



Modeling and simulation of gene regulatory networks 4

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INRIA Grenoble - Rhône-Alpes and IBIS



- IBIS: systems biology group at INRIA/Université Joseph Fourier/CNRS
 - Analysis of bacterial regulatory networks by means of models and experiments
 - Biologists, computer scientists, mathematicians, physicists, ...

<http://team.inria.fr/ibis>

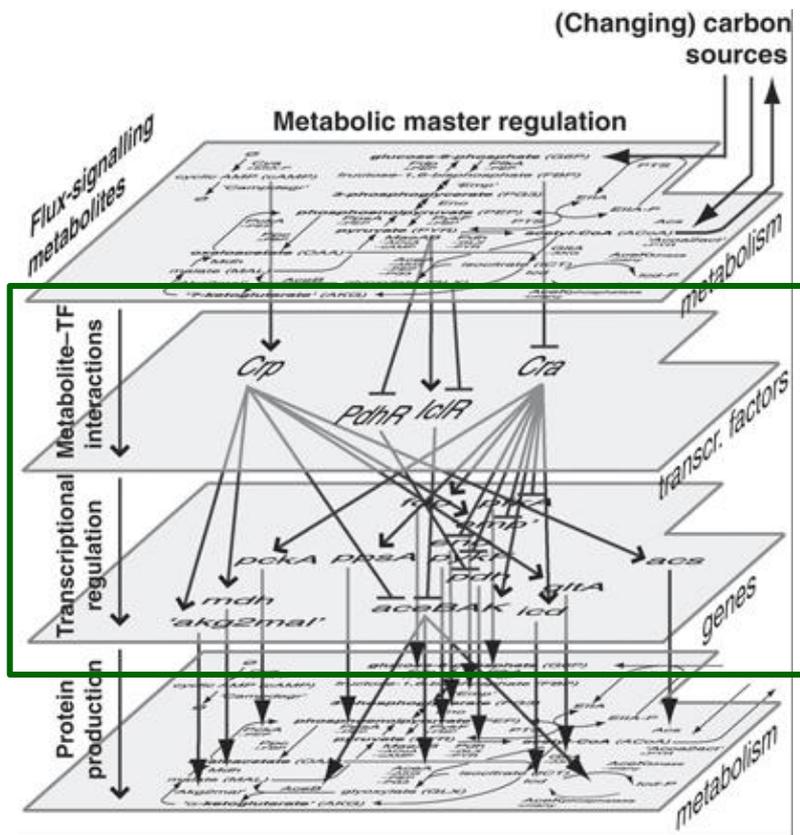


Overview

1. Gene regulatory networks in bacteria
2. Quantitative modeling of gene regulatory networks
3. Qualitative modeling of gene regulatory networks
- 4. Identification of gene regulatory networks**
5. Towards integrated models of the cell

Gene regulatory networks

- Gene regulatory networks control changes in gene expression levels in response to environmental perturbations



- Gene regulatory networks consist of genes, gene products, signalling metabolites, and their mutual regulatory interactions

Global regulators of transcription involved in glucose-acetate diauxie in *E. coli*

Kotte et al. (2010), *Mol. Syst. Biol.*, 6:355

Modeling of gene regulatory networks

- Well-established theory for modeling of gene regulatory networks using ordinary differential equation (ODE) models

Bolouri (2008), *Computational Modeling of Gene Regulatory Networks*, Imperial College Press

Polynikis et al. (2009), *J. Theor. Biol.*, 261(4):511-30

- Practical problems encountered by modelers:
 - Knowledge on molecular mechanisms rare
 - **Quantitative information on kinetic parameters and molecular concentrations absent**
 - Large models

Lack of quantitative information: strategies

- Three main strategies to deal with lack of quantitative data:
 - Test of parameter sensitivity
 - Model reduction and simplification
 - Parameter estimation from time-series data

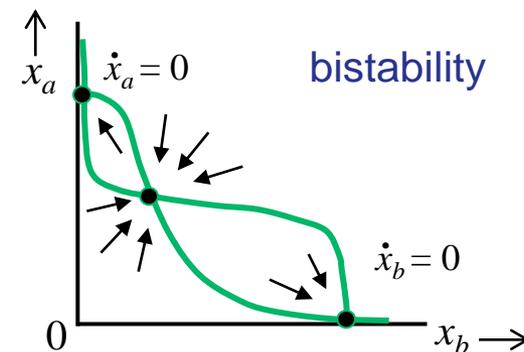
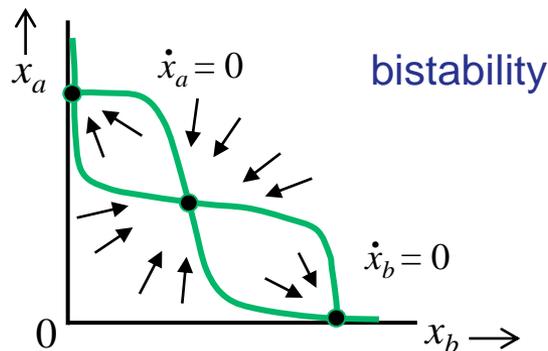
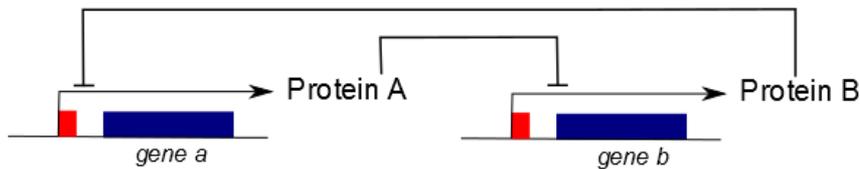
De Jong and Ropers (2006), *Brief. Bioinform.*, 7(4):354-363

Test of parameter sensitivity

- Important dynamic properties are expected to be **robust** over large ranges of parameter values

Important dynamic properties should be insensitive to moderate variations in parameter values

Stelling *et al.* (2004), *Cell*, 118(6):675-685



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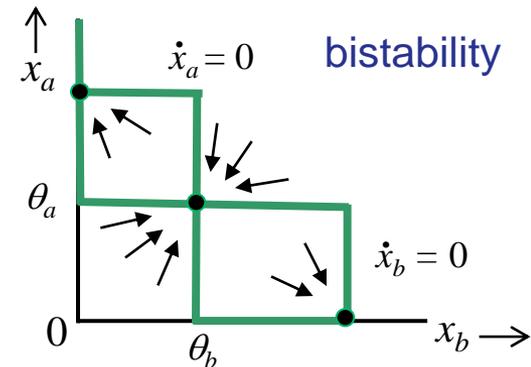
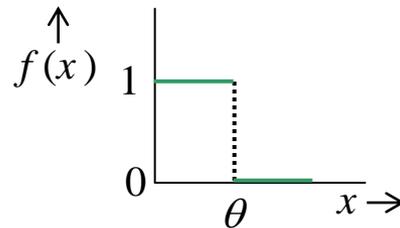
- Large variety of techniques for assessing sensitivity of models to changes in parameter values

Saltelli *et al.* (2008), *Global Sensitivity Analysis: The Primer*. John Wiley & Sons.

Model reduction and simplification

- Use model reduction and simplification to obtain models that can be analyzed with less information on parameter values
 - Piecewise-linear instead of nonlinear models
 - Also: Boolean models

$$\begin{aligned}\dot{x}_a &= \kappa_a f(x_b) - \gamma_a x_a \\ \dot{x}_b &= \kappa_b f(x_a) - \gamma_b x_b\end{aligned}$$



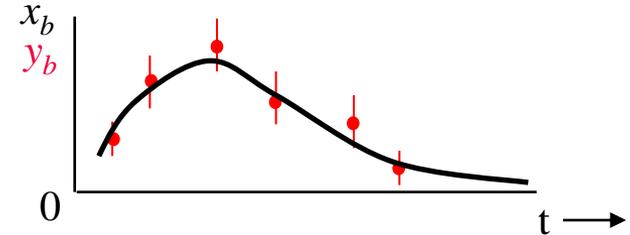
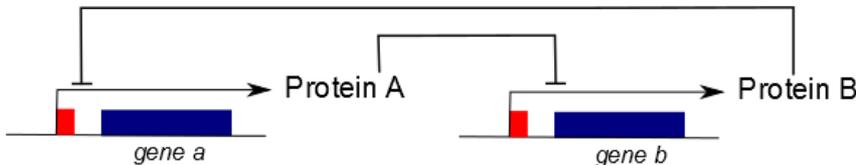
Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29
de Jong et al. (2004), *Bull. Math. Biol.*, 66(2):301-40

Parameter estimation

- **Estimate** parameter values from experimental time-series data
Systems identification in control and engineering

Walter and Pronzato (1997), *Identification of Parametric Models*, Springer

- Given model structure, search parameter values for which model predictions best fit experimental data



- Minimization of objective function, for instance sum of squared errors:
$$\sum_t (x(t, \theta) - y(t))^2$$

Possibility to add constraint or penalty terms to restrict parameter space

Parameter estimation problem

- Differential algebraic equation (DEA) models

$$\mathbf{A} \frac{d}{dt} \mathbf{x}(t, \mathbf{p}) = \mathbf{f}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p}), \quad t_0 \leq t \leq t_e$$
$$\mathbf{x}(t_0, \mathbf{p}) = \mathbf{x}_0$$

- Selection matrix $\mathbf{A} \in \mathbb{R}^{n \times n}$
- State variables $\mathbf{x} : \mathbb{R} \times \mathbb{R}^m \rightarrow \mathbb{R}^n$
- Input variables $\mathbf{u} : \mathbb{R} \rightarrow \mathbb{R}^l$
- Parameters $\mathbf{p} \in \mathbb{R}^m$
- Rate functions $\mathbf{f} : \mathbb{R}^n \times \mathbb{R}^l \times \mathbb{R}^m \rightarrow \mathbb{R}^n$

Ashyraliyev et al. (2009), *FEBS J*, 276(4):886–902

Parameter estimation problem

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- Observables: $\mathbf{g}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p})$

$$\mathbf{g} : \mathbb{R}^n \times \mathbb{R}^l \times \mathbb{R}^m \rightarrow \mathbb{R}^q$$

- (Non)linear constraints: $\mathbf{c}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p}) \geq 0$

Parameter estimation problem

- Model predictions at time t_i

$$\mathbf{g}^i = \mathbf{g}(\mathbf{x}(t_i, \mathbf{p}), \mathbf{u}(t_i), \mathbf{p})$$

- Measurements of observables at time t_i

$$y_j \sim \mathcal{F}(\mu_j, \sigma_j)$$

$$\mathbf{y}^i = \mathbf{y}(t_i)$$

- Model discrepancies

$$\mathbf{G} = [\mathbf{g}^1, \dots, \mathbf{g}^N]$$

$$\mathbf{Y} = [\mathbf{y}^1, \dots, \mathbf{y}^N]$$

$$\mathbf{E}(\mathbf{p}) = | \mathbf{G} - \mathbf{Y} |$$

Parameter estimation problem

- Objective function

$$V(\mathbf{p}) = \sum_{i=1}^N \sum_{j=1}^q \frac{(g_j^i - y_j^i)^2}{(\sigma_j^i)^2} = \mathbf{E}(\mathbf{p})^T \mathbf{W} \mathbf{E}(\mathbf{p})$$

$$y_j \sim \mathcal{N}(\mu_j, \sigma_j) \text{ iid}$$

Other objective functions possible, more adapted to other measurement models or practical considerations!

- **Parameter estimation problem:**

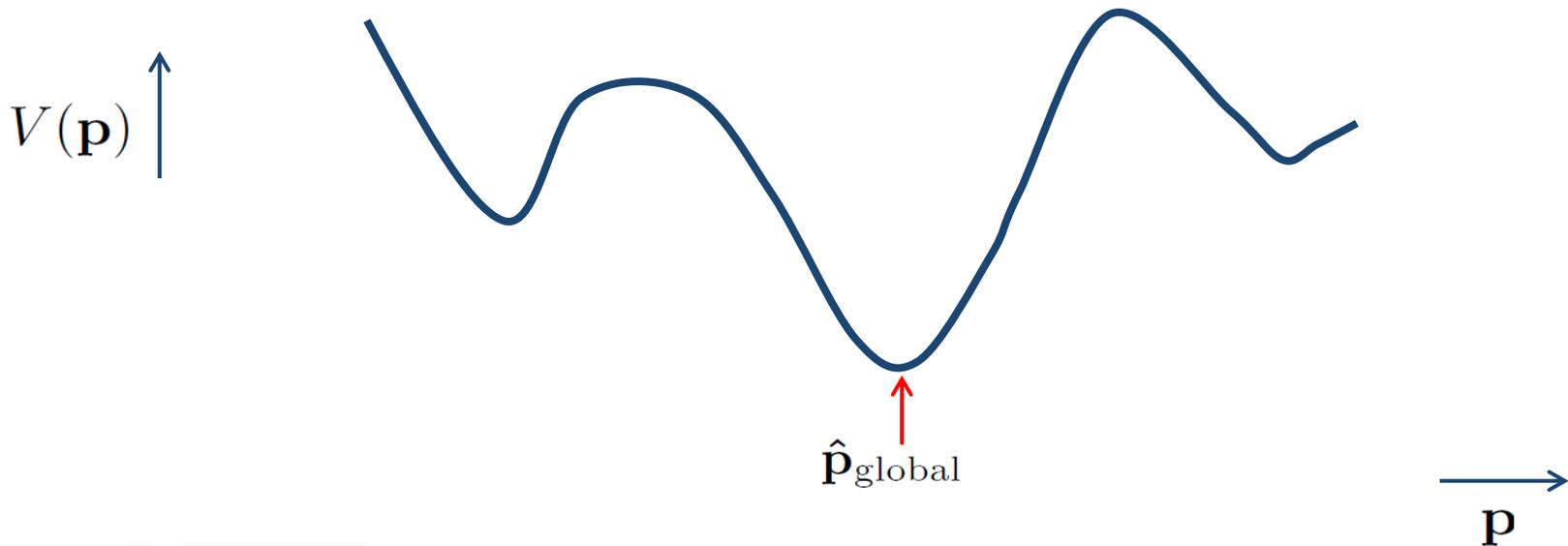
$$\hat{\mathbf{p}} = \arg \min_{\mathbf{p}} V(\mathbf{p})$$

Parameter estimation methods

- Parameter estimation is a complex optimization problem
- Methods for solving optimization problem:
 - **Global methods:**

$$\hat{\mathbf{p}}_{\text{global}} = \arg \min_{\mathbf{p}} V(\mathbf{p})$$

for all \mathbf{p} in parameter space

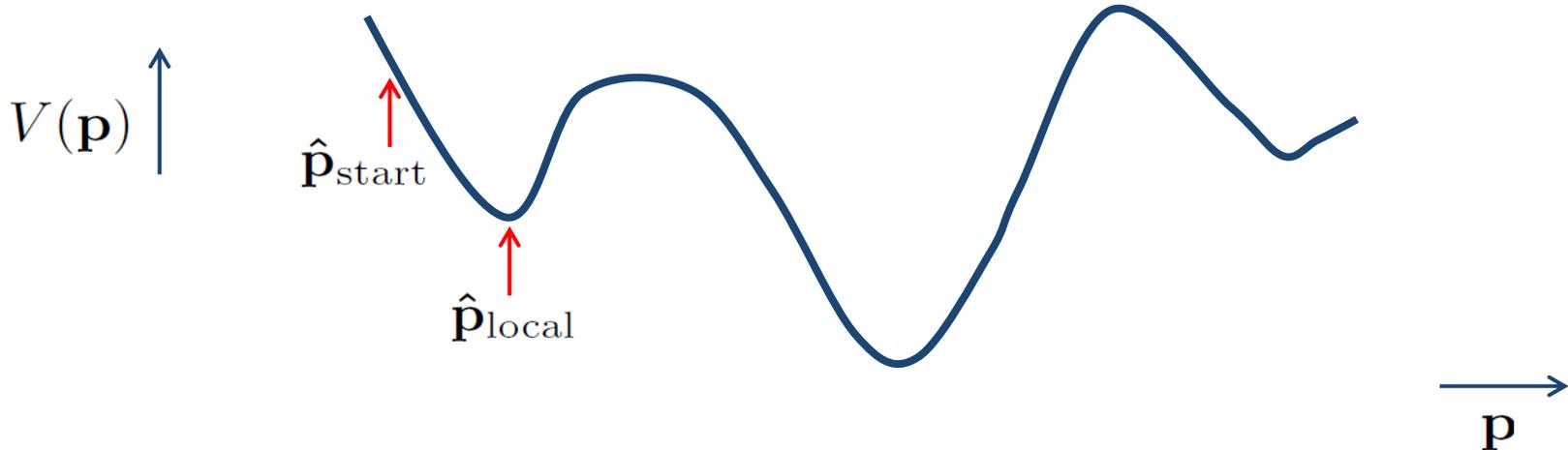


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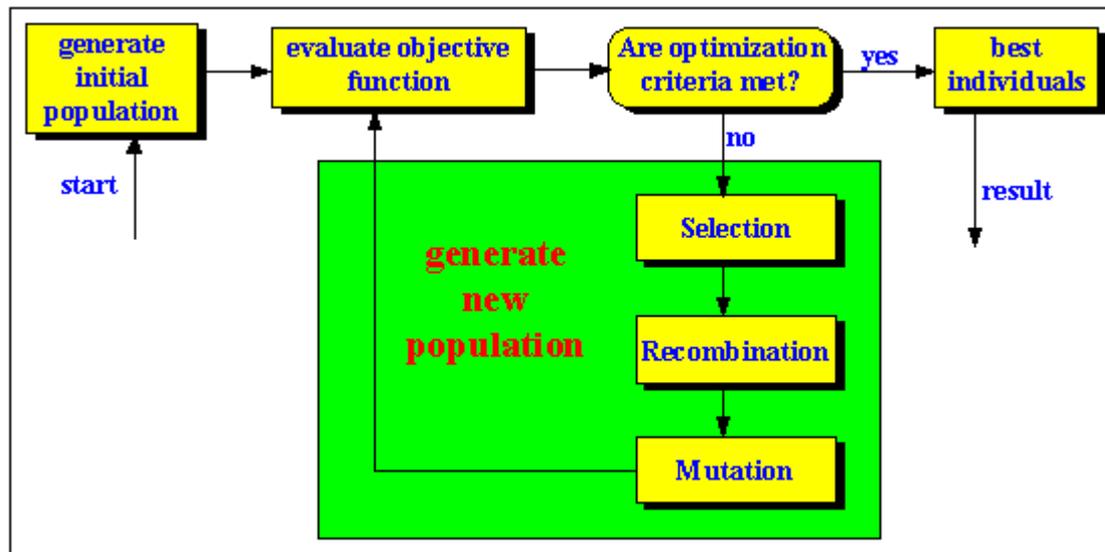
$$\hat{\mathbf{p}}_{\text{local}} = \arg \min_{\mathbf{p}} V(\mathbf{p})$$

for all \mathbf{p} in a neighborhood of $\hat{\mathbf{p}}_{\text{start}}$



Global optimization methods

- Variety of global optimization methods:
 - Evolutionary algorithms



Ashyraliyev et al. (2009), *FEBS J*, 276(4):886–902

Global optimization methods

- Variety of global optimization methods:
 - Evolutionary algorithms
 - Simulated annealing
 - ...
- Search of entire parameter space, but generally no convergence proof
- Mostly stochastic algorithms

