Accurate stochastic simulation algorithm for multiscale models of infectious disease

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1. Research gap

Stochastic simulation algorithms (SSA) for ***multiscale models*** of infectious diseases are paid much attention as:

1. small populations or noise play a crucial rule in real life;
2. disease dynamics are inherently multiscale (e.g. within-host + across-population dynamics).

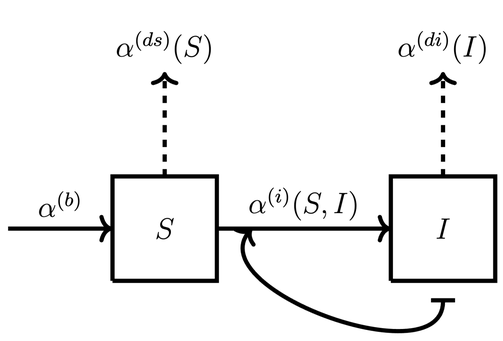
Computational challenges when simulating models across different scales (usually non-Markovian) ⇒ innovations needed!

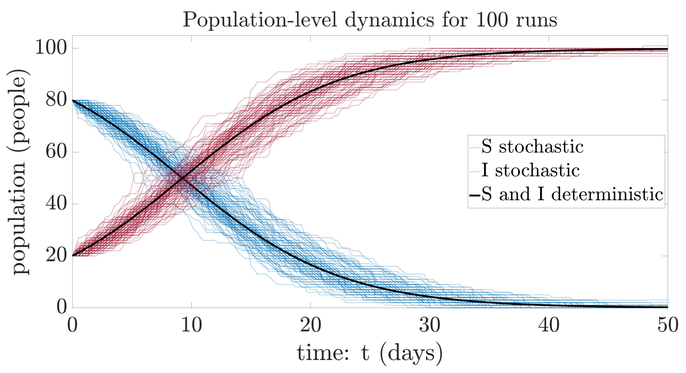
2. Contribution of our work

- Development of ***a novel exact SSA***, applied to a showcase multiscale system with deterministic within-host model and stochastic population-level formulation;
- ***Accuracy***, given the within-host information is harvested at a reasonable resolution;
- ***Generality***, our SSA can be applied to other multiscale systems in (or outside) the realm of infectious diseases.

3. Stochastic population-level model

The S (susceptible) $-$ I (infectious) model. **Calendar time: t.**



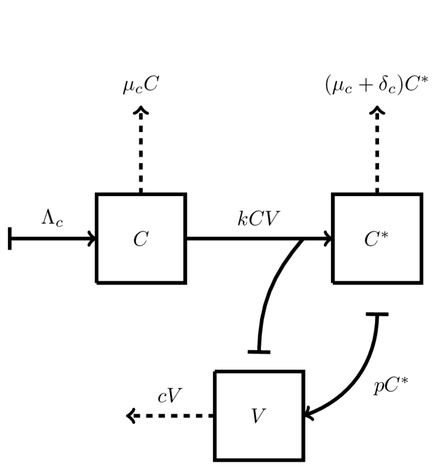


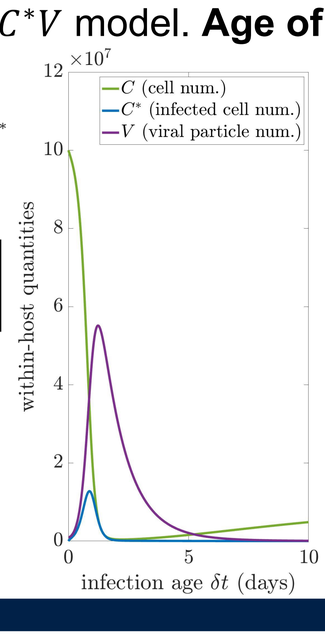
$P_{(s+m,i+n)} \stackrel{\text{def}}{:=}$ transition probability of the process from $(S,I)=(s,i)$ to $(S,I)=(s+m,i+n)$.

$$\frac{\mathrm{d}P_{(s,i)}}{\mathrm{d}t} = \alpha^{(b)}P_{(s-1,i)}(t) + \alpha^{(ds)}(s+1)P_{(s+1,i)}(t) + \alpha^{(di)}P_{(s,i+1)}(t) + \alpha^{(i)}(s+1,i-1)P_{(s+1,i-1)}(t) - P_{(s,i)}(t)\left[\alpha^{(b)} + \alpha^{(ds)}(s) + \alpha^{(di)}(i) + \alpha^{(i)}(s,i)\right]$$

