CRISMA Laboratory
UPMC Critical Care

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Multi-scale modeling of Influenza a virus and its containment

Towards System Biology Workshop

Grenoble, May 2011

Gilles Clermont, MD

CRISMA Center

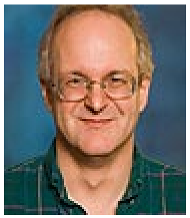
Center for Inflammation and Regenerative Modeling

Critical Care Medicine, Mathematics, Industrial Engineering

University of Pittsburgh

Acknowledgments

- **Colleagues**






- **Trainees**
  - Baris Hancioglu
  - Ian Price
  - David Dreisigmeyer
  - Sarah Lukens
  - Jay Depasse

- **NIH(GM)/NSF(DMS)**

Epidemic Influenza

- **In a “normal” season**
  - Up to 30 million infections in the US
  - 100,000 attributable hospitalizations
  - 35,000 attributable deaths
  - 3B (direct) -15B (total) in societal costs
- **Most deaths are due to secondary infections (pneumonia)**
- **Target population (old, sick and the very young)**

Pandemic 2009 H1N1

- **In the US**
  - 61M cases, 12,700 deaths
- **Severe illness**
  - The Australia-New Zealand experience (NEJM)
    - 722 cases (29 cases/M)
    - 14.3% mortality
  - The Canadian experience (JAMA)
    - 215 cases
    - 14.3% mortality
  - Our own experience Pittsburgh/UPMC
    - 24 admissions to adult ICU starting in august 2009
    - 75% mortality
- **Target population**
  - Young adult, pregnant women

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes
The major outcomes studied ... trauma, defined as an injury sev... 15.[6]

Meta-analysis
Our statistical apprach was to as... chute and control groups by od... the precision of estimates by 95... We chose the Mantel-Haenszel... geneity, and sensitivity and su... fixed effects weighted regression... causes of heterogeneity. We sel... assess publication bias visually ... tests to test it quantitatively. Stat... was the tool for all statistical ana...

Results

Our search strategy did not ... controlled trials of the parachut...

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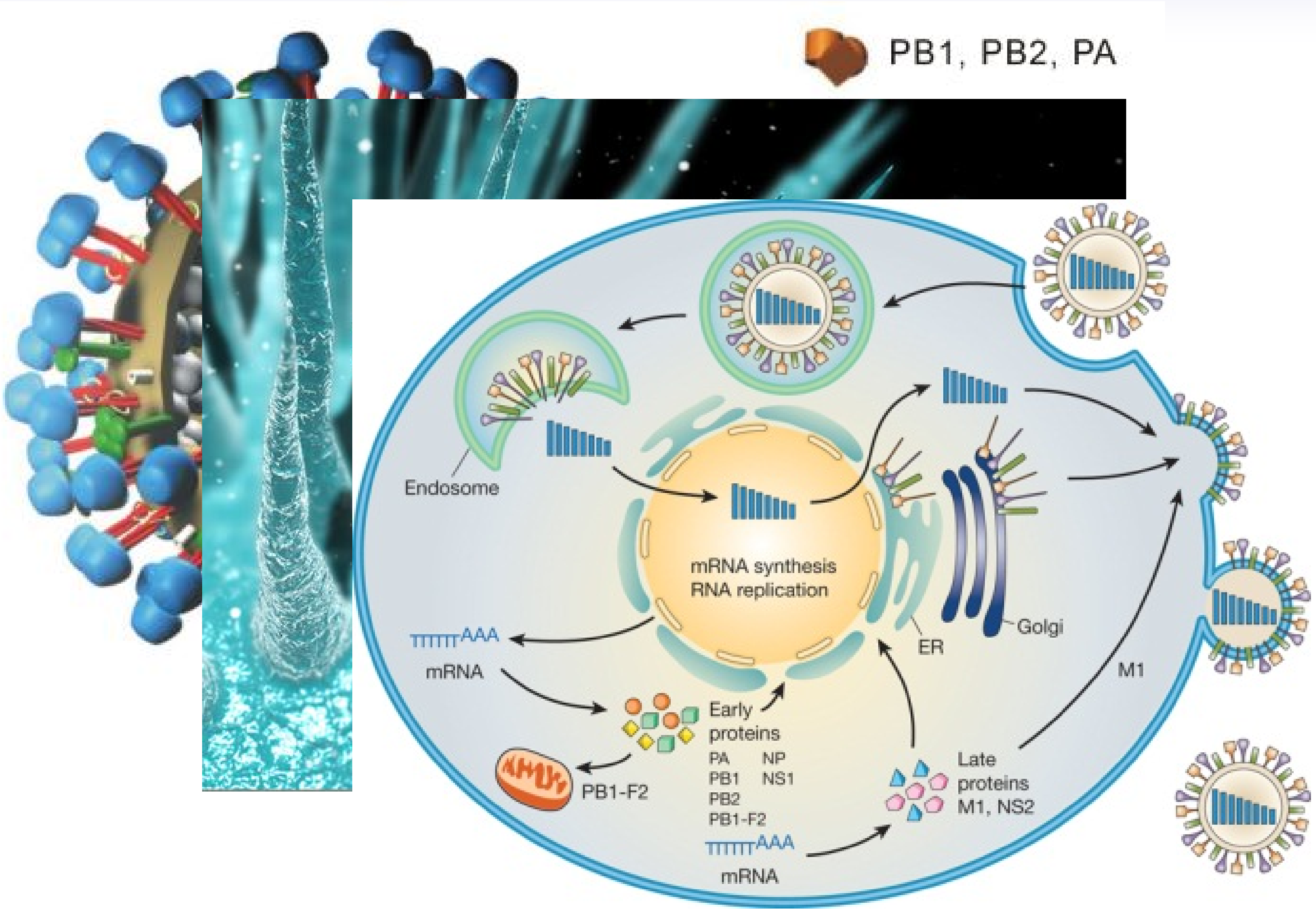
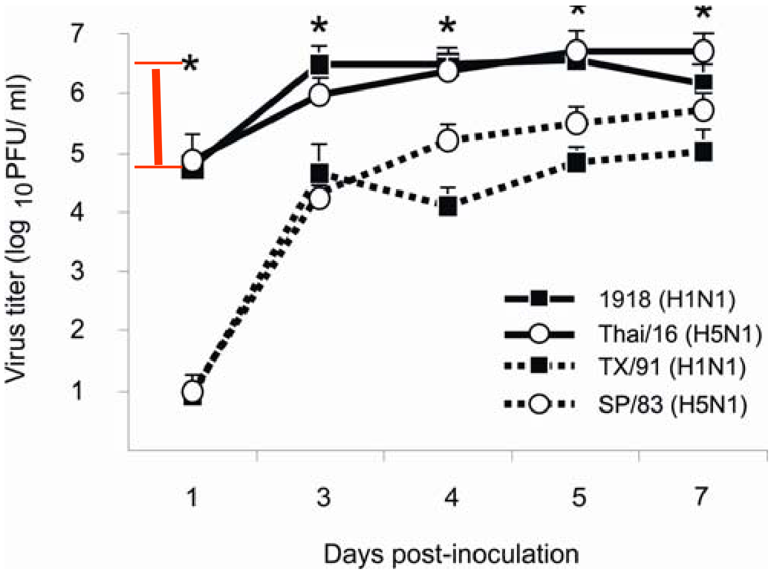
Gordon C S Smith
professor

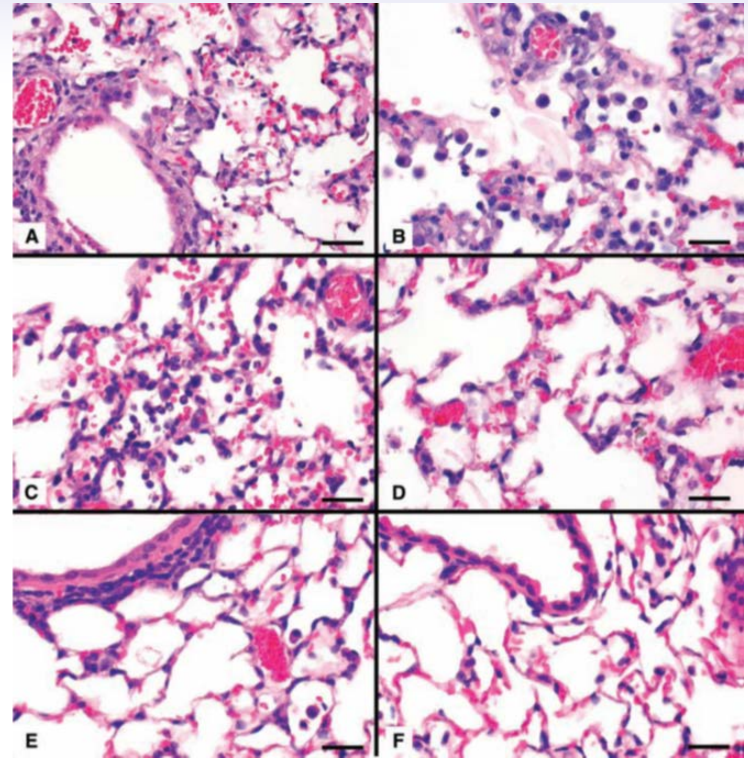
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

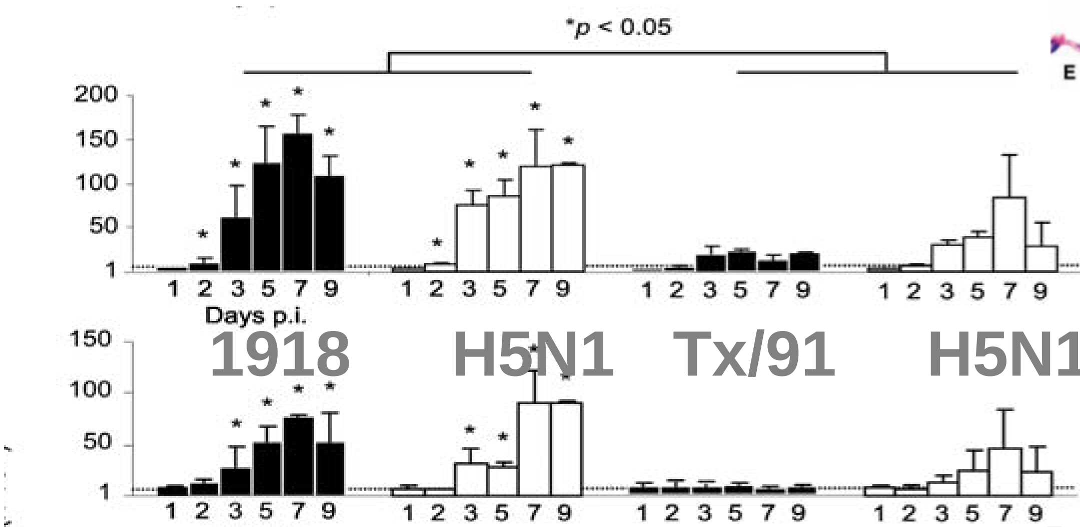
Influenza A virus



Pandemic influenza is an inflammatory disease





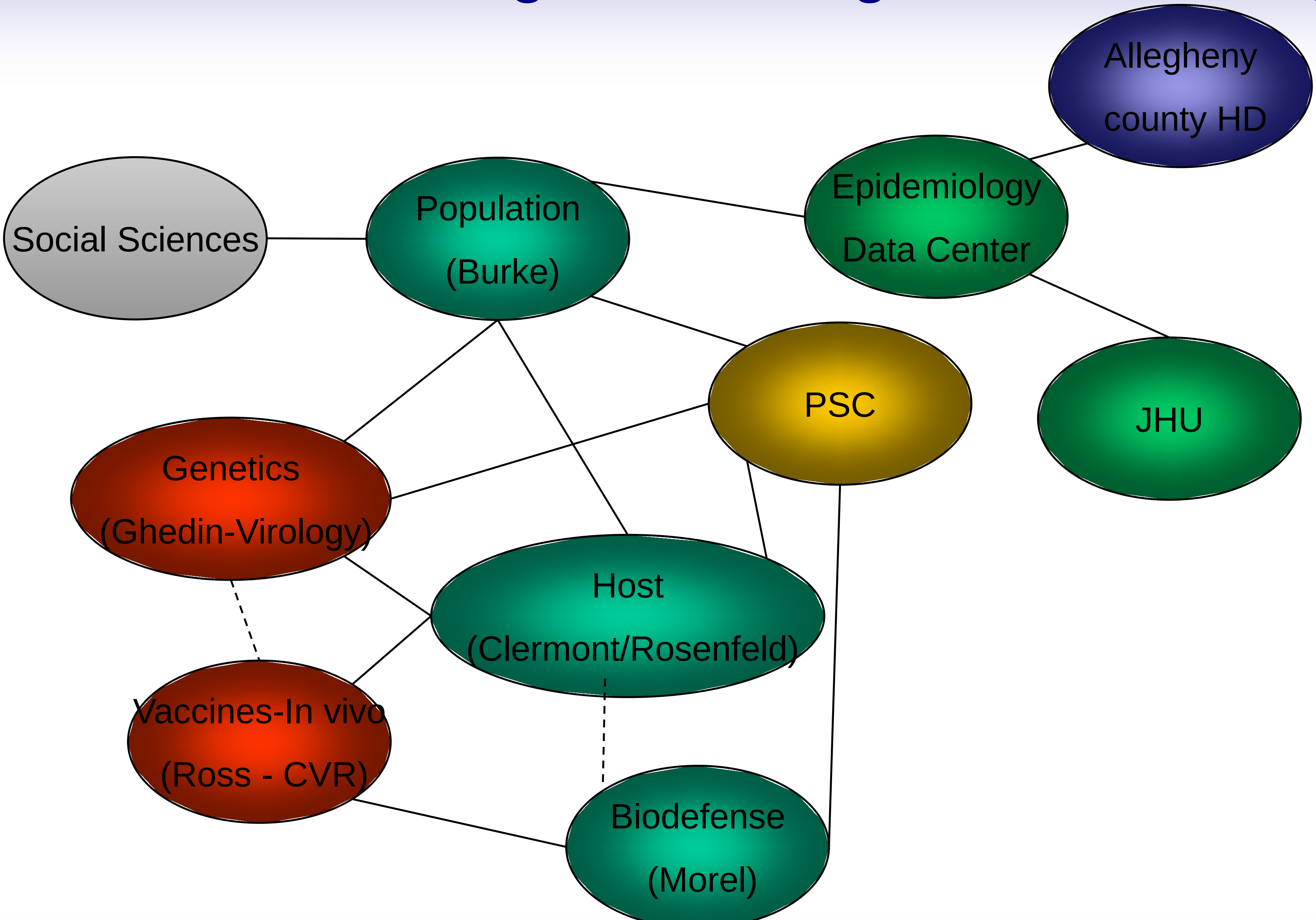


Macrophages (CD11b+, CD11c-, Ly6G/C-, CD4-, CD8-)

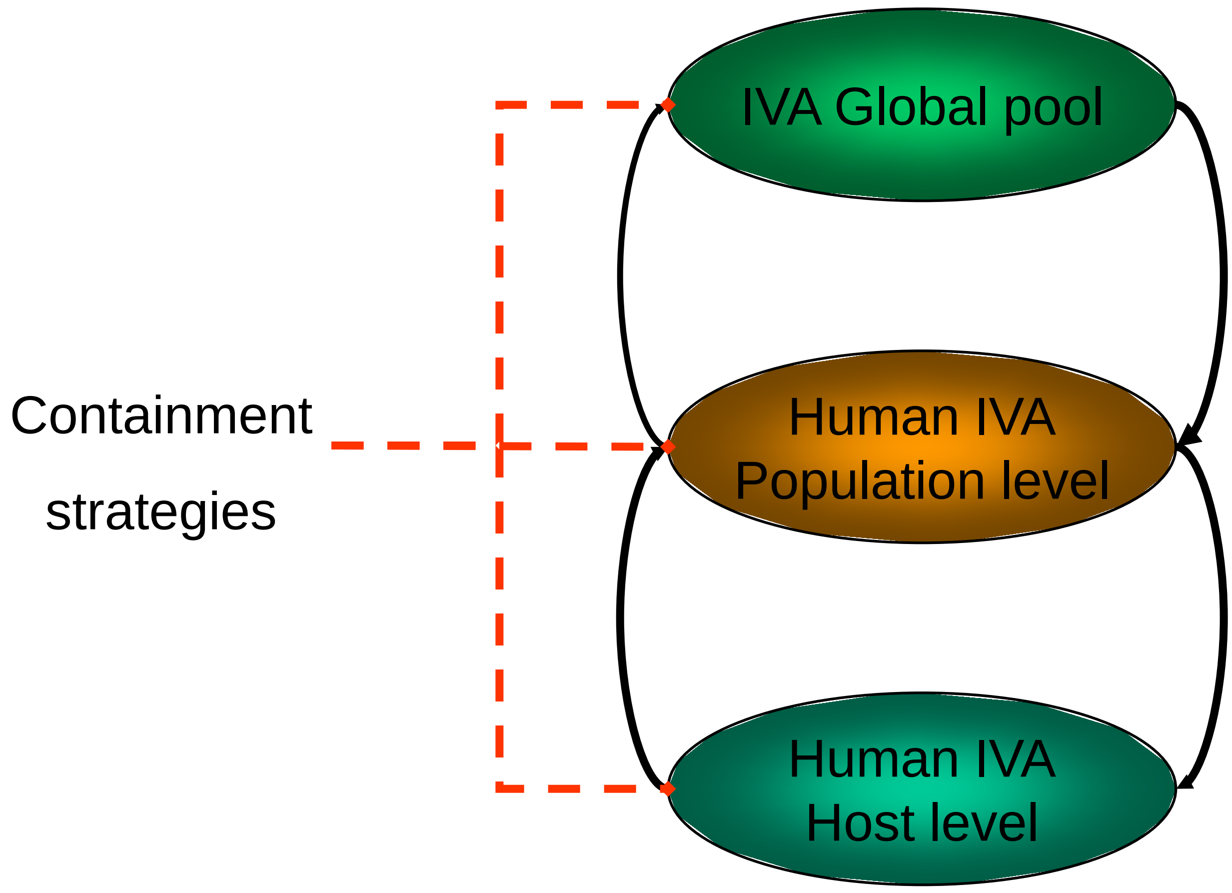
Neutrophils (CD11b+, CD11c-, Ly6G/C+, CD4-, CD8-)

Perrone et al., PLoS Pathogens 2008

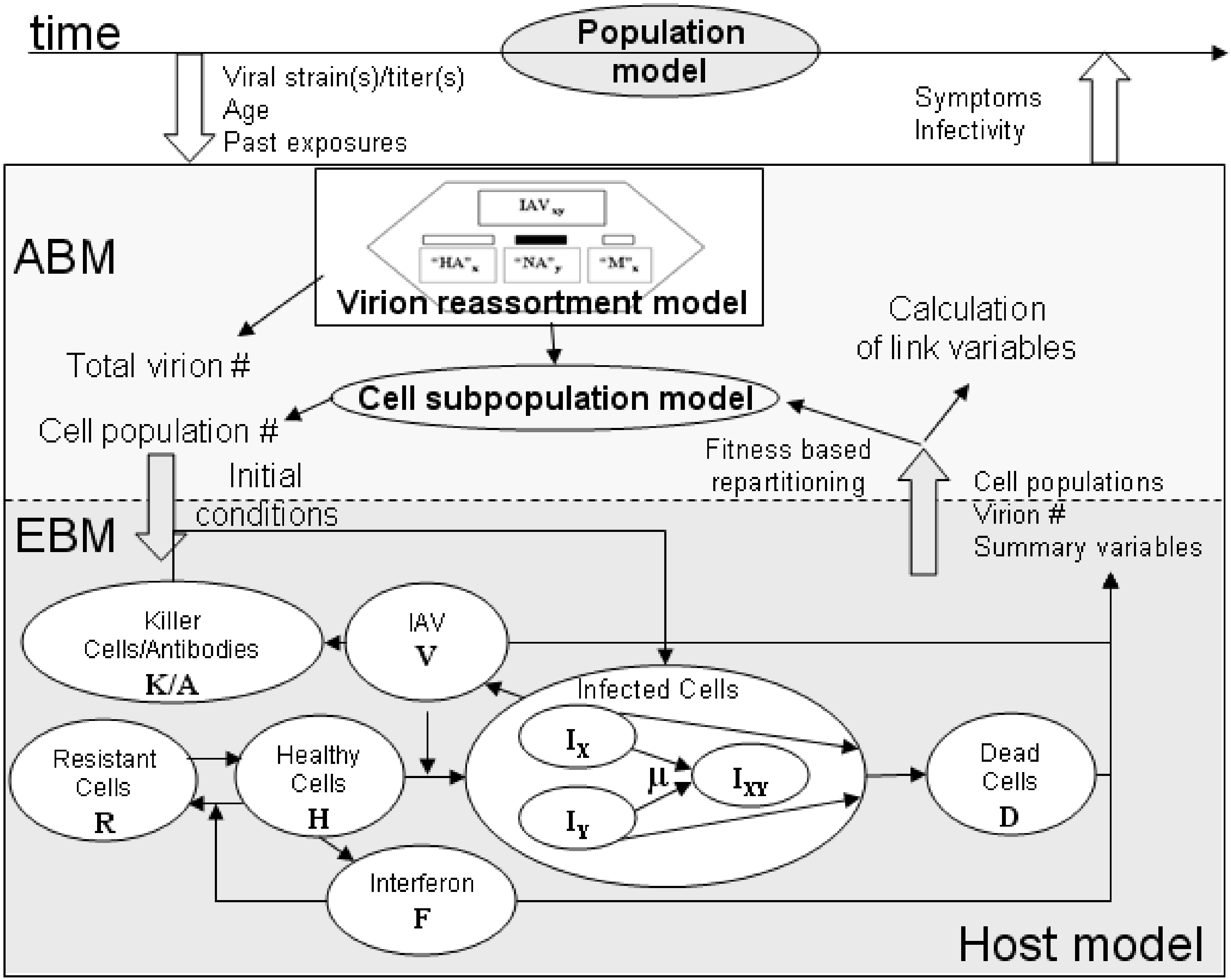
Influenza modeling in Pittsburgh



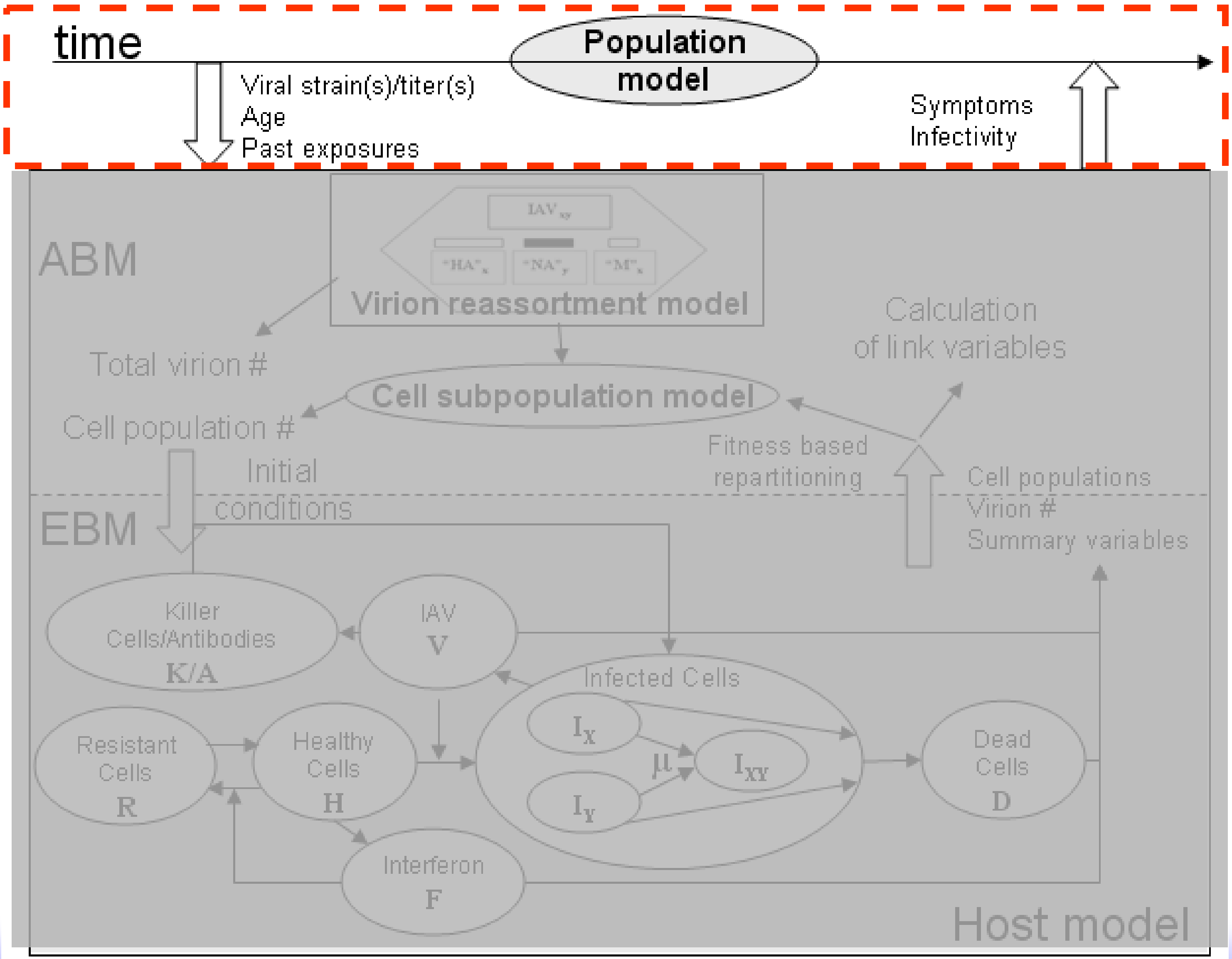
Multiscale modeling



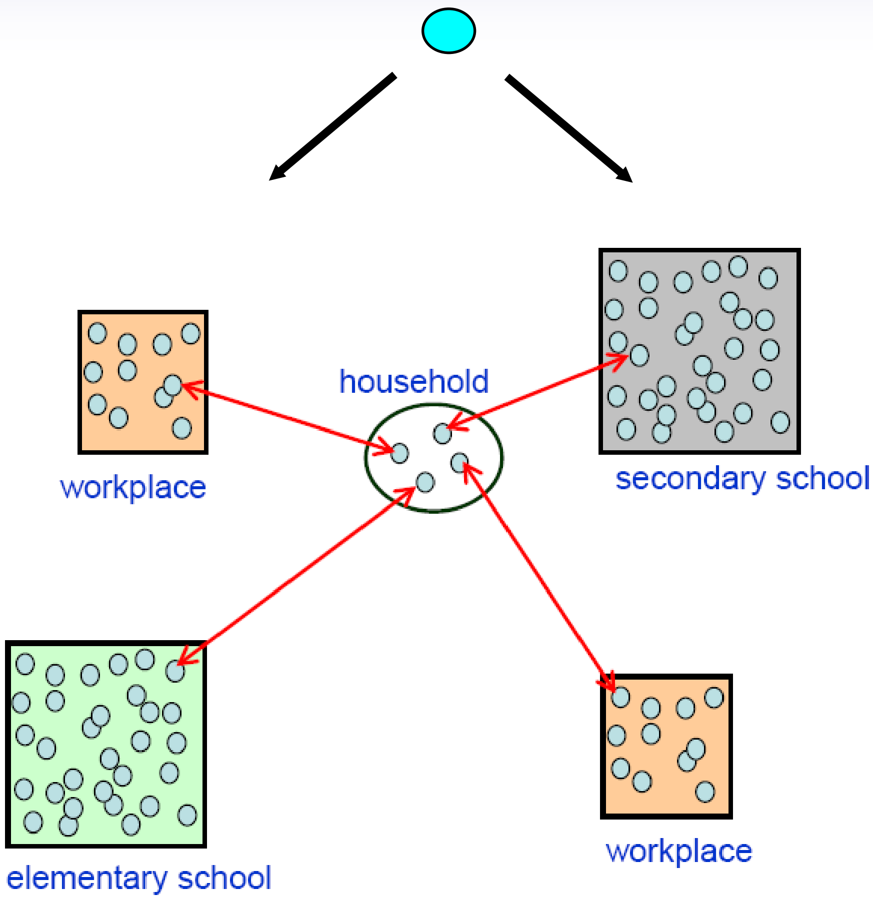
Multiscale modeling – MIDAS



Multiscale modeling – Population



Population-level models (SIR)



