Modeling & Simulation (Computational Immunology)

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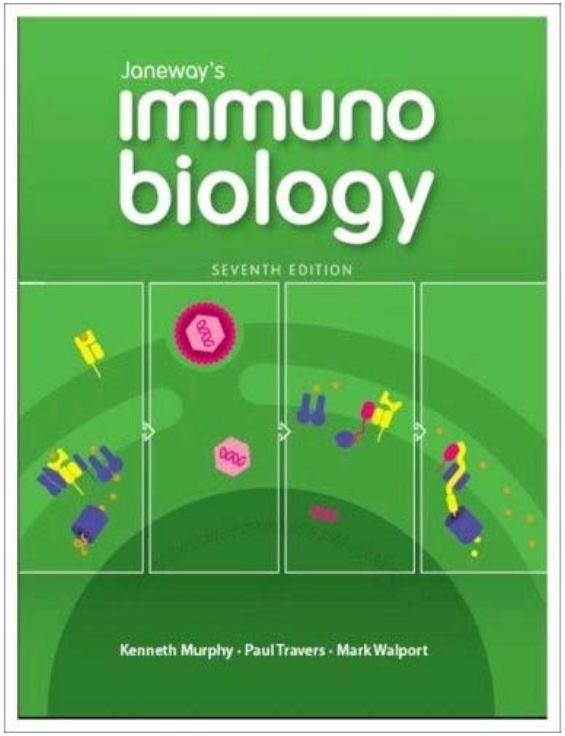
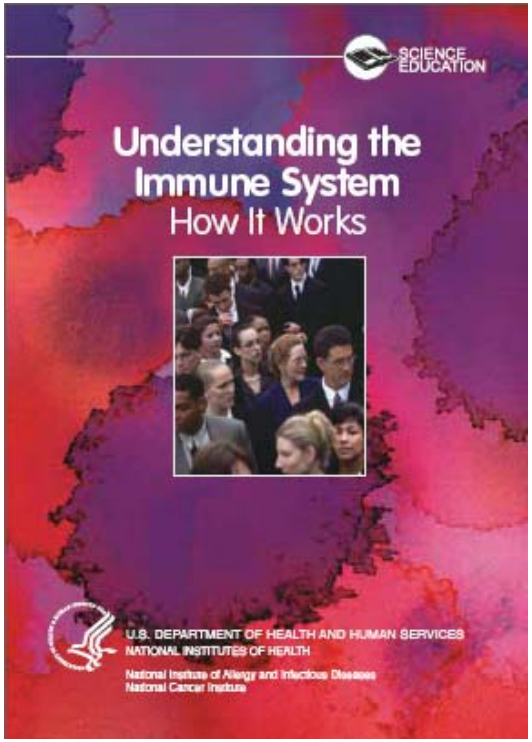
Modeling the immune response

If you want more information on the biology…





Janeway's Immunobiology

- or -

http://www3.niaid.nih.gov/topics/immuneSystem

The Immune System

Science that began with Jenner in 1796

- A network of cells, tissues, and organs that work together to defend the body against attacks by "foreign" invaders.
  - Primarily microbes (germs)—tiny, infection-causing organisms such as bacteria, viruses, parasites, and fungi.
- Provides basis for vaccines (e.g., flu shot)
- Implicated in disease:
  - Autoimmune (Lupus, MS, Rheumatoid Arthritis)
  - Sepsis, Cancer

Understanding will lead to better diagnostics and therapies

Immune System Reacts against Antigens

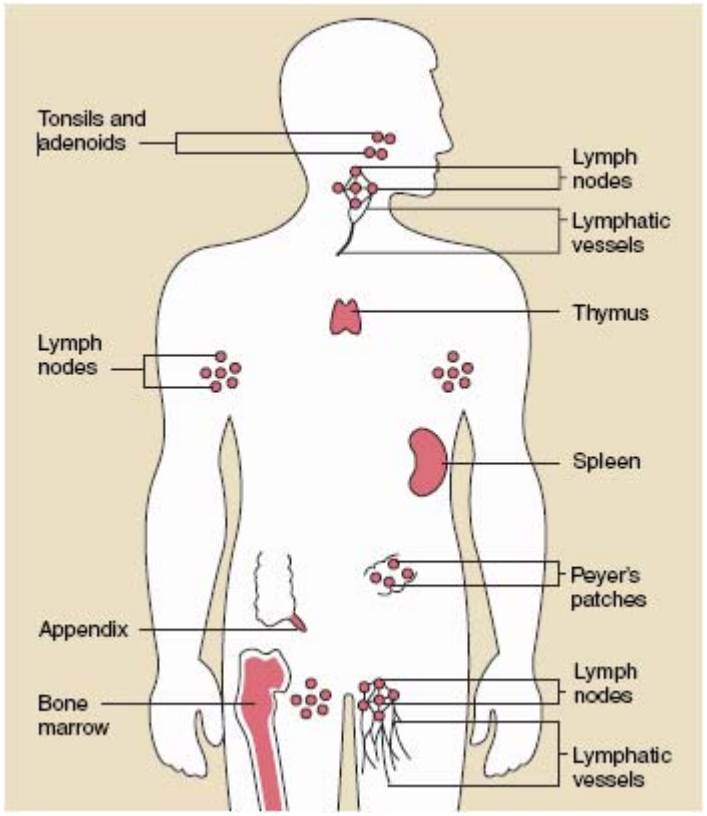
Differentiates between our own cells (self) and foreign cells (non-self)

- **Antigen**: anything that triggers immune response
  - Can be (part of) microbe such as virus. Tissues/cells from another person can also carry non-self markers and act as antigens.
- Mistaking self for non-self results in autoimmune disease
  - E.g., some forms of arthritis and diabetes
- May respond to harmless foreign substance (ragweed pollen)
  - Produces allergy (this antigen is called an allergen)

Understanding will lead to better diagnostics and therapies

A Spatially Distributed System

The organs of the immune system are positioned throughout the body



Called “lymphoid organs”, since home to lymphocytes
(small white blood cells that are key players in the immune system)

Why Model the Immune System?

Experiments provide only a static window onto the real dynamics of immunity

- Immune response involves the collective and coordinated response of $\approx 10^{12}$ cells and molecules
- Distributed throughout body
  - blood, lymph nodes, spleen, thymus, bone marrow, etc.
- Interactions involve feedback loops and non-linear dynamics
- Experiments often require artificial constructs
- High variability observed in experimental results

What is a mathematical model?

"Essentially, all models are wrong, but some are useful."
-George Box, University of Wisconsin

A mathematical model uses mathematical language to describe a system. It consists of a collection of variables and rules governing their values.

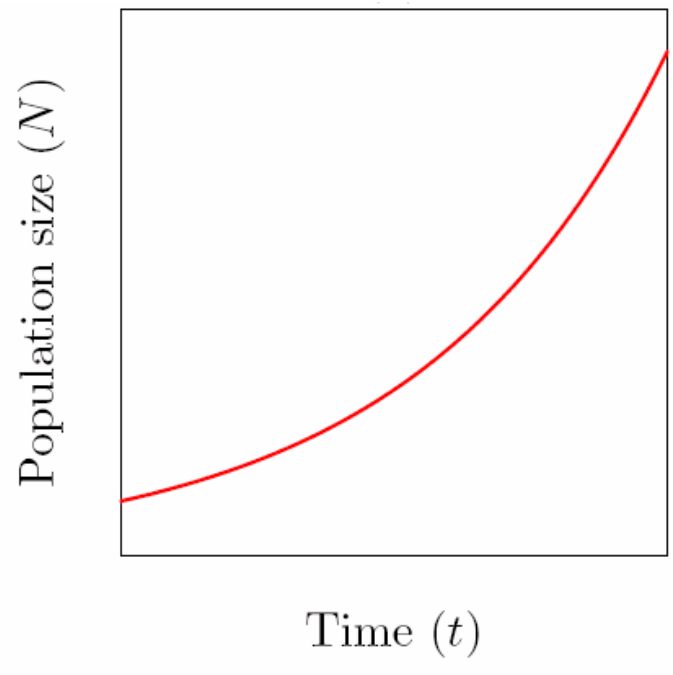
Models are **based on assumptions** inspired by observing some real phenomena in the hope that the model behavior resembles the real behavior.

