Lotka-Volterra predator-prey systems modeling virus dynamics in marine ecosystems and HIV infection

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Outline

Bacteria and Virus Communities

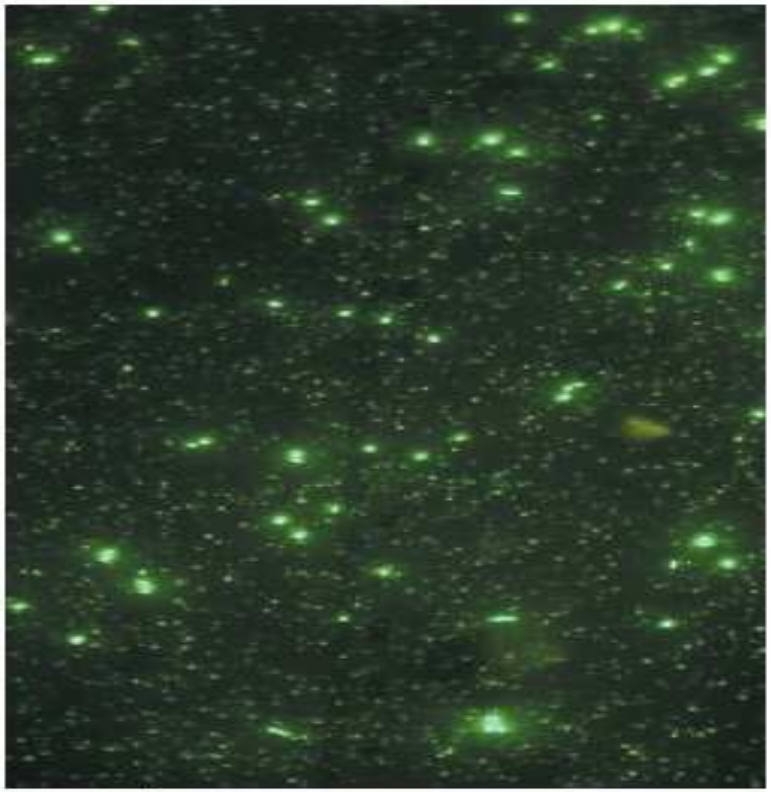


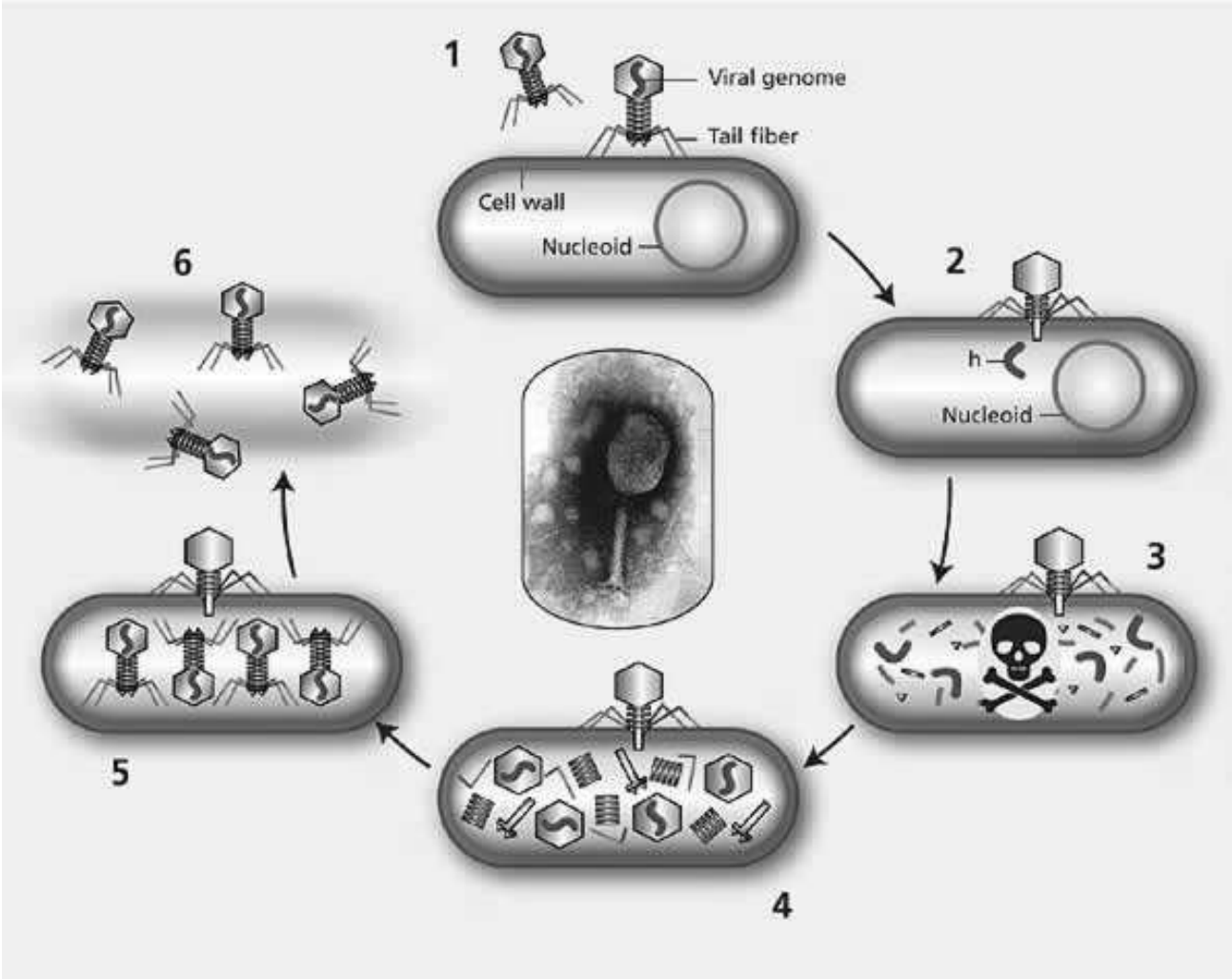
Figure 1 | Ocean inhabitants. A photomicrograph of a seawater sample taken off the coast of California. The larger dots are bacteria (about 0.5 micrometres in diameter) and the smaller ones are viruses; both are stained with the DNA-specific stain SYBR Green. The bacteria predominantly belong to the SAR11 group. Zhao and colleagues' results[3] suggest that many of the viruses are pelagiphages that infect SAR11 bacteria.

10^9 Bacterial per liter in sea water.

10^{10} Virus or more per liter.

Virus that parasitize Bacteria are called Bacteriophage, or more briefly, phage.

