System Identification for Genetic Regulatory Networks

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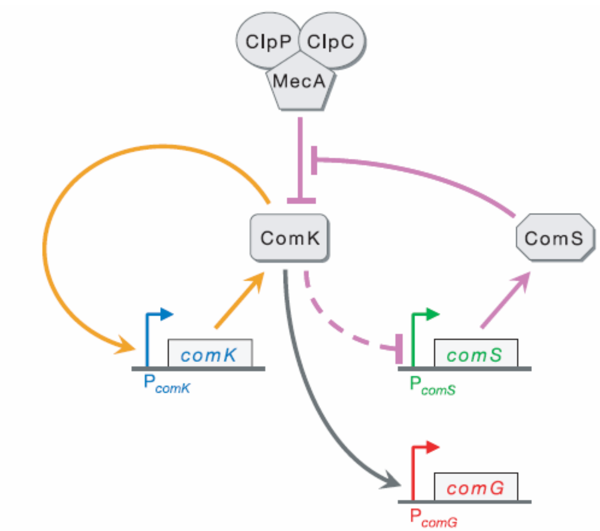
Dynamic Networks



Suel, Garcia-Ojalvo, Liberman, Elowitz – Nature 2006

http://maps.google.com

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Given a genetic network structure, how do we build an accurate model?

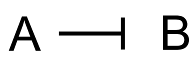
We'll use a simple genetic network as a case study and ask:

1. Is it possible to estimate parameters accurately even when measurements are noisy?

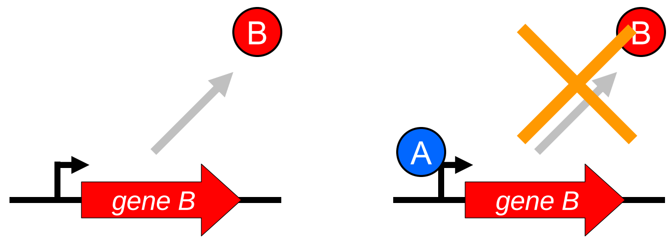
2. If we can choose an input to the system (even if it's very simple), what should we choose?

Bistable Switches Can Encode Low and High States

Genetic "Logic"

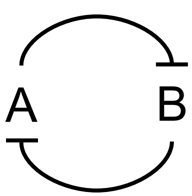


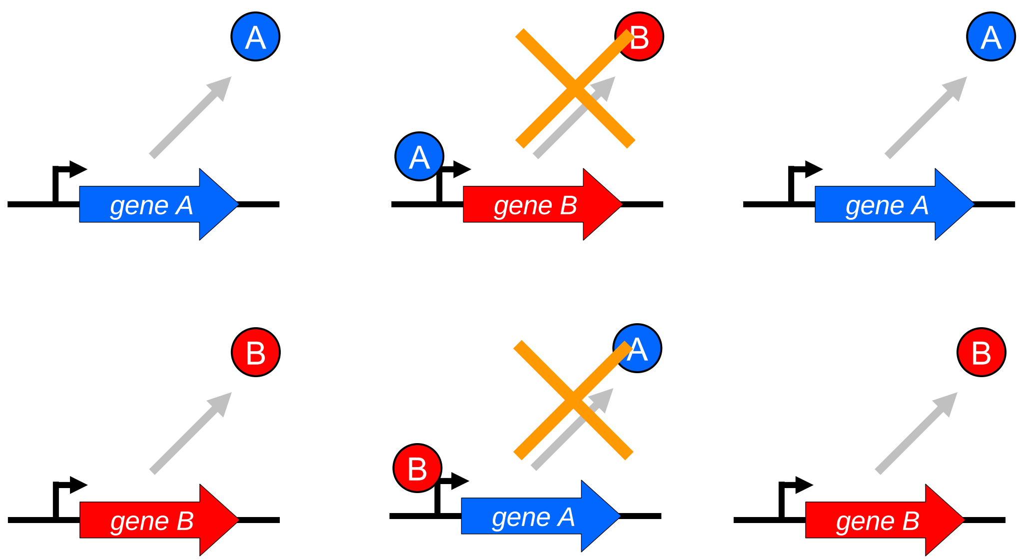
A represses B



A	B
0	1
1	0

Bistable Switch



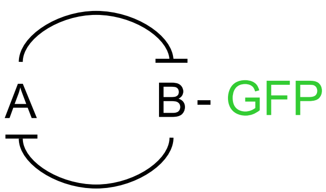


Lots of A
No B

Lots of B
No A

A Synthetic Genetic Bistable Switch

Gardner, Cantor, Collins – Nature 2000



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Last Updated: Thursday, 12 January 2006, 11:04 GMT

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Taiwan breeds green-glowing pigs

By Chris Hogg
BBC News, Hong Kong

Scientists in Taiwan say they have bred three pigs that glow in the dark.

They claim that while other researchers have bred partly fluorescent pigs, theirs are the only pigs in the world which are green through and through.

When lit up in the dark, the pigs glow green

The pigs are transgenic, created by adding genetic material from jellyfish into a normal pig embryo.

The researchers hope the pigs will boost the island's stem cell research, as well as helping with the study of human disease.

The researchers, from National Taiwan University's Department of Animal Science and Technology, say that although the pigs glow, they are otherwise no different from any others.

Taiwan is not claiming a world first. Others have bred partially fluorescent pigs before. But the researchers insist the three pigs they have produced are better.

They are the only ones that are green from the inside out. Even their heart and internal organs are green, they say.

In daylight, their eyes and skin are green-tinged

To create them, DNA from jellyfish was added to about 265 pig embryos which were implanted in eight different pigs.

Four of the pigs became pregnant and three male piglets were born three months ago.

Green generation

SEE ALSO:
- Green-tinged farm points the way — 28 Apr 04 | Science/Nature
- Cloning gets specific — 29 Jun 00 | Science/Nature
- Scientists produce five pig clones — 14 Mar 00 | Science/Nature

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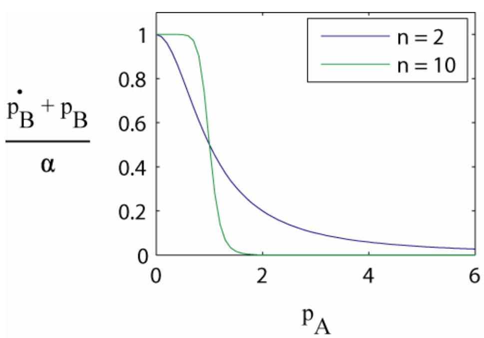
A Mathematical Model for a Bistable Switch

$$\dot{p}_A = \frac{\alpha}{1 + (p_B)^n} - p_A$$

$$\dot{p}_B = \frac{\alpha}{1 + (p_A)^n} - p_B$$

p_A concentration of protein A
p_B concentration of protein B
α effective protein production rate
n cooperativity



Assumptions:
- System is symmetric
- Translation dynamics are fast
- Continuous dynamics
- many more…

