Towards the Mathematics of Multivalent Binding Processes

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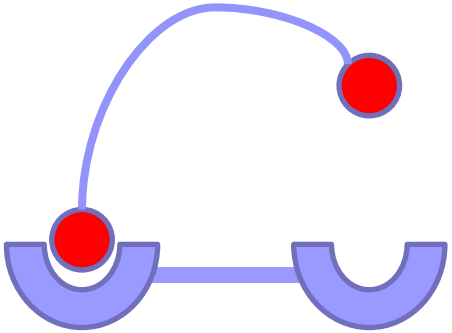
October 2011
MolMod
Workshop Heidelberg



$$U \underset{k_{off1}}{\overset{k_{on1}}{\rightleftharpoons}} M \underset{k_{off2}}{\overset{k_{on2}}{\rightleftharpoons}} B$$

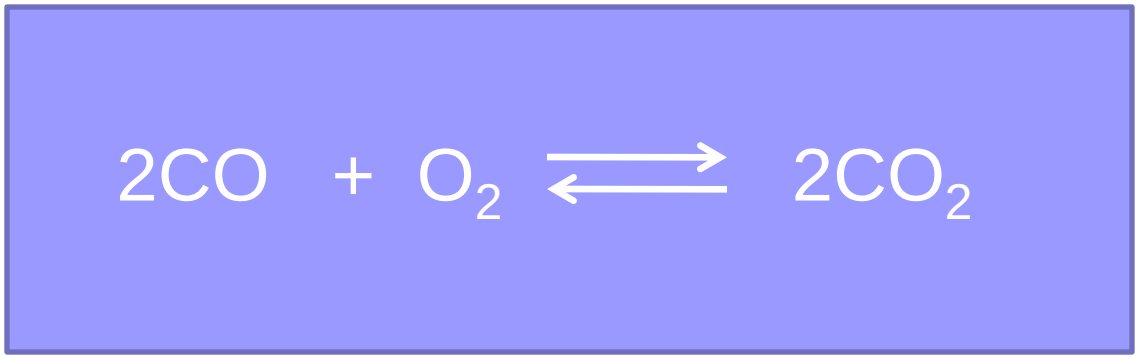
Transition Rates

Infinitesimal Generator

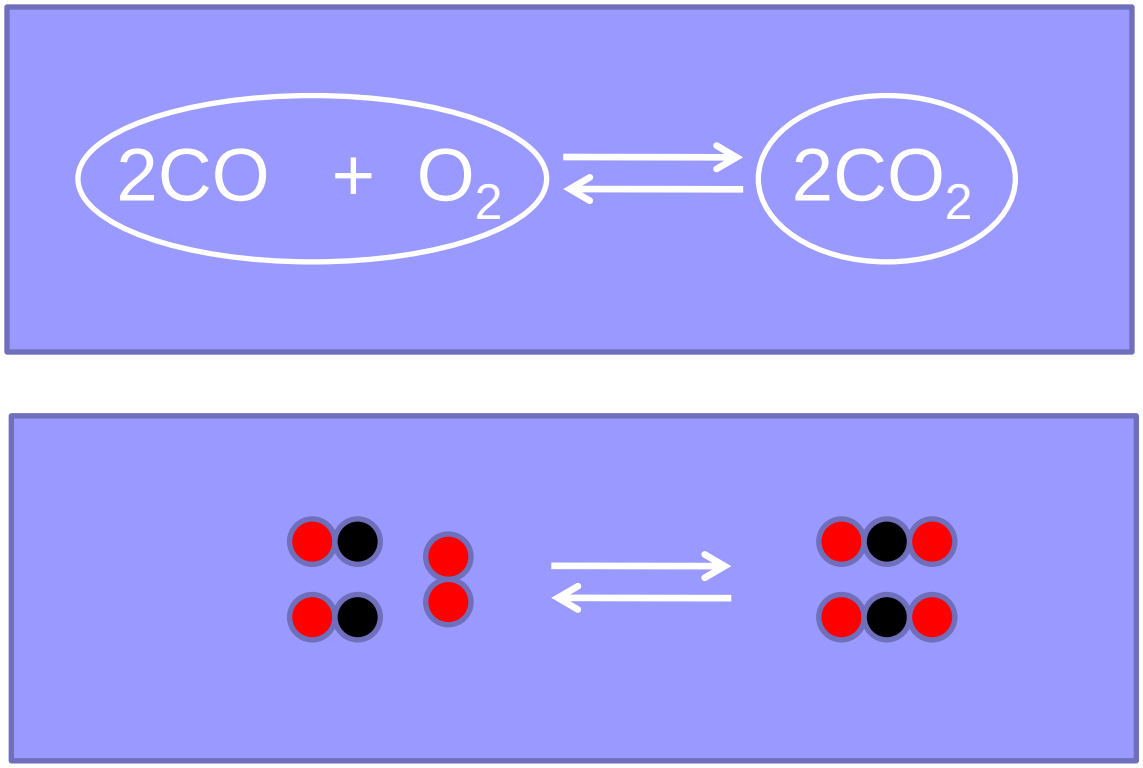
Algorithmic Approach

Estimation of Timescales

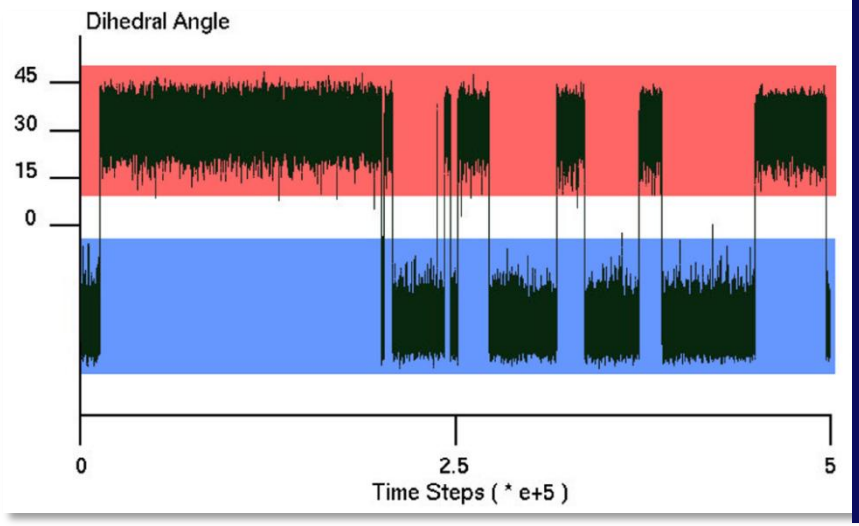
Reaction Kinetics

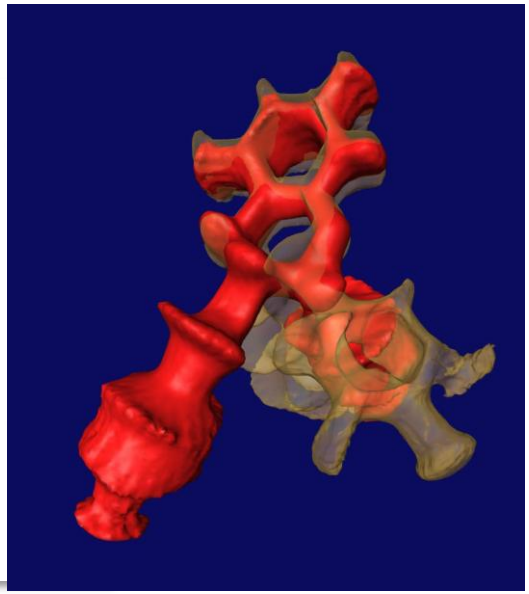


Reaction Kinetics

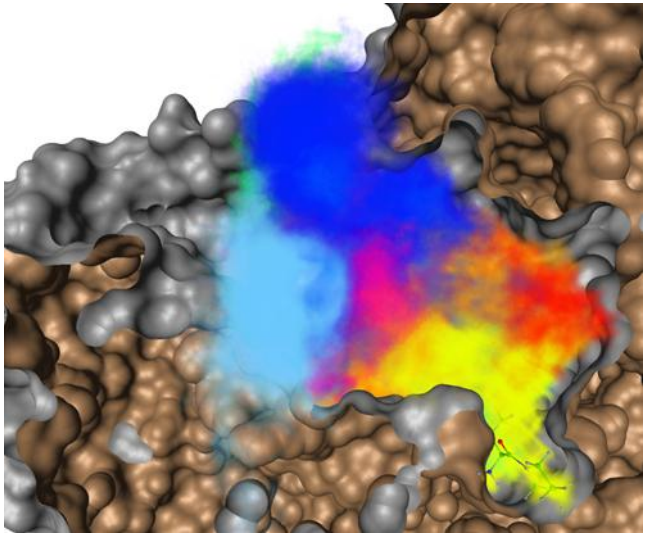


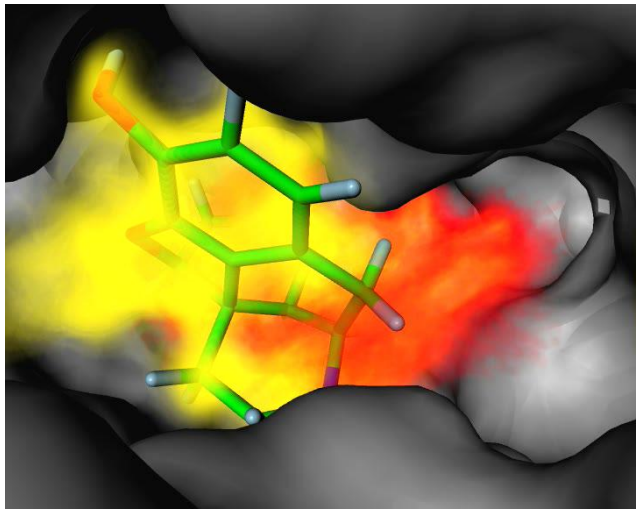
Molecular Kinetics



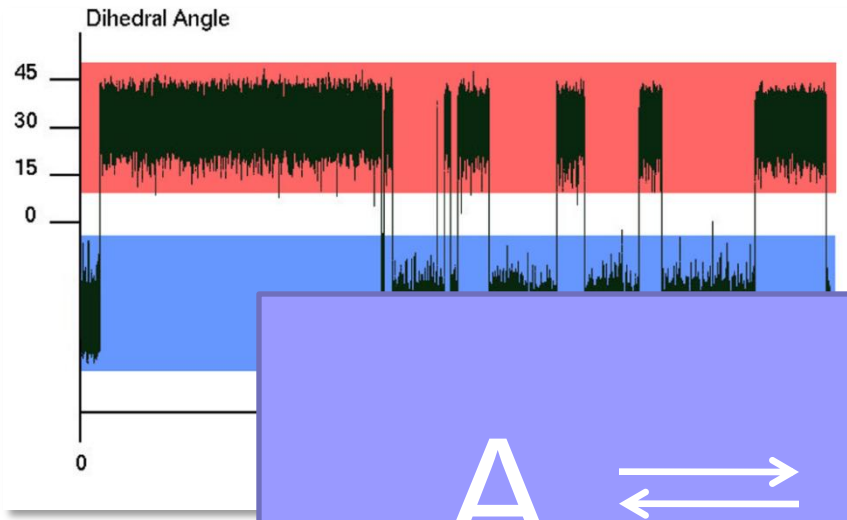


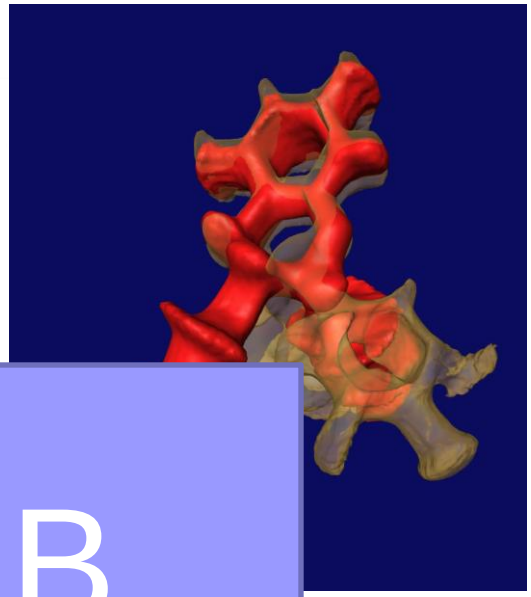
Deuflhard, Dellnitz, Junge, Schütte, 1999