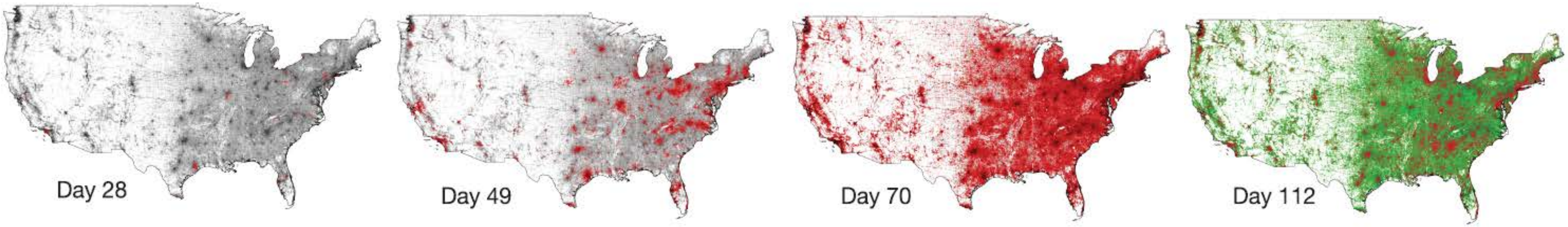
- **Susceptibles**
  - P(Infection|Environment)
- **Infected**
  - P(Duration)
  - ?? P(Death)
- **Recovered**
  - P(Susceptible)?=0
- **Resistant**
  - P(immune)

- Human activity (travel)
- Geography/weather

Population-level models

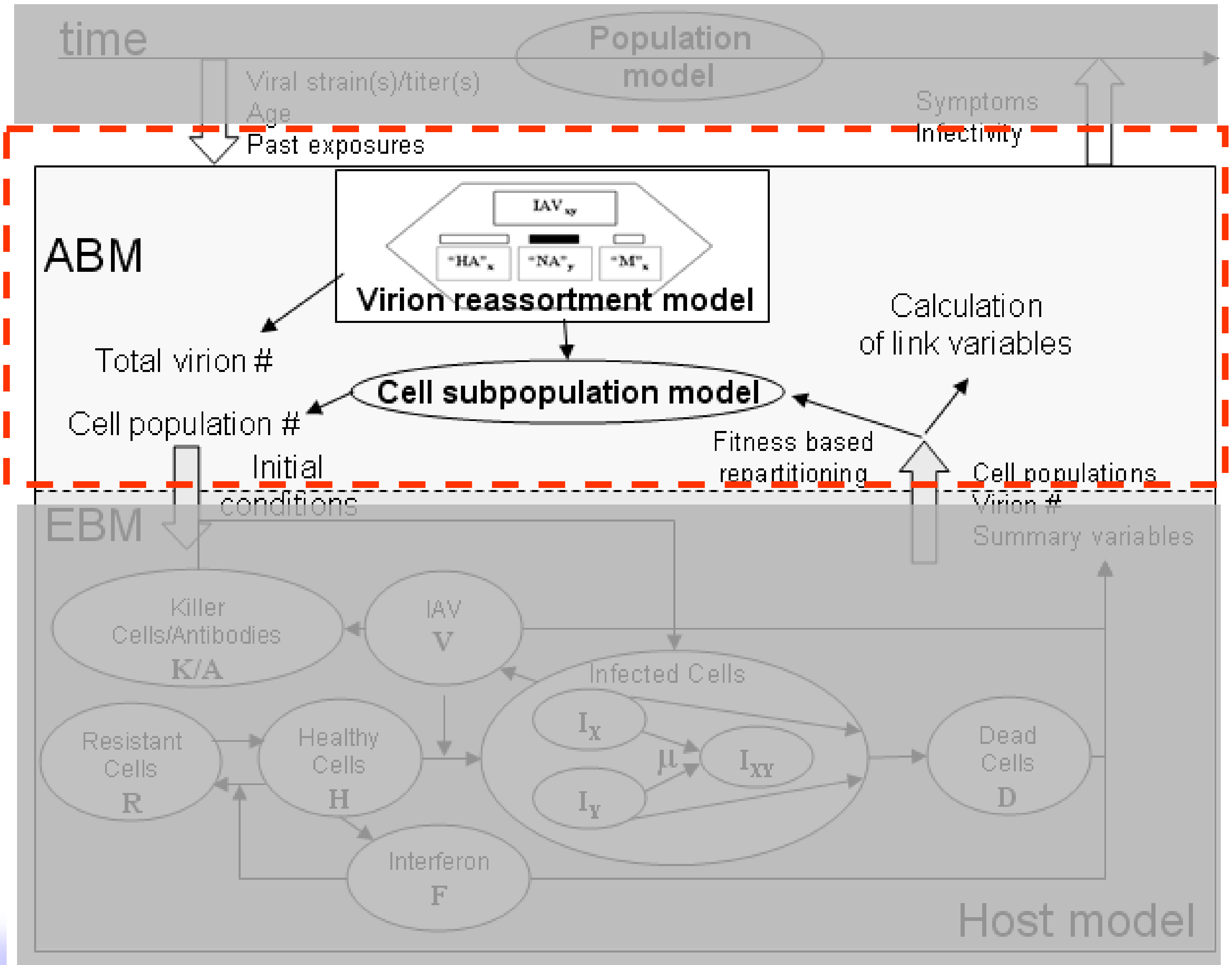
Agent-based model (FRED)

- Sophisticated cellular automata
- Stochastic - Distribution driven
  - Age, household size, school sizes…
  - Transmission, duration of disease…
- Computational requirements
  - 32 nodes
  - 75GB (3e8 agents)
  - 5 hours

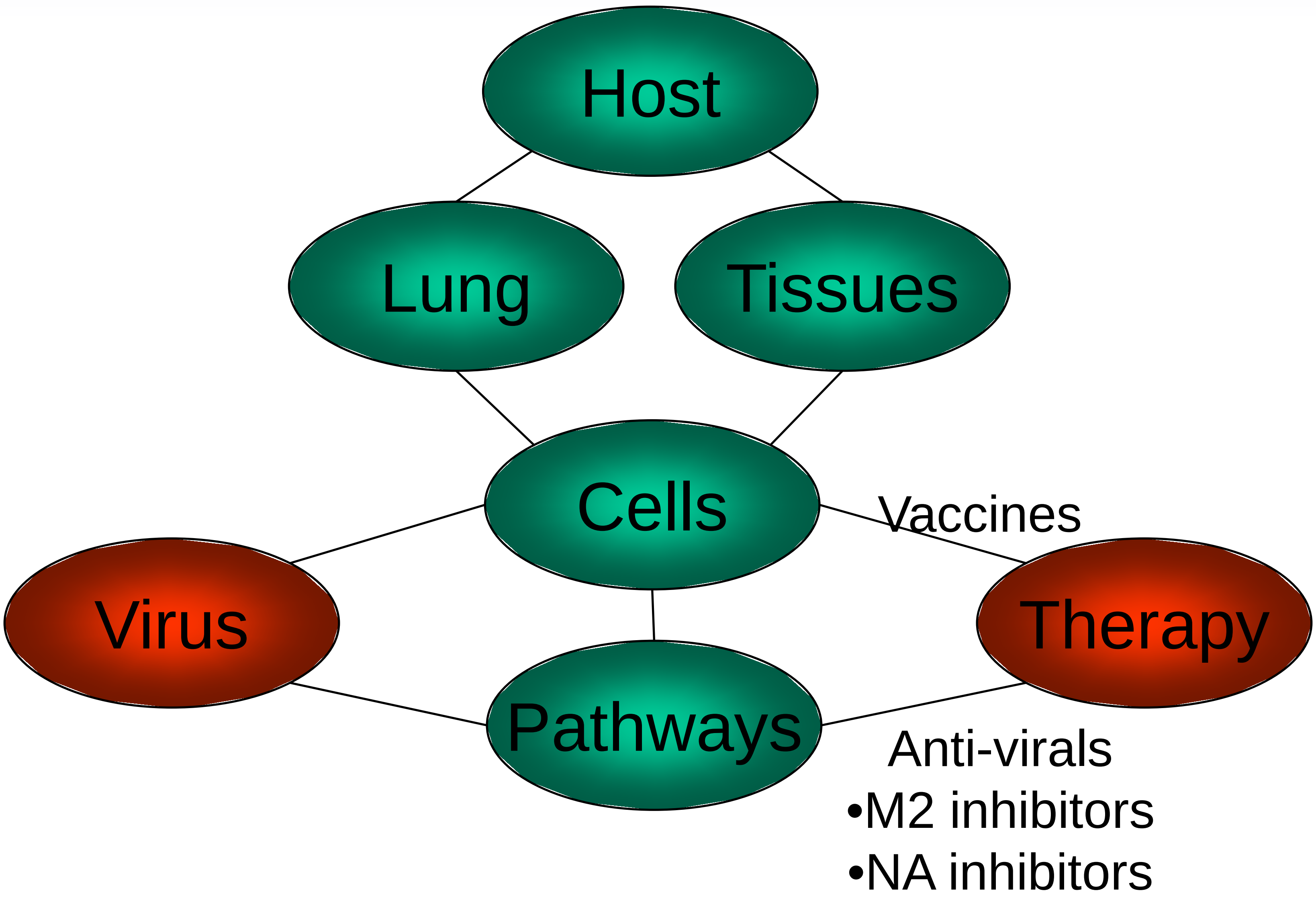


Ferguson et al. Nature 2005

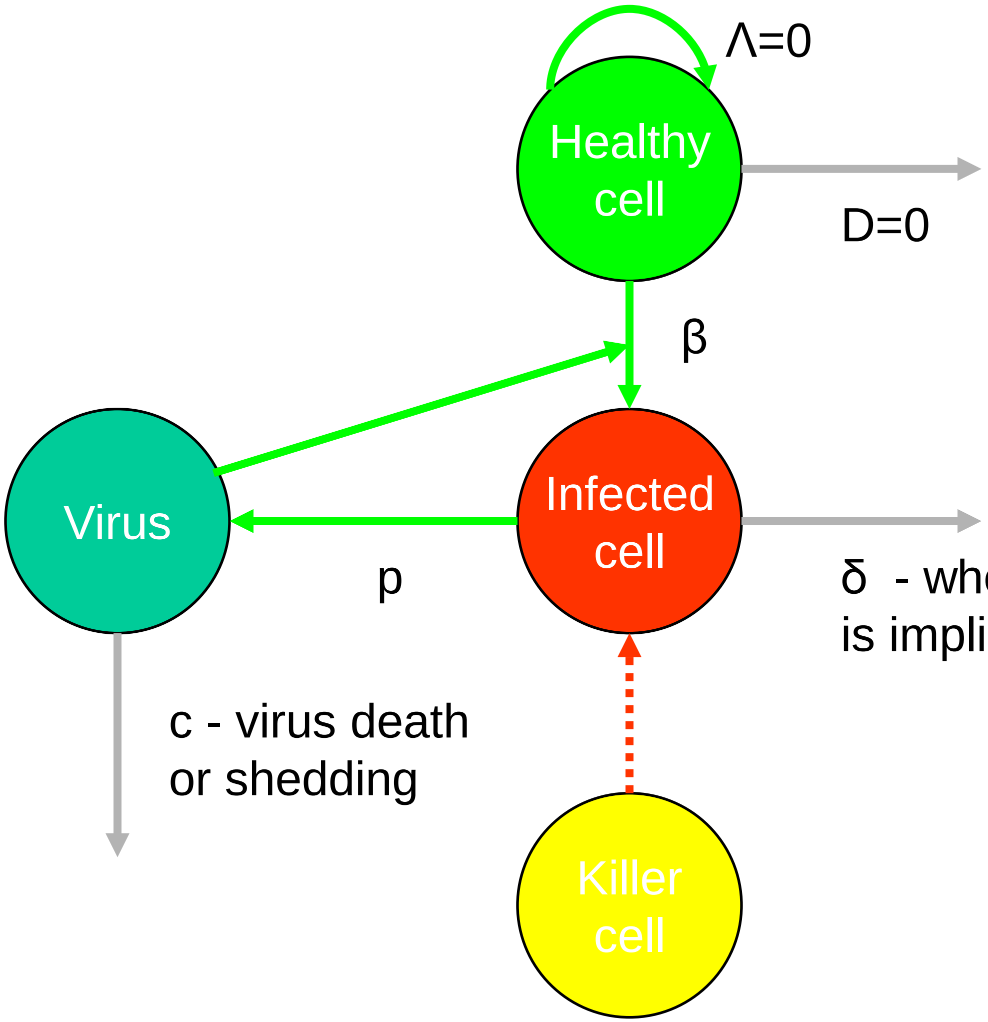
Multiscale modeling – Viral evolution



Multiscale modeling - Host



The simplest viral model – ever ! (v1.0)

