Mecanistic (compartmental) models in life science

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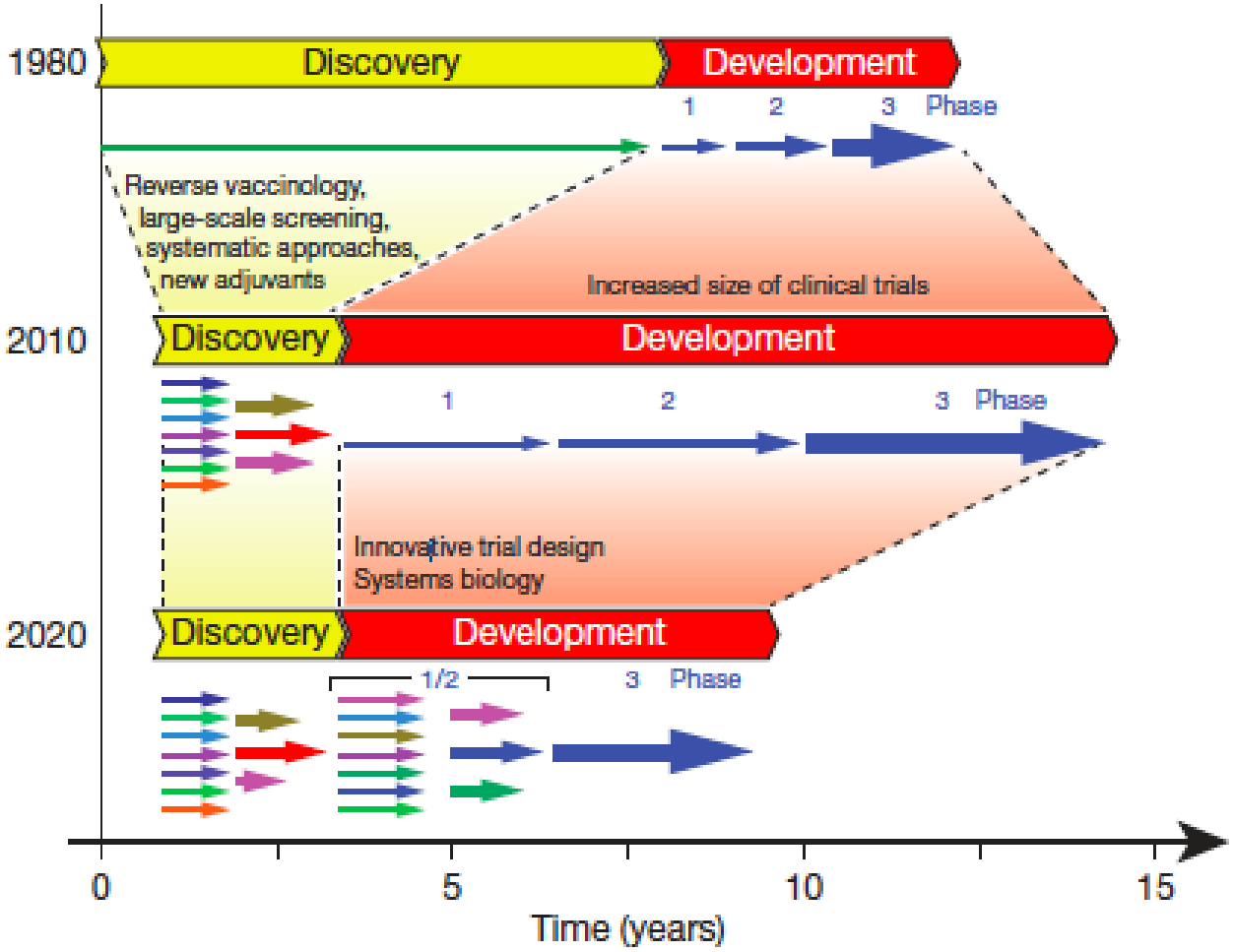
Motivation: All models are wrong, but some are useful!



Rappuoli R, Aderem A. A 2020 vision for vaccines against HIV, tuberculosis and malaria. Nature 2011;473:463–469.

Compartmental models: how

- Delimit the problem of interest you want to study
- Collect available data/Generate data
- Identify the main actors contributing to the observed phenomena:
  - Cell types (e.g. in immunology…)
  - Subset of the population (e.g. in epidemiology…)
  - …
- Clarify the interactions among the actors
- Translate in equations

Observables

Compartments

ODE
Compartments → State variables
Interactions → Coefficients

Compartmental models ODE based: why

- Use previous knowledge about the question of interest
- Easily integrate additional knowledge when available to improve the model
- Clearly understand the interactions, the biological meaning of parameters
- Improved comprehension of the outputs
- Longitudinal data → dynamical systems → ODE
- Many powerful tools exist to analyze and solve ODE (R, Python, Matlab…)

What do we expect from a model?

Modeling imply high semplification of the mechanism underlying the case studyed → we could not include every variable in the model because it will be impossible to use in practice.

BUT

With a good balance between parsimony and exhaustiveness, models can be succesfully used to:

- Improve the understanding of a phenomena
- Test multiple hypotheses under different scenarios
- Suggest experiments to better collect data to explain some outputs
- Predict the evolution after the observed horizon
- Personalized medicine

Class overview

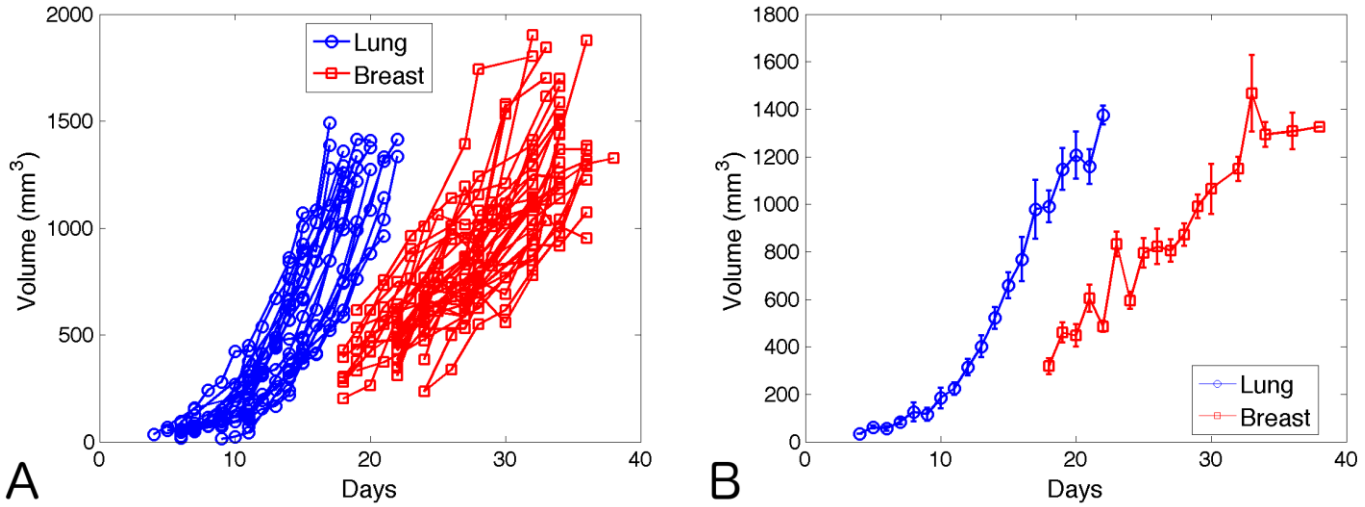
In this class we are going to introduce mechanistic modeling in life science and talk about the forward problem:

- How to build a model starting from a case study:
  - What are the main actors and their interactions?
  - Which questions we want to answer?
- Which structural problems should be taken into account before using the model
- Model simulation to produce the outcome of some measurements: calibration

Examples from the literature: tumor growth

Tumor growth is the result of several complex biological processes (regulation of proliferation, angiogenesis,…).
But: all these processes together produce a macroscopic expansion of the tumor volume, which can be described with simple laws. Two main goals:

- Testing growth hypotheses
- Predict future course of tumor progression with or without therapy



Brute data sets from lung breast experiments.
A. All animals' growth curves. B. Average curves.

Benzekry, Sébastien, et al. "Classical mathematical models for description and prediction of experimental tumor growth." *PLoS Comput Biol* 10.8 (2014): e1003800.

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Examples from the literature: tumor growth

$V = \text{tumor volume}$

Exponential model:

$$\begin{cases} \frac{dV}{dt} = aV \\ V(t=0) = V_0 \end{cases}$$

Ok for description of the first proliferation phase
But it has been observed that the relative growth rate decreases with time!

Logistic model:

$$\begin{cases} \frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right) \\ V(t=0) = V_0 \end{cases}$$

