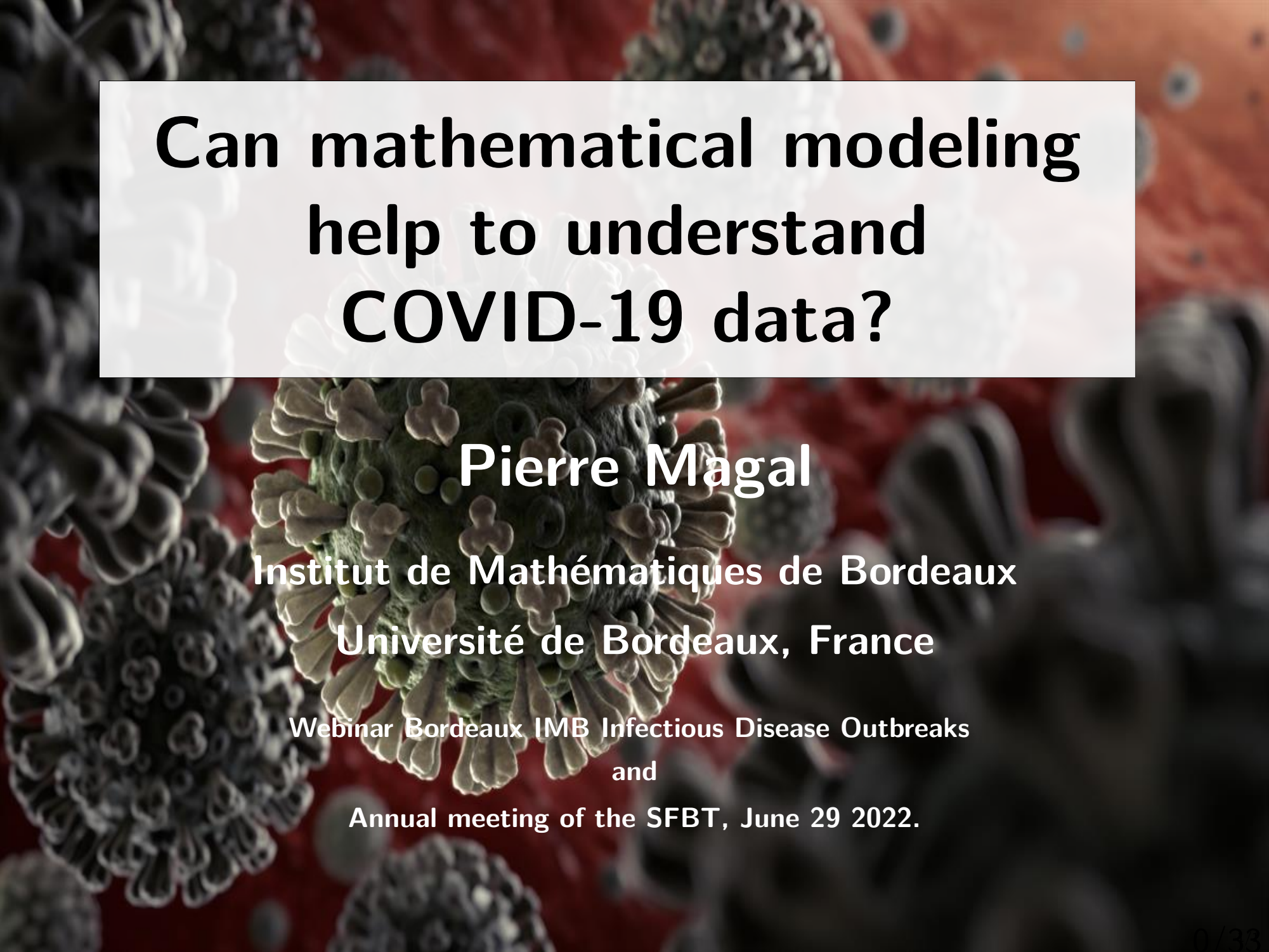

Can mathematical modeling help to understand COVID-19 data?

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Webinar Bordeaux IMB Infectious Disease Outbreaks

and

Annual meeting of the SFBT, June 29 2022.

Scope & aims

- How to recover information from the **cumulative number of reported cases data**?
- We want to use simple models with a **limited number of parameters**.
- Here the parameters include part of the **initial conditions**.
- We want to **reconstruct** and **forecast** the epidemic.

PART I:
Unreported cases for COVID-19

Example of unreported cases

A published study[1] traced COVID-19 infections resulting from a business meeting in Germany attended by a person who was infected but had no symptoms at the time. Four people were eventually infected from this single contact.

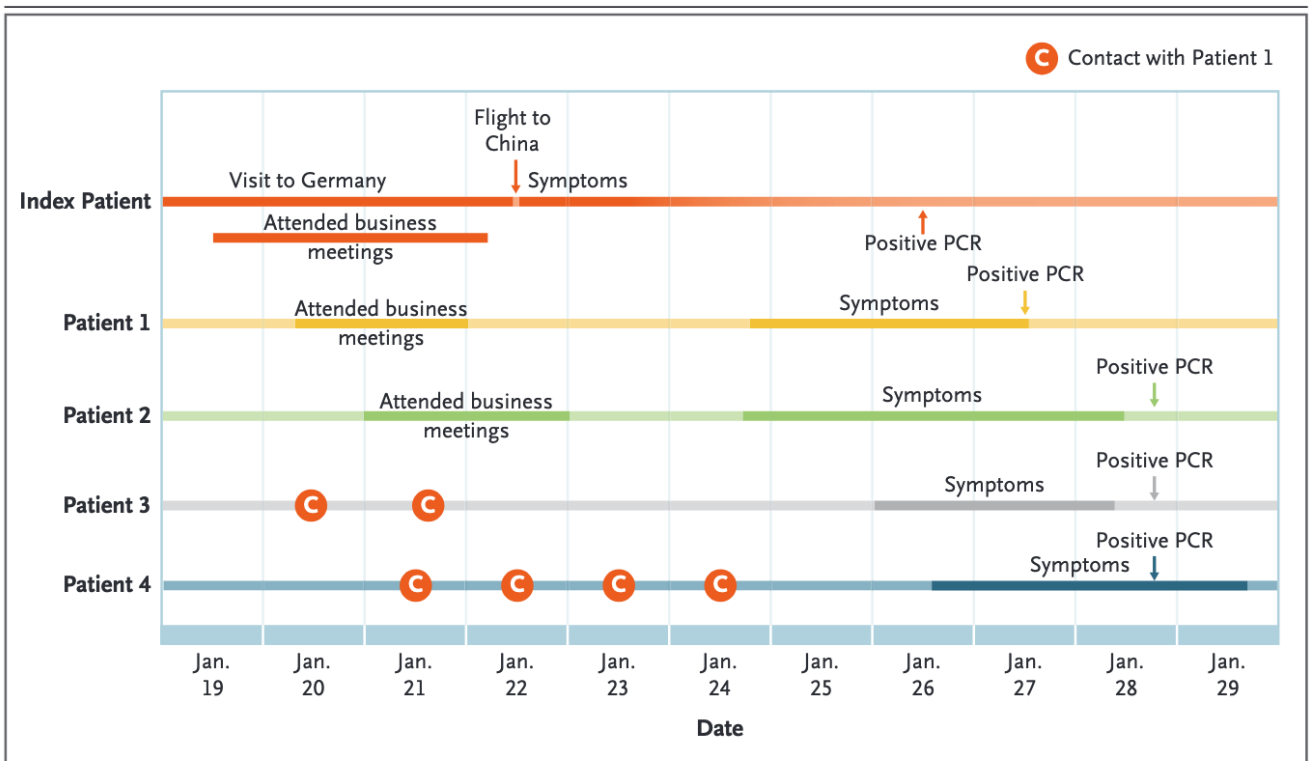


Figure 1. Timeline of Exposure to Index Patient with Asymptomatic 2019-CoV Infection in Germany.

[1] **Rothe, et al.** (2020), Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *New England Journal of Medicine*, **382(10)**, 970-971.

Example of unreported cases

A team in Japan[2] reports that 13 people evacuated from *Diamond Princess* were infected, 4 of whom, or 31 $\%$, never developed symptoms.

On the French *aircraft carrier Charles de Gaulle*, clinical and biological data for all 1739 crew members were collected on arrival at the Toulon harbor and during quarantine: 1121 crew members (64%) were tested positive for COVID-19 using RT-PCR, and among these, 24% were asymptomatic[3].

[2] **H. Nishiura, N. M. Linton, & A. R. Akhmetzhanov** (2020), Serial interval of novel coronavirus (COVID-19) infections, *Int. J. Infect. Dis.*, **93**, 284-286.

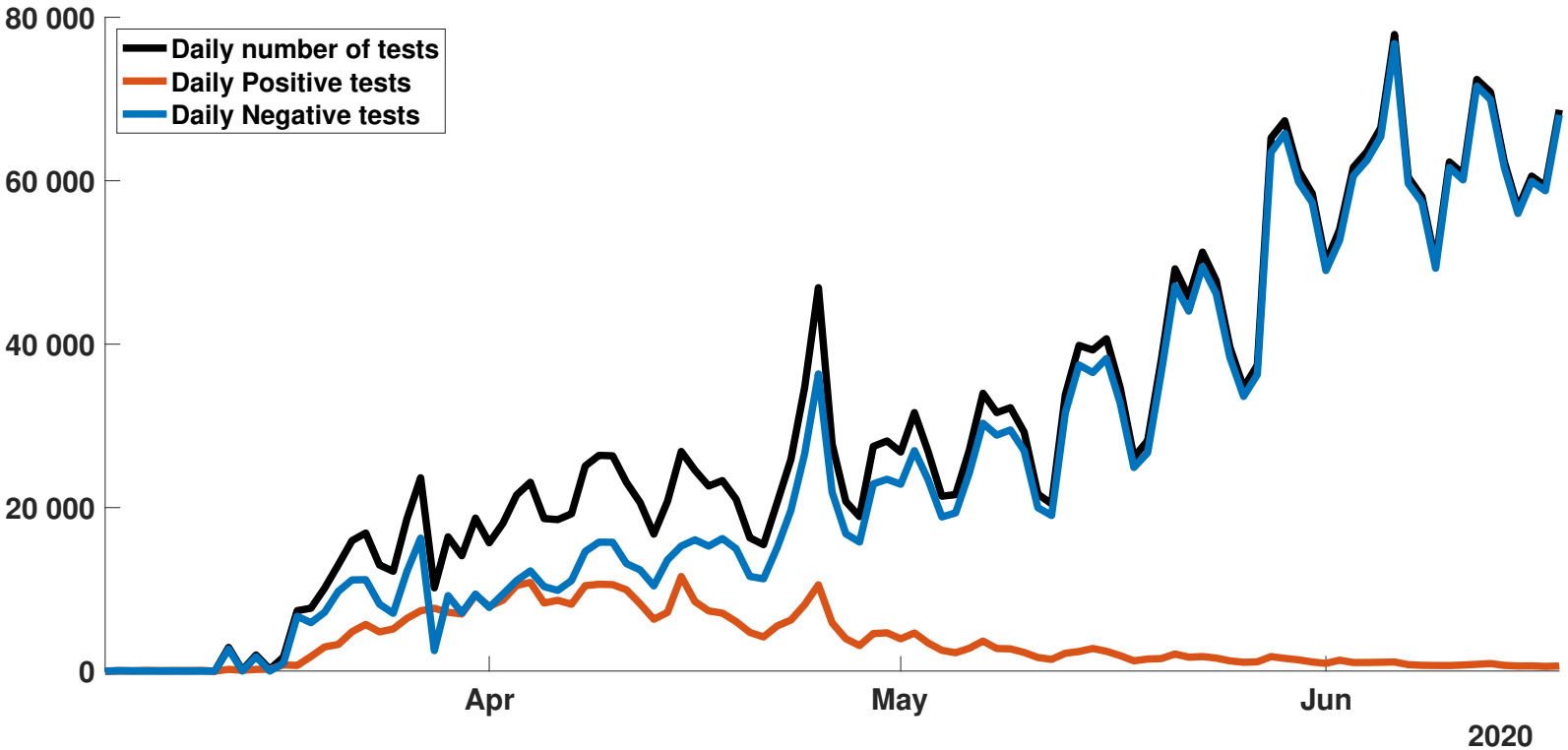
[3] **O. Bylicki, N. Paleiron, and F. Janvier** (2021), An Outbreak of Covid-19 on an Aircraft Carrier. *New Engl. J. Med.*, **384(10)**, 976–977.

What are the unreported cases?

- **Mild symptoms** induce unreported cases because people will only get tested in case of severe symptoms.
- Unreported cases are partly due to a low daily number of tests.

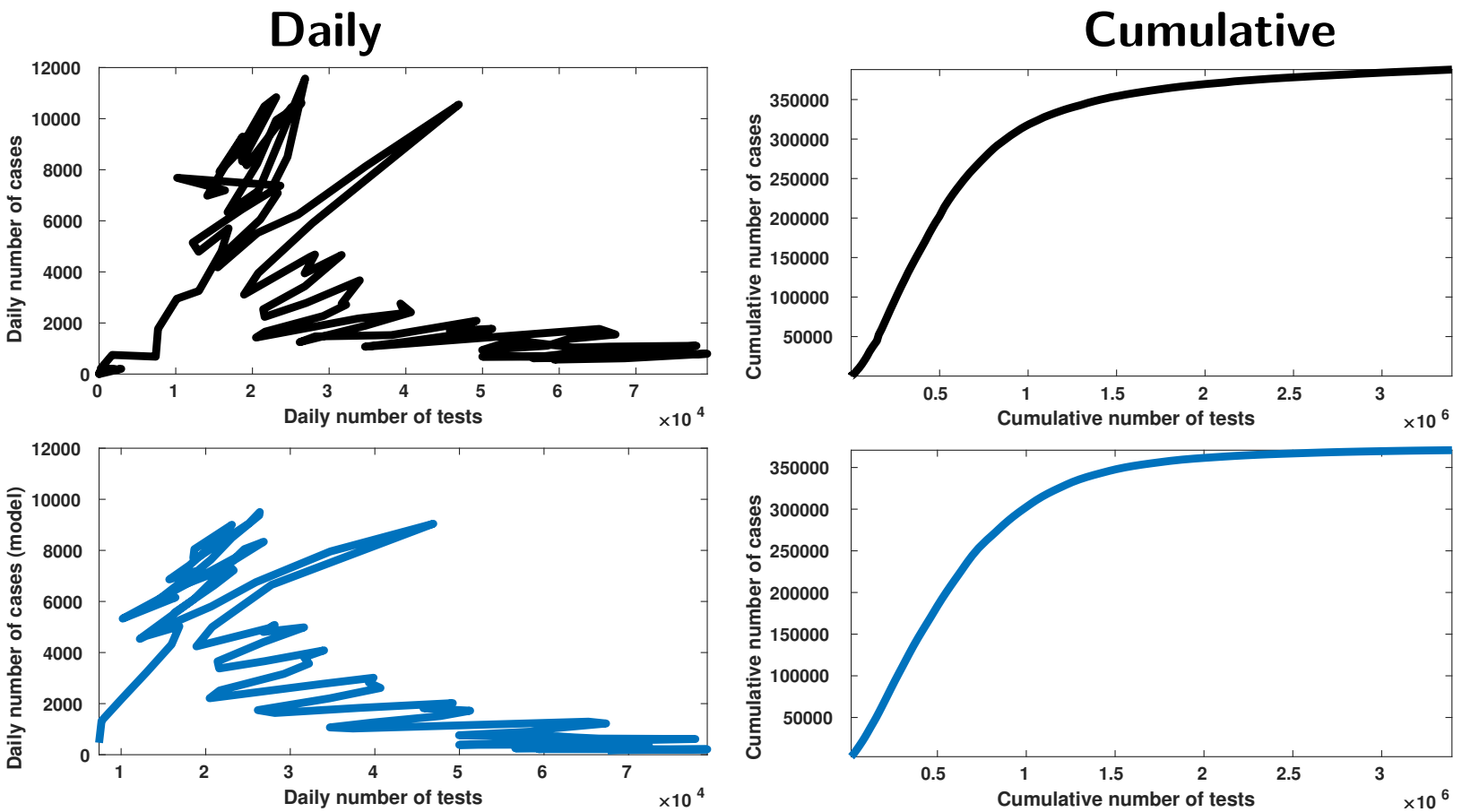
Testing data for New York state

The dynamic of the daily number of tests is connected to the dynamic of the daily number of reported cases in a complex way[4].



