Multi-strain virus dynamics with mutations: A global analysis

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Example: HIV infection

HIV infects T-cells (immune cells).

$$T + V \to T^*$$

1. Virus is a retrovirus: it carries single-stranded RNA instead of double-stranded DNA.

2. After infection, viral RNA is copied to DNA which is then integrated into the cell's DNA. This process is error-prone and leads to mutations!

3. Now infected cell starts producing viral proteins, which assemble into new viruses.

4. Utimately, infected cell dies and releases new viruses.

Other examples:

Influenza infects epithelial cells, Malaria parasite infects red blood cells.

Single-strain virusmodel

Standard model (see e.g. Perelson etal, Nowak etal).

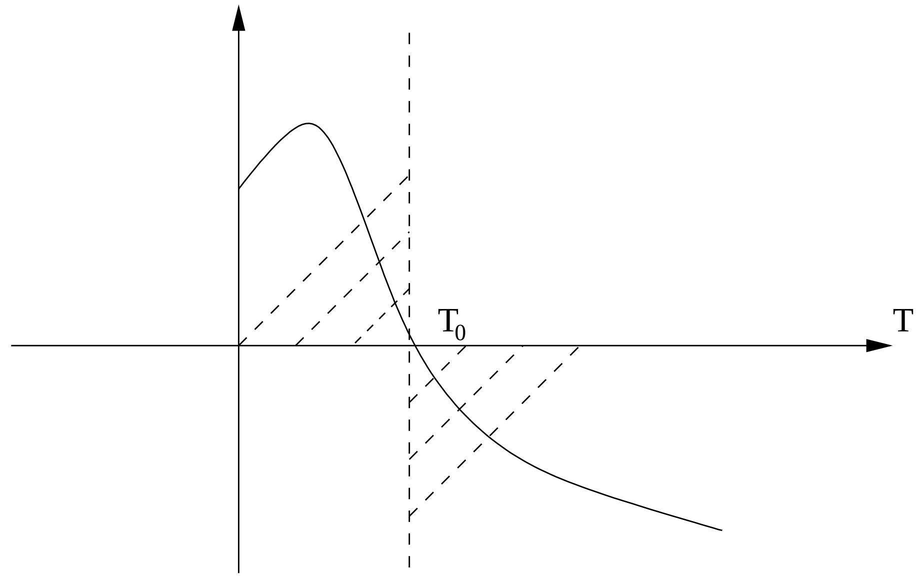
$$
\begin{aligned}
\dot{T} &= f(T) - kVT, \quad \text{healthy T-cells} \\
\dot{T}^* &= kVT - \beta T^*, \quad \text{infected T-cells} \\
\dot{V} &= N\beta T^* - \gamma V, \quad \text{viruses}
\end{aligned}
$$

$f(T)$ is the growth rate of an uninfected population of T-cells.

As it is typically unknown, we only assume a sector condition:

$$
\exists T_0 > 0 : f(T)(T - T_0) < 0, \quad T \neq T_0,
$$

so that $T(t) \to T_0$ as $t \to \infty$ for $\dot{T} = f(T)$.



Examples from literature:

1. Linear: $a - bT$.

2. Logistic: $rT(1 - T/T_{\max})$.

Corrected single-strain virus model

$$
\begin{aligned}
\dot{T} &= f(T) - kVT \\
\dot{T}^* &= kVT - \beta T^* \\
\dot{V} &= N\beta T^* - \gamma V - kVT
\end{aligned}
$$

$-kVT$ in V-equation accounts for loss of virus particle upon infection.

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$-kVT$ in V-equation accounts for loss of virus particle upon infection.

All subsequent results remain valid with or without $-kVT$ term, so we drop it henceforth.

Steady States

1. Disease-free steady state

$$E_0 = (T_0, 0, 0),$$

always exists.