Ashyraliyev *et al.* (2009), *FEBS J*, 276(4):886–902

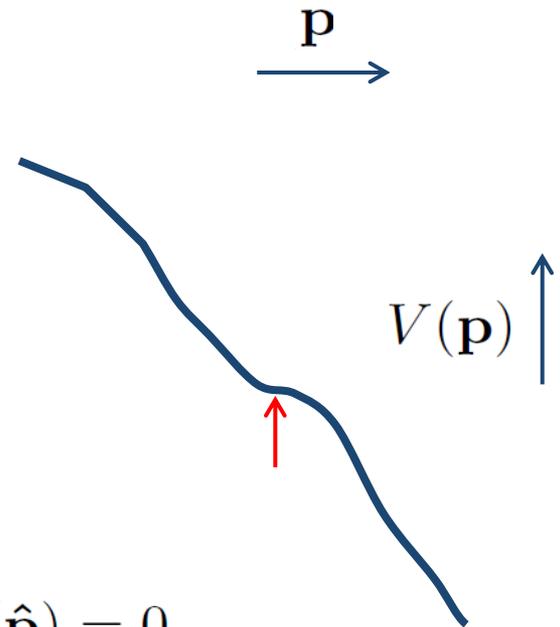
Local optimization methods

- Variety of local optimization methods
 - Gradient methods

Gradient: $\nabla V(\mathbf{p}) = \left[\frac{\partial}{\partial p_i} V(\mathbf{p}) \right]$

Hessian: $\nabla^2 V(\mathbf{p}) = \left[\frac{\partial}{\partial p_i \partial p_j} V(\mathbf{p}) \right]$

Necessary condition for local minimum: $\nabla V(\hat{\mathbf{p}}) = 0$

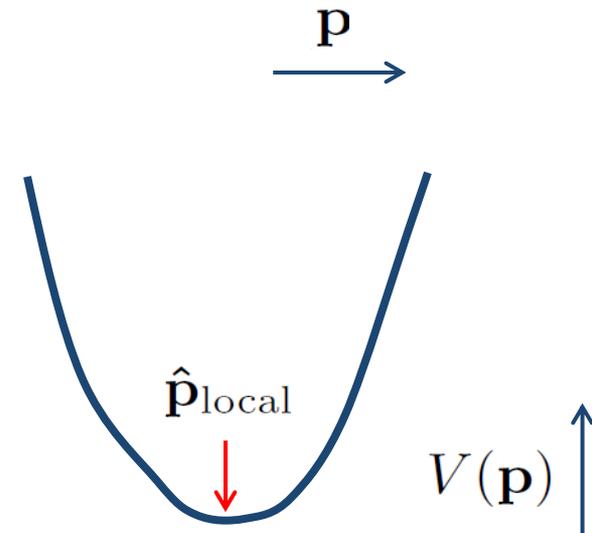


Local optimization methods

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Necessary condition for local minimum: $\nabla V(\hat{\mathbf{p}}) = 0$

Sufficient condition for local minimum:

$$\nabla V(\hat{\mathbf{p}}) = 0 \quad \text{and} \quad \mathbf{p}^T \nabla^2 V(\hat{\mathbf{p}}) \mathbf{p} > 0 \quad \text{for all } \mathbf{p}$$

Local optimization methods

- Variety of local optimization methods
 - Gradient methods

$$\mathbf{p}_{\text{new}} = \mathbf{p} + \alpha d\mathbf{p}, \quad V(\mathbf{p}_{\text{new}}) < V(\mathbf{p})$$

Steepest descent

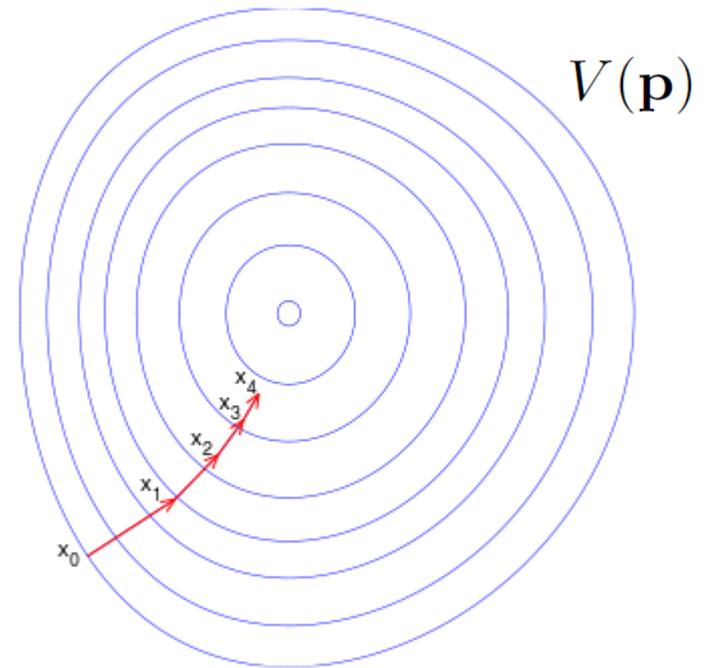
$$d\mathbf{p} = -\nabla V(\mathbf{p})$$

Newton's method

$$d\mathbf{p} = -\nabla^{-2}V(\mathbf{p}) \nabla V(\mathbf{p})$$

Other choices for $d\mathbf{p}$

Adaptive choice of α



Local optimization methods

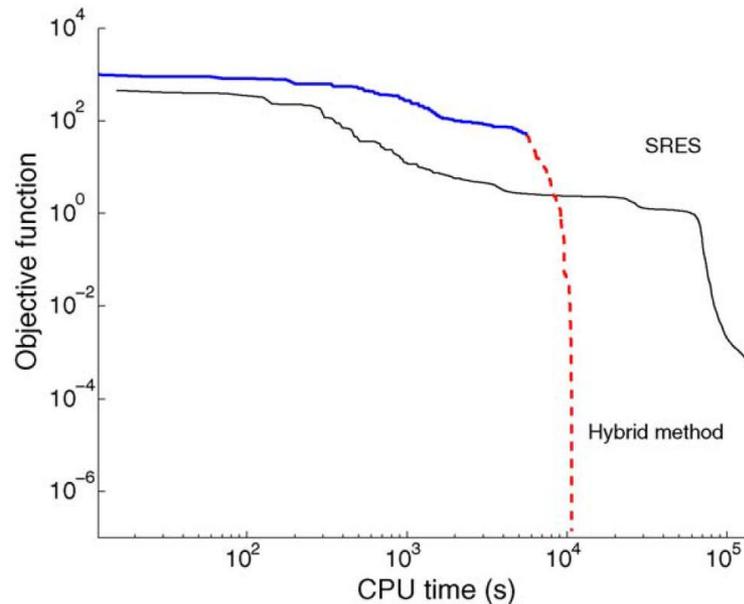
- Variety of local optimization methods
 - Gradient methods
 - Direct search
 - ...
- Local search of parameter space, but proof of (speed of) convergence
- Mostly deterministic algorithms

Ashyraliyev *et al.* (2009), *FEBS J*, 276(4):886–902

Hybrid optimization method

- **Hybrid optimization:** global followed by local optimization
- In practice, hybrid optimization methods work well on large nonlinear models used in systems biology

Test on benchmark identification problems



Rodriquez-Fernandez *et al.* (2006), *Biosystems*, 83: 248–65

Constrained optimization methods

- Differential algebraic equation (DEA) models

$$\mathbf{A} \frac{d}{dt} \mathbf{x}(t, \mathbf{p}) = \mathbf{f}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p}), \quad t_0 \leq t \leq t_e$$
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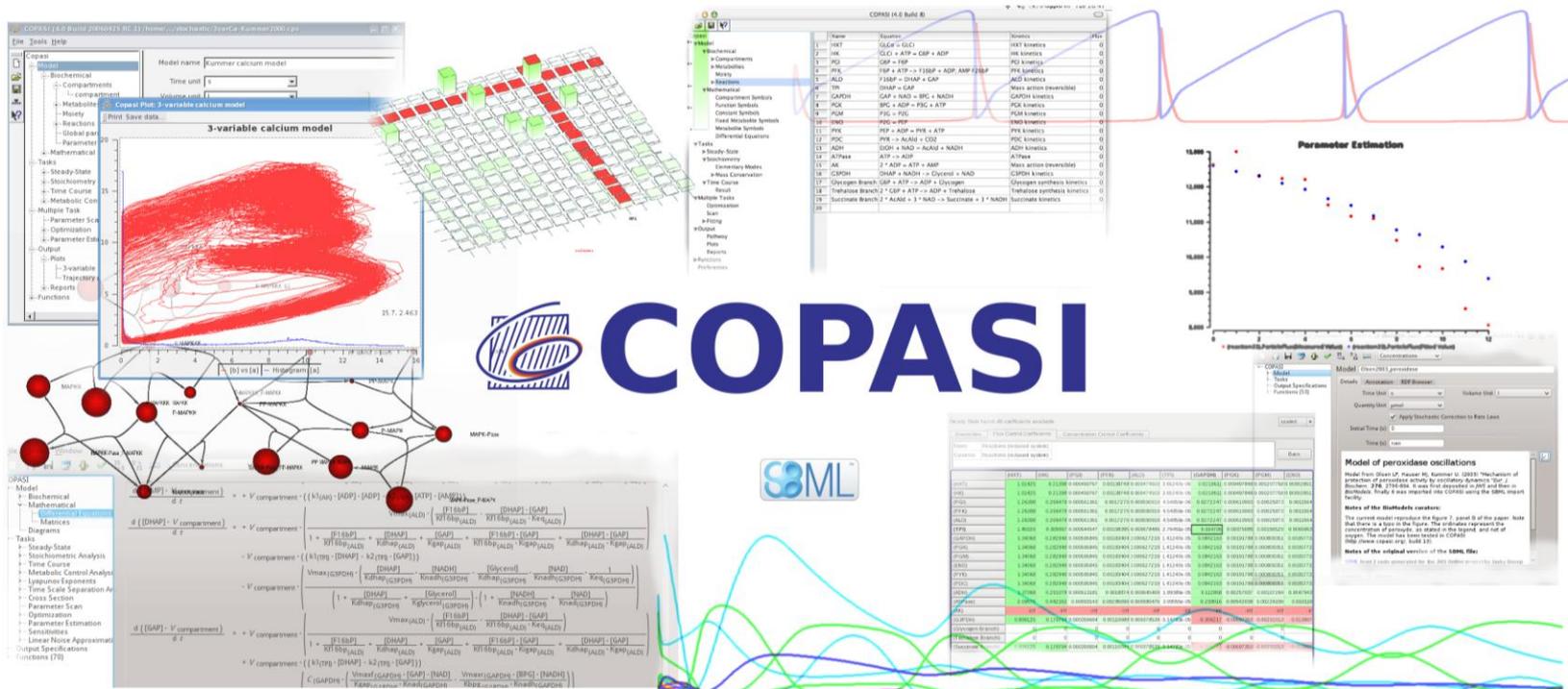
- (Non)linear constraints:

$$\mathbf{c}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p}) \geq 0$$

- Constraints can be implemented in different ways
 - Penalty term in objective function
 - Search in subspace defined by (in)equality constraints
 -

Parameter estimation tools

- Large number of dedicated parameter estimation tools in systems biology, in addition to general-purpose tools

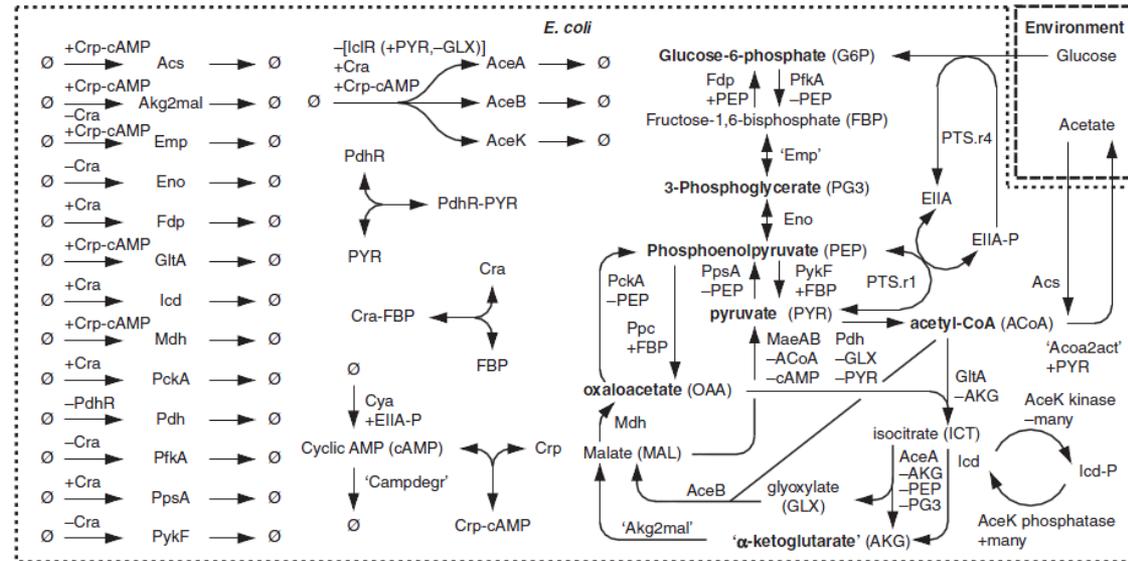
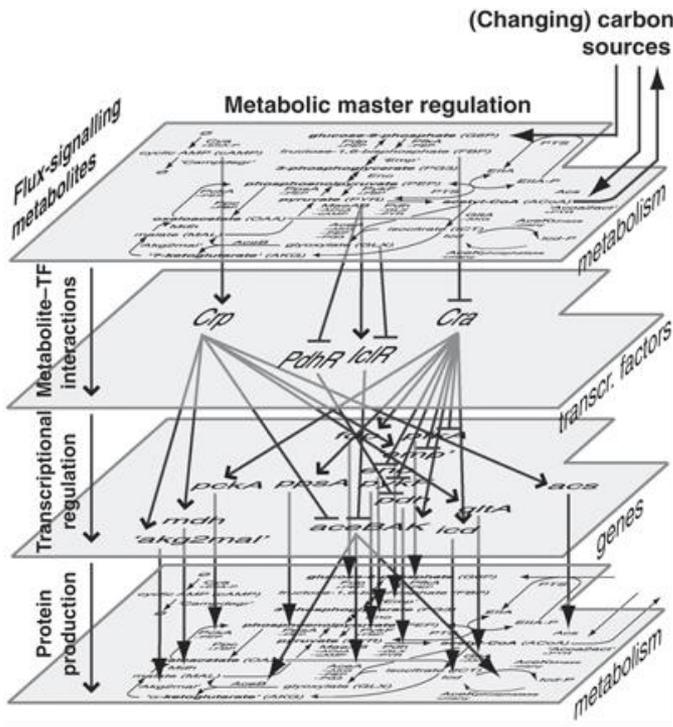


Hoops et al. (2006), *Bioinformatics*, 22:3067-74

Integrated model of *E. coli* metabolism

- Coupling of gene expression and metabolism into a single integrated model of *E. coli* metabolism

Kinetic model with 47 variables and 193 parameters



Kotte et al. (2010), *Mol. Syst. Biol.*, 6: 355

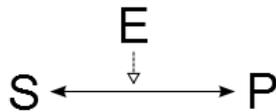
Multi-scale network of *E. coli* metabolism

- Estimation of model parameters using steady-state data: algebraic equations

Published data sets for balanced growth on either glucose or acetate

$$N \cdot v = 0$$

- **Divide-and-conquer strategy** based on model structure
 1. Estimate reaction rates at steady state
 2. Identify model parameters for individual reactions from reaction rate estimations and measurements of concentrations
 3. Re-estimate integrated model



$$v(s, p) = \frac{V_m^+ \cdot s / K_{m1} - V_m^- \cdot p / K_{m2}}{1 + s / K_{m1} + p / K_{m2}}$$

Kotte *et al.* (2009), *Bioinformatics*, 25(4):519-25

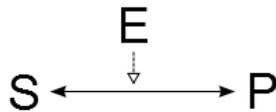
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$$f_{E,Pdh} = \frac{x_{Pdh} p_{Pdh,kcat} \frac{x_{PYR}}{p_{Pdh,K_{PYR}}} \left(1 + \frac{x_{PYR}}{p_{Pdh,K_{PYR}}}\right)^{p_{Pdh,n}-1}}{\left(1 + \frac{x_{PYR}}{p_{Pdh,K_{PYR}}}\right)^{p_{Pdh,n}} + p_{Pdh,L} \left(1 + \frac{x_{GLX}}{p_{Pdh,K_{GLX}}} + \frac{x_{PYR}}{p_{Pdh,K_{I,PYR}}}\right)^{p_{Pdh,n}}}$$

$$f_{E,PfkA} = \frac{x_{PfkA} p_{PfkA,kcat} \frac{x_{G6P}}{p_{PfkA,K_{G6P}}} \left(1 + \frac{x_{G6P}}{p_{PfkA,K_{G6P}}}\right)^{p_{PfkA,n}-1}}{\left(1 + \frac{x_{G6P}}{p_{PfkA,K_{G6P}}}\right)^{p_{PfkA,n}} + p_{PfkA,L} \left(1 + \frac{x_{PEP}}{p_{PfkA,K_{PEP}}}\right)^{p_{PfkA,n}}}$$

Kotte et al. (2010), *Mol. Syst. Biol.*, 6: 355

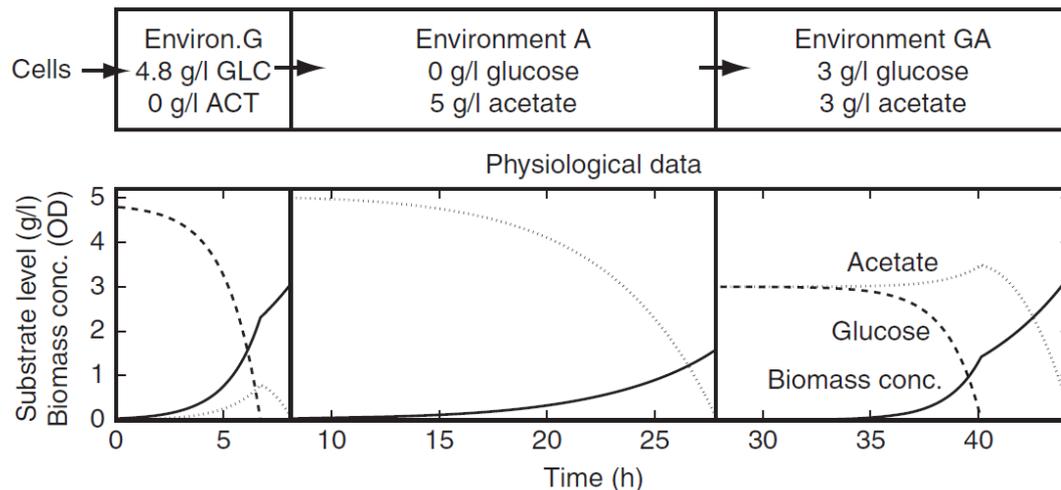
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Published data sets for balanced growth on either glucose or acetate

$$N \cdot v = 0$$

- Model reproduces known physiological behavior of *E. coli*: diauxic growth and carbon catabolite repression



Kotte *et al.* (2010), *Mol. Syst. Biol.*, 6: 355

Identifiability analysis

- Parameter p_j is (globally) **identifiable**, if it can be uniquely determined from given model input $\mathbf{u}(t)$ and error-free data
- Model is (globally) identifiable, if all of its parameters are
- **A-priori identifiability** analysis
 - Structural problems of model

$$\frac{d}{dt}x(t, \mathbf{p}) = p_1 \cdot x + p_2 \cdot x$$

Given measurements of x , it is not possible to obtain independent estimates of both parameters

Walter and Pronzato (1997), *Identification of Parametric Models*, Springer

Identifiability analysis

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- Model is (globally) identifiable, if all of its parameters are
- **A-priori identifiability** analysis
 - Structural problems of model
- **Practical or a-posteriori identifiability** analysis
 - Problems with precision and quality of data
 - Correlation between variables
- Parameter p_j is practically identifiable if its confidence interval is of finite size
- Model is practically identifiable, if all of its parameters are

Identifiability analysis using profile likelihood

- Objective function

$$V(\mathbf{p}) = \sum_{i=1}^N \sum_{j=1}^q \frac{(g_j^i - y_j^i)^2}{(\sigma_j^i)^2} = \mathbf{E}(\mathbf{p})^T \mathbf{W} \mathbf{E}(\mathbf{p})$$

$$y_j \sim \mathcal{N}(\mu_j, \sigma_j) \text{ iid}$$

is proportional to **log-likelihood**

Minimization of $V(\mathbf{p})$ corresponds to maximum likelihood estimation

- Profile likelihood for parameter p_i ranging over interval $p_i = \tilde{p}_i \in [\underline{p}, \bar{p}]$ is defined as

$$V_{PL}(\tilde{p}_i) = \min_{\mathbf{p} \in \mathbb{R}^m, p_i = \tilde{p}_i} V(\mathbf{p})$$

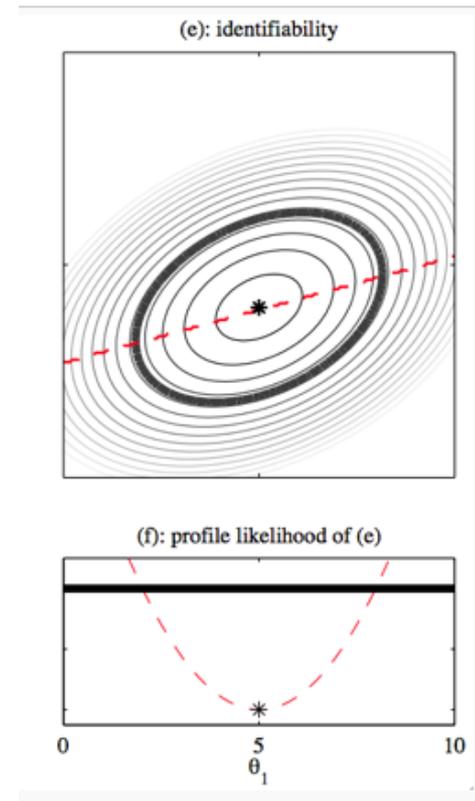
- Likelihood-based confidence interval $\{\mathbf{p} \mid V(\mathbf{p}) - V(\hat{\mathbf{p}}) < \alpha\}$

Threshold given by distribution

Raue *et al.* (2009), *Bioinformatics*, 25(15):1923-9

Identifiability analysis using profile likelihood

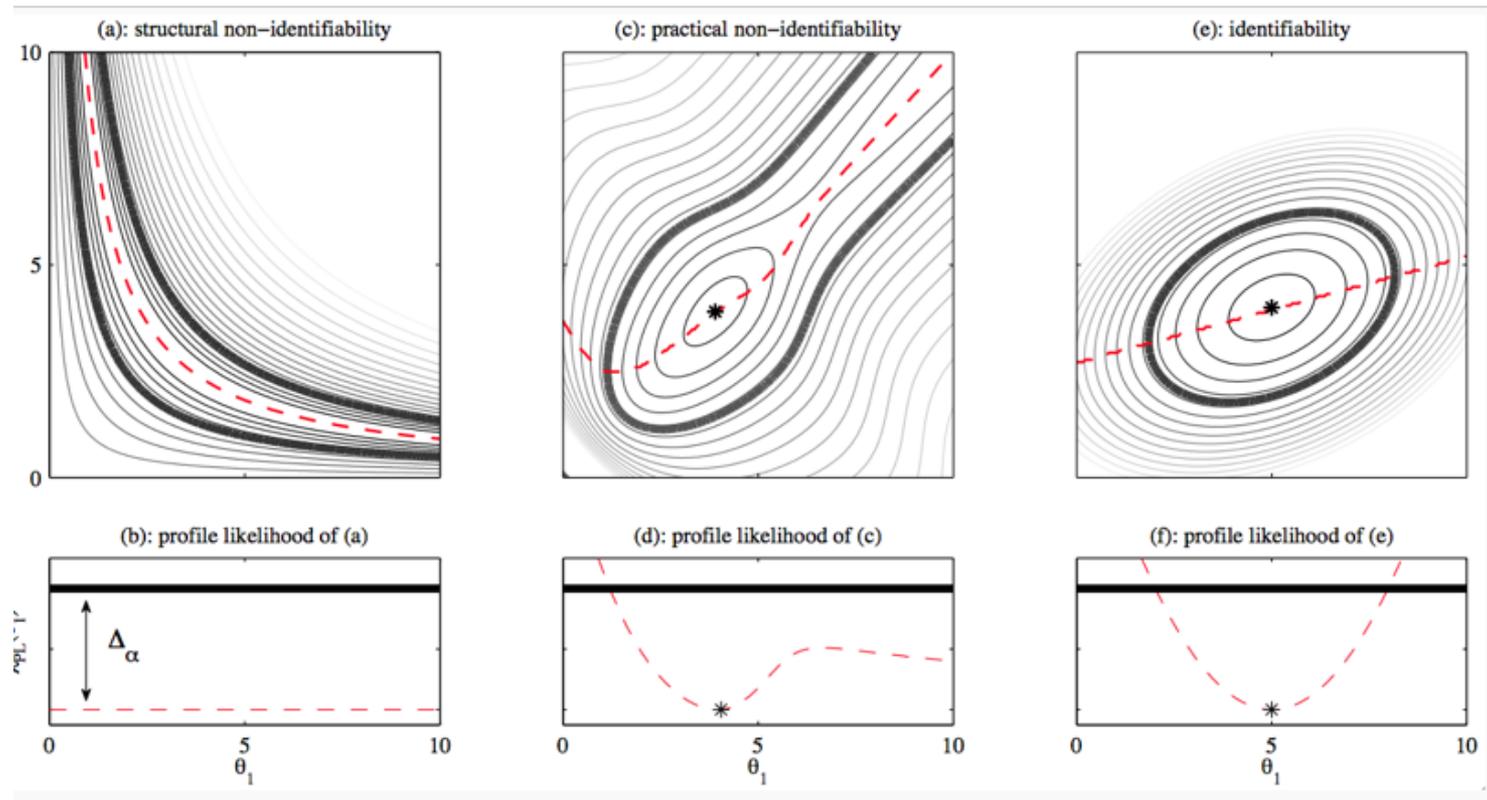
- Intuition: for each parameter, explore the parameter space in direction of least increase of objective function



Raue et al. (2011), *IET Syst. Biol.*, 5(2):120-30

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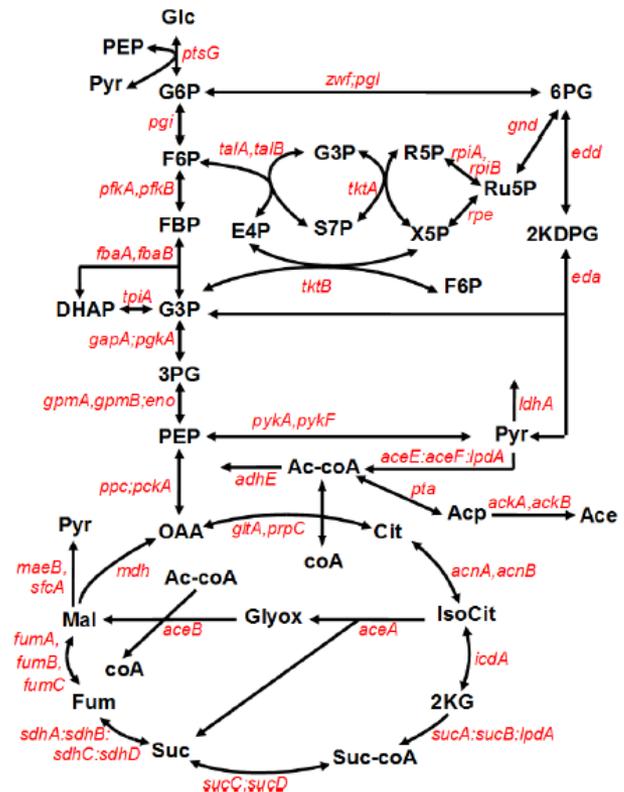
Identifiability analysis of *E. coli* metabolism

