### Mathematical Epidemiology for Security Analysts

- extended version

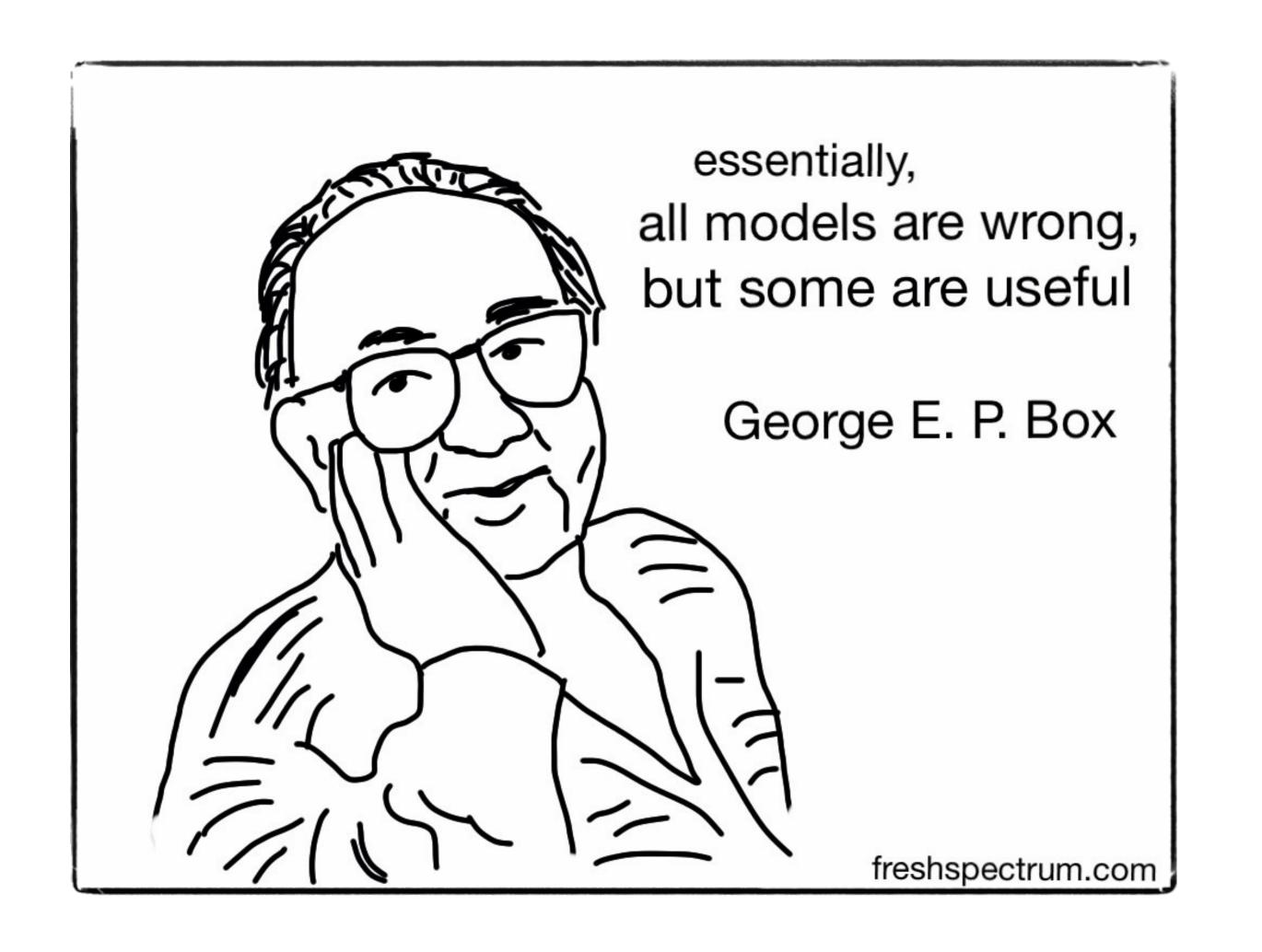
#### Tomáš Rosa, Ph.D.

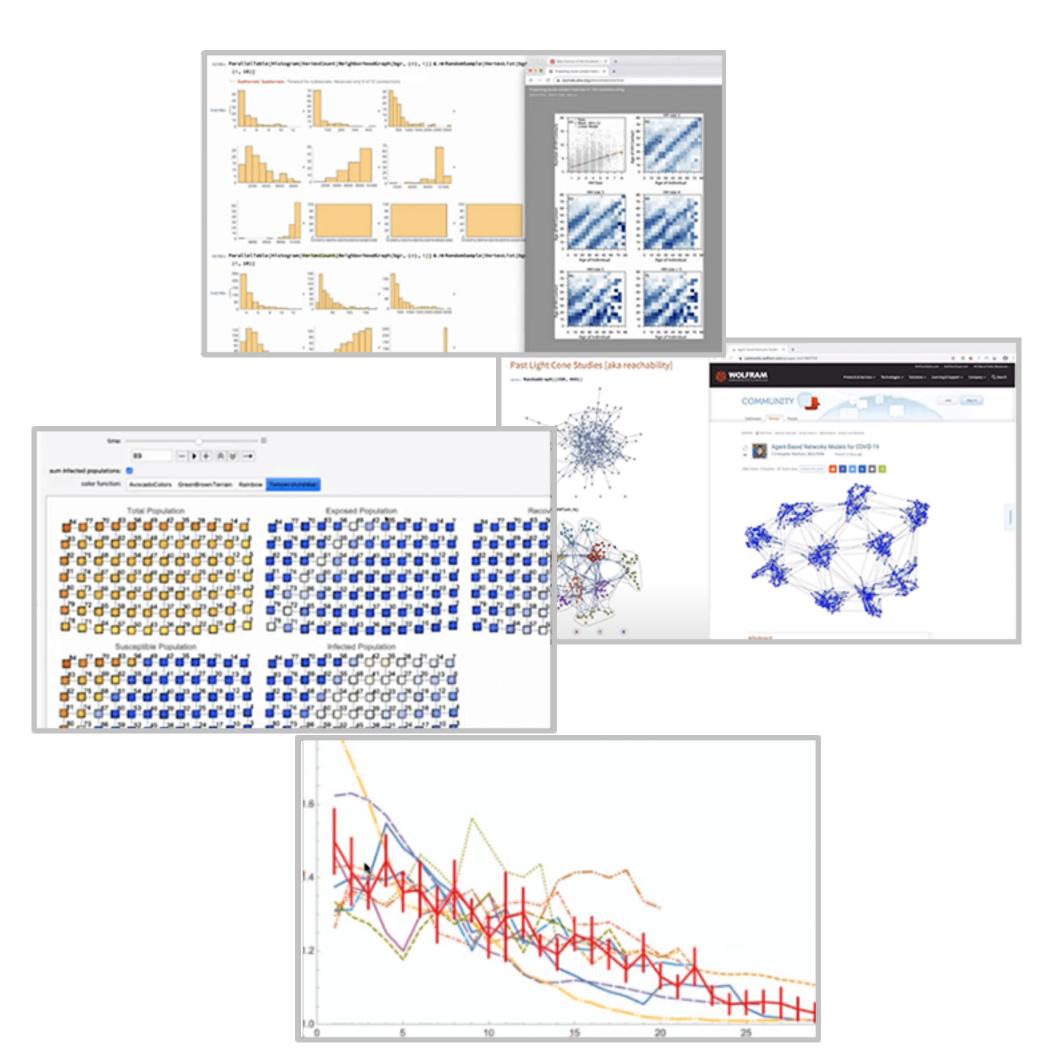
Cryptology and Biometrics Competence Centre of Raiffeisen BANK International in Prague

# 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"?



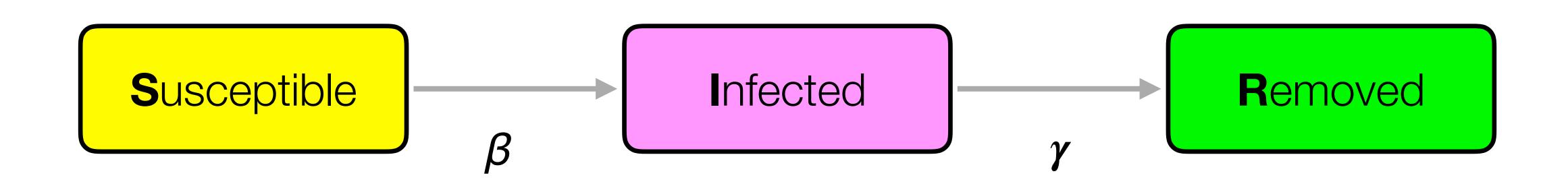


### We focus on compartmental models, today

- · Suitable for strategic modelling of a disease under the community spread mode
  - mechanistic principle, also invoking the law of mass action in various forms
  - deterministic computation of "precise averages"
  - reversibility by going back-and-forth in time (e.g. going backwards to the patient zero)
  - allow for strategy verification and testing of control mechanisms
  - excellent to understand the mechanical "Rules of Contagion" (noting [Kucharski, 2020])
- Other approaches include: stochastic models, network graphs, agent-based simulations, phenomenological growth models, ad hoc statistical estimations, etc.

#### SIR Compartmental Epidemic Model

- based on Kermack-McKendrick theory since 1927

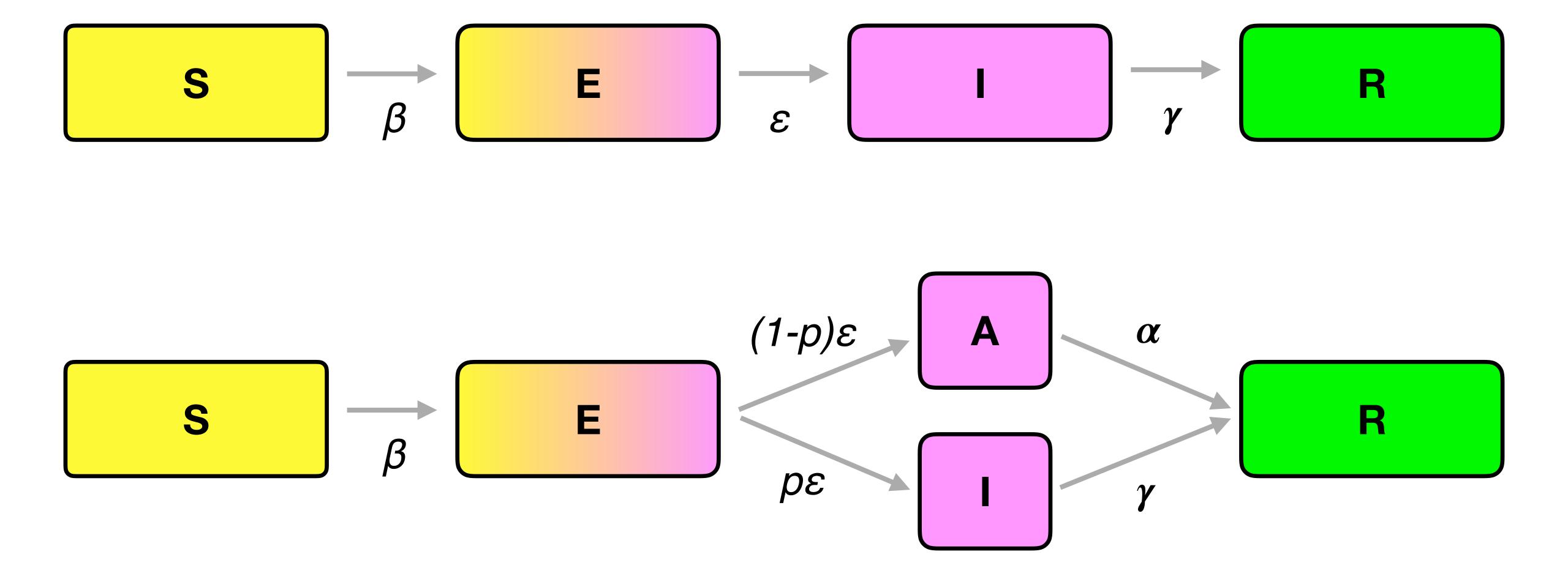


$$\frac{dS(t)}{dt} = -\frac{\beta}{N}I(t)S(t) \qquad \frac{dI(t)}{dt} = \frac{\beta}{N}I(t)S(t) - \gamma I(t) \qquad \frac{dR(t)}{dt} = \gamma I(t)S(t) - \gamma I(t) \qquad \frac{dR(t)$$

#### Towards Quantitative Answers

- · We focused on a very simple model to grasp the core principles of mechanistic modelling
  - this is also enough to get a qualitative idea of epidemics behaviour in general
- To closer describe the *quantitative* aspects of the particular disease, e.g. COVID-19 (or swine flu, etc.), we shall continue with adding further compartments
  - e.g. **SEIR** by adding **E** ~ **Exposed** for those **infected**, **but not infectious**, **yet**
  - the core principles are still valid, we just make the model more complex
  - be careful not to make it overly complicated; we shall stick with the simplest model providing an acceptable data fit

#### Towards COVID-19 Realities - SEIR and SEAIR



# Ordinary Differential Equations - What do they say here?

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

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

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

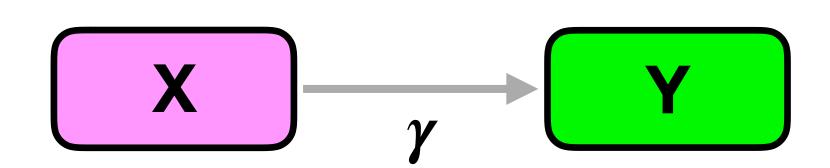
$$\frac{dX(t)}{dt} = \Lambda + \alpha X(t) + \beta X(t)Y(t)$$

- 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
  - A 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
  - $\beta$  analogous to  $\alpha$ , this time for a **mass** action ("degree-two") growth/decrease process

### Understanding (Isolated) Spontaneous Flow

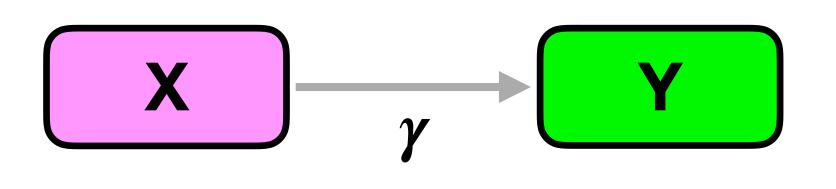
#### For an illustration, let us have

$$\frac{dX(t)}{dt} = -\gamma X(t) \text{ and } \frac{dY(t)}{dt} = \gamma X(t)$$



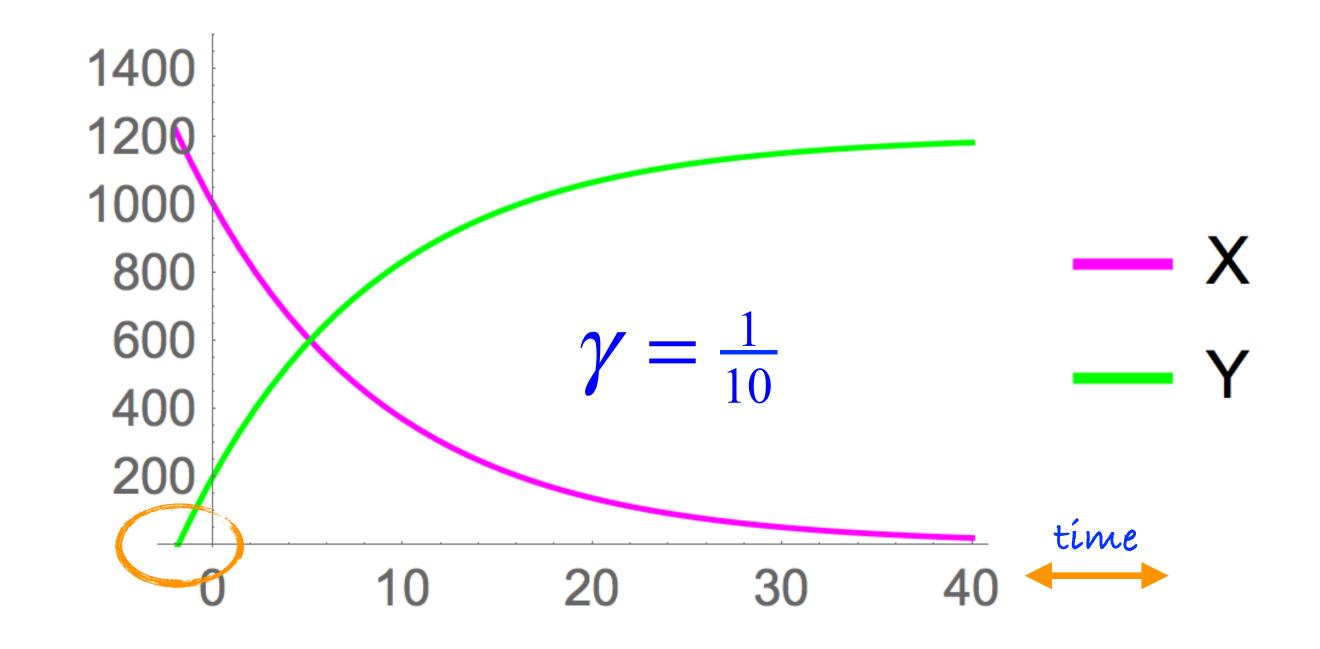
- We have two connected population decrease/growth sub-models
  - the solution is easy to find analytically
- · Be careful the constant relative rate assumption is helpful, but it is just an approximation
  - this is in turn equivalent to the exponential waiting time distribution, as noted below

### Analytical Solution of (Isolated) Spontaneous Flow



$$X(t) = X_0 e^{-\gamma t}$$

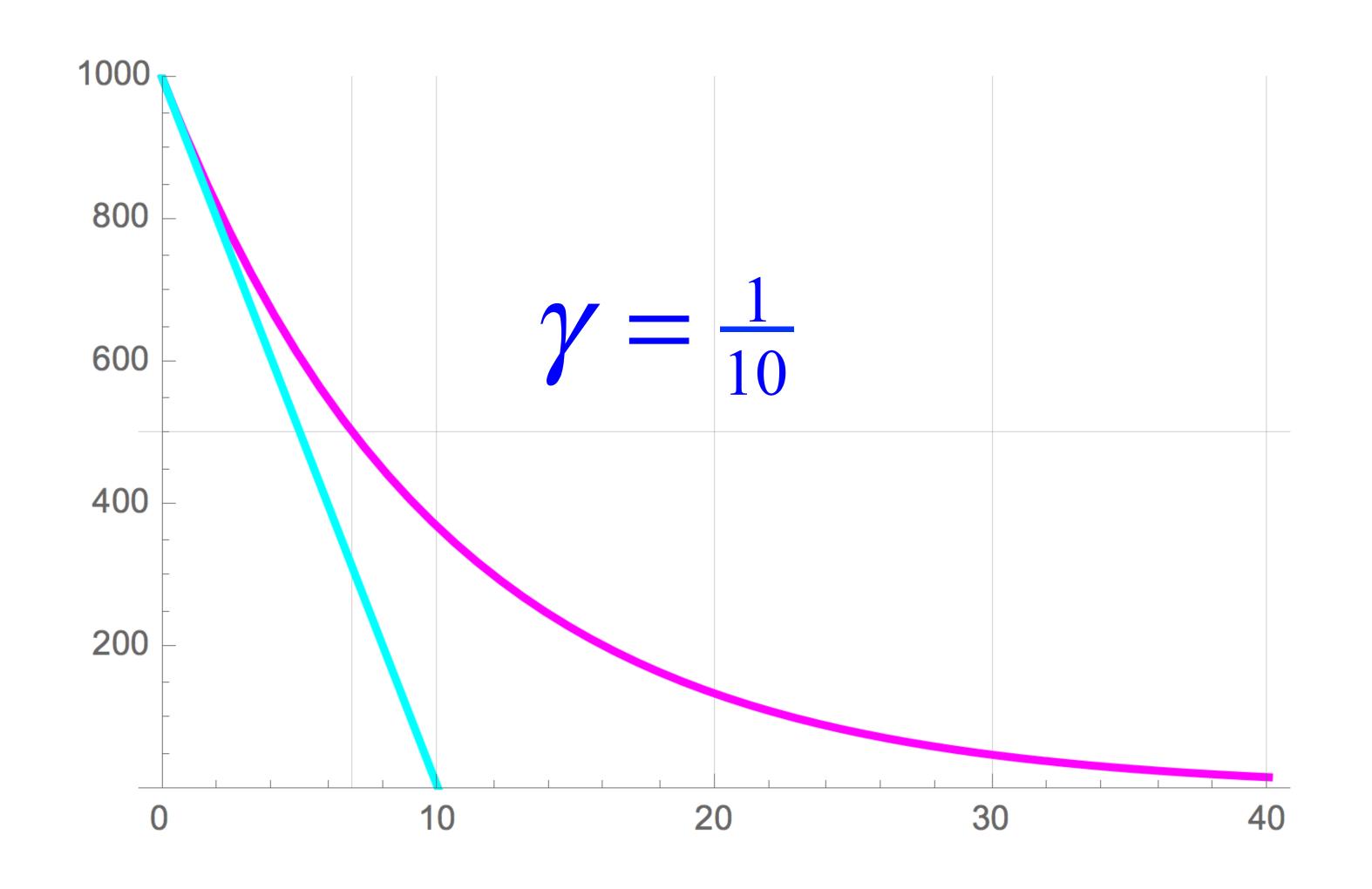
$$Y(t) = X_0 (1 - e^{-\gamma t}) + Y_0$$



- Having fitted the initial conditions  $(X_0, Y_0)$  and  $\gamma$ , we can run the model back and forth
  - the initial conditions can be further given for any time instant, not just in t=0
- · This is an example of deterministic models reversibility which is in turn very interesting in itself
  - sure, be careful about the interpretation of the results, e.g. What would y(t) < 0 remind us?

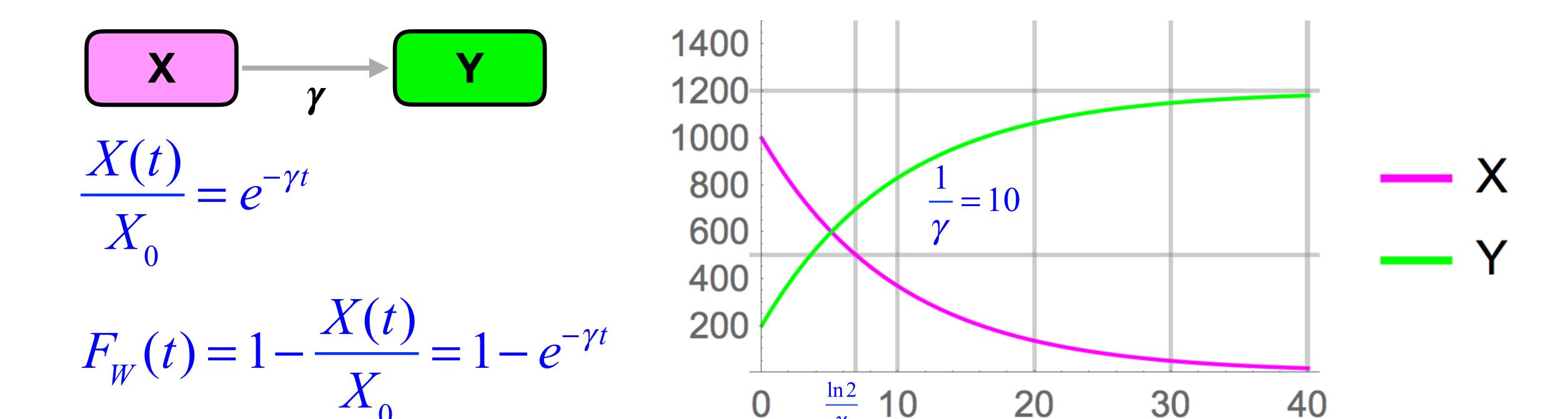
### Cautionary Note: Exponential vs Linear Decrease

- exponential decrease speed also decreases exponentially



time	ехр	lin
0	1000	1000
1	905	900
2	819	800
3	741	700
4	670	600
5	607	500
6	549	400
7	497	300
8	450	200
9	407	100
10	368	0

# Fitting the $\gamma$ Rate



- $F_W(t)$  is then the cumulative distribution function of a random variable W denoting the waiting time until a randomly chosen member of X leaves this compartment
  - this is the exponential distribution with  $\mathbf{E}[W] = 1/\gamma$  and median  $m[W] = (\ln 2)/\gamma$
- · So, we can fit the rate  $\gamma$  as the reciprocal of the (estimated) mean time of staying in the compartment X

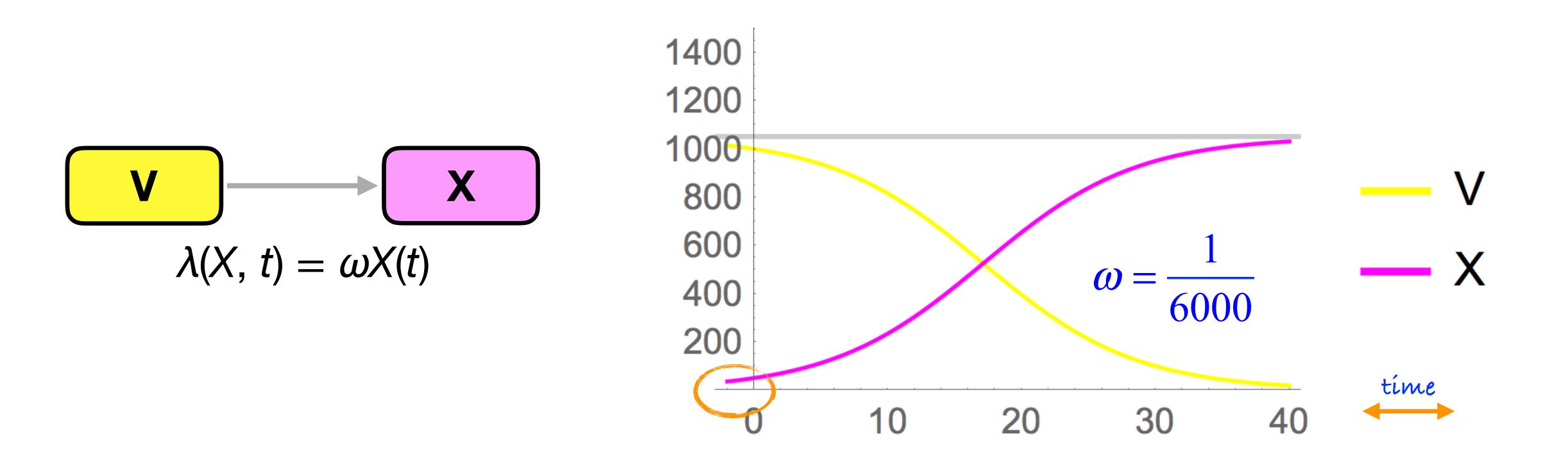
#### Understanding (Isolated) Induced Flow

$$\frac{dV(t)}{dt} = -\lambda(X,t)V(t) = -\frac{\beta}{N}X(t)V(t)$$

$$\frac{dX(t)}{dt} = \lambda(X,t)V(t) = \frac{\beta}{N}X(t)V(t)$$

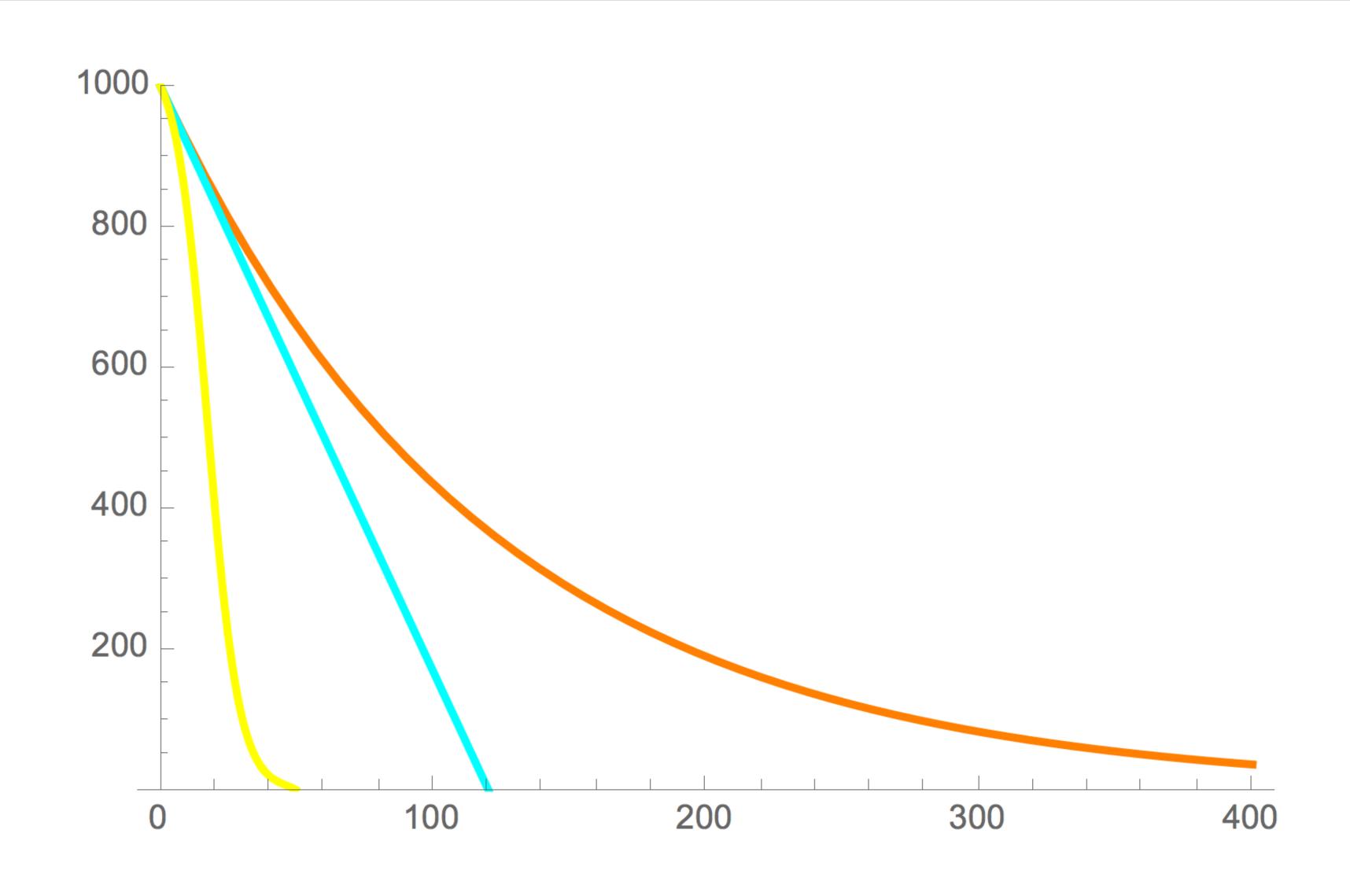
- In epidemiology,  $\lambda(X, t)$  is also called *infection force* 
  - it brings a nonlinear term invoking the law of mass action mechanism
- Note X(t)V(t) is corresponds to the number of possibly infective edges in the *complete bipartite contact graph* (assuming ideal mixing)  $K_{S(t),I(t)}$  of the population network in the given time instant
  - $\beta$  / N is the *probabilistic* instantaneous relative rate of the infection spreading through these edges

