environmental bioinformatics
Computational Toxicology Center

A Closed-Loop Identification Protocol (CLIP) for Nonlinear Biological Networks

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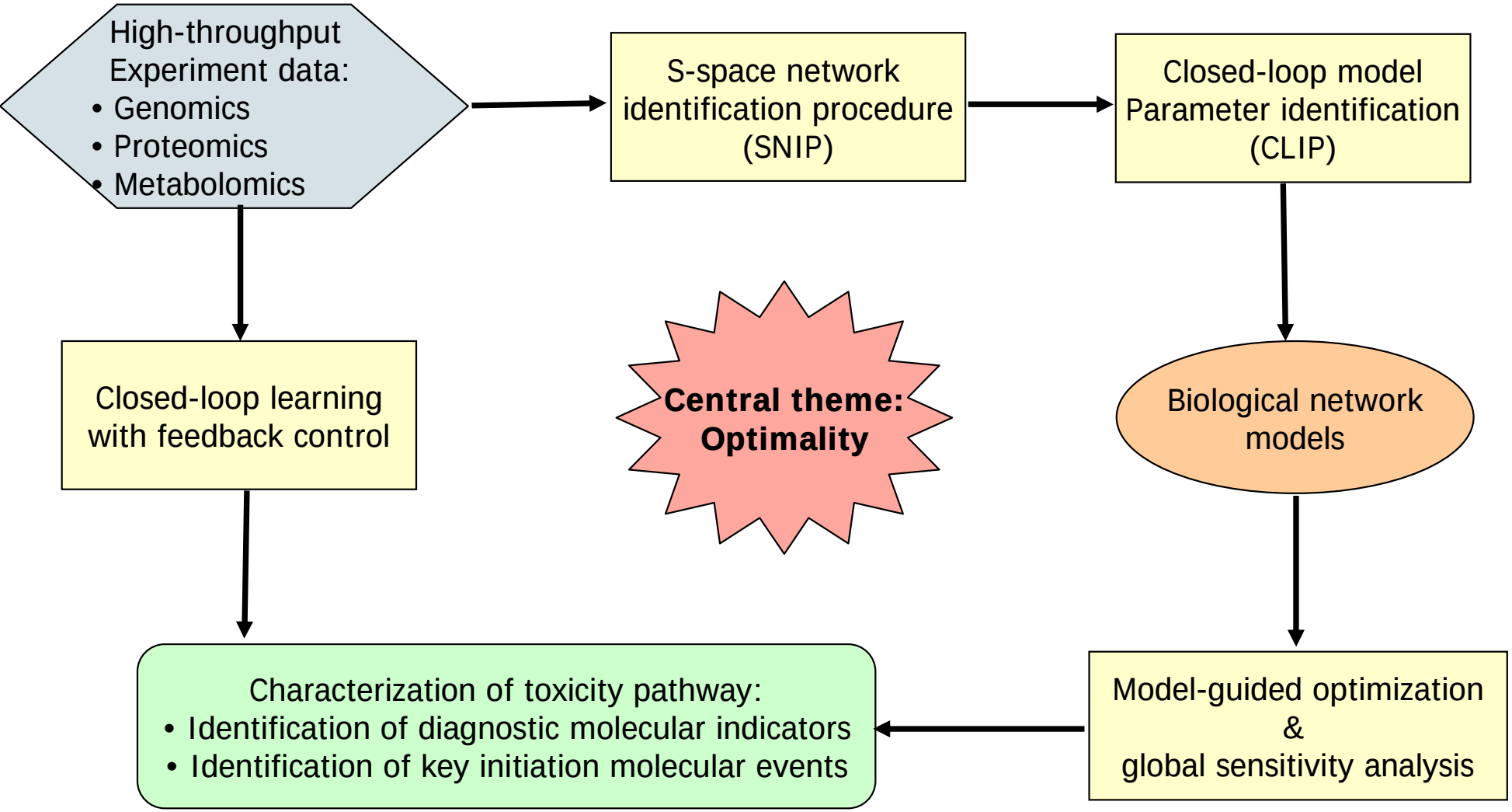
Optimal analysis, identification, and control of complex biological networks



Part A: the S-Space Network Inference Procedure (SNIP)

Objective:

- Understand who is talking to who from laboratory data
- How do they talk with each other (linear, nonlinear, independent, cooperative)?

Characteristics of the problem:

- Nonlinearity
- Dynamics mixed with network structure
- Unknown/unmeasured species
- Biological and measurement noise
- Positive and negative feedbacks, autoregulations
- Laboratory constraints
- Network scale (can be large)
- Diffusion

General strategy: perturbation + analysis

Quantitative vs. qualitative methods

Model-based vs. model-independent methods

Linear vs. nonlinear methods

Time-dependent vs. time-independent methods

Time-independent:

- **Experimentally easier**
- **Smaller information content**

Time-dependent:

- **Large information content**
- **Experimentally more difficult**
- **More difficulties in information extraction**

Existing techniques

Cluster analysis (qualitative, indirect information)

Boolean approaches (discrete assumption)

Bayesian methods (probabilistic in nature)

Dynamic modeling approaches (need model)

Correlation metric construction

- **Need random time-series perturbation**
- **Precise measurements faster than system's relaxation**
- **Perturbation around system's steady state**

Jacobian matrix methods

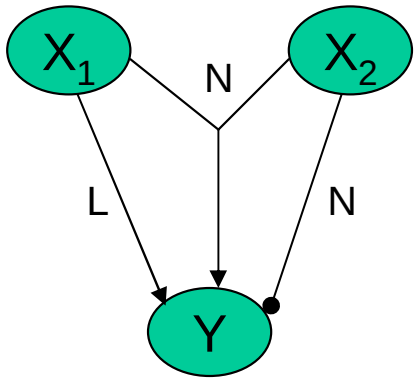
- **Linear approximation requires small perturbations, can be sensitive to noise**
- **Can become under-determined problem, need knowledge or assumptions to overcome**

The SNIP algorithm

Goals:

- Enable reliable ID from large perturbations
- Obtain linear & nonlinear interactions
- Model-independent
- Reveal independent and cooperative relationships
- Robust to noise
- Robust to unknown & unmeasured species

A toy network (1)



A three component network

Steady state relationship:

$y=x_1+3x_1x_2-5x_2^2$

Encode x_1 with $m_1(s)=\left[1+0.5\cos\left(2\times 2\pi s\right)\right]$

S is experiment index
Perturbations are time-independent

$$x_1 = x_1^* m_1(s) = 2\left[1+0.5\cos\left(2\times 2\pi s\right)\right]$$

$$y(s) = 4\cos(2\times 2\pi s)+3$$

Fourier decoding of y(s) in S

y depends linearly on x_1

A toy network (2)

Encode X_2 with $m_2(s) = [1 + 0.5\cos(5 \times 2\pi s)]$

$$y(s) = 8 + 3\cos(5 \times 2\pi s) - 5[1 + 0.5\cos(5 \times 2\pi s)]^2$$

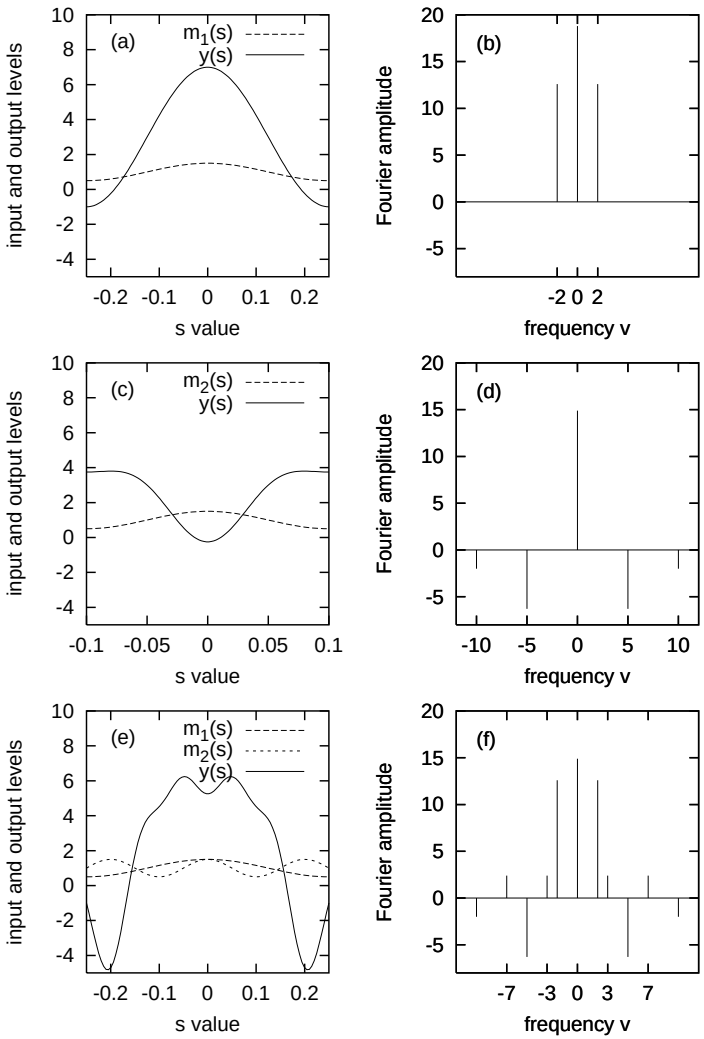
Fourier decoding of y(s) in S

y depends nonlinearly on x_2

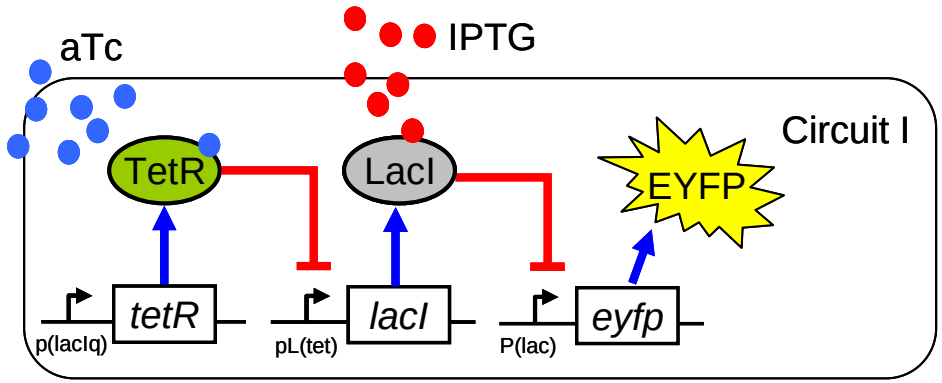
Encode X_1 (with m_1) and
X_2 (with m_2) simultaneously

Fourier decoding of y(s) in S

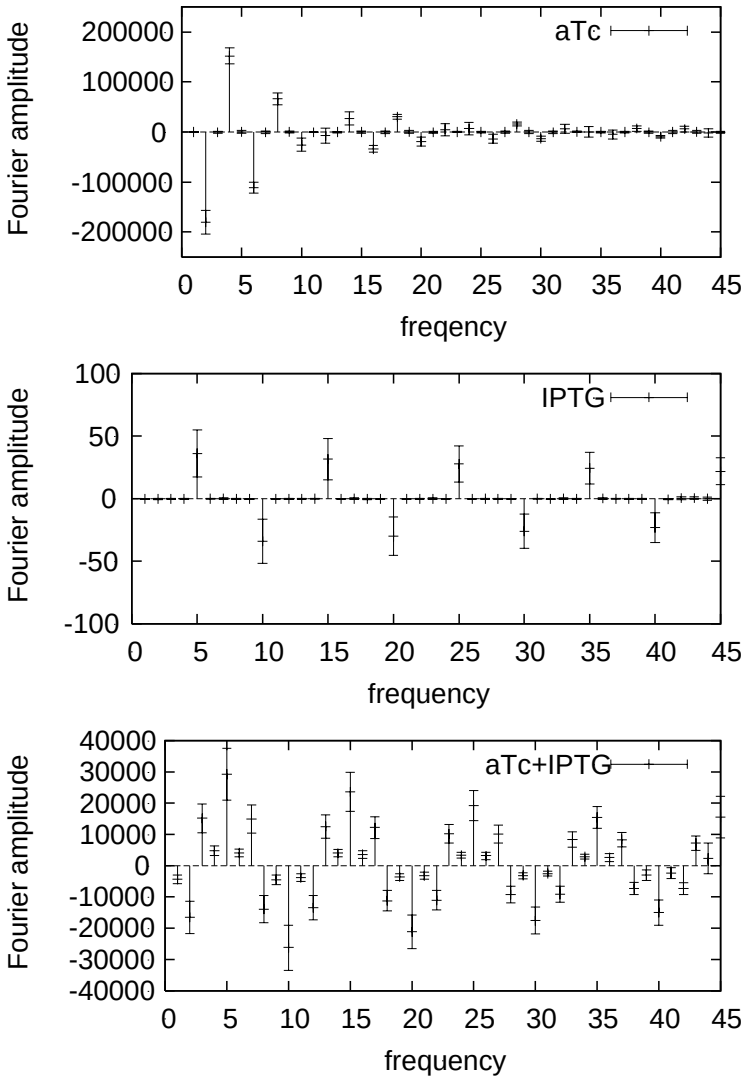
Cooperative effects of x_1 and x_2 on y



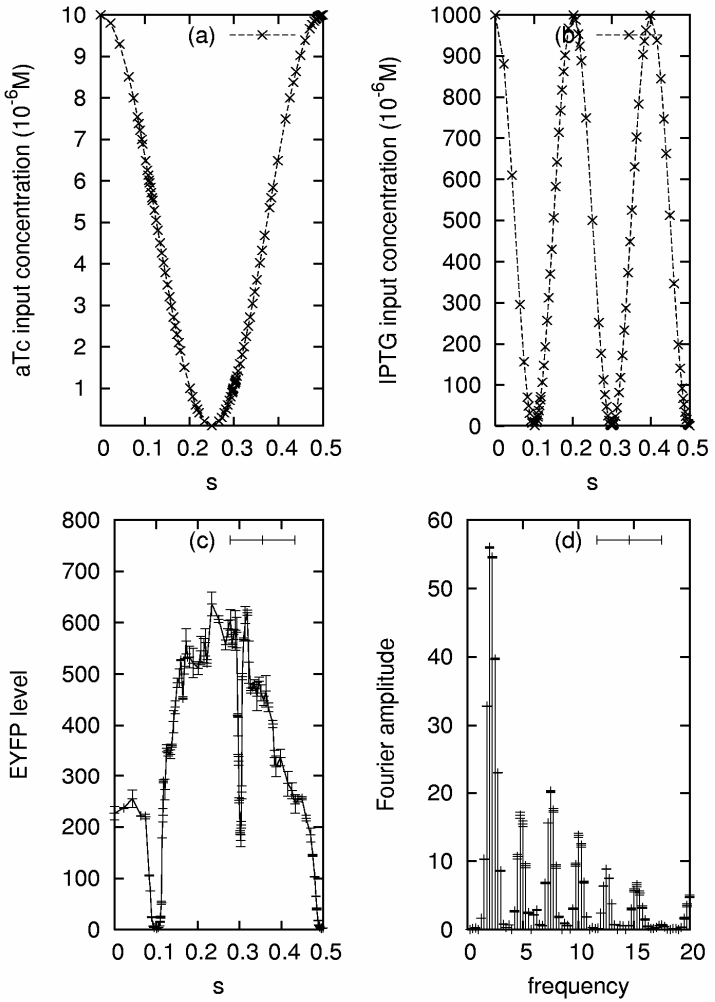
SNIP application to a simulated genetic inverter

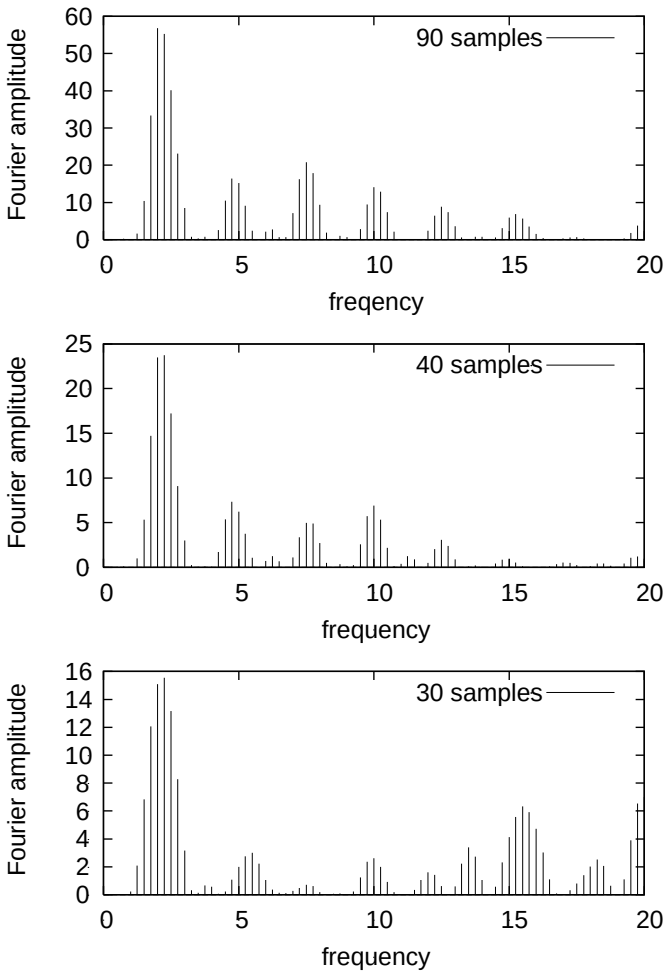


Encode: aTc & IPTG
Measure: EYFP



Laboratory SNIP application to the genetic inverter





Part B: The Closed-loop identification Protocol (CLIP)

General objective:

Optimal biochemical/biophysical model parameter identification from minimal laboratory data

Characteristics of the problem:

- System nonlinearity
- Limited number & type of experiments
- Considerable biological & measurement noise

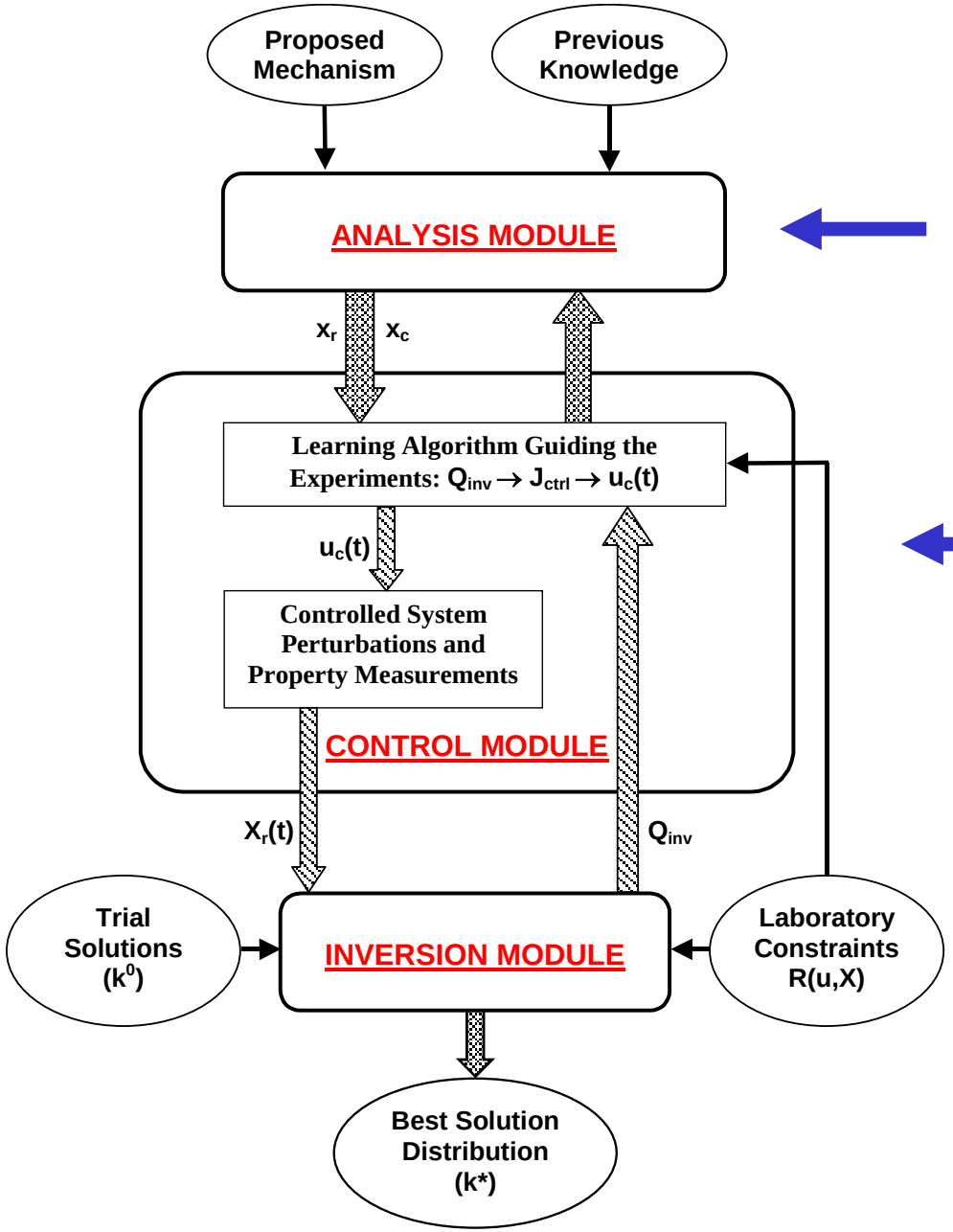
Problems with traditional identification methods:

- Provide only one or a few solutions for each parameter
- Assume linear propagation of laboratory data to inverted parameters
- Mostly based on linear system identification theory

General features of CLIP:

- Global and nonlinear identification
- Recover the full distribution of consistent solutions for each parameter
- Iteratively search for the most informative experiments
- Maximally reduce parameter uncertainty

The CLIP operation



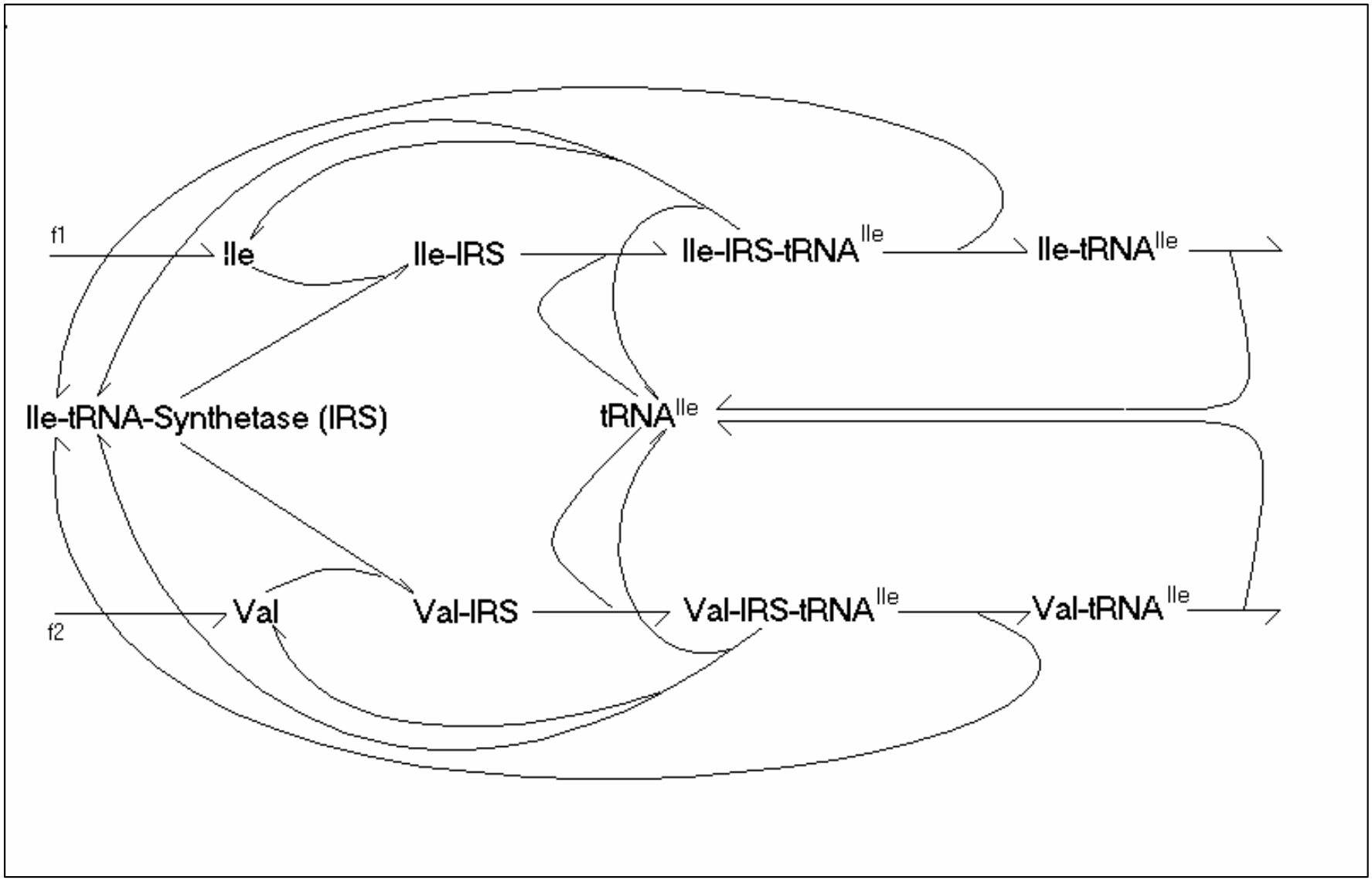
Pre-lab analysis and experimental design

