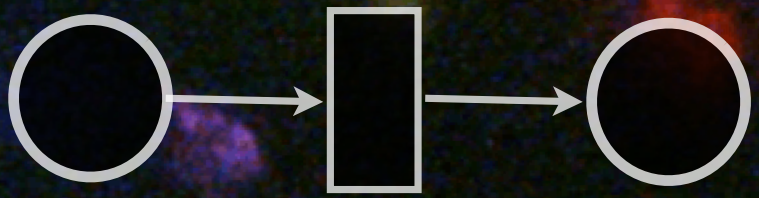
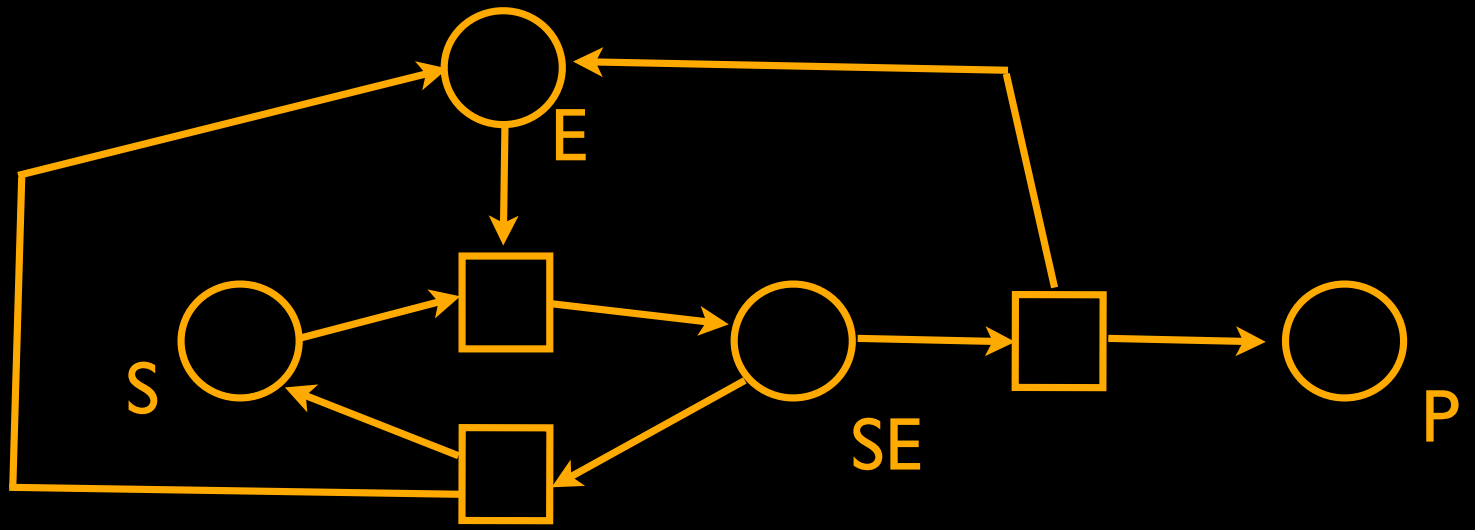
Why aren't Petri nets widely used in biological research ?



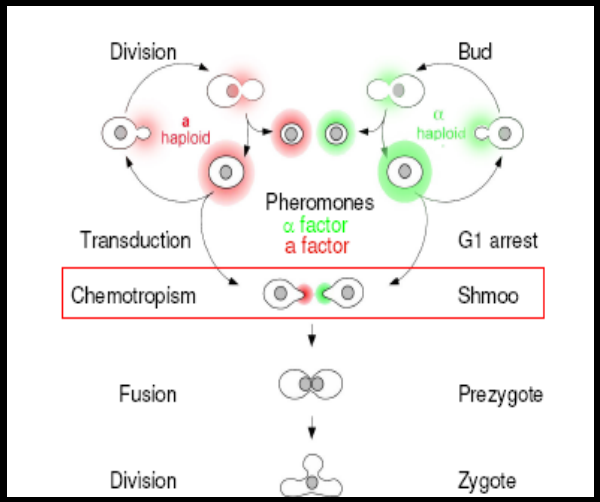
Jorge Carneiro
Instituto Gulbenkian de Ciência, Portugal
http://qobweb.igc.gulbenkian.pt

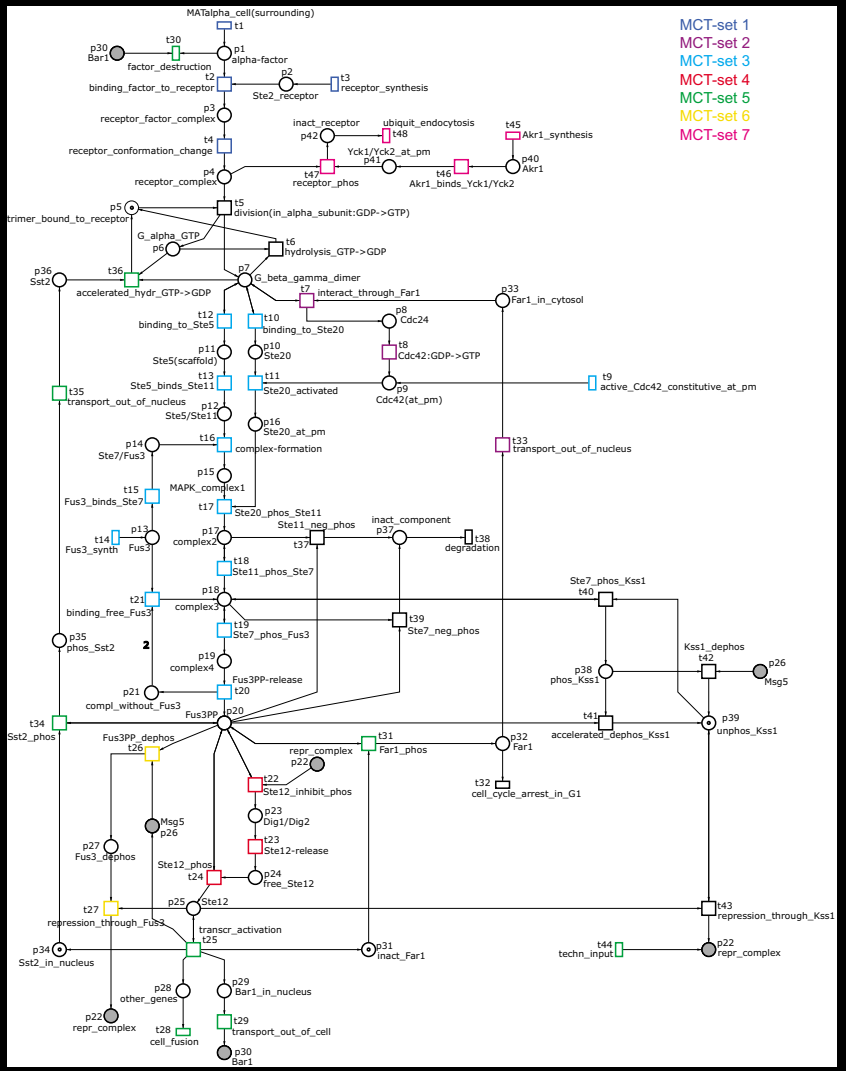
(Stochastic) Petri nets were naturally applied to modelling of metabolic networks, signal transduction pathways and gene regulatory networks

$$S + E \rightleftarrows [SE] \rightarrow P + E$$



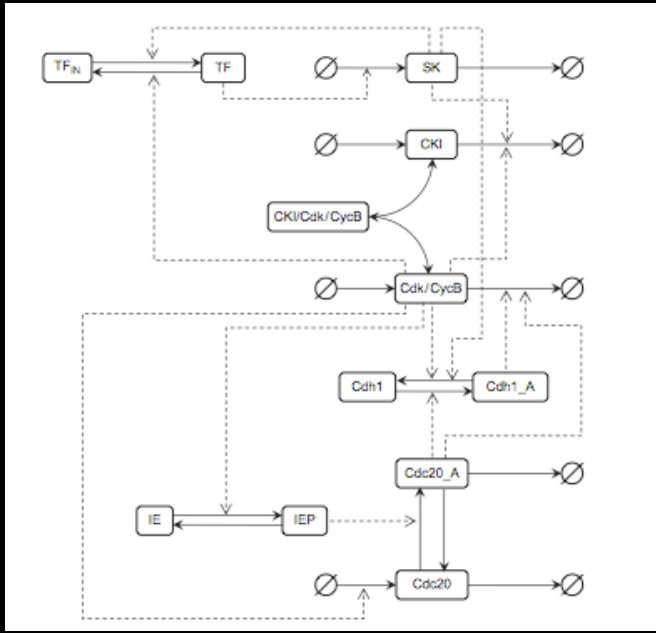
Application of Petri net based analysis techniques to signal transduction pathways

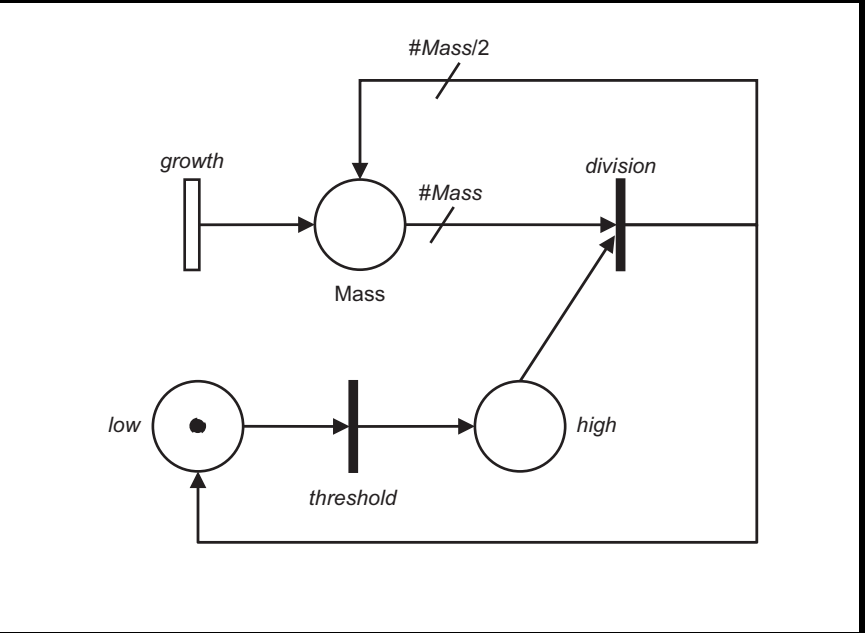


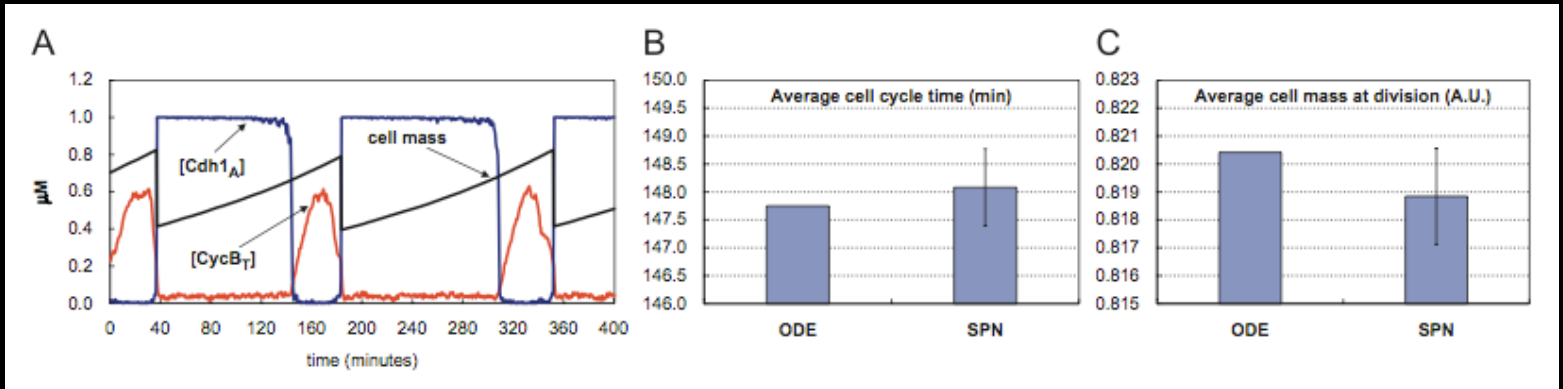


Sackmann et al. *BMC Bioinformatics* (2006), **7**:482

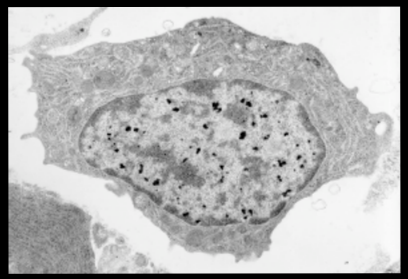
Stochastic Petri Net extension of a yeast cell cycle model

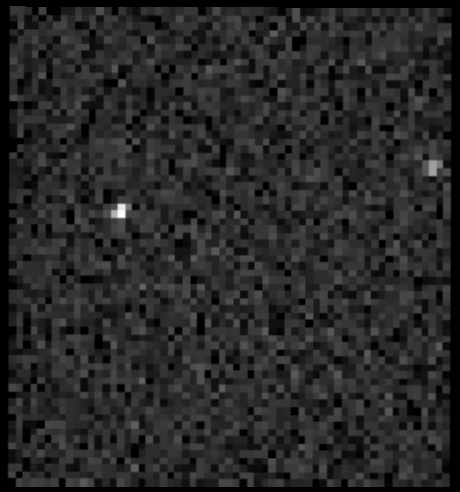


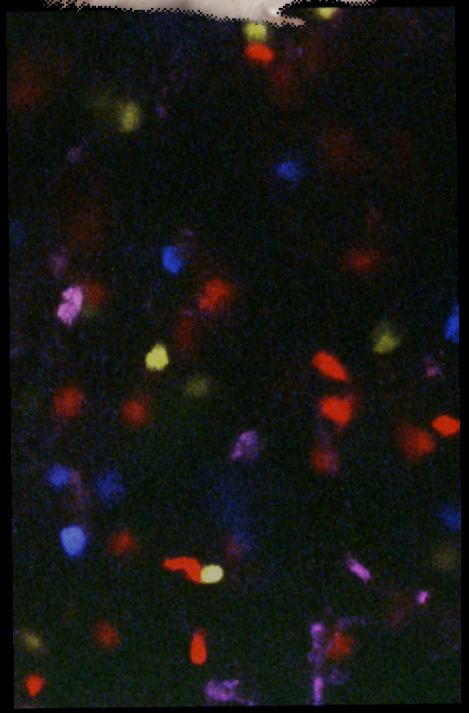




Mura & Csikasz-Nagy et al. *J Theor Biol* (2008), **254**: 850





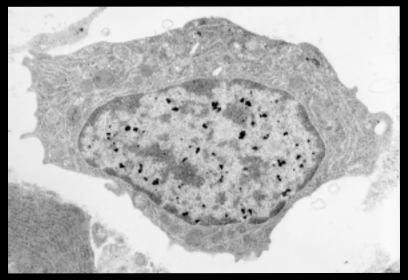


A few examples of biological processes that I am trying to model by Stochastic Petri Nets

V(D)J recombination

Ion channel dynamics

Cell population dynamics



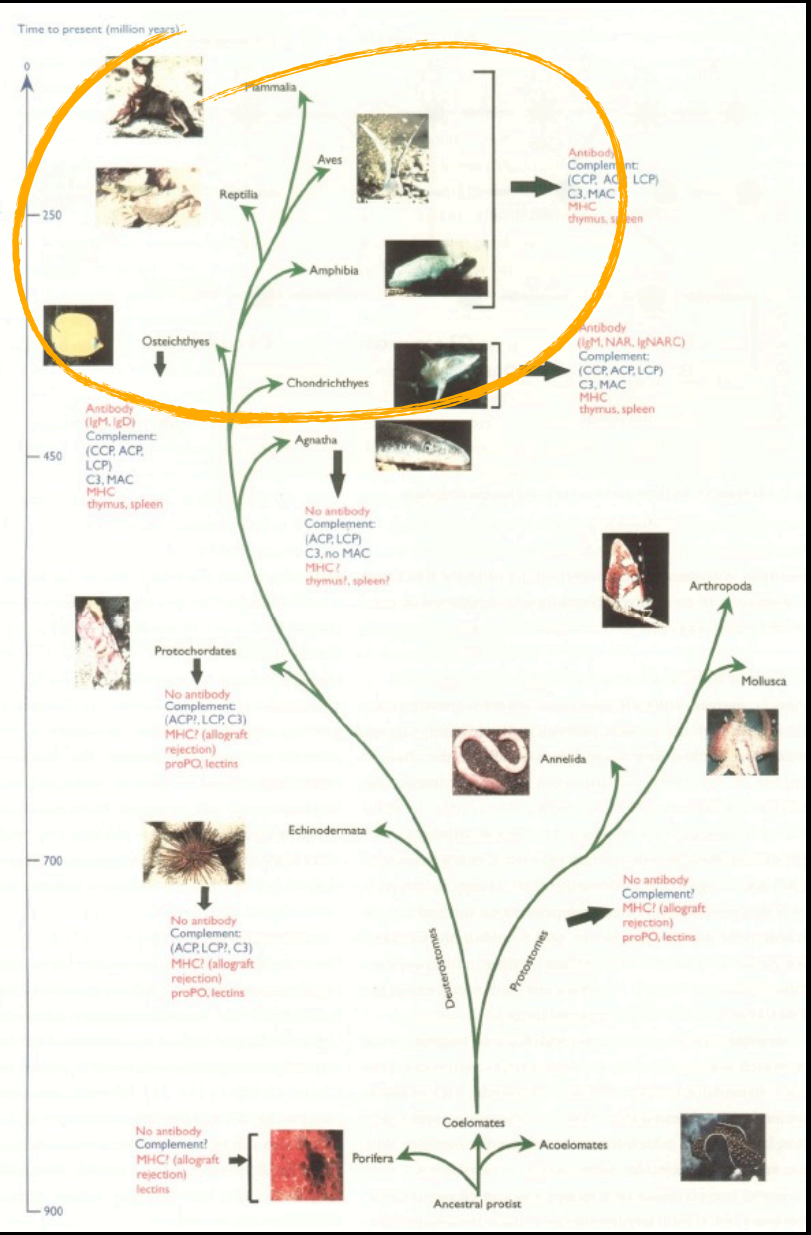
V(D)J recombination

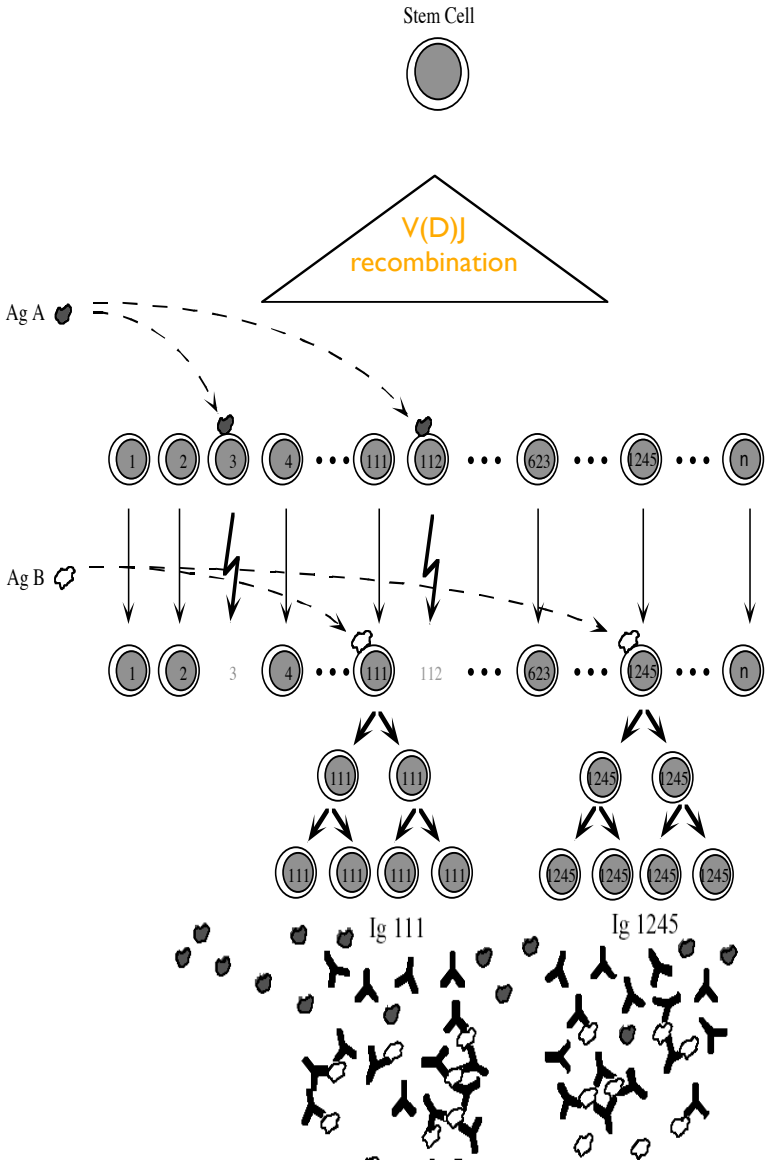
a.k.a.

Making an antibody gene

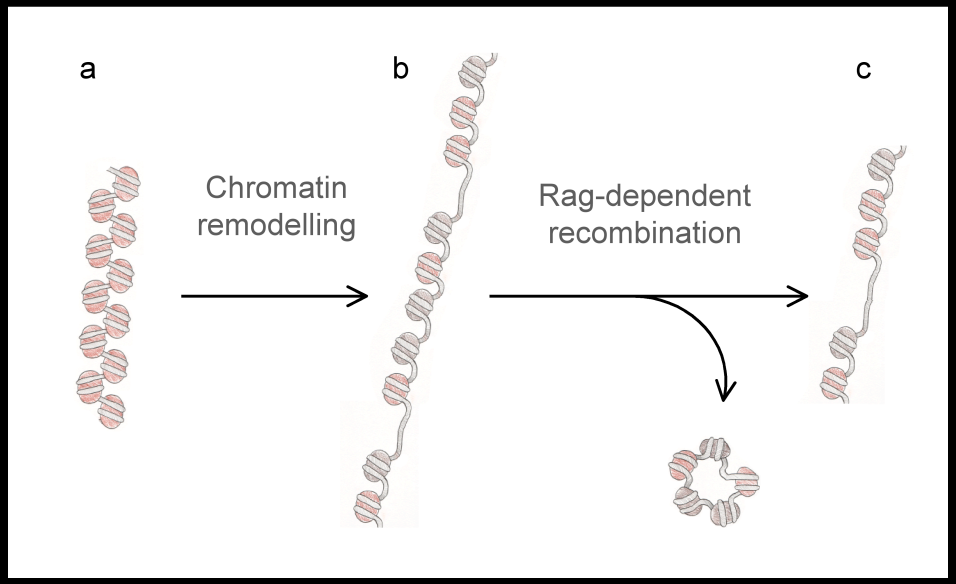
a.k.a.

