

A new method for tackling the stochastic dynamics of viral infection

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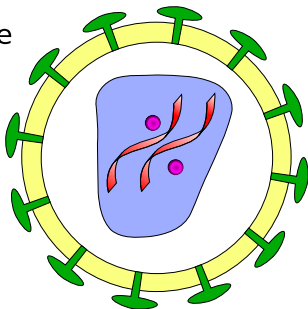
The Human Immunodeficiency Virus



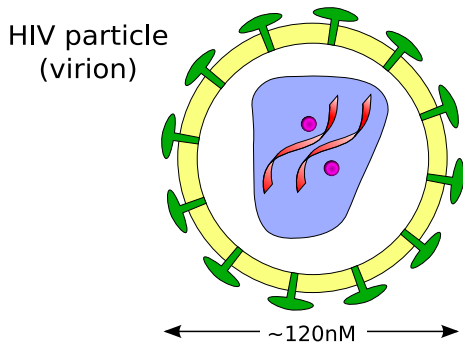
- First isolated in 1983 by Françoise Barre-Sinoussi and Luc Montagnier, for which they received half of this year's Nobel Prize in Medicine.

The Human Immunodeficiency Virus

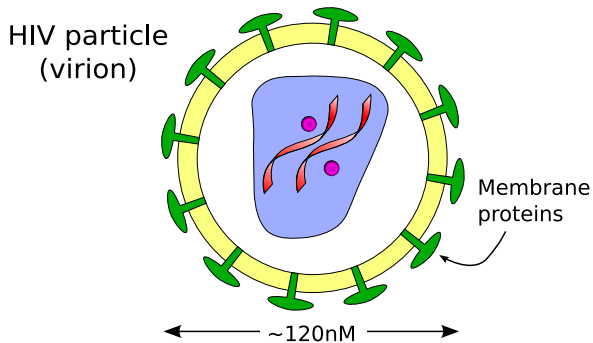
HIV particle
(virion)



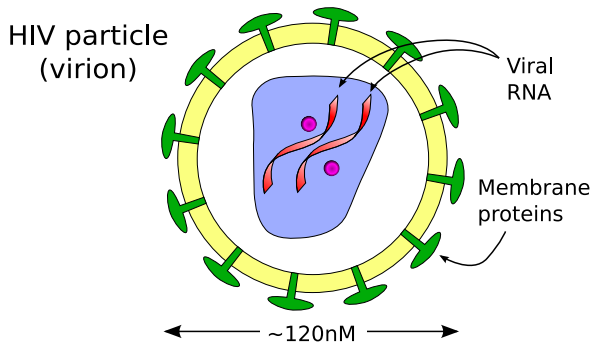
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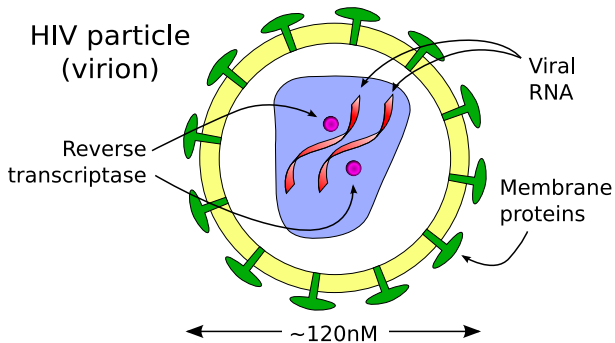
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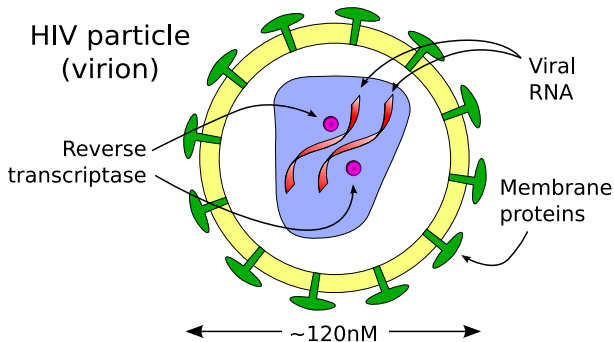
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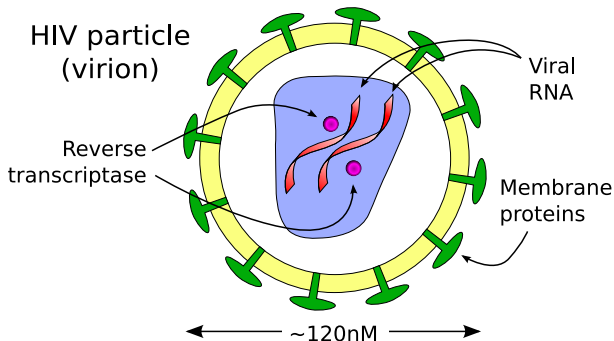


