Multi-strain virus dynamics with mutations: A global analysis

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Example: HIV infection

HIV infects T-cells (immune cells).

\[ T + V \rightarrow T^* \]

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. Ultimately, infected cell dies and releases new viruses.

Other examples:

Influenza infects epithelial cells, Malaria parasite infects red blood cells.
Single-strain virus model

Standard model (see e.g. Perelson et al, Nowak et al).

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

\(f(T)\) 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 \(T(t) \rightarrow T_0\) as \(t \rightarrow \infty\) for \(\dot{T} = f(T)\).
Examples from literature:

1. Linear: $a - bT$.

2. Logistic: $rT(1 - T/T_{\text{max}})$.
Corrected single-strain virus model

\[
\begin{align*}
\dot{T} &= f(T) - kVT \\
\dot{T}^* &= kVT - \beta T^* \\
\dot{V} &= N\beta T^* - \gamma V - kVT
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\(-kVT\) 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

\[ R^0 := \frac{kN}{\gamma} T_0 = \frac{T_0}{\bar{T}} > 1. \]
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 $\text{int}(\mathbb{R}_+^3)$. Conclude via Lasalle.
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

\[
\dot{T} = f(T) - \sum_{i=1}^{n} k_i V_i T
\]
\[
\dot{T}_i^* = k_i V_i T - \beta_i T_i^*, \quad i = 1, \ldots, n
\]
\[
\dot{V}_i = N_i \beta_i T_i^* - \gamma_i V_i, \quad i = 1, \ldots, n
\]

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

\[
\mathcal{R}_i^0 := \frac{k_i N_i}{\gamma_i} T_0 = \frac{T_0}{T_i} > 1.
\]
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.**

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

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

\[
\dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+ \\
\dot{T^*} = KVT - BT^*, \quad T^* \in \mathbb{R}_+^n \\
\dot{V} = P(\mu) \hat{N} BT^* - \Gamma V, \quad V \in \mathbb{R}_+^n,
\]

where

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

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 \( f'(\tilde{T}_i) \leq 0 \)) 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):

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

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 \( i \rightarrow j \) 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

\[ \exists \text{ nonzero } B_{k_1 k_2}, B_{k_2 k_3}, \ldots, B_{k_{l-1} k_l} \text{ with } i = k_1 < \cdots < k_l = j. \]
For small $\mu > 0$, by continuity of $\sigma (A(\mu)) = \bigcup_i \sigma (A_i(\mu))$:

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

**Prop 1**

1. $A(\mu)$ has eigenvector $(v_1, v_2, \ldots, v_k) > 0$ 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 $(v_1, v_2, \ldots, v_k) \geq 0$ 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 $j = i + 1, \ldots, k$ 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 \( \frac{1}{T_j(\mu)} \) is eigenvalue of \( A(\mu) \) with eigenvector \( > 0 \).

2. \( E_j(\mu) \geq 0 \) iff \( \frac{1}{T_j(\mu)} \) is eigenvalue of \( A(\mu) \) with eigenvector \( \geq 0 \).

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

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

Not surprisingly, our next question will be whether it is still GAS. But first, some examples...
Examples of extreme cases

1. $Q$ irreducible $\iff A(\mu)$ 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 \( \iff A(\mu) \) 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:

\[
A(\mu) = \begin{pmatrix}
\tilde{T}_1^{-1}(\mu) & 0 & 0 & \cdots & 0 \\
+ & \tilde{T}_2^{-1}(\mu) & 0 & \cdots & 0 \\
0 & \cdots & \cdots & \cdots & \vdots \\
\vdots & \cdots & \cdots & \cdots & \vdots \\
0 & 0 & \cdots & + & \tilde{T}_n^{-1}(\mu)
\end{pmatrix}
\]

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

Mutation is “uni-directional”.

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Main result

\[ \dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+ \]
\[ \dot{T}^* = KVT - BT^*, \quad T^* \in \mathbb{R}_+^n \]
\[ \dot{V} = P(\mu)\hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}_+^n, \]

Let

\[ \bar{T}_1 < \bar{T}_2 < \cdots < \bar{T}_{n-1} < \bar{T}_n < T_0, \]
\[ (f(T) - f(\bar{T}_1))(T - \bar{T}_1) \leq 0, \quad f'(\bar{T}_1) \leq 0 \]

and

\[ U = \{(T, T^*, V) \in \mathbb{R}_+^{2n+1} | \ T_1^* + V_1 > 0\} \]
Main result (cont.)

**Thm**

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

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: