STOCHASTIC HIV REBOUND DURING POST TREATMENT-INTERRUPTION

The Role of Immune Pressure

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Alan Perelson

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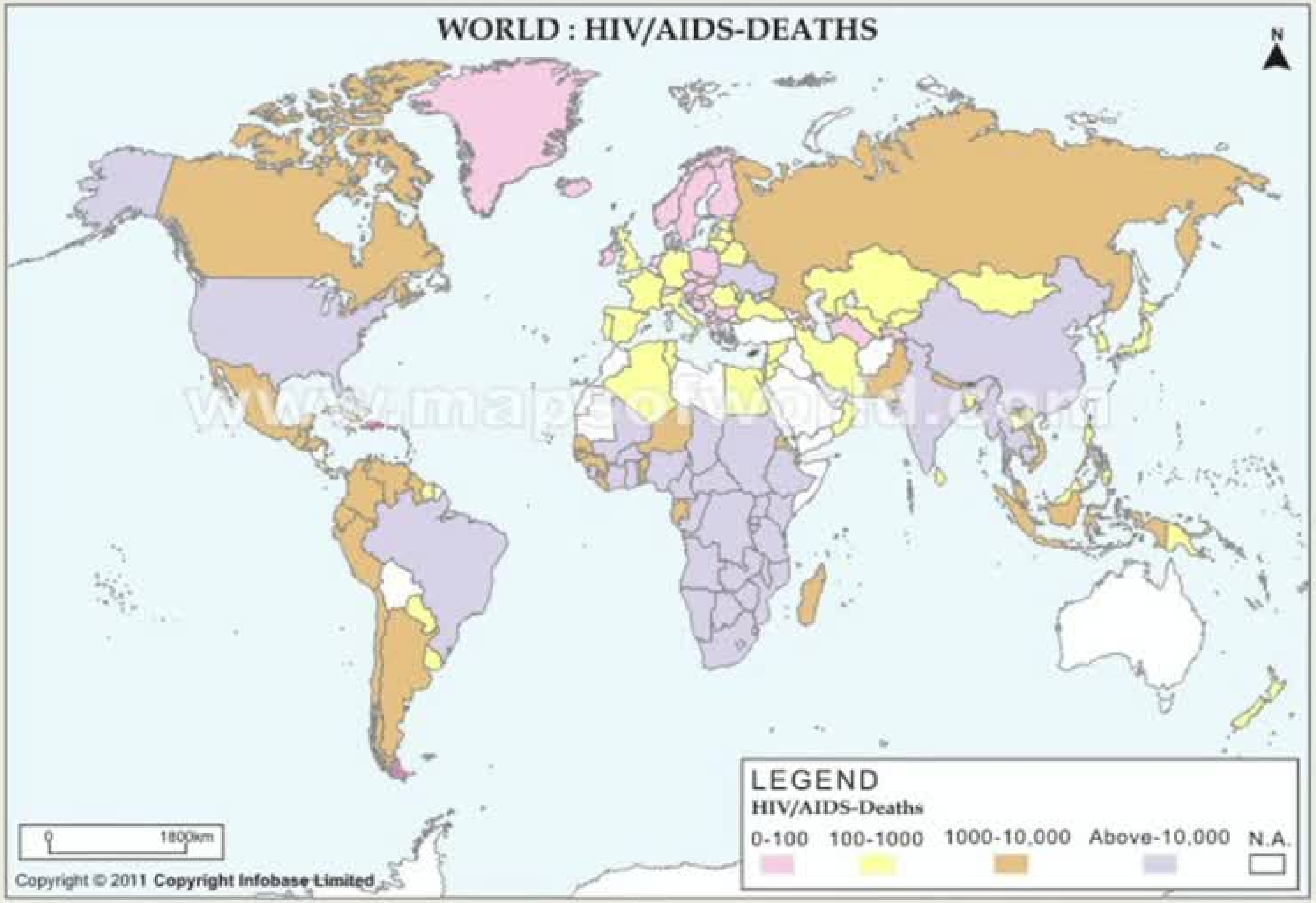
EST. 1943

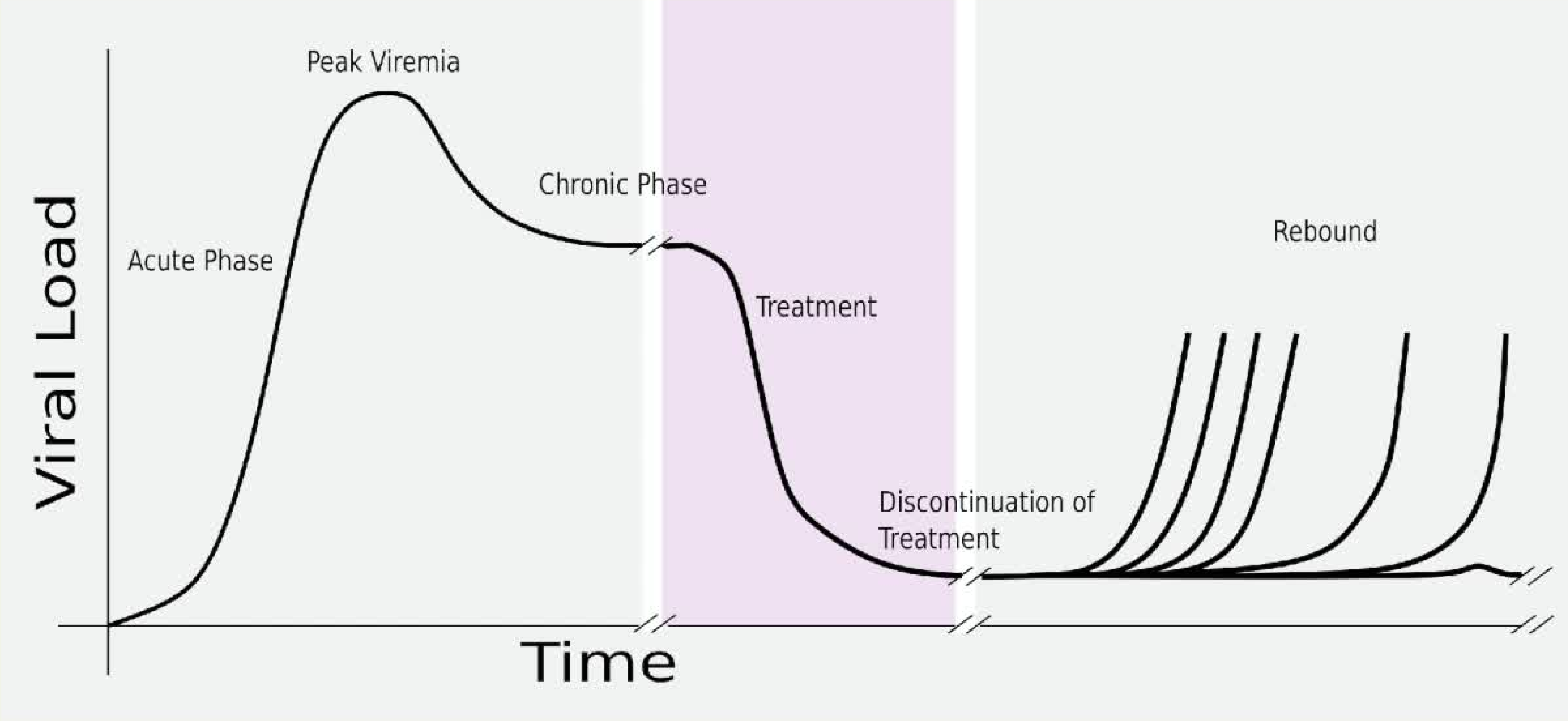
HIV : Human Immunodeficiency Virus

- Retrovirus prevalent worldwide
- 36.9 million people at end of 2017
- 940,000 deaths in 2017
- Requires life-long treatment

