ESTIMATING PARAMETERS OF CHAOTIC SYSTEMS IN PHARMACOLOGY

IMMANUEL FREEDMAN, PH. D SMIEEE, HARLEYSVILLE PA USA

SYSTEMS, SIGNALS & ALGORITHMS CONSULTANT

ROBERT BIES (U. BUFFALO), NIKHIL PILLAI (U. BUFFALO)

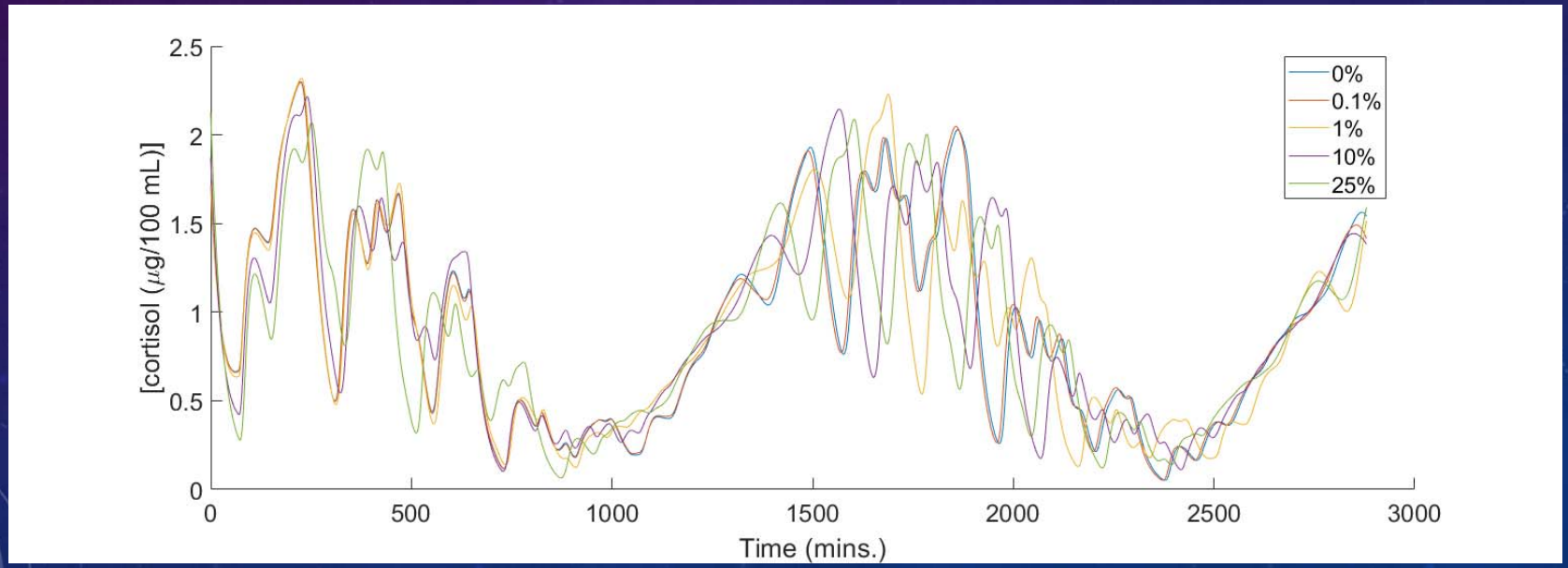
SORREL SCHWARTZ (U. GEORGETOWN), THANG HO (VERTEX)

LEARNING OBJECTIVES

- Introduce challenges of chaotic dynamical systems identification
- Illustrate applications to Quantitative Systems Pharmacology
- Understand adaptive chaos synchronization combined with grid search

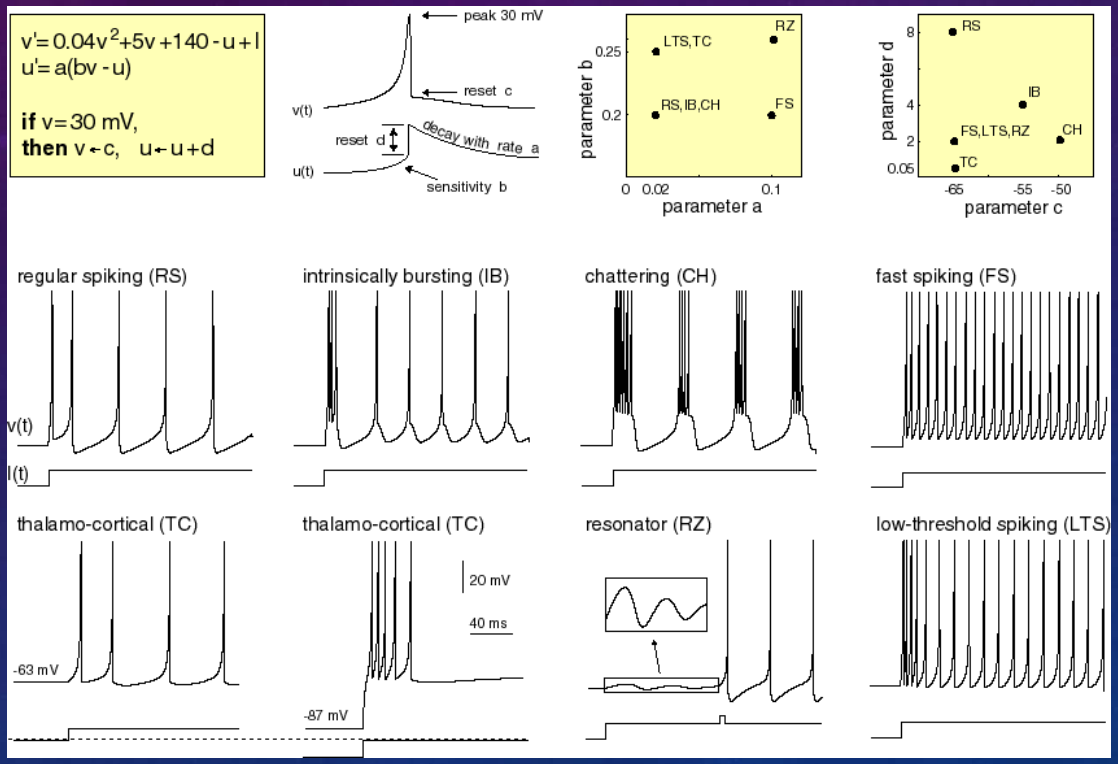
BOUNDED CHAOTIC DYNAMICAL SYSTEMS

A bounded chaotic dynamical system has terms exponentially sensitive to initial conditions



EXEMPLARY CHAOTIC SYSTEMS IN PHARMACOLOGY

IZHEKIVICH CORTICAL NEURON



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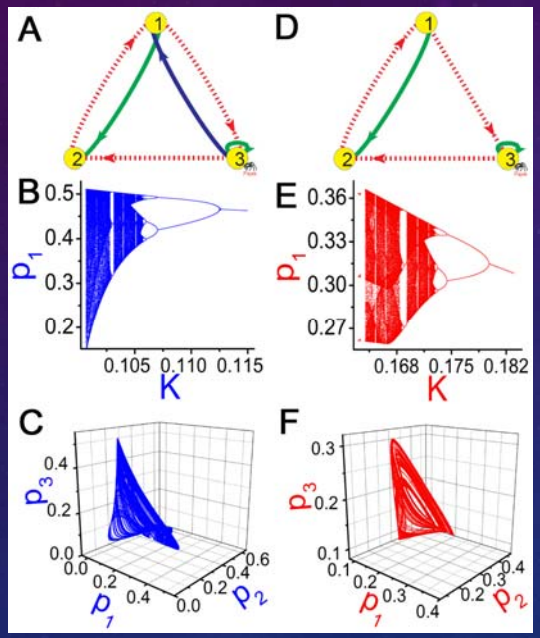
EXEMPLARY CHAOTIC SYSTEMS IN PHARMACOLOGY

THREE-NODE CHAOTIC MOTIFS IN SYSTEMS BIOLOGY



- (A, D) 3-node Gene Regulatory Networks
- (B, E) Bifurcation diagrams
- (C, F) Chaotic attractors

Solid (dashed) = active (repressive) interactions

Zhang Z. et al., PLoS ONE 2012; 7(7): e39355.

KEY CHALLENGES IN PARAMETER ESTIMATION

- Solutions may be multimodal and non-convex
- Optimizers may converge to local solutions
- Objective functions may be very flat near the solutions
- Models may be over-determined
- Models may be poorly scaled
- Solutions may not be smoothly differentiable
- Some parameter combinations may be sloppy

Rodriguez-Fernandez, M. et al. BMC Bioinformatics 2006;7:483
Gutenkunst R.N. et al., PLoS Comput Biol 2007;3(10): e189

DOKOUTMETZIDIS CORTISOL MODEL

DELAYED FEEDBACK WITH CIRCADIAN CYCLE

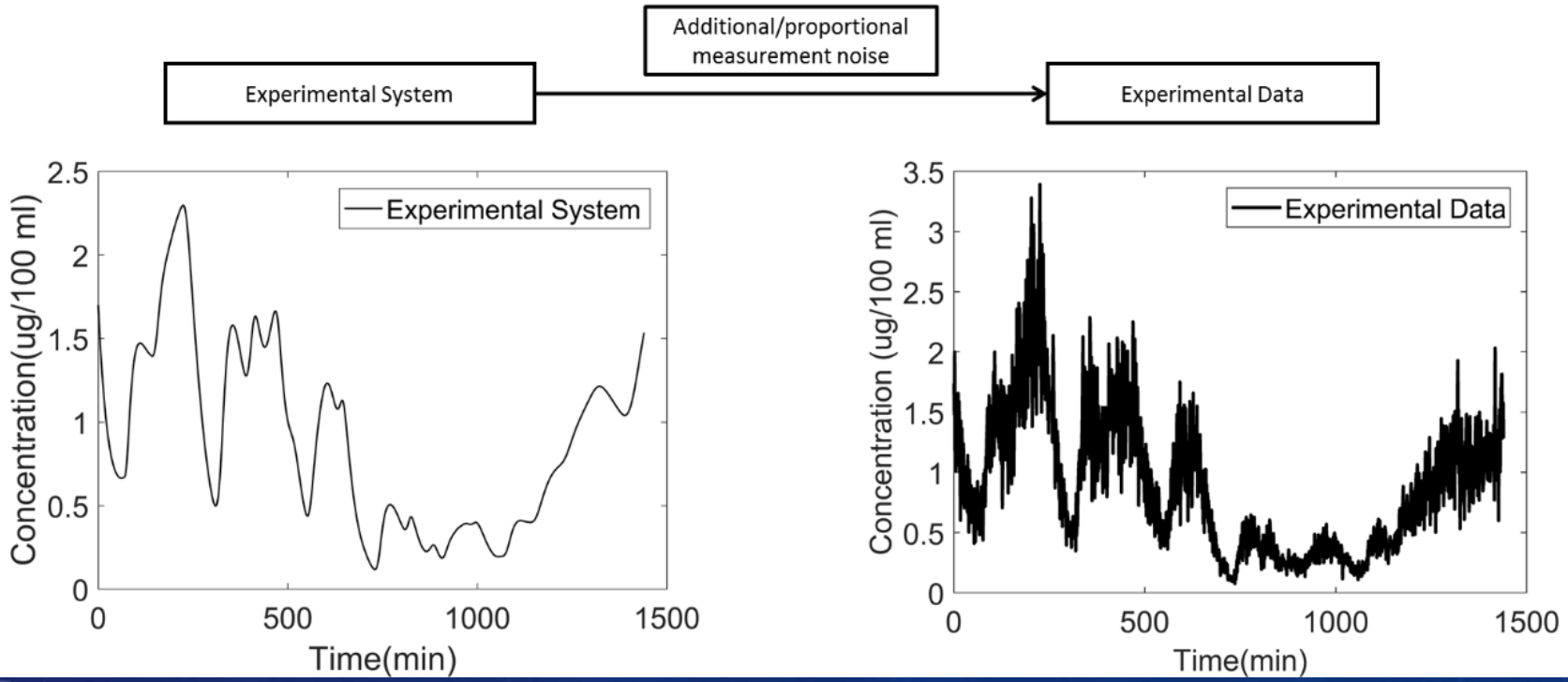
$$\frac{dC(t)}{dt} = q_1 \cdot \frac{a^n \cdot C(t-\tau)}{a^n + C(t-\tau)^n} - q_2 \cdot C(t)$$

$$a = A \cdot cos\left[(t-f) \cdot \frac{2\pi}{1440}\right] + B$$

Dokoumetzidis, A. et al. , Br J Clin Pharmacol. 2002 Jul; 54(1): 21–29.

NOISY CORTISOL MODEL

20% PROPORTIONAL ERROR



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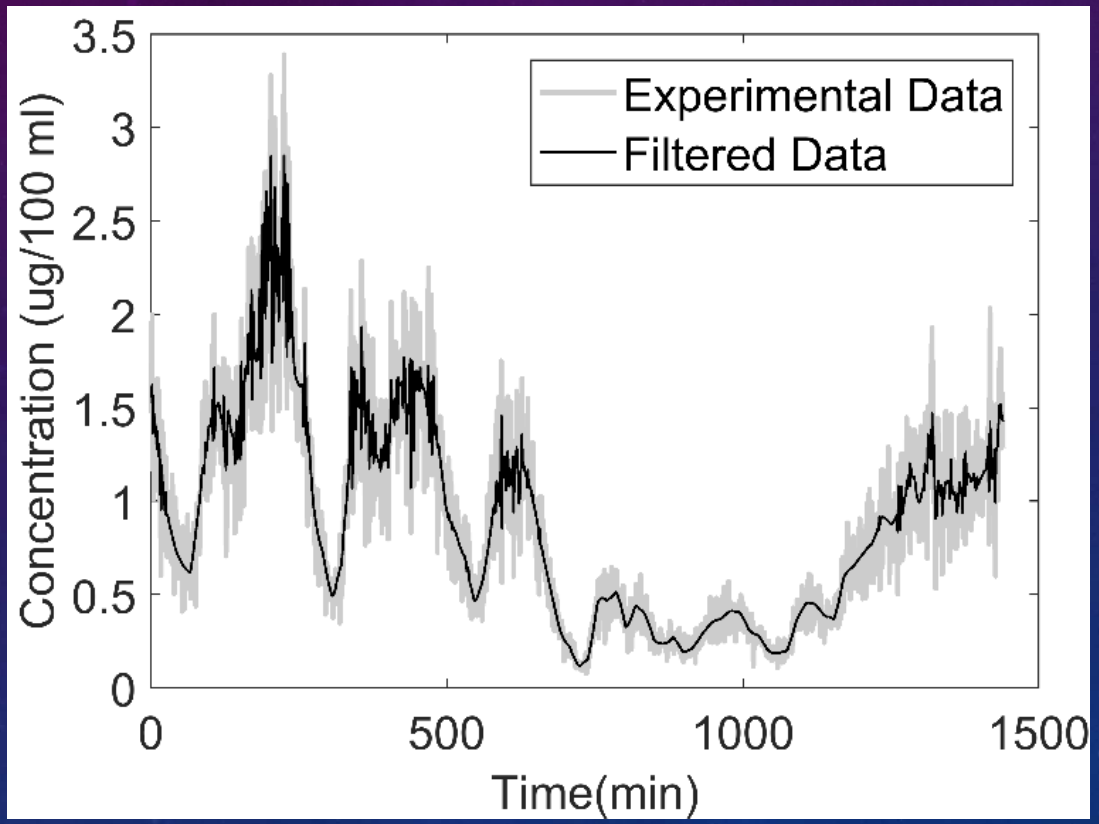
NOISE FILTERING BY WAVELET THRESHOLDING



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NOISELESS SYSTEM LINEAR IN THE PARAMETERS

$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}, \boldsymbol{p})$$

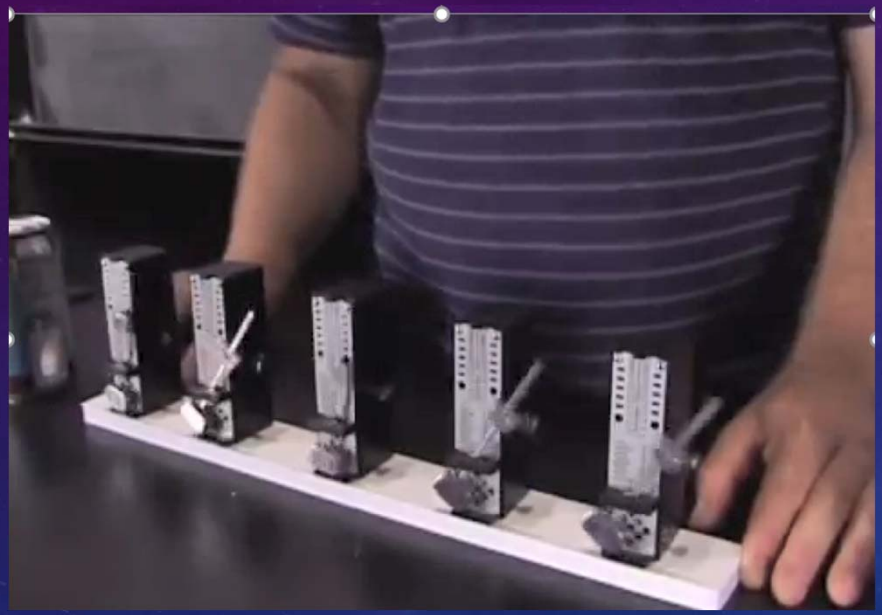
where $F_i(x,p) = c_i(x) + \sum_{j=1}^{m} p_{ij} f_{ij}(x)\,, i = 1,2 \cdots, n$

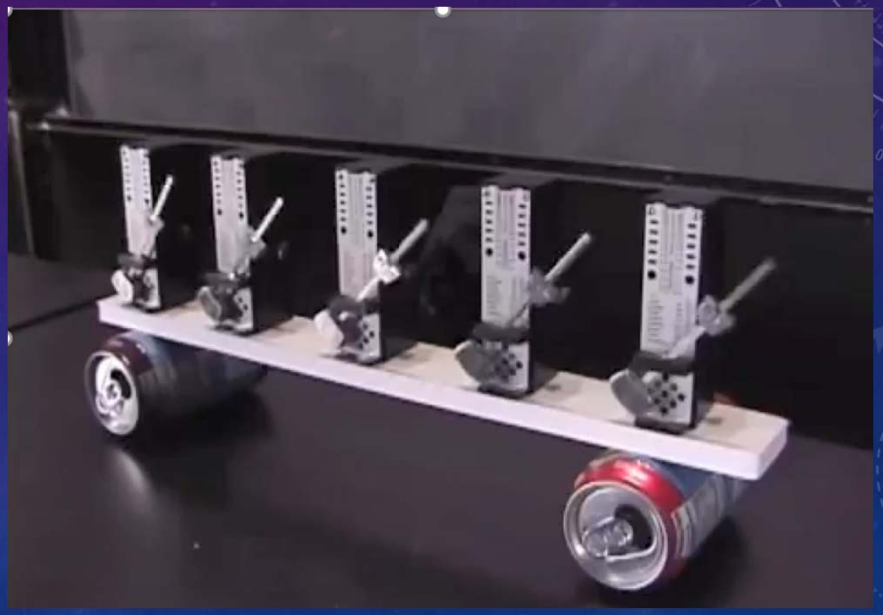
Here, *c* and *f* are nonlinear functions and p are *nm* parameters to be estimated in a bounded set U.

The vector functions ***F*** satisfy a uniform Lipschitz condition in U.

SYNCHRONIZATION OF METRONOMES

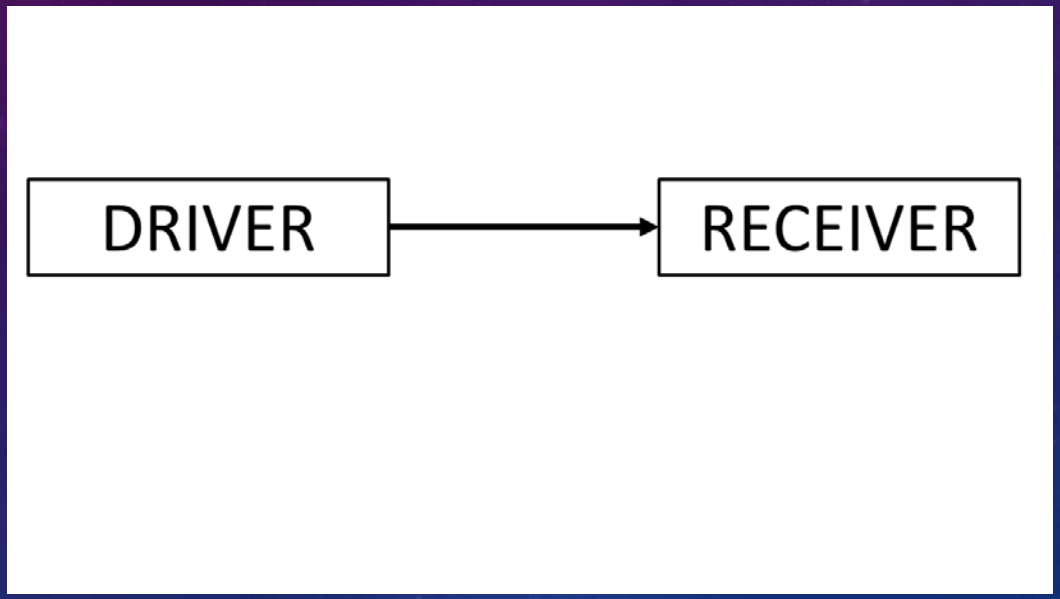
HARVARD NATURAL SCIENCES DEMONSTRATION





Phase synchronization of bidirectionally coupled metronomes at 176 beats per minute
https://www.youtube.com/watch?v=Aaxw4zbULMs

UNIDIRECTIONAL COUPLING



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ADAPTIVE CHAOS SYNCHRONIZATION

Augmented system with unidirectional adaptive coupling to residuals

$$\dot{\boldsymbol{y}} = \boldsymbol{F}(\boldsymbol{y}, \boldsymbol{q}) + \boldsymbol{\varepsilon}(\boldsymbol{y} - \boldsymbol{x})$$

$$\dot{\epsilon_i} = -\gamma_i {e_i}^2, \mathrm{i} = 1,2,\cdots,n$$

$$\dot{q_{ij}} = -\delta_{ij}\varepsilon_i f_{ij}(y), i = 1,2,\cdots,n$$

where $e_i = (y_i - x_i)$ and the $\gamma_i > 0, \delta_{ij} > 0, i = 1,2,\cdots,n$ are arbitrary constants which we selected as γ_i=Γ and δ_{ij}=δ for all i, j.

Huang, D. (2004), retrieved from https://arxiv.org/abs/nlin/0405015

LYAPUNOV FUNCTION

$$V = \frac{1}{2}\sum_{i=1}^{n} e_i^2 + \sum_{i=1}^{n}\sum_{j=1}^{m} \frac{1}{\delta_{ij}}\left(q_{ij} - p_{ij}\right)^2 + \frac{1}{2}\sum_{i=1}^{n} \frac{1}{\gamma_i}(e_i + L)^2$$

$V \geq 0, \acute{V} \leq 0$ on every trajectory, with exact equality only when the residuals are zero and the parameters are identical.

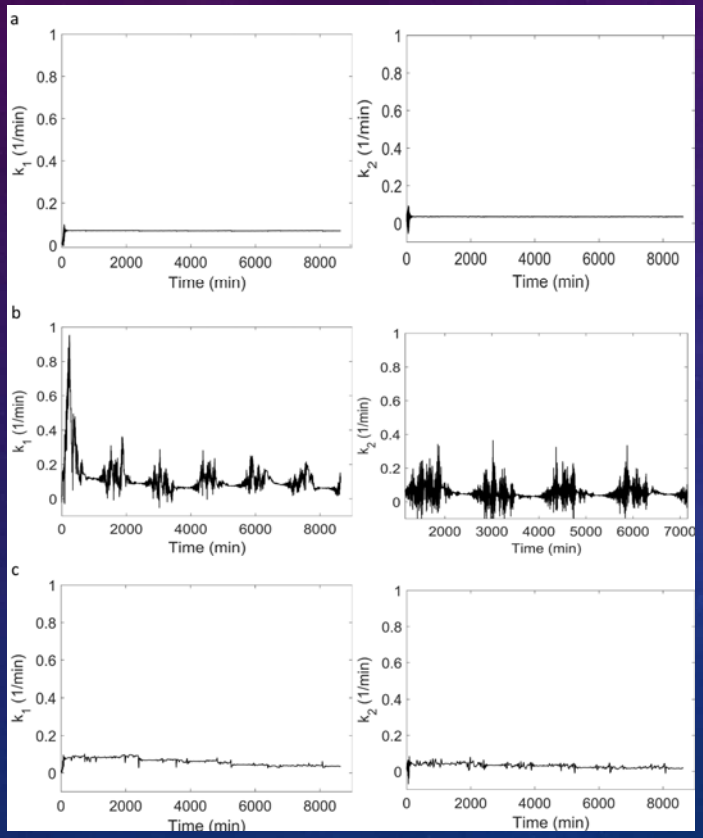
Huang, D. (2004), retrieved from https://arxiv.org/abs/nlin/0405015

CONVERGENCE PROPERTIES

The Lasalle invariance principle guarantees asymptotic convergence of the augmented system to the experimental system parameters from arbitrary starting values.

ADAPTIVE CHAOS SYNCHRONIZATION

CONVERGENCE OF LINEAR PARAMETERS FOR DENSE DATA



- (a) Noiseless data sampled at 1 minute intervals
- (b) Noisy data (20% proportional noise) sampled at 1 minute sampling intervals
- (c) Noiseless data sampled at 45 minute sampling intervals

The parameters were extracted as the median of the fluctuating values for the last cycle.

