Mathematical Modelling in Physiology: Biomedical applications
Moscow, 21-24.03.2016

# Mathematical modelling of immuno-physiological processes in virus infections:

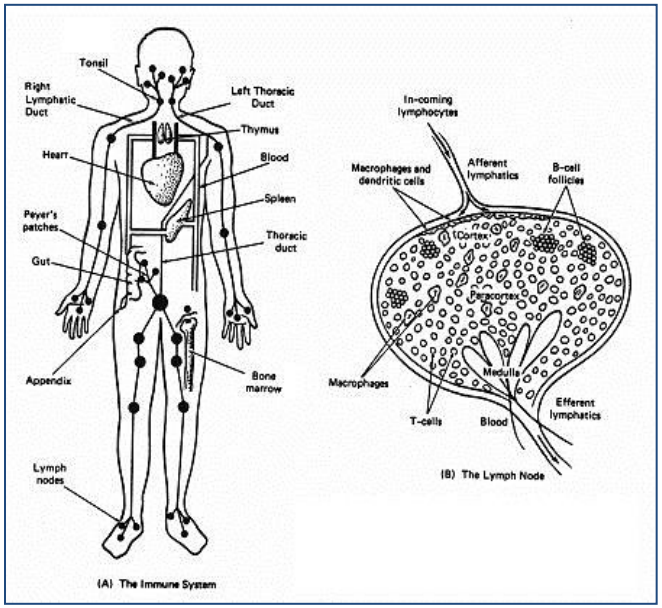
## a question driven data-based approach

*Gennady Bocharov*

Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow

# The Immune System

1)




**Physical**

•Transport

(1% of cells traverse the whole lymphoid system per hour)

•Diffusion

**Chemical**

• Ligand-receptor

• Signal transduction

• Peptide synthesis

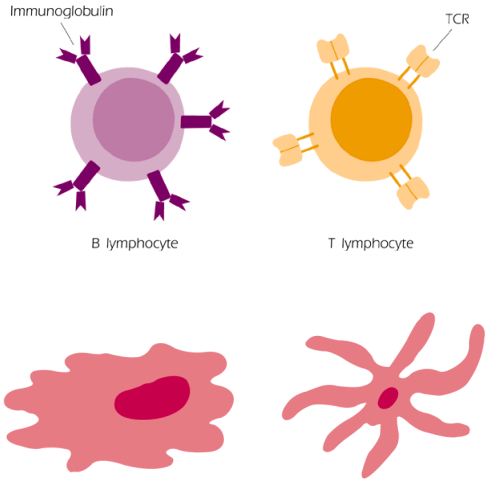
**Biological**

•Gene regulation

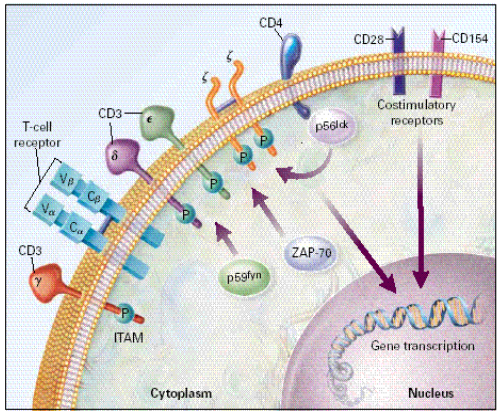
•Generation of antigen receptor diversity

•Cell division (~6 hrs)

•Cell differentiation




2)




3)

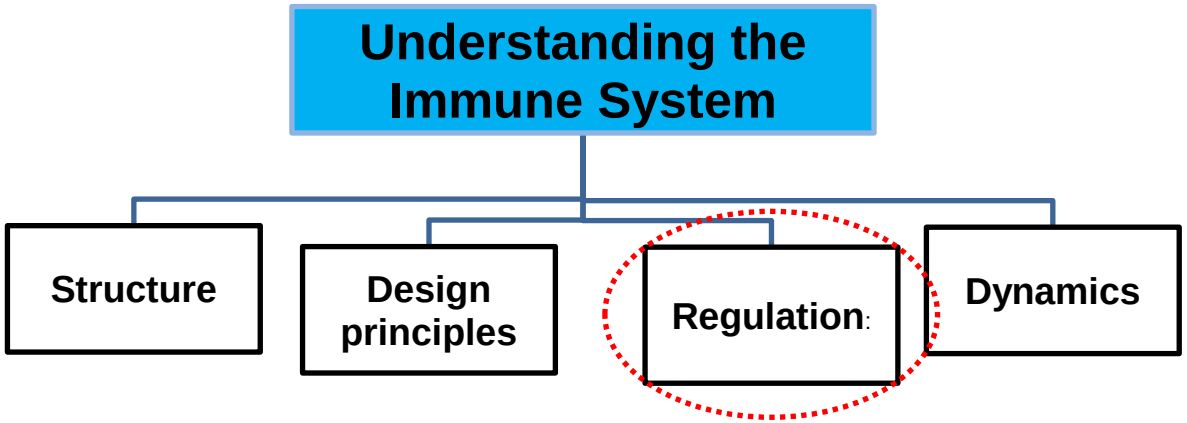
- **Sources of heterogeneity**:

1) *Physical compartments (lymph node, spleen, blood, etc.)*
2) *Distinct cell populations (e.g. lymphocytes, Macrophages)*
3) *Heterogeneity w.r.t. the expression of specific markers (CCR5) or fluorescent labels (CFSE, BrdU)*
4) *…*

**The fundamental challenge to applied mathematicians is to understand immunology in new ways by using models, computational techniques & algorithms**

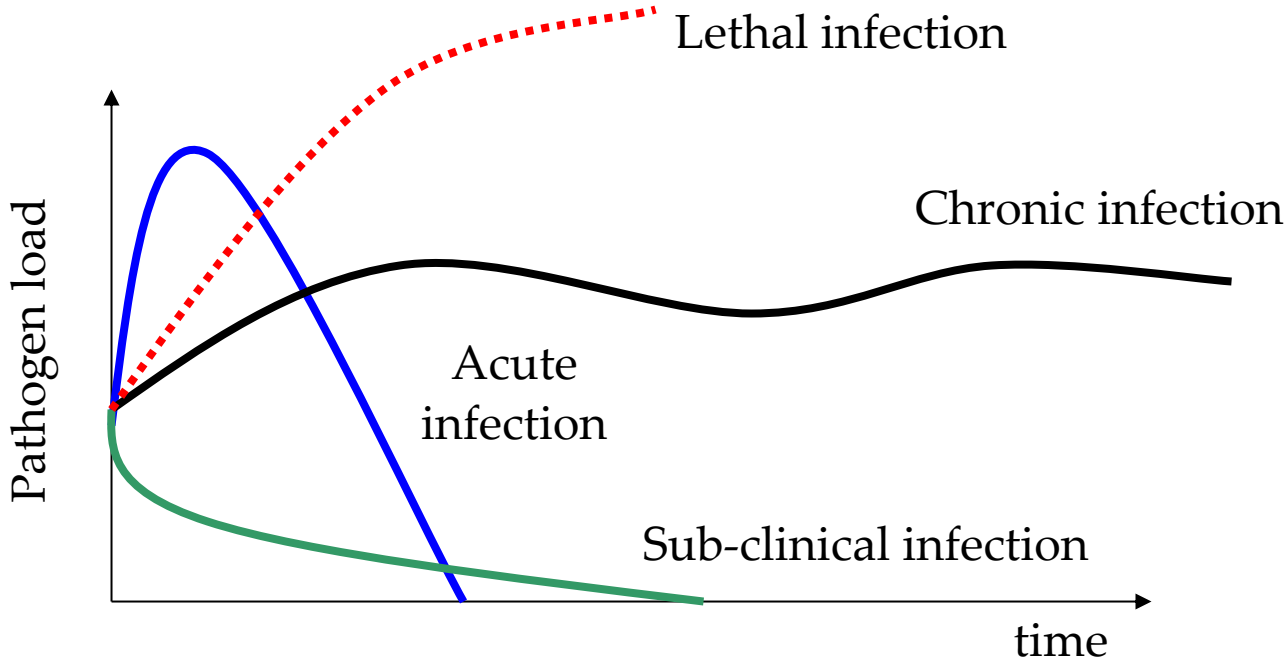
# Challenges in understanding the IS

"…The many immunological observations and results from in vitro or in vivo experiments vary and their interpretations differ enormously. A major problem is that within a normal distribution of biological phenomena that are measurable with many methods virtually anything can be shown or is possible.." *R. M. Zinkernagel. Immunity Against Infections & Vaccines: Credo 2004. Scand J Immunol. 2004, 60: 9–13*




- **Infectious disease model: key components**
- **Antiviral immune response: kinetic regulation**
- **Optimal model structure: information-theoretic criteria**
- **Cell growth analysis: asymmetric division**

# Dynamic patterns of infectious diseases




**Chronic persistence:**

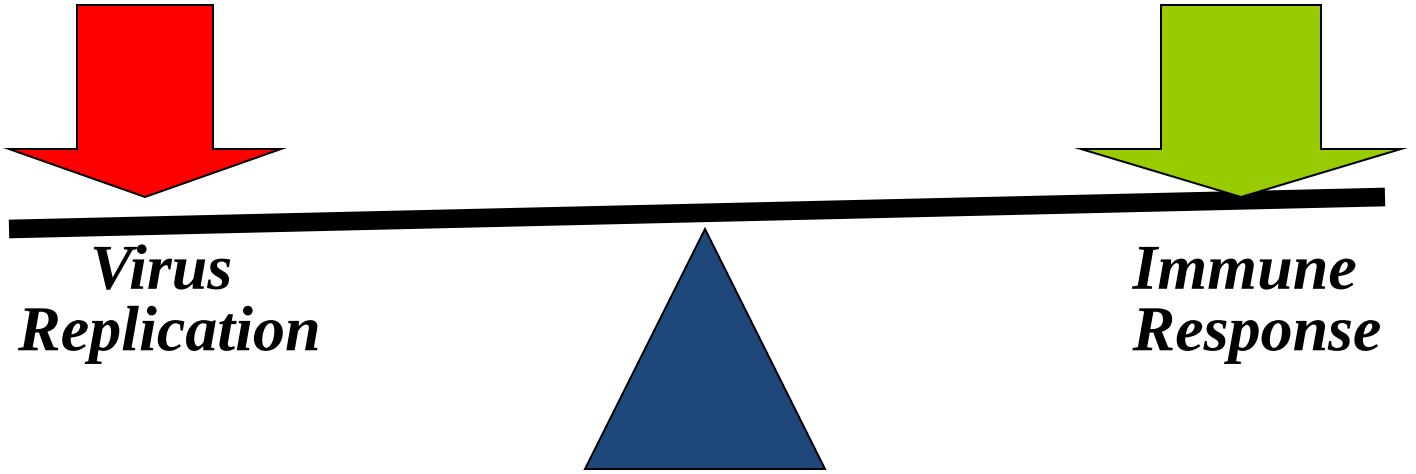
**Why? How to cure it?**

Objective:
to stimulate the
specific immune response
=> Exacerbation

# Topics

- **Infectious disease model: key components**
- Antiviral immune response: kinetic regulation
- Optimal model structure: information-theoretic criteria
- Cell growth analysis: asymmetric division

# The „numbers game“ perspective: virus & host factors in the outcome of infection




**The clinician‘s perspective:**

- Cytopathicity of virus
- Latency
- Persistence
- Replication rate
- Tropism
- Immunopathology
- Health condition of the infected individual

**The mathematical view:**

$$\frac{d}{dt}V(t) = \left(\beta - \gamma \cdot F(t)\right) \cdot V(t)$$

$$\frac{d}{dt}F(t) = \rho \cdot C(t) - \eta \cdot \gamma \cdot F(t) \cdot V(t) - \mu_f \cdot F(t)$$

$$\frac{d}{dt}C(t) = \xi(m) \cdot \alpha \cdot V(t-\tau) \cdot F(t-\tau) - \mu_f \cdot \left(C - C^*\right)$$

$$\frac{d}{dt}m(t) = \sigma \cdot V(t) - \mu_m \cdot m(t)$$

$$V(t_0) = V_0, \quad F(t_0) = F_0, \quad C(t_0) = C_0, \quad m(t_0) = m_0,$$
$$V(t) = 0, \quad F(t) = F_0 \quad \text{при } t \in [t_0 - \tau, t_0)$$

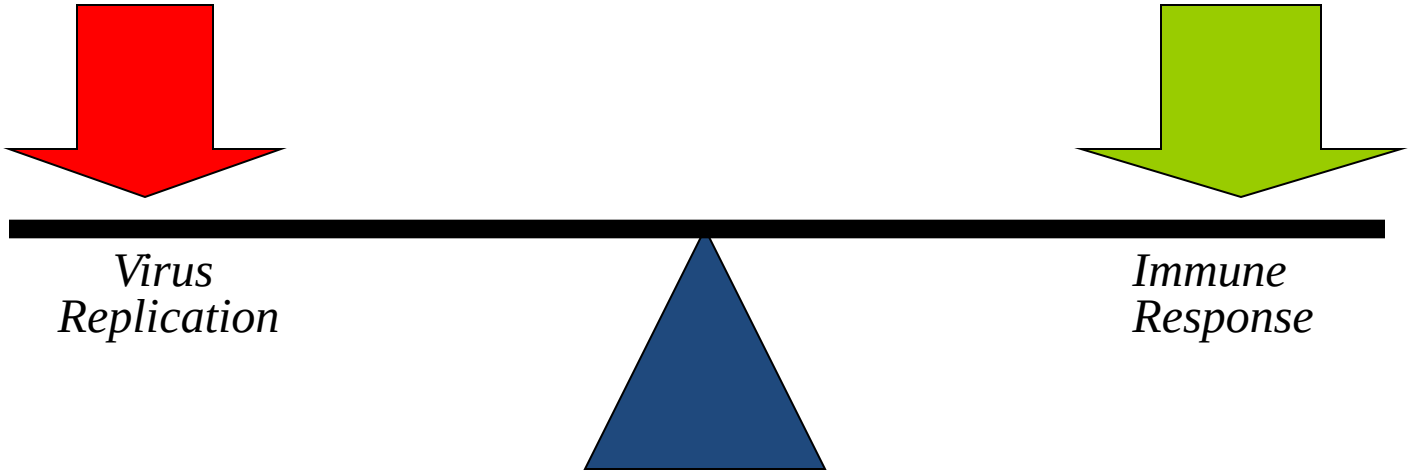
# Modelling in immunology: Experimental and Mathematical Approaches

Nobel Prize Laureate
Rolf M. Zinkernagel

Academician
Guri I. Marchuk

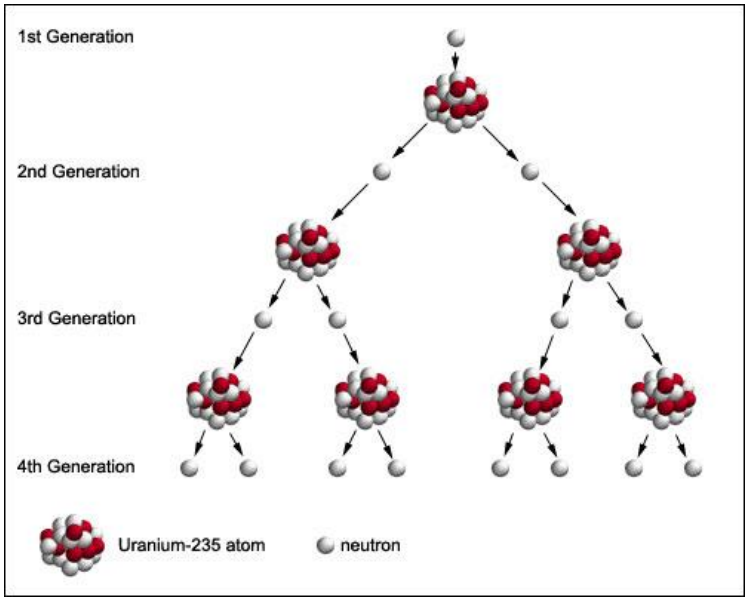
„**The outcome of infection results from the ´*numbers games*´ between infectious agent and the immune system**.“

