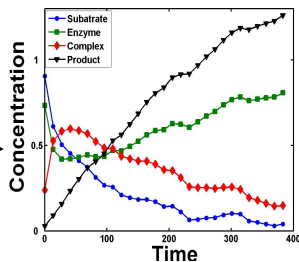


# Computational determination of enzyme reaction mechanisms

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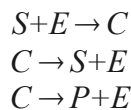
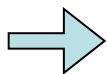
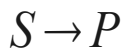
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High and Low throughput experiments generate time series of multiple chemical species



Is it possible to infer a potential reaction mechanism in a few steps?

Biochemical pathways are composed of elementary chemical reactions



Enzyme  $E$  catalyzes the conversion of Substrate  $S$  into Product  $P$

Rate of change of chemical species with time can be represented as polynomials with law of mass action kinetics

$$\frac{dS}{dt} = -k_1 ES + k_2 C$$

$$\frac{dX_i}{dt} = F_i(X, a_i) = \sum a_{ij} \Phi_j(X, b)$$

$a$  – Parameters,  $b$  – Order

$\Phi$  – Reaction function

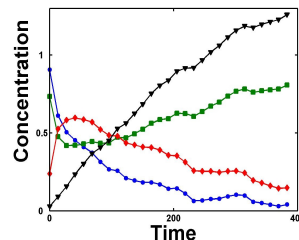
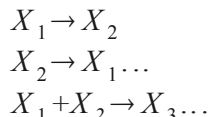
Each reaction function represents an elementary chemical reaction

1

Our method deduces a mechanism by systematic selection of chemical reactions from a dictionary of reactions

Dictionary of elementary chemical reactions captures all possible models

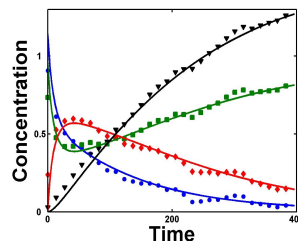
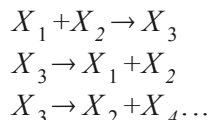
Over fitting due to all possible models



Systematic selection of reactions assessed with fitting provides the best model

Final model

Good fit with a final model



4

5

Selection is driven by Information Criterion  $C_{IC}$

$$C_{IC} = \frac{1}{N} (e^{q^T} \cdot e^{q}) + 2q$$

Information Criterion

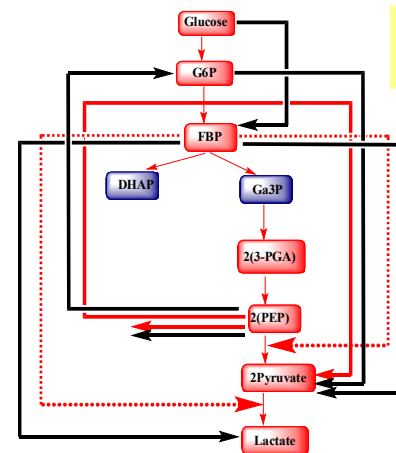
$q$  = No. of chemical reactions,  
 $N$  = No. of time points  $\times$  No. of species

$$e = (dX_i(t_j) / dt)_{j=1}^N - \Phi \cdot a_i = \text{Fitting error}$$

6

Our methodology deduced Glycolytic pathway

Pathway  
Our method



Our method has identified optimal experimental conditions to obtain maximal information

Very robust to noise – 85% accuracy even in the presence of 45% noise in the data

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Future directions

- Analyze the effect of missing chemical species
- Include allosteric kinetics in addition to mass action kinetics
- Apply to complex biochemical pathways



Reference: *Proteomics*, 2007, 7, 828-838  
Funded by NSF Grant IIS-0513701