GenPCCA: Markov State Models for Non-Equilibrium Steady States

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joint work with: S. Röblitz, C. Schütte, L. Reinmiedl, RG A. Gleixner, N. Djurdjevac-Conrad stochastic process -> finite Markov chain with transition matrix P

1) Cyclic behaviour in molecular processes

2) Robust Perron Cluster Analysis (PCCA+)

3) From Eigendecompositions to Schur Decompositions

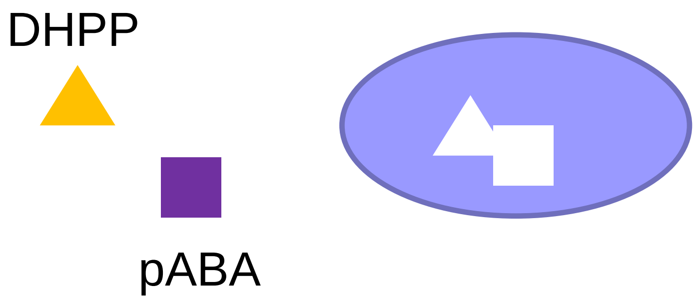
4) Generalized PCCA for Dominant Cycles
(function-based clustering)

5) Example

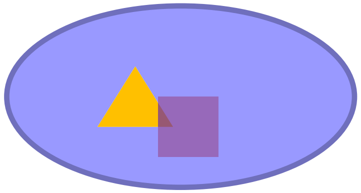
optimizing dihydropterat-synthetase

Durmaz, 2016

dihydropterat-synthetase
(catalytic reaction)

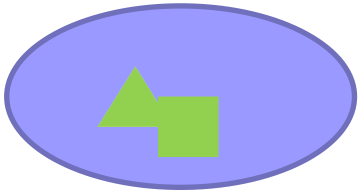


dihydropterat-synthetase
(catalytic reaction)



complex

dihydropterat-synthetase
(catalytic reaction)



complex

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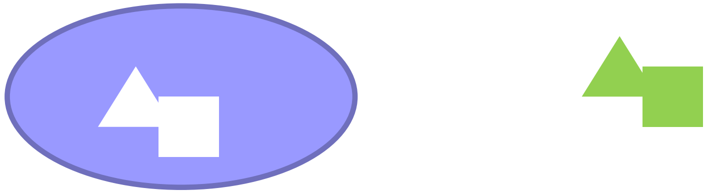
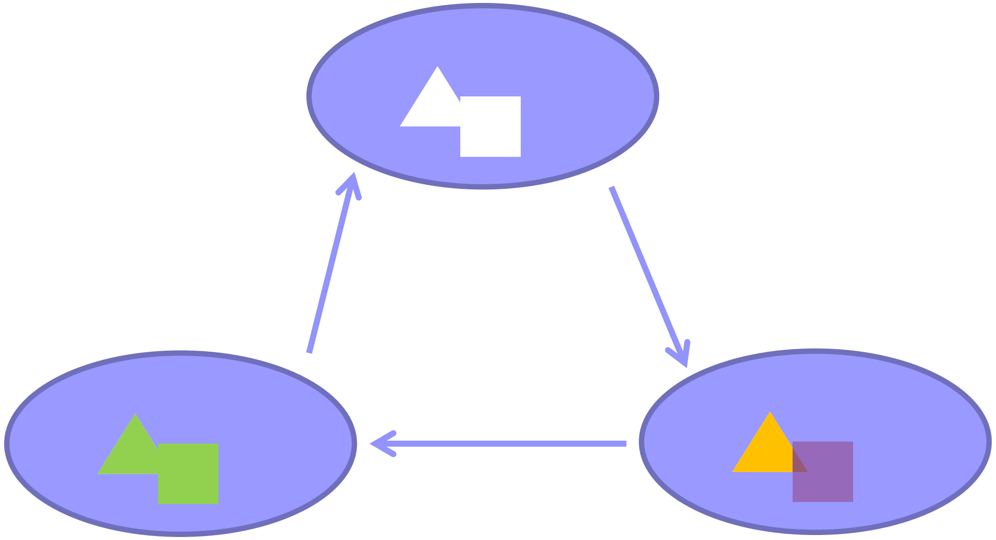
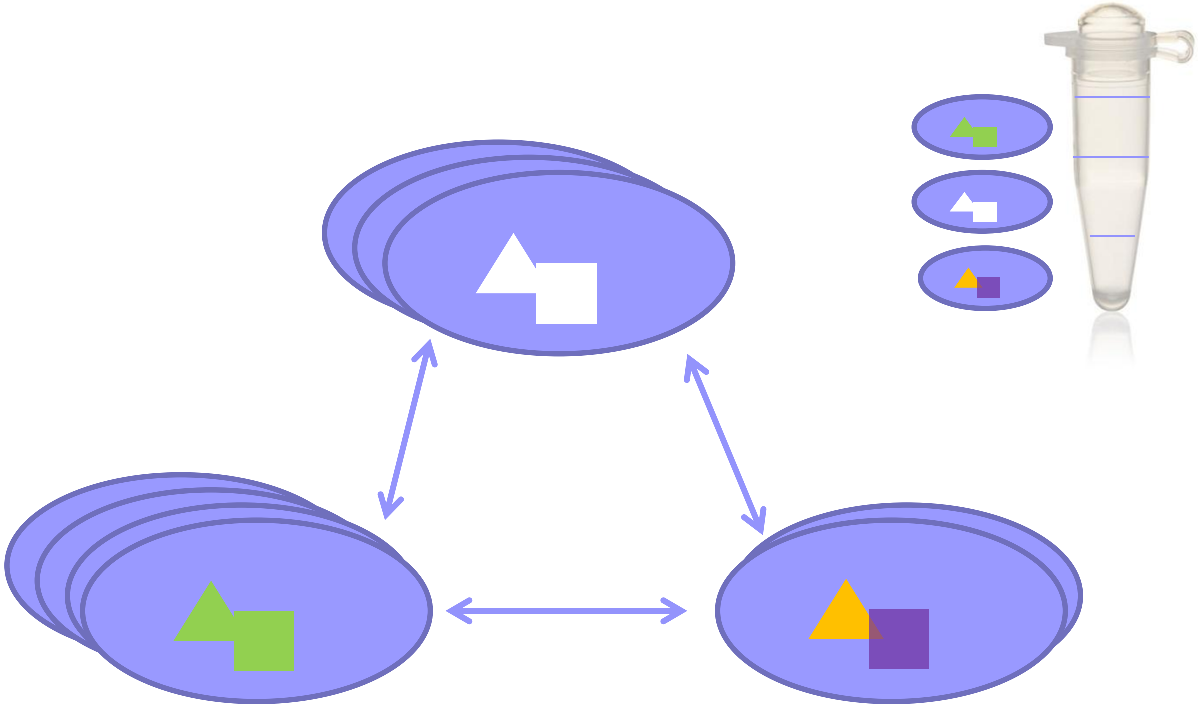


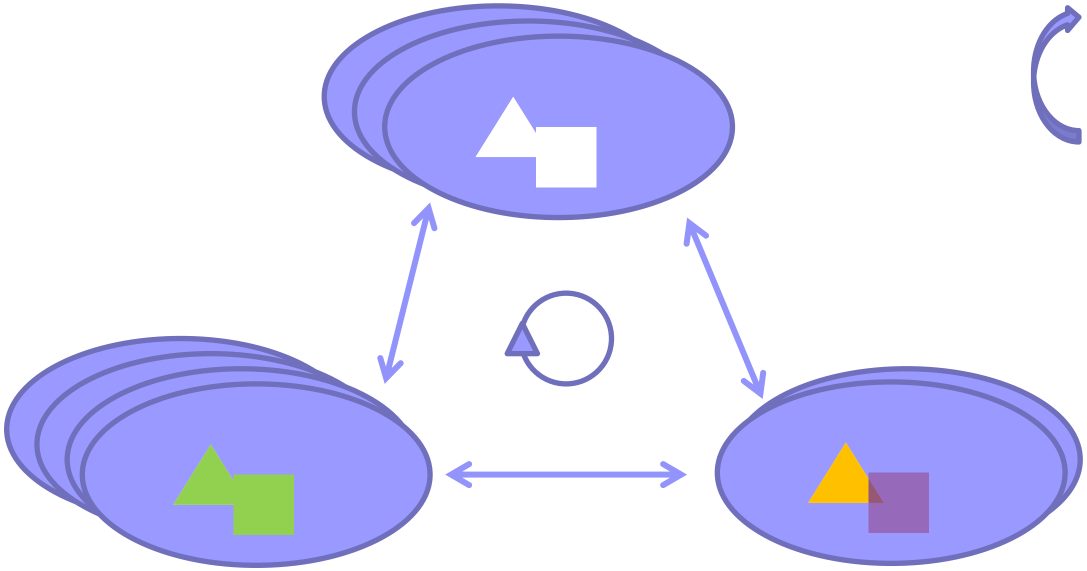
product
(-> acid folique)

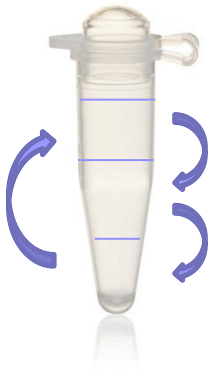


catalytic cycle

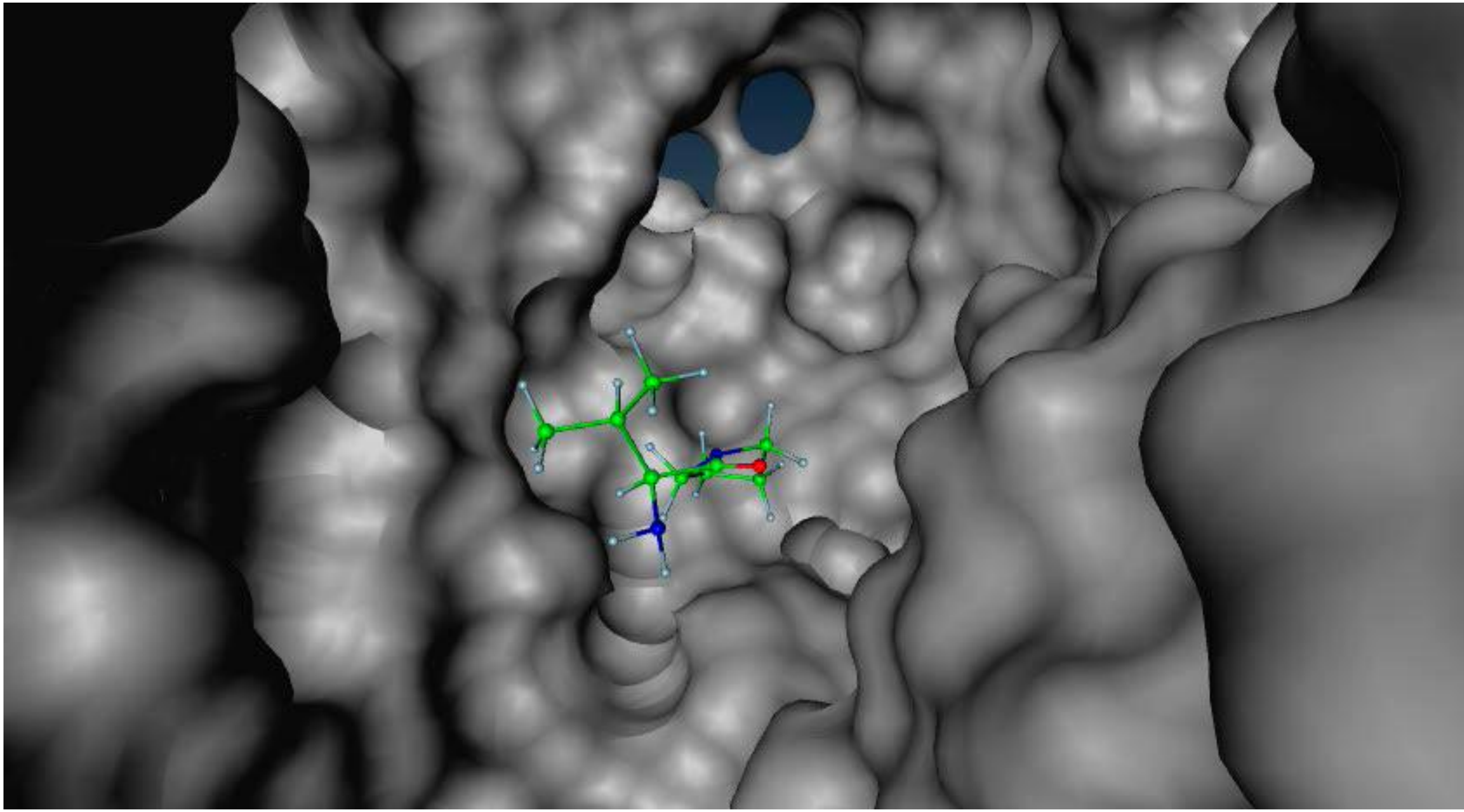


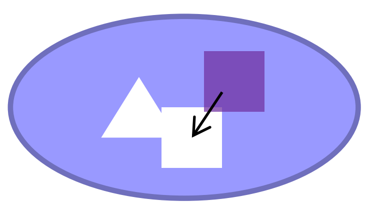
stationary distribution





NESS
(non-equilibrium steady state)





detailed molecular description
of the system (transitions P)

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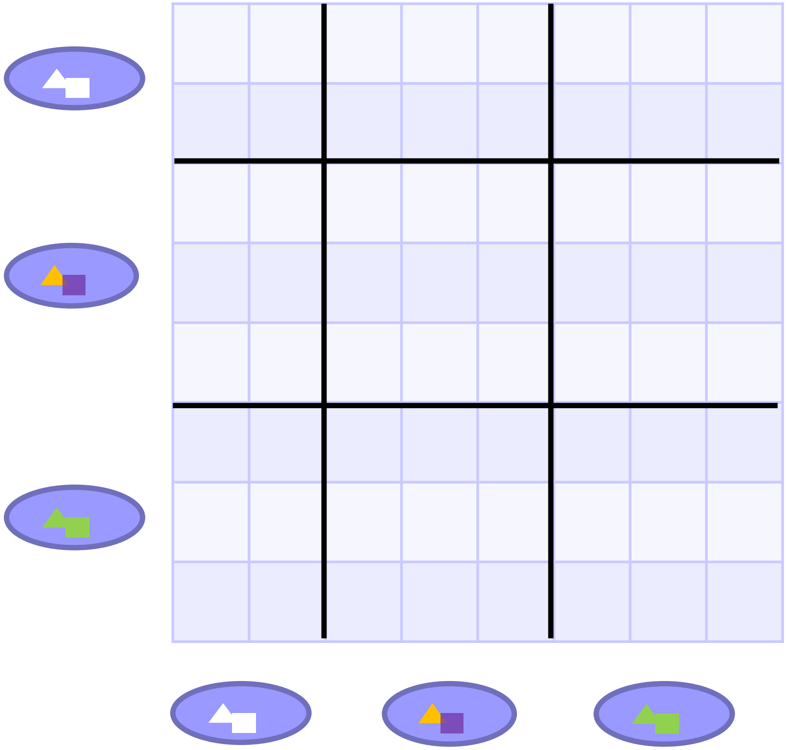
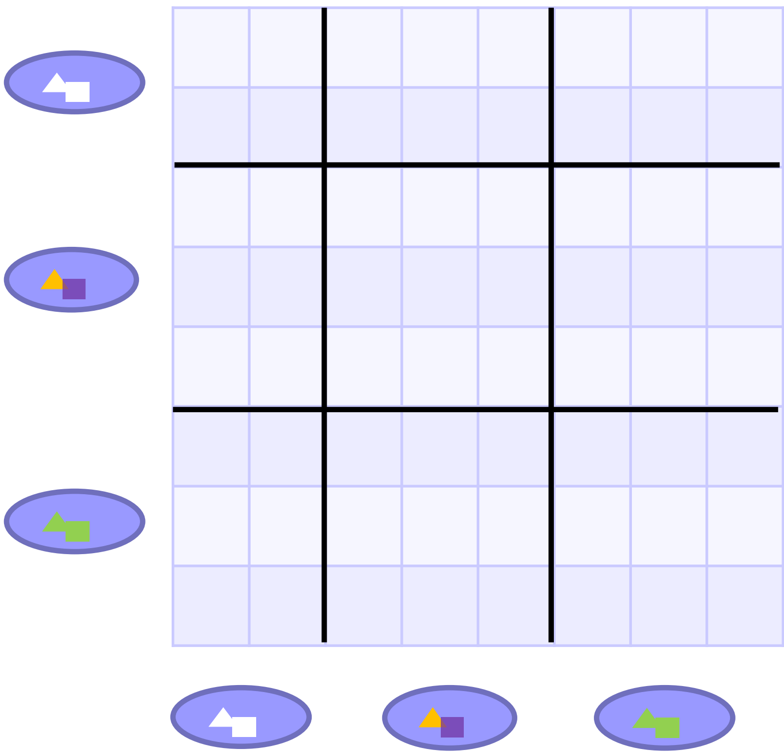


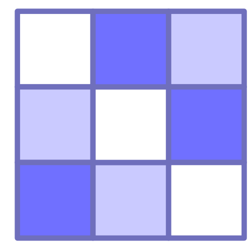
clustering

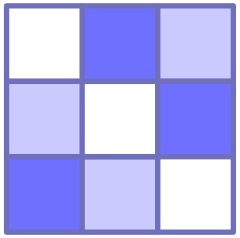
detailed molecular description
of the system (transitions P)



clustering/
projection

efficiency of
catalytic cylce





efficiency = non-reversibility of P_C

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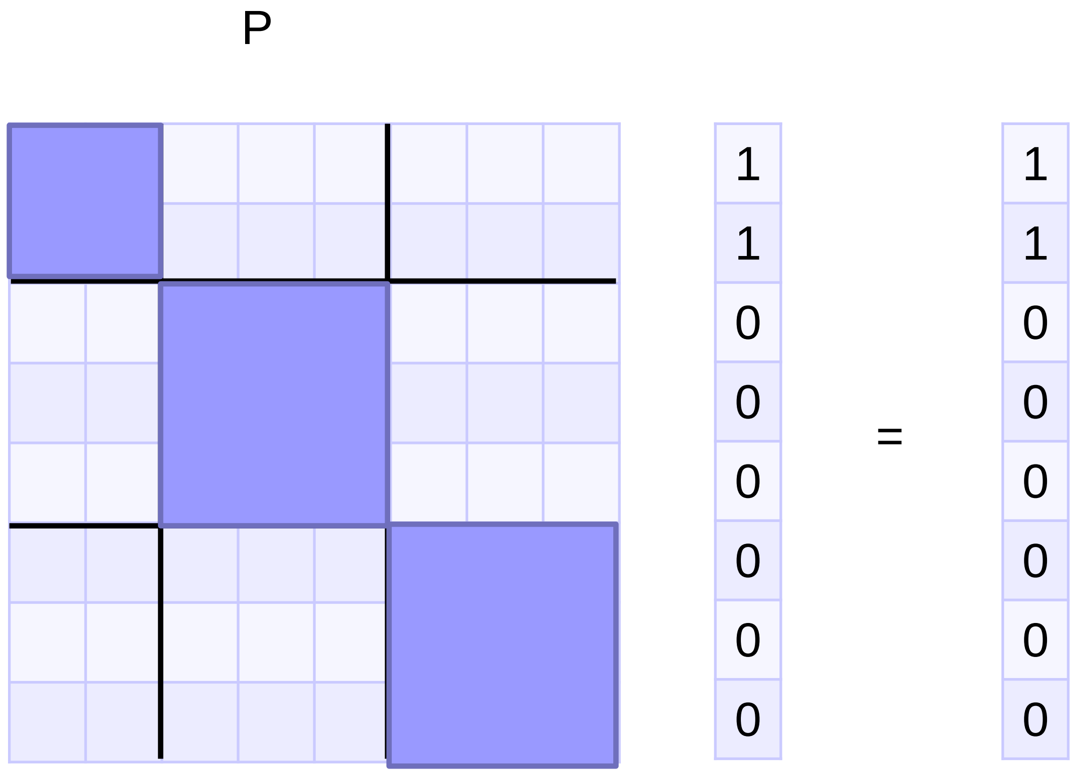
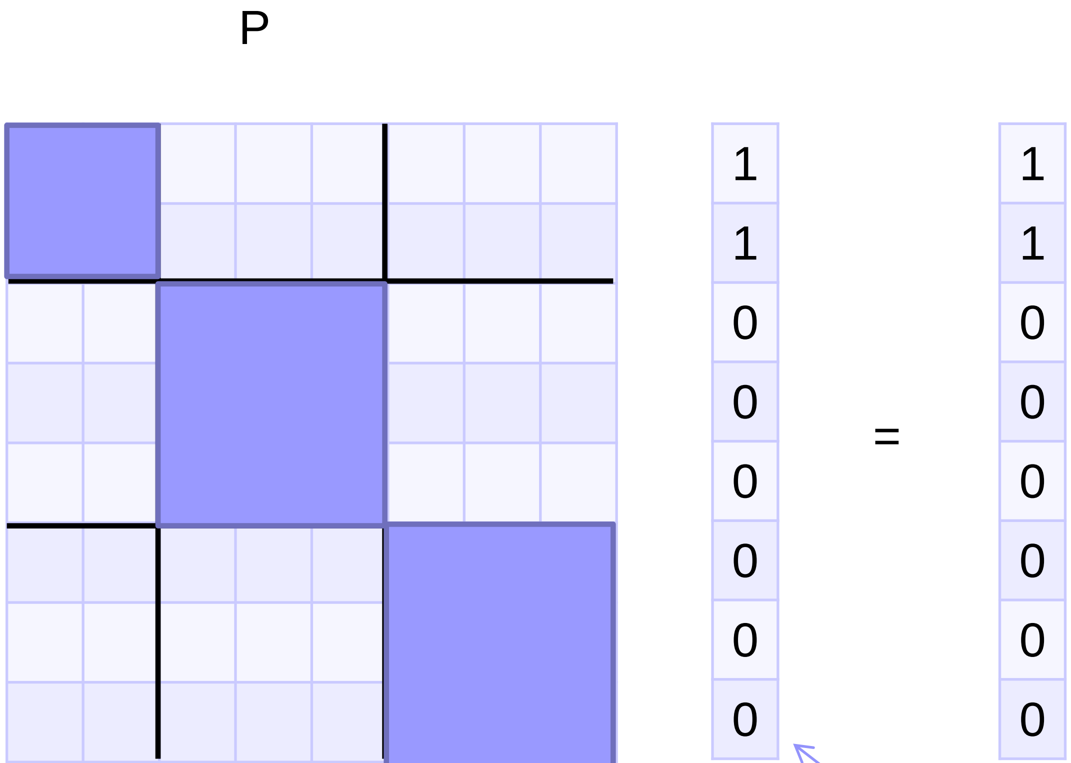
5) Example

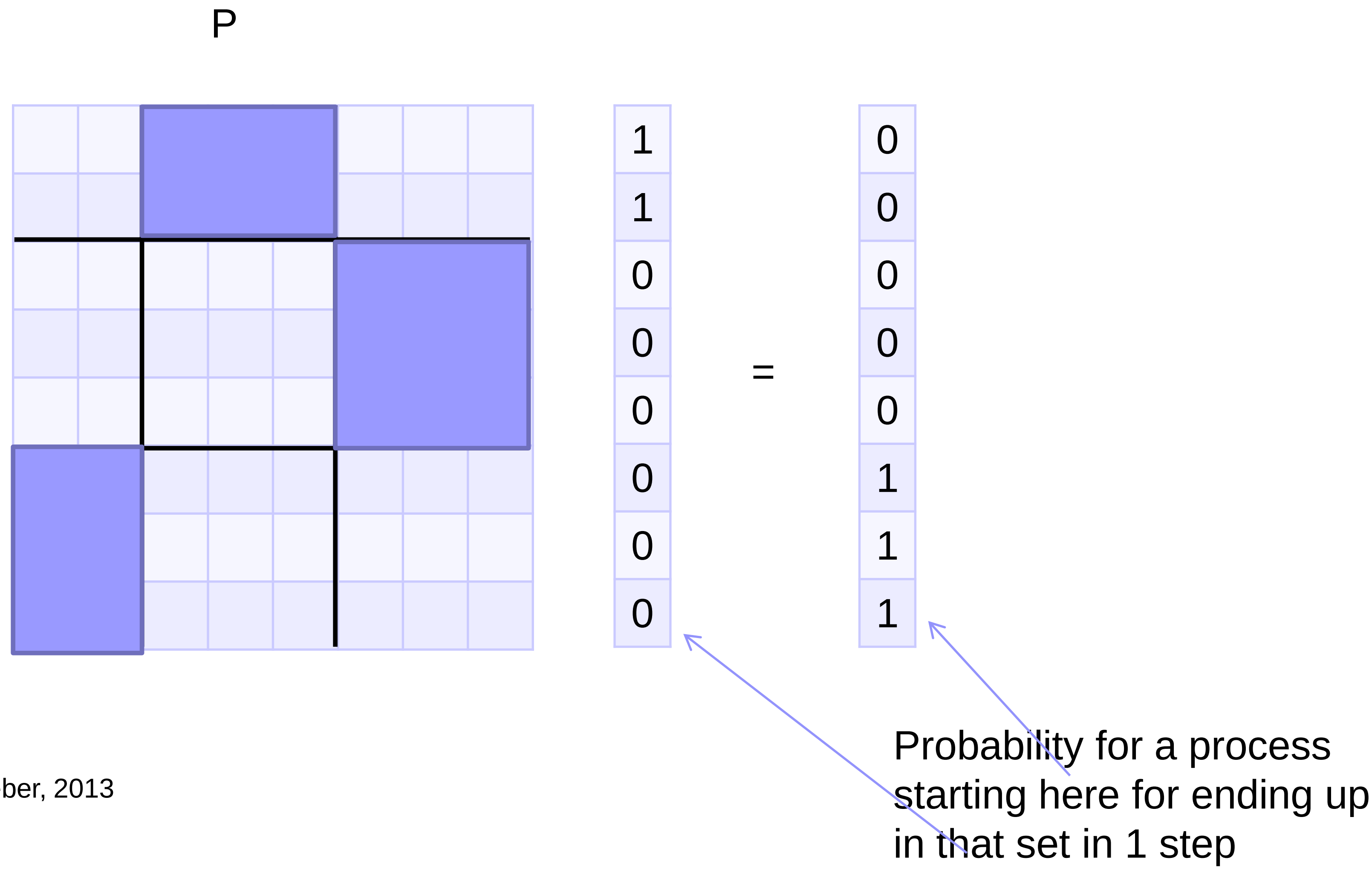


Weber, Galliat, 2002
Deuflhard, Weber, 2005
Weber, 2006
Röblitz, Weber, 2013

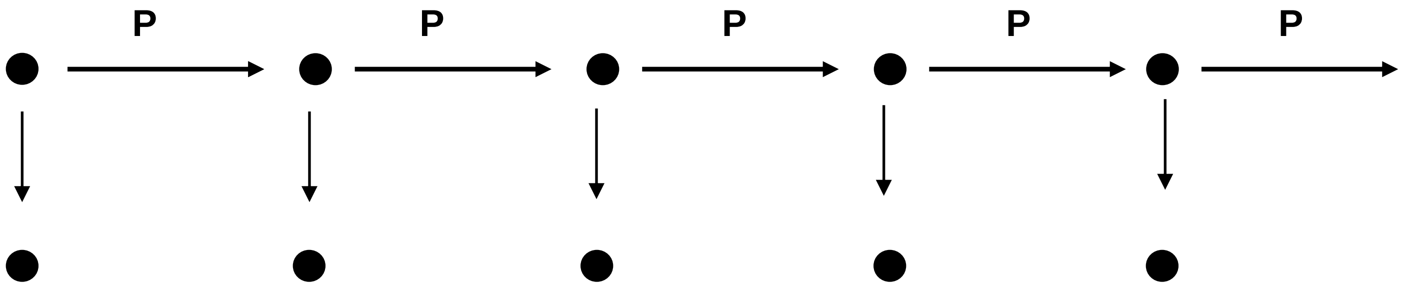


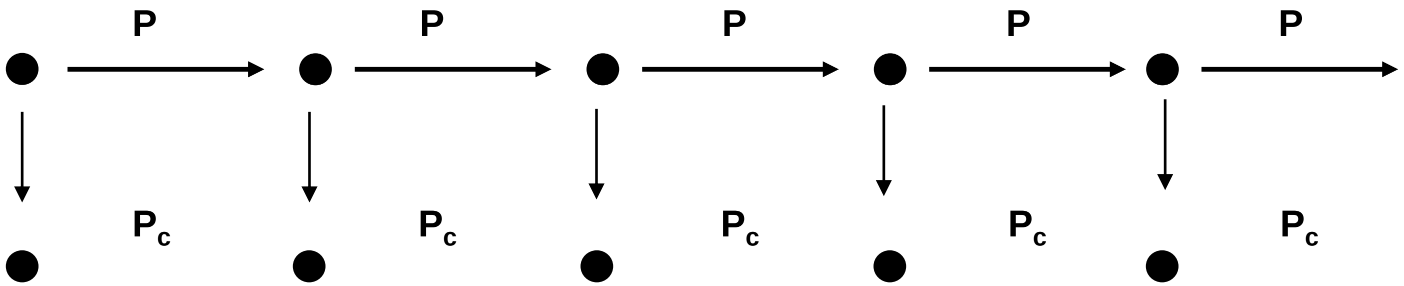
Probability for a process starting here for ending up in that set in 1 step

