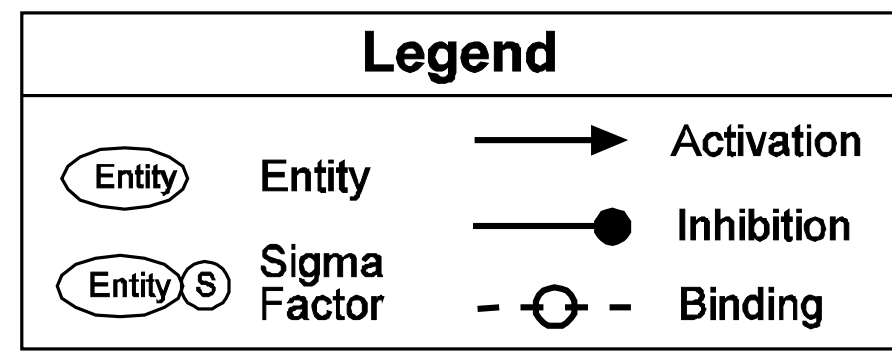
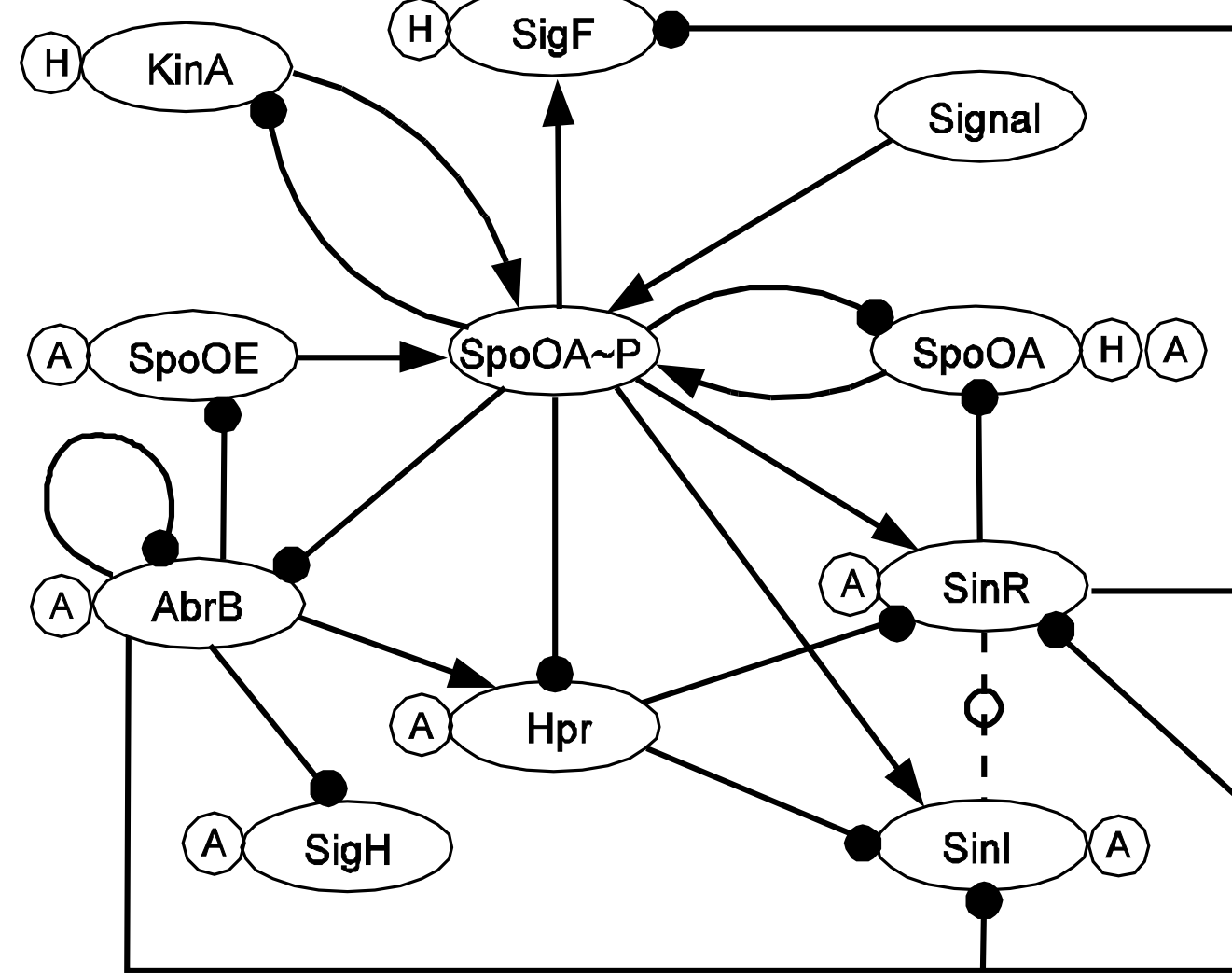


p1

Sporulation in *B. subtilis*



t1

Boolean Model Construction

- Each entity's behaviour described using truth tables.
- Logic minimisation used to extract fundamental behaviour.
- Result is Boolean equations in disjunctive normal form.
- Example: AbrB**

