Evolution of HIV-1 Across the Within and Between-Host Scales: The Role of Transmission Bottlenecks

SIAM Conference on Applications of Dynamical Systems
MS12 Advances in Infectious Disease Modeling
Sunday May 17th, 2019

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Multi-Scale Evolution

- Within-host
  - HIV-1 is a rapidly replicating retrovirus
  - Estimated 10^8 newly infected cells per day
- Transmission Bottleneck
  - In the majority of cases, new infections are started by a single virus strain
- Between-host
  - 1.8 million new HIV infections in 2017

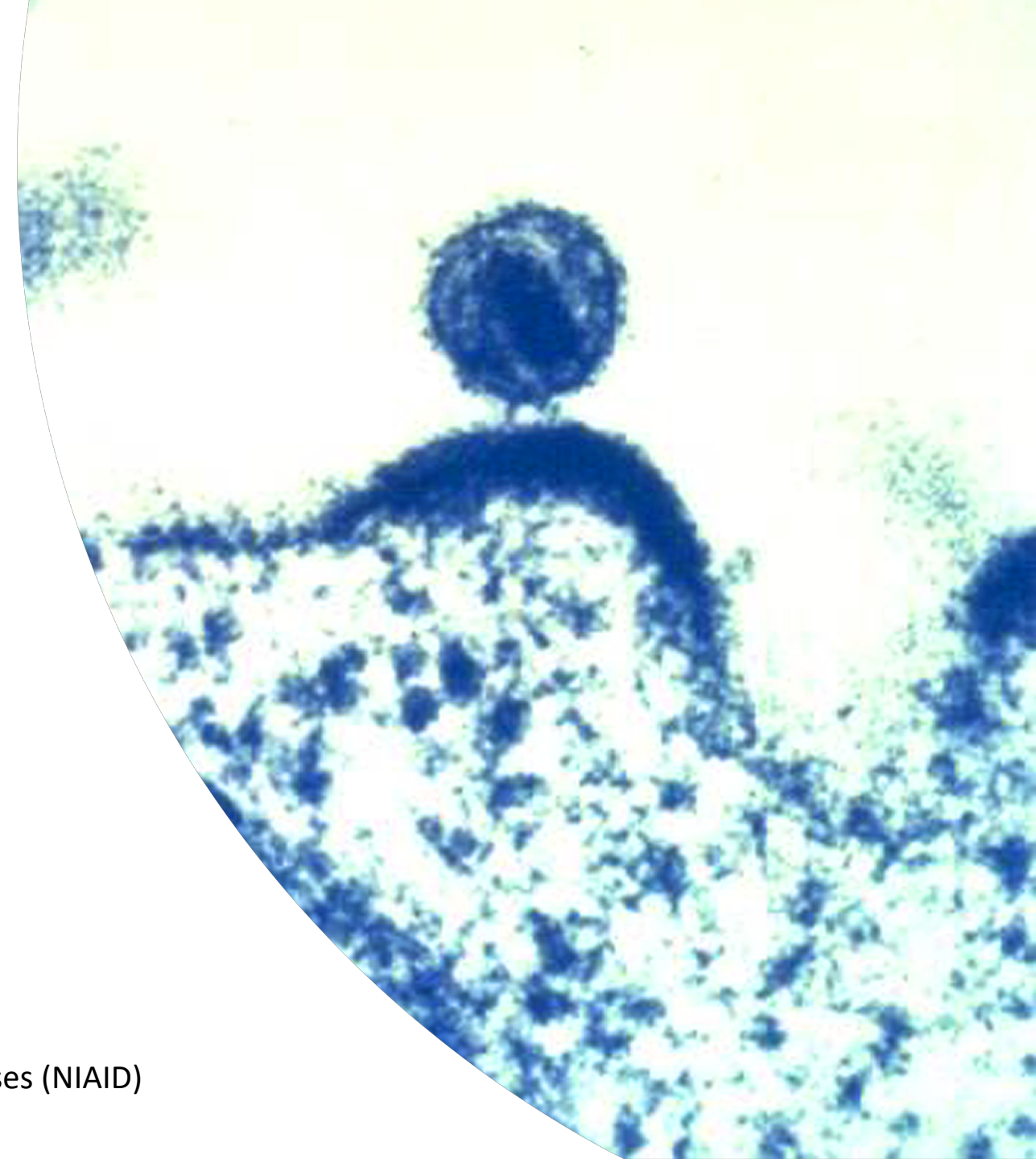
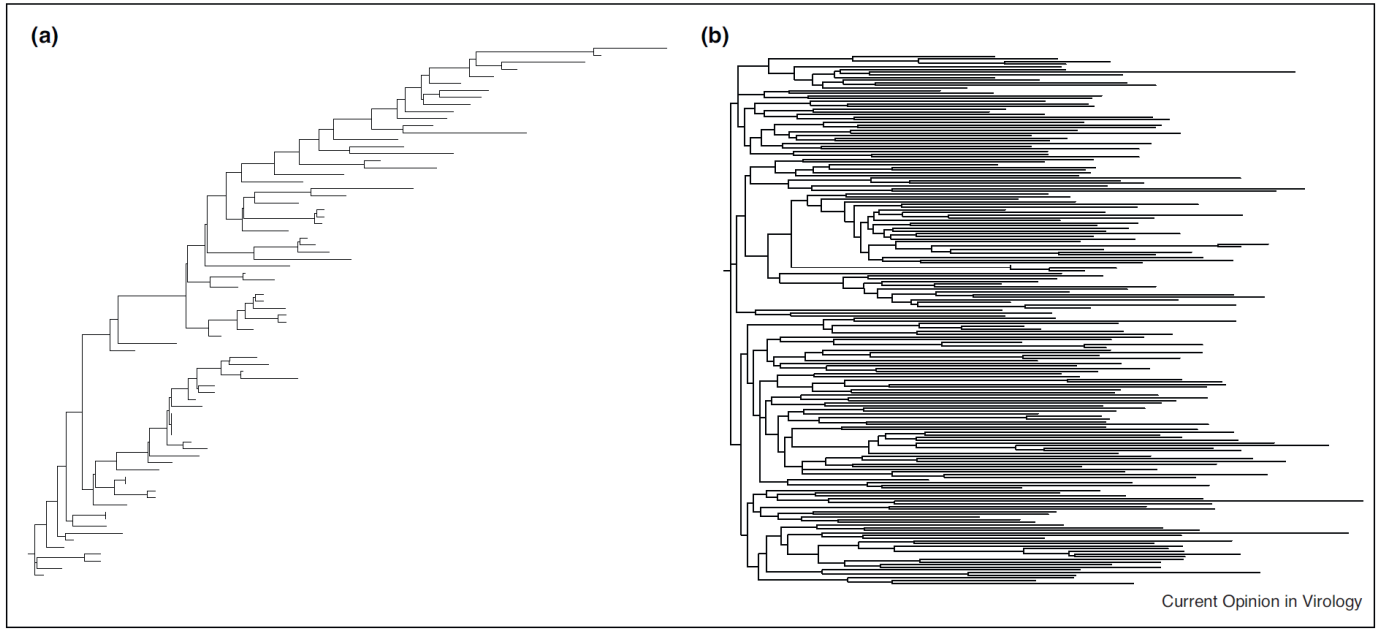


Photo Credit: National Institute of Allergy and Infectious Diseases (NIAID)

Multi-Scale Evolution: Transmission Bottleneck

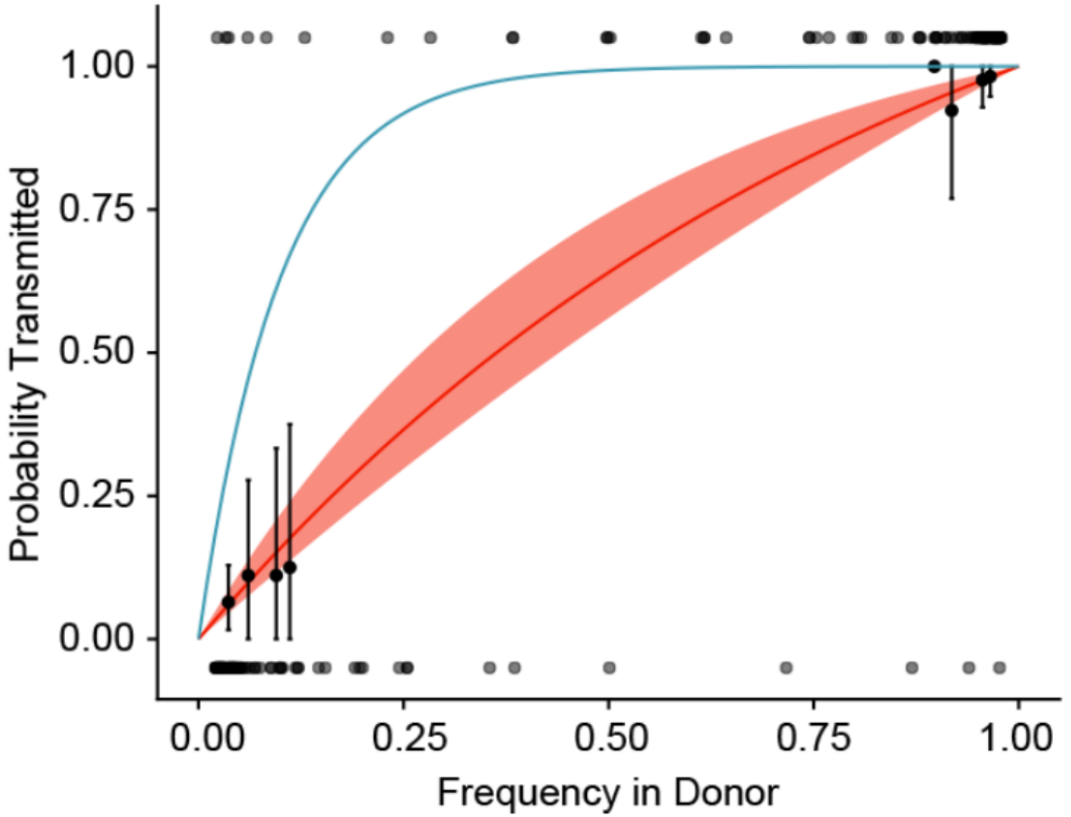
- The rate of evolution of the virus is 2 to 6 times greater within than between hosts.
- A current hypothesis: The HIV-1 latent reservoir acts to archive less-evolved virus for later transmission.
- We offer a complimentary hypothesis: traits for efficiency of transmission, across the bottleneck, are not under direct selection and are thus subject to drift within-host



Theys K., et. al., *The impact of HIV-1 within-host evolution on transmission dynamics*, Current Opinion in Virology Dec; 28:92-101. doi: 10.1016/j.coviro.2017.12.001 (2018)

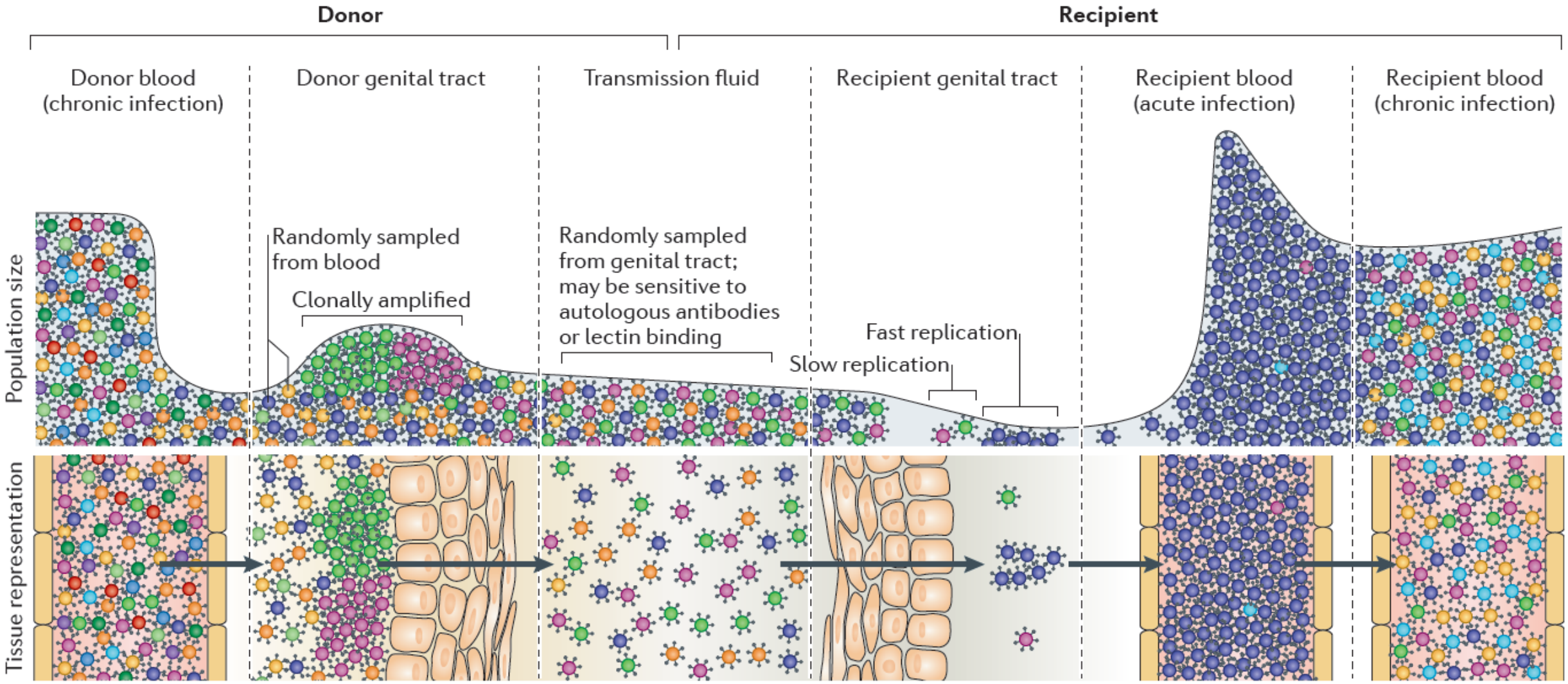
Multi-Scale Evolution: Insights from Influenza

- Within-host evolution of influenza virus is consistent with a neutral model of evolution
- Uncertainty of the between-host bottleneck size
- Rare variants have a low probability of transmission
- Influenza evolution is dominated by stochasticity on local scales and positive selection on global scales



McCrone J., et. al., *Stochastic processes constrain the within and between host evolution of influenza virus.* 2018;7:e35962. doi: 10.7554/eLife.35962 (2018)

Multi-Scale Evolution: Transmission Bottleneck



Joseph S., et. al., *Bottlenecks in HIV-1 transmission: insights from the study of founder viruses*, Nat Rev Microbiol. 2015 Jul;13(7):414-25. doi: 10.1038/nrmicro3471. (2015)

Questions

Does allowing transmission fitness to evolve within-host without direct selection pressure have the effect of slowing the observed rate of evolution over epidemic time?

