# Modeling & Simulation (Computational Immunology)


**Steven H. Kleinstein**


Department of Pathology
Yale University School of Medicine

steven.kleinstein@yale.edu


March 29, 2010

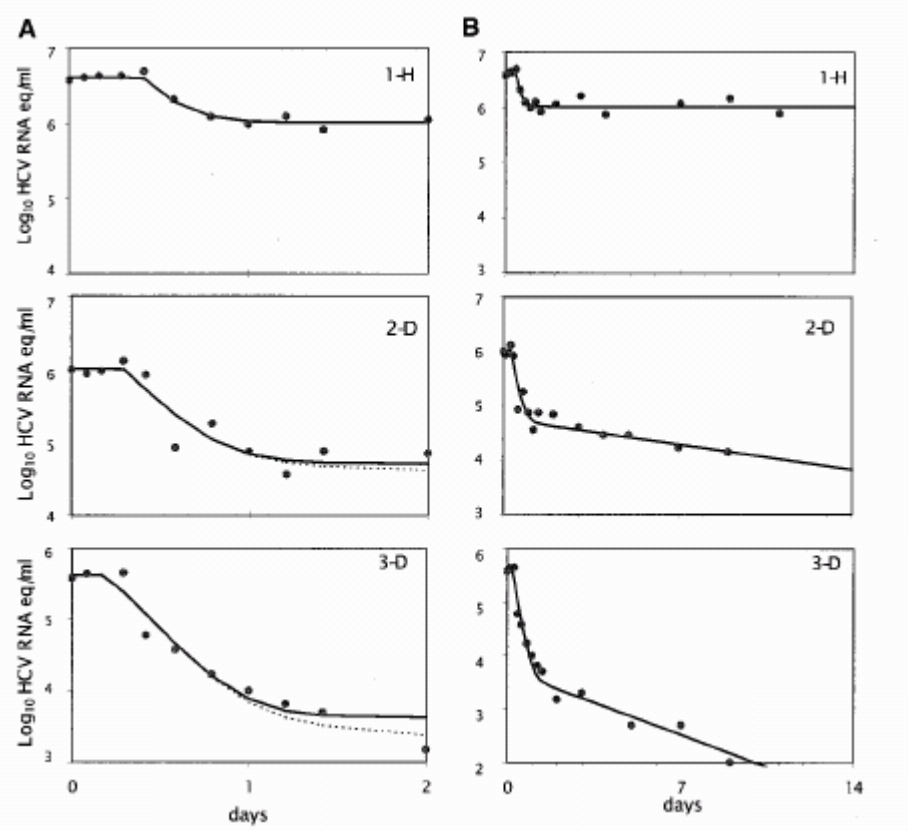
# Hepatitis C Viral Dynamics and Interferon-α Therapy

Modeling 23 patients during 14 days of therapy (daily doses)

**Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon-α Therapy**

Avidan U. Neumann,*† Nancy P. Lam,*‡ Harel Dahari, David R. Gretch, Thelma E. Wiley, Thomas J. Layden, Alan S. Perelson

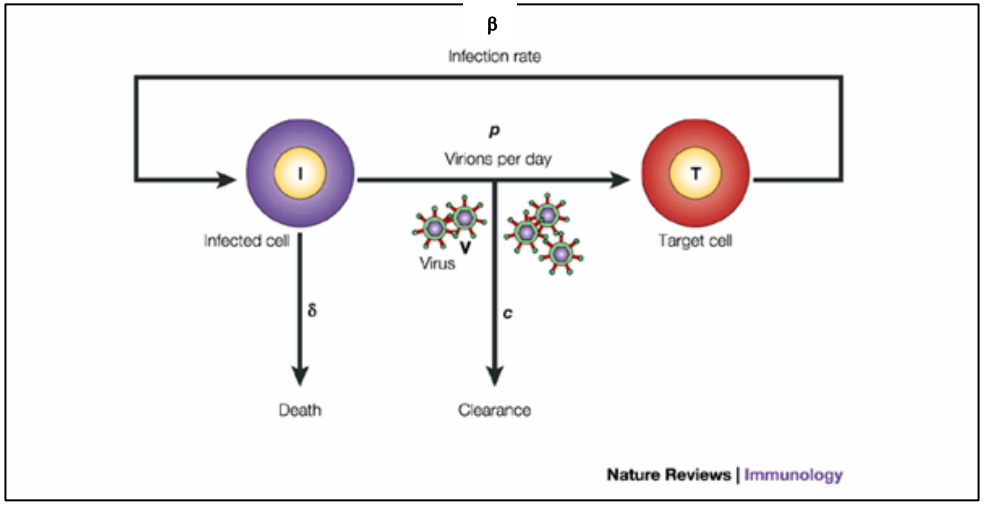
SCIENCE VOL 282 2 OCTOBER 1998




Short delay followed by biphasic decline in viral load

# Model of Hepatitis C Viral Dynamics

Includes virus along with target (T) and infected (I) cells




Target Cells $dT/dt = s - dT$ ? (1)

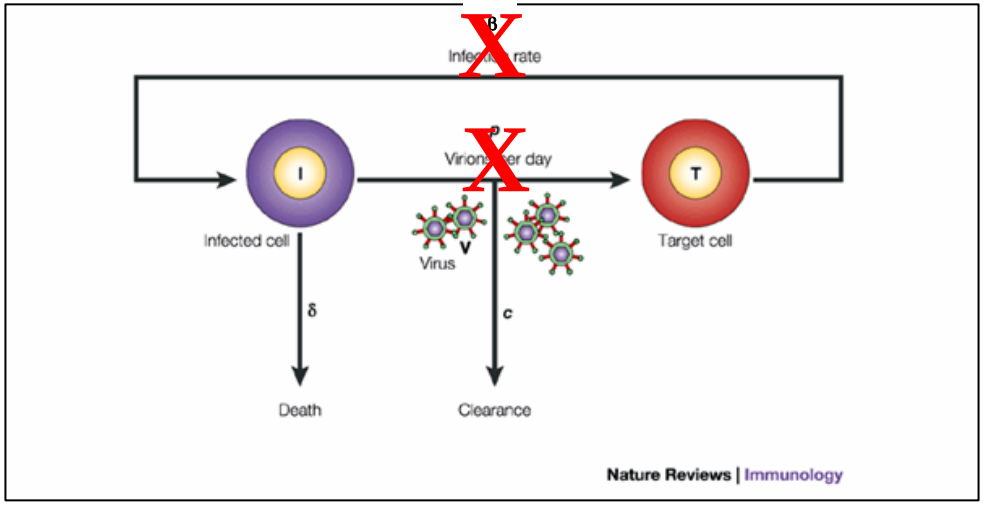
Infected Cells $dI/dt =$ ? $- \delta I$ (2)

Virus (HCV RNA) $dV/dt = pI - cV$ (3)

Before therapy, virus load is approximately constant

# Model of Interferon-α Therapy

Includes virus along with target (T) and infected (I) cells




Target Cells $$dT/dt = s - dT - \beta VT \quad (1)$$

Infected Cells $$dI/dt = \beta VT - \delta I \quad (2)$$

Virus (HCV RNA) $$dV/dt = pI - cV \quad (3)$$

Therapy can reduce the rate of infection, or production of virions

# Hepatitis C Viral Dynamics and Interferon-α Therapy

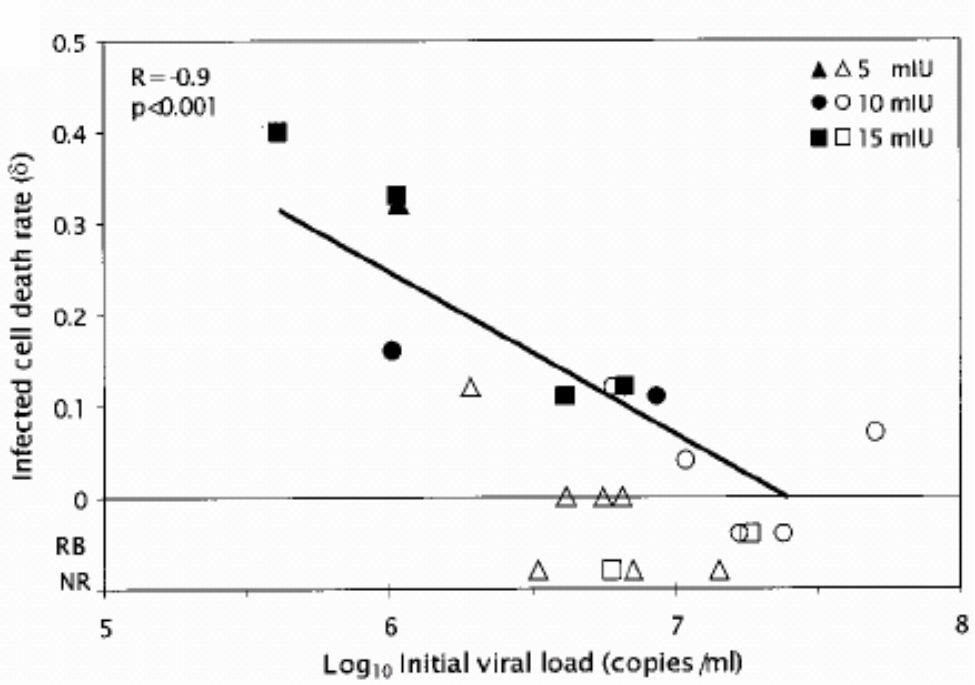
## Modeling 23 patients during 14 days of therapy (daily doses)