#### Isolated Mass Action Solution Example



- · Solution found numerically, though this particular one can still be found analytically
  - leading to the logistic equation / curve
  - contains not so surprising (almost) exponential episodes followed by somewhat relaxed regions

### Exponential, Linear, and Mass Action Slopes Comparison



### Cautionary Note on $\beta$ Parameter

- In our setup,  $\beta$  is the average rate of sufficient (for infection) contacts of one particular individual in the whole population (no matter in what compartment does this individual belong to)
- Note that many authors use a "reduced", per capita value of  $\beta' = \beta / N$ , where N is the population size
  - frequent and more correct in textbooks; also in our toy example  $\omega = \beta / N$
  - less frequent in many COVID-19 papers or computational approaches; so, we stay with the non-reduced variant here
  - anyway, be very careful of what is what this can be decided from equations

### The Basic and Effective Reproduction Number vs. Beta

- the forward and backward fitting approaches

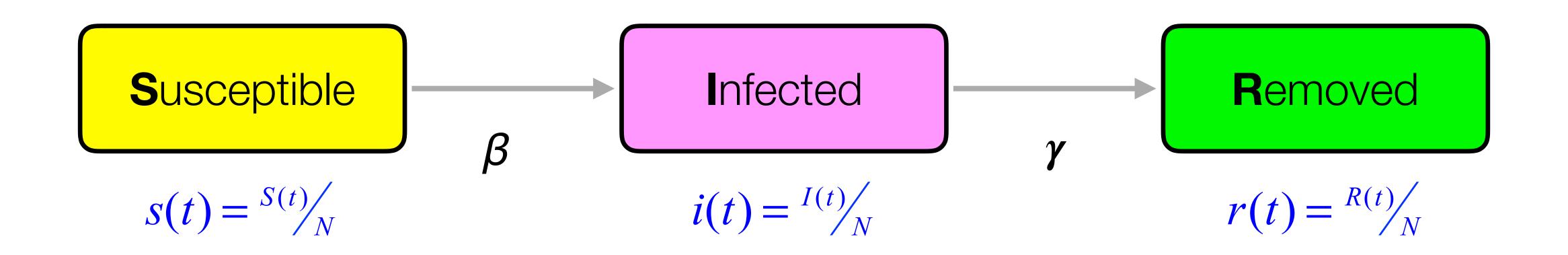
$$\mathcal{R}_{0} = \frac{\beta}{\gamma}$$

$$\mathcal{R}_{e}(t) = \mathcal{R}_{0} \frac{S(t)}{N}$$

\*) In this particular model

- In *quantitative* analysis,  $\beta$  is found by fitting the model to the observations data set
  - the aforementioned equation is then used for the basic reproduction number  $\mathbf{R}_0$  estimation
  - this is usually the appropriate approach there
- For *qualitative* investigation or if we have an independent  $\mathbf{R}_0$  estimate anyway, we can reverse this
  - we take the average infectious time  $1/\gamma$  together with the estimated  $R_0$  and compute  $\beta$
  - be careful about a possible chicken-egg circle than

### Going Dimensionless



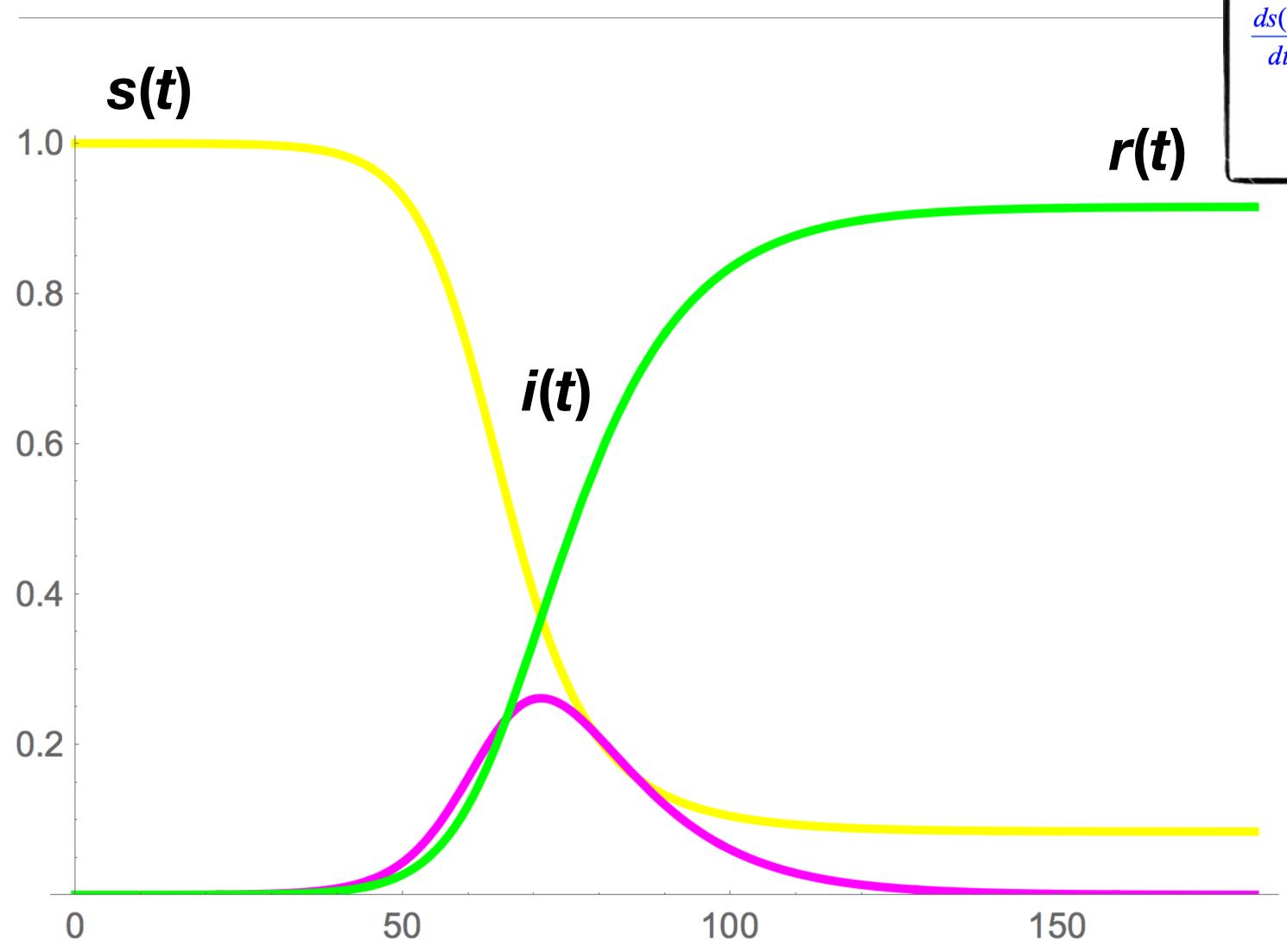
$$\frac{ds(t)}{dt} = -\beta i(t)s(t) \qquad \frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t) \qquad \frac{dr(t)}{dt} = \gamma i(t)$$

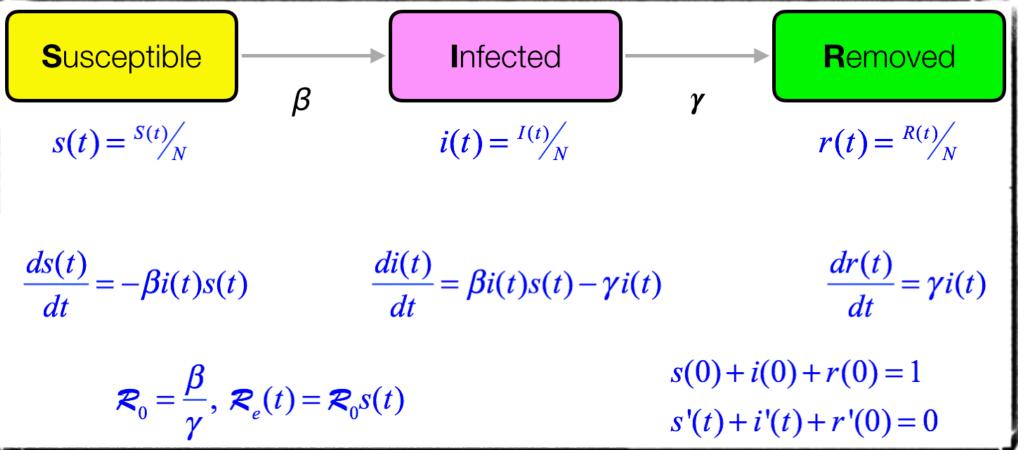
$$\mathcal{R}_0 = \frac{\beta}{\gamma}, \, \mathcal{R}_e(t) = \mathcal{R}_0 s(t)$$

