Modeling Disease Evolution at Multiple Levels

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Outline

- Natural Selection at Multiple Scales
- An Example of Linking Within- and Between-Host Scales
- A Dream of Linking Intra-Cellular, Within- and Between-Host Scales
- What We Need to Understand Better

Levels of Selection

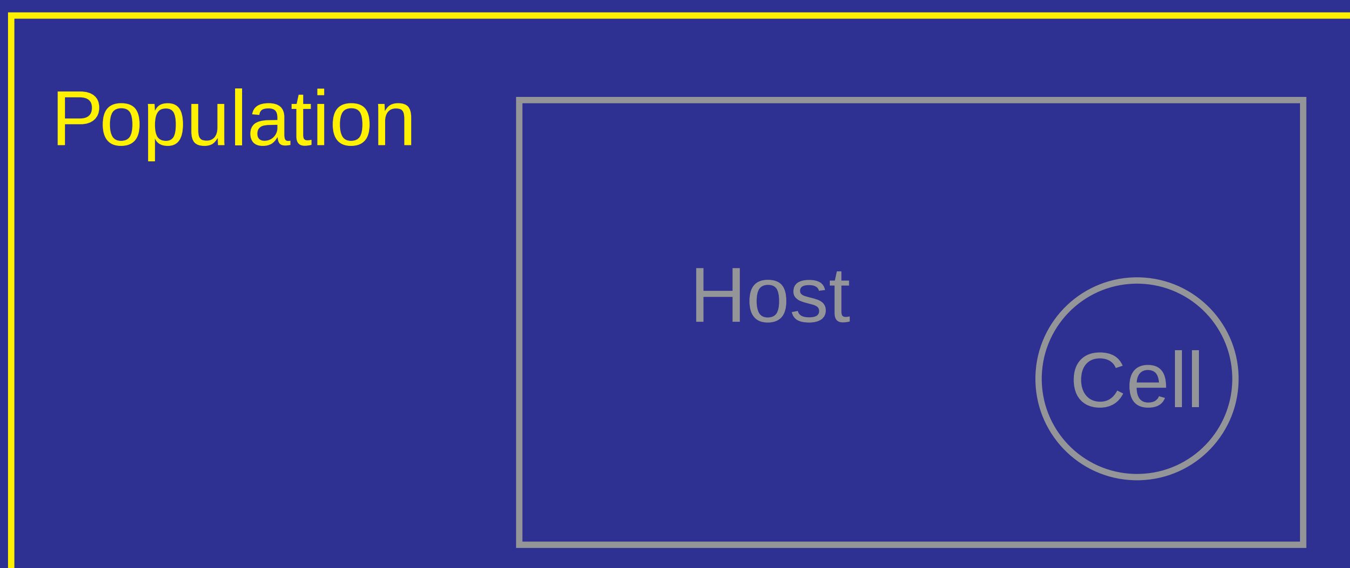
Natural selection can function at a number of different levels

- Within-Host: Competition for resources the virus can utilize within an individual host

Levels of Selection

Natural selection can function at a number of different levels

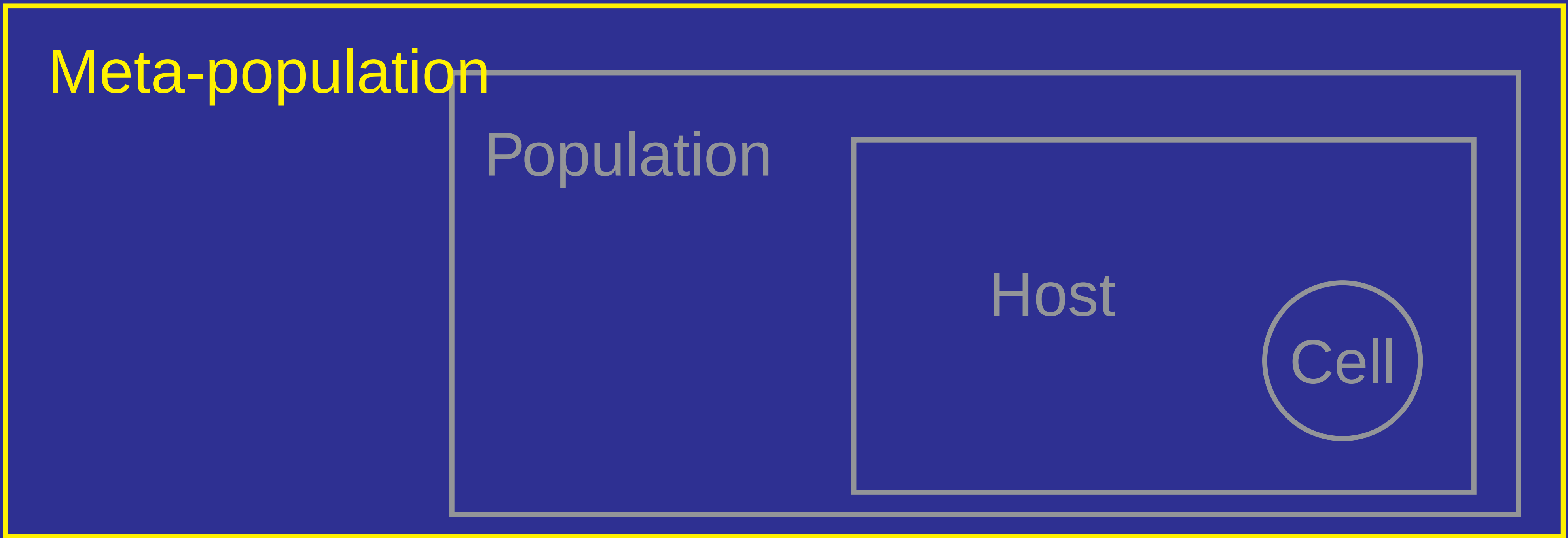
- Between-Hosts: Competition between infections for uninfected hosts (Classical View)



Levels of Selection

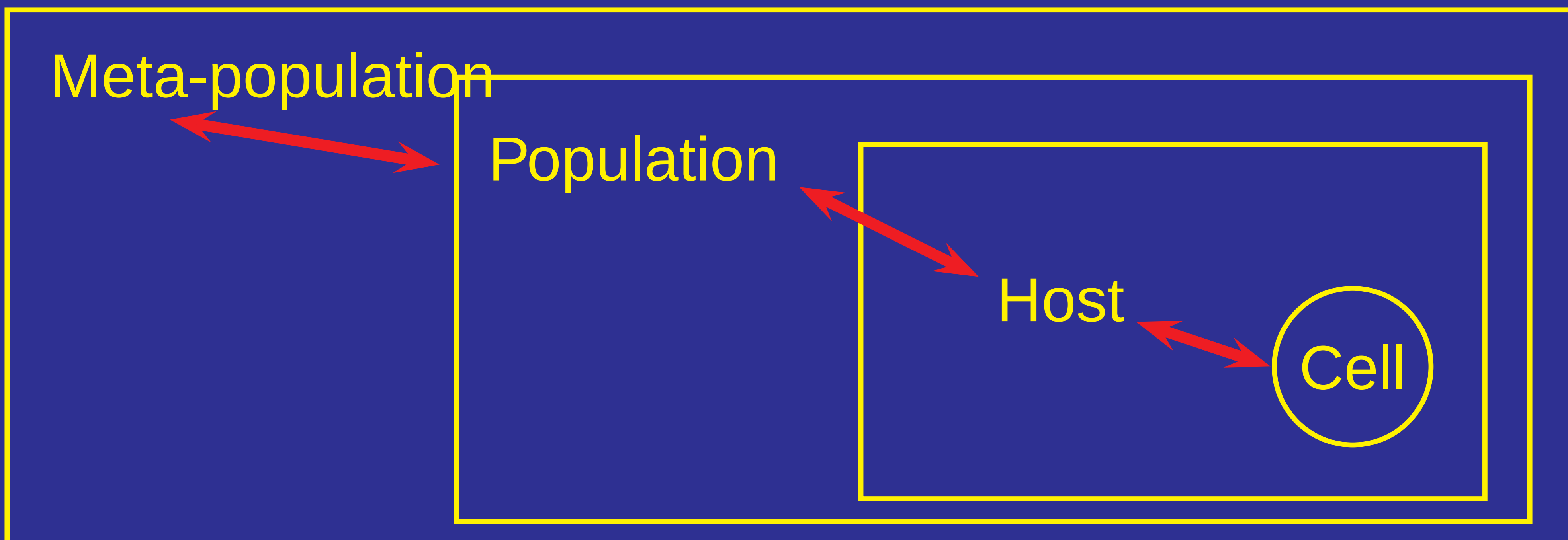
Natural selection can function at a number of different levels