Mathematical modeling is process of constructing, testing, and improving mathematical models

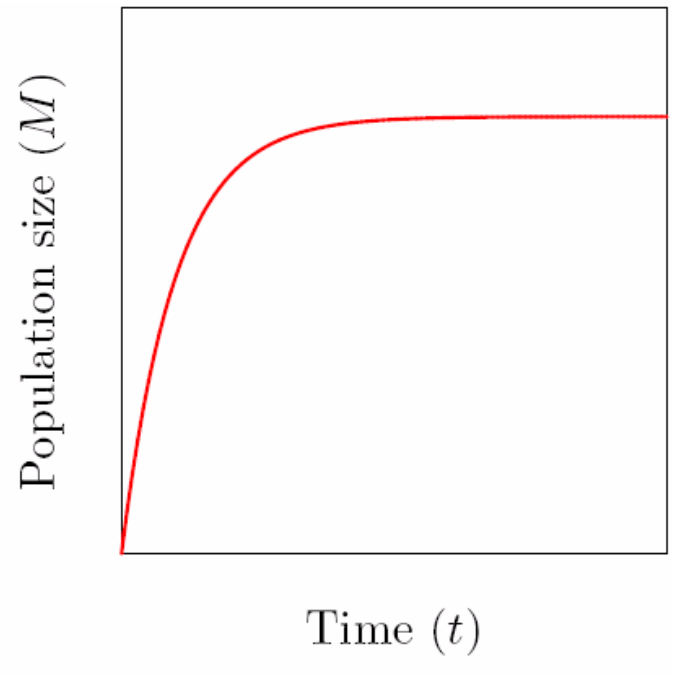
What is a dynamic model?

A set of equations written to describe behavior of system over time

Exponential growth of virus



White blood cells produced by bone marrow

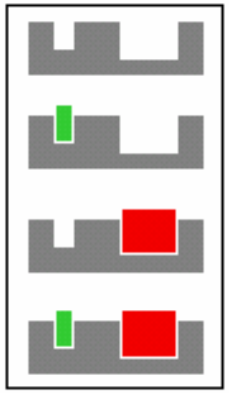


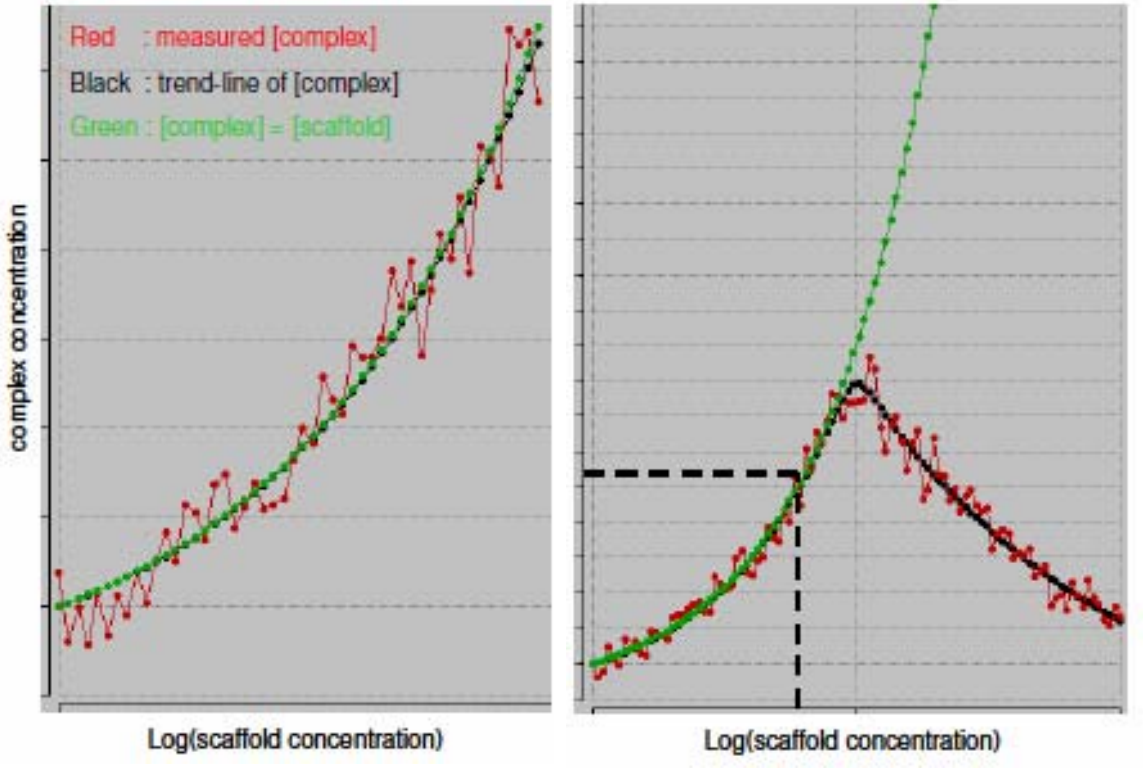
Equations are usually simulated to study system behavior

Mechanistic modeling vs. curve fitting

Only mechanistically correct models extrapolate reliably

Gene transcriptionally activated by complex of three proteins, and one acts as scaffold





Figures from: Hamid Bolouri

Interpolation (i.e. within sample predictions) vs.
Extrapolation (i.e. out of sample predictions, as in the right panel)

Types of Dynamic Models

Choosing the type of model is an important first step

- **Continuous**: time or state variables (often called 'density')
  - Ordinary differential equations
- **Discrete**: time or state variables
  - assume a small set of qualitative states e.g. active or inactive
  - changes in state are given by discrete (logical) rules

- **Deterministic**: no randomness is involved in the development of future states of the system
  - Given model structure, parameter values, and initial conditions, there is no variation in output
- **Stochastic**: the next state of is not fully determined by the previous state – probability is involved
  - can take into account the fluctuations in mRNA/protein/cell numbers and external noise

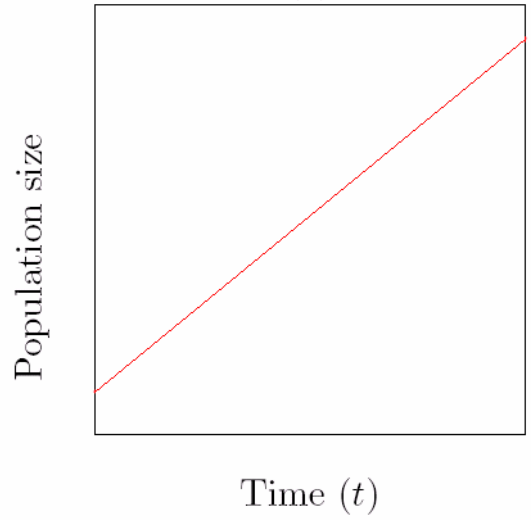
Spatial structure can also important

Ordinary Differential Equations (ODEs)

Continuous and Deterministic

Production rate

$$\frac{dB}{dt} = p \quad \Rightarrow \quad B(t) = B(0) + pt \quad \Rightarrow$$



Change in number of B cells per time

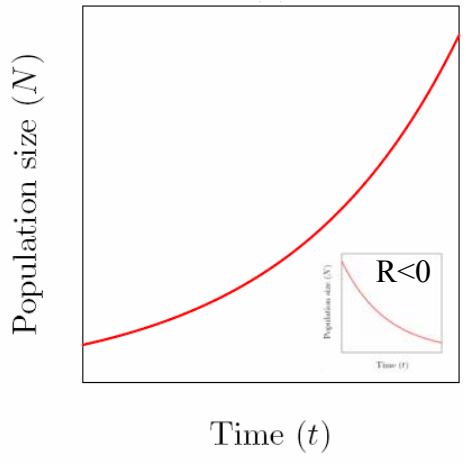
$$\frac{dB}{dt} = \lim_{t \to 0} \frac{B(t + \Delta t) - B(t)}{\Delta t}$$

Most models used in practice not solvable → **simulate**

Exponential growth (and decay)

