Mathematical Epidemiology for KoroNERV-20
- key elementary models and ideas

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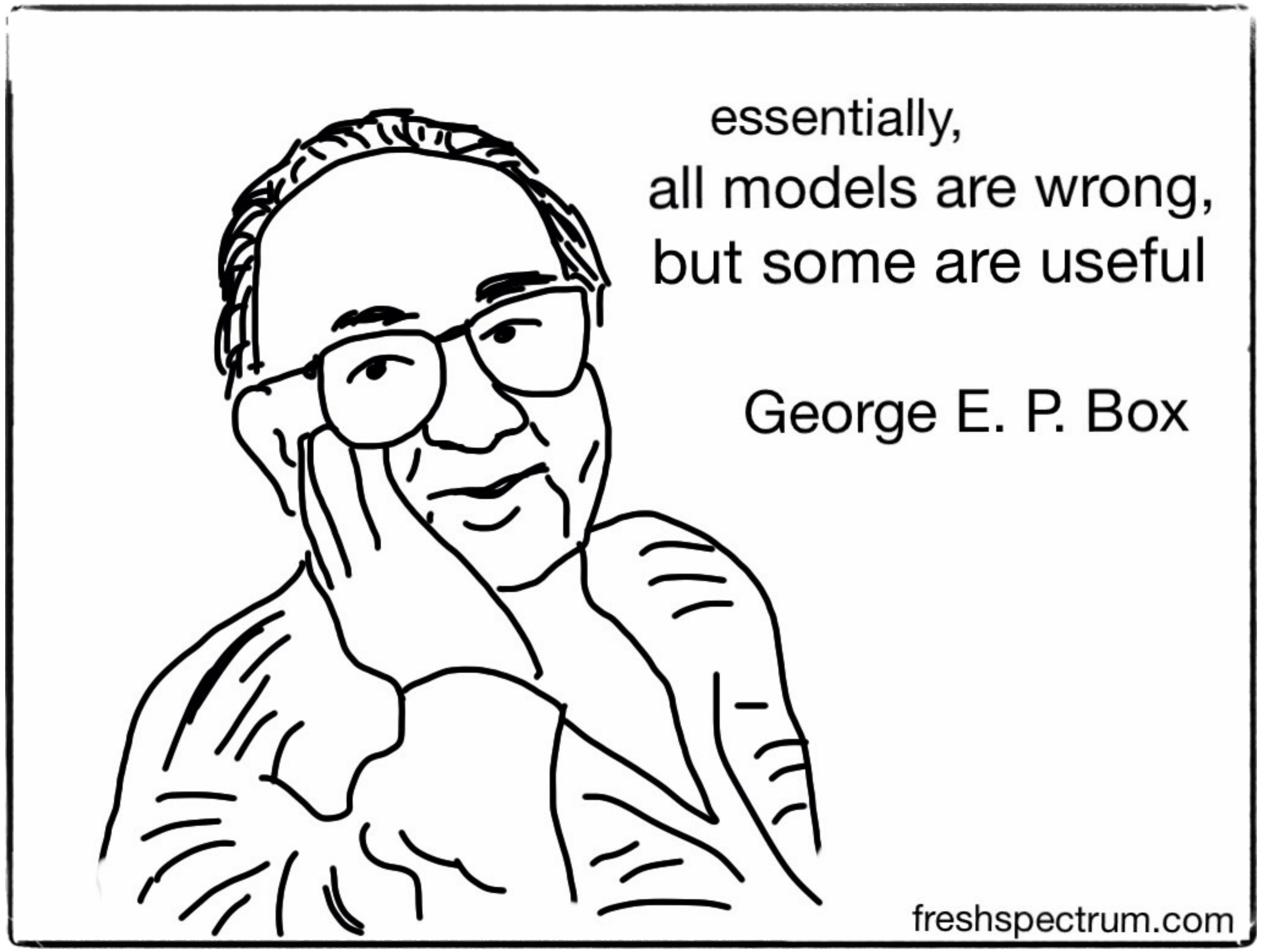
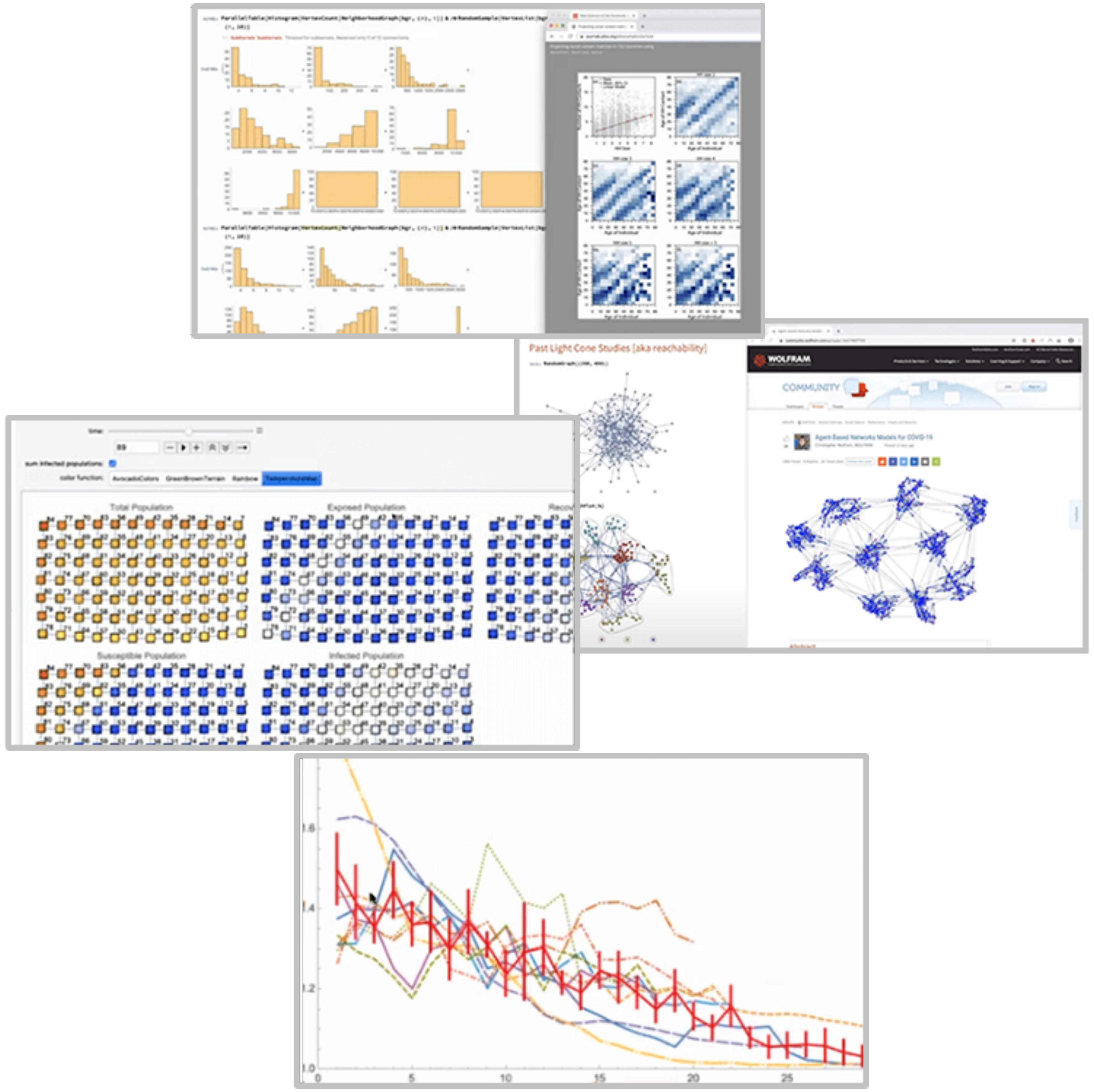
So… why?

