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Differential-Equations Modelling and Covid-19

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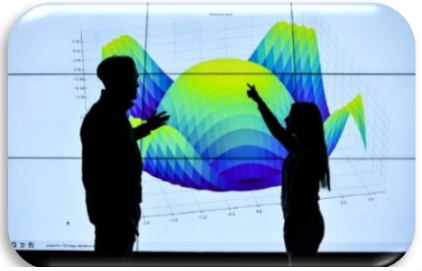

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Overview

- Disease-spread models
  - Reproduction number
- Dynamical systems
  - Herd immunity
- SEIR model for Covid-19
  - Connecting models to data

Motivation

IEMAG report NPHET

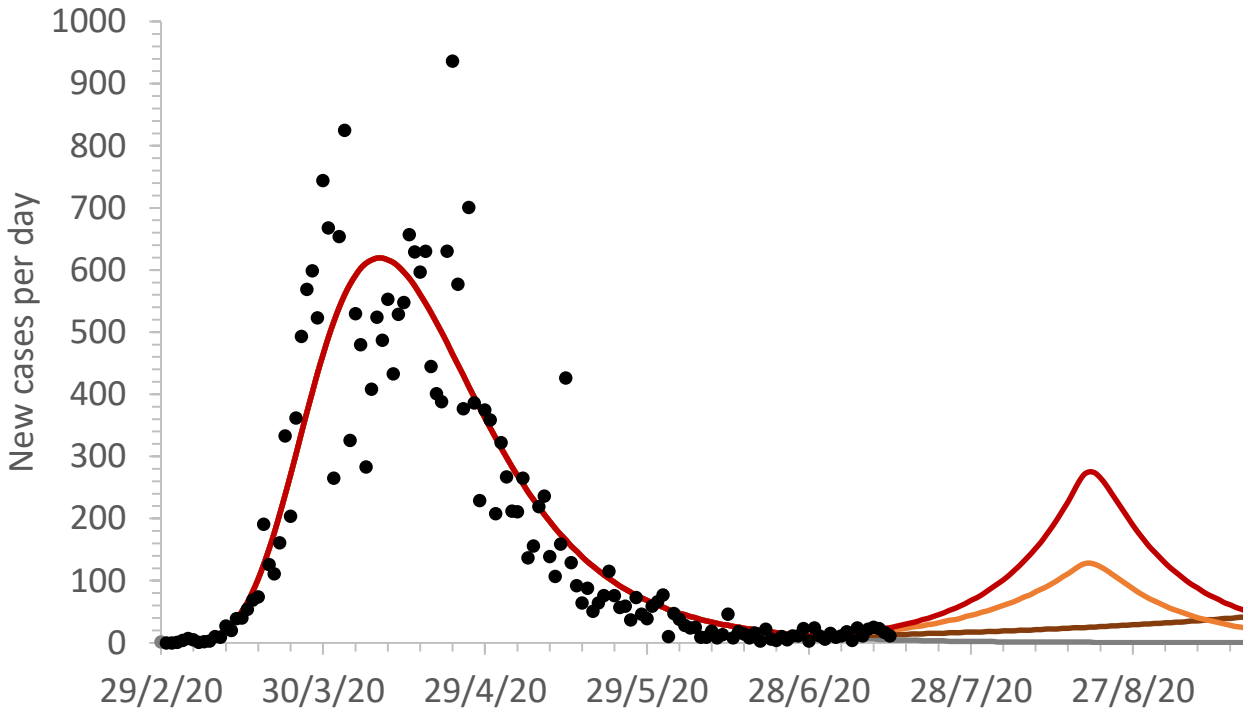
13 July 2020

Motivation

What might happen as we ease restrictions?

If R had been 0.5 until 29 June 2020 and rises above 1 thereafter

Coronavirus **COVID-19** Public Health Advice



Model projections of the number of new symptomatic infections per day. R is assumed to be 0.5 from 28 March to 29 June, and rises to 1.2, 1.6 or 1.8 thereafter; for R=1.6 and 1.8 a stay-at-home restriction is re-imposed 7 weeks later, restoring R to 0.5

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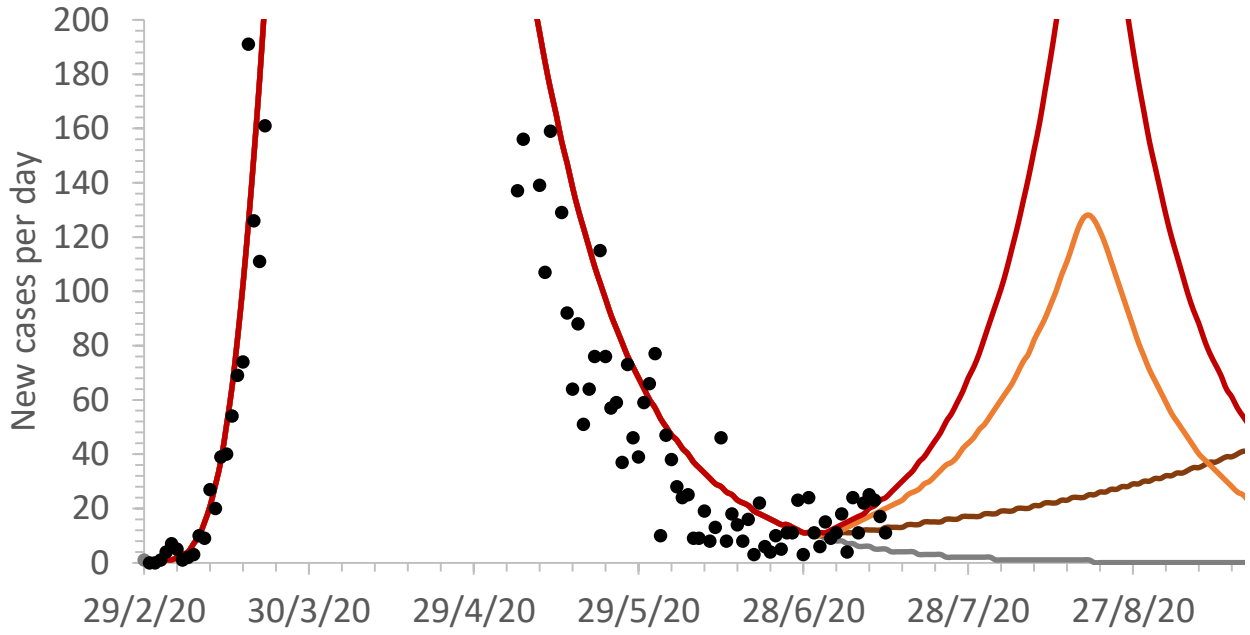

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Disease-spread models

- Start with an oversimplified exponential model.
- Define $S(t)$ to be the number of susceptible (healthy) people in the population.
- Note: assuming $S(t)$ is a continuous variable, but people are discrete.
- If infection occurred randomly, the number of susceptible people would change in time according to an exponential decay law:

$$\frac{dS}{dt} = -k\,S,$$

where k is a positive rate constant

Disease-spread models

- The SI model

- For diseases that spread due to social contacts, the rate of change of $S(t)$ depends on how many infected people there are in the population.

- Note: assumes that the population is *well-mixed,* so that any two members have equal chance of contact

- Then the rate of change of $S(t)$ can be written as

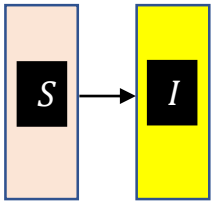
$$\frac{dS}{dt} = -k(t)\, S,$$

where $k(t)$ is a time-varying rate. Usual form:

$$\frac{dS}{dt} = -\left(M\, q \frac{I(t)}{N}\right) S,$$

where $M\ dt$ is the average number of contacts of a person in (small) time interval dt, q is the probability of transmission when a susceptible person meets an infected person, and $I(t)/N$ is the fraction of infected people is the population of size N.

Disease-spread models



- The SI model

- Writing $\beta = Mq$ (called the *contact rate*), we have

$$\frac{dS}{dt} = -\frac{\beta}{N} S\, I,$$

with the corresponding equation for $I(t)$ being

$$\frac{dI}{dt} = \frac{\beta}{N} S\, I.$$

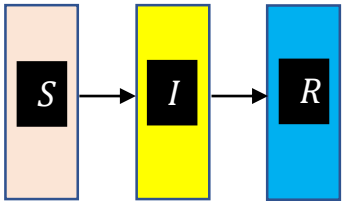
- Note that in this model, $S(t) + I(t) = N$, where the population size N is assumed to be constant.

- Sometimes we work with the fraction $\rho(t) = I(t)/N$ of infected people in the population. Using $S = N - I = N(1 - \rho)$, we can rewrite the $I(t)$ equation as

$$\frac{d\rho}{dt} = \beta\rho(1 - \rho) \quad \text{for} \quad \rho(t),$$

which can be solved to give a closed-form expression for $\rho(t)$.

Disease-spread models



- The SIR model

- The SI model assumes that an infected person remains infectious forever, and so the long-time limit of the model, once infection begins, is $\rho \to 1$.

- In the SIR model, we assume that an infected person spontaneously recovers (and stops being infectious) at a *recovery rate* γ, i.e. that they recover after a time that, on average, is $1/\gamma$.

