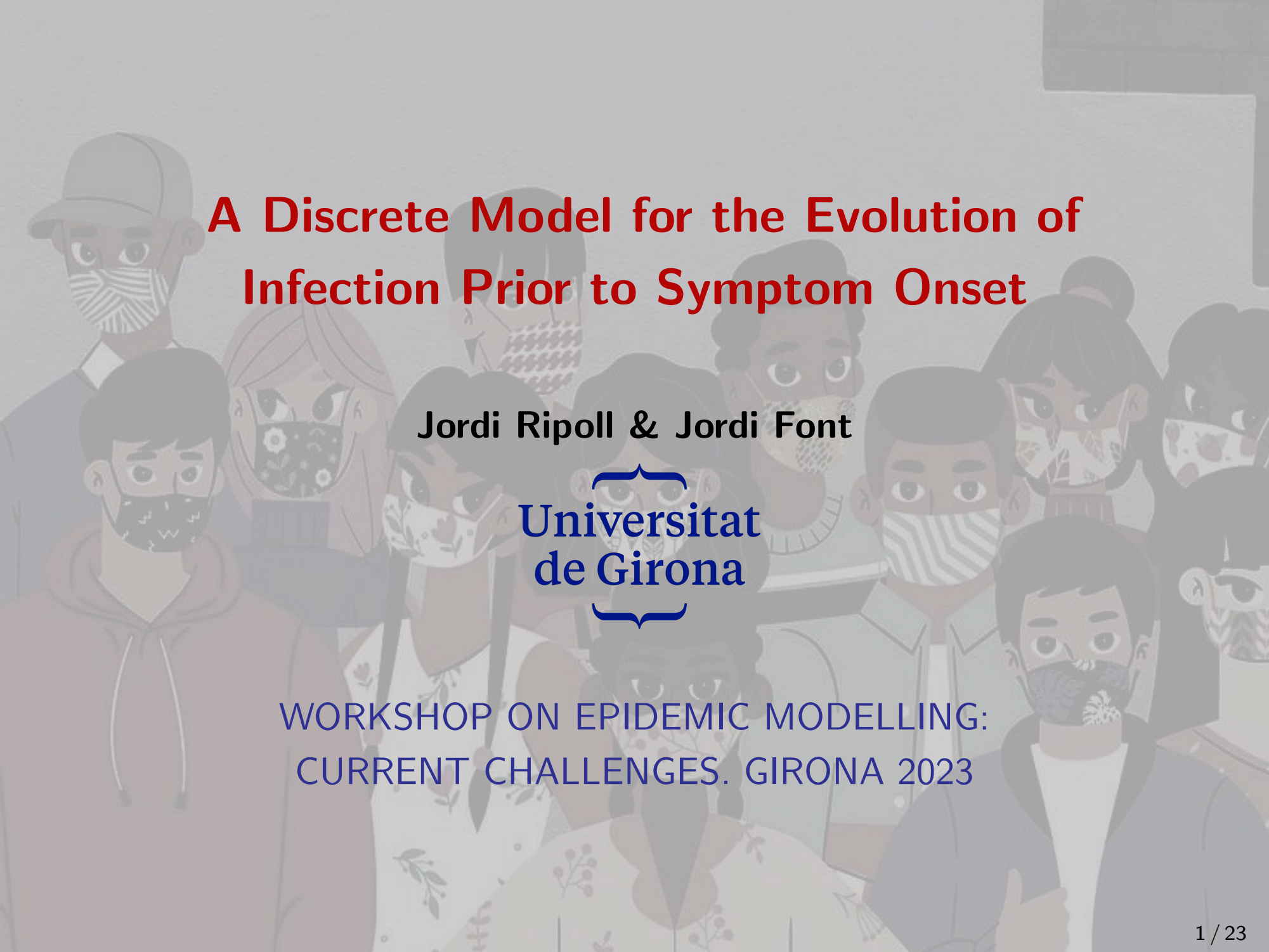

A Discrete Model for the Evolution of Infection Prior to Symptom Onset

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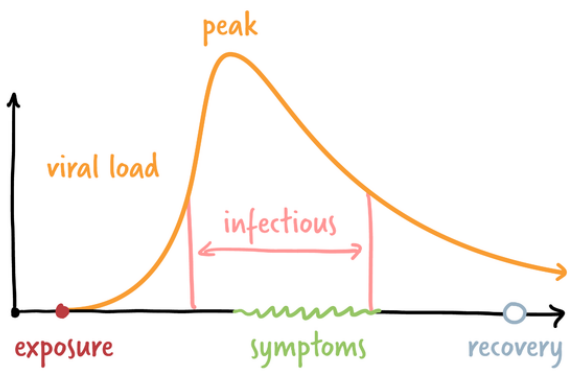
WORKSHOP ON EPIDEMIC MODELLING: CURRENT CHALLENGES. GIRONA 2023

Discrete-time Epidemic Model

Introduction. Discrete model single-epidemic outbreak

- Key-feature: infection prior to symptom onset.
- Diseases with asymptomatic carriers: *typhoid*, *HIV*, *C. difficile*, *influenza*, *cholera*, *tuberculosis and COVID-19*.
- Non-linear **Markov chain**. Transitions based on geometric or negative-binomial probability distributions and infection process on a Poisson distribution (*# of contacts per day*).
- We focus on two epidemiological indicators: transmission potential ($\mathcal{R}_0$) and the severity of the pathogen (*virulence*).



Discrete-time Epidemic Model

Introduction (cont')

Non-linear epidemic model in discrete-time $t = 0, 1, 2, \ldots$ days.

- **Markov chain**. State variables according to the disease progression. Fraction of individuals: Susceptible, Exposed (latent who are not infectious), Asymptomatic (but with transmission), Symptomatic (I infectious), Removed (alive and immune) and Deceased (disease-related).
- Total pop. $S_t + E_t + A_t + I_t + R_t + D_t = 1$, $t \geq 0$.
- **Linear transitions** between states based on the geometric distribution $\mathbb{P}(X = k) = p(1-p)^{k-1}$, $k \geq 1$, $\mathbb{E}[X] = \frac{1}{p}$, $\text{Var}(X) = \frac{1-p}{p^2}$, for some generic probability p.
- Fixed probabilities of the model: $0 < \alpha, \delta, \gamma, p, q < 1$.

Discrete-time Epidemic Model

Flow diagram of the SEA-RID non-linear Markov chain

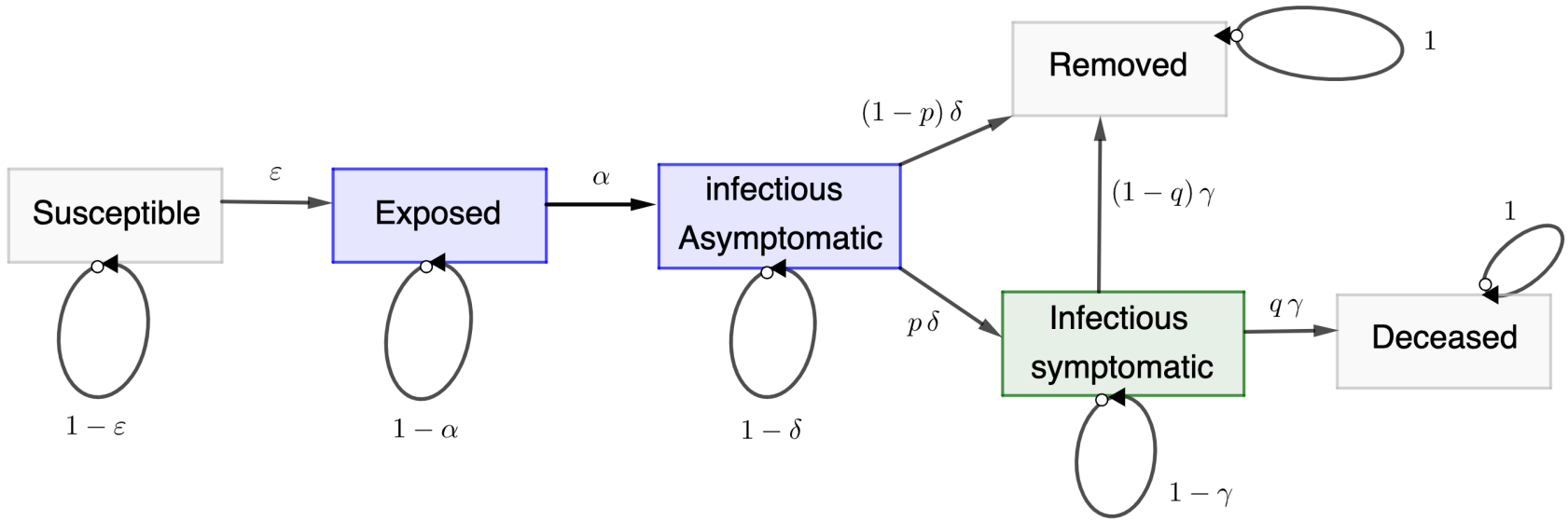


Figure: Infection process with probability $\varepsilon = 1 - e^{-(\beta_1 A + \beta_2 I)/(1-D)}$ depending on the number of infectious hosts, either asymptomatic or symptomatic, over alive population. No demographic turnover. Complete immunity along each epidemic outbreak. Virulence: $q\gamma$.

Discrete-time Epidemic Model

Model equations. Force of infection

- Force of infection $\varepsilon_t = 1 - e^{-(\beta_1 A_t + \beta_2 I_t)/(1-D_t)}$, $\beta_1, \beta_2 > 0$.
- System for each epidemic outbreak (*single wave*):

$$\begin{cases} S_{t+1} = (1-\varepsilon_t) S_t \\ E_{t+1} = \varepsilon_t S_t + (1-\alpha) E_t \\ A_{t+1} = \alpha E_t + (1-\delta) A_t \\ I_{t+1} = p\delta A_t + (1-\gamma) I_t \\ R_{t+1} = (1-p)\delta A_t + (1-q)\gamma I_t + R_t \\ D_{t+1} = q\gamma I_t + D_t \end{cases}, \quad t \geq 0 \, .$$

- Probability of developing symptoms p and *case fatality ratio* q, the proportion of symptomatic cases that result in death.

Discrete-time Epidemic Model

Model equations. Limitations

The introduced model has several limitations:

- It is **deterministic**, although it has many underneath probabilistic models, so no random variation.
- It is **rather homogeneous** in many aspects: no age, no space, no time-since-exposure, no different susceptibility ...
