LiSyM
Liver Systems Medicine

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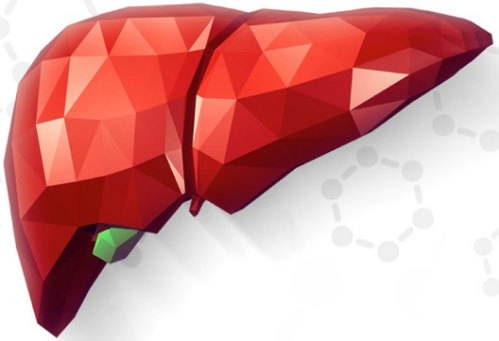
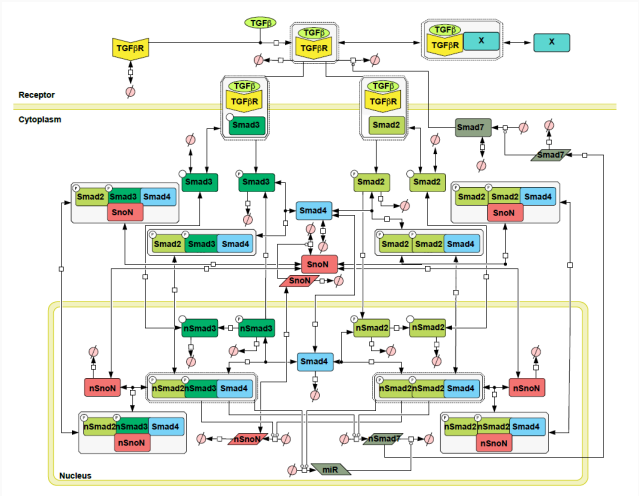
Model-based detection of progression-caused alterations in cellular information processing



First LiSyM Jamboree & SAB Meeting

16 th May 2017 | Jens Timmer | University of Freiburg

Chronic Liver Disease Progression - The Modeller's Perspective



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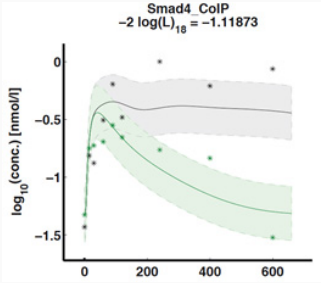
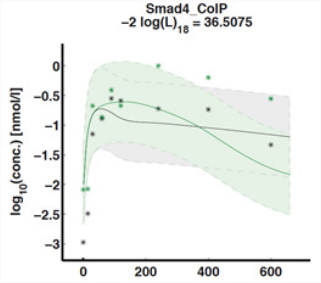
Chronic Liver Disease Progression - The Modeller's Perspective

Same model structure but different behaviors

Primary hepatocytes



Hepa 1-6



Parameter Estimation in Nonlinear, Partially Observed, Noisy, Non-autonomous, Stiff, Sparse Dynamical Systems

Dynamics:

$$\dot{\vec{x}} = \vec{f}(\vec{x}, \vec{p}, \vec{u}), \quad \vec{x}(t_0) = \vec{x}_0 \quad \vec{x} \in \mathbb{R}^n_+$$

Observations:

$$\vec{y}(t_i) = \vec{g}(\vec{x}(t_i), \vec{p}) + \vec{\epsilon}(t_i), \quad \vec{\epsilon}(t_i) \sim N(0, \Sigma_i), \quad \vec{y} \in \mathbb{R}^m_+$$

Negative log-likelihood:

$$\chi^2(\vec{p}, \vec{x}_0) = \sum_{i=1}^{N} \sum_{j=1}^{M} \left(\frac{(y_j^D(t_i) - g_j(\vec{x}(t_i; \vec{p}, \vec{x}_0)}{\sigma_{ij}} \right)^2$$

Parameters fitted on logarithmic scale

Chronic Liver Disease Progression - The Modeller's Perspective

Hypothesis:

Disease progression = Alterations in cellular information processing

Hierarchy of possibilities to reflect this in the models

- Changes in initial values $\vec{x}_0$: Different expression levels of involved proteins
- Changes in kinetic parameters $\vec{p}$: Different expression levels of enzymes, scaffolds or transporters
- Changes in topological structure of pathway $f(.)$: Other proteins involved

All alterations in the model can be related to biology

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Strategy

- Fit models for different stages of disease progression
- Look for differences in initial values, parameters, model structure
- Challenge: Experimental data $\Longrightarrow$ there will always be differences
- Required: A systematic procedure to detect ”real” differences
- Since differences are related to biology:

Model-based functional genomics/proteomics

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Finding the Differences

- Performing a plethora of t-tests is not an option
- Idea:
  For parameter p_i^j at disease stage j write parameter $p_i^{j'}$ at disease stage j' as

$$p_i^{j'} = \tilde{r}_i \, p_i^j$$

  On log-scale:

  $r_i = \log \tilde{r}_i, \quad r_i = 0$ means no difference for parameter p_i between stages j and j'

- Challenge: How to find the real differences

Regularisation

Extend the log-likelihood

$$\chi^2_{k,\lambda} = \chi^2 + \lambda \sum_i |r_i|^k$$

Goal:

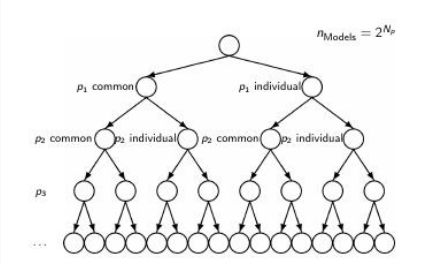
- The statistically minimum number of necessary differences, a sparse solution
- numerically efficient

How to choose k and λ ?

