A Graphical Representation for Biological Processes in the Stochastic pi-Calculus

Andrew Phillips, Luca Cardelli, Giuseppe Castagna

5.11.2007

Outline

- introduction
- stochastic pi-calculus
- graphical calculus
- example: bistable gene network
- conclusion

Introduction

- graphical representation for biological systems
  - static
  - dynamic
- formalism: graphical calculus
- equivalent to stochastic π

- highlight existence of cycles
- animate interactions between system components
- accessibility to non-computer scientists

The Stochastic π-Calculus

a variant with internal transitions and recursive definitions

System

- system $E \vdash P$
- constant environment E
- process P

Biological settings

- process P represents a molecule (gene, protein, etc.)
- an action describes what a molecule can do

The Stochastic π-Calculus

Environment

$$
\begin{array}{lll}
E ::= & X(m) = P & \text{Definition, } \mathrm{fn}(P) \subseteq m \\
\mid & E_1, E_2 & \text{Union} \\
\mid & \emptyset & \text{Empty}
\end{array}
$$

- definition parametrized by m

The Stochastic π-Calculus

Action

$$\begin{array}{lll} \pi ::= & \tau_r & \text{Delay} \\ | & !x(n) & \text{Output} \\ | & ?x(m) & \text{Input} \end{array}$$

- delay action τ_r
  - represents a change in internal structure
  - the rate r characterises an exponential distribution
  - average duration of the interaction $1/r$
- input and output
  - on a common channel x
  - an interaction of two molecules
  - rate(x) . . . the interaction rate
- fits the biological reality well

The Stochastic π-Calculus

Process

$$
\begin{array}{rrll}
P, Q ::= & P|Q & \text{Parallel} \\
| & M & \text{Choice} \\
| & X(n) & \text{Instance} \\
| & \nu x P & \text{Restriction} \\
M ::= & \pi.P + M & \text{Action} \\
| & 0 & \text{Null}
\end{array}
$$

- parallel composition $P_1|\ldots|P_M$
  - existence of M molecules in parallel
- choice $\pi_1 P_1 + \ldots + \pi_N P_N$
  - ability to react in N different ways
- definition recorded in environment
- restriction used to represent complexes with a private communication $\nu x(P|Q)$

The Stochastic π-Calculus

Execution rules

generally $E \vdash P \xrightarrow{\alpha} E \vdash P'$

Graphical representation

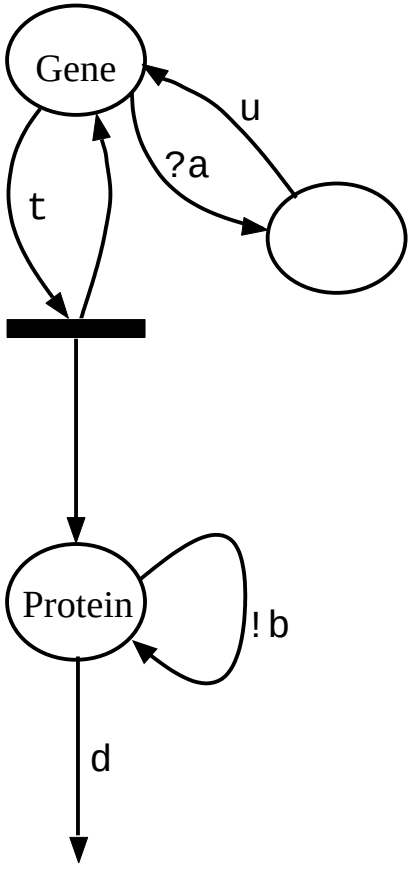
- processes as *nodes*
- *edges* to nested process
- definition in the environment assigns a unique *identifier* to a node
- static visualisation only

The Stochastic π-Calculus

Example of graphical representation

$Gene(a, b) = \tau_t.(Gene(a, b)|Protein(b)) + ?a.\tau_u.Gene(a, b)$

$Protein(b) = !b.Protein(b) + \tau_d$



Graphical Calculus

- reduction equivalent to stochastic π-calculus
- the same expressive power
- each choice defined separately in the environment
- each node unique identifier
- static and also dynamic visualisation

Graphical Calculus

Process

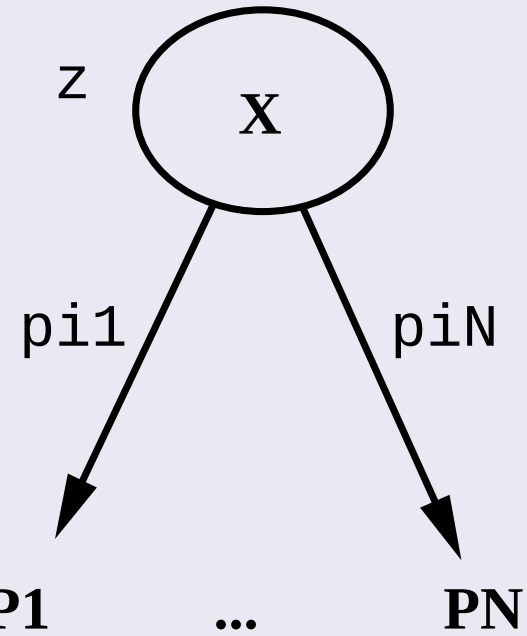
$$
\begin{array}{lll}
P, Q ::= & P|Q & \text{Parallel} \\
| & 0 & \text{Null} \\
| & X(n) & \text{Instance} \\
| & \nu x P & \text{Restriction}
\end{array}
$$

Environment

$$
\begin{array}{lll}
E ::= & X(m) = D & \text{Definition, } \mathrm{fn}(P) \subseteq m \\
| & E_1, E_2 & \text{Union} \\
| & \emptyset & \text{Empty} \\
D ::= & P & \text{Process} \\
| & M & \text{Choice} \\
| & \nu x D & \text{Restriction} \\
M ::= & \pi.P + M & \text{Action} \\
| & 0 & \text{Null}
\end{array}
$$

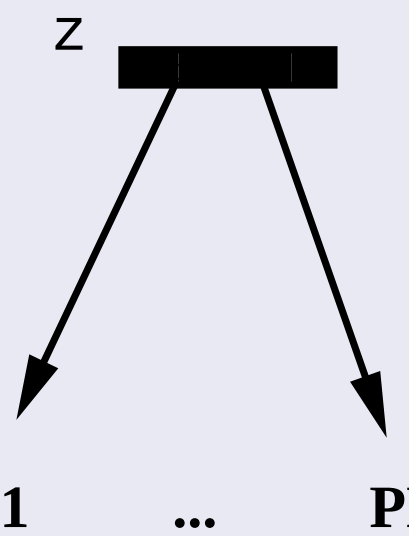
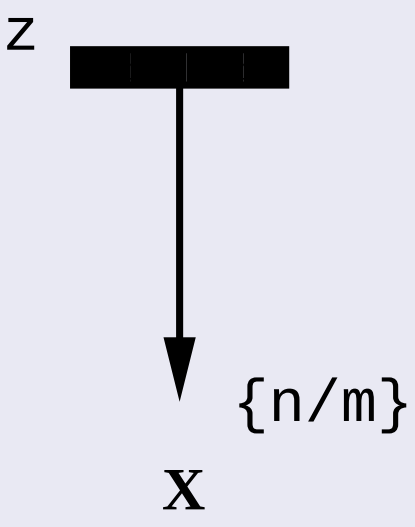
Graphical Calculus

Graphical representation - environment

E	Choice $X(m)=\nu\, z(pi1.P1+...+piN.PN)$	Process $X(m)=P$	Union $E1,...,EN$
E		**P**	**E1 ... EN**

Graphical Calculus

Graphical representation - process

P	Null *v z 0*	Parallel *v z(P1|...|PM)*	Instance *X(m)=P |− vzX(n)*
P			

Graphical Calculus

Dynamic graphical representation of processes

P	Null *v z 0*	Parallel *v z(P1|...|PM)*	Instance *X(m)=P |− vzX(n)*
P		z **P1** **...** **PN**	**X** {n/m} z

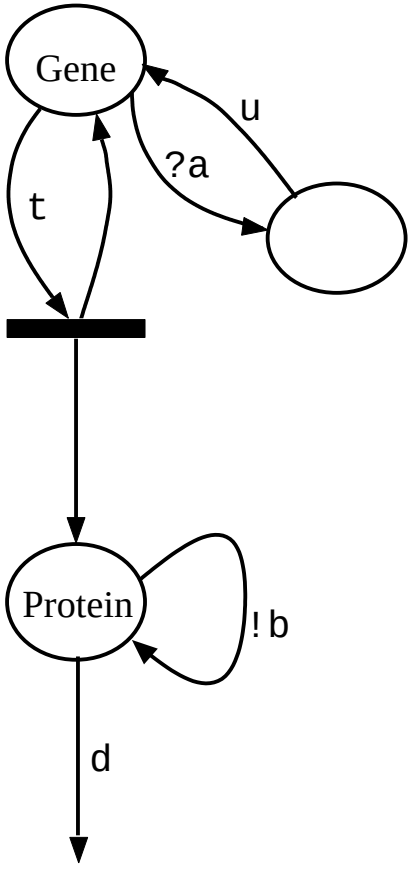
- substitution token $\{n/m\}$ next to instance
- dotted edge from restricted name z to processes
- node highlighted when at least one token present and any restricted names are connected to the token – the process is "active"

The Stochastic π-Calculus

Gene example of graphical representation

$Gene(a, b) = \tau_t.(Gene(a, b)|Protein(b)) + ?a.\tau_u.Gene(a, b)$

$Protein(b) = !b.Protein(b) + \tau_d$



Graphical Calculus

Gene example

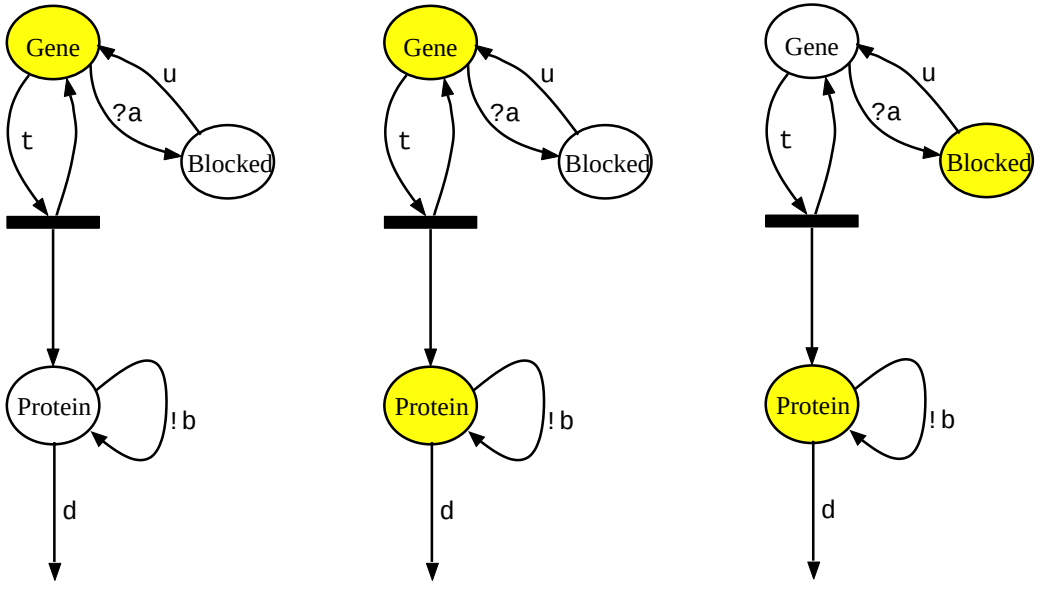
$Gene(a,b) = \tau_t.(Gene(a,b)|Protein(b)) + ?a.Blocked(a,b)$

$Blocked(a,b) = \tau_u.Gene(a,b)$

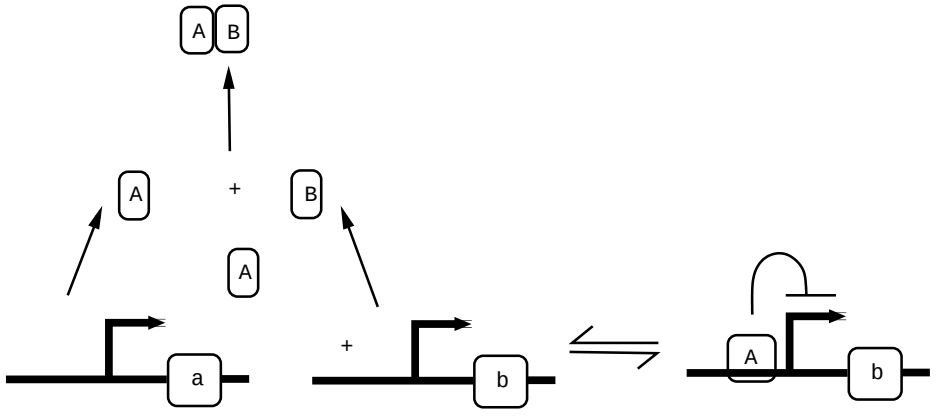
$Protein(b) = !b.Protein(b) + \tau_d$

Example of behaviour

$1 \xrightarrow{t} 2 \xrightarrow{?a} 3 \xrightarrow{u} 2$



Bistable Gene Network



z=inhibit, bind

$a(z) = \tau_{tA}.(A(z)|a(z))$

$A(z) = \nu u(\tau_{d_A} + !bind(u).A_B(u) + !inhibit(u).A_b(u, inhibit, bind))$

$A_b(u, inhibit, bind) = ?u.A(z)$

$A_B(u) = \tau_{dAB}$

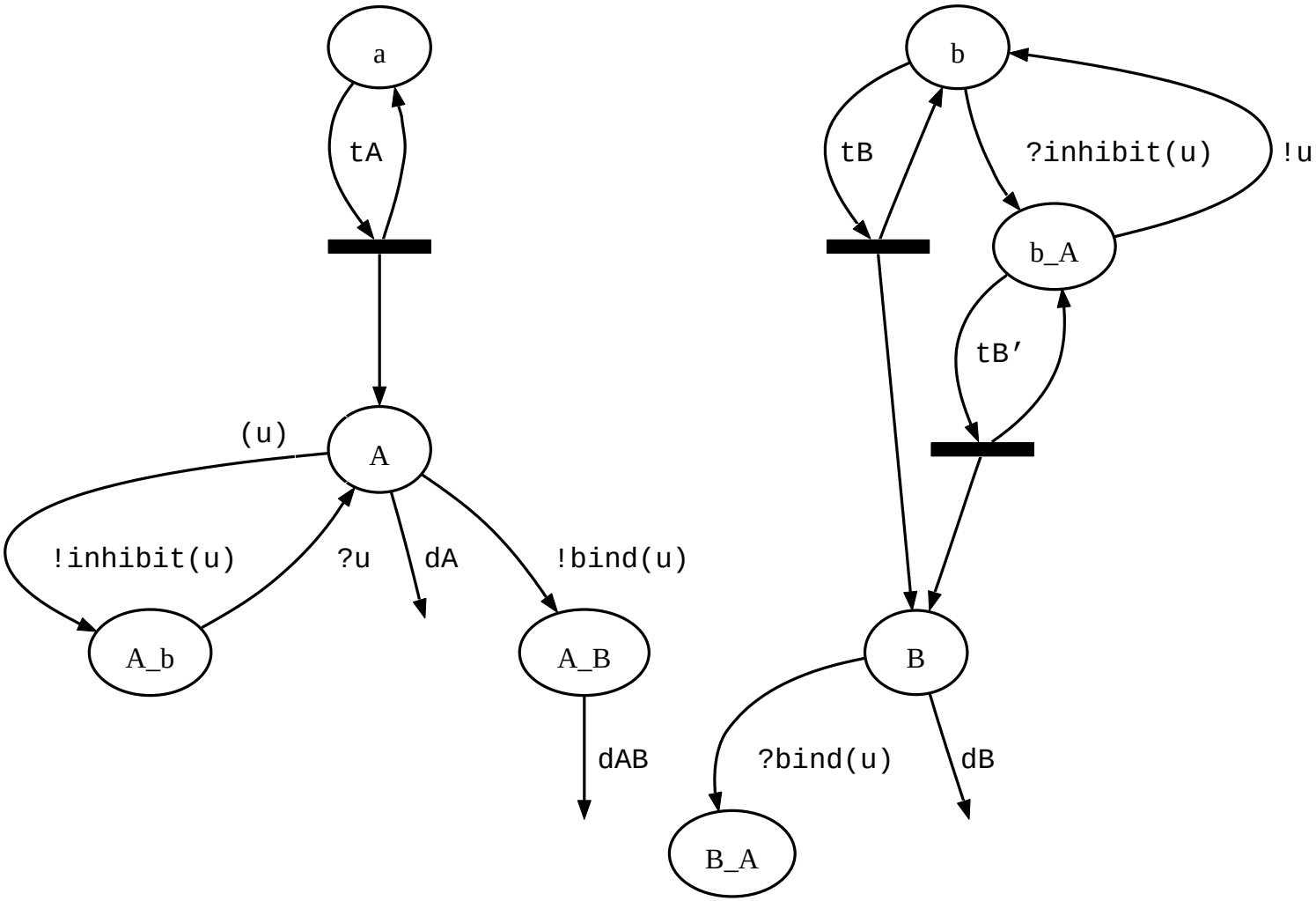
$b(z) = \tau_{tB}.(B(z)|b(z)) + ?inhibit(u).b_A(u)$

$b_A(u) = \tau_{tB'}.(B(z)|b_A(u)) + !u.b(z)$

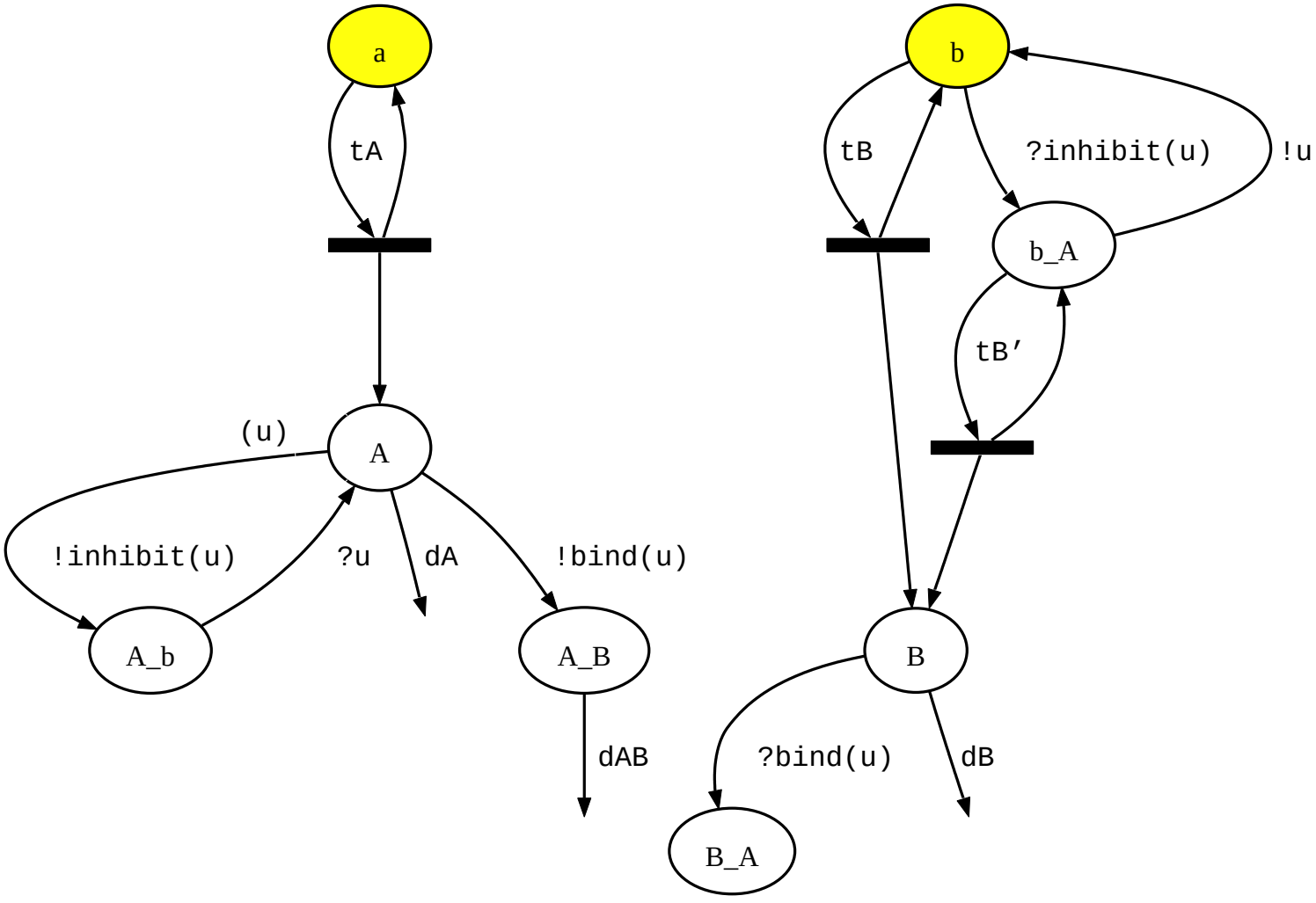
$B(z) = \tau_{dB} + ?bind(u).B_A(u)$

$B_A(u) = 0$

Bistable Gene Network

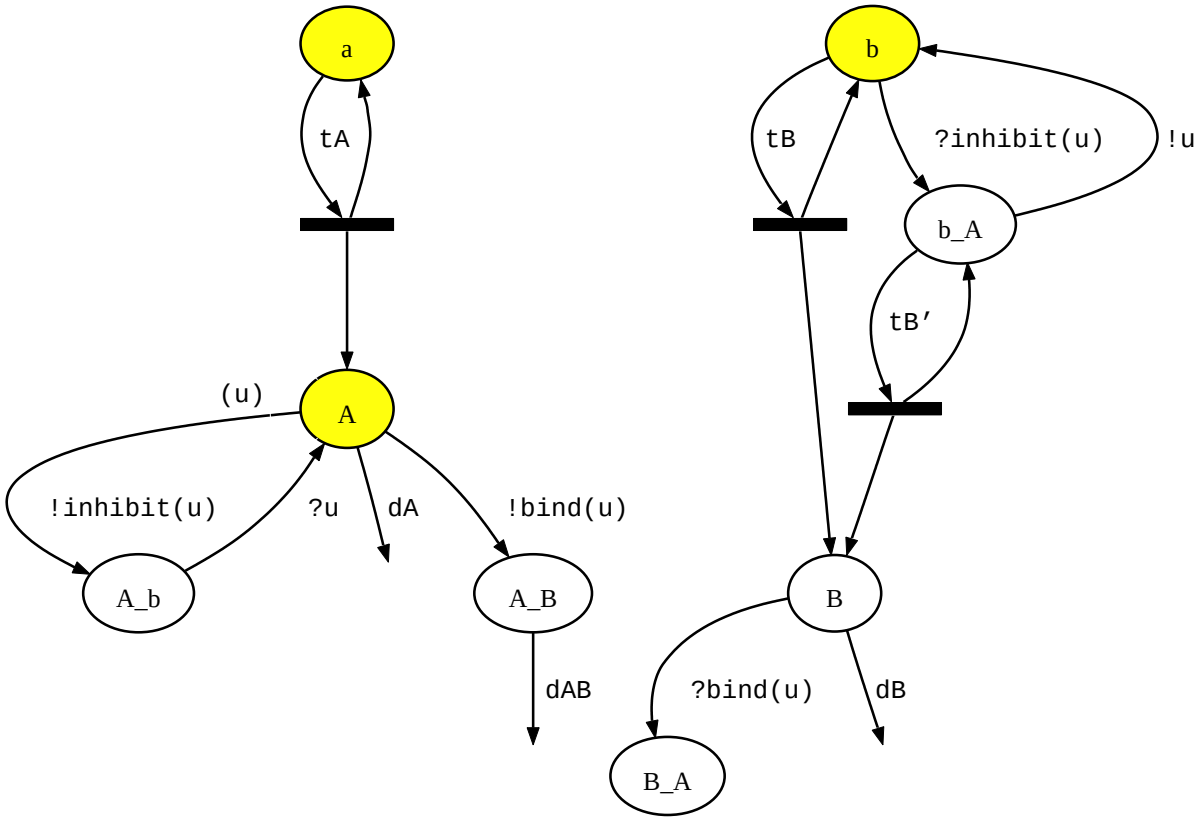


Bistable Gene Network - First Possible Behaviour



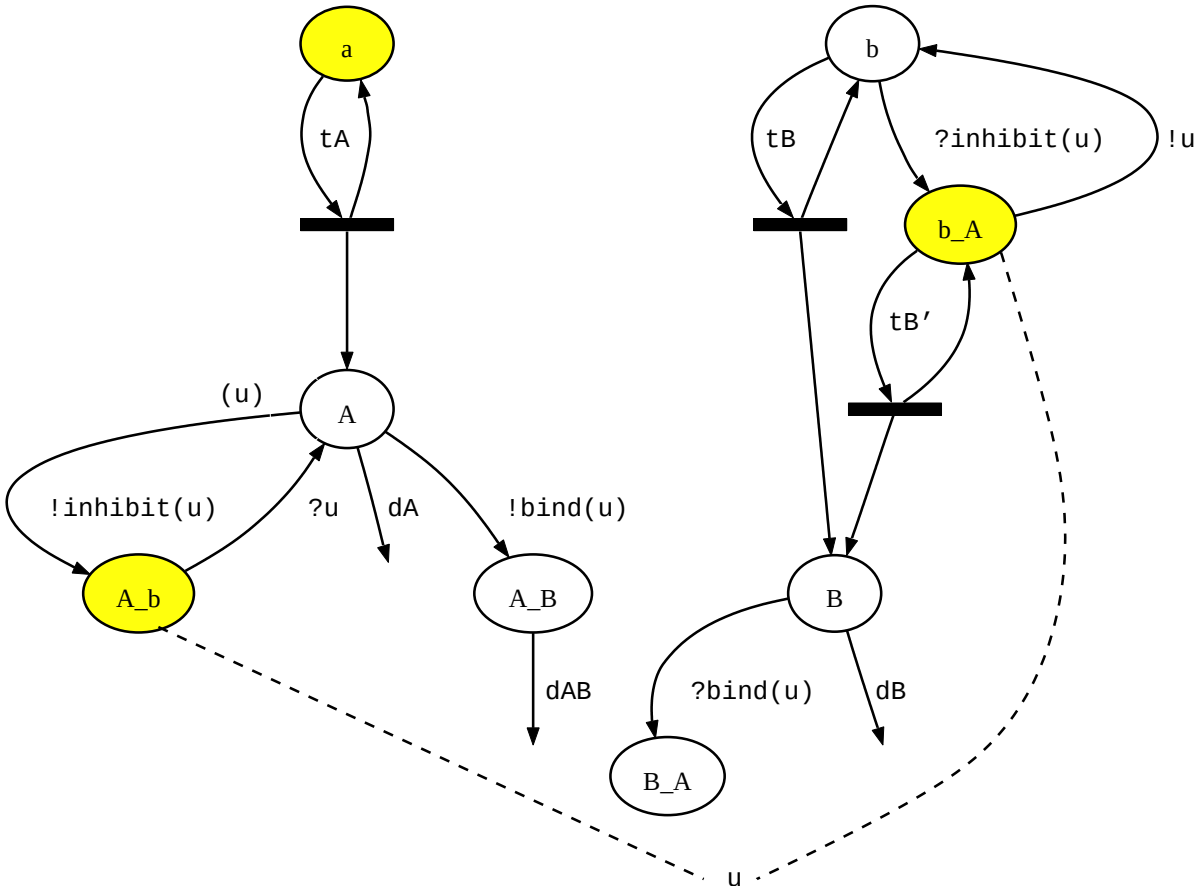
Bistable Gene Network - First Possible Behaviour

t_a (A is transcribed first)

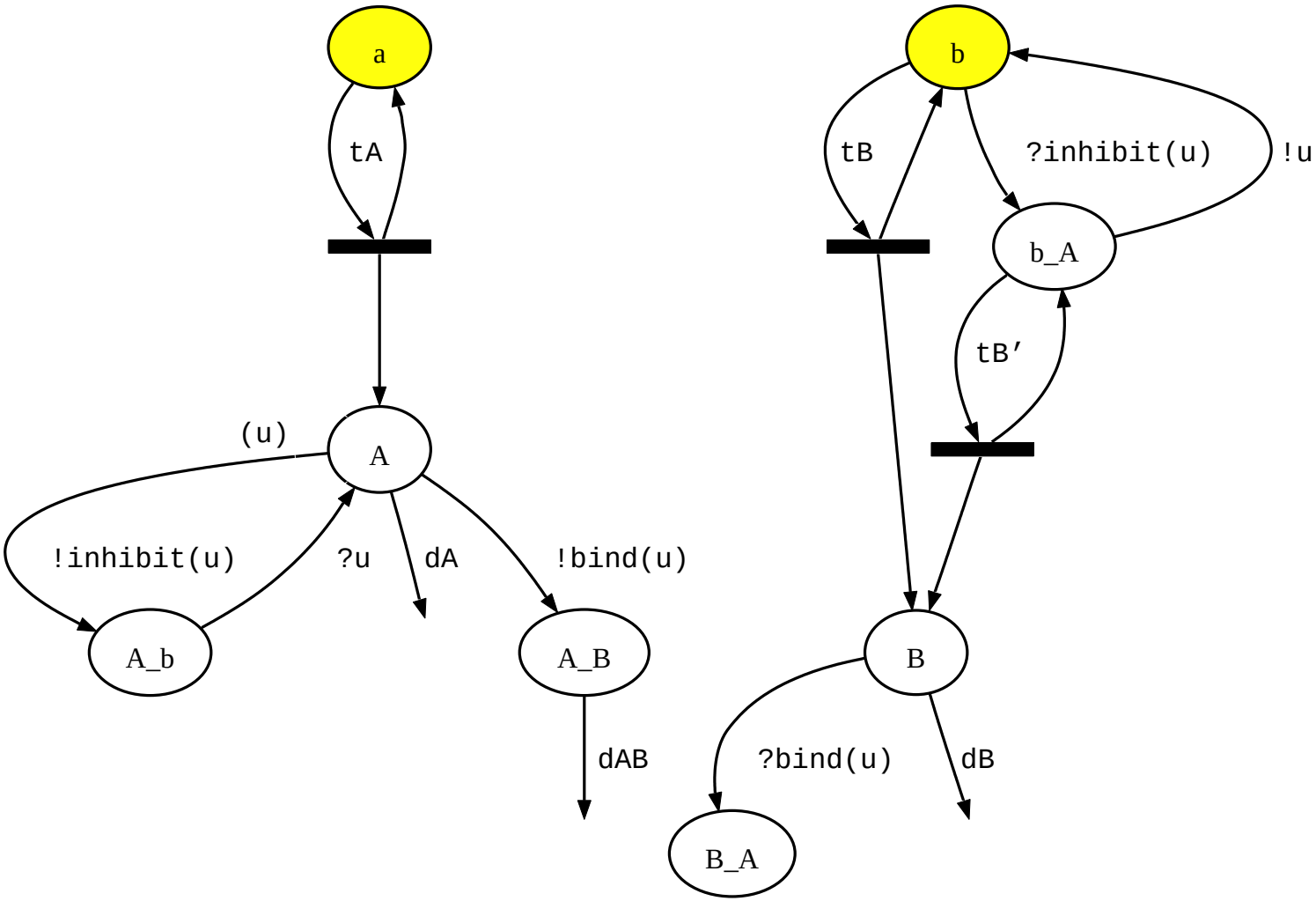


Bistable Gene Network - First Possible Behaviour

inhibit (*A* binds to gene *b* and inhibits production of protein *B*)

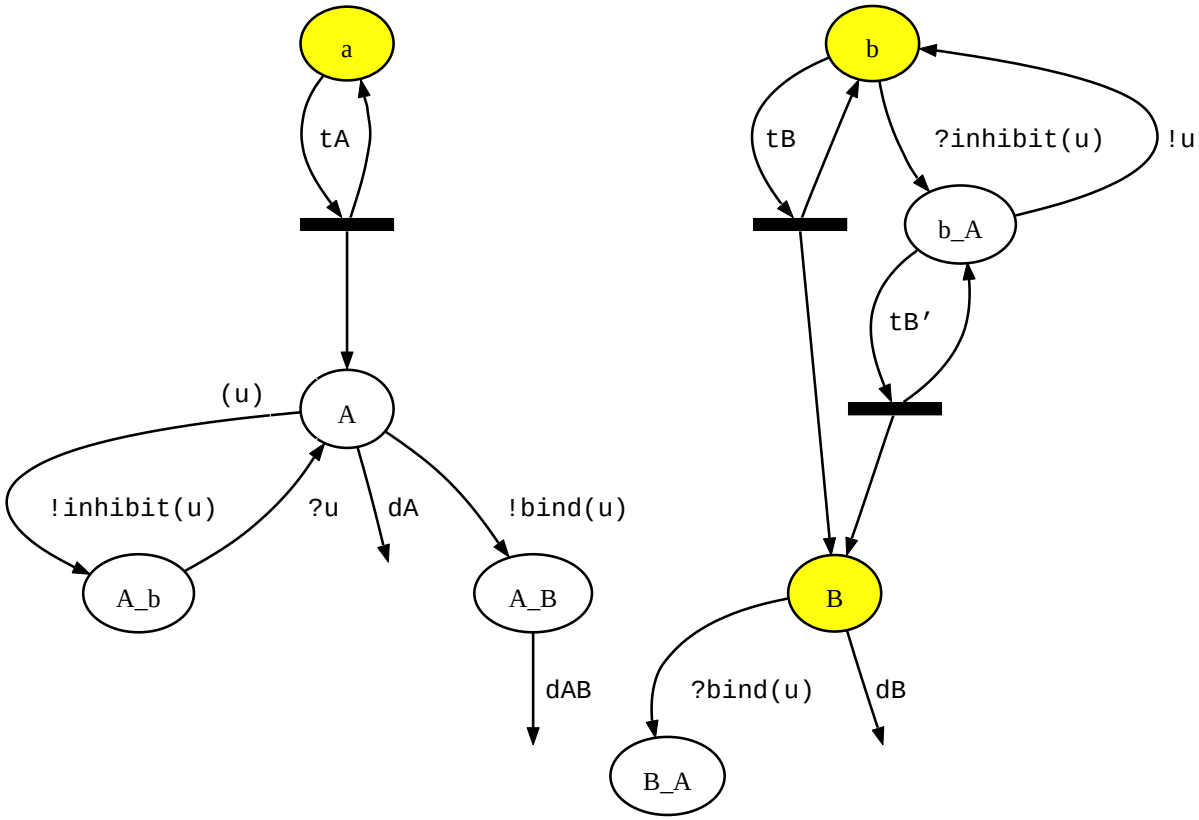


Bistable Gene Network - Second Possible Behaviour



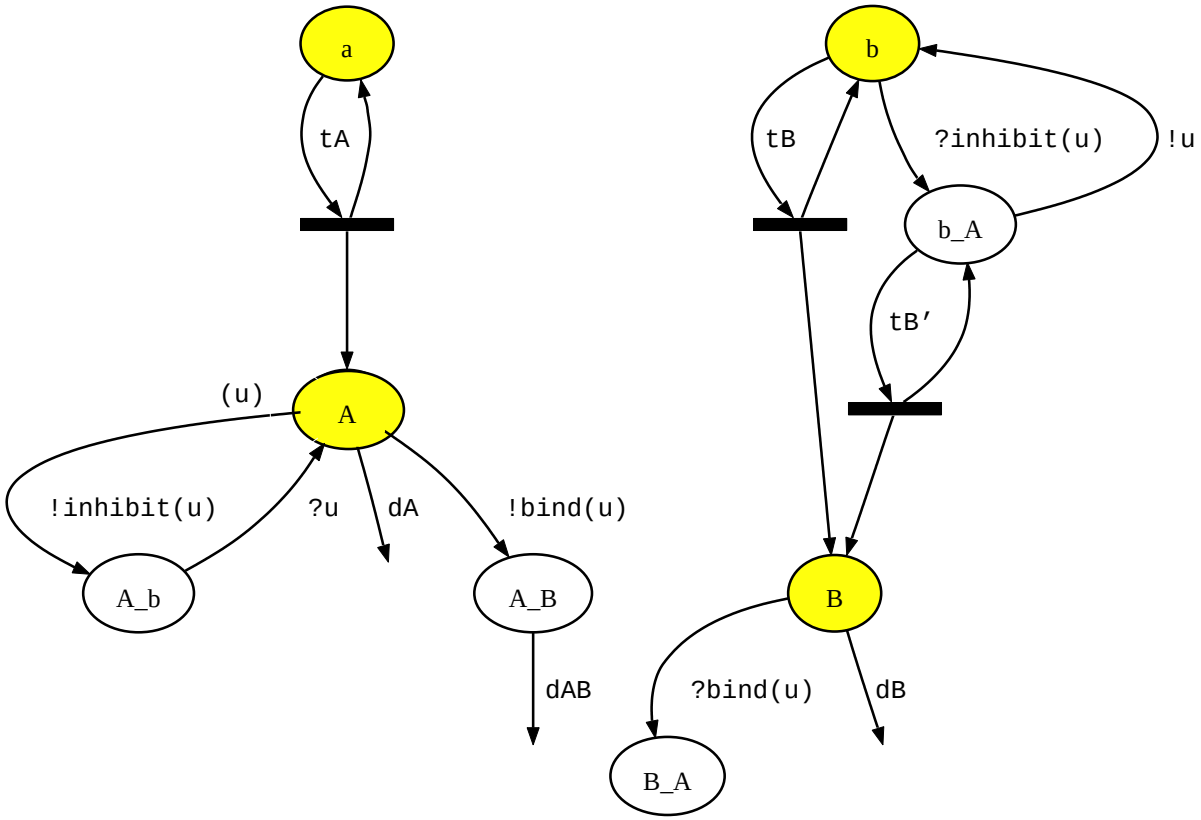
Bistable Gene Network - Second Possible Behaviour

t_b (B is transcribed first)



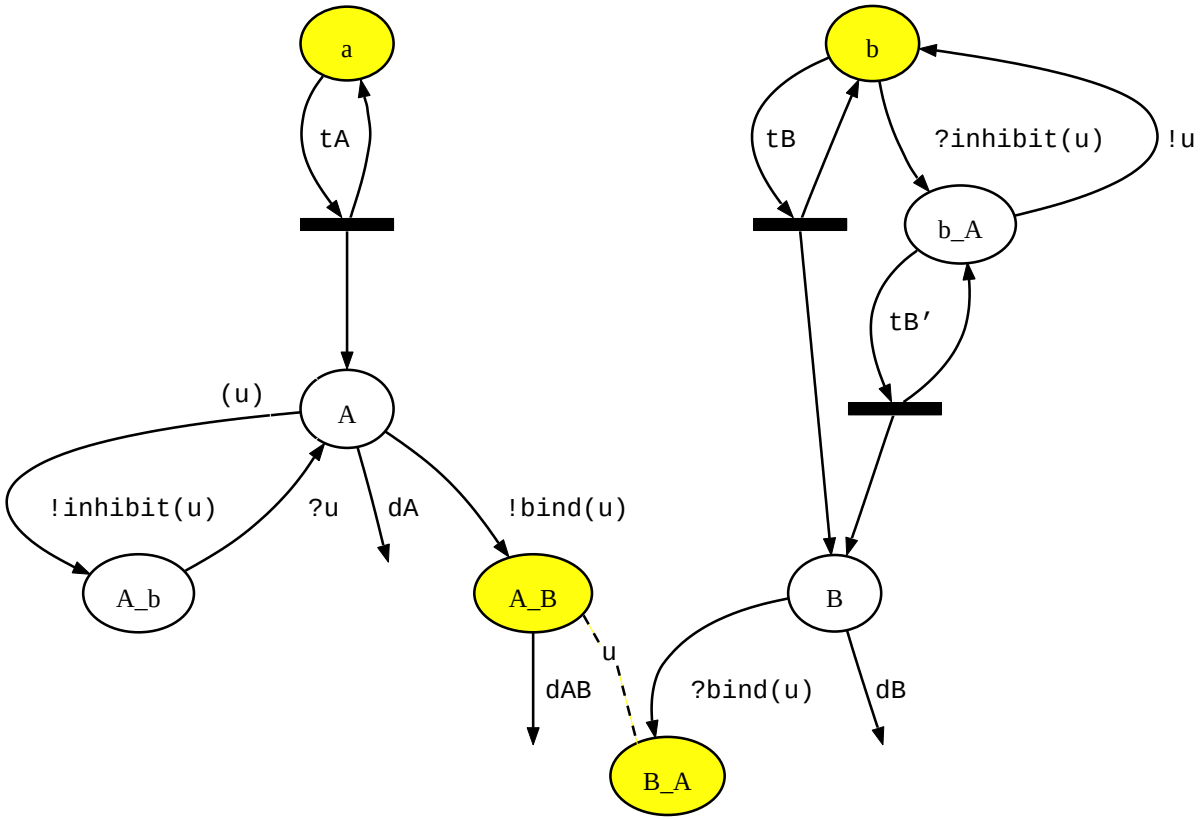
Bistable Gene Network - Second Possible Behaviour

t_a (A is transcribed then)



Bistable Gene Network - Second Possible Behaviour

bind (protein A binds to protein B)



Conclusion

- graphical calculus
- expressive power of stochastic pi-calculus
- static and dynamic visualisation
- examples
  - bistable gene network
  - mapk cascade
- SPiM
  - tool
  - programming language
  - graph generation
  - simulation