# Replication rate in virus persistence: pro & contra




- Experimental studies with LCMV infection in mice: a faster speed of virus replication is an advantage for a virus in overcoming the immune system control and establishing the persistent infection – the tolerance by exhaustion (Moskophidis et al., *Nature* (1993) 362: 758-761)
- Theoretical study of virus infection model: a slow virus replication favors the long-term persistence (Marchuk and Belykh, 1980)

# Mathematical immunology and the nuclear chain reaction




## George Irving Bell

**4.08.1926-28.05.2000**

- Harvard University (Physics) - 1947
- Division “T” Los Alamos Scientific Laboratory - 1947
- **“Nuclear Reactor Theory”** - 1970
- Quantitative models in immunology - 1970
- Theoretical Biology & Biophysics. Los Alamos NL - 1974
- Humane genome Project – 1988

## Guri Ivanovich Marchuk

**8.06.1925-24.03.2013**

- Leningrad University (Mathematics/mechanics) – 1949
- Division ”B” Nuclear Power Plant Ceneter - 1953
- **“Numerical Methods in the Analysis of the Nuclear Reactors”** – M. 1959
- Mathematical modeling in immunology - 1975
- Institute of Numerical Mathematics, Academy of Sciences (1980)

# Basic scheme of an infectious disease

**G.I. Bell**:

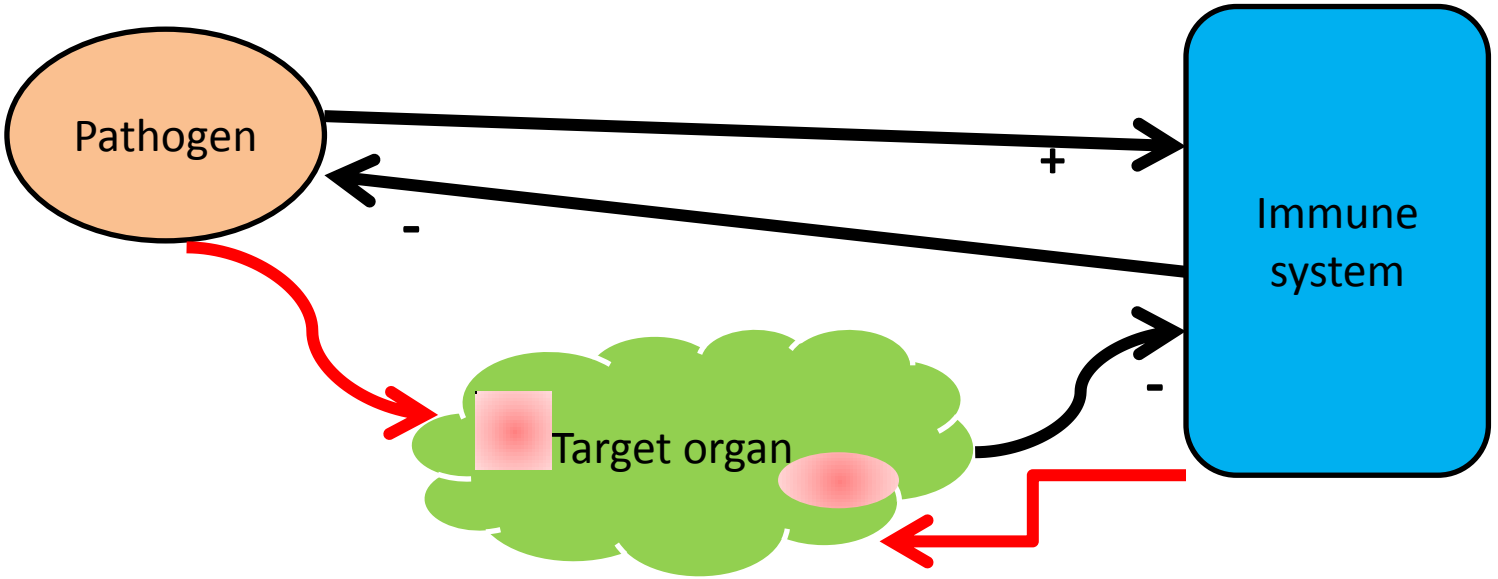
**Predator-prey equations simulating an immune (1973)**

- *Population dynamics of Replicating antigens and Antibodies*
- *Lotka-Volterra-type of ODEs*

**G.I. Marchuk:**

**Mathematical model of infectious disease (1974)**

- *System of delay differential equations*
- *Target organ damage*
- *Negative feedback of the organ damage on the immune system*



# Basic model of the infectious disease (1975)

State space variable

1. Pathogen population
2. Antibodies
3. Plasma cells
4. Tissue damage

System of Delay-Differential Equations

$$\frac{d}{dt}V(t) = (\beta - \gamma \cdot F(t)) \cdot V(t)$$

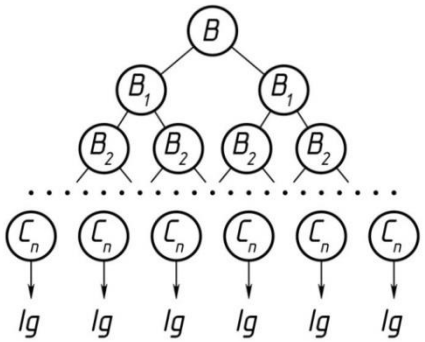
$$\frac{d}{dt}F(t) = \rho \cdot C(t) - \eta \cdot \gamma \cdot F(t) \cdot V(t) - \mu_f \cdot F(t)$$

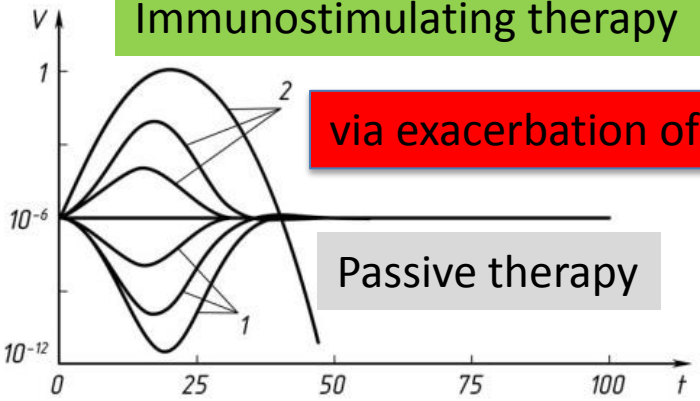
$$\frac{d}{dt}C(t) = \xi(m) \cdot \alpha \cdot V(t-\tau) \cdot F(t-\tau) - \mu_f \cdot (C - C^*)$$

$$\frac{d}{dt}m(t) = \sigma \cdot V(t) - \mu_m \cdot m(t)$$

Initial data

$$V(t_0) = V_0, \quad F(t_0) = F_0, \quad C(t_0) = C_0, \quad m(t_0) = m_0,$$
$$V(t) = 0, \quad F(t) = F_0 \quad \text{for} \quad t \in [t_0 - \tau, t_0)$$

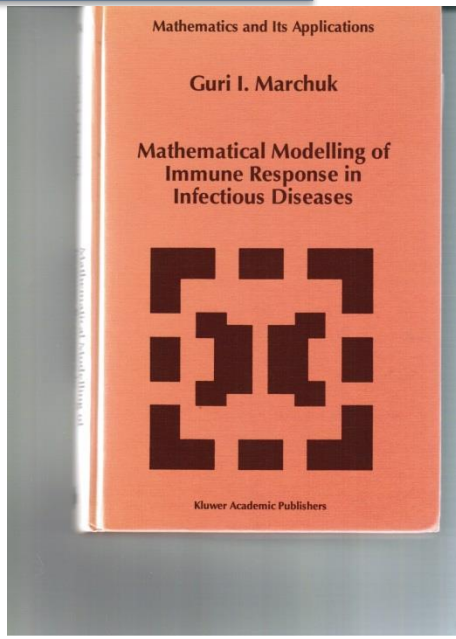



Immunostimulating therapy

via exacerbation of the chronic infection

Passive therapy



# Fundamental modelling issues

- The immune system can be considered as *an ensemble of individual cells*, which differ in a number of physiologically relevant traits: the spatial position (***z***), the receptors' specificity (*s*), the number of specific receptors (*r*), etc. => ***Heterogeneity***

- One can describe the immune system by a state vector listing the number of individual cells of each "type" ***n***(*t*,***Z***,*s*,*r*,…) depending on a number of continuous as well as discrete variables

- Using conservation principle the equation for the density function n(t, ***x***) with ***x*** standing for the vector of traits can be written as

$$\frac{\partial n}{\partial t} + \nabla(\mathbf{v}n) = \mathbf{Birth} - \mathbf{Death} + \mathbf{Migration} + \mathbf{Reactions}, \quad \nabla = \left(\frac{\partial}{\partial x_1}, \frac{\partial}{\partial x_2}, \ldots, \frac{\partial}{\partial x_K}\right), \quad \mathbf{v} = [v_1, v_2, \ldots, v_K]^{\mathrm{T}}, \quad v_i = \frac{dx_i}{dt}$$

- "Typical" equation for population dynamics:

$$\frac{d}{dt}(\text{Population size}) = \mathbf{f}\left(growth, death, migration, \ldots\right)$$

# Maximum likelihood parameter estimation

$$\frac{d}{dt}\mathbf{y}(t) = \mathbf{f}\left(\mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}\right), \quad t \in [t_0, T], \quad \tau > 0$$

$$\mathbf{y} \in R^{n_\mathbf{Y}}, \quad \mathbf{p} \in R^{n_\mathbf{p}}$$

$$\mathbf{y}(t) = \varphi(t),\ t \in [t_0 - \tau, t_0].$$

- Observation data $\left\{t_j, \mathbf{y}_j\right\}_{j=1}^{n_{obs}}$

- Likelihood function

$$\mathbf{y}_j \sim \mathcal{N}\left(\mathbf{y}(t_j), \Sigma_j\right)$$

$$\mathcal{H}\left(\mathbf{y}_j; \mathbf{p}\right) = \frac{1}{\sqrt{(2\pi)^{n_y} \det \Sigma_j}} \exp\left\{-\frac{1}{2}\left[\mathbf{y}(t_j) - \mathbf{y}_j\right]^{\mathrm{T}} \Sigma_j^{-1} \left[\mathbf{y}(t_j) - \mathbf{y}_j\right]\right\}$$

$$\mathcal{L}(\mathbf{p}) = \prod_{j=1}^{n_{obs}} \mathcal{H}\left(\mathbf{y}_j; \mathbf{p}\right)$$

$$\mathbf{p}^* = \arg\max_{\mathbf{p} \in D} \mathcal{L}(\mathbf{p})$$

# Topic

- Infectious disease model: key components
- **Antiviral immune response: kinetic regulation**
- Optimal model structure: information-theoretic criteria
- Cell growth analysis: asymmetric division

# Experimental System:
## Lymphocytic choriomeningitis virus (LCMV) infection of C57BL/6 mice

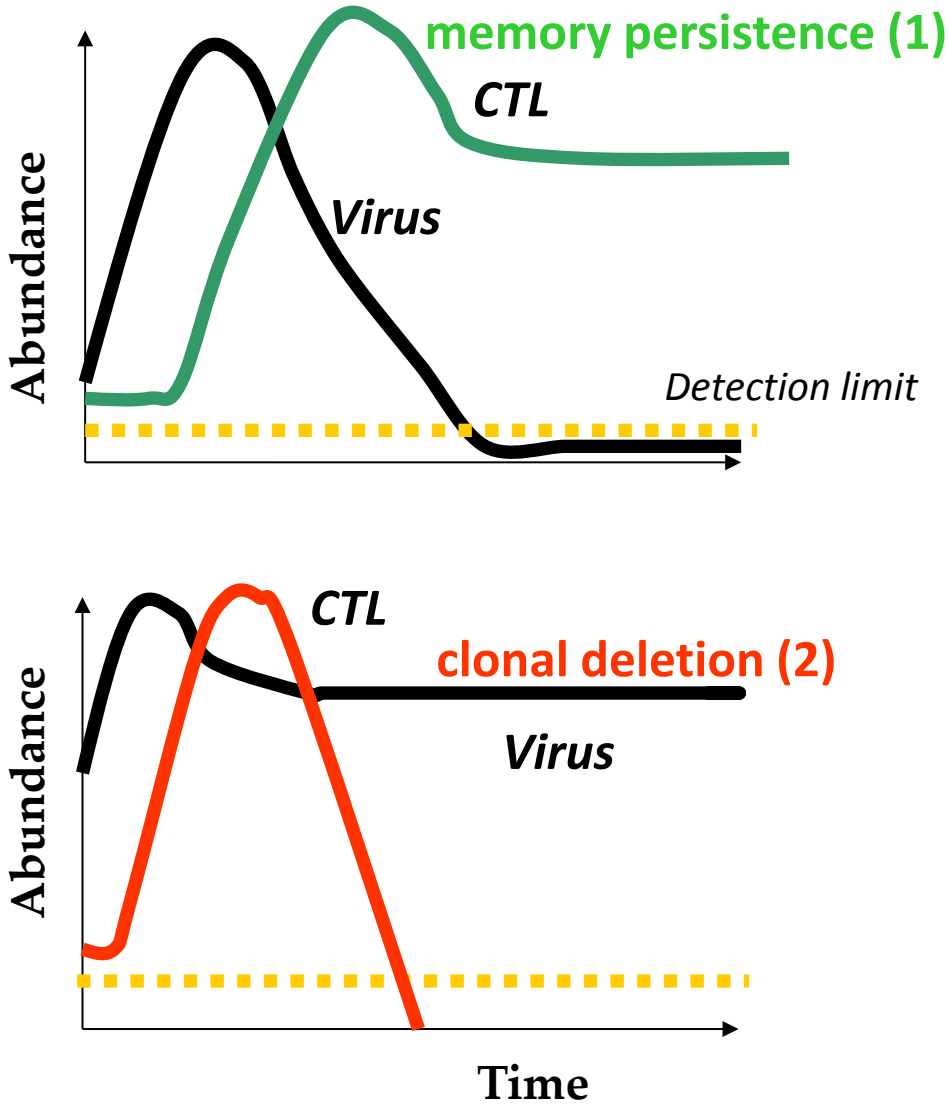
- **Family**: *arenaviruses*
- **Strains:** *Docile, Traub, WE, Aggressive, Armstrong, Clone 13*
- **Host**: *mice, hamsters*

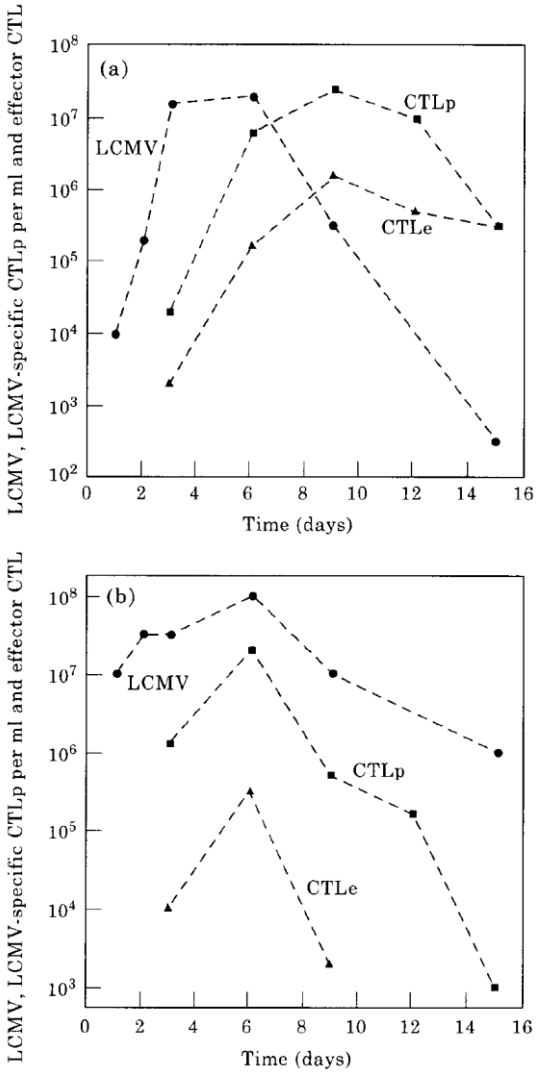
  (***Humans****: acute hemorrhagic fevers – Lassa fever*)
- **Target cells**: primarily infects & replicates in *macrophages*, *lymphocytes*
- **Cytopathicity in vivo:** *non-cytopathic RNA virus*
- **CTL responses** play a dominant role in virus clearance: *appear early and high*
- **Neutralizing antibody response**: appear only *late* after infection
- **Immunopathology:** *spleen, liver, central nervous system, etc.*

