HOW TO USE UQ & GSA TOOLS TO STUDY EPIDEMICS ?

EXAMPLE ON COVID-19

—

Joint work with C. Prieur, B. Iooss & F. Gamboa

To appear in *Basics and trends in sensitivity analysis, Theory and practice in R*

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Important disclaimer

What will be presented here is by no means an attempt to forecast anything about Covid

The goal is just to illustrate how UQ & GSA can be used on particular models used in epidemiology …

… and inspire you for dealing with UQ, GSA & data calibration in your own simulation models

Outline

Modified SIR model for Covid-19

Prior UQ & GSA with independent parameters

Data calibration and posterior UQ & GSA

1

MODIFIED SIR MODEL FOR COVID-19

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Compartmental models

Basic principle: the total population is divided into several categories (the « compartments »)

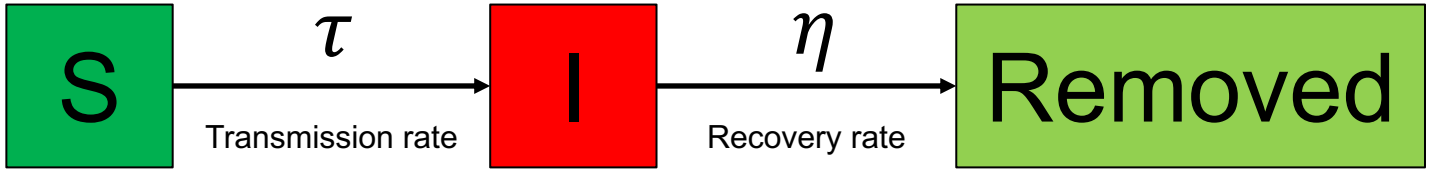
- **People may progress between compartments**
- **We study the evolution of the number of individuals inside each compartment over time**

The most basic compartmental model is the so-called SIR model

- 3 compartments : Susceptible (S), Infectious (I) and Recovered or **Removed** (R)

- Hypothesis
  - Total population is constant (no births / deaths modeled)
  - Recovery is permanent (immunity)
  - We can observe the number of infected individuals (more on this later)

Compartmental models: SIR

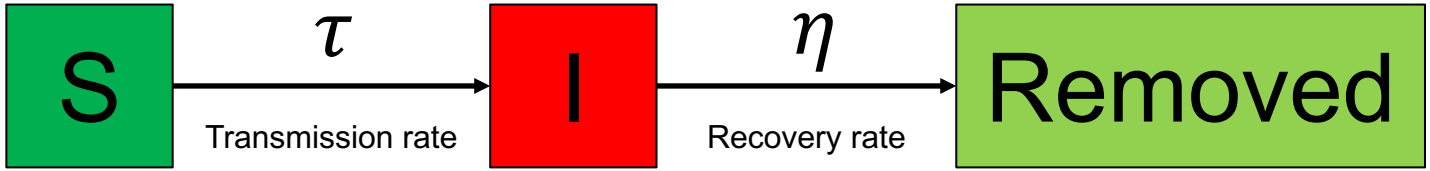


$$\frac{dS(t)}{dt} = -\tau S(t)I(t)$$

$$\frac{dI(t)}{dt} = \tau S(t)I(t) - \eta I(t)$$

$$\frac{dR(t)}{dt} = \eta I(t)$$

Compartmental models: SIR



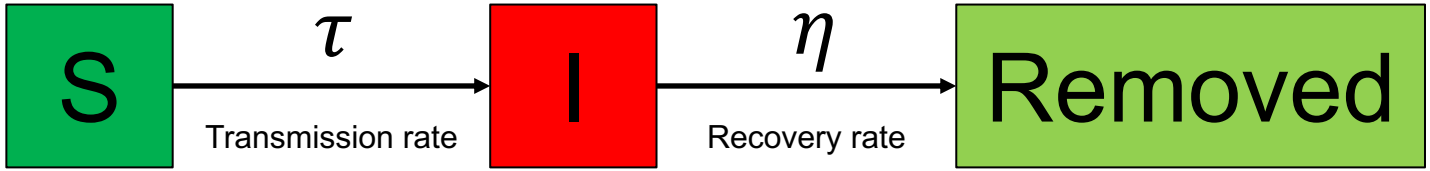
$$\frac{dS(t)}{dt} = -\tau S(t)I(t)$$

proportional to the number of contacts

$$\frac{dI(t)}{dt} = \tau S(t)I(t) - \eta I(t)$$

$$\frac{dR(t)}{dt} = \eta I(t)$$

Compartmental models: SIR



$$\frac{dS(t)}{dt} = -\tau S(t)I(t)$$

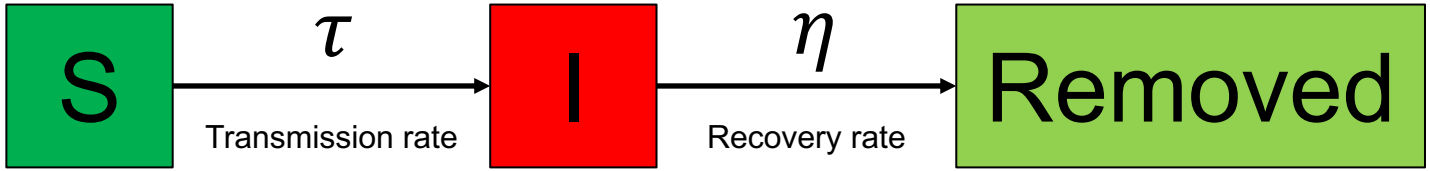
proportional to the number of contacts

$$\frac{dI(t)}{dt} = \tau S(t)I(t) - \eta I(t)$$

$$\frac{dR(t)}{dt} = \eta I(t)$$

redundant since population is constant

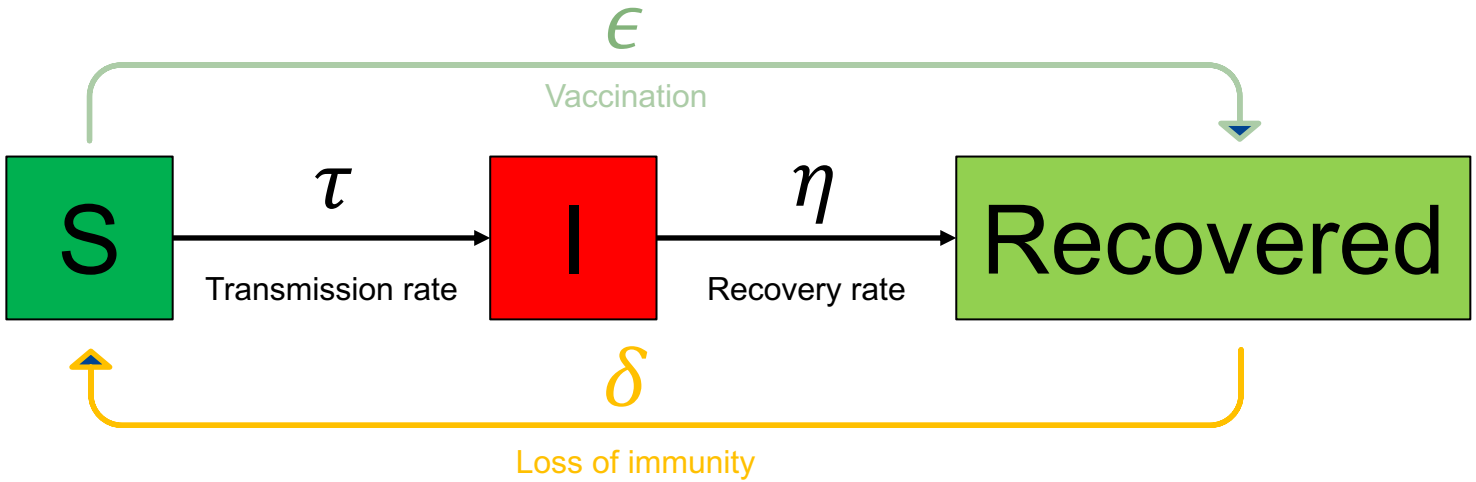
Compartmental models: SIR



$$\frac{dS(t)}{dt} = -\tau S(t)I(t)$$

$$\frac{dI(t)}{dt} = \tau S(t)I(t) - \eta I(t)$$

Compartmental models: SIR – additional mechanisms



$$\frac{dS(t)}{dt} = -\tau S(t)I(t) - \epsilon S(t) + \delta R(t)$$
$$\frac{dI(t)}{dt} = \tau S(t)I(t) - \eta I(t)$$
$$\frac{dR(t)}{dt} = \eta I(t) + \epsilon S(t) - \delta R(t)$$

Compartmental models: SIR

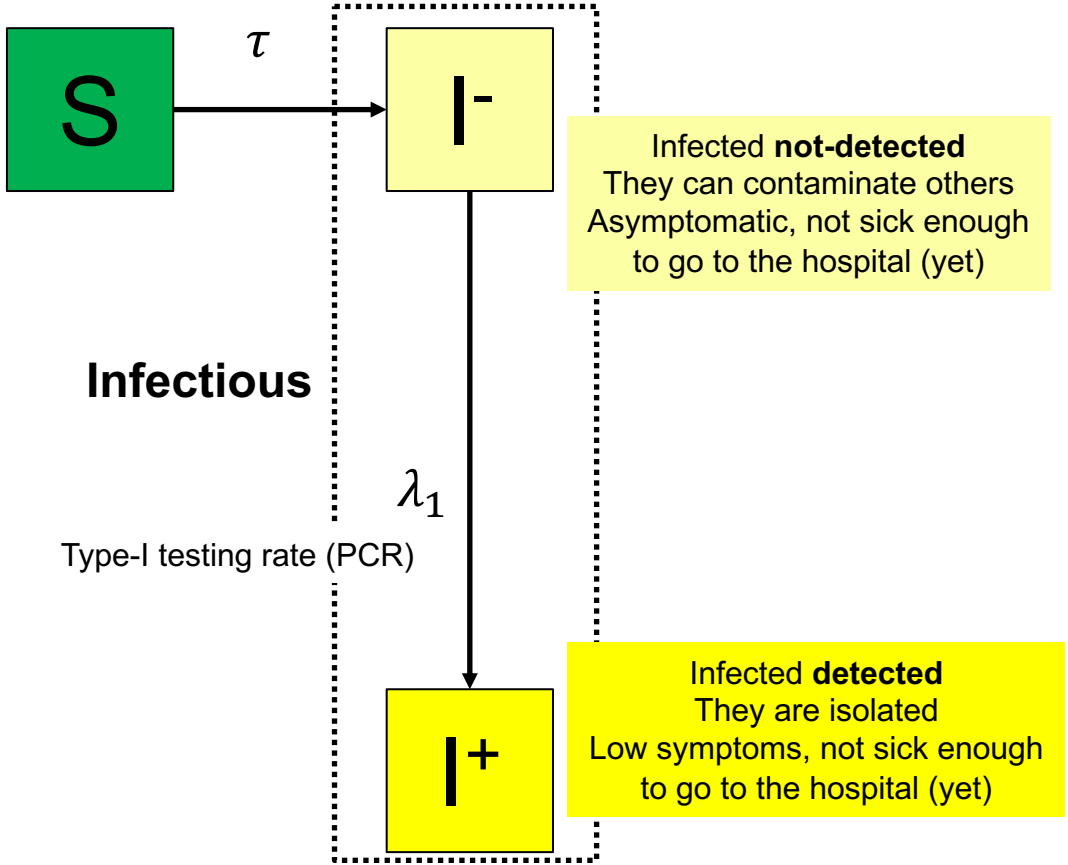
Age and spatial behaviors can be added

- PDEs instead of ODEs
- Many more parameters inside the equations
- Contact matrices between age classes & regions

For the Covid-19 epidemics, two additional mechanisms must be accounted for

- Specificity of Covid-19
  - Asymptomatic individuals play a major role
  - Symptomatic individuals are not all tested and reported
  - Data from hospitals, ICU, testing
- The transmission rate changes over time due to the lockdown

Compartmental models: modified SIR



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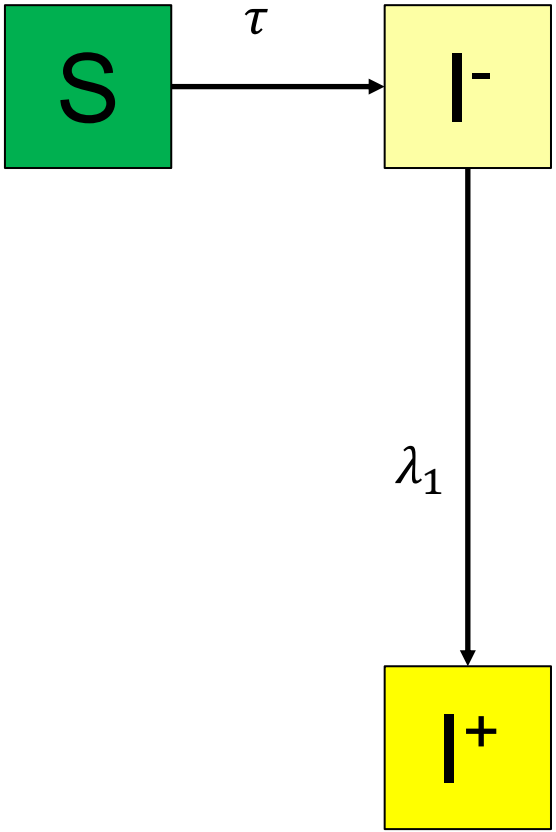
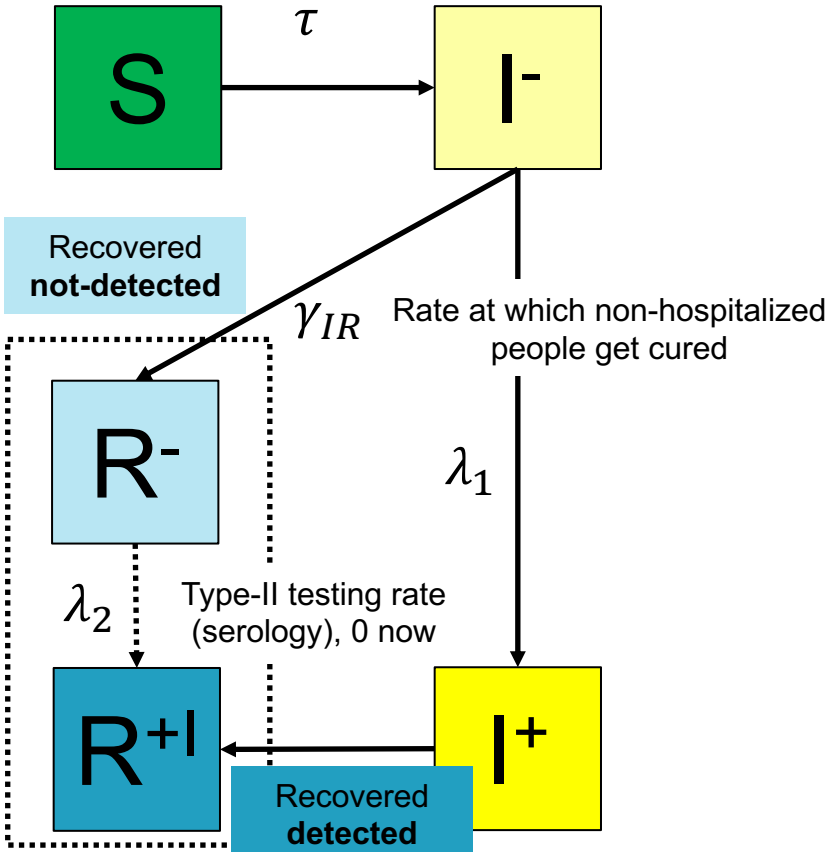
Compartmental models: modified SIR



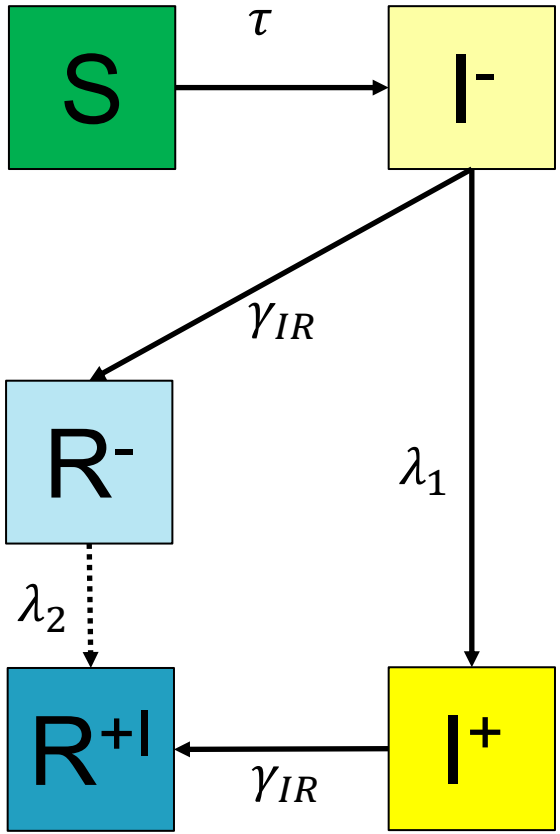
I individuals can recover, or get sicker and go to the hospital

Compartmental models: modified SIR



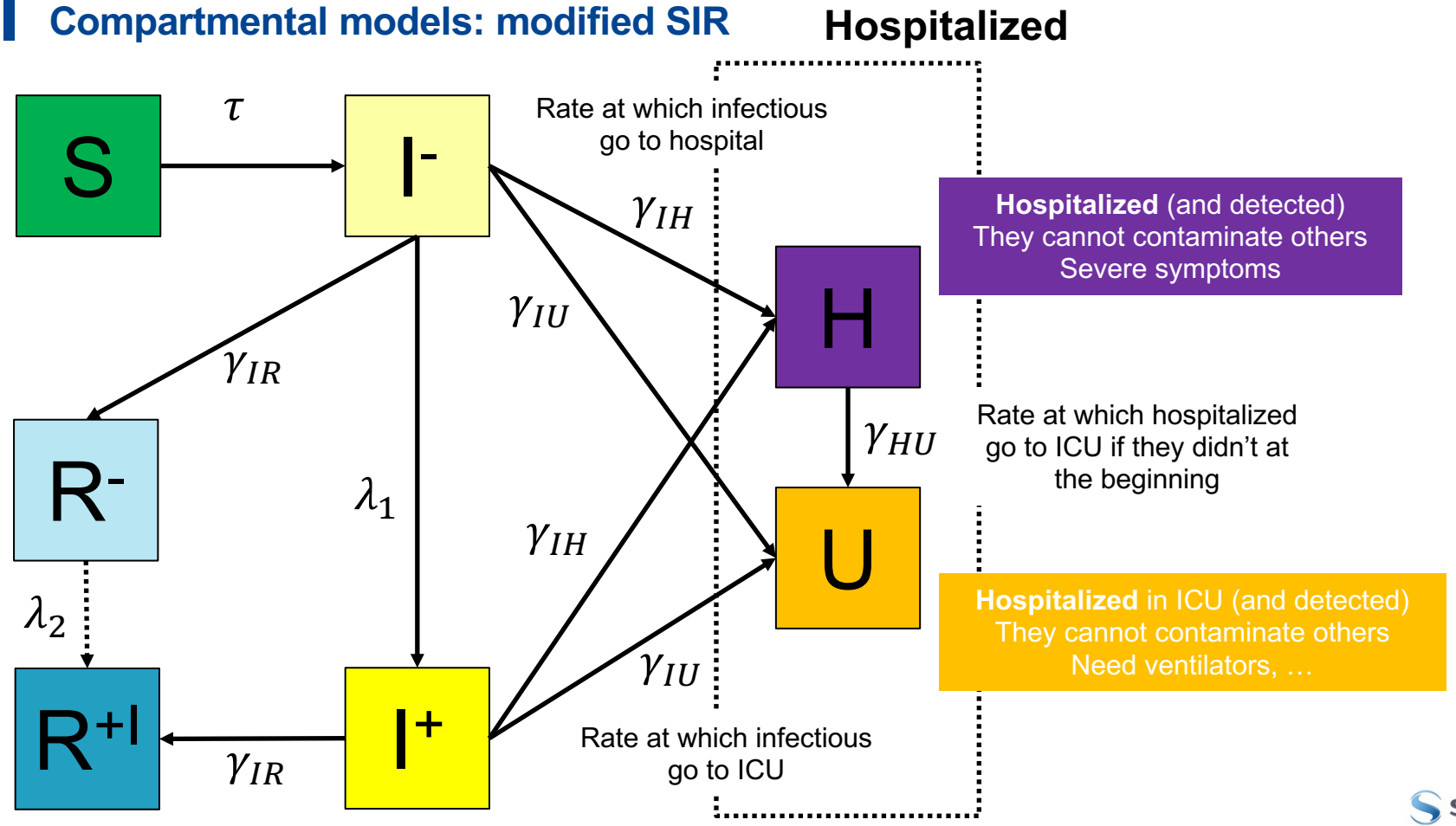
I individuals can **recover**, or get sicker and go to the hospital

Compartmental models: modified SIR

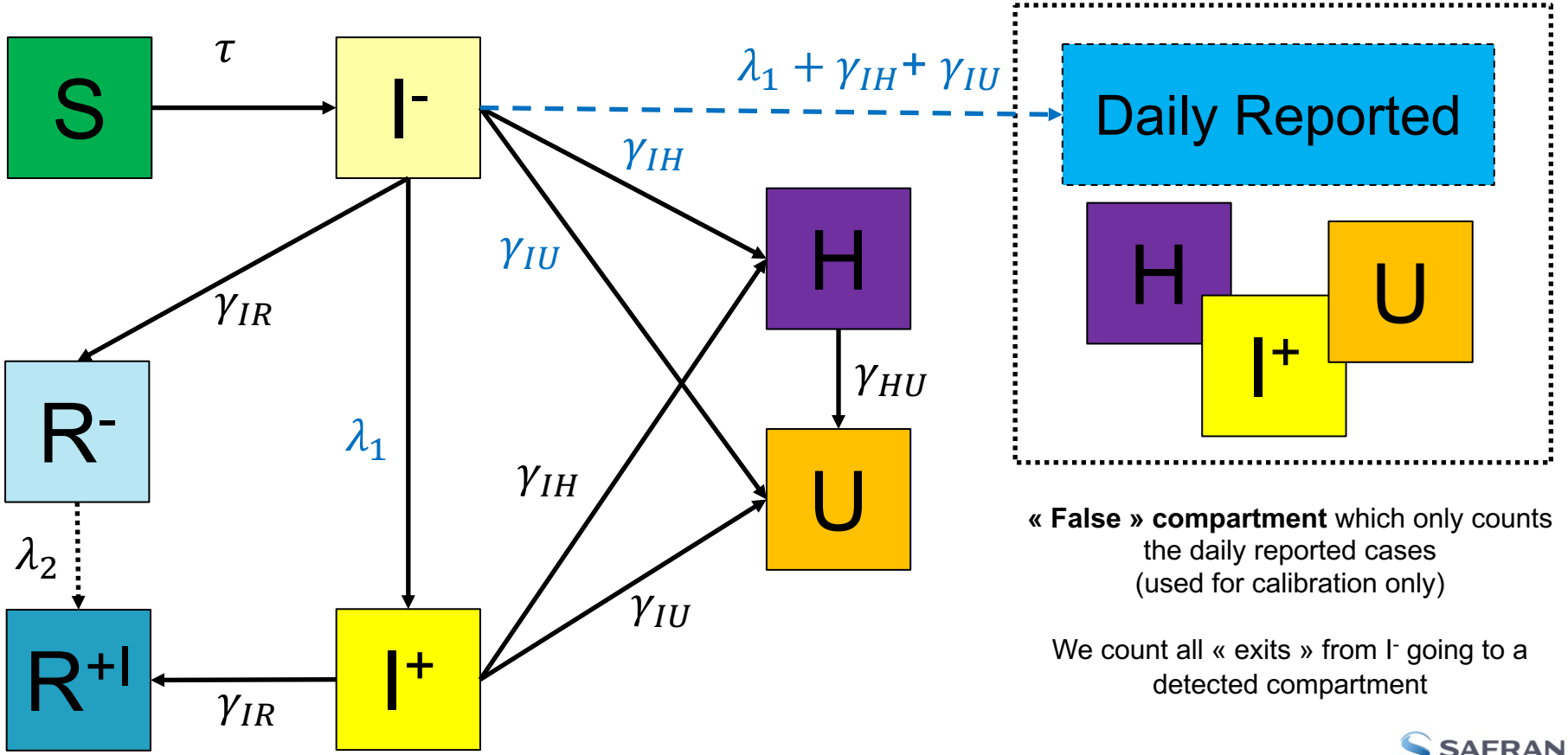


I individuals can recover, or get sicker and **go to the hospital**

Compartmental models: modified SIR



Compartmental models: modified SIR

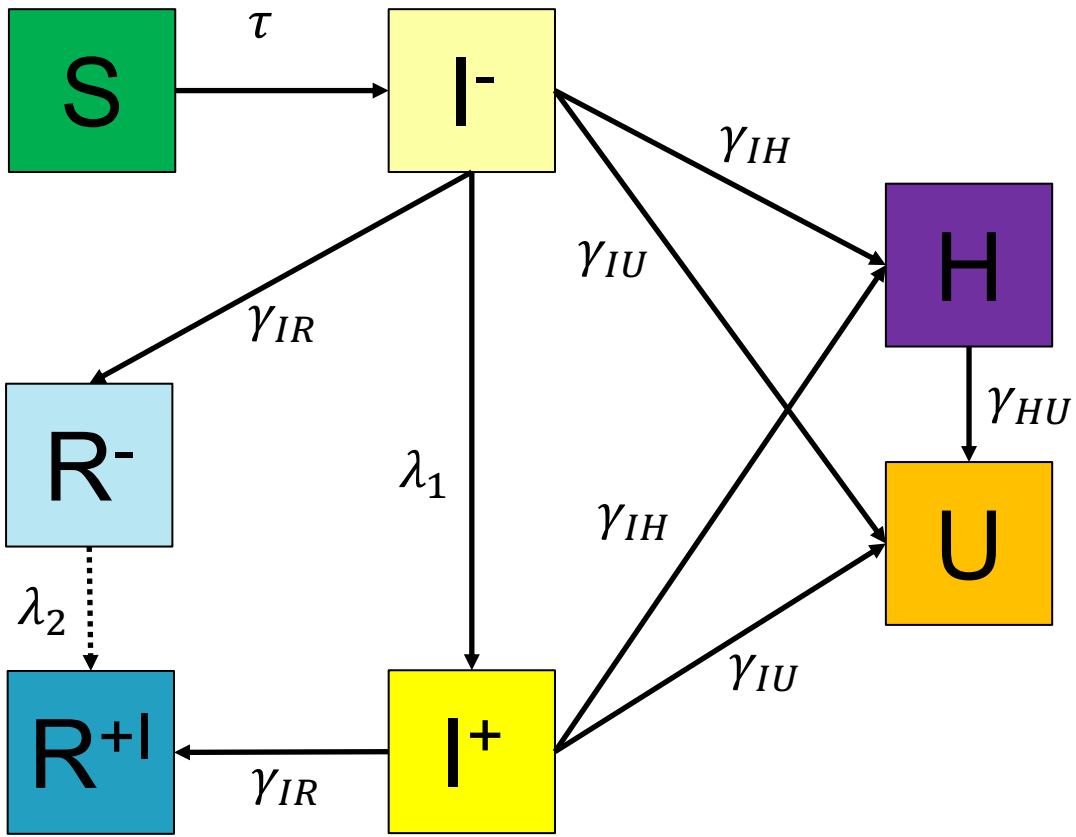


« False » compartment which only counts the daily reported cases (used for calibration only)

We count all « exits » from I- going to a detected compartment

Compartmental models: modified SIR

H & U individuals can recover, or die



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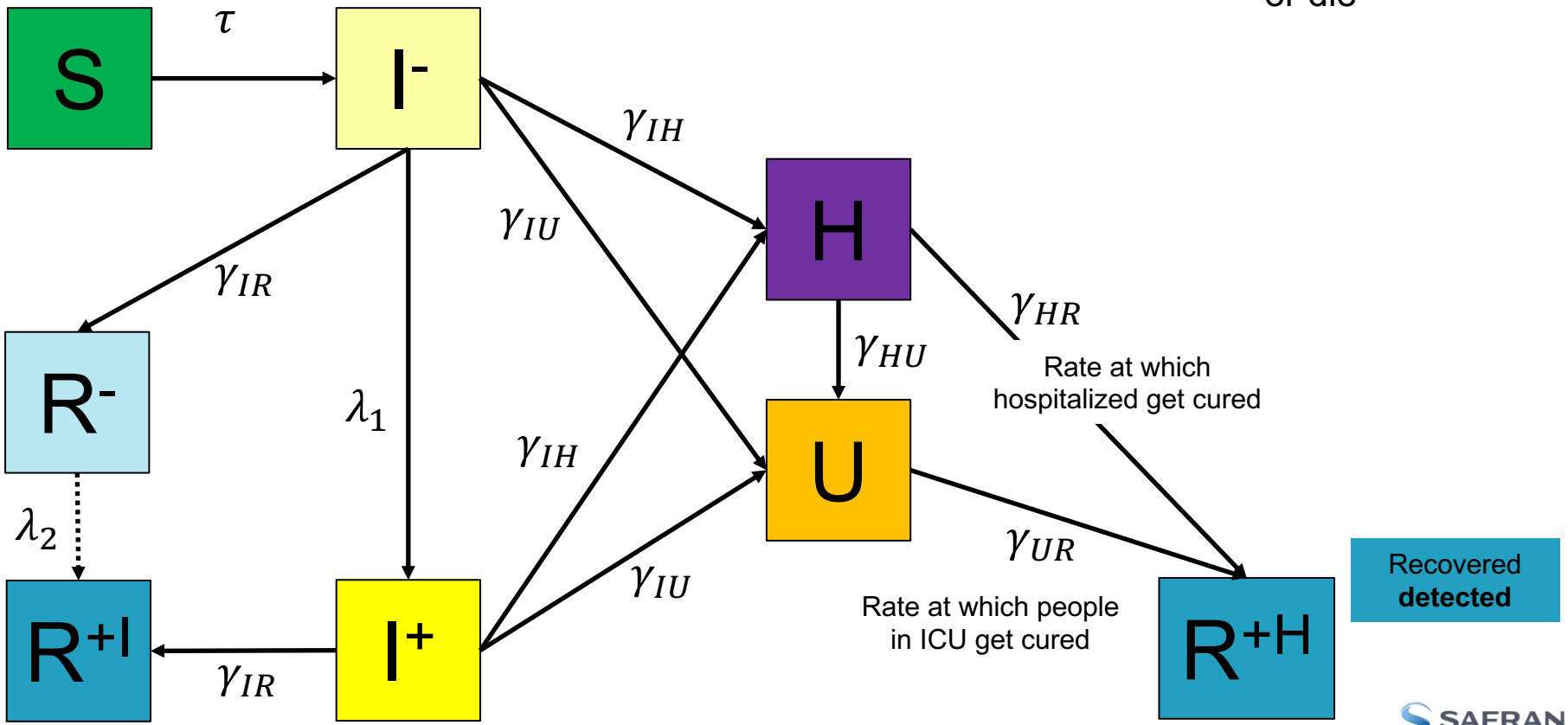
Compartmental models: modified SIR

H & U individuals can **recover**, or die



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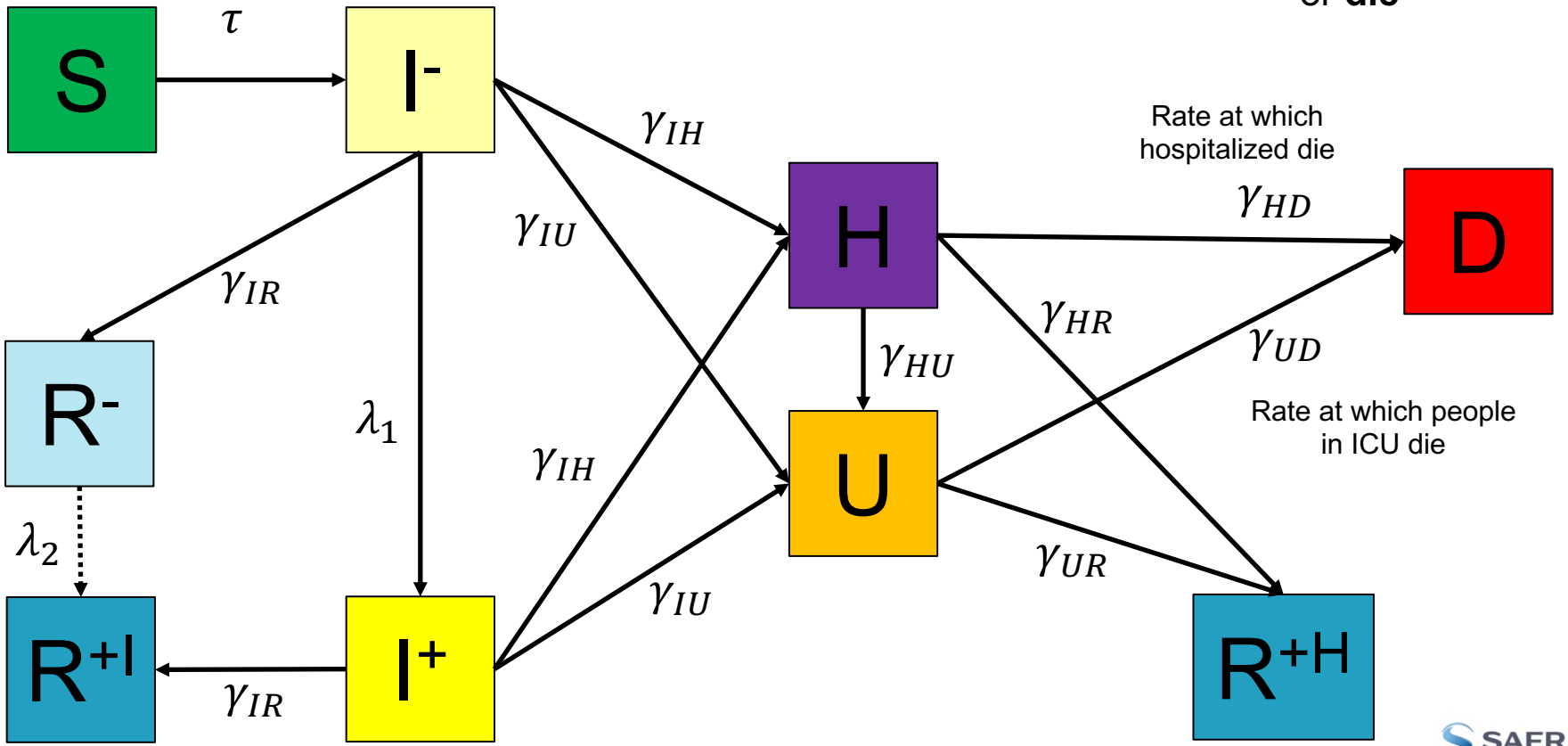
Compartmental models: modified SIR

H & U individuals can recover, or **die**



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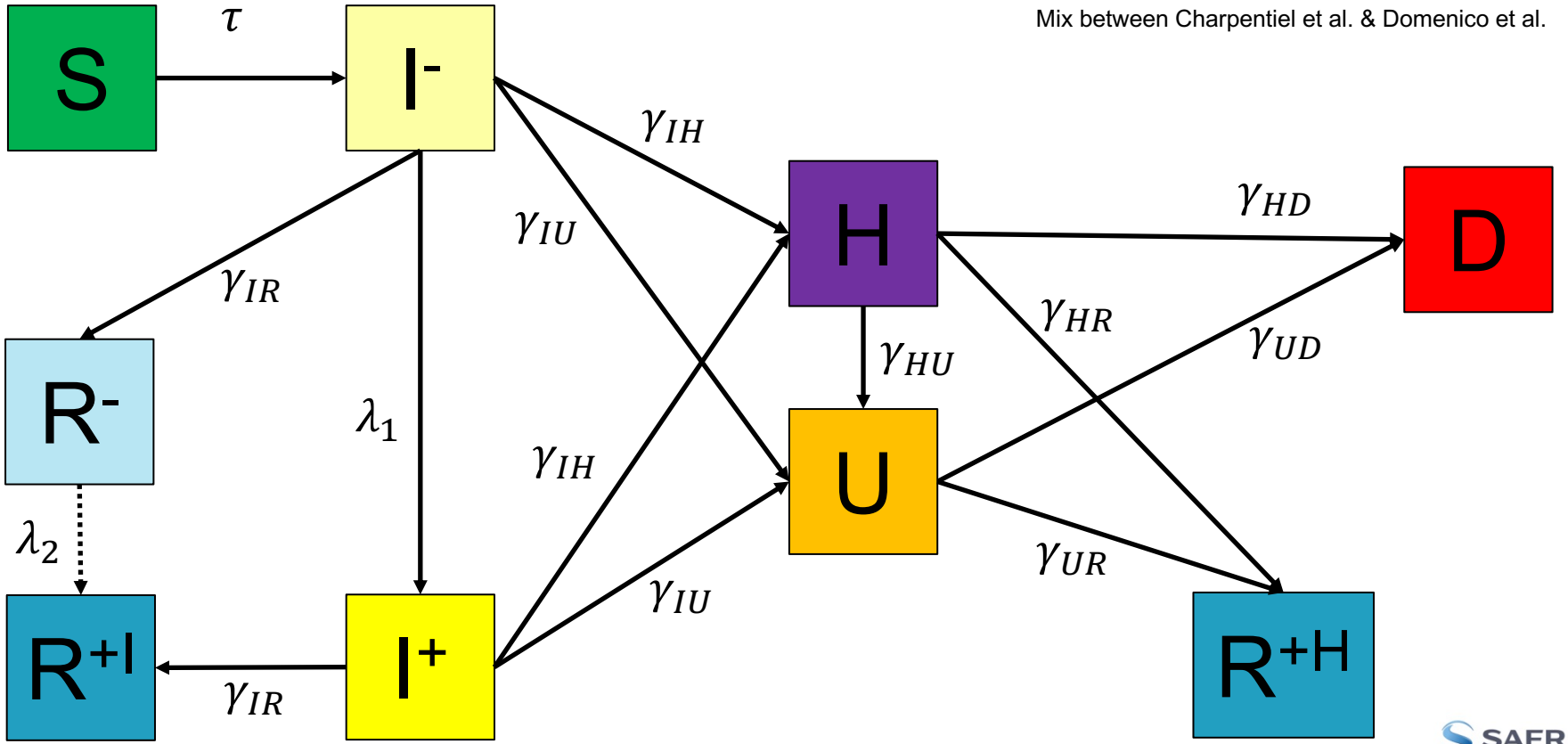
Compartmental models: modified SIR – final model

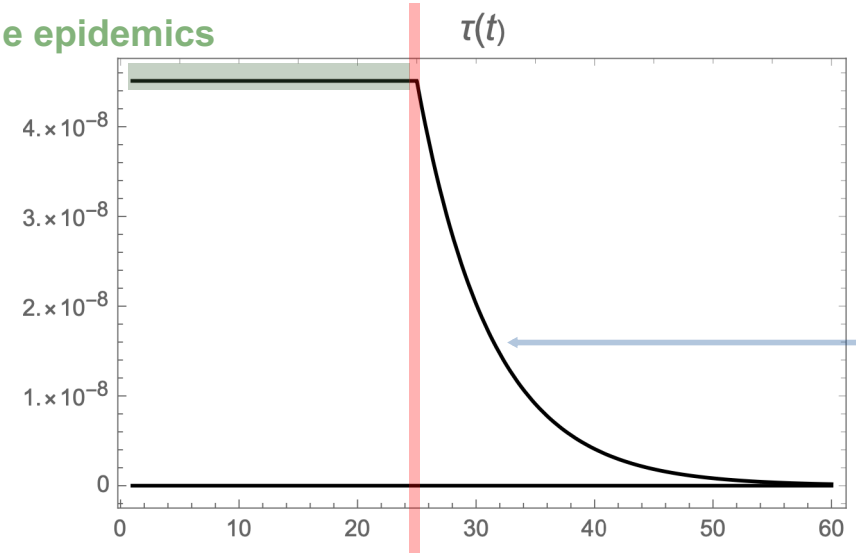


Mix between Charpentiel et al. & Domenico et al.

Compartmental models: modified SIR – about the transmission rate

A large number of papers use a parametric form for the transmission rate

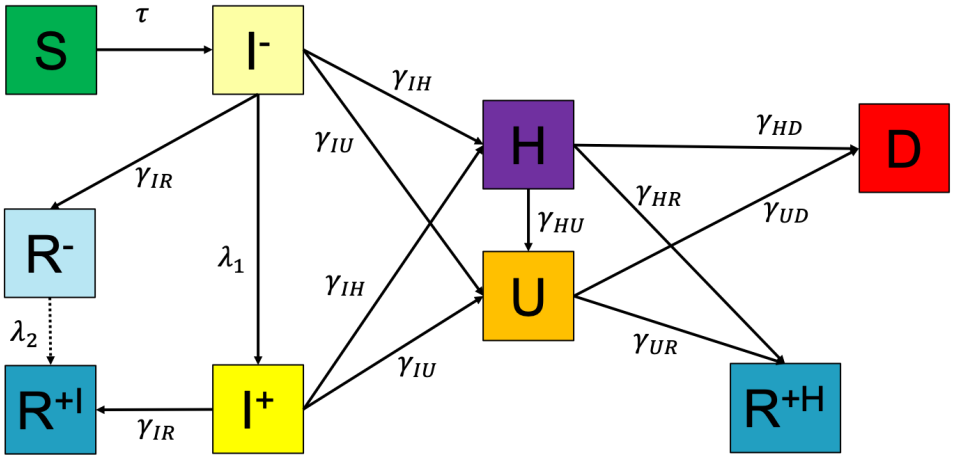
- Constant during the outbreak
- Exponential decay once the social distancing measures take effect



$$\tau(t) = \tau_0, \quad 0 \le t \le N$$
$$\tau(t) = \tau_0 \exp\left(-\mu(t-N)\right), \quad t > N$$

Liu et al. (a) & Liu et al. (b)

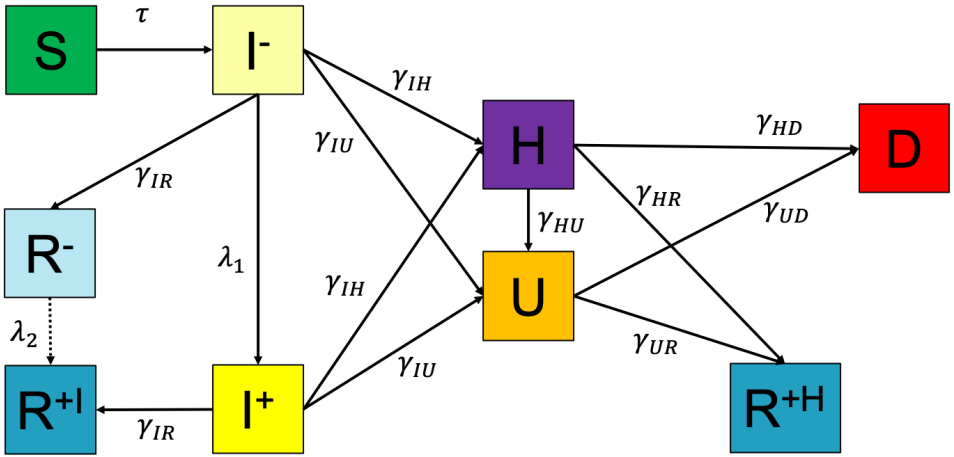
Compartmental models: modified SEIR – parameterization



More interpretable parameters

p_a	p_H	p_U	p_{HU}	p_{HD}	p_{UD}
Conditioned on being infected, the probability of having light symptoms or no symptoms	Conditioned on being mild/severely ill, the probability of needing hospitalization	Conditioned on going to hospital, the probability of needing ICU	Conditioned on being hospitalized but not in ICU, the probability of needing ICU	Conditioned on being hospitalized but not in ICU, the probability of dying	Conditioned on being admitted to ICU, the probability of dying

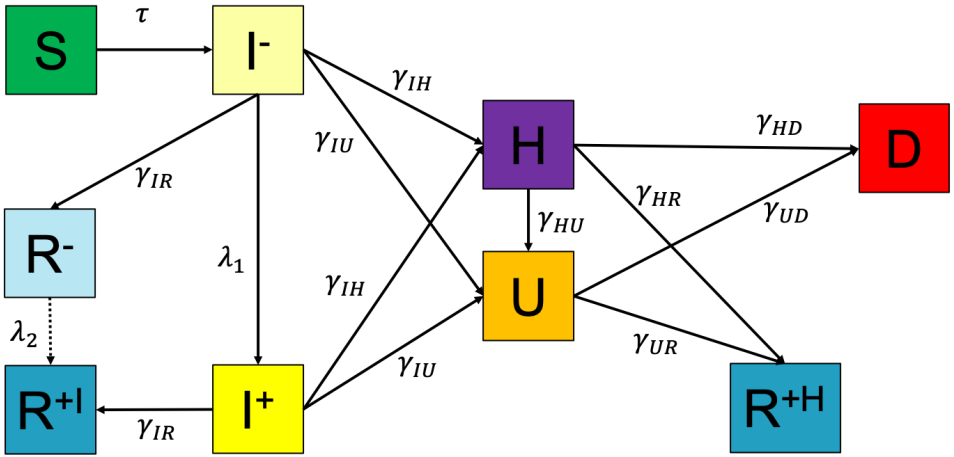
Compartmental models: modified SEIR – parameterization



More interpretable parameters

N_a	N_s	N_{IH}	N_{HD}	N_{HU}	N_{UD}	N_{HR}	N_{UR}
If asymptomatic, number of days until recovery	If symptomatic, number of days until recovery without hospital	If severe symptomatic, number of days until hospitalization	If in H, number of days until death	If in H but not in ICU, number of days until ICU	If in ICU, number of days until death	If hospitalized but not in ICU, the number of days until recovery	If in ICU, number of days until recovery

Compartmental models: modified SEIR – parameterization



More interpretable parameters

$$
\begin{aligned}
\gamma_{IR} &= (1-p_a)(1-p_H)/N_s + p_a/N_a \\
\gamma_{IH} &= (1-p_a)p_H(1-p_U)/N_{IH} \\
\gamma_{IU} &= (1-p_a)p_H p_U/N_{IH} \\
\gamma_{HR} &= (1-p_{HD})/N_{HR} \\
\gamma_{HD} &= p_{HD}/N_{HD} \\
\gamma_{HU} &= p_{HU}/N_{HU} \\
\gamma_{UR} &= (1-p_{UD})/N_{UR} \\
\gamma_{UD} &= p_{UD}/N_{UD}
\end{aligned}
$$

λ_1

$\lambda_2 \ (= 0)$

$\mathcal{R}_0,\ t_0,\ \mu,\ N,\ I_0^-$

Compartmental models: modified SIR – uncertainties

Some remarks on this type of results

- **All the parameters on the model have uncertainty !**
  - Some are related to the lack of knowledge on the virus
  - Others depend on the effect of social distancing, isolation and testing strategy
- **The uncertainty can be reduced by calibration but not completely**
- **It is of particular interest to know which parameters have the highest impact on the predictions**
  - E.g. for political & health strategies
- The previous simulation is performed when we have data: what does it look like at the very beginning of the epidemics ?
  - **In particular if we account for the prior uncertainties (i.e. when no calibration is available yet)**

2

PRIOR UQ & GSA

Prior UQ & GSA

Imagine this is mid-January in France

- We do not know precisely many characteristics of the virus
- The starting date of the virus is not known
- The effect of social distancing / isolation is not well understood
- **You want to have an idea of the potential height of the « wave »**

We model our uncertainties on the parameters with probability distributions

Prior UQ & GSA

Parameter	Physical Meaning	Probability Distribution
p_a	Conditioned on being infected, the probability of having light symptoms or no symptoms	Uniform 0.5 – 0.9
p_H	Conditioned on being mild/severely ill, the probability of needing hospitalization	Uniform 0.15 – 0.2
p_U	Conditioned on being mild/severely ill, the probability of needing ICU	Uniform 0.15 – 0.2
p_{HU}	Conditioned on being hospitalized but not in ICU, the probability of needing ICU	Uniform 0.15 – 0.2
p_{HD}	Conditioned on being hospitalized but not in ICU, the probability of dying	Uniform 0.15 – 0.25
p_{UD}	Conditioned on being admitted to ICU, the probability of dying	Uniform 0.2 – 0.3
N_a	If asymptomatic, number of days until recovery	Uniform 8 – 12 (days)
N_s	If symptomatic, number of days until recovery without hospital	Uniform 8 – 12 (days)
N_{IH}	If severe symptomatic, number of days until hospitalization	Uniform 8 – 12 (days)
N_{HD}	If in H, number of days until death	Uniform 15 – 20 (days)
N_{HU}	If in H but not in ICU, number of days until ICU	Uniform 1 – 10 (days)
N_{UD}	If in ICU, number of days until death	Uniform 8 – 12 (days)
N_{HR}	If hospitalized but not in ICU, the number of days until recovery	Uniform 15 – 25 (days)
N_{UR}	If in ICU, number of days until recovery	Uniform 15 – 20 (days)
λ_1	Type I testing rate	Uniform 10^{-4} – 10^{-3}
$\mathcal{R}_0$	Basic reproducing nb.	Uniform 3 – 3.5
t_0	Starting date of epidemics	Uniform 25/01 – 10/02
μ	Decaying rate for transmission (soc. dist. / lockdown)	Uniform 0.03 – 0.08
N	Date of effect for soc. dist. / lockdown	Uniform 20 – 50 (days)
I_0^-	Number of infected undetected at the start of epidemics	Uniform 1 – 100

Independence assumption

Prior UQ & GSA

Imagine this is mid-January in France

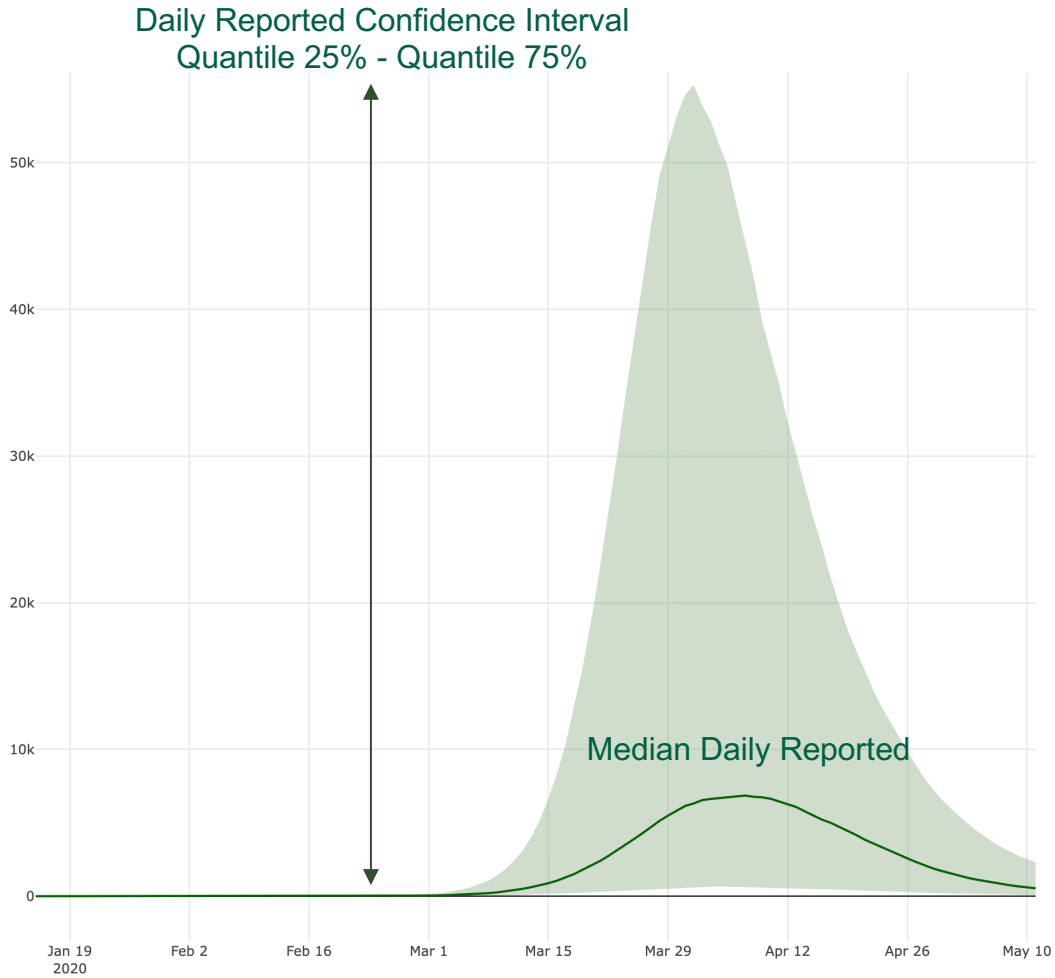
- We do not know precisely many characteristics of the virus
- The starting date of the virus is not known
- The effect of social distancing / isolation is not well understood
- **You want to have an idea of the potential height of the « wave »**

We model our uncertainties on the parameters with probability distributions

We can then compute the uncertainties on our model predictions

- Generate a random value of the parameters according to their probability distribution
- Run the simulation & collect the curves of the epidemics
- Repeat until you get a large sample (e.g. 5000)

Prior UQ & GSA



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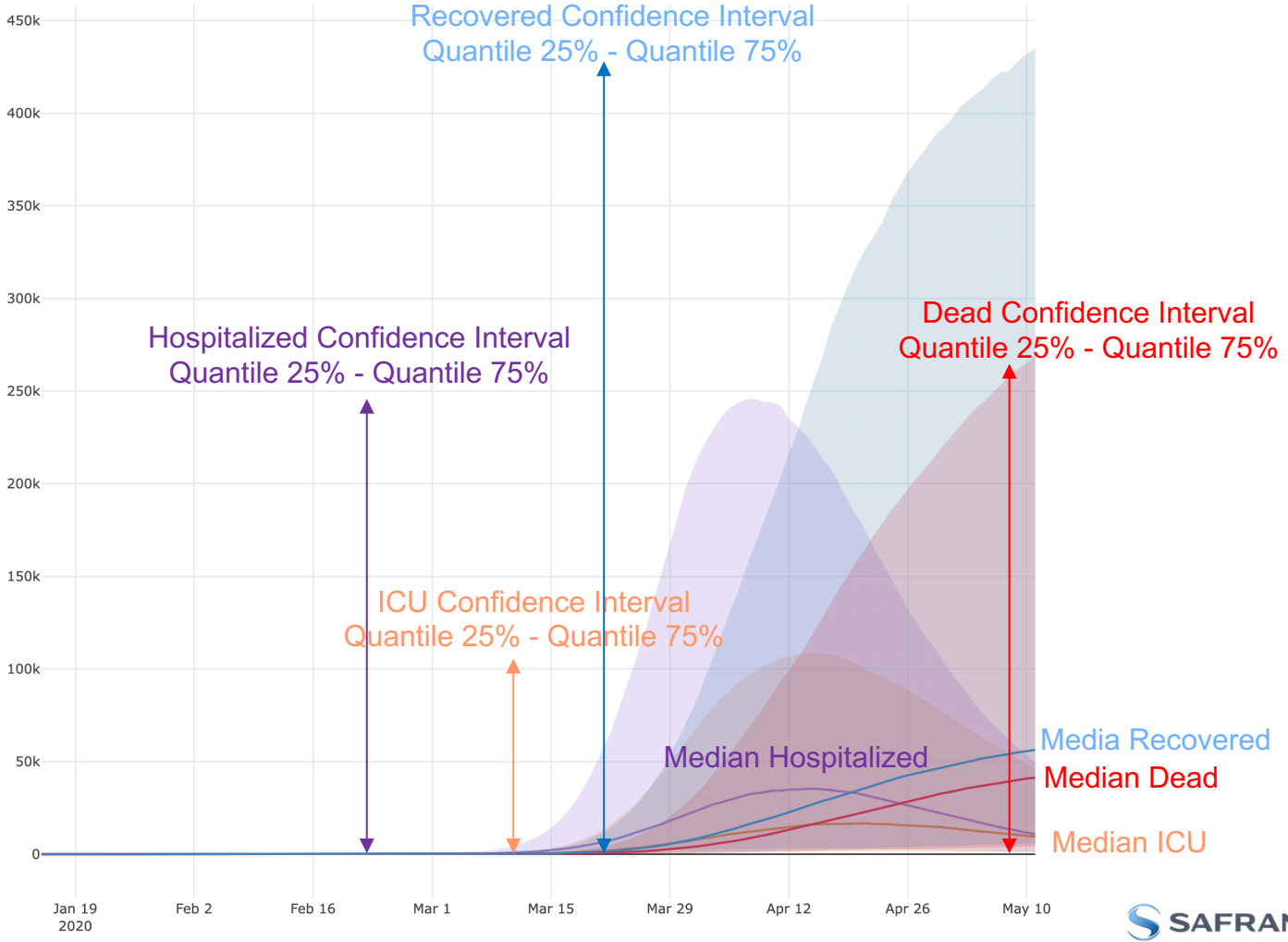
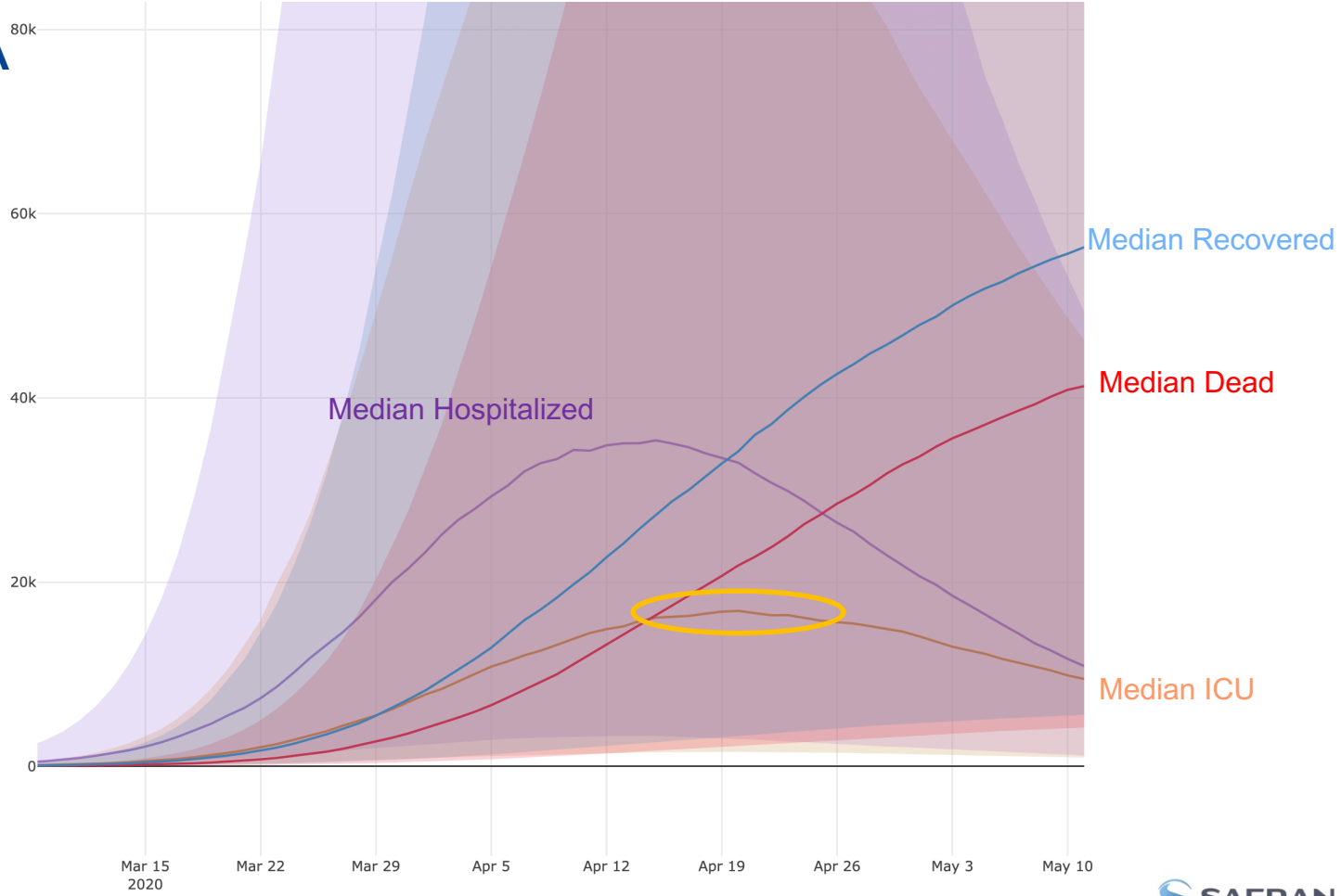
Prior UQ & GSA



Prior UQ & GSA

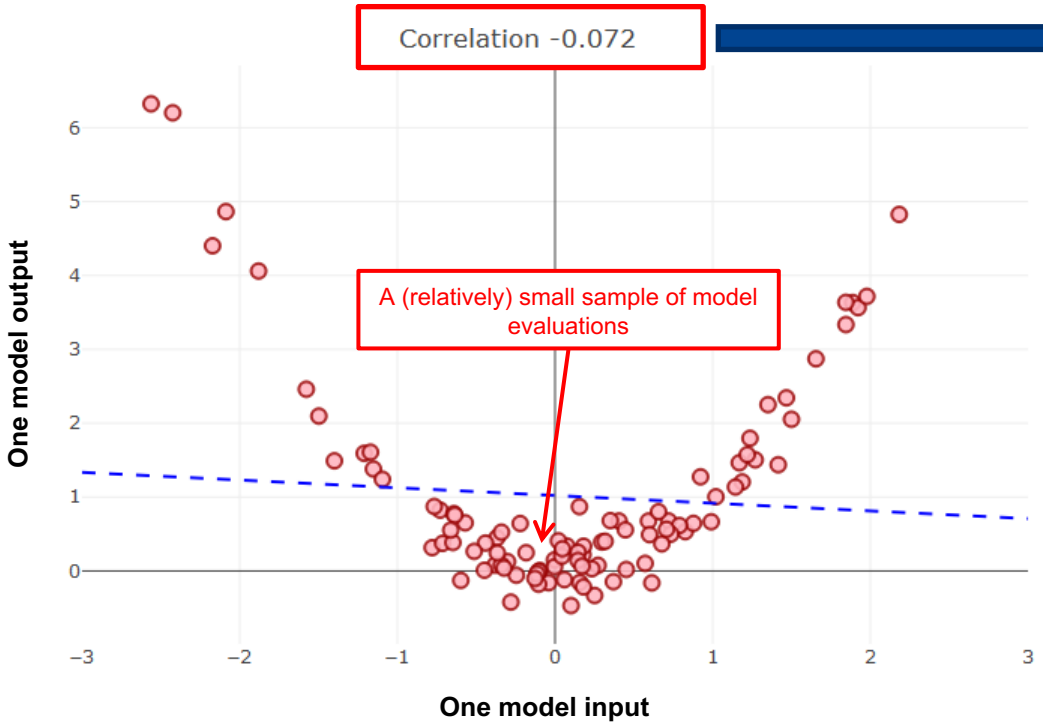


Prior UQ & GSA

The total number of parameters is large (20)

- Before performing GSA & calibration (expensive), we may start by a first **screening phase**
- Screening = using a relatively small number of model evaluations to quickly identify non-influential parameters
- Here we use a modern screening tool : HSIC
  - Principle : we will use a statistical test to check if we can **detect independence** between the outputs and some parameters
  - The test is based on the HISC criterion, which is a measure of **nonlinear correlation**

Prior UQ & GSA – HSIC in a nutshell



The correlation here is almost zero.