Iterative experiment optimization and data acquisition

Global parameter identification

Isoleucyl-tRNA synthetase proofreading valyl-tRNA^{Ile}

M. Okamoto & M. Savageau. *Biochemistry* 23:1701-1709 (1984)



Kinetic equations (10 species, 16 rate constants)

$$dx_1/dt = k_{-3}x_5 + k_{-4}x_6 + (k_7 + k_1)x_7 + (k_8 + k_2)x_8 - k3x_1x_3 - k4x_1x_4 - k_{-7}x_1x_9 - k_{-8}x_1x_{10}$$
$$dx_2/dt = (k_{-5} + k_1)x_7 + (k_{-6} + k_2)x_8 + k_9x_9 + k_{10}x_{10} - k_5x_2x_5 - k_6x_2x_6$$
$$dx_3/dt = f_1 + k_{-3}x_5 + k_1x_7 - k_3x_1x_3$$
$$dx_4/dt = f_2 + k_{-4}x_6 + k_2x_8 - k_4x_1x_4$$
$$dx_5/dt = k_3x_1x_3 + k_{-5}x_7 - k_{-3}x_5 - k_5x_2x_5$$
$$dx_6/dt = k_4x_1x_4 + k_{-6}x_8 - k_{-4}x_6 - k_6x_2x_6$$
$$dx_7/dt = k_5x_2x_5 + k_{-7}x_1x_9 - (k_{-5} + k_7 + k_1)x_7$$
$$dx_8/dt = k_6x_2x_6 + k_{-8}x_1x_{10} - (k_{-6} + k_8 + k_2)x_8$$
$$dx_9/dt = k_7x_7 - k_{-7}x_1x_9 - k_9x_9$$
$$dx_{10}/dt = k_8x_8 - k_{-8}x_1x_{10} - k_{10}x_{10}$$

x_1 = [IRS] x_2 = [$tRNA^{Ile}$] x_3 = [Ile] x_4 = [Val] x_5 = [Ile-IRS] x_6 = [Val-IRS]
x_7 = [Ile-IRS-$tRNA^{Ile}$] x_8 = [Val-IRS-$tRNA^{Ile}$] x_9 = [Ile-$tRNA^{Ile}$] x_{10} = [Val-$tRNA^{Ile}$]

The task:

Obtain the rate constant k_1, k_2, k_5, k_{-5}, k_6, k_{-6}

Experimental capabilities and restrictions:

- Positive influx of x_1, x_3, x_4
- Finite concentration measurements
- Laboratory noise

The analysis module: estimating the most informative experiments

- **Estimate the best molecules for monitoring system behavior**
- **Determine the best molecular targets for perturbing the system**

Sensitivity analysis by Random-Sampling High Dimensional Model Representation (RS-HDMR)

$$\sigma^2_{total} = \sum_{i=1}^{n} \sigma_i^2 + \sum_{1 \le i < j \le n} \sigma_{ij}^2 + \dots$$

The inversion module: identifying the rate constant distribution

The Genetic Algorithm (GA)

Mutation

1101 1111+1100 0010

1101 1101+1100 0110

Crossover

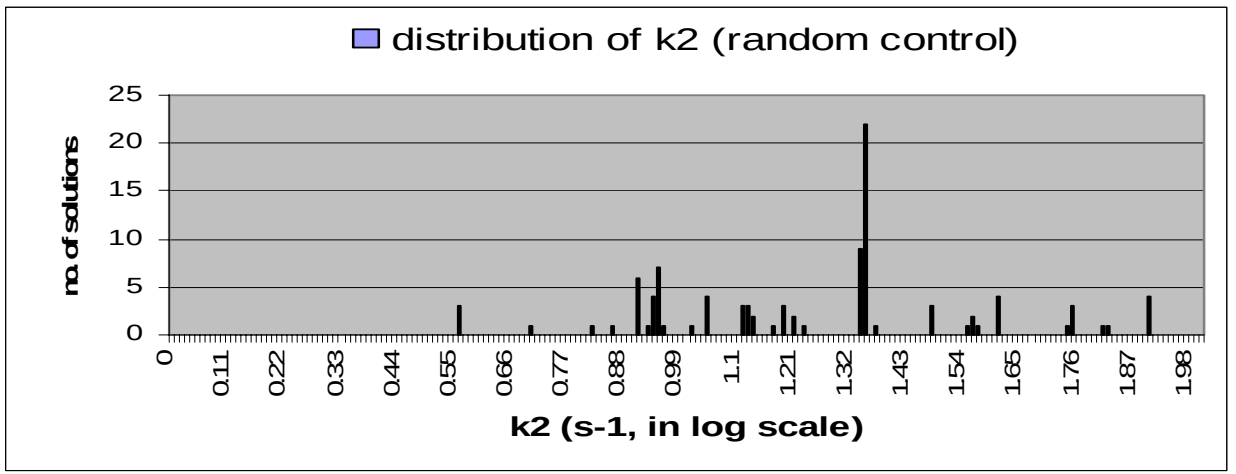
1101 1100 + 1111 **0010**

1101 **0010** + 1111 1100

Cost function of the inversion GA

$$J_{inv}^{i,p} = \frac{1}{N}\sum_{n=1}^{N} \frac{1}{T}\sum_{t=t_1}^{t_T} \left(X_{n,t}^{i,lab} - X_{n,t}^{i,p,cal}\right) / \varepsilon_n^i$$