- Between-Populations: Competition for populations of hosts (meta-population)



Levels of Selection

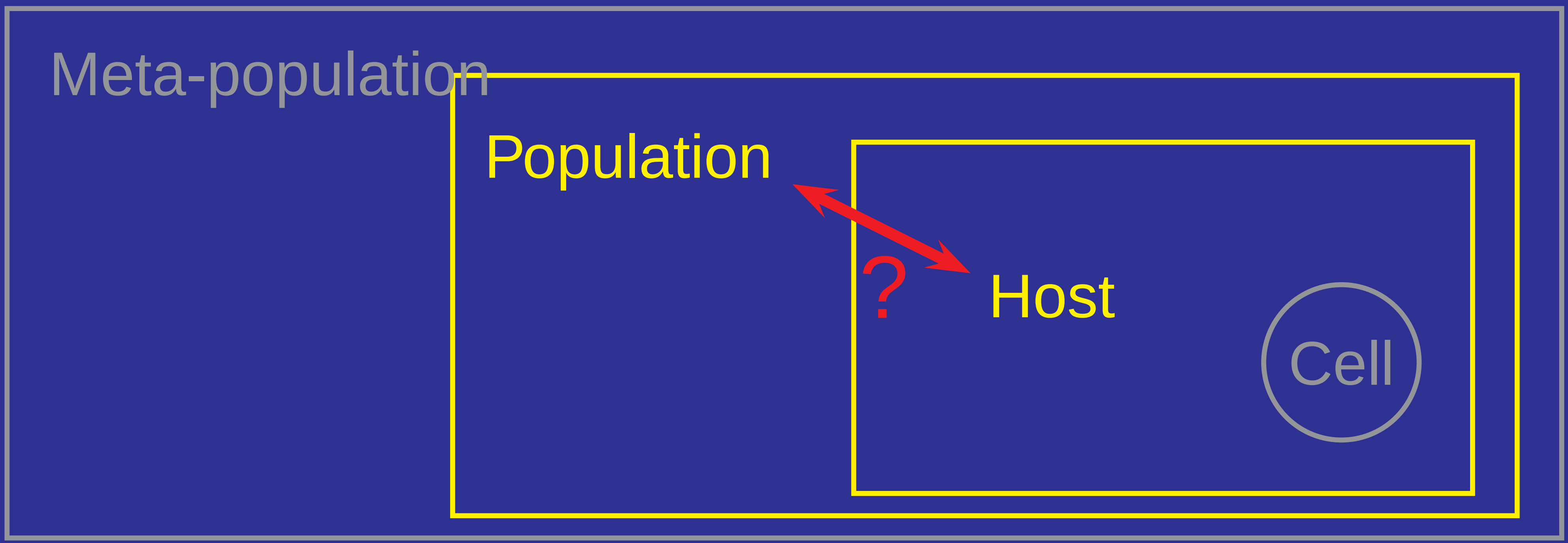
Given the complexity of the biology at each level, it is unlikely the optimal strategy at one level would be the same for another.



Levels of Selection: Within-Host vs. Between Host

E.g., consider virion production rate within a cell p.

The ESS p value at the within-host level $\neq$ ESS p value at the between-host level

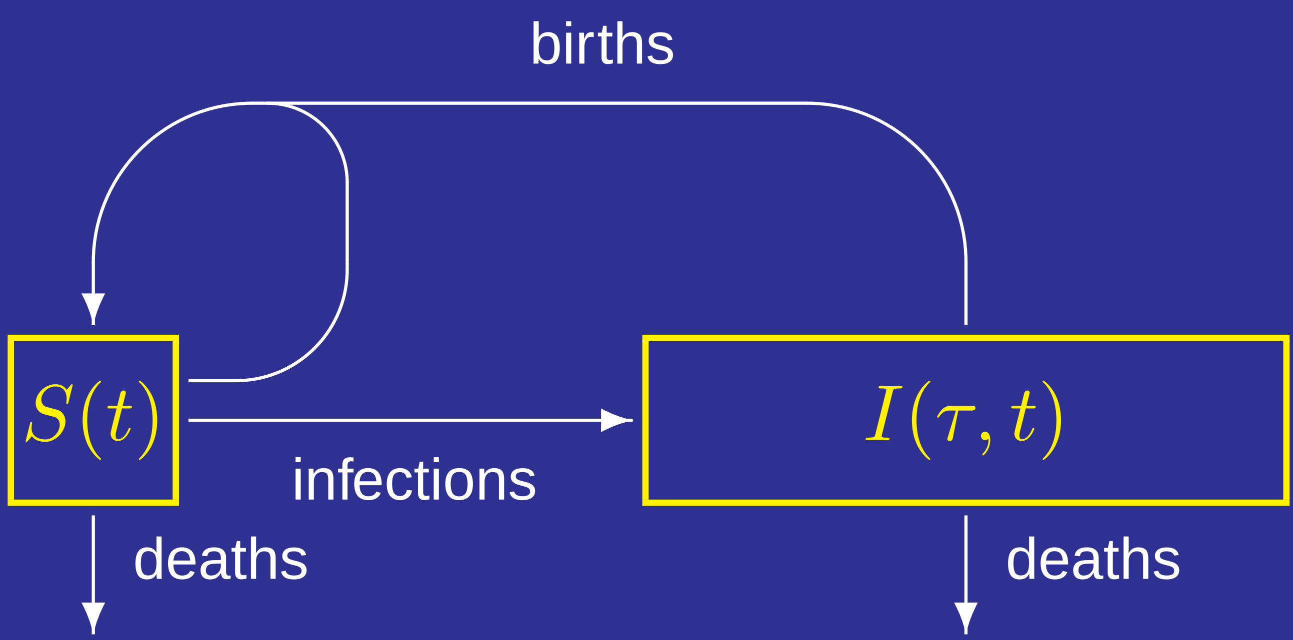


Gilchrist and Coombs (2006); Coombs, Gilchrist, and Ball (2007)

Selection at the Between and Within Host Scales

Between Host Model

Diagram of a simple structured model



- **S**usceptible & **I**nfectious classes
- Direct transmission of infection between hosts
- Infectious class structured by age of infection τ

Between Host Model

Formal model definition

$$\frac{dS}{dt} = b\left(S(t) + \int_0^\infty I(\tau,t)d\tau\right) - S(t)\left(\int_0^\infty \beta(\tau)I(\tau,t)d\tau + m\right)$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial \tau} = -(\alpha(\tau) + m)I(\tau,t)$$

$$I(0,t) = S(t)\int_0^\infty \beta(\tau)I(\tau,t)d\tau.$$

Where,

$\tau =$ age of a host's infection

$m =$ Host background mortality rate

$\alpha =$ Host mortality rate due to parasitic infection (virulence)

$\beta =$ Transmission rate of infection between hosts

Between Host Pathogen Fitness

Invasion analyses of the model indicates that natural selection will favor the maximization of R_0