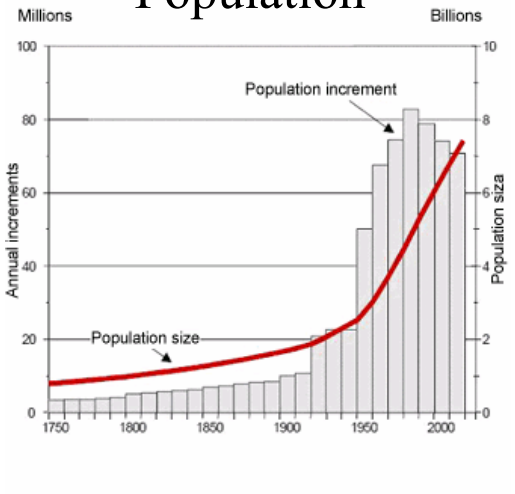
Continuous and Deterministic

$$\frac{dB}{dt} = rB$$



$$N(t) = N(0)e^{rt}$$

Human Population



How long for population to double?

$$2N(0) = N(0)\mathrm{e}^{rt}$$

$$\ln 2 = rt$$

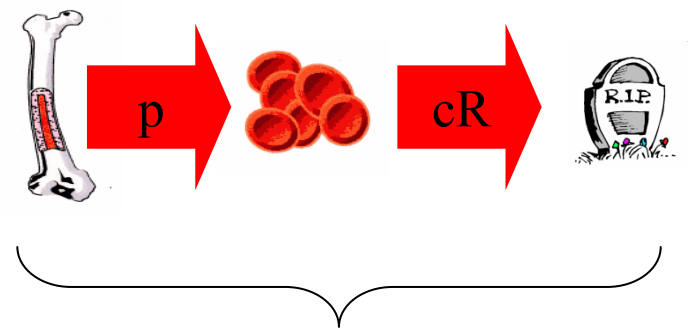
$$t = \ln[2]/r$$

Doubling time: time for population to reach 2x initial value
Half-life: time for population to reach 50% of initial value

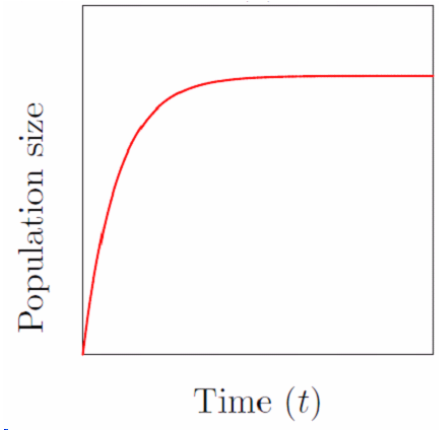
Steady-state

Population sizes remain constant at steady-state

Red Blood Cell production



$$\frac{dR}{dt} = p - cR$$



$$0 = p - cR$$

$$R = p/c$$

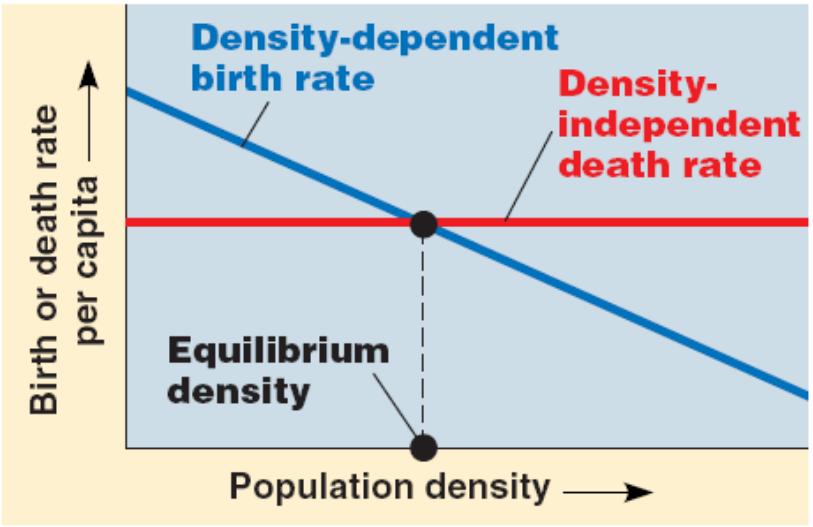
How many cells at steady-state?

Solve for steady state by setting derivatives equal to zero

Density dependence

Birth (or death) rate may depend on population size

$$\frac{dN}{dt} = bN \qquad -dN$$



$$N = K\left(1 - \frac{d}{b}\right)$$

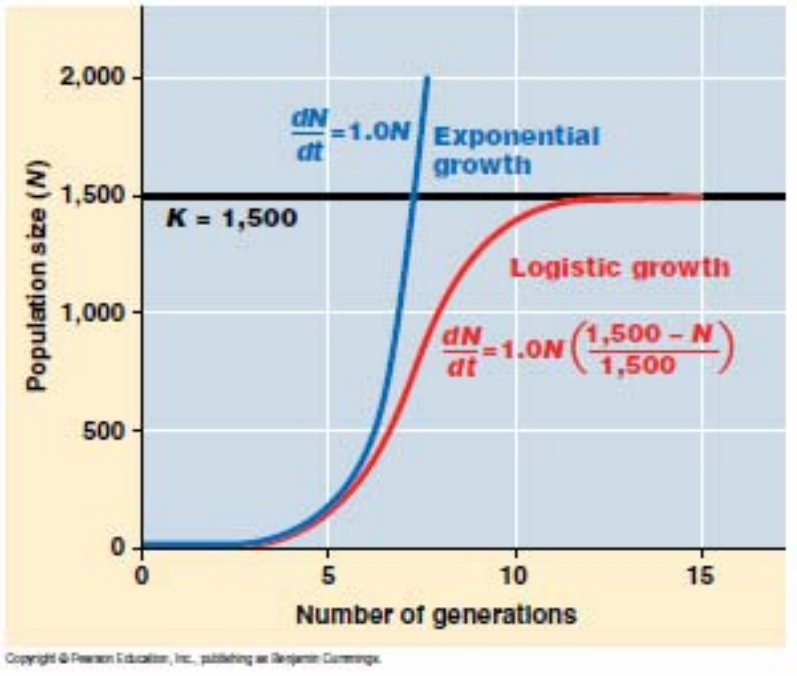
Stable steady-state: small perturbations return to same state

Logistic Model (S-shaped curve)

Includes density-dependent birth and death (r = b - d)

$$\frac{dN}{dt} = rN\left(1-\frac{N}{K}\right)$$

Initial stage of growth is approximately exponential; growth slows as saturation begins, and then stops at maturity.

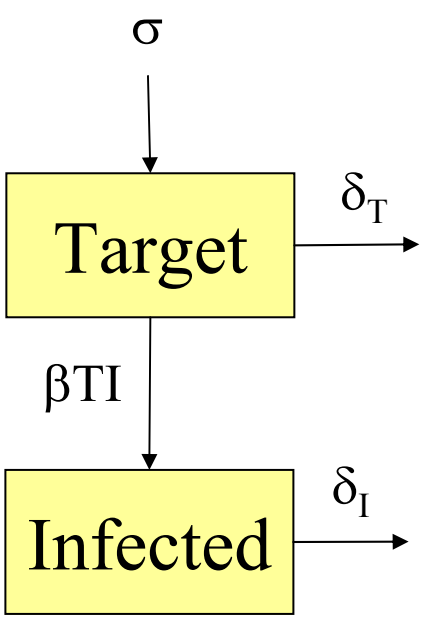


Is this a "model" if can't explain why birth/death rate *r~N/K?*
phenomenological model

Carrying capacity (K): population size that can be sustained indefinitely

Modeling Interactions

Law of mass action: encounters between elements occur randomly



Target cells (T) become infected cells (I)