- The SIR equations are

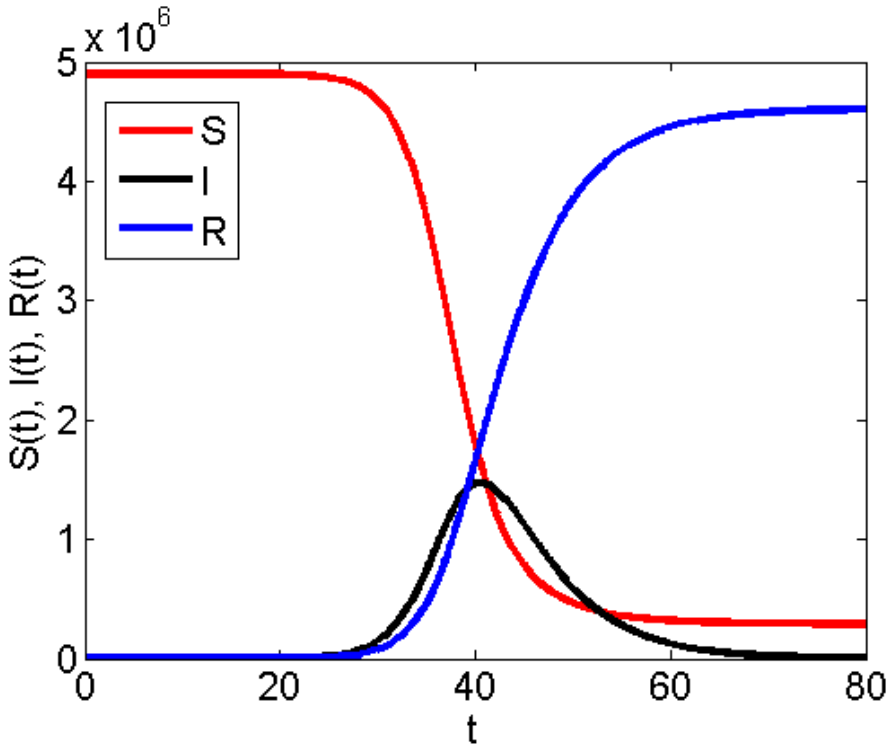
$$\frac{dS}{dt} = -\frac{\beta}{N}SI, \qquad \frac{dI}{dt} = \frac{\beta}{N}SI - \gamma I, \qquad \frac{dR}{dt} = \gamma I,$$

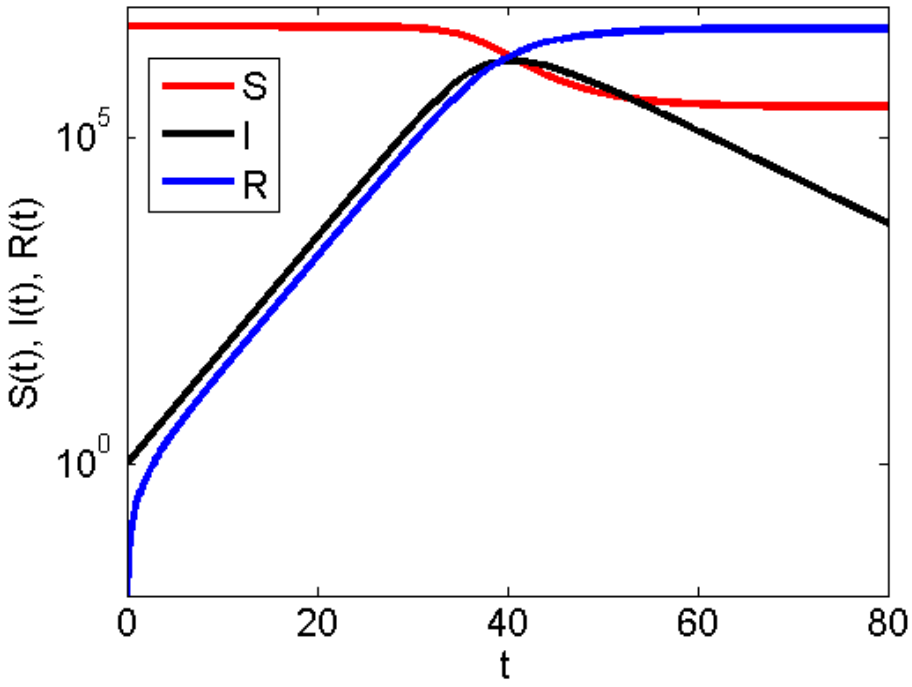
where $S(t)$, $I(t)$ and $R(t)$ are the number of people in the respective compartments, with

$$S(t) + I(t) + R(t) = N.$$

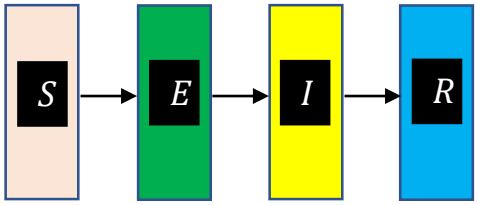
Examples of numerical solutions for SIR

- $N = 4.9 \times 10^6,\ \beta = 0.6,\ \gamma = 0.2,\ \Delta t = 0.01$





Disease-spread models



- Many extensions exist.

- For example, the SEIR model includes an “exposed” state, with another timescale, which models the individuals who have had contact with an infected person, but are not yet themselves infectious (capable of transmitting the disease)

$$\frac{dS}{dt} = -\frac{\beta}{N}SI, \qquad \frac{dE}{dt} = \frac{\beta}{N}SI - \frac{1}{L}E, \qquad \frac{dI}{dt} = \frac{1}{L}E - \gamma I, \qquad \frac{dR}{dt} = \gamma I,$$

  where L is the (average) *latent period.*

- As before, the sum of the four compartment populations adds up to the total (constant) population:

$$S(t) + E(t) + I(t) + R(t) = N.$$

- Note: the timescales we use are all average periods, while the model assumes exponentially-distributed residence times in compartments.

Reproduction number

- The *basic reproduction number* R_0 is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population.

- See J. M. Heffernan et al., "Perspectives on the basic reproductive ratio", J. Royal Soc. Interface, 2, 281 (2005) for a discussion of the next-generation matrix approach.

- In simple models, R_0 can also be calculated as the sum over compartments of the product of:
    - the fraction of infectives that flow through the compartment
    - the average time spent in that compartment
    - the contact rate for that compartment

Reproduction number

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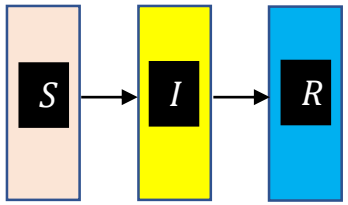
- Example: SIR model



$$\frac{dS}{dt} = -\frac{\beta}{N}SI, \qquad \frac{dI}{dt} = \frac{\beta}{N}SI - \gamma I, \qquad \frac{dR}{dt} = \gamma I,$$

  - the fraction of infectives that flow through the I compartment: 1
  - the average time spent in I compartment: $1/\gamma$
  - the contact rate for I compartment: β

- So $R_0 = \beta/\gamma$ for the SIR model

Reproduction number

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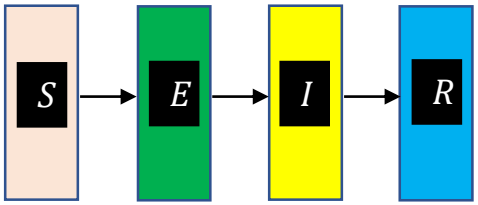

    - the fraction of infectives that flow through the I compartment: 1
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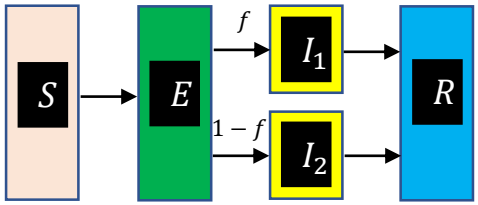
Reproduction number

- In simple models, R_0 can also be calculated as the sum over compartments of the product of:
  - the fraction of infectives that flow through the compartment
  - the average time spent in that compartment
  - the contact rate for that compartment

- Example: SEIIR model



  - the fraction of infectives that flow through the I_1 compartment: f
  - the fraction that flow through the I_2 compartment: $1-f$
  - the average time spent in either I compartment: $1/\gamma$
  - the contact rate for I_1 compartment: $h\beta$; for I_2 it is β

- So $R_0 = \frac{fh\beta}{\gamma} + \frac{(1-f)\beta}{\gamma} = (fh + 1 - f)\beta/\gamma$ for this SEIIR model

Overview

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Dynamical Systems

- From Wikipedia: "A *dynamical system* is a system in which a function describes the time dependence of a point in a geometrical space. At any given time, a dynamical system has a state given by a tuple of real numbers (a vector) that can be represented by a point in an appropriate state space (a geometrical manifold). The evolution rule of the dynamical system is a function that describes what future states follow from the current state."

- One-dimensional example:

$$\frac{dx}{dt} = F\big(x(t)\big) \text{ for } x(t),$$

  where the function $F(x)$ is given.

- A *fixed point* x^* is a value such that if $x(t^*) = x^*$ at some time t^*, then $x(t) = x^*$ for all $t \geq t^*$.

- Fixed points can be determined by solving the equation

$$F(x^*) = 0.$$

Dynamical Systems

- Example: the SI disease-spread model

$$\frac{d\rho}{dt} = \beta\rho(1-\rho) \quad \text{for } \rho(t) = I(t)/N,$$

has two fixed points, at $\rho^* = 0$ and at $\rho^* = 1$.

- The early-time dynamics can be understood by making the approximation $\rho \approx 0$ on the right-hand side of the differential equation, and retaining the first non-zero term (i.e. use a Taylor series expansion about the fixed point $\rho^* = 0$ and retain only the first nontrivial term):

$$\frac{d\rho}{dt} \approx \beta\rho,$$

which gives early-time exponential growth of infection:

$$\rho(t) \approx \rho(0)\exp(\beta\, t)\,.$$

Dynamical Systems

- Generalizing to higher-dimensional systems

- m-dimensional example:

$$\frac{dx}{dt} = F\big(x(t)\big) \text{ for } x(t) \in \mathbb{R}^m,$$

  where the function $F: \mathbb{R}^m \mapsto \mathbb{R}^m$, is given.
- Example: SIR model, where $x(t) = [S(t), I(t), R(t)]$.

  Linearize the system about the fixed point x^*:

$$\frac{dx}{dt} \approx F(x^*) + J.\,(x(t) - x^*),$$

  where the J is the Jacobian matrix evaluated at x^*:

$$J_{ij} = \left.\frac{\partial F_i}{\partial x_j}\right|_{x^*}.$$

Dynamical Systems

- Letting $y(t) = x(t) - x^*$ be the deviation from the fixed point, then (in the generic case where the eigenvectors of J span $\mathbb{R}^m$), the solution of the linearized system is

$$y(t) = \sum_{i=1}^{m} \xi_i \, e^{s_i t} \, u_i \,,$$

where s_i and u_i are the i^{th} eigenvalue and corresponding eigenvector of J, and ξ_i is the i^{th} coefficient in the expansion of the initial condition over the spanning basis:

$$y(0) = \sum_{i=1}^{m} \xi_i \, u_i .$$

- The fixed point is *asymptotically stable* if $\mathrm{Re}(s_i) < 0$ for all $i = 1,2, \ldots, m$.