**LCMV infection of mice: a "Gold Standard" of experimental immunology**

# Relevant patterns of LCMV infection dynamics

The kinetics of the T cell response falls in between two extremes
**expansion=>contraction=>**



# Phenomenology of the LCMV-host interaction

**Phenotypes of "virus-host" relationships:**

1. acute infection followed by LCMV clearance in two weeks
2. temporary persistence up to 2 or 3 months
3. life-long persistence

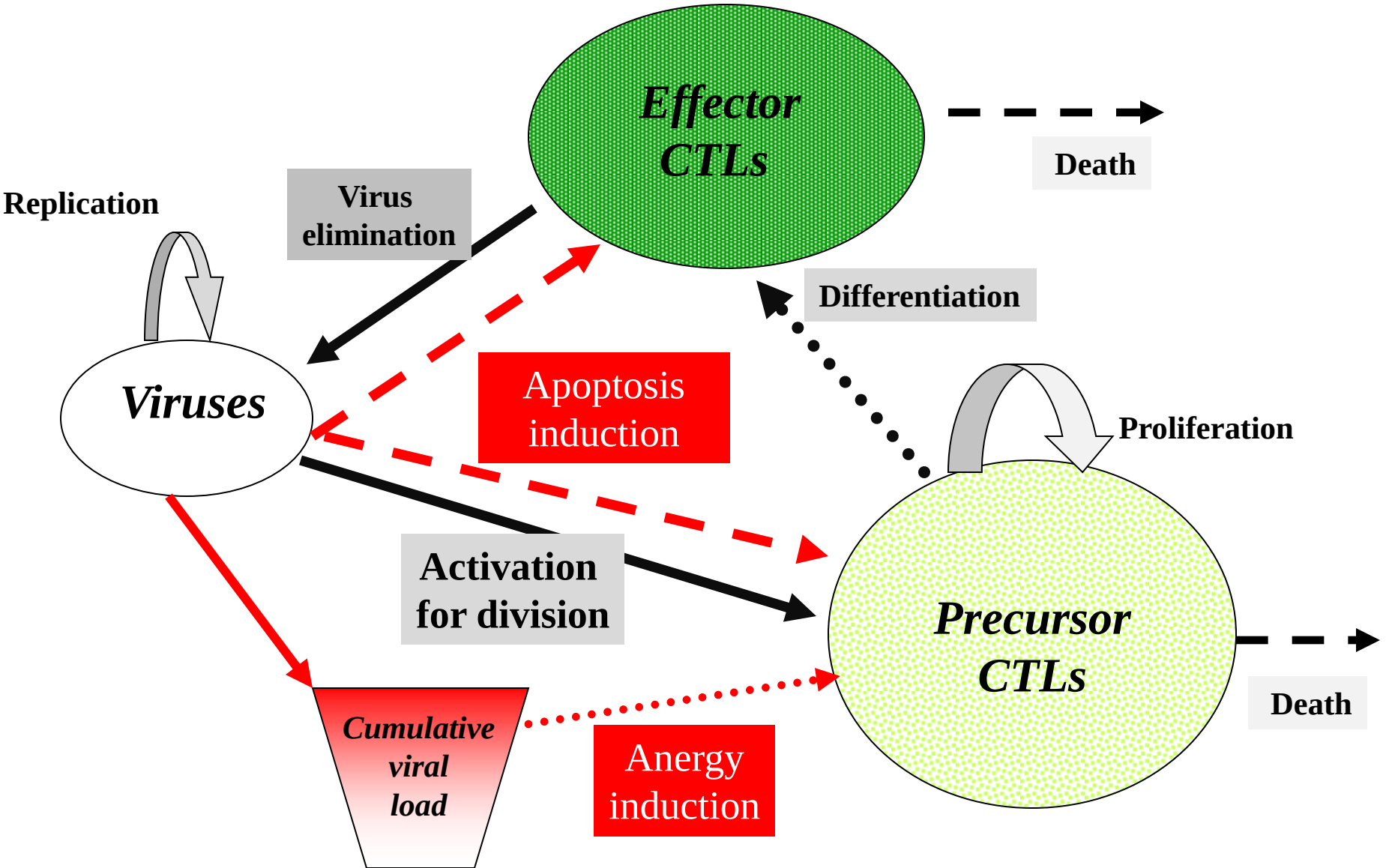
**Final stages of antiviral CTL responses:**

1. Creation of the CTL memory
2. Almost complete loss of the entire LCMV-specific precursor CTRL repertoire
3. Complete exhaustion of precursor CTLs

**Persistence**:

depends on particular combination of virus & host parameters

# Mechanistic view of the LCMV infection fate decision



# Time-dependent variables of the DDE model

$V(t)$ – **virus** titer in spleen at time $t$ (*pfu/ml*)

$E_p(t)$ – number of virus-specific **precursor CTLs** in spleen at time $t$ (*cell/ml*)

$E(t)$ – number of virus-specific **effector CTLs** in spleen at time $t$ (*cell/ml*)

$W(t)$ – cumulative virus antigen load in spleen at time $t$

Replication

Elimination

$$\frac{\mathrm{d}}{\mathrm{d}t}V(t) = \beta V(t)\left(1 - \frac{V(t)}{V_{\mathrm{mvc}}}\right) - \gamma_{\mathrm{VE}}E_{\mathrm{e}}(t)V(t),$$

AICD - Apoptosis

$$\frac{\mathrm{d}}{\mathrm{d}t}E_{\mathrm{p}}(t) = \alpha_{E_{\mathrm{p}}}(E_{\mathrm{p}}^0 - E_{\mathrm{p}}(t)) + b_{\mathrm{p}}g_{\mathrm{p}}(W)V(t-\tau)E_{\mathrm{p}}(t-\tau) - \alpha_{\mathrm{AP}}V(t-\tau_{\mathrm{A}})V(t)E_{\mathrm{p}}(t),$$

Homeostasis

Clonal expansion

$$\frac{\mathrm{d}}{\mathrm{d}t}E_{\mathrm{e}}(t) = b_{\mathrm{d}}g_{\mathrm{e}}(W)V(t-\tau)E_{\mathrm{p}}(t-\tau) - \alpha_{\mathrm{AE}}V(t-\tau_{\mathrm{A}})V(t)E_{\mathrm{e}}(t) - \alpha_{E_{\mathrm{e}}}E_{\mathrm{e}}(t),$$

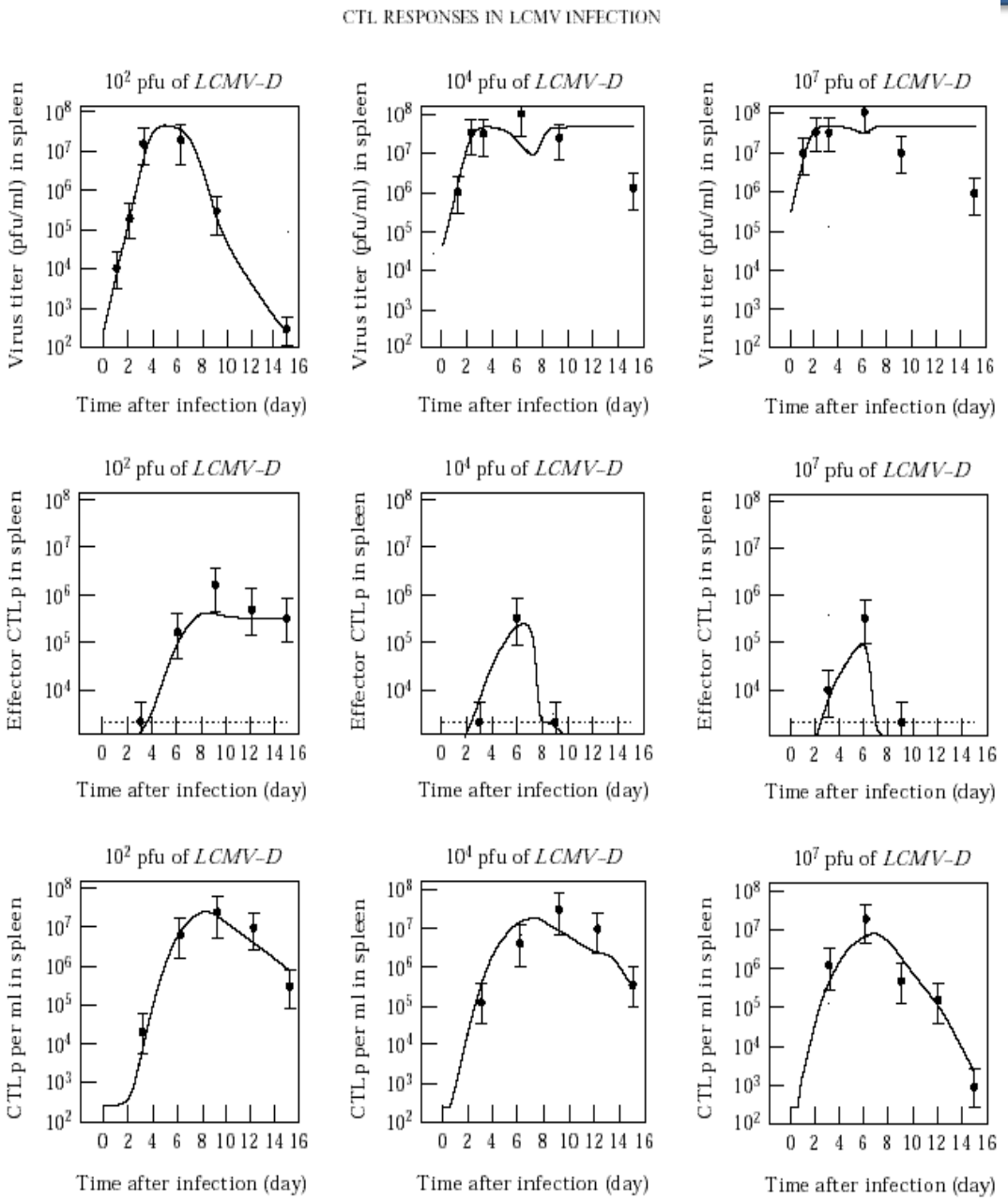
AICD - Apoptosis

$$\frac{\mathrm{d}}{\mathrm{d}t}W(t) = b_W V(t) - \alpha_W W(t),$$

where $g_{\mathrm{p}}(W) = 1/(1 + W/\theta_{\mathrm{p}})^2$ and $g_{\mathrm{e}}(W) = 1/(1 + W/\theta_{\mathrm{E}})^2$.

Anergy

# Model calibration




$$V_{Spleen}(day\ 0) = \frac{0.37 \cdot \mathbf{IS}}{(1 + \mathbf{IS}/0.84 \cdot 10^5)}$$

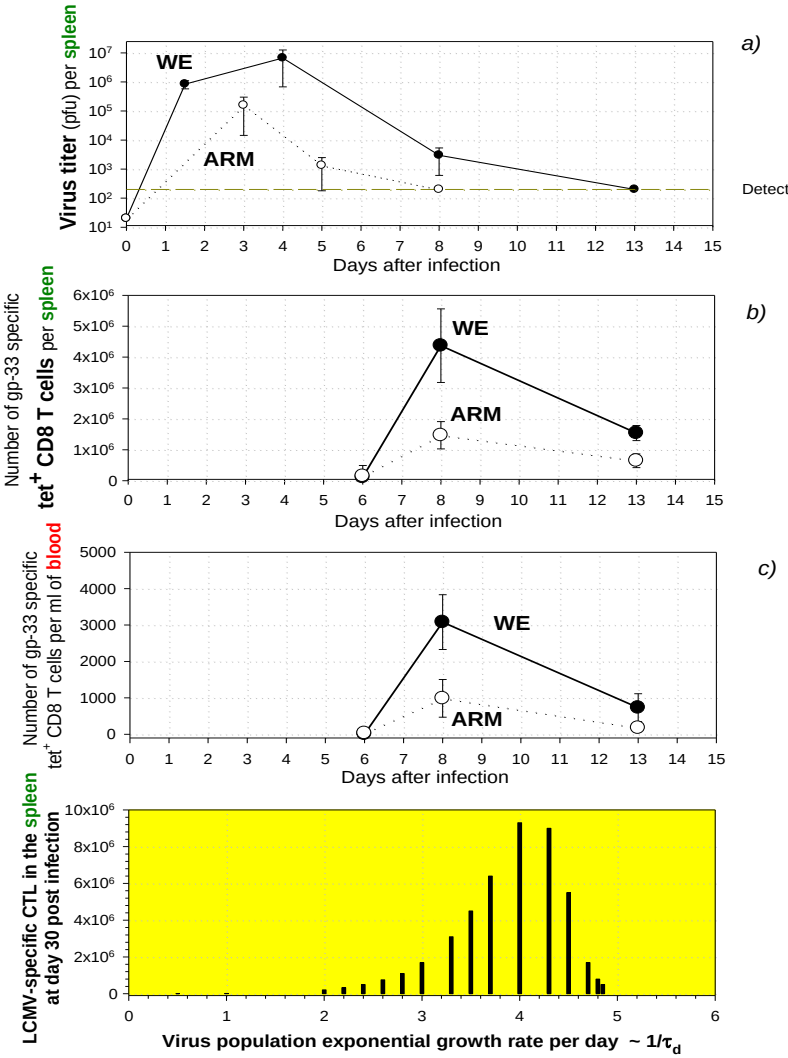
*J. theor. Biol.* (1998) **192**, 283–308

**Modelling the Dynamics of LCMV Infection in Mice: Conventional and Exhaustive CTL Responses**

G. A. Bocharov*

# Virus growth rate and CTL expansion

Fig. Clonal expansion of gp-33 specific CTL after i.v. infection with 200 pfu of LCMV-WE versus LCMV-Armstrong




JOURNAL OF VIROLOGY, Mar. 2004, p. 2247–2254 Vol. 78, No. 5
0022-538X/04/$08.00+0 DOI: 10.1128/JVI.78.5.2247–2254.2004


Underwhelming the Immune Response: Effect of Slow Virus Growth on CD8+-T-Lymphocyte Responses

Gennady Bocharov,[1,2]†‡ Burkhard Ludewig,[3]†* Antonio Bertoletti,[4] Paul Klenerman,[5] Tobias Junt,[3] Philippe Krebs,[3]‡ Tatyana Luzyanina,[6] Cristophe Fraser,[1] and Roy M. Anderson[1]

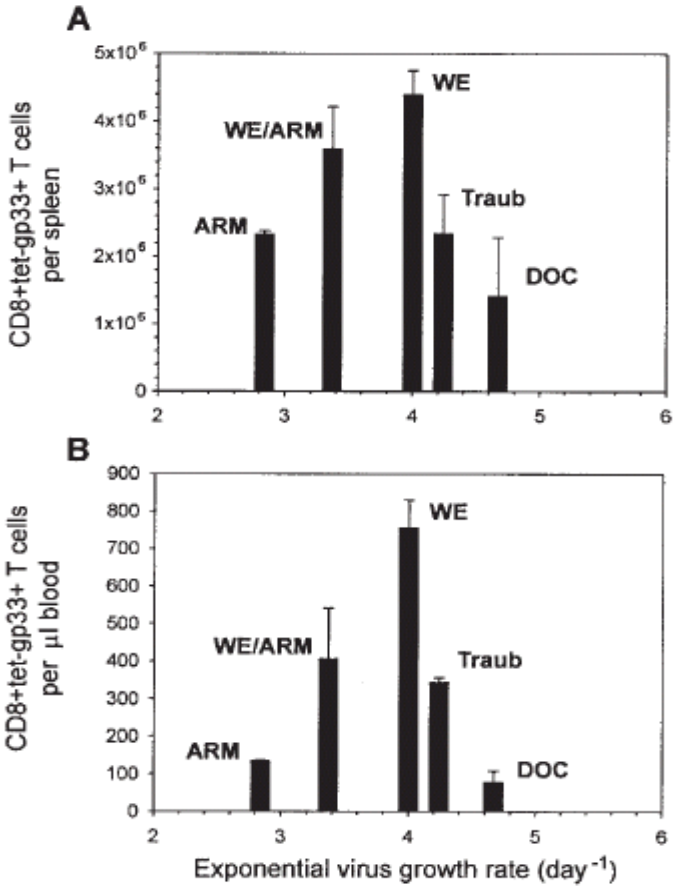
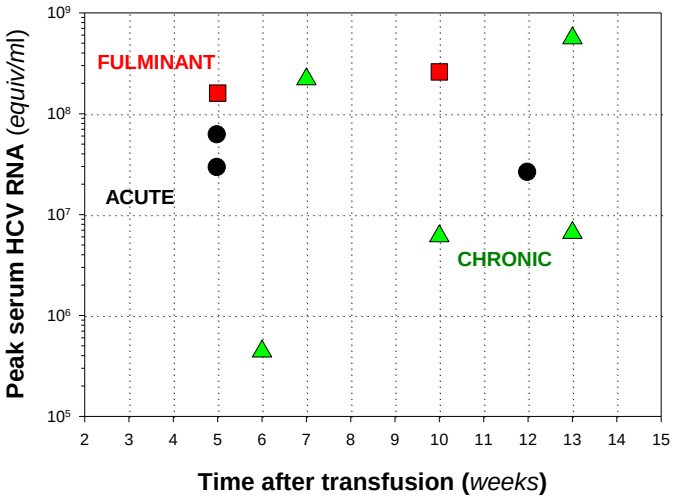



FIG. 2. Bell-shaped relationship between initial virus growth rate and peak CTL responses in spleen (A) and blood (B) established using data on CTL expansion in C57BL/6 mice infected with distinct LCMV strains exhibiting different growth rates. The error bars indicate standard errors. Variation in the LCMV growth rate can have either an enhancing or a down-regulating effect on the clonal burst size of virus-specific CTLs. Virus replication above a threshold is required for strong CTL response. LCMV-WE appears to be an "optimally" replicating strain in C57BL/6 mice, as it induces the strongest CTL response.

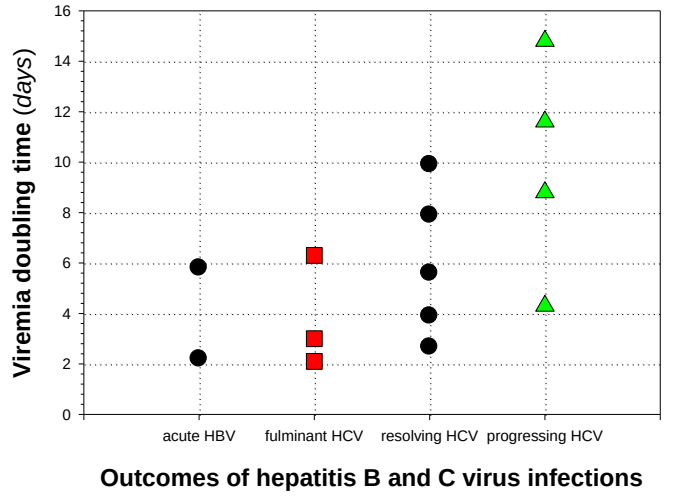
# Published clinical observations: the effect of the virus growth rate




a)

**A reduction in virus growth rate between infected subjects is associated with a spectrum of disease outcomes**:

- *fulminant hepatitis* ($\tau_2$~ **2.1** to **6.2** days)
- *acute resolving hepatitis* ($\tau_2$~ **2.3** to **10** days)
- *chronic progressing hepatitis* ($\tau_2$~ **4** to **615** days)



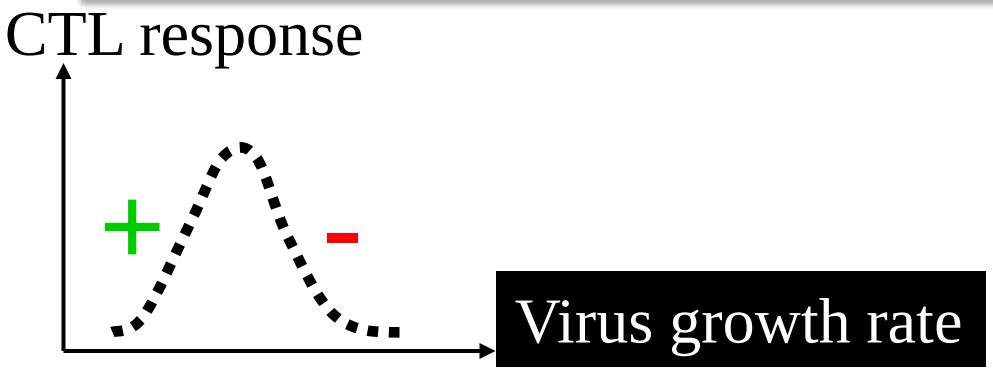

b)

The genomic analysis of immune response in chimpanzees infected with HCV virus showed that HCV **replication below a threshold level** required for activation of genes involved in antigen presentation **results in virus persistence** (Su et al. *PNAS USA* (2002): **99**: 15669-15674)


Farci et al. *Science* (2000) **288**: 339-344

Webster et al. *Hepatology* (2000) **32**: 1117-1124

# Slowly does it…




- Viruses that replicate slowly invoke a weak adaptive immune response
- A ***bell-shaped*** relationship between the virus growth rate and the peak T cell response
- Speed of viral replication represents an important ***'kinetic' mechanism*** influencing the pathogenesis and duration of virus persistence within the human host

HIGHLIGHTS



IMMUNE EVASION

## Slowly does it…

A new study published in the *Journal of Virology* shows that viruses that replicate slowly invoke a weak adaptive immune response, specifically a weak cytotoxic T-lymphocyte response, which could contribute to virus persistence and chronic disease.

Two facets of the CTL response can affect virus clearance. Specific CTL clones are amplified in response to antigen stimulation — the magnitude of amplification of CTLs increases with increasing antigen concentrations. Viruses that replicate rapidly produce large amounts of antigen, which can overwhelm the specific CTL response. This physical deletion of CTLs — known as exhaustion — results in virus persistence.

Using lymphocytic choriomeningitis virus (LCMV) infection of mice as a model, the amplification of CTLs in response to LCMV strains that have different replication rates was assessed. A bell-shaped response was found: both slow and fast replicating virus strains produced weaker $CD8^+$ T-cell responses compared with a strain that had an intermediate replication rate.

What about hepatitis C virus, which replicates more slowly than LCMV? Available data sets were analysed, and slower virus replication correlated with virus persistence. For hepatitis B virus, one well-documented study of virus kinetics and CTL response has been analysed. A predator–prey model was constructed by Bocharov *et al.* — with the CTLs as predators, and the virus as prey — and calibrated using this available HBV data set.

The model was used to predict the effect of changes in virus replication kinetics on the CTL response. Reducing the virus replication rate led to a weaker CTL response, which could result in virus persistence. Certain individuals — 'high-responders' — have a more efficient CTL response, presumably through genetic variation. Even with a simulated high-responder, a slowly replicating virus strain elicited only a weak and transient CTL response. This model predicts that the transition from acute to chronic HBV infection could result from a decrease in the replication rate of the virus.

The mathematical model used is reductionist and cannot take into account every aspect of the complex interactions between the virus and the immune system. However, models are useful for predicting and planning experimental work, and this modelling approach could be implemented for other important viruses, such as HIV or cytomegalovirus. This report clearly indicates that the kinetics of virus replication could be important for the outcome of the infection. Slow viruses could sneak past immune surveillance and establish persistence, and therapies that downregulate virus replication could also result in virus persistence and chronic disease.

*Susan Jones*

**References and links**

**ORIGINAL RESEARCH PAPER** Bocharov, G. *et al.* Underwhelming the immune response: effect of slow virus growth on $CD8^+$-T-lymphocyte responses. *J. Virol.* **78**, 2247–2254 (2004)

# Integration of mathematical modelling into the immunological mainstream

William E. **Paul** (June 12, 1936 – September 18, 2015)

PNAS

## Feedback regulation of proliferation vs. differentiation rates explains the dependence of CD4 T-cell expansion on precursor number

Gennady Bocharov[a,1,2], Juan Quiel[b], Tatyana Luzyanina[c], Hagit Alon[d], Egor Chiglintsev[e], Valery Chereshnev[f], Martin Meier-Schellersheim[b], William E. Paul[b,2], and Zvi Grossman[b,d,1,2]

[a]Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow 119333, Russia; [b]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; [c]Institute of Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino 142290, Russia; [d]Tel Aviv University School of Medicine, Tel Aviv 69978, Israel; [e]Novosibirsk State University, Novosibirsk 630090, Russia; and [f]Institute of Immunology and Physiology, Ural Branch Russian Academy of Sciences, Ekaterinburg 620219, Russia

Contributed by William E. Paul, January 7, 2011 (sent for review November 16, 2010)

PNAS

## Antigen-stimulated CD4 T-cell expansion is inversely and log-linearly related to precursor number

Juan Quiel[a], Stephane Caucheteux[a], Arian Laurence[b], Nevil J. Singh[c], Gennady Bocharov[d], Shlomo Z. Ben-Sasson[a], Zvi Grossman[a], and William E. Paul[a,1]

Laboratories of [a]Immunology and [c]Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; [b]Molecular Immunology and Inflammation Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892; and [d]Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow 119333, Russia

Contributed by William E. Paul, January 7, 2011 (sent for review November 11, 2010)

Thus, the immune system offers challenges sufficient to test the growing power of mathematical attack on a biological problem. It is to the quantitative prediction of the outcome of given perturbations in the immune system that we envisage our mathematical/ modeling colleagues will apply themselves. There is a richness of opportunities and a myriad of challenges. Good luck!!!!!

*Math. Model. Nat. Phenom.*
Vol. 7, No. 5, 2012, pp. 4–6

# Topic

- Infectious disease model: key components
- Antiviral immune response: kinetic regulation
- **Optimal model structure: information-theoretic criteria**
- Cell growth analysis: asymmetric division

# Fundamental modelling issues

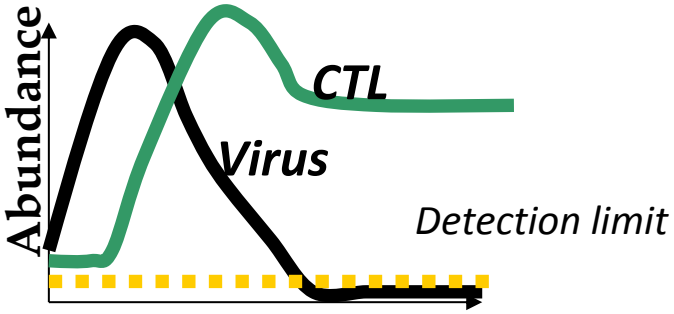
- "Typical" equation for population dynamics:

$$\frac{\Delta N}{\Delta t} = \mathbf{f}\left(growth, death, migration, ...\right)$$

**General problem:** various functional forms can be suggested for the same process…

- ***Which model is better:*** that having the fewer parameters or that based more closely on the biology of the system?
- Is it possible to distinguish between the important and the unimportant assumptions in a model?

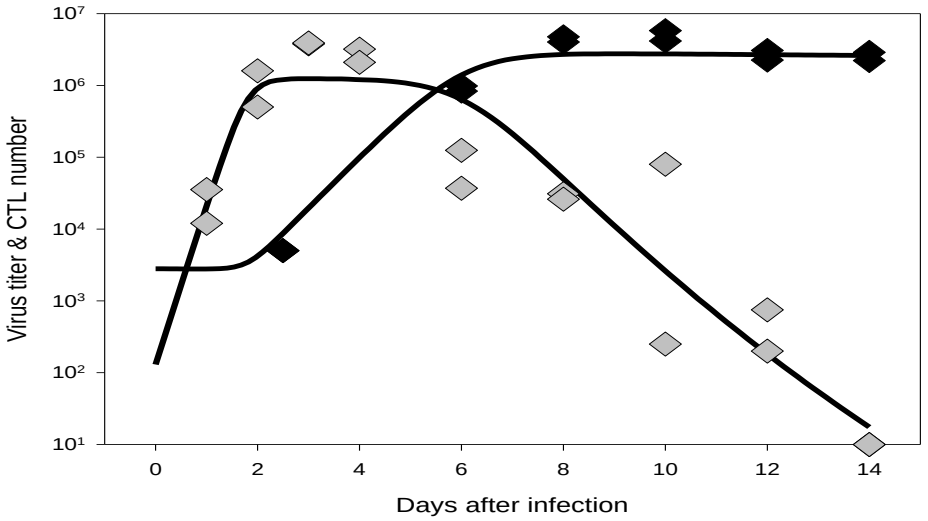
# Virus - CTL dynamics: typical kinetics

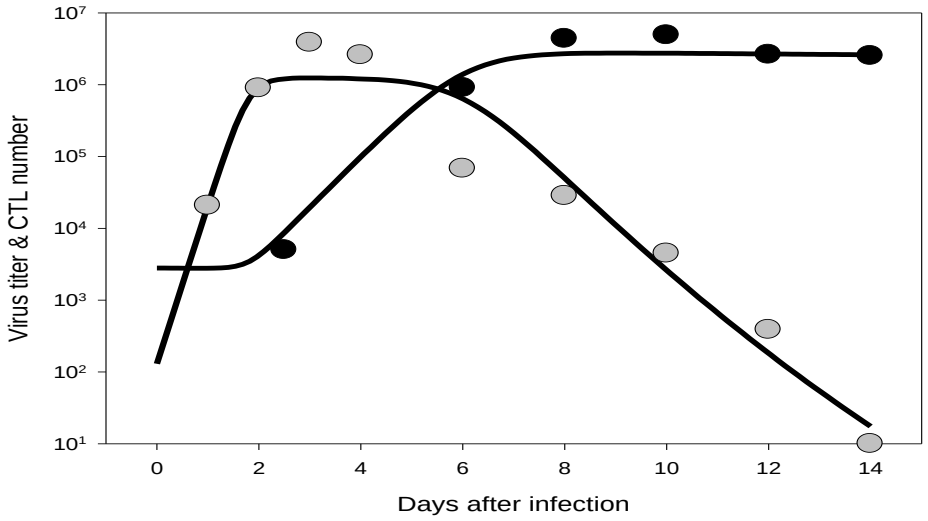



Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
Journal of Computational and Applied Mathematics 184 (2005) 50–76
JOURNAL OF COMPUTATIONAL AND APPLIED MATHEMATICS
www.elsevier.com/locate/cam

Computational approaches to parameter estimation and model selection in immunology

C.T.H. Baker[a,b,*], G.A. Bocharov[a,b,c], J.M. Ford[d], P.M. Lumb[b], S.J. Norton[b], C.A.H. Paul[a], T. Junt[e], P. Krebs[e], B. Ludewig[e,f]



# Hierarchy of models for LCMV-CTL data

Complexity

5 parameters

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_1 \cdot V(t) \cdot E(t) - \alpha_E \cdot E(t)$$

*Predator-Prey*

6 parameters

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t)}{\theta_{sat} + V(t)} E(t) - \alpha_E \cdot E(t)$$

*PP+Holling type II response*

7 parameters

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t-\tau)}{\theta_{sat} + V(t)} E(t-\tau) - \alpha_E \cdot E(t)$$

*…+ time lag in the CTL division*

8 parameters

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t-\tau)}{\theta_{sat} + V(t)} E(t-\tau) - \alpha_E \cdot E(t) + T^*$$

*…+ CTL homeostasis*

9 parameters

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot \left(1 - V(t)/K\right) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_1 \cdot V(t) \cdot E(t) - \alpha_E \cdot E(t) + T^* - r_m \cdot E(t)$$
$$\frac{d}{dt}E_m(t) = r_m \cdot E(t) - \alpha_m \cdot E_m(t)$$

*…+ CTL memory population*

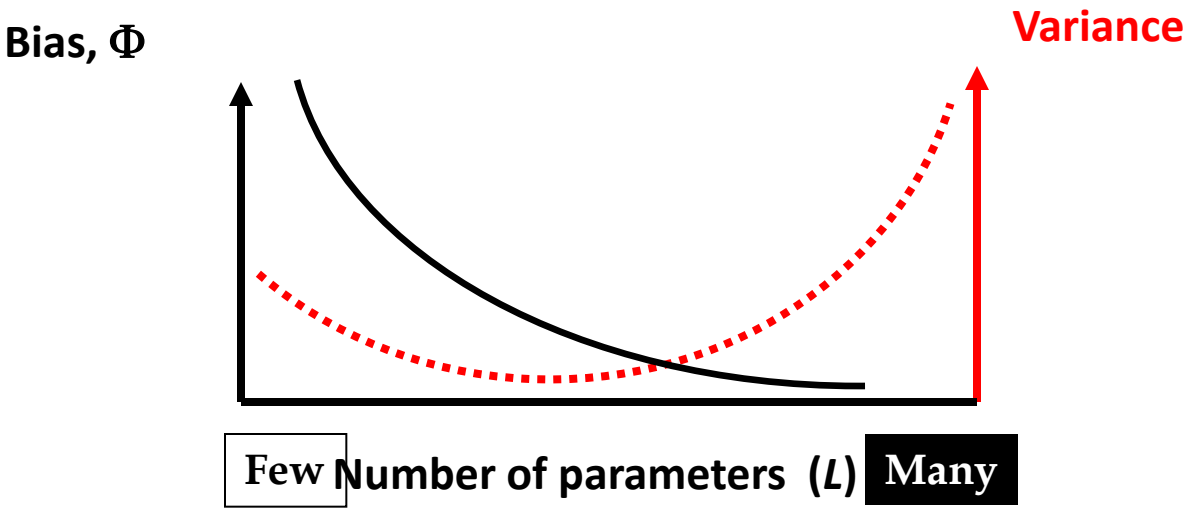
# Model selection: accuracy & parsimony

Given a set of related models – how to rank them by giving each a score?