[4] **Q. Griette and P. Magal** (2021) Clarifying predictions for COVID-19 from testing data: the example of New York State, *Infectious Disease Modelling*, **6**, 273-283.

Testing data for New York state[5]

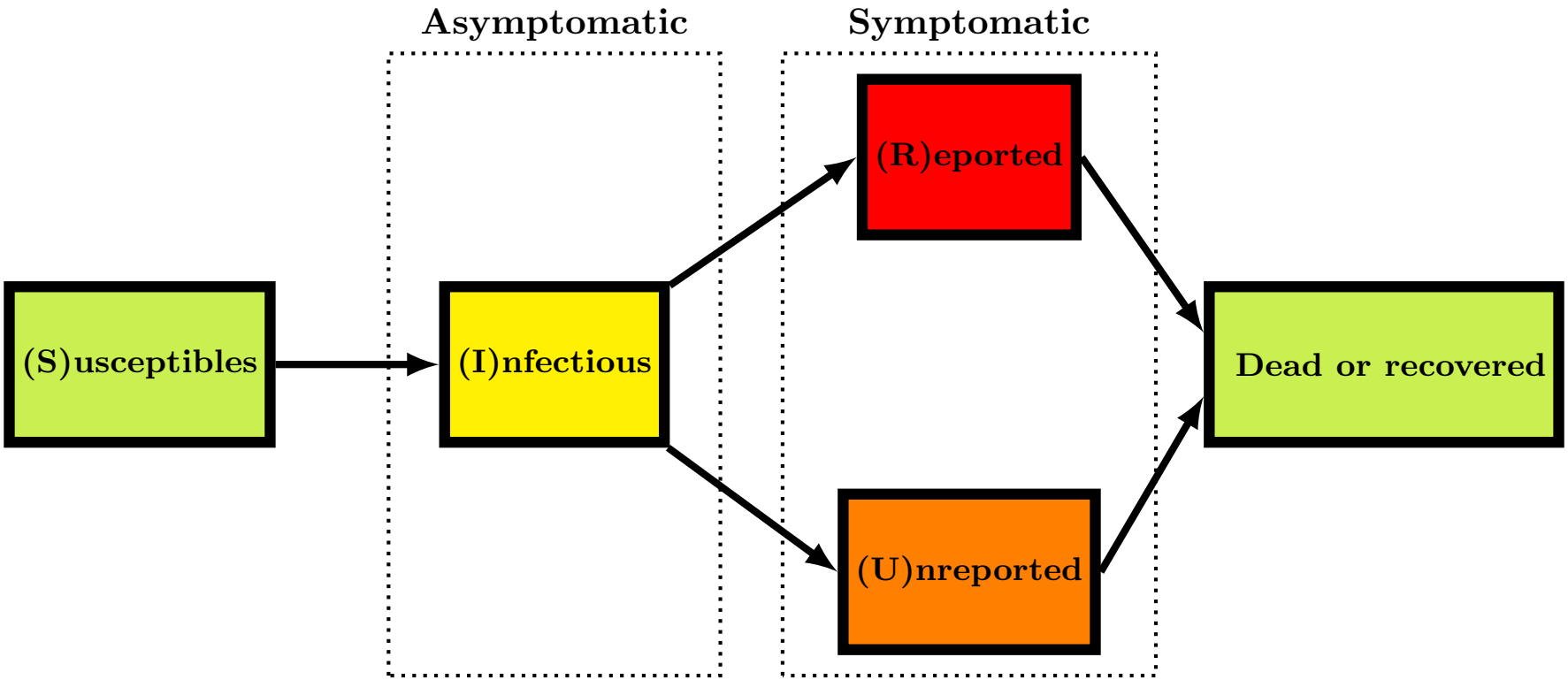


The **black curves** are produced by using **the data only**. The **blue curves** are produced by using **the model** with **the testing data**.

[5] **Q. Griette and P. Magal** (2021) Clarifying predictions for COVID-19 from testing data: the example of New York State, *Infectious Disease Modelling*, **6**, 273-283.

PART II:
An epidemic model with unreported cases

Epidemic with Unreported Cases[6,7]



[6] **Z. Liu, P. Magal, O. Seydi, and G. Webb** (2020), Understanding unreported cases in the 2019-nCov epidemic outbreak in Wuhan, China, and the importance of major public health interventions, *Biology*, **9(3), 50**.

[7] **J. Arino, F. Brauer, P. van den Driessche, J. Watmough and J. Wu** (2006), Simple models for containment of a pandemic, *Journal of the Royal Society Interface*, **3(8)**, 453-457.

Epidemic model

Transmissions between infectious and susceptible individuals are described by

$$\begin{cases} S'(t) = -\tau(t)\, S(t)\, I(t), \\ I'(t) = \tau(t)\, S(t)\, I(t) - \nu\, I(t), \end{cases} \tag{1}$$

where

- $\tau(t)$ is the rate of transmission.
- $1/\nu$ is the average duration of the asymptomatic infectious period.
- $\tau(t)\, S(t)\, I(t)$ is the flux of S-individuals becoming infected at time t.
- $\nu\, I(t)$ is the flux of I-individuals leaving the I-compartment.

Initial distribution of the model

The system (1) is complemented with the initial distribution of the model

$$S(t_0) = S_0 \geq 0,\ I(t_0) = I_0 \geq 0. \tag{2}$$

The parameter

$$t_0$$

is also unknown.

That is the time t_0 from which the epidemic model (1) becomes applicable.

Connecting the data and the model[8,9]

To connect the data and the model (1) we use the following equation

$$\mathrm{CR}'(t) = f\,\nu\,I(t), \text{ for } t \geq t_0, \tag{3}$$

where f is the **fraction of reported individuals**.

We assume that

- f is the fraction of patients with **severe symptoms**.
- $1 - f$ is the fraction of of patients with **mild symptoms**.

[8] **Z. Liu, P. Magal, O. Seydi, and G. Webb** (2020), Understanding unreported cases in the 2019-nCov epidemic outbreak in Wuhan, China, and the importance of major public health interventions, *Biology*, **9(3), 50**.

[9] **P. Magal, and G. Webb** (2018) The parameter identification problem for SIR epidemic models: Identifying Unreported Cases, *Journal of Mathematical Biology* **77(6-7)**, 1629–1648.

Given Parameters

- Number of susceptible individuals when the epidemic starts

$$S_0 = 67 \text{ millions for France.}$$

- Time from which the epidemic model starts to be valid, also called initial time of the model t_0.
- The average duration of the infectiousness $\frac{1}{\nu} = 3$ days.
- The fraction of reported individuals $f = 0.9$.

Computed parameters

- I_0 the number of asymptomatic infectious patients at the start of the epidemic.
- $\tau(t)$ the rate of transmission.

What factors govern the transmission rate $\tau(t)$?

As explained in Magal and Ruan[10] by using stochastic individual based models

$$\tau(t) = \frac{1}{\text{the average duration of a contact}} \times \text{the probability of transmission.}$$

Contact patterns are impacted by **social distancing measures**.

The average number of contacts per unit of time depends on the **density of population**[11,12].

---

[10] **P. Magal and S. Ruan** (2014), Susceptible-Infectious-Recovered Models Revisited: From the Individual Level to the Population Level, *Mathematical Biosciences* **250**, 26-40.

[11] **J. Rocklöv, & H. Sjödin.** (2020), High population densities catalyse the spread of COVID-19. *J Travel Med*, **27(3)** , taaa038.

[12] **H. Seligmann, N. Vuillerme & J. Demongeot** (2020), Summer COVID-19 third wave: faster high altitude spread suggests high UV adaptation, *medRxiv*.

What factors govern the transmission rate $\tau(t)$?

- The probability of transmission depends of the virulence of the pathogen which can depend on the **temperature, the humidity, and the Ultraviolet**[13,14].

- The probability of transmission depends of the susceptibility of the individuals
  - **Blood group**[15] : Blood group O is associated with a lower susceptibility to SARS-CoV2;
  - **Genetic lineage**[16] A gene cluster inherited from Neanderthal has been identified as a risk factor for severe symptoms.

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[13] **J. Demongeot, Y. Flet-Berliac, & H. Seligmann** (2020), Temperature Decreases Spread Parameters of the New Covid-19 Case Dynamics, *Biology*, **9**, 94.

[14] **J. Wang, et al** (2020), High temperature and high humidity reduce the transmission of COVID-19. *Available at SSRN 3551767*.

[15] **P. Guillon, et al.** (2008), Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies, *Glycobiology* **18.12**, 1085-1093.

[16] **H. Zeberg and S. Pääbo,** (2020), The major genetic risk factor for severe COVID-19 is inherited from Neanderthals, *Nature*.

PART III:
Single epidemic wave

Modeling the exponential phase

At the early stage of the epidemic, we can assume that $S(t)$ is constant, and equal to S_0. We can also assume that $\tau(t)$ remains constant equal to $\tau_0 = \tau(t_0)$. Therefore, by replacing these parameters into the I-equation of system (1) we obtain

$$I'(t) = (\tau_0 S_0 - \nu) I(t).$$

Therefore

$$I(t) = I_0 \exp\left(\chi_2 \left(t - t_0\right)\right),$$

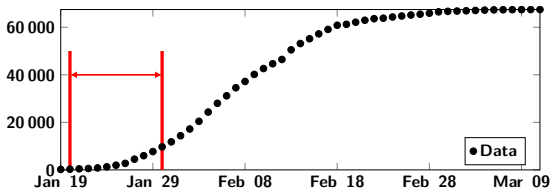
where

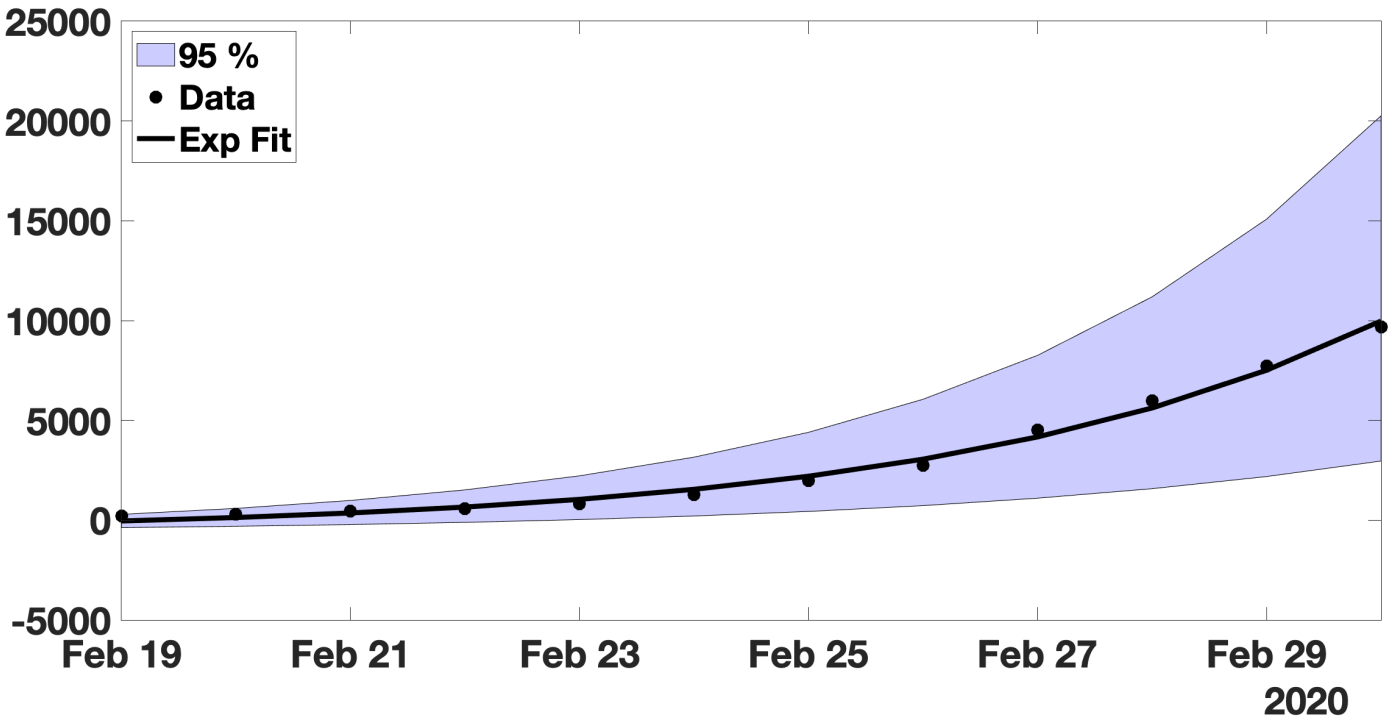
$$\chi_2 = \tau_0 S_0 - \nu.$$

By using (3), we obtain

$$\mathrm{CR}(t) = \chi_1 e^{\chi_2 t} - \chi_3. \tag{4}$$

Application to COVID-19 in mainland China [17,18]





[17] **Z. Liu, P. Magal, O. Seydi, and G. Webb** (2020), Understanding unreported cases in the 2019-nCov epidemic outbreak in Wuhan, China, and the importance of major public health interventions, *Biology*, **9(3), 50**.

[18] **J. Demongeot, Q. Griette and P. Magal** (2020), SI epidemic model applied to COVID-19 data in mainland China, *Royal Society Open Science* 7:201878.

Initial number of infected and transmission rate

Remember that (3) and (4) are respectively

$$\mathrm{CR}'(t) = f\,\nu\,I(t), \text{ for } t \geq t_0, \quad \text{and} \quad \mathrm{CR}(t) = \chi_1 e^{\chi_2 t} - \chi_3.$$

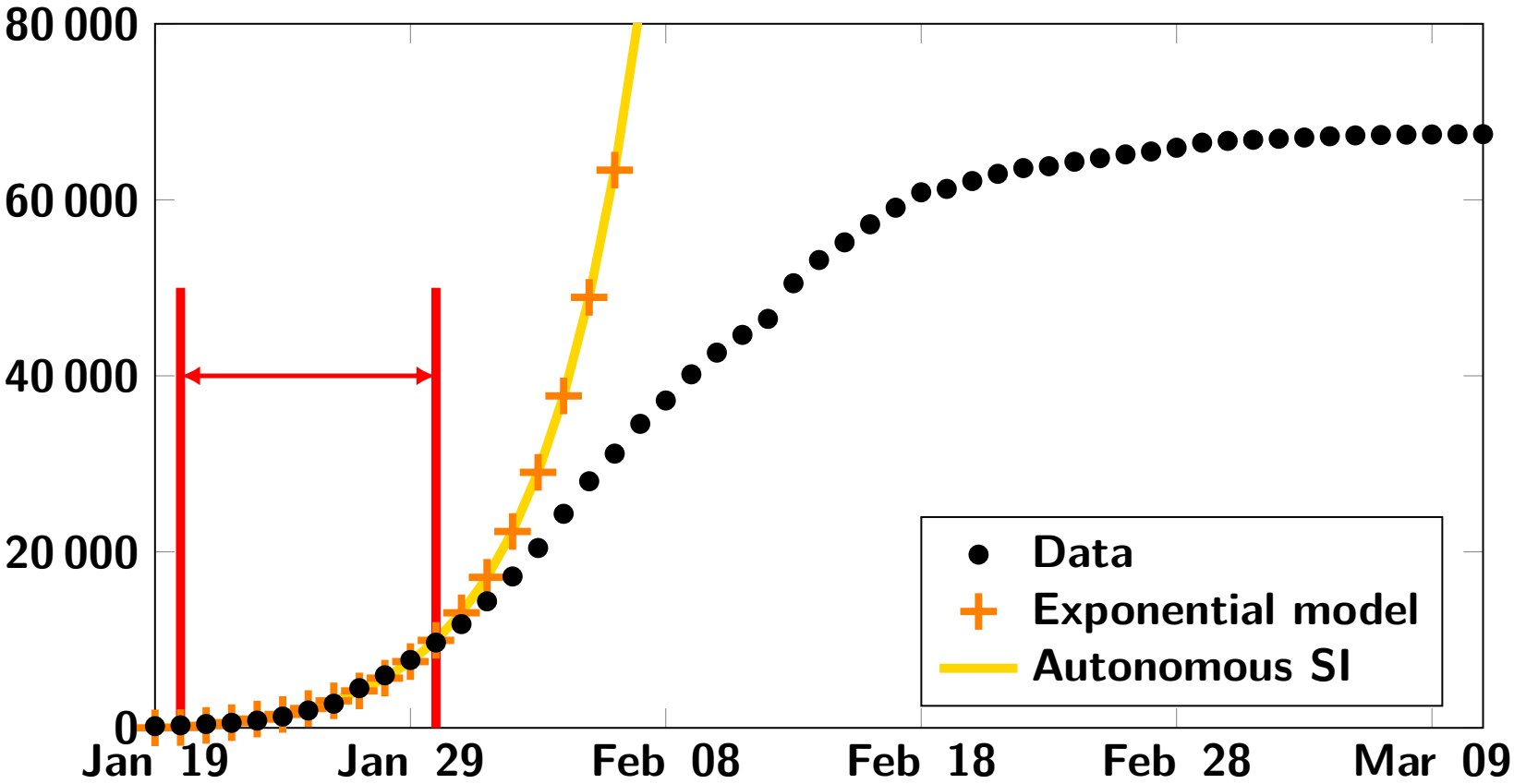
By using (3) and (4) we obtain

$$I_0 = \frac{\mathrm{CR}'(t_0)}{\nu\,f} = \frac{\chi_1\,\chi_2 e^{\chi_2\,t_0}}{\nu\,f},$$

and by using (4)

$$\tau_0 = \frac{\chi_2 + \nu}{S_0}.$$

Why do we need a time-dependent transmission rate?



PART IV:
Multiple epidemic waves

Earlier results with a transmission rate reconstructed from the data

This problem has already been considered in several articles. In the early 70s, London and Yorke[19,20] discussed the time dependent rate of transmission in the context of measles, chickenpox and mumps.

Motivated by applications to the data for COVID-19 the group of Bakhta, Boiveau, Maday, & Mula[21] also obtained some new results about reconstructing the rate of transmission.

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[19] **W. P. London, and J. A. Yorke** (1973), Recurrent outbreaks of measles, chickenpox and mumps: I. Seasonal variation in contact rates. *Am J Epidemiol*, **98(6)**, 453-468.

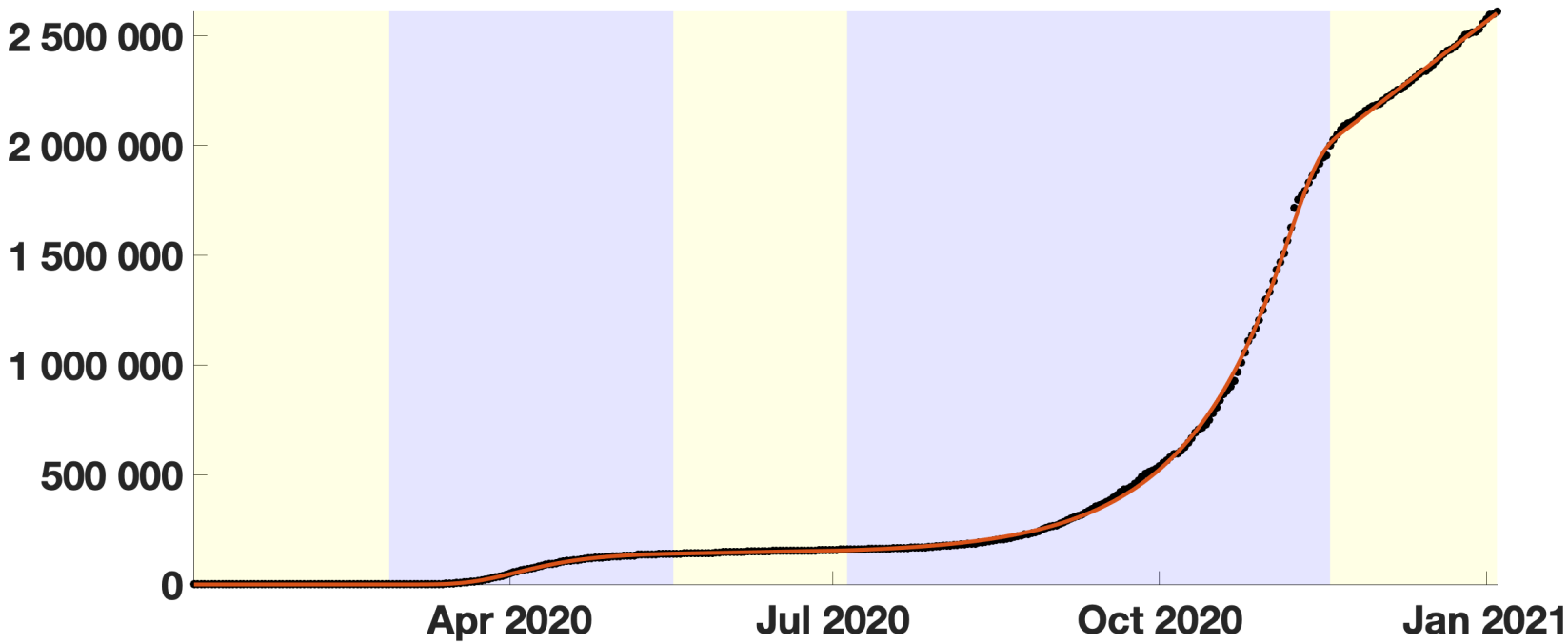
[20] **J. A. Yorke, and W. P. London** (1973), Recurrent outbreaks of measles, chickenpox and mumps: II. Systematic differences in contact rates and stochastic effects. *Am J Epidemiol*, **98(6)**, 469-482.

[21] **A. Bakhta, T. Boiveau, Y. Maday, & O. Mula** (2021), Epidemiological Forecasting with Model Reduction of Compartmental Models. Application to the COVID-19 Pandemic. *Biology*, **10(1)**, 22.