Typical rate constant distribution after random perturbation



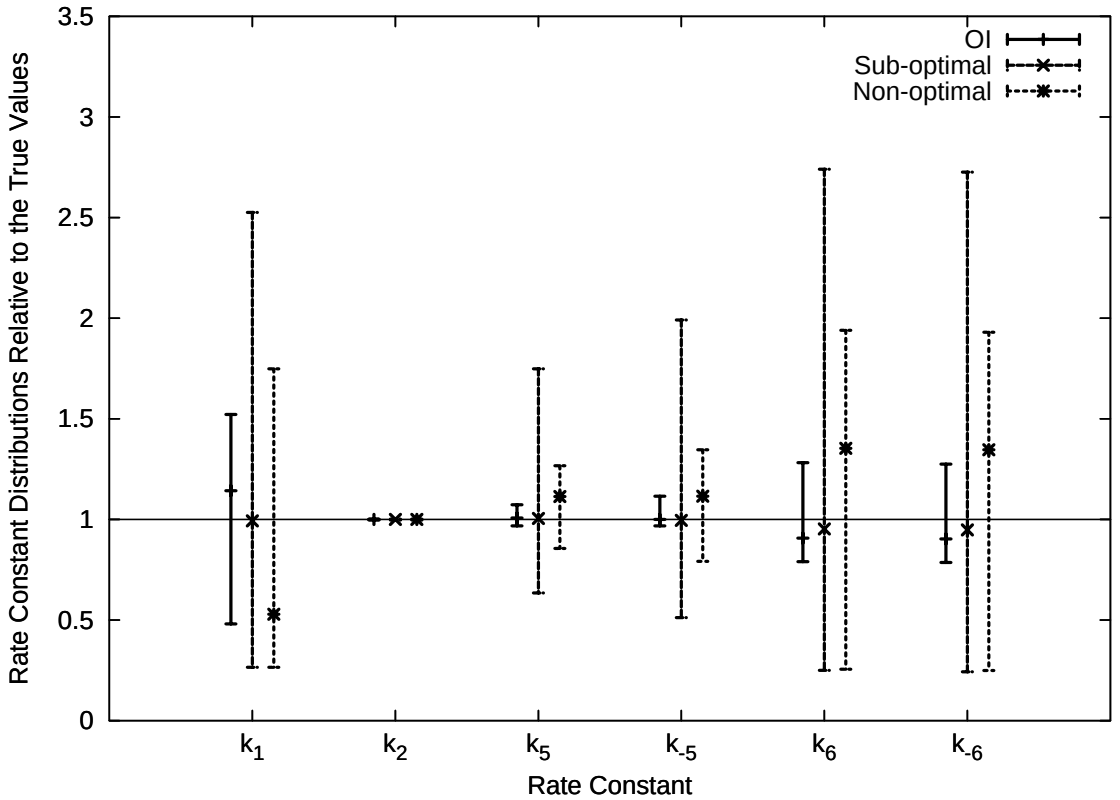
The control module: squeezing on the rate constant distribution

Cost function of the control GA

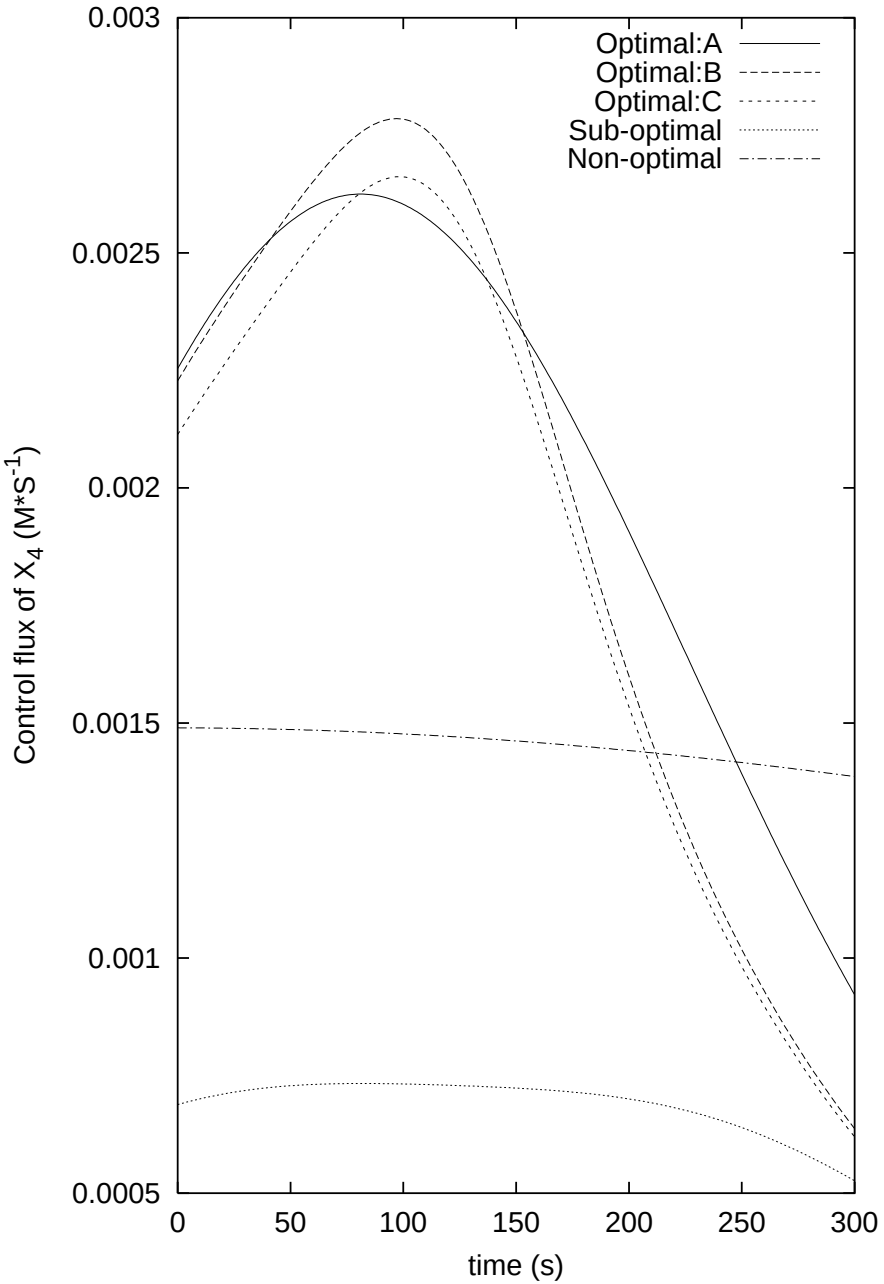
$$J^i_{ctrl} = Q^i_{inv} - \omega R[u^i_c(t), X^i_r(t)]$$