- It is **autonomous**, i.e. time-independent model parameters.
- As mentioned earlier, no demographic turnover and no loss of immunity. It is independent of within-host dynamics ...

... but discrete-time is not a limitation at all.

Future work: age-classes (kids, adults and older people).

Discrete-time Epidemic Model

Recurrent sequences formulation. Extension to initial histories

- $R_t = 1 - (S_t + E_t + A_t + I_t + D_t)$ and $D_t = q\gamma \sum_{j=1}^{\infty} I_{t-j}$. Then, using the model equations recursively we get to:

$$\begin{cases} S_t = \prod_{j=1}^{\infty}(1-\varepsilon_{t-j}) = \exp\left(-\sum_{j=1}^{\infty} \frac{\beta_1 A_{t-j} + \beta_2 I_{t-j}}{1-D_{t-j}}\right) \\ E_t = \sum_{j=1}^{\infty}(1-\alpha)^{j-1}\varepsilon_{t-j} S_{t-j} \\ A_t = \alpha \sum_{j=1}^{\infty}(1-\delta)^{j-1} E_{t-j} \\ I_t = p\delta \sum_{j=1}^{\infty}(1-\gamma)^{j-1} A_{t-j} \end{cases}, \quad t \geq 1 \, .$$

Discrete-time Epidemic Model

Non-linear renewal equation (asymptomatics)

- Reduction to a scalar **non-linear discrete renewal equation** for A_t:

$$A_t = \alpha \sum_{j=1}^{\infty} (1-\delta)^{j-1} \sum_{k=1}^{\infty} (1-\alpha)^{k-1} \varepsilon_{t-j-k} \prod_{n=1}^{\infty} (1-\varepsilon_{t-j-k-n})$$

with
$\varepsilon_t = 1 - \exp\left(-(\beta_1 A_t + \beta_2 p\delta \sum_{j=1}^{\infty} (1-\gamma)^{j-1} A_{t-j})/(1-D_t)\right)$
and $D_t = pq\delta\gamma \sum_{k=1}^{\infty} (1-\gamma)^{k-1} \sum_{j=1}^{\infty} A_{t-j-k}$.