Parameter Identification Problem: Find α and n given measurements of p_A and p_B

Measurement Noise

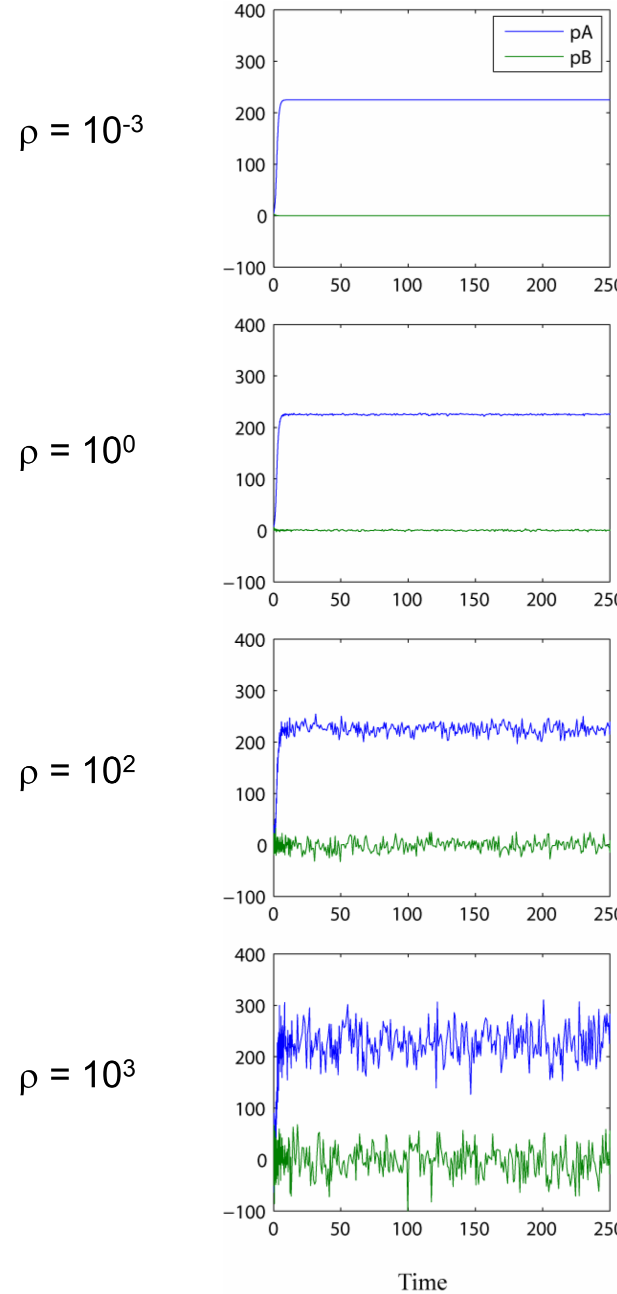
$$\frac{d}{dt}\begin{bmatrix} p_A \\ p_B \\ \alpha \\ n \end{bmatrix} = \begin{bmatrix} \frac{\alpha}{1+(p_B)^n} - p_A \\ \frac{\alpha}{1+(p_A)^n} - p_B \\ 0 \\ 0 \end{bmatrix}$$

$$\dot{x} = f(x)$$

Output Equation:

$$y = \begin{bmatrix} p_A \\ p_B \end{bmatrix} + noise$$

Guassian white noise with variance ρ



Generate Simulation Data to Try Out Parameter ID Methods

$p_A(0)$, $p_B(0)$, α, n picked randomly from a probability distribution

Integrate ODEs with these initial conditions and parameters

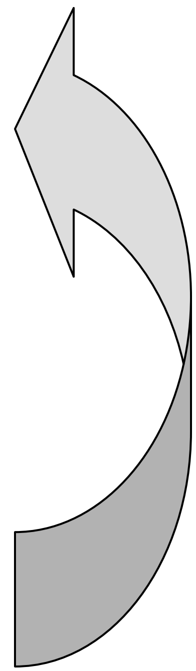
$$\frac{d}{dt}\begin{bmatrix} p_A \\ p_B \\ \alpha \\ n \end{bmatrix} = \begin{bmatrix} \frac{\alpha}{1+(p_B)^n} - p_A \\ \frac{\alpha}{1+(p_A)^n} - p_B \\ 0 \\ 0 \end{bmatrix}$$

$$\dot{x} = f(x)$$

Noise is added to the state measurements

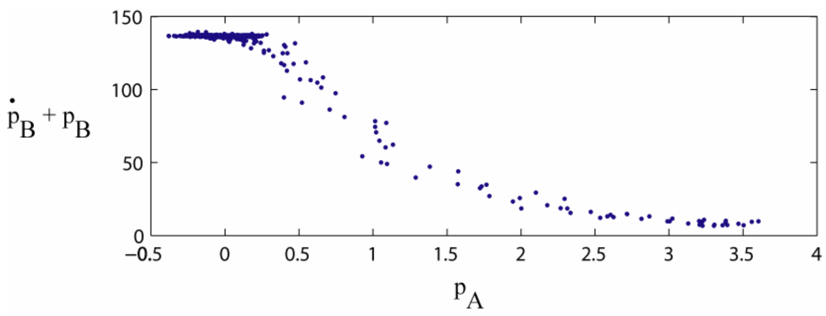
Run parameter identification algorithm
Errors are

$$|\hat{\alpha} - \alpha| \quad |\hat{n} - n|$$



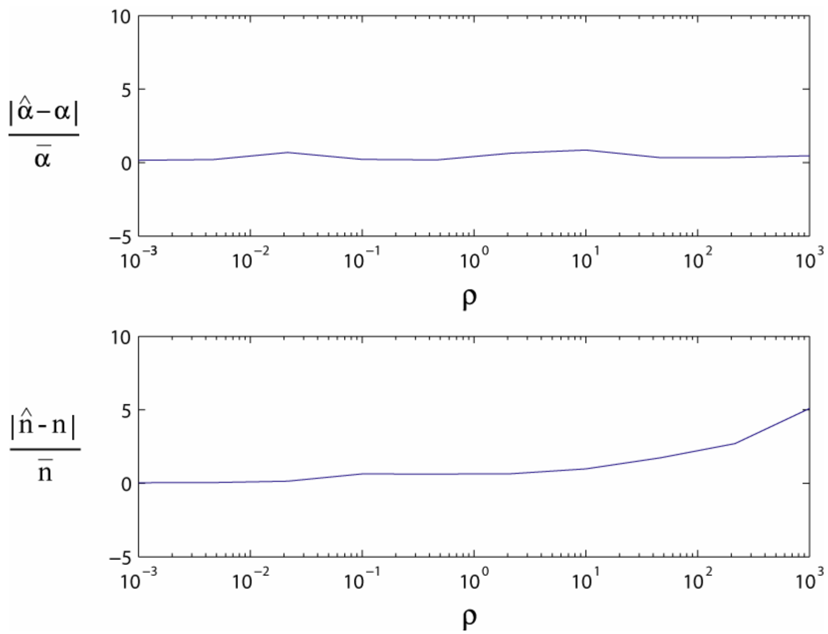
Run many times
Find average error

Nonlinear Least Squares Fit is Very Sensitive to Noise



Isolate nonlinear term by calculating derivative
Fit the curve to data, best fit gives α and n
Sources of noise:
- Sensor noise (ρ = 0.02 here)
- Errors in taking derivative

$$\dot{p}_B + p_B = \frac{\alpha}{1 + (p_A)^n}$$

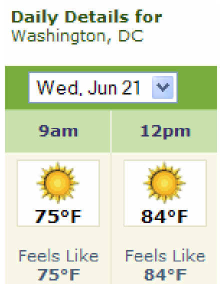


$\hat{\alpha}$ estimate
α actual value
$\bar{\alpha}$ average (from probability distribution)

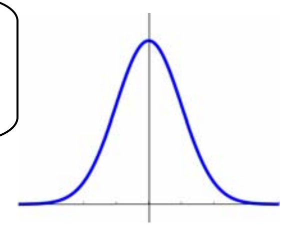
Kalman Filter is an Optimal Linear Estimator

Kalman filter is an optimal recursive data processing algorithm
It predicts the state and then corrects its estimate based on sensor measurements

Goal: $\lim_{t\to\infty} x(t) - \hat{x}(t) = 0$



It's hot outside! I think it's around 85 degrees.