| Regimen | Patient | Initial VL ($10^6$ copies per milliliter) | Delay (hours) | Virion clearance ($c$) (1/day) | ± error | Efficacy ($\varepsilon$) Percent | ± error | Infected cell death ($\delta$) (1/day) | ± error | Production ($10^9$ copies per day) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A | 5.6 | 8 | 5.9 | 1.1 | 79 | 4.0% | 0 | 0.01 | 495 |
| 1 | B | 1.9 | 8 | 6.4 | 1.8 | 75 | 7.0% | 0.12 | 0.02 | 290 |
| 1 | C | 14.2 | NR | NR | | NR | | NR | | NR |
| 1 | D | 7.1 | NR | NR | | NR | | NR | | NR |
| 1 | E | 1.1 | 11 | 7.0 | 0.6 | 86 | 0.1% | 0.32 | 0.04 | 125 |
| 1 | F | 6.5 | 7 | 5.0 | 0.8 | 89 | 8.0% | 0 | 0.01 | 601 |
| 1 | G | 3.3 | NR | NR | | NR | | NR | | NR |
| 1 | H | 4.1 | 10 | 6.9 | 0.2 | 75 | 1.0% | 0 | 0.01 | 498 |
| 1: Mean | ±SD | 5.5 ± 4.1 | 9 ± 1.5 | 6.2 ± 0.8 | | 81 ± 8% | | 0.09 ± 0.14 | | 402 ± 191 |
| 2 | A | 6.1 | 7 | 3.6 | 0.2 | 86 | 0.5% | 0.12 | 0.01 | 410 |
| 2 | B | 16.7 | 9 | 6.0 | 0.3 | 98 | 0.4% | RB | | 1409 |
| 2 | C | 8.6 | 8 | 6.8 | 0.8 | 96 | 1.0% | 0.11 | 0.03 | 1089 |
| 2 | D | 1.0 | 7 | 5.6 | 0.5 | 95 | 1.0% | 0.16 | 0.04 | 92 |
| 2 | E | 59.0 | 10 | 11.2 | 0.6 | 99.7 | 0.01% | 0.07 | 0.02 | 12191 |
| 2 | F | 10.9 | 7 | 4.4 | 0.1 | 96 | 0.9% | 0.04 | 0.01 | 965 |
| 2 | G | 23.8 | 7 | 4.8 | 0.1 | 92 | 0.8% | RB | | 1780 |
| 2 | H | 2.7 | 9 | 7.9 | 1.0 | 99.3 | 0.2% | ND | | 324 |
| 2: Mean | ±SD | 16.1 ± 18.9 | 8 ± 1 | 6.3 ± 2.4 | | 95 ± 4% | | 0.1 ± 0.05 | | 2282 ± 4045 |
| 3 | A | 6.7 | 8 | 3.7 | 0.3 | 99.7 | 0.4% | 0.12 | 0.04 | 405 |
| 3 | B | 4.1 | 11 | 9.5 | 3.7 | 91 | 2.0% | 0.11 | 0.03 | 761 |
| 3 | C | 5.8 | 13 | 5.7 | 0.7 | 98 | 0.5% | ND | | 523 |
| 3 | D | 0.4 | 5 | 6.0 | 0.8 | 99.0 | 0.2% | 0.4 | 0.05 | 42 |
| 3 | E | 18.3 | 7 | 6.0 | 0.9 | 97.5 | 1.6% | RB | | 2136 |
| 3 | F | 1.1 | 14 | 5.8 | 0.6 | 90 | 0.3% | 0.33 | 0.03 | 112 |
| 3 | G | 6.0 | NR | NR | | NR | | NR | | NR |
| 3: Mean | ±SD | 6.0 ± 5.9 | 9.5 ± 3.5 | 6.1 ± 1.9 | | 96 ± 4% | | 0.24 ± 0.15 | | 663 ± 769 |
| All: Mean | ±SD | 9.4 ± 12.4 | 8.7 ± 2.3 | 6.2 ± 1.8 | | — | | 0.14 ± 0.13 | | 1276 ± 498 |

Average virion production rate of $1.3 \times 10^{12}$ virions per day

# Hepatitis C Viral Dynamics and Interferon-α Therapy

Modeling 23 patients during 14 days of therapy (daily doses)




Suggests immune control has important role in lowering viral load

Patients with undetectable HCV after 3 months of therapy (filled symbols) had significantly faster cell death rates

# Immune System **Adapts** to Pathogenic Challenge

Secondary responses are quantitatively and qualitatively different

**Faster kinetics, greater magnitude**

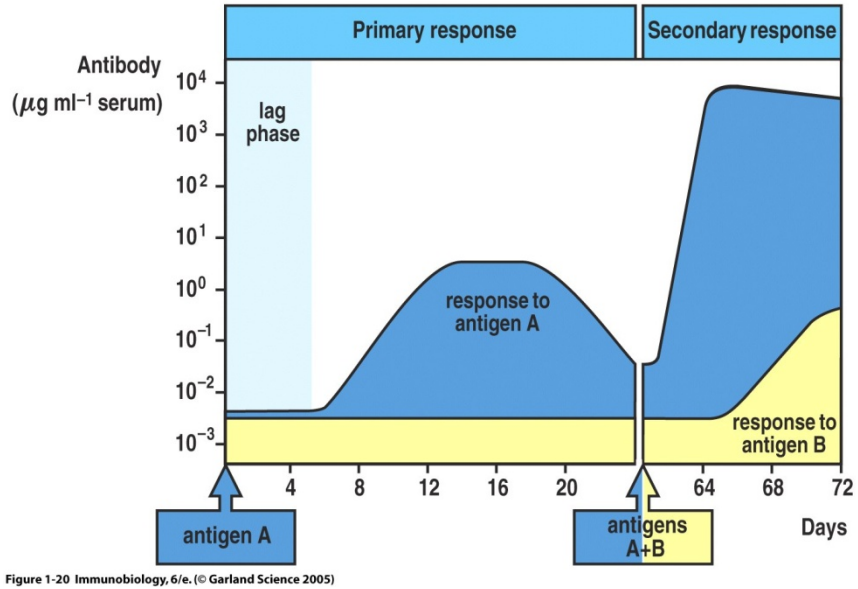



Figure 1-20 Immunobiology, 6/e. (© Garland Science 2005)

**Increased affinity**

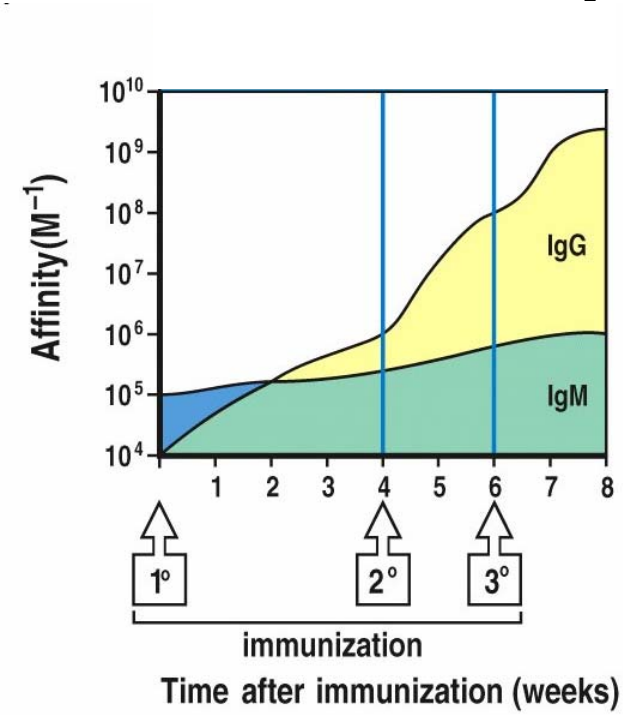
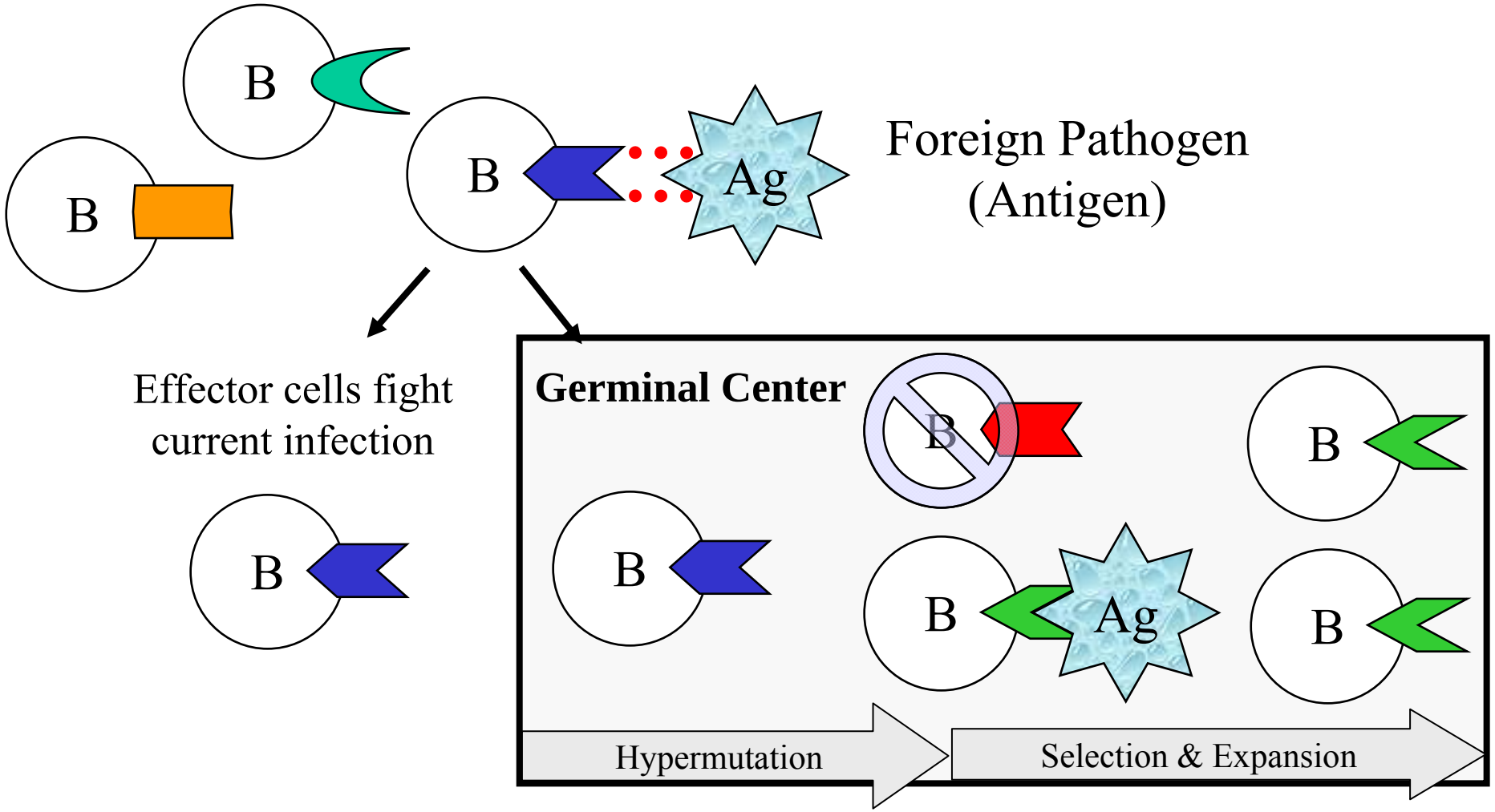