- The COVID-19 pandemic threatens *not only* our health, economy, sport, culture, … it is a **global security threat**
  - models are essential to create a broad platform to understand, discuss, and solve it
  - the more we rely on models, the more we shall ask about their own security and safety aspects
  - understanding the internal *code of epidemic* allows for much better analyses, forecasts, and preparedness also in other areas - for instance, finance, banking, and industry

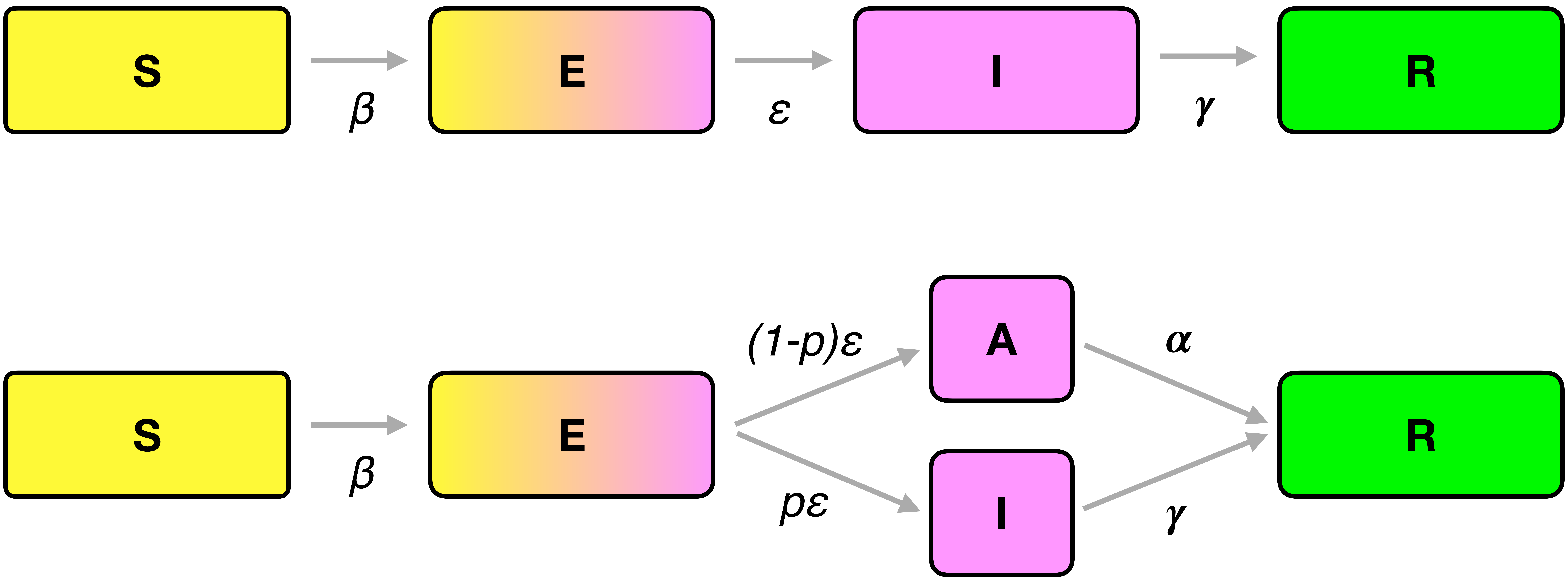
Have you said “modelling”?





SIR Compartmental Epidemic Model
- based on Kermack-McKendrick theory since 1927

Towards COVID-19 Realities



Ordinary Differential Equations - What do they say here?

$$X(t+\Delta t) = X(t) + [\Lambda + \alpha X(t) + \beta X(t)Y(t)]\Delta t$$

$$\frac{X(t+\Delta t) - X(t)}{\Delta t} = \Lambda + \alpha X(t) + \beta X(t)Y(t)$$

$$\lim_{\Delta t \to 0} \frac{X(t+\Delta t) - X(t)}{\Delta t} = \frac{dX(t)}{dt}$$

$$\frac{dX(t)}{dt} = \Lambda + \alpha X(t) + \beta X(t)Y(t)$$

- General form of ODE as used in many deterministic models of biological processes
  - incorporates various kinds of growth/decrease action and handles the infinitesimal time steps correctly
  - Λ is an *instantaneous **absolute** rate of change* of a “degree-zero” growth/decrease process
  - α is an *instantaneous **relative** rate of change* of a “degree-one” growth/decrease process
  - β analogous to α, this time for a **mass action** (“degree-two”) growth/decrease process

SIR Compartmental Epidemic Model
- based on Kermack-McKendrick theory since 1927

$$\frac{dS(t)}{dt} = -\frac{\beta}{N} I(t)S(t) \qquad \frac{dI(t)}{dt} = \frac{\beta}{N} I(t)S(t) - \gamma I(t) \qquad \frac{dR(t)}{dt} = \gamma I(t)$$

$$\mathcal{R}_0 = \frac{\beta}{\gamma},\ \mathcal{R}_e(t) = \mathcal{R}_0 \frac{S(t)}{N}$$

$$S(0) + I(0) + R(0) = N$$

$$S'(t) + I'(t) + R'(0) = 0$$

All Those "***R***"s

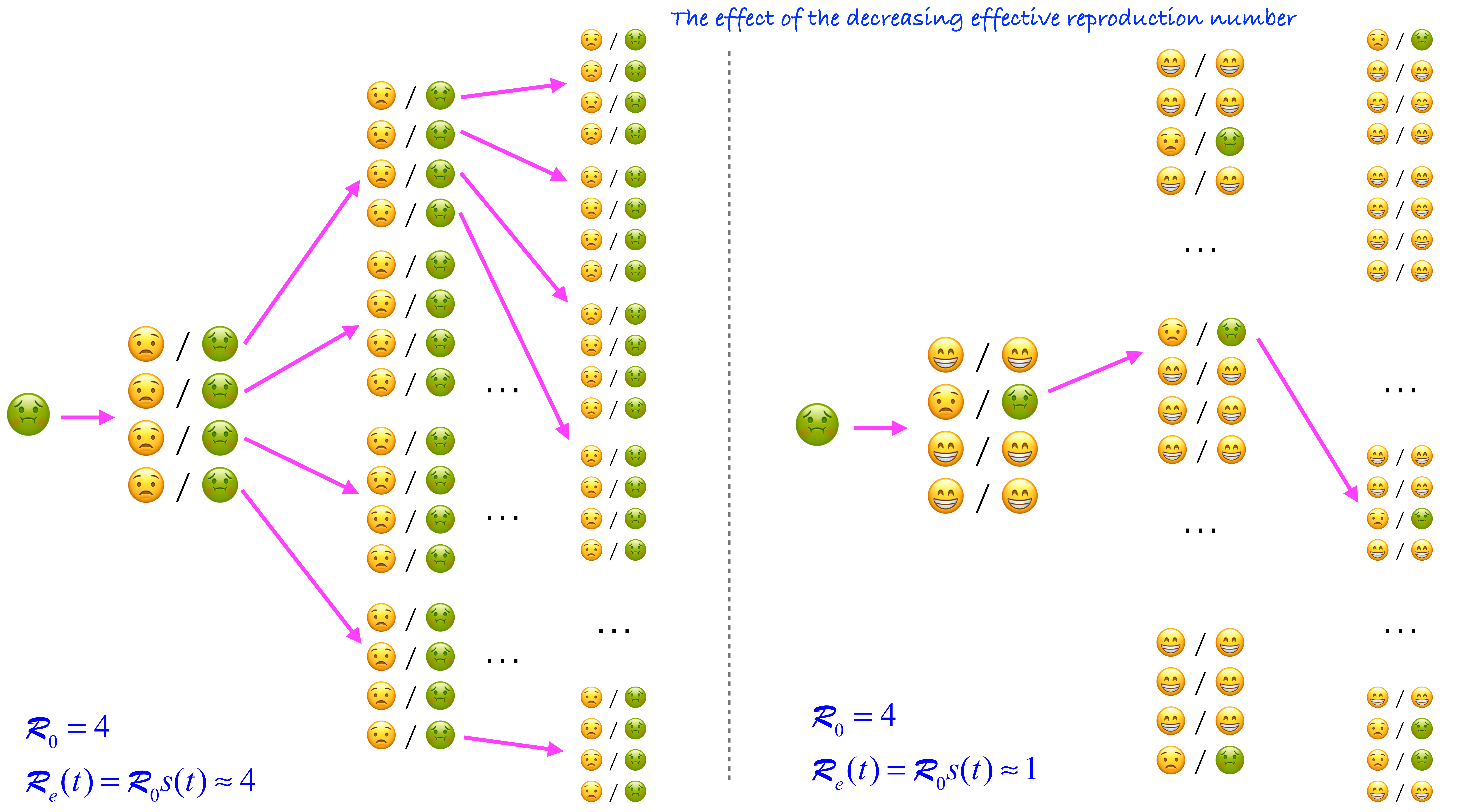
$$\mathcal{R}_0 = \frac{\beta}{\gamma}$$

$$\mathcal{R}_e(t) = \mathcal{R}_0 \frac{S(t)}{N} = \mathcal{R}_0 s(t)$$

$$controlled - \mathcal{R}_0 = \frac{\beta_t}{\gamma_t}$$

*) in this particular model

- Basic reproduction number $\mathbf{R}_0$
  - inherent model constant, describes important qualitative aspects, e.g. equilibria and their stability
- Effective reproduction number $\mathbf{R}_e(t)$
  - what we observe in daily experience
- Controlled reproduction number $\mathbf{R}_{0,t}$
  - what we aim for with our interventions


