FROM PETRI NETS TO PARTIAL DIFFERENTIAL EQUATIONS AND BEYOND

- BIOMODEL ENGINEERING FOR MULTI-SCALE SYSTEMS BIOLOGY -

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OUTLINE

- BACKGROUND
  - modelling, what for?
  - how many model types do we need?
  - some case studies

- FRAMEWORK
  - unifying paradigms: QPN - SPN - CPN

- COLOUR AND MULTI-SCALE SYSTEM
  - replication
  - encoding space

- SUMMARY & OUTLOOK
  - open problems
  - next steps
BACKGROUND
MODELLING = FORMAL KNOWLEDGE REPRESENTATION

- natural biosystem
- observed behaviour
- predicted behaviour
- model-based experiment design
- wetlab experiments
- formalizing understanding
- analysis simulation
- model validation

MODELLING

MODEL VALIDATION = CONFIDENCE INCREASE
MODELLING = FORMAL KNOWLEDGE REPRESENTATION

DESCRIPTIVE

natural biosystem

model-based experiment design

observed behaviour

predicted behaviour

model (knowledge)

analysis simulation

formalizing understanding

wetlab experiments

model validation

PREDICTIVE

EXPLANATORY

MODEL VALIDATION = CONFIDENCE INCREASE
MODELLING = BLUEPRINT FOR SYSTEM CONSTRUCTION

RELIABLE AND ROBUST ENGINEERING REQUIRES VERIFIED MODELS
WHAT KIND OF MODEL SHOULD BE USED?
(BIOCHEMICAL NETWORKS)
\[
\begin{align*}
\frac{d\alpha}{dt} &= -\nu_1 \\
\frac{d\text{Ste}_2}{dt} &= -\nu_2 + \nu_3 - \nu_5 \\
\frac{d\text{Ste}_2\text{active}}{dt} &= \nu_2 - \nu_3 - \nu_4 \\
\frac{d\text{Sst}_2\text{active}}{dt} &= \nu_4 - \nu_47 \\
\frac{dG\alpha\beta\gamma}{dt} &= -\nu_6 + \nu_9 \\
\frac{dG\alpha\text{GTP}}{dt} &= \nu_6 - \nu_7 - \nu_8 \\
\frac{dG\alpha\text{GDP}}{dt} &= \nu_7 + \nu_8 - \nu_9 \\
\frac{dG\beta\gamma}{dt} &= \nu_6 - \nu_9 - \nu_1 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_37 \\
&\quad - \nu_42 + \nu_43 \\
\frac{d\text{Ste}_5}{dt} &= -\nu_12 + \nu_13 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_3 \\
\frac{d\text{Ste}_7}{dt} &= -\nu_1 + \nu_13 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_32 \\
\frac{dG\beta\gamma}{dt} &= -\nu_14 + \nu_15 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_32 \\
\frac{d\text{Fus}_3}{dt} &= -\nu_14 + \nu_15 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_29 \\
\frac{d\text{Ste}_1}{dt} &= -\nu_18 + \nu_19 - \nu_1 + \nu_23 + \nu_27 + \nu_32 \\
\nu_1 &= \alpha[t] \cdot \text{Bar}_1\text{active}[t] \cdot k_1 \\
\nu_2 &= \text{Ste}_2[t] \cdot \alpha[t] \cdot k_2 \\
\nu_3 &= \text{Ste}_2\text{active}[t] \cdot k_3 \\
\nu_4 &= \text{Ste}_2\text{active}[t] \cdot k_4 \\
\nu_5 &= \text{Ste}_2[t] \cdot k_5 \\
\nu_6 &= \text{Ste}_2\text{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6 \\
\nu_7 &= G\alpha\text{GTP}[t] \cdot k_7 \\
\nu_8 &= G\alpha\text{GTP}[t] \cdot \text{Sst}_2\text{active}[t] \cdot k_8 \\
\nu_9 &= G\alpha\text{GDP}[t] \cdot G\beta\gamma[t] \cdot k_9 \\
0 &= \alpha\beta\gamma[t] \cdot C[t] \cdot k_{10} \\
\nu_12 &= \text{Ste}_5[t] \cdot \text{Ste}_1\text{l}[t] \cdot k_{12} \\
\nu_13 &= A[t] \cdot k_{13} \\
\nu_14 &= \text{Ste}_7[t] \cdot \text{Fus}_3[t] \cdot k_{14} \\
\nu_15 &= A[t] \cdot k_{15} \\
\nu_16 &= \alpha[t] \cdot C[t] \cdot k_{16} \\
\nu_17 &= C[t] \cdot k_{17} \\
\nu_18 &= D[t] \cdot \text{Ste}_20[t] \cdot k_{18}
\end{align*}
\]
BIO NETWORKS, SOME PROBLEMS

- knowledge
  - uncertain
  - growing, changing
  - distributed over independent data bases, papers, journals, . . .