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

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

# SIR Solution Example





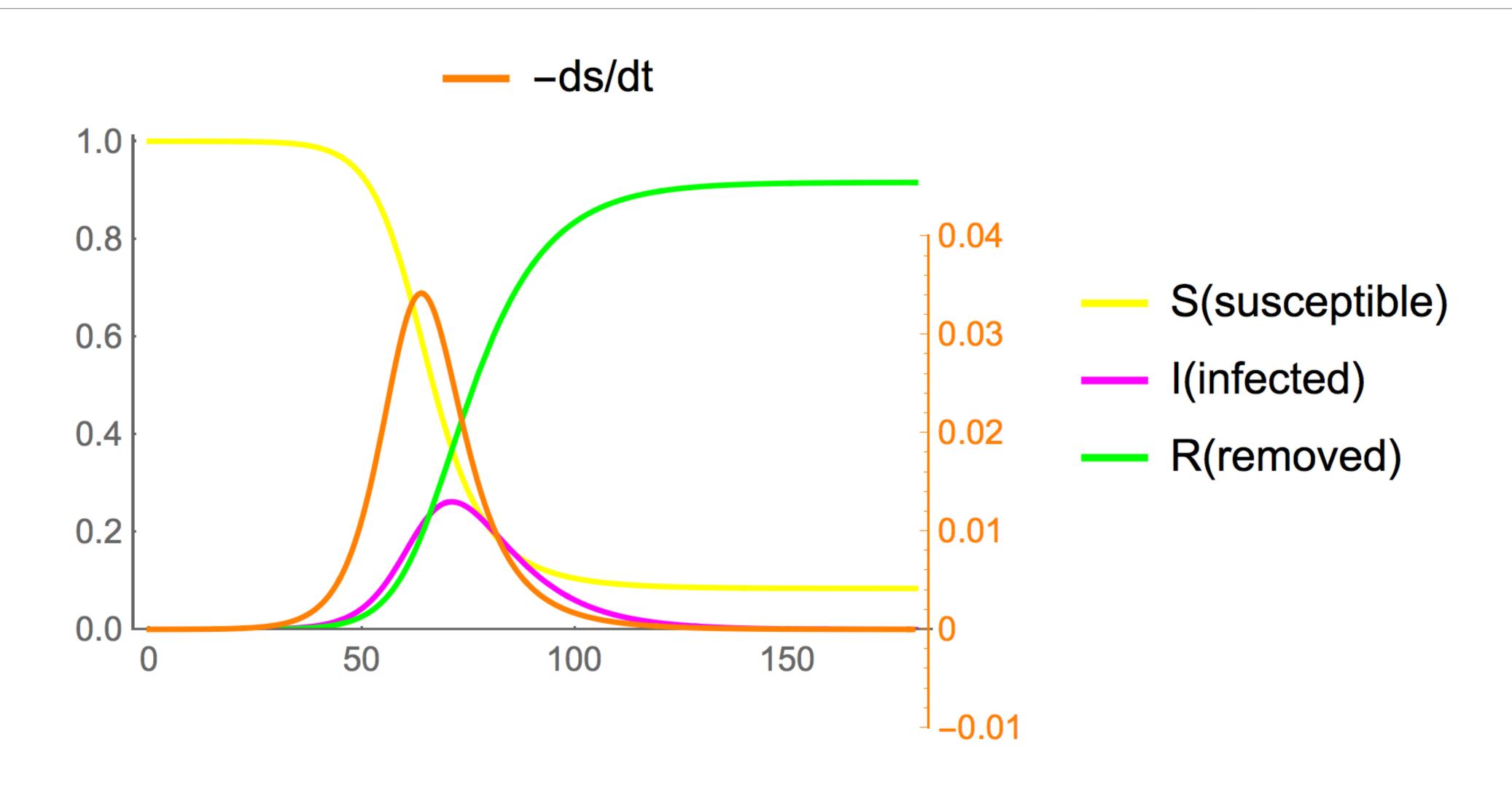
$$I(0) = 10^{-5}$$

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

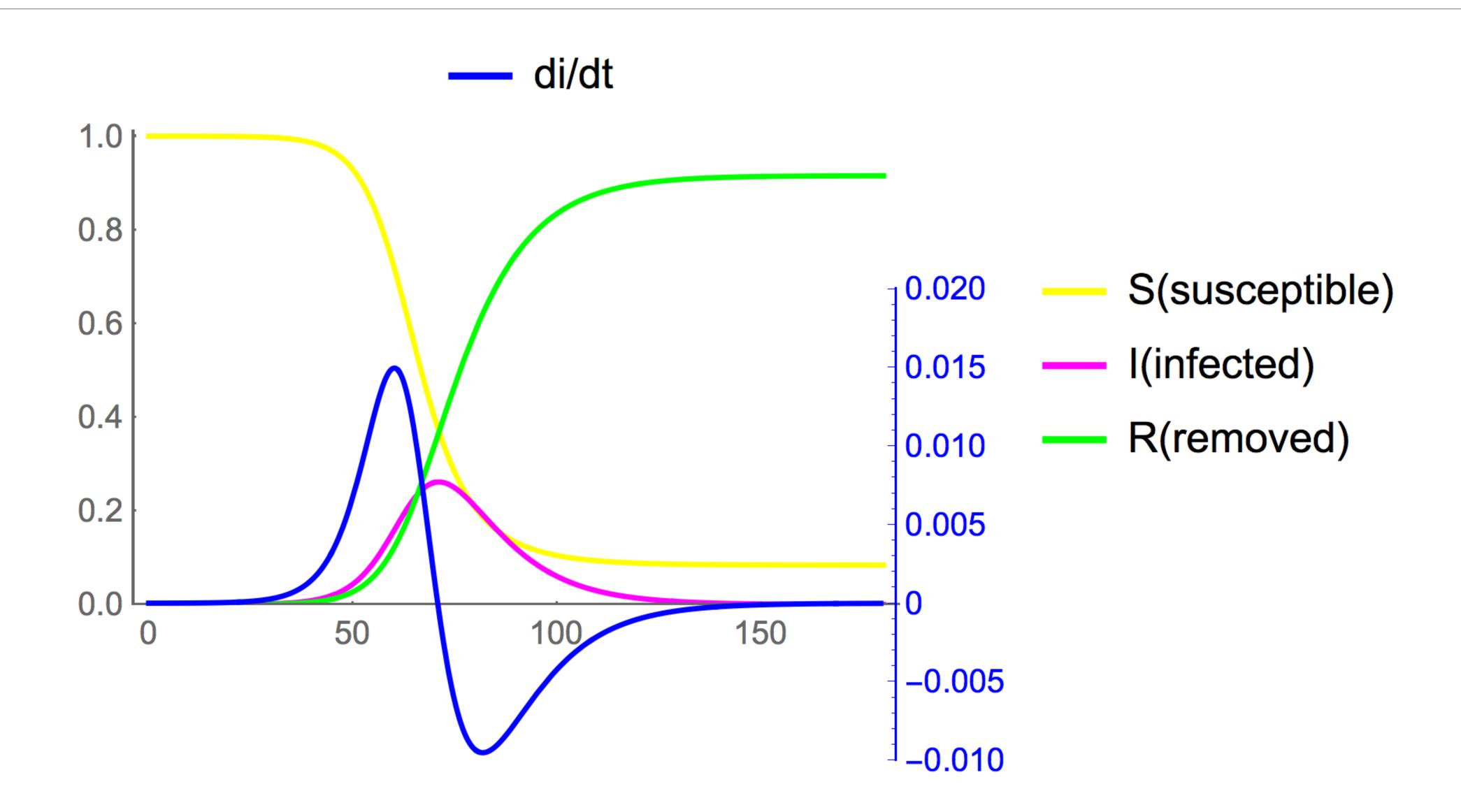
$$\gamma = \frac{1}{10}$$

$$R_0 = 2.70$$

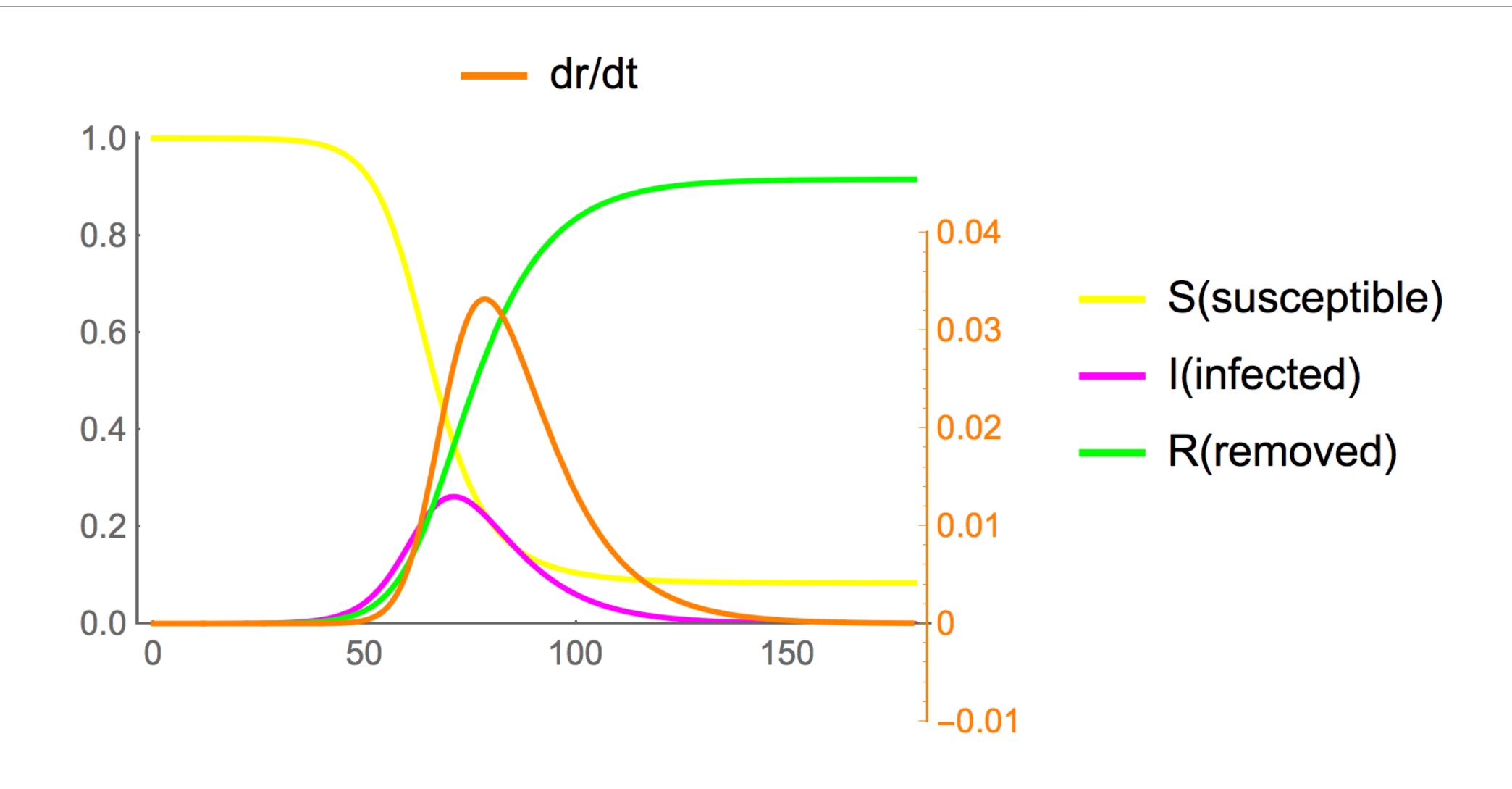
#### Considering the s(t) Derivative ~ Incidence



#### Considering the *i*(*t*) Derivative ~ Prevalence Change Rate



# Considering the r(t) Derivative ~ Removed Change Rate



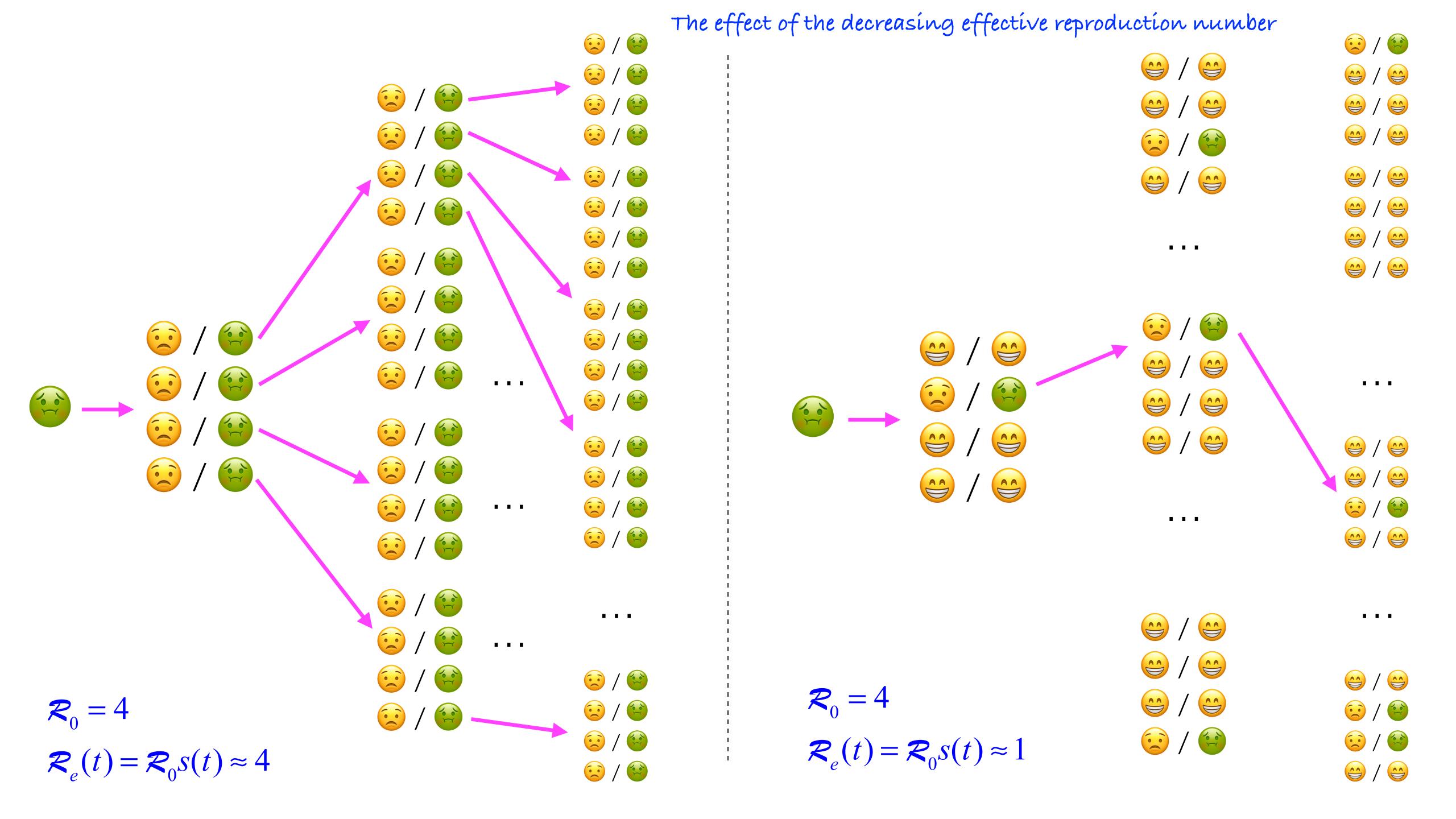
#### All Those "R"s

$$\mathcal{R}_{0} = \frac{\beta}{\gamma}$$

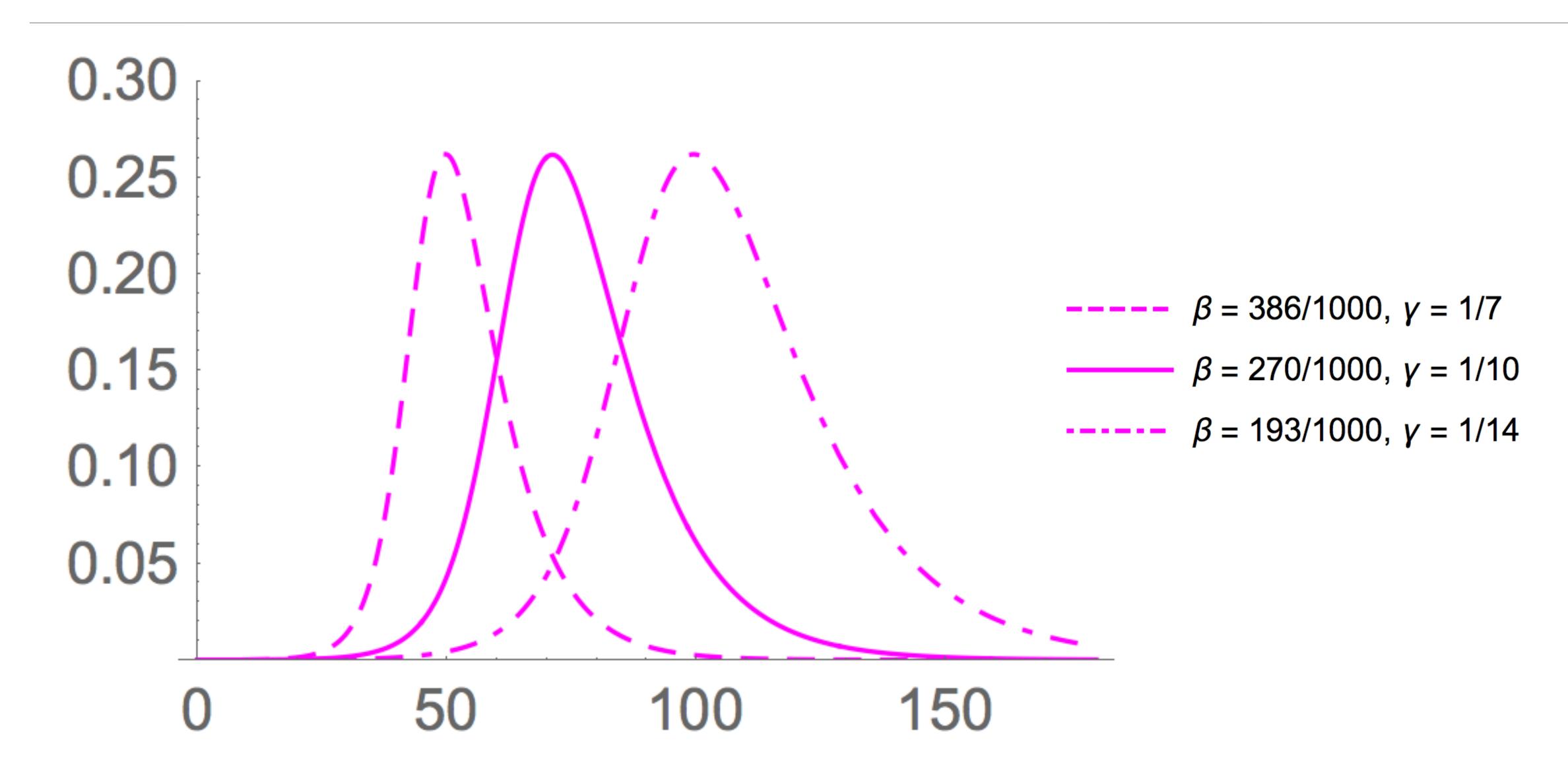
$$\mathcal{R}_{e}(t) = \mathcal{R}_{0} \frac{S(t)}{N} = \mathcal{R}_{0} s(t)$$

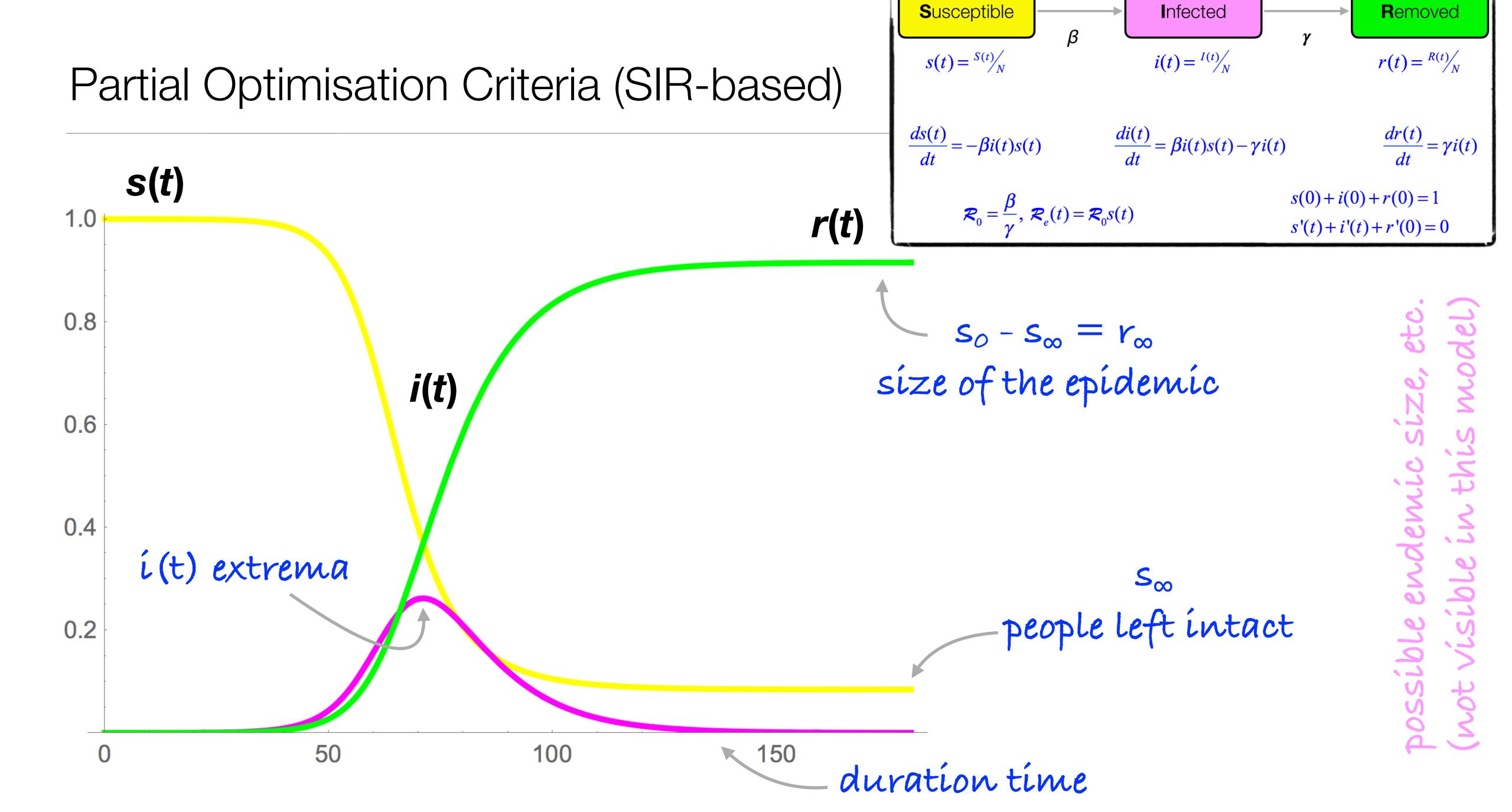
$$controlled - \mathcal{R}_{0} = \frac{\beta_{t}}{\gamma}$$

