

How to use simulation models

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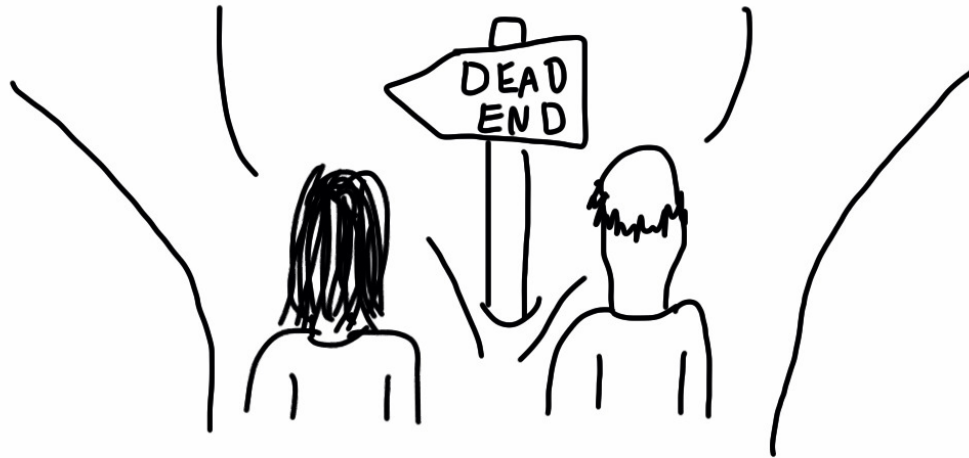
2019-07-11

Why model (infectious diseases)?

- What can we do with models?
- What questions can they help answer?

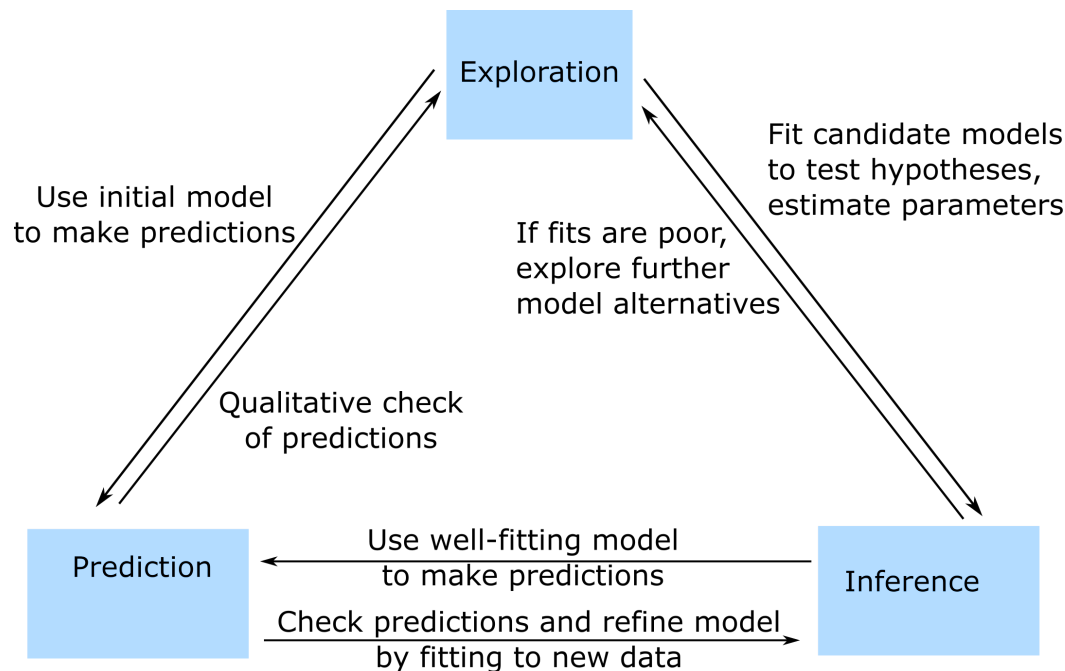
According to the sign
we should go right

But our model
says left



Model uses

- **Exploration:** We can build and analyze models to better understand the complex dynamics of a system and generate hypotheses.
- **Prediction & What-if scenarios:** We can perform virtual experiments and make predictions.
- **Hypothesis testing & Parameter Estimation:** We can fit models to data (inference) to test mechanisms/hypotheses and to estimate parameters.

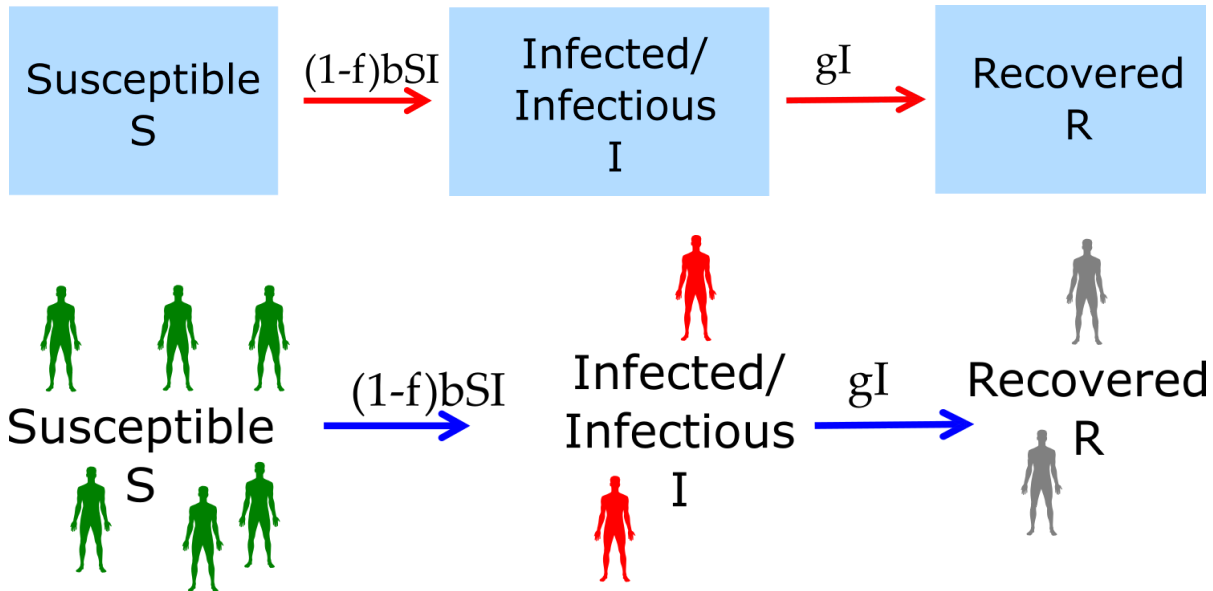


Model-aided exploration and hypothesis generation

Model-aided exploration - an example

- For a single infectious disease outbreak, more intervention/control (through e.g. drugs or social distancing) is generally better.
- If multiple outbreaks are likely and no control is possible beyond the first outbreak (e.g. because of drug resistance or resource limitation) how does the best control strategy change?
- Use a simple model to understand/explore optimal intervention strategies for multi-outbreak settings.
- Details: Handel et al "*What is the best control strategy for multiple infectious disease outbreaks?*" Proceedings of the Royal Society B 2007.

Using a model to answer the question



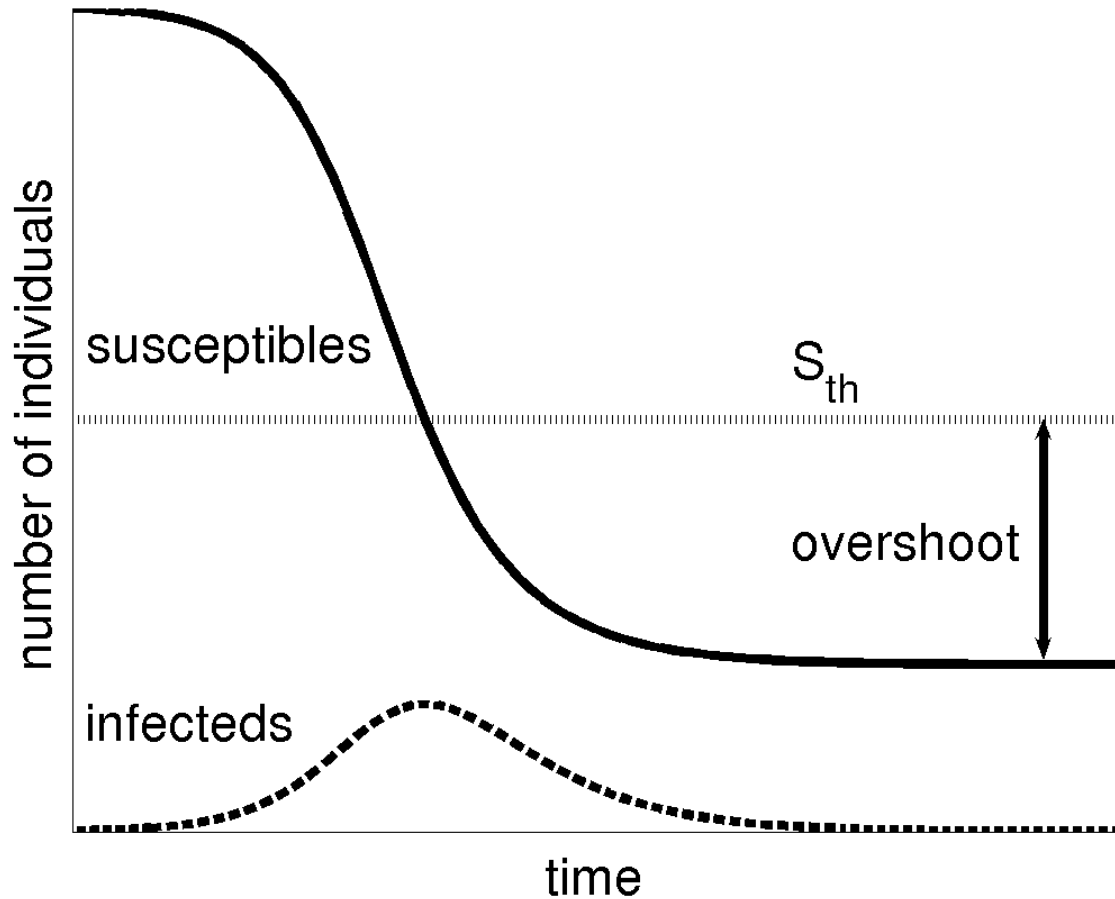
Basic SIR model with control.