- various, mostly ambiguous representations
  - verbose descriptions
  - diverse graphical representations
  - contradictory and / or fuzzy statements

- network structure
  - tend to grow fast
  - dense, apparently unstructured
  - hard to read

MODELS ARE PATCHWORKS FULL OF ASSUMPTIONS
**Bio Network Representations Should be**

- **Readable & unambiguous**
  - \( \Rightarrow \text{fault avoidant model construction} \)

- **Various abstraction levels**

- **Locality - causality - concurrency**

- **Compositional**

- **Executable**
  - \( \Rightarrow \text{to experience the model, spec. causality} \)

- **Analysable, with unifying power**
  - \( \Rightarrow \text{formal = mathematical representations} \)
  - \( \Rightarrow \text{high-level description for various analysis approaches} \)

- **As simple as possible**
  - \( \Rightarrow \text{how many model types do we need} \)
MODELLING = ABSTRACTION

- hierarchical organisation of components -> model variables
  - genes, molecules, organelles, cells, tissues, organs, organisms

- functionality of atomic events
  - chemical reactions with/out stoichiometry, conformational change, transport, . . .

- time
  - qualitative versus quantitative models

- individual vs population behaviour

- (hierarchical) space

- observables

- shape and volume of components

- biosystem development
Bio Networks

.. .

Are networks of biochemical reactions

.. .

Naturally expressible as Petri nets

\[ 2 \text{NAD}^+ + 2 \text{H}_2\text{O} \rightarrow 2 \text{NADH} + 2 \text{H}^+ + \text{O}_2 \]
PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

- places -> model variables
  -> (bio-) chemical compounds
  -> proteins
  -> protein conformations
  -> complexes
  -> genes, ... etc.
  ... in different locations

- transitions -> atomic events
  -> (stoichiometric) chemical reaction
  -> complexation / decomplexation
  -> phosphorylation / dephosphorylation
  -> conformational change
  -> transport step, ... etc.
  ... in different locations
BIO PETRI NETS - SOME EXAMPLES
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]

[Koch, Heiner 2010]
Ex2 - Apoptosis in Mammalian Cells

[GON 2003]

[HEINER, KOCH, WILL 2004]
[Gilbert, Heiner, Ross, Fulton, Gu, Trybiolo 2008]
[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILIO 2008]
One pathway

Mitogens
Growth factors

receptor

Ras

Raf

MEK

ERK

cytoplasmic substrates

Elk
SAP

Gene
EX4 - RKIP SIGNALLING PATHWAY

[Cho et al. 2003]
Ex4 - RKIP Signalling Pathway, Petri Net

\[ mi \rightarrow si \]

\[
\begin{align*}
  & \text{Raf-1Star} & \text{RKIP} \\
  & s1 & s2 \\
  & k1 & k2 \\
  & \text{ERK-PP} & \\
  & s9 \\
  & k8 \\
  & \text{MEK-PP} & \text{RKIP-P} \\
  & s8 & s11 \\
  & k6 & k9 \\
  & \text{MEK-PP}_{\text{ERK}} & \text{RKIP-P}_{\text{RP}} \\
  & s7 & s10 \\
  & k7 & k10 \\
  & \text{ERK} & \text{RP} \\
  & s5 & s10 \\
  & k5 \\
  & \text{Raf-1Star}_{\text{RKIP} \text{ERK-PP}} \\
  & s3 & s4 \\
  & k3 & k4 \\
  & \text{MEK-PP}_{\text{ERK}} \\
  & s8 \\
  & k6 \\
  & \text{MEK-PP} \\
  & s7 \\
\end{align*}
\]

[Heiner, Gilbert 2006]

[Heiner, Donaldson, Gilbert 2010]
Ex4 - RKIP Signalling Pathway, Hierarchical Petri Net

[Heiner, Gilbert 2006]
[Heiner, Donaldson, Gilbert 2010]
EX5 - SIGNALLING CASCADE

RasGTP

Raf

RafP

Phosphatase1

MEK

MEKP

MEKPP

Phosphatase2

ERK

ERKP

ERKPP

Phosphatase3
EX5 - SIGNALLING CASCADE

[GILBERT, HEINER, LEHRACK 2007]

[HEINER, GILBERT, DONALDSON 2008]
Ex6 - *Halobacterium Salinarum*

[Marwan, Oesterhelt 1999]
Ex7 - Pain Signalling


Modules: 38
Places: 713
Transitions: 775
Pages: 325
Nesting depth: 4
THE FRAMEWORK
CRUCIAL POINT

STATE-DEPENDENT RATE FUNCTION

LAMBDA OF EXPONENTIAL WAITING TIME

CTMC

STRENGTH OF CONTINUOUS FLOW

ODEs

-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

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March 2012
KEY IDEA

MODELS SHARING STRUCTURE

QUANTITATIVE MODEL = QUALITATIVE MODEL + RATE FUNCTIONS (KINETICS)
**FRAMEWORK 2010**

**QUALITATIVE**

- **LTS / PO**
  - **CTL, LTL**

**STOCHASTIC**

- **CTMC**
  - **CSL, PLTLc**

**HYBRID**

- Approximation

**CONTINUOUS**

- **ODEs**
  - **PLTLc**

- **time-free**
- **timed, quantitative**

- Abstraction
- Extension

**continuous state space**

**discrete state space**
ABOUT THE RELATION
STOCHASTIC VS CONTINUOUS
STOCHASTIC SIMULATION

Stochastic Output – 1 Level

Time (s)

Concentration (Levels)
STOCHASTIC SIMULATION

Stochastic Output – 10 Levels

Concentration (Levels)

Time (s)
Stochastic Simulation - 100 Levels

Concentration (Levels)

Time (s)
Deterministic Simulation

Deterministic Output

Concentration (µMol)

Time (s)
ABOUT THE RELATION
QUALITATIVE VS CONTINUOUS
EX7 - HYPOXIA

[YU ET AL. 2007]
Ex7 - HYPOXIA

(a) $O_2$

(b) $k_5, k_6, k_{29}, k_{30}$

(c) $(b) + k_{19}$

(d) $(c) + k_{16}$

(e) $(d) + k_{13}$

(f) $(e) + k_{13}$
Ex7 - HYPOXIA
COLOURED FRAMEWORK 2011

LTS / PO
CTL, LTL

QUALITATIVE

COLOURED

STOCHASTIC

CTMC
CTMC

CSL, PLTLc
CSL, PLTLc

HYBRID

approximation

COLOURED

CONTINUOUS

ODEs
ODEs

PLTLc
PLTLc

continuous state space

discrete state space

time-free

timed, quantitative

abstraction

extension

approximation

abstraction

extension
COLOUR -
WHAT FOR?
**Ex1: Prey - Predator**

**Sub-system 1**
- **Reproduction of Prey**
  - Prey 1
  - Prey 2
- **Predator Death**
  - Predator 1
  - Predator 2
- **Consumption of Prey**
  - 2

**Sub-system 2**
- **Reproduction of Prey**
  - Prey 1
  - Prey 2
- **Predator Death**
  - Predator 1
  - Predator 2
- **Consumption of Prey**
  - 2

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March 2012
**Ex1: Prey - Predator**

- **definitions**
  
  ```
  colourset CS = 1-2;
  var x : CS;
  ```

- **better:**
  
  ```
  const SIZE = 2;
  colourset CS = 1-SIZE;
  var x : CS;
  ```

- **changing SIZE adapts the model to various scenarious**
Ex2 - C. Elegans

[Li et al. 2009]
[Bonzanni et al. 2009]
**Ex3 - Halobacterium Salinarum**

[Marwan 2010]

- **Cluster type 1/2:** 400/850
- **Places:** 12,426
- **Transitions:** 16,577
- **Unfolding:** 6 sec
- **Stoch. simulation:** 10-15h

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Methylation site 2

CheY binding site

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March 2012
Ex4: Diffusion - 1D

cAMP_1

\[ t_{1\_1\_2} \]

cAMP_2

\[ t_{1\_2\_3} \]

cAMP_3

\[ t_{1\_3\_4} \]

cAMP_4

\[ t_{1\_4\_5} \]
**Ex4: Diffusion - 1D**

- **definitions**
  - `const D1 = 5; // grid size`
  - `colorset CS = 1-D1; // grid positions`
  - `var x, y : CS;`

- **function** `neighbour1D (CS x, a) bool:`
  - // a is neighbour of x
  - `(a=x-1 | a=x+1) & (1<=a) & (a<=D1);`

```plaintext
[neighbour1D(x,y)]
```

Diagram:
- Node `t1` with variable `x` and edge labeled `100` connecting to node with `100`.
- Node labeled `CS` connecting to `t1` with edge labeled `y`.
**Ex4: Diffusion - 1D, ODEs**

\[
\begin{align*}
\frac{dc_1}{dt} &= k \cdot c_2 - k \cdot c_1 \\
\frac{dc_2}{dt} &= k \cdot c_1 + k \cdot c_3 - 2 \cdot k \cdot c_2 \\
\frac{dc_3}{dt} &= k \cdot c_2 + k \cdot c_4 - 2 \cdot k \cdot c_3 \\
\frac{dc_4}{dt} &= k \cdot c_3 + k \cdot c_5 - 2 \cdot k \cdot c_4 \\
\frac{dc_5}{dt} &= k \cdot c_4 - k \cdot c_5
\end{align*}
\]
Ex4: Diffusion - 1D

15 Grid Positions
Ex4: Diffusion - 1D

150 Grid Positions, no scaling
**Ex4: Diffusion - 1D**

150 Grid Positions, Scaling of Initial Marking and Rates
Ex4: Diffusion - 2D4 Neighbourhood

Scheme
Ex4: Diffusion - 2D8 Neighbourhood

Scheme
Ex4: Diffusion - 2D

- Scheme

- Definitions

  ```
  const D1 = 5; // grid size first dimension
  const D2 = 5; // grid size second dimension
  colorset CD1 = 1-D1; // row index
  colorset CD2 = 1-D2; // column index
  colorset Grid2D = CD1 x CD2; // 2D grid
  
  var x, a : CD1;
  var y, b : CD2;
  ```
**Ex4: Diffusion - 2D4 Neighbourhood**

- **four neighbours**

  ```
  function neighbour2D4 (CD1 x, CD2 y, CD1 a, CD2 b) bool:
  // (a,b) is one of the up to four neighbours of (x,y)
  (a=x & b=y-1) | (a=x & b=y+1)
  | (b=y & a=x-1) | (b=y & a=x+1);
  ```

![Diagram of the neighbour2D4 function with cAMP and Grid2D nodes connected by edges labeled with (x,y) and (a,b).]
- eight neighbours

  function neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b) bool:

  // (a,b) is one of the up to eight neighbours of (x,y)
  (a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)
  & !(a=x & b=y))
  & (1<=a & a<=D1) & (1<=b & b<=D2);

```
[neighbour2D8(x,y,a,b)]

(x,y) 100

Grid2D 100`(3,3) cAMP

(a,b)
t1
```
Ex4: Diffusion - 2D8 Neighbourhood
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000000' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000006' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000010' matrix
**Ex4: Diffusion - 2D4 Neighbourhood, 15x15**

`'data.dat.00000015' matrix`
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15x15

'data.dat.00000020' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000030' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000040' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 15x15

'data.dat.00000050' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 30x30

'data.dat.00000050' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 60x60

'data.dat.00000050' matrix
Ex4: Diffusion - 2D4 Neighbourhood, 120x120

'data.dat.00000050' matrix
EX5 - PLANAR CELL POLARITY

[BioPPN 2011]
[CMSB 2011]
Ex5 - Planar Cell Polarity
Ex5 - Planar Cell Polarity

grid size: 40 x 40
PLACES: 164,000
TRANSITIONS: 229,686
unfolding: 2 min
cont. simulation: 2 h

[BioPPN 2011]
[CMSB 2011]
Ex6 - Mobility / Motility

-> Gradients

[Dagstuhl 2011]
get multiple copies of patterns
   -> Halo model, new order of net sizes

encode locality
   -> Ca channel models
   -> cell tissue + communication between cells
   -> motility, gradients, . . .

dynamic membrane systems

differentiate between submodels within a master net
   -> T-invariants
   -> generated models in conformance with wet-lab data
   -> mutants
   -> algorithmic folding

...
SUMMARY
& OUTLOOK
**Modelling = Abstraction**

- hierarchical organisation of components -> model variables
  
  genes, molecules, organelles, cells, tissues, organs, organisms

- functionality of atomic events
  
  chemical reactions with/out stoichiometry, conformational change, transport, . . .

- time
  
  qualitative versus quantitative models

- individual vs population behaviour

- (hierarchical) space

- observables

- shape and volume of components

- biosystem development
MULTI-SCALE CHALLENGES

- repetition ... of components
- variation
- spacial organisation
- hierarchical organisation
- communication
- mobility / motility
- replication / deletion
- pattern formation
- differentiation
- semi-regular/irregular/dynamic organisation
How dynamic has a model to be?

Modification over time may include:

- addition/subtraction of model components
- rewiring yielding new structures
- parameter modification (e.g. triggered by mutation)
- model translocation (model passing, nets in nets)
- reorganizing the hierarchical structure, adding, removing levels
SUMMARY

- representation of bio networks by Petri nets
  - partial order representation
  - formal semantics
  - unifying view
  - better comprehension
  - sound analysis techniques

- purposes
  - animation
  - model validation against consistency criteria
  - to experience the model
  - to increase confidence
  - qualitative / quantitative behaviour prediction
  - experiment design, new insights

- step-wise model development
  - qualitative model
  - discrete quantitative model
  - continuous quantitative model
  - discrete Petri nets
  - stochastic Petri nets
  - continuous Petri nets = ODEs, hybrid models
  - locality and space
  - coloured Petri nets
OUTLOOK

THANKS!

HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE