# Modeling formalisms and Small models of inflammation

*Gilles Clermont*

Medical Director, Center for Inflammation and Regenerative modeling
Department of Critical Care Medicine, University of Pittsburgh

# Objectives

- What is a model.
- Modeling formalisms
- Specific models
- Population variability

# What is a model

$$Y(state) \xrightarrow{Model} X(observations)$$

- Simplified representation of a complicated reality (the system)
- Captures (describes) key behaviors of reality
- Two basic choices:
  - Level of system specification
    - Pathways vs Cells vs Organs vs Organism
    - Multiscale
  - Modeling framework specification
    - Mathematical/statistical/others

# Why a model?

- Predictions
  - Survival
  - Hurricane path and strength
- Insight/interpretation
  - What-if scenarios?
  - “Rank” drivers of outcome

# Model structure
# Variables and Parameters

$$Y = mX+b$$

- Variables (Y, X) are:
  - Input into the model, output from the model (state)
  - Independent predictors
  - Observable from the system
- Parameters (m, b) are:
  - Integral part of the specification of the model
  - Adjusted to have model “fit” the data
    - Poor fit suggest the model does not capture the behavior of the system

# Scale and granularity

**Top-down**
- Abstract
- Few variables and parameters
- May or may not offer useful predictions

**Data-rich**
- Data-driven
- Biological correspondence may be difficult
- Black-box

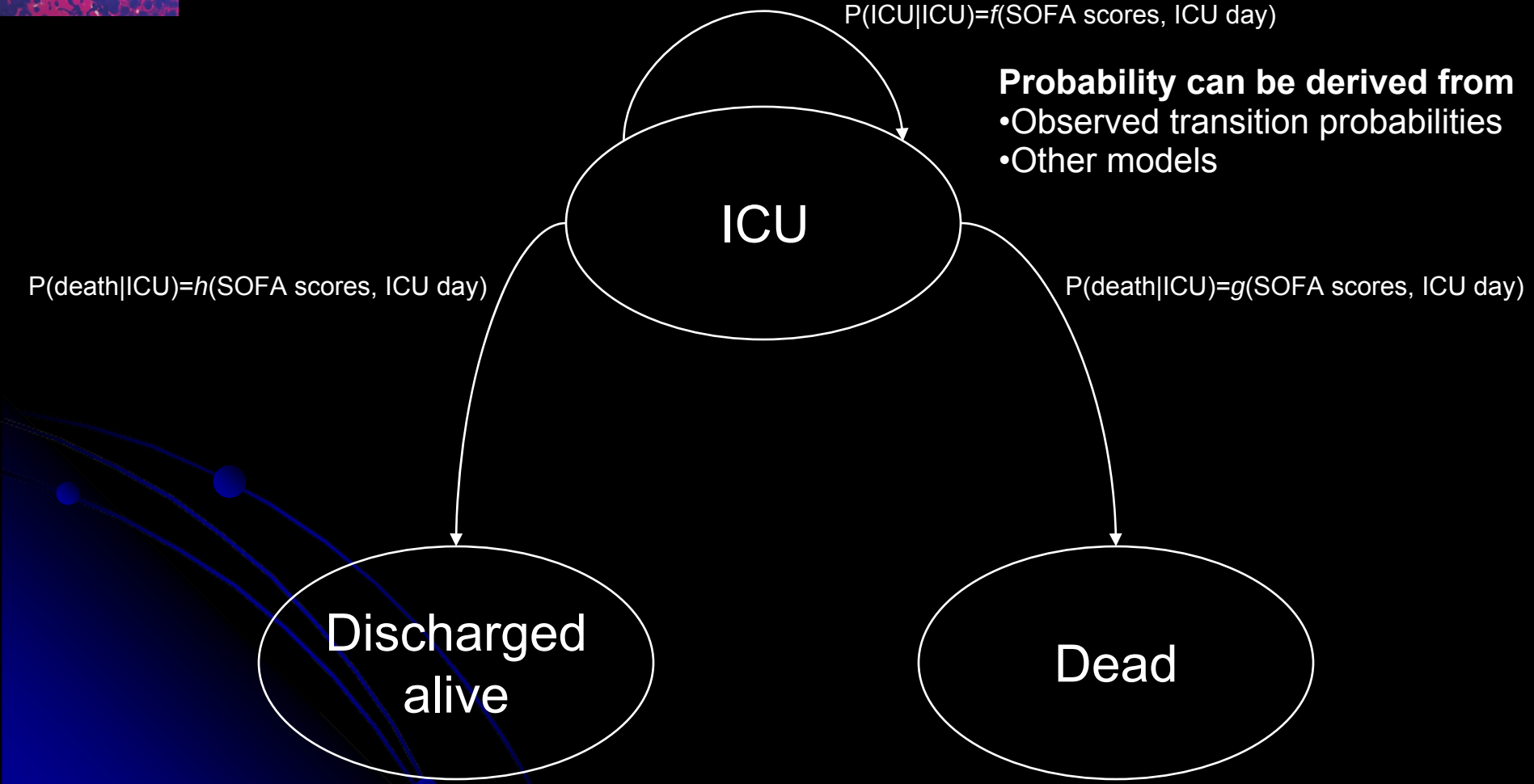
**Knowledge-rich**
- Causal
- Extensive use of prior knowledge
- White-box

**Bottom-up**
- As close to reality as possible
- Broad knowledge-gaps
- Computational intractability

# Statistical (data-driven) models

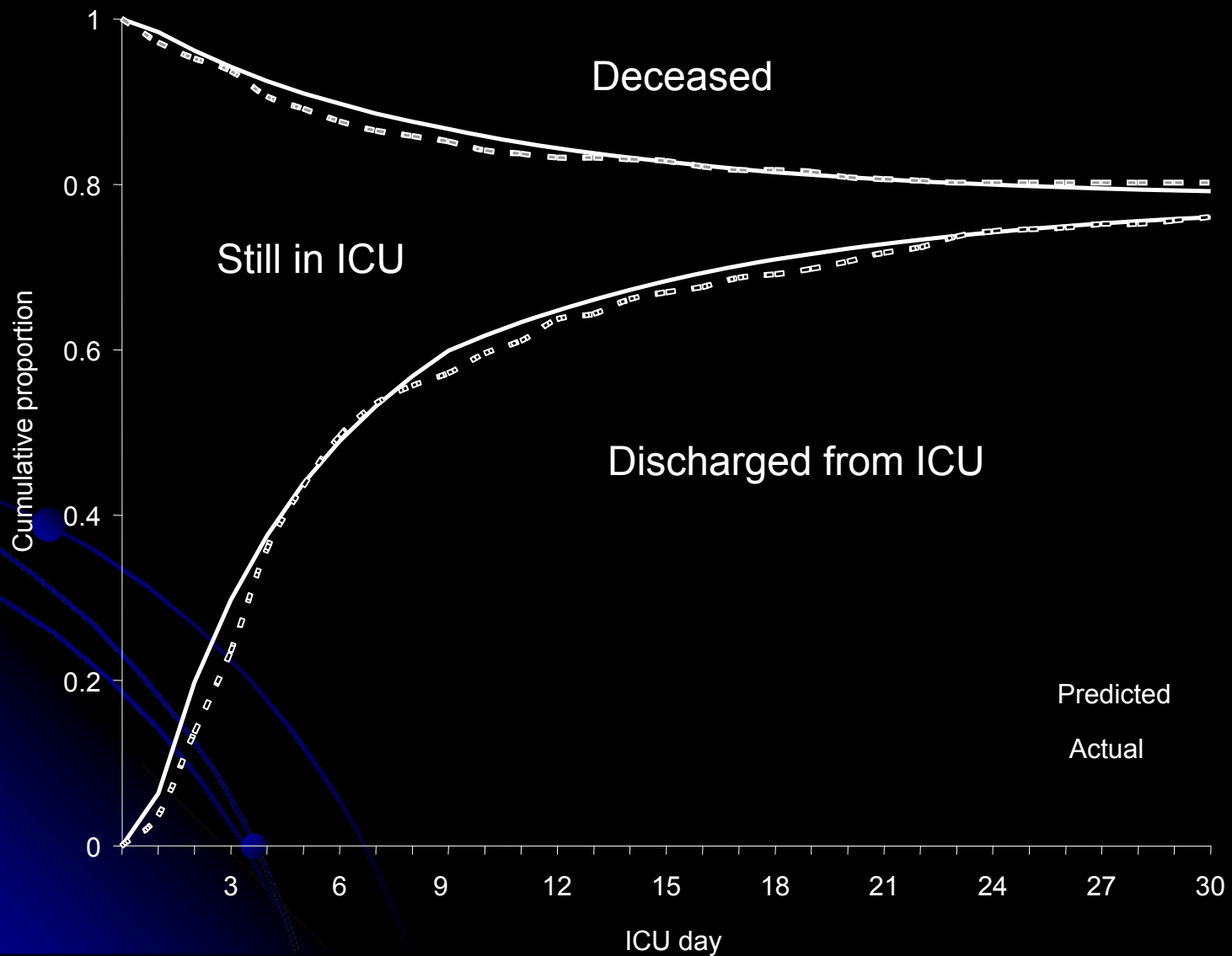
- What they can do
  - Classify
    - Discriminate (ROC)
    - Cluster
  - Predict (calibration, e.g. $R^2$)
- What form do they take
  - Regression
  - Machine learning
    - Neural networks
    - Graphical
    - Many others
  - Combinations

# Time-dependent statistical predictions




**Probability can be derived from**
- Observed transition probabilities
- Other models

# Actual vs predicted



# Statistical models

- Advantages
  - Good to predict population outcome
  - Take advantage of associations
- Disadvantages
  - Not as good to predict the outcome of an individual, except at extreme of predictions
  - Knowledge poor, no inclusion of a priori known mechanisms
  - Require large amount of data
  - Subject to assumptions (e.g. distribution of data) that may not always be fulfilled
  - Require careful approach to missing data

# Equation-based models

- Non-dynamical
  - Describes relationships between variables
    - Typically algebraic
  - Description of steady-states, transients unimportant
  - Most traditional physiologic model
    - Cardiopulmonary physiology
- Dynamical
  - Difference equations
  - Differential equations
    - Time-dependence (Ordinary DE)
    - Time and space-dependence (Partial DE)

# Equation-based models

- Knowledge-rich
- Basic laws (rules) of the system are provided a priori
  - Also true of agent-based models
- Clear sense of causality
- May or may not be constructed as to reflect physical reality
  - Can be very high level
- Although basically deterministic, can clearly accommodate stochastic elements, thus uncertain knowledge
- Well developed mathematical theory

# Scale and granularity

**Top-down**
- Abstract
- Few variables and parameters
- May or may not offer useful predictions

**Data-rich**
- Data-driven
- Biological correspondence may be difficult
- Black-box

**Knowledge-rich**
- Causal
- Extensive use of prior knowledge
- White-box

**Bottom-up**
- As close to reality as possible
- Broad knowledge-gaps
- Computational intractability

# Equation-based models - caveats

- Even small systems can have large number of parameters
  - Parameter reduction techniques are available
- Many of the parameters are not known
  - Even if we think we have good literature documentation
    - Biological data was typically not collected with modeling in mind
  - Molecule half-life
  - Reaction rates
- Models are typically underspecified: many different combination of parameters can explain data equally well
- Structure vs parameters problem
- Underlying assumptions may not be fulfilled (e.g. continuity)