$$\dot{S} = -(1-f)bSI$$

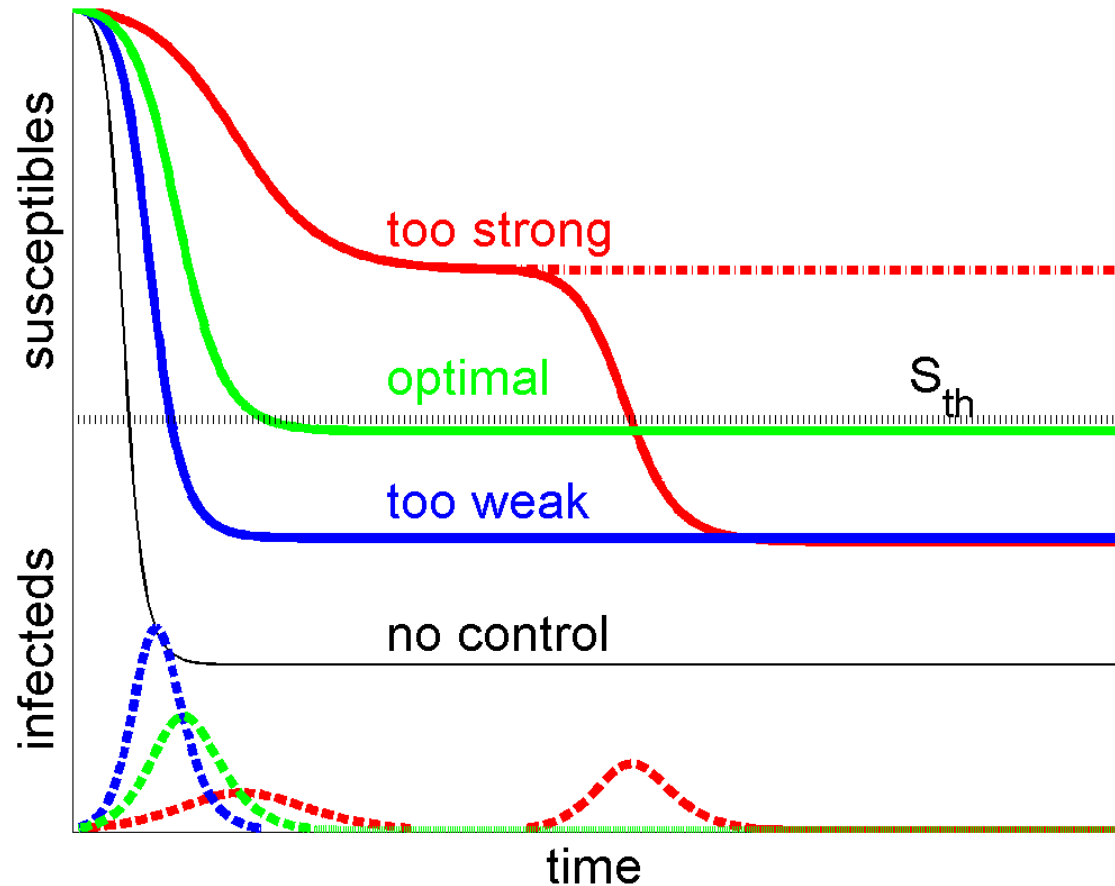
$$\dot{I} = (1-f)bSI - gI$$

$$\dot{R} = gI$$

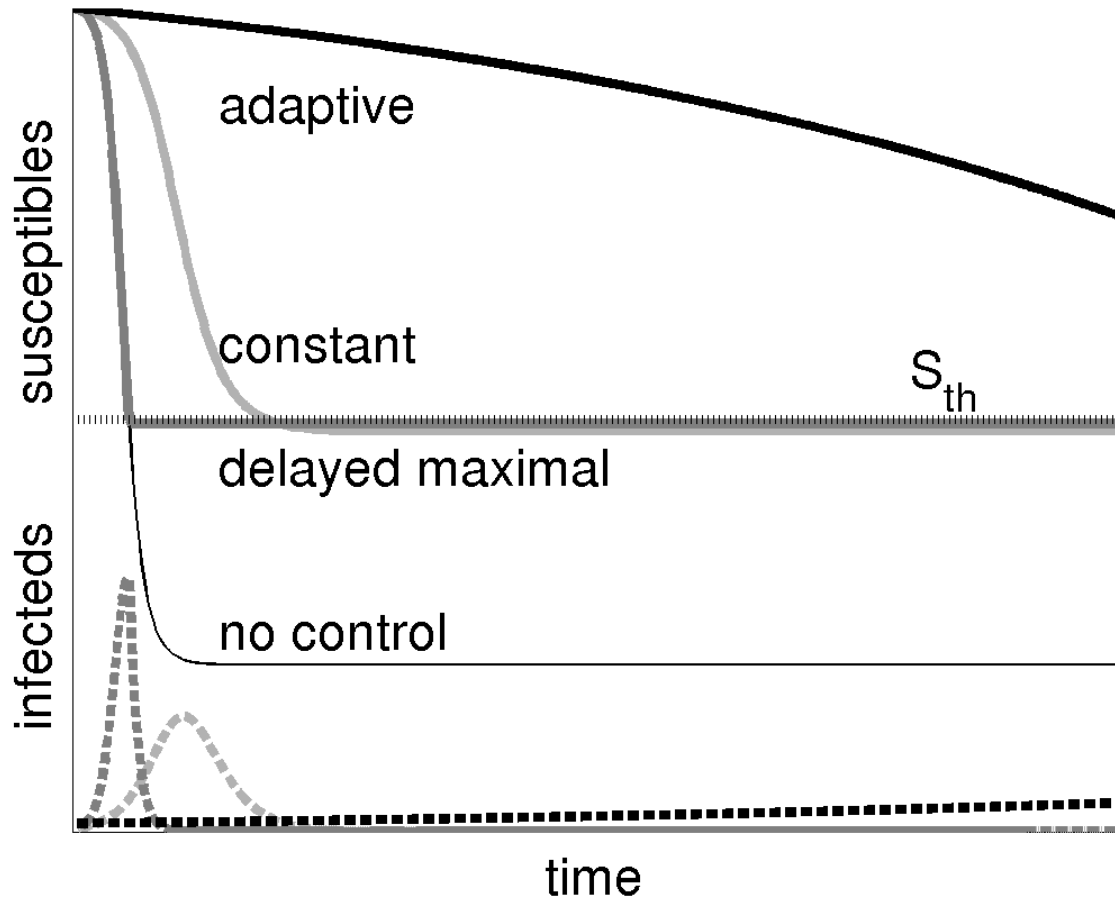
The overshoot concept



Control during multiple outbreaks

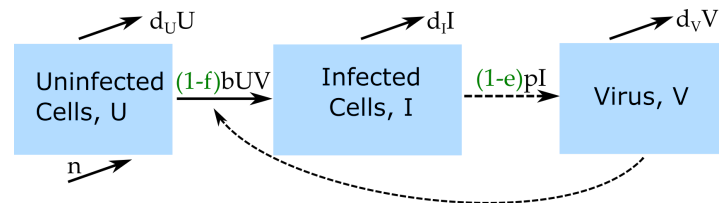
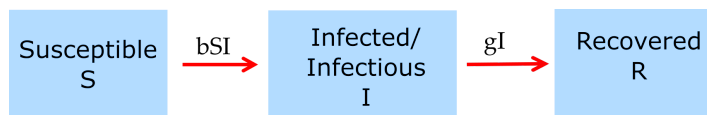