4. Deterministic within-host model

The target cell-limited CC^*V model. **Age of infection: δt.**





C: number of uninfected cells
C^*: number of infected cells
V: number of virus particles

$$\frac{\mathrm{d}C}{\mathrm{d}(\delta t)} = \Lambda_c - kCV - \mu_c C$$
$$\frac{\mathrm{d}C^*}{\mathrm{d}(\delta t)} = kCV - (\mu_c+\delta_c)C^*$$
$$\frac{\mathrm{d}V}{\mathrm{d}(\delta t)} = pC^* - cV$$

5. Coupling the within-host model to the population-level one: a multiscale showcase

Transmission propensity $\alpha^{(i)} := \beta s i$.

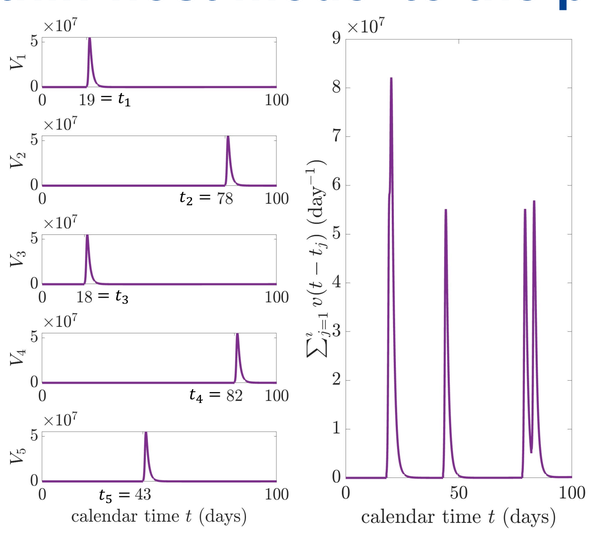
Model coupling:

Agent j's transmission coefficient β_j depends on its instantaneous within-host viral load $\mathrm{V}_j(\delta t_j)$:

$$\boldsymbol{\beta_j(t) = lV_j(\delta t_j) \stackrel{\text{def}}{:=} v(t-t_j)},$$

where t is the current calendar time and t_j is the calendar time of agent j's initial infection.

$\Rightarrow \boldsymbol{\alpha^{(i)}(s,i;t) = s\sum_{1\le j\le i} v(t-t_j)}$.



$$P_{(s+1,i)}(t+\Delta t) = \alpha^{(b)}\Delta t$$
$$P_{(s-1,i)}(t+\Delta t) = \alpha^{(ds)}(s)\Delta t$$
$$P_{(s,i-1)}(t+\Delta t) = \alpha^{(di)}(i)\Delta t$$
$$P_{(s-1,i+1)}(t+\Delta t) = \underbrace{s\sum_{j=1}^{i} v(t-t_j)\,\Delta t}_{\alpha(s,i;t)}$$

non-Markovian!!

$$P_{(s,i)}(t+\Delta t) = 1 - s\sum_{j=1}^{i} v(t-t_j)\Delta t$$

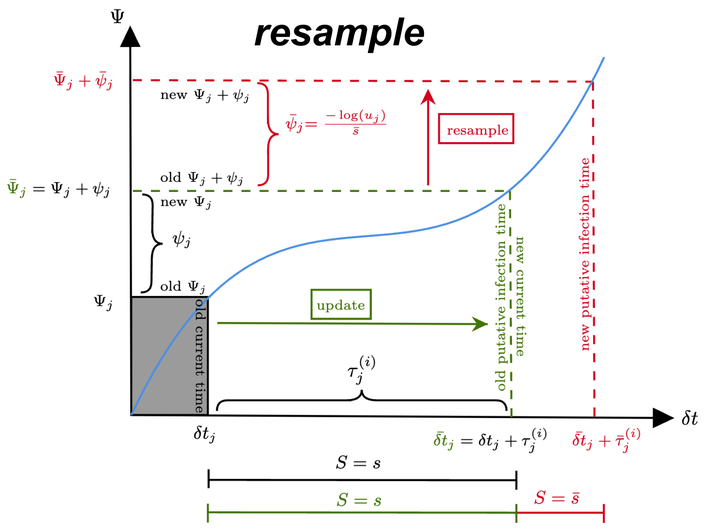
Survival distribution function $SDF_s(T^{(i)};t) \stackrel{\text{def}}{:=} 1 - CDF_s(T^{(i)};t)$: the probability that no infections have occurred in $(t, t+T^{(i)})$ as $\Delta t \to 0$. We have