- The fixed point is *unstable* (with early-stage exponential growth) if $\mathrm{Re}(s_i) > 0$ for at least one $i \in \{1,2, \ldots, m\}$.

Dynamical Systems

- Example: SIR model, where $x(t) = [S(t), I(t), R(t)]$, so $m = 3$.

- The full SIR equations are

$$\frac{dS}{dt} = -\frac{\beta}{N} SI, \qquad \frac{dI}{dt} = \frac{\beta}{N} SI - \gamma I, \qquad \frac{dR}{dt} = \gamma I.$$

- Linearizing about $x^* = [N, 0, 0]$:

$$\frac{dS}{dt} \approx -\beta I, \qquad \frac{dI}{dt} = \beta I - \gamma I, \qquad \frac{dR}{dt} = \gamma I,$$

so Jacobian is

$$J = \begin{bmatrix} 0 & -\beta & 0 \\ 0 & \beta - \gamma & 0 \\ 0 & \gamma & 0 \end{bmatrix},$$

with eigenvalues $0, 0$ and $\beta - \gamma$.

Dynamical Systems

- Thus, the all-healthy fixed point $x^* = [N, 0, 0]$ is:

  stable if $\beta - \gamma < 0$, i.e., if the reproduction number $R_0 = \frac{\beta}{\gamma} < 1$,

  unstable if $\beta - \gamma > 0$, i.e., if the reproduction number $R_0 > 1$

- In the unstable case, the exponential growth rate is given by the eigenvalue $\beta - \gamma = \gamma(R_0 - 1)$.

Dynamical Systems

H. W. Hethcote, "The mathematics of infectious diseases," SIAM Review, 42, 599-653 (2000)

- Herd immunity

- Back to the full SIR equations:

$$\frac{dS}{dt} = -\frac{\beta}{N}SI, \qquad \frac{dI}{dt} = \frac{\beta}{N}SI - \gamma I, \qquad \frac{dR}{dt} = \gamma I,$$

with $R_0 > 1$.

- The rate of change of $I(t)$ switches from positive to negative when $\frac{\beta}{N}S - \gamma$ changes sign, which is when

$$S = \frac{1}{R_0}N,$$

or when the fraction of the population that has been infected equals $1 - \frac{1}{R_0}$.

- Exercise: derive the equation $\frac{dI}{dS} = -1 + \frac{\gamma}{\beta}\frac{N}{S}$ and solve for $I(S)$. Hence show that the final number of susceptibles, $S_\infty = \lim_{t\to\infty} S(t)$, is the unique root in $(0, 1/R_0)$ of the equation $S_\infty - \frac{N}{R_0}\ln\left(\frac{S_\infty}{S(0)}\right) - S(0) - I(0) = 0$.

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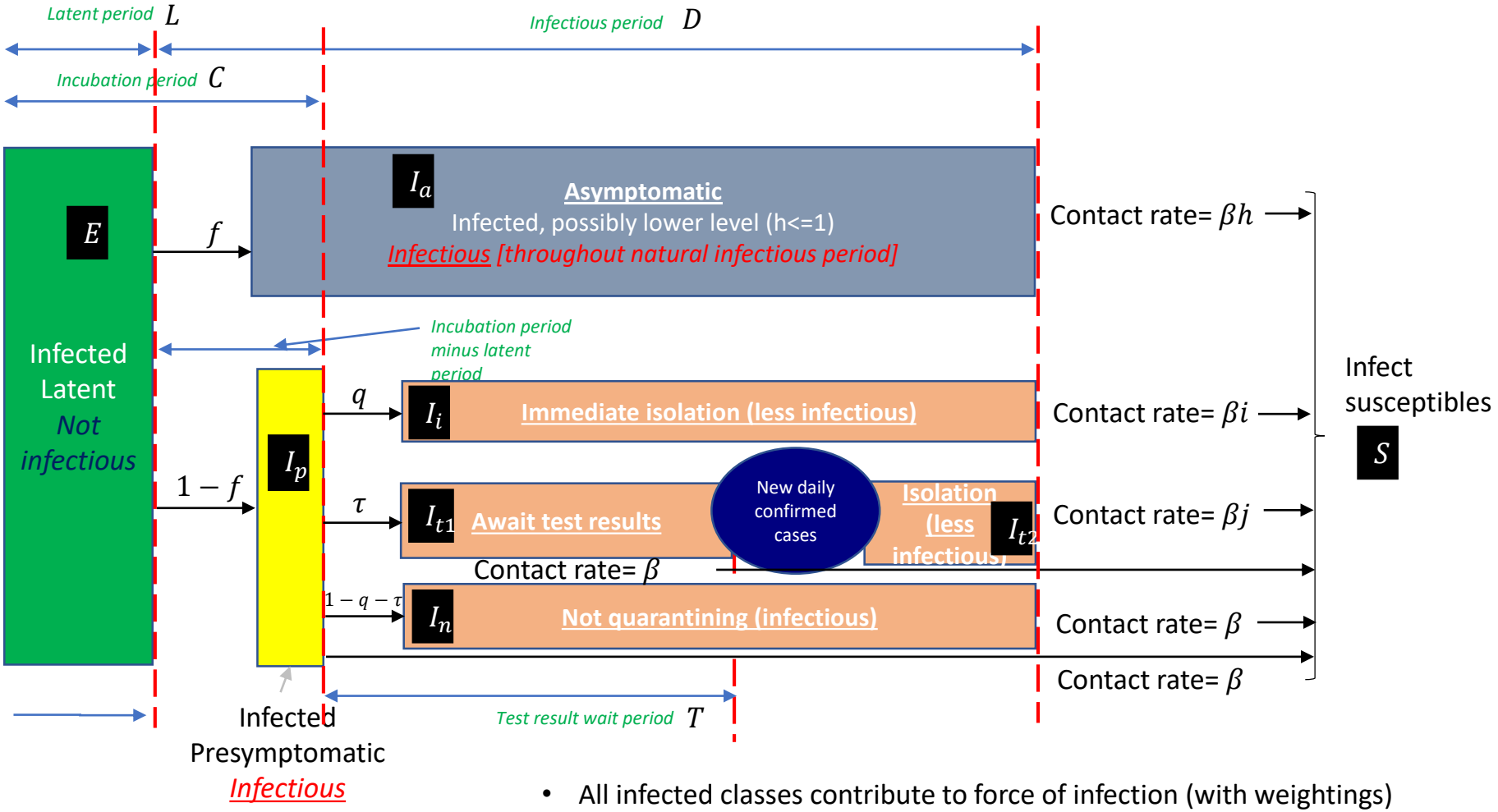
IEMAG SEIR model

www.gov.ie/en/publication/dc5711-irish-epidemiology-modelling-advisory-group-to-nphet-technical-notes/



- All infected classes contribute to force of infection (with weightings)
- Infected individuals move from the infected classes to Removed (not shown)

IEMAG SEIR model

www.gov.ie/en/publication/dc5711-irish-epidemiology-modelling-advisory-group-to-nphet-technical-notes/

$$\frac{dS}{dt} = -\beta S\left(I_p + hI_a + iI_i + I_{t1} + jI_{t2} + I_n\right)/N$$

$$\frac{dE}{dt} = \beta S\left(I_p + hI_a + iI_i + I_{t1} + jI_{t2} + I_n\right)/N - \frac{1}{L}E$$

$$\frac{dI_p}{dt} = \frac{(1-f)}{L}E - \frac{1}{C-L}I_p$$

$$\frac{dI_a}{dt} = \frac{f}{L}E - \frac{1}{D}I_a$$

$$\frac{dI_i}{dt} = \frac{q}{C-L}I_p - \frac{1}{D-C+L}I_i$$

$$\frac{dI_{t1}}{dt} = \frac{\tau}{C-L}I_p - \frac{1}{T}I_{t1}$$

$$\frac{dI_{t2}}{dt} = \frac{1}{T}I_{t1} - \frac{1}{D-C+L-T}I_{t2}$$

$$\frac{dC_c}{dt} = \frac{1}{T}I_{t1}$$

$$\frac{dI_n}{dt} = \frac{(1-q-\tau)}{C-L}I_p - \frac{1}{D-C+L}I_n$$

$$\frac{dR}{dt} = \frac{1}{D}I_a + \frac{1}{D-C+L}I_i + \frac{1}{D-C+L-T}I_{t2} + \frac{1}{D-C+L}I_n$$

IEMAG SEIR model

- Plausible ranges of timescale parameters obtained from extensive literature review

[1] John M Griffin, Aine Collins, Kevin Hunt, David McEvoy, Miriam Casey, Andrew Byrne, Conor G McAloon, Ann Barber, Elizabeth Lane, David McEvoy, and Simon J More. A rapid review of available evidence on the serial interval and generation time of COVID-19. *medRxiv doi:10.1101/2020.05.08.20095075*, 2020.