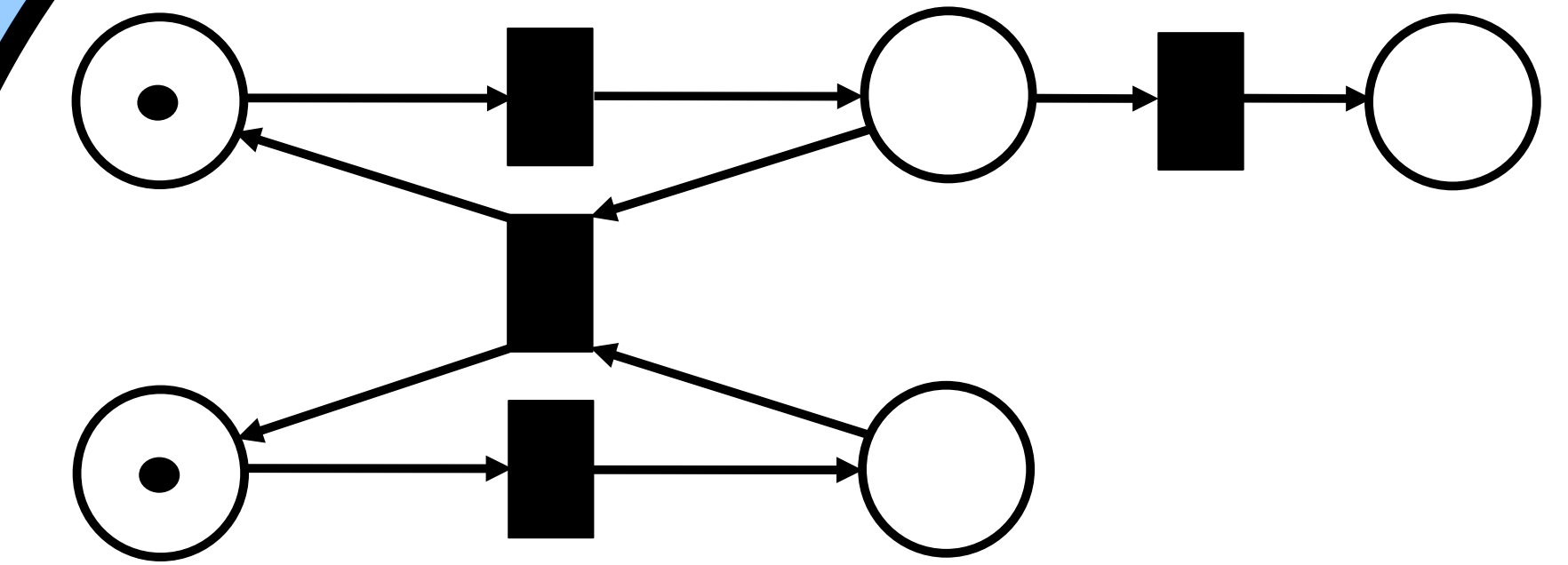
SigA	AbrB	SpoOA~P	AbrB
0	0	0	0
0	0	1	0
0	1	0	0
0	1	1	0
1	0	0	1
1	0	1	0
1	1	0	0
1	1	1	0

$$\text{AbrB} = \text{SigA} \overline{\text{AbrB}} \text{SpoOA}\sim\text{P}$$

$$\overline{\text{AbrB}} = \overline{\text{SigA}} + \overline{\text{AbrB}} + \overline{\text{SpoOA}\sim\text{P}}$$

p2

Petri Nets



- Graphical notation with mathematical semantics.
- Able to model choice, synchronization and concurrent activities.
- Wide range of techniques for analysis.
- Comprehensive tool support.

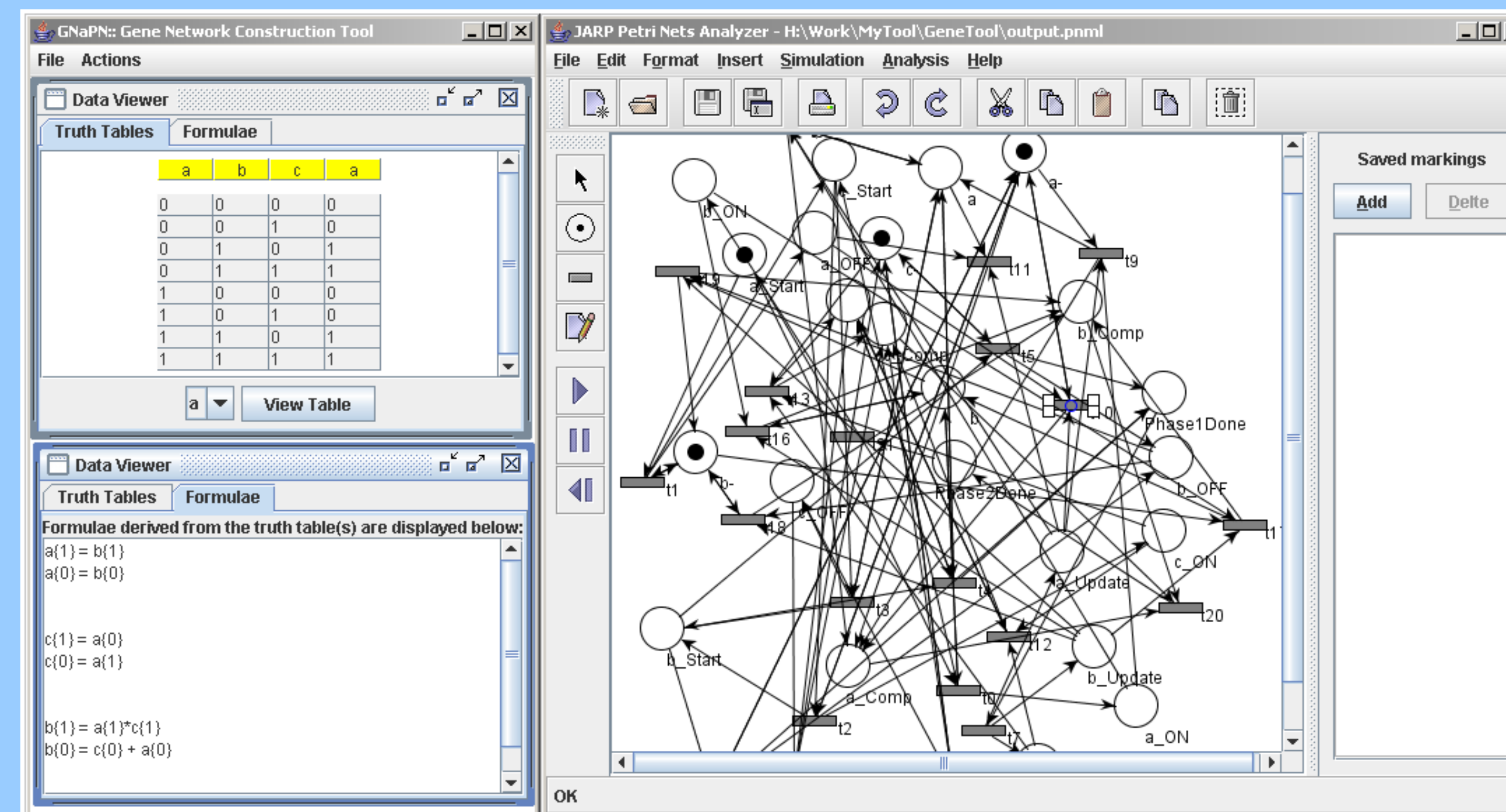
t4

Discussion

- New compact qualitative model for Petri nets.
- Supported by software tool to automate model construction.
- Cater for incomplete and inconsistent data.
- Both synchronous and asynchronous semantics considered.
- Detailed case study of sporulation in *B. subtilis*.
- Recent extensions to framework:
 - New Petri net model for multi-valued networks developed.
 - Applied to case study on *E. coli*.
 - Investigating application of temporal logic.
 - Modular model construction and analysis.