The sparse data were densified to 5 minute sampling intervals via a cubic Piecewise Continuous Hermite Interpolating Polynomial.

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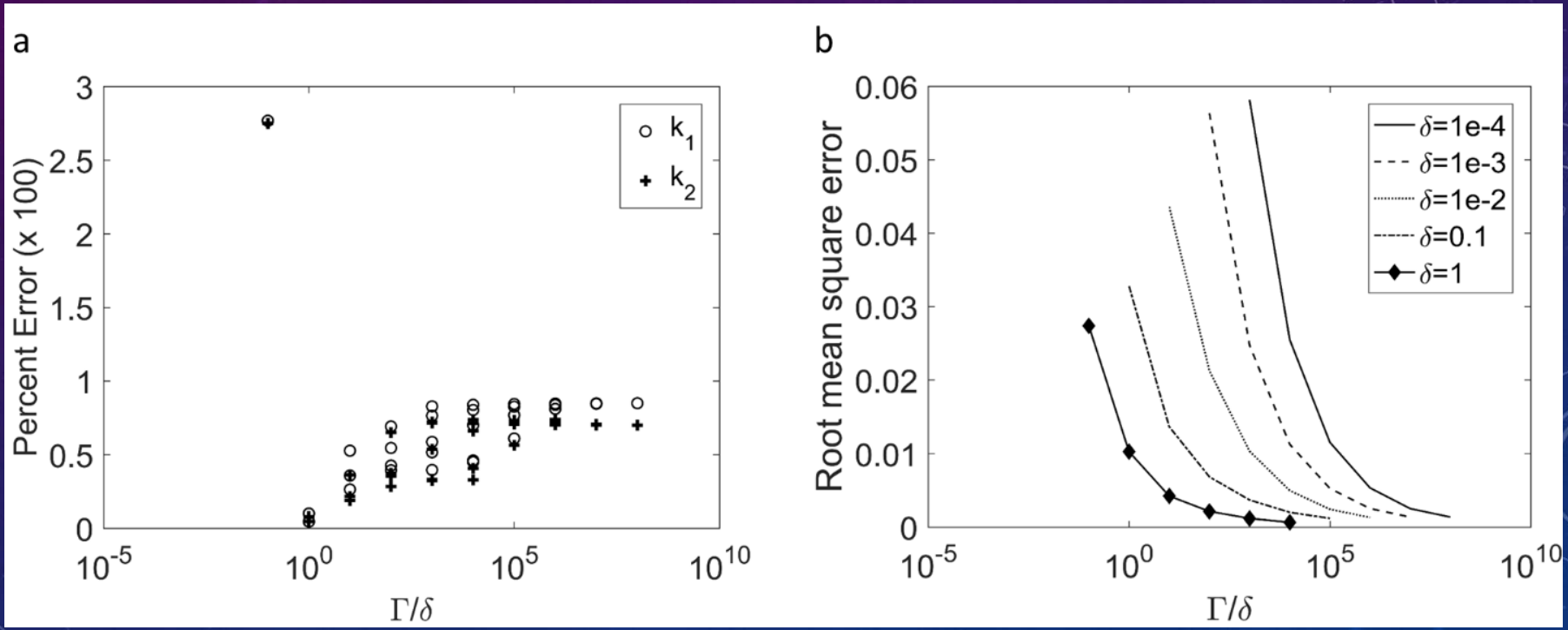
ADAPTIVE CHAOS SYNCHRONIZATION

ERROR METRICS



Γ/δ is the ratio of adaptive coupling strength to parameter learning rate

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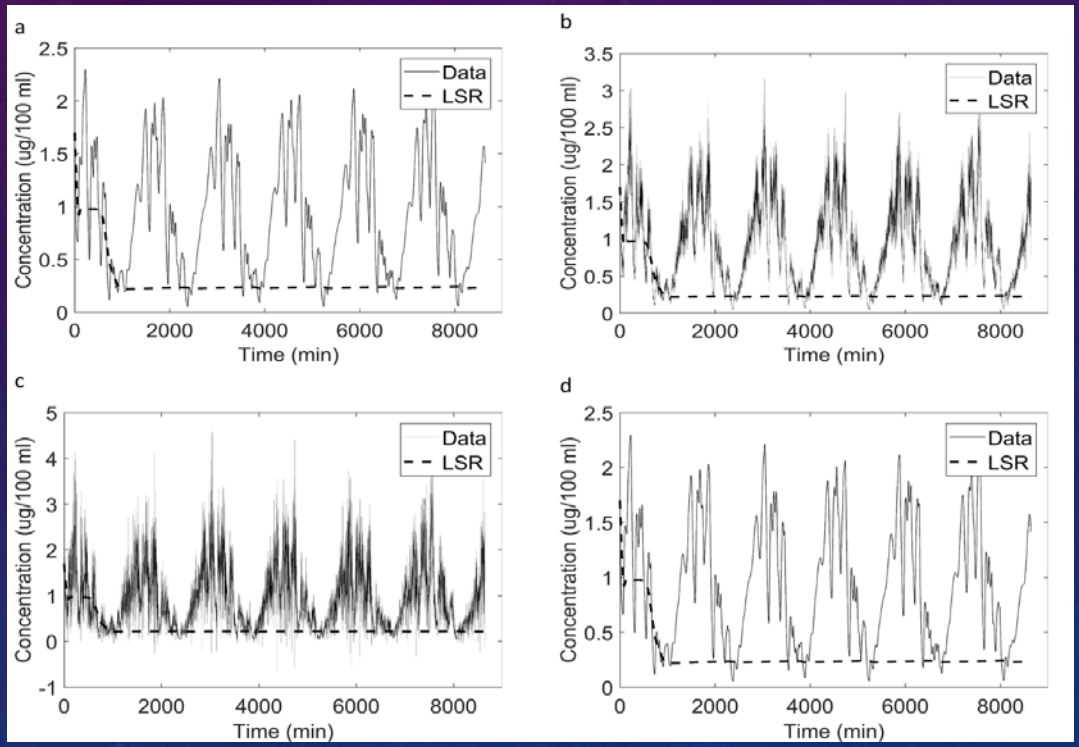
NON-LINEAR LEAST SQUARES & COARSE-TO-FINE GRID SEARCH

ALL NON-FIXED PARAMETERS OF SPARSE NOISY CORTISOL SYSTEM



20% proportional error ; 45 minute sampling interval

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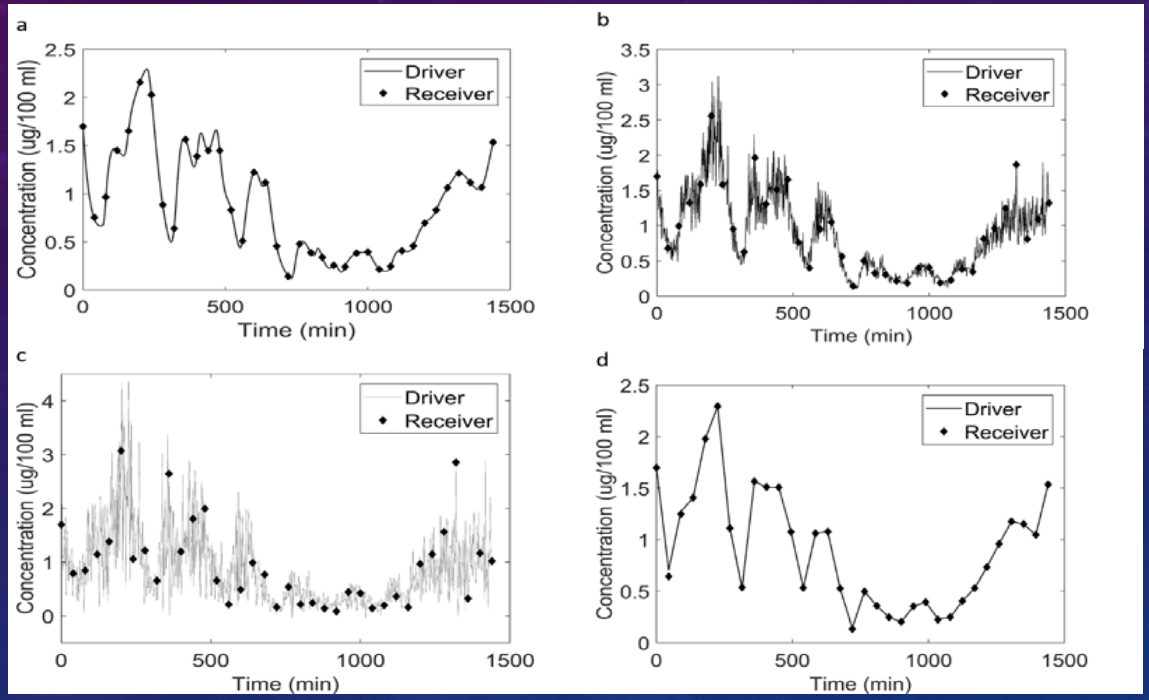
CHAOS SYNCHRONIZATION & COARSE-TO-FINE GRID SEARCH

ALL NON-FIXED PARAMETERS OF SPARSE NOISY CORTISOL SYSTEM



20% proportional error ; 45 minute sampling interval

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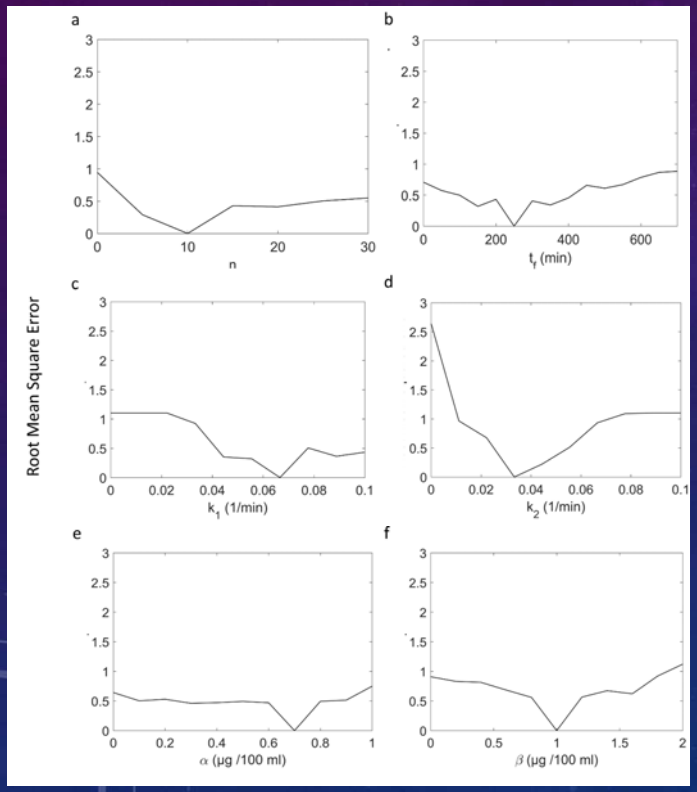
CHAOS SYNCHRONIZATION & COARSE-TO-FINE GRID SEARCH

