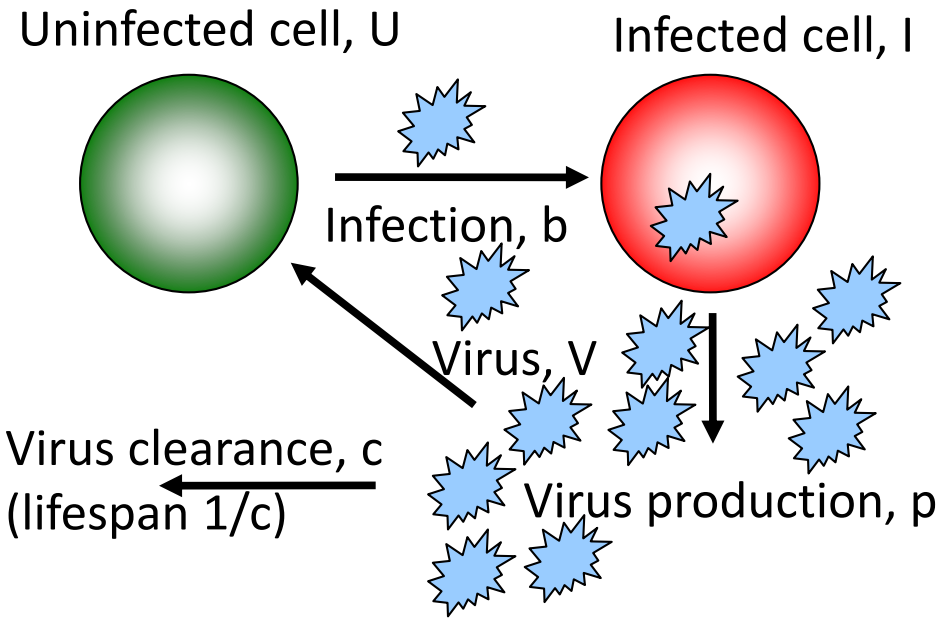
Modeling HCV and HIV

2017 MITII Summer School on Immune Response Modeling

Author: Andreas Handel, Department of Epidemiology and Biostatistics, University of Georgia
ahandel@uga.edu

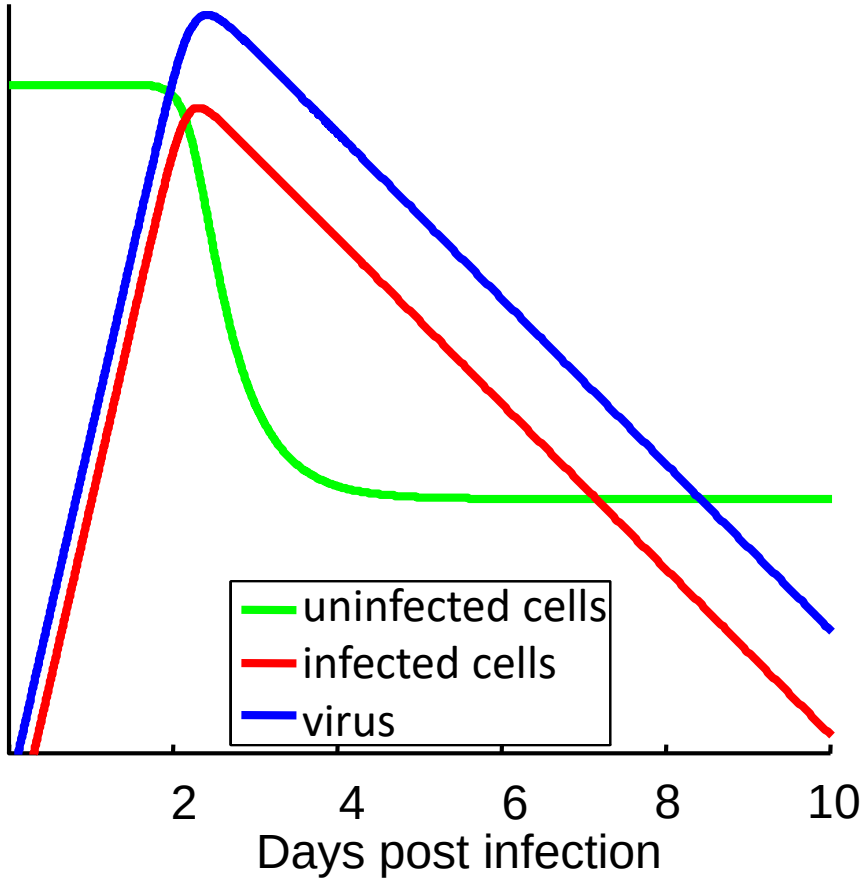
Recap – acute viral infection



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

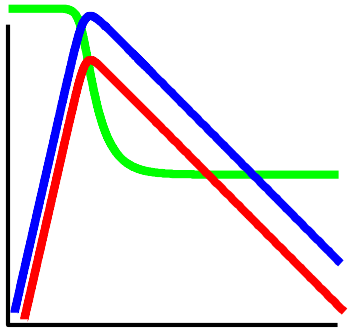
$$\dot{I} = bUV - \delta I$$

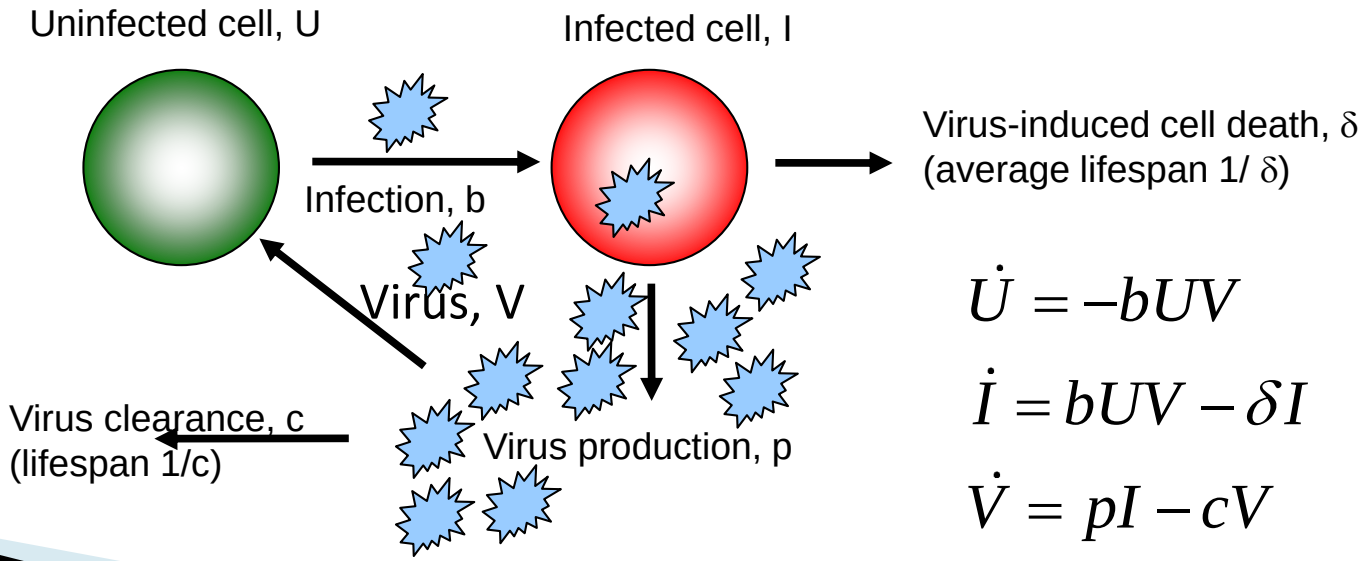
$$\dot{V} = pI - cV$$



Modeling a persistent virus infection

- So far, our model only describes an acute virus infection (e.g. influenza)
- How can we extend the model to allow for persistent infections (e.g. HCV, HIV)?