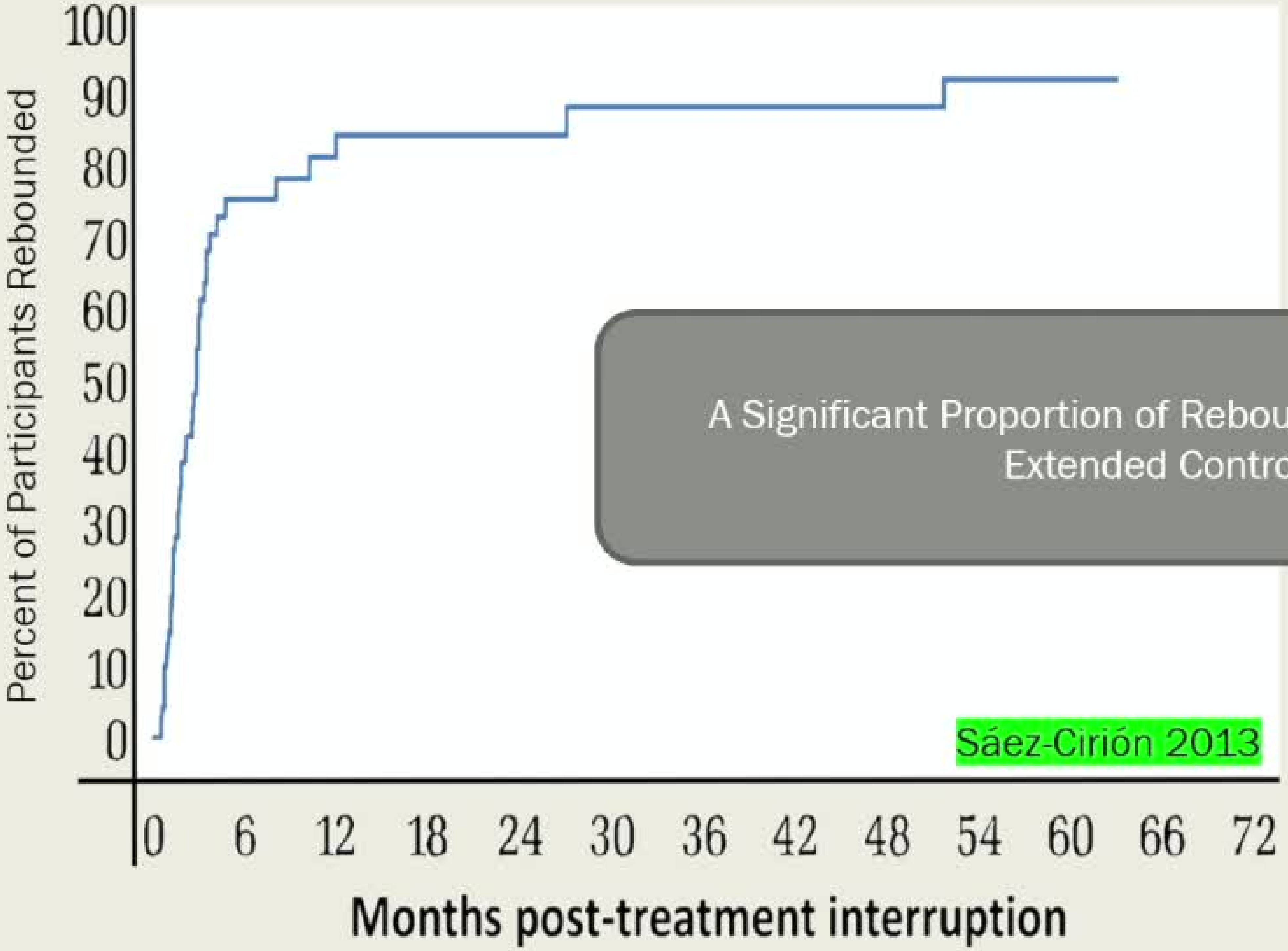


WHO Global Health Observatory (GHO) data

HIV Infection



Rebound Times Have Large Variation

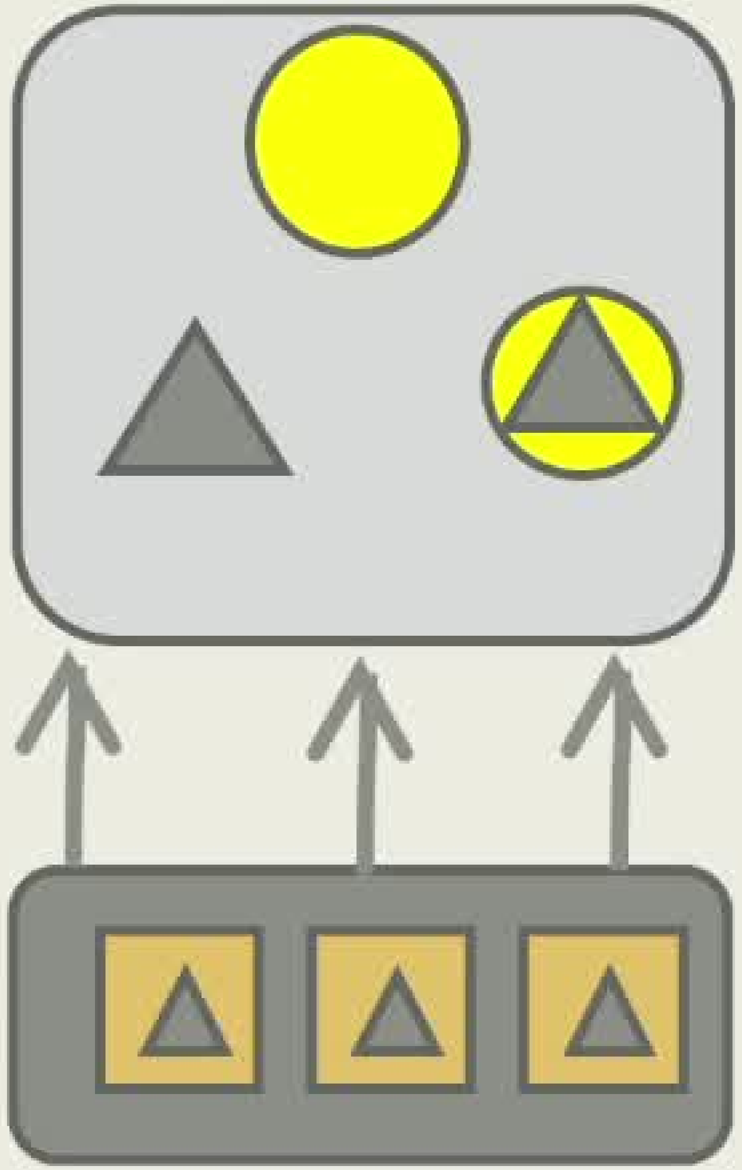


A Significant Proportion of Rebounders Experience Extended Control

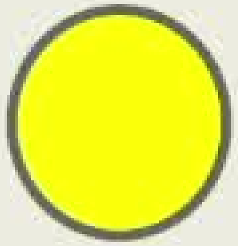
Concept and Goals

- Use mathematical models to understand how the immune system interacts with HIV
- Understand variations in rebound times following the discontinuation of treatment

Single Compartment In-host HIV-model



Infected cells



Effector cells

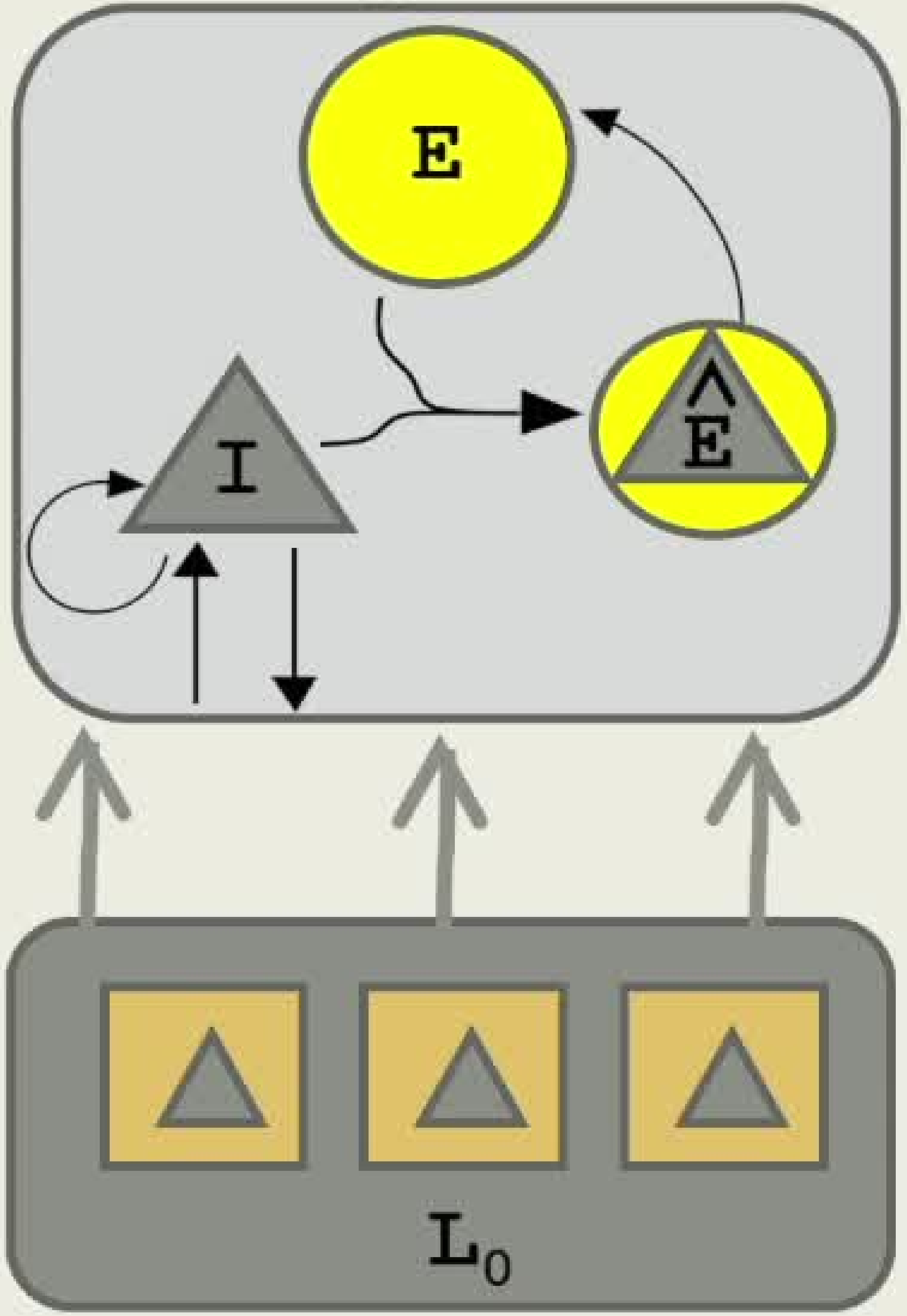
Bound E-cells

Latently infected

Assumptions

- Small compartment like a lymph node
- Finite effector cells
- Non-dynamic T-cell population
- Inexhaustible latent reservoir
- It takes time for an effector cell to kill an infectious cell