- Basic reproduction number R<sub>0</sub>
  - 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  $R_{0,t}$ 
  - what we aim for with our interventions



# Same $\mathbf{R}_0$ , Different Timing





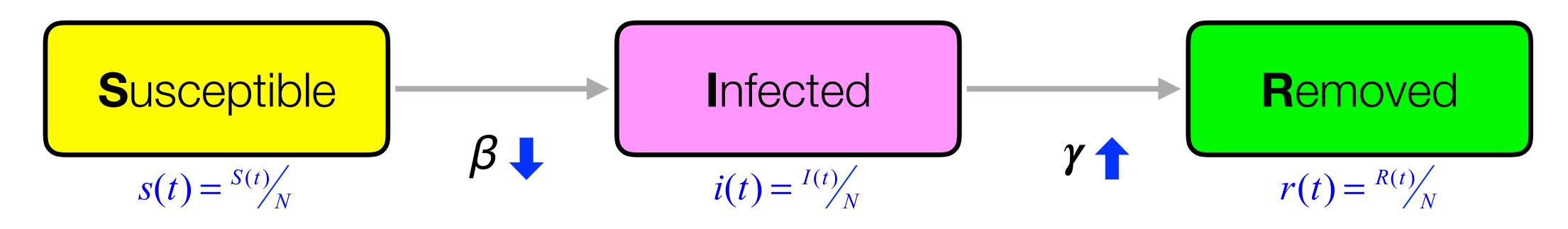
### Anti-Epidemic Interventions

#### transmission rate intervention

- moderating contact rate
- decreasing infection probability

#### removal rate intervention 1

- broad testing
- contact tracing
- vaccination



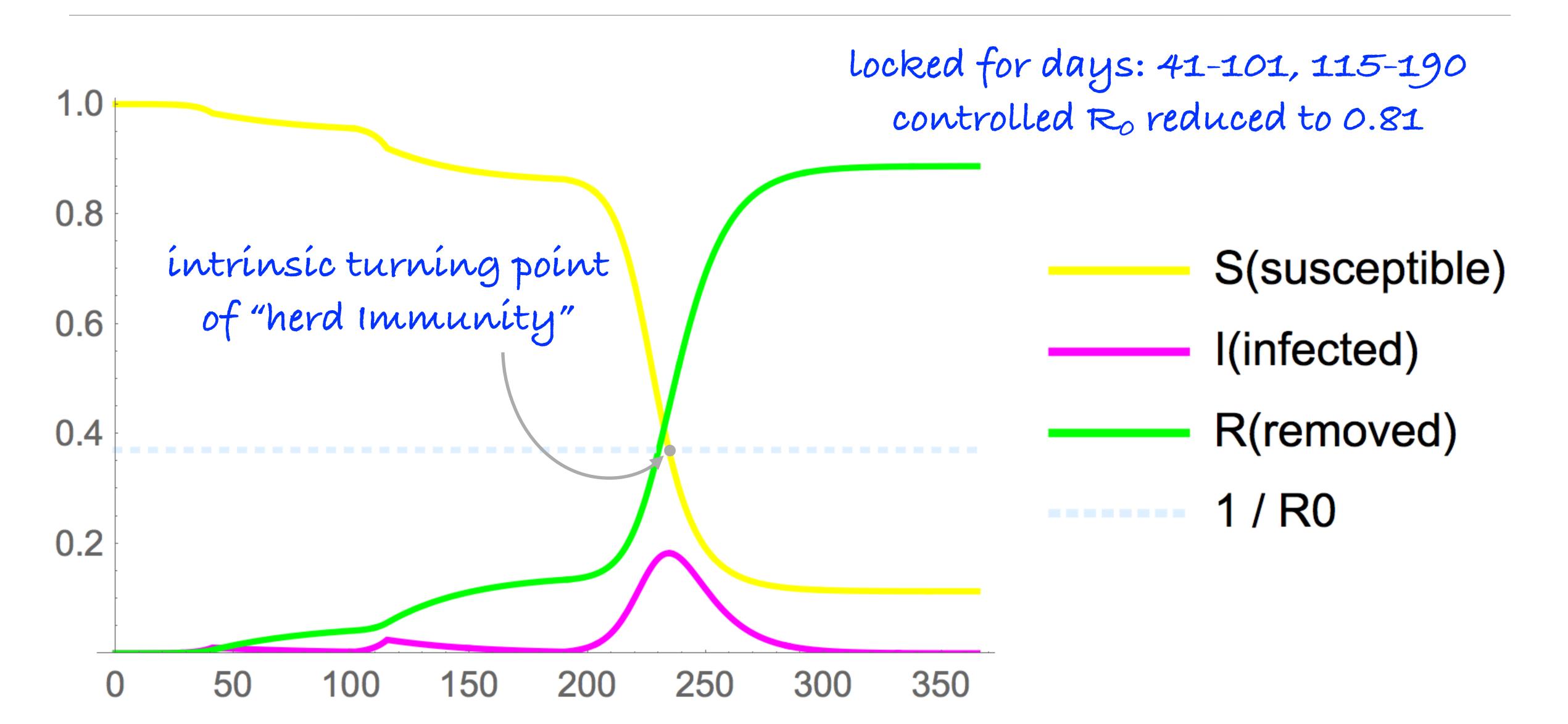
$$\frac{ds(t)}{dt} = -\beta i(t)s(t) \qquad \qquad \frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t) \qquad \qquad \frac{dr(t)}{dt} = \gamma i(t)s(t) - \gamma i(t) \qquad \qquad \frac{dr(t)}{dt} = \gamma i(t)s(t) - \gamma i(t) -$$

$$Recall black {\cal R}_0 = rac{eta}{\gamma}, \ {\cal R}_e(t) = {\cal R}_0 s(t)$$
  $s'(t) + i'(t) + r'(t) = 0$ 

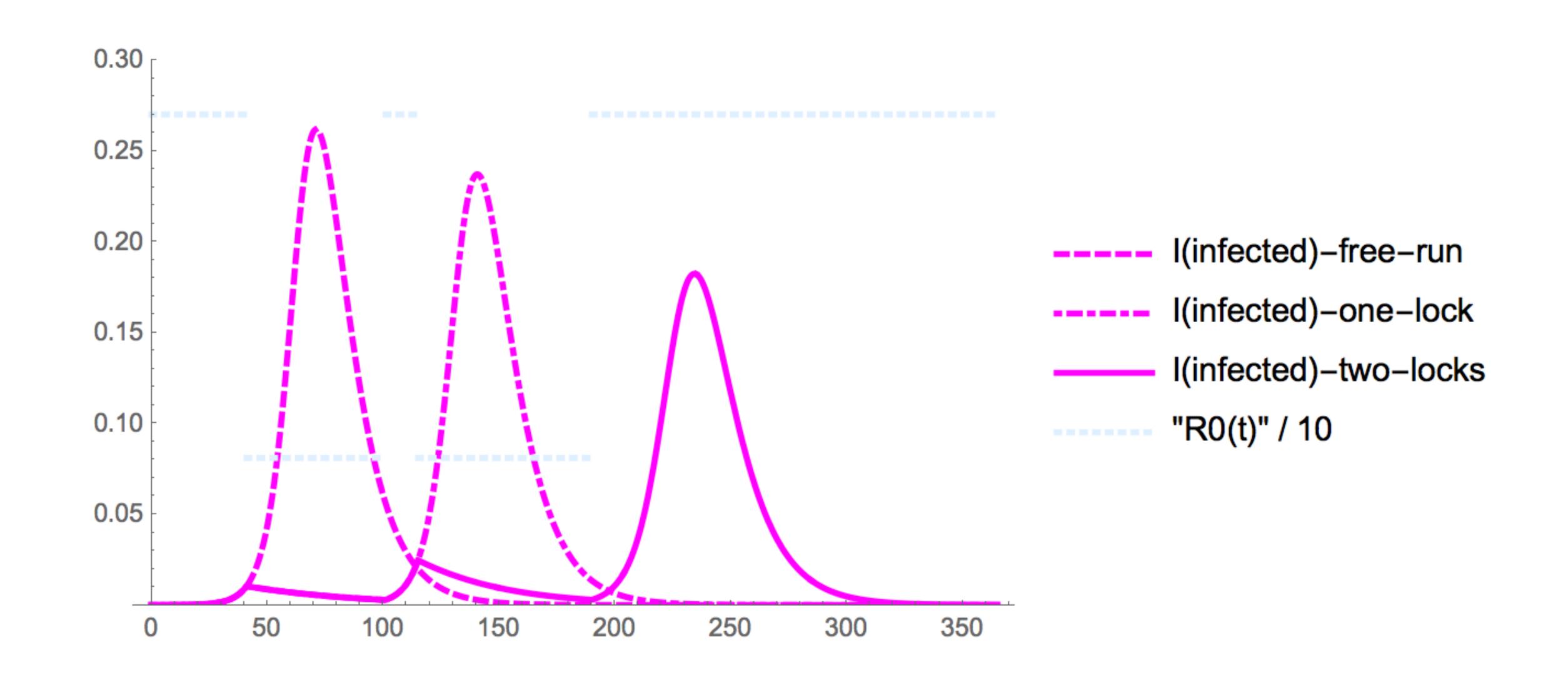
### Lockdown as an Algorithmic Trade-Off

- · 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)

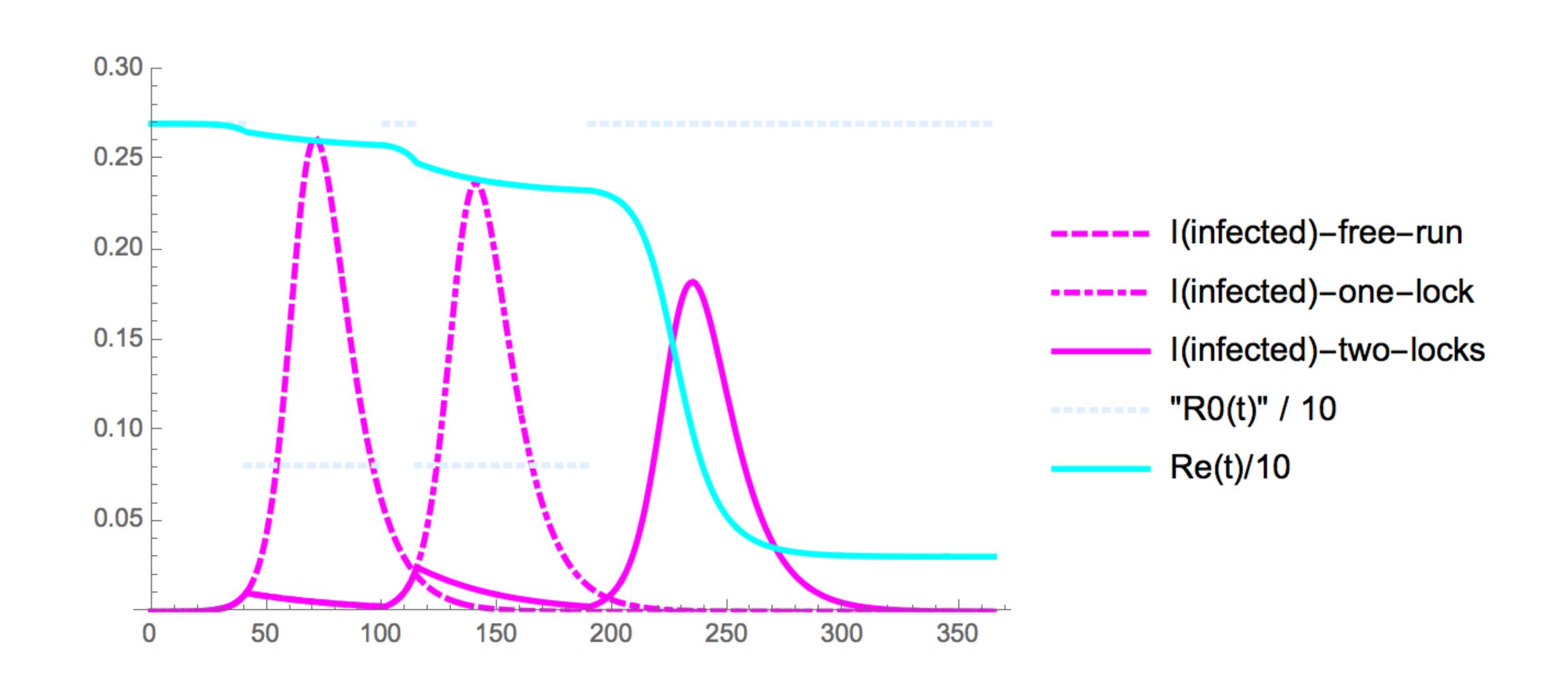
#### Example: Qualitative Study of Two Ideal Consecutive Lockdowns



