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

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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: (#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 Framework

- Model design
  - Observed, hidden variables. Dependency model
  - Posterior uncertainty
    - Reduced on $X$, but not on $Y$
  - Information Gain Scores
    - $S(A; \text{Data}) < S(B; \text{Data})$
    - $\Rightarrow$ OK$>$ Should do $B$
  - Run overnight, sift through raw data, (hopefully) help intuition along

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

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The Need for Experimental Design

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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). Learn structure from changes in measurements

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For given model: Short(est) sequences of experiments leading to identification?
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ODE Model

\[
\begin{align*}
    dx(t) &= f(x(t))dt + dW(t) \\
    E[x(t)] &\to x_0 \ (t \to \infty)
\end{align*}
\]

1. Linearize around steady state: \( x(t) \to x(t) - x_0 \).
2. System matrix \( A = (df_i/dx_{0,j})_{ij} \).
3. Disturb system by \( u(t) \equiv u_* \), measure new steady state:
   \[
   dx(t) = Ax(t) - u(t) + dW(t), \quad x_* = \lim_{t \to \infty} E[x(t)]
   \]
4. Motivates linear model for measurements:
   \[
   u_* = Ax_* + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2 I)
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### Linearized ODE Model

**ODE Model**

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**x(t)** Expression levels \(n\) genes

**f(·)** Non-linear model

**x_0** Unperturbed steady state

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- \( x(t) \) Expression levels \( n \) genes
- \( f(\cdot) \) Non-linear model
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Bayesian Linear Model

- **Likelihood** \( P(D|A) = \prod_k N(u_k|Ax_k, \sigma^2 I) \). Prior \( P(A) \)

  Bayesian Posterior: \( P(A|D) \propto P(D|A)P(A) \)

  Why not just (penalized) maximum likelihood estimation:

  \[ \hat{A} = \text{argmax} \ P(D|A)P(A) \]?

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

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

Laplace Prior

$$P(A) = \prod_{ij} P(a_{ij}), \quad P(a_{ij}) = \frac{\tau}{2} e^{-\tau |a_{ij}|}$$
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Approximate Inference: Rough Idea

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

$$P(\mathbf{a}|\mathbf{D}) \propto P(\mathbf{D}|\mathbf{a}) \prod_i P(\mathbf{a}_i)$$

**Hard “just” because $P(\mathbf{a}_i)$ are not Gaussian**

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

$$P(\mathbf{a}|\mathbf{D}) \approx Q(\mathbf{a}) \propto P(\mathbf{D}|\mathbf{a}) \prod_i \tilde{P}(\mathbf{a}_i|\mathbf{b}_i, \pi_i)$$

- Expectation Propagation: iterates moment matching over $i$:
  Update variational parameters $\mathbf{b}_i, \pi_i$ s.t.:

  $$Q_{old}(\mathbf{a})P(\mathbf{a}_i)/\tilde{P}(\mathbf{a}_i) \leftrightarrow Q_{new}(\mathbf{a})$$ [same moments]
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Sparse Bayesian Linear Model

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Information Gain Score

\[ S(u_*, x_* | D) = D[Q'(A | D \cup \{(u_*, x_*)\}) \| Q(A | D)] \]

\(D[Q' \| Q]\): Information gained in \(Q \rightarrow Q'\).
Efficient exact computation for Gaussians \(Q, Q'\)

- But outcome \(x_*\) unknown before experiment \(u_*\) done!?
  ⇒ Use expected score under current knowledge \(Q(x_* | D, u_*).\)
  Exact sampling: \(A \sim Q(\cdot | D), x_* = A^{-1} u_*\)

- Score many candidates \(u_*\) very efficiently:
  Pick maximizer of \(E_{Q(x_* | D, u_*)}[S(u_*, x_* | D)]\)
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Robust, efficient code will be released:
Predictable running time. Easy to use for non-experts

- Free parameters $\sigma^2$, $\tau$:
  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)
  - Discrete or point process observations
Our Approach As Black Box

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**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)

- Pool of 200 \( u_\ast \) (unit norm; 3 non-zeros, sparsity for biological relevance) randomly drawn

- Noise variance \( \sigma^2 \) estimated from simpler random networks. Prior precision \( \tau \) set by heuristic
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Network from joint posterior $Q(A)$?
Rank edges $i \leftarrow j$ by $Q(\{|a_{ij}| > 0.1\})$

- ROC curve: false positive rate $\rightarrow$ true positive rate.
  iAUC: area under ROC curve, up to # FPs = # edges.
  Random ranking has iAUC = 0.02
- About 25% edges have value $\approx 0$ in true $A$ (at steady state), not detectable by linearized model. Excluded from iAUC computation
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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 $\leq 3$ (unrealistic in scale-free networks), we do not [comparison done on such graphs].
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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
- Markov Chain Monte Carlo (Park, Casella, 05)
  Much slower than our method (too slow for large-scale experimental design). Hard to assess convergence even for experts
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Conclusions

- **Fast accurate** approximate inference, experimental design in disturbed linearized ODE setup
- Network sparsity is key prior assumption. Experimental design can lead to large savings
- Can be used with time-course measurements just as well
- Robust, easy-to-use method. **Code** with Matlab interface will be released
- Linearized ODE approach is limited:
  - Small, controlled $u_*$ to stay in linearity region (experimental techniques?), but large $u_*$ for better SNR
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- Bayesian inference and experimental design for (simple) non-linear ODEs of biochemical kinetics?
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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