- ***the goodness of fit*** – the size of the minimized least squares (or maximized likelihood) function
- ***the principle parsimony*** – **a proper balance between under-fitting and over-fitting**

## General principle:

***A model should be "as simple as possible yet as complex as necessary" (Denis Noble et al. 2005) with respect to the included variables, model structure and the number of parameters for adequate representation of the data***



# Criteria for discriminating between models – model selection

- Kullback-Leibler information distance between models ***f*** and ***g*** is defined as the multidimensional integral:

$$I(f,g)=\int f(x)\log\left(\frac{f(x)}{g(x|\theta)}\right)dx$$

•**Akaike** (1973) found a rigorous way to estimate the Kullback-Leibler directed distance of the candidate model ***g*** to the truth ***f model*** based on the empirical **log-likelihood function** $\mathcal{L}(\mathbf{p})$ at its maximum point $\mathcal{L}_*=\mathcal{L}(\mathbf{p}_*)$

•The ***Akaike's Information Criterion*** makes use of an estimate of the ***expected, relative distance*** between the fitted model and the unknown true mechanism that actually generated the ***observed*** data ($n_{obs}$)

$$\mu_{AIC}=n_{obs}\cdot\ln\left(\mathcal{L}(\mathbf{p}^*)\right)+2(n_{\mathbf{p}}+1)$$

•The **Kolomogorov complexity – Minimum Description Length** principle by Jorma Rissanen "Modelling by the Shortest Data Description" (1978)

$$MDL=-\ln\left(\mathcal{L}(\mathbf{p}^*)\right)+0.5\cdot n_{\mathbf{p}}\cdot\ln(n_{obs}/(2\pi))+\ln\int_{\Omega}\sqrt{\det(\mathbf{I}(\mathbf{p}))}d\mathbf{p}$$

# Model Ranking

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_1 \cdot V(t) \cdot E(t) - \alpha_E \cdot E(t)$$

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t)}{\theta_{sat} + V(t)} E(t) - \alpha_E \cdot E(t)$$

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t-\tau)}{\theta_{sat} + V(t)} E(t-\tau) - \alpha_E \cdot E(t)$$

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot (1 - V(t)/K) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_2 \frac{V(t-\tau)}{\theta_{sat} + V(t)} E(t-\tau) - \alpha_E \cdot E(t) + T^*$$

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot \left(1 - {V(t)}/{K}\right) - \gamma \cdot V(t) \cdot E(t)$$
$$\frac{d}{dt}E(t) = b_1 \cdot V(t) \cdot E(t) - \alpha_E \cdot E(t) + T^* - r_m \cdot E(t)$$
$$\frac{d}{dt}E_m(t) = r_m \cdot E(t) - \alpha_m \cdot E_m(t)$$

Bias $\Phi_{OLS}(\mathbf{p}^*)$ | $\mu$ *Information loss*

| | | |
|---|---|---|
| Model 2 | $7.8 \times 10^{11}$ | *440* |
| Model 3 | $1.6 \times 10^{12}$ | *461* |
| Model 1 | $6.5 \times 10^{12}$ | *465* |
| Model 4 | $1.6 \times 10^{12}$ | *475* |
| Model 5 | $1.6 \times 10^{12}$ | *531* |

Ranking: M2>M3>M1>M4>M5

**=> The best model is Model 2**

# Uncertainty in parameter estimates: 95% Confidence Intervals

| *Parameter* [95%CI] | Model 1 | Model 2 |
|---|---|---|
| *Virus growth rate constant* | $4.61 \in$ **[3.7, 6.5]** | $4.51 \in$ **[4.2, 4.8]** |
| *CTL activation rate constant* | $9.2 \times 10^{-7}$ **[$6.8 \cdot 10^{-7}$, $1.4 \cdot 10^{-6}$]** | $1.42 \in$ **[1.36, 1.48]** |
| *CTL death rate constant* | $0.093 \in$ **[$10^{-10}$, 0.2]** | $0.2 \in$ **[0.15, 0.26]** |

# The ‘best’ model for the given data

$$\beta = 4.51; \quad K = 4.69 \cdot 10^{6}; \quad \gamma = 8 \cdot 10^{-5}$$

$$b_2 = 1.42; \quad \theta_{sat} = 3.23 \cdot 10^{-176} \approx 0; \quad \alpha_E = 0.2$$

$$\frac{d}{dt}V(t) = \beta \cdot V(t) \cdot \left(1 - V(t)/K\right) - \gamma \cdot V(t) \cdot E(t)$$

$$\frac{d}{dt}E(t) = b_2 \frac{V(t)}{\theta_{sat} + V(t)} E(t) - \alpha_E \cdot E(t)$$

Therefore, the equation for CTL dynamics can be reduced to

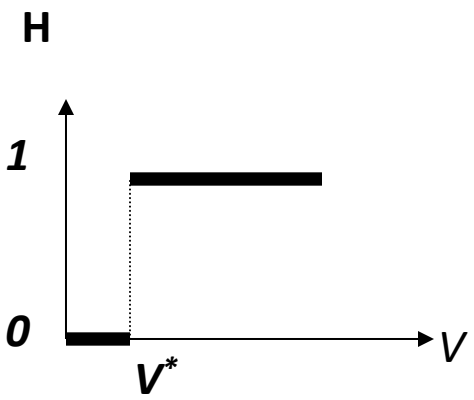
$$\frac{d}{dt}E(t) = b_2 \cdot E(t) \cdot \mathrm{H}(V - V^*) - \alpha_E \cdot E(t)$$

where $\mathrm{H}(\cdot)$ is the Heaviside's step function with $V^*$ assuming the value $\sim \theta_{\mathrm{sat}}$

Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
Journal of Computational and Applied Mathematics 184 (2005) 50–76
JOURNAL OF COMPUTATIONAL AND APPLIED MATHEMATICS
www.elsevier.com/locate/cam

Computational approaches to parameter estimation and model selection in immunology

C.T.H. Baker[a,b,*], G.A. Bocharov[a,b,c], J.M. Ford[d], P.M. Lumb[b], S.J. Norton[b], C.A.H. Paul[a], T. Junt[e], P. Krebs[e], B. Ludewig[e,f]

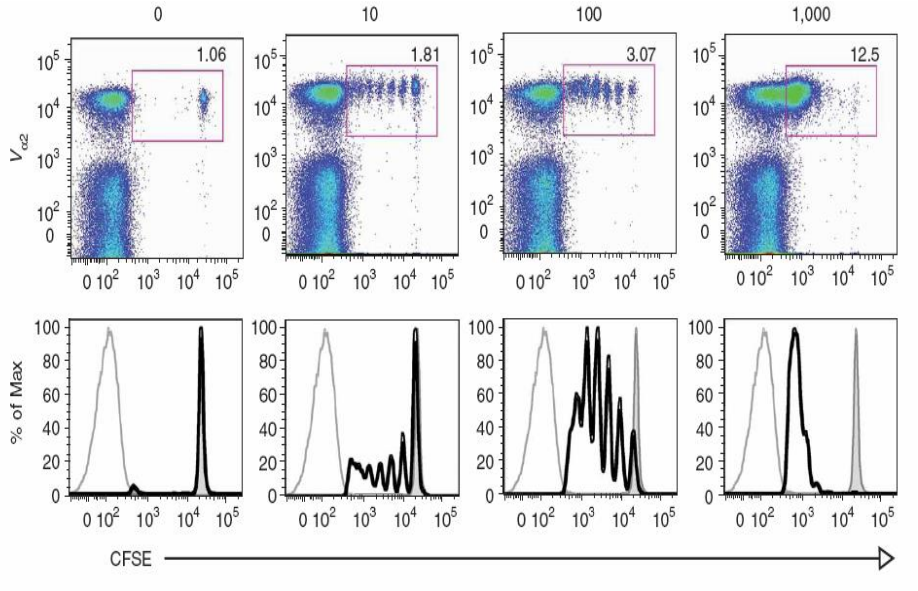


# Topic

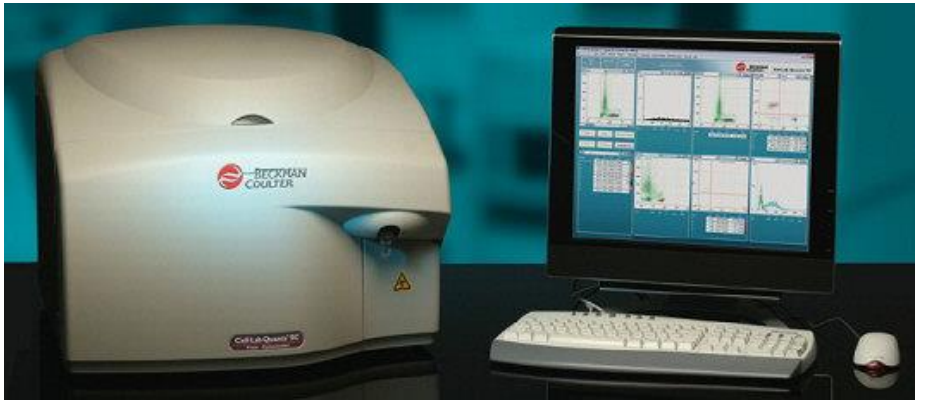
- Infectious disease model: key components
- Antiviral immune response: kinetic regulation
- Optimal model structure: information-theoretic criteria
- **Cell growth analysis: asymmetric division**

# CFSE Proliferation Assay:

analysis of antigen specific and non-specific T cell proliferation.




From: *Quah et al., Nat Protoc.2007;2:2049*



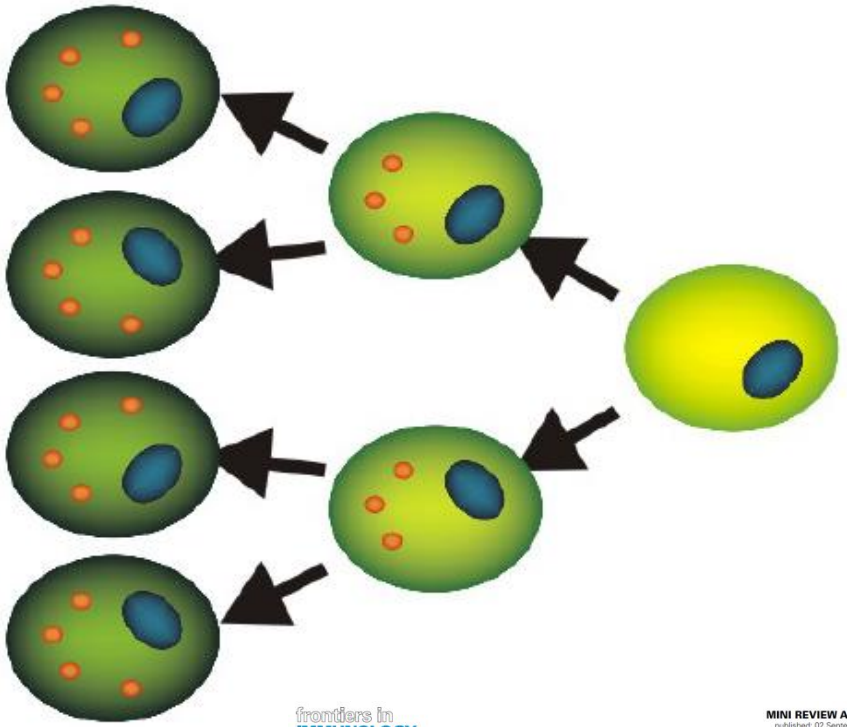

http://www.biochemmack.ru/product/citometry/cytometr/CellLabQuantaSC/.

- **Major assumption**: **cell division is symmetric, i.e. the label is halved in the two daughter cells**
- **Cell biology axiom**: **a random and uneven partition of mass between the sister cells**

*R. Sennerstam, partition of (mass) protein to sister cell pairs at mitosis: a re-evaluation. J Cell Sci 1988, 90:301*

- **Does this matter?**

# Symmetric cell division: 50% vs 50%



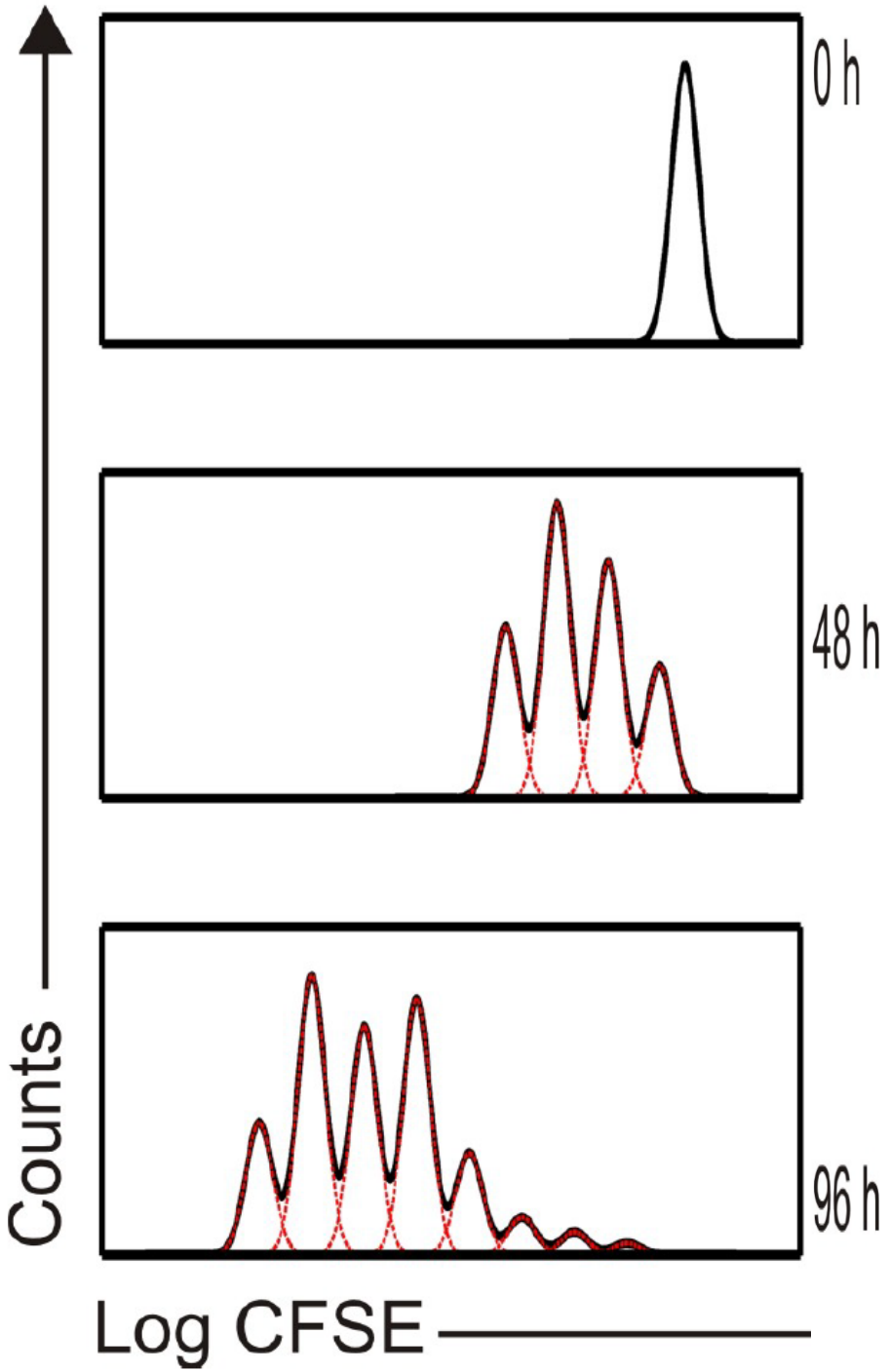
frontiers in IMMUNOLOGY

MINI REVIEW ARTICLE
published: 02 September 2013
doi: 10.3389/fimmu.2013.00264

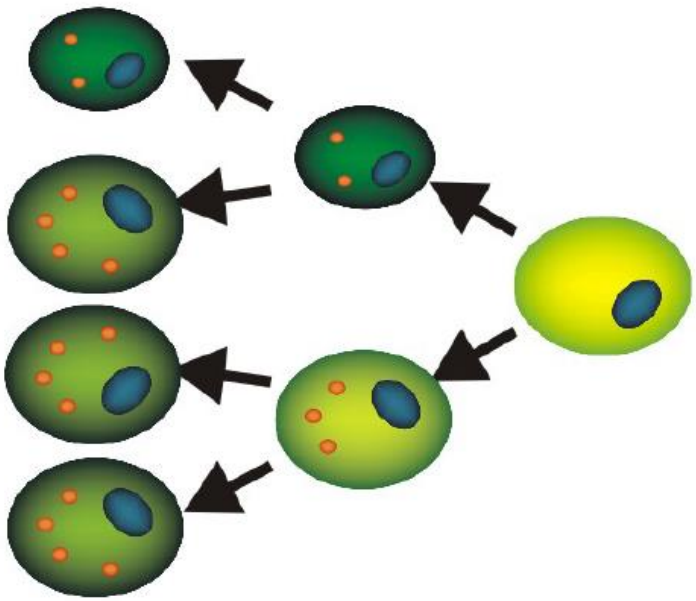
Asymmetry of cell division in CFSE-based lymphocyte proliferation analysis

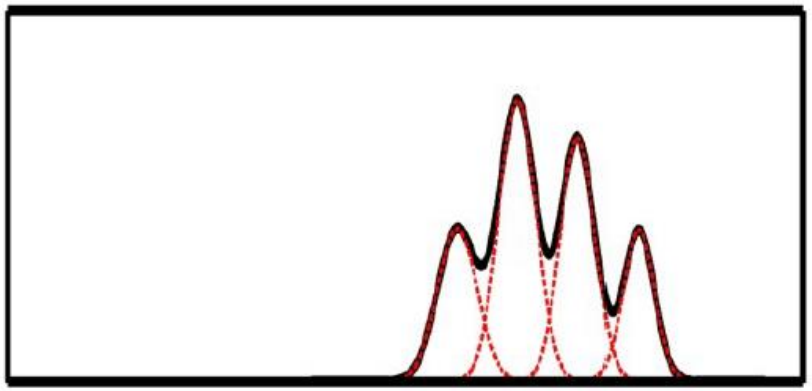
*Gennady Bocharov[1]*, Tatyana Luzyanina[2], Jovana Cupovic[3] and Burkhard Ludewig[3]*

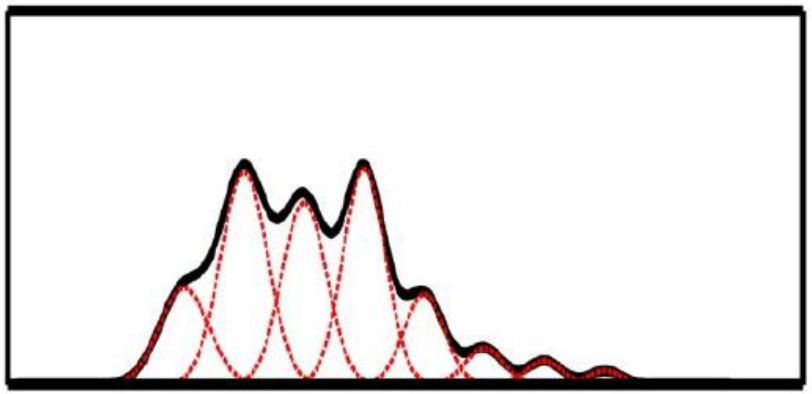
[1] Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow, Russia
[2] Institute of Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino, Russia
[3] Institute of Immunobiology, Kantonal Hospital St. Gallen, St. Gallen, Switzerland



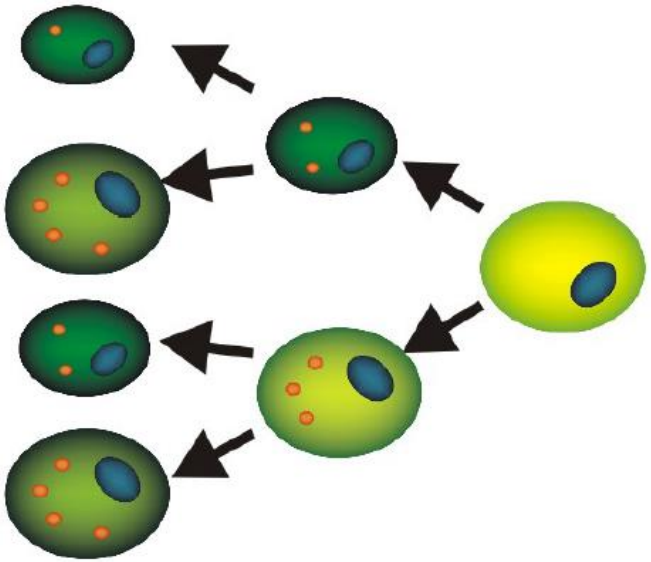
# Low asymmetry of the division: 46% vs 54%

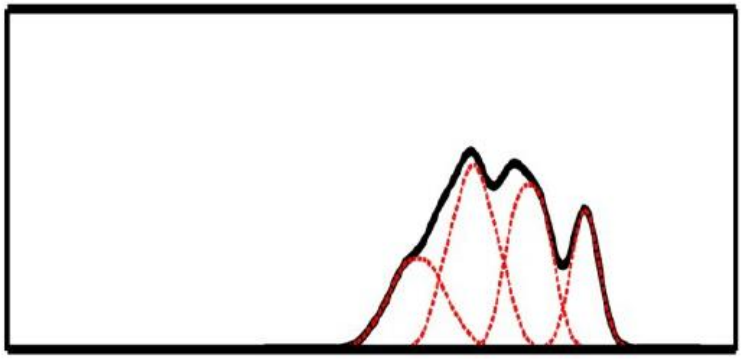


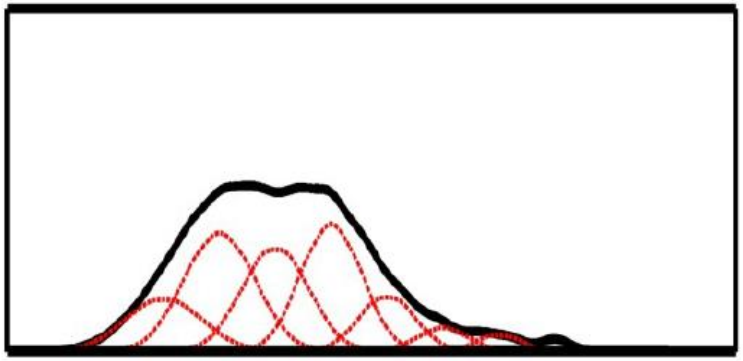




Higher asymmetry of division:
42% vs 58%

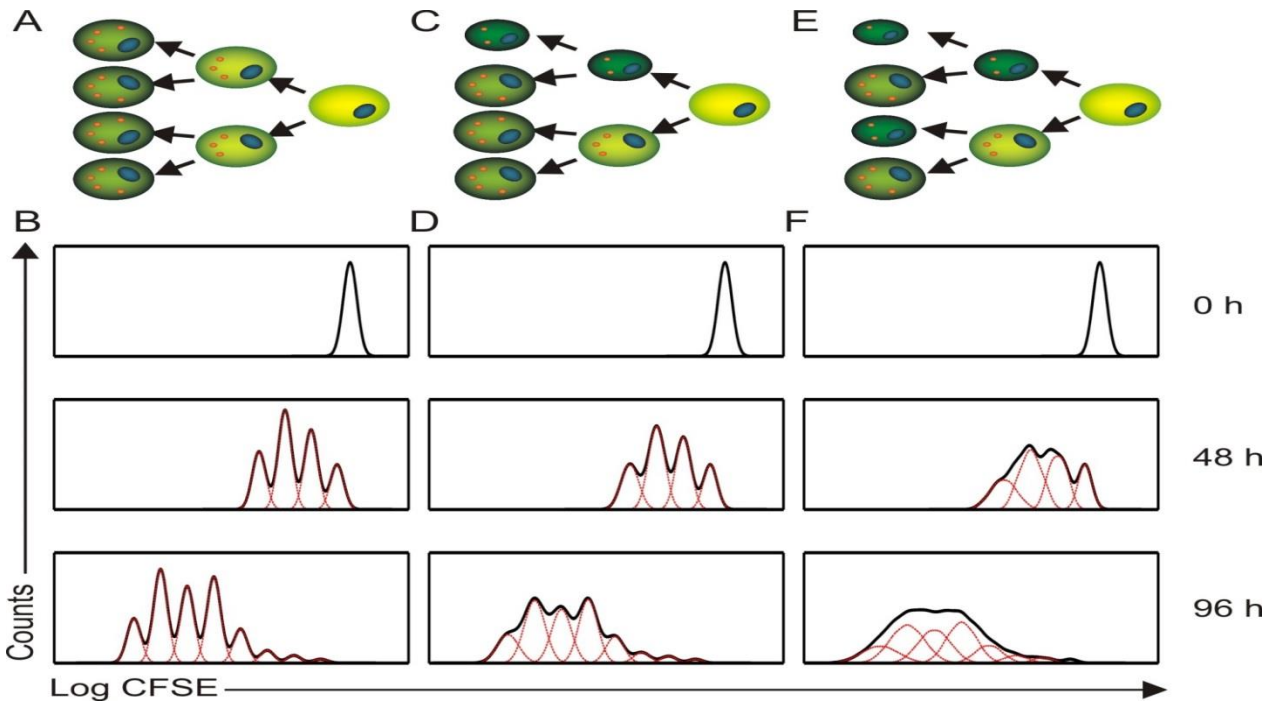


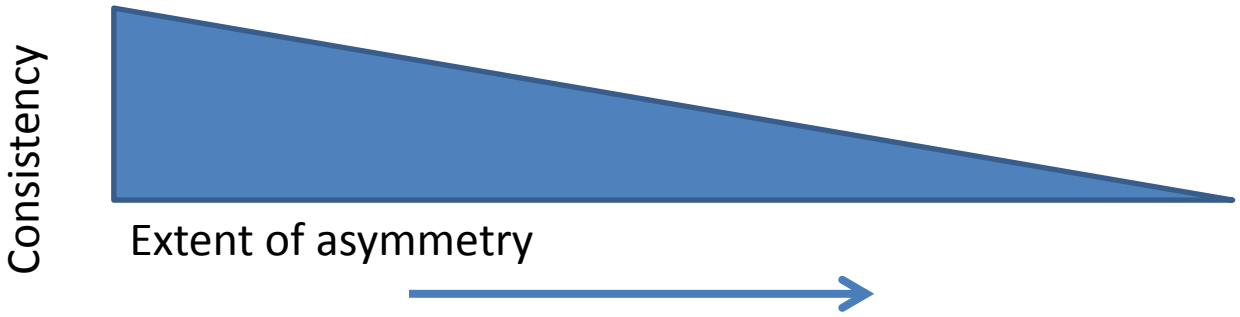




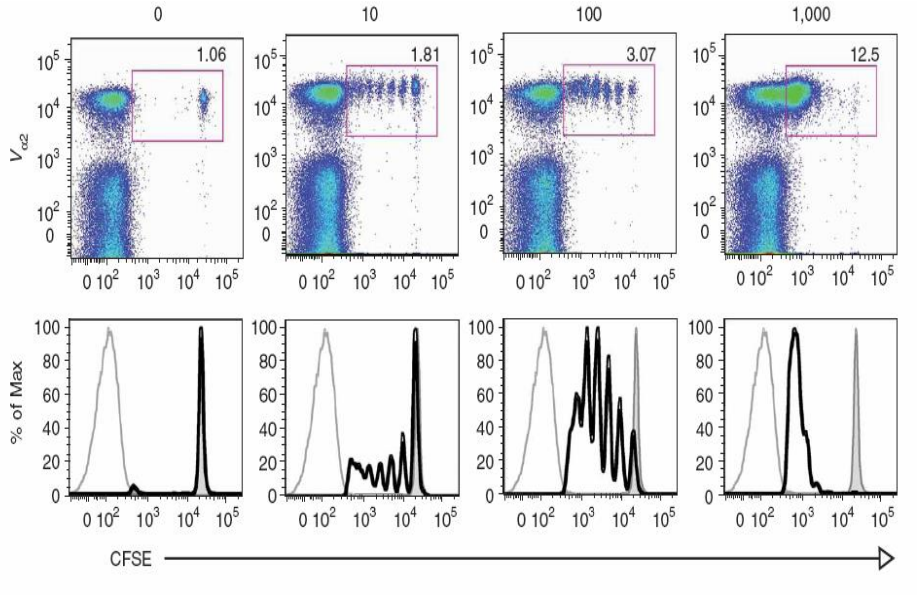
# Ssoftware for CFSE histogram decomposition

FlowJo is a product of Tree Star, Inc.
www.flowjo.com
1-541-201-0022
flowjo@treestar.com
TN.Proliferation.20100424



# Raw data

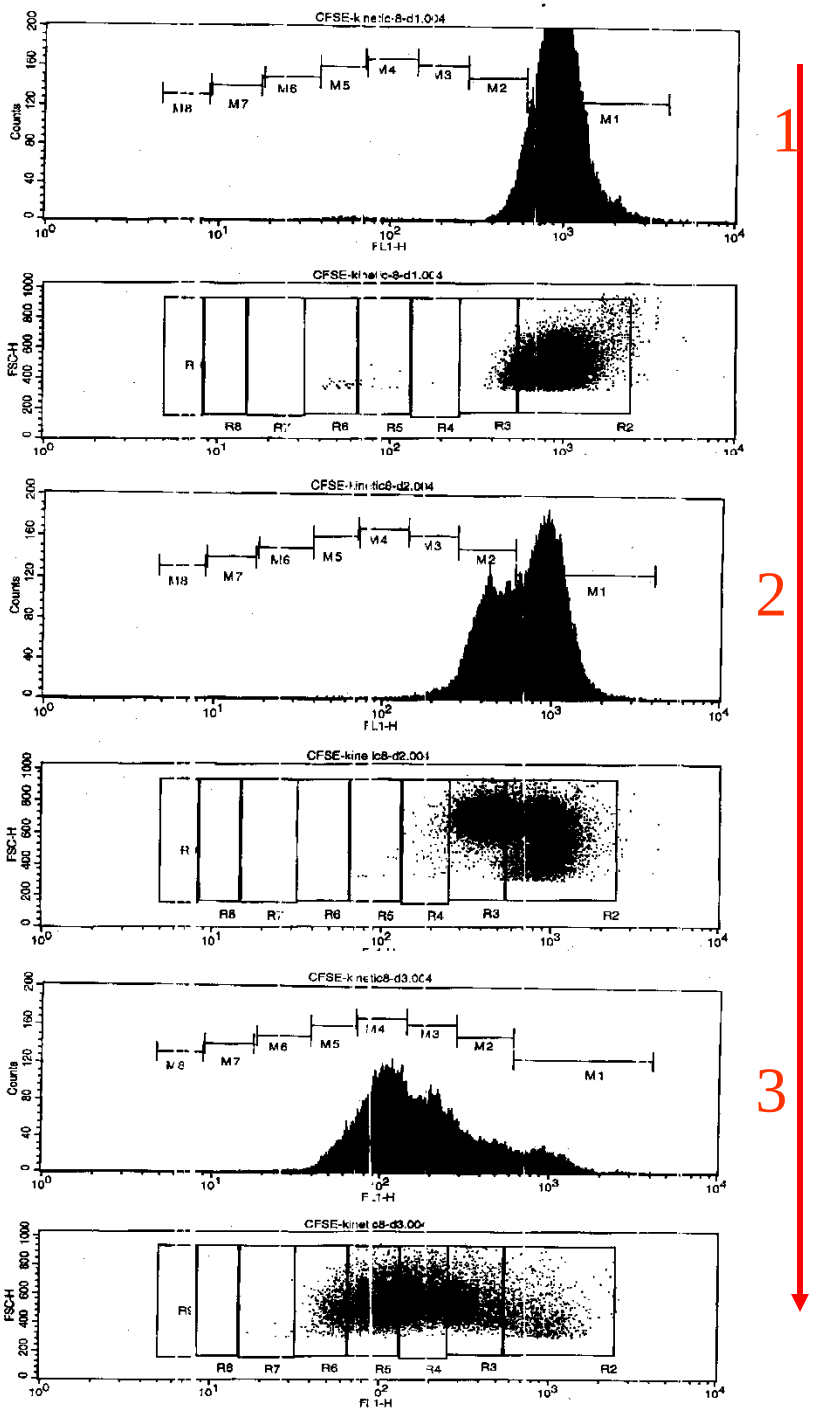



Quah et al., Nat Protoc.2007;2:2049

FlowJo is a product of Tree Star, Inc.
www.flowjo.com
1-541-201-0022
flowjo@treestar.com
TN.Proliferation.20100424

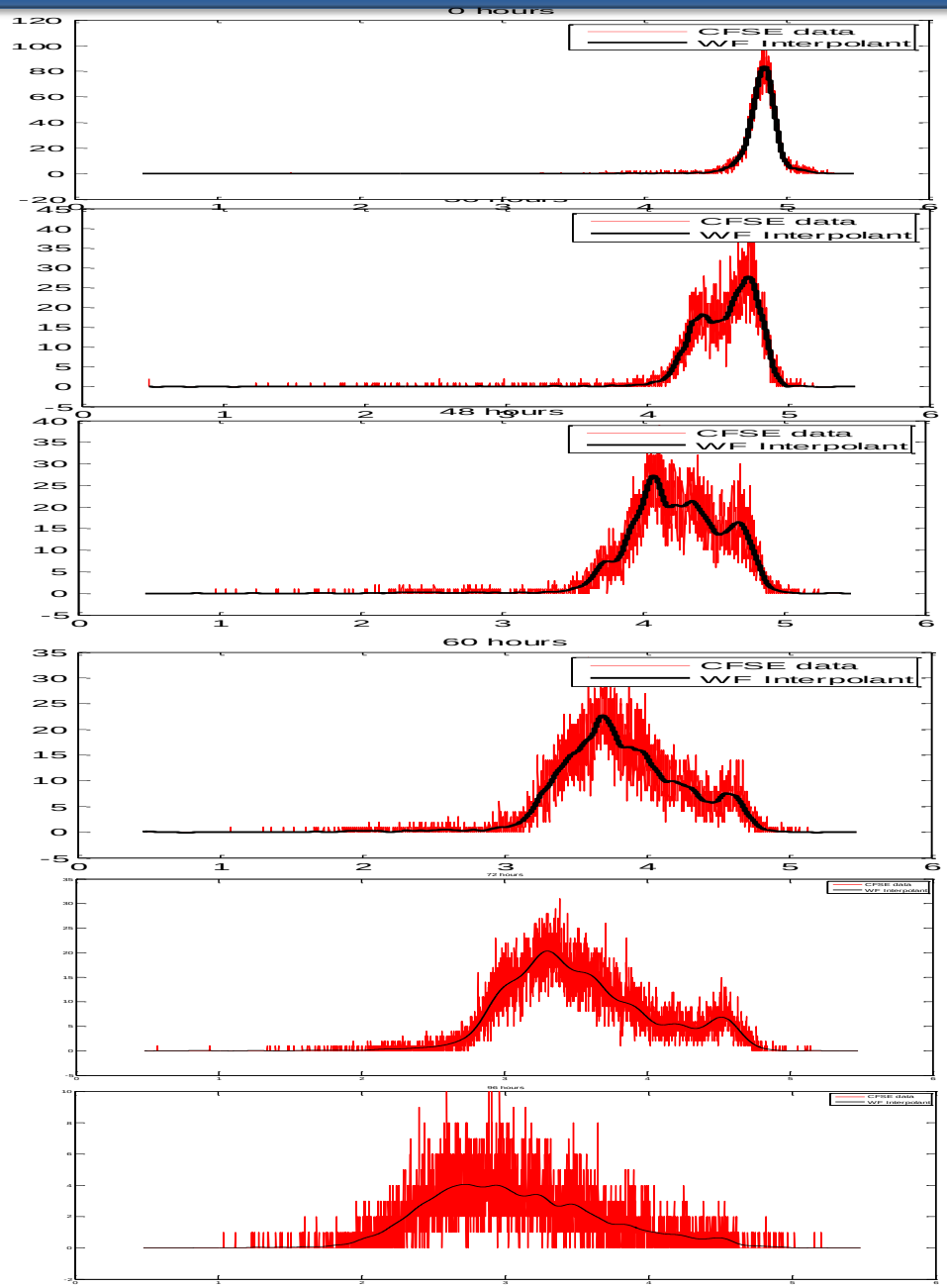

Problem: an interpretation of flow cytometry data

# Evolution of histograms of CFSE-labeled PHA-stimulated peripheral blood mononuclear cells generated by flow cytometry




Data from S. Ehl (Children's Hospital, Freiburg University)
Request: to characterize the individual's immune responsiveness

# Proliferation of retrogenic CD8+ T cells




48

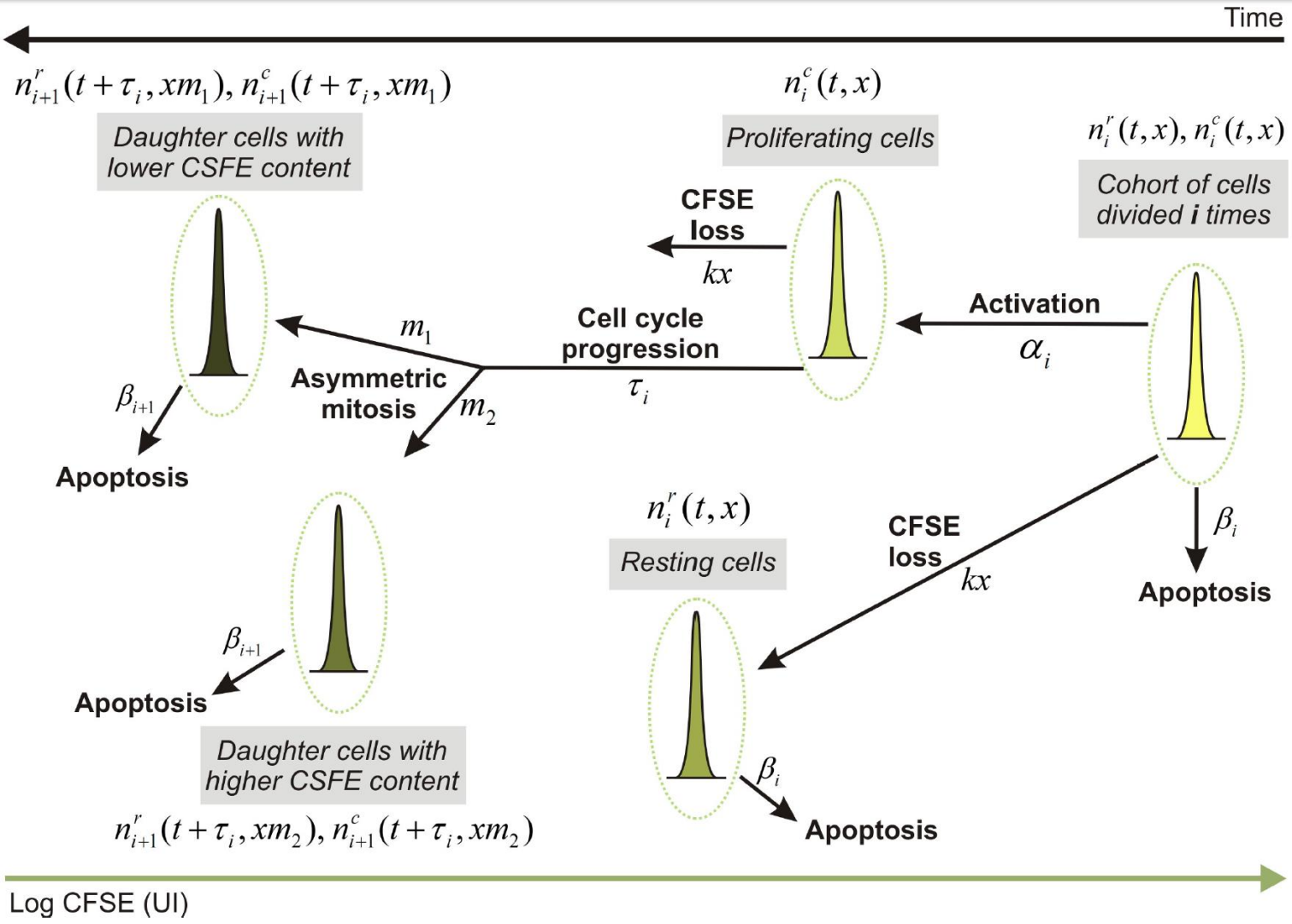
60

72

96

Time (hours)

# Division- and CFSE-label structured mathematical model



# Delay-hPDE model with asymmetric division

J. Math. Biol. (2014) 69:1547–1583
DOI 10.1007/s00285-013-0741-z
Mathematical Biology

**Mathematical models for CFSE labelled lymphocyte dynamics: asymmetry and time-lag in division**

Tatyana Luzyanina · Jovana Cupovic · Burkhard Ludewig · Gennady Bocharov

$$n_i(t,x) = n_i^r(t,x) + n_i^c(t,x), \quad i = 0,1\ldots, i_p - 1,$$

$$n_{i_r}(t,x) = n_{i_r}^r(t,x)$$

$$\frac{\partial}{\partial t} n_0^r(t,x) - k\frac{\partial}{\partial x}\left(x n_0^r(t,x)\right) = -(\alpha_0 + \beta_0) n_0^r(t,x),$$

$$\frac{\partial}{\partial t} n_i^r(t,x) - k\frac{\partial}{\partial x}\left(x n_i^r(t,x)\right) = -(\alpha_i + \beta_i) n_i^r(t,x) +$$

$$+ \alpha_{i-1} e^{k\tau_{i-1}}\left(\frac{1}{m_1} n_{i-1}^r(t-\tau_{i-1}, e^{k\tau_{i-1}}\frac{x}{m_1}) + \frac{1}{1-m_1} n_{i-1}^r(t-\tau_{i-1}, e^{k\tau_{i-1}}\frac{x}{1-m_2})\right), \; i = 1,2,\ldots, i_r,$$

$$\frac{\partial}{\partial t} n_i^c(t,x) - k\frac{\partial}{\partial x}\left(x n_i^c(t,x)\right) = \alpha_i\left(n_i^r(t,x) - e^{k\tau_i} n_i^r(t-\tau_i, e^{k\tau_i} x)\right), \; i = 0,1,\ldots, i_r - 1,$$

$$n_0^r(s,x) = 0, \; s \in [-\tau_0, 0); \; n_0^r(0,x) = n^0(x);$$

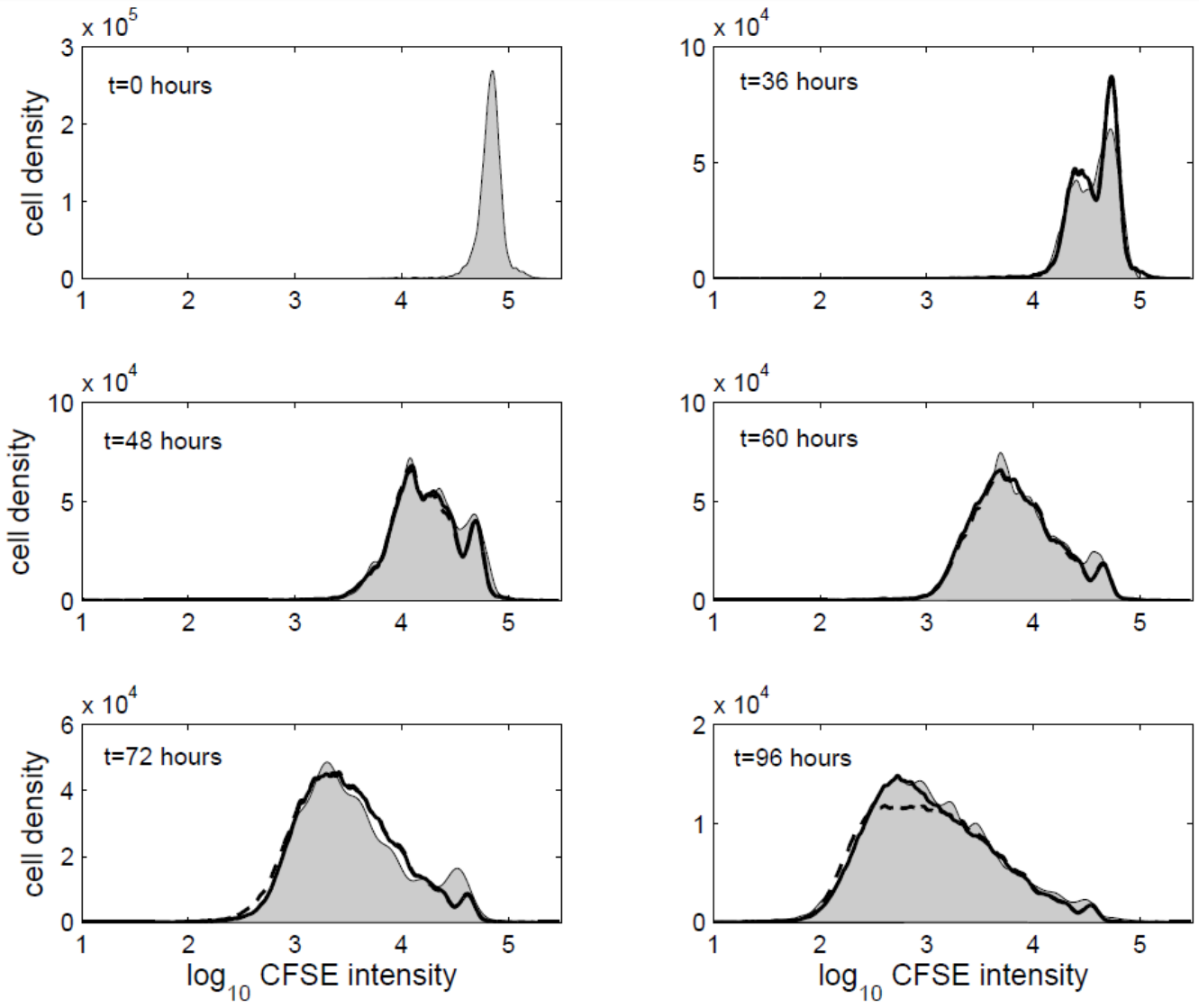
$$n_i^r(s,x) = 0, \; s \in [-\tau_i, 0], \; i = 1,2,\ldots, i_r;$$