Is the difference between within- and between host evolutionary rates sensitive to the size and composition of the bottleneck Inoculum?

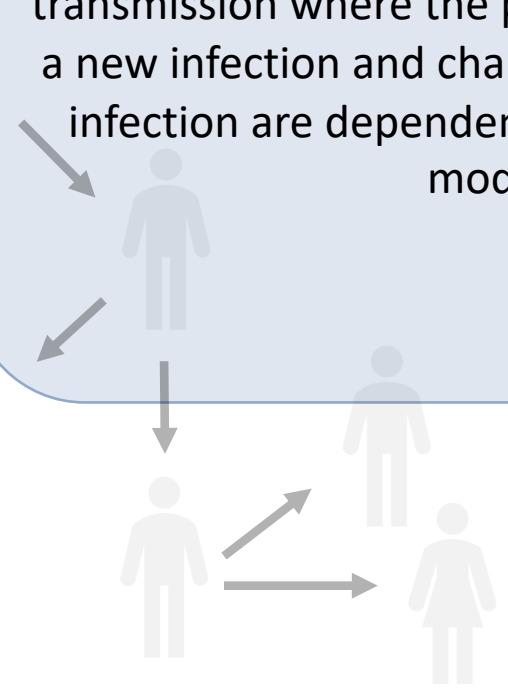
Methods: Overview

Within-host

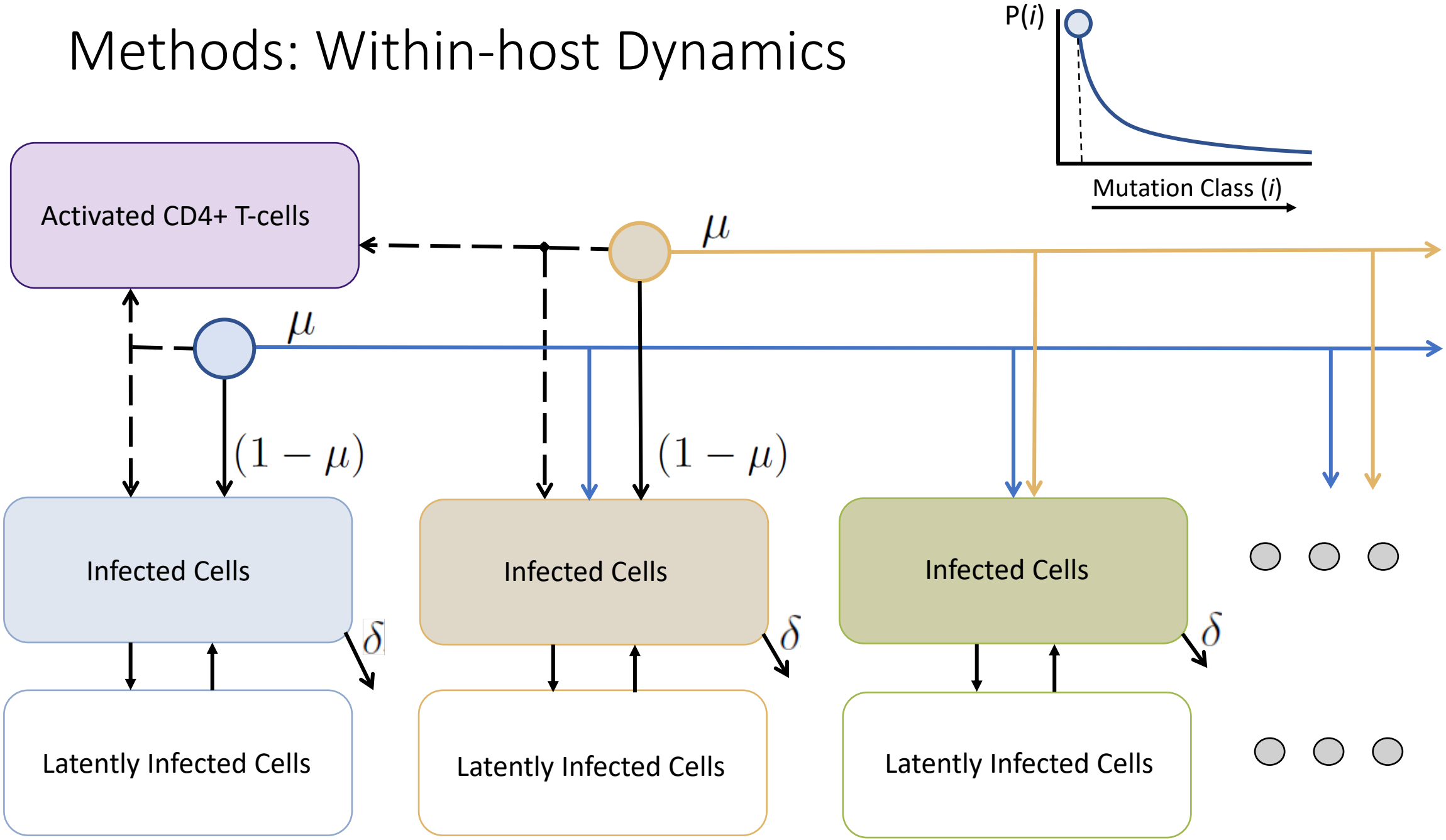
Deterministic host-cell-limited model of viral dynamics with fitness evolution and a latent reservoir

Between-host

Stochastic branching process model of disease transmission where the probability of founding a new infection and characteristics of the new infection are dependent on the within-host model



Methods: Within-host Dynamics



Methods: Fitness Evolution Within-host

$$\dot{x} = \lambda - dx - x\sum_{i}^{n} \beta y_i$$

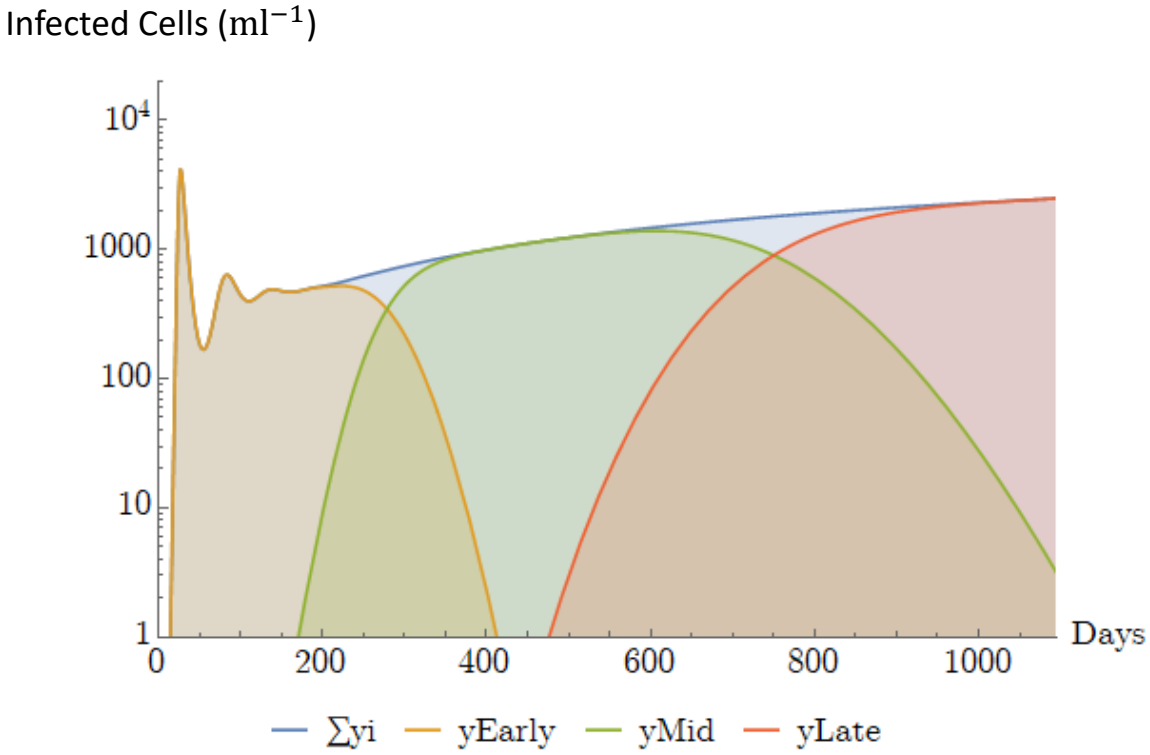
μ

$$\dot{y}_i = x(1-\mu)\beta y_i + x\mu \sum_{j=1}^{n} \beta K(i-j) y_j - \delta_i y_i - \gamma y_i + \alpha l_i$$

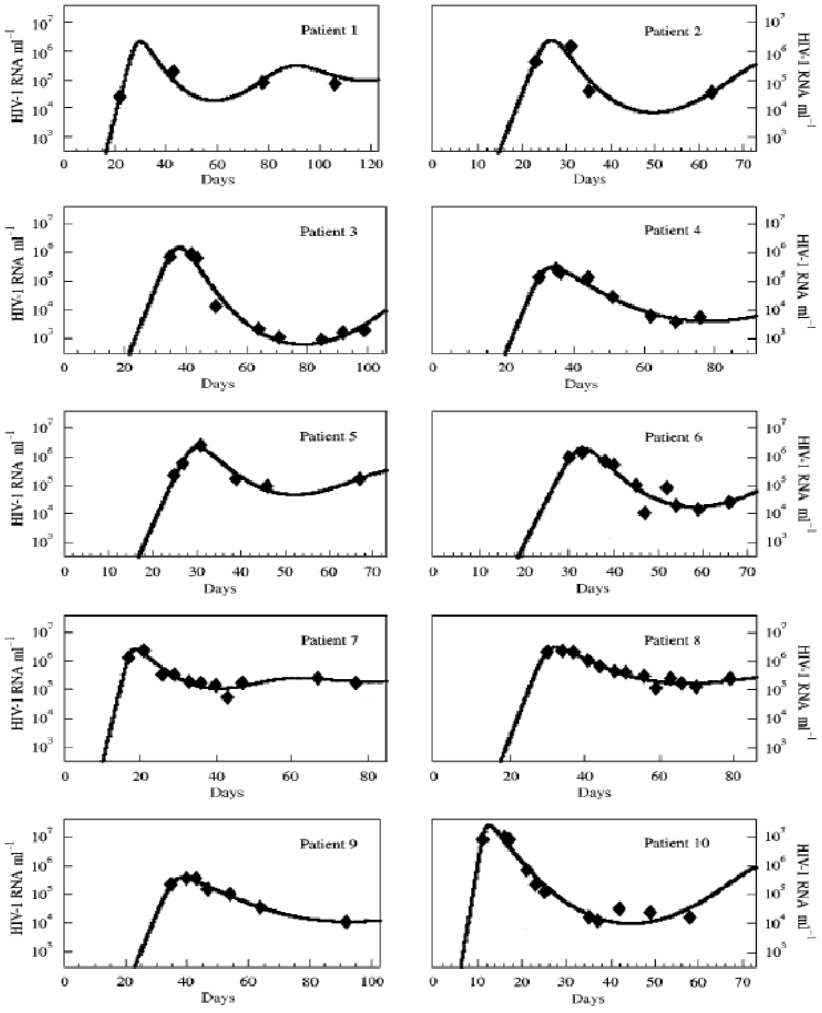
$$\dot{l}_i = \gamma y_i + (\rho - \alpha) l_i.$$

