

Within-host viral infection dynamics and evolution

The surprising complexity of the classical world

Tim Vaughan, Alexei Drummond, Peter Drummond



September 13, 2011



Goals of study

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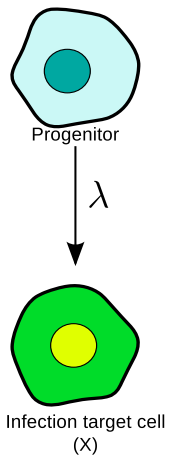
- Model effects of mutation due to different microscopic mechanisms
- Examine correlations arising between genetically distinct viral subpopulations
- Determine extent to which mutation mechanism affects these correlations

Part I

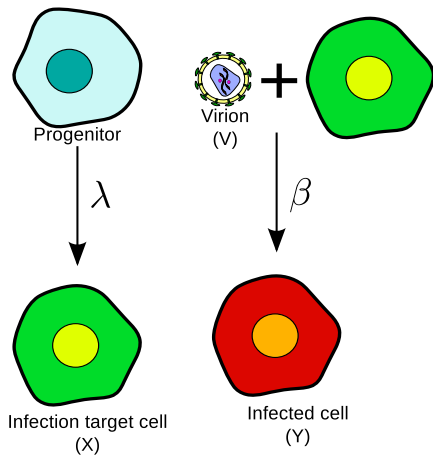
Demographic fluctuations

Primitive infection processes

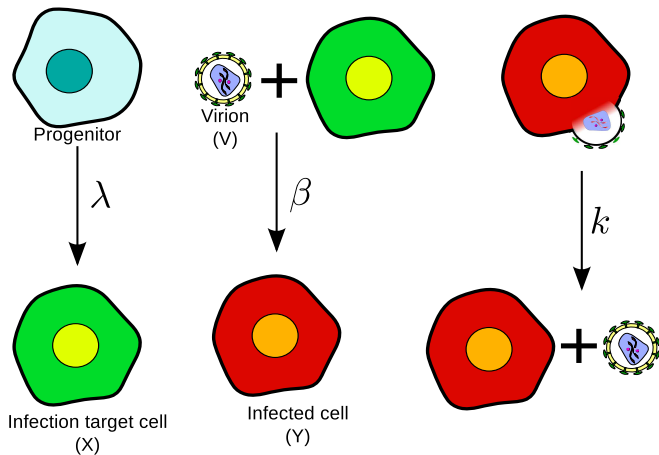
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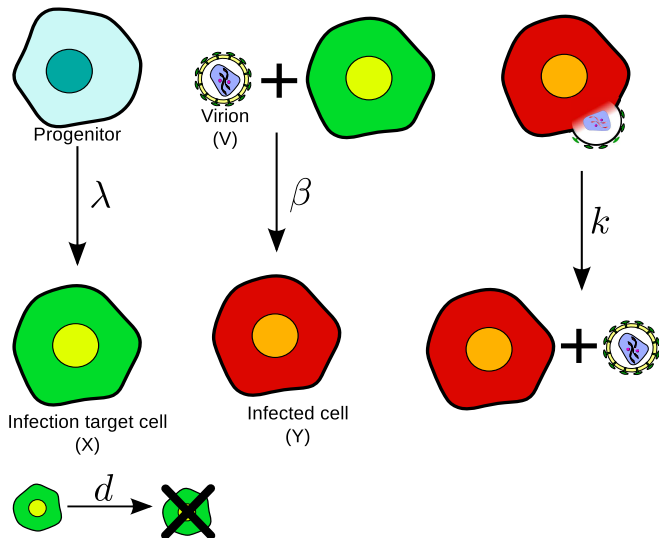
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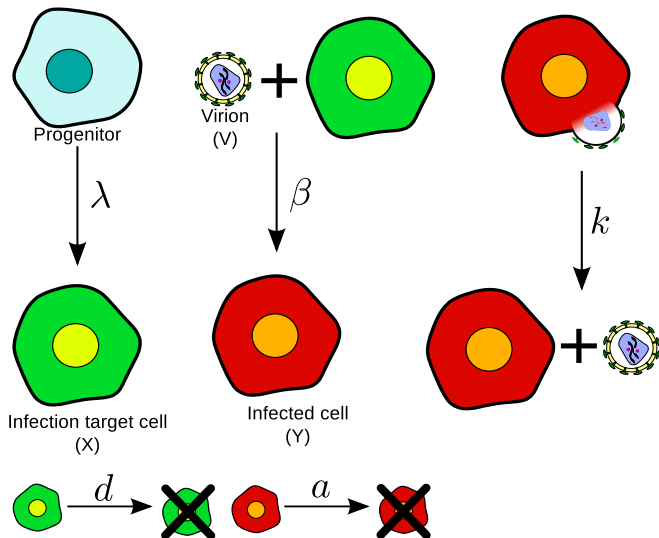
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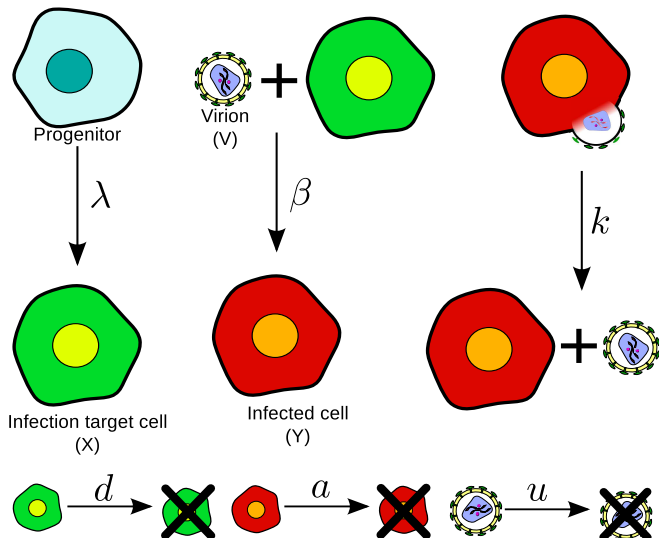
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Values of rate constants