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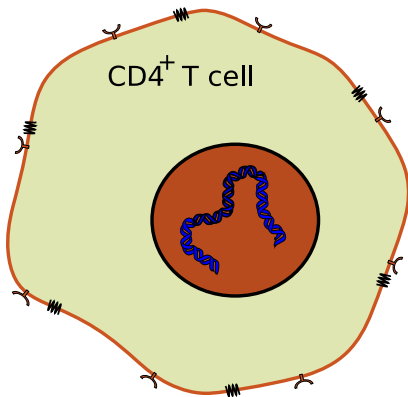
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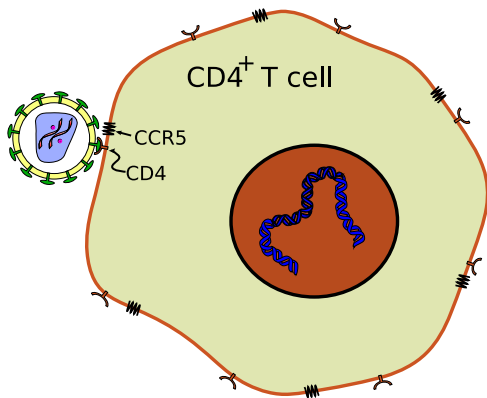


- Genome $\simeq 10^4$ bases long – equivalent to just under 2.5kB.
- Responsible for the deaths of over 2 million people in 2007.
(UNAIDS/WHO)

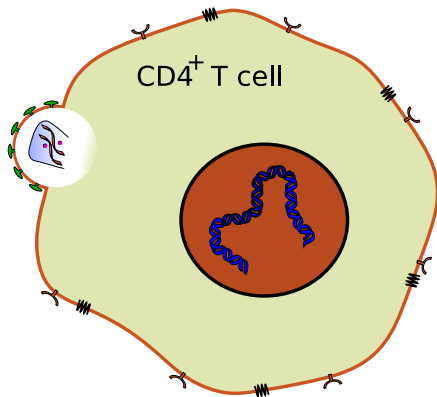
The HIV infection process



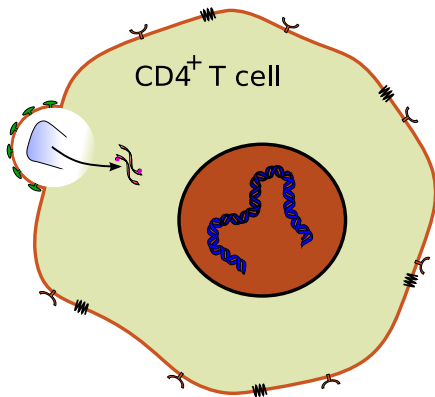
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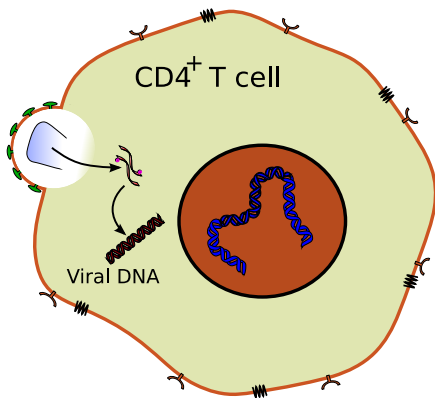
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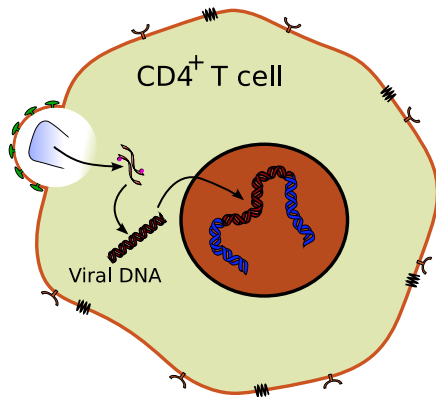
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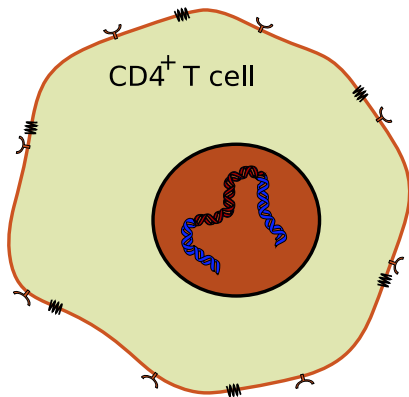
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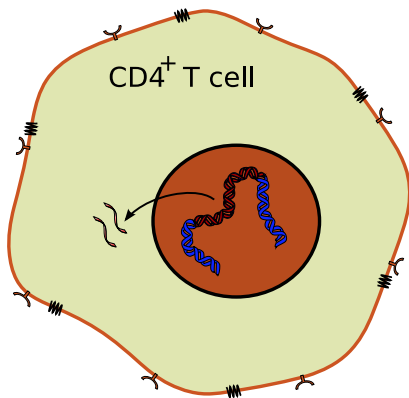
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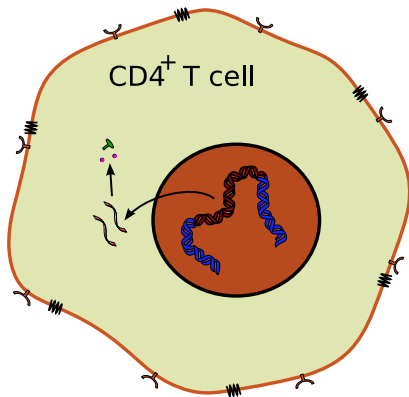
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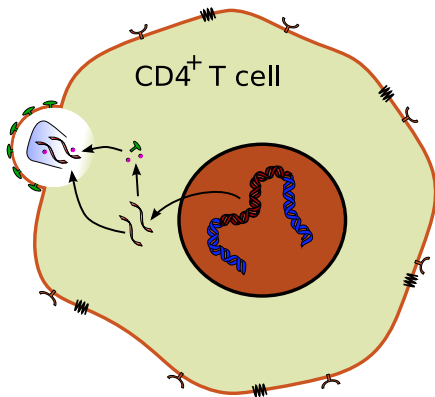
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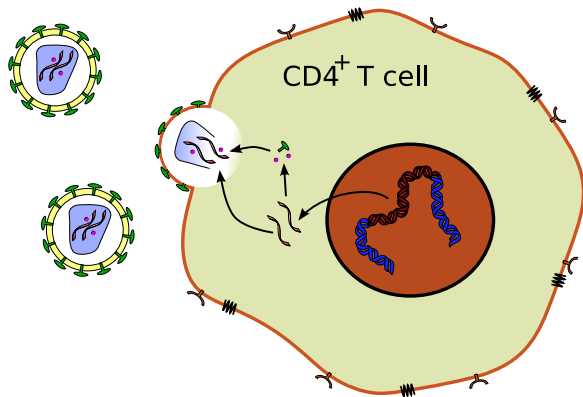
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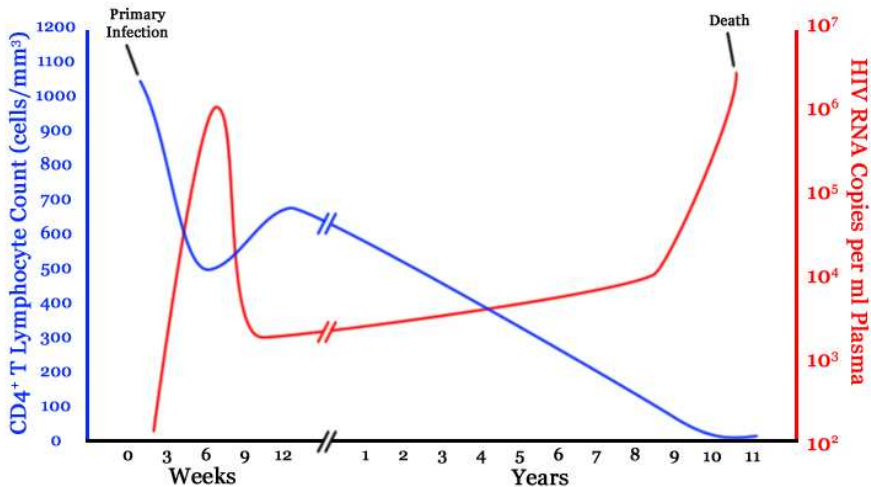
The HIV infection process



The HIV infection process



The HIV infection time-course



Deterministic models of infection dynamics

- Many deterministic models of HIV infection dynamics have been suggested. For example, [Perelson et al. \(1993\)](#), [Schenzle \(1994\)](#), [Phillips et al. \(1996\)](#), [Nowak et al. \(1996\)](#).

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These correlations are completely ignored by deterministic models.

Stochastic approaches



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Need a systematic *scalable* approach to deal with the large populations present in viral infections.

The Poisson Representation

Gardiner, Chaturvedi (1977)

- A probability distribution over discrete variables can be expressed in terms of an over-complete set of Poissonian basis functions:

$$P(\mathbf{N}, t) = \int d^{2M} \mathbf{x} f(\mathbf{x}, t) p_0(\mathbf{x}; \mathbf{N}) \quad (1)$$

where

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The dynamics of many birth/death master equations can be *exactly* described by diffusion processes!

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Must employ sophisticated integration techniques in these cases.

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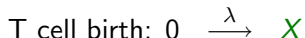
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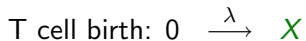
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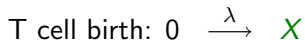
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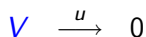
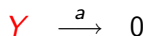
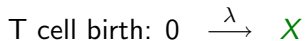
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Integrating by parts yields an FPE, equivalent to the following Itô SDEs:

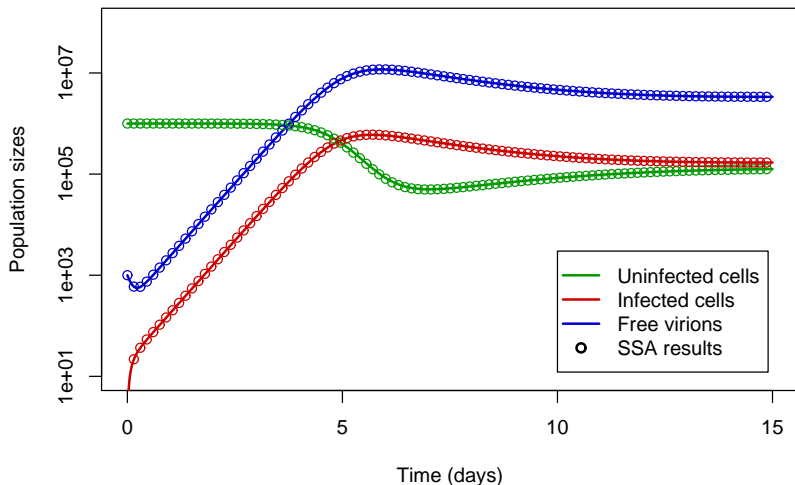
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$$dv = (ky - uv - \beta xv) dt + \frac{\beta v}{\sqrt{2}} (idW_1^I(t) + dW_2^I(t)) \\ + \sqrt{\frac{ky}{2}} (dW_1^P(t) - idW_2^P(t))$$

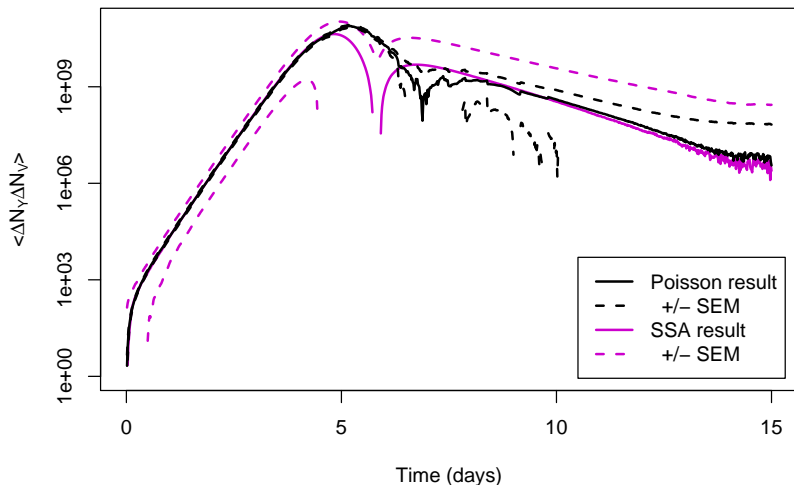
Example 1: Results – Mean population sizes

- Dynamics of means achieve perfect agreement with SSA results. (Model parameters from [Nowak and May, \(2000\).](#))



Example 1: Results – Infected cell / virion correlations

- Covariance between N_Y and N_V in close agreement with SSA result, given error bounds due to finite ensemble sizes.