Input (u)

Plant

$\dot{x} = f(x, u)$

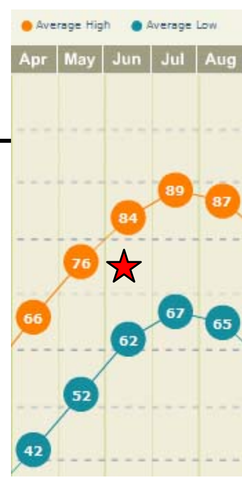
Sensors

$y = Cx + w$

Noisy measurements (y)

Estimator

State estimate ($\hat{x}$)

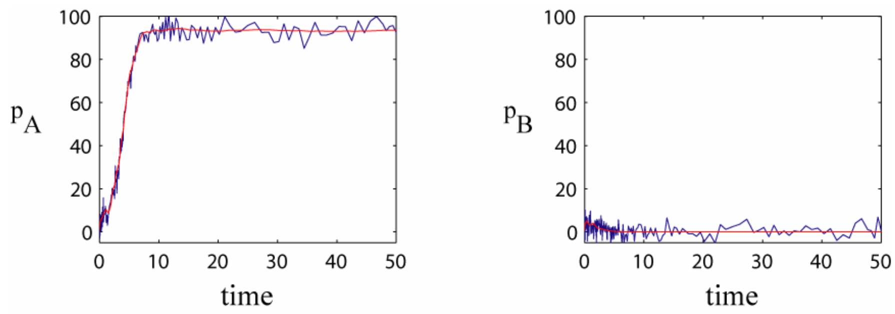


$\dot{\hat{x}} = f(\hat{x}, u) + L(y - C\hat{x})$

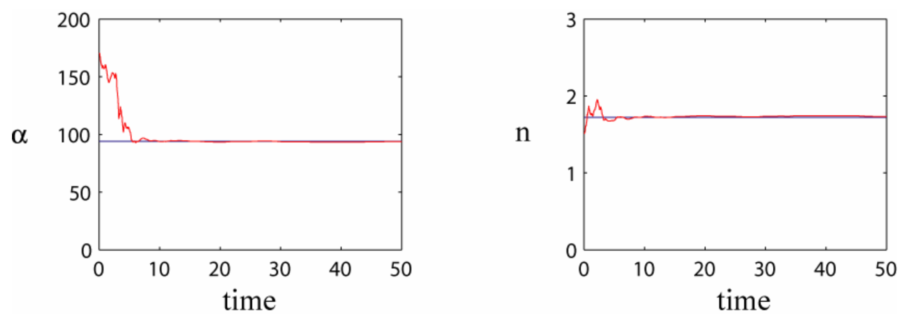
Measure of confidence in sensor measurements

Weather data from http://www.weather.com

Extended Kalman Filter Can Be Used to Identify Model Parameters

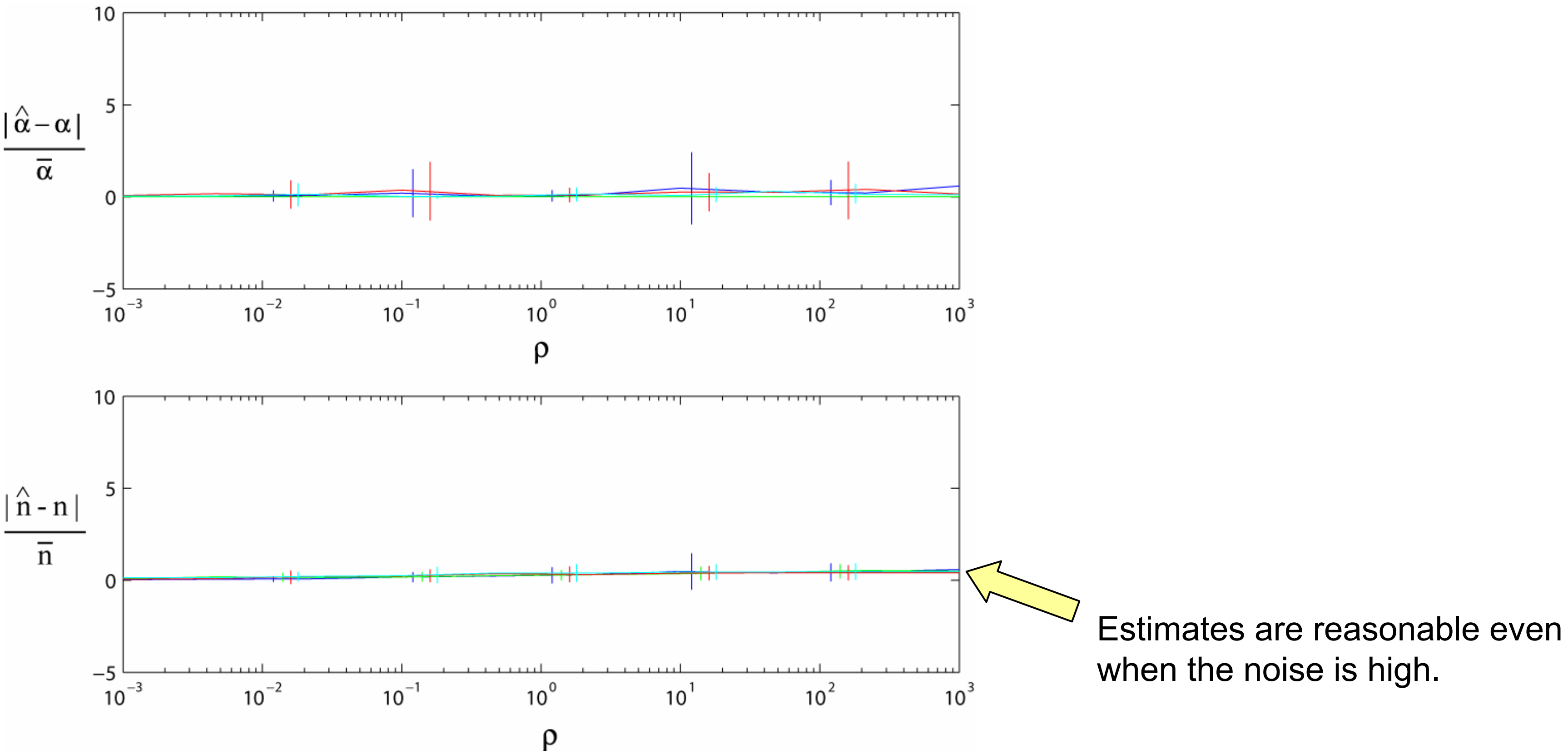


State estimate
Measured state



Parameter estimate
Actual parameter value

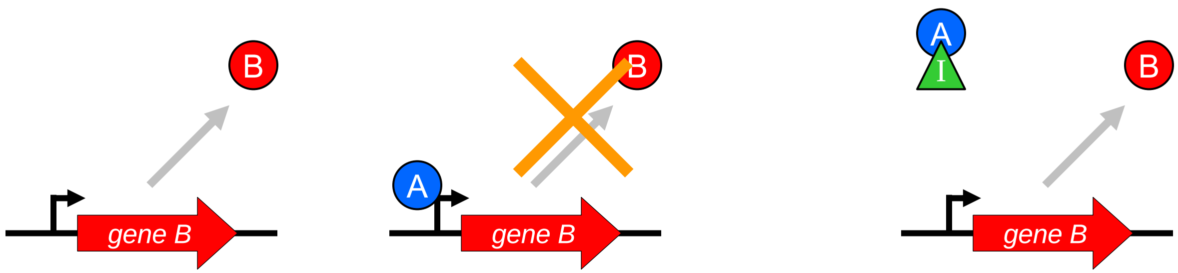
Extended Kalman Filter Gives Good Parameter Estimates Even When Noise is High



Using Inputs to Improve Parameter Identification

If we have control over the input to the system will this help us to identify parameters?

Inducers as Inputs



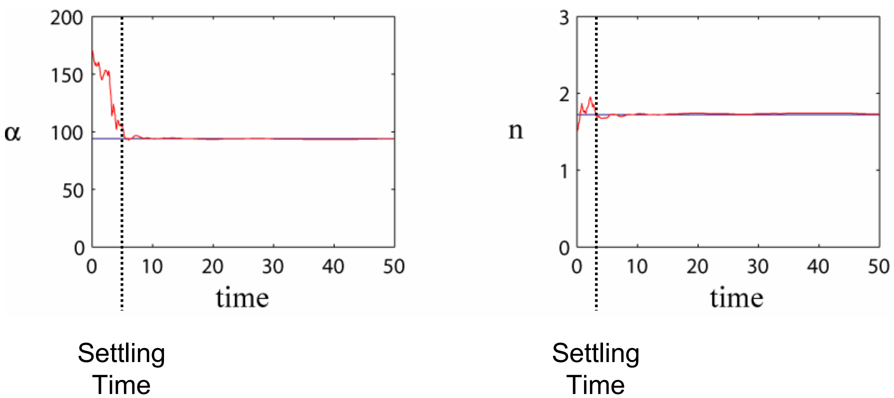
$$\dot{p}_A = \frac{\alpha}{1 + (u\ p_B)^n} - p_A$$
$$\dot{p}_B = \frac{\alpha}{1 + (p_A)^n} - p_B$$

$$u = \frac{\beta}{1+\left(\frac{I}{K}\right)^m}$$

$0 < u \leq \beta$
for plausible values of I

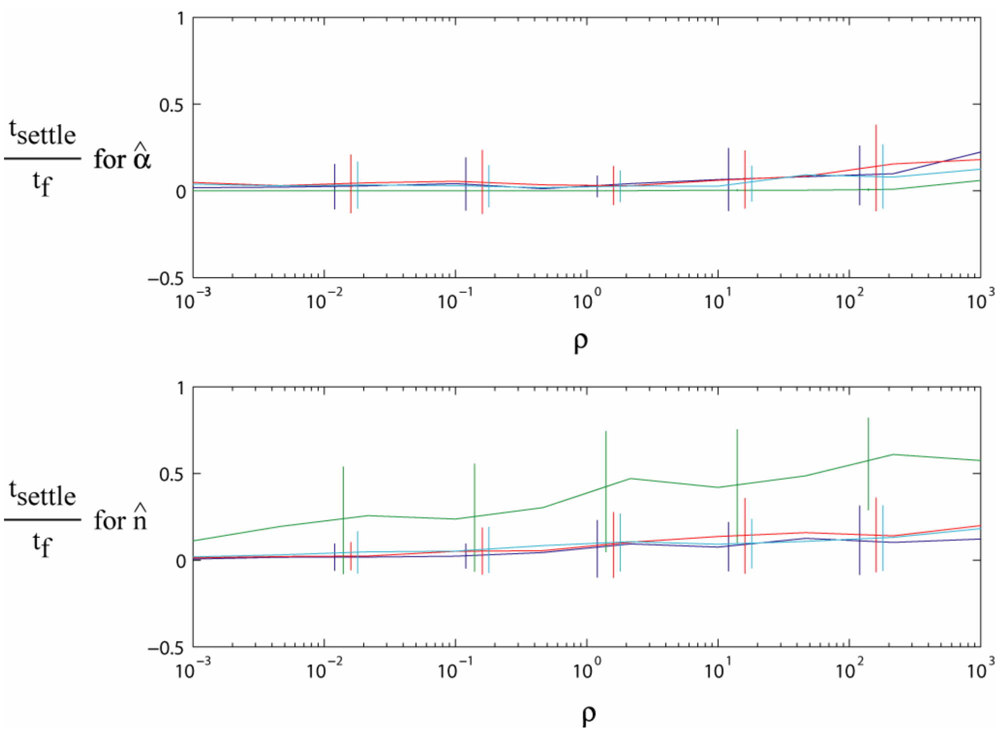
Optimization based approach to selecting inputs

Number of Data Points Required to Obtain a Good Estimate Depends Upon the Input



Parameter estimate

Actual parameter value



piecewise constant

u = 0 (saturating level of inducer)

u = 3.2 (optimal constant input)

u = 10 (no inducer added)

There is a distinct advantage to choosing inputs carefully.

Summary

Case study of parameter identification for bistable switch

By using dynamical models to estimate parameters we see a dramatic reduction in estimation error

Choosing appropriate inputs can reduce the estimation time

Acknowledgements

Richard Murray	Caltech (Control & Dynamical Systems)
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