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

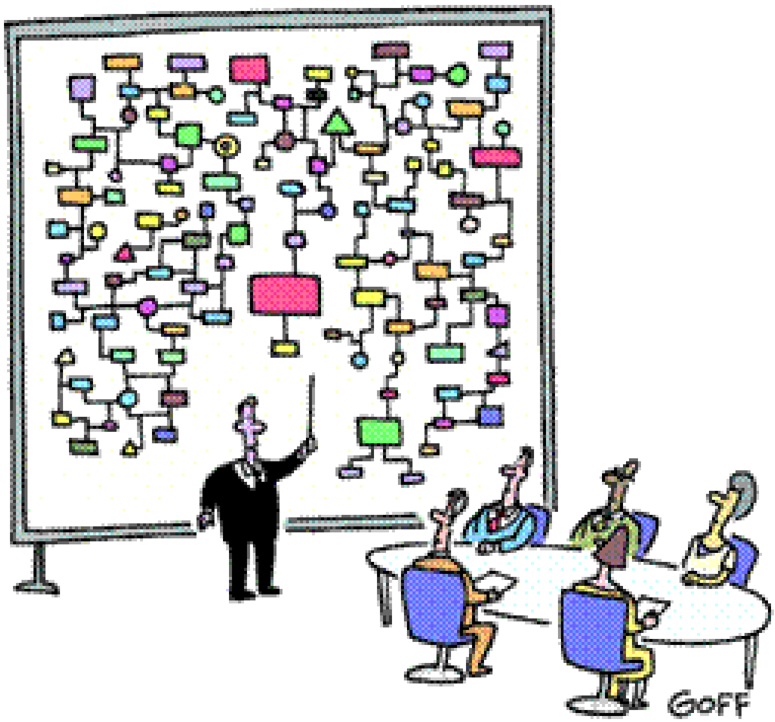
mary-ann.blaetke@ovgu.de

Motivations

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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

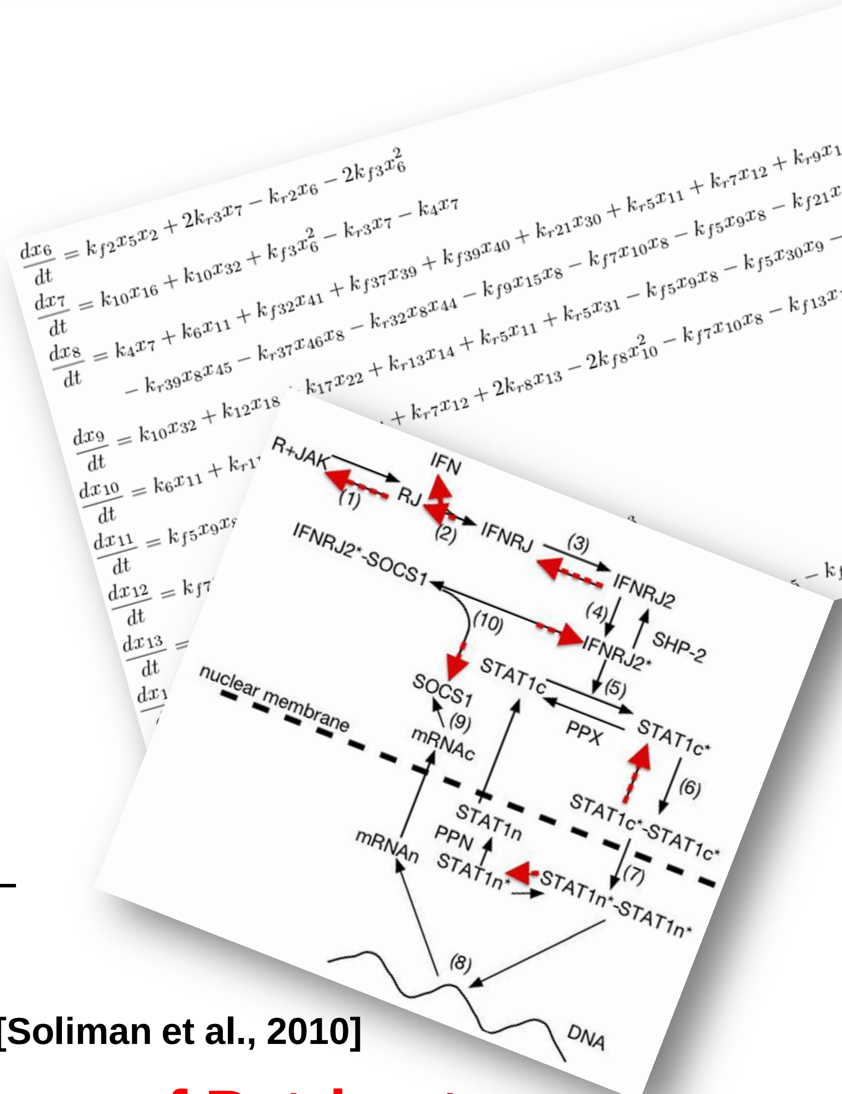


"And that's why we need a computer."

⇒ 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]

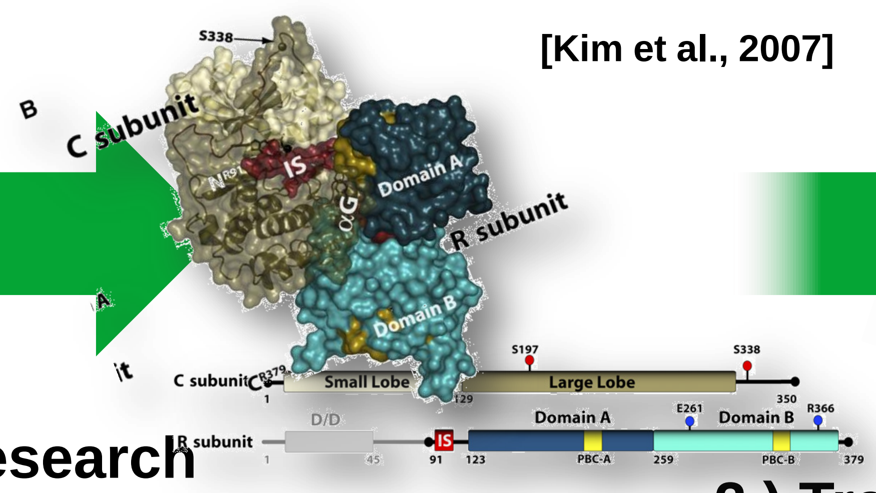
⇒Our Idea: Using the power of Petri nets to Model Molecular Networks

[Heiner et al., 2010]

Modular Petri net Modeling Concept

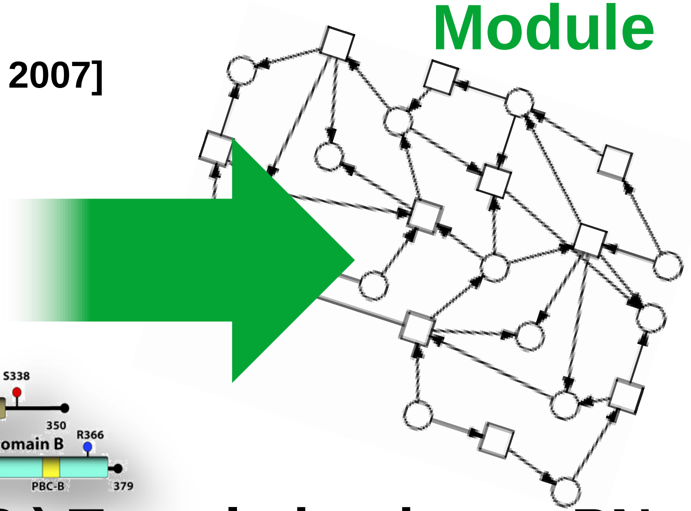
Network Structure of a Module and Properties

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



[Kim et al., 2007]

Module



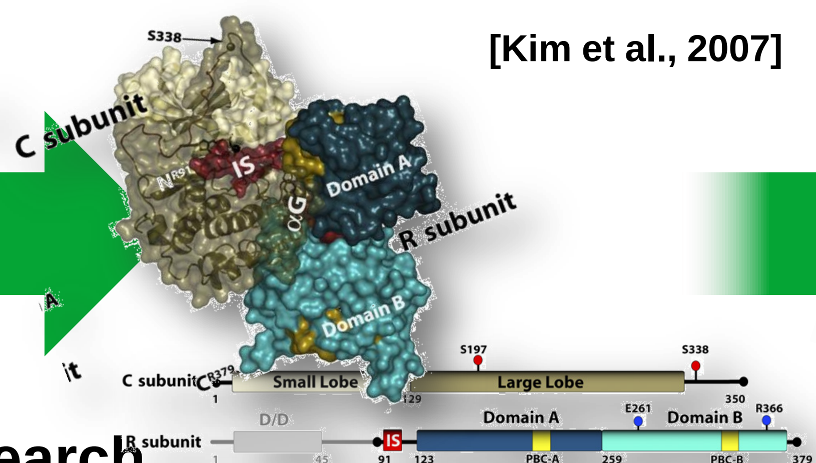
1.) Literature Research

2.) Translation into a PN

Network Structure of a Module and Properties

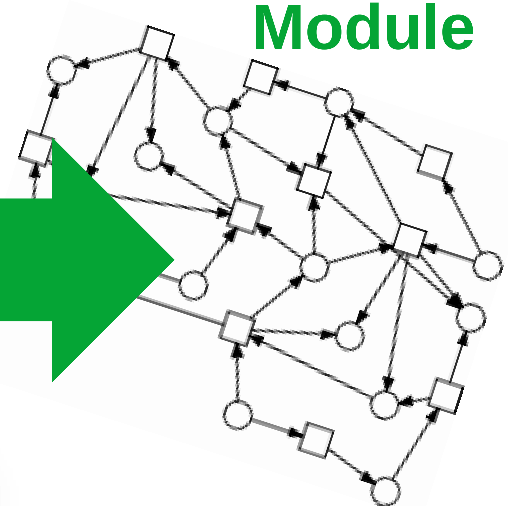
- Domain-related representation of a protein, its interactions and intermolecular changes by a Petri net
  - Place – Specific state of a protein domain (or a non-protein)
  - Transitions – Shifts between different states
  - Principle of double-entry bookkeeping -> shared copies of identical subnets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

1.) Literature Research



[Kim et al., 2007]

Module

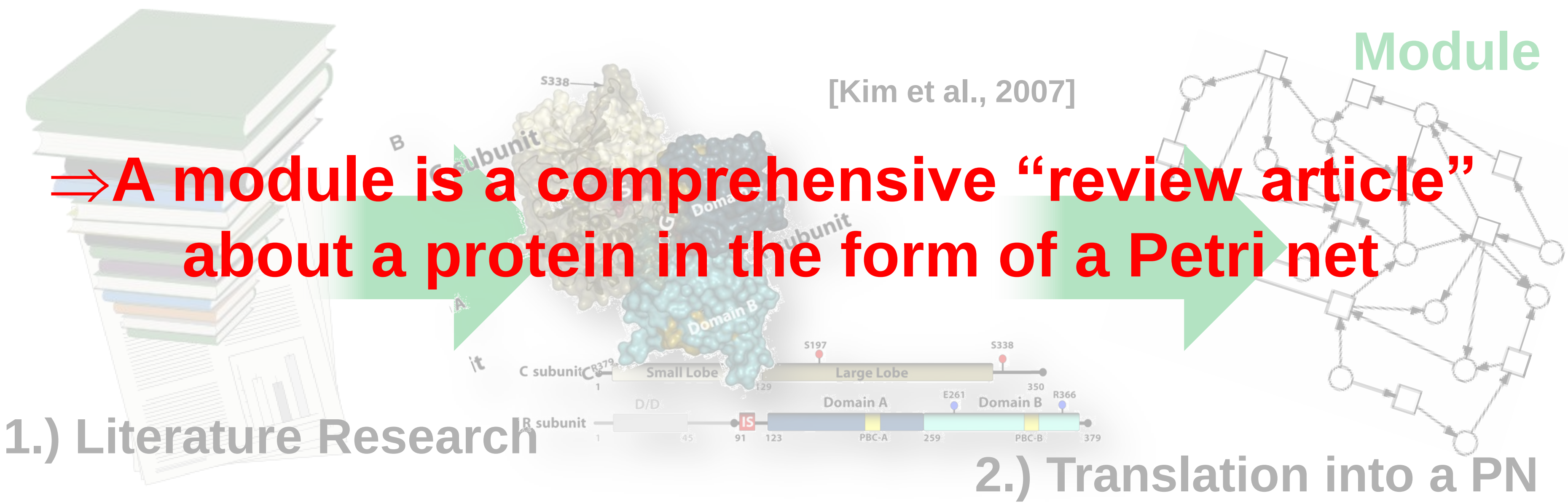


2.) Translation into a PN

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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

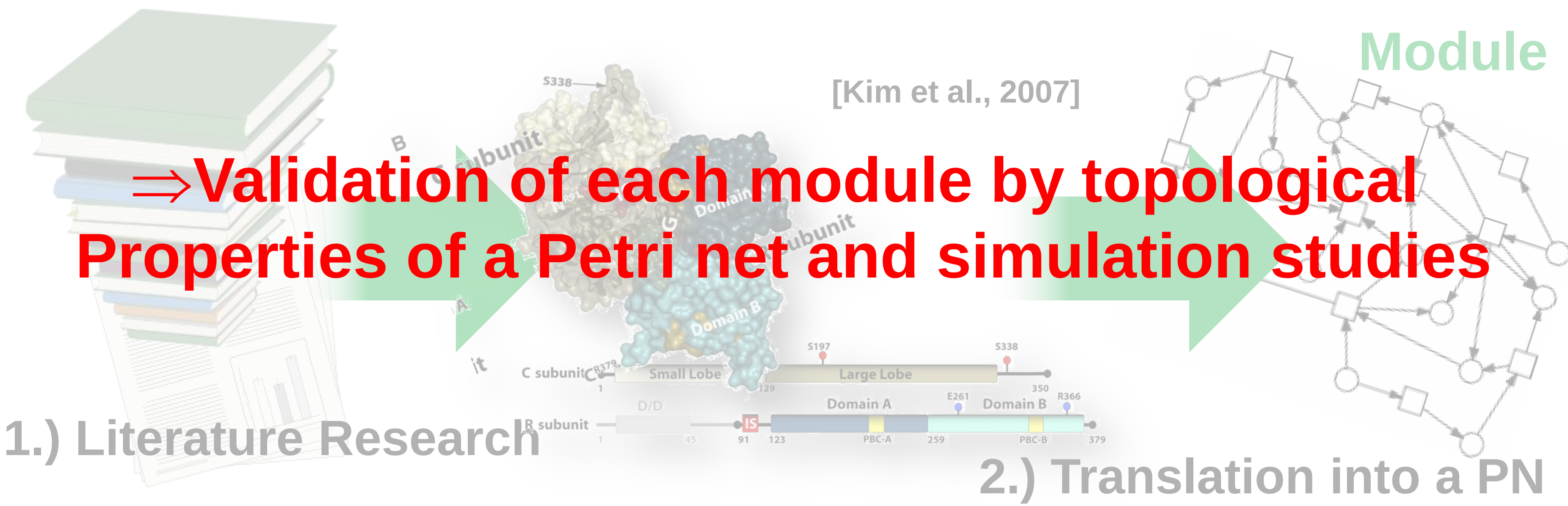


⇒A module is a comprehensive “review article” about a protein in the form of a Petri net

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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

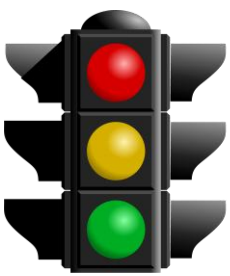
Validation of a Module

- 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

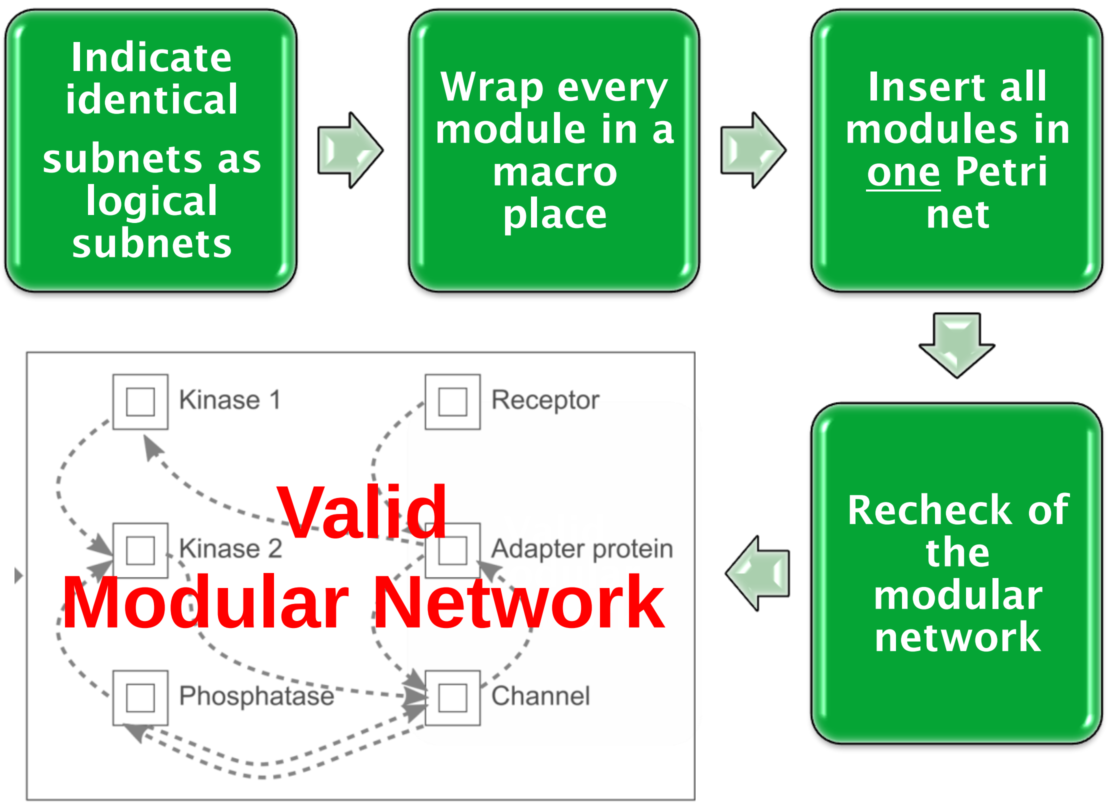
variable

must be fulfilled

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



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

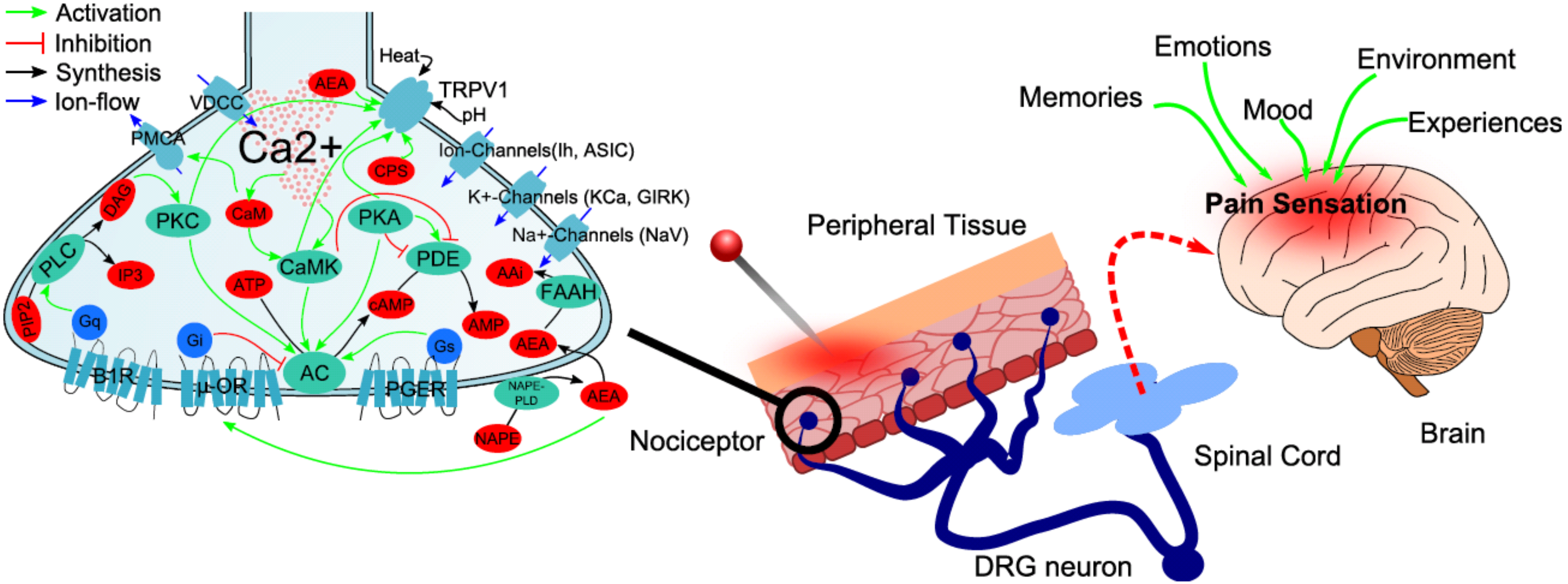
must be fulfilled ⇒ 1:1 Transfer

Case Study – Pain Signaling

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

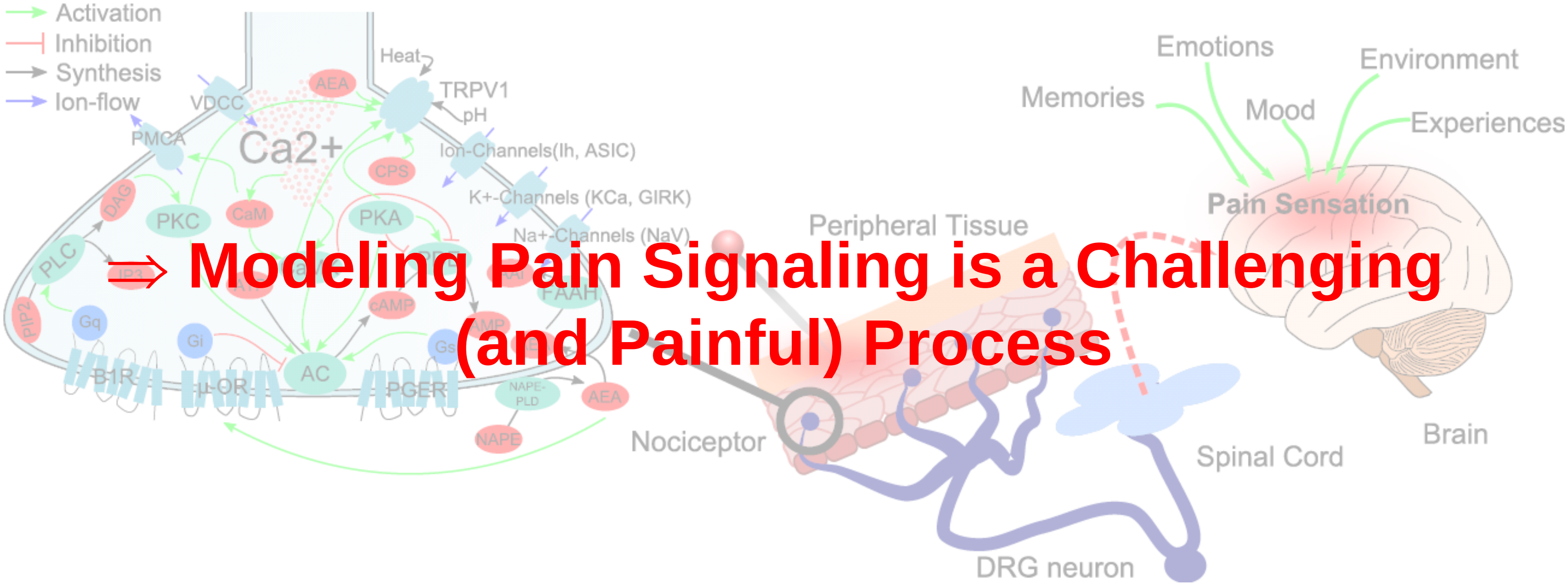