Example 2: Modelling HIV infection with mutation

- Both reverse and forward transcription processes are error-prone – recent experiments indicate that each replication has a $\sim 20\%$ chance of introducing a mutation. [Keele et al., PNAS \(2008\)](#)

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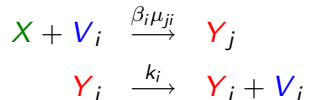
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- Poisson approach will allow us to focus resources on this aspect of the stochastic HIV dynamics, rather than worrying about population size.

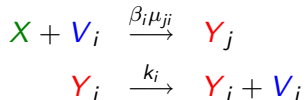
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This leads to the following stochastic quasi-species-like equations:

$$\begin{aligned} dx &= (\lambda - dx - \sum_j \beta_j v_j x) dt + \frac{x}{\sqrt{2}} \left(idW_1^I(t) - dW_2^I(t) \right) \\ dy_i &= \left(\sum_j \beta_j \mu_{ij} x - a_i y_i \right) dt + \sqrt{\frac{k_i y_i}{2}} \left(dW_{1,i}^P + idW_{2,i}^P \right) \\ dv_i &= (k_i y_i - u_i v_i - \beta_i v_i x) dt + \frac{\beta_i v_i}{\sqrt{2}} \left(idW_1^I(t) + dW_2^I(t) \right) \\ &\quad + \sqrt{\frac{k_i y_i}{2}} \left(dW_{1,i}^P(t) - idW_{2,i}^P(t) \right) \end{aligned}$$

Example 2: Results - Viral population diversity

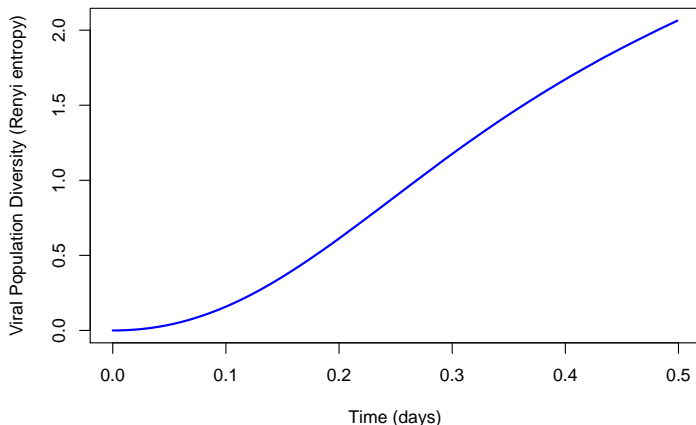
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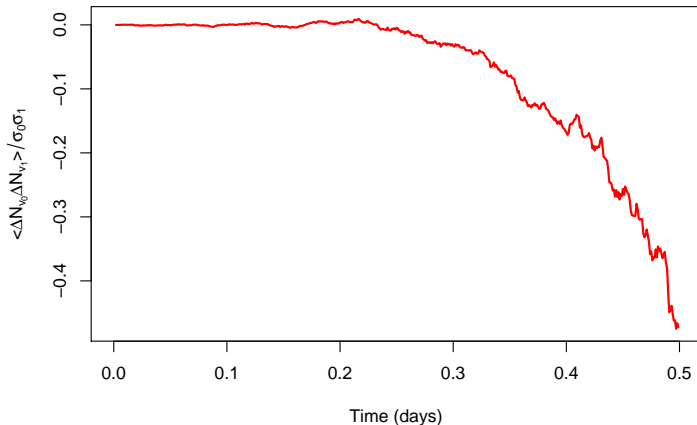
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Example 2: Results - Correlated viral fluctuations

- Can observe the development of negative correlations between viral populations separated by a single point mutation:



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Thank-you!