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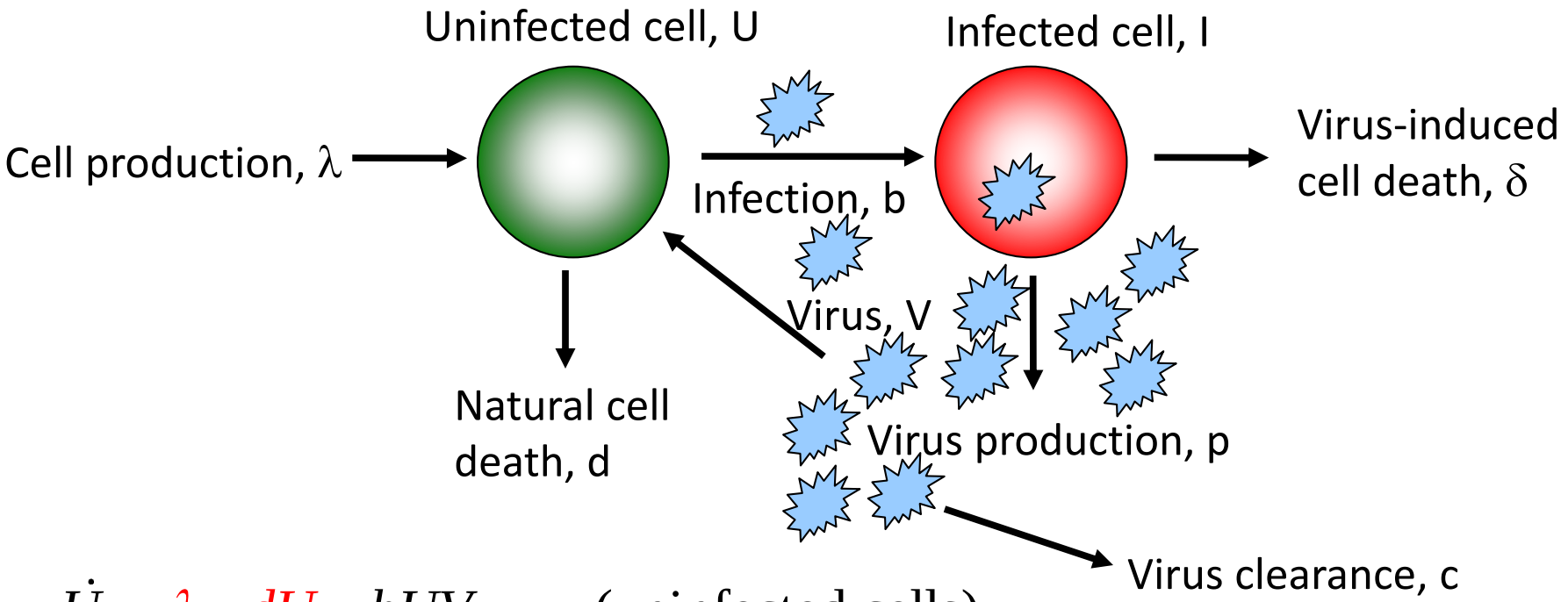
Modeling a persistent virus infection



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

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

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

Steady states

- At a steady state (endemic state, equilibrium), the population numbers don't change.
- What does that mean for our model equations?

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

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

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

Steady states

- At a steady state, the populations/variables do not change: $\dot{U} = \dot{I} = \dot{V} = 0$
- The differential equations now become algebraic equations and we can solve for the variables at steady state.

$$\dot{U} = 0 = \lambda - dU - bUV \quad \text{(uninfected cells)}$$
$$\dot{I} = 0 = bUV - \delta I \quad \text{(infected cells)}$$
$$\dot{V} = 0 = pI - cV \quad \text{(free virus)}$$

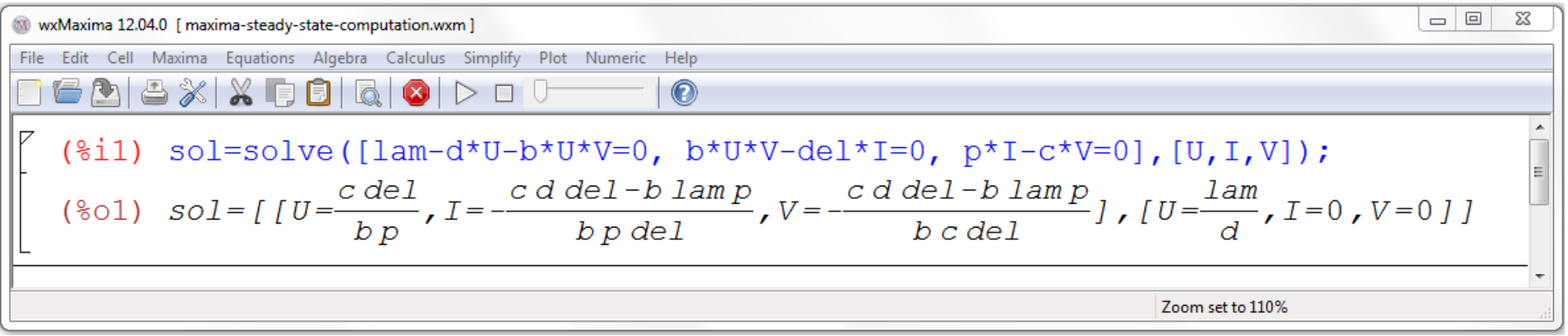
- What do we need to do?

Quick detour – analytical calculations

- Finding the value of 3 variables from 3 simple algebraic equations is straightforward and can be done analytically.
- Even if things are straightforward, they can sometimes be tedious/messy – it would be nice if we didn't have to do it by hand.
- R can't do analytical calculations, but other software packages can. The "big 2" are Maple and Mathematica. Both can do lots of stuff and are relatively expensive.
- A free alternative is Maxima (http://maxima.sourceforge.net/). It's not as powerful as Mathematica/Maple, but if you just need to do a few simple analytical calculations, it might be good enough.
- Other packages seem to exist, see: http://en.wikipedia.org/wiki/Comparison_of_computer_algebra_systems - but I don't have experience with any others.

Quick detour – analytical calculations

- The Maxima code to compute the steady state:



$$\dot{U} = 0 = \lambda - dU - bUV \quad \text{(uninfected cells)}$$

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$$U_s = \frac{c\delta}{bp}, \quad I_s = \frac{pb\lambda - dc\delta}{bp\delta}, \quad V_s = \frac{pb\lambda - dc\delta}{bc\delta}$$

Steady states - comments

- For the model without cell birth/death (acute infection), there is only the non-infection steady state.
- The SS can be a dynamical equilibrium, with ongoing virus production, cell birth and death, etc.
- We could compute stability of steady states.

