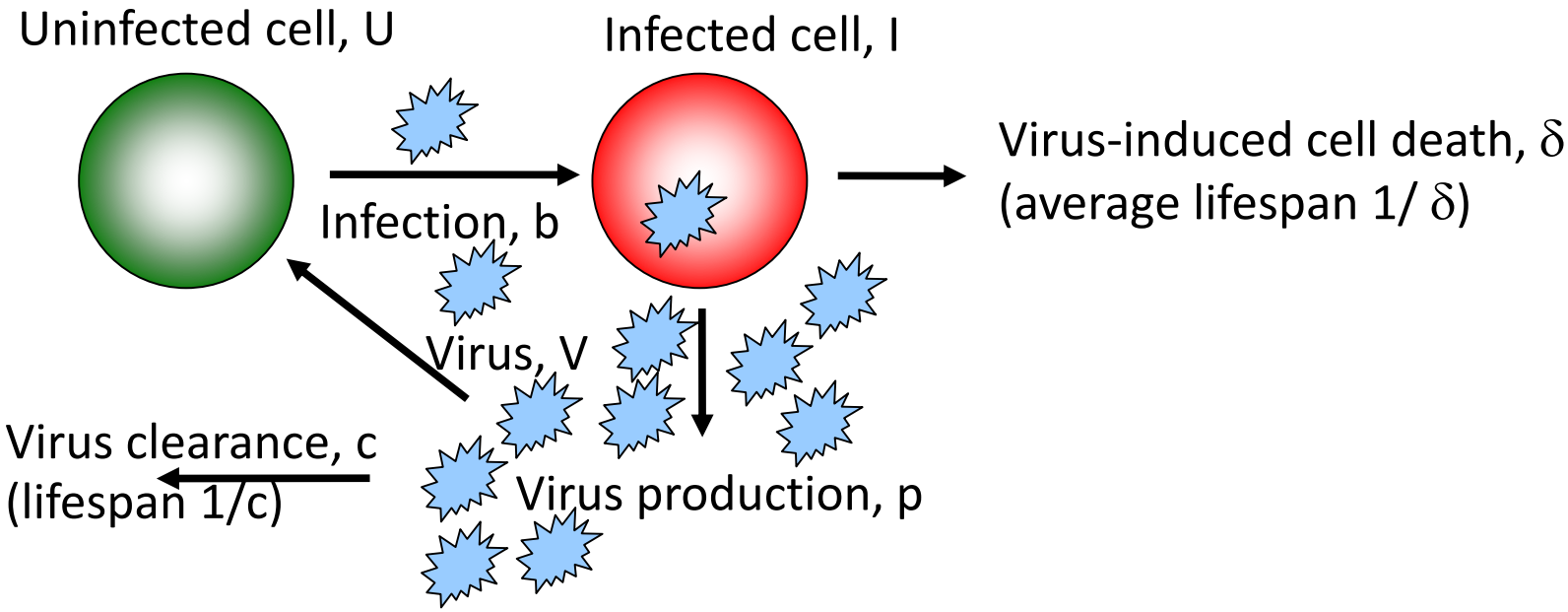
$$\dot{U} = -bUV \qquad \text{(uninfected cells)}$$