New fitness classes arise during viral replication

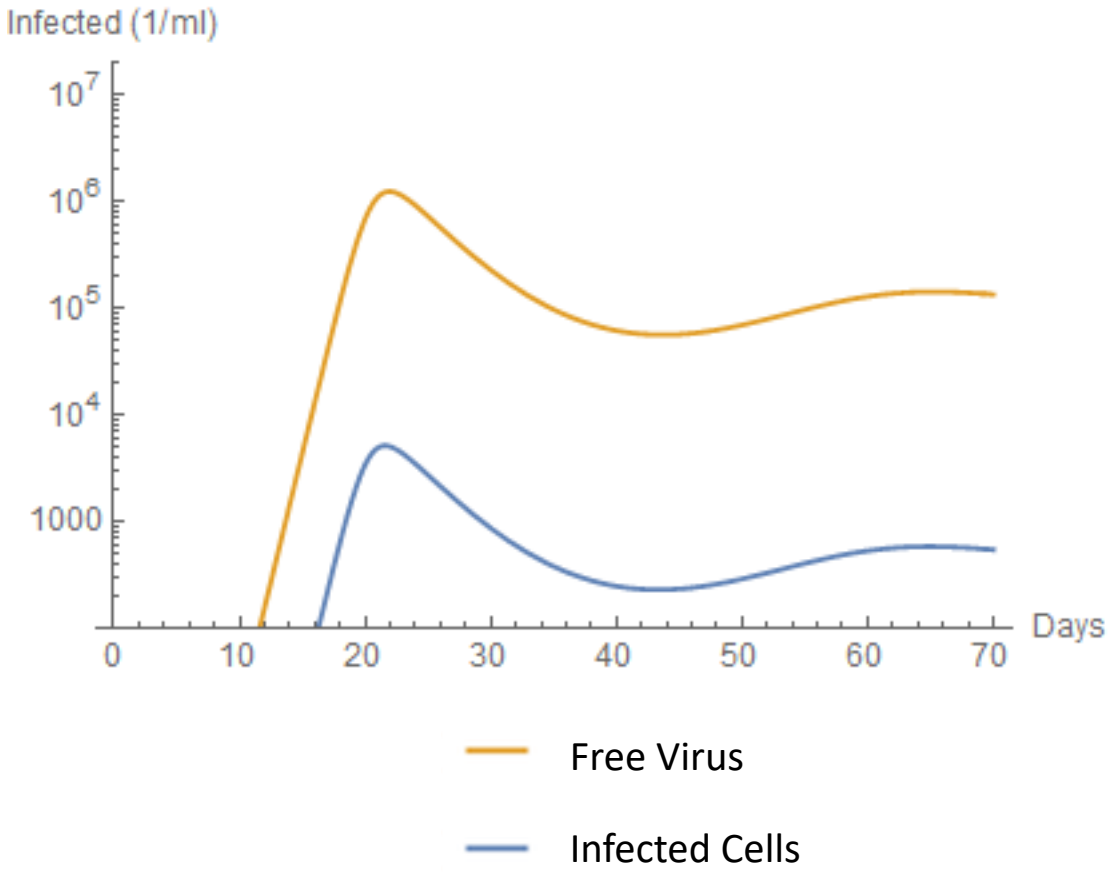
Increased fitness is included as a decreased removal rate of infected cells



Methods: Model Parameters



Stafford, et. al., *Modeling Plasma Virus Concentration during Primary HIV Infection*, J. theor. Biol. (2000) 203:285-301. doi:10.1006/jtbi.2000.1076



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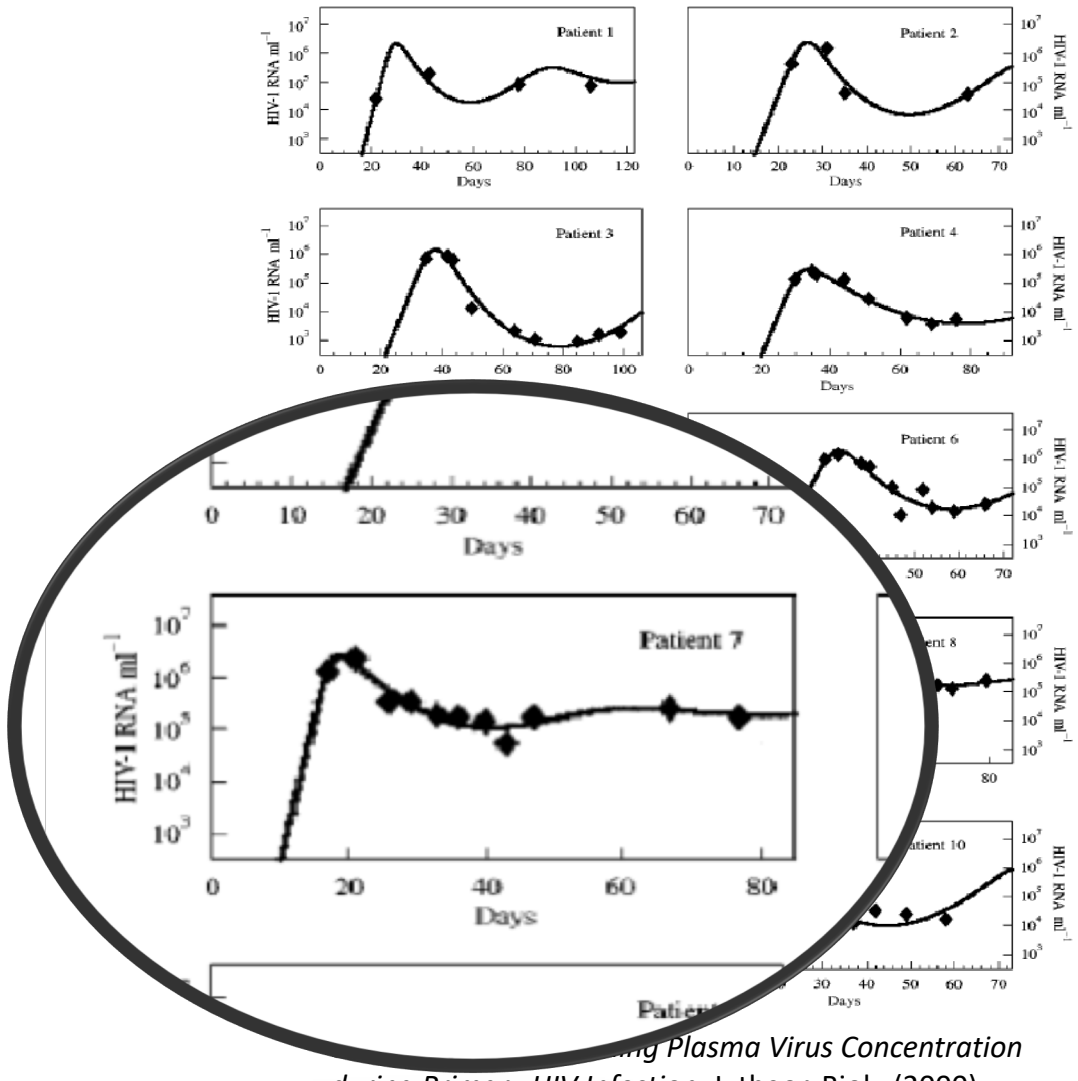

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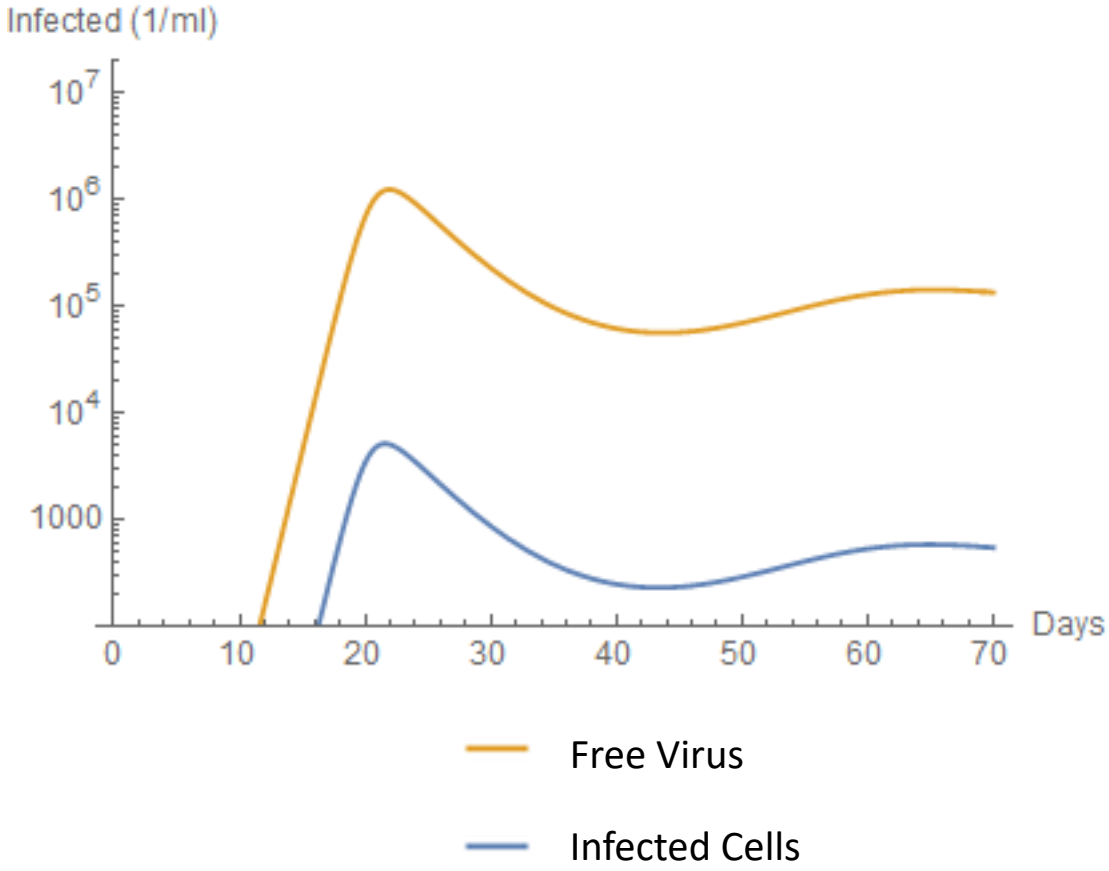
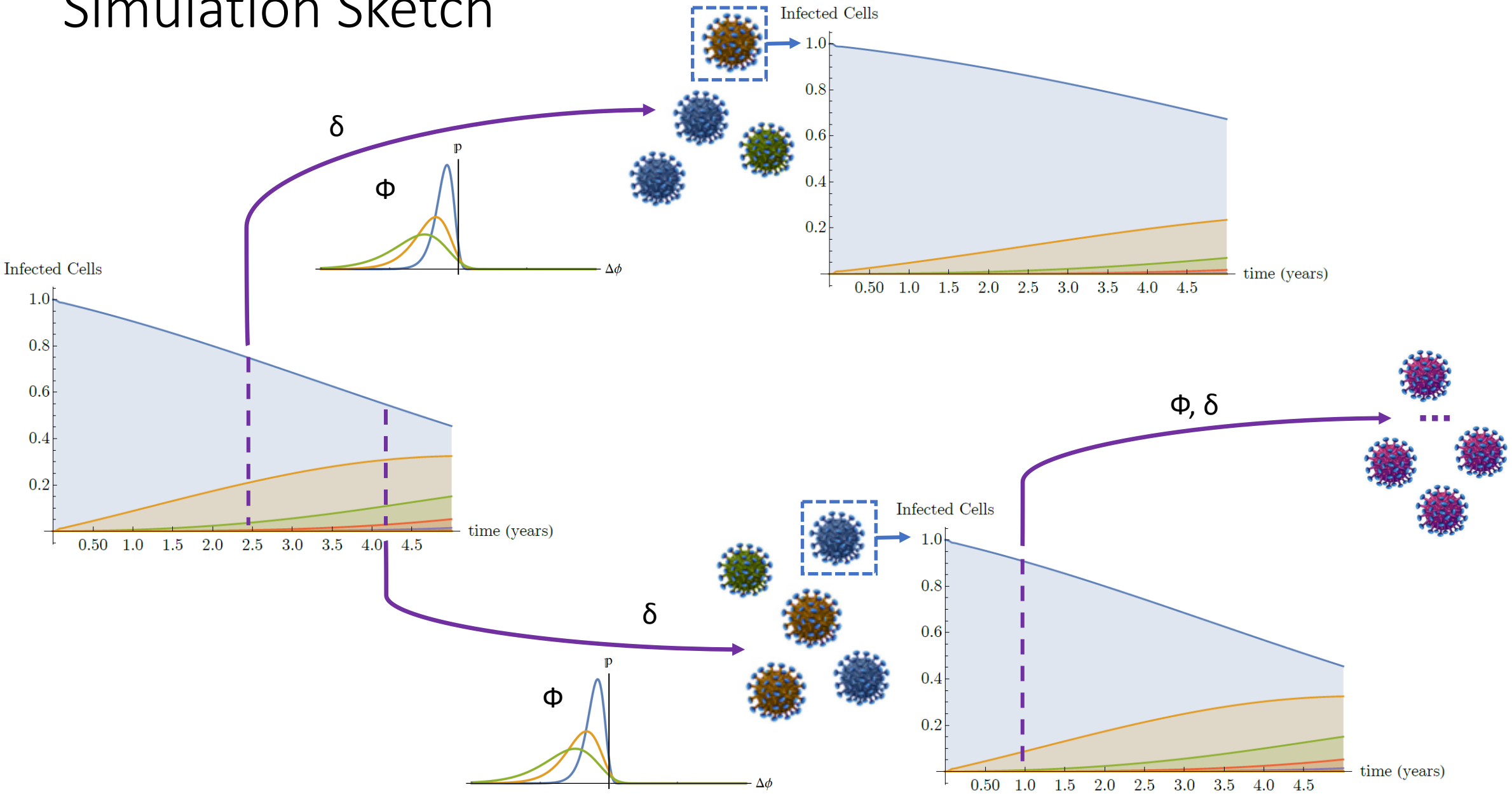