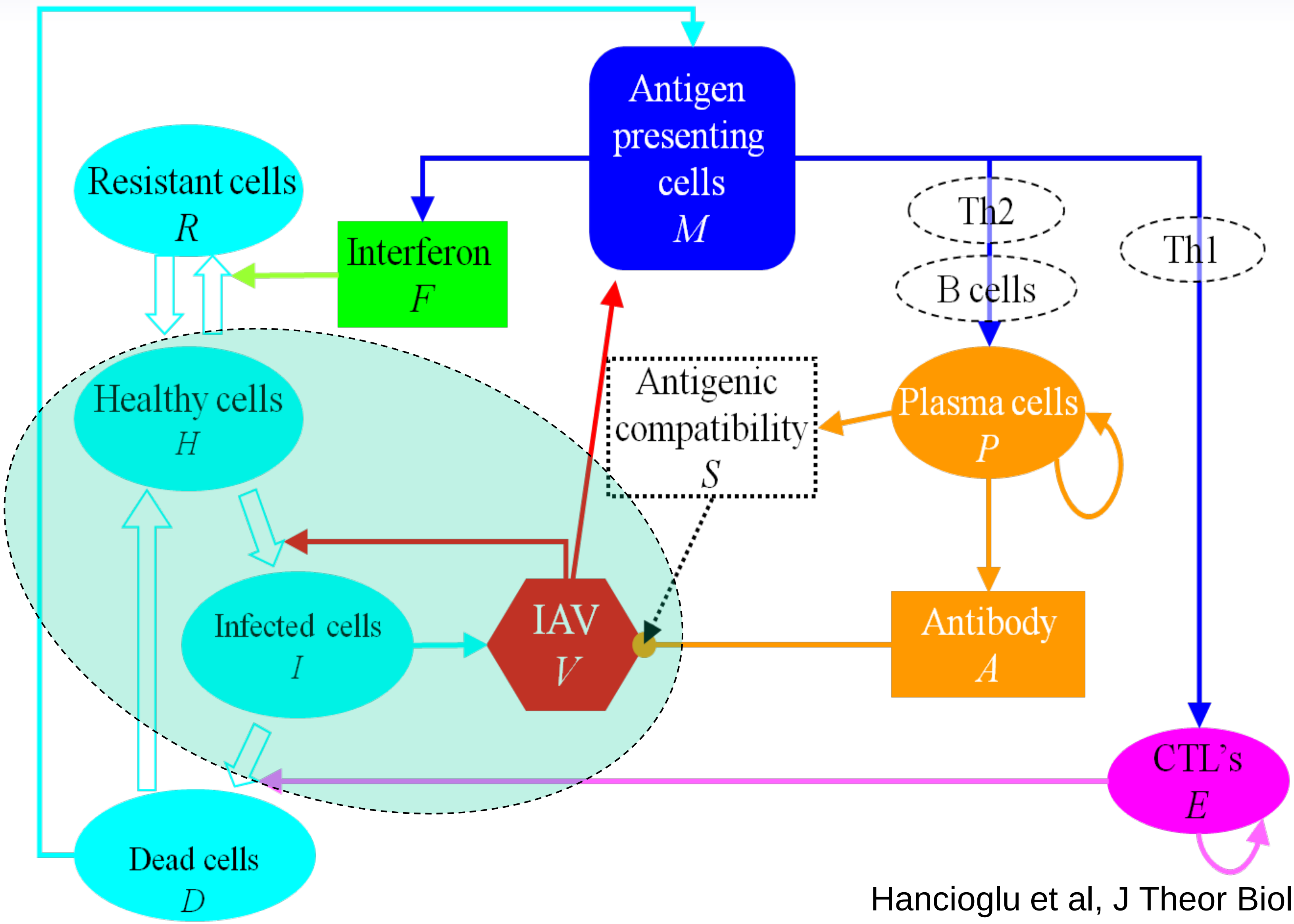


$$\frac{dH}{dt} = -\beta HV$$

$$\frac{dI}{dt} = \beta HV - \delta I$$

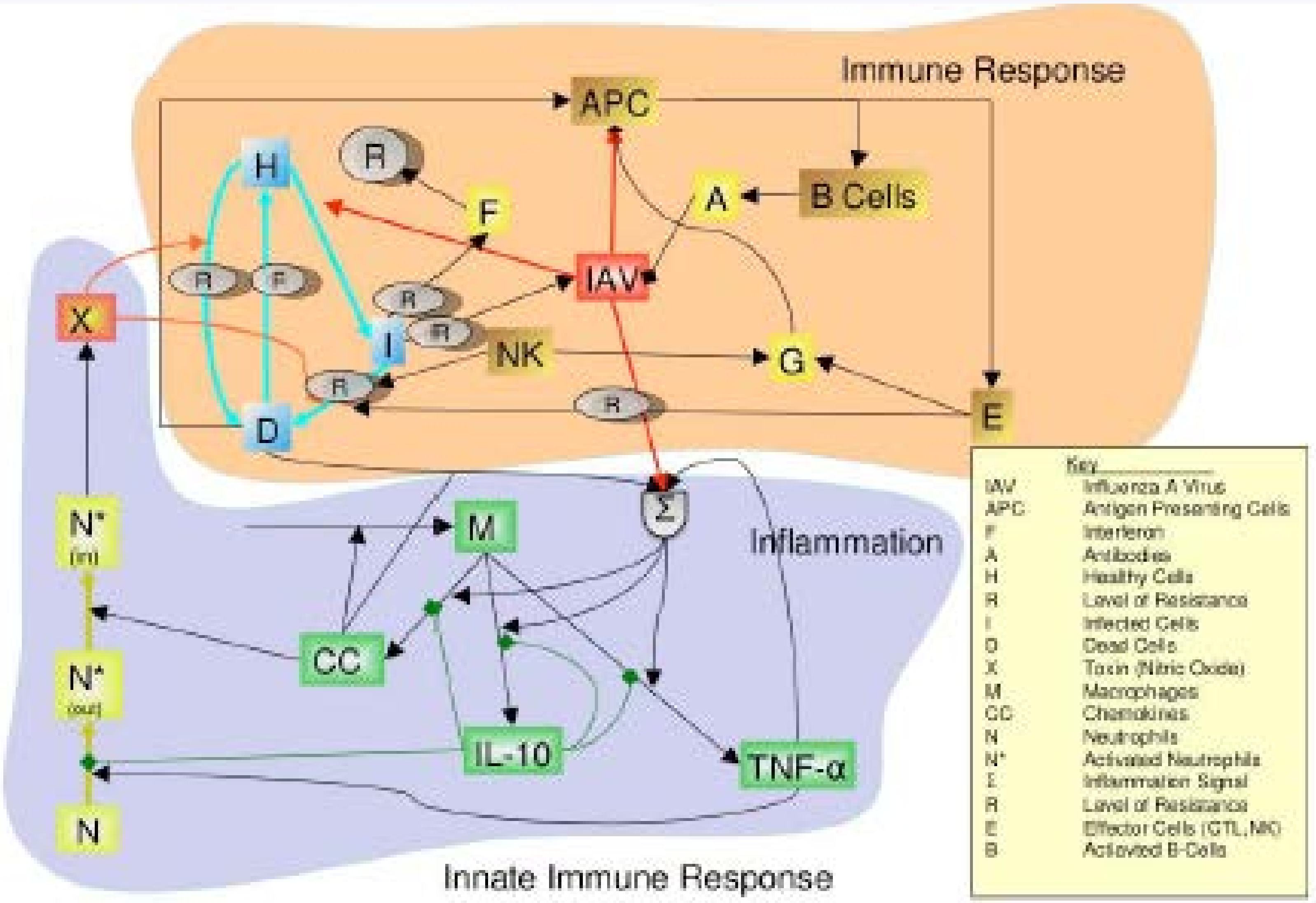
$$\frac{dV}{dt} = pI - cV$$

IVA-host model 2.0



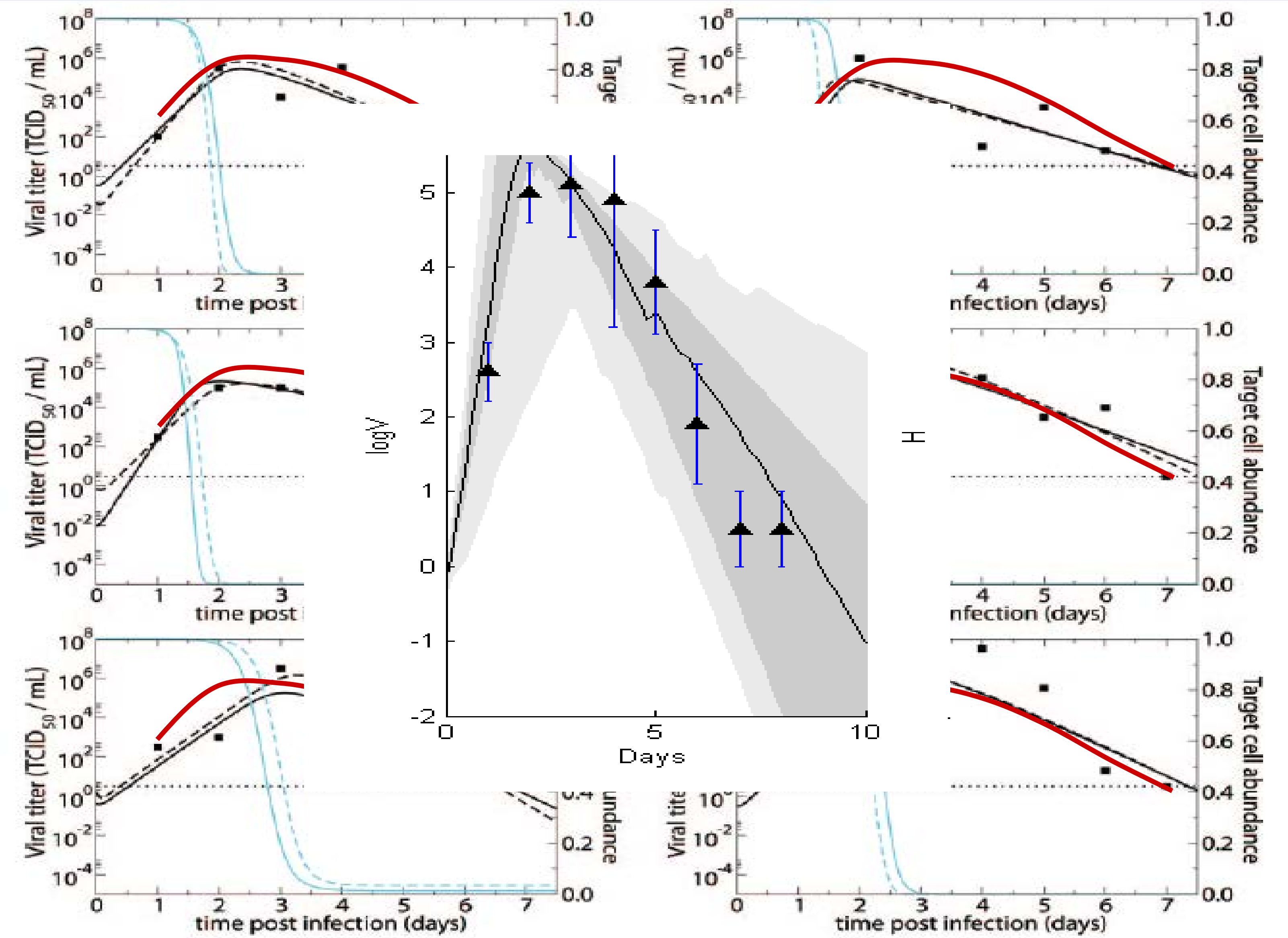
Hancioglu et al, J Theor Biol 2007

Host-level model 3.0



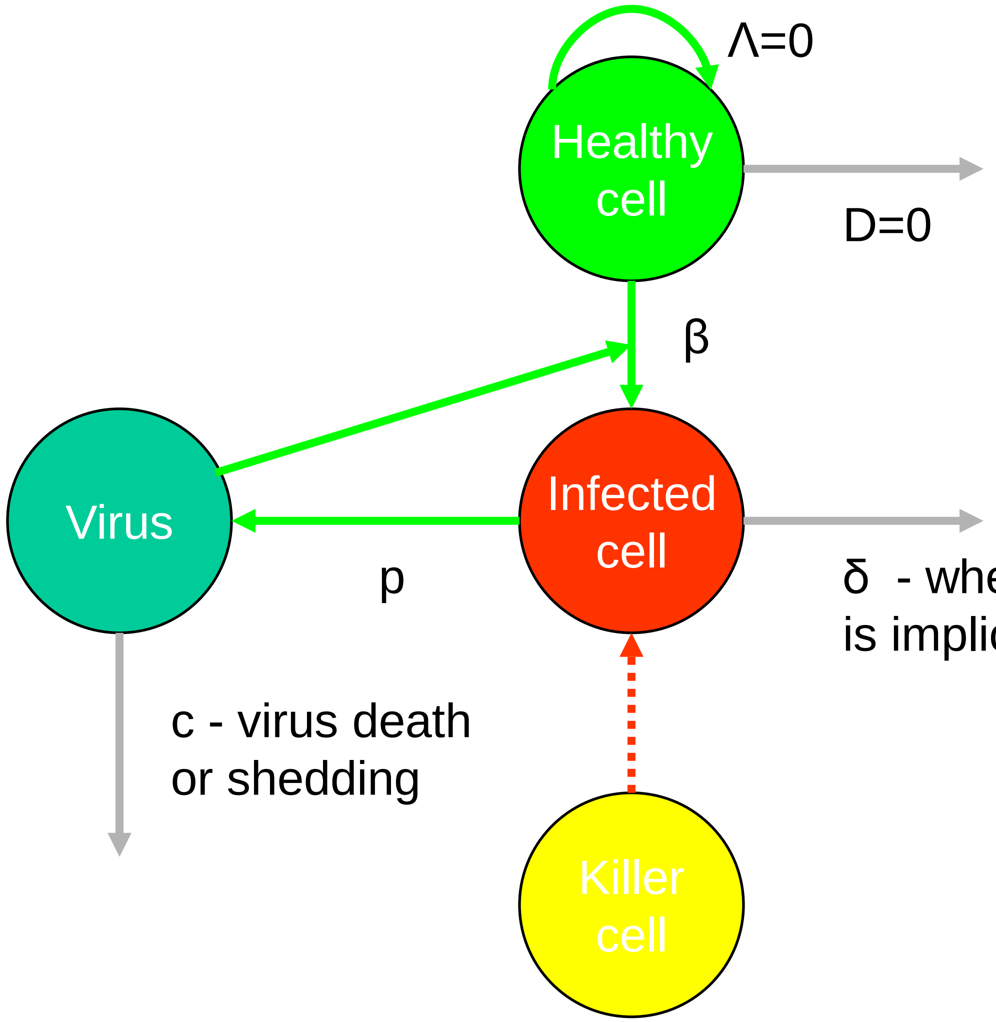
Price et al. JCC 2008

Looking at individuals



Baccam et al. Virology 2007

The estimation problem



$$\frac{dH}{dt} = -\beta HV$$

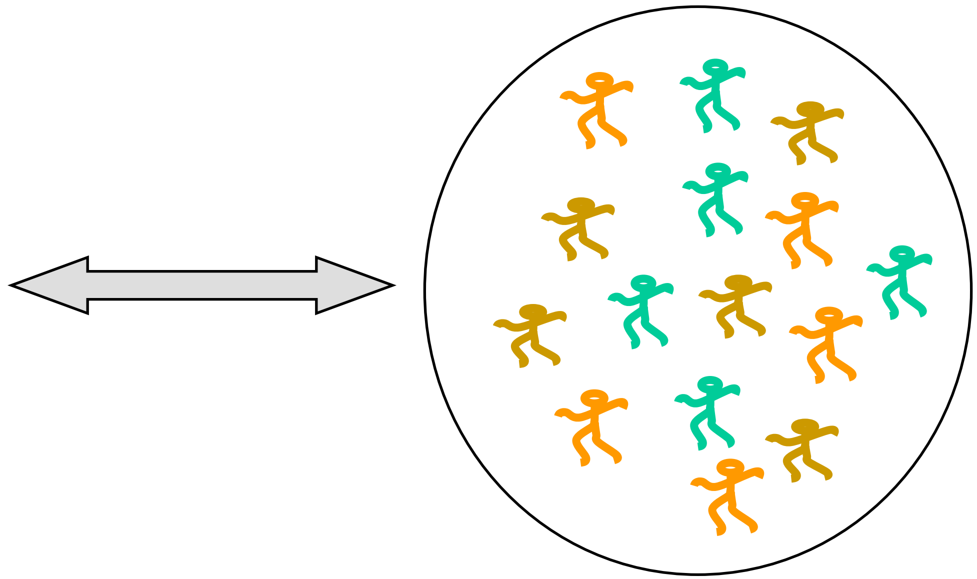
$$\frac{dI}{dt} = \beta HV - \delta I$$

$$\frac{dV}{dt} = pI - cV$$

δ - where active cell killing is implicit in this death rate

Population ensemble models

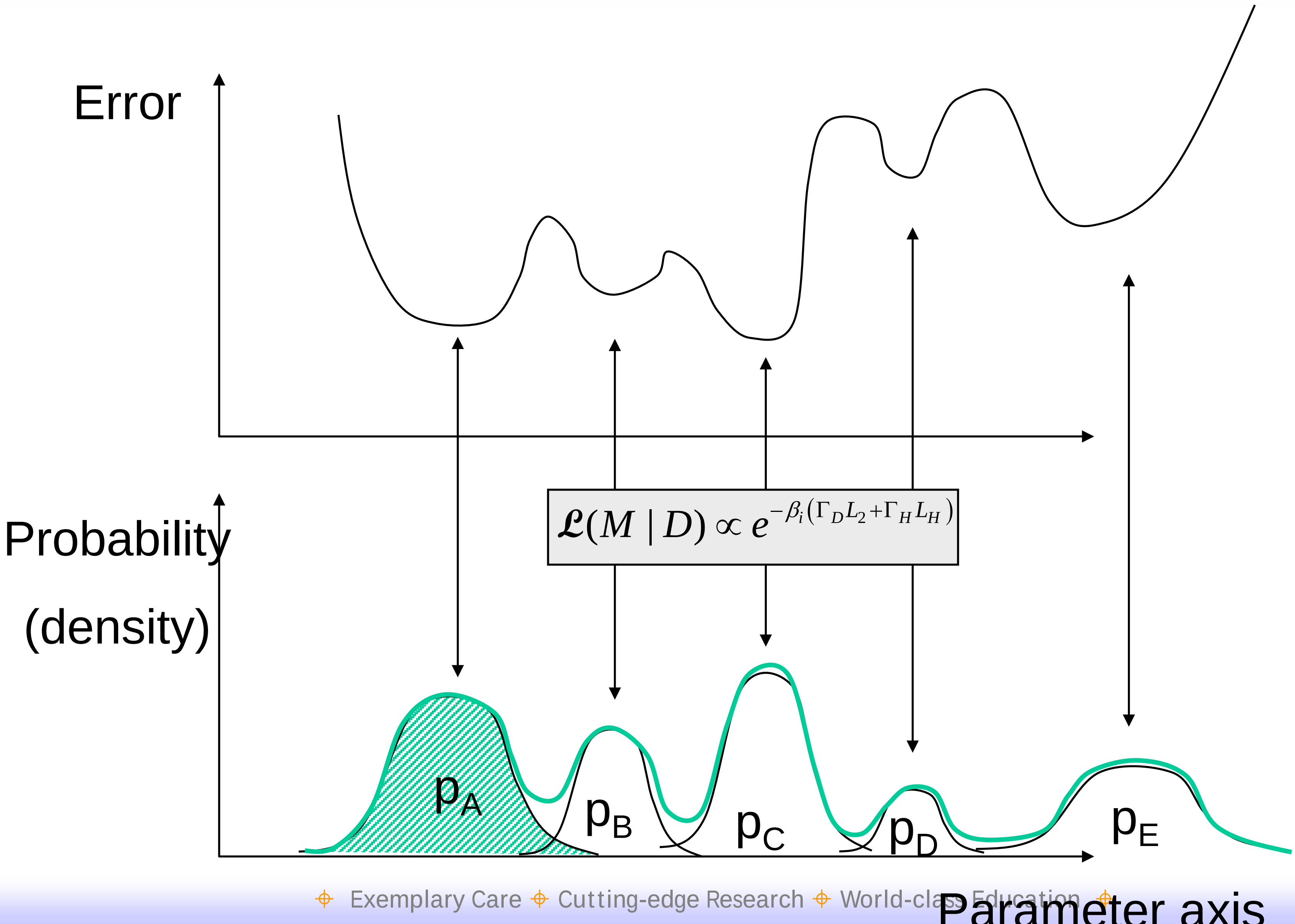
$\mathcal{E}(M_n)$



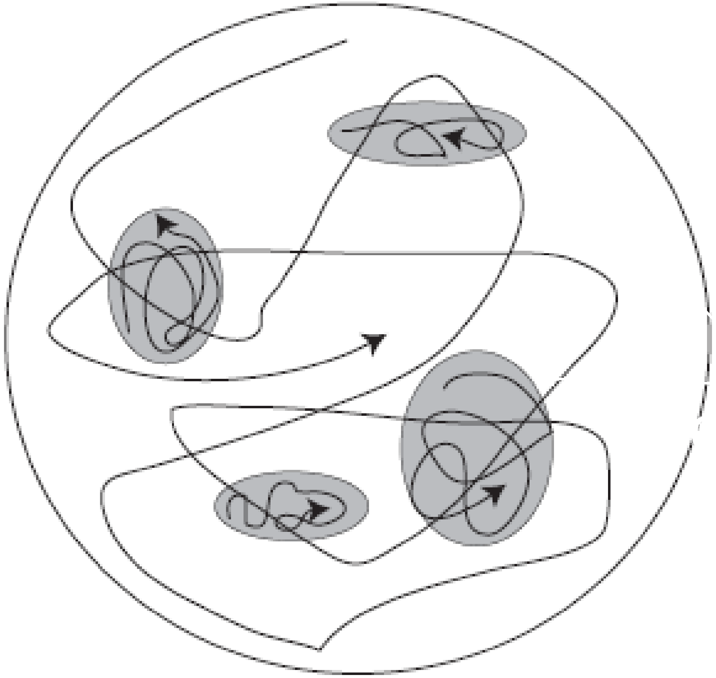
$\mathcal{E}(M_n)$ ≡ Metamodel or Ensemble

Many many more models than individuals

Creating the ensemble



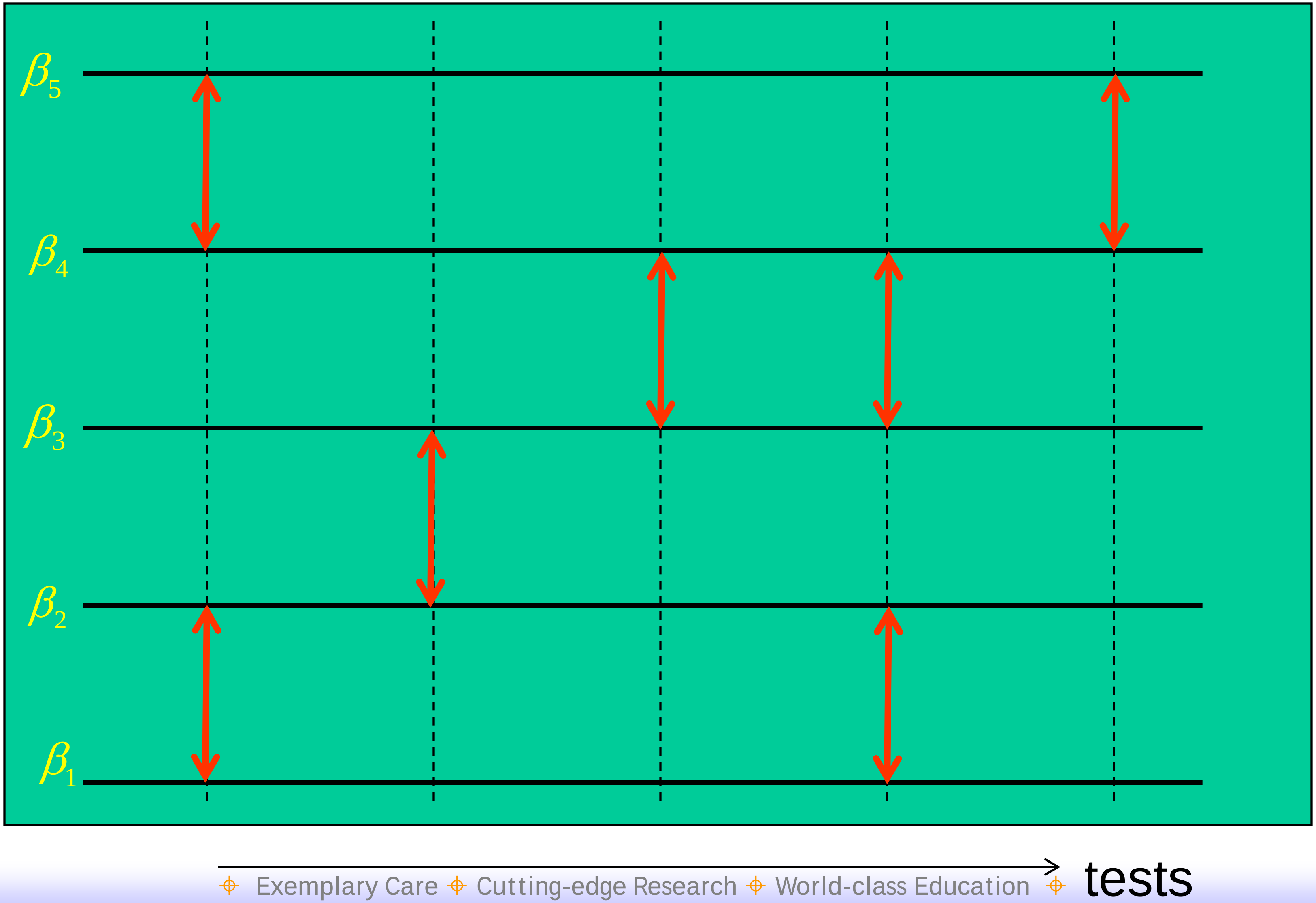
Calculating the Ensemble



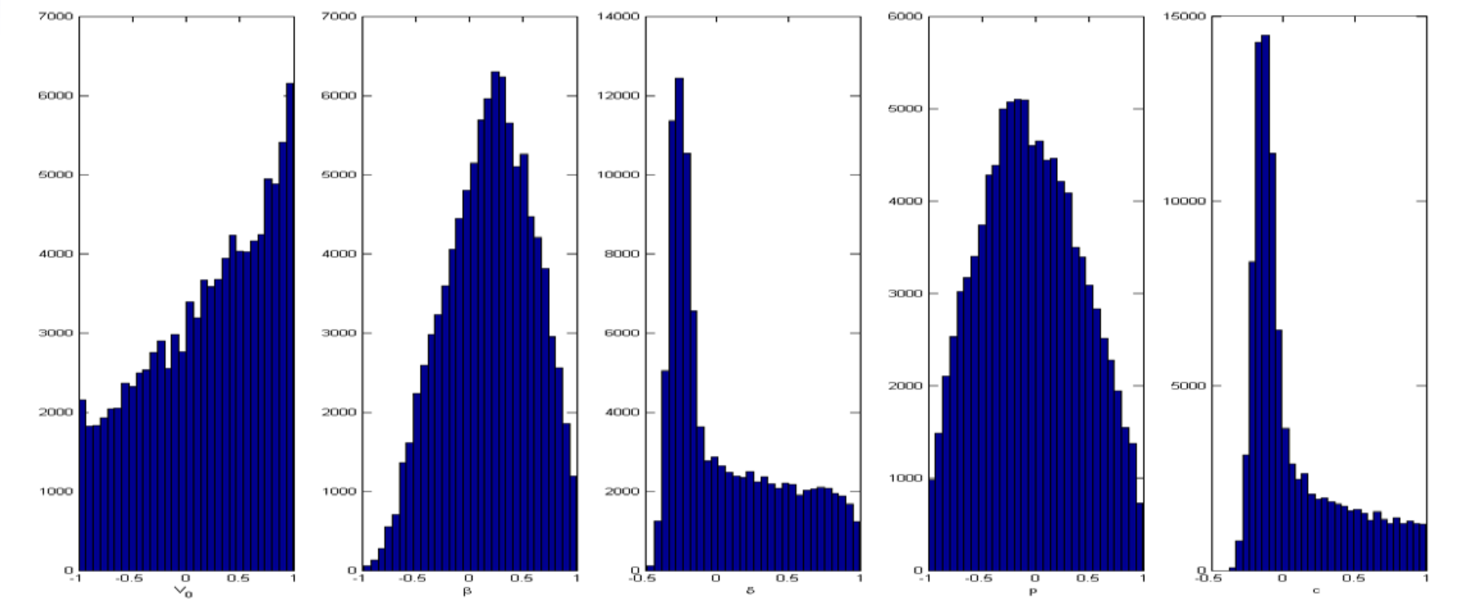
- **MH-type algorithm**
- **Parallel tempering/ Replica exchange as mixing method**