- The other variables are computed in order as I_t, S_t and E_t.

Discrete-time Epidemic Model

Non-linear renewal equation (asymptomatics). 5 terms

- *Probabilistic interpretation of the renewal equation:*

$$A_t = \sum_{j,k\geq 1}$$

probability of being susceptible until time $t-j-k$ $\times$

prob. per time-unit of becoming infected at $t-j-k$ $\times$

probability latent period is k days $\times$

probability infectious asymptomatic period is j days $\times$

mean infectious asymptomatic period $=$

$$\sum_{j,k\geq 1} \prod(1-\varepsilon_\diamond) \times \varepsilon_\diamond \times \alpha(1-\alpha)^{k-1} \times \delta(1-\delta)^{j-1} \times \frac{1}{\delta}$$

Discrete-time Epidemic Model

Basic reproduction number $\mathcal{R}_0$. Two natural viewpoints

We can compute the basic reproduction number for the present model once we have decided what is an infection event:

1. Infection event is meant as the **exposition** to the pathogen of a susceptible host becoming an asymptomatic individual.

2. Infection event is meant as the **onset of symptoms** for a host who has been exposed to the pathogen in the past.

Discrete-time Epidemic Model

Linearization: $E_0 + A_0 + I_0 \ll 1$. 1st viewpoint

At the disease-free SS, $\varepsilon_t \simeq \beta_1 A_t + \beta_2 p\delta \sum_{j=1}^{\infty} (1-\gamma)^{j-1} A_{t-j}$.

Linear discrete **renewal equation** (3 *geometric distributions*):

$$A_t = \sum_{j=1}^{\infty} \delta(1-\delta)^{j-1} \sum_{k=1}^{\infty} \alpha(1-\alpha)^{k-1} \Big(\frac{\beta_1}{\delta} A_{t-j-k} + \frac{\beta_2 p}{\gamma} \sum_{n=1}^{\infty} \gamma(1-\gamma)^{n-1} A_{t-j-k-n} \Big)$$

- **Basic reproduction number:** spectral radius of the 1-dim. next-generation operator. $\mathcal{R}_{0,a} = \frac{\beta_1}{\delta} + \frac{\beta_2 p}{\gamma}$, as *the expected secondary asymptomatic cases produced by asymptomatic primary case*. Abstract setting [Diekmann 1990].

