

A discrete-time Epidemic Model for presymptomatic transmission

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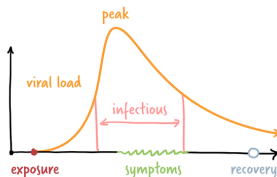
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Discrete-time Epidemic Model

Introduction

- Simple discrete model for each epidemic outbreak.
- States according to the pathogen load: non-infectious asymptomatic phase, **infectious asymptomatic phase** (key-feature, mild or no symptoms), infectious symptomatic phase and immune phase (natural immunity).
- Neither interventions nor vaccination. No demographic turnover. *Reinfections will be considered later on.*



Discrete-time Epidemic Model

Introduction (cont')

Non-linear epidemic model in discrete-time $t = 0, 1, 2, \dots$ 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, i.e. $\mathbb{P}(X = t) = p(1 - p)^{t-1}$, $\mathbb{E}[X] = \frac{1}{p}$, $\text{Var}(X) = \frac{1-p}{p^2}$, for some generic probability p .
- Fixed probabilities of the model: $0 < \alpha, \delta, \gamma, p, q < 1$.

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Recalling some definitions

- Incidence: # of new cases per day in the interval $(t, t + 1]$:
 $\varepsilon_t S_t N = (S_t - S_{t+1})N$, where N is the population size.
- Total # of cases until time t : $\sum_{j=0}^{\infty} \varepsilon_{t-j} S_{t-j} N = (1 - S_{t+1})N$.
- Force of infection ε_t : **probability per unit of time** of the susceptible becoming infected (starting the latent phase).
- β_1, β_2 are the infection transmission rates [1/time] (*contact rate* \times *infectiveness*). If $A_t + I_t + D_t \ll 1$, then we have
$$\varepsilon_t = 1 - e^{-(\beta_1 A_t + \beta_2 I_t)/(1 - D_t)} \simeq \beta_1 A_t + \beta_2 I_t.$$

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

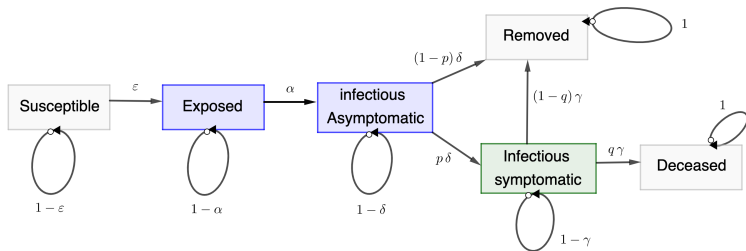


Figure: Infection process with probability $\varepsilon = 1 - e^{-(\beta_1 A + \beta_2 I)/(1-D)}$ depending on the # of infectious individuals over alive population, see [PNAS 21], and transmission rates β_1, β_2 . No demographic turnover. Complete immunity along each epidemic outbreak. Virulence: $q\gamma$.

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Model equations. Force of infection ε_t

- Mean latent period $\frac{1}{\alpha}$, mean infectious A/S period $\frac{1}{\delta}$ and $\frac{1}{\gamma}$, prob. developing symptoms p , survival probability $1 - q$.
- **Non-linear infection process** with density-dependent probability $\varepsilon_t = 1 - e^{-(\beta_1 A_t + \beta_2 I_t)/(1 - D_t)}$, with $\beta_1, \beta_2 > 0$.
- System for each epidemic outbreak (*single wave*): $t \geq 0$,

$$\left\{ \begin{array}{l} S_{t+1} = (1 - \varepsilon_t)S_t \\ E_{t+1} = \varepsilon_t S_t + (1 - \alpha)E_t \\ A_{t+1} = \alpha E_t + (1 - \delta)A_t \\ I_{t+1} = p\delta A_t + (1 - \gamma)I_t \\ R_{t+1} = (1 - p)\delta A_t + (1 - q)\gamma I_t + R_t \\ D_{t+1} = q\gamma I_t + D_t \end{array} \right.$$

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Equilibria and initial history

- Mean incubation period $\frac{1}{\alpha} + \frac{1}{\delta}$, i.e time to onset symptoms.
- Total mean infectious period $\frac{1}{\delta} + \frac{1}{\gamma}$, either as A or I .
- States with viral load: E, A, I .
- **Disease-free steady state:** $(S^*, 0, 0, 0, R^*, D^*)$, with $S^* + R^* + D^* = 1$. No endemic equilibrium in here.
- Extension of the initial condition at $t = 0$ to a discrete history in $(-\infty, 0]$ such that $(S_{-\infty} = 1, 0, 0, 0, 0, 0)$.
- Sequence of waves: initial condition of wave $(w + 1)$ may correspond with the final size of previous wave w : $(S_{\infty}^w, \simeq 0, \simeq 0, \simeq 0, R_{\infty}^w, D_{\infty}^w)$.

