Experimental Design for Efficient Identification of Gene Regulatory Networks using Sparse Bayesian Models

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MAX-PLANCK-GESELLSCHAFT

Outline

1. The Need for Experimental Design
2. System Identification of Genetic Regulation
3. Sparse Bayesian Linear Model
4. Experiments
5. Related Work. Conclusions

Why Experimental Design?

- Large-scale genome-wide experiments:
  Affordable today in fully automatized labs
- Solve problems by complete enumeration or random shooting?
  - Guaranteed to run out of steam on hard problems
  - Cutting-edge experiments always hard/expensive
  - Even for large labs: $(\#\mathrm{Results})/\$$ counts!
- Sequential Optimal Design
  Plan next experiment based on all previous outcomes
  ⇒ Every smart biologist does that anyway!
- Can optimal design be semi-automatized on a dumb machine?
  What general framework allows us to do that?

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Bayesian Optimal Design

Smart Biologist

- Which variables could explain my data? How could dependencies look like?
- X look well-determined. Did not learn much about Y
- I think: Exp. A (B) would tell me more about X (Y) now $\Rightarrow$ Of course I do B!
- 1000s of X, Y. Combinatorial number of possible interactions $\Rightarrow$ Human intuition

Bayesian Framework

- Model design
  Observed, hidden variables. Dependency model
- Posterior uncertainty
  Reduced on X, but not on Y
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  $S(A; \mathrm{Data}) < S(B; \mathrm{Data})$
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Gene Regulatory Networks

- Genes can regulate other genes
  Protein from gene A can be transcription factor:
  up-/down-regulates transcription of gene B.
  Causal link $A \rightarrow B$ in gene regulatory network
- Affordable Measurements
  m-RNA concentrations (micro-arrays), protein concentrations
  $\leftrightarrow$ Expression levels $x_A(t)$, $x_B(t)$
- System Identification
  Interventionist. Disturb system (without breaking it).
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Linearized ODE Model

ODE Model

$$d\boldsymbol{x}(t) = \boldsymbol{f}(\boldsymbol{x}(t))dt + d\boldsymbol{W}(t)$$
$$\mathrm{E}[\boldsymbol{x}(t)] \to \boldsymbol{x}_0 \ (t \to \infty)$$

$\boldsymbol{x}(t)$	Expression levels n genes
$\boldsymbol{f}(\cdot)$	Non-linear model
$\boldsymbol{x}_0$	Unperturbed steady state

1. Linearize around steady state: $\boldsymbol{x}(t) \to \boldsymbol{x}(t) - \boldsymbol{x}_0$.
   System matrix $\boldsymbol{A} = (df_i/dx_{0,j})_{ij}$
2. Disturb system by $\boldsymbol{u}(t) \equiv \boldsymbol{u}_*$, measure new steady state:

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3. Motivates linear model for measurements:

$$\boldsymbol{u}_* = \boldsymbol{A}\boldsymbol{x}_* + \varepsilon, \quad \varepsilon \sim N(\boldsymbol{0}, \sigma^2 \boldsymbol{I})$$

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Bayesian Linear Model

- Likelihood $P(D|\boldsymbol{A}) = \prod_k N(\boldsymbol{u}_k|\boldsymbol{A}\boldsymbol{x}_k, \sigma^2\boldsymbol{I})$. Prior $P(\boldsymbol{A})$

$$\text{Bayesian Posterior :} \quad P(\boldsymbol{A}|D) \propto P(D|\boldsymbol{A})P(\boldsymbol{A})$$

Why not just (penalized) maximum likelihood estimation:

$$\hat{\boldsymbol{A}} = \operatorname{argmax} P(D|\boldsymbol{A})P(\boldsymbol{A}) \ ?$$

- Estimation is not sufficient here
  Optimal design fundamentally needs uncertainty quantification
  $\Rightarrow$ Posterior $P(\boldsymbol{A}|D)$ is just that
- Decisions are needed after many fewer than n experiments.
  $\Rightarrow$ "Objective" classical estimation theory breaks down
- Besides: Is $\boldsymbol{A}$ really completely unknown . . . ?

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A Sparsity Prior Distribution

- All biological regulatory networks are sparsely connected
  $\Rightarrow$ $\boldsymbol{A}$ should have many very small entries
- Encoding sparsity of $\boldsymbol{A}$ is a must!
  $\Rightarrow$ Sparsity-enforcing prior distribution $P(\boldsymbol{A})$

Laplace Prior

$$P(\boldsymbol{A}) = \prod_{ij} P(a_{ij}), \quad P(a_{ij}) = \frac{\tau}{2} e^{-\tau |a_{ij}|}$$