Target $\frac{dT}{dt} = \sigma - \delta_T T - \beta T I$

Infected $\frac{dI}{dt} = \beta T I - \delta_I I$

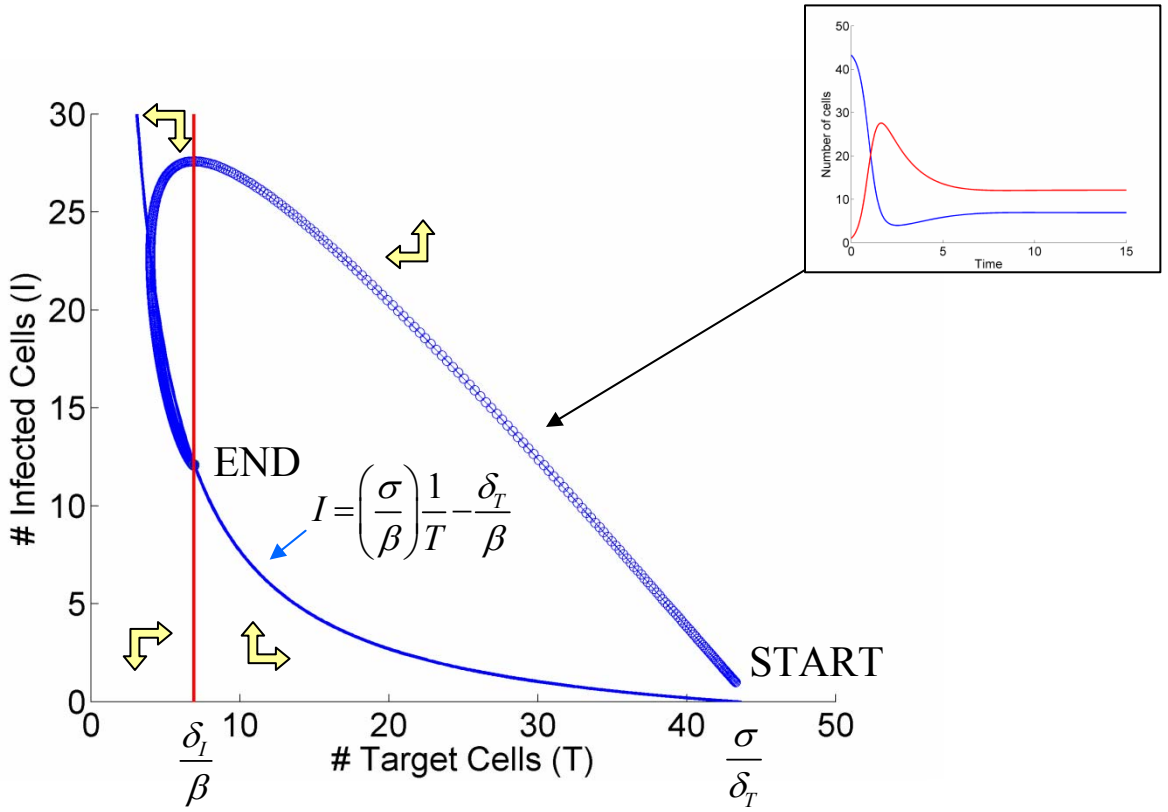
The law of mass action is also called the mean-field assumption

Phase Plane Analysis

Nullclines plot where derivatives are zero (cross at steady-state)

Target $\frac{dT}{dt} = \sigma - \delta_T T - \beta T I$

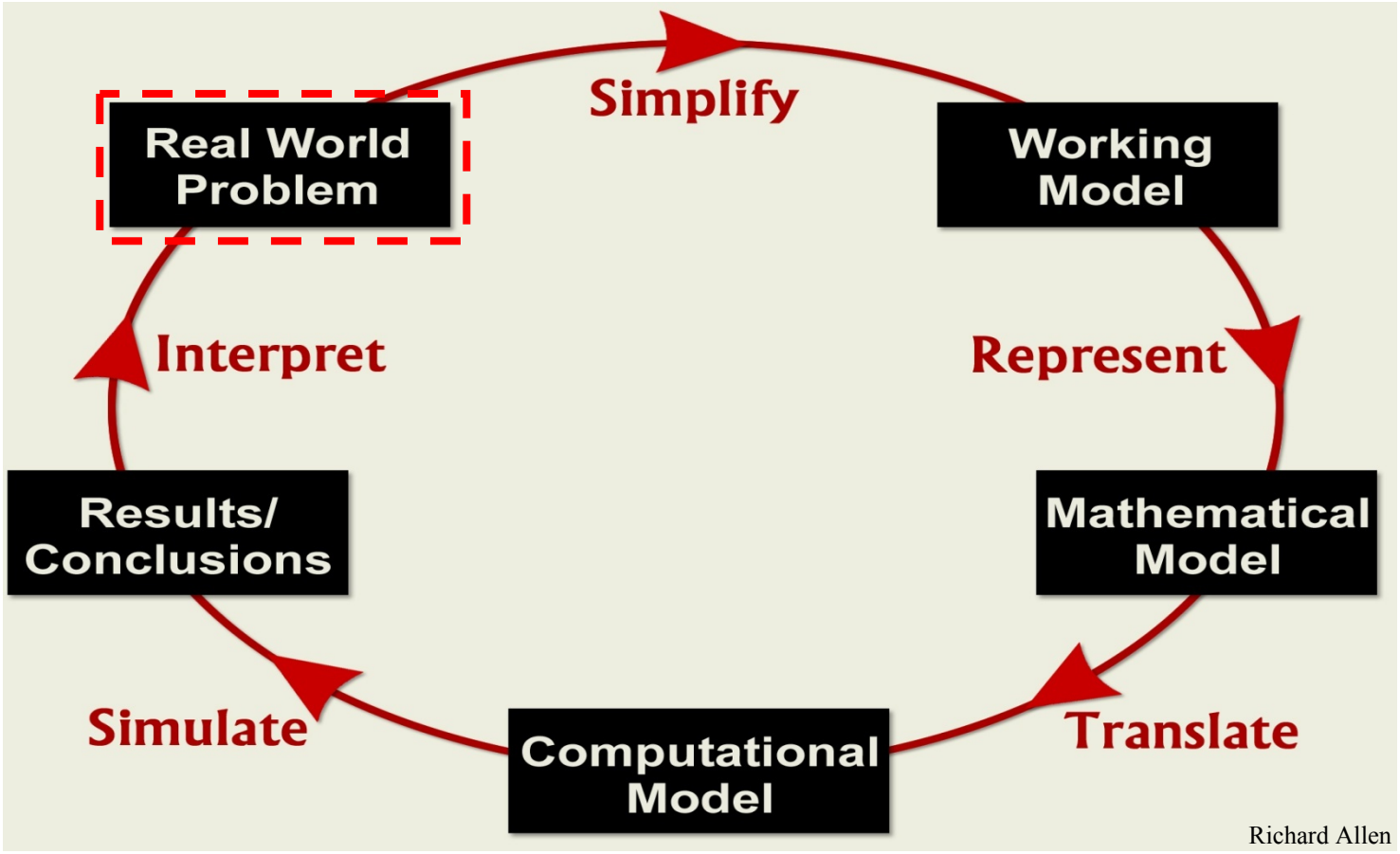
Infected $\frac{dI}{dt} = \beta T I - \delta_I I$



Phase portraits plot typical trajectories in the state space

The Modeling Process

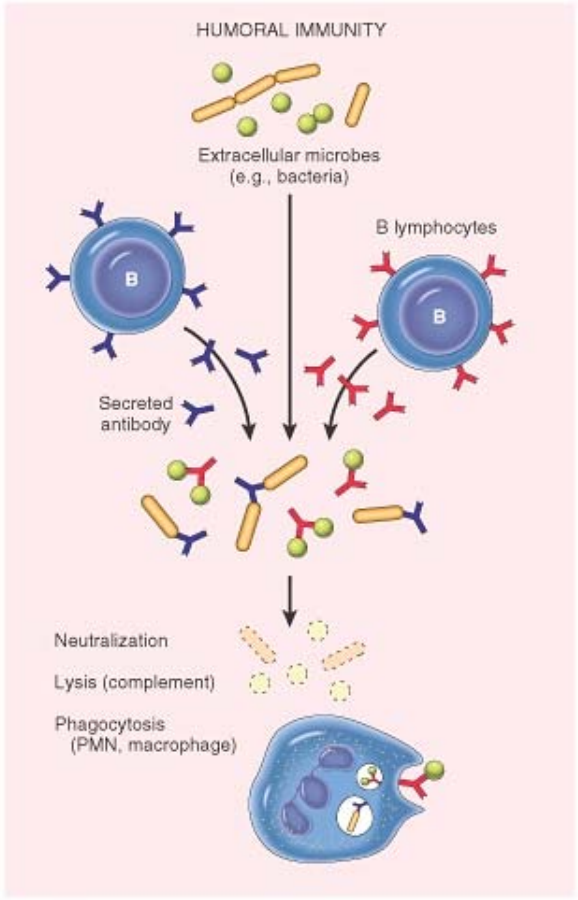
Starts with a specific scientific question



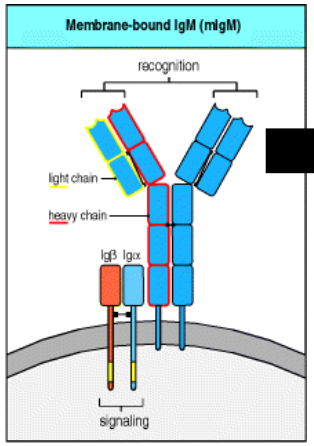
Model should produce predictions that suggest new experiments

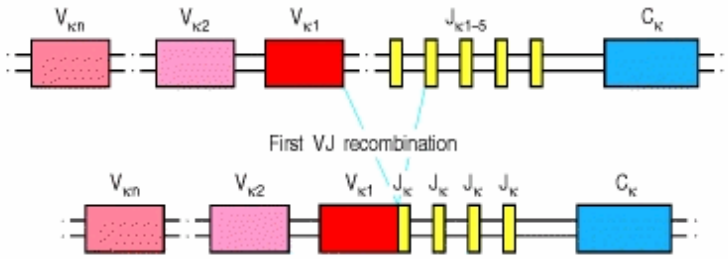
B cells "recognize" antigens thorough antibody receptor

First phase of diversification occurs in bone marrow while cell is maturing



Rearrangement generates diverse receptors:





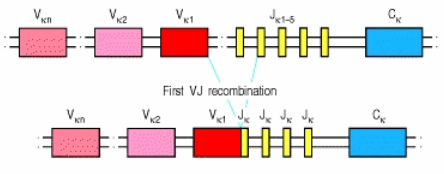
Number of functional gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	40	30	65
Diversity (D)	0	0	27
Joining (J)	5	4	6

Second phase of diversification (by somatic hypermutation) follows activation

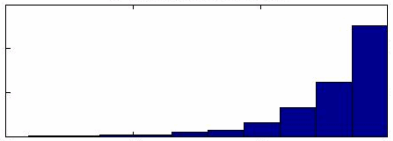
The Modeling Process: V(D)J Recombination

How are VJ segments chosen to generate an Ig light chain?



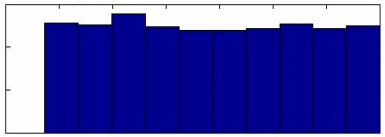
Hypothesis: VJ chosen randomly with equal probability

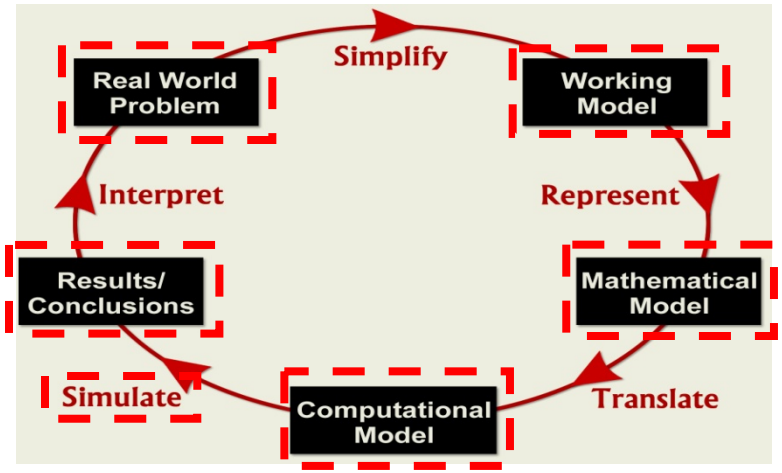
Observed V usage



?

Predicted V usage





$Pr[V_n] = 1/N$; $P[J_m] = 1/M$

randInteger(N) = floor(N * rand()) + 1

Model should produce predictions that suggest new experiments

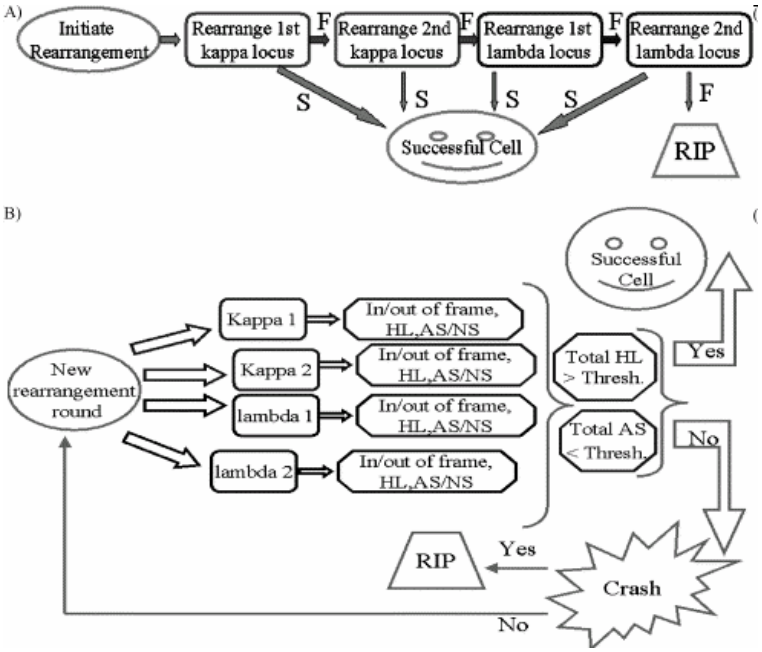
The Modeling Process: V(D)J Recombination

Extend rearrangement model to cover different alleles

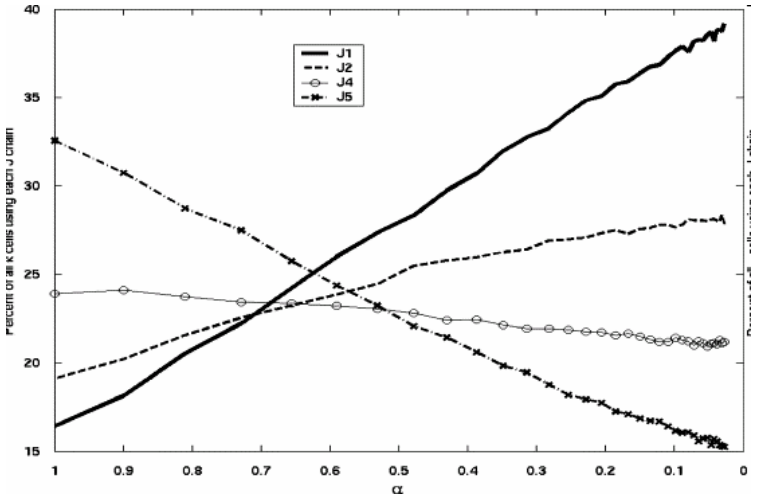
seminars in IMMUNOLOGY, Vol. 14, 2002: pp. 169–190
doi:10.1016/S1044–5323(02)00041-6, available online at http://www.idealibrary.com on IDEAL®

Analysis of B cell receptor production and rearrangement Part I. Light chain rearrangement☆

Yoram Louzoun[a,], Tzivia Friedman[a], Eline Luning Prak[b], Sam Litwin[c] and Martin Weigert[a]*



A probabilistic model of allelic exclusion fails to explain the status of receptor genes and the receptor phenotype of most B cells… we have revived the purely probabilistic approach in a model that now includes receptor editing and allows for some multi-receptor B cells. **We find that this model can explain the observed properties of B cells when the frequency of self-reactive B cells is high…**



Alpha reflects degree of sequentiality for Jκ rearrrangement.

Revised model of rearrangement suggest new experiments

Things to ask before any modeling study

Frank Tobin (2009): Modeling is Powerful BUT Has Far to Go

BioITWorld.com

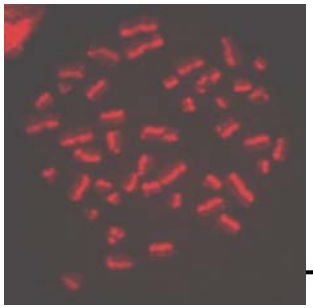
1. Why do you want to do modeling?
2. How will you know if you succeed?
3. What will you do with the model once you have it? For what decisions will it be used or what confirmatory experiments will get performed?