Choosing k

$$\chi^2_{k,\lambda} = \chi^2 + \lambda \sum_i |r_i|^k$$

- $k = 0$: gives sparsity, but NP-hard
- $k = 2$: efficient, but not sparse
- $k = 1$: also sparse, but treatable



A lot of numerical details ...

- Non-differentiable objective function at $r_i = 0$: sub-gradients
- Constrained optimisation: Karush-Kuhn-Tucker criterion
- Uniqueness of reduction: profile likelihood

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Choosing λ

$$\chi^2_{1,\lambda} = \chi^2 + \lambda \sum_i |r_i|^1$$

- Estimate parameters individually for all disease stages from $\chi^2_{1,0}$
- Scan λ from 0 to higher values
- Estimate parameters based on regularised $\chi^2_{1,\lambda}$
- Will lead to increasing number of $r_i = 0$
- Apply likelihood ratio test between $\chi^2_{1,0}$ and $\chi^2_{1,\lambda}$
- If not significant $r_i = 0$ is justified, otherwise: stop
- Use profile likelihood to find out whether reduction is unique

Merkle et al. 2016, PLoS Comput Biol 12(8): e1005049.
Steiert et al. 2016, Bioinformatics 32, 2016, i718-i726

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Summary

- There is still need to develop new modeling techniques in systems medicine
- Since differences in parameters at different disease stages reflect biology
  - understand mechanisms
  - identify biomarkers
  - identify intervention points
- Systems are non-linear: points of maximal differences are not necessarily points of most effective interactions
- It needs the model

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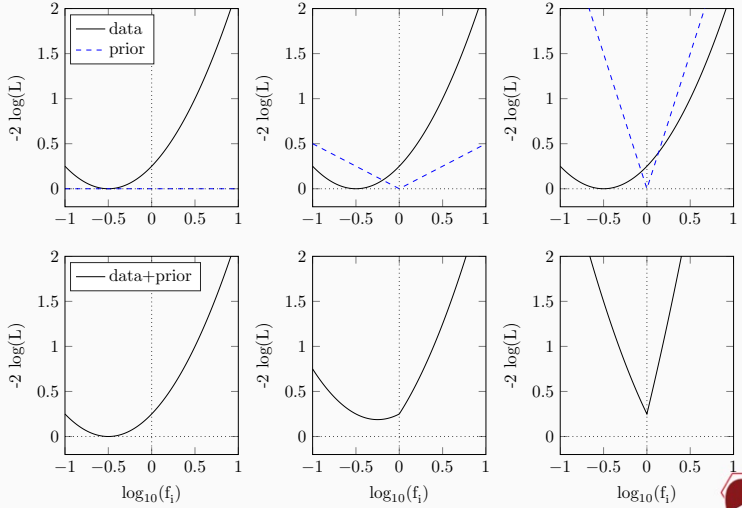
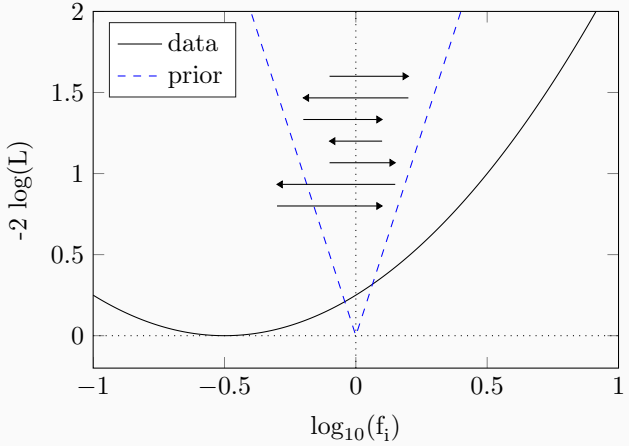
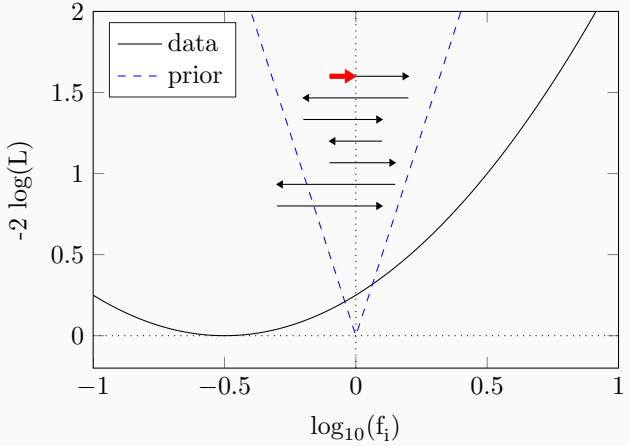
Regularization: example



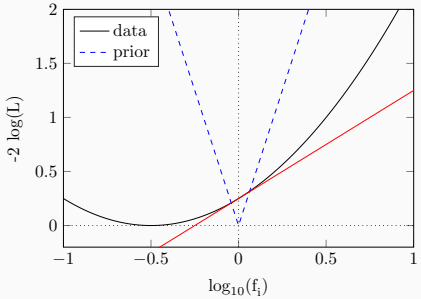
Regularization: step size



Regularization: step size



Regularization: convergence



Karush–Kuhn–Tucker convergence criterion

$$\begin{cases} \nabla_i \chi^2(\hat{p}_i) + \lambda \operatorname{sign}(\hat{p}_i) = 0, & |\hat{p}_i| > 0 \\ |\nabla_i \chi^2(\hat{p}_i)| \leq \lambda, & \hat{p}_i = 0 \end{cases}$$