Parameter	Description	Value
λ^*	T cell production rate	$2.5 \times 10^8/\text{day}$
β^*	T cell infection rate	$5 \times 10^{-13}/\text{T cell/virion/day}$
k	virion production rate	$10^3/\text{infected T cell/day}$
d	T cell death rate	$10^{-3}/\text{T cell/day}$
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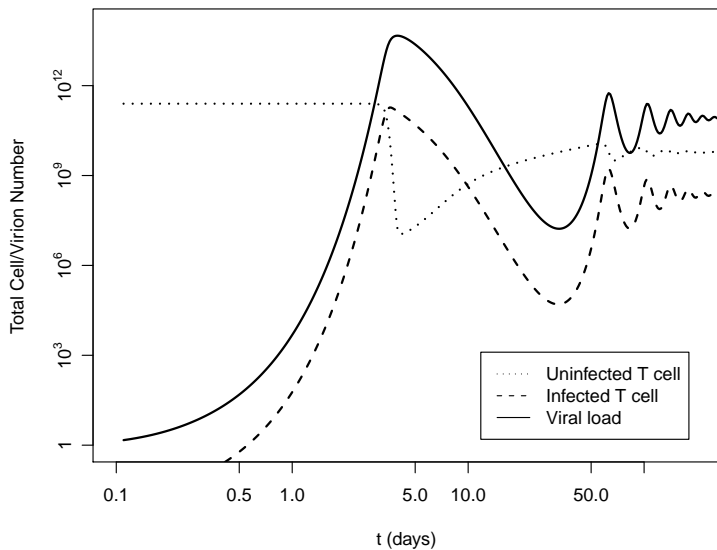
Deterministic Model

$$\dot{x} = \lambda - \beta xv - dx$$

$$\dot{y} = \beta xv - ay$$

$$\dot{v} = ky - \beta xv - uv$$

Deterministic predictions



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- We need to relax this assumption to consider the effect of integer numbers of cells and virions.
- This leads naturally to the question of *when* microscopic interactions occur.
- Assume reactions occur at *known rates* (dependent on population sizes) but at completely *unknown times*: i.e. Poisson stochastic processes.