The effect of the decreasing effective reproduction number
$\mathcal{R}_0 = 4$
$\mathcal{R}_e(t) = \mathcal{R}_0 s(t) \approx 4$
$\mathcal{R}_0 = 4$
$\mathcal{R}_e(t) = \mathcal{R}_0 s(t) \approx 1$

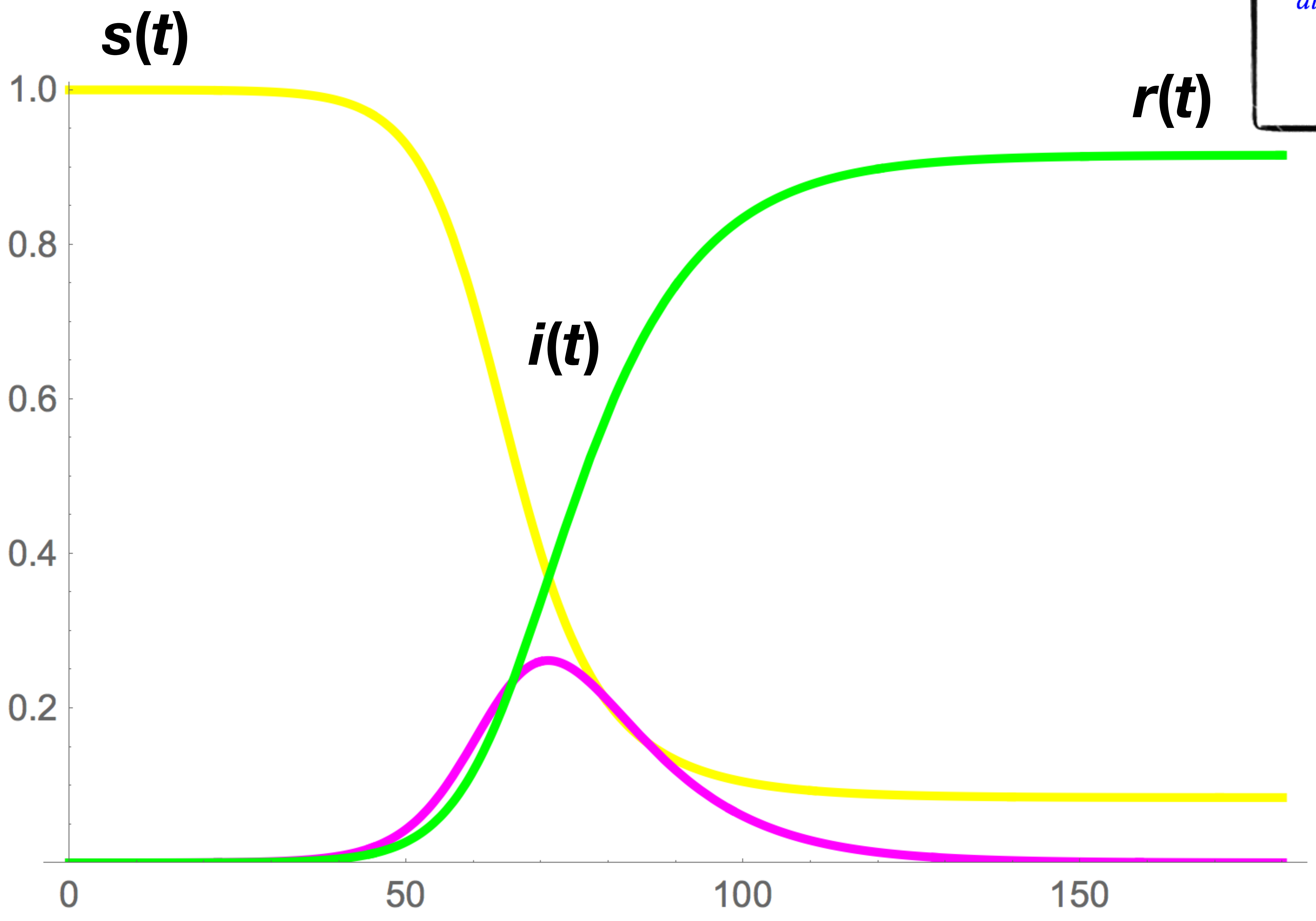
SIR Solution Example

$s(t) = {}^{S(t)}/_{N}$ $\quad i(t) = {}^{I(t)}/_{N}$ $\quad r(t) = {}^{R(t)}/_{N}$

$$\frac{ds(t)}{dt} = -\beta i(t)s(t) \qquad \frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t) \qquad \frac{dr(t)}{dt} = \gamma i(t)$$

$$\mathcal{R}_0 = \frac{\beta}{\gamma},\ \mathcal{R}_e(t) = \mathcal{R}_0 s(t)$$

$$s(0) + i(0) + r(0) = 1$$
$$s'(t) + i'(t) + r'(0) = 0$$



$$I(0) = 10^{-5}$$

$$\beta = \frac{27}{100}$$

$$\gamma = \frac{1}{10}$$

$$\mathcal{R}_0 = 2.70$$

Partial Optimisation Criteria (SIR-based)

$s(t) = S(t)/N$ $\quad i(t) = I(t)/N$ $\quad r(t) = R(t)/N$

$$\frac{ds(t)}{dt} = -\beta i(t) s(t) \qquad \frac{di(t)}{dt} = \beta i(t) s(t) - \gamma i(t) \qquad \frac{dr(t)}{dt} = \gamma i(t)$$

$$\mathcal{R}_0 = \frac{\beta}{\gamma},\ \mathcal{R}_e(t) = \mathcal{R}_0 s(t)$$

$$s(0) + i(0) + r(0) = 1$$
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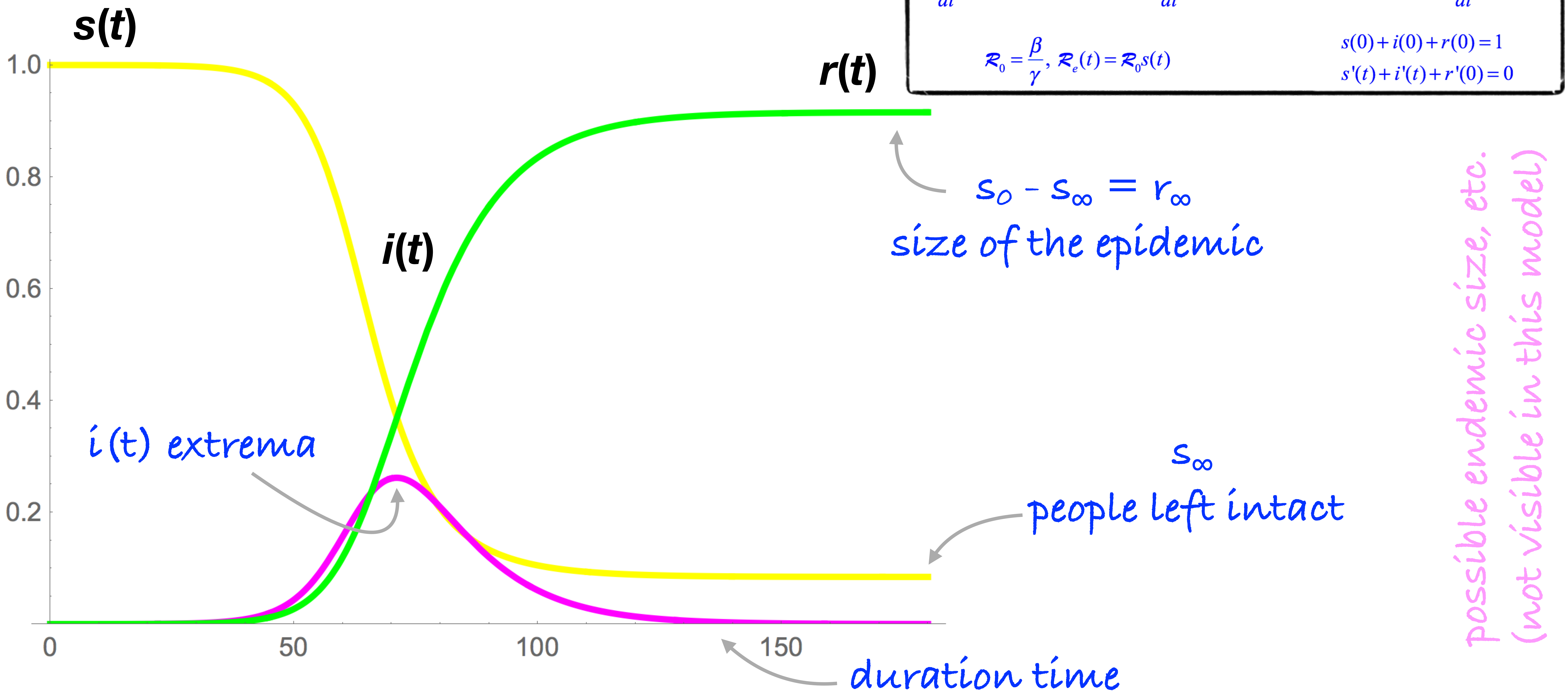