But there is clearly a dependence between this output and this input !

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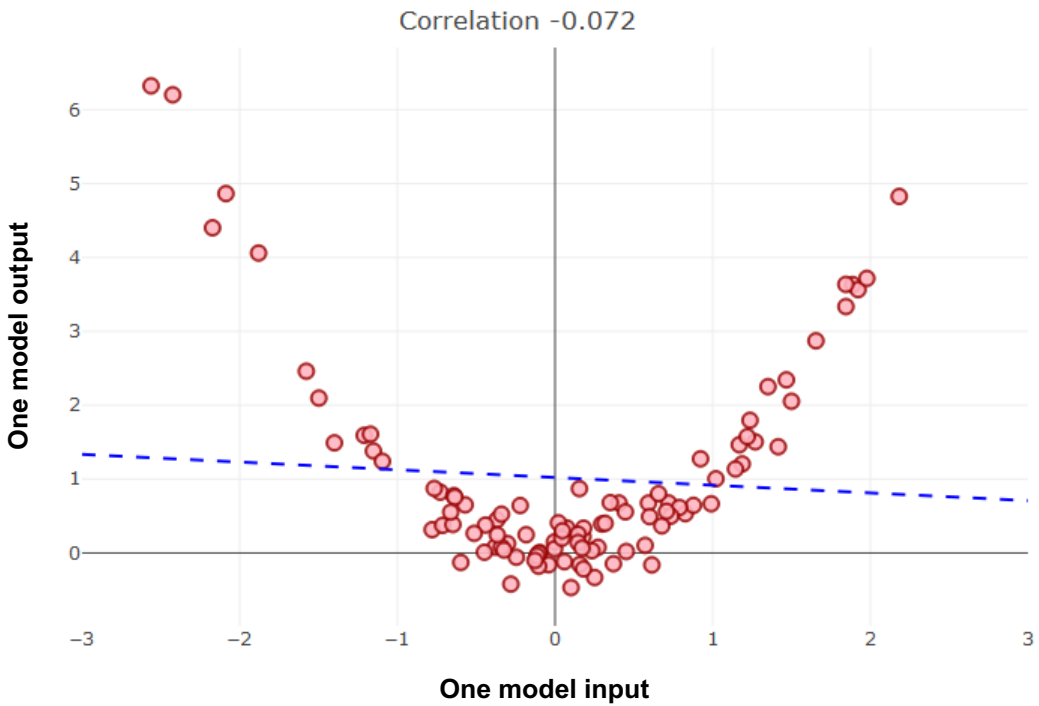
Prior UQ & GSA – HSIC in a nutshell



HSIC principle: search inside a large ensemble of potential nonlinear functions if one fits the sample.

In practice:

1. Transform the input with a nonlinear function
2. Transform the output with a nonlinear function
3. Compute the **correlation between the transformed variables**
4. Repeat for all the nonlinear functions inside your prescribed ensemble
5. The final criterion is the **maximum correlation** among all those calculated

If your ensemble is infinite and sufficiently large, you can detect dependence.

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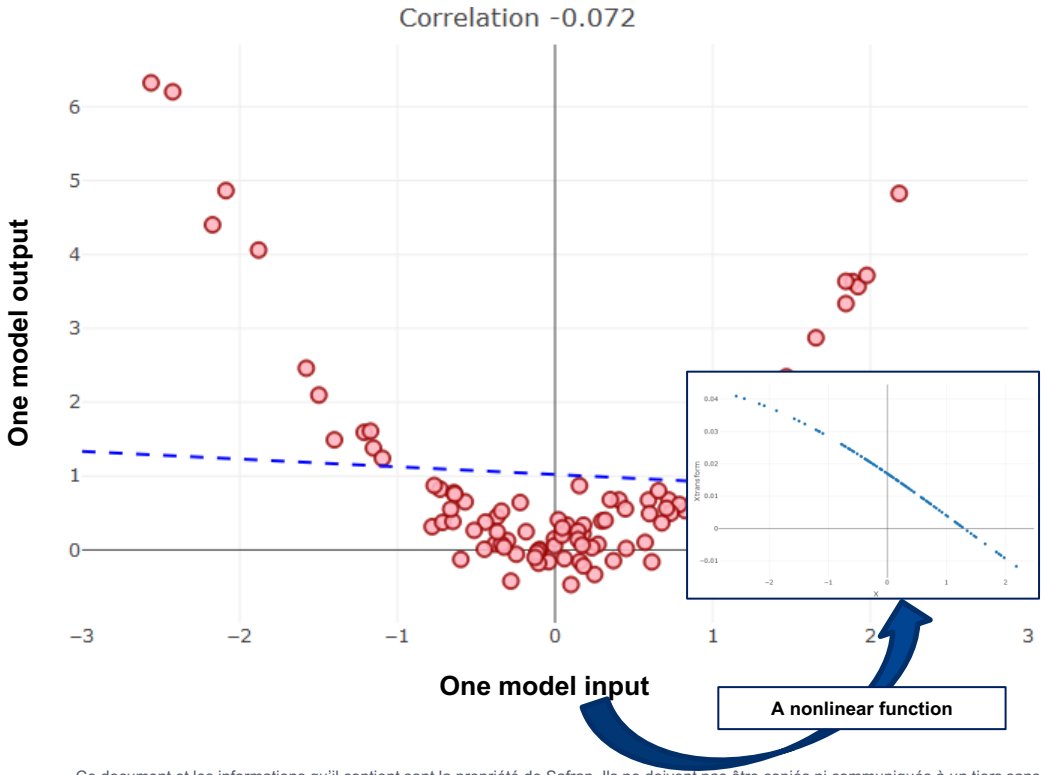
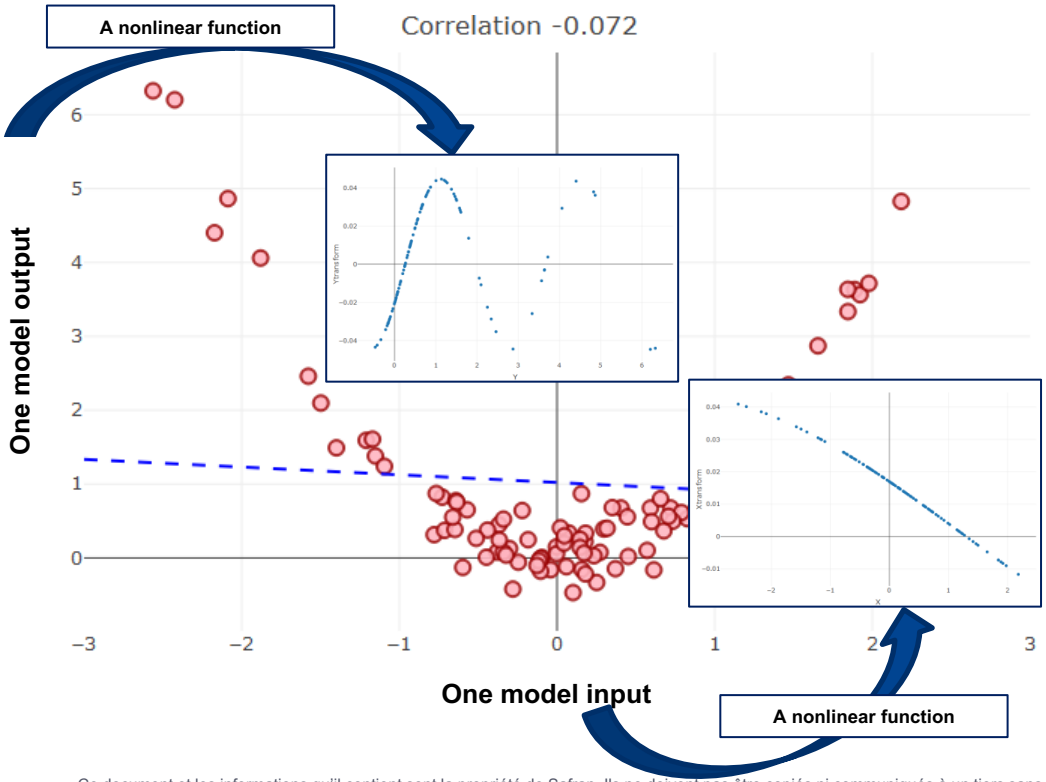
Prior UQ & GSA – HSIC in a nutshell



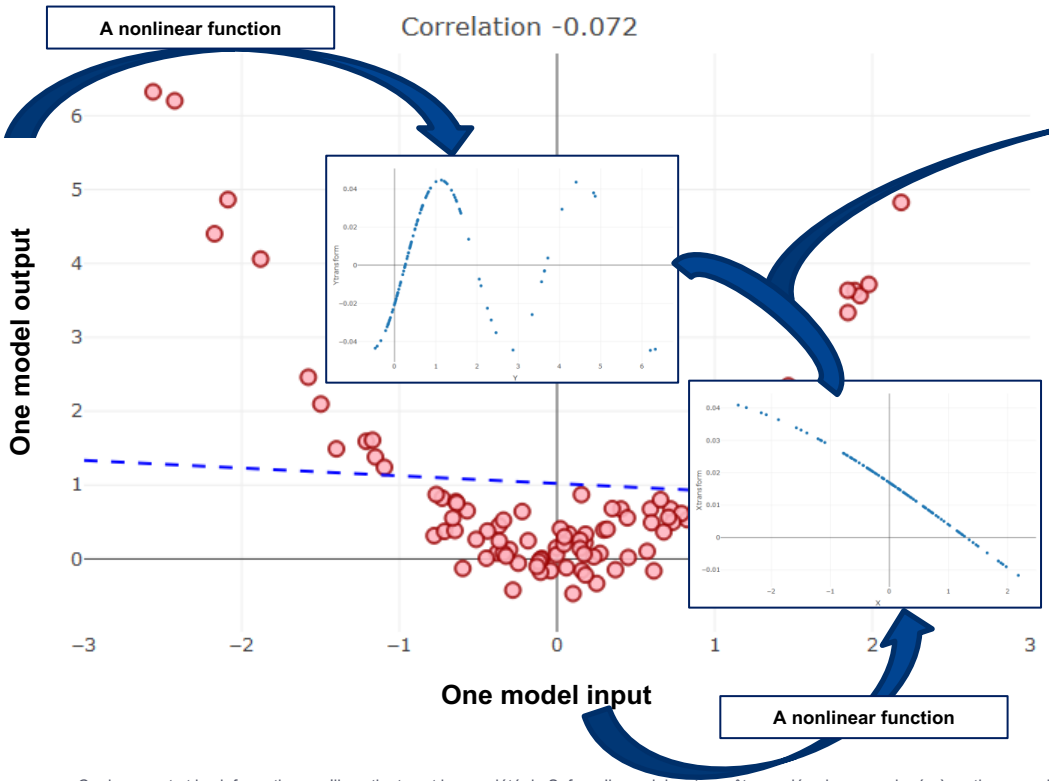
Transform the input with a nonlinear function from the ensemble

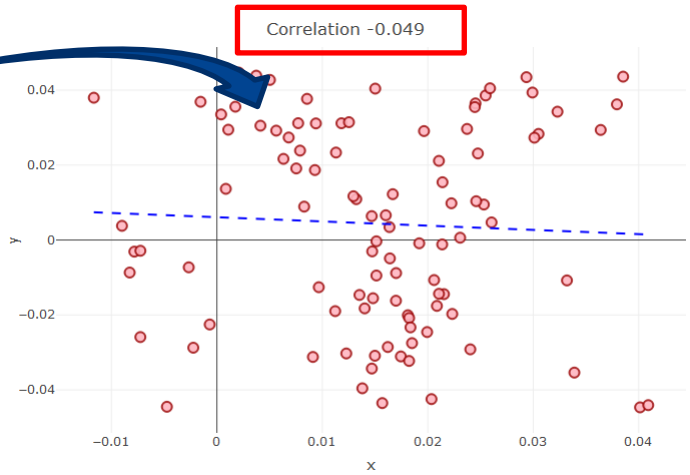
Prior UQ & GSA – HSIC in a nutshell



Transform the output with a nonlinear function from the ensemble

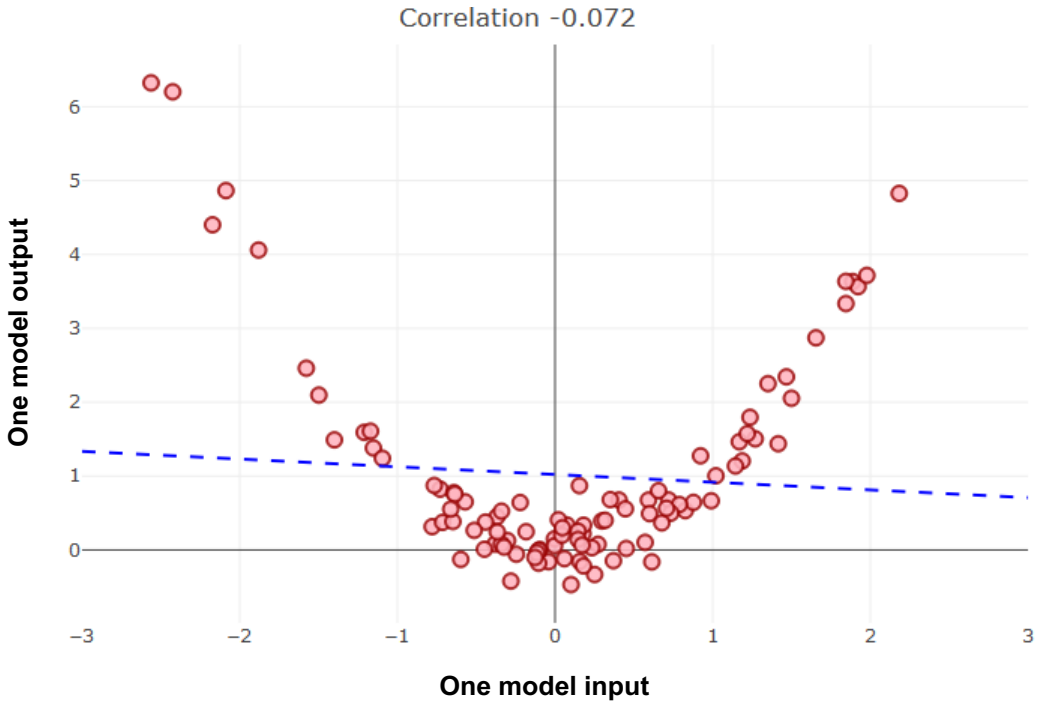
Prior UQ & GSA – HSIC in a nutshell





Compute the correlation between the transforme variables and store it.

Prior UQ & GSA – HSIC in a nutshell



We then test other nonlinear functions

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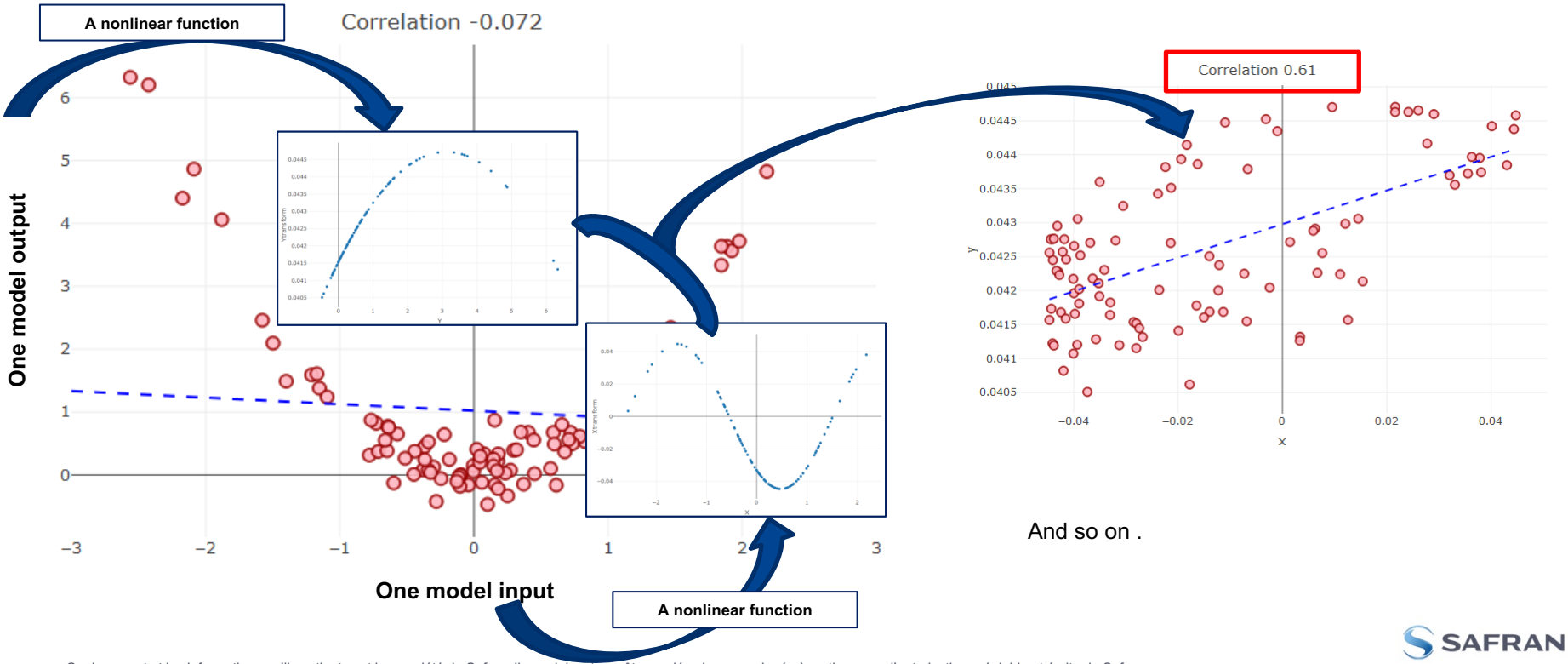
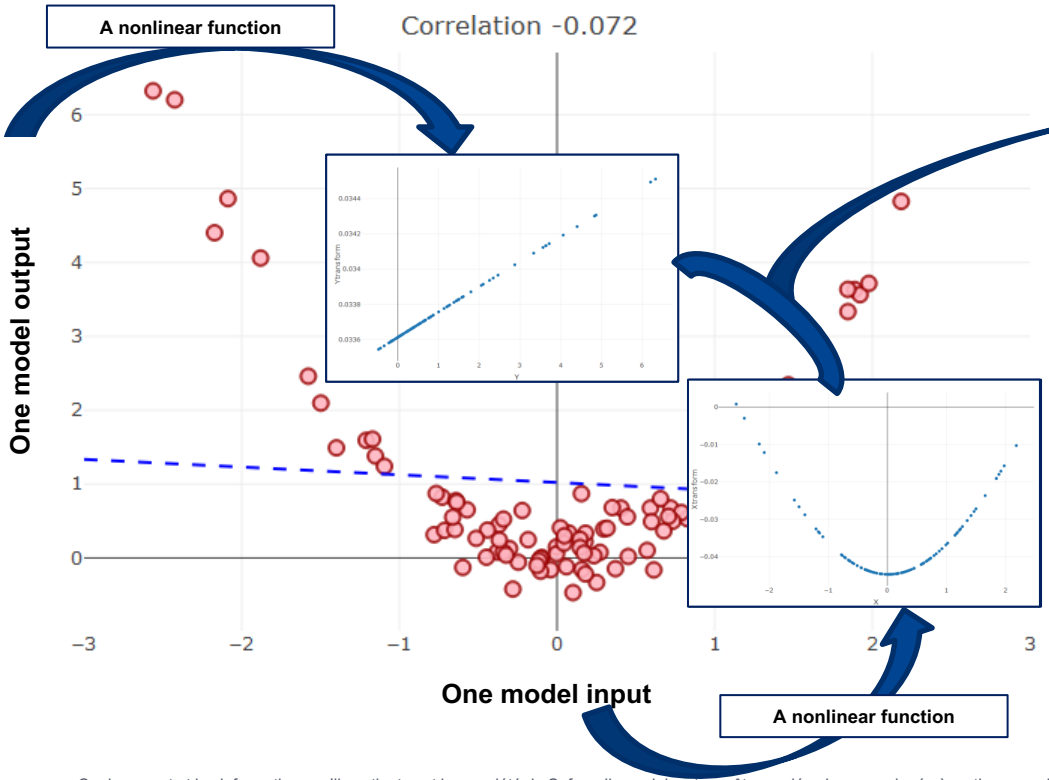
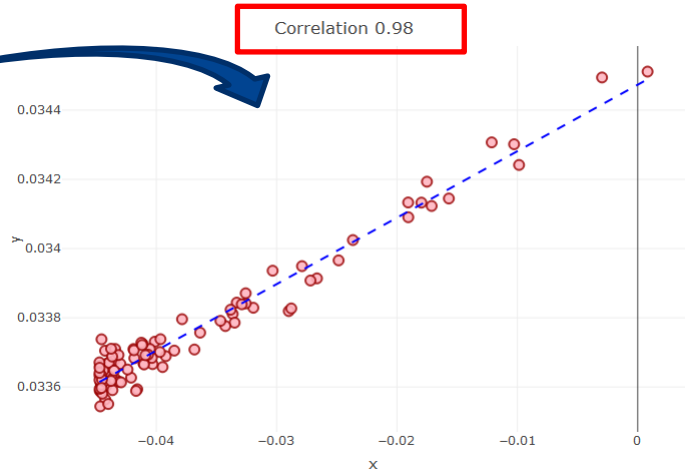
Prior UQ & GSA – HSIC in a nutshell



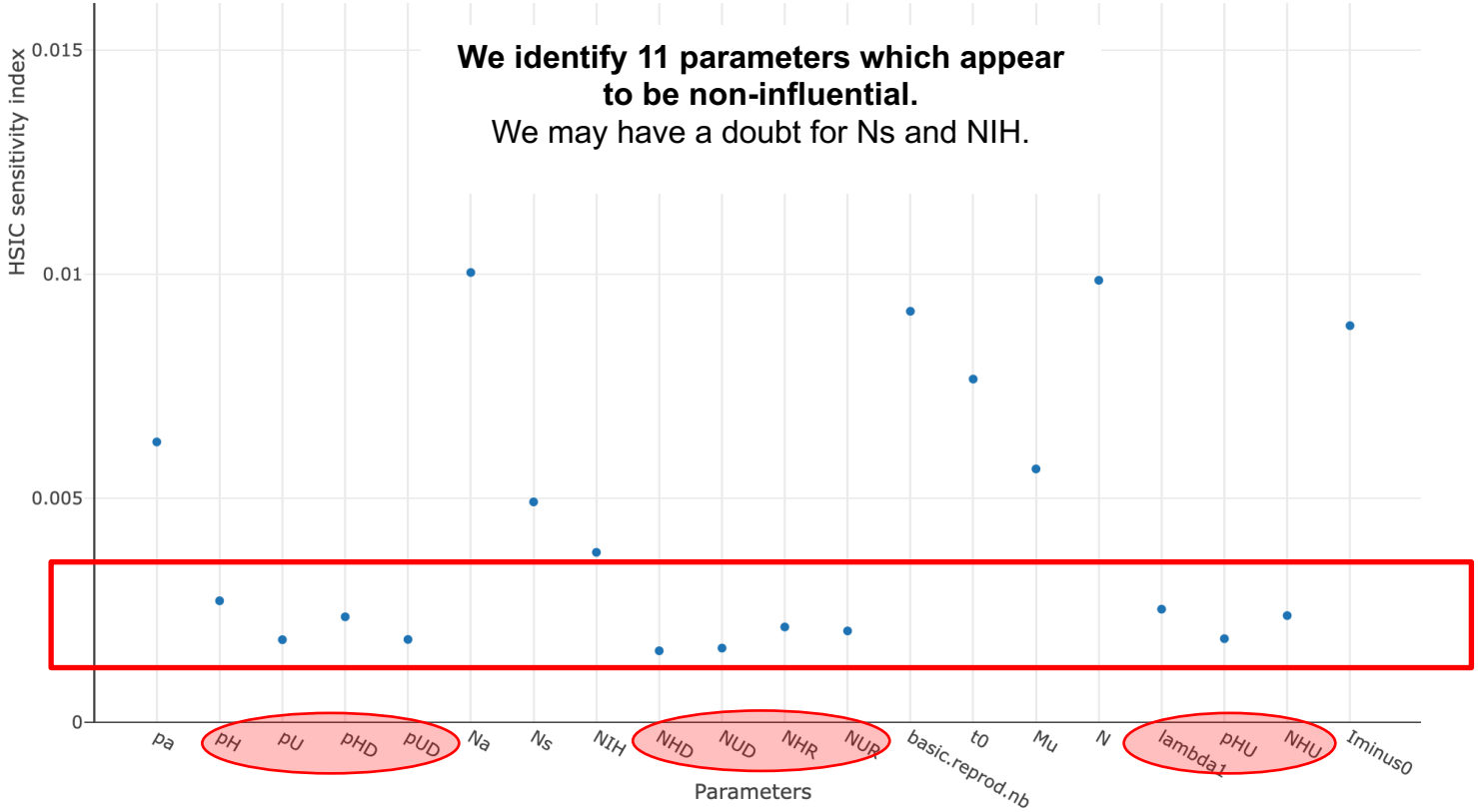
Prior UQ & GSA – HSIC in a nutshell





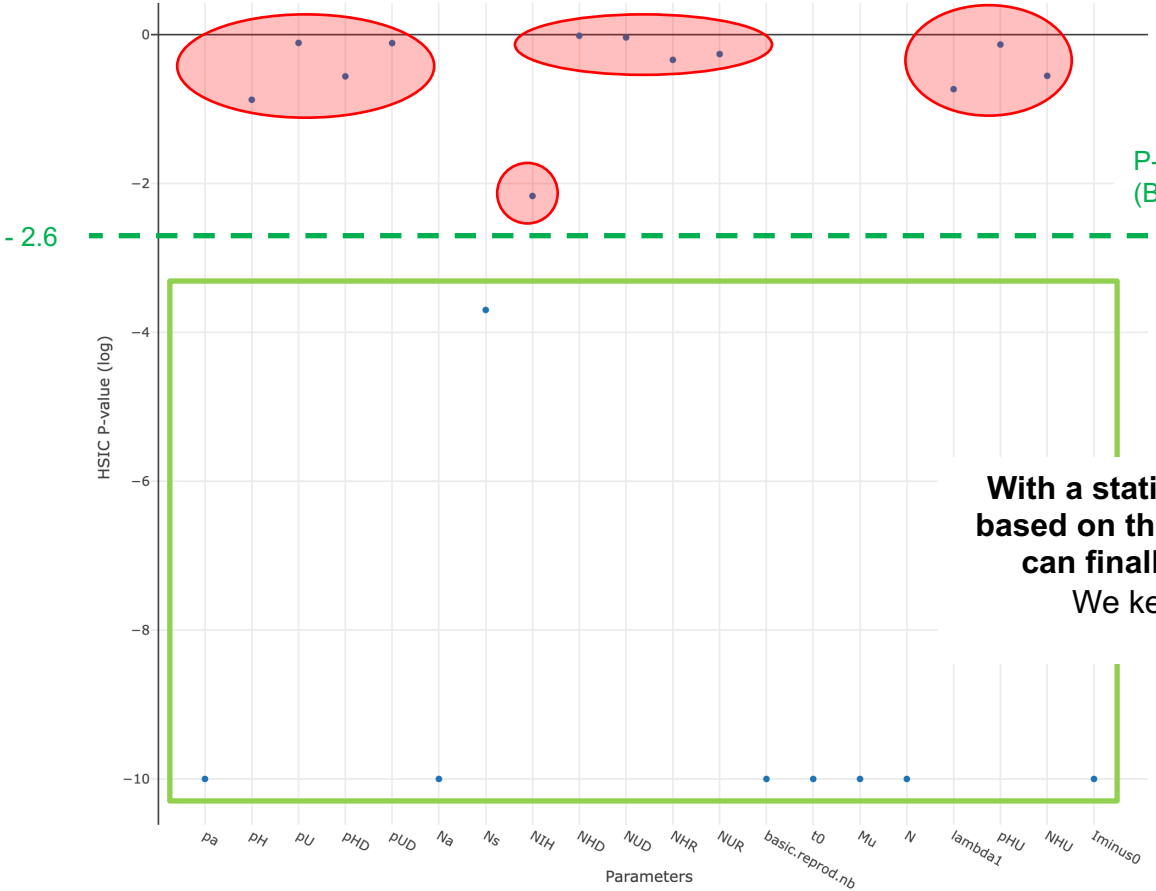
For example with these two nonlinear functions we find a very likely dependence !

Prior UQ & GSA – HSIC on our model



Output curves are aggregated and we use a PCA kernel D. 2015

Prior UQ & GSA – HSIC on our model



P-value limit for the statistical test = 0.05 / 20
(Bonferroni correction)

With a statistical test of independence based on the computed HSIC values we can finally discard 12 parameters.
We keep Ns but discard NIH.

Prior UQ & GSA

The total number of parameters is large (20)

- Before performing GSA & calibration (expensive), we may start by a first screening phase
- Screening = using a relatively small number of model evaluations to quickly identify non-influential parameters
- Here we use a modern screening tool : HSIC
  - Principle : we will use a statistical test to check if we can detect independence between the outputs and some parameters
  - The test is based on the HISC criterion, which is a measure of nonlinear correlation

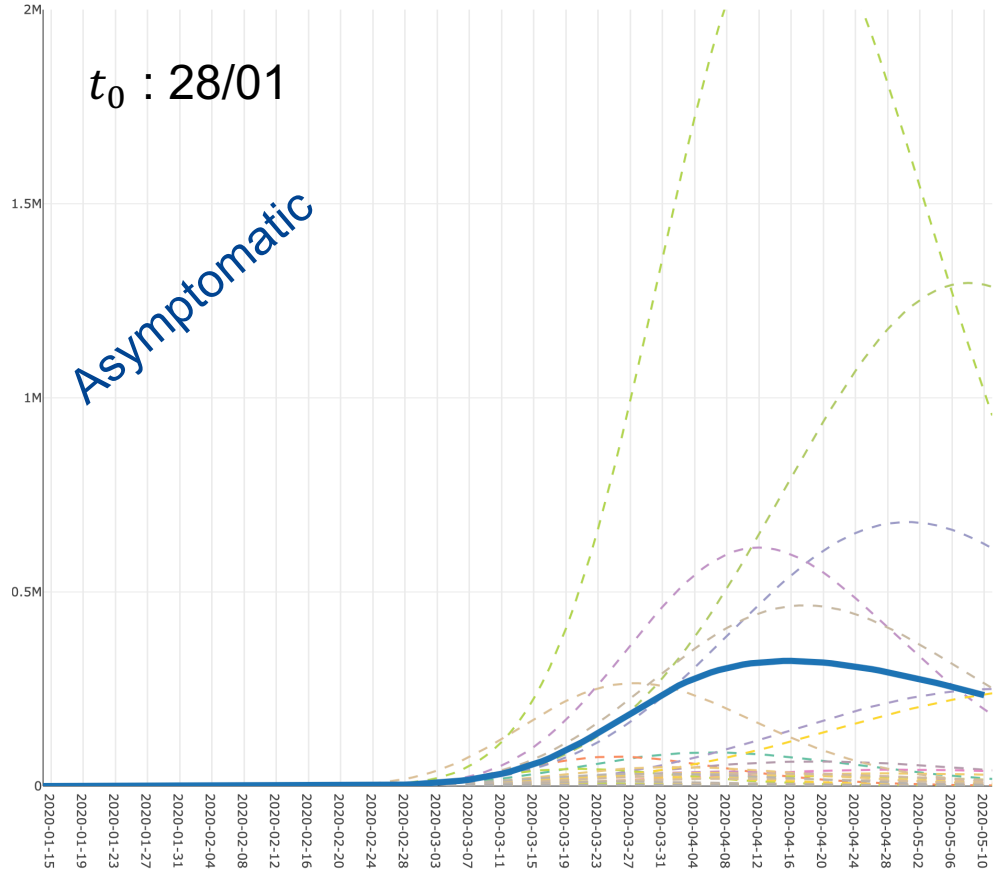
We have identified 8 influential parameters via screening

- The discarded ones are now fixed to their mean values till the end
- For each remaining parameter, we compute
  - Its **main effect** (Sobol first-order index)
  - Its **total effect**, i.e. we account for its impact via main effect + all interaction it may have with others (Sobol total index)
  - By computing their difference we can see the strength of interactions in the model

- We can also investigate how the impact changes over time

- NB: we can use Sobol indices because the parameters are assumed to be independent

Prior UQ & GSA – Quick recap on main effects (Sobol first order)



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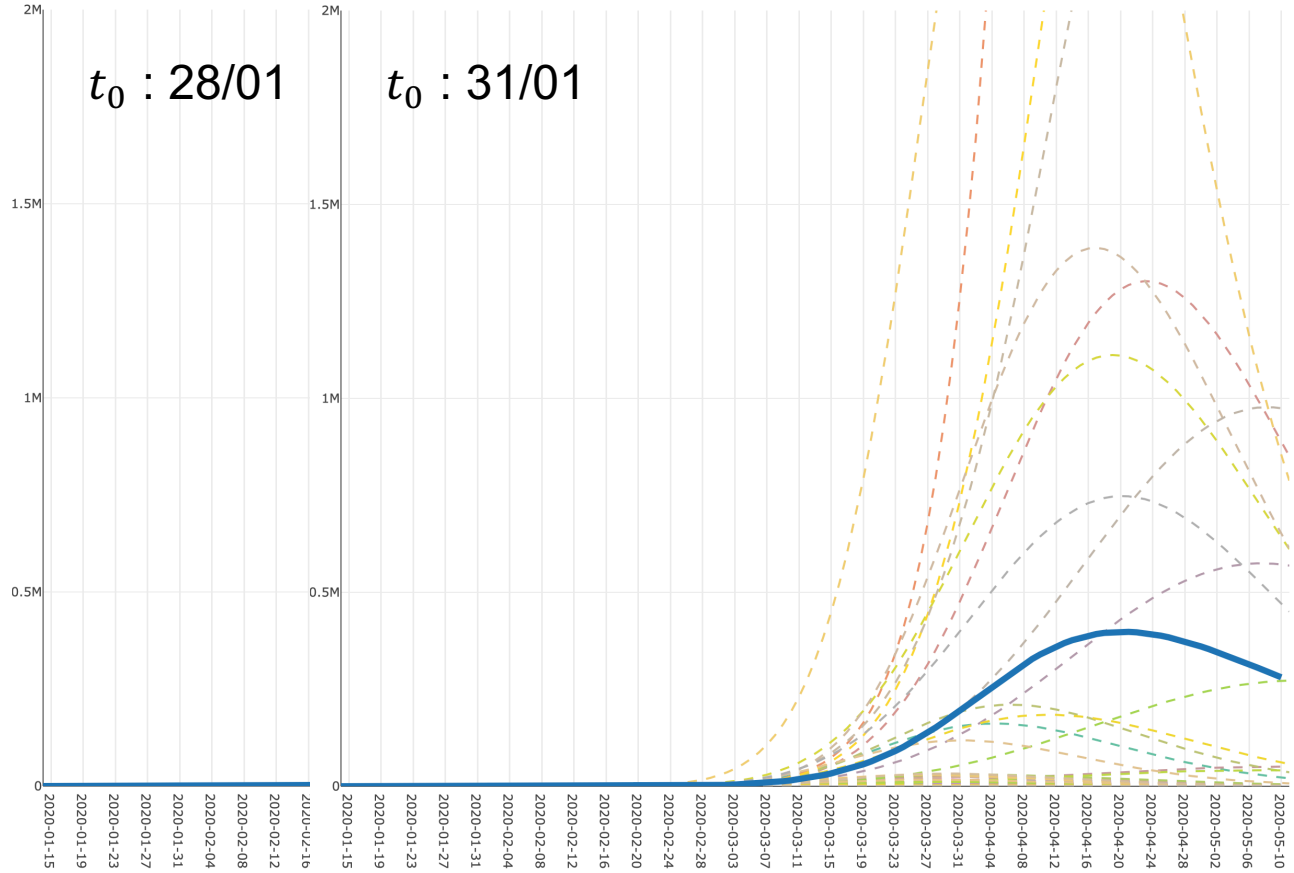

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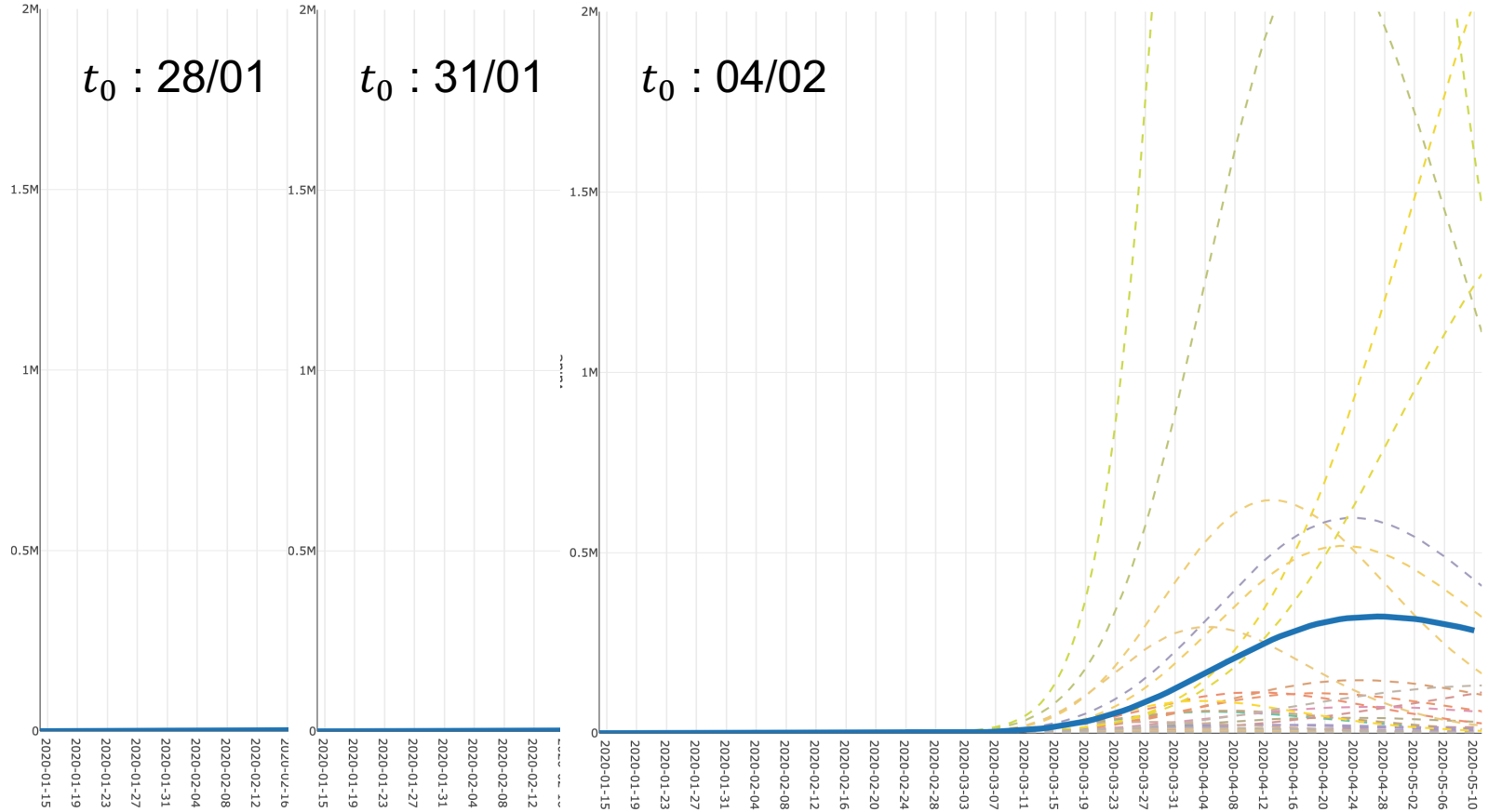
Prior UQ & GSA – Quick recap on main effects (Sobol first order)