Ways to implement optimal control



Model Exploration - more examples

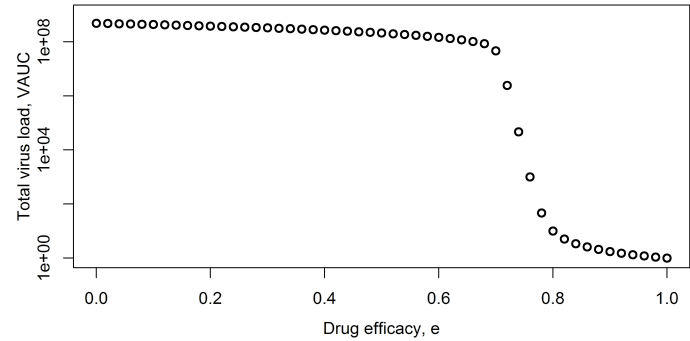
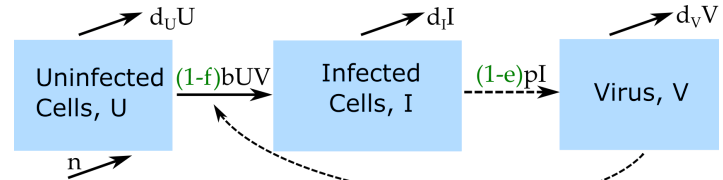
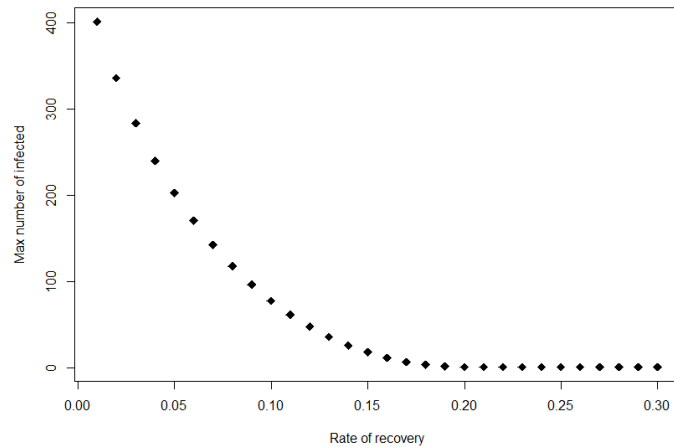
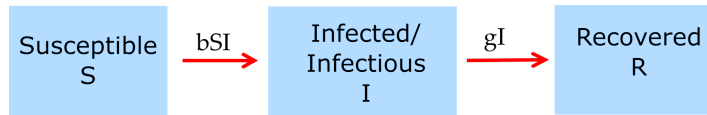
- Looking at the dynamics (time-series) of a model can be useful.
- Often, we are not mainly interested in the time series, but instead some more specific quantity, e.g. total number of infected/pathogens, steady state values, etc.
- We usually want to know how such outcome(s) of interest vary with some parameter(s).
- What do we need to do to answer such questions?



Model Exploration

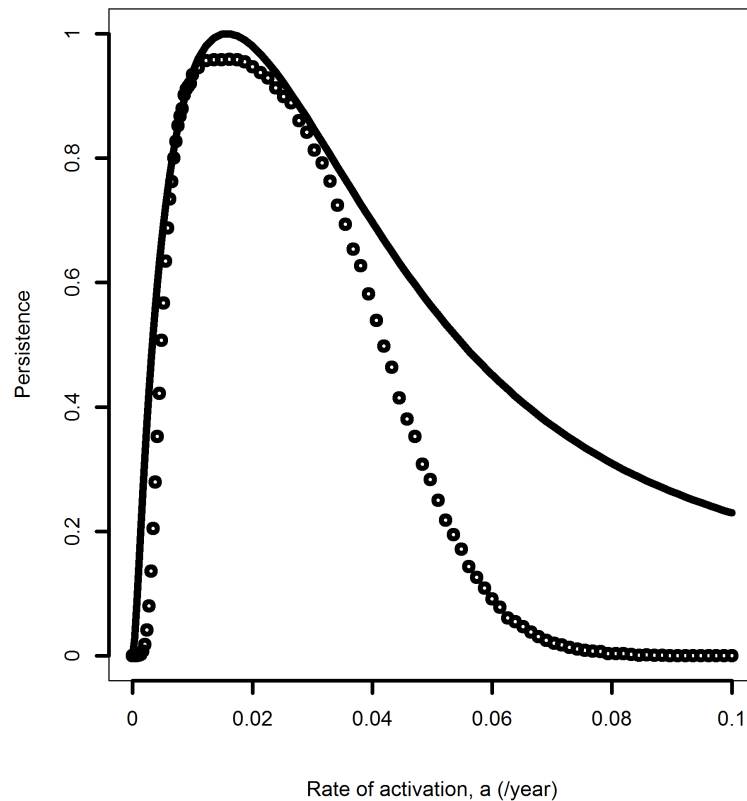
1. Choose some parameter values.
2. Run the simulation model.
3. Record quantities/outcomes of interest.
4. Choose another set of parameter values (usually we only vary one at a time).
5. Repeat steps 2-4 until you got all parameter-outcome pairs of interest.
6. Report (e.g. plot) your findings.

Model Exploration



Model Exploration - Example 2

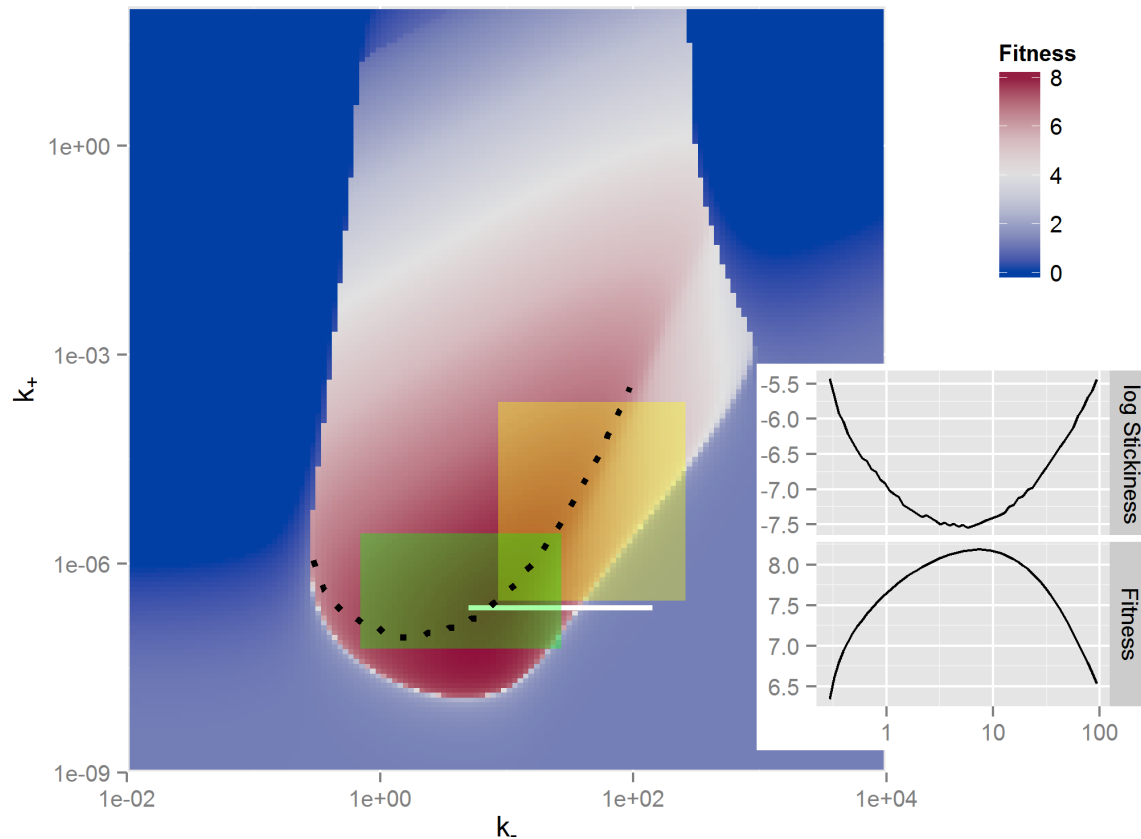
Persistence of TB in a population as a function of latent activation rate. Zheng et al (2014) PLoS One.



Model Exploration - Example 3

Virus fitness as function of virion binding (k_+) and release (k_-) rates.

Handel et al (2014) Proc Royal Soc Interface.



Exploration - summary

- If the system/question is very simple, we might not need a model (e.g. for a single outbreak, all things equal we know more control is better).
- Infectious disease systems are often complex. If we know little about our system and its behavior, building and exploring simple models is often a useful first step.

Exploration - practice

- We could do the model exploration by hand through the DSAIDE/DSAIRM GUI.
- We could automate it by writing R code that loops over parameters and repeatedly calls the underlying model (see e.g. 'Level 2' in the package tutorial).
- The *Model Exploration* app allows you to do such exploration graphically.