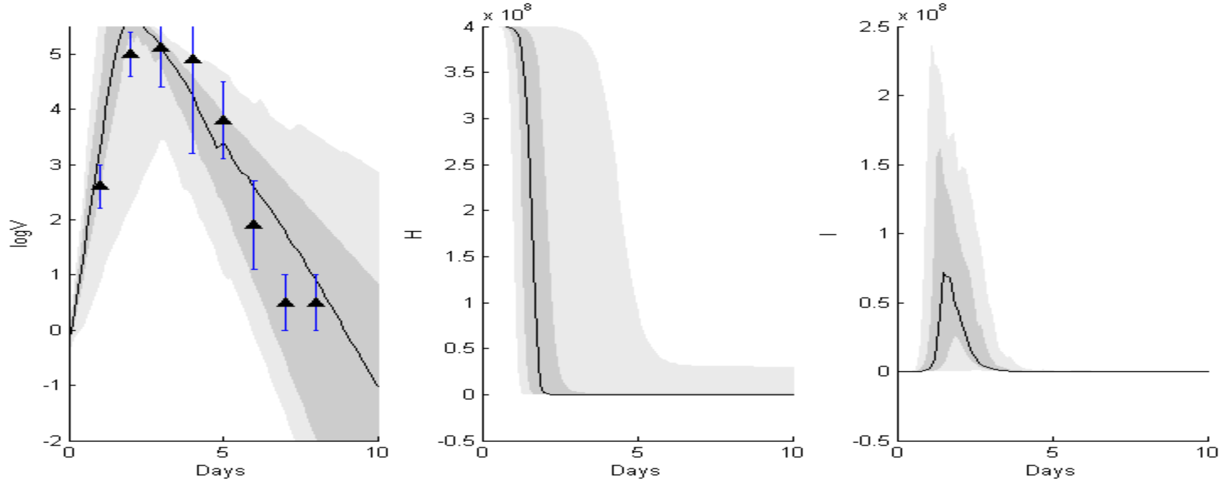
Earl, Deem 2006

Chain mixing

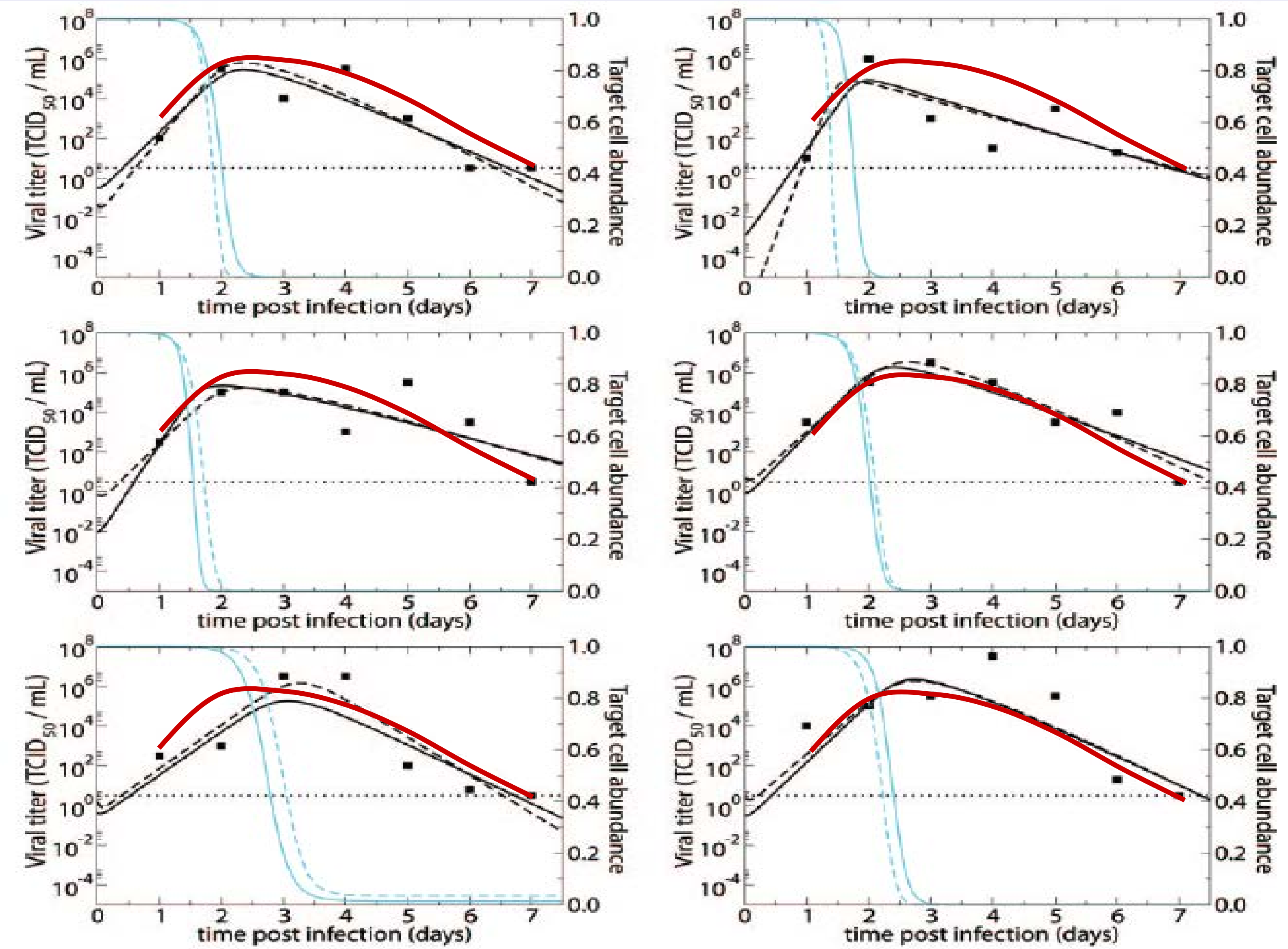


The population ensemble



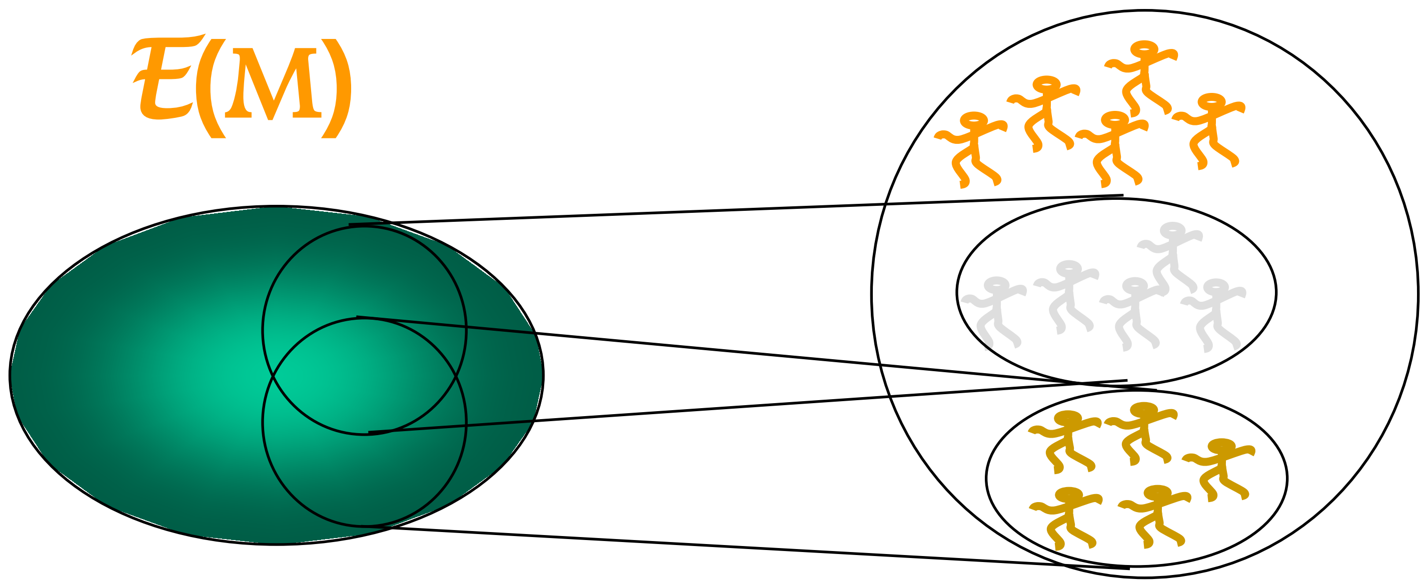


Looking at a population



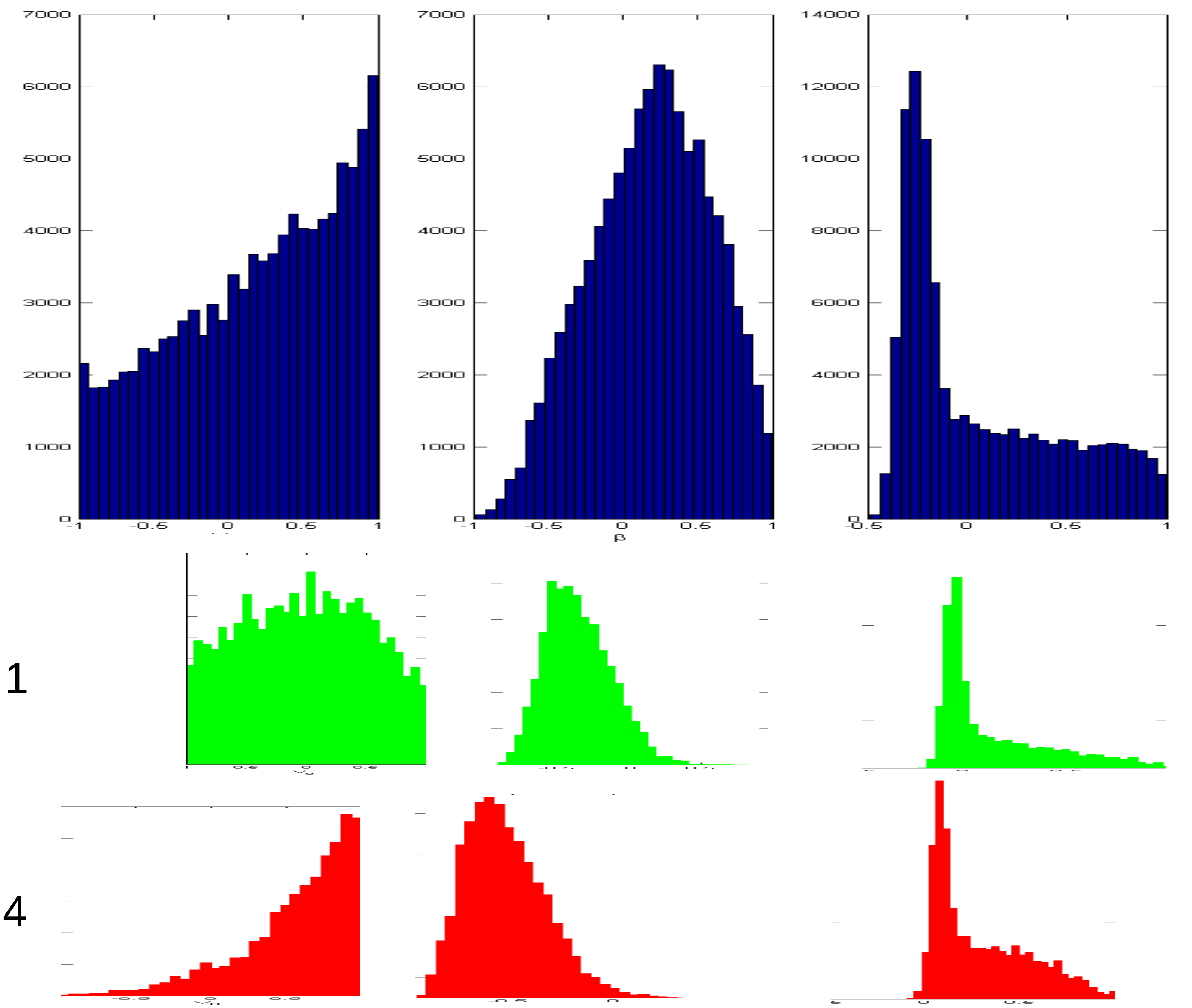
Baccam et al. Virology 2007

Probabilistic ensembles – for subpopulations



- **Sparsity -> pooling "similar" patients may be good enough**
  - The clinician does this

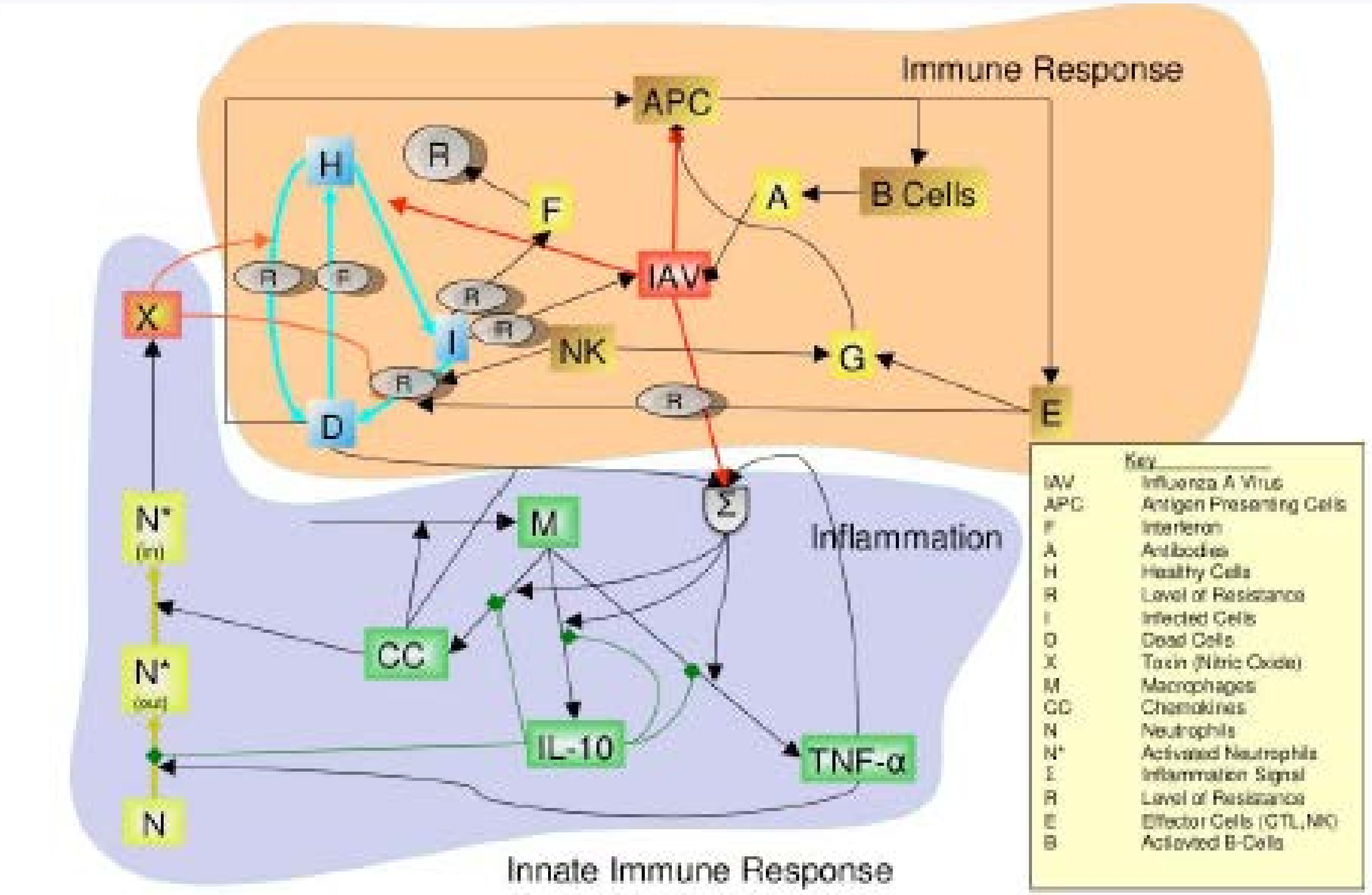
A population ensemble



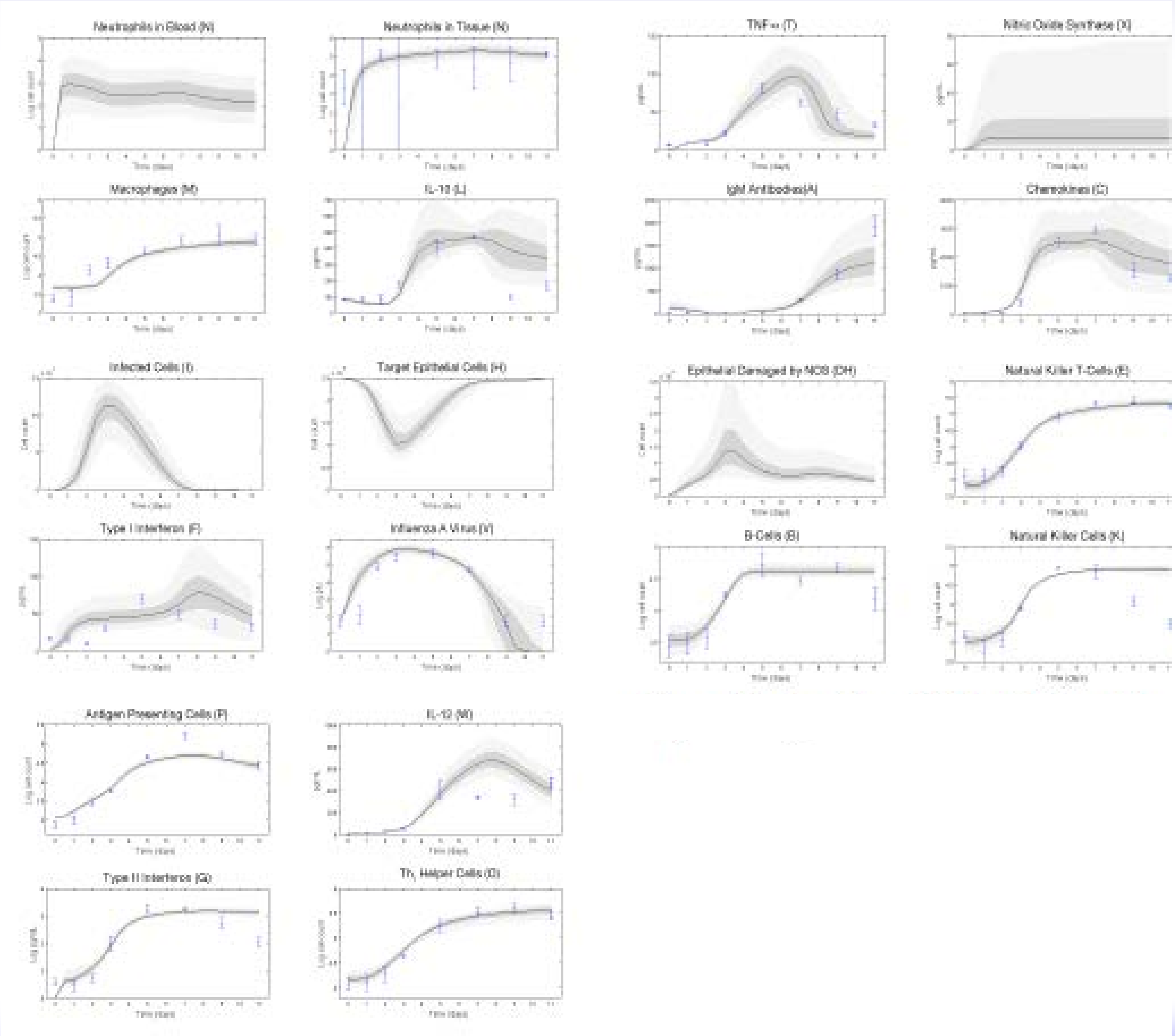
Patient 1

Patient 4

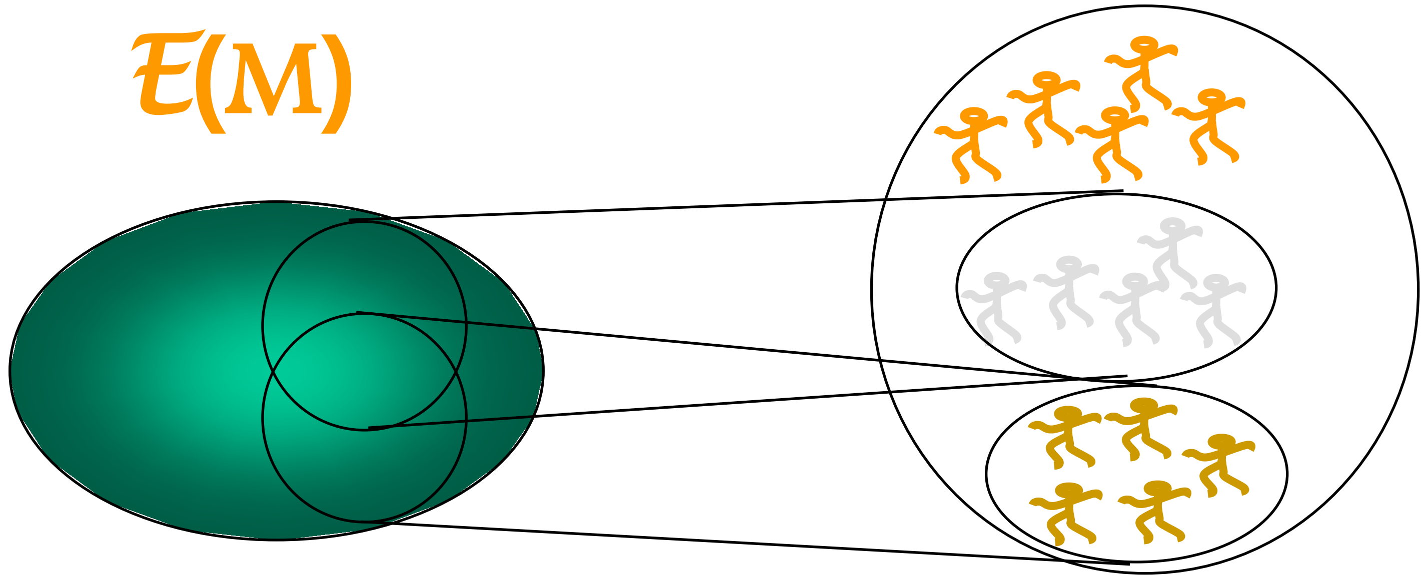
Host-level models



V3.0 ensemble

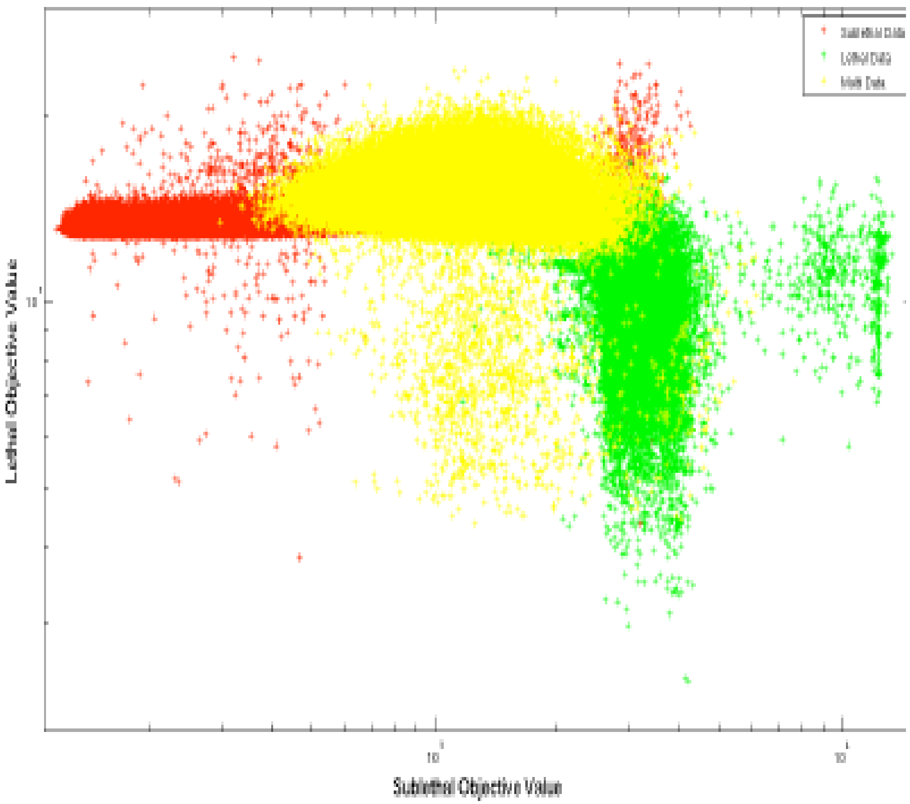


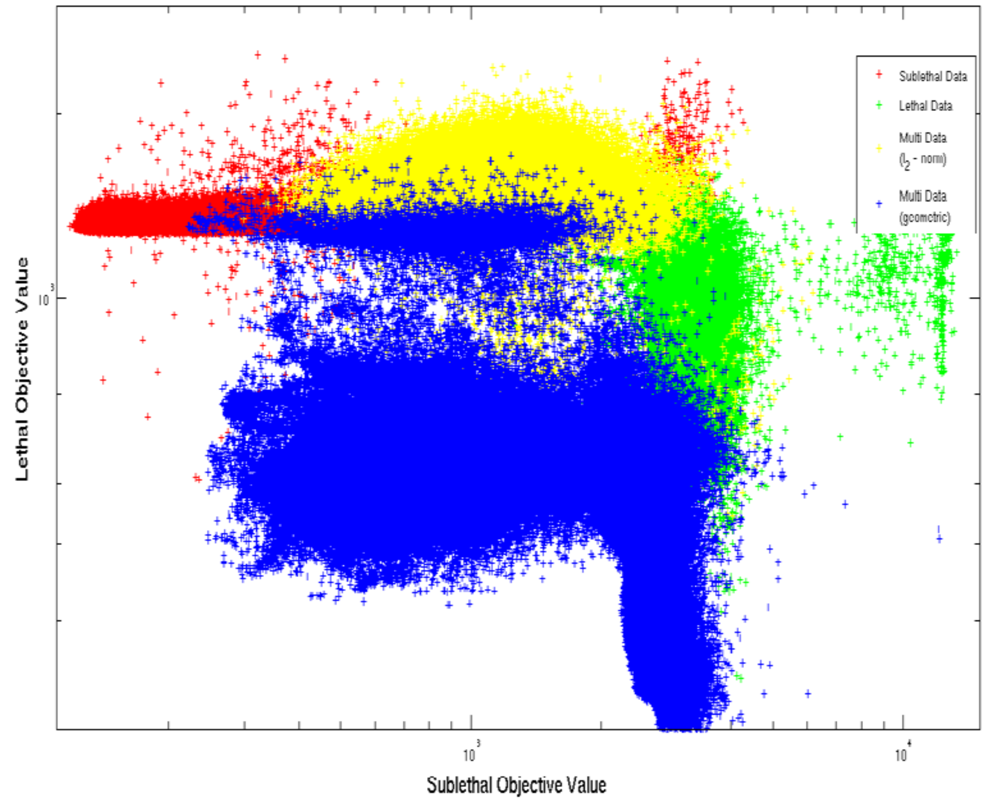
Probabilistic ensembles – for subpopulations



- **Sparsity -> pooling "similar" patients may be good enough**
  - The clinician does this

