A Bayesian active learning strategy for sequential experimental design in systems biology

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Seminar MIA-T, INRA,
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Sequential experimental design for systems biology

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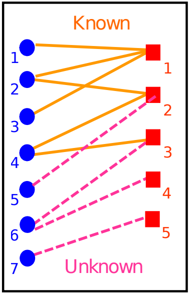

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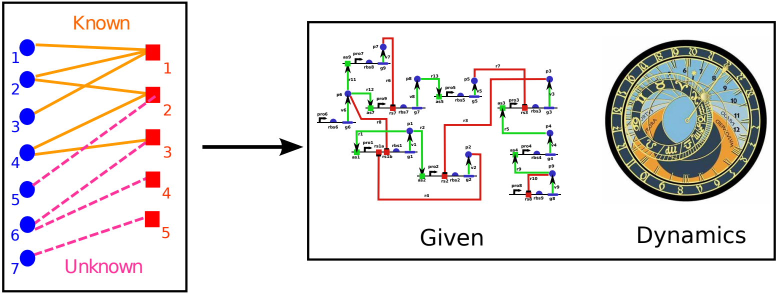

Context

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(regulation, triggering, transport, . . .)

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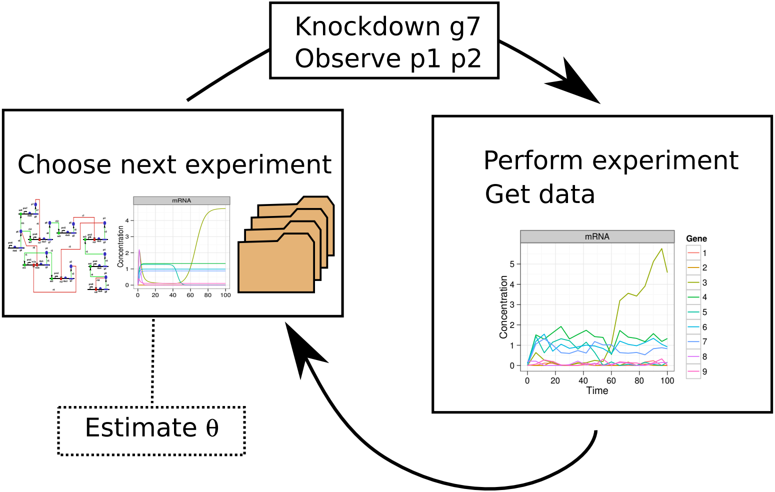
A challenging issue

- Data fit: need to estimate kinetic parameters
- Hard problem: many interacting species
- Dream challenge (IBM, EMBL):
  - simulated data
  - molecular perturbation
  - budget constraint

Context


Knockdown g7
Observe p1 p2
Choose next experiment
mRNA
Concentration
Perform experiment
Get data
mRNA
Concentration
Time
Gene
Estimate θ

Outline

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2. Problem formulation and proposed method

3. Simulation results

Problem set up

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- Model kinetic parameters: $\theta \in \Theta \subseteq \mathbb{R}^p$, unknown θ^*

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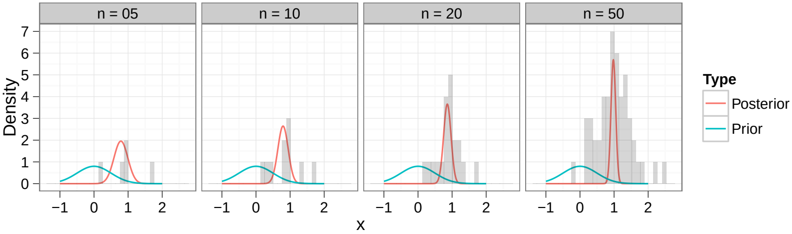
Experimental design: estimate θ^*

- Sequentially choose experiments
- Experimental cost, limited budget

Brief recall on Bayesian update



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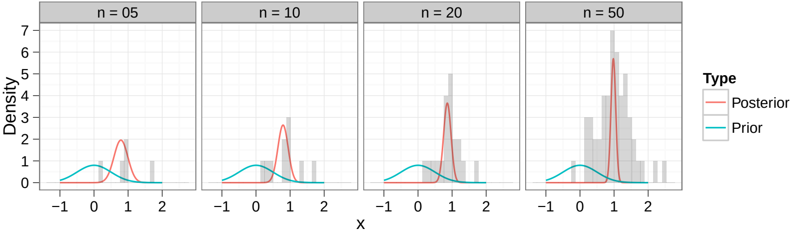

- Bayes rule: prior π, data o from experiments e

$$P(\theta|o;e) = \frac{P(o|\theta;e)\,\pi(\theta)}{\int_{\theta'} P(o|\theta';e)\,\pi(\theta')d\theta'}$$