Anti-Epidemic Interventions

transmission rate intervention ⬇

- moderating contact rate
- decreasing infection probability

removal rate intervention ⬆

- broad testing
- contact tracing
- vaccination

Susceptible → β ⬇ → **Infected** → γ ⬆ → **Removed**

$s(t) = S(t)/N$ $i(t) = I(t)/N$ $r(t) = R(t)/N$

$$\frac{ds(t)}{dt} = -\beta i(t)s(t) \qquad \frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t) \qquad \frac{dr(t)}{dt} = \gamma i(t)$$

$$\mathcal{R}_0 = \frac{\beta}{\gamma}, \; \mathcal{R}_e(t) = \mathcal{R}_0 s(t)$$

$$s(0) + i(0) + r(0) = 1$$

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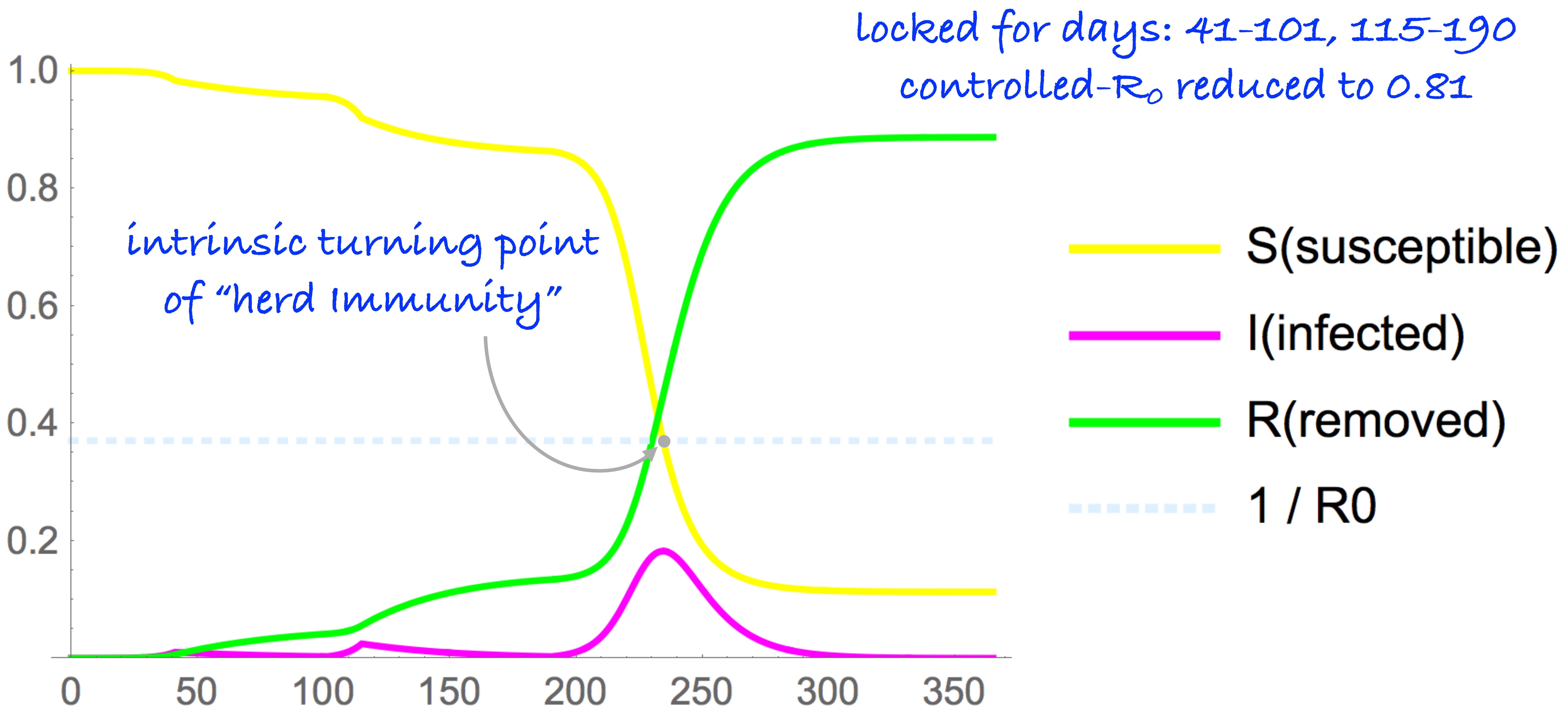
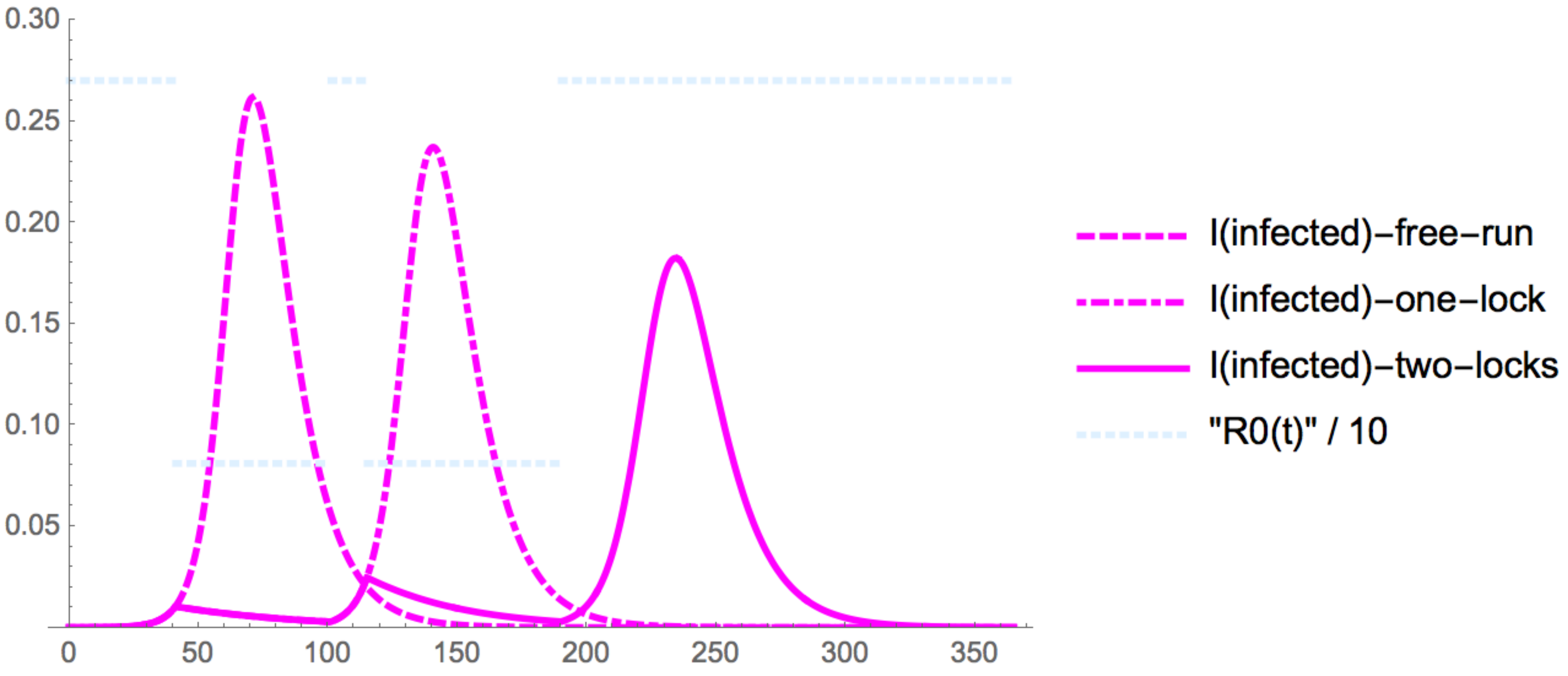
Lockdown as an Algorithmic Trade-Off

- Saying it "*buys time*" is a bit misleading from the model perspective
- It actually costs time and *trades the time for*
  - moderation of the prevalence extrema (one-time lockdown)
  - moderation of the final size of the epidemic (perpetual lockdown)
- To be effective, it needs a combination
  - vaccination (ideal)
  - tracing, quarantine, and isolation (have to be rather strict)
  - long-term intensive, yet-bearable hygienic measures (erode with time)

Example: Qualitative Study of Two Ideal Consecutive Lockdowns



Locked in Lockdowns



Real-World Lockdown *Serious Modelling Example* (UK)

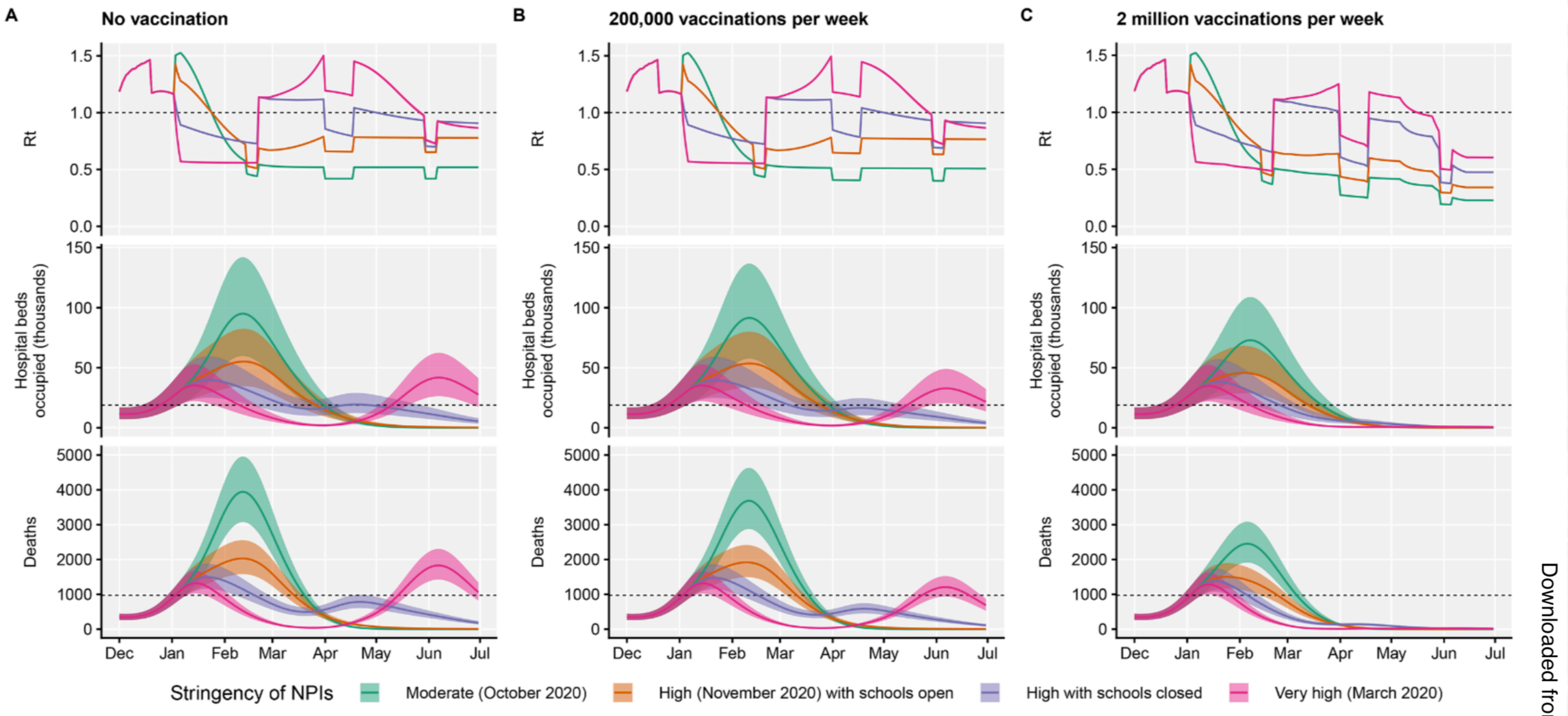


Fig. 4. Projections of epidemic dynamics under different control measures. We compare four alternative scenarios for non-pharmaceutical interventions from 1 January 2021: (i) mobility returning to levels observed during relatively moderate restrictions in early October 2020; (ii) mobility as observed during the second lockdown in England in November 2020, then gradually returning to October 2020 levels from 1 March to 1 April 2021, with schools open; (iii) as (ii), but with school

[https://science.sciencemag.org/content/early/2021/03/03/science.abg3055]

Basic Vaccination Inequalities

$$\mathcal{R}_e(t) = \mathcal{R}_0 s(t) = \mathcal{R}_0(s_0 - p(t))$$

$$\approx \mathcal{R}_0(1 - p(t)) \text{ for } s_0 \approx 1$$

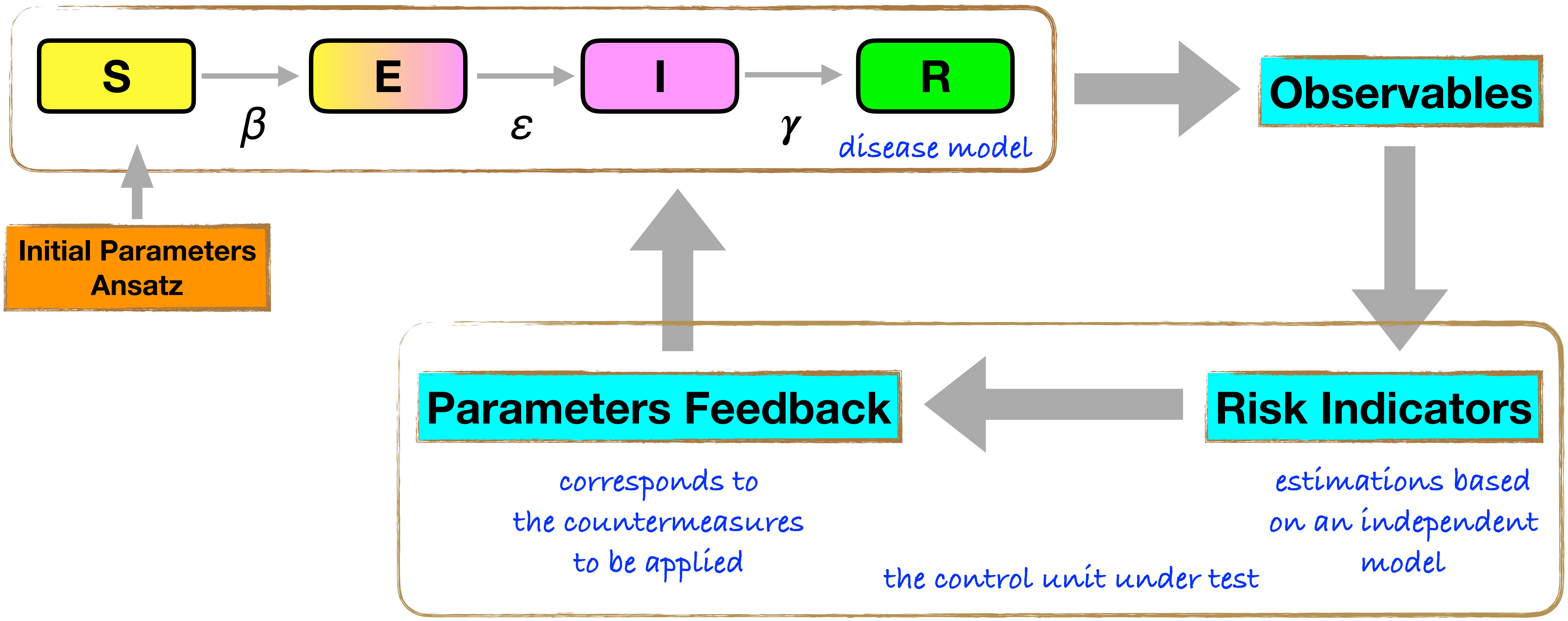
$$\mathcal{R}_e(t) < 1 \Leftrightarrow p(t) > 1 - \frac{1}{\mathcal{R}_0}$$

$$\text{resp. } p_\varepsilon(t) > \frac{1}{\varepsilon}\left(1 - \frac{1}{\mathcal{R}_0}\right)$$

- Assumptions:
  - vaccine distributed *uniformly among yet-susceptible* people
  - vaccine efficacy ε
  - immunity does not vanish in near time (circa one year, at least)
- Recovered people fraction bearing natural immunity then sums up with the vaccinated fraction
  - not shown here for clarity

For instance, AZD 1222 with 63.09% efficacy [WHO] eliminates $\mathcal{R}_0 < 2.7$.

Countermeasures Safety Check by Simulated Test Runs



*) Note the SEIR model is just an example

Transparency Required

- We shall generally *trust the mathematics, not necessarily the mathematicians*
  - similarly as we do in pharmaceutical research - we rely on pharmacology, not necessarily the pharmacologists

What information is publicly available during the evaluation of a new medicine and once a decision has been made?