Figure 10-31 Immunobiology, 6/e. (© Garland Science 2005)

Affinity Maturation is Fundamental to Adaptive Immunity

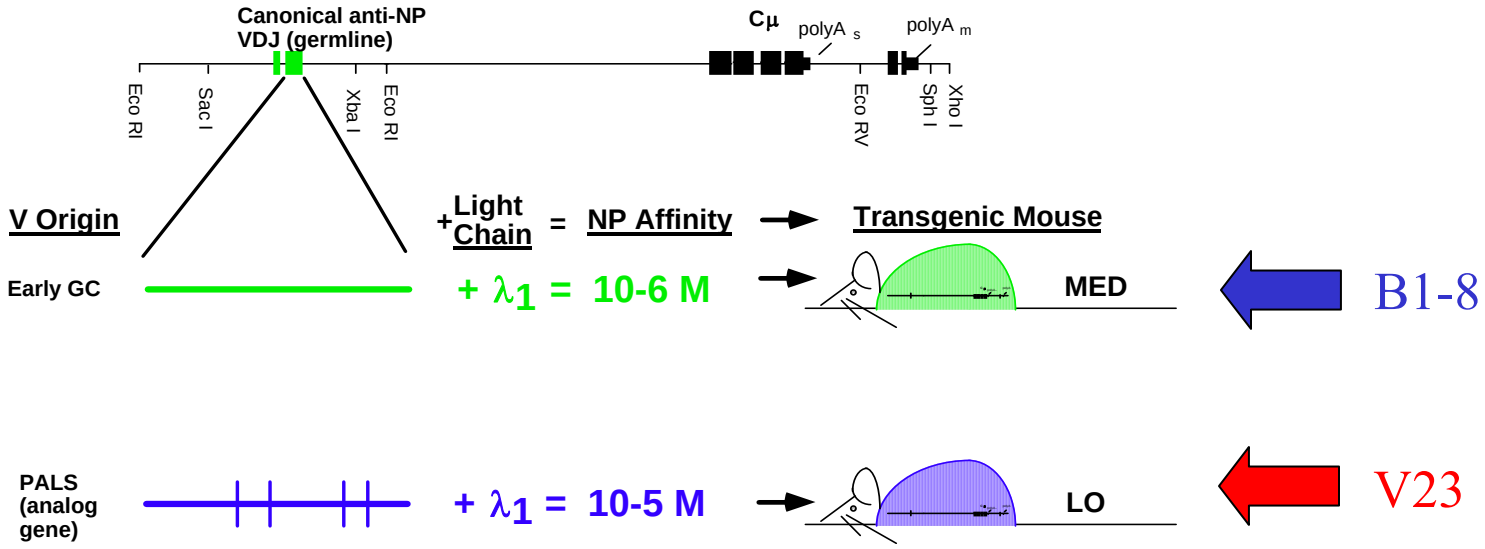
# Germinal Centers are Site of Affinity Maturation

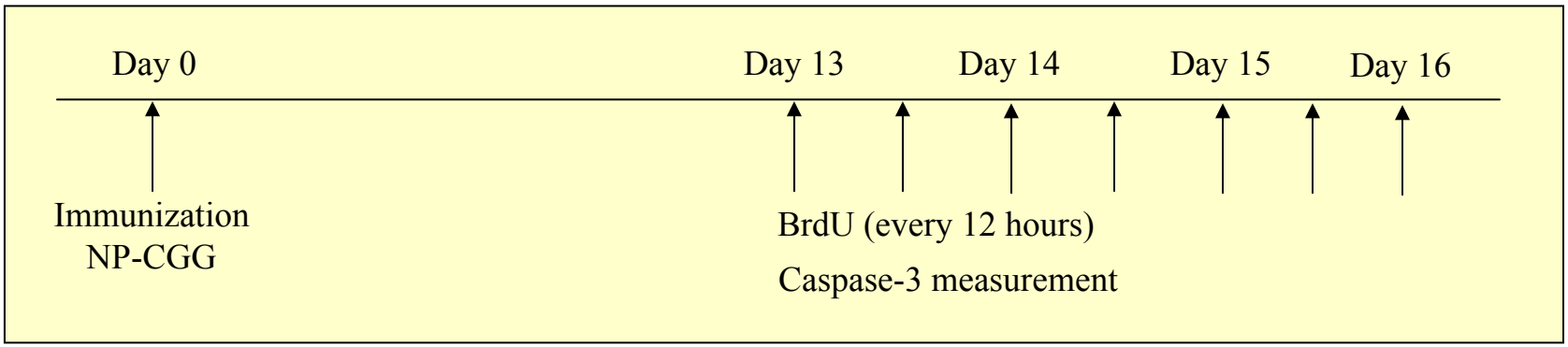



Affinity maturation accomplished through somatic hypermutation of B cell receptor, followed by expansion of rare higher-affinity mutants

