Tackling the Within-Host Stochastic Dynamics of HIV Infection

Why Virology needs Theoretical Physicists

Tim Vaughan, Peter Drummond, Alexei Drummond

15th of May, 2009

HIV – Current State of Pandemic

World Health Organization

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

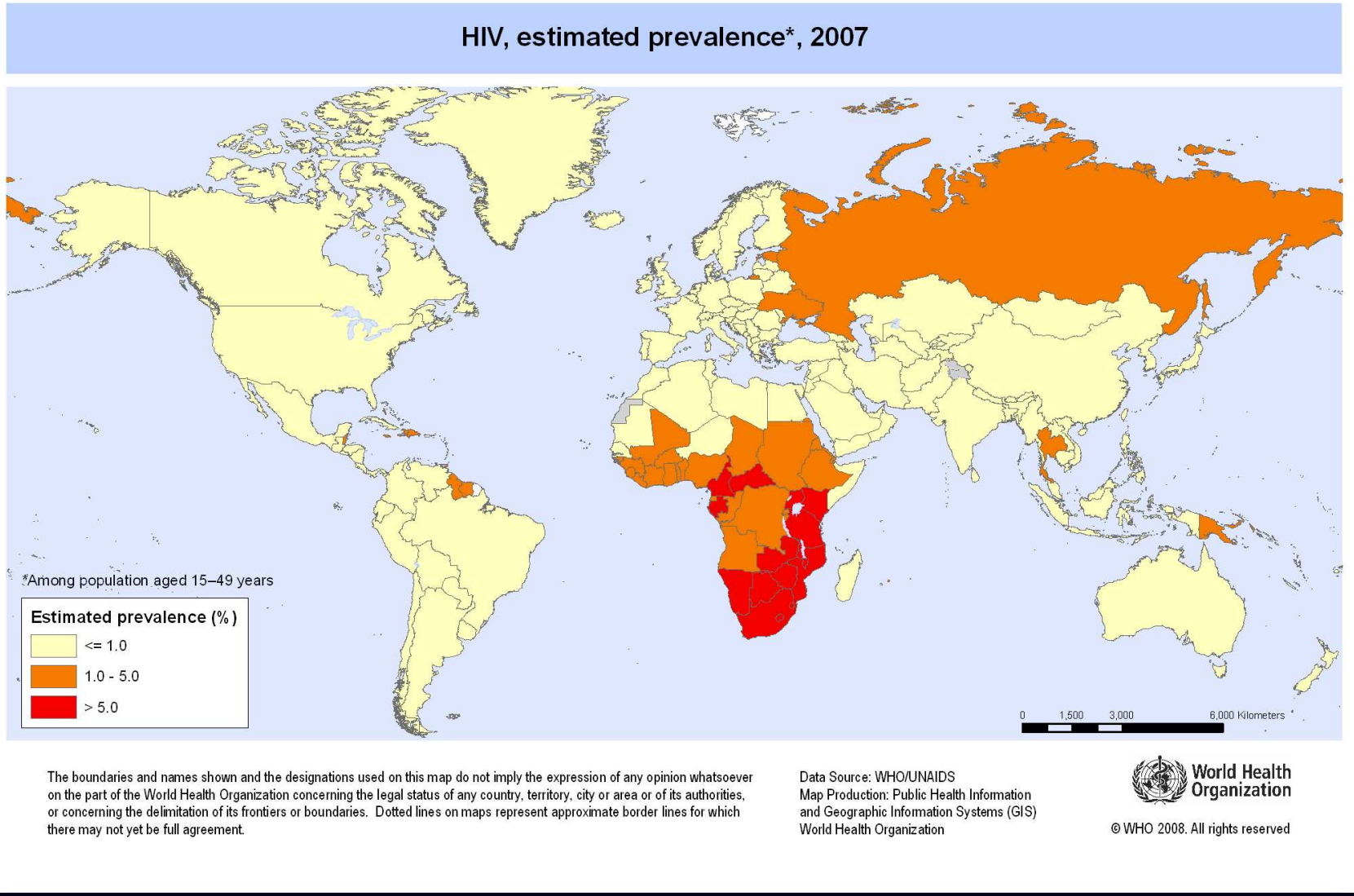
Global summary of the AIDS epidemic, December 2007

Number of people living with HIV in 2007	Total	33 million [30 – 36 million]
	Adults	30.8 million [28.2 – 34.0 million]
	Women	15.5 million [14.2 – 16.9 million]
	Children under 15 years	2.0 million [1.9 – 2.3 million]
People newly infected with HIV in 2007	Total	2.7 million [2.2 – 3.2 million]
	Adults	2.3 million [1.9 – 2.8 million]
	Children under 15 years	370 000 [330 000 – 410 000]
AIDS deaths in 2007	Total	2.0 million [1.8 – 2.3 million]
	Adults	1.8 million [1.6 – 2.1 million]
	Children under 15 years	270 000 [250 000 – 290 000]

HIV – Current State of Pandemic

Globally, nearly 1 in every 100 people are HIV-positive.

HIV – Current State of Pandemic



HIV – A Brief History

1920–1940 Cross-species transmission from chimpanzees in Cameroon. Korber et al., Science (2000), Keele et al., Science (2006)

HIV – A Brief History

1981 First recorded cases of previously-unknown immune deficiency disease by CDC.

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1982 CDC records approximately 800 cases and coins the name AIDS.

HIV – A Brief History

1983 Parisian lab headed by Luc Montagnier at the Pasteur Institute isolates a virus from the T cells of an AIDS suferer. Baré-Sinoussi et al., Science (1983)

HIV – A Brief History

Luc Montagnier

2008

(Medicine)

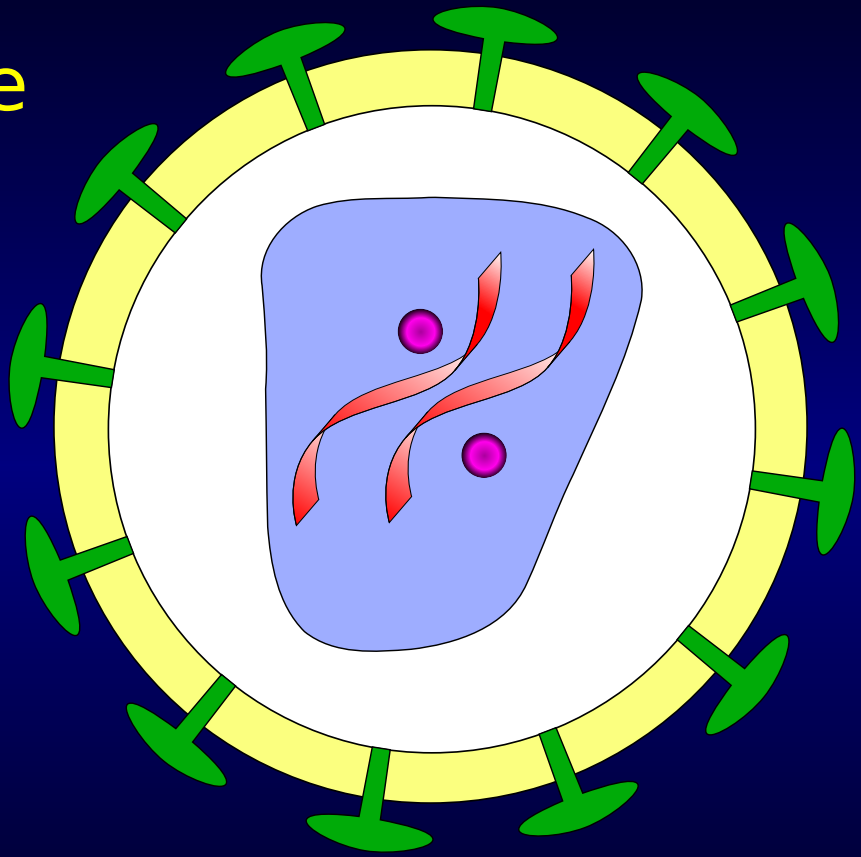
Françoise Barré-Sinoussi

HIV – A Brief History

1984 American scientist Robert Gallo, also doing breakthrough research on HIV, concludes that the virus is responsible for AIDS and predicts that a vaccine should be available in *two years*.

... But what is it?

HIV particle
(virion)



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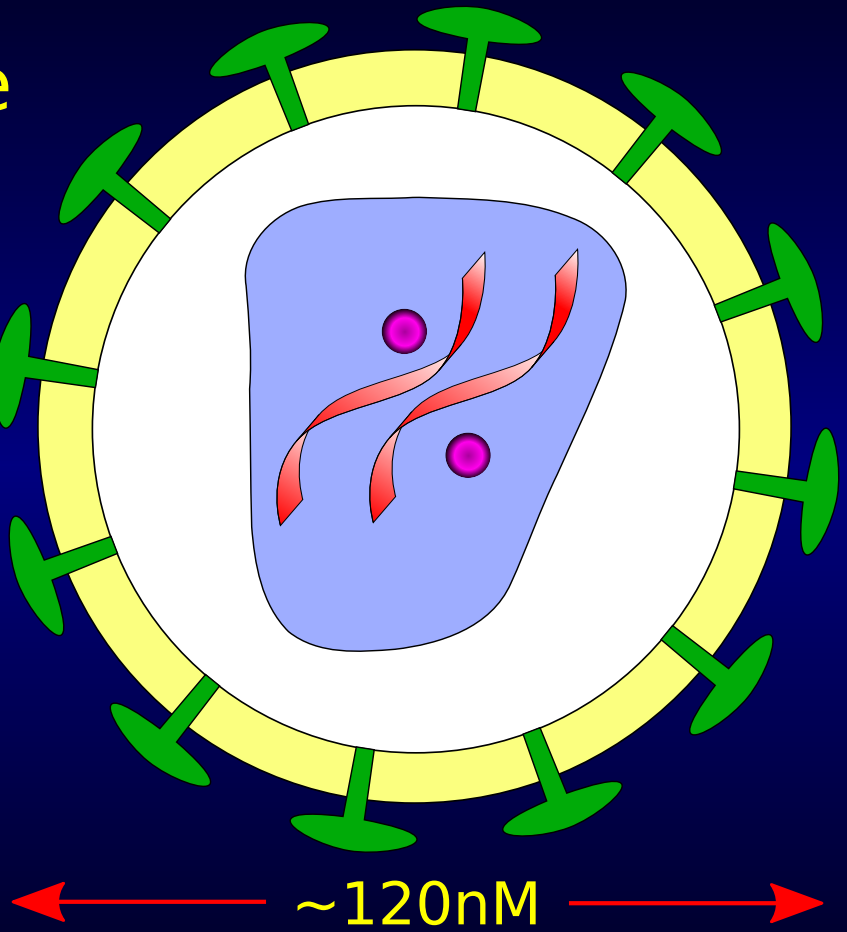

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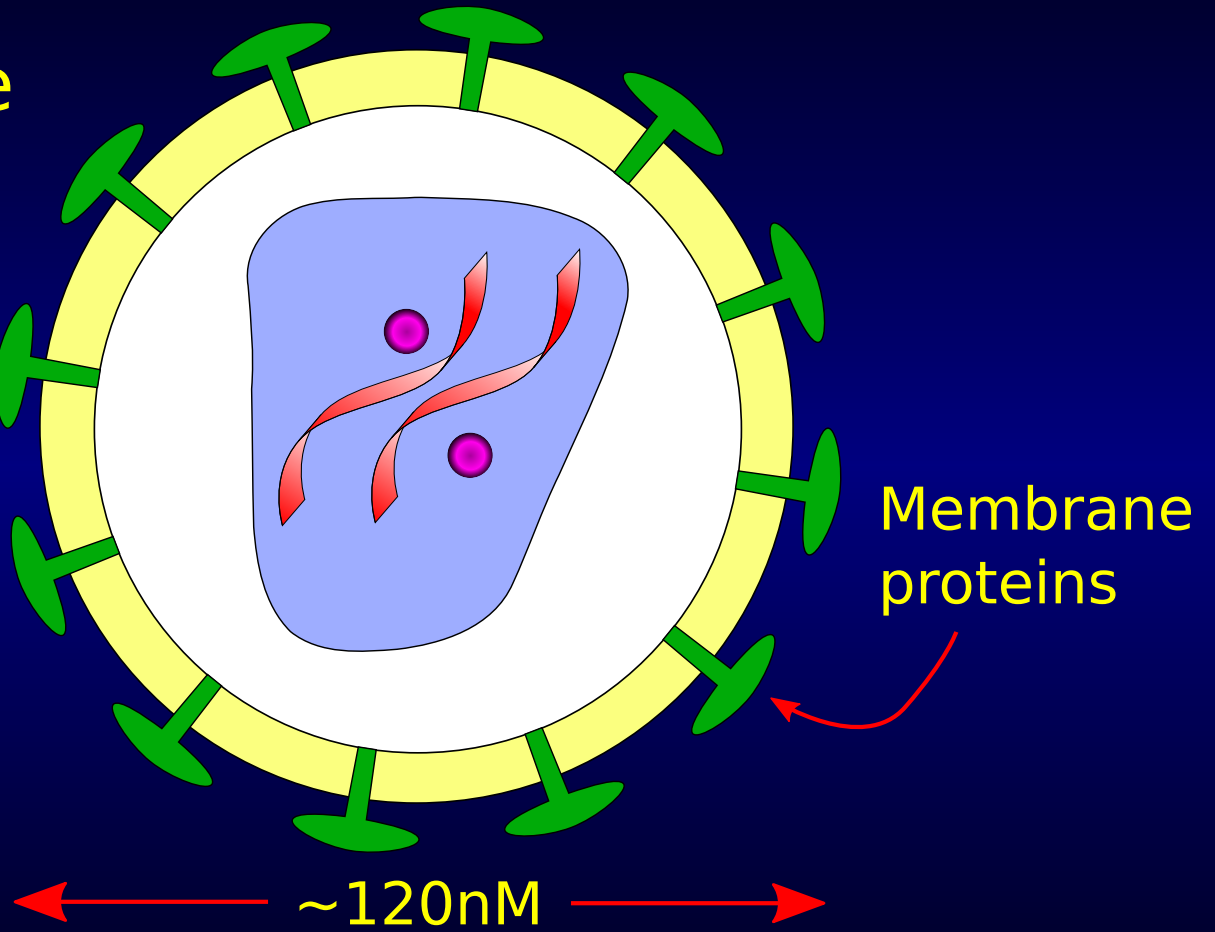

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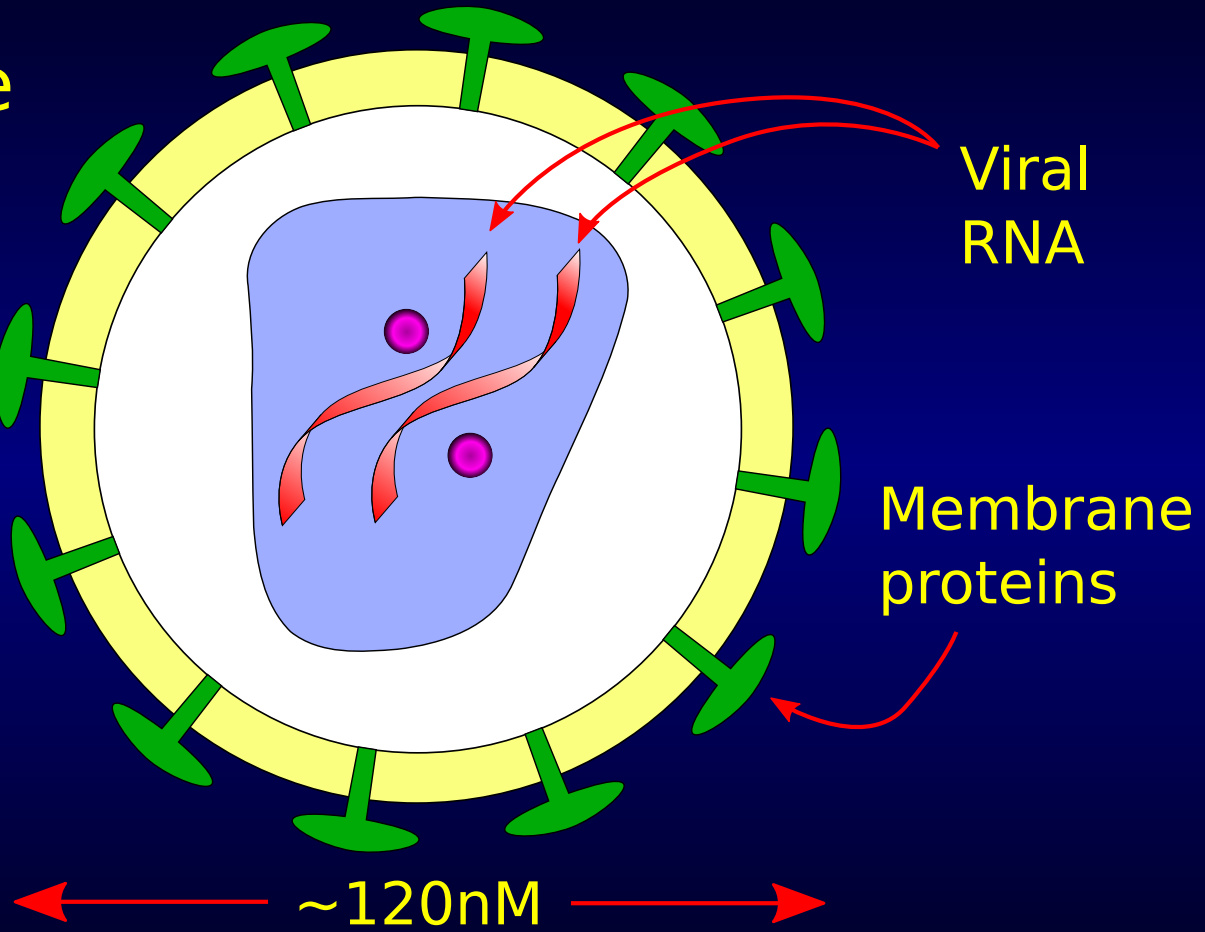

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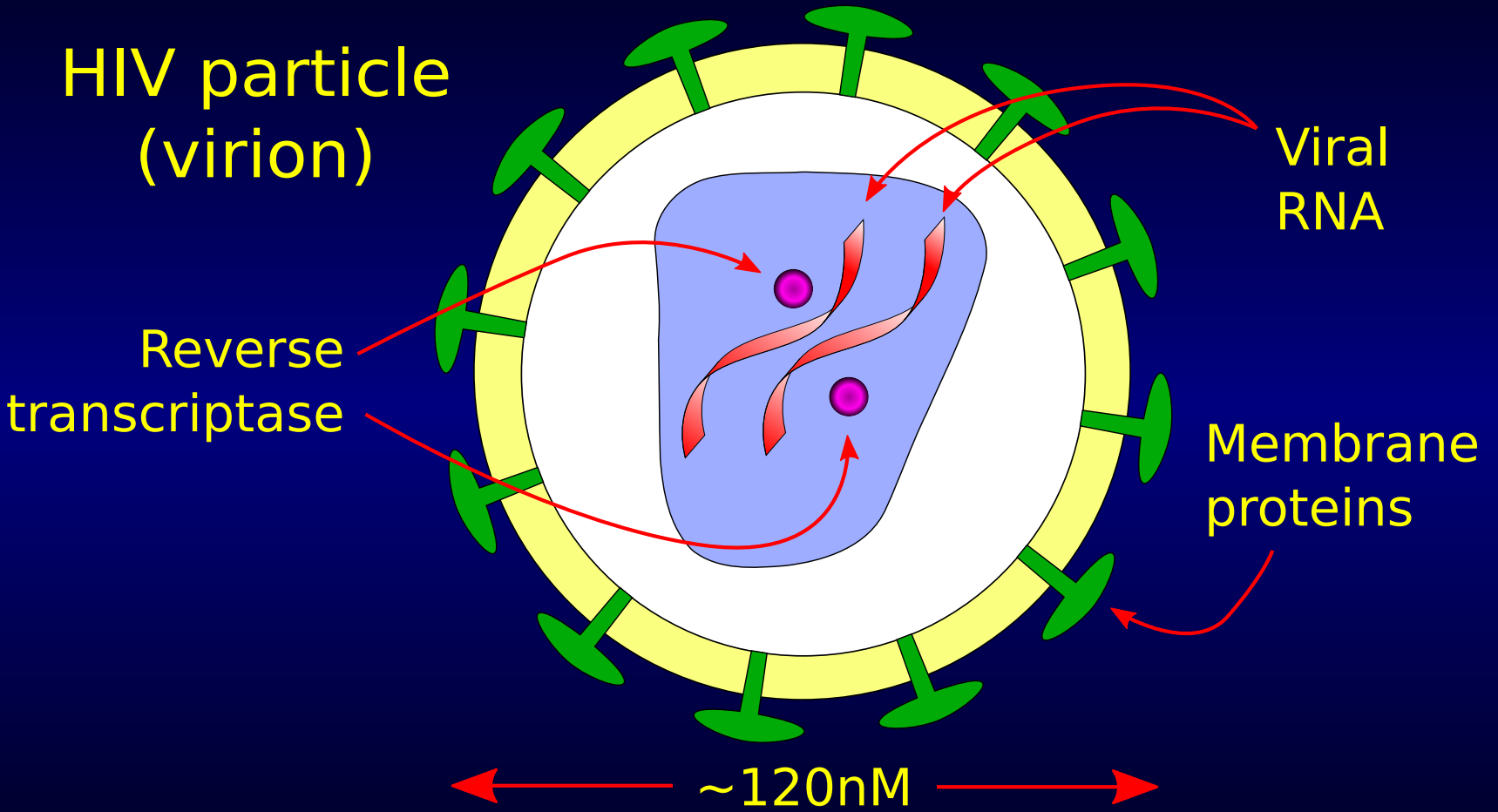
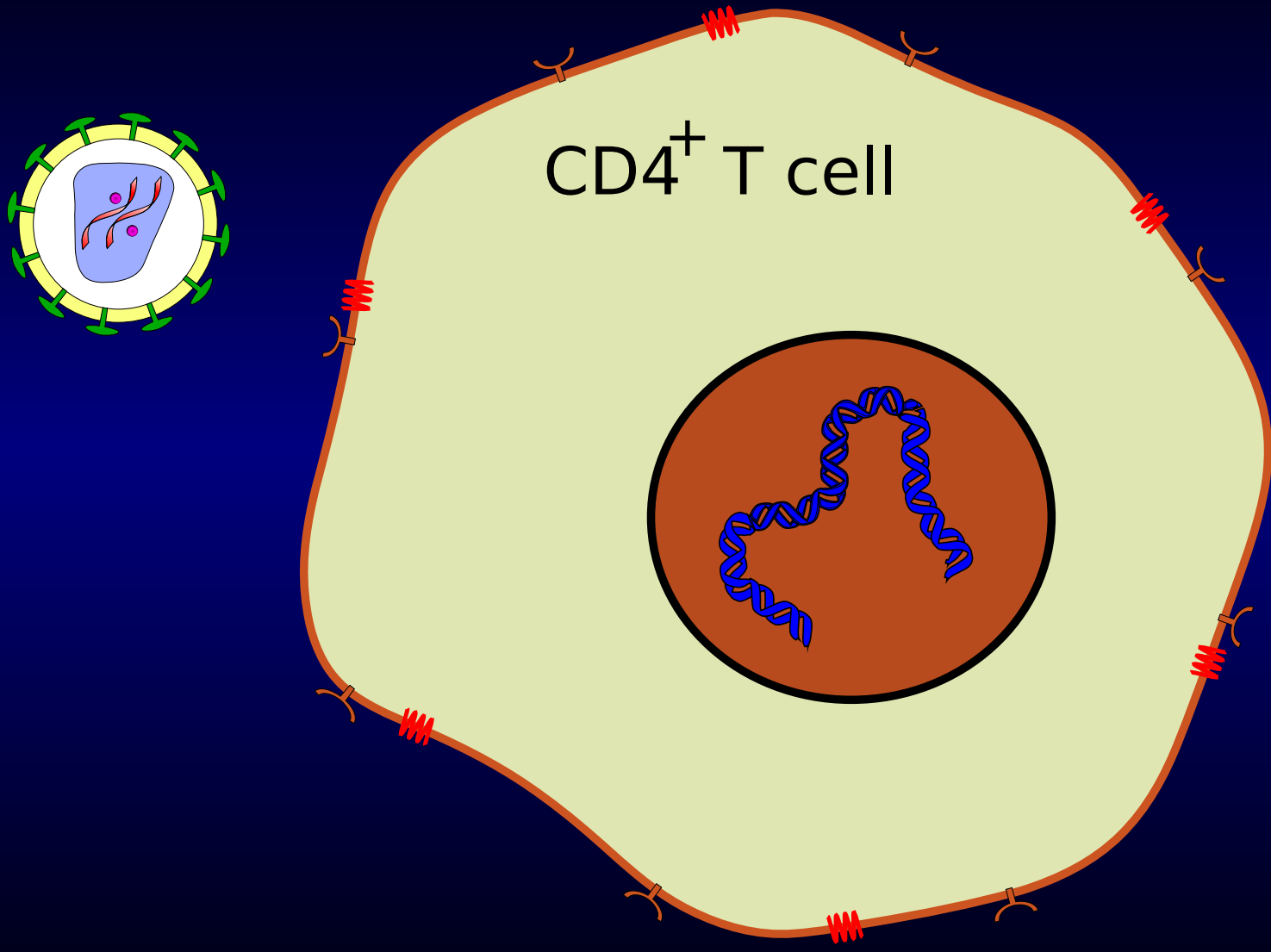


Microscopic View of the Infection Process



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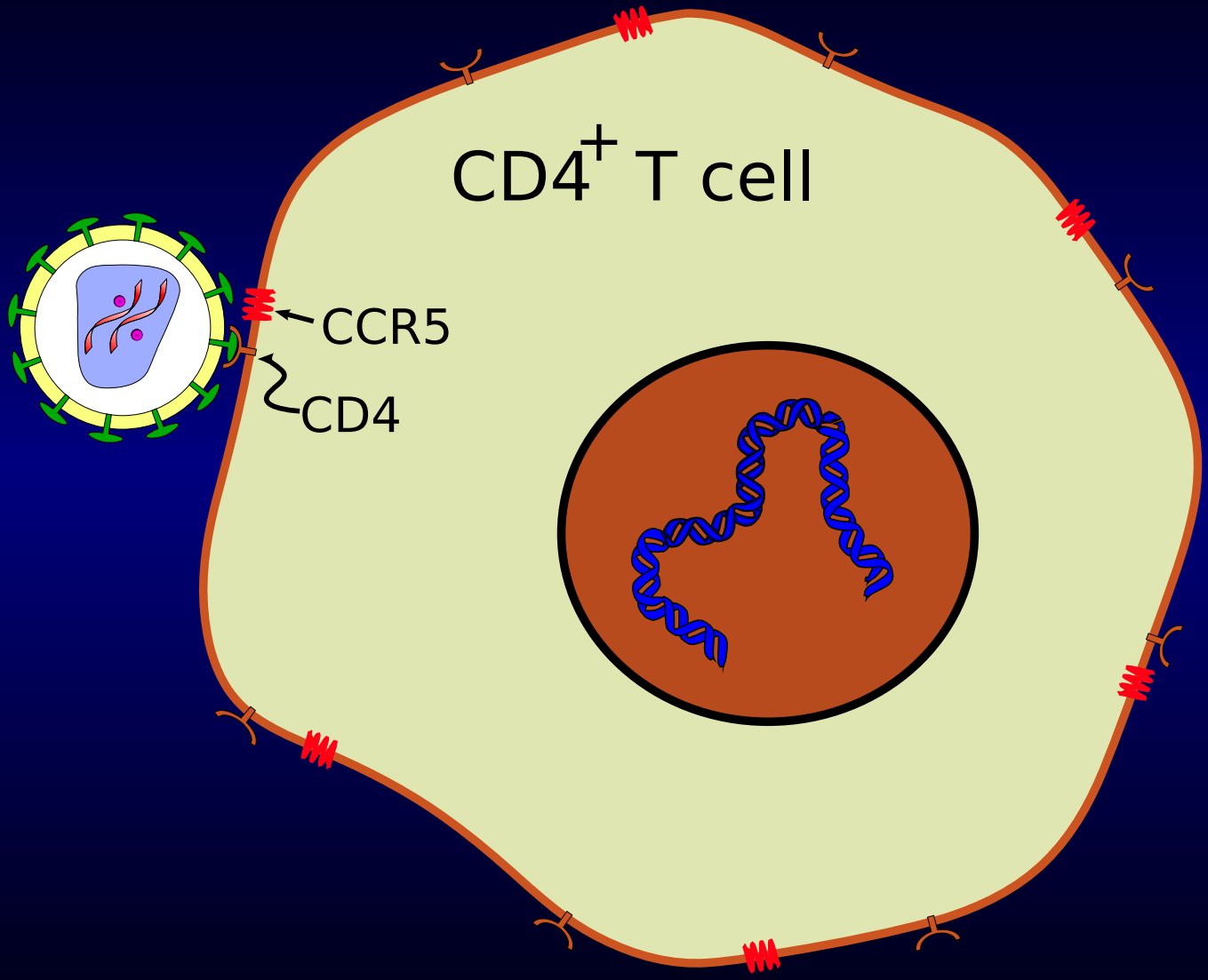

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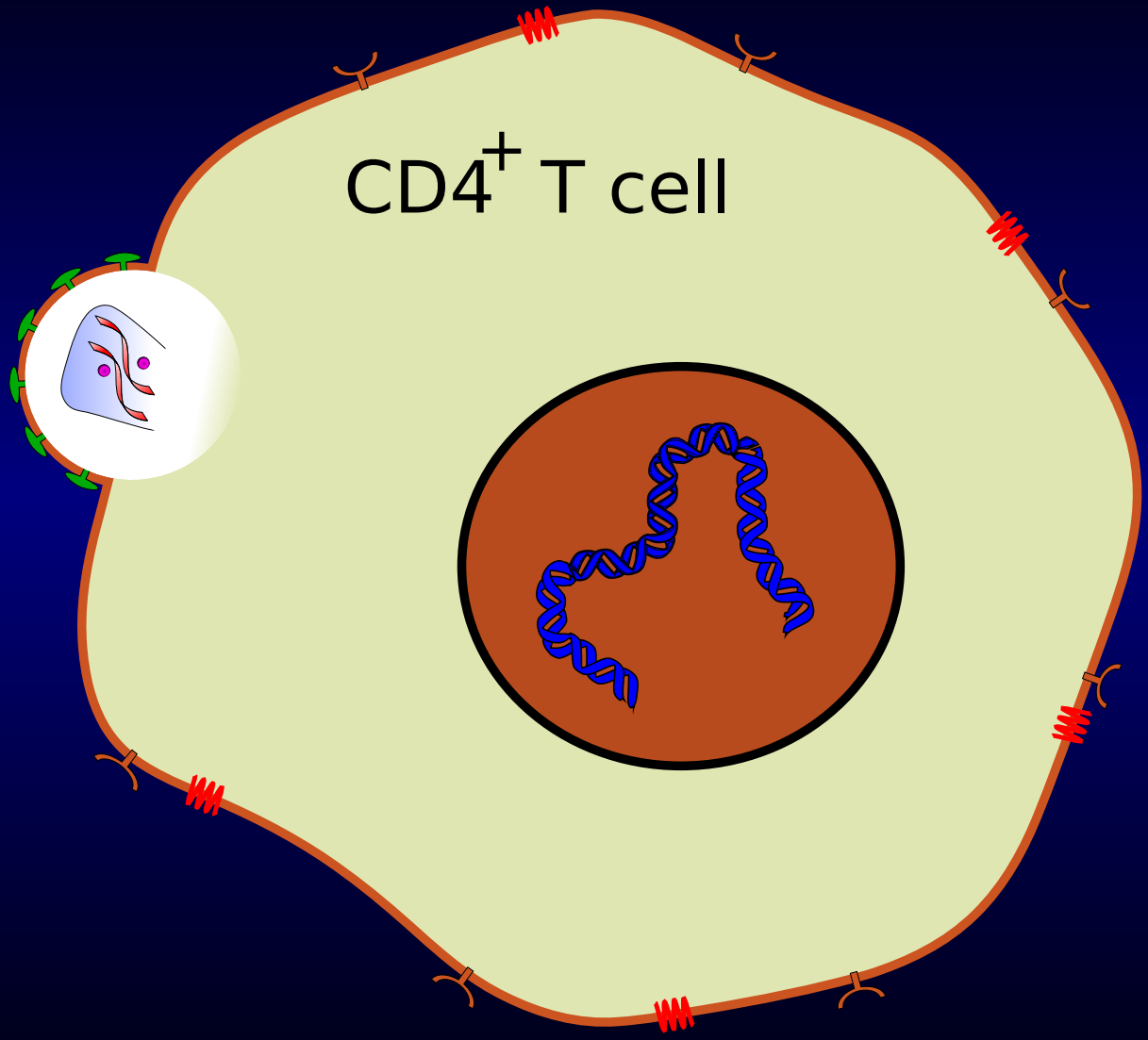

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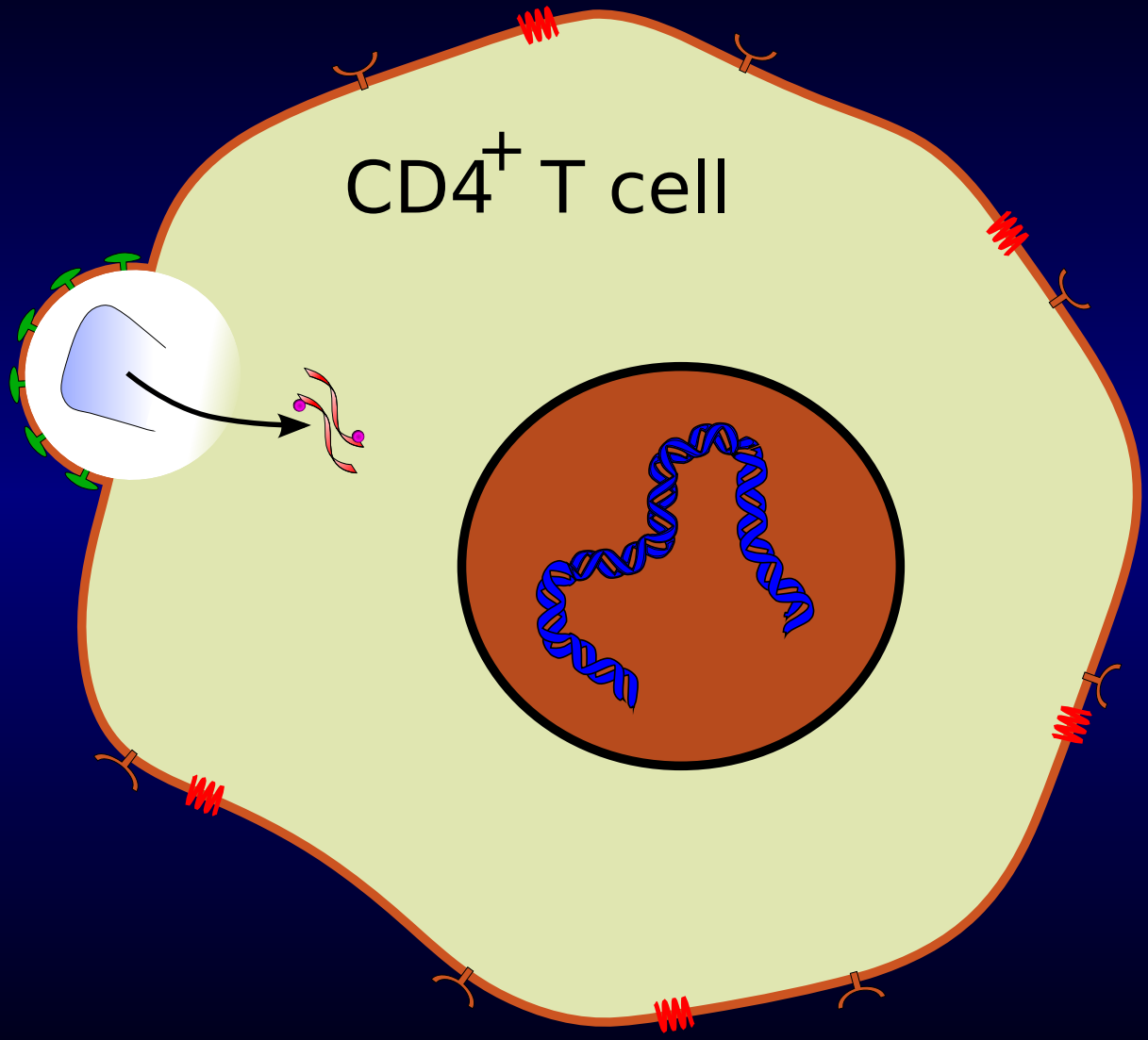

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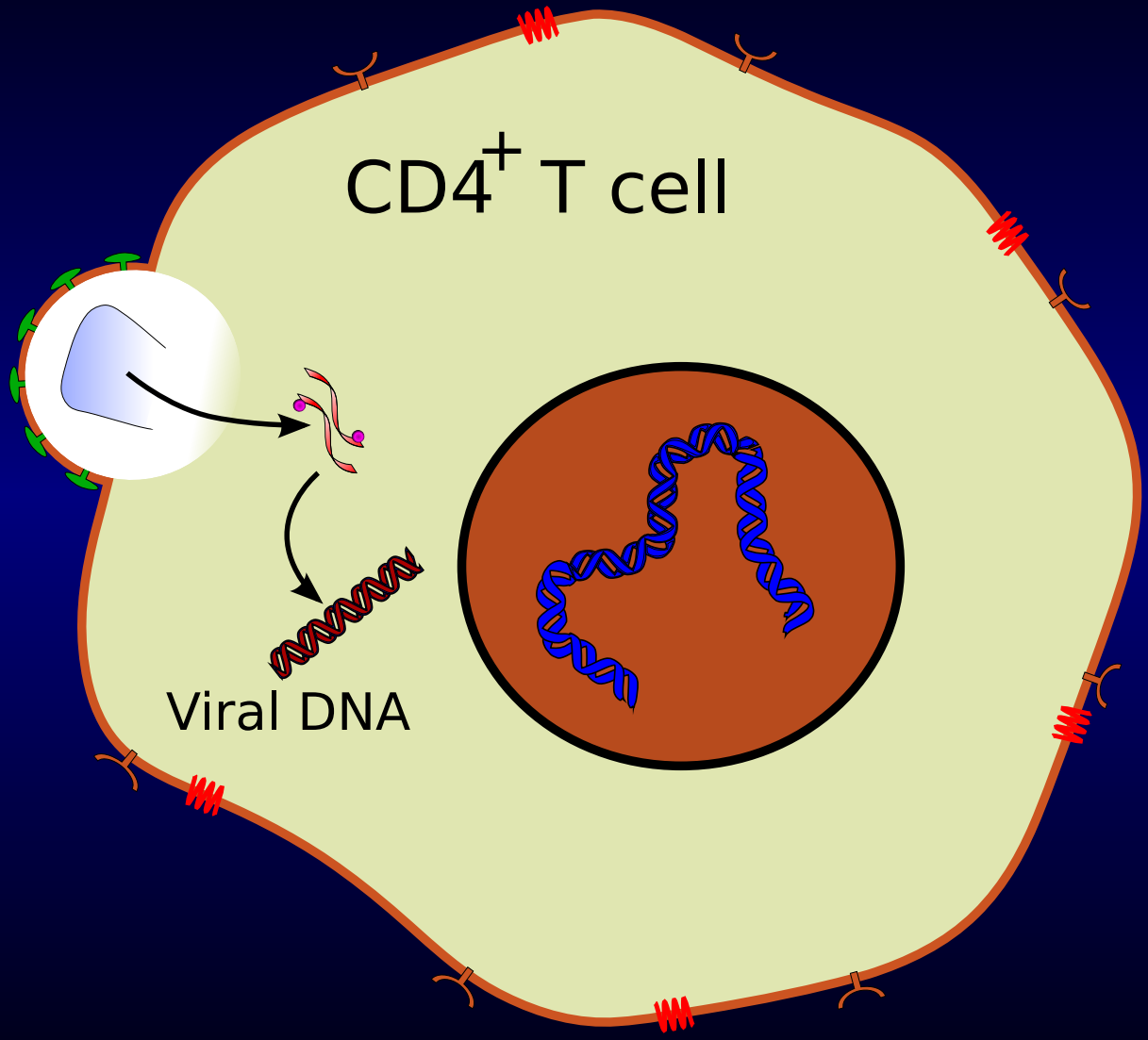

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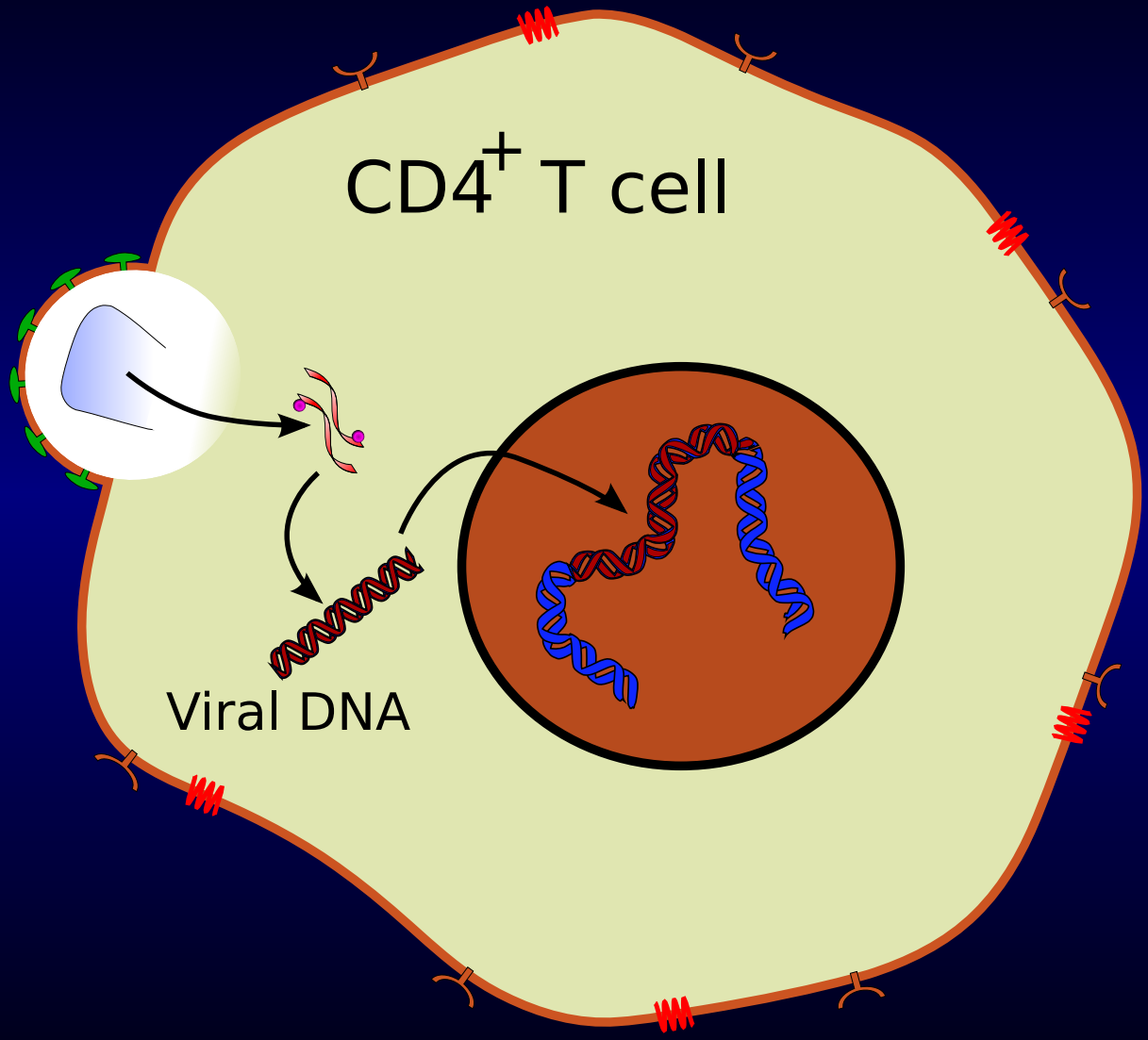

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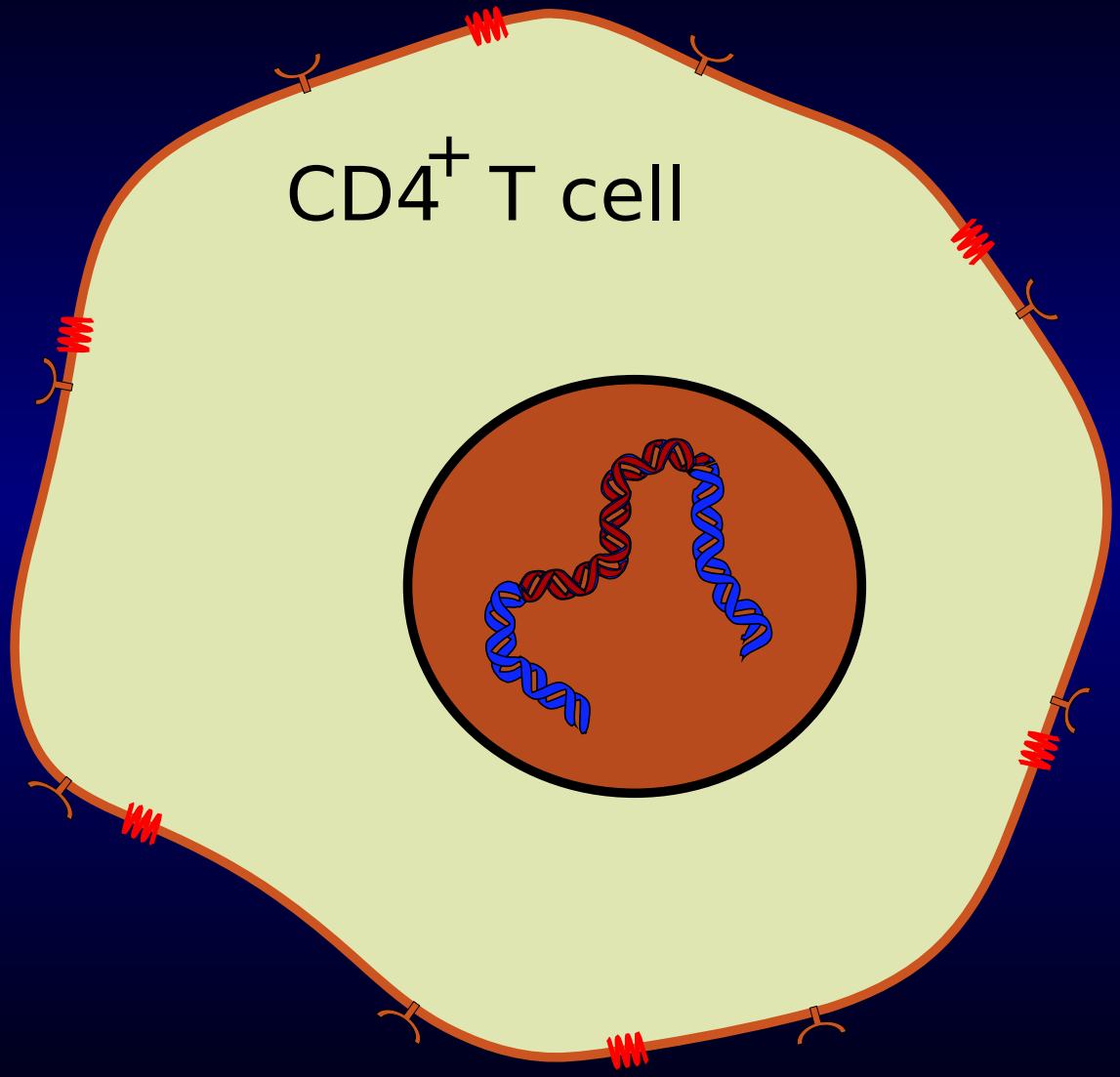

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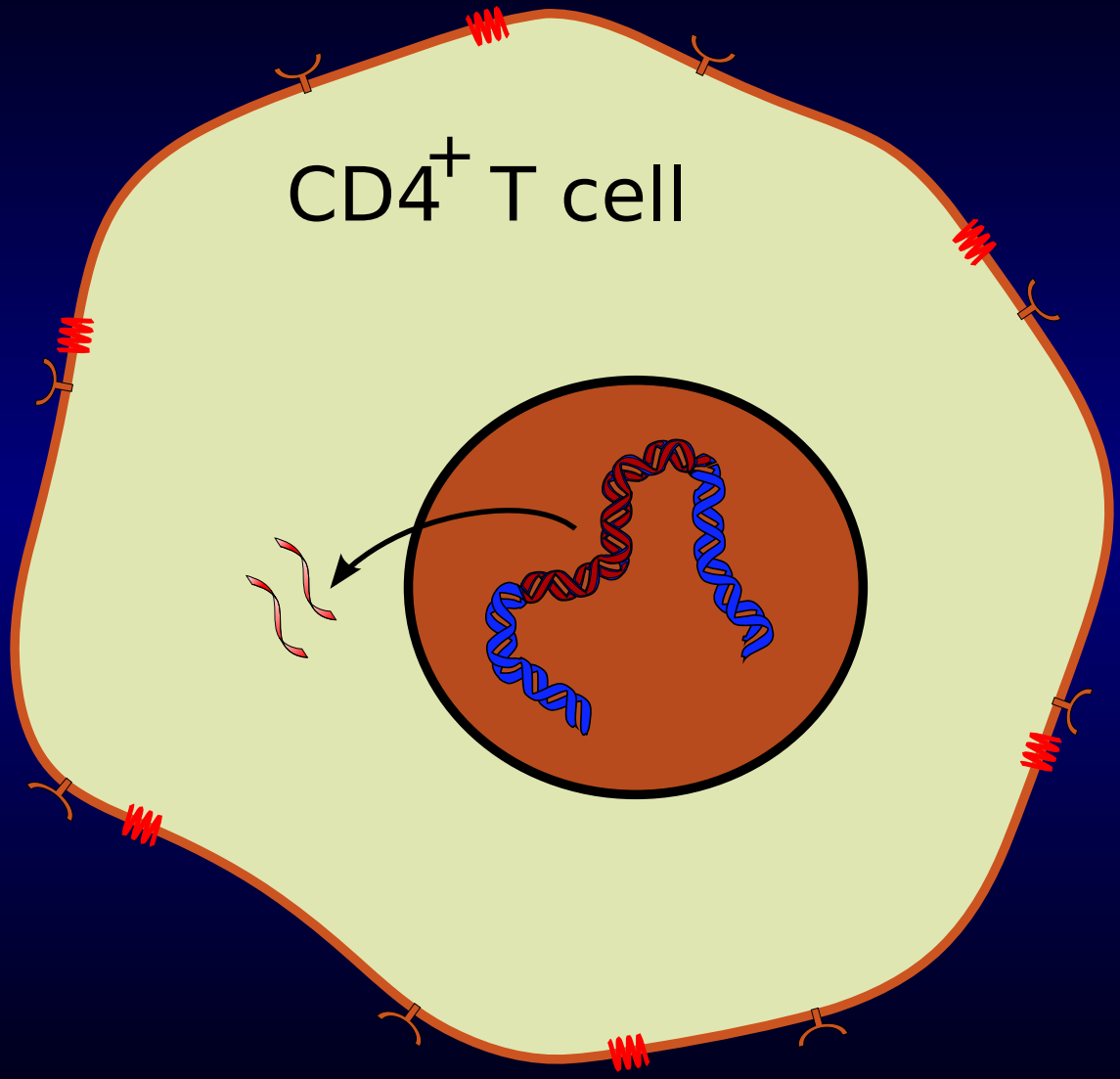

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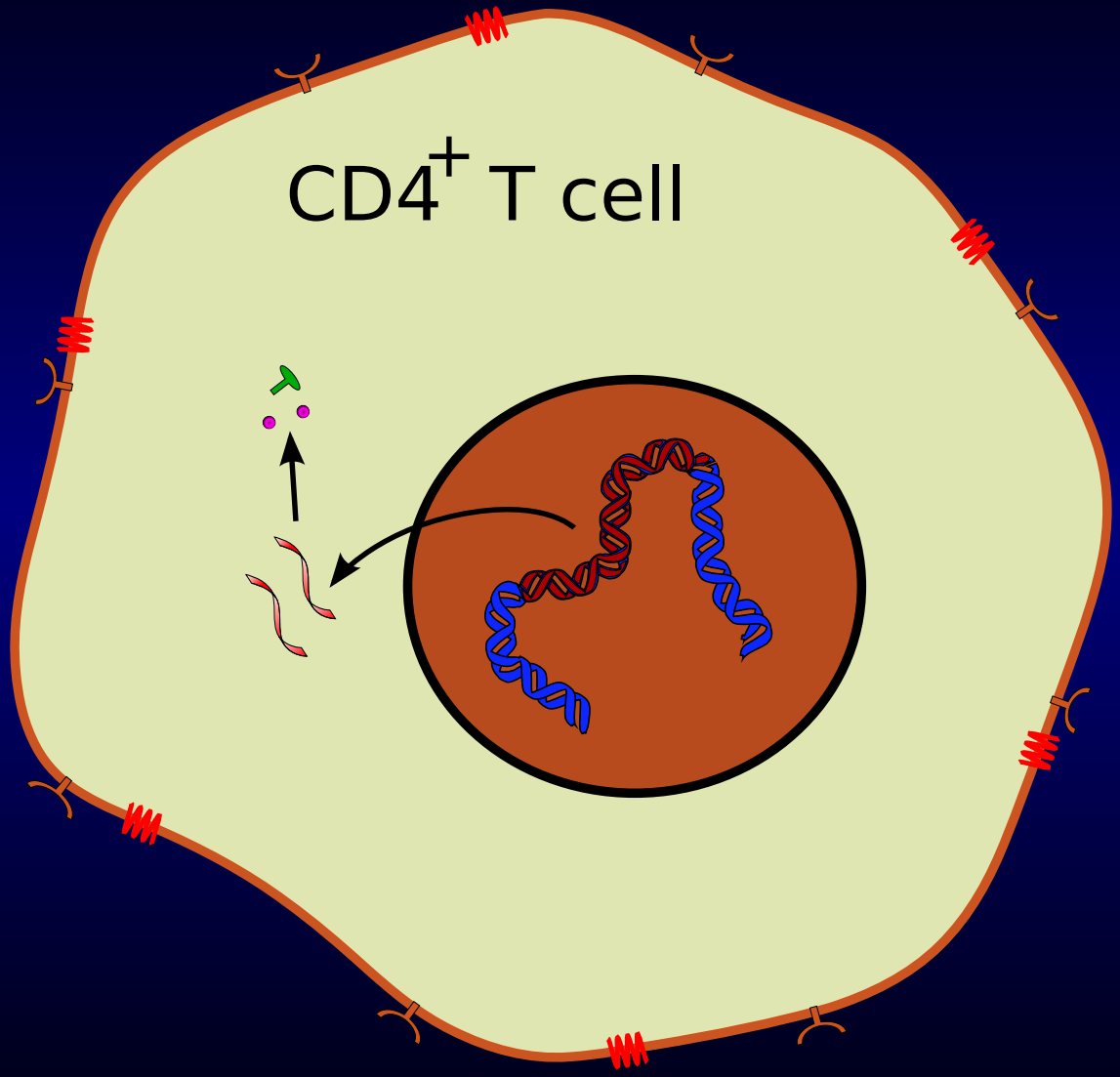