Beware motivation: “We want to create a model of process X…”

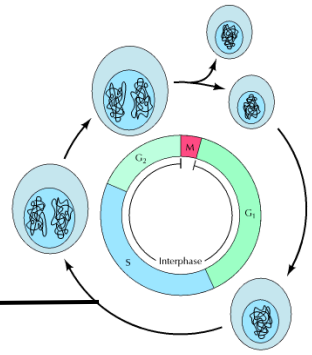
Understanding cell proliferation and death

BrdU (thymidine analog) incorporated into cell DNA during S-phase

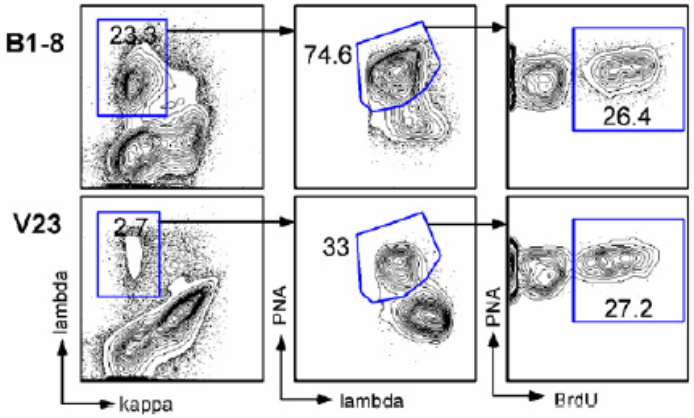
Flow cytometry to quantify antigen-specific germinal center B cells…

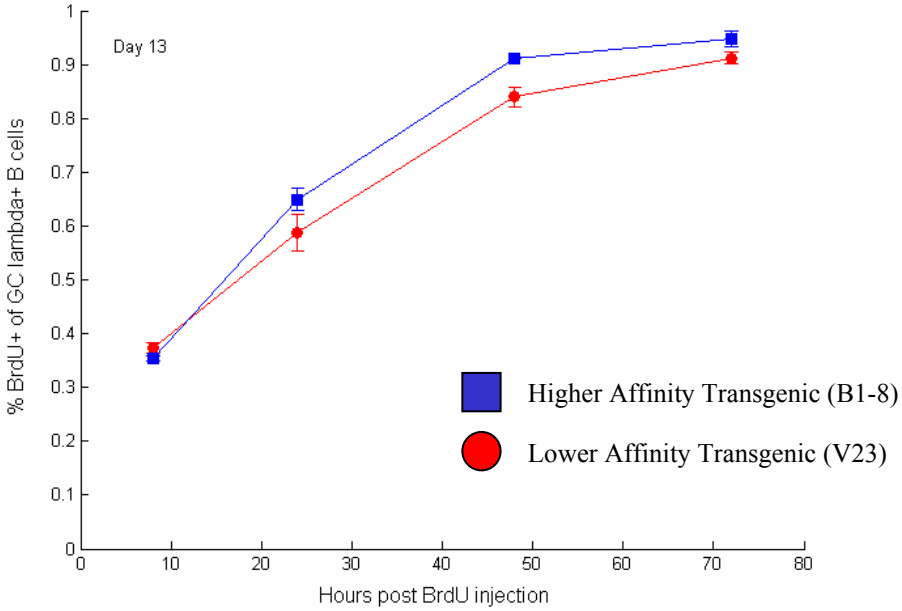


BrdU incorporated during S phase



science.csustan.edu/confocal/Images/SCE/index.SCE.htm





Labeling curves look similar – suggests same proliferation rate?

Understanding cell proliferation and death

At steady-state, rate at which the fraction of BrdU labeled cells increases is indicative of the sum of the per cell proliferation and death rates

Quantification of Cell Turnover Kinetics Using 5-Bromo-2′-deoxyuridine[1]

Sebastian Bonhoeffer,* Hiroshi Mohri,† David Ho,† and Alan S. Perelson[2]*‡

The Journal of Immunology, 2000, 164: 5049–5054.

Rapid Turnover of T Lymphocytes in SIV-Infected Rhesus Macaques

Hiroshi Mohri, Sebastian Bonhoeffer, Simon Monard, Alan S. Perelson, David D. Ho*

www.sciencemag.org • SCIENCE • VOL. 279 • 20 FEBRUARY 1998

International Immunology, Vol. 15, No. 3, pp. 301–312
doi:10.1093/intimm/dxg025, available online at www.intimm.oupjournals.org

Asynchronous differentiation models explain bone marrow labeling kinetics and predict reflux between the pre- and immature B cell pools

Ramit Mehr[1], Gitit Shahaf[1], Alex Sah[2] and Michael Cancro[2]

The Journal of Immunology

Taking Advantage: High-Affinity B Cells in the Germinal Center Have Lower Death Rates, but Similar Rates of Division, Compared to Low-Affinity Cells[1]

Shannon M. Anderson,* Ashraf Khalil,† Mohamed Uduman,‡§ Uri Hershberg,*†§ Yoram Louzoun,¶ Ann M. Haberman,† Steven H. Kleinstein,‡§ and Mark J. Shlomchik[2]*†

Oncogene (2005) 24, 7514–7523
© 2005 Nature Publishing Group All rights reserved 0950-9232/05 $30.00
www.nature.com/onc

Reduced cell turnover in lymphocytic monkeys infected by human T-lymphotropic virus type 1

Christophe Debacq[1,5], Jean-Michel Héraud[2,5], Becca Asquith[3], Charles Bangham[3], Fabrice Merien[2], Vincent Moules[4], Franck Mortreux[4], Eric Wattel[4], Arsène Burny[1], Richard Kettmann[1], Mirdad Kazanji[2] and Luc Willems*[,1]

Models of BrdU incorporation integral part of many studies

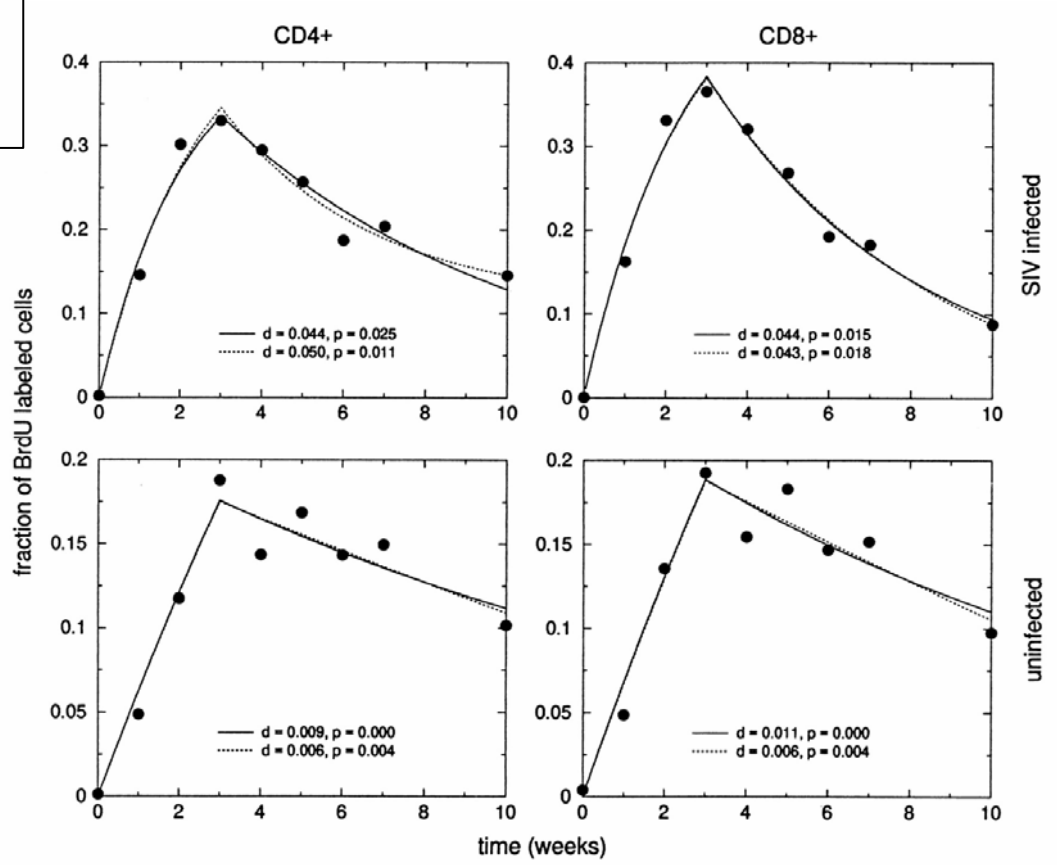
BrdU labeling of CD4+ and CD8+ T lymphocytes