# How does affinity impact cell-fate decisions?

Follow fate of higher and lower affinity B cells using transgenic mice

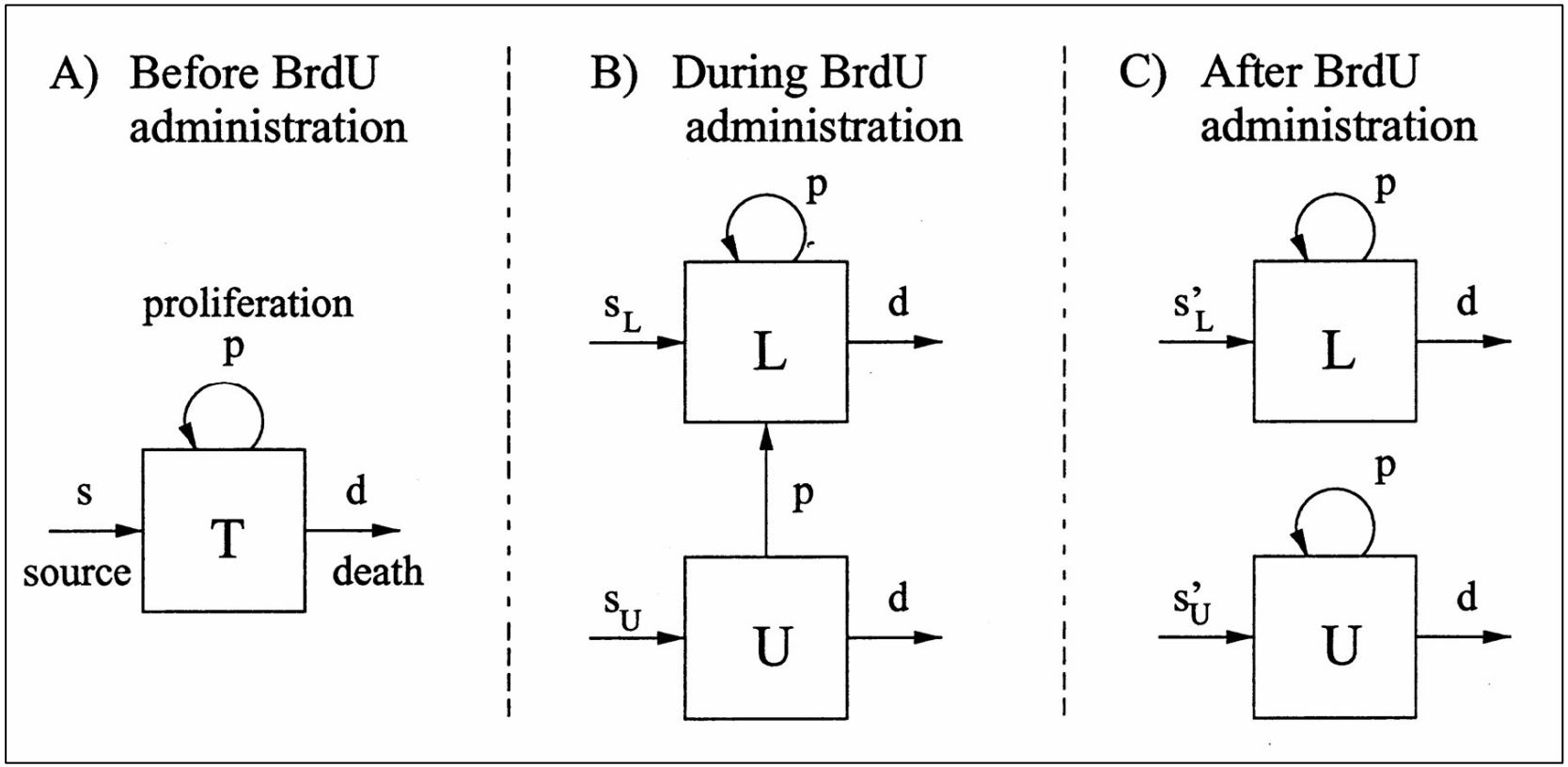



Is selection driven by a proliferative vs. survival advantage?

# Basic Model of BrdU Labeling

Many experiments stop administering label after some time

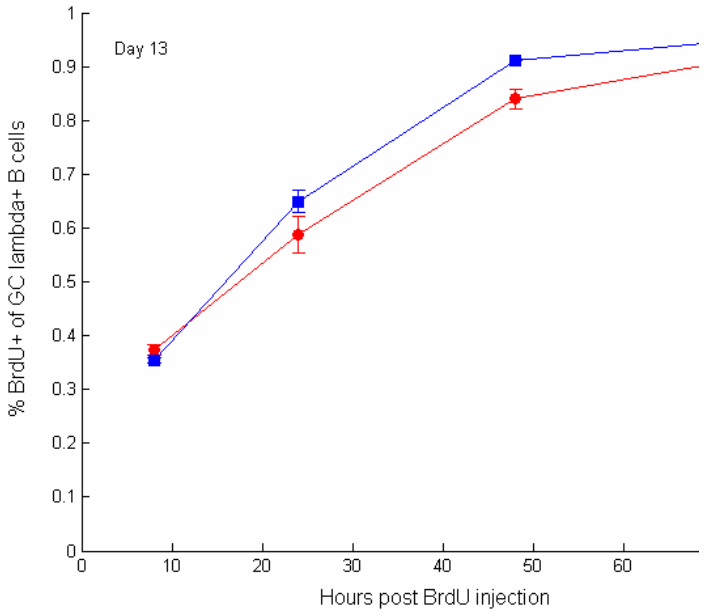


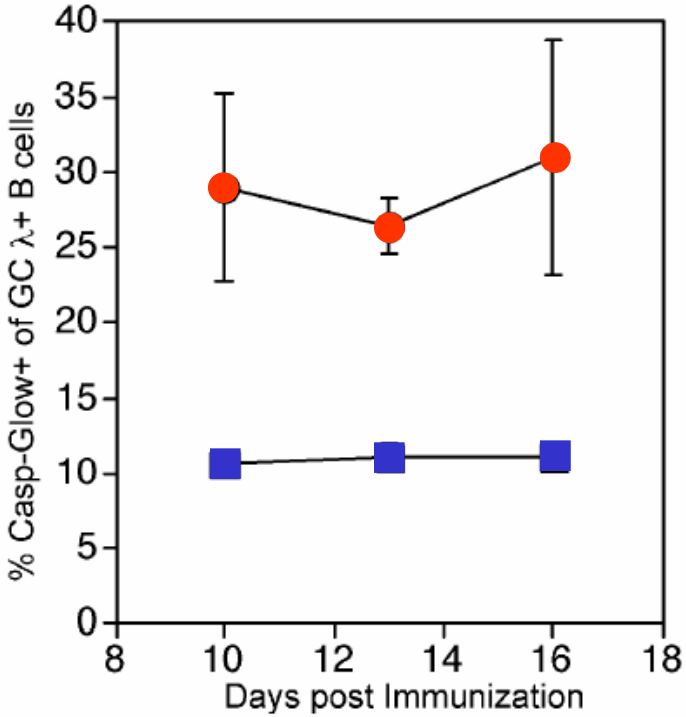

We can express these as sets of ordinary differential equations

# How do proliferation and death depend on affinity?

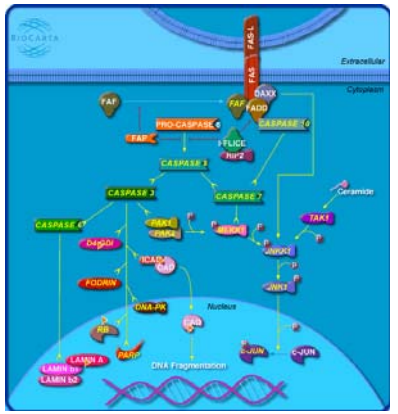
Higher Affinity Transgenic (B1-8) Lower Affinity Transgenic (V23)

