A SEIR-SEI model calibration for the Zika virus epidemic in Brazil

Americo Cunha Jr

Universidade do Estado do Rio de Janeiro — UERJ
NUMERICO – **Nu**cleus of **M**odeling and **E**xper**i**mentation with **Co**mputers
http://numerico.ime.uerj.br

In collaboration with: Eber Dantas (UERJ)
Michel Tosin (UERJ)

ICVRAM-ISUMA
UNCERTAINTIES
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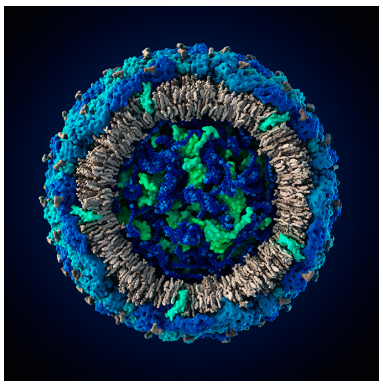
Outline

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

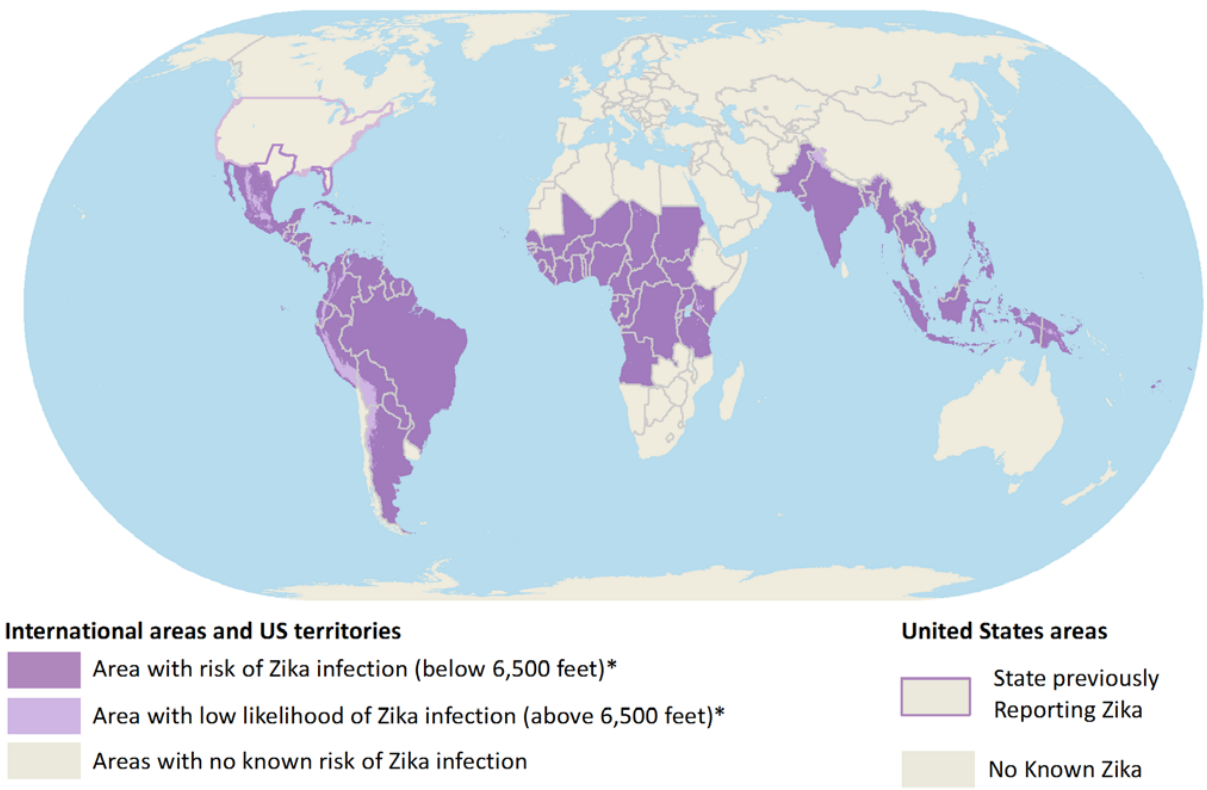


Zika virus

Aedes aegypti

Global outbreak of Zika virus

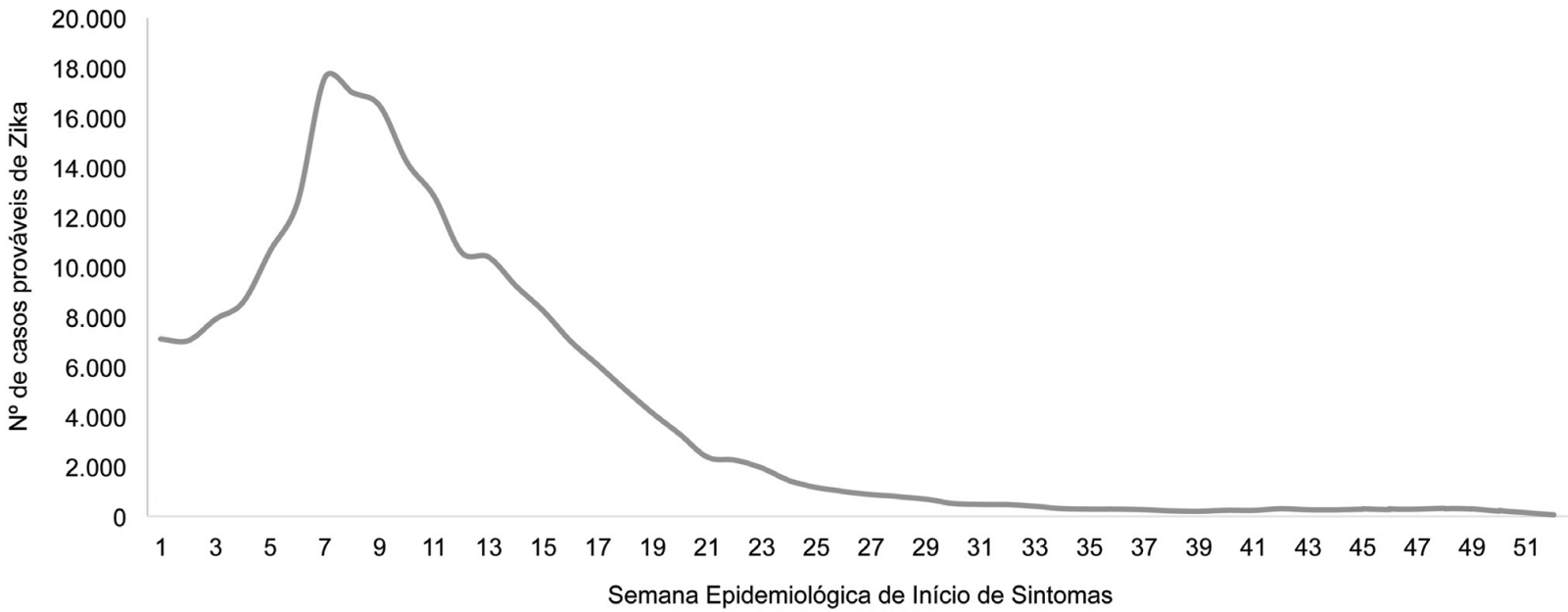
World Map of Areas with Risk of Zika



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

Research objectives

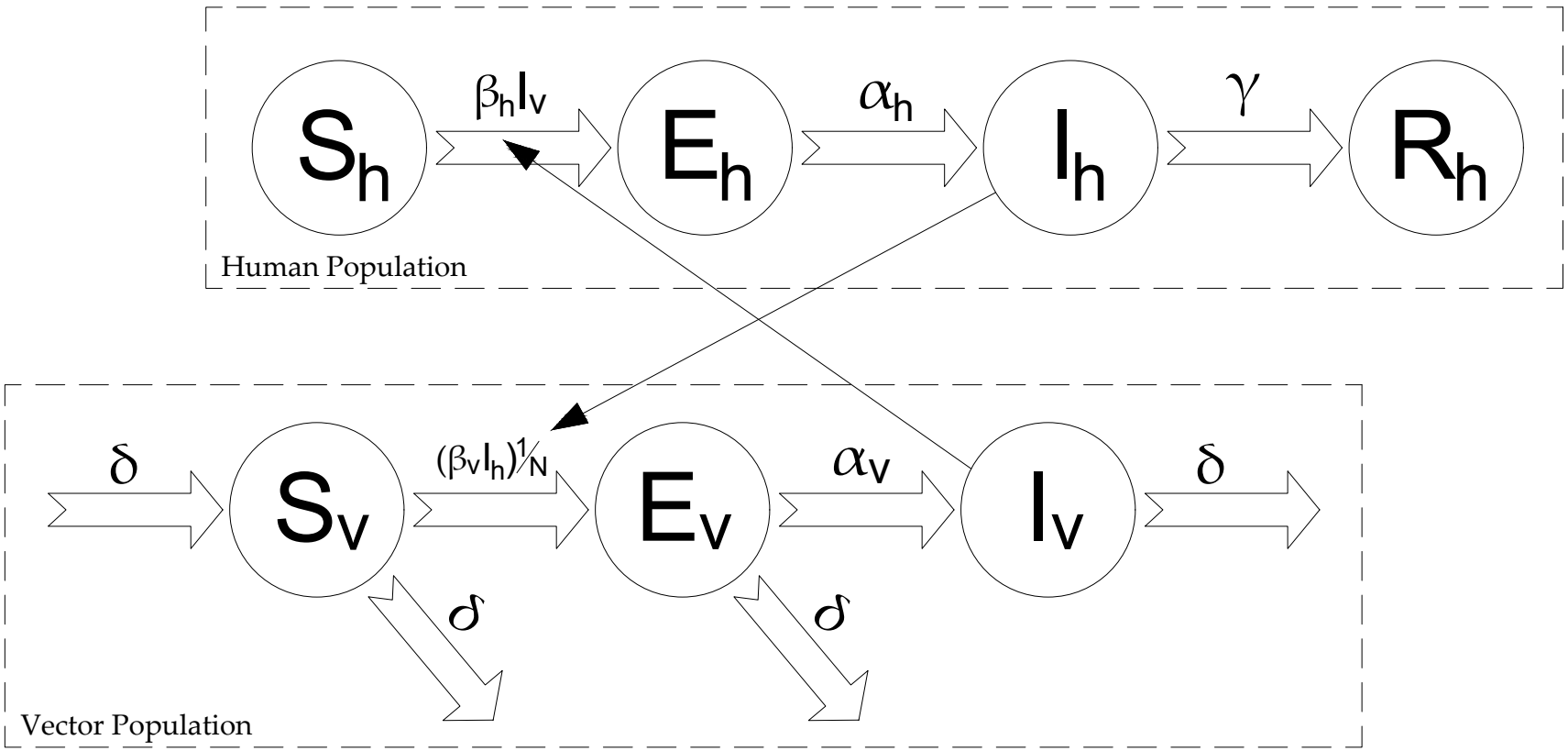
The objectives of this research are:

- Develop an epidemic model to describe the Zika virus outbreak 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

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

$$\frac{\mathrm{d}E_h}{\mathrm{d}t} = \beta_h\, S_h\, I_v - \alpha_h\, E_h \qquad \frac{\mathrm{d}E_v}{\mathrm{d}t} = \beta_v\, S_v\, \frac{I_h}{N} - (\delta + \alpha_v)\, E_v$$

$$\frac{\mathrm{d}I_h}{\mathrm{d}t} = \alpha_h\, E_h - \gamma\, I_h \qquad \frac{\mathrm{d}I_v}{\mathrm{d}t} = \alpha_v\, E_v - \delta\, I_v$$

$$\frac{\mathrm{d}R_h}{\mathrm{d}t} = \gamma\, I_h \qquad \frac{\mathrm{d}C}{\mathrm{d}t} = \alpha_h\, E_h$$

+ 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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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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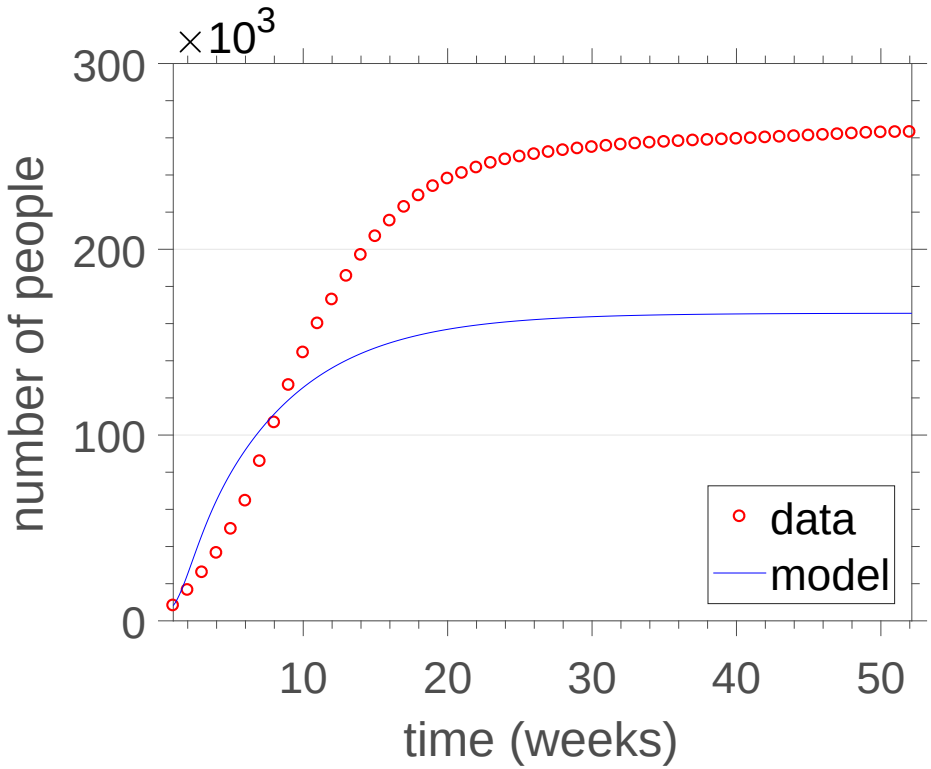
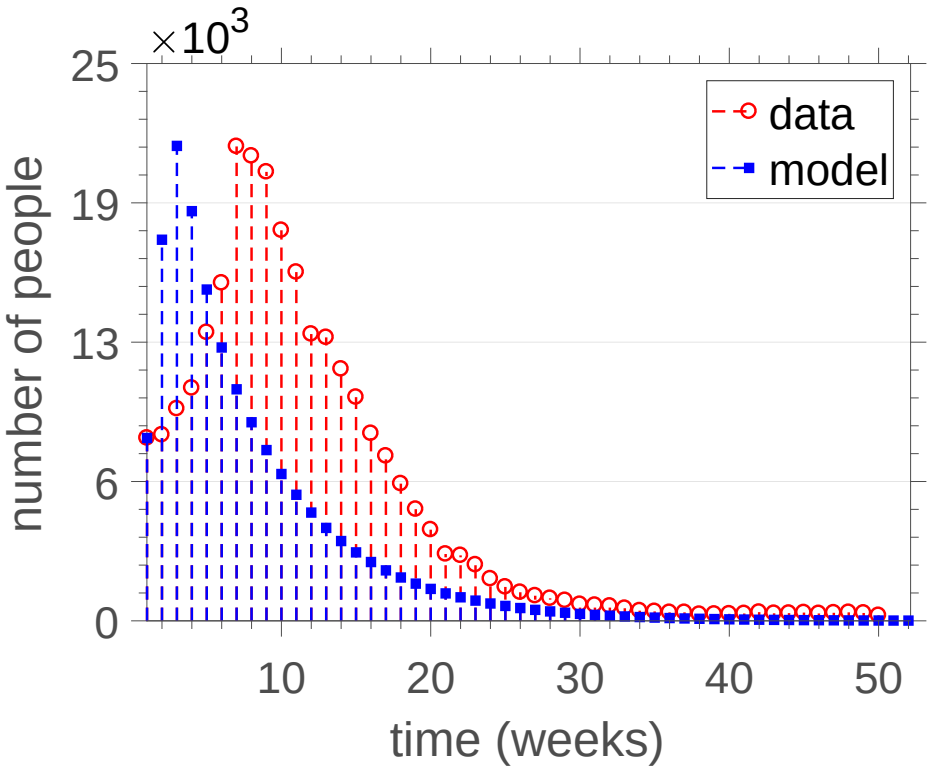
Nominal model: predictions vs observations

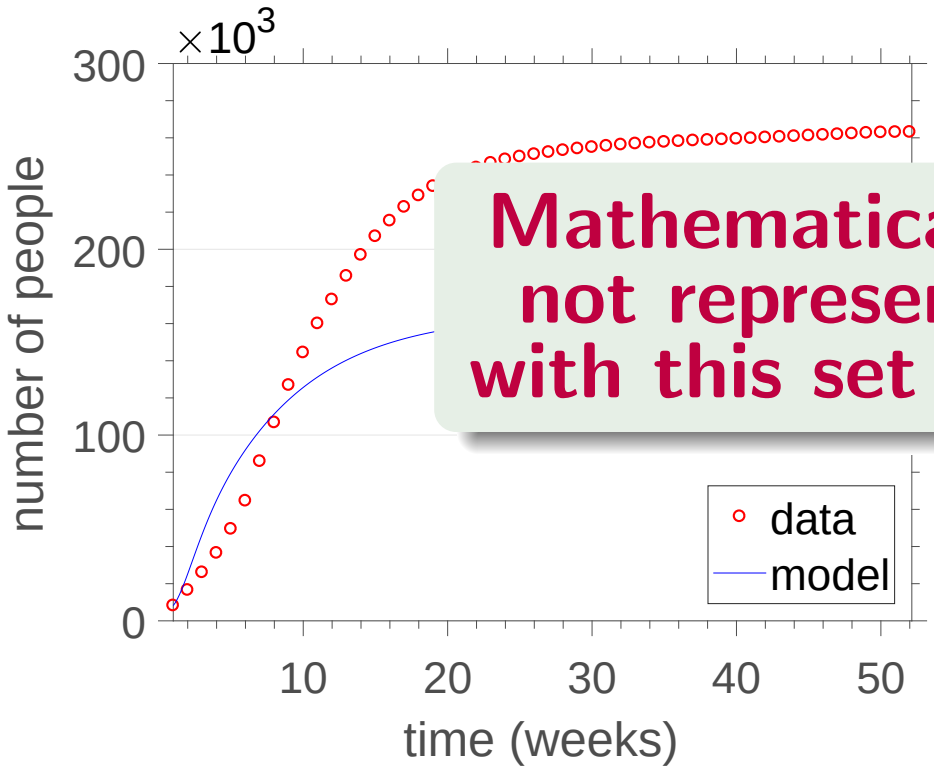


Cumulative number of infectious

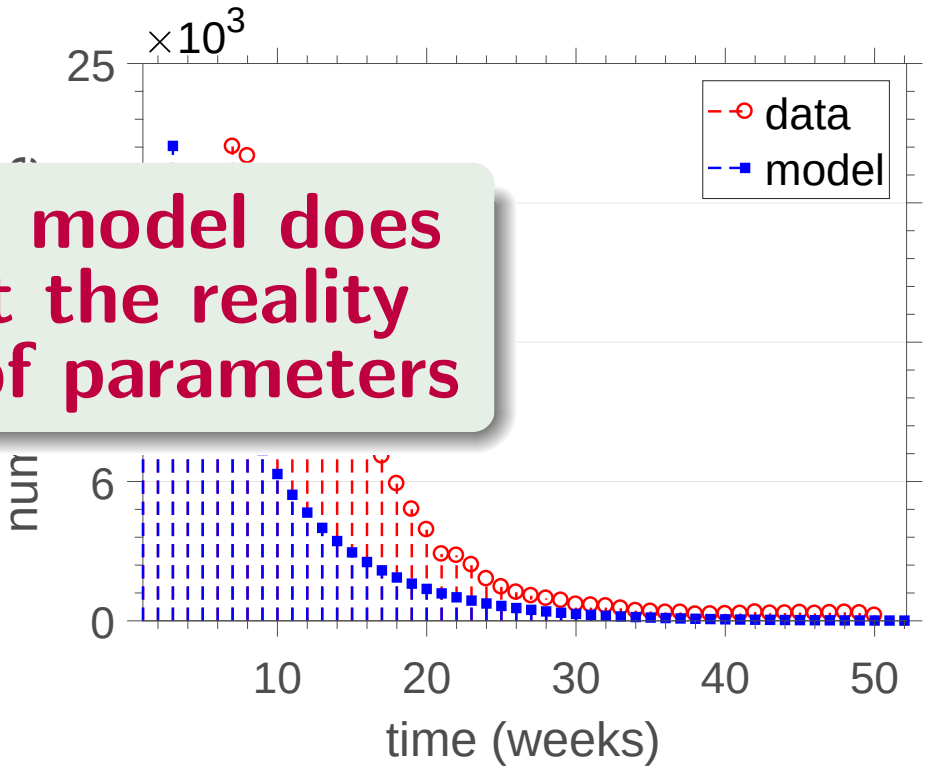


New infectious cases

Nominal model: predictions vs observations



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



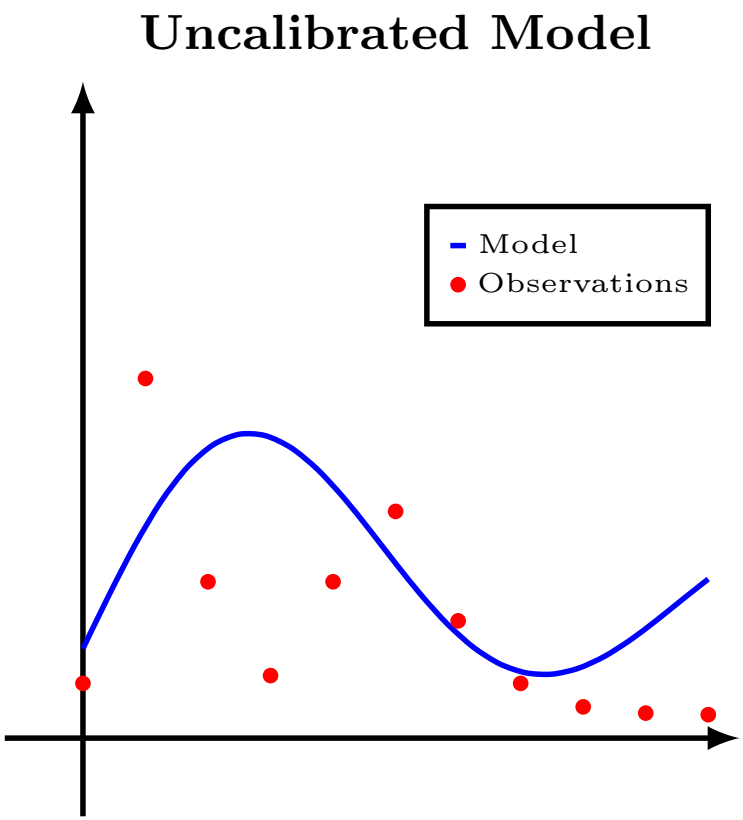
Cumulative number of infectious

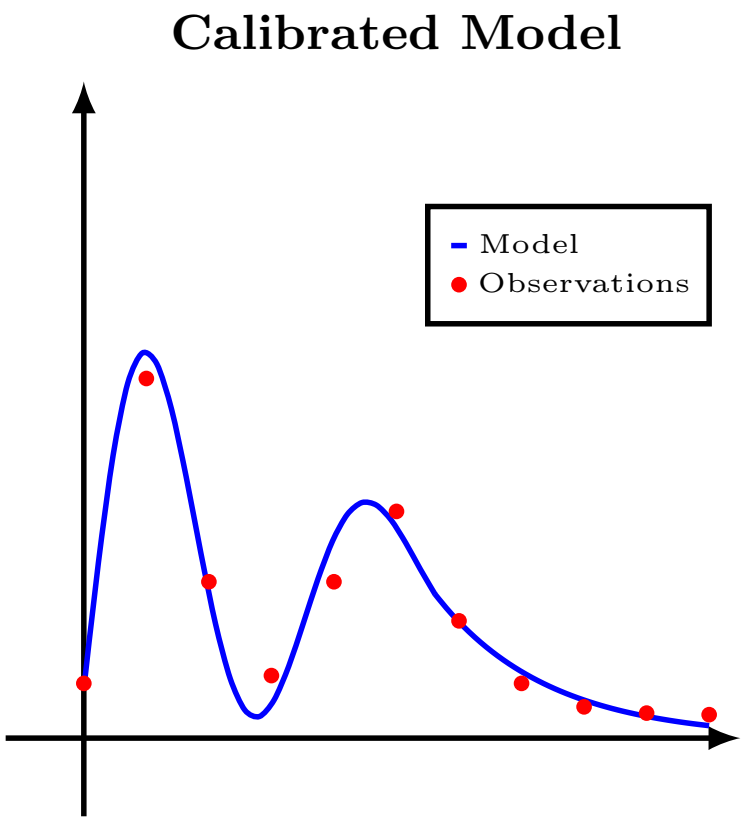
New infectious cases

Section 3

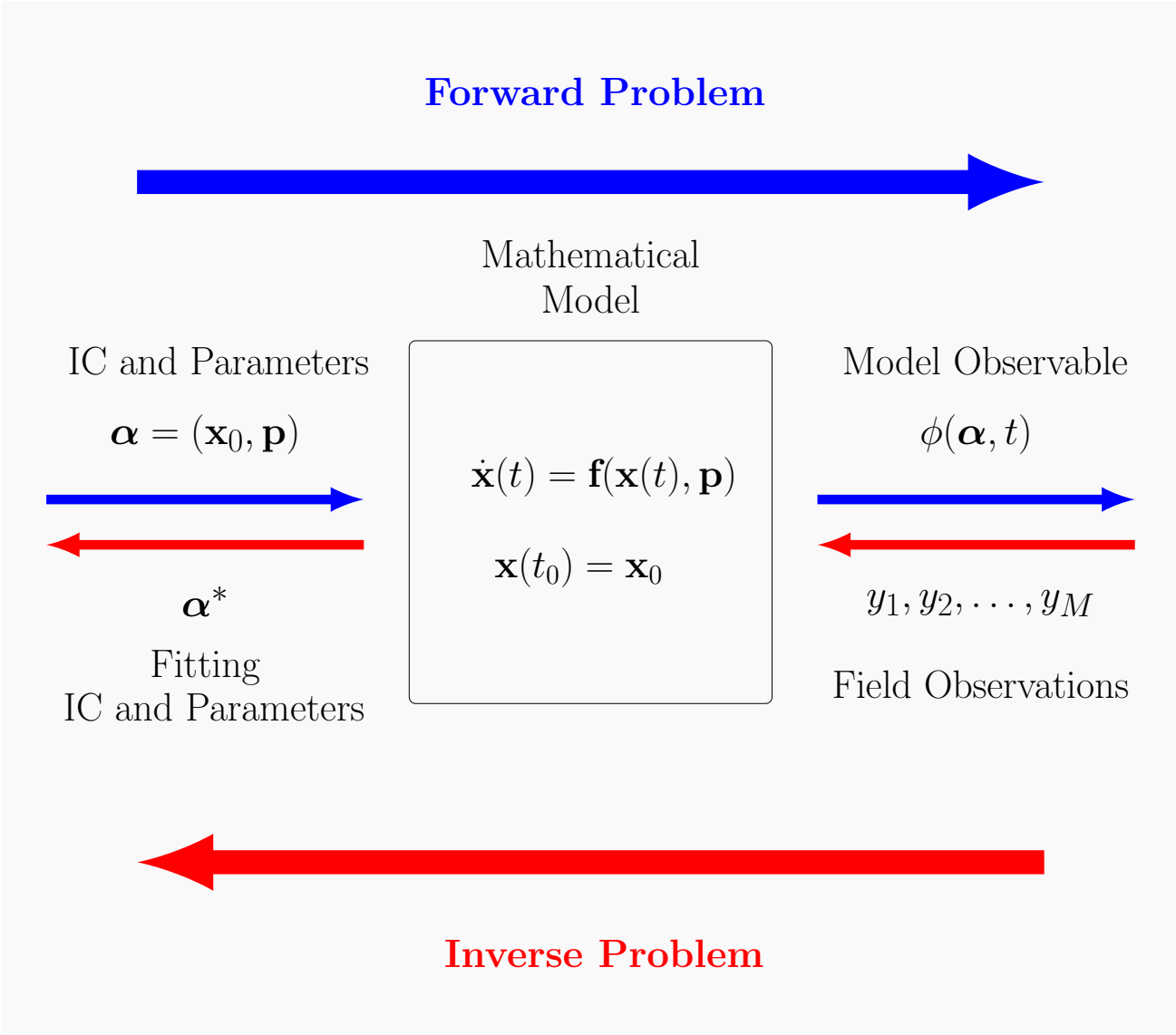
Inverse Problem

Model calibration





Forward and inverse problems



Inverse problem formulation

Find a vector of parameters such that

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

- 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:

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

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

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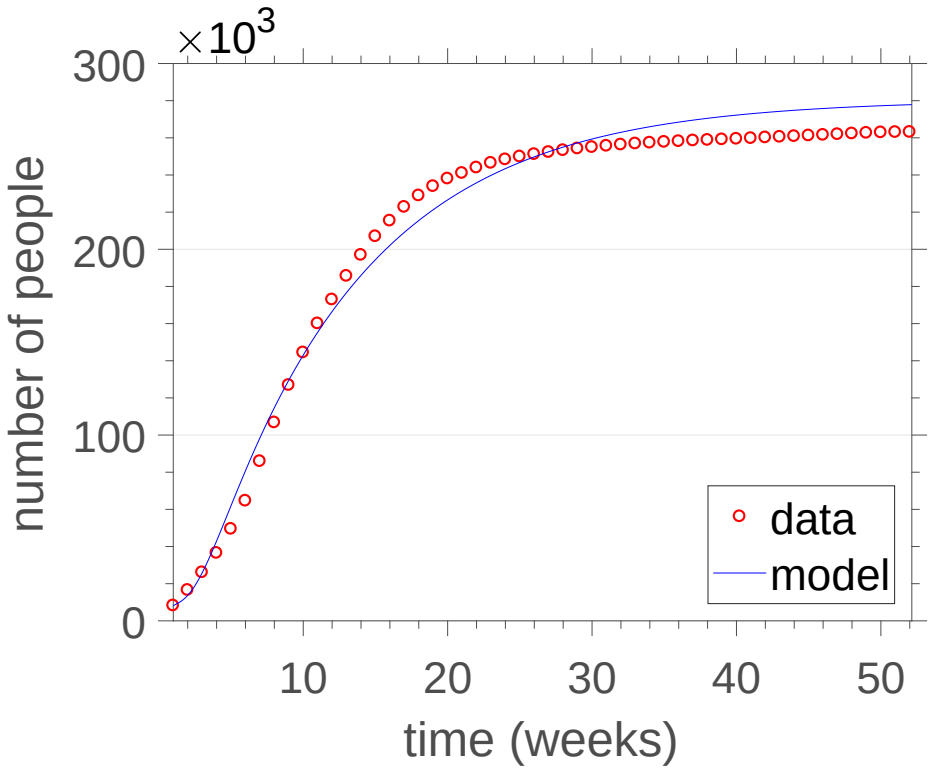
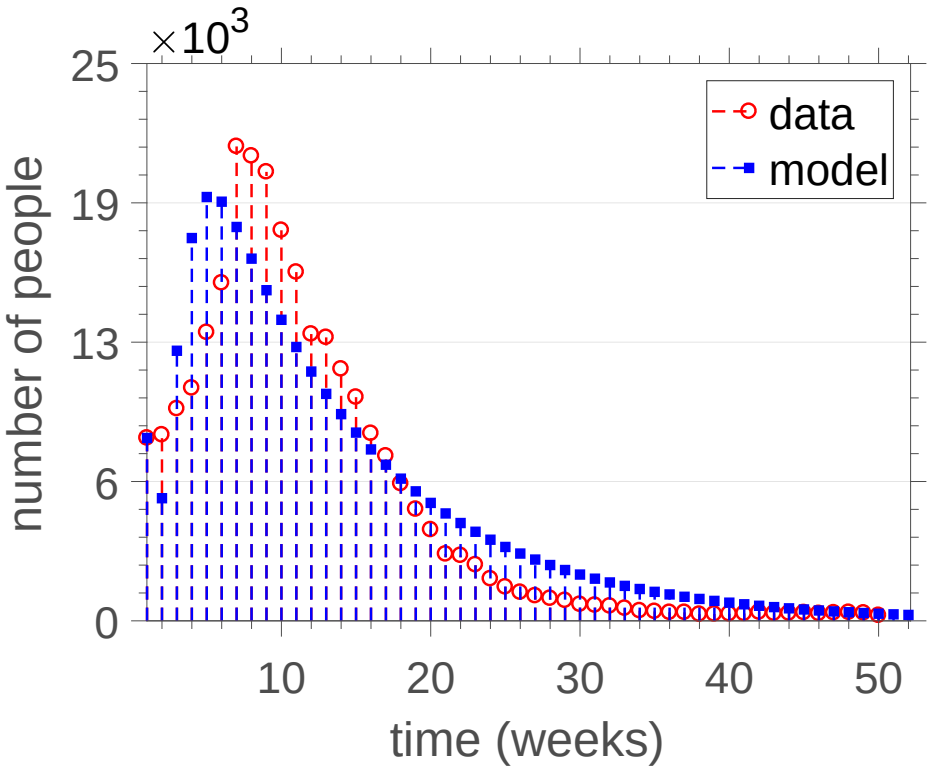
$\Longrightarrow$ Q-wellposed: existence, uniqueness, unimodality and local stability

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

Calibrated model: predictions vs observations



Cumulative number of infectious



New infectious cases

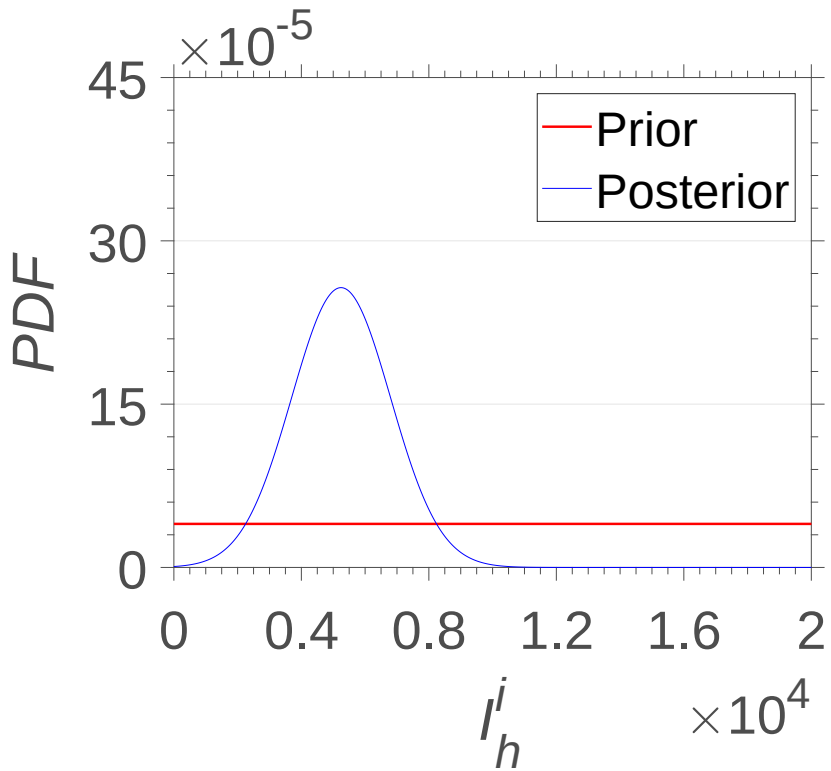
Bayesian updating (ongoing research)

Bayesian formalism for model calibration:

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

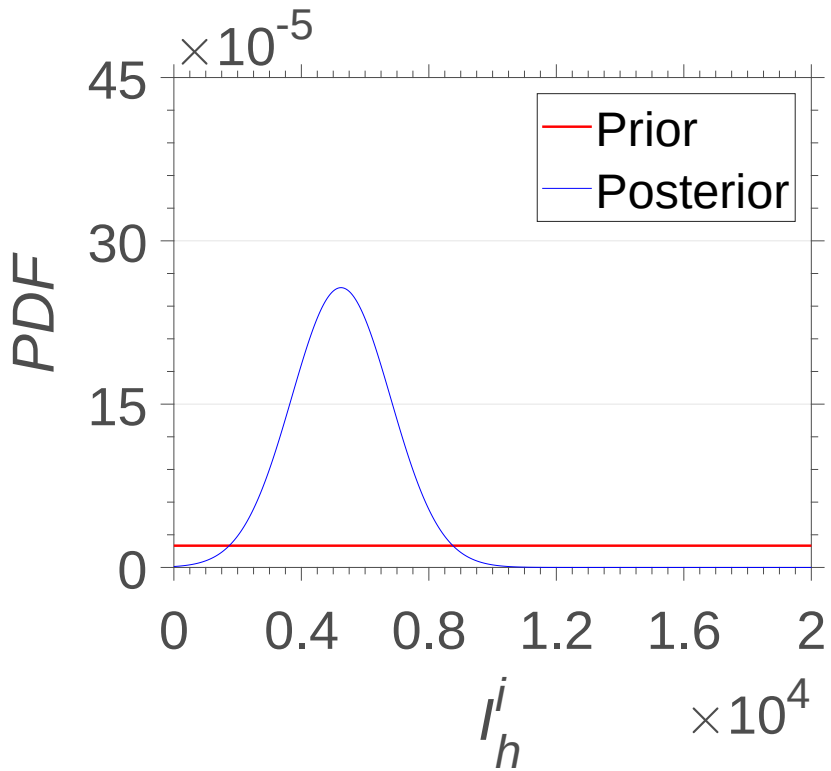
- additive noise hypothesis
- likelihood: Gaussian (MaxEnt principle)
- prior: uniform / gamma

Uniform priors for initial infectious



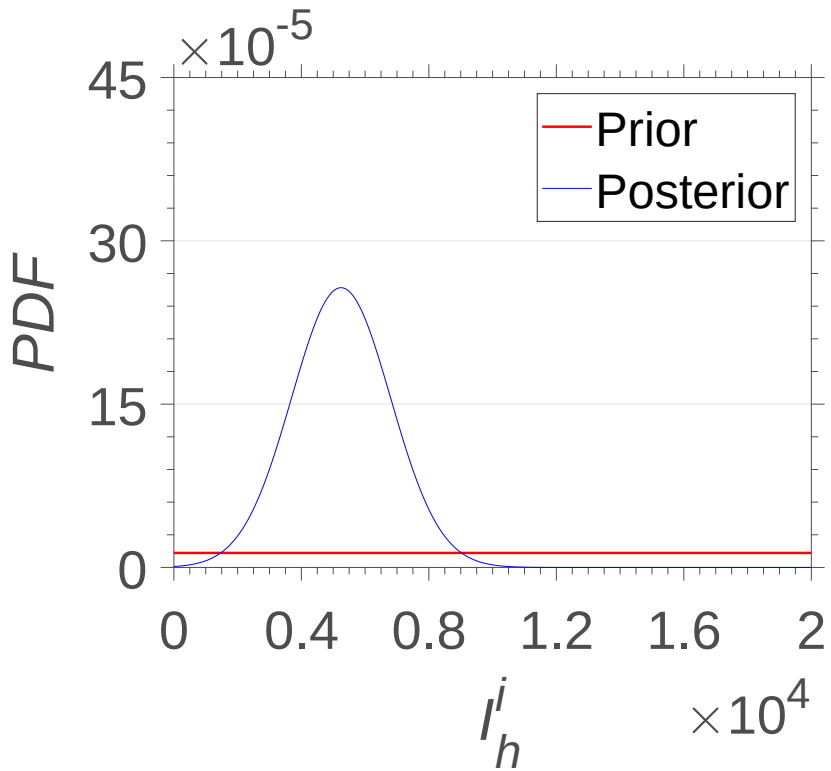
$\text{Uniform}(0, 25k)$

Uniform priors for initial infectious



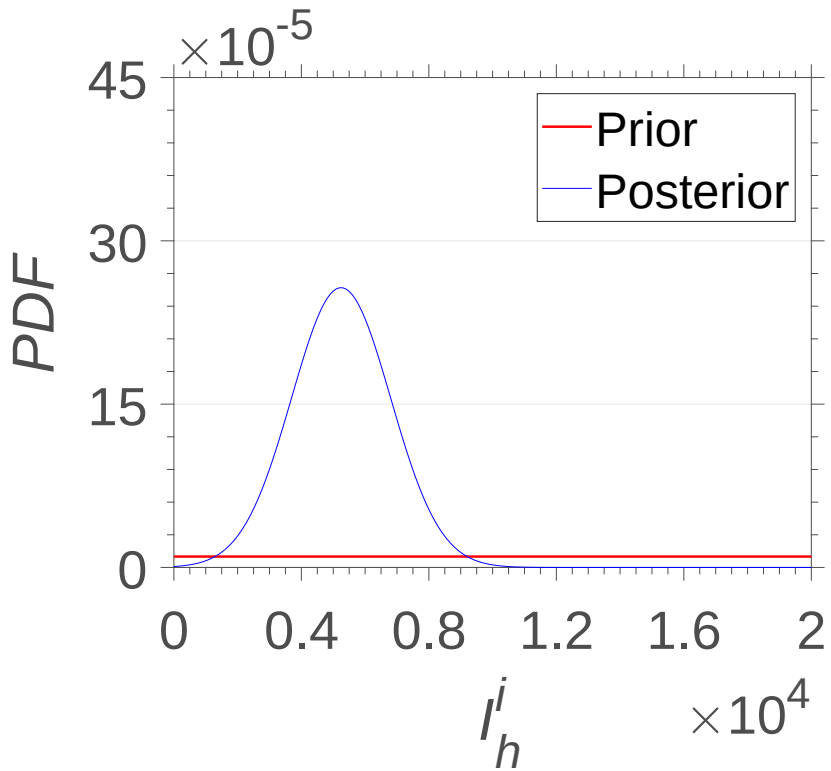
$\text{Uniform}(0, 50k)$

Uniform priors for initial infectious



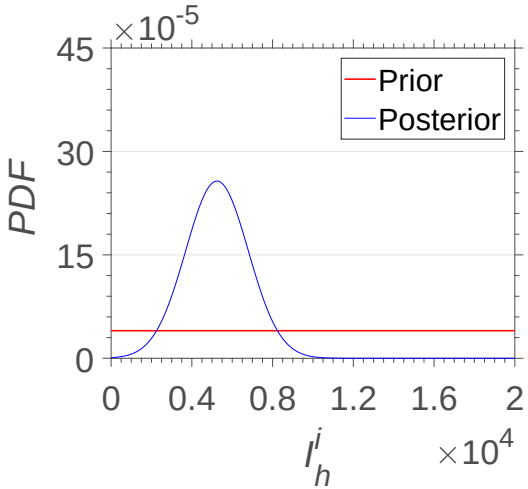
$\text{Uniform}(0, 75k)$

Uniform priors for initial infectious

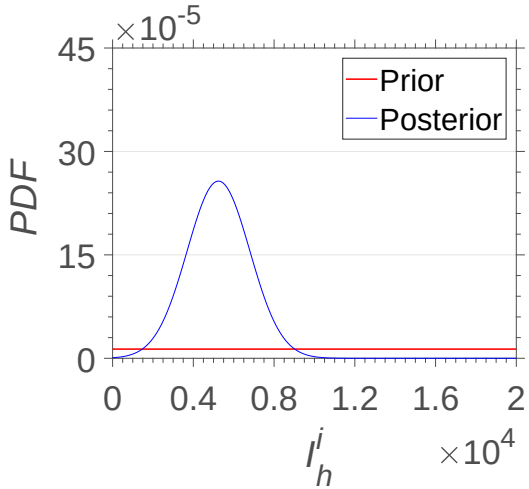


$\text{Uniform}(0, 100k)$

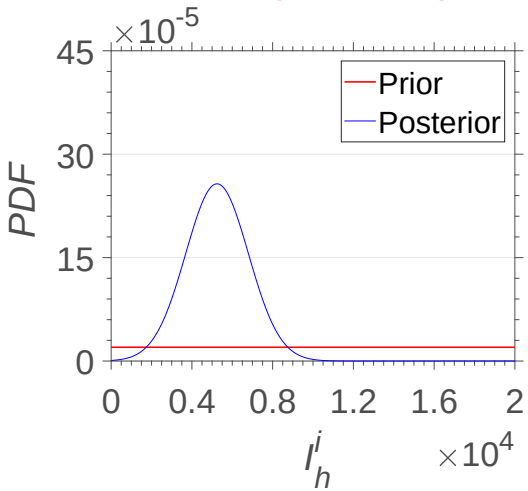
Uniform priors for initial infectious



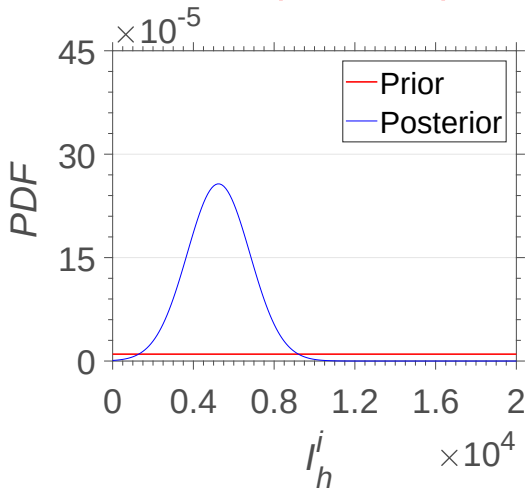
Uniform$(0, 25k)$



Uniform$(0, 75k)$

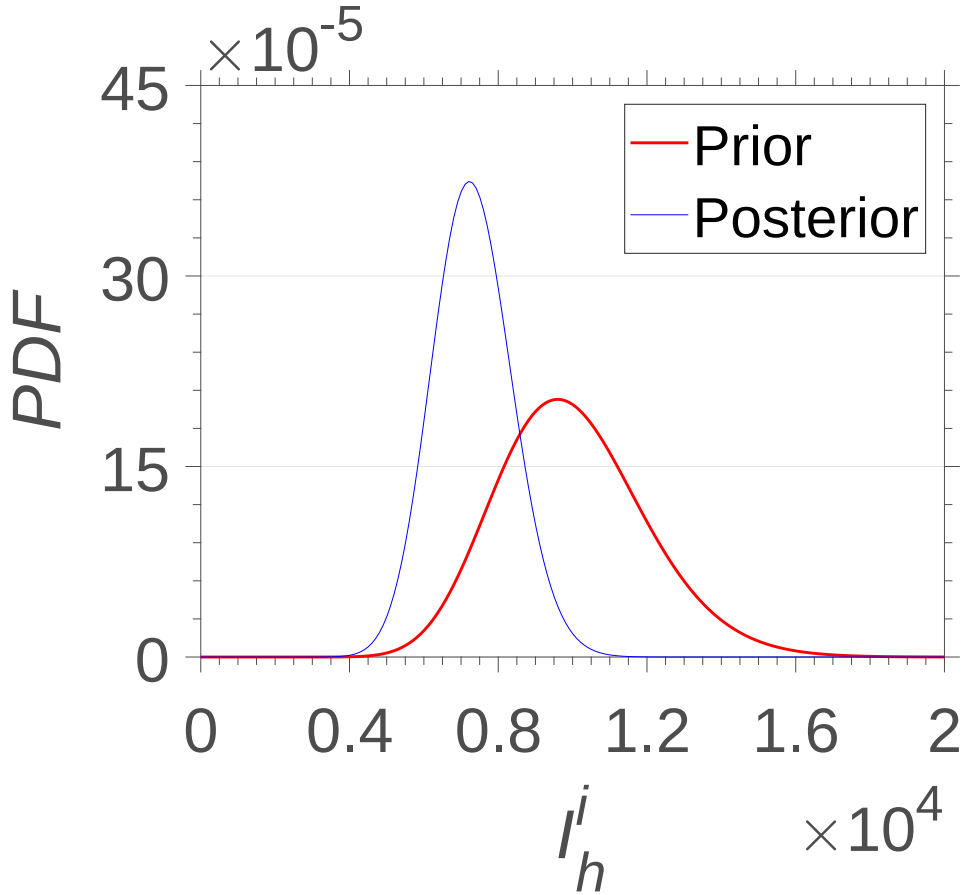


Uniform$(0, 50k)$



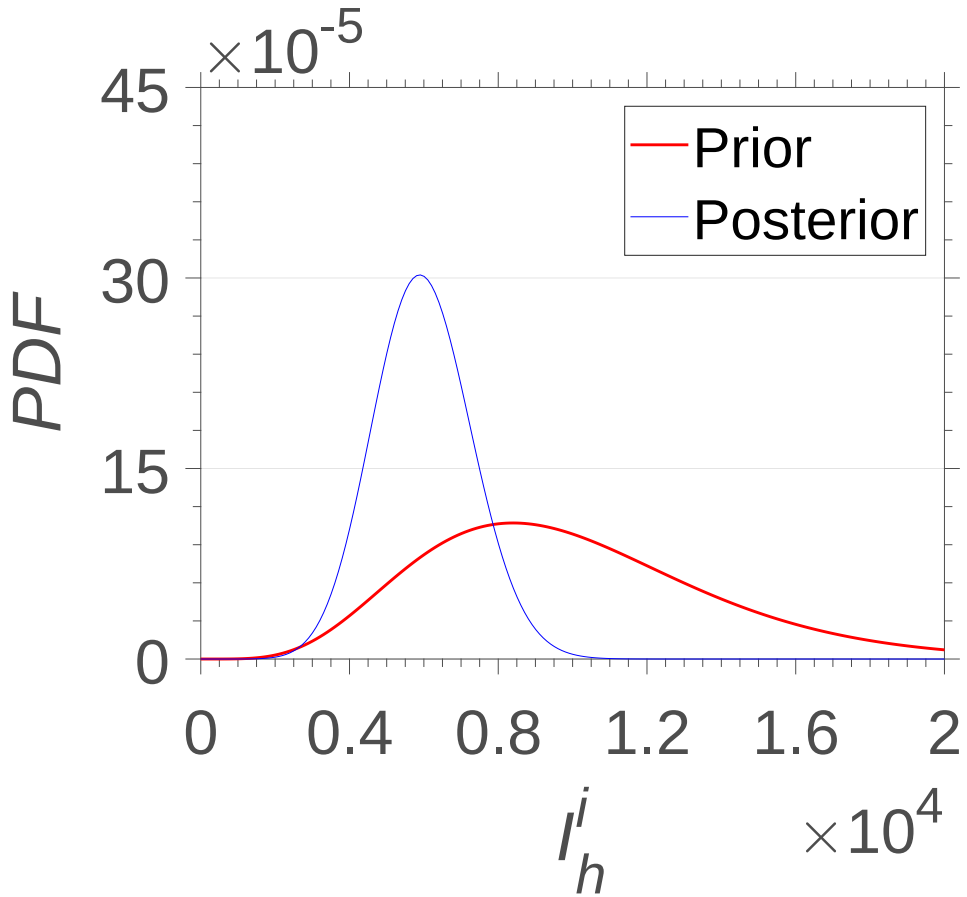
Uniform$(0, 100k)$

Gamma priors for initial infectious



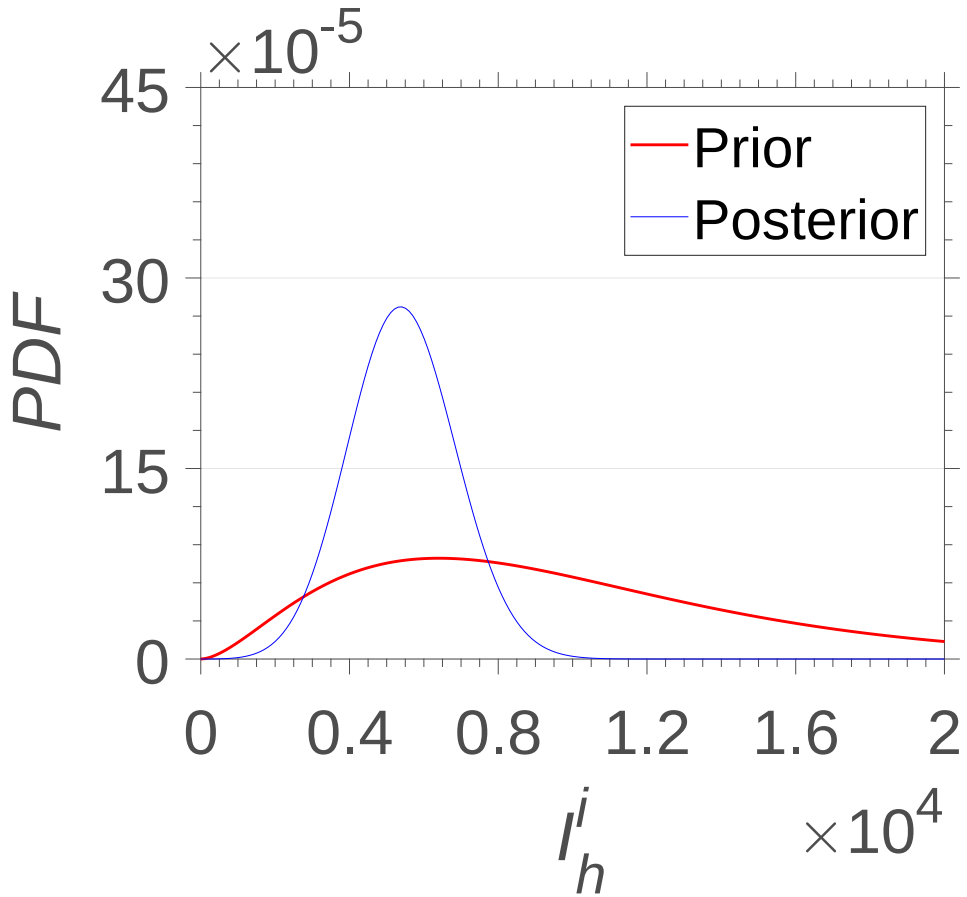
$\delta = 20\%$

Gamma priors for initial infectious



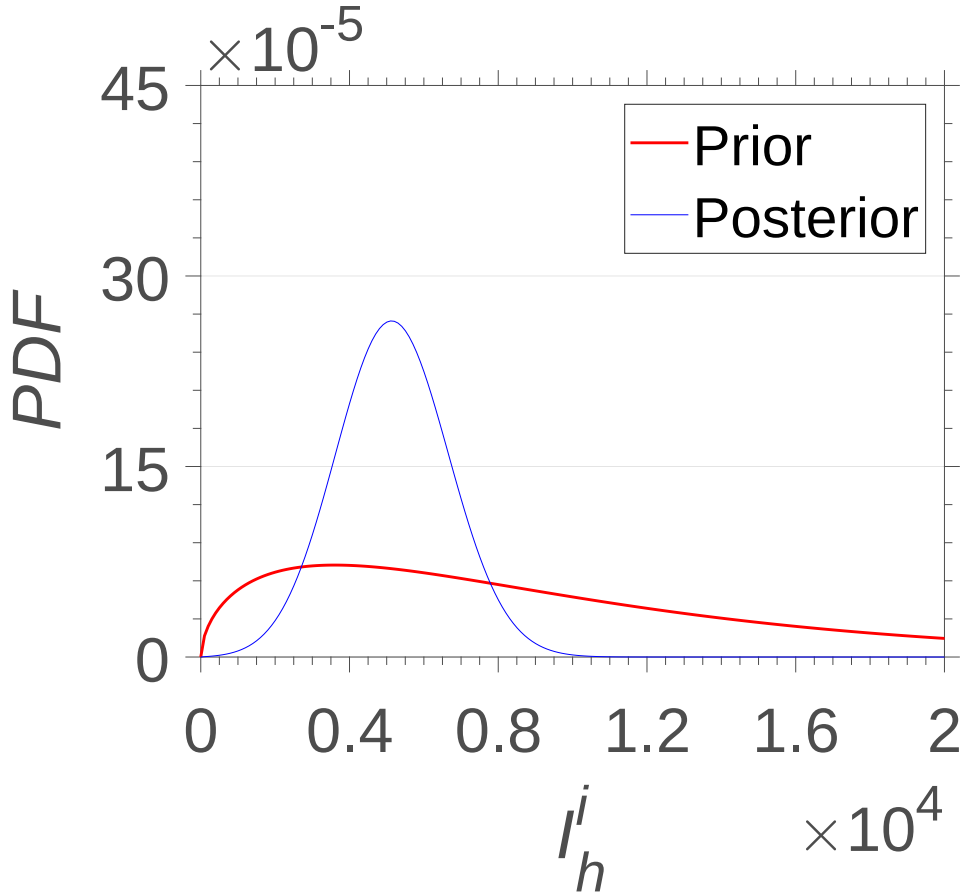
$\delta = 40\%$

Gamma priors for initial infectious



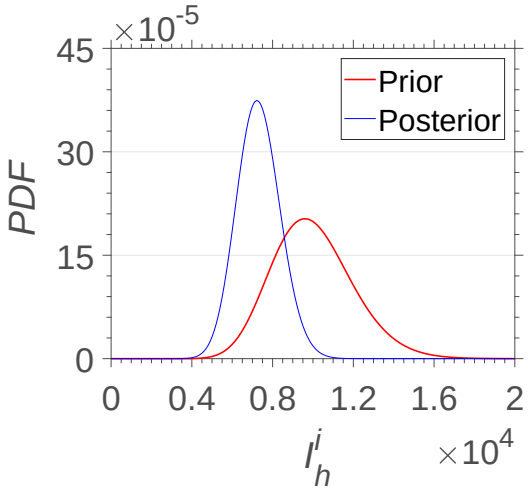
$\delta = 60\%$

Gamma priors for initial infectious

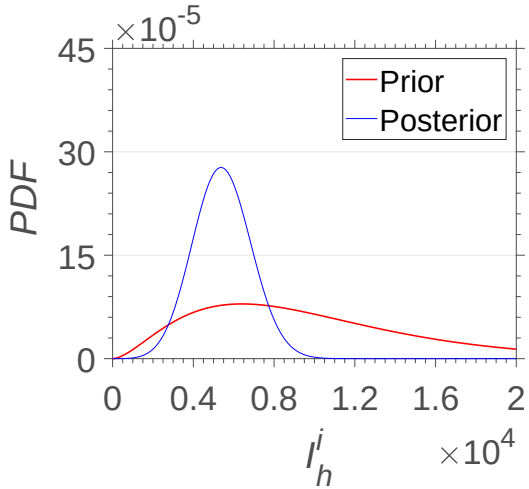


$\delta = 80\%$

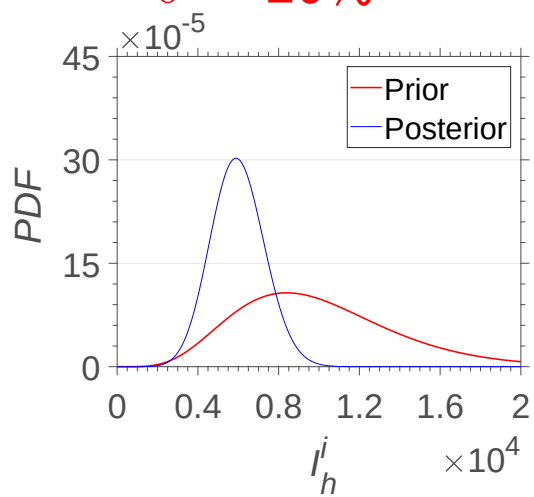
Gamma priors for initial infectious



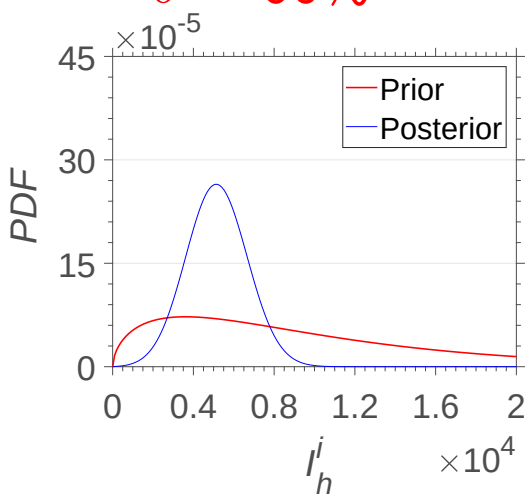
$\delta = 20\%$



$\delta = 60\%$



$\delta = 40\%$



$\delta = 80\%$

Section 4

Uncertainty Quantification

Uncertainties in the mathematical model

The mathematical model is subjected to uncertainties:

- **model uncertainty**
  - lack of knowledge about dynamical system (significative, but ignored in a first analysis)
- **data uncertainty**
  - model parameters (pronounced)
  - initial conditions (very pronounced)

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

Stochastic model of uncertainties

- random parameters:

$$\boldsymbol{X} = (S_h^0, E_h^0, I_h^0) \quad \text{(initial conditions)}$$

- initial conditions constraint:

$$0 \leq E_h^0 \leq X_{max} \quad \text{and} \quad 0 \leq I_h^0 \leq X_{max}$$

$$\mathcal{K}: \quad S_h^0 + E_h^0 + I_h^0 = N - R_h^0 \quad \text{(afine manifold)}$$

- initial conditions distributions:

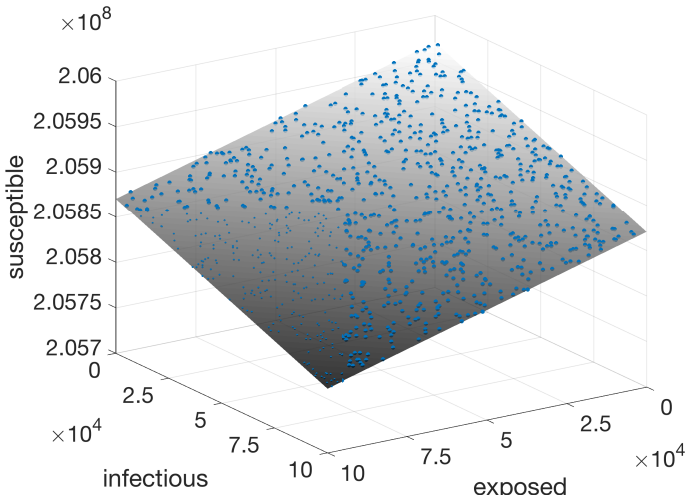
$$\boldsymbol{X} \sim \text{Uniform}(\mathcal{K})$$

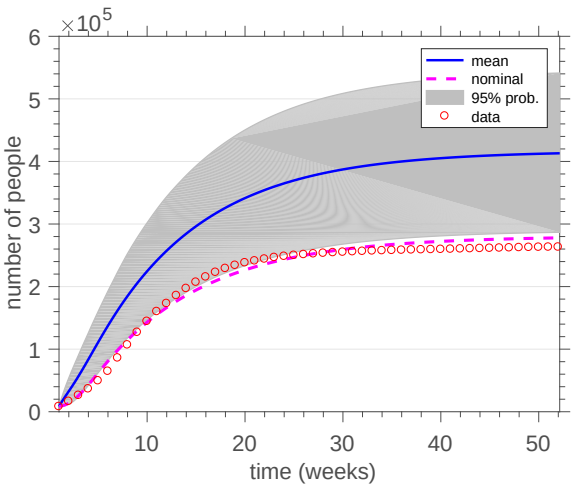
- model response:

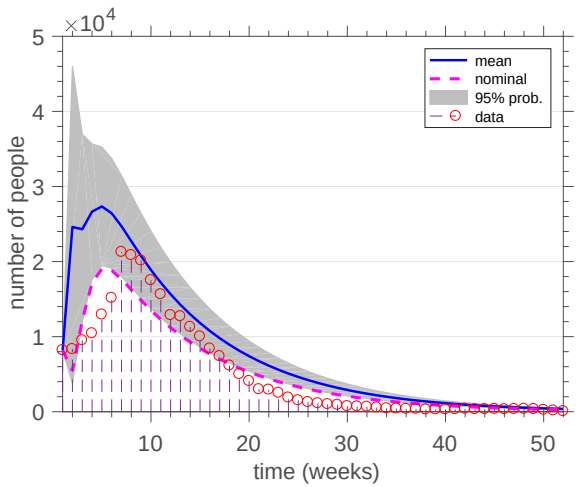
$$\boldsymbol{U} = h(\boldsymbol{X}) \quad \text{(random vector)}$$