$$Q^i_{inv} = 1/[\frac{1}{M}\sum_{m=1}^{M}\frac{(k^i_{m,\max} - k^i_{m,\min})}{(k^i_{m,\max} + k^i_{m,\min})}]$$

Rate constant distribution after 500 experiments



Convergence of the optimal perturbations



Problems with CLIP:

1. Large number of experiments
2. Expensive computation

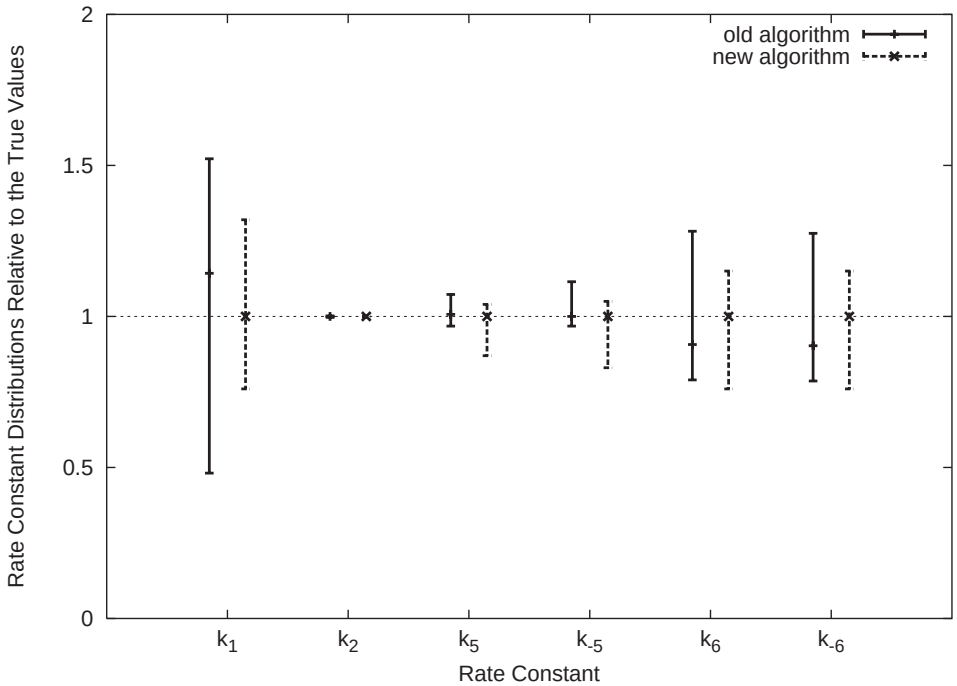
Proposed solution:

1. Replace the GA by the simplex algorithm in the control module
2. Modify the cost function in the inversion module

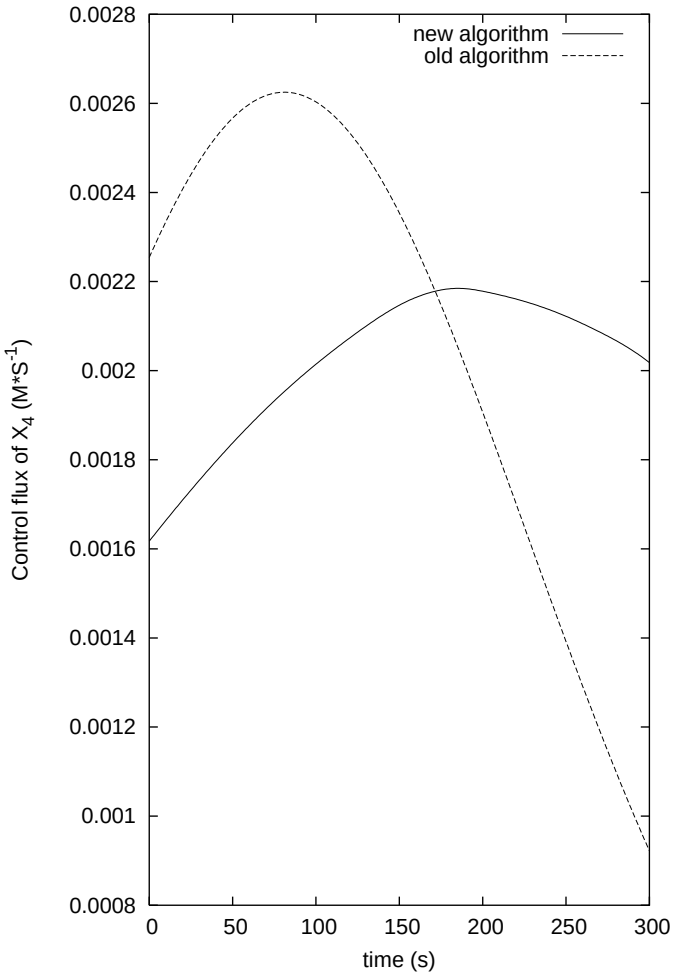
$$J_{inv}^{i,p} = \frac{1}{T}\frac{1}{N}\sum_{t=t_1}^{t_T}\sum_{n=1}^{N}\exp[(X_{n,t}^{i,lab} - X_{n,t}^{i,p,cal})/\varepsilon_n^i]\times[\prod_{m=1}^{M}(\frac{k_m^U - k_m^S + 1}{k_m^U - k_m^L + 1})^w]$$

The Simplex-CLIP algorithm

The inversion quality



Optimal perturbation



The Simplex-CLIP: 10 times less experiments, 20 times less computational cost

Problems with the simplex-CLIP:

- Simplex algorithm lacks sufficient global search ability
- Considerable number of experiments

Question: what makes an optimal perturbation optimal?