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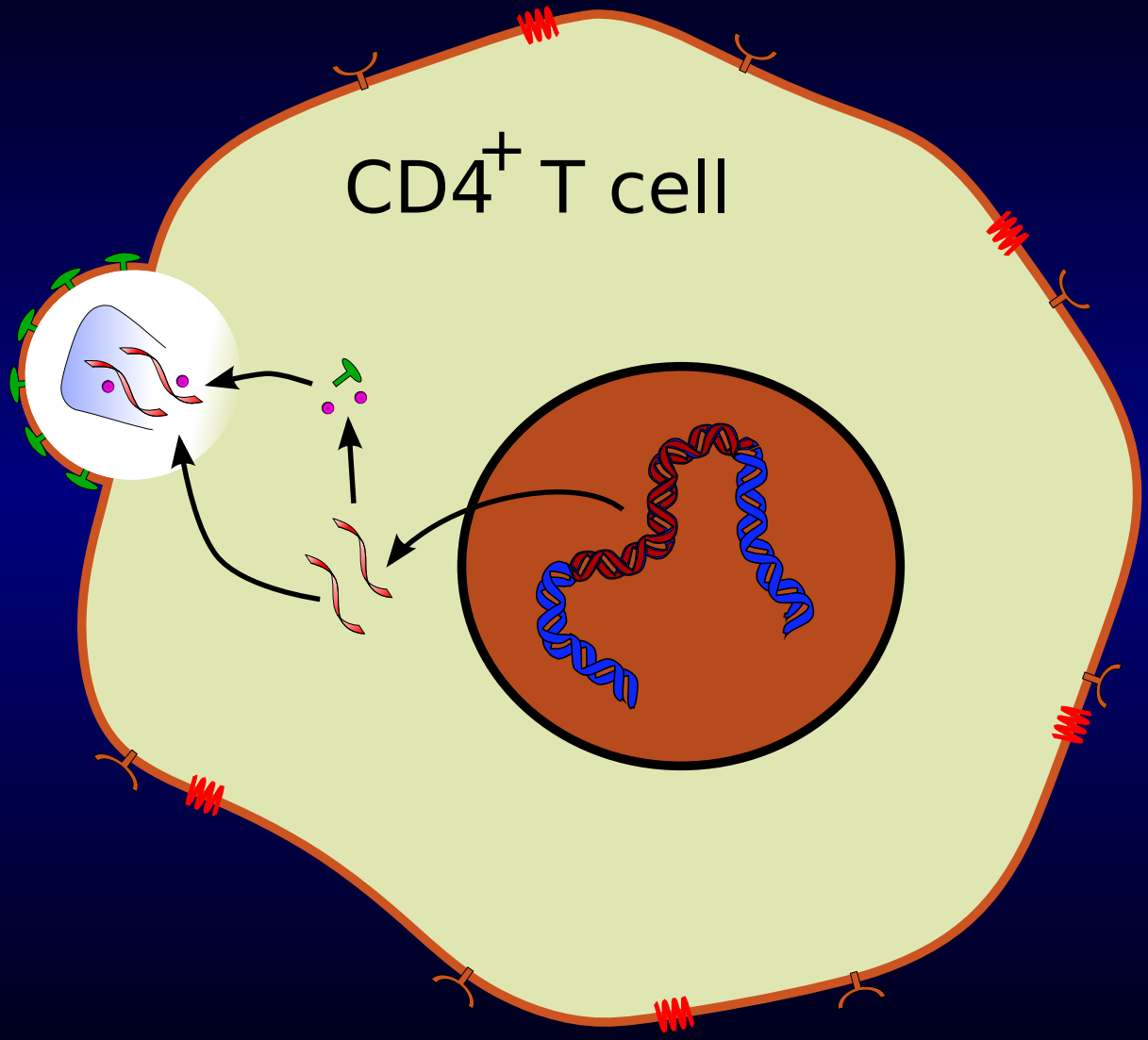

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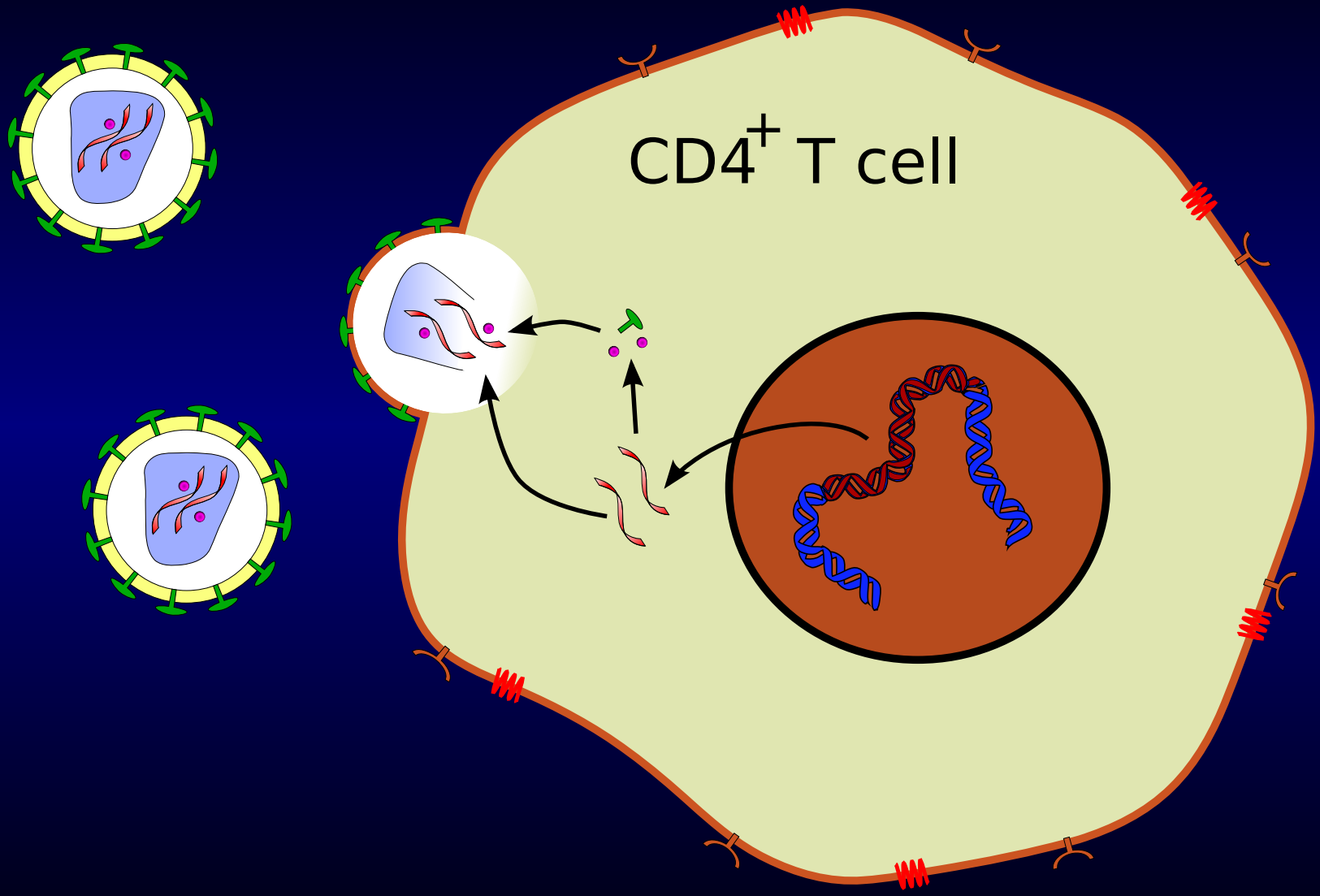
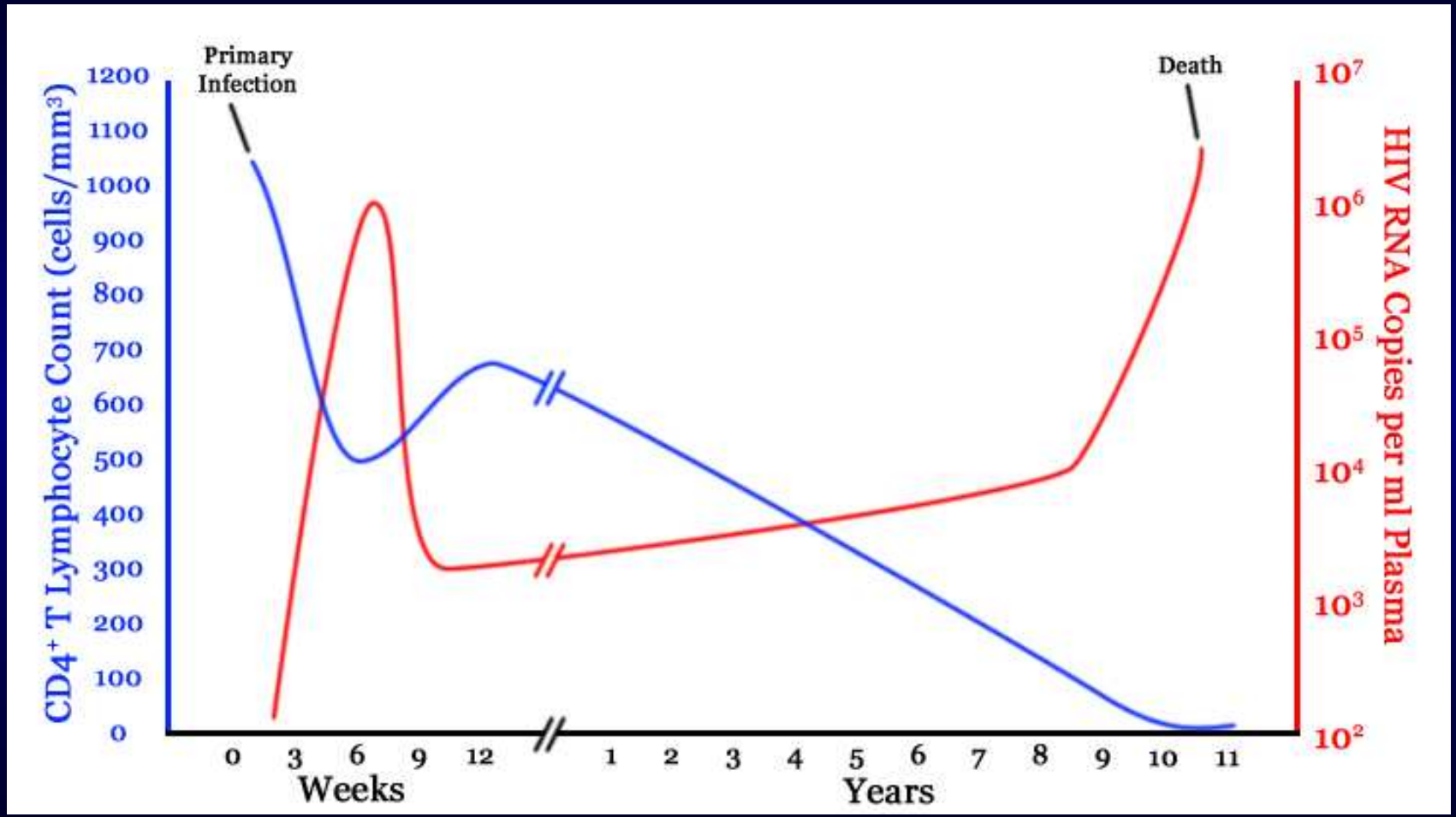


Qualitative Features of Infection Dynamics



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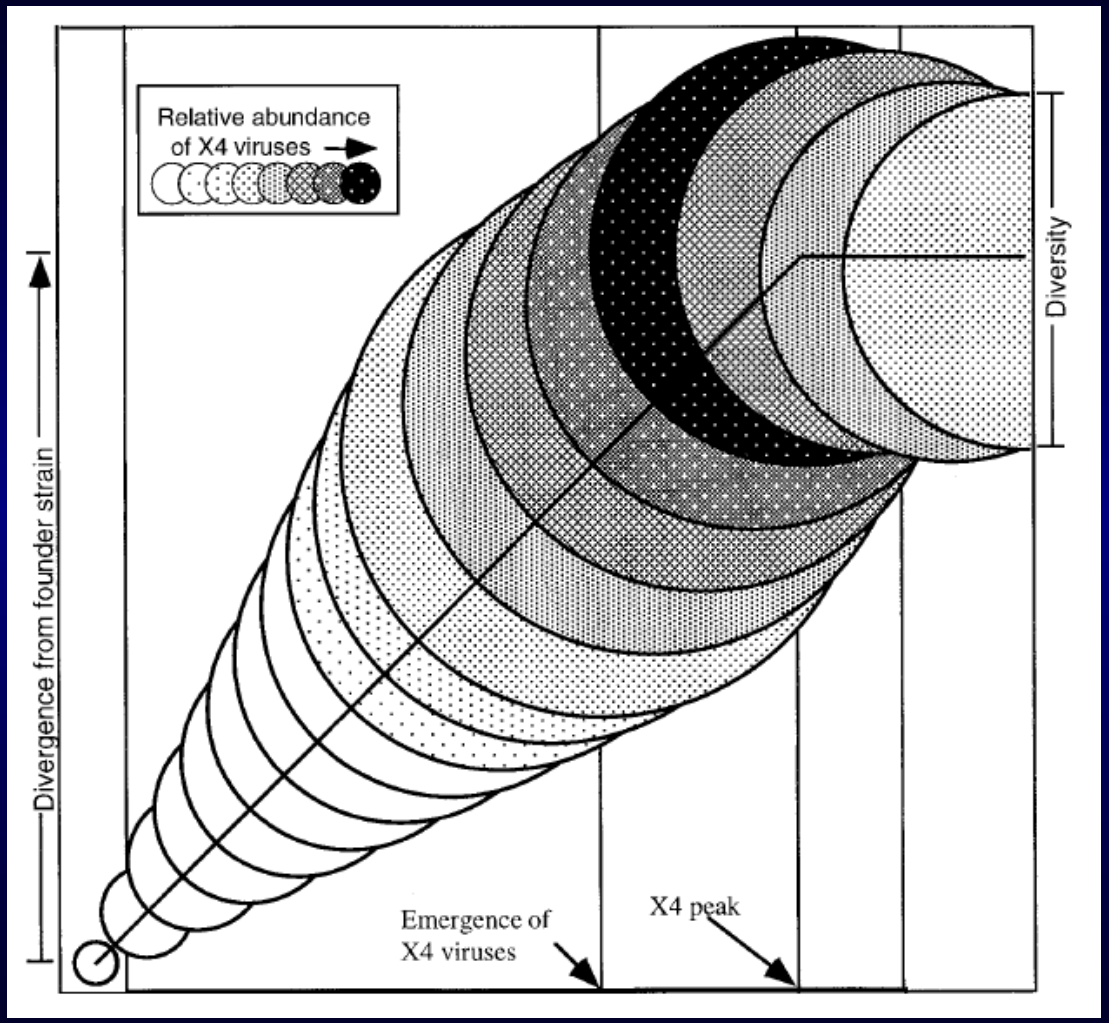

Shankarappa et al., J. Virol. (1999)

Why Create Mathematical Models?

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The implementation of qualitative hypothesies in terms of precise mathematical models is *required* in order to quantitatively compare predictions with experimental outcomes.

Simple Deterministic Models

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- Assumes uniform (well mixed) system and no mutation.

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Deterministic models cannot capture many important features of within-host viral dynamics:

- Fluctuations in set-point of viral load,
- Demographic viral extinction events,
- Fluctuations in small populations – important when considering mutating viral quasi-species.

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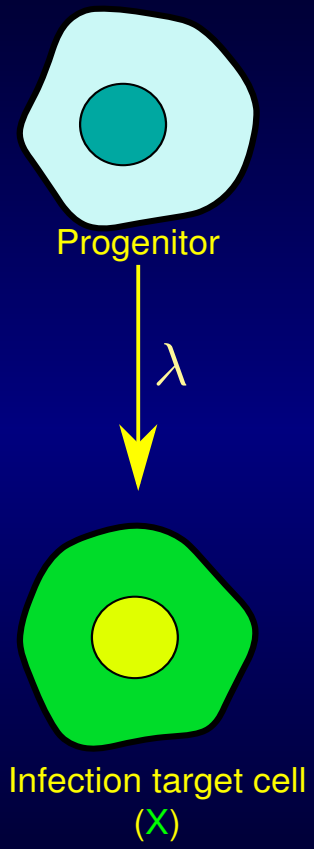

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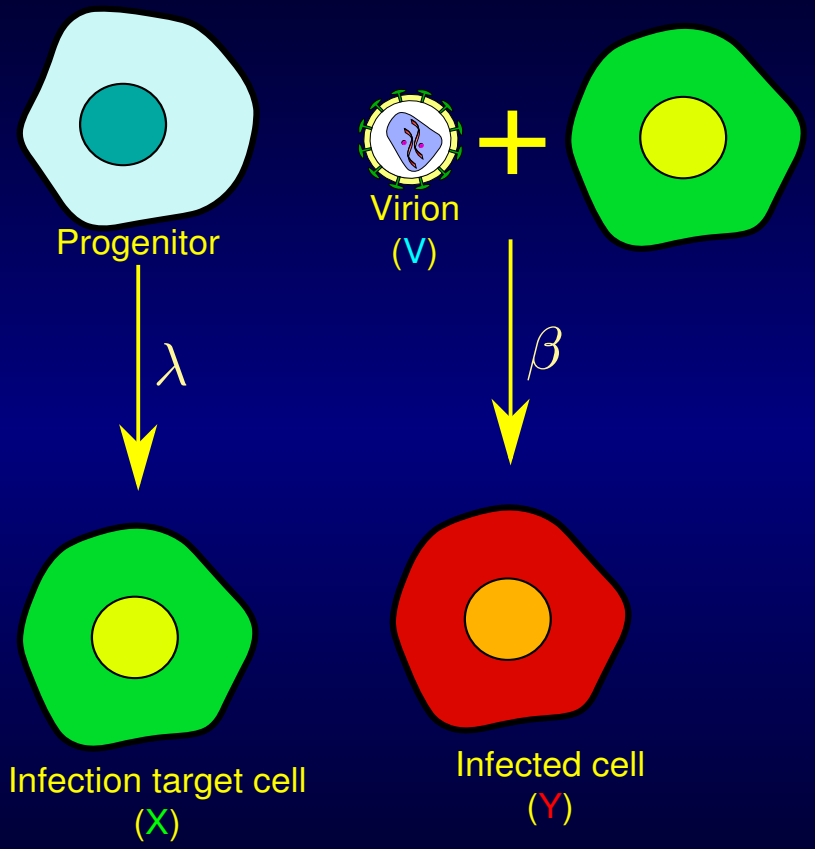

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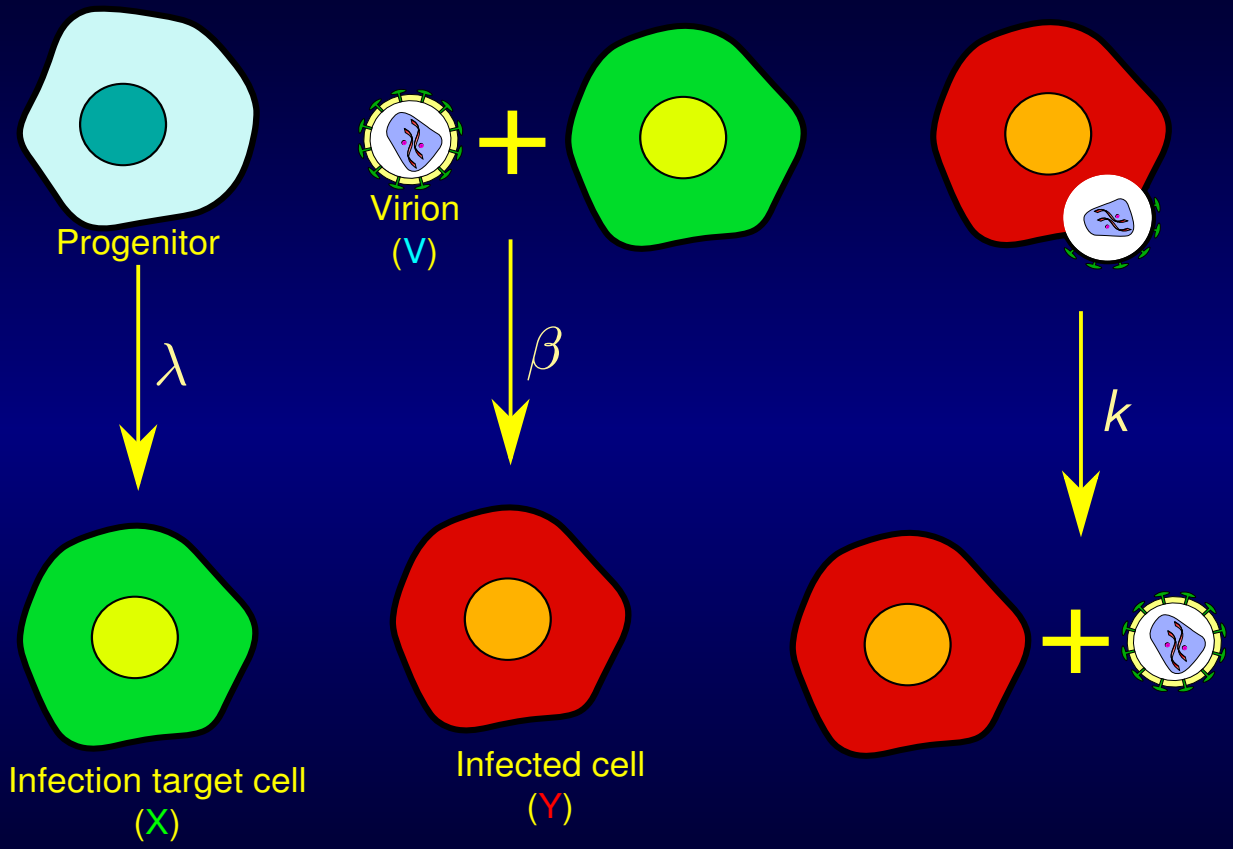

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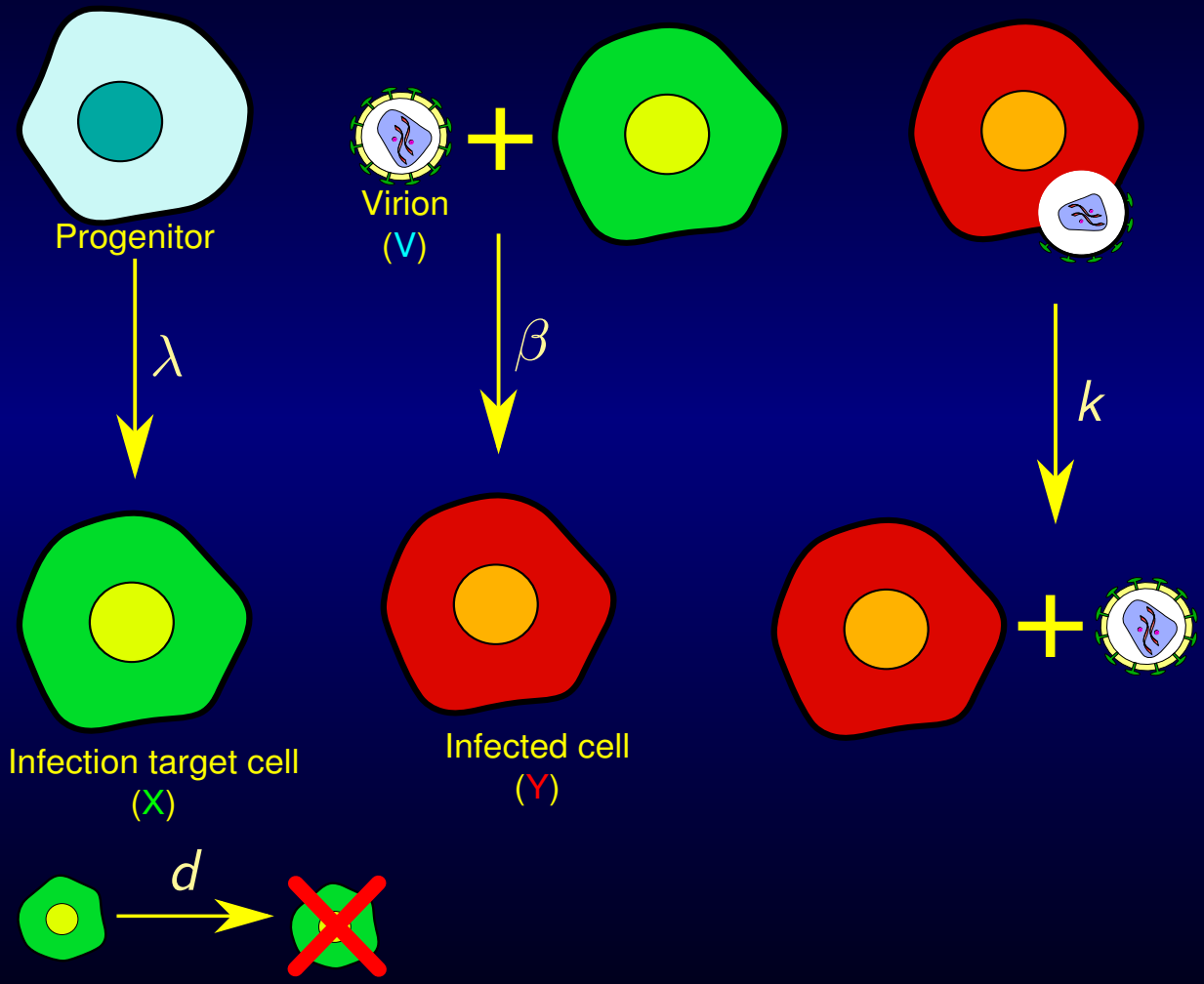

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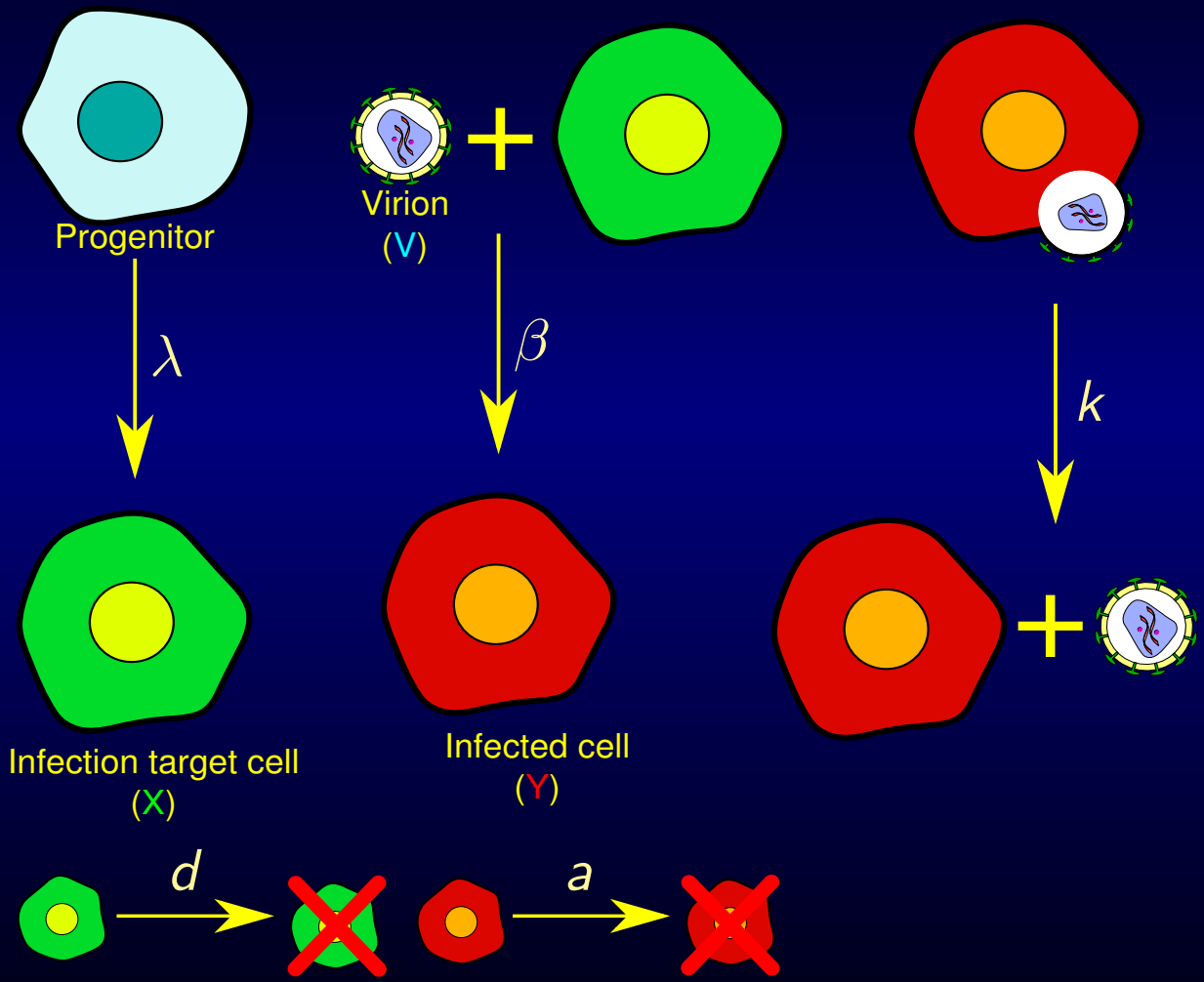

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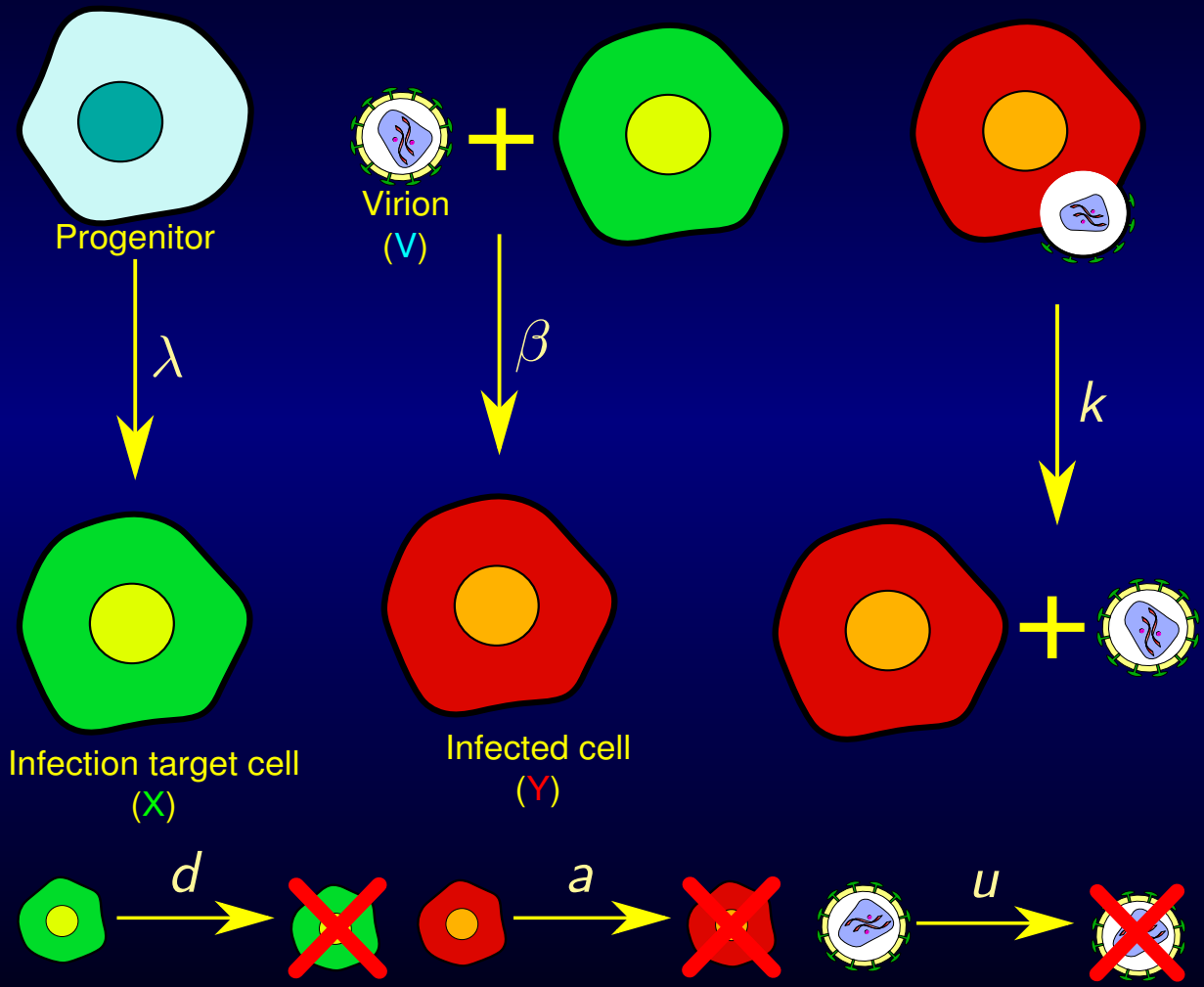

Stochastic Model

Chemical Master Equation

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\begin{aligned}
\dot{P}(\vec{n}) \quad = \quad & \lambda \left[P(\vec{n}_{-x}) - P(\vec{n}) \right] \\
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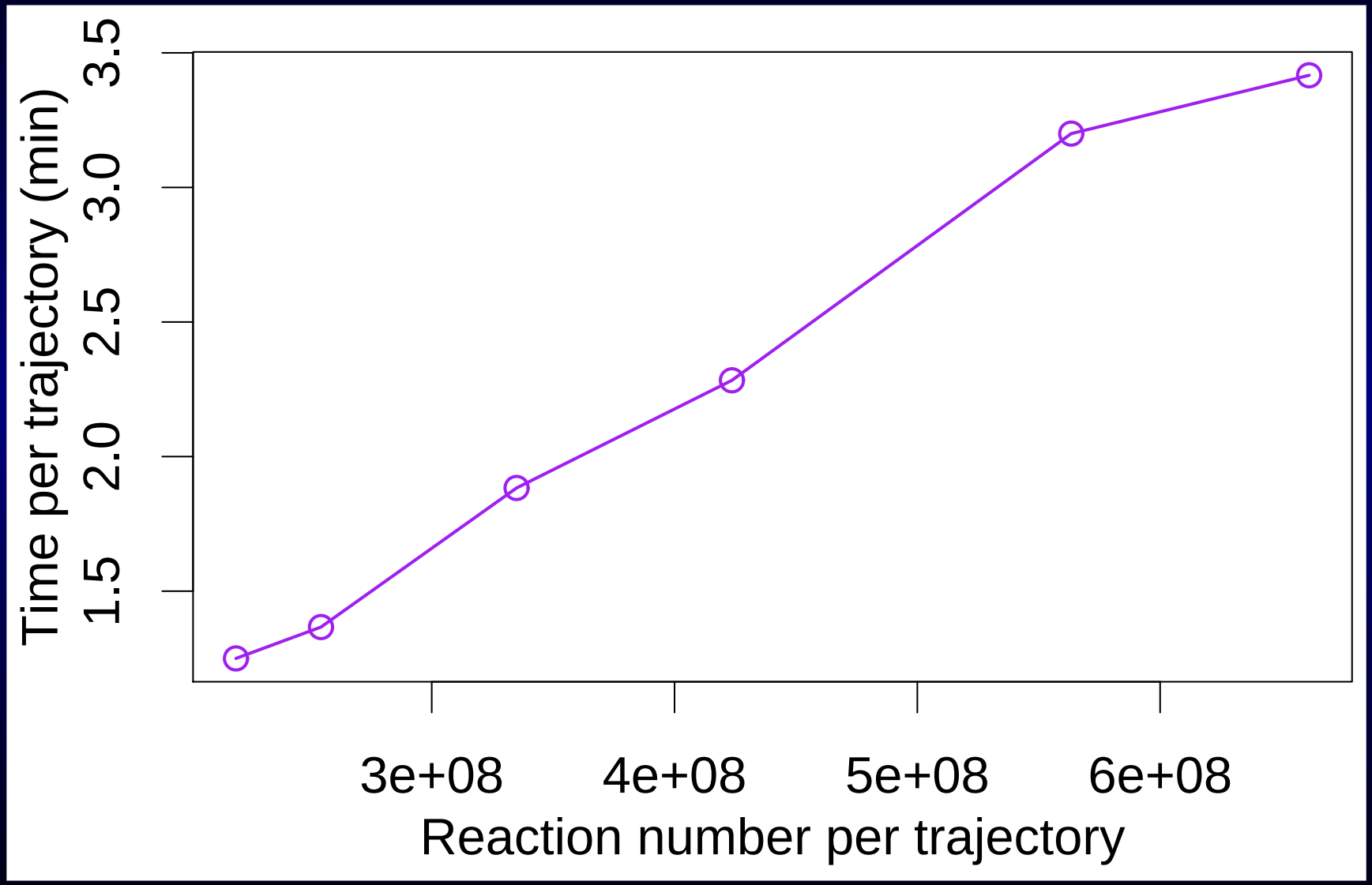
So what's the problem?

Stochastic simulations are HARD.

Standard Monte Carlo approaches do not scale



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The Poisson Representation

$$P(\vec{n}, t) = \int \mathrm{d}^{2M} f(\vec{\alpha}, t) \Lambda(\vec{\alpha}, \vec{n})$$

where

$$\Lambda(\vec{\alpha}, \vec{n}) = \prod_{k=1}^{M} e^{-\alpha_k} \frac{\alpha^{n_k}}{n_k!}$$

The Poisson Representation

- By expanding both sides of a master equation and making use of the following identities,

$$\begin{aligned}(n_k+1)\Lambda(\vec{\alpha},\vec{n}_{+k}) &= \alpha_k\Lambda(\vec{\alpha},\vec{n}) \\ \Lambda(\vec{\alpha},\vec{n}_{-k}) &= (1+\frac{\partial}{\partial\alpha_k})\Lambda(\vec{\alpha},\vec{n}),\end{aligned}$$

one obtains the following integro-differential equation:

$$\int \mathrm{d}^{2M}\vec{\alpha}\dot{f}(\vec{\alpha},t)\Lambda(\vec{\alpha},\vec{n}) = \int \mathrm{d}^{2M}\vec{\alpha}f(\vec{\alpha},t)\mathcal{L}'\Lambda(\vec{\alpha},\vec{n})$$

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For binary reactions, this has the form of a Fokker-Planck equation describing the evolution of the probability distribution of a continuous diffusion process.

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- The evolution of diffusion processes can be exactly determined through the numerical integration of Stochastic Differential Equations (SDEs).

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- The evolution of diffusion processes can be exactly determined through the numerical integration of Stochastic Differential Equations (SDEs).
- The computational complexity of this process has *no clear dependence* on number of particles/cells/virions being simulated.

Fokker-Planck Equation for Stochastic Virus Model

$$
\begin{aligned}
\dot{f}(x, y, v, t) \quad = \quad & \Big[- \partial_x (\lambda - dx - \beta x v) \\
& - \partial_y (\beta x v - a y) \\
& - \partial_v (k y - u v - \beta x v) \\
& - \partial_x \partial_v \beta x v + \partial_y \partial_v k y \Big] f(x, y, v, t)
\end{aligned}
$$

Stochastic DEs for Virus Model

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \beta xv + \sqrt{\frac{\beta}{2}} x(i\zeta_1(t) - \zeta_2(t)) \\
\dot{y} &= \beta xv - ay + \sqrt{\frac{ky}{2}} (\zeta_3(t) + i\zeta_4(t)) \\
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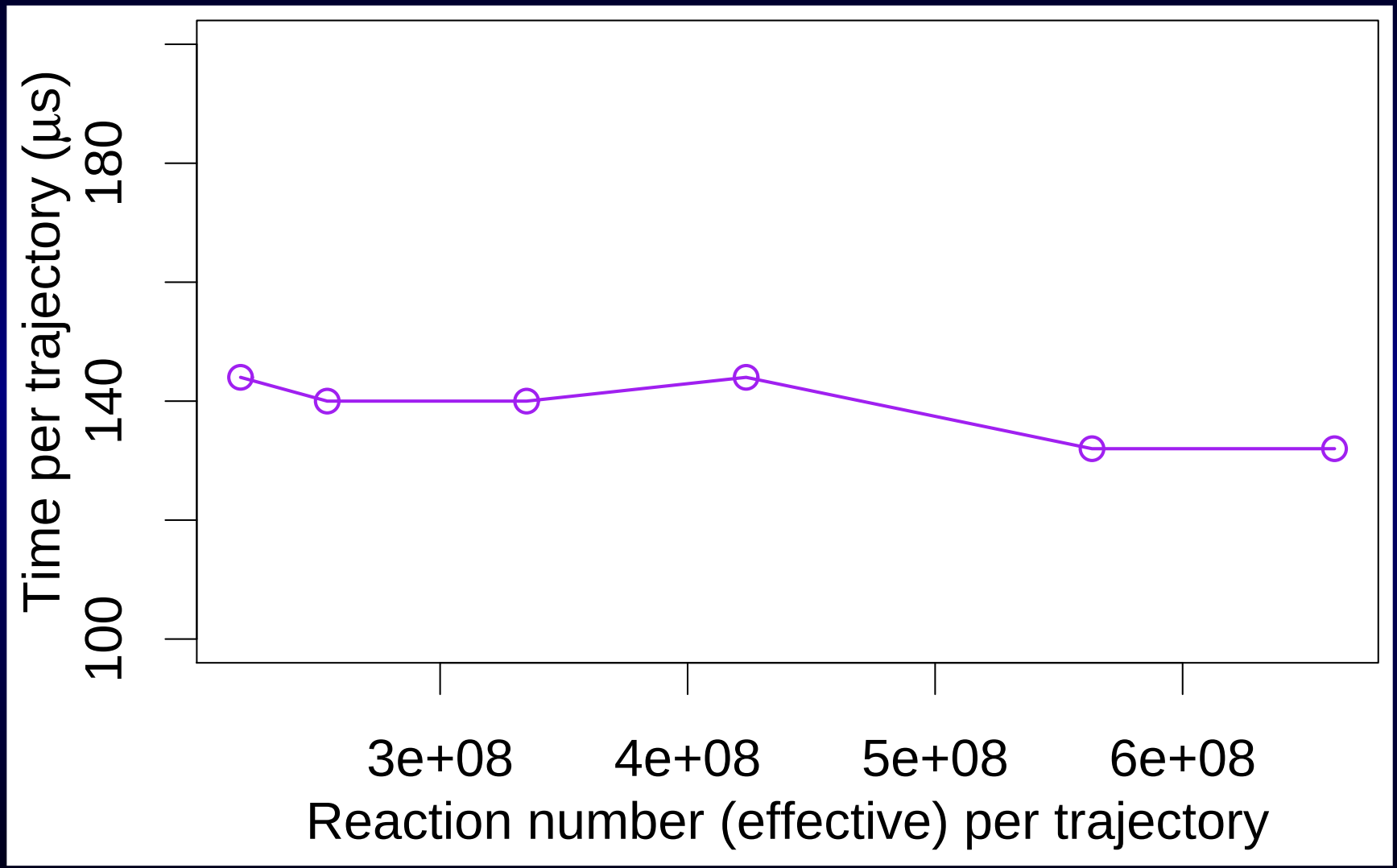
$$\langle x \rangle_s = \langle n_x \rangle \qquad \langle x^2 \rangle_s = \langle n_x (n_x - 1) \rangle$$

Poisson Representation approach *scales*



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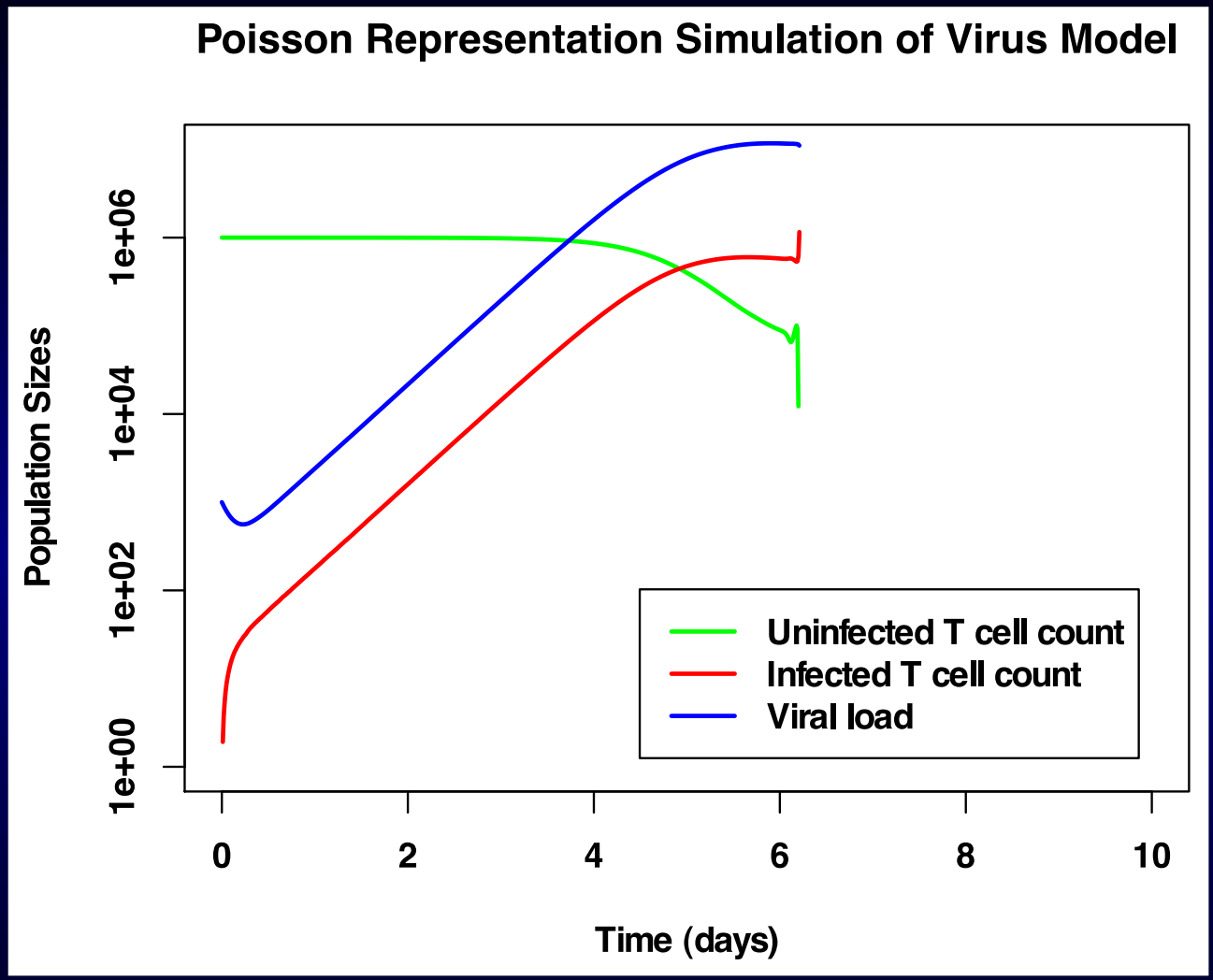
Poisson Representation Simulation of Virus Model
Population Sizes
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Time (days)
Uninfected T cell count
Infected T cell count
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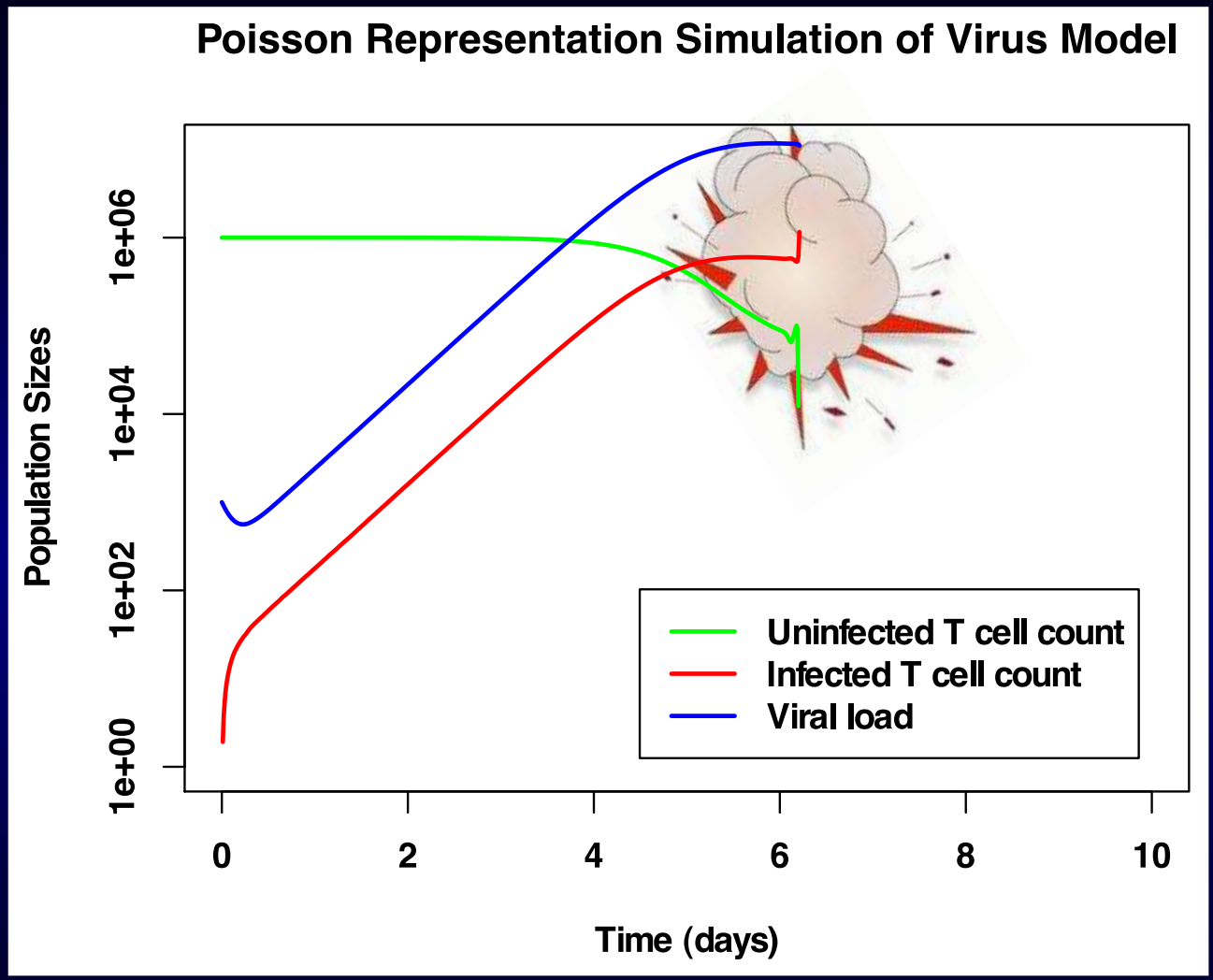
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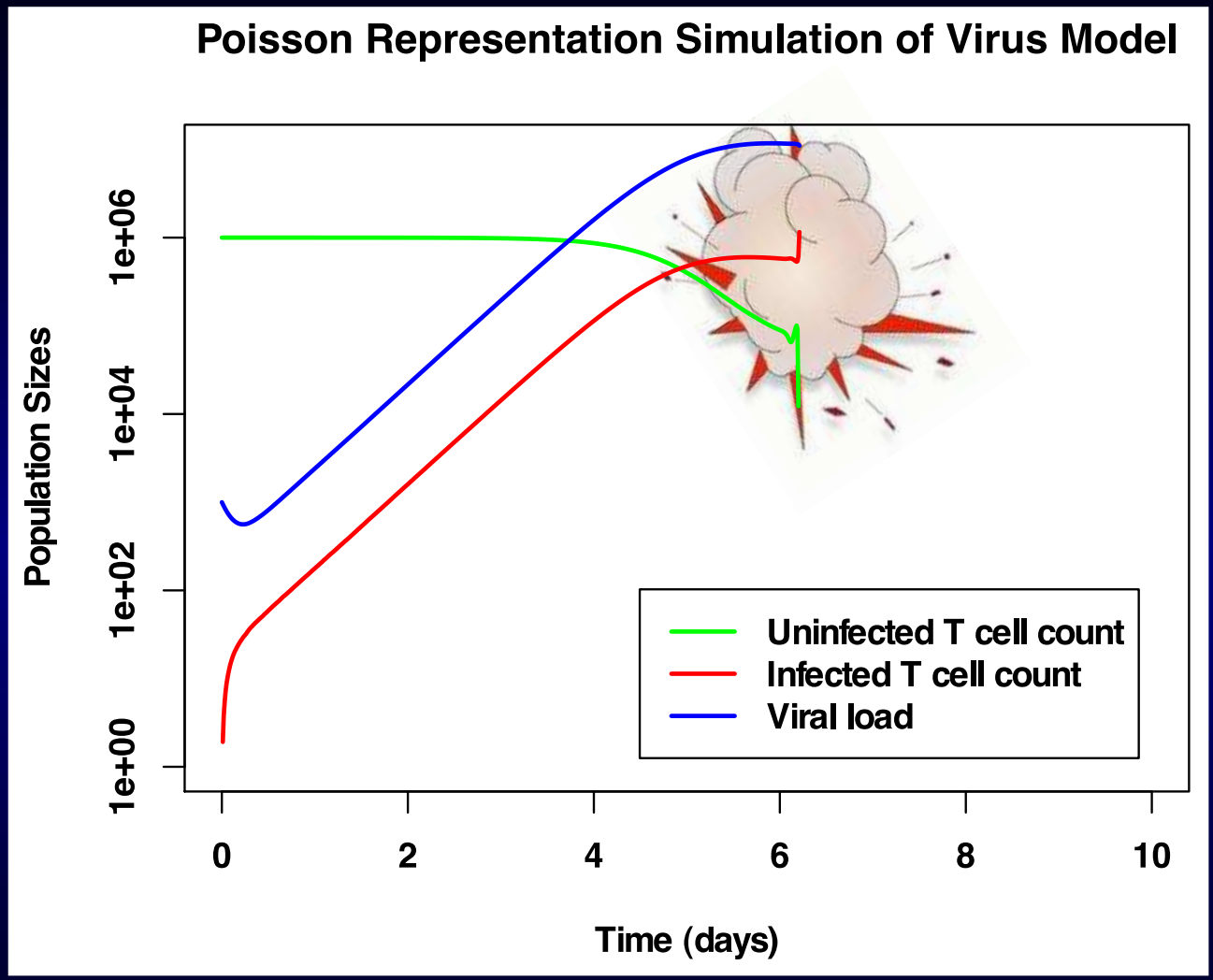

What's happened?

There's a Devil in the Details

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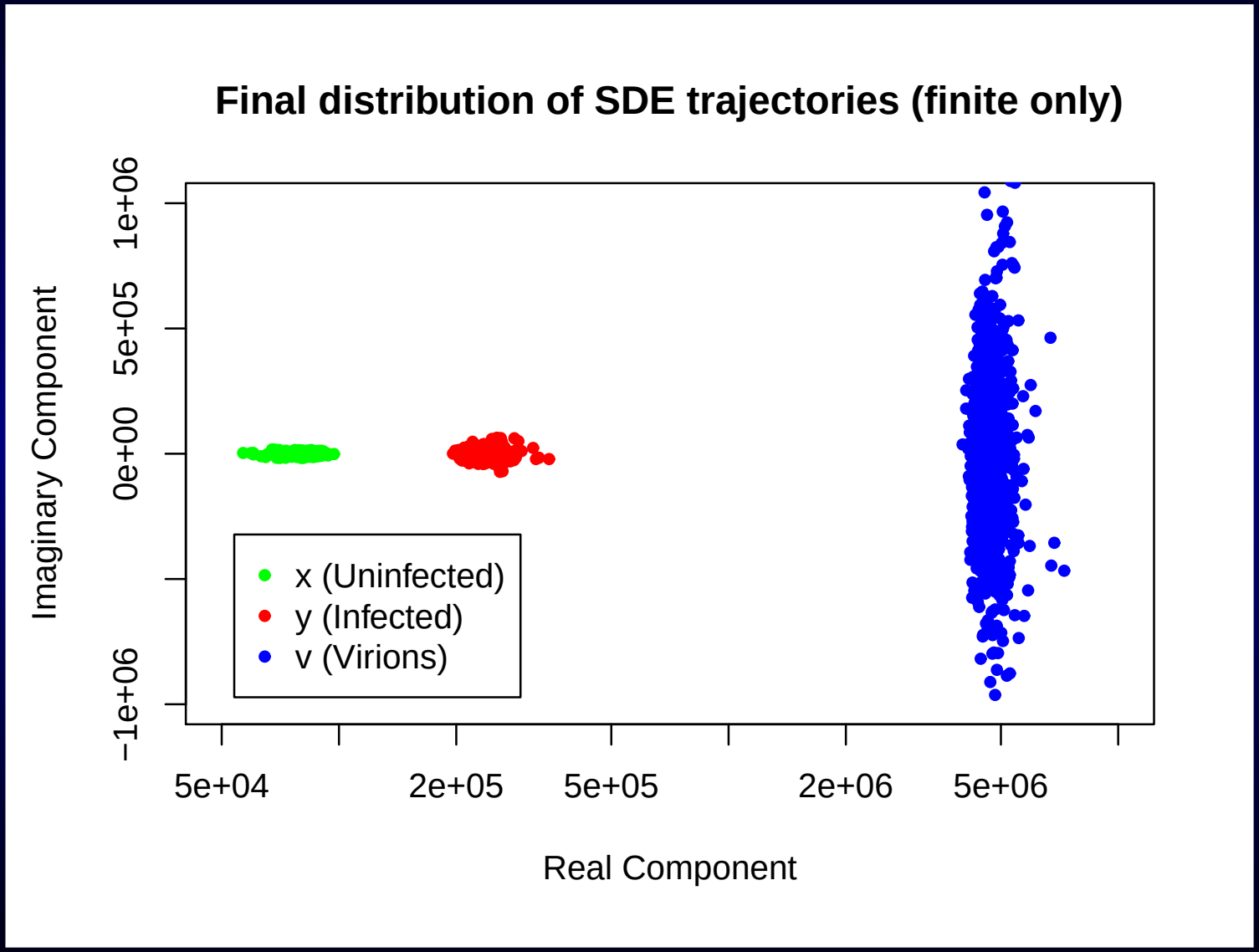
- systematic errors in results.