SIV-infected and an uninfected macaque. Data are from Mohri et al., Science (1998)

Rapid Turnover of T Lymphocytes in SIV-Infected Rhesus Macaques

Hiroshi Mohri, Sebastian Bonhoeffer, Simon Monard, Alan S. Perelson, David D. Ho*

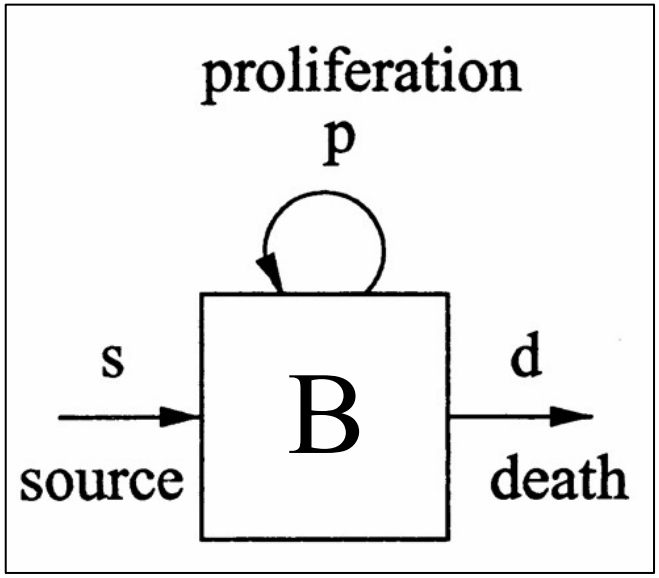
www.sciencemag.org • SCIENCE • VOL. 279 • 20 FEBRUARY 1998



Is there a difference in cell turnover?

Model of BrdU Labeling

Start with a basic model of cell population dynamics…



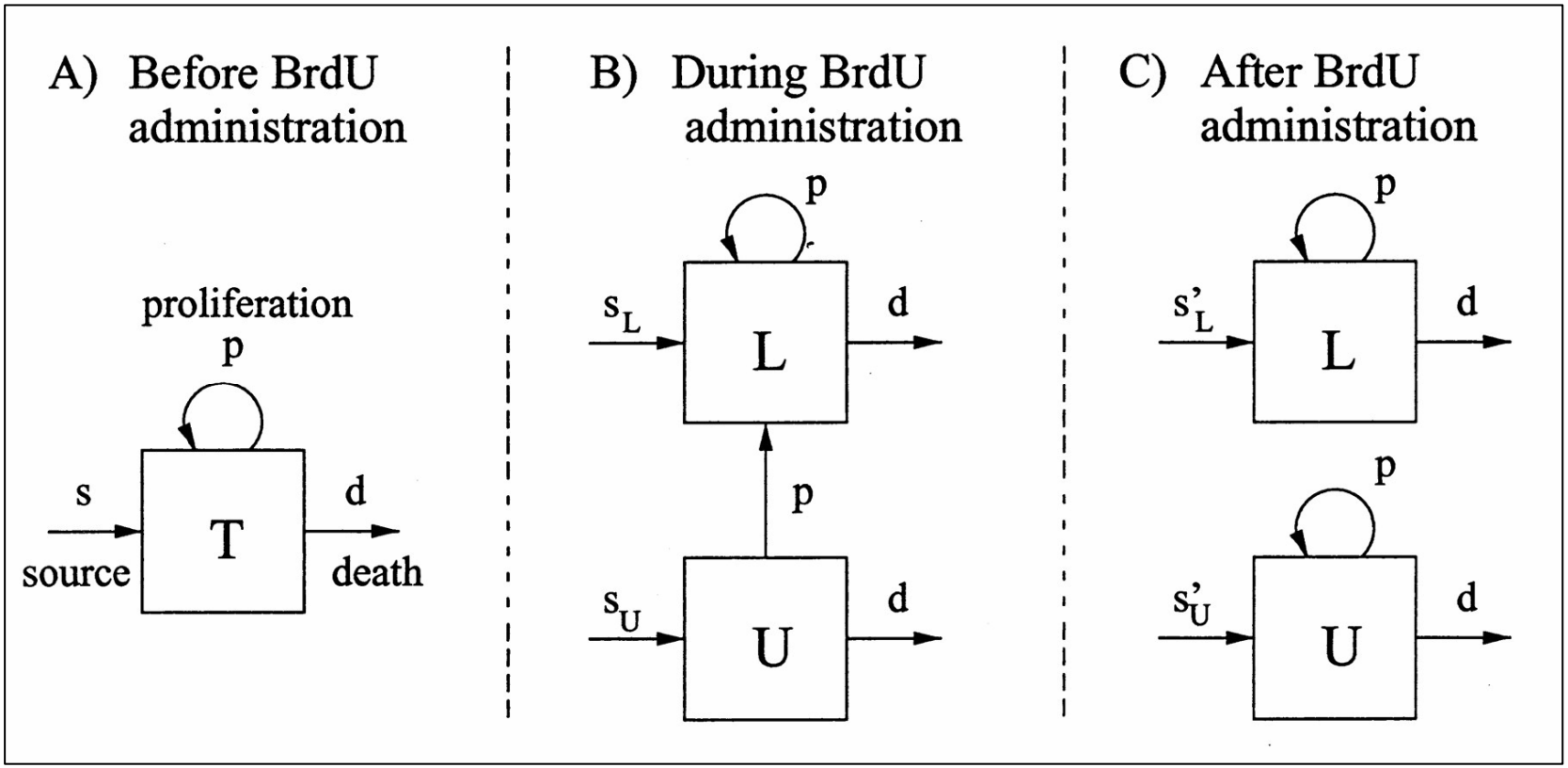
Rate of change in B cell population

$$\frac{dB}{dt} = s + pB - dB$$

Often can often assume population in steady-state (i.e., constant)

Model of BrdU Labeling

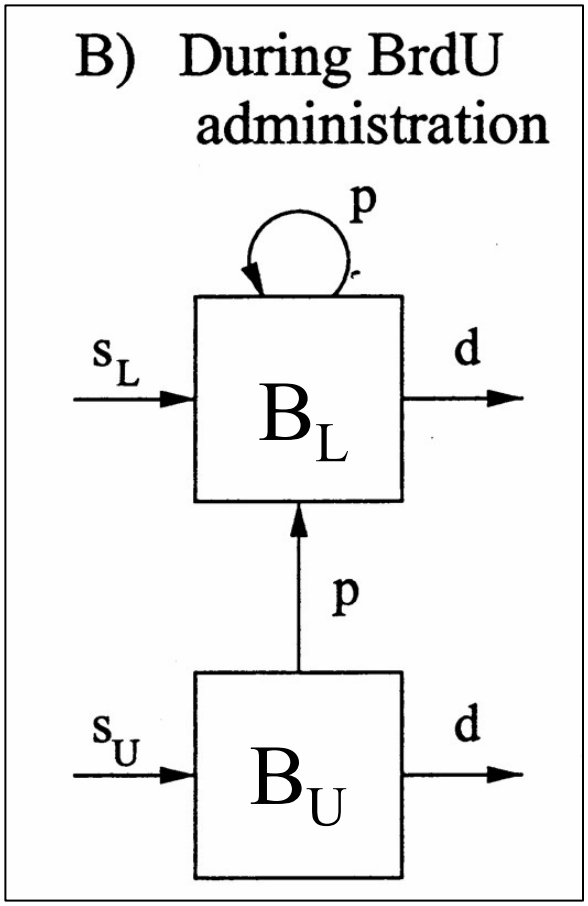
Many experiments stop administering label after some time



