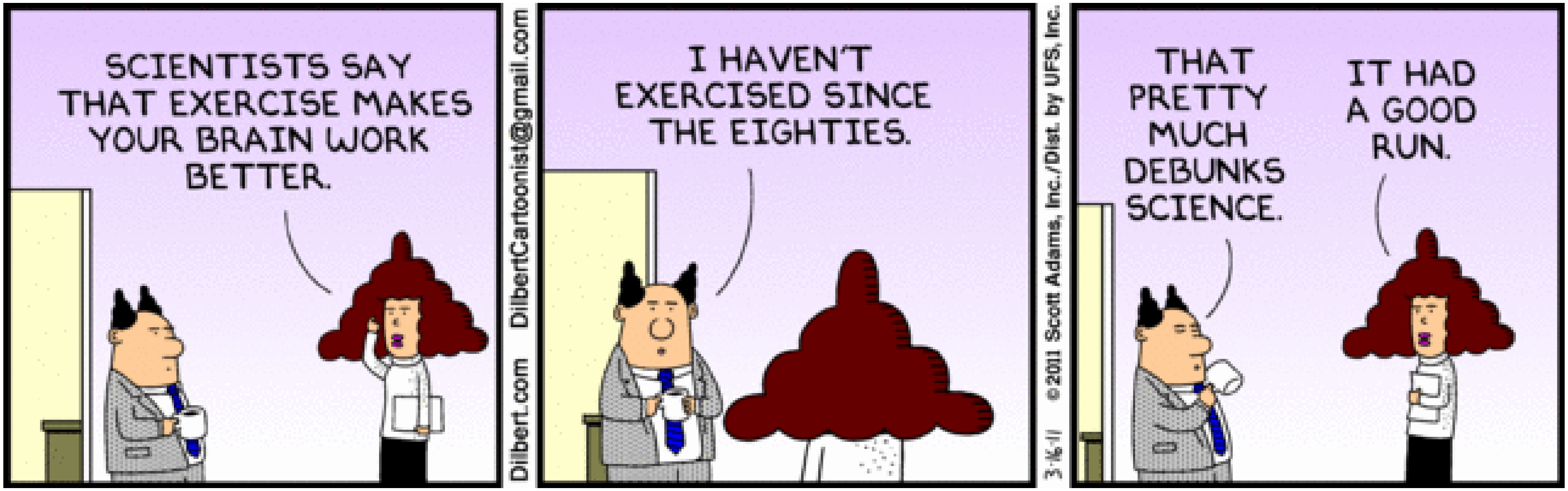
Introduction to Simulation Modeling

for within-host infections

Andreas Handel

2020-07-20 08:53:15

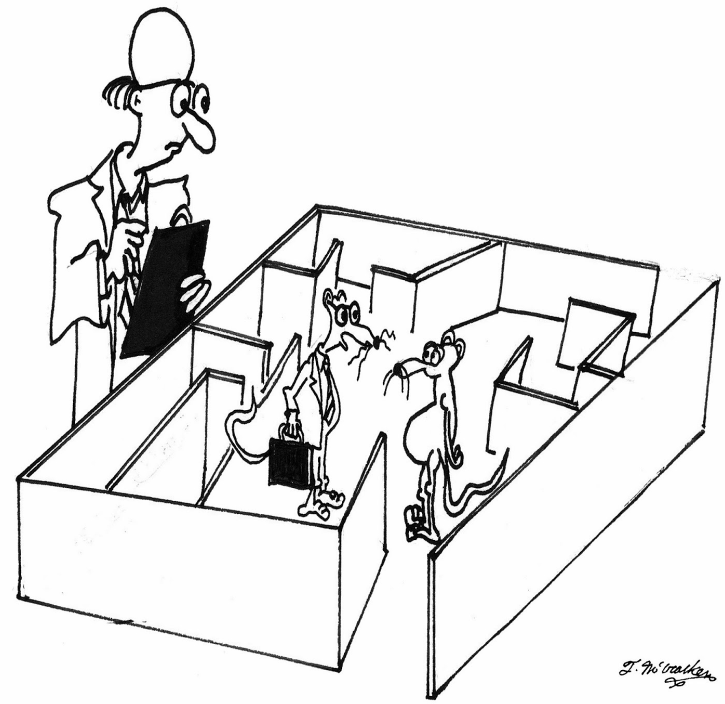
Science needs data



dilbert.com

Experimental studies

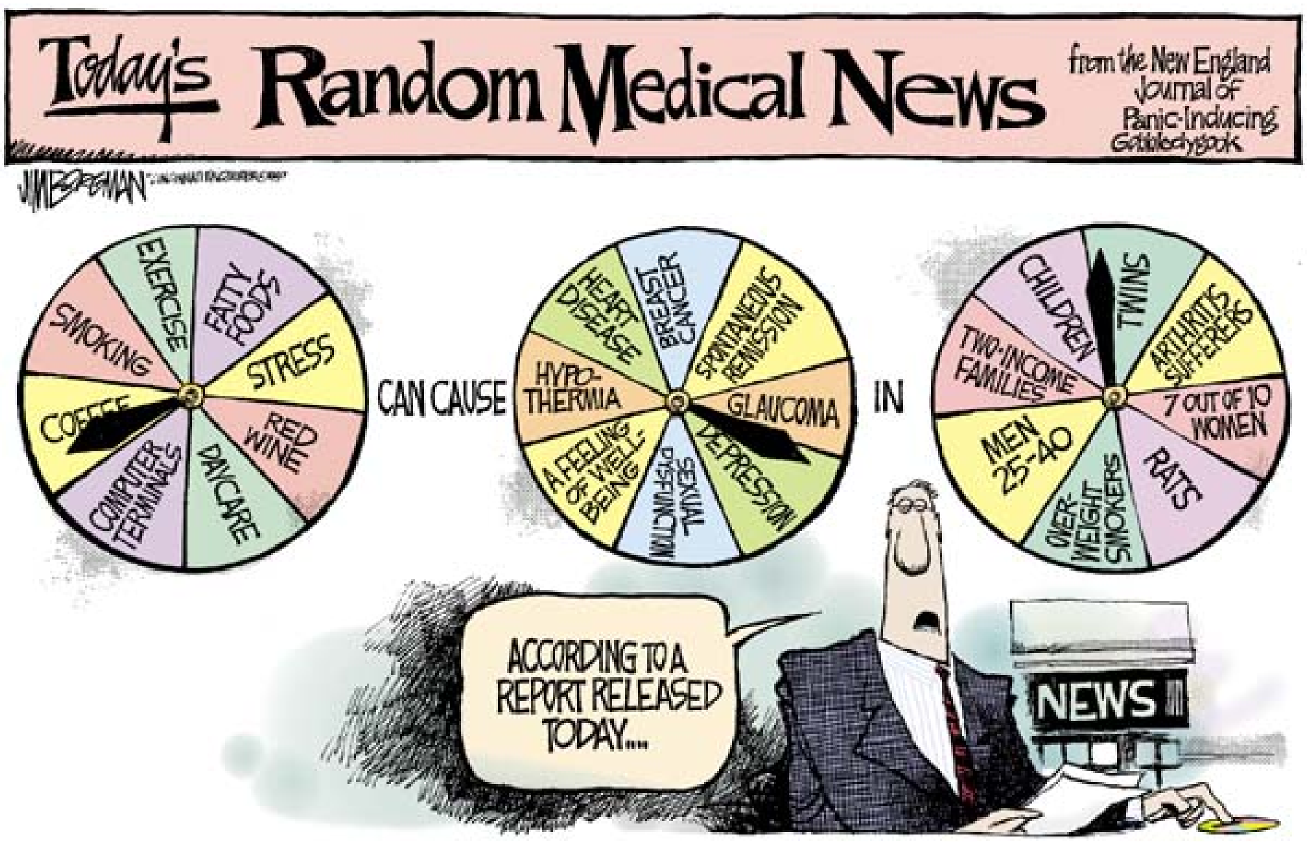
- The approach used in almost all bench/lab sciences.
- Clinical trials in Public Health and Medicine.