Simulation Sketch



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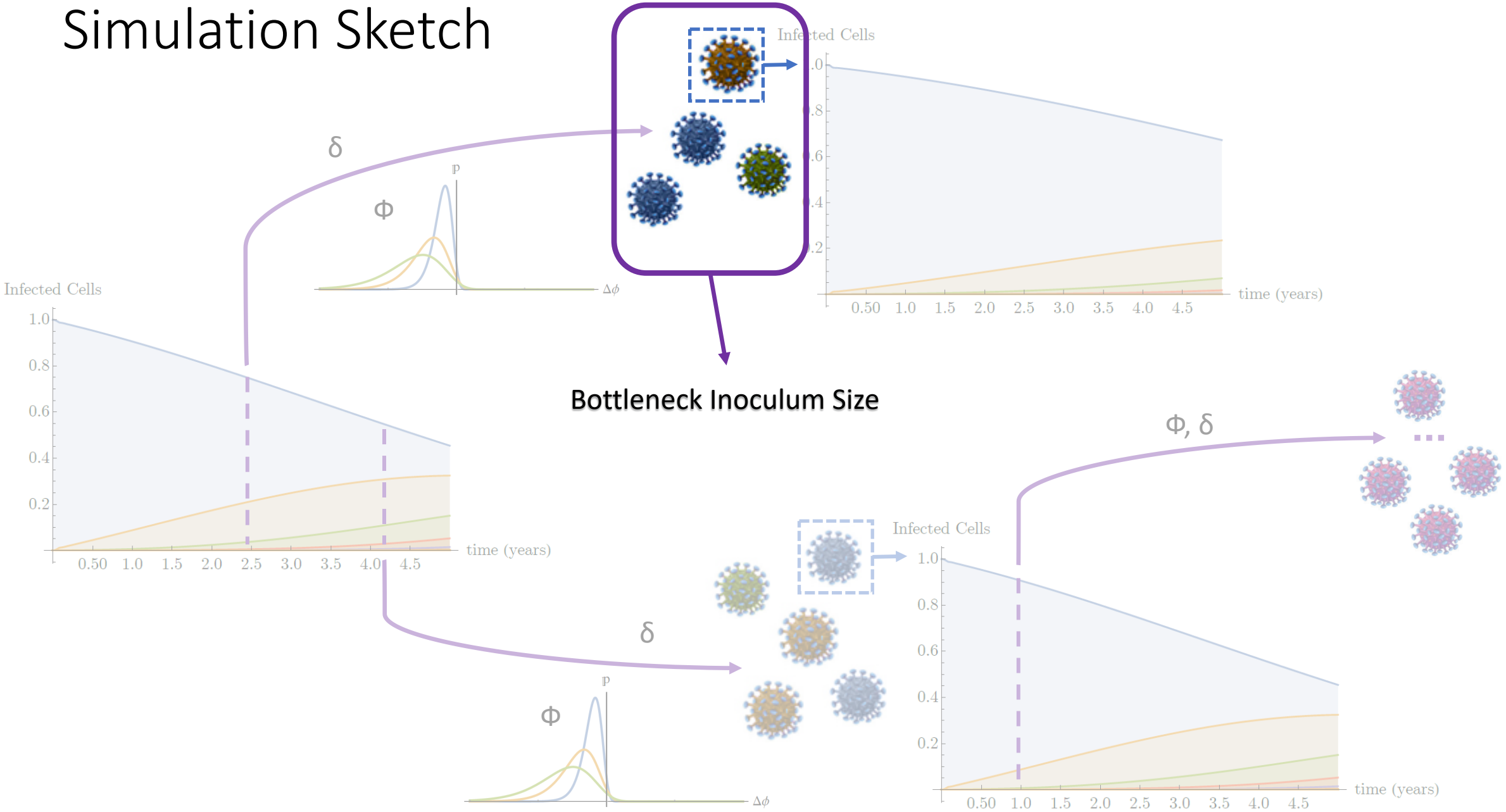

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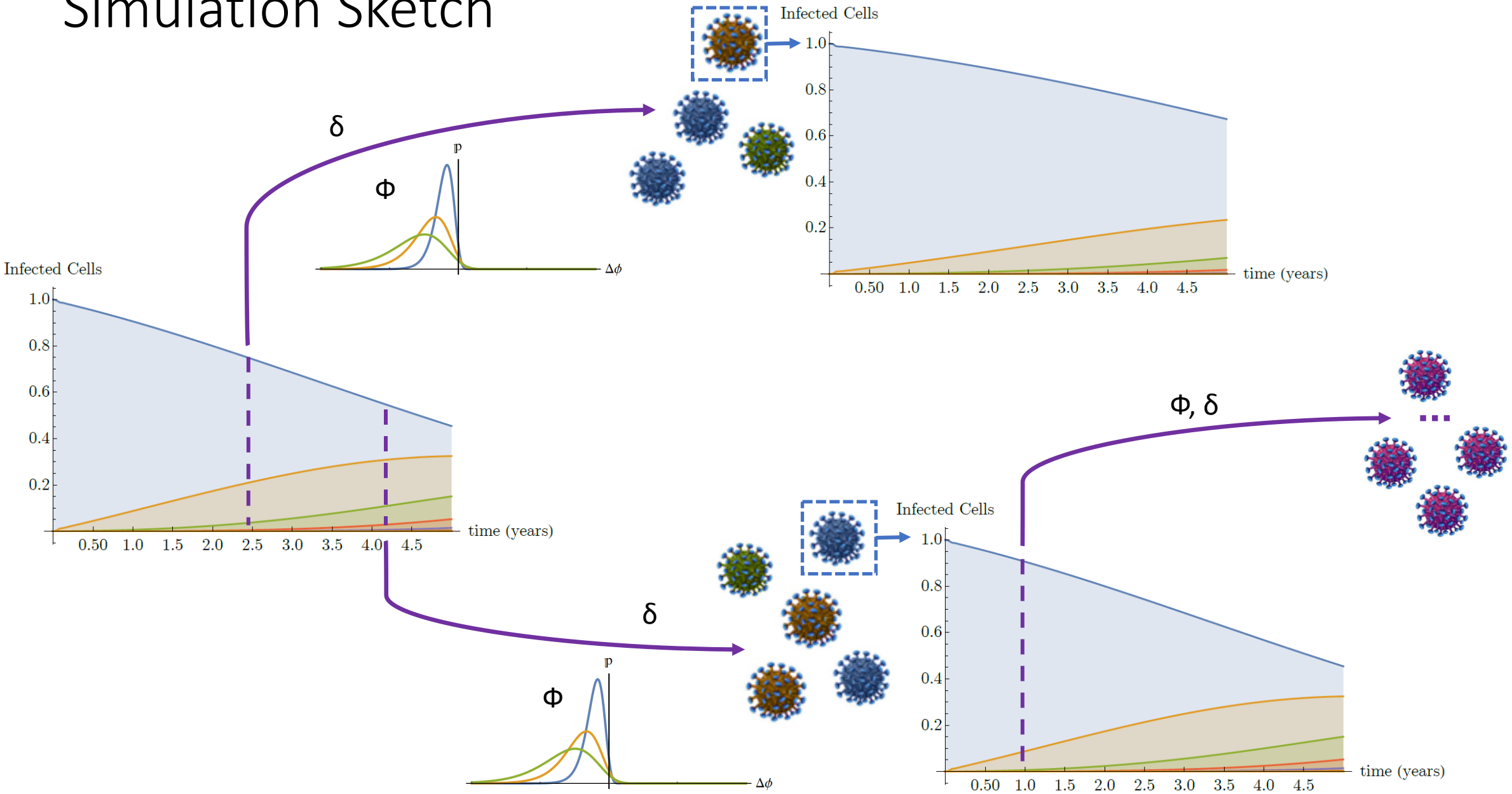
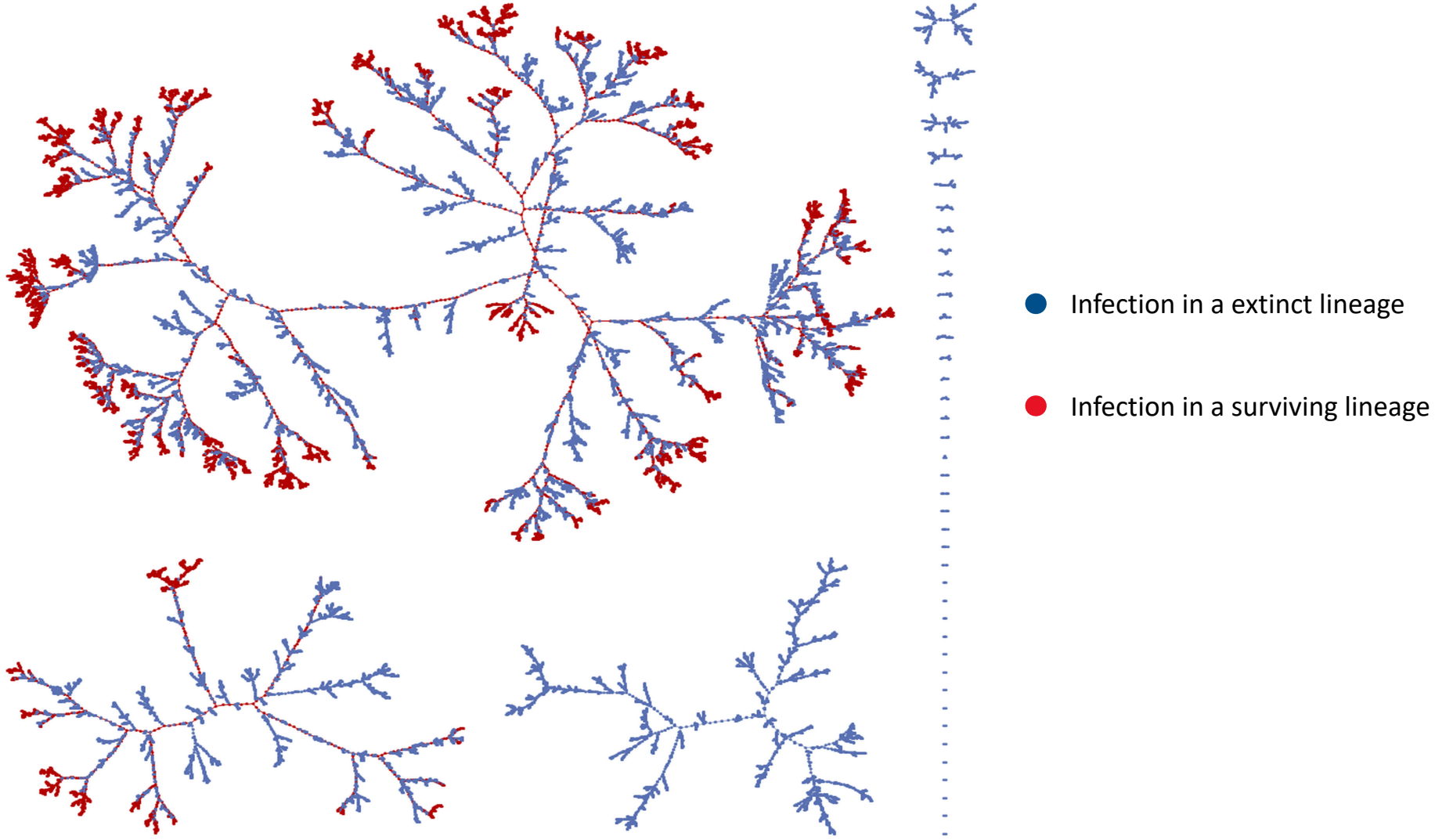
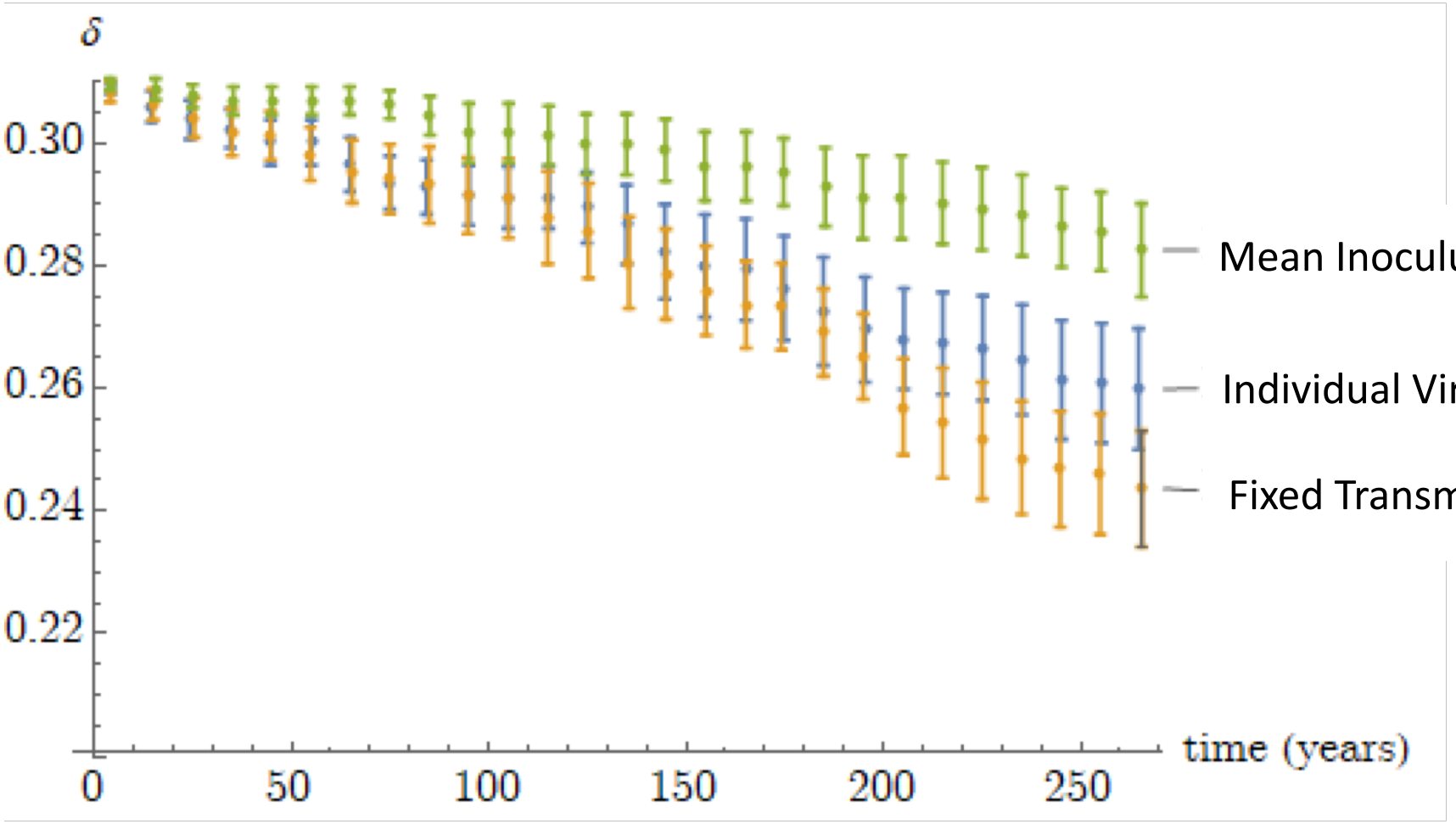