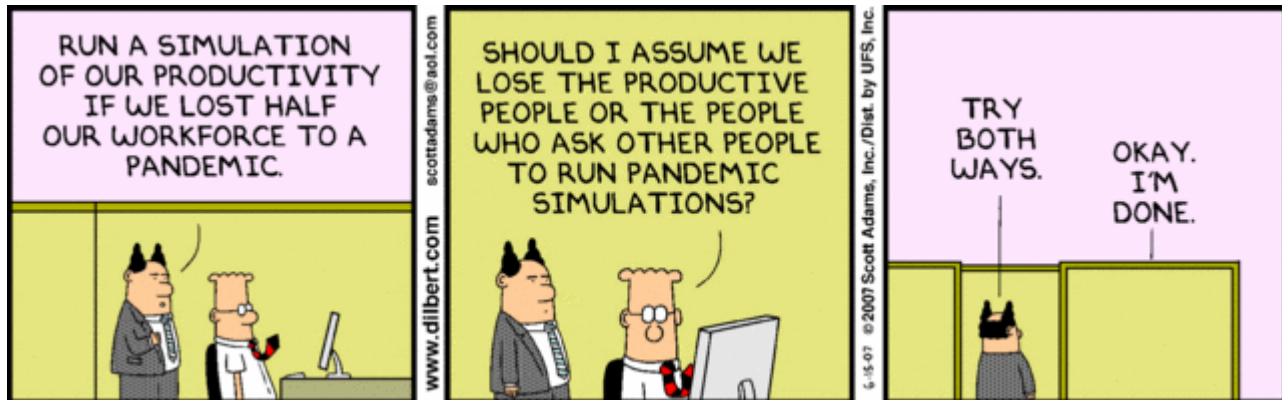
Model-based predictions

Model Predictions/Virtual Experiments

- We saw how we can use models to explore how outcomes of interest change with parameters.
- Model exploration is often useful to gain general insights into a system early on.
- Once we built up our understanding and have a model that we think approximates reality reasonably well, we can potentially move on to making predictions and explore 'what-if' scenarios (virtual experiments).

Prediction types

- Predictions can be of different types:
 - **Qualitative:** Try to predict shape/direction of an outcome (similar to the 'exploration' model use).
 - **Semi-quantitative:** Try to predict the approximate or relative size of an outcome.
 - **Quantitative:** Try to predict (with confidence intervals) the magnitude of an outcome.



Semi-quantitative prediction example

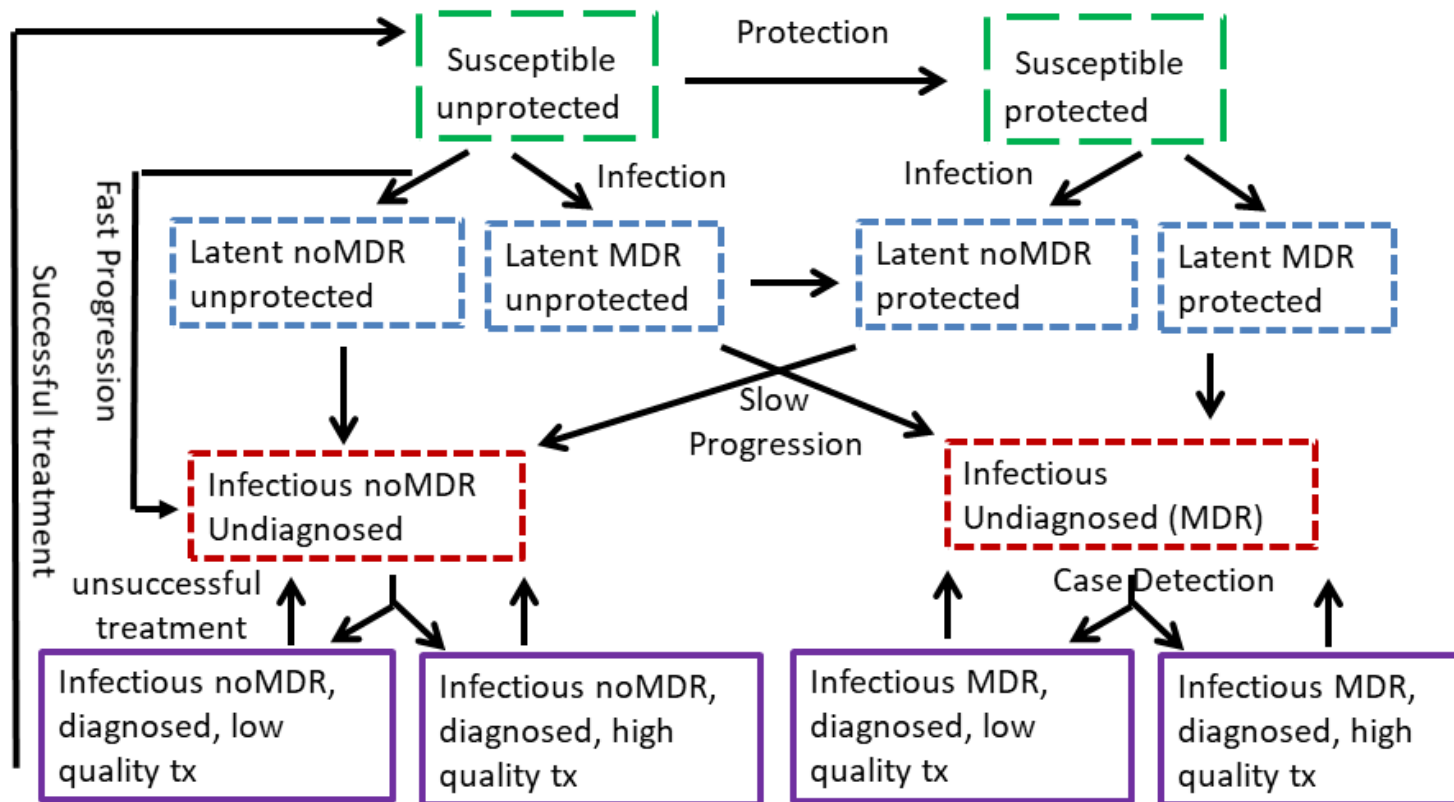
- Multi-group effort to use computer models to predict how different interventions affect TB incidence and prevalence in 2025.



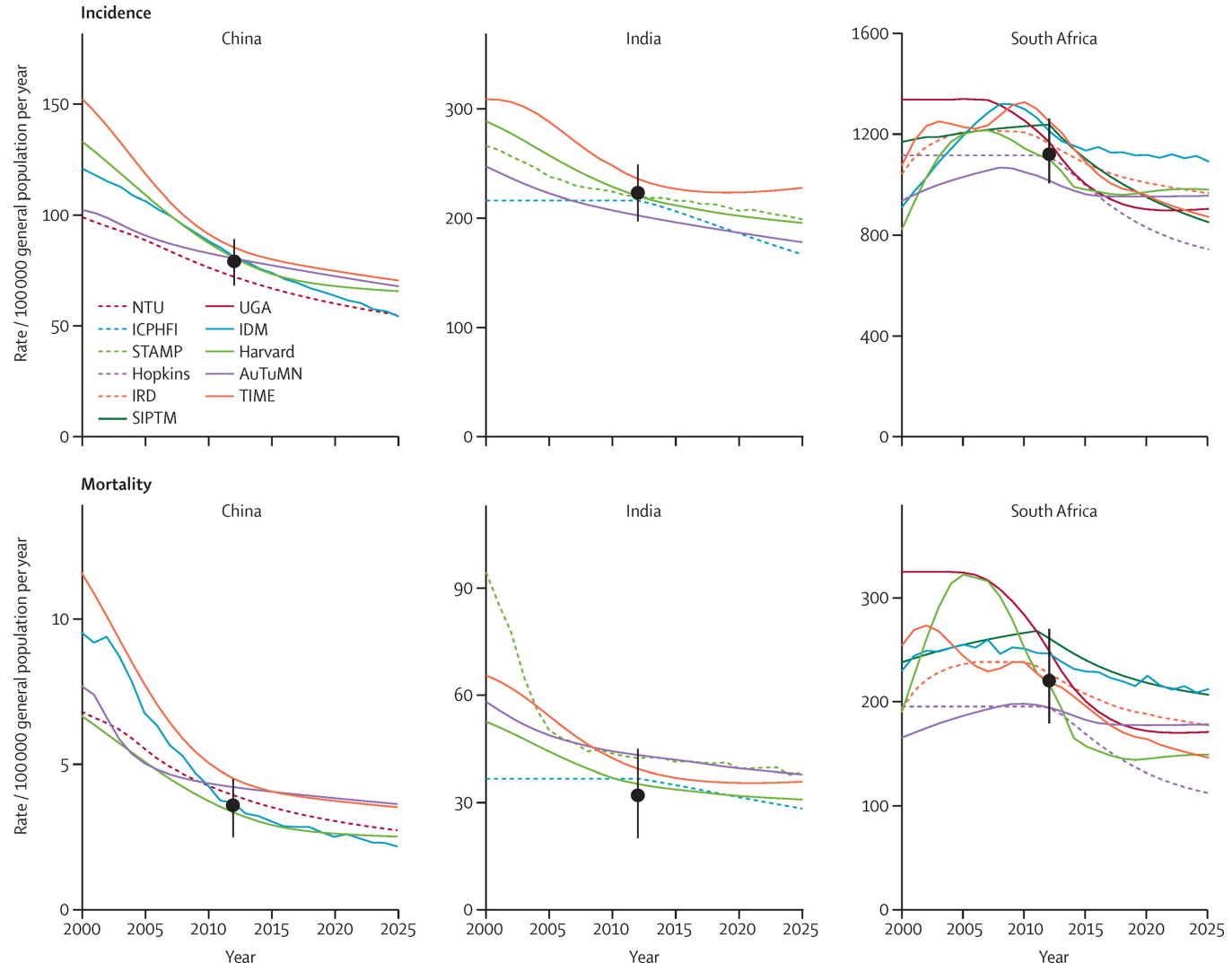
- More details:
 - Houben et al "*Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models.*" Lancet Global Health, 2016.
 - Menzies et al "*Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models.*" Lancet Global Health, 2016.

