Two-level Evolution of Chronic Viral Infections and the Effect of the Population-level Control

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Introduction and Motivation

- Chronic viral infection can persist in an infected person for years.
- During this time the virus evades the host's immune system by evolving new phenotypes (cf. HIV).
- New strains can be *transmitted*.
- Treatment/prophylaxis introduce additional evolutionary pressure, facilitating appearance of new, *resistant* virus strains.

Introduction and Motivation

We aim at

developing a unified framework for modeling and analyzing the interplay between local, within-host mutation dynamics and global, population-level distribution of different virus strains while taking into account the effects of treatment and prophylaxis.

At this stage we

- consider two models: a *baseline* and an *extended* one;
- compute the equilibrium distribution of virus strains;
- characterize the effect of using therapeutic and prophylactic controls;
- carry out extensive numerical analysis.

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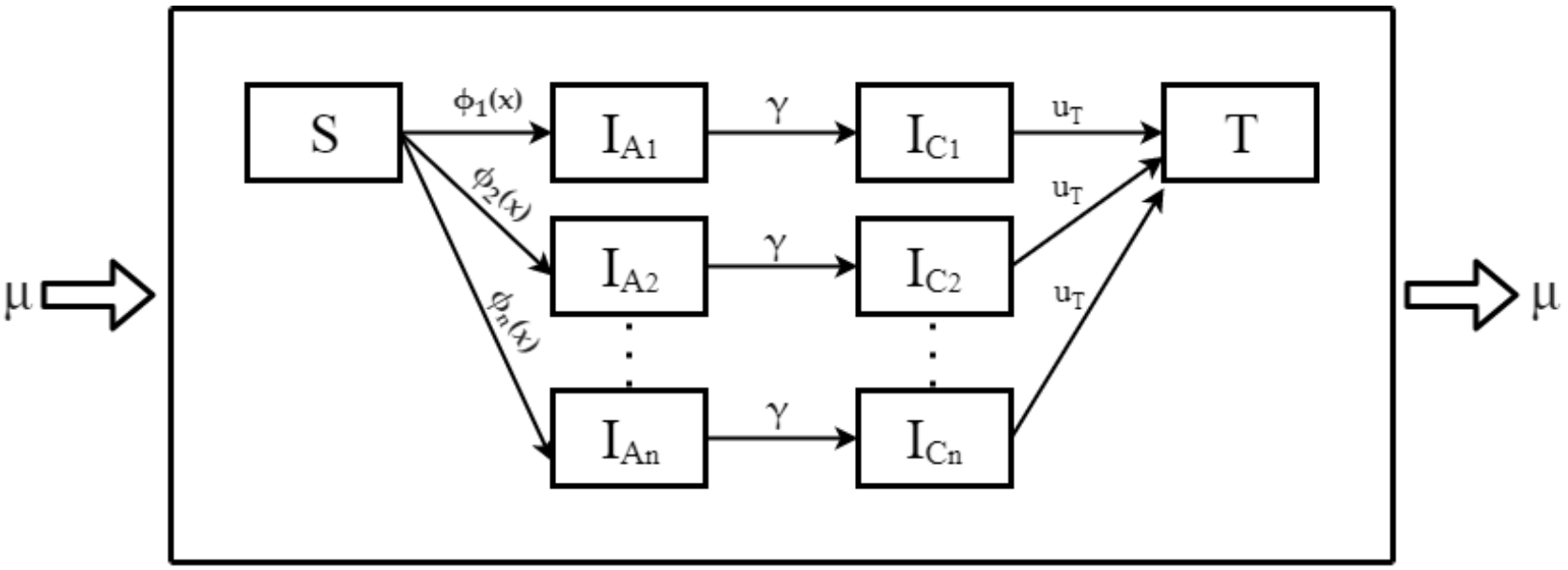
Baseline model



$$\dot{I}_{Ai} = \phi_i(X)S - \gamma I_{Ai} - \mu I_{Ai}$$

$$\dot{I}_{Ci} = \gamma I_{Ai} - u_T I_{Ci} - \mu I_{Ci}$$

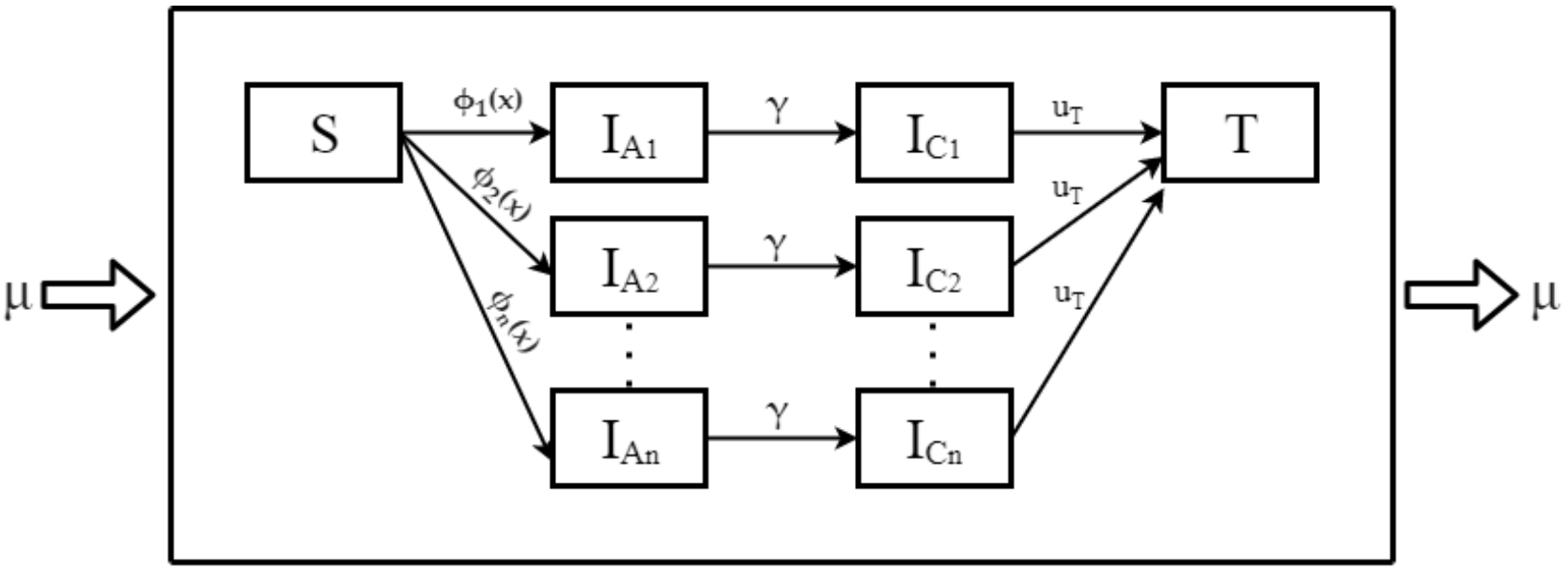
$$\dot{T} = u_T \sum_{i=1}^{n} I_{Ci} - \mu T$$

$$\dot{S} = \mu - \sum_{i=1}^{n} \phi_i(X)S - \mu S$$

- Genotypic variability.
- No phenotypic variability
- Transmission rate:

$$\phi_i(X) = \beta_C \left(\xi I_{Ai} + \sum_{j=1}^{n} \alpha_{ij} I_{Cj} \right)$$

Baseline model



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Baseline model

$$\dot{I}_{\mathrm{A}i} = \phi_i(X)S - \gamma I_{\mathrm{A}i} - \mu I_{\mathrm{A}i}$$

$$\dot{I}_{\mathrm{C}i} = \gamma I_{\mathrm{A}i} - u_{\mathrm{T}} I_{\mathrm{C}i} - \mu I_{\mathrm{C}i}$$

$$\dot{T} = u_{\mathrm{T}} \sum_{i=1}^{n} I_{\mathrm{C}i} - \mu T$$

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- Transmission rate:

$$\phi_i(X) = \beta_{\mathrm{C}} \left(\xi I_{\mathrm{A}i} + \sum_{j=1}^{n} \alpha_{ij} I_{\mathrm{C}j} \right)$$

Mutation coefficients α_{ij}

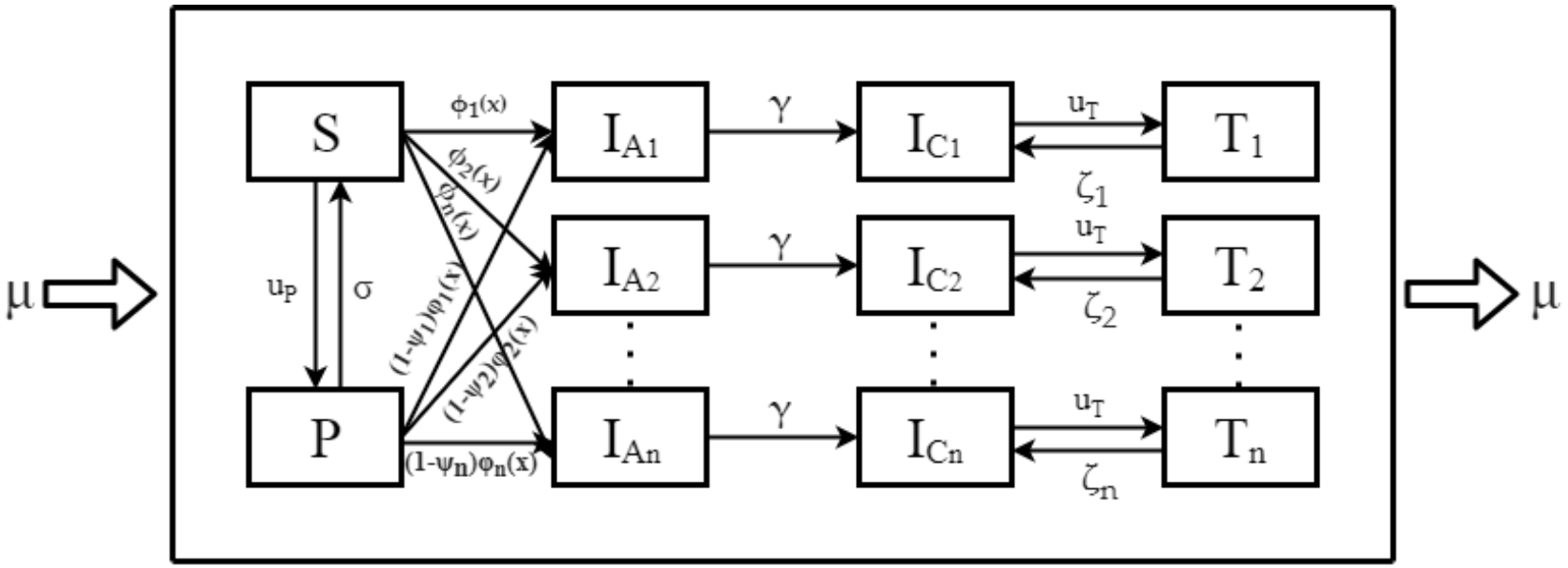
$\alpha_{ij} \in [0, 1]$ denotes the average fraction of type i viruses in the viral population of an individual initially infected by the type j virus.

A1. $\sum_{i=1}^{n} \alpha_{ij} = 1$ for all $j = 1, \ldots, n$.

A2. $\alpha_{ii} \neq 0$ for all $i = 1, \ldots, n$.

$\mathrm{A} = [\alpha_{ij}]_{i,j=1,\ldots,n}$ is a *column stochastic matrix*.

Extended model



$$\dot{I}_{\mathrm{A}i} = \phi_i(X)S + (1-\psi_i)\phi_i(X)P - \gamma I_{\mathrm{A}i} - \mu I_{\mathrm{A}i}$$

$$\dot{I}_{\mathrm{C}i} = \gamma I_{\mathrm{A}i} + \zeta_i T_i - u_{\mathrm{T}} I_{\mathrm{C}i} - \mu I_{\mathrm{C}i}$$

$$\dot{T}_i = u_{\mathrm{T}} I_{\mathrm{C}i} - \zeta_i T_i - \mu T_i$$

$$\dot{S} = \mu - u_{\mathrm{P}} S - \sum_{i=1}^{n} \phi_i(X)S + \delta P - \mu S$$

$$\dot{P} = u_{\mathrm{P}} S - \sum_{i=1}^{n} (1-\psi_i)\phi_i(X)P - \delta P - \mu P$$

- Phenotypic variability:
  - Variable contagiousness;
  - Variable resistance to prophylactic measures;
  - Variable resistance to therapeutic measures.

