Dynamics of Zika Virus in Brazil

Model Calibration and Uncertainty Quantification

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numerico.ime.uerj.br

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Rio de Janeiro - RJ, Brazil

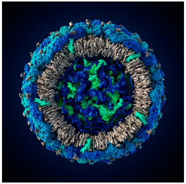
Outline

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 130,000 confirmed cases in Brazil since 2015
- International consensus that ZIKV is a cause of:
  - Guillain–Barré syndrome
  - Microcephaly

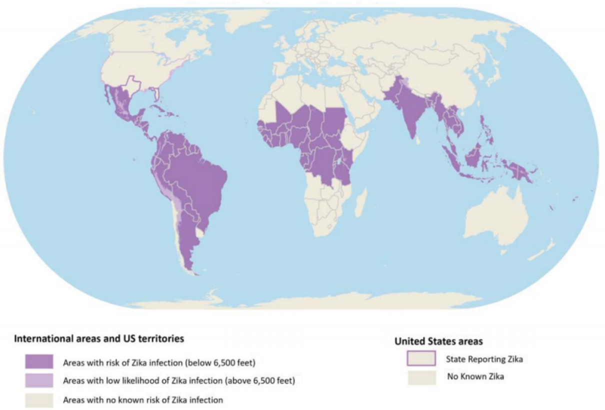


Zika virus

Aedes aegypti

Global outbreak of Zika virus

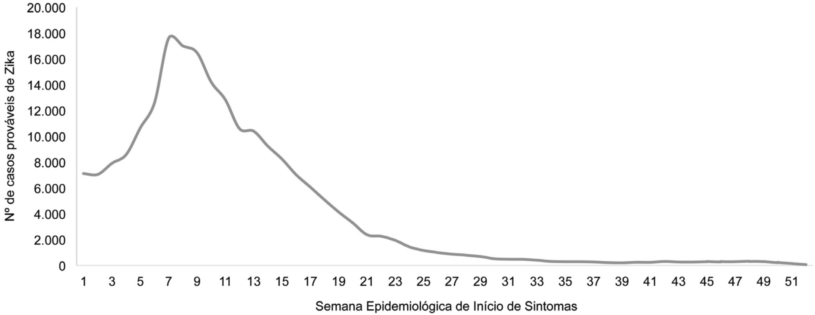
World Map of Areas with Risk of Zika



Centers for Disease Control and Prevention, *World Map of Areas with Risk of Zika, August 2017.*

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)

- Mainly spread by *Aedes* mosquitoes as well as Zika virus
- More than 219,000 probable cases reported in Brazil until Epidemiological Week 35 of 2017
- 310 confirmed deaths until EW 35 of 2017 or in investigation

Dengue virus

Aedes aegypti

Research objectives

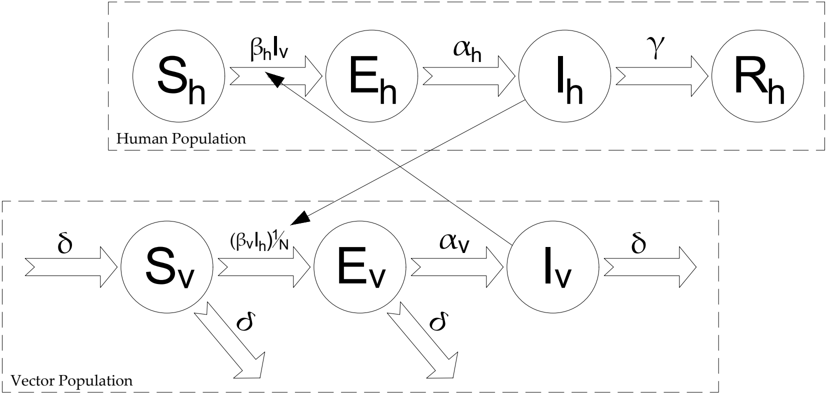
The objectives of this research are:

- Develop an epidemic model to describe the Zika virus outbreak of 2016 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

SEIR-SEI 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.**

Dynamic system associated to the SEIR-SEI model

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = -\beta_h\, S_h\, I_v$$

$$\frac{\mathrm{d}E_h}{\mathrm{d}t} = \beta_h\, S_h\, I_v - \alpha_h\, E_h$$

$$\frac{\mathrm{d}I_h}{\mathrm{d}t} = \alpha_h\, E_h - \gamma\, I_h$$

$$\frac{\mathrm{d}R_h}{\mathrm{d}t} = \gamma\, I_h$$

$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = \delta - \beta_v\, S_v\, \frac{I_h}{N} - \delta\, S_v$$

$$\frac{\mathrm{d}E_v}{\mathrm{d}t} = \beta_v\, S_v\, \frac{I_h}{N} - (\delta + \alpha_v)\, E_v$$

$$\frac{\mathrm{d}I_v}{\mathrm{d}t} = \alpha_v\, E_v - \delta\, I_v$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \alpha_h\, E_h$$

\+ 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.**

SEIR-SEI model parameters

Model parameters and outbreak data are obtained from:

- open scientific literature

- Brazilian health system

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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

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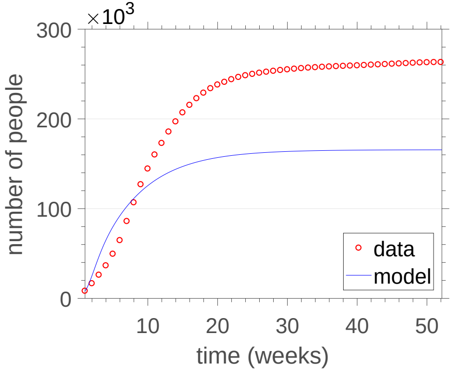
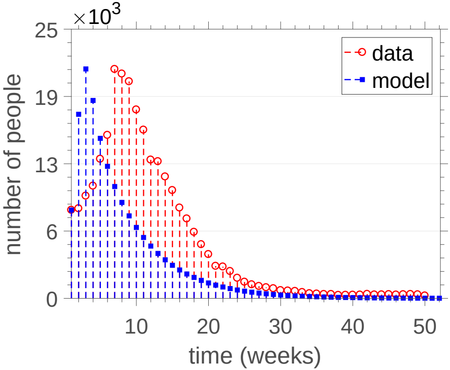
Cumulative infectious and new infectious

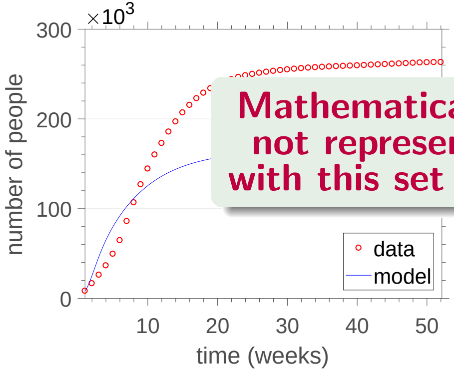


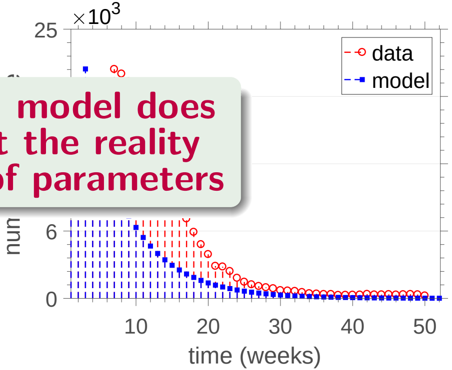
Cumulative number of infectious



New infectious cases

Cumulative infectious and new infectious





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

Cumulative number of infectious

New infectious cases

Section 3

V&V and Calibration

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

Verification and Validation (V&V)

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- Validation
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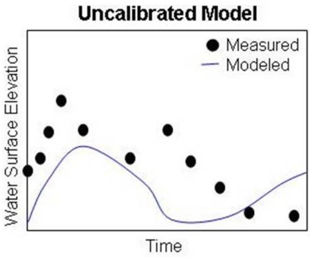
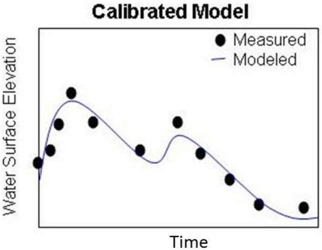
  It is an exercise in *physics*.

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

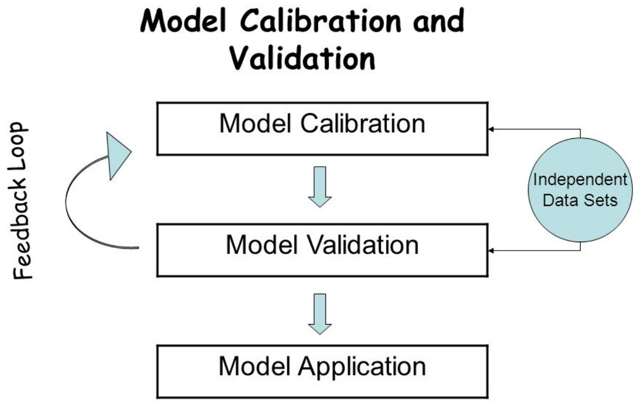
Calibration of the model





* Pictures from *Introduction to stormwater modeling*, Minnesota Stormwater Manual

Calibration vs Validation



* Picture from *NHI course on Travel Demand Forecasting*

Forward and inverse problem for SEIR-SEI dynamic system

Forward Problem

Mathematical Model

IC and Parameters

$\boldsymbol{\alpha} = (\mathbf{x}_0, \mathbf{p})$

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{p})$$

$$\mathbf{x}(t_0) = \mathbf{x}_0$$

Model Observable

$\phi(\boldsymbol{\alpha}, t)$

$\boldsymbol{\alpha}^*$

Fitting IC and Parameters

$y_1, y_2, \ldots, y_M$

Field Observations

Inverse Problem

An inverse problem for SEIR-SEI model calibration

Given a collection of field data

$$\mathbf{y}_1, \; \mathbf{y}_2, \; \cdots, \; \mathbf{y}_M,$$

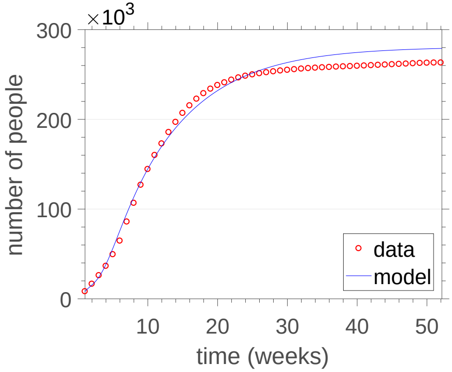
find a set of fitting parameters and initial conditions such that

$$\boldsymbol{\alpha}^* = \arg\min_{\boldsymbol{\alpha}} \left\{ \sum_{n=1}^{M} \left| y_n - \phi\left(\boldsymbol{\alpha}, t_n\right) \right|_2^2 \right\}.$$

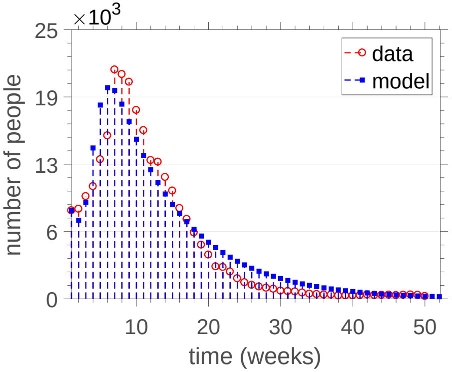
Solved using a bounded trust-region-reflective algorithm.

Coleman, T.F., and Li, Y., *An Interior Trust Region Approach for Nonlinear Minimization Subject to Bounds.* **SIAM Journal on Optimization, 6:418–445, 1996.**

Cumulative infectious and new infectious



Cumulative number of infectious



New infectious cases

First calibration

First calibration skills

- Reasonable parameters
- Cumulative number of infectious overshoots data by only 6%
- Peak value of New Cases differs from the data maximum by 7.87%
- Human IC sum differ 9.82% from the total population

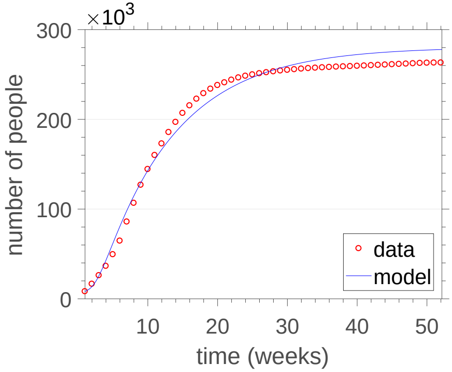
$$S_h^i + E_h^i + I_h^i + R_h^i \neq N$$

- Vector IC sum to 0.99

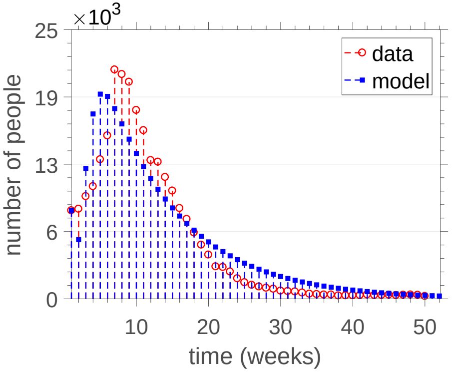
$$|S_h^i + E_h^i + I_h^i - 1| > \texttt{tol}$$

- Initial infectious humans is approximately 253,360 individuals

Cumulative infectious and new infectious



Cumulative number of infectious



New infectious cases

Second calibration

Second calibration skills

- Reasonable parameters
- Cumulative number of infectious overshoots data by only 5.74%
- Vector IC sum to 0.999

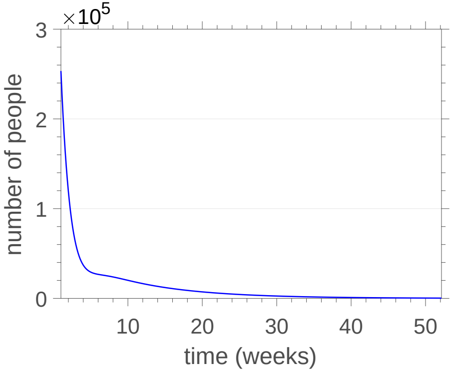
$$|S_h^i + E_h^i + I_h^i - 1| < \texttt{tol}$$

- Initial infectious humans is approximately 10,000 individuals
- Human IC sum is equal to total population