Discrete-time Epidemic Model

Progression over time of the infection $E \to A \to I$

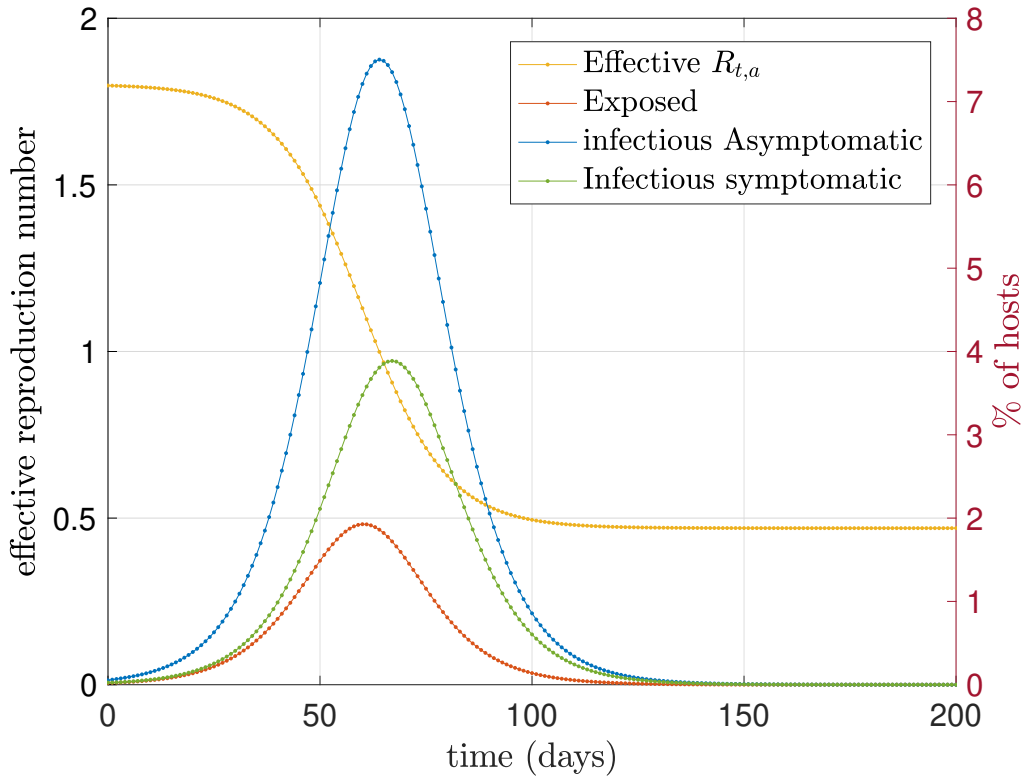


Figure: Size of the peaks: $E_{60} = 1.93\%$, $A_{64} = 7.5\%$, $I_{67} = 3.89\%$, and $\mathcal{R}_{t,a} = \frac{1-e^{-\beta_1 A_t/(1-D_t)}}{A_t} \cdot \frac{S_t}{\delta} + p\frac{1-e^{-\beta_2 I_t/(1-D_t)}}{I_t} \cdot \frac{S_t}{\gamma}$, giving the transmission potential of the disease at the t-th day, that starts at $t = 0$ as $\mathcal{R}_{0,a}$.

Discrete-time Epidemic Model

Alternative basic reproduction numbers

- Before tackling computation from 2nd viewpoint, consider the **2-dimensional linear discrete renewal equation**:

$$\begin{cases} I_t = p\delta \sum_{j=1}^{\infty} (1-\gamma)^{j-1} A_{t-j} \\ A_t = \sum_{j=1}^{\infty} (1-\delta)^{j-1} \sum_{k=1}^{\infty} \alpha(1-\alpha)^{k-1} \left(\beta_1 A_{t-j-k} + \beta_2 I_{t-j-k} \right) \end{cases}$$

- *Joint basic reproduction number*: spectral radius of the 2-dim. next-generation operator $\tilde{\mathcal{R}}_0 = \frac{\beta_1}{2\delta} + \sqrt{\left(\frac{\beta_1}{2\delta}\right)^2 + \frac{\beta_2 p}{\gamma}}$.

Discrete-time Epidemic Model

Renewal equation (symptomatics). 2nd viewpoint

- Linear operator $(\mathcal{K}\phi)_t$. Reduce to a single renewal eq. for I_t if $\frac{\beta_1}{\delta} < 1$: $I_t = \beta_2 p \delta \sum_{j=1}^{\infty} (1-\gamma)^{j-1} \left((Id - \beta_1 \mathcal{K})^{-1} \mathcal{K} I \right)_{t-j}$.
- Then, the **basic reproduction number** is given by $\mathcal{R}_{0,s} = \frac{\beta_2}{\gamma} p \sum_{n=1}^{\infty} (\frac{\beta_1}{\delta})^{n-1} = \frac{\beta_2}{\gamma} \frac{p}{1-\beta_1/\delta}$, interpreted as *the expected # of symptomatic individuals that a symptomatic individual will produce*. Sum of pre-symptomatic cases.
- As expected, the three expressions of $\mathcal{R}_0$ are such that
$$\text{sign}(\mathcal{R}_{0,a} - 1) = \text{sign}(\mathcal{R}_{0,s} - 1) = \text{sign}(\tilde{\mathcal{R}}_0 - 1),$$
and they are related via a function of $\frac{\beta_1}{\delta}$ and $\frac{\beta_2 p}{\gamma}$.