We can express these as sets of ordinary differential equations

Model of BrdU Labeling

Split the B cell population into Labeled (B_L) and Unlabeled (B_U) subsets



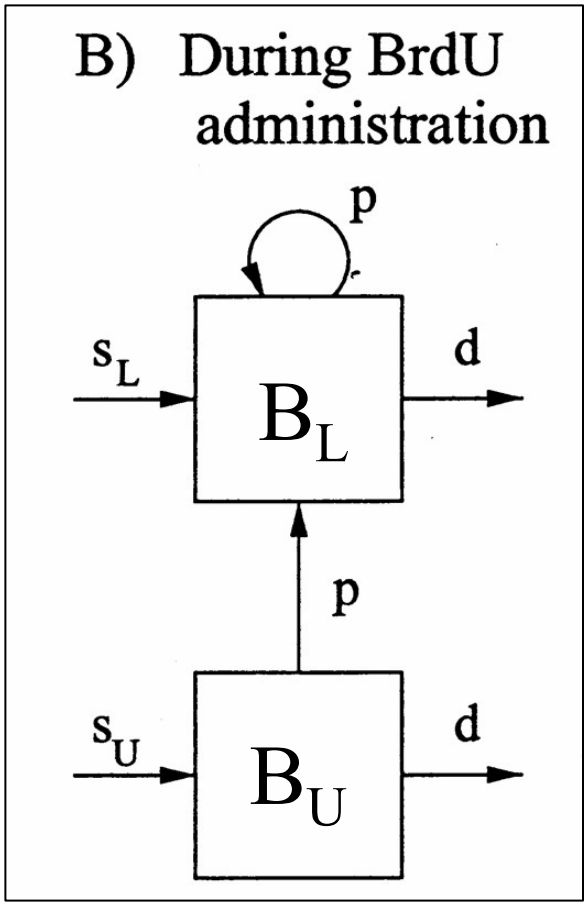
$$\frac{dB_U}{dt} = s_u - pB_U + dB_U$$

$$\frac{dB_L}{dt} = s_l + 2pB_U + pB_L - dB_L$$

Solve or simulate these equations over time

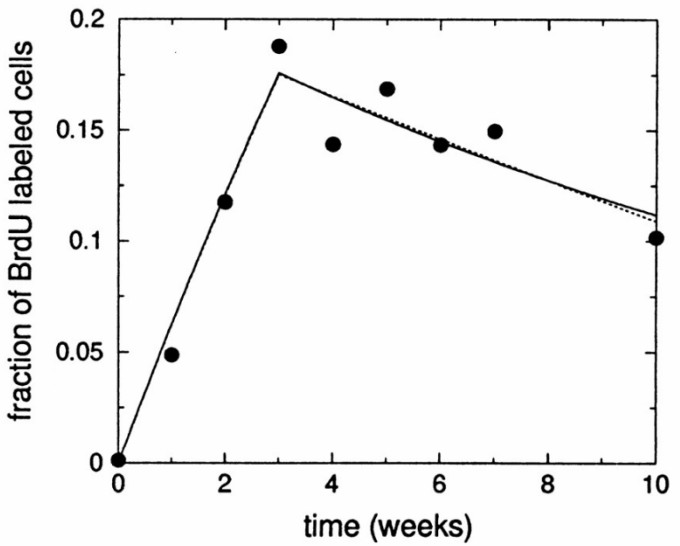
Model of BrdU Labeling

Many experiments stop administering label after some time



$$f_L(t) = A_1(1 - e^{-(d+p)t})$$

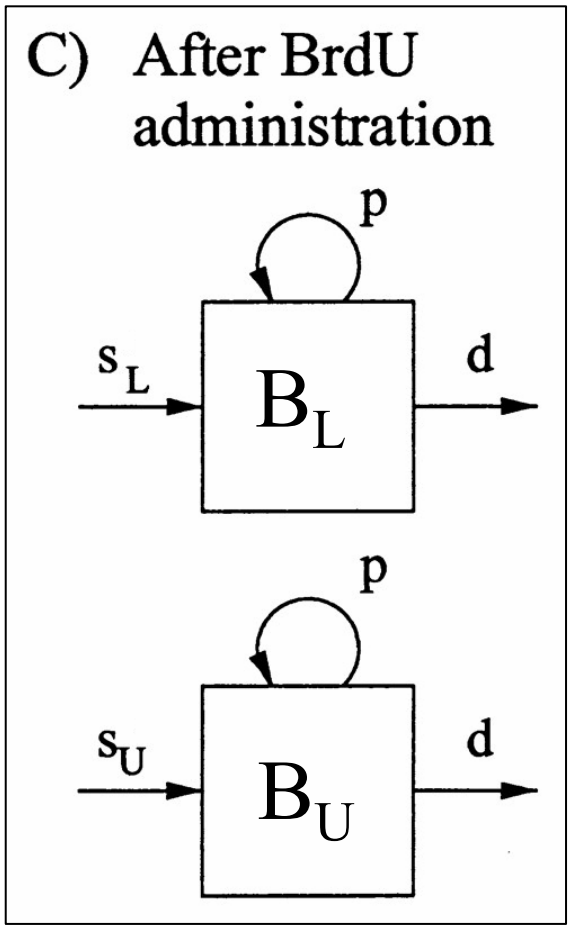
$$A_1 = 1 - \frac{s_U}{(s_U + s_L)} \times \frac{(d-p)}{(d+p)}$$



Labeling curve reflects both proliferation AND death

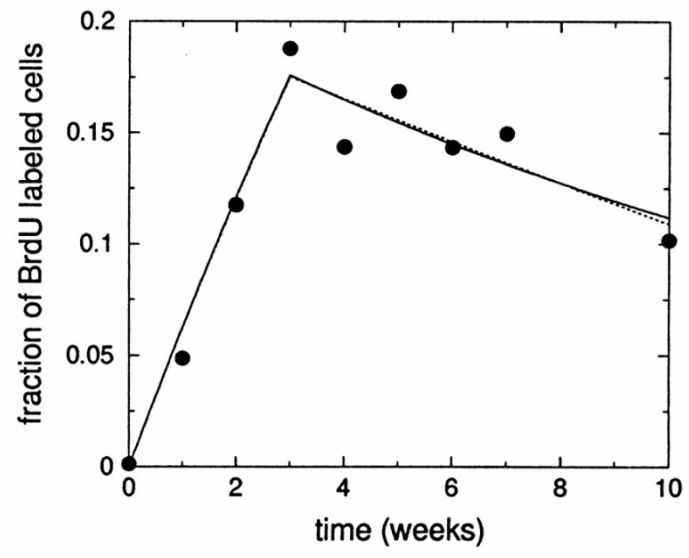
Model of BrdU DE-Labeling

Stop administering label after some time (t_e)



$$f_L(t) = A_2 + A_3 e^{-(d-p)(t-t_e)})$$

$$A_2 = \frac{s_L}{(s_U + s_L)}, A_3 = f_L(t_e) - A_2$$

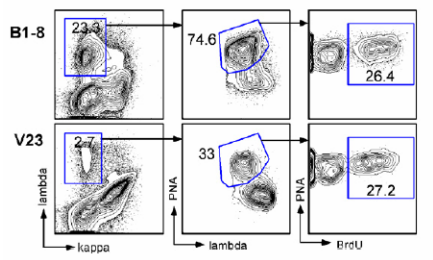


Can estimate proliferation AND death

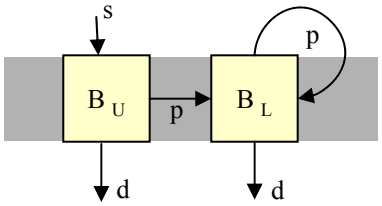
Interaction of Computation & Experiment

Compare simulation and experiment using least-squares objective

Experimental Observations



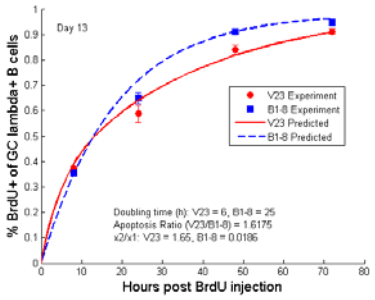
Computational Model



Least-squares objective function

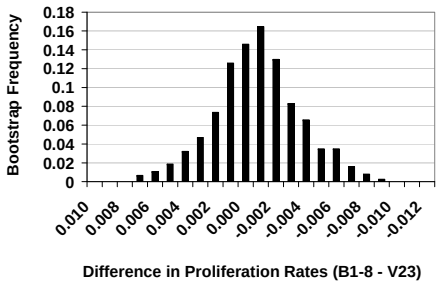
$$E = \sum_i \frac{(y_i - \hat{y}_i)^2}{VAR(y_i)}$$

Fit Model to Data



New Experiments

Model Predictions



Bootstrapping Confidence Intervals

Continuous cycle of modeling and experimentation

For more information…

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PLoS COMPUTATIONAL BIOLOGY

Message from ISCB

Getting Started in Computational Immunology

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Feel free to email me with any questions!

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