BioPPN Workshop, 20 June 2011

Pain Signaling - A Case Study of the Modular Petri Net Modeling Concept with Prospect to a Protein-Oriented Modeling Platform

Mary Ann Blätke, Sonja Meyer, Wolfgang Marwan
Motivations
Motivation

- Monolithic pathway models are not always easy to handle
  - Hard to maintain, update and curate
  - Coupling of different pathway models is far from trivial

⇒ Our Idea: Modular representation of proteins with a defined connection interface
Motivation

- ODEs are not always the best choice (see also Ref. [2])
  - Difficult analysis of topological network properties
  - Mathematical structure hides biological information
  - Transformation into a reaction network is not unique
  - Difficult to understand for “wet-lab” biologists

\[ \Rightarrow \text{Our Idea: Using the power of Petri nets to Model Molecular Networks} \]
Modular Petri net Modeling Concept
Network Structure of a Module and Properties

- Domain–related representation of a protein, its interactions and intermolecular changes by a Petri net

1.) Literature Research

2.) Translation into a PN

[Kim et al., 2007]
Network Structure of a Module and Properties

- Domain–related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non–protein)
  - Transitions – Shifts between different states
  - Principle of double–entry bookkeeping → shared copies of identical subnets among interacting protein

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Network Structure of a Module and Properties

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- Domain–related representation of a protein, its interactions and intermolecular changes by a Petri net
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  - Principle of double–entry bookkeeping –> shared copies of identical subnets among interacting protein

⇒ A module is a comprehensive “review article” about a protein in the form of a Petri net

2.) Translation into a PN

[Kim et al., 2007]
Validation of a Module

- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non-protein)
  - Transitions – Shifts between different states
  - Principle of double-entry bookkeeping ➔ shared copies of identical subnets among interacting protein

Validation of each module by topological Properties of a Petri net and simulation studies

1.) Literature Research
2.) Translation into a PN
Validation of a Module

Properties

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**Covered with P-INv:**
- Set of all possible states of a domain of the module-protein, an interactive protein or of the non-protein

**Stochastic simulation studies**
- Dynamic behavior of the modules has to reflect the assigned function of the protein
Generation of a Modular Network

- Generation of a modular network from a set of modules
- Identical copies of subnets and places of non-proteins build the connection interface among the modules

Valid Modular Network
Properties of the Modular Network

- Modules:

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- Modular network:

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must not be fulfilled ⇒ 1:1 Transfer

variable ⇒ Determined by the intersection of the modules

must be fulfilled ⇒ 1:1 Transfer
Case Study – Pain Signaling
Pain Signaling

- Serious clinical and public health issues
- No sufficient mechanism-based pain therapy
- Complex and diverse molecular mechanisms of parallel, convergent and concurrent processes
- But: Molecular processes are not very well understood
Pain Signaling

- Serious clinical and public health issues
- No sufficient mechanism-based pain therapy
- Complex and diverse molecular mechanisms of parallel, convergent and concurrent processes
- But: Molecular processes are not very well understood

⇒ Modeling Pain Signaling is a Challenging (and Painful) Process
Modules

- 38 Modules based on literature
  - Enzymes (PKA, PKC, AC etc.)
  - Receptors (GPCRs)
  - Ca(2+)–Channels
  - Etc.

- Validated by:
  - Structural analysis
  - Simulation studies

- All modules are valid!

Literature

320 scientific articles
Example: mueOR + Gi–Protein
Example: mueOR + Gi-Protein

Diagram showing the interaction between morphine and the opioid receptor, involving Gi-Protein and the binding of GDP and GTP.
Other Examples: Protein kinase A
Other Examples: TRPV1 – Ion–Channel
Top-Level of the Nociceptive Network

The nociceptive network is valid!
Top-Level of the Nociceptive Network

⇒ The nociceptive network is valid!

Predicted properties have been confirmed by structural analysis

Modules: 38
Places: 713
Transitions: 775
Pages: 325
Nesting Depth: 4
Conclusion and Outlook
Advantages

- Modules are...
  - interactive reviews of spread information about a protein
  - easy to update, to extend,
  - to couple by identical matching subnets => straight forward generation of modular networks
  - reusable in other networks
- Extend the modular core network with gene expression, degradation, translocation modules…
Outlook: “Pain Model”

- Identification of possible targets for therapeutic intervention strategies
  - Completion
  - Parameterization and Validation
  - Stochastic Simulation studies
  - Extension to colored Petri nets to represent multiple copies of Proteins and DRG neuron populations
Outlook: Modular Modeling Concept

- Network reconstruction coupled with modular modeling concept
- Advanced analysis of structural motifs
- Other case studies: pain signaling, EGF pathway...

[Heinrich et al., 2003]
Outlook: Modular Modeling Concept

Modeling platform for protein modules:

- Organization of the modules
- Module + data set offering detailed information
- Strict naming convention
- Automatic generation of modular networks from a set of approved curated modules
  - Iterative search of coupling partners
  - Pathway oriented suggestion using tags
Acknowledgement

- Supervisor: Wolfgang Marwan
- Software-/ Petri Net Support: Monika Heiner + Co-workers
- Biological Expertise: MOPS Consortia
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Petri Net Tutorial

Scaling up from single molecules to multicellular systems: modelling over time and space with advanced Petri net techniques

Molecular Signaling Network

Multicellular Organisms

Spatiotemporal Cell Motility and Gradient Formation

At 12th International Conference on Systems Biology (ICSB 2011), Heidelberg

27./28. August 2011

Organized by Monika Heiner, David Gilbert and Mary Ann Blätke

Schedule
Saturday, August 27, 2011:
14.30 - 19.00 h - Foundations of Advanced Petri Nets
Sunday, August 28, 2011:
9.00 - 13.30 h - Further Advanced Petri Net Techniques and Applications

Registration:
www.icsb-2011.net

Contact/Information:
mary-ann.blatke@ovgu.de
http://www-dsz.informatik.tu-cottbus.de/BME/ICSB2011
www.icsb-2011.net
THANK YOU

www.ovgu.de

Bundesministerium für Bildung und Forschung

MaCS

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Interaction Matrix

Protein Module Database

SEARCH FOR MODULE
GENERATE NETWORK

Interaction Matrix in the Background of the Database

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Iterative Search of Coupling Partners

1.) Search Interacting Proteins

Method: Iterative Network Generation
1. Stringency: Human
2. Start-Protein: ADCY5

2. Iteration

1. Iteration
- OPRD1
- GNAI1
- OPRK1
- OPRM1

Start-Protein
- GNAs1
- PRKCA
- PRKCZ
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- TRPV1

2. Iteration

3. Iteration

2.) List of Interacting Proteins

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3.) Export of the Generated Network