Results: Simulated Transmission Trees



Results: Evolution of increased death rate (δ)



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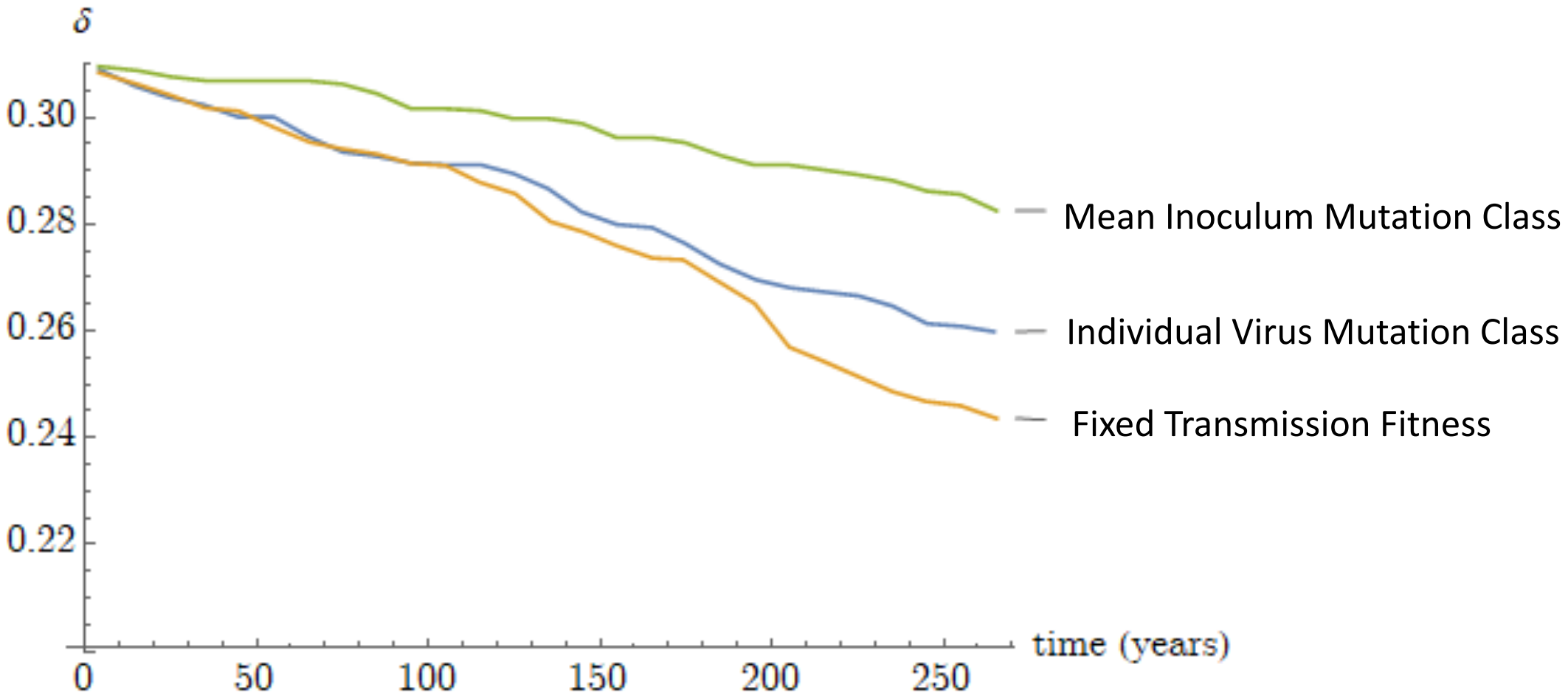
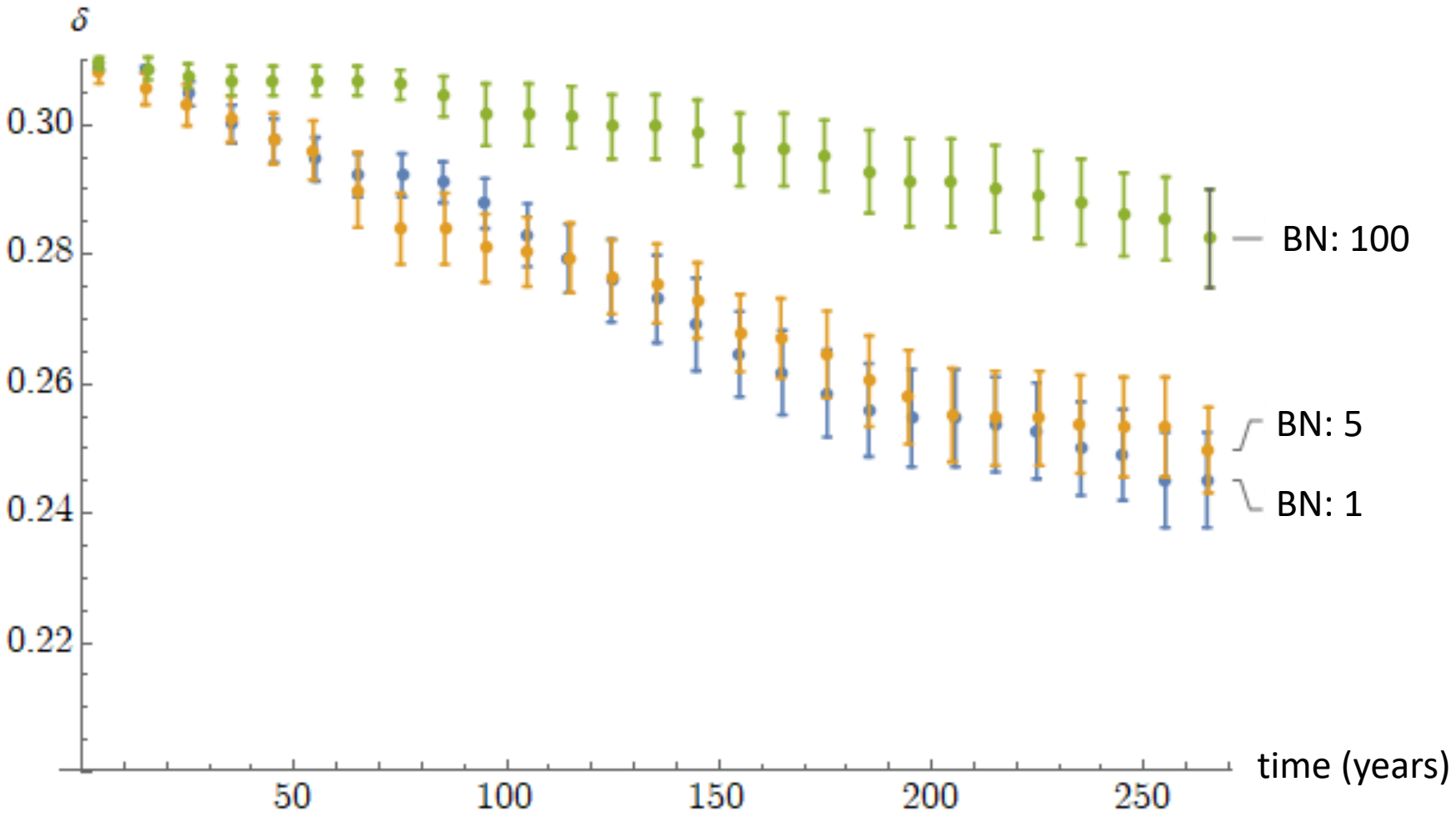


Results: Bottleneck Inoculum Size



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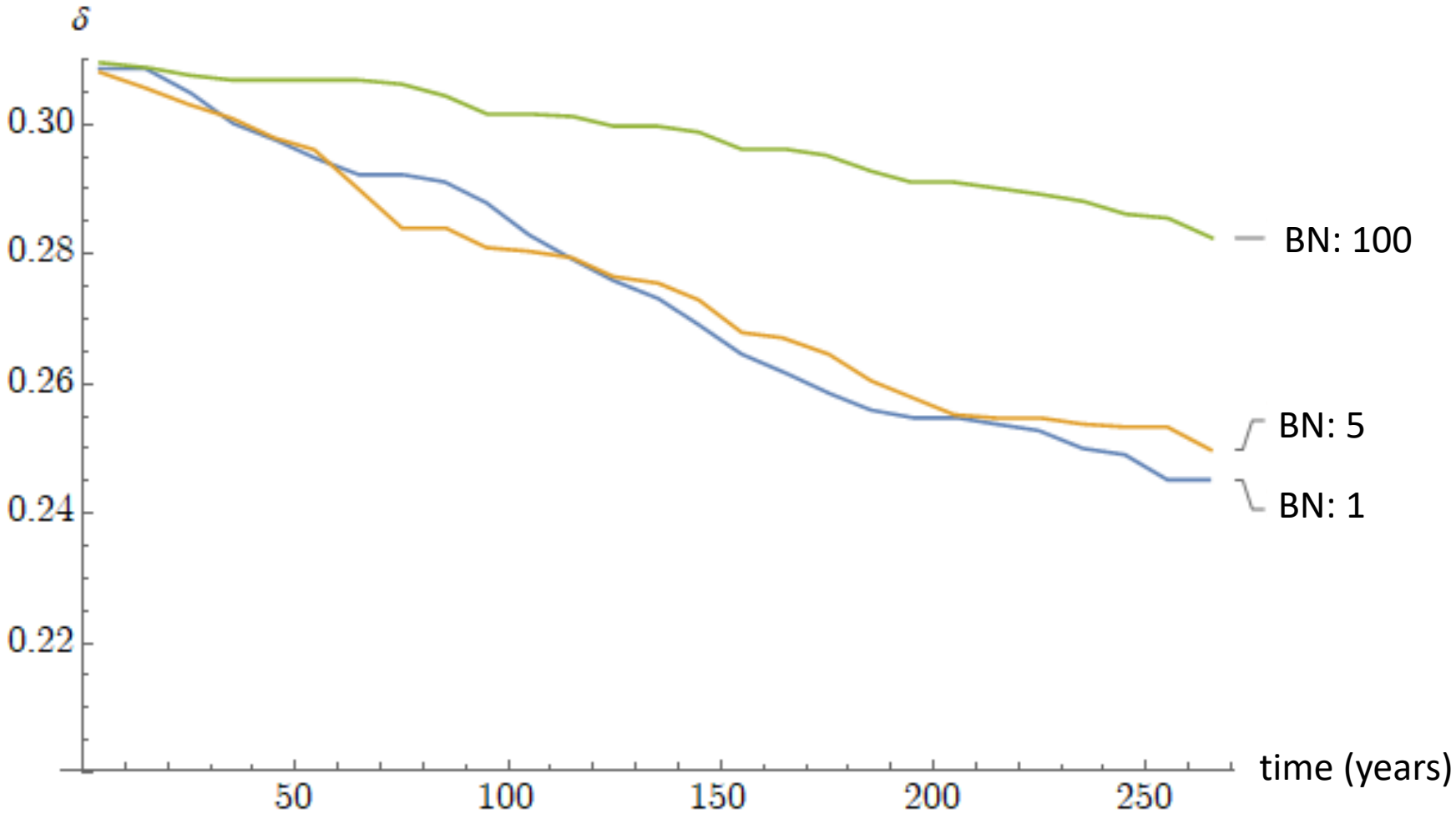

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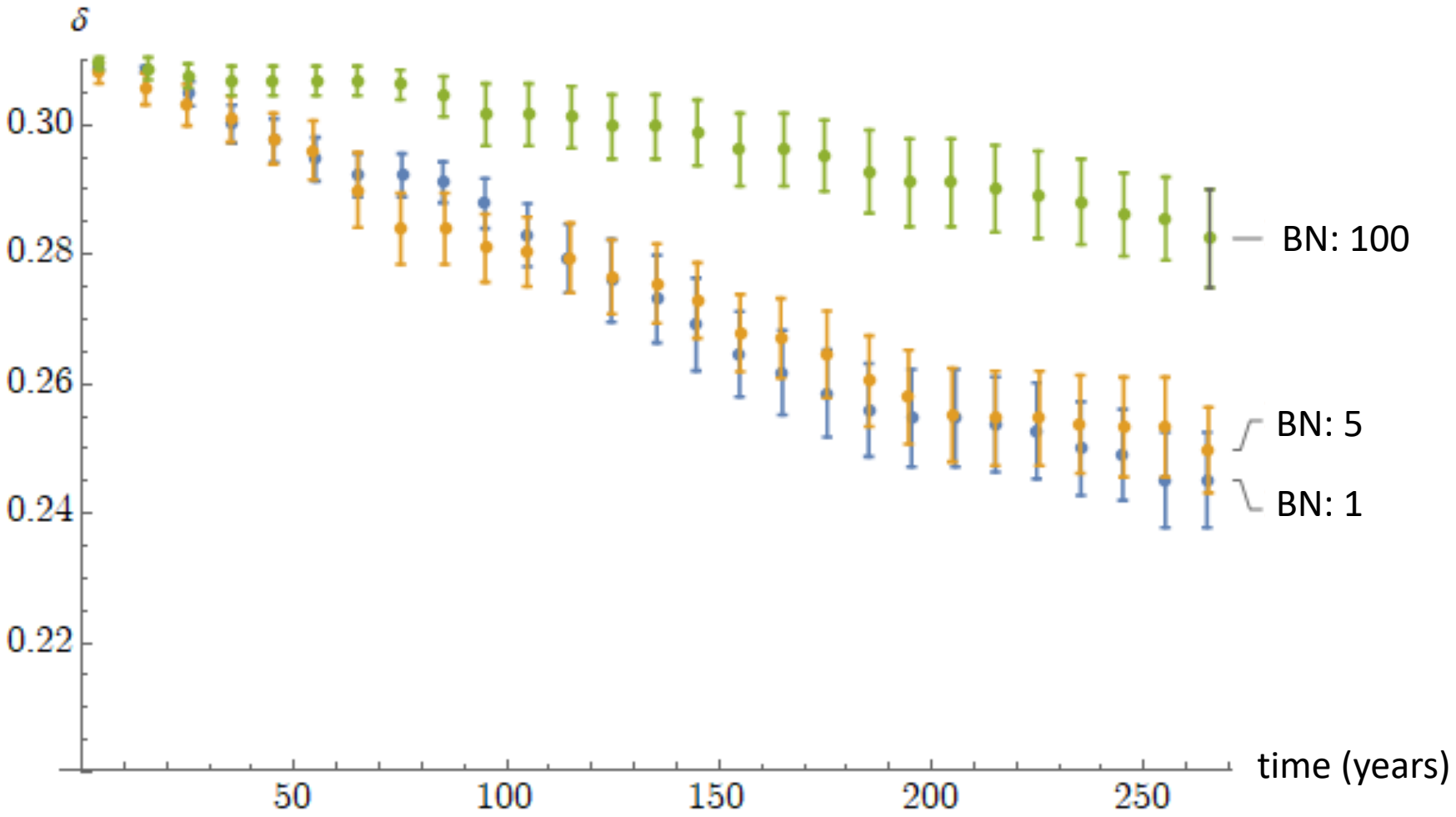
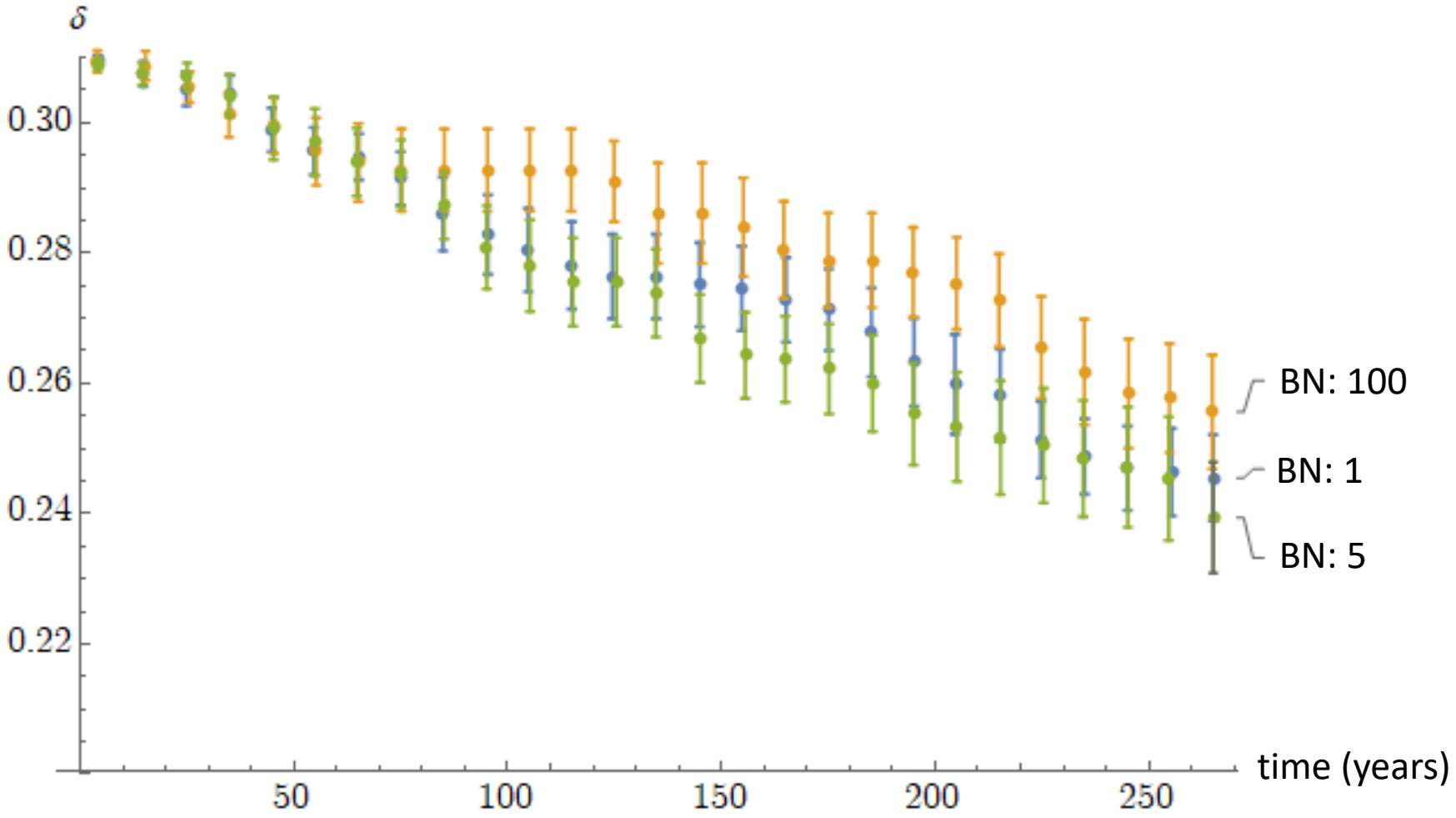


Results: Fixed Transmission Fitness



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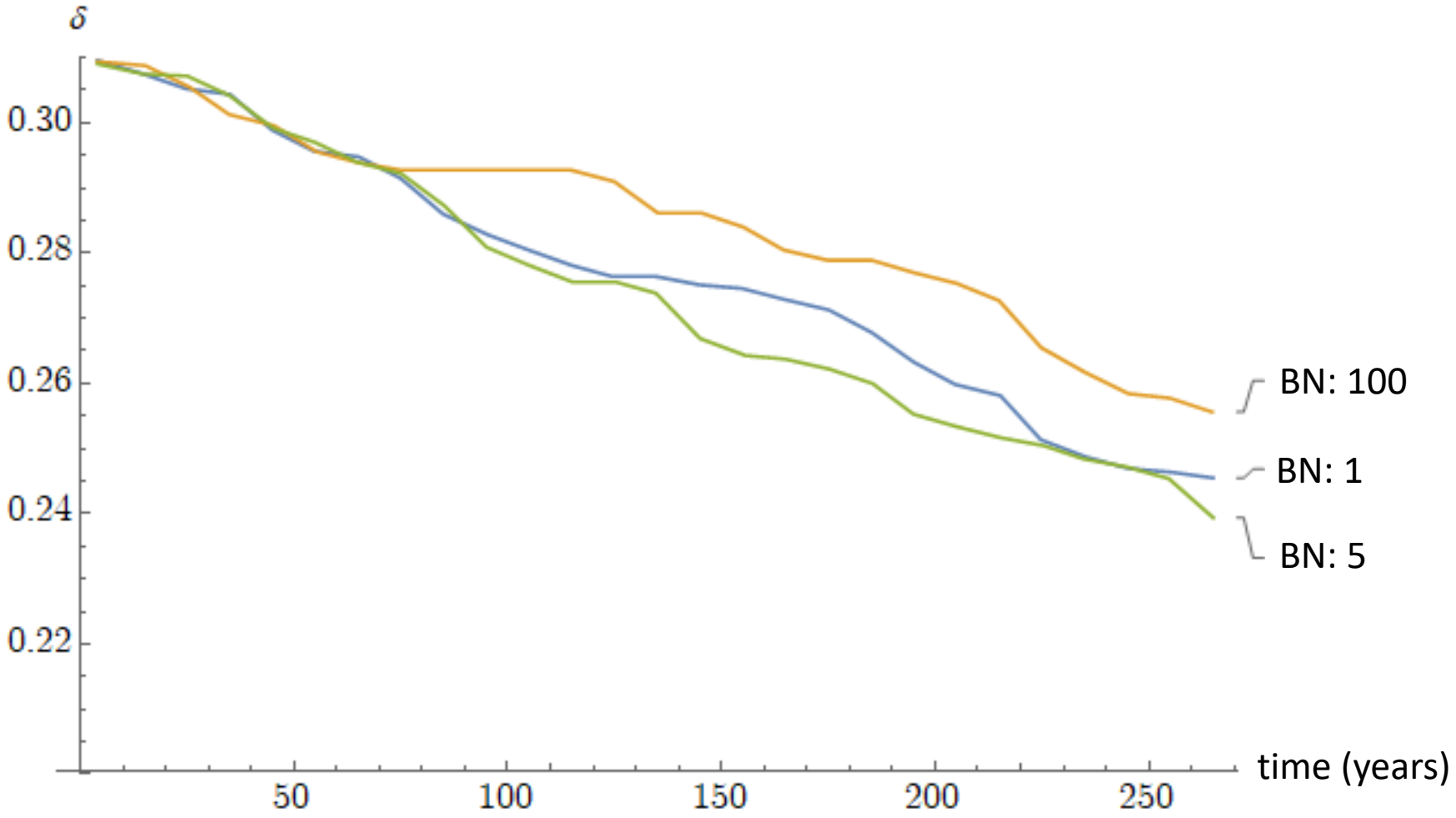
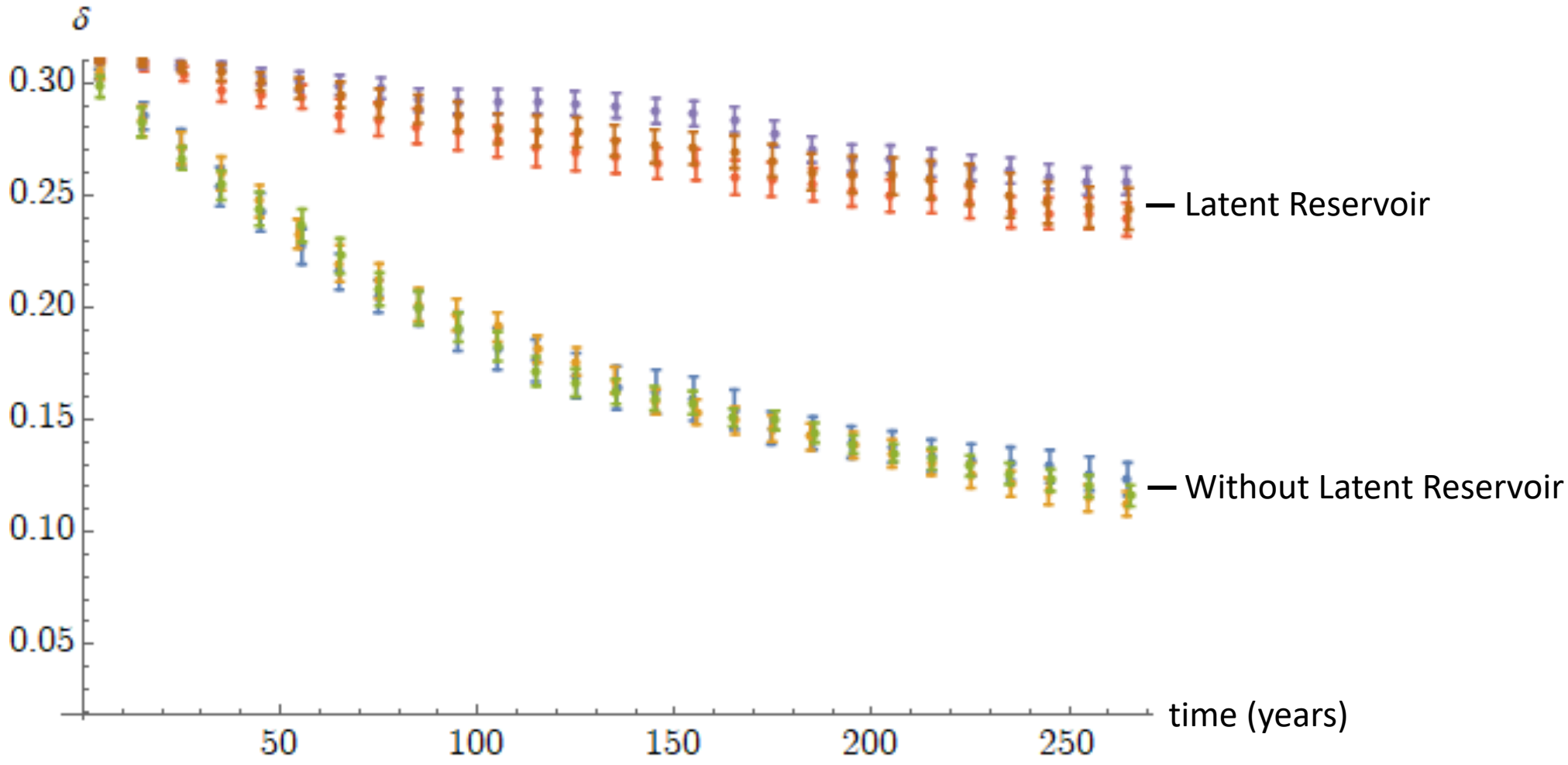