$$n_i^c(s,x) = 0, \; s \in [-\tau_i, 0], \; i = 0,1,\ldots, i_r - 1;$$

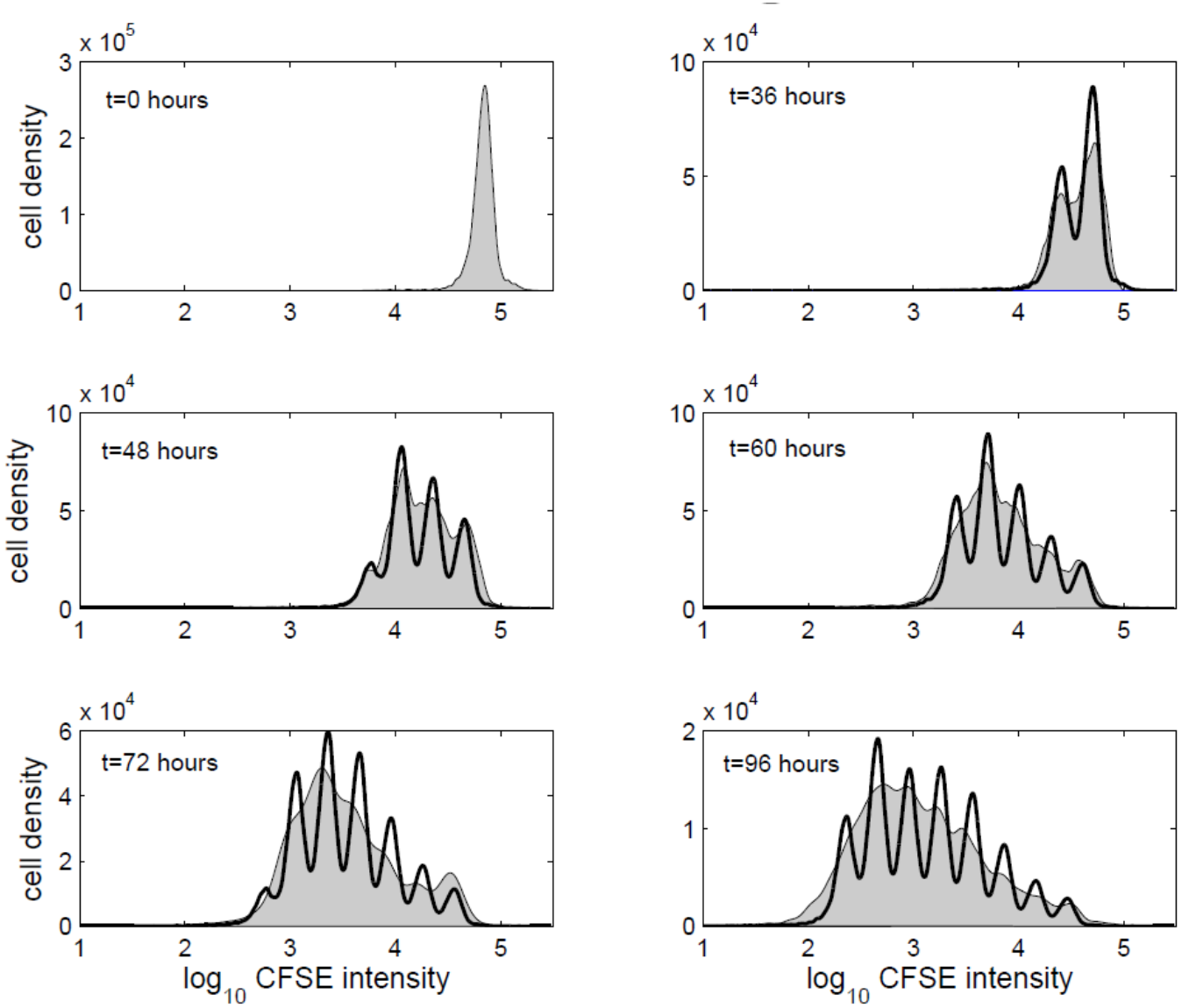
$$n_i^r(t, x_{\max}) = n_i^c(t, x_{\max}) = 0, \; t \geq 0;$$

$$v(0) n_i^r(t,0) = v(0) n_i^c(t, x0) = 0, \; t \geq 0;$$

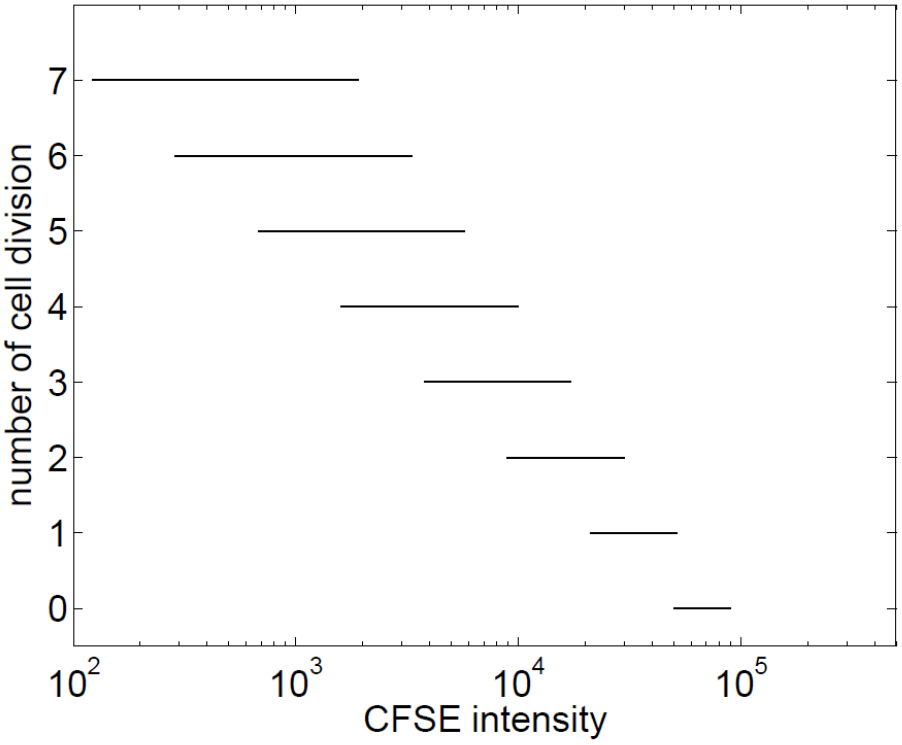
# Label- and division- structured delay model for an asymmetric cell division



# Label- and division- structured symmetric cell division



# Generations overlap




J. Math. Biol. (2014) 69:1547–1583
DOI 10.1007/s00285-013-0741-z

Mathematical Biology

**Mathematical models for CFSE labelled lymphocyte dynamics: asymmetry and time-lag in division**

Tatyana Luzyanina · Jovana Cupovic · Burkhard Ludewig · Gennady Bocharov

frontiers in IMMUNOLOGY

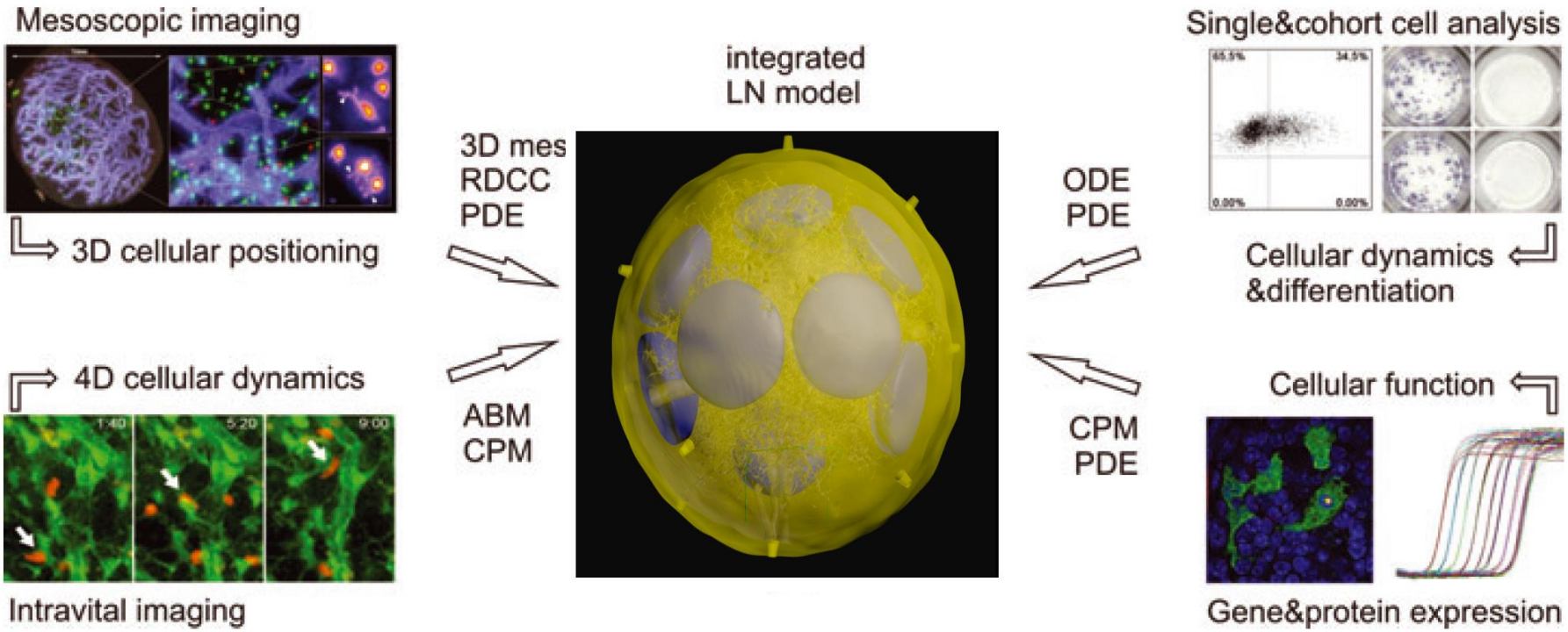
MINI REVIEW ARTICLE
published: 02 September 2013
doi: 10.3389/fimmu.2013.00264

Asymmetry of cell division in CFSE-based lymphocyte proliferation analysis

*Gennady Bocharov[1]*, Tatyana Luzyanina[2], Jovana Cupovic[3] and Burkhard Ludewig[3]*

[1] *Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow, Russia*
[2] *Institute of Mathematical Problems in Biology, Russian Academy of Sciences, Pushchino, Russia*
[3] *Institute of Immunobiology, Kantonal Hospital St. Gallen, St. Gallen, Switzerland*

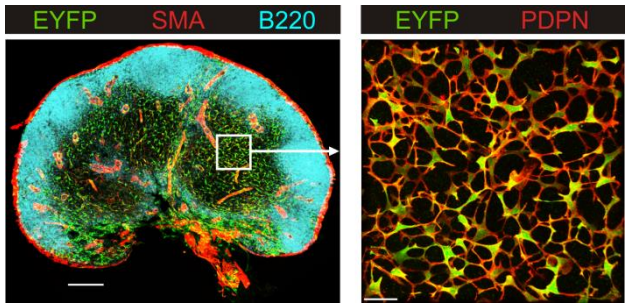
# Embedding the cell population dynamics models into the spatial contexts of the lymphoid organs




Burkhard Ludewig et al. DOI: 10.1002/eji.201242508 Eur. J. Immunol. 2012. 42: 3116–3125

European Journal of Immunology

A global "imaging" view on systems approaches in immunology



# "Space" is the current frontier in Systems Immunology

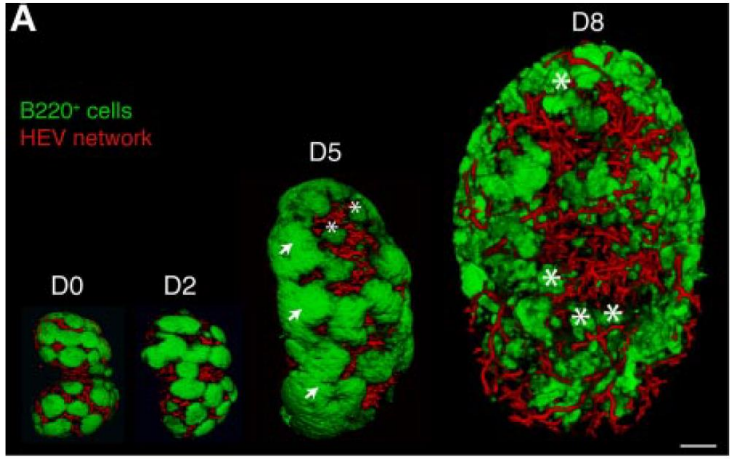
**Analyses of the dynamic cell behavior to predict the immune function in health and disease**

Technologies to observe and understand cells in motion (*Tang et al.*, 2013, EJI):

- Data capturing and processing: new computational tools to deal with the **vast amount** of data generated by imaging

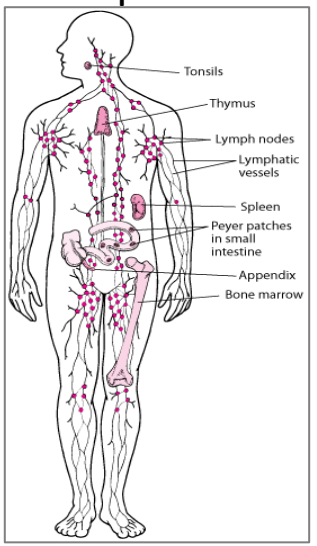
**Capturing the structure-function relationship in a computationally efficient manner is the key to successful systems immunology**

- Requires **anatomically based mathematical models** integrating the interaction processes across multiple scales (multi-physics):




(From: Kumar et al, 2008 EJI)

- **Tissue properties**
- **Blood and lymph flow patterns**
- **Fluid-tissue interactions**
- **Systemic cell re-circulation**
- **Within organs cell migration**



# 3D modelling of the lymph node structure

*Math. Model. Nat. Phenom.*
**Vol. 6, No. 7, 2011, pp. 13-26**
DOI: 10.1051/mmnp/20116702

## Reaction-Diffusion Modelling of Interferon Distribution in Secondary Lymphoid Organs

**G. Bocharov[1*†], A. Danilov[1*†], Yu. Vassilevski[1], G.I. Marchuk[1], V.A. Chereshnev[2] and B. Ludewig[3]**

*Computation* **2015**, *3*, 222-234; doi:10.3390/computation3020222

OPEN ACCESS

*computation*

**ISSN 2079-3197**
www.mdpi.com/journal/computation

*Communication*

## Computational Approach to 3D Modeling of the Lymph Node Geometry

**Alexey Kislitsyn [1,†], Rostislav Savinkov [1,†], Mario Novkovic [2,†], Lucas Onder [2] and Gennady Bocharov [3,*]**

*ISSN 0012-4966, Doklady Biological Sciences, 2011, Vol. 439, pp. 194–196. © Pleiades Publishing, Ltd., 2011.*
*Original Russian Text © G.A. Bocharov, A.A. Danilov, Yu.V. Vassilevski, G.I. Marchuk, V.A. Chereshnev, B. Ludewig, 2011, published in Doklady Akademii Nauk, 2011, Vol. 439, No. 3, pp. 413–415.*

**PHYSIOLOGY**

## Simulation of the Interferon-Mediated Protective Field in Lymphoid Organs with Their Spatial and Functional Organization Taken into Consideration

**G. A. Bocharov[a], A. A. Danilov[a], Yu. V. Vassilevski[a], Academician G. I. Marchuk[a], Academician V. A. Chereshnev[b], and B. Ludewig[c]**

Submitted:

## Data-driven modelling of the FRC network for studying the fluid flow in the conduit system

Rostislav Savinkov[a,b], Alexey Kislitsyn[a,b], Daniel J. Watson[c], Raoul van Loon[c], Igor Sazonov[c], Mario Novkovic[d], Lucas Onder[d], Gennady Bocharov[a,*]

[a] *Institute of Numerical Mathematics of the RAS, Moscow, Russian Federation*
[b] *Lomonosov Moscow State University, Moscow, Russian Federation*
[c] *College of Engineering, Swansea University, Swansea, Wales, U.K.*
[d] *Institute of Immunobiology, Kantonsspital St. Gallen, St. Gallen, Switzerland*

# Collaboration & Support

- Institute of Immunobiology, St. Gallen Hospital:
*Burkhard Ludewig, Jovana Cupovic, Lucas Onder, Mario Novkovic, Philippe Krebs, Tobias Junt*

- Mathematics Department, The University of Manchester:
*Christopher T.H. Baker*

- Mathematics Department, The University of Chester:
*Neville J. Ford*

- Institute of Mathematical Problems in Biology, RAS:
*Tatyana Luzyanina*

- Children's Hospital, Freiburg University:
*Stephan Ehl*

- Infection Biology Laboratory, Universitat Pompeu Fabra, Barcelona, Spain:
*Andreas Meyerhans*

**Support:**

- **Russian Science Foundation**
- **Program of the Russian Academy of Sciences "Basic Research for Medicine"**
- **Russian Foundation of Basic Research**
- **Swiss National Science Foundation, the 6th Framework Program of the EC (AIDS-CoVAC)**

Thank you very much
for your attention!