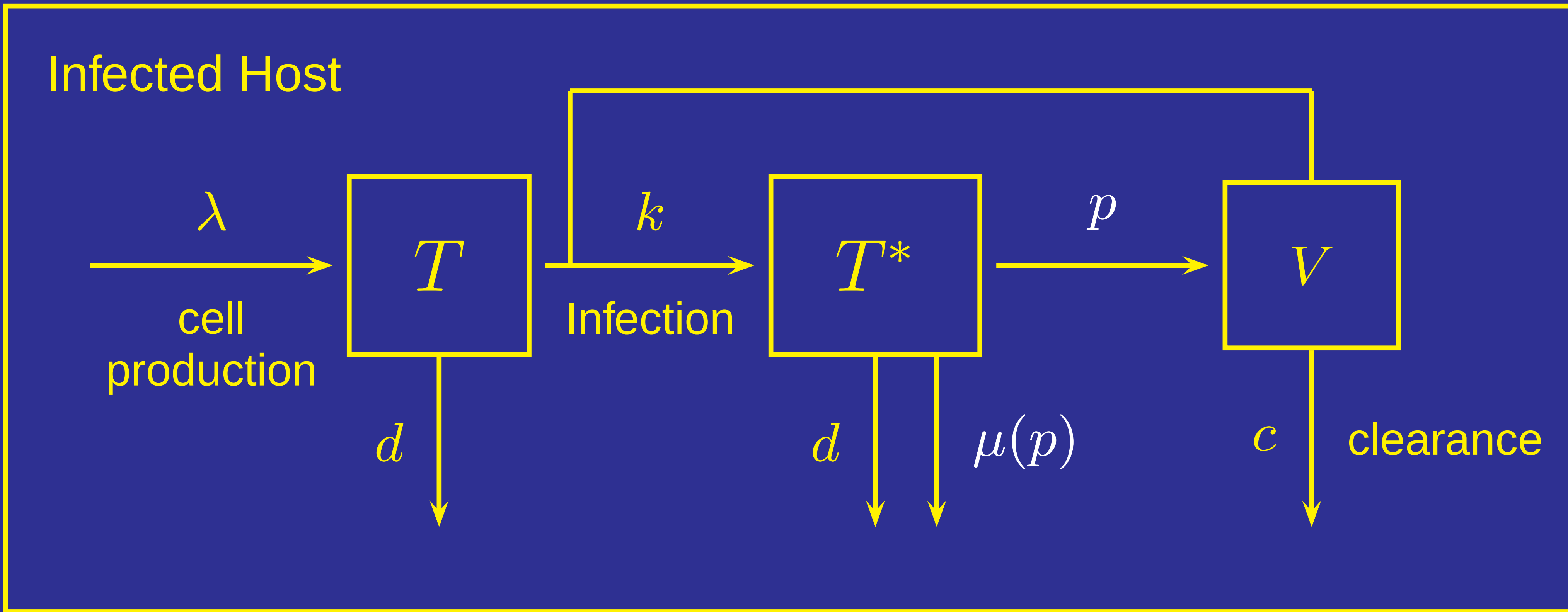
$$R_0 \propto \int_0^\infty \beta(\tau) \exp\left[-\int_0^\tau (\alpha(z) + m) dz\right] d\tau$$

$$= \frac{\beta}{\alpha + m},$$

when β, α, and m are static.

Within-Host Model

$$dT/dt = \lambda - k\,V\,T - d\,T$$
$$dT^*/dt = k\,V\,T\; - (\mu(p) + d)T^*$$
$$dV/dt = p\,T^* - c\,V,$$



Within-Host Selection

- Within-host selection favors the maximization of the reproductive ratio of an infected cell ρ:

$$\rho = \frac{k}{c}\frac{p}{\mu(p) + d}$$
$$= \frac{1}{\hat{T}}$$

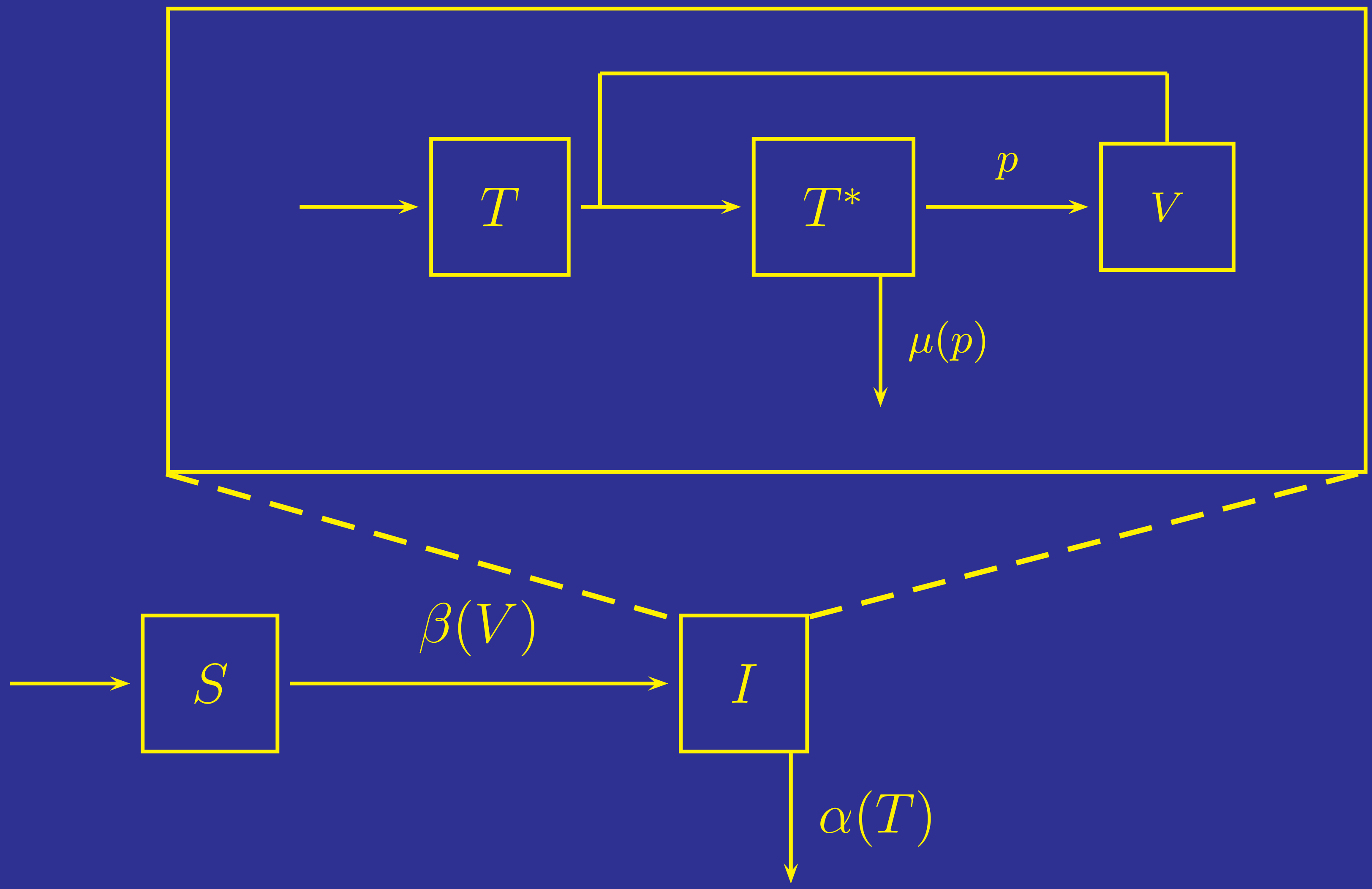
- Strain which maximizes $\rho(p)$
  - Minimizes $\hat{T}(p)$
  - Competitively excludes other competitors within host.

Gilchrist *et al.* (2004)