$$\dot{I} = bUV - \delta I \qquad \text{(infected cells)}$$

$$\dot{V} = pI - cV - bUV \qquad \text{(free virus)}$$

Sometimes, but not always ok to ignore

Simple model for acute virus infection



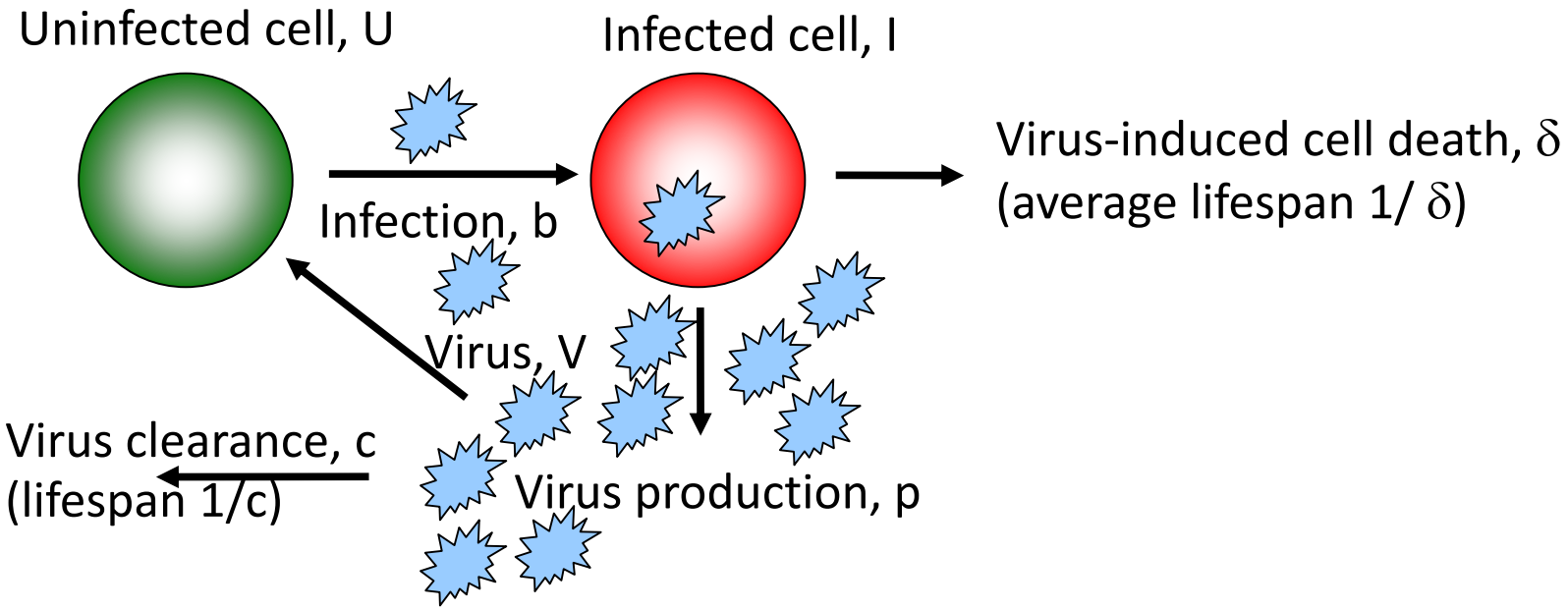
$$\dot{U} = -bUV \qquad \text{(uninfected cells)}$$

$$\dot{I} = bUV - \delta I \qquad \text{(infected cells)}$$

$$\dot{V} = pI - cV - \gamma bUV \qquad \text{(free virus)}$$

Might be needed if we express virus load not in units of infectious virions, but something else (for instance Plaque Forming Units, as done in experiments)