Modeling HCV & Drug Treatment

Using simple models to study HCV

- Hepatitis C virus (HCV) causes a persistent infection
- It can be modeled by a set of equations such as the ones we just looked at
- We are interested in the effect of drug treatment on virus load

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

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

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

Modeling HCV

- Before treatment start, the infection is chronic, i.e. at steady state:

$$\dot{U} = 0 = \lambda - dU - bUV$$

$$\dot{I} = 0 = bUV - \delta I$$

$$\dot{V} = 0 = pI - cV$$

$$U_s = \frac{c\delta}{bp}, \quad I_s = \frac{\lambda}{\delta} - \frac{dc}{bp}, \quad V_s = \frac{p\lambda}{c\delta} - \frac{d}{b}$$

Modeling interferon treatment

- Treatment with interferon (IFN) was found to lead to decline in virus load, but mechanism was not known

IFN might reduce susceptibility of cells to infection

$$\dot{U} = \lambda - dU - (1-f)bUV$$

$$\dot{I} = (1-f)bUV - \delta I$$

$$\dot{V} = (1-e)pI - cV$$

IFN might reduce production of virions

Based on Neumann et al. (1998) Science

Modeling interferon treatment

- We will use the mechanistic model to test different hypotheses:
  - Hypothesis 1: IFN reduces susceptibility of cells to infection
  - Hypothesis 2: IFN reduces virus production
  - Hypothesis 3: Both H1 and H2
  - Hypothesis 4: Neither H1 or H2
  - Hypothesis 5: Either H1 or H2
- How do we use the models to test this?

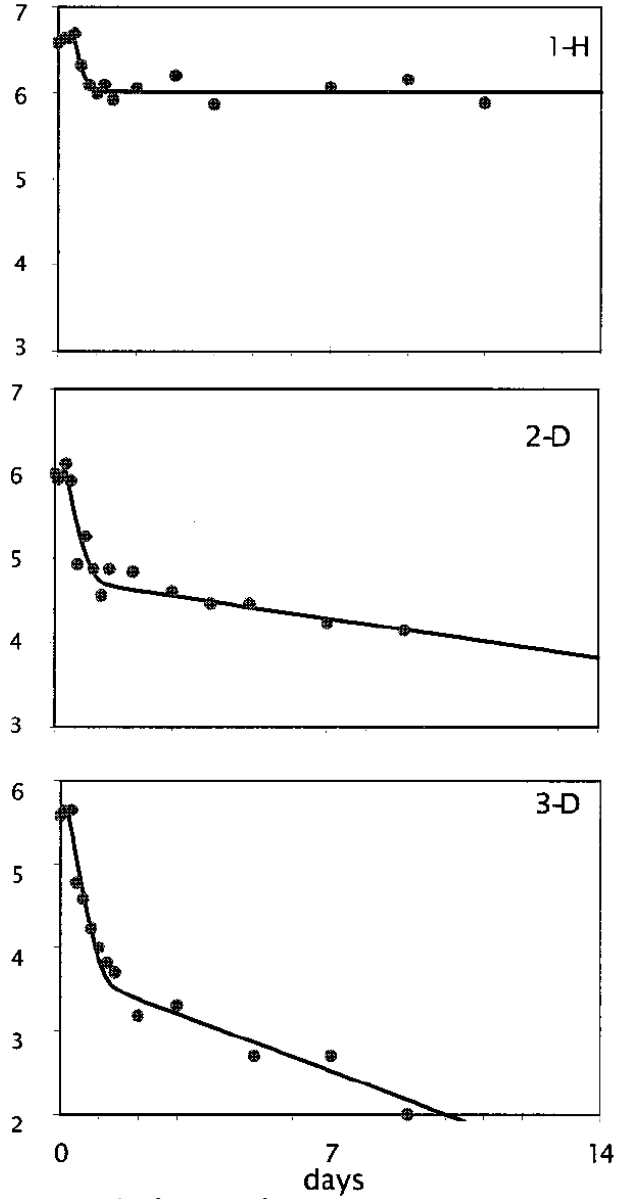
Testing the mechanisms of IFN treatment

- Open and run SISMID-U4-hcv1.r
- Actual data for virus after treatment looks like this:
- Run simulation for different IFN mechanisms/hypotheses. What do you conclude?

$$\dot{U} = \lambda - dU - (1-f)bUV$$

$$\dot{I} = (1-f)bUV - \delta I$$

$$\dot{V} = (1-e)pI - cV$$



Neumann et al. (1998) Science

Modeling IFN treatment

- *Neumann et al. (1998, Science)* also used the model to estimate parameters, such as the lifespan of an infected cell ($1/\delta$), the lifespan of a virion (1/c) and the efficacy, ***e***, of different doses of IFN.
- To do so, they fitted the model to data. We won't do that now, we will be covering data fitting later.

More detailed IFN model

- In the previous model, the strength of the drug was assumed to not change over time $\dot{U} = \lambda - dU - bUV$
- But drug decays over time $\dot{I} = bUV - \delta I$

$$\dot{V} = (1-e)pI - cV$$

- Especially important if drug is given rarely, as in newer versions of IFN treatment for HCV
- A more detailed model will include the kinetics of the drug (pharmacokinetics, PK) and will also model how drug efficacy depends on drug concentrations (pharmacodynamics, PD)

PK/PD models

- A lot of PK/PD modeling exists, it's a field with its own journals
- For infectious diseases, most PK/PD studies deal with bacterial infections and antibiotics
- The "PK/PD guys" rarely interact with immunologists/virologists and vice versa
- Most models either include detailed PK/PD but no immune response, or IR but no PK/PD
- An area ripe for future experimental and modeling studies

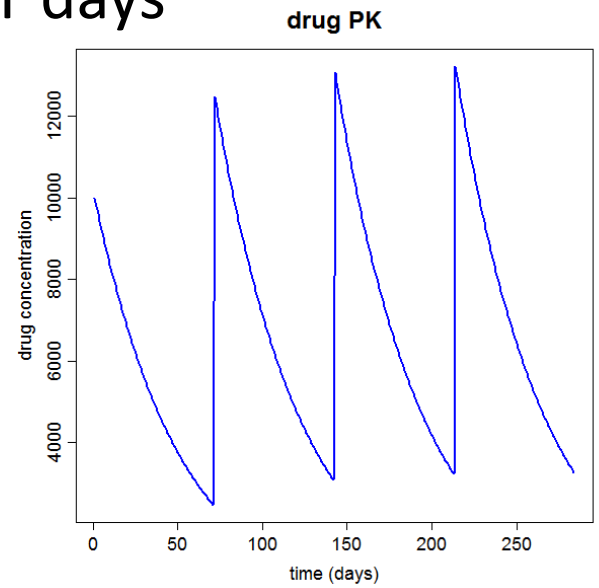
Some more on that: Handel et al. (2009) Journal of Theoretical Biology

Pharmacokinetics

- Simplest model: drug decays at a constant rate and is given at concentration C_0 is every T days

$$\dot{C} = -d_C C$$

$$C = C + C_0 \quad \text{every T days}$$

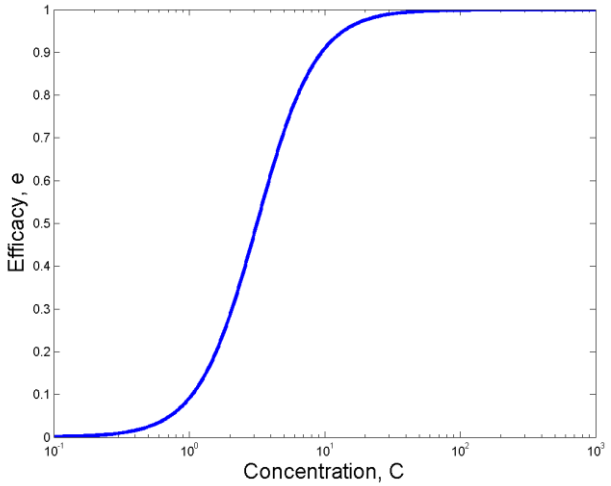


- More complicated/realistic models are possible that take into account movement of drug from absorption site to site of action.