A stochastic description

With these goals in mind, we assemble the

Chemical Master Equation (CME)

$$\begin{aligned}\frac{\partial}{\partial t} P(N_x, N_y, N_v) = & \lambda [P(N_x - 1, N_y, N_v) - P(N_x, N_y, N_v)] \\ & + \beta [(N_x - 1)(N_v - 1)P(N_x - 1, N_y + 1, N_v - 1) \\ & \quad - N_x N_y P(N_x, N_y, N_v)] \\ & + k N_y [P(N_x, N_y + 1, N_v - 1) - P(N_x, N_y, N_v)] \\ & + d [(N_x + 1)P(N_x + 1, N_y, N_v) - N_x P(N_x, N_y, N_v)] \\ & + a [(N_y + 1)P(N_x, N_y + 1, N_v) - N_y P(N_x, N_y, N_v)] \\ & + u [(N_v + 1)P(N_x, N_y, N_v + 1) - N_v P(N_x, N_y, N_v)]\end{aligned}$$

Traditional Monte Carlo approach

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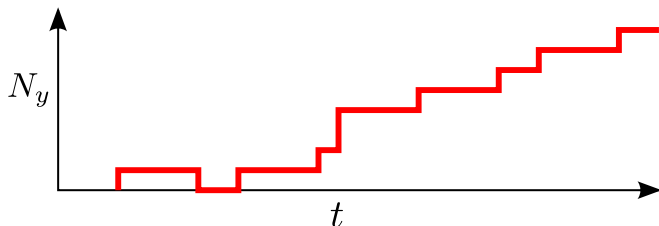
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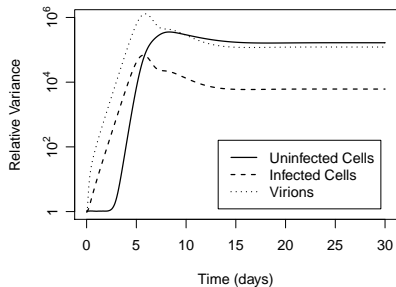
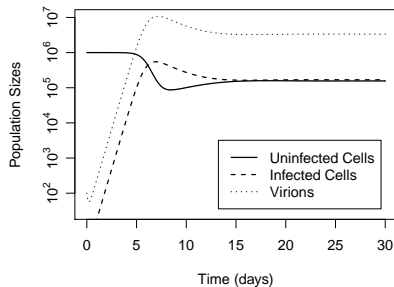
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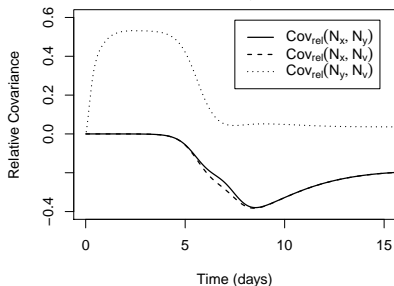
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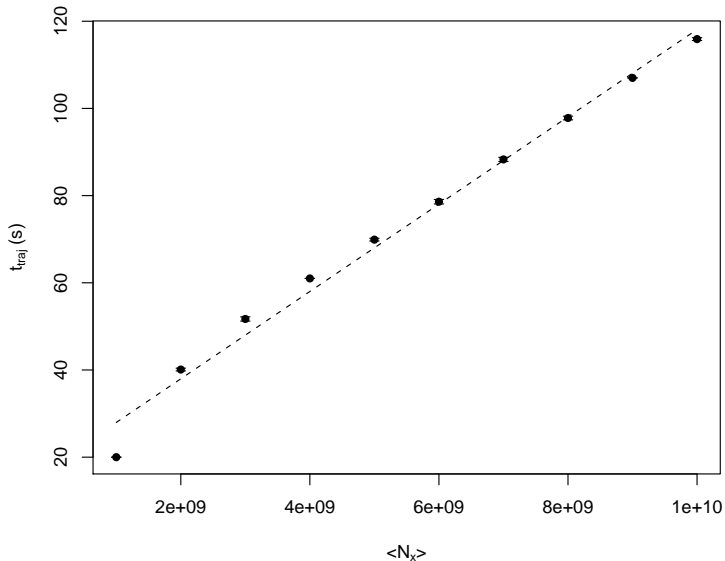
SSA results for small system



$$\text{Cov}_{\text{rel}}(N_i, N_j) \equiv \frac{\langle N_i N_j \rangle}{\langle N_i \rangle \langle N_j \rangle} - 1$$



Computational burden of the SSA



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- 3 Map the FPE to stochastic differential equations (SDEs) and solve numerically.

