

OTTO VON GUERICKE  
UNIVERSITÄT  
MAGDEBURG

**BioPPN 2012, Hamburg**

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

**Mary Ann Blätke**

# OUTLINE

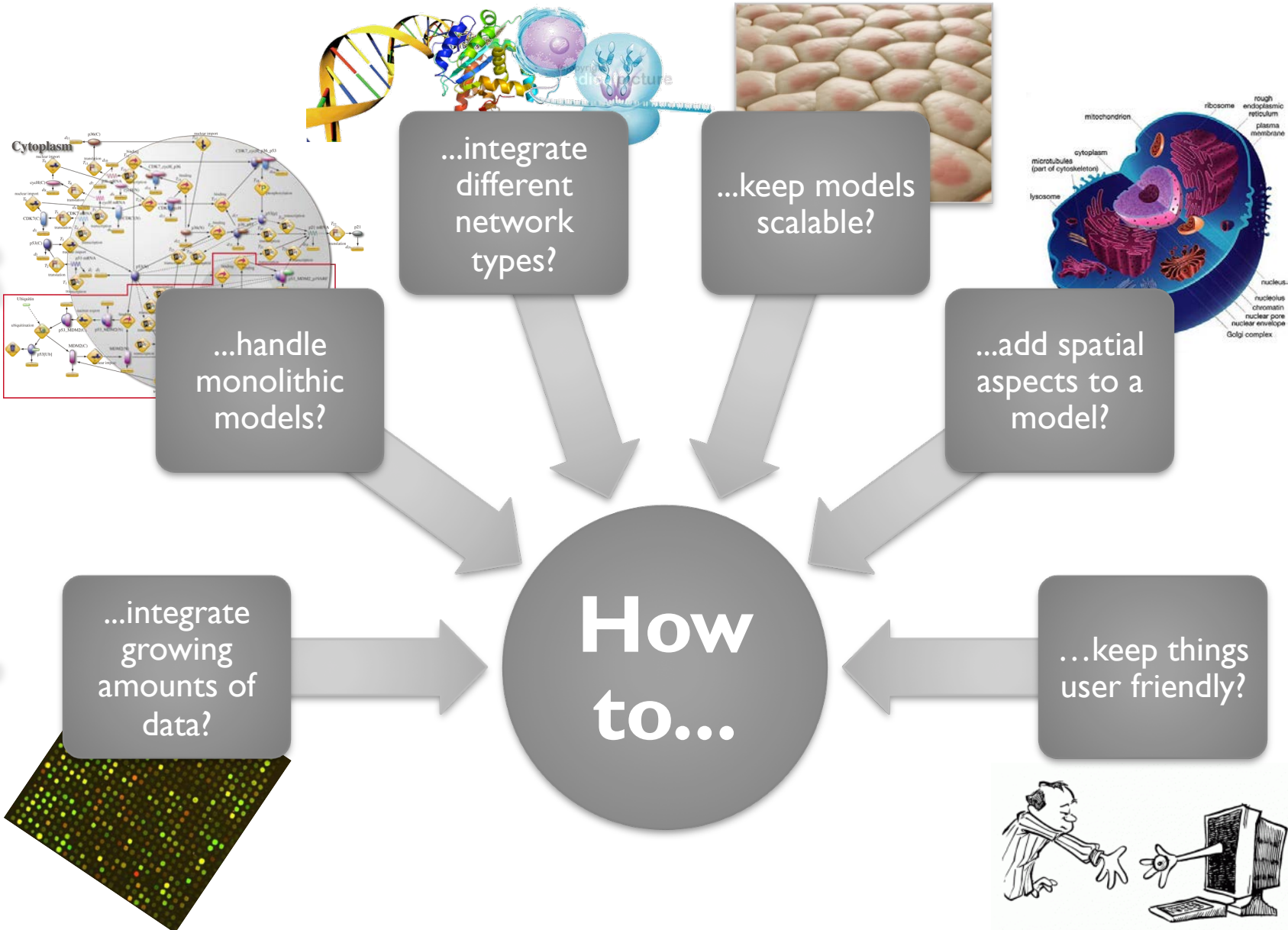
- **Conceptual Thoughts...**
- **Proof of Principle: JAK-STAT...**
- **More Than Organizing Modules...**
- **Sneak Peak & Summary...**



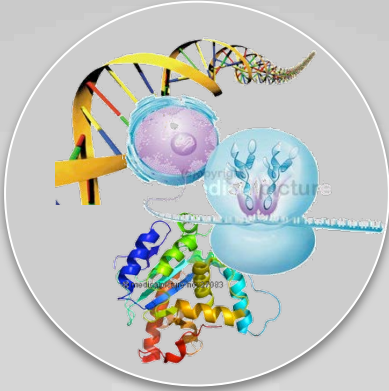
# CONCEPTUAL THOUGHTS...



# PROBLEMS IN SYSTEMS BIOLOGY

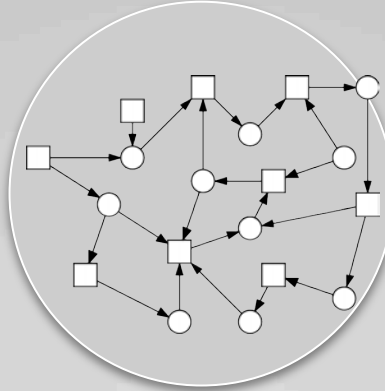


# FOUNDATION OF OUR CONCEPT



## 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

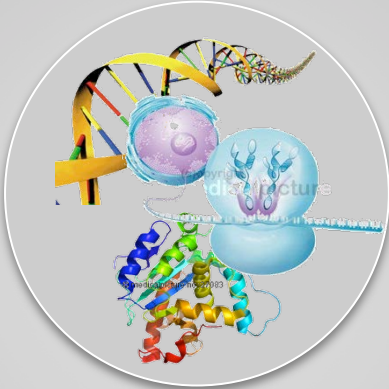


## Database

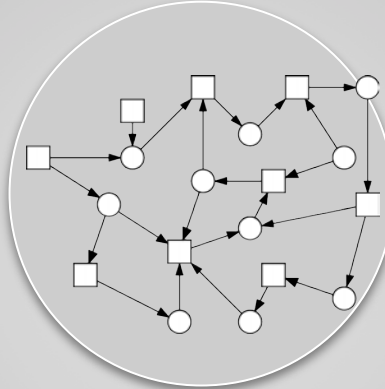
- Organization of modules
- Easy handling of meta-data
- Public access



# 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 an 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?

## 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 an Petri net

## 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)
- Representing a biomolecule and its direct interaction with other biomolecules in the form of an Petri net

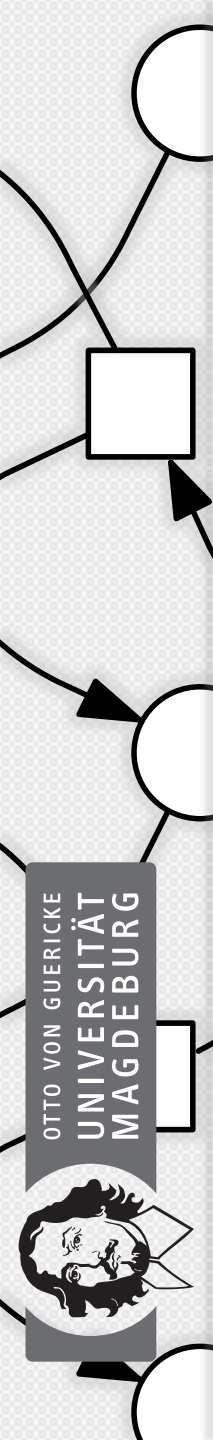
**=> Modules serve as interactive wiki-like articles**

## Design Principle

**=> 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...

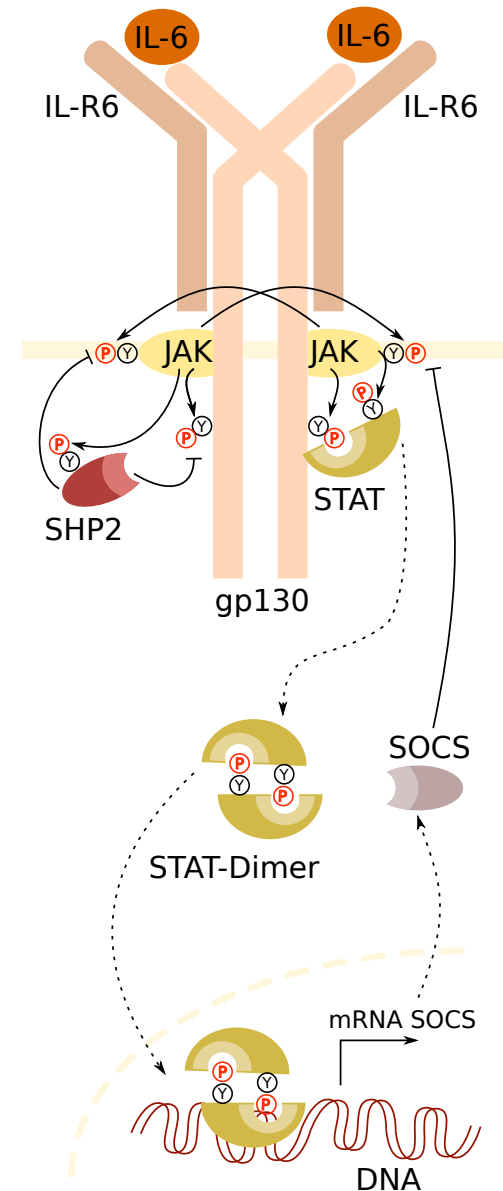
Joint work with Anna Dittrich and Fred Schaper



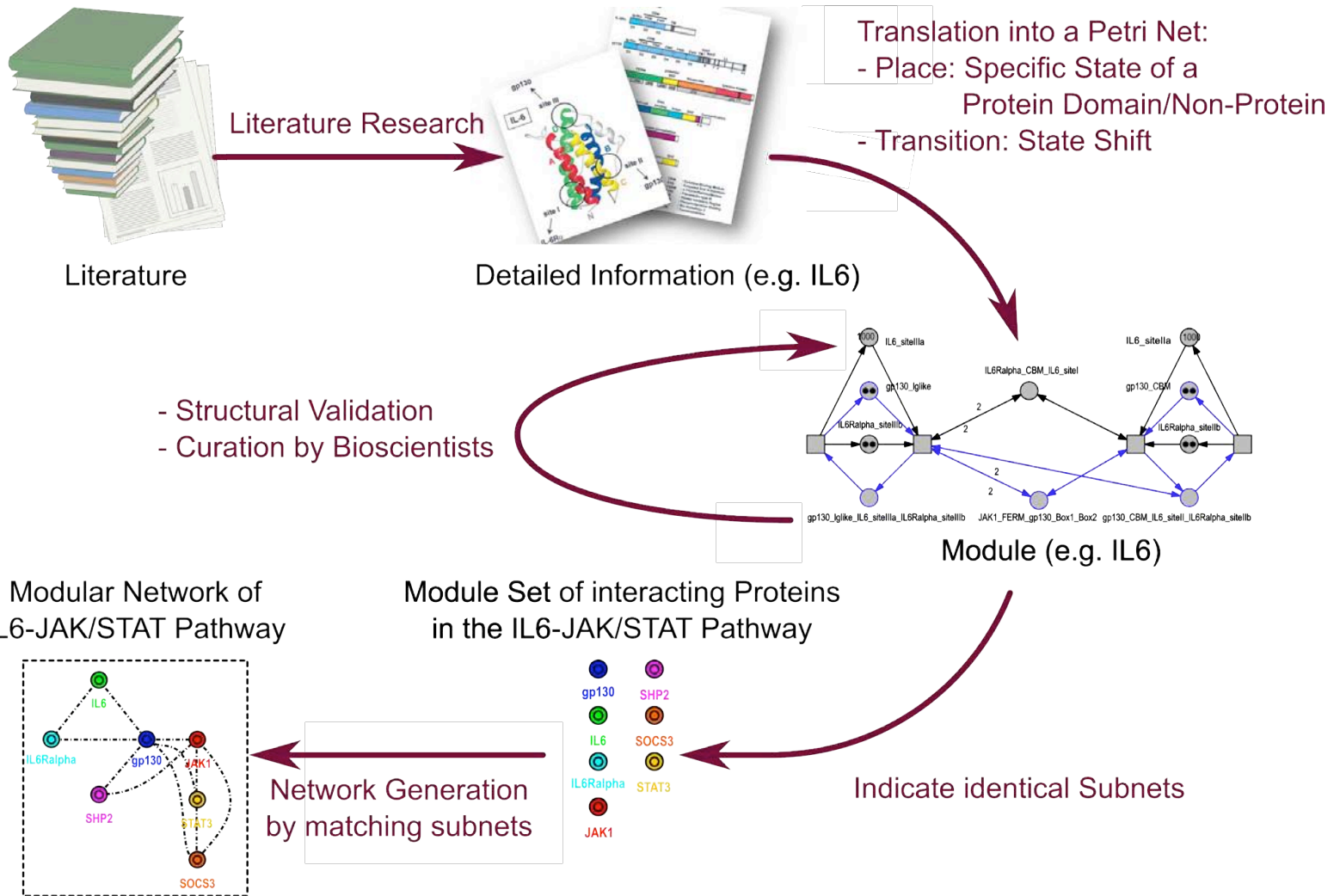
# JAK-STAT PATHWAY

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

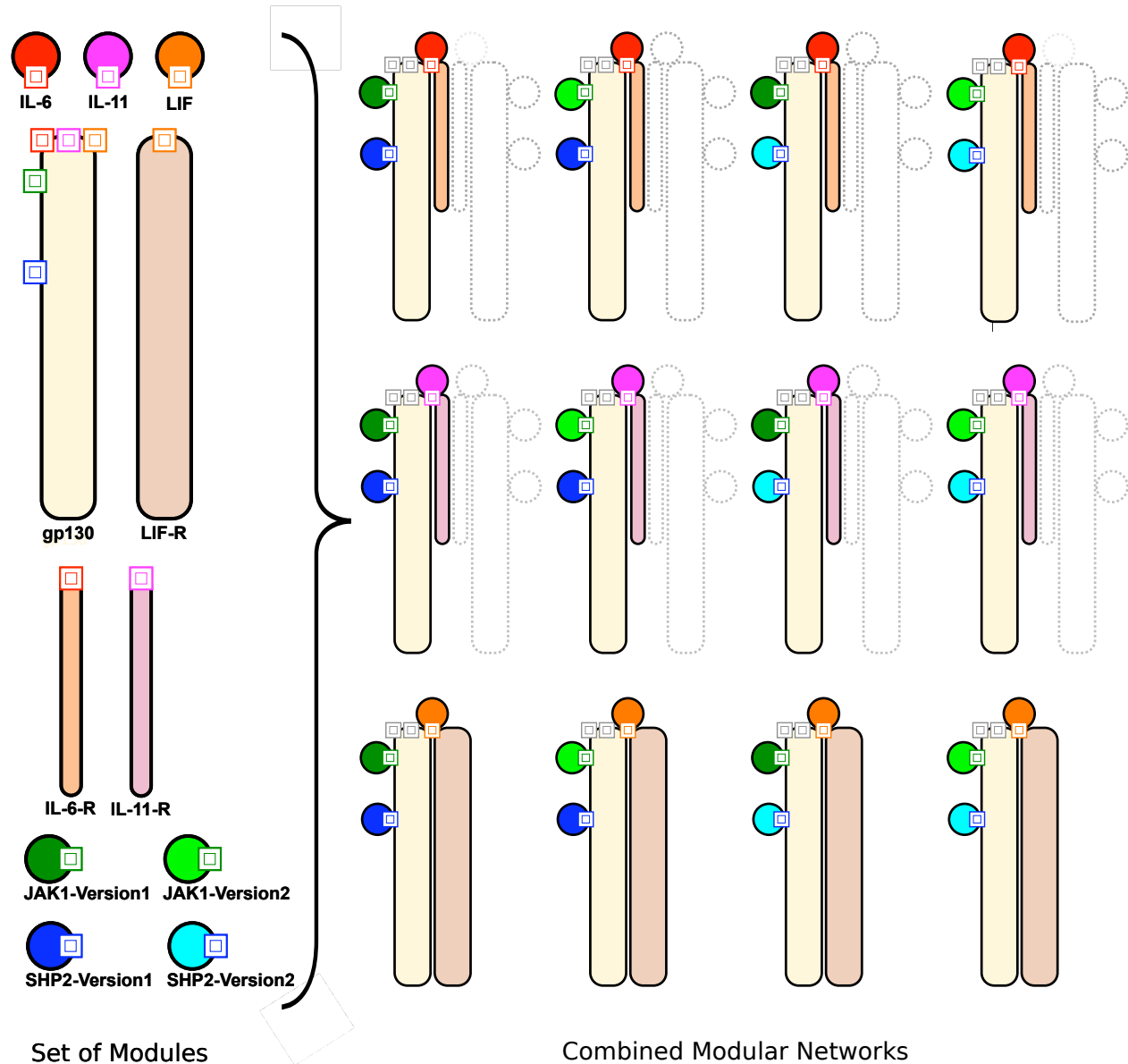
=> **Several isoforms, different cytokine receptors and ligands**



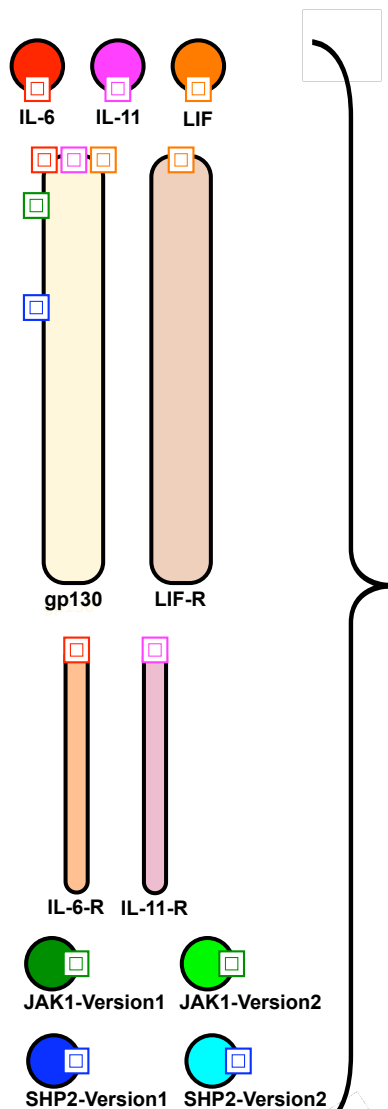
# CONSTRUCT A PROTEIN MODULE



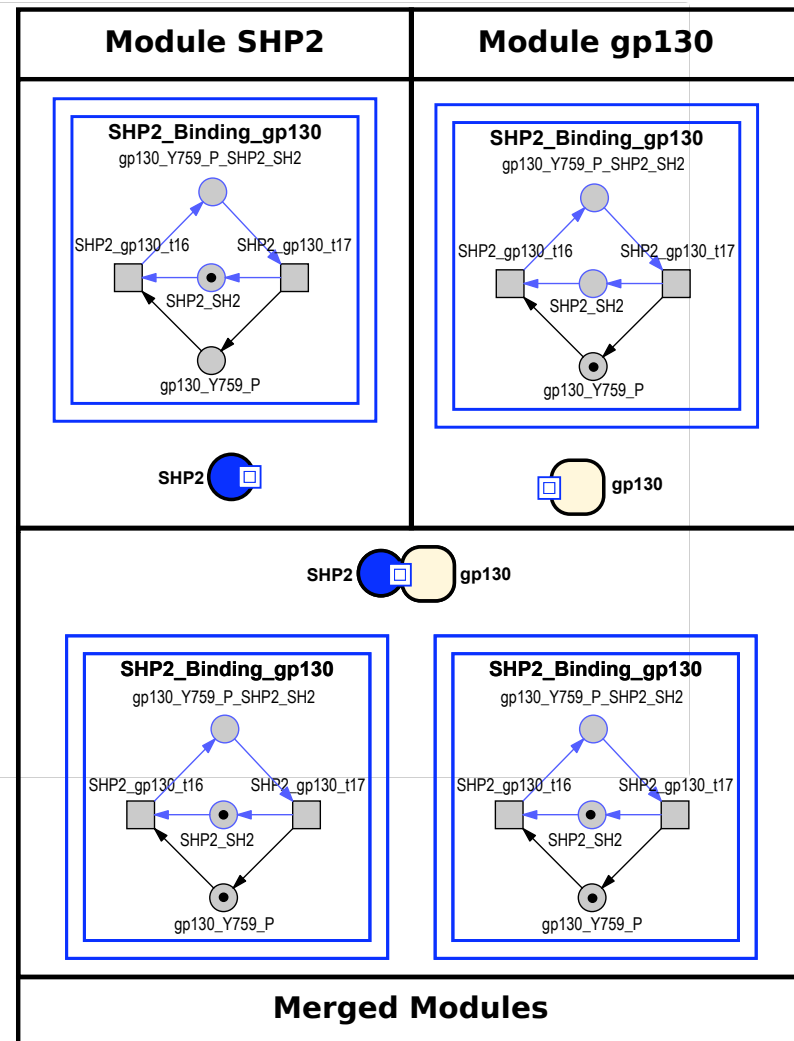
# COMBINATORICS OF JAK-STAT



# COMBINATORICS OF JAK-STAT



Set of Modules

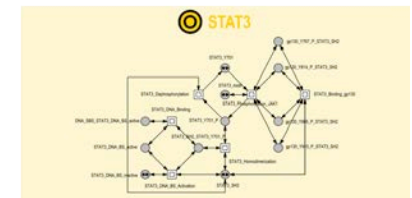
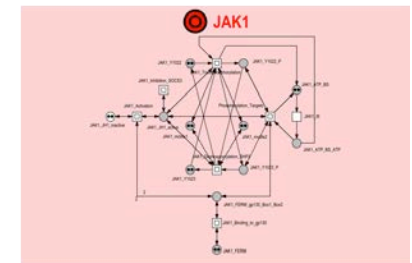
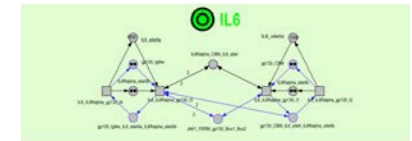
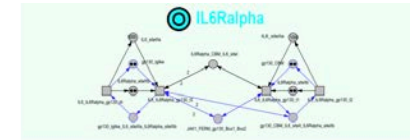
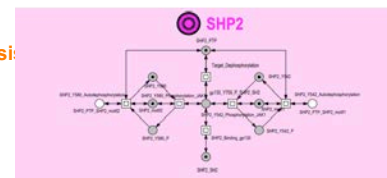
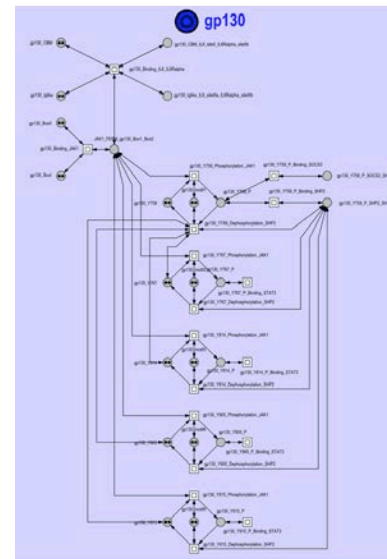
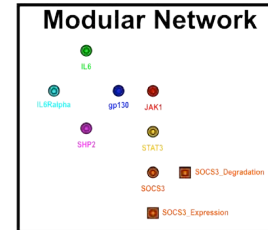
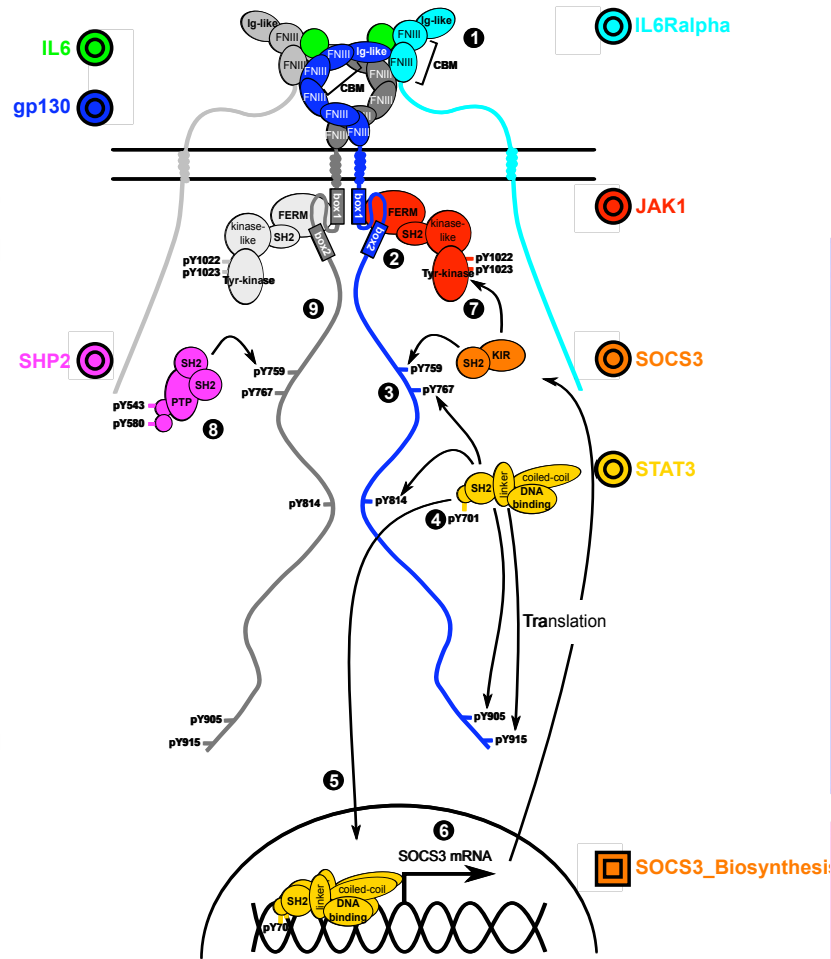


Combined Modular Networks



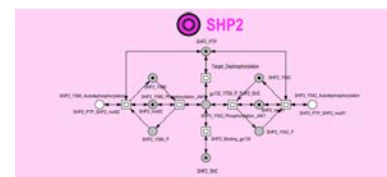
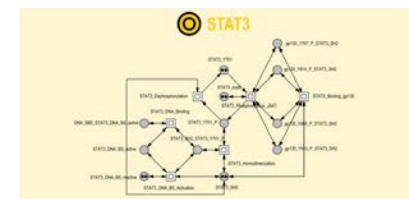
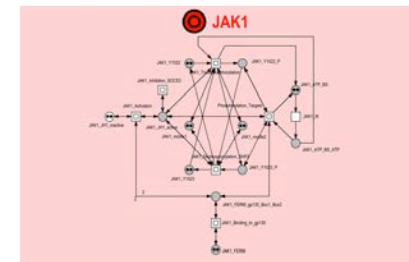
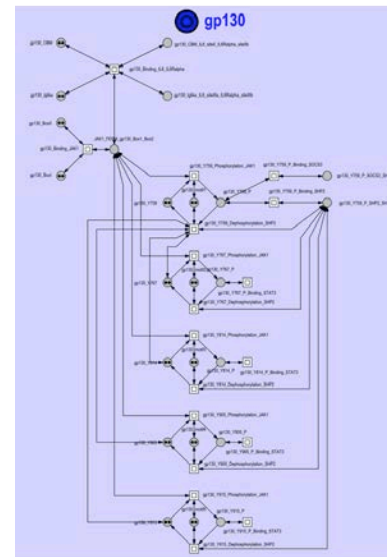
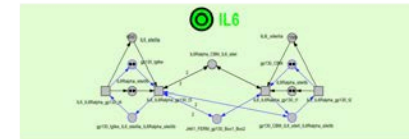
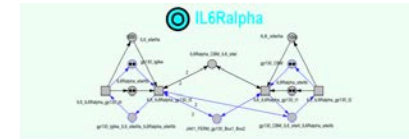
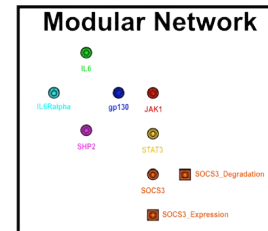


# JAK-STAT IN IL-6 SIGNALING

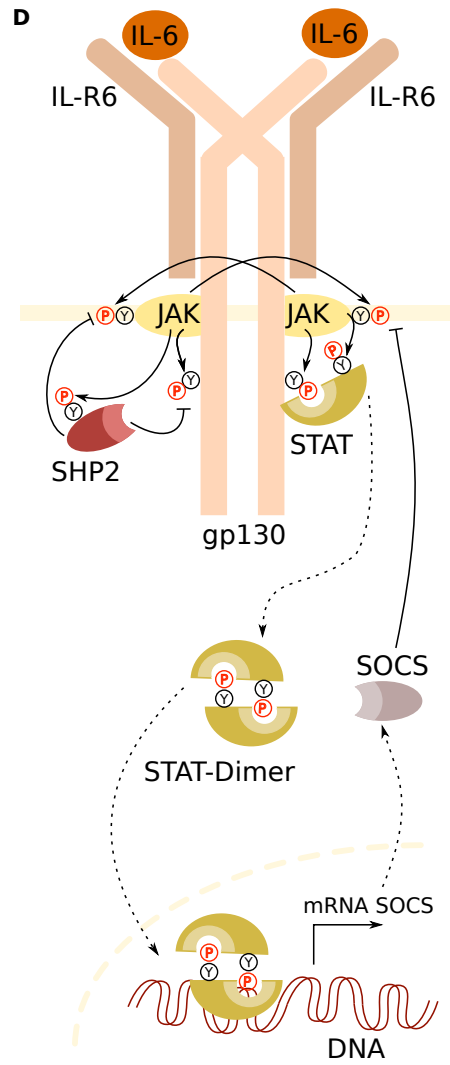
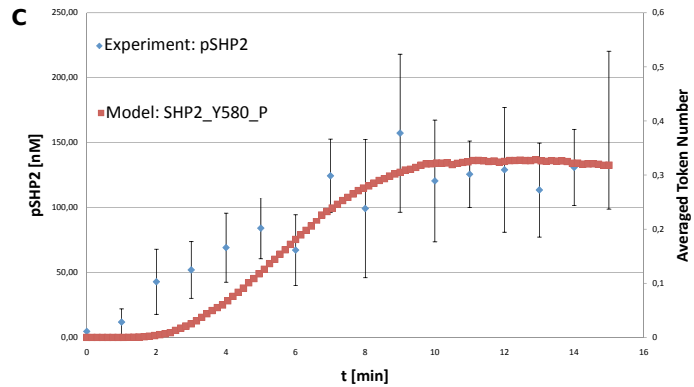
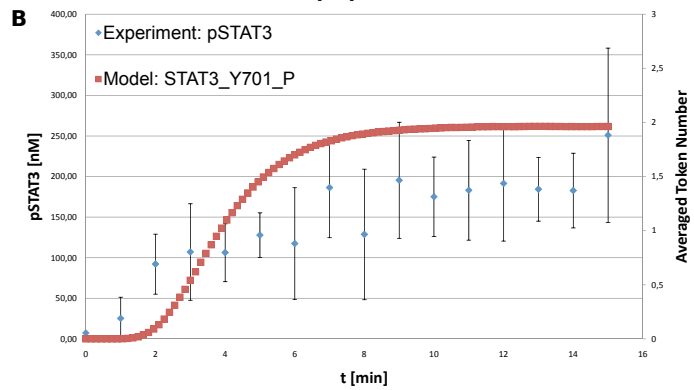
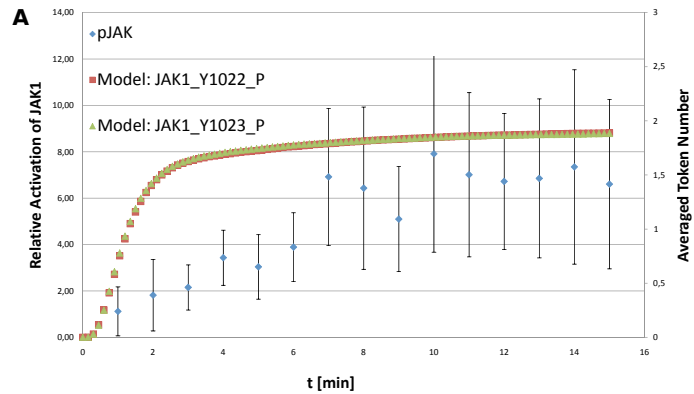


# JAK-STAT IN IL-6 SIGNALING

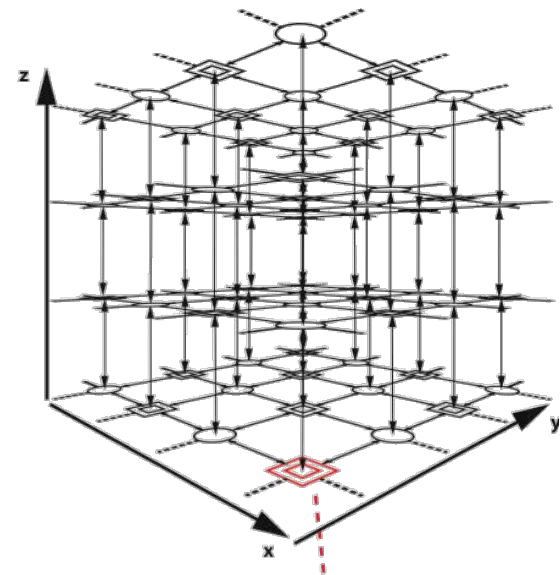
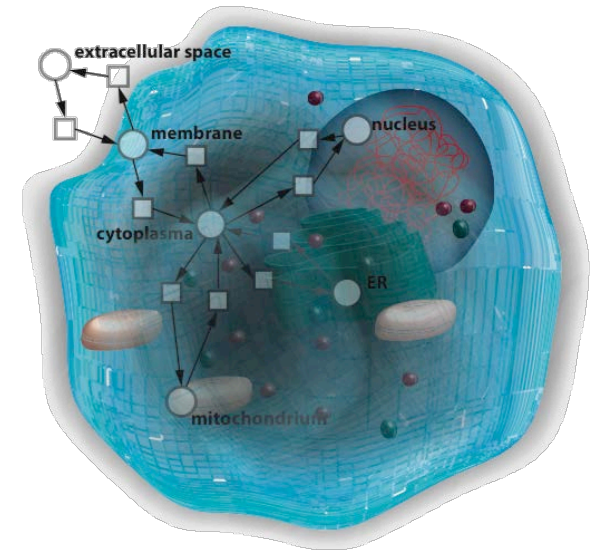
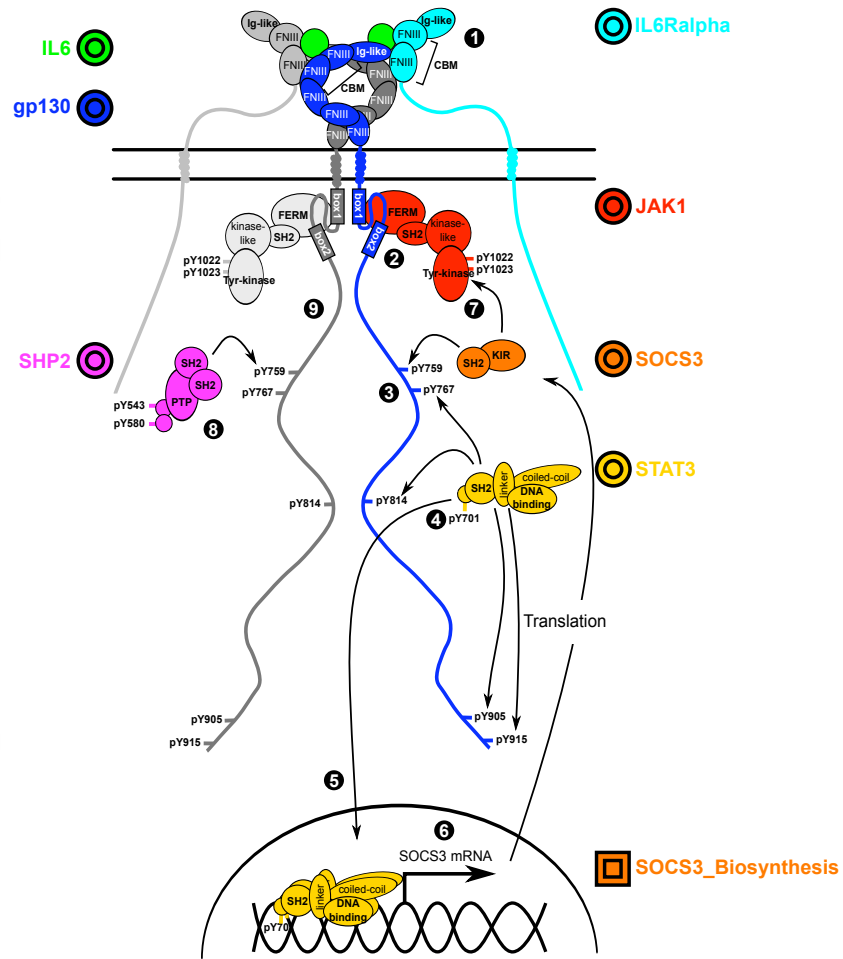
- Network dimension:
  - Protein modules: 7
  - Extension:
    - 1x degradation module,
    - 1 x mRNA module
  - Places: 92
  - Transition: 102
  - Edges: 487
  - Pages: 58
  - Nesting Depth: 4



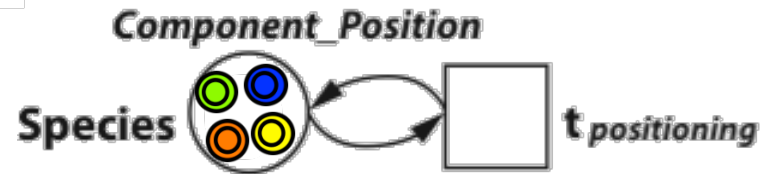
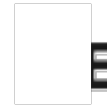
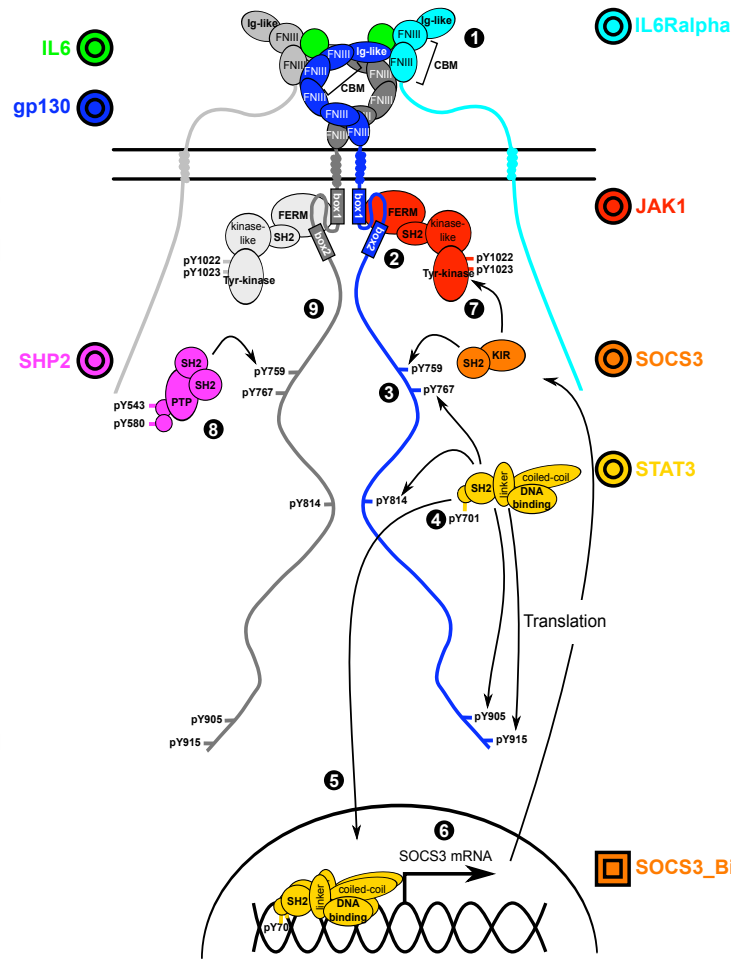
# RUN THE MODEL



# ENCODING SPACE VIA COLOUR



# 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

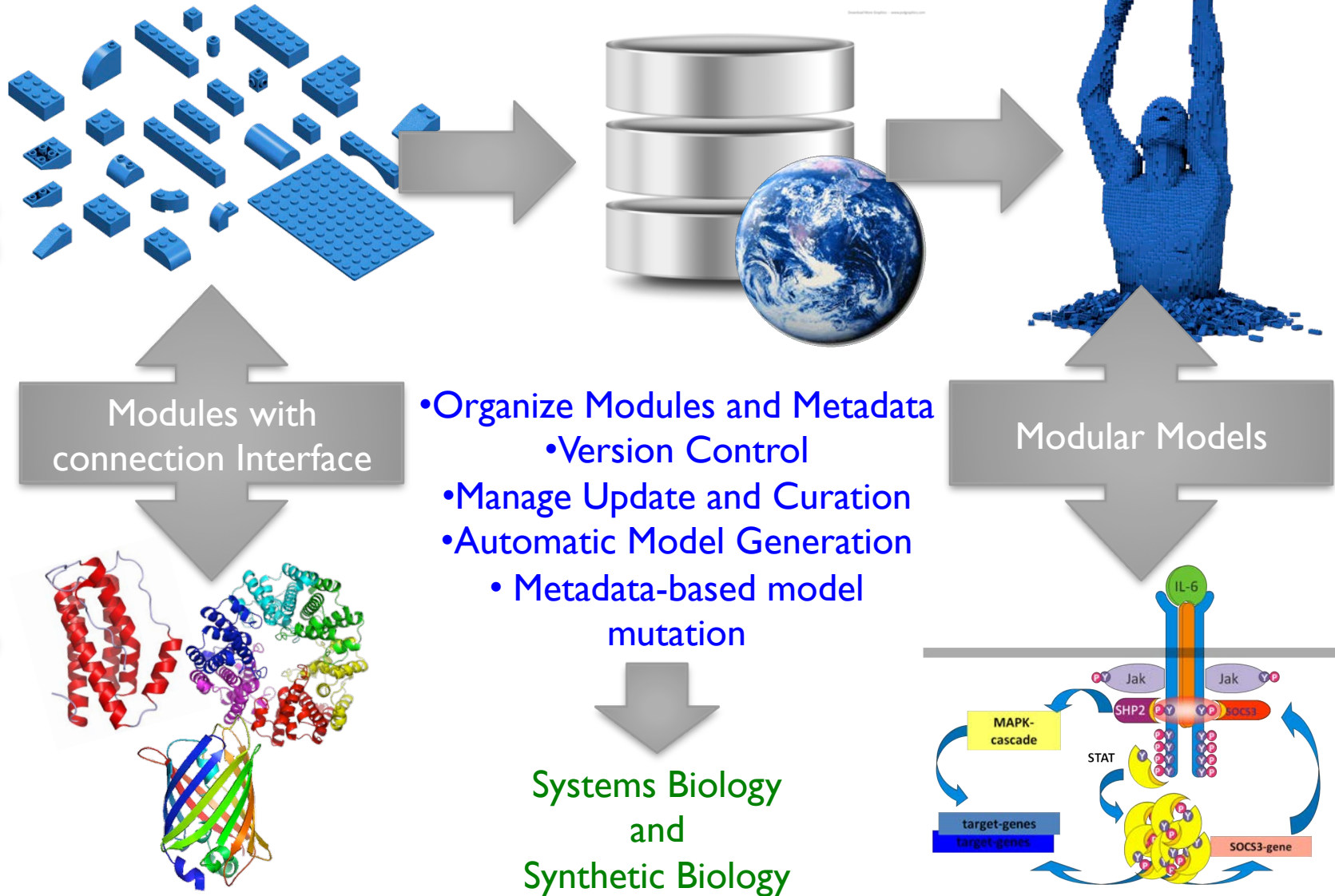




# MORE THAN ORGANIZING MODULES...

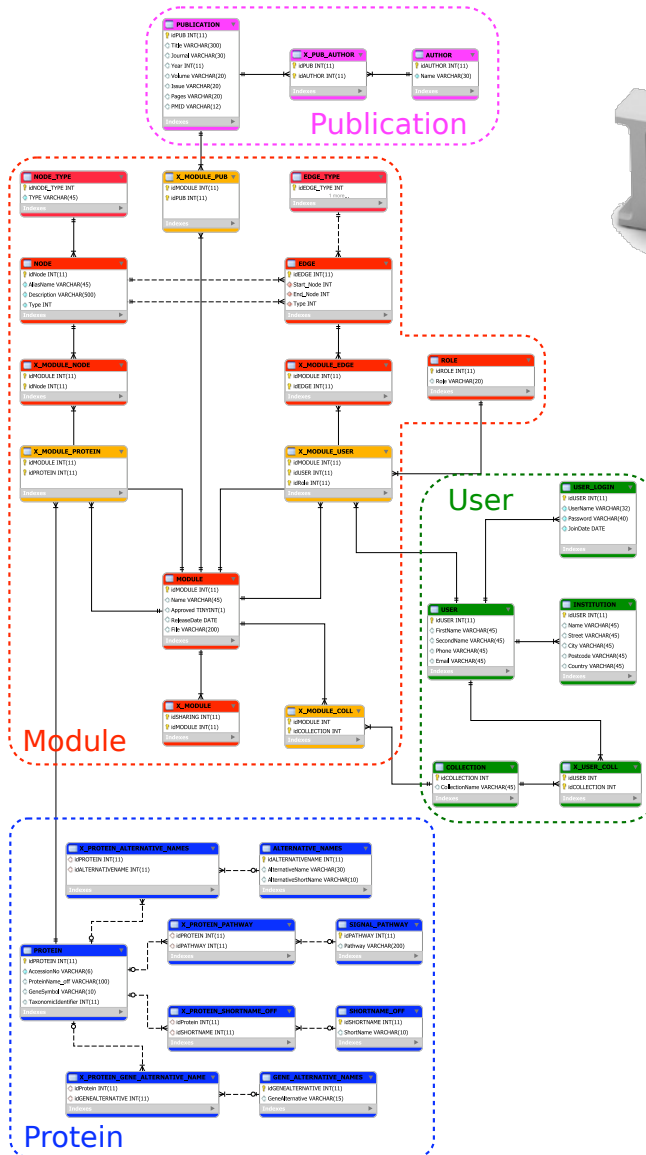


# ASSEMBLING MODELS FROM MODULES

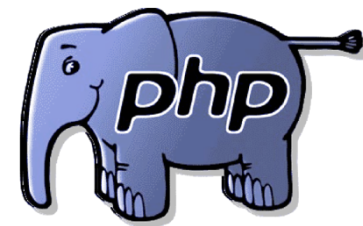




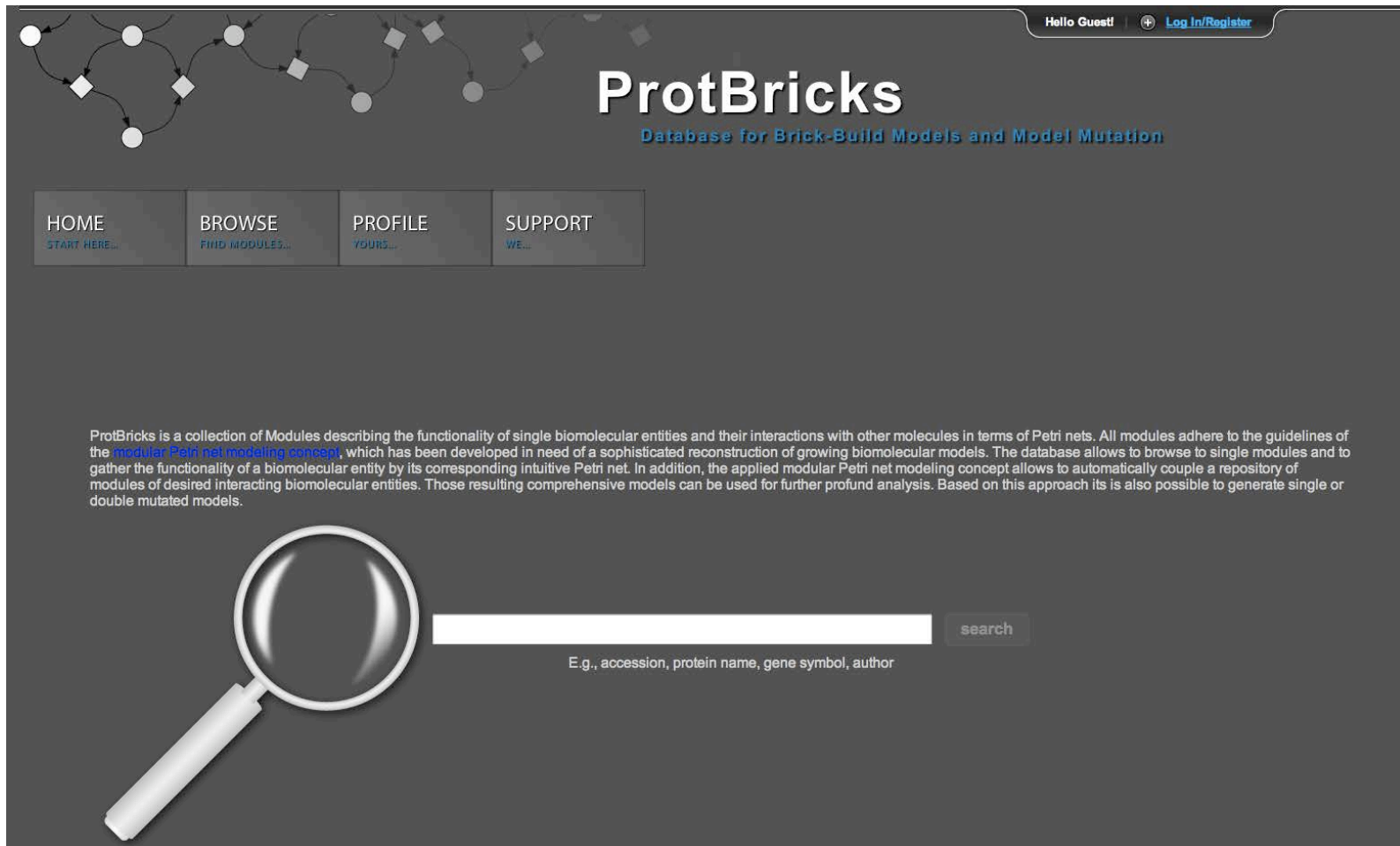
# THE CORE...



JavaScript



# USER-INTERFACE



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## ProtBricks

Database for Brick-Build Models and Model Mutation


**HOME**  
START HERE...

**BROWSE**  
FIND MODULES...

**PROFILE**  
YOURS...

**SUPPORT**  
WE...

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 modeling concept](#), 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 its is also possible to generate single or double mutated models.