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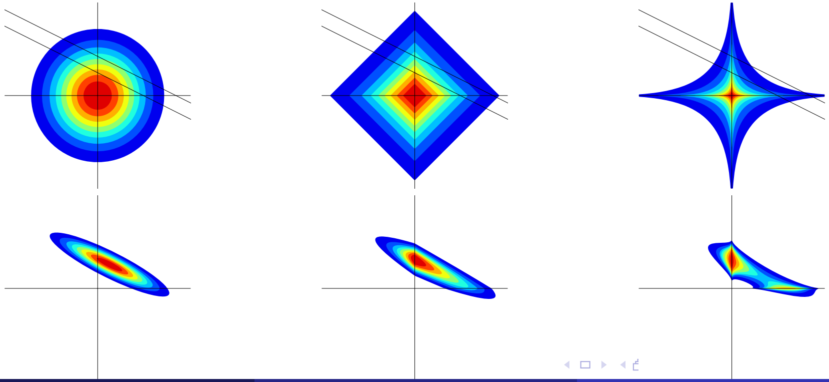

Approximate Inference: Rough Idea

- Bayesian posterior for one row $\boldsymbol{a}$ of $\boldsymbol{A}$

$$P(\boldsymbol{a}|D) \propto P(D|\boldsymbol{a}) \prod_i P(a_i)$$

Hard "just" because $P(a_i)$ are not Gaussian

- Moment matching idea: $P(D|\boldsymbol{a})P(a_i)$ not Gaussian either. Gaussian with same moments have form $P(D|\boldsymbol{a})\tilde{P}(a_i|b_i, \pi_i)$.

$$P(\boldsymbol{a}|D) \approx Q(\boldsymbol{a}) \propto P(D|\boldsymbol{a}) \prod_i \tilde{P}(a_i|b_i, \pi_i)$$

- Expectation Propagation: iterates moment matching over i: Update variational parameters b_i, π_i s.t.:

$$Q_{old}(\boldsymbol{a})P(a_i)/\tilde{P}(a_i) \longleftrightarrow Q_{new}(\boldsymbol{a}) \text{ [same moments]}$$

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$$S(\boldsymbol{u}_*, \boldsymbol{x}_* | D) = \mathrm{D}[Q'(\boldsymbol{A} | D \cup \{(\boldsymbol{u}_*, \boldsymbol{x}_*)\}) \,\|\, Q(\boldsymbol{A} | D)]$$

$\mathrm{D}[Q' \,\|\, Q]$: Information gained in $Q \to Q'$.
Efficient exact computation for Gaussians Q, Q'

- But outcome $\boldsymbol{x}_*$ unknown before experiment $\boldsymbol{u}_*$ done!?
  $\Rightarrow$ Use expected score under current knowledge $Q(\boldsymbol{x}_* | D, \boldsymbol{u}_*)$.
  Exact sampling: $\boldsymbol{A} \sim Q(\cdot | D)$, $\boldsymbol{x}_* = \boldsymbol{A}^{-1}\boldsymbol{u}_*$
- Score many candidates $\boldsymbol{u}_*$ very efficiently:
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Our Approach As Black Box

- Robust, efficient code will be released:
  Predictable running time. Easy to use for non-experts
- Free parameters σ^2, τ:
  Bayesian automatic selection, given related task data
- Applies to time series data just as well (if linear model does)
- Encompasses generalized linear models:
  - Non-Gaussian noise (outliers)
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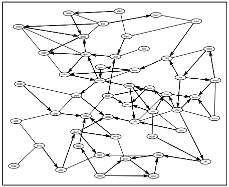
Experimental Setup

Common practice: validate on data from realistic simulation.

- Sample small-world network, $n = 50$ genes



- Model with Hill-type kinetics, parameters randomly drawn (similar to Kholodenko *et.al.*, 02)

$$f_i(\boldsymbol{x}) = -V_{di}\frac{x_i}{d_i + x_i} + V_{si}\prod_{j\in\mathcal{A}_i}\frac{1 + A_{ij}\left(\frac{x_j}{\kappa_{ij}}\right)^{n_{ij}}}{1 + \left(\frac{x_j}{\kappa_{ij}}\right)^{n_{ij}}}\prod_{j\in\mathcal{I}_i}\frac{1}{1 + \left(\frac{x_j}{\kappa_{ij}}\right)^{n_{ij}}}$$

- Pool of 200 $\boldsymbol{u}_*$ (unit norm; 3 non-zeros, sparsity for biological relevance) randomly drawn
- Noise variance σ^2 estimated from simpler random networks. Prior precision τ set by heuristic

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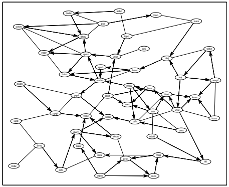

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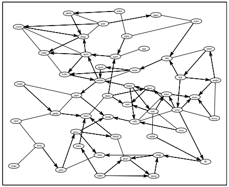

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Decision and Evaluation

- Network from joint posterior $Q(\boldsymbol{A})$?
  Rank edges $i \leftarrow j$ by $Q(\{|a_{ij}| > 0.1\})$
- ROC curve: false positive rate → true positive rate.
  iAUC: area under ROC curve, up to # FPs $=$ # edges.
  Random ranking has iAUC $= 0.02$
- About 25% edges have value ≈ 0 in true $\boldsymbol{A}$ (at steady state), not detectable by linearized model. Excluded from iAUC computation