### Example: Infectious Compartment Comparative Close-Up

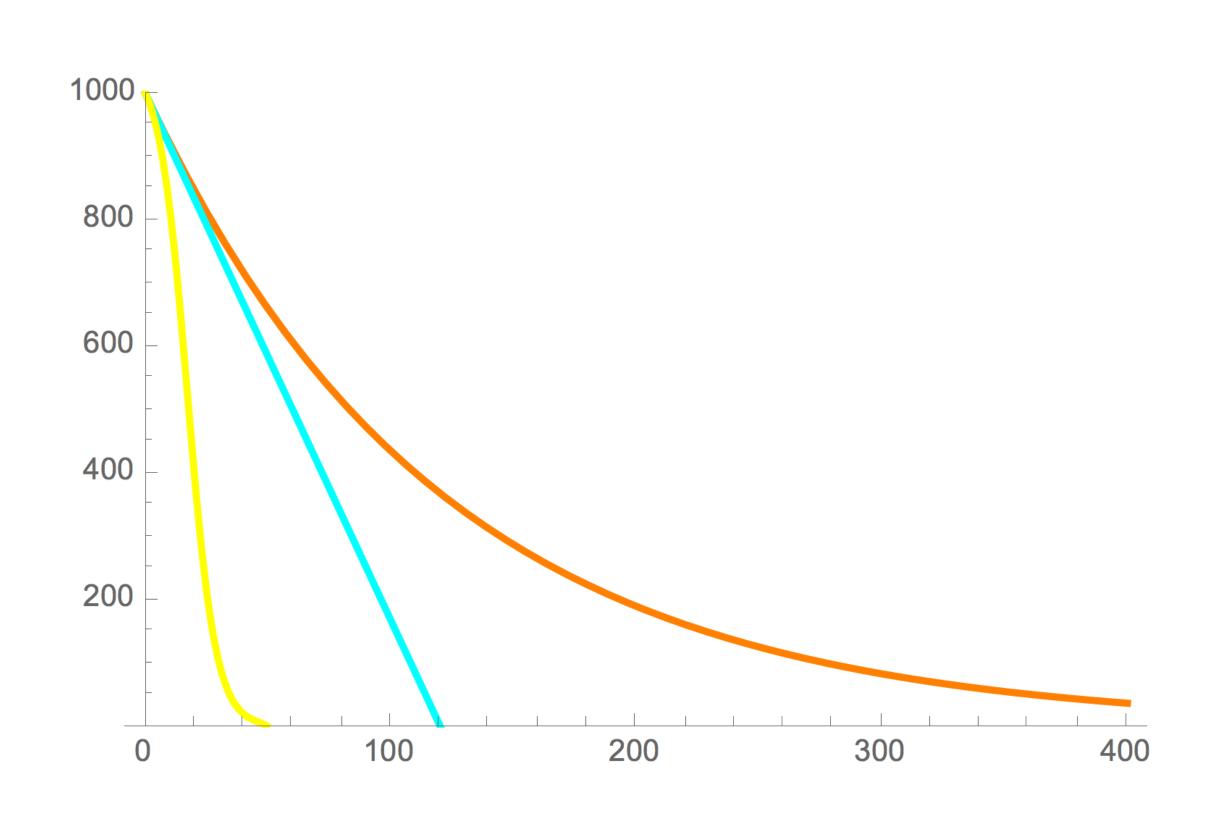


#### Locked in Lockdowns - Effective Reproduction Number Noted



# Why the Viral Load is Soooo Important

- There is a big difference in between the locked (decreasing) and the released (growing) prevalence slopes; assume  $R_e > 1$ 
  - the exponential decrease slows down exponentially, since only a degree-one factor withdraws infectious people (if testing and tracing is not working perfectly)
  - the growth is then a degree-two mass action process boosted by the instantaneous viral load
  - for the idea, recall our experiments with the isolated flows before



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

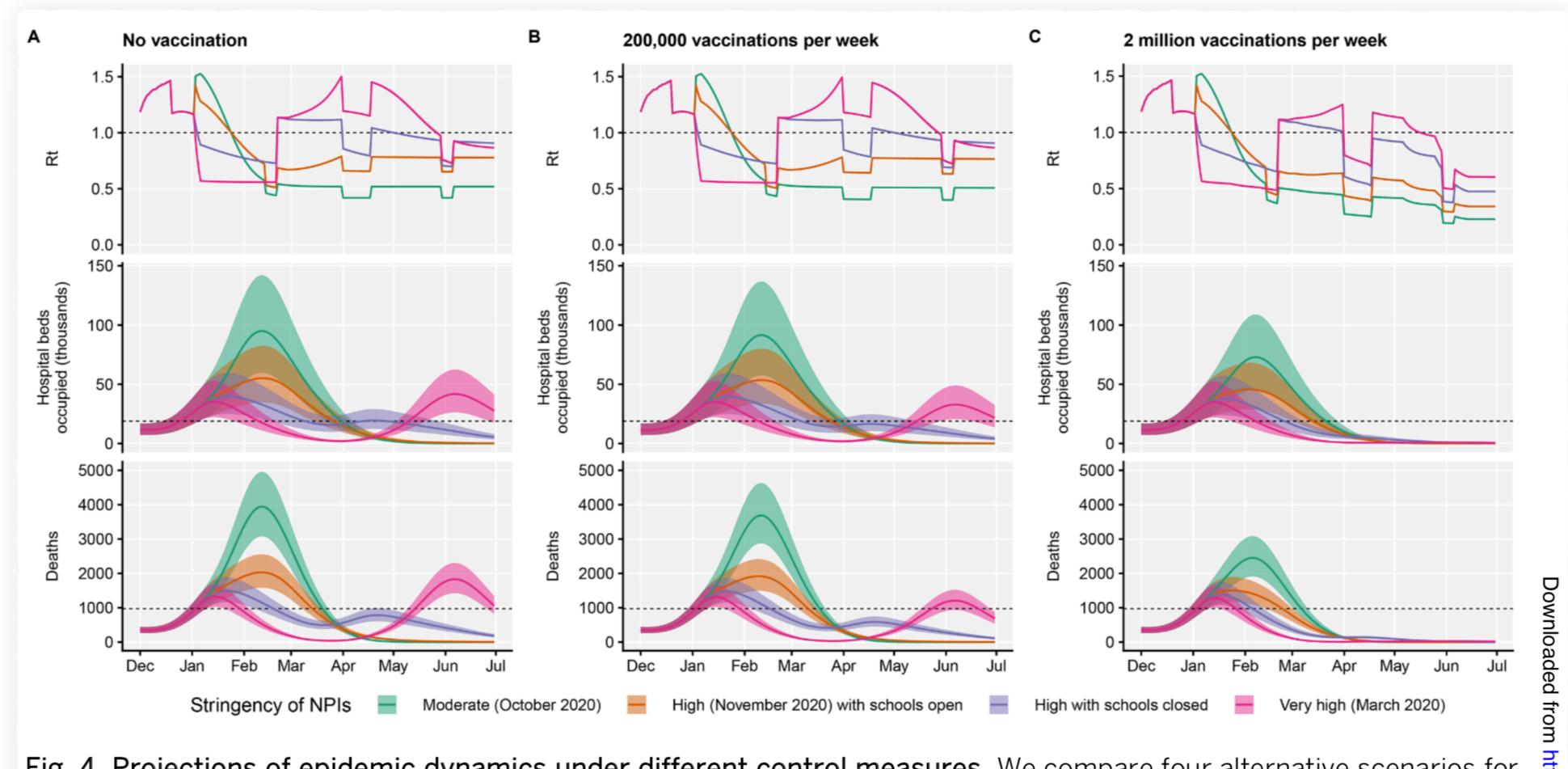


Fig. 4. Projections of epidemic dynamics under different control measures. We compare four alternative scenarios for non-pharmaceutical interventions from 1 January 2021: (i) mobility returning to levels observed during relatively moderate restrictions in early October 2020; (ii) mobility as observed 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

#### Basic Vaccination Inequalities

$$\mathcal{R}_{e}(t) = \mathcal{R}_{0}s(t) = \mathcal{R}_{0}(s_{0} - p(t))$$

$$\approx \mathcal{R}_{0}(1 - p(t)) \text{ for } s_{0} \approx 1$$

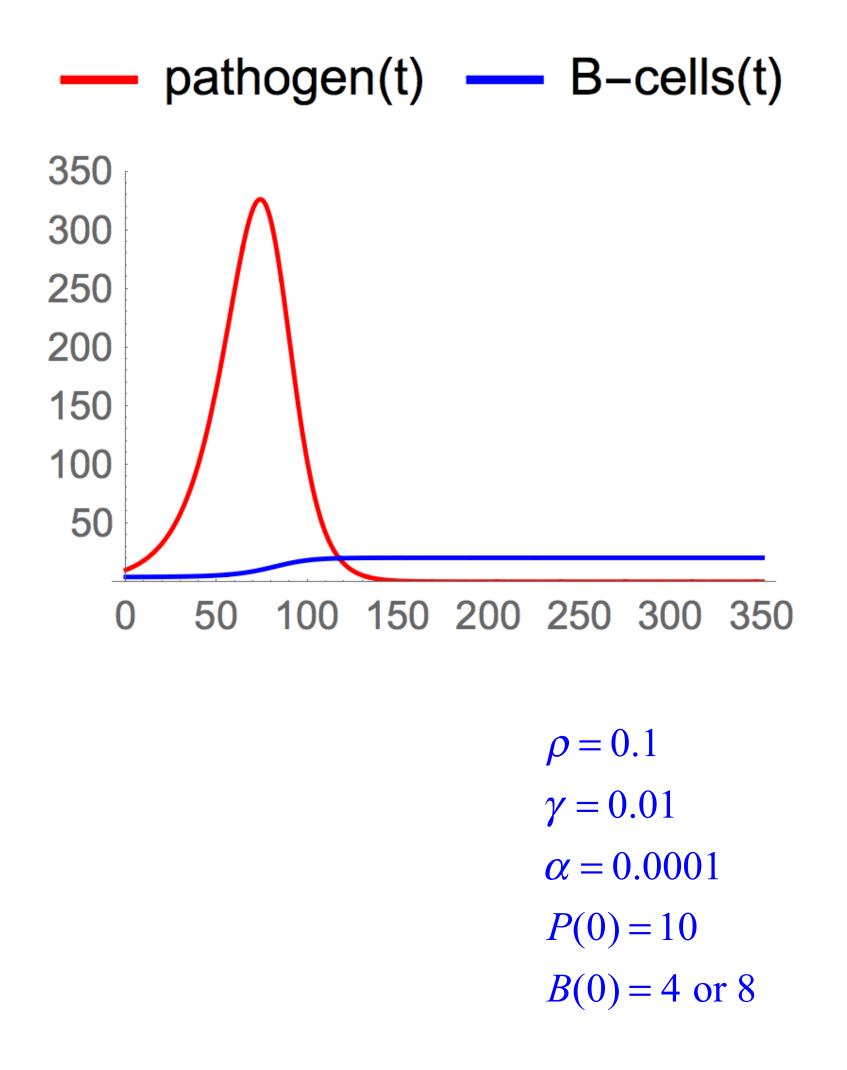
$$\mathcal{R}_{e}(t) < 1 \Leftrightarrow p(t) > 1 - \frac{1}{\mathcal{R}_{0}}$$

$$\text{resp. } p_{\varepsilon}(t) > \frac{1}{\varepsilon} \left(1 - \frac{1}{\mathcal{R}_{0}}\right)$$

- Assumptions:
  - vaccine distributed *uniformly among* yet-susceptible people
  - vaccine efficacy  $\varepsilon$
  - 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

#### In Vivo Models

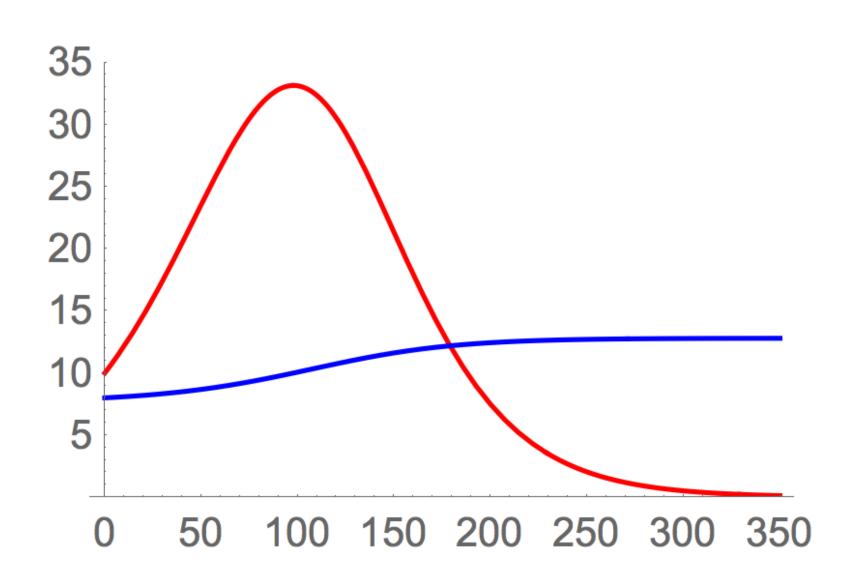
- mathematical epidemiology meets the body



#### Gilchrist - Sasaki model

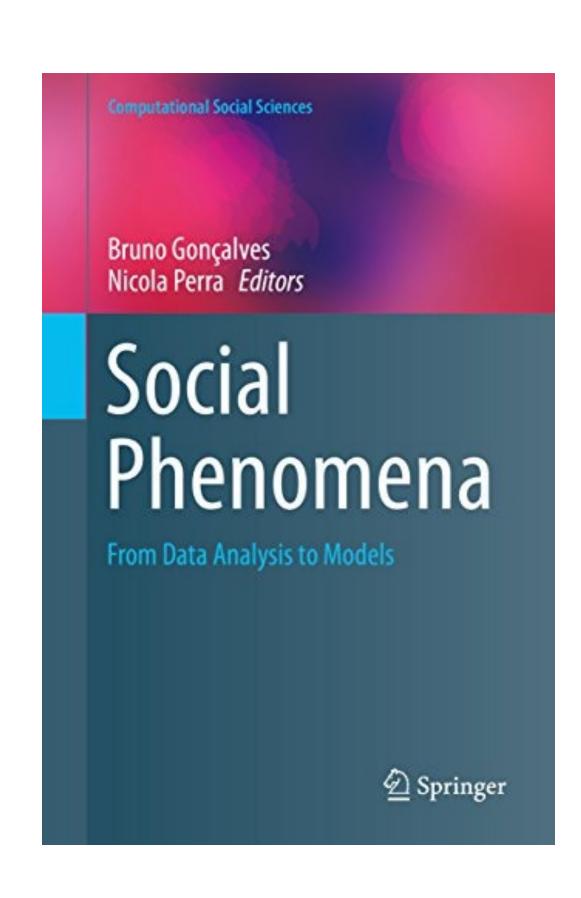
$$\frac{dP(t)}{dt} = \rho P(t) - \gamma B(t) P(t)$$

$$\frac{dB(t)}{dt} = \alpha B(t) P(t)$$



#### Computational Social Sciences

- mathematical epidemiology meets the people



- · Mathematical modelling of the whole society
  - epidemiology in demographic context
  - anti-epidemic measures simulation
  - non-compliance impacts, backward bifurcation effect
  - generalised contagion of (mis)information, behaviour patterns, etc.
  - financial security

## Qualitative Realities



Trust the mathematics, not so the mathematicians.

