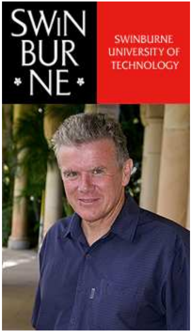
Within-host viral infection dynamics and evolution

The surprising complexity of the classical world

Tim Vaughan, Alexei Drummond, Peter Drummond

September 13, 2011



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- Model effects of mutation due to different microscopic mechanisms

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- Determine extent to which mutation mechanism affects these correlations

Part I

Demographic fluctuations

Primitive infection processes

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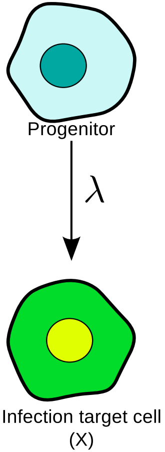

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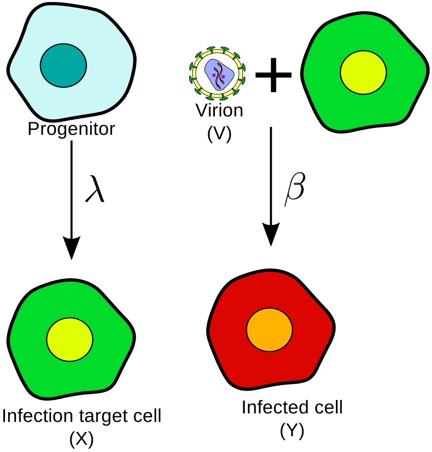

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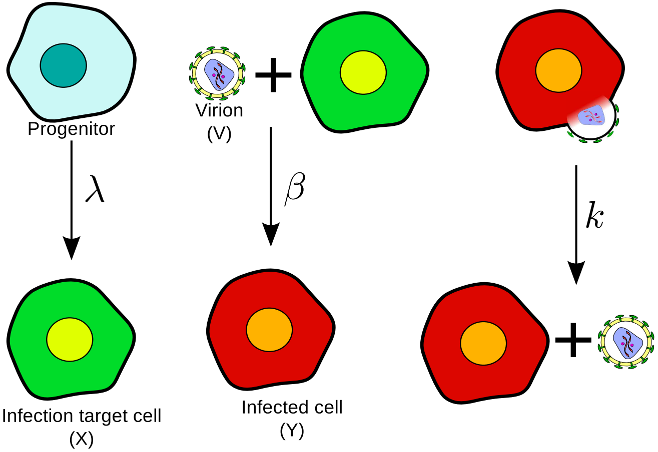

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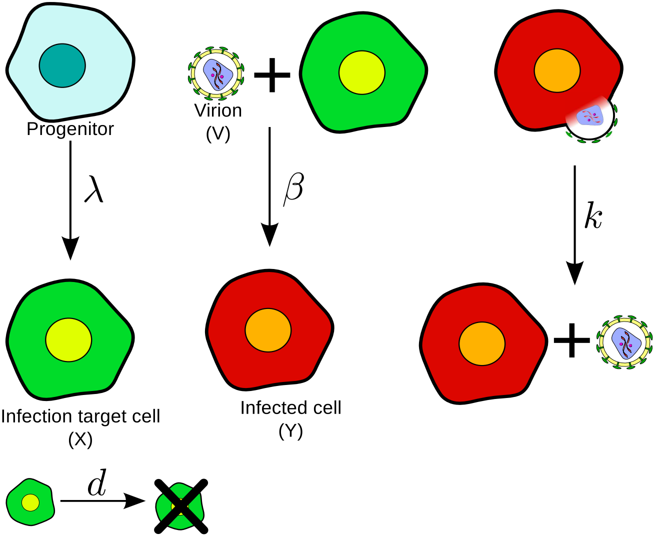


Progenitor

λ

Virion
(V)