- Simplified model of central carbon metabolism in *E. coli*
- Model at steady state and lin-log kinetics for describing reactions

$$v = \text{diag}(e) \cdot (a + B^x \cdot \ln x + B^u \cdot \ln u)$$

$$N \cdot v = 0$$

- Measurements:
 - Metabolite concentrations u, x
 - Enzyme concentrations e
 - Metabolic fluxes (reaction rates at steady state) J
- Parameters to estimate: $a \quad B^x \quad B^u$



Berthoumieux *et al.* (2011), *Bioinformatics*, 27(13):i186–93

Identifiability analysis of *E. coli* metabolism

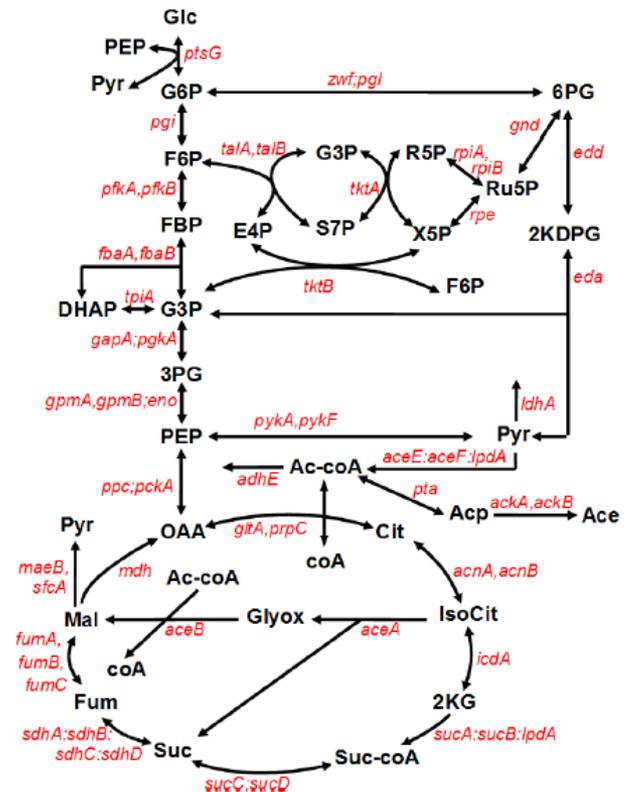
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$$N \cdot v = 0$$

- Solution by minimal regression

More complicated methods if data are incomplete



Berthoumieux *et al.* (2011), *Bioinformatics*, 27(13):i186–93

Identifiability analysis of *E. coli* metabolism

- Simplified model of central carbon metabolism in *E. coli*
- Most parameters are not identifiable as determined from profile likelihood!

Reactions	Metabolites																							
	Glc	PEP	G6P	Pyr	F6P	FBP	DHAP	3PG	AcoA coA	6PG	Ru5P	R5P	S7P	2KG	Suc	Fum	Mal	ATP ADP	Cit	NADPH NADP	NADH NAD	FAD	Ace	
	0.29	-0.89	0.79	1.87	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	-0.33	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	-0.16	0	0	0.04	-0.28	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0	0	0	0	
	0	0	0	0	0	-0.3	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	-0.07	0.22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	-0.18	0	-0.05	0	0	0	0	0	0	0	0	0	0.32	0	0	-0.17	0	0	
	0	0.26	0	0	0	0	0	-0.12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0.12	0	0.49	0	-0.19	0	0	0	0	0	0	0	0	0	0	0	0.16	0	0	0	0	0	
	0	0	0	0.64	0	0	0	0.05	0	0	0	0	0	0	0	0	0	0	0	0	-0.21	0	0	
	0	0	-0.22	0	0	0	0	0	-0.24	0	0	0	0	0	0	0	0	0	0	-0.01	0	0	0	
	0	0	0	0	0	0	0	0	0.48	-0.09	0	0	0	0	0	0	0	0	0	-0.01	0	0	0	
	0	0	0	0	0	0	0	0	0	0.46	0	-0.39	0	0	0	0	0	0	0	0	0	0	0	
	0	0	-0.74	0	0	0	0	0	0	0.3	-0.16	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0	0	0.01	-0.1	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	-0.32	0	0	0	0	0	0	0.51	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	-0.58	0	0	0	0	0	0.35	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	0	0	0	0	0	0.22	0	0	0	0	-0.001	0	0	0	0	0.49	0	-0.01	0	0	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0.99	0	0	0	0	0.55	0	0	0	0	
	0	0	0	0	0	0	0	0	0.08	0	0	0	0	-0.09	0	0	0	0	0	-0.59	0	0	0	
	0	0	0	0	0	0	0	0	0	0	0	0	0	1.26	0.3	0	0	0	0	0	0	-0.48	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.08	-0.44	0	0	0	0	0	0	0.4	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.46	0.1	0	0	0	0	0	0	0
	0	0.15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.01	0	0.31	0	-0.12	0	0	
	0	0.29	0	0	-0.13	0	0	0	0	0	0	0	0	0	0	0	0.1	-1.15	0.21	0	0	0	0	
	0	0	0	-0.31	0	0	0	0	-0.21	0	0	0	0	0	0	0	0.38	0	0	0.36	-0.05	0	0	
	0	0	0	0	0	0	0	0	-0.11	0	0	0	0	0	0.26	0	-0.18	0	0	0	0	0	0	
	0	0.1	-0.09	0.04	-0.06	0	0	0.17	0.1	0	0	0.09	0	-0.01	0	0	0	-0.46	0	-0.003	0.01	0	0	
	0	0	0	-0.03	0	0	0	0	0	0	-0.93	0	0	0	0	0	0	0	0	0	0	0	0	
	0	0	0	-0.06	0	0	0	0	-0.01	0	0	0	0	0	0	0	0	0.21	0	-0.25	-2.03	0	2.19	
	0	0	0	2.67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.11	0	0	
	0	0	0	0	0	0	0	0	0.91	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

27/31 nonidentifiable reactions

73/100 nonidentifiable parameters

Berthoumieux et al. (2013), *J. Math. Biol.*, 67:1759-1832

Structural vs parametric identification

- **Parametric identification** assumes model structure given
- **Structural identification** provides joint estimate of model structure and parameters

$$\mathbf{A} \frac{d}{dt} \mathbf{x}(t, \mathbf{p}) = \mathbf{f}(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), \mathbf{p}), \quad t_0 \leq t \leq t_e$$
$$\mathbf{x}(t_0, \mathbf{p}) = \mathbf{x}_0$$

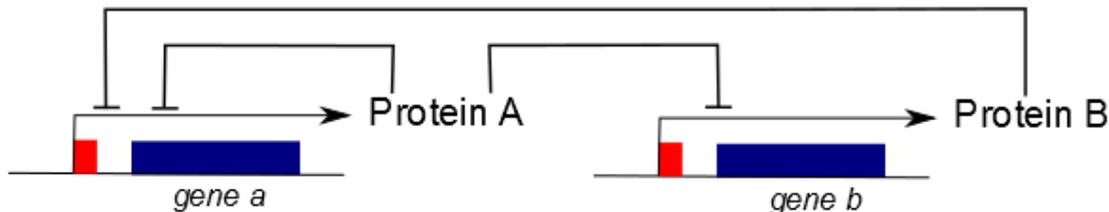
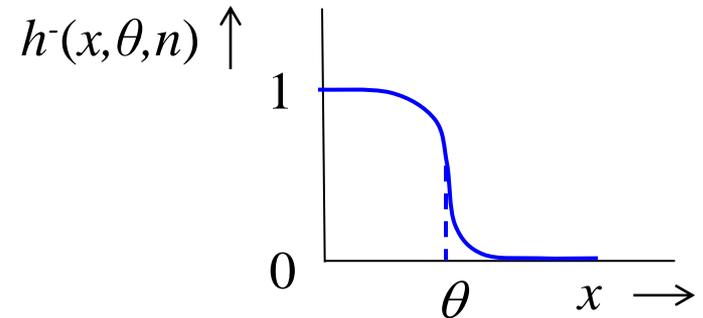
- Structural identification very difficult problem, based on exploration of *a-priori* defined model space

Structural vs parametric identification

- Method for **structural and parametric identification** of gene regulatory networks from time-series data
 - Exploits monotonicity properties of switch-like regulation functions g to invalidate interactions

$$\dot{x}_a = \kappa_a h^-(x_a, \theta_{a2}, n) h^-(x_b, \theta_b, n) - \gamma_a x_a$$

$$\dot{x}_b = \kappa_b h^-(x_a, \theta_{a1}, n) - \gamma_b x_b$$



x : protein concentration
 θ : threshold concentration
 κ, γ : rate constants
 n : steepness parameter

Porreca et al. (2010), *Bioinformatics*,
26(9):1239-45

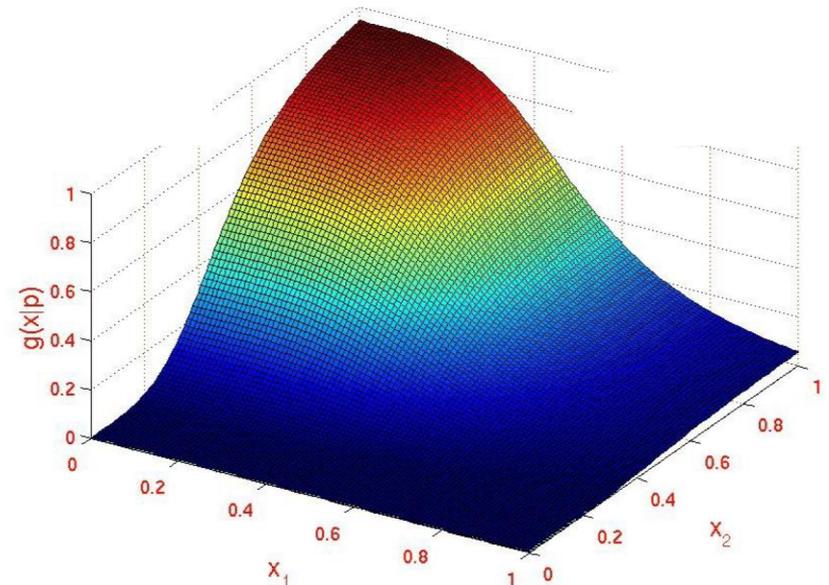
Structural vs parametric identification

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Observations $x_1 \uparrow$, $x_2 \downarrow$ and $g(x_1, x_2) \uparrow$ rule out pattern x_1 activator and x_2 inhibitor

$$\dot{x}_3 = g(x_1, x_2, p) - \gamma_3 x_3$$

$$g(x_1, x_2, p) \neq \kappa_3 h^+(x_1, \theta_1, n) h^-(x_2, \theta_2, n)$$



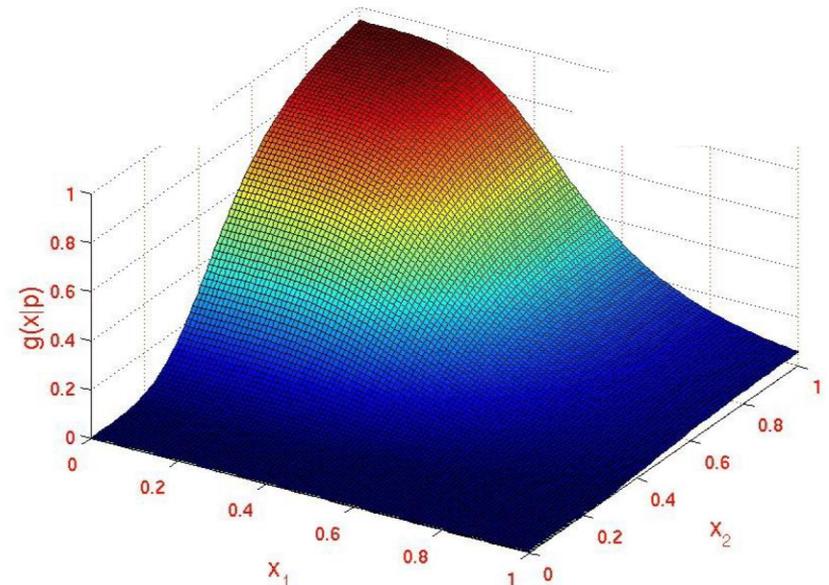
Porreca et al. (2010), *Bioinformatics*,
26(9):1239-45

Structural vs parametric identification

- Method for **structural and parametric identification** of gene regulatory networks from time-series data
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 - Looks for simplest interaction structures consistent with data

Subpatterns of inconsistent patterns
are also inconsistent

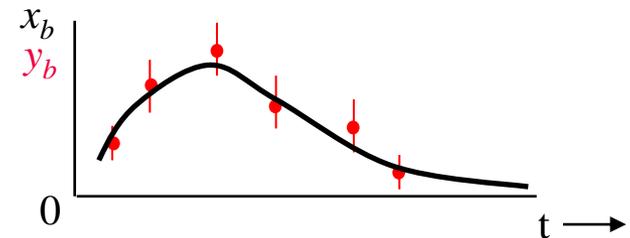
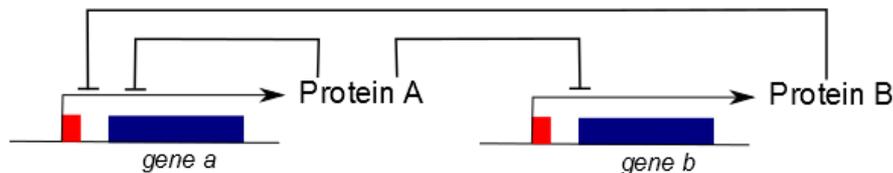
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Porreca *et al.* (2010), *Bioinformatics*,
26(9):1239-45

Structural vs parametric identification

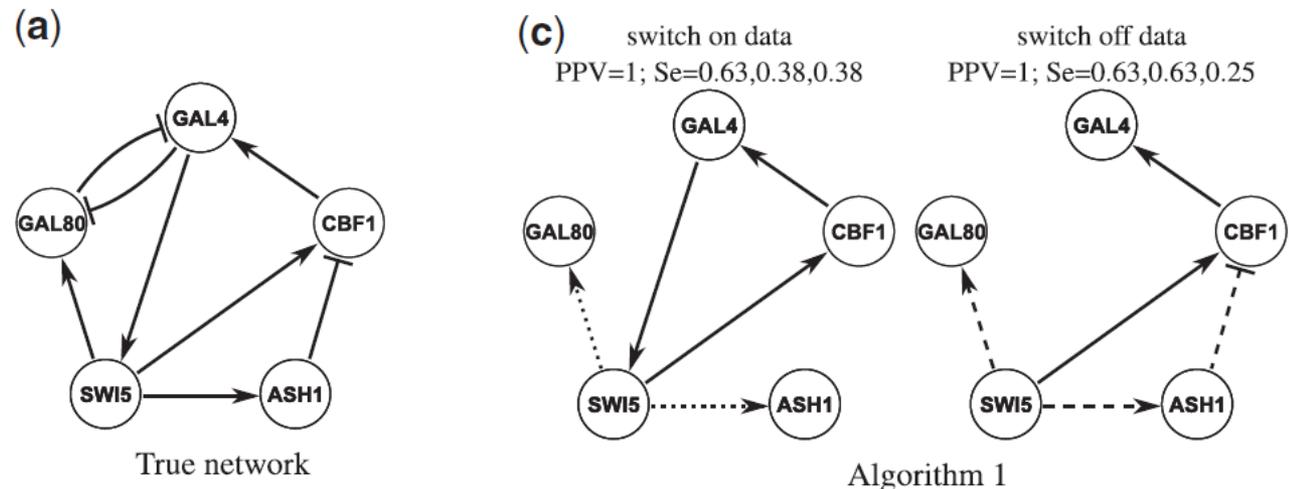
- Method for **structural and parametric identification** of gene regulatory networks from time-series data
 - Exploits monotonicity properties of switch-like regulation functions g to invalidate interactions
 - Looks for simplest interaction structures consistent with data
 - Estimate parameters for selected interaction structure



Porreca et al. (2010), *Bioinformatics*,
26(9):1239-45

Structural vs parametric identification

- Method for **structural and parametric identification** of gene regulatory networks from time-series data
 - Exploits monotonicity properties of switch-like regulation functions g to invalidate interactions
 - Looks for simplest interaction structures consistent with data
 - Estimate parameters for selected interaction structure
 - Good results on benchmark data set in yeast



Porreca *et al.* (2010), *Bioinformatics*,
26(9):1239-45

Structural vs parametric identification

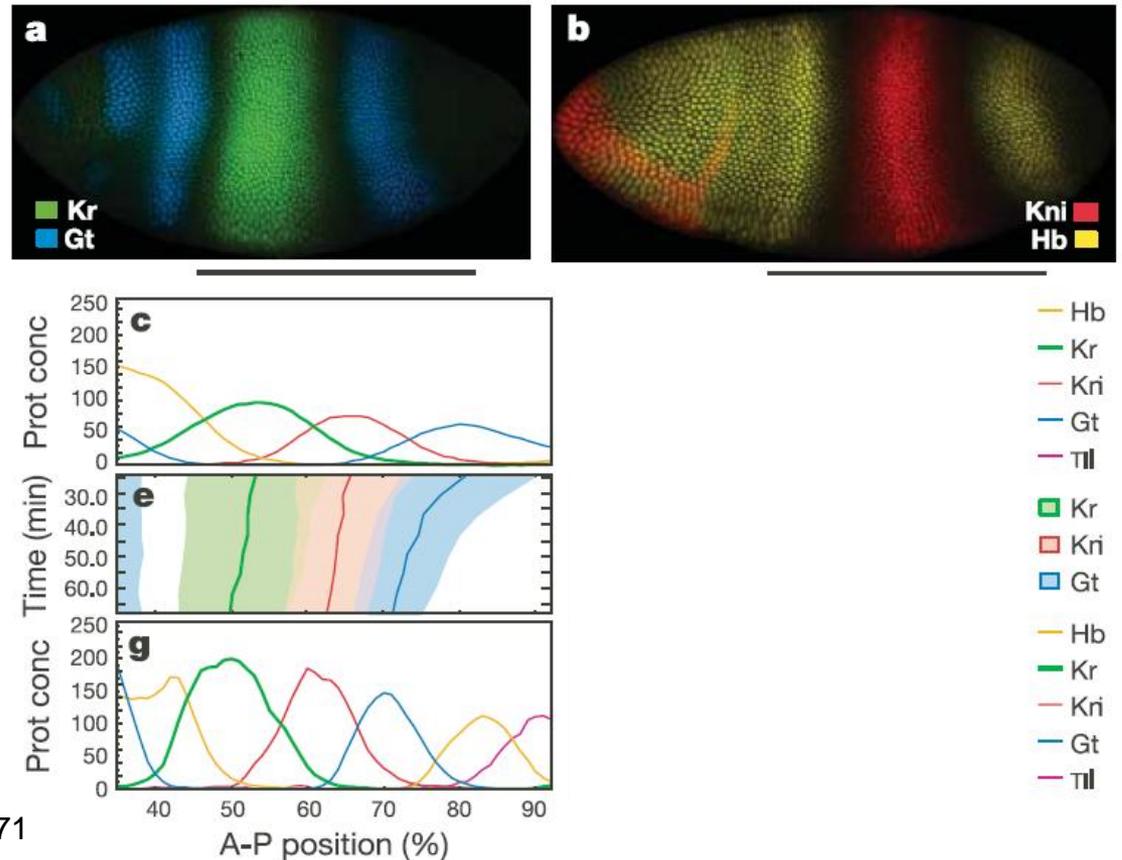
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$$\mathbf{x}(t_0, \mathbf{p}) = \mathbf{x}_0$$

