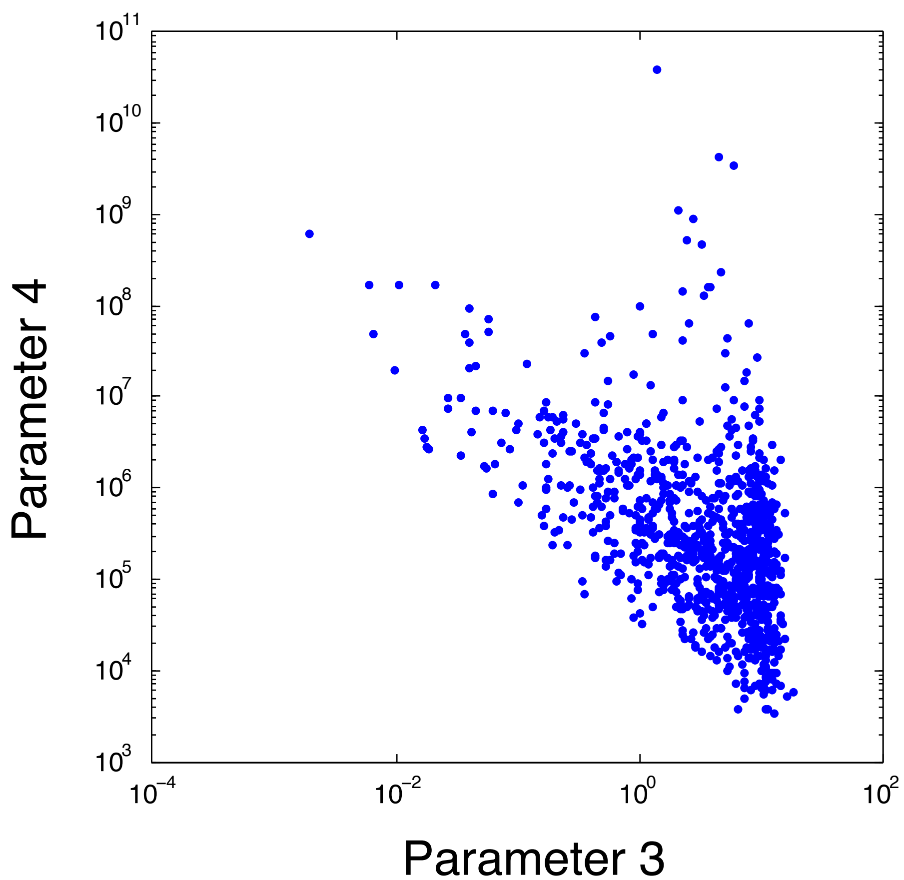
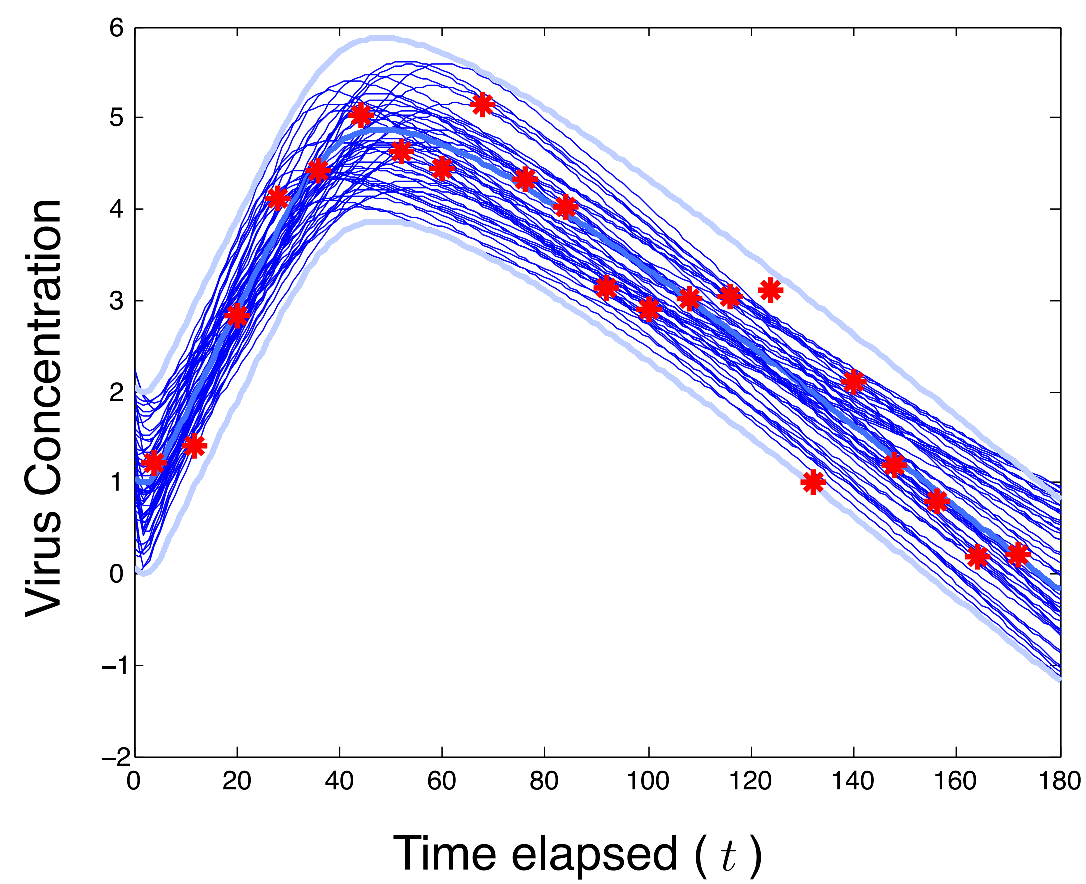
A Practical Algorithm
for
"Practical" Parameter Identifiability Analysis





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National Institute of Informatics

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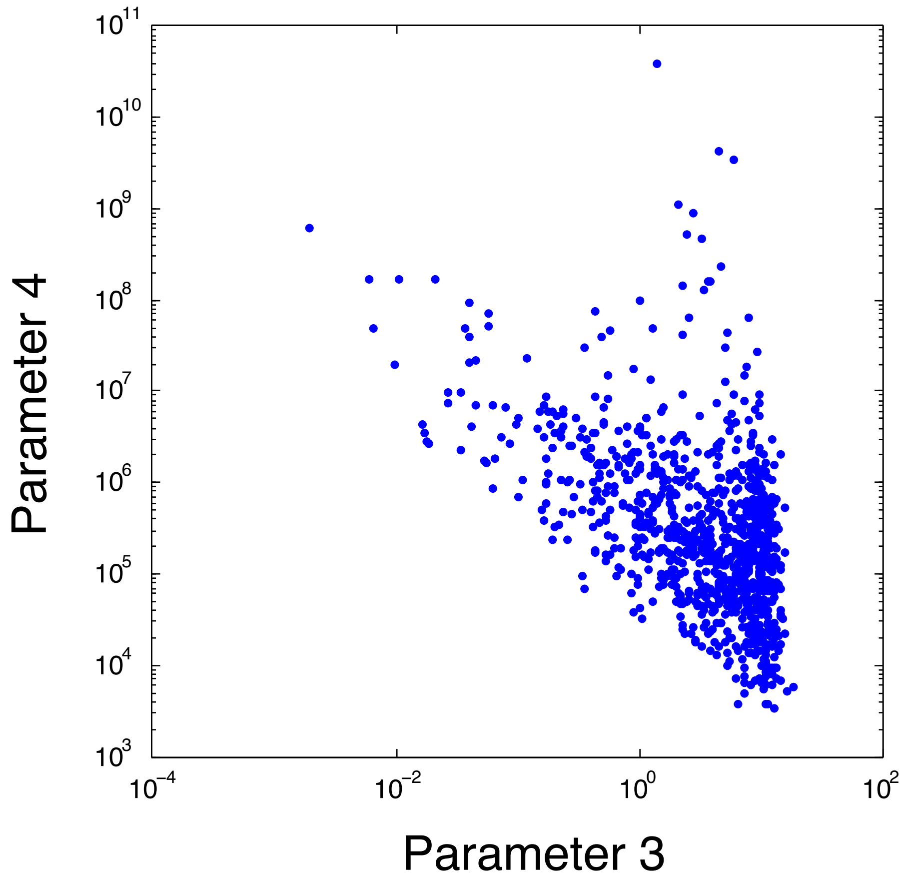

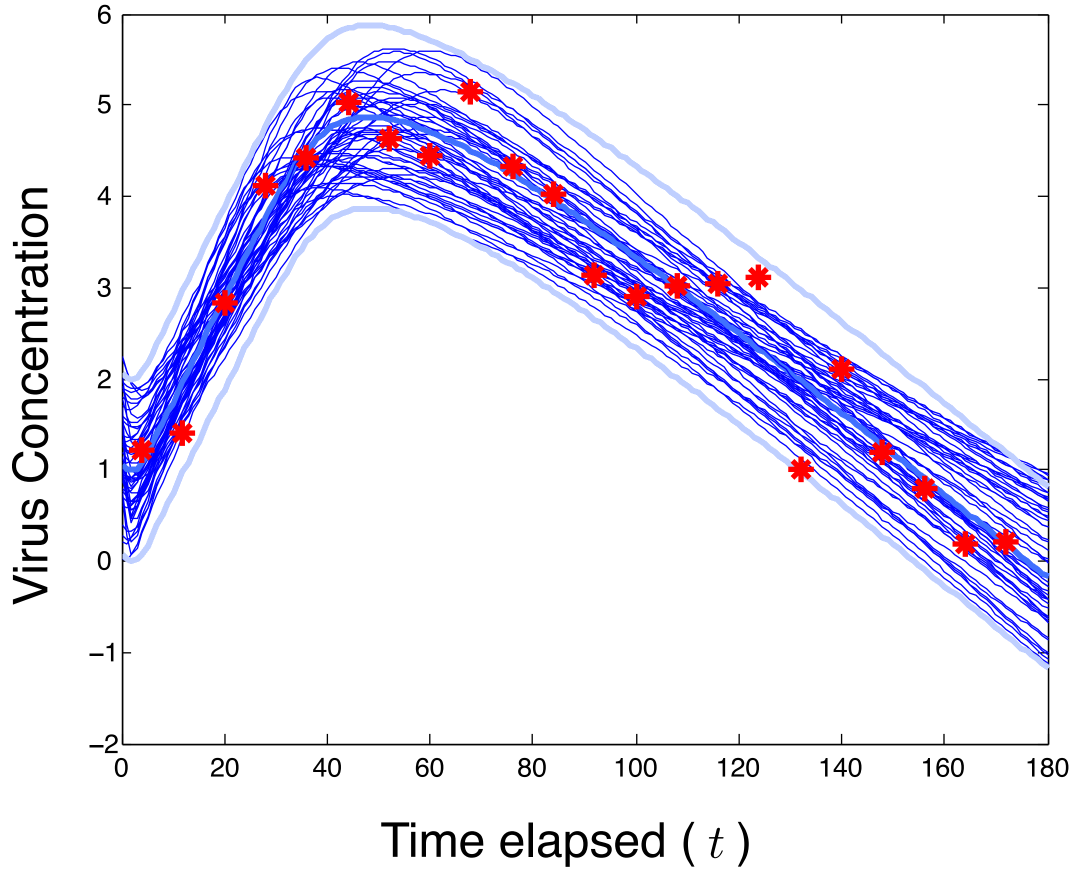

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Parameter Identifiability Analysis

Parameter Identifiability Analysis

Hongyu Miao, Xiaohua Xia, Alan S. Perelson, and Hulin Wu.
On Identifiability of Nonlinear ODE Models and Applications in Viral Dynamics. SIAM REVIEW, 53(1):3–39, 2011.

Structural Parameter Identifiability Analysis

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Structural Parameter Identifiability Analysis

Assuming there is no variability of data, can we uniquely estimate model parameters?

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Structural Parameter Identifiability Analysis

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Practical Parameter Identifiability Analysis

Given a certain level of variability of data, how precisely can we estimate model parameters?

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Practical Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost

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Practical Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Fisher Information Matrix	not-Robust ✗	

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Practical Parameter Identifiability Analysis

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Fisher Information Matrix	not-Robust ✗	Fast ✓

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Practical Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Fisher Information Matrix	not-Robust ✗	Fast ✓
Monte Carlo / Bootstrap method		

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Example 0 : Influenza Kinetics model (Baccam et al.)

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$$\frac{du_1}{dt} = -x_1 u_1 u_4$$
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$$\frac{du_3}{dt} = \frac{1}{x_2} u_2 - \frac{1}{x_3} u_3$$
$$\frac{du_4}{dt} = \frac{x_4}{x_5} u_3 - x_6 u_4$$

$$u_1(t=0) = x_5$$
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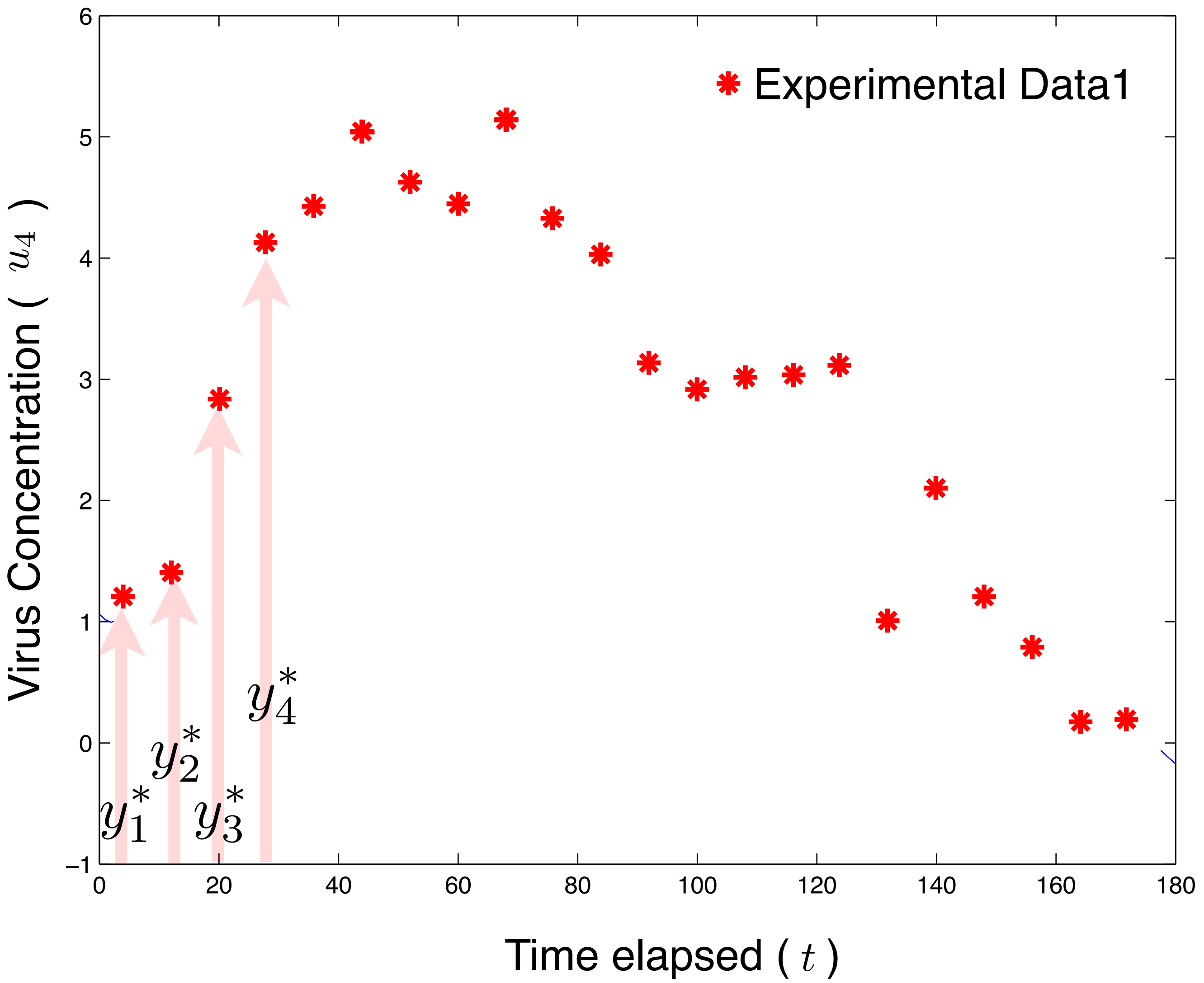
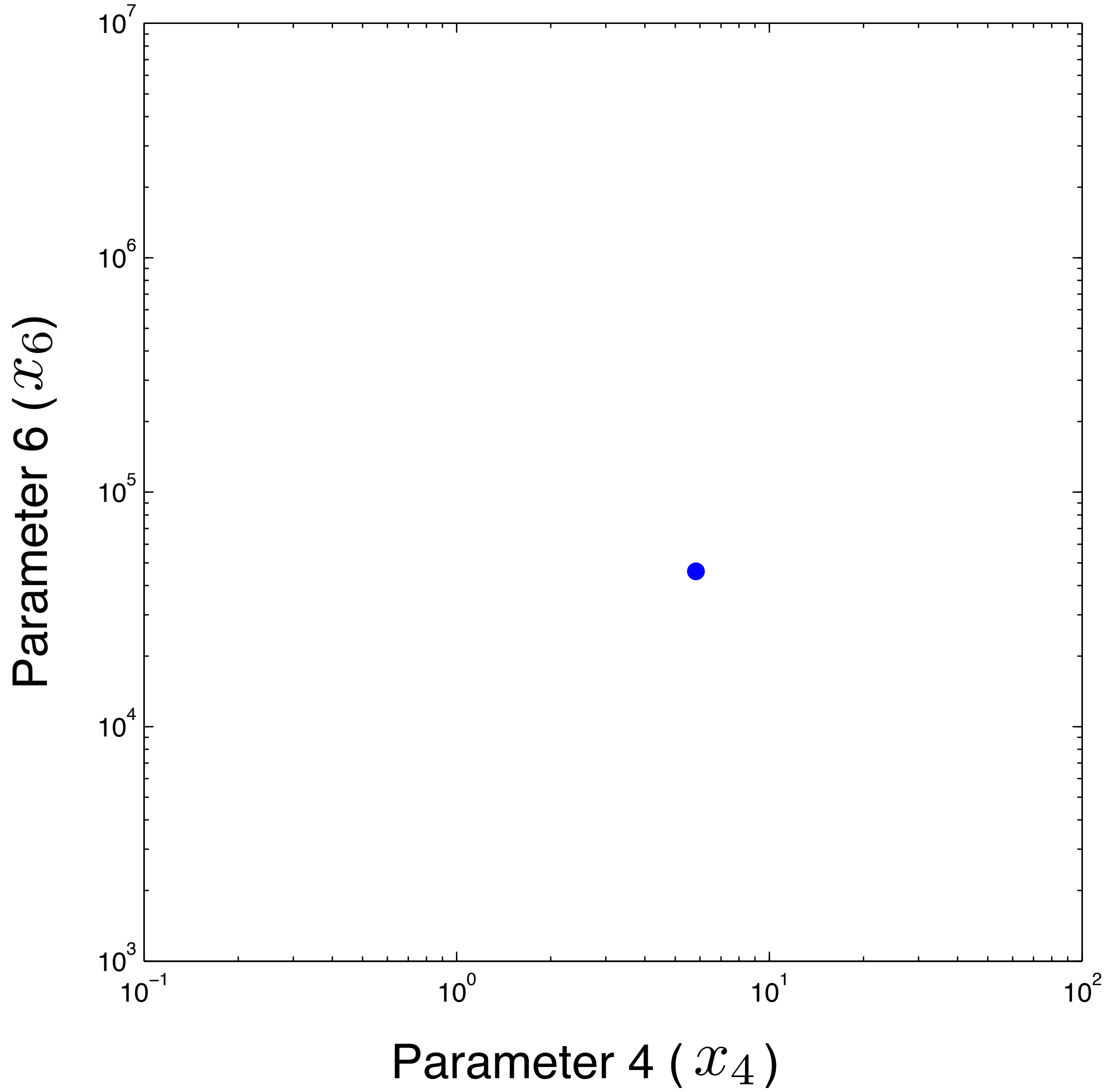
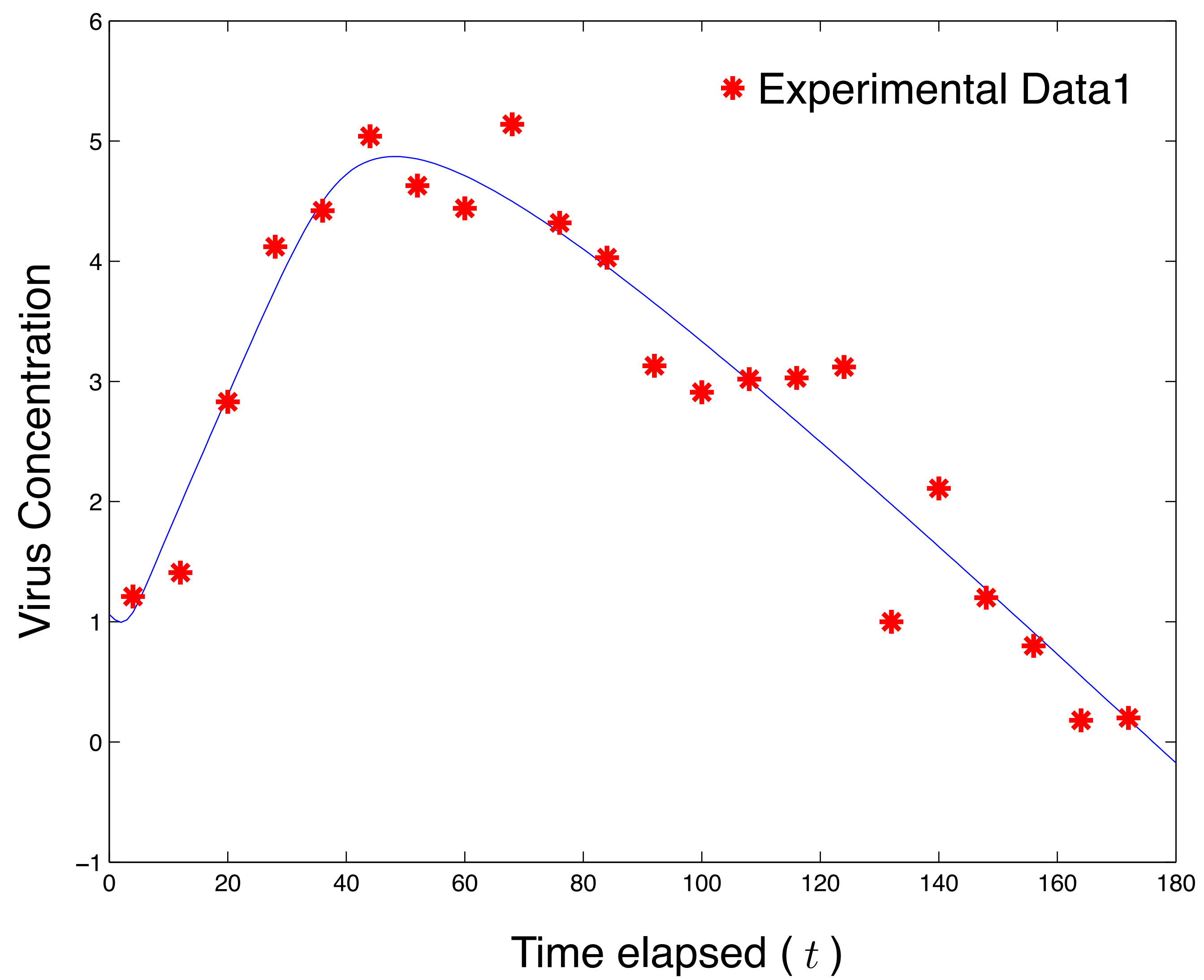


Monte Carlo / Bootstrap method

Monte Carlo / Bootstrap method





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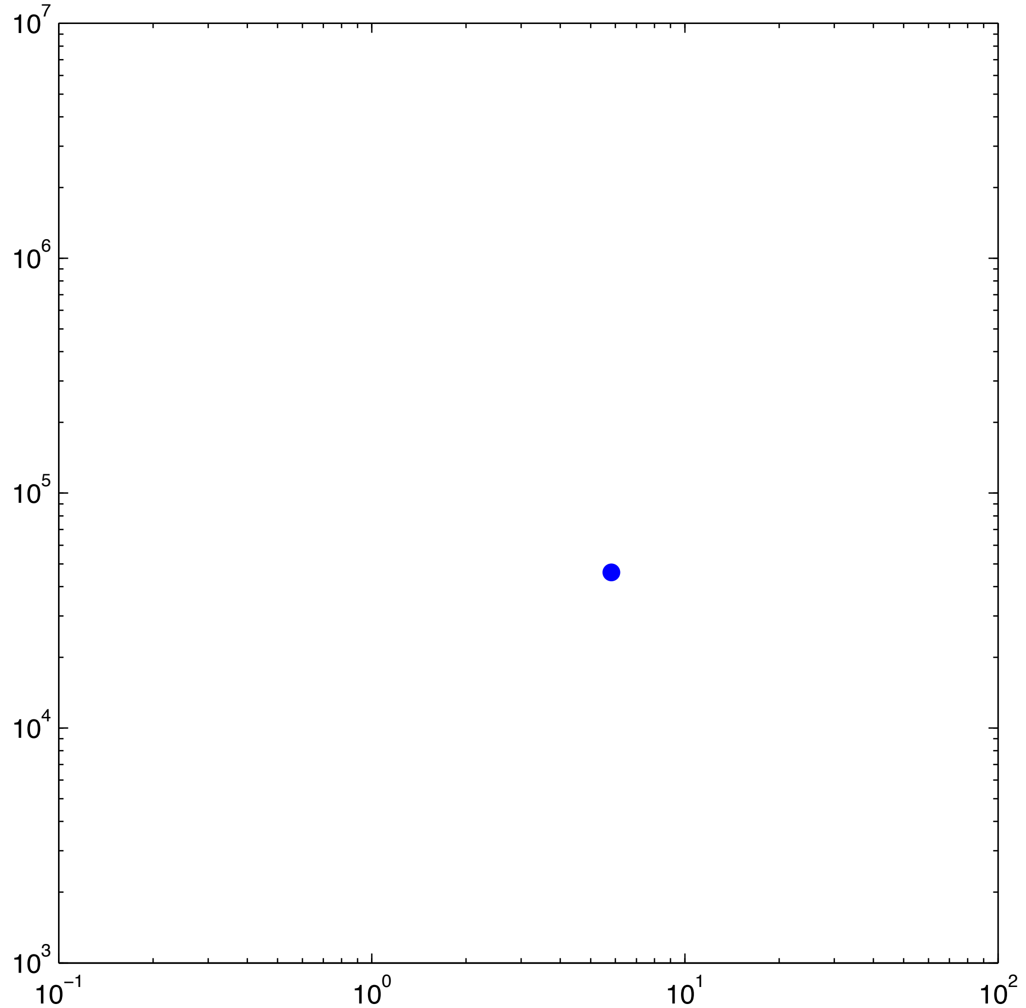
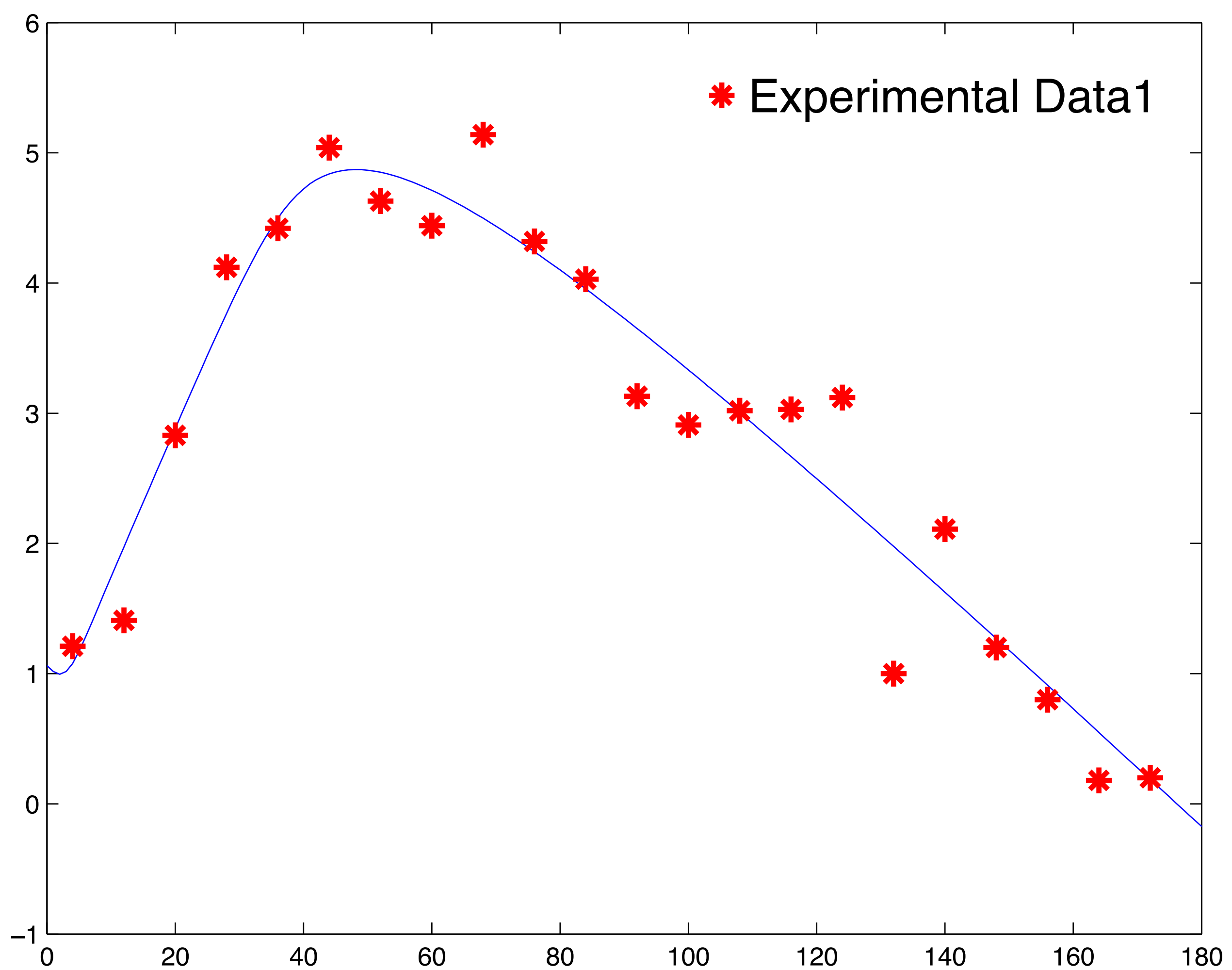
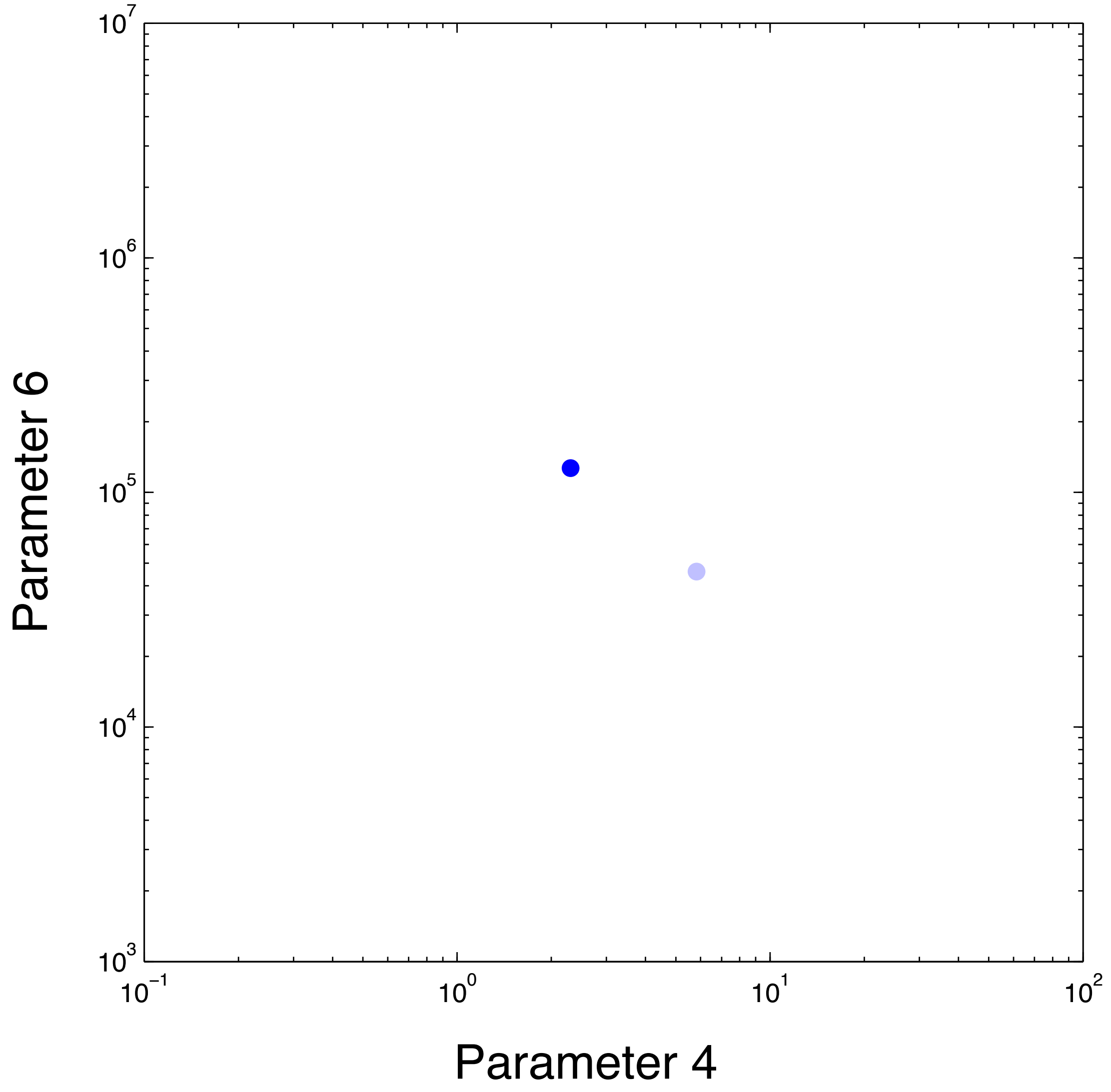
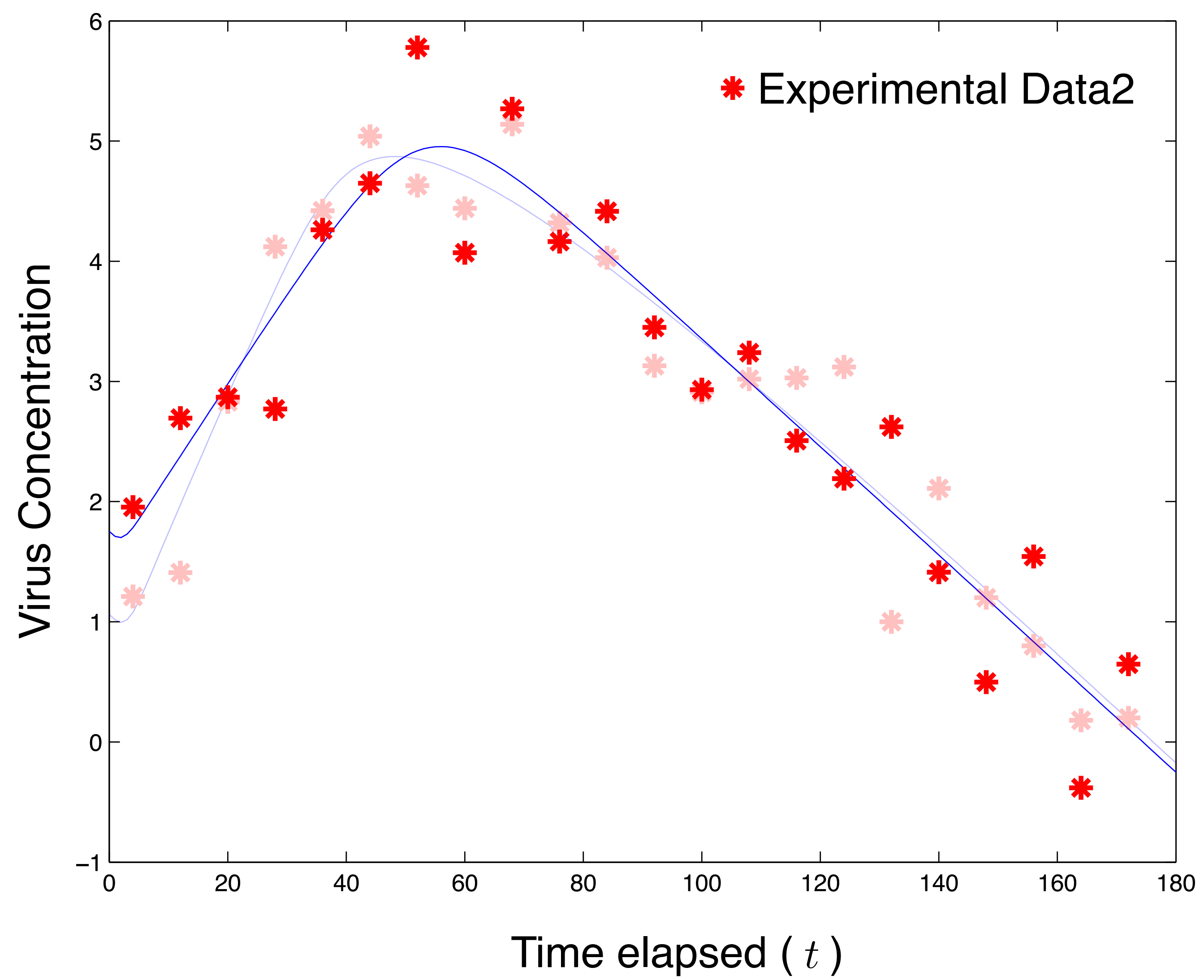




Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*_{\text{exp1}}||_2$

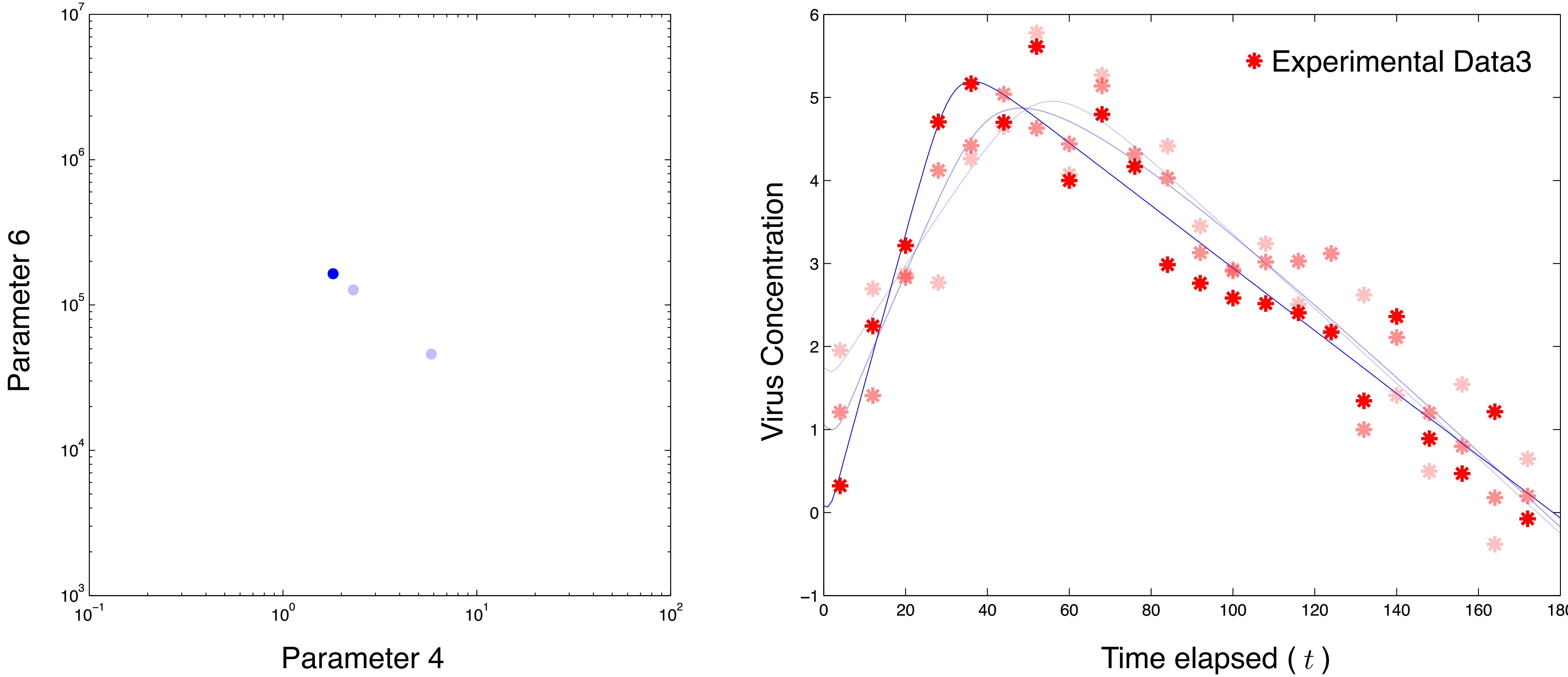
Monte Carlo / Bootstrap method





Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*_{\text{exp2}}||_2$

Monte Carlo / Bootstrap method



Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*_{\text{exp3}}||_2$

Monte Carlo / Bootstrap method

We do not usually have enough sets of experimental data to conduct statistical analyses on the sets of parameters found from them...

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Artificially create data.

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↓

Artificially create data.

Explicitly specify variability level and distribution

↙

Monte Carlo method

Monte Carlo / Bootstrap method

We do not usually have enough sets of experimental data to conduct statistical analyses on the sets of parameters found from them...

Artificially create data.