Simple model for acute virus infection



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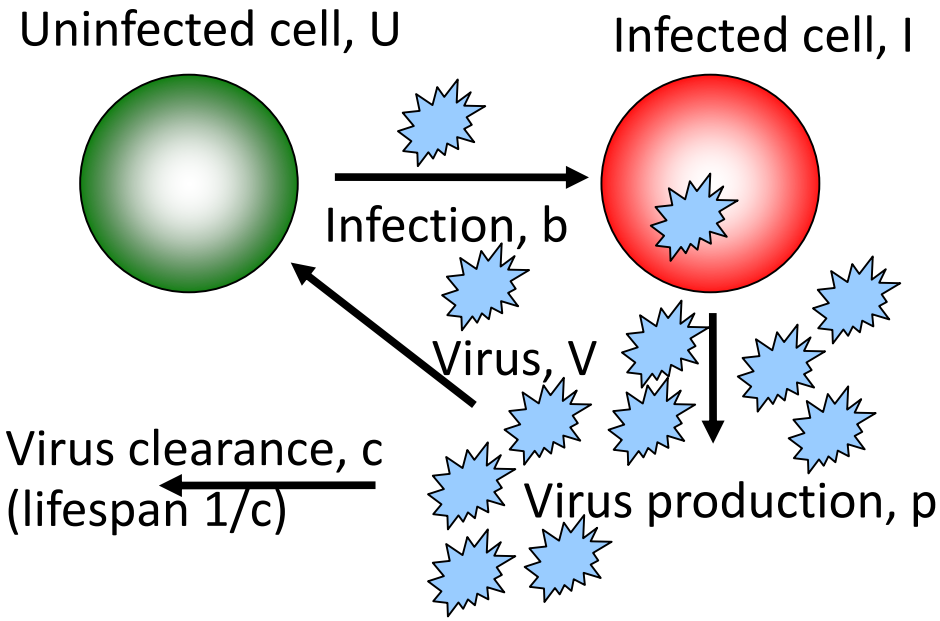
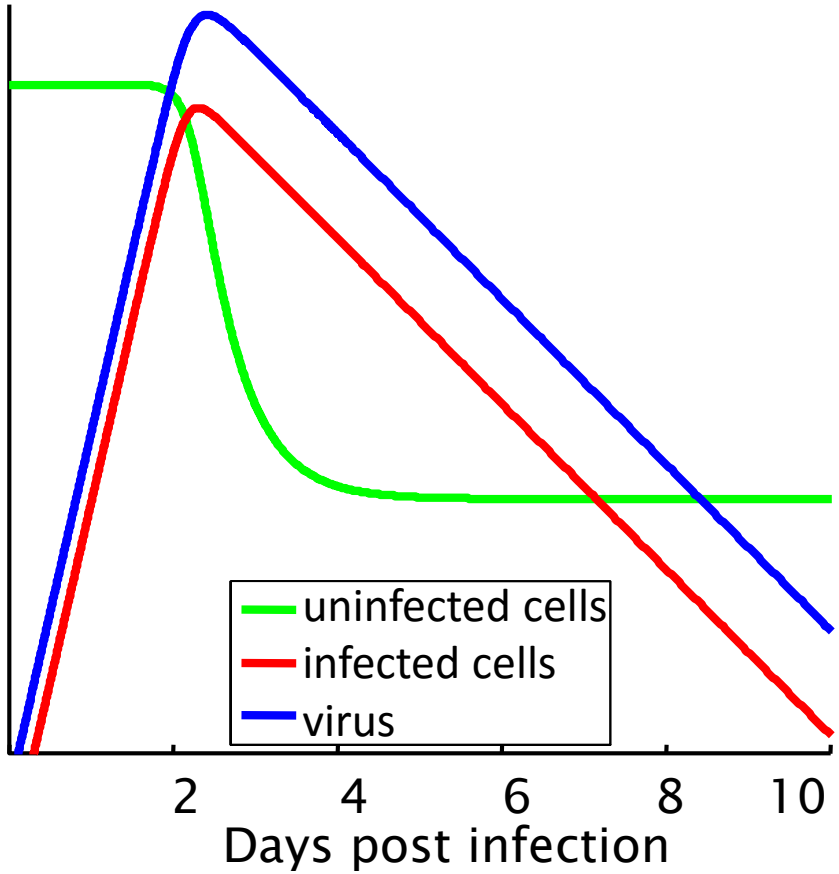
Simple model for acute virus infection