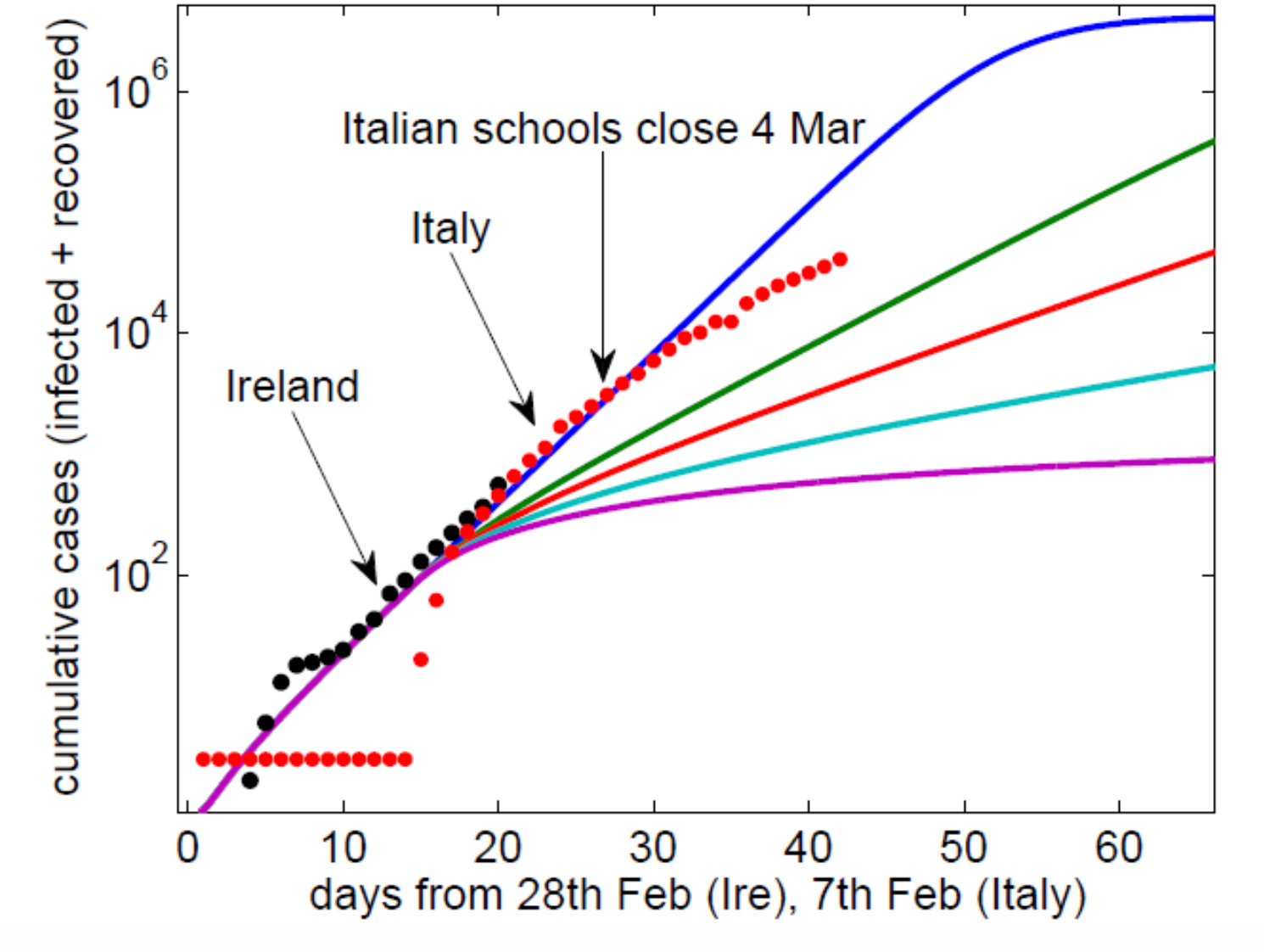
[2] Conor G McAloon, Aine Collins, Kevin Hunt, Ann Barber, Andrew Byrne, Francis Butler, Miriam Casey, John M Griffin, Elizabeth Lane, David McEvoy, Patrick Wall, Martin J Green, Luke O'Grady, and Simon J More. The incubation period of COVID-19: A rapid systematic review and meta-analysis of observational research. *medRxiv doi:10.1101/2020.04.24.20073957*, 2020.

[3] Andrew W Byrne, David McEvoy, Aine Collins, Kevin Hunt, Miriam Casey, Ann Barber, Francis Butler, John Griffin, Elizabeth Lane, Conor McAloon, Kirsty O'Brien, Patrick Wall, Kieran Walsh, and Simon More. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic covid-19 cases. *medRxiv doi:10.1101/2020.04.25.20079889*, 2020.

- Contact rate β to be calibrated.

- Non-pharmaceutical interventions (NPIs) modelled as time-varying $\beta(t)$.

IEMAG SEIR model



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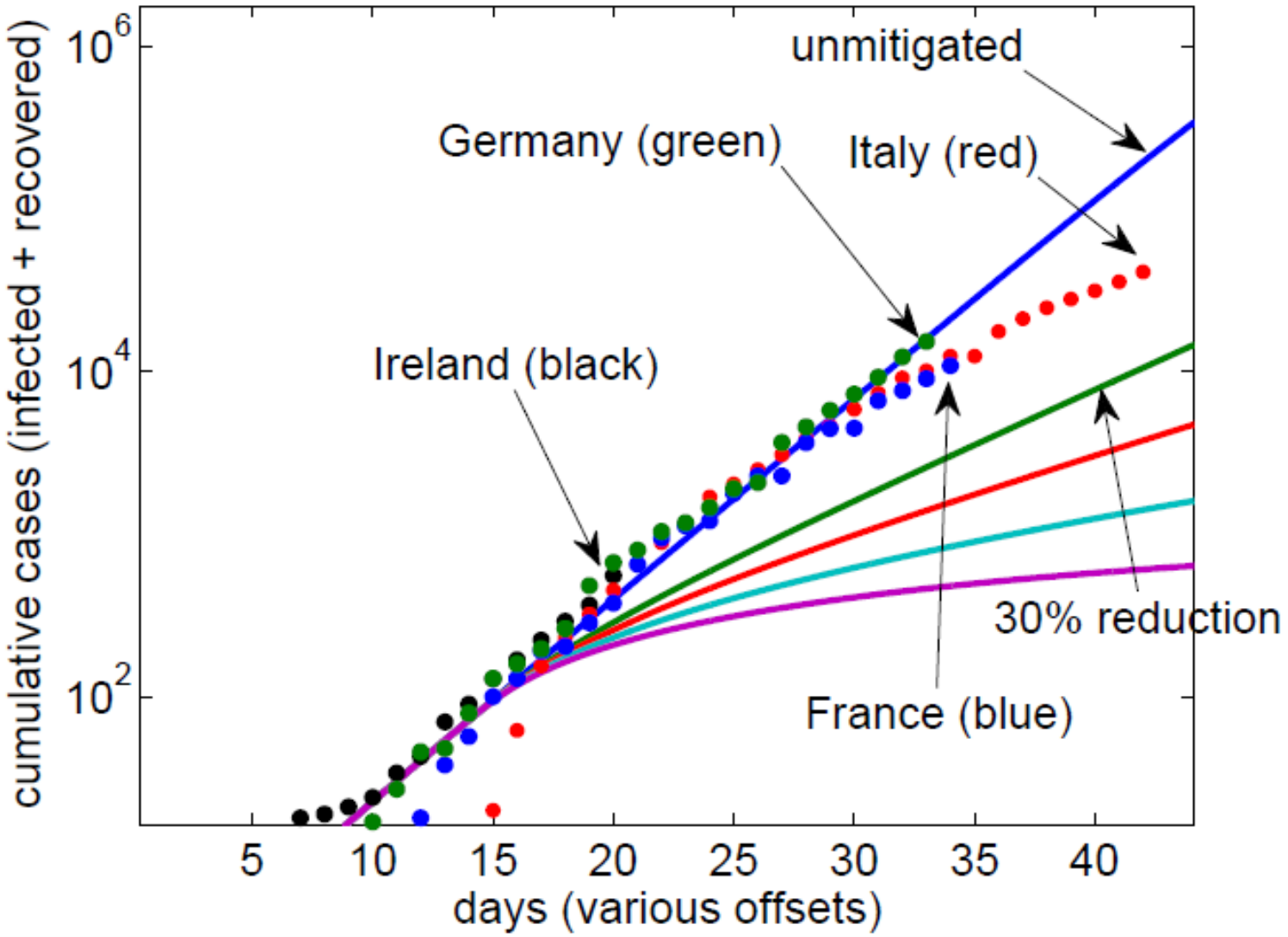


IEMAG SEIR model

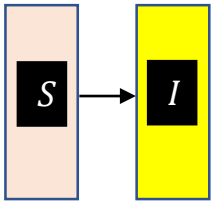
- First choice: constant rate β, fitted to match the early-stage exponential growth

- Second choice: As NPIs took effect, the best fit across several statistical models was produced by a Poisson model with rate following a Gompertz function

$$C_c(t) \approx \theta_1 \, e^{-\theta_2 \theta_3^t}$$

- Inverse problem: given a (smooth) fit to the data, can we invert the differential equations to determine the time-varying $\beta(t)$?

Inverting the SI model



- The SI model with time-varying $\beta(t)$ can be written as

$$\frac{dI}{dt} = \frac{\beta}{N} S\, I = \frac{\beta}{N}(N - I)I.$$

- Inverse problem: given the observed $I(t)$, what is $\beta(t)$?

- Explicit answer:

$$\beta(t) = \frac{dI}{dt}\frac{N}{(N - I)I}.$$

- Similar idea for the full SEIR model, just more complicated…

- See, for example, A. Mummert, "Studying the recovery procedure for the time-dependent transmission rate(s) in epidemic models", J. Math. Biol., 67, 483 (2013).