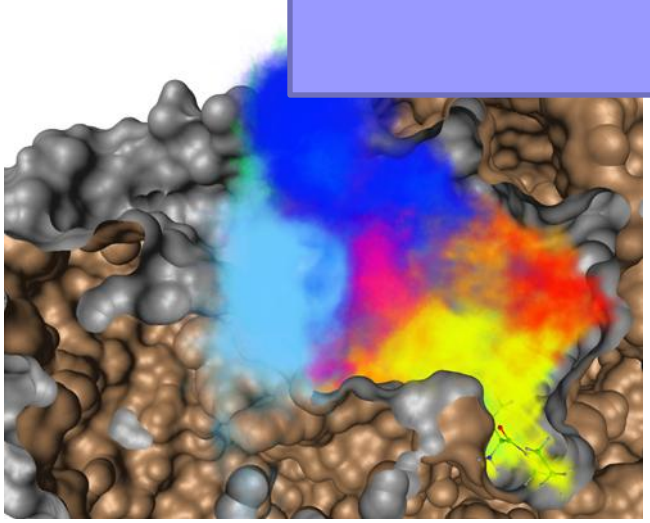


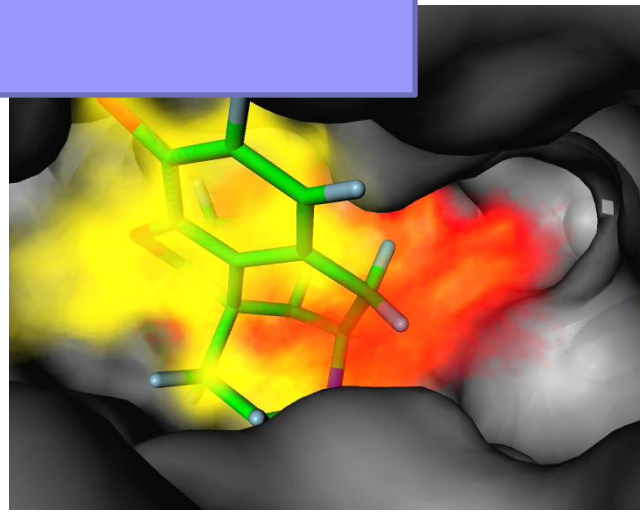
Molecular Kinetics





$$A \rightleftharpoons B$$





Deuflhard, Dellnitz, Junge, Schütte, 1999

Concentration vector (statistical weights)

$$x(t) \in \mathbb{R}^n$$

Concentration vector (statistical weights)

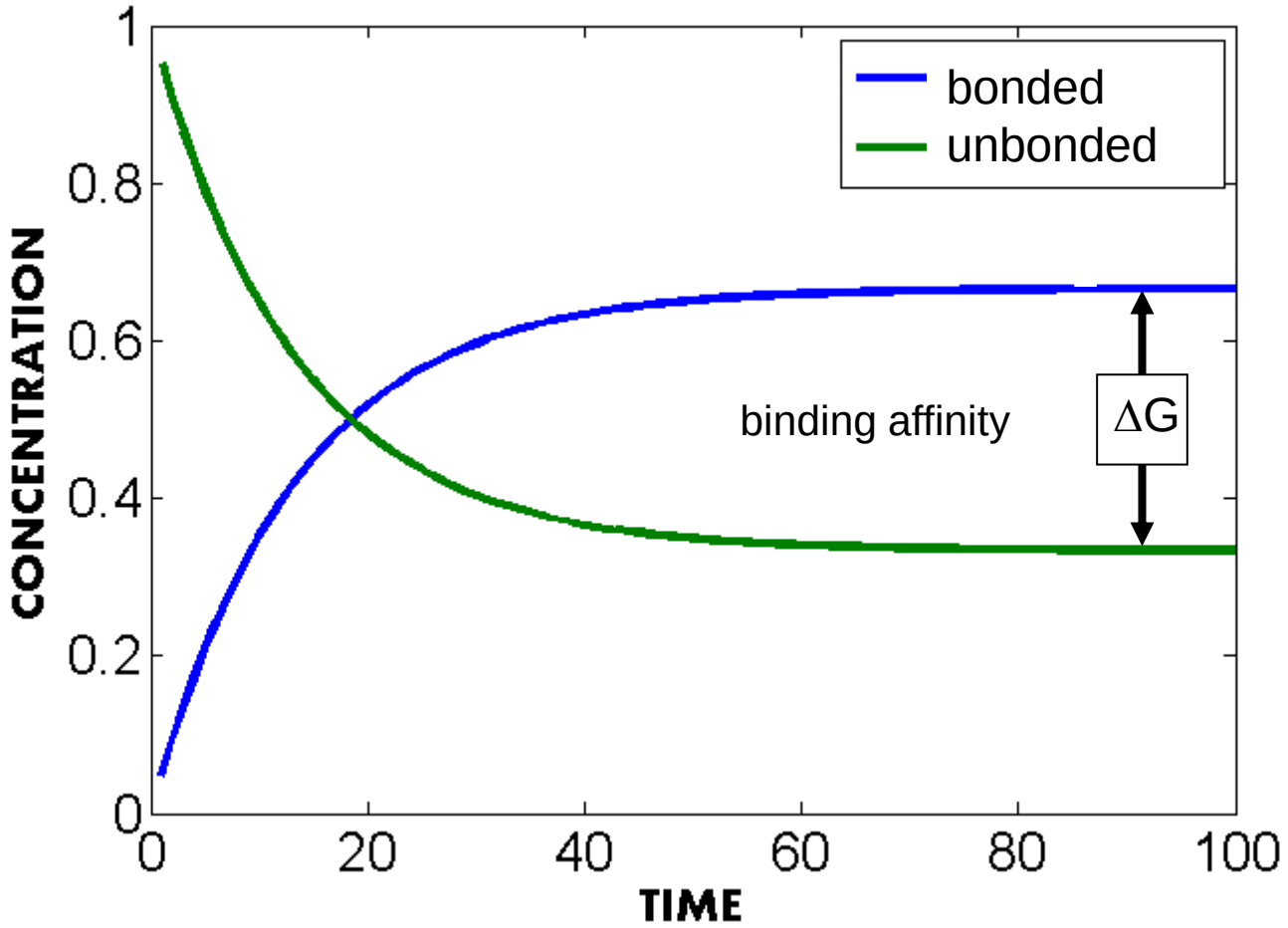
$$x(t) \in \mathbb{R}^n$$

Reaction rates (transition rates)

$$\dot{x}^{\perp} = x^{\perp} Q_c$$

$$Q_c \in \mathbb{R}^{n \times n}$$

Stationarity $\pi^{\perp} Q_c = 0$



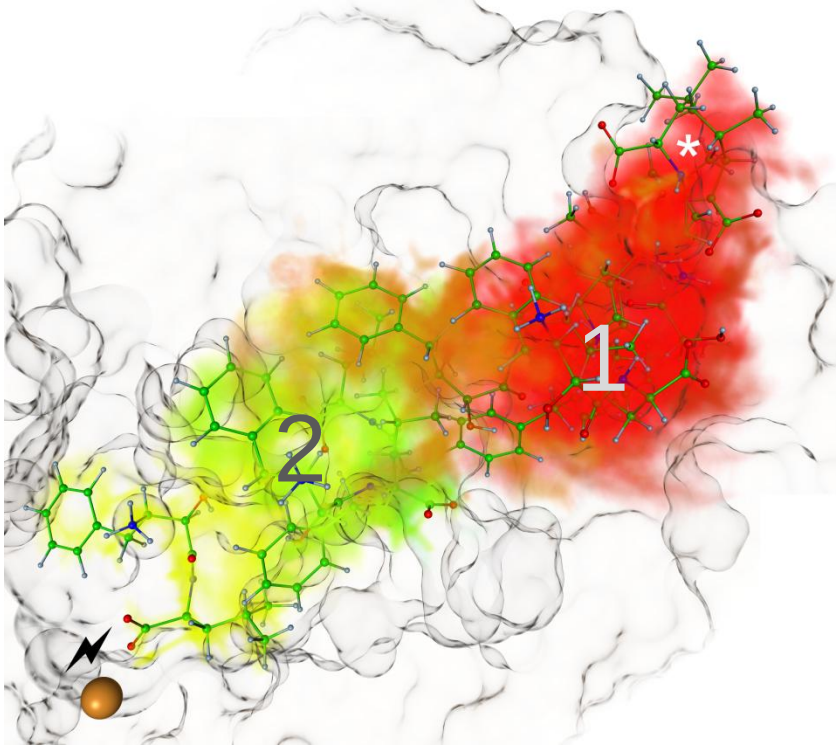
Stationarity

$$\pi^{\perp} Q_c = 0$$

Reversibility (detailed balance condition)

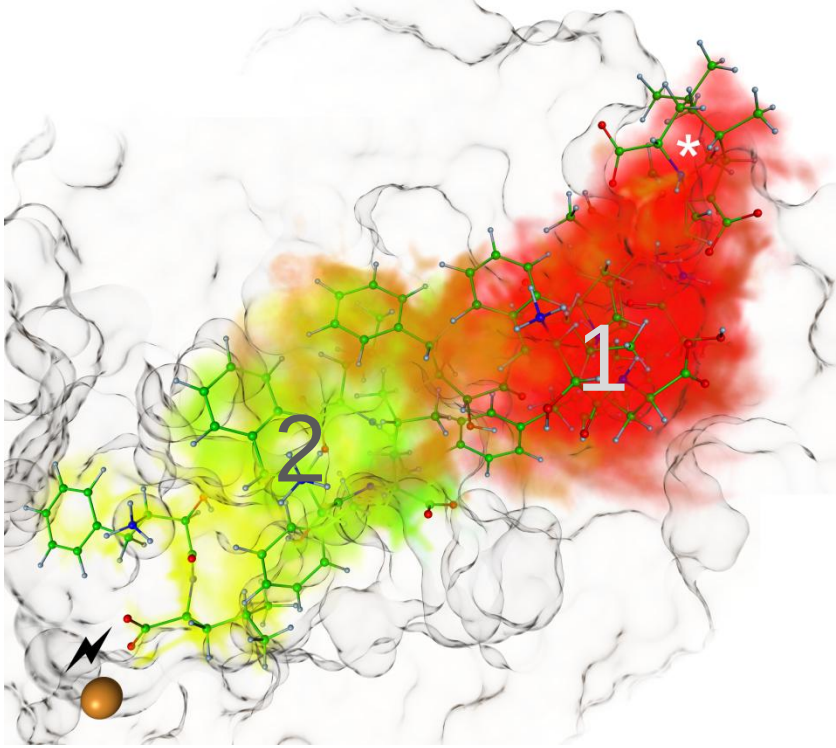
$$Q_c(i,j)\pi_i = Q_c(j,i)\pi_j$$

$$1 \rightleftharpoons 2$$

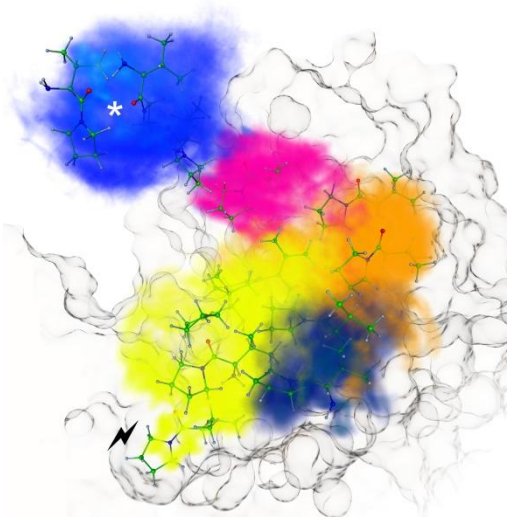


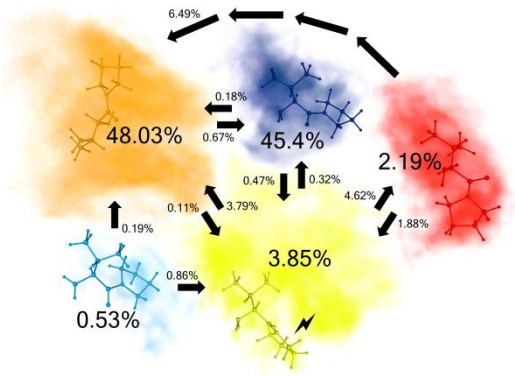
$$Q_c = \begin{pmatrix} -\pi_2 & \pi_2 \\ \pi_1 & -\pi_1 \end{pmatrix}$$

$$1 \rightleftharpoons 2$$



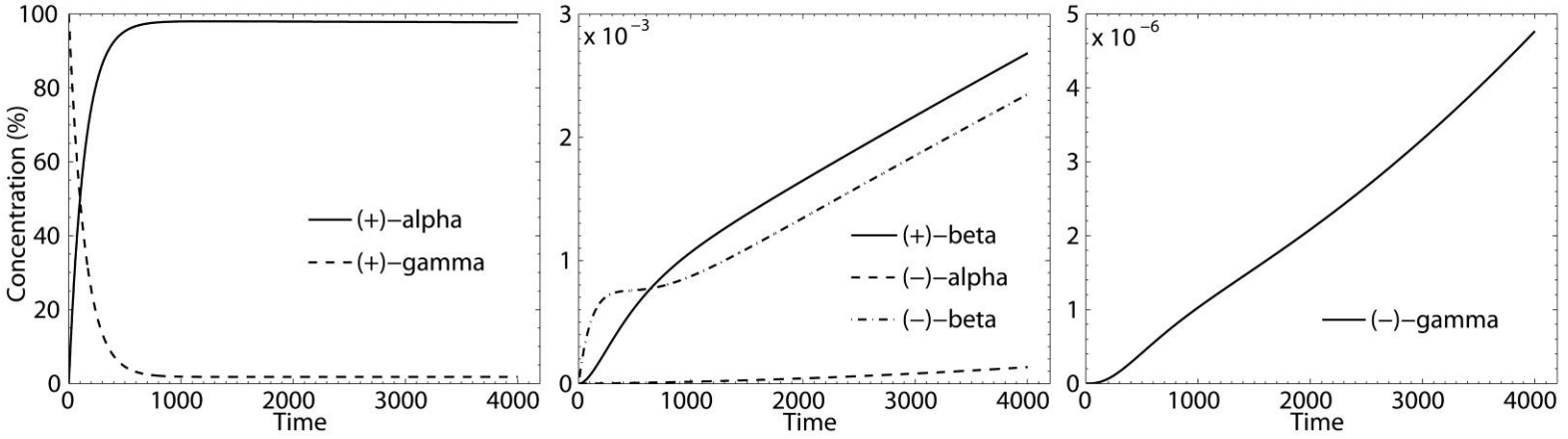
$$Q_c = \mu \begin{pmatrix} -\pi_2 & \pi_2 \\ \pi_1 & -\pi_1 \end{pmatrix}$$





Bujotzek, Wb, 2009

Wb, Becker, Köppen, Durmaz , 2008



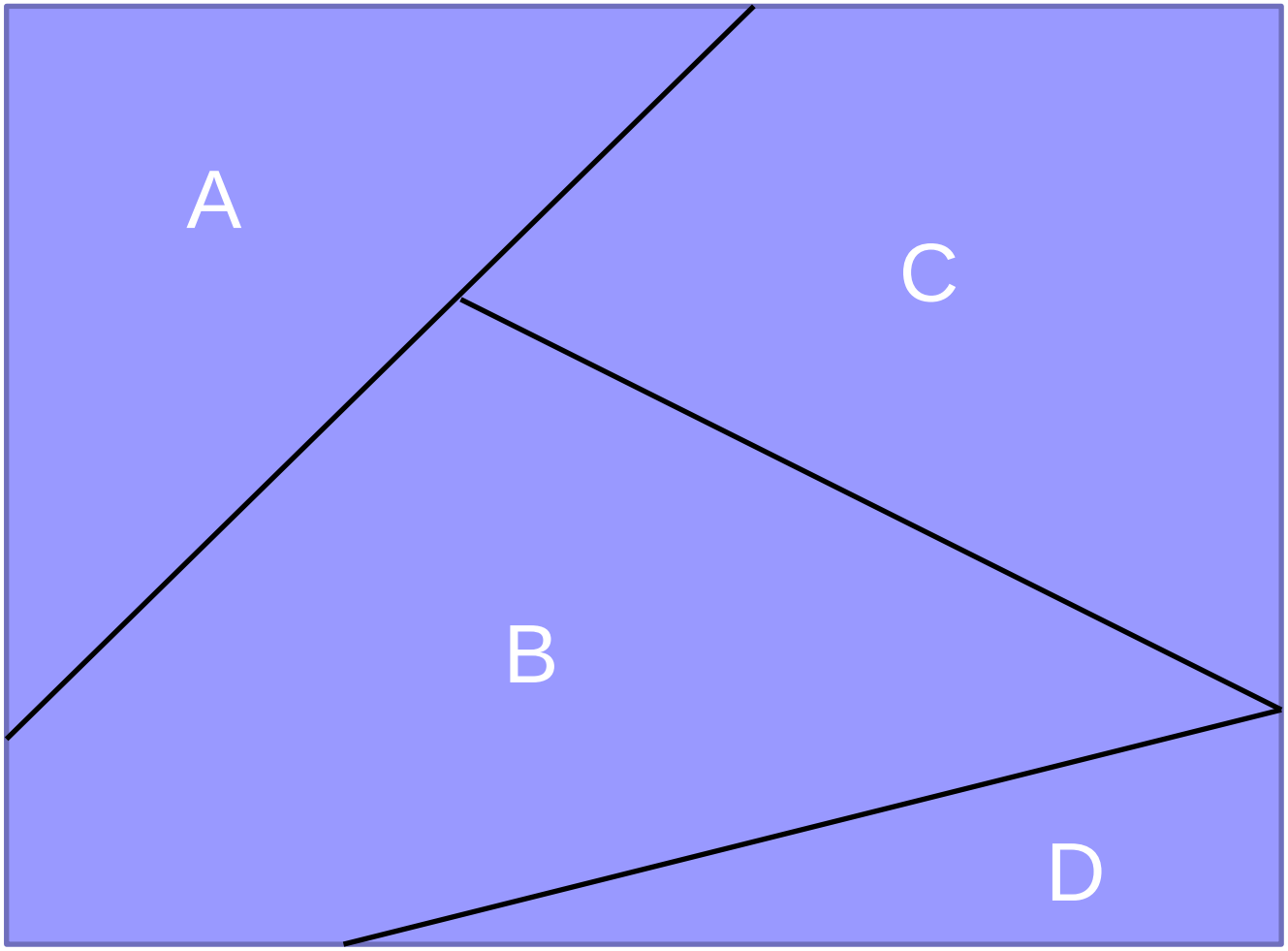
Transition Rates

Infinitesimal Generator

Algorithmic Approach

Estimation of Timescales

Ω



Conformations can‘t be defined in advance!
They have to be defined in such a way that transition rates exist!

Conformations are membership functions

$$\chi_i : \Omega \rightarrow [0,1]$$

partition of unity

$$\sum_{i=1..n} \chi_i(q) = 1$$

Q_c corresponds to a propagation in $\mathbb{R}^n$

assumption (not necessary)

$\mathcal{Q}$ corresponds to a propagation in Ω

Q_c corresponds to a propagation in $\mathbb{R}^n$

assumption (not necessary)

$\mathfrak{Q}$ corresponds to a propagation in Ω

Optional: Wb, 2010

- infinitesimal genarator in (q,p)-space
- optimal lag-time
- transitions are (rare) jumps