- Potentially most powerful because we have most control.
- Not always possible.



"THEY TESTED SOME BRAIN BOOSTING PILLS ON ME AND NOW I'M SELLING MAPS. WANT TO BUY ONE?"

Observational studies

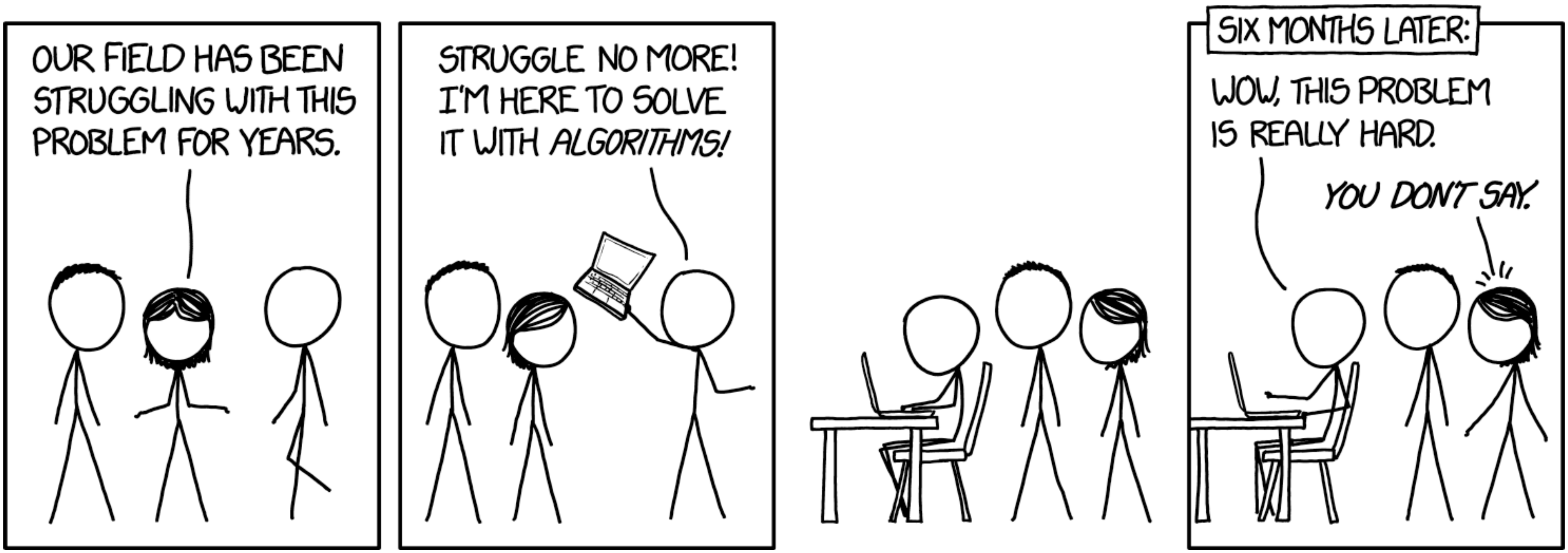
- Widely used in Public Health and other areas (e.g. Medicine, Sociology, Geology).
- Not as powerful as experimental studies.
- Often the only option.



