Colored Petri Nets for Multiscale Systems Biology

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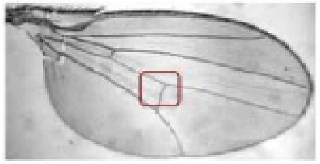
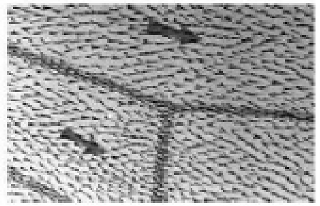
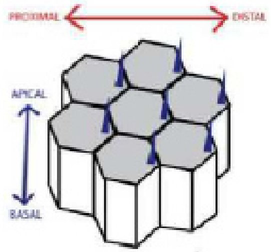
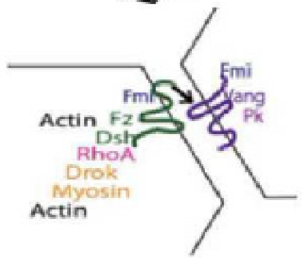
Outline

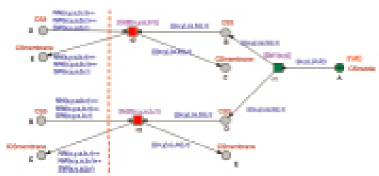
- Multiscale Systems Biology
- Colored Petri nets
- Colored Petri net framework
- Key techniques
- Analysis techniques
- Applications
- Summary











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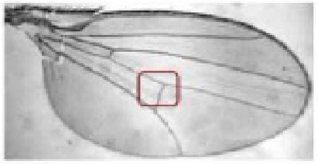
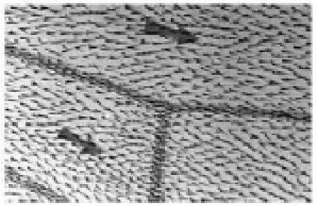
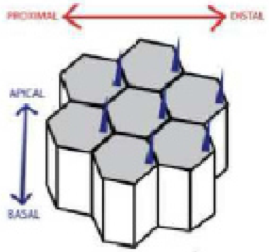
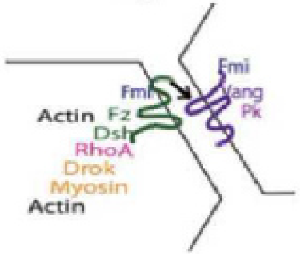
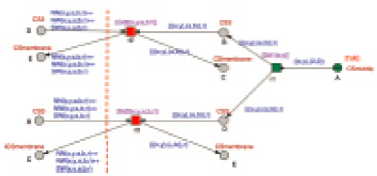




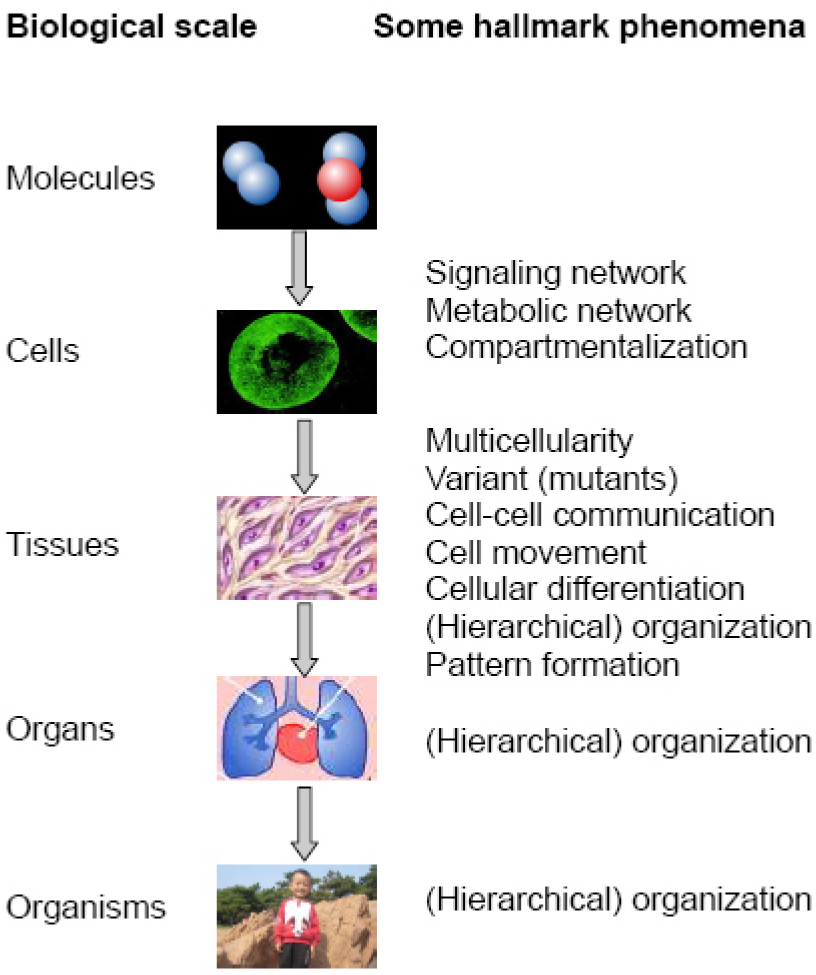






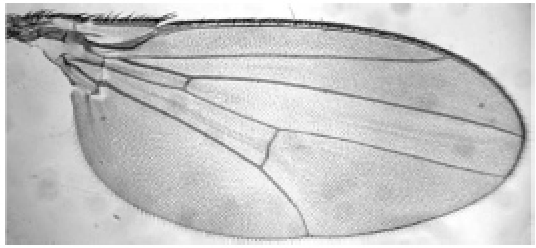
Systems Biology

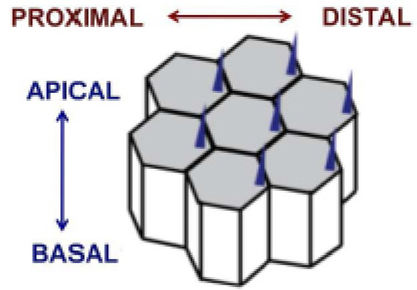
- understand biology at a system level [Kitano 2002]
- take into account complex interactions at different scales of biological organization [Popel et al. 2009]

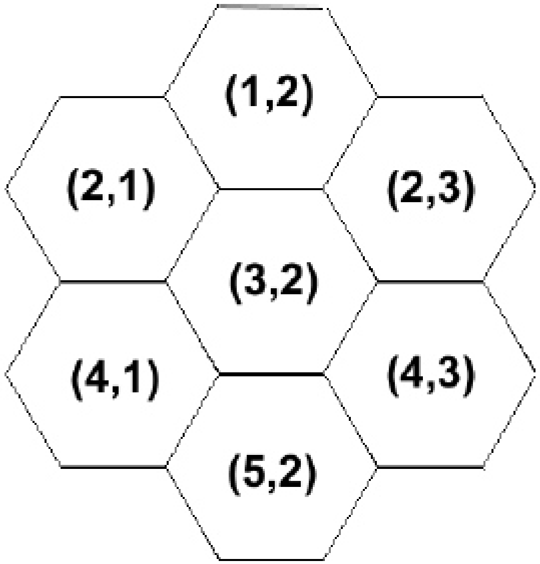


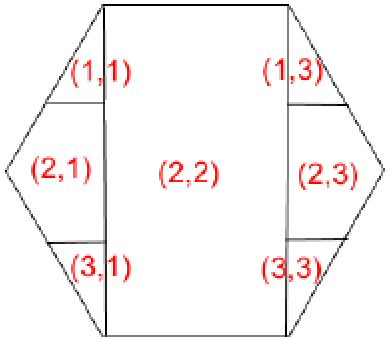
Multiscale challenges

- Repetition
- Variation
- Organization
- Hierarchical organization
- Communication
- Movement
- Replication
- Deletion
- Differentiation
- Dynamic (variable) grid size
- Pattern formation









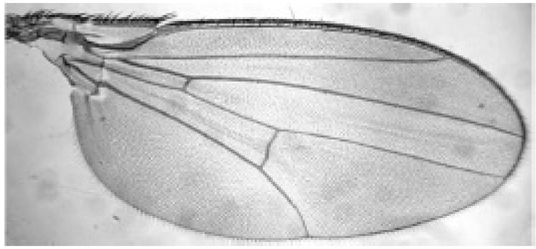
Cell(3,2)

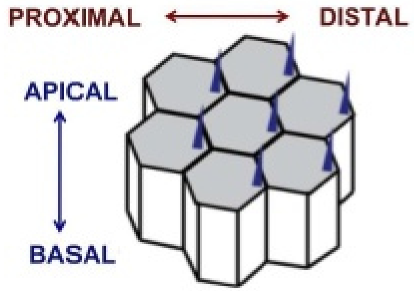
[Gao et. al. 2011]

Modeling challenges

How to

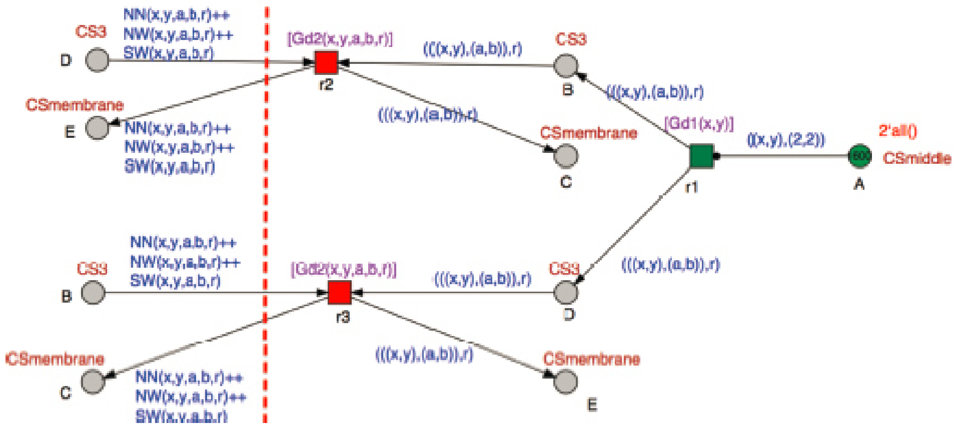
- ☐ Design & construct models
- ☐ Simulate models
- ☐ Analyze models
- ☐ Visualize results





To use

- ☐ Colored Petri nets



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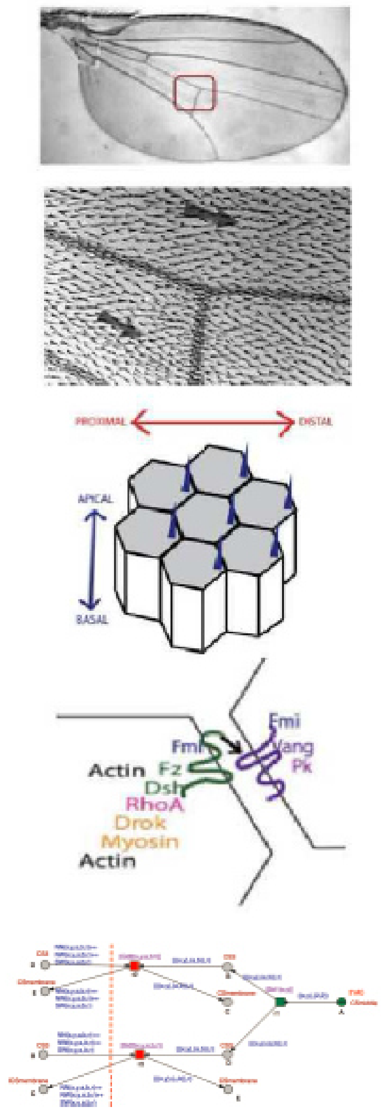
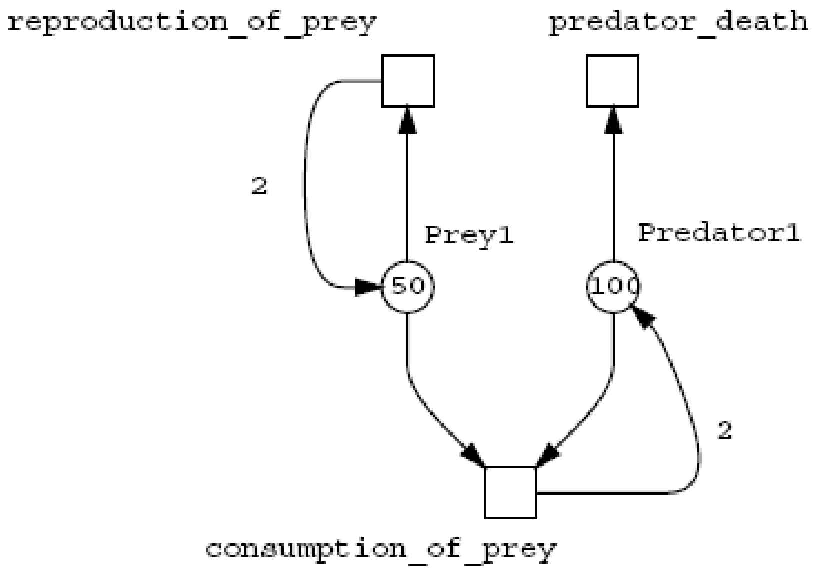


