Towards a mechanistic understanding of membrane permeability from weighted ensemble simulations in Orion

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Outline

Background on membrane permeation

Our kinetic model of permeability

Evaluation of our kinetic model

Permeation trajectories of a few molecules

Preliminary statistical analysis of our model

Conclusions and future directions

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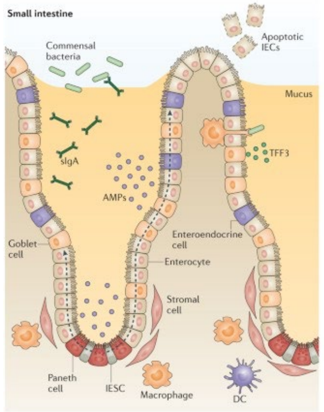
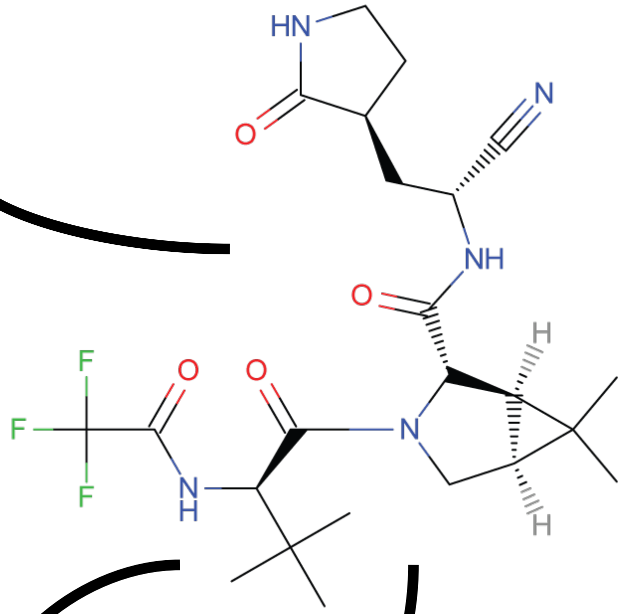
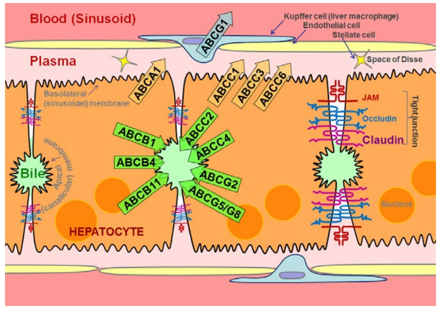
Membrane barriers that drug molecules must cross

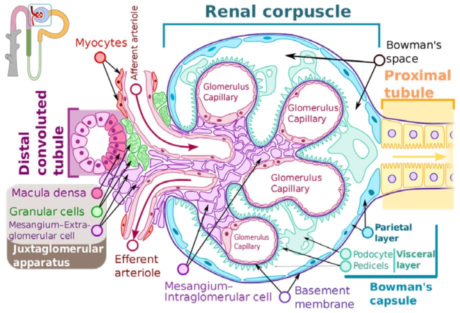


gastrointestinal epithelial cells

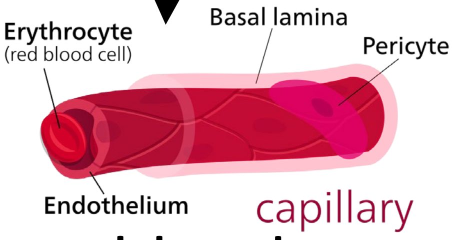




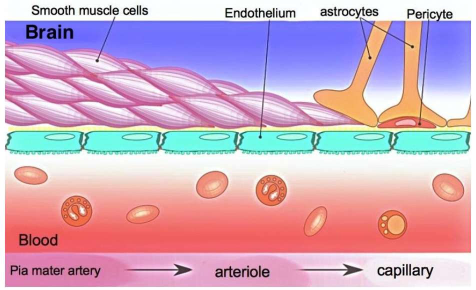
liver cell membrane



kidney cell



blood capillary wall



restrictive organ barriers (BBB)

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Images adapted from: Peterson & Artis, Nat. Immunol., 2014; Wikipedia

How do drugs cross membrane barriers?

Active transport

OPINION

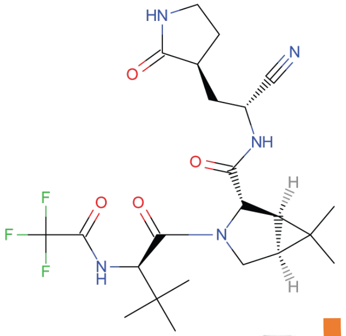
Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule?