Difficulties with Poisson representation approach

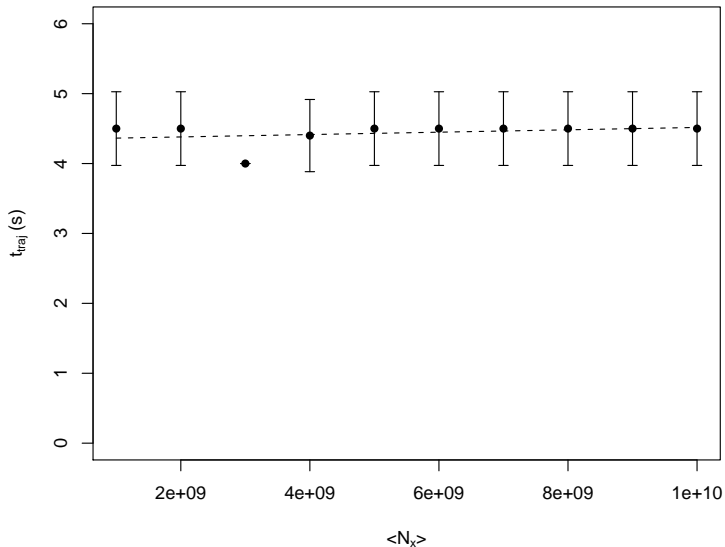
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- Can in principle address with stochastic gauges ([Drummond, 2004](#)), but there are an infinite number of different gauges and no a priori way of assessing performance of a particular gauge is currently known.

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 - ⇒ Fewer trajectories needed to sample the distribution.
- 2 Integration algorithms for continuous variable SDEs involve approximating the integral using a series of finite time steps, *the size of which does not explicitly depend on the magnitude of the variables involved.*

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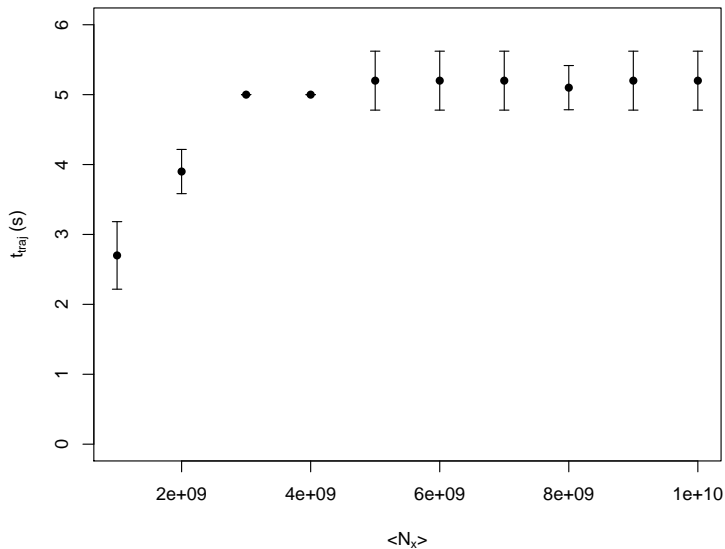
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- Finite time step approximation to stochastic trajectory for N_x can be generated by iterating:

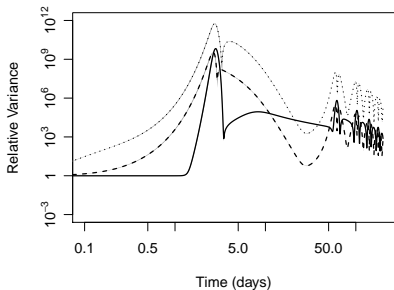
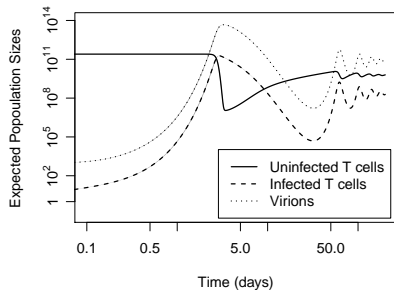
$$N_x(t + (q + 1)\tau) = N_x(t + q\tau) + m_q$$

with each m_q chosen from a Poisson distrib. with mean $\tau\lambda$.
(Gillespie, 2001)

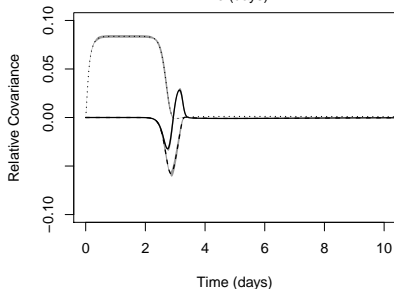
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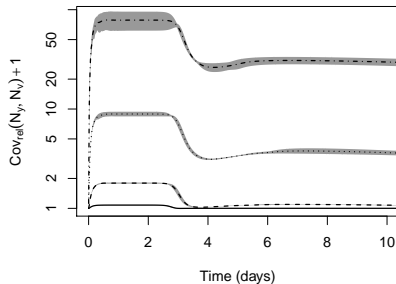
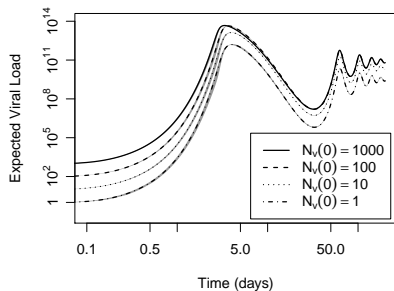
τ -leaping results for full-sized model



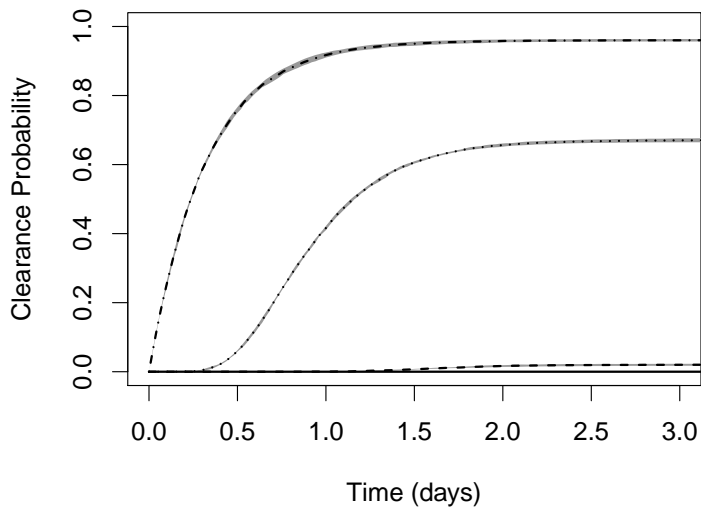
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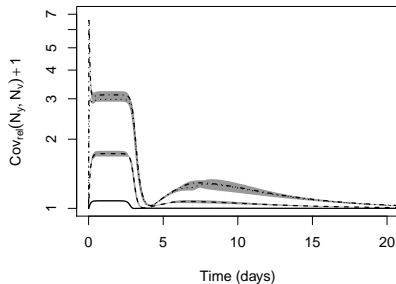
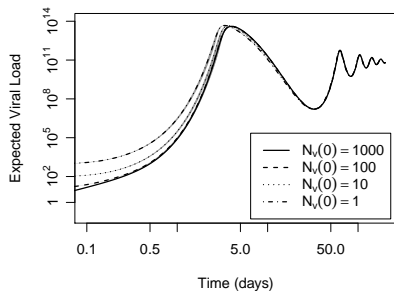
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Part II