Pain Signaling

- 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

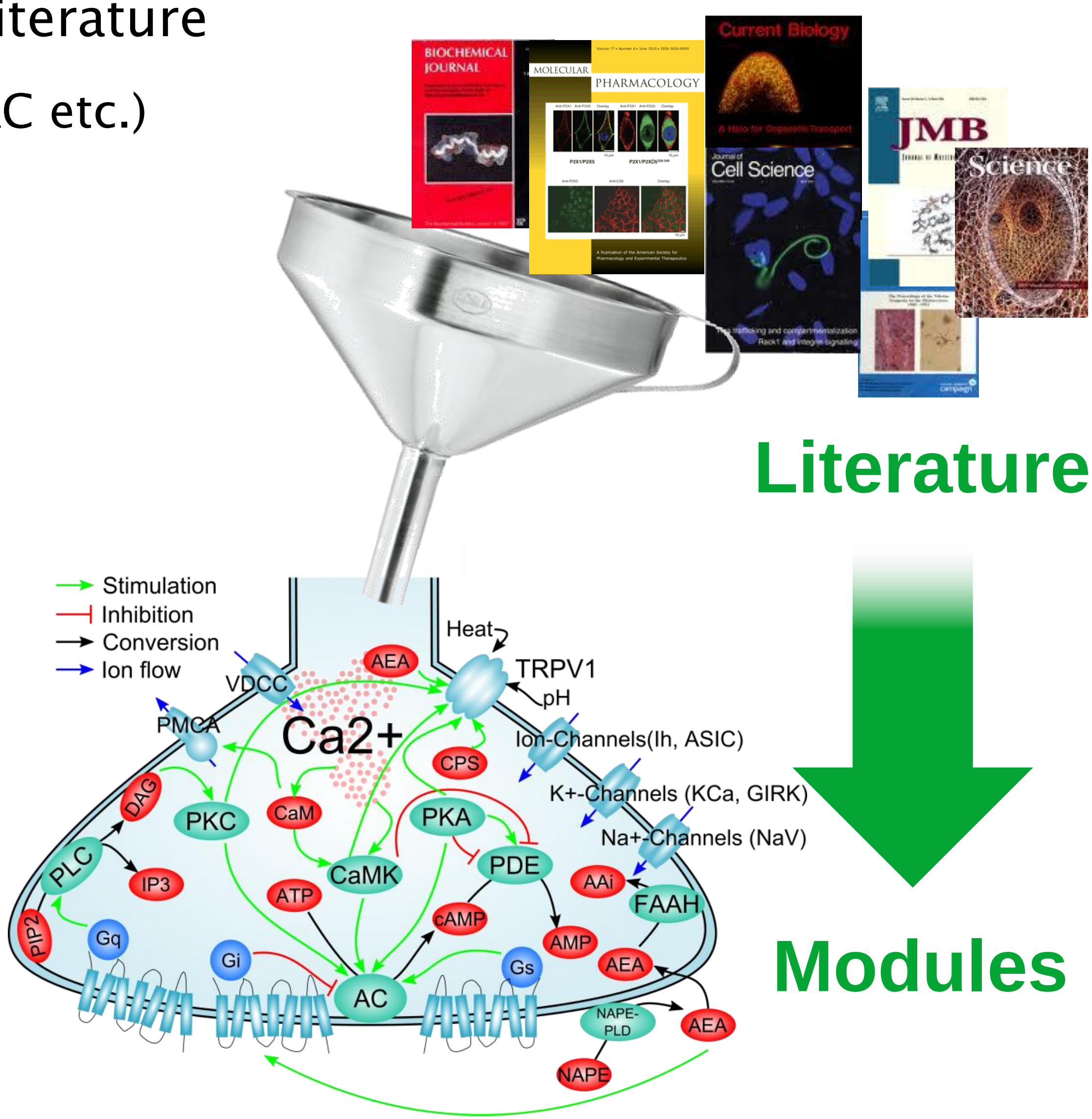


⇒ Modeling Pain Signaling is a Challenging (and Painful) Process

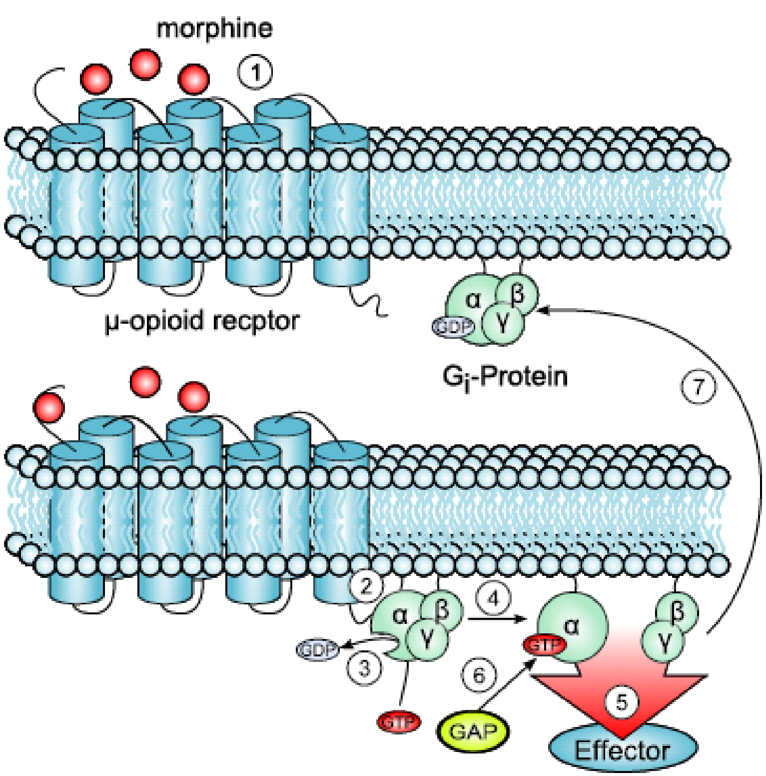
Modules

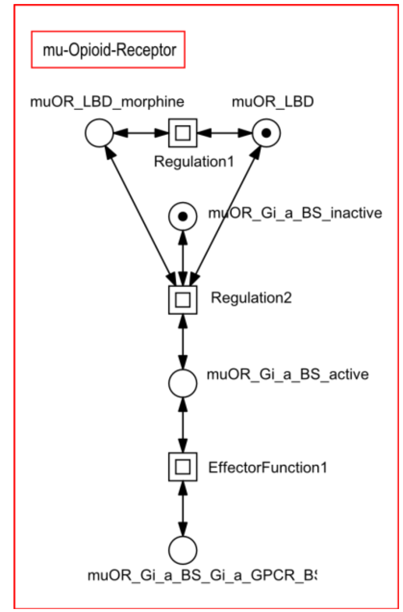
- 38 Modules based on literature
  - Enzymes (PKA, PKC, AC etc.)
  - Receptors (GPCRs)
  - Ca(2+)-Channels
  - Etc.
- Validated by:
  - Structural analysis
  - Simulation studies
- All modules are valid !