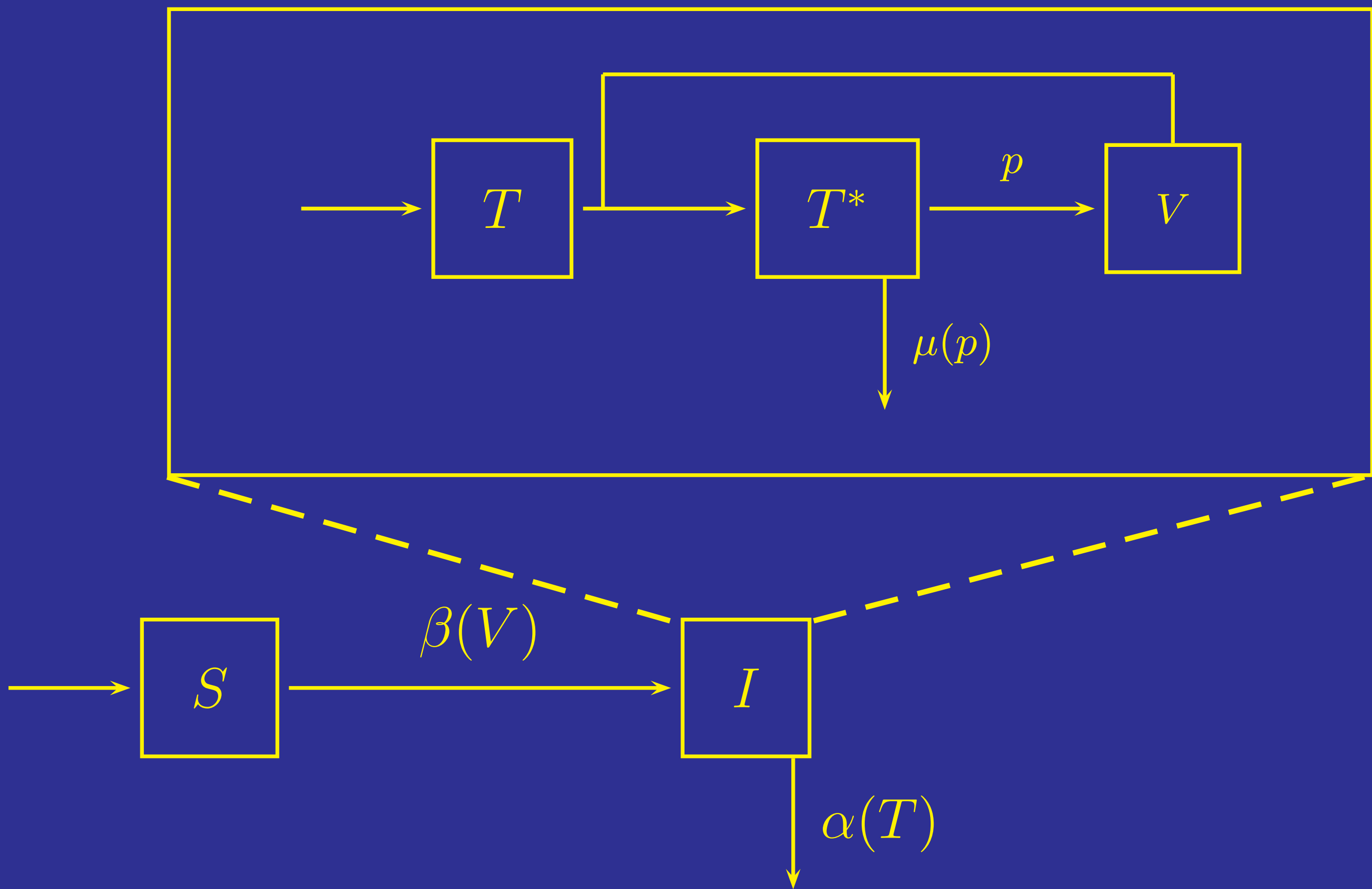
Linking Within- and Between-Host Scales

Linking Within & Between-Host Scales

Nest within-host model inside between-host model



Linking Within & Between-Host Scales

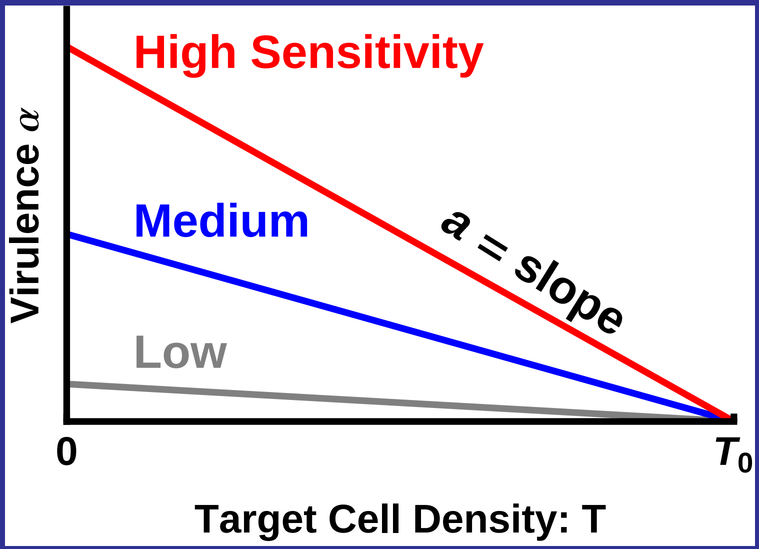


$$\alpha(T) = a\,(T_0 - T) \qquad \beta(V) = bV$$

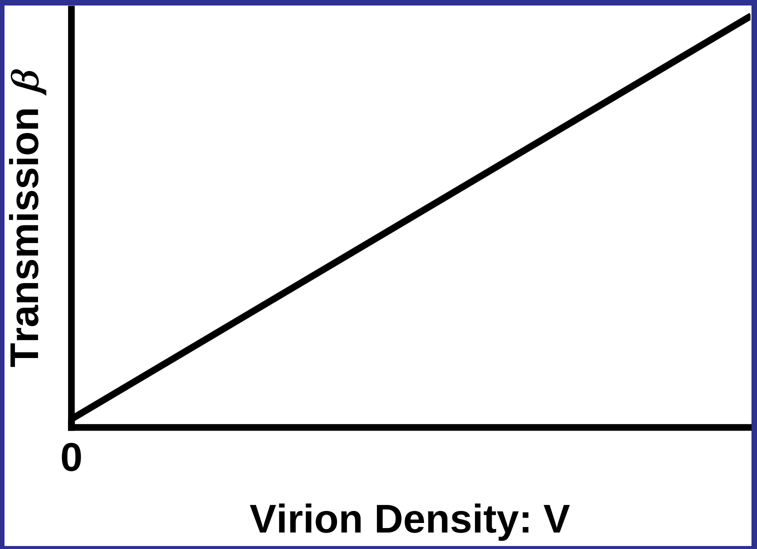
Linking Within & Between-Host Scales

$$\alpha(T) = \underbrace{a}_{\text{Sensitivity}} (T_0 - T) \qquad \beta(V) = bV$$

Virulence vs. Target Cell



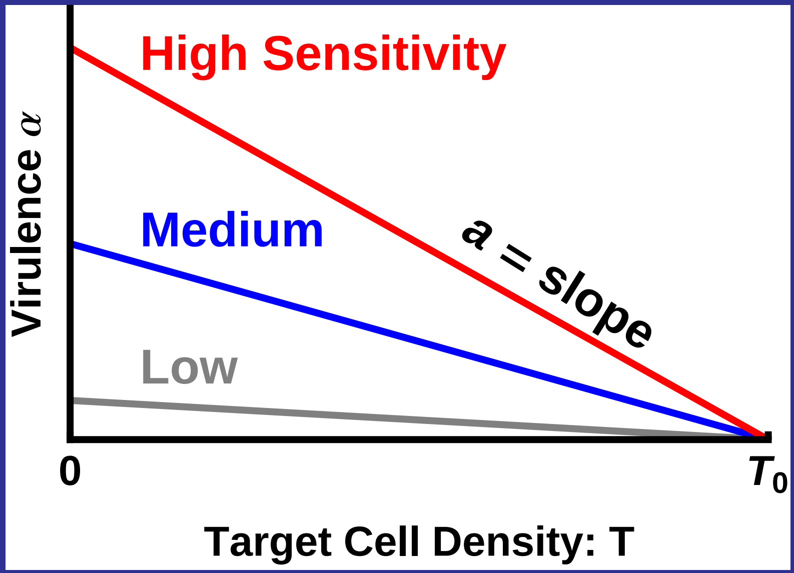
Transmission vs. Virion

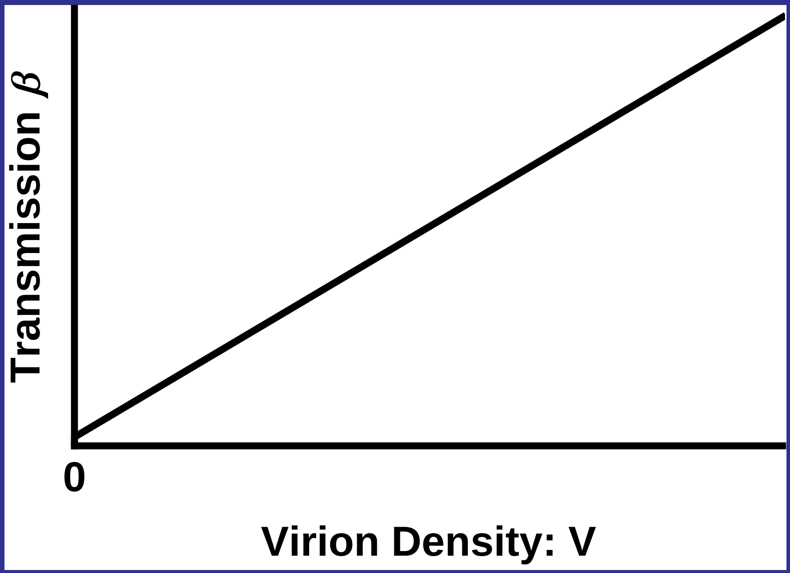


Between Host Pathogen Fitness

Let $p^\bullet$ be the virion production rate which maximizes,

$$R_0(p) \propto \int_0^\infty \beta(V(\tau|p)) \exp\left[-\int_0^\tau (\alpha(T(z|p)) + m) dz\right] d\tau$$