UGA model

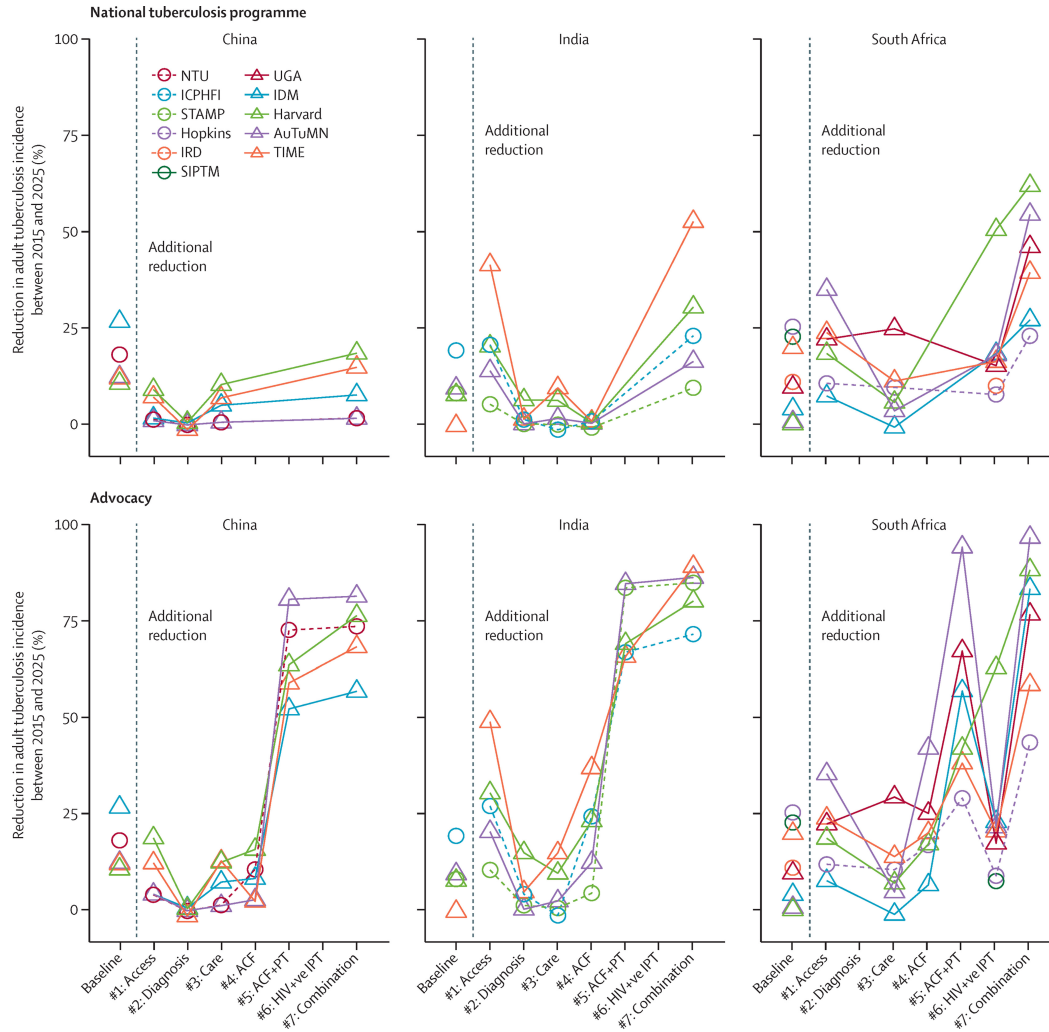
- Ordinary differential equation (ODE) model with a total of 72 compartments/equations.



Model calibration



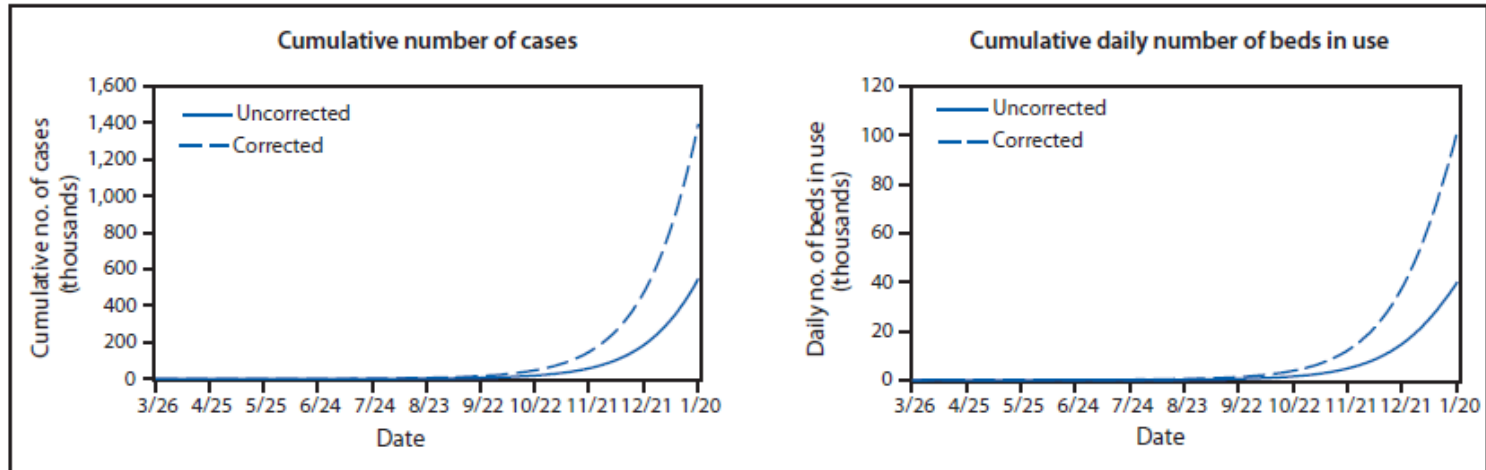
Model predictions



Quantitative prediction example

- Trying to predict the 2014 Ebola outbreak.
- Many different groups built models to try and predict the outbreak dynamics and impact of interventions.