Genetic correlations

Mutation in HIV replication

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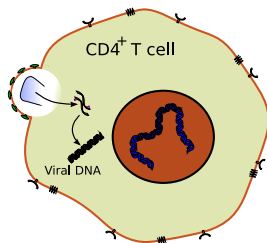
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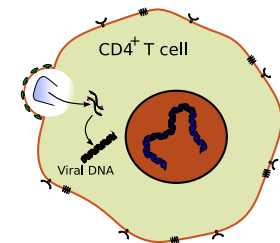
Reverse Transcription

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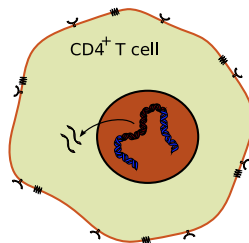
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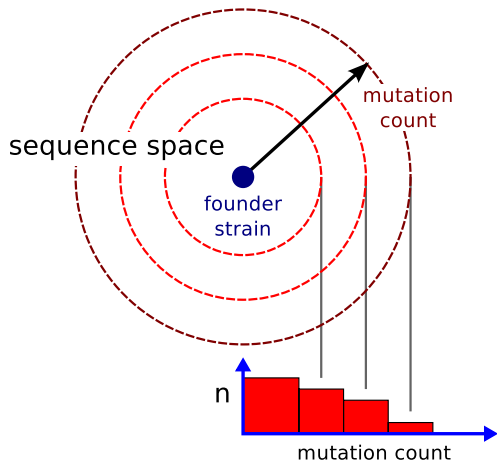
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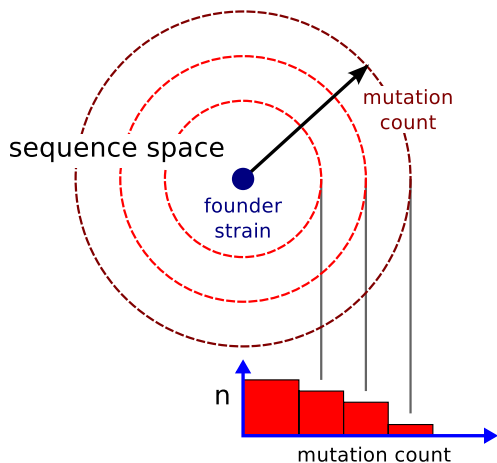
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 - \implies stochastic simulation (even τ -leaping) without further simplification is unwieldy at best.

Sequence space projection

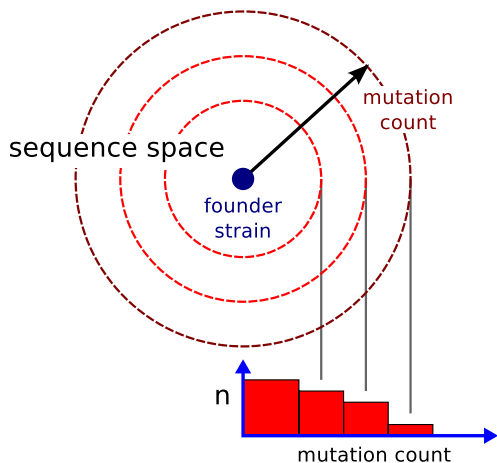


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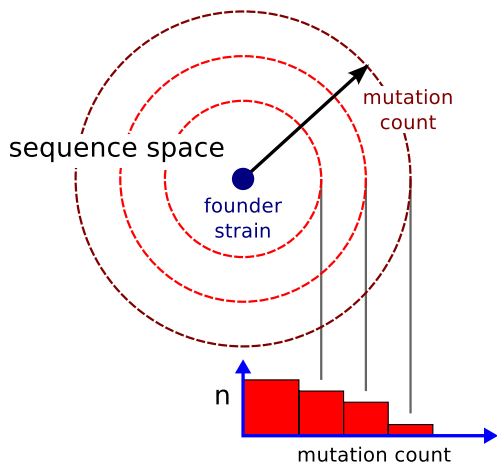
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Thank-you!