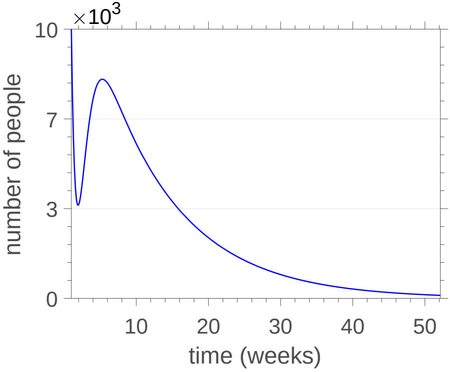
$$S_h^i + E_h^i + I_h^i + R_h^i = N$$

- 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

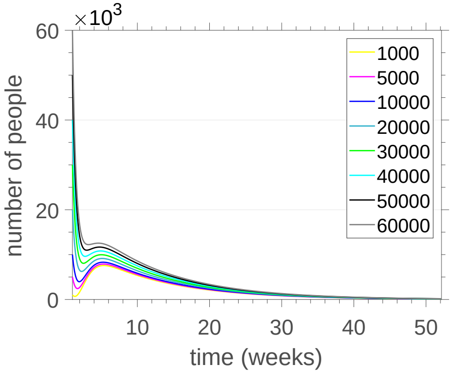


First calibration

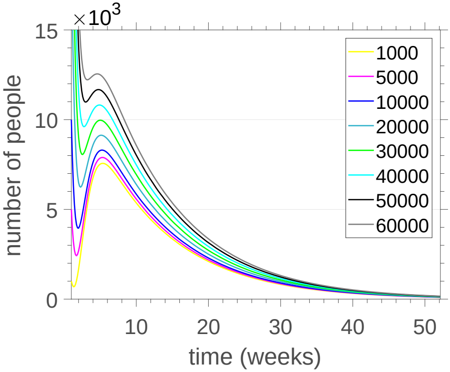


Second calibration

Comparison of infectious humans curves

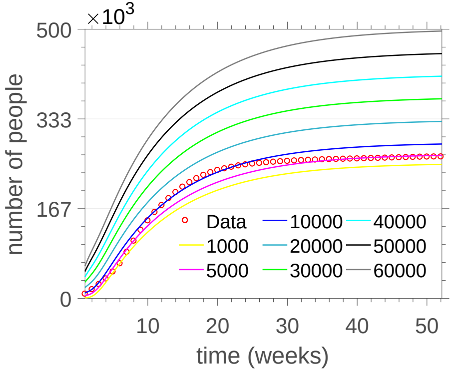


Curves for various initial infectious humans values

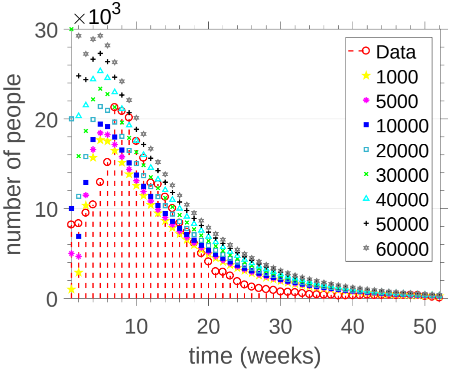


Zoom in the local peak region of the image to the left

Comparison of comulative and new infectious curves



Cumulative number of infectious

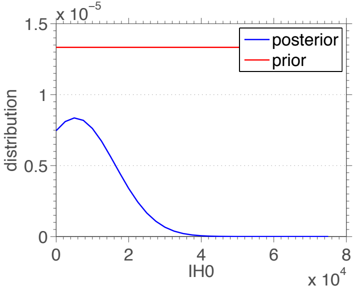


New infectious cases

Ongoing research: Bayesian updating

Bayesian formalism for model calibration:

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



uniform prior

Section 4

Uncertainty Quantification

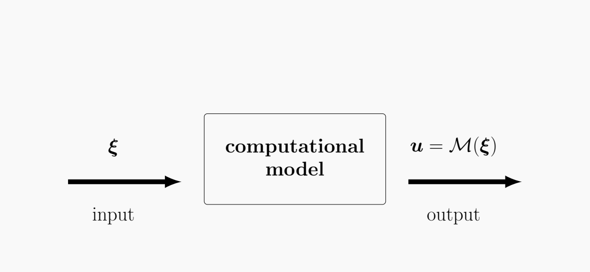
Uncertainties in the mathematical model

The mathematical model is subjected to uncertainties:

- **model uncertainty**
  - due to lack of knowledge of physics
  - ignored in a first analysis
- **data uncertainty**
  - due to model parameters variabilites
  - initial infected humans
    (most pronounced)

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

Computation under uncertainty



1. Data Representation: characterize inputs uncertainties
2. Uncertainty Propagation: quantify output uncertainties
3. Certification: establish acceptable levels of uncertainty

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

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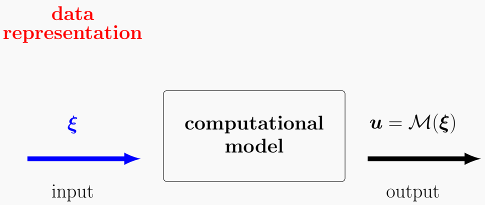

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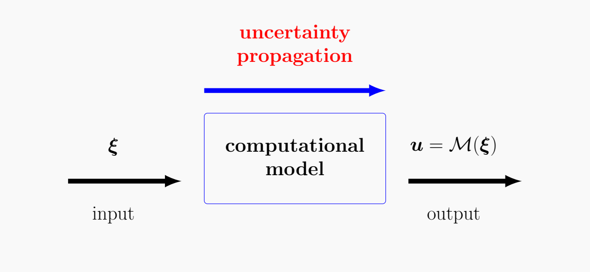

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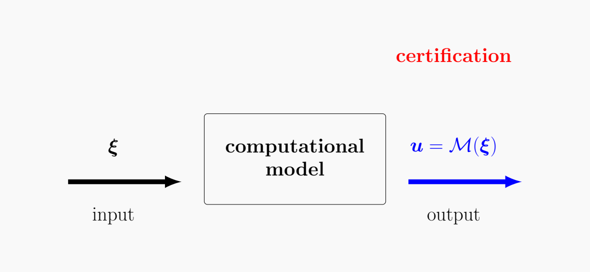

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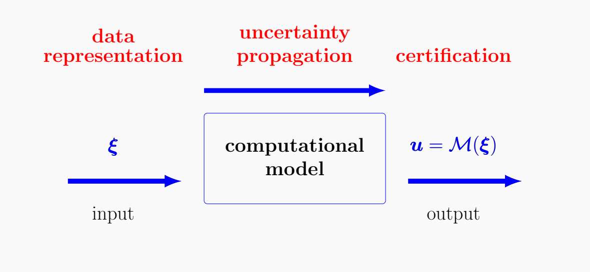

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Construction of a stochastic model

Parametric probabilistic approach: $(\Omega, \Sigma, \mathcal{P})$

- initial infected humans I_{h0} is a random variable

$$\omega \in \Sigma \mapsto X(\omega) \in \mathbb{R}$$

- model response is a random process

$$(\omega, t) \in \Sigma \times \mathcal{T} \mapsto \boldsymbol{U}(\omega, t) \in \mathbb{R}^8$$

- model response is function of model parameter

$$\boldsymbol{U} = h(X)$$

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

Known information about X:

$$\mathrm{Supp}\, p_X = [a, b] \subset [0, +\infty) \implies \int_a^b p_X(x)\, dx = 1$$

Constrained optimization problem:

Maximize

$$\mathcal{S}\left(p_X\right) = -\int_a^b p_X(x) \ln\left(p_X(x)\right) dx,$$

such that

$$\int_a^b p_X(x)\, dx = 1.$$

MaxEnt optimization problem

Lagrangian:

$$\mathcal{L}\left(p_X, \lambda_0\right) = -\int_{x=a}^{b} p_X(x)\, \ln\left(p_X(x)\right) dx - (\lambda_0 - 1)\left(\int_{a}^{b} p_X(x)\, dx - 1\right)$$

MaxEnt optimization problem

Lagrangian:

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Necessary conditions for an extreme:

$$\frac{\partial \mathcal{L}}{\partial p_X}\left(p_X, \lambda_0\right) = 0$$

and

$$\frac{\partial \mathcal{L}}{\partial \lambda_0}\left(p_X, \lambda_0\right) = 0$$

MaxEnt optimization problem

$$\frac{\partial \mathcal{L}}{\partial p_X}(p_X, \lambda_0) = 0 \quad \Longrightarrow \quad p_X(x) = \mathbb{1}_{[a,b]}(x)\, e^{-\lambda_0}$$

$$\frac{\partial \mathcal{L}}{\partial \lambda_0}(p_X, \lambda_0) = 0 \quad \Longrightarrow \quad \int_{x=a}^{b} p_X(x)\, dx = 1$$

MaxEnt optimization problem

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Hence,

$$\int_{x=a}^{b} \mathbb{1}_{[a,b]}(x)\, e^{-\lambda_0}\, dx = 1 \quad \Longrightarrow \quad e^{-\lambda_0} = \frac{1}{b-a},$$

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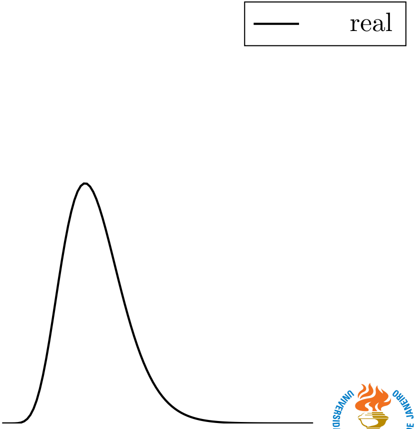
so that

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

X has uniform distribution on $[a, b]$.

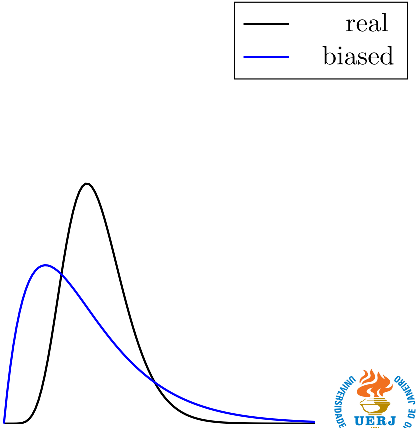
Philosophy of MaxEnt Principle

- The parameter of interest has a unknown distribution



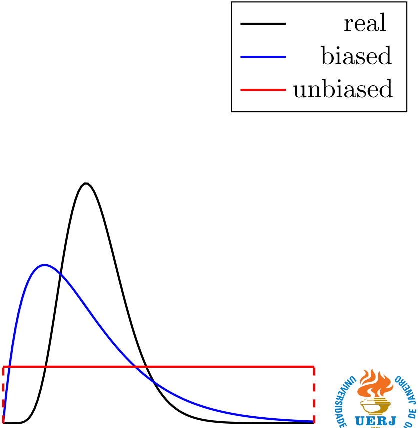
Philosophy of MaxEnt Principle

- 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
$\boldsymbol{X}_1$	$\boldsymbol{U} = h(\boldsymbol{X})$	$\boldsymbol{U}_1 = h(\boldsymbol{X}_1)$
$\vdots$		$\vdots$
$\boldsymbol{X}_M$	**computational model**	$\boldsymbol{U}_M = h(\boldsymbol{X}_M)$
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 $\boldsymbol{U}$

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:

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

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

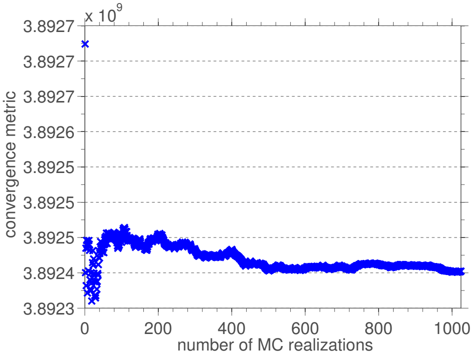
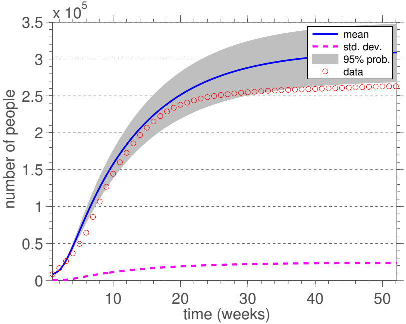


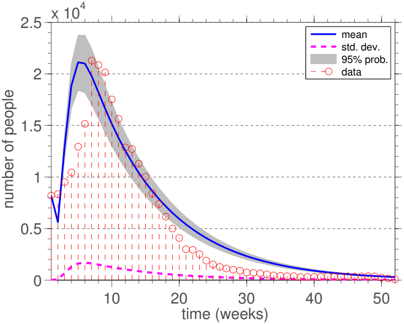
Figure: MC convergence metric as function of the number of realizations.

Cumulative and new infectious confidence band

$$X \sim Uniform(0, 75) \times 10^3$$



Cumulative number of infectious



New infectious cases

Section 5

Final Remarks

Concluding remarks

Contributions and conclusions:

- Development of a SEIR-SEI epidemic model to describe Zika virus outbreak in Brazil
- Calibration of this SEIR-SEI model with epidemic real data
- Construction of a probabilistic model to describe uncertainties

Ongoing research:

- Bayesian updating to improve the model calibration
- Describe model and other parameters uncertainties

Future directions:

- Design of experiments via Active Subspace
- Data-driven identification of epidemiological models

Acknowledgments

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CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

Uncertainties 2018

http://icvramisuma2018.org

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*, 2017 (under review).

Number of new cases of infectious per epidemiological week

Number of new cases per week

A set of 52 points to represent the number of new infectious cases of Zika fever at each week is defined as follows:

$$\mathcal{N}_w = C_w - C_{w-1} \,,$$
$$\mathcal{N}_1 = C_1 \,,$$

where C_w is the cumulative number of infectious humans in the wth epidemiological week.

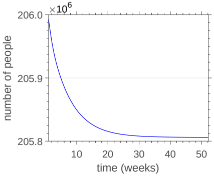
Nominal parameters and initial conditions

Nominal parameters and initial conditions

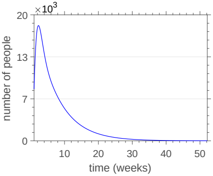
$\boldsymbol{\alpha}$	value	unit
α_h	$1/5.9$	days^{-1}
α_v	$1/9.1$	days^{-1}
γ	$1/7.9$	days^{-1}
δ	$1/11$	days^{-1}
β_h	$1/11.3$	days^{-1}
β_v	$1/8.6$	days^{-1}
N	206×10^6	people
S_h^i	205,953,959	people
E_h^i	8,201	people
I_h^i	8,201	people
R_h^i	29,639	people
S_v^i	0.99956	——
E_v^i	2.2×10^{-4}	——
I_v^i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

Curves for nominal inputs

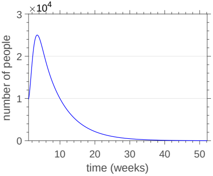
Curves for nominal inputs



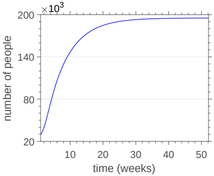
Susceptible humans



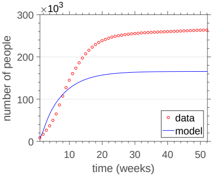
Exposed humans



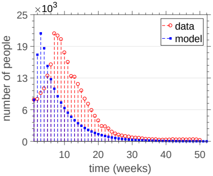
Infectious humans



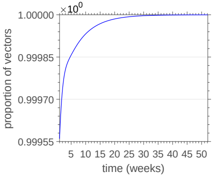
Recovered humans



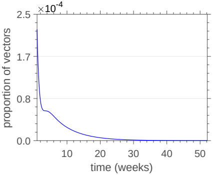
Cumulative infectious



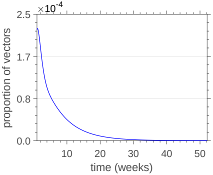
New cases



Susceptible vectors



Exposed vectors



Infectious vectors

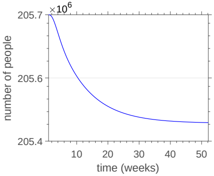
First calibration parameters and initial conditions