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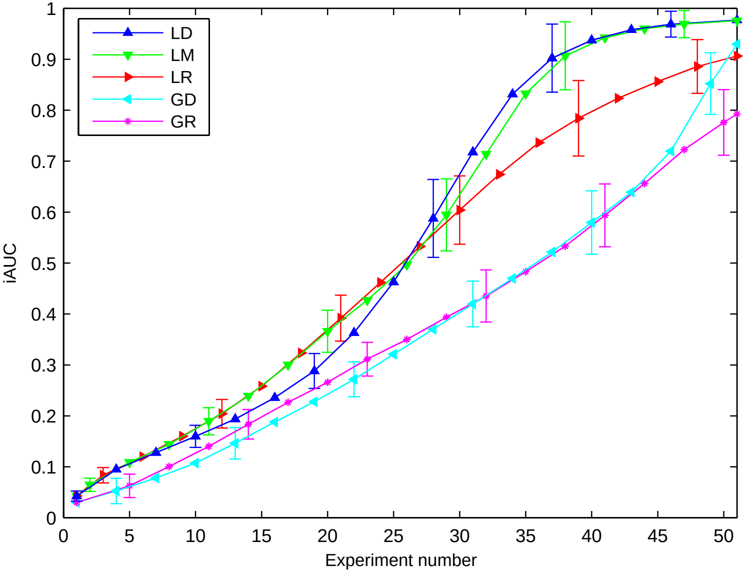
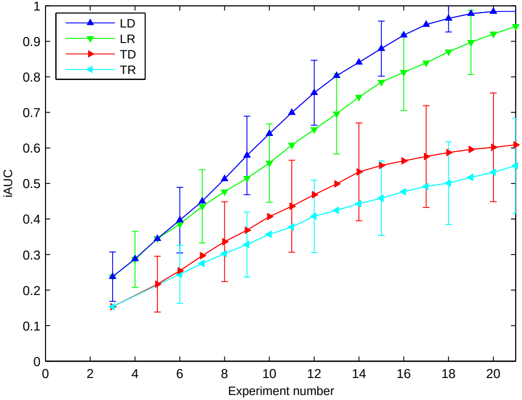
Results


LD
LM
LR
GD
GR
iAUC
Experiment number
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
5
10
15
20
25
30
35
40
45
50

Comparison Tegnér *et.al.*

- Tegnér *et.al.*(PNAS 03): most cited work on experimental design for network identification.
- We do not use quantizations: our method works better and is 2 orders of magnitude faster
- They require node in-degree ≤ 3 (unrealistic in scale-free networks), we do not [comparison done on such graphs]



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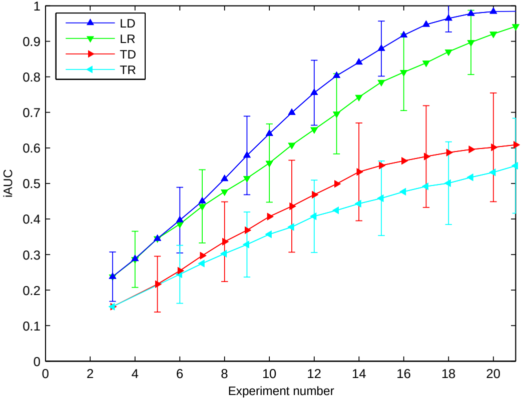

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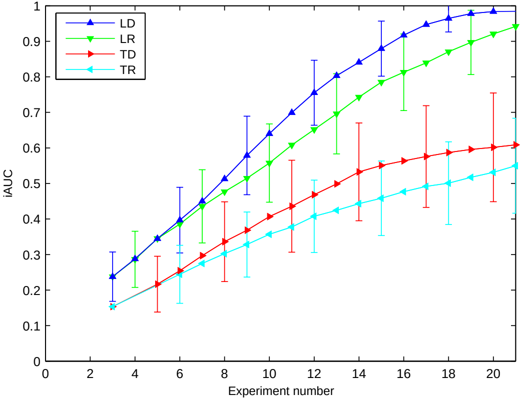

Related Work

- Much work on disturbed linearized ODE models.
  Estimation, no inference, no experimental design (except Tegnér *et.al.*)
- Sparse Bayesian Learning (Tipping, 01; Rogers, Girolami, 05)
  No experimental design. Uses non-log-concave Student-*t* prior.
  EP more general than SBL
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Conclusions

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- Can be used with time-course measurements just as well
- Robust, easy-to-use method. Code with Matlab interface will be released
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Conclusions (II)

- Other applications of sparse (generalized) linear models, in systems biology and beyond (natural image statistics, neural spike coding, adaptive control, *etc*)
- Applications to dynamical or nonparametric models?
- Submitted for journal publication
- Details:
  M. Seeger, F. Steinke, K. Tsuda
  Bayesian Inference and Optimal Design in the Sparse Linear Model, AI and Statistics 2007
  `www.kyb.tuebingen.mpg.de/bs/people/seeger`
- Useful for your work? Do not hesitate to get in touch