Pharmacodynamics

- One frequently used model is known as the E-max model:

$$e(C) = \frac{C^n}{C^n + C_{50}}$$



n determines how quickly ***e(C)*** increases with C

Concentration at which drug efficacy is 50%

- Since *C(t)* changes with time according to the PK equations, drug efficacy also changes with time

PK/PD model for IFN treatment

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

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

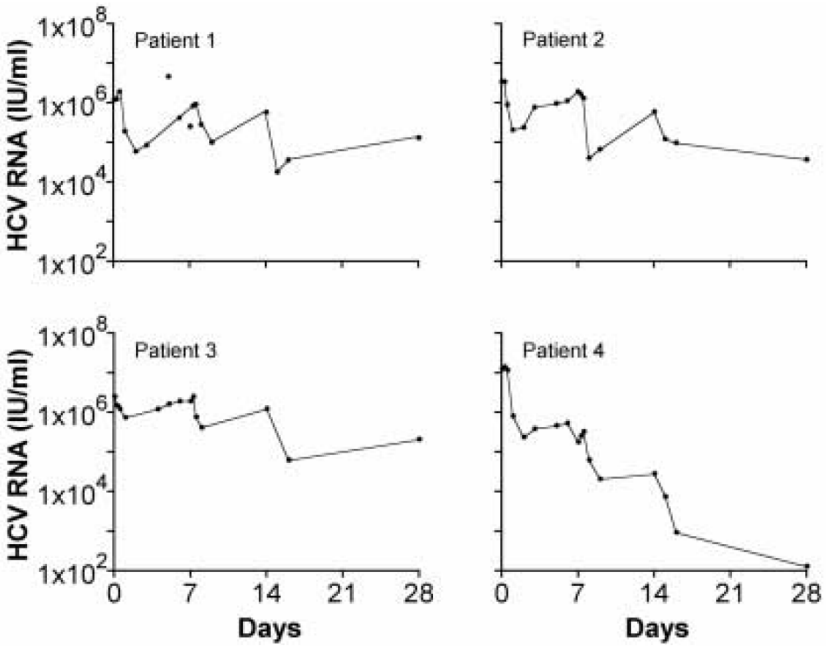
$$\dot{V} = (1-e)pI - cV$$

$$e = \frac{C^n}{C^n + C_{50}}$$

$$\dot{C} = -d_C C, \quad C = C + C_0 \quad \text{every T days}$$

PK/PD for HCV model – R example

- Load and run SISMID-U4-hcv2.r
- Make sure you understand the code. Some new stuff is in there, e.g. a loop that repeatedly calls the ODE solver
- Change different PK and PD parameters and see how it affects the results
- This is how some of the data look like:



Powers et al. (2003) Seminars in Liver Disease

PK/PD models for HCV

- More detailed PK/PD models for IFN treatment in HCV can be found in: *Powers et al. (2003) Seminars in Liver Disease, Talal et al. (2006) Hepatology*
- Those PK/PD models were shown to agree better with the data compared to models that had constant IFN efficacy

Combination therapy for HCV

- In addition to IFN-alpha, patients started to receive ribavirin
- Ribavirin alone does not or only transiently reduces virus load
- Ribavirin in combination with IFN sometimes leads to improved long-term virus decline
- The mechanism of ribavirin action was not well known
- We can use a model to study how ribavirin works and how to optimize combination treatment

Based on Dixit et al. (2004) Nature

Combination therapy for HCV

- Assumption: Ribavirin leads to the production of mutated, non-infectious virions

$$\dot{U} = \lambda - dU - bUV_I$$

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

$$\dot{V}_I = (1-r)(1-e)pI - cV_I \qquad \text{(infectious virus)}$$

$$\dot{V}_{NI} = r(1-e)pI - cV_{NI} \qquad \text{(non-infectious virus)}$$

- We need to keep track of non-infectious virus since experiments measure viral RNA levels

Combination therapy for HCV

- Simplifying assumption: Over the duration of treatment, the number of uninfected cells changes little and remains at its steady-state level:

$$U_s = \frac{c\delta}{bp}$$

$$\dot{I} = bU_s V_I - \delta I$$

$$\dot{V}_I = (1-r)(1-e)pI - cV_I$$

$$\dot{V}_{NI} = r(1-e)pI - cV_{NI}$$

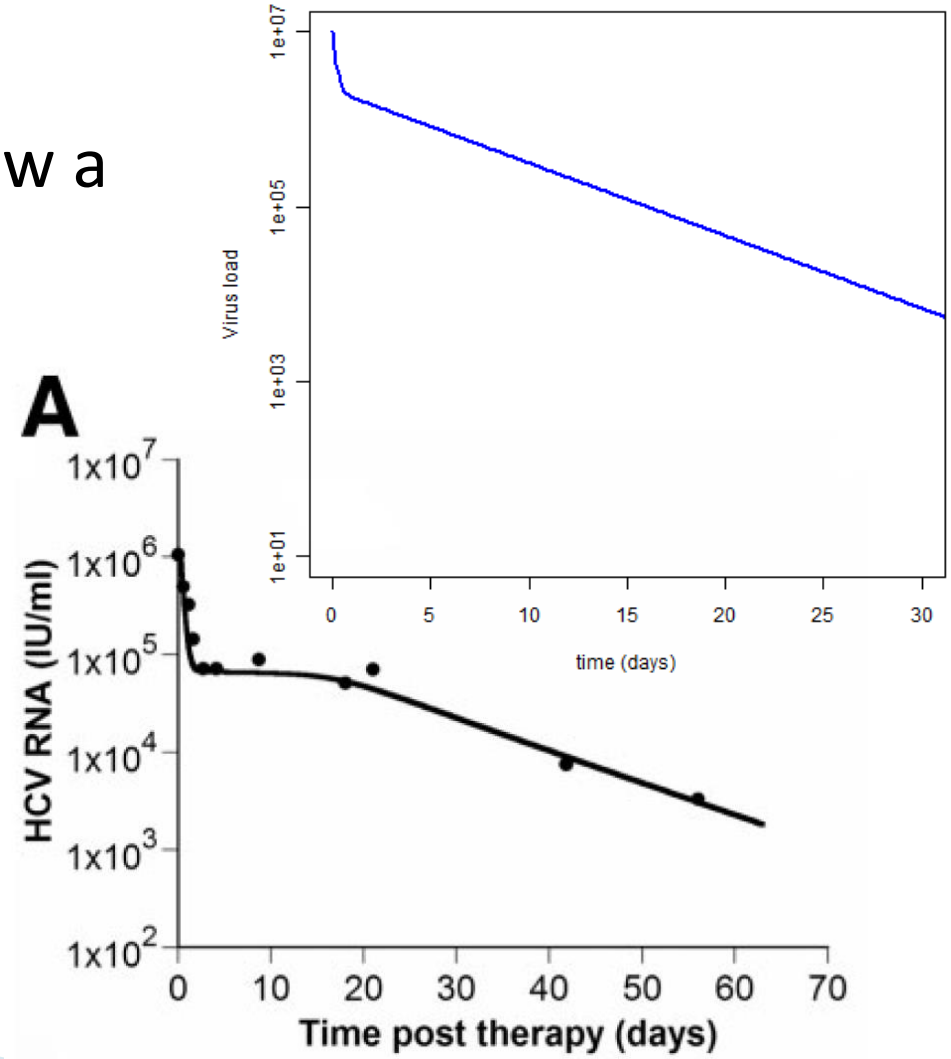
- We also assume that PK/PD does not play an important role

Combination therapy – R Example

- Load and run SISMID-U4-hcv3.r
- Data show that if IFN is effective (high $\boldsymbol{e}$), ribavirin has little effect on virus load, but if IFN is less effective, the addition of ribavirin makes a difference. Test if the model can reproduce this.
- *Dixit et al. (2004, Nature)* also fitted the model to data and used it to make predictions about long-term treatment outcomes.