Jim Borgman

Simulation/modeling studies

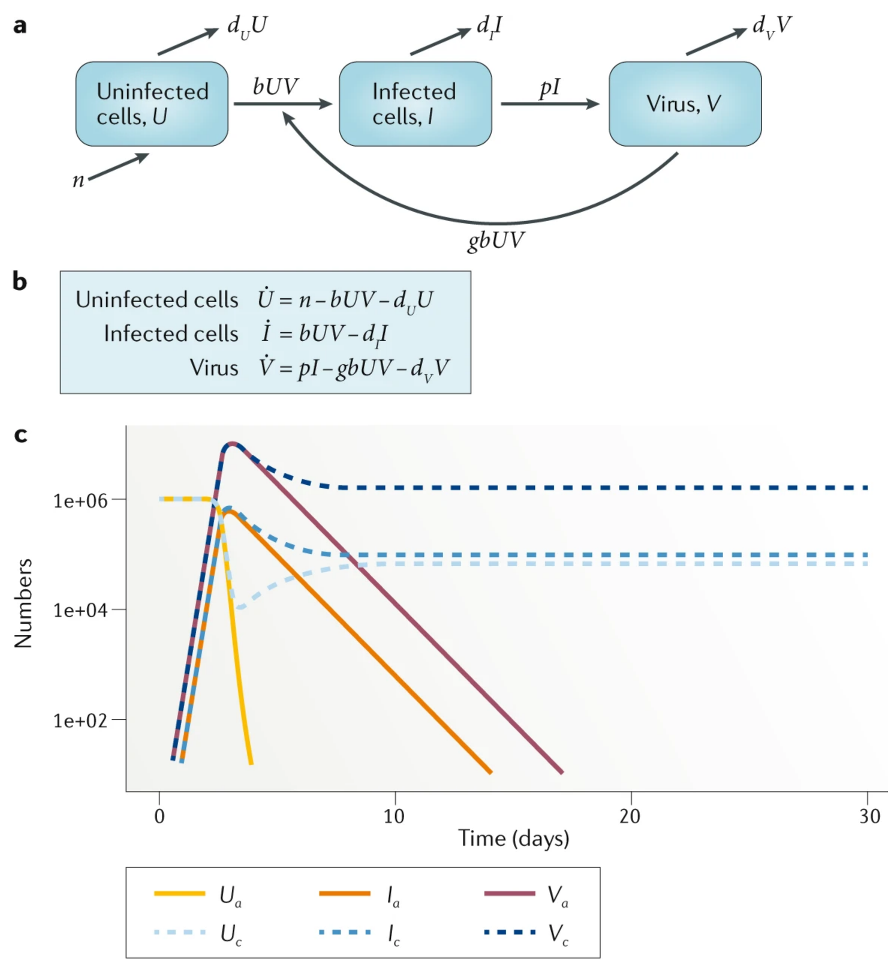
- Computer models can represent a real system.
- Simulated data is not as good as real data.
- Often the only option.



xkcd.com

Modeling definition

- The term **modeling** usually means (in science) the description and analysis of a system using mathematical or computational models.



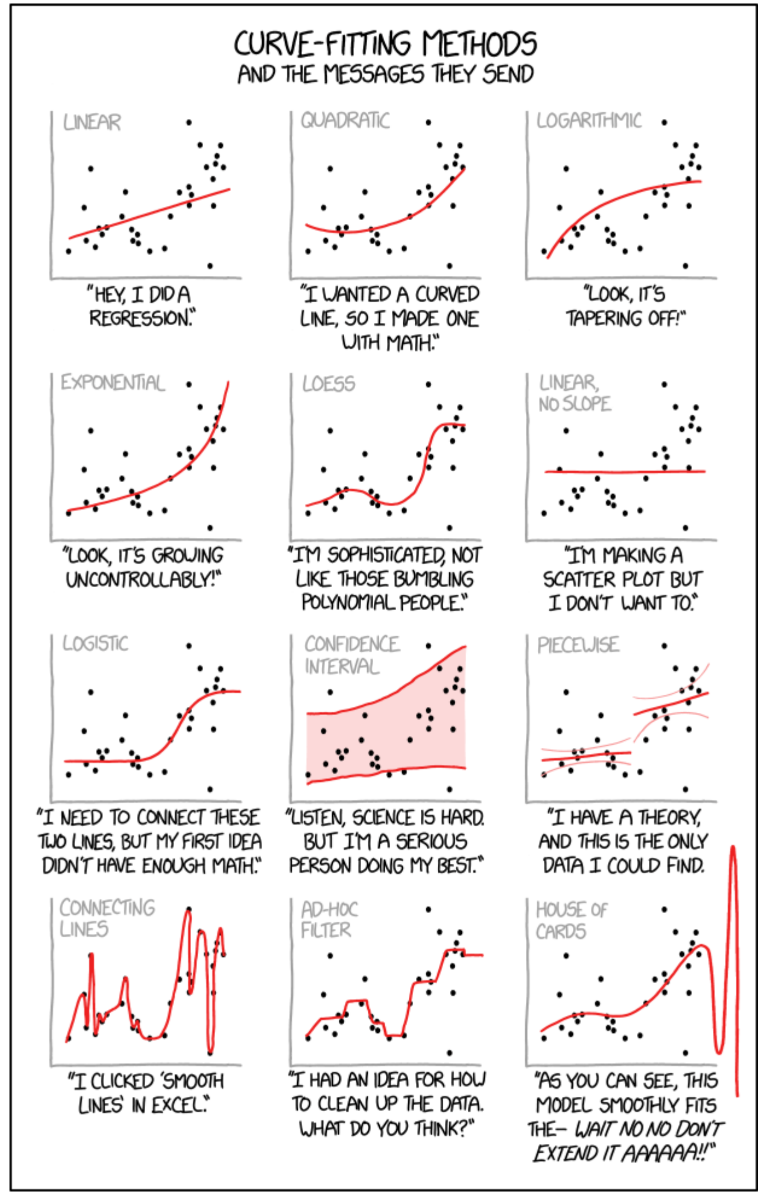
Lorem ipsum

A way to classify models

- **Phenomenological/non-mechanistic/(statistical) models**
  - Look at patterns in data
  - Do not describe mechanisms leading to the data
- **Mechanistic/process/simulation models**
  - Try to represent simplified versions of mechanisms
  - Can be used with and without data

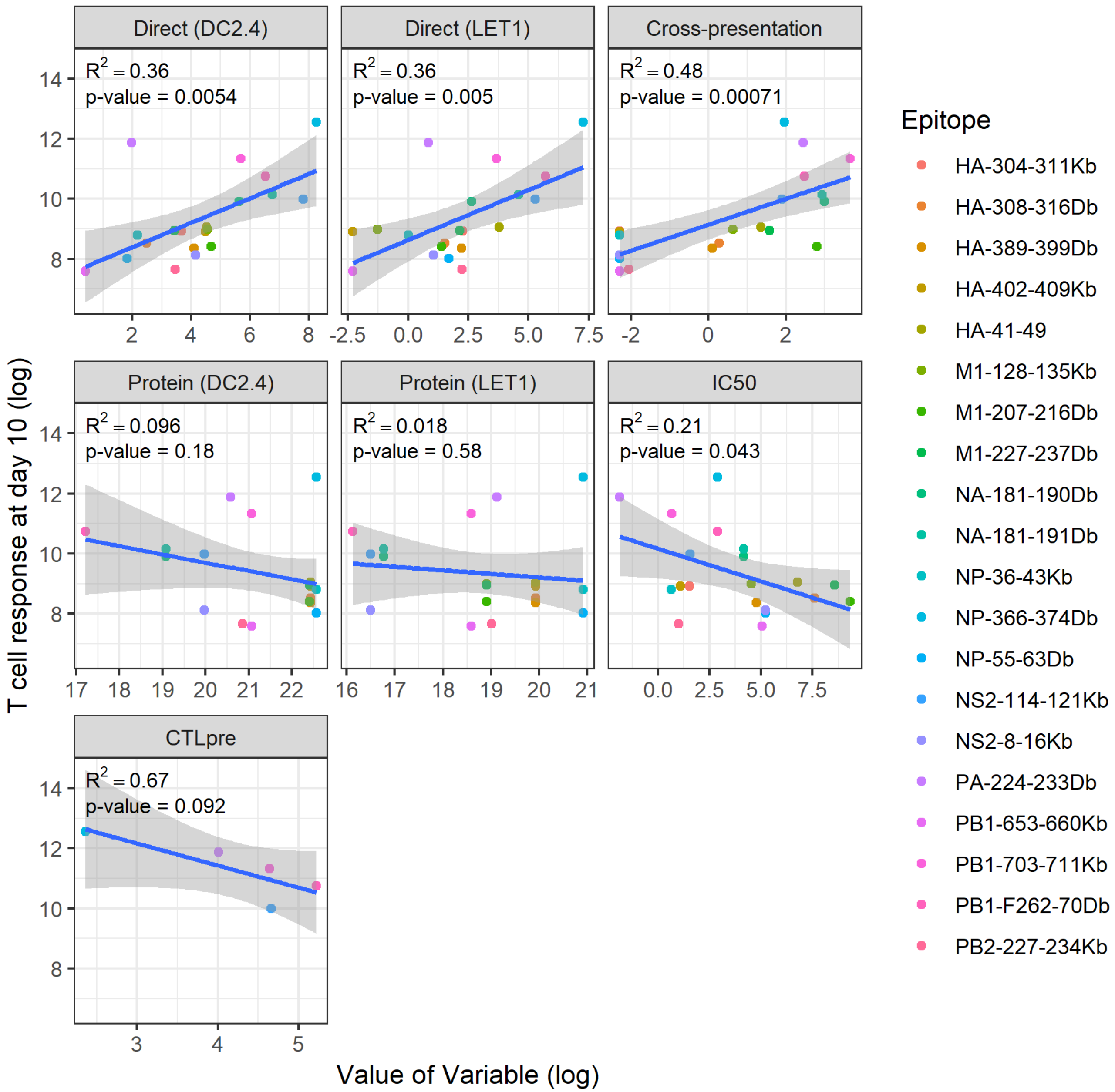
Phenomenological models

- You might be familiar with statistical models (that includes Machine Learning, AI, Deep Learning,…).
- Most of those models are phenomenological/non-mechanistic (and static).
- Those models are used extensively in all areas of science.
- The main goal of these models is to understand data/patterns and make predictions.



xkcd.com

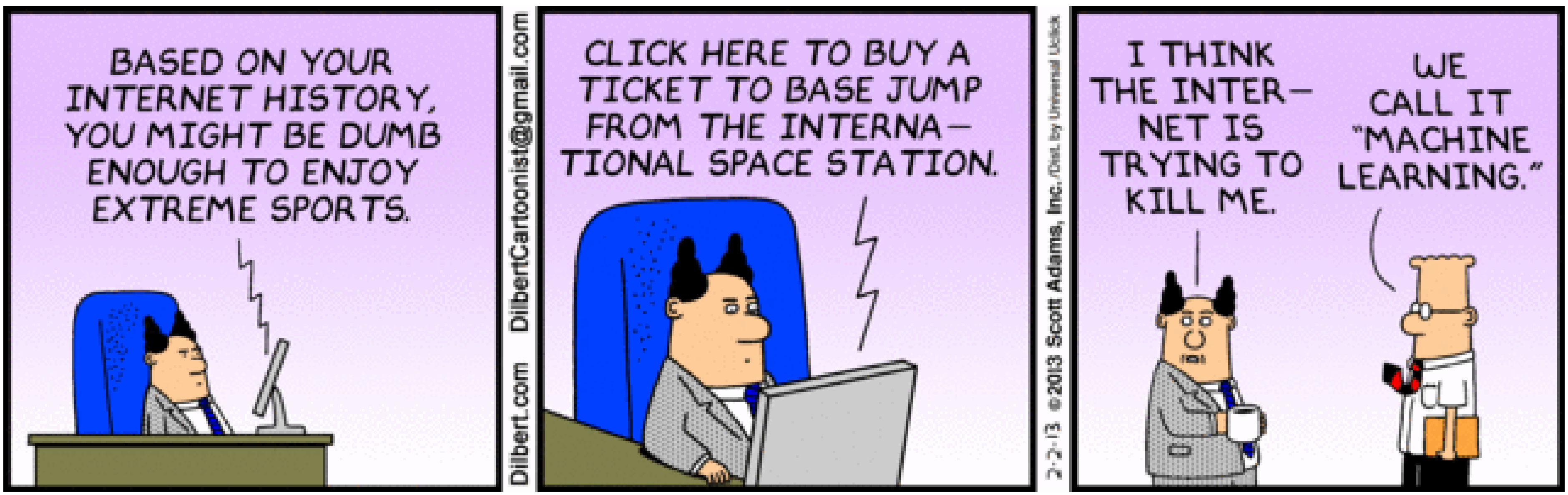
Non-mechanistic model example



Wu et al 2019 Nature Communications.