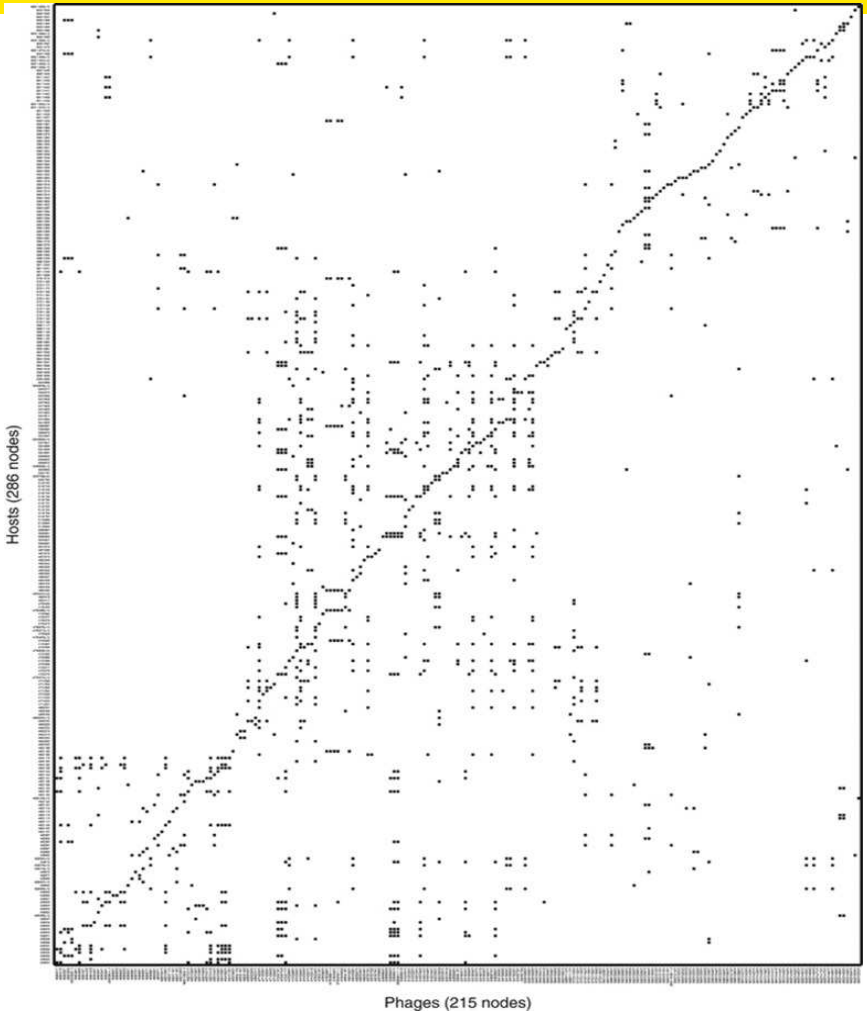
Virus Life Cycle: adsorption to lysis



Latent Period: time from adsorption to burst $\approx 20 - 40$ min.

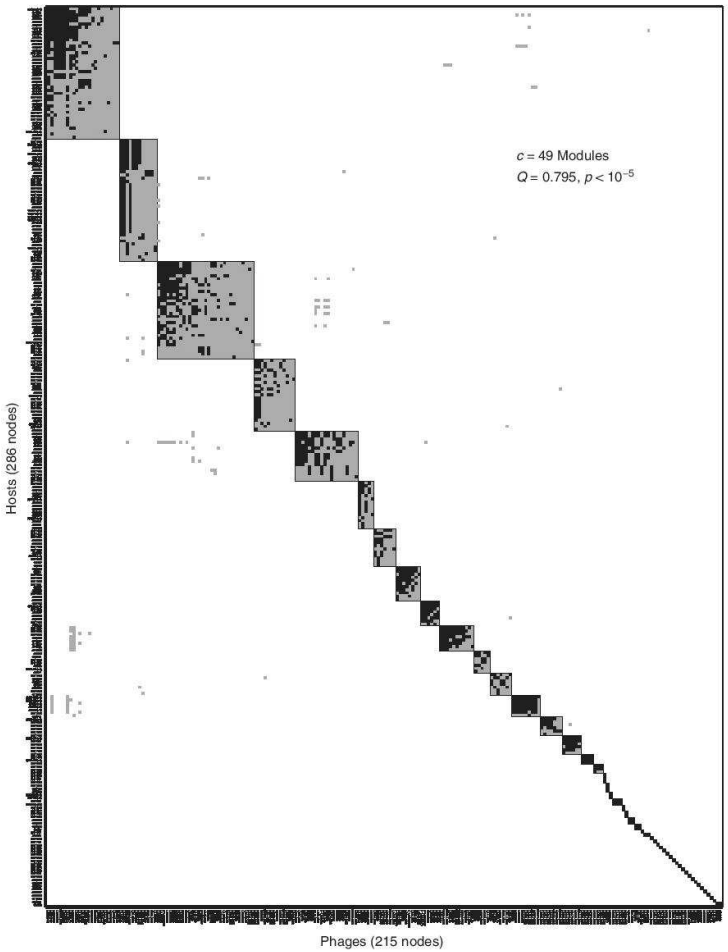
Burst size: 10-1000 virus.

Infection network of marine bacteria & virus



Multi-scale structure and geographic drivers of cross-infection within marine bacteria and phages, Flores,Valverde,Weitz, ISME 2013.
data from: Bacteriophage sensitivity patterns among bacteria isolated from marine waters, Moebus & Nattkemper, 1981

Infection Network after resorting for modularity



Multi-scale structure and geographic drivers of cross-infection within marine bacteria and phages, Weitz et al, ISME 2013,

Nested Infection Networks in Bacteria-Virus systems

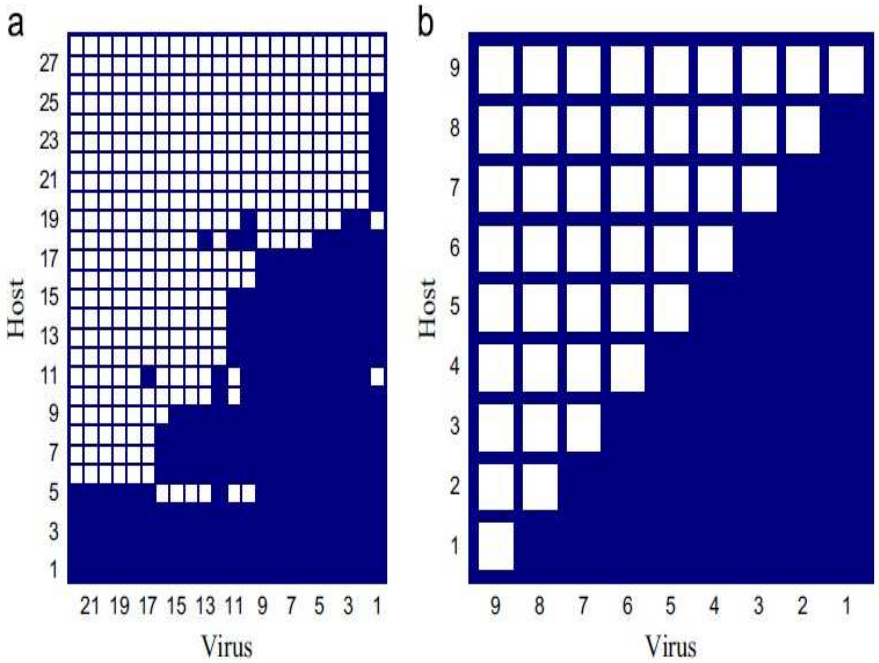


Fig. 1. (a) Infection network from an experimental study presenting a statistically nested pattern (original data from Stenholm et al., 2008 and reanalyzed in Flores et al., 2011). The numbers identify different types of viruses and hosts. (b) Perfectly nested infection network. For a perfectly nested network, the numbers correspond to the rank (i.e., number of interactions). White squares denote that a given virus can infect the host.

Infection Networks and Presence-Absence Matrices

Bacteria types $B_i,\ 1 \le i \le n$ and virus types $V_j,\ 1 \le j \le m$.

Network matrix

$$M_{ij} = \left\{ \begin{array}{cc} 1 & V_j \text{ infects } B_i \\ 0 & V_j \text{ does not infect } B_i \end{array} \right\}$$

Nested Infection Networks

Table: Nested Network

B_1	x	x	x
B_2		x	x
B_3			x
	V_1	V_2	V_3

$$M = \begin{pmatrix} 1 & 1 & 1 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix}$$

Weitz et al* show that community persistence is facilitated by **trade-offs**:

- bacterial growth rate increases as the number of virus that infect it increases.
- infection efficiency of virus should decrease with increasing host range.

* Jover L.F., Cortez M.H., Weitz J.S. (2013) Mechanisms of multi-strain coexistence in host phage systems with nested infection networks, J. Theor. Biology 332: 65-77.

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Networks inspired by “Kill the Winner” hypothesis

Table: One-to-One Network

B_1	x		
B_2		x	
B_3			x
	V_1	V_2	V_3

Table: One-to-One with a generalist

B_1	x			x
B_2		x		x
B_3			x	x
B_4				x
	V_1	V_2	V_3	Z

$Z =$ Zooplankton.

F. Thingstad, (2014), A theoretical analysis of how strain-specific viruses can control microbial species diversity, Proc. Nat. Acad. Science

General Lotka-Volterra Model of Bacteria & Virus

$$\frac{dB_i}{dt} = \underbrace{B_i\left(r_i - \sum_{k=1}^{n} a_{ik}B_k\right)}_{\text{growth and competition}} - \underbrace{B_i\sum_{j=1}^{m} M_{ij}\phi_{ij}V_j}_{\text{infection by virus}}, 1 \le i \le n,$$

$$\frac{dV_j}{dt} = \underbrace{V_j\sum_{i=1}^{n}\beta_{ij}\phi_{ij}M_{ij}B_i}_{\text{virus reproduction}} - \underbrace{d_jV_j}_{\text{virus decay}}, 1 \le j \le m$$

where

$\phi_{ij} =$ affinity, or attack rate, of V_j for B_i.

$\beta_{ij} =$ "burst size" of V_j progeny released upon lysis of B_i.

In order to focus on virus-bacteria infection network, simplify competition among bacteria: $a_{ij} = a = 1,\ \forall i, j$. Set $\Phi_{ij} = M_{ij}\phi_{ij}$.

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Basic Dynamical Features of the Model

- Positive solutions, $B_i(0), V_j(0) > 0, \forall i, j$, exist globally in time and $B_i(t), V_j(t) > 0, \ \forall i, j, \ t > 0$.
- Solutions are attracted to a compact subset of $\mathbb{R}_+^{m+n}$.
- Persistence* of all bacteria and virus types requires existence of an equilibrium with all positive components!

*(uniform) persistence: $\exists \epsilon > 0$, such that $\liminf_{t\to\infty} X(t) > \epsilon, \forall X \in \{B_i, V_j\}$, provided all initial data are positive

Volterra's Lyapunov Function

Assume the existence of an equilibrium $E^* = (B^*, V^*)$ with $B_i^*, V_j^* > 0, \forall i, j$. Let $U(x, x^*) = x - x^* - x^* \log(x/x^*),\ x, x^* > 0$ and

$$V = \sum_i c_i U(B_i, B_i^*) + \sum_j d_j U(V_j, V_j^*)$$

for suitable $c_i > 0, d_j > 0$. Then

$$\begin{aligned} \frac{dV}{dt} &= -\sum_{i=1}^{n} c_i (B_i - B_i^*) \sum_{k=1}^{n} (B_k - B_k^*) + \sum_{j=1}^{m} (V_j - V_j^*) \sum_{i=1}^{n} (d_j \beta_{ij} - c_i) \Phi_{ij} (B_i - B_i^*) \\ &= -\left(\sum_{i=1}^{n} (B_i - B_i^*) \right)^2, \text{ if } 0 = (d_j \beta_{ij} - c_i) \Phi_{ij},\ c_i = 1,\ 1 \le i \le n,\ 1 \le j \le m. \end{aligned}$$

For example: $\beta_{ij} = \beta_j,\ \forall i, j.$ Burst size independent of host.

LaSalle Invariance Principle

Theorem: Let $\frac{dx}{dt} = f(x)$ be an ODE defined on a set $G \subset \mathbb{R}^n$. Let $V : G \to \mathbb{R}$ be continuously differentiable. If for some solution $x(t)$, the derivative $\frac{dV}{dt}$ of the map $t \to V(x(t))$ satisfies the inequality $\frac{dV}{dt} \leq 0$ then the omega limit set ω of the solution satisfies

$$\omega \cap G \subset \{x \in G : \nabla V(x) \cdot f(x) = 0\}$$

In our example $\frac{dV}{dt} = -\left(\sum_{i=1}^{n}(B_i - B_i^*)\right)^2$ so

$$\omega \subset \{(B, V) \in \mathbb{R}^{m+n} : \sum_i B_i \equiv \sum_i B_i^*\}$$

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Main Result

Theorem: Assume there is a positive equilibrium E^* and $\beta_{ij} = \beta_j$. Then

- E^* is locally stable.
- Positive solutions are weakly persistent: $0 < \liminf_{t\to\infty} x(t),\ x \in \{B_i, V_j\}$.
- On the omega limit set of a positive solution:
  1. $\sum_i (B_i(t) - B_i^*) = 0$.
  2. solutions satisfy the **limiting system**:

$$\begin{aligned} \frac{dB_i}{dt} &= -B_i \cdot \sum_{j=1}^{m} \Phi_{ij}(V_j - V_j^*),\ 1 \le i \le n \\ \frac{dV_j}{dt} &= \beta_j V_j \sum_{k=1}^{n} \Phi_{kj}(B_k - B_k^*),\ 1 \le j \le m. \end{aligned}$$

- If E^* is unique positive equilibrium then $\lim_{t\to\infty} \frac{1}{t}\int_0^t (B(s), V(s))ds = E^*$ holds for every positive solution and the system is uniformly persistent.

