Petri Net Tutorial – Part 1:

BioModel Engineering via Modular, Protein-oriented Modeling

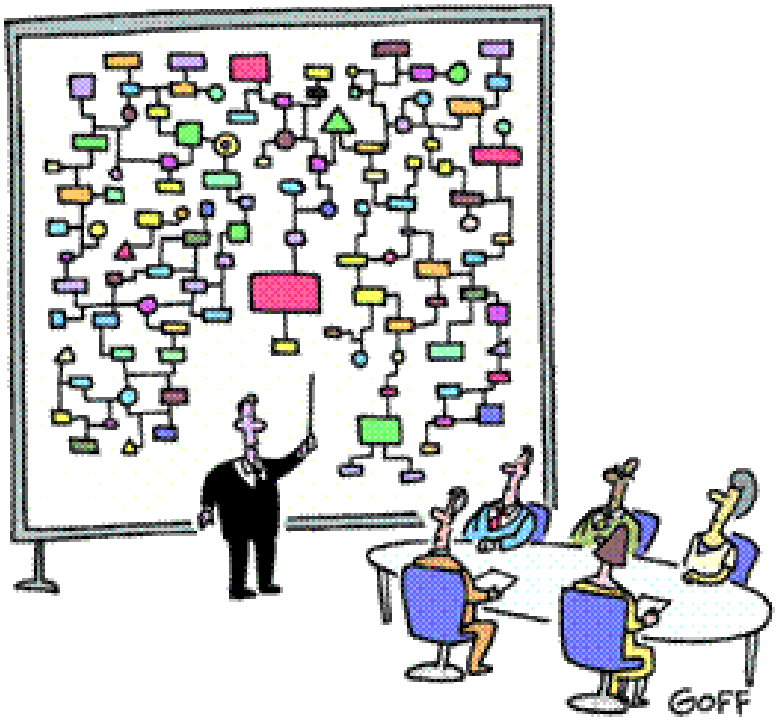
Mary Ann Blätke

@ ICSB 2011, Heidelberg

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

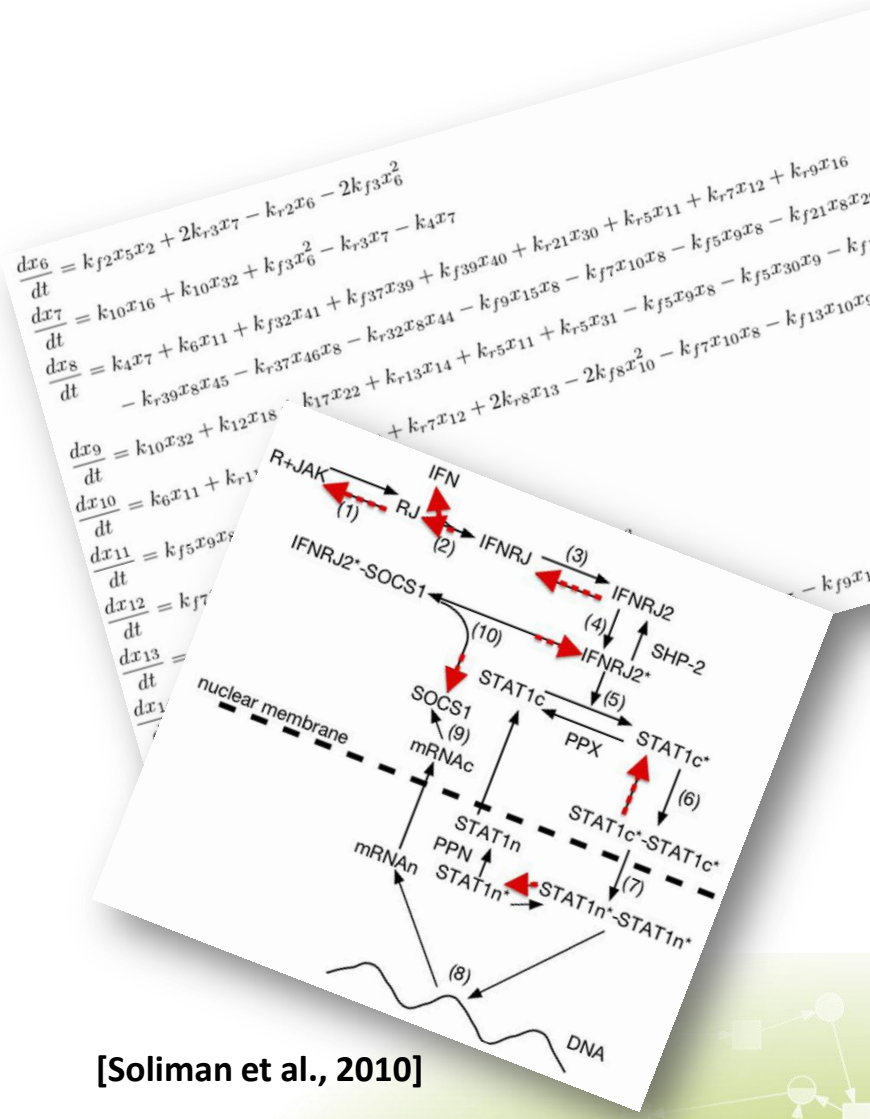


"And that's why we need a computer."

⇒ 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



[Soliman et al., 2010]

⇒Our Idea: Using the power of Petri nets to model molecular networks **[Heiner et al., 2010]**

BioModel Engineering via Modular, Protein-oriented Modelling

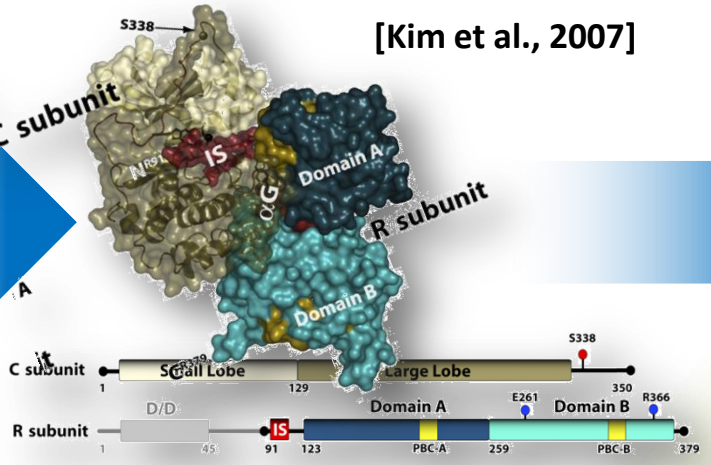
Modular Petri net Modeling Concept

Structure of a Module and Properties

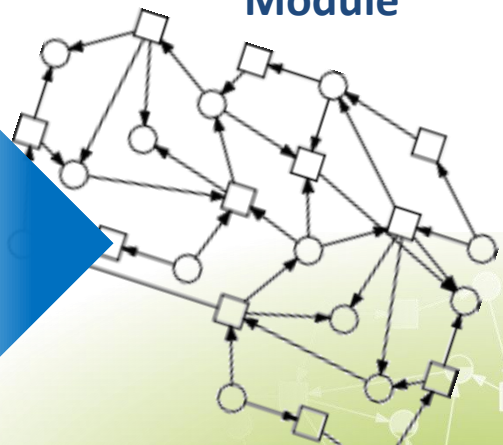
- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net

1.) Literature Research

[Kim et al., 2007]



Module



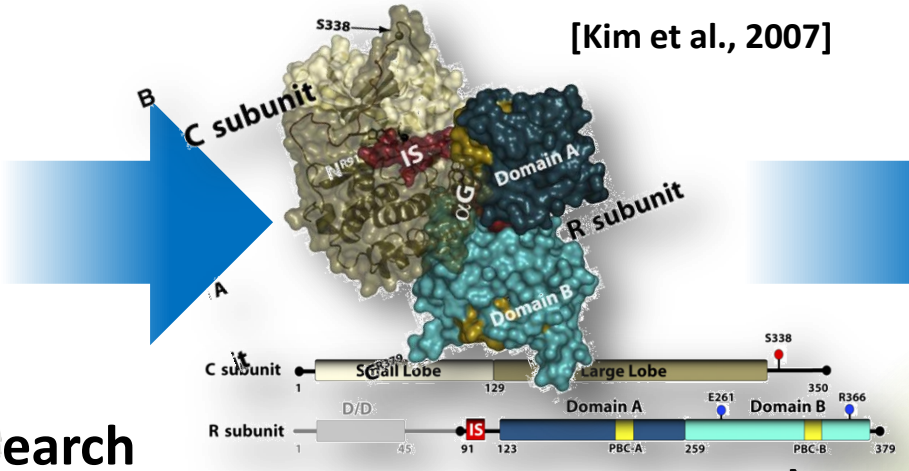
2.) Translation into a PN

Structure of a Module and Properties

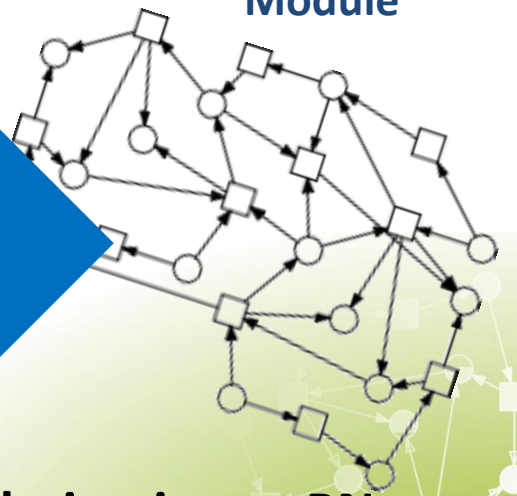
- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non-protein)
  - Transitions – Shifts between different states
  - Principle of double-entry bookkeeping -> shared copies of identical subnets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

1.) Literature Research

[Kim et al., 2007]



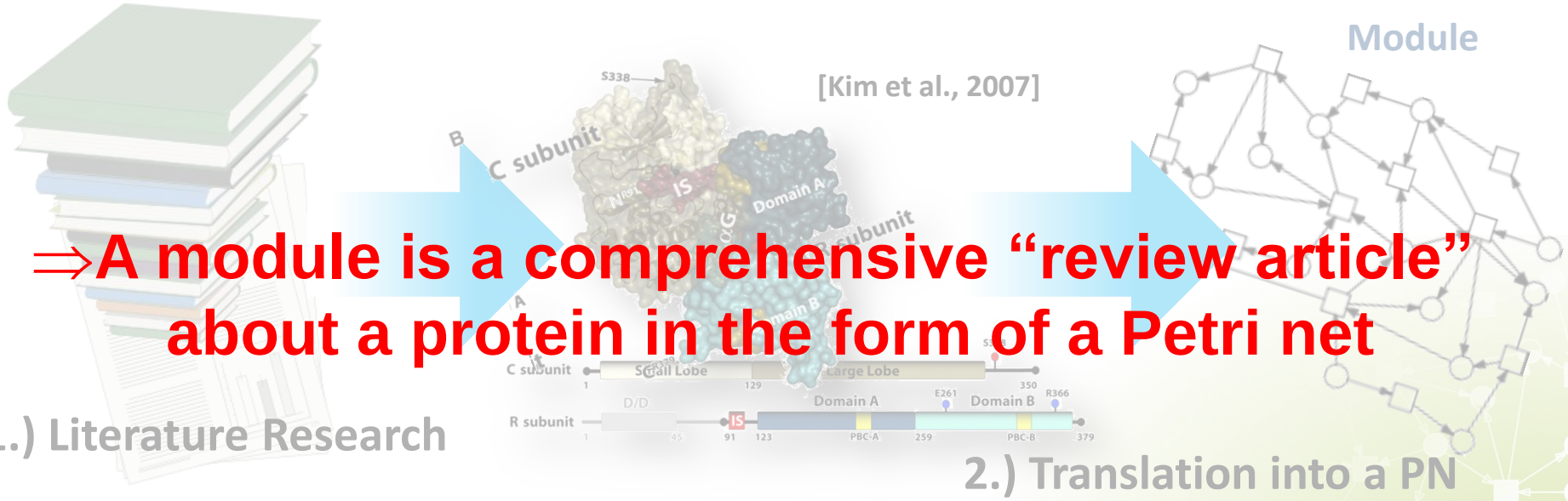
Module



2.) Translation into a PN

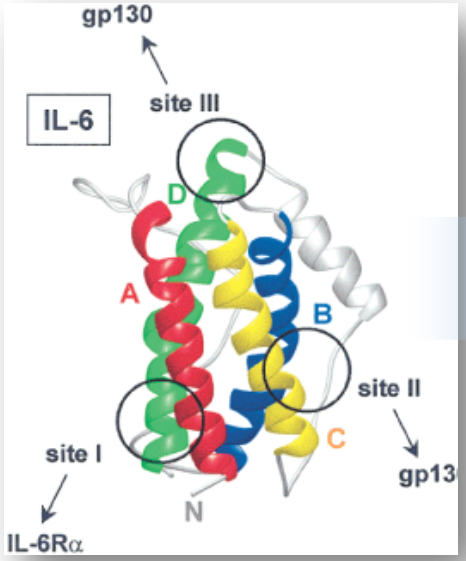
Structure of a Module and Properties

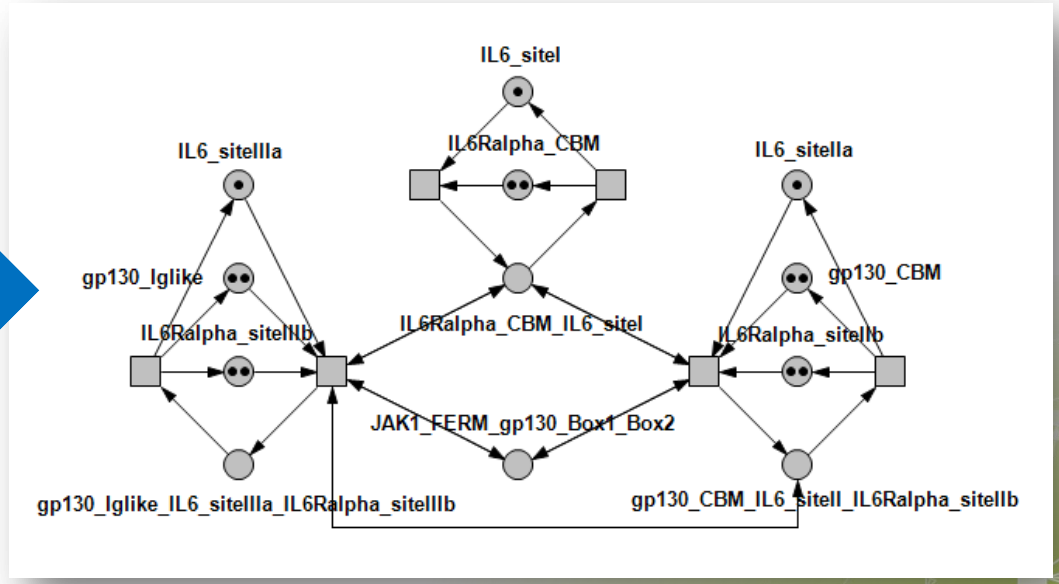
- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non-protein)
  - Transitions – Shifts between different states



Validation of a Module

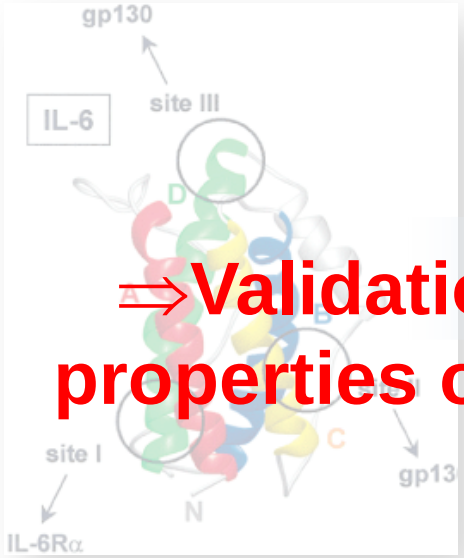
- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non-protein)
  - Transitions – Shifts between different states
  - Principle of double-entry bookkeeping -> shared copies of identical subnets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

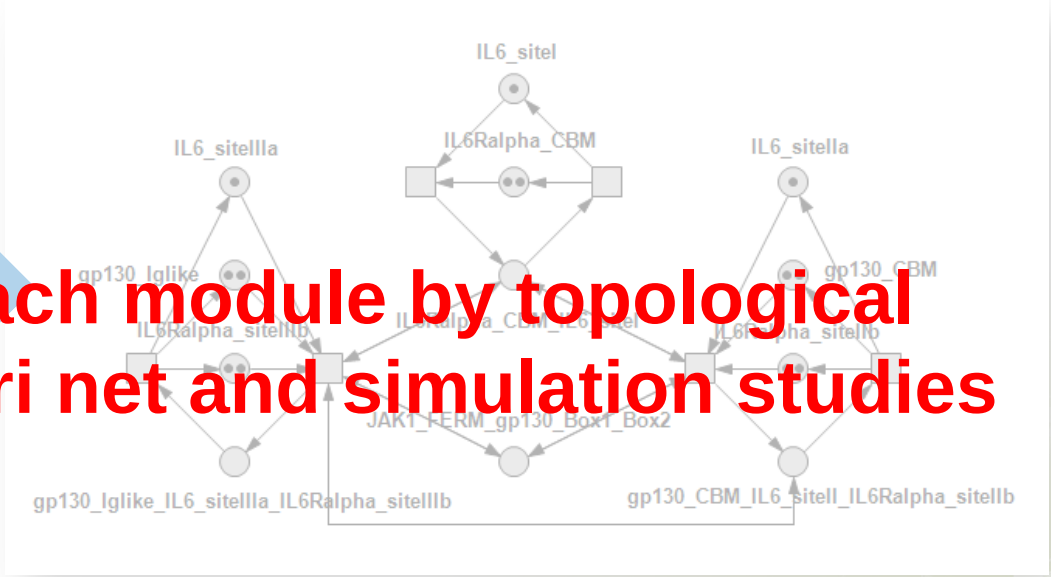




Validation of a Module

- 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

Validation of a Module

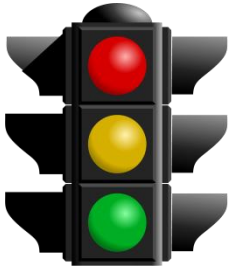
- Properties:

PUR	ORD	HOM	NBM	CSV	SCF	FT0	TF0	FP0	PF0	CON	SC
N	Y	Y	N	N	N	N	N	Y	Y	Y	N

DTP	CPI	CTI	SCTI	SB	k-B	1-B	DCF	DSt	DTr	LIV	REV
N	Y	N	N	Y	Y	Y	N	Y	N	N	N

Covered with P-INV:

- **Set of all possible states of a domain of the module-protein, an interactive protein or of the non-protein**



must not be fulfilled

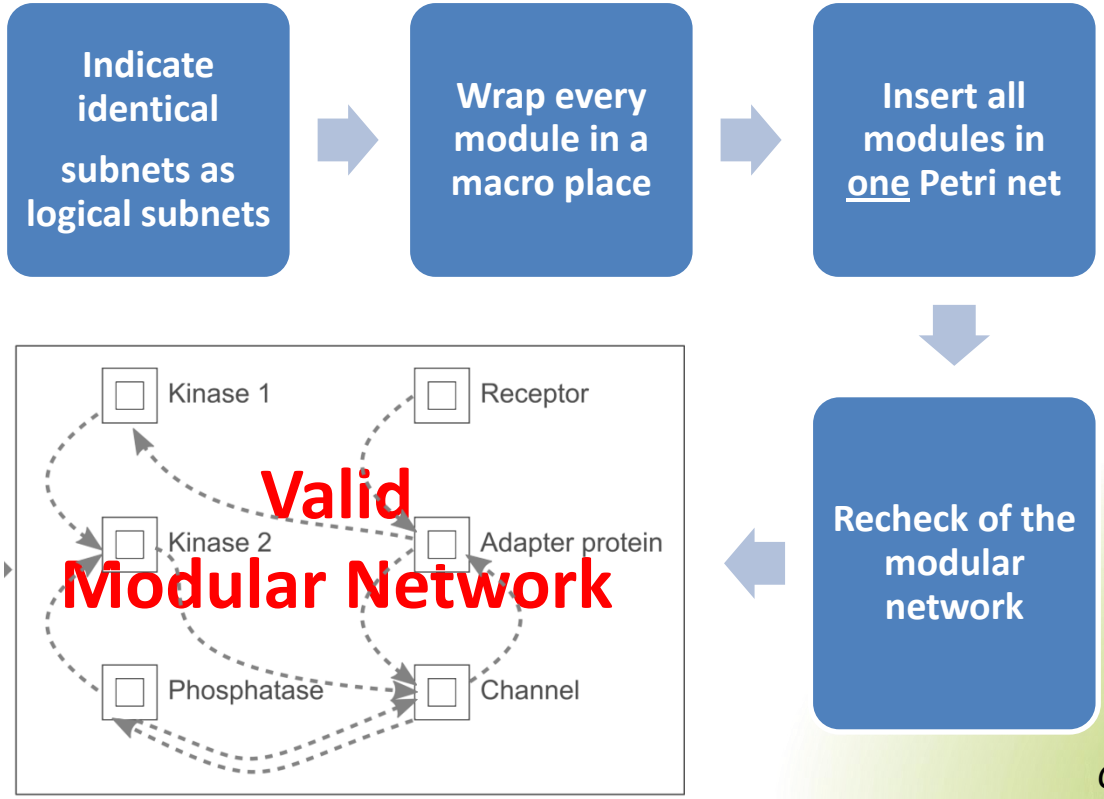
variable

must be fulfilled

- Stochastic simulation studies:
  - Dynamic behavior of the modules has to reflect the assigned function of the proteins

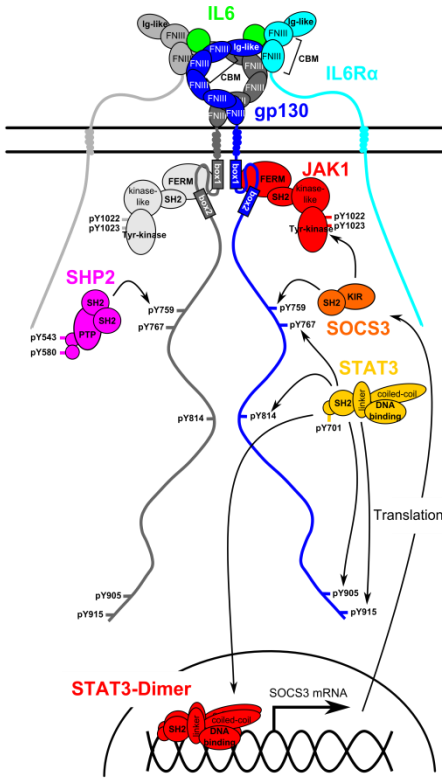
Generation of a Modular Network

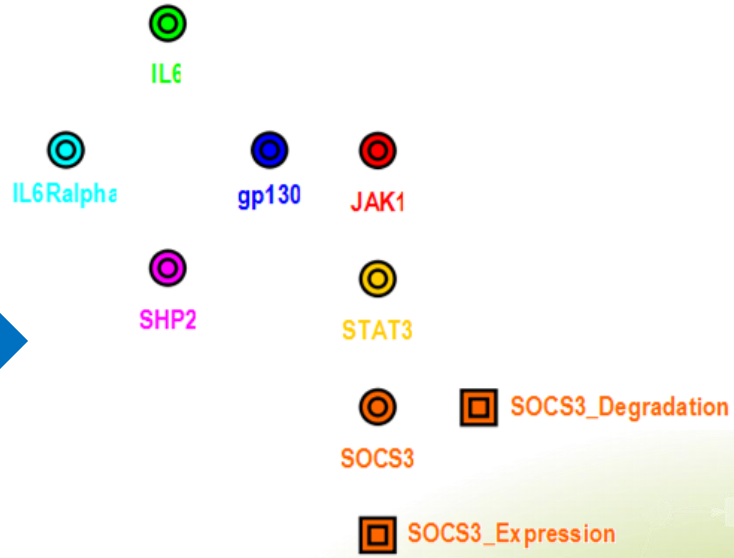
- Generation of a modular network from a set of modules
- Identical copies of subnets and places of non-proteins build the connection interface among the modules



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

- Modules:

PUR	ORD	HOM	NBM	CSV	SCF	FT0	TF0	FP0	PF0	CON	SC
N	Y	Y	N	N	N	N	N	Y	Y	Y	N

DTP	CPI	CTI	SCTI	SB	k-B	1-B	DCF	DSt	DTr	LIV	REV
N	Y	N	N	Y	Y	Y	N	Y	N	N	N

TRANSFER

- Modular network:

PUR	ORD	HOM	NBM	CSV	SCF	FT0	TF0	FP0	PF0	CON	SC
N	Y	Y	N	N	N	N	N	Y	Y	Y	N

DTP	CPI	CTI	SCTI	SB	k-B	1-B	DCF	DSt	DTr	LIV	REV
N	Y	N	N	Y	Y	N	N	N	N	N	N

must not be fulfilled ⇒ 1:1 Transfer

variable ⇒ Determined by the intersection of the modules

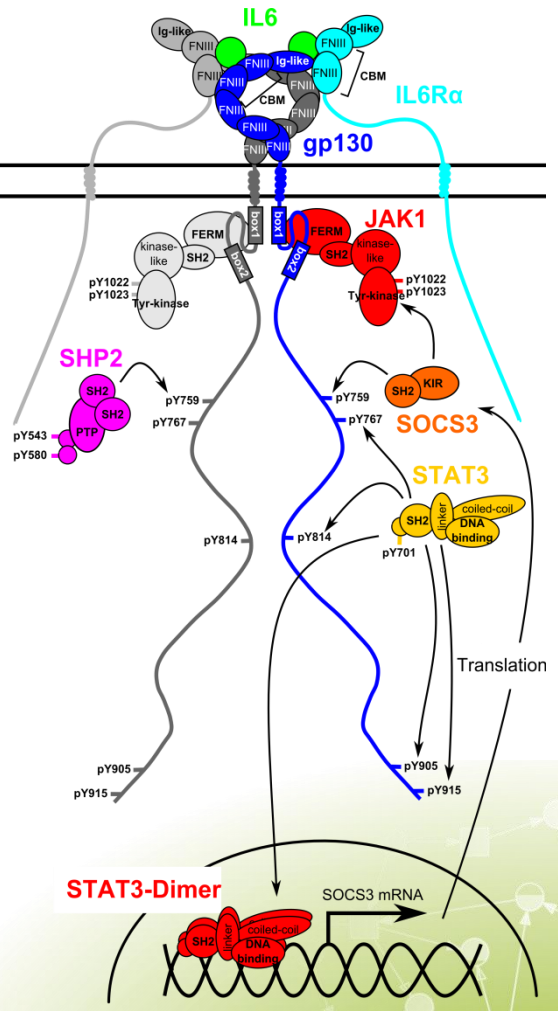
must be fulfilled ⇒ 1:1 Transfer

BioModel Engineering via Modular, Protein-oriented Modelling

Case Study - JAK-STAT Pathway...

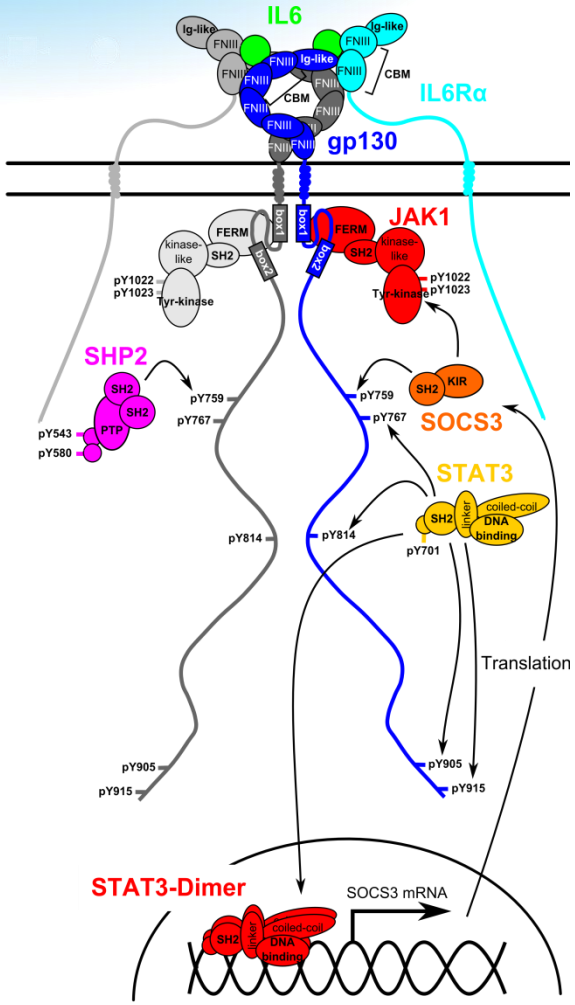
Biomolecular Network

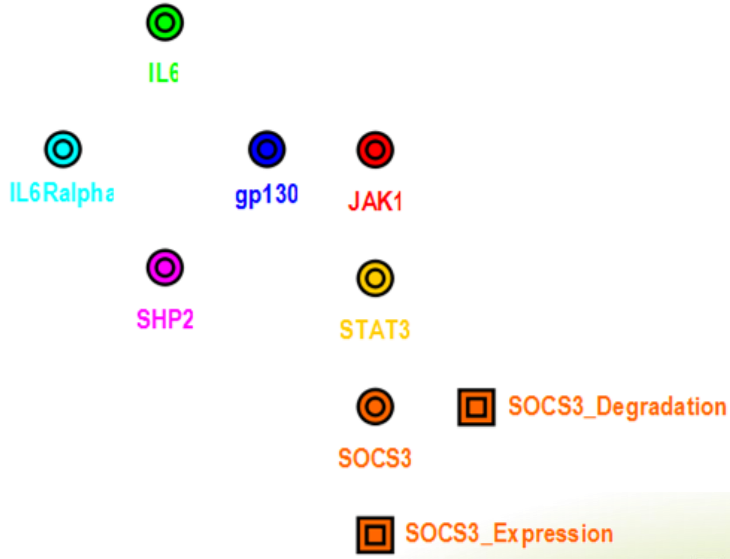
- Main Components: Receptor, JAK, STAT
  - Receptor – Il6-Receptor (here)
  - JAK – Janus- Kinase
  - STAT – Signal Transducer and Activator of Transcription
- Inflammation and the immune response, haematopoiesis, liver and neuronal regeneration, embryonal development and fertility…



[Heinrich et al., 2003]

Modular Model

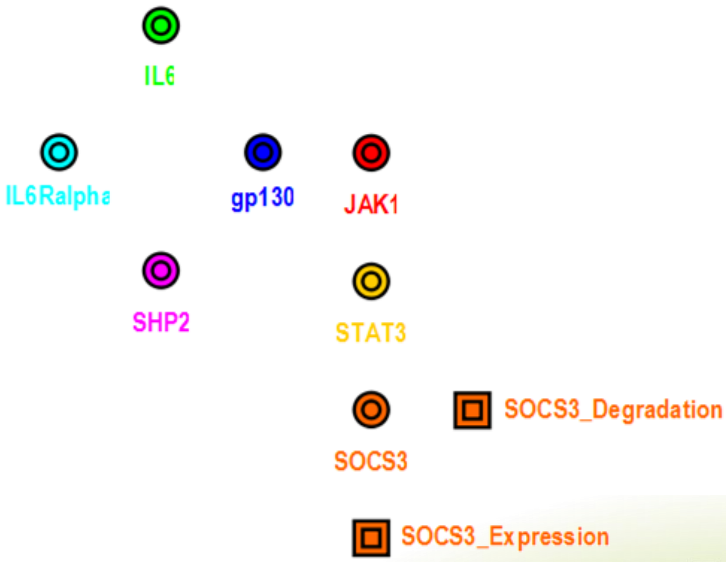




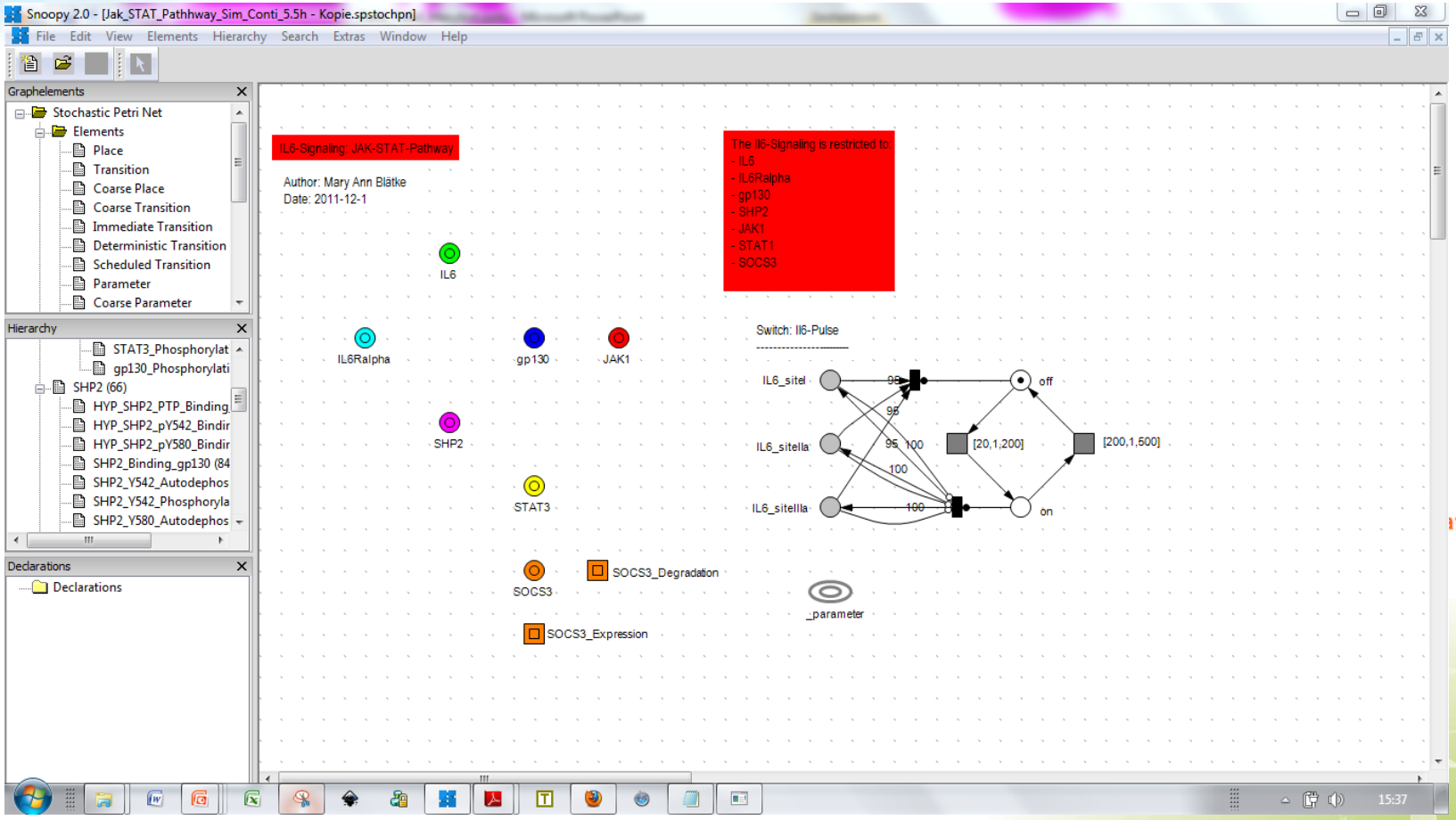
[Heinrich et al., 2003]

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

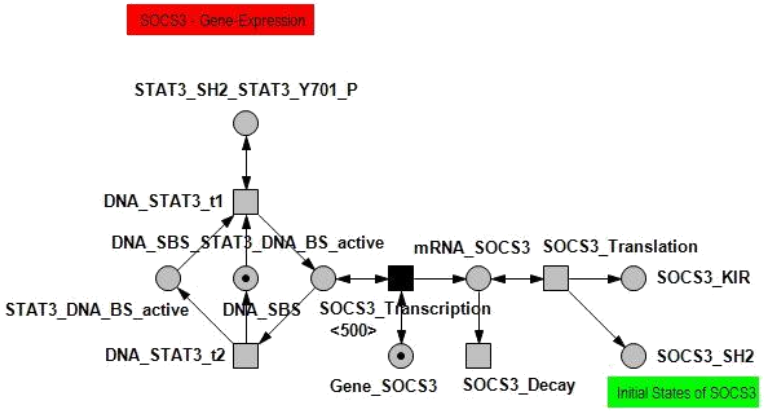


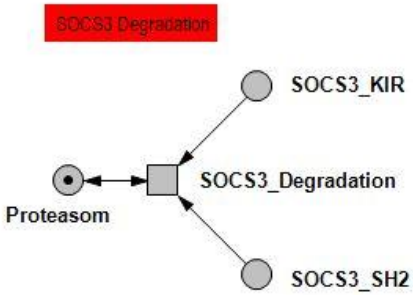
BioModel Engineering via Modular, Protein-oriented Modelling

Summary & Outlook

ADVANTAGES

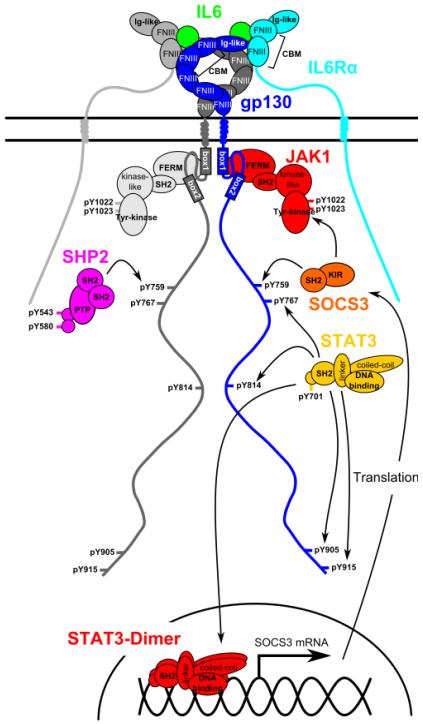
- Modules are…
  - interactive reviews of spread information about a protein
  - easy to update, to extend,
  - to couple by identical matching subnets => straight forward generation of modular networks
  - reusable in other networks
- Extend the modular core network with gene expression, degradation,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



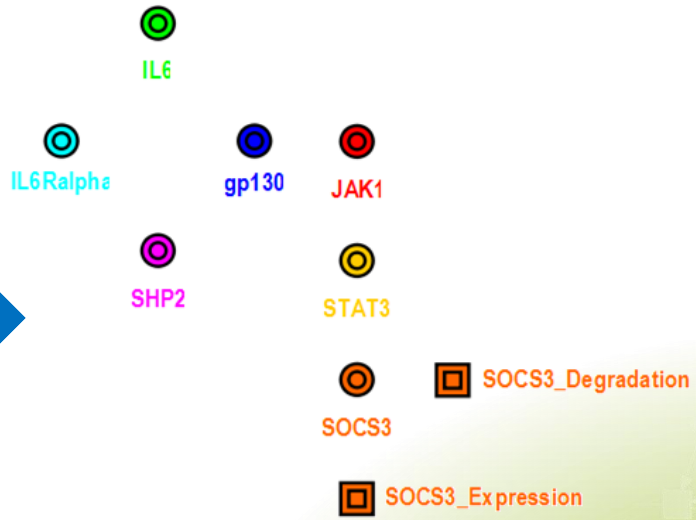


Outlook: Modular Modeling Concept

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

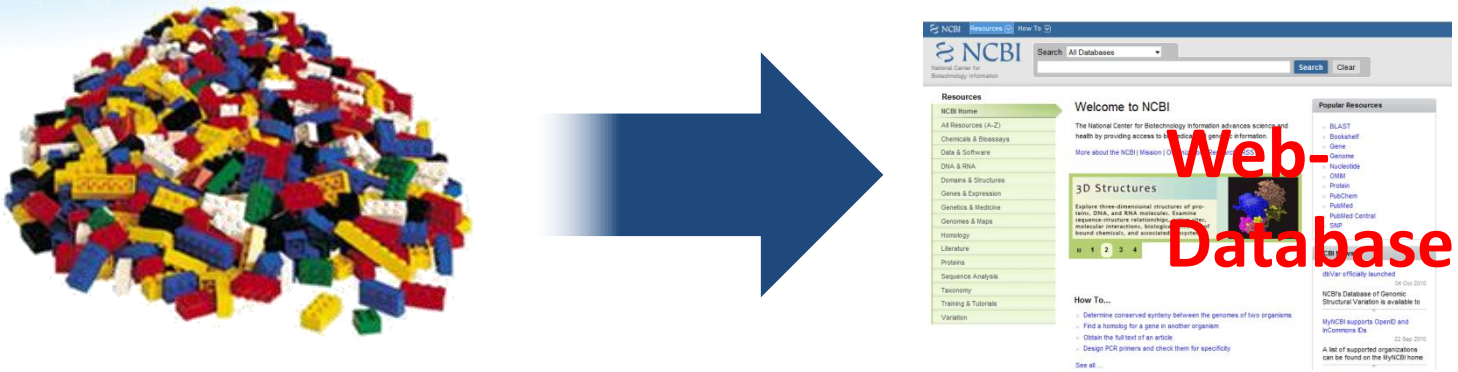


[Heinrich et al., 2003]



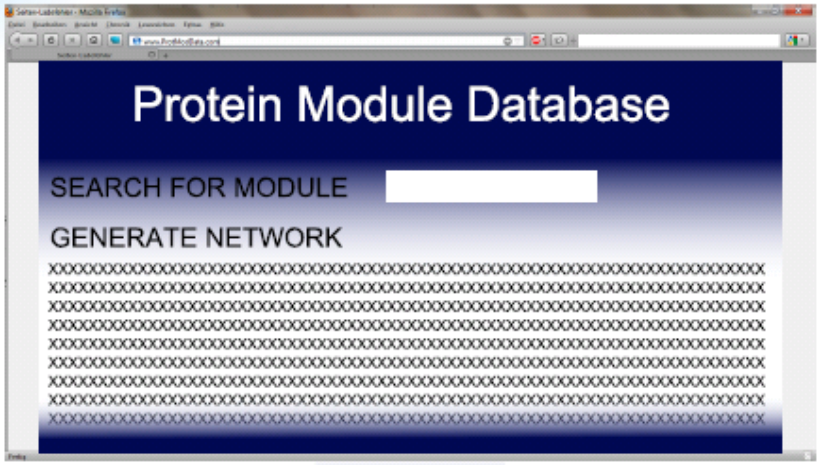
Outlook: Database Concept

- 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

Outlook: Database Concept



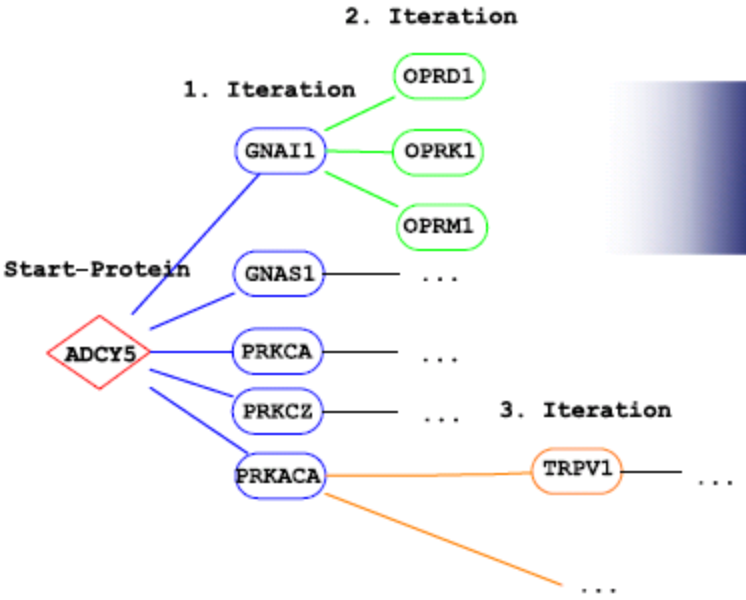
Interaction Matrix in the Background of the Database

	ADCY5	GNAI1	GNAS1	OPRD1	OPRK1	OPRM1	PRKACA	PRKCA	PRKCZ	TRPV1
ADCY5	-									
GNAI1		-								
GNAS1			-							
OPRD1				-						
OPRK1					-					
OPRM1						-				
PRKACA							-			
PRKCA								-		
PRKCZ									-	
TRPV1										-
...										

Iterative Search of Coupling Partners

1.) Search Interacting Proteins

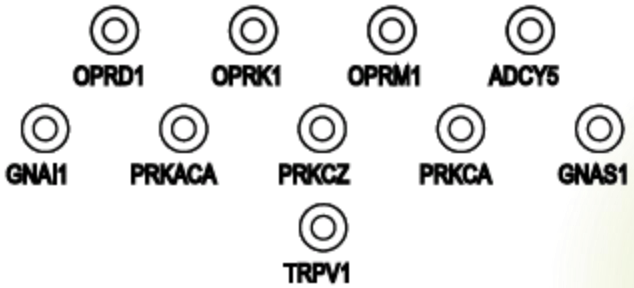
Method: Iterative Network Generation
1. **Stringency: Human**
2. **Start-Protein: ADCY5**

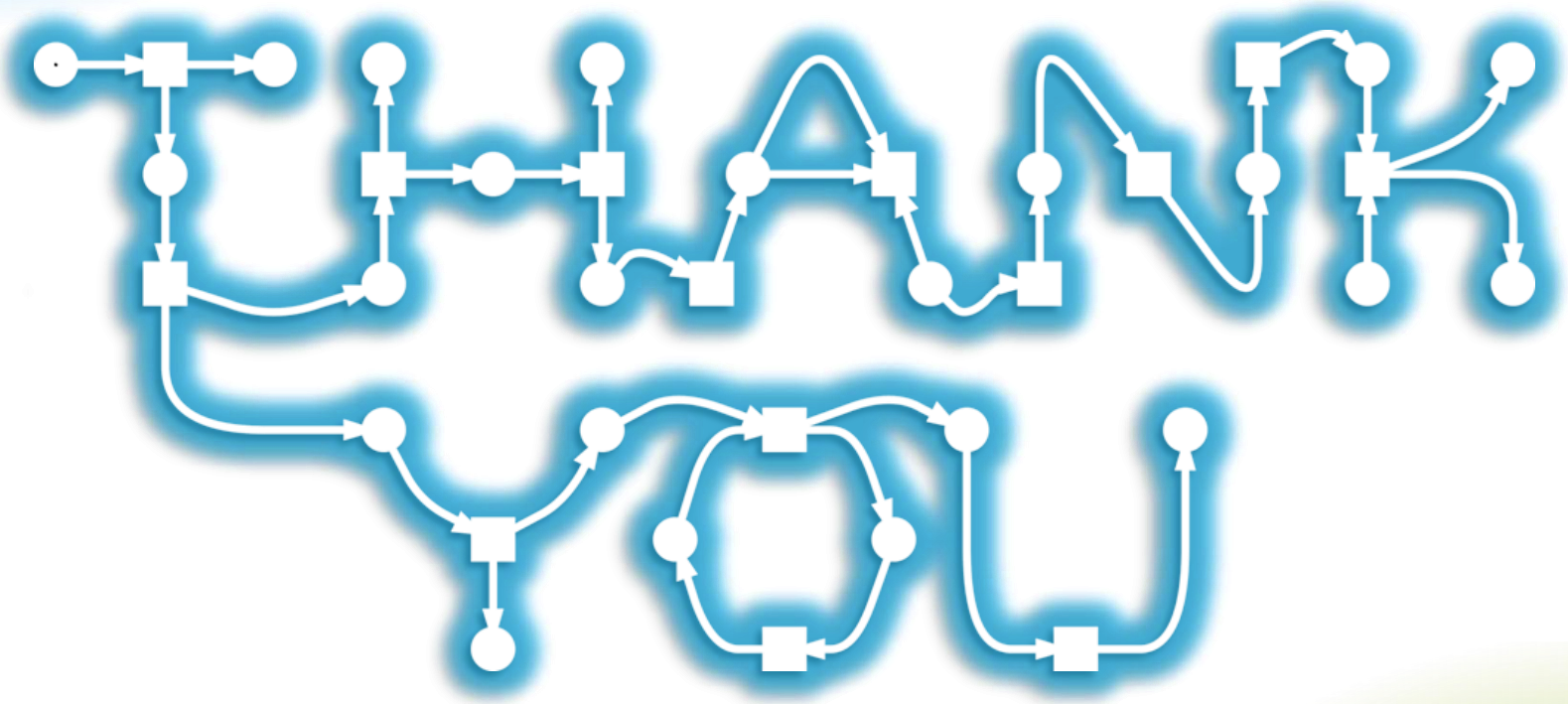


2.) List of Interacting Proteins

Accession No.	Gene Symbol	Organism	Author	Version	Approved	
O95622	ADCY5	Human	Author1	1	Yes	☑
				2	No	☐
			Author2	1	Yes	☐
P63096	GNAI1	Human	Author 3	1	Yes	☑
G5JWF2	GNAS1	Human	Author 4	1	Yes	☑
P41143	OPRD1	Human	Author 3	1	Yes	☑
P41145	OPRK1	Human	Author 5	1	No	☑
P63096	OPRM1	Human	Author 5	1	Yes	☑
P17612	PRKACA	Human	Autho6	1	Yes	☐
			Author7	1	Yes	☑
P17252	PRKCA	Human	Author1	1	Yes	☑
Q05513	PRKCZ	Human	Author1	1	Yes	☑
Q8NER1	TRPV1	Human	Author8	1	No	☐
				2	No	☐
			Author3	1	Yes	☑
				2	No	☐
...	...	...	...	...	...	☐

3.) Export of the Generated Network




THANK
YOU