Multiobjective estimation

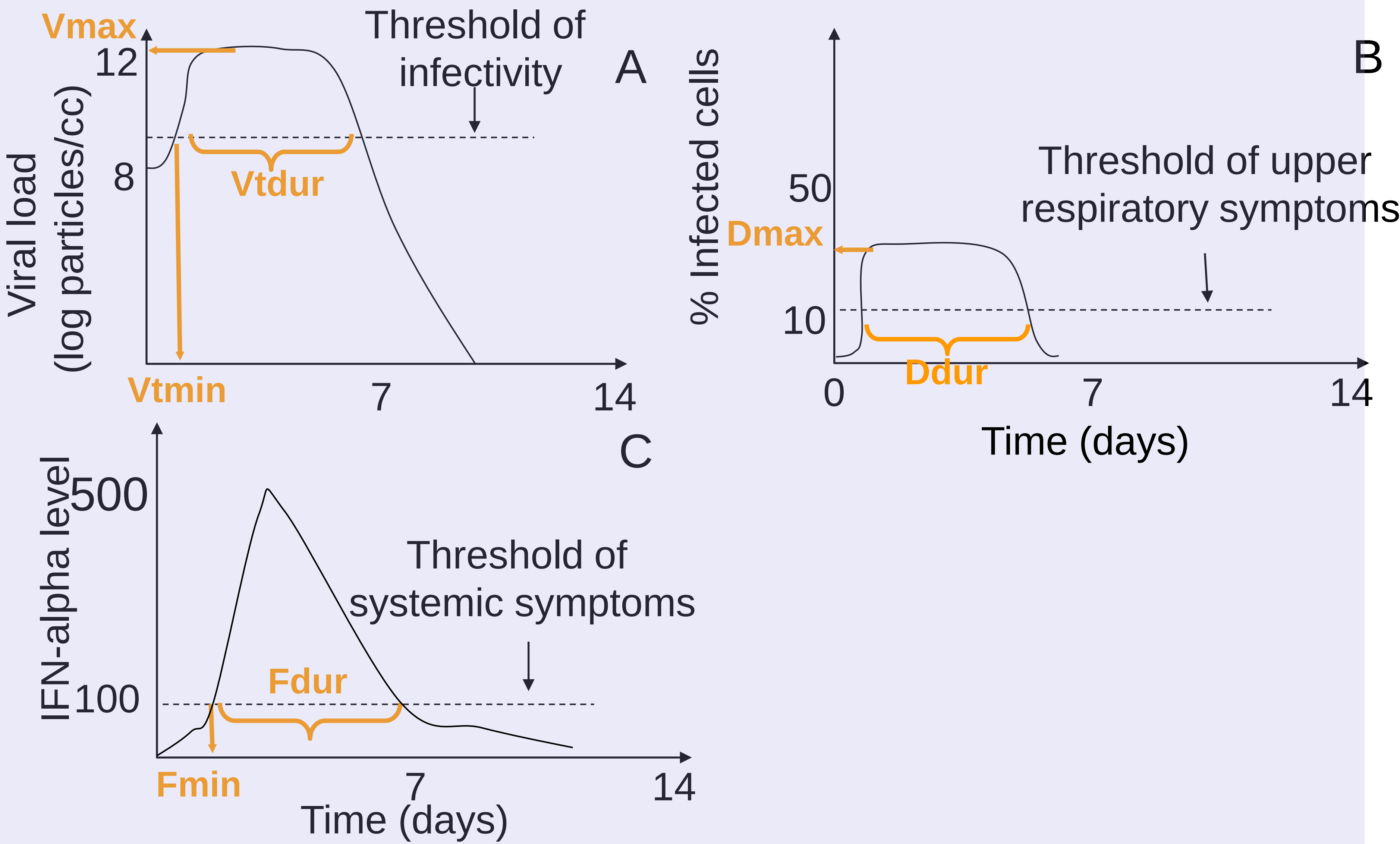




$$E = \sqrt{E_a^2 + E_b^2}$$

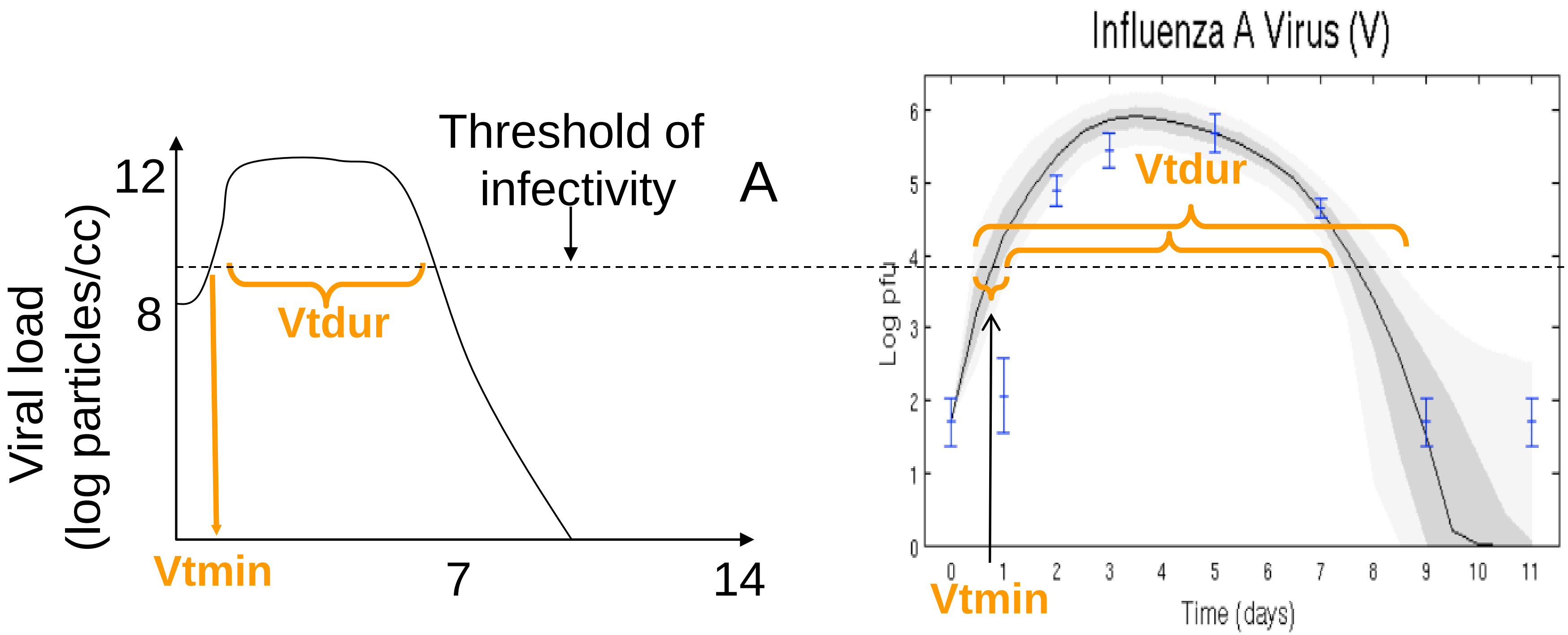
$$E = E_a^{\alpha} E_b^{\beta}$$

Linking scales of description



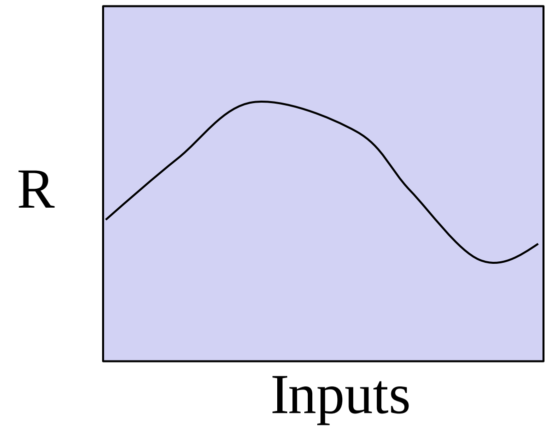
Linking scales of description

- Transmission = infectivity x upper respiratory symptoms
- Behavior (stay home or not)= systemic symptoms



Linking scales of description

- Integrated run (explicit hybrid) = not practical
- Look-up tables = fast but memory hungry
- Response surfaces = forward simulations, polynomial fit, algebraic computation

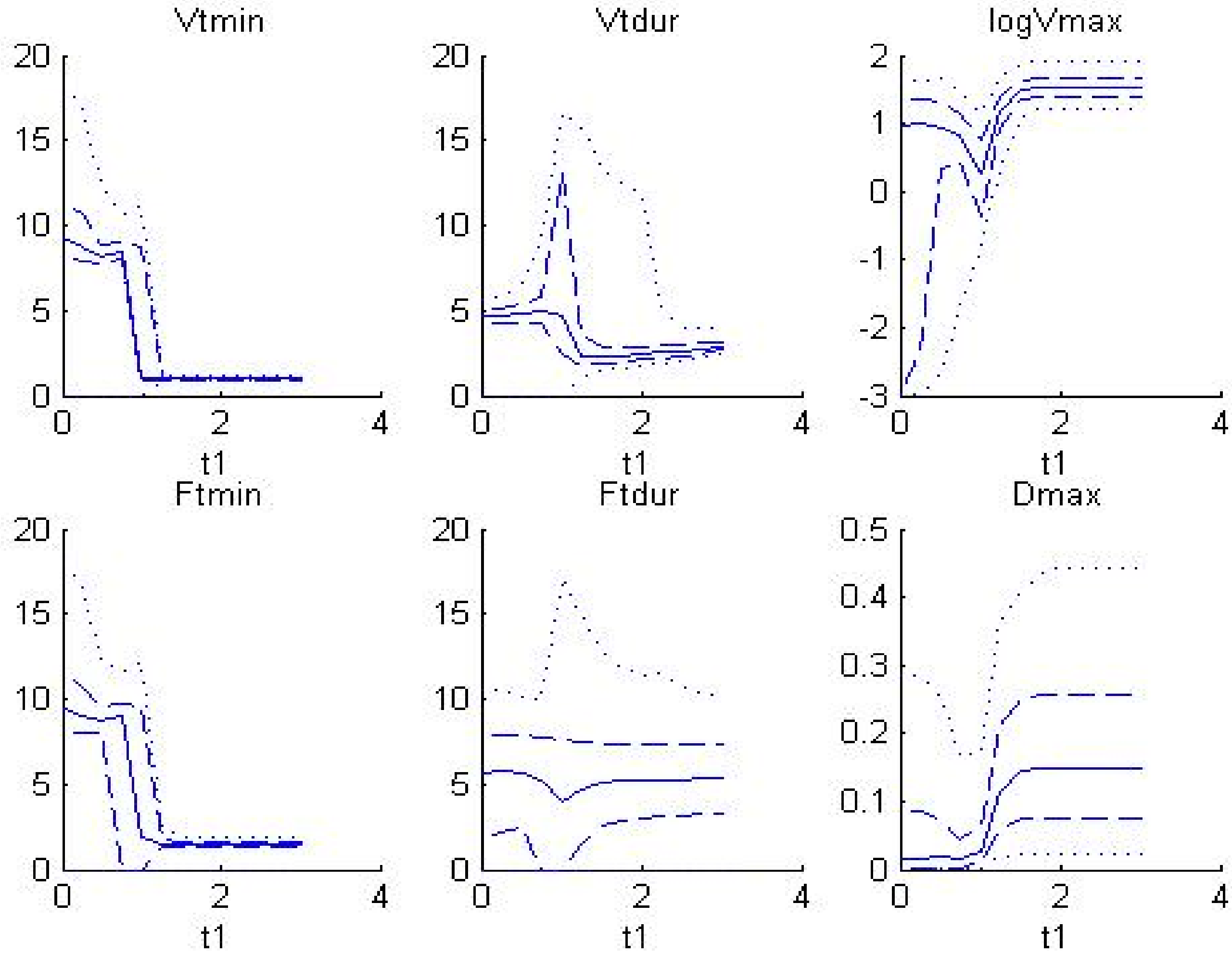


$$R = f(\text{Inputs})$$

$$R \in \left\{\mu_{\text{Transmissibility}}, \mu_{\text{Behavior}}, \mu_{\text{Resistance}}, \sigma_{\text{Transmissibility}}, \sigma_{\text{Behavior}}, \sigma_{\text{Resistance}}\right\}$$

$$\text{Inputs} \in \left\{\text{Viral load, burst size, viral adhesion, existing antibodies, ..}\right\}$$

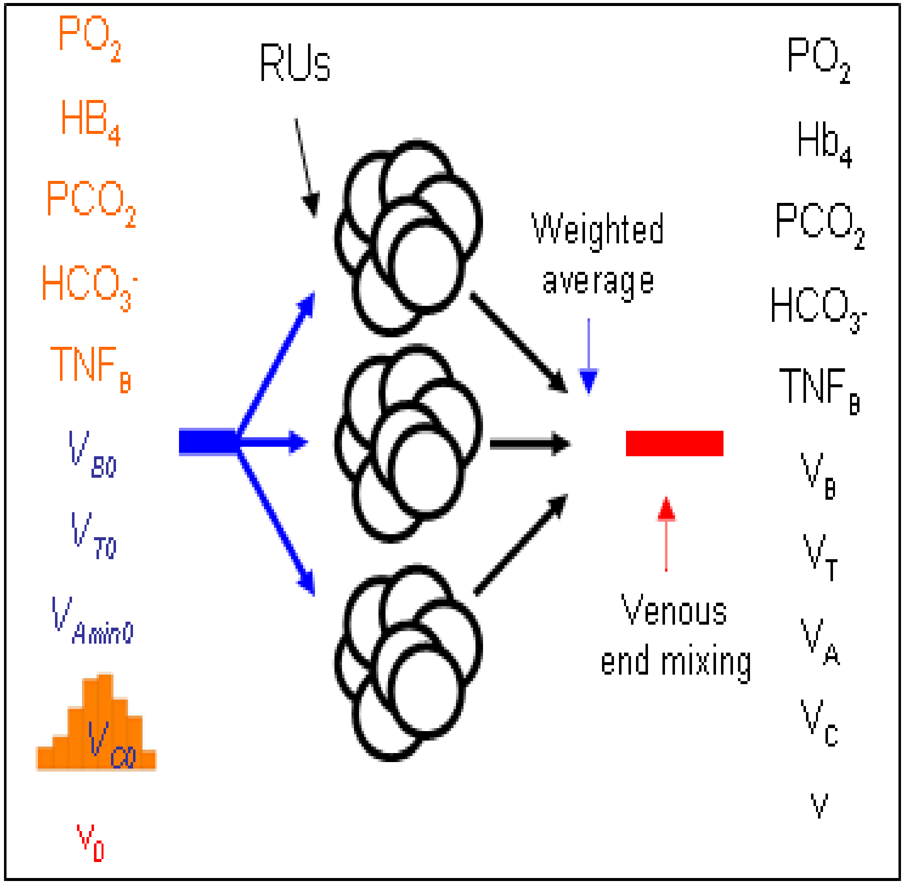
Predicted impact of therapy



Virulent pathogen

A multiscale lung model

- Inflammation occurs in the tissue barrier between air and blood.
- Tissue swelling impairs gas diffusion. Extreme inflammatic of a respiratory unit (~25 alvec 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.



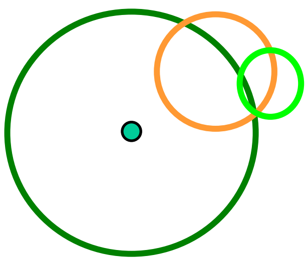
Reynolds et al, J Theor Biol 2009

Knowledge and successful translation

Empirical

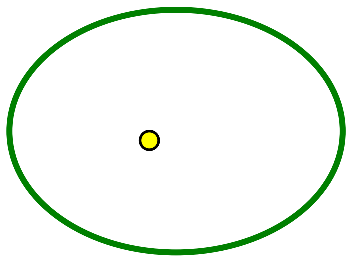
Epicycles

- to XVII century



Kepler/Newton

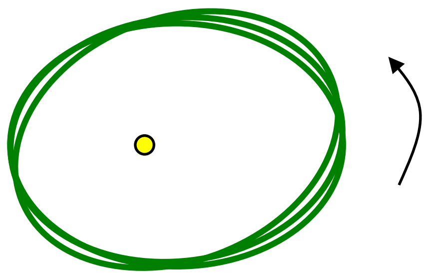
Ellipses



First interaction between a physical law and empiric observation

GR - Einstein

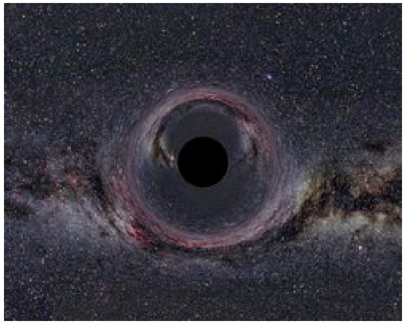
Precessing ellipses



Discrepancy between predictions and empiric observation

QG - ??

Black hole physics



Discrepancy between gravity and other forces of nature

Depth of knowledge

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Abstract submissions are encouraged and will be published in the Journal of Critical Care

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