Maximal volume or carrying capacity

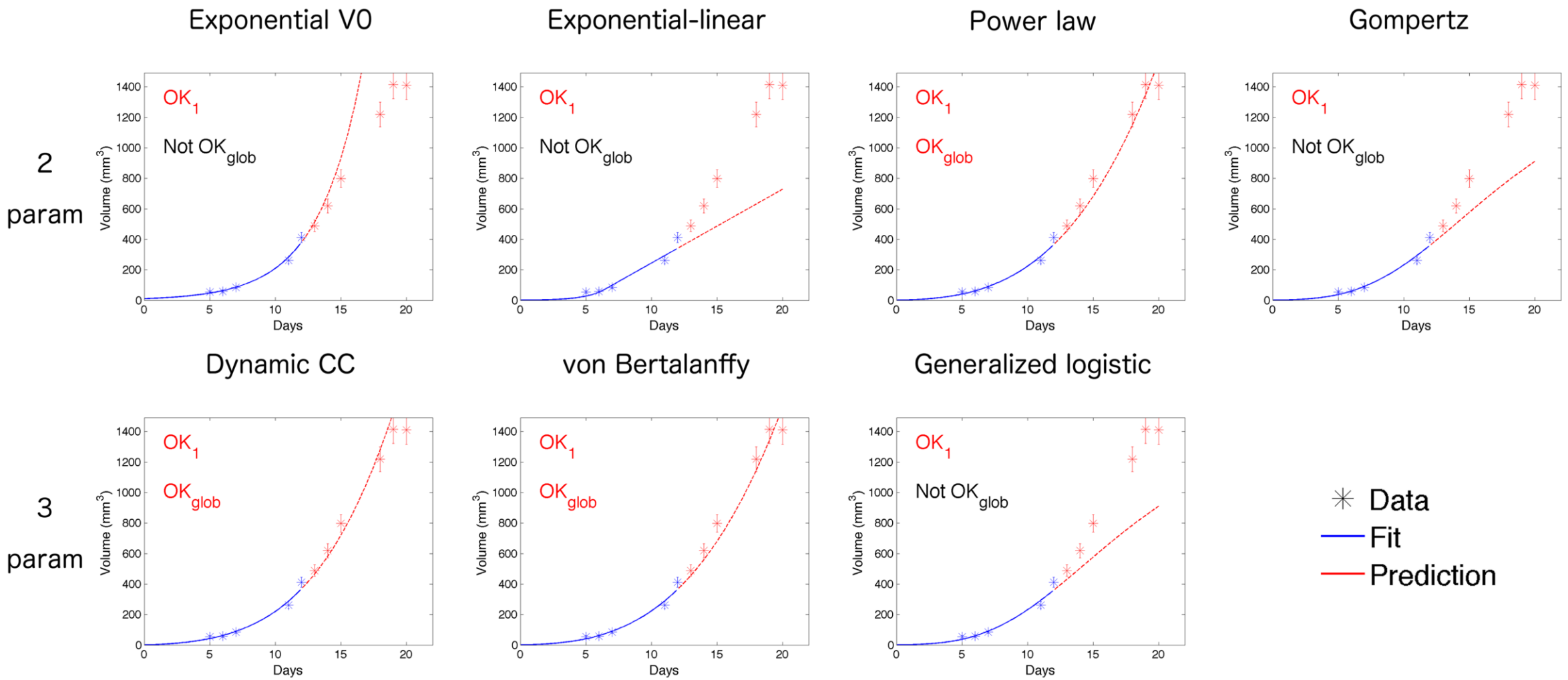
Gompertz model:

$$\begin{cases} \frac{dV}{dt} = ae^{-\beta t}V \\ V(t=0) = V_0 \end{cases}$$

Exponential decay of a

Initial proliferation rate

Examples from the literature: tumor growth

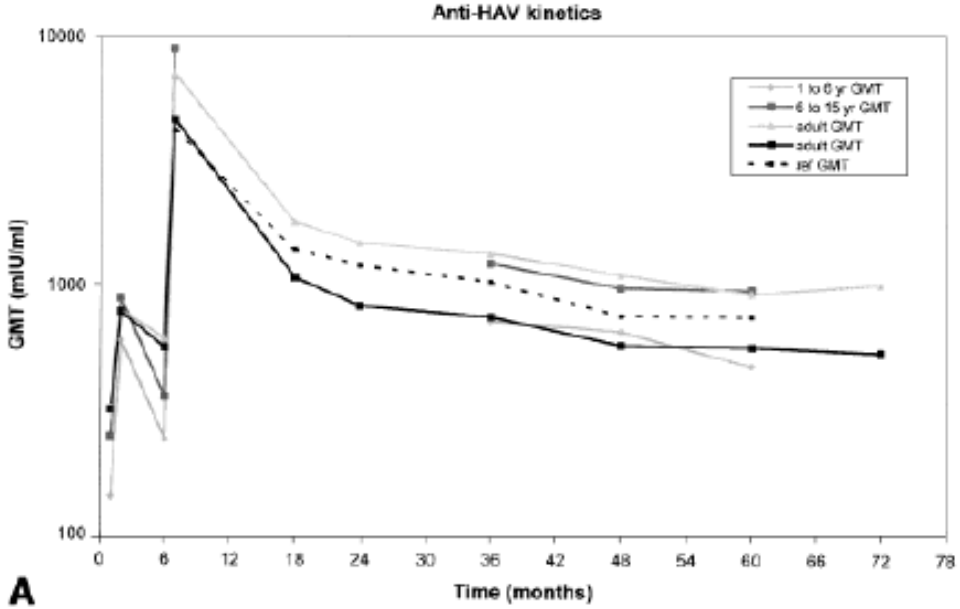


Representative examples of performances of varius models for the lung data set. Five data points were used to estimate the animal parameters and predict future growth.

Examples from the literature: antibodies dynamic upon vaccination

Vaccine induced immunity is typically evaluated by means of the antibody titers, secreted by B-lymphocytes. It has been experimentally observed the existance of B-cells with an increased life span (bone marrow). Understanding and predicting the long-term persitance of humoral immunity after vaccination is crucial:

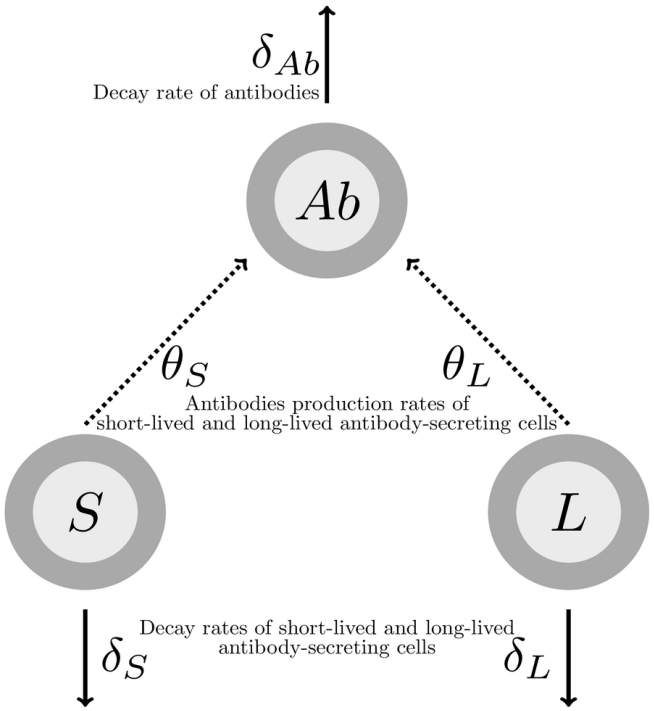
- **Immunology**: quantitative research over time-scales+understanding epidemiology
- **Vaccinology**: help in clinical trial for immunity conferred prediction
- **Health policy**: make recommendations on booster vaccination



Long-term kinetics for anti HAV

Van Damme, P., et al. "Long-term persistence of antibodies induced by vaccination and safety follow-up, with the first combined vaccine against hepatitis A and B in children and adults." *Journal of medical virology* 65.1 (2001): 6-13.

Examples from the literature: antibodies dynamic upon vaccination



$$\begin{cases} \dot{S} = -\delta_S S \\ \dot{L} = -\delta_L L \\ \dot{Ab} = \theta_S S + \theta_L L - \delta_{Ab} Ab \\ S(0) = S_0, L(0) = L_0, Ab(0) = Ab_0 \end{cases}$$

$$Ab(t) = \frac{\phi_S}{\delta_{Ab} - \delta_S} e^{-\delta_S t} + \frac{\phi_L}{\delta_{Ab} - \delta_L} e^{-\delta_L t} + \left(Ab_0 - \frac{\phi_S}{\delta_{Ab} - \delta_S} - \frac{\phi_L}{\delta_{Ab} - \delta_L} \right) e^{-\delta_{Ab} t}$$

$$\phi_S = \theta_S S_0 \qquad \phi_L = \theta_L L_0$$

Asymptotic model:

$$Ab(t) = \frac{\phi_S}{\delta_{Ab} - \delta_S} e^{-\delta_S t} + \frac{\phi_L}{\delta_{Ab}} + \left(Ab_0 - \frac{\phi_S}{\delta_{Ab} - \delta_S} - \frac{\phi_L}{\delta_{Ab}} \right) e^{-\delta_{Ab} t}$$

Andraud, Mathieu, et al. "Living on three time scales: the dynamics of plasma cell and antibody populations illustrated for hepatitis a virus." *PLoS Comput Biol* 8.3 (2012): e1002418.