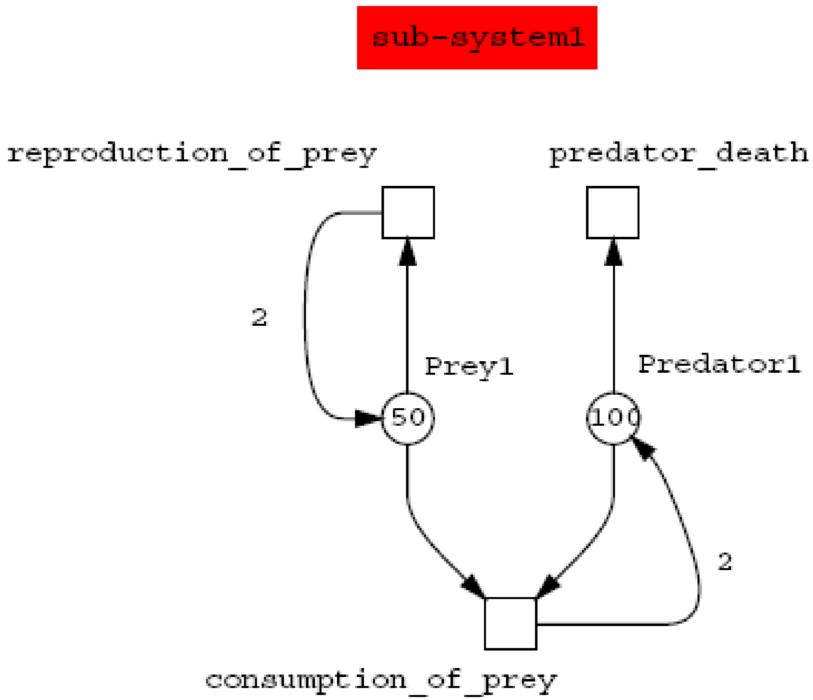
Colored Petri nets

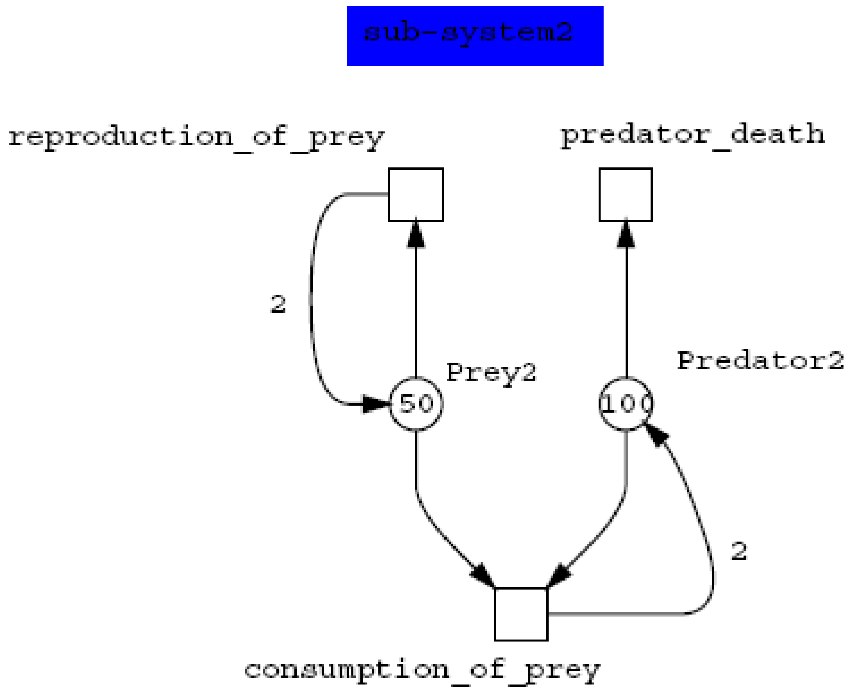


Chemical reactions:

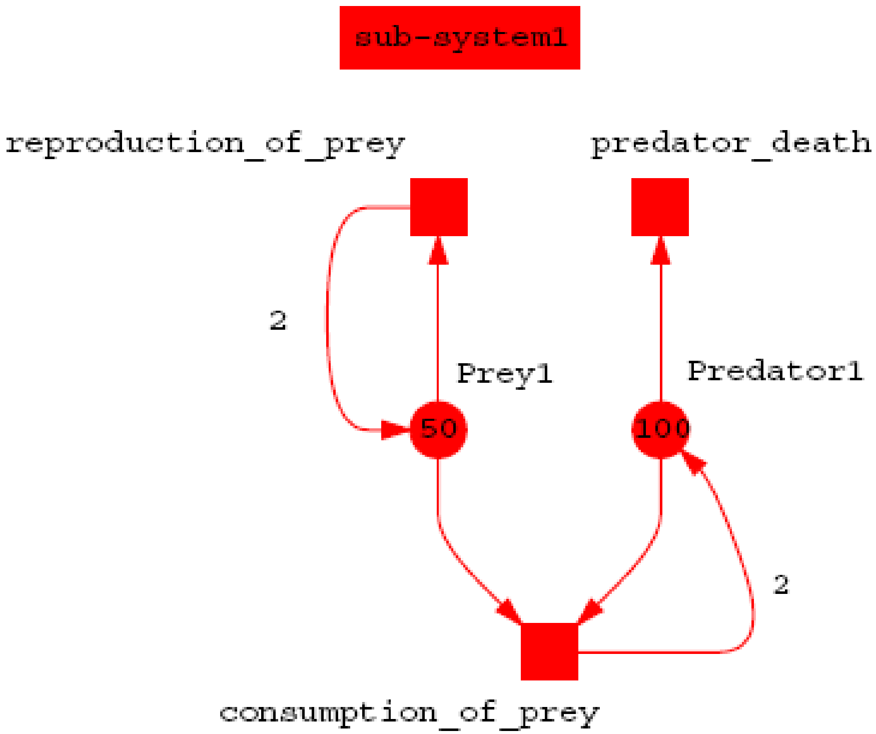
- Prey → 2Prey
- Prey + Predator → 2Predator
- Predator → λ

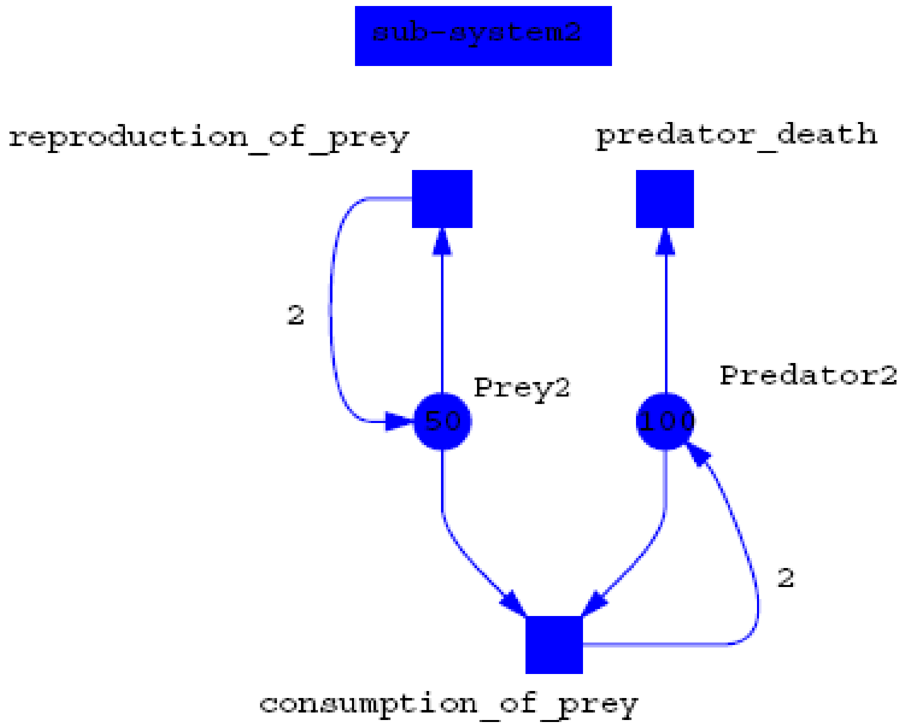
Colored Petri nets





Colored Petri nets

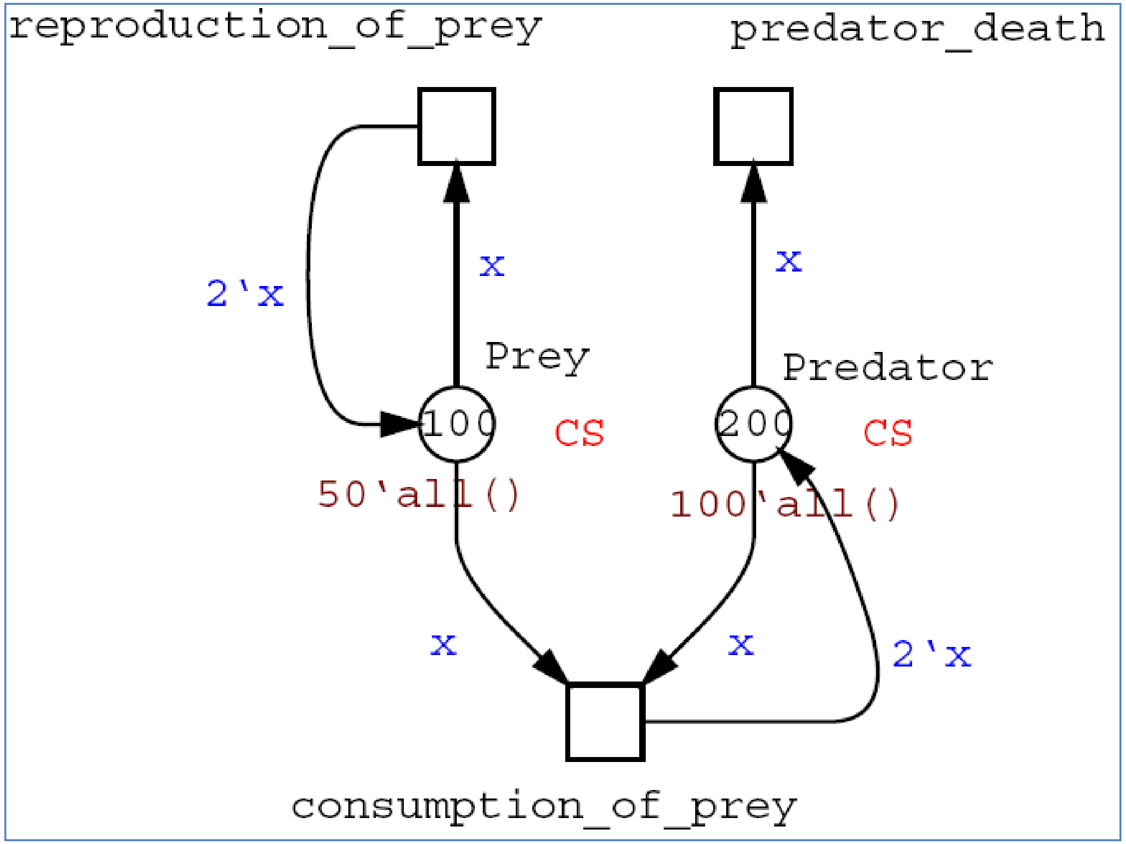




Colored Petri nets

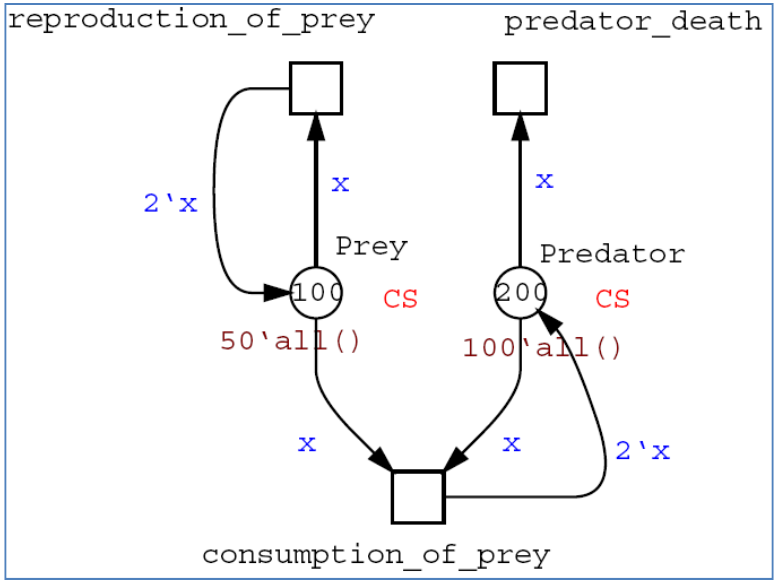
Declarations:

- colorset CS = red, blue;
- variable x : CS



- Changing color sets adapts the model to various scenarios

Colored Petri nets － basic notions



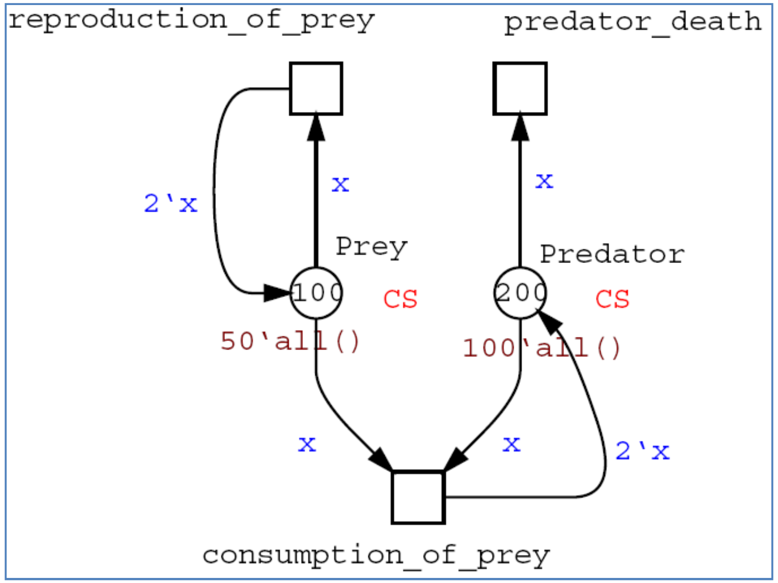
Declarations:

- colorset CS = red, blue;
- variable x : CS

Notions:

- Multiset
  - a set in which there can be several occurrences for the same element
  - denoted by m(s1)\`s1++ m(s2)\`s2++···
  - Example: {a, a, b, b, b} == 2\`a++3\`b

Colored Petri nets － basic notions



Declarations:

- colorset CS = red, blue;
- variable x : CS

Notions:

- Place/transition/arc
- Color sets
- Guards: Boolean expressions
- Arc expressions: result type = type of connected place
- Initial marking: initialization expressions