Epidemic and Endemic phases in France

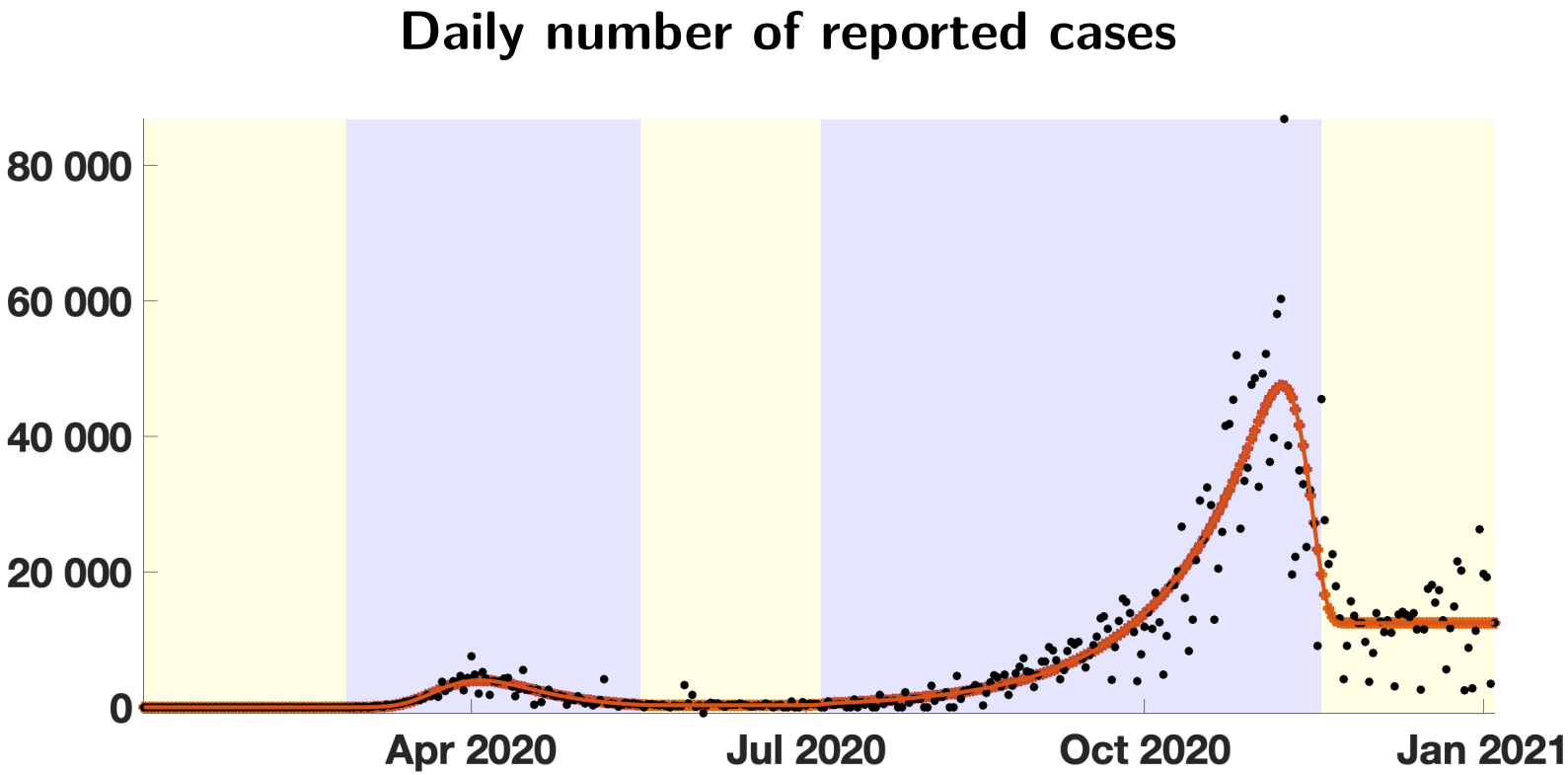
We fit a Bernoulli-Verhulst model during each epidemic phase. Then we extend the model by lines outside the epidemic phases. We regularize the junction points by a convolution with a Gaussian function with standard deviation of 7 days.

Cumulative number of reported cases



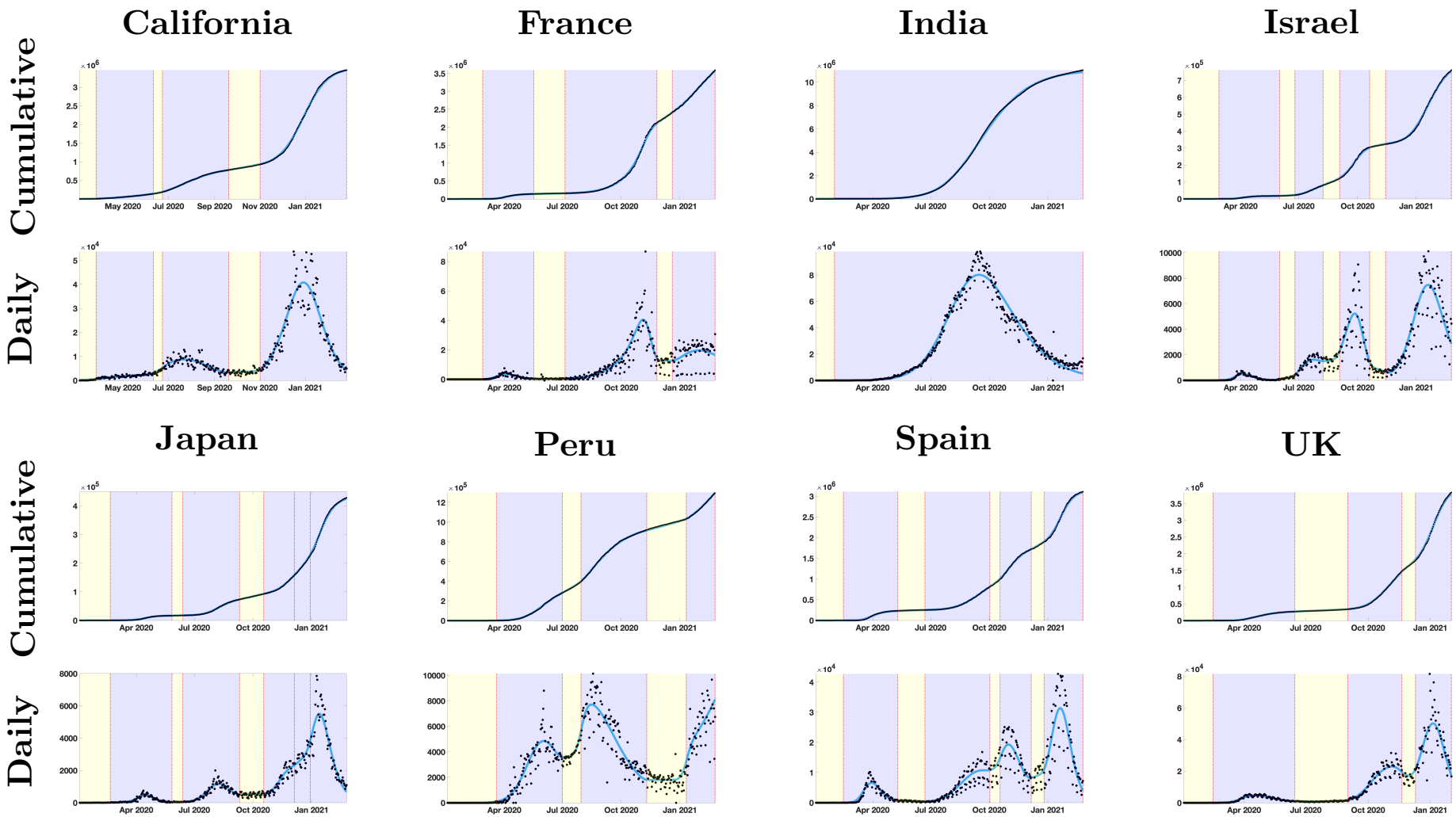
The red curve corresponds to the phenomenological model and the black dots correspond to the data of the number of cumulative cases. **We use** $16 = 2 \times 5 + 3 \times 2$ **parameters for more than 365 points.**

Epidemic and Endemic phases in France



The red curve corresponds to the first derivative of the phenomenological model and the black dots correspond to the data of the daily number of cases.