Non-mechanistic models - Advantages

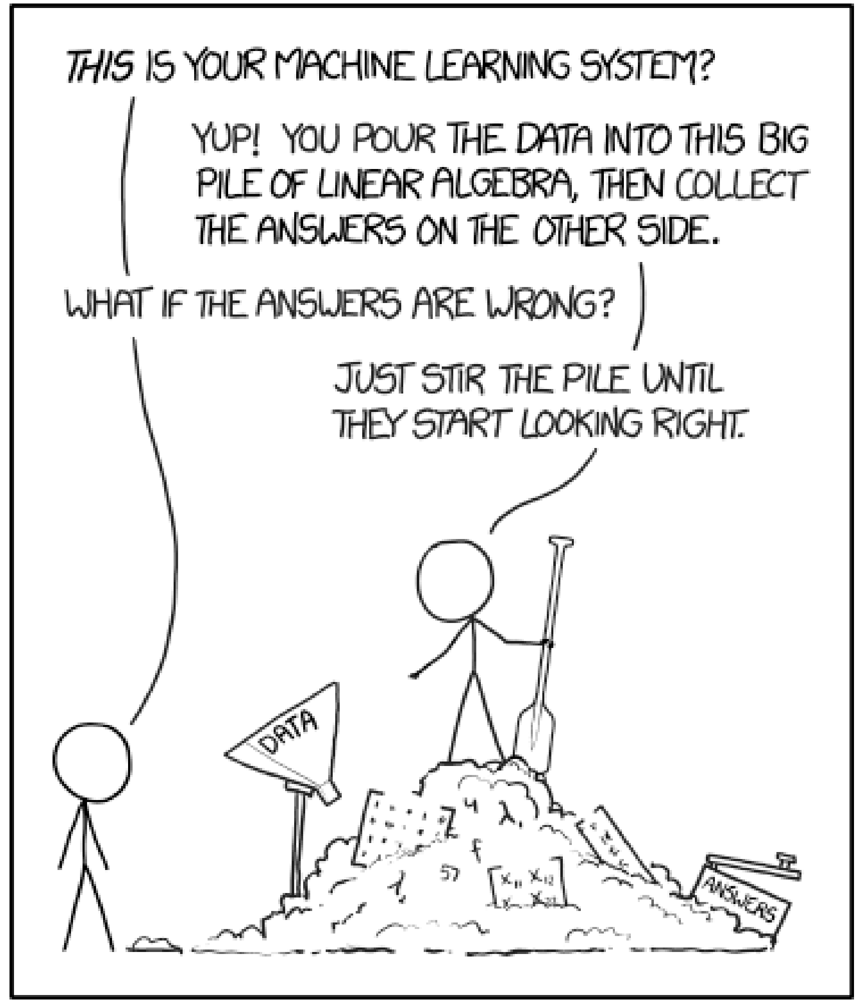
- Finding correlations/patterns is (relatively) simple.
- Some models are very good at predicting (e.g. Netflix, Google Translate).
- Sometimes we can go from correlation to causation.
- We don't need to understand all the underlying mechanisms to get actionable insights.



dilbert.com

Non-mechanistic models - Disadvantages

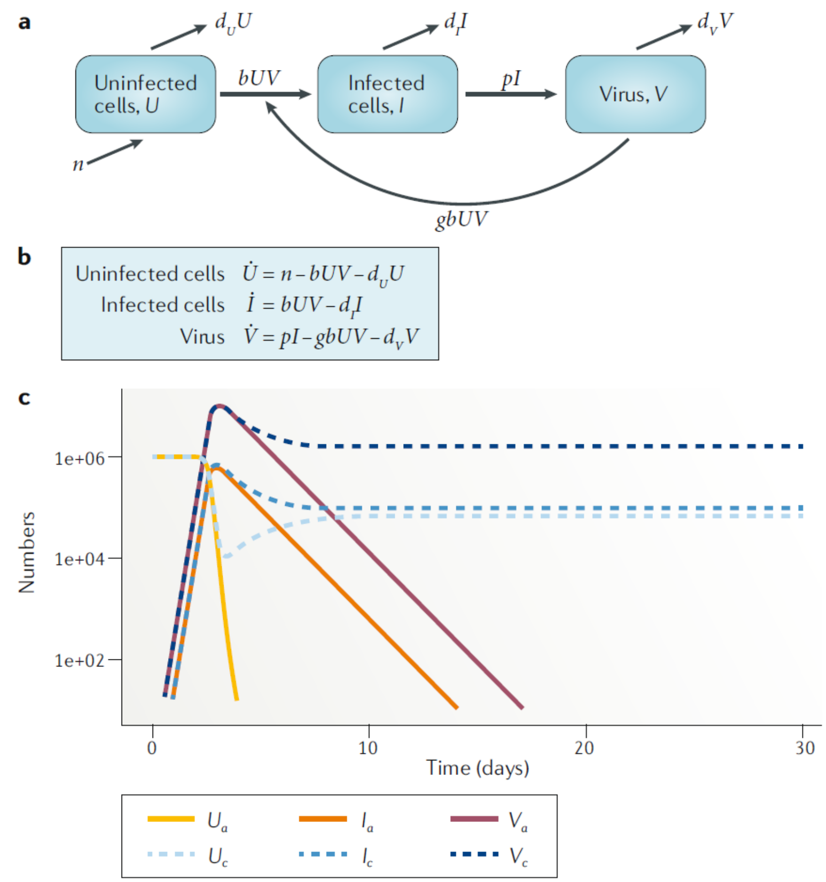
- The jump from correlation to causation is always tricky (bias/confounding/systematic errors).
- Even if we can assume a causal relation, we do not gain a lot of mechanistic insights or deep understanding of the system.