Discrete-time Epidemic Model

Evolution of infection transmission. Virulence-transmission tradeoff

- Weighted **mean transmission rate** $\bar{\beta} = \frac{\beta_1}{1+p} + \frac{\beta_2 p}{1+p}$, *average between pre-symptomatic and post-symptomatic*.
- Provided that hosts can develop symptoms $p > 0$ and die from the disease $q > 0$, virulence is positively correlated with transmission as $q\gamma = p \cdot c\bar{\beta}^2 \leq 1\,,\ c > 0\,.$
- We **optimize** $\mathcal{R}_0$ for transmission rate of the symptomatic phase: $\mathcal{R}_{0,a}(\beta_2) = \frac{\beta_1}{\delta} + \frac{\beta_2 q}{c\bar{\beta}^2} = \frac{\beta_1}{\delta} + \frac{\beta_2 q}{c}\left(\frac{1+p}{\beta_1+\beta_2 p}\right)^2$. Global maximum such that $\beta_2^* > \beta_2^* p = \beta_1$.
- Accordingly, we get an optimal (intermediate) virulence $q\gamma^* = p \cdot c(\bar{\beta}^*)^2 = p \cdot c\left(\frac{2\beta_1}{1+p}\right)^2$.

Discrete-time Epidemic Model

Optimal virulence under tradeoff

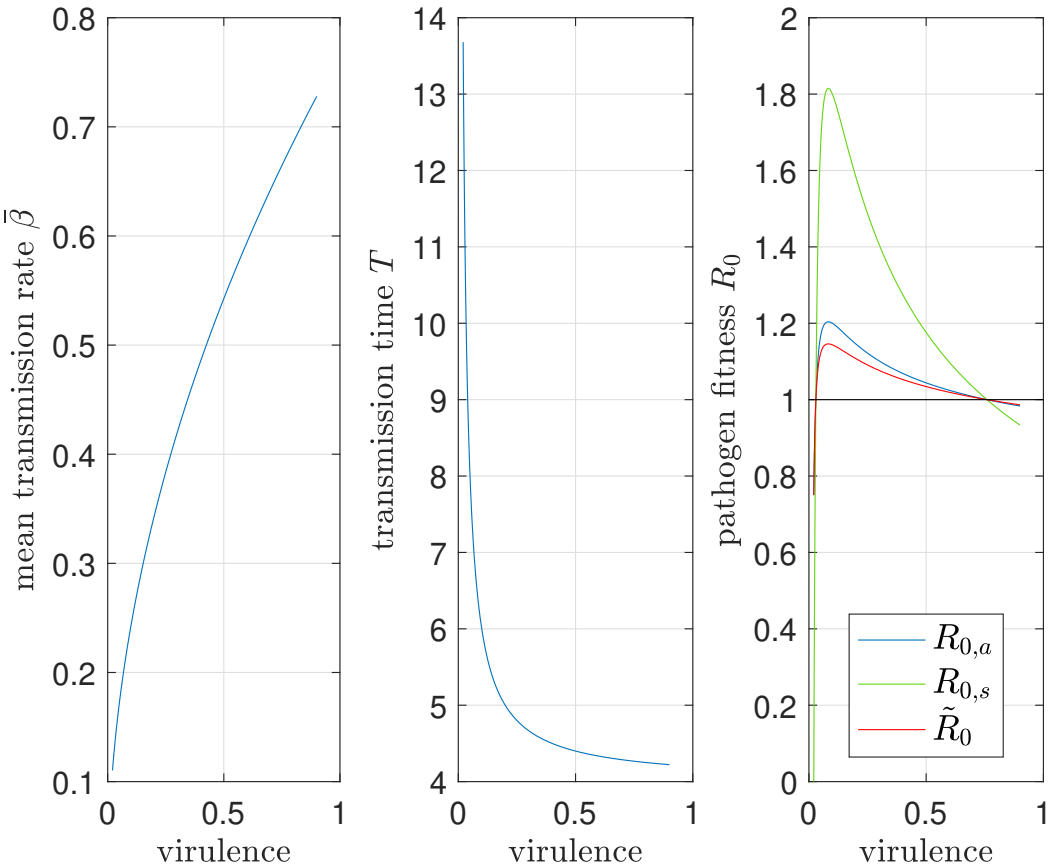


Figure: Plots in virulence $q\gamma$, prob. of dying due to disease symptoms. Left: mean trans. rate $\bar{\beta} = \sqrt{\frac{q\gamma}{pc}}$ days^{-1}. C: trans. time $T = \frac{1}{\delta} + \frac{q}{q\gamma}$ days. Right: basic reproduction numbers and optimal virulence $q\gamma^* = 0.08$.

Discrete-time Epidemic Model

Evolutionary outcomes

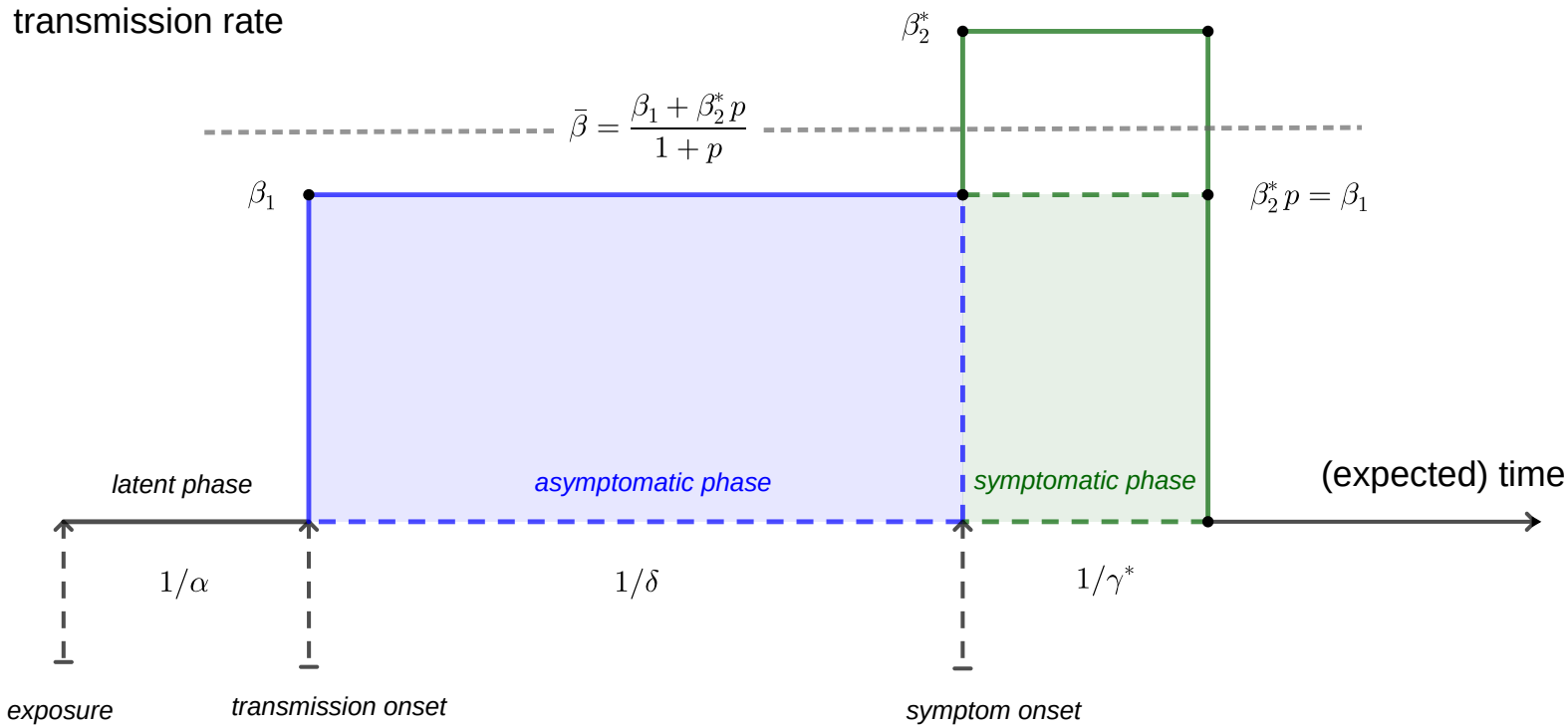


Figure: At maximal $\mathcal{R}_0$, transmission rate is always higher in the symptomatic phase $\beta_2^* > \beta_2^* p = \beta_1$, yet most of the infections take place prior to symptom onset if longer asymptomatic phase $\frac{1}{\delta} > \frac{1}{\gamma^*}$.

Discrete-time Epidemic Model

Final size of symptomatic hosts

- S_t is bounded in the interval:
$$\exp\left(-\sum_{n=1}^{\infty}\frac{\beta_1 A_{t-n}+\beta_2 I_{t-n}}{1-D_\infty}\right) \leq S_t \leq \exp\left(-\sum_{n=1}^{\infty}\beta_1 A_{t-n}+\beta_2 I_{t-n}\right)$$
- It turns out that $\lim_{t\to\infty}\sum_{n=1}^{\infty}\beta_1 A_{t-n}+\beta_2 I_{t-n} = (\frac{\beta_1}{\delta}+\frac{\beta_2 p}{\gamma})(1-S_\infty)$.
- Finally, we get an **interval for** S_∞ solving 2 equations:

$$e^{-\mathcal{R}_{0,a}\frac{1-S_\infty}{1-pq(1-S_\infty)}} \leq S_\infty \leq e^{-\mathcal{R}_{0,a}(1-S_\infty)}.$$

- If $pq \ll 1$ we recover the classical equation.
- Final size of the symptomatic hosts is $\frac{\gamma}{(1-p)\delta+\gamma}(1-S_\infty)$.

Discrete-time Epidemic Model

Enhanced model. Sub-stages & loss of immunity

- From *geometric distribution* (discrete analog to exp. dist.) to *negative binomial distribution* (discrete analog to the Gamma distribution) and reinfection probability θ:

$$
\begin{cases}
S_{t+1} = (1-\varepsilon_t)S_t + \theta R_t \\
E^1_{t+1} = \varepsilon_t S_t + (1-\alpha)E^1_t \,, \quad E^i_{t+1} = \alpha E^{i-1}_t + (1-\alpha)E^i_t \\
A^1_{t+1} = \alpha E^n_t + (1-\delta)A^1_t \,, \quad A^i_{t+1} = \delta A^{i-1}_t + (1-\delta)A^i_t \\
I^1_{t+1} = p\delta A^n_t + (1-\gamma)I^1_t \,, \quad I^i_{t+1} = \gamma I^{i-1}_t + (1-\gamma)I^i_t \\
R_{t+1} = (1-p)\delta A^n_t + (1-q)\gamma I^n_t + (1-\theta)R_t \\
D_{t+1} = q\gamma I^n_t + D_t
\end{cases}
$$

$i = 2 \ldots n$.

Discrete-time Epidemic Model

Enhanced model (cont')

- Underneath prob. model: $\mathbb{P}(X = k) = \binom{k-1}{n-1} p^n (1-p)^{k-n}$, $k \geq n$, $\mathbb{E}[X] = \frac{n}{p}$, $\mathrm{Var}(X) = n\frac{1-p}{p^2}$.
- Basic reproduction number from the asymptomatic point of view is analogous

$$\mathcal{R}_{0,a} = \frac{\beta_1 n}{\delta} + \frac{\beta_2 p\, n}{\gamma}\,.$$

- One can write analogous but more involved non-linear and linear **renewal equations** for the enhanced model.

SUMMARY:

A Discrete Model for the Evolution of Infection Prior to Symptom Onset

- Discrete epidemic models are simple yet powerful dynamical systems to describe *Inf. Diseases*. Suitable for discrete data.
- Reduction of the epidemic model to a non-linear **renewal equation** with a meaningful probabilistic interpretation.
- Computation and interpretation of the **basic reproduction number** from asymptomatic and symptomatic viewpoints.
- Maximization of $\mathcal{R}_0$ giving the **optimal virulence** level. Transmission higher in the symptomatic phase yet most of the infections take place prior to symptom onset.
- Determination of the **final size** of symptomatic hosts.

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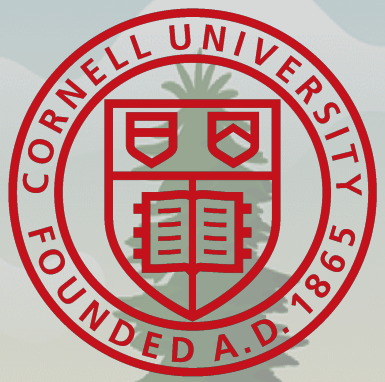
Thank you for listening!



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