Phenomenological Model[22]



[22] **Q. Griette, J. Demongeot and P. Magal** (2021), What can we learn from COVID-19 data by using epidemic models with unidentified infectious cases? *Mathematical Biosciences and Engineering*, **19(1)**: 537–594.

Instantaneous reproduction number

We use our method to compute the transmission rate, and we consider the **instantaneous reproduction number**

$$\mathbf{R_e(t)} = \tau(\mathbf{t})\mathbf{S(t)}/\nu,$$

and the **quasi-instantaneous reproduction number**

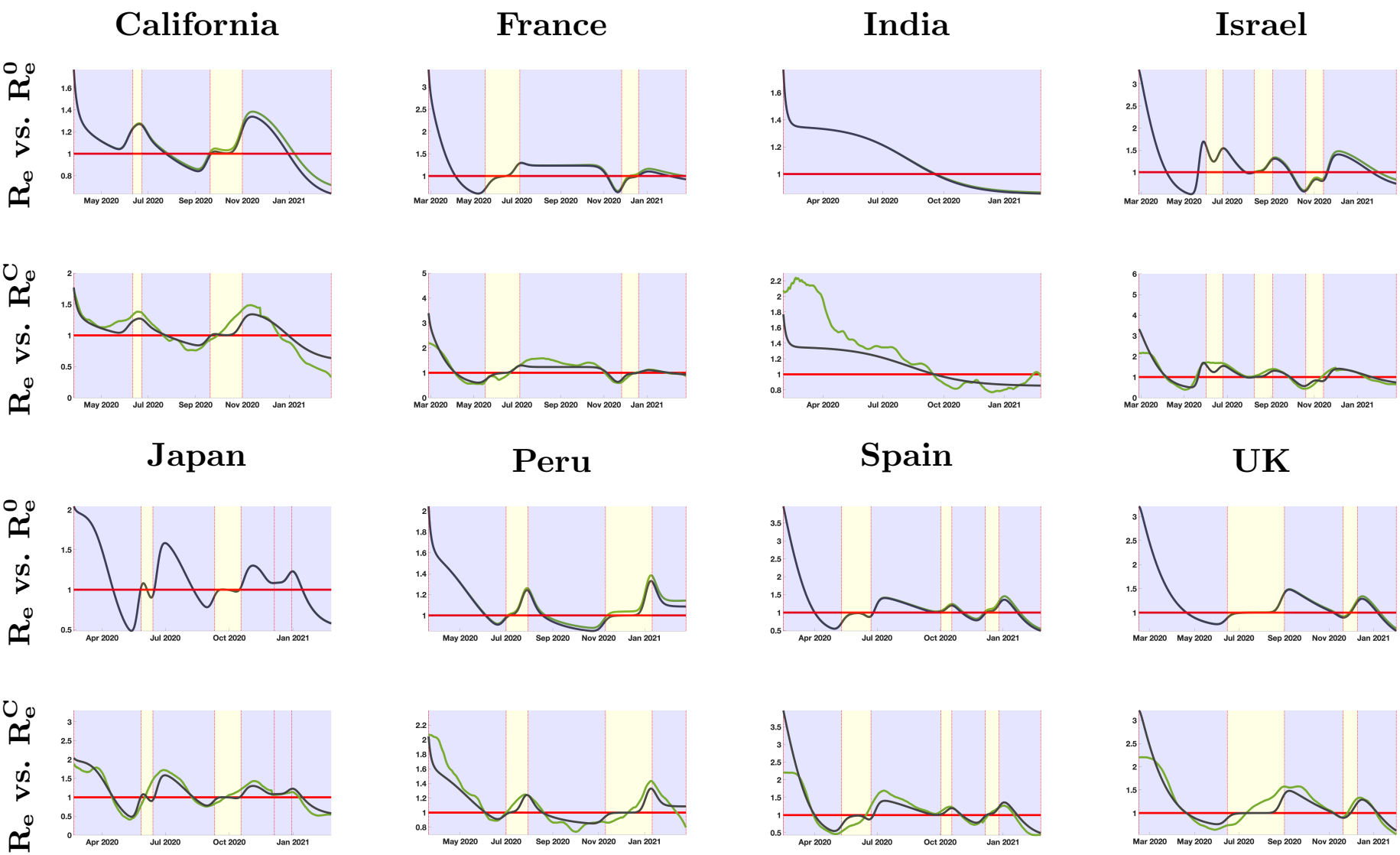
$$\mathbf{R_e^0(t)} = \tau(\mathbf{t})\mathbf{S_0}/\nu,$$

We compare the above indicators with $\mathbf{R_e^C(t)}$ the classical notion of **instantaneous reproduction number**[23,24].

[23] **T. Obadia, R. Haneef, & P. Y. Boëlle** (2012), The R_0 package: a toolbox to estimate reproduction numbers for epidemic outbreaks. *BMC medical informatics and decision making*, **12(1)**, 1-9.

[24] **A. Cori, N. M. Ferguson, C. Fraser, & S. Cauchemez** (2013), A new framework and software to estimate time-varying reproduction numbers during epidemics. *American journal of epidemiology*, **178(9)**, 1505-1512.

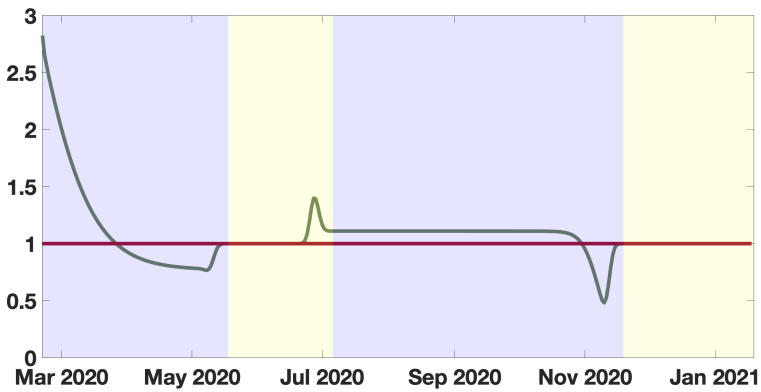
Instantaneous reproduction numbers[25]



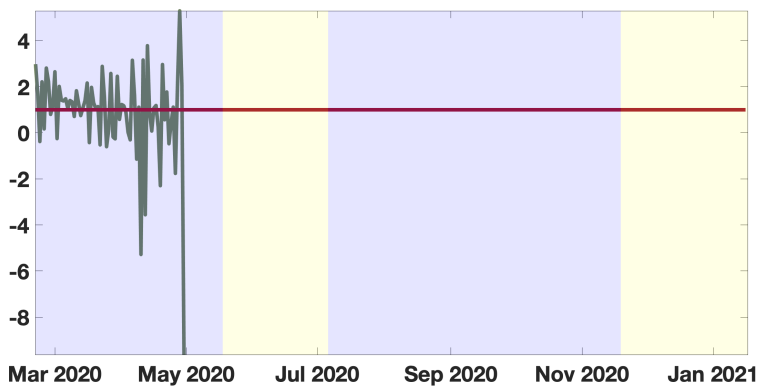
[25] **Q. Griette, J. Demongeot and P. Magal** (2021), What can we learn from COVID-19 data by using epidemic models with unidentified infectious cases? *Mathematical Biosciences and Engineering*, **19(1)**: 537–594.

Why do we need a phenomenological model to regularize the data?

With phenomenological model



Without phenomenological model



Conclusions

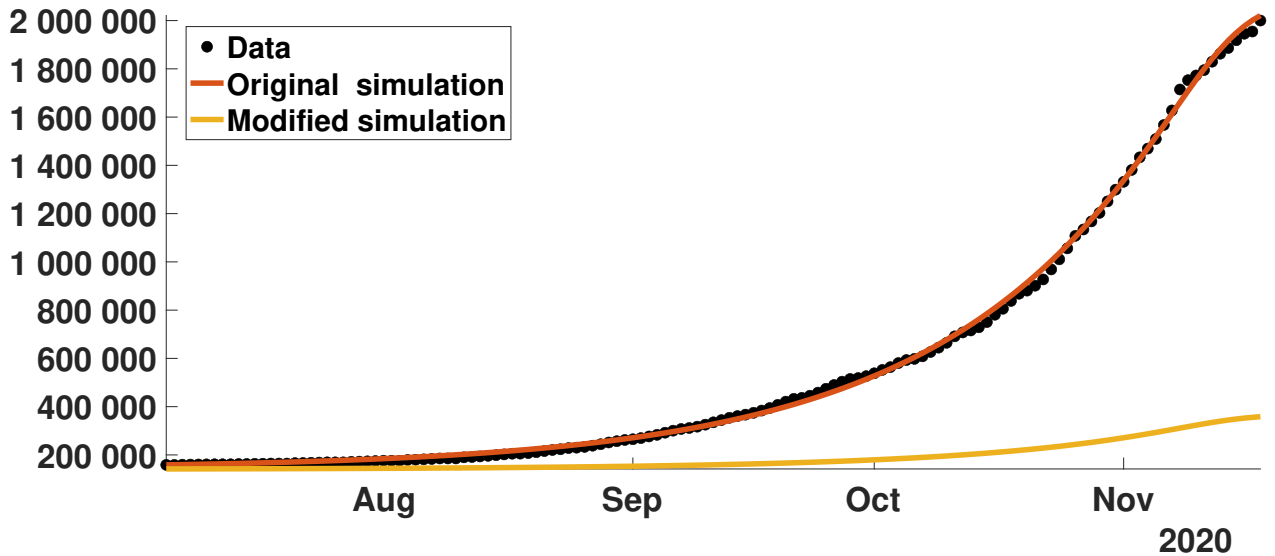
The population of susceptible patients is almost unchanged after the epidemic passed. Therefore, the system behaves almost like the non-autonomous system

$$I'(t) = \tau(t) S_0 I(t) - \nu I(t), \forall t \geq t_0, \text{ and } I(t_0) = I_0,$$

This means that $I(t)$ depends linearly on I_0.

Conclusions

The average daily number of cases during the endemic phases matters a lot.[26]



We start the simulation at time $t_0 =$ July 05 with the initial value $I_0 = \dfrac{\mathrm{CR}'(t_2)}{\nu f}$

for **red curve** and with $I_0 = \dfrac{1}{10}\dfrac{\mathrm{CR}'(t_2)}{\nu f}$ for **yellow curve**.

[26] **Q. Griette, J. Demongeot and P. Magal** (2021) A robust phenomenological approach to investigate COVID-19 data for France, *Mathematics in Applied Sciences and Engineering*, **2(3)**, 149-218.

Conclusions

How to extend the same kind of idea to large systems?

In Liu et al. [27] we consider a 2-dimensional example. This example corresponds to a system of the form

$$\mathrm{I}'(\mathrm{t}) = \mathrm{L}\,\mathrm{I}(\mathrm{t})$$

where $\mathrm{L} \in \mathrm{M}_n(\mathbb{R})$ is a n by n matrix with non negative off diagonal elements.

Then we use the **Perron-Frobenius theorem**, and assume that an **asynchronous exponential growth regime** that is

$$\mathrm{I}(\mathrm{t}) = \mathrm{e}^{\lambda_0 \mathrm{t}} \mathrm{I}_0 \in \mathbb{R}^n$$

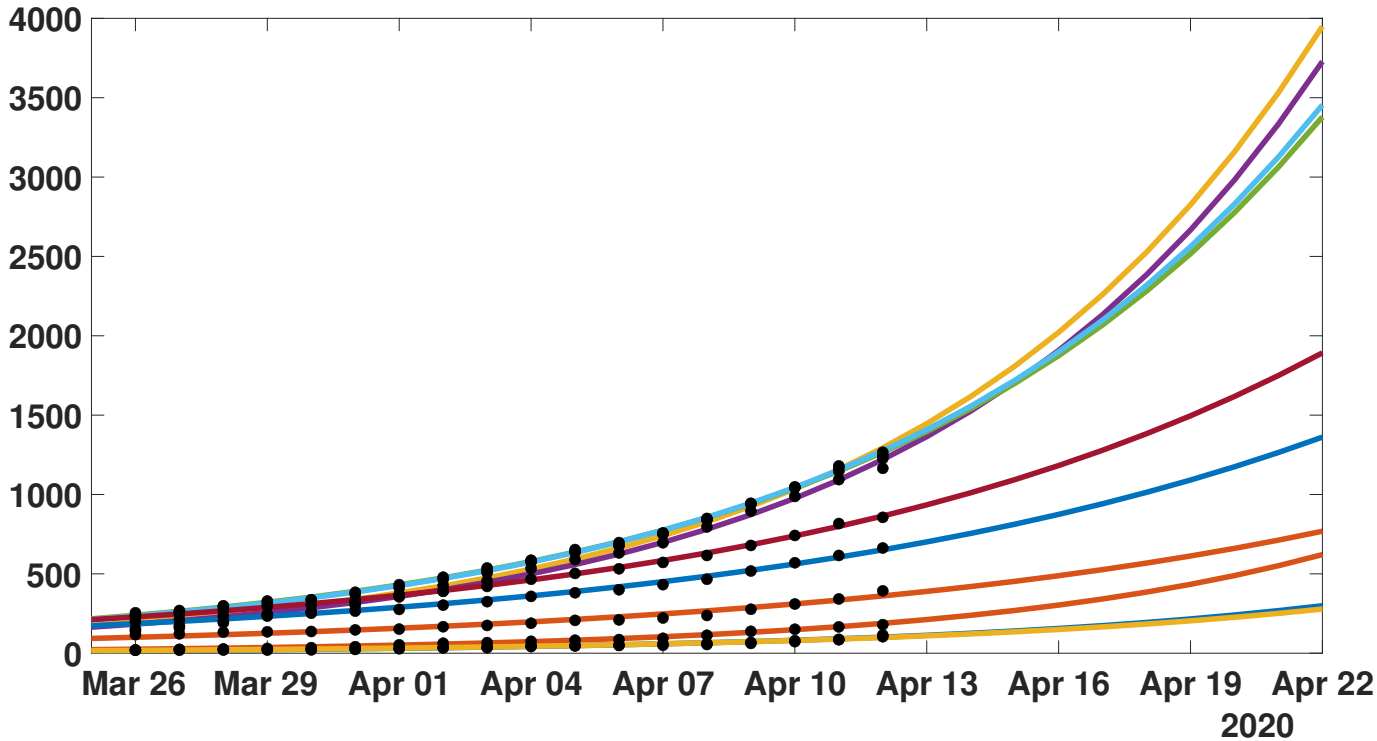
which gives

$$\lambda_0 \mathrm{I}_0 = \mathrm{L}\,\mathrm{I}_0, \text{ with } \mathrm{I}_0 \geq 0 \text{ and } I_0 \neq 0.$$

[27] **Z. Liu, P. Magal, O. Seydi, and G. Webb** (2020), Understanding unreported cases in the 2019-nCov epidemic outbreak in Wuhan, China, and the importance of major public health interventions, *Biology*, **9(3), 50**.

Conclusions

In the figure below we use an exponential fit for age group data for Japan[28]. **The exponential growth depend on the age group.**



We observe the transient behavior of a linear system with a weak coupling between compartments!

[28] **Q. Griette, P. Magal and O. Seydi** (2020), Unreported cases for Age Dependent COVID-19 Outbreak in Japan, *Biology* **9, 132**.


Thank you for your attention