PARAMETER SENSITIVITY ANALYSIS



- Sensitivity analysis for parameter (a) n, (b) t_f, (c) k_1, (d) k2, (e) α and (f) β.
- Increments of 0.01/min in either input or output rate constant significantly impacted affected the predicted concentration.
- An increment of 100 minutes in phase had a relatively small effect on the predicted concentrations.
- Varying parameters α, β and n has a moderate impact on predicted concentration.

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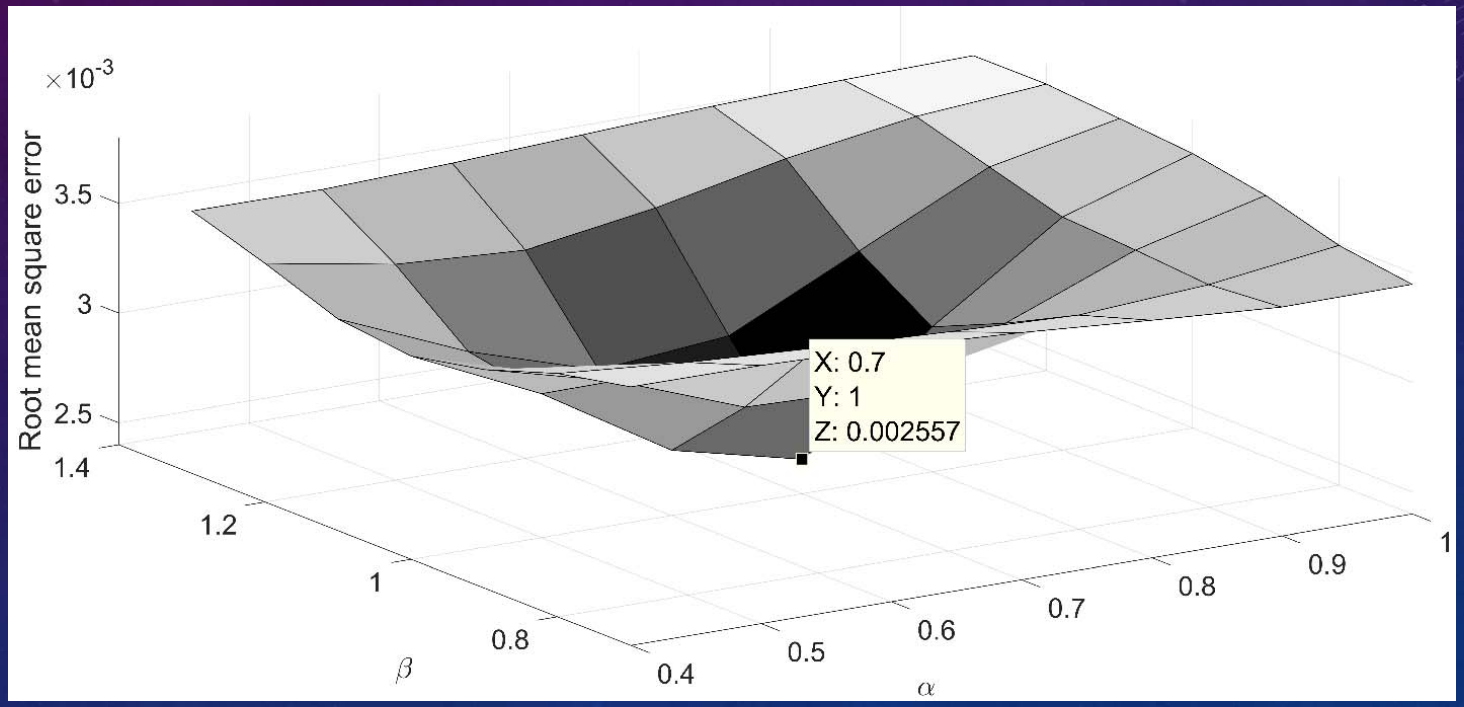
CHAOS SYNCHRONIZATION & GRID SEARCH

ROOT MEAN SQUARE ERROR SURFACE



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SUMMARY AND CONCLUSION

- Wavelet thresholding provides effective denoising that retains geometric details.
- Adaptive chaos synchronization for linear parameters combined with coarse-to-fine grid search for non-linear parameters provides accurate estimates of all parameters for an exemplary chaotic dynamical system.

NB: Adaptive chaos synchronization may be iterated to improve accuracy, especially when the data sets span a small number of cycles.

BOOK CHAPTER OPPORTUNITY

AAPS PHARMACO-IMAGING FOCUS GROUP

- Title: Applied Imaging in Systems Pharmacology
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freedman@freedmanpatent.com +1 215-527-1779