**Flow cytometry used to look at antigen-specific germinal center B cells…**



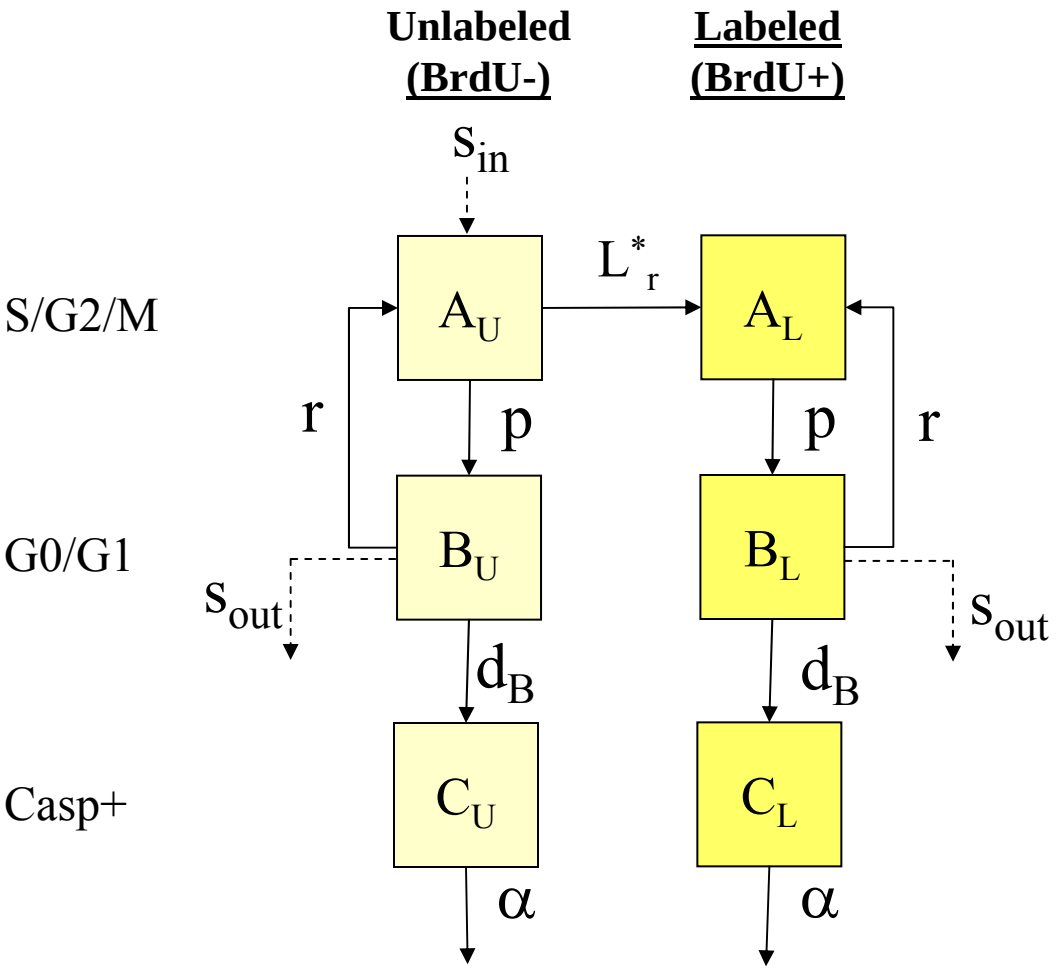

Caspase label tracks dying cells



Updates to basic BrdU model: caspase compartment, BrdU pulse

# The ABC Model

**A**: Dividing (S/$G_2$/M); **B**: Non-Dividing ($G_0$/$G_1$); **C**: CaspGLOW+ cells




$$\frac{dA_U}{dt} = s_{in} + rB_U - \left(p + d_A + L_r^*\right)A_U$$

$$\frac{dB_U}{dt} = 2pA_U - \left(r + d_B + s_{out}\right)B_U$$

$$\frac{dC_U}{dt} = d_A A_U + d_B B_U - \alpha C_U$$

$$\frac{dA_L}{dt} = rB_L + L_r^* A_U - \left(p + d_A\right)A_L$$

$$\frac{dB_L}{dt} = 2pA_L - \left(r + d_B + s_{out}\right)B_L$$

$$\frac{dC_L}{dt} = d_A A_L + d_B B_L - \alpha C_L$$

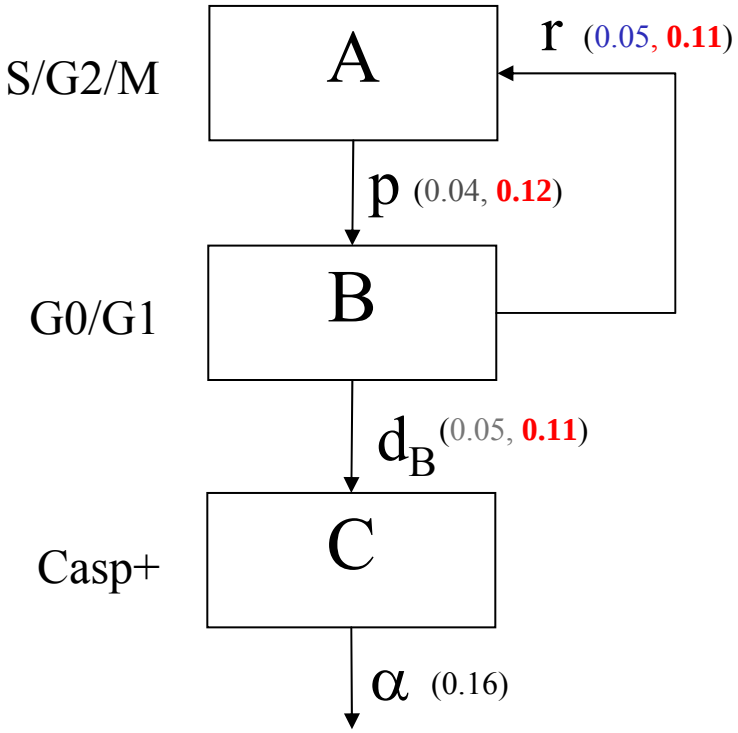
$$L_r^* = \begin{cases} L_r \text{ if } T_i \le t \le \left(T_i + L_t\right) \\ \text{for some BrdU injection } T_i \\ 0 \text{ otherwise} \end{cases}$$

$$\%\text{BrdU+} = \frac{A_L + B_L + C_L}{A_U + B_U + C_U + A_L + B_L + C_L} \times 100\%$$

$$\%\text{CaspGLOW+} = \frac{C_U + C_L}{A_U + B_U + C_U + A_L + B_L + C_L} \times 100\%$$

# Model estimates proliferation and death rates

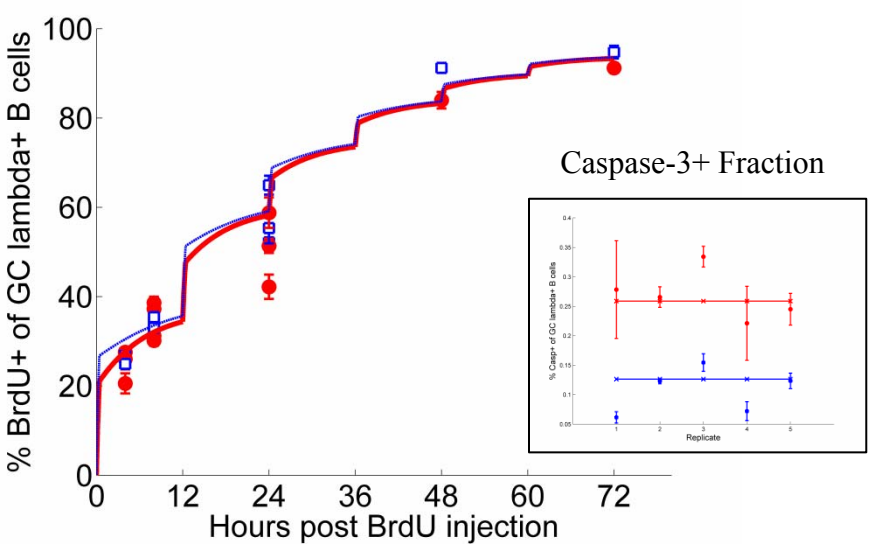
■ Higher Affinity Transgenic (B1-8) ● Lower Affinity Transgenic (V23)




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]**

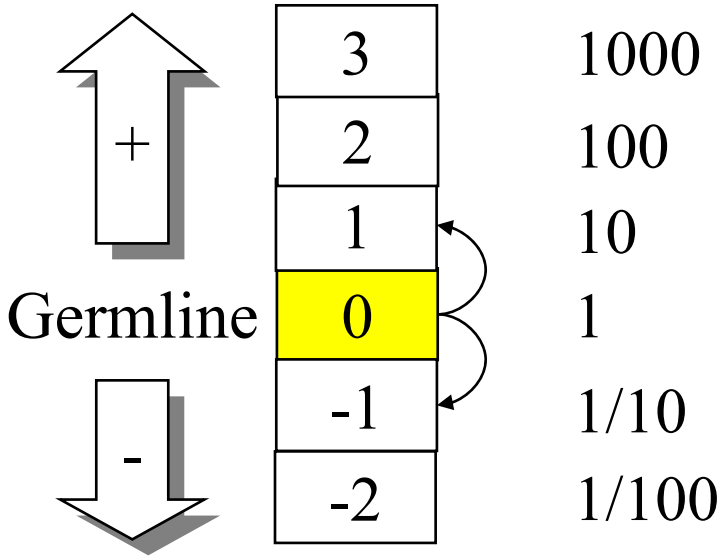
Shannon M. Anderson,* Ashraf Khalil,† Mohamed Uduman,‡§ Uri Hershberg,*† Yoram Louzoun,¶ Ann M. Haberman,† Steven H. Kleinstein,‡§ and Mark J. Shlomchik*†




Lower affinity cells have intrinsically **higher death** rate, AND **increased proliferation**

# Immune response as optimization problem

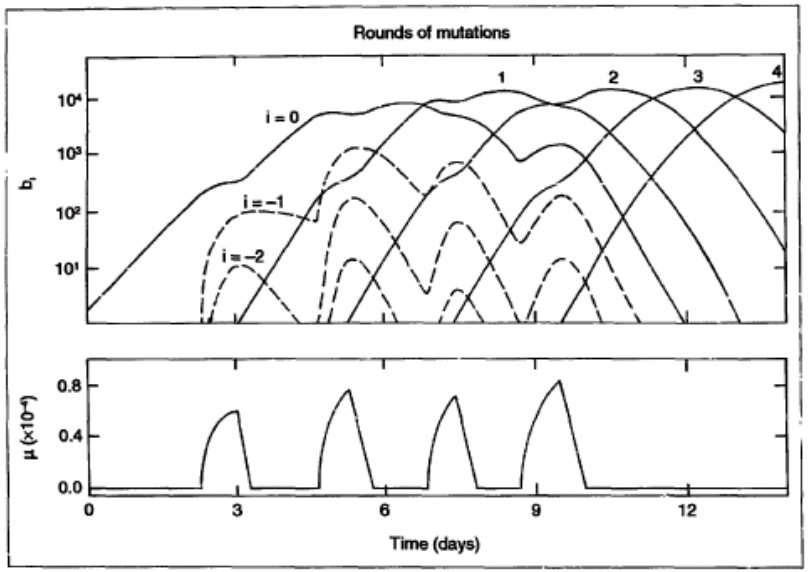
Affinity class framework groups B cells with similar on/off-rates




**Cyclic re-entry of germinal center B cells and the efficiency of affinity maturation**

Thomas B. Kepler and Alan S. Perelson

$$\frac{db_i}{dt} = b_i\theta_i\left\{-k_d(1-h_i) + k_p h_i\left(2m_u - 1\right)\right\} + 2k_p\sum_{j\neq i} m_u b_j h_i \theta_i$$




Optimal mutation schedule is phasic (on-off cycles)

# But, what should we optimize?

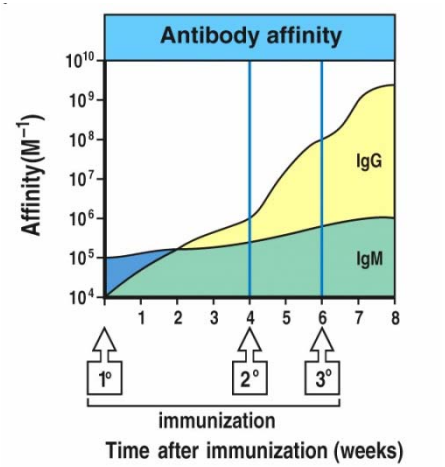



Figure 10-31 Immunobiology, 6/e. (© Garland Science 2005)

*Immunology and Cell Biology* (1998) **76**, 373–381

**Theoretical Article**

Predicted and inferred waiting times for key mutations in the germinal centre reaction: Evidence for stochasticity in selection