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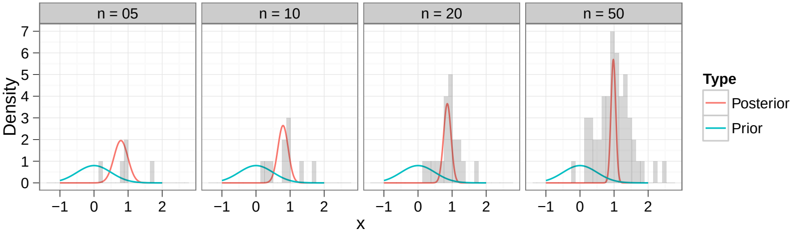

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- Numerical integration

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- average over possible observations

$$E_{o \sim P(o | \theta^*; e)} E_{\theta \sim P(\theta | o; e)} \left[\ell(\theta, \theta^*) \right]$$

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$$E_{o\sim P(o|\theta^*;e)}E_{\theta\sim P(\theta|o;e)}\left[\ell(\theta, \theta^*)\right]$$

- average using current state of knowledge

$$R(e;\pi) = E_{\theta'\sim\pi}E_{o\sim P(o|\theta';e)}E_{\theta\sim P(\theta|o;e)}\left[\ell(\theta, \theta')\right]$$

Main idea

- sequence of posteriors

$$\pi_k(\theta) = \frac{P(o_{k-1}|\theta; e_{k-1})\,\pi_{k-1}(\theta)}{\int_{\theta'} P(o_{k-1}|\theta'; e_{k-1})\,\pi_{k-1}(\theta')d\theta'}$$

- reference risk

$$R(\pi_k) = E_{\theta\sim\pi_k} E_{\theta'\sim\pi_k}\left[\ell(\theta,\theta')\right]$$

- next experiment choice

$$e_{k+1} = \arg\max_{e\in\mathcal{E}} \; \frac{R(\pi_k) - R(e;\pi_k)}{C_e}$$

Numerical evaluation of the $R(e;\pi)$

$$R(e;\pi) = \int_{\theta,\theta'} \ell(\theta,\theta') \int_{o} \frac{P(o|\theta;e)\,\pi(\theta)\,P(o|\theta';e)\,\pi(\theta')}{\int_{\theta''} P(o|\theta'';e)\,\pi(\theta'')d\theta''}\,d\theta\,d\theta'$$

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- draw a sample $\{\theta_i\}_{i=1\ldots N}$ from π;

$$R(e;\pi) \simeq R^N(e;\pi) = \frac{1}{N^2}\sum_{i,j=1}^{N} \ell(\theta_i,\theta_j)\, w_{ij}(e)$$

where $w_{ij}(e) = \int_o \frac{P(o|\theta_i;e)\,P(o|\theta_j;e)}{\sum_{k=1}^{N} P(o|\theta_k;e)}\, do$

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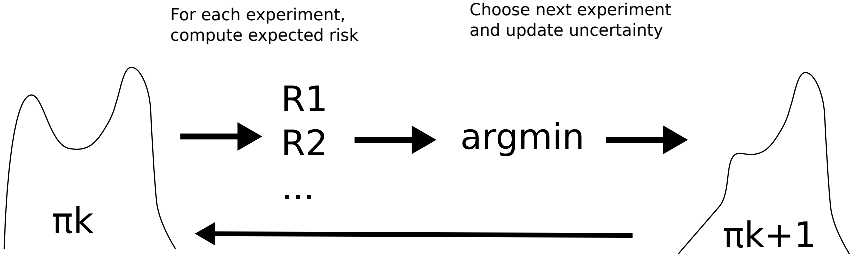
- draw a sample $\{o_u^i\}_{u=1,\cdots,M}$ from each $P(o|\theta_i;e)$

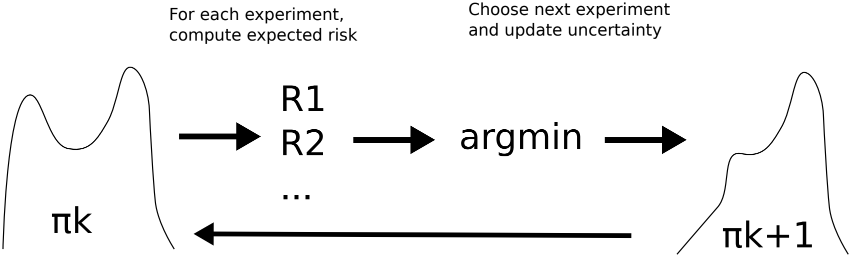
$$w_{ij}(e) \simeq w_{ij}^M(e) = \frac{1}{M}\sum_{u=1}^{M} \frac{P(o_u^i|\theta_j;e)}{\sum_{k=1}^{N} P(o_u^i|\theta_k;e)}$$

Summary


For each experiment,
compute expected risk
Choose next experiment
and update uncertainty
πk
R1
R2
...
argmin
πk+1

Sequential design

Summary



Conceptual advantage

Provides a unique criterion for experimental design

Expectation approximation

Computationally intensive, accuracy difficult to monitor

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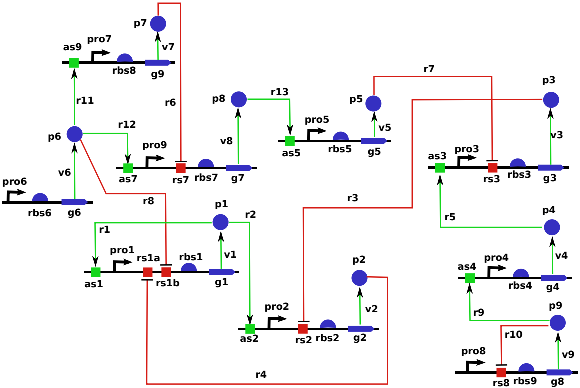
Dream sub-challenge 1



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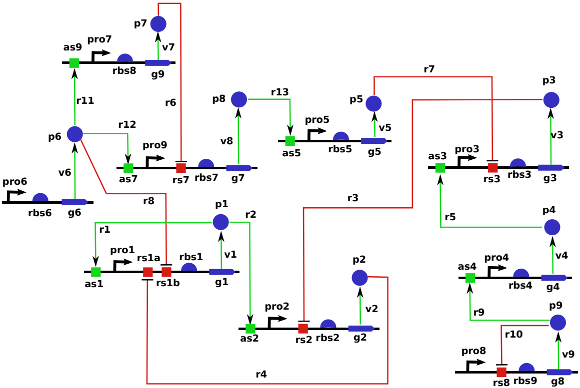


45 kinetic parameters, 9 genes, 18 molecular species

Limited budget

Estimate true kinetic parameter

Estimate concentration time course for an unseen experiment

Exploring the space of parameters

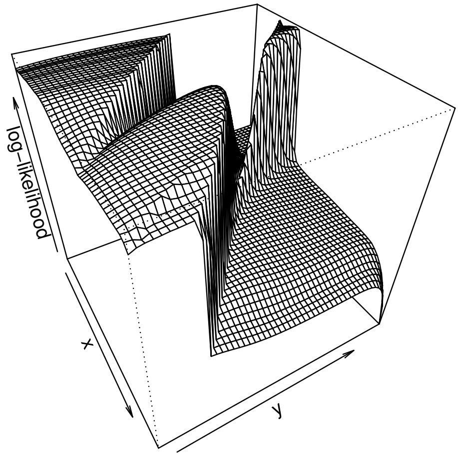
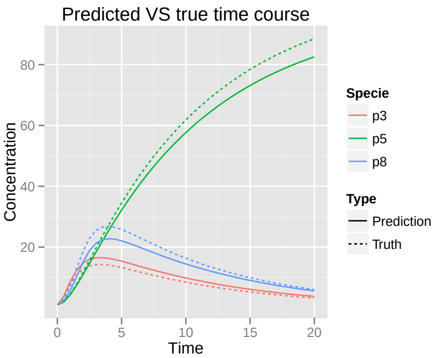


Figure : Posterior surface along a 2D space.

Challenge results

Rank	Dparam	Dprot
1	0.0229	0.0024
2	0.8404	0.0160
3	0.1592	0.0354
4	0.0899	0.0475
5	0.1683	0.0979
6	0.0453	0.1988
7	0.1702	0.3625
8	**0.8128**	**0.3564**
9	0.3766	0.8180
10	0.0699	19.3233
11	0.1883	3.2228
12	5.0278	14.7744



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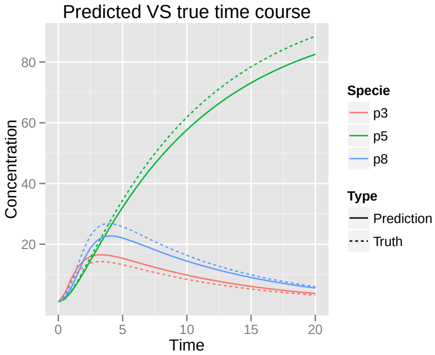

Reproduce global dynamical behaviour

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Winner of dream network parameter inference challenge 6

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Experimental Design for Parameter Estimation of Gene Regulatory Networks

Bernhard Steiert[1,2,3]*, Andreas Raue[1,2.], Jens Timmer[1,2,3,4,5], Clemens Kreutz[1,2.]

1 Institute for Physics, University of Freiburg, Freiburg, Germany, 2 Freiburg Center for Systems Biology, University of Freiburg, Freiburg, Germany, 3 Freiburg Institute for Advanced Studies, University of Freiburg, Freiburg, Germany, 4 BIOSS Centre for Biological Signalling Studies, University of Freiburg, Freiburg, Germany, 5 Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

Table 1. Overview of the criteria that were considered for the final decisions.

Abbreviaton	Detailed explanation
(WT)	Wild-type measurements provide the largest data-points to credits ratio.
(P. mRNA)	Protein data has a better data-points to credits ratio than mRNA data. However, the species to be measured have to be specified and choosing the wrong time-courses can yield only little information gain.
(MA)	For microarray data, there is no decision required about which compounds should be measured. This makes the design more robust. If there are fast processes, high-density time resolution is favorable in comparison to low-density measurements.
(OptPerPL)	Perturbation experiments D are selected as maximally informative based on the PL, if the score R(D) in (13) is optimal.
(GelShift)	Because a single time course data set is not informative enough to resolve the practical non-identifiability, this parameter was measured directly by a gel-shift experiment.
(Module)	The parameters to be bought are in a sub-module of bad estimates and therefore there is hope to improve identifiability of the whole module.
(LocMin)	If several local minima have been detected with similar agreement to the data, designs are chosen which optimally discriminate between the local minima.
(SwitchDyn)	The model shows qualitatively different dynamics and a perturbation is able to switch the model's behavior.
(Extra)	The experiment or the parameter values are important for improving the accuracy of the demanded model extrapolation.
(Budget)	Sometimes, experiments are advantageous because the remaining credits allow a more flexible planning or the budget can be spent more comprehensively.

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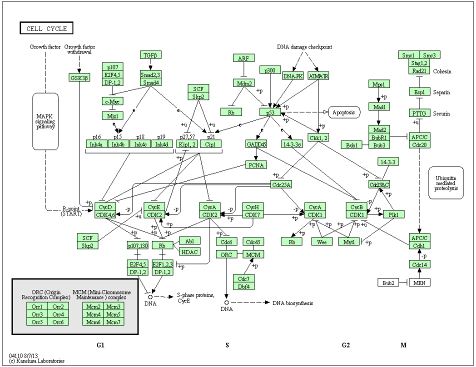
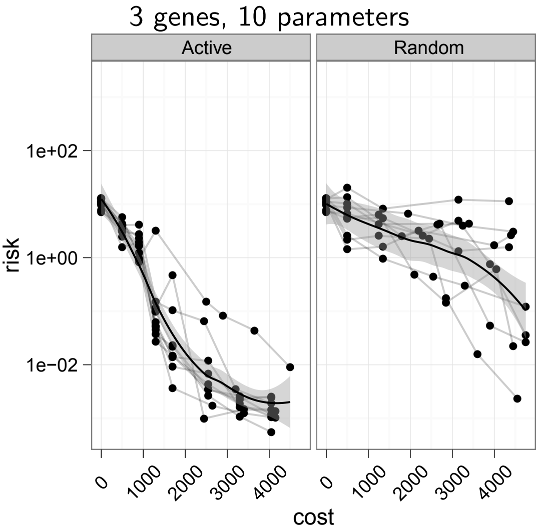
Kegg cell cycle, 124 genes



Simulations on a subnetwork



Estimate a single parameter?

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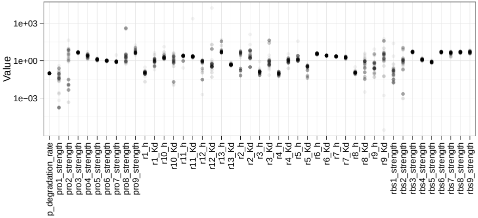

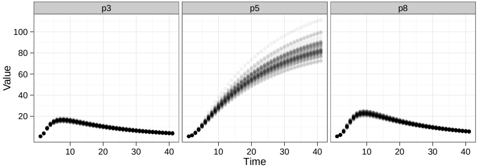

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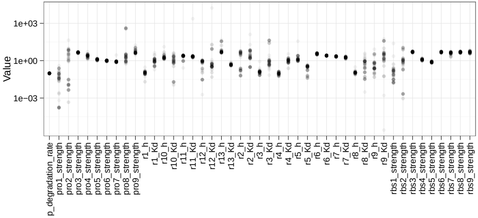

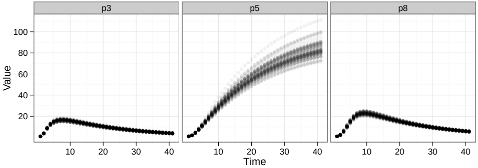

- Already pointed out in the literature
- Mispecified model, stochastic dynamics, real data . . .

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  - Subjectivity, robustness
  - Scale
  - Accessibility to non specialists

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- Computational challenges
  - Numerical integration in high dimensions
  - Uncertainty propagation in dynamical systems

Submition to BMC systems biology
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Many thanks to Christian Lajaunie and Jean-Philippe Vert.

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