- Monte Carlo is used for propagation of uncertainties

Uncertainty propagation





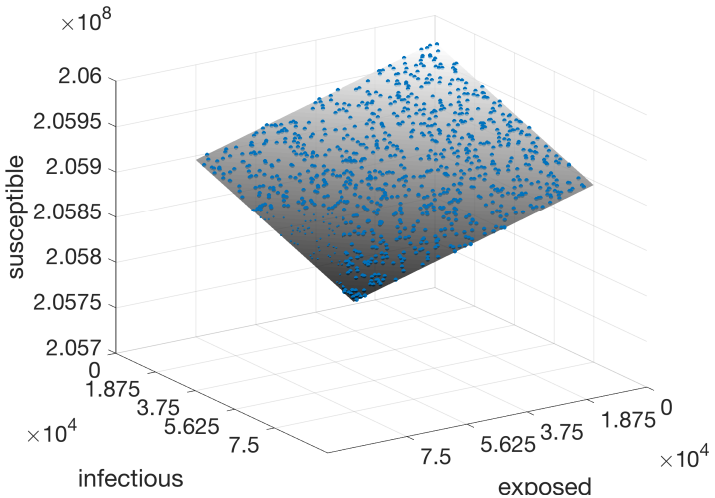


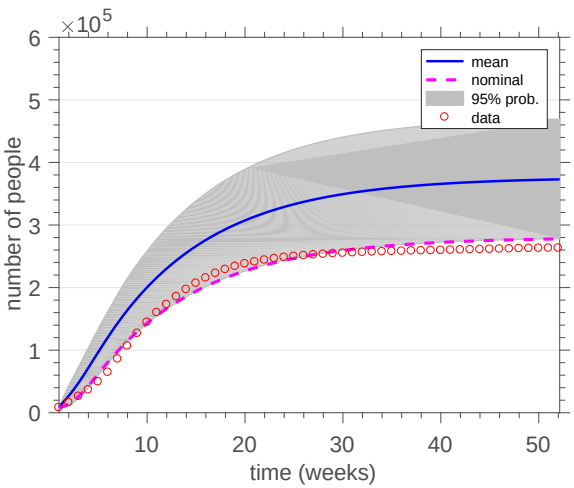
Cumulative infectious

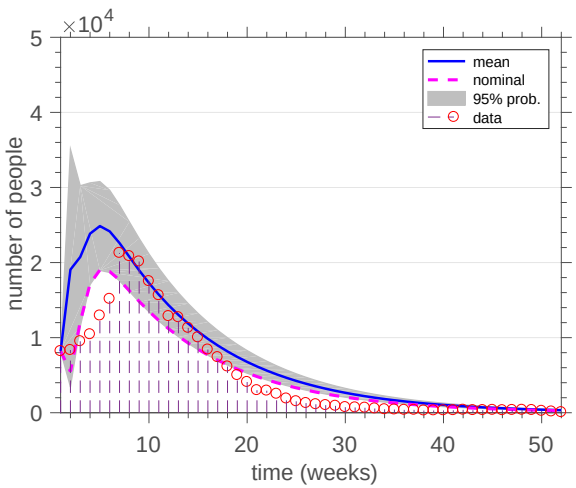
New infectious cases

$$X_{max} = 100 \times 10^3$$

Uncertainty propagation





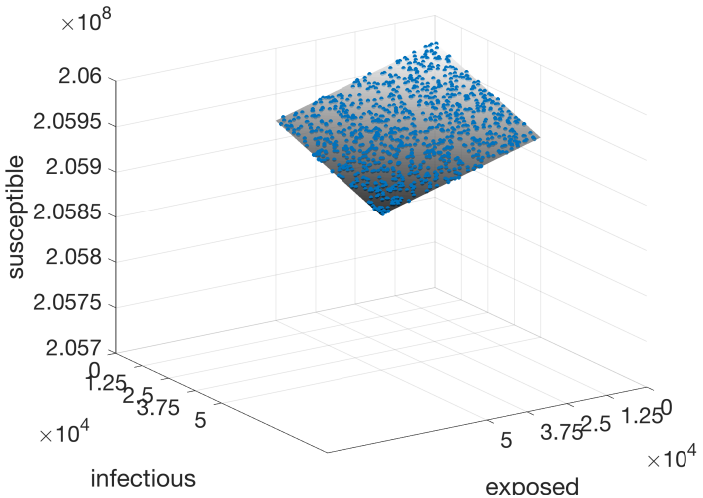


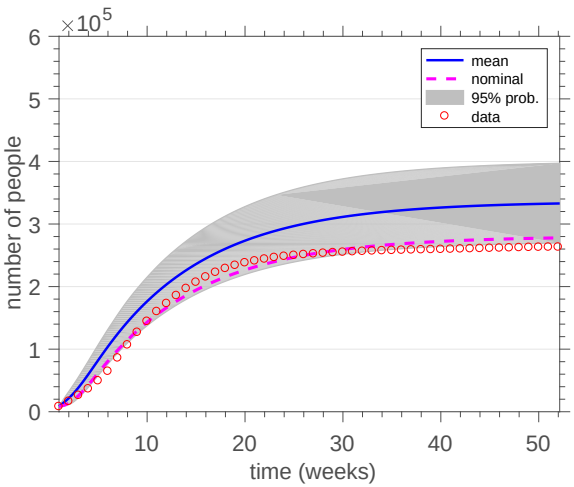
Cumulative infectious

New infectious cases

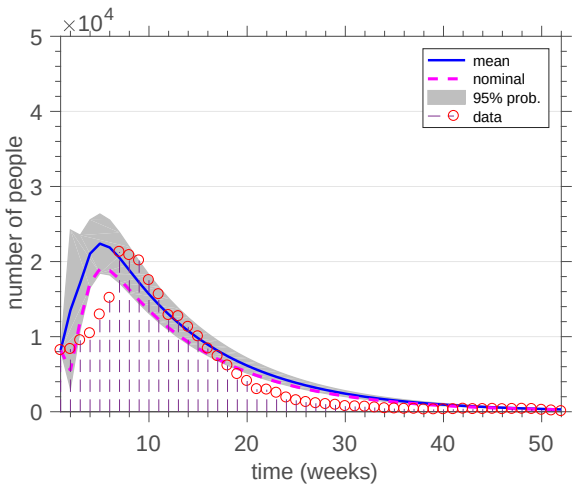
$$X_{max} = 75 \times 10^3$$

Uncertainty propagation





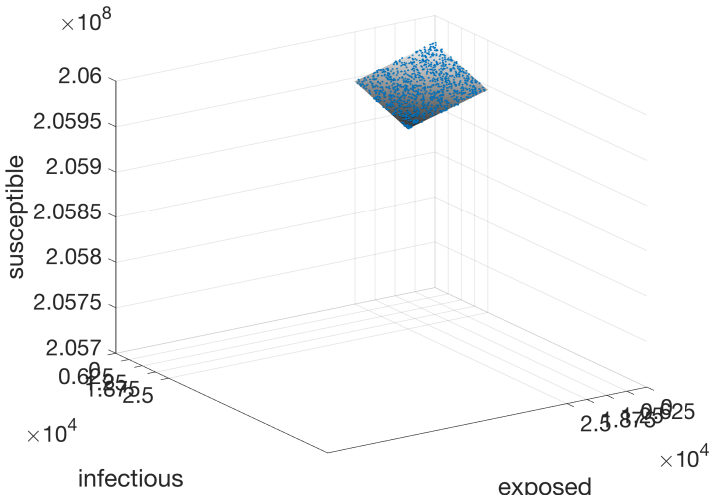
Cumulative infectious

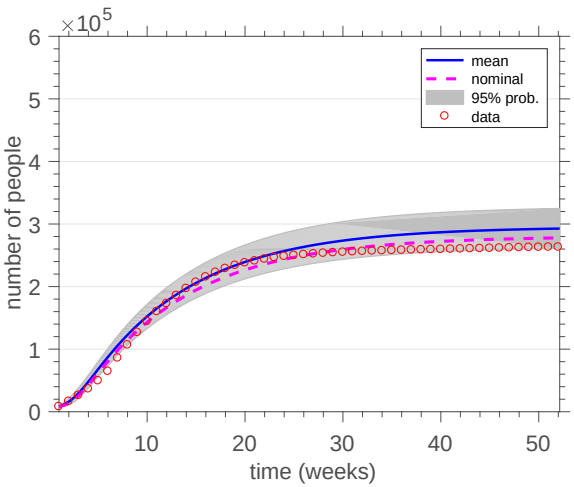


New infectious cases

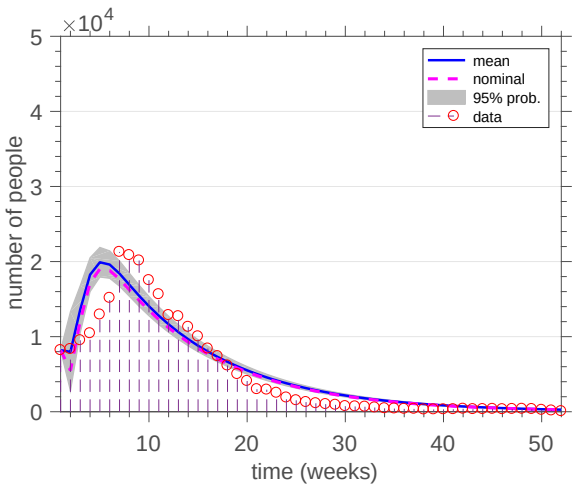
$$X_{max} = 50 \times 10^3$$

Uncertainty propagation





Cumulative infectious

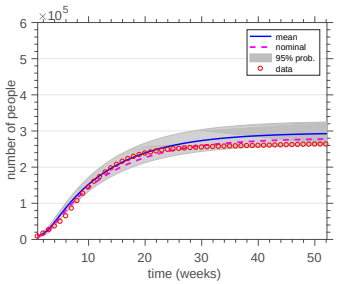


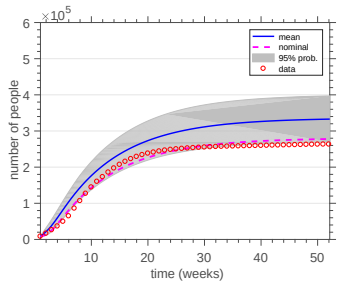
New infectious cases

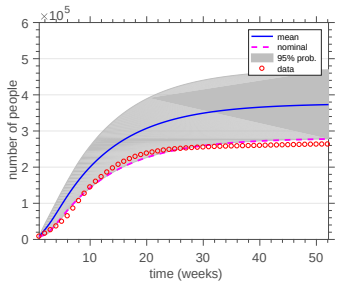
$$X_{max} = 25 \times 10^3$$

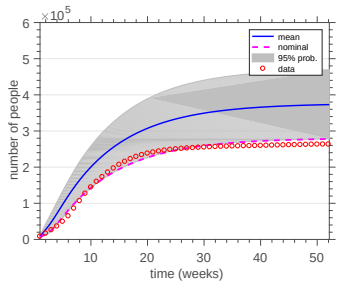
Uncertainty propagation

Cumulative infectious

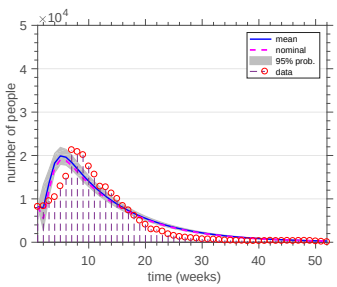


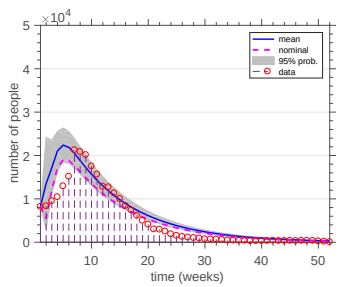


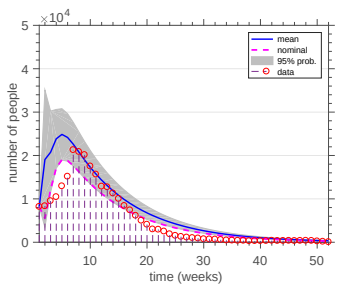


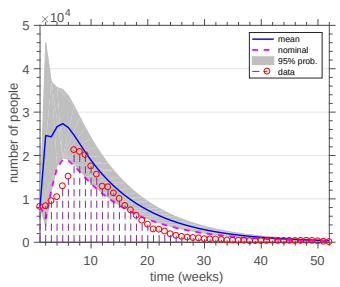


New infectious cases









$X_{max} = 25 \times 10^3$ $X_{max} = 50 \times 10^3$ $X_{max} = 75 \times 10^3$ $X_{max} = 100 \times 10^3$

Section 5

Final Remarks

Concluding remarks

Contributions:

- 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

Monica Heilbron Prize

Eber and Michel received the Monica Heilbron Prize for best scientific initiation work of 2017 at UERJ.

Acknowledgments

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FAPERJ
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CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

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Thank you for your attention!

americo@ime.uerj.br

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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). https://hal.archives-ouvertes.fr/hal-01456776v3


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

Complementary Theory

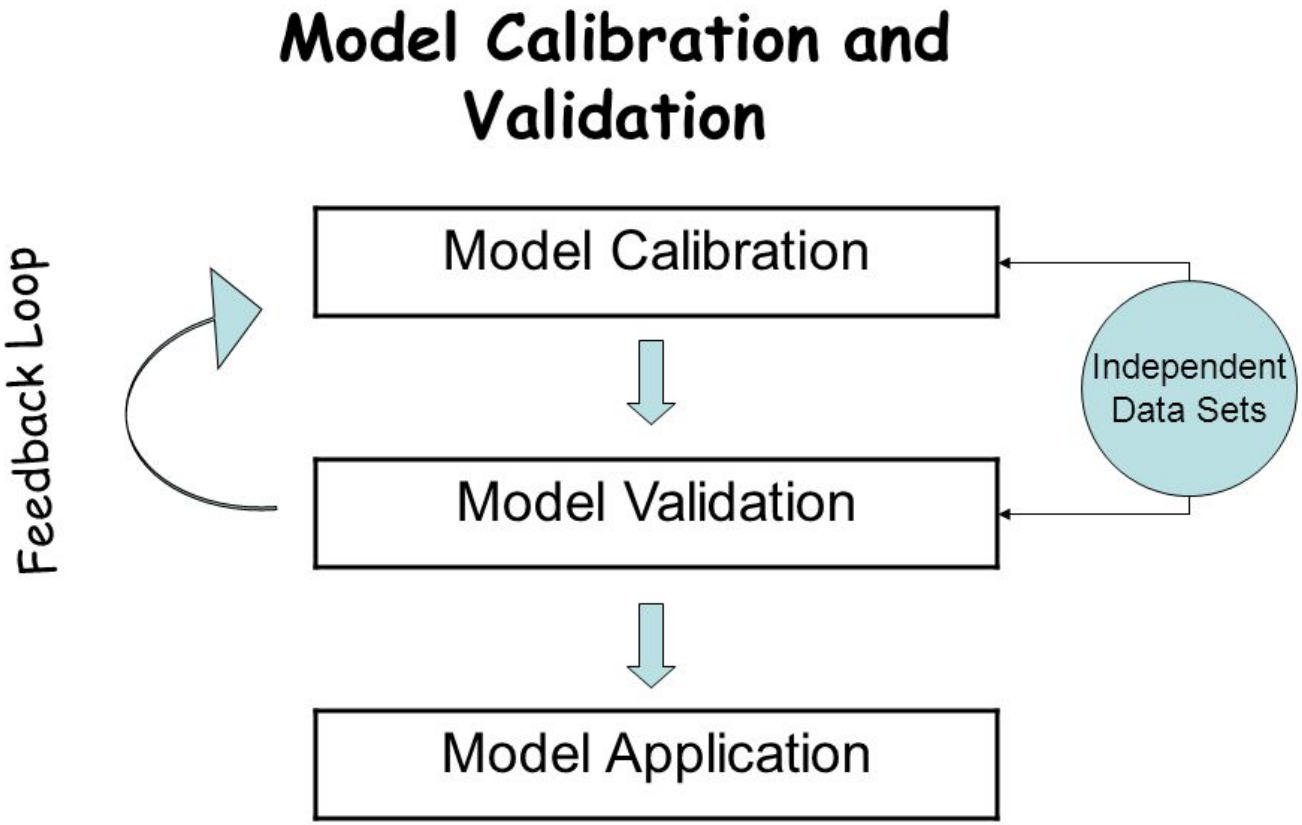
Number of new cases per week

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.

Calibration vs Validation



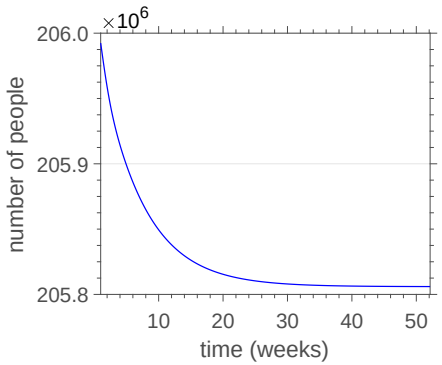
* Picture from *NHI course on Travel Demand Forecasting*

Results for Nominal Model

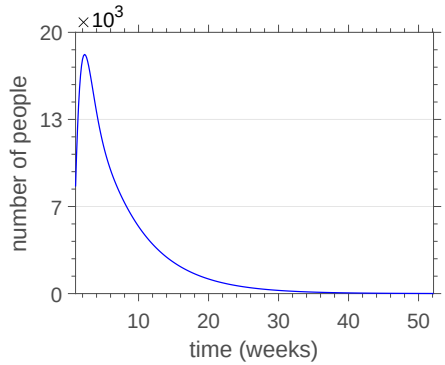
Nominal parameters and initial conditions