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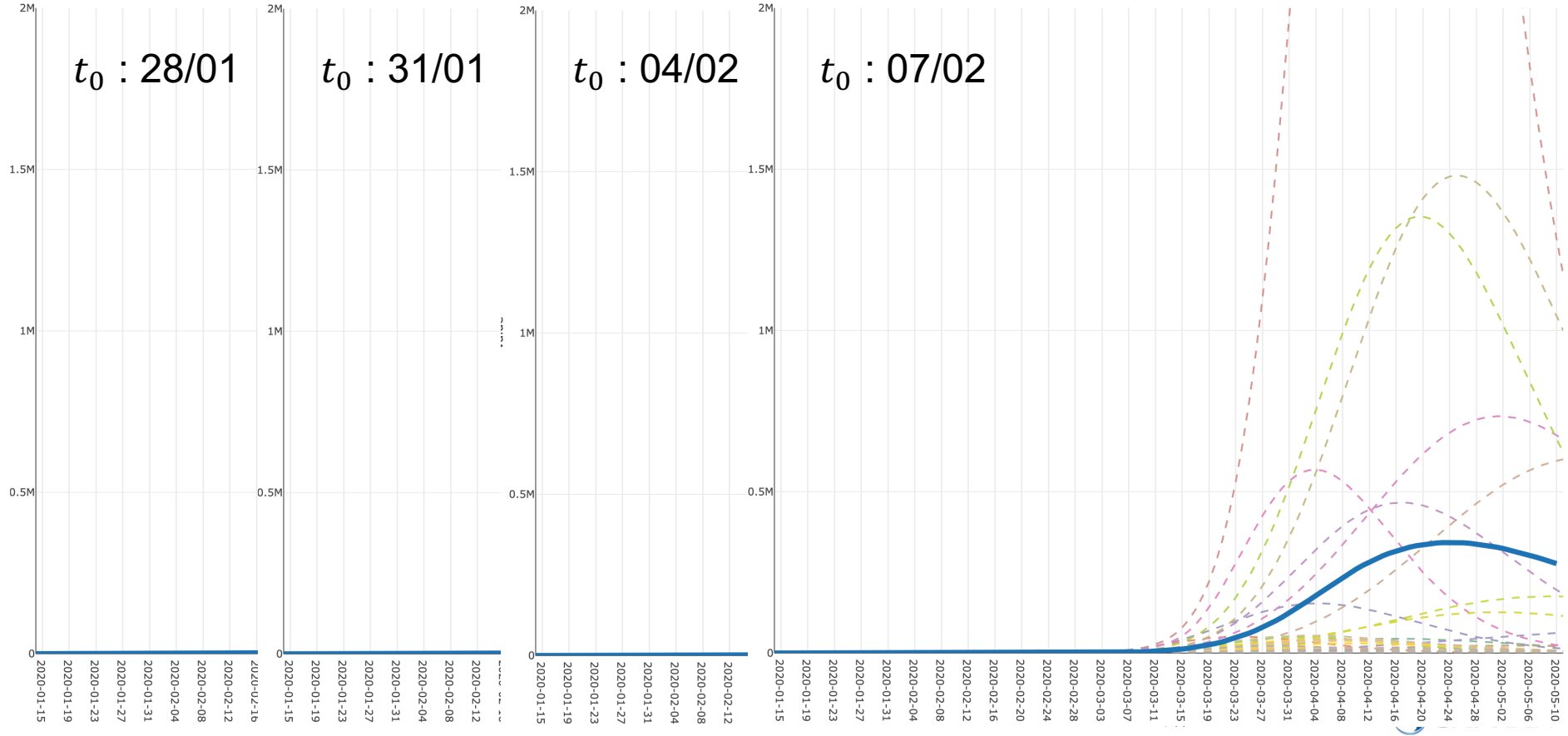

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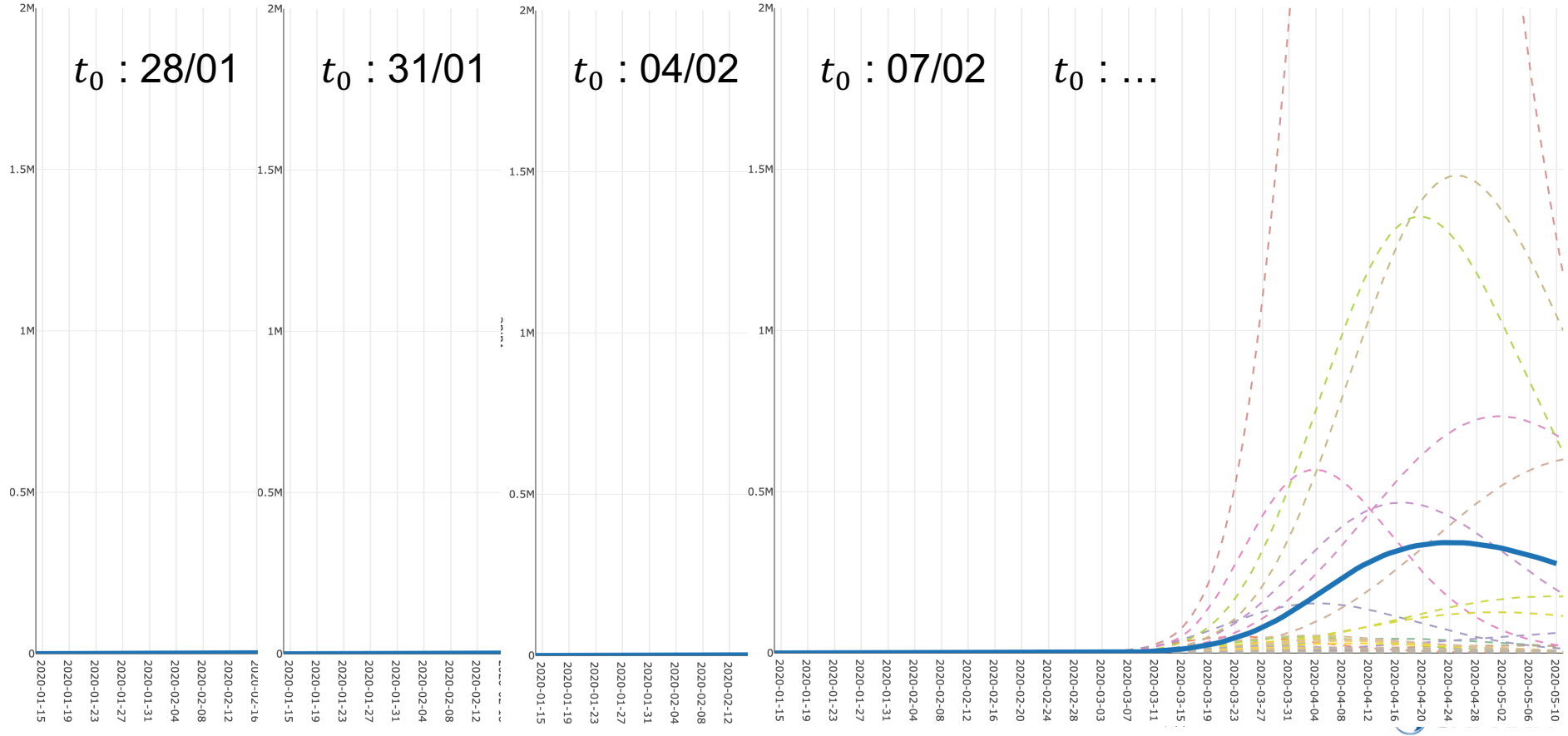
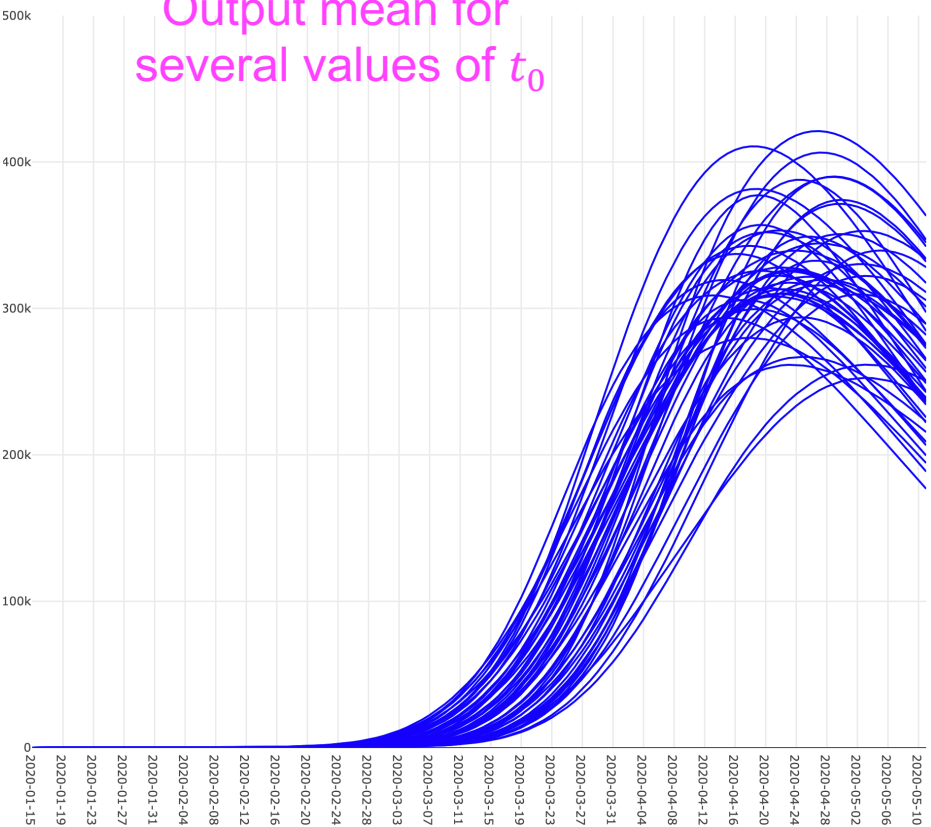


Prior UQ & GSA – Quick recap on main effects (Sobol first order)

Output mean for several values of t_0



Prior UQ & GSA – Quick recap on main effects (Sobol first order)

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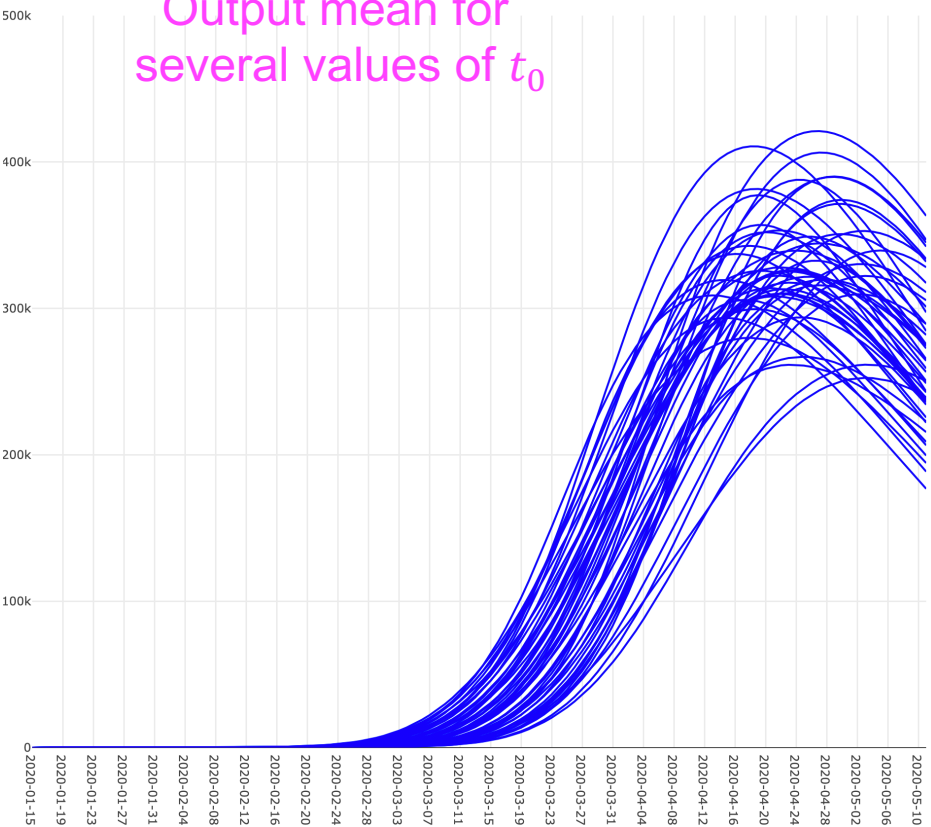
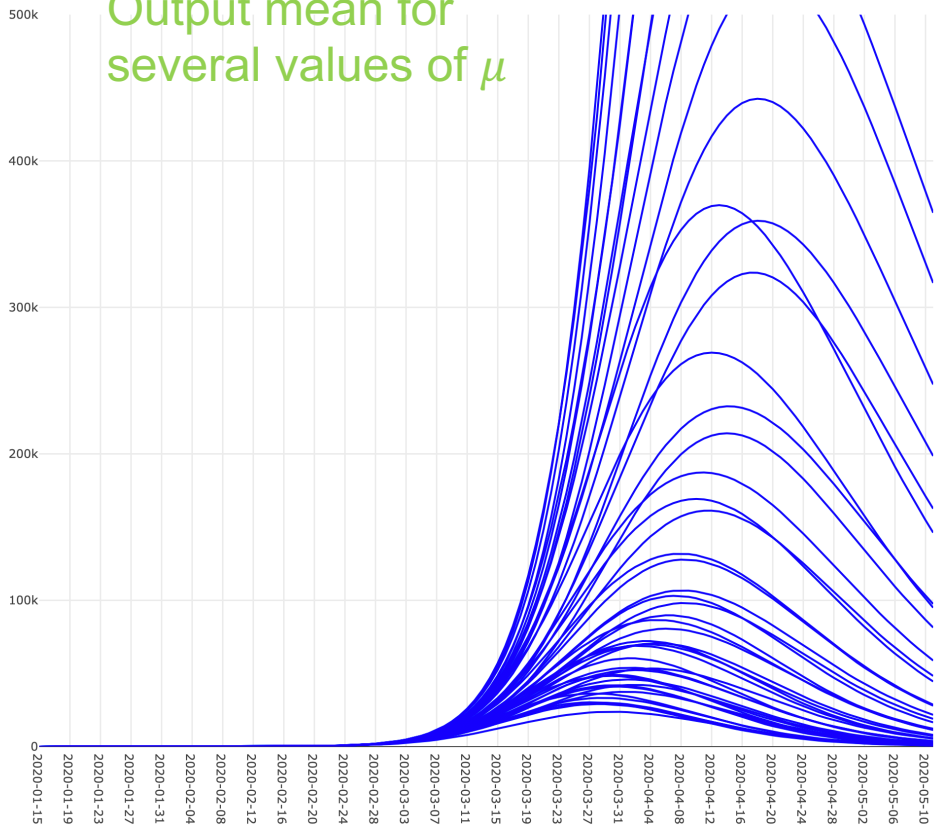


Output mean for several values of μ



Prior UQ & GSA – Quick recap on main effects (Sobol first order)

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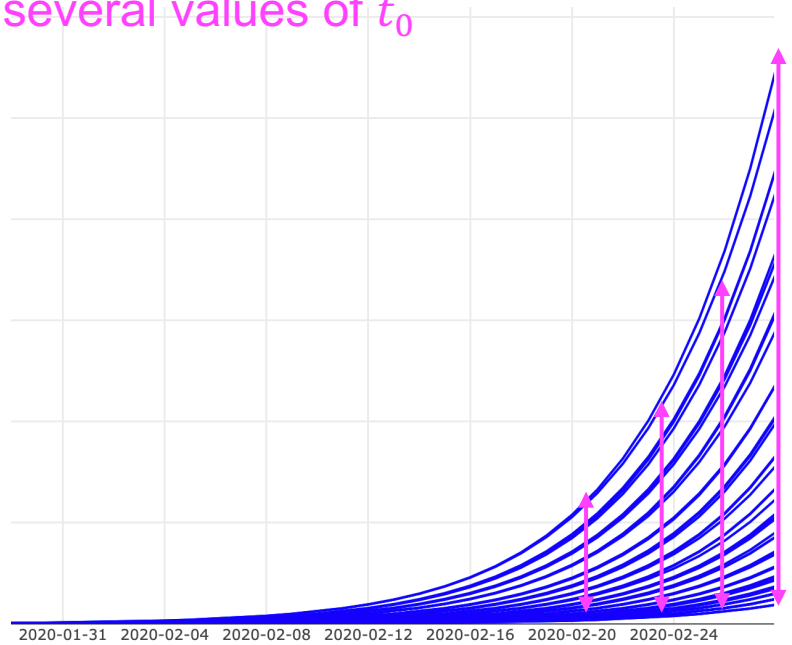
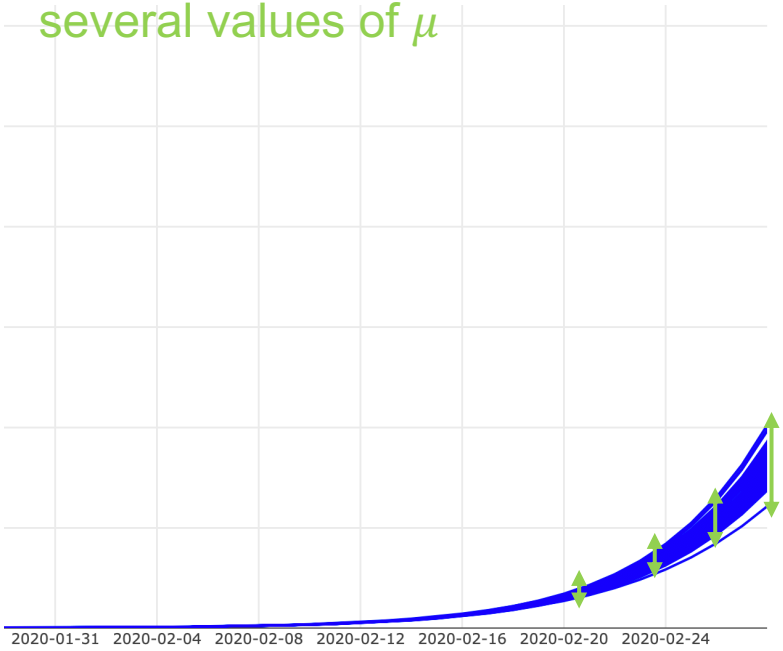