Colored Petri nets － basic notions

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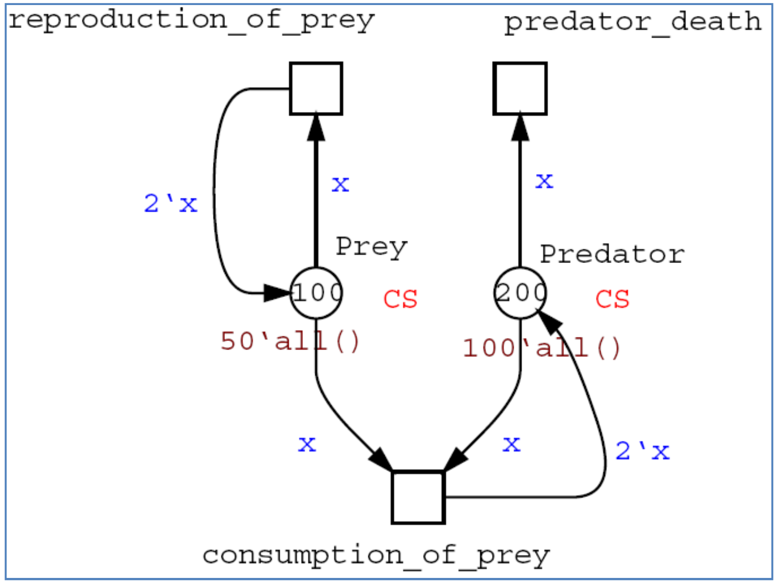


Declarations:

- colorset CS = red, blue;
- variable x : CS

Notions:

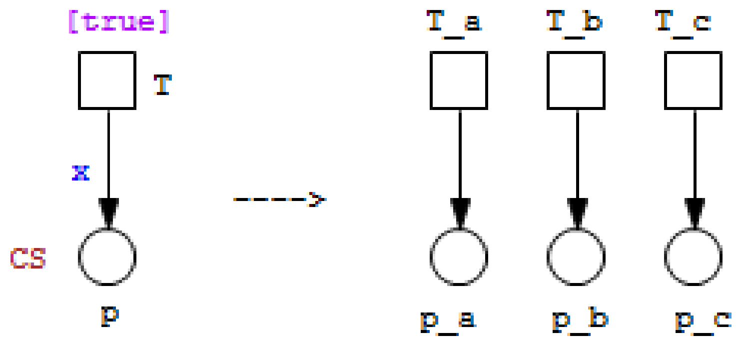
- Color sets
  - Define how many components/subsystems (cells) in a colored Petri net model
  - Each component (cell) is a color

  - Simple types: dot, integer, string, Boolean, enumeration, index
  - Compound types: product, union

Colored Petri nets － basic notions

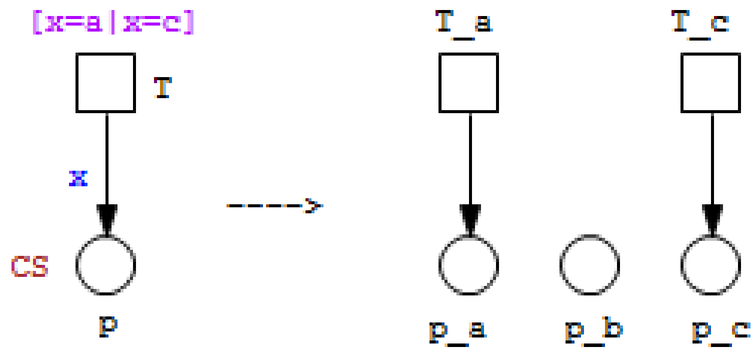
Declarations:

- colorset CS = a,b,c;
- variable x : CS

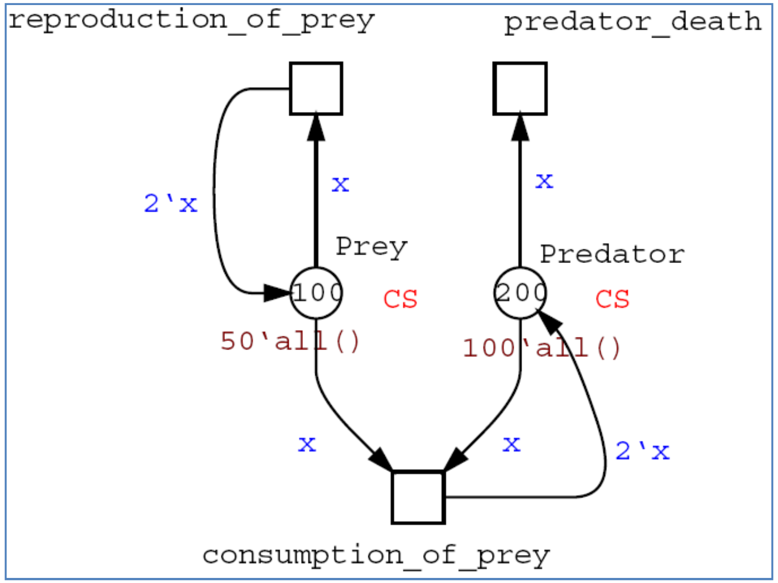


Notions:

- Guard
  - Boolean expression (true/false)
  - Select those uncolored transitions where the guard is evaluated to true



Colored Petri nets – basic notions



Declarations:

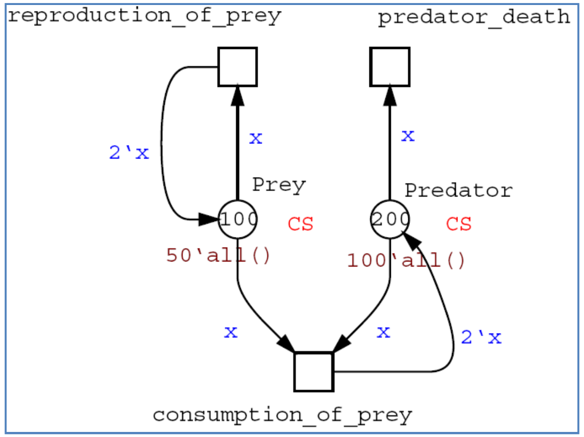
- colorset CS = red, blue;
- variable x : CS

Notions:

- Arc expressions
  - usually variables of color sets
  - e.g., x, 2`x
  - result type = type of connected place
- Initial marking
  - A multiset expression
  - 50`all() == 50`a ++ 50`b

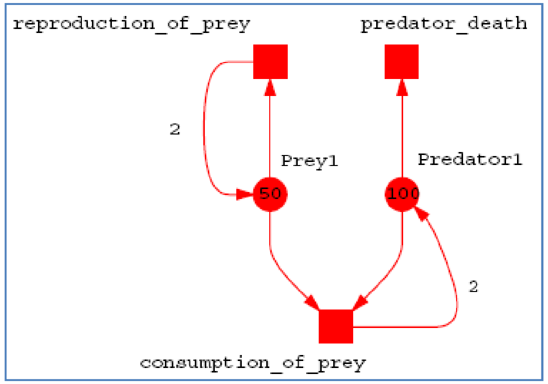
Colored Petri nets – basic notions

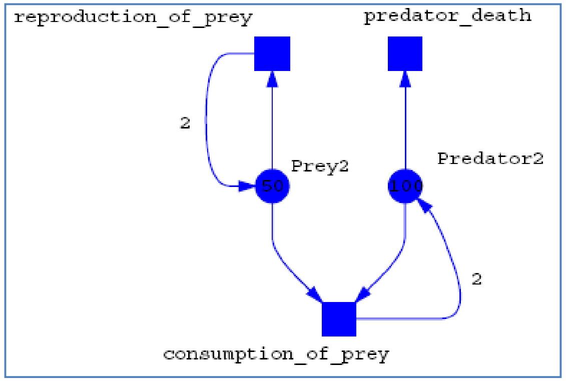
- Folding/unfolding
- Place/transition instances



Questions:

- Automatic folding
- Automatic unfolding





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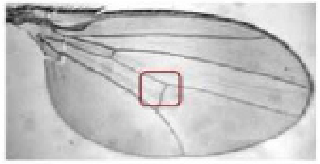

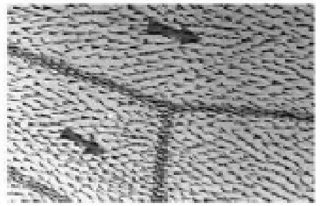

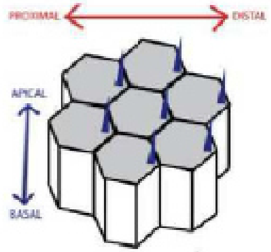

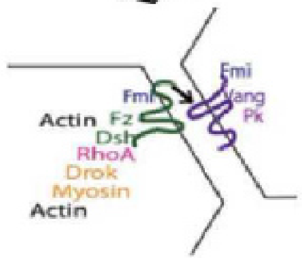

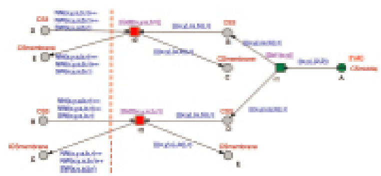

Colored Petri net framework

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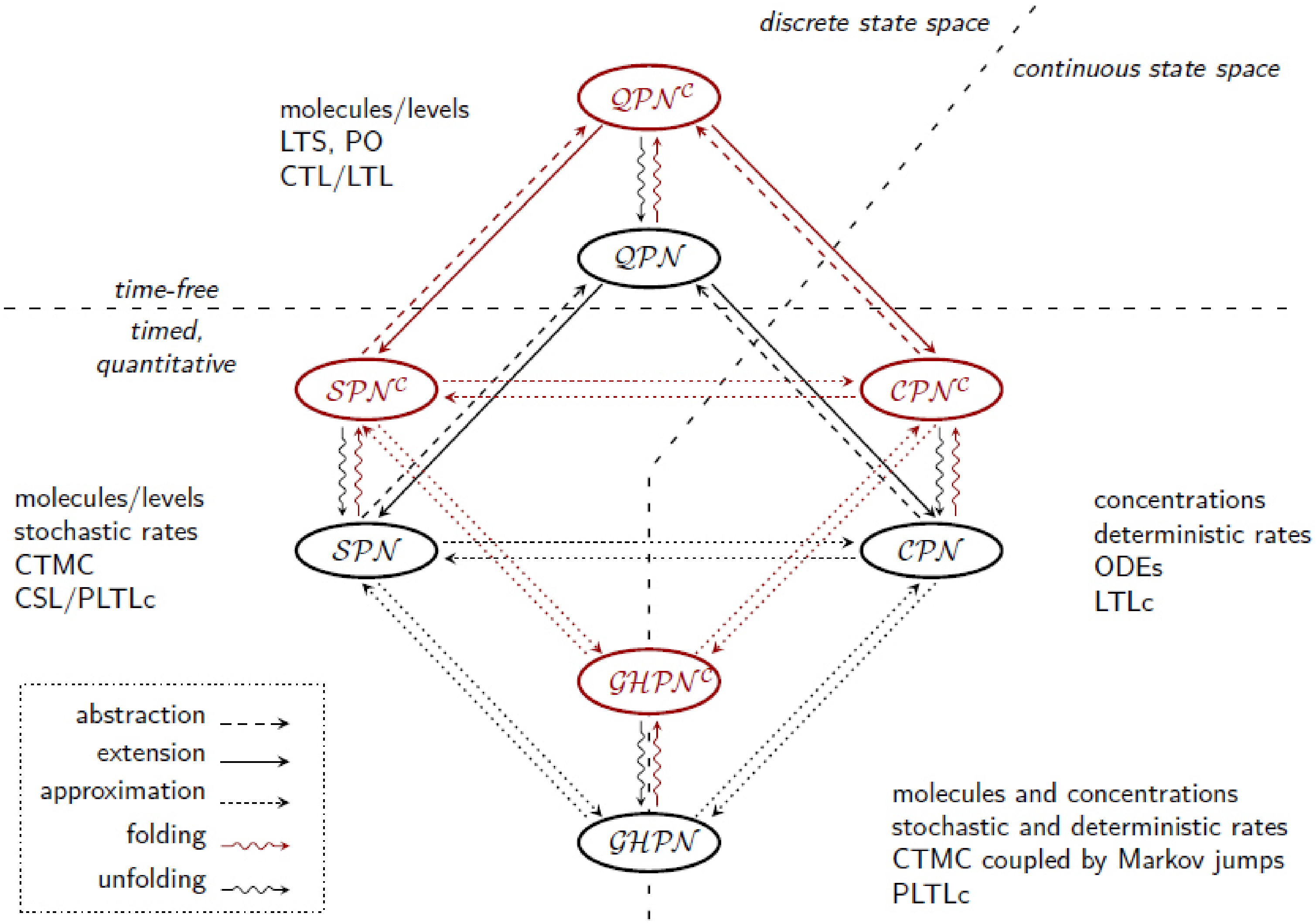

•*Fei Liu. Colored Petri Nets for Systems Biology; PhD thesis, BTU Cottbus, Dep. of CS, January 2012.*

•*M Heiner, M. Herajy, F. Liu, C. Rohr. Snoopy – a unifying Petri net tool; In Proc. PETRI NETS 2012, Hamburg, Springer, LNCS, volume 7347, 398–407, June 2012.*

Colored Petri net － implementation

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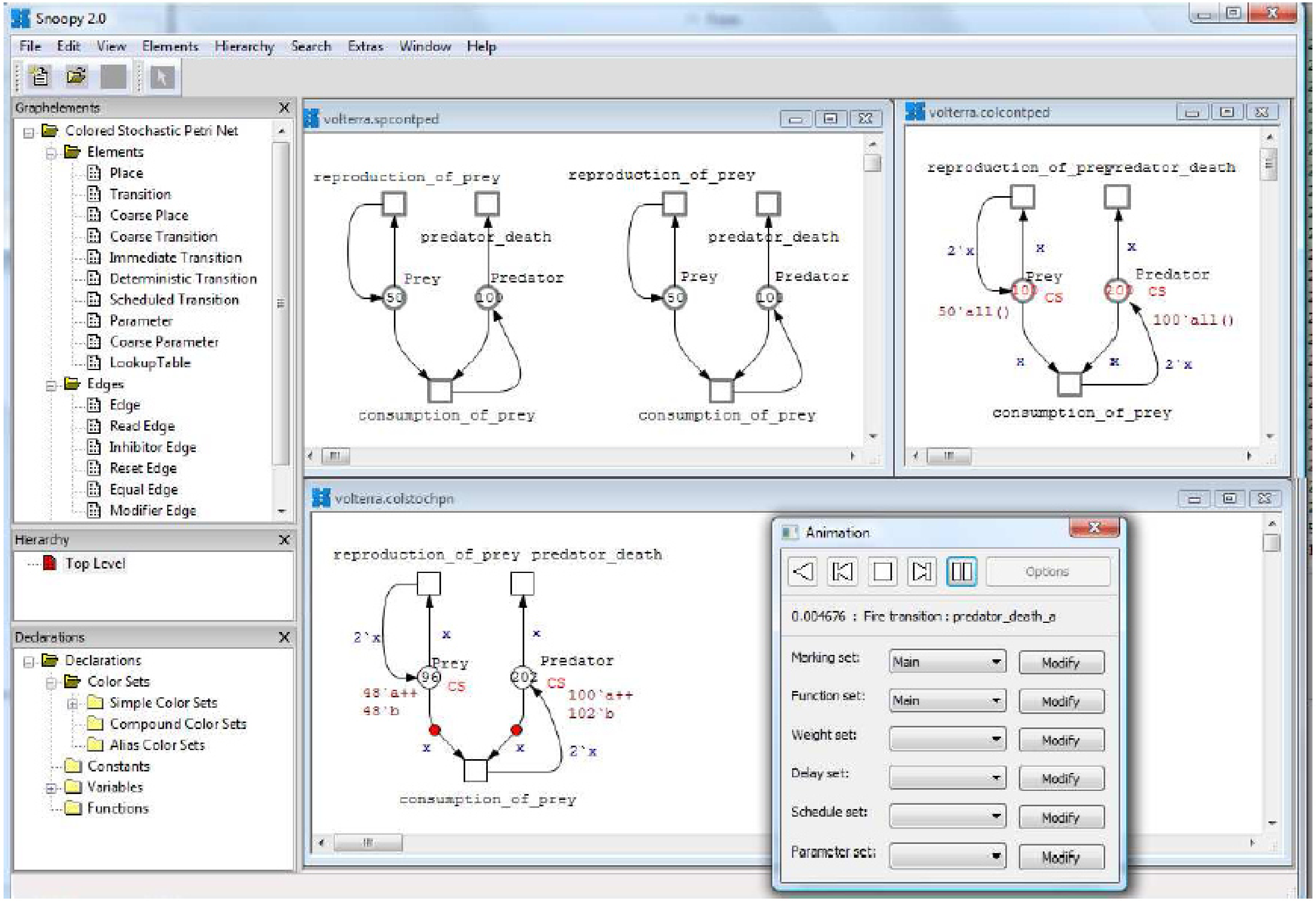
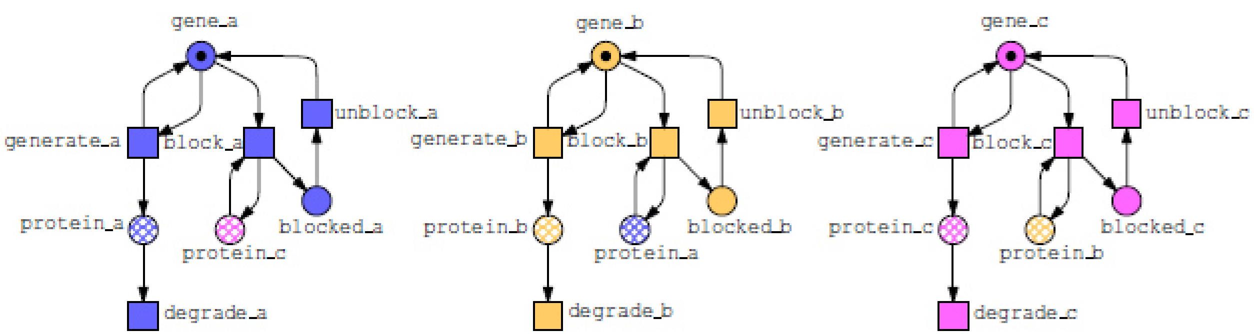
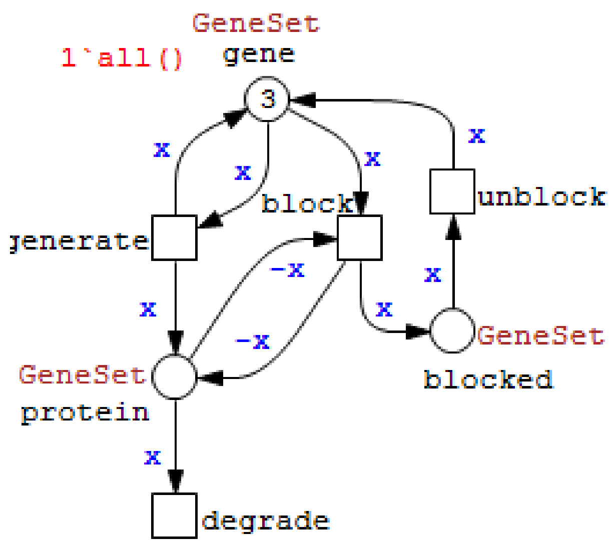


Colored qualitative Petri net (QPNC)

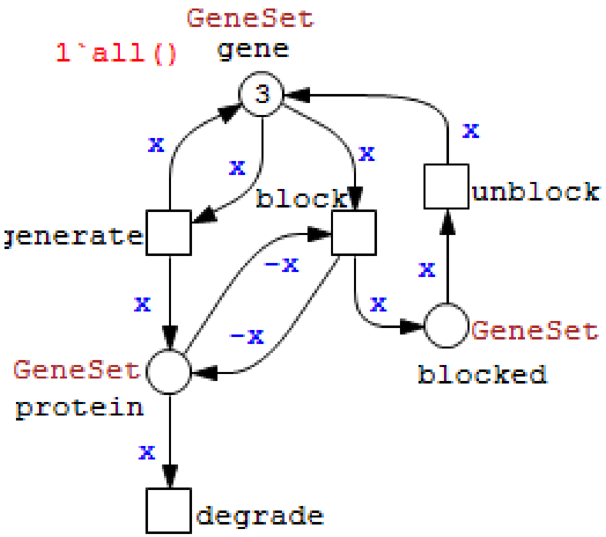
- Colored extension of QPN
- Special arcs: inhibitor, read, equal, reset
- Animation built in Snoopy
- Export (unfold) to external analysis tools

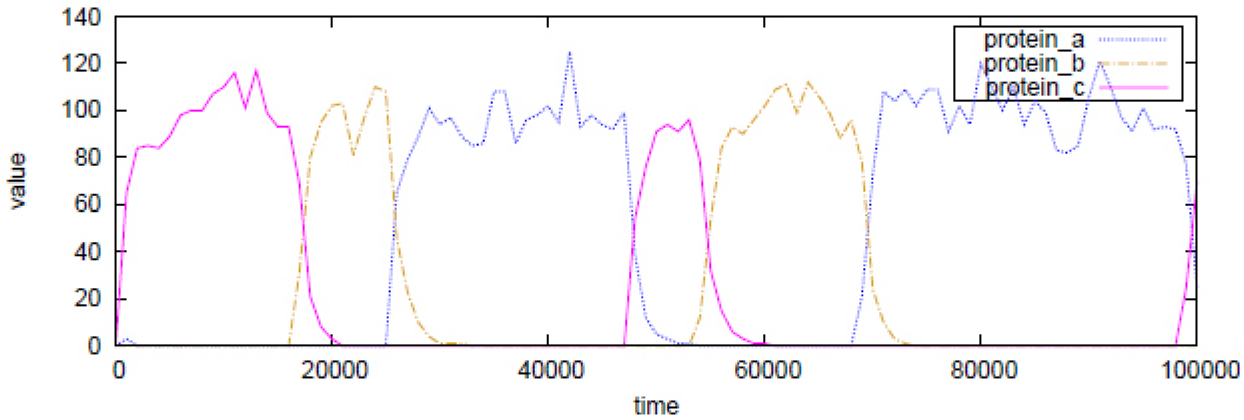




Colored stochastic Petri net (SPNC)

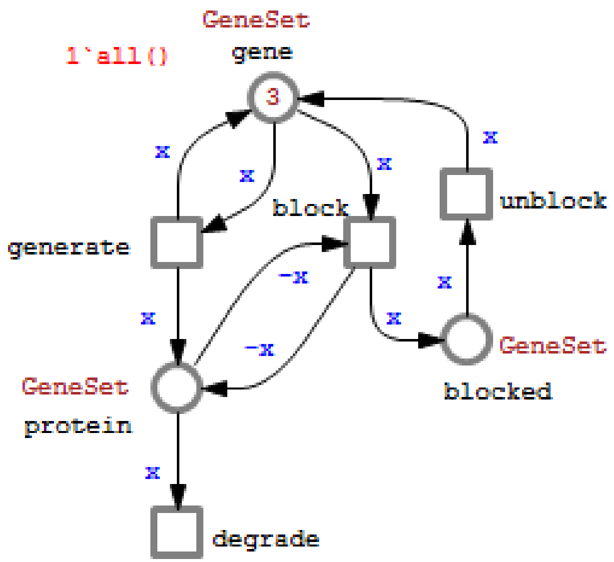
- Colored extension of SPN
- Transition: stochastic rate with an exponential probability distribution
- Semantics: continuous time Markov chains (CTMCs)
- Special arcs, modifier arcs
- Special transitions: immediate, deterministic, scheduled
- Animation/stochastic simulation built in Snoopy
- Export (unfold) to external analysis tools

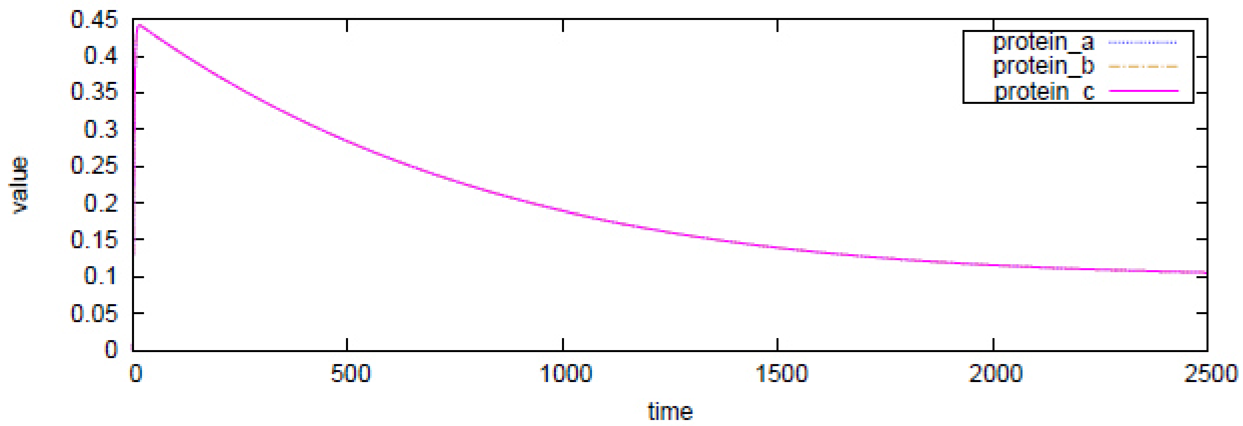




Colored continuousPetri net (CPNC)

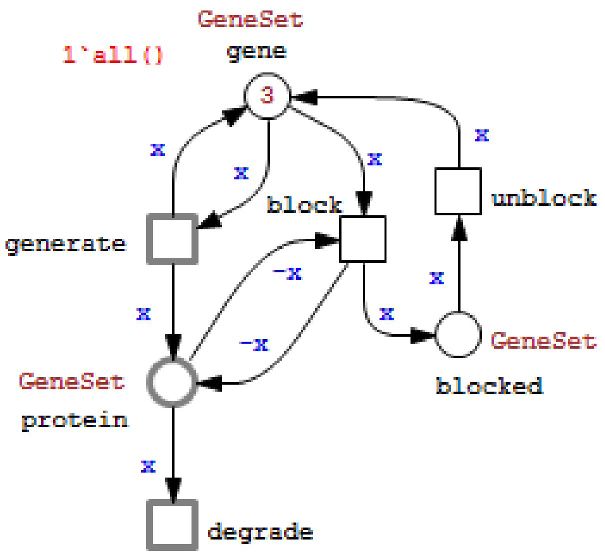
- Colored extension of CPN
- Place: real values
- Transition: deterministic rates
- Semantics: a set of ordinary differential equations (ODEs)
- Special arcs: inhibitor, reader, modifier
- Continuous simulation built in Snoopy
- Export (unfold) to external analysis tools

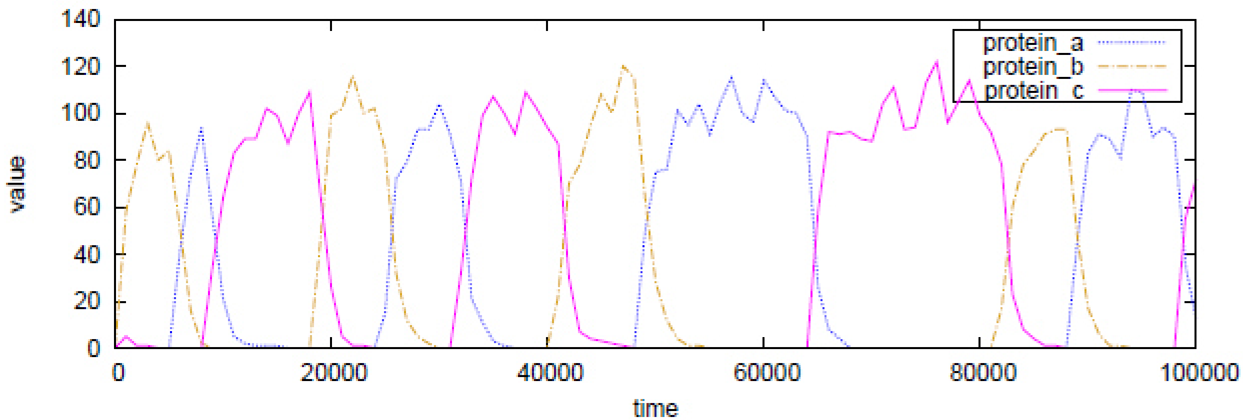




Colored hybrid Petri net (HPNC)