First calibration parameters and IC

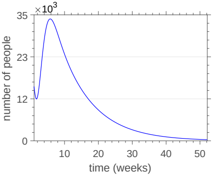
α	TRR input	**lb**	**ub**	TRR output
α_h	$1/5.9$	$1/12$	$1/3$	$1/12$
α_v	$1/9.1$	$1/10$	$1/5$	$1/10$
γ	$1/7.9$	$1/8.8$	$1/3$	$1/8.8$
δ	$1/11$	$1/21$	$1/11$	$1/16.86$
β_h	$1/11.3$	$1/16.3$	$1/8$	$1/16.3$
β_v	$1/8.6$	$1/11.6$	$1/6.2$	$1/11.6$
S_h^i	205,953,959	$0.9 \times \mathrm{N}$	N	205,700,000
E_h^i	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

Curves for first calibration inputs

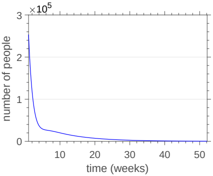
Curves for first calibration inputs



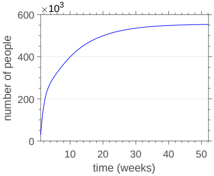
Susceptible humans



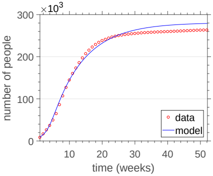
Exposed humans



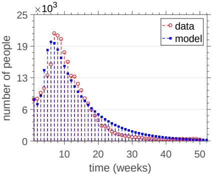
Infectious humans



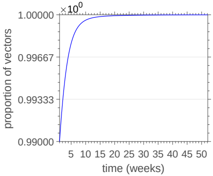
Recovered humans



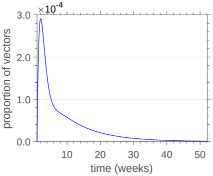
Cumulative infectious



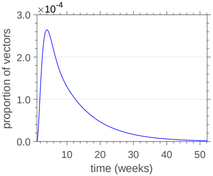
New cases



Susceptible vectors



Exposed vectors



Infectious vectors

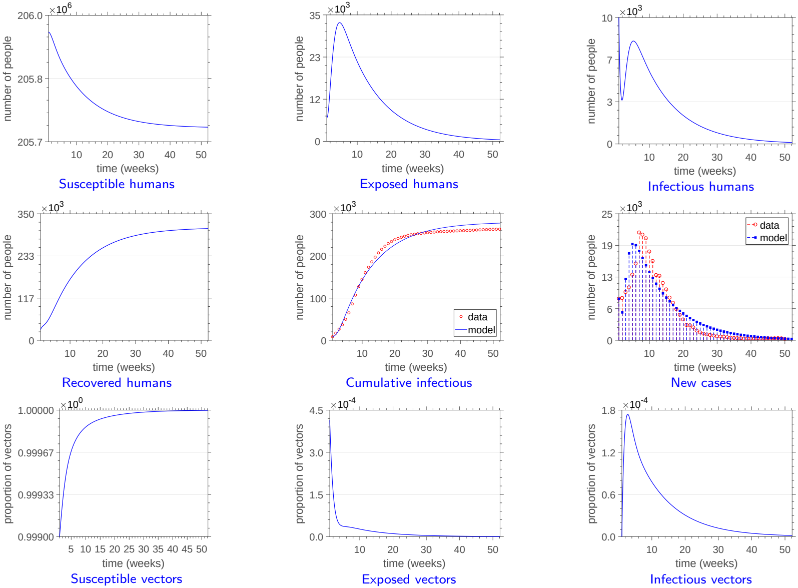
Second calibration parameters and initial conditions

Second calibration parameters and IC

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

Curves for second calibration inputs

Curves for first second inputs



References from images and data

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, April 2017, by *CDC* at goo.gl/5U6pdL
- Zika 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 goo.gl/JbLzWL