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Results for Nested Network

$$\begin{aligned}\frac{dB_i}{dt} &= B_i\left(r_i - \sum_{k=1}^{n} B_k\right) - B_i \sum_{j\geq i} \phi_j V_j,\ 1 \leq i \leq n,\\ \frac{dV_j}{dt} &= \beta_j \phi_j V_j \sum_{k\leq j} B_k - d_j V_j, \qquad 1 \leq j \leq n\end{aligned}$$

Burst and attack rates of virus j independent of host: $\beta_{ij} = \beta_j,\ \phi_{ij} = \phi_j$.

$$e_j \equiv \frac{\beta_j \phi_j}{d_j} = \text{infection efficiency of virus } j$$

Weitz trade-off assumptions:

(a) $r_1 > r_2 > \cdots > r_n$: bacterial growth rate decreases with increasing defence against infection.

(b) $e_1 > e_2 > \cdots > e_n$: viral infection efficiency decreases with (increasing) host range.

Then a unique positive equilibrium exists which is globally asymptotically

Proof Sketch

An omega limit set is contained in $\sum_{i=1}^{n} B_i = \sum_{i=1}^{n} B_i^*$, solutions are bounded for all $t \in \mathbb{R}$, and satisfy the limiting system:

$$\begin{aligned} \frac{dB_i}{dt} &= -B_i \sum_{j \geq i} \phi_j (V_j - V_j^*), \ 1 \leq i \leq n, \\ \frac{dV_j}{dt} &= \beta_j \phi_j V_j \sum_{k \leq j} (B_k - B_k^*), \quad 1 \leq j \leq n \end{aligned}$$

- Observe that $\frac{dV_n}{dt} \equiv 0$ so $V_n(t)$ is constant.
- Then $\frac{dB_n}{dt} = -B_n \phi_n (V_n - V_n^*)$ which, because $B_n(t)$ is bounded, implies that $V_n \equiv V_n^*$ and that $B_n(t)$ is constant.
- Therefore, $\sum_{i=1}^{n-1} B_i(t)$ is constant.
- Then $\frac{dV_{n-1}}{dt} = \beta_{n-1} \phi_{n-1} V_{n-1} \sum_{k \leq n-1} (B_k - B_k^*) = 0$, else $V_{n-1}(t)$ is not bounded. So $\sum_{k \leq n-1} (B_k - B_k^*) = 0$ and $V_{n-1}(t)$ is constant.
- Therefore, $B_n(t) \equiv B_n^*$ because $\sum_{k=1}^{n} (B_k - B_k^*) = 0$. Now iterate!

Results for One-to-One Network

$$\begin{aligned}\frac{dB_i}{dt} &= B_i(r_i - \sum_{j=1}^{n} B_j) - B_i V_i \\ \frac{dV_i}{dt} &= e_i d_i V_i(B_i - \frac{1}{e_i}),\ 1 \le i \le n.\end{aligned}$$

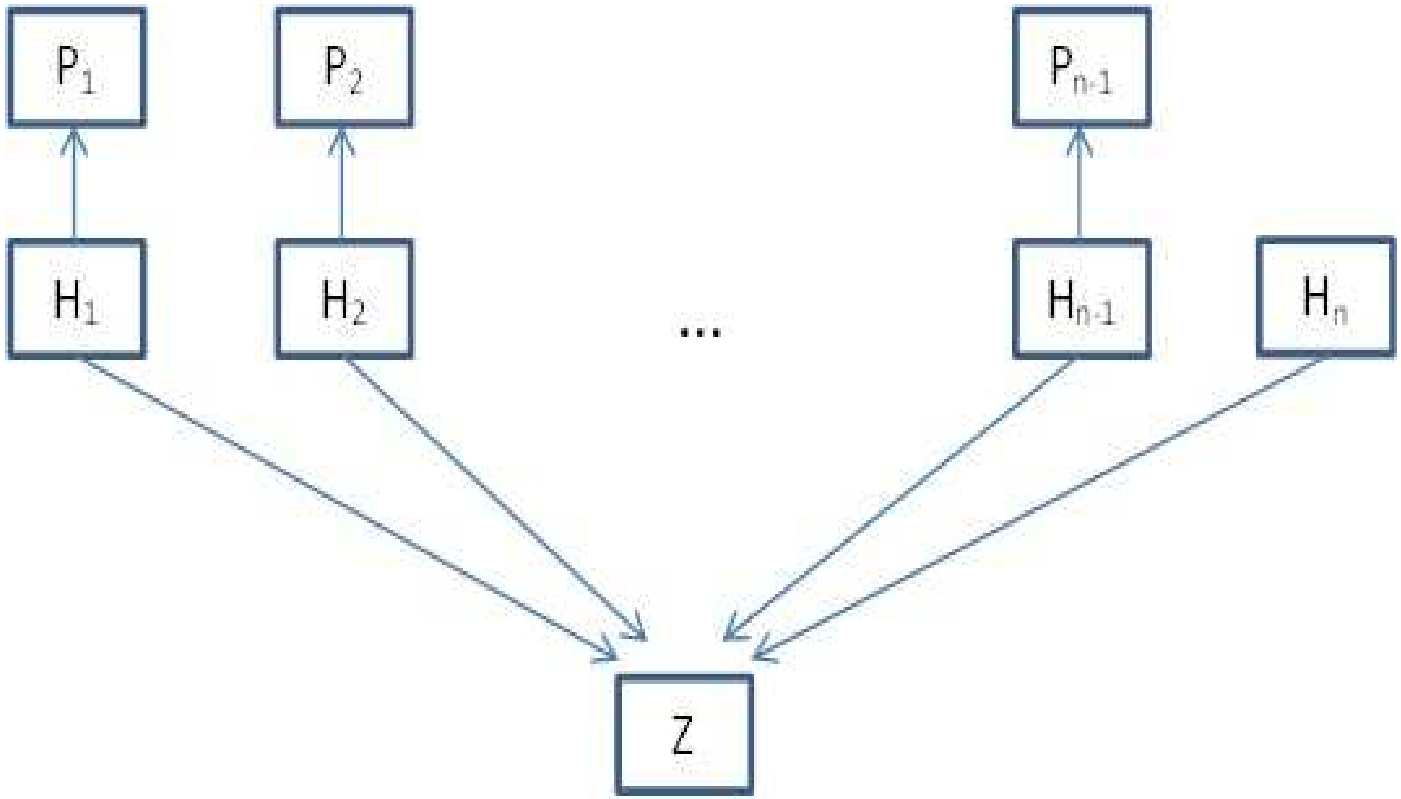
Unique positive equilibrium E^* if and only if: $\sum_{i=1}^{n} \frac{1}{e_i} < r_j,\ 1 \le j \le n$.

Theorem: The ω-limit set of a positive solution is either E^* or it consists of non-constant bounded solutions, $(B(t), V(t))$, satisfying $\sum_{i=1}^{n} B_i(t) = \sum_{i=1}^{n} B_i^*,\ t \in \mathbb{R}$ and $\forall i$, $(B_i(t), V_i(t))$ is a positive solution of the conservative planar system

$$\begin{aligned}\frac{dB_i}{dt} &= B_i\,(V_i^* - V_i) \\ \frac{dV_i}{dt} &= e_i d_i V_i\,(B_i - B_i^*)\,.\end{aligned}$$

All positive solutions converge to E^* if $n \le 3$.