2. A second disease steady state

$$E = (\bar{T}, \bar{T}^*, \bar{V})$$

exists iff basic reproduction number

$$\mathcal{R}^0 := \frac{kN}{\gamma} T_0 = \frac{T_0}{\bar{T}} > 1.$$

Global asymptotic stability

Thm Let E exist and assume sector condition:

$$(f(T) - f(\bar{T}))(T - \bar{T}) \leq 0.$$

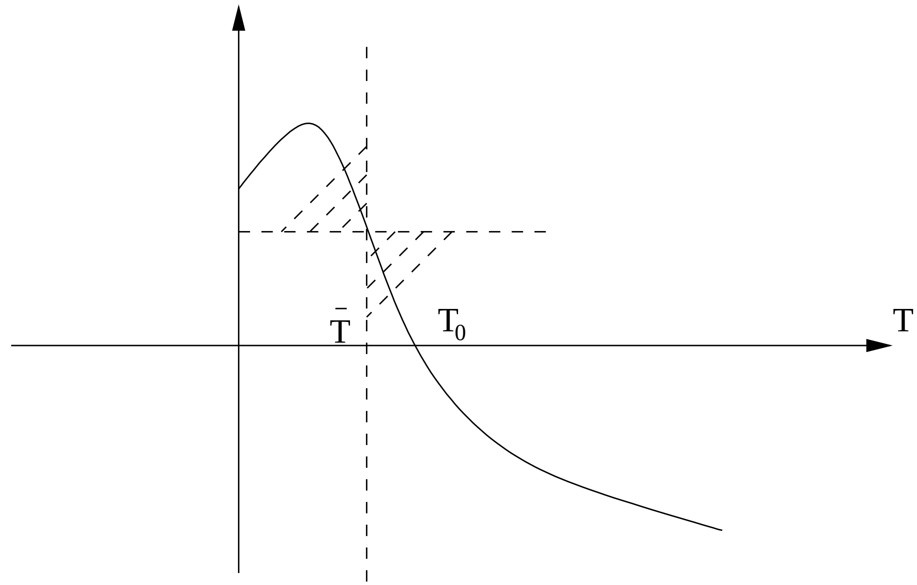
Then E is GAS for IC $T^*(0) + V(0) > 0$.

Pf.

$$W = \int_{\bar{T}}^{T} \left(1 - \frac{\bar{T}}{\tau}\right) d\tau + \int_{\bar{T}^*}^{T^*} \left(1 - \frac{\bar{T}^*}{\tau}\right) d\tau + \frac{\beta}{N\beta} \int_{\bar{V}}^{V} \left(1 - \frac{\bar{V}}{\tau}\right) d\tau.$$

Then $\dot{W} \leq 0$ on $\mathrm{int}(\mathbb{R}^3_+)$. Conclude via Lasalle.

Sector condition



Note: In PDL+Smith, SIAM J Appl Math 64 (2003), 1313-1327, it was shown that stable oscillatory solutions can occur if the sector condition fails (e.g. if $f(T)$ is logistic like in Perelson's standard model, but not if $f(T)$ is linear like in Nowak's model!)

Results there were not based on Lyapunov approach, but on fact that system is 3D competitive dynamical system, for which a Poincaré-Bendixson theory is available.

Multi-strain model without mutations

$$
\begin{aligned}
\dot{T} &= f(T) - \sum_{i=1}^{n} k_i V_i T \\
\dot{T}_i^* &= k_i V_i T - \beta_i T_i^*, \quad i = 1, \ldots, n \\
\dot{V}_i &= N_i \beta_i T_i^* - \gamma_i V_i, \quad i = 1, \ldots, n
\end{aligned}
$$

Steady States: Disease-free E_0 (as before) and n single-strain disease steady states E_i on boundary iff basic reproduction numbers

$$
\mathcal{R}_i^0 := \frac{k_i N_i}{\gamma_i} T_0 = \frac{T_0}{\bar{T}_i} > 1.
$$

Competitive exclusion

Order wlog: $\bar{T}_1 < \bar{T}_2 \leq \cdots \leq \bar{T}_{n-1} \leq \bar{T}_n < T_0$,

Equivalently: $1 < \mathcal{R}_n^0 \leq \mathcal{R}_{n-1}^0 \leq \cdots \leq \mathcal{R}_2^0 < \mathcal{R}_1^0$.

