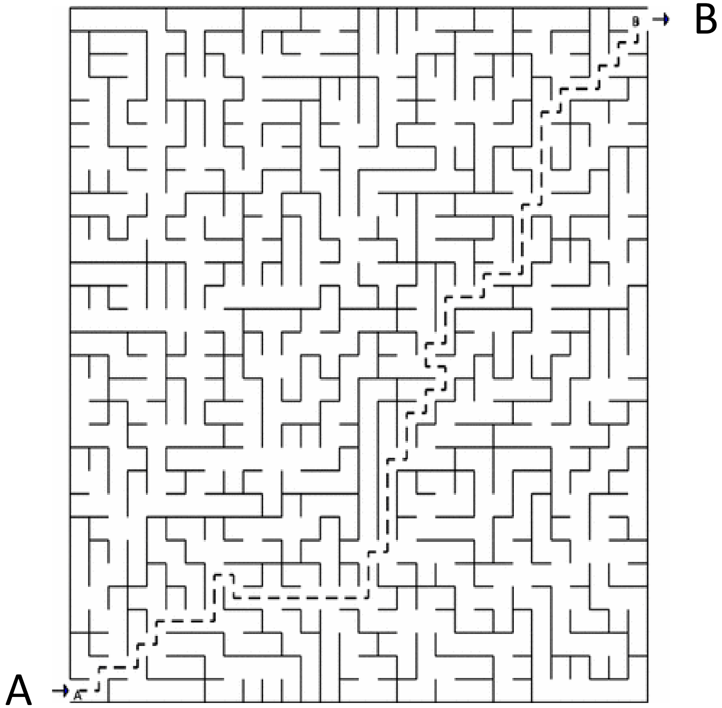
Learning Rates and Pathways of Molecular Conformational Changes

MARCUS WEBER (ZIB, BERLIN)
BIOINFORMATICS IN BERGEN BIB2023
24.05.2023

Reaction Pathways



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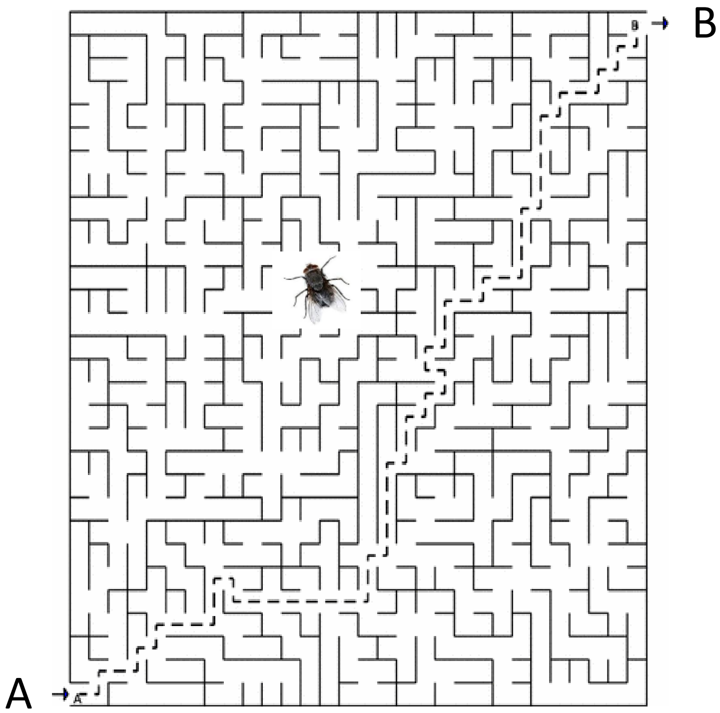

What is the probability to reach B and not reach A?

Close A. What is the mean residence time in the maze?

How much does this „microstate“ belong to the „macrostate“ B?

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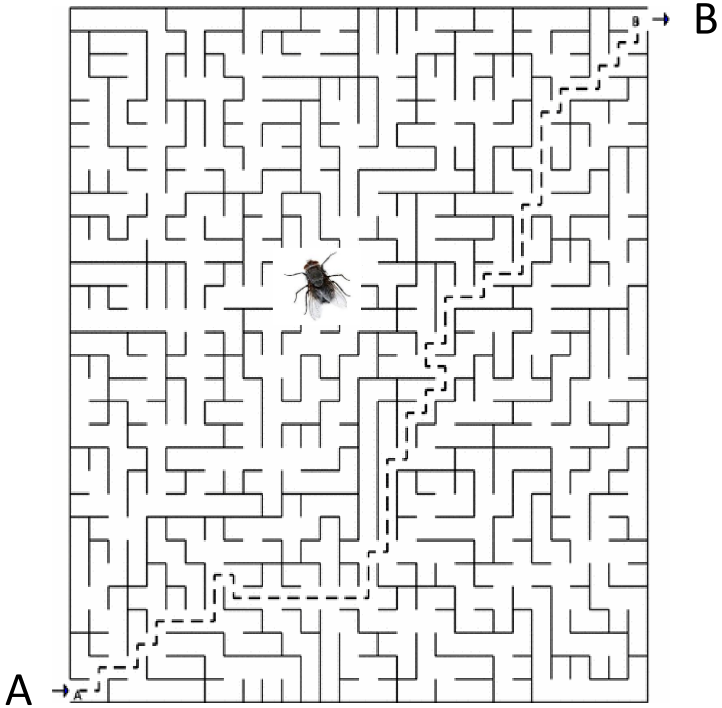
Reaction Pathways



What is the probability to reach B and not reach A? $Q\chi = 0$

Close A. What is the mean residence time in the maze? $Q(1-\chi) = -c_1$

How much does this „microstate“ belong to the „macrostate“ B? $Q\chi \approx 0$

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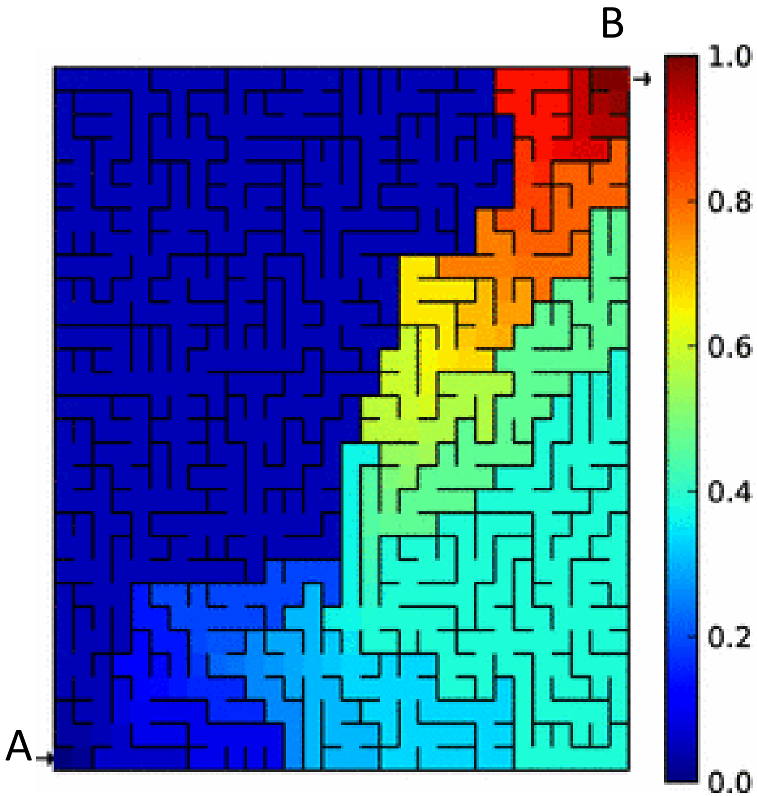

$$\chi_B\colon \mathbb{R}^n \to [0,1]$$

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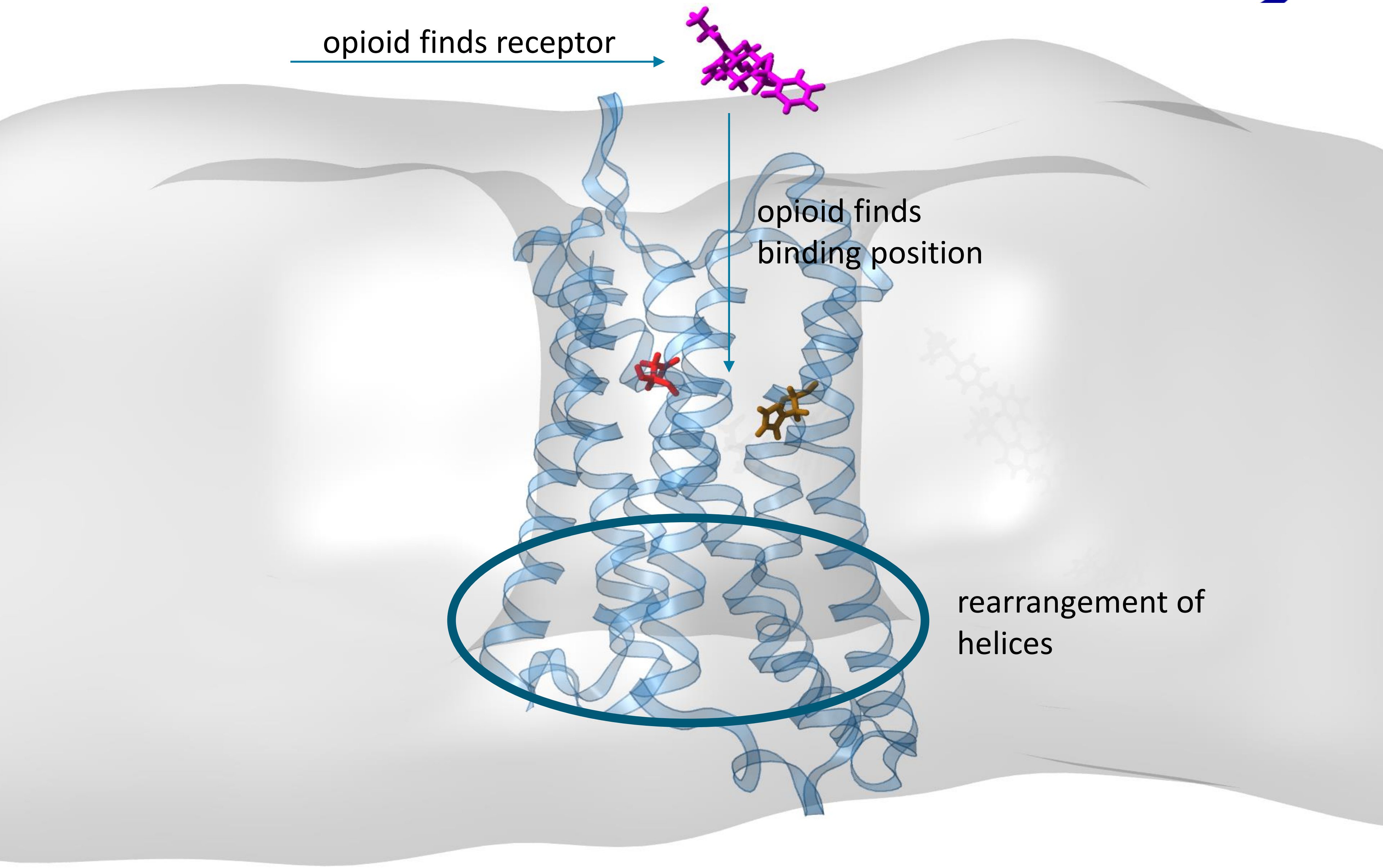
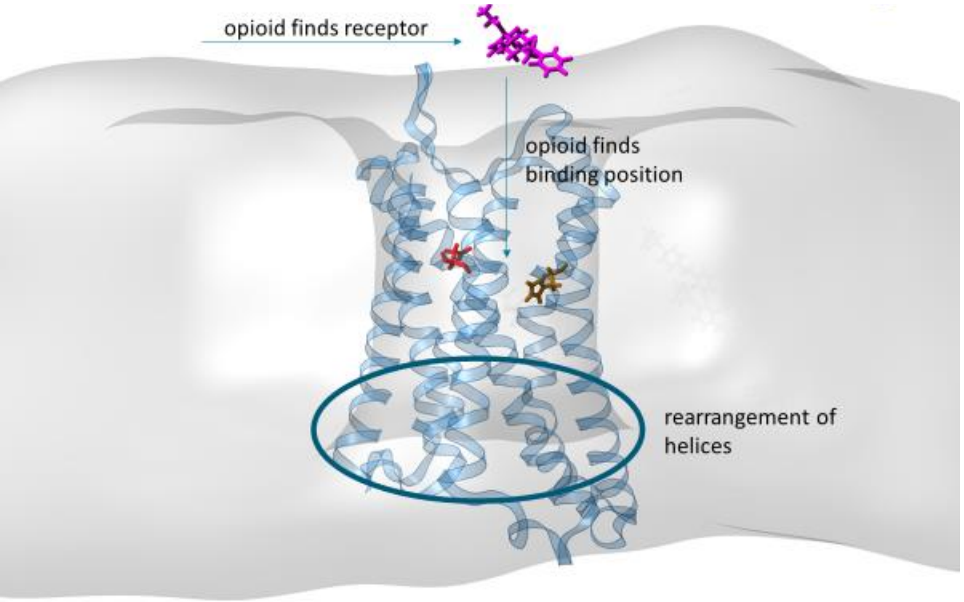
What happens at the opioid receptor?



Research questions

- transition rates (on- versus off-process)
- definition of what is on/off/intermediate
- binding path
- which coordinates can be used to identify the macrostate(s)?
- which “coordinates“ influence macroscopic changes?



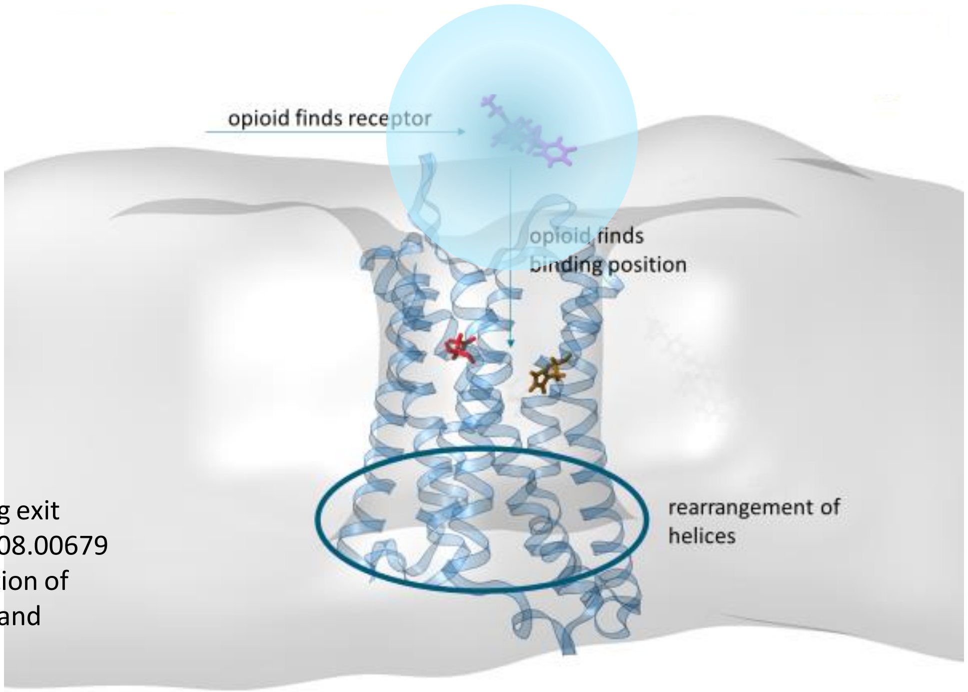
Research questions

- transition rate and times (on- versus off-process) $c_1, \frac{1}{c_1}\chi$
- definition of what is on/off/intermediate χ
- binding path $-\nabla\chi$
- which coordinates can be used to identify the macrostate(s)? χ(x)
- which “coordinates“ influence macroscopic changes?

$$\chi: \mathbb{R}^{3N} \to [0,1]$$

membership function

(projection without memory)



M.Weber, N. Ernst: A fuzzy-set theoretical framework for computing exit rates of rare events in potential-driven diffusion processes, arXiv:1708.00679
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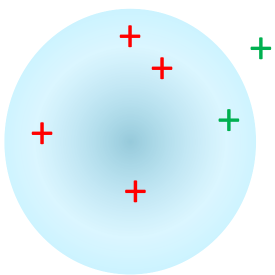

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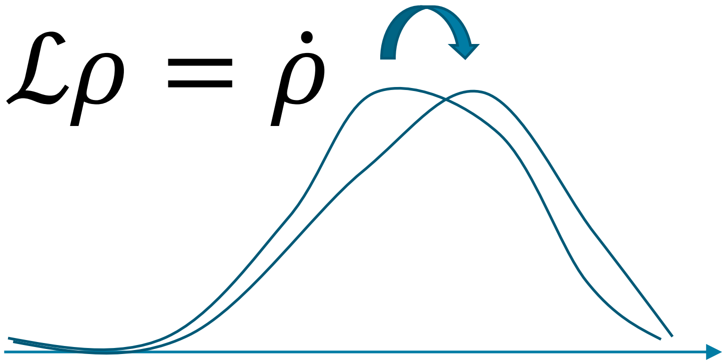
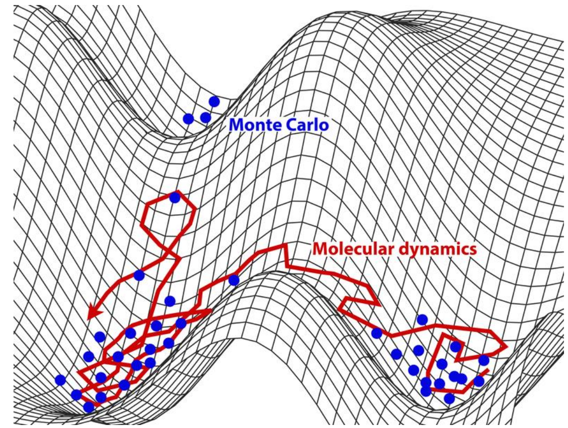
Density based point of view

$$\mathcal{L}\rho = \dot{\rho}$$





https://commons.wikimedia.org/wiki/File:Sampling_in_Monte_Carlo_and_molecular_dynamics.png

$$\mathcal{L} = "OLD"$$

$$\mathcal{L}^* = -\nabla V(x)\,\nabla \, + \frac{\sigma^2}{2}\Delta$$

L. Donati, M. Heida, B. G. Keller, M. Weber: Estimation of the infinitesimal generator by square-root approximation. *J. Phys.: Condens. Matter*, 30(42):425201, 2018

M. Weber: A Subspace Approach to Molecular Markov State Models via a New Infinitesimal Generator, Habilitation Thesis, Freie Universität Berlin, 2011

Solving a PDE

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$$\mathcal{L}^*\chi = -\alpha\chi + c_2$$

$\chi: \mathbb{R}^{3N} \rightarrow [0,1]$

$\alpha = c_1 + c_2$

Solving a PDE

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$$\mathcal{L}^*\chi = -c_1\chi + c_2(1-\chi)$$

$\cdot\, e^{-c_1 t}$

$p_\chi(x,t) := \chi(x)e^{-c_1 t}$

Solving a PDE

$$\mathcal{L}^* p_\chi = -c_1 p_\chi + c_2 p_\chi \frac{1-\chi}{\chi}$$

$$p_\chi(x,t) := \chi(x) e^{-c_1 t}$$

Solving a PDE

$$\mathcal{L}^* p_\chi - c_2 p_\chi \frac{1-\chi}{\chi} = -c_1 p_\chi$$

$$p_\chi(x,t) := \chi(x) e^{-c_1 t}$$

Solving a PDE

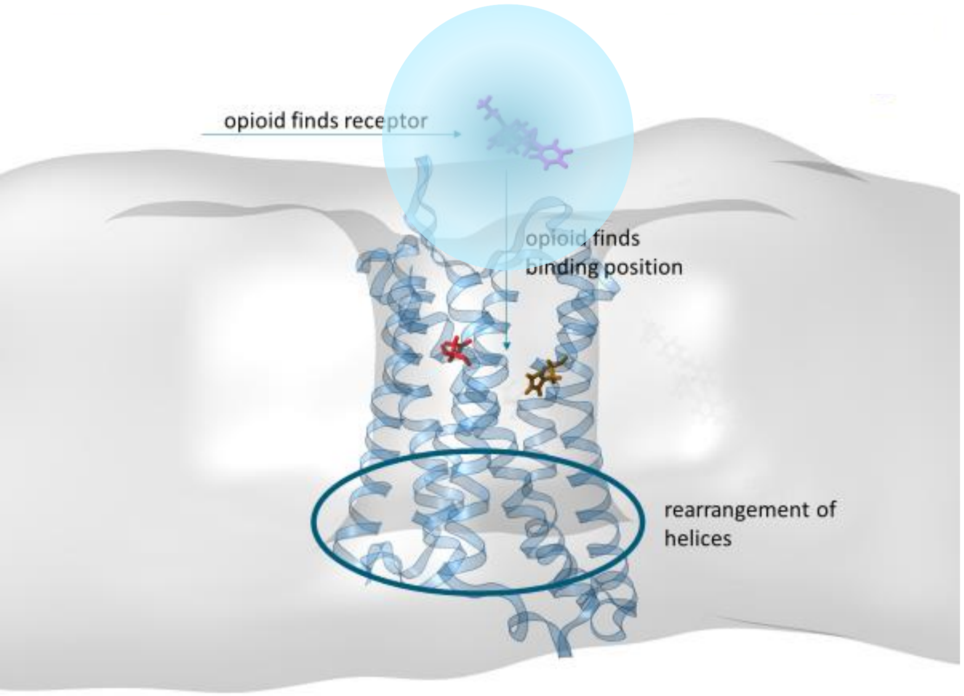
$$\mathcal{L}^* p_\chi - c_2 p_\chi \frac{1-\chi}{\chi} = \frac{\partial p_\chi}{\partial t}$$

$$p_\chi(x,0) = \chi(x)$$

Feynman-Kac

$$p_\chi(x,\tau) = E\left[\chi(x_\tau)\cdot \exp\left(-c_2\int_0^\tau \frac{1-\chi(x_r)}{\chi(x_r)}\right) \mid x_0 = x\right]$$

$$p_\chi(x,t) := \chi(x)e^{-c_1 t}$$



Koopman Operator

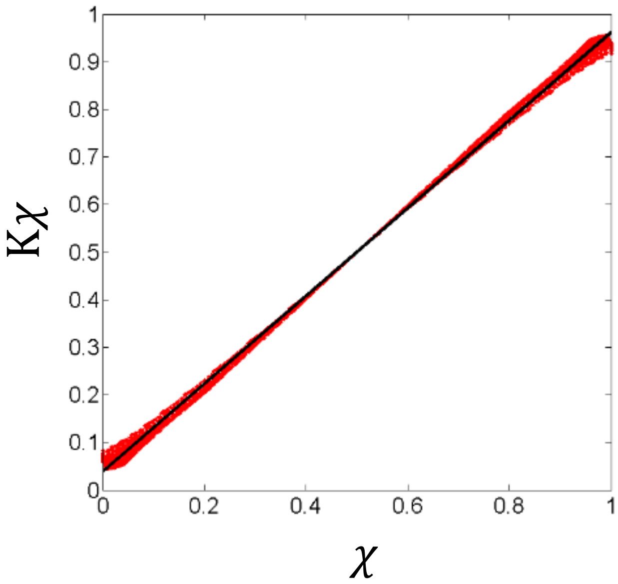
$$(Kf)(x) = E[f(x_\tau)|x_0 = x]$$

$$K = \exp(\tau\mathcal{L}^*)$$

Computation &
Theory

Algorithmic Idea

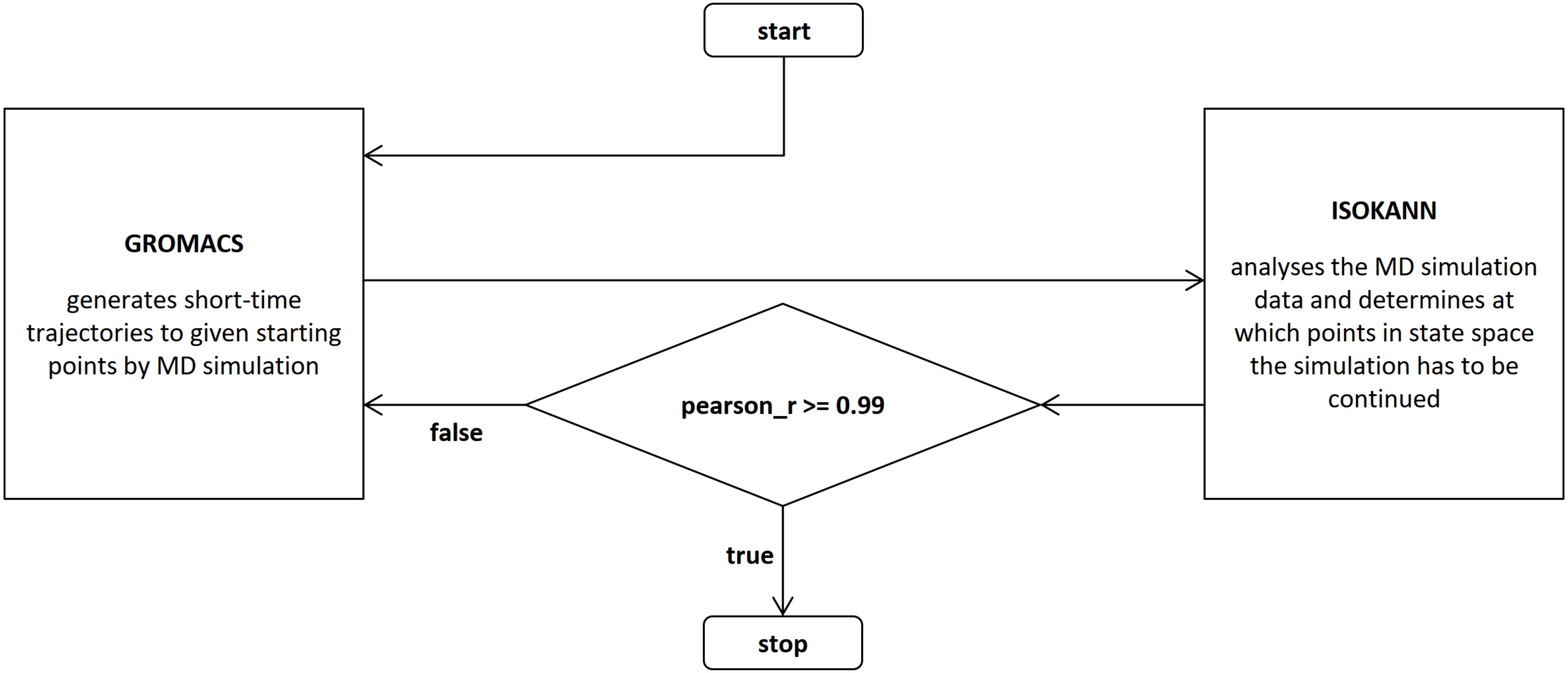
$$\mathcal{L}^*\chi = -\alpha\chi + c_2$$
$$\alpha = c_1 + c_2$$



$$K\chi = \exp(\tau\mathcal{L}^*)\,\chi$$
$$= e^{-\tau\alpha}\chi + \frac{c_2}{\alpha}\left(1 - e^{-\tau\alpha}\right)$$
$$= \gamma_1\chi + \gamma_2$$

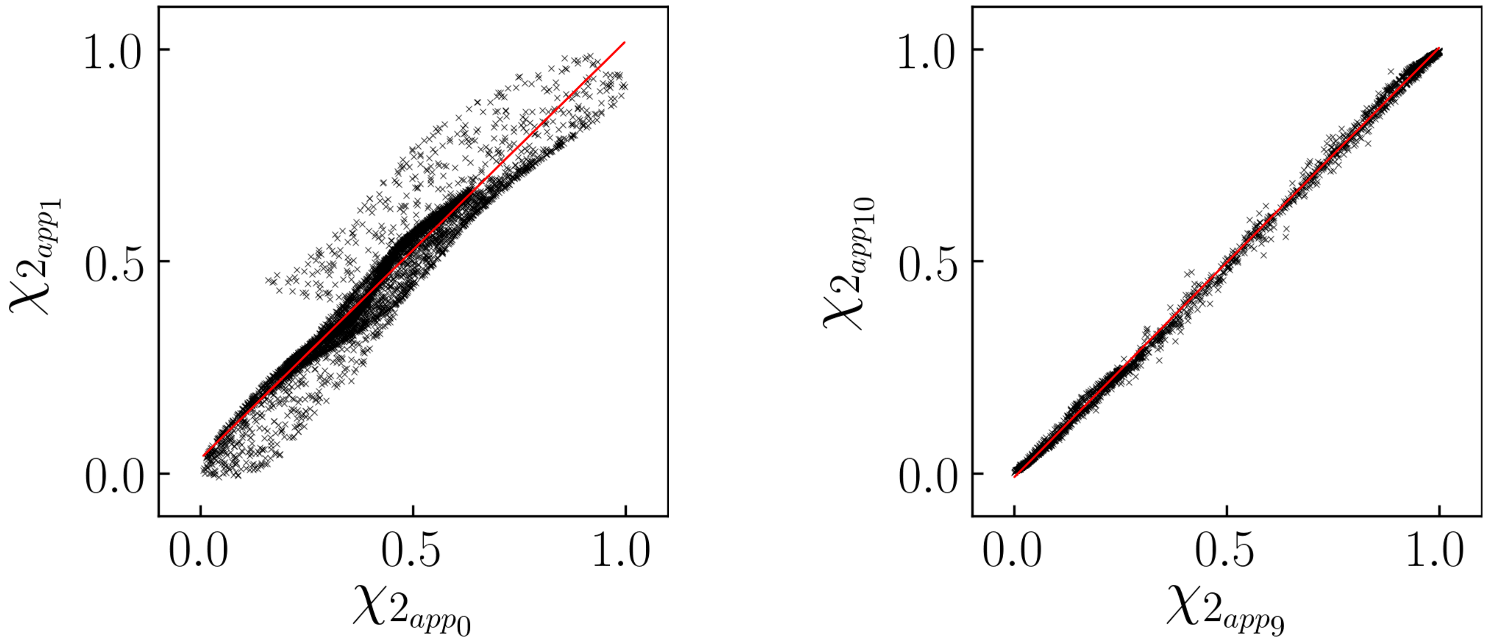
„metastability“

Algorithm ISOKANN



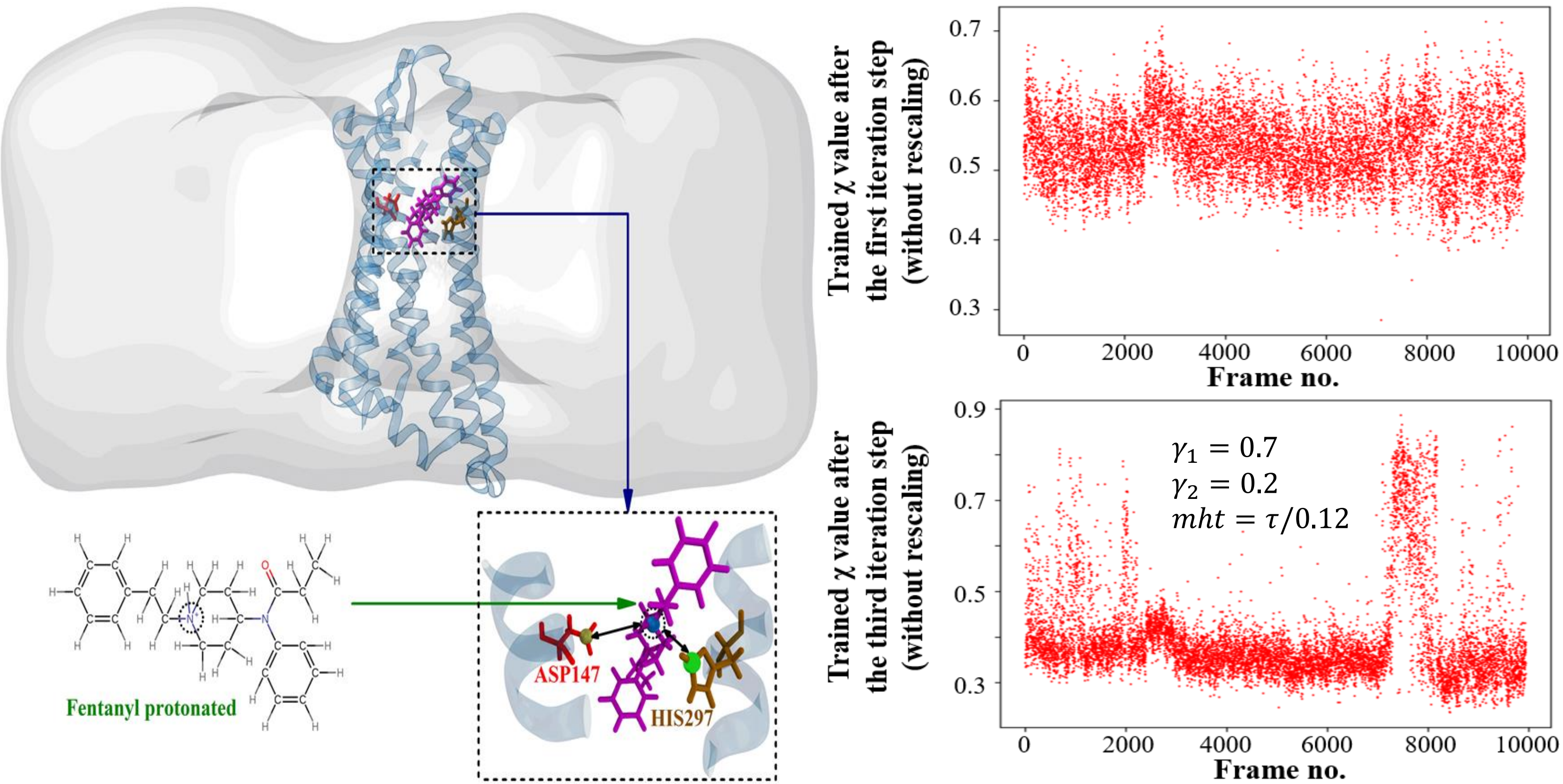
R. J. Rabben, Master Thesis 2022**.**

Stopping criterion



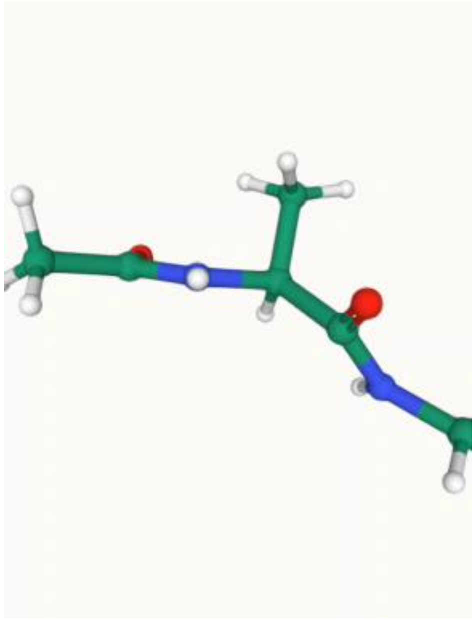
R. J. Rabben, Bachelor Thesis 2019**.**

Results



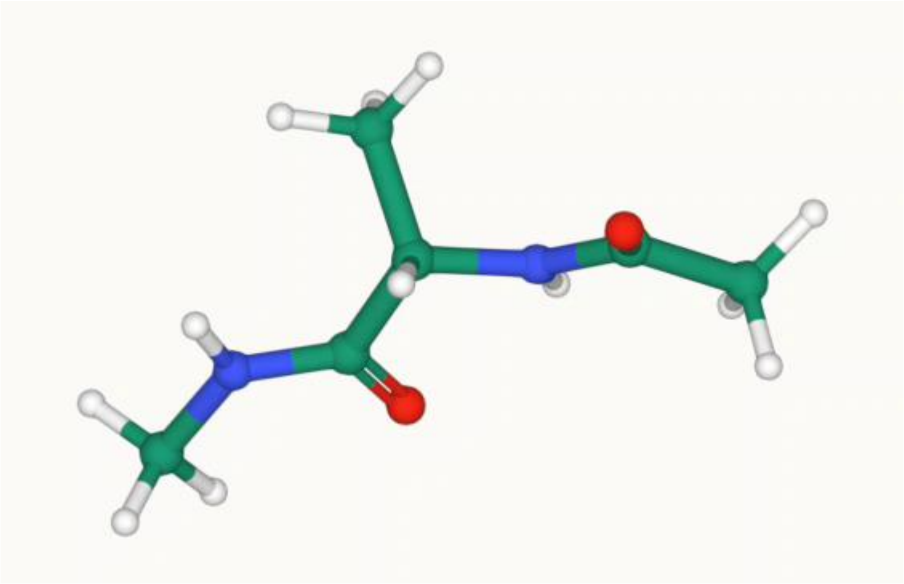
R. J. Rabben, S. Ray, M. Weber: ISOKANN: Invariant subspaces of Koopman Operators learned by a Neural Network.
The J. of Chem. Phys., 153(11):114109, 2020.

Movie



A. Sikorski 2023

Movie



A. Sikorski 2023

Thank you!

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Computational Molecular Design @ ZIB

financial support / guests with scholarships:

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- UniSysCat (Elizaveta Kobeleva)
- MaRDI research data management (Marco Reidelbach)
- Charité (partial payment of patent)

+ guests from universities (Konstantin Fackeldey, Amir Niknejad, …)