Results for Kill the Winner Network

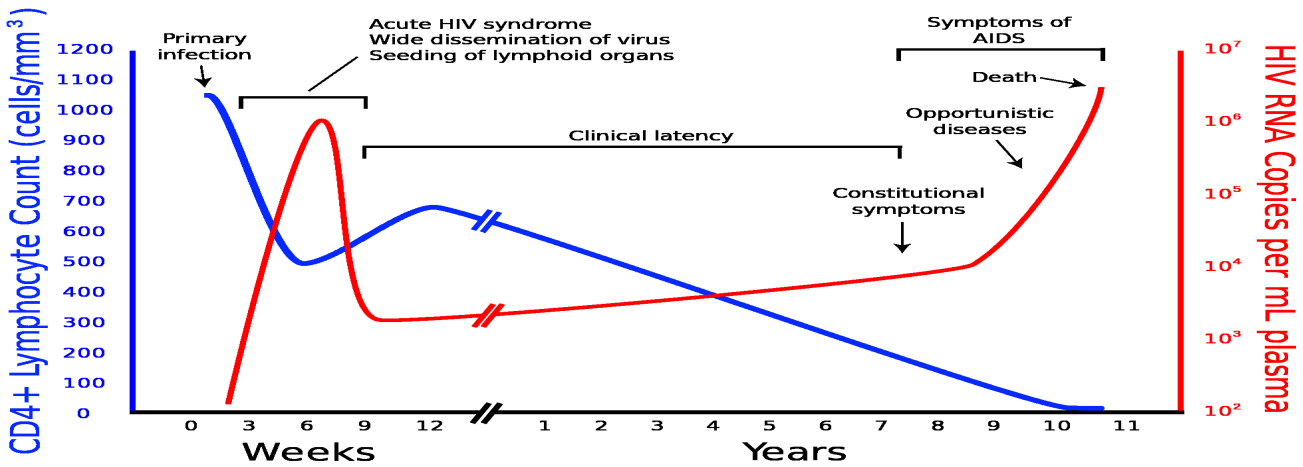


Results are similar to those for one-to-one network.
$H = B =$ bacteria, $P = V =$ virus, $Z =$ zooplankton

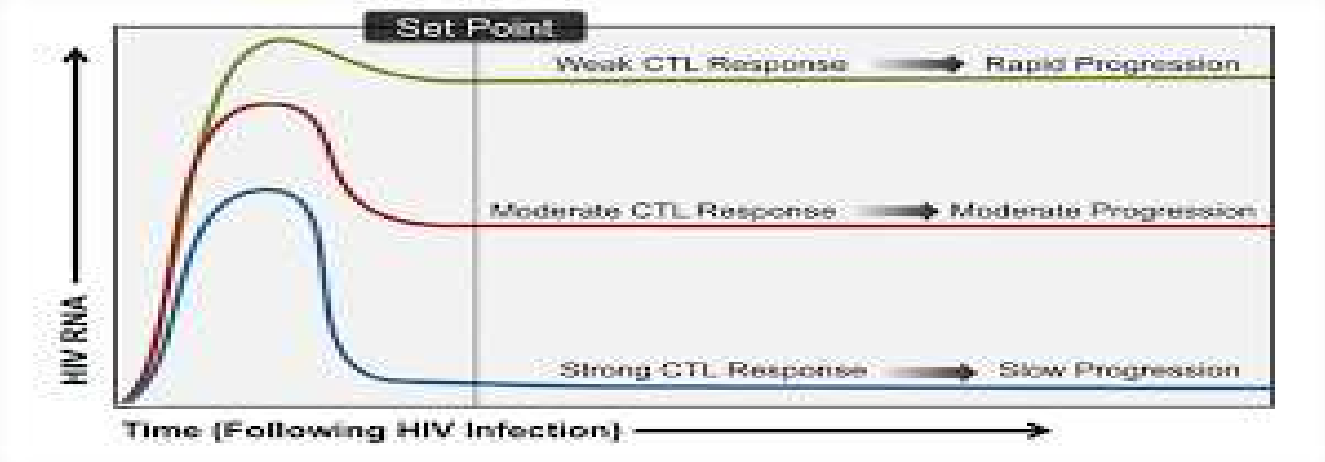
Summary

- Trophic Network structure influences persistence of stable bacteria-virus communities
- Volterra's Lyapunov function together with the LaSalle invariance principle provide effective tools for understanding bacteria-virus and predator-prey systems.

HIV & CTL (Cytotoxic T Lymphocyte) Immune Response



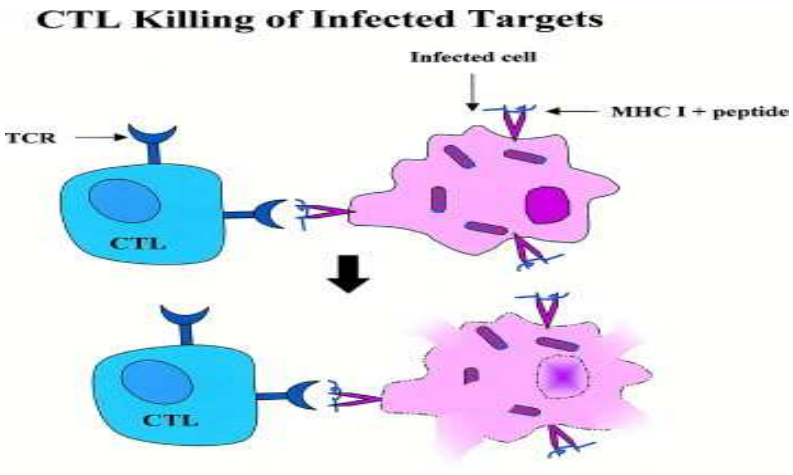
Progression of HIV infection

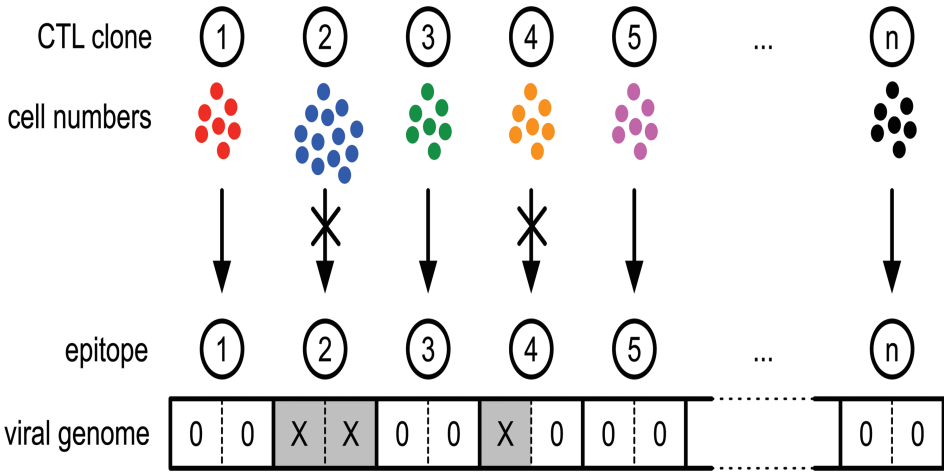


Importance of CTL Immune Response

CTL recognition & killing of infected cell

epitope: the part of an antigen that is recognized by the immune system.

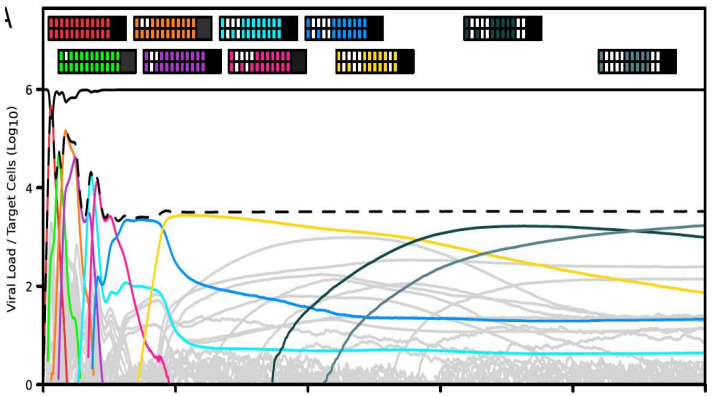




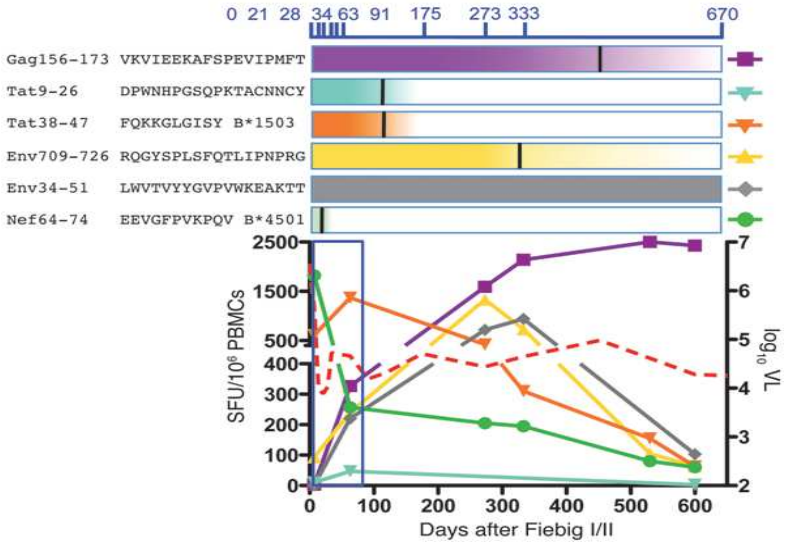
CTL recognizes epitope, kills infected cell & proliferates clones

CTL clones target distinct epitopes, but mutations can confer resistance

CTL/HIV Interactions, Dynamics & Diversity



(a) HIV/CTL evolution (van Deutekom et al.)



(b) Shifting immunodominance (Liu et al.)

- Patterns of multi-epitope CTL response and HIV escape?
- Understanding complex HIV-CTL dynamics & evolution is important for designing vaccine/immunotherapy.

General multi-variant virus-immune response model

$$\frac{dX}{dt} = b - dX - X\sum_{i=1}^{m} k_i V_i,$$

$$\frac{dY_i}{dt} = k_i V_i X - \delta_i Y_i - Y_i \sum_{j=1}^{n} r_{ij} Z_j, \quad i = 1, \ldots, m$$

$$\frac{dV_i}{dt} = p_i Y_i - c_i V_i, \quad i = 1, \ldots, m$$

$$\frac{dZ_j}{dt} = q_j Z_j \sum_{i=1}^{m} r_{ij} Y_i - \mu_j Z_j, \quad j = 1, \ldots, n.$$

- $X =$ target cells
- $Y_i =$ cells infected with strain i
- $V_i =$ virus strain i
- $Z_j =$ CTL immune response variant
- $r_{ij} =$ recognition/attack rate of CTL Z_j on infected cell Y_i.
- (r_{ij}): $m \times n$ virus-immune interaction network.

Quasi-steady state and rescaling

- Fast virus dynamics: $\frac{dV_i}{dt} = 0 \;\Rightarrow\; V_i(t) \propto Y_i(t)$
- Rescale parameters and variables $X \to x$, $Y_i \to y_i$.

$$\dot{x} = 1 - x - x\sum_{i=1}^{m} \mathcal{R}_i y_i,$$

$$\dot{y}_i = \gamma_i y_i \left(\mathcal{R}_i x - 1 - \sum_{j=1}^{n} a_{ij} Z_j \right), \quad i = 1, \ldots, m$$

$$\dot{Z}_j = \frac{\sigma_j}{\rho_j} Z_j \left(\sum_{i=1}^{m} a_{ij} y_i - \rho_j \right), \quad j = 1, \ldots, n.$$

- a_{ij} is rescaled attack/recognition rate of Z_j on y_i. Matrix (a_{ij}) captures network structure.
- Each virus strain y_i has *epitope set* $\Lambda_i \subseteq [1, n]$: $j \in \Lambda_i$, if $a_{ij} > 0$.

Feasible equilibria and positivity class uniqueness

Classify equilibria $\mathcal{E}^* = (x^*, y^*, Z^*)$ in $\mathbb{R}^{1+m+n}_+$ by "**persistent variant sets**":

$$\Omega_y = \{i \in [1,m] : y_i^* > 0\}, \quad \Omega_z = \{j \in [1,n] : Z_j^* > 0\}$$

Positivity class corresponding to $\mathcal{E}^*$:

$$\Gamma_\Omega = \{(x,y,z) \in \mathbb{R}^{1+m+n}_+ : y_i > 0 \iff y_i^* > 0,\ z_j > 0 \iff z_j^* > 0\}$$

Positivity class uniqueness:

- For any other equilibria $\mathcal{E}^\diamond$ in Γ_Ω, $x^\diamond = x^*$
- If $\mathcal{E}^*$ is the unique equilibrium in Γ_Ω, then either $|\Omega_y| = |\Omega_z|$ or $|\Omega_y| = |\Omega_z| + 1$.

Saturated equilibria

Following Hofbauer and Sigmund (1998), we call $\mathcal{E}^*$ *saturated* if:

$$\left.\frac{\dot{y}_i}{\gamma_i y_i}\right|_{\mathcal{E}^*} = \mathcal{R}_i x^* - 1 - \sum_{j\in\Omega_z} a_{ij} Z_j^* \le 0, \quad \forall i \notin \Omega_y,$$

$$\left.\frac{\rho_j \dot{Z}_j}{\sigma_j Z_j}\right|_{\mathcal{E}^*} = \sum_{i\in\Omega_y} a_{ij} y_i^* - \rho_j \le 0, \quad \forall j \notin \Omega_z.$$

Note that these are "invasion eigenvalues" of "missing populations". An equilibrium with all positive components is saturated.