search

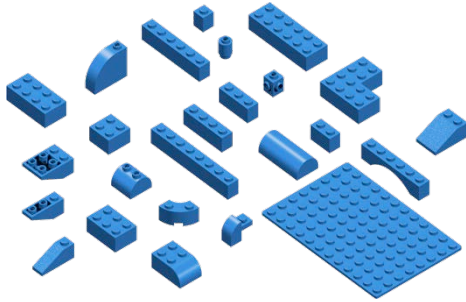
E.g., accession, protein name, gene symbol, author

# SNEAK PEAK & SUMMARY...



# METADATA-DRIVEN MODEL MUTATION

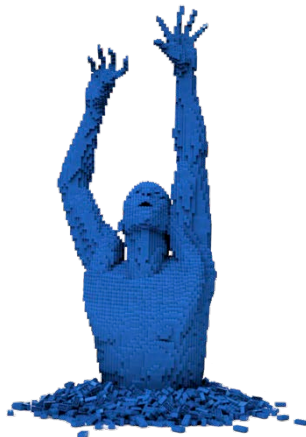
1. Choose a set of modules



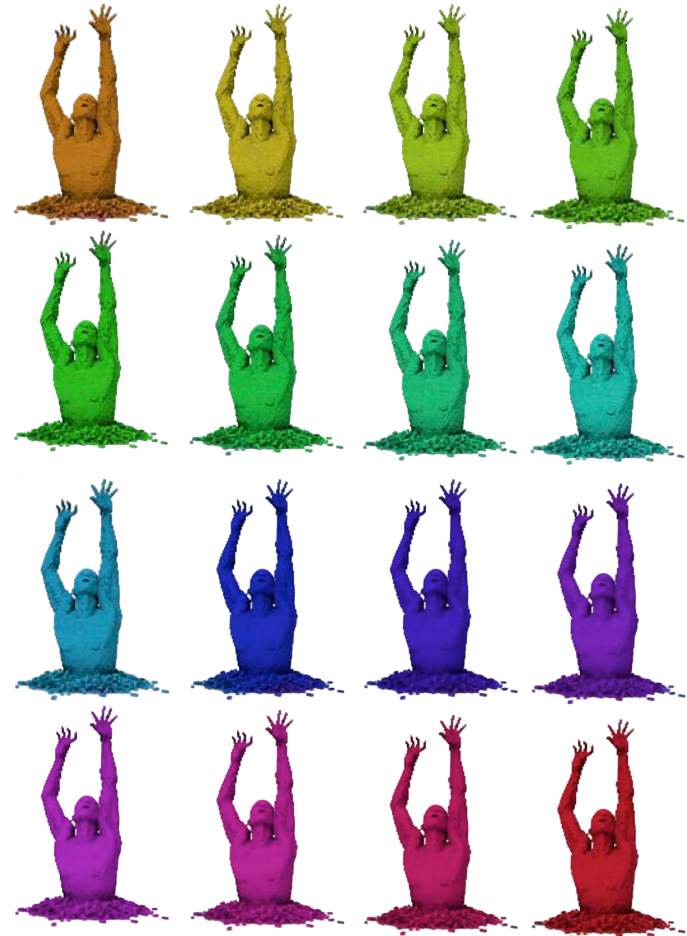
**+ Metadata**



2. Automatic network generation



3. Use metadata to generate biologically functional mutations



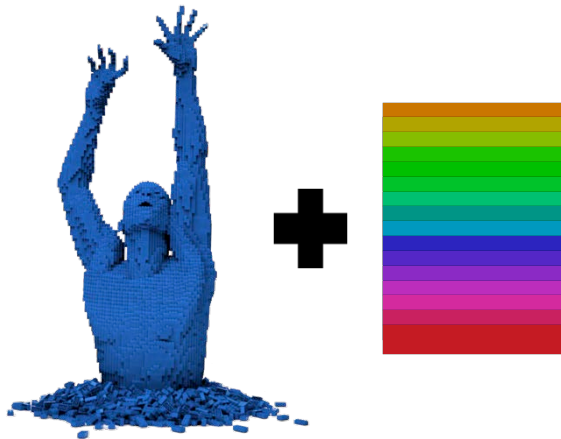
**Mutated networks with different properties**



# METADATA-DRIVEN MODEL MUTATION

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**

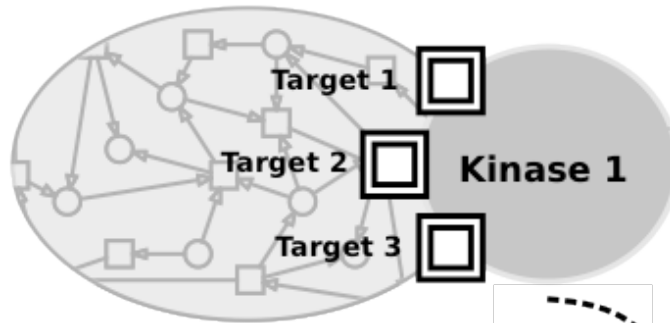
**Mutated networks with different  
properties**