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

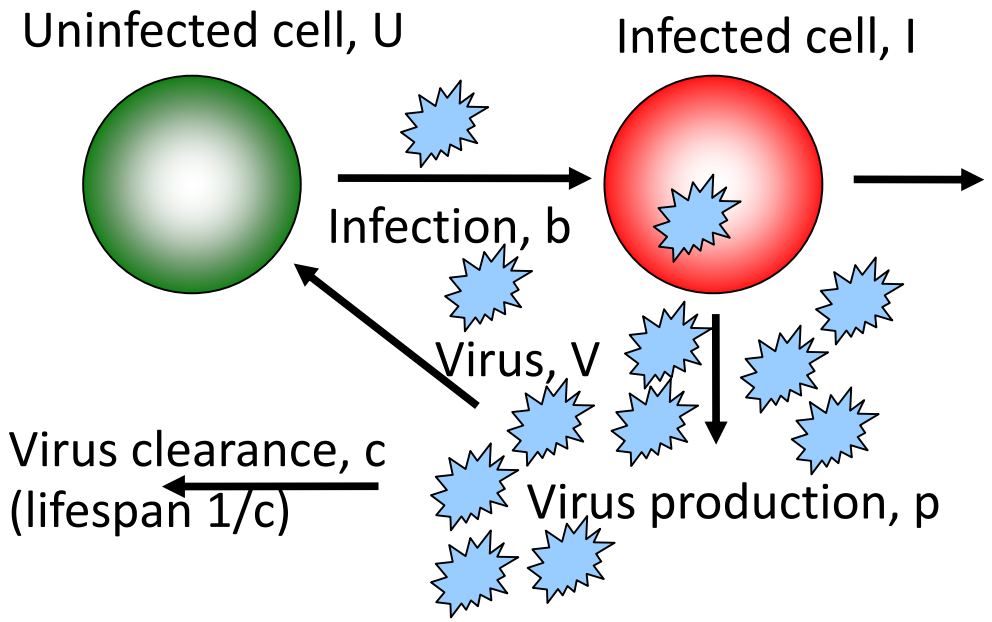
$$\dot{I} = bUV - \delta I$$

$$\dot{V} = pI - cV$$



Diagrams and equations

- It's often useful to go from figures/diagrams to equations and back.
- For this model, I used pretty(?) figures



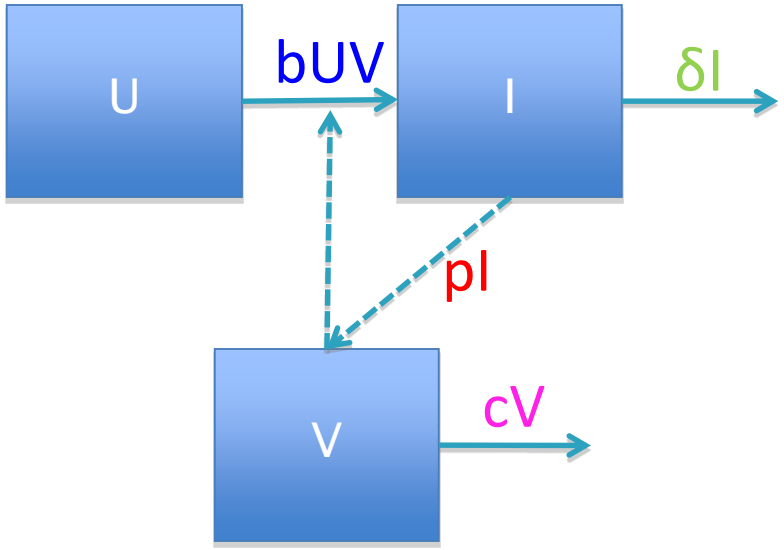
$$\dot{U} = -bUV$$

$$\dot{I} = bUV - \delta I$$

$$\dot{V} = pI - cV$$

Diagrams and equations

- Another way to illustrate equations is to draw box diagrams.



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

Change of hosts in each compartment at a given time

$$\dot{I} = bUV - \delta I$$

Specifying the change: Influx and outflow for each compartment

$$\dot{V} = pI - cV$$

A word on notation

- I'm trying to be (somewhat) consistent
- If you go to the literature, you will find many different notations

$$\dot{T} = s - \nu T - \beta TV \quad \text{(uninfected target cell)}$$
$$\dot{T}^* = \beta TV - dT^* \quad \text{(infected target cells)}$$
$$\dot{V} = NdT^* - cV \quad \text{(free virus)}$$