Random cutting and pasting of DNA

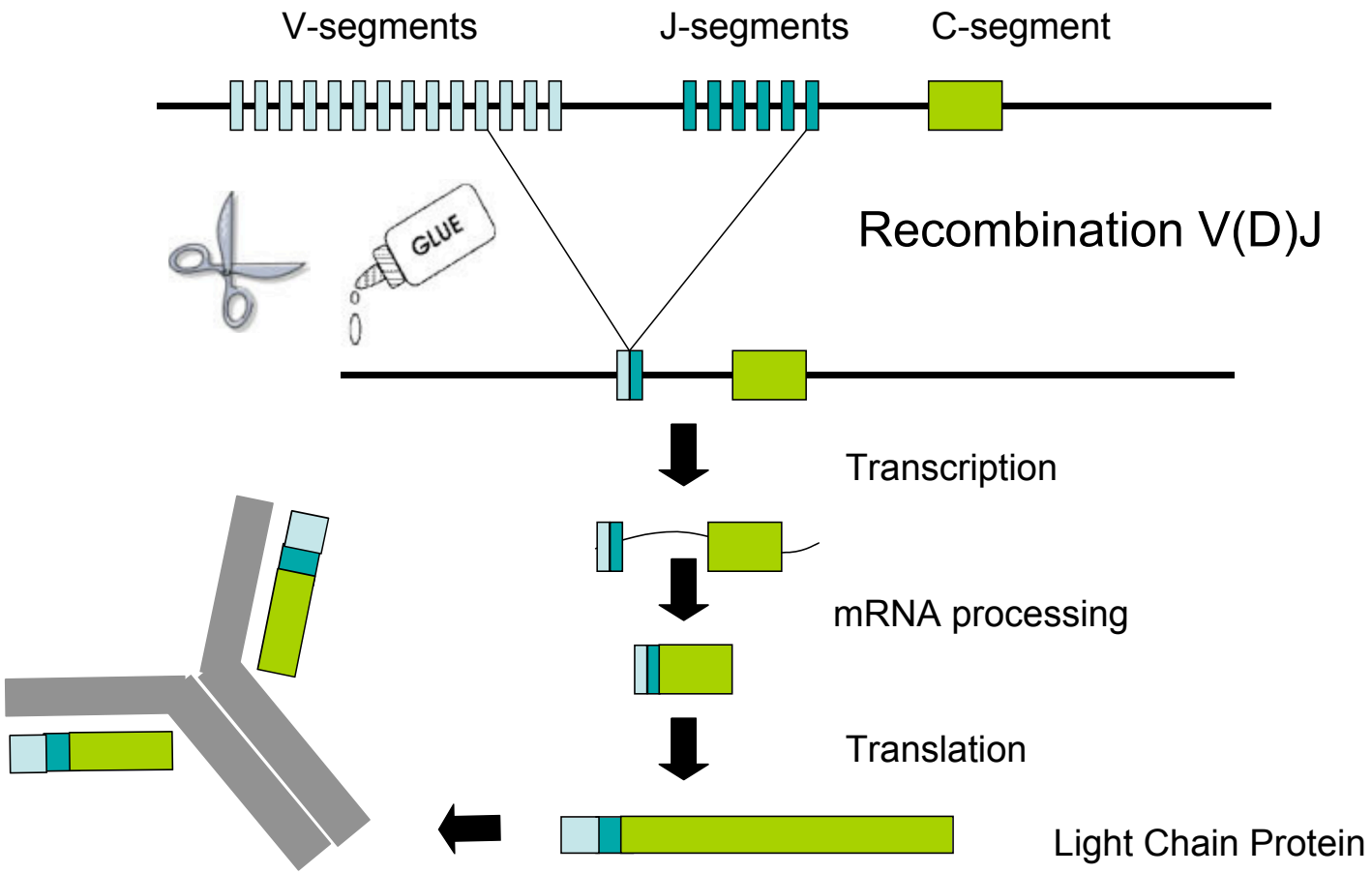

Time to present (million years)
0
250
450
700
900
Mammalia
Aves
Reptilia
Amphibia
Osteichthyes
Chondrichthyes
Agnatha
Antibody
(IgM, IgD)
Complement:
(CCP, ACP, LCP)
C3, MAC
MHC
thymus, spleen
No antibody
Complement:
(ACP, LCP)
C3, no MAC
MHC?
thymus?, spleen?
Arthropoda
Protochordates
No antibody
Complement:
(ACP?, LCP, C3)
MHC? (allograft rejection)
proPO, lectins
Mollusca
Annelida
Echinodermata
No antibody
Complement:
(ACP, LCP?, C3)
MHC? (allograft rejection)
proPO, lectins
Deuterostomes
Protostomes
No antibody
Complement?
MHC? (allograft rejection)
proPO, lectins
No antibody
Complement?
MHC? (allograft rejection)
lectins
Porifera
Coelomates
Acoelomates
Ancestral protist


Stem Cell
V(D)J
recombination
Ag A
Ag B
1
2
3
4
111
112
623
245
n
Ig 111
Ig 1245

V(D)J recombination



A Cartoon of V(D)J recombination

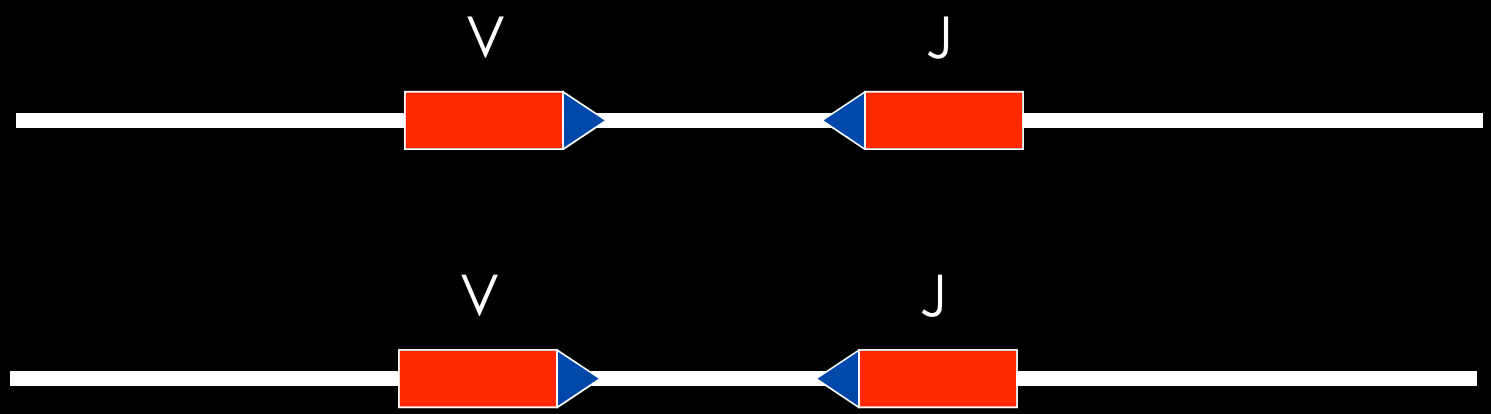


Lymphocytes must have only one antigen receptor

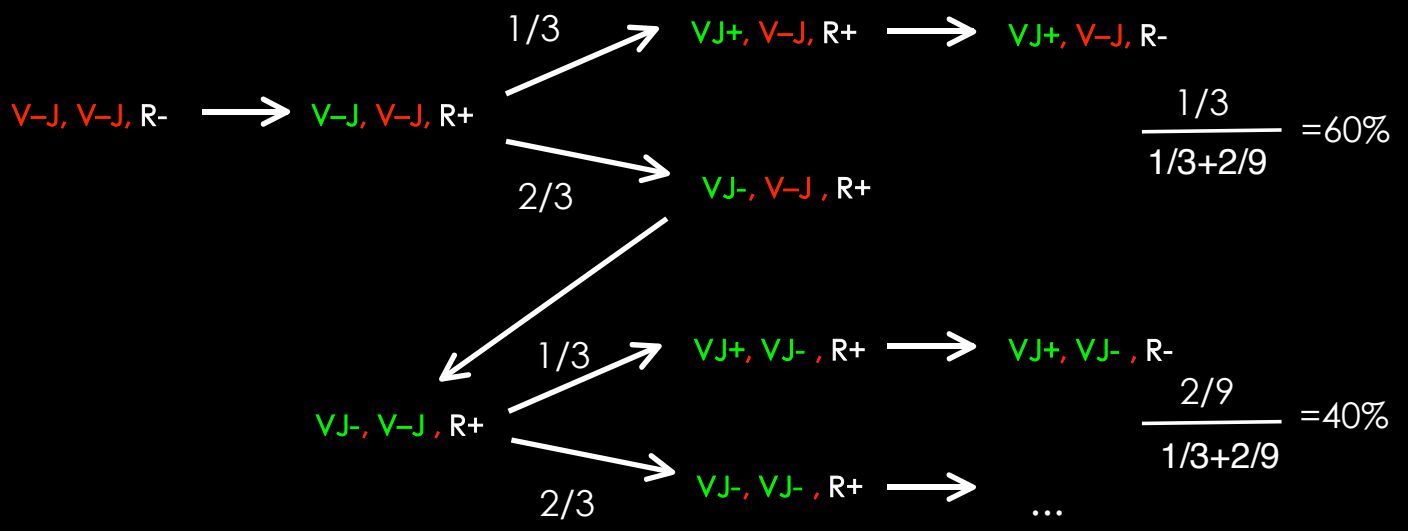
Yield and allelic exclusion constrain the kinetics of V(D)J recombination

Maximize diversity and allelic exclusion in the output of the reaction

A toy VJ locus model

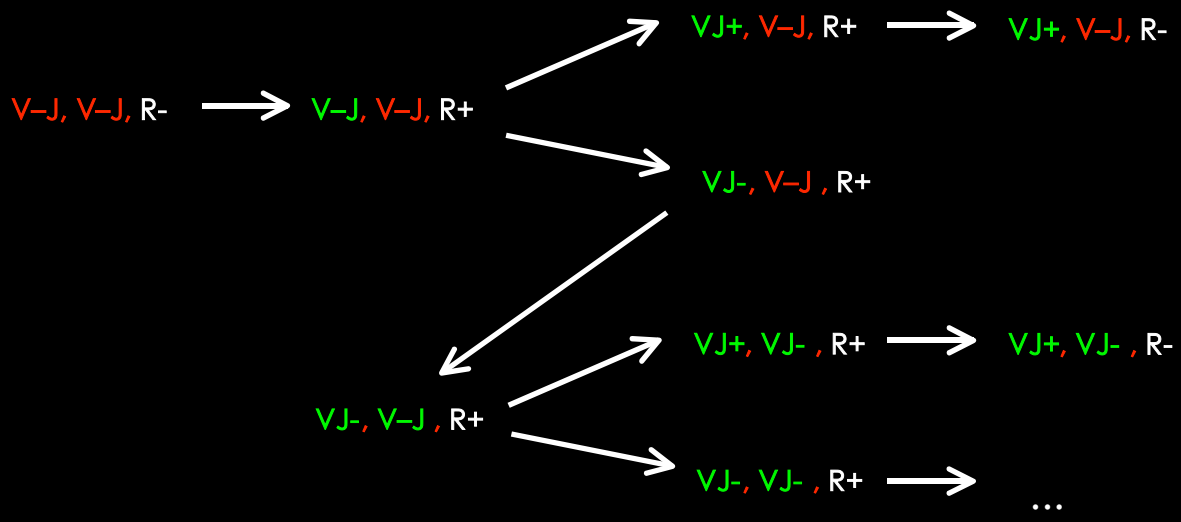


A toy VJ locus model



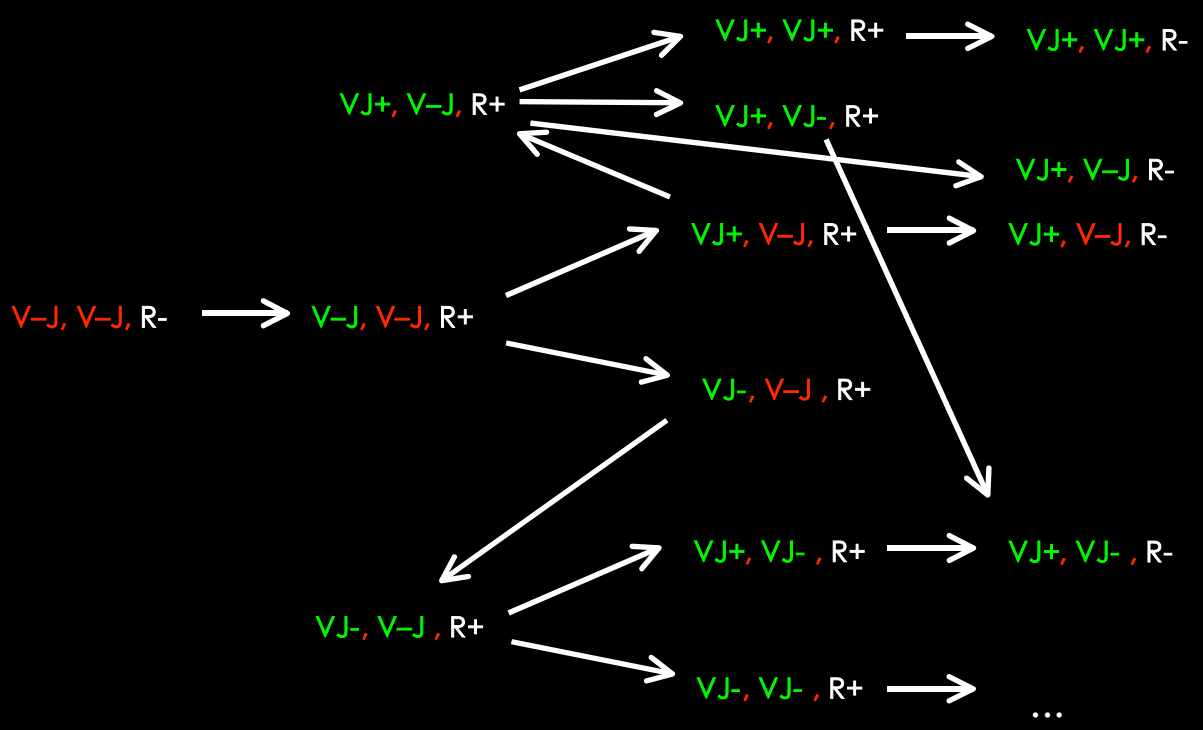
[Rajewsky]

A toy VJ locus model



[Rajewsky]

A toy VJ locus model



Boucontet et al. *J. Immunol.* (2005) **234**: 153
Sepúlveda et al. *J.Theor. Biol.* (2005) **174**: 3912

Continuous time Markov chain (CTMC)

$$\mathbf{S_t} = \mathbf{S_0}.Exp(\mathbf{Q}t)$$

$$\mathbf{Q} = \left\{q_{i,j}\right\}$$

0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	-d	0	0	0	0	0	0	0	0	0	0	0	0
0	2W	-2o-2W	0	0	2o	0	0	0	0	0	0	0	0
2c	0	0	-2c	0	0	0	0	0	0	0	0	0	0
0	2c	0	2d	-2c-2d-2r	0	0	0	0	2(1-f)r	0	0	0	2fr
0	0	2c	0	2W	-2c-2o-2r-2W	0	0	2o	0	2(1-f)r	0	0	0
0	0	0	2c	0	0	-2c	0	0	0	0	0	0	0
0	0	0	0	2c	0	d	-2c-d-2r	0	0	0	0	0	0
0	0	0	0	0	0	0	W	-2r-W	0	0	0	0	0
0	0	0	0	0	0	0	0	0	-2c-2d	0	2c	0	0
0	0	0	0	0	0	0	0	0	2W	-2c-2o-2W	0	2c	0
0	0	0	0	0	0	0	0	0	0	0	-2d	0	0
0	0	0	0	0	0	0	0	0	0	2o	2W	-4o-2W	0
0	0	0	0	0	0	0	0	0	0	0	0	0	-2d
0	0	0	0	0	0	0	0	0	0	0	0	0	2(w+W)
0	0	0	0	0	0	0	0	0	2c	0	0	0	0
0	0	0	0	0	0	0	0	0	0	2c	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	2c
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0

Boucontet et al. *J. Immunol.* (2005) **234**: 153
Sepúlveda et al. *J.Theor. Biol.* (2005) **174**: 3912

Modelling V(D)J recombination using CTMC

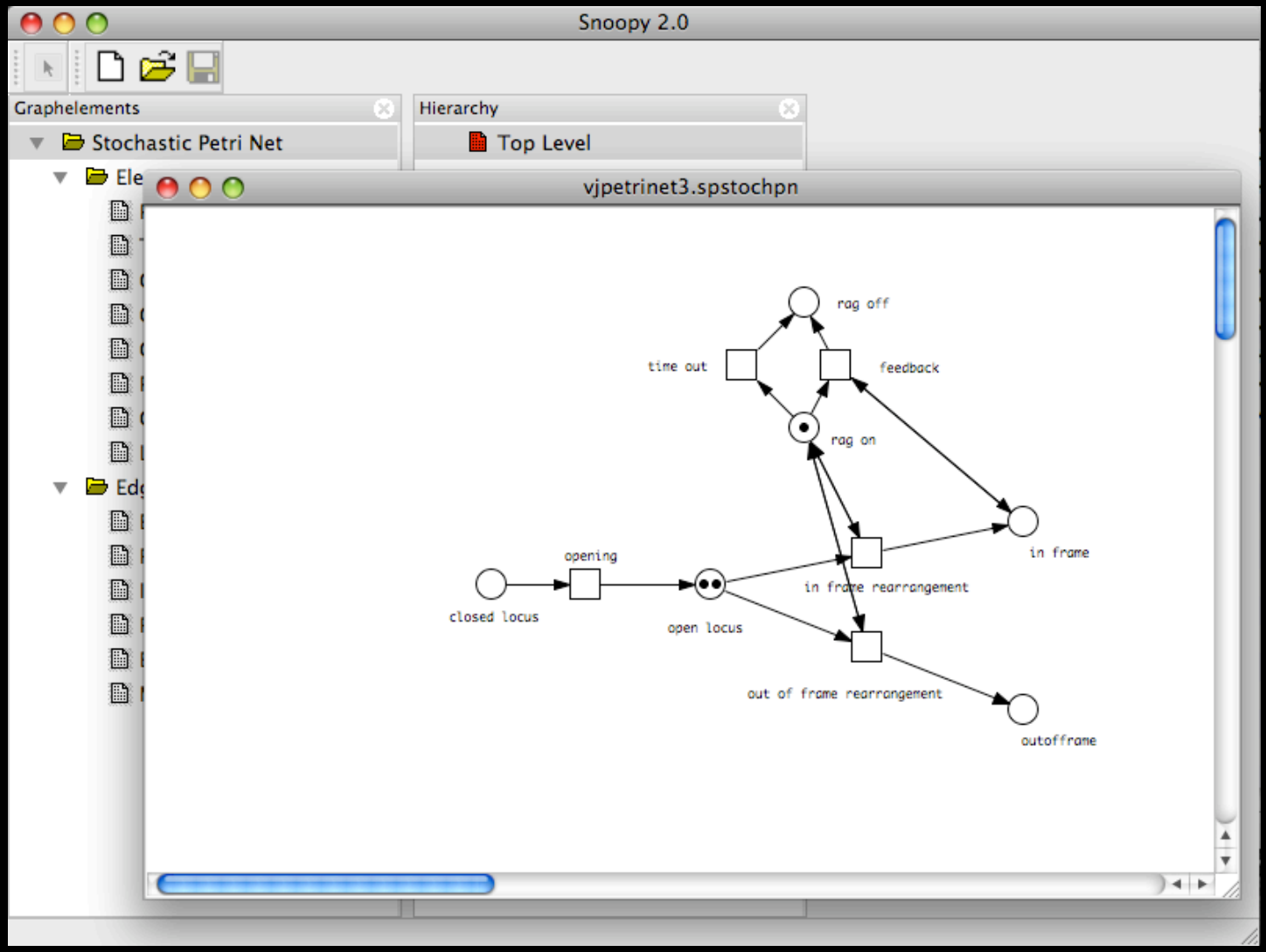
Theoretically sound but,

Hard to handle

Entering terms in large transition matrices is error prone

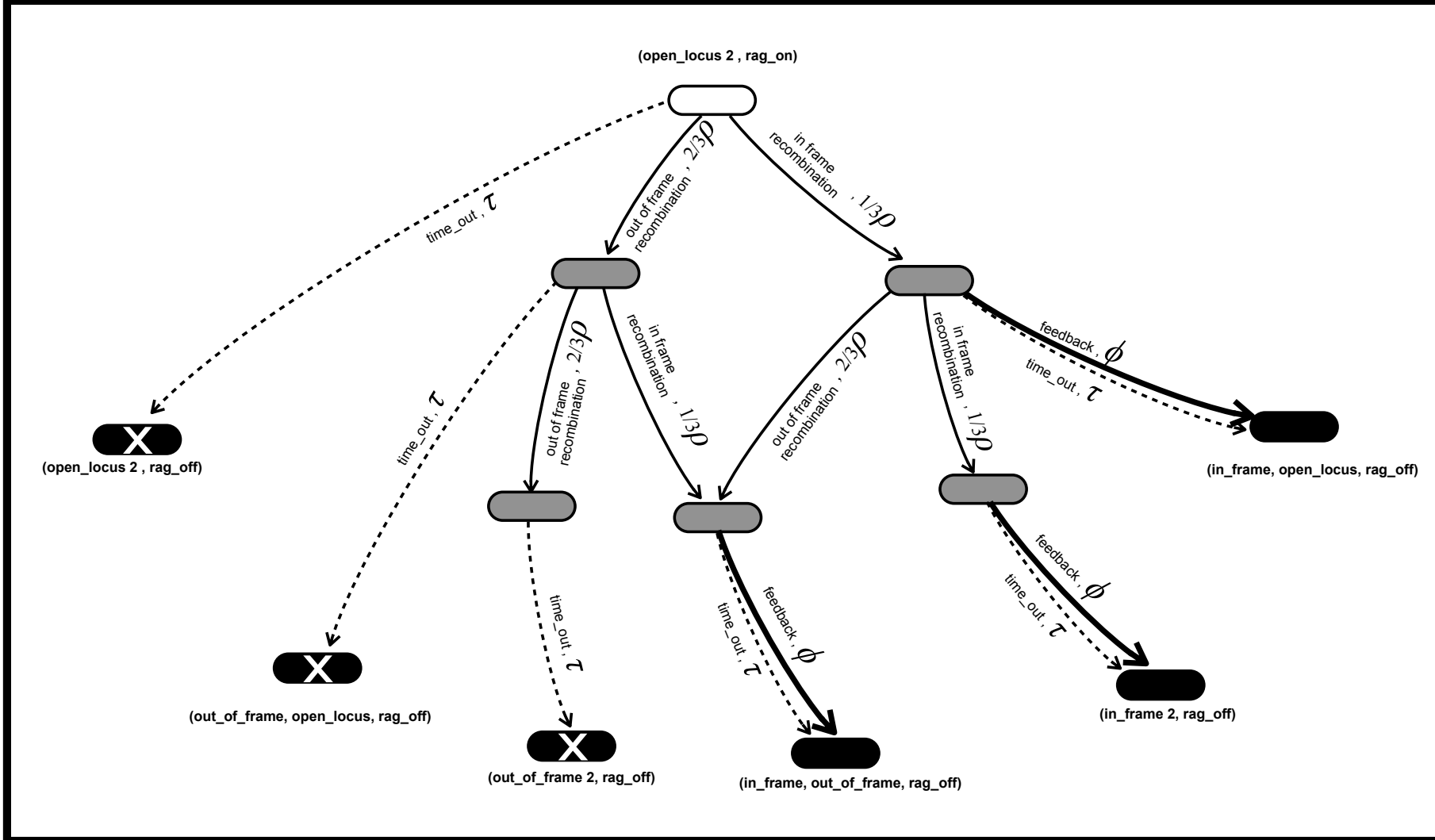
Model (re)design is painful

CTMC equivalent stochastic Petri net



Petri net editor and simulator

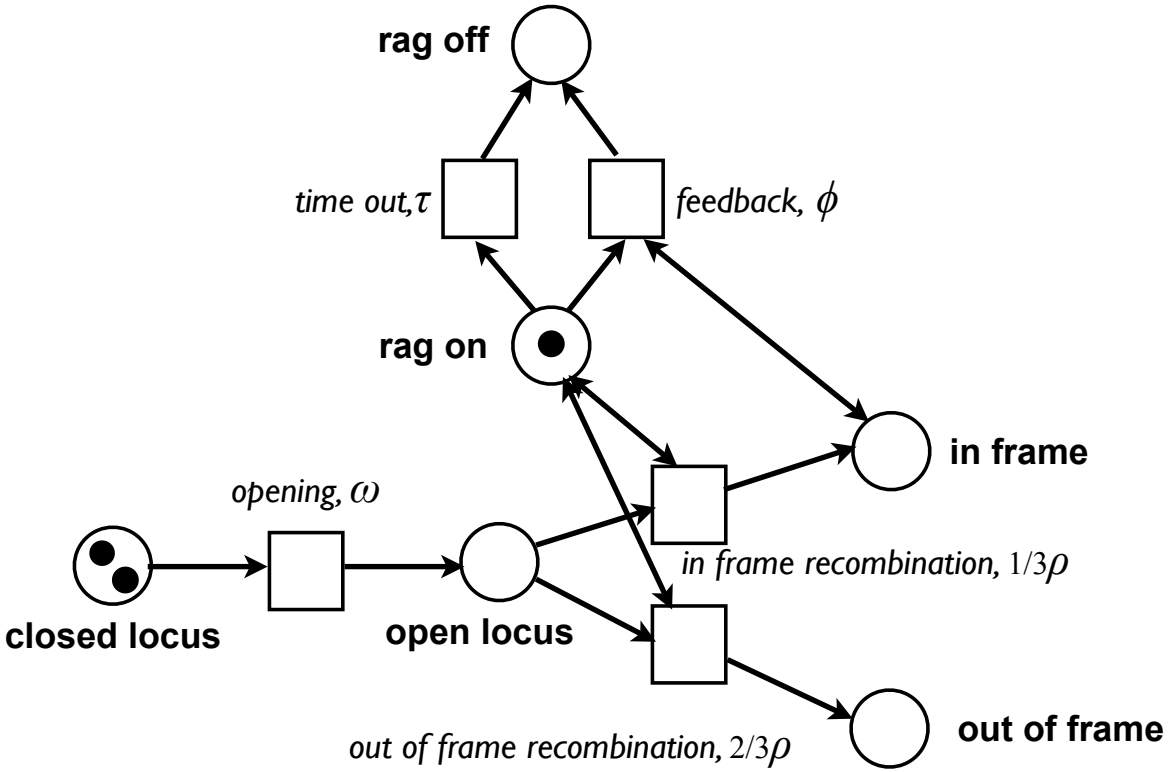
Snoopy 2.0: http://www-dssz.informatik.tu-cottbus.de/software/snoopy.html



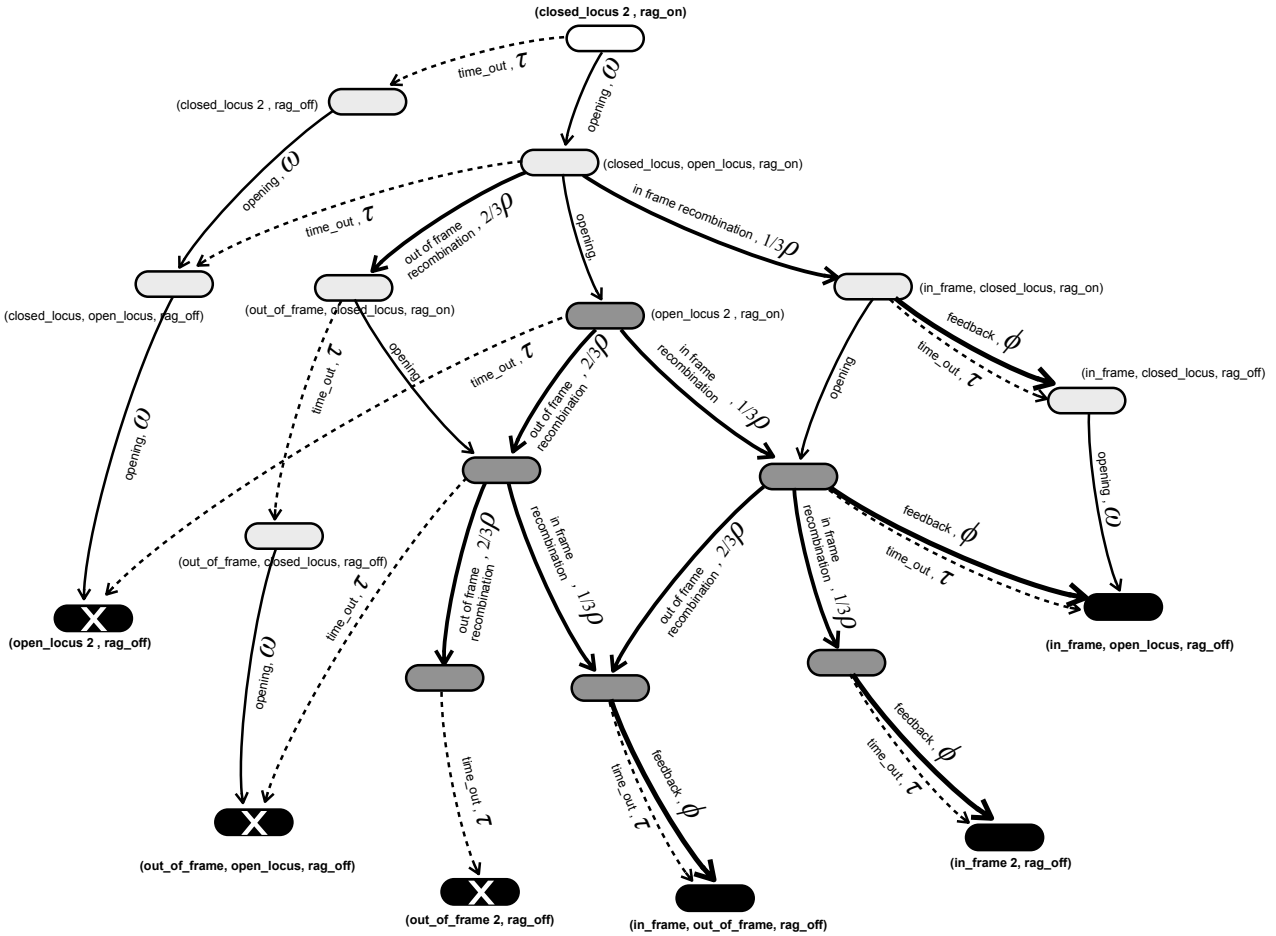
Petri net analyser

Charlie: http://www-dssz.informatik.tu-cottbus.de/software/charlie.html

Asynchronous allele accessiblity with feedback



A toy VJ locus model



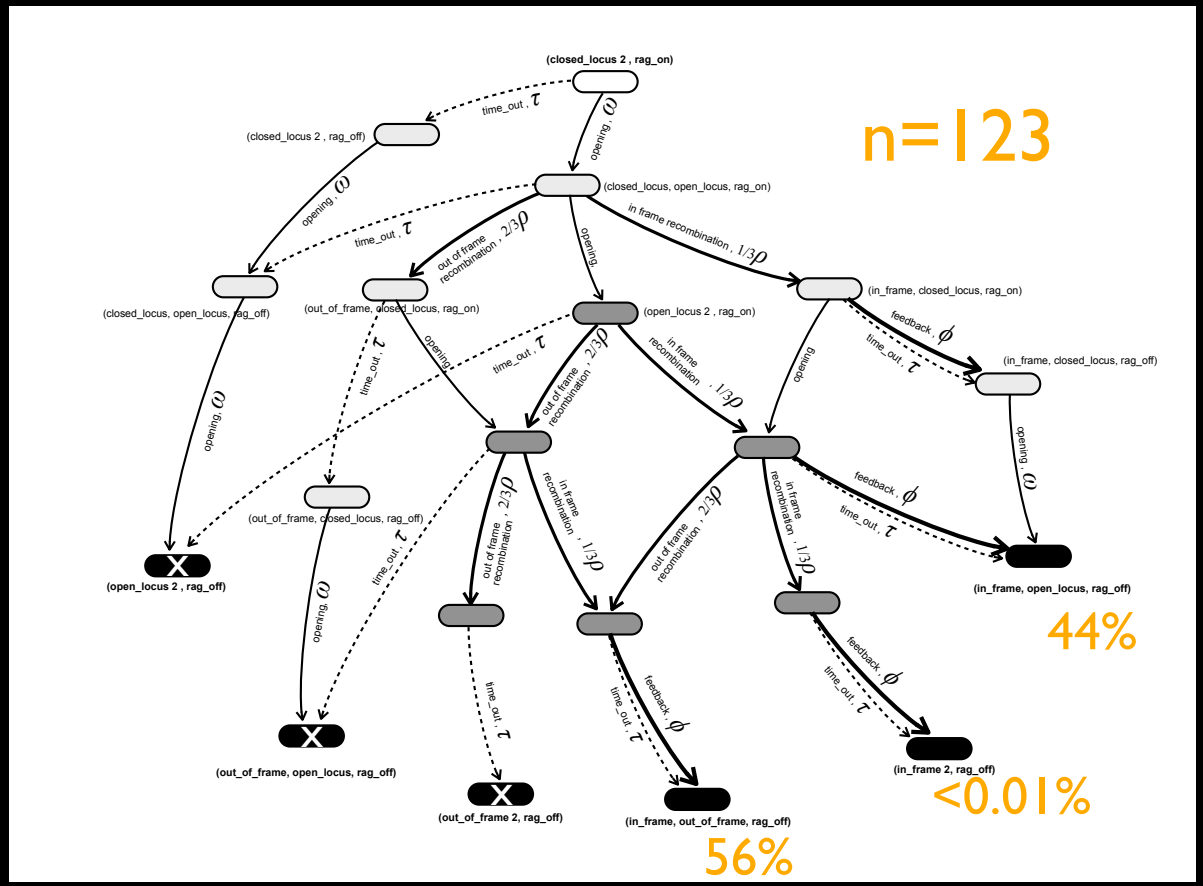
Reachability is excellent,

but ...

How can we estimate the parameters that explain the experimentally observed output of the V(D)J reaction ?

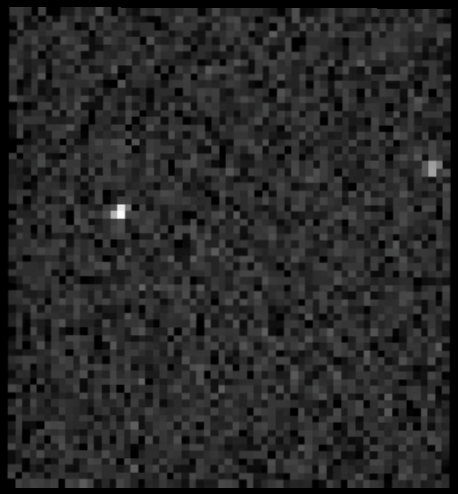
How can we estimate the parameters that explain the experimentally observed output of the V(D)J reaction ?

Locus configuration in γδ thymocytes

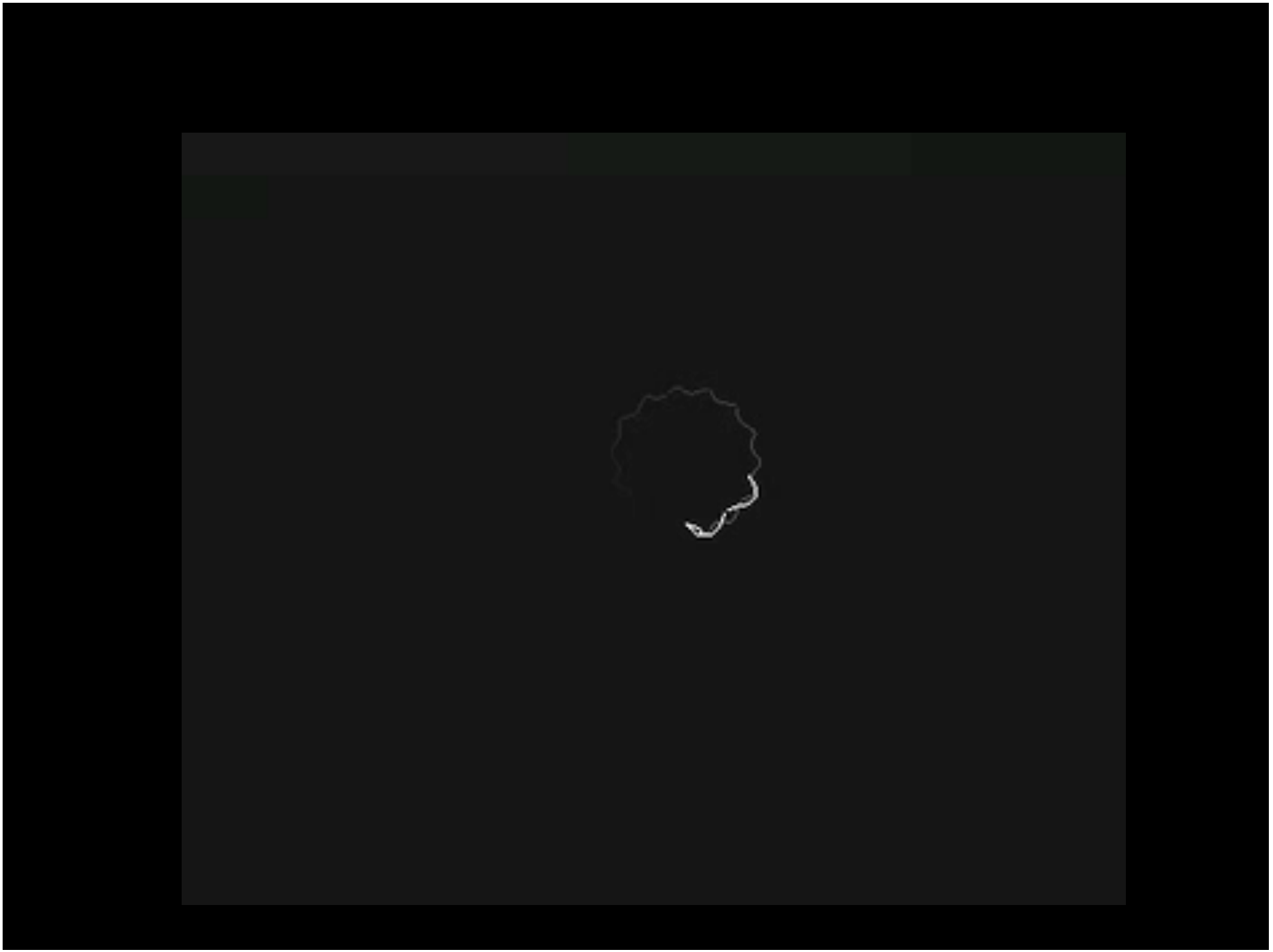


How likely are these experimental values given the model ?

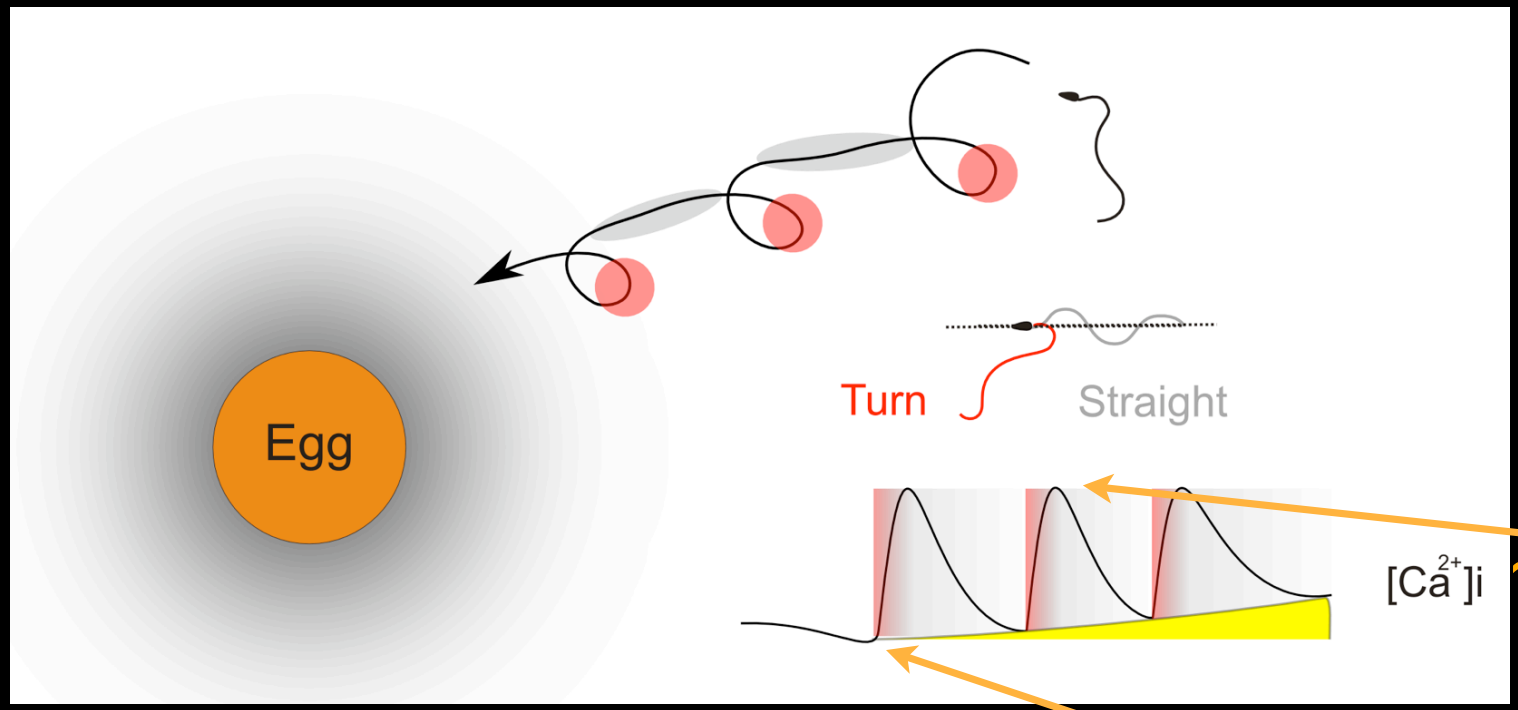
Parameter estimation based on data is not available (or is not straightforward) in none of the Petri net tools I tried



Ion channel dynamics

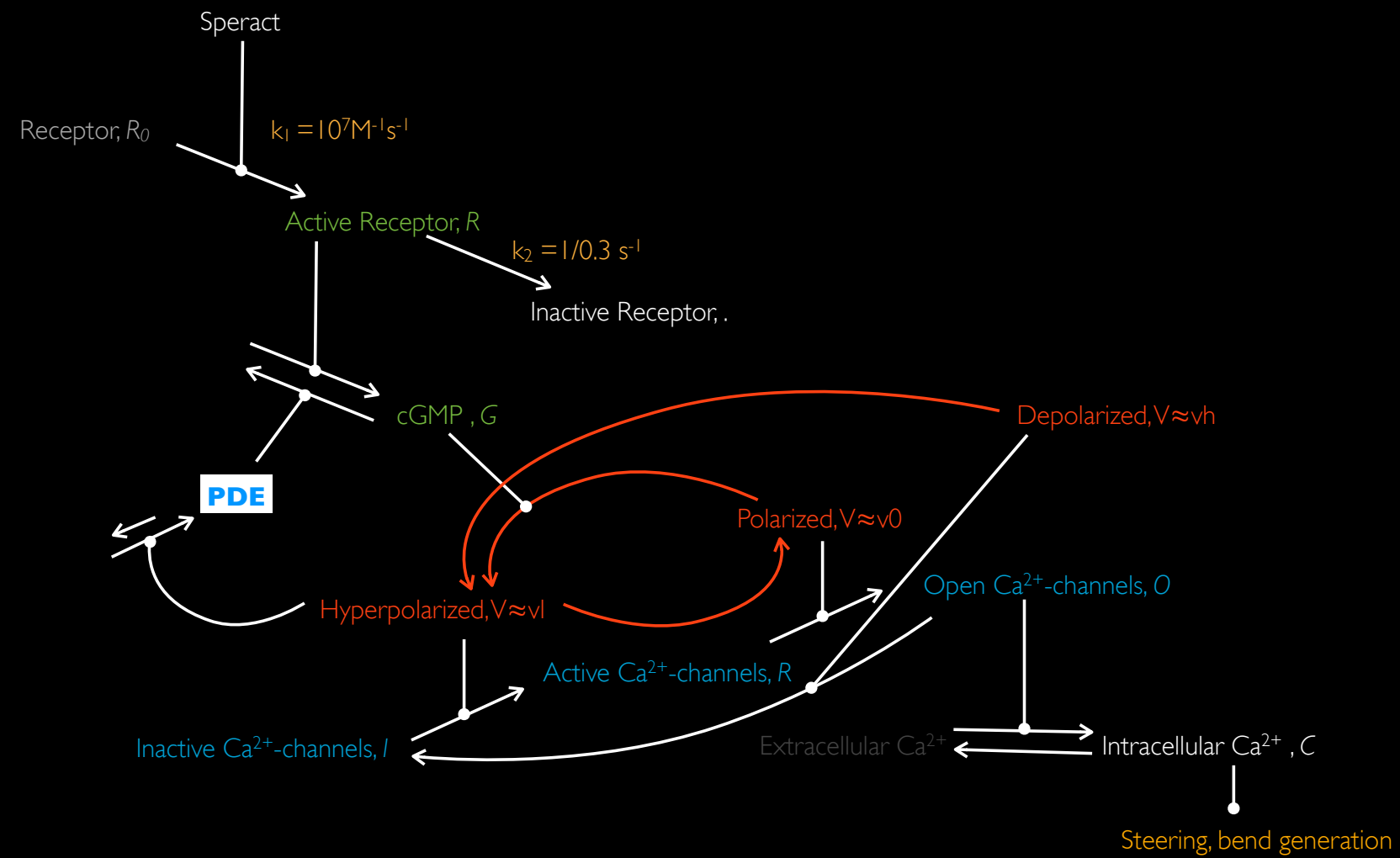


Ion (Ca^{2+}) channel dynamics controls sperm chemotaxis

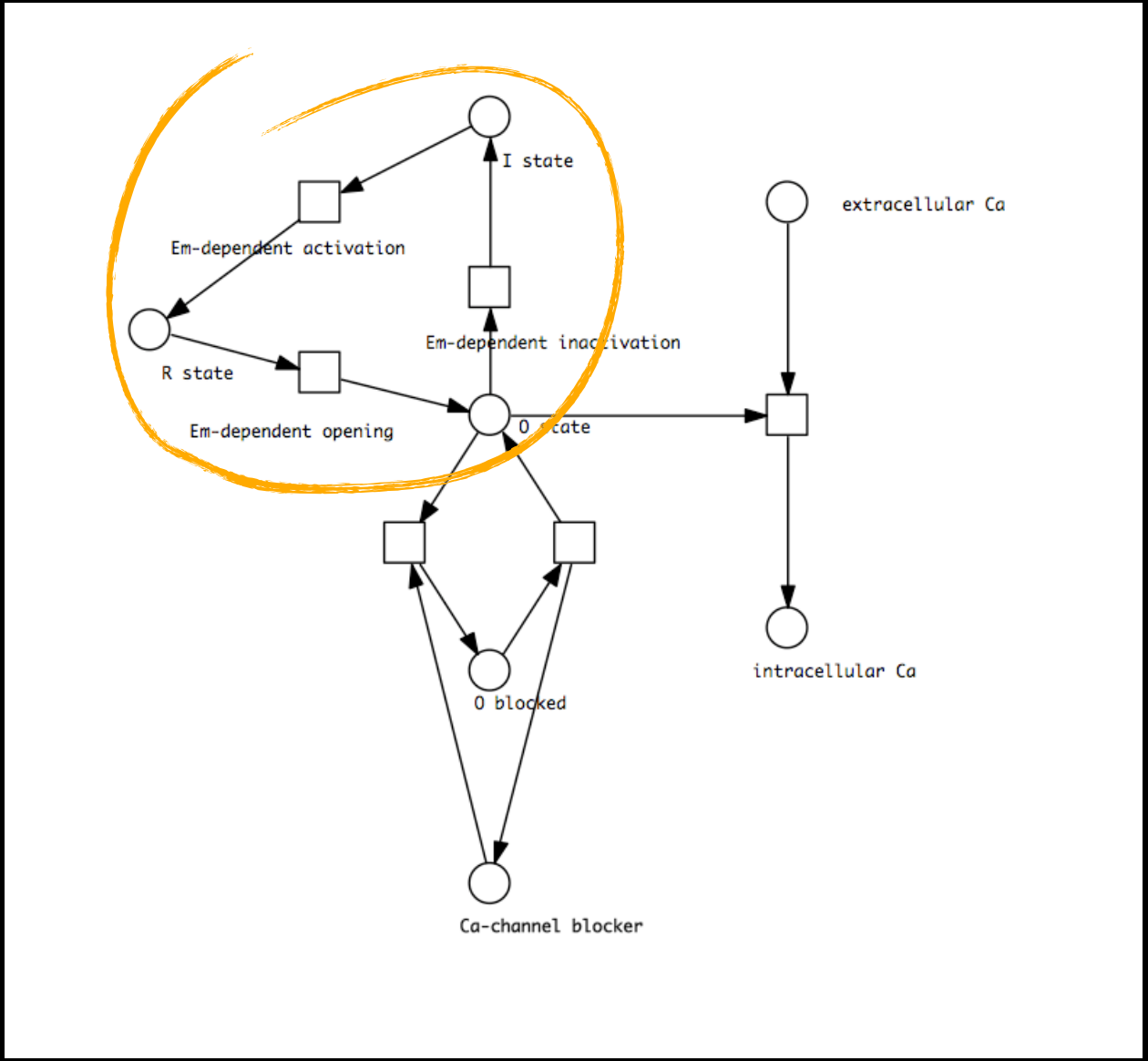


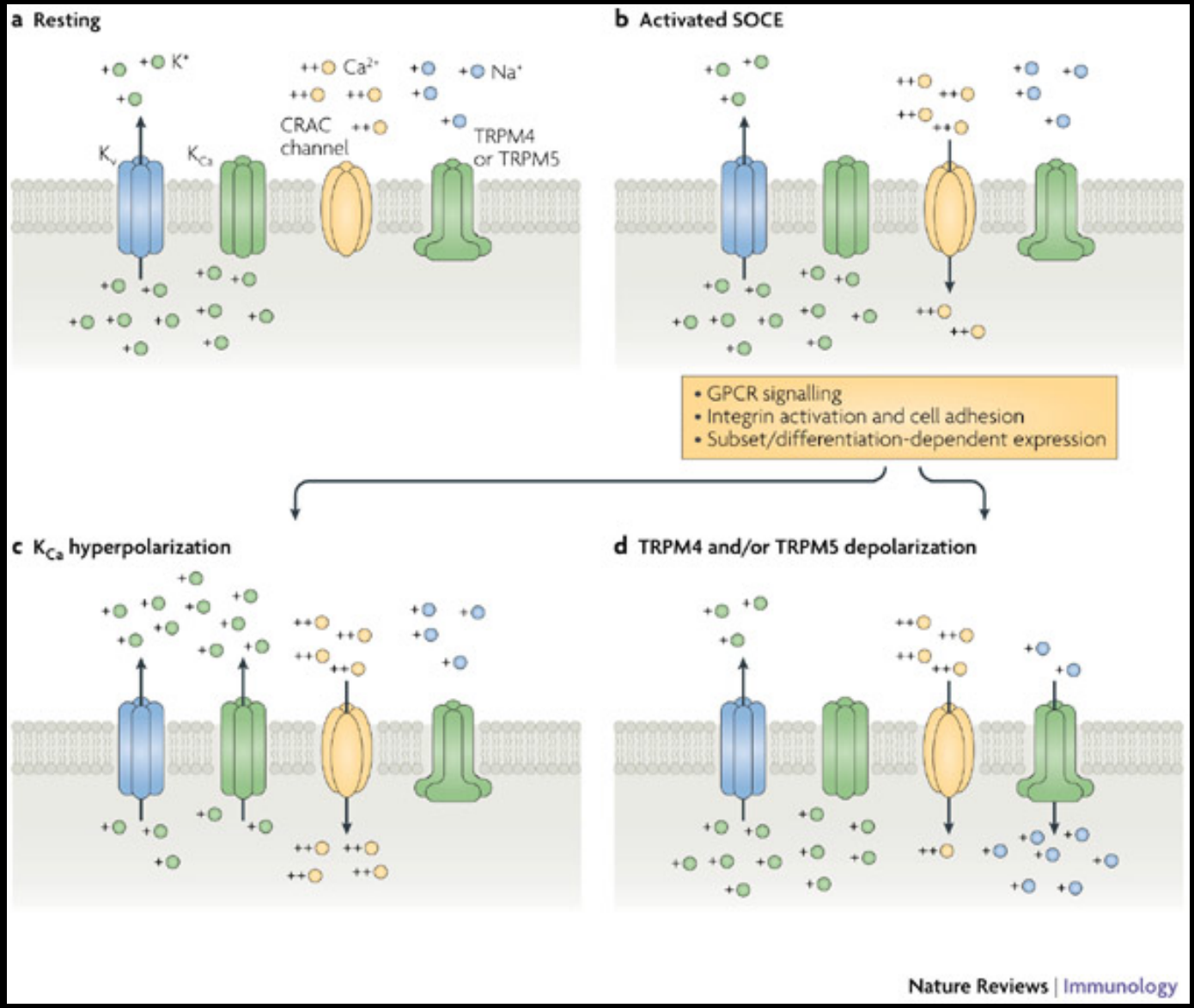
Guerrero et al. *Biochem. Soc.Trans.* (2010) **in press**

Ion (Ca^{2+}) channel dynamics controls sperm chemotaxis



SPN representation of ion (Ca^{2+}) channel dynamics



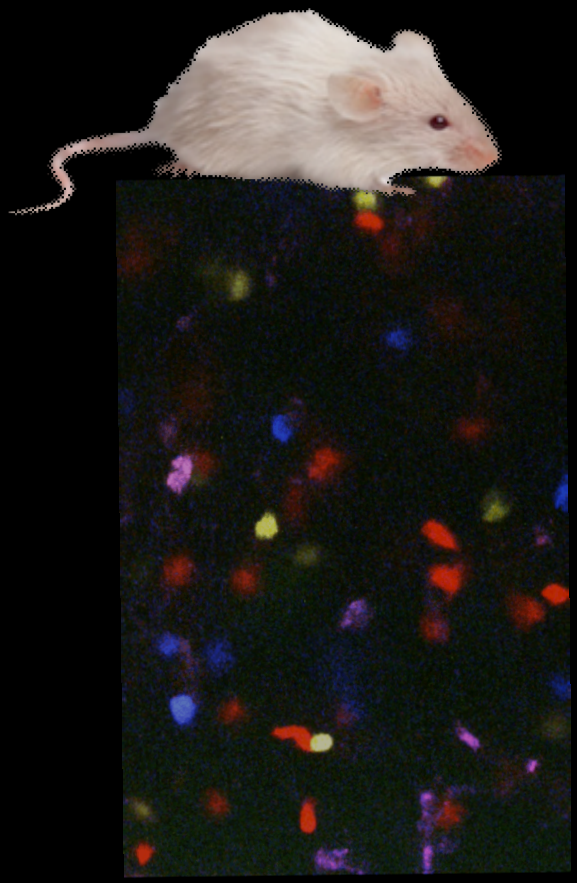

a Resting
K+
Ca2+
Na+
CRAC channel
TRPM4 or TRPM5
Kv
KCa
b Activated SOCE
• GPCR signalling
• Integrin activation and cell adhesion
• Subset/differentiation-dependent expression
c KCa hyperpolarization
d TRPM4 and/or TRPM5 depolarization
Nature Reviews | Immunology

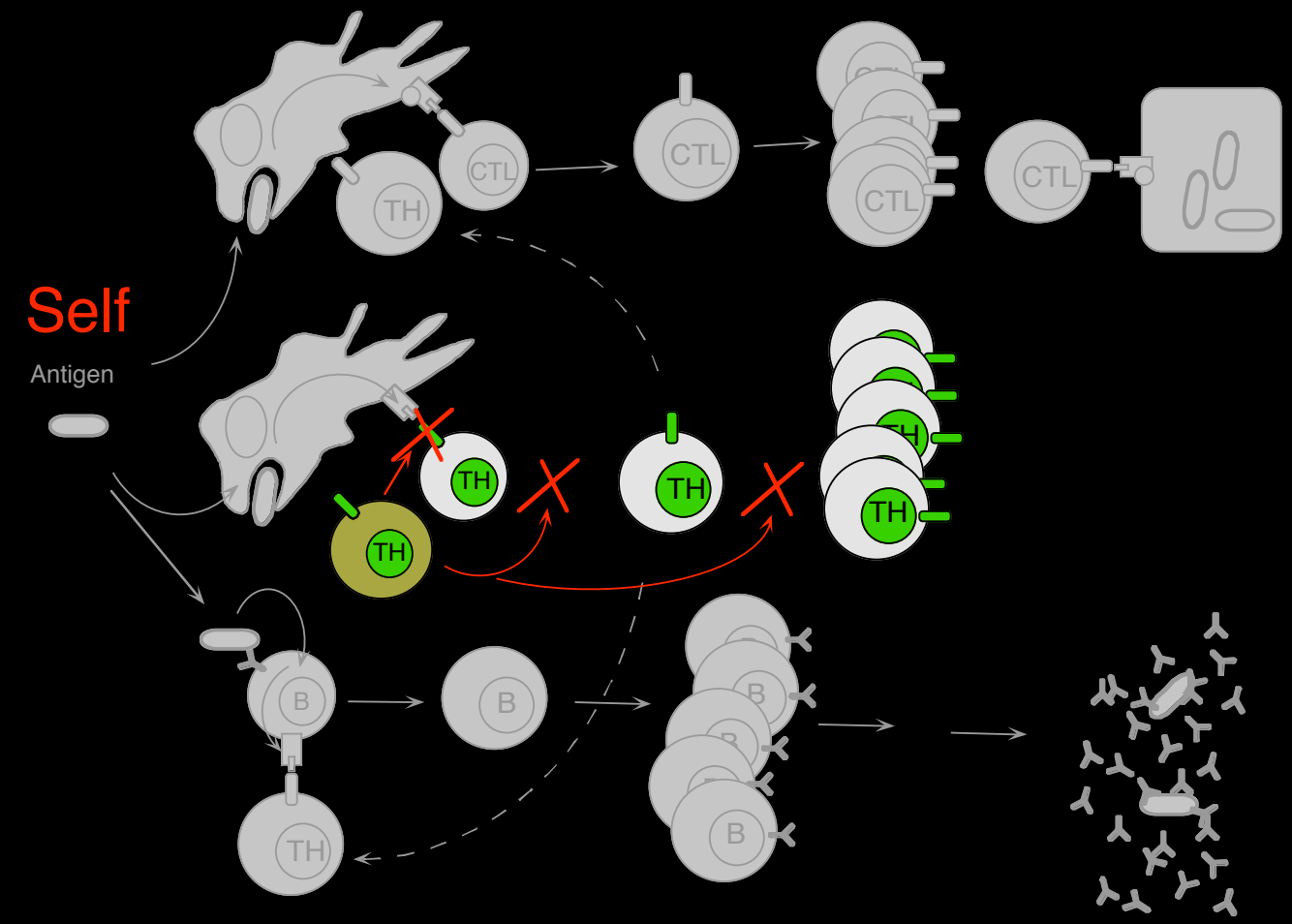
How can one estimate the model parameters based on experimental data ?

How can *Em* be represented in a SPN framework ?

One would like to avoid representing all the ions...

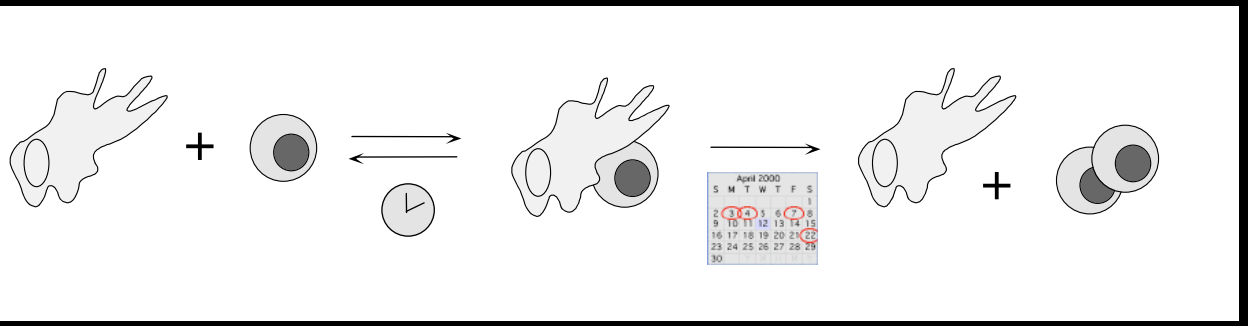
Modelling T-cell interactions and dynamics involved in autoimmunity

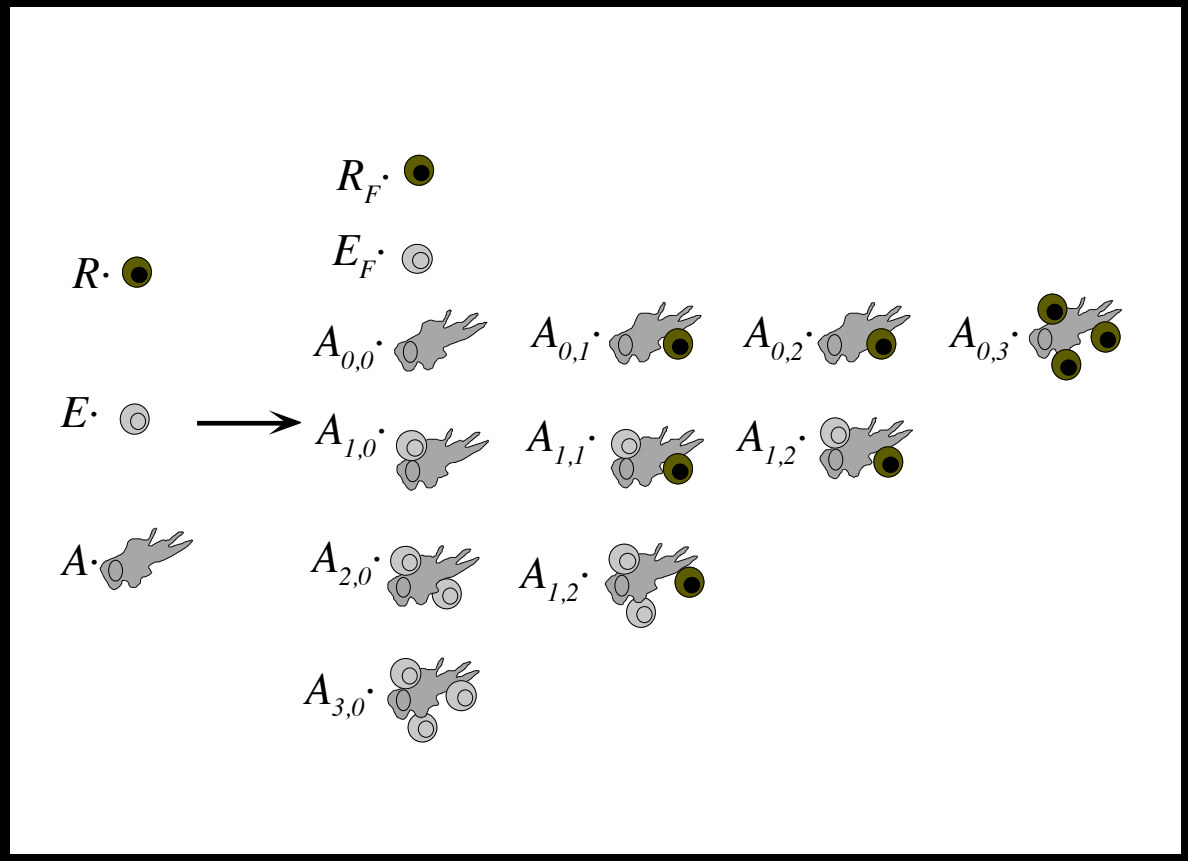




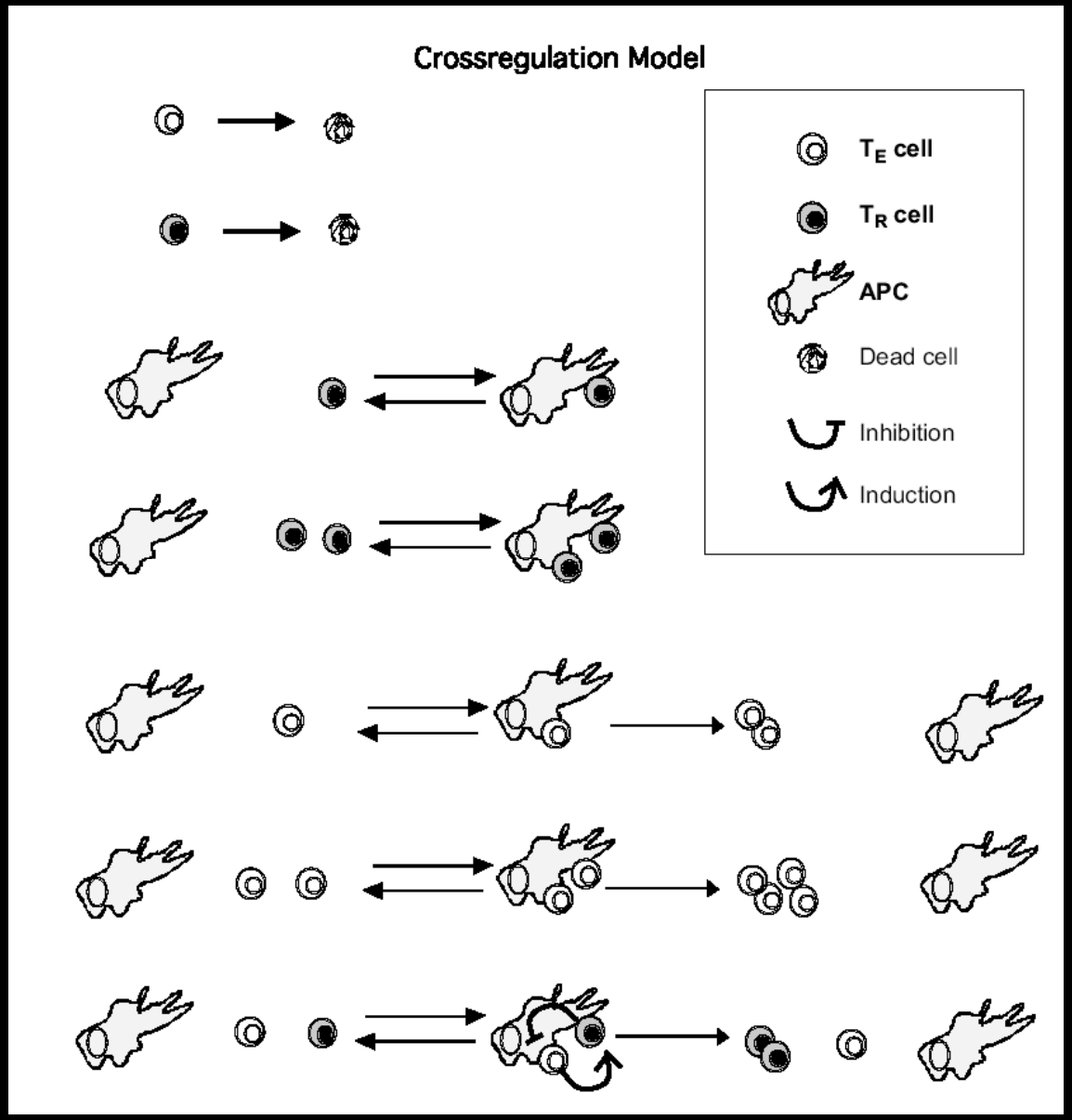
Sakaguchi et al. *Annu. Rev. Immunol.* (2004) 22: 531

Carneiro et al. *Immunol. Reviews* (2007) **216**: 48





Leon et al. *J. Theor. Biol.* (2000) **207**: 231



Carneiro et al. *Immunol. Reviews* (2007) **216**: 48

The crossregulation model was formulated in terms of ordinary differential equations

$$\frac{dE}{dt} = p_E \cdot E_A - d_E \cdot E$$

$$\frac{dR}{dt} = p_R \cdot R_A - d_R \cdot R$$

$$C = \frac{1 + K(A+T) - \sqrt{(1+K(A+T))^2 - 4ATK^2}}{2K}$$

$$E_C = \frac{E}{T}C \quad , \quad R_C = \frac{R}{T}C$$

$$\varepsilon = \frac{E_C}{A} \quad , \quad \rho = \frac{R_C}{A}$$

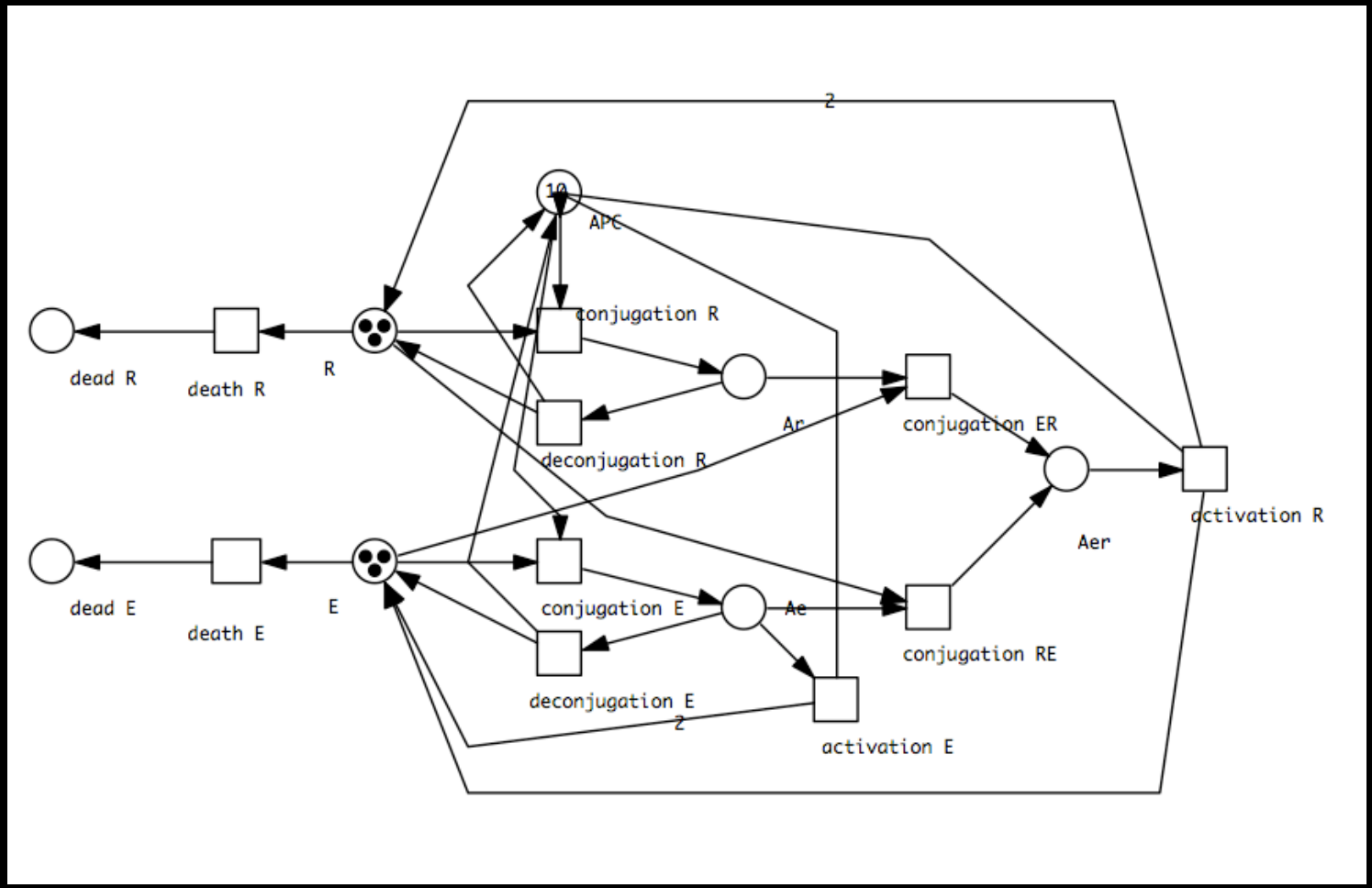
$$E_A = E_C\left(1 - \frac{2\rho}{2-\varepsilon}\right)$$

$$R_A = R_C\left(\frac{2\varepsilon}{2-\rho}\right)$$

Carneiro et al. *Immunol. Reviews* (2007) **216**: 48

How much would stochasticity and discreteness affect the results ?

The crossregulation model formulated as a SPN

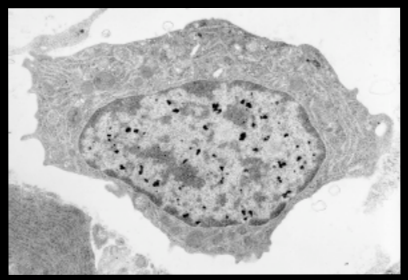


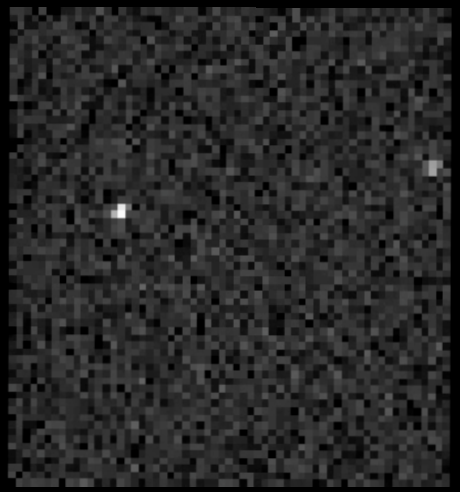
SPN representation for two sites per APC is cumbersome !

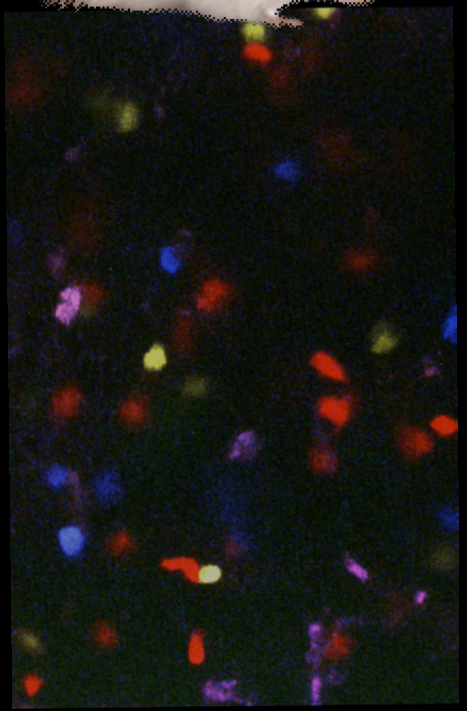
The crossregulation model formulated as a SPN

How to study the dependence on number of sites
without redrawing the structure ?

Why aren't Petri nets widely used in biological research ?







Difficulties in adopting SPN framework

A personal experience

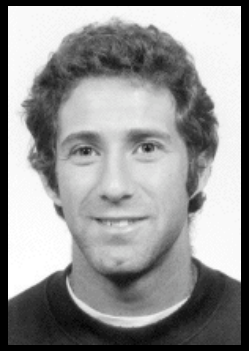
V(D)J recombination ~ how to estimate parameters ?

Ion channel dynamics ~ how to represent Em ?

T-cell population dynamics ~ SPN is too complex !

Acknowledgements

Adan Guerrero
Alberto Darszon
Chris Hood
Takuya Nishigaki
(IBT/UNAM, Cuernavaca,Mex)



Nuno Sepúlveda

Kalet Leon

Pablo Pereira, Laurent Boucontet
Pasteur Institute

Lisa Bergman, Jocelyne Demengeot
(IGC,Portugal)

Email: jcarneir@igc.gulbenkian.pt
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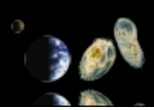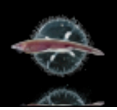
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