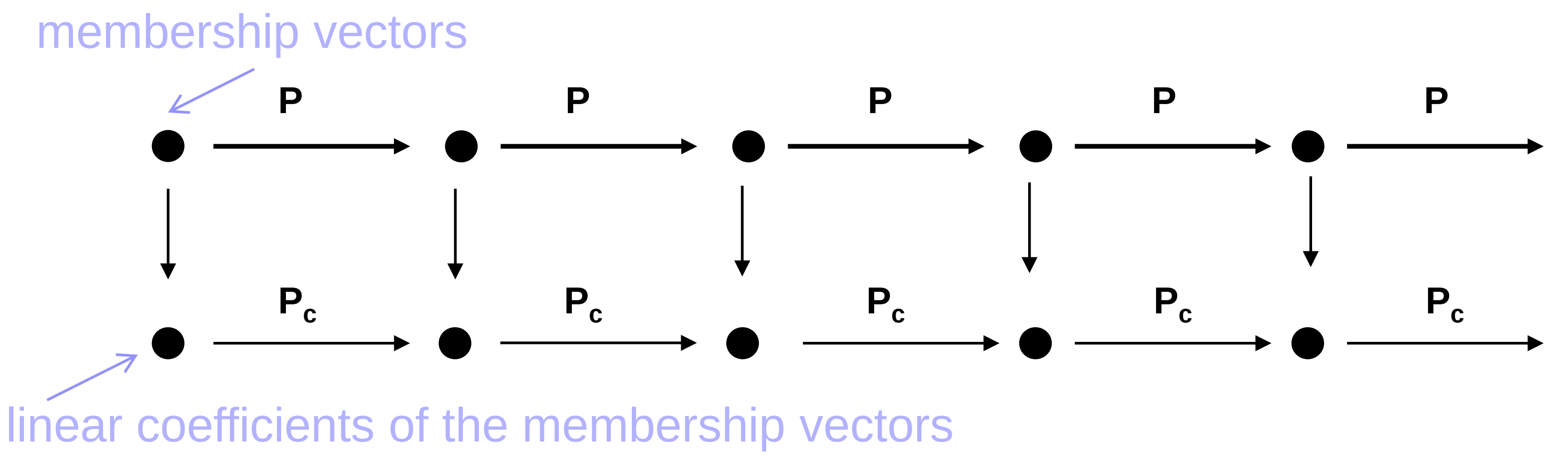
Weber, Galliat, 2002
Deuflhard, Weber, 2005
Weber, 2006
Röblitz, Weber, 2013



Röblitz, Weber, 2013


P
P
P
P
P


P
P
P
P
P
P_c
P_c
P_c
P_c
P_c



- P_c is a Galerkin discretization of P
- Membership vectors form an invariant subspace X of P
- starting point of P-chain inside the invariant subspace

Weber, 2011
Röblitz, Weber, 2013
Fackeldey, Weber, 2016

$$PX = X\Lambda$$

$$\chi = XA$$

X orthogonal matrix with regard to the stationary distribution (separability = orthogonality of A)

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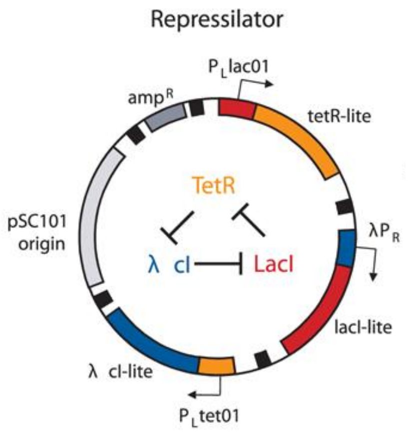
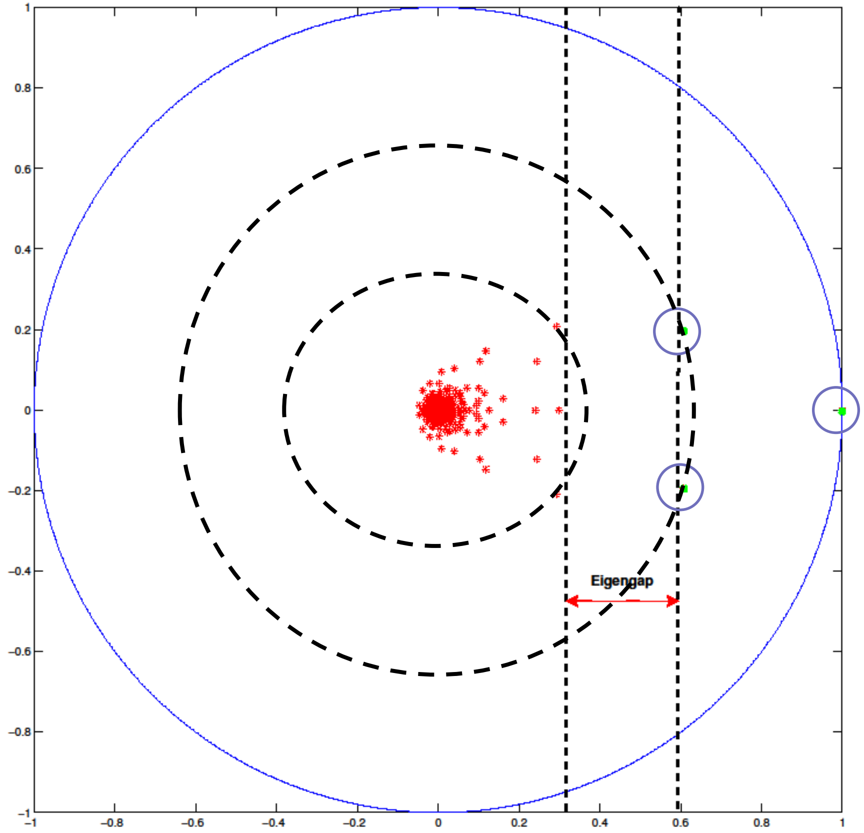




Reinmiedl, 2016
Elowitz, Stanislas, Leibler, 2000

$$PX = X\Lambda$$

diagonal matrix??

X **orthogonal matrix** with regard to the stationary distribution

Schur decomposition

$$PX = X\Lambda$$

+	+	+	+	+	+	+	+
	+	+	+	+	+	+	+
		+	+	+	+	+	+
			+	+	+	+	+
				+	+	+	+
					+	+	+
						+	+
							+

Schur decomposition

$$PX = X\Lambda$$

+	+	+	+	+	+	+	+
	+	+	+	+	+	+	+
		+	+	+	+	+	+
			+	+	+	+	+
				+	+	+	+
					+	+	+
						+	+
							+

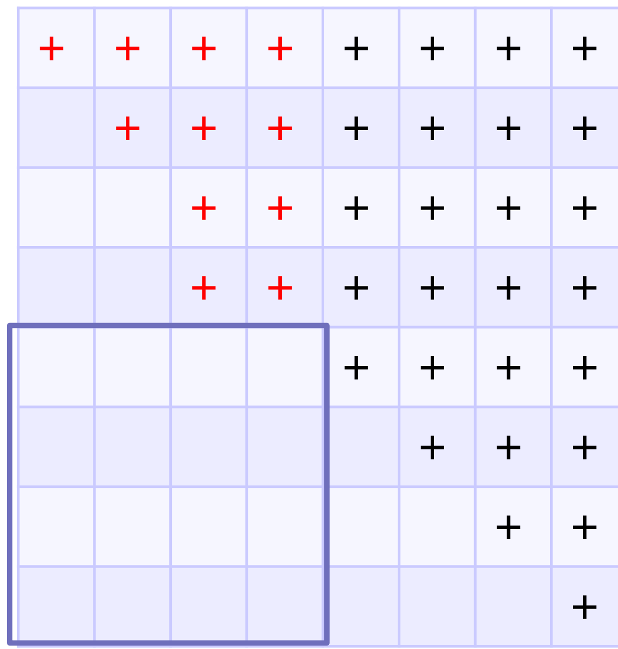
real Schur decomposition

$$PX = X\Lambda$$

+	+	+	+	+	+	+	+
	+	+	+	+	+	+	+
		+	+	+	+	+	+
		+	+	+	+	+	+
				+	+	+	+
					+	+	+
						+	+
							+

real Schur decomposition

$$PX = X\Lambda$$



„Schur = Eigen“ for reversible matrices

Schur is well-conditioned

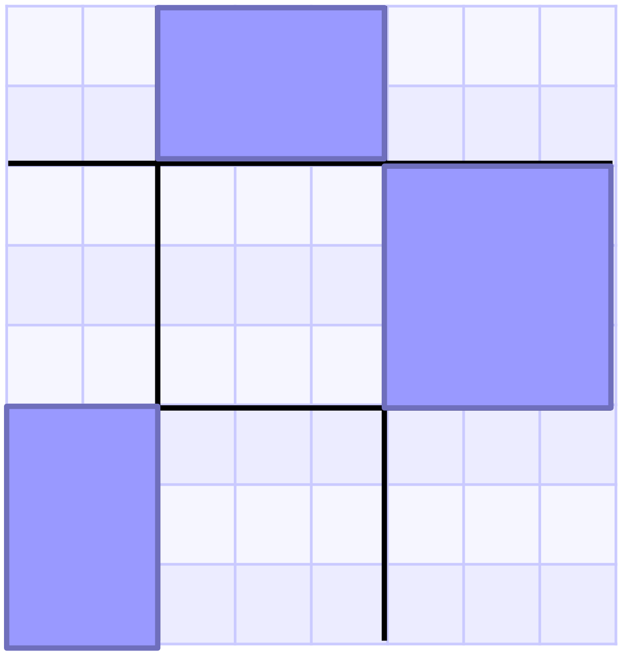
Schur always exists

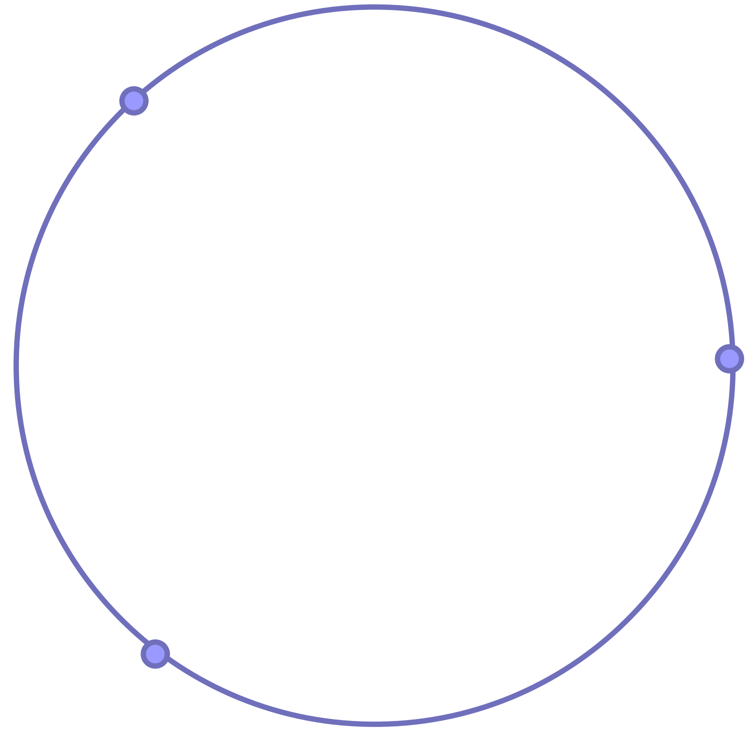
Schur is not unique

Schur values of P become Schur values of P_C

$$T = \begin{pmatrix} 5/12 & 5/12 & 1/6 \\ 1/4 & 1/4 & 1/2 \\ 1/3 & 1/3 & 1/3 \end{pmatrix}$$

P





P_C

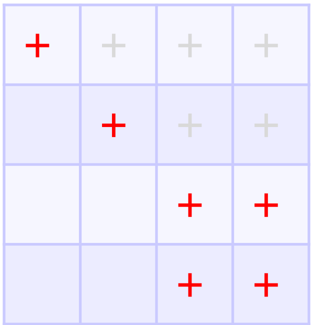
0	1	0
0	0	1
1	0	0

Non-reversibility $n = \|DP_C - (DP_C)^T\|_{F,\mu}$ of P_C is a consequence of the non-diagonality of the Schur matrix and the „separability / orthogonality“ of the clusters.

$$n = \sqrt{2 \sum_{i>j} \left|\Lambda_{ij} - \Lambda_{ji}\right| \cdot \|A^{(i)} \times A^{(j)}\|_{\mu}^{2}}$$

Djurdjevac-Conrad, Schütte, Weber, 2016

Λ



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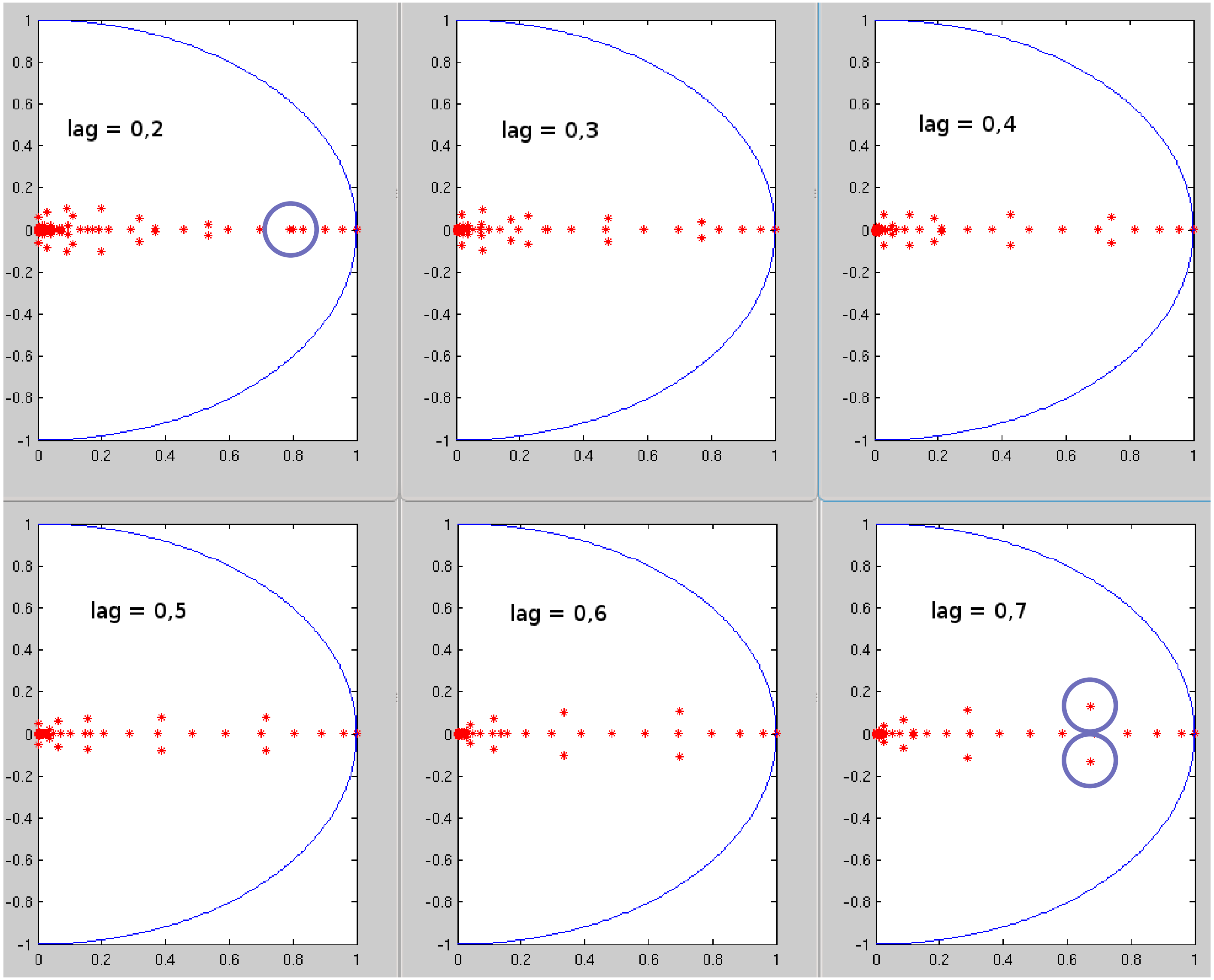

Reinmiedl, 2016

SDE Hindemarsh-Rose (neuronal excitation)

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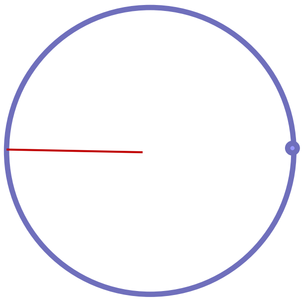
Preparation of the invariant space:

```
Pd=diag(sqrt(sd))*P*diag(1./sqrt(sd));
[Q, R]=schur(Pd);
[Q, R]=SRSchur(Q, R);
X=diag(1./sqrt(sd))*Q;
```

X orthogonal with regard to the stationary distribution
SRSchur sorts the eigenvalues

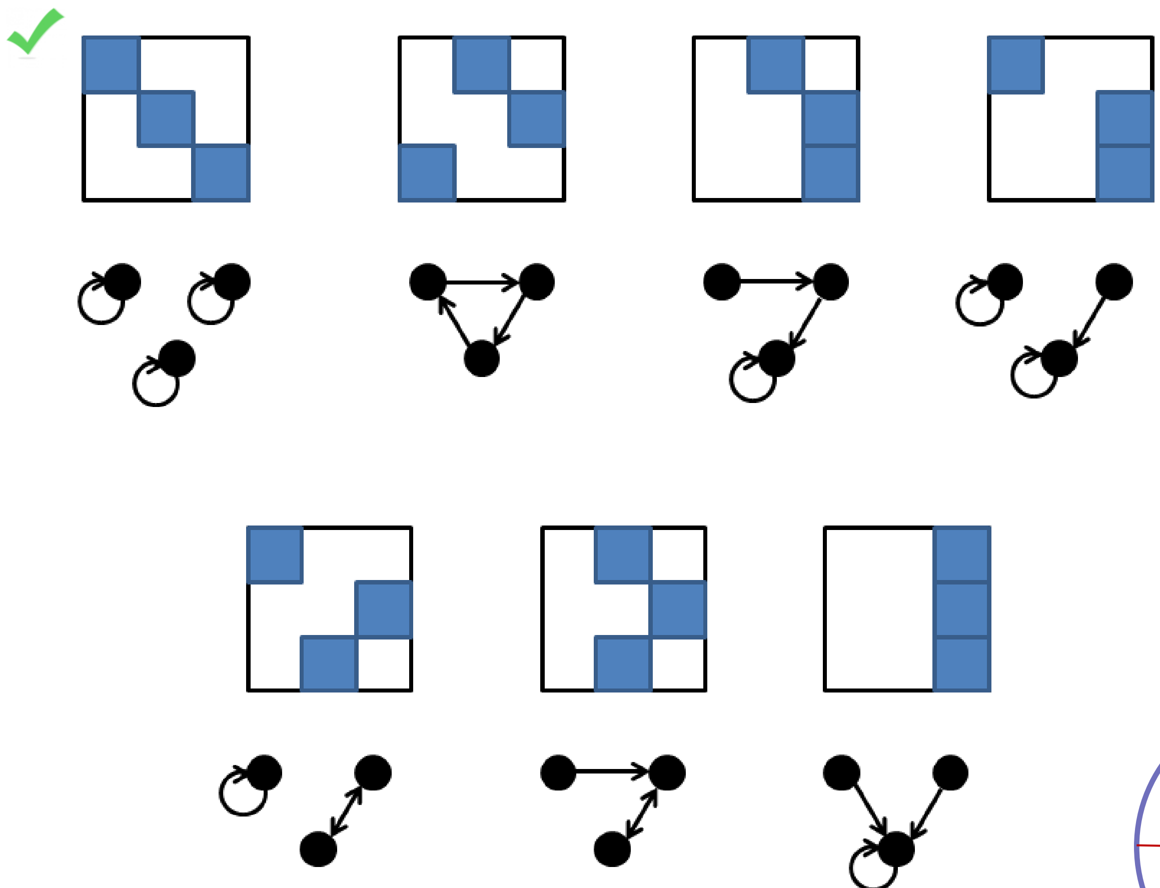
```
function [val,pos] = select(r)
 %[val pos] = min(abs(1-r)); %Metastability
 [val, pos]=max(abs(r)); %Permutation Matrices
 %[val, pos]=max(abs(r-(real(r)<0).*real(r))); % LOG
 %...
```