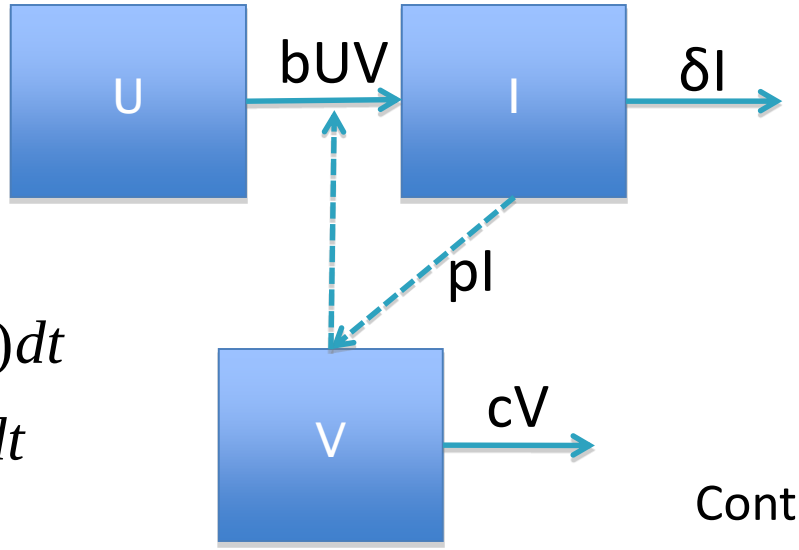
$$\dot{x} = \lambda - dx - \beta xv \quad \text{(uninfected cells)}$$
$$\dot{y} = \beta xv - ay \quad \text{(infected cells)}$$
$$\dot{v} = \kappa y - uv \quad \text{(free virus)}$$

Diagrams and Models

- If we show a model with boxes, we usually imply that we use a compartmental model where we track total numbers in each box/compartment but not individuals.
- We did not specify some other aspects of implementation.

Discrete in time,
Difference Equation

$$U_{t+dt} = U_t - (bUV)dt$$
$$I_{t+dt} = I_t + (bUV - \delta I)dt$$
$$V_{t+dt} = V_t + (pI - cV)dt$$



$$\dot{U} = -bUV$$
$$\dot{I} = bUV - \delta I$$
$$\dot{V} = pI - cV$$

Continuous in time, ODE

Simple virus model - R Example

- Open **SISMID-U2-virus.r**
- The script implements the simple virus model as discrete time and continuous time models.
- Read through the program and try to understand it.
- See how results change as you change some of the parameter values.
- Play around with the time step for the discrete model and see what it does.
- You can also change some of the initial conditions (U0, I0, V0).

Discussion

- Mechanistic, dynamical models are useful for studying infectious diseases.
- Such models come in all kinds of forms.
- Models can quickly become complex and hard to analyze. For within-host models, one of the main "source of complexity" is the immune response.
- No matter how detailed, a model is always a simplified abstractions of the real biology/system.
- Finding the right model (type, complexity) for the question at hand is the challenge and "art" of modeling.

What's next

- We will revisit and extend the models discussed here in various ways as we study specific pathogens (HCV, HIV, Influenza, Malaria, TB) in some more detail.
- We will discuss more details about the biology of the within-host infectious disease processes for those pathogens.
- We will apply models to these pathogens to gain general conceptual insights, to study treatment/intervention and to estimate parameters.
- We will focus on compartmental, deterministic ODE models.
- We will spend one session briefly going over alternative (more complicated) modeling approaches.

Further reading – modeling in biology

- *Britton (2003) "Essential mathematical biology" Springer:* Relatively easy, not too math heavy.
- *Allman and Rhodes (2004) "Mathematical Models in Biology: An Introduction" Cambridge U Press:* Integrates MATLAB into the text/exercises.
- *Ellner and Guckenheimer (2006) "Dynamic Models in Biology" Princeton University Press:* Nice integration of mathematical analysis and computer modeling, topics very broad.
- *Otto and Day (2007) "A Biologist's Guide to Mathematical Modeling in Ecology and Evolution" Princeton University Press:* Some good background/primers on math topics, explanations on how to model, not much infectious disease specific material.

Further reading – within-host

- *Nowak and May (2000) "Virus dynamics" Oxford U. Press*
- *Anderson and May (1991) "Infectious Diseases of Humans – Dynamics and Control" Oxford U. Press*
  Keeling and Rohani (2008) "Modeling Infectious Diseases" Princeton U. Press
  (these books are about ID modeling on the population level, not individual hosts. But a lot of the concepts and math/equations are the same)
- *Alan Perelson (2002) "Modelling Viral and Immune System Dynamics", Nature Reviews Immunology*
- A few names in the field: Rustom Antia, Becca Asquith, Rob de Boer, Sebastian Bonhoeffer, Denise Kirschner, Angela McLean, Martin Nowak, Alan Perelson, Ruy Ribeiro, Dominik Wodarz, many more….