Output mean for several values of μ



Zoom at the beginning of the simulation

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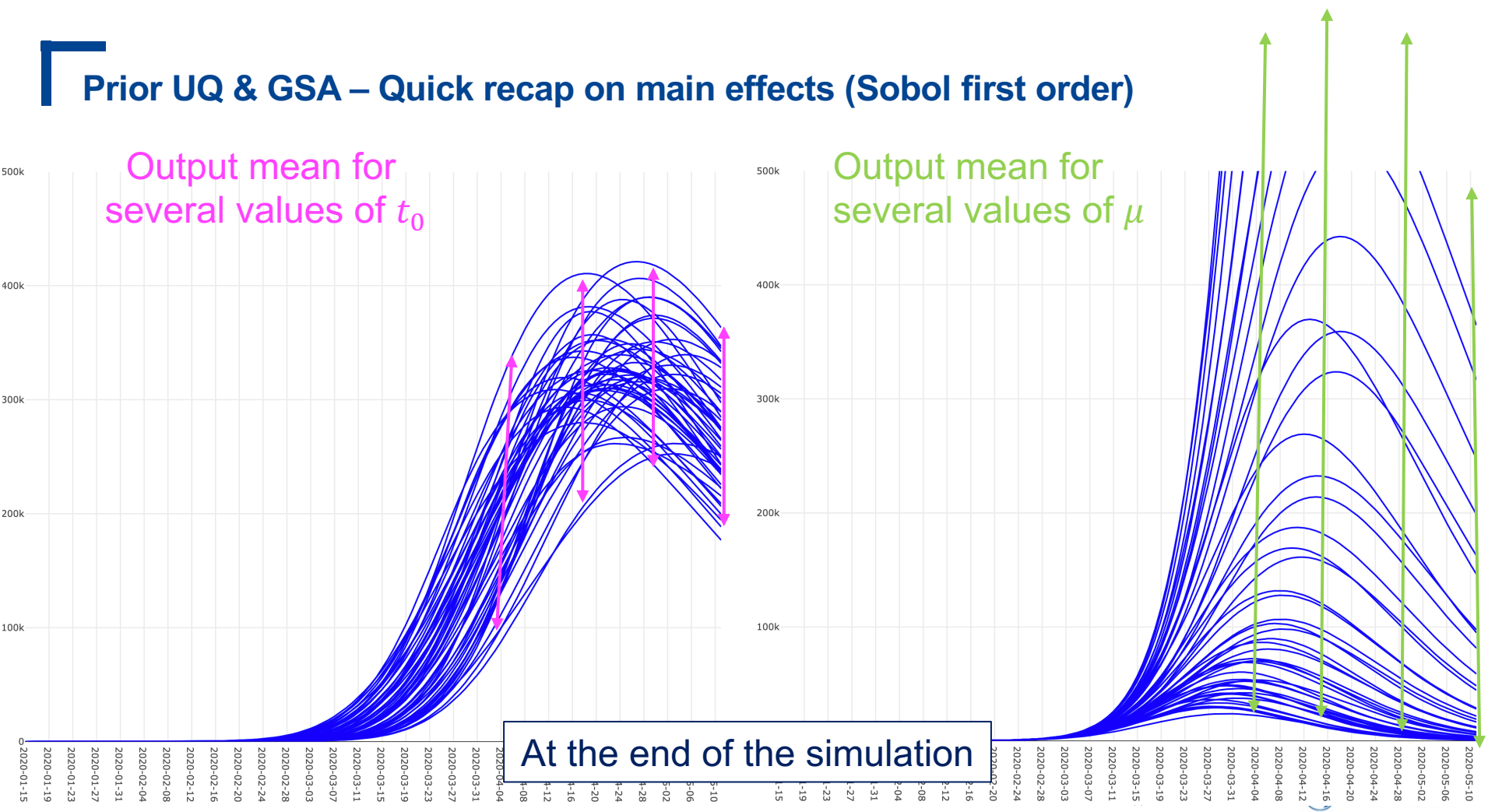
Prior UQ & GSA – Quick recap on main effects (Sobol first order)

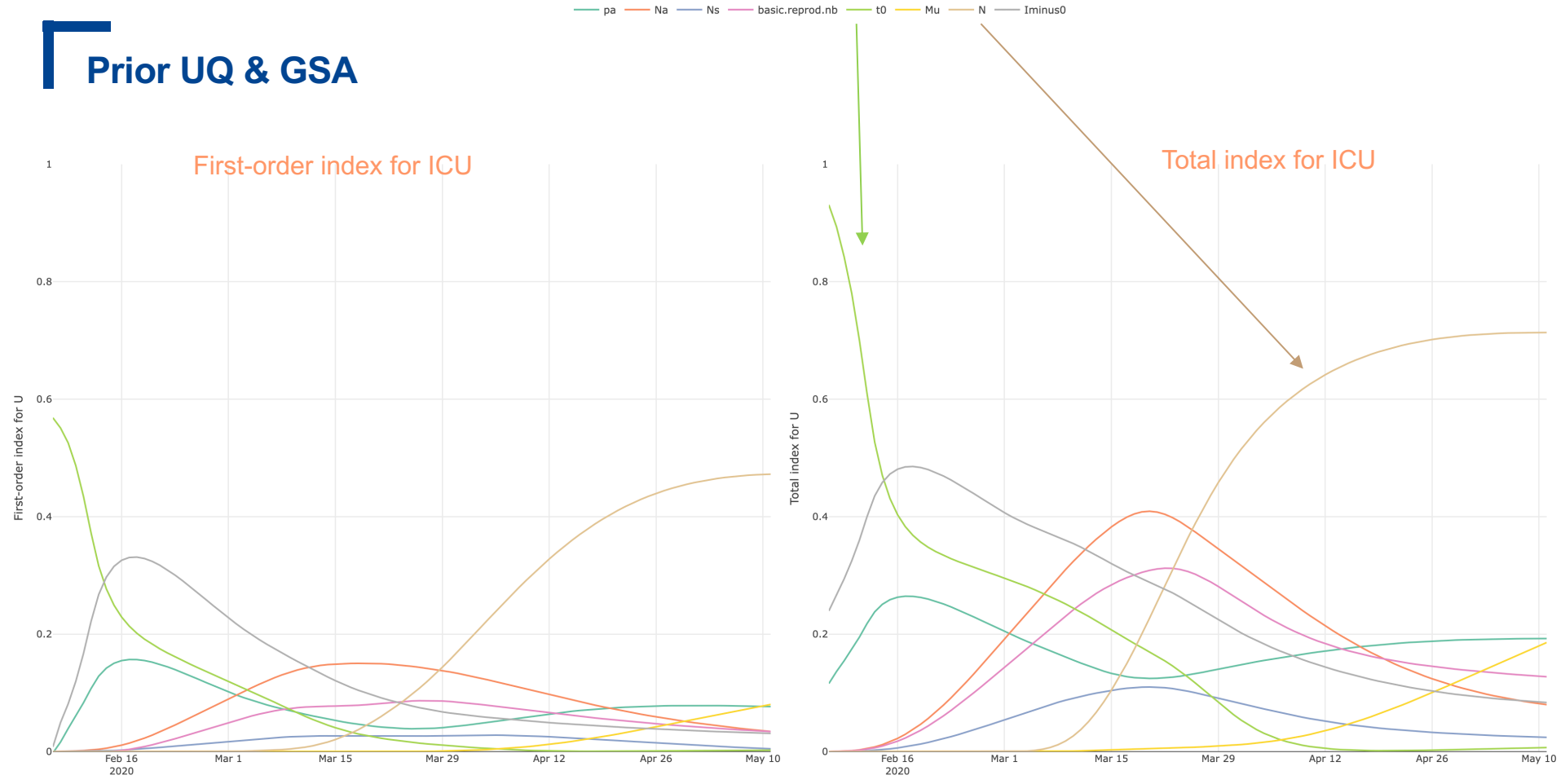
Output mean for several values of t_0

Output mean for several values of μ



At the end of the simulation

Prior UQ & GSA



Prior UQ & GSA – conclusion

Uncertainties on predictions are very large

- Small uncertainties on parameters lead to high uncertainties on the number of cases
- This is typical for SIR-like models (exponential behavior)

Few main effects, lots of interactions

- As expected, starting date and decay of transmission arise (first-order)
- All other parameters have an influence via interactions

After some time, we start collecting data → we can update our knowledge on some parameters

3

DATA CALIBRATION

POSTERIOR UQ & GSA

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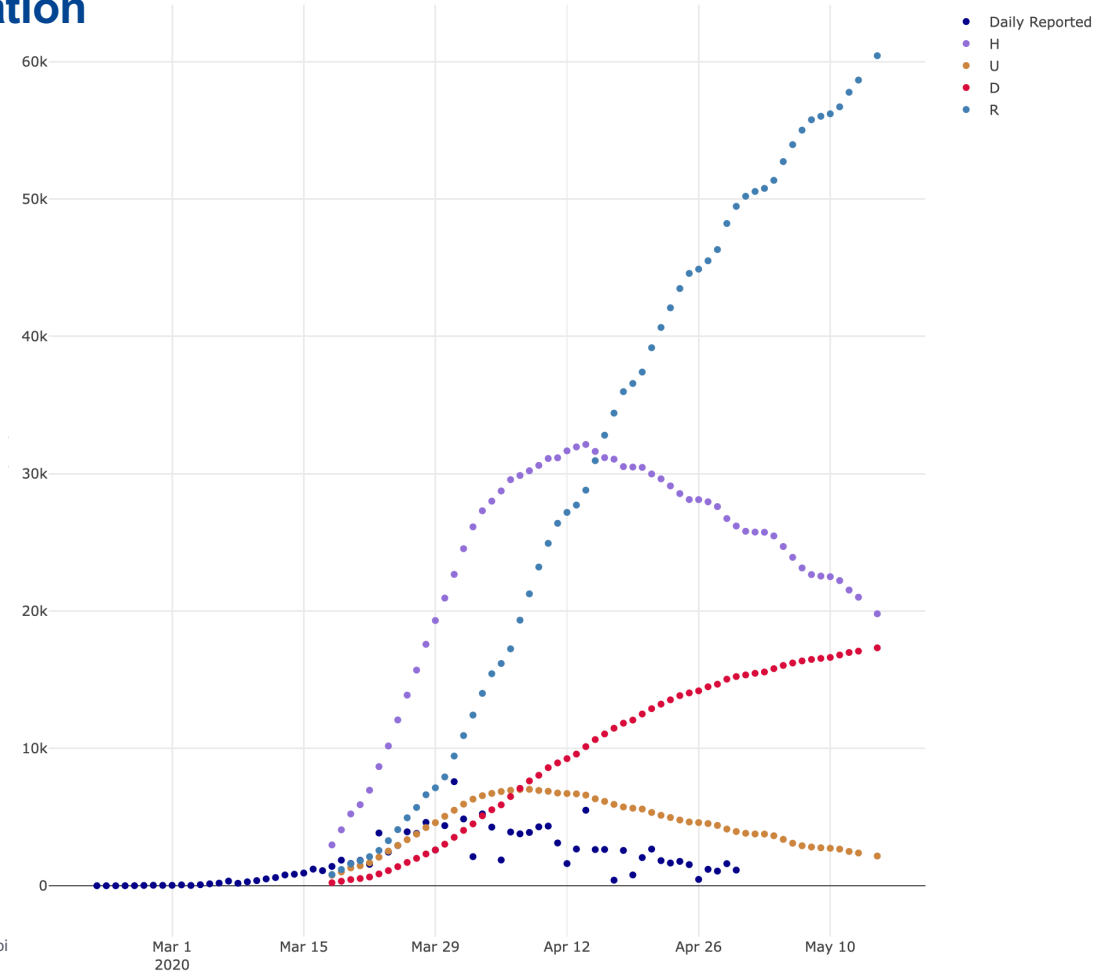
Posterior UQ & GSA – data calibration

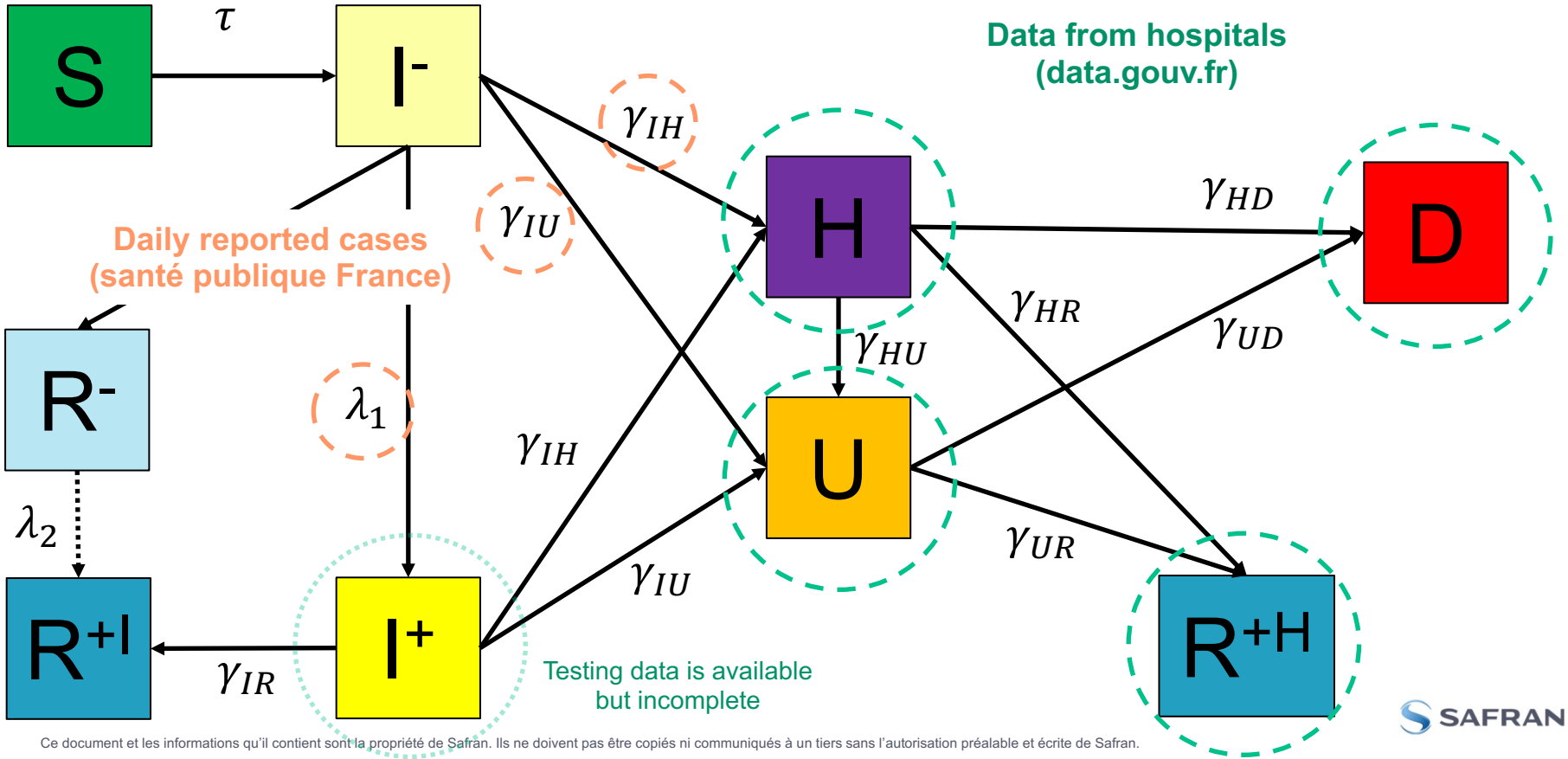
After some time, we start collecting data

- Daily reported cases (DR)
- **Now we can also incorporate H, U, D and R^{+H}**



Sources:
Santé Publique France
Data.gouv.fr

Compartmental models: modified SEIR – available data



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Posterior UQ & GSA – data calibration

After some time, we start collecting data

> Daily reported cases (DR), H, U, D and R+H

We can use these data to update our knowledge on the uncertain parameters

> We use a Bayesian approach for this calibration

$$p(\theta|\text{data}_1, \ldots, \text{data}_n) \propto p(\text{data}_1, \ldots, \text{data}_n|\theta)\, p(\theta)$$

Posterior distribution on the parameters (i.e. « updated » knowledge via calibration)

Likelihood

Prior distribution on the parameters

Posterior UQ & GSA – data calibration

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Posterior distribution on the parameters (i.e. « updated » knowledge via calibration)

Likelihood

Prior distribution on the parameters

> The likelihood is given by an assumption on how collected data and the SIR-model are related

$$\text{data}_i = \text{SIR}(\theta, t_i) + \sqrt{\text{data}_i}\,\epsilon_i$$

Gaussian error with zero mean and st. dev. σ

Posterior UQ & GSA – data calibration

After some time, we start collecting data

> **Daily reported cases (DR), H, U, D and R+H**

We can use these data to update our knowledge on the uncertain parameters

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Posterior distribution on the parameters (i.e. « updated » knowledge via calibration)

Likelihood

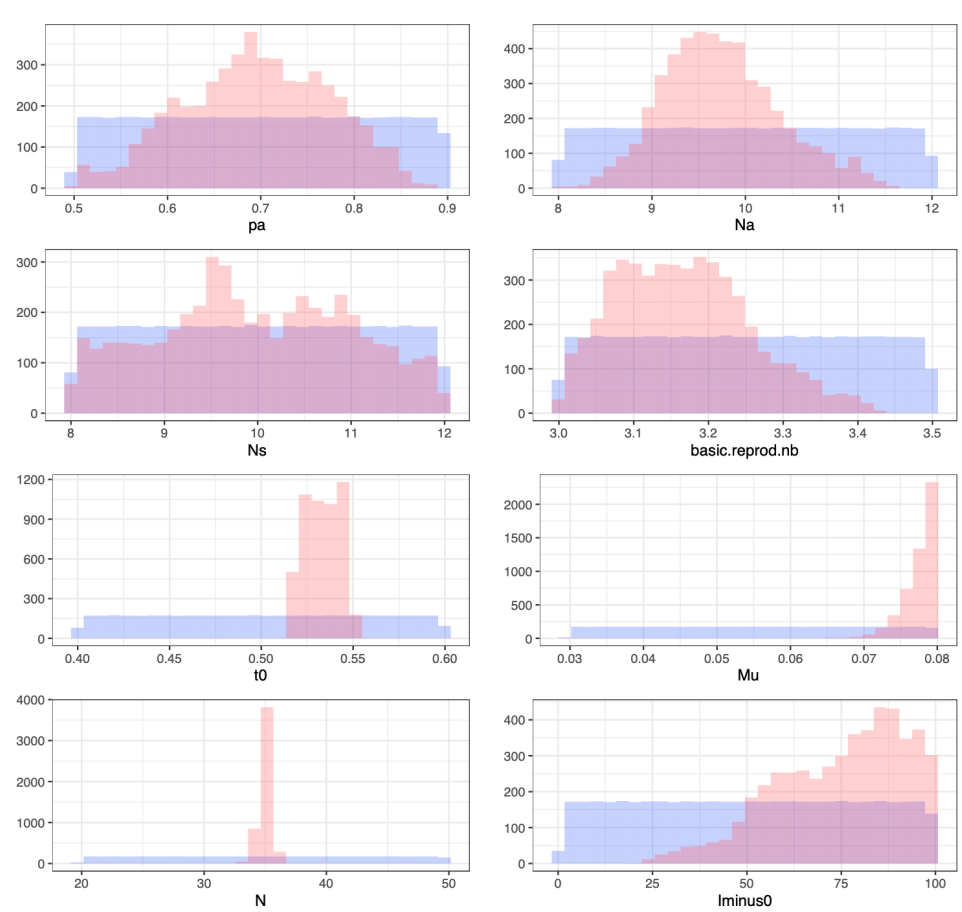
Prior distribution on the parameters

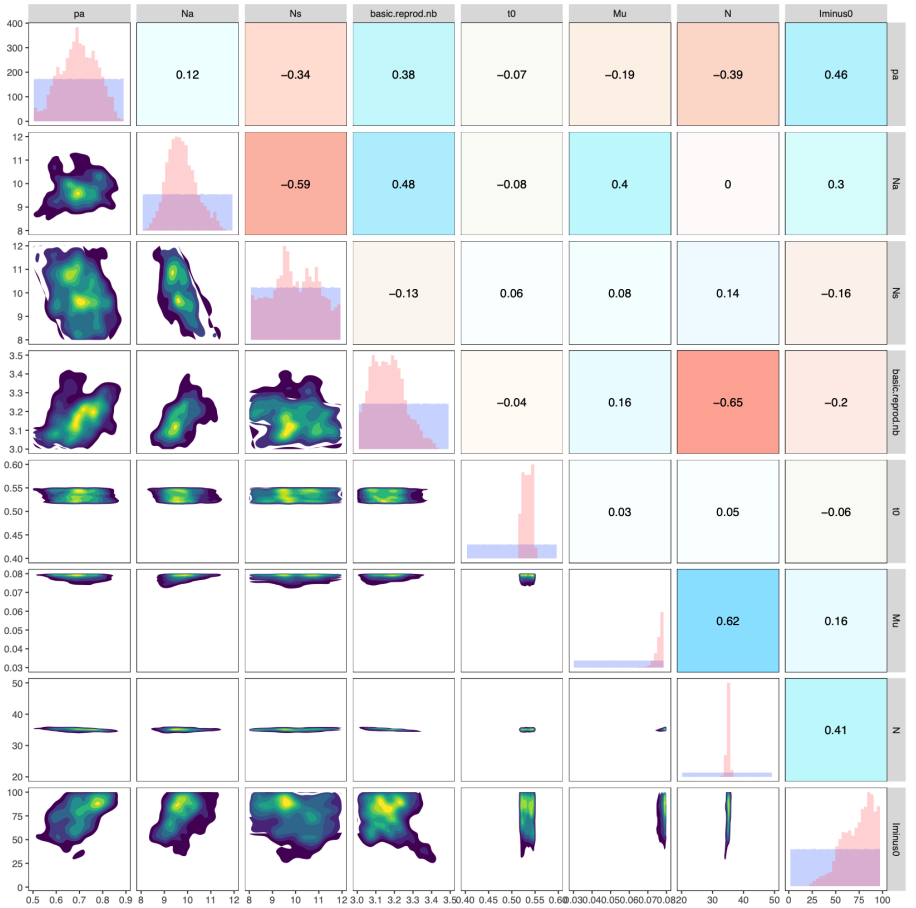
> The likelihood is given by an assumption on how collected data and the SIR-model are related

> The posterior distribution is not tractable, we use a MCMC sampling algorithm

- Metropolis-Hastings tuned for the problem

Posterior UQ & GSA – data calibration



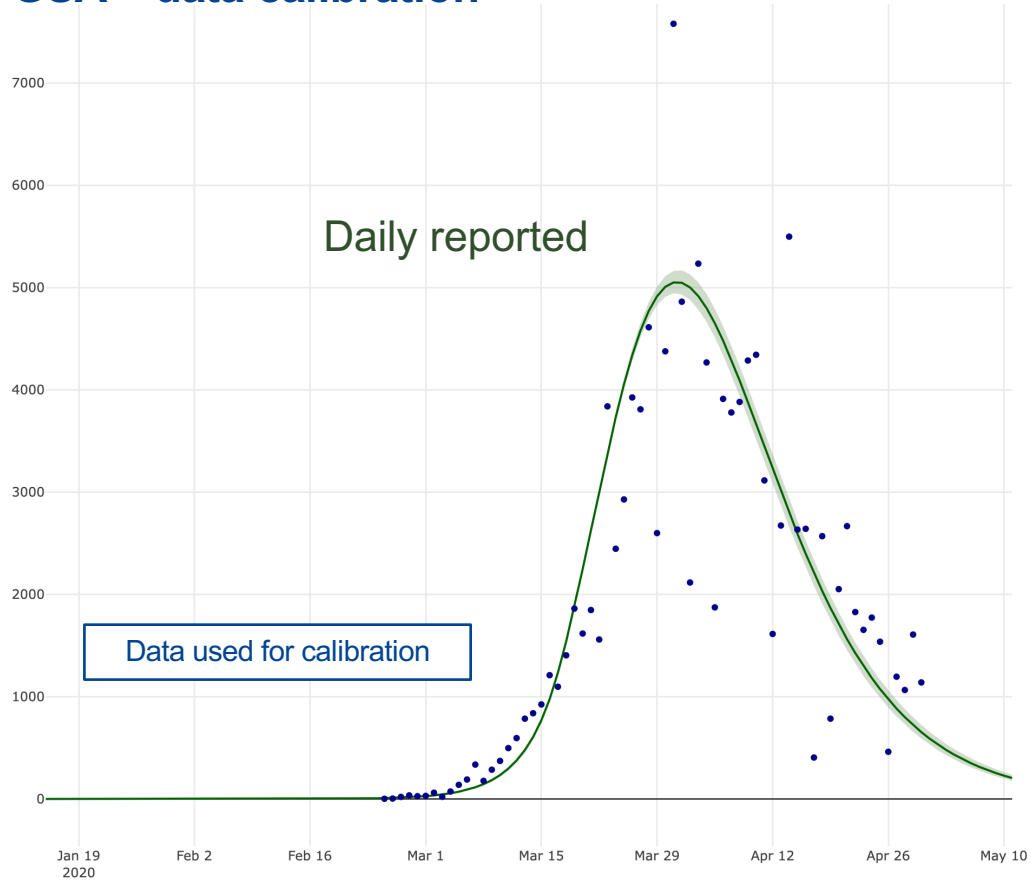


Posterior UQ & GSA – propagation on number of cases

Once we have the posterior sample, we can propagate it through the model

- Simply run the SIR+ model for each parameter value in the MCMC sample
- Collect the number of cases in each compartment
- Also include observed data which were used for calibration

Posterior UQ & GSA – data calibration



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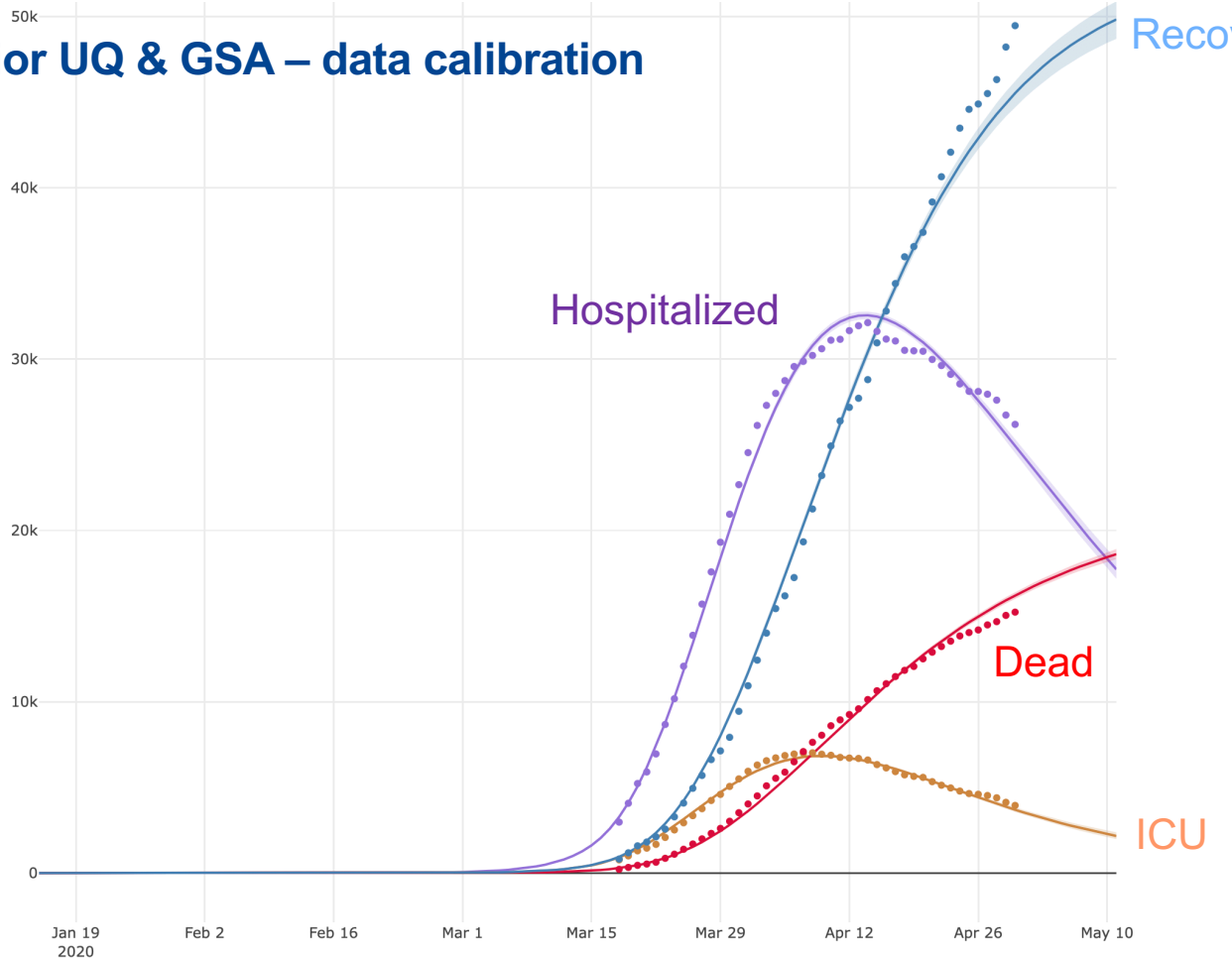

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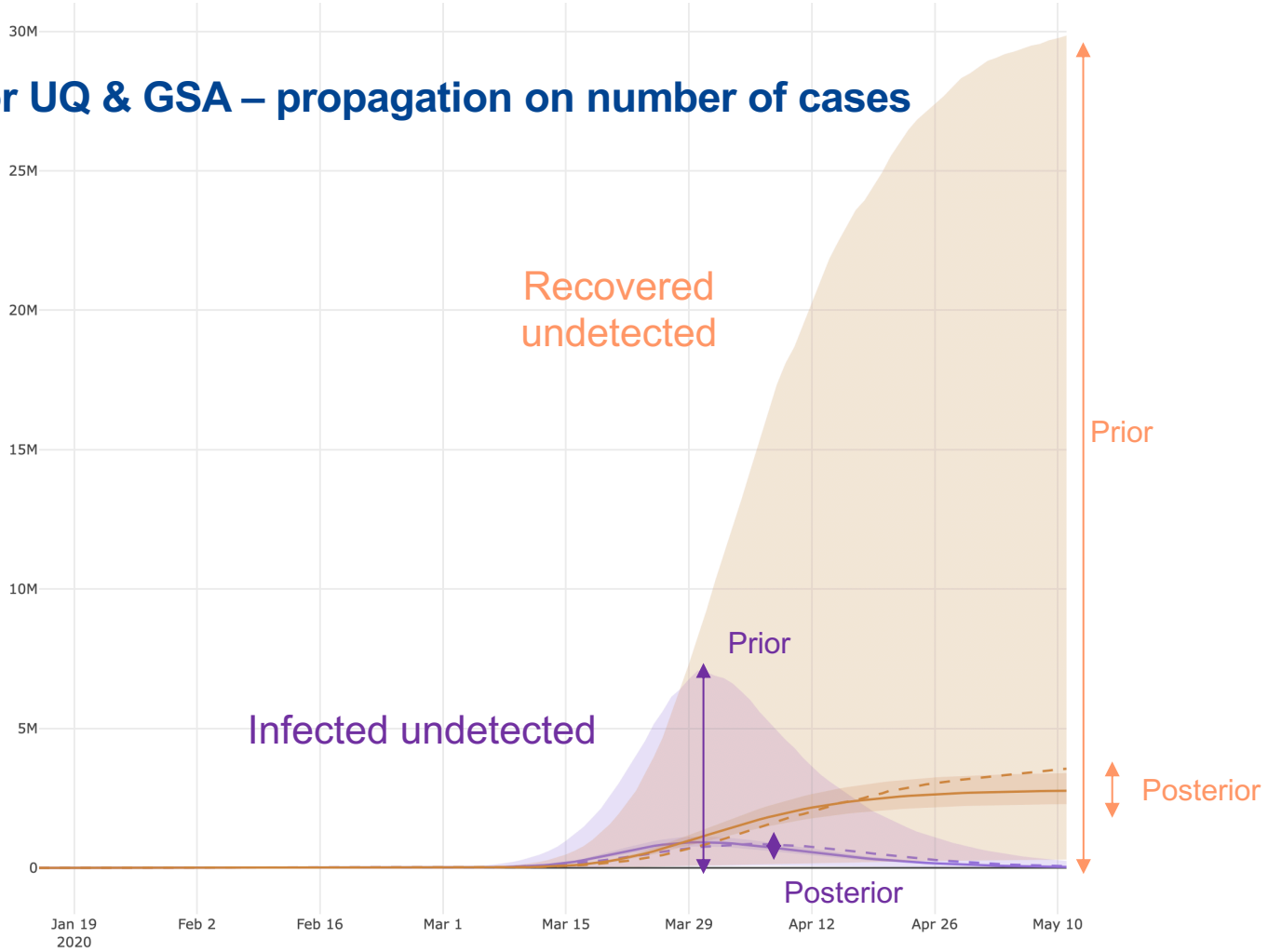
Posterior UQ & GSA – propagation on number of cases



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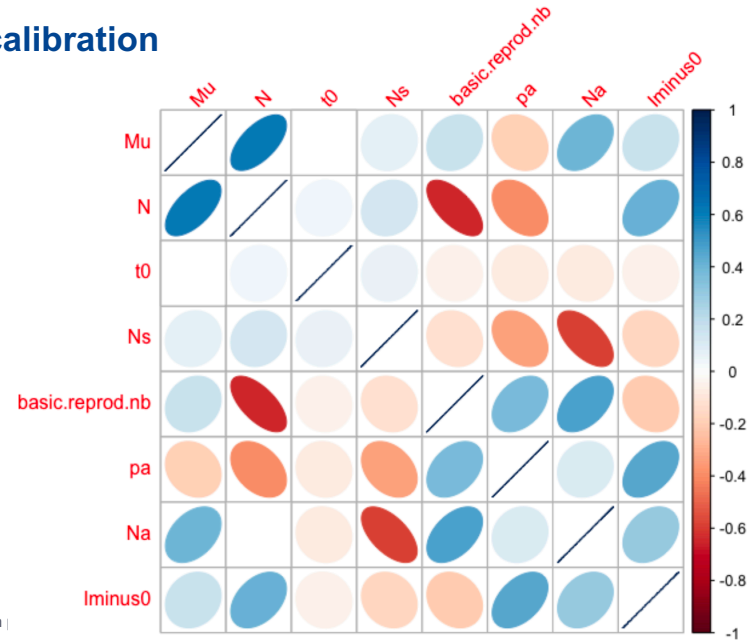
We can also compute the impact of each parameter after calibration

- **But this time they are correlated due to calibration**



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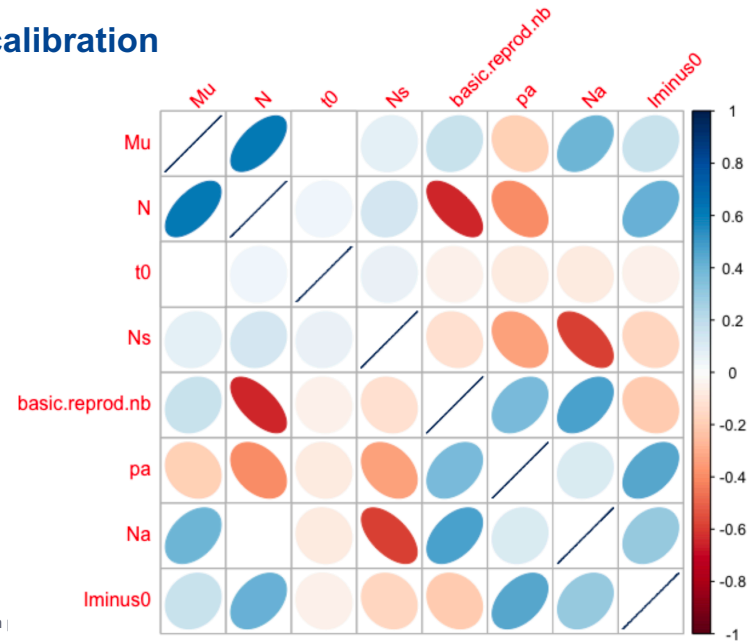
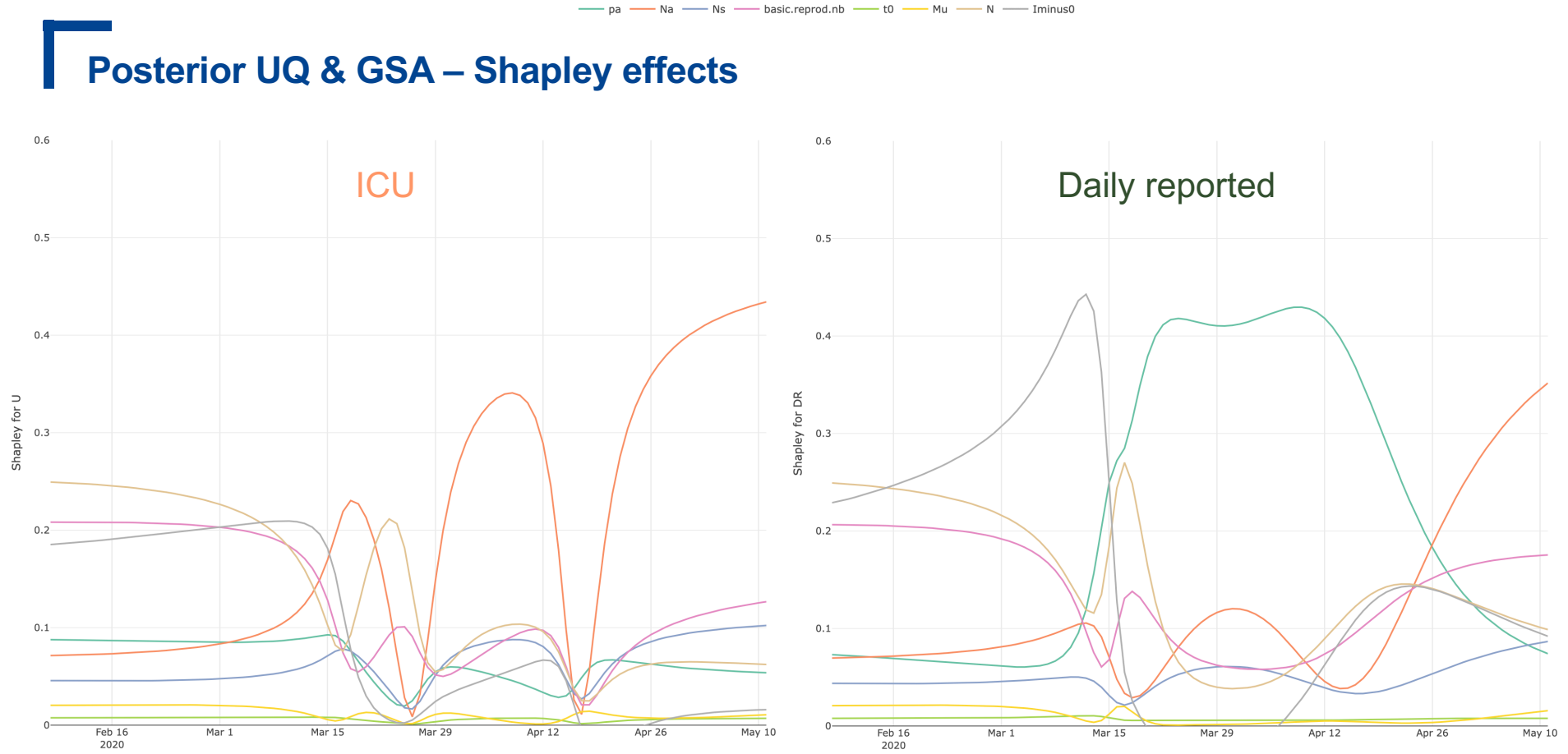
We can also compute the impact of each parameter after calibration

- But this time they are correlated due to calibration
- **We cannot use Sobol indices**
- **We resort to Shapley effects**
  - Interactions & correlations are distributed evenly among parameters



Posterior UQ & GSA – Shapley effects



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Conclusion

We have illustrated standard tools from UQ & GSA on a simplified Covid-19 model

- Define the representative model (modified SIR model)
- Prior to data acquisition, uncertainty propagation and sensitivity analysis
- Bayesian calibration with available data
- New uncertainty propagation and sensitivity analysis with updated distributions
- **The approach is general to any study of infectious diseases**
  - More complex SIR model (latency phase, calibration and seasonality for deaths, …)
- **Many tools in R package sensitivity**

! such models are highly sensitive to parameters

What we did not illustrate here (although crucial when dealing with more complex models)

- The computational time to solve the SIR ODE is very small
- This is not the case with more complex models (i.e. solid/fluid mechanics, …)
- **There are thus additional steps**
  - The expensive model is replaced by a surrogate model
  - It is built with an initial design of experiments generated in the parameter space
  - It may be enriched by sequential model runs (refinement in regions where calibration is promising)
  - It is used in all UQ & GSA methods instead of the initial model

Thank you for your attention

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[5] Z. Liu, P. Magal, and G. F. Webb. Predicting the number of reported and unreported cases for the COVID-19 epidemics in China, South Korea, Italy, France, Germany and United Kingdom. Preprint, 2020, URL https://www.medrxiv.org/content/early/2020/04/10/2020.04.09.20058974.

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