- Colored extension of GHPN
- Place: real/integer values
- Transition: deterministic/stochastic rates
- Semantics: ODEs/CTMC
- Special arcs: inhibitor, reader, equal, reset, modifier
- Hybrid simulation built in Snoopy
- Export (unfold) to external analysis tools





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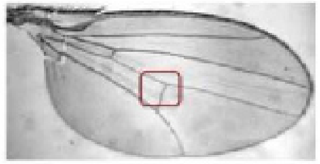
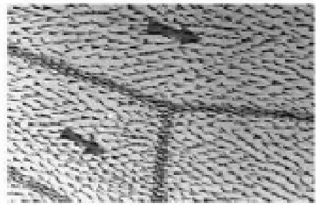
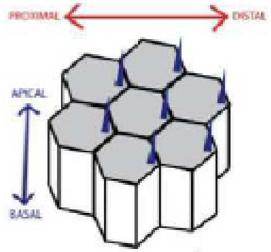
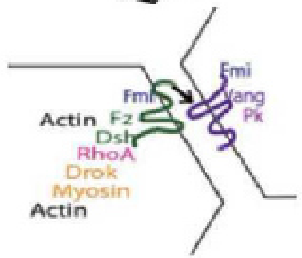
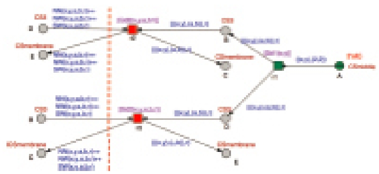










Key techniques

Annotation language of colored Petri nets

$$
\begin{array}{rcl}
\langle \text{Type} \rangle & ::= & \langle \text{SimpleType} \rangle \mid \langle \text{CompoundType} \rangle \\
\langle \text{SimpleType} \rangle & ::= & \langle \text{TypeIdentifier} \rangle \mid \langle \text{StructuredType} \rangle \\
\langle \text{TypeIdentifier} \rangle & ::= & \langle \text{UnsignedInteger} \rangle \mid \langle \text{Boolean} \rangle \mid \langle \text{String} \rangle \\
\langle \text{UnsignedInteger} \rangle & ::= & \text{``int''} \\
\langle \text{Boolean} \rangle & ::= & \text{``bool''} \\
\langle \text{String} \rangle & ::= & \text{``string''} \\
\langle \text{StructuredType} \rangle & ::= & \langle \text{Enumeration} \rangle \mid \langle \text{Index} \rangle \\
\langle \text{Enumeration} \rangle & ::= & \langle \text{IdentifierList} \rangle \\
\langle \text{IdentifierList} \rangle & ::= & \langle \text{Identifier} \rangle \mid \langle \text{IdentifierList} \rangle \text{``,''} \langle \text{Identifier} \rangle \\
\langle \text{Index} \rangle & ::= & \langle \text{Identifier} \rangle \text{``[''} \langle \text{IndexSpecifier} \rangle \text{``]''} \\
\langle \text{IndexSpecifier} \rangle & ::= & \text{``int''} \\
\langle \text{CompoundType} \rangle & ::= & \langle \text{Product} \rangle \mid \langle \text{Union} \rangle \\
\langle \text{Product} \rangle & ::= & \langle \text{Type} \rangle \text{``}\times\text{''} \langle \text{Type} \rangle \mid \langle \text{Product} \rangle \text{``}\times\text{''} \langle \text{Type} \rangle \\
\langle \text{Union} \rangle & ::= & \langle \text{Type} \rangle \mid \langle \text{Union} \rangle \text{``,''} \langle \text{Type} \rangle
\end{array}
$$

Key techniques

Annotation language of colored Petri nets

$$
\begin{array}{rcl}
\langle \text{ColorExpr} \rangle & ::= & \langle \text{MultiSetExpr} \rangle \\
\langle \text{MultiSetExpr} \rangle & ::= & \langle \text{Predicate} \rangle \mid \langle \text{MultiSetExpr} \rangle \langle \text{MSAdditionOp} \rangle \langle \text{Predicate} \rangle \\
\langle \text{MSAdditionOp} \rangle & ::= & \text{``++''} \\
\langle \text{Predicate} \rangle & ::= & \langle \text{SeparatorExpr} \rangle \mid \text{``[''} \langle \text{OrExpr} \rangle \text{``]''} \langle \text{SeparatorExpr} \rangle \\
\langle \text{SeparatorExpr} \rangle & ::= & \langle \text{TupleExpr} \rangle \mid \langle \text{SeparatorExpr} \rangle \langle \text{SeparatorOp} \rangle \langle \text{TupleExpr} \rangle \\
\langle \text{SeparatorOp} \rangle & ::= & \text{``\`{}''} \\
\langle \text{TupleExpr} \rangle & ::= & \langle \text{OrExpr} \rangle \mid \text{``(''} \langle \text{CommaExpr} \rangle \text{``)''} \\
\langle \text{CommaExpr} \rangle & ::= & \langle \text{TupleExpr} \rangle \mid \langle \text{CommaExpr} \rangle \langle \text{CommaOp} \rangle \langle \text{TupleExpr} \rangle \\
\langle \text{CommaOp} \rangle & ::= & \text{``,''} \\
\langle \text{OrExpr} \rangle & ::= & \langle \text{AndExpr} \rangle \mid \langle \text{OrExpr} \rangle \langle \text{OrOp} \rangle \langle \text{AndExpr} \rangle \\
\langle \text{OrOp} \rangle & ::= & \text{``}|\text{''} \\
\langle \text{AndExpr} \rangle & ::= & \langle \text{EqualExpr} \rangle \mid \langle \text{AndExpr} \rangle \langle \text{AndOp} \rangle \langle \text{EqualExpr} \rangle \\
\langle \text{AndOp} \rangle & ::= & \text{``\&''} \\
\langle \text{EqualExpr} \rangle & ::= & \langle \text{RelationExpr} \rangle \mid \langle \text{EqualExpr} \rangle \langle \text{EqualOp} \rangle \langle \text{RelationExpr} \rangle \\
\langle \text{EqualOp} \rangle & ::= & \text{``}=\text{''} \mid \text{``}<>\text{''} \\
\langle \text{RelationExpr} \rangle & ::= & \langle \text{AddExpr} \rangle \mid \langle \text{RelationExpr} \rangle \langle \text{RelationOp} \rangle \langle \text{AddExpr} \rangle \\
\langle \text{RelationOp} \rangle & ::= & \text{``}<\text{''} \mid \text{``}<=\text{''} \mid \text{``}>=\text{''} \mid \text{``}>\text{''} \\
\langle \text{AddExpr} \rangle & ::= & \langle \text{MultiplicityExpr} \rangle \mid \langle \text{AddExpr} \rangle \langle \text{AddOp} \rangle \langle \text{MultiplicityExpr} \rangle \\
\langle \text{AddOp} \rangle & ::= & \text{``}+\text{''} \mid \text{``-''}
\end{array}
$$

Key techniques

- Annotation language of colored Petri nets

  - Flex scanner & Bison parser

  - C++ vs ML (functional programming) language

F Liu, M Heiner and C Rohr: Manual for Colored Petri Nets in Snoopy; Technical report 02-12, Brandenburg University of Technology Cottbus, Department of Computer Science, March 2012.

Key techniques

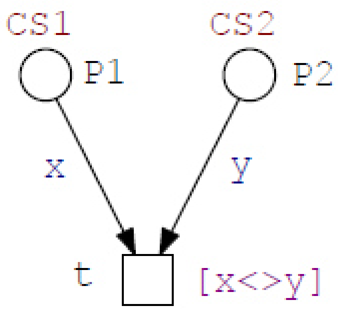
- Unfolding algorithm

  - reuse analysis techniques and tools for standard Petri nets
  - reuse stochastic or continuous simulation algorithms

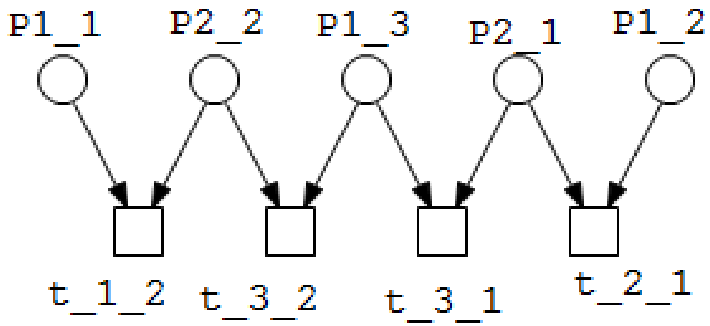
F Liu, M Heiner and M Yang: An efficient method for unfolding colored Petri nets; In Proceedings of the 2012 Winter Simulation Conference (WSC 2012), Berlin, IEEE, 978-1-4673-4781-5/12, 2012.

Key techniques

- Unfolding algorithm
  - compute all instances (bindings) for every transition
  - bind every variable to each color of its color set
  - the combination of color sets if the guard is always true

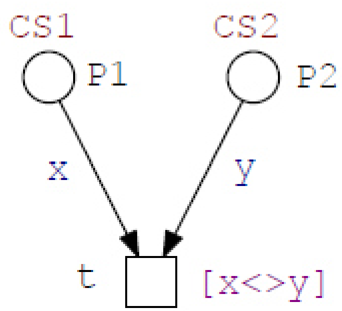



```
Declarations:
colorset CS1=int with 1,2,3;
colorset CS2=int with 1,2;
variable x:CS1;
variable y:CS2;
```



Key techniques

- Unfolding algorithm
  - the number of instances for a transition is constrained by its guard
  - A constraint satisfaction approach
    - the guard is not always true
    - all the variables in the guard have finite integer domains

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Declarations:
colorset CS1=int with 1,2,3;
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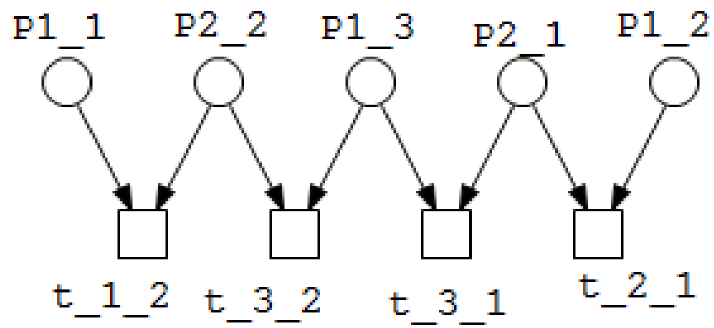
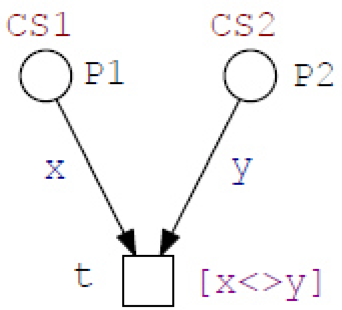
```



Key techniques

- Unfolding algorithm
  - get the guard of a transition
  - get all variables in this guard
  - define the color set of each variable as its domain in CSP
  - define the guard as a constraint of CSP
  - solve CSP using constraint solvers, e.g. Gecode




```
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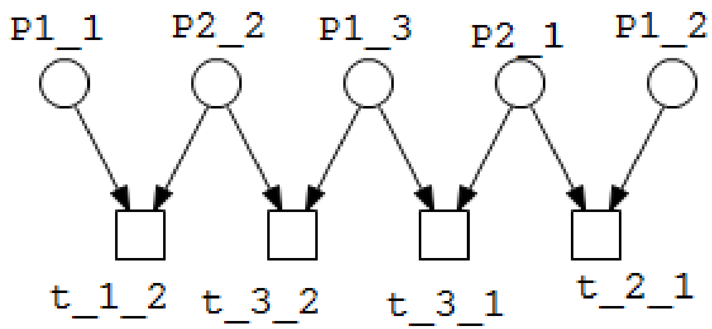
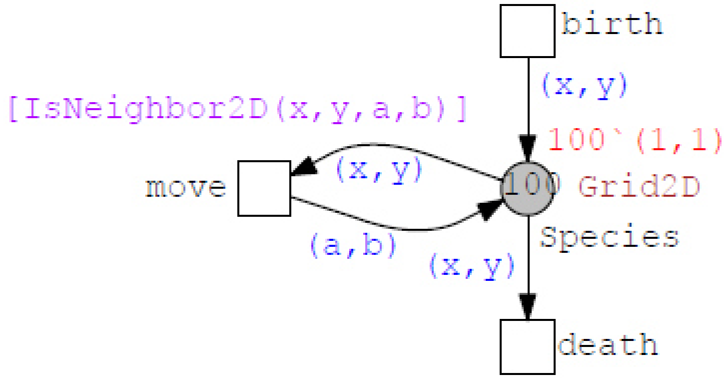


Unfolding algorithm



Size			Unfolding time	
$M \times N$	Places	Transitions	without CSP	with CSP
10×10	100	884	4 seconds	1 seconds
50×50	2,500	24,404	34 minutes	8 seconds
100×100	10,000	98,804	11 hours	43 seconds
200×200	40,000	397,604	$\diamond$	4 minutes

* done on PC, Intel(R) Xeon(R) CPU 2.83GHz, RAM 4.00GB. $\diamond$ we did not get the result within 24 hours.