Thm Let all E_i exist and assume sector condition for $\bar{T}_1$:

$$(f(T) - f(\bar{T}_1))(T - \bar{T}_1) \leq 0.$$

Then E_1 is GAS for IC $T_1^*(0) + V_1(0) > 0$.

Pf.

$$\tilde{W} = W + \sum_{i=2}^{n} \left(T_i^* + \frac{1}{N_i} V_i \right).$$

Then $\dot{\tilde{W}} \leq 0$. Conclude via Lasalle.

Including mutations

$$\begin{aligned}\dot{T} &= f(T) - k'VT, \quad T \in \mathbb{R}_+ \\ \dot{T}^* &= KVT - BT^*, \quad T^* \in \mathbb{R}^n_+ \\ \dot{V} &= P(\mu)\hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}^n_+,\end{aligned}$$

where

$$P(\mu) = I + \mu Q, \;\; Q \text{ mutation matrix has 0 column sums.}$$

What happens to the equilibria E_i when $\mu > 0$? (E_0 unaffected)

For small $\mu > 0$, they still exist assuming hyperbolicity (e.g. when $f'(\bar{T}_i) \leq 0$) by the Implicit Function Theorem.

But, are they still in closed orthant? More careful analysis required; Q plays key role.

Define: $A(\mu) = \Gamma^{-1}\hat{N}P(\mu)K$, non-negative matrix, and wlog rewrite (by relabeling indices):

$$A(\mu) = \begin{pmatrix} A_1(\mu) & 0 & \dots & 0 \\ \mu B_{2,1} & A_2(\mu) & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \mu B_{k,1} & \mu B_{k,2} & \dots & A_k(\mu) \end{pmatrix},$$

where each diagonal block $A_i(\mu)$ is irreducible.

[Recall that $X \in \mathbb{R}^{n\times n}$ is irreducible iff its digraph (n nodes, directed edge $i \to j$ iff $X_{ji} \neq 0$) is strongly connected.]

Note: For $\mu = 0$, $A(0) = \Gamma^{-1}\hat{N}K$ is diagonal with (shuffled) diagonal entries:

$$0 < \frac{1}{\bar{T}_n} < \frac{1}{\bar{T}_{n-1}} < \cdots < \frac{1}{\bar{T}_1},$$

Def: strain group j is reachable from strain group $i < j$ if

$\exists$ nonzero $B_{k_1 k_2}, B_{k_2 k_3}, \ldots, B_{k_{l-1} k_l}$ with $i = k_1 < \cdots < k_l = j$.

For small $\mu > 0$, by continuity of $\sigma\left(A(\mu)\right) = \cup_i \sigma\left(A_i(\mu)\right)$:

$$0 < \frac{1}{\tilde{T}_n(\mu)} < \frac{1}{\tilde{T}_{n-1}(\mu)} < \cdots < \frac{1}{\tilde{T}_1(\mu)}, \quad \tilde{T}_i(0) = \bar{T}_i.$$

Prop 1

1. $A(\mu)$ has eigenvector $(v_1, v_2, ..., v_k) > 0$ iff $\frac{1}{\tilde{T}_1(\mu)}$ is dominant eigenvalue of $A_1(\mu)$, and all strain groups $j \geq 2$ are reachable from strain group 1;

2. $A(\mu)$ has an eigenvector $(v_1, v_2, ..., v_k) \geq 0$ for each eigenvalue $\frac{1}{\tilde{T}_r(\mu)}$ for which $\frac{1}{\tilde{T}_r(\mu)}$ is a dominant eigenvalue of some $A_i(\mu)$, and $s(A_j(\mu)) < \frac{1}{\tilde{T}_r(\mu)}$ for all $j = i+1, ..., k$ such that strain group j is reachable from strain group i; $v_j > 0 (= 0)$ if group j is reachable (not reachable) from strain group i.