How can we remove these boundary terms?

Possibility 1: Trajectory Truncation



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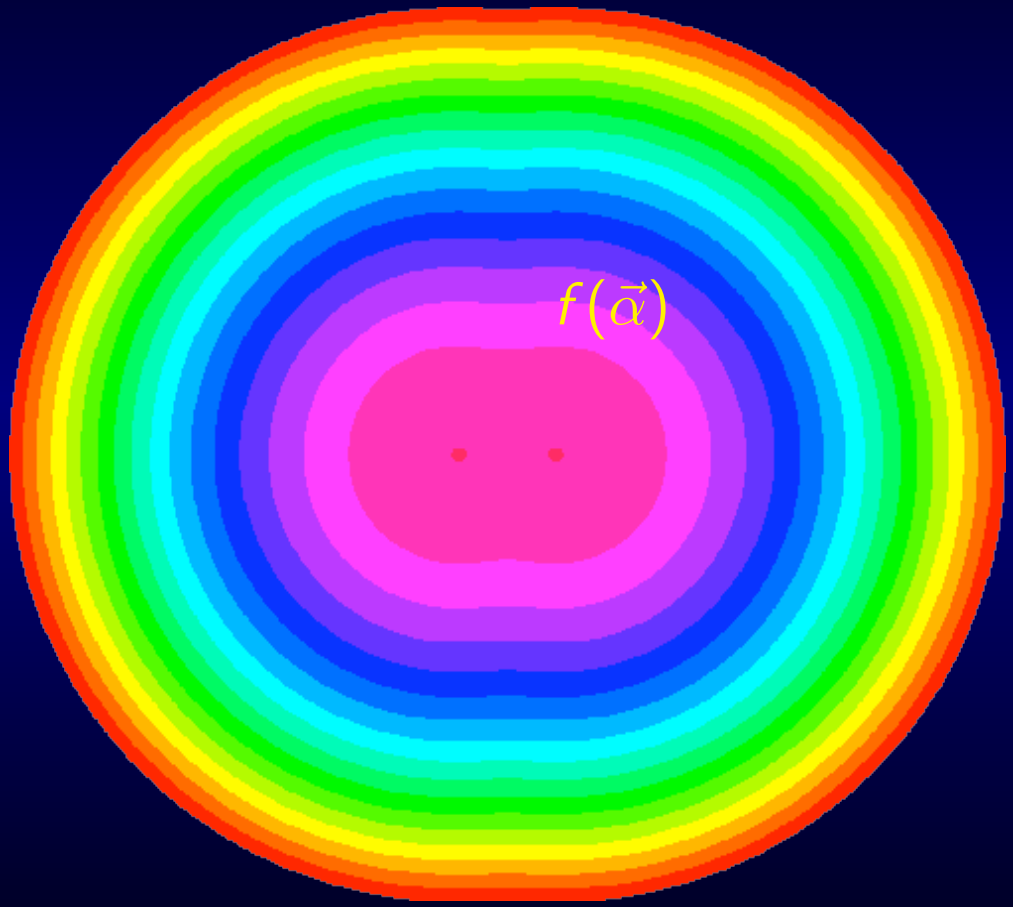

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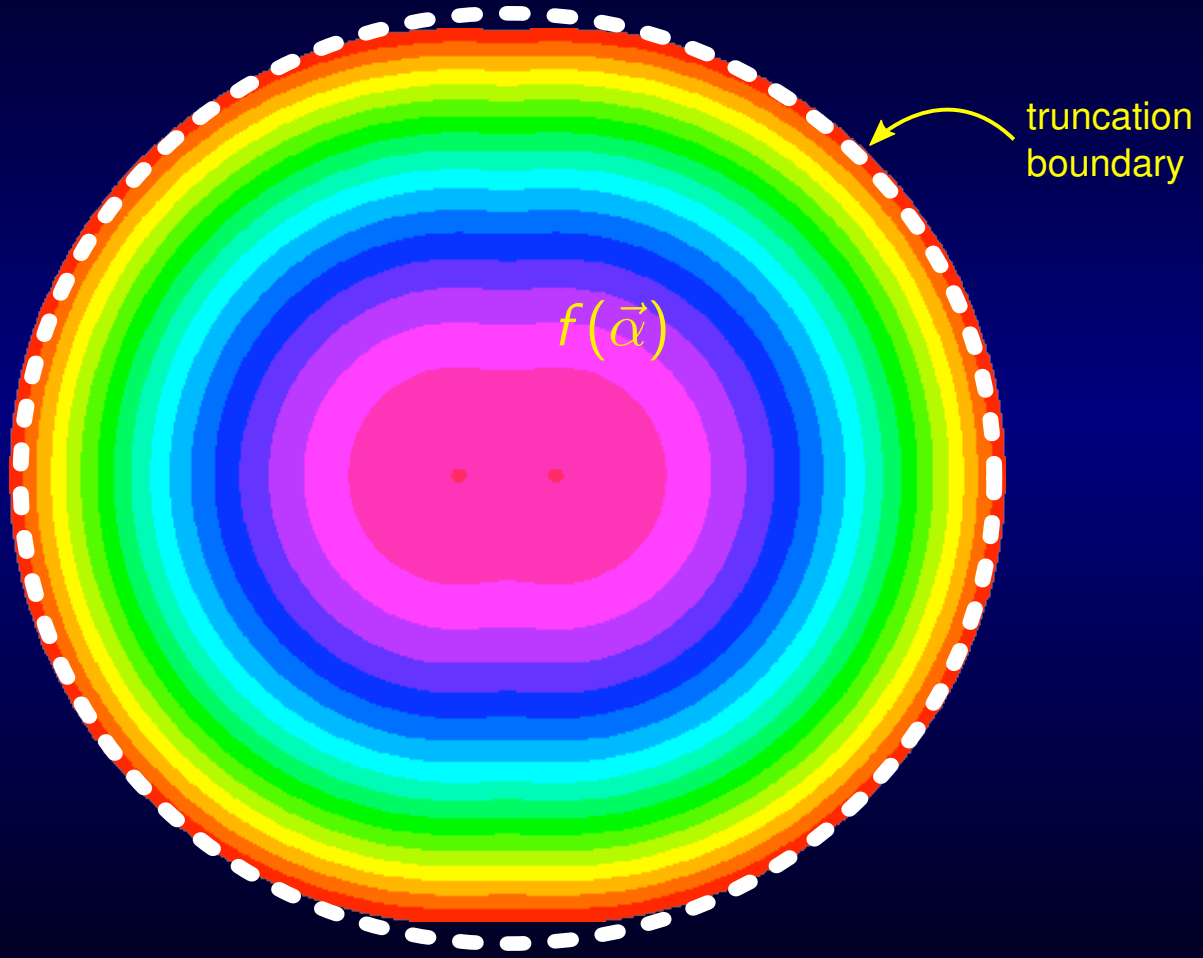

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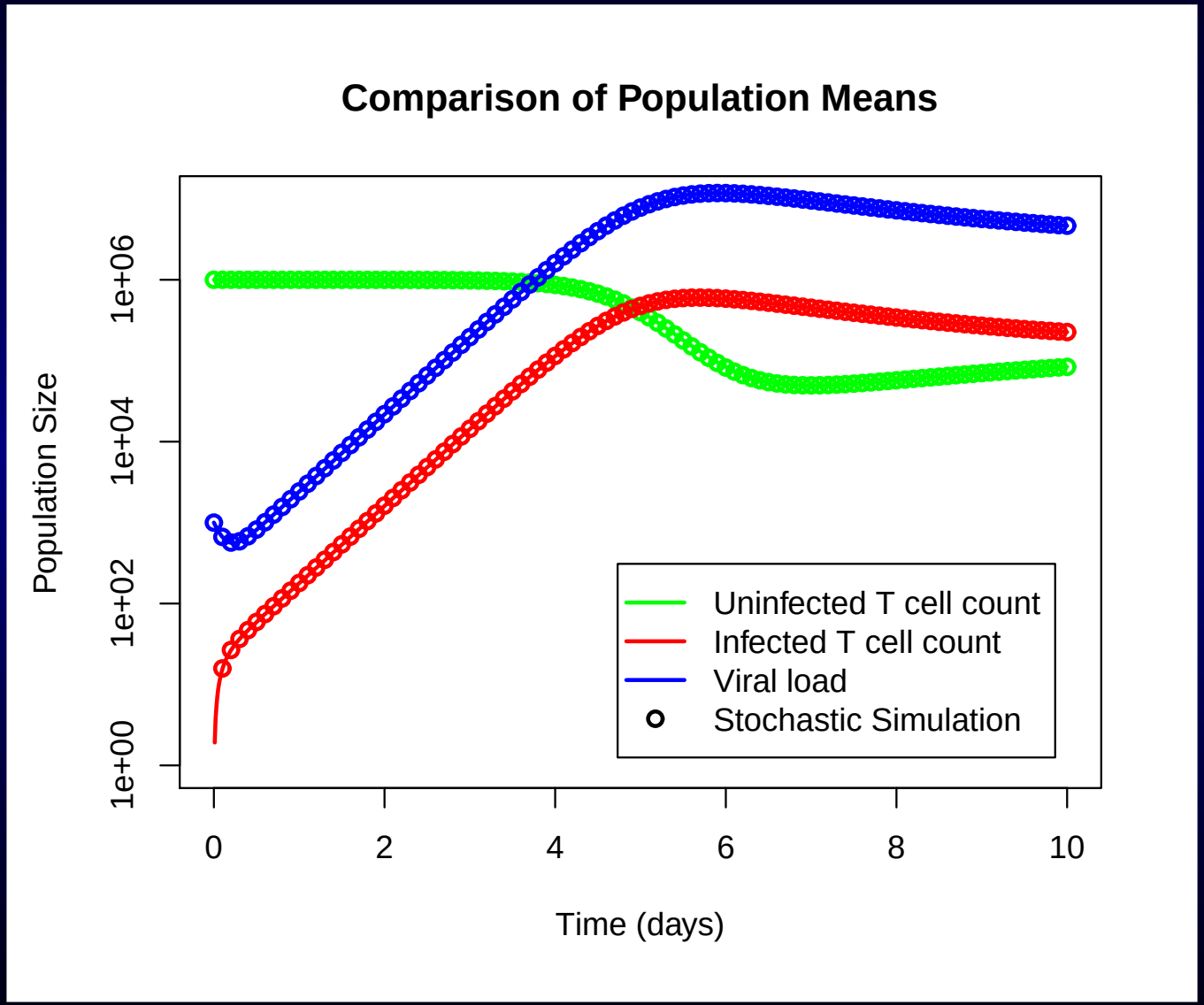

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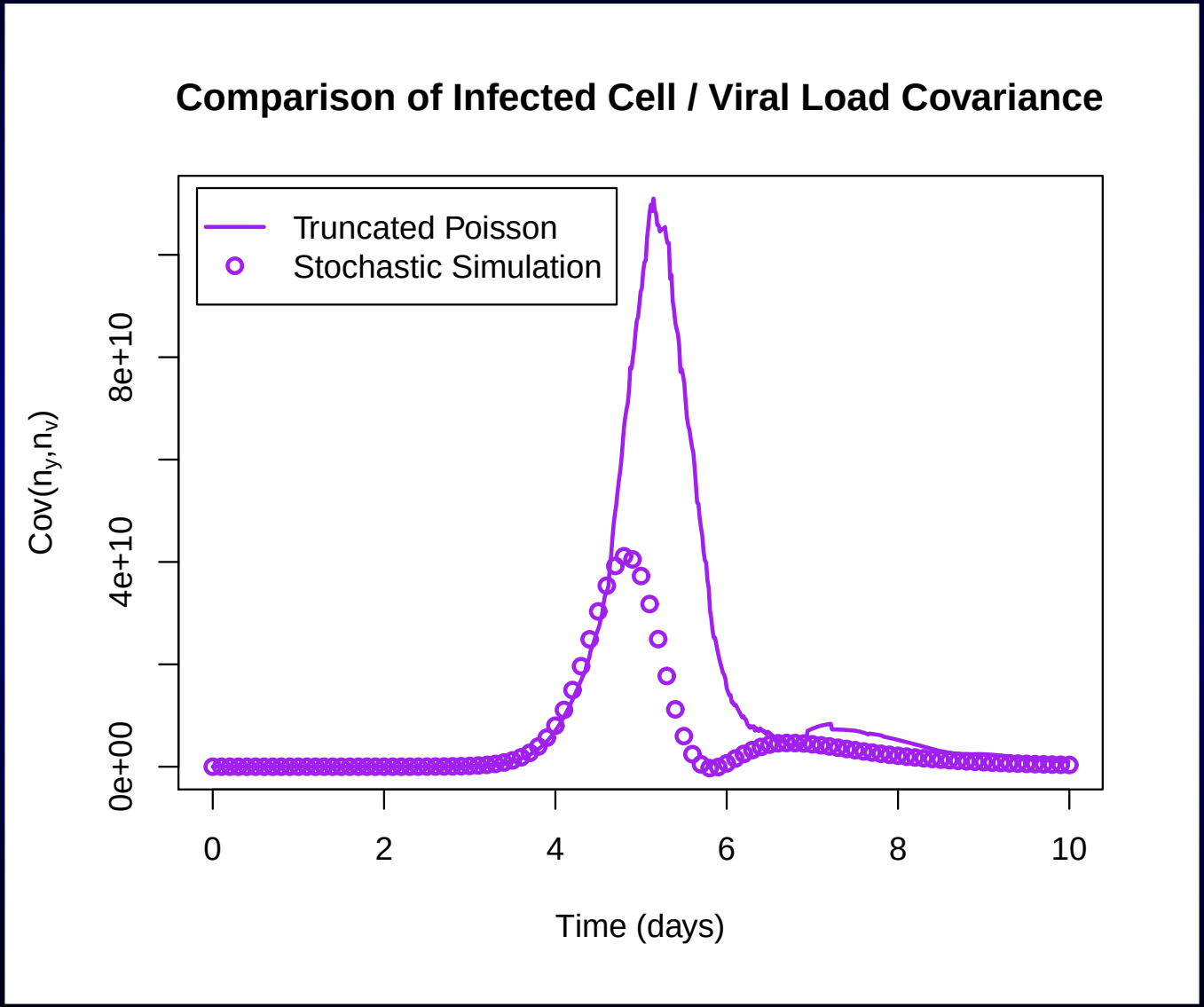

Possibility 2: Diffusion Gauges

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$$\iff \qquad \dot{f}(\vec{\alpha}, t) = \left[-\sum_j \partial_{\alpha_j} A_j + \frac{1}{2} \sum_{jk} \partial_{\alpha_j} \partial_{\alpha_k} D_{jk} \right] f(\vec{\alpha}, t)$$

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- We are therefore free to rotate B matrices so as to improve the stability of the SDEs by reducing the likelihood of trajectories entering the negative half of the complex plane.

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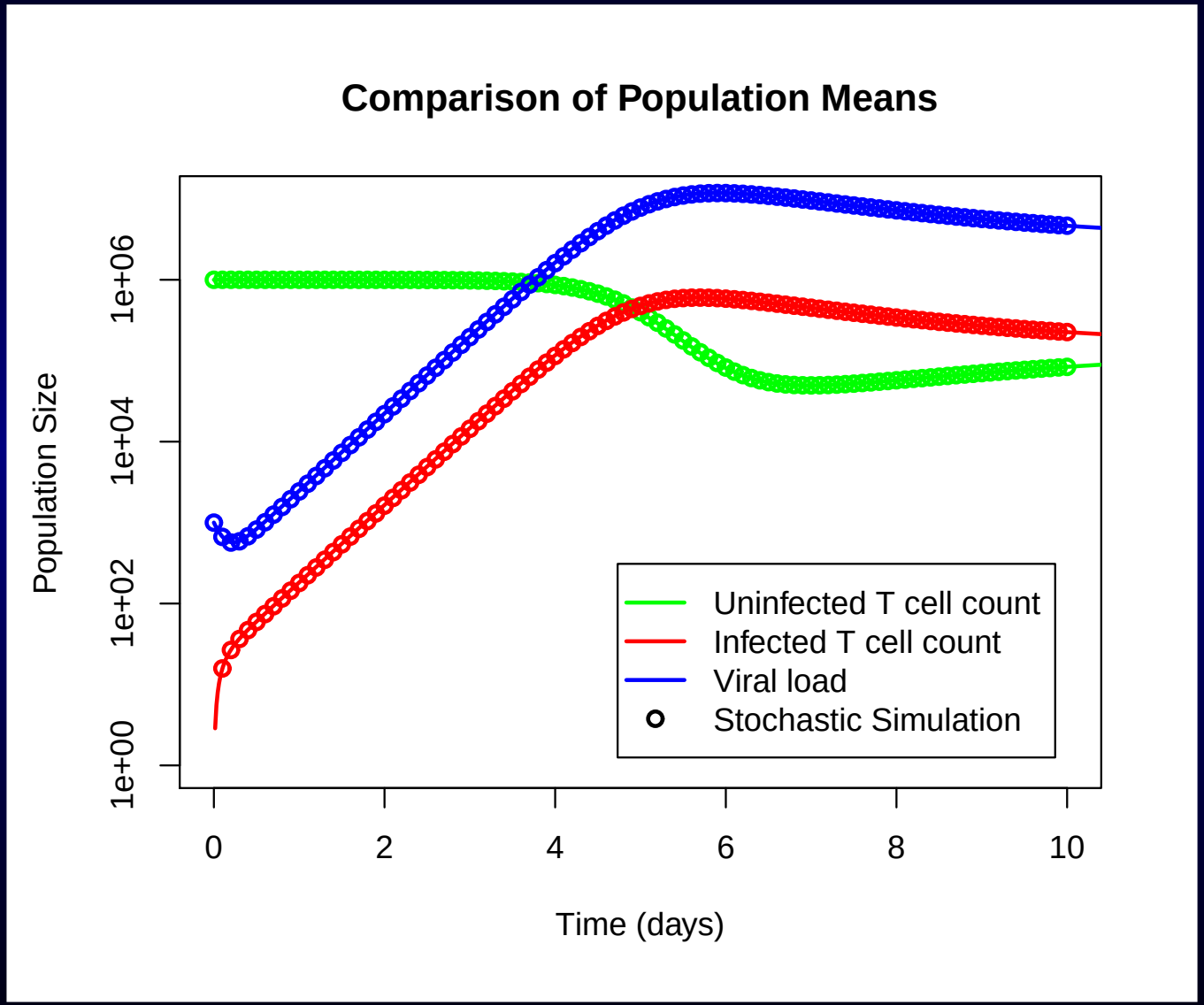