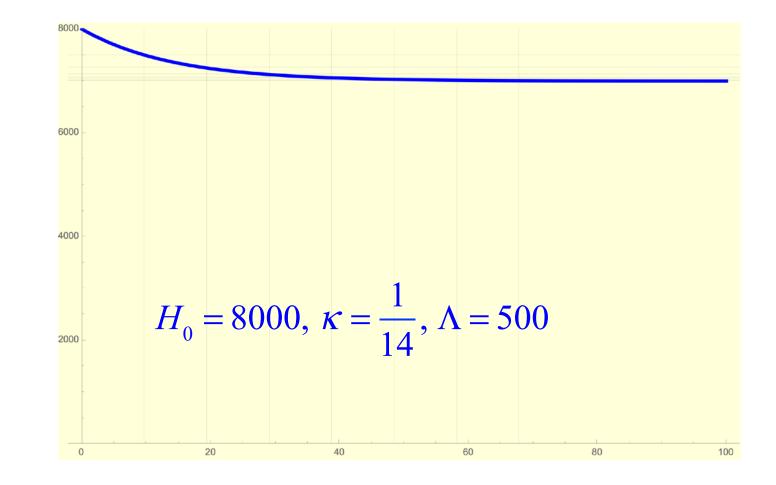
## Consider a "Constant In, Fraction Out" Mechanism

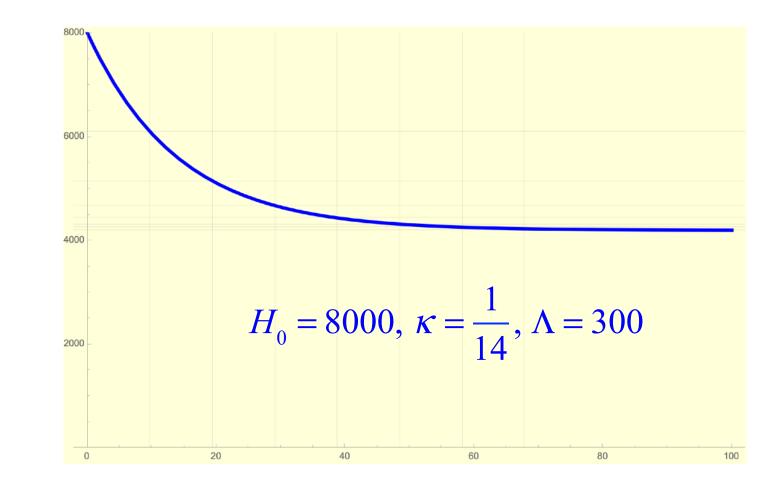
$$\frac{dH(t)}{dt} = \Lambda - \kappa H(t)$$

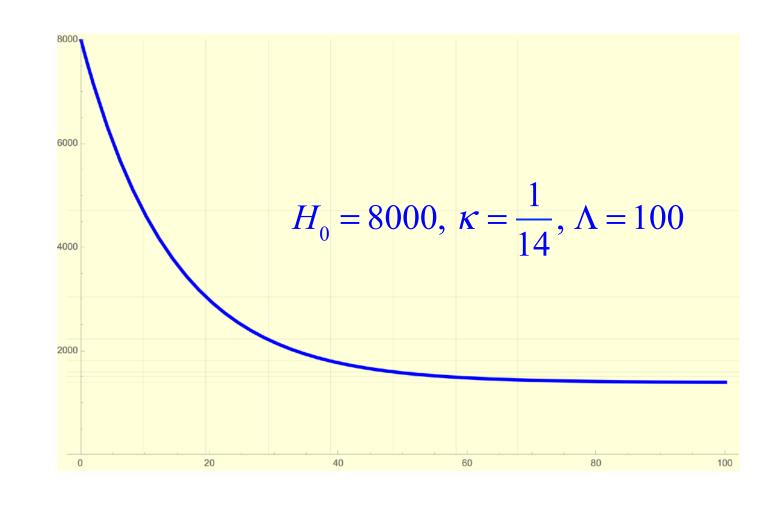
$$H(t) = H_0 e^{-\kappa t} + \frac{\Lambda}{\kappa} (1 - e^{-\kappa t})$$

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

- simplified mechanics of hospital occupancy under stationary incidence levels
- illustrates expectable behaviour under (quasi)endemic conditions
- asymptotically stable equilibrium  $\Lambda/\kappa$







# Prevalence Decrease Roadmap - Reality versus Mighty Wish

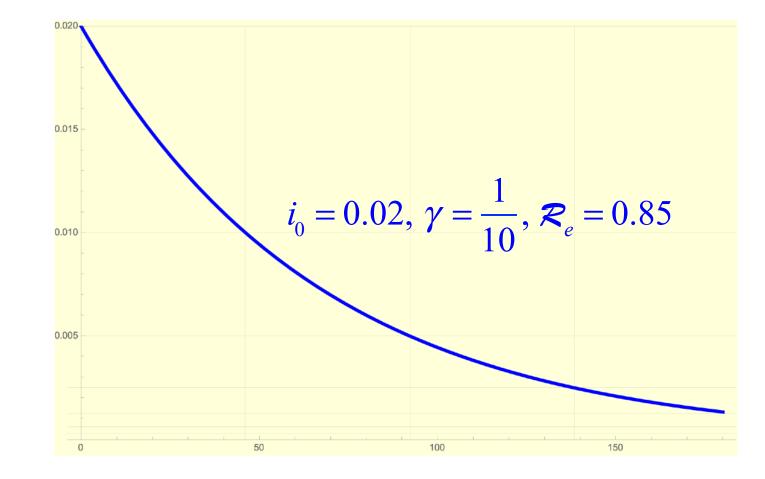
- also relevant for the important viral load estimates

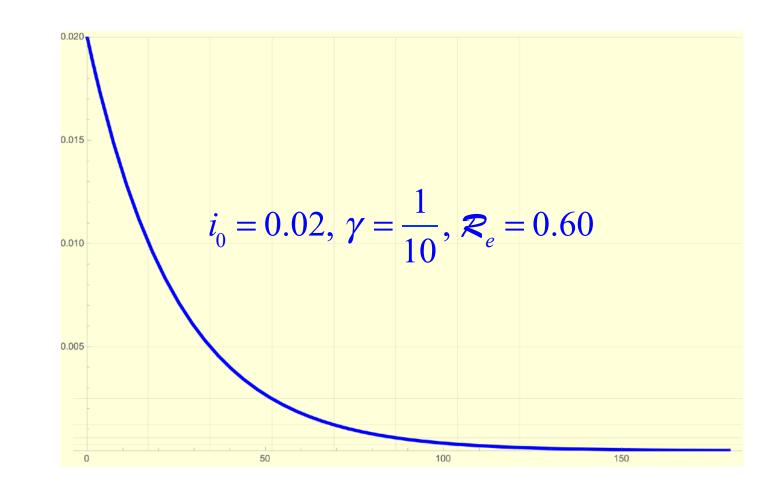
$$\frac{di(t)}{dt} = \beta i(t)s(t) - \gamma i(t)$$

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

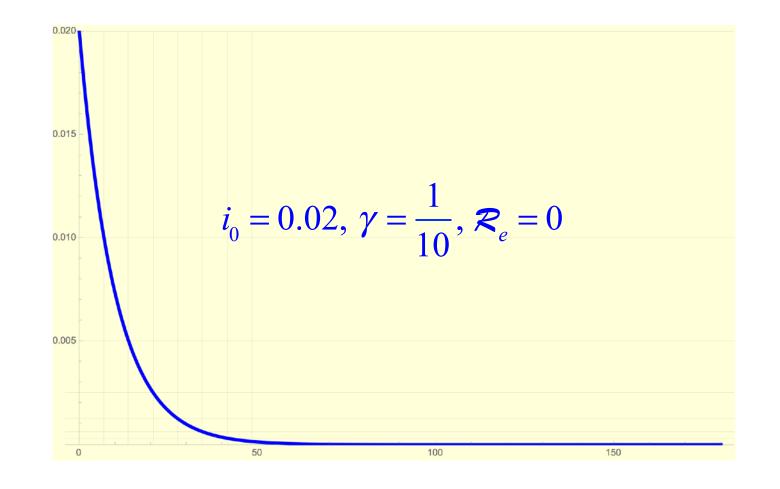
stationary 
$$\mathcal{R}_e$$
:  $i(t) = i_0 e^{-\gamma(1-\mathcal{R}_e)t}$ 

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





- 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  $ds(t)/dt = -\gamma R_e(t)i(t)$
- asymptotically stable equilibrium 0 for  $R_{\rm e} < 1$



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

Filtered Markov style mechanistic short-time any-time **BISOP** Mechanistic ÚZIS (Z)SEIAR Mechanistic long-time "A" MUNI **IDEA** Mechanistic  $RI(t) = 6\log_2 Z_t + C_0$ 

PES

## AES ~ Anti-Epidemic System (PES\* in Czech)

- · Two important modules, together creating a sort of epidemics modelling and control
  - Risk Index is its sensing part
  - AES transitions rules and countermeasures matrix is its acting part
- Considering its deemed importance, the whole scheme would deserve somehow deeper elaboration
  - RI is described quite briefly without e.g. calibration details and selected model discussion
  - the acting part design is hidden completely, relation of countermeasures to RI is just stated
  - verification of interaction with a suitable long-term epidemic model to check this is an optimal control strategy is missing this would bring either vital plausibility arguments or adjustments

#### Risk Index in Brief

$$RI(t) = 6\log_2 Z_t + C_0$$
, so we have  $RI(t_b) - RI(t_a) = 6\log_2 \frac{Z_{t_b}}{Z_{t_a}}$ 

- $Z_t$  is a random variable (process) estimating the number of serious COVID-19 cases emerging during the following 30 days since the base time t
  - $Z_t$  is based on four measurable (not fully independent) factors according to a mixed model (cf. the reference below)
  - RI is not(!) a percent-based measure
  - the logarithmic nature of its relative increase/decrease is the only relevant interpretation
- · Some details are given in Kulveit, J. and Gavenčiak, T.: Odvození indexu rizika pro epidemii COVID-19 v České republice
  - updated by Májek, O., Kulveit, J., Přibylová, L., Hajnová, V., Jarkovský, J., and Dušek, L.: *Metodika pro výpočet indexu rizika COVID-19*, v. 2.3, 27.12.2020



Jde to pomalu. Dnes jsme cvičili povel "K noze!"

\*) It goes slowly. Today, we exercised the "HEEL!" command.

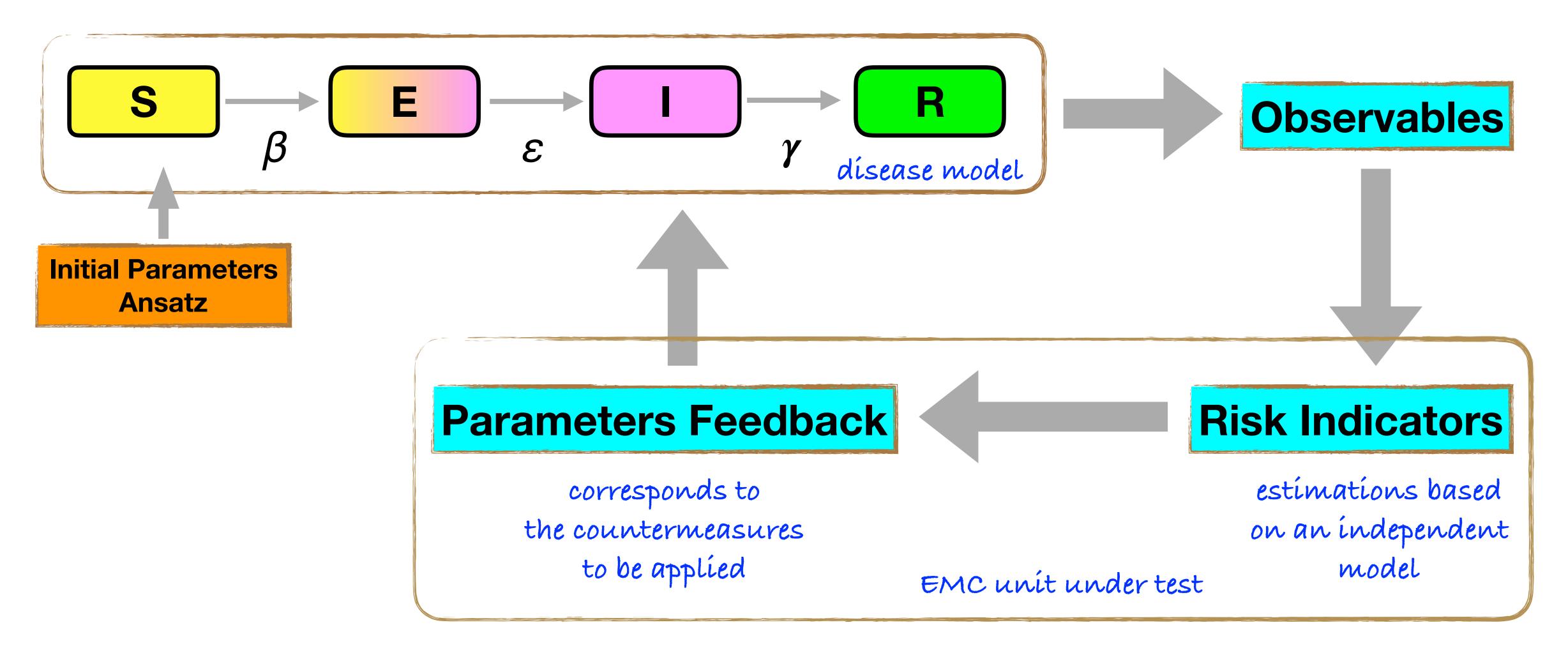
## Security and Safety Aspects of Epidemics Modelling and Control

- Backdoor elimination by design and full transparency
  - invoking generalised Kerckhoffs's principle (since 1883)
  - note the ability to recompute a just-stated mathematical expression is not a transparency as we understand it today
  - discussion of the model calibration is an important part of its description (similar to e.g. S-Boxes in crypto)
- · Input data sensitivity analysis, integrity protection, and fault prevention
  - imagine a whole state is governed by a simple equation and its data source; What could we do then?

## Integrity and Non-Repudiation of EMC

- Long established objectives in data-driven control mechanisms
  - calling for Epidemics Modelling and Control security and safety
- Mechanistic models offer interesting properties for this
  - going back-and-forth in time allows for better hypothesis testing and data validation
  - invertibility allows for verification of public data (including e.g. newspaper predictions) with a presumed model
  - parameters feed-back allows for simulated control strategy testing

### EMC Simulated Test Runs



## Transparency Required

- Again, 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.

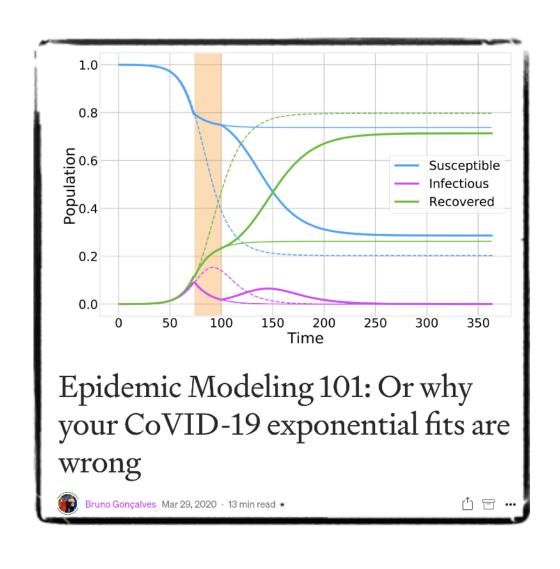
The list of new medicines that are being evaluated by the <a href="CHMP">CHMP</a> is available on the EMA website and updated every month.