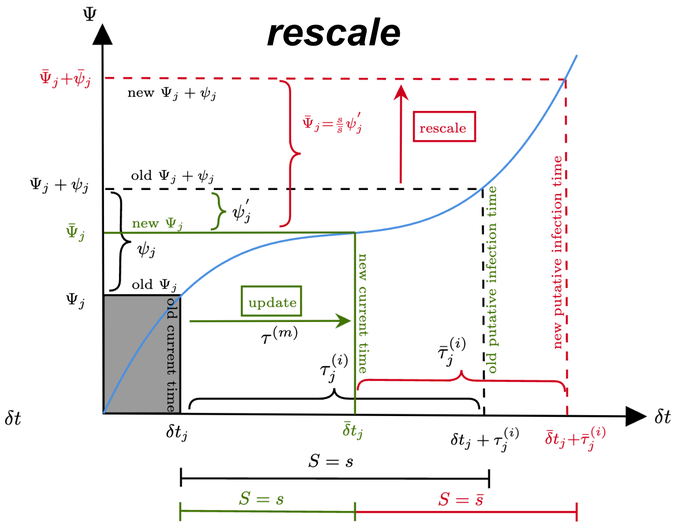
$$\boldsymbol{SDF_s(T^{(i)};t) = \exp[-s\sum_{1\le j\le i}\Psi(T^{(i)};t)]},$$

where $\boldsymbol{\Psi(T^{(i)};t) \stackrel{\text{def}}{:=} \int_0^{T^{(i)}} v(\eta+\delta t_j)\mathrm{d}\eta}$ is stored in a lookup table.

6. Novel SSA for the multiscale system

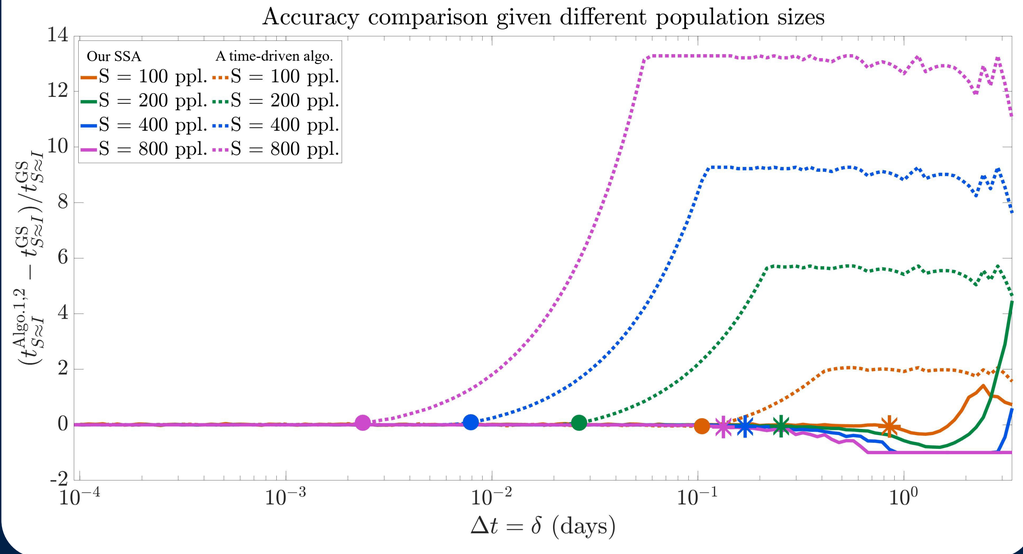
Our SSA updates from event to event via ***a generalised next-reaction method***. Putative times (for non-Markovian events) are initially sampled (based on SDF_s and Ψ). After an event happens, we need to ***resample*** the putative time for that event and ***rescale*** the putative times for all the other events. For non-Markovian events:





7. Novel SSA is exact

We compare the accuracy of our SSA to an existing time-driven algorithm with a constant time step Δt (which is proven to be exact, i.e. 'golden-standard' (GS) as $\Delta t \to 0$). δ denotes the resolution of the within-host Ψ in our SSA.



8. Conclusion and future directions

We developed ***a novel accurate SSA for multiscale systems***, incorporating within-host viral load dynamics into individual infection rates in a population-scale infectious disease model. It is ***general*** and can be applied to other multiscale systems with different underlying sub-models.

Future directions: 1). Non-deterministic, noisy within-host model for the whole population; 2). Infectious individuals with varying within-host time scales; 3). Heterogeneous populations, such as those with age structures; 4). Investigating the efficiency of our SSA.

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