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A DATABASE-SUPPORTED MODULAR MODELLING PLATFORM FOR SYSTEMS AND SYNTHETIC BIOLOGY

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OUTLINE

• Conceptual Thoughts...

• Proof of Principle: JAK-STAT...

• More Than Organizing Modules...

• Sneak Peak & Summary...
Conceptual Thoughts...
PROBLEMS IN SYSTEMS BIOLOGY

How to...

- Integrate different network types?
- Keep models scalable?
- Add spatial aspects to a model?
- Keep things user friendly?
- Handle monolithic models?
- Integrate growing amounts of data?
FOUNDATION OF OUR CONCEPT

Modules
• Stick to natural building-blocks
• Manageable and handy in size
• Easy to update, maintain, curate
  • Reusable, recombinable

Petri Nets
• Formal language and unifying framework
  • Strict syntax
  • Easy and intuitive modelling
  • Scalable (coloured PN)
  • Powerful tools

Database
• Organization of modules
• Easy handling of meta-data
• Public access
FOUNDATION OF OUR CONCEPT

- Modules
- Petri Nets
- Database

=> Comprehensive and Unifying Modelling Framework
**What is a Module?**

**Self-Contained and Object-Oriented Entities/Models**

- Object oriented = centred around a biomolecule (gene, mRNA, protein)
- Representing a biomolecule and its direct interaction with other biomolecules in the form of a Petri net
Module Types

Molecular Interactions

Protein Module
- Petri Net
- Binding and Unbinding Reactions
- Formation and Cleavage of Covalent Bonds
- Conformational Changes
- Documentation & Searchable Metadata

Protein Degradation Module
- Petri Net
- Inactivation & Degradation
- Documentation & Searchable Metadata

Gene Module
- Petri Net
- Transcriptional Activity
- Binding and Unbinding of Proteins
- Covalent Modification
- Documentation & Searchable Metadata

RNA Module
- Petri Net
- Transcription
- Processing of RNA (Alternative Splicing)
- Binding and Unbinding Reactions
- Translation
- Degradation
- Documentation & Searchable Metadata

Causal Dependencies

Causal Interaction Module
- Petri Net
- Causal Influences on Molecular and Cellular Processes
- Documentation & Searchable Metadata

Allelic Influence Module
- Petri Net
- Allelic Influences on Molecular and Cellular Processes
- Documentation & Searchable Metadata
**What is a Module?**

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**Design Principle**

- Simple rules for the design of each module type
- Structural Petri net properties
- Defined connection interfaces (shared subnets) used to couple the modules

**Documentation and Metadata**

- Commented lists of places and transitions
- Literature citations
- Links to protein, sequence database entries etc.
**What is a Module?**

**Self-Contained and Object-Oriented Entities/Models**

- Object oriented = centred around a biomolecule (gene, mRNA, protein)
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=> Modules serve as interactive wiki-like articels

**Design Principle**

- Simple rules for the design of each module type
- Structural Petri net properties
- Defined connection interfaces (shared subnets) used to couple the modules

=> Modularity of any resulting biomodel mirrors the modular composition of the living system at the molecular level

**Documentation and Metadata**

- Commented lists of places and transitions
- Literature citations
- Links to protein, sequence database entries etc.
Proof of Principle: JAK-STAT...

Joint work with Anna Dittrich and Fred Schaper
JAK-STAT Pathway

- Major signalling pathway
- Dysfunctionality leads to cancers, immune deficiencies syndromes
- Main Components:
  - Cytokine Receptors
  - JAK – Janus- Kinase
  - STAT – Signal Transducer and Activator of Transcription

=> Several isoforms, different cytokine receptors and ligands
CONSTRUCT A PROTEIN MODULE

- Literature Research
  - Literature
  - Detailed Information (e.g. IL6)
    - Structural Validation
    - Curation by Bioscientists

Translation into a Petri Net:
- Place: Specific State of a Protein Domain/Non-Protein
- Transition: State Shift

Module (e.g. IL6)

Network Generation by matching subnets

Module Set of interacting Proteins in the IL6-JAK/STAT Pathway

Modular Network of IL6-JAK/STAT Pathway

Indicate identical Subnets
COMBINATORICS OF JAK-STAT

IL-6  IL-11  LIF

gp130  LIF-R

IL-6-R  IL-11-R

JAK1-Version1  JAK1-Version2
SHP2-Version1  SHP2-Version2

Set of Modules

Combined Modular Networks
COMBINATORICS OF JAK-STAT

Set of Modules

Combined Modular Networks

Module SHP2

Module gp130

Merged Modules

SHP2 BINDING gp130

SHP2 BINDING gp130

SHP2 BINDING gp130

SHP2 BINDING gp130
JAK-STAT in IL-6 Signaling

Modular Network

IL6Ralpha

JAK1

SOCS3

STAT3

SOCS3 mRNA

SOCS3_Biosynthesis

IL6

gp130

SHP2
JAK-STAT in IL-6 Signaling

- Network dimension:
  - Protein modules: 7
  - Extension:
    - 1x degradation module,
    - 1x mRNA module
  - Places: 92
  - Transition: 102
  - Edges: 487
  - Pages: 58
  - Nesting Depth: 4
**Run the Model**

(A) Relative Activation of JAK1

(B) Experiment: pSTAT3

(C) Experiment: pSHP2

(D) IL-6 receptor (IL-R6) binding and activation of JAK-STAT signaling pathway.

- IL-6 binds to IL-R6, activating the JAK-STAT pathway.
- JAK kinases are phosphorylated, leading to the activation of STAT proteins.
- STAT proteins dimerize and translocate to the nucleus, interacting with SOCS and other proteins.
- DNA binding and transcriptional regulation.
ENCODING SPACE VIA COLOUR

[Diagram with various biological components and interactions, including "IL6", "gp130", "SHP2", "JAK1", "SOCS3", and "STAT3". The diagram illustrates the biochemical pathway involving these components, with labels such as "extracellular space", "membrane", "cytoplasm", and "nucleus". The pathway is color-coded to represent different stages and components, such as "SOCS3 mRNA" and "SOCS3 Biosynthesis".]
ENCODING SPACE VIA COLOUR

Module_ID := (Protein_1, Protein_2,…,Protein_i)
Compartment := (extracellular, membrane, cytoplasm, Nucleus,…)
xGrid :=(1,2,…,m)
yGrid :=(1,2,…,n)
zGrid :=(1,2,…,o)

Component_Position :=Module_ID x Compartment x xGrid x yGrid x zGrid

=> Modules can only interact on the same or neighbouring position
=> Modules that interact can only move together
=> Else modules can move independently
MORE THAN ORGANIZING MODULES...
ASSEMBLING MODELS FROM MODULES

- Organize Modules and Metadata
- Version Control
- Manage Update and Curation
- Automatic Model Generation
  - Metadata-based model mutation

Systems Biology and Synthetic Biology
The Core...
**User-Interface**

ProtBricks is a collection of Modules describing the functionality of single biomolecular entities and their interactions with other molecules in terms of Petri nets. All modules adhere to the guidelines of the *Modular Petri net methodology*, which has been developed in need of a sophisticated reconstruction of growing biomolecular models. The database allows to browse to single modules and to gather the functionality of a biomolecular entity by its corresponding intuitive Petri net. In addition, the applied modular Petri net modeling concept allows to automatically couple a repository of modules of desired interacting biomolecular entities. Those resulting comprehensive models can be used for further profound analysis. Based on this approach it is also possible to generate single or double mutated models.
Sneak Peak & Summary...
METADATA-DRIVEN MODEL MUTATION

1. Choose a set of modules

2. Automatic network generation

+ Metadata

3. Use metadata to generate biologically functional mutations

Mutated networks with different properties
3. Use Metadata to generate biologically functional mutations

4. Implicit generation of a coloured Petri Net

Wt and mutated model defined by colour

Use predicates and guards to realise in silico mutation

Mutated networks with different properties
APPLICATION FOR SYNTHETIC BIOLOGY...

Natural Network 1
- Target 1
- Target 2
- Kinase 1
- Target 3

Natural Network 2
- Target 4
- Target 5
- Target 6

Artificial Network with Altered Properties
- Target 1
- Target 2
- Kinase 2'
- Target 4
- Target 6

Target 1 + Target 2

Target 5
Comprehensive and Unifying Modelling Framework

- Handle large and growing network by natural modularization
- Represent different networks by different module types
- Integrate different modules by defined connection interfaces
- Reusable, recombinable
- Organization of modules and their metadata
- Version control
- Automatic model generation
- Automatic metadata-driven model mutation
- In silico synthetic biology
- Coloured extension: scalability and space
• Cooperation Partners
  ◦ Monika Heiner and Co-Workers, BTU Cottbus
  ◦ David Gilbert, Brunel University London
  ◦ Fred Scharper and Co-Workers, OvGU Magdeburg
  ◦ Tim Hucho, University of Cologne

• Projects
  ◦ Consortium „Modelling of Pain Switches”

• Graduate School
  ◦ IMPRS Magdeburg