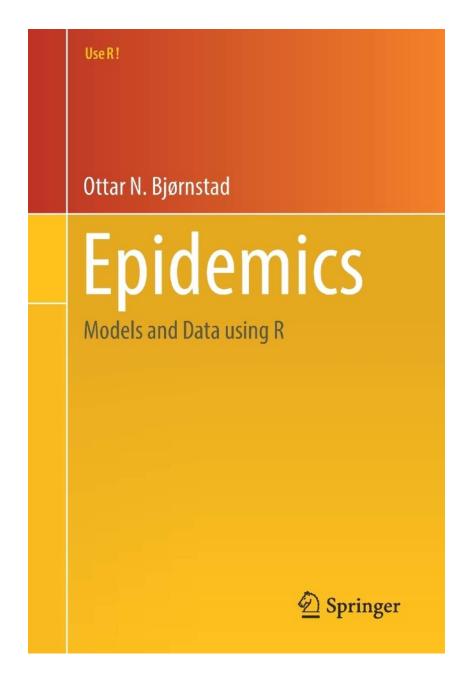
EMA also publishes the agendas and minutes of all its committees' meetings, where information on the stage of the assessment can be found.

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

## How to Start Experimenting I

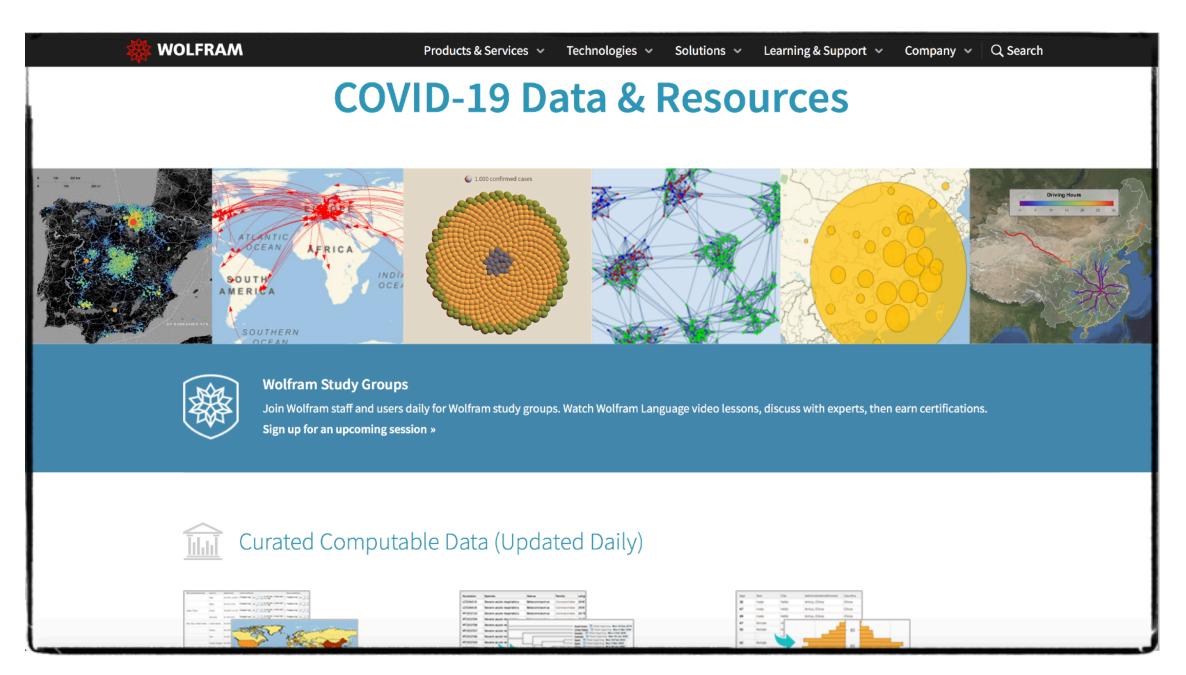
- Computationally oriented introduction by physicist and data scientist Bruno Gonçalves with GitHub support (just grab your Python and start exploring)
  - https://medium.com/data-for-science/epidemic-modeling-101-or-why-your-covid19-exponential-fits-are-wrong-97aa50c55f8
- Should you rather prefer R, there is an excellent book by mathematical biologist Ottar N. Bjørnstad





## How to Start Experimenting II

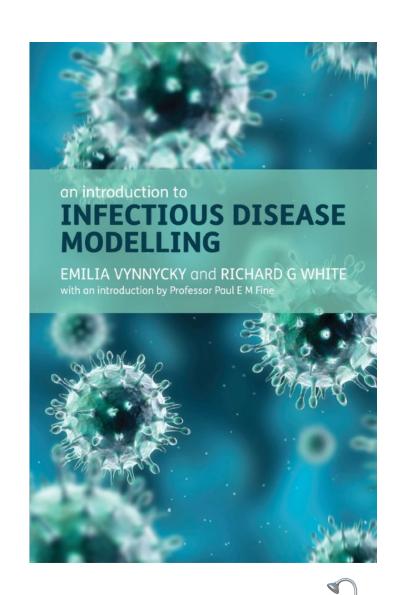
- Wolfram's Mathematica is the long-standing hallmark for the applied mathematical analysis, also including epidemiological modelling, now
  - for the Raspberry PI platform, it is available for free!

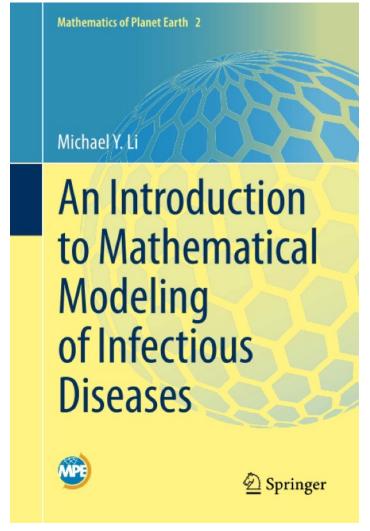


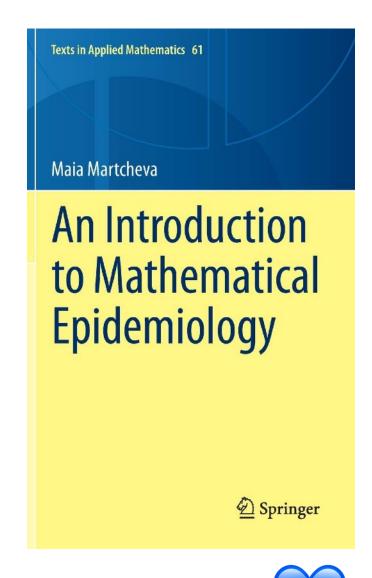


https://www.wolfram.com/covid-19-resources/

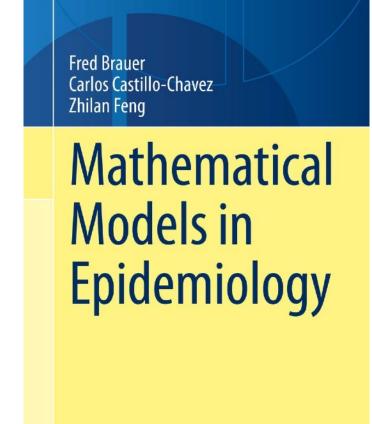
## Mathematical Epidemiology Bookshelf



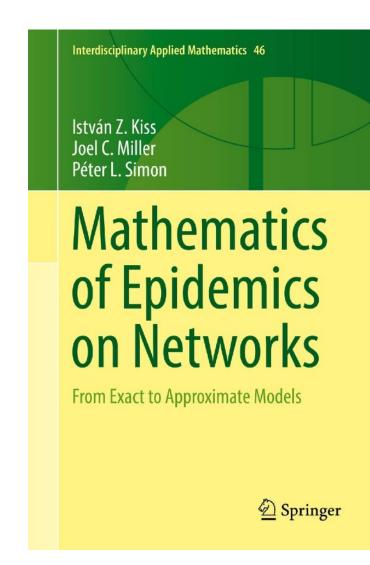


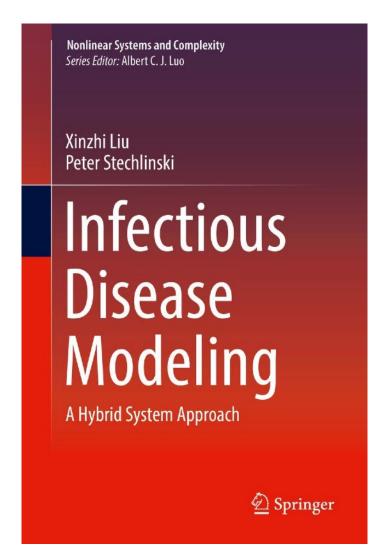






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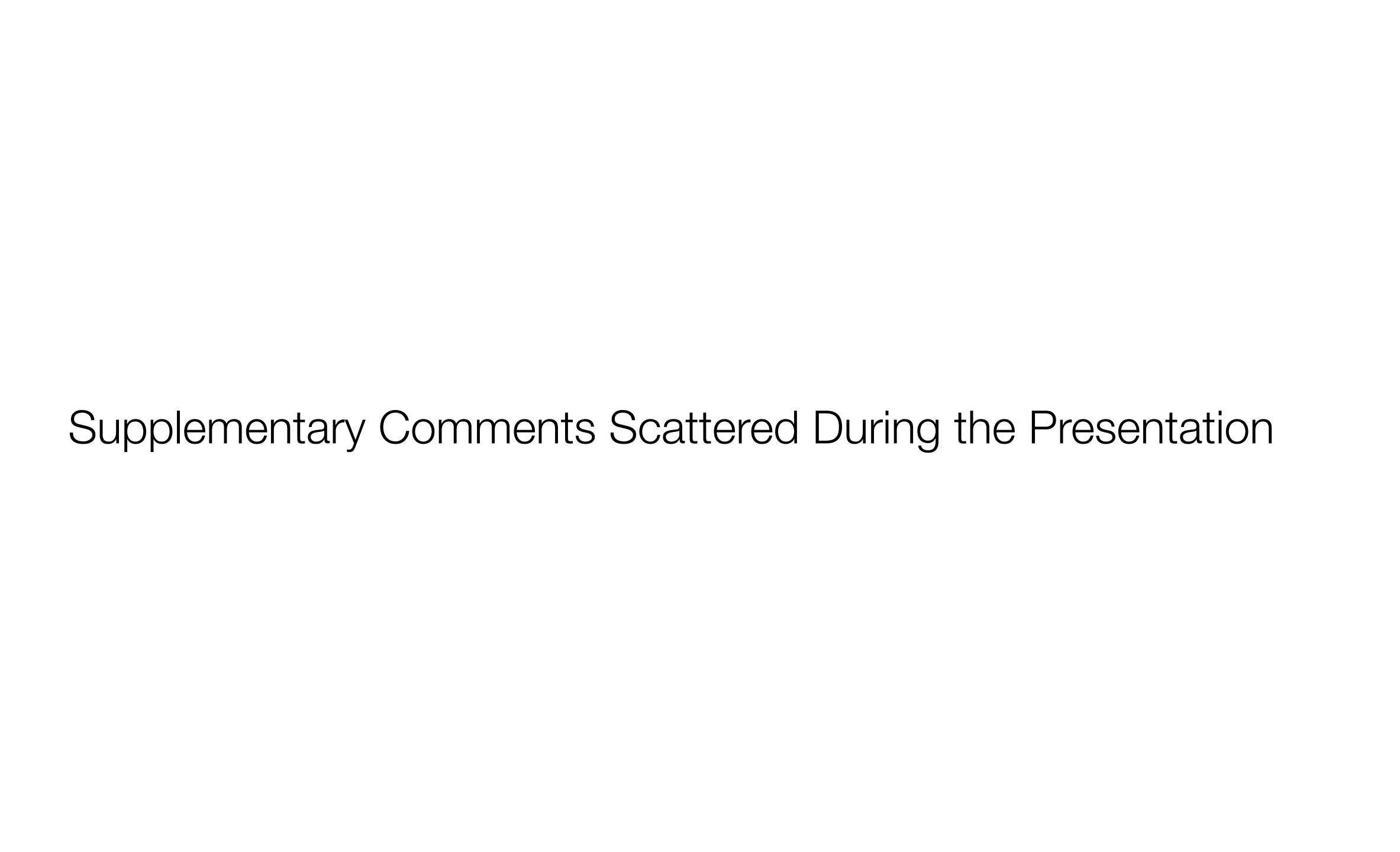






#### Conclusion

- Mathematical modelling is the key part to create a platform where many experts from different areas can share and dispute their ideas
  - as 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



#### You Have Been Warned

Today, with this topic, be really careful what you do and what you say.

Somebody could take it seriously.

## The more we think, the more we get...

- · Mathematically speaking, these models are quite simple
  - this is on purpose, as we want to go as simply as it gets (but not simpler)
  - the real potential is, however, in the interpretation
- · Let us e.g. consider the compartment-size-dependent derivatives
  - by fitting the model, we get useful insights into the infection spread
  - for instance, how close/far are we to the herd immunity?
  - daily change rates after a lock-down on/off are also shedding further light on the real situation (does not seem to be interpreted correctly in media, though)

## Understanding Mathematical Treatment

Primarily, it is not about the original cause.

The main goal is to moderate the reproduction parameters, and the remedy can be then a very tradeoff in between several factors.

## Let's Talk About Strategy!

- There is a natural **intrinsic turning point** of the epidemic that is given solely by the *initial* basic reproduction number reciprocal (as the remaining susceptible fraction)
- Until we reach that point, the community-spreading epidemic will be bouncing up and down with each and every lockdown release and reinforcement, respectively
- It is true that each and every wave following a (full) lockdown release will be milder in terms of its peak and the total number of people affected
- · In principle, we could beat the epidemic this way
- The problem is, relying solely on perpetual on/off lockdowns would take enormous amount of time, probably exhausting the state in other ways
  - also the possibly vanishing immunity is of a very big concern here

#### Mix of Bearable Countermeasure That Can Persist

- Apparently, we shall control the epidemic parameters permanently, not allowing them to relax back towards their free unmoderated values
  - this way, the herd immunity threshold, given by controlled-Ro, is also shifted as well
  - ideally, we could break the community spread mode at all, by e.g. tracing-out the disease
- These countermeasure shall, however, last until the very end (be careful of what does this mean) of the epidemic, so they shall be both **effective and bearable**
- Reliable contact tracing and quarantine count into this
- Vaccination is then an emergency wormhole that helps to skip a long track on the way to the intrinsic turning point (i.e. the herd immunity)

## In Vivo Models - When Population Models Meet In-depth Approach

- · Still, the same principles of dynamical systems modelling and control can be applied
  - the most important conclusion is these models can (and shall) be interconnected
  - not only for analysis and prediction, but also for **testing of in-depth anti- epidemic measures**
- Example Designing the strategy for the "Back to School" approach
  - design of optimal testing tactics based not only on the population model, but also on the in vivo SARS-CoV-2 kinetics
  - verification of the suggested control system by an in-depth disease model

## Example of In-Depth Modelling and Verification Approach

- Used here just to show the nice and desirable application of the modelling approach
  - the authors apply it also for the control mechanism verification, as well



## Finally, Let's Talk About the Approach

- Whenever stating any important results, define the model used and the input data
  - this is a common practice in mathematical modelling
  - now, it is extremely important, as the results do have serious impacts
  - otherwise, anybody can state just almost anything and deny it later
  - The more you feel like a professional, the more rigorous arguments you shall present then!

## Foremost experts are about to make a decision



#### Remember

# proof V GTFO

## Revision History

- 2021/01/28: initial version, based on former lecture on contact tracing impact
- 2021/02/05: alpha version for steering committee
- 2021/02/12: alpha 2, graphs recalibration for slightly adjusted parameters
- 2021/02/16: mathematical virology noted; release version 1
- 2021/03/12: reverse update from the simplified version; release version 1.1
- 2021/03/24: some qualitative realities included; release version 1.2
- 2021/03/30: KoroNERV-20 presentation flash-back; release version 1.3