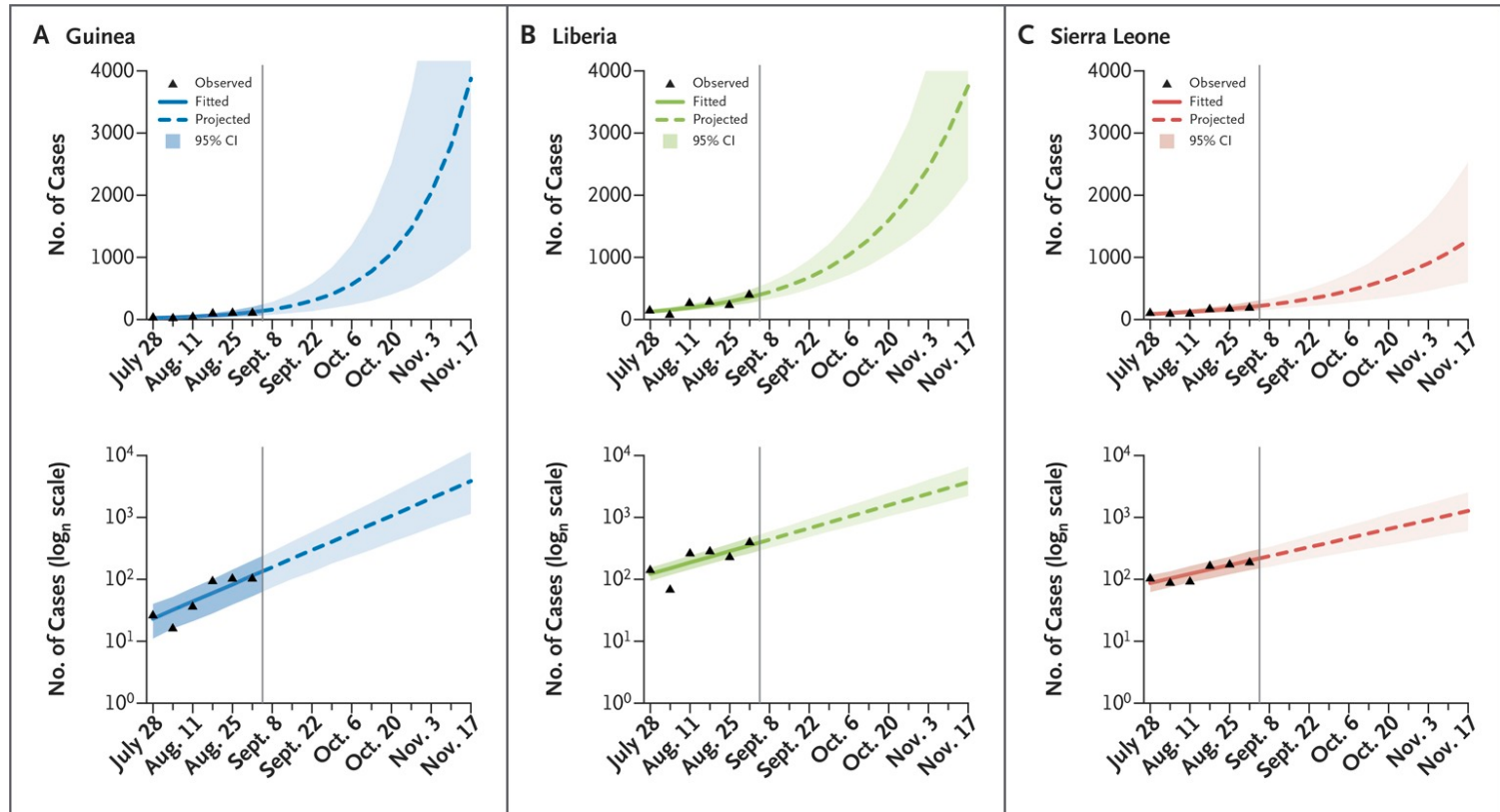
Ebola prediction model 1



Meltzer et al 2014 MMWR
(<https://www.cdc.gov/mmwr/preview/mmwrhtml/su6303a1.htm>)

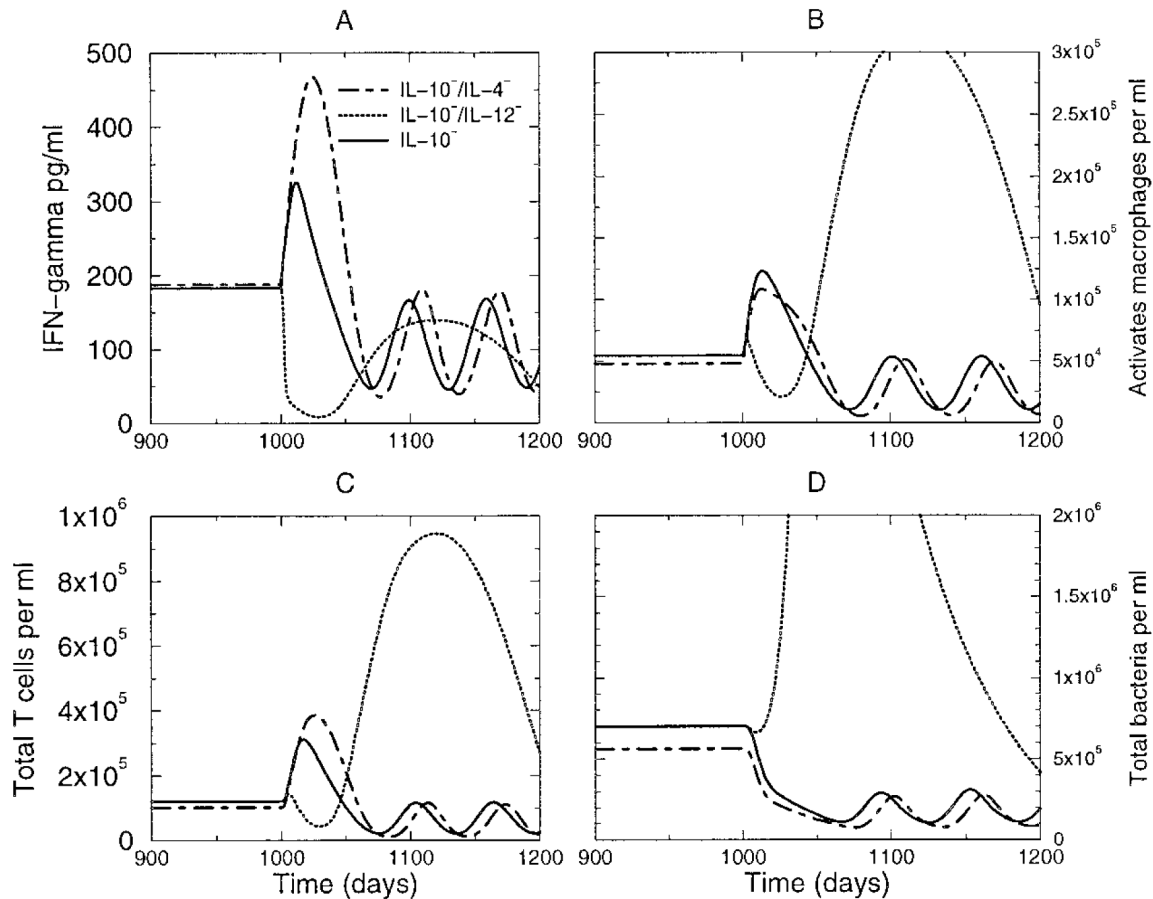
"CDC model predicts 1.4 million cases of Ebola by January!"

Ebola prediction model 2



WHO Ebola Response Team, NEJM 2016
(<https://www.nejm.org/doi/full/10.1056/NEJMoa1411100>)

Within-host model prediction example



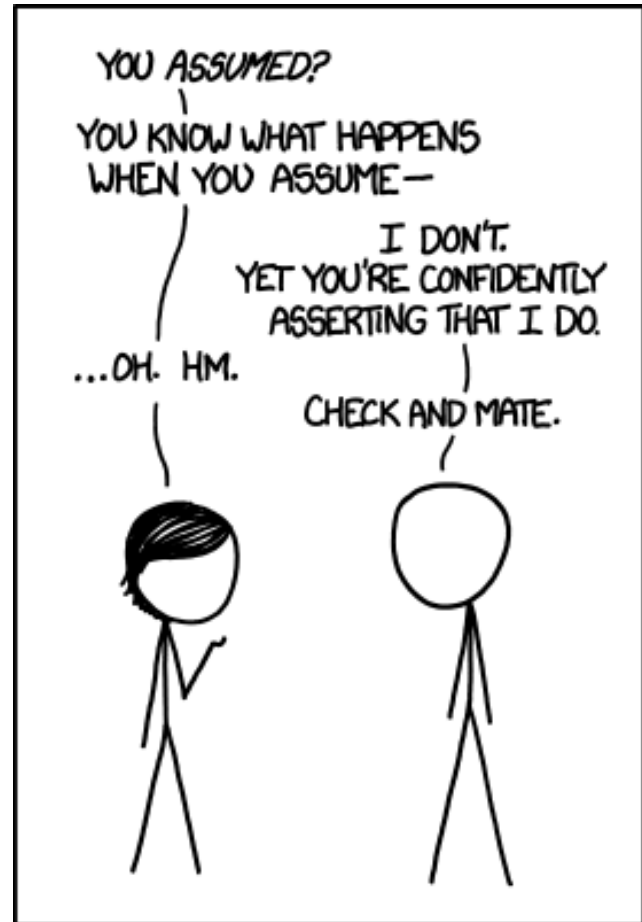
Prediction of TB infection outcomes for depletion of certain cytokines.
Wigginton and Kirschner (2001) J Immunology.

Prediction - comments

- Simple models are best for qualitative and semi-quantitative predictions.
 - If we increase vaccination, does incidence/prevalence drop faster or slower than linear?
 - As we increase drug dose, how does it affect pathogen load?
- If we want to make precise and detailed predictions, we generally need very detailed (complex) models.
 - Detailed models are 'data hungry' and often the data are not available.
 - Detailed models are difficult to write and analyze.

Prediction - comments

All models makes simplifying assumptions. Thus, predictions are only reliable if the underlying model is a good approximation of the real system.