EMA provides a high level of transparency about its medicine assessment by publishing of meeting agendas and minutes, reports describing how the medicine was assessed and the clinical study results submitted by medicine developers in their applications.

The list of new medicines that are being evaluated by the CHMP is available on the EMA website and updated every month.

EMA also publishes the agendas and minutes of all its committees' meetings, where information on the stage of the assessment can be found.

Once a decision has been taken on the authorisation or refusal of a marketing authorisation, EMA publishes a comprehensive set of documents called the European public assessment report (EPAR). This includes the public CHMP assessment report, which describes in detail the data assessed and why the

[https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/how-ema-evaluates-medicines#outcome-section]

Qualitative Realities

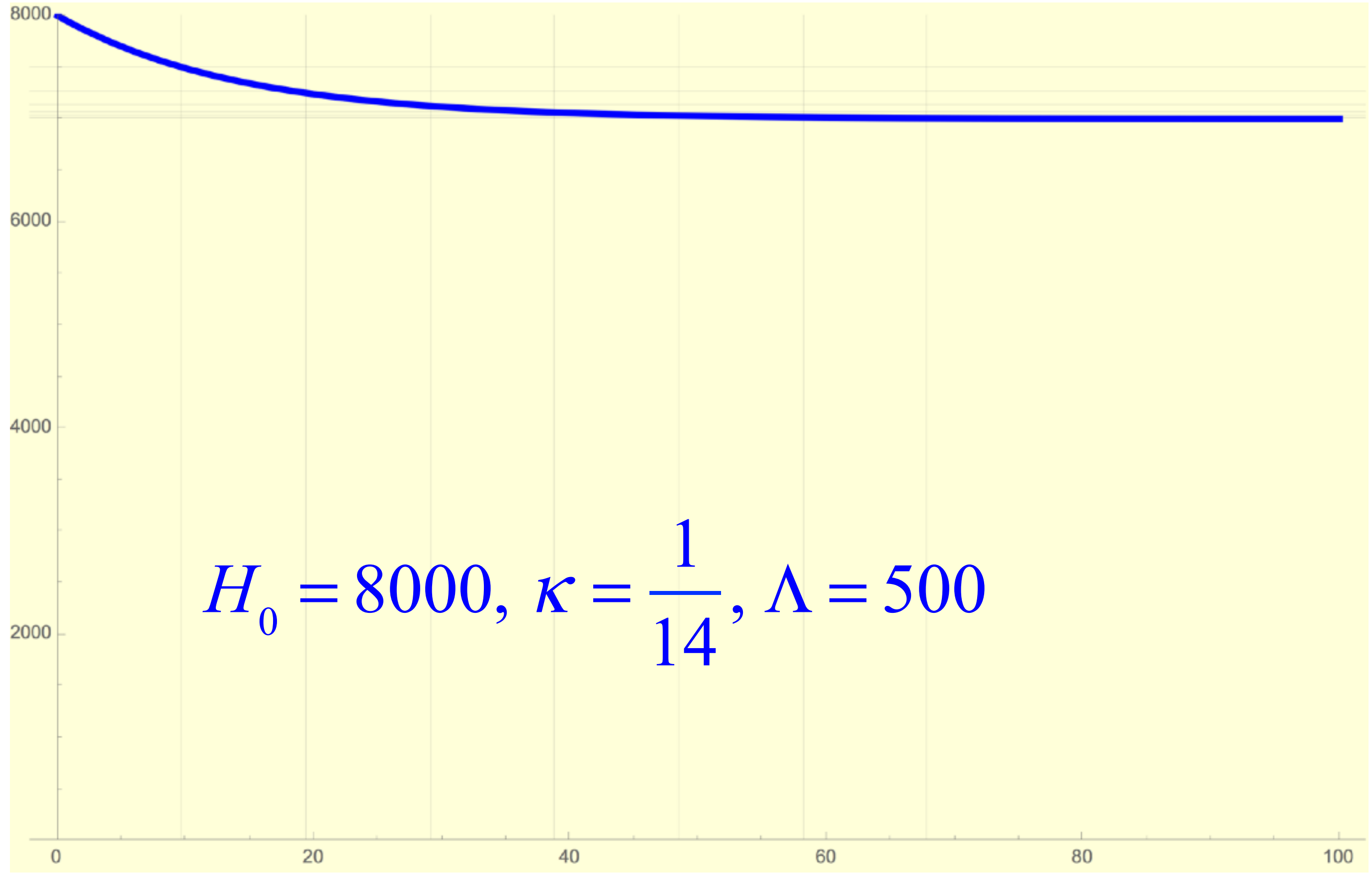
Consider a “Constant In, Fraction Out” Mechanism

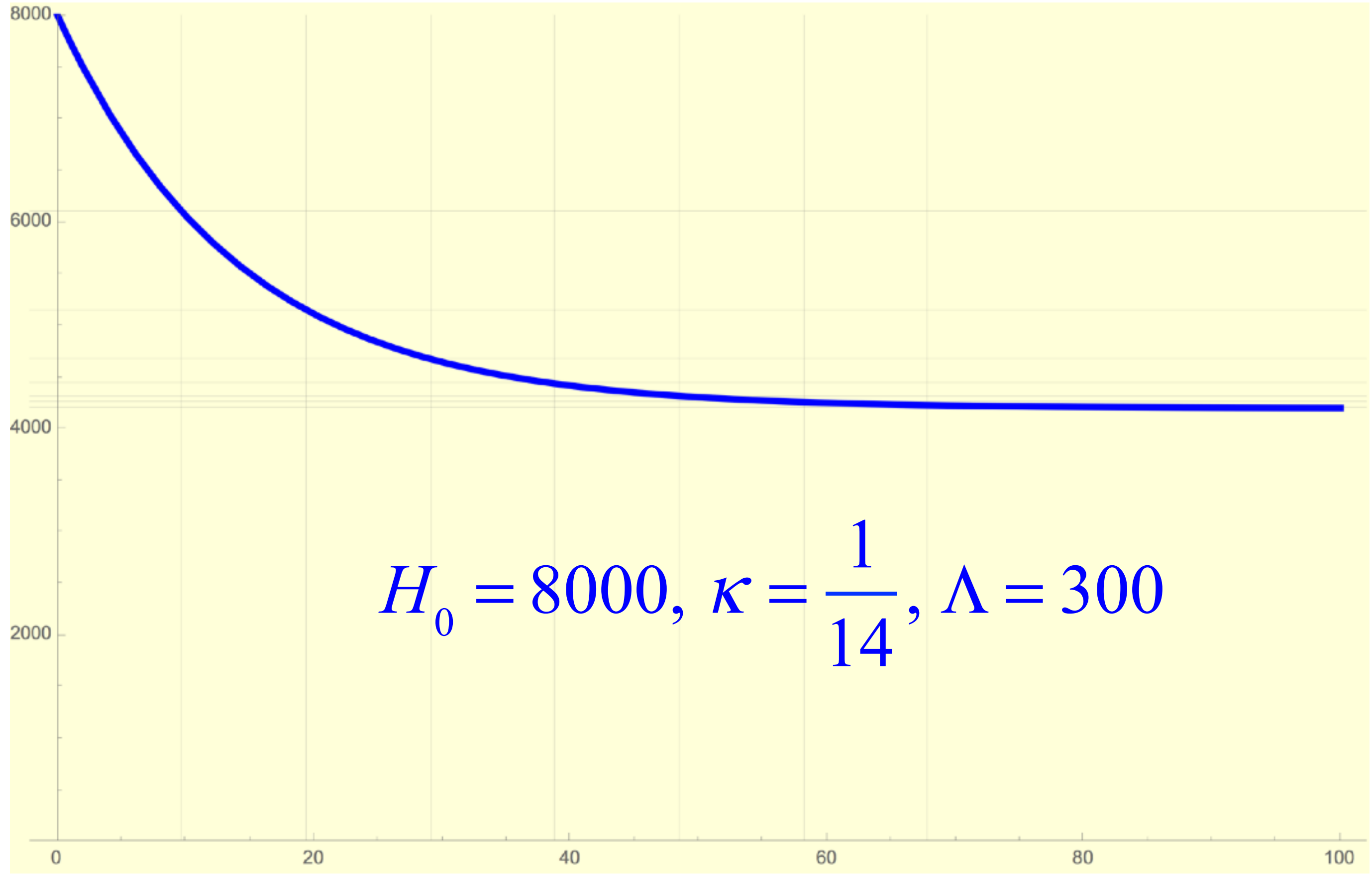
$$\frac{dH(t)}{dt} = \Lambda - \kappa H(t)$$

