Dynamics of Viral Infection and Evolution

Greyson R Lewis[1], Wallace F Marshall[1,2], Barbara A Jones[3]
[1]Biochemistry and Biophysics, University of California - San Francisco, CA
[2]Chan Zuckerberg Biohub, San Francisco, CA
[3]IBM Research Almaden, San Jose, CA

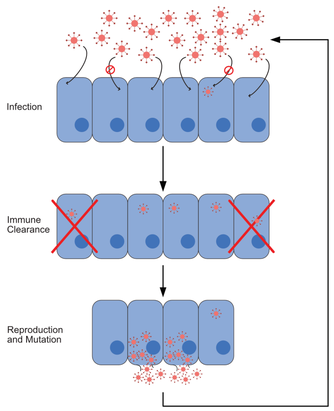
UCSF University of California San Francisco

IBM Research

CENTER FOR CELLULAR CONSTRUCTION

Introduction

RNA viruses exhibit high mutation rates that lead to the formation of closely-related clouds of offspring called "quasispecies," which can be found within hosts during infections. Here, we report dynamics and steady-state results of a model for within-host viral infection and evolution. As in prior work [1], we simulate host-viral interactions as a three-step cycle: infection, immune response, and replication with mutation.



Viruses are described by *m*, the maximum-length alignment between a static host-cell receptor (length 50) and a variable viral binding protein (length 100).

The host is a self-replenishing pool of 1000 cells, which viruses attempt to infect at the beginning of each cycle and may be destroyed by the immune response if infected.

We vary host conditions via two parameters: *T*, the permissivity (*m*-selectiveness) of viral entry; and *A*, the maximal immune response.

Methods

Probabilities of viruses infecting, evading an immune response, and remaining in the cell after not replicating are calculated iteratively using the following equations:

$$\Lambda_m^0 = \Psi_m^R$$

$$\Lambda_{\mathrm{m}}^{\mathrm{i+1}} = \frac{1}{c}\mathrm{P_m}[1-[1-\mathrm{e_m}(1-\sum_{m=0}^{50}\Lambda_m^{\mathrm{i}})]^{\mathrm{c}}] + \Lambda_{\mathrm{m}}^{\mathrm{i}}$$

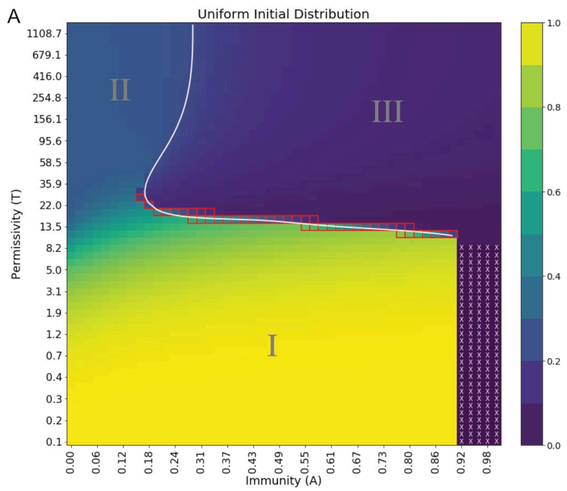
$$\psi^I(m) = \Lambda_m^{i=N}$$

$$\psi^{\Xi}(m) = \psi^I(m)(1-\Xi_m)$$

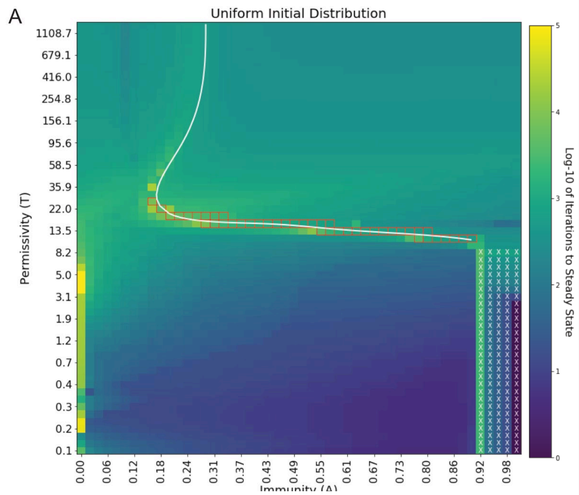
$$\psi^R(m) = \psi^{\Xi}(m)(1-e_m)\,p$$

I, Ξ, and R correspond to infection, the immune response, and proportion of viruses remaining.

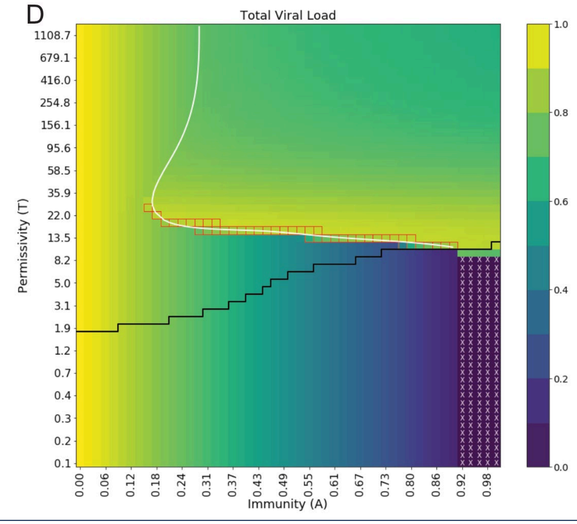
Virus-cell matches at steady state exhibits phase transition



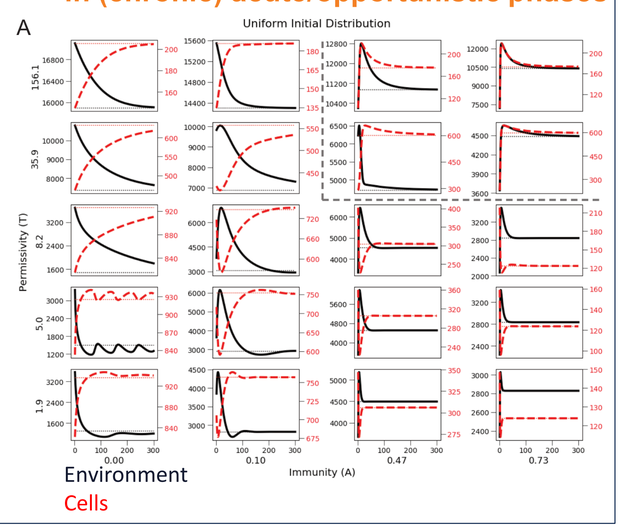
Iterations to steady-state mirrors phase boundary



Total viral load (cells + env) shows regions of varying immune dependence



Viral load dynamics are (un)correlated in (chronic) acute/opportunistic phases



References
[1] BA Jones, J Lessler, S Bianco, JH Kaufman. Statistical Mechanics and Thermodynamics of Viral Evolution. *PLoS ONE* 10 (9): e0137482.

Contact Information
Barbara Jones bajones@us.ibm.com
Greyson Lewis greyson.lewis@gmail.com

Contact us for a preprint!

Dynamics and Convergence

Probability distributions are calculated iteratively via the above equations with a uniform initial distribution. Each full cycle is a single time step, and this defines the dynamics. Every initial condition (T, A) reaches a steady state, and we define convergence when system variables varying less than a set epsilon per iteration (with the exception of some cyclical states at A=0).

Results and Discussion

We find a phase transition of varying order in the mean match number phase space: first-order for the horizonal phase boundary and increasing in order with increasing *T* after the phase boundary becomes vertical.

Viral loads are strongly immunity-dependent, except in phase III. Based on this, slower convergence than phase I, and additional confirmation from other properties, we suggest the following correspondences:

Phase I - Acute infections (e.g., flu, Covid-19);
Phase II – Opportunistic infections (e.g., JC virus);
Phase III – Chronic infections (e.g., Hepatitis C).

At the first-order phase boundary, we unexpectedly find bimodal match number distributions, both in simulations and at steady state. We interpret this as phase coexistence, often seen at such transitions.

Additionally, this region contains points of extended convergence (bright yellow), taking tens of thousands of iterations to shift from metastability to steady state. We believe this signals glassy dynamics.

Note fast initial time scales followed by much slower ones at longer times in the dynamics of viral loads.

We continue to investigate the implications of zero-sum vs. correlated growth of viral load outside and within the chronic infection region (phase III) and welcome suggestions for linking our model to experiments.

We acknowledge support from: the Center for Cellular Construction (NSF DBI-1548297, all), NIH grant R35 GM130327 (WFM), the Chan Zuckerberg Biohub (WFM), Aspen Center for Physics (NSF PHY-1607611, BAJ), the NSF GRFP (Grant No. 1650113, GRL), and NIGMS (T32GM008284, GRL).