Modelling the evolutionary and epidemiological dynamics of influenza outbreaks

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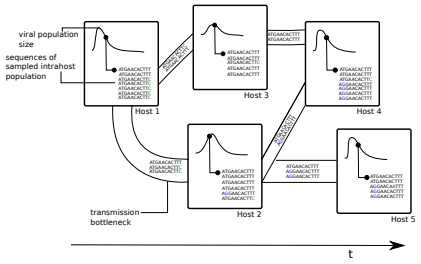
1. INTRODUCTION

- The rapid evolution of influenza viruses causes their epidemiological and evolutionary dynamics to occur on the same timescale.
- We develop a model of viral evolution that unifies dynamics on both scales, given genetic data taken from within-host viral populations from infected hosts sampled during an epidemic.

2. INTRA- AND INTER-HOST DYNAMICS



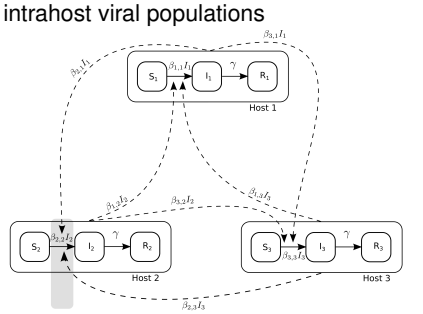
3. MULTISCALE MODEL

- The within-host viral phylogeny, while shaped by host immunity and population genetic processes for the duration of the infection, is additionally affected by transmission bottlenecks and the host's position in the transmission chain
- Transmission between hosts is dependent on the genetic diversity that is generated within-host.

4. MODEL

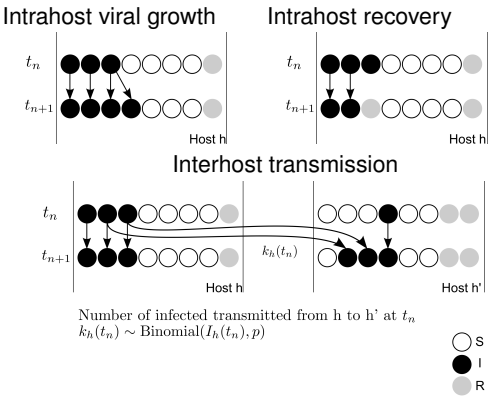
Viral population size changes according to stochastic SIR epidemic process

(a) Compartmental model for evolution of intrahost viral populations



The within-host infection rate $S_h \to I_h$ depends on the infected population sizes of all hosts

(b) Events

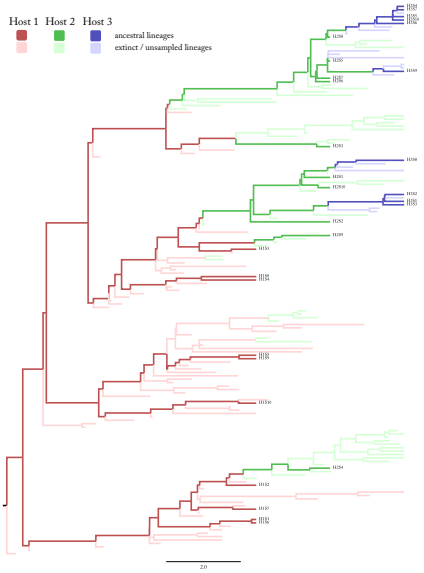


(c) Transition probabilities

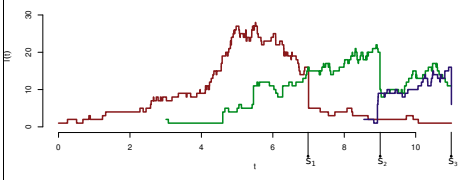
$$P(\Delta S_h(t) = i, \Delta I_h(t) = j \mid S_1(t), I_1(t), ..., S_{N_h}(t), I_{N_h}(t))$$
$$= \begin{cases} \frac{\beta_{h,h'}}{N} S_h(t) I_{h'}(t) \Delta t + o(\Delta t), & h = h' : (i,j) = (-1,1) \\ & h \neq h' : (i,j) = (-k_{h'}(t), k_{h'}(t)) \\ & h' \in \{1, ..., N_h\} \\ \gamma I_h(t) \Delta t + o(\Delta t), & (i,j) = (0,-1) \\ 1 - (\sum_k \frac{\beta_{h,k}}{N} S_h(t) I_k(t) \Delta t & \\ + \gamma I_h(t) \Delta t) + o(\Delta t), & (i,j) = (0,0) \end{cases}$$

The intrahost population trajectories are simulated via the Gillespie algorithm.

(d) Ancestral tree of intrahost viral sequences



(e) Infected population size trajectories



- We assume a multi-scale viral metapopulation representing the demographic structure of the host population and the in-host structure
- Each host contains N cells which follow stochastic SIR dynamics (a, b, c), where $I_h(t)$ represents the viral population size in host h
- An infection event (within or between hosts) corresponds to the splitting of a lineage in the viral phylogeny (b)
- This process generates an underlying ancestral tree $\mathcal{G}$ of sequences sampled from the within-host viral populations (e.g. (d)) shaped by a demographic history (e.g. (e)) generated by (a,b,c)
- The tree likelihood with mutation model parameters μ and sequence data $\mathcal{D}$: $P(\mathcal{D} \mid \mathcal{G}, \mu) = \sum_{\mathcal{D}_A \in \mathbf{D}_A} \prod_{\{i,j\} \in e} \prod_{l=1}^{L} [\mathrm{e}^{(-\mathbf{Q}\mu |e_{ij}|)}]_{D_{i,l}, D_{j,l}}$

5. INFERENCE

Parameters:
Ancestral tree:
$\Theta_G = \{\gamma, \boldsymbol{\beta}, p, \mathcal{T}\}$
Mutation model: μ
where γ is the removal rate, $\boldsymbol{\beta}$ is a matrix of transmission / infection rates, p is the bottleneck size parameter, $\mathcal{T}$ is the topology of the tree, and μ is the mutation rate.

Bayesian MCMC scheme with ABC step to sample parameters given sequences $\mathcal{D}$, in host partitions $\mathbf{P}$, sampled at times $\mathbf{S}$:
$p(\Theta_G, \mu, \mathcal{G} | \mathcal{D}, \mathbf{P}, \mathbf{S}, N) \propto p(\mathcal{D} \mid \mathcal{G}, \mu) p(\mathcal{G} \mid \Theta_G, \mathbf{P}, \mathbf{S}, N) p(\mu) p(\Theta_G)$
To update Θ_G, we use an approximate method:

- Propose a move $\Theta'_G \leftarrow \Theta_G$
- Simulate $\mathcal{G}^*$ given $\Theta'_G, \mathbf{P}, \mathbf{S}, N$ as in (4)
- Calculate distance $\rho(\mathcal{G}, \mathcal{G}^*)$
- IF $\rho(\mathcal{G}, \mathcal{G}^*) \leq \epsilon$
- Accept Θ'_G with probability $\alpha = \min\left(1, \frac{p(\Theta'_G)}{p(\Theta_G)}\right)$.

6. ONGOING WORK

- Optimising and running the model on within-host viral populations sampled from horses during an equine influenza outbreak in Newmarket, UK

7. ACKNOWLEDGEMENTS

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