IEMAG SEIR model

www.gov.ie/en/publication/dc5711-irish-epidemiology-modelling-advisory-group-to-nphet-technical-notes/

1. Asuming $C_r(t) = G(t)$, solve the algebraic equation (10) for $I_{t1}(t)$.
2. Using $I_{t1}(t)$ from step 1, solve the differential equation (7) for $I_{t2}(t)$.
3. Using $I_{t1}(t)$ from step 1, solve the algebraic equation (6) for $I_p(t)$.
4. Using $I_p(t)$ from step 3, solve the differential equation (5) for $I_i(t)$.
5. Using $I_p(t)$ from step 3, solve the differential equation (8) for $I_n(t)$.
6. Using $I_p(t)$ from step 3, solve the algebraic equation (3) for $E(t)$.
7. Using $E(t)$ from step 6, solve the differential equation (4) for $I_a(t)$.
8. Combine equations (1) and (2) to give

$$\frac{dS}{dt} = -\frac{dE}{dt} - \frac{1}{L}E \tag{12}$$

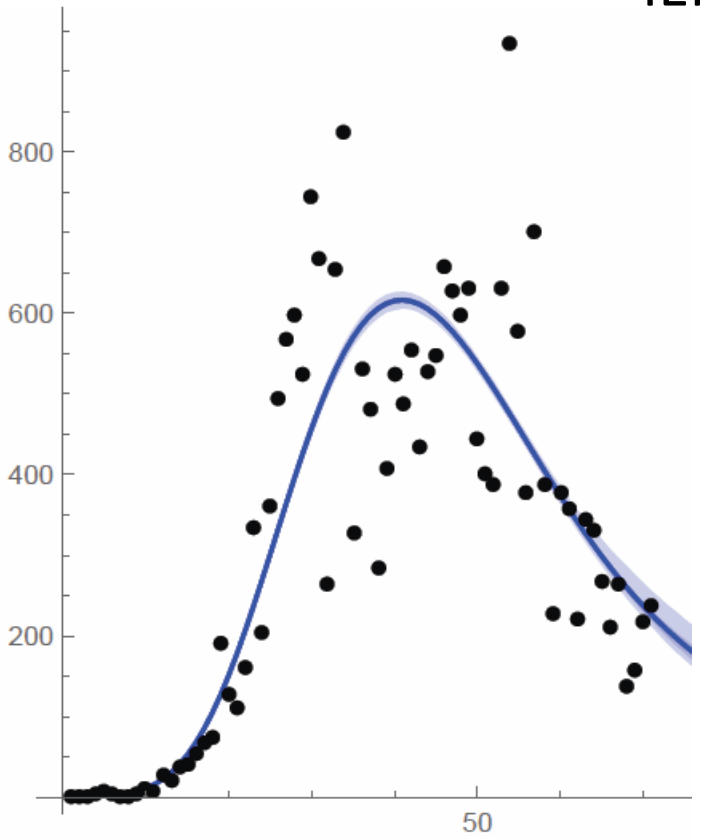
   and, using $E(t)$ from step 6, solve this differential equation for $S(t)$.

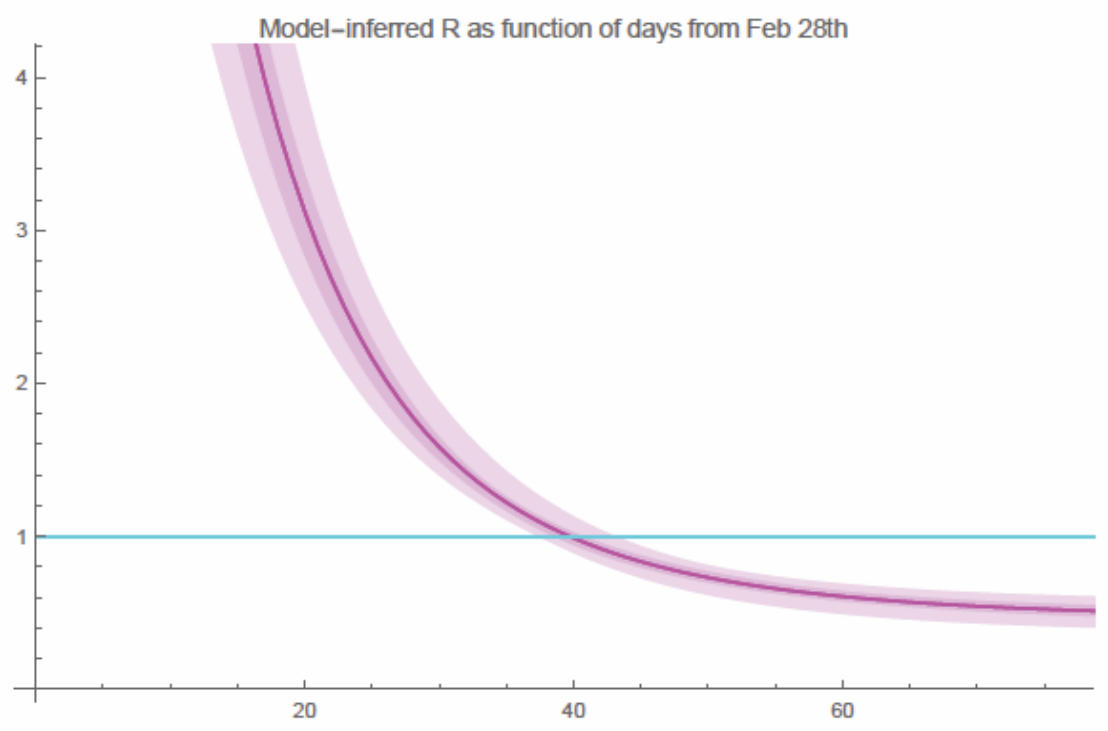
9. Using the results of steps 2, 3, 4, 5, 7 and 8, solve equation (1) for the inferred time-dependent transmission rate $\beta(t)$:

$$\beta(t) = -N\frac{dS}{dt}\left(I_p + hI_a + iI_i + I_{t1} + jI_{t2} + I_n\right)^{-1}. \tag{13}$$

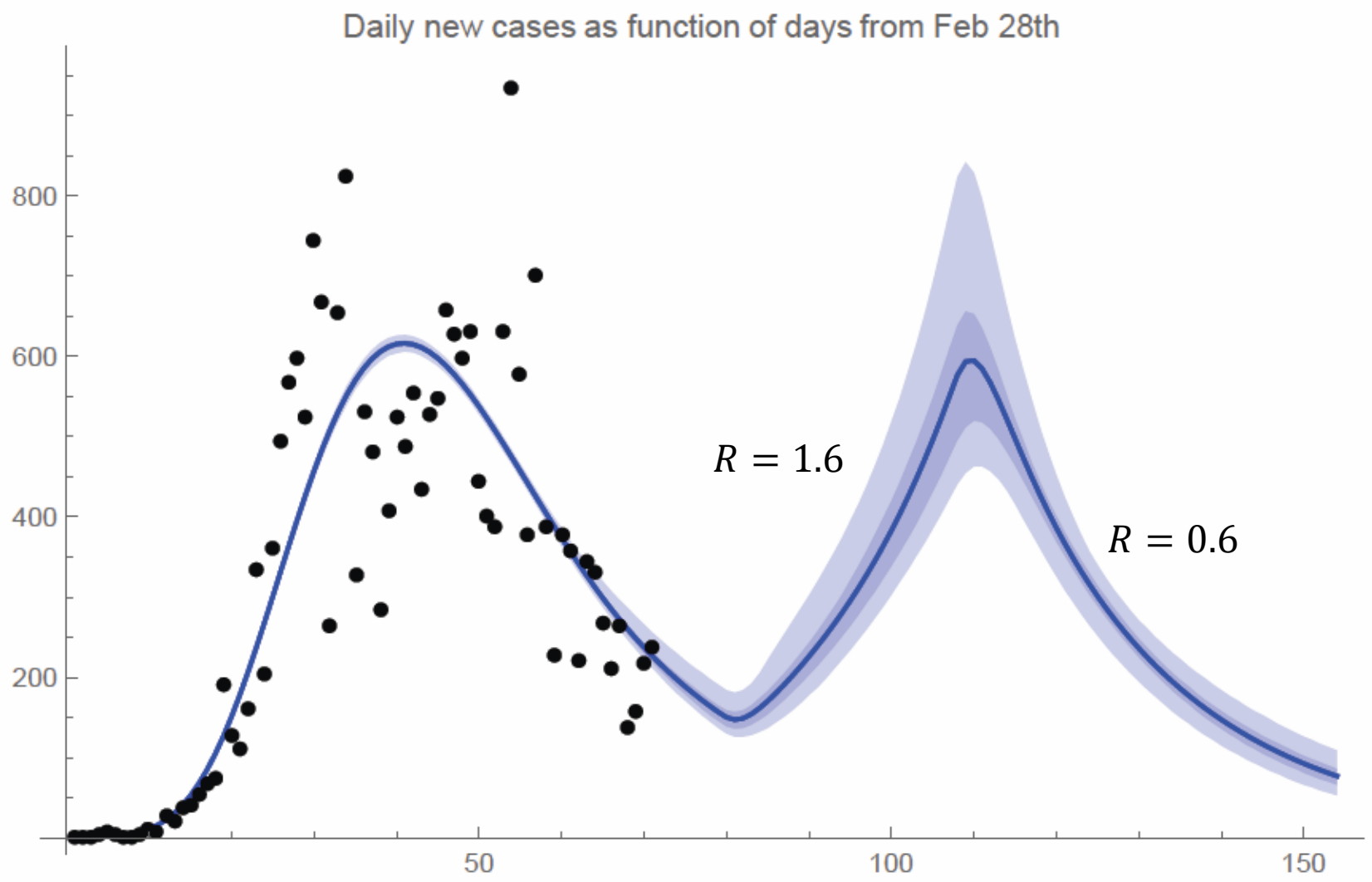
IEMAG SEIR model

www.gov.ie/en/publication/dc5711-irish-epidemiology-modelling-advisory-group-to-nphet-technical-notes/