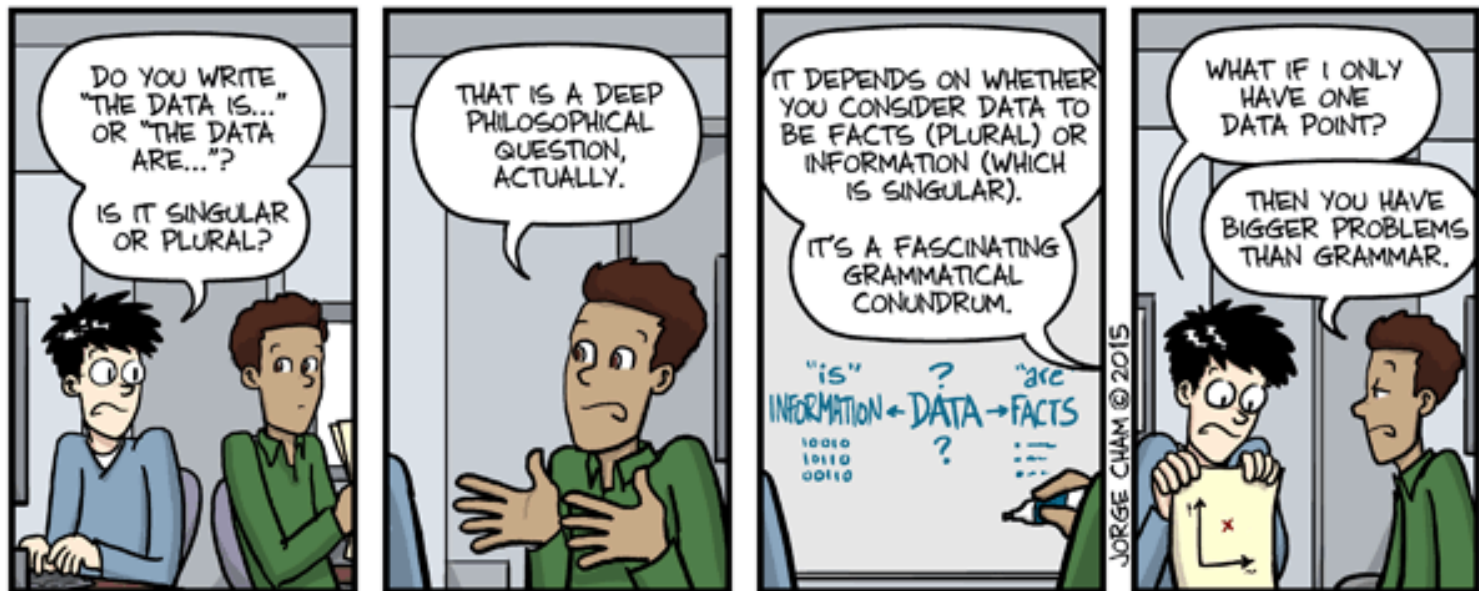
Prediction - practice

- The *Antiviral treatment* DSAIRM app allows you to make predictions regarding the impact of drug treatment.
- The *ID Control for multiple outbreaks* DSAIDE app allows you to explore the example given above in more detail.

Model fitting

Fitting models to data

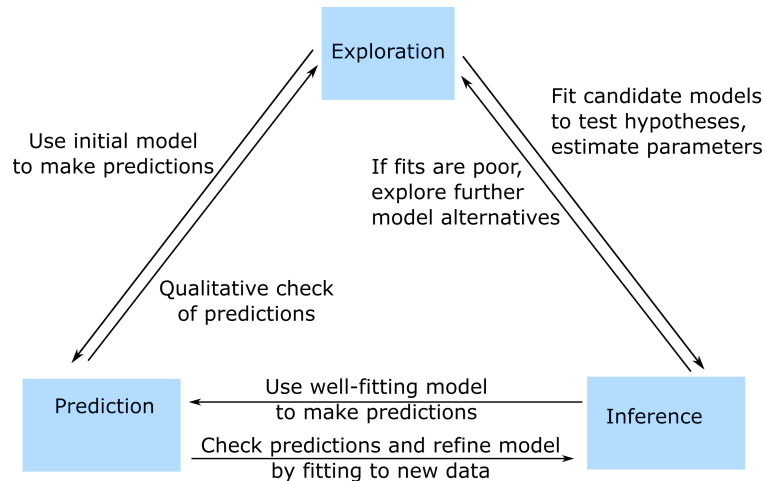
- We build models based on what we assume/know goes on in a specific system.
- We can use models to explore systems and make specific predictions.
- This can be done in the absence of data.
- Adding data to the mix allows us to do more. If we have the right data, we can fit models to it.



JORGE CHAM © 2015

Model testing/validation

- At some point, we need to bring our model results in contact with data to see how our model performs.
- Ideally, there is a loop/spiral:
 1. formulate assumptions/hypotheses
 2. build and analyze model(s)
 3. generate hypotheses/make predictions
 4. compare to data
 5. repeat



Model testing/validation

- The same loop happens in all of science, just often without the explicit use of mathematical models:
 1. have (specify) assumptions about system
 2. generate hypotheses/predictions based on implicit models
 3. do experiment(s)
 4. compare hypotheses/predictions to data
 5. repeat

Hypothesis testing with non-mechanistic models

- We usually test hypotheses by collecting data and performing statistical tests to see if there is a pattern (H_1) or not (H_0).
- The statistical tests can discriminate between no pattern and some kind of pattern/correlation.
- If data was collected properly, one can often conclude that there is a causal link. But one can't say much about the mechanisms leading to the observed patterns.

Hypothesis testing with mechanistic models

- With mechanistic simulation models, we can directly **test hypotheses/mechanisms**: We can formulate different models, each representing a set of hypotheses/mechanisms. The quality of fit of each model to the data lends support to specific models/mechanisms.
- The mechanism(s) of the best fitting model are more likely to be correct than those of the less good fitting models.

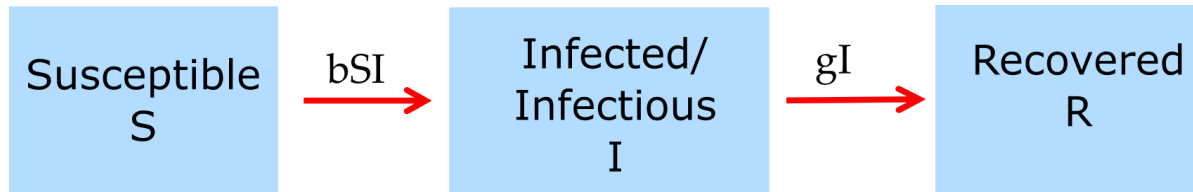
Model fitting example 1

- Norovirus can cause infection through a common source (e.g. food), or transmit person-to-person.
- The Question: For a given Norovirus outbreak, is transmission purely person-person, or is there also a common source?
- The approach: build models for each hypothesis, fit to data and evaluate.