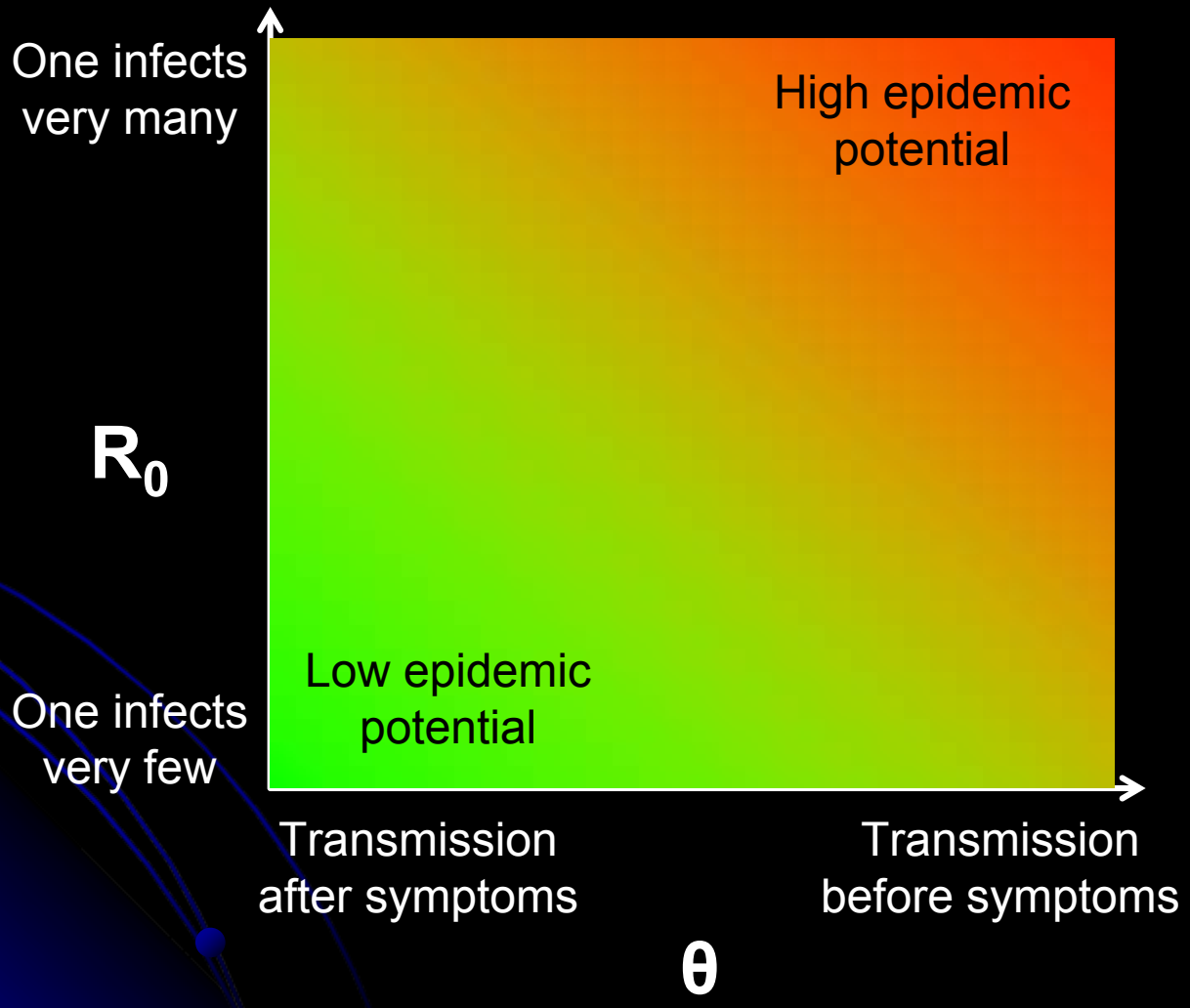
# Viral Models – Population based

- Largely empirical
  - Susceptible, Infected, Recovered/resistant
- Yet, knowledge of basic determinant of such models is important
  - $R_0$, $\theta$
  - Social networks
  - Health delivery services infrastructure

# Motivation for biological models

- Explain input to larger models
- Explain manifestation of disease
  - Disease severity
  - Age, co-morbidity
- Explore modifiers of disease that act at the individual level
  - Susceptibility
  - Transmissibility
  - Vaccine effect
  - Antibiotics

# Population models



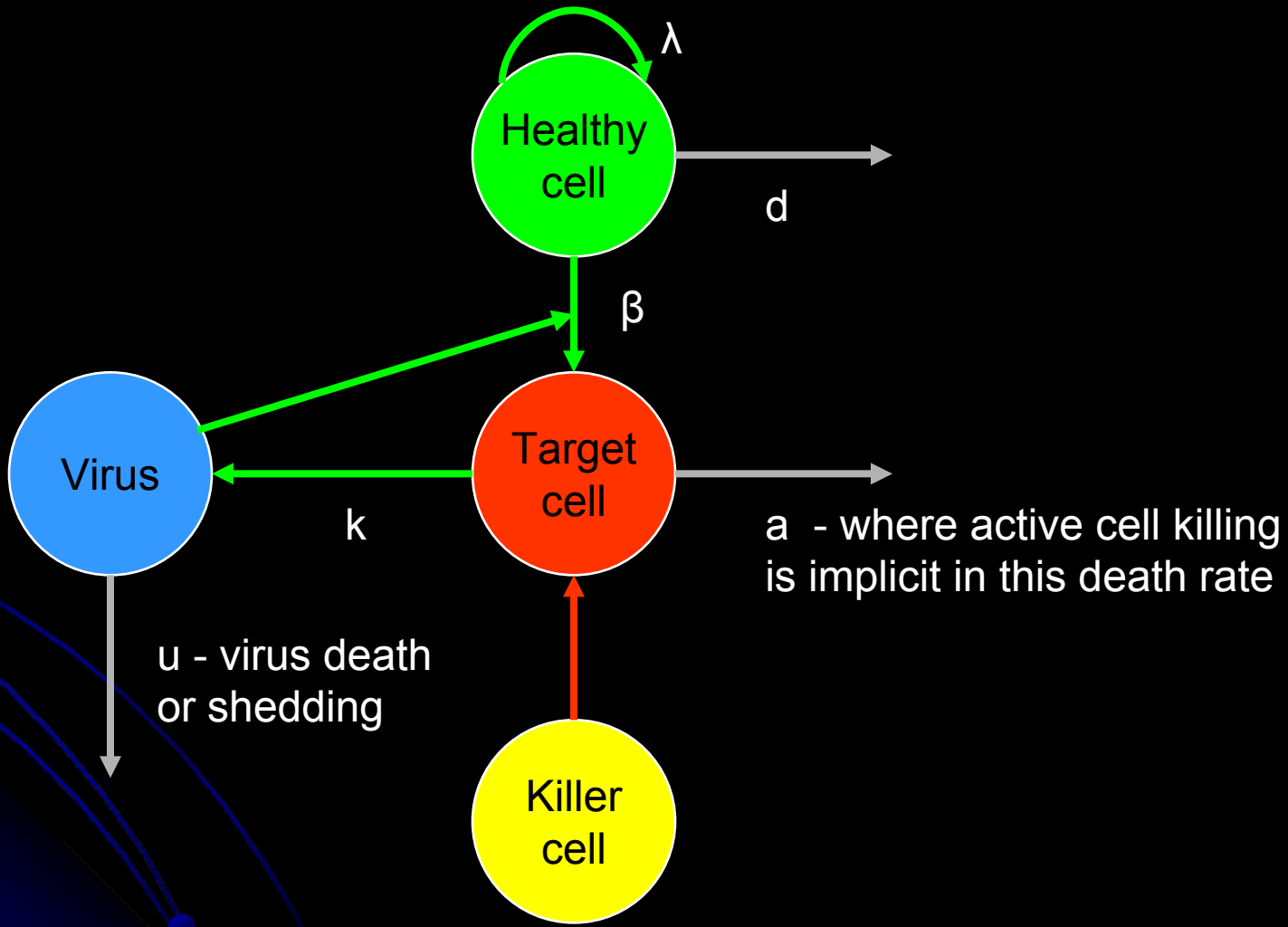
# Biological models

- Models of Host-Virus interaction
- HIV (a lot), as well as other retroviruses
- Influenza, HBV, West Nile, Smallpox
- Little traction in translational research
  - Exception is multiple interruptions of therapy in HIV carriers

# Biological Models of viral infections

- Since early 1990's
- HIV
  - Nowak, Perelson, Kirschner, Wodarz
  - Object
    - HIV/CD4+ interaction
    - Optimizing therapy
    - Dynamics of viral mutation and multiple infections
- Influenza
  - Bocharov, Hancioglu, Beauchemin
- Hepatitis B, C
  - Bocharov

# The simplest viral model (v0.1)



# The "reaction" formulation

X: healthy cell
Y: infected cell
V: virus
R: killer cell

$$* \xrightarrow{\lambda} x$$

$$y \xrightarrow{k} v$$

$$v + x \xrightarrow{\beta} y$$

$$x \xrightarrow{d} *, \quad v \xrightarrow{u} *, \quad y \xrightarrow{a} *$$

$$\dot{x} = \lambda - \beta v x - d x$$

$$\dot{y} = \beta v x - a y$$

$$\dot{v} = k y - u v - \beta v x$$

# With a killer cell (r)

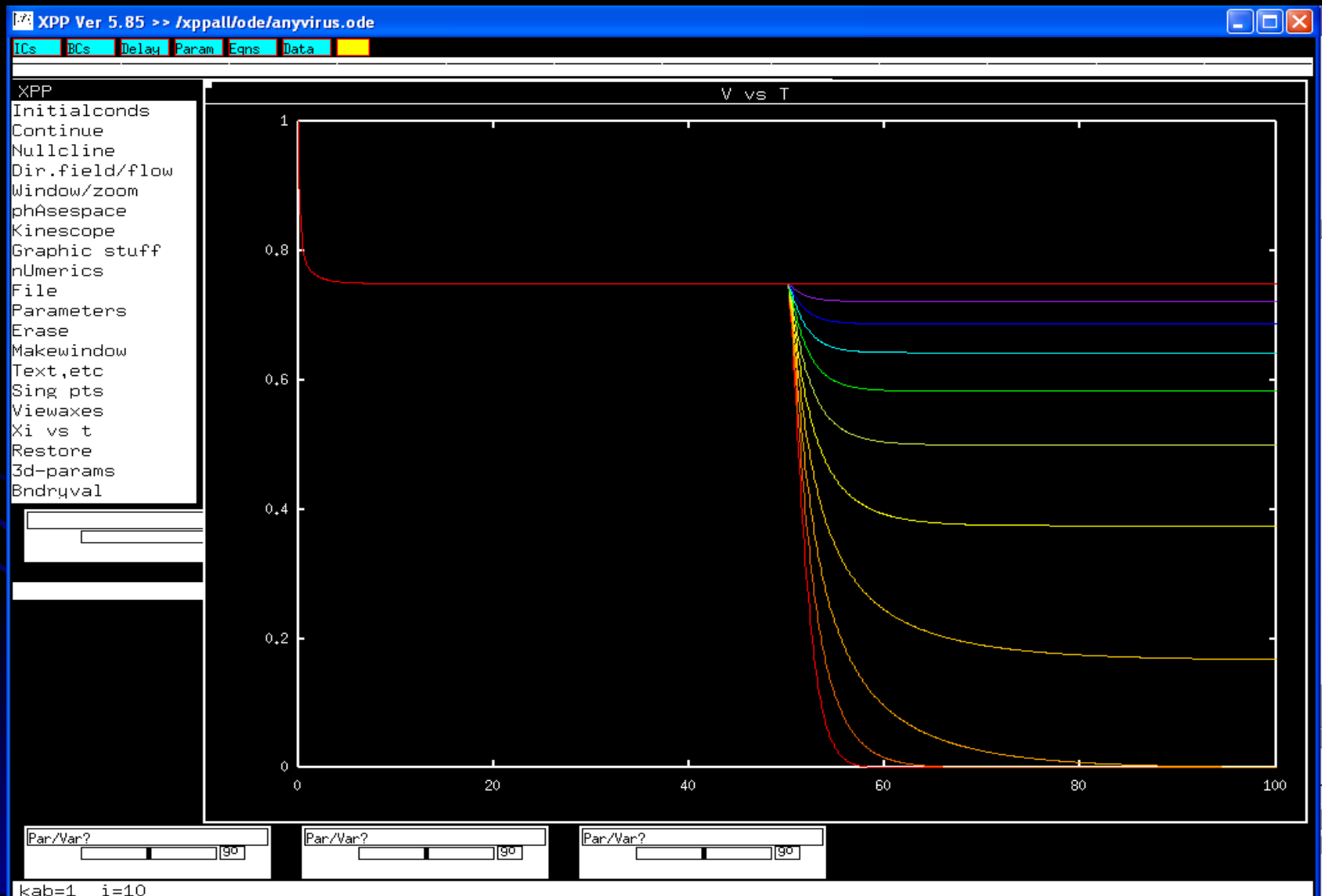
$$
\begin{aligned}
&* \xrightarrow{\lambda} x \\
&y \xrightarrow{k} v \\
&v + x \xrightarrow{\beta} y \\
&x \xrightarrow{d} *, \; v \xrightarrow{u} *, \; y \xrightarrow{a} *
\end{aligned}
$$

$$
\begin{aligned}
\dot{x} &= \lambda - \beta v x - d x \\
\dot{y} &= \beta v x - a y \\
\dot{v} &= k y - u v - \beta v x
\end{aligned}
$$

$$
\begin{aligned}
&y + r \xrightarrow{\gamma} r \\
&* \xrightarrow{c} r \\
&r \xrightarrow{f} *
\end{aligned}
$$

$$
\begin{aligned}
\dot{y} &= \beta v x - a y - \gamma r y \\
\dot{r} &= c - f r
\end{aligned}
$$