Extended model

Using matrix notation we write down $3n + 2$ DEs

$$
\begin{aligned}
\dot{\mathrm{I}}_A &= \mathrm{B_C}\,(\xi\,\mathrm{I}_A + \mathrm{A}\,\mathrm{I_C})\,S + \mathrm{B_C}\,(\mathrm{E} - \Psi)\,(\xi\,\mathrm{I_A} + \mathrm{A}\,\mathrm{I_C})\,P - (\gamma + \mu)\,\mathrm{I_A} \\
\dot{\mathrm{I}}_\mathrm{C} &= \gamma\,\mathrm{I}_A + \mathrm{Z}\mathrm{T} - (u_T + \mu)\,\mathrm{I_C} \\
\dot{\mathrm{T}} &= u_\mathrm{T}\,\mathrm{I_C} - (\mu\,\mathrm{E} + \mathrm{Z})\,\mathrm{T} \\
\dot{S} &= \mu + \delta P - \mathbf{1}_{[1\times n]}\,\mathrm{B_C}\,(\xi\,\mathrm{I_A} + \mathrm{A}\,\mathrm{I_C})\,S - (u_\mathrm{P} + \mu)S \\
\dot{P} &= u_\mathrm{P} S - \mathbf{1}_{[1\times n]}\,\mathrm{B_C}\,(\mathrm{E} - \Psi)\,(\xi\,\mathrm{I_A} + \mathrm{A}\,\mathrm{I_C})\,P - (\delta + \mu)P,
\end{aligned}
$$

where

$$
\mathrm{I}_A = \begin{bmatrix} I_{A1} \\ \vdots \\ I_{An} \end{bmatrix} \text{ (same } \mathrm{I_C}, \mathrm{T}\text{), and } \mathrm{B_C} = \begin{bmatrix} \beta_{\mathrm{C}1} & & 0 \\ & \ddots & \\ 0 & & \beta_{\mathrm{C}n} \end{bmatrix} \text{ (same } \mathrm{Z}, \Psi\text{).}
$$

Baseline model: R_0

Basic reproduction number

For any choice of parameters $\alpha_{ij} \geq 0$ such that $\sum_i \alpha_{ij} = 1$ and $\alpha_{ii} \neq 0$ for all $i, j = 1, \ldots, n$, the *controlled* basic reproduction number for the baseline system is given by

$$R_0(u_{\mathrm{T}}) = \beta_{\mathrm{C}} \frac{\xi(u_{\mathrm{T}} + \mu) + \gamma}{(\gamma + \mu)(u_{\mathrm{T}} + \mu)}.$$

Sensitivity coefficient: R_1

$$R_0(u_{\mathrm{T}}) = R_0 + R_1^T u_{\mathrm{T}} + \mathcal{O}(u_{\mathrm{T}}^2) \qquad : \text{see } ([a])$$

$$\approx \beta_{\mathrm{C}} \frac{\xi\mu + \gamma}{(\gamma + \mu)\mu} - \frac{\beta_{\mathrm{C}}\gamma}{\mu^2 (\gamma + \mu)} u_{\mathrm{T}}.$$

[a] *DG, Bulla, Romero-Severson*, Systematic evaluation..., **JTB**, Vol. 462, 2019.

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Baseline model: X_{EE}

Endemic equilibrium

Let A be an irreducible non-negative column stochastic matrix s. t. $\alpha_{ii} \neq 0$ for all $i = 1, ..., n$. Then the endemic equilibrium for the baseline syst. exists and is unique if $R_0 > 1$.

Let, furthermore, $v^\top = [v_1, \ldots, v_n]$ be the normalized right dominant eigenvector of A satisfying $\sum_{i=1}^{n} v_i = 1$. The components of the endemic equilibrium state are given by

$$I^*_{\mathrm{A}i} = \frac{\mu}{(\gamma+\mu)}\left(1 - \frac{1}{R_0}\right) v_i, \quad I^*_{\mathrm{C}i} = \frac{\gamma\mu}{(\gamma+\mu)(u_{\mathrm{T}}+\mu)}\left(1 - \frac{1}{R_0}\right) v_i,$$

$$T^* = \frac{\gamma u}{(\gamma+\mu)(u_{\mathrm{T}}+\mu)}\left(1 - \frac{1}{R_0}\right), \qquad S^* = \frac{1}{R_0}.$$

Extended model: R_0

Basic reproduction number

The controlled basic reproduction number of the extended system is given by

$$R_0(u_{\mathrm{T}}, u_{\mathrm{P}}) = \frac{\bar{\beta}_{\mathrm{C}}(\gamma + \xi\mu)}{(\gamma+\mu)\mu}\rho\left(Q(u_{\mathrm{P}})N(u_{\mathrm{T}})\right),$$

where $\bar{\beta}_{\mathrm{C}} = \max_i \beta_{\mathrm{C}i}$,

$$\bar{\mathrm{B}}_{\mathrm{C}} = \bar{\beta}_{\mathrm{C}}^{-1}\,\mathrm{B}_{\mathrm{C}},$$

$$Q(u_{\mathrm{P}}) = \bar{\mathrm{B}}_{\mathrm{C}}\,[\,\mathrm{E}_n - P_{DFE}(u_{\mathrm{P}})\Psi],$$

$$N(u_{\mathrm{T}}) = \tfrac{1}{\gamma+\xi\mu}\,[\xi\mu\,\mathrm{E}_n + \gamma\,\mathrm{A}\Delta(u_{\mathrm{T}})], \text{ and}$$

$$\Delta(u_{\mathrm{T}}) = (\,\mathrm{Z} + (\mu + u_{\mathrm{T}})\,\mathrm{E}_n)^{-1}(\,\mathrm{Z} + \mu\,\mathrm{E}_n).$$

Extended model: Sensitivity analysis

Sensitivity coefficients R_1^T and R_1^P

Let A be irreducible and let w_0 and v_0 be the right and the left dominant eigenvectors of $Q(0)N(0) = \bar{\mathrm{B}}_{\mathrm{C}}\,\bar{\mathrm{A}}$, corresponding to $\rho\left(\bar{\mathrm{B}}_{\mathrm{C}}\,\bar{\mathrm{A}}\right)$ and normalized such that $w_0^\top v_0 = 1$. The controlled basic reproduction number $R_0^\beta(u_{\mathrm{T}}, u_{\mathrm{P}})$ can be written as

$$R_0^\beta(u_{\mathrm{T}}, u_{\mathrm{P}}) = R_0^\beta + R_{1,\mathrm{T}}^\beta u_{\mathrm{T}} + R_{1,\mathrm{P}}^\beta u_{\mathrm{P}} + \mathcal{O}(\|(u_{\mathrm{T}}, u_{\mathrm{P}})\|^2), \qquad (1)$$

where $R_0^\beta = \frac{\bar{\beta}_{\mathrm{C}}(\gamma+\xi\mu)}{(\gamma+\mu)\mu}\rho(\bar{\mathrm{B}}_{\mathrm{C}}\,\bar{\mathrm{A}})$,

$$R_{1,\mathrm{T}}^\beta = -w_0^\top\left[R_0^\beta\,\mathrm{E}_n - \frac{\xi}{(\gamma+\mu)}\,\mathrm{B}_{\mathrm{C}}\right](\mathrm{Z} + \mu\,\mathrm{E}_n)^{-1}v_0, \text{ and}$$

$$R_{1,\mathrm{P}}^\beta = -R_0^\beta\frac{1}{(\delta+\mu)}w_0^\top\Psi v_0.$$

Two controls: which one is more efficient?

Simplified model: no variability in transmission rates

Assume $\mathrm{B_C} = \beta_{\mathrm{C}}\,\mathrm{E}_n$. The control u_{T} is locally more efficient than u_{P} if it holds that

$$\frac{\gamma}{\gamma+\xi\mu} w_0^\top (\,\mathrm{Z} + \mu\,\mathrm{E}_n)^{-1} v_0 > \frac{1}{(\delta+\mu)} w_0^\top \Psi v_0. \qquad (*)$$

Note: $\tau_i = 1/(\zeta_i + \mu)$ and $\pi = 1/(\delta+\mu)$ are the average duration of being either on treatment or on prophylaxis and recall that $w_0^\top = [1, \ldots, 1]$. Then we can write $(*)$ as

$$\sum_i \frac{\gamma}{\gamma+\xi\mu} \tau_i v_{0i} > \sum_i \psi_i \pi v_{0i}.$$

Protection conferred by treatment/prophylaxis against the ith strain.

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Two controls: which one is more efficient?

Full scale model

u_{T} is locally more efficient than u_{P} if

$$\sum_i \left[1 - \frac{\beta_{\mathrm{A}i}\theta_{\mathrm{A}}}{R_0^{\beta}}\right] \tau_i w_{0i} v_{0i} > \sum_i \psi_i \pi w_{0i} v_{0i},$$

where $\theta_{\mathrm{A}} = 1/(\gamma + \mu)$ is the average duration of the acute stage.

The parameters $R^{\beta}_{1,\mathrm{T}}$ and $R^{\beta}_{1,\mathrm{P}}$ are the sum of products *average duration of the medical intervention* $\times$ *protection conferred by the intervention* taken with the weights corresponding to the stationary distribution of the virus strains.

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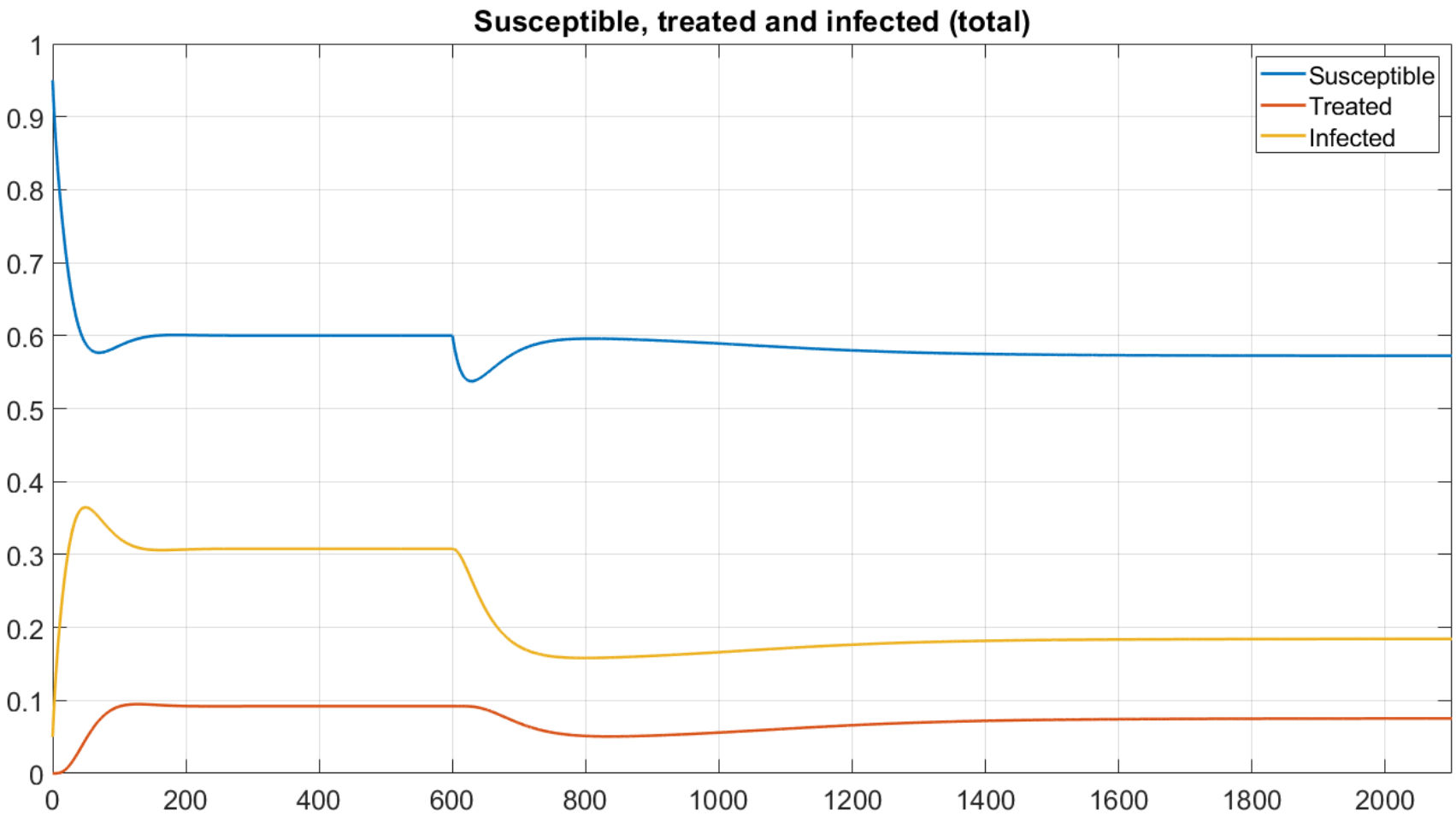
Numerical results: Setup