Further extending the HCV model

- The previous model produces a biphasic decline in virus load
- Some patients show a tri-phasic decline
- Something to do with the immune response?



Further extending the HCV model

- Claim: allowing for proliferation of uninfected and infected cells can explain the data (no IR needed)

$$\dot{U} = \lambda - dU - bUV_I + g_U U\left(1 - \frac{U+I}{U_0}\right)$$

$$\dot{I} = bUV_I - \delta I + g_I I\left(1 - \frac{U+I}{U_0}\right)$$

$$\dot{V}_I = (1-r)(1-e)pI - cV_I$$

$$\dot{V}_{NI} = r(1-e)pI - cV_{NI}$$

Homeostatic feedback loop

Number of cells below which the homeostatic regulation starts

Based on Dahari et al. (2007) Hepatology

On your own – triphasic HCV decline

- Harder version: Use SISMID-U4-hcv3.r as starting point. Extend the model to the one shown on the previous slide. Easier version: Load and run SISMID-U4-hcv4.r
- Observe the tri-phasic decline
- When/why does the tri-phasic decline occur?
- How does the dynamics depend on the efficacy of IFN and ribavirin?
- How do other model parameters influence the dynamics?
- Hint: A more detailed discussion of the model (and answers to these questions) can be found in *Dahari et al. (2007) Hepatology*

Discussion

- Simple models have real value! They can be used to gain insights into mechanisms
- Models that do not agree with data can be used to reject specific hypotheses
- Models can make predictions which can be tested in further experiments
- By fitting models to data one can estimate important parameters, such as drug efficacy, rate of virion production, etc.
- All these models are very simple and ignore the immune response. Nevertheless, they seem to be useful tools to obtain novel insights ("Models are always wrong but sometimes surprisingly useful").

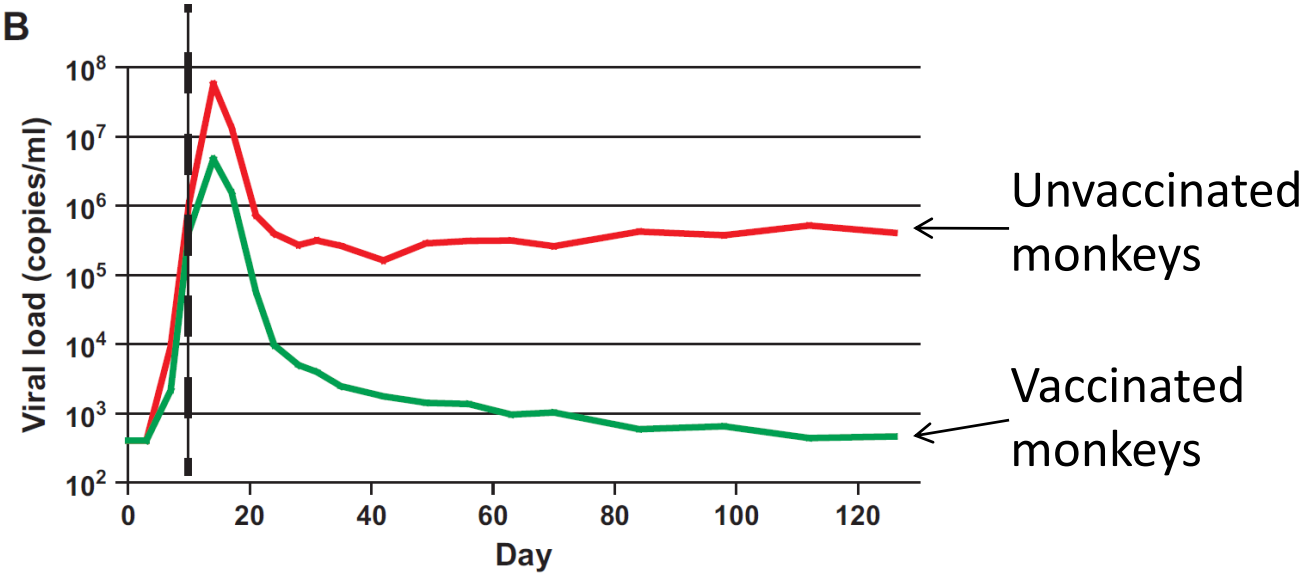
Modeling HIV

Simple HIV models

- We just saw how several simple models were able to produce useful results and match data
- Similar models have been used extensively for HIV
- Like the HCV models, some HIV models do not include an immune response (mainly Alan Perelson & Co., see e.g. *Ho et al. 1995 Nature, Perelson et al. (1996) Science, (1997) Nature*)

Simple HIV models

- The HIV models without immune response were able to provide useful insights.
- But: Data show that the immune response, especially CTL, are important and influence the infection dynamics.



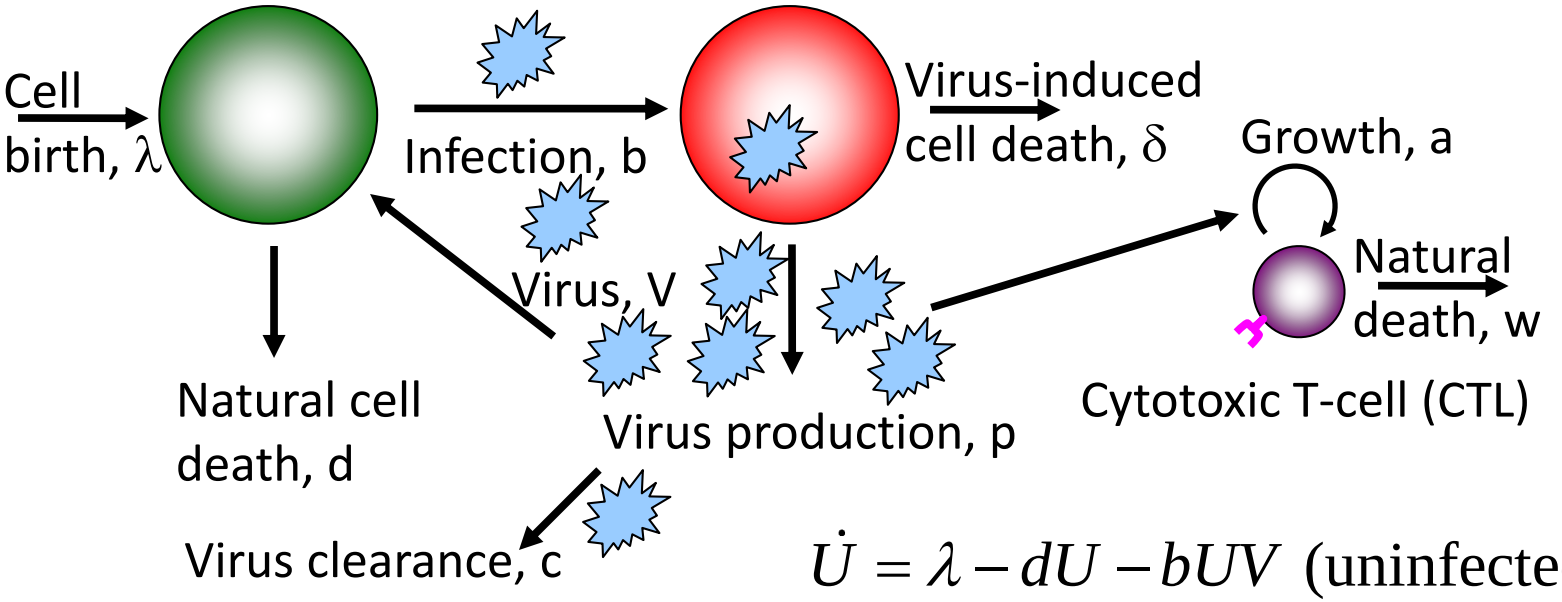
From *Davenport et al. (2007) Immunological Reviews*

HIV models with a CTL response

- The data suggest that we should include a CTL response in our model
- We start with our previous, simple model that we used for HCV
- It's often not clear how to best model the immune response, usually it's done in a very abstract manner
- We assume that CTL undergo per-capita expansion proportional to virus load and die at a fixed rate
- This leads to a predator-prey (Lotka-Volterra) type system
- See e.g. *Wei et al. 1995 Nature, Nowak & Bangham 1996 Science* for application of such models to HIV

HIV models with a CTL response

- CTL have a per-cell growth proportional to viral load and die at a fixed rate.



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

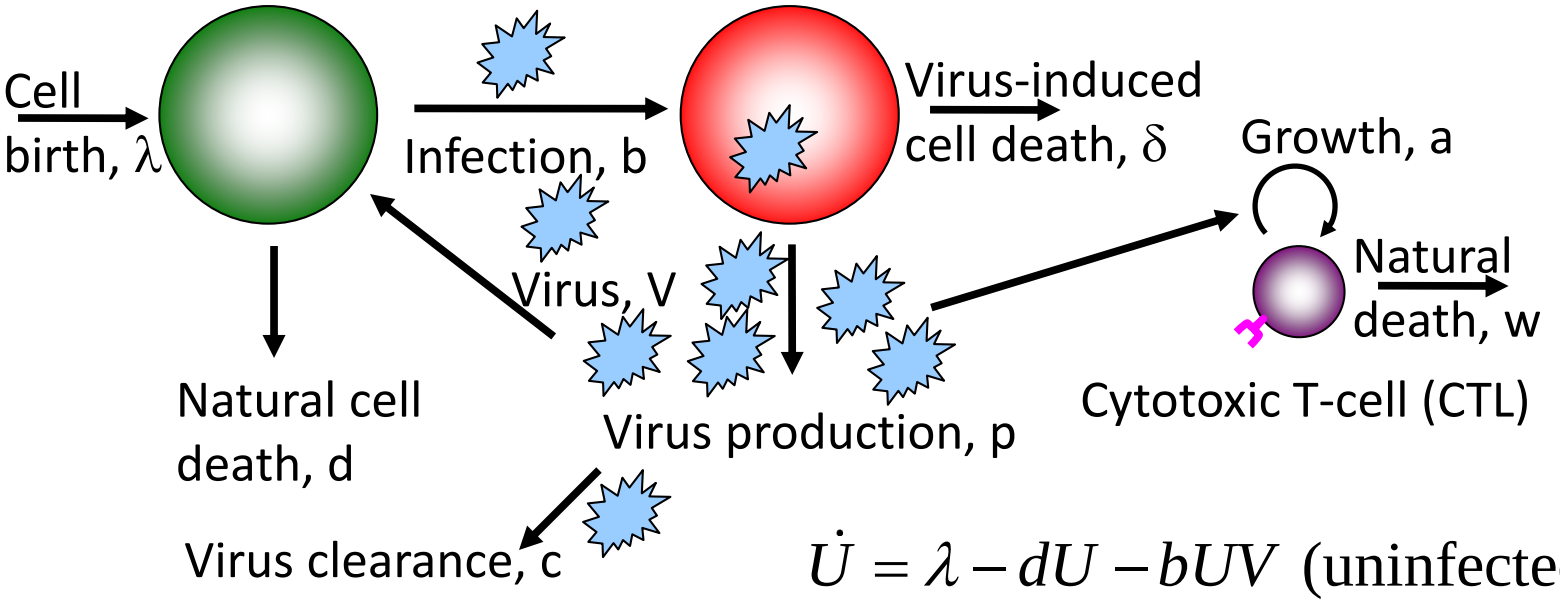
$$\dot{I} = bUV - \delta I \quad \text{(infected cells)}$$

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

$$\dot{Y} = ? \quad \text{(adaptive IR/CTL)}$$

HIV models with a CTL response

- CTL have a per-cell growth proportional to viral load and die at a fixed rate.



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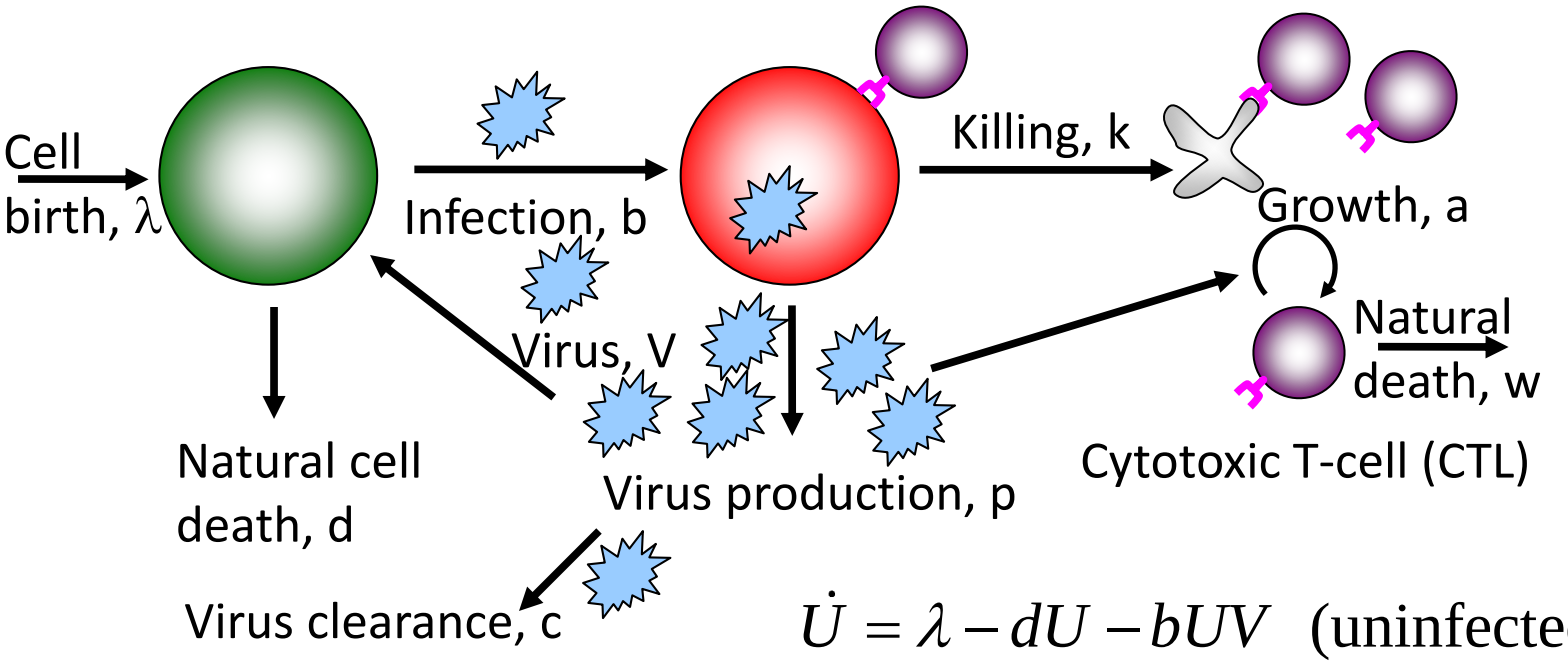
$$\dot{I} = bUV - \delta I \quad \text{(infected cells)}$$