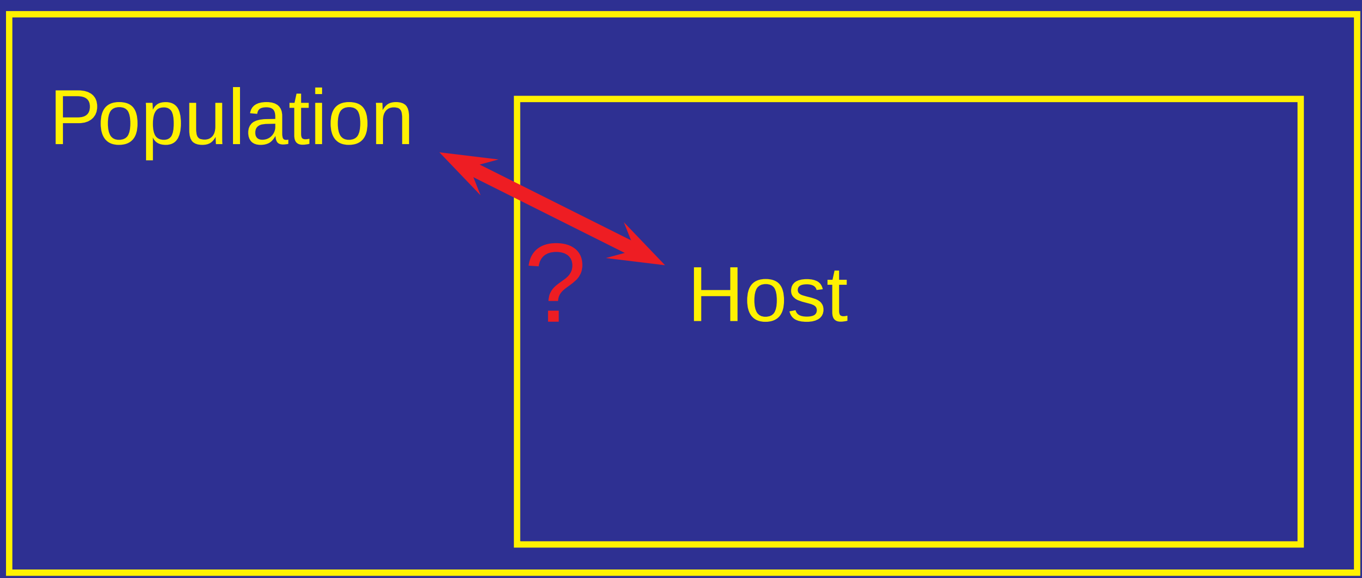


Levels of Selection

Between-Host: $R(p)$ maximized at $p = p^{\bullet}$

Within-Host: $\rho(p)$ maximized at $p = p^{*}$

In general, $p^{\bullet} \neq p^{*}$ and which one wins depends on sensitivity of host to loss of parasitized resource.

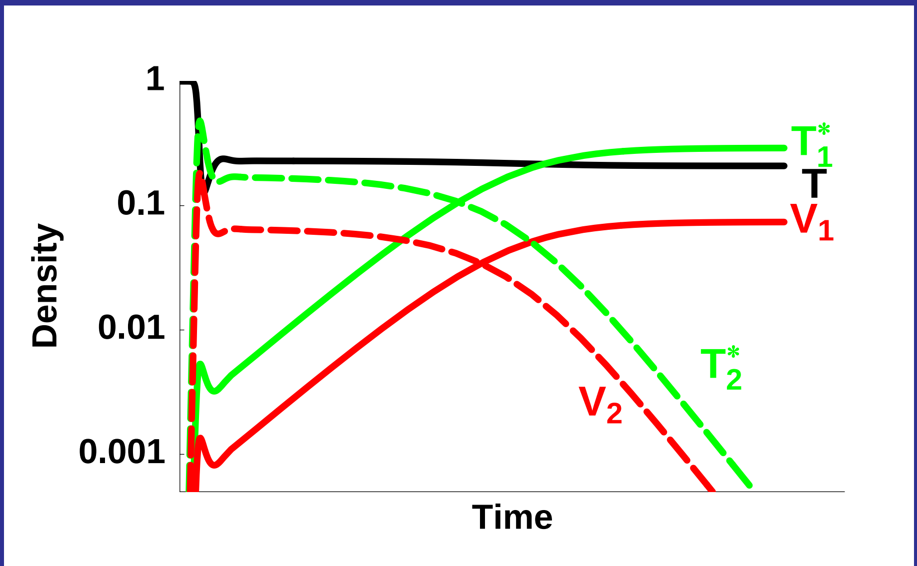


Resolution of Selection Conflict

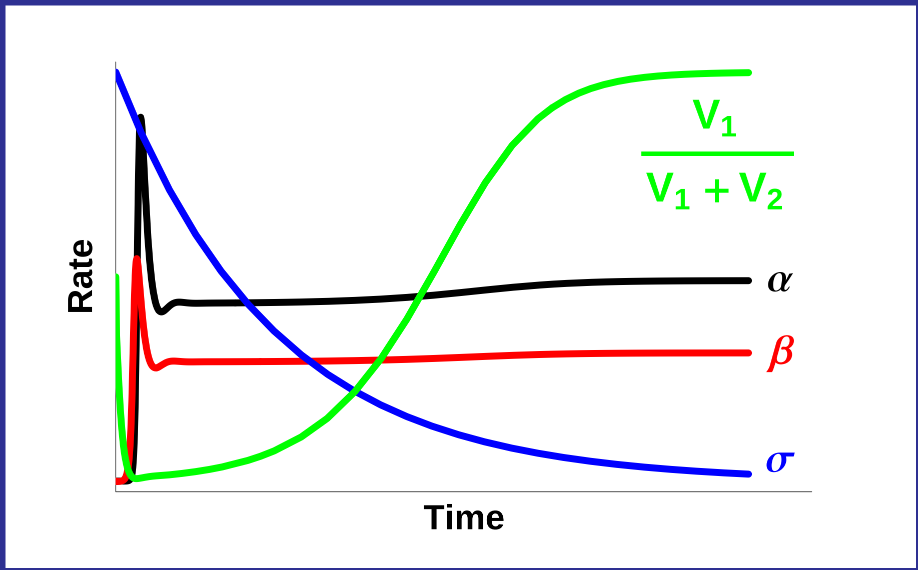
Approach

- Within-host model dynamics with two strains
- Mutation between strains
- Infection inoculum of reflects strain mix in infecting host

Within-Host Dynamics



Between-Host Parameters



Coombs, Gilchrist, and Ball (2007)

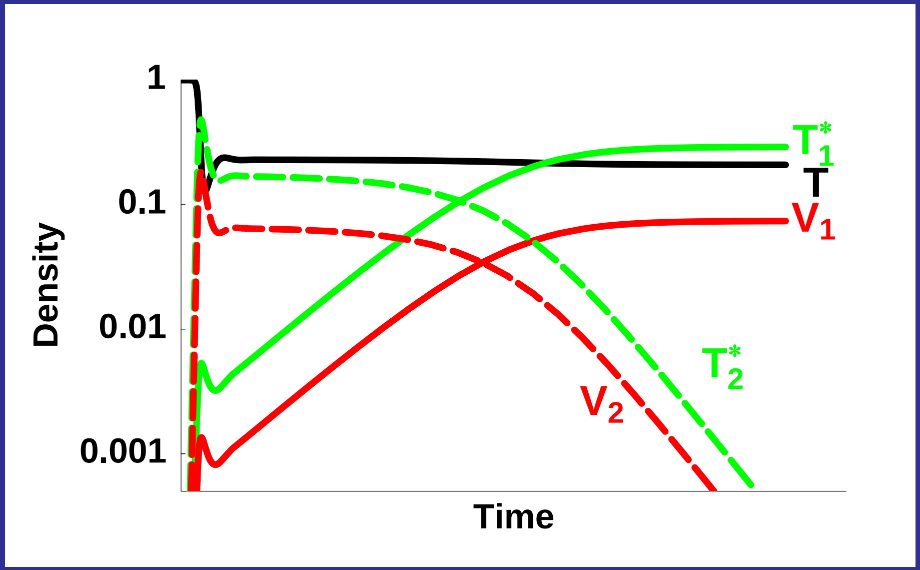
Analyzing Model: Two Strains

Basic trade-off of increasing p:

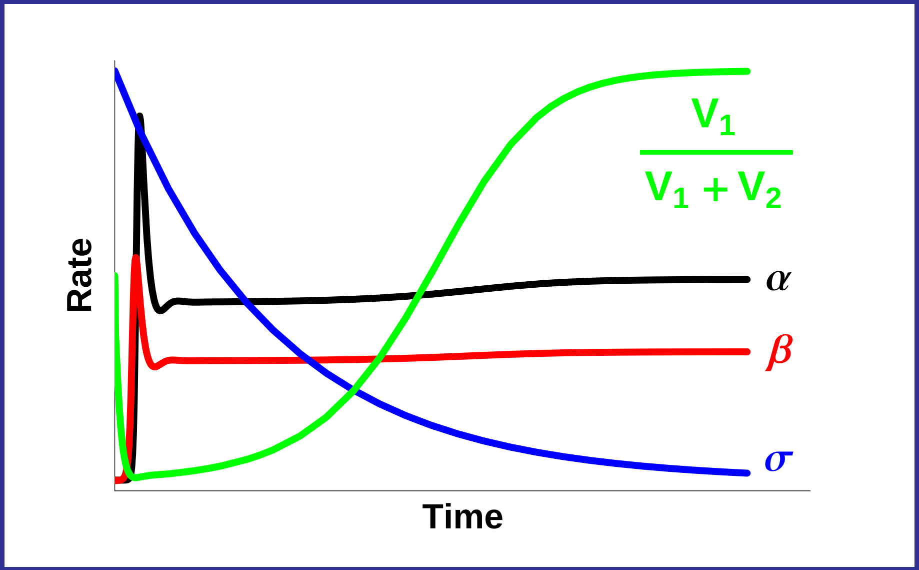
Initial Spike: Max $V(t)$ increases, increasing early β

Competitive Exclusion: Rate of exclusion increases, decreasing later β.