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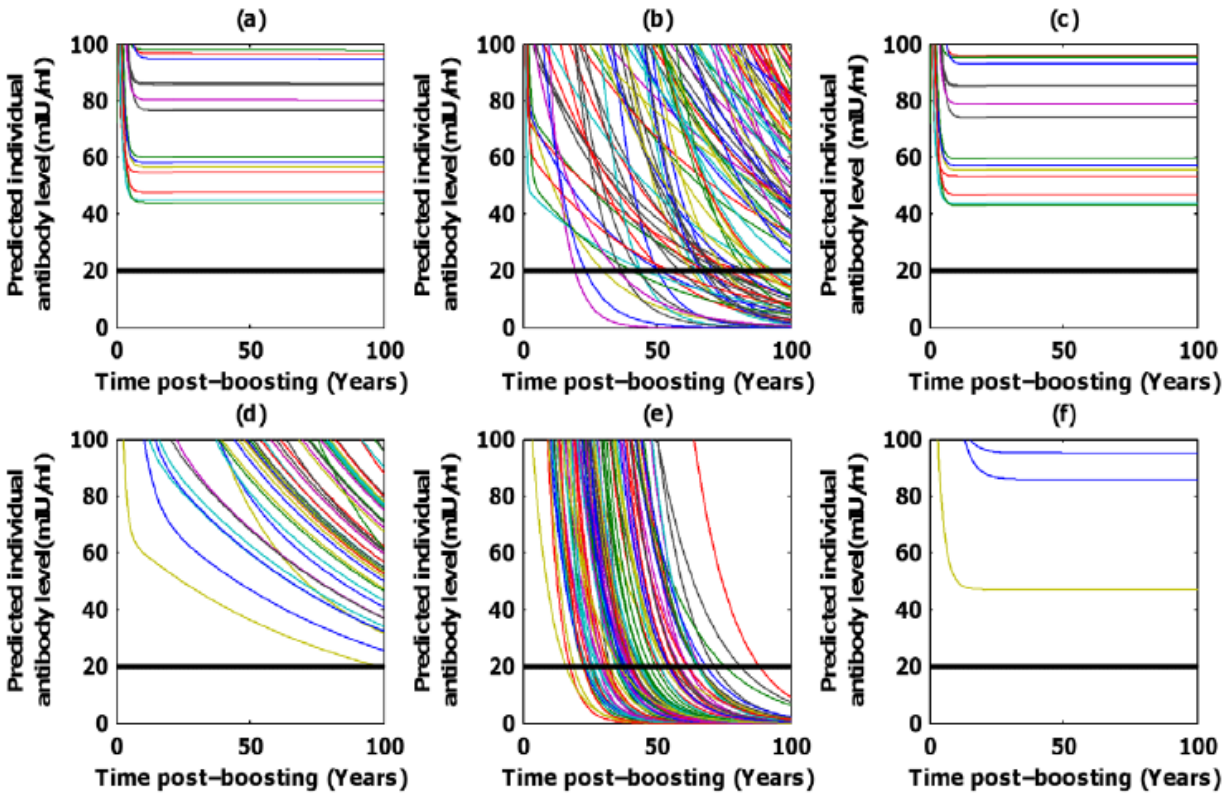
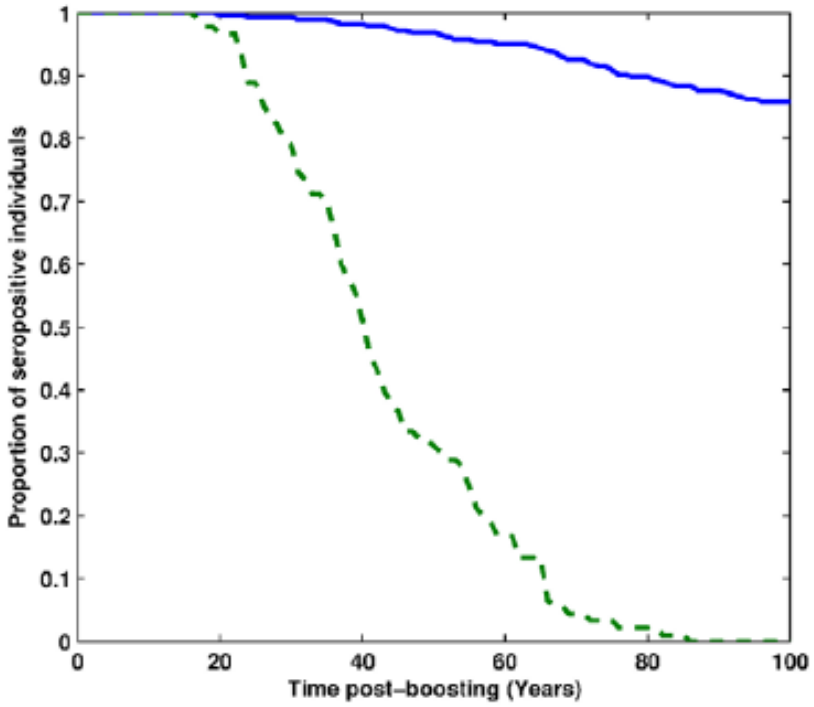
Examples from the literature: antibodies dynamic upon vaccination



Individual prediction plots with a focus around the positivity threshold (20 mIU/ml, black line). (a,c,b) HavrixTM 1440 dataset, (d,e,f) HavrixTM 720 dataset; (a,d) complete model, (b,e) plasma-cell driven kinetics model, (c,f) asymptotic model.



Predicted proportion of seropositive patients according to time post vaccination from the plasma-cell driven kinetics model (full blue line: HavrixTM 1440 dataset , dashed green line: HavrixTM 720 dataset).