# The reverse transcriptase example



# A (slightly) more realistic model

- HIV infects CD4+ cells
- These CD4+ cells are responsible for the clonal expansion of cytotoxic T lymphocytes
- Could “controlling” virus expression allow sufficient CD4+ activation to allow sufficient CTL to maintain a chronic carrier state – given a fixed antigenic mutation rate?

# Lessons learned from biological models of HIV

- Rapid drift, a major impediment for vaccine development, is our worse enemy - preserved ability of clonal development of CTLs
- Models have predicted that an optimal strategy for HIV containment would include:
  - Early HAART (highly active anti retroviral therapy) intervention
  - Frequent interruptions of therapy to minimize drift while CTL clones are enrolled (Structure Treatment Interruption, DRUGS 2002)

# Translation (STI strategy)

- SMART, OPTIMA (in unsuppressed HIV)

**Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults (Review)**

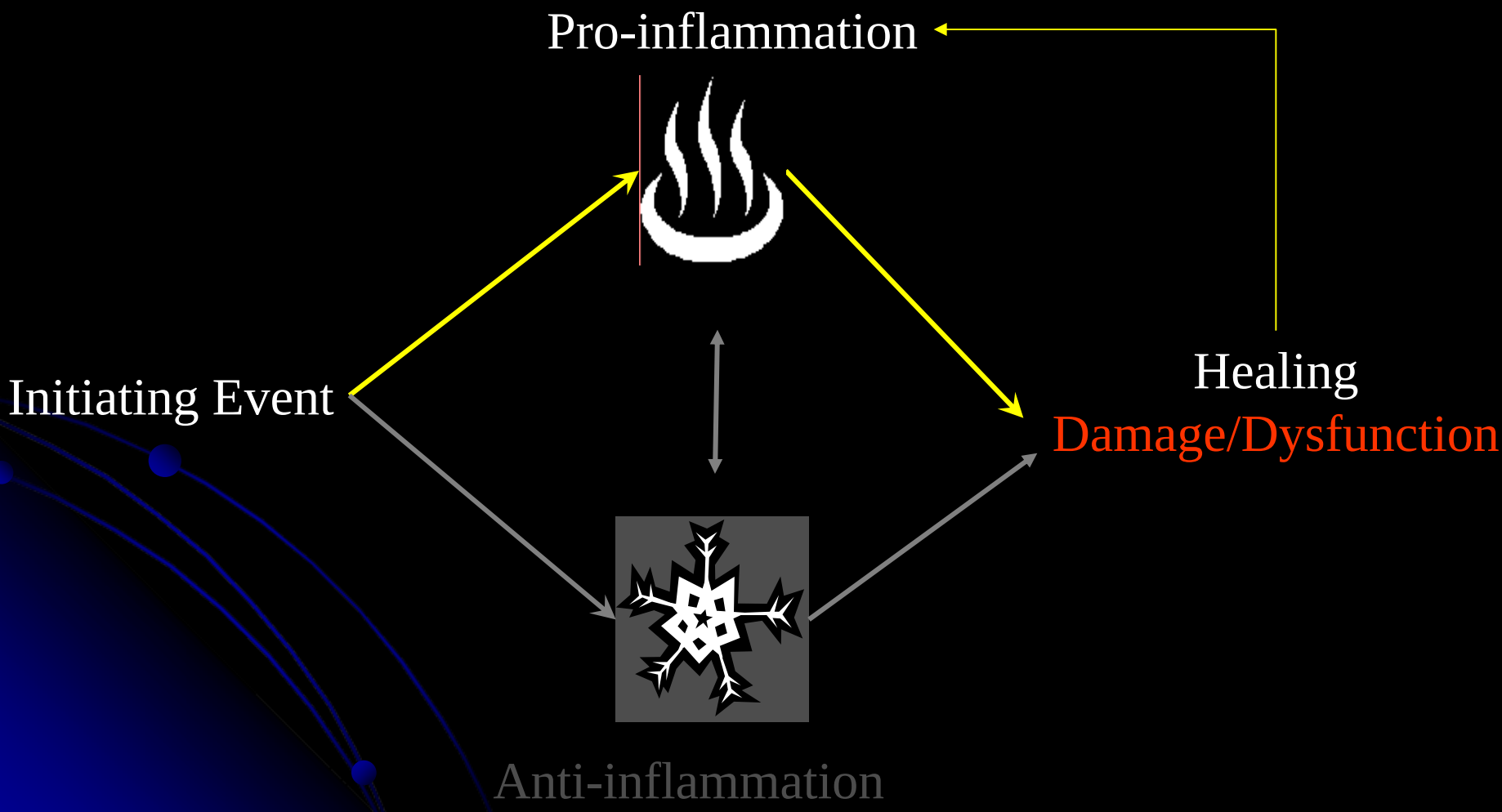
Pai NP, Tulsky JP, Lawrence J, Colford Jr JM, Reingold AL

- STACCATO (Lancet 8/2006)

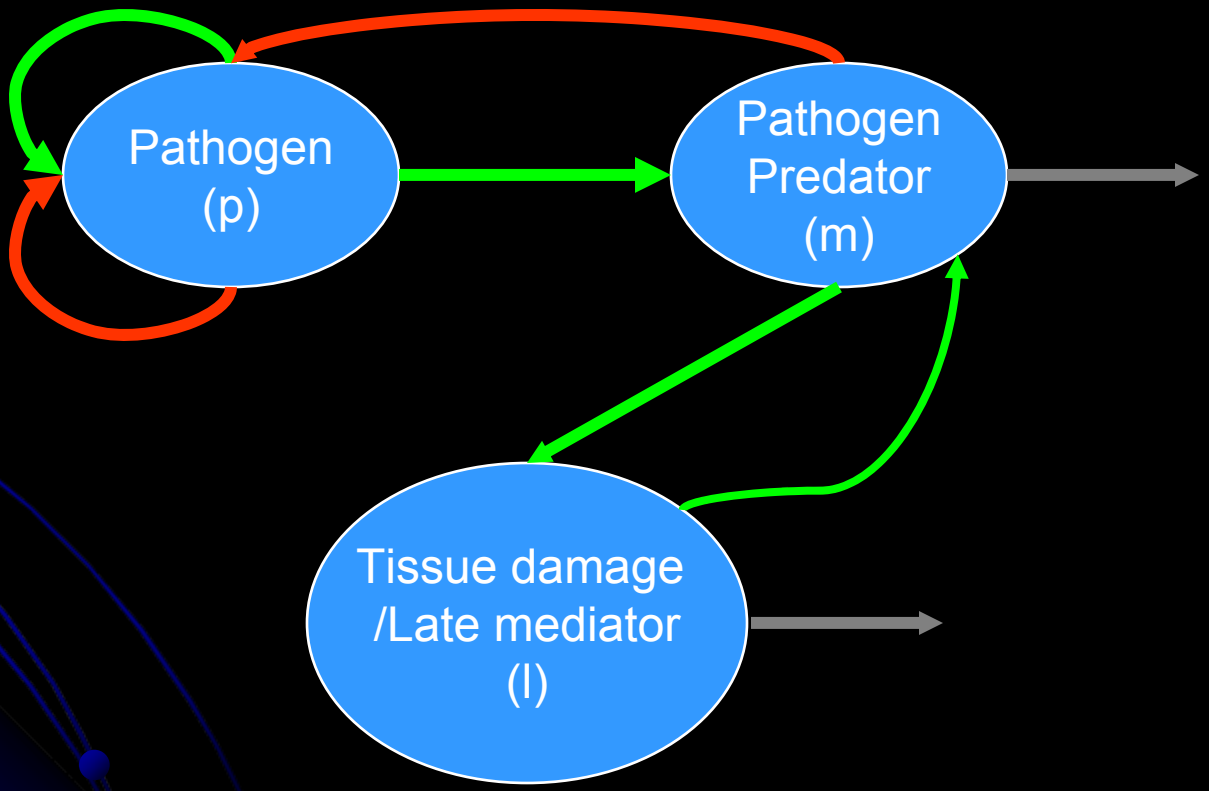
**CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial**

*Jintanat Ananworanich, Angèle Gayet-Ageron, Michelle Le Braz, Wisit Prasithsirikul, Ploenchan Chetchotisakd, Sasisopin Kiertiburanakul, Warangkana Munsakul, Phitsanu Raksakulkarn, Somboon Tansuphasawasdikul, Sunee Sirivichayakul, Matthias Cavassini, Urs Karrer, Daniel Genné, Reto Nüesch, Pietro Vernazza, Enos Bernasconi, Dominic Leduc, Claudette Satchell, Sabine Yerly, Luc Perrin, Andrew Hill, Thomas Perneger, Praphan Phanuphak, Hansjakob Furrer, David Cooper, Kiat Ruxrungtham, Bernard Hirschel, the Staccato Study Group*, the Swiss HIV Cohort Study**

# Inflammation – a reduced model



# Inflammation – a reduced model



# The reaction system

$$p \rightarrow 2\ p$$

$$p + p \rightarrow p$$

$$p + m \rightarrow m$$

$$m + p \rightarrow 2\ m$$

$$m + m \rightarrow m$$

$$m \rightarrow *$$

$$m \rightarrow m + l$$

$$l \rightarrow *$$

# The DE formulation

$$\frac{dp}{dt} = k_p p(1-p) - k_{pm} mp \quad (1)$$

$$\frac{dm}{dt} = (k_{mp} p + l) m(1-m) - m \quad (2)$$

$$\frac{dl}{dt} = k_{lm} f(m) - k_l l \quad (3)$$

$$f(m) = 1 + \tanh\left(\frac{m-\theta}{w}\right), \quad (4)$$

*p* is pathogen, *m* is a pathogen predator, *l* is a late mediator, possibly tissue dysfunction. So, 3 variables, 7 parameters.

*Kumar et al. J Theoretical Biol 2004*

# Possible “steady-state” behaviors

$$0 = k_p p(1-p) - k_{pm} mp \quad (1)$$

$$0 = (k_{mp} p + l) m(1-m) - m \quad (2)$$

$$0 = k_{lm} f(m) - k_l l \quad (3)$$

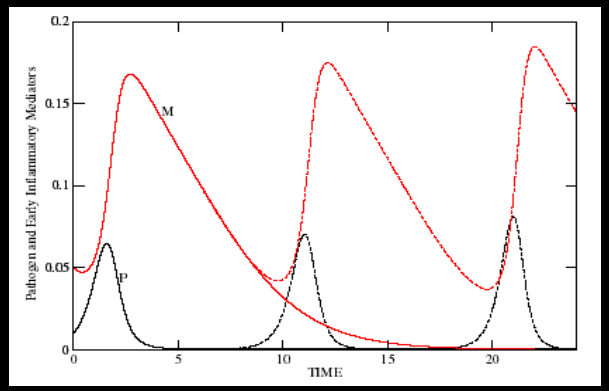
Up to five solutions = fixed points or orbits

- A solution is a combination of *p*, *m* and *l* that fulfills all equations simultaneously
- Each solution depends on the actual parameter values

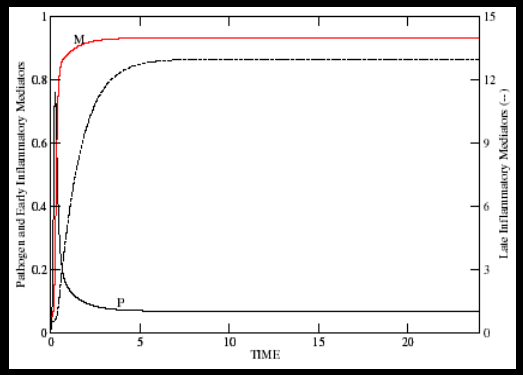
# What are possible outcomes?