Construct Lyapunov function W:

$$W = x - x^* \ln\frac{x}{x^*} + \sum_{i,j}\left(\frac{y_i}{\gamma_i} + \frac{\rho_j Z_j}{\sigma_j}\right) - \sum_{\substack{i\in\Omega_y,\\ j\in\Omega_z}}\left(\frac{y_i^*}{\gamma_i}\ln\frac{y_i}{y_i^*} + \frac{\rho_j Z_j^*}{\sigma_j}\ln\frac{Z_j}{Z_j^*}\right)$$

$$\frac{d}{dt}W = -\frac{1}{x^* x}(x - x^*)^2 + \sum_{i\notin\Omega_y} y_i\left(\mathcal{R}_i x^* - 1 - \sum_{j\in\Omega_z} a_{ij} Z_j^*\right) + \sum_{j\notin\Omega_z} Z_j\left(\sum_{i\in\Omega_y} a_{ij} y_i^* - \rho_j\right)$$

$\Rightarrow \frac{d}{dt}W \le 0$ if $\mathcal{E}^*$ saturated.

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There exists a saturated equilibria

Proof, using a homotopy argument and topological degree theory, follows the one given for Lotka-Volterra systems in Josef Hofbauer and Karl Sigmund text *E*volutionary Games and Population Dynamics Cambridge University Press, 1998.

A locally stable equilibrium is necessarily saturated; the existence of Lyapunov function W implies that a saturated equilibrium is locally stable.

Theorem on Equilibria Stability & Persistent Variants

Theorem (Browne & H.S., 2018)

If $\mathcal{E}^* = (x^*, y^*, Z^*)$ is saturated, then $\mathcal{E}^*$ is locally stable and $x(t) \to x^*$ as $t \to \infty$. Furthermore, if $\mathcal{E}^*$ is "strictly saturated" and is the unique equilibrium in positivity class Γ_Ω, then

i) $y_i, Z_j \to 0$ *for all* $i \notin \Omega_y, j \notin \Omega_z$.

ii) $\frac{1}{t}\int_0^t y_i(s)ds \to y_i^*,\ i \in \Omega_y,\ \frac{1}{t}\int_0^t Z_j(s)ds \to Z_j^*,\ j \in \Omega_z$

iii) y_i, Z_j *are uniformly persistent for all* $i \in \Omega_y, j \in \Omega_z$.

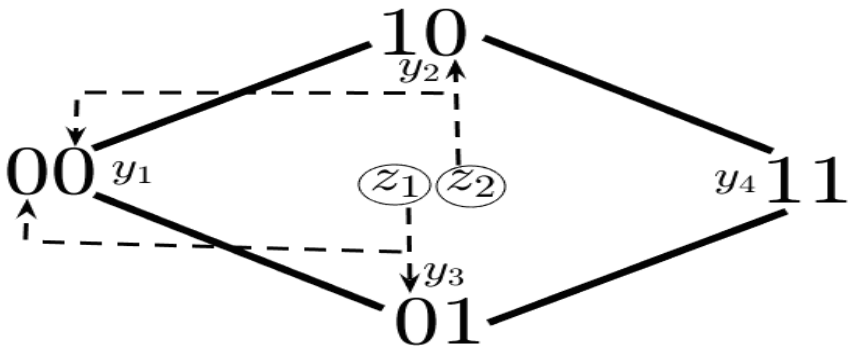
iv) *If* $|\{i \in \Omega_y : \Lambda_i \cap \Omega_z \neq \emptyset\}| \leq 2$ (≤ 2 *persistent virus strains under immune attack), then* $\mathcal{E}^*$ *is GAS.*

- Proof uses Lyapunov function and LaSalle's invariance principle.

Special Case

1. there are n "viral epitopes", recognition sites on infected cell, labeled $1, 2, \cdots, n$.
2. each epitope is either "wild-type" 0 or "mutated" 1.
3. CTL cell Z_j recognizes only epitope j if it is not mutated.
4. to each infected cell is associated a sequence $(i_1, i_2, \cdots, i_n) \in \{0,1\}^n$. ($2^n$ infected cell types.)
5. fitness (virus productivity) of infected cell with sequence $(i_1, i_2, \cdots, i_n)$ is $f^d \mathcal{R}_1$, $f \in (0,1)$ where $d = \sum_{j=1}^n i_j$.
6. Z_j targets its epitope at rate independent of infected cell type: $a_{ij} = a_j$.
7. Reproductive number $\mathcal{I}_j$ of Z_j is a_j/ρ_j (attack rate/removal rate).
8. Dominance hierarchy: $\mathcal{I}_1 > \mathcal{I}_2 > \cdots > \mathcal{I}_n$.

example: 2 immune types, 4 infected cell types



Note that:

- y_2 and y_3 have same fitness.
- But y_2 is immune to dominant CTL z_1 while y_3 is not!

Uniform fitness costs for full n-epitope network

Let y_1 be wild strain $(0, 0, \cdots, 0)$ with fitness $\mathcal{R}_1$ and

$$d(y_i, y_1) = |(i_1, i_2, \cdots, i_n)|_{l^1} = p \Rightarrow \mathcal{R}_i = \mathcal{R}_1 f^p, |\Lambda_i| = n - p,\ 1 \le i \le 2^n$$

$$\dot{x} = 1 - x - x \sum_{i=1}^{2^n} \mathcal{R}_i y_i,$$

$$\dot{y}_i = \gamma_i y_i \left(f^p \mathcal{R}_1 x - 1 - \sum_{j \in \Lambda_i} z_j \right),\ 1 \le i \le 2^n,\ d(y_i, y_1) = p \in [0, n]$$

$$\dot{z}_j = \sigma_j \mathcal{I}_j z_j \left(\sum_{i: j \in \Lambda_i} y_i - 1/\mathcal{I}_j \right),\ j = 1, \ldots, n,\ \Lambda_i = \{i_1, \ldots, i_{n-p}\}.$$

