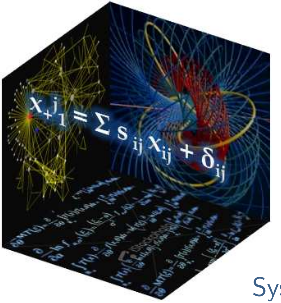
University of Strathclyde Engineering

Parameter Estimation for Kinetic Reaction Networks in Systems Biology



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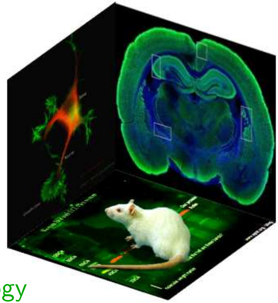
Industrial Control Centre, EEE

20 January 2009

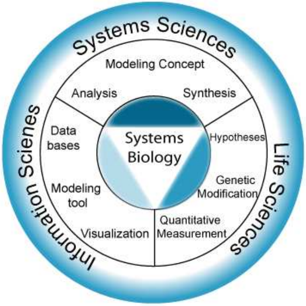


Systems Theory for Systems Biology

Systems Biology Concept

Quantitative, dynamical & spatial Biology
$\Rightarrow$ mathematical modelling

- Main Components
  - Quantitative, dynamical experiments
  - Modelling
  - Model analysis
  - Experiment design
- Integrative Approach: Life sciences, natural sciences, math, engineering



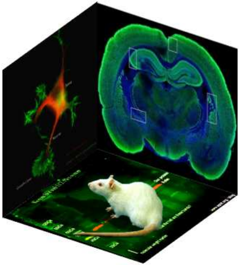
www.sysbio.de

Goal: Better understanding of complex biological systems

Main bottleneck: Experimental quantification

Part I:
Modelling rat behaviour

1. Water maze experiment
2. Random walk model
3. Conclusions

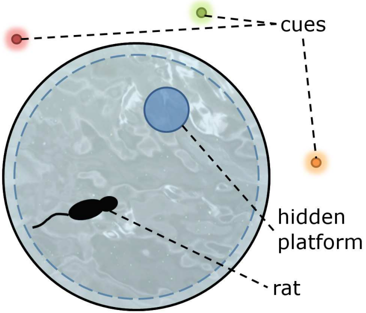


Part II:
Parameter estimation with observer

1. Problem statement
2. Method outline
3. Conclusions

Part I: Modelling rat behaviour

Morris water maze: Study spatial learning and memory



One procedure:

- Rat swims in pool & tries to find the hidden platform.
- Training ⇒ memory
- Performance

study

Different experiments

- Brain regions, neurological pathways
- Disorders, e.g. trauma, Alzheimer, ...
- Drugs, genes & proteins

Introduction to the Morris water maze

Morris water maze: Study spatial learning and memory

Literature: performance only

- Escape latencies
- Time in different areas
- No detailed dynamics

This project: dynamic Model

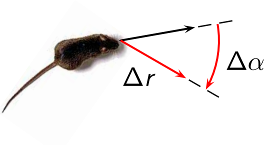
- Search strategies
- Learning protocols
- $\Rightarrow$ Deeper understanding!

(Loading movie)

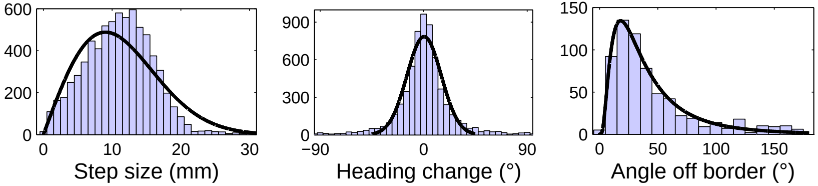
by Jean-Etienne Poirrier,
University of Liège, Belgium

Dynamic model of rat behaviour

Modified random walk model of rat:



Domain	Process	Variable	Distribution
Border	Move forward	Step size	Rayleigh
	Leave border	Likelihood	Constant
		Angle off border	Lognormal
Interior	Move forward	Step size	Rayleigh
	Turn	Heading change	Normal (mean dep. on prev. change)



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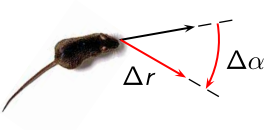
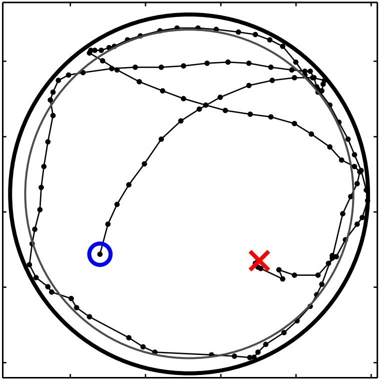
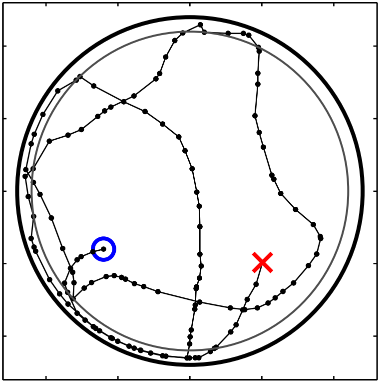


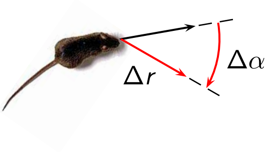


Laboratory rat



Computational model

Summary rat model & outlook

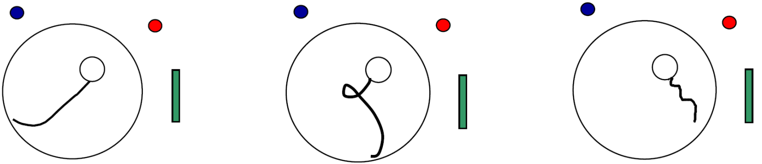


Current model:

- Explains rat movements with random walk

Further model development:

- Search strategies (Approach & stability, turning, scanning)



- Learning protocols (Random vs. determined, mental map)

Understand spatial learning and memory

Experiment: Morris water maze
Theory: Computational model

Part II: Molecular systems biology

"Biology: Life on Earth" ed.5
by Gerald & Teresa Audesirk
Prentice-Hall Inc. 1999

A cell does

- Take in & break down nutrients
- Receive & process signals (e.g. hormones)
- Read and run the genetic code

Interaction of molecular components

- Channels, enzymes, ...
- Receptors, kinases, ...
- Transcription factors, ...

Modelled as systems of biochemical reactions

Reaction kinetic model

Reaction kinetic model:

$$\alpha_1 S_1 + \ldots + \alpha_{n_s} S_{n_s} \xrightarrow{p} \beta_1 P_1 + \ldots + \beta_{n_p} P_{n_p}$$

Dynamic model of biology

- Ordinary differential equations:

$$\dot{c} = Nv(c, p)$$

- Reaction kinetics:

$$v_i = V_i \prod \frac{c_j^{\eta_{ij}}}{K_{ij}^{\eta_{ij}} + c_j^{\eta_{ij}}}$$

Given: structure   Unknown: reaction constants

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?

Given: structure

Unknown: reaction constants

The challenge

Systems biology needs

- Accurate and reliable parameter estimation methods

Technical systems

- High degree of freedom for excitation
- Quasi continuous data
- Linearised and/or discretised
- Accurate methods

Biological systems

- Limited excitation: often step or pulse
- Sparse & noisy data
- Nonlinear, but special: monotone, positive, ...
- Heuristic methods

Systems theory for systems biology?

- Exploit biology specific property

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Parameter estimation method

1. Extend state space $\Longrightarrow$ parameter independent form
2. Design observer $\Longrightarrow$ state estimate of extended trajectory
3. Determine parameters based on above state estimate

$$\begin{tikzcd}
\dot c = Nv(c,p) \arrow[r, "x = \Psi(c,p)"'] & \dot x = f(x) \arrow[r, "z = \Phi(\tilde x)"'] & \dot z = Az + B\phi(z) \arrow[d, dashed, "\text{design}"] \\
 & & \begin{aligned}\dot{\tilde z} &= A\tilde z + B\phi(\tilde z)\\ &\quad + L(\theta)(y-\tilde y)\end{aligned} \arrow[d, dashed, "\textit{estimate}"] \\
p(t) & \tilde x(t) \arrow[l, "p = \Psi^{\mathrm{inv}}(x)"'] & \tilde z(t) \arrow[l, "\tilde x = \Phi^{inv}(z)"']
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design

$$\dot{\tilde{z}} = A\tilde{z} + B\phi(\tilde{z}) + L(\theta)(y - \tilde{y})$$

estimate

$$\tilde{x} = \Phi^{inv}(z) \qquad \tilde{z}(t)$$

1. Extend state space

$$x = \begin{bmatrix} c \\ v \end{bmatrix} \text{ then } \frac{d}{dt}\log(v) \Rightarrow \begin{bmatrix} \dot{c} = Nv \\ \dot{v} \neq \dot{v}(p) \end{bmatrix}$$

- Parameter est. $\rightarrow$ state estimation
- c-dynamics & output linear

Parameter estimation method

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2. Observer: Dynamic system estimating x

Problem: Observability map

$$\Phi(x) = \begin{bmatrix} y_1 & \cdots & y_1^{(r_1)} & \cdots & y_m^{(r_m)} \end{bmatrix}$$

singular ouside manifold $\mathcal{M}: \{x | \dot{p} = 0\}$

Solution: Special observers

- 1. Lie algebraic methods
  - Transform $z = \Phi(x)$ & global inversion of Φ
- 2. Dissipative methods
  - Avoids transformation with $\Phi \Rightarrow$ LMI design

$z = \Phi(\tilde{x})$

$$\dot{z} = Az + B\phi(z)$$

design

$$\dot{\tilde{z}} = A\tilde{z} + B\phi(\tilde{z}) + L(\theta)(y - \tilde{y})$$

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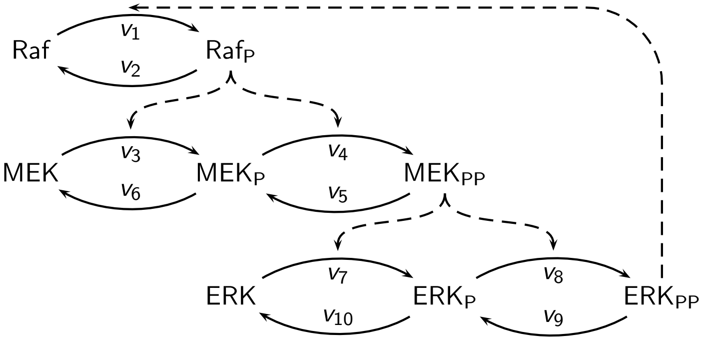
Example: MAP kinase model

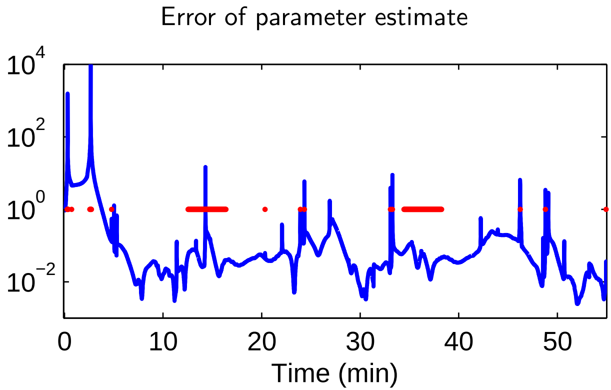
- Important module in signal transduction
  cell growth & differentiation, cell cycle, apoptosis, . . . → cancer
- 8 species, 10 reactions, 21 parameters ⇒ 29 extended states



[Kholodenko, EurJBiochem 267:1583–1588, 2000]

Example: MAP Kinase results

- Accurate parameter estimation: convergence into an ϵ-ball
- Avoid: error peaks where poorly observable (we know where)



Conclusions & Outlook

Advantage

- Optimal & unique solution guaranteed
- Identifiability = observability

Disadvantage

- Dense time course data needed

Challenges

- Noise sensitive $\Longrightarrow$ pre-filtering
- Continuous measurement $\Longrightarrow$ interpolation

Conclusion

- Uses structural information
- Exploits particular nonlinearity of biological systems

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Thanks

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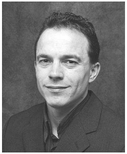

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[1] H. Conzelmann, **D. Fey**, and E. D. Gilles. "Exact model reduction of combinatorial reaction networks". *BMC Systems Biology*, 2:78, 2008.

[2] **D. Fey**, R. Findeisen, and E. Bullinger. "Parameter estimation in kinetic reaction models using nonlinear observers is facilitated by model extensions". In *17th IFAC World Congress, Seoul, Korea*, pages 313–318, 2008.

[3] **D. Fey**, R. Findeisen, and E. Bullinger. "Identification of biochemical reaction networks using a parameter-free coordinate system". In P. A. Iglesias and B. Ingalls, editors, *Control-Theoretic Approaches in Systems Biology*, pages 293–310. MIT press, 2009. in print.

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