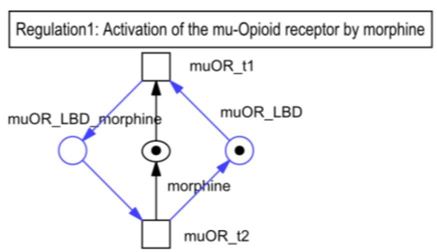
320 scientific articles

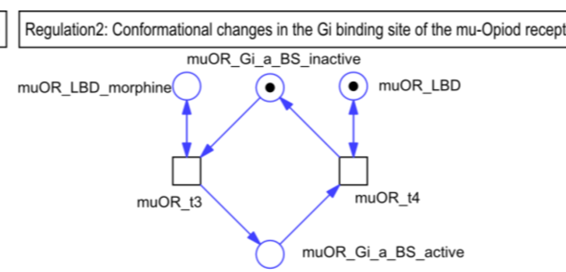


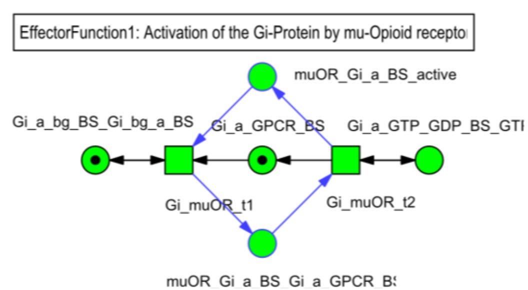
Example : mueOR + Gi–Protein



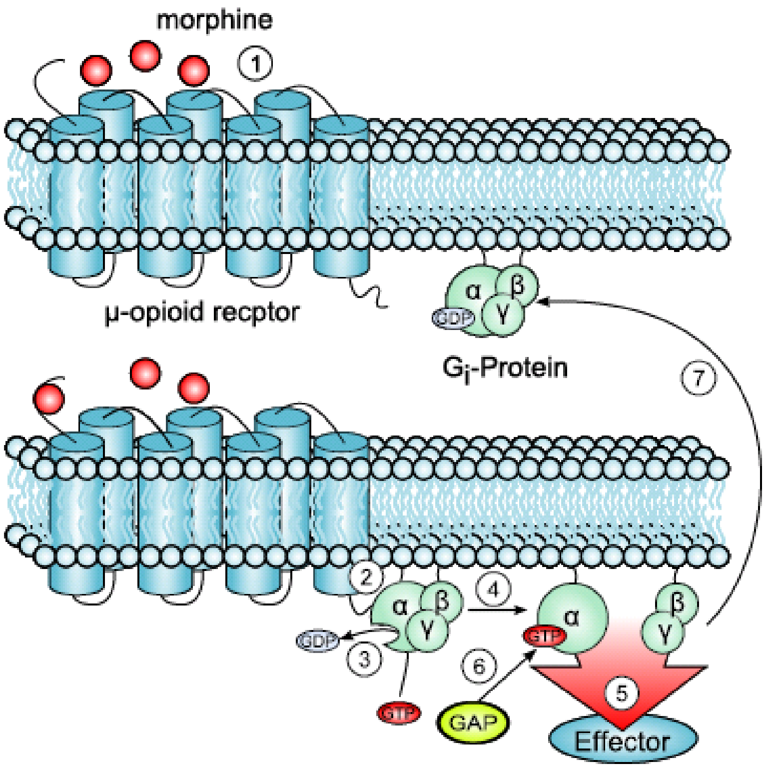


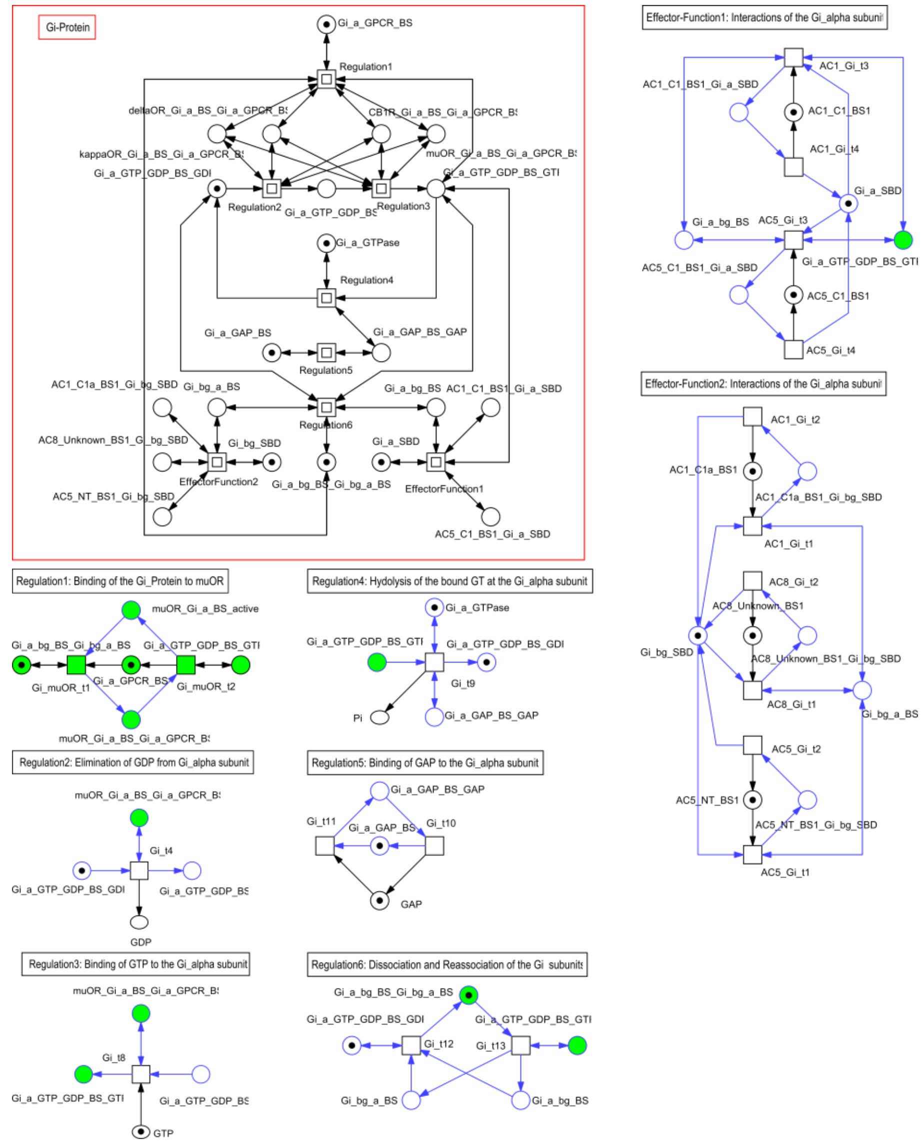




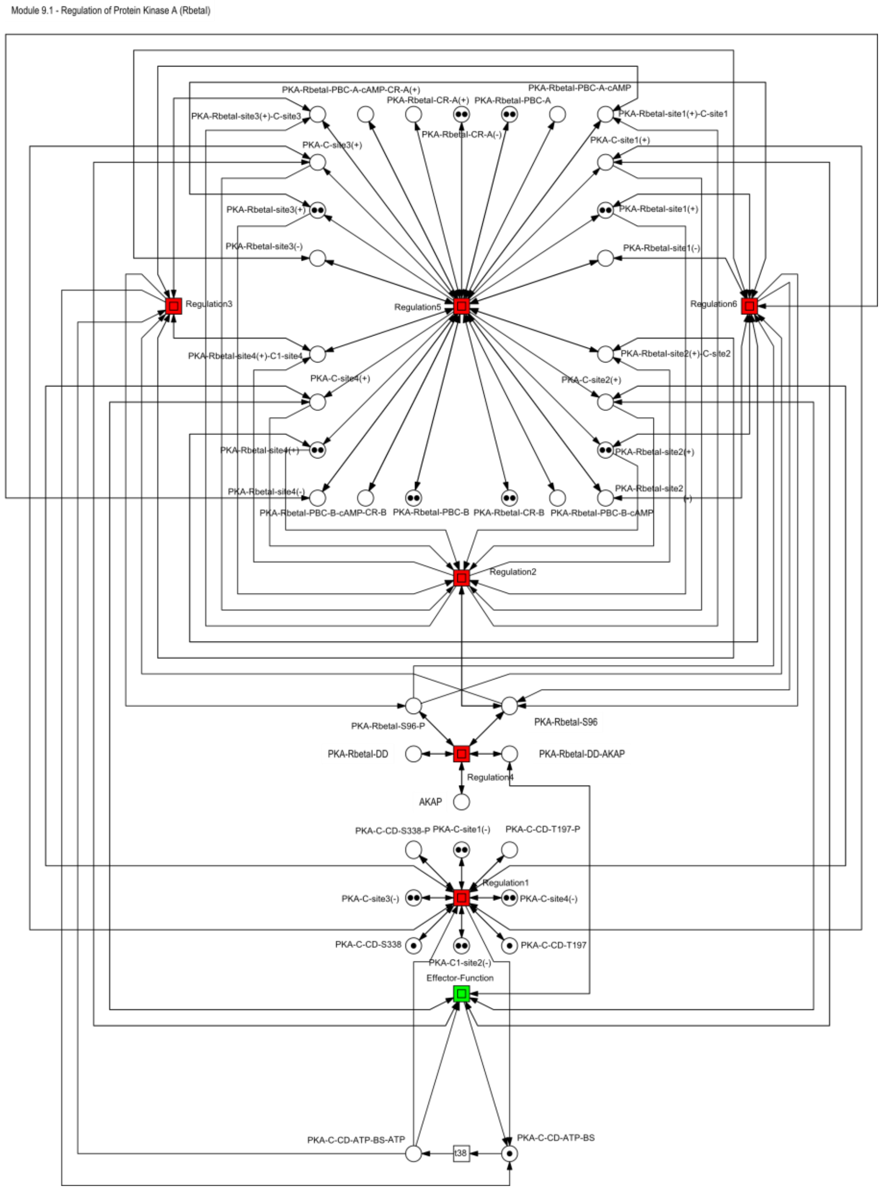


Example : mueOR + Gi-Protein





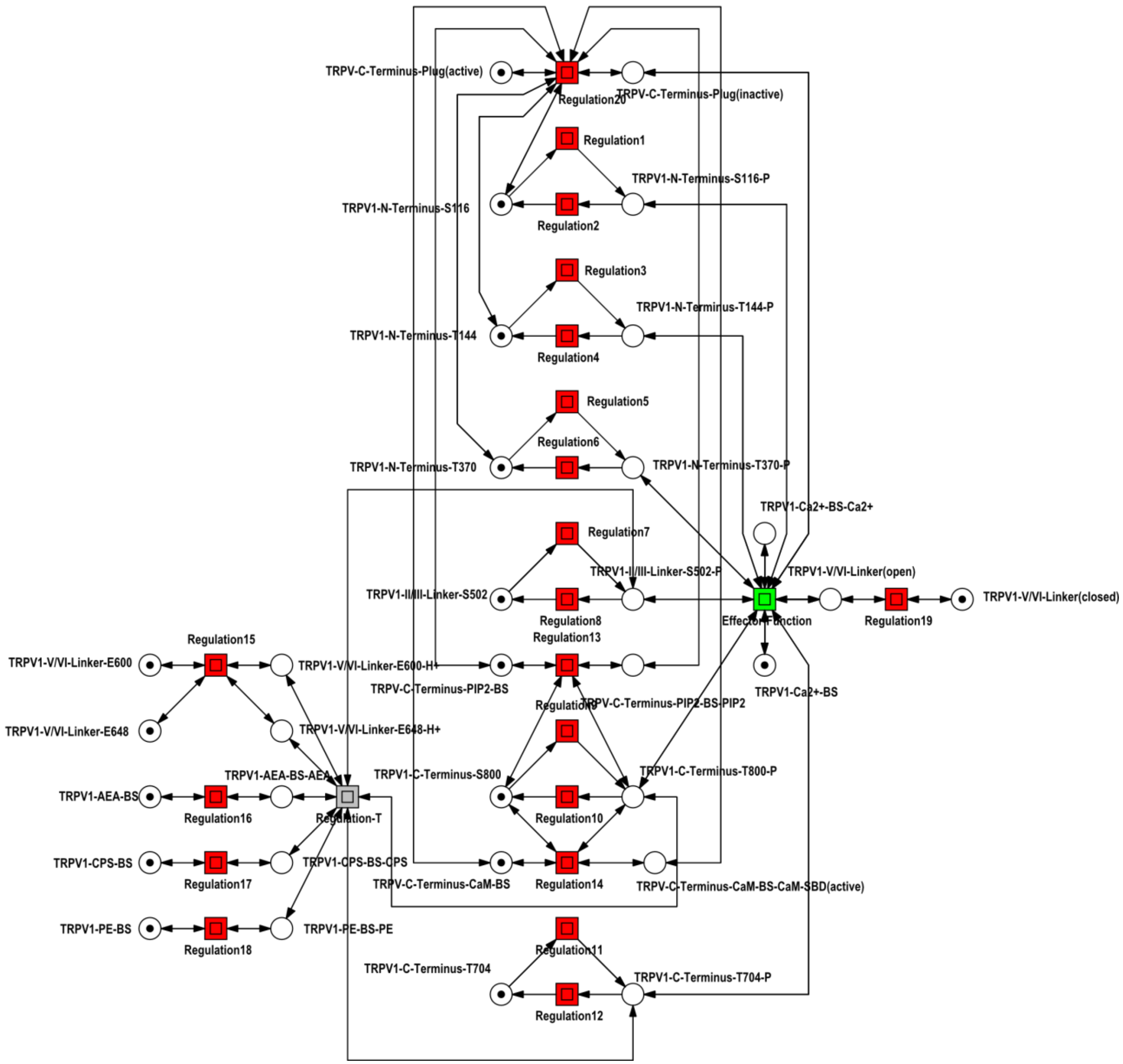
Other Examples: Protein kinase A



OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

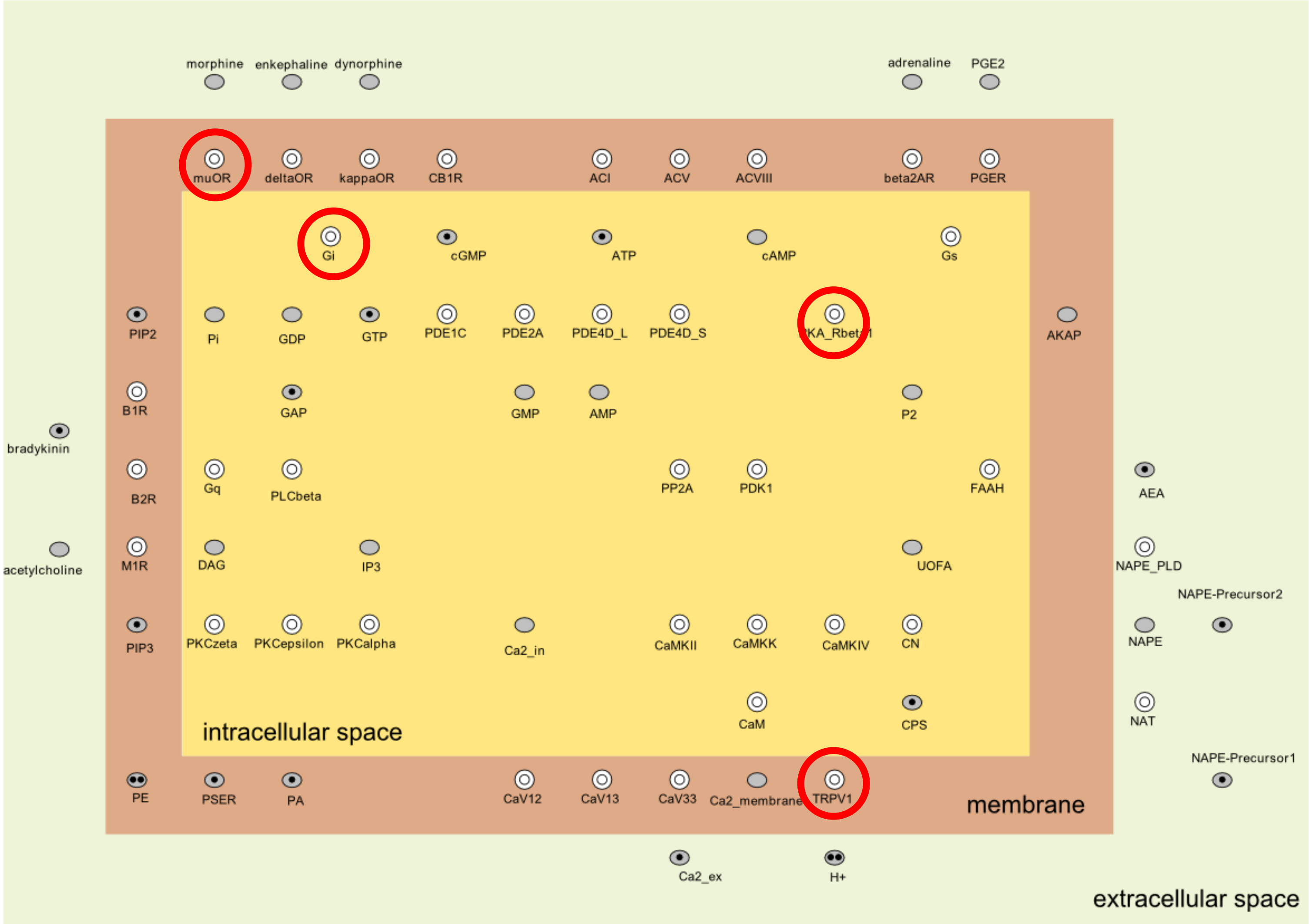
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

Other Examples: TRPV1– Ion–Channel



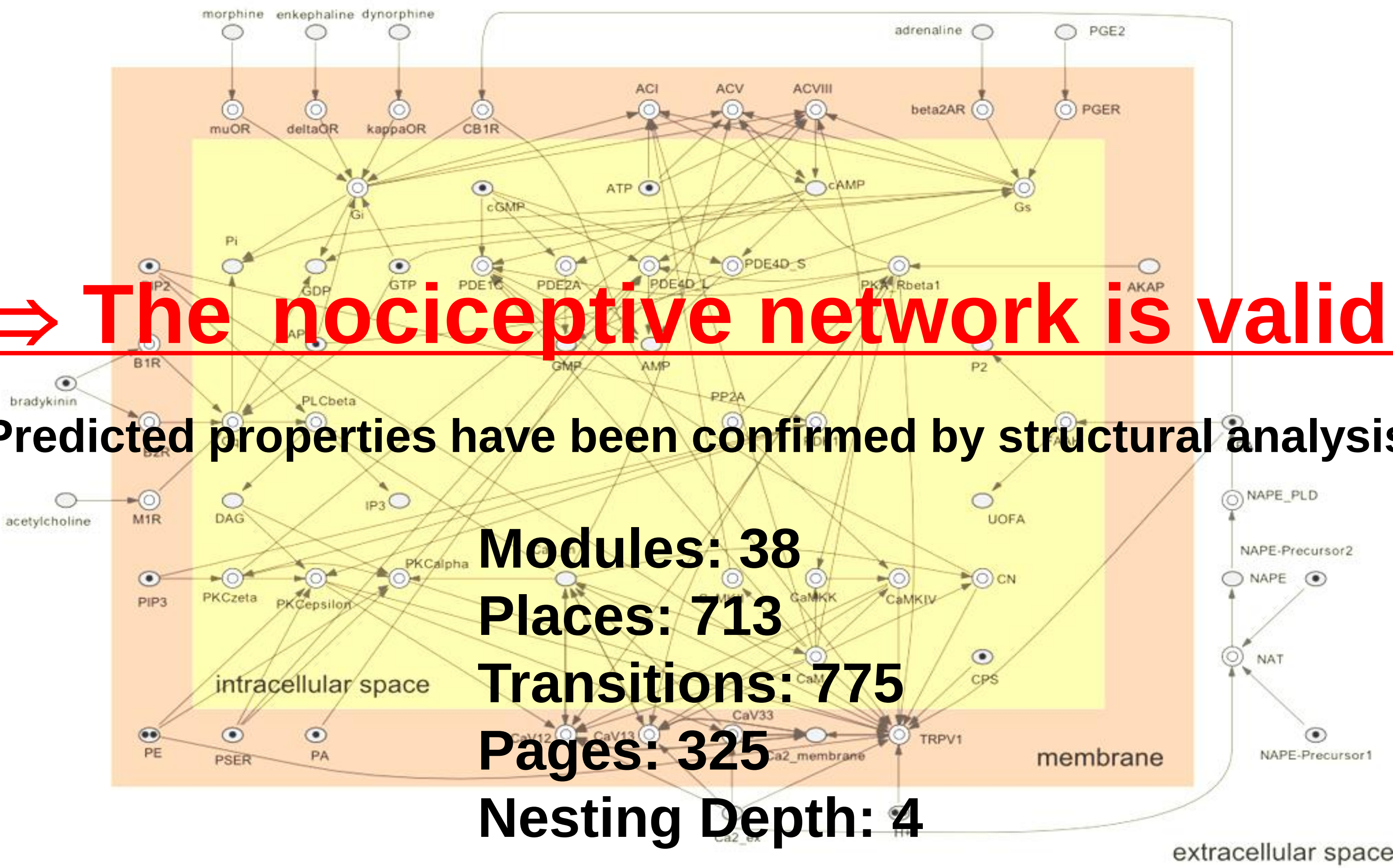
OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

Top-Level of the Nociceptive Network



OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

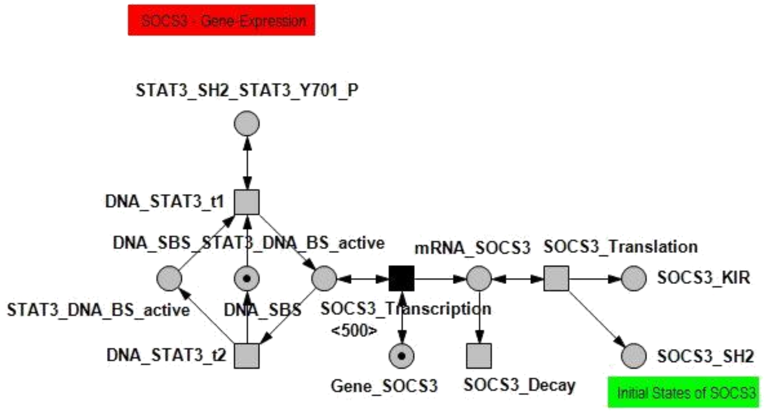
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

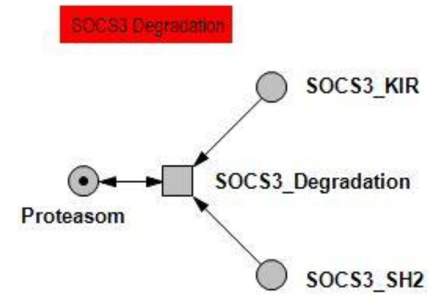
Conclusion and Outlook

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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…





OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

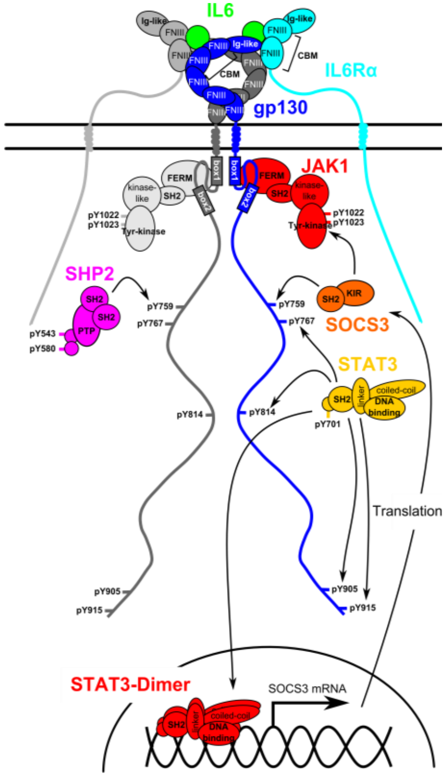
Outlook: "Pain Model"

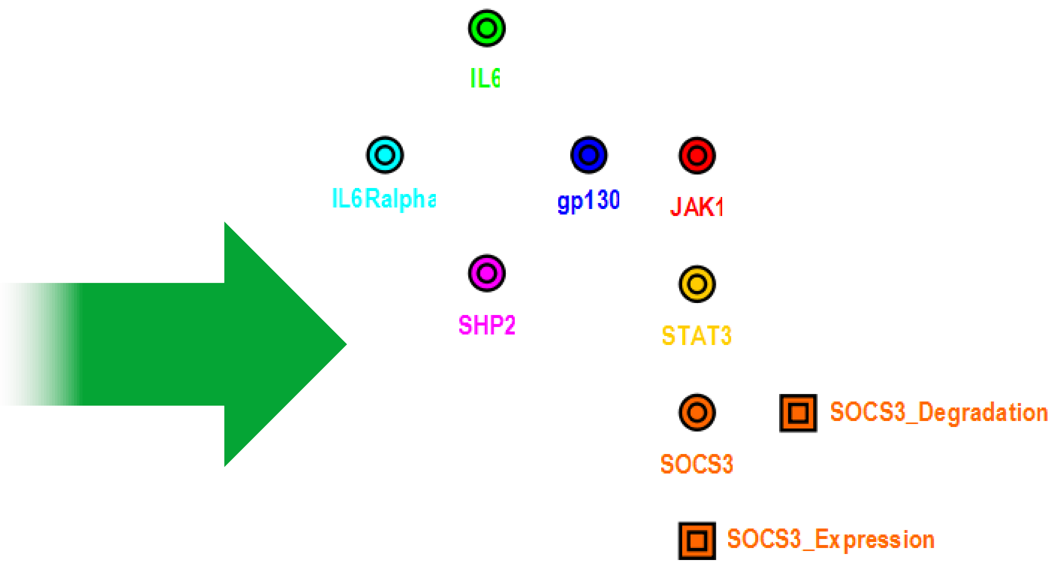
- Identification of possible targets for therapeutic intervention strategies
  - Completion
  - Parameterization and Validation
  - Stochastic Simulation studies
  - Extension to colored Petri nets to represent multiple copies of Proteins and DRG neuron populations

...Petri Net Therapy

Outlook: Modular Modeling Concept

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

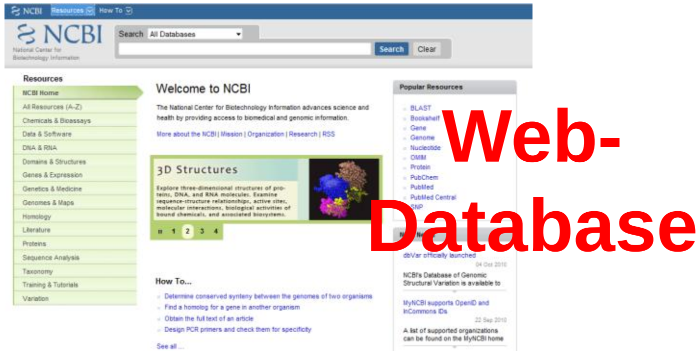




[Heinrich et al., 2003]