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- Colored Petri net framework
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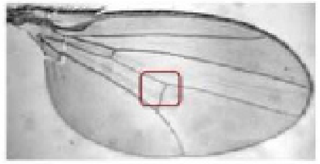

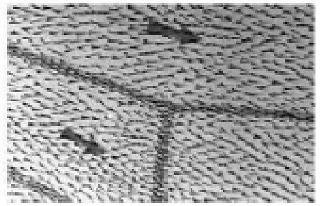

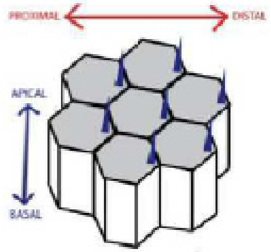

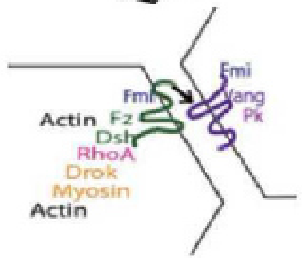

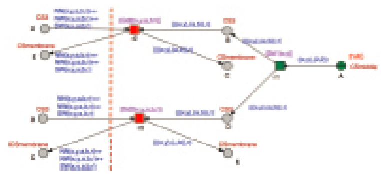

Analysis capabilities

- built in Snoopy
  - animation (QPN^C/SPN^C)
  - simulation ($SPN^C/CPN^C/HPN^C$)

- external analysis tools
  - structural analysis (all net classes): Charlie
  - CTL model checking (QPN^C): Marcie
  - numerical CSL model checking (SPN^C): Marcie
  - simulative PLTLc model checking (SPN^C): Marcie
  - simulative PLTLc model checking ($SPN^C/CPN^C/HPN^C$): MC2 tool

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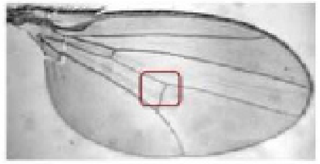
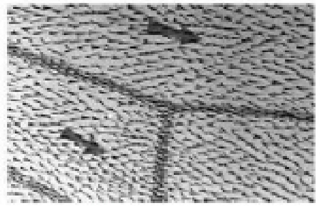
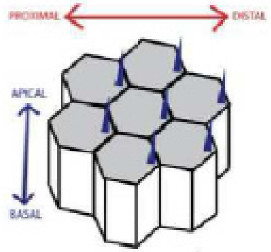
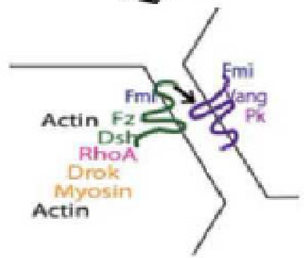
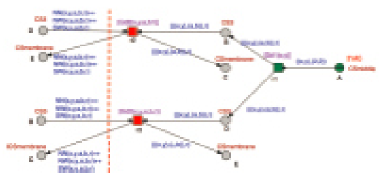


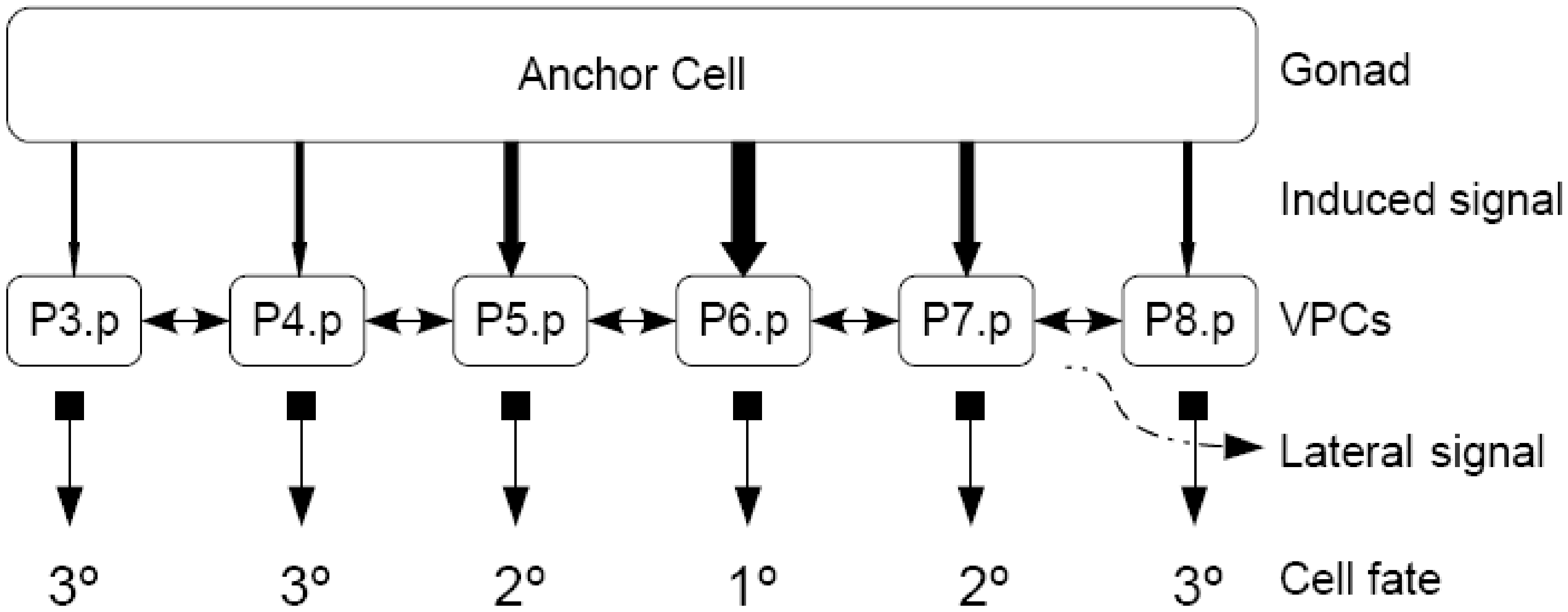


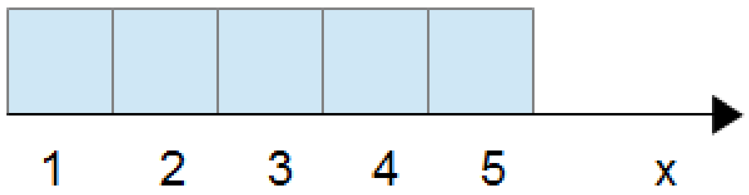






Ex1- C. Elegans Vulval Development





Ex1- C. Elegans Vulval Development

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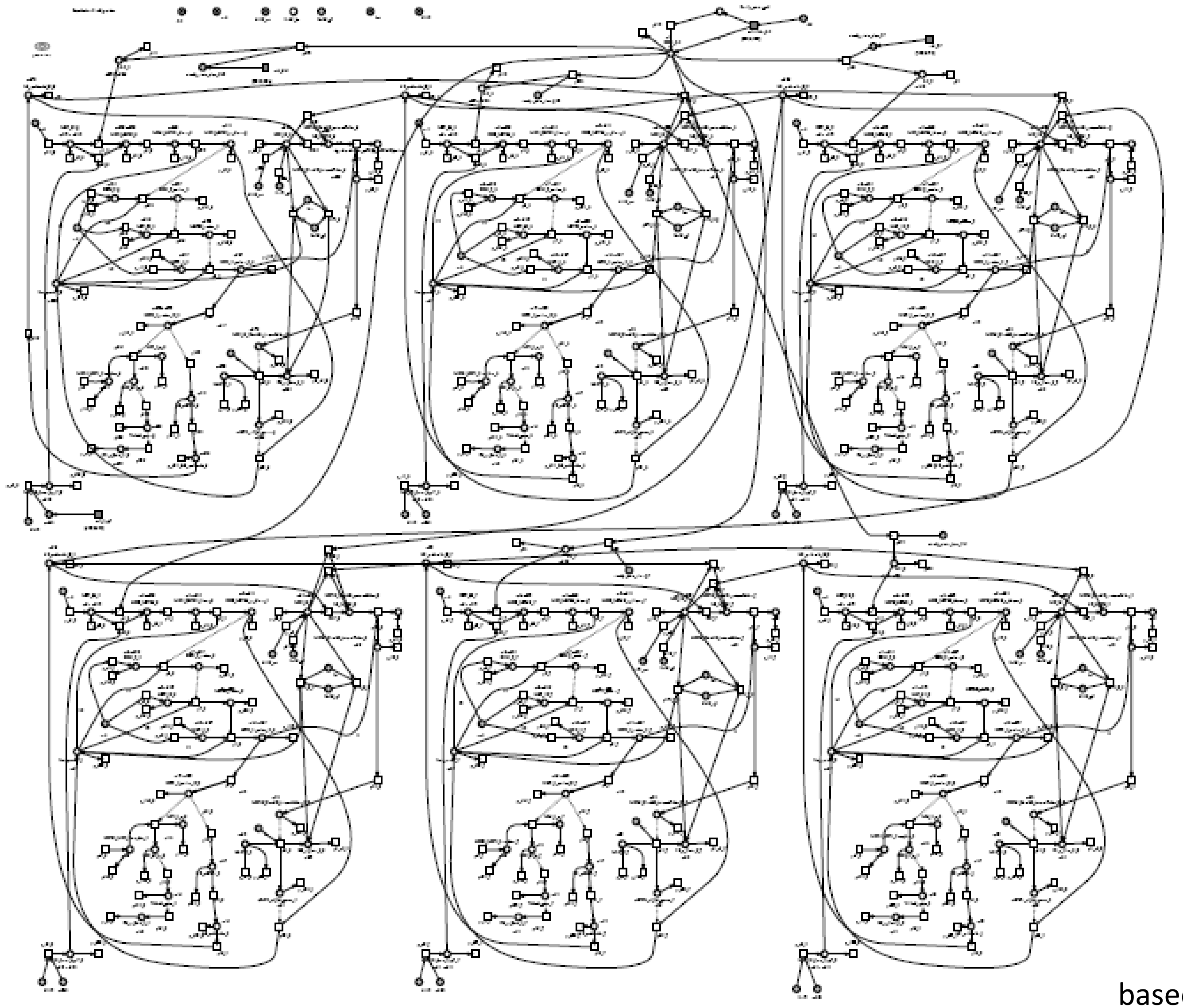
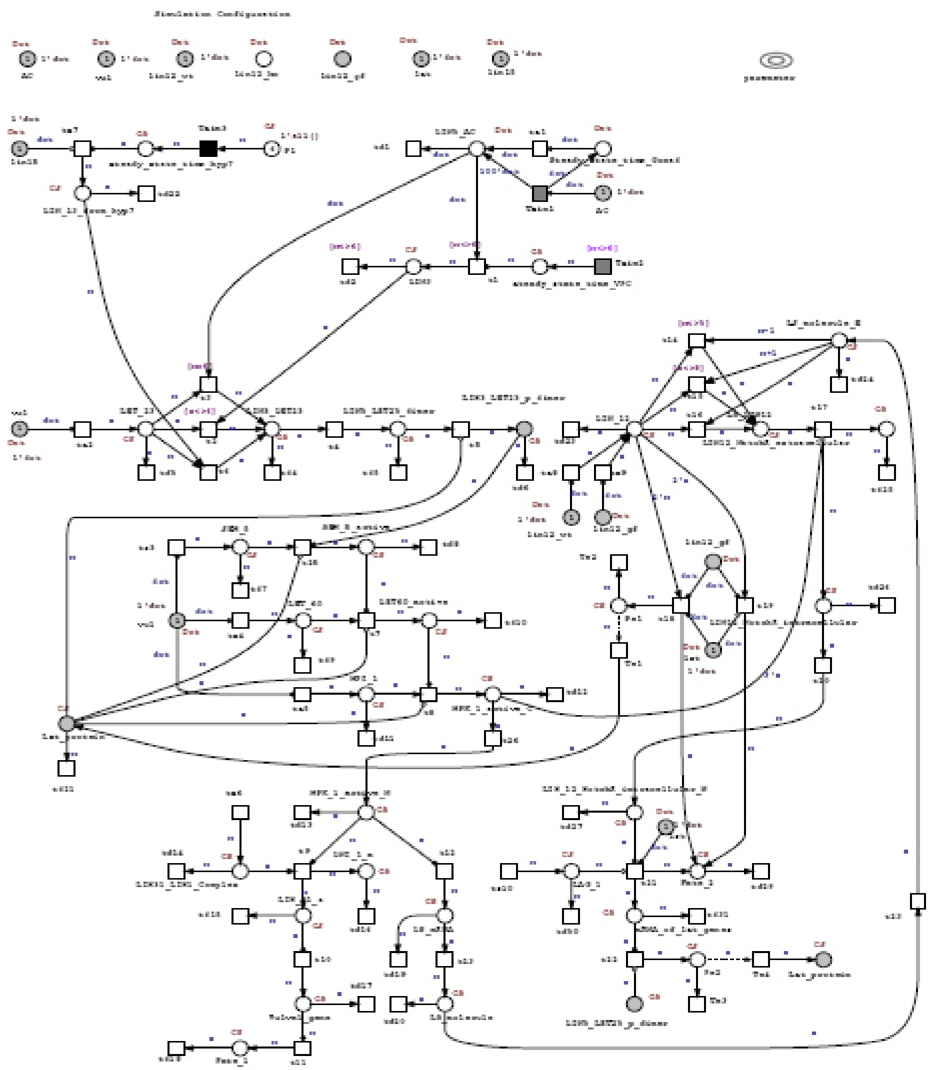


based on [Li et al. 2009]