- Structural identification very difficult problem, based on exploration of a-priori-defined model space
- In certain cases, structural identification reduces to parametric identification

Parameter estimation from *Drosophila* data

- Measurement of protein concentrations of gap genes during development of *Drosophila* embryo



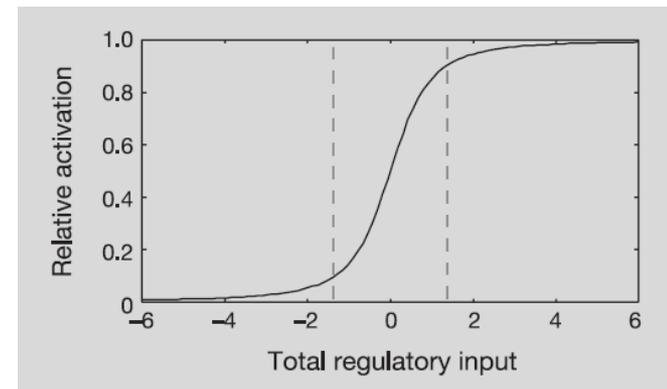
Jaeger et al. (2004), *Nature*, 430(6997):368-71

Parameter estimation from *Drosophila* data

- Neural-network-like model of connections between gap genes
 - Model with 58 nuclei and 7 variables (proteins) per nucleus
 - Free diffusion of proteins because at early stages of development embryo is syncytium (multinucleate cell)
 - Sigmoidal response functions
 - Connectivity pattern encoded in parameter matrix T , so parametric **and** structural identification

$$\frac{dv_i^a}{dt} = R_a g(u^a) + D^a [(v_{i-1}^a - v_i^a) + (v_{i+1}^a - v_i^a)] - \lambda_a v_i^a$$

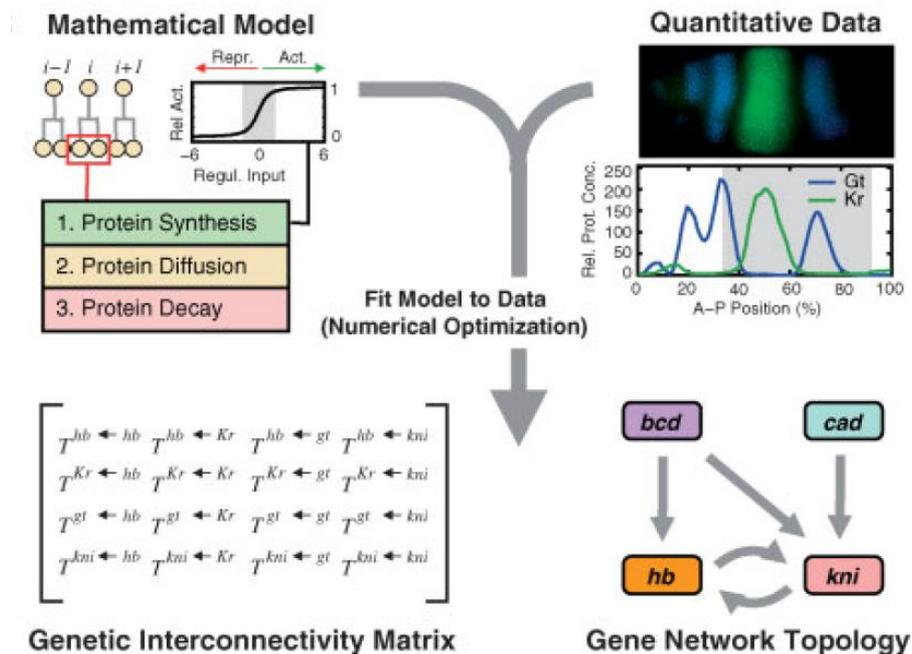
$$u^a = \sum_b T^{ab} v_i^b + m^a v_i^{Bcd} + h^a$$



Jaeger et al. (2004), *Nature*, 430(6997):368-71

Parameter estimation from *Drosophila* data

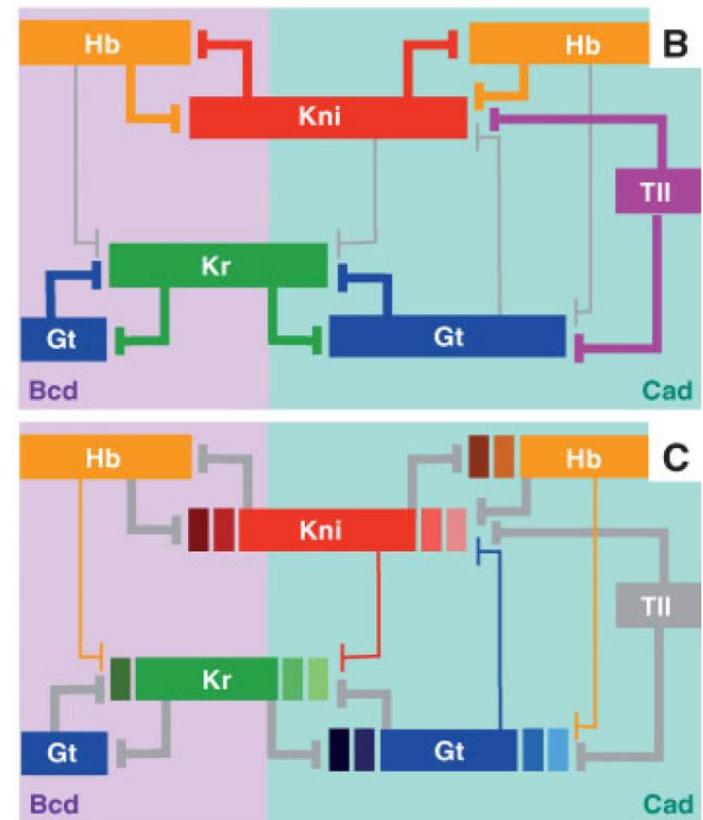
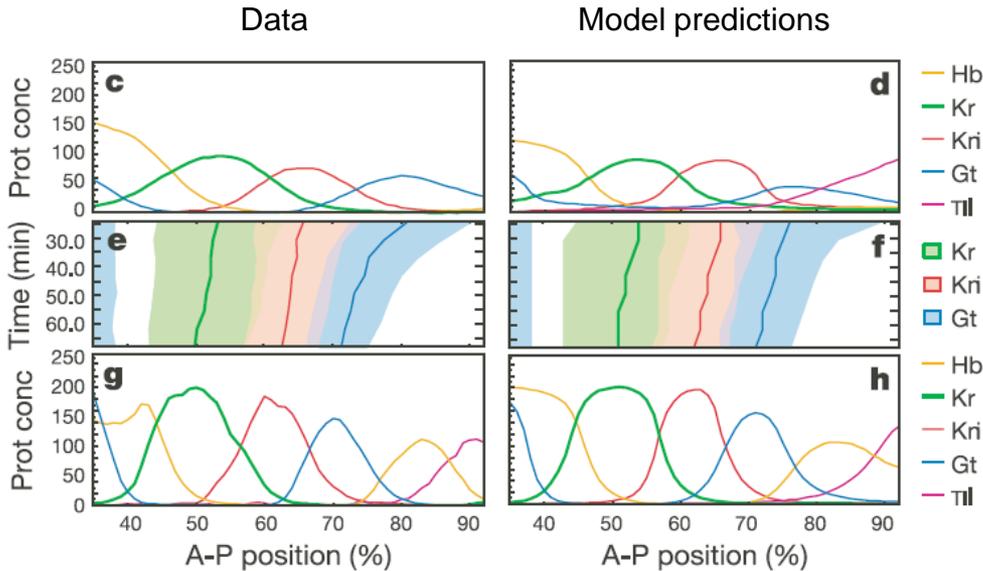
- Neural-network-like model of connections between gap genes
- Brute-force parameter estimation by fitting model to data
Parallelized simulated annealing



Jaeger and Reinitz (2006), *BioEssays*, 28(11):1102-11

Shifts in gap gene domains

- What is function of **cross-inhibition** between gap genes?
 Model predicts that they are important for shift in gap gene domains after their initial establishment



Conclusions

- Identification of models requires estimation of parameters
 - Optimization problem: minimization of objective function
 - Large variety of methods available: global vs local, deterministic vs stochastic, ...
- Identifiability issues: structural and practical identifiability
- Structural vs parametric identification
- Other issues: optimal experimental design, ensemble models
- Large-scale parameter estimation problems in systems biology are very difficult to solve
 - Clever tricks
 - Model-dependent heuristics
 - Model reduction, ...

Internships in IBIS

- Challenging problems for biologists, physicists, computer scientists, mathematicians, ...
- ... in a multidisciplinary working environment
- Contact: Hidde.de-Jong@inria.fr and ibis.inrialpes.fr



Courtesy Guillaume Baptist (2008)

Merci !



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