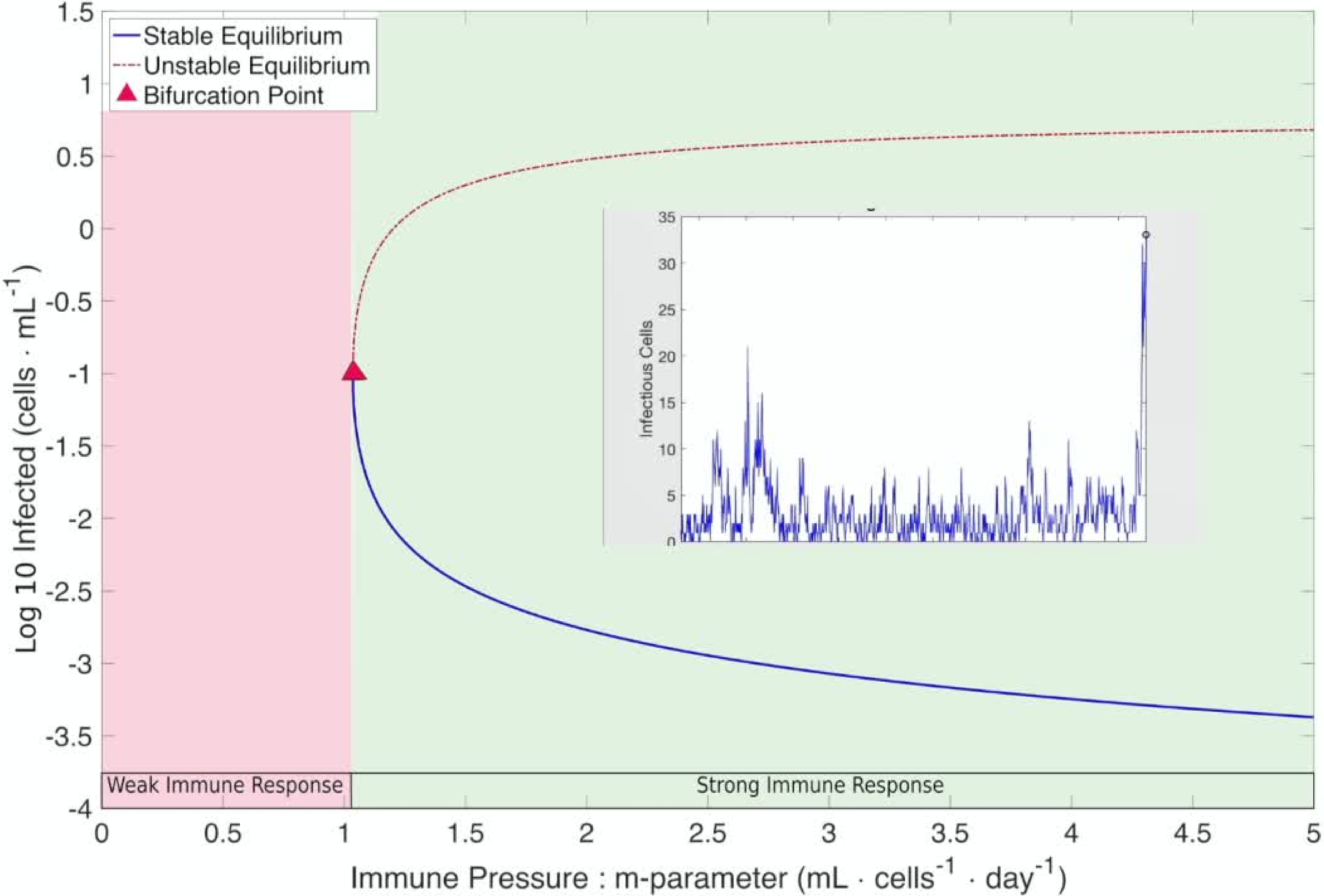
Single Compartment In-host HIV-model



$$\frac{dI}{dt} = \alpha + (\lambda - \delta)I - mIE$$

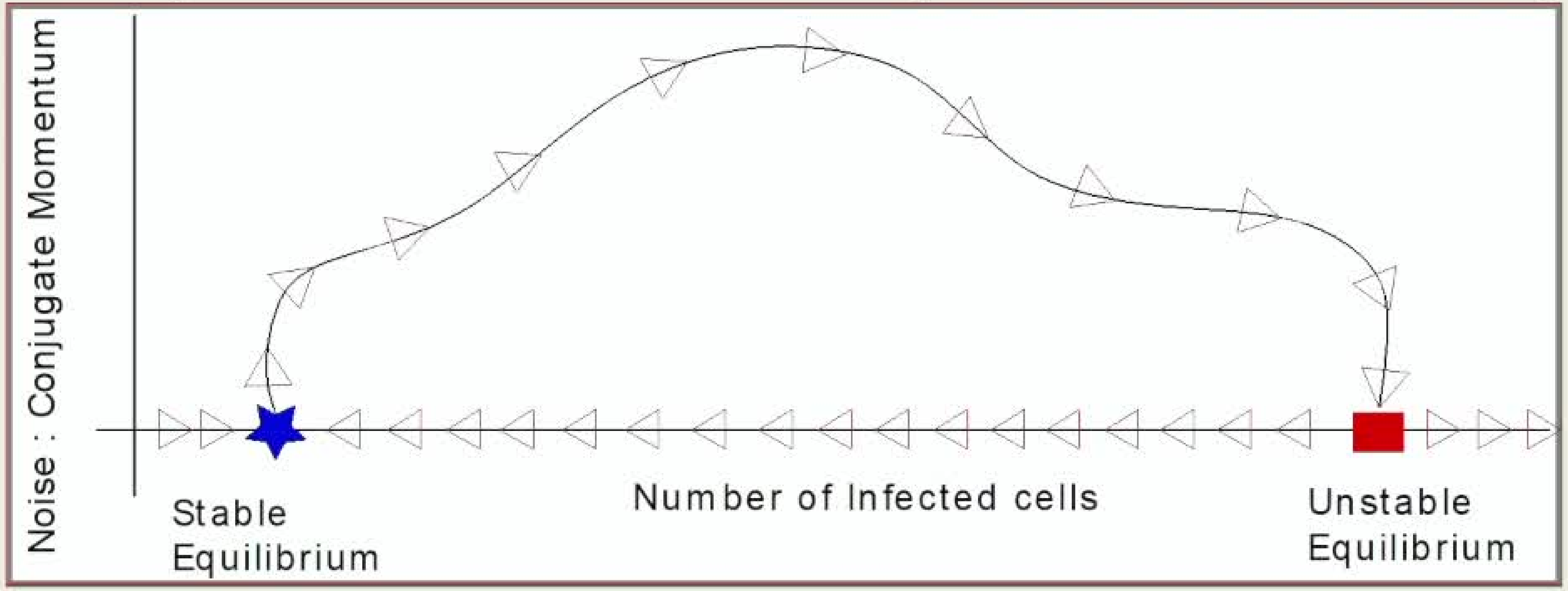
$$\frac{dE}{dt} = \omega\left(E_0 - E\right) - mIE$$

Finite Effector Cell



Stable Equilibrium
Unstable Equilibrium
Bifurcation Point
Log 10 Infected (cells · mL^{-1})
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
Infectious Cells
35
30
25
20
15
10
5
0
Weak Immune Response
Strong Immune Response
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Immune Pressure : m-parameter (mL · cells^{-1} · day^{-1})

Escape From Stable EQ to Unstable EQ



- Stochastic formulation will reveal a Hamiltonian system
- Hamiltonian system has conjugate momentum or noise-dimension for each state variable
- Equilibrium points become unstable saddle points
- **The minimum action path** leading from the deterministically stable to the deterministically unstable equilibrium point can be used to **approximate escape times**

Master Equation ⟶ Fokker-Planck

$$\begin{aligned}\dot{P}(I,E;t) = {}& \delta[(I+1)P(I+1,E;t) - IP(I,E;t)] + \alpha N[P(I-1,E;t) - P(I,E;t)] \\ &+ \lambda[(I-1)P(I-1,E;t) - IP(I,E;t)] \\ &+ mN^{-1}[(E+1)(I+1)P(I+1,E+1;t) - EIP(I,E;t)] \\ &+ \omega[(E_0 - E + 1)P(I,E-1;t) - (E_0 - E)P(I,E;t)]\end{aligned}$$

$$P(I,E;t) \approx \rho(x,y)\, N^{-2}$$

Fokker-Planck ⟶ Hamiltonian

$$\frac{\partial \rho^*}{\partial t} = -\frac{\partial}{\partial x}\left[V_x \rho^*\right] - \frac{\partial}{\partial y}\left[V_y \rho^*\right] + \frac{1}{2N}\left[\frac{\partial^2}{\partial x^2}\left[D_{xx}\rho^*\right] + \frac{\partial^2}{\partial y^2}\left[D_{yy}\rho^*\right] + 2\frac{\partial^2}{\partial x \partial y}\left[D_{xy}\rho^*\right]\right]$$

$$-\frac{\partial S}{\partial t} = V_x p_x + V_y p_y + \frac{1}{2}D_{xx}p_x^2 + \frac{1}{2}D_{yy}p_y^2 + D_{xy}p_x p_y$$

$\frac{\partial S}{\partial x} = p_x \text{ and } \frac{\partial S}{\partial y} = p_y$: Conjugate Momentum

$\mathcal{H}\left(\bar{x}, \frac{\partial S}{\partial \bar{x}}, t\right) + \frac{\partial S}{\partial t} = 0$: Hamilton-Jacobi EQ