One answer: it maximizes the system's sensitivity with respect to variations in the rate constants?

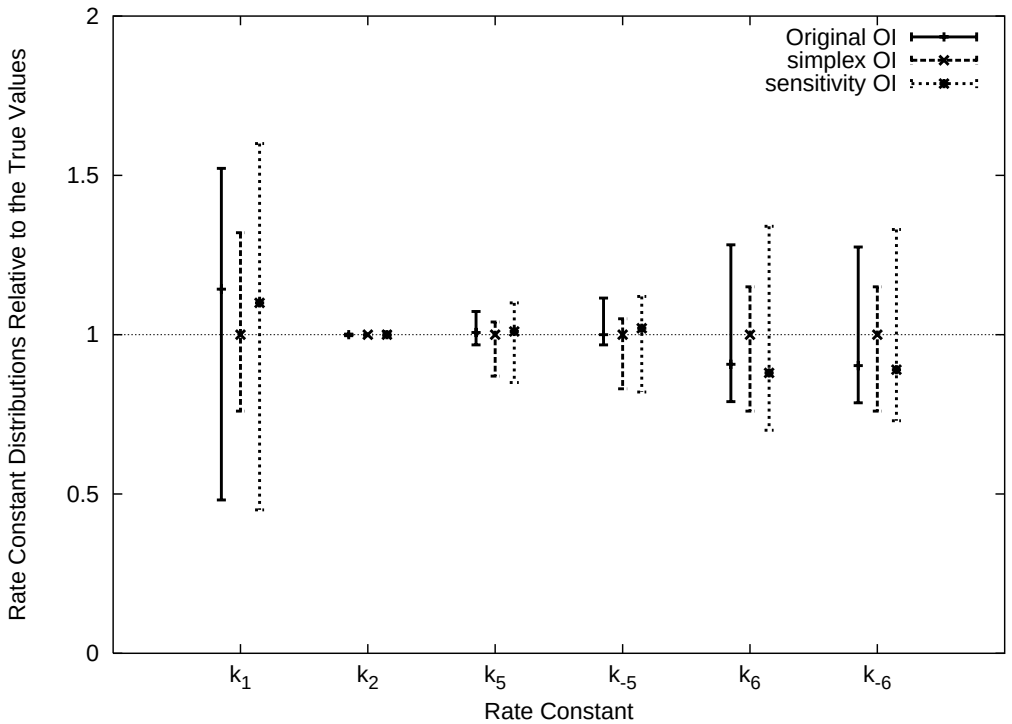
Proposed solution: estimate the optimal perturbation using global sensitivity maximization

Advantage:

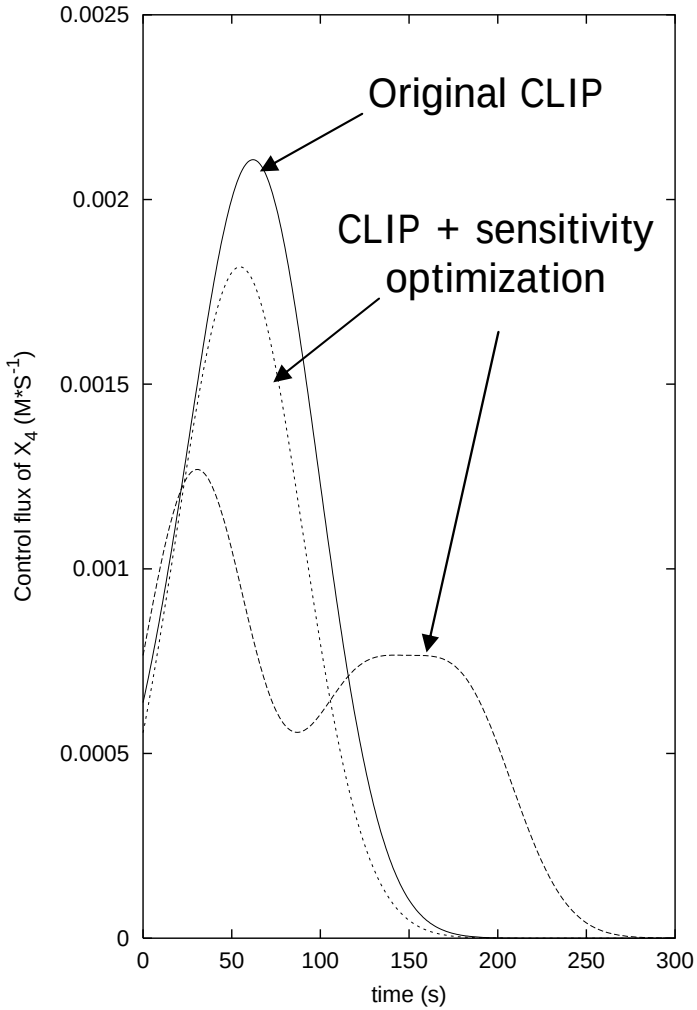
- No experiment needed for sensitivity maximization!
- Global search
- Inexpensive computation

Effect of sensitivity optimization for CLIP

Inversion quality



Optimal perturbation



CLIP + sensitivity optimization: ONE laboratory experiment and >100 times less computational time

X.Feng, H. Rabitz, et al. A closed-loop identification protocol for nonlinear dynamical systems. *J. Phys. Chem. A* **110:**7755-7762 (2006)

Future Directions

- SNIP
  - quantitative relationship extraction
  - Encoding experiment optimization
  - Simulation on larger networks (scalability)
- CLIP
  - Simulation on larger networks (scalability)
  - Model discrimination
- Application to toxicity pathways

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