β

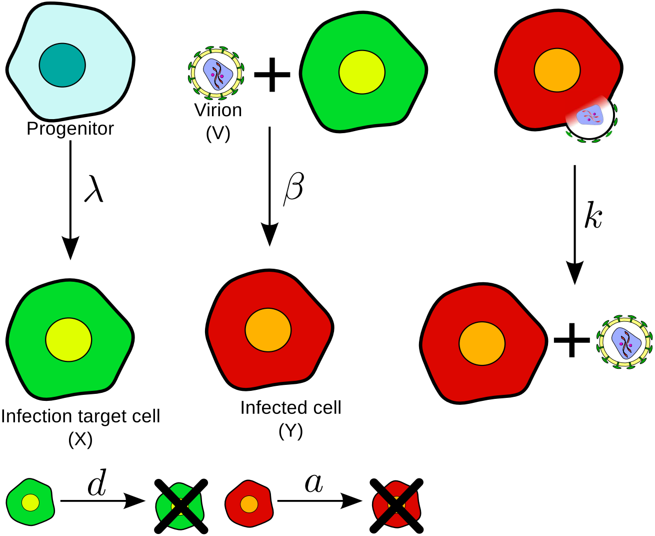
k

Infection target cell
(X)

Infected cell
(Y)

d

Primitive infection processes



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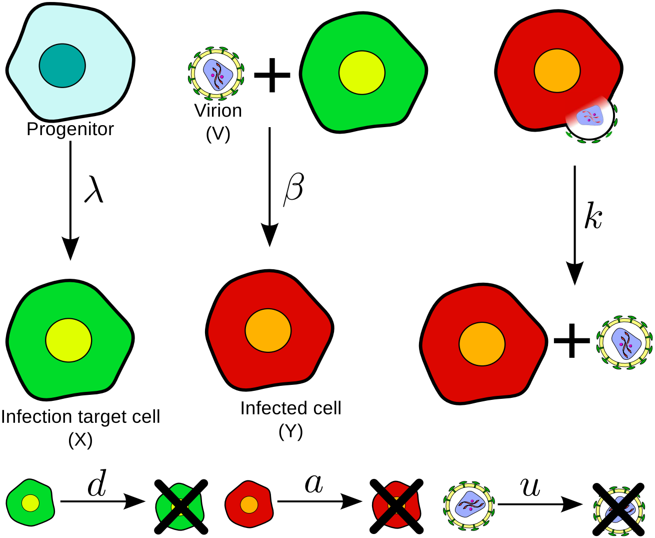

Values of rate constants

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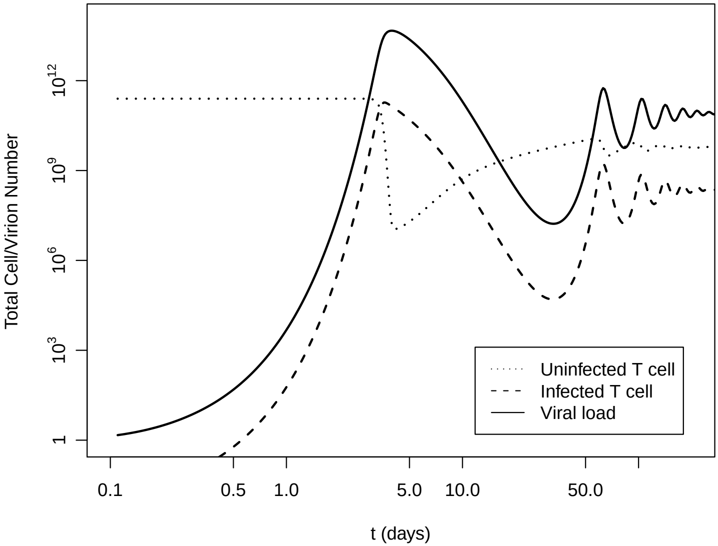
Deterministic Model

$$\begin{aligned}\dot{x} &= \lambda - \beta x v - d x\\ \dot{y} &= \beta x v - a y\\ \dot{v} &= k y - \beta x v - u v\end{aligned}$$

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) \quad = \quad & \lambda \big[P(N_x - 1, N_y, N_v) - P(N_x, N_y, N_v) \big] \\
& + \beta \big[(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) \big] \\
& + k N_y \big[P(N_x, N_y + 1, N_v - 1) - P(N_x, N_y, N_v) \big] \\
& + d \big[(N_x + 1) P(N_x + 1, N_y, N_v) - N_x P(N_x, N_y, N_v) \big] \\
& + a \big[(N_y + 1) P(N_x, N_y + 1, N_v) - N_y P(N_x, N_y, N_v) \big] \\
& + u \big[(N_v + 1) P(N_x, N_y, N_v + 1) - N_v P(N_x, N_y, N_v) \big]
\end{aligned}
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Traditional Monte Carlo approach

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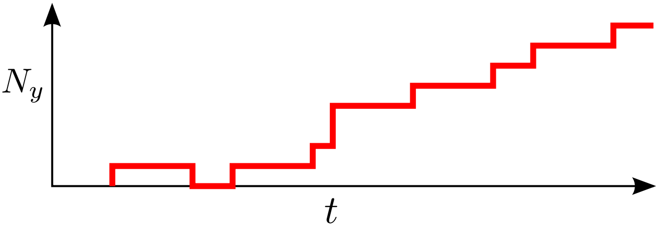
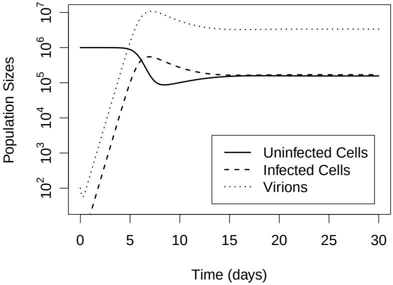
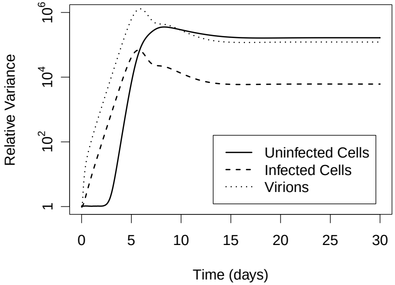
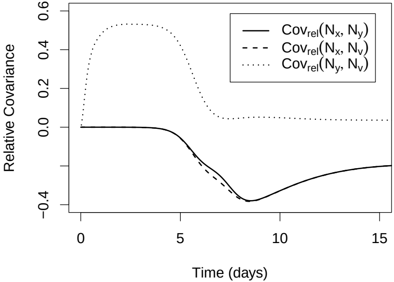


SSA results for small system

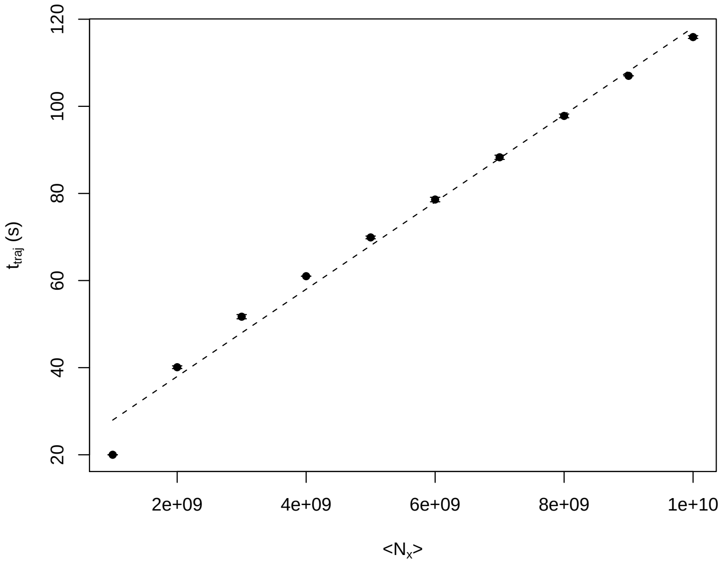




$$\mathrm{Cov}_{\mathrm{rel}}(N_i, N_j) \equiv \frac{\langle N_i N_j \rangle}{\langle N_i \rangle \langle N_j \rangle} - 1$$