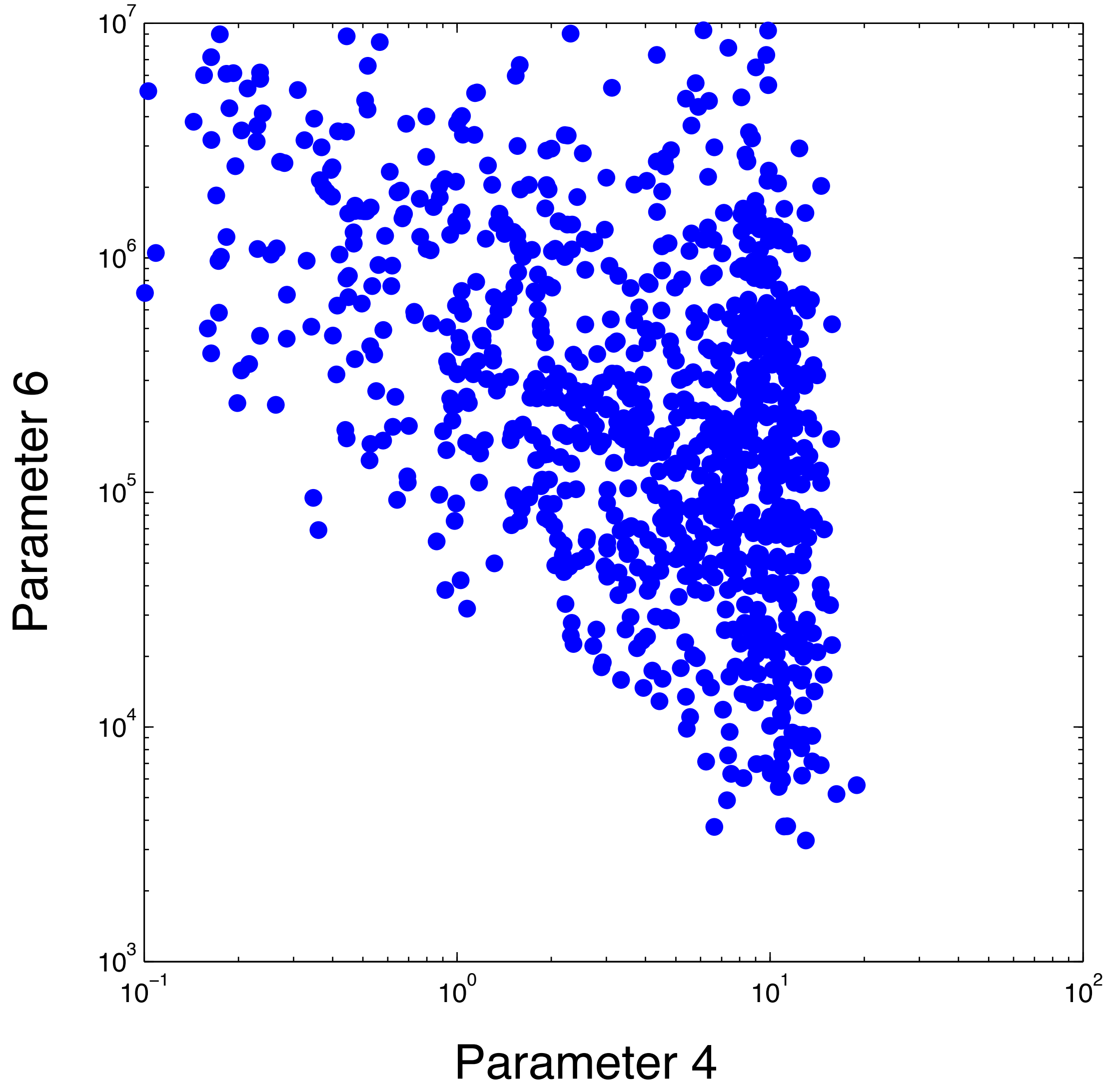
Explicitly specify variability level and distribution

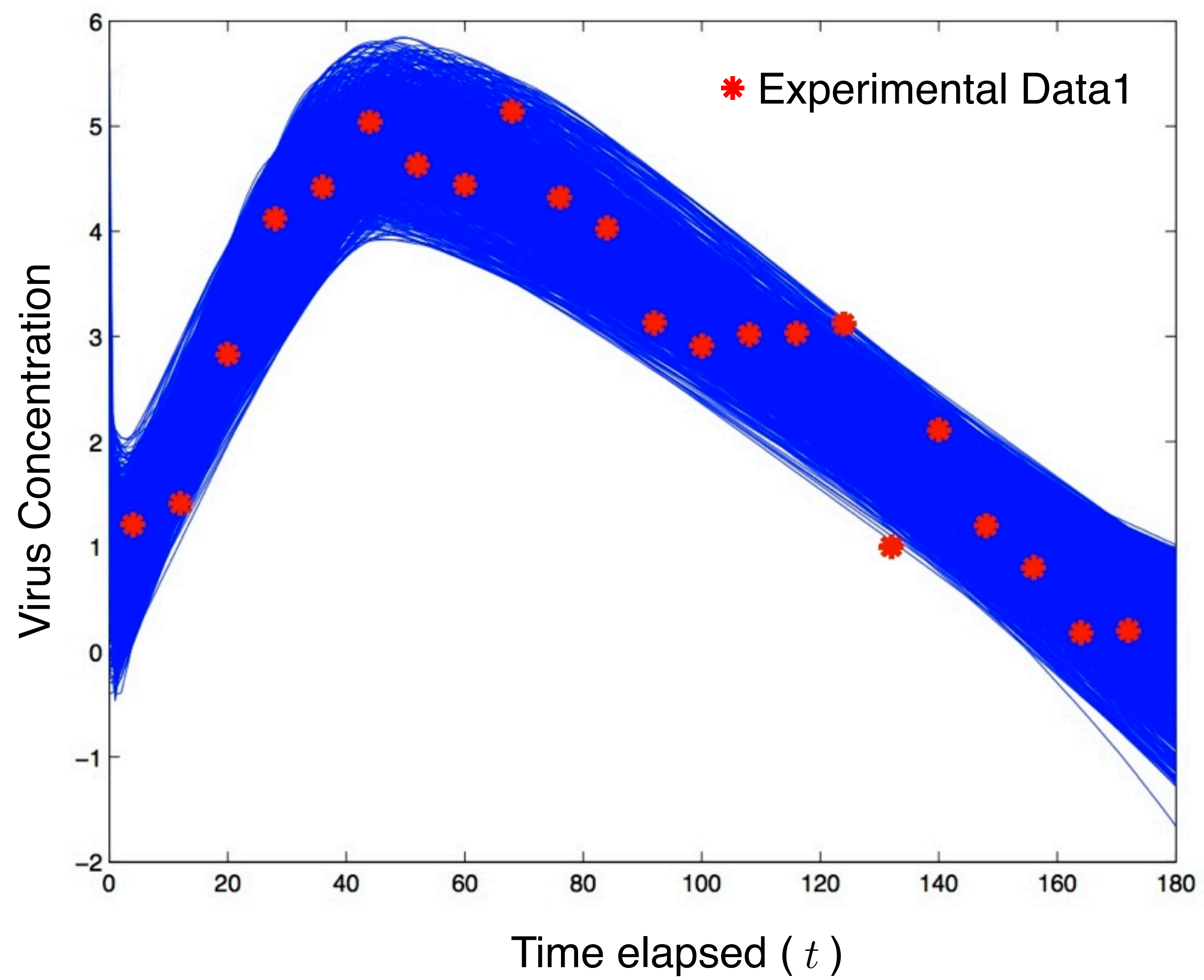
Resample residuals

Monte Carlo method

Bootstrap method

Monte Carlo / Bootstrap method





Monte Carlo / Bootstrap method

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$$\vdots$$

Monte Carlo / Bootstrap method

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Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*_{\text{exp3}}||_2$

$\vdots$

Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*_{\text{exp1000}}||_2$

Monte Carlo / Bootstrap method

Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*||_2$

Monte Carlo / Bootstrap method

Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*||_2$

Gauss Newton method

$$\boldsymbol{x}_{\mathrm{new}} = \boldsymbol{x}_{\mathrm{old}} + (J^{\mathrm{T}}J)^{-1}(J^{\mathrm{T}}(\boldsymbol{f}(\boldsymbol{x}_{\mathrm{old}}) - \boldsymbol{y}^*))$$

Monte Carlo / Bootstrap method

Find $\boldsymbol{x}$ that minimizes $||\boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{y}^*||_2$

Levenberg-Marquardt method

$$\boldsymbol{x}_{\mathrm{new}} = \boldsymbol{x}_{\mathrm{old}} + (J^{\mathrm{T}}J + \lambda I)^{-1}(J^{\mathrm{T}}(\boldsymbol{f}(\boldsymbol{x}_{\mathrm{old}}) - \boldsymbol{y}^*))$$

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Approximating the Jacobian matrix

is computationally **expensive**...

Conventional Algorithm

Conventional Algorithm

Jacobian matrix:

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_m} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_m} \end{bmatrix}$$

Conventional Algorithm

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$$\begin{matrix} \frac{\partial f_1}{\partial x_1} \\ \frac{\partial f_2}{\partial x_1} \\ \vdots \\ \frac{\partial f_n}{\partial x_1} \end{matrix}$$

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$$\begin{bmatrix} \frac{\partial f_1}{\partial x_1} \\ \frac{\partial f_2}{\partial x_1} \\ \vdots \\ \frac{\partial f_n}{\partial x_1} \end{bmatrix} \approx$$

Conventional Algorithm

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$$\begin{bmatrix} \boldsymbol{\frac{\partial f_1}{\partial x_1}} \\ \boldsymbol{\frac{\partial f_2}{\partial x_1}} \\ \vdots \\ \boldsymbol{\frac{\partial f_n}{\partial x_1}} \end{bmatrix} \approx \quad \boldsymbol{f}(x_1, x_2, \cdots x_m)$$

Conventional Algorithm

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Conventional Algorithm

Jacobian matrix:

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_m} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_m} \end{bmatrix}$$

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$$i = 1, 2, \ldots, m$$

Conventional Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

Conventional Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

(Number of parameters + 1)

Conventional Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

(Number of parameters + 1) x Number of iterations

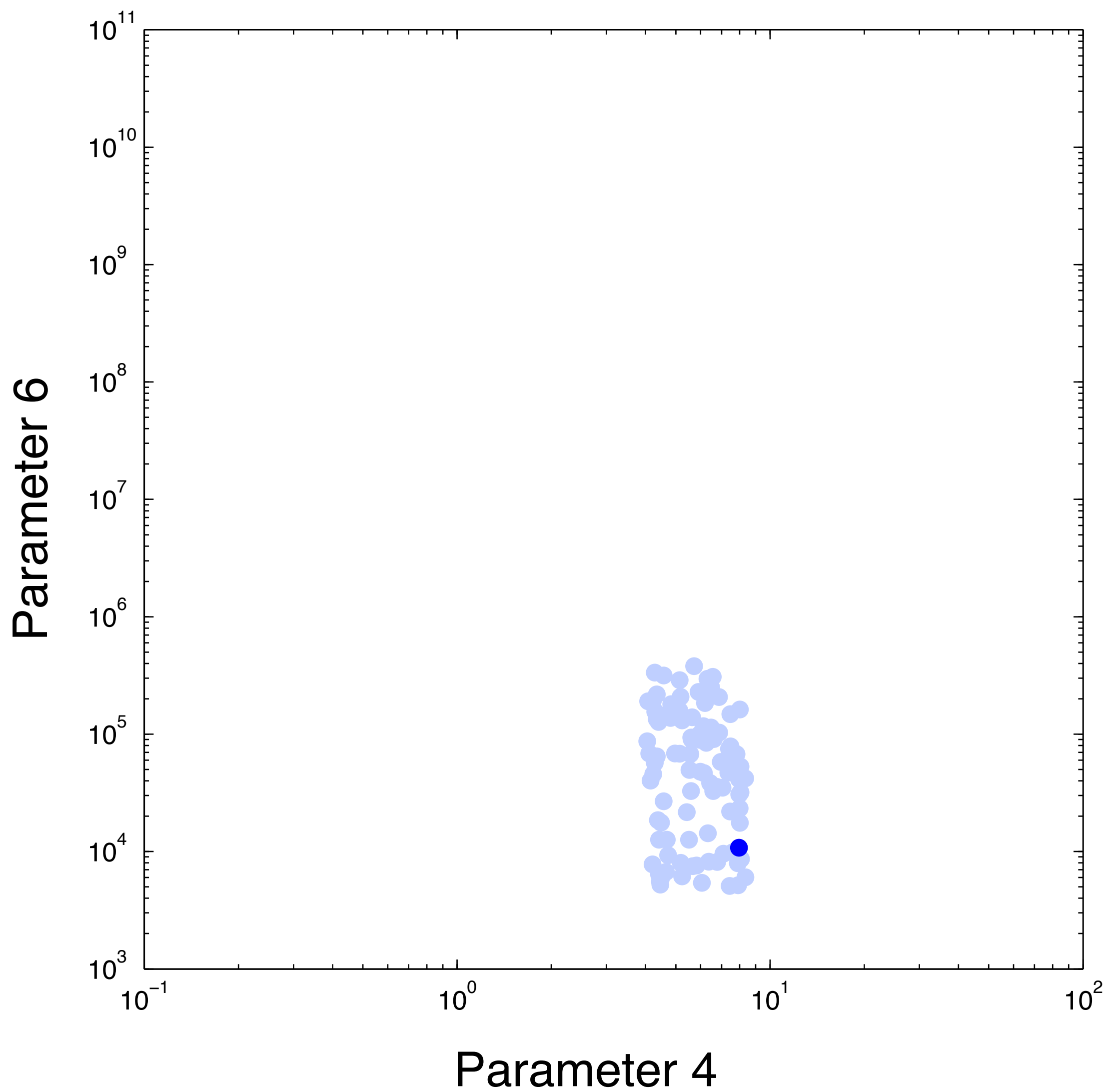
Conventional Algorithm

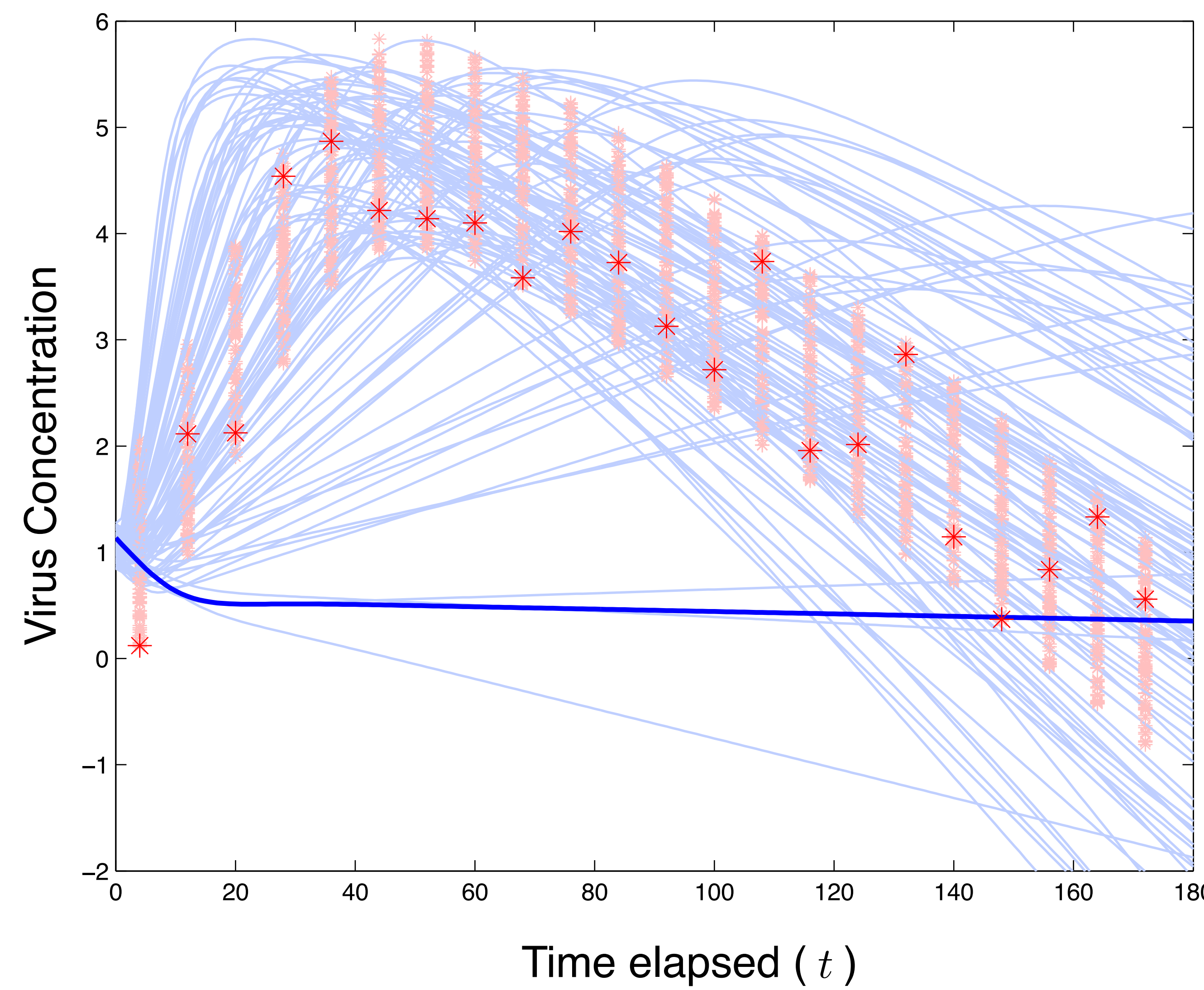
Number of simulations needed to obtain 1,000 sets of parameters.

(Number of parameters + 1) x Number of iterations x 1,000

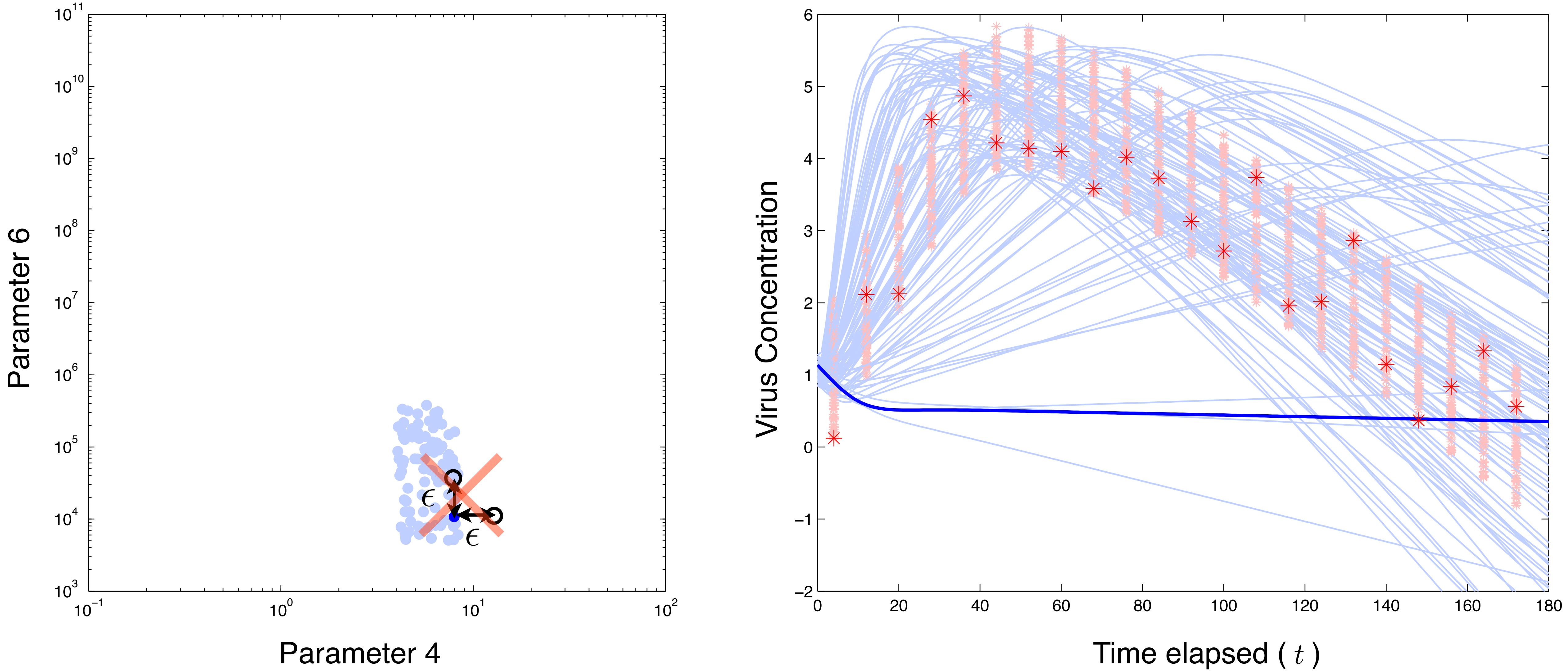
New Algorithm

New Algorithm





New Algorithm



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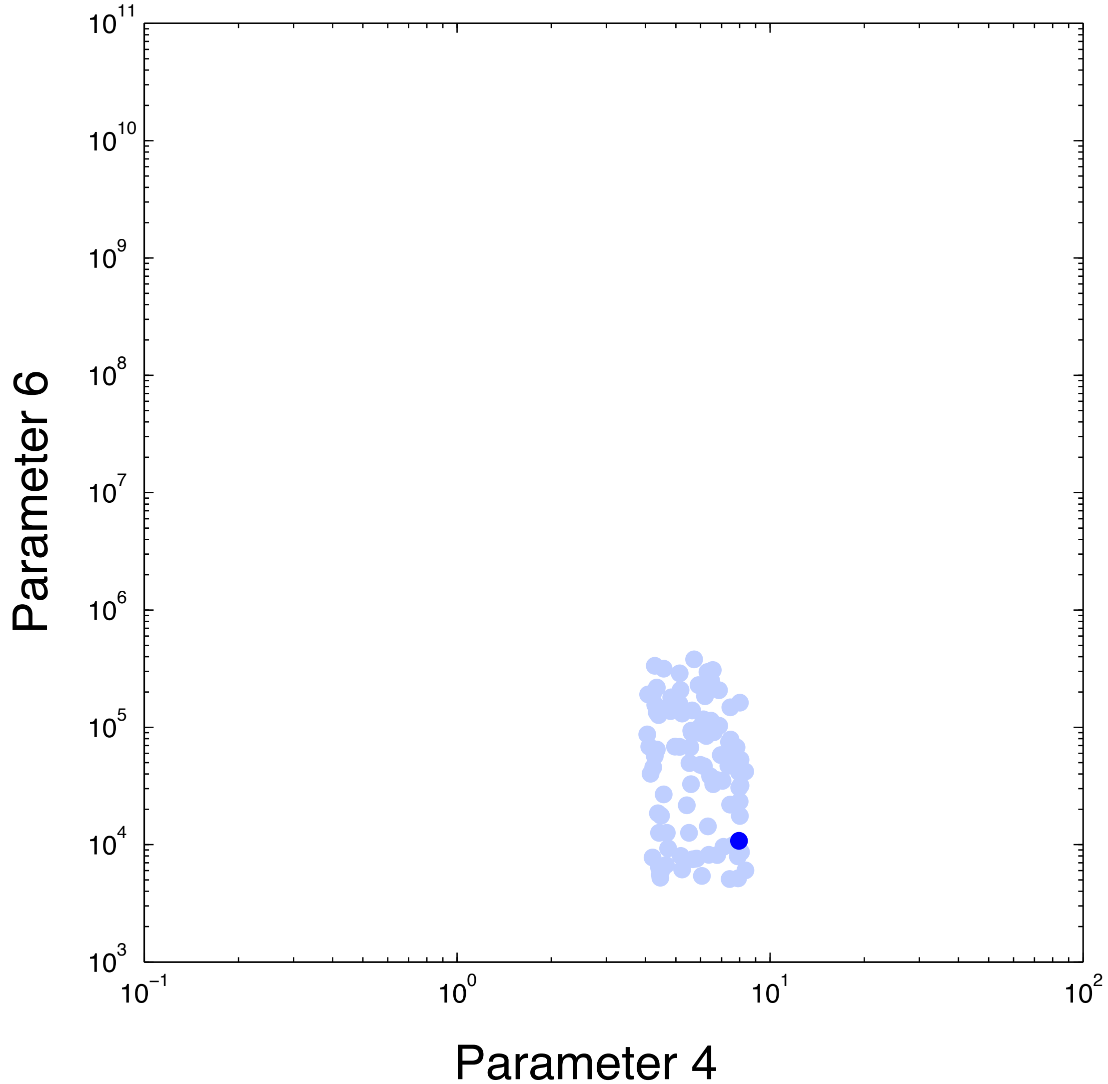

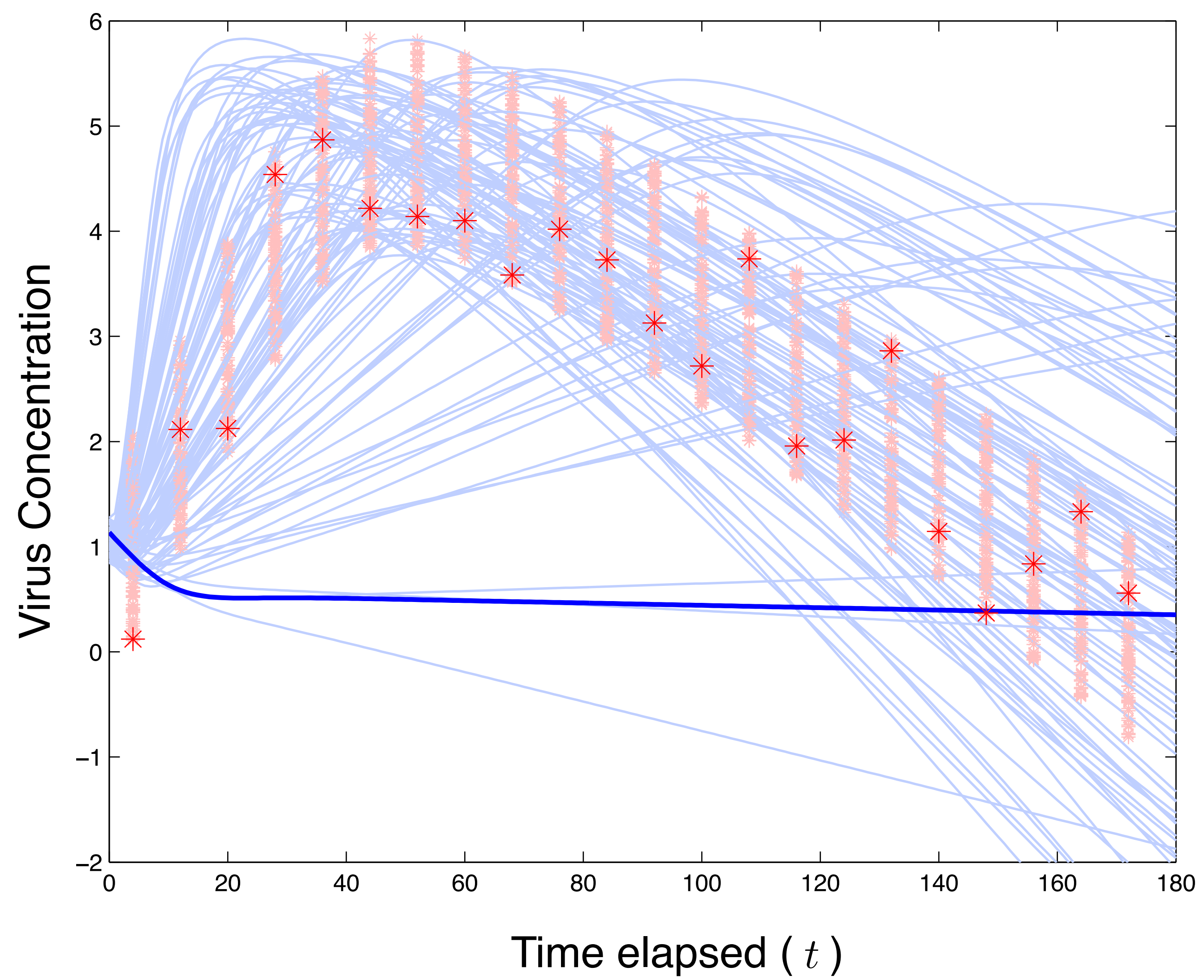

New Algorithm

Approximating the Jacobian matrix using the **neighbours**...

New Algorithm

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Jacobian is like... Slope

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$$\text{Slope} \approx \frac{\text{Rise}}{\text{Run}}$$

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Jacobian is like...

$$\text{Slope} \approx \frac{\text{Rise}}{\text{Run}}$$

Rise: $\Delta \boldsymbol{y} = \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\boldsymbol{x}_{\text{neighbour}})$

New Algorithm

Approximating the Jacobian matrix using the **neighbours**...

Jacobian is like... $\text{Slope} \approx \dfrac{\text{Rise}}{\text{Run}}$

Rise: $\Delta \boldsymbol{y} = \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\boldsymbol{x}_{\text{neighbour}})$

Run: $\Delta \boldsymbol{x} = \boldsymbol{x} - \boldsymbol{x}_{\text{neighbour}}$

New Algorithm

Approximating the Jacobian matrix using the **neighbours**...

Jacobian is like...

$$J_{\text{approx}} = \frac{\Delta \boldsymbol{y}}{\Delta \boldsymbol{x}}$$

Rise: $\Delta \boldsymbol{y} = \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\boldsymbol{x}_{\text{neighbour}})$

Run: $\Delta \boldsymbol{x} = \boldsymbol{x} - \boldsymbol{x}_{\text{neighbour}}$

New Algorithm

Approximating the Jacobian matrix using the **neighbours**...

$$\Delta \boldsymbol{y} \quad = J_{\text{approx}} \Delta \boldsymbol{x}$$

$$\Delta \boldsymbol{y} = \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\boldsymbol{x}_{\text{neighbour}})$$

$$\Delta \boldsymbol{x} = \boldsymbol{x} - \boldsymbol{x}_{\text{neighbour}}$$

New Algorithm

Approximating the Jacobian matrix using the **neighbours**...

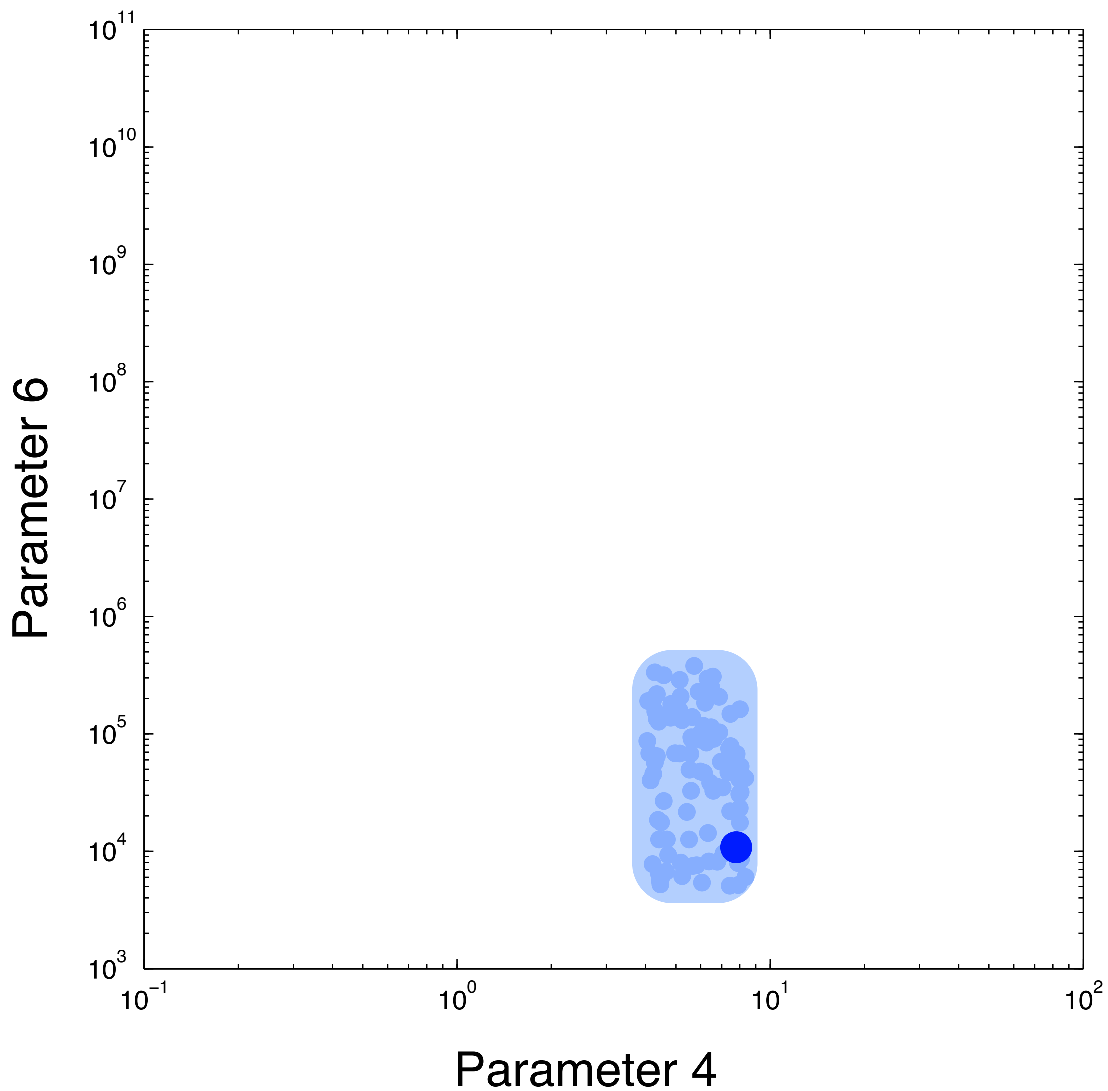
$$\Delta \boldsymbol{y}^{(i)} = J_{\mathrm{approx}} \Delta \boldsymbol{x}^{(i)}$$

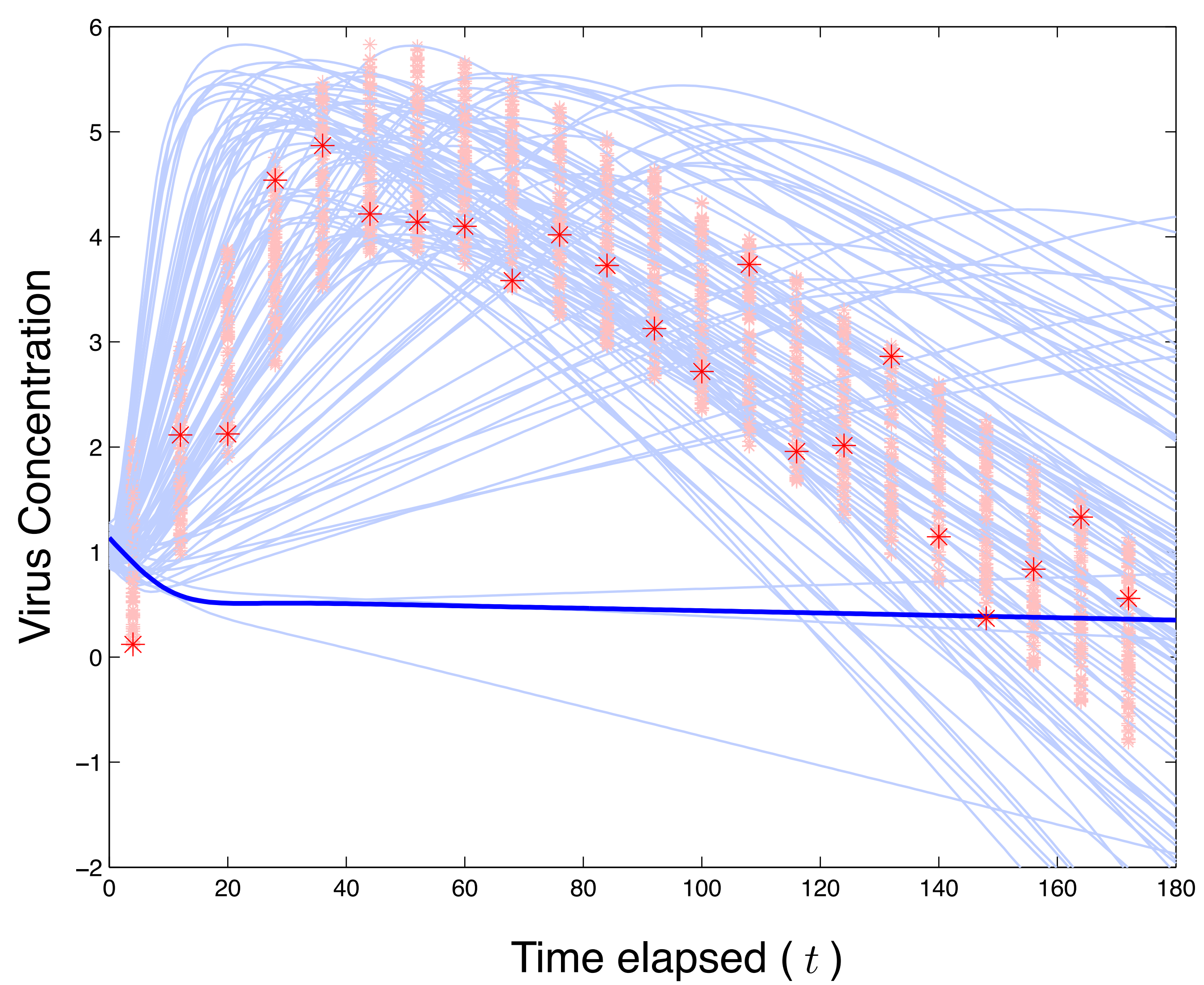
$$\text{for } i = 1, 2, \ldots, n_{\mathrm{neighbour}}$$

$$\Delta \boldsymbol{y}^{(i)} = \boldsymbol{f}(\boldsymbol{x}) - \boldsymbol{f}(\boldsymbol{x}^{(i)}_{\mathrm{neighbour}})$$

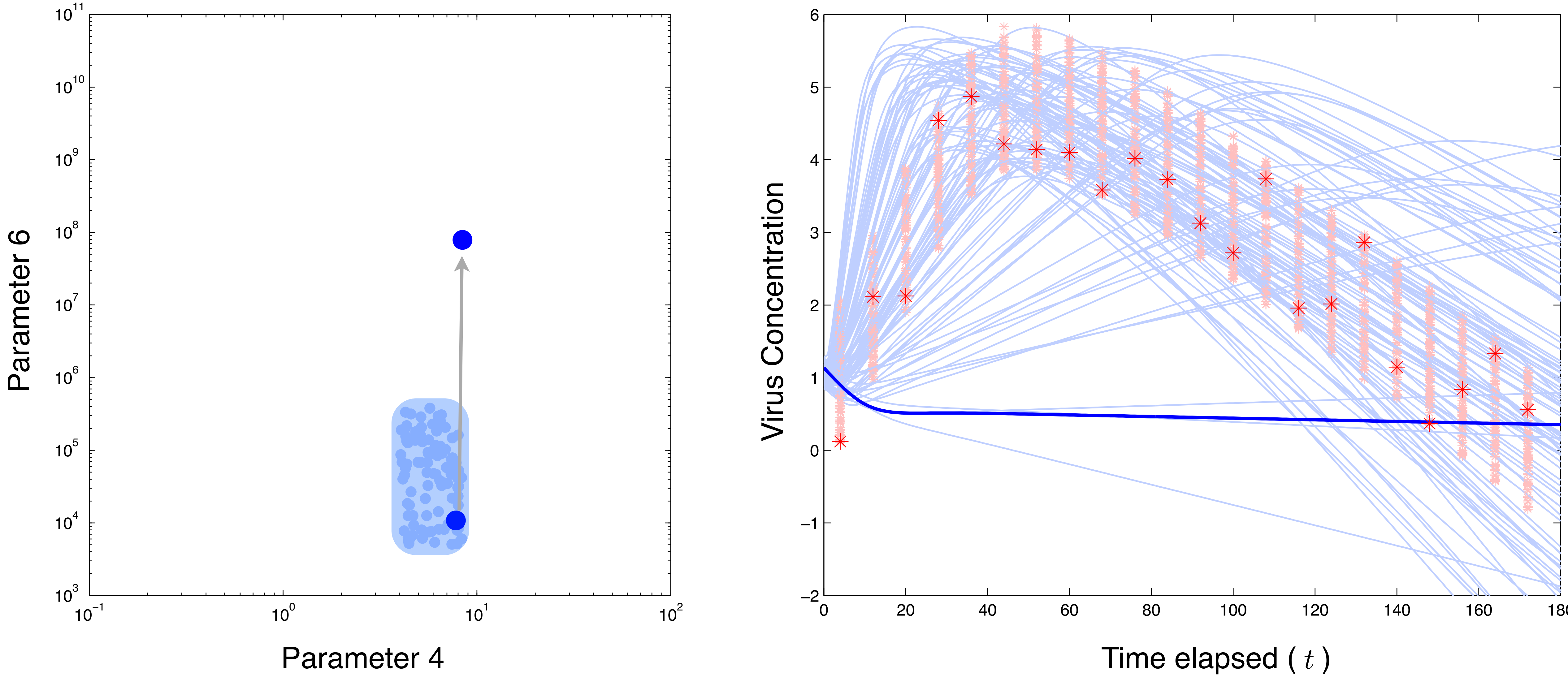
$$\Delta \boldsymbol{x}^{(i)} = \boldsymbol{x} - \boldsymbol{x}^{(i)}_{\mathrm{neighbour}}$$

