Uncertainty quantification in the Brazilian outbreak of Zika virus

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NUMERICO – **Nu**cleus of **M**odeling and **E**xpe**ri**mentation with **Co**mputers
http://numerico.ime.uerj.br

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Michel Tosin (UERJ)

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New York City, USA

In honor to the 70th birthday of Prof. Christian Soize

Outline

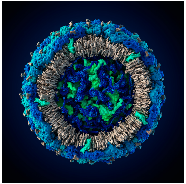
1. Introduction
2. Dynamic Model
3. Inverse Problem
4. Sensitivity Analysis
5. Uncertainty Quantification
6. Final Remarks

Section 1

Introduction

Zika virus (ZIKV)

- Member of *Flaviviridae* virus family
- First isolated in 1947 at Uganda, Africa
- Mainly spread by *Aedes* mosquitoes
- W.H.O declared it a public health emergency of international concern
- More than 140,000 confirmed cases in Brazil since 2015
- International consensus that ZIKV is a cause of:
    - Guillain–Barré syndrome
    - Microcephaly

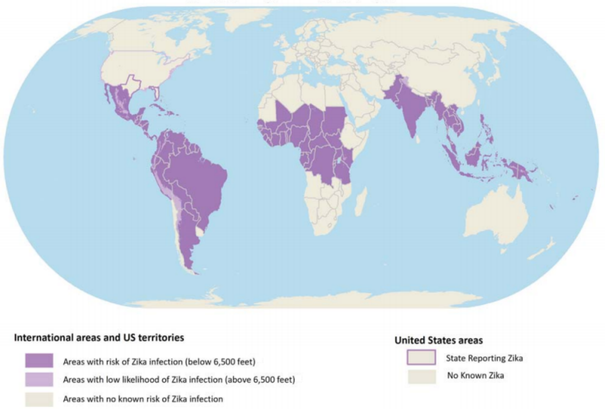


Zika virus

Aedes aegypti

Global outbreak of Zika virus

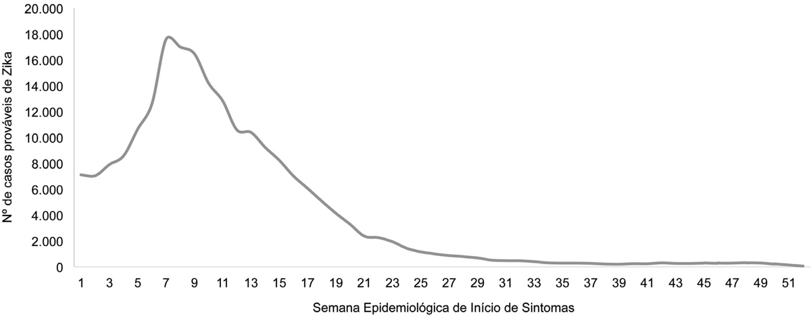
World Map of Areas with Risk of Zika



Centers for Disease Control and Prevention, *World Map of Areas with Risk of Zika, March 2018.*

Zika virus outbreak in Brazil

New cases in Brazil by epidemiological week of 2016



Secretaria de Vigilância em Saúde. *Zika virus - Boletim Epidemiológico v. 48*, n. 14, 2017.

ISSN: 2358-9450

Dengue virus (DENV)

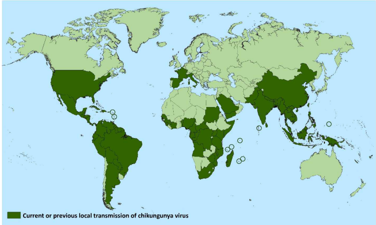
- Member of *Flaviviridae* virus family
- Mainly spread by *Aedes* mosquitoes, as in the case for Zika virus
- Probable cases in Brazil:
  - $>$ 170,000 in 2018
  - $>$ 250,000 in 2017
  - $>$ 3 million in 2016 and 2015

Dengue virus

Aedes aegypti

Other Arbovirus

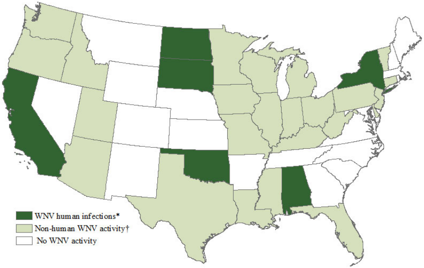
- **AR**thropod-**BO**rne virus
- Yellow Fever: South America and Africa
  (261 deaths in Brazil in 2017)
- Chikungunya: worldwide
  ($>$ 204,000 confirmed cases in Brazil since 2015)
- Rift Valley fever: Africa and Arabian Peninsula
  (ongoing outbreak in Kenya by June 2018)



Chikungunya cases (May 2018)

Other Arbovirus

- Japanese encephalitis: Southeast Asia, Western Pacific
- West Nile virus: widely established from Canada to Venezuela
- Both transmitted by the *Culex* mosquitoes



West Nile virus activity in USA (July 2018)

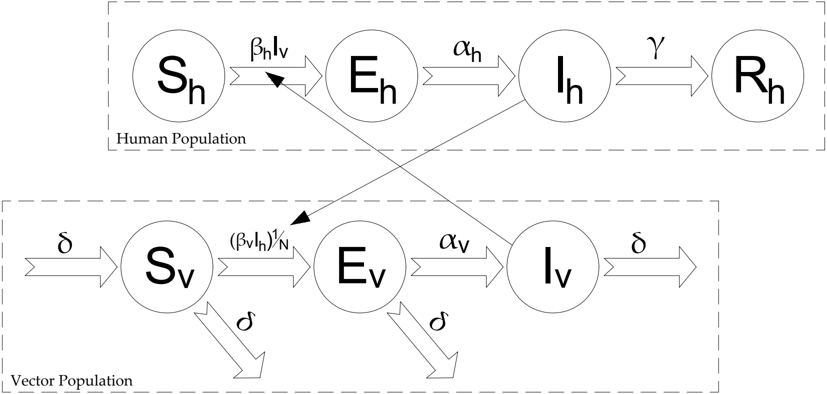
Research objectives

- Develop an epidemic model to describe the recent outbreak of Zika virus in Brazil
- Verify (qualitatively and quantitatively) the epidemic model capacity of prediction
- Calibrate this epidemic model with real data to obtain reliable predictions
- Construct a stochastic model to deal with data uncertainties and made more robust predictions

Section 2

Dynamic Model

SEIR-SEI model for Zika virus dynamics



A. J. Kucharski et al. *Transmission Dynamics of Zika Virus in Island Populations: A Modelling Analysis of the 2013–14 French Polynesia Outbreak.* **PLOS Neglected Tropical Diseases, 2016.**

Associated dynamical system

$$\frac{dS_h}{dt} = -\beta_h\, S_h\, I_v$$

$$\frac{dE_h}{dt} = \beta_h\, S_h\, I_v - \alpha_h\, E_h$$

$$\frac{dI_h}{dt} = \alpha_h\, E_h - \gamma\, I_h$$

$$\frac{dR_h}{dt} = \gamma\, I_h$$

$$\frac{dS_v}{dt} = \delta - \beta_v\, S_v\, \frac{I_h}{N} - \delta\, S_v$$

$$\frac{dE_v}{dt} = \beta_v\, S_v\, \frac{I_h}{N} - (\delta + \alpha_v)\, E_v$$

$$\frac{dI_v}{dt} = \alpha_v\, E_v - \delta\, I_v$$

$$\frac{dC}{dt} = \alpha_h\, E_h$$

$+$ initial conditions

S - Population of susceptible
E - Population of exposed
I - Population of infected
R - Population of recovered
N - Population of humans

C - Infected humans cumulative
α - Incubation ratio
δ - Vector lifespan ratio
β - Transmition rate
γ - Recovery rate

h - Human-related
v - Vector-related

A. J. Kucharski et al. *Transmission Dynamics of Zika Virus in Island Populations: A Modelling Analysis of the 2013–14 French Polynesia Outbreak.* **PLOS Neglected Tropical Diseases, 2016.**

Model parameters and outbreak data

- open scientific literature

- Brazilian health system

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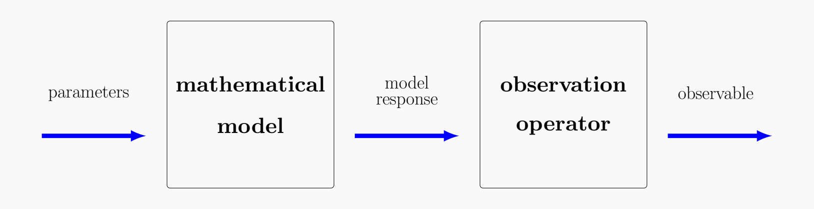
FIOCRUZ
Fundação Oswaldo Cruz

parameter	value	unit
α_h	$1/5.9$	days^{-1}
α_v	$1/9.1$	days^{-1}
γ	$1/7.9$	days^{-1}
δ	$1/11$	days^{-1}
β_h	$1/11.3$	days^{-1}
β_v	$1/8.6$	days^{-1}
N	206×10^6	people

Quantities of interest (QoI)



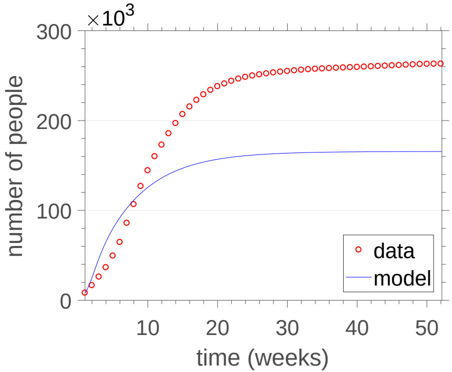
QoI 1: cumulative number of infectious

$$C_t = \int_{\tau=0}^{t} \alpha_h \, E_h(\tau) \, d\tau$$

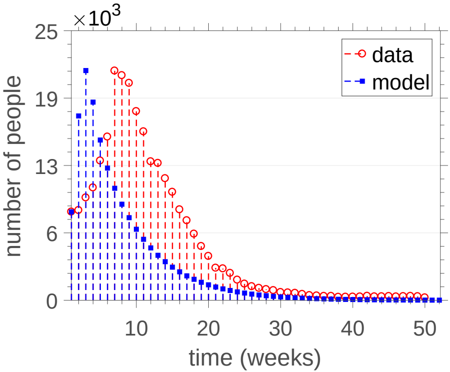
QoI 2: new infectious cases

$$\mathcal{N}_w = C_w - C_{w-1}, \quad (w = 2, 3, \cdots, 52)$$
$$\mathcal{N}_1 = C_1$$

Time series for QoI's

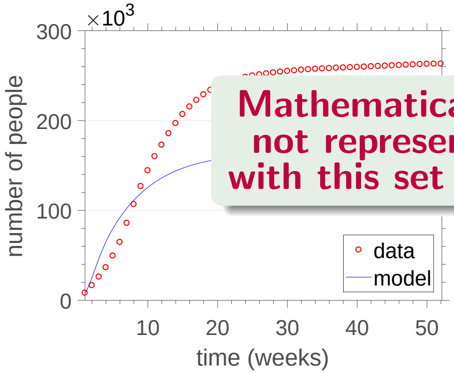


cumulative number of infectious

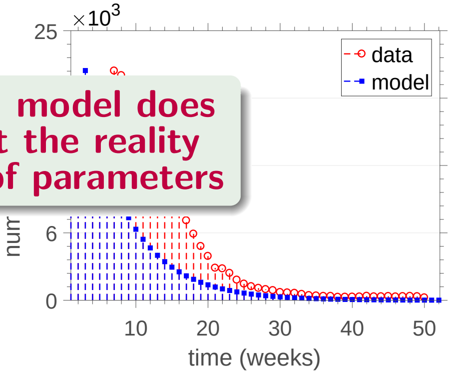


new infectious cases

Time series for QoI’s



cumulative number of infectious



new infectious cases

Mathematical model does not represent the reality with this set of parameters

Section 3

Inverse Problem

Verification and Validation (V&V)

- Verification
  Are we solving the equation *right*?

- Validation
  Are we solving the *right* equation?

G. Iaccarino *Quantification of Uncertainty in Flow Simulations Using Probabilistic Methods*,
VKI Lecture Series, Stanford University, 2008

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- Validation
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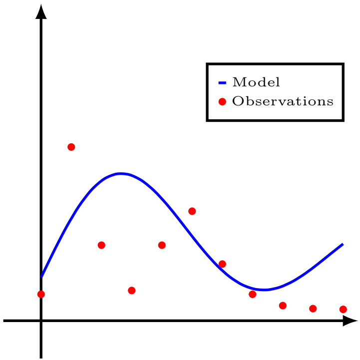
  It is an exercise in *physics*.

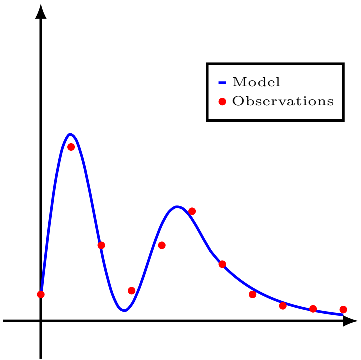
G. Iaccarino *Quantification of Uncertainty in Flow Simulations Using Probabilistic Methods*,
VKI Lecture Series, Stanford University, 2008

Calibration of the model

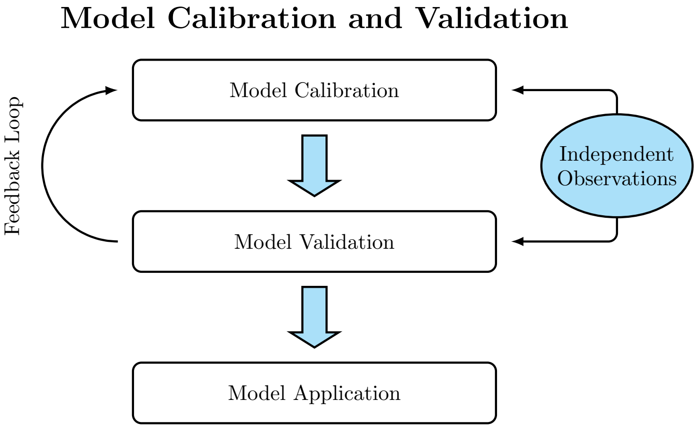
Uncalibrated Model



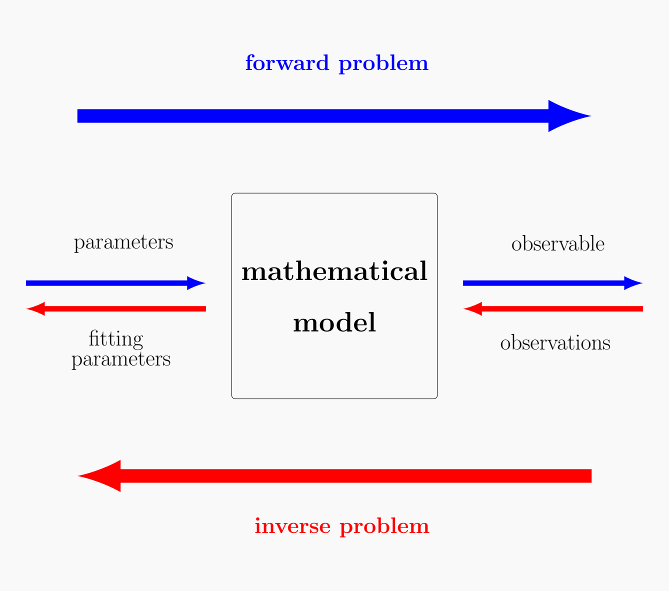
Calibrated Model



Calibration vs Validation



Forward and inverse problem



Inverse problem formulation

- data space: $F = \mathbb{R}^M$
- parameter space: $C = \left\{ \boldsymbol{\alpha} \in \mathbb{R}^{12} \mid \boldsymbol{\alpha}_{min} \leq \boldsymbol{\alpha} \leq \boldsymbol{\alpha}_{max} \right\}$
- observation vector: $\boldsymbol{y} = (y_1, y_2, \cdots, y_M) \in F$
- prediction vector: $\boldsymbol{\phi}(\boldsymbol{\alpha}) = (\phi_1, \phi_2, \cdots, \phi_M) \in F$
- misfit function:

$$J(\boldsymbol{\alpha}) = ||\boldsymbol{y} - \boldsymbol{\phi}(\boldsymbol{\alpha})||_F^2 = \sum_{m=1}^{M} \Big| y_m - \phi_m(\boldsymbol{\alpha}) \Big|^2$$

Find a vector of parameters such that

$$\boldsymbol{\alpha}^* = \arg\min_{\boldsymbol{\alpha} \in C} J(\boldsymbol{\alpha}).$$

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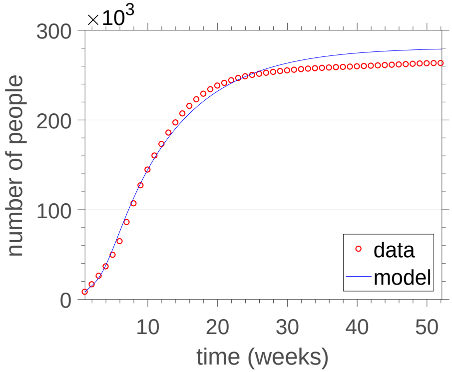
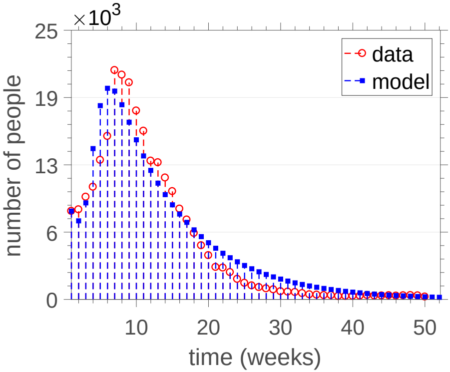
$\Longrightarrow$ Q-wellposed: existence, uniqueness, unimodality and local stability

$\Longrightarrow$ Solution algorithm: bounded trust-region-reflective

First calibration



cumulative number of infectious

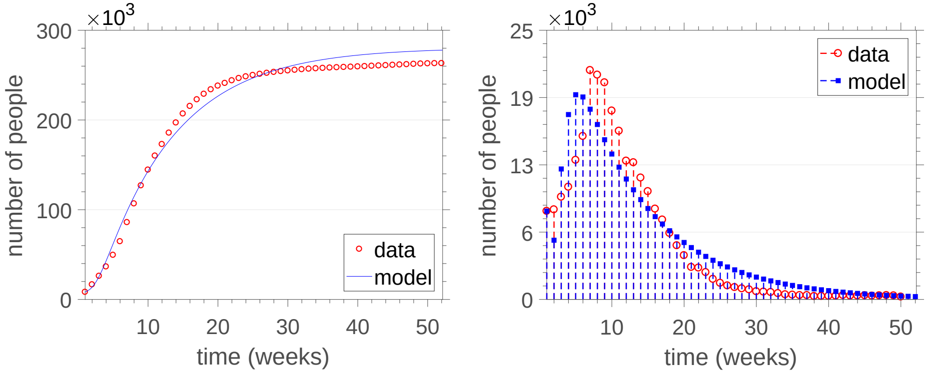


new infectious cases

Remarks on first calibration

- Reasonable parameters
- cumulative number of infectious overshoots data by only 6%
- Peak value of New Cases differs from the data maximum by 7.87%
- Initial infectious humans is approximately 253,360 individuals

Second calibration

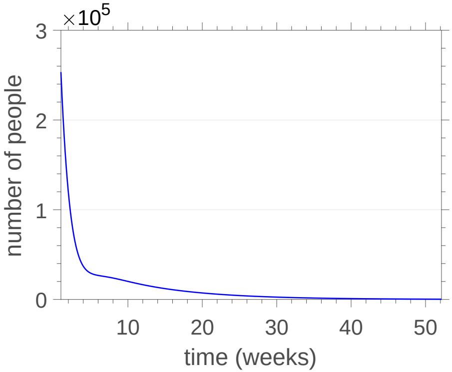


cumulative number of infectious   new infectious cases

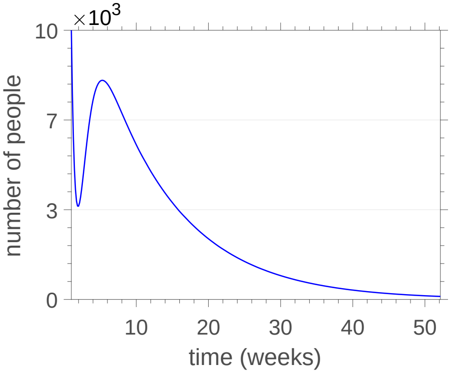
Remarks on second calibration

- Reasonable parameters
- cumulative number of infectious overshoots data by only 5.74%
- Initial infectious humans is approximately 10,000 individuals
- Peak value of new infectious cases differs from the data maximum by 10.57%
- Peak of new infectious cases occurs two weeks before the peak of the data

Comparison of infectious humans curves

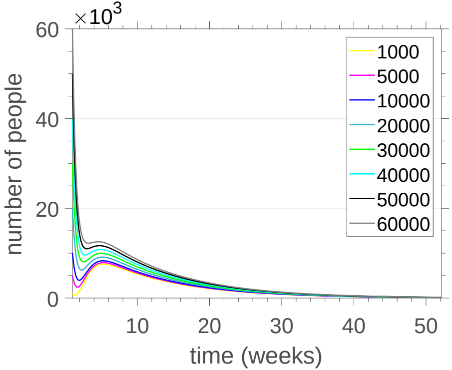


First calibration

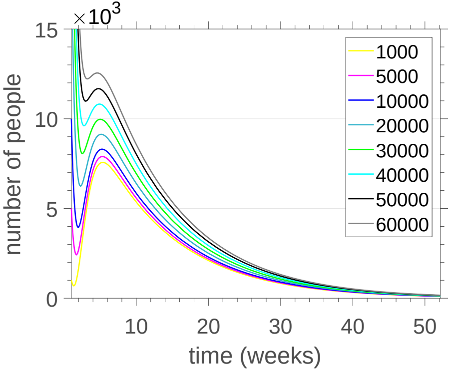


Second calibration

Comparison of infectious humans curves

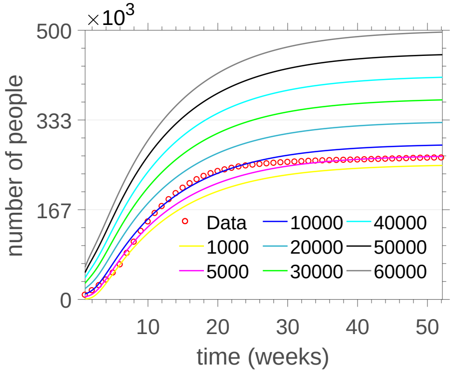


Curves for various initial infectious humans values

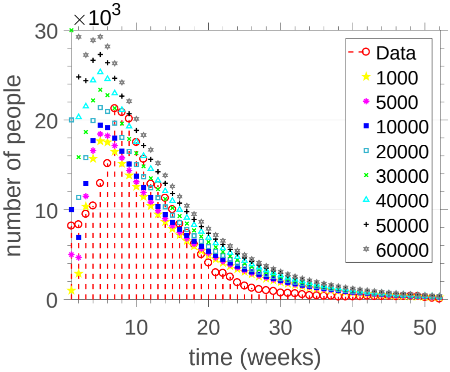


Zoom in the local peak region of the image to the left

Comparison of cumulative and new infectious curves



cumulative number of infectious



new infectious cases

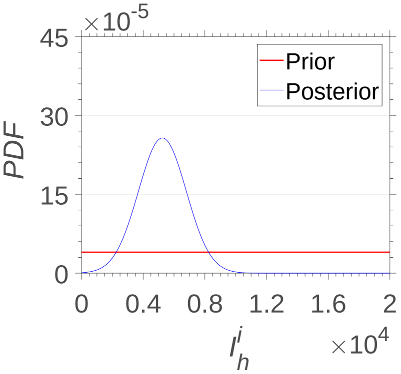
Bayesian updating (ongoing research)

Bayesian formalism for model calibration:

$$\underbrace{\pi(\text{model} \mid \text{data})}_{\textit{posterior}} \propto \underbrace{\pi(\text{data} \mid \text{model})}_{\textit{likelihood}} \times \underbrace{\pi(\text{model})}_{\textit{prior}}$$

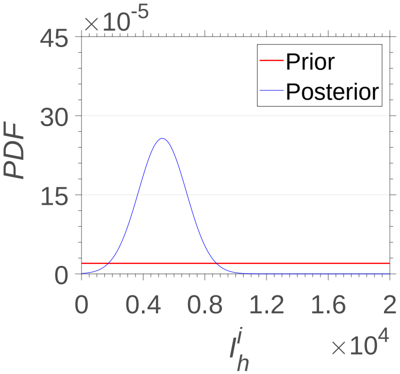
- additive noise hypothesis
- likelihood: Gaussian (MaxEnt principle)
- prior: uniform / gamma

Uniform priors for initial infectious



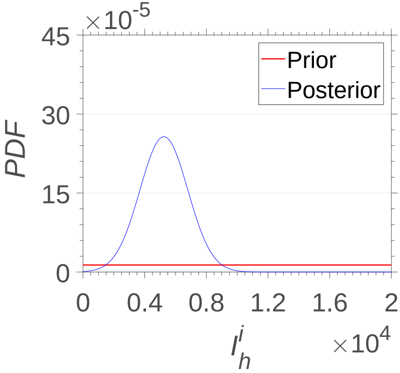
Uniform$(0, 25k)$

Uniform priors for initial infectious



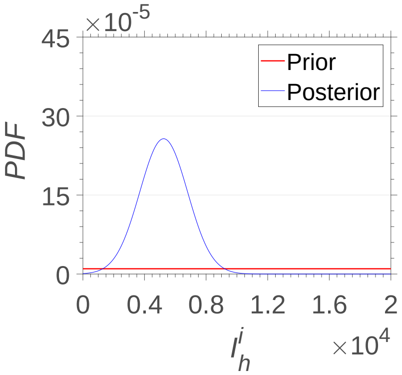
Uniform$(0, 50k)$

Uniform priors for initial infectious



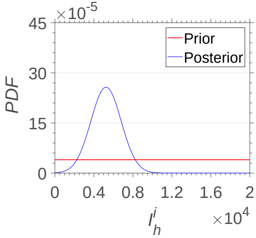
Uniform$(0, 75k)$

Uniform priors for initial infectious

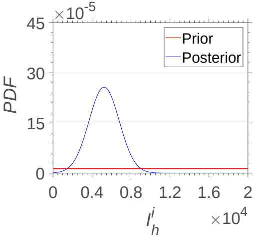


Uniform$(0, 100k)$

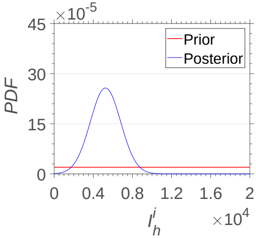
Uniform priors for initial infectious



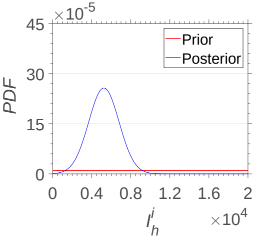
Uniform$(0, 25k)$



Uniform$(0, 75k)$

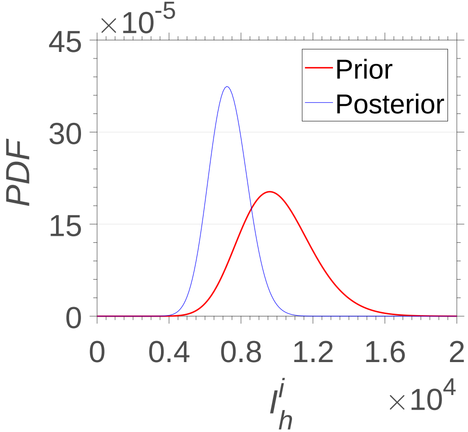


Uniform$(0, 50k)$



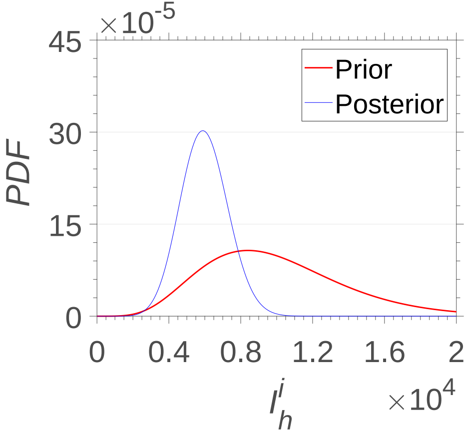
Uniform$(0, 100k)$

Gamma priors for initial infectious



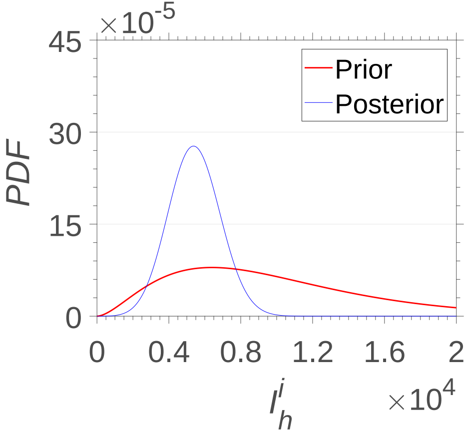
$\delta = 20\%$

Gamma priors for initial infectious



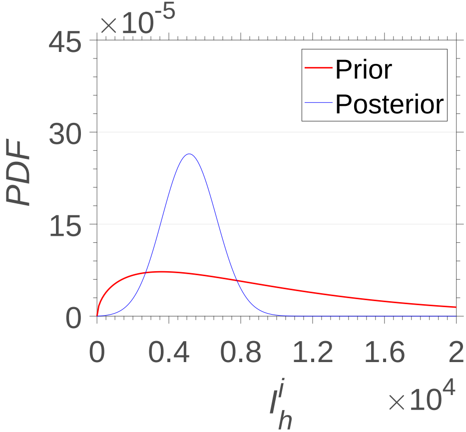
$\delta = 40\%$

Gamma priors for initial infectious



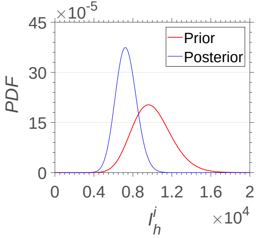
$\delta = 60\%$

Gamma priors for initial infectious

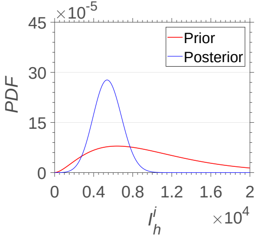


$\delta = 80\%$

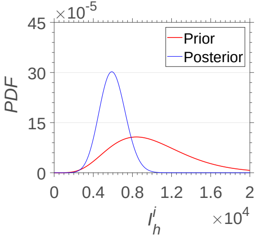
Gamma priors for initial infectious



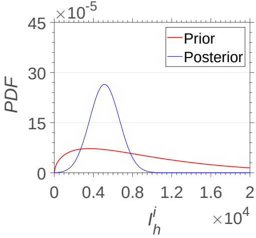
$\delta = 20\%$



$\delta = 60\%$



$\delta = 40\%$

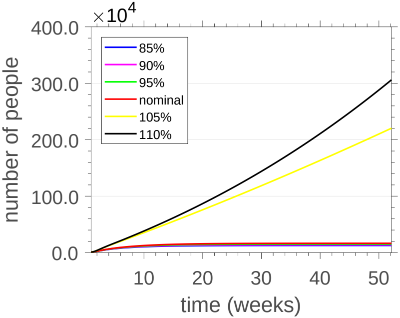


$\delta = 80\%$

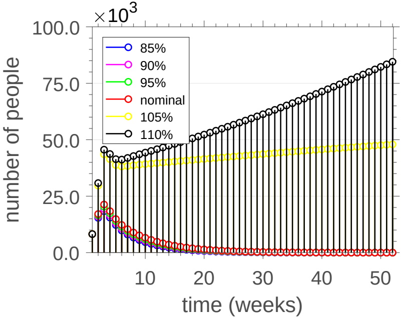
Section 4

Sensitivity Analysis

Sensitivity curves for β_h

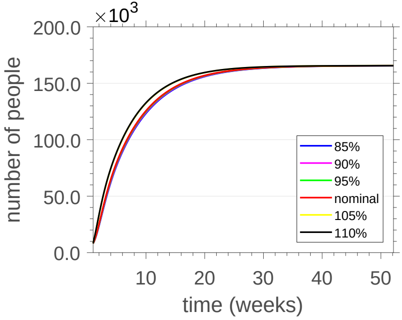


cumulative number of infectious

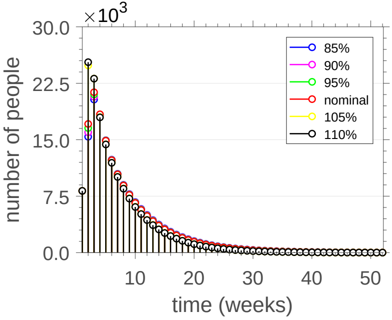


new infectious cases

Sensitivity curves for α_h

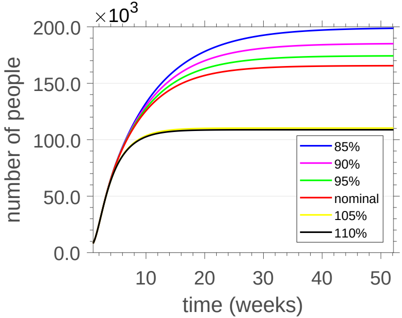


cumulative number of infectious

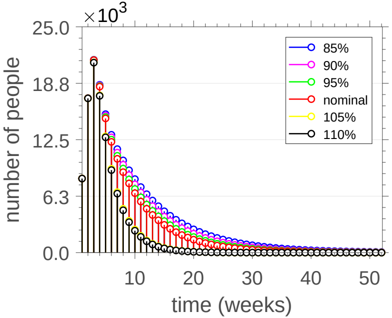


new infectious cases

Sensitivity curves for γ

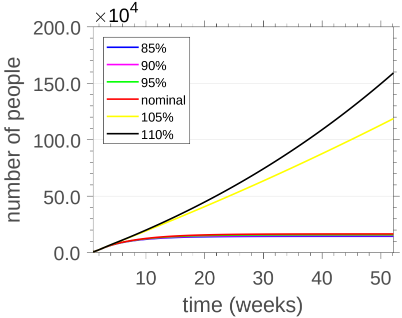


cumulative number of infectious

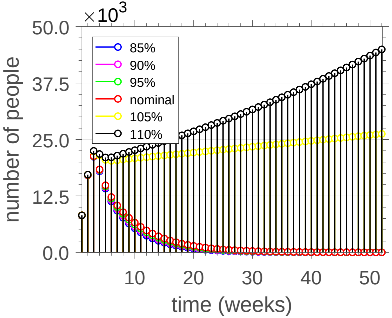


new infectious cases

Sensitivity curves for β_v

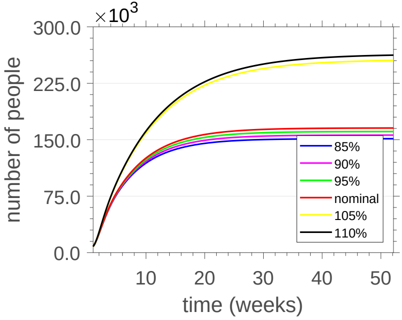


cumulative number of infectious

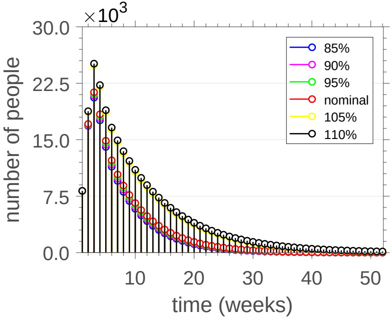


new infectious cases

Sensitivity curves for α_v

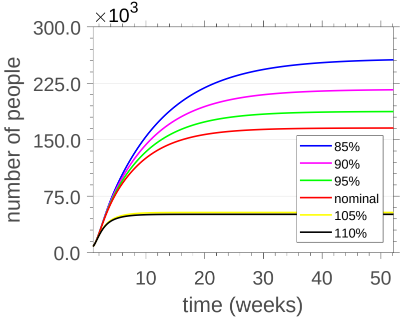


cumulative number of infectious

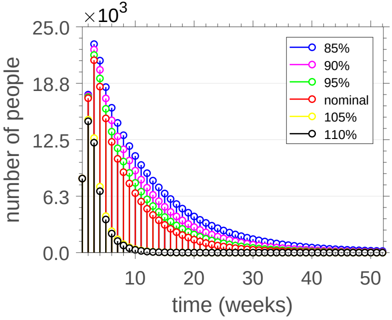


new infectious cases

Sensitivity curves for δ



cumulative number of infectious



new infectious cases

Section 5

Uncertainty Quantification

Uncertainties in the mathematical model

- **model uncertainty** (lack of knowledge of physics)
  $\longrightarrow$ ignored in a first analysis
- **data uncertainty** (model parameters variabilites)
  $\longrightarrow$ parametric probabilistic approach
  $\longrightarrow$ transmition rates β_h and β_v as random variables
  $\longrightarrow$ maximum entropy principle for model construction

C. Soize, *Uncertainty Quantification: An Accelerated Course with Advanced Applications in Computational Engineering*, Springer, 2017.

Maximum Entropy Principle (MaxEnt)

Among all the probability distributions, consistent with the known information about a random parameter, choose the one which corresponds to the maximum of entropy (MaxEnt).

MaxEnt distribution = most unbiased distribution

Entropy of the random variable X is defined as

$$\mathcal{S}\left(p_X\right) = -\int_{\mathbb{R}} p_X(x) \ln\left(p_X(x)\right) dx,$$

"measure for the level of uncertainty"

MaxEnt optimization problem

Maximize

$$\mathcal{S}\left(p_X\right) = -\int_{\mathbb{R}} p_X(x) \ln\left(p_X(x)\right) dx,$$

respecting $N+1$ constraints (known information) given by

$$\int_{\mathbb{R}} g_k\left(X\right) p_X(x)\, dx = m_k, \qquad k = 0, \cdots, N,$$

where the g_k are known real functions, with $g_0(x) = 1$.

MaxEnt optimization problem

Maximize

$$\mathcal{S}\left(p_X\right) = - \int_{\mathbb{R}} p_X(x) \ln\left(p_X(x)\right) dx,$$

respecting $N+1$ constraints (known information) given by

$$\int_{\mathbb{R}} g_k\left(X\right) p_X(x)\, dx = m_k, \qquad k = 0, \cdots, N,$$

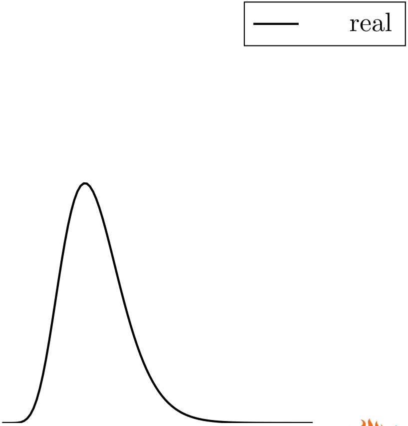
where the g_k are known real functions, with $g_0(x) = 1$.

MaxEnt general solution

$$p_X(x) = \mathbb{1}_{\mathcal{K}}(x) \exp\left(-\lambda_0\right) \exp\left(-\sum_{k=1}^{N} \lambda_k\, g_k(x)\right)$$

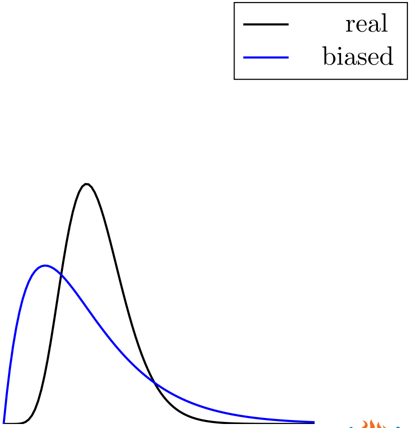
Philosophy of MaxEnt Principle

- The parameter of interest has a unknown distribution



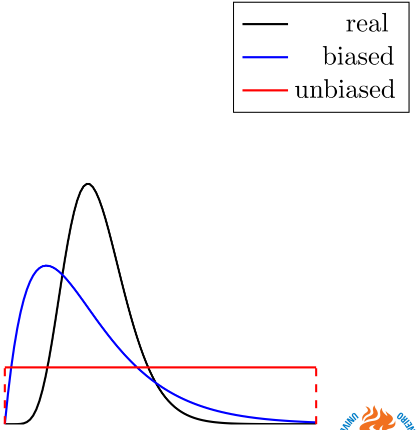
Philosophy of MaxEnt Principle

- The parameter of interest has a unknown distribution
- Distributions arbitrarily chosen can be coarse and biased



Philosophy of MaxEnt Principle

- The parameter of interest has a unknown distribution
- Distributions arbitrarily chosen can be coarse and biased
- A conservative strategy is to use the most unbiased (MaxEnt) distribution



Uncertainty propagation through the model

Monte Carlo Method

pre-processing	**processing**	**post-processing**
generation of scenarios	solution of model equations	computation of statistics
$\boldsymbol{X}_1$ $\vdots$ $\boldsymbol{X}_M$	$\boldsymbol{U} = h(\boldsymbol{X})$	$\boldsymbol{U}_1 = h(\boldsymbol{X}_1)$ $\vdots$ $\boldsymbol{U}_M = h(\boldsymbol{X}_M)$
$\longrightarrow$	$\boxed{\textbf{computational model}}$	$\longrightarrow$
known $F_{\boldsymbol{X}}$		estimated $F_{\boldsymbol{U}}$
generator of random vector $\boldsymbol{X}$	deterministic solver of $\boldsymbol{u} = h(\boldsymbol{x})$	statistical inference to estimate convergence and distribution of $\boldsymbol{U}$

Probabilistic model 1

Random variables: β_h and β_v

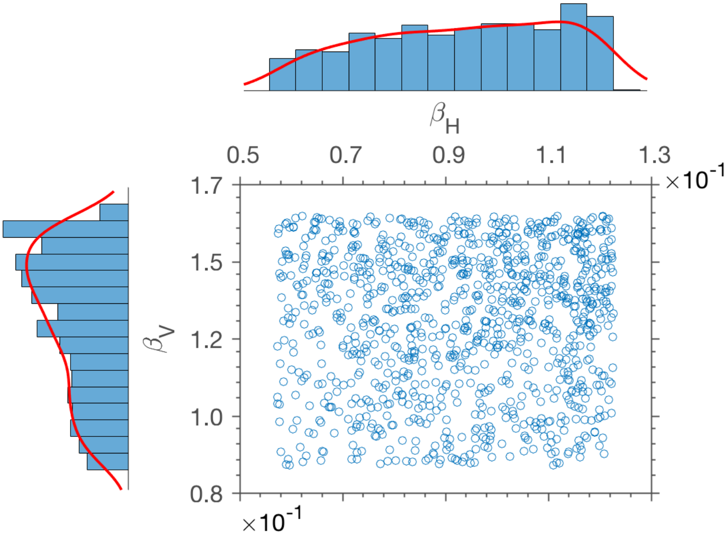
Available information: support and mean (nominal) value

MaxEnt distribution

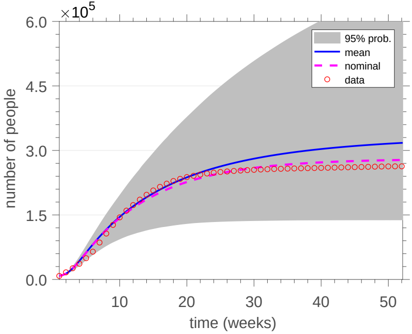
$$p_X(x) = \mathbb{1}_{[a,b]}(x) \, \exp\left(-\lambda_0 - \lambda_1 \, x\right)$$

"truncated exponential (2 parameters)"

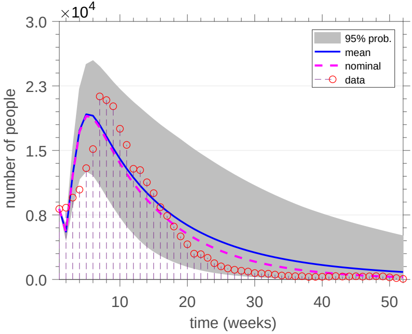
Transmission rates marginal PDFs



Confidence band for the QoIs



cumulative number of infectious



new infectious cases

Probabilistic model 2

Random variables: β_h and β_v

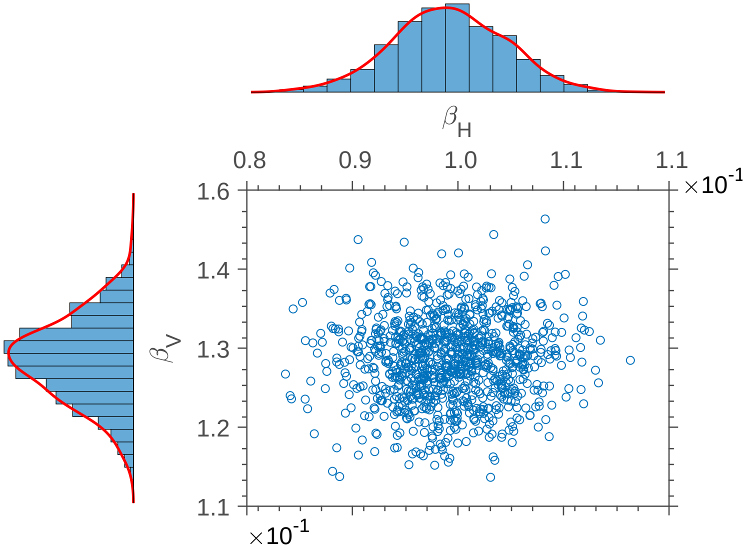
Available information: support, mean (nominal) value and dispersion

MaxEnt distribution

$$p_X(x) = \mathbb{1}_{[a,b]}(x)\, \exp\left(-\lambda_0 - \lambda_1\, x - \lambda_2\, x^2\right)$$

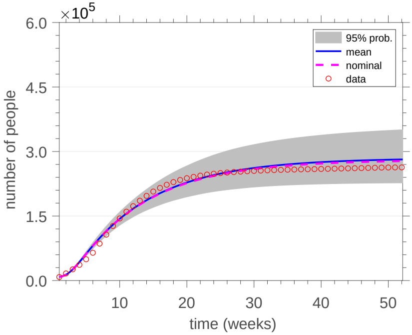
"truncated exponential (3 parameters)"

Transmission rates marginal PDFs

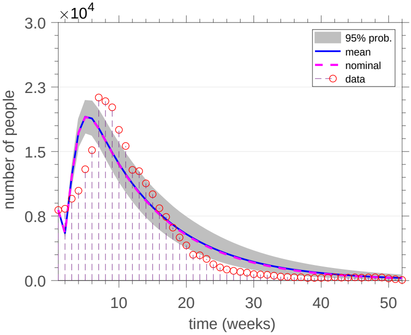


Confidence band for the QoIs

dispersion = 5%



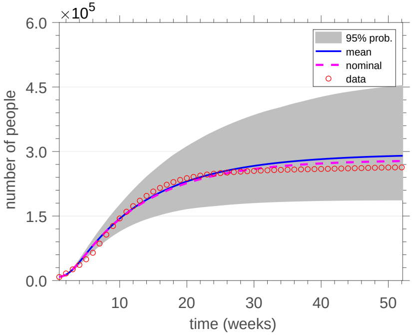
cumulative number of infectious



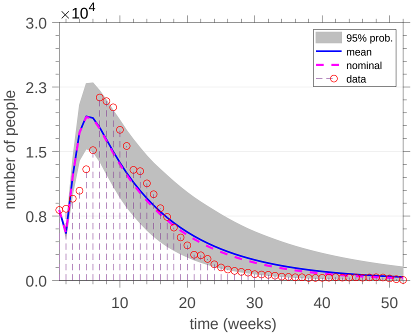
new infectious cases

Confidence band for the QoIs

dispersion = 10%



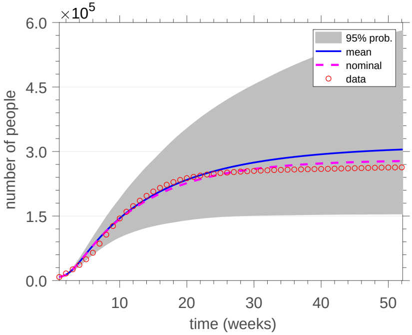
cumulative number of infectious



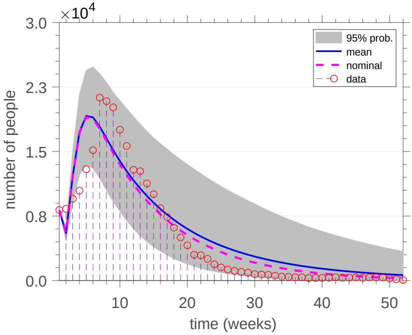
new infectious cases

Confidence band for the QoIs

dispersion = 15%



cumulative number of infectious



new infectious cases

Probabilistic model 3

Random variables: β_h, β_v and δ

Available information for β_h and β_v: support, mean (nominal) value

Distribution for β_h and β_v

$$p_X(x) = \mathbb{1}_{[a,b]}(x)\, \exp\left(-\lambda_0 - \lambda_1\, x - \lambda_2\, x^2\right)$$

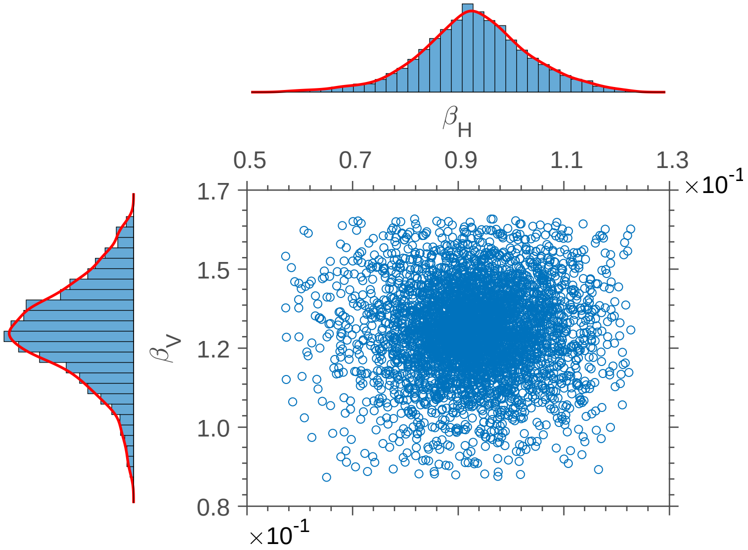
Available information for δ: support

MaxEnt distribution for δ

$$p_X(x) = \mathbb{1}_{[a,b]}(x)\, \frac{1}{b-a}$$

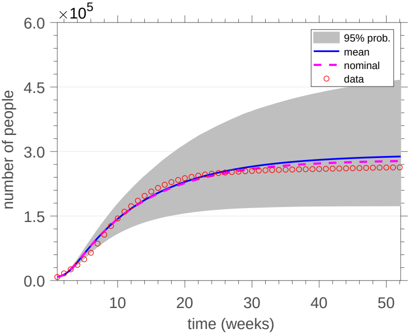
"uniform"

Transmission rates marginal PDFs

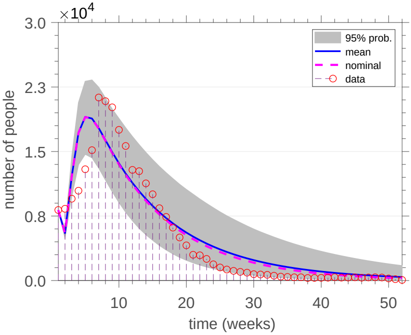


Confidence band for the QoIs

random dispersion



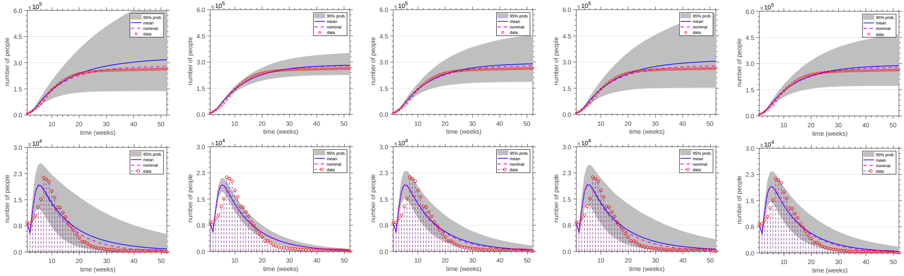
cumulative number of infectious



new infectious cases

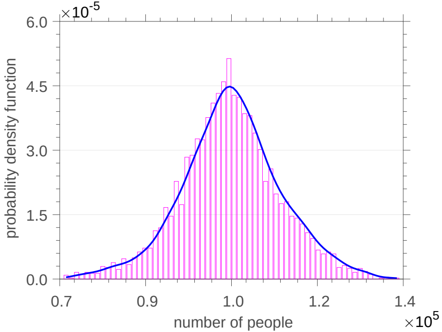
Confidence band for the QoIs

no dispersion | $\delta = 5\%$ | $\delta = 10\%$ | $\delta = 15\%$ | $\Delta \sim U(5\%, 15\%)$



Evolution of QoIs PDFs

Epidemiological Week 13

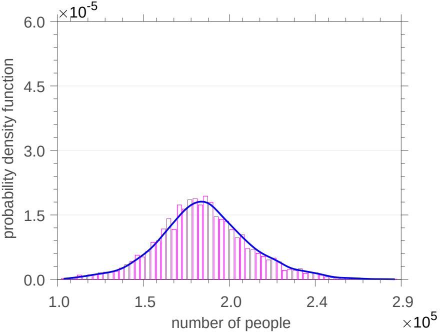


cumulative number of infectious

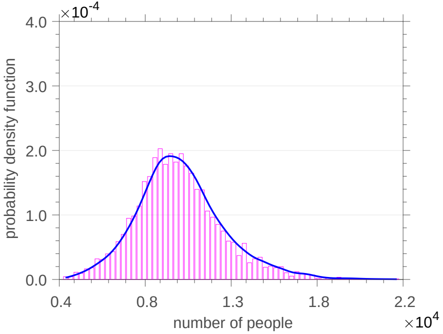
new infectious cases

Evolution of QoIs PDFs

Epidemiological Week 26



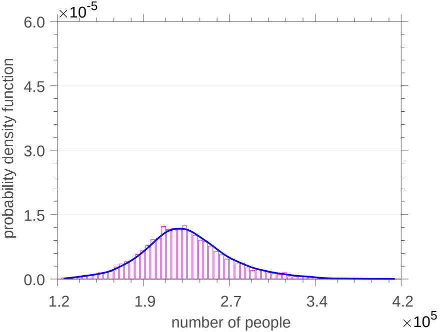
cumulative number of infectious



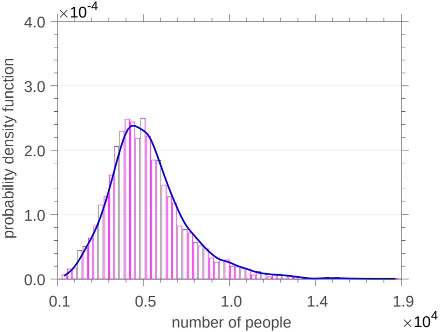
new infectious cases

Evolution of QoIs PDFs

Epidemiological Week 39



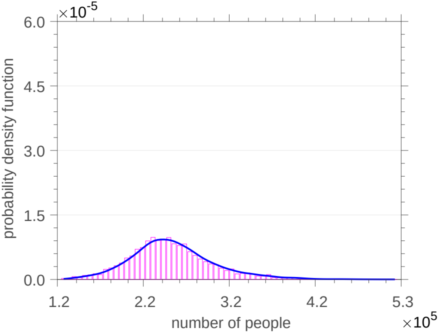
cumulative number of infectious



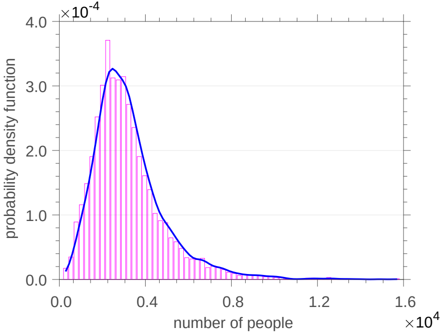
new infectious cases

Evolution of QoIs PDFs

Epidemiological Week 52

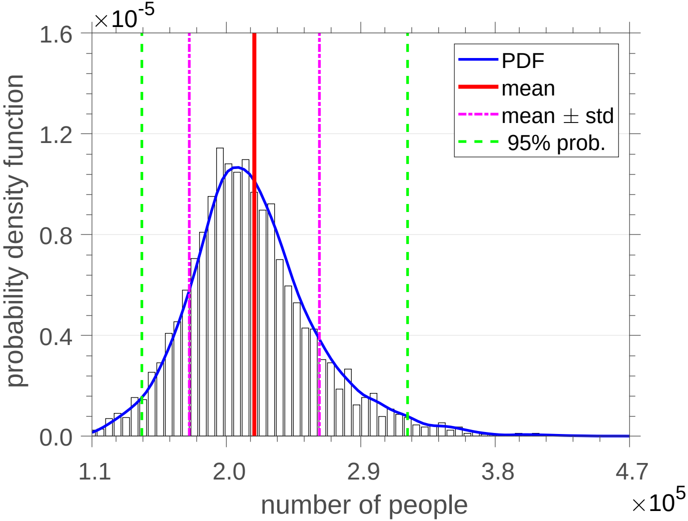


cumulative number of infectious

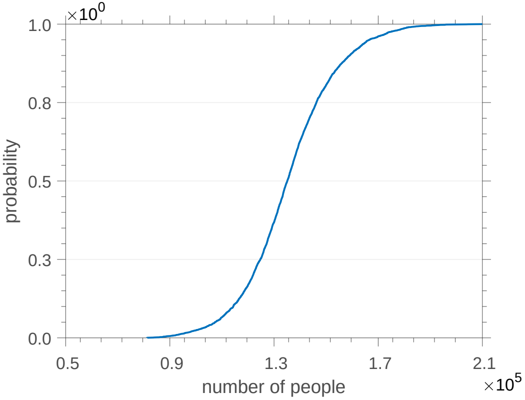


new infectious cases

Time-averaged cumulative infectious



Cumulative infectious CDF until EW 20

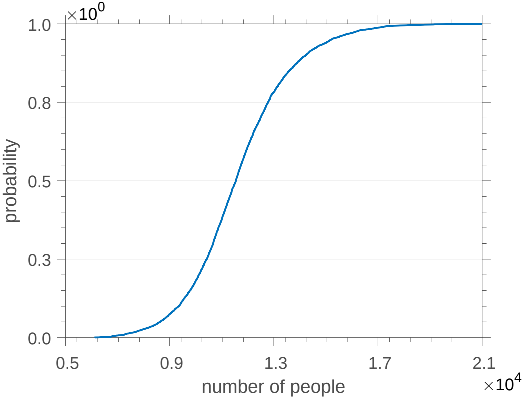


Statistics of C

$$
\begin{aligned}
\text{mean} &= 13{,}480 \\
\text{std. dev.} &= 17{,}451 \\
\text{skewness} &= 0.2471 \\
\text{kurtosis} &= 3.6356 \\
P(C \geq c^*) &= 56.05\%
\end{aligned}
$$

$c^* = 131{,}550$

New cases CDF until 20th EW



Statistics of $\mathcal{N}_w$

$$
\begin{aligned}
\text{mean} &= 11{,}466 \\
\text{std. dev.} &= 1{,}924 \\
\text{skewness} &= 0.4872 \\
\text{kurtosis} &= 3.9084 \\
\mathrm{P}(\mathcal{N}_w \geq N^*) &= 13.43\%
\end{aligned}
$$

$N^* = 13{,}500$

Section 6

Final Remarks

Concluding remarks

Contributions:

- Development of an epidemic model to describe Brazilian outbreak of Zika virus
- Calibration of this model with real epidemic data
- Construction of a parametrric probabilistic model of uncertainties

Ongoing research:

- Bayesian updating to improve the model calibration
- Quantify model discrepancy in a nonparametric way

Future directions:

- Investigate the effectiveness of different control strategies
- Scenarios exploration with active subspace method
- Data-driven identification of epidemiological models

Acknowledgments

Invitation for the minisymposium:

- Profª. Marta Rosales
- Prof. Marcelo Piovan

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CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

UERJ UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO

Thank you for your attention!

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www.americocunha.org

E. Dantas, M. Tosin and A. Cunha Jr,
Calibration of a SEIR–SEI epidemic model to describe Zika virus outbreak in Brazil,
Applied Mathematics and Computation, 338: 249-259, 2018.
https://doi.org/10.1016/j.amc.2018.06.024

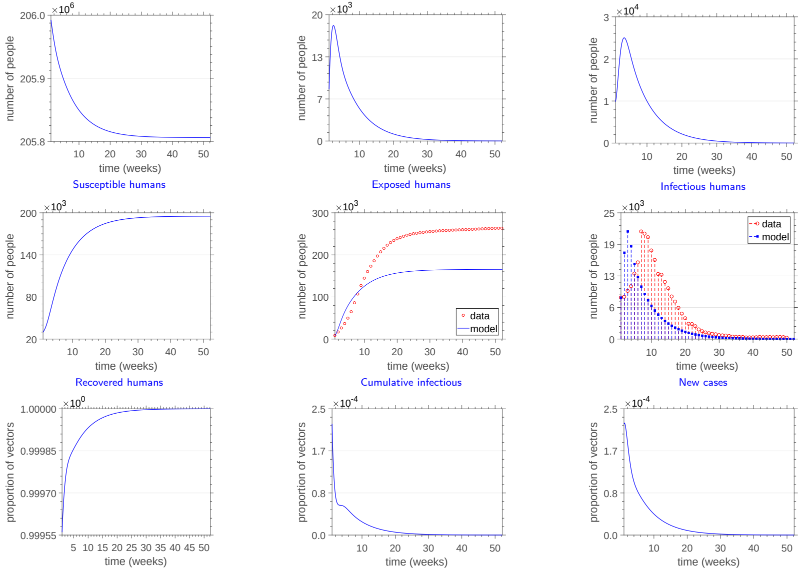
E. Dantas, M. Tosin and A. Cunha Jr,
Uncertainty quantification in the nonlinear dynamics of Zika virus, 2018
(in preparation).

nominal parameters

Nominal parameters and initial conditions

$\boldsymbol{\alpha}$	value	unit
α_h	$1/5.9$	days^{-1}
α_v	$1/9.1$	days^{-1}
γ	$1/7.9$	days^{-1}
δ	$1/11$	days^{-1}
β_h	$1/11.3$	days^{-1}
β_v	$1/8.6$	days^{-1}
N	206×10^6	people
S_h^i	205,953,959	people
E_h^i	8,201	people
I_h^i	8,201	people
R_h^i	29,639	people
S_v^i	0.99956	——
E_v^i	2.2×10^{-4}	——
I_v^i	2.2×10^{-4}	——

Model response with nominal parameters



Susceptible humans

Exposed humans

Infectious humans

Recovered humans

Cumulative infectious

New cases

Susceptible vectors

Exposed vectors

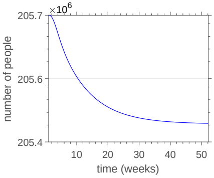
Infectious vectors

first calibration

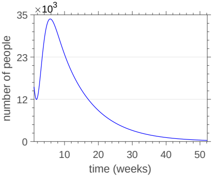
First calibration parameters and initial conditions

α	TRR input	**lb**	**ub**	TRR output
α_h	$1/5.9$	$1/12$	$1/3$	$1/12$
α_v	$1/9.1$	$1/10$	$1/5$	$1/10$
γ	$1/7.9$	$1/8.8$	$1/3$	$1/8.8$
δ	$1/11$	$1/21$	$1/11$	$1/16.86$
β_h	$1/11.3$	$1/16.3$	$1/8$	$1/16.3$
β_v	$1/8.6$	$1/11.6$	$1/6.2$	$1/11.6$
S_h^i	205,953,959	$0.9 \times \mathrm{N}$	N	205,700,000
E_h^i	8,201	0	N	15,089
I_h^i	8,201	0	N	253,360
S_v^i	0.99956	0.99	0.999	0.99
E_v^i	2.2×10^{-4}	0	1	0
I_v^i	2.2×10^{-4}	0	1	0

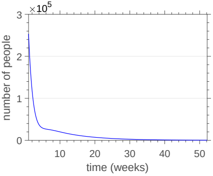
Model response for first calibration



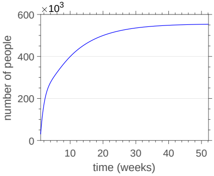
Susceptible humans



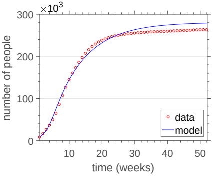
Exposed humans



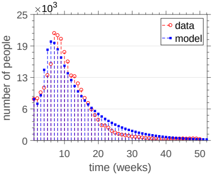
Infectious humans



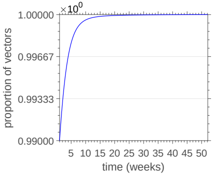
Recovered humans



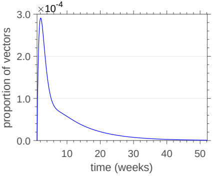
Cumulative infectious



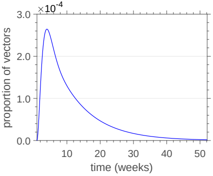
New cases



Susceptible vectors



Exposed vectors



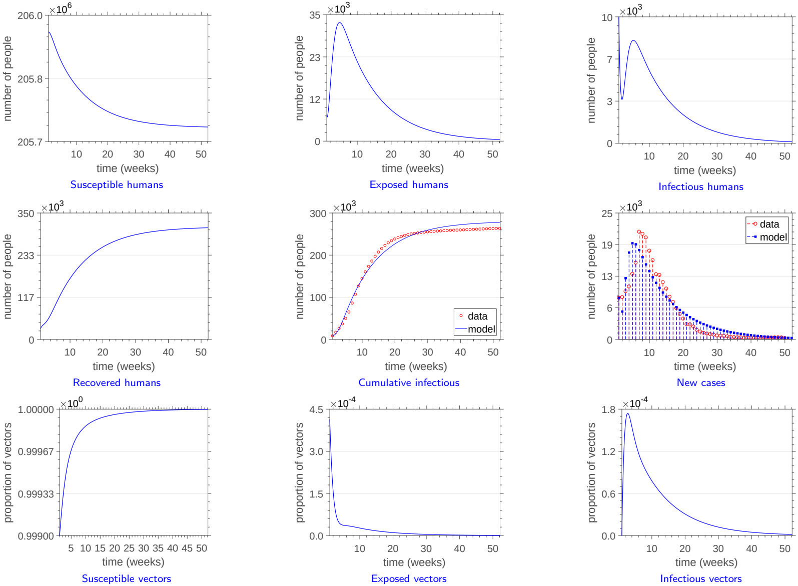
Infectious vectors

second calibration

Second calibration parameters and initial conditions

α	TRR input	**lb**	**ub**	TRR output
α_h	$1/5.9$	$1/12$	$1/3$	$1/12$
α_v	$1/9.1$	$1/10$	$1/5$	$1/10$
γ	$1/7.9$	$1/8.8$	$1/3$	$1/3$
δ	$1/11$	$1/21$	$1/11$	$1/21$
β_h	$1/11.3$	$1/16.3$	$1/8$	$1/10.40$
β_v	$1/8.6$	$1/11.6$	$1/6.2$	$1/7.77$
S_h^i	205,953,959	$0.9 \times \mathrm{N}$	N	205,953,534
E_h^i	8,201	0	10,000	6,827
I_h^i	8,201	0	10,000	10,000
S_v^i	0.9996	0.99	0.999	0.999
E_v^i	2.2×10^{-4}	0	1	4.14×10^{-4}
I_v^i	2.2×10^{-4}	0	1	0

Model response for second calibration



Monte Carlo convergence

Study of convergence for MC simulation

Stochastic dynamic model:

$$\dot{\boldsymbol{U}}(t,\omega) = f(\boldsymbol{U}(\omega,t))$$

Convergence metric for of Monte Carlo simulation:

$$\mathtt{conv}(n_s) = \left(\frac{1}{n_s} \sum_{n=1}^{n_s} \int_{t_0}^{t_f} \parallel \boldsymbol{U}(t,\omega_n) \parallel^2 \; dt \right)^{1/2}$$

C. Soize, *A comprehensive overview of a non-parametric probabilistic approach of model uncertainties for predictive models in structural dynamics.* **Journal of Sound and Vibration**, 288: 623–652, 2005.

Study of convergence for MC simulation

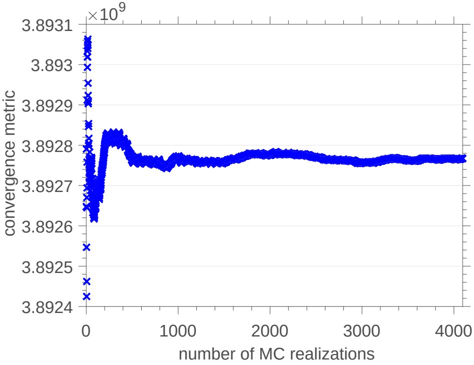


Figure: MC convergence metric as function of the number of realizations.

references

References from images and data

- Zika Virus 3D Model by *visual-science. com* at goo.gl/CwHe6v
- Hi-resolution female Aedes aegypti mosquito by *CDC* at goo.gl/WxWrjz
- World Map of Areas with Risk of Zika, March 2018, by *CDC* at bit.ly/2uTsalT
- Dengue Virus 3D Model by *hhmi. org* at goo.gl/6MvNMP
- Aedes aegypti mosquito by *denguevirusnet. com* at goo.gl/gHXoSA
- New Cases data in Brazi/2016 by *Secretaria de Vigilância em Saúde* at bit.ly/2LxMZ0i