Computational burden of the SSA



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

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- Derivation of FPE involves an “integration by parts” step which assumes tails of $f(\alpha_x, \alpha_y, \alpha_v)$ decay rapidly as $|\vec{\alpha}| \to \infty$. Violation of this assumption can lead to large sampling errors and/or systematic errors in results.

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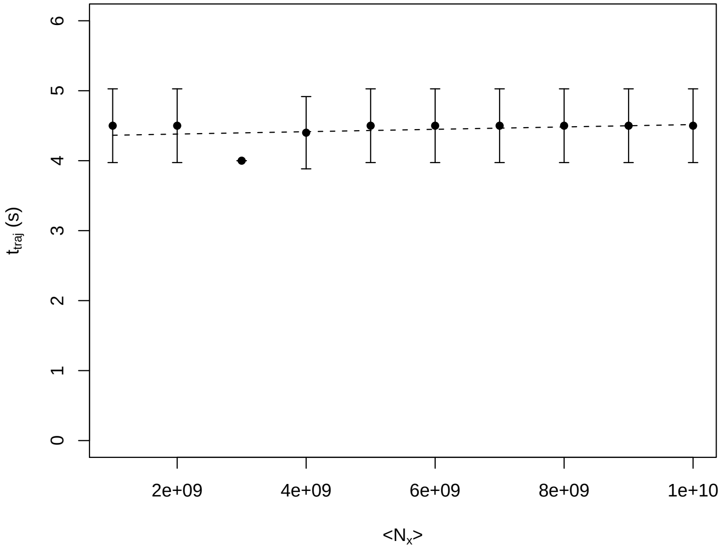
- Can in principle address with stochastic gauges (Drummond, 2004), but there are an infinite number of different gauges and no a priori way of assessing performance of a particular gauge is currently known.

Why does Poisson rep. offer scaling improvement?



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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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- 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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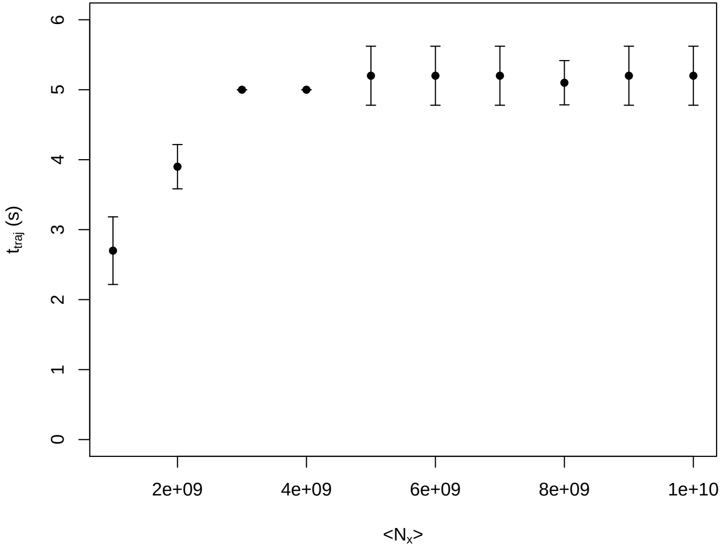
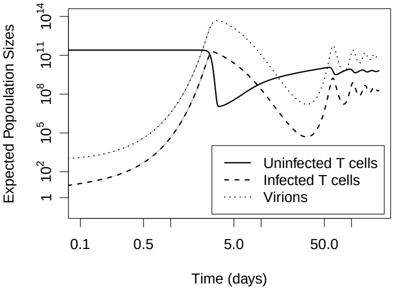
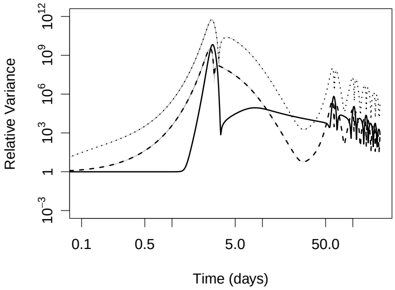