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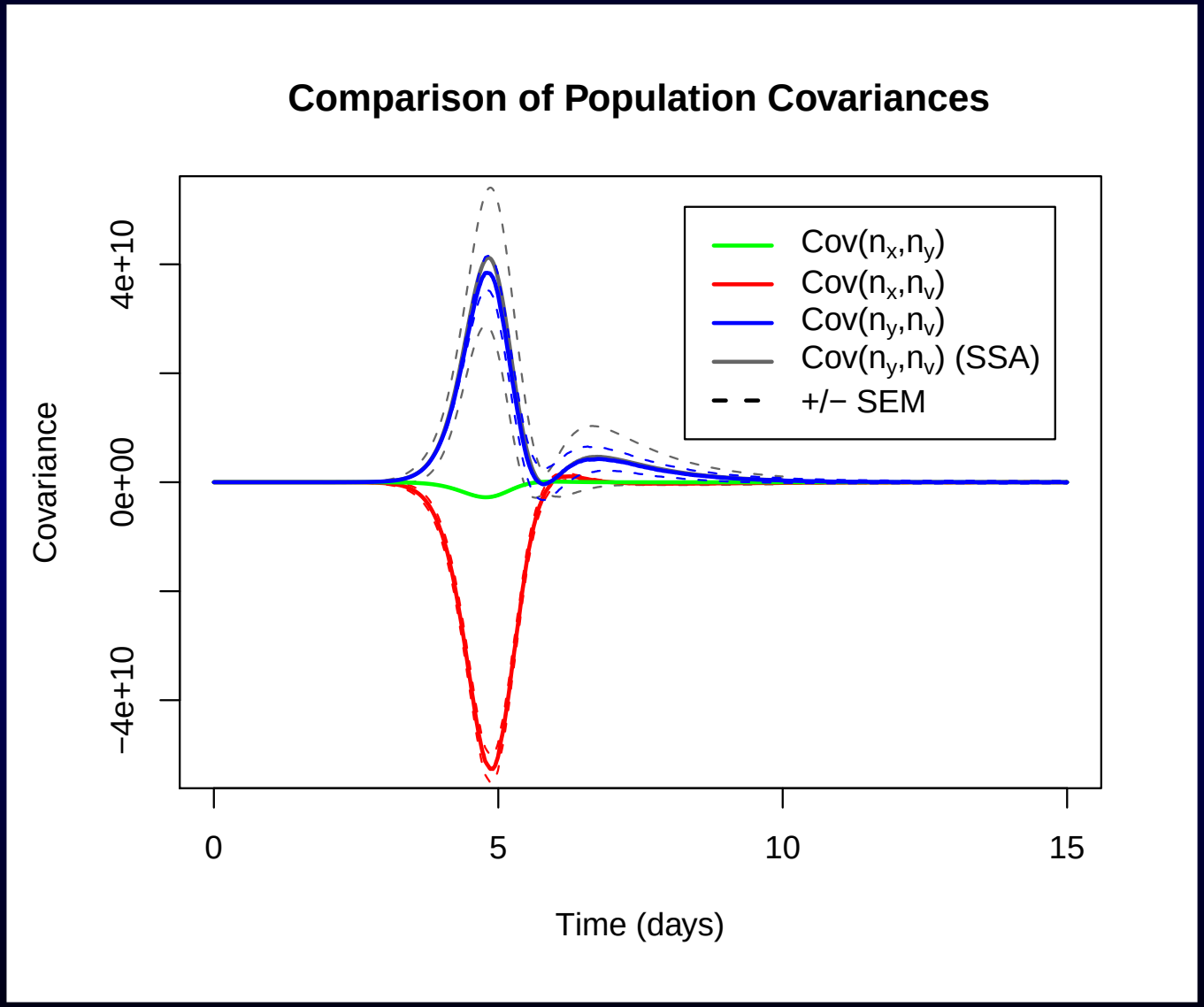

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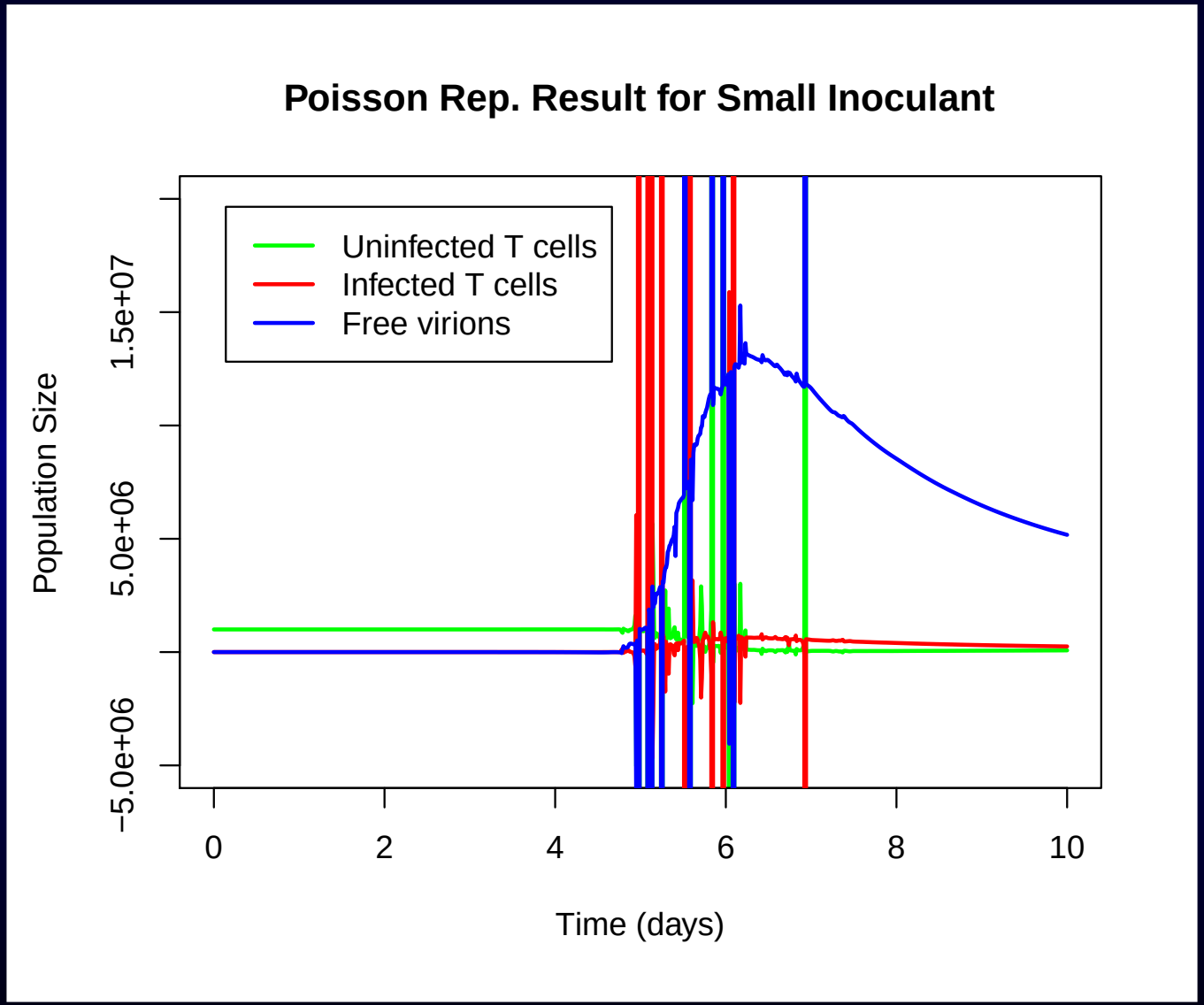

Possibility 3: Drift Gauges

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- Provide one with a means of stabilising the SDEs by adding arbitrary 'gauge' functions to their drift terms.

Possibilities 3: Drift Gauges

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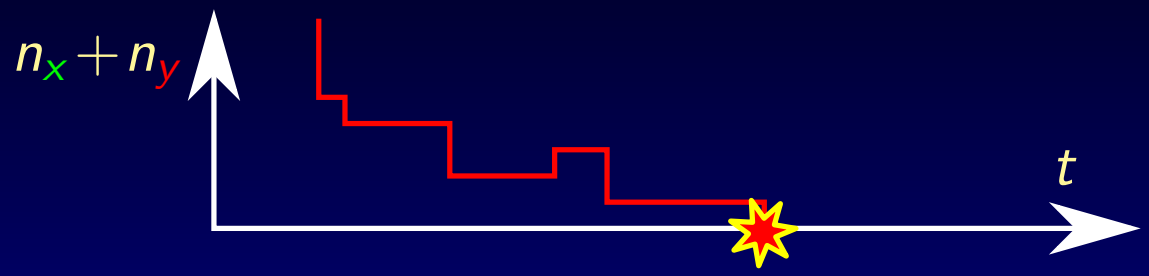
Fluctuations in $\Omega(t)$ may increase sampling algorithms and lead to boundary terms.

Unfortunately, no gauge function has yet been identified which eliminates boundary terms due both to the vanilla Poisson SDEs and the evolution of $\Omega(t)$ in the stochastic viral model.

Possibility 4: State-space Segmentation



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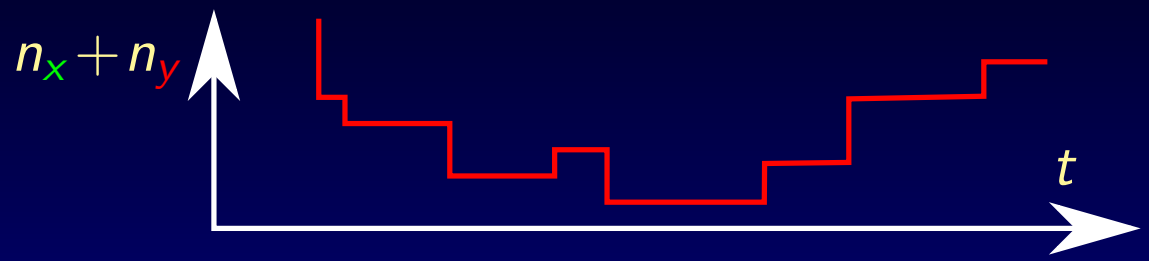

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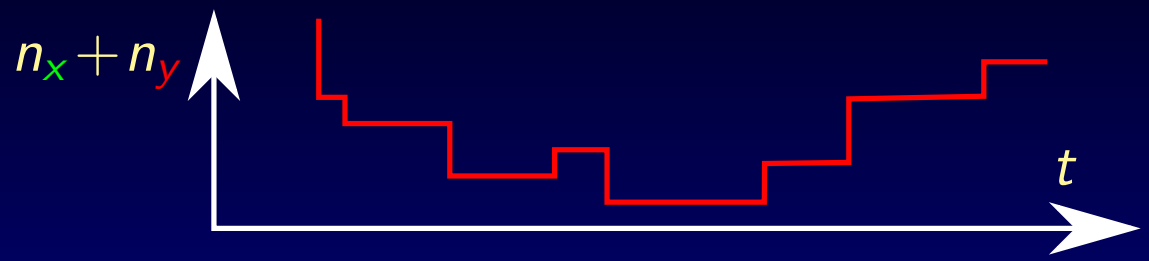

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- By explicitly excluding the $n_x + n_y$ state from the Poisson Representation expansion, one obtains a modified FPE which describes the evolution of weighted stochastic trajectories.
- The weights are necessary to properly include the effect of possibl extinction in the final results.

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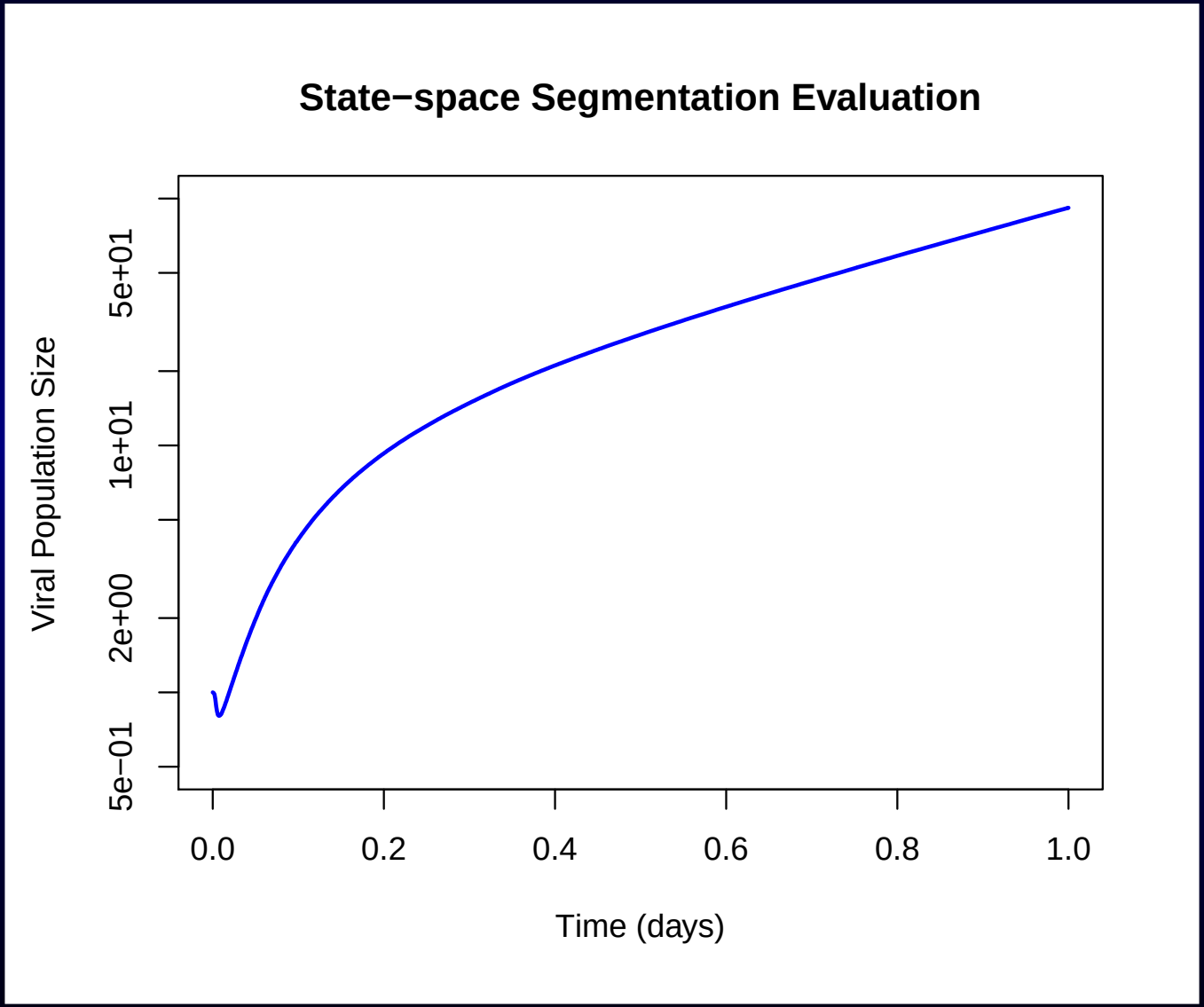

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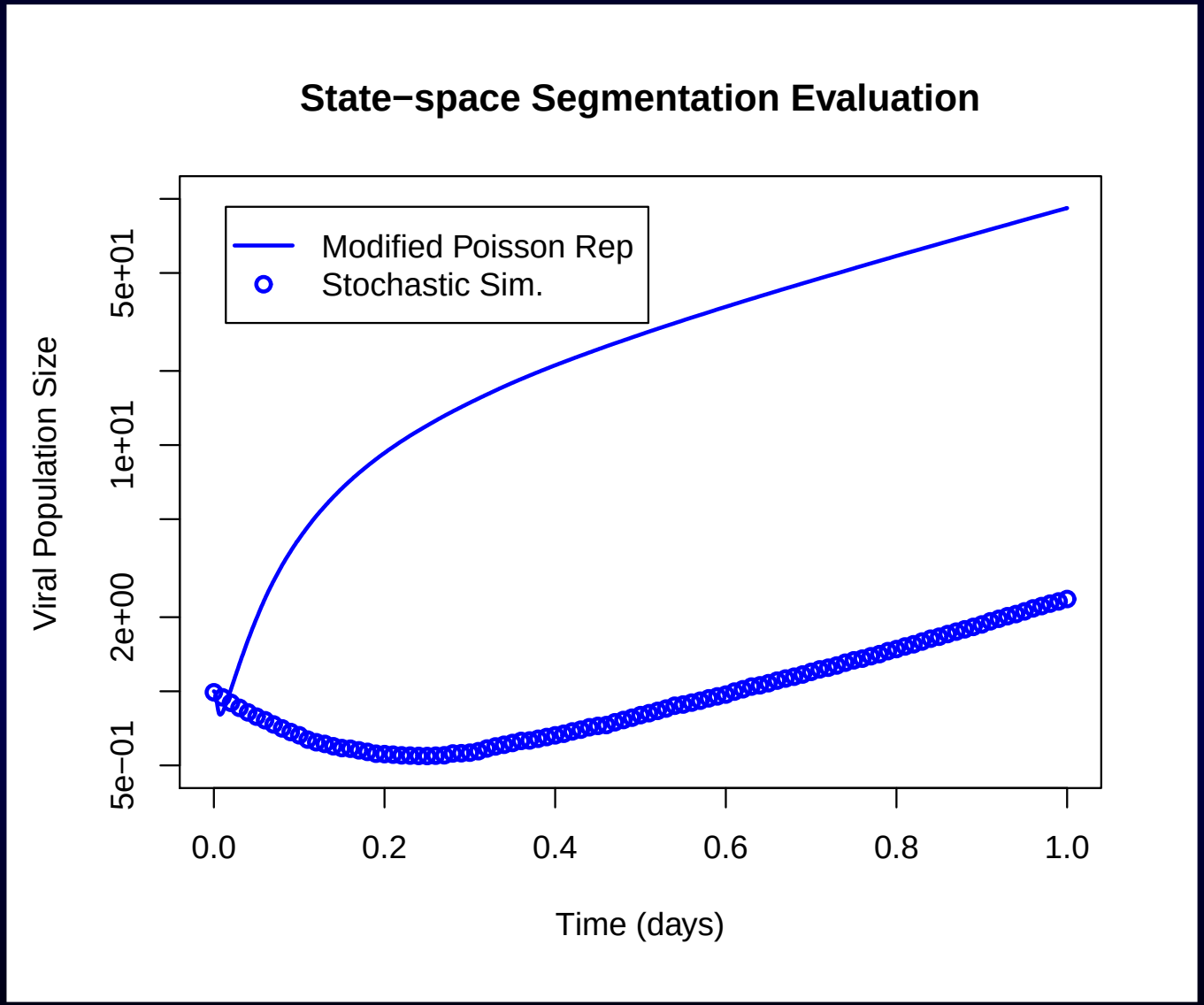

Conclusion

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Obtaining exact numerical results for even simple stochastic models of viral infection is a worthy but extremely hard problem.

The Future

- Begining to seriously consider. . .

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The Brute Force Equation

Stochastic Simulation + Swinburne Supercomputer = Results

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Wish us luck!