PETRI NET TUTORIAL – PART 1:

BIOMODEL ENGINEERING VIA MODULAR, PROTEIN-ORIENTED MODELING

MARY ANN BLÄTKE

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BIOMODEL ENGINEERING VIA MODULAR, PROTEIN-ORIENTED MODELLING

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

⇒ Our Idea: Using the power of Petri nets to model molecular networks [Heiner et al., 2010]
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MODULAR PETRI NET MODELING CONCEPT
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]
**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 proteins

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1.) Literature Research

2.) Translation into a PN

[Kim et al., 2007]
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

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

1.) Literature Research
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)
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_validation of each module by topological properties of a Petri net and simulation studies_
# 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 proteins
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

Indicate identical subnets as logical subnets
Wrap every module in a macro place
Insert all modules in one Petri net

Valid Modular Network

Recheck of the modular network
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

[Heinrich et al., 2003]
# Properties of the Modular Network

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- **TRANSFER** must not be fulfilled \(\Rightarrow\) **1:1 Transfer**
- **variable** \(\Rightarrow\) **Determined by the intersection of the modules**
- **must be fulfilled** \(\Rightarrow\) **1:1 Transfer**

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CASE STUDY - JAK-STAT PATHWAY...
BIOMOLECULAR NETWORK

- Main Components: Receptor, JAK, STAT
  - Receptor – Il6-Receptor (here)
  - JAK – Janus- Kinase
  - STAT – Signal Transducer and Activator of Transcription

- Inflammation and the immune response, haematopoiesis, liver and neuronal regeneration, embryonal development and fertility...

[Heinrich et al., 2003]
MODULAR MODEL

[Heinrich et al., 2003]
MODEL DIMENSION

- Protein modules: 7
- Extension:
  - 1x degradation module,
  - 1 x gene expression module
- Places: 92
- Transition: 102
- Edges: 487
- Pages: 58
- Nesting Depth: 4
LIVE DEMONSTRATION
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: 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: DATABASE 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

Web-Database
OUTLOOK: DATABASE CONCEPT

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. Interaction
     1. Interaction
       GNAI1
       OPRK1
       OPRM1
     Start-Protein
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     PRKCA
     ... 
     3. Interaction
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     TRPV1
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3.) Export of the Generated Network

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