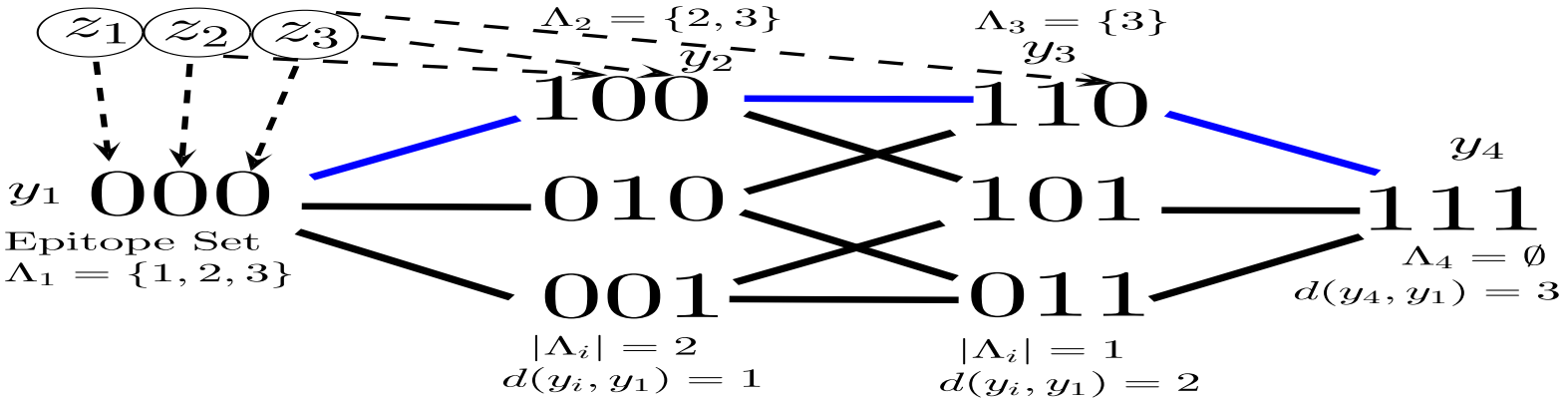
Convergence to perfectly nested network

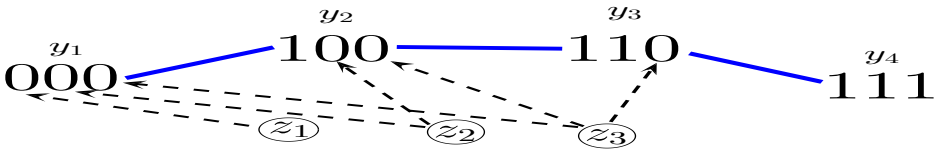
- Under uniform mutational fitness costs, the system of 2^n virus strains converges to a perfectly nested network with less than or equal to $n+1$ persistent virus strains.

Theorem (Full ("hypercube") network $\rightarrow$ Nested network (Browne & H.S. 2018))

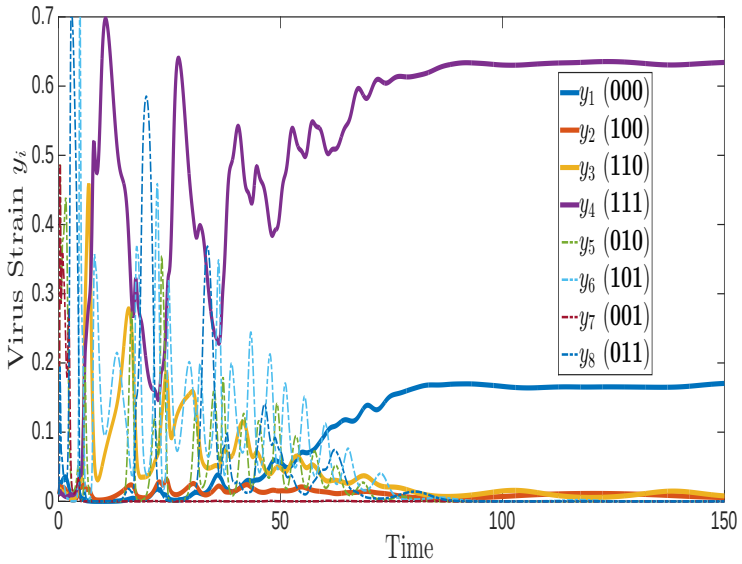
Consider full network on n epitopes ($m = 2^n$) with equal fitness costs and strict immunodominance hierarchy. Suppose y_i, $i \in [1, n+1]$, is indexed so that $\Lambda_i = \{i, \ldots, n\}$ for $i = 1, \ldots, n$, $\Lambda_{n+1} = \emptyset$. Then $y_i(t) \to 0$ as $t \to \infty$ for all $i \in [n+2, 2^n]$, and the results for nested subnetwork hold in full network, i.e. y_i, z_i are uniformly persistent for $1 \le i \le k \le n$ when $\mathcal{R}_k > \mathcal{Q}_k$ (and y_{k+1} is also persistent if $\mathcal{R}_{k+1} > \mathcal{Q}_k$).

Convergence to perfectly nested network

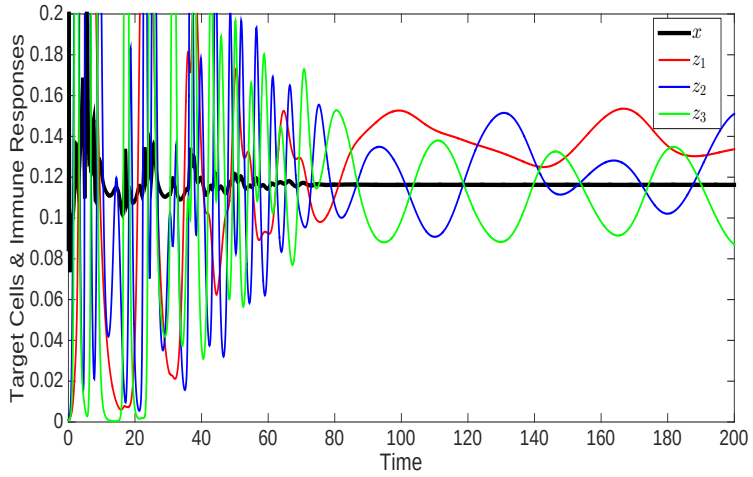




Convergence to nested network: $x(0) = 1,\ y_i(0) = 10^{-2},\ z_j(0) = 10^{-3}$

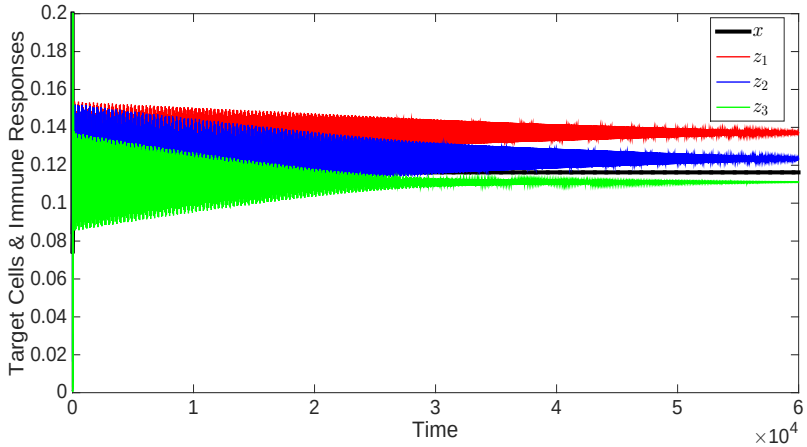


(a) Virus Strains y_i



(b) Immune response z_j

- Example dynamics for $n = 3$ epitopes. Convergence to "nested equilibrium" $\widetilde{\mathcal{E}}_4$ where $y_1, y_2, y_3, y_4, z_1, z_2$ persist.



Virus-immune network models: conclusions & limitations

Conclusions:

- Virus/immune network models motivated by HIV/CTL dynamics & evolution. Can be applied to other complex prey-predator systems, e.g. bacteria/phage.
- Diverse virus “quasi-species” and immune response variant network can be built through viral resistance mutations at multiple epitopes.
- Immunodominance hierarchy most important factor determining escape pathway (network structure).

Limitations:

- Model is deterministic & no explicit mutation.
- Assumptions on interaction rate forms, no intracellular or immune activation delay.

Grazie per l'attenzione

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