Within-Host Dynamics



Between-Host Parameters



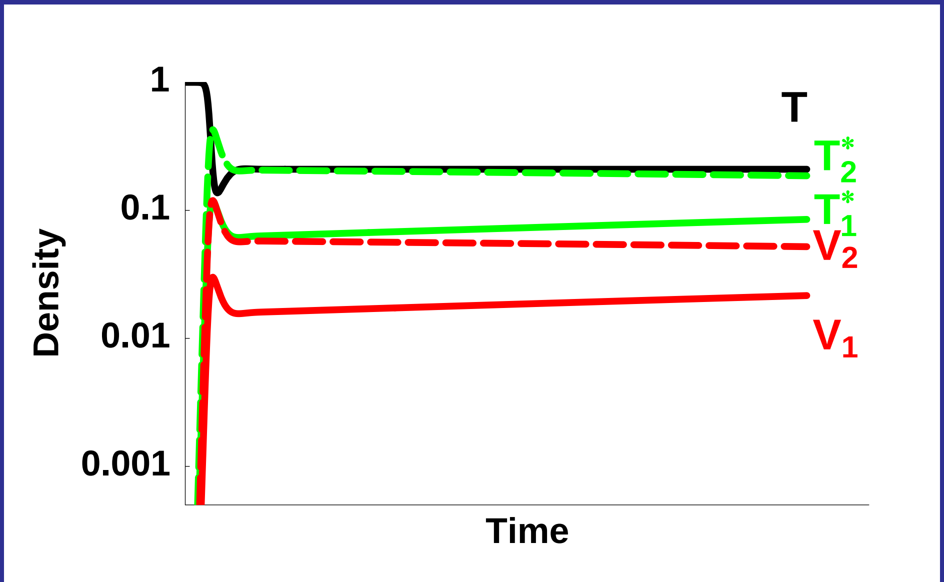
Model Behavior: Production Rate p

Similar Production Rates: $p_1 \lesssim p_2$

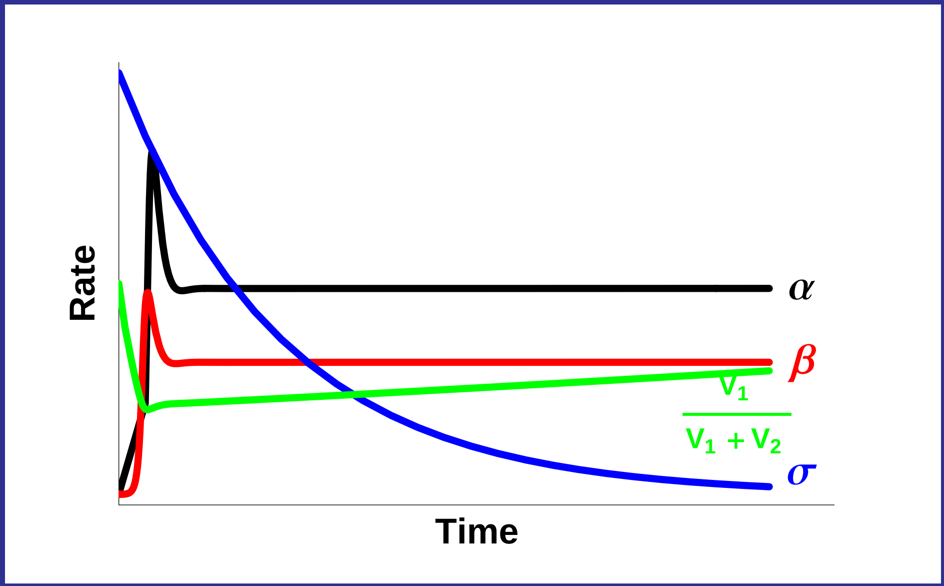
Spike Advantage: Small

Competitive Exclusion: Slow

Within-Host Dynamics



Between-Host Parameters



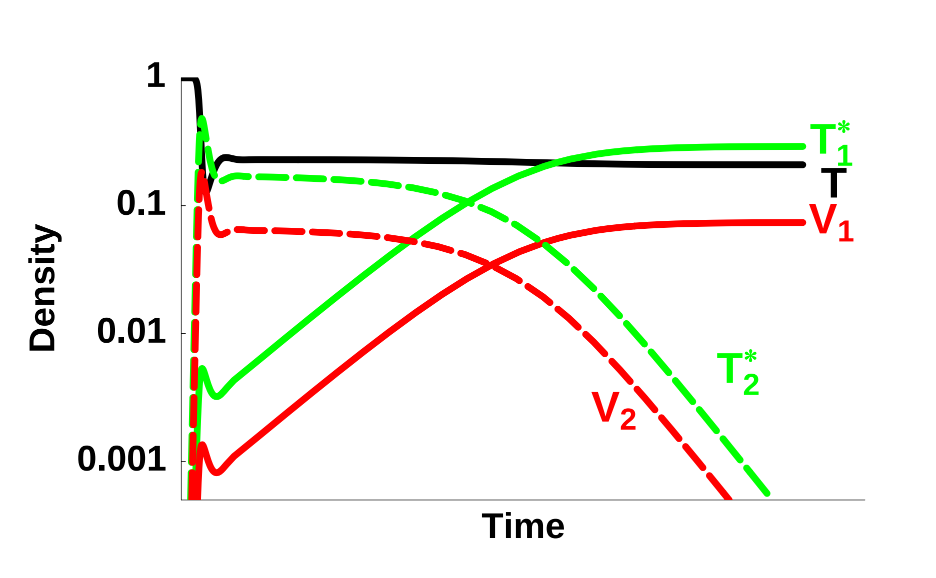
Model Behavior: Production Rate p

Different Production Rates: $p_1 < p_2$

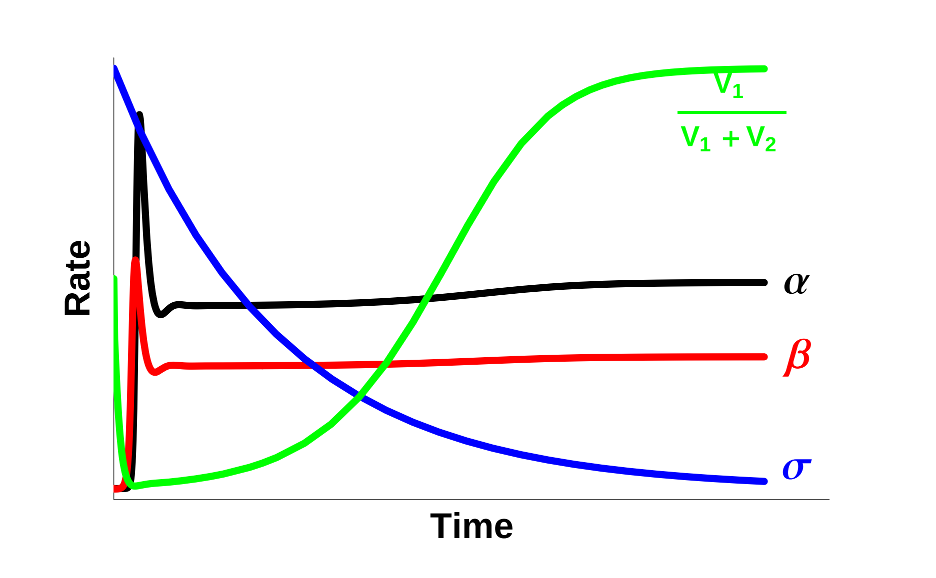
Spike Advantage: Moderate

Competitive Exclusion: Moderate

Within-Host Dynamics



Between-Host Parameters



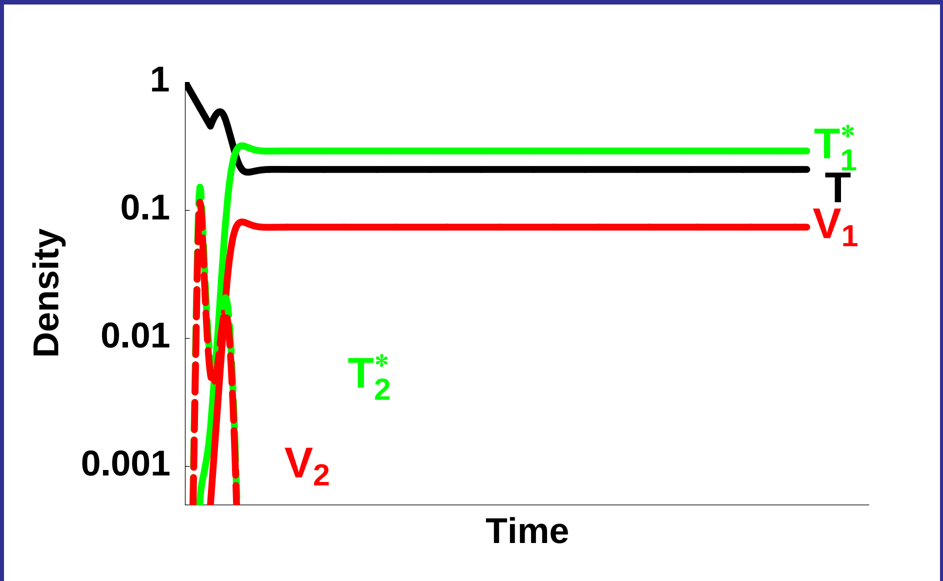
Model Behavior: Production Rate p

Very Different Production Rates: $p_1 \ll p_2$

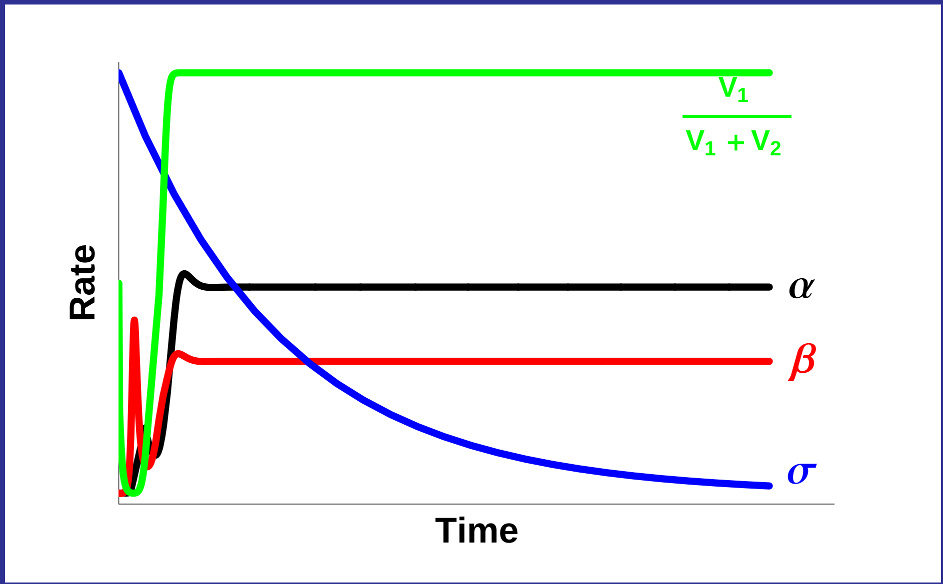
Spike Advantage: Moderate

Competitive Exclusion: Fast

Within-Host Dynamics



Between-Host Parameters



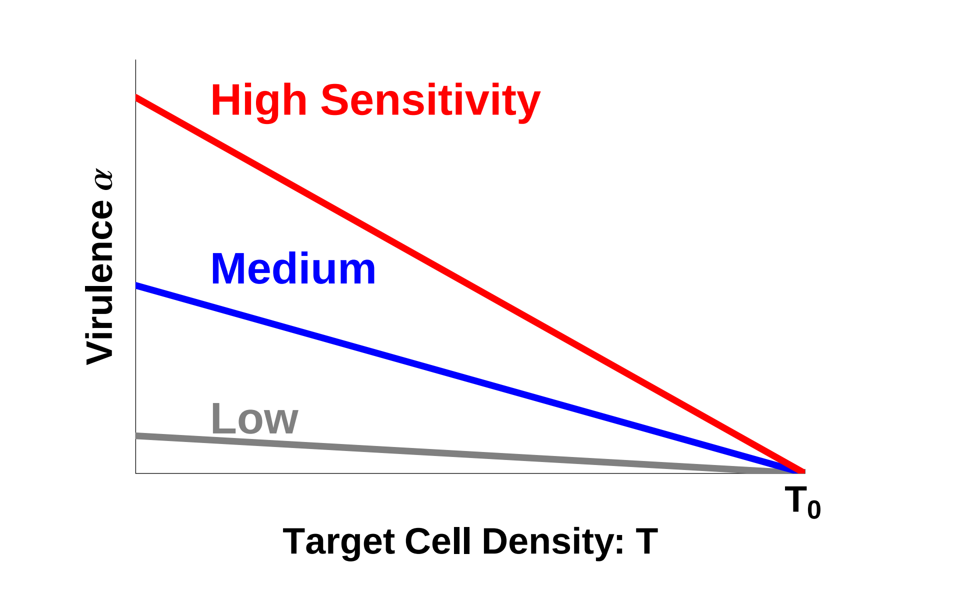
Model Results: Importance of Spike vs. Exclusion