Results: Latent Reservoir



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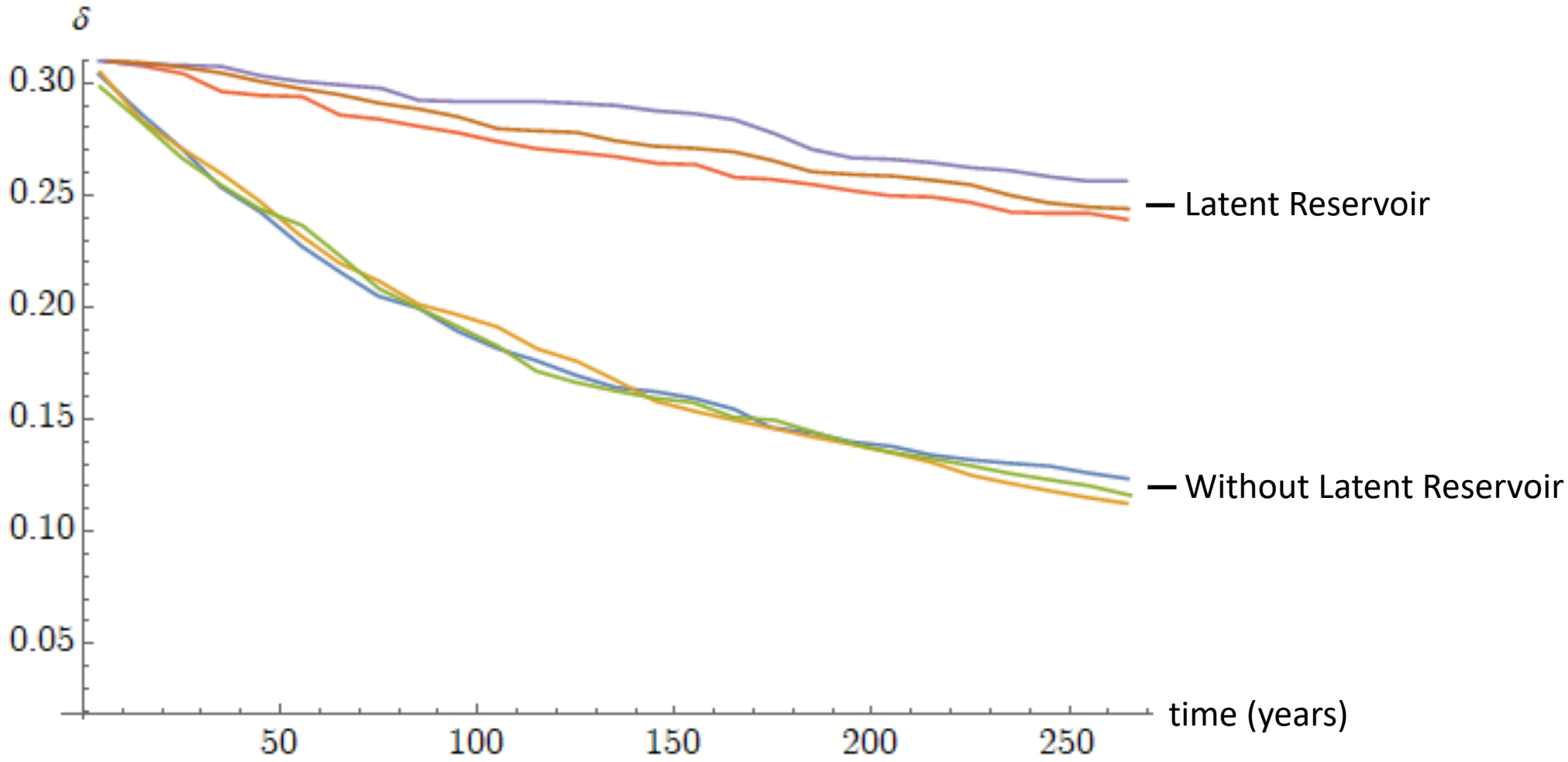

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Is the difference between within- and between host evolutionary rates sensitive to the size and composition of the bottleneck Inoculum

Results

Does allowing transmission fitness to evolve within-host without selection have the effect of slowing the observed rate of evolution over epidemic time?

- Changes are sensitive to the within-host viral distribution

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Results

Does allowing transmission fitness to evolve within-host without selection have the effect of slowing the observed rate of evolution over epidemic time?

- Changes are sensitive to the within-host viral distribution

Is the difference between within- and between host evolutionary rates sensitive to the size and composition of the bottleneck Inoculum

- Yes, the rates of evolution are sensitive to the size and composition of the transmission bottleneck Inoculum
- Our results **suggest** that bottleneck effects could amplify the changes in the observed rate of between-host evolution beyond that of the archival effects of the latent reservoir alone

Acknowledgments

Lindi Wahl

Wahl Research Group

Art Poon

Poon Lab

NSERC CRSNG

CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada

Discussion

- Our modeling suggests the observed between-host rate of evolution is dependent on how well adapted the virus is to the host, and therefore slows over the course of the epidemic
- This dependence on how well adapted the virus to the host raises the question whether will allowing different hosts with distinct immune HLA types will reproduce the additional explanation for the difference in evolutionary rates, ‘adapt and revert’

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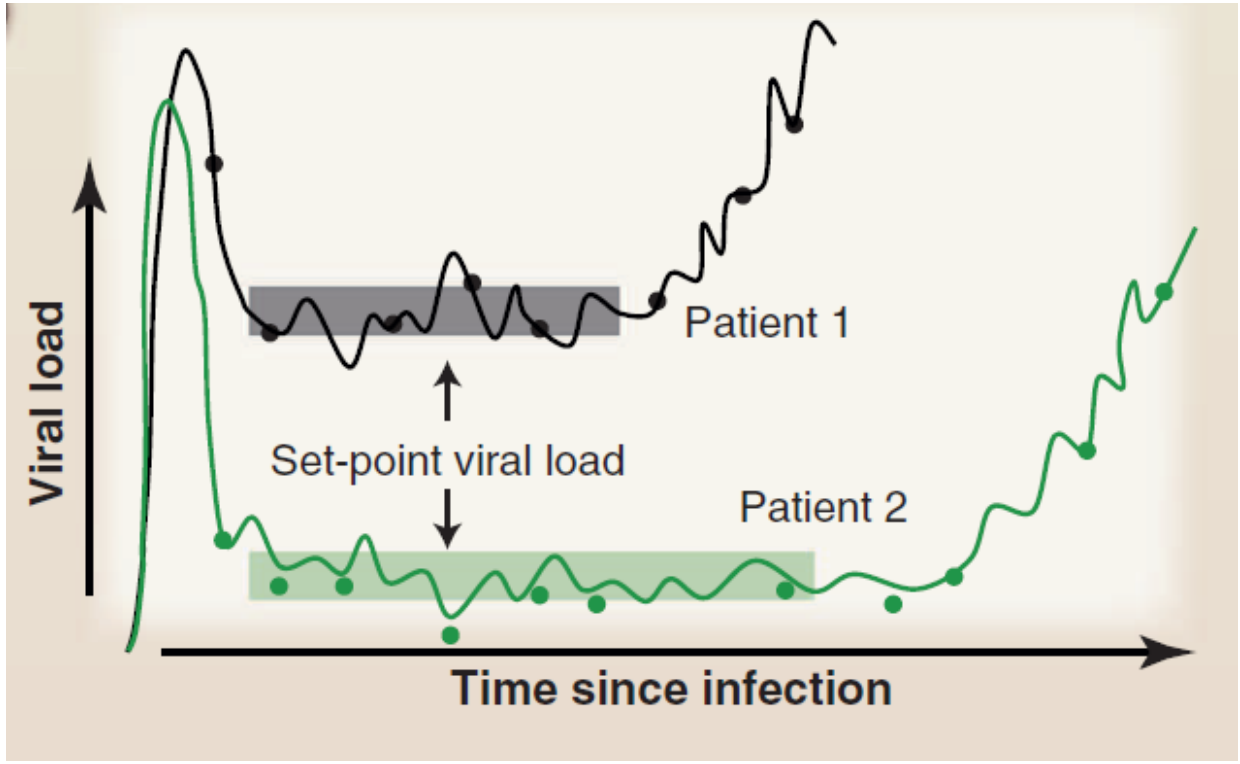
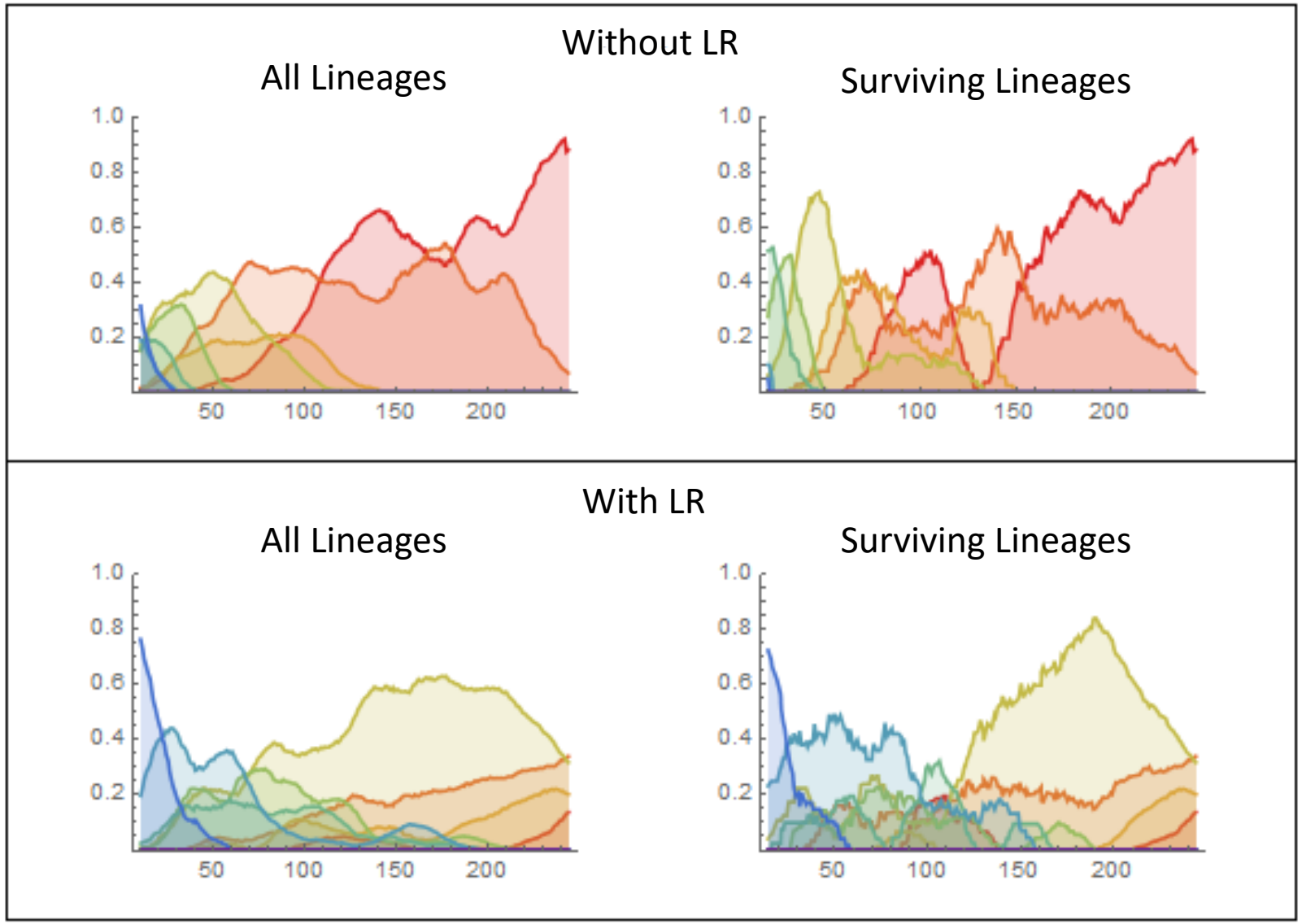
Introduction: Within-host