We consider a model where

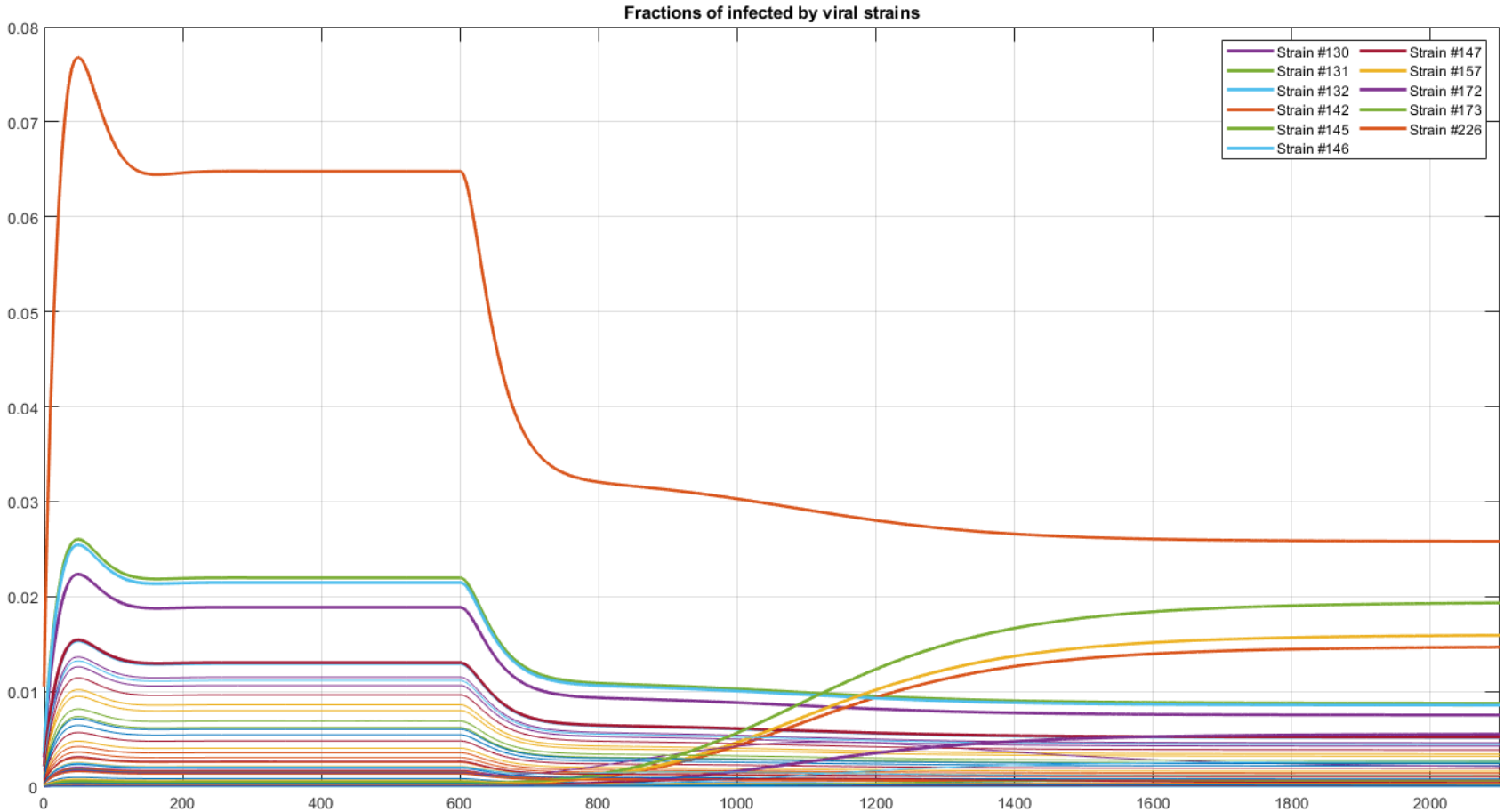
- 226 virus strains,
- 4 infection stages: 1 acute and 3 chronic,
- infected either develop or not develop their own antibodies,
- 5 levels of prophylaxis depending on the concentration of the aB in the blood,
- people on prophylaxis can get infected as well, although at reduced (and strain-dependent) rate.

In total, there are 4076 DEs.

Numerical results



Numerical results: distribution of strains



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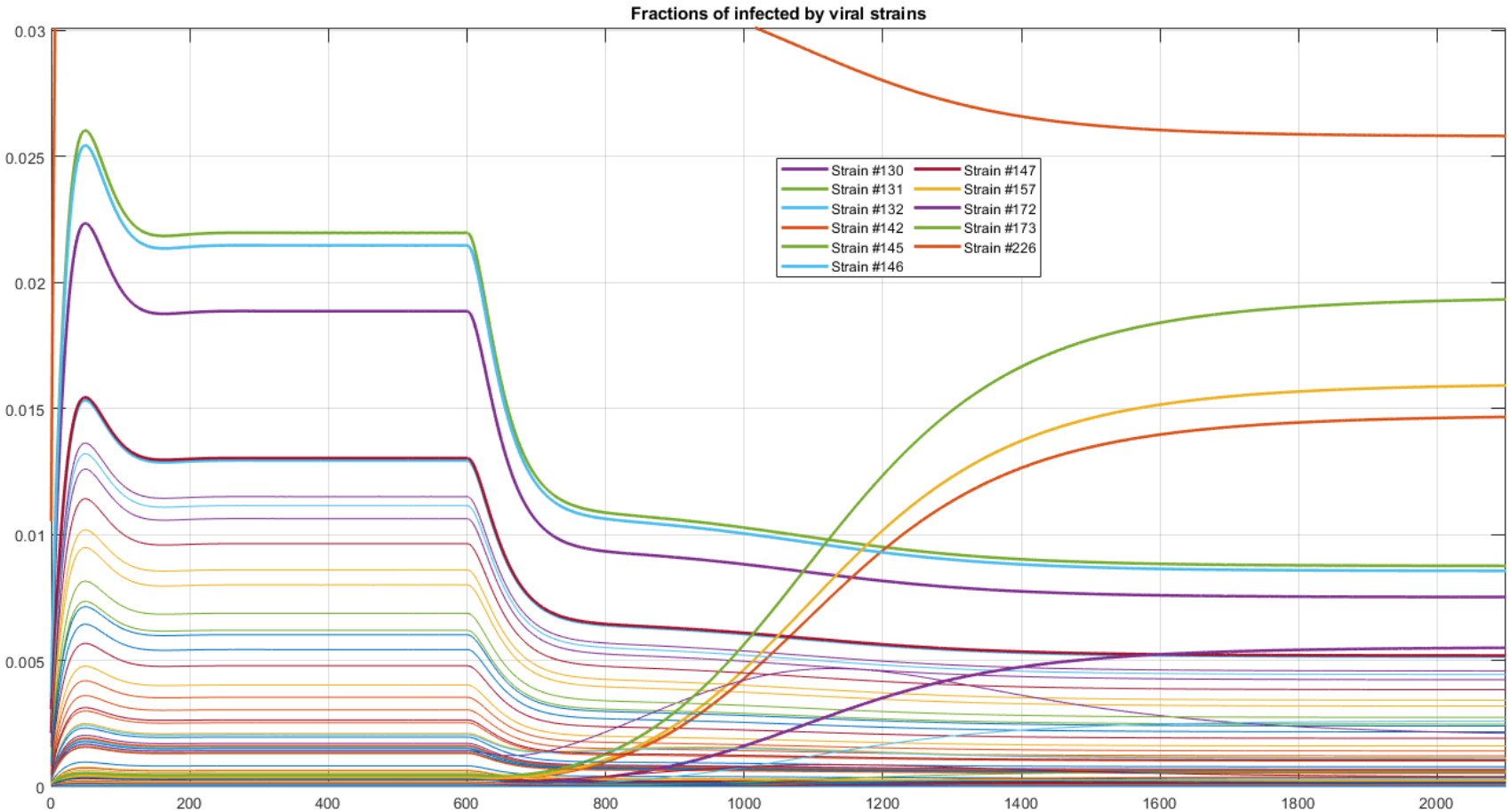

Conclusions

There are a number of issues to be resolved:

- Classification of virus strains
- Determining the mutation probabilities:
  - averaged Markov model evolution? transition rates?
  - estimation of the evolutionary distance, ...
- Protection given by prophylaxis:
  - strain-specific protection,
  - pharmacokinetics, etc...

Conclusions

- Gromov, Romero-Severson, Within-host phenotypic evolution and the population-level control of chronic viral infections by treatment and prophylaxis. *Submitted,* Oct. 2019. Available on `arXiv.org`
- Romero-Severson, Gromov, Wagh, Korber, Broadly neutralizing antibodies for HIV prevention. . . , *In preparation*, 2020.

Conclusions

Thank you!