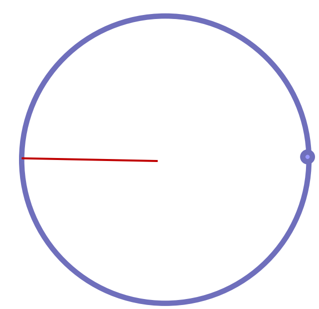


Brandts, 2001
Fackeldey, Weber, 2016

Why taking the absolute value?

sources/sinks = redundancy





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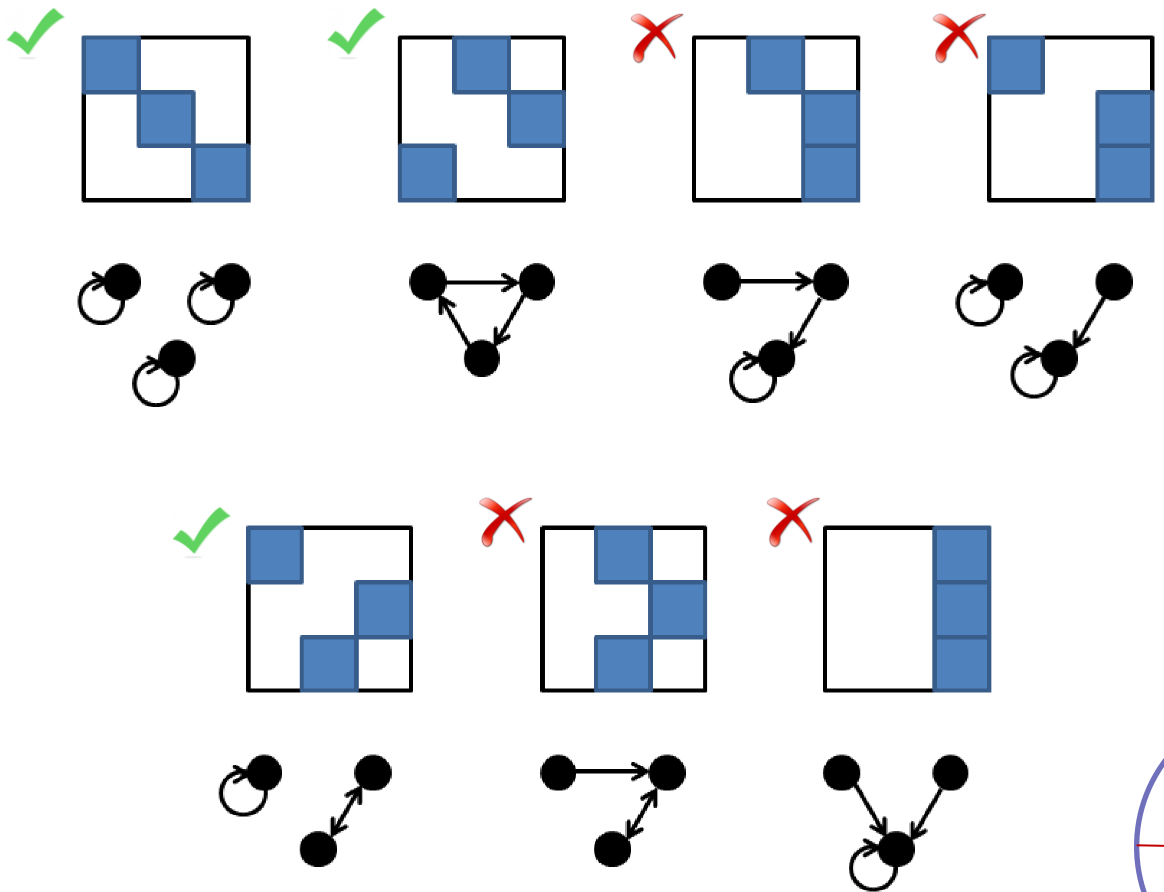
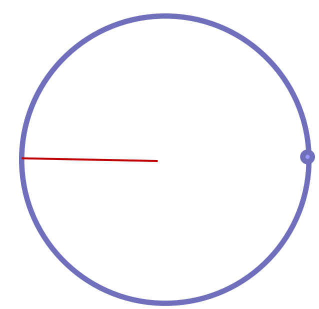
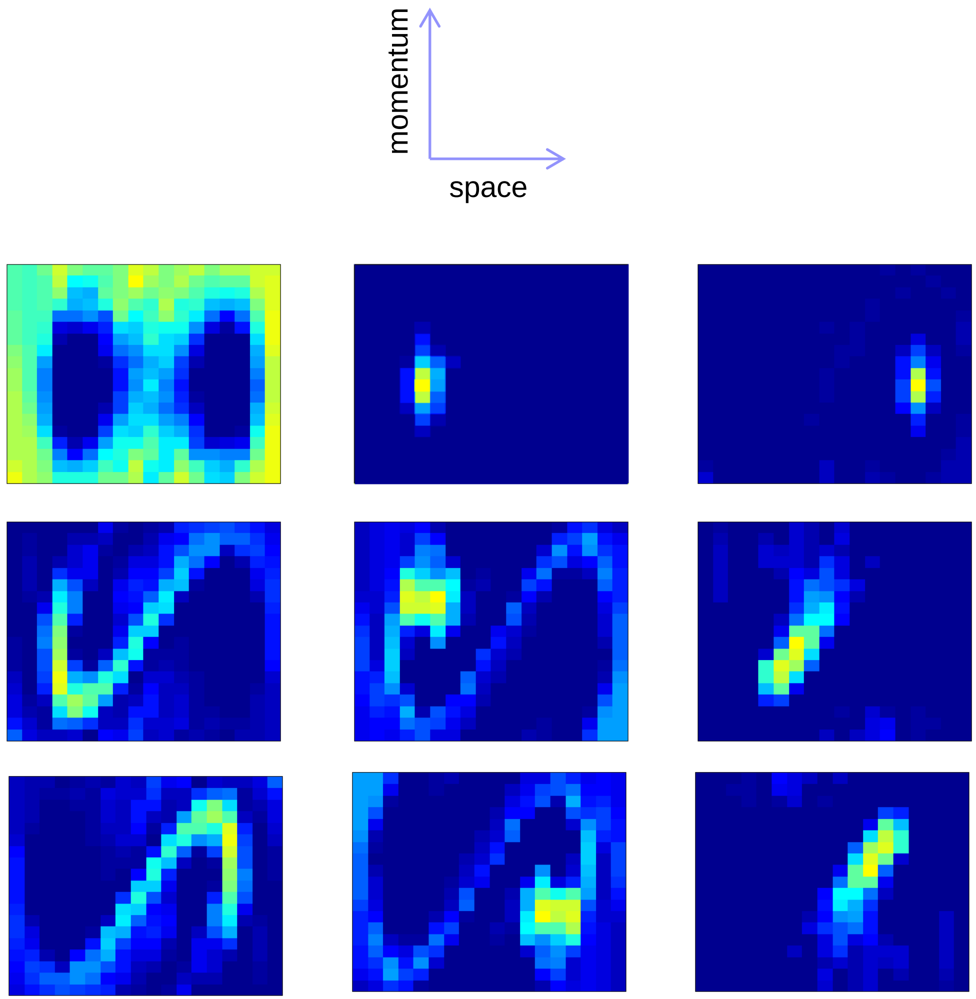
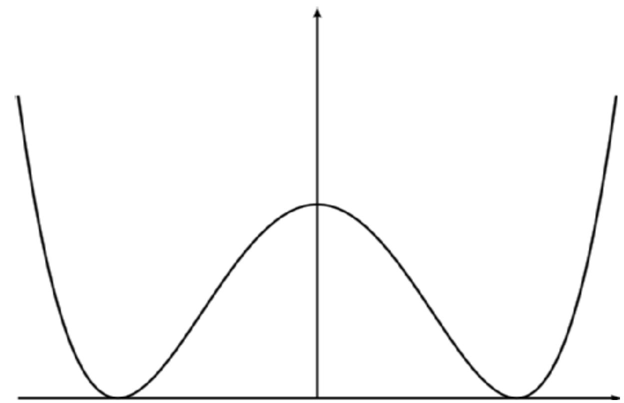






Djurdjevac-Conrad, Schütte, Weber, 2016



low-friction Langevin dynamics

1	0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	0
0	0	1	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0
0	0	0	0	0	1	0	0	0
0	0	0	1	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	1
0	0	0	0	0	0	1	0	0

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Djurdjevac-Conrad, Schütte, Weber, 2016

Λ

+	+	+	+
	+	+	+
		+	+
		+	+

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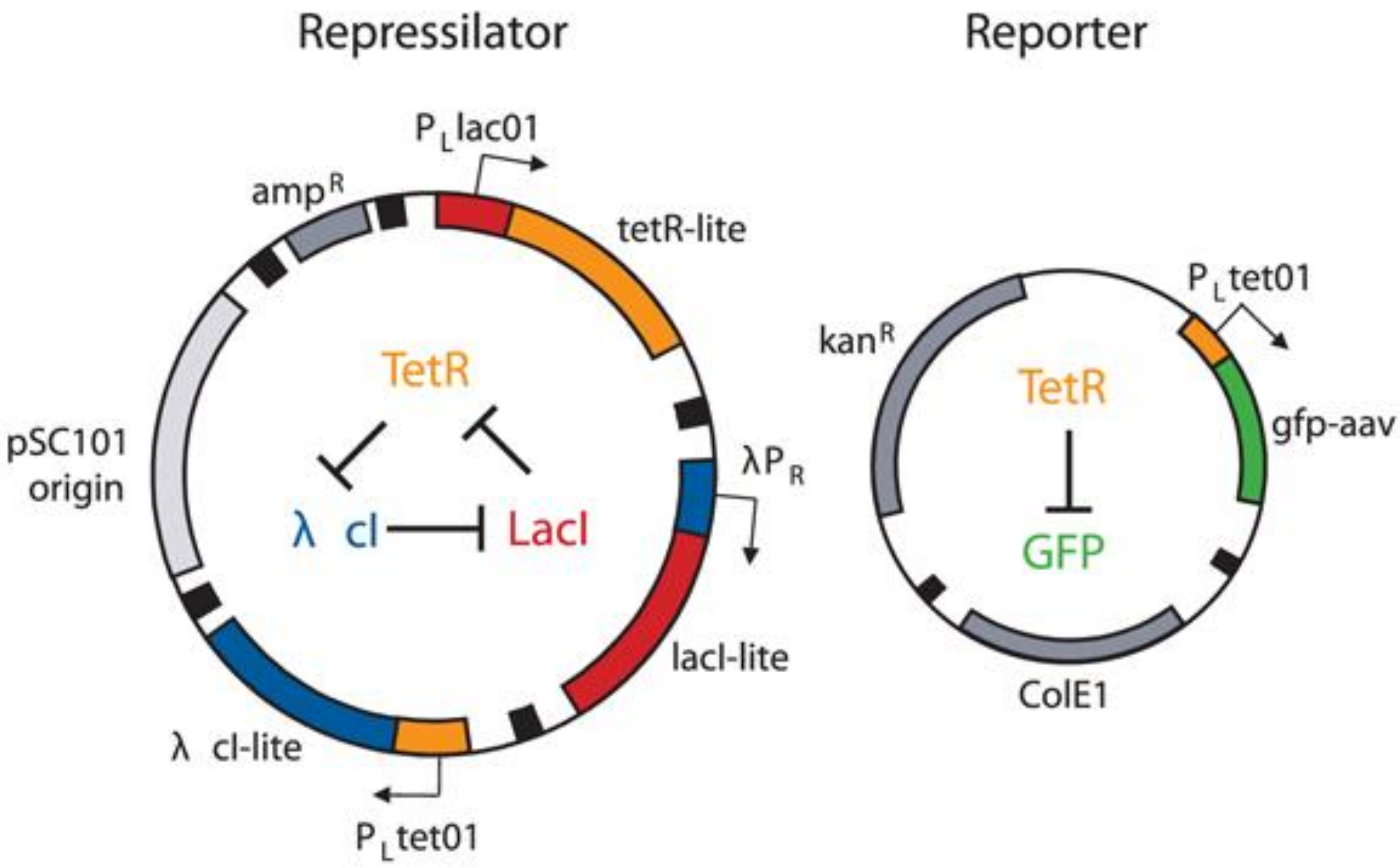
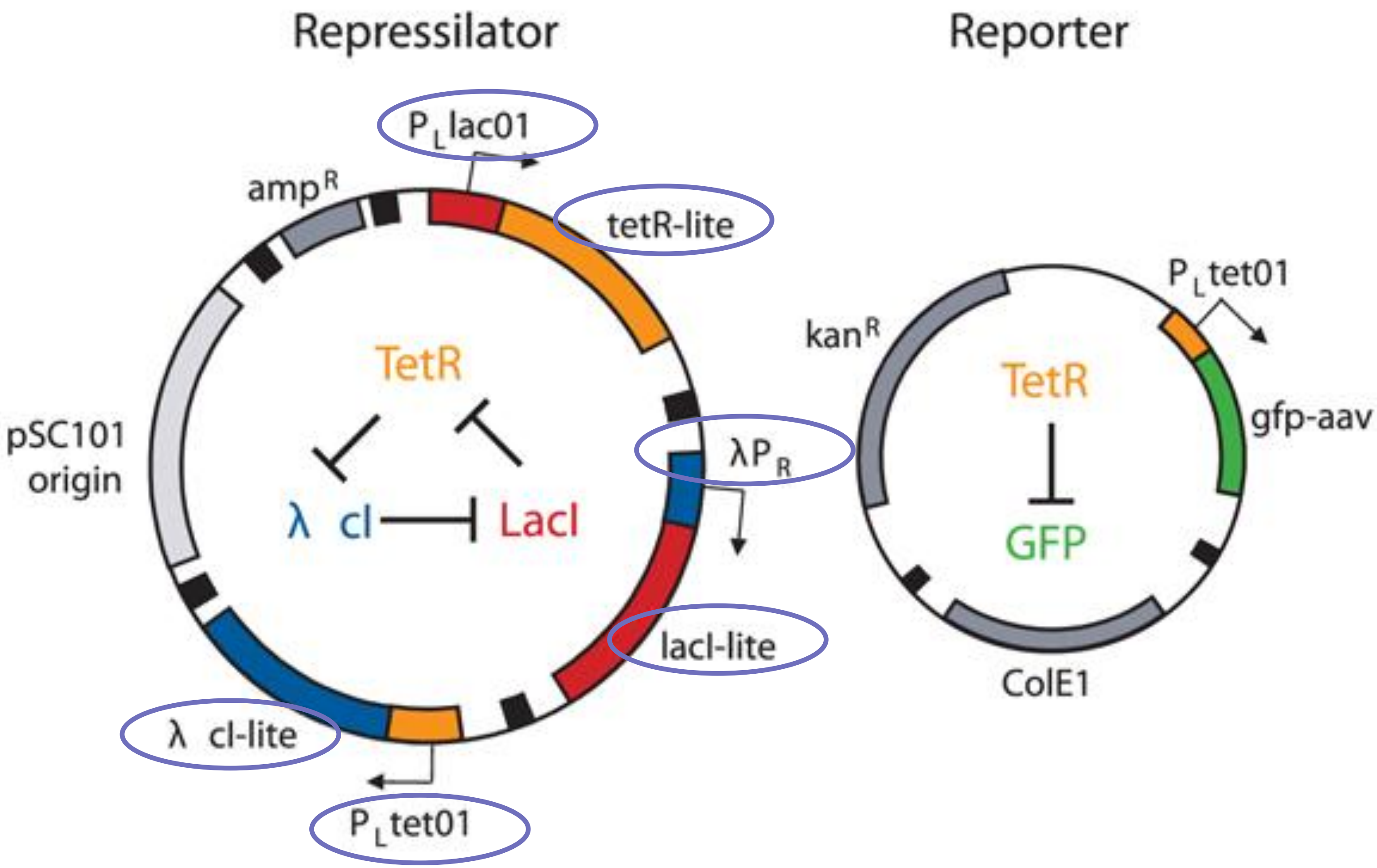


A Synthetic Oscillatory Network of Transcriptional Regulators; Michael Elowitz and Stanislas Leibler; Nature. 2000 Jan 20;403(6767):335-8.



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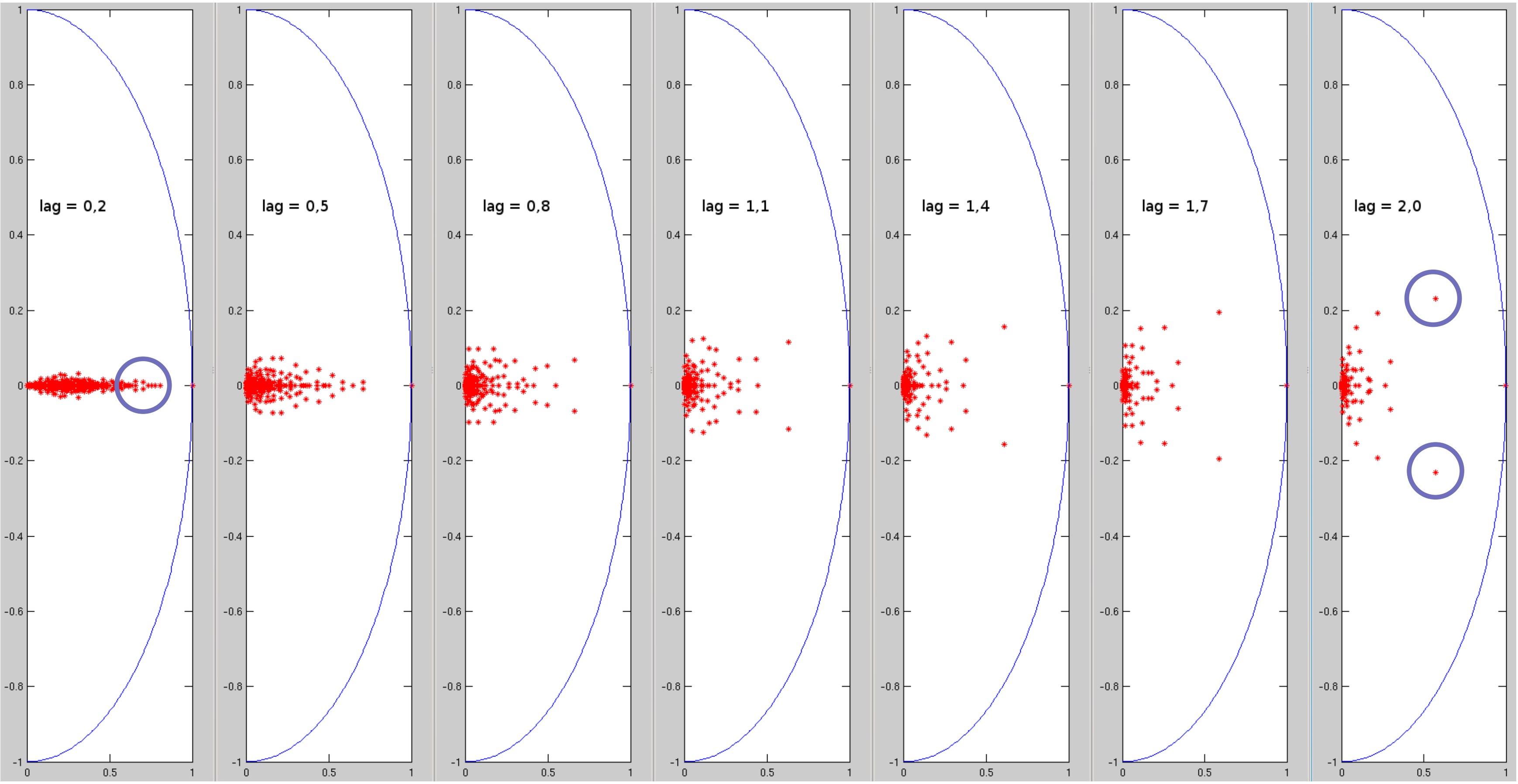
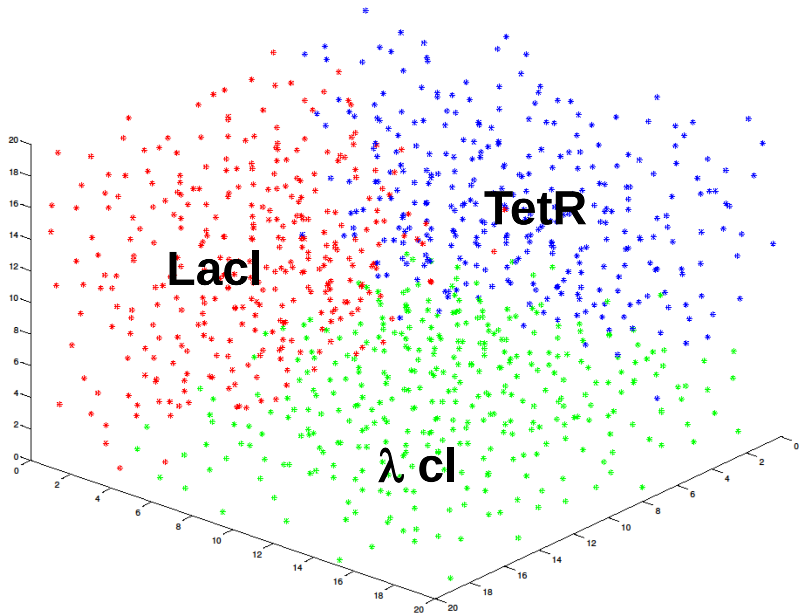
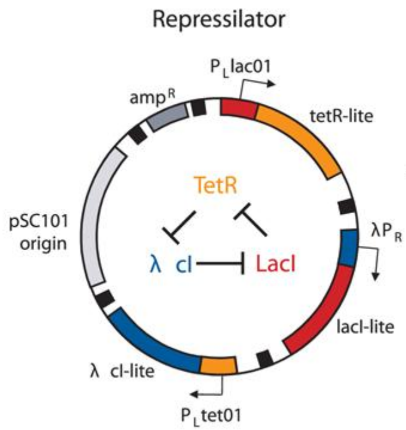


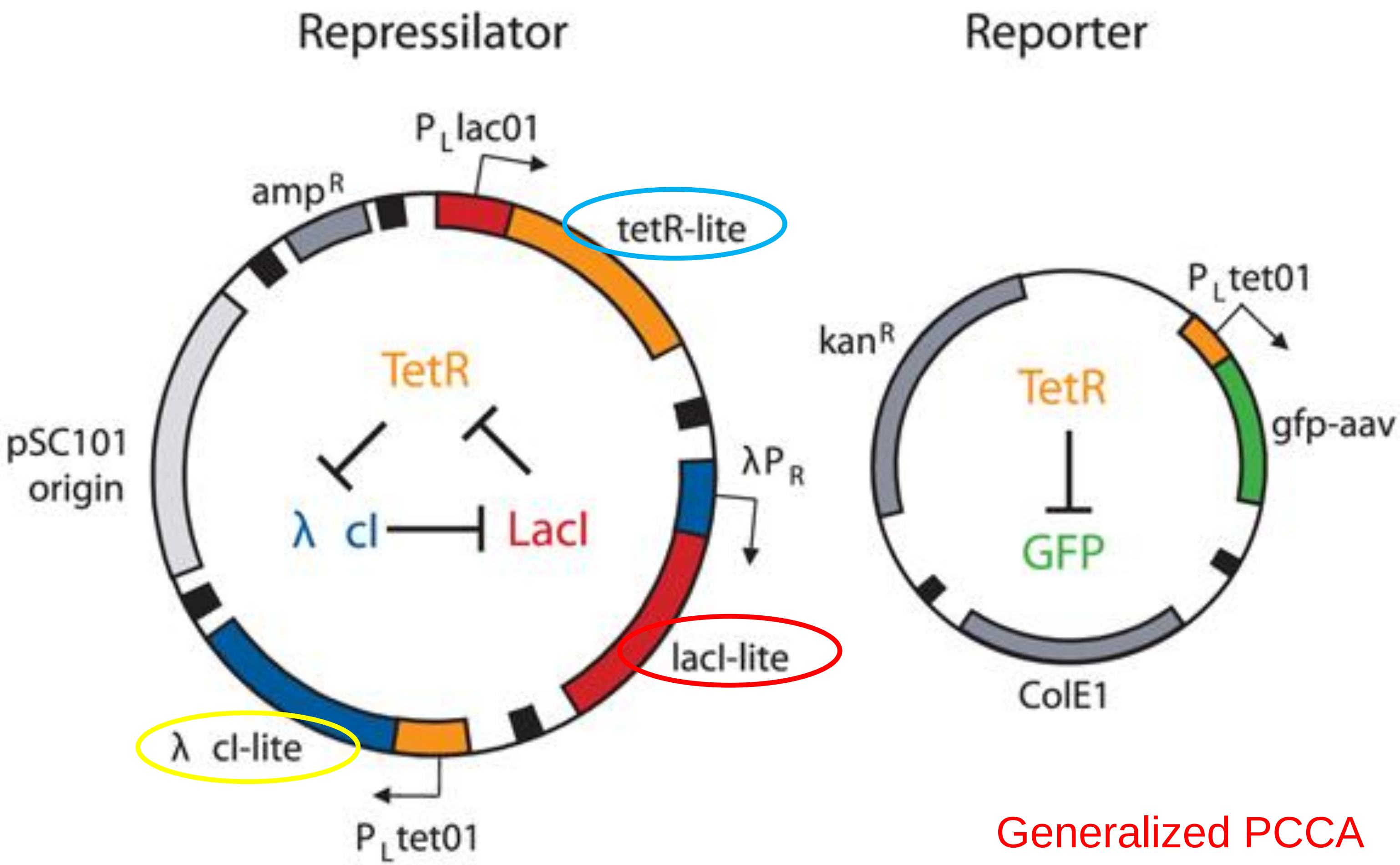
Reinmiedl, 2016

Generalized PCCA





Reinmiedl, 2016
Beckenbach, Eifler, Fackeldey, Gleixner, Grever, Weber, Witzig, 2016 (subm.)



Generalized PCCA
(n=0.005)

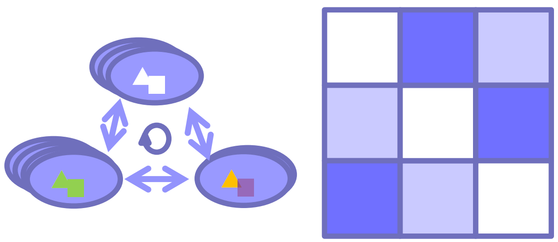
Reinmiedl, 2016
Beckenbach, Eifler, Fackeldey, Gleixner, Grever, Weber, Witzig, 2016 (subm.)

Information „to go“

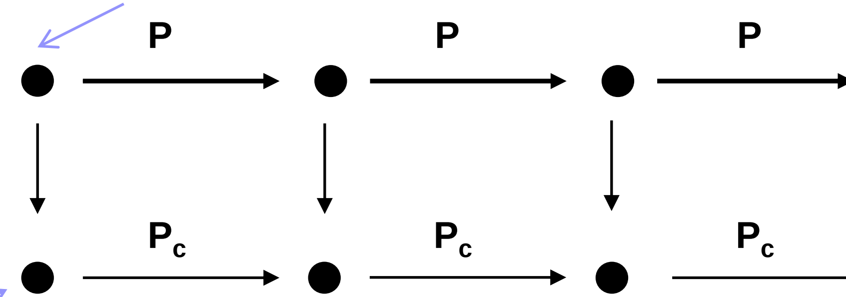
$$\chi = XA$$

membership vectors

$$PX = X\Lambda$$



efficiency = non-reversibility



linear coefficients of the membership vectors

$$n = \sqrt{2\sum_{i>j}\left|\Lambda_{ij} - \Lambda_{ji}\right| \cdot \|A^{(i)} \times A^{(j)}\|_{\mu}^{2}}$$