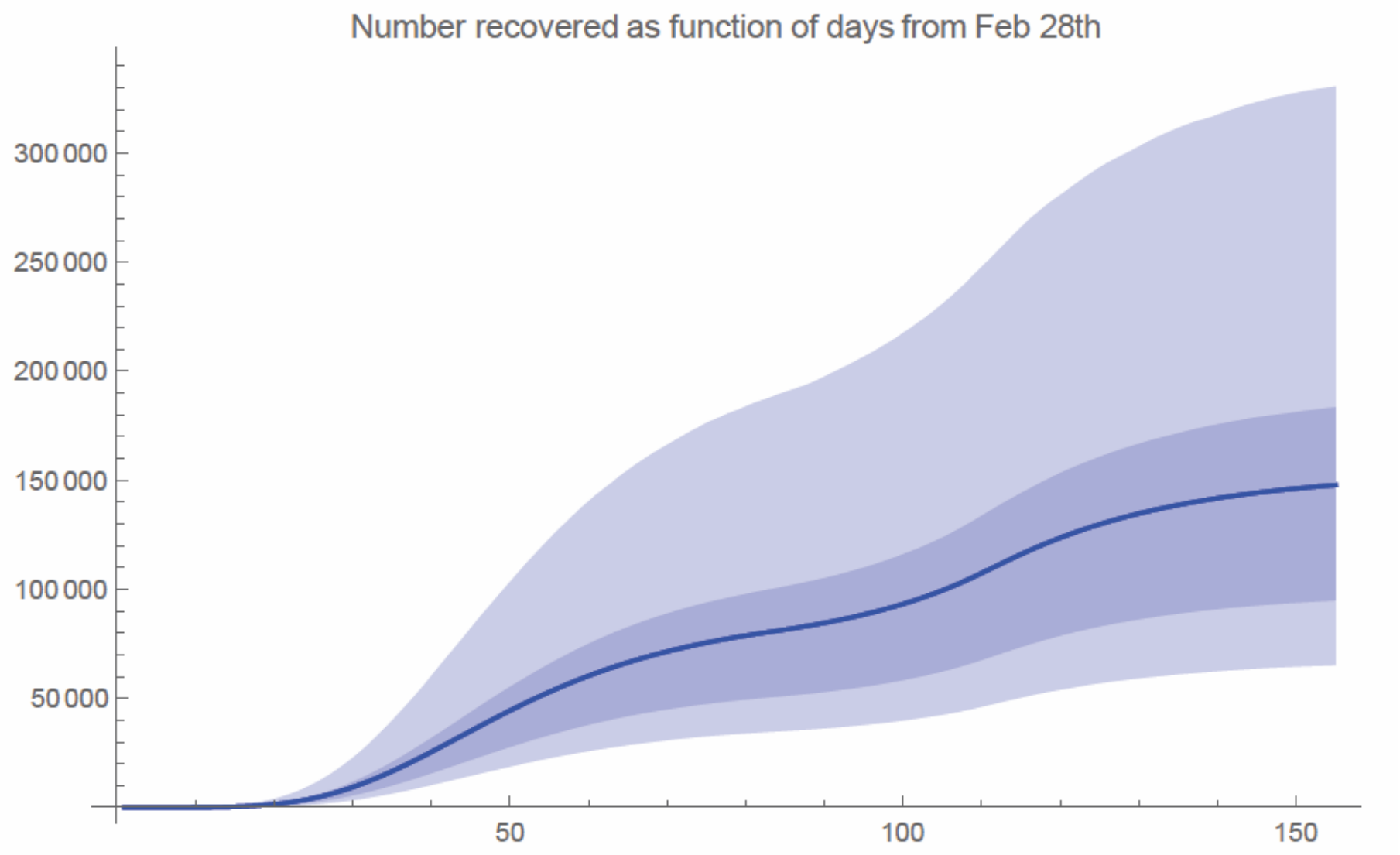




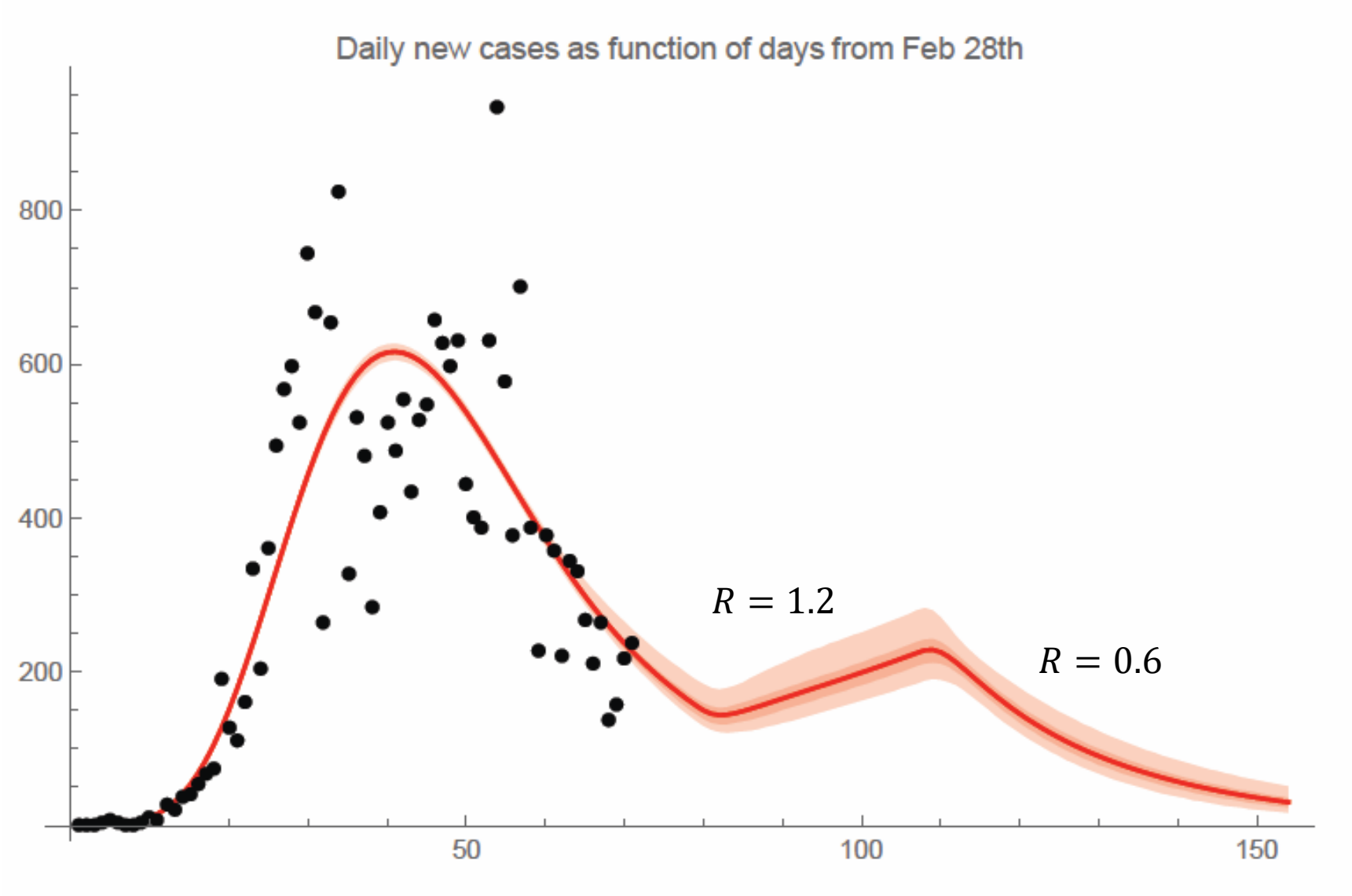
IEMAG SEIR model: scenario projections



IEMAG SEIR model : scenario projections

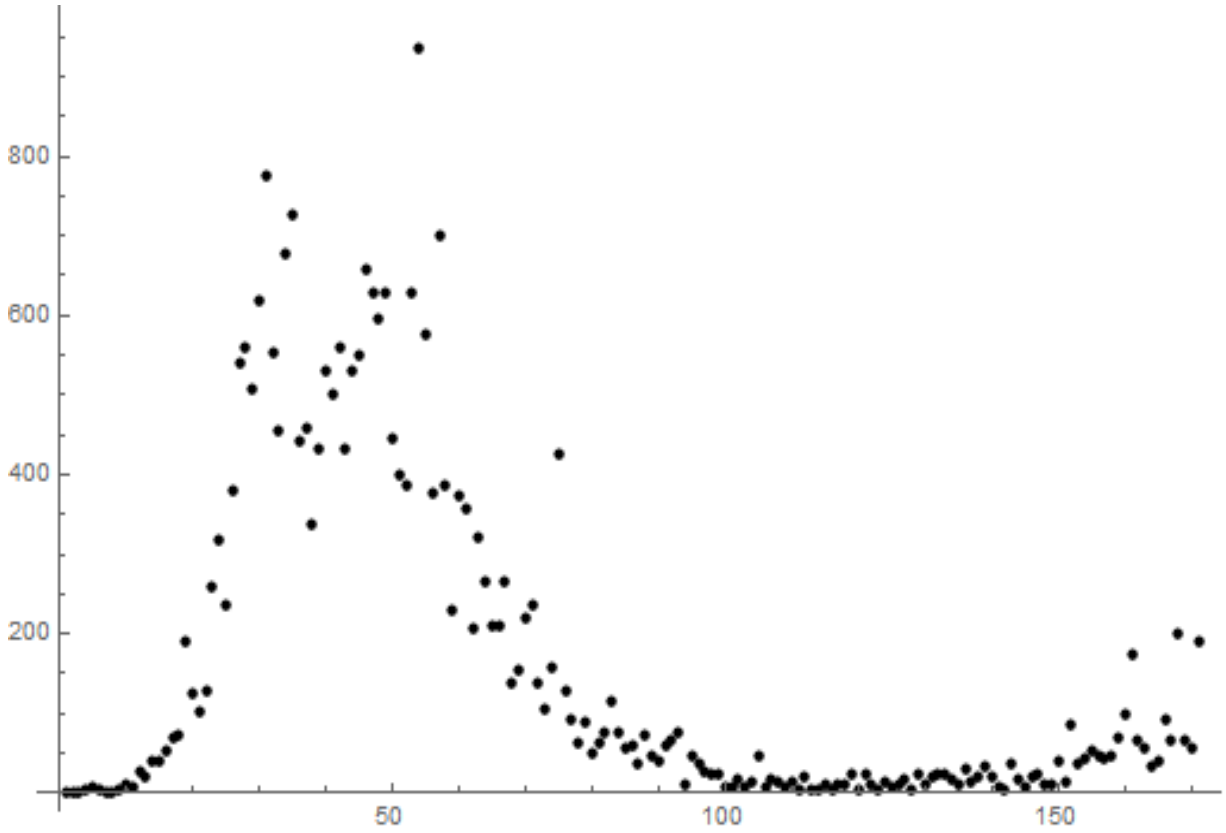


IEMAG SEIR model : scenario projections



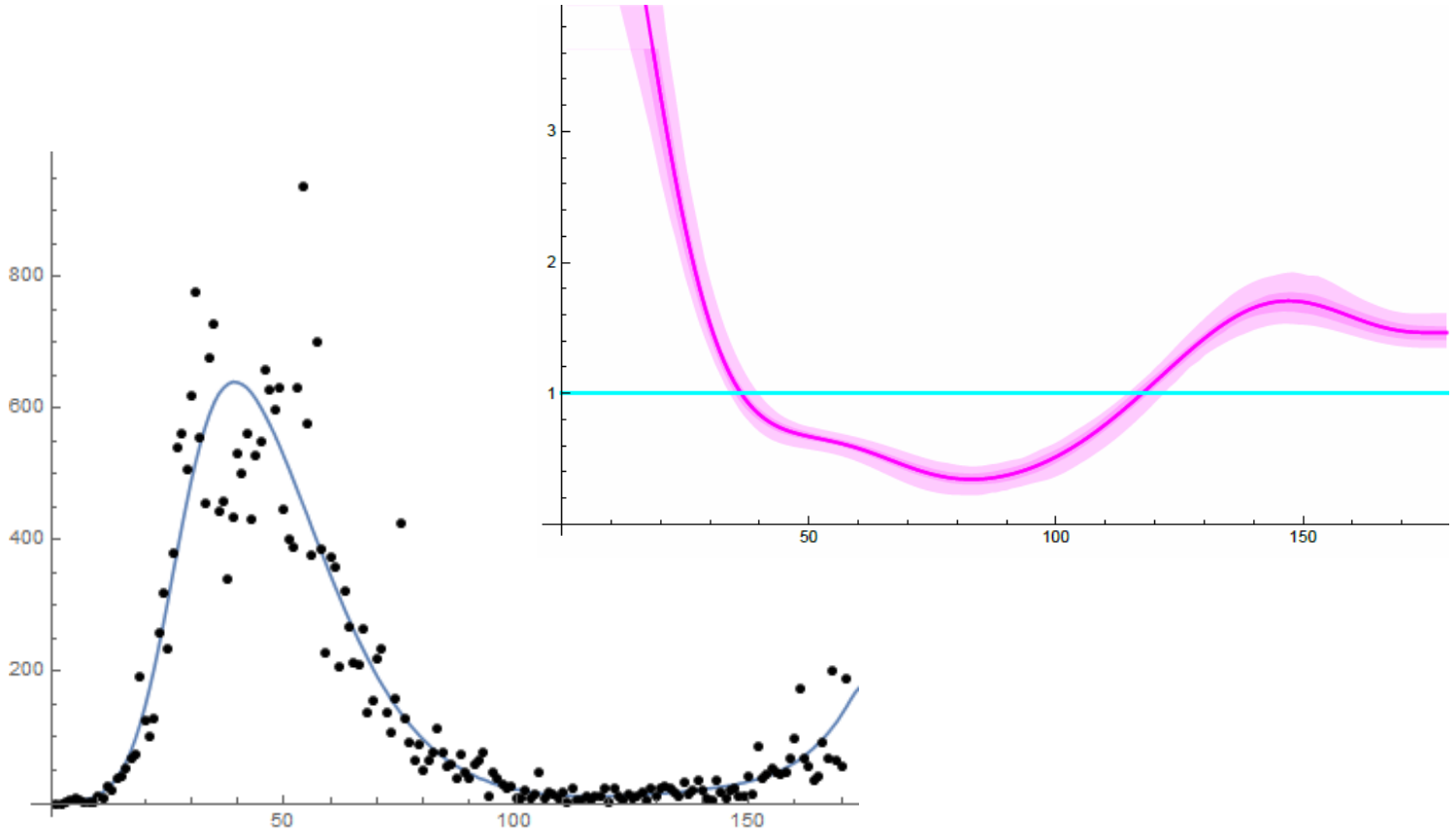