$\boldsymbol{\alpha}$	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}	——

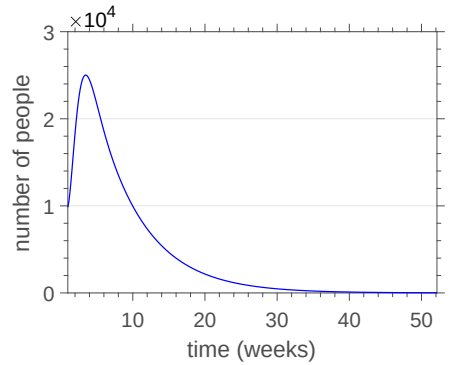
Curves for nominal model



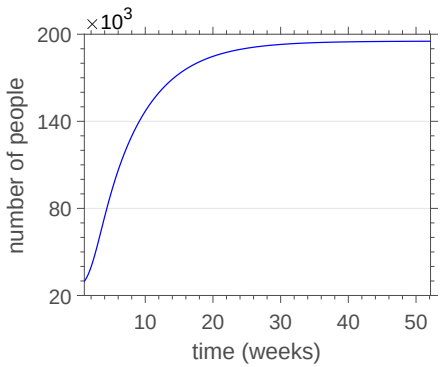
Susceptible humans



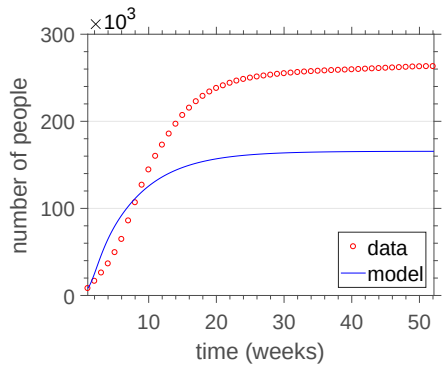
Exposed humans



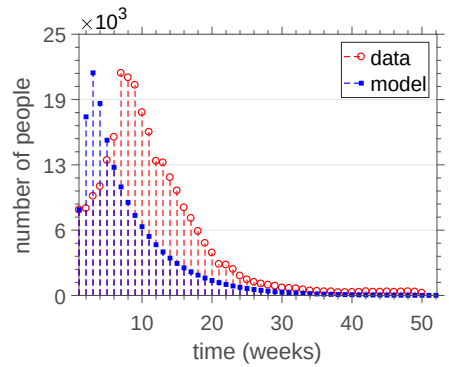
Infectious humans



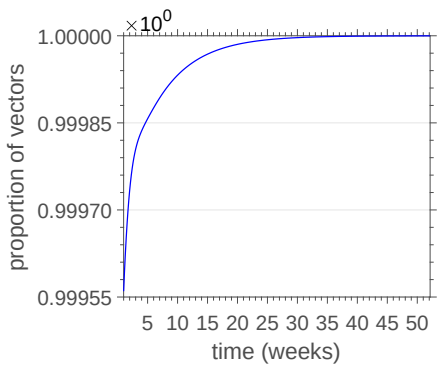
Recovered humans



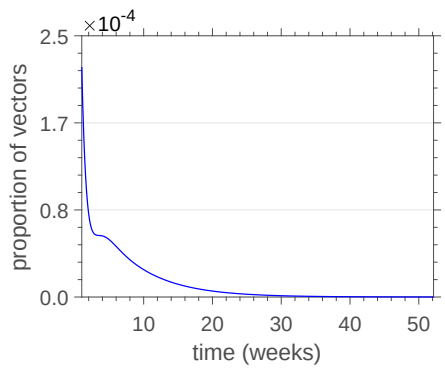
Cumulative infectious



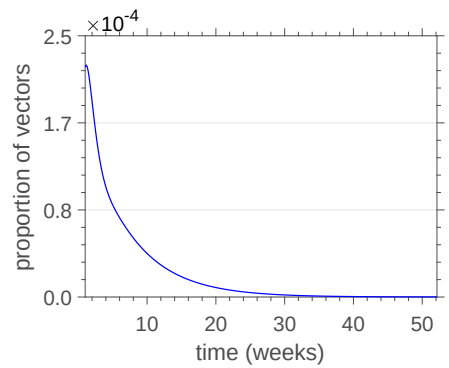
New cases



Susceptible vectors



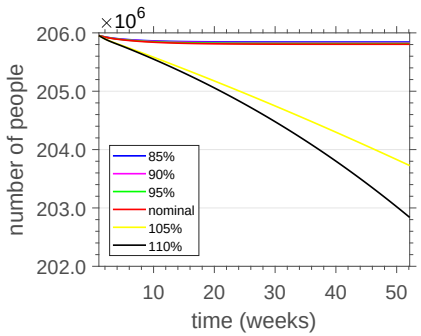
Exposed vectors



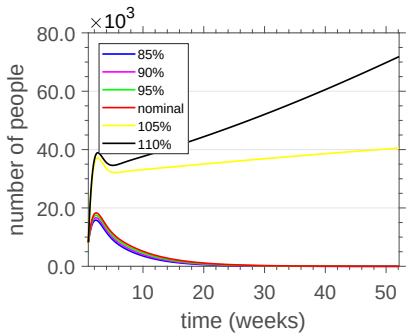
Infectious vectors

Analysis of Sensitivity

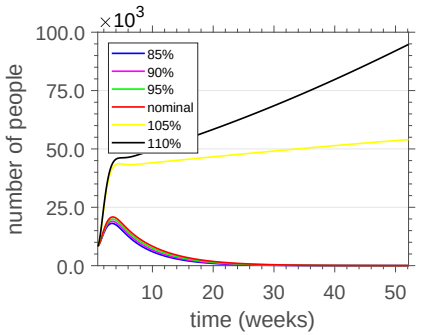
Sensitivity curves for β_h



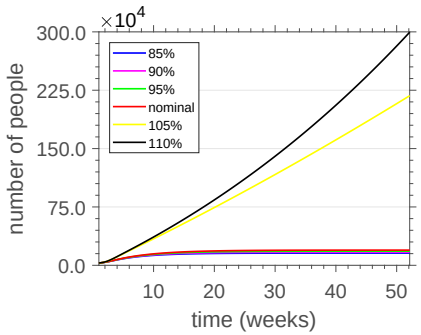
Susceptible humans



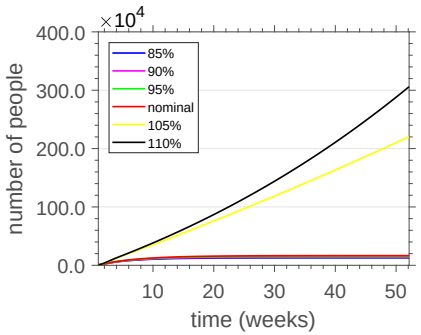
Exposed humans



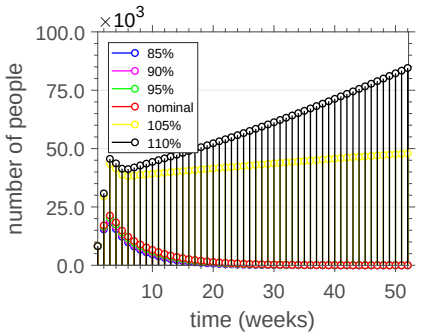
Infectious humans



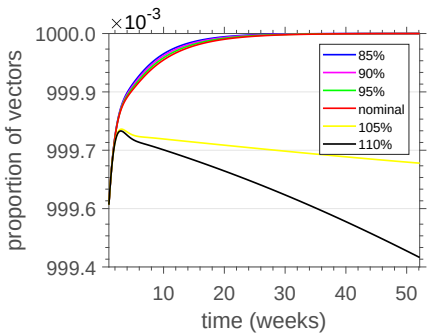
Recovered humans



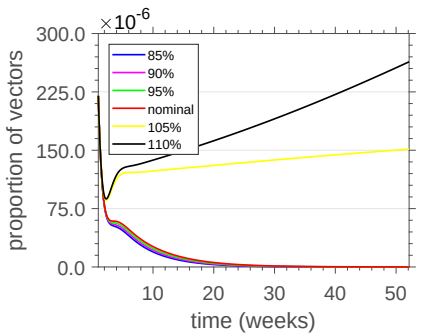
Cumulative infectious



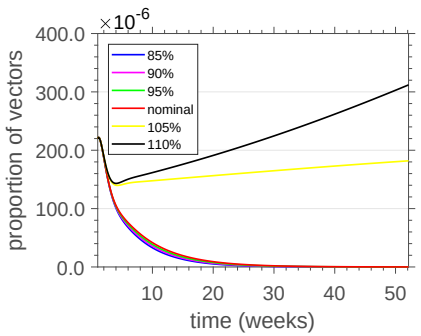
New cases



Susceptible vectors

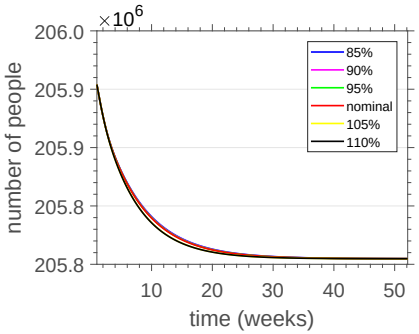


Exposed vectors

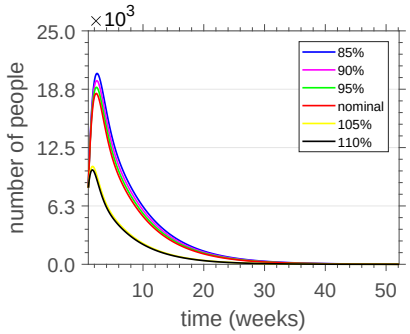


Infectious vectors

Sensitivity curves for α_h



Susceptible humans



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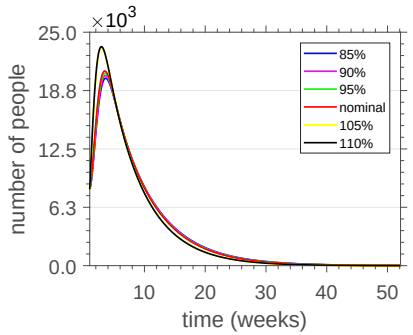
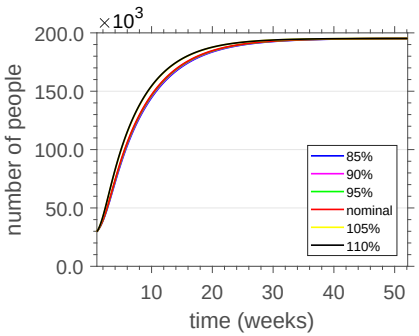
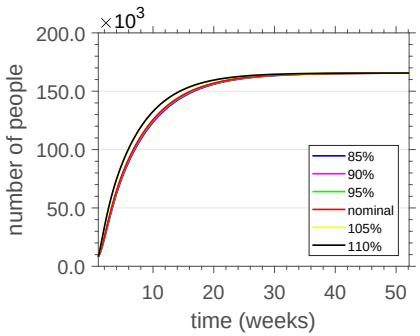


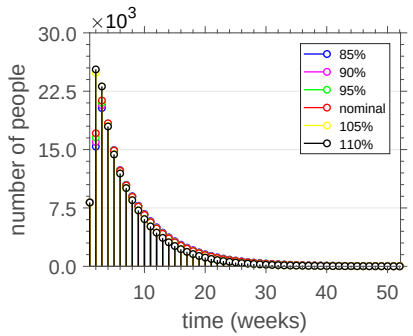
Infectious humans



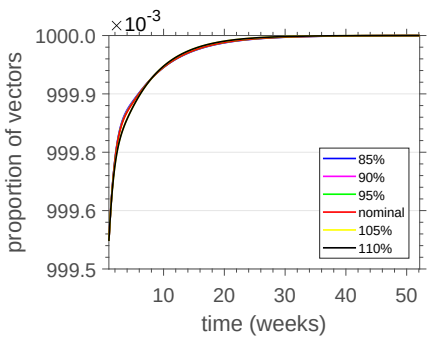
Recovered humans



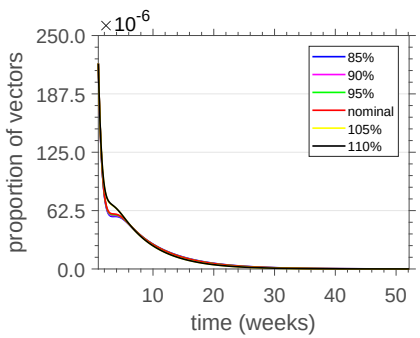
Cumulative infectious



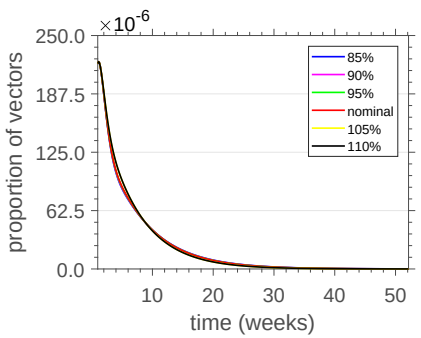
New cases



Susceptible vectors

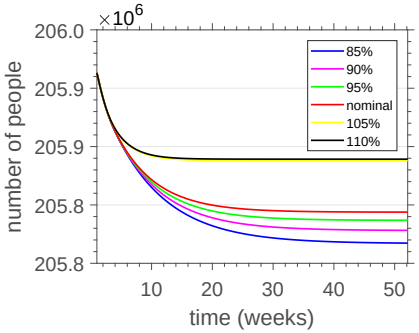


Exposed vectors

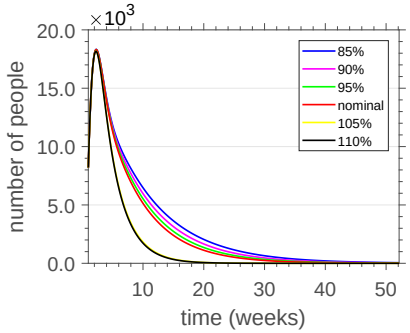


Infectious vectors

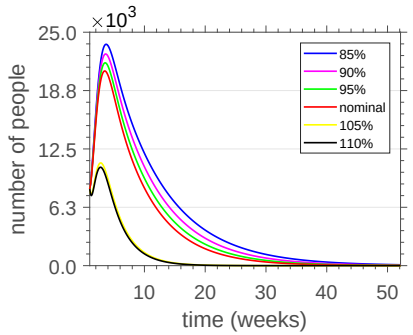
Sensitivity curves for γ



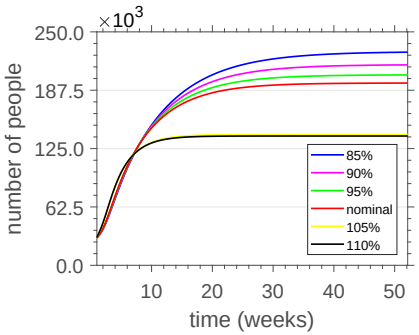
Susceptible humans



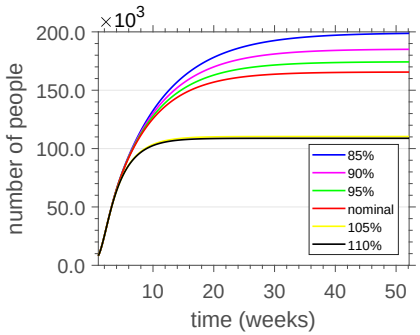
Exposed humans



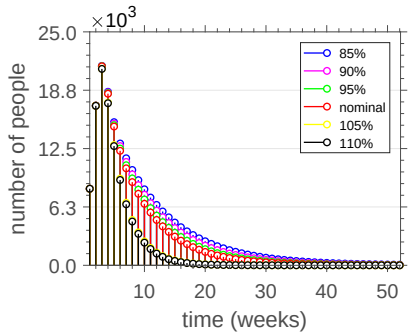
Infectious humans



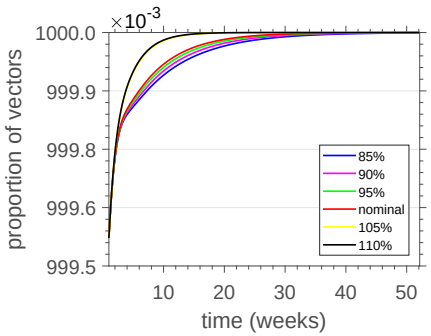
Recovered humans



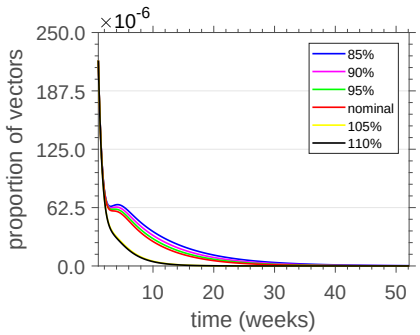
Cumulative infectious



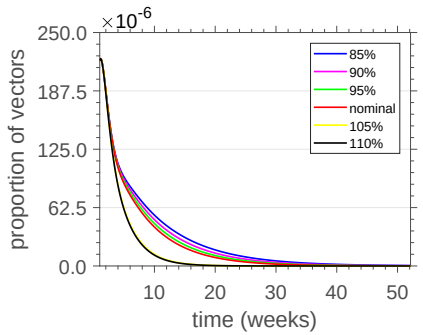
New cases



Susceptible vectors

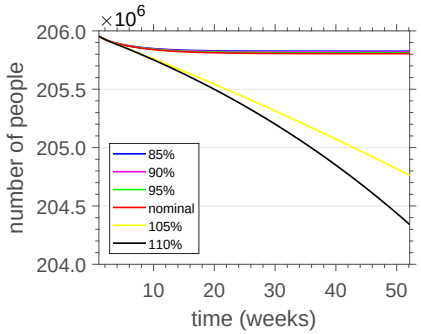


Exposed vectors

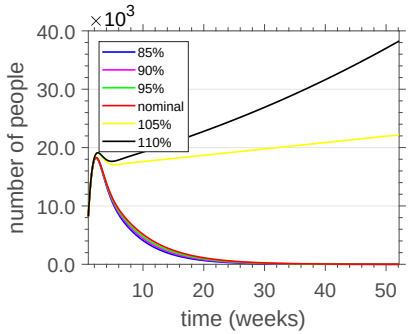


Infectious vectors

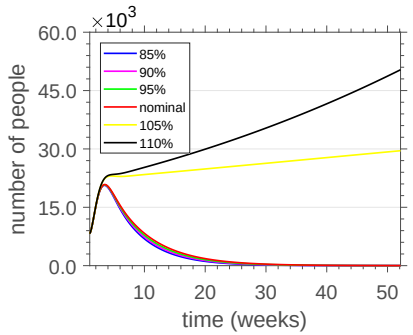
Sensitivity curves for β_v



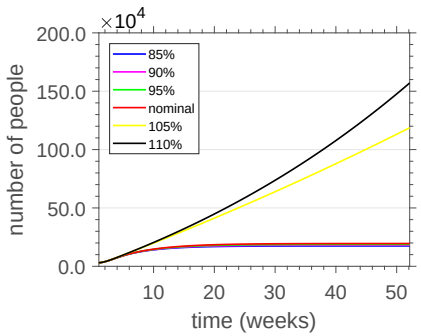
Susceptible humans



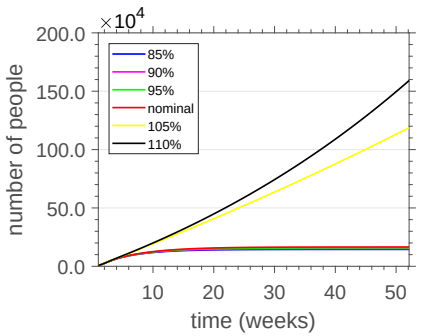
Exposed humans



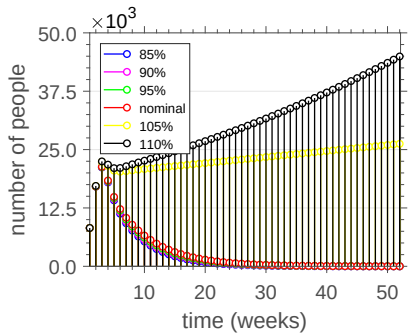
Infectious humans



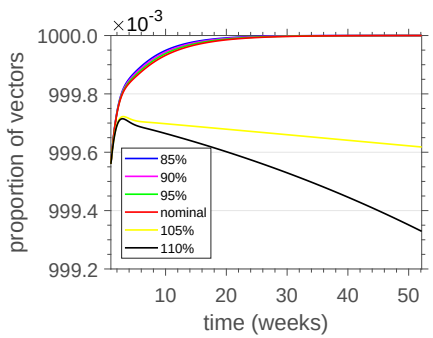
Recovered humans



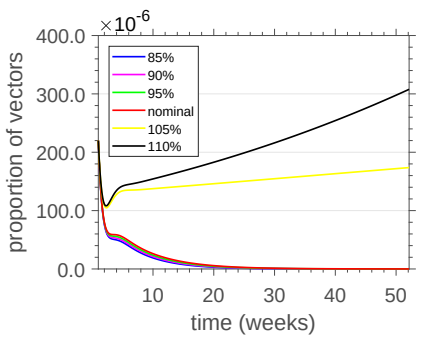
Cumulative infectious



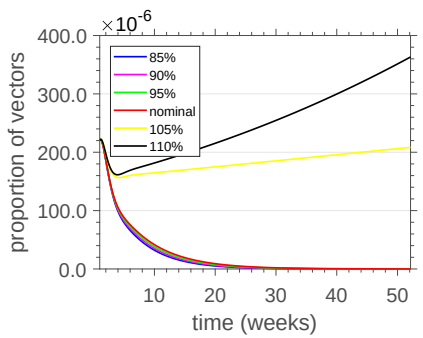
New cases



Susceptible vectors

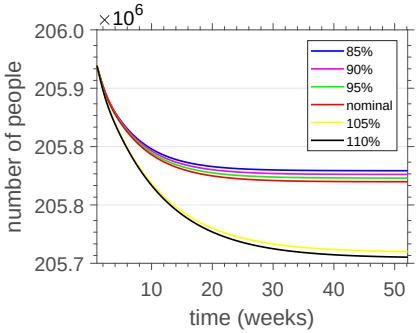


Exposed vectors

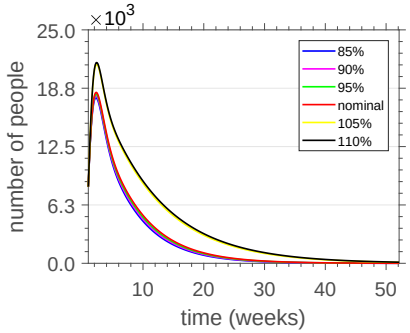


Infectious vectors

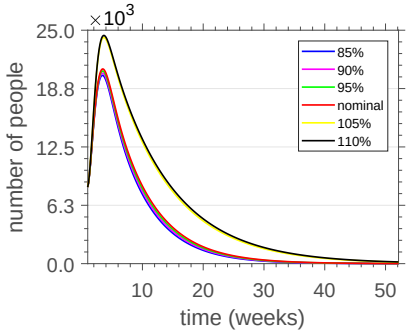
Sensitivity curves for α_v



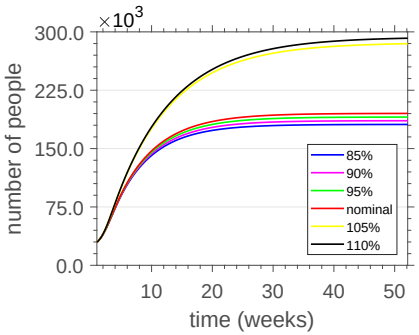
Susceptible humans



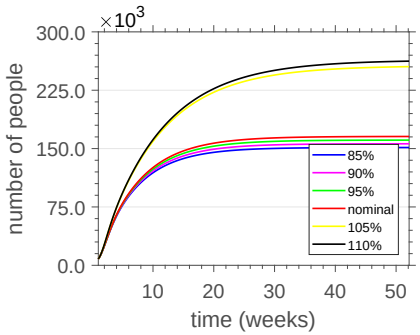
Exposed humans



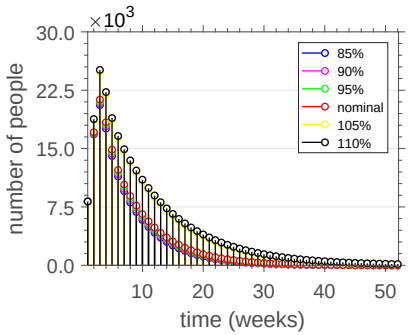
Infectious humans



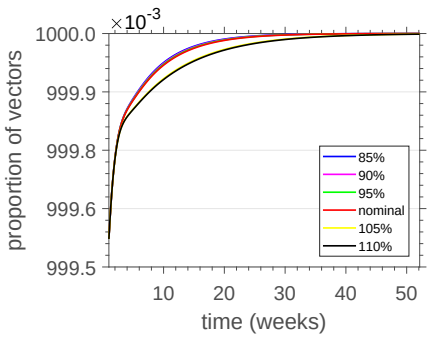
Recovered humans



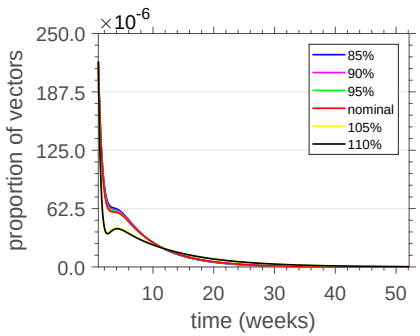
Cumulative infectious



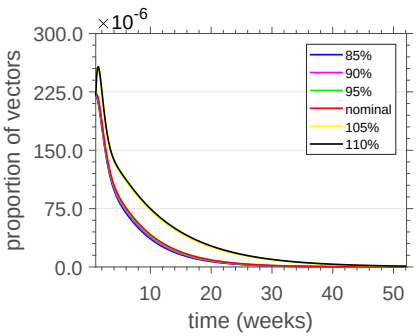
New cases



Susceptible vectors

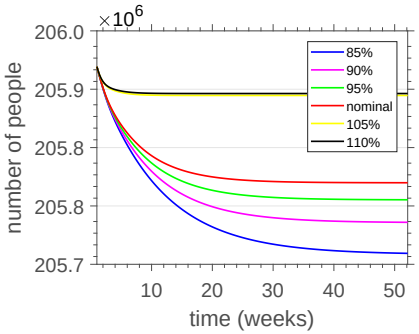


Exposed vectors

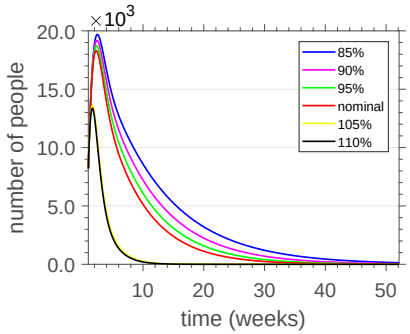


Infectious vectors

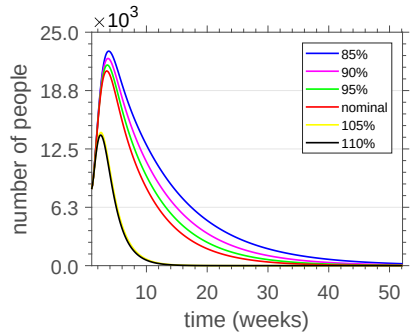
Sensitivity curves for δ



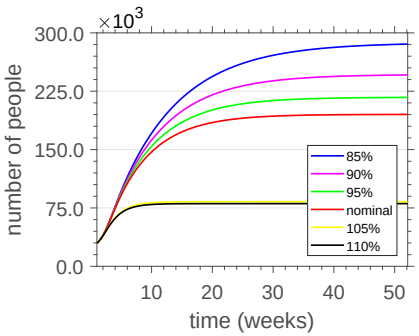
Susceptible humans



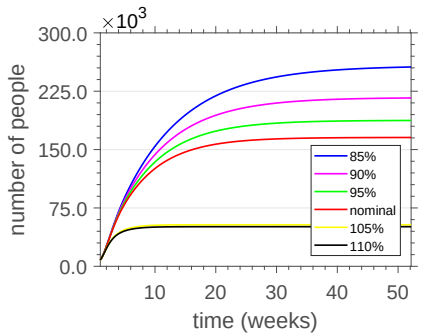
Exposed humans



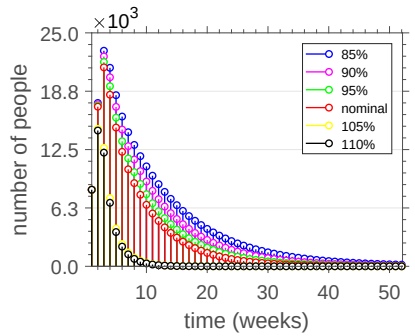
Infectious humans



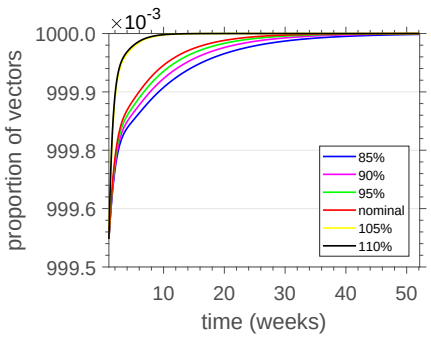
Recovered humans



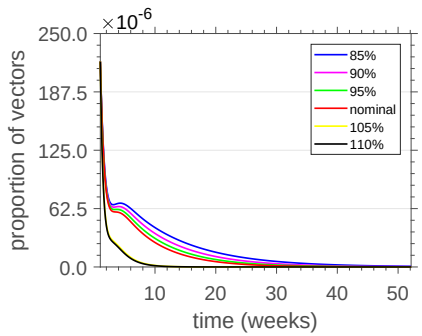
Cumulative infectious



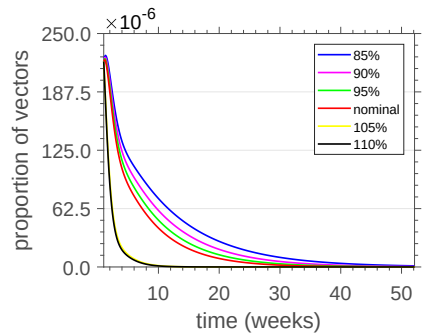
New cases



Susceptible vectors



Exposed vectors



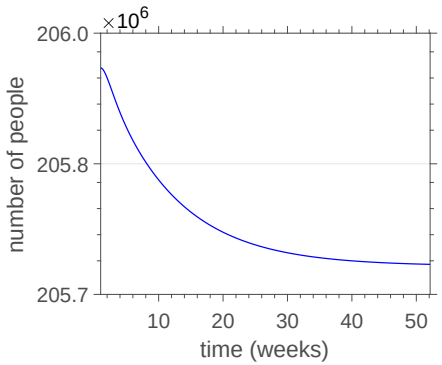
Infectious vectors

Results of Model Calibration

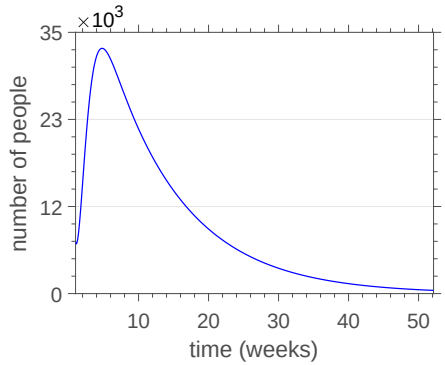
Calibration parameters and IC

$\boldsymbol{\alpha}$	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	$0.9 \times$ 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

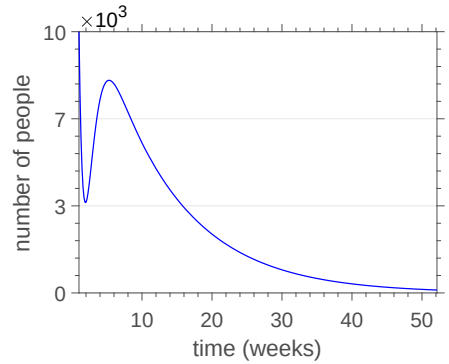
Curves for calibrated model



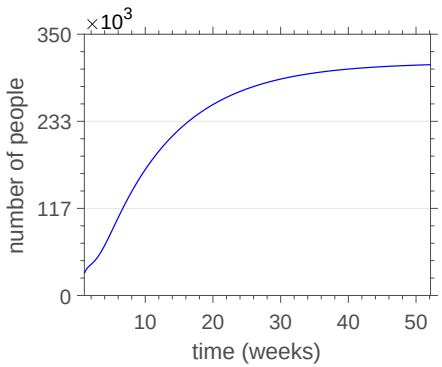
Susceptible humans



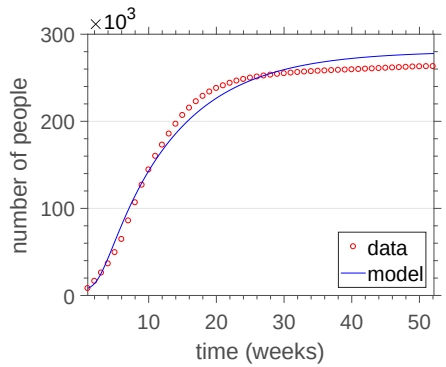
Exposed humans



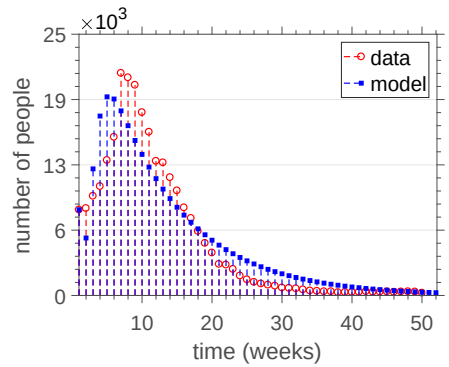
Infectious humans



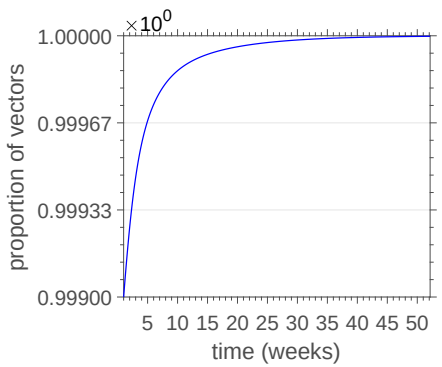
Recovered humans



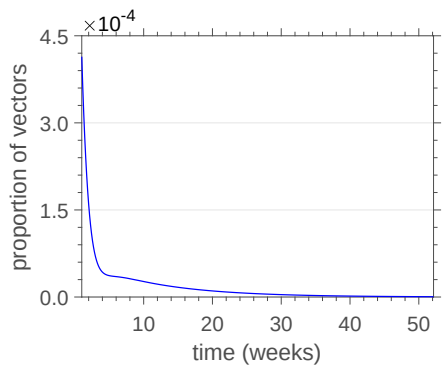
Cumulative infectious



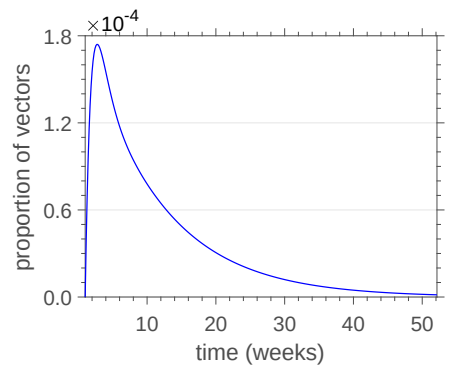
New cases



Susceptible vectors



Exposed vectors



Infectious vectors