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

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

Acknowledgement

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

www.ovgu.de

Bundesministerium für Bildung und Forschung

Magdeburg Centre for Systems Biology MaCS

FORSCHUNGSEINHEITEN FORSYS DER SYSTEMBIOLOGIE

mary-ann.blaetke@ovgu.de

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

Acknowledgement

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

www.ovgu.de

Bundesministerium für Bildung und Forschung

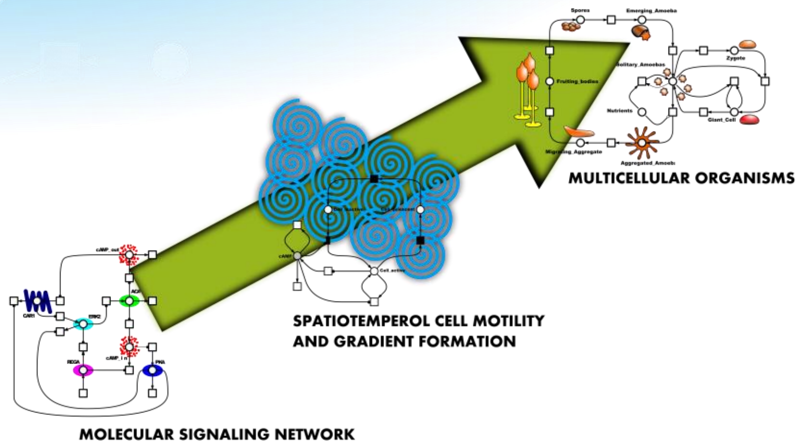
Magdeburg Centre for Systems Biology MaCS

FORSCHUNGSEINHEITEN FORSYS DER SYSTEMBIOLOGIE

mary-ann.blaetke@ovgu.de

Petri Net Tutorial

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



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:

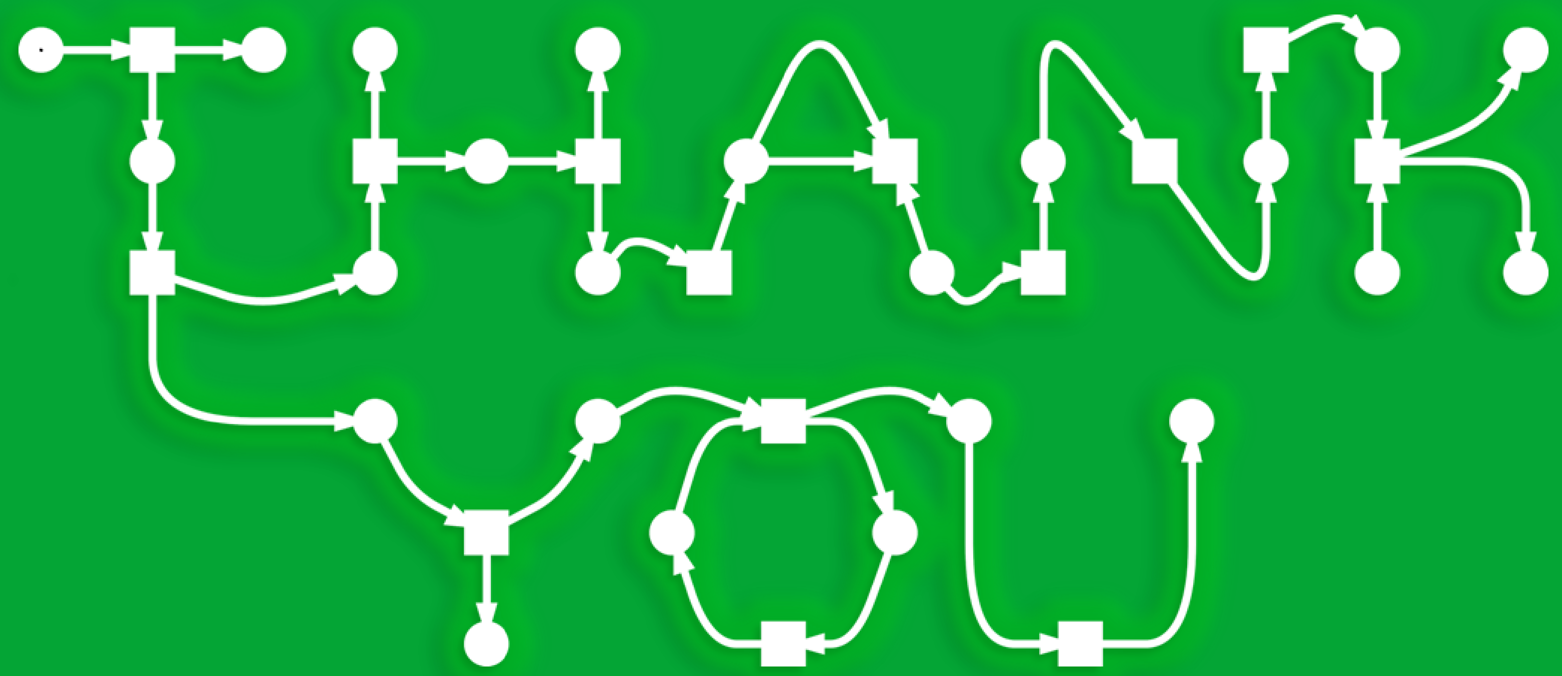
www.icsb-2011.net

Contact/ Information:

mary-Ann.Blaetke@OVGU.DE
http://www-dssz.informatik.tu-cottbus.de/BME/ICSB2011
www.icsb-2011.net

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN



www.ovgu.de

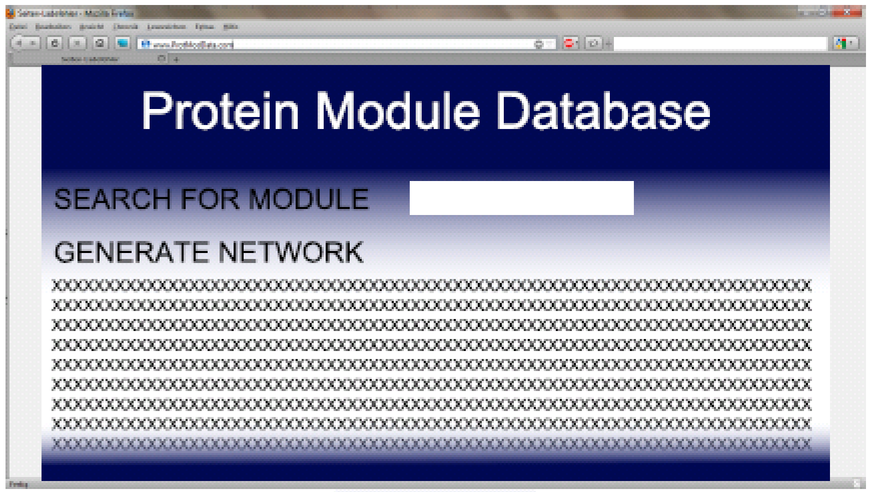
Bundesministerium für Bildung und Forschung

Magdeburg Centre for Systems Biology MaCS

FORSCHUNGSEINHEITEN FORSYS DER SYSTEMBIOLOGIE

mary-ann.blaetke@ovgu.de

Interaction Matrix



Interaction Matrix in the Background of the Database

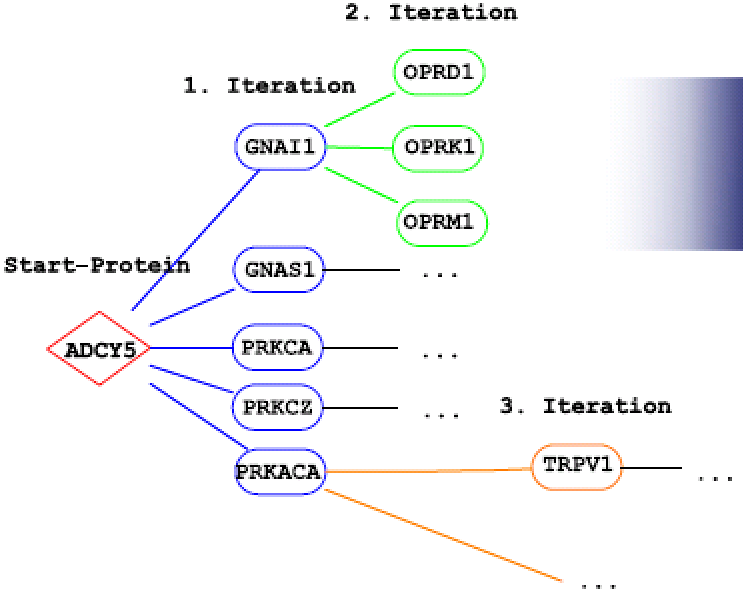
	ADCY5	GNAI1	GNAS1	OPRD1	OPRK1	OPRM1	PRKACA	PRKCA	PRKCZ	TRPV1
ADCY5	-									
GNAI1		-								
GNAS1			-							
OPRD1				-						
OPRK1					-					
OPRM1						-				
PRKACA							-			
PRKCA								-		
PRKCZ									-	
TRPV1										-
...										

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
NAT FAKULTÄT FÜR NATURWISSENSCHAFTEN

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