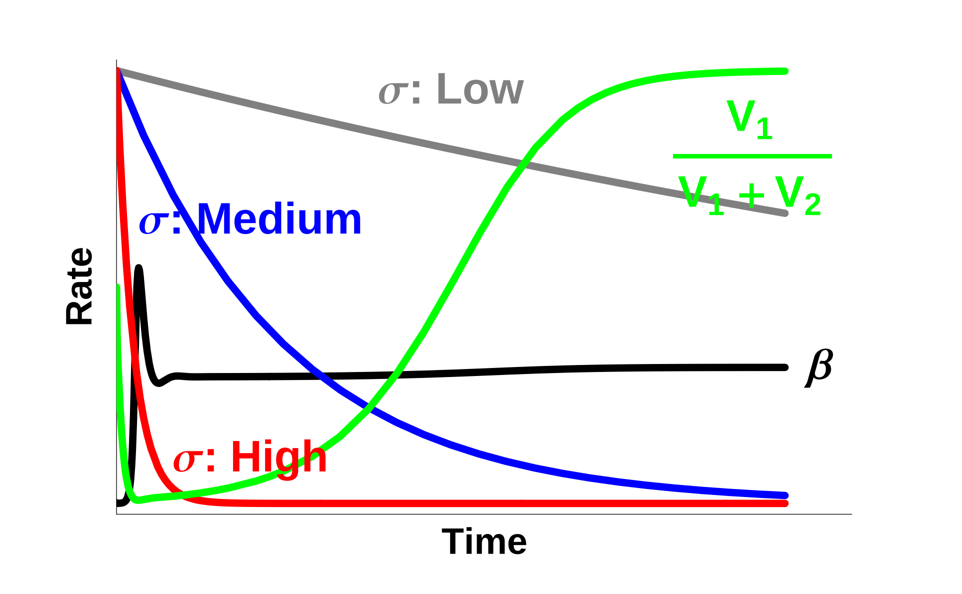
Sensitivity of host to T loss affects importance of spike

Low Sensitivity: Within-Host Optimum p^* favored

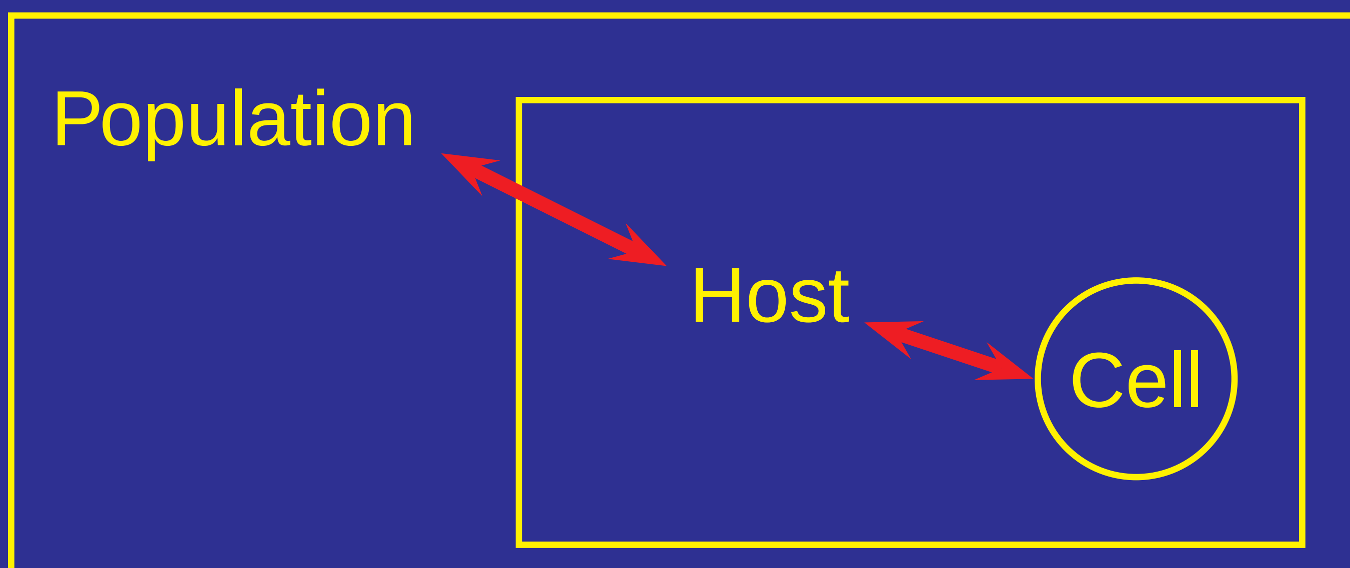
Medium Sensitivity: Intermediate $p^* > p > p^\bullet$ favored

High Sensitivity: Between-Host optimum $p^\bullet$ favored





Including Intra-Cellular Scale



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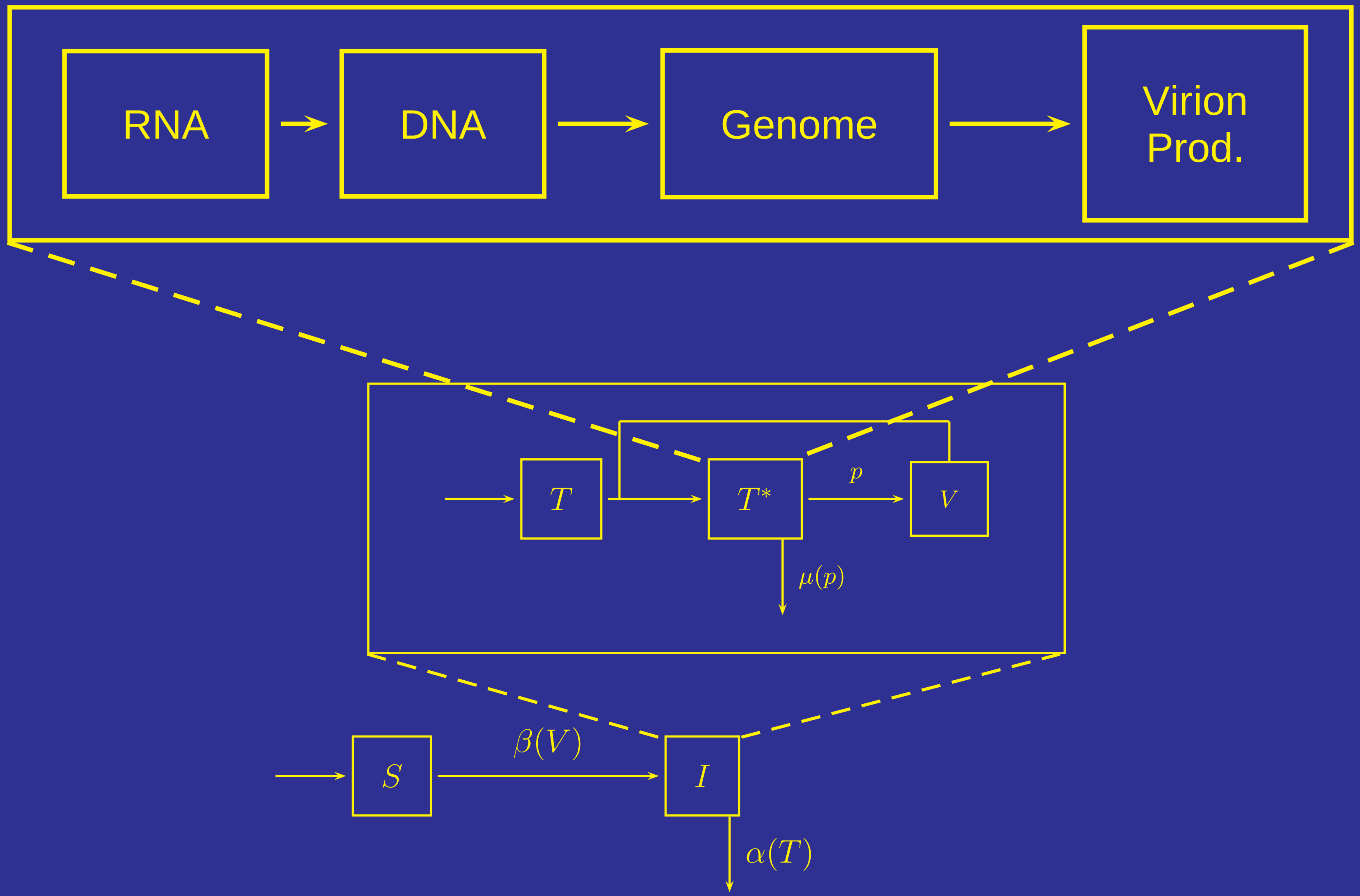

e.g. see Rong et al. (2007)

What We Need to Understand Better

- How can we include stochastic effects
  - Birth-death processes at each scale
  - Distribution of mutation effects on p
  - Transmission between hosts
  - Genetic drift

  in a biologically sensible and mathematically managable manner

What We Need to Understand Better

- How does cell mortality change with virion production rate? I.e. what does $\mu(p)$ look like
- How sensitive is the host to resource loss? I.e. What does $\alpha(T)$ look like?
- How much heterogeneity is there between hosts
- More general modeling tools for dynamics and data analyses

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