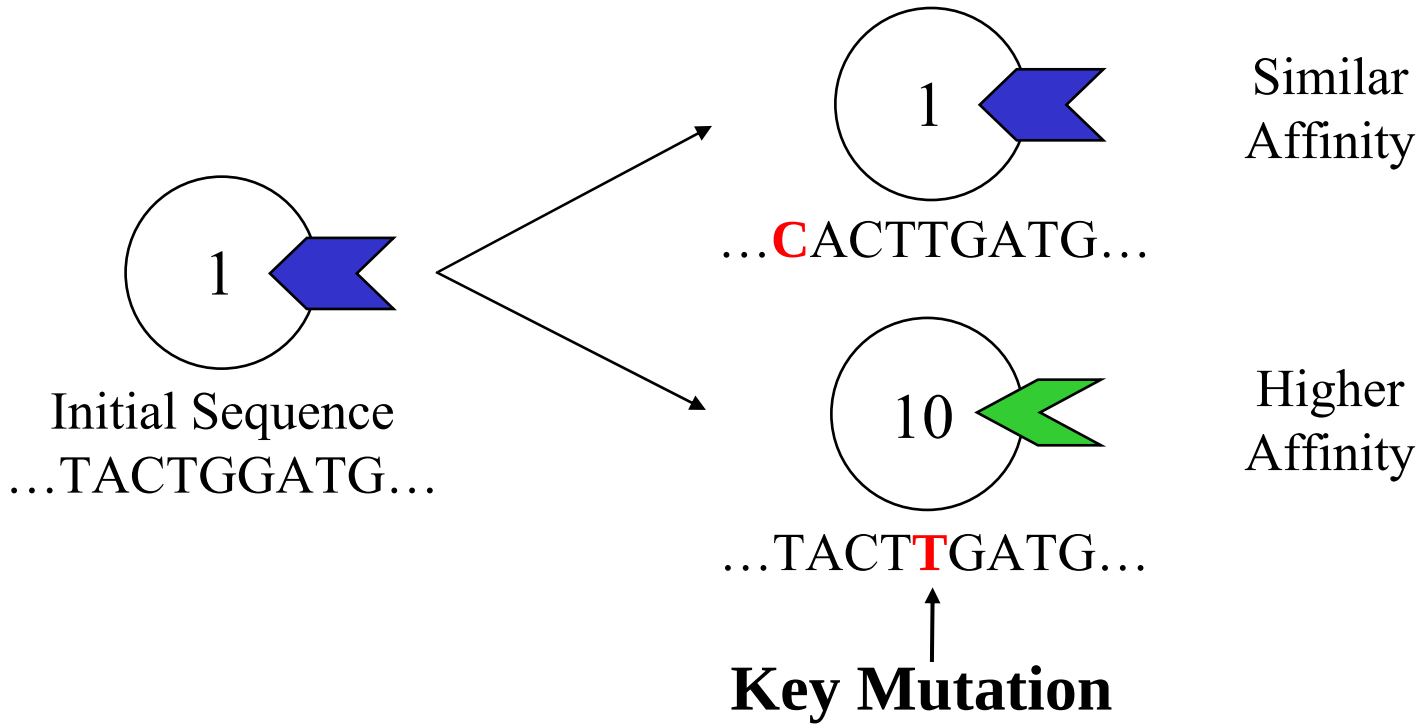
MICHAEL D RADMACHER,[1] GARNETT KELSOE[2] and THOMAS B KEPLER[1]

[1]*Biomathematics Graduate Program, Department of Statistics, North Carolina State University, Raleigh, North Carolina, and* [2]*Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, Maryland, USA*

How efficient is affinity maturation? Optimal?

# Quantitative Affinity Maturation

Consider well-studied antigen NP: (4-hydroxy-3-nitrophenyl)acetyl

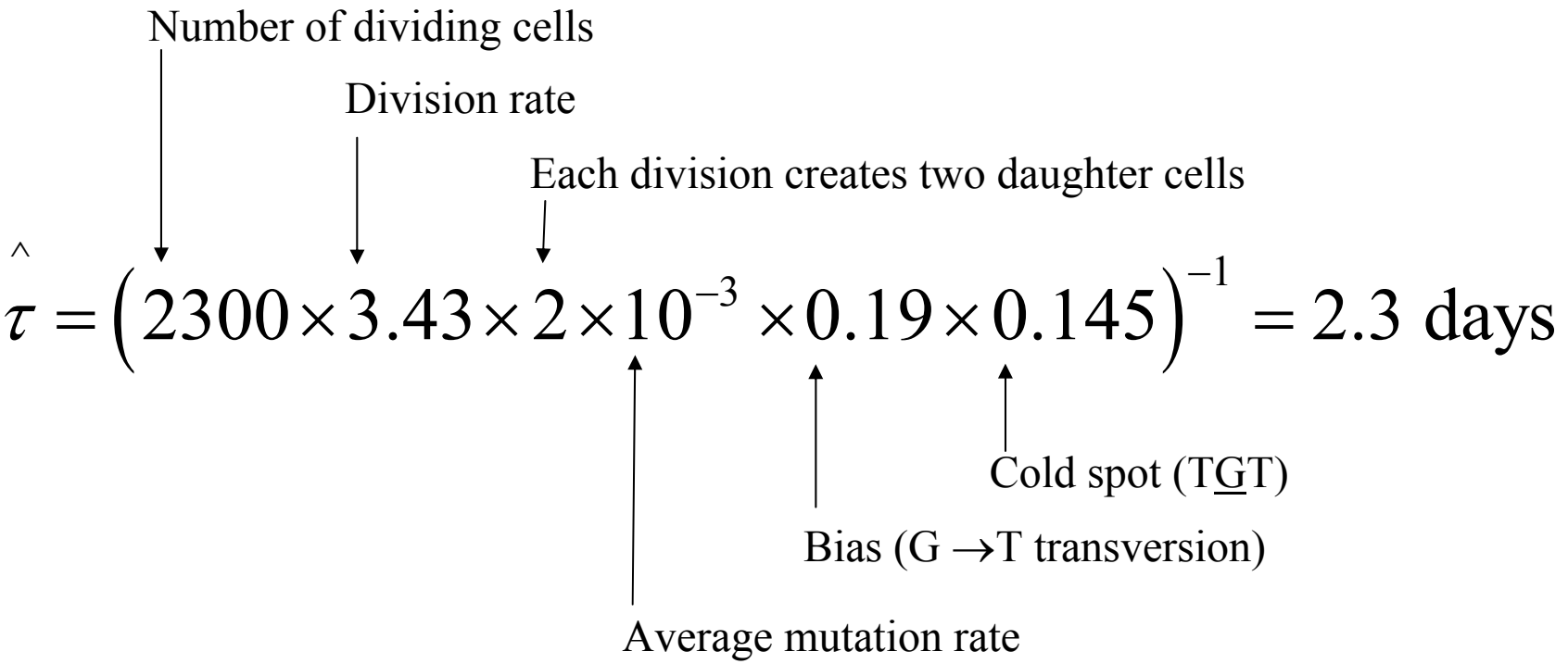



**Key Mutation** increases affinity 10-fold

( majority of high-affinity antibodies observed in the anti-NP response contains this mutation)

# Mean waiting time for key mutations

The position 33 mutation, a transversion from G to T in the second nucleotide of the codon, produces a 10-fold increase in binding affinity of the Ig for NP




Predicted waiting time for key mutations is 2.3 days

# Appearance time for key mutations

Experimental sequence data from germinal center microdissections

| GC | Strain | Day | Ig sequences* | Position 33 mutations |
|---|---|---|---|---|
| 61AM40 | BL/6 | 8 | 8 | 0 |
| 61AM41 | BL/6 | 8 | 10 | 0 |
| 61AM14 | BL/6 | 8 | 12 | 0 |
| 61AM16 | BL/6 | 8 | 12 | 0 |
| L1AB01 | BL/*6.lpr* | 10 | 9 | 0 |
| L1AB02 | BL/*6.lpr* | 10 | 10 | 10 |
| L1AB03 | BL/*6.lpr* | 10 | 3 | 0 |
| L1AB04 | BL/*6.lpr* | 10 | 7 | 0 |
| 61AB08 | BL/6 | 10 | 4 | 0 |
| L1AD01 | BL/*6.lpr* | 14 | 12 | 0 |
| L1AD02 | BL/*6.lpr* | 14 | 11 | 11 |
| L1AD03 | BL/*6.lpr* | 14 | 10 | 8 |
| L1AD05 | BL/*6.lpr* | 14 | 11 | 0 |
| 61AD01 | BL/6 | 14 | 8 | 3 |
| 61AD02 | BL/6 | 14 | 10 | 0 |
| 61AA02 | BL/6 | 16 | 8 | 8 |

*Sequences are available from EMBL/Gen Bank/DDBJ under accession numbers DS13953 and X67341-X67391.