New Algorithm

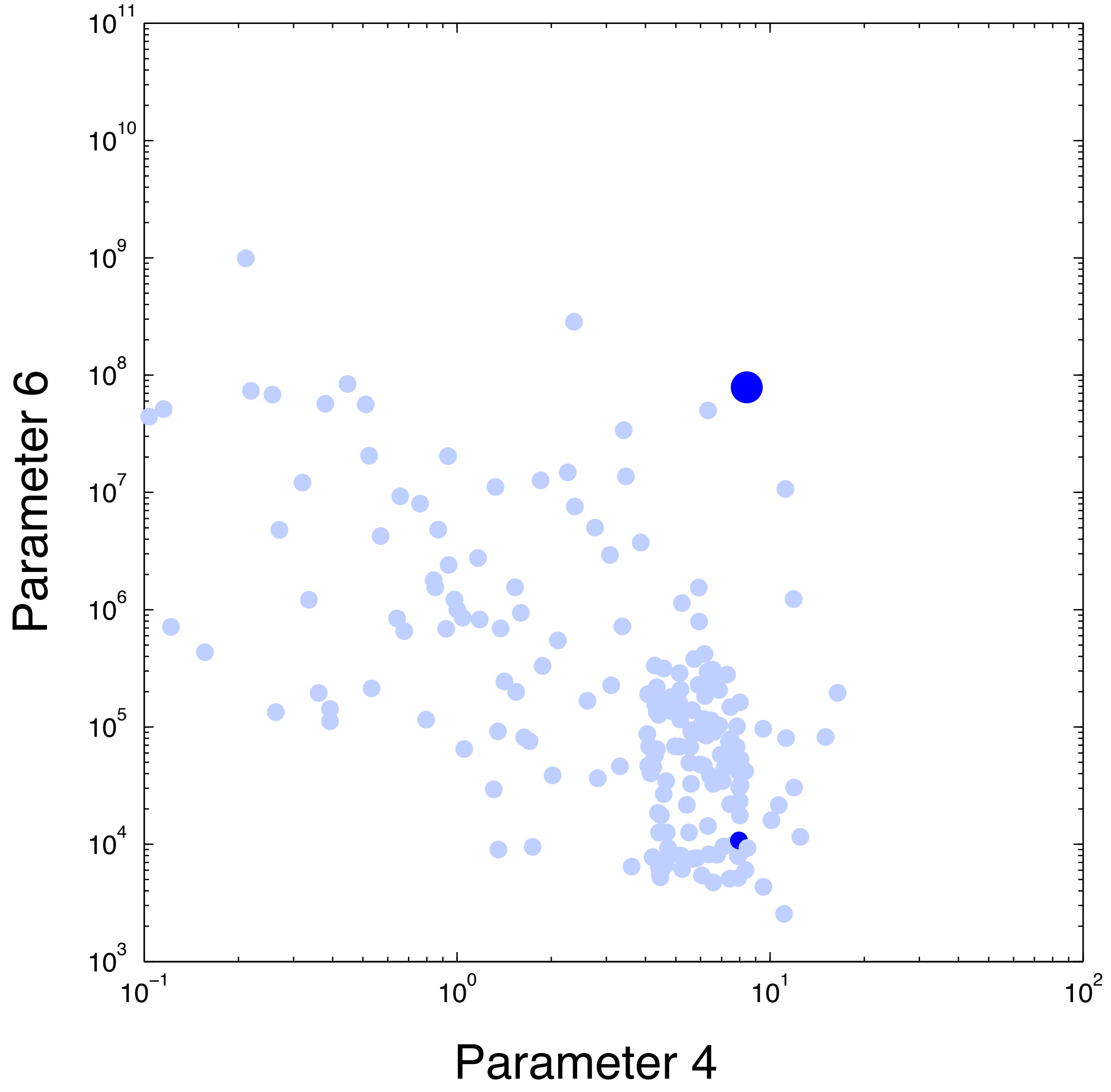


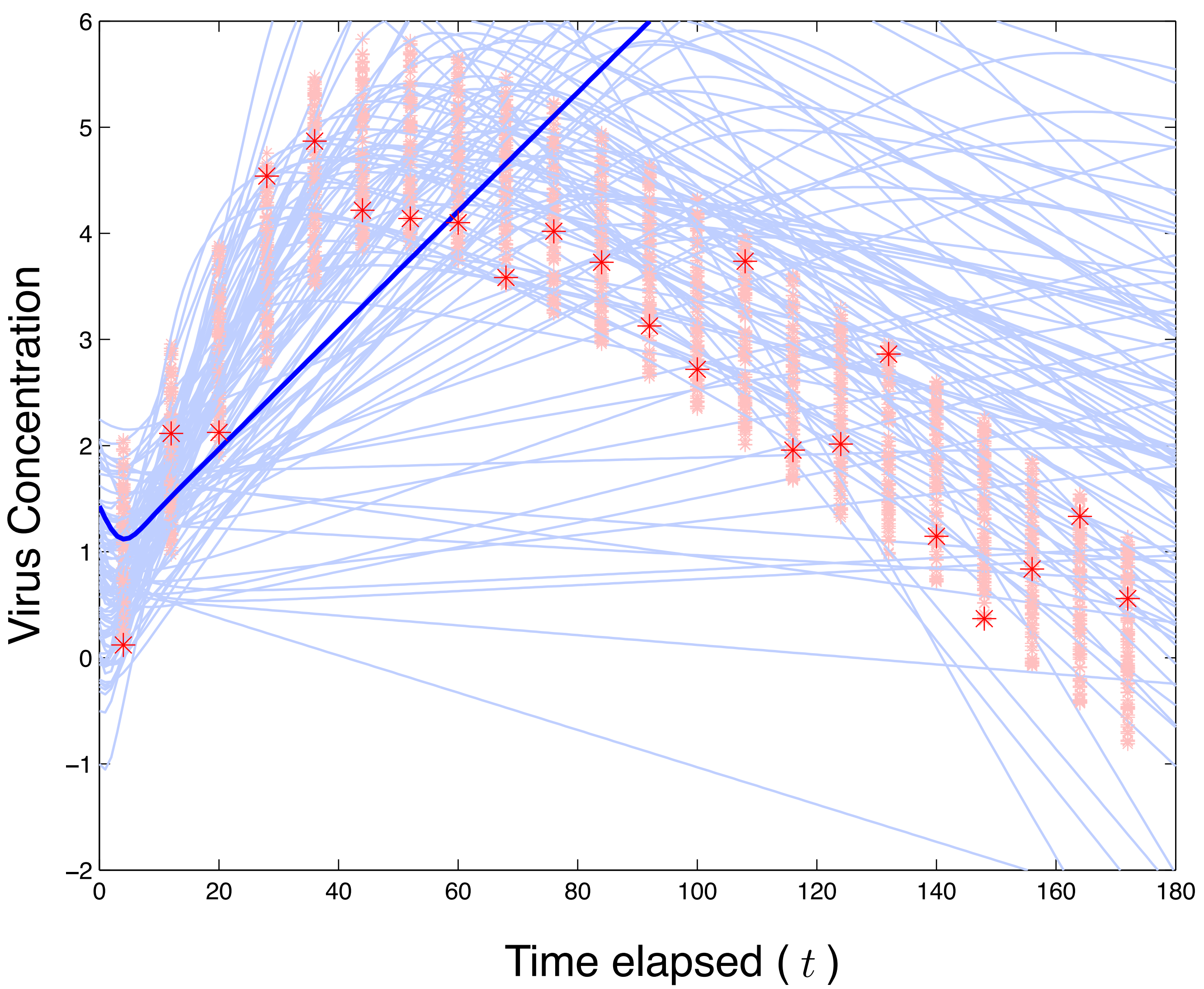


New Algorithm

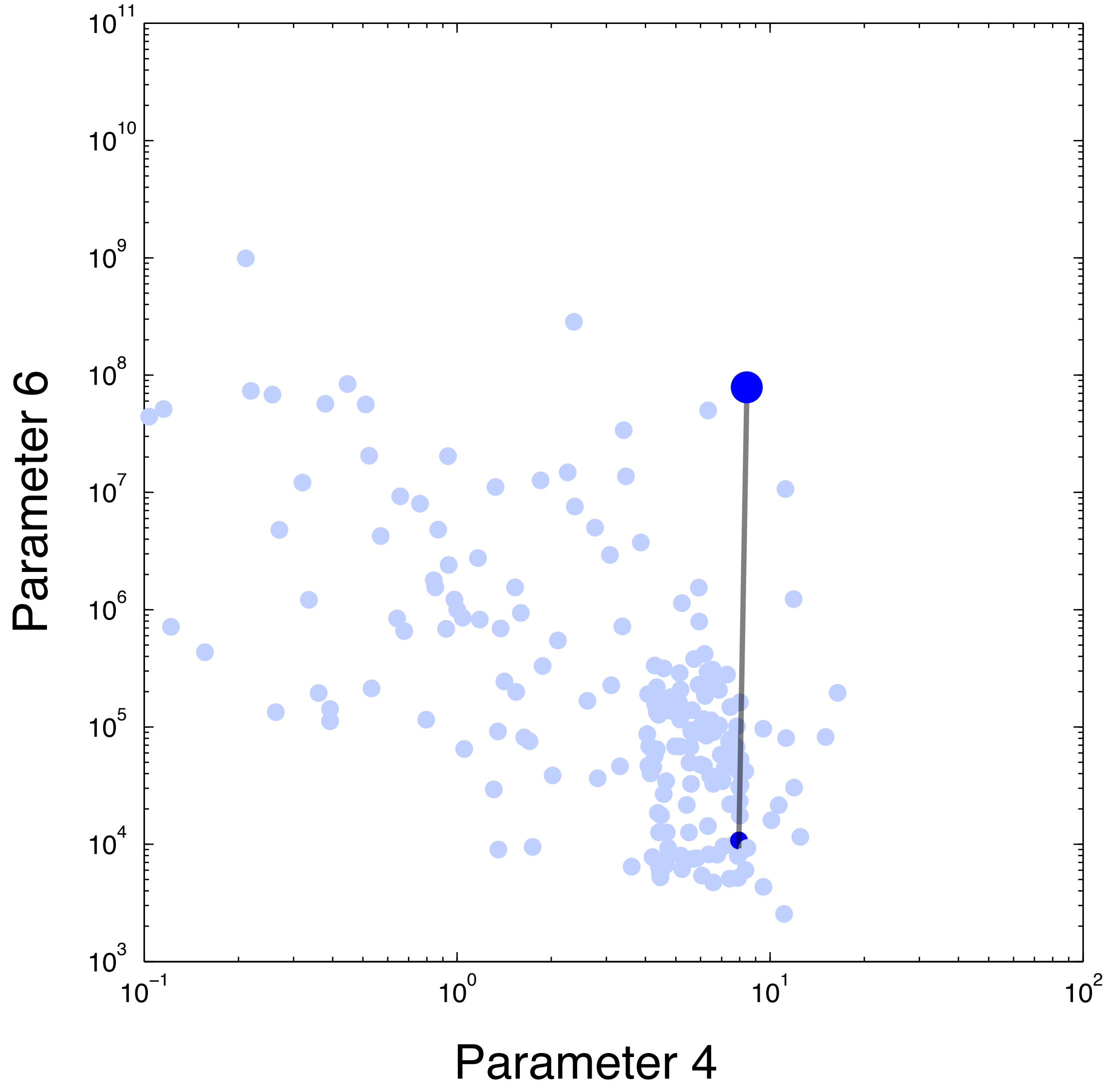


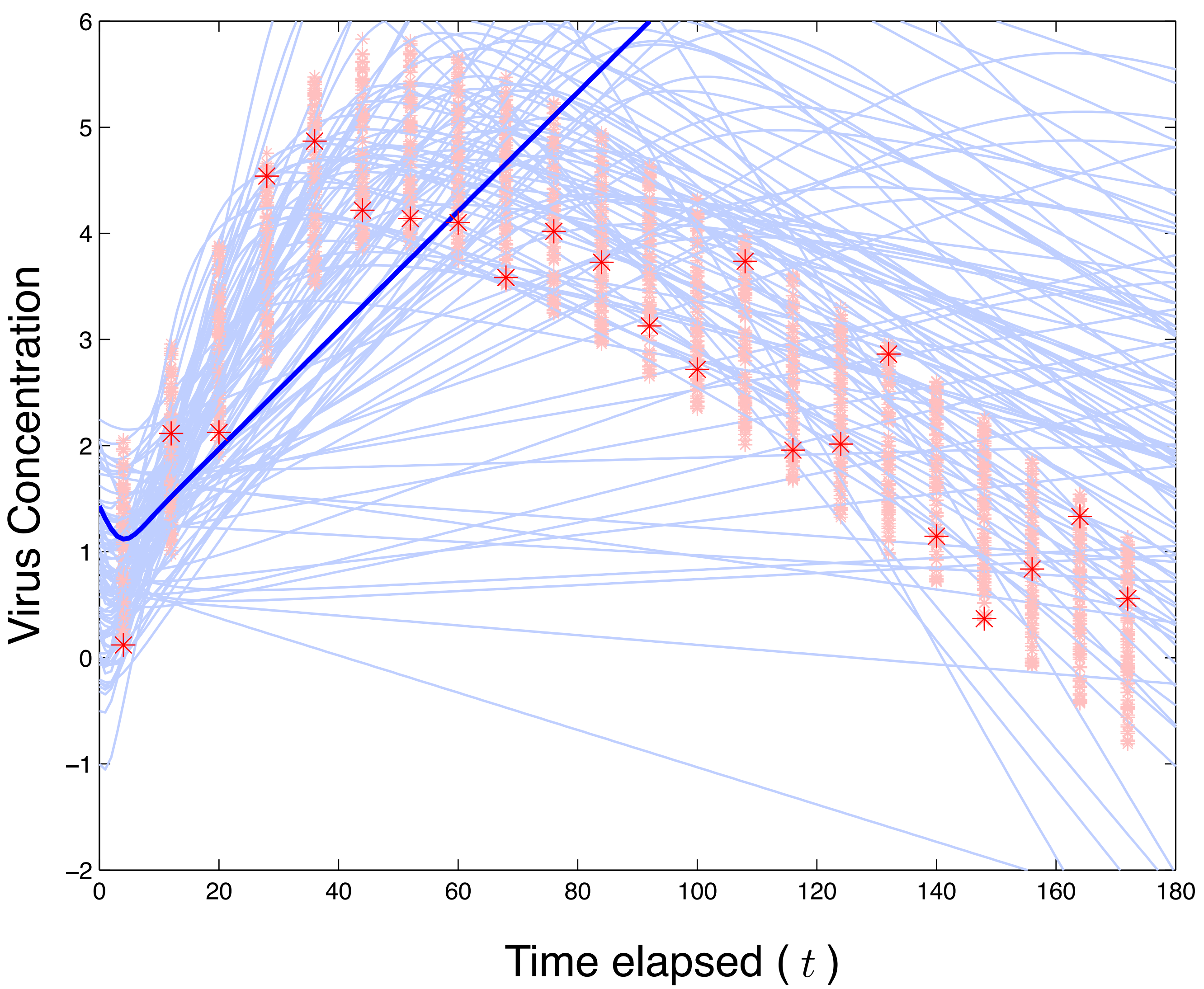
New Algorithm



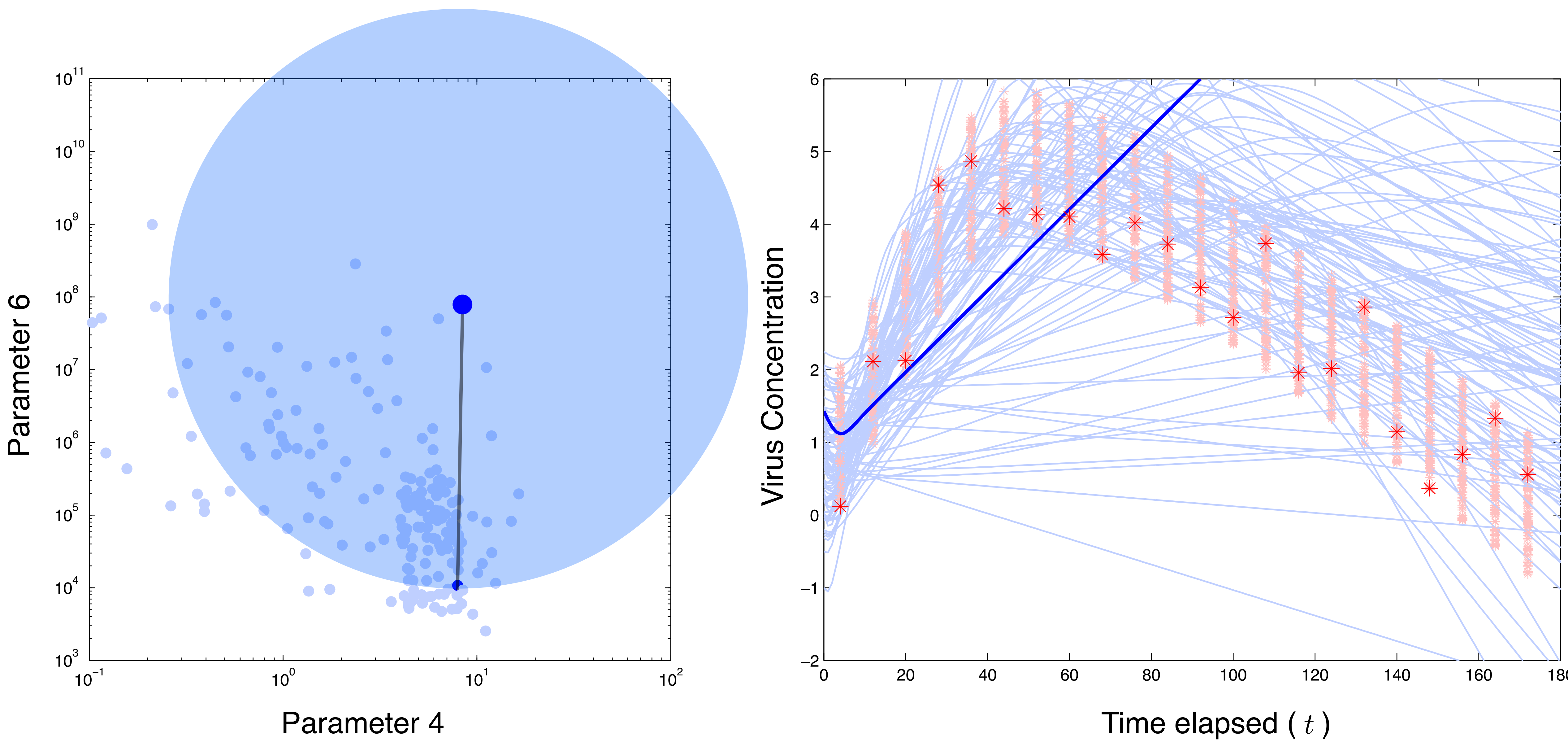


New Algorithm

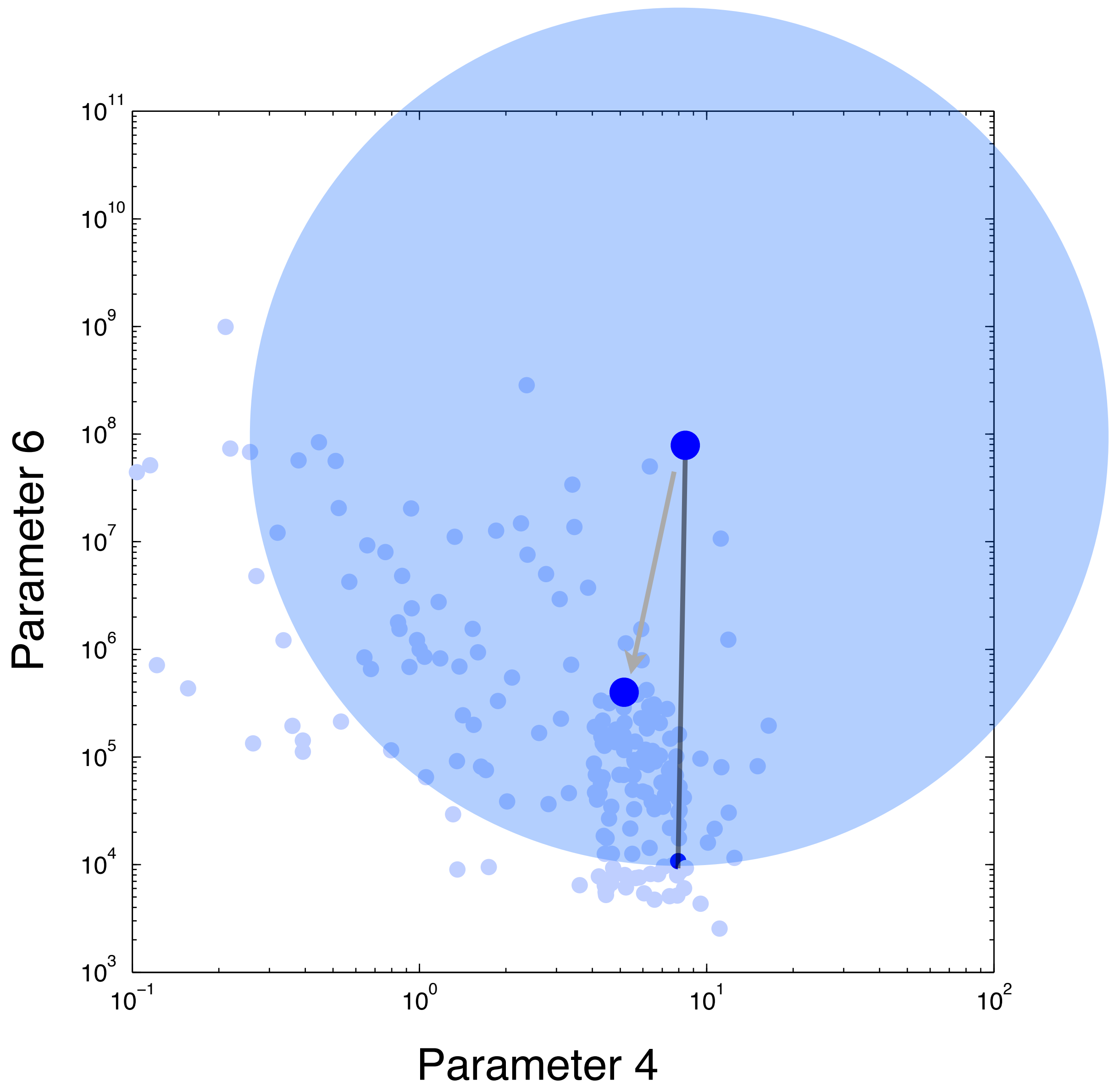


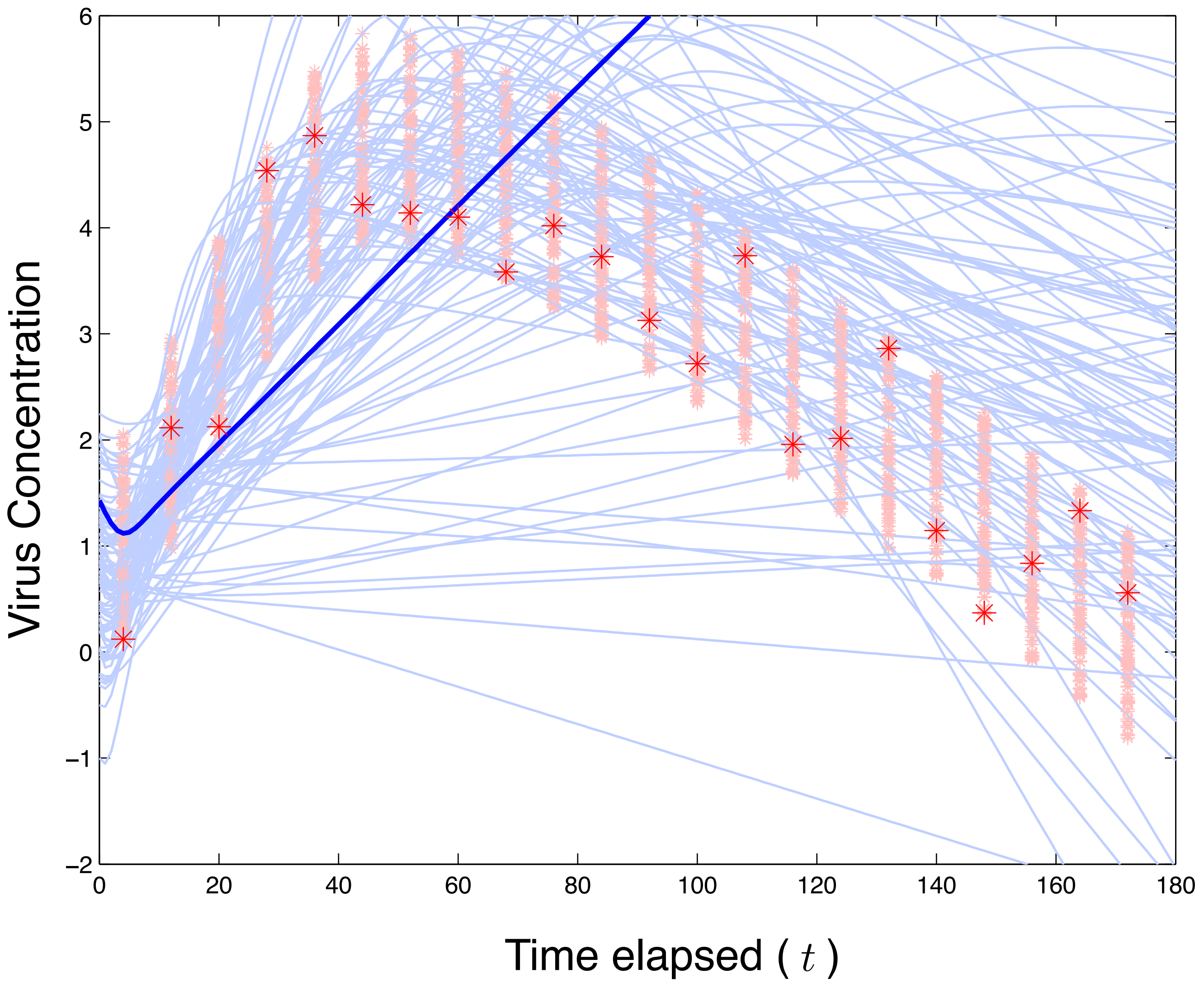


New Algorithm

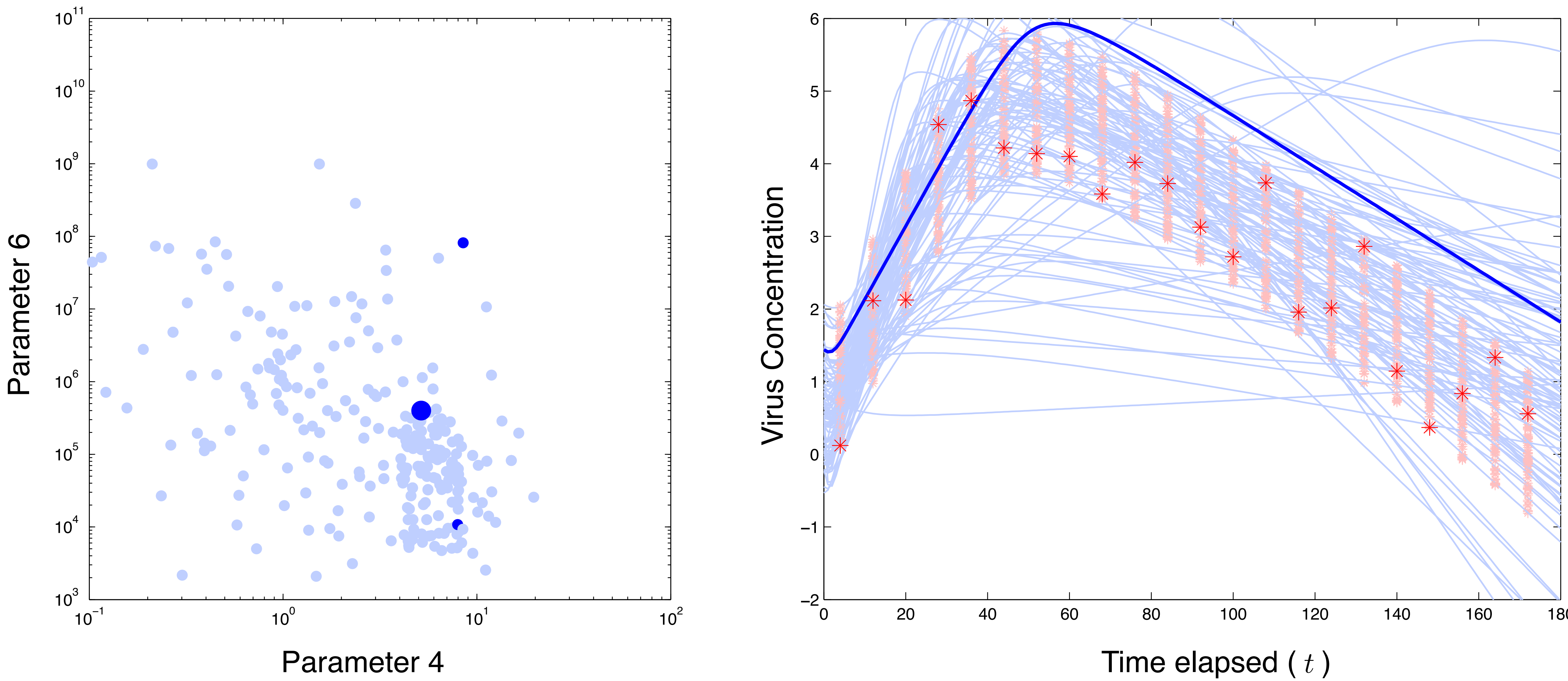


New Algorithm





New Algorithm



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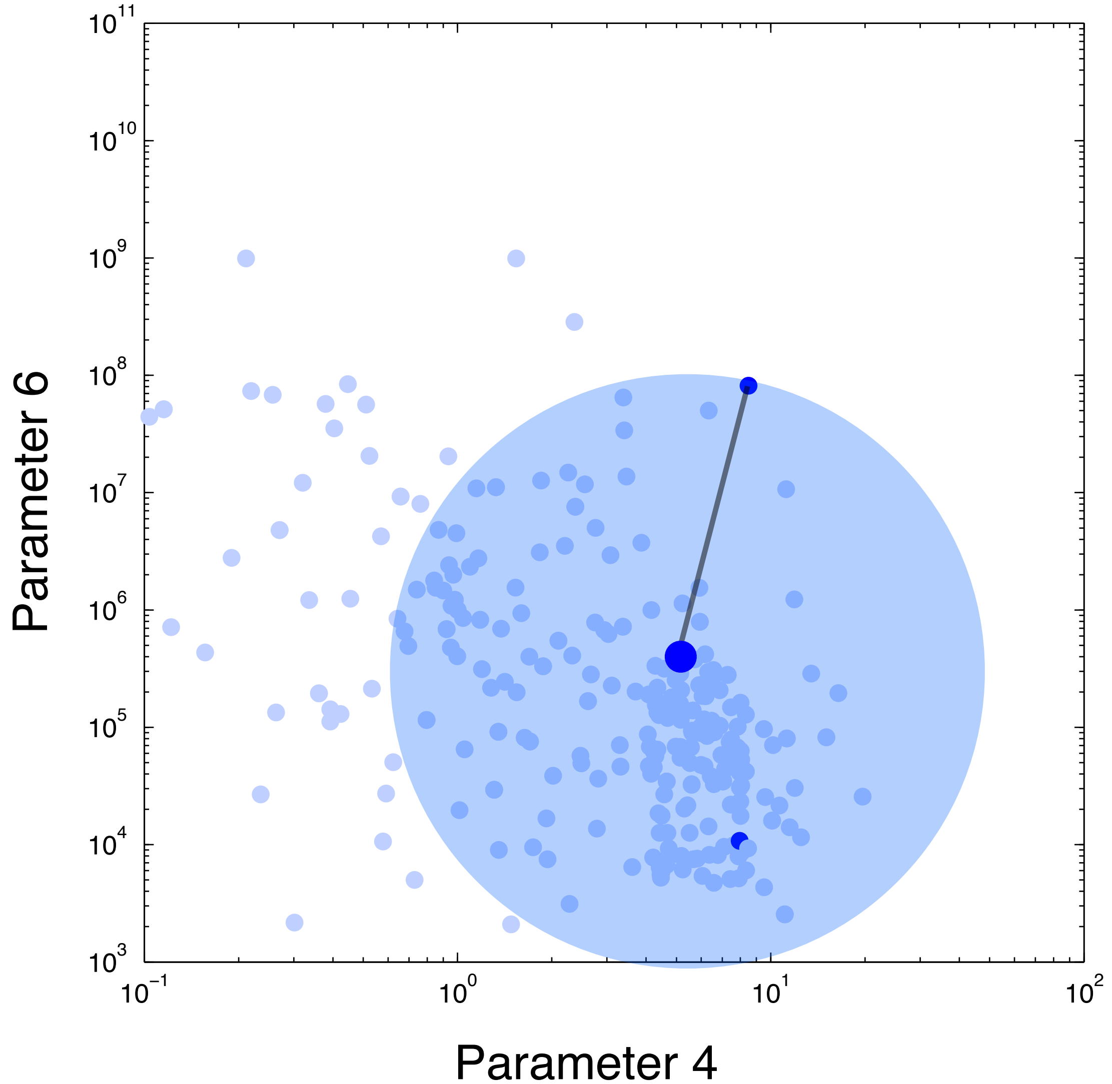
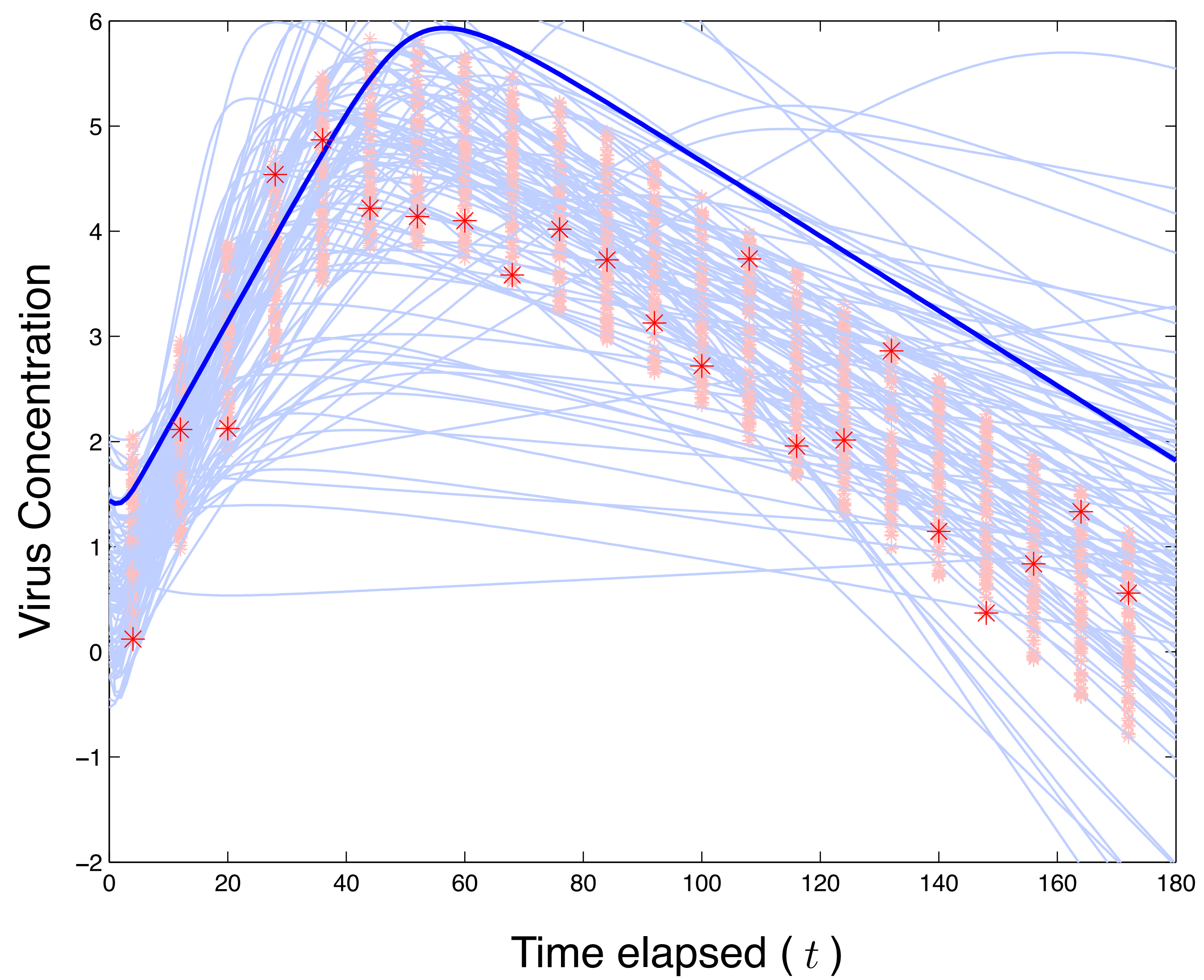
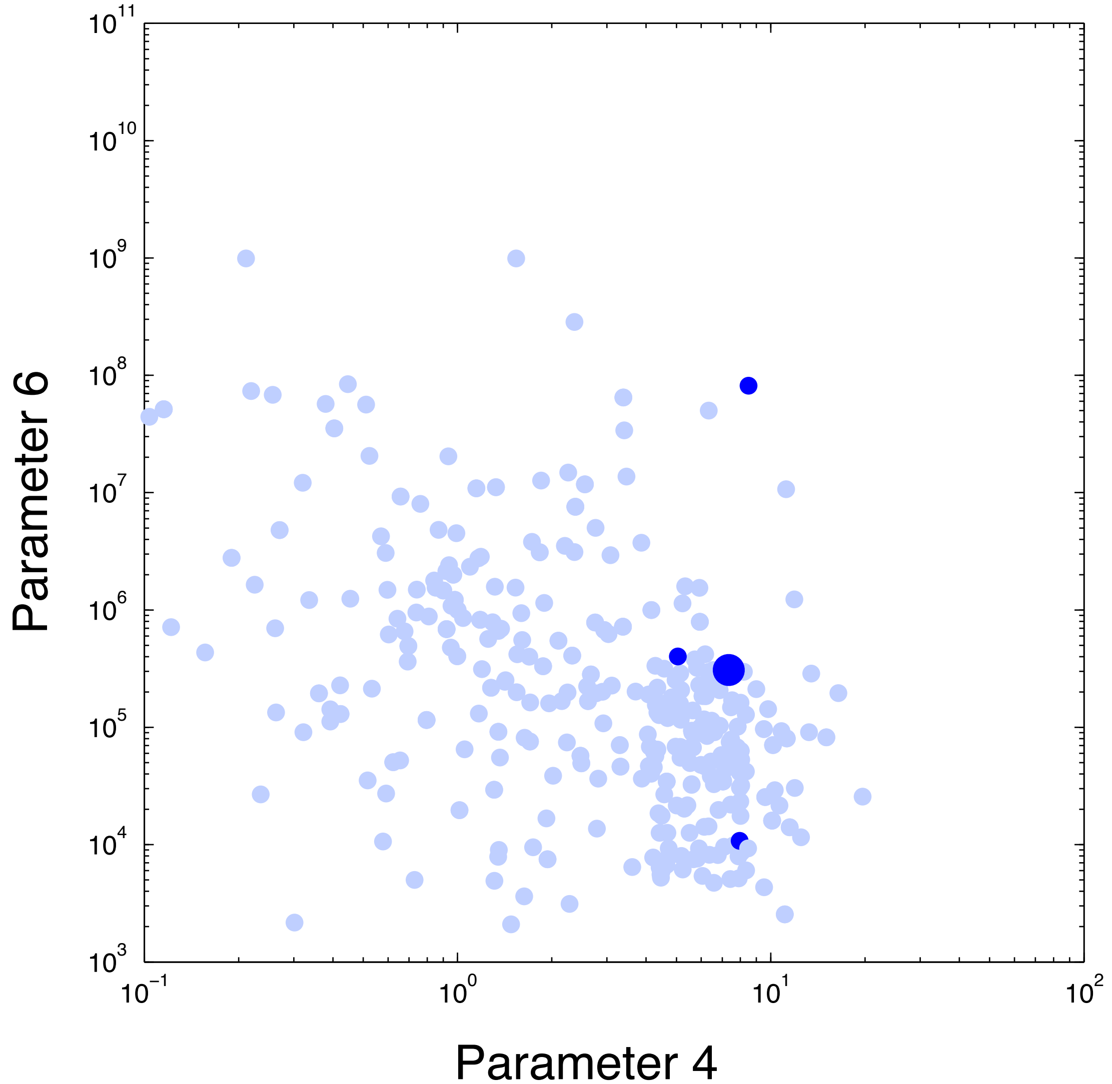
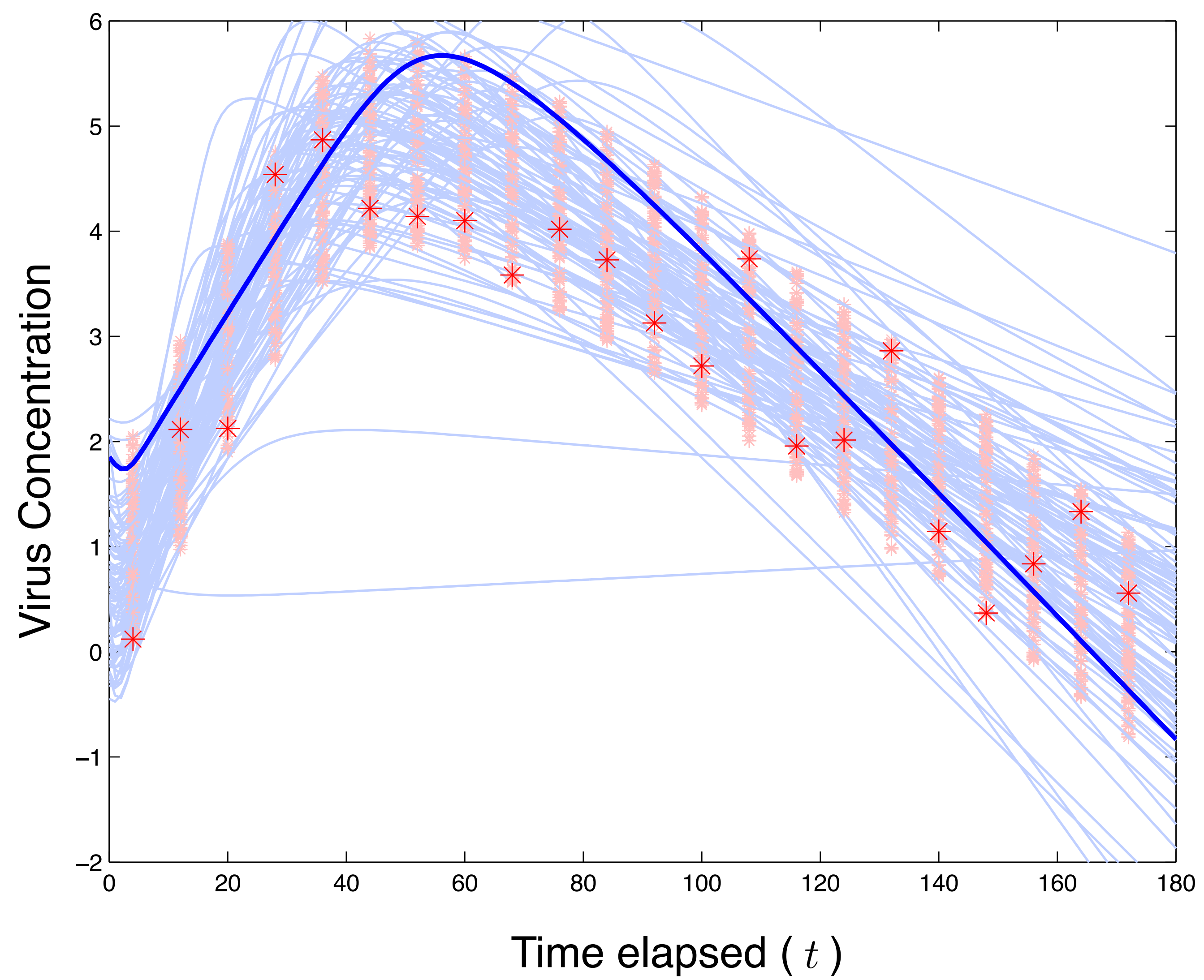