FP3

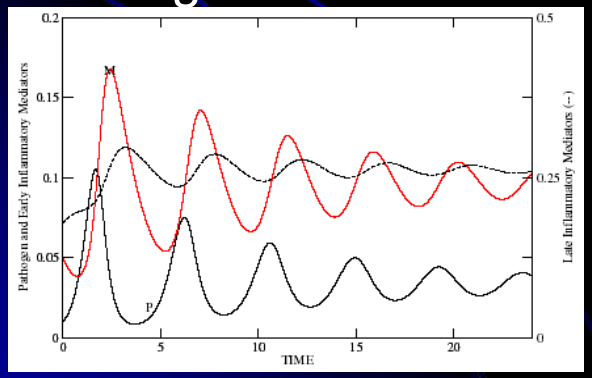
Cure




Persistent Infectious death

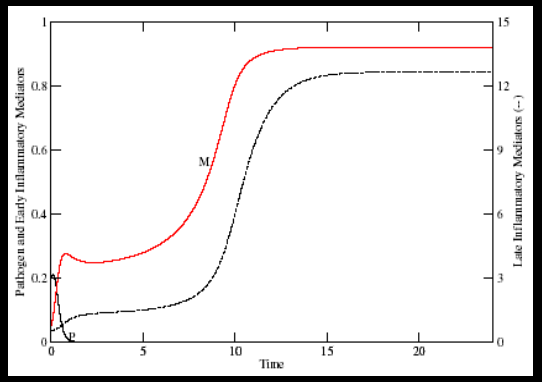



Low grade infection



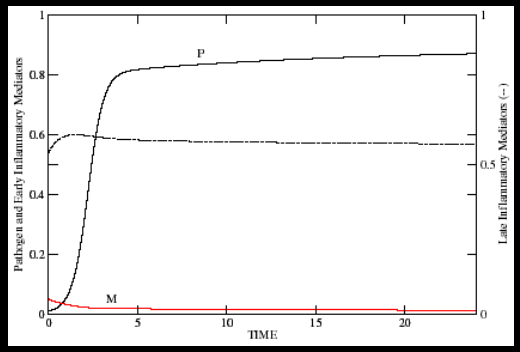

FP5

Sterile death

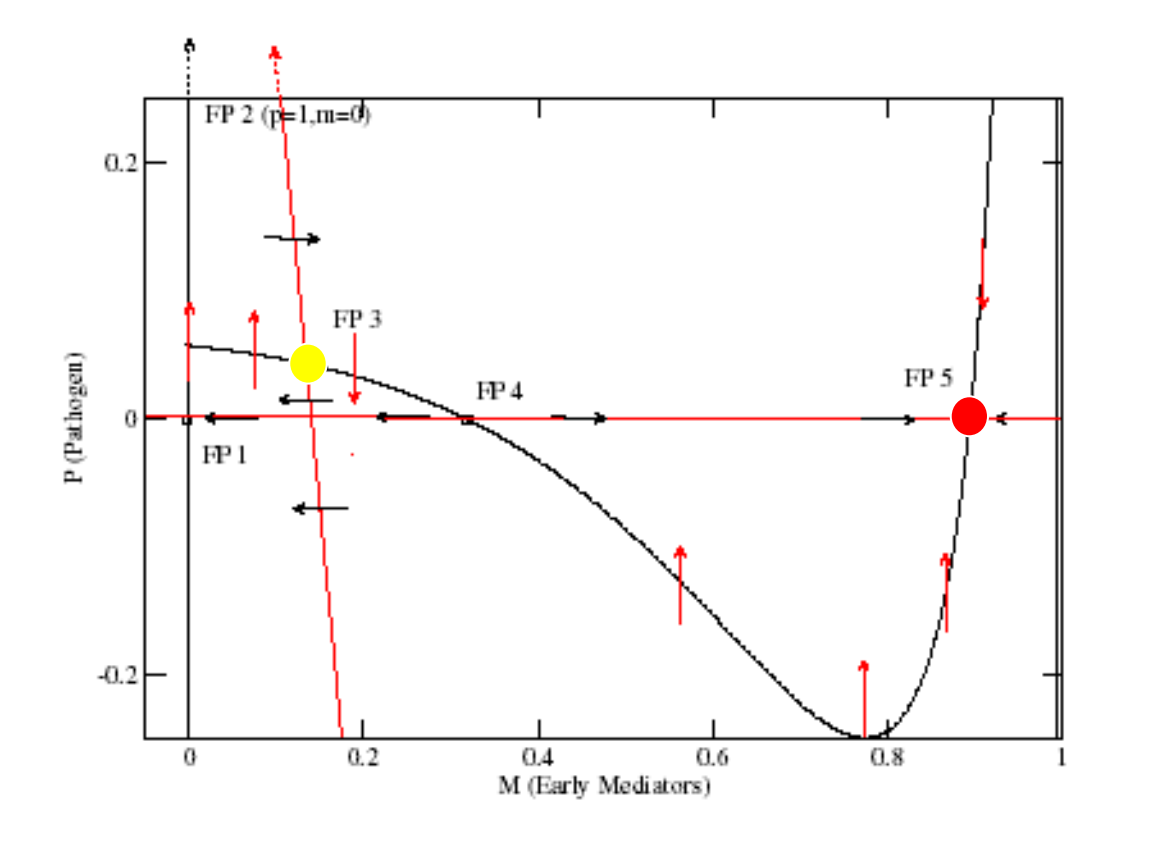



FP2

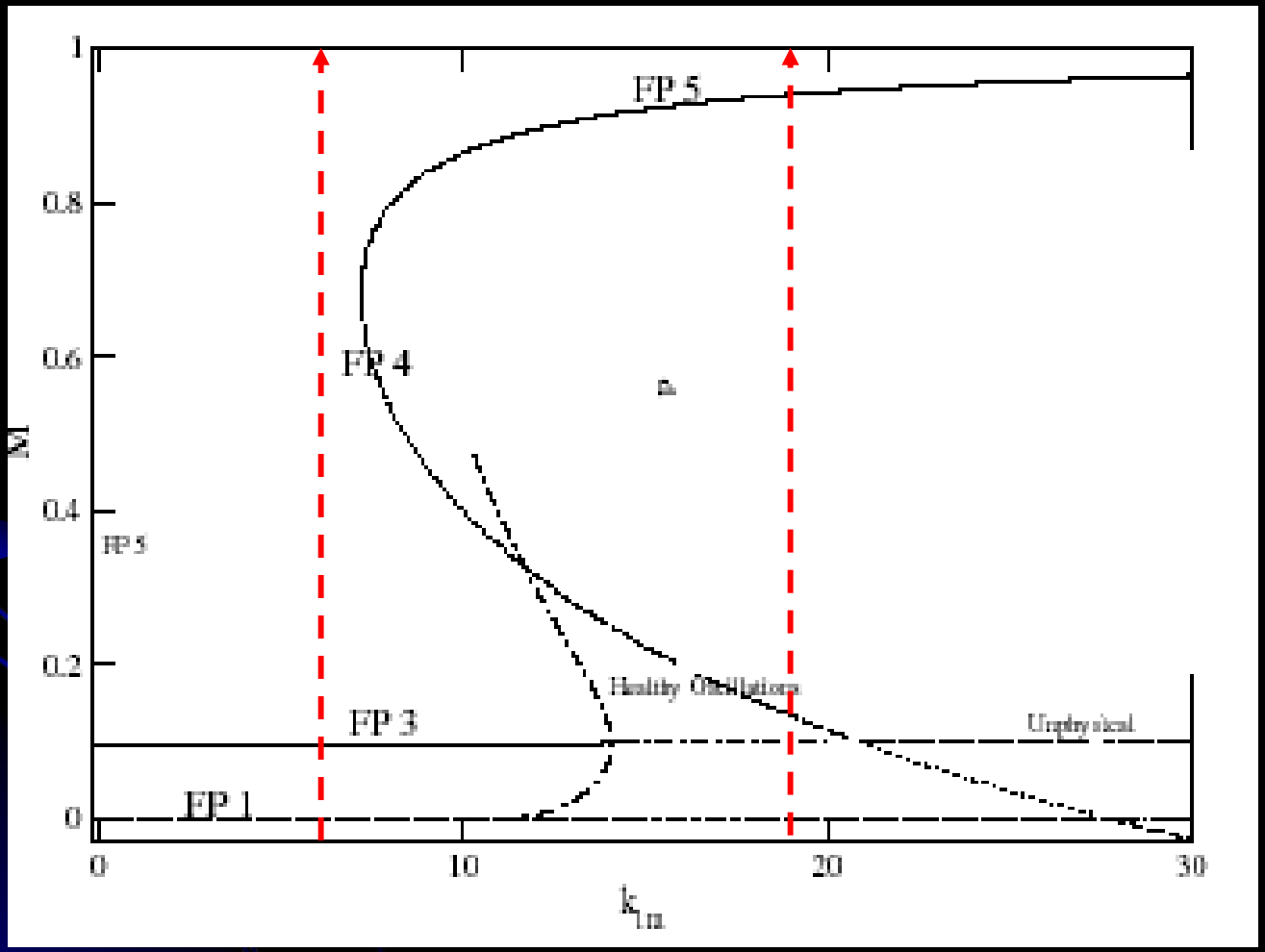
Immune failure death



# The notion of stable/unstable regimen



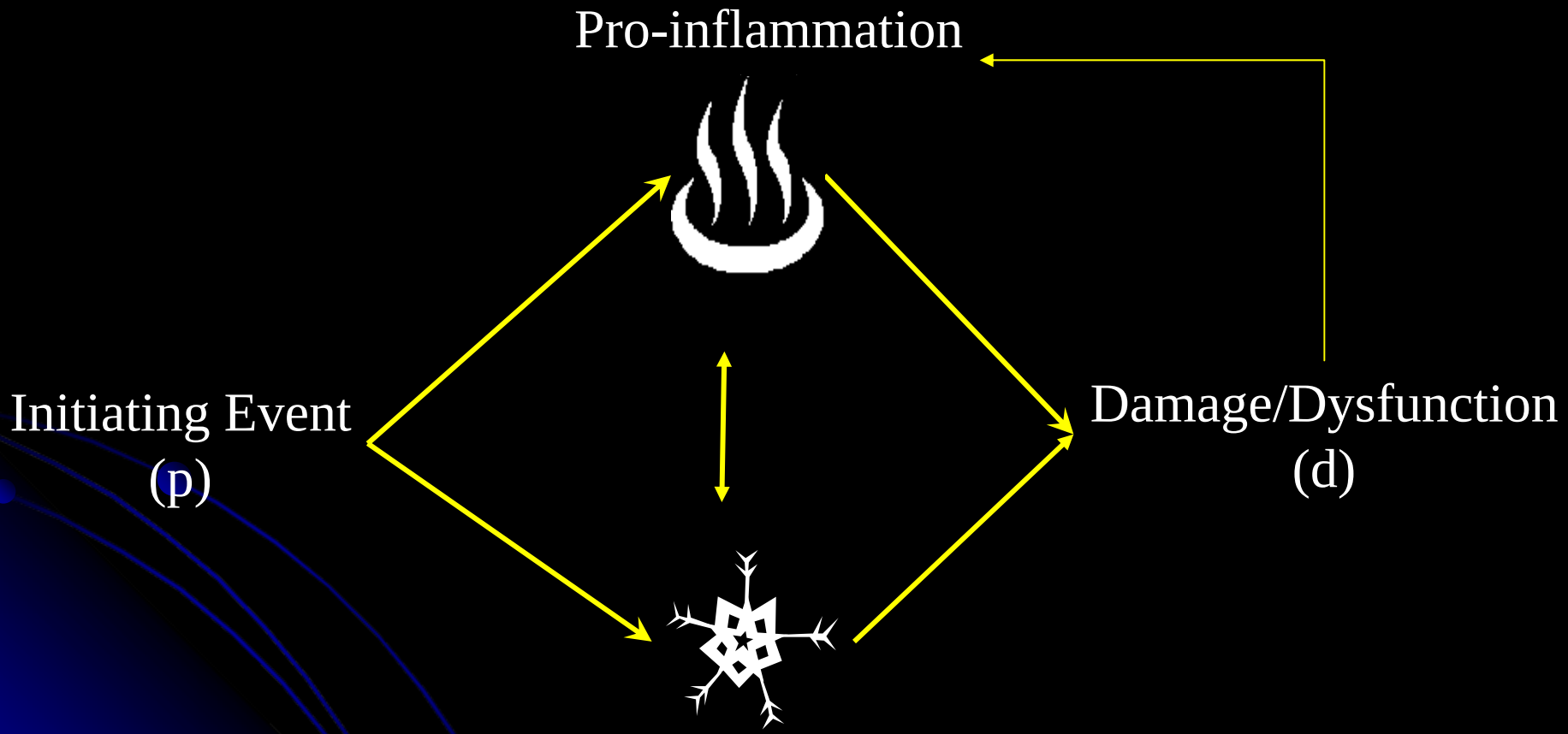
# The need for a "late mediator"



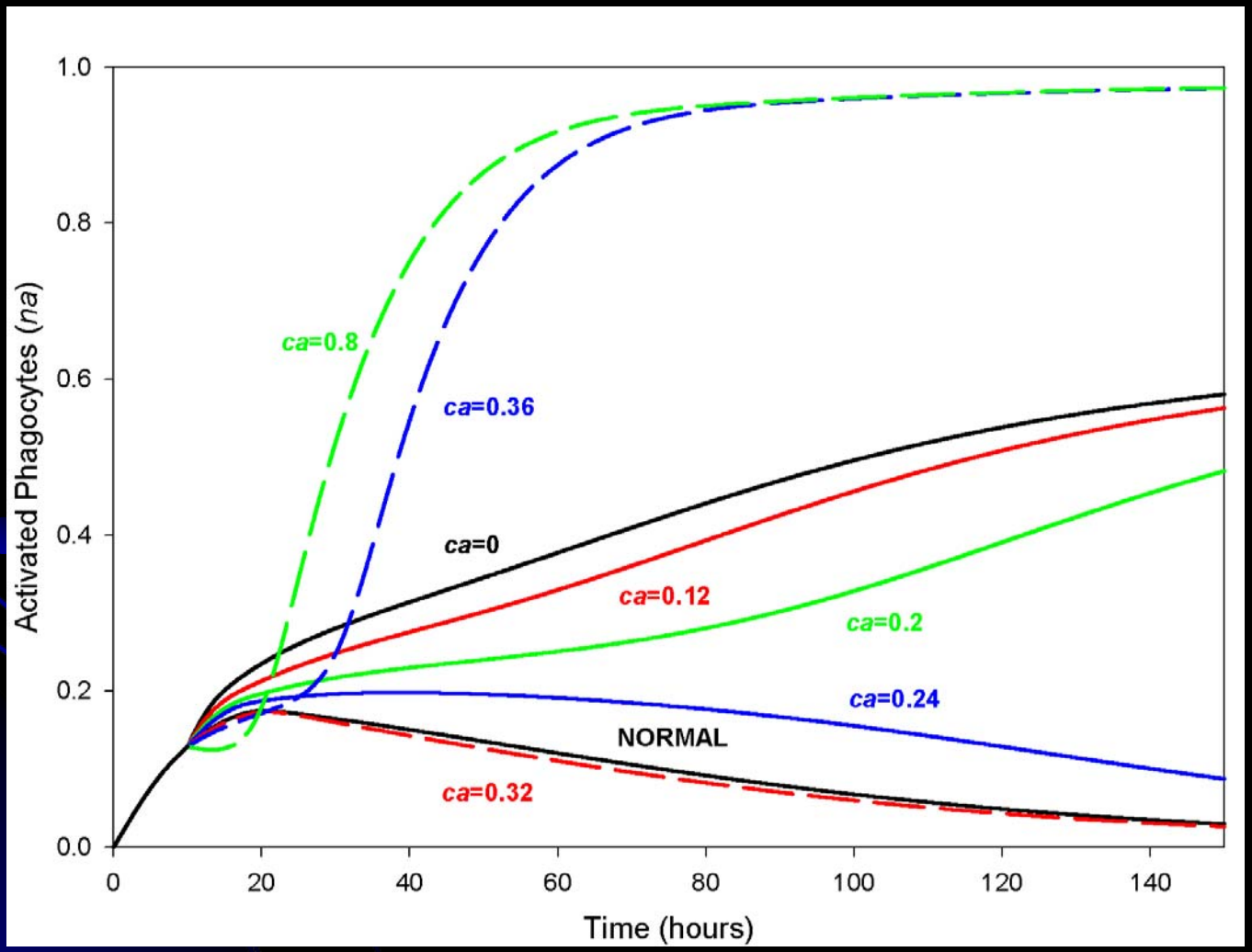
# Insights from a simple model

- Only 3 (4) regimen are ever possible
  - Cure
  - Oscillations with low grade pathogens
  - Aseptic death
  - Immunesuppression (septic death)
- There are specific conditions for the existence of those regimen
- There cannot be “aseptic” death if collateral damage production does not exceed a certain threshold

# The role of anti-inflammatories



# Manipulating anti-inflammatories

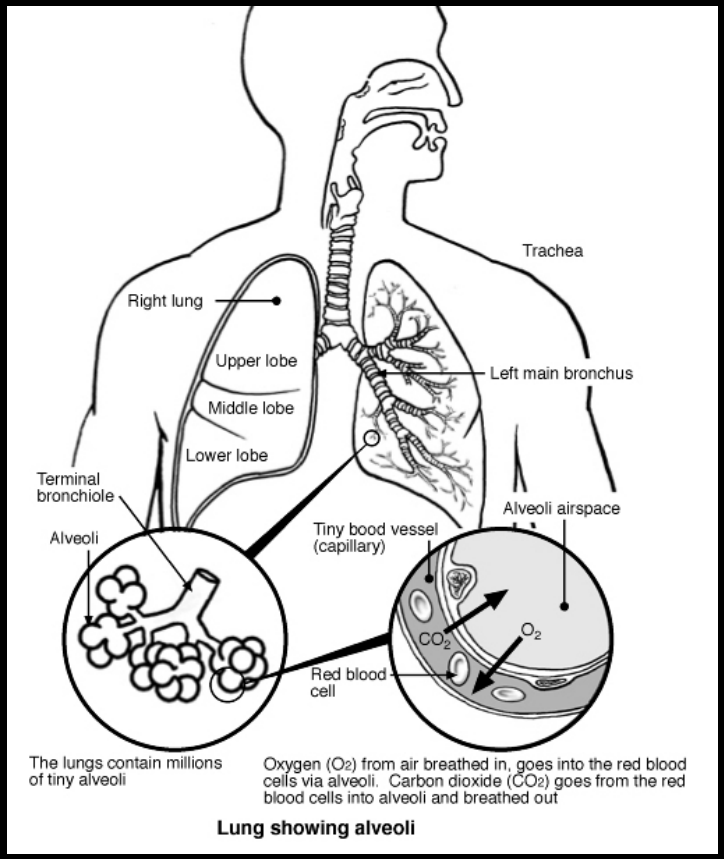


# Why complicate things

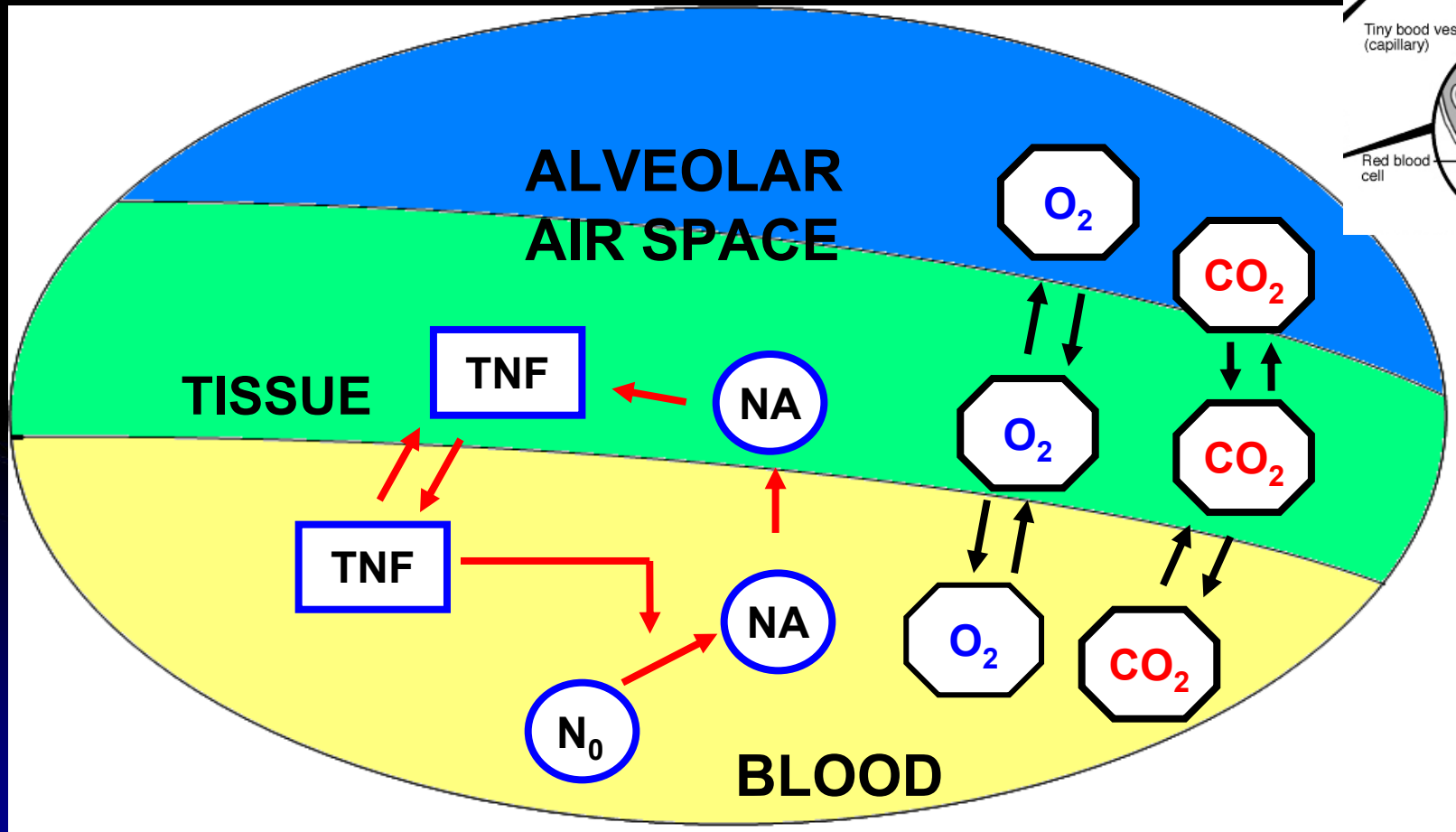
- To calibrate a model, we need to confront it to data
- To “intervene” in the dynamics in a realistic way, more realistic “handles” are needed
- Variability
- Not all “modules” need to be equally complicated
- The analysis of large models:
  - May rapidly become intractable
  - May not yield useful results

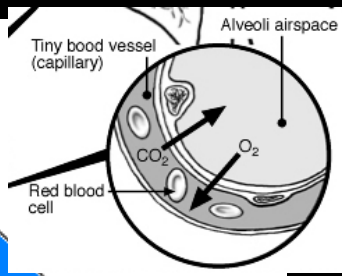
# Multiscale models – the lung

- Oxygen and carbon dioxide exchange
- Inflammation occurs in the tissue barrier between air and blood.
- Tissue swelling impairs gas diffusion. Extreme inflammation of a respiratory unit (~25 alveoli) can completely stop gas exchange (shunt).
- The global impact of inflammation depends on the combined contribution of respiratory units (RU) with diverse anatomical and physiologic properties.

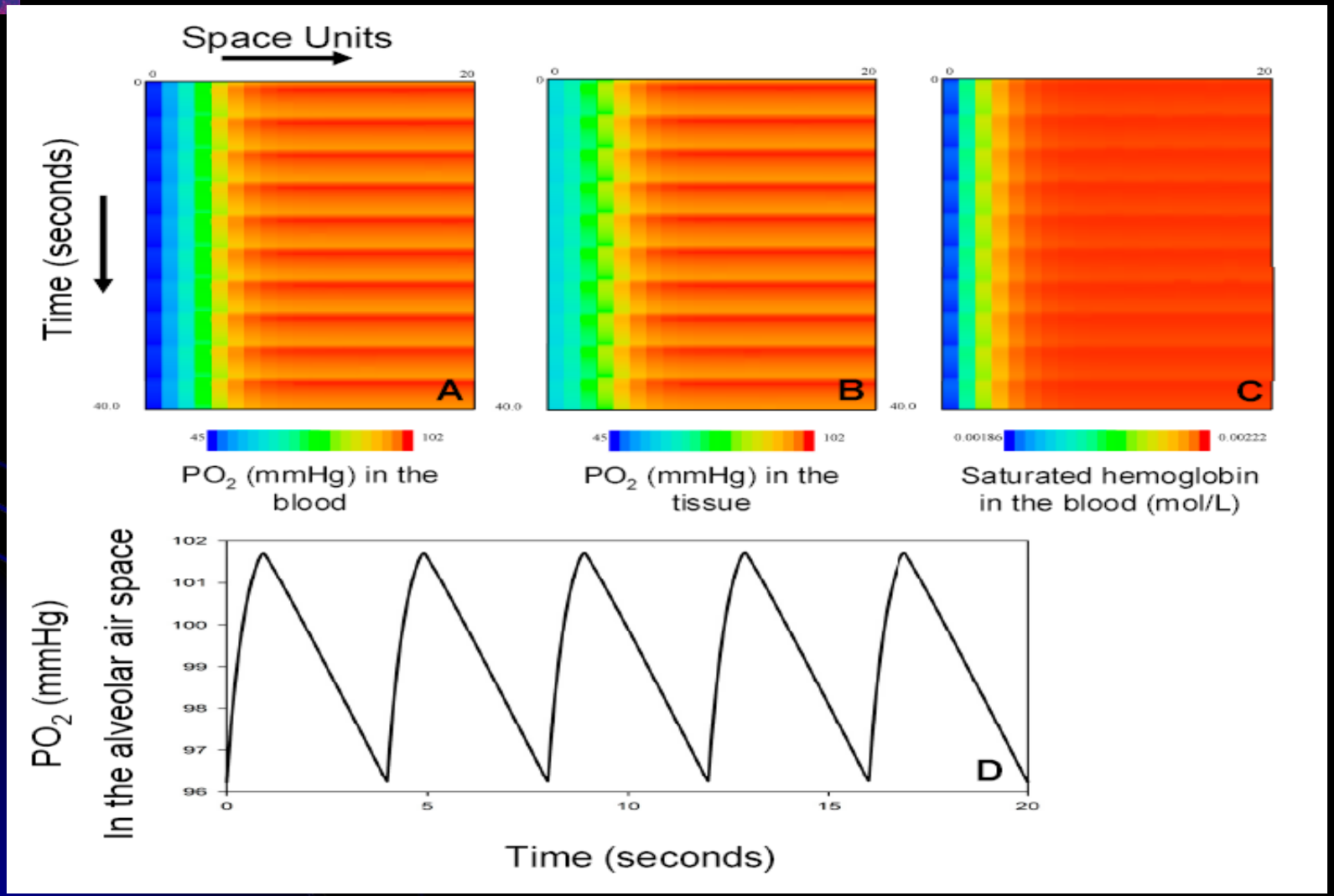


# Model schematics



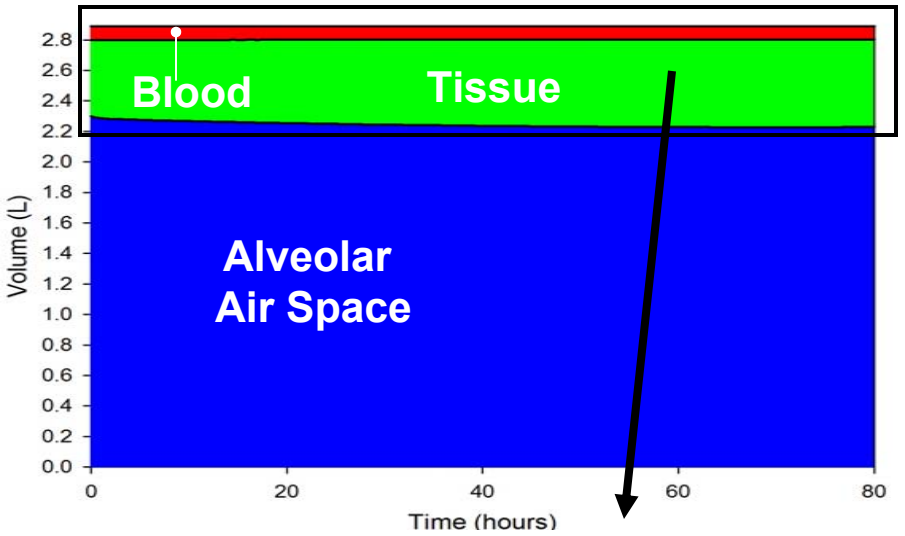



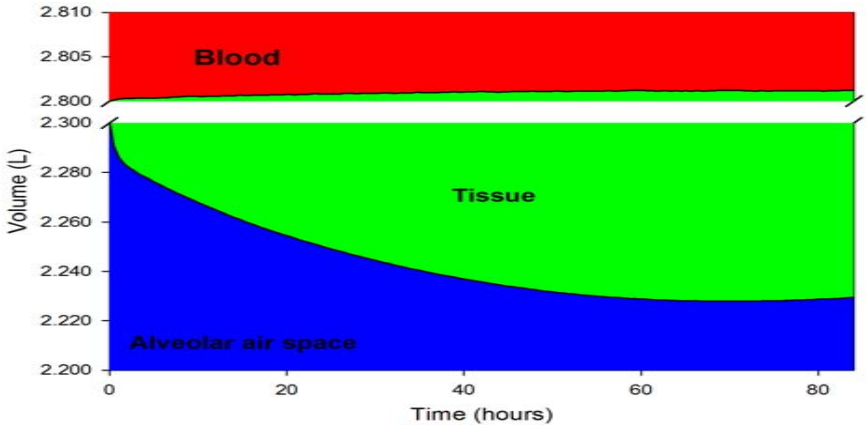
# Simulation results
# Gas exchange – single unit



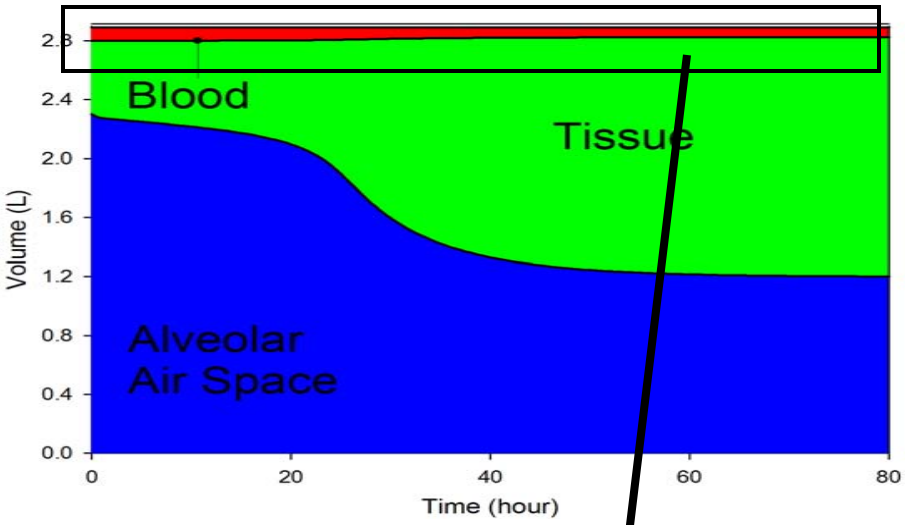
# Simulation results
# Lung volumes – single unit

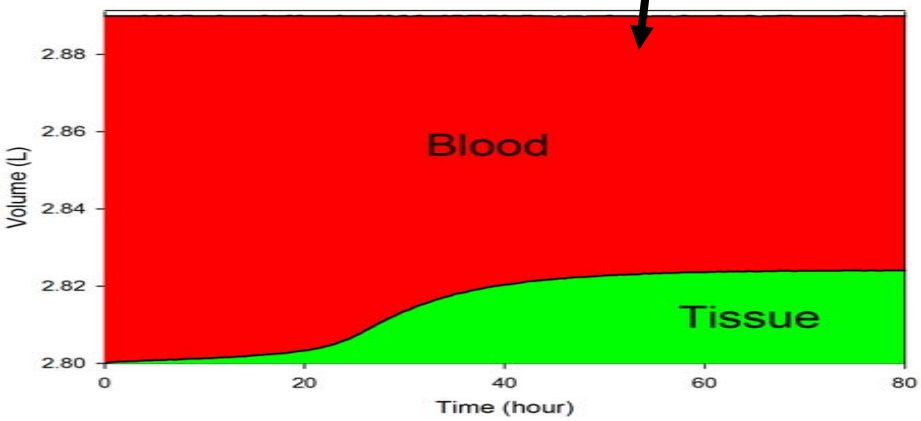
## Non-Lethal



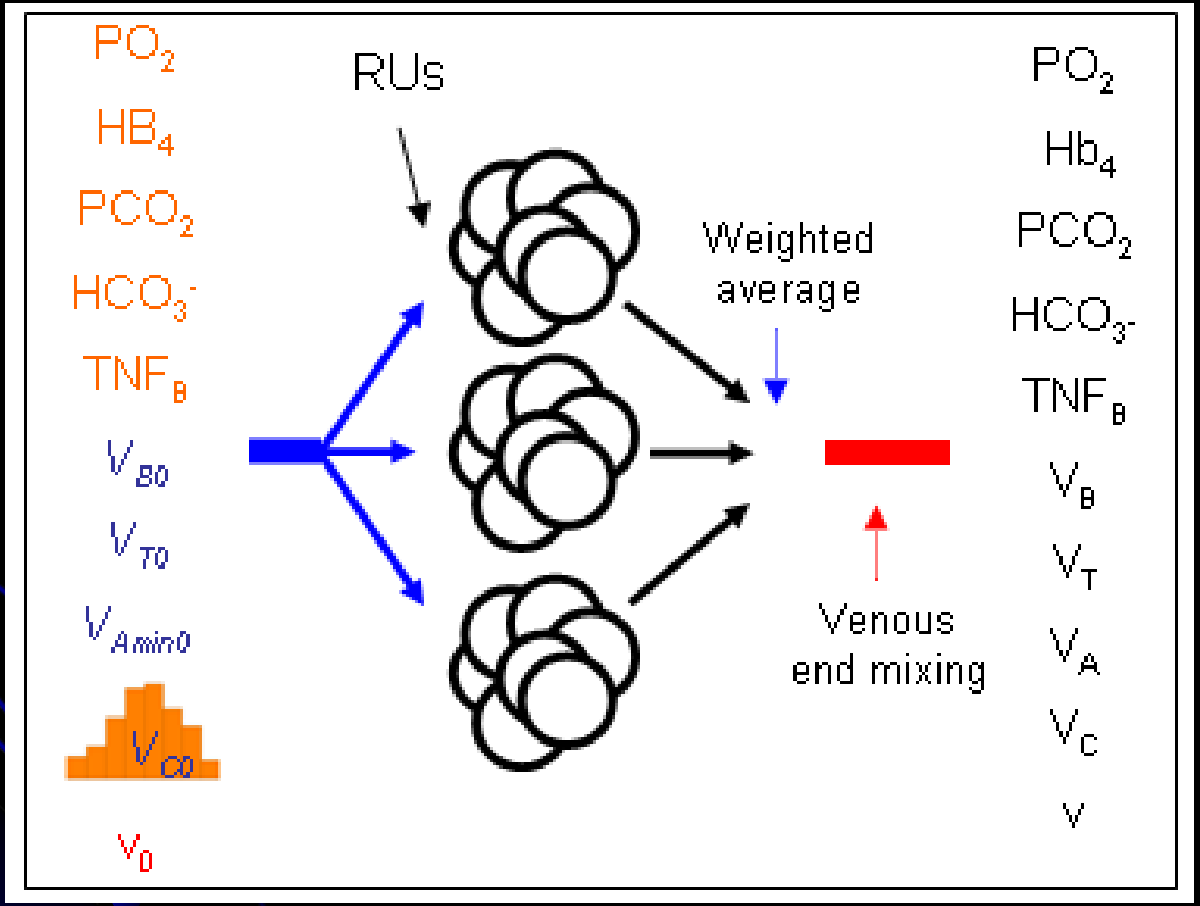




## Lethal

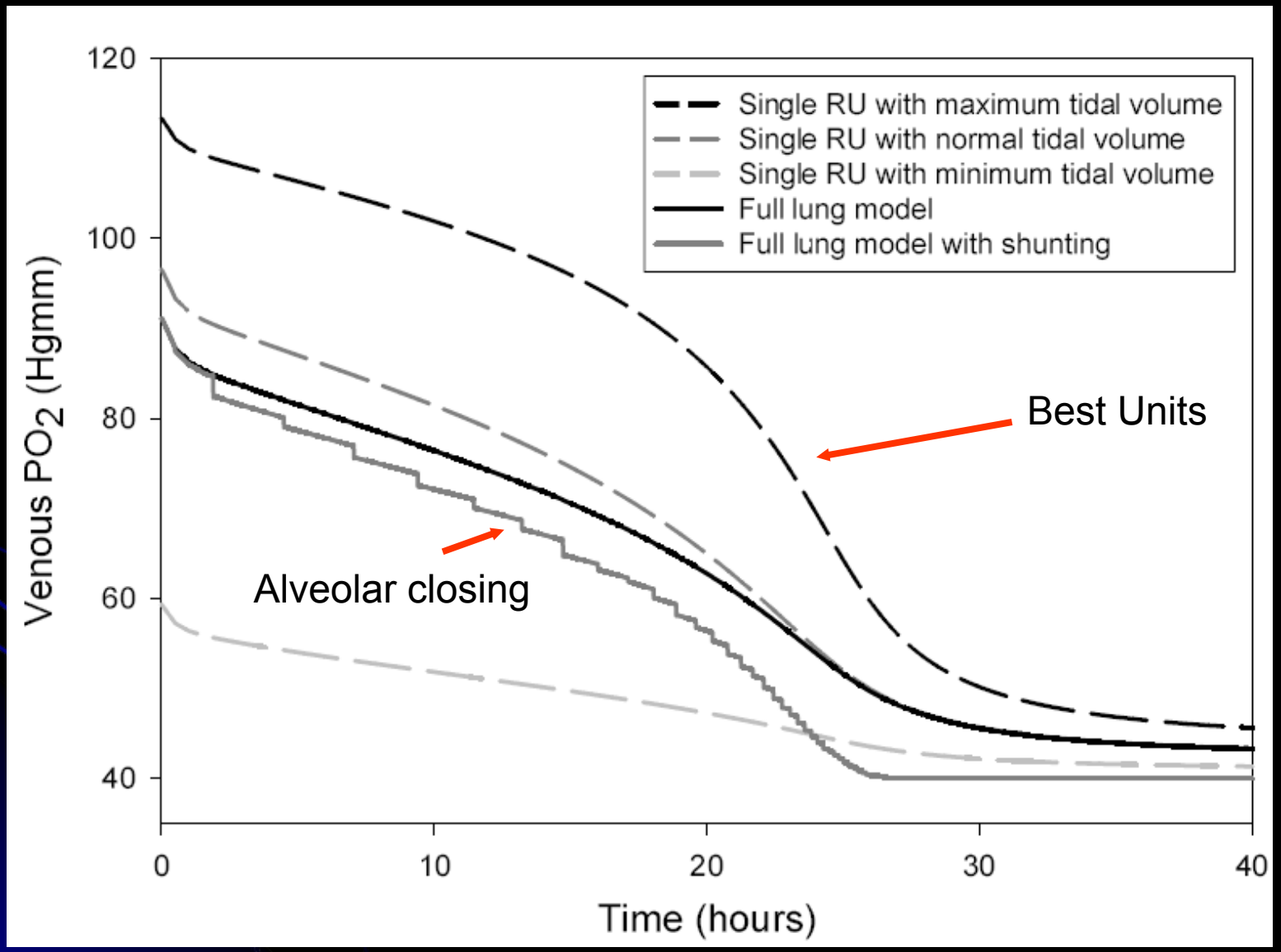


# Full lung model
# Assembling heterogeneous units



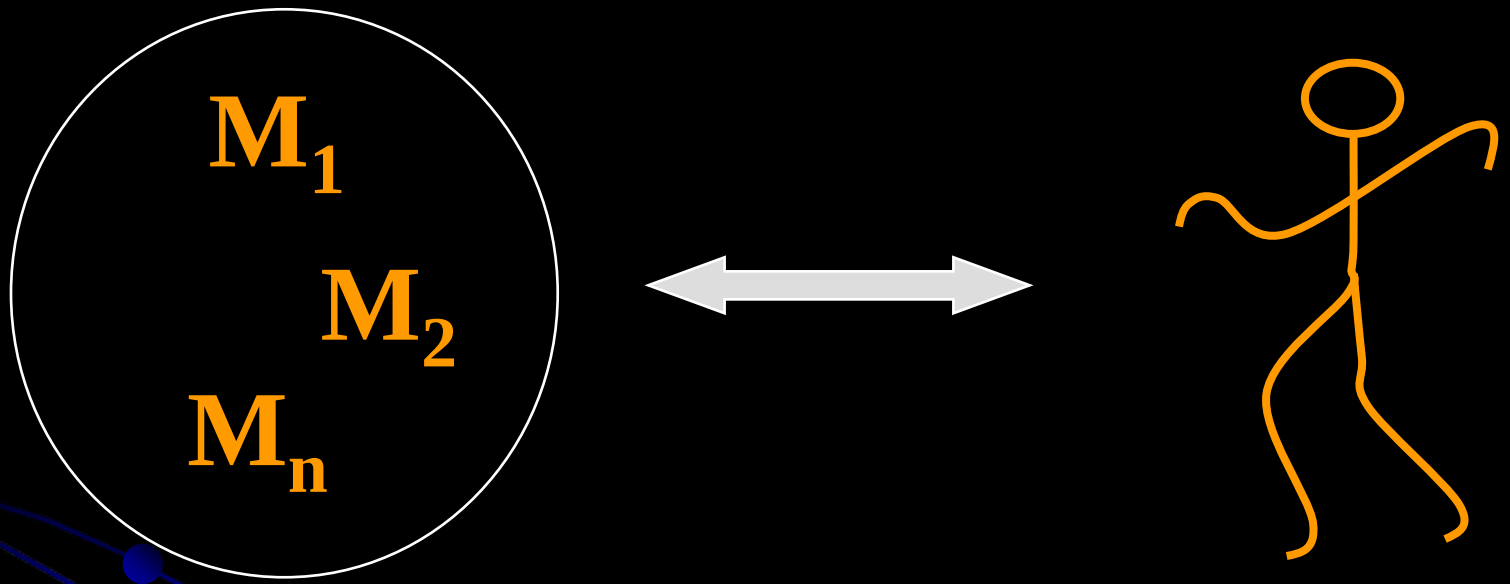
# Simulation - Full lung model



# Optimization

- Parameter identification
  - Inverse problem / data assimilation
  - Variability
- Control
  - Modify inputs to a model to achieve a desired outcome

# Patient-specific metamodel



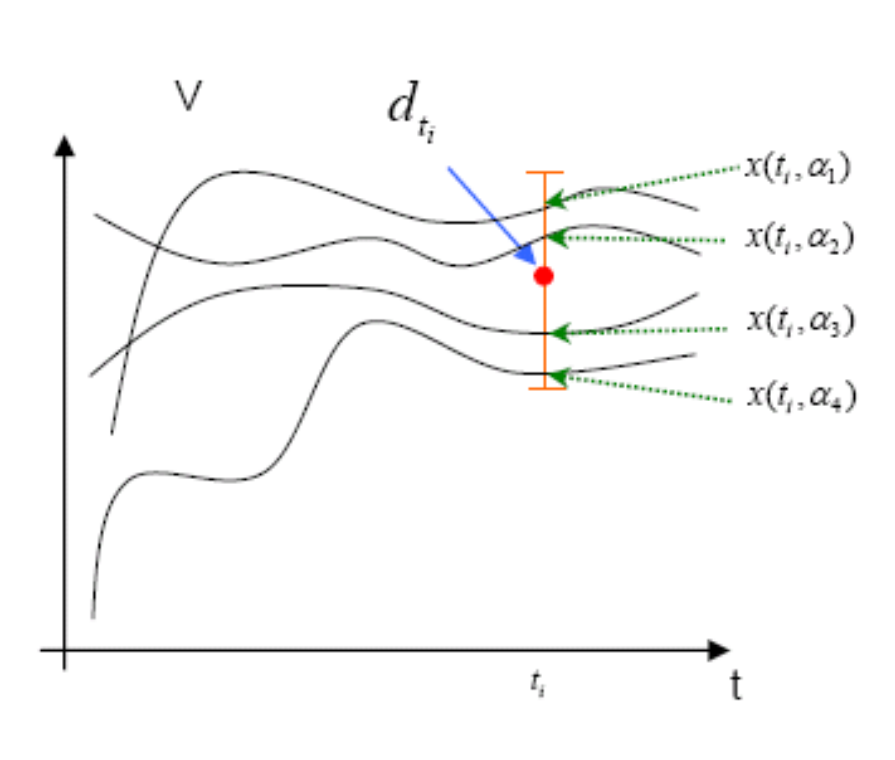

$\mathcal{E}(M_n) \equiv$ Metamodel or Ensemble

Where the individual models vary in their mathematical structure and parameters

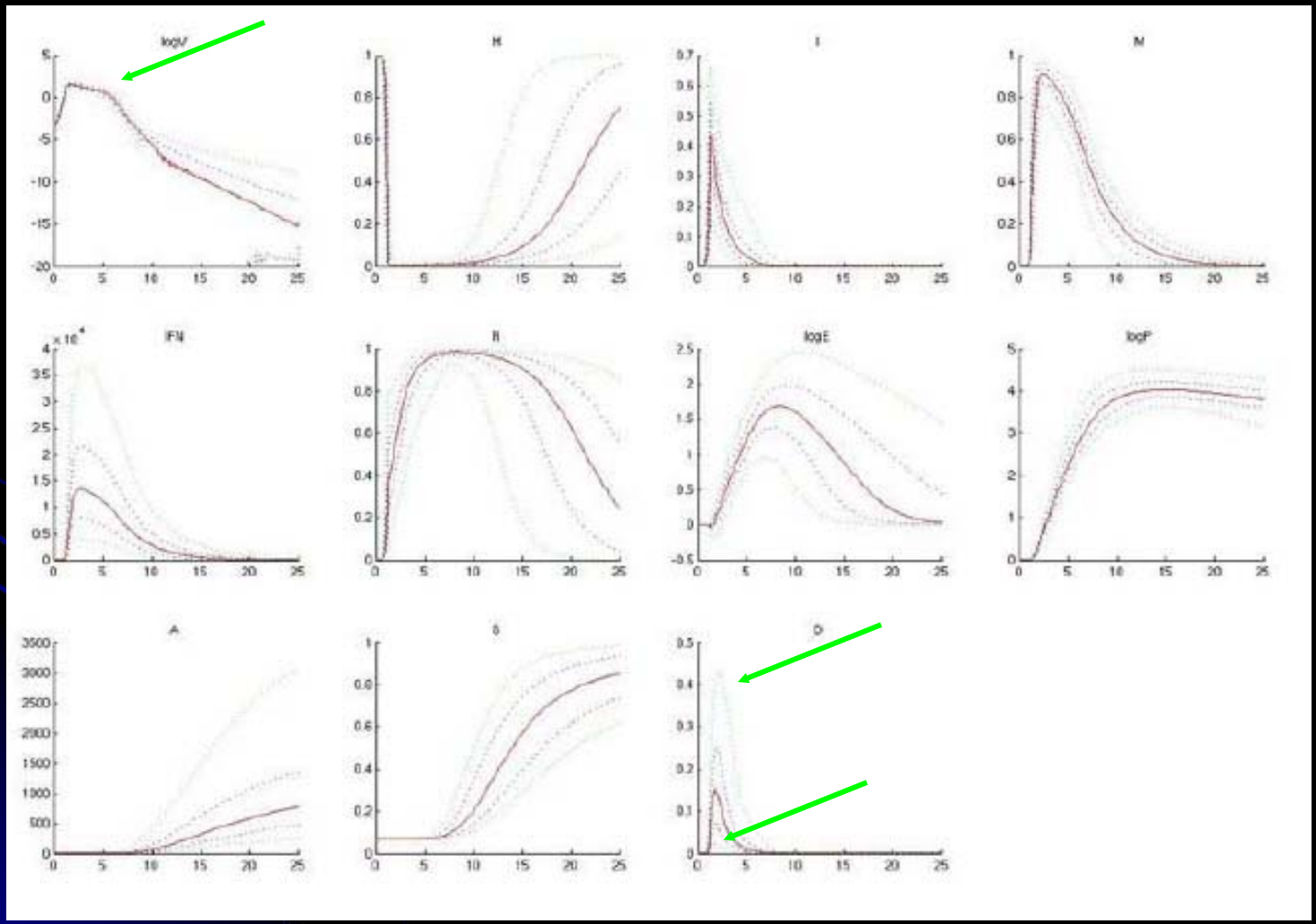
# Population variability in the response to Influenza virus

- Uncertainty in available data: measurement error
- Inter-individual variations

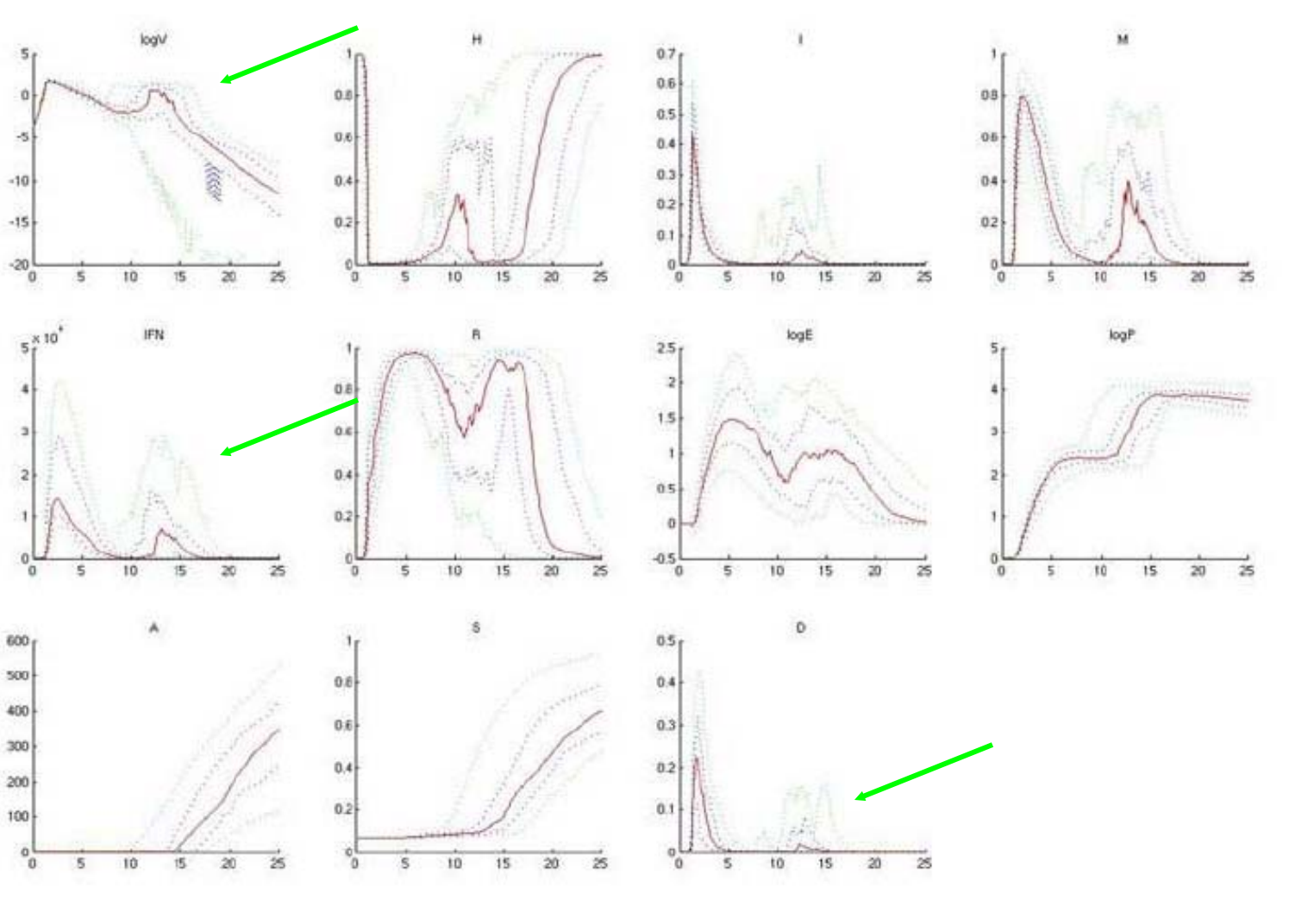
Best approached with stochastic methods



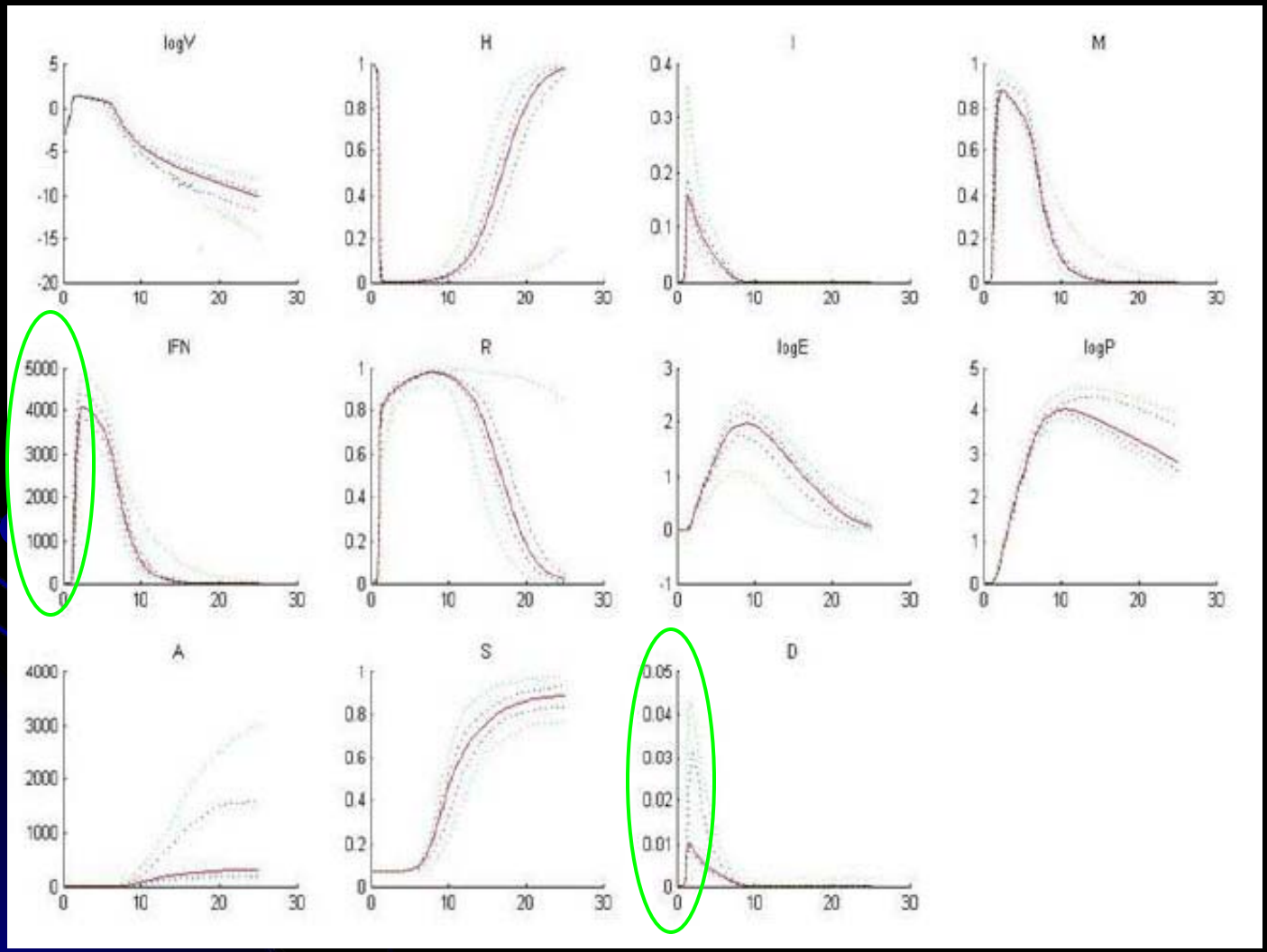
# Variability in the normal response



# Recurrence of disease…



# …and Superspreaders



# Conclusions

- Inflammation has several different components
- Inflammation is a multiscale problem
- A variety of modeling formalisms can be used