How does this compare with predicted waiting of 2.3 days

# Arrival time of founder key mutant

Two-stage model of B cell mutation and clonal expansion

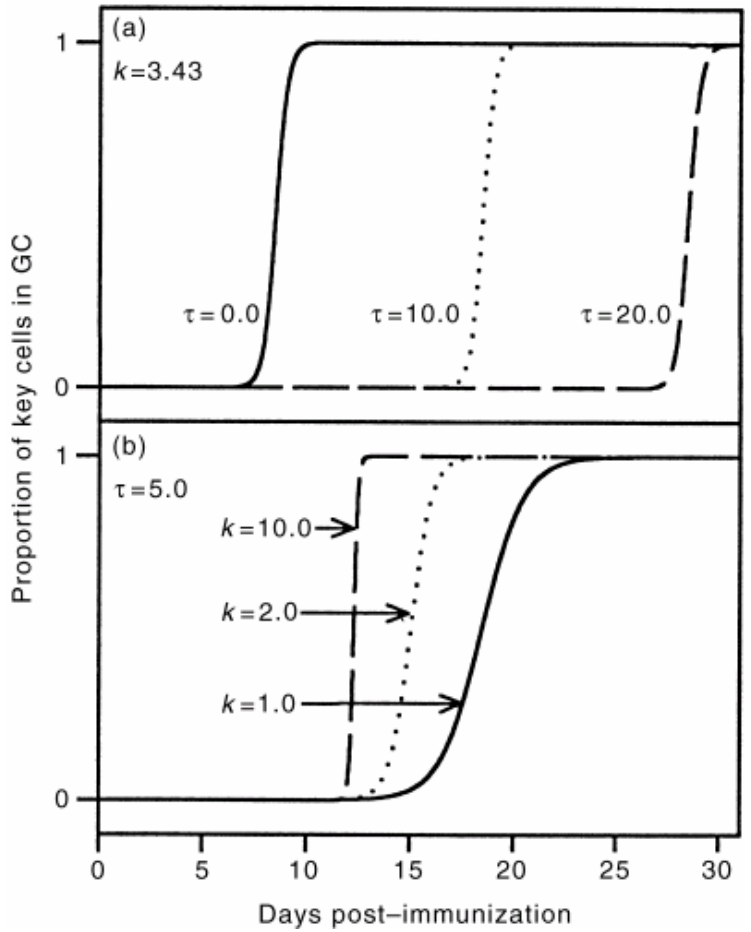
**Stage 0:**
Mutation begins ~ day 6.5

**Stage I:**
Arrival times are exponentially distributed ($\tau$)

**Stage II:**
Growth of the key mutant clone is logistic

$$\frac{d\rho}{dt} = k\rho(1-\rho), \quad \text{for } t > \tau^*$$

Arrival time of key mutant




Estimate $\tau$ and k by fitting to experimental data

# Maximum likelihood parameter estimates

Give average appearance time ($\tau$) and proliferation rate (k)…

Observation time

Fraction of key mutants at $t_i$ if first appear at time $\tau_i^*$

Probability to NOT appear by time $t_i$

$$L = \prod_i \left\{ \int_0^{t_i} \left[ b\left(x_i \mid n_i, \rho_i\left(k, \tau_i^*, t_i\right)\right) \cdot f\left(\tau_i^* \mid \tau\right) \right] d\tau_i^* \quad + I(x_i = 0) \exp\left(-\frac{t_i}{\tau}\right) \right\},$$

Probability to first appear at time $\tau i^*$

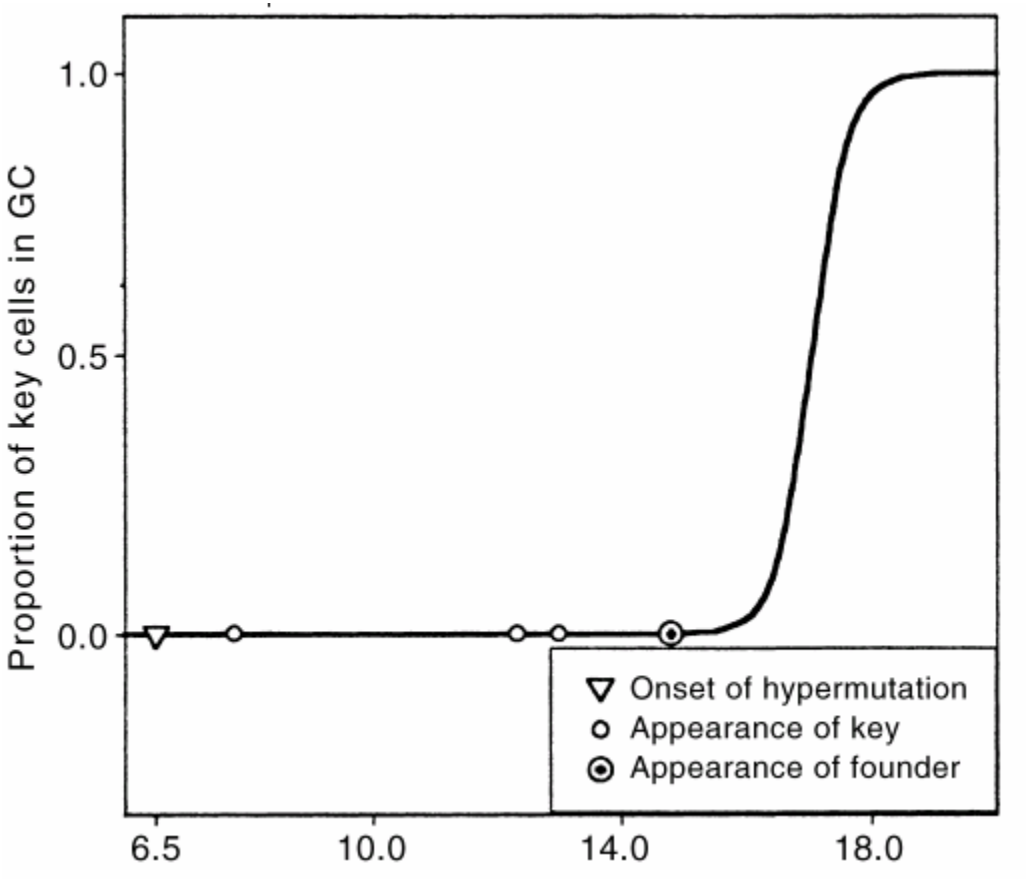
Binomial probability (finding $x_i$ key mutants when sampling $n_i$ sequences)

Appearance time of founder key mutant

Maximize likelihood (L) over $\tau$ and k

# First key mutant produced earlier than founder

Appearance of founder key mutant is 8.3 days vs. 2.3 days for first key mutant




**Why?**

Stochastic selection

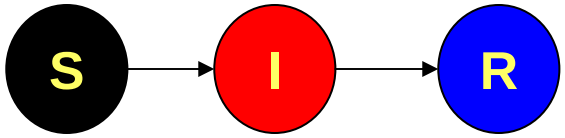
Emigration

Lethal/Blocking mutations

On average, 2.6 key mutants arise that are not perpetuated within the GC before one appears that leads to domination of the GC

# The SIR Model of Epidemics

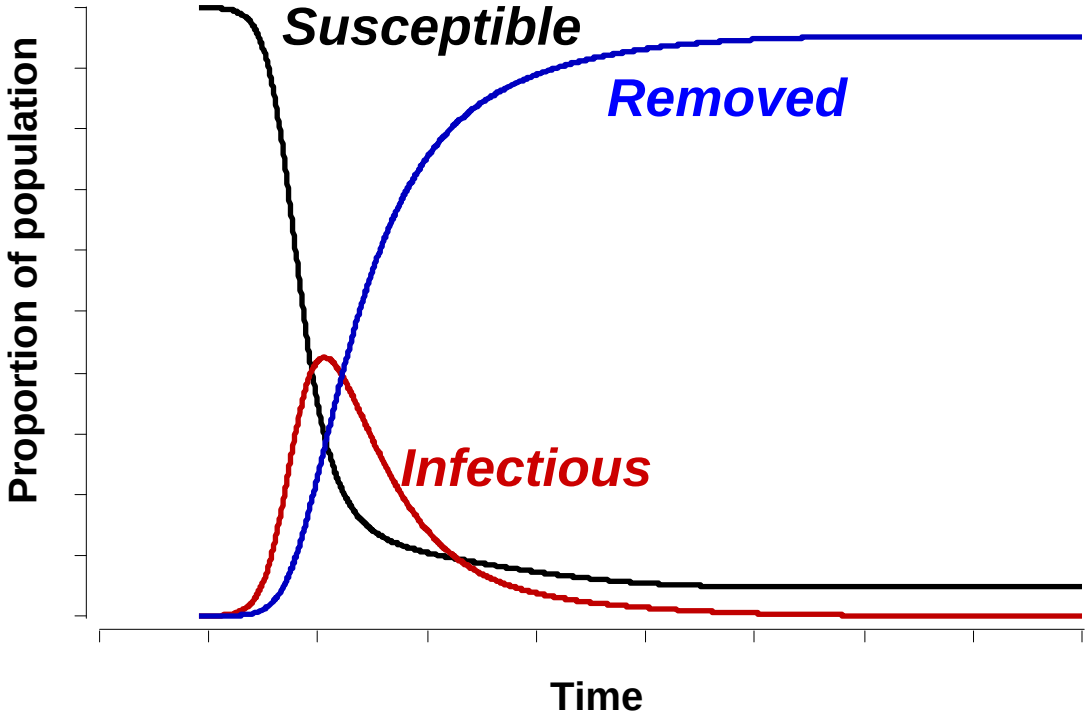
Model for many infectious diseases including measles




