Challenges in Dynamical Systems Inference:

New Approaches for Parameter and Uncertainty Estimation

Matthias Chung

Department of Mathematics
Computational Modeling & Data Analytics Division
Academy of Integrated Science
Virginia Tech
mcchung@vt.edu

January 2020 @ Universität Potsdam

Challenges in Dynamical Systems Inference:

New Approaches for Parameter and Uncertainty Estimation

Matthias Chung

Department of Mathematics
Computational Modeling & Data Analytics Division
Academy of Integrated Science
Virginia Tech
mcchung@vt.edu

January 2020 @ Universität Potsdam

acknowledgment & funding

VIRGINIA TECH

Technische Universität Berlin

Alexander von Humboldt Stiftung / Foundation

NSF
DMS 1723005 & I/UCRC 1650463

NIH National Institutes of Health
R21 GM107683-01

USDA
NIFA: 2016-08687

mcchung@vt.edu

collaborators

- John Bardsley, University of Montana
- Mickael Binois, Argonne National Lab
- Bobby Gramacy, Virginia Tech
- Amber Smith, University of Tennessee, Memphis
- Romcholo Macatula, Virginia Tech
- Mihai Pop, University of Maryland College Park
- Justin Krueger, Virginia Tech
- Honghu Liu, Virginia Tech
- Eldad Haber, University of British Columbia
- Julianne Chung, Virginia Tech
- Lars Ruthotto, Emory University

mcchung@vt.edu

outline

``All models are wrong, but some are useful, ...

(George Box)

mcchung@vt.edu

``All models are wrong, but some are useful, ...

(George Box)

... and some are dangerous."

(Lenny Smith)

mcchung@vt.edu

``All models are wrong, but some are useful, ...

(George Box)

... and some are dangerous."

(Lenny Smith)

Outline

1. robust ODE/DDE solvers
2. dynamical systems parameter estimation
3. surrogate data
4. optimal experimental design

mcchung@vt.edu

① robust `lsfem` solvers for

- ordinary & delay differential equations (ODE/DDE)
- initial & boundary value problems (IVP/BVP)
- differential algebraic equations (DAE)

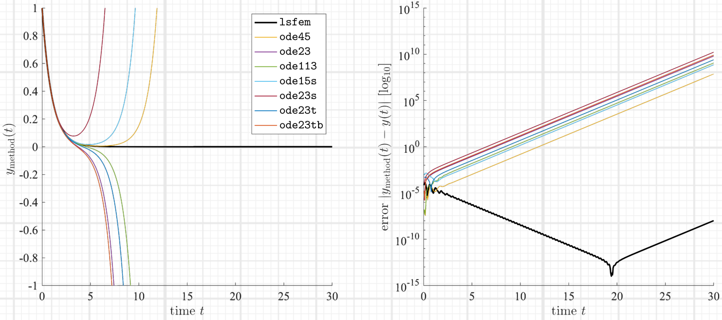
G Hairer, SP Nørsett, and E Wanner. *Solving Ordinary Differential Equations I: Nonstiff Problems*. 2nd ed. Berlin: Springer, 1993.

mcchung@vt.edu

① robust `lsfem` solvers for

- ordinary & delay differential equations (ODE/DDE)
- initial & boundary value problems (IVP/BVP)
- differential algebraic equations (DAE)

Example $y' = y - 2\mathrm{e}^{-t}$, $y(0) = 1$ with exact solution $y(t) = \mathrm{e}^{-t}$



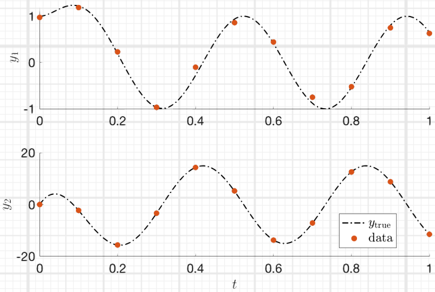
Hairer, Nørsett, and Wanner 1993.

mcchung@vt.edu

① ODE: Burlisch-Bock parameter estimation problem

$$y' = \begin{bmatrix} 0 & 1 \\ \mu^2 & 0 \end{bmatrix} y - \begin{bmatrix} 0 \\ (\mu^2 + \rho^2) \sin \rho t \end{bmatrix} \qquad y(0) = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$t \in [0, 1]$ with $\mu = \rho = 15$. Estimate true μ for data



Hans Georg Bock. Recent advances in parameteridentification techniques for ode. In: *Numerical treatment of inverse problems in differential and integral equations*. Springer, 1983, pp. 95–121.

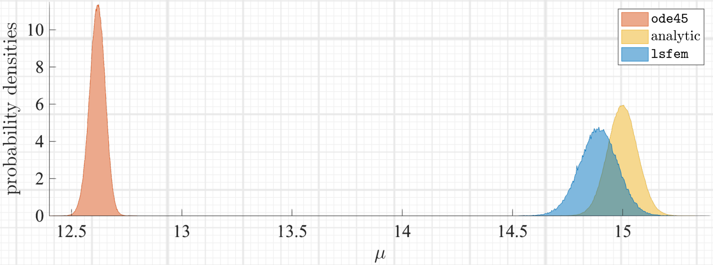
R Bulirsch. Die Mehrzielmethode zur numerischen Lösung von nichtlinearen Randwertproblemen und Aufgaben der optimalen Steuerung. In: *Report der Carl-Cranz-Gesellschaft* 251 (1971).

 mcchung@vt.edu

① ODE: Burlisch-Bock parameter estimation problem

$$y' = \begin{bmatrix} 0 & 1 \\ \mu^2 & 0 \end{bmatrix} y - \begin{bmatrix} 0 \\ (\mu^2 + \rho^2) \sin \rho t \end{bmatrix} \qquad y(0) = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$t \in [0, 1]$ with $\mu = \rho = 15$. Results using MCMC method

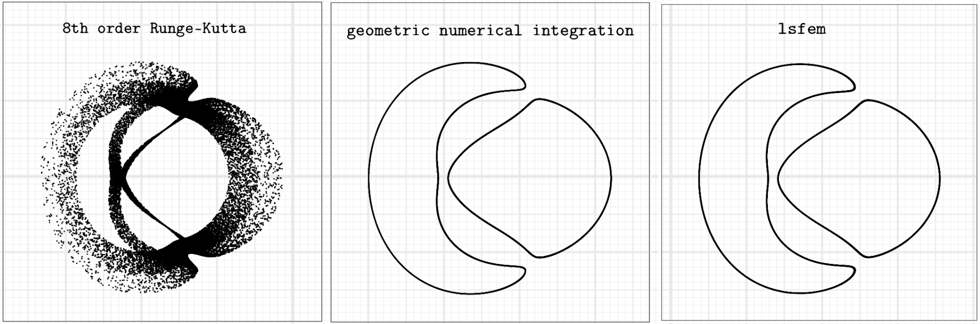


Bock 1983.

Bulirsch 1971.

mcchung@vt.edu

① Hénon-Heiles Hamiltonian system

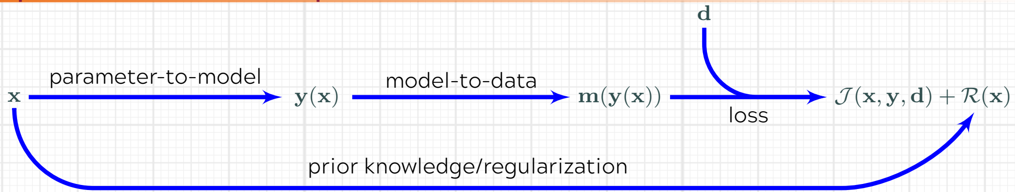


$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} -y_3 - 2\lambda y_3 y_4 \\ -y_4 - \lambda(y_3^2 - y_4^2) \\ y_1 \\ y_2 \end{bmatrix} \quad \text{wrt.} \quad \begin{bmatrix} y_1(0) \\ y_2(0) \\ y_3(0) \\ y_4(0) \end{bmatrix} = 0.18 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix}, \lambda = 1 \text{ and } t \in [0, 100, 000]$$

E Hairer and M Hairer. GniCodes—Matlab programs for geometric numerical integration. In: *Frontiers in Numerical Analysis (Durham, 2002)*. Universitext. Springer, Berlin, 2003, pp. 199–240.

mcchung@vt.edu

② parameter estimation problem



- $\mathbf{x} \in \mathbb{R}^n$ parameter
- $\mathbf{y} : \mathbb{R}^n \to \mathcal{Y}$ model, e.g., ODE, DDE, PDE
- $\mathbf{m} : \mathcal{Y} \to \mathbb{R}^m$, projection onto data, e.g., ODE evaluated at discrete time points
- $\mathbf{d} \in \mathbb{R}^m$
- e.g., $\mathcal{J}(\mathbf{x}) = \|\mathbf{m}(\mathbf{y}(\mathbf{x})) - \mathbf{d}\|_2^2$, where $\|\cdot\|_2$ Euclidean norm
- $\mathcal{R} : \mathbb{R}^n \to \mathbb{R}$ regularization/prior knowledge (e.g., sparsity $\|\cdot\|_1$)
- Interpretation as MAP estimate in a Bayesian framework

mcchung@vt.edu

② parameter estimation via principal differential analysis (PDA)

VIRGINIA TECH

$$\widehat{\mathbf{x}} = \arg\min_{\mathbf{x}} \|\mathbf{m}(\mathbf{y}(t)) - \mathbf{d}\|_2^2 \quad \text{subject to } \mathbf{y}'(t) = \mathbf{f}(t, \mathbf{y}(t); \mathbf{x}), \qquad \mathbf{y}(t_0) = \mathbf{y}_0$$

"derivation":

M Chung, J Krueger, and M Pop. Identification of microbiota dynamics using robust parameter estimation methods. In: *Mathematical Biosciences* 294 (2017), pp. 71–84.

Jim O Ramsay. Principal differential analysis: Data reduction by differential operators. In: *Journal of the Royal Statistical Society. Series B (Methodological)* (1996), pp. 495–508.

A.A. Poyton, M.S. Varziri, K.B. McAuley, P.J. McLellan, and J.O. Ramsay. Parameter estimation in continuous-time dynamic models using principal differential analysis. In: *Comput. Chem. Eng.* 30.4 (2006), pp. 698–708.

mcchung@vt.edu

② parameter estimation via principal differential analysis (PDA)

VIRGINIA TECH

$$(\widehat{\mathbf{x}}, \widehat{\mathbf{y}}) = \underset{\mathbf{x},\mathbf{y}}{\arg\min} \; \|\mathbf{m}(\mathbf{y}(t)) - \mathbf{d}\|_2^2 + \lambda \|\mathbf{y}'(t) - \mathbf{f}(t, \mathbf{y}(t); \mathbf{x})\|_{\mathcal{L}^2}^2 \quad \text{subject to } \mathbf{y}(t_0) = \mathbf{y}_0$$

"derivation":

1. relax ODE constraint

Chung, Krueger, and Pop 2017.

Ramsay 1996.

Poyton, Varziri, McAuley, McLellan, and Ramsay 2006.

mcchung@vt.edu

② parameter estimation via principal differential analysis (PDA)

$$(\widehat{\mathbf{x}}, \widehat{\mathbf{q}}) = \underset{\mathbf{x},\mathbf{q}}{\arg\min}\ \|\mathbf{m}(\mathbf{s}(t;\mathbf{q})) - \mathbf{d}\|_2^2 + \lambda \|\mathbf{s}'(t;\mathbf{q}) - \mathbf{f}(t, \mathbf{s}(t;\mathbf{q}); \mathbf{x})\|_{\mathcal{L}^2}^2, \quad \text{subject to } \mathbf{s}(t_0) = \mathbf{y}_0$$

"derivation":

1. relax ODE constraint
2. restrict to parameterized finite function space

Chung, Krueger, and Pop 2017.

Ramsay 1996.

Poyton, Varziri, McAuley, McLellan, and Ramsay 2006.

mcchung@vt.edu

② parameter estimation via principal differential analysis (PDA)

VIRGINIA TECH

$$(\widehat{\mathbf{x}}, \widehat{\mathbf{q}}) = \underset{\mathbf{x},\mathbf{q}}{\arg\min}\ \|\mathbf{m}(\mathbf{s}(t;\mathbf{q})) - \mathbf{d}\|_2^2 + \lambda\|\mathbf{s}'(\mathbf{T};\mathbf{q}) - \mathbf{f}(\mathbf{T},\mathbf{s}(\mathbf{T};\mathbf{q});\mathbf{x})\|_2^2 \quad \text{subject to } \mathbf{s}(t_0) = \mathbf{y}_0$$

"derivation":

1. relax ODE constraint
2. restrict to parameterized finite function space
3. discretize $\mathbf{T} = [T_1, \ldots, T_M]^\top$

Chung, Krueger, and Pop 2017.

Ramsay 1996.

Poyton, Varziri, McAuley, McLellan, and Ramsay 2006.

② parameter estimation via principal differential analysis (PDA)

$$(\widehat{\mathbf{x}}, \widehat{\mathbf{q}}) = \arg\min_{\mathbf{x},\mathbf{q}} \|\mathbf{m}(\mathbf{s}(t;\mathbf{q})) - \mathbf{d}\|_2^2 + \lambda \|\mathbf{s}'(\mathbf{T};\mathbf{q}) - \mathbf{f}(\mathbf{T}, \mathbf{s}(\mathbf{T};\mathbf{q});\mathbf{x})\|_2^2 \quad \text{subject to } \mathbf{s}(t_0) = \mathbf{y}_0$$

"derivation":

1. relax ODE constraint
2. restrict to parameterized finite function space
3. discretize $\mathbf{T} = [T_1, \ldots, T_M]^\top$

advantages:

- simultaneous parameter and approximate ODE solve
- robustness in parameter estimates

Chung, Krueger, and Pop 2017.

Ramsay 1996.

Poyton, Varziri, McAuley, McLellan, and Ramsay 2006.

mcchung@vt.edu

② generalized Lotka-Volterra simulation study

Consider the 4 state Lotka-Volterra system

$$\mathbf{y}' = \operatorname{diag}(\mathbf{y})\,(\mathbf{r} + \mathbf{A}\mathbf{y}), \qquad \mathbf{y}(0) = \mathbf{y}_0$$

with

$$\mathbf{r} = \begin{bmatrix} 2 \\ 1 \\ 0 \\ -3 \end{bmatrix}, \quad \mathbf{A} = \begin{bmatrix} 0 & -0.6 & 0 & -0.2 \\ 0.6 & 0 & -0.6 & -0.2 \\ 0 & 0.6 & 0 & -0.2 \\ 0.2 & 0.2 & 0.2 & 0 \end{bmatrix}, \quad \mathbf{y}_0 = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \end{bmatrix}.$$

Goal: Estimating $\mathbf{x} = [\mathbf{r}; \operatorname{vec}(\mathbf{A}); \mathbf{y}_0]$ give data.

mcchung@vt.edu

Average relative error:

$$e_r = \frac{1}{80}\sum_{j=1}^{80}\left|\frac{m_j(\mathbf{y}) - d_j}{d_j}\right|$$

Study 1 (0% noise):

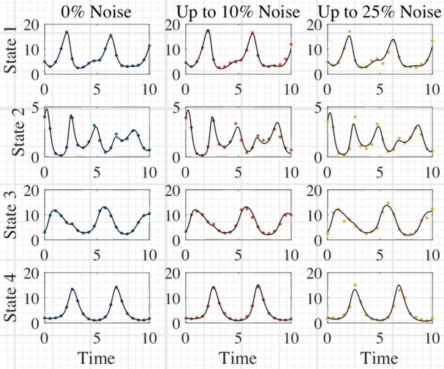
$$e_r \approx 0.0331$$

Study 2 (up to 10% noise):

$$e_r \approx 0.0926$$

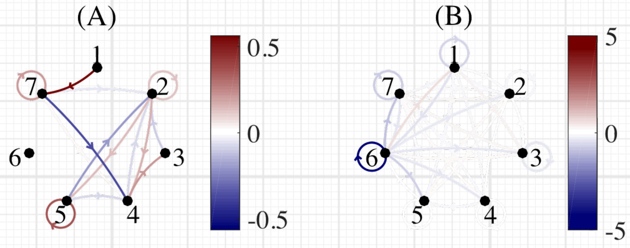
Study 3 (up to 25% noise):

$$e_r \approx 0.1511$$



dynamics vs. data

mcchung@vt.edu



PDA (A) versus published interaction matrix (B)

1. Blautia
2. Barnesiella
3. Unclassified Mollicutes
4. Undefined Lachnospiraceae
5. Unclassified Lachnospiraceae
6. Coprobacillus
7. Other

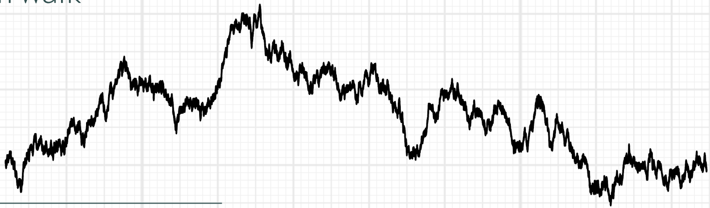
C G Buffie, I Jarchum, et al. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. In: *Infect. Immun.* 80.1 (2012), pp. 62–73; R R Stein, V Bucci, et al. Ecological modeling from time-series inference: insight into dynamics and stability of intestinal microbiota. In: *PLoS Comput. Biol.* 9.12 (2013), e1003388; C G Buffie, V Bucci, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. In: *Nature* 517.7533 (2015), pp. 205–208.

mcchung@vt.edu

A Gaussian process is a collection of random variables $g(t)$; any finite number $\{g(t_i)\}_{i=1}^m$ of which have a joint Gaussian distribution, i.e., for finite $\mathbf{t} = [t_1, \ldots, t_m]^\top \in \mathbb{R}^m$, the joint distribution is Gaussian,

$$g(\mathbf{t}) \sim \mathcal{N}([\mu(t_i)]_{i=1}^m, [\kappa(t_i, t_j)]_{i,j=1}^m)$$

e.g., random walk



C E Rasmussen and C K I Williams. *Gaussian Process for Machine Learning*. MIT press, 2006.

 mcchung@vt.edu

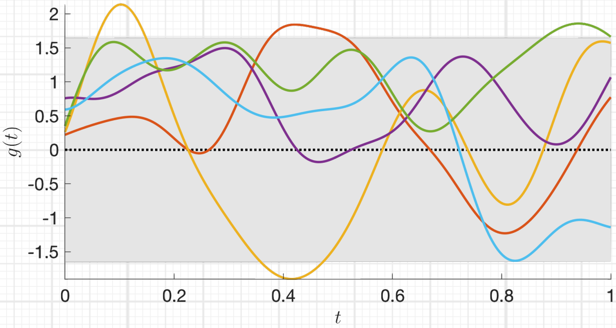
③ Gaussian process prior

Kernel $\kappa(t, \tilde{t})$ is real, symmetric, non-negative, integrable function

mcchung@vt.edu

Kernel $\kappa(t,\tilde{t})$ is real, symmetric, non-negative, integrable function

squared exponential kernel $\kappa(t,\tilde{t}) = \tau^2 \exp\left(-\frac{1}{2\ell^2}\left\|t-\tilde{t}\right\|_2^2\right)$ $(\tau = 1)$

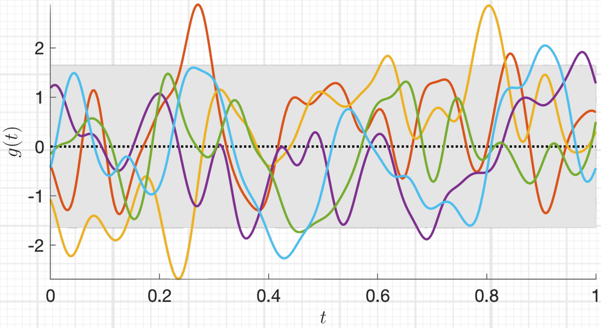


$\ell^2 = 0.01$ (length scale parameter)

mcchung@vt.edu

Kernel $\kappa(t,\tilde{t})$ is real, symmetric, non-negative, integrable function

squared exponential kernel $\kappa(t,\tilde{t}) = \tau^2 \exp\left(-\frac{1}{2\ell^2}\left\|t-\tilde{t}\right\|_2^2\right) \qquad (\tau = 1)$

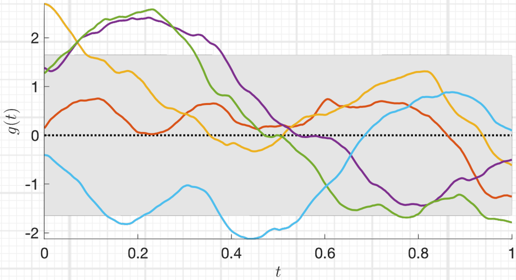


$\ell^2 = 0.001$ (length scale parameter)

mcchung@vt.edu

Kernel $\kappa(t, \tilde{t})$ is real, symmetric, non-negative, integrable function

Matérn kernel $\kappa(t,\tilde{t}) = \frac{2^{1-\nu}}{\Gamma(\nu)} \left(\frac{\sqrt{2\nu|t-\tilde{t}|}}{\ell} \right)^{\nu} K_\nu \left(\frac{\sqrt{2\nu|t-\tilde{t}|}}{\ell} \right)$

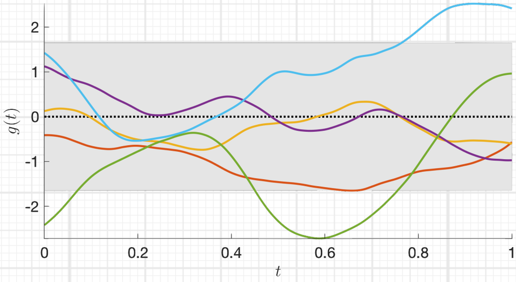


Γ Gamma function, K_ν modified Bessel function, $\nu = 1/2$

mcchung@vt.edu

Kernel $\kappa(t,\tilde{t})$ is real, symmetric, non-negative, integrable function

Matérn kernel $\kappa(t,\tilde{t}) = \frac{2^{1-\nu}}{\Gamma(\nu)}\left(\frac{\sqrt{2\nu|t-\tilde{t}|}}{\ell}\right)^{\nu} K_\nu\left(\frac{\sqrt{2\nu|t-\tilde{t}|}}{\ell}\right)$



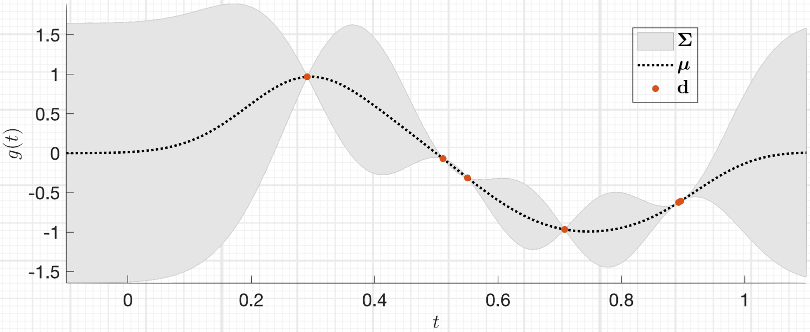
Γ Gamma function, K_ν modified Bessel function, $\nu = 3/2$

mcchung@vt.edu

joint distribution at $\mathbf{t}$ and $\mathbf{T}$: $$\begin{bmatrix}\mathbf{d}\\ \mathbf{g}\end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix}\mathbf{0}_m\\ \mathbf{0}_M\end{bmatrix}, \begin{bmatrix}\boldsymbol{\Sigma}_{\mathbf{t}} & \boldsymbol{\Sigma}_{\mathbf{tT}}\\ \boldsymbol{\Sigma}_{\mathbf{Tt}} & \boldsymbol{\Sigma}_{\mathbf{T}}\end{bmatrix}\right)$$

conditional (predictive) distribution

$$(\mathbf{g}|\mathbf{d}) \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}), \quad \text{with } \boldsymbol{\mu} = \boldsymbol{\Sigma}_{\mathbf{Tt}}\boldsymbol{\Sigma}_{\mathbf{t}}^{-1}\mathbf{d} \quad \text{and } \boldsymbol{\Sigma} = \boldsymbol{\Sigma}_{\mathbf{T}} - \boldsymbol{\Sigma}_{\mathbf{Tt}}\boldsymbol{\Sigma}_{\mathbf{t}}^{-1}\boldsymbol{\Sigma}_{\mathbf{tT}}$$



mcchung@vt.edu

For predictive Gaussian process $\mathbf{g} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ for given data $(\mathbf{t}, \mathbf{d})$ and model $\mathbf{y}$ solve

$$\widehat{\mathbf{x}} = \arg\min_{\mathbf{x}} \|\mathbf{m}(\mathbf{y}(t, \mathbf{x})) - \mathbf{g}\|^2_{\boldsymbol{\Sigma}^{-1}} + \mathcal{R}(\mathbf{x})$$

Algorithm: sampled GP weighted least squares

input: model $\mathbf{y}$, projection $\mathbf{m}$, $\boldsymbol{\mu}$, $\boldsymbol{\Sigma}$, initial guess $\mathbf{x}_0$

1: **parallel for** $j = 1$ **to** J **do**

2: **sample** $\mathbf{g}_j$ **from Gaussian process** $\mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$

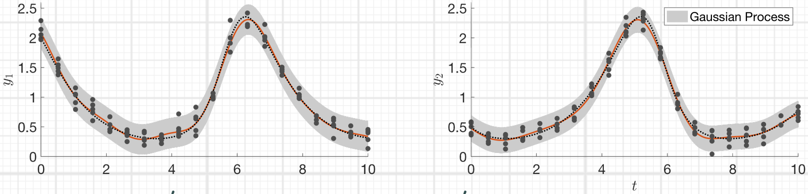
3: **solve** $\widehat{\mathbf{x}}_j = \arg\min_{\mathbf{x}} \|\mathbf{m}(\mathbf{y}(t, \mathbf{x})) - \mathbf{g}_j\|^2_{\boldsymbol{\Sigma}^{-1}} + \mathcal{R}(\mathbf{x})$

4: **end parallel for**

output: $\{\widehat{\mathbf{x}}_j\}_{j=1}^{J}$

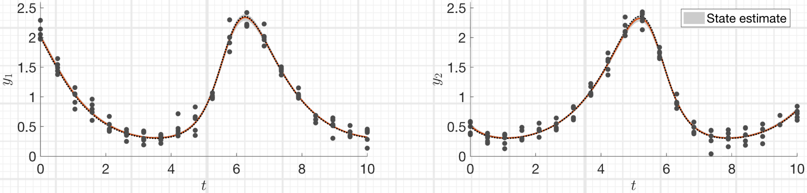
M Chung, M Binois, et al. Parameter and Uncertainty Estimation for Dynamical Systems Using Surrogate Stochastic Processes. In: *arXiv preprint arXiv:1802.00852* (2018).

VIRGINIA TECH



$$y_1' = -y_1 + x_1 y_1 y_2 \qquad y_2' = y_2 - x_2 y_1 y_2$$

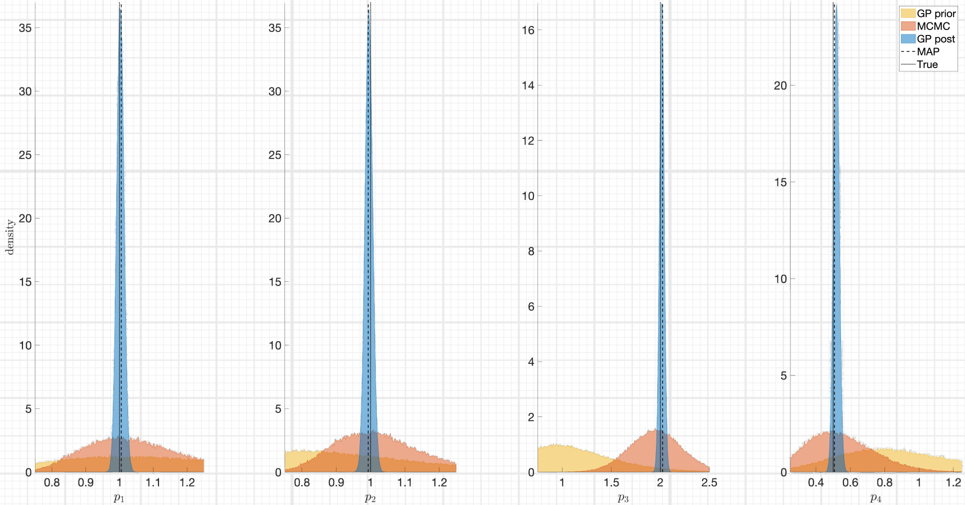
unknow parameter $\mathbf{x} = [x_1, x_2, y_1(0), y_2(0)]^\top$



Matthias Chung, Mickaël Binois, et al. Parameter and uncertainty estimation for dynamical systems using surrogate stochastic processes. In: *SIAM Journal on Scientific Computing* 41.4 (2019), A2212–A2238.

 mcchung@vt.edu

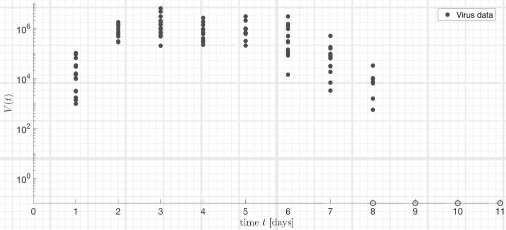
③ Lotka-Volterra UQ



marginal 1D densities with GP and with MCMC

mcchung@vt.edu

③ motivating example: influenza virus data & model

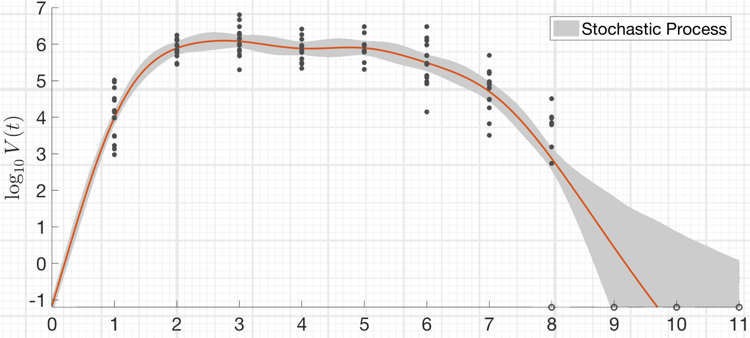


$$T' = -\beta T V$$
$$I_1' = \beta T V - \kappa I_1$$
$$I_2' = \kappa I_1 - \frac{\delta I_2}{K_d + I_2}$$
$$V' = \rho I_2 - c V$$

- T target cells
- I_1 and I_2 infected cells
- V virus
- β "contact rate"
- κ rate (eclipse)
- ρ virus production rate
- c clearance rate
- δ density dependent clearance
- K_d half-saturation constant

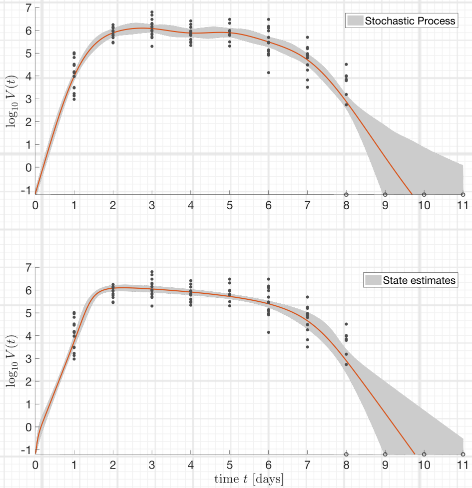
Chung, Binois, et al. 2019.

③ influenza virus GP



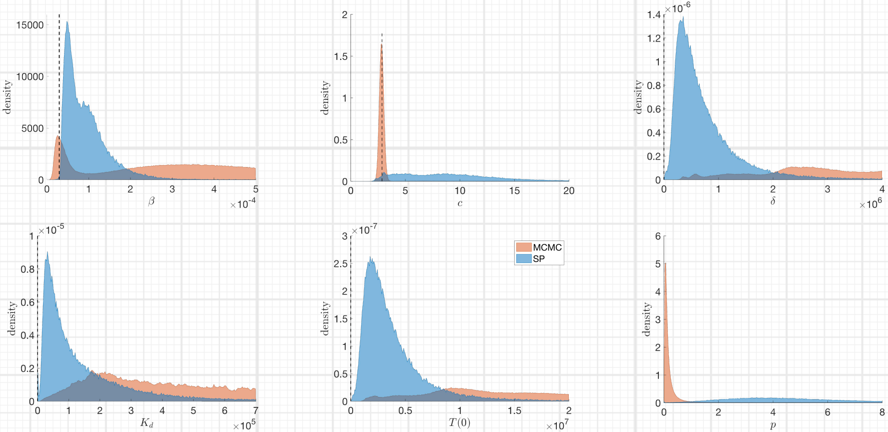
mcchung@vt.edu

③ influenza virus GP



mcchung@vt.edu

③ influenza virus GP



marginal 1D densities with GP and with MCMC

mcchung@vt.edu

VIRGINIA TECH

$$\widehat{\mathbf{x}} \quad = \arg\min_{\mathbf{x}} \tfrac{1}{2} \overbrace{\|\mathbf{y}(\quad \mathbf{x}) - \mathbf{d} \quad \|^2_{\boldsymbol{\Gamma}_\varepsilon^{-1}}}^{\mathcal{J}(\mathbf{x})} + \tfrac{1}{2} \overbrace{\|\mathbf{L}\mathbf{x}\|_2^2}^{\mathcal{R}(\mathbf{x})}$$

subject to $\mathbf{C}_{\rm e}\mathbf{x} - \mathbf{c}_{\rm e} = \mathbf{0}$ and $\mathbf{C}_{\rm i}\mathbf{x} - \mathbf{c}_{\rm i} \geq \mathbf{0}$,

- $\mathbf{C}_{\rm e}, \mathbf{C}_{\rm i}, \mathbf{c}_{\rm e}, \mathbf{c}_{\rm i}$ constraints

E Haber, L Horesh, and L Tenorio. Numerical methods for experimental design of large-scale linear ill-posed inverse problems. In: *Inverse Problems* 24.5 (2008), p. 055012.

M Chung and E Haber. Experimental Design for Biological Systems. In: *SIAM Journal on Control and Optimization* 50.1 (2012), pp. 471–489.

$$\widehat{\mathbf{x}}(\mathbf{p}) = \arg\min_{\mathbf{x}} \frac{1}{2}\overbrace{\|\mathbf{y}(\mathbf{p},\mathbf{x}) - \mathbf{d}(\mathbf{p})\|^2_{\boldsymbol{\Gamma}_{\boldsymbol{\varepsilon}}^{-1}(\mathbf{p})}}^{\mathcal{J}(\mathbf{x})} + \frac{1}{2}\overbrace{\|\mathbf{L}\mathbf{x}\|_2^2}^{\mathcal{R}(\mathbf{x})}$$

subject to $\mathbf{C}_{\mathrm{e}}\mathbf{x} - \mathbf{c}_{\mathrm{e}} = \mathbf{0}$ and $\mathbf{C}_{\mathrm{i}}\mathbf{x} - \mathbf{c}_{\mathrm{i}} \geq \mathbf{0}$,

- $\mathbf{C}_{\mathrm{e}}, \mathbf{C}_{\mathrm{i}}, \mathbf{c}_{\mathrm{e}}, \mathbf{c}_{\mathrm{i}}$ constraints
- $\mathbf{p} \in \Omega$ design parameter (Ω set of feasible design parameter)

Haber, Horesh, and Tenorio 2008.

Chung and Haber 2012.

Bayes risk approach (average design)

$$\min_{\mathbf{p}\in\Omega} \quad \mathcal{J}(\mathbf{p}) = \tfrac{1}{2}\,\mathbb{E}\,\|\widehat{\mathbf{x}}(\mathbf{p}) - \mathbf{x}_{\mathrm{true}}\|_2^2 + \mathcal{R}_{\mathbf{p}}(\mathbf{p}) \qquad \text{subject to}$$

$$\widehat{\mathbf{x}}(\mathbf{p}) = \arg\min_{\mathbf{x}} \overbrace{\tfrac{1}{2}\,\|\mathbf{y}(\mathbf{p},\mathbf{x}) - \mathbf{d}(\mathbf{p})\|^2_{\boldsymbol{\Gamma}_{\boldsymbol{\varepsilon}}^{-1}(\mathbf{p})}}^{\mathcal{J}(\mathbf{x})} + \overbrace{\tfrac{1}{2}\,\|\mathbf{L}\mathbf{x}\|_2^2}^{\mathcal{R}(\mathbf{x})}$$

$$\text{subject to}\ \ \mathbf{C}_{\mathrm{e}}\mathbf{x} - \mathbf{c}_{\mathrm{e}} = \mathbf{0} \text{ and } \mathbf{C}_{\mathrm{i}}\mathbf{x} - \mathbf{c}_{\mathrm{i}} \geq \mathbf{0}\,,$$

- $\mathbf{C}_{\mathrm{e}}, \mathbf{C}_{\mathrm{i}}, \mathbf{c}_{\mathrm{e}}, \mathbf{c}_{\mathrm{i}}$ constraints
- $\mathbf{p} \in \Omega$ design parameter (Ω set of feasible design parameter)
- $\mathbb{E}$ expected value (sampling of expected value via training data $\mathbf{x}^j_{\mathrm{true}}$, with $j = 1, \ldots, M$)
- $\mathcal{R}_{\mathbf{p}}$ regularization (cost) on design parameter $\mathbf{p}$

Haber, Horesh, and Tenorio 2008.

Chung and Haber 2012.

mcchung@vt.edu

Bayes risk approach (average design)

$$\min_{\mathbf{p}\in\Omega} \quad \mathcal{J}(\mathbf{p}) = \tfrac{1}{2}\,\mathbb{E}\,\|\widehat{\mathbf{x}}(\mathbf{p}) - \mathbf{x}_{\text{true}}\|_2^2 + \beta\|\mathbf{p}\|_1 \qquad \text{subject to}$$

$$\widehat{\mathbf{x}}(\mathbf{p}) = \arg\min_{\mathbf{x}} \overbrace{\tfrac{1}{2}\,\|\mathbf{y}(\mathbf{p},\mathbf{x}) - \mathbf{d}(\mathbf{p})\|^2_{\boldsymbol{\Gamma}_{\boldsymbol{\varepsilon}}^{-1}(\mathbf{p})}}^{\mathcal{J}(\mathbf{x})} + \overbrace{\tfrac{1}{2}\,\|\mathbf{L}\mathbf{x}\|_2^2}^{\mathcal{R}(\mathbf{x})}$$

$$\text{subject to} \;\; \mathbf{C}_\text{e}\mathbf{x} - \mathbf{c}_\text{e} = \mathbf{0} \text{ and } \mathbf{C}_\text{i}\mathbf{x} - \mathbf{c}_\text{i} \geq \mathbf{0}\,,$$

- $\mathbf{C}_\text{e}, \mathbf{C}_\text{i}, \mathbf{c}_\text{e}, \mathbf{c}_\text{i}$ constraints
- $\mathbf{p} \in \Omega$ design parameter (Ω set of feasible design parameter)
- $\mathbb{E}$ expected value (sampling of expected value via training data $\mathbf{x}_{\text{true}}^j$, with $j = 1, \ldots, M$)
- $\mathcal{R}_\mathbf{p}$ regularization (cost) on design parameter $\mathbf{p}$

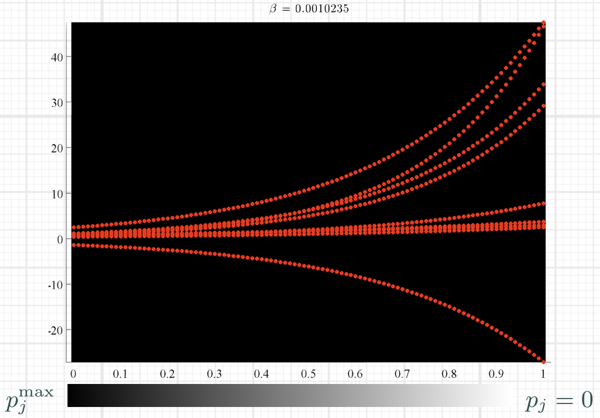
Haber, Horesh, and Tenorio 2008.

Chung and Haber 2012.

mcchung@vt.edu

④ Exponential growth

$y' = xy$ unknown parameter x

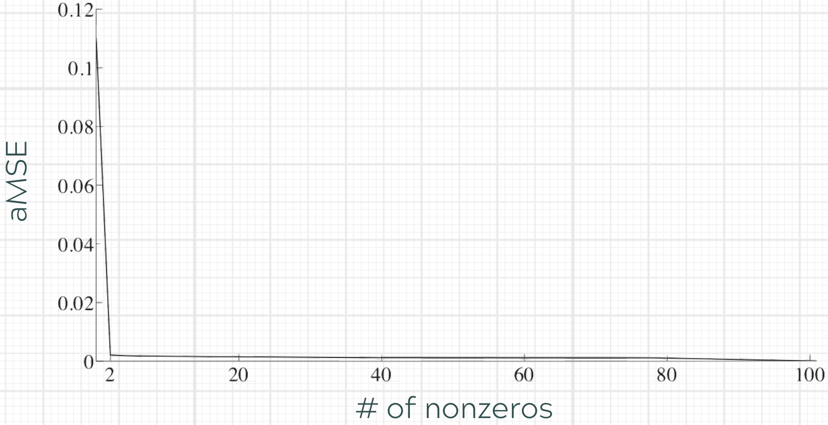


samples = 10, discretization 101, no noise, and $\mathbf{L} = 0.1\mathbf{I}_n$

mcchung@vt.edu

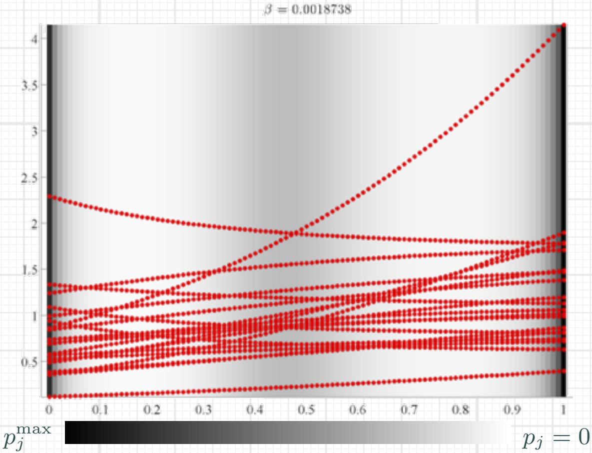
④ Exponential growth

$y' = xy$ unknown parameter x



mcchung@vt.edu

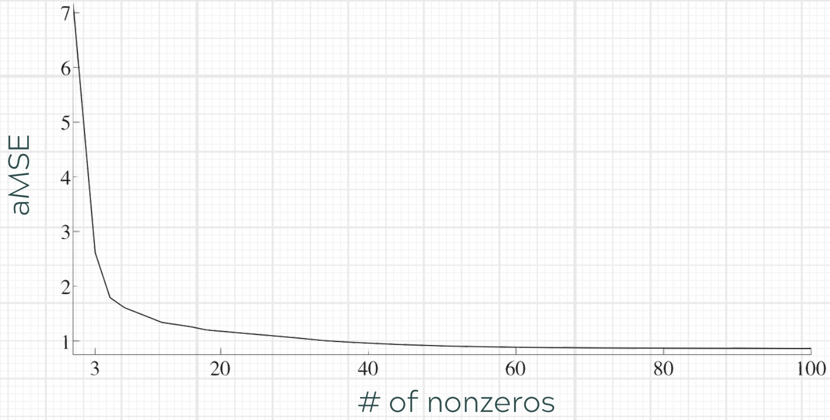
$y' = x_1 y - x_2 y^2$ unknown parameter $\mathbf{x} = [x_1, x_2]^\top$



samples = 20, discretization 101, no noise, and $\mathbf{L} = 0.1\mathbf{I}_n$

④ Logistic growth

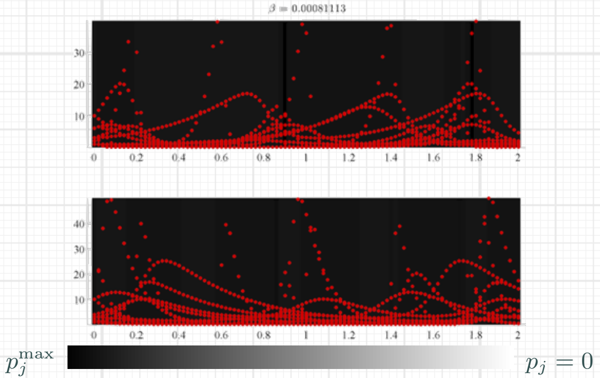
$$y' = x_1 y - x_2 y^2 \qquad \text{unknown parameter } \mathbf{x} = [x_1, x_2]^\top$$



mcchung@vt.edu

$$y_1' = x_1 y_1 - x_2 y_1 y_2$$
$$y_2' = -x_3 y_2 + x_4 y_1 y_2$$

$$\mathbf{x} = [x_1, x_2, x_3, x_4]^\top$$



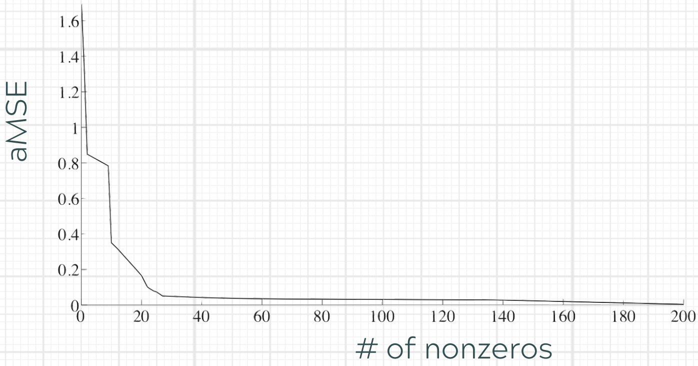
samples = 10, discretization 202, no noise, and $\mathbf{L} = 0.1\mathbf{I}_n$

mcchung@vt.edu

④ Lotka-Volterra

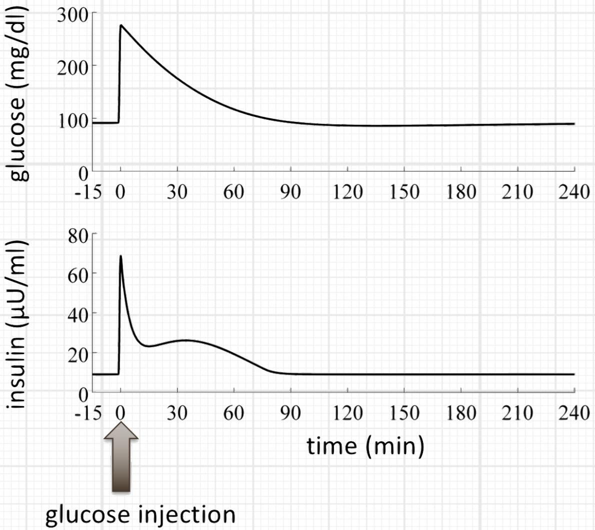
$$y_1' = x_1 y_1 - x_2 y_1 y_2$$
$$y_2' = -x_3 y_2 + x_4 y_1 y_2$$

$$\mathbf{x} = [x_1, x_2, x_3, x_4]^\top$$



mcchung@vt.edu

④ intravenous glucose tolerance test (IVGTT)



mcchung@vt.edu

VIRGINIA TECH

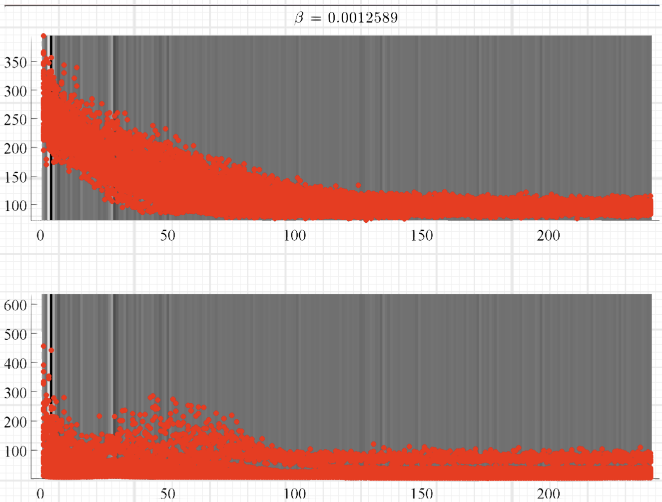
Minimal Model

$$\dot{G}(t) = -x_1 + X(t)G(t) + x_1 G_b$$
$$\dot{I}(t) = -\gamma \max(G(t) - h, 0)t - n(I(t) - I_b)$$
$$\dot{X}(t) = -x_2 X(t) + x_3(I(t) - I_b)$$

G, I, X	blood glucose, plasma insulin, effective insulin
G_b, I_b	basal level of glucose and insulin
γ	pancreatic insulin release rate
h	pancreatic threshold
n	degradation rate of insulin
x_1	glucose effectiveness
x_2	degradation rate of effective insulin
x_3	stimulation sensitivity of insulin

R N Bergman, L S Phillips, and C Cobelli. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. In: *The Journal of clinical investigation* 68.6 (1981), pp. 1456–1467.

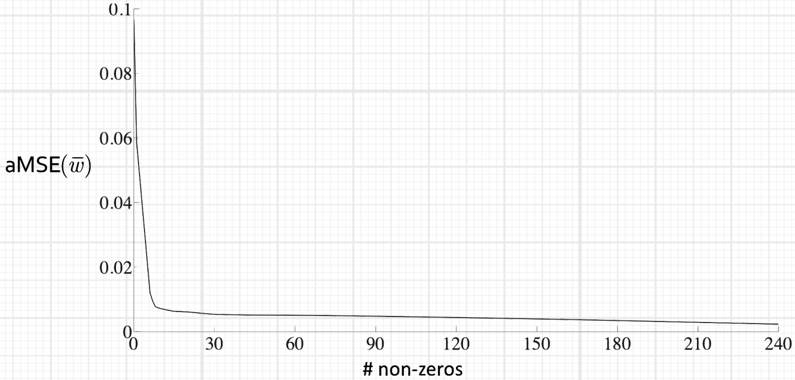
mcchung@vt.edu



54 samples, discretization 241

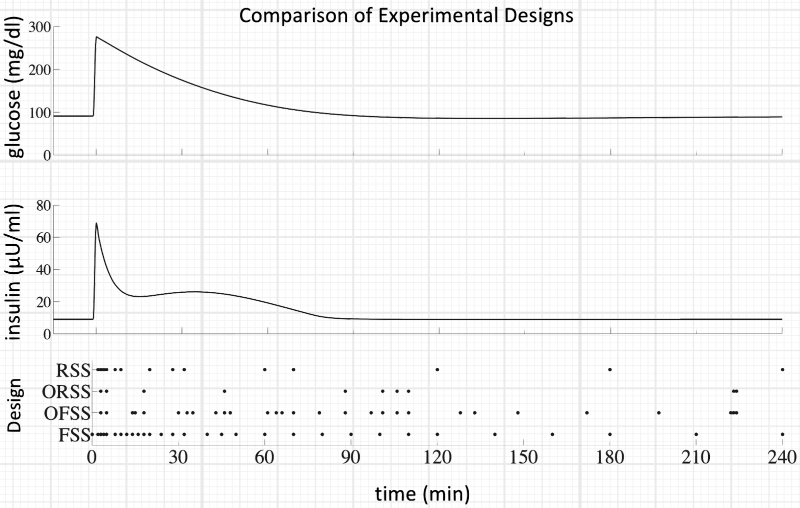
mcchung@vt.edu

④ IVGTT: sparsity vs. error

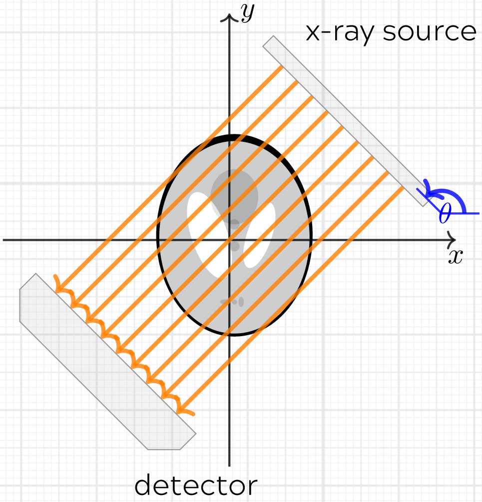


mcchung@vt.edu

④ IVGTT: proposed design



mcchung@vt.edu



$$\mathbf{d}(\theta) = \mathbf{T}\mathbf{R}(\theta)\mathbf{x}_{\text{true}} + \boldsymbol{\varepsilon}(\theta)$$

- $\mathbf{x}_{\text{true}} \in \mathbb{R}^n$ true object
- θ angle
- $\mathbf{R}(\theta) \in \mathbb{R}^{n \times n}$ rotation of object
- $\mathbf{T} \in \mathbb{R}^{n_r \times n}$ transmission process

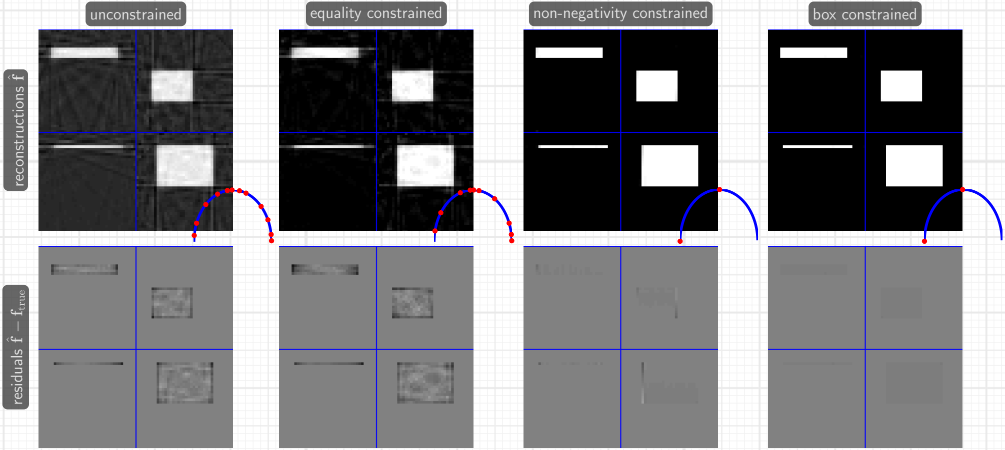
Where and how often should be measured for good recovery?

Design constraints

- time
- cost
- health risk
- limited resources

L Ruthotto, J Chung, and M Chung. Optimal Experimental Design for Inverse Problems with State Constraints. In: *SIAM Journal on Scientific Computing* 40.4 (2018), B1080–B1100.

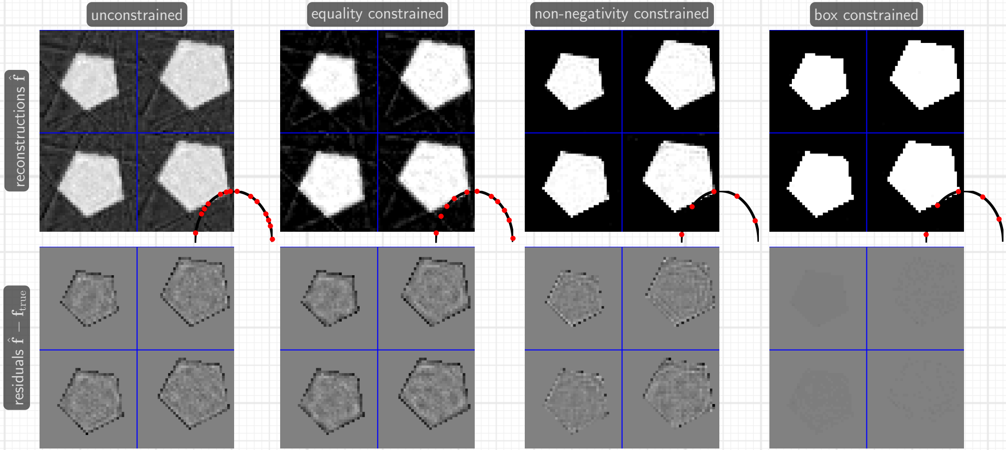
④ tomography results: rectangles



intuitive optimal angles $[0, 90]$ $[0, 90]$ (non-negative) $[0, 90]$ (box)

 mcchung@vt.edu

④ tomography results: pentagons

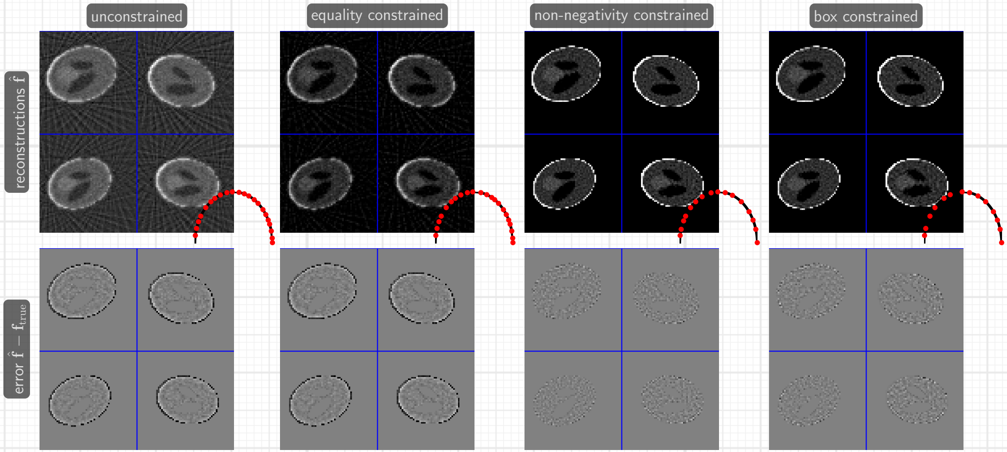


intuitive optimal angles $[27, 63, 99, 135, 171]$

$[25, 64, 99, 136, 171]$ (non-negative) $[27, 62, 99, 134, 171]$ (box)

mcchung@vt.edu

④ tomography results: Shepp-Logan phantom



mcchung@vt.edu

④ conclusion & outlook

VIRGINIA TECH

Take-home message

- flexible and robust differential equation solvers
- efficient parameter estimation method using PDA
- robust parameter estimation via surrogate data
- new computational framework for optimal experimental design

Outlook

- computational methods for finite element methods for ODE/DDE/DAE
- Gaussian processes for ODE PE, inverse problems, model reduction, missing data problems
- apply OED to various system setups

Thank you for your attention!

mcchung@vt.edu

④ References I

Bardsley, J M, A Solonen, H Haario, and M Laine. Randomize-then-optimize: A method for sampling from posterior distributions in nonlinear inverse problems. In: *SIAM Journal on Scientific Computing* 36.4 (2014), A1895–A1910.

Bergman, R N, L S Phillips, and C Cobelli. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. In: *The Journal of clinical investigation* 68.6 (1981), pp. 1456–1467.

Bock, Hans Georg. Recent advances in parameteridentification techniques for ode. In: *Numerical treatment of inverse problems in differential and integral equations*. Springer, 1983, pp. 95–121.

mcchung@vt.edu

- Buffie, C G, V Bucci, R R Stein, P T McKenney, L Ling, A Gobourne, D No, H Liu, M Kinnebrew, A Viale, E Littmann, M R van den Brink, R R Jenq, Y Taur, C Sander, J R Cross, N C Toussaint, J B Xavier, and E G Pamer. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. In: *Nature* 517.7533 (2015), pp. 205–208.
- Buffie, C G, I Jarchum, M Equinda, L Lipuma, A Gobourne, A Viale, C Ubeda, J Xavier, and E G Pamer. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. In: *Infect. Immun.* 80.1 (2012), pp. 62–73.
- Bulirsch, R. Die Mehrzielmethode zur numerischen Lösung von nichtlinearen Randwertproblemen und Aufgaben der optimalen Steuerung. In: *Report der Carl-Cranz-Gesellschaft* 251 (1971).

mcchung@vt.edu

④ References III

Calvetti, D and E Somersalo. *Introduction to Bayesian Scientific Computing: Ten Lectures on Subjective Computing*. New York: Springer, 2007. ISBN: 0387733930.

Chung, M, M Binois, RB Gramacy, DJ Moquin, AP Smith, and AM Smith. Parameter and Uncertainty Estimation for Dynamical Systems Using Surrogate Stochastic Processes. In: *arXiv preprint arXiv:1802.00852* (2018).

Chung, M and E Haber. Experimental Design for Biological Systems. In: *SIAM Journal on Control and Optimization* 50.1 (2012), pp. 471–489.

Chung, M, J Krueger, and M Pop. Identification of microbiota dynamics using robust parameter estimation methods. In: *Mathematical Biosciences* 294 (2017), pp. 71–84.

mcchung@vt.edu

Chung, Matthias, Mickaël Binois, Robert B Gramacy, Johnathan M Bardsley, David J Moquin, Amanda P Smith, and Amber M Smith. Parameter and uncertainty estimation for dynamical systems using surrogate stochastic processes. In: *SIAM Journal on Scientific Computing* 41.4 (2019), A2212–A2238.

Haber, E, L Horesh, and L Tenorio. Numerical methods for experimental design of large-scale linear ill-posed inverse problems. In: *Inverse Problems* 24.5 (2008), p. 055012.

Hairer, E and M Hairer. GniCodes—Matlab programs for geometric numerical integration. In: *Frontiers in Numerical Analysis (Durham, 2002)*. Universitext. Springer, Berlin, 2003, pp. 199–240.

Hairer, G, SP Nørsett, and E Wanner. *Solving Ordinary Differential Equations I: Nonstiff Problems*. 2nd ed. Berlin: Springer, 1993.

 mcchung@vt.edu

Poyton, A.A., M.S. Varziri, K.B. McAuley, P.J. McLellan, and J.O. Ramsay. Parameter estimation in continuous-time dynamic models using principal differential analysis. In: *Comput. Chem. Eng.* 30.4 (2006), pp. 698–708.

Ramsay, Jim O. Principal differential analysis: Data reduction by differential operators. In: *Journal of the Royal Statistical Society. Series B (Methodological)* (1996), pp. 495–508.

Rasmussen, C E and C K I Williams. *Gaussian Process for Machine Learning*. MIT press, 2006.

Ruthotto, L, J Chung, and M Chung. Optimal Experimental Design for Inverse Problems with State Constraints. In: *SIAM Journal on Scientific Computing* 40.4 (2018), B1080–B1100.

Smith, R C. *Uncertainty Quantification: Theory, Implementation, and Applications*. Vol. 12. SIAM, 2013.

mcchung@vt.edu

④ References VI

- Stein, R R, V Bucci, N C Toussaint, C G Buffie, G Rätsch, E G Pamer, C Sander, and J B Xavier. Ecological modeling from time-series inference: insight into dynamics and stability of intestinal microbiota. In: *PLoS Comput. Biol.* 9.12 (2013), e1003388.
- Tenorio, L. *An Introduction to Data Analysis and Uncertainty Quantification for Inverse Problems*. Vol. 3. SIAM, 2017.
- Wahba, G. Smoothing noisy data with spline functions. In: *Numerische Mathematik* 24.5 (1975), pp. 383–393.

mcchung@vt.edu