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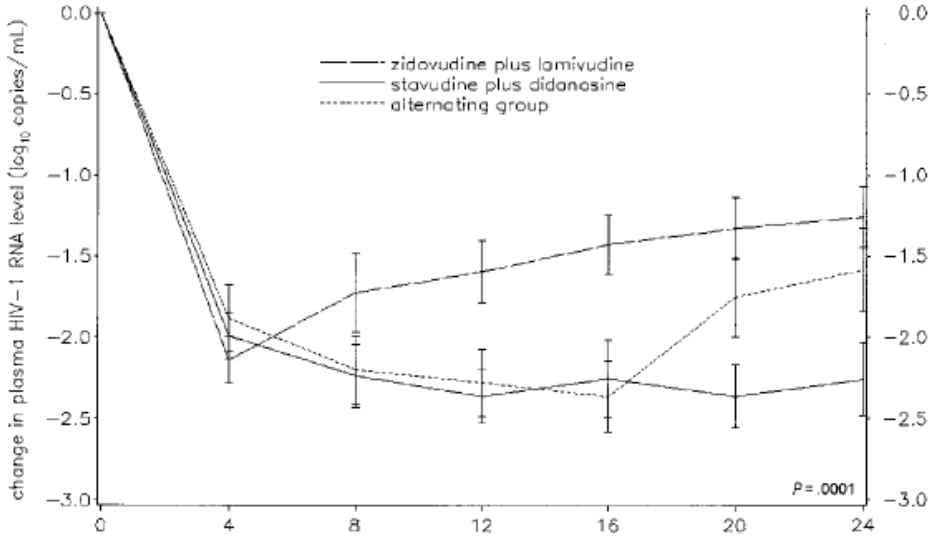
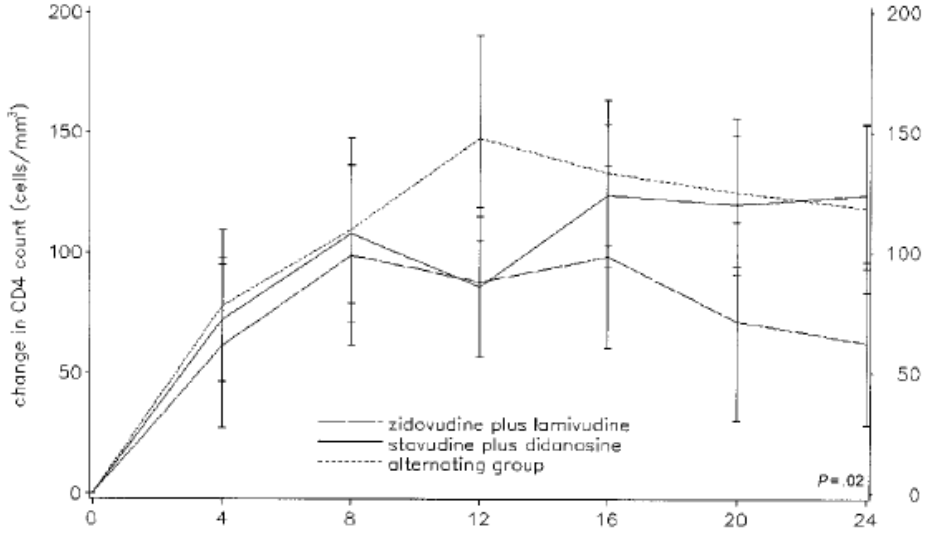
Examples from the literature: HIV and personalized medicine

HIV-infected patients can be treated but not cured with antiretroviral therapy, and guidelines for medical treatments are usually based on empirical results of clinical trials. Several biological processes should be considered: interactions of the viruses and the host immune system, mechanisms of action of the drugs, viral and host characteristics



Viral load



CD4+ T cells

Molina, Jean-Michel, et al. "The ALBI trial: a randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with human immunodeficiency virus." *The Journal of infectious diseases* 180.2 (1999): 351-358.

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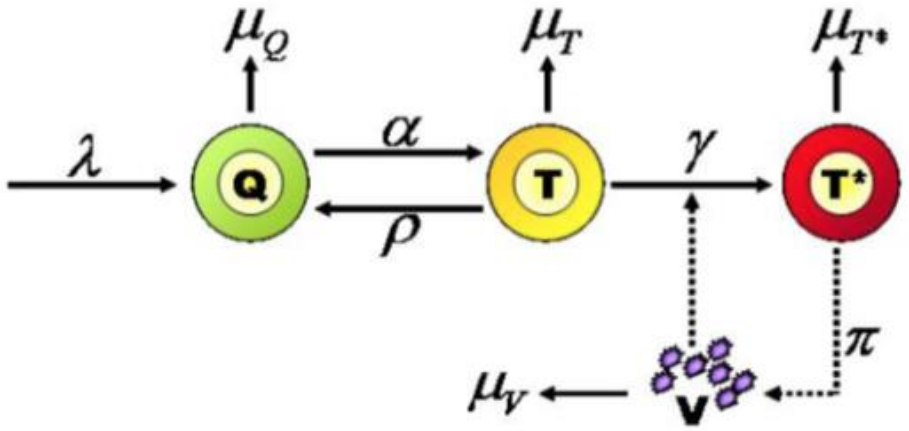
Examples from the literature: HIV and personalized medicine

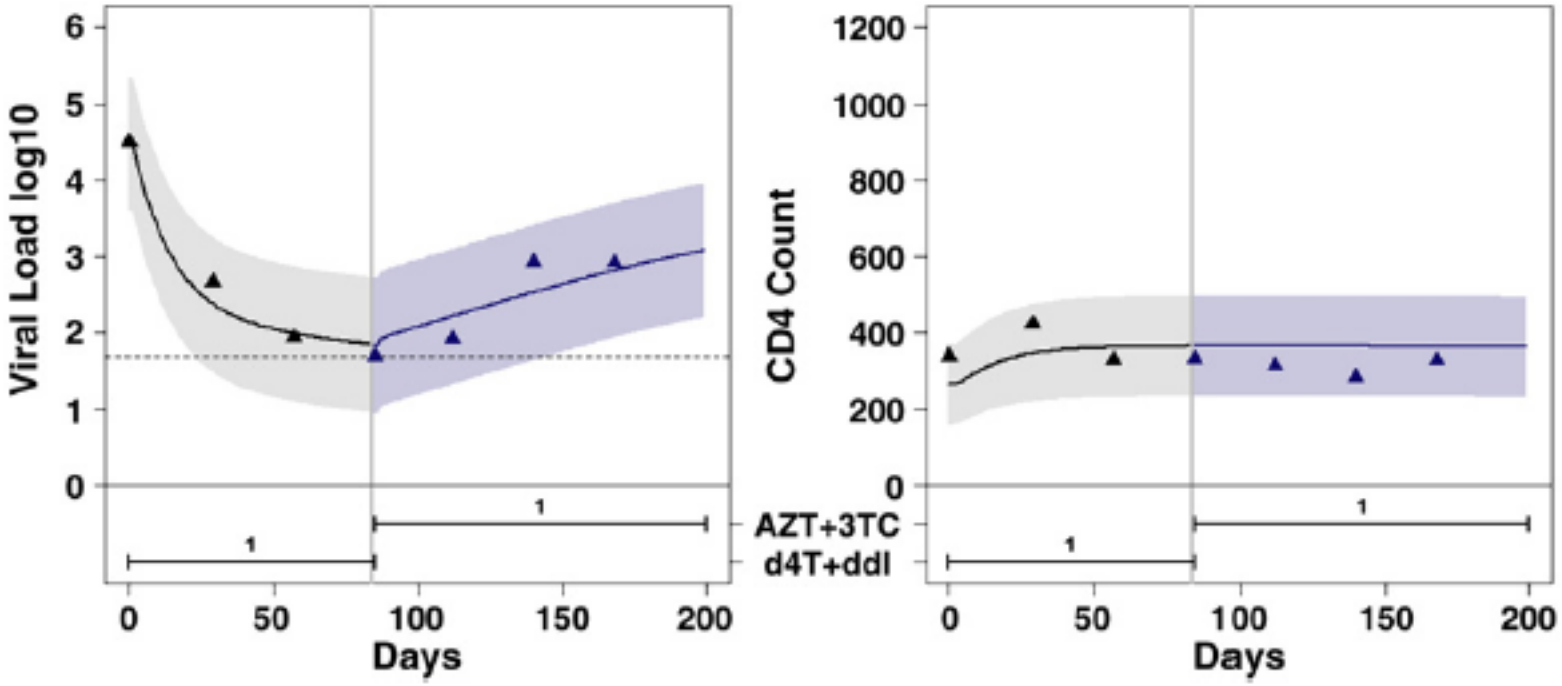


$$\begin{cases} \frac{dQ}{dt} &= \lambda - \mu_Q Q - \alpha Q + \rho T \\ \frac{dT}{dt} &= \alpha Q - \rho T - \mu_T T - \gamma V T \\ \frac{dT^*}{dt} &= \gamma V T - \mu_{T^*} T^* \\ \frac{dV}{dt} &= \pi T^* - \mu_V V \end{cases}$$

$Q =$ quiescient CD4+T cells
$T =$ activated uninfected CD4+T cells
$T^* =$ activated infected CD4+T cells
$V =$ viruses concentration

Prague, Mélanie, Daniel Commenges, and Rodolphe Thiébaut. "Dynamical models of biomarkers and clinical progression for personalized medicine: The HIV context." *Advanced drug delivery reviews* 65.7 (2013): 954-965.

Examples from the literature: HIV and personalized medicine



Viral load (log10 copies/ml) and CD4 count (cells/l) predictions for patients at median of the final HIV viral load distribution for patients in ALBI switch. Black lines are fits, blue line on the left of the horizontal line is prediction. Shaded zone represents the 95% measurement error predictive interval.

Understand:

- The effect of a specific drug, and more drugs when combined (synergism, antagonism…)
- The reaction of each patient
- The best posology, in a personalized manner

↓

- ☐ PK/PD
- ☐ In silico trials

Is your model reliable?

We have identified a specific problem to study and decided how to model it as a compartmental model: can we really use this model? Can we rely on its outputs and predictions?