- Rapidly replicating virus
  - Immune escape
  - Host cell competition
- Approximately ten thousand nucleotides long
- Set-point viral load (SpVL) is a key correlate to virulence
- Has a long lived and evolutionarily stable latent reservoir

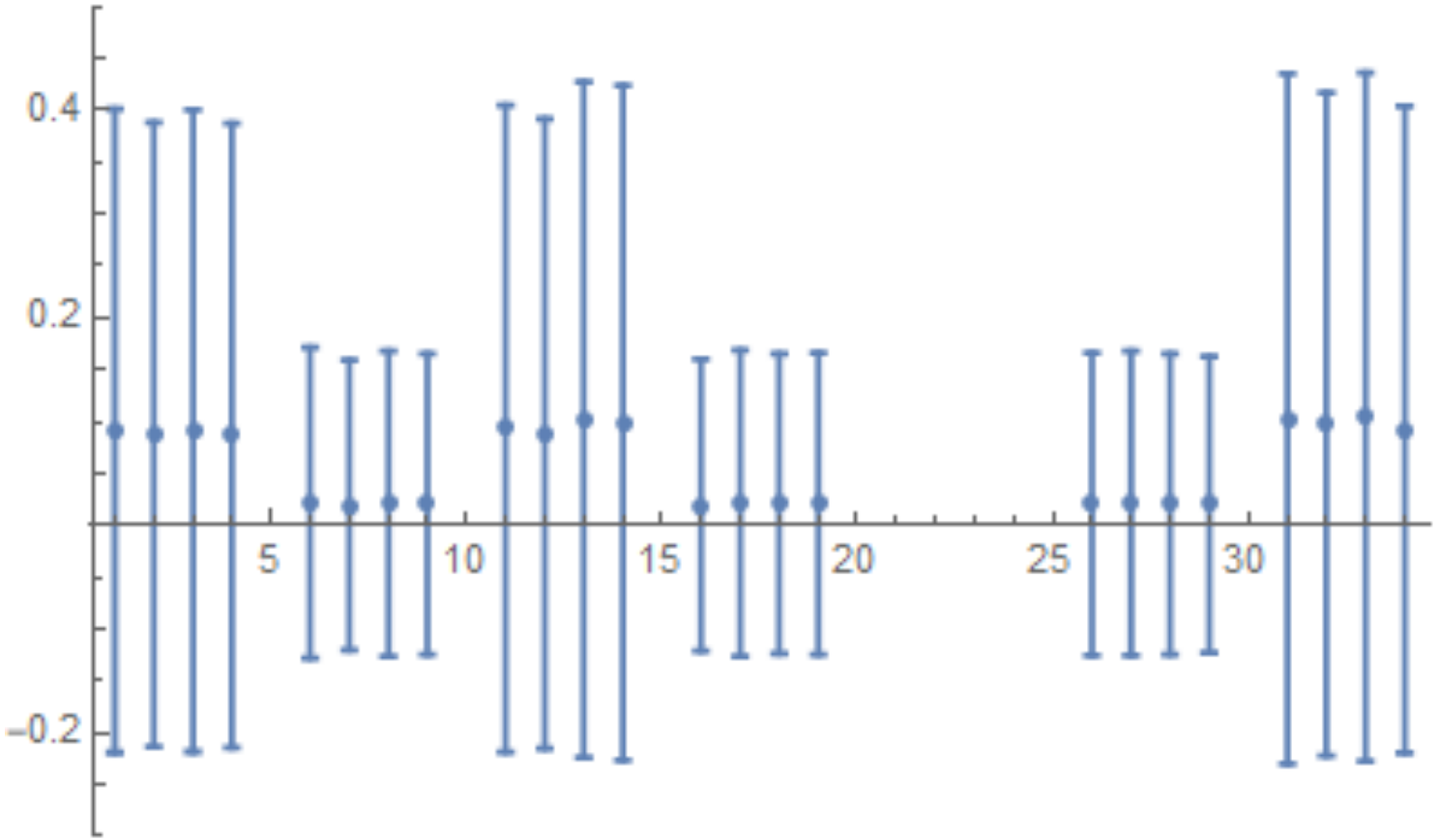


Fraser, C., Lythgoe, K, Leventhal, G, et. al. *Virulence and pathogenesis of HIV-1 infection: an evolutionary perspective*., Science. **343**, 6177, pp. 1243727 (2014).

Evolution of intermediate SpVL



Mean Transmitted Mutation Class



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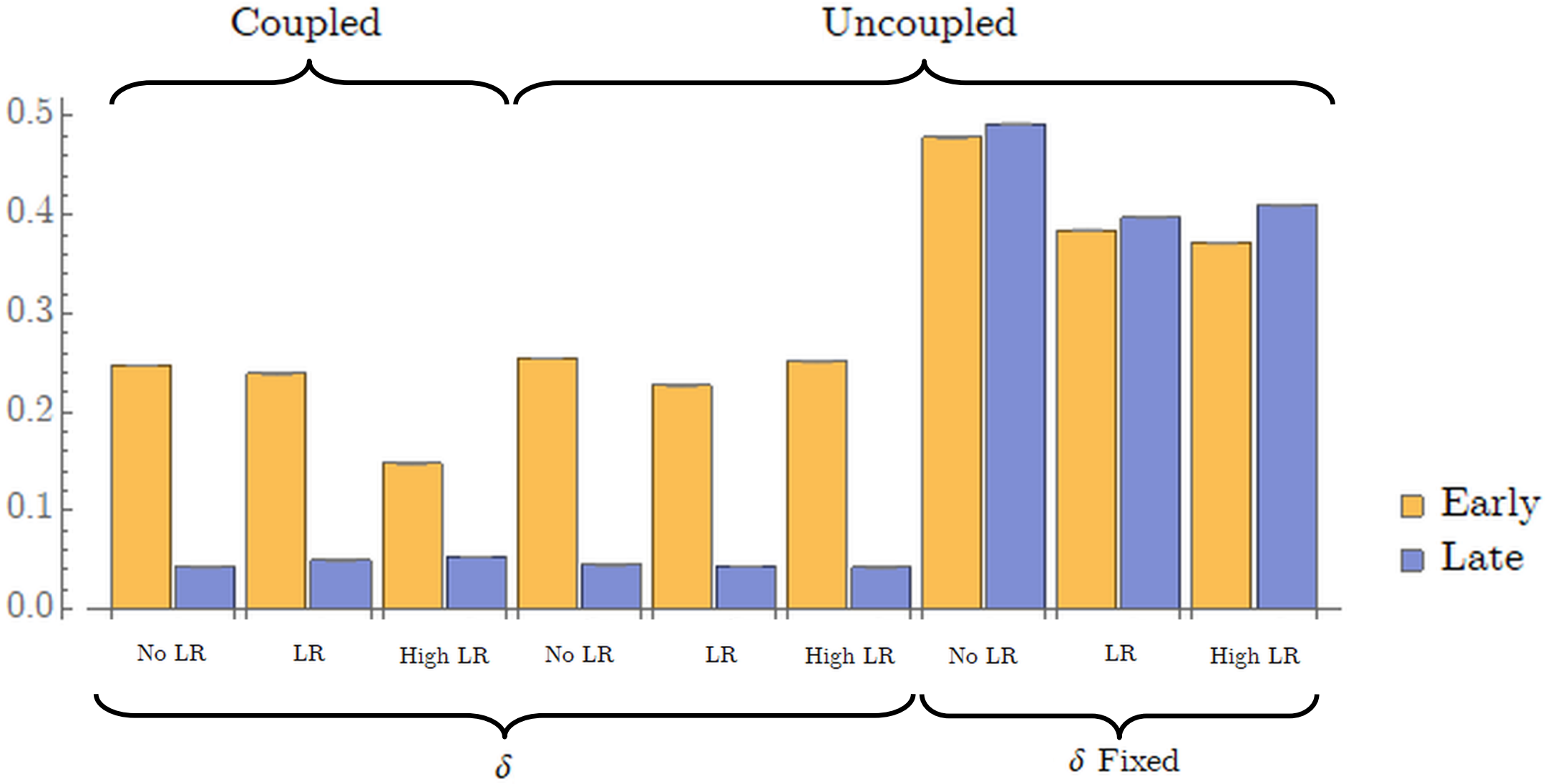
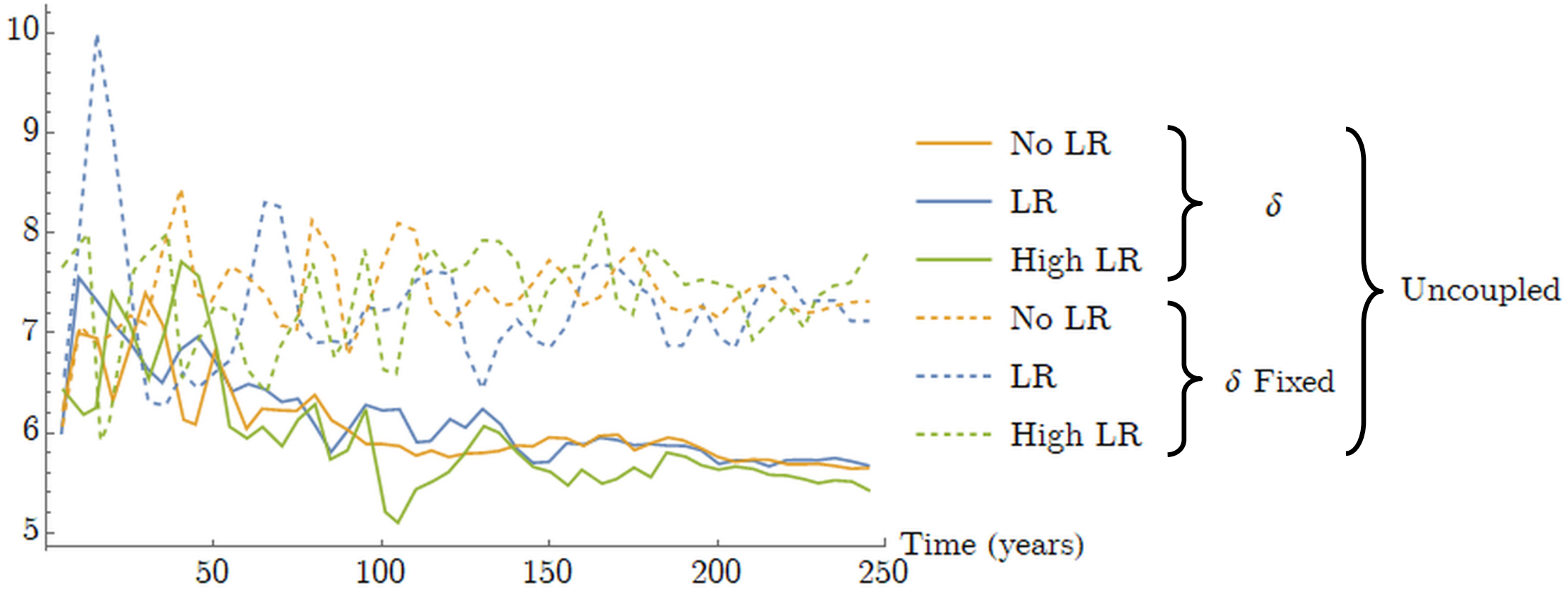


Within-host Diversity



Within-host Model

$$\dot{x} = \lambda - dx - x\sum_{i}^{n} \beta(i, \beta_0) y_i$$

$$\dot{y_i} = \alpha l_i - \delta y_i - \gamma l_i + x(1-\mu)\beta(i, \beta_0) y_i + x\mu \sum_{j=1}^{n} \beta(j, \beta_0) K(i-j) y_j$$

$$\dot{l_i} = \gamma y_i + (\rho - \alpha) l_i$$