IEMAG SEIR model

- From late June, the daily number of cases began to grow again.
- A new fitting approach required.

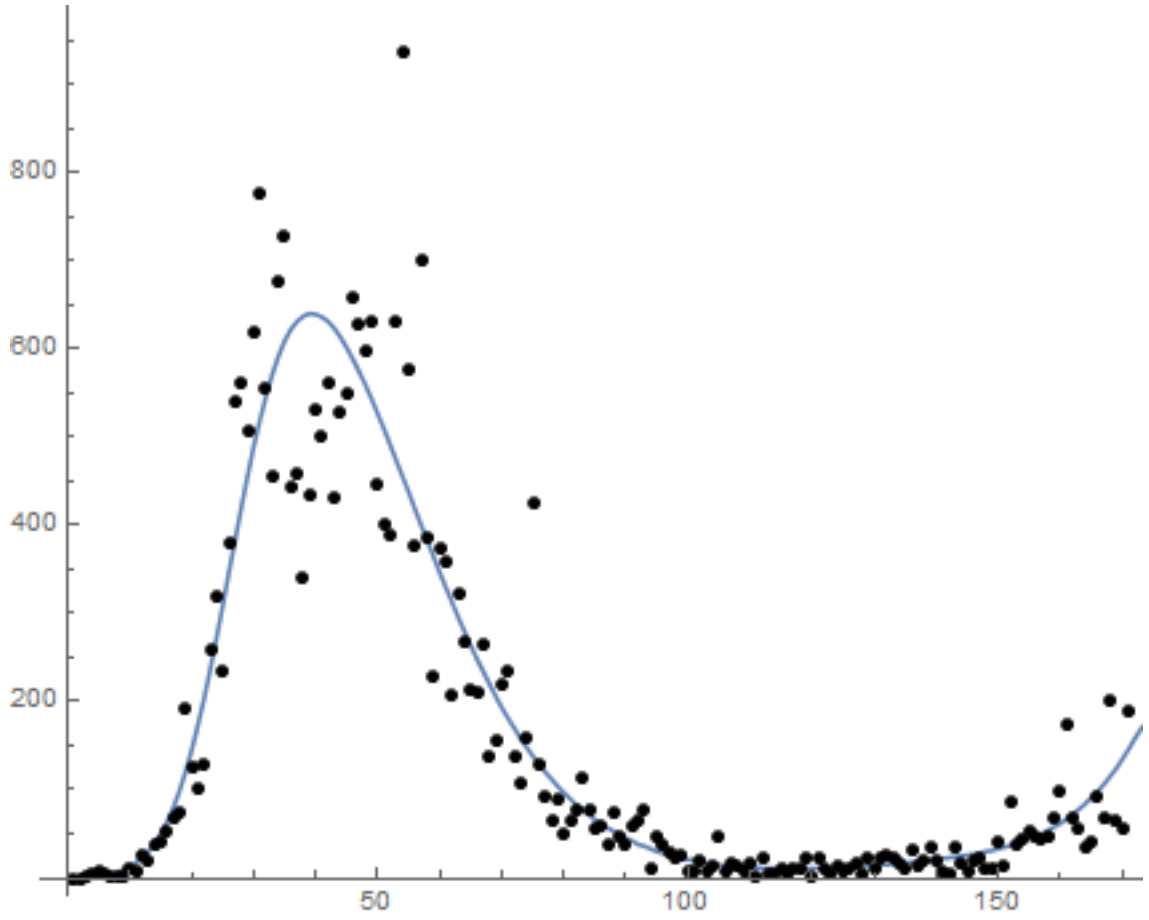


IEMAG SEIR model

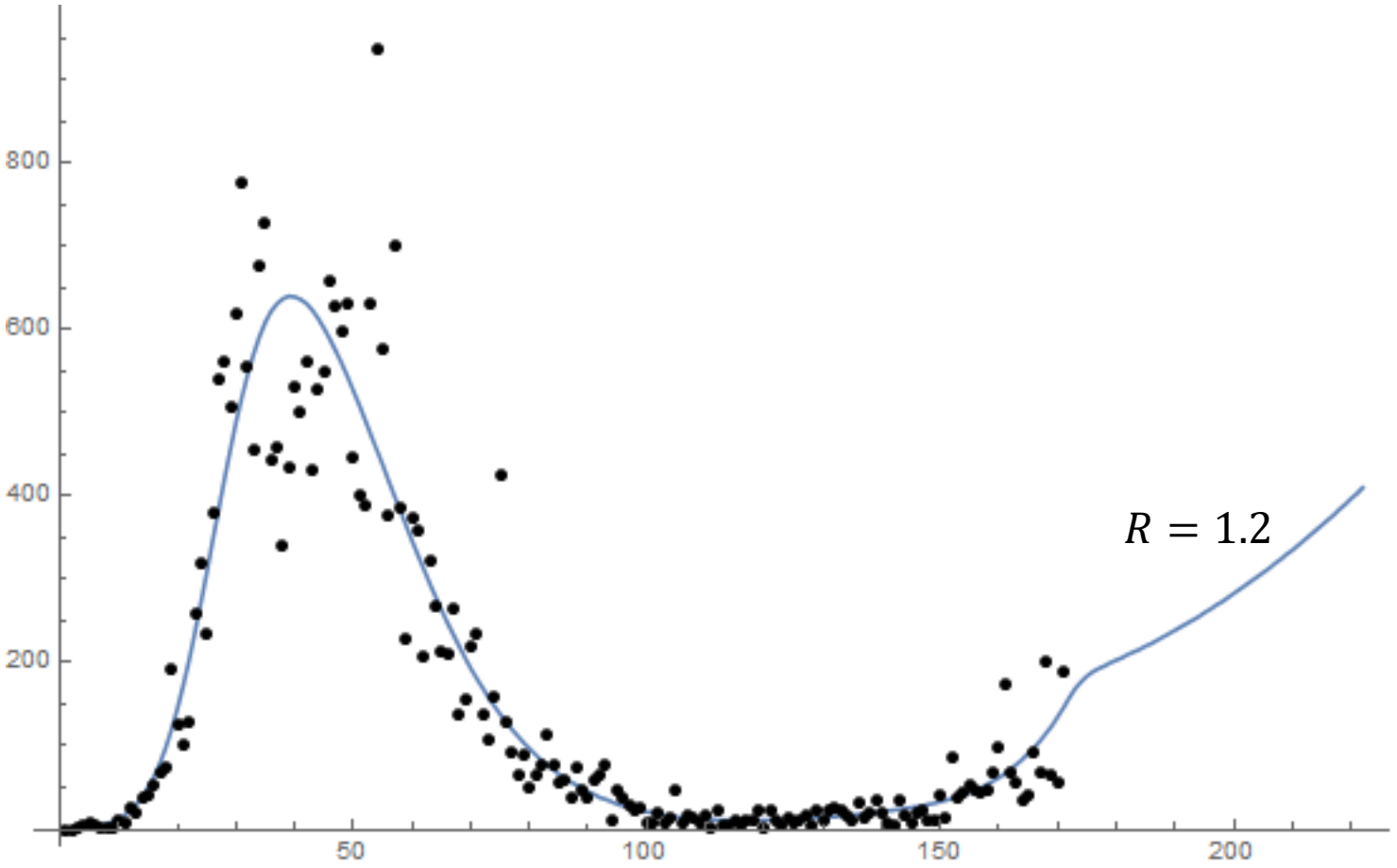
- Third choice: use GAM to produce a spline-based smooth fit for the inversion process.



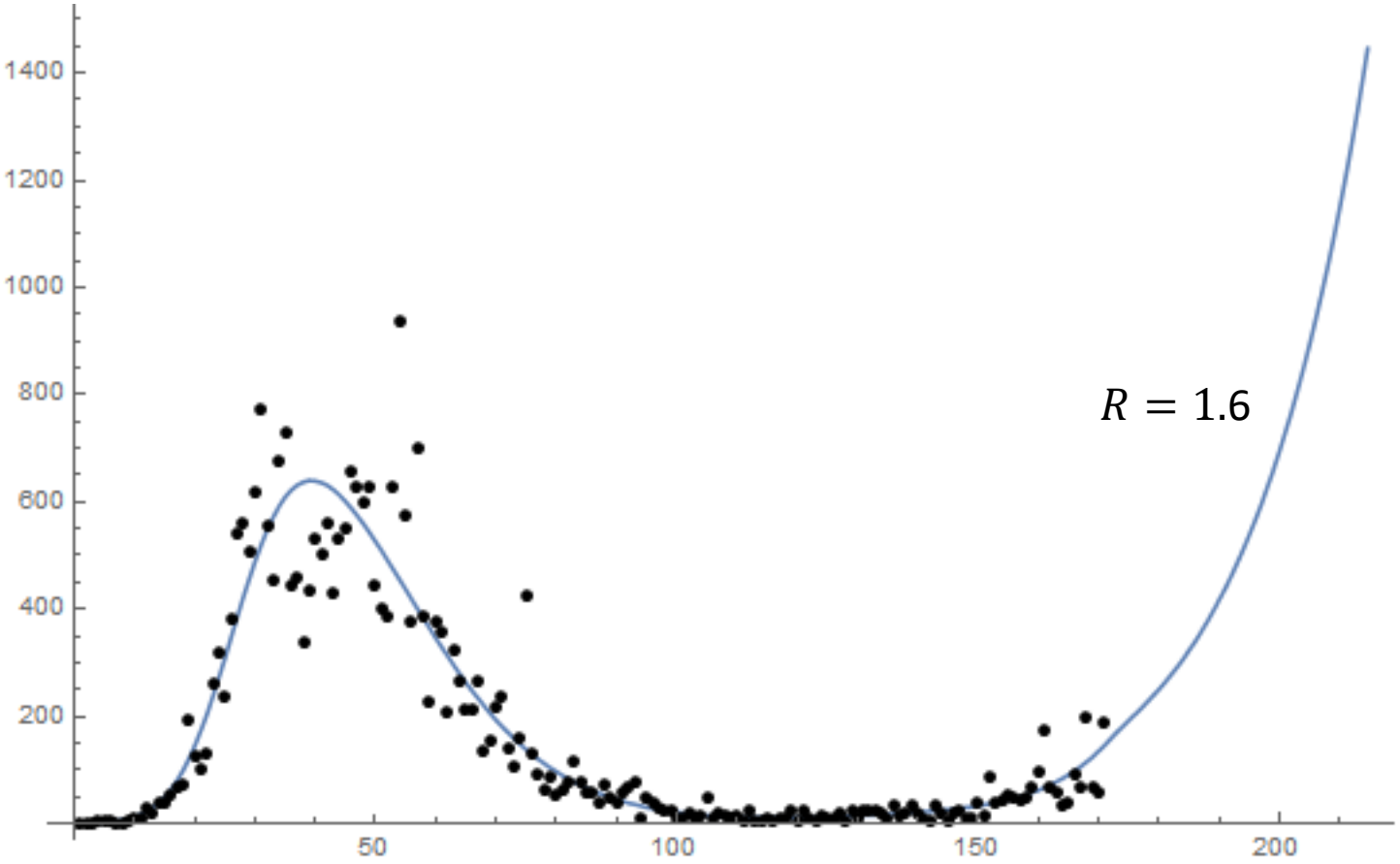
IEMAG SEIR model



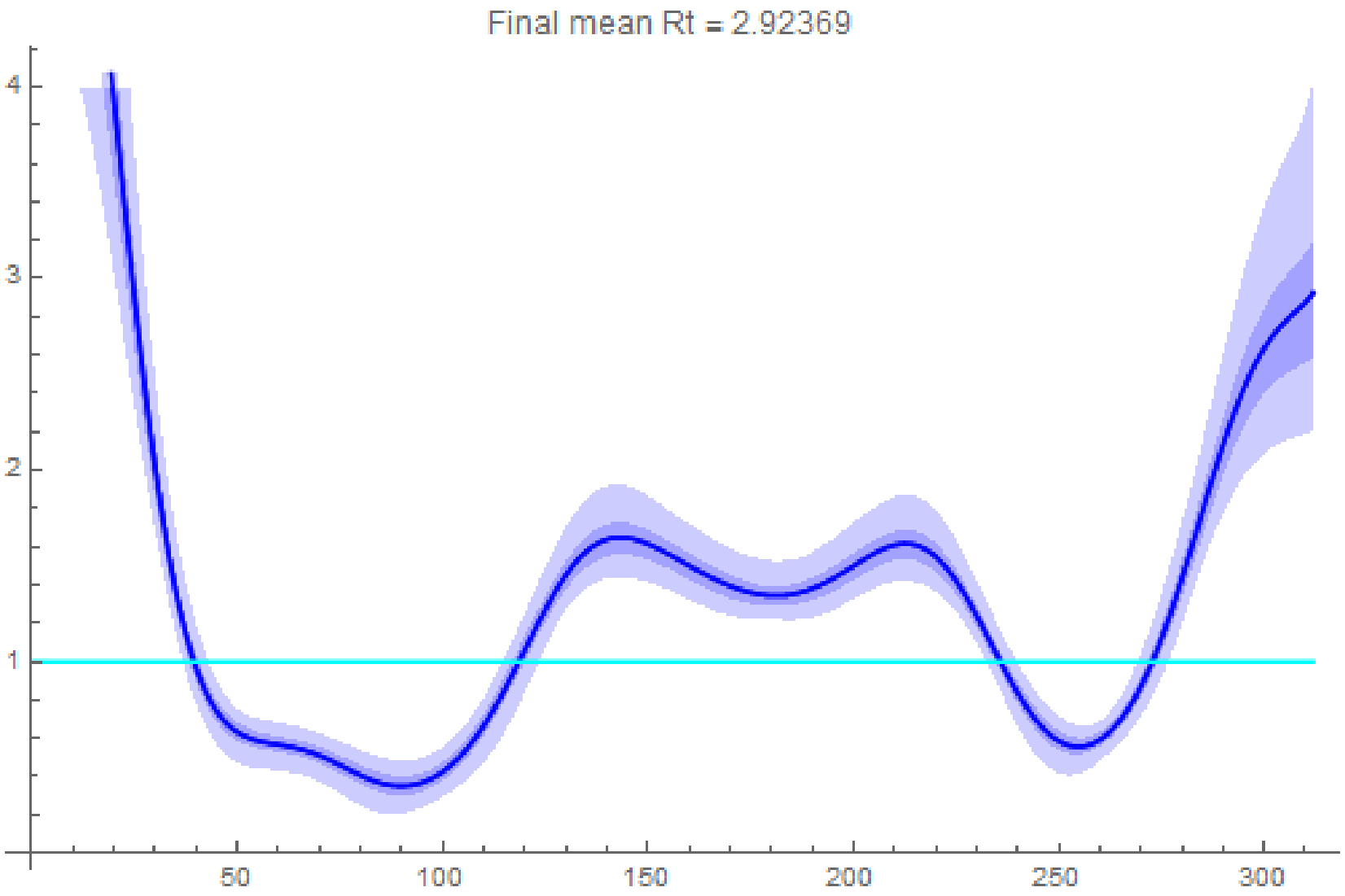
IEMAG SEIR model : scenario projections



IEMAG SEIR model : scenario projections



IEMAG SEIR model



Overview

- Disease-spread models
  - Reproduction number
- Dynamical systems
  - Herd immunity
- SEIR model for Covid-19
  - Connecting models to data

Perspectives

- Population-level differential-equation models are relatively simple to run and calibrate, but can give some insights into the role of parameters.
- The focus is on scenario analysis, not on “prediction”.
- The underlying spreading process is highly uncertain, so stochastic modelling needed to improve upon these deterministic models
- Other extensions and models:
  - Beyond homogeneous: cohorting, e.g., on the basis of age and/or geography
  - Beyond continuous: Agent-based models

Thanks to…

- IEMAG members, especially Brendan Murphy, Chris Brunsdon, Jim Duggan and Cathal Walsh

- The Irish mathematical sciences community

- Special thanks to Claire Gormley, Nial Friel, Norma Bargary, David O'Sullivan, Joey O'Brien, Leah Keating, Ali Faqeeh and everyone in my group

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Differential-Equations Modelling and Covid-19

James Gleeson

MACSI, Department of Mathematics and Statistics
University of Limerick

Joint work with Brendan Murphy, Joseph O'Brien, David O'Sullivan and IEMAG colleagues

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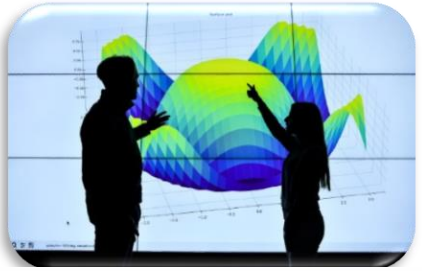

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