Q_c corresponds to a propagation in $\mathbb{R}^n$

projection χ

$\mathfrak{Q}$ corresponds to a propagation in Ω

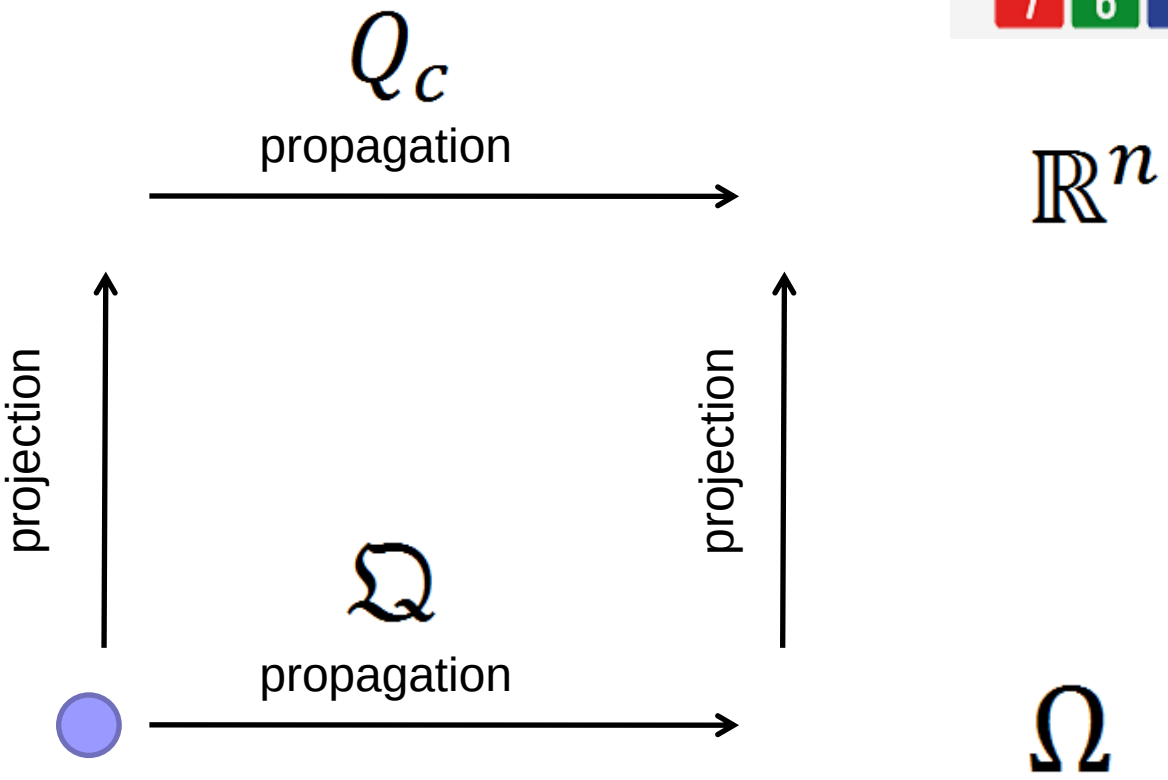
Kube, Wb, 2007
Wb, Kube, 2008
Wb, 2010

Q_c corresponds to a propagation in $\mathbb{R}^n$

χ projection χ

$\mathfrak{Q}$ corresponds to a propagation in Ω

Kube, Wb, 2007
Wb, Kube, 2008
Wb, 2010


Q_c
propagation
$\mathbb{R}^n$
projection
projection
$\mathcal{Q}$
propagation
Ω

Galerkin discretization

$$Q_c = \langle \chi, \chi \rangle_\pi^{-1} \langle \chi, \mathcal{Q} \chi \rangle_\pi$$

infinitesimal generator and eigenfunctions

$$\chi = \mathrm{X}\mathrm{A}$$

Conformations are membership functions

$$\chi_i : \Omega \to [0,1]$$

partition of unity

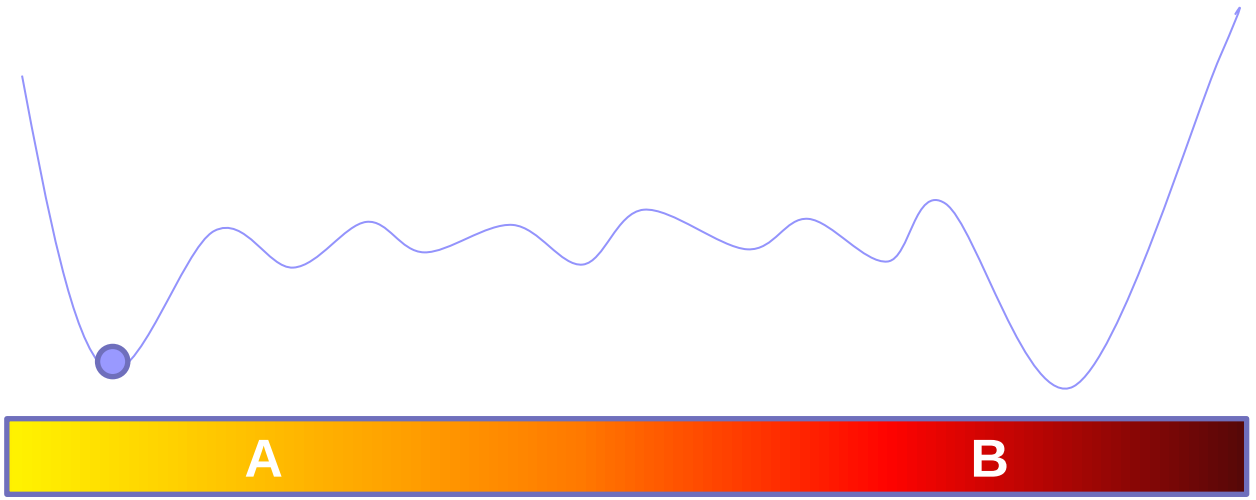
$$\sum_{i=1..n} \chi_i(q) = 1$$

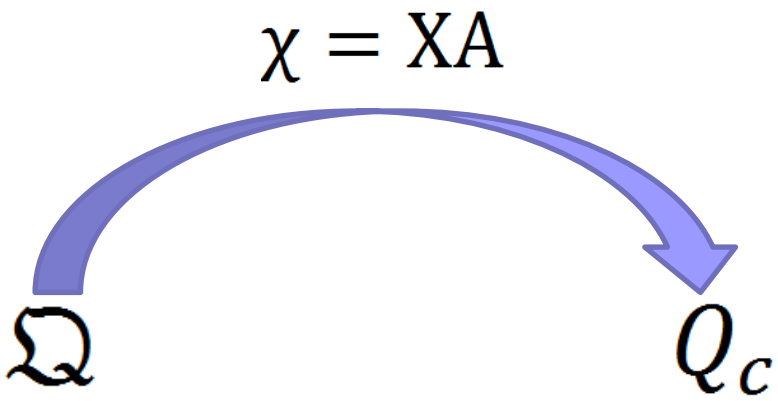
existing transition rates

$$\chi = \mathrm{X}\mathrm{A}$$

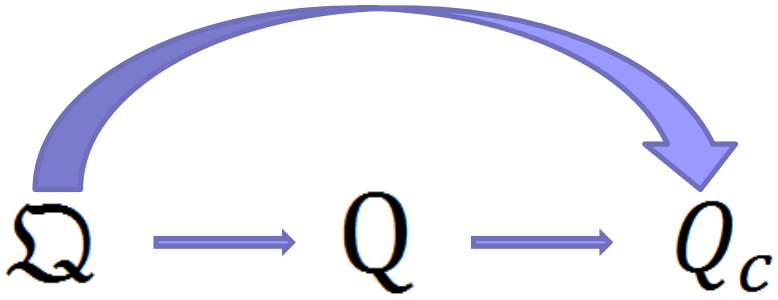
PCCA+
Deuflhard, Wb, 2005
Wb, 2006
Wb, 2010

diffusive transitions „transition region“	„soft“ membership functions
jump-like transitions „barrier crossing“	„hard“ membership functions



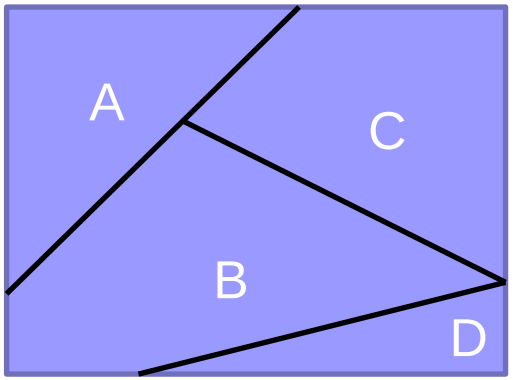

$\chi = \mathrm{XA}$
$\mathcal{Q}$
Q_c

$$\chi = \mathrm{X}\mathrm{A}$$



$$\mathrm{X} = \phi\mathrm{C} \qquad \chi = \phi\mathrm{C}\mathrm{A}$$

basis functions



$\mathcal{Q}$ Q_c

infinitesimal generators
commuting diagram
„process“-based interpretation

Q

Galerkin discretization
projection error
no process-based sampling

Faradjian, Elber, 2004
Swope, Pitera, 2004
Chodera, Swope, Pitera, Dill, 2006
Haack, 2008
Vanden-Eijnden, Venturoli, 2009
Sarich, Noé, Schütte, 2009
Wb, 2010

et al.

How to make the matrix Q interpretable?

Milestoning: count „first hitting events“ only (combine short trajectories to a long trajectory)

Optimal lag-time: choose minimal lag-time with Chapman-Kolmogorov property, estimate Q from multiple lagtime simulations

Error estimation: choose discretization sets, s.t projection error is small, i.e., determine this error