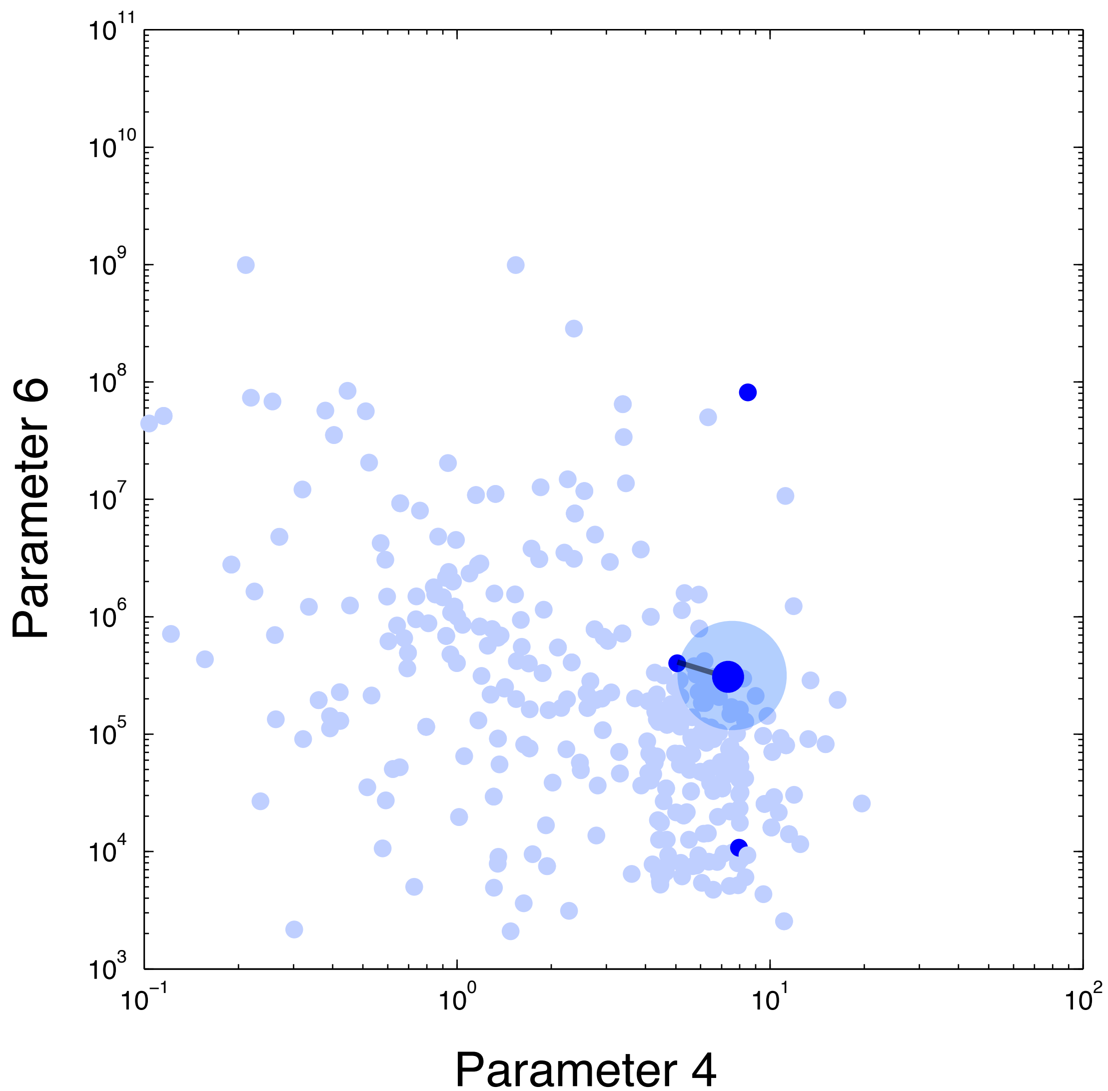


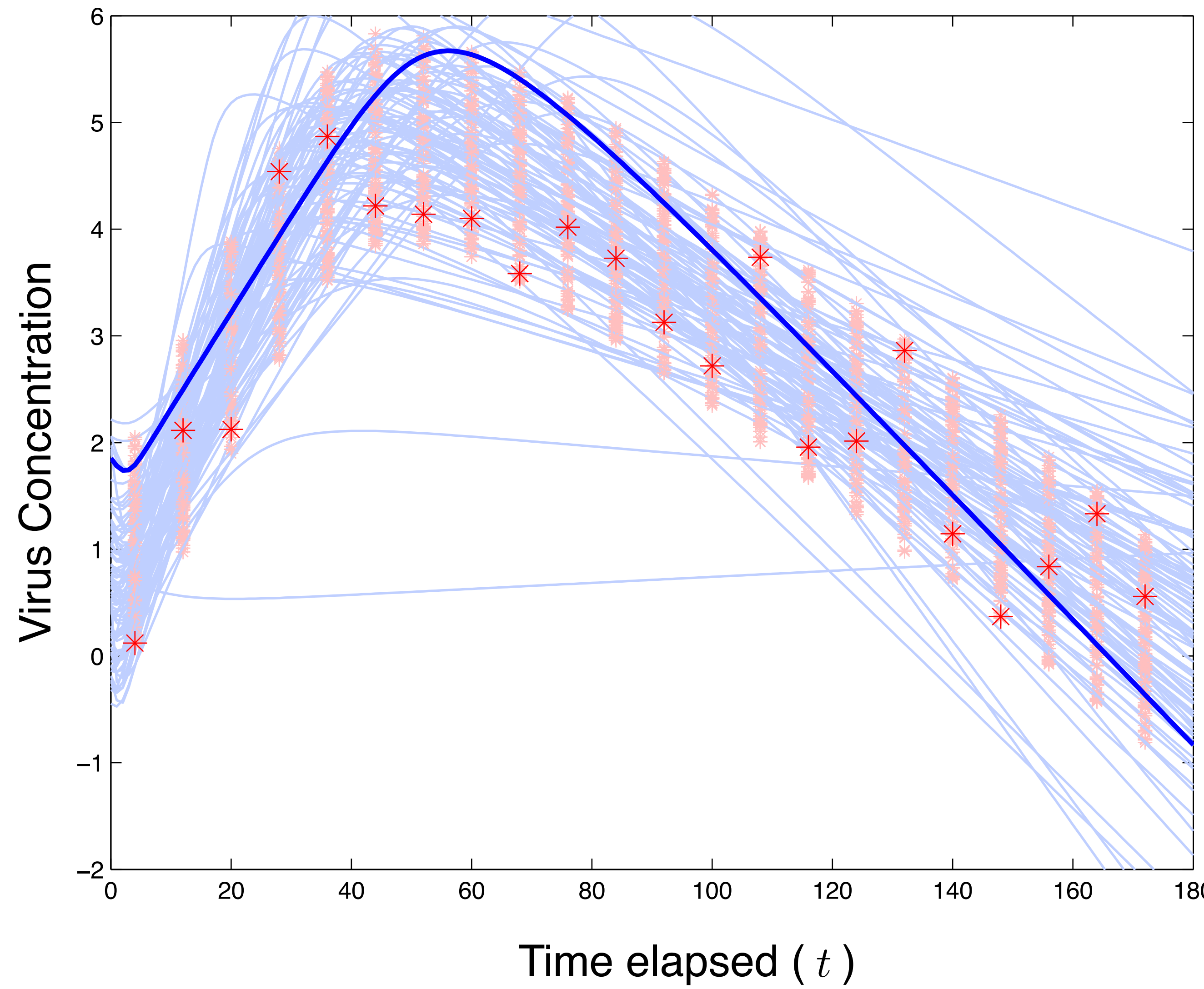
New Algorithm



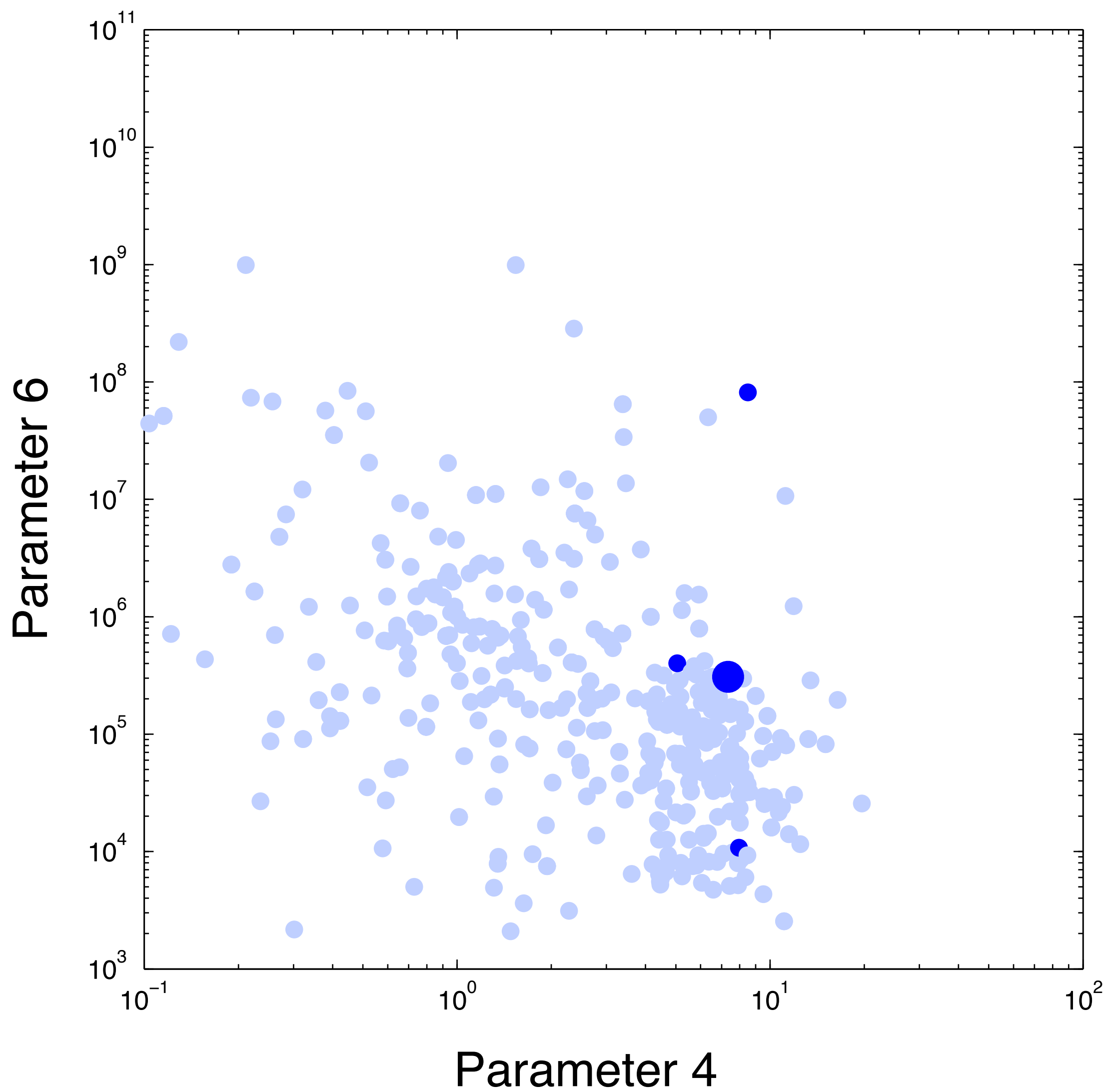


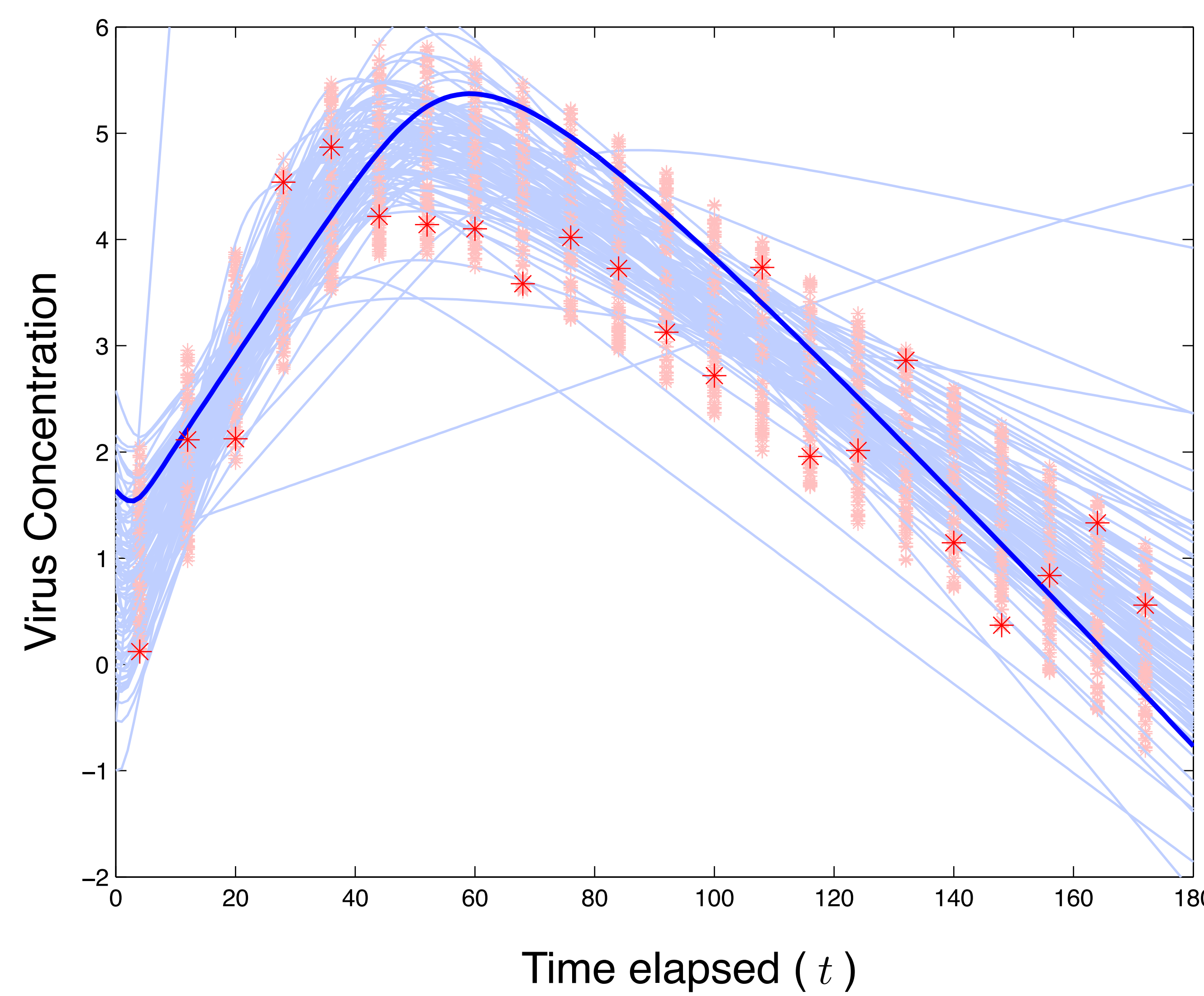
New Algorithm





New Algorithm





New Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

New Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

1

New Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

1 x Number of iterations

New Algorithm

Number of simulations needed to obtain 1,000 sets of parameters.

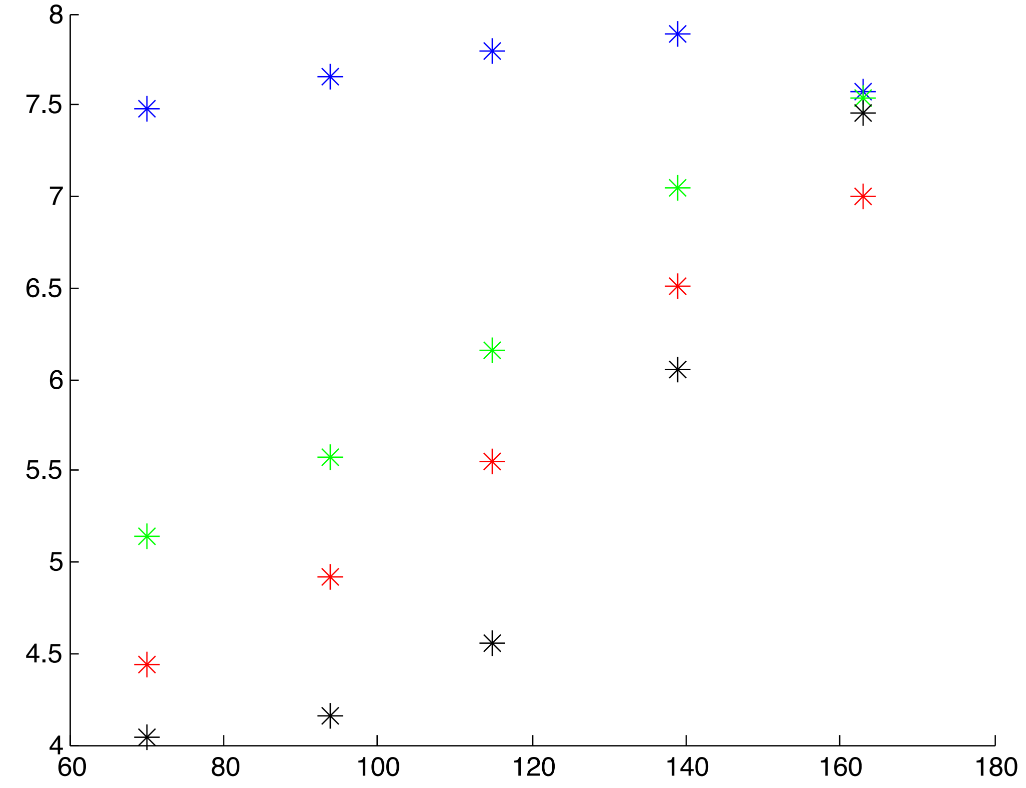
1 x Number of iterations x 1,000

Example 1 HIV kinetics model of Miao et al.

Example 1 HIV kinetics model of Miao et al.

$$\frac{du_1}{dt} = (x_1 - x_5 u_2 - x_6 u_3 - x_7 u_4) u_1$$
$$\frac{du_2}{dt} = (x_2 + x_5 u_1 - x_8 u_3) u_2 + \frac{1}{4} x_7 u_4 u_1$$
$$\frac{du_3}{dt} = (x_3 + x_6 u_1 - x_9 u_2) u_3 + \frac{1}{4} x_7 u_4 u_1$$
$$\frac{du_4}{dt} = (x_4 + \frac{1}{2} x_7 u_1) u_4 + (x_8 + x_9) u_3 u_2$$

$$u_1(t=0) = x_{10}$$
$$u_2(t=0) = x_{11}$$
$$u_3(t=0) = x_{12}$$
$$u_4(t=0) = x_{13}$$



Hongyu Miao, Carrie Dykes, Lisa M. Demeter, James Cavenaugh, Sung Yong Park, Alan S. Perelson, and Hulin Wu. Modeling and Estimation of Kinetic Parameters and Replicative Fitness of HIV-1 from Flow-Cytometry-Based Growth Competition Experiments. Bulletin of Mathematical Biology, 70:1749– 1771, 2008.

Example 1 HIV kinetics model of Miao et al.

$$\frac{du_1}{dt} = (x_1 - x_5 u_2 - x_6 u_3 - x_7 u_4) u_1$$

$$\frac{du_2}{dt} = (x_2 + x_5 u_1 - x_8 u_3) u_2 + \frac{1}{4} x_7 u_4 u_1$$

$$\frac{du_3}{dt} = (x_3 + x_6 u_1 - x_9 u_2) u_3 + \frac{1}{4} x_7 u_4 u_1$$

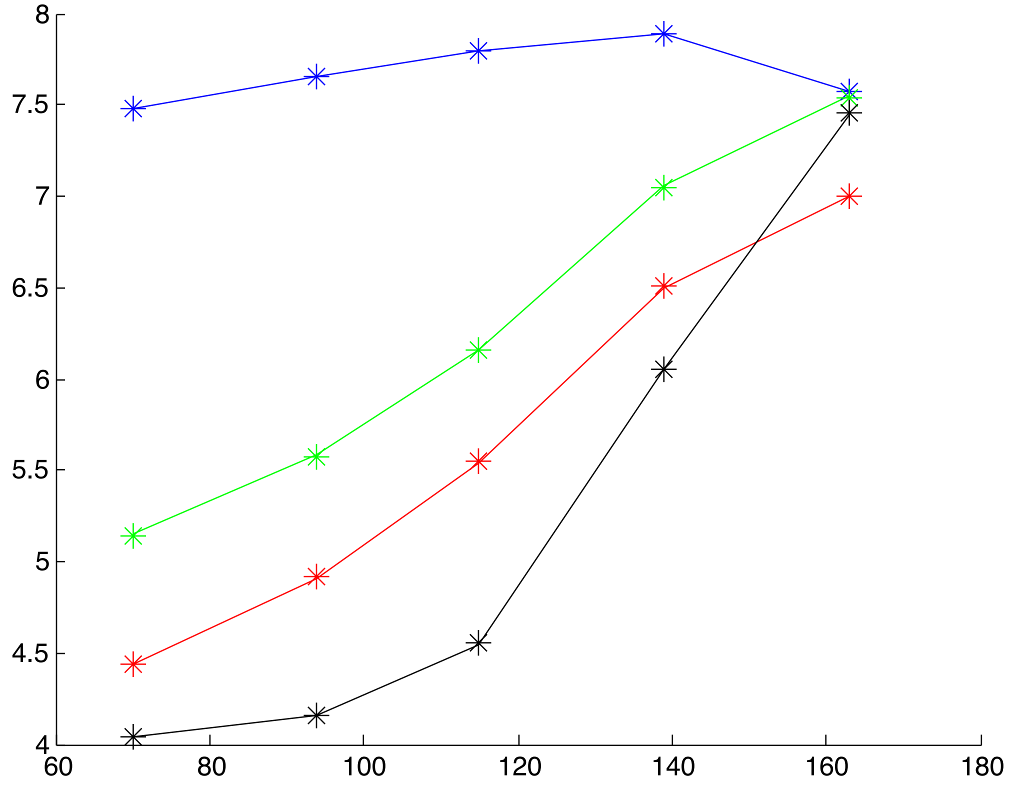
$$\frac{du_4}{dt} = (x_4 + \frac{1}{2} x_7 u_1) u_4 + (x_8 + x_9) u_3 u_2$$

$$u_1(t=0) = x_{10}$$

$$u_2(t=0) = x_{11}$$

$$u_3(t=0) = x_{12}$$

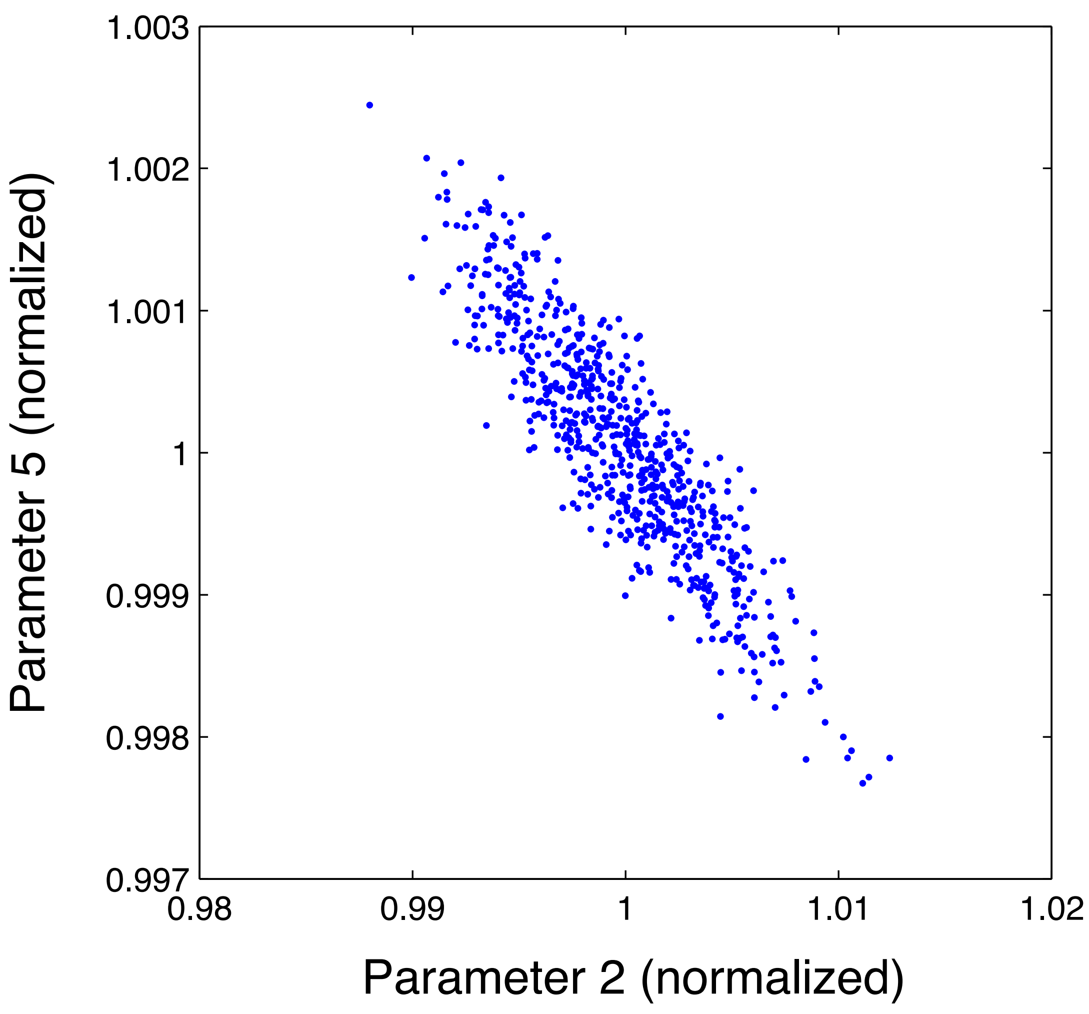
$$u_4(t=0) = x_{13}$$



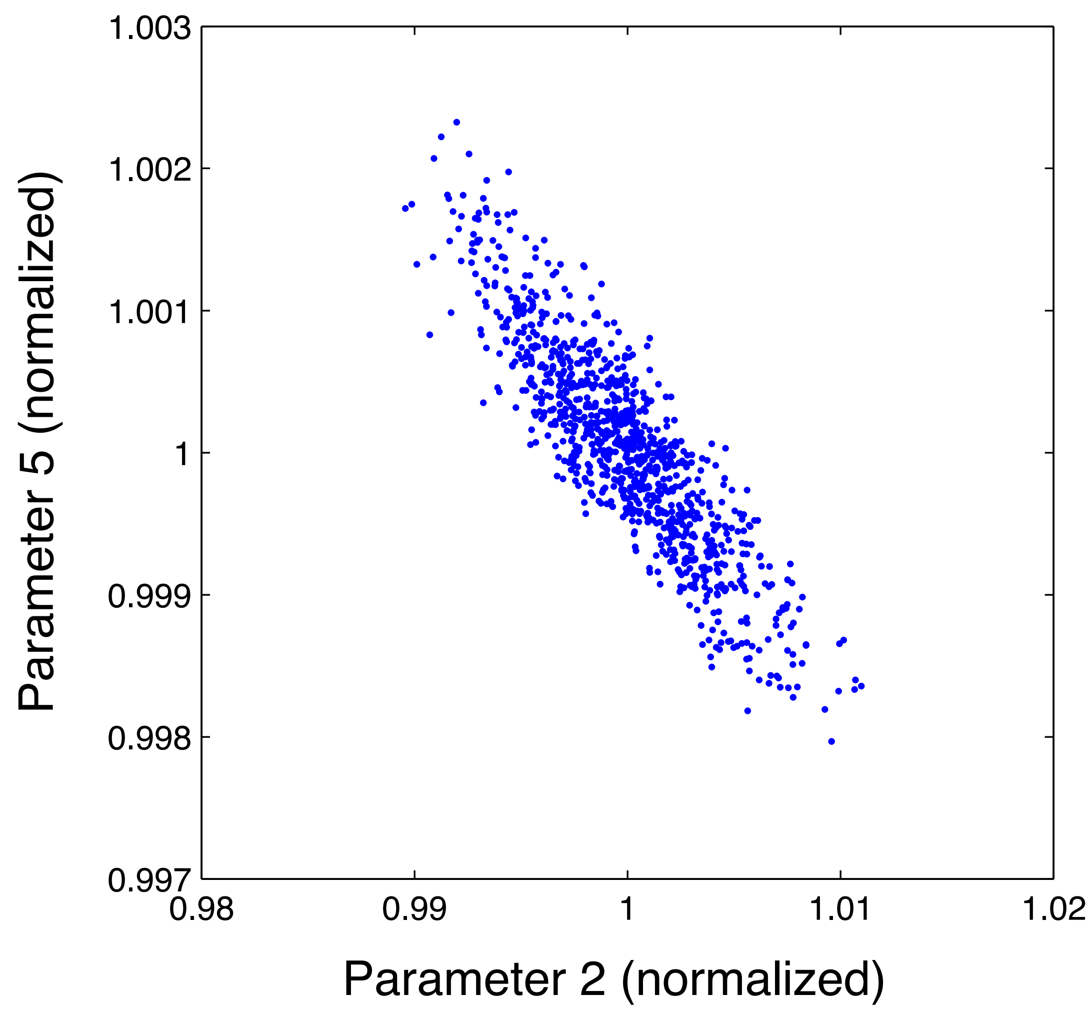
Hongyu Miao, Carrie Dykes, Lisa M. Demeter, James Cavenaugh, Sung Yong Park, Alan S. Perelson, and Hulin Wu. Modeling and Estimation of Kinetic Parameters and Replicative Fitness of HIV-1 from Flow-Cytometry-Based Growth Competition Experiments. Bulletin of Mathematical Biology, 70:1749– 1771, 2008.

Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm

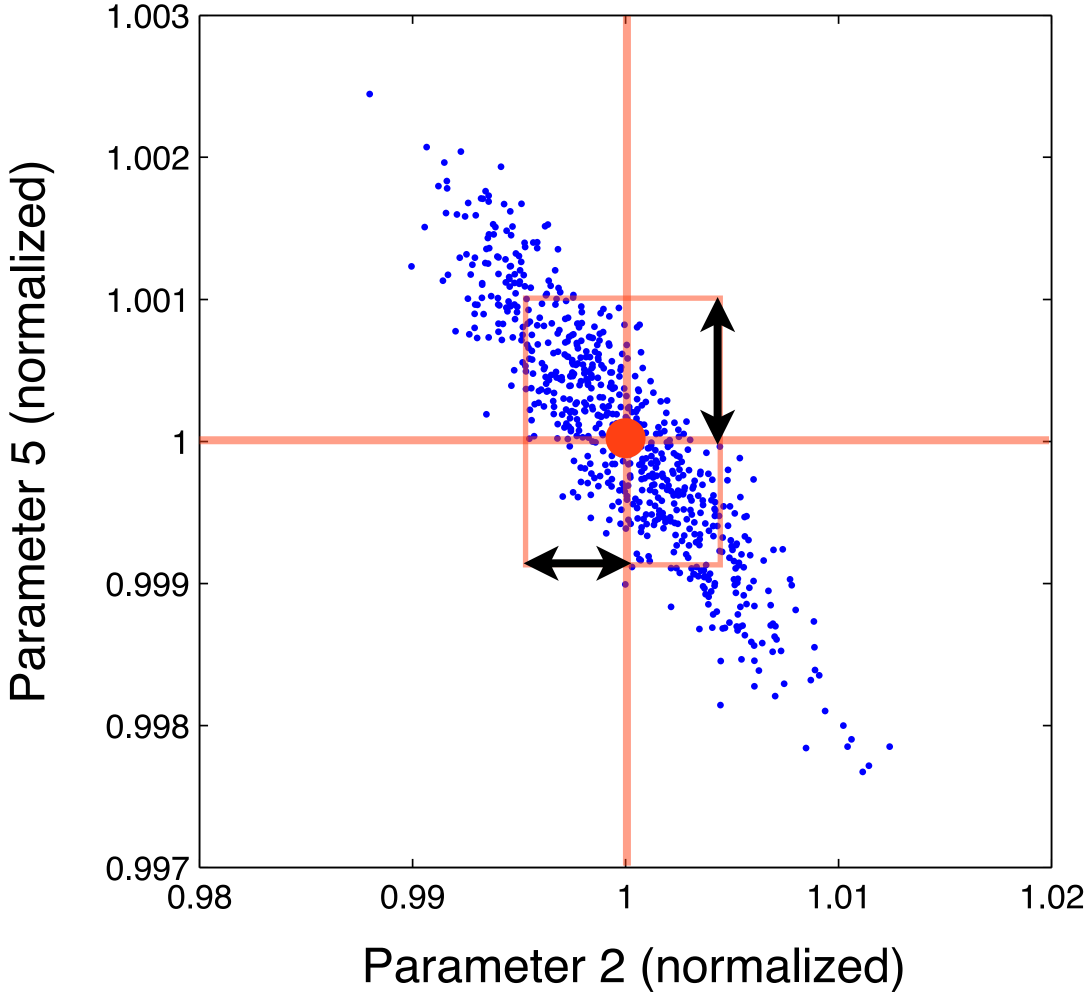


New Algorithm



Example 1 HIV kinetics model of Miao et al.

Average **R**elative Parameter **E**stimation Error

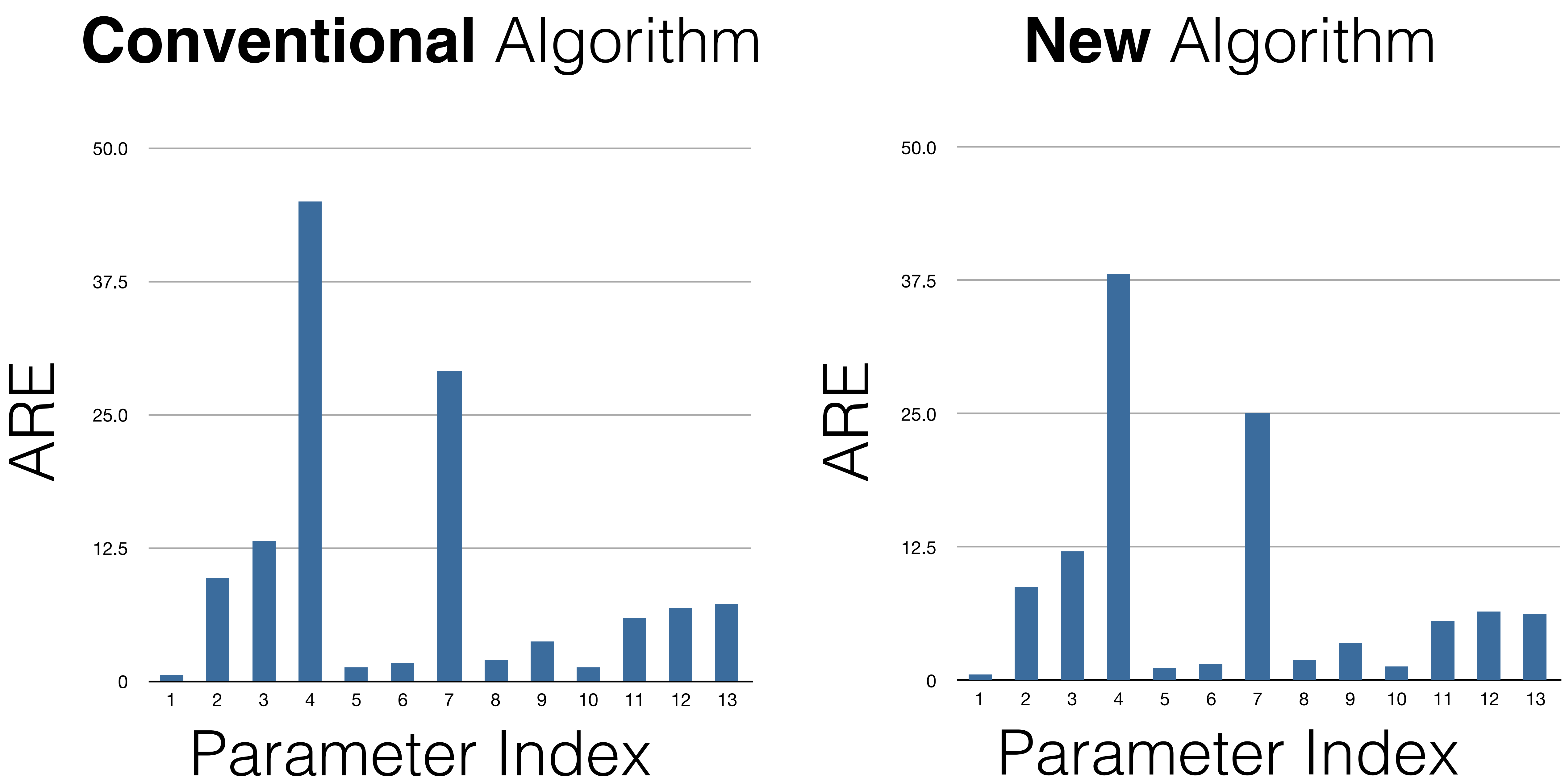


ARE of the i th parameter

$$\frac{1}{N}\sum_{j=1}^{N}\frac{x_{ij}-x_i^*}{x_i^*}\times 100\%$$

Hongyu Miao, Xiaohua Xia, Alan S. Perelson, and Hulin Wu.
On Identifiability of Nonlinear ODE Models and Applications in Viral Dynamics. SIAM REVIEW, 53(1):3–39, 2011.

Example 1 HIV kinetics model of Miao et al.



Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm		**New** Algorithm
	Number of simulations	
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm		**New** Algorithm
131,508	Number of simulations	
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm		**New** Algorithm
131,508	Number of simulations	11,280
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm		**New** Algorithm
131,508	Number of simulations	11,280
2 hours	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 1 HIV kinetics model of Miao et al.

Conventional Algorithm		**New** Algorithm
131,508	Number of simulations	11,280
2 hours	CPU time	**10 min**

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 2 Benchmark Problem of Moles et al.

Example 2 Benchmark Problem of Moles et al.

$$
\begin{aligned}
\frac{du_1}{dt} &= x_1/(1 + (p/x_2)^{x_3} + (x_4/s)^{x_5}) - x_6 u_1 \\
\frac{du_2}{dt} &= x_7/(1 + (p/x_8)^{x_9} + (x_{10}/u_7)^{x_{11}}) - x_{12} u_2 \\
\frac{du_3}{dt} &= x_{13}/(1 + (p/x_{14})^{x_{15}} + (x_{16}/u_8)^{x_{17}}) - x_{18} u_3 \\
\frac{du_4}{dt} &= x_{19}/(x_{20} + u_1) u_1 - x_{21} u_4 \\
\frac{du_5}{dt} &= x_{22}/(x_{23} + u_2) u_2 - x_{24} u_5 \\
\frac{du_6}{dt} &= x_{25}/(x_{26} + u_3) u_3 - x_{27} u_6 \\
\frac{du_7}{dt} &= x_{28}/x_{29} u_4 (s - u_7)/(1 + s/x_{29} - u_7/x_{30}) \\
&\quad - x_{31}/x_{32} u_5 (u_7 - u_8)/(1 + u_7/x_{32} + u_8/x_{33}) \\
\frac{du_8}{dt} &= x_{31}/x_{32} u_5 (u_7 - u_8)/(1 + u_7/x_{32} + u_8/x_{33}) \\
&\quad - x_{34}/x_{35} u_6 (u_8 - p)/(1 + u_8/x_{35} + p/x_{36})
\end{aligned}
$$

Carmen G. Moles, Pedro Mendes, and Julio R. Banga. Parameter Estimation in Biochemical Pathways: A Comparison of Global Optimization Methods. Genome Research, 13:2467–2474, 2003.

Example 2 Benchmark Problem of Moles et al.

$$\frac{du_1}{dt} = x_1/(1 + (p/x_2)^{x_3} + (x_4/s)^{x_5}) - x_6 u_1$$

$$\frac{du_2}{dt} = x_7/(1 + (p/x_8)^{x_9} + (x_{10}/u_7)^{x_{11}}) - x_{12} u_2$$

$$\frac{du_3}{dt} = x_{13}/(1 + (p/x_{14})^{x_{15}} + (x_{16}/u_8)^{x_{17}}) - x_{18} u_3$$

$$\frac{du_4}{dt} = x_{19}/(x_{20} + u_1)u_1 - x_{21} u_4$$

$$\frac{du_5}{dt} = x_{22}/(x_{23} + u_2)u_2 - x_{24} u_5$$

$$\frac{du_6}{dt} = x_{25}/(x_{26} + u_3)u_3 - x_{27} u_6$$

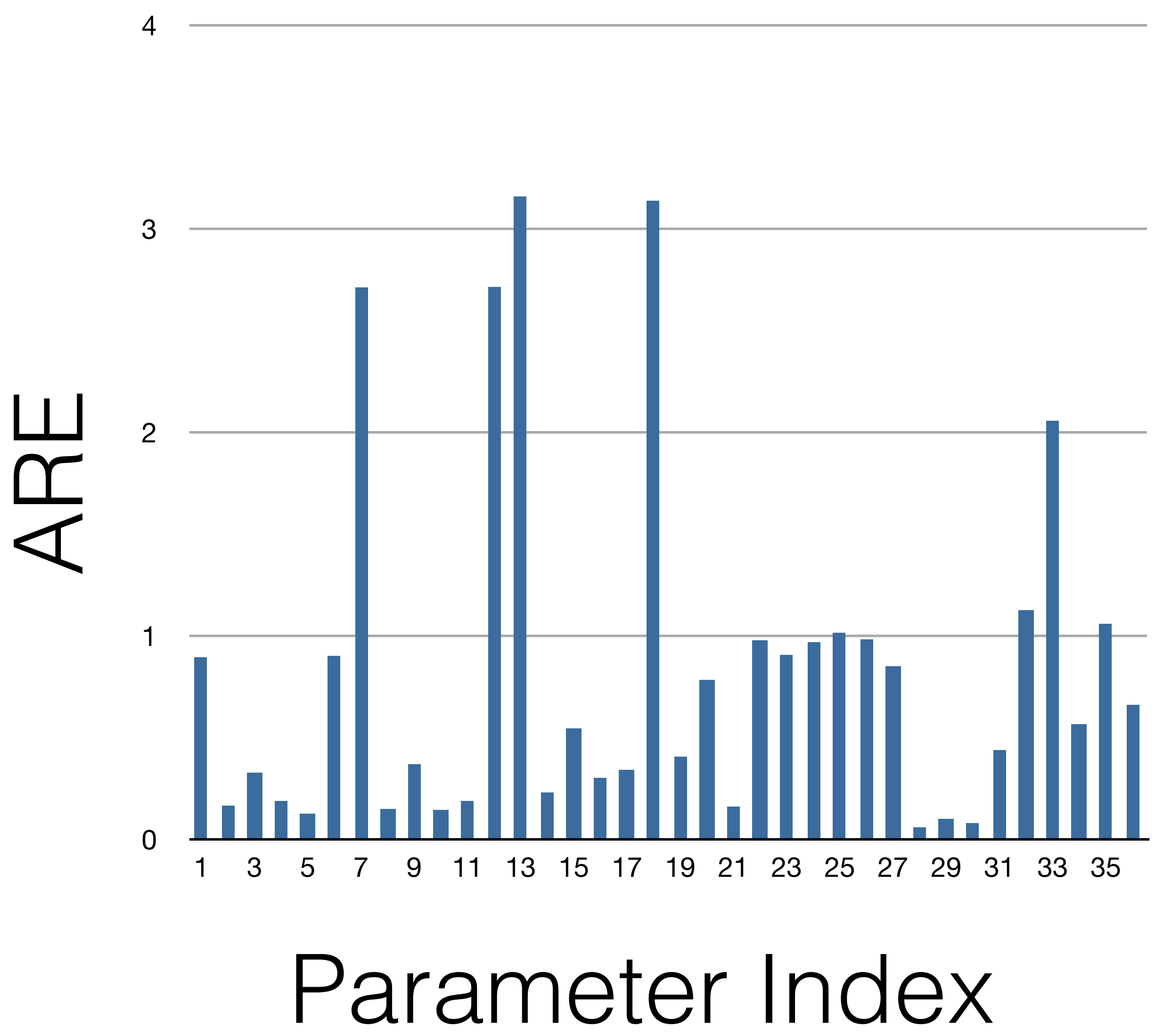
$$\frac{du_7}{dt} = x_{28}/x_{29} u_4 (s - u_7)/(1 + s/x_{29} - u_7/x_{30}) - x_{31}/x_{32} u_5 (u_7 - u_8)/(1 + u_7/x_{32} + u_8/x_{33})$$

$$\frac{du_8}{dt} = x_{31}/x_{32} u_5 (u_7 - u_8)/(1 + u_7/x_{32} + u_8/x_{33}) - x_{34}/x_{35} u_6 (u_8 - p)/(1 + u_8/x_{35} + p/x_{36})$$

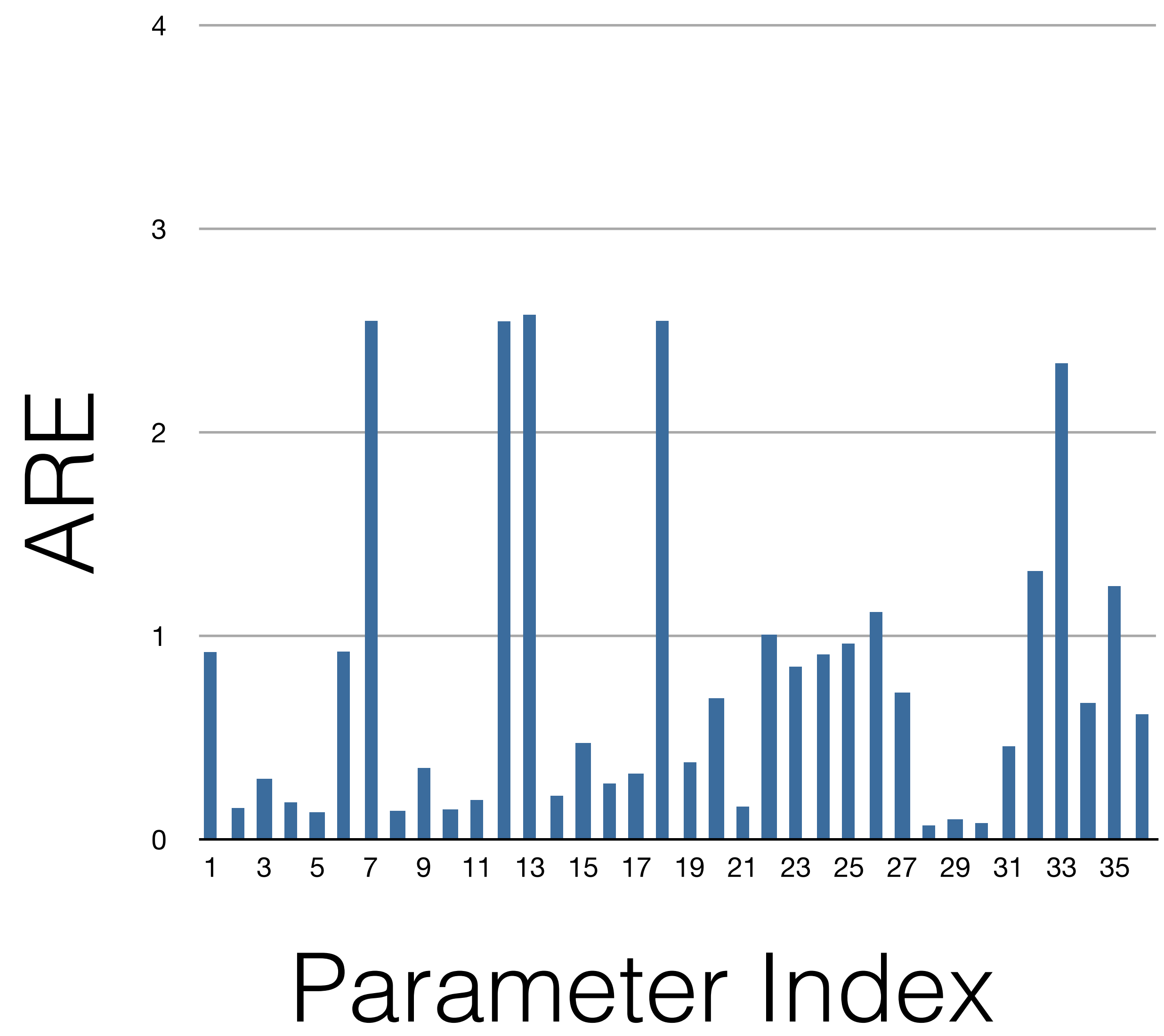
Carmen G. Moles, Pedro Mendes, and Julio R. Banga. Parameter Estimation in Biochemical Pathways: A Comparison of Global Optimization Methods. Genome Research, 13:2467–2474, 2003.

Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm



New Algorithm



Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm		**New** Algorithm
	Number of simulations	
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm		**New** Algorithm
174,586	Number of simulations	
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm		**New** Algorithm
174,586	Number of simulations	3,167
	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm		**New** Algorithm
174,586	Number of simulations	3,167
3 days	CPU time	

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Example 2 Benchmark Problem of Moles et al.

Conventional Algorithm		**New** Algorithm
174,586	Number of simulations	3,167
3 days	CPU time	**1.5 hours**

CPU time measured on Intel Xeon 2.66GHz Processor on Mac Pro

Conclusion

“Practical” Parameter Identifiability Analysis

"**Practical**" Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method		

"Practical" Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✔	

“Practical” Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✓	Impractically Slow... ✗

“**Practical**” Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✔	Impractically Slow... ✘
Monte Carlo / Bootstrap method + **New Algorithm**		

“**Practical**” Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✓	Impractically Slow... ✗
Monte Carlo / Bootstrap method + **New Algorithm**	Robust ✓	

“**Practical**” Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✓	Impractically Slow... ✗
Monte Carlo / Bootstrap method + **New Algorithm**	Robust ✓	Practically acceptable computational cost ✓

Practical Parameter Identifiability Analysis

	Nonlinear Model	Computational Cost
Monte Carlo / Bootstrap method	Robust ✓	Impractically Slow… ✗
Monte Carlo / Bootstrap method + **New Algorithm**	Robust ✓	Practically acceptable computational cost ✓

Research funded and supported by

Natural Science and Engineering Research Council of Canada

Department of Applied Mathematics, University of Waterloo