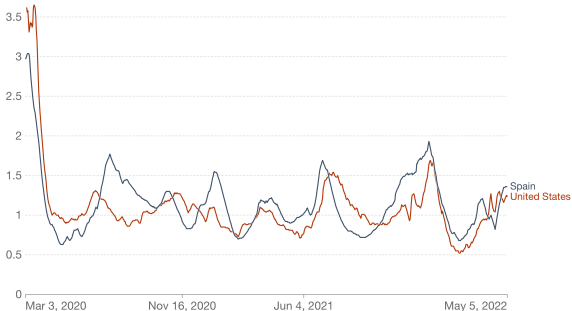
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COVID-19: 6 waves already, 7th wave?

Estimate of the effective reproduction rate (R) of COVID-19

The reproduction rate represents the average number of new infections caused by a single infected individual. If the rate is greater than 1, the infection is able to spread in the population. If it is below 1, the number of cases occurring in the population will gradually decrease to zero.

Our World
in Data



Source: Arroyo-Marioli F, Bullano F, Kucinskas S, Rondón-Moreno C (2021) Tracking R of COVID-19: A new real-time estimation using 16 BY Kalman filter.

Figure: ourworldindata.org/ [▶ Link](#)

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Recurrent sequences formulation

- Firstly, reduction to 4 state variables:

$R_t = 1 - (S_t + E_t + A_t + I_t + D_t)$ and $D_t = q\gamma \sum_{j=1}^{\infty} I_{t-j}$. Then,

using the model equations recursively we get to:

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

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Renewal equation (asymptomatics)

- Moreover, 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 $D_t = p q \delta \gamma \sum_{k=1}^{\infty} (1 - \gamma)^{k-1} \sum_{j=1}^{\infty} A_{t-j-k}$.

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

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Renewal equation (asymptomatics) cont'

- *Probabilistic interpretation of the renewal equation:*

$$\begin{aligned} A_t &= \sum_{j,k \geq 1} \\ &\text{probability of being susceptible at time } t - j - k \quad \times \\ &\text{prob. per time-unit of becoming infected at } t - j - k \quad \times \\ &\text{probability latent period is } k \quad \times \\ &\text{probability infectious asymptomatic period is } j \quad \times \\ &\text{mean infectious asymptomatic period} \quad = \\ &\sum_{j,k \geq 1} \prod (1 - \varepsilon_\diamond) \times \varepsilon_\diamond \times \alpha(1 - \alpha)^{k-1} \times \delta(1 - \delta)^{j-1} \times \frac{1}{\delta} \end{aligned}$$

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Linearization: $E_0 + A_0 + I_0 \ll 1$

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*):

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

- **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 an *asymptomatic primary* case. Abstract setting [Diekmann 1990].

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Alternative basic reproduction numbers

- Different reproduction numbers can be defined depending on what is understood as an *infection event*. See [BCR17].
- **2-dimensional linear discrete renewal equation:**

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

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

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Renewal equation (symptomatics)

- Moreover, we can reduce to a single renewal equation for I_t

$$\text{if } \frac{\beta_1}{\delta} < 1: I_t = \beta_2 p \delta \sum_{j=1}^{\infty} (1 - \gamma)^{j-1} ((Id - \beta_1 \mathcal{K})^{-1} \mathcal{K} I)_{t-j}.$$

- Then, the **basic reproduction number** is given by

$$\mathcal{R}_{0,s} = \frac{\beta_2}{\gamma} p \sum_{n=1}^{\infty} \left(\frac{\beta_1}{\delta}\right)^{n-1} = \frac{\beta_2}{\gamma} \frac{p}{1 - \beta_1/\delta},$$

interpreted as *the expected # of symptomatic individuals that a symptomatic individual will produce.*

- 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 $\frac{\beta_2 p}{\gamma}$.

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Trade-offs and evolutionary aspects

- One can find similar models in the lit., but we pay attention to the interpretation of different meaningful \mathcal{R}_0 's.
- Weighted **mean transmission rate** $\bar{\beta} = \frac{\beta_1}{1+p} + \frac{\beta_2 p}{1+p}$.
- **Measure of virulence.** Provided individuals can develop symptoms ($p > 0$), the disease-induced mortality $q\gamma$ is positively correlated with the mean transmission $\bar{\beta}$, e.g. the trade-off $q\gamma = p(c_1\bar{\beta}^2 + c_0)$, $c_1, c_0 > 0$.
- Scenario: (constant) Transmission rate is higher in the *symptomatic phase*, yet the accumulated number of infections is larger in the *asymptomatic phase*.

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Virulence-transmission trade-off

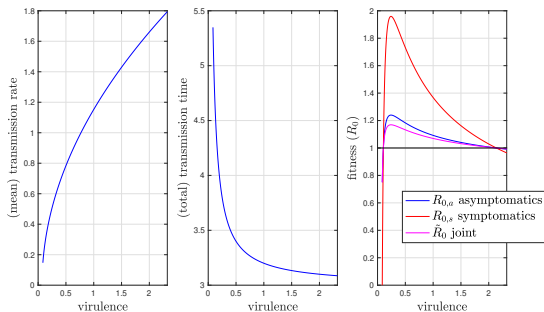


Figure: Left: mean transmission rate $\bar{\beta}$ vs. virulence (*disease-induced mortality*). Center: transmission time (asymptomatic + symptomatic phases $1/\delta + 1/\gamma$) vs. virulence. Right: fitness measure as the *basic reproduction number* vs. virulence. Optimal virulence at $q\gamma = 0.2421$

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Trade-offs and evolutionary aspects (cont')

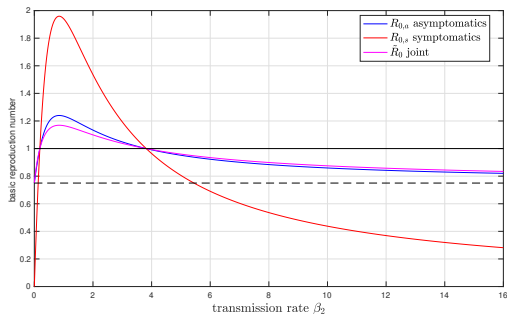


Figure: $\mathcal{R}_0(\beta_2)$. Global maximum at β_2^* s.t. always $\beta_1 < \beta_2^* p$, and $\frac{\beta_1}{\delta} > \frac{\beta_2^* p}{\gamma^*}$ if e.g. $\beta_1^2 > \frac{q(1+p)^2}{2p\epsilon_1} \delta$, so a larger A-phase $\frac{1}{\delta} > \frac{1}{\gamma^*}$. Values: $\beta_1 = 0.25$, $p = 0.7$, $\beta_2^* p = 0.5929$ and around 60% of infections take place prior to symptom onset. **Does evolution lead to this maximum?**

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Final size of the epidemics $1 - S_\infty$ (cont')

- 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 $\lim_{t \rightarrow \infty} \sum_{n=1}^{\infty} \beta_1 A_{t-n} + \beta_2 I_{t-n} = \left(\frac{\beta_1}{\delta} + \frac{\beta_2 p}{\gamma}\right)(1 - S_\infty)$.
- 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 for $1 - S_\infty$. Notice $\mathcal{R}_{0,a}$ has a central role over the other expressions for the basic reproduction number.

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Extension of the model

- From *Geometric distributions* (discrete analog of Exp. dist.) to *Negative Binomial distributions* (discrete analog of the Gamma dist.) and reinfection probability θ : $i = 2 \dots n$





$$\left\{ \begin{array}{l} S_{t+1} = (1 - \varepsilon_t)S_t + \theta R_t \\ E_{t+1}^1 = \varepsilon_t S_t + (1 - \alpha)E_t^1, \quad E_{t+1}^i = \alpha E_t^{i-1} + (1 - \alpha)E_t^i \\ A_{t+1}^1 = \alpha E_t^n + (1 - \delta)A_t^1, \quad A_{t+1}^i = \delta A_t^{i-1} + (1 - \delta)A_t^i \\ I_{t+1}^1 = p\delta A_t^n + (1 - \gamma)I_t^1, \quad I_{t+1}^i = \gamma I_t^{i-1} + (1 - \gamma)I_t^i \\ R_{t+1} = (1 - p)\delta A_t^n + (1 - q)\gamma I_t^n + (1 - \theta)R_t \\ D_{t+1} = q\gamma I_t^n + D_t \end{array} \right.$$

- $\mathbb{P}(X = t) = \binom{t-1}{n-1} p^n (1-p)^{t-n}$, $\mathbb{E}[X] = \frac{n}{p}$, $\text{Var}(X) = n \frac{1-p}{p^2}$.

References

-  Reproduction number for an age of infection structured model, *Math. Model. Nat. Phenom.* 16 (2021)
C. Barril, À. Calsina, S. Cuadrado, J. Ripoll
-  Efficient numerical computation of the basic reproduction number for structured populations, *J. Comput. Appl. Math.* 384, (2021).
D. Breda, F. Florian, J. Ripoll, R. Vermiglio
-  A practical approach to R_0 in continuous-time ecological models. *Math. Meth. Appl. Sci.* 41 (18), 8432–8445, (2017)
C. Barril, À. Calsina, J. Ripoll
-  The discrete-time Kermack–McKendrick model: A versatile and computationally attractive framework for modeling epidemics, *PNAS 2021 Vol. 118 No. 39*.
Odo Diekmann et al.

References (cont')

-  On the reproduction number of a gut microbiota model, *B. Math. Biol.* 79(11), 2727–2746, (2017)
C. Barril, À. Calsina, J. Ripoll
-  Dynamics in a simple evolutionary-epidemiological model for the evolution of an initial asymptomatic infection stage, PNAS 2020
Simon A. Levin et al.
-  Evidence for transmission of COVID-19 prior to symptom onset. *eLife* 2020; 9:e57149
Tindale et al.
-  Evolution of Acute Infections and the Invasion-Persistence Trade-Off, Vol. 173 No. 4, *The American Naturalist*, 2009.
A.A. King et al.

Books



Data-driven Modelling of Structured Populations. A Practical Guide to the Integral Projection Model. Springer, 2016.

S.P. Ellner, D.Z. Childs, M. Rees



Matrix population models. Construction, analysis, and interpretation, Sinauer, 2001.

H. Caswell



An Introduction to Mathematical Population Dynamics. Along the trail of Volterra and Lotka, Springer, New York, 2014.

M. Iannelli, A. Pugliese