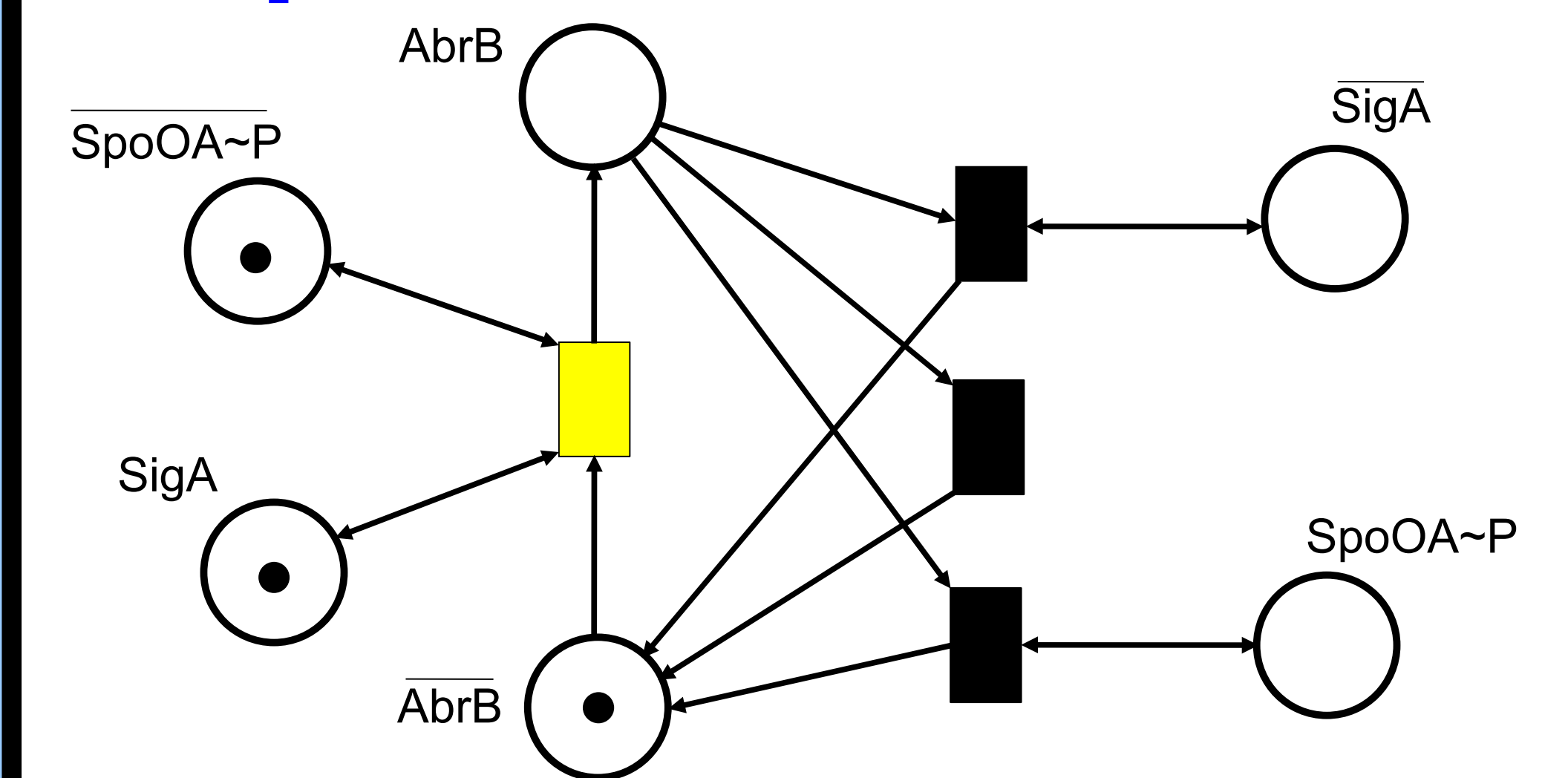
Qualitatively Analysing Genetic Regulatory Networks using Petri Nets: A Case Study of Sporulation in *B. subtilis*

Jason Steggles, Richard Banks, Oliver Shaw and Anil Wipat
Bioinformatics, November 2006



t2

Equations to Petri Net Model



Size of model: 75 places and 91 transitions

p4

Mutant Analysis

- Systematically knockout and overexpress each entity as done in laboratory experiments.
- Observe how this affects sporulation.

Entity	Knock out	Overexpressed
KinA	No sporulation	Normal
SpoOA	No sporulation	Normal
AbrB	No sporulation	No sporulation
SpoOE	Normal	No sporulation
SigH	No sporulation	Normal
SinR	Normal	No sporulation

- Observe that AbrB is only entity to have affect in both cases.
- Explained by AbrB being at the centre of three competing feedback loops.

Dynamic Property Analysis

- Consider properties between entities.
 - Example:** Mutual exclusion of SpoOA~P and SigF
- Q: Can SpoOA~P and SigF be active at the same time?

Use model checking to check constraint:

$$(\text{SpoOA}\sim\text{P} + \text{SigF}) = 2$$

No reachable marking found which satisfies the above constraint.

SpoOA~P and SigF are mutually exclusive.

p3

Model Analysis

Wide range of techniques for analysing Petri net model:

- Validation:**
 - Does model exhibit reasonable behaviour, e.g. sporulation occurs under correct conditions?
 - Perform simulations and observe attractor cycles.
- Dynamic properties:**
 - Reachability analysed using model checking.
 - Properties of entities considered, e.g. mutual exclusion.
- Mutant analysis:**
 - Entity knockout and overexpression.
 - Investigate effect using model checking.
 - Formulate hypotheses for laboratory testing.