3. All other eigenvectors of $A(\mu)$, $\mu > 0$ are not sign definite.

Prop 2

1. $E_j(\mu) > 0$ iff $\frac{1}{\tilde{T}_j(\mu)}$ is eigenvalue of $A(\mu)$ with eigenvector > 0.

2. $E_j(\mu) \geq 0$ iff $\frac{1}{\tilde{T}_j(\mu)}$ is eigenvalue of $A(\mu)$ with eigenvector ≥ 0.

3. $E_j(\mu) \notin \mathbb{R}_+^{2n+1}$ iff $\frac{1}{\tilde{T}_j(\mu)}$ is eigenvalue of $A(\mu)$ with eigenvector which is not sign-definite.

Note that $E_1(\mu)$ always persists, either > 0, or ≥ 0.

Not surprisingly, our next question will be whether it is still GAS.

But first, some examples...

Examples of extreme cases

1. Q irreducible $\Leftrightarrow A(\mu)$ irreducible as well:

Then by the Perron-Frobenius Thm, $A(\mu)$ has dominant eigenvalue $1/\tilde{T}_1(\mu)$ with positive eigenvector; there are no other non-negative eigenvectors.

Then $E_1(\mu) > 0$ is only remaining non-negative steady state for $\mu > 0$.

So only E_1 persists, others disappear.

Interpretation: Q irreducible means that every strain type can mutate (directly or indirectly) to any other strain type.

Examples of extreme cases (cont.)

2. Q is lower triangular $\Leftrightarrow A(\mu)$ lower triangular as well:

If diagonal entries of $A(\mu)$ are arranged in decreasing order, and for each pair $i < j$, j is reachable from i, then $E_1(\mu) > 0$ and $E_k(\mu) \geq 0$ for $k = 2, \ldots, n$.

So all steady states persist.

Ex:

$$A(\mu) = \begin{pmatrix} \tilde{T}_1^{-1}(\mu) & 0 & 0 & \ldots & 0 \\ + & \tilde{T}_2^{-1}(\mu) & 0 & \ldots & 0 \\ 0 & \ddots & \ddots & \ldots & \vdots \\ \vdots & \ldots & \ddots & \ddots & \vdots \\ 0 & 0 & \ldots & + & \tilde{T}_n^{-1}(\mu) \end{pmatrix}$$

Interpretation: This means that strain type i can only mutate (directly or indirectly) to "downstream" strain types $j > i$.

Mutation is "uni-directional".

Main result

$$\begin{aligned}
\dot{T} &= f(T) - k'VT, \quad T \in \mathbb{R}_+ \\
\dot{T}^* &= KVT - BT^*, \quad T^* \in \mathbb{R}^n_+ \\
\dot{V} &= P(\mu)\hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}^n_+,
\end{aligned}$$

Let

$$\bar{T}_1 < \bar{T}_2 < \cdots < \bar{T}_{n-1} < \bar{T}_n < T_0,$$

$$(f(T) - f(\bar{T}_1))(T - \bar{T}_1) \le 0, \;\; f'(\bar{T}_1) \le 0$$

and

$$U = \{(T, T^*, V) \in \mathbb{R}^{2n+1}_+ | \;\; T^*_1 + V_1 > 0\}$$

Main result (cont.)

Thm

$$\exists \mu_0 > 0, \quad E_1(\mu) \in C([0, \mu_0] \to U) :$$

1. $E_1(\mu)$ is steady state for all $\mu \in [0, \mu_0]$ with $E_1(0) = E_1$.

2. $E_1(\mu)$ is GAS for IC in U.

Proof requires use of a perturbation result of the GAS + hyperbolic steady state E_1 for unperturbed system where $\mu = 0$, see:

Smith and Waltman, Perturbation of a globally stable steady state, Proc. AMS 127 (1999), 447-453.