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

$$\dot{Y} = aVY - wY \quad \text{(adaptive IR/CTL)}$$

HIV models with a CTL response

- CTL kill infected cells at some fixed rate



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

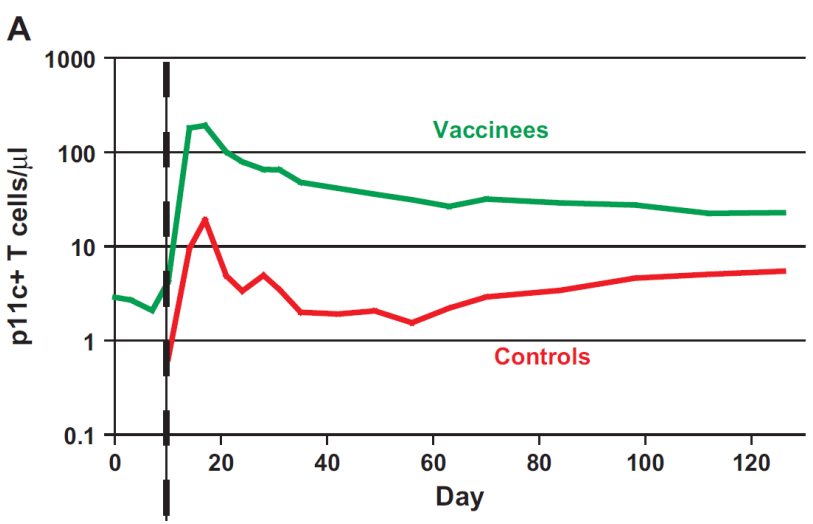
$$\dot{I} = bUV - \delta I - kIY \quad \text{(infected cells)}$$

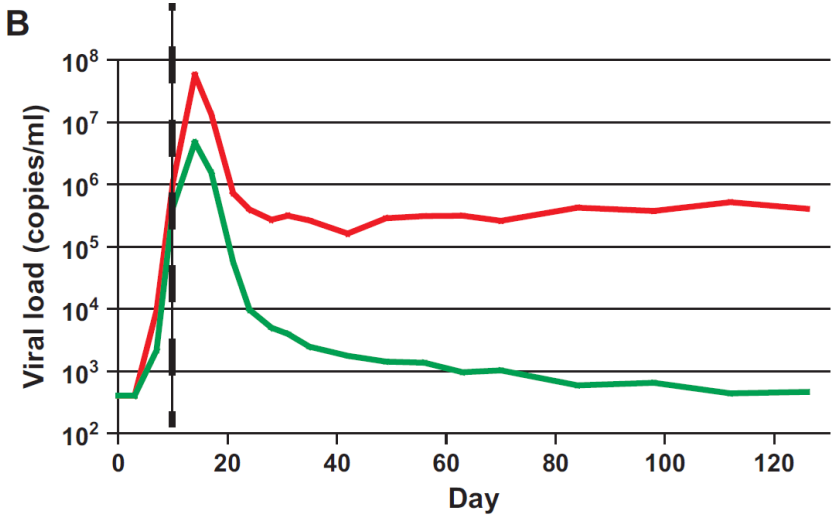
$$\dot{V} = pI - cV \quad \text{(free virus)}$$

$$\dot{Y} = aVY - wY \quad \text{(adaptive IR/CTL)}$$

R Example - HIV models and data

- Open and run SISMID-U4-hiv1.r
- To simulate vaccination, one can set **CTL0** to a larger value or increase activation rate (***α***) or killing rate (***k***) of CTL
- Compare the results with the data. Try to see if you can tweak model parameters or the CTL equation to get something that looks like the data





From *Davenport et al. (2007) Immunological Reviews*

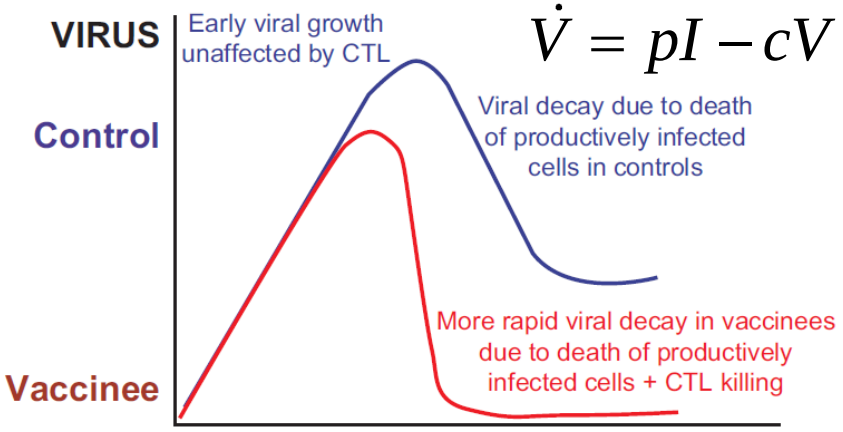
Problems with the models

- Models lead to oscillations in cells/virus
- Models predict that more CTL lead to more rapid virus decline. The data do not show this

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

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

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



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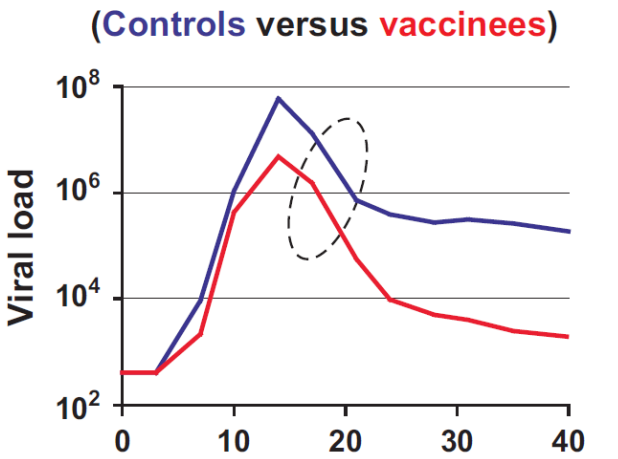


Same decay rate of virus in control and vaccinated animals NOT consistent with CTL killing of productively infected cells.

Developing a new model

- Maybe CTL are not the only important IR component and we should build a model that includes the innate response, B-cells/antibodies, etc.
- Or maybe we have all the important "players" but the way we built the model is wrong
- Let's try to see if we can modify the model to obtain results that are in better agreement with data
- For more, see ***"Understanding the Failure of CD8 T-cell Vaccination against HIV"*, Rob de Boer (2007), Journal of Virology.** (Note: We will use notation that differs from Rob's paper)

Problems with mass-action assumption

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

$$\dot{E} = bUV - gE \quad \text{(latently infected cells - same as } L \text{ previously)}$$

- The rate at which virus infects target cells is ***bU***
- If there are 10x more target cells, infection occurs at 10x the rate
- This is only realistic if the "bottleneck" in the infection process is finding uninfected cells
- If there is an abundance of uninfected cells, other factors become rate-limiting
- The infection rate should approach some maximum value for large ***U***

The new model – infection process

$$\dot{U} = \lambda - dU - \frac{bUV}{h_b + U} \qquad \text{(uninfected cells)}$$

$$\dot{E} = \frac{bUV}{h_b + U} - gE \qquad \text{(latently infected cells)}$$

$$U \ll h_b \rightarrow bV, \quad U \gg h_b \rightarrow \frac{b}{h_b} UV = \tilde{b}UV$$