There are many assessments one can do to test the reliability of a model and our confidence. We will mainly discuss about the following topics:

1. Structural identifiability
2. Practical identifiability
3. Sensitivity analysis
4. Calibration

Structural identifiability analysis

ODE system: the model

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}(t), \Psi) \\ \mathbf{x}(0) = \mathbf{g}(\Psi) \end{cases}$$

With:

$$\mathbf{x}(t) = (x_1(t), \ldots, x_k(t)) \quad \text{and} \quad \Psi = (\psi_1, \ldots, \psi_p)$$

State variables

Unknown parameters

Structural identifiability analysis

System-Experiment model

$$\Sigma(\Psi) = \begin{cases} \text{ODE system} \\ \mathbf{y}(t) = \mathbf{h}(\mathbf{x}(t), \Psi) \end{cases}$$

With: $\mathbf{y}(t) = (y_1(t), \ldots, y_n(t))$ ⟵ Observables

We want to answer the following question:

Assuming perfect experimental data (noise free and continuous in time), and an error-free model structure, are we able to recover unique values for unknown model parameters?

Structural identifiability analysis

3 possible answers:

- The system-experiment model is structurally globally identifiable:
- The system-experiment model is structurally locally identifiable
- The system-experiment model is structurally not identifiable

Mathematically:

$$\Sigma(\Psi) = \Sigma(\Psi^*) \Rightarrow \Psi = \Psi^* \Rightarrow \mathrm{GI}$$
$$\Sigma(\Psi) = \Sigma(\Psi^*) \Rightarrow \Psi \in \mathrm{V}^*, |\mathrm{V}^*| < \infty \Rightarrow \mathrm{LI}$$
$$\Sigma(\Psi) = \Sigma(\Psi^*) \text{ has infinite solutions } \Rightarrow \mathrm{NotI}$$

Structural identifiability analysis

Structural identifiability is a theoretical property of the model structure and a necessary condition for recovering the uniquely unknown model parameters:

If a system-experiment is not identifiable, then any parameter estimation would be random and not reliable!!!

In this case, one can:

- Try to simplify the model (i.e. reduce *k*)
- Fix some parameter values, for example from the literature (i.e. reduce *p*)
- Design new experiments to measure additional quantities (i.e. improve *n*)

Structural identifiability analysis: some softwares

- Identifiabilityanalysis package:
  - Implemented in Mathematica
  - Freely available at http://www.fcc.chalmers.se/software/other-software/identifiabilityanalysis/
  - Based on probabilistic semi-numerical algorithm
  - Fully authomatic, quick results, easy to use

- DAISY package:
  - Implemented in REDUCE 3.8
  - Freely available at http://www.dei.unipd.it/~pia/
  - Based on a differential algebra algorithm
  - Completely automatized software

Practical identifiability analysis

Let us suppose that our model is structurally globally identifiable: are you sure that you will be able to correctly estimate the model parameters?

Sensitivity analysis

Sensitivity analysis is another theoretical approach to evaluate a model and understand if we can use it in practice to gain understanding of the problem it is supposed to model.

Sensitivity analysis aim at answering the following question:

How model parameters affect the output dynamics?

Question: can you see why answering that question can give additional information about practical identifiability?

Sensitivity analysis

Many methods exists to assess sensitivity analysis and, as for structural identifiability, we can talk about local and global sensitivity analysis.

In this class we are just going to discuss about local sensitivity analysis

The first step to perform a local sensitivity analysis of a model consists in identifying a reasonabe range for each parameter, i.e. reasonable lower and upper bounds of their values. For instance, this can come from the literature.

Local sensitivity analysis

A classical method for assessing local sensitivity analysis is to evaluate the normalized sensitivity coefficients, corresponding to the normalized partial derivatives of the observables with respect to the model parameters.

Mathematically:

$$\Sigma(\Psi) = \begin{cases} \text{ODE system} \\ \mathbf{y}(t) = \mathbf{h}(\mathbf{x}(t), \Psi) \end{cases}$$

$$\frac{\psi_i}{y_j(t,\Psi)} \frac{\partial y_j(t,\Psi)}{\partial \psi_i} \text{ evaluated at } \Psi = \Psi^*$$

Zi, Zhike. "Sensitivity analysis approaches applied to systems biology models." *IET systems biology* 5.6 (2011): 336-346.

Local sensitivity analysis

For example, Matlab function sens_ind:

https://fr.mathworks.com/matlabcentral/fileexchange/1480-sensitivity-analysis-for-odes-and-daes

Local sensitivity analysis

A more intuitive way to perform local sensitivity analysis is to plot the solution of the system given the parameters (i.e. from the model to the observables), then vary one parameter at a time in their reasonable range to see the effect over the solution.

In addition, understand how the variation of a single parameter affects the output, is one simple approach for model calibration.

Model calibration

Model calibration is the last step one could consider before trying a formal approach for proper parameter estimation (which is the content of the next lesson).

Model calibration is based on output simulation through the proposed model:

Is the model able to reproduce trajectories which are reasonable compared to the observed ones?

Question: what do you need and need to know to perform model calibration?