τ-leaping results for full-sized model





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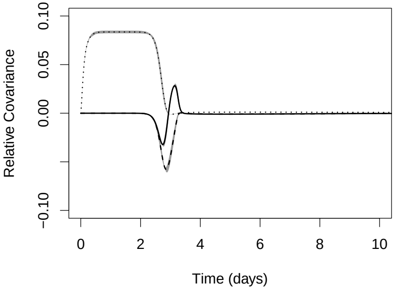
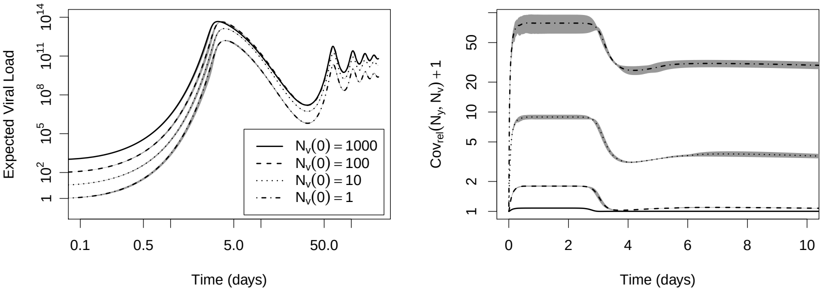


Impact of initial population size



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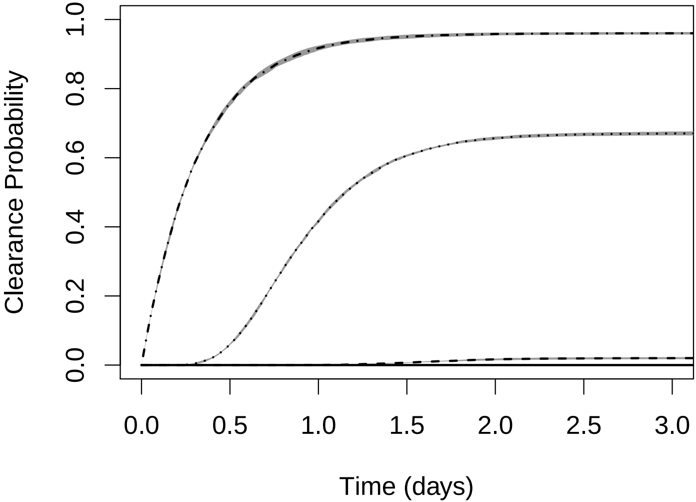

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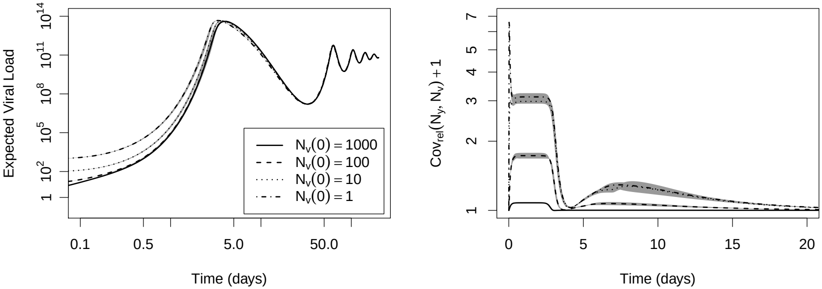