- The new formulation introduces saturation.
- If ***U*** is high, the virus infects at maximum rate ***b***
- If ***U*** is low, the infection rate is $\boldsymbol{bU/h_b < b}$
- The constant $\boldsymbol{h_b}$ controls the level of ***U*** where saturation sets in

The new model – virus dynamics

- For the virus, we make a quasi-steady state assumption: We assume that virus clearance is fast and virus load therefore follows almost instantaneously the dynamics of the infected cells

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

$$\text{assume (sloppy) } \dot{V} = 0 \quad \rightarrow \quad V = \frac{p}{c} I$$

CTL killing in the old model

$$\dot{I} = gE - \delta I - kIY \quad \text{(productively infected cells)}$$

- Mass-action problem again: A CTL kills at rate ***kI***
- 10x more infected cells leads to 10x faster killing
- Only realistic if finding infected cells is the rate-limiting step
- For high infected cell numbers, killing rate should saturate at some maximum value

CTL killing in the old model

$$\dot{I} = gE - \delta I - kYI \quad \text{(productively infected cells)}$$

- Another mass-action problem: 10x more CTL lead to 10x faster killing - only realistic up to a point
- If there are lots of CTL, further increasing their number likely won't increase the rate of removal/death of infected cells
- For high CTL numbers, killing rate should again saturate at some maximum value

The new model – CTL killing

$$\dot{I} = gE - \delta I - \frac{kIY}{h_k + I + Y} \quad \text{(productively infected cells)}$$

$$I + Y, h_k \rightarrow kY, \qquad Y + I, h_k \rightarrow kI$$

- If infected cells (CTL) are abundant, killing depends only on the constant ***k*** and CTL (infected cells)
- The constant h_k regulates when the different saturation regimes set in
- One could have made a model where killing saturates as k_1Y and k_2I and where different constants h_1 and h_2 regulate the saturation for ***Y*** and ***I***
- One could have used a similar term for the infection process (but Rob didn't so I won't either)

$$\frac{bUV}{h_b + U + V}$$

The new model – CTL dynamics

$$\dot{Y} = aVY - wY = a\frac{p}{c}IY - wY \quad \text{(old model)}$$

$$\dot{N} = -\frac{aNI}{h_a + N + I} \quad \text{(non-activated/naive CTL)}$$

$$\dot{Y} = \frac{aN}{h_a + N + I}I + \frac{mIY}{h_m + Y + I} - d_Y Y \quad \text{(activated CTL)}$$

The new model

$$\dot{U} = \lambda - dU - \frac{bUV}{h_b + U}$$ (uninfected cells)

$$\dot{E} = \frac{bUV}{h_b + U} - gE - d_E E$$ (latently infected cells)

$$\dot{I} = gE - \delta I - \frac{kIY}{h_k + I + Y}$$ (productively infected cells)

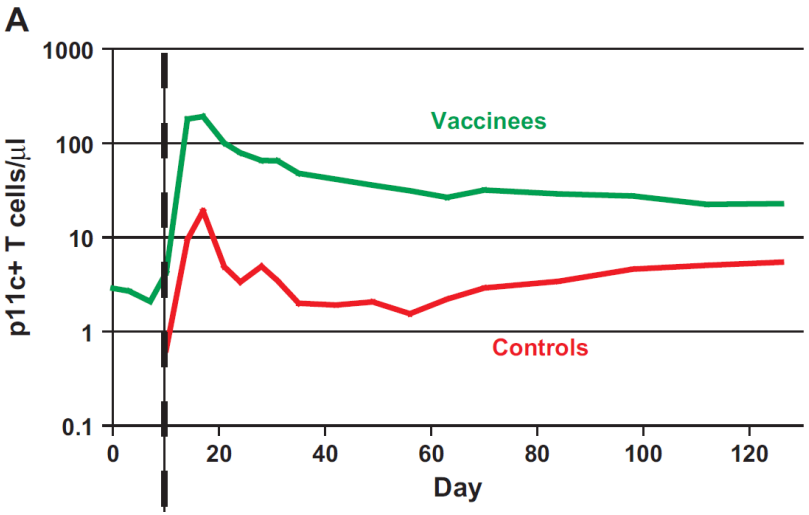
$$\dot{N} = -\frac{aNI}{h_a + N + I}$$ (non-activated/naive CTL)

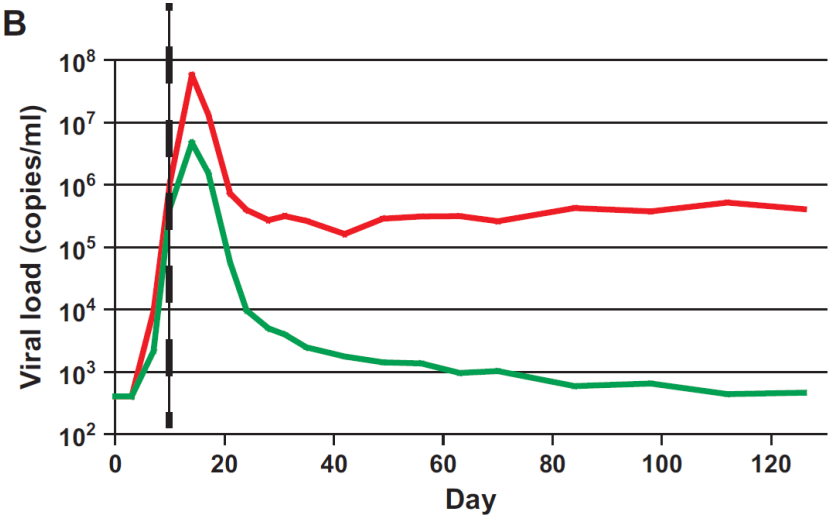
$$\dot{Y} = \frac{aN}{h_a + N + I} I + \frac{mIY}{h_m + Y + I} - d_Y Y$$ (activated CTL)

$$V = \frac{p}{c} I$$ (virus - not a differential equation)

R Example – new HIV model

- Open and run SISMID-U4-hiv2.r
- Play around with parameters, see how close you can get to the data





Discussing the new HIV model

- For some parameter combinations, the new model can remove the oscillations and reproduce the constant virus decline, independent of CTL response.
- The new model does not fully reproduce the data. We can't get increased CTL numbers and less virus for the vaccination scenario.
- There are many parameters, some of them have no direct biological meaning and their values are not known.
- To estimate all the parameters through model fitting, one would need a lot of data.

Discussing the new HIV model

- The simpler models and this one consider exactly the same “players” (virus, target cells, CTL)
- Results change solely based on different choices for model implementation!
- This shows how tricky the business of setting up models can be.

Possible thoughts

- These models are getting complicated!
- These models are way too simple, the real biology of infections is much more complex!
- I agree!

General Discussion

- Simple models can be quite powerful and have been used to produce important insights.
- Obviously, such simple models have limitations and can only be used to address certain questions.
- For instance if one is interested in the effects of the immune response, the model obviously needs to contain an IR.

General Discussion

- If you get a result for a specific model formulation (e.g. mass-action, exponential distribution for life-span), it doesn't mean you'll get the same for a slightly different model formulation (**unfortunately**).
- Similar to the experimental situation: Results for a specific mouse strain and a specific pathogen isolate might change if you go to a different model system.
- In principle, one would need to try a lot of different model formulations (equations or host/pathogen).
- Nobody does that. So for both experimental and modeling papers, results should not be over-generalized (unless you want to publish in a top tier journal….).

Further reading

- The papers mentioned on some of the slides give details about the HCV and HIV models
- The references mentioned in the introductory lecture
- A main person behind a lot of the HCV and HIV models is **Alan Perelson**. Check some of his most-cited work for interesting and relatively simple models applied to HCV and HIV