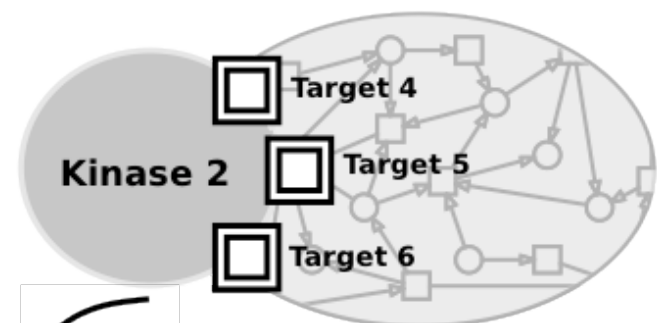


# APPLICATION FOR SYNTHETIC BIOLOGY...

Natural Network 1

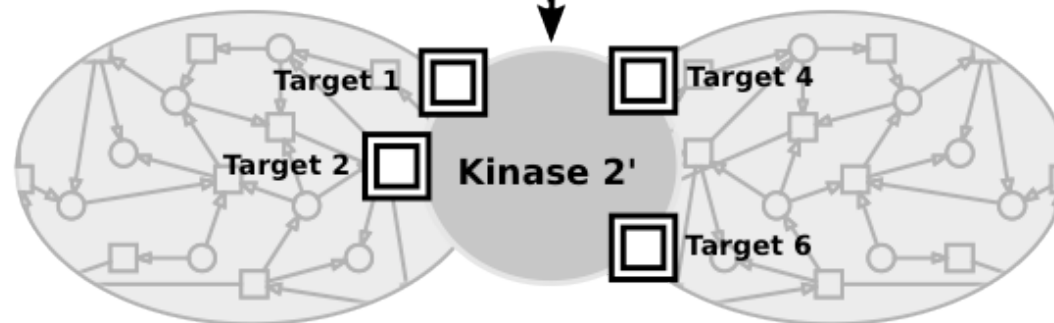


Natural Network 2



Target 1  +  
Target 2  +

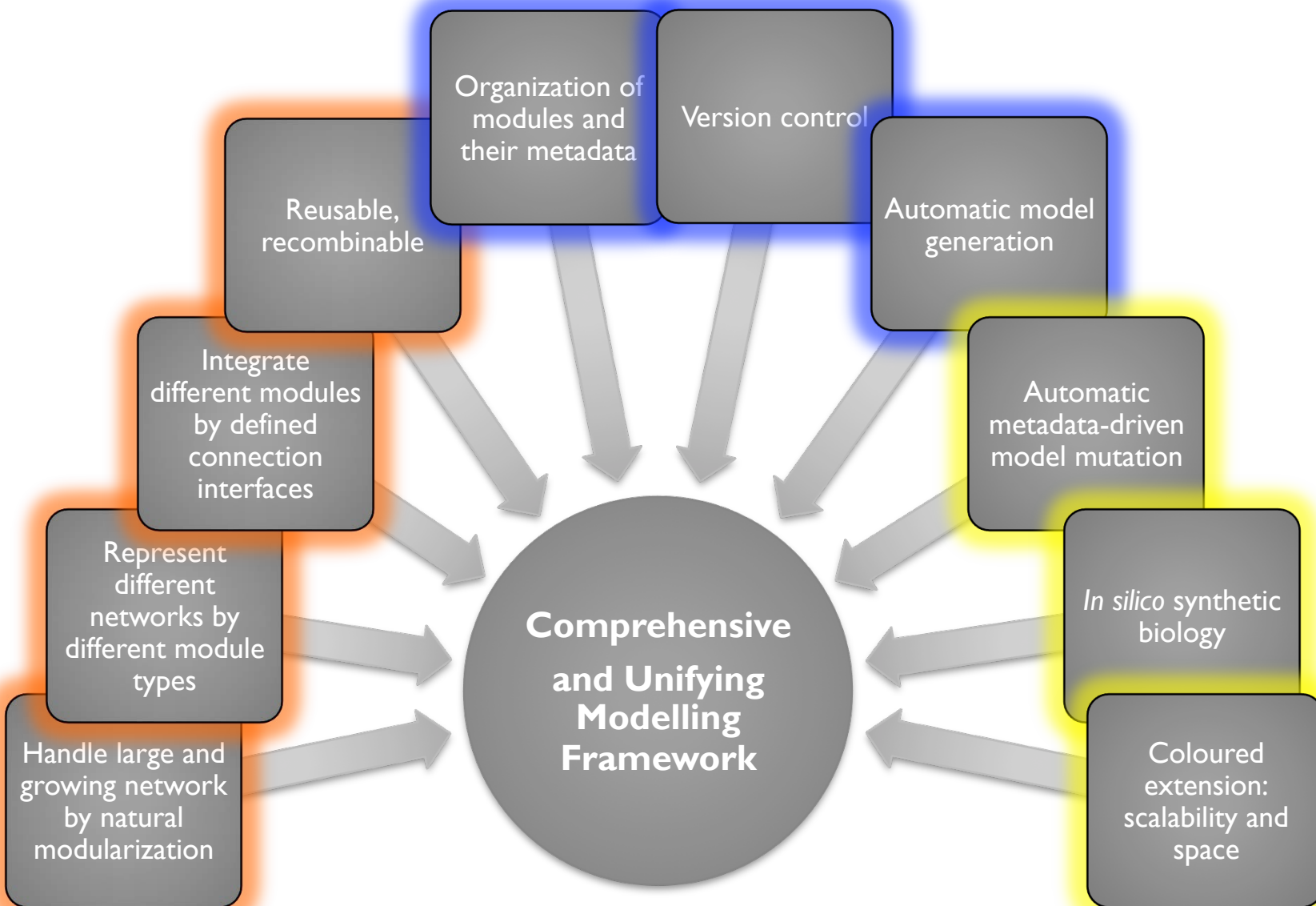
  Target 5



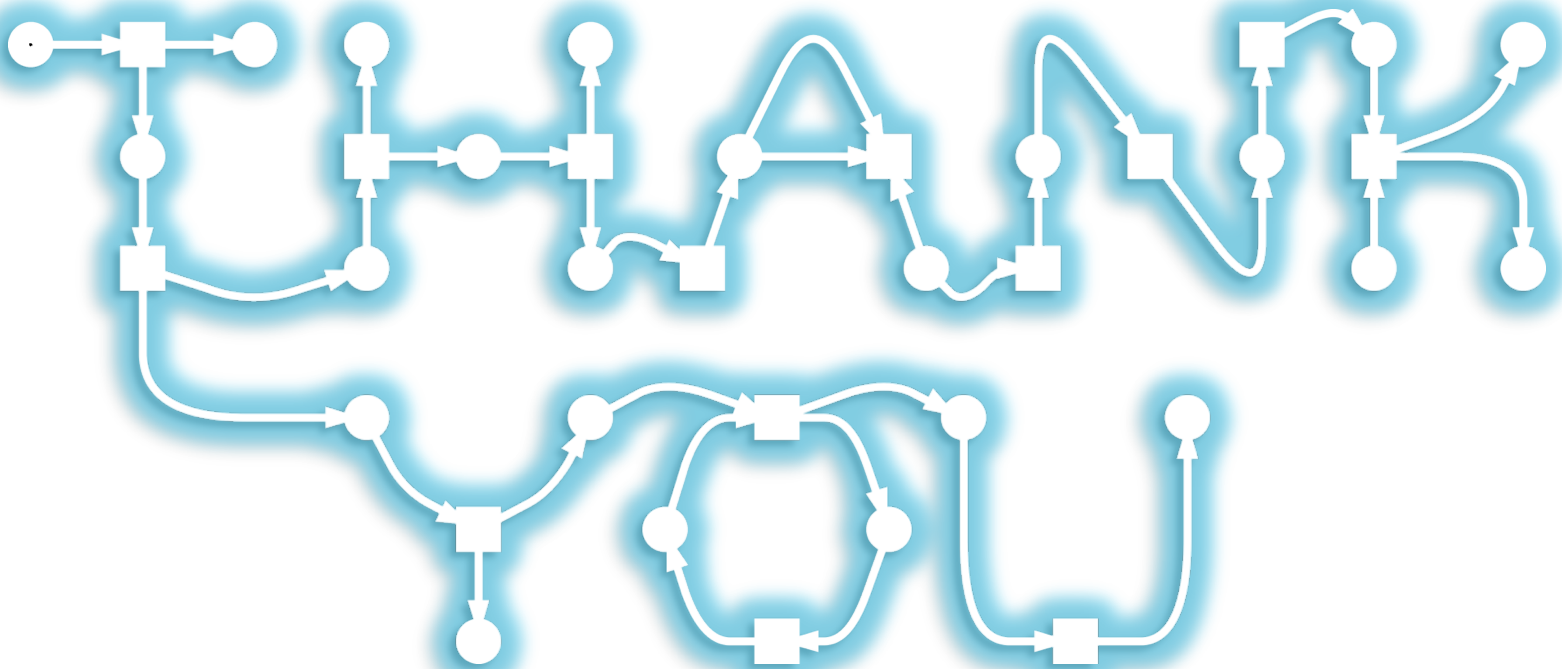
Artificial Network with Altered Properties



# SUMMARY







- 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



Federal Ministry  
of Education  
and Research