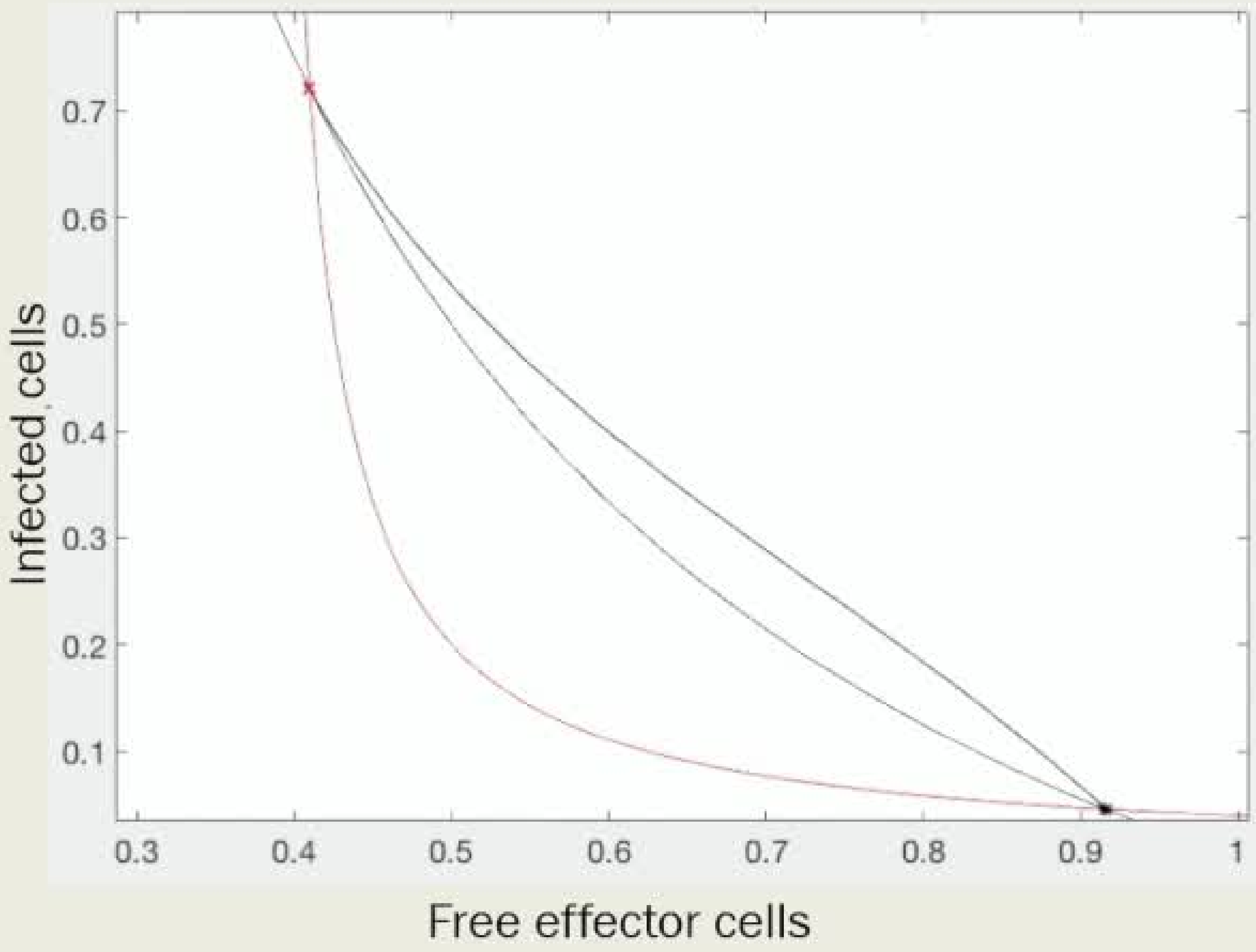
Hamiltonian

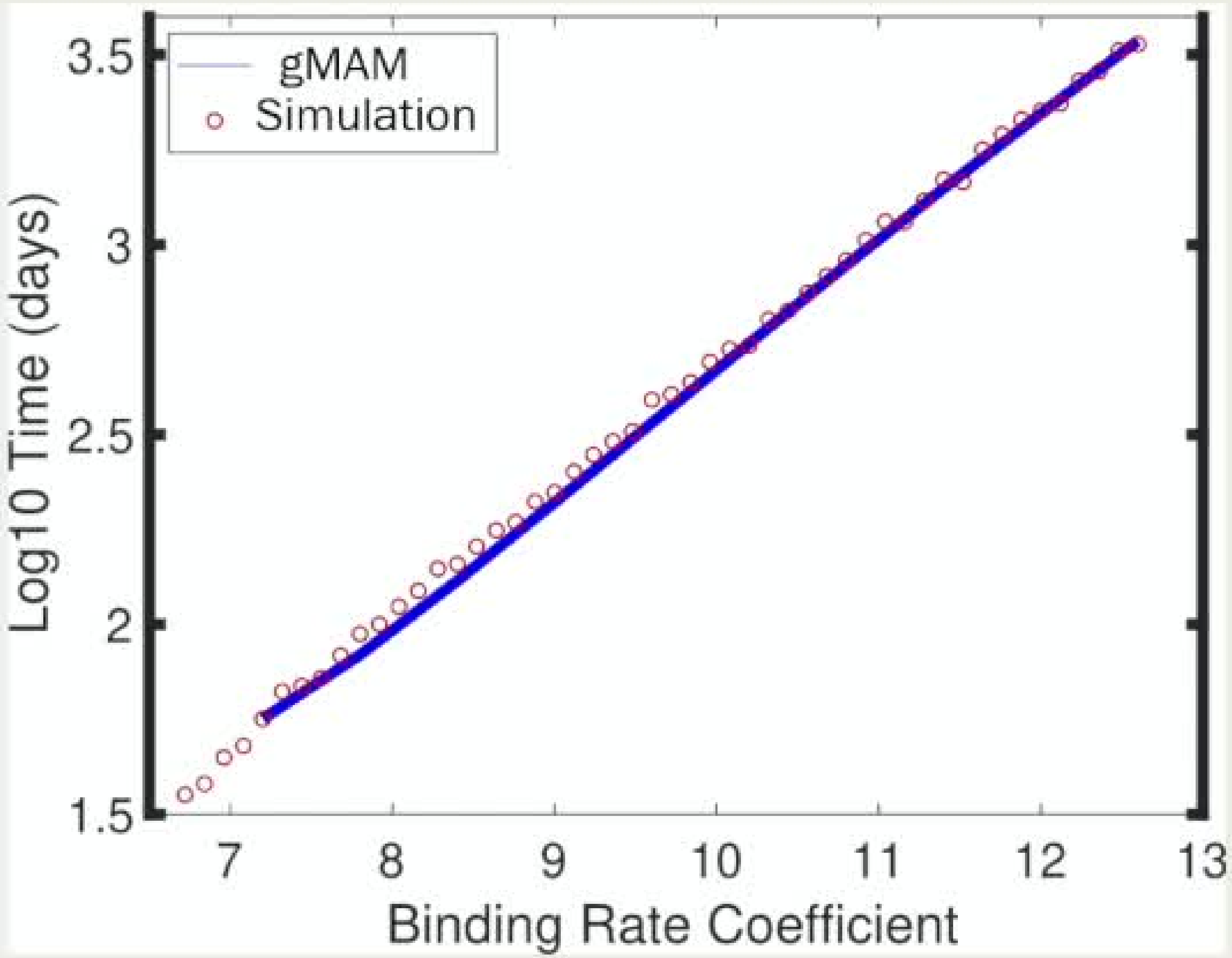
$$\mathcal{H} = V_x p_x + V_y p_y + \frac{1}{2} D_{xx} p_x^2 + \frac{1}{2} D_{yy} p_y^2 + D_{xy} p_x p_y$$

$$\begin{aligned} V_x &= -\delta x + \alpha + \lambda x - mxy \\ V_y &= -mxy + \omega(e_0 - y) \\ D_{xx} &= \delta x + \alpha + \lambda x + mxy \\ D_{yy} &= mxy + \omega(e_0 - y) \\ D_{xy} &= mxy. \end{aligned}$$

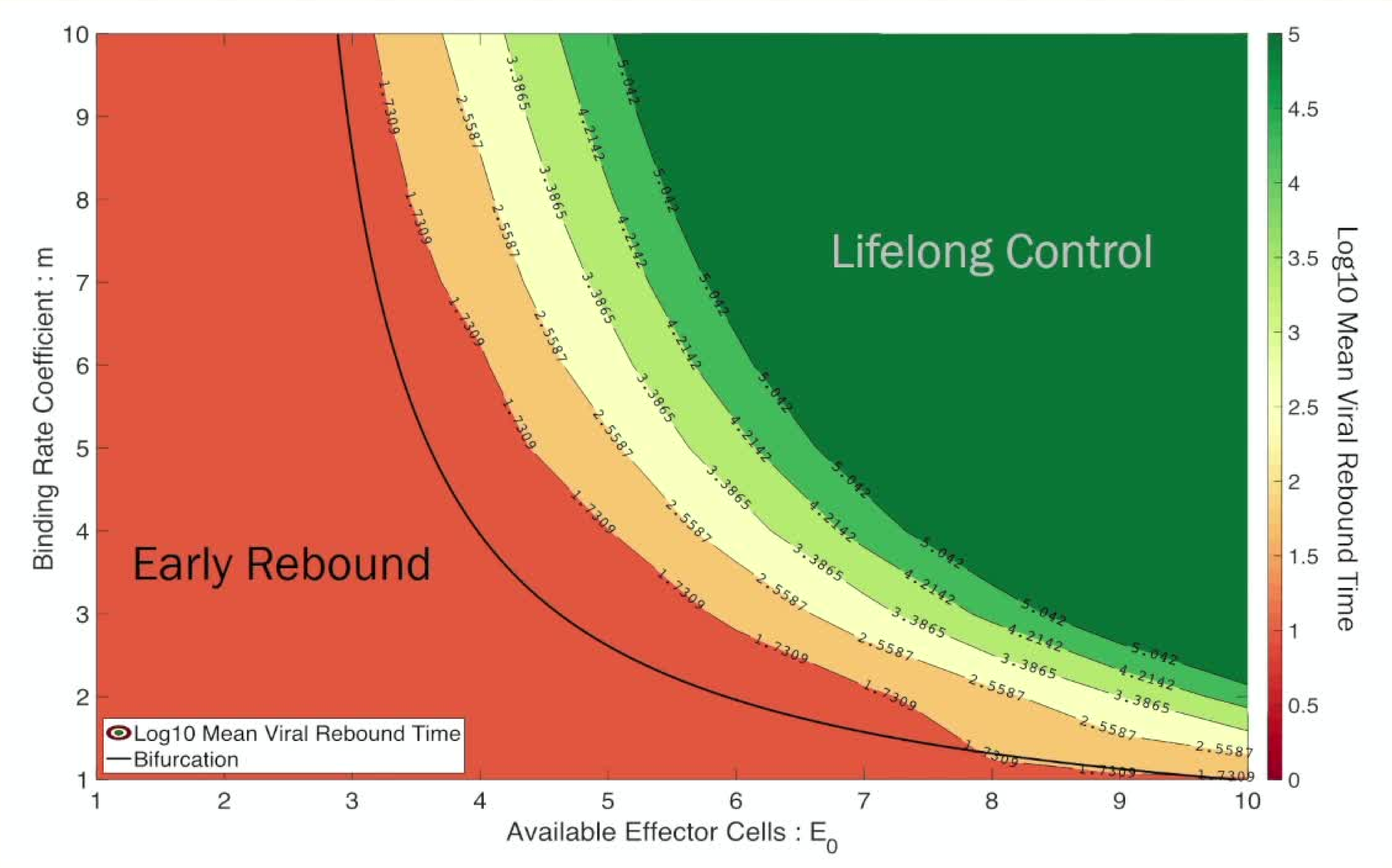
$$\frac{\partial S}{\partial x} = p_x \text{ and } \frac{\partial S}{\partial y} = p_y$$

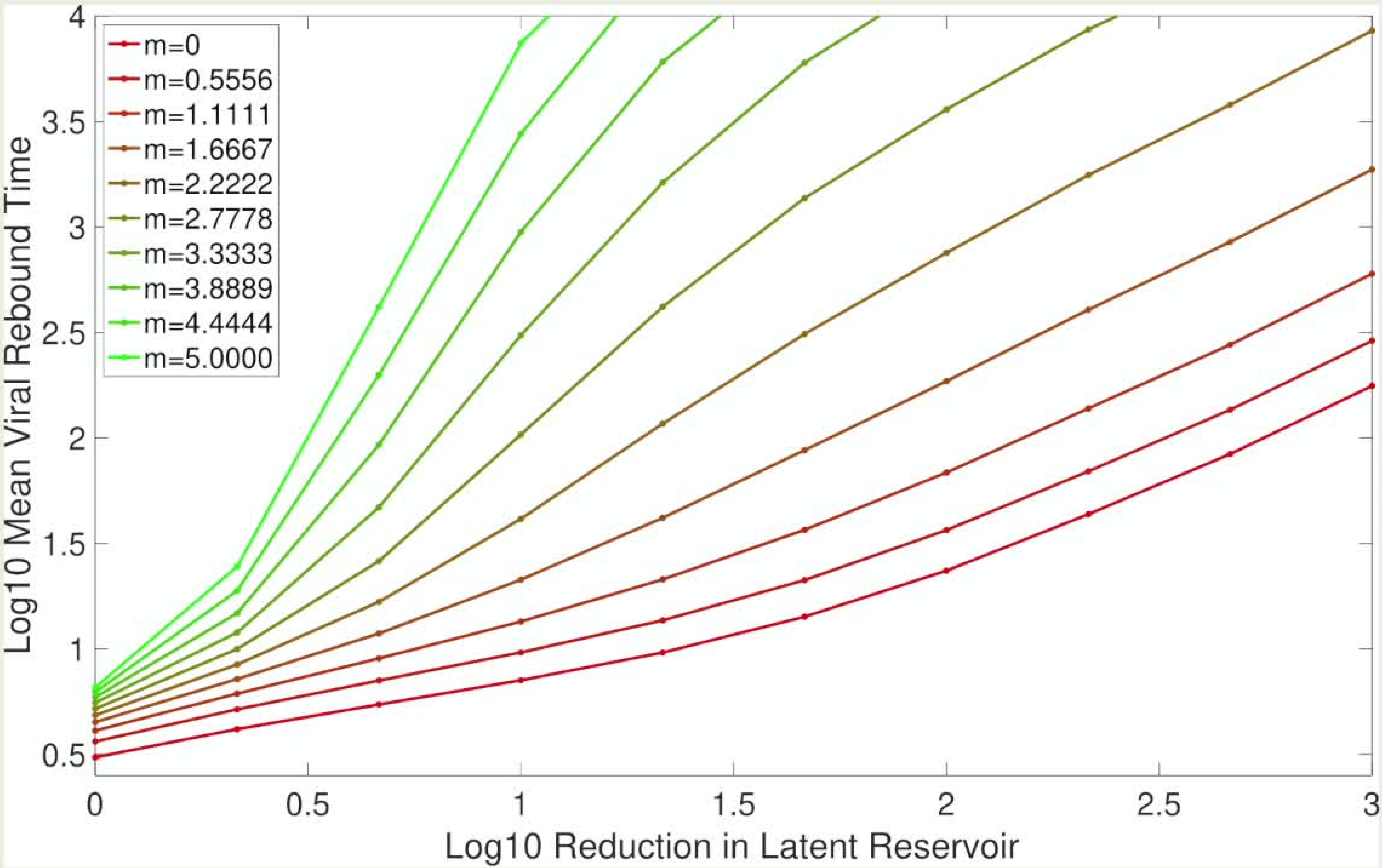
Comparison with Stochastic Simulation





Heymann 2007


Lifelong Control
Early Rebound
Binding Rate Coefficient : m
Available Effector Cells : E_0
Log10 Mean Viral Rebound Time
Log10 Mean Viral Rebound Time
Bifurcation
1.7309
2.5587
3.3865
4.2142
5.042



m=0
m=0.5556
m=1.1111
m=1.6667
m=2.2222
m=2.7778
m=3.3333
m=3.8889
m=4.4444
m=5.0000
Log10 Mean Viral Rebound Time
Log10 Reduction in Latent Reservoir
0.5
1
1.5
2
2.5
3
3.5
4
0
0.5
1
1.5
2
2.5
3

Implications

- Host variation in immune pressure can explain the large spread in rebound times
  - *Model can explain both quick rebound and long term control*
  - *Increased immune pressure increases sensitivity to changes in the latent reservoir*
- Supports the idea that the immune response is important in understanding PTC
  - *Work by Borducchi/Barouch*
  - *Expansion of the model can be used to help guide clinical questions*
- Hamiltonian methods make model comparison more practical
  - *Does not rely on stochastic simulations*

Acknowledgments

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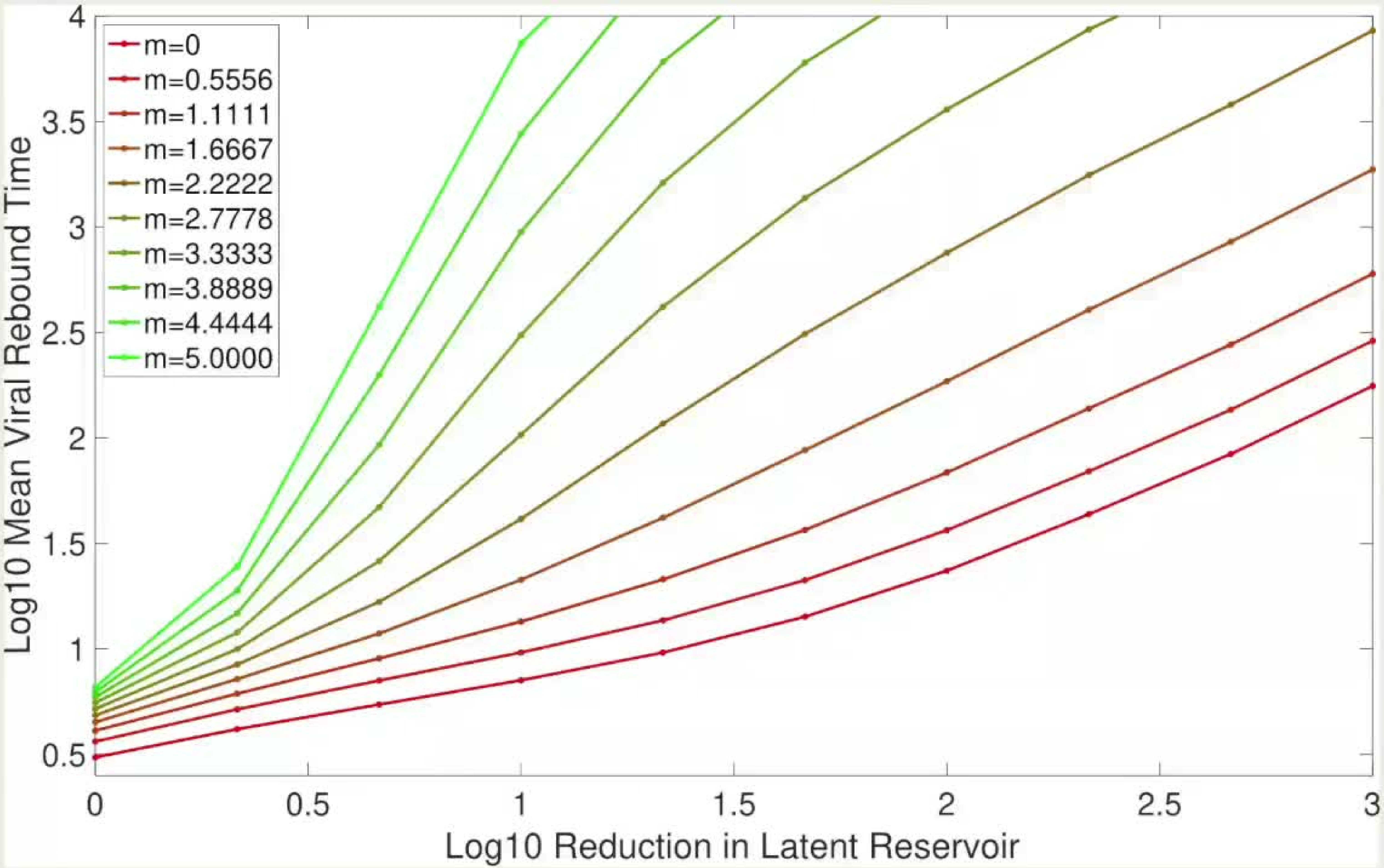
Group: Theoretical Biology and Biophysics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Log10 Reduction in Latent Reservoir
0.5
1
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3.5
4
0
0.5
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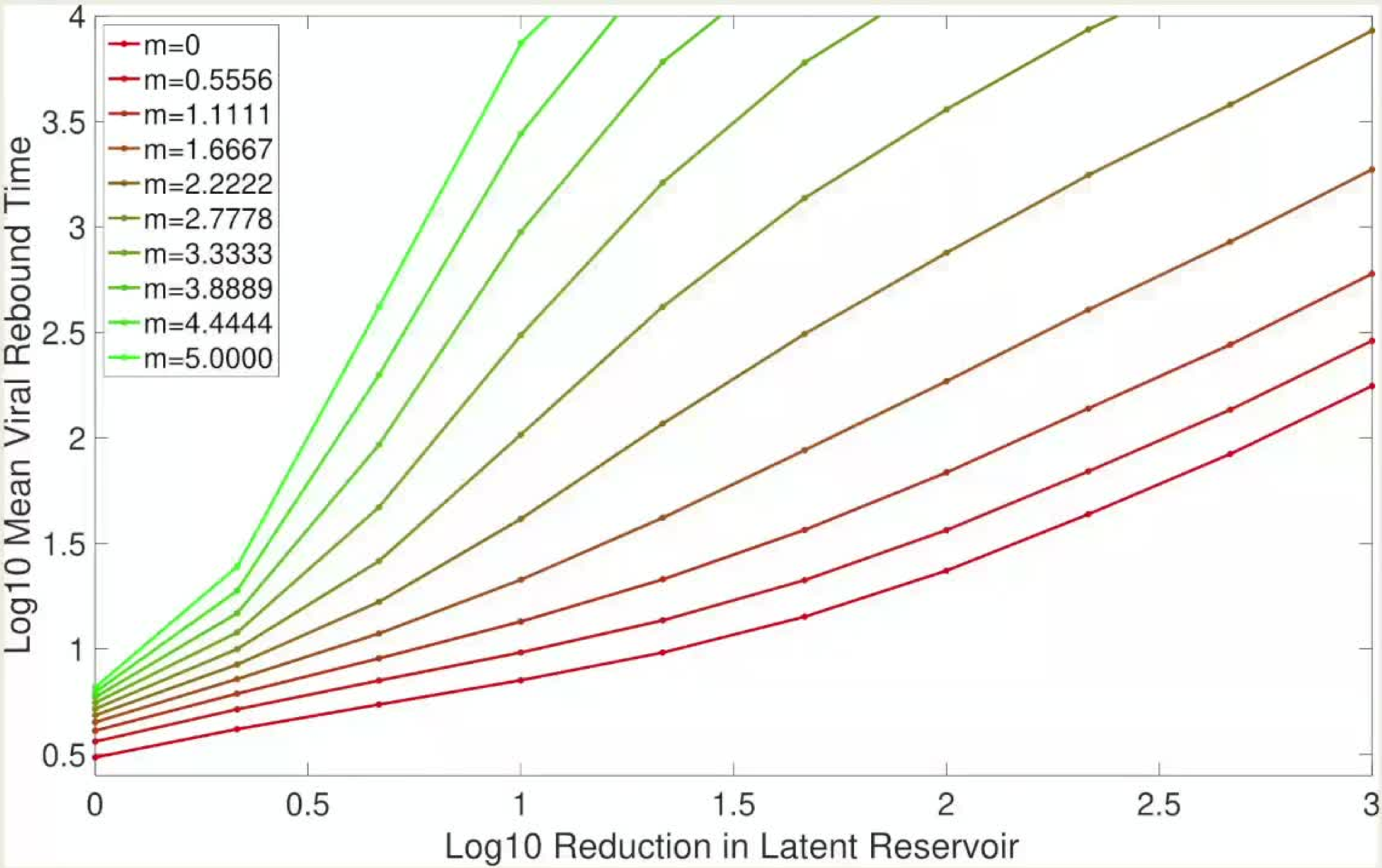
1.5
2
2.5
3



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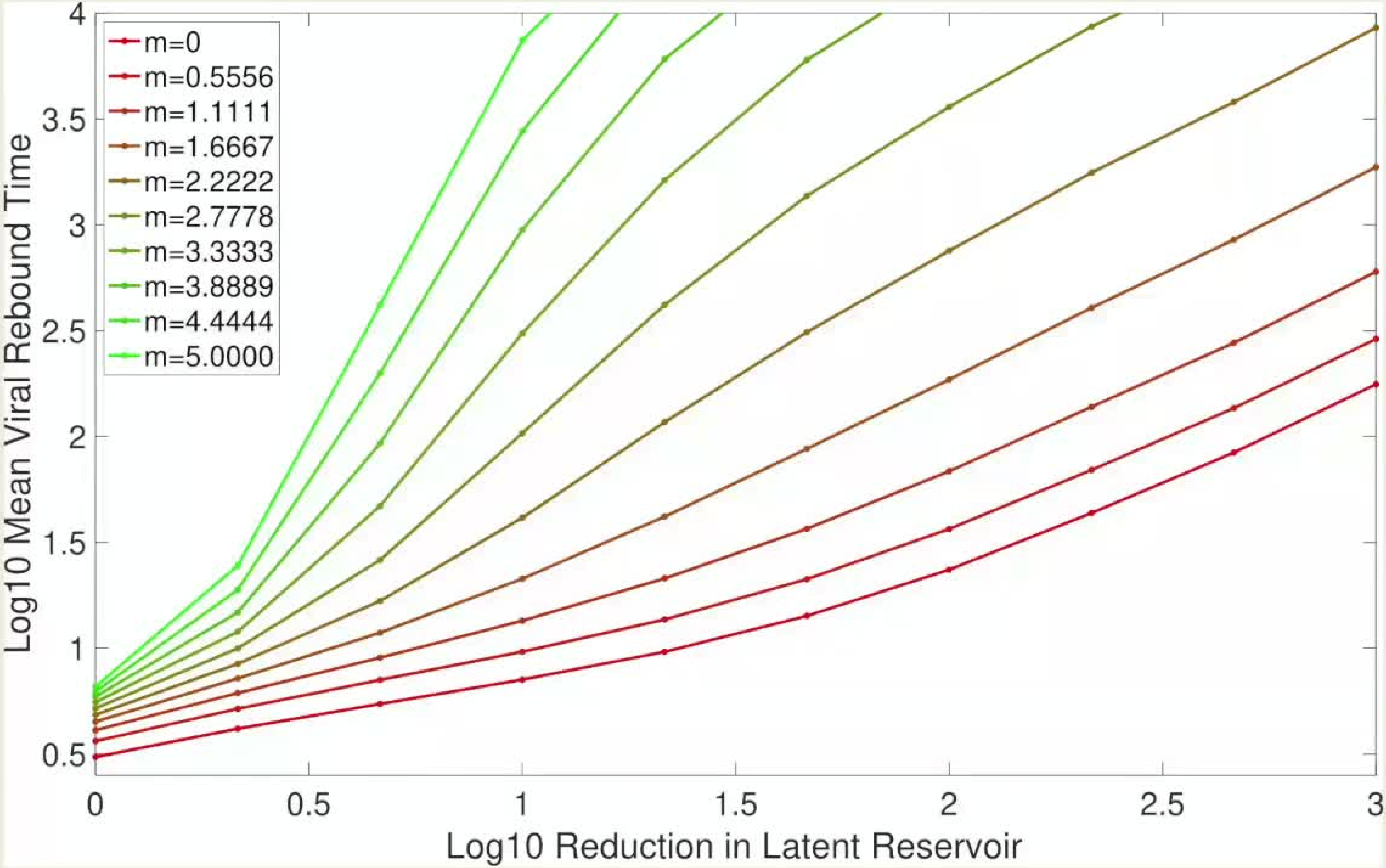

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1
1.5
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2.5
3
3.5
4
0
0.5
1
1.5
2
2.5
3

Master Equation

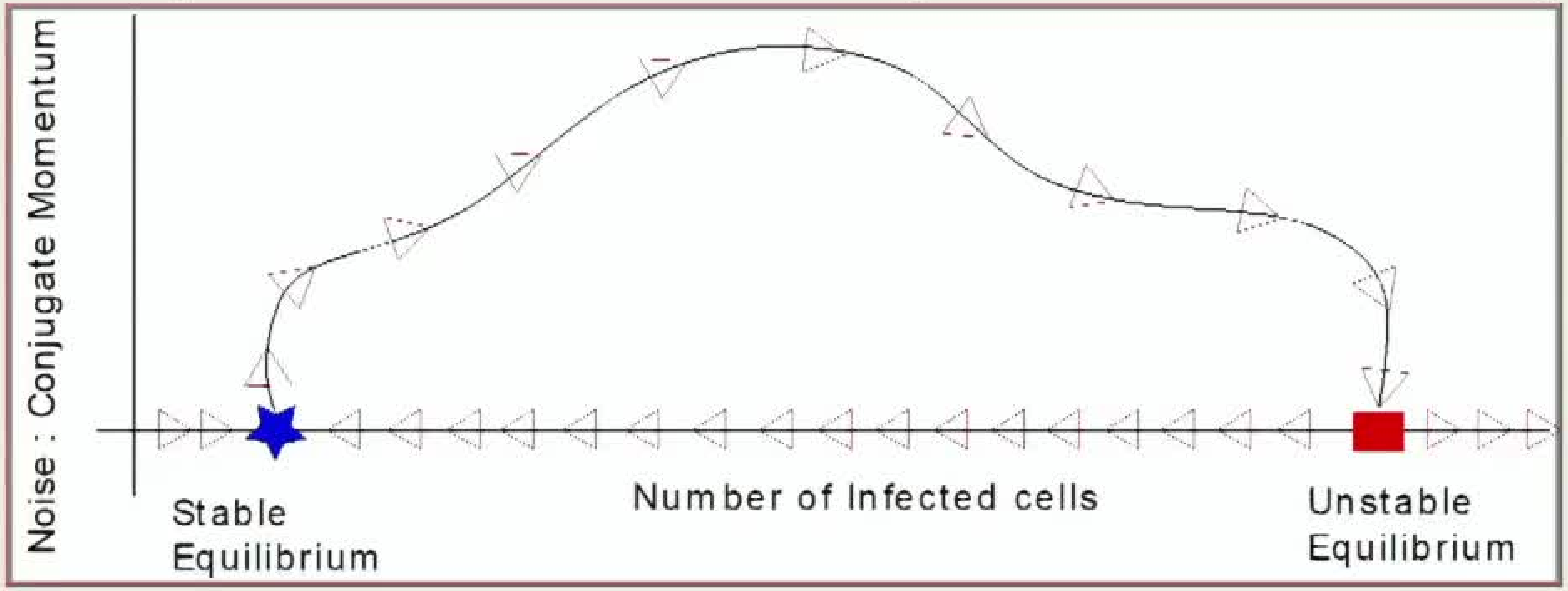
General Discrete Master Equation:

$$\frac{dP(\mathbf{X},t)}{dt} = \sum_{\mathbf{r}} \left[W(\mathbf{X}\text{-}\mathbf{r};\mathbf{r}) P(\mathbf{X}\text{-}\mathbf{r},t) - W(\mathbf{X};\mathbf{r}) P(\mathbf{X},t) \right]$$

HIV-model Master Equation:

$$\begin{aligned}
\dot{P}(I,E;t) = {} & \delta[(I+1)P(I+1,E;t) - IP(I,E;t)] + \alpha N[P(I-1,E;t) - P(I,E;t)] \\
& + \lambda[(I-1)P(I-1,E;t) - IP(I,E;t)] \\
& + mN^{-1}[(E+1)(I+1)P(I+1,E+1;t) - EIP(I,E;t)] \\
& + \omega[(E_0 - E + 1)P(I,E-1;t) - (E_0 - E)P(I,E;t)]
\end{aligned}$$

Escape From Stable EQ to Unstable EQ



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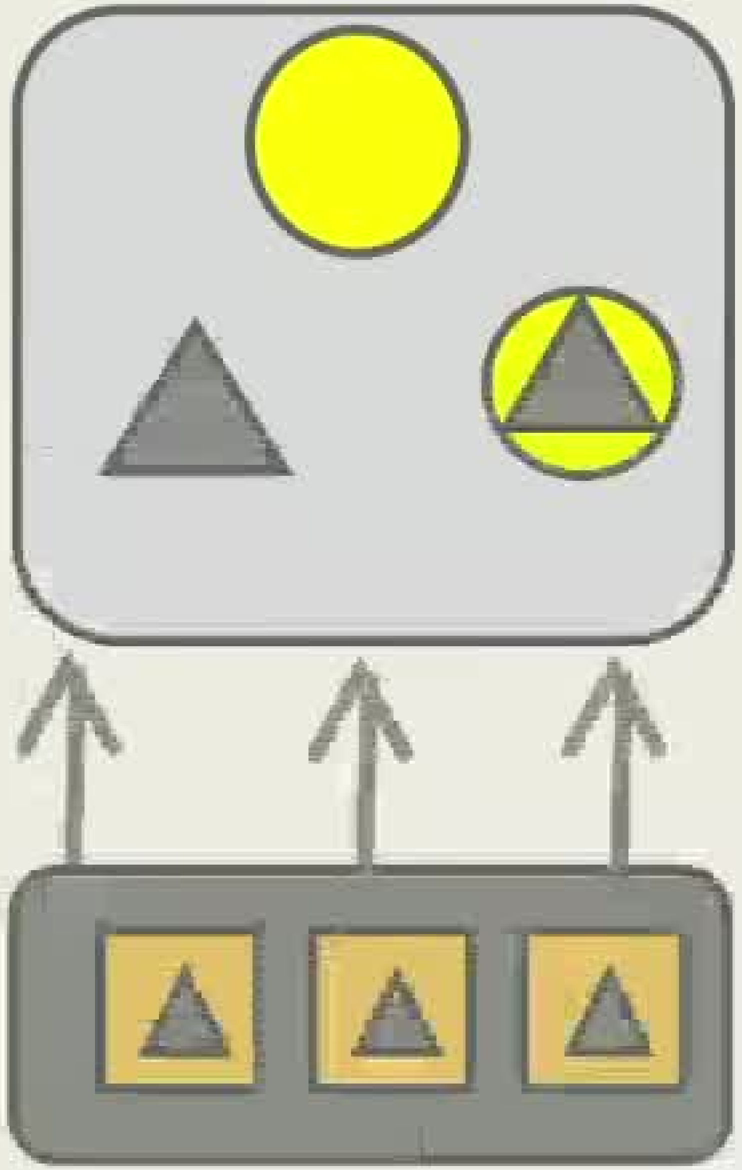

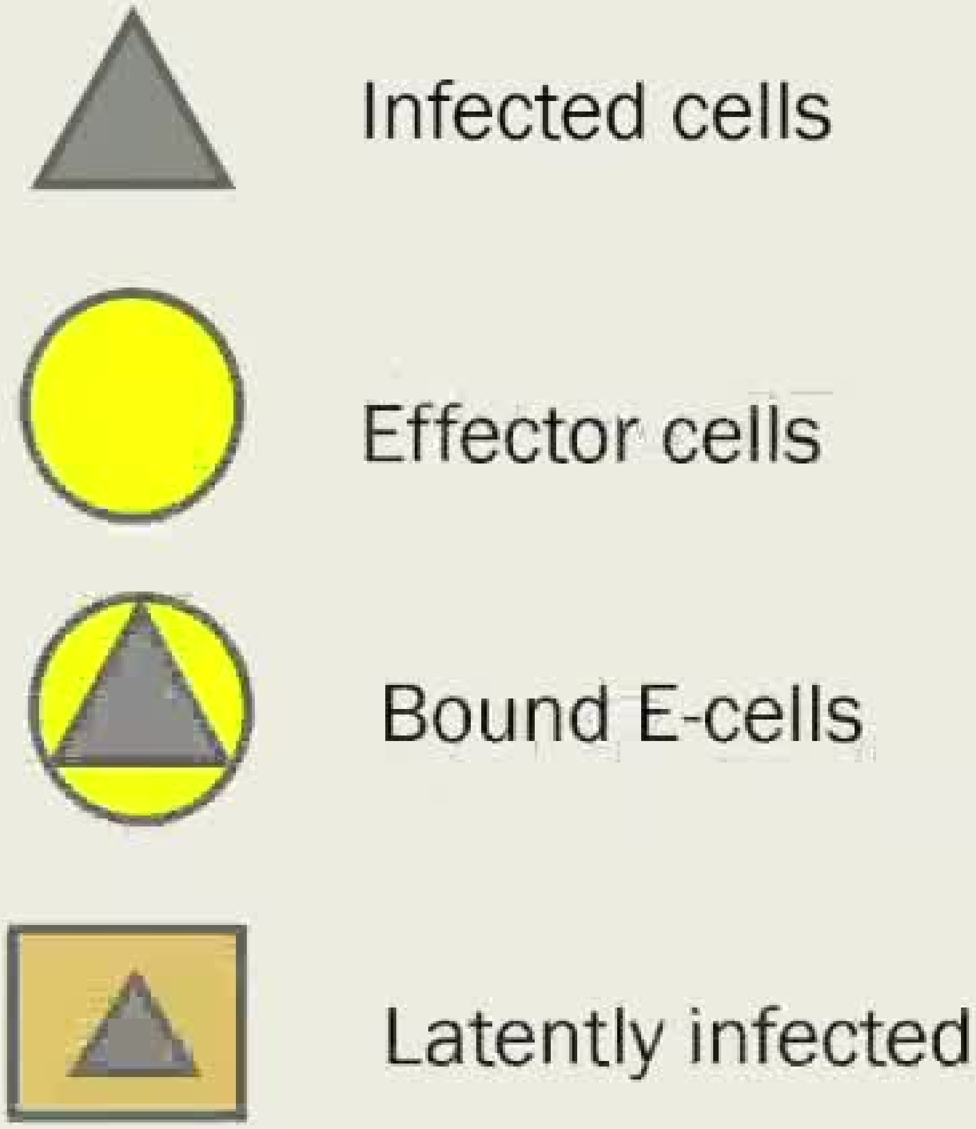

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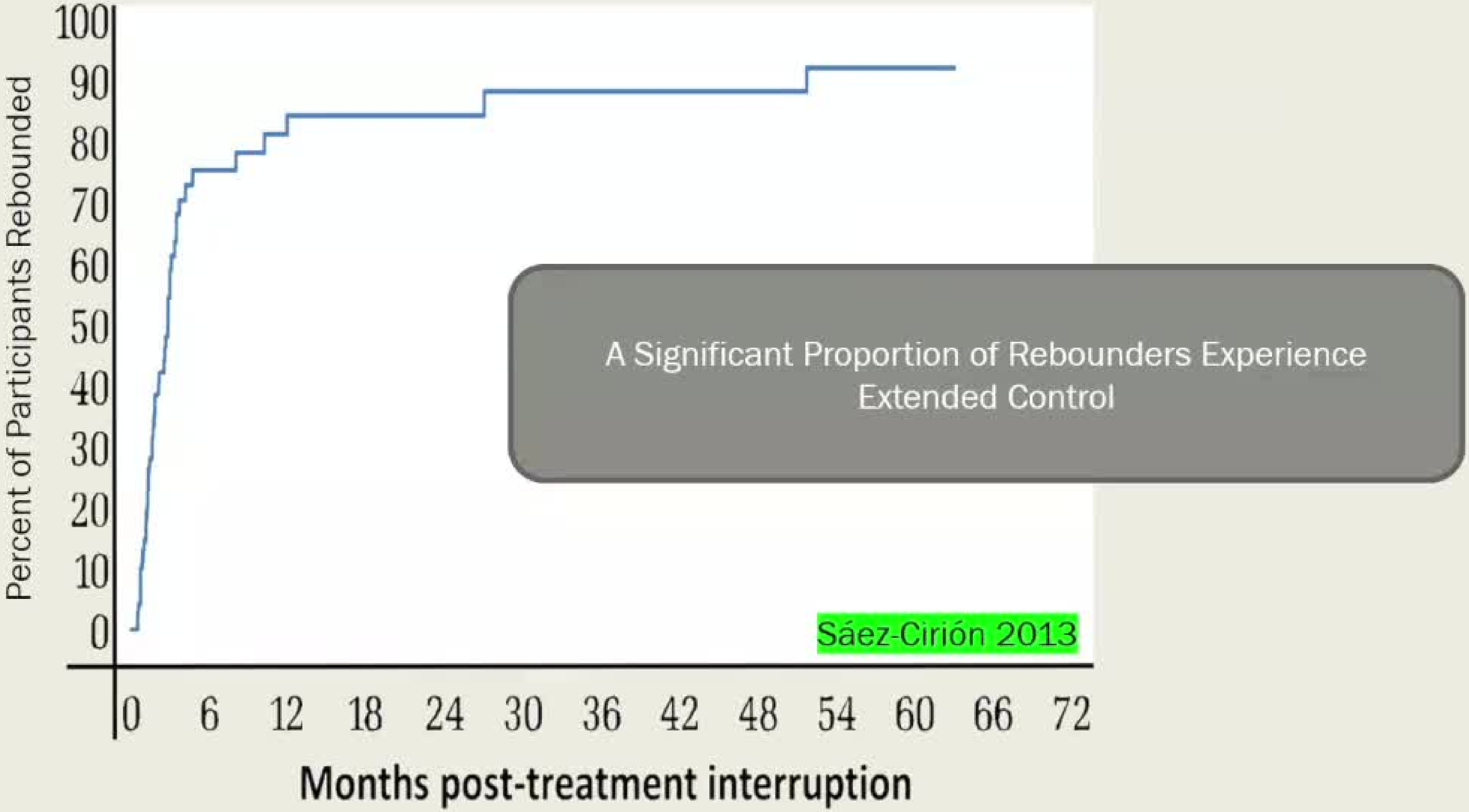
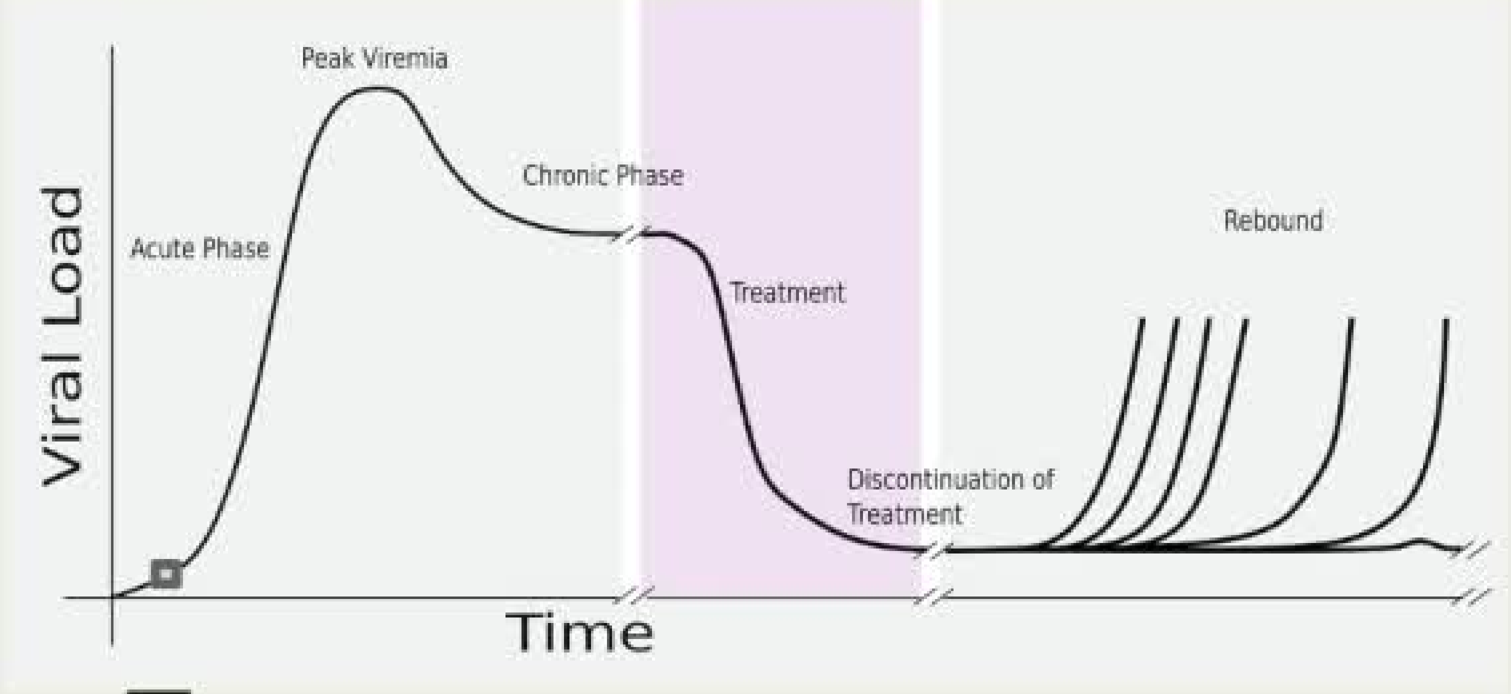
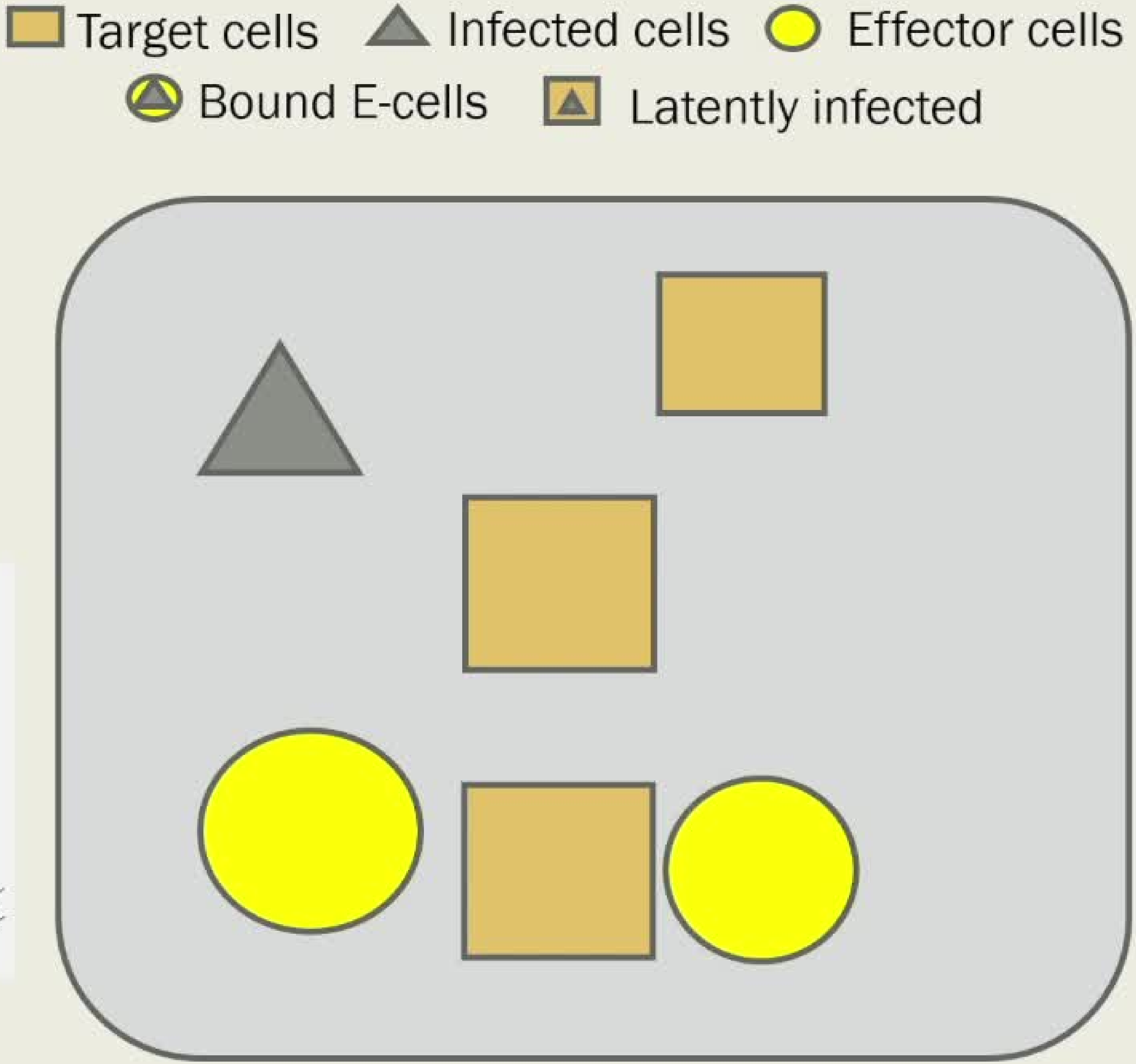