$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \mu I$$

$$\frac{dR}{dt} = \mu I$$



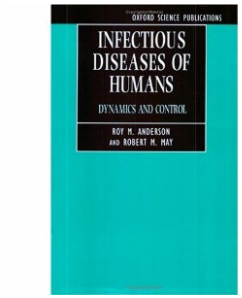

Other versions allow recovered individual to be re-infected

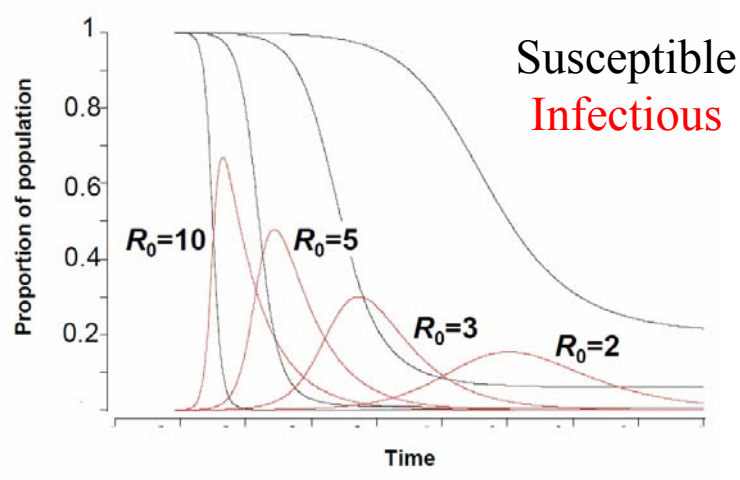
# The basic reproductive ratio: $R_0$

average number of secondary cases caused by an infectious individual in a totally susceptible population

$$R_0 = \frac{\beta}{\mu} \times S(0)$$

$R_0 < 1$: disease dies out
$R_0 > 1$: disease can invade



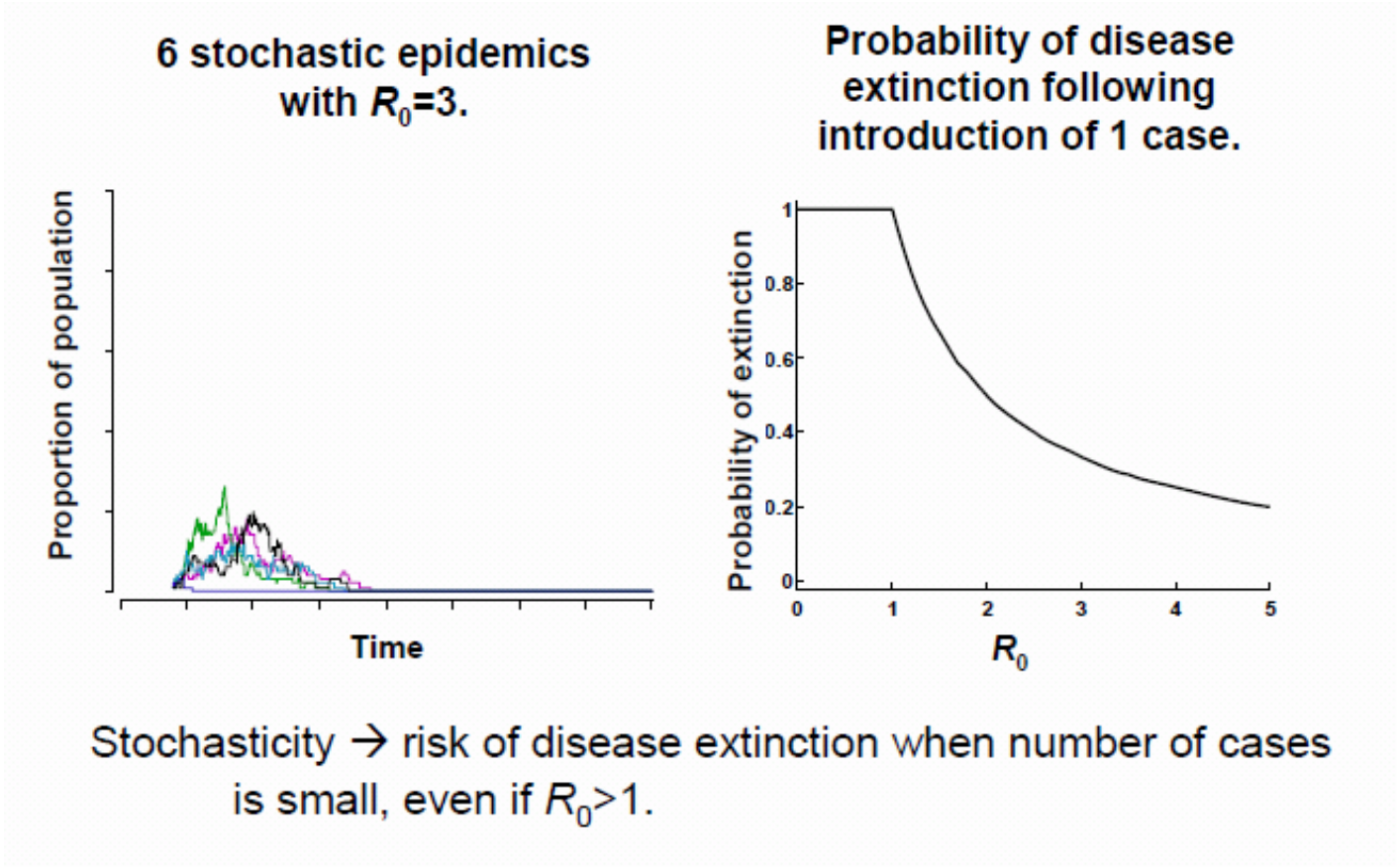




| The value of $R_0$ for some well-known diseases | |
|---|---|
| Disease | $R_0$ |
| AIDS | 2 to 5 |
| Smallpox | 3 to 5 |
| Measles | 16 to 18 |
| Malaria | > 100 |

$R_0$ indicates whether population at risk from disease

# ODEs are deterministic

Predicts epidemic even with non-zero chance that disease dies out




Stochasticity → risk of disease extinction when number of cases is small, even if $R_0$>1.

Simulate using stochastic approach – Gillepsie Method

# Random Numbers

Starting with the same seed will give you equivalent stream

**Uniform deviates: [0,1)**

Linear congruential generator

$$I_{j+1} = aI_j + c \pmod{m}$$

$I_0$ is the seed (common to use system clock)

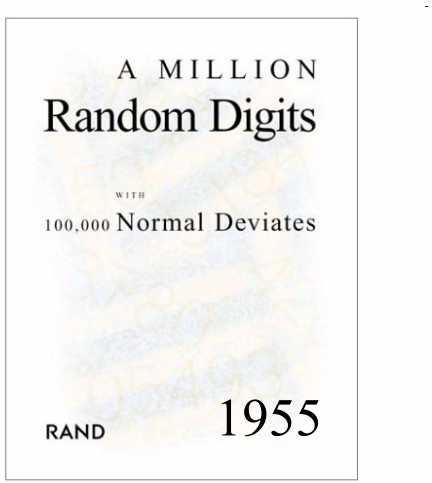
$I_{j+1} = 3I_j + 7 \pmod{10}$

Produces: 6,5,2,3

**Period**: time before stream repeats itself (maximum m)

Fast, but sequential calls can be correlated, so not used much

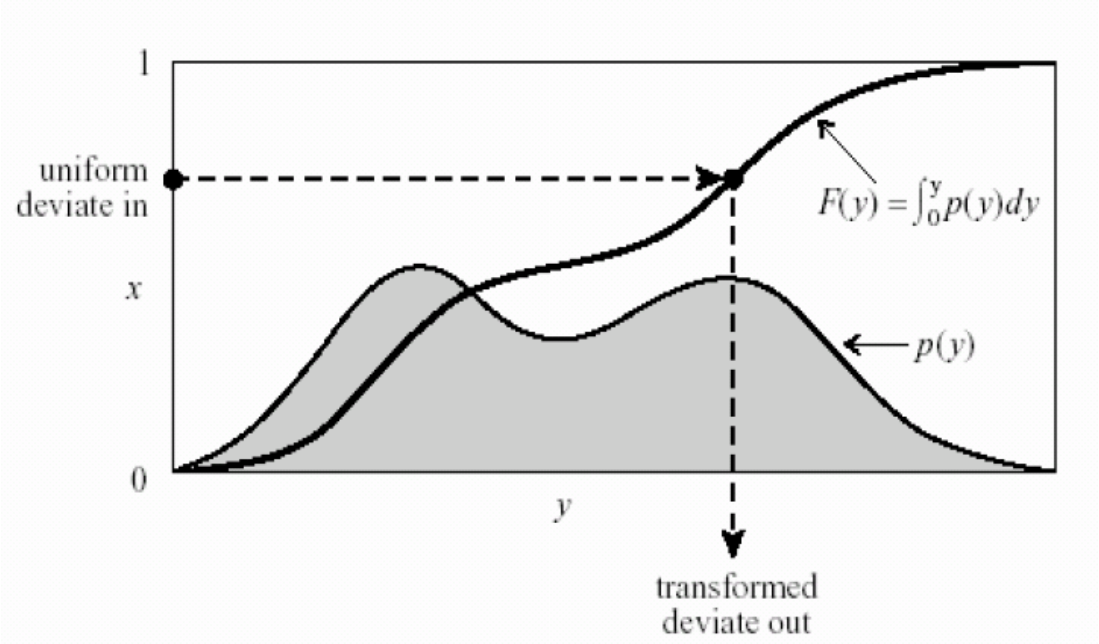
**Mersenne Twister**
**(period $2^{19937}$-1)**




Be careful on computer clusters (streams can be correlated)

# Simulating from other distributions

**Transformation Method**: indefinite integral of p(y) must be known and invertible




$$\text{Exponential}(\alpha) = -\frac{1}{\alpha}\ln\left[\text{Uniform}(0,1)\right]$$

Transformation to generate exponential distribution (Poisson process)

# *For more information…*

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Message from ISCB

## Getting Started in Computational Immunology

**Steven H. Kleinstein***

Interdepartmental Program in Computational Biology and Bioinformatics, and Department of Pathology, Yale University School of Medicine, New Haven, Connecticut, United States of America

**Feel free to email me with any questions!**

**steven.kleinstein@yale.edu**