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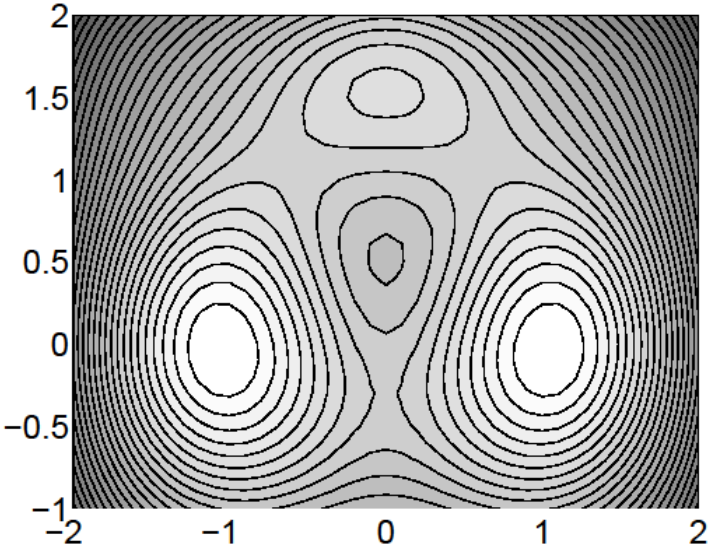
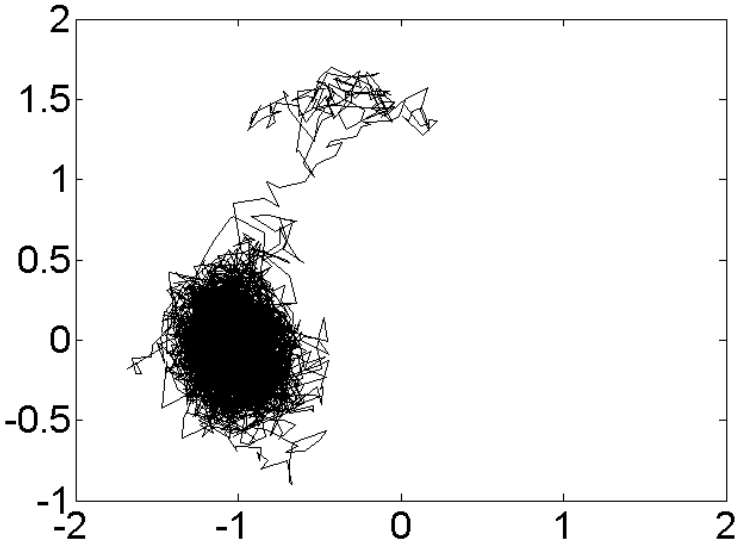
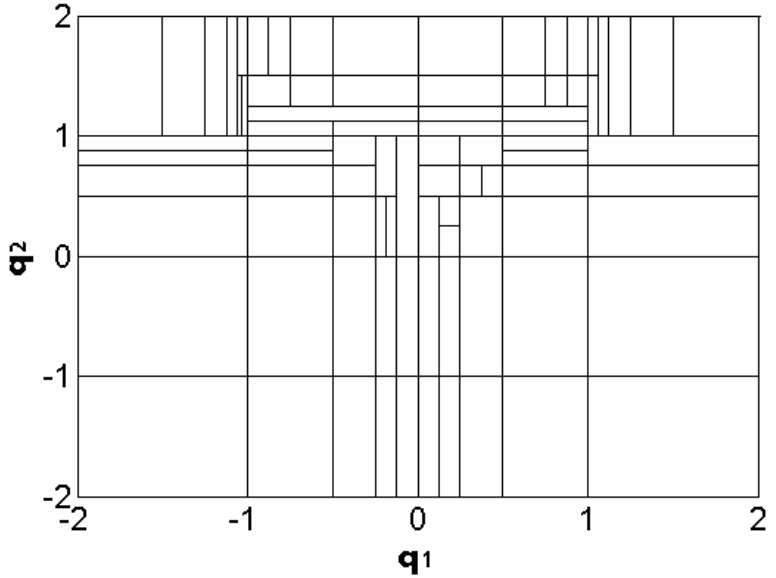
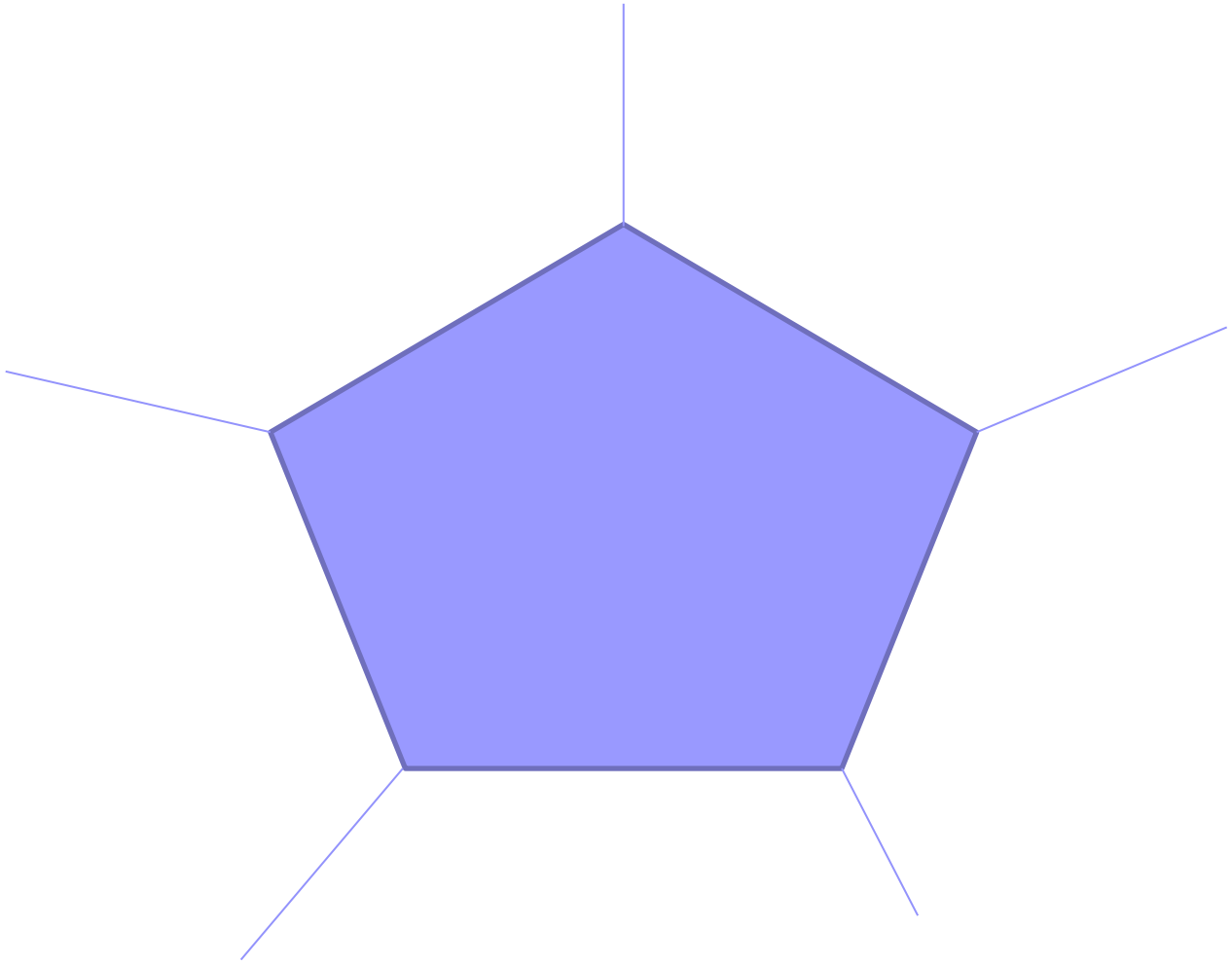

2
1.5
1
0.5
0
−0.5
−1
−2
−1
0
1
2

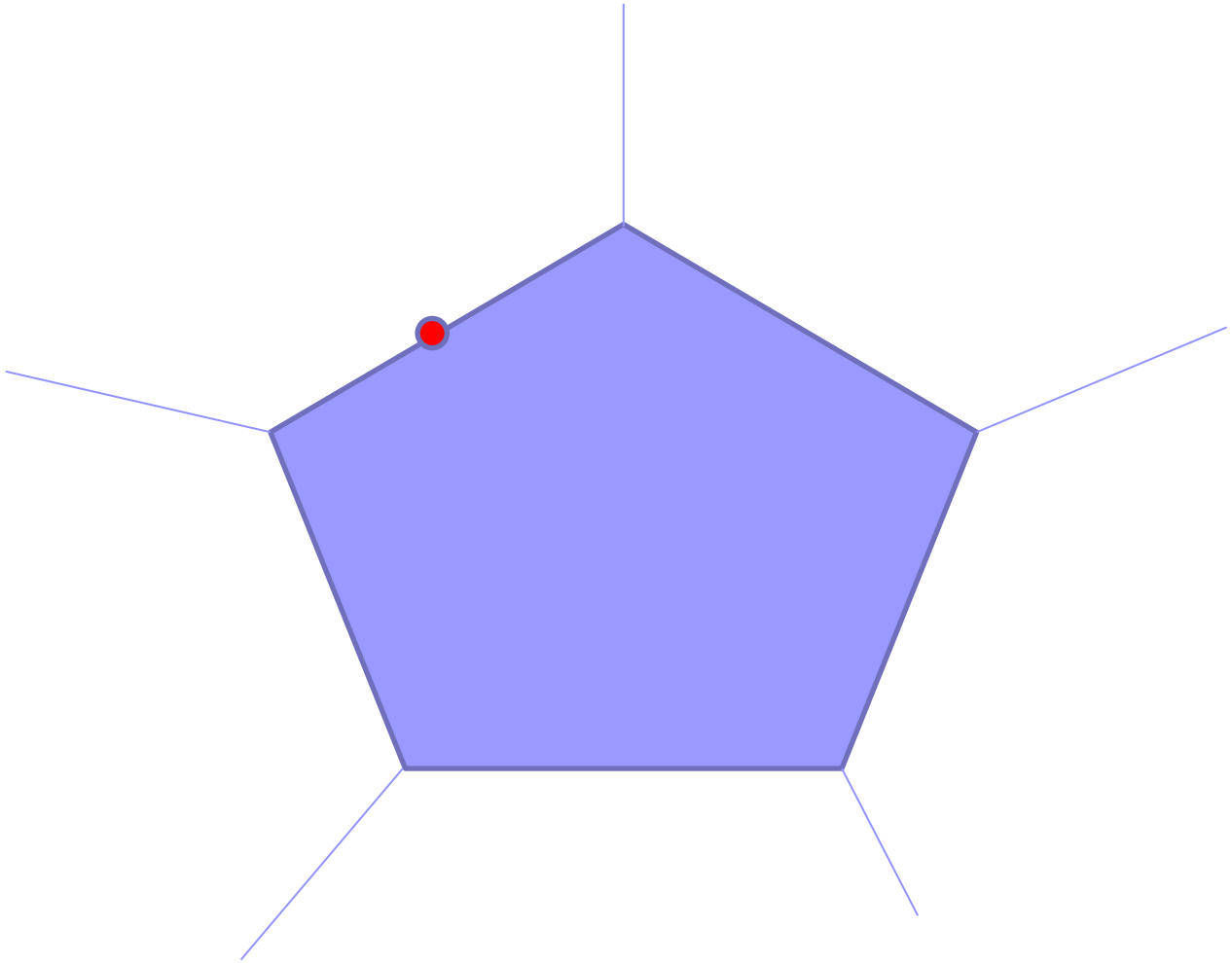

2
1.5
1
0.5
0
-0.5
-1
-2
-1
0
1
2


2
1
0
-1
-2
-2
-1
0
1
2
q2
q1



instantaneous change of densities …

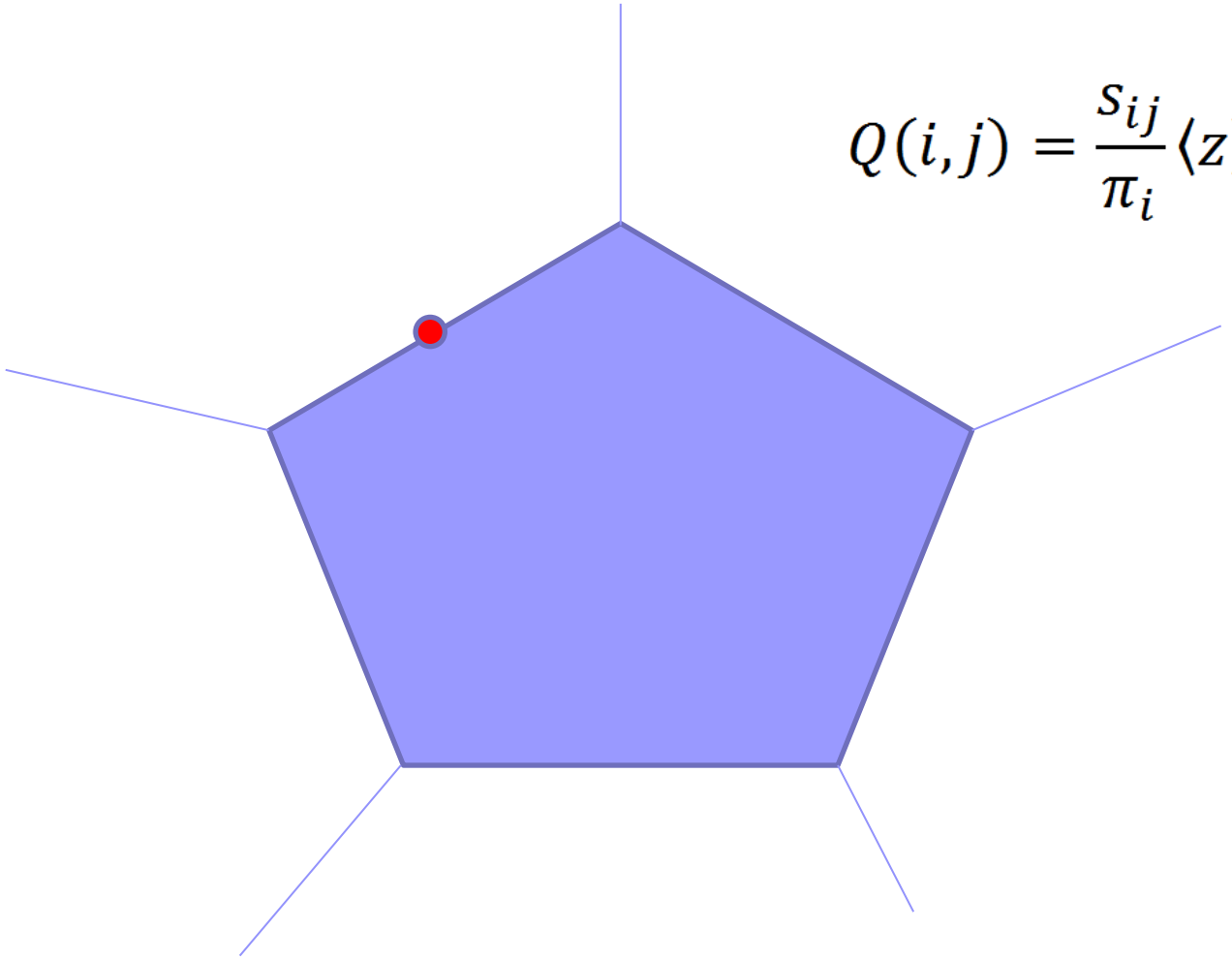
Theorem of Gauß



instantaneous change of densities …

Theorem of Gauß

$$Q(i,j) = \frac{s_{ij}}{\pi_i}\langle z \rangle_{ij}$$



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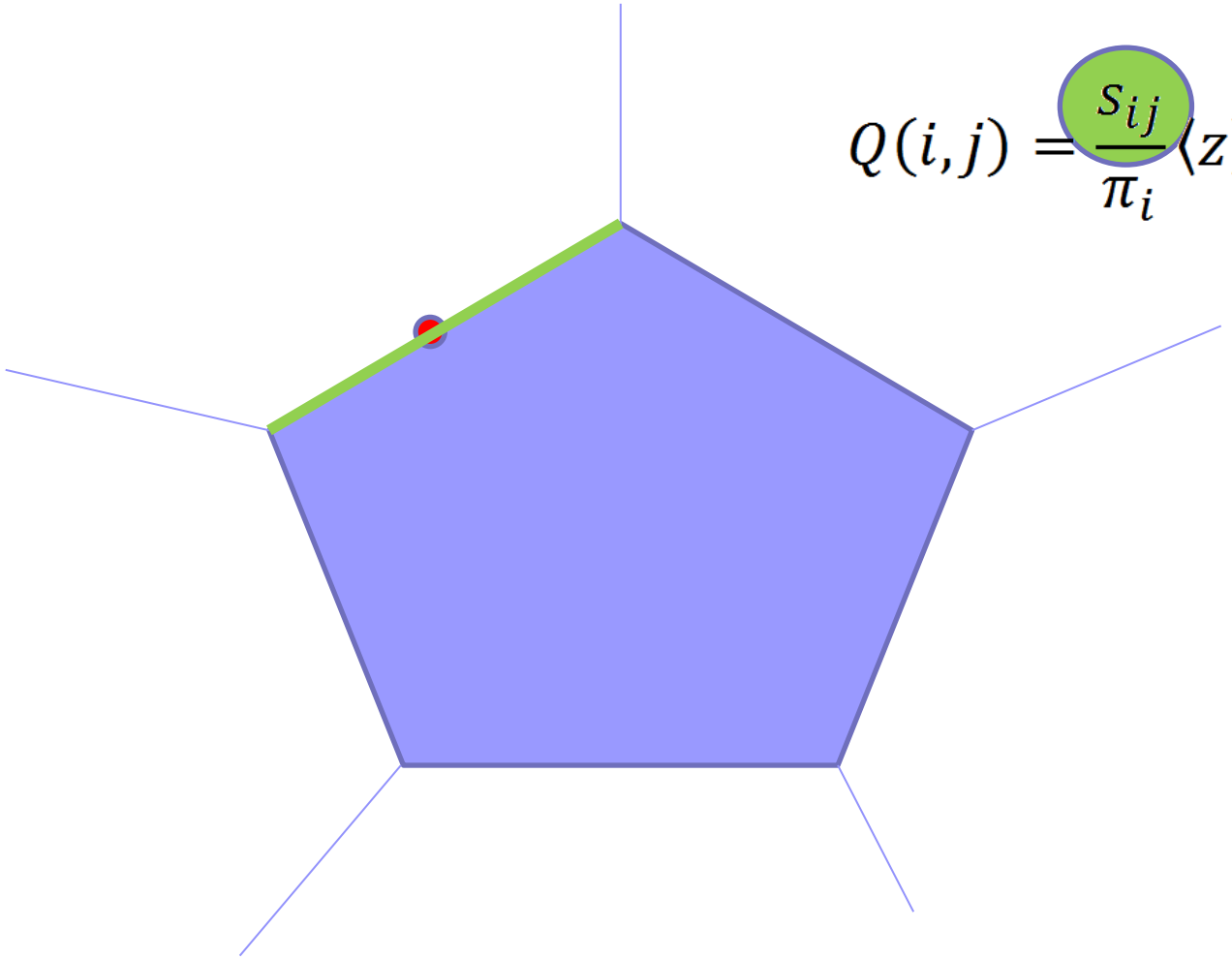

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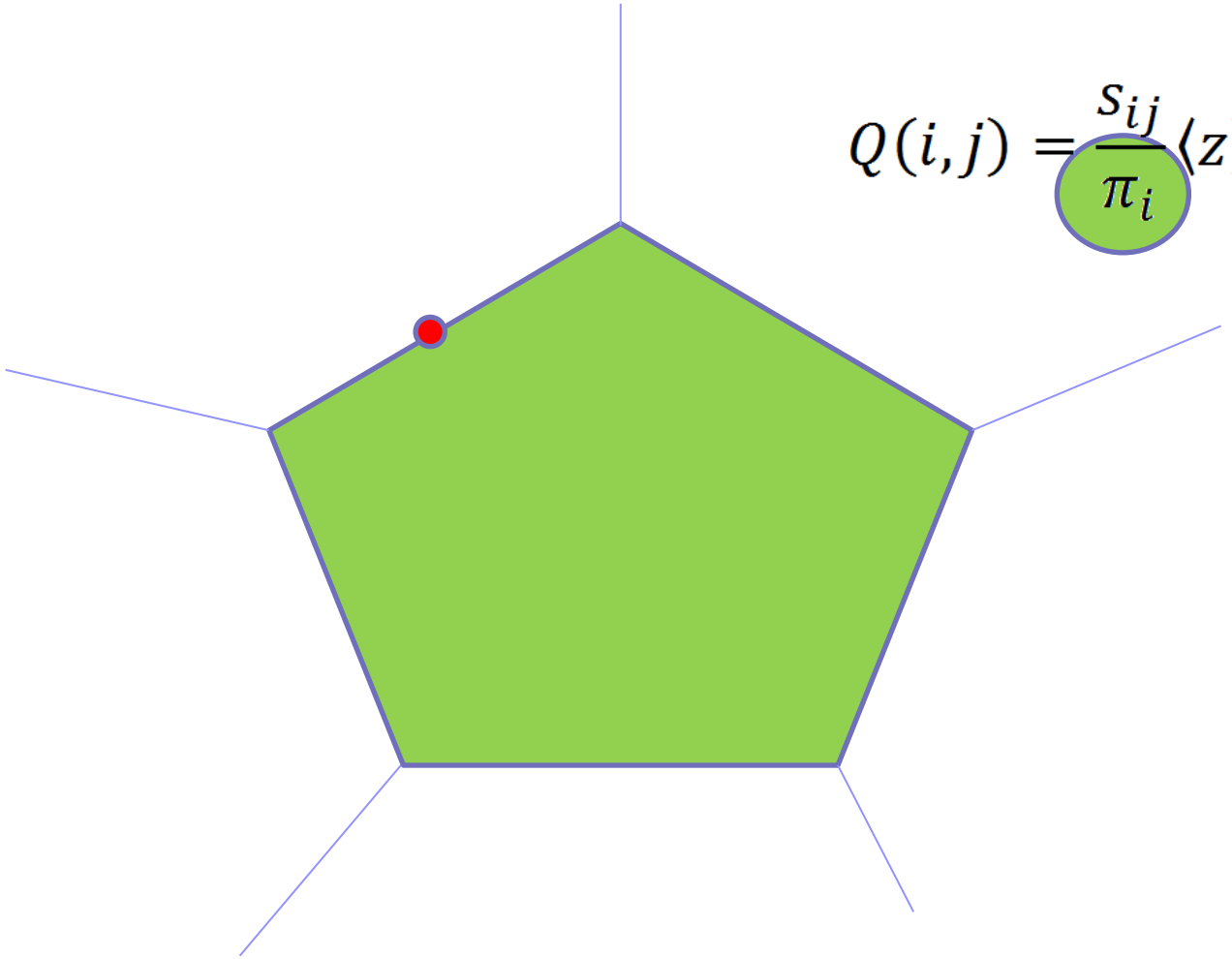

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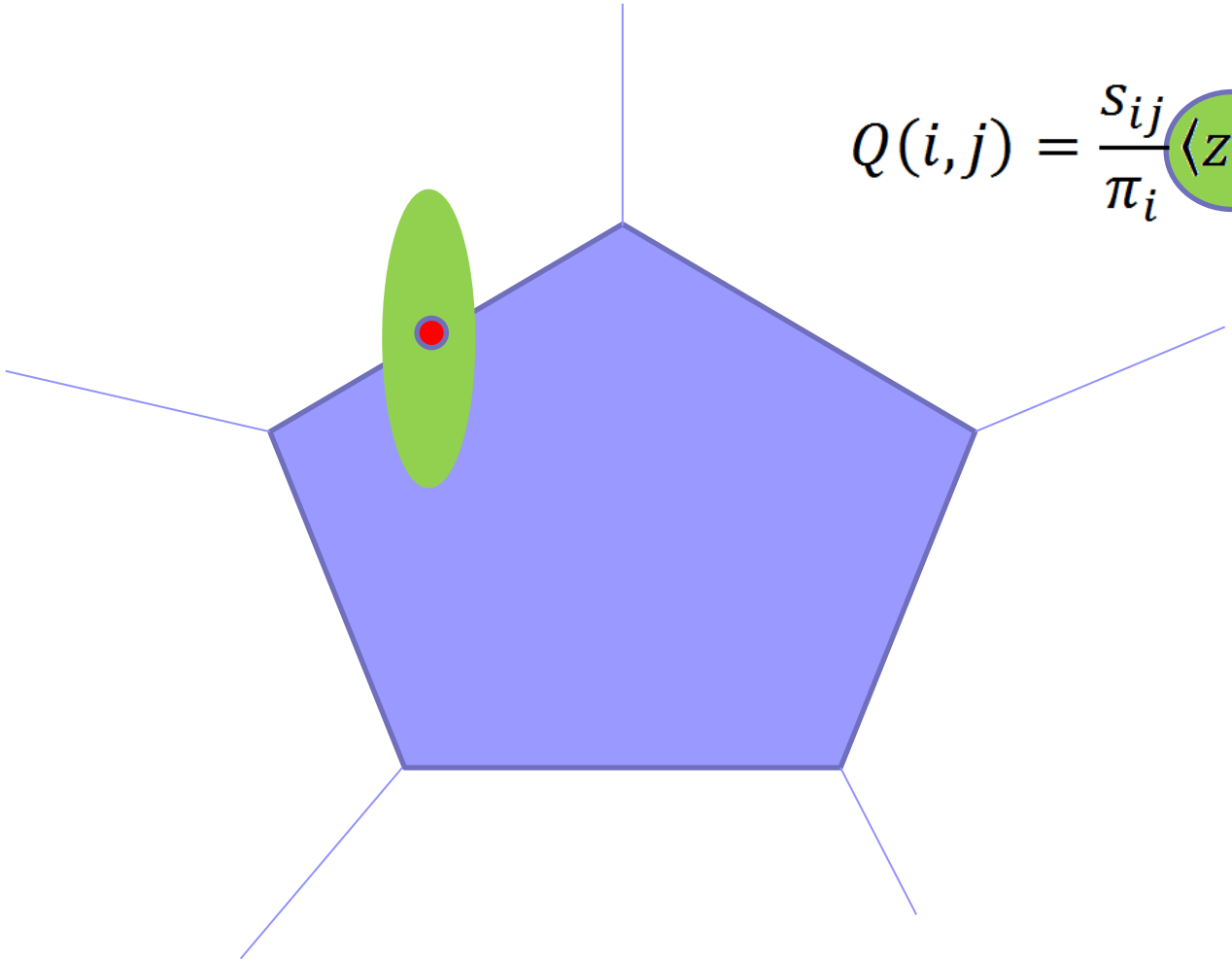
Wb, 2010



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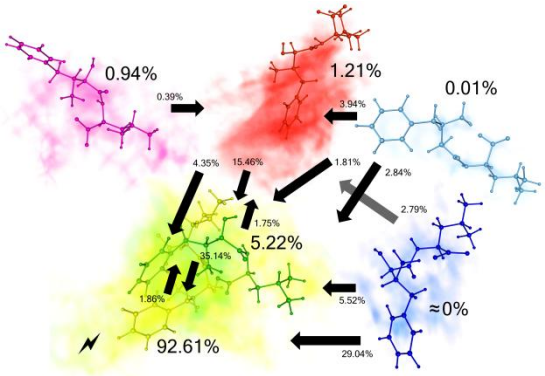
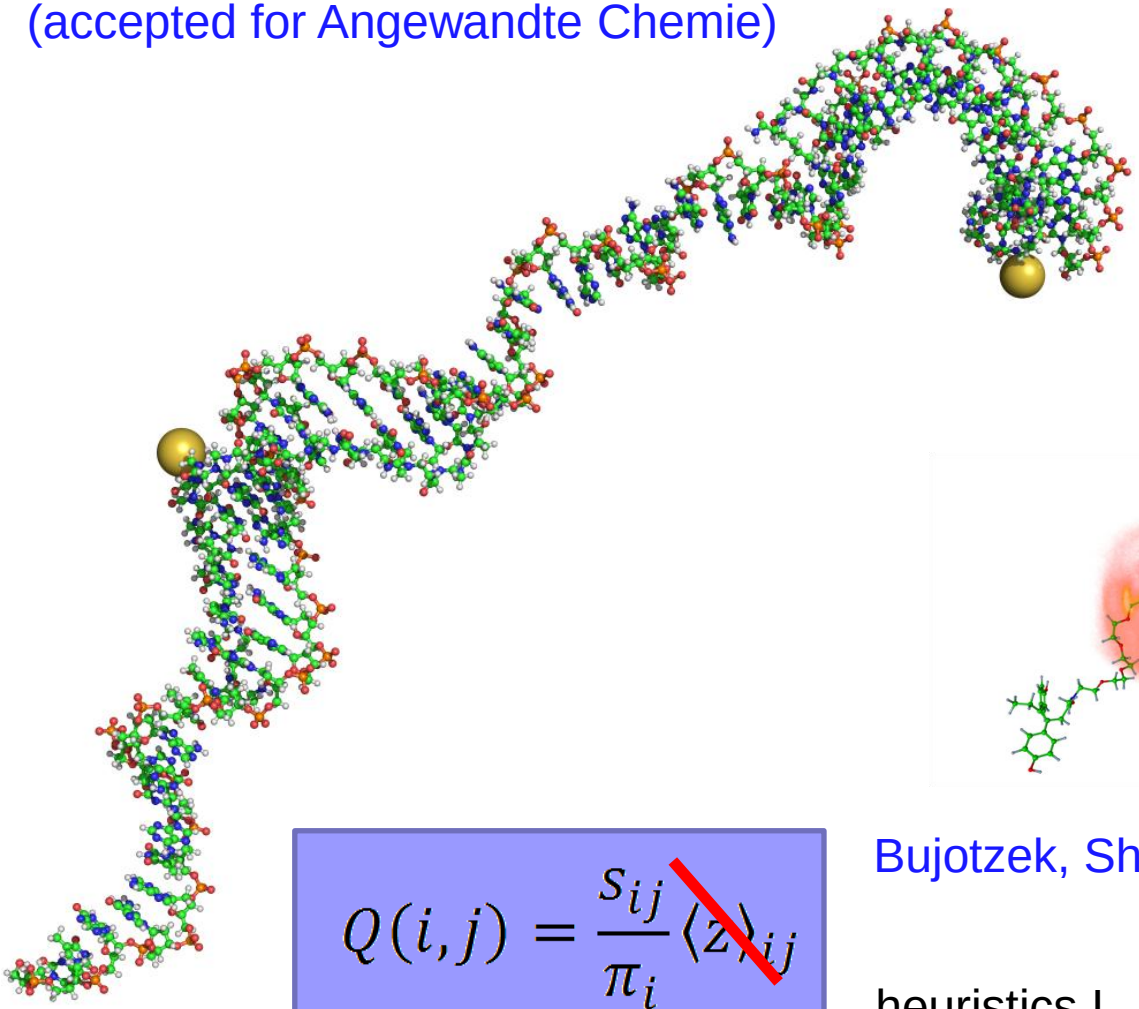
Theorem of Gauß

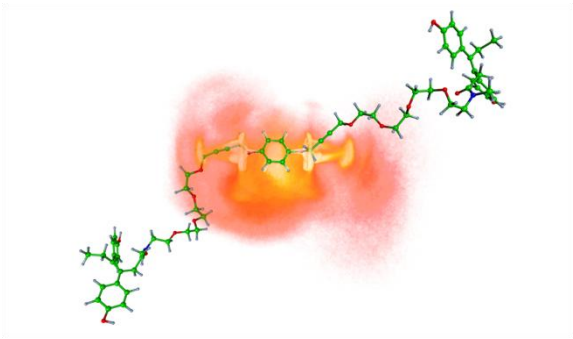


Example: APN binding path

Method	Complexity	Computing Time
Long-time MD	$O(1/(1-\lambda_2))$	$\lambda_2 \approx 1$, unsolvable (hundred years)
Conformation Dynamics (w/o Gauß)	O(m/r)	m=335, worst ratio $r=10^{-7}$ (months)
Theorem of Gauß	O(m*f)	m=335, f=22 (one week)

Abendroth, Bujotzek, Shan, Haag, W., Seitz, 2011
(accepted for Angewandte Chemie)





$$Q(i,j) = \frac{s_{ij}}{\pi_i}\langle z \rangle_{ij}$$

μ

Bujotzek, Shan, Haag, Wb, 2011

heuristics I

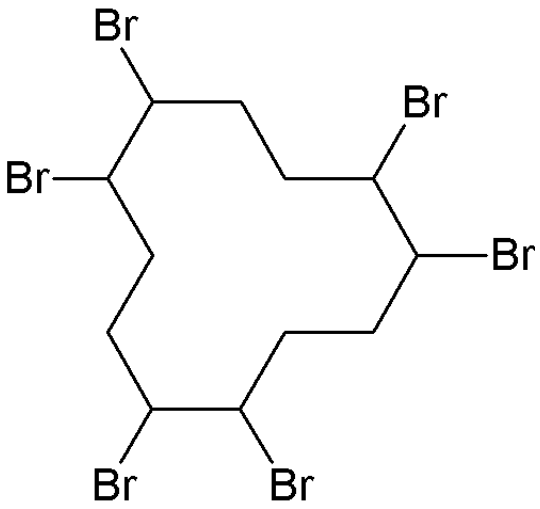
Transition Rates

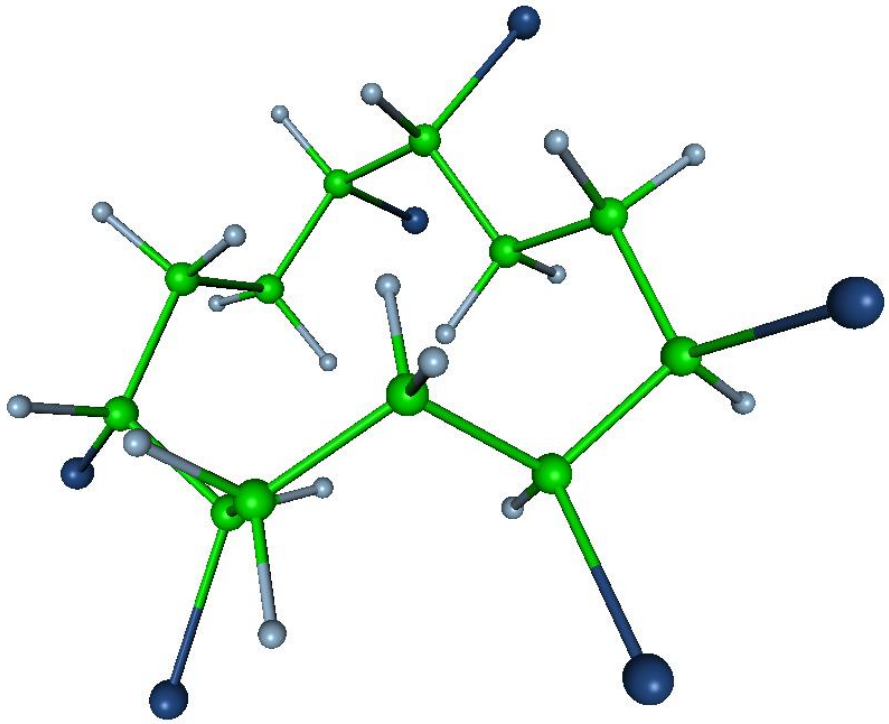
Infinitesimal Generator

Algorithmic Approach

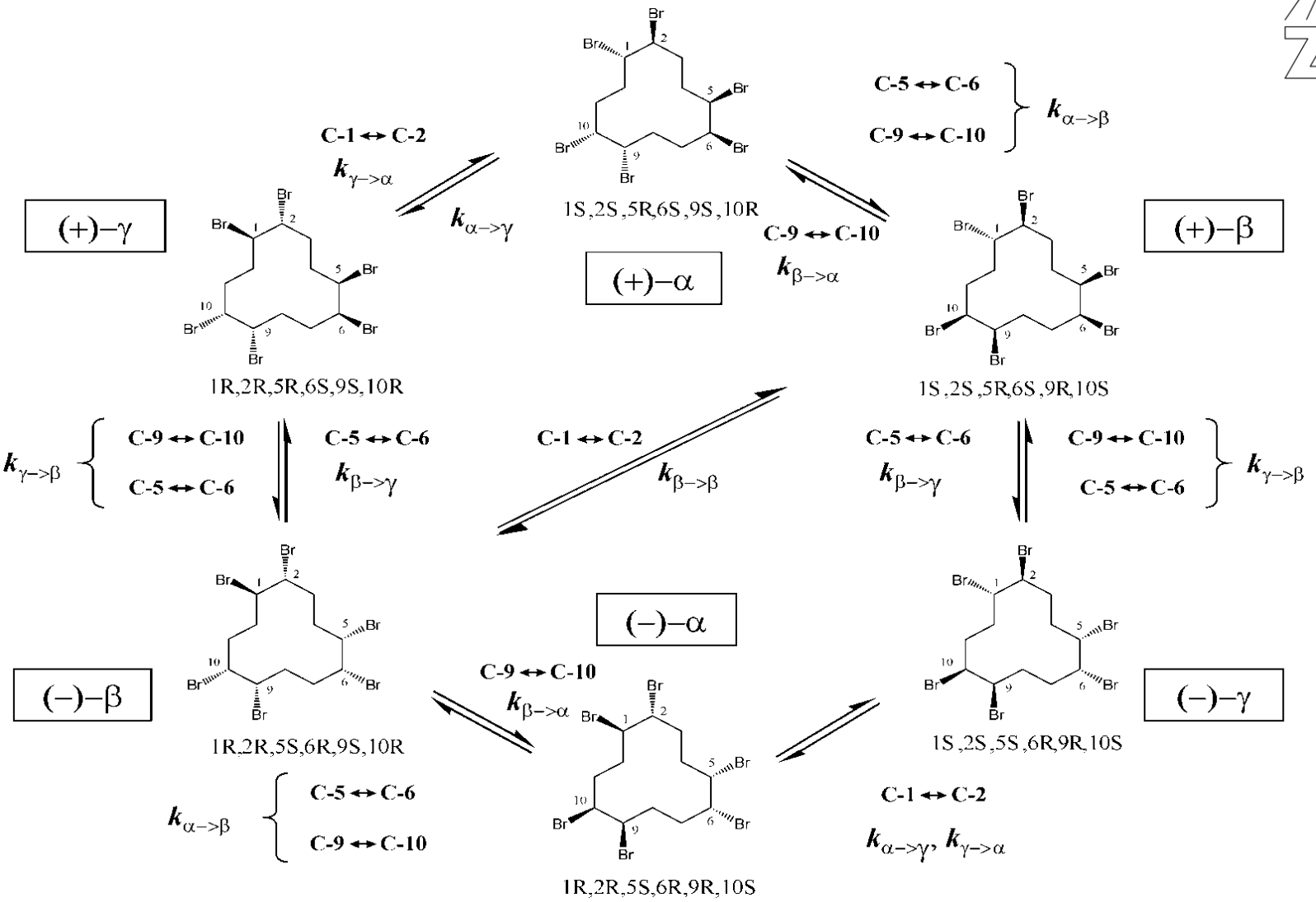
Estimation of Timescales

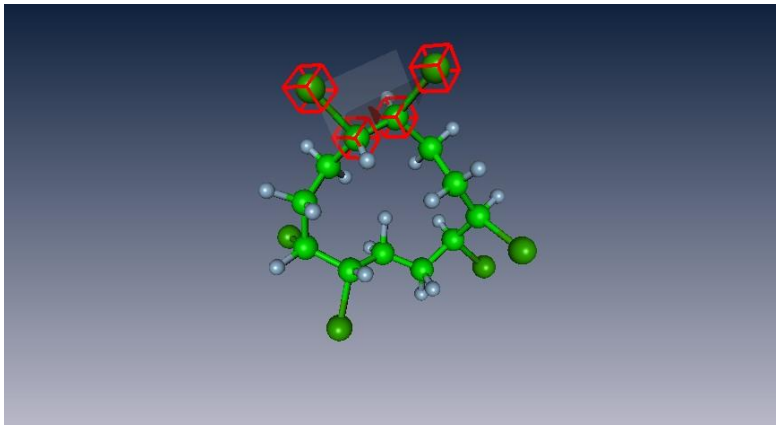
Interconversion of HBCD

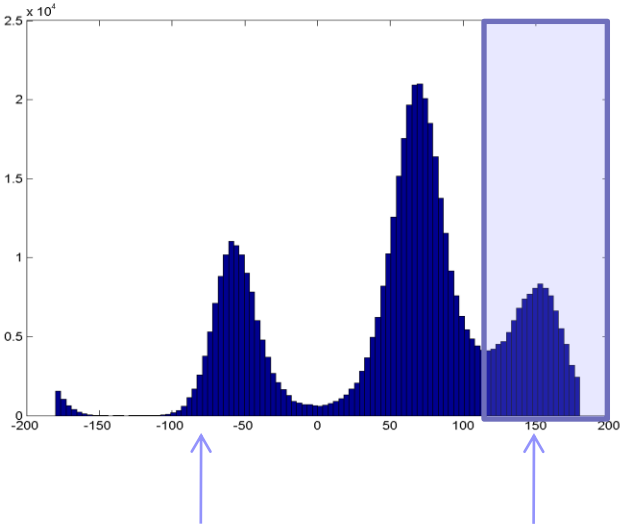




Wb, Becker, Köppen, Durmaz , 2008

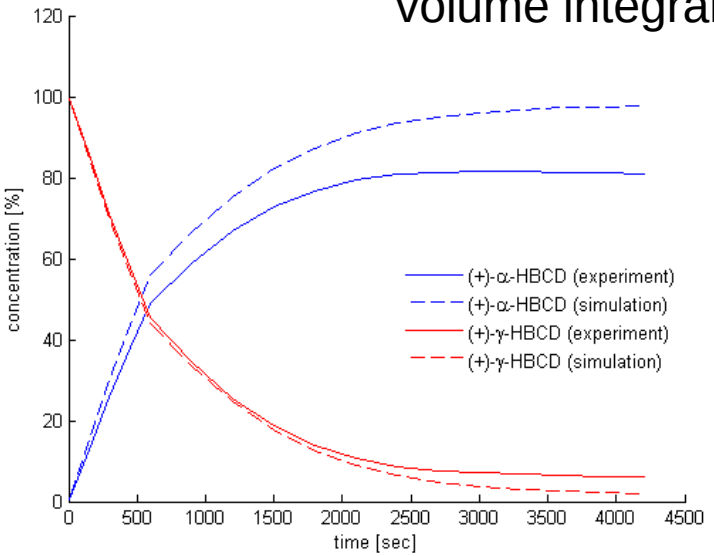

C-1 ↔ C-2
$k_{\gamma->\alpha}$
$k_{\alpha->\gamma}$
C-5 ↔ C-6
C-9 ↔ C-10
$k_{\alpha->\beta}$
(+)−γ
(+)−α
(+)−β
C-9 ↔ C-10
$k_{\beta->\alpha}$
1S,2S,5R,6S,9S,10R
1R,2R,5R,6S,9S,10R
1S,2S,5R,6S,9R,10S
$k_{\gamma->\beta}$
C-9 ↔ C-10
C-5 ↔ C-6
C-5 ↔ C-6
$k_{\beta->\gamma}$
C-1 ↔ C-2
$k_{\beta->\beta}$
C-5 ↔ C-6
$k_{\beta->\gamma}$
C-9 ↔ C-10
C-5 ↔ C-6
$k_{\gamma->\beta}$
(−)−α
(−)−β
(−)−γ
C-9 ↔ C-10
$k_{\beta->\alpha}$
1R,2R,5S,6R,9S,10R
1S,2S,5S,6R,9R,10S
$k_{\alpha->\beta}$
C-5 ↔ C-6
C-9 ↔ C-10
C-1 ↔ C-2
$k_{\alpha->\gamma}$, $k_{\gamma->\alpha}$
1R,2R,5S,6R,9R,10S





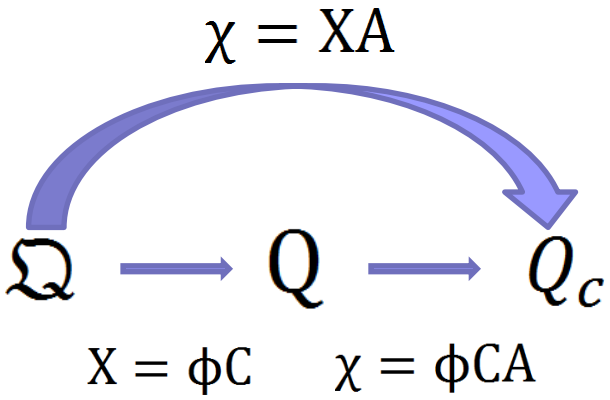
volume integral „surface“ integral

heuristics II



Interconversion rates	chemical experiment	theory	
$k_{\alpha\to\gamma}$	$1{,}4\times10^{-4}$	$1{,}65\times10^{-4}$	
$k_{\alpha\to\beta}$	$1{,}9\times10^{-5}$	$0{,}8\times10^{-5}$	
$k_{\beta\to\alpha}$	$1{,}2\times10^{-4}$	$0{,}4\times10^{-4}$	
$k_{\beta\to\gamma}$	$1{,}7\times10^{-4}$	$2{,}1\times10^{-5}$	
$k_{\gamma\to\beta}$	$1{,}5\times10^{-4}$	$1{,}6\times10^{-5}$	
$k_{\gamma\to\alpha}$	$1{,}5\times10^{-3}$	$1{,}5\times10^{-3}$	←
$k_{\beta\to\beta}$	$1{,}1\times10^{-3}$	$0{,}9\times10^{-3}$	←

Conclusion



Theory

pro Q is a Galerkin discretization: Theorem of Gauß

con Q is not a rate matrix: handle projection error

Experiment

pro main processes identified, correct sorting

con modelling errors: force field

heuristics: anisotropic velocity fields, surface integral

Thank you for your attention!