Part II

Genetic correlations

Mutation in HIV replication

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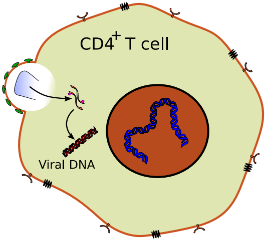

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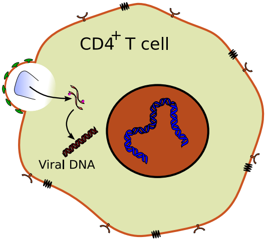

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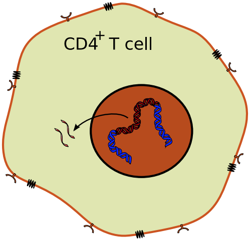

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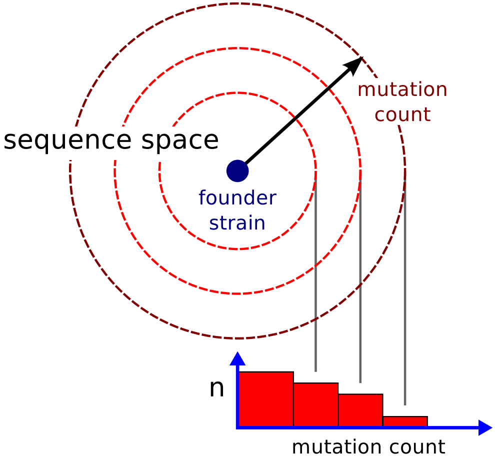
$\Longrightarrow$ stochastic simulation (even τ-leaping) without further simplification is unwieldy at best.

Sequence space projection



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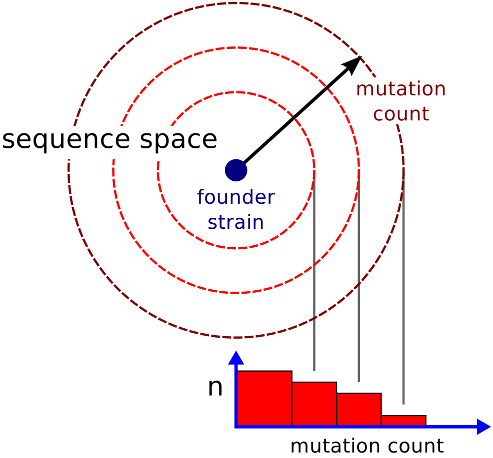

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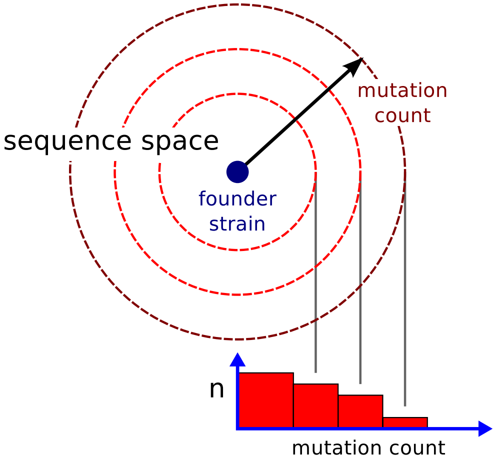

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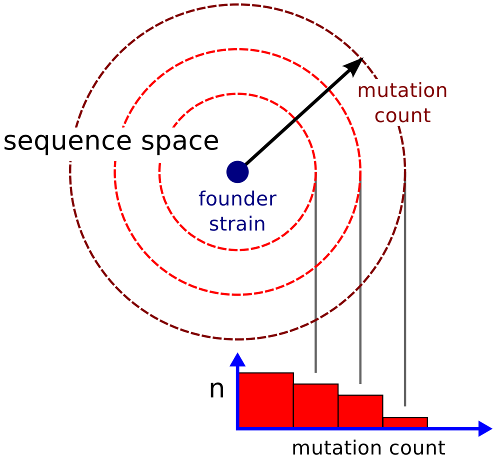

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Thank-you!