Model/Hypothesis 1

Person-person transmission is the only transmission mechanism



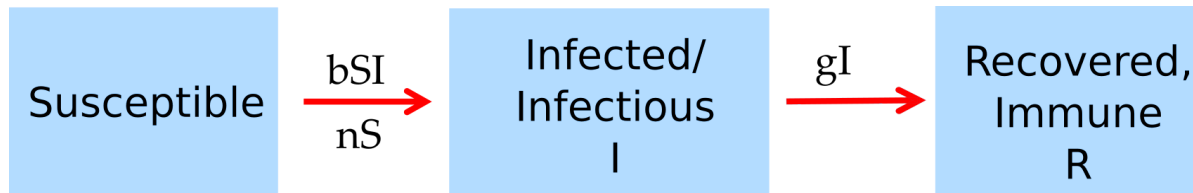
$$\dot{S} = -bSI$$

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

$$\dot{R} = gI$$

Model/Hypothesis 2

Environmental transmission is **also** an important transmission mechanism



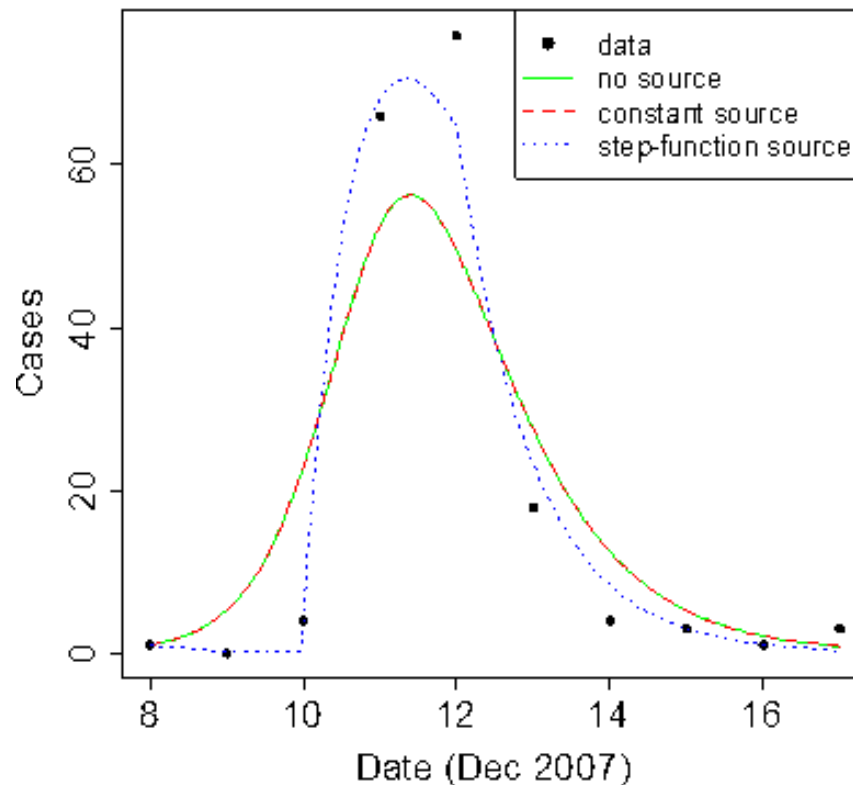
$$\dot{S} = -\mathbf{nS} - bSI$$

$$\dot{I} = \mathbf{nS} + bSI - gI$$

$$\dot{R} = gI$$

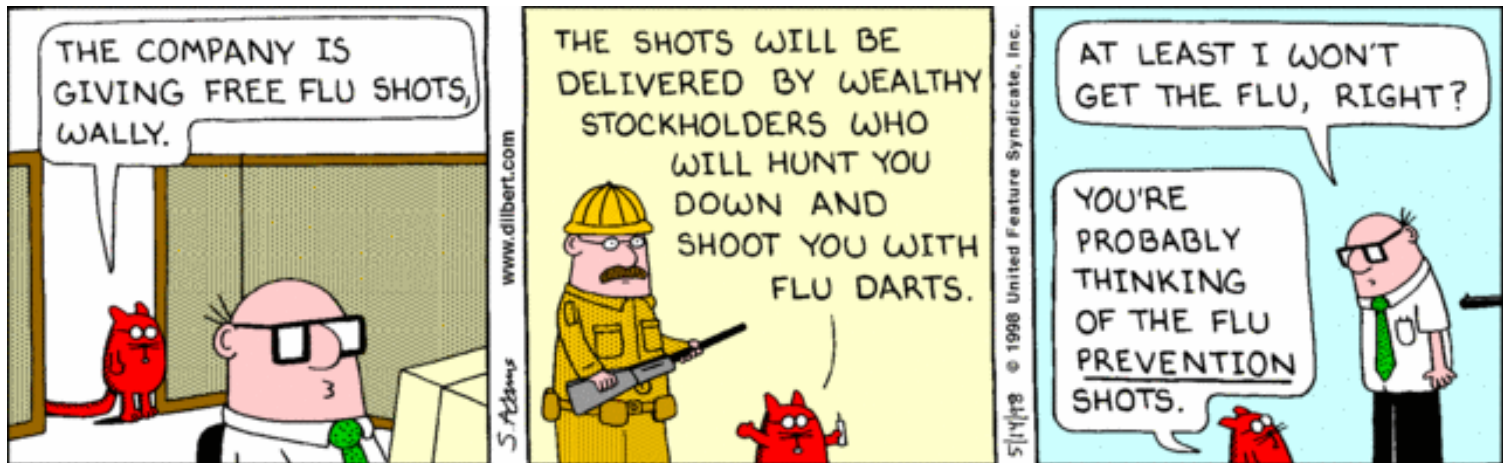
Model fits

- Model with constant source (red, $n > 0$ for duration of outbreak) did not perform better than the no source model (green, $n = 0$).
- Model with extra source between Dec 10-12 (blue, $n > 0$ between 12/10-12/12, 0 otherwise) did best (AIC comparison).



Model fitting example 2

- Investigate the mechanism of drug action of neuraminidase inhibitors against influenza.
- The Question: What is the mechanism of action of neuraminidase inhibitors, is it reducing virus production of infected cells or infection of uninfected cells?
- The approach: build models for each mechanism/hypothesis, fit to data and evaluate.



Model/Hypothesis 1

Neuraminidase reduces infection rate of uninfected cells.

$$\dot{U} = -b(\mathbf{1} - \mathbf{e})UV$$

$$\dot{I} = b(\mathbf{1} - \mathbf{e})UV - d_I I$$

$$\dot{V} = pI - d_V V - gb(\mathbf{1} - \mathbf{e})UV$$

Model/Hypothesis 2

Neuraminidase reduces rate of virus production by infected cells.

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

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

$$\dot{V} = p(\mathbf{1} - \mathbf{f})I - d_V V - gbUV$$

Model fits

Solid lines show best fits of model with mechanism 1, dashed lines show model with mechanism 2. Statistical comparison suggests model/mechanism 2 explains the data better ($AICc_1 = -56$ and $AICc_2 = -82$).

Parameter estimates

- By fitting models, we can also **estimate biologically meaningful parameters**.
- The parameters in our models often represent important biological quantities (e.g. the duration of the infectious period).
- Fitting returns estimates for the best-fit parameter values.
- If we believe the model is a decent representation of the real system, we might consider the estimated parameter to be reliable.

In example 1, an estimate of $g=0.5/\text{day}$ means the estimated duration of the infectious period is 2 days.

$$\begin{aligned}\dot{S} &= -nS - bSI \\ \dot{I} &= nS + bSI - \mathbf{g}I \\ \dot{R} &= \mathbf{g}I\end{aligned}$$

In example 2, an estimate of $f=0.98$ means the drug reduces virus production by 98%.

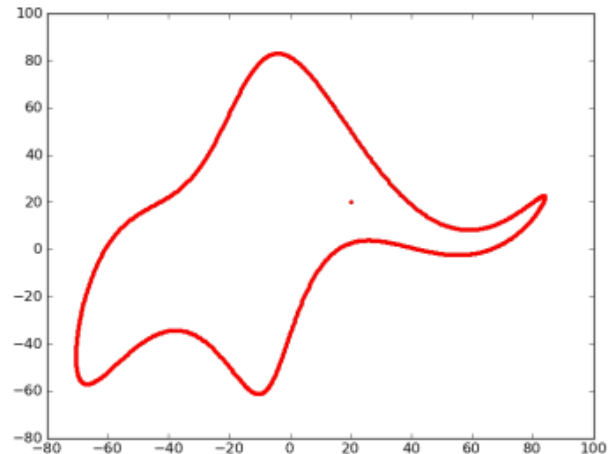
$$\begin{aligned}\dot{U} &= -bUV \\ \dot{I} &= bUV - d_I I \\ \dot{V} &= p(\mathbf{1} - \mathbf{f})I - d_V V - gbUV\end{aligned}$$

Fitting comments

- Fitting mechanistic models is conceptually the same as fitting regression models, but technically more challenging.
- If a non-mechanistic model doesn't fit well, we only learned that we need another model.
- If a mechanistic model that was built based on our best knowledge doesn't fit well, we have learned something useful!
- Complex models with many parameters can provide good fits for spurious reasons.
- It is important to keep models simple to prevent overfitting.

With four parameters I can fit an elephant, and with five I can make him wiggle his trunk.

John von Neumann



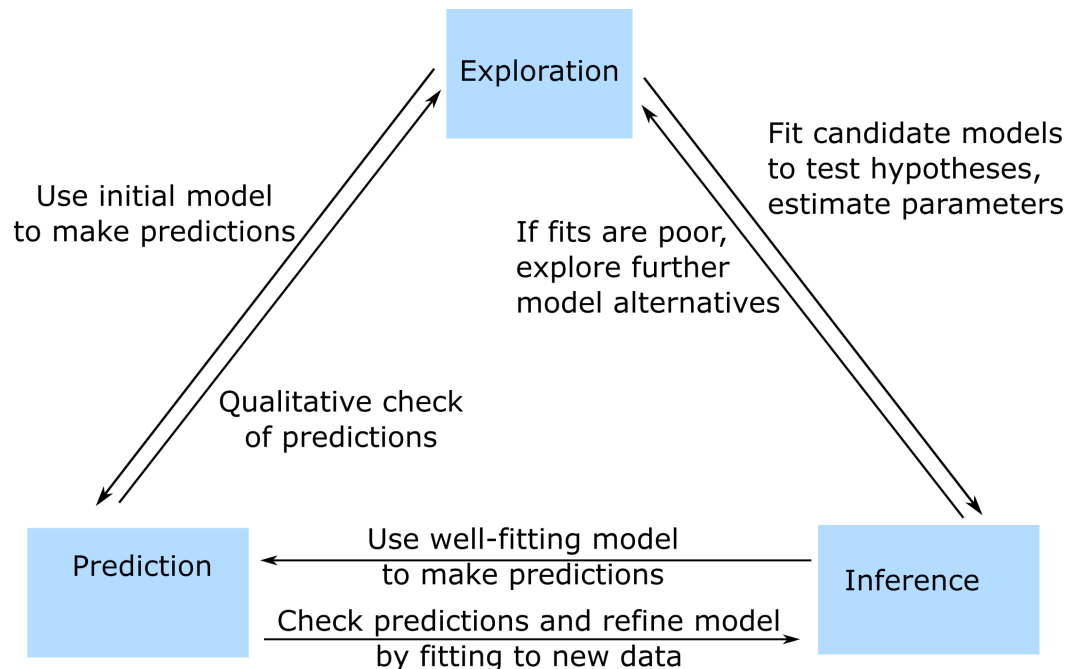
<https://bit.ly/31UB3v9>

Fitting - practice

- The *Basic Model fitting* app in DSAIRM provides an introduction, the other apps in the *Model fitting* section teach further concepts.
- The apps in the *Model fitting* section of DSAIDE teach some concepts of model fitting.

Model uses - summary

- Simulation models can be built and analyzed without fitting to data.
- 'Data-free' model use allows exploration and potentially prediction.
- Hypothesis/mechanism testing and parameter estimation are possible if models are combined with data.
- A project often uses models for several of the described approaches.



Literature

- Joshua Epstein, "Why model", <http://jasss.soc.surrey.ac.uk/11/4/12.html>
- Rob May, "Uses and Abuses of Mathematics in Biology",
doi:10.1126/science.1094442
- Fred Brauer, "Mathematical epidemiology is not an oxymoron",
doi:10.1186/1471-2458-9-S1-S2
- Garnett et al, "Mathematical models in the evaluation of health
programmes", doi:10.1016/S0140-6736(10)61505-X