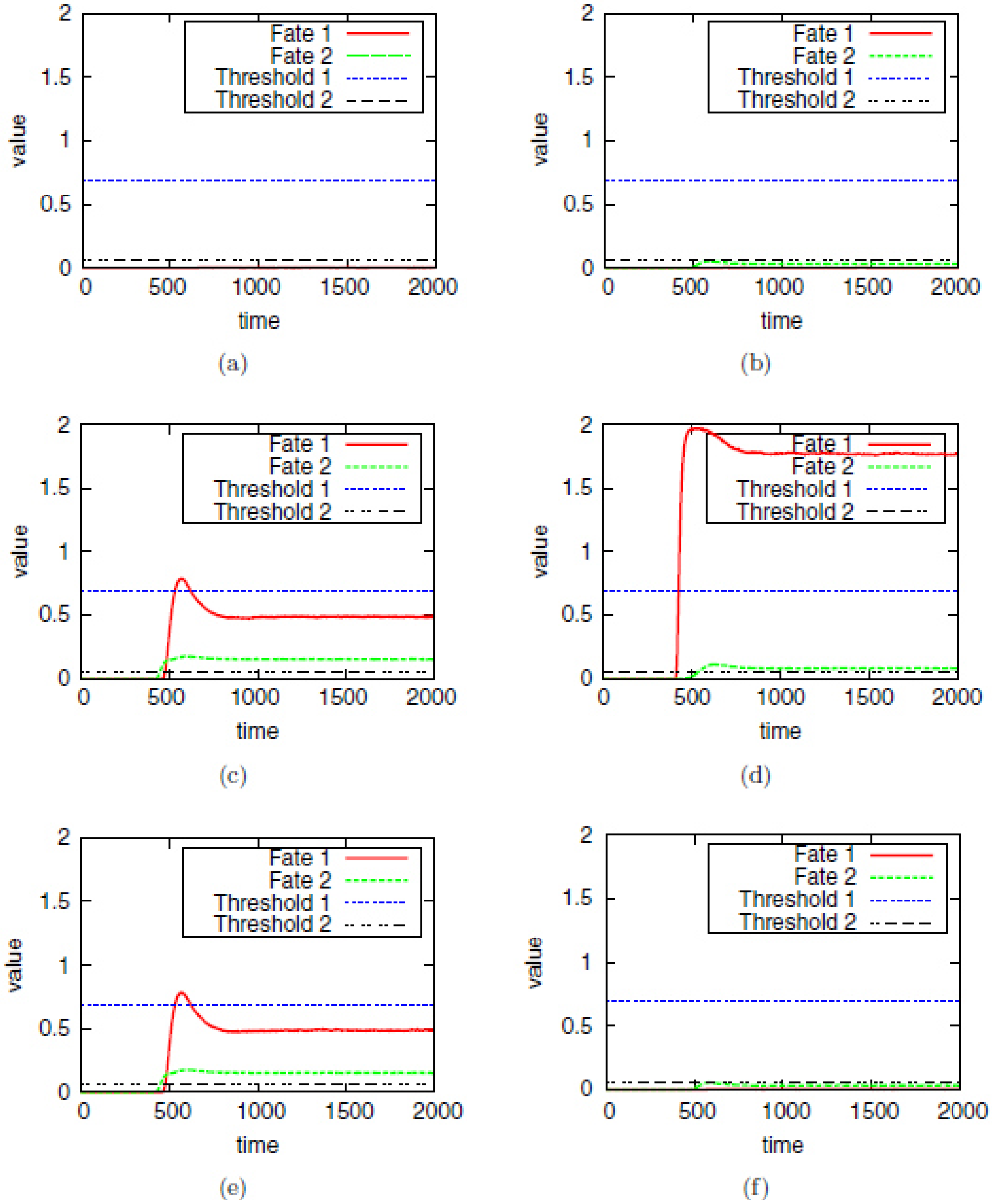
Ex1- C. Elegans Vulval Development



- Declarations:
  colorset Dot = with dot;
  colorset CS = integer with 3-8;
  variable x : CS;

F Liu, M Heiner and M Yang: Modeling and analyzing biological systems using colored hierarchical Petri nets, illustrated by C. elegans vulval development; WSPC Journal of Biological Systems, 22(3):463–493, online May 2014.

Ex1- C. Elegans Vulval Development



Ex2- Planar Cell Polarity in Drosophila Wing

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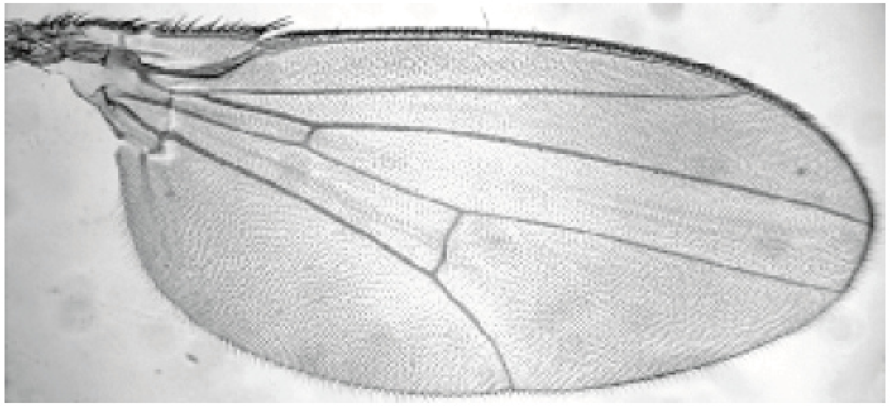
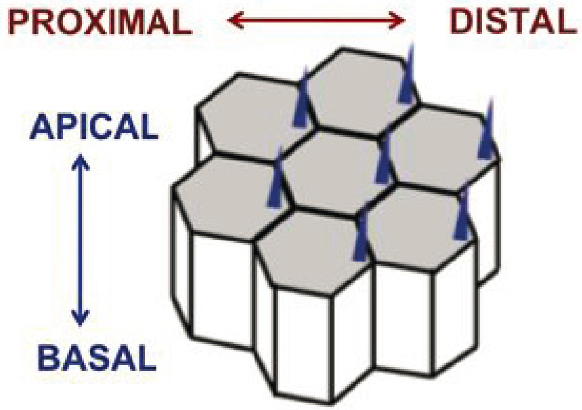
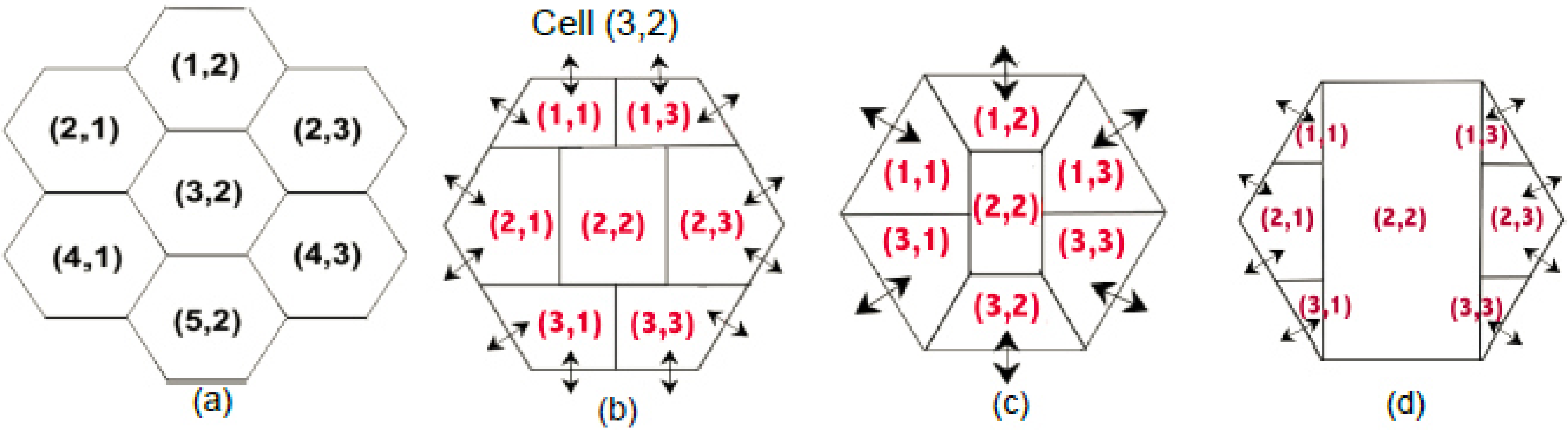
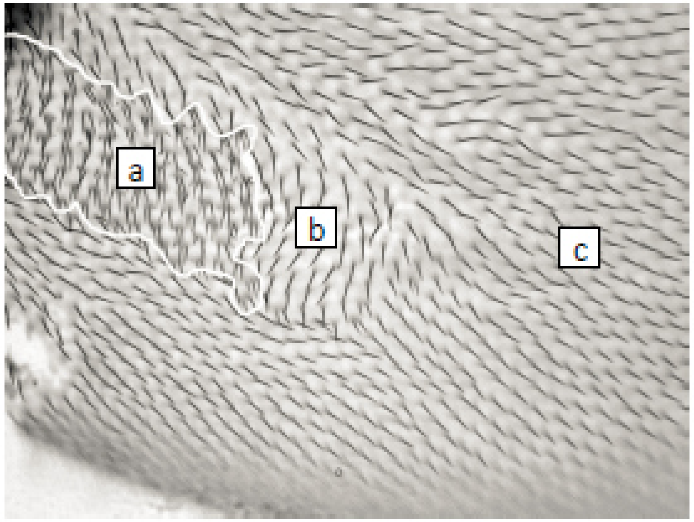


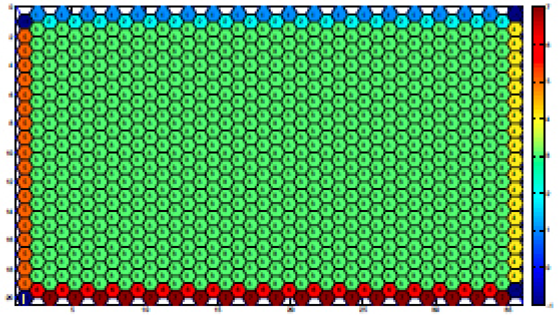


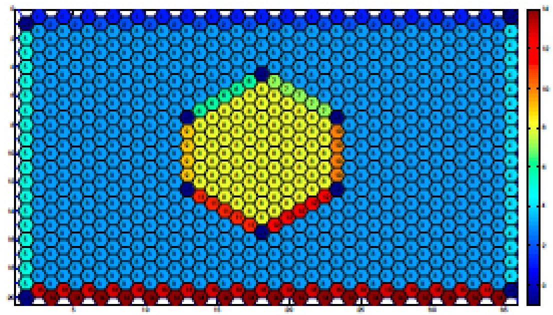


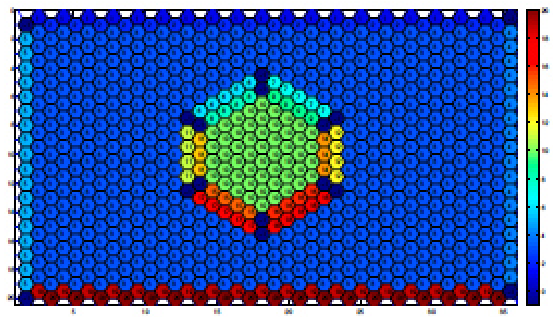
Q Gao, D Gilbert, M Heiner, F Liu, D Maccagnola and D Tree: Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing; IEEE/ACM Transactions on Computational Biology and Bioinformatics, 10(2):337-351, 2013

Ex1- Planar Cell Polarity in Drosophila Wing

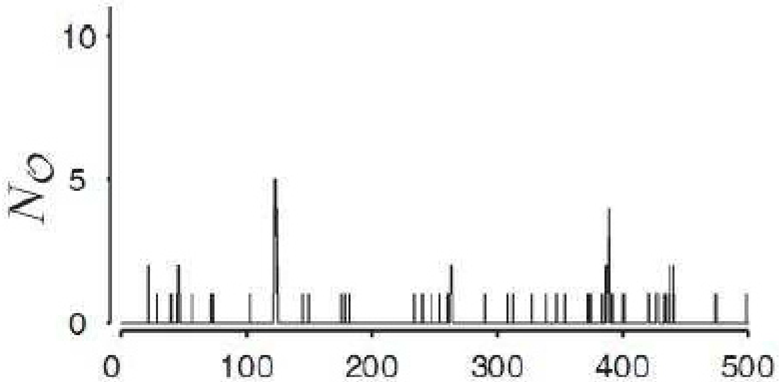


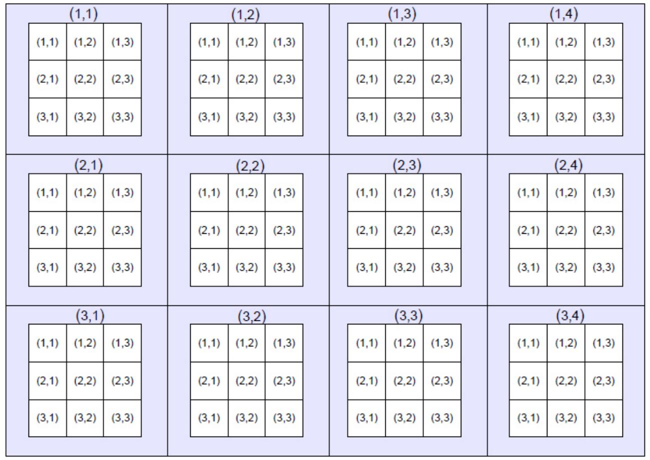






Ex3 - Ca2+ release sites

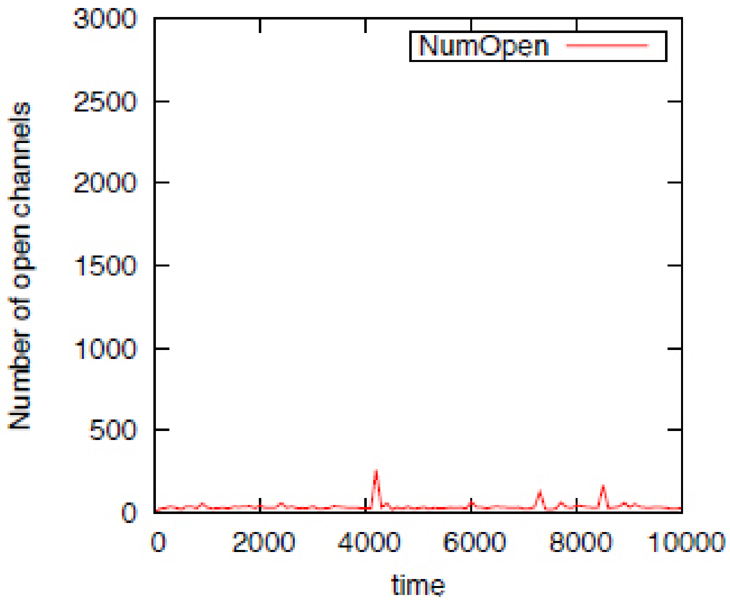




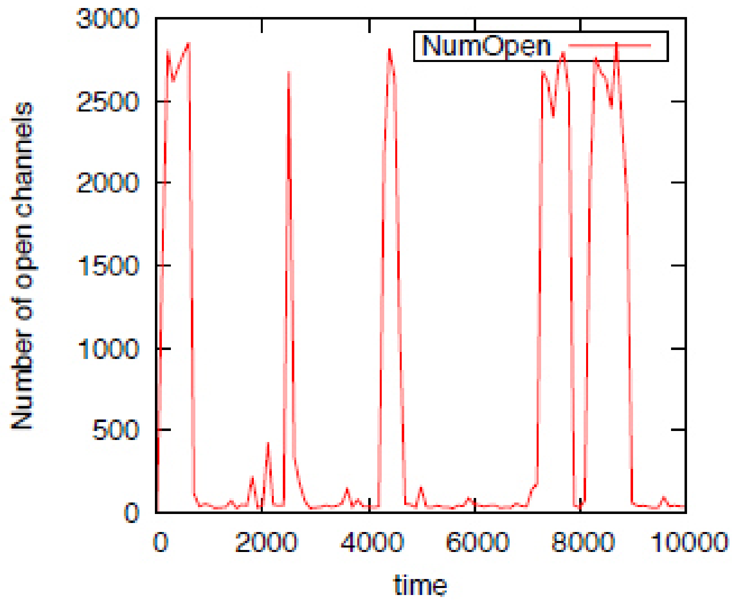
- A cluster: a group of strongly coupled channels
- An array of weakly coupled clusters

F Liu and M Heiner: Multiscale modelling of coupled Ca2+ channels using coloured stochastic Petri nets; IET Systems Biology, 7(4):106 - 113, August 2013.