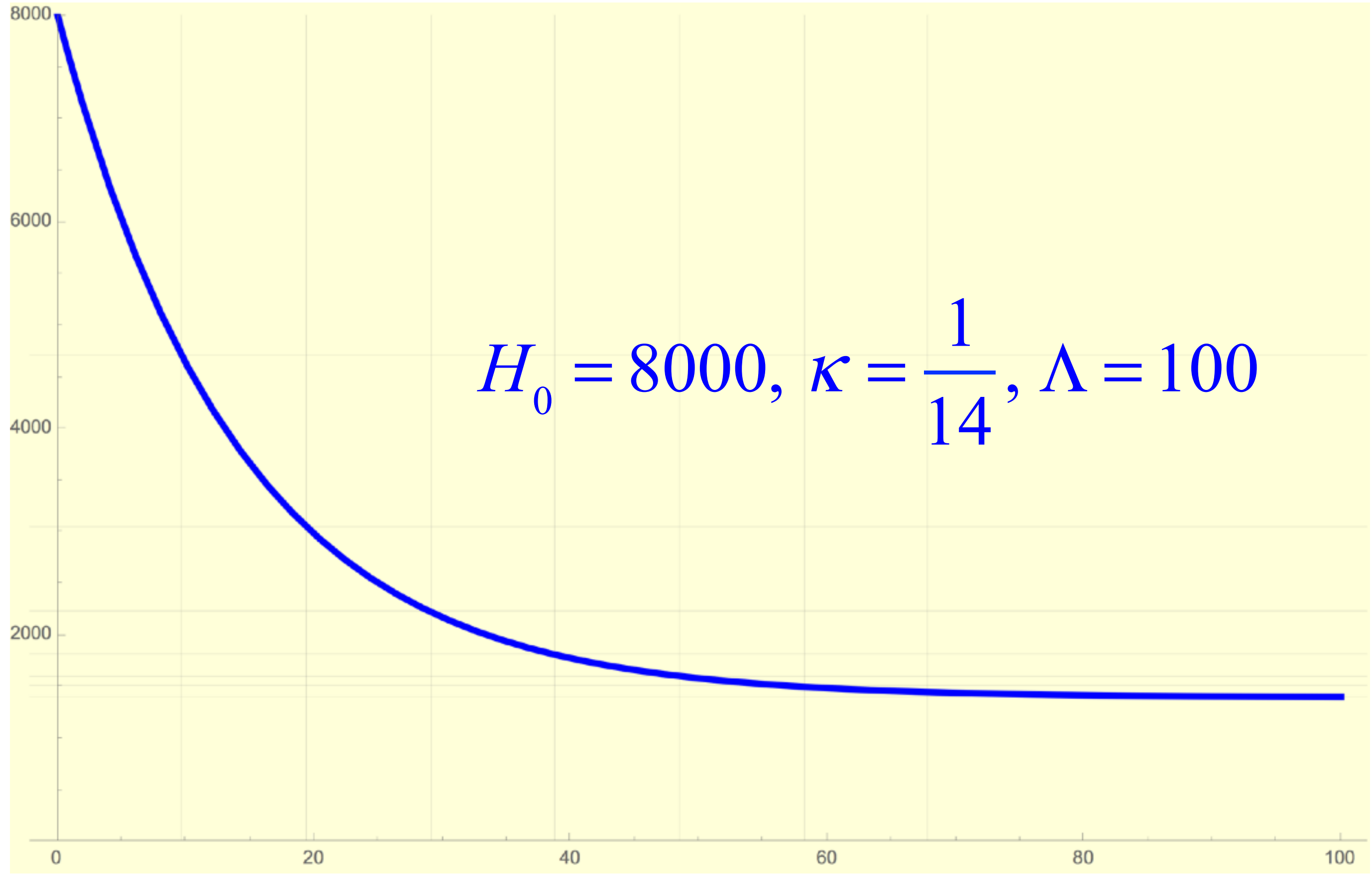
$$H(t) = H_0 e^{-\kappa t} + \frac{\Lambda}{\kappa}(1 - e^{-\kappa t})$$

$$t_{1/2} = \frac{\ln 2}{\kappa}$$

- simplified mechanics of hospital occupancy under stationary incidence levels
- illustrates expectable behaviour under (quasi)endemic conditions
- asymptotically stable equilibrium Λ/κ







KNM-D1

Prevalence Decrease Roadmap - Reality versus Mighty Wish

- also relevant for the important viral load estimates

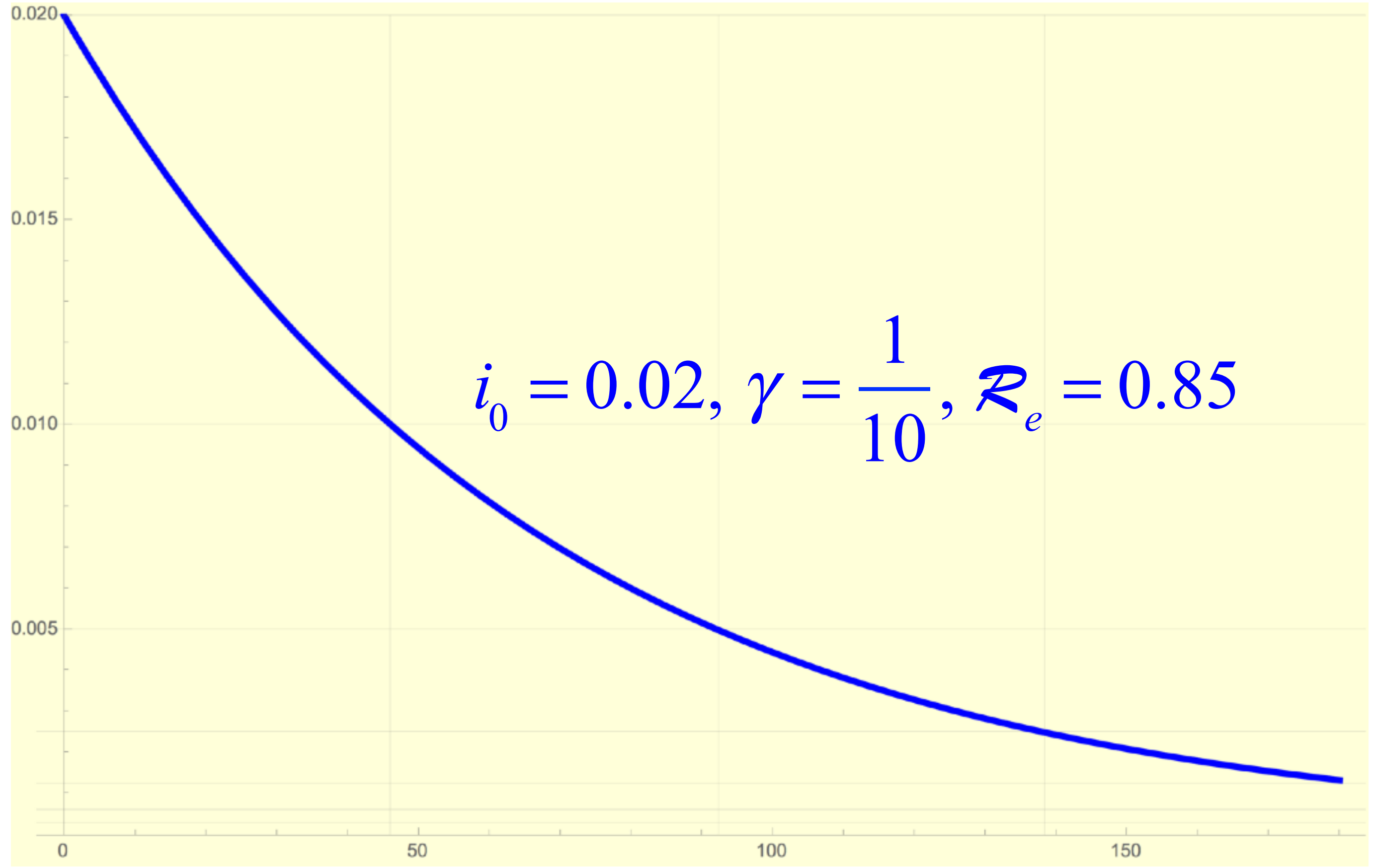
$$\frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t)$$