Infection Event

- Virus introduced to host



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The Role of Immune Pressure

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This is a sketch of a typical HIV infection with treatment during the chronic phase. Note that after discontinuation of treatment there is a large spread among rebounders; some rebound in weeks, and some take years

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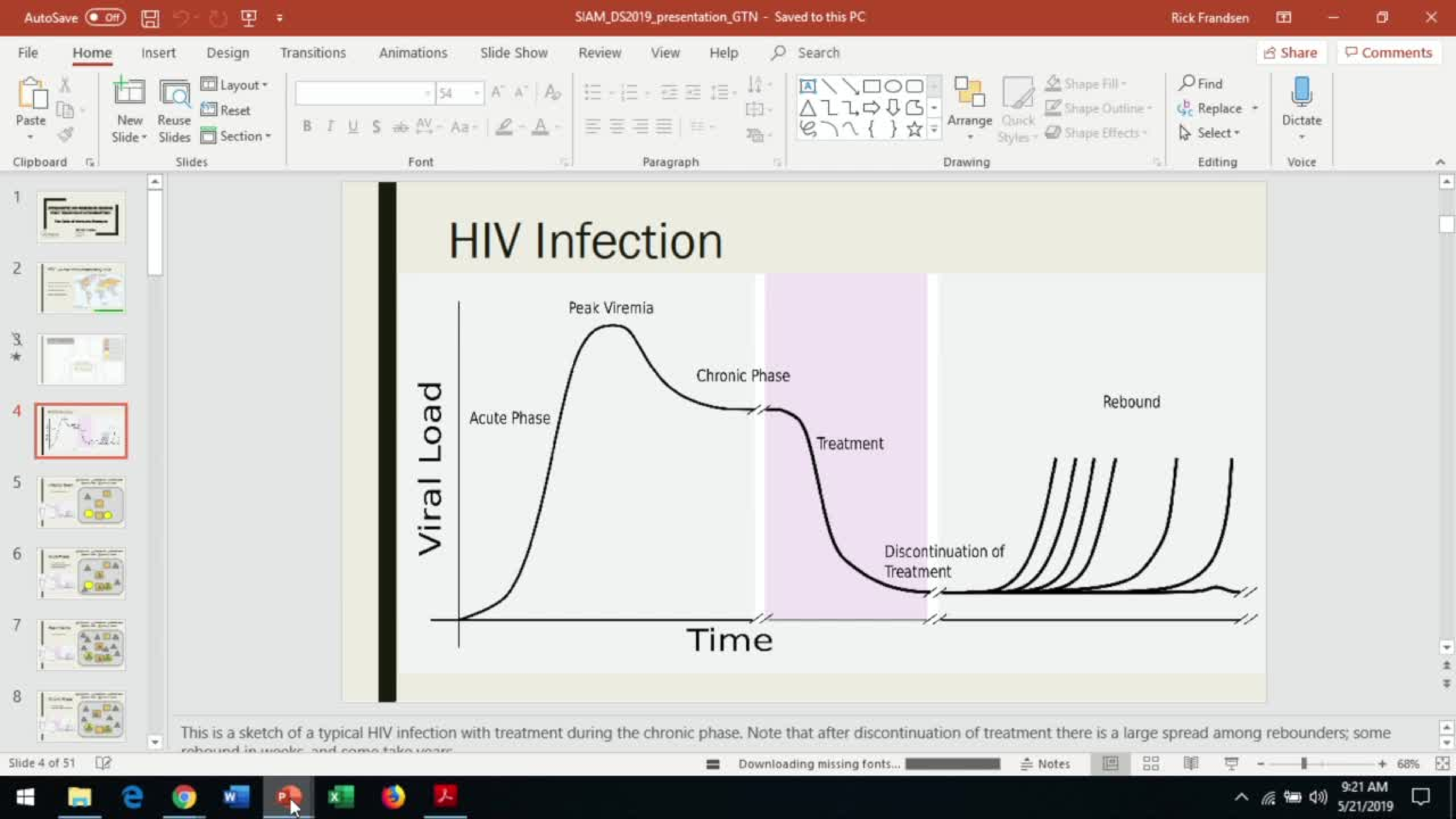
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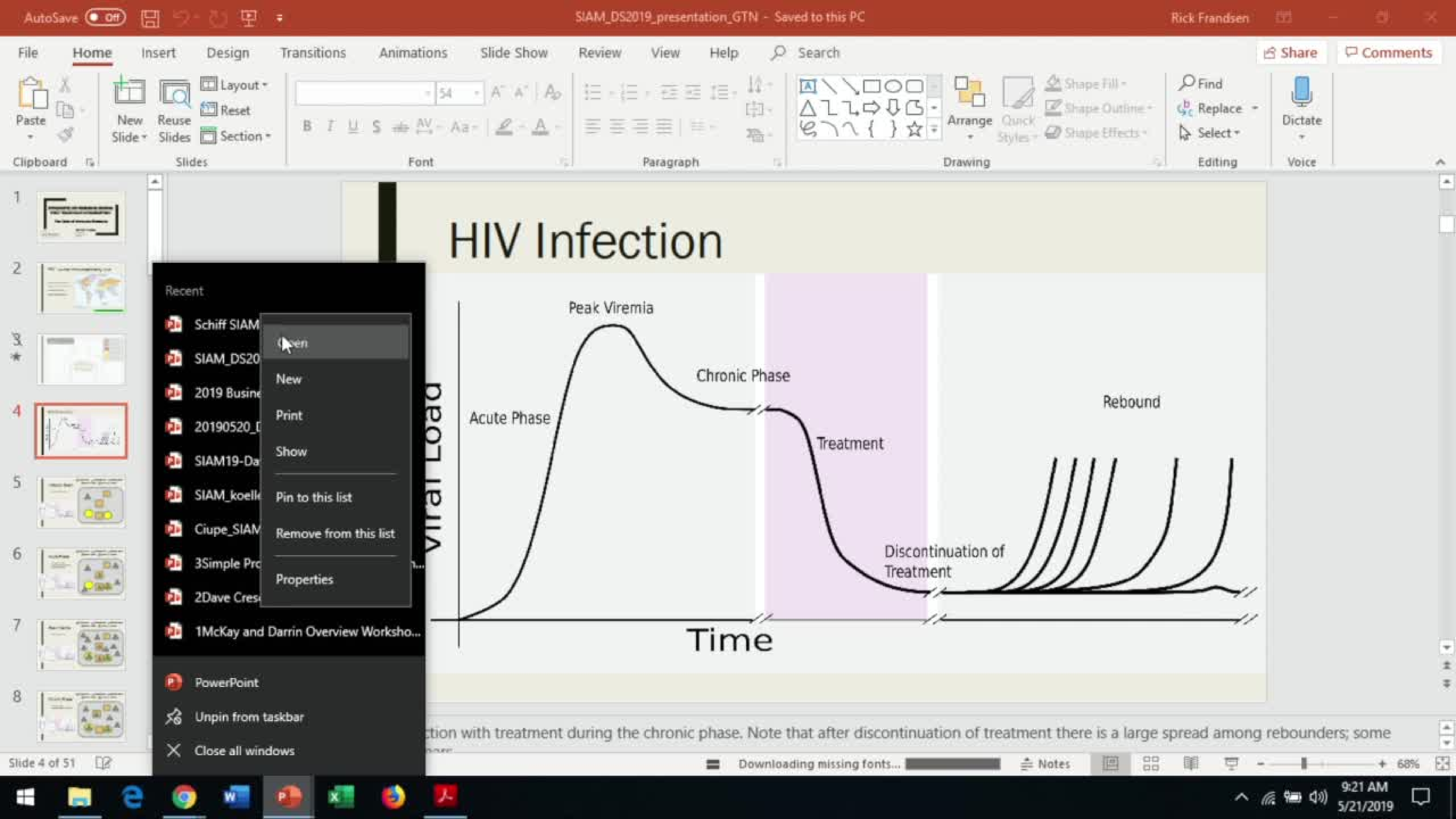
HIV Infection
Peak Viremia
Chronic Phase
Acute Phase
Treatment
Rebound
Discontinuation of Treatment
Viral Load
Time
This is a sketch of a typical HIV infection with treatment during the chronic phase. Note that after discontinuation of treatment there is a large spread among rebounders; some
Slide 4 of 51



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HIV Infection
Peak Viremia
Chronic Phase
Acute Phase
Treatment
Rebound
Discontinuation of Treatment
Viral Load
Time
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