xkcd.com

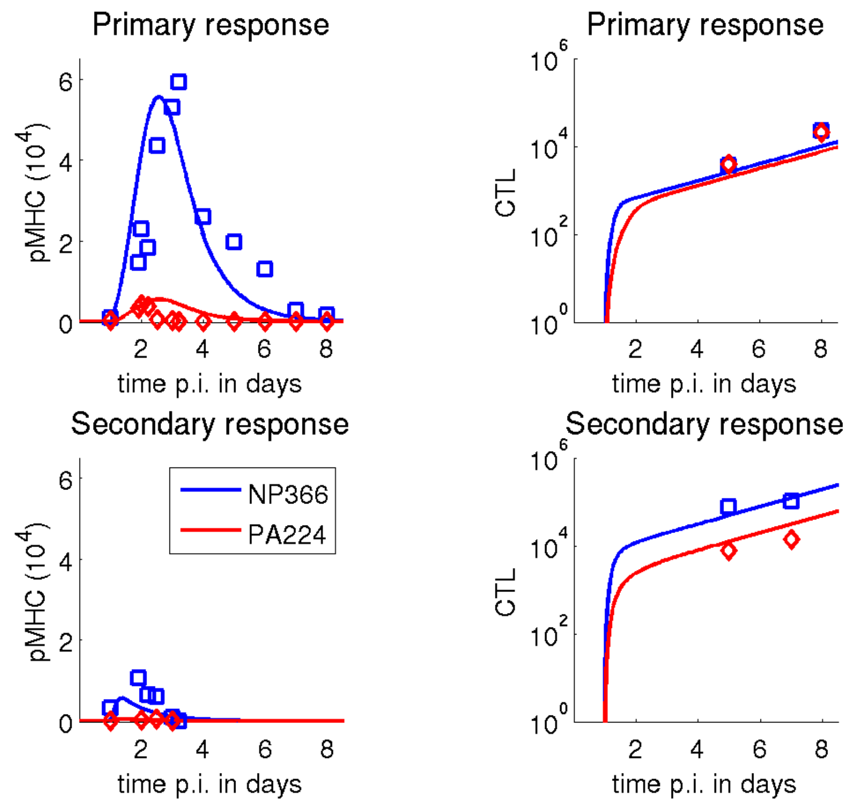
Mechanistic models

- We formulate explicit mechanisms/processes driving the system dynamics.
- This is done using mathematical equations (often ordinary differential equations), or computer rules.
- Also called **systems/dynamic(al)/(micro)simulation/process/mathematical/ODE/… models.**



Mechanistic model example

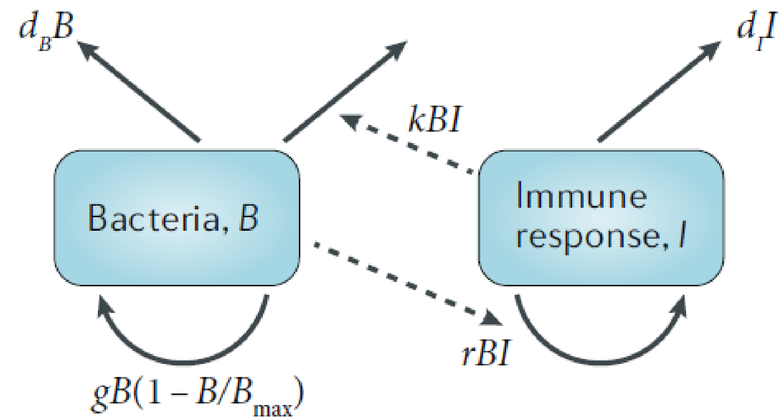
$$\dot{V} = rV - kVT^*$$
$$\dot{P} = fV - dP$$
$$\dot{T} = -aPT$$
$$\dot{T}^* = aPT + gT^*$$



Handel & Antia 2008 J Vir

Mechanistic models - Advantages

- We get a potentially deeper, mechanistic understanding of the system.
- We know exactly how each component affects the others in our model.

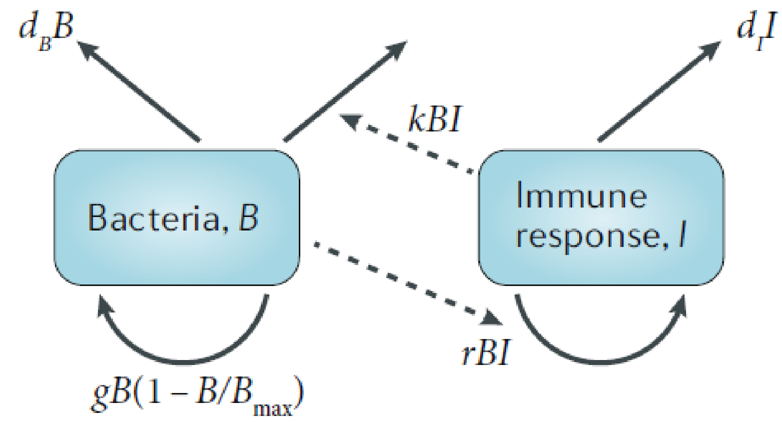


Bacteria $\dot{B} = gB(1 - \frac{B}{B_{max}}) - d_B B - kBI$

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

Mechanistic models - Disadvantages

- We need to know (or assume) something about the mechanisms driving our system to build a mechanistic model.
- If our assumptions/model are wrong, the “insights” we gain from the model are spurious.