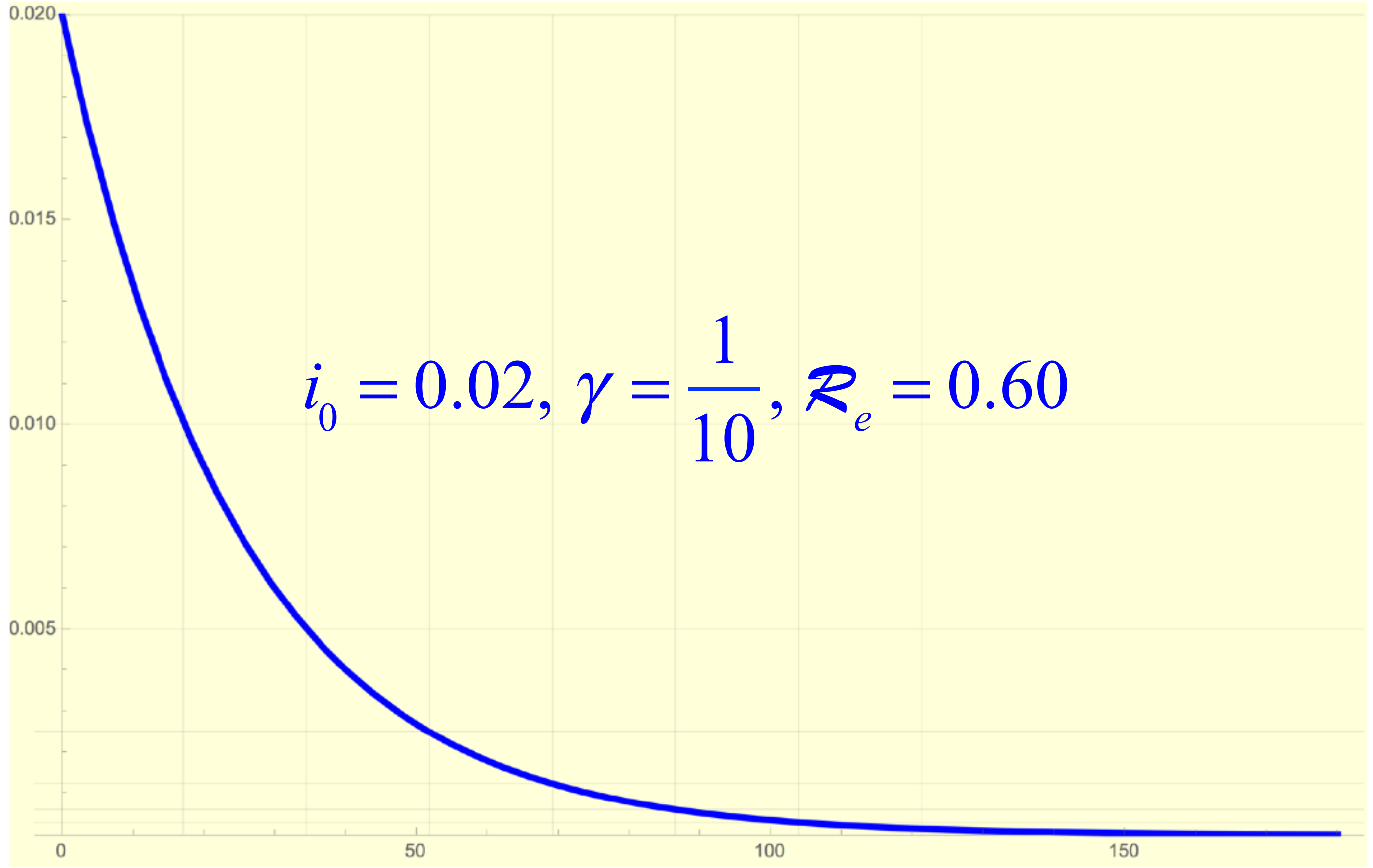
$$= -\gamma i(t)(1 - \frac{\beta}{\gamma} s(t)) = -\gamma i(t)(1 - \mathcal{R}_e(t))$$

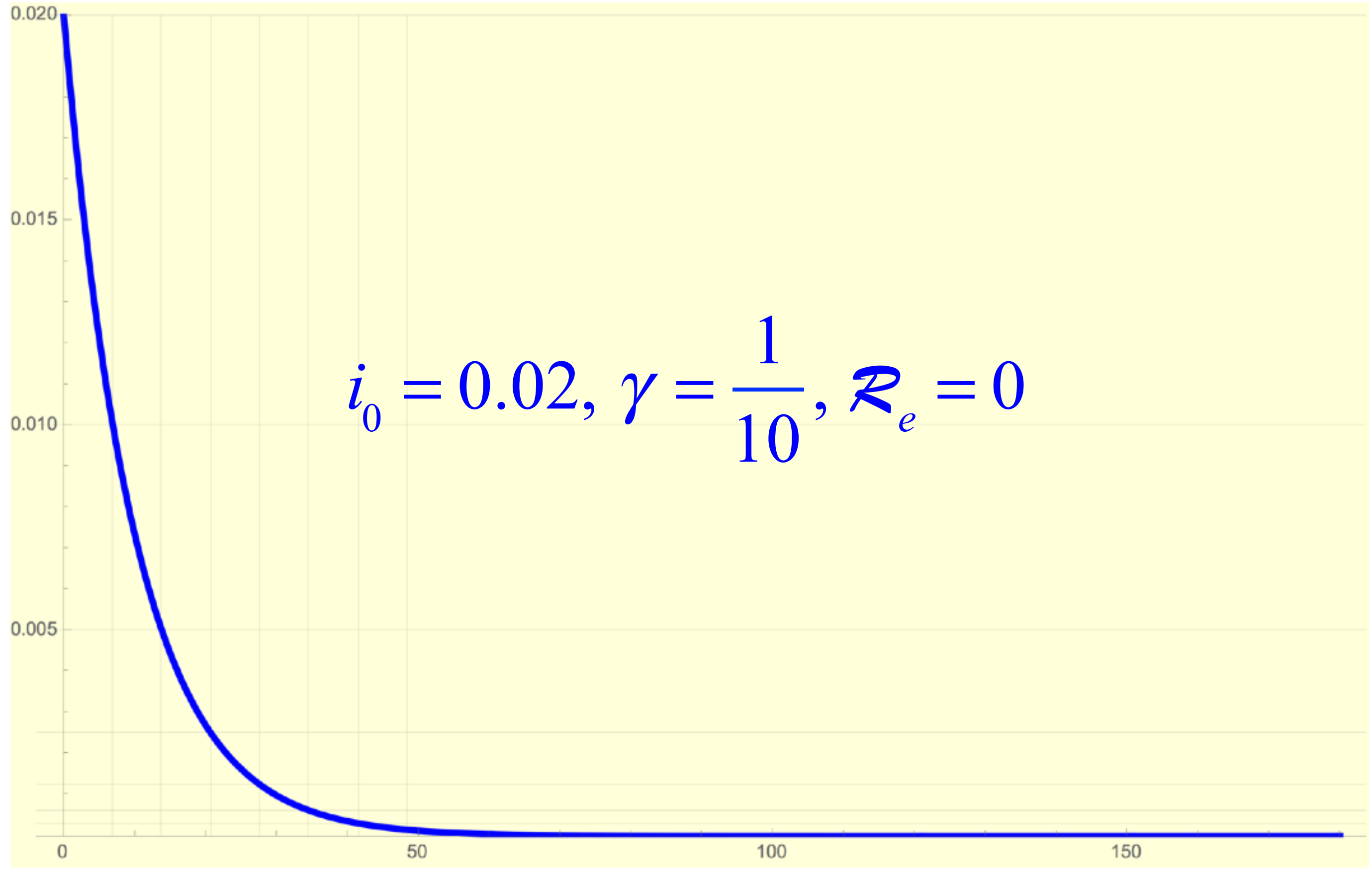
$$\text{stationary } \mathcal{R}_e : \; i(t) = i_0 e^{-\gamma(1-\mathcal{R}_e)t}$$

$$t_{1/2} = \frac{\ln 2}{\gamma}(1 - \mathcal{R}_e)^{-1}$$

- discloses the mechanics behind expectable prevalence decrease trajectory
- *stationary* effective reproduction number assumption is plausible enough for the qualitative assessment
- for the incidence viewpoint note then $ds(t)/dt = -\gamma \boldsymbol{R}_e(t) i(t)$
- asymptotically stable equilibrium 0 for $\boldsymbol{R}_e < 1$







CZ Models - Most probably incomplete picture (*unintentionally*)

Markov style short-time

ÚZIS

Mechanistic long-time

Filtered mechanistic any-time

BISOP

(Z)SEIAR

MUNI

Mechanistic "A"

IDEA

$$RI(t) = 6\log_2 Z_t + C_0$$

PES

Mechanistic "B"

Conclusion

- Mathematical modelling is the key part to create a platform where many experts from different areas can *share and dispute* their ideas
    - since mathematics is the ultimate language of this universe
- The more important decisions are to be made, the more we shall talk about the security and safety of our models
    - simply put **trust, but test**
    - mechanistic models do offer incredible opportunities to verify vital components of other models, here e.g. the reproduction number and risk index estimates as well as countermeasures effect

Revision History

- 2021/03/26: fork from the extended *Mathematical Epidemiology for Security Analysts* version

- 2021/03/30: release version 1