Ex3 - Ca2+ release sites



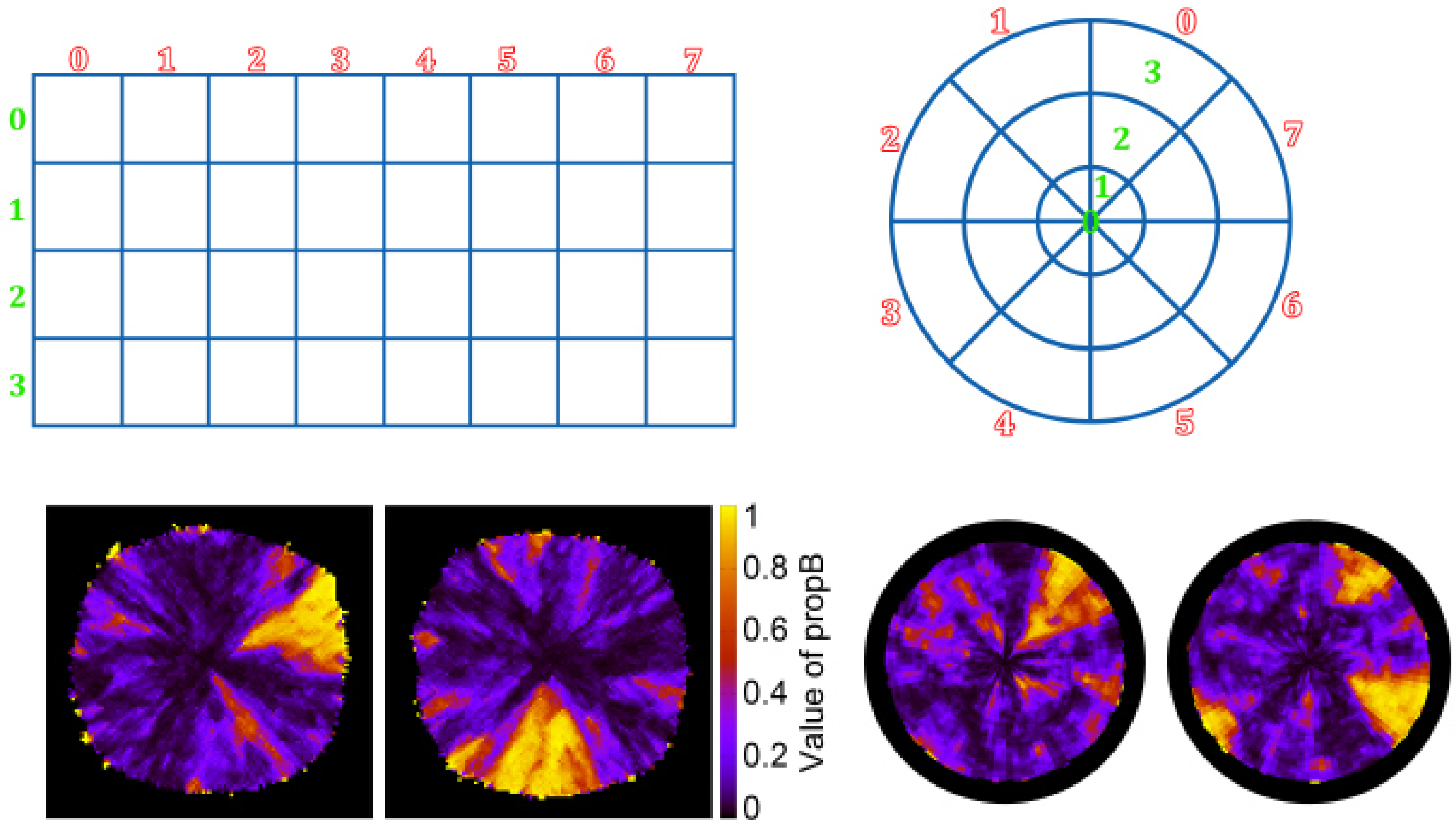
(a)



(b)

- Ignoring/considering the effect of neighboring clusters
- Few/frequent waves

Ex3 − Phase variation in a cell colony



O Pârvu, D Gilbert, M Heiner, F Liu, N Saunders and S Shaw: Spatial-temporal modelling and analysis of bacterial colonies with phase variable genes; ACM Transactions on Modeling and Computer Simulation (TOMACS), 25(2):25p., May 2015.

Ex4 − the Brusselator

- The PDEs of the Brusselator

$$\frac{\partial U}{\partial \tau} = A - (B+1)U + U^2V + \nabla^2 U$$
$$\frac{\partial V}{\partial \tau} = BU - U^2V + D\nabla^2 V$$

$$B = (\mu + 1) * (1 + \eta)^2$$

- The chemical reactions and diffusion

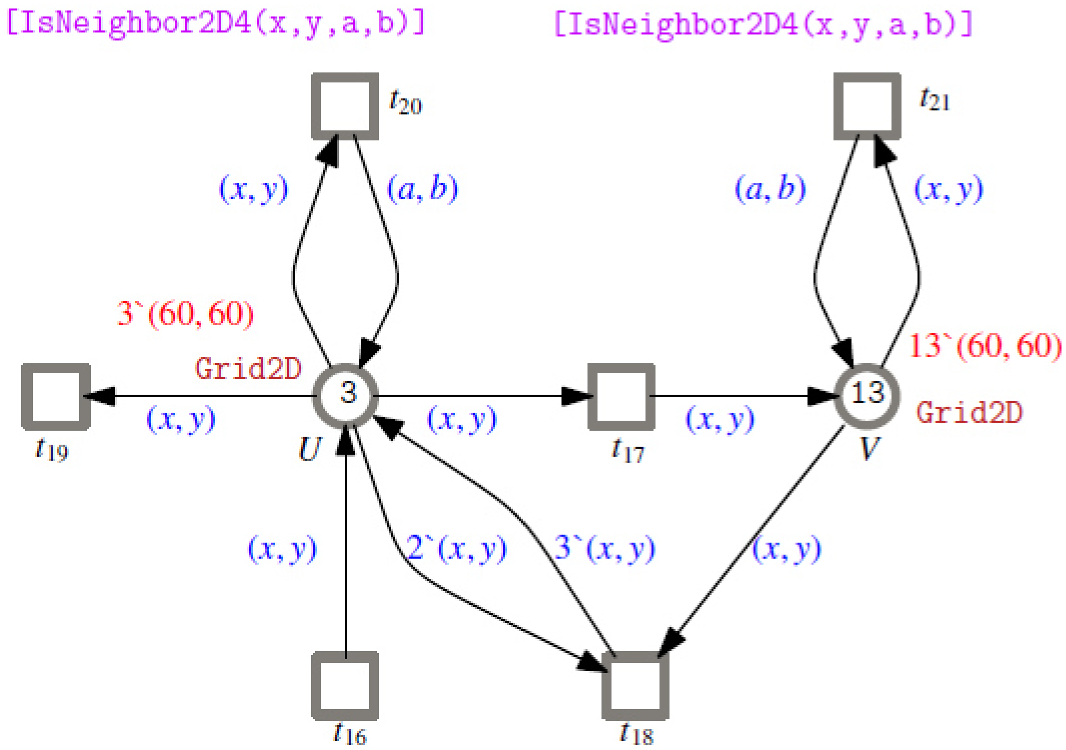
$$\phi \xrightarrow{A} U_{xy}$$
$$U_{xy} \xrightarrow{B} V_{xy}$$
$$2U_{xy} + V_{xy} \xrightarrow{1} 3U_{xy}$$
$$U_{xy} \xrightarrow{1} \phi$$

$$U_{xy} \xrightarrow{1/h^2} U_{ab}$$
$$V_{xy} \xrightarrow{D/h^2} V_{ab}.$$

F Liu, MA Blätke, M Heiner and M Yang:
Modelling and simulating reaction–diffusion systems using coloured Petri nets;
Computers in Biology and Medicine, 53:297–308, October 2014

Ex4 – the Brusselator

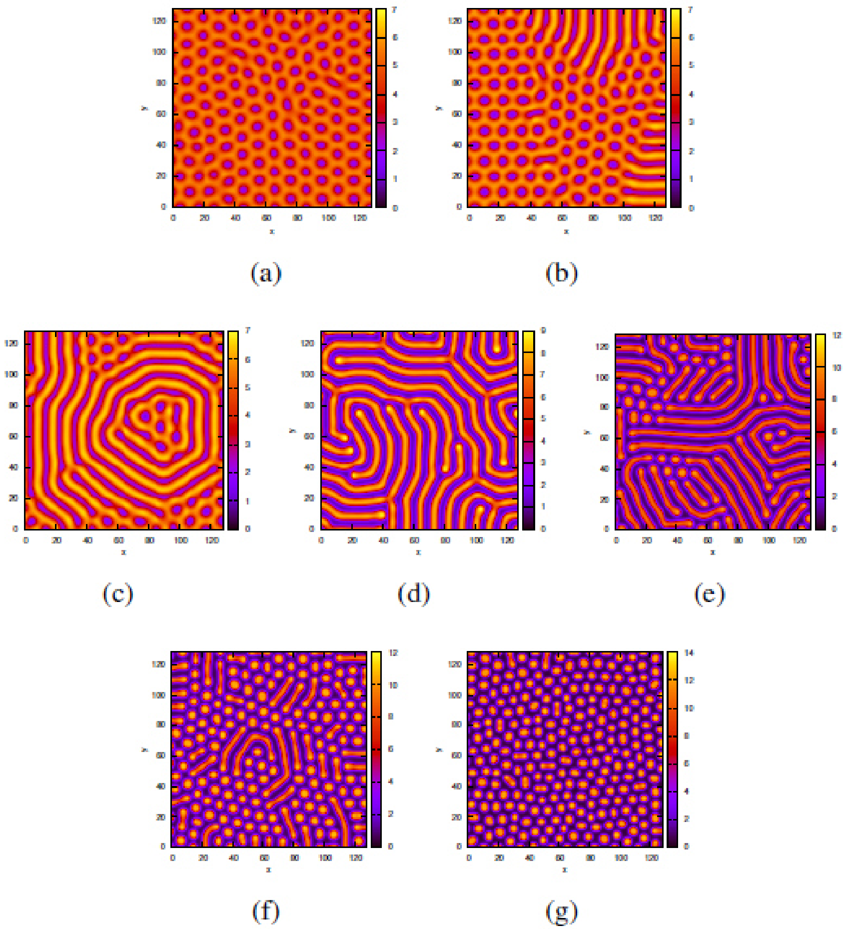
- The colored Petri net model of the Brusselator



transition	rate function
t_{16}	A
t_{17}	$B * U$
t_{18}	$U * U * V$
t_{19}	U
t_{20}	$U/(h * h)$
t_{21}	$D * V/(h * h)$

Ex4 － the Brusselator

- The colored Petri net model of the Brusselator



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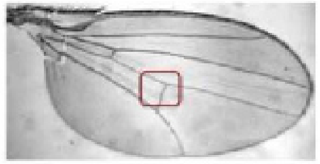

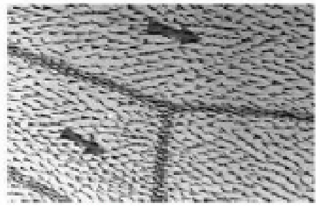

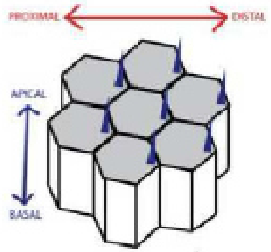

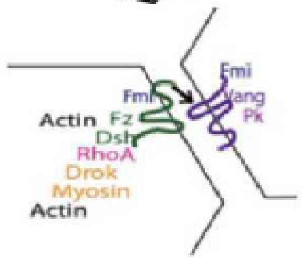

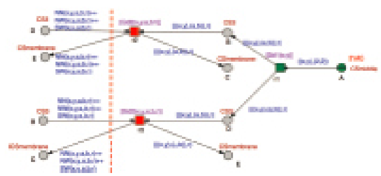

Multiscale challenges vs colored Petri nets

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- Repetition
- Variation
- Organization
- Hierarchical organization
- Communication
- Movement
- Replication
- Deletion
- Differentiation
- Dynamic (variable) grid size
- Pattern formation

- Colors
- Choose a group of colors
- Ordered color sets
- Ordered product color sets
- Exchange colors
- Change a color to another
- Create a new color in a color set
- Remove a color from a color set
- Change a color to another
- Dynamic color sets
- Combination

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- Federal Ministry of Education and Research, Germany (0315449H)
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- Molecular Network Group, Otto-von-Guericke-Universität, Germany
- Computational Systems and Synthetic Biology Research Group, Brunel University, UK
- Department of Computer Science, Port Said University, Egypt

Thank you for your attention！

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- *Q Gao et al. Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing; IEEE/ACM Transactions on Computational Biology and Bioinformatics. 2012*
- *F Liu and M Heiner: Multiscale modelling of coupled Ca2+ channels using coloured stochastic Petri nets; IET Systems Biology, 2013.*
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