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

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

Non-mechanistic vs Mechanistic models

- Non-mechanistic models (e.g. regression models, machine learning) 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.

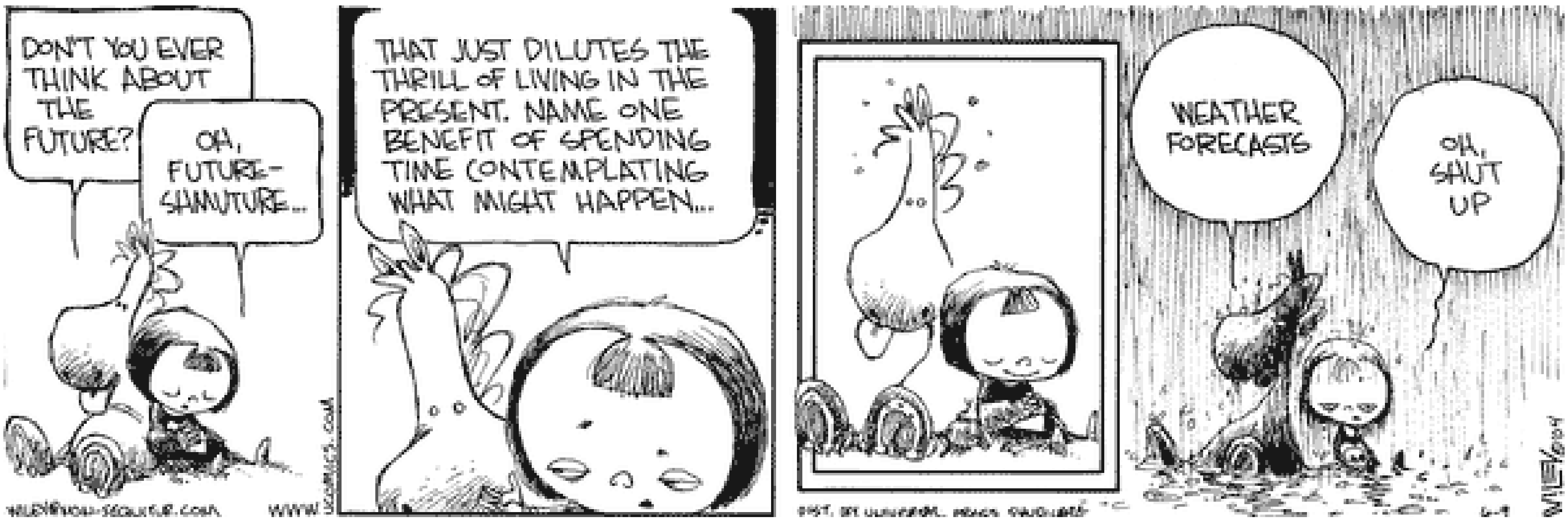
Ideally, you want to have both in your ‘toolbox’.

Simulation models

- We will focus on **mechanistic simulation models.**
- The hallmark of such models is that they explicitly (generally in a simplified manner) model processes occuring in a system.

Simulation modeling uses

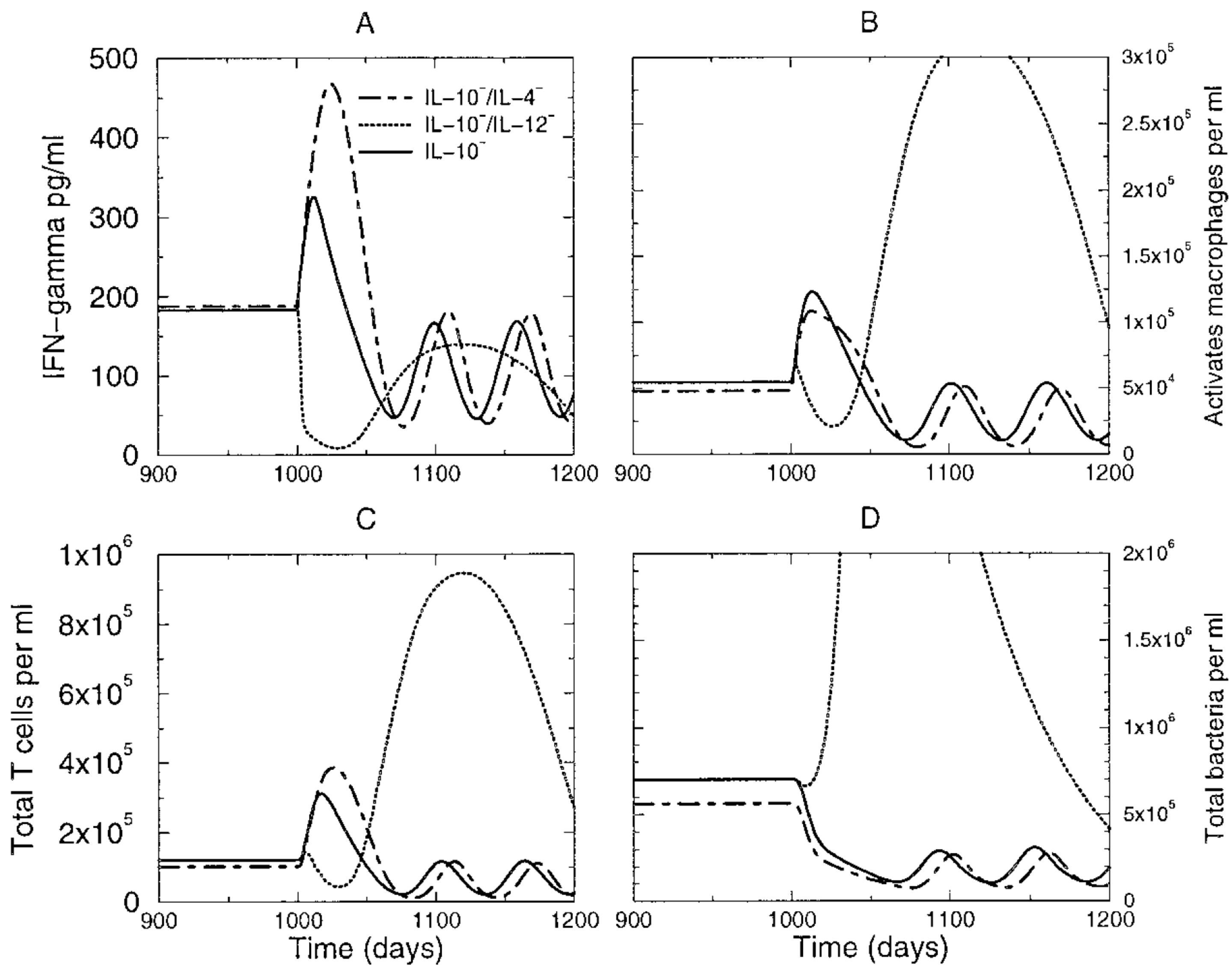
- Weather forecasting.
- Simulations of a power plant or other man-made system.
- Predicting the economy.
- Infectious disease transmission.
- Immune response modeling.
- …



www.gocomics.com/nonsequitur

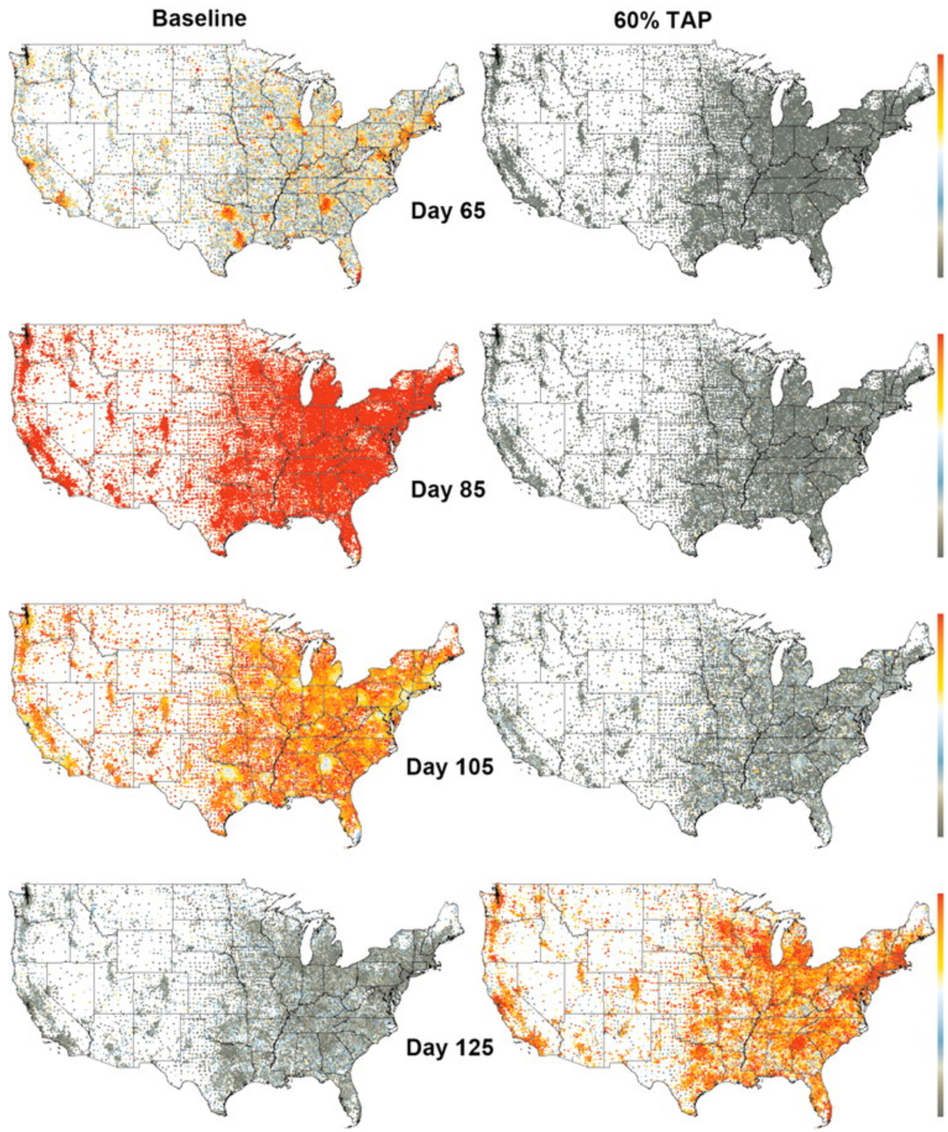
Real-world examples

Using a TB model to explore/predict cytokine-based interventions (Wigginton and Kirschner, 2001 J Imm).



Real-world examples

Targeted antiviral prophylaxis against an influenza pandemic (Germann et al 2006 PNAS).



Within-host and between-host modeling

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

The same types of simulation models are often used on both scales.

Population level modeling history

- 1766 - Bernoulli "An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it" (see Bernoulli & Blower 2004 Rev Med Vir)
- 1911 – Ross "The Prevention of Malaria"
- 1920s – Lotka & Volterra "Predator-Prey Models"
- 1926/27 - McKendrick & Kermack "Epidemic/outbreak models"
- 1970s/80s – Anderson & May
- Lot's of activity since then
- See also Bacaër 2011 "A Short History of Mathematical Population Dynamics"

Within-host modeling history

- The field of within-host modeling is somewhat recent, with early attempts in the 70s and 80s and a strong increase since then.
- HIV garnered a lot of attention starting in the late 80s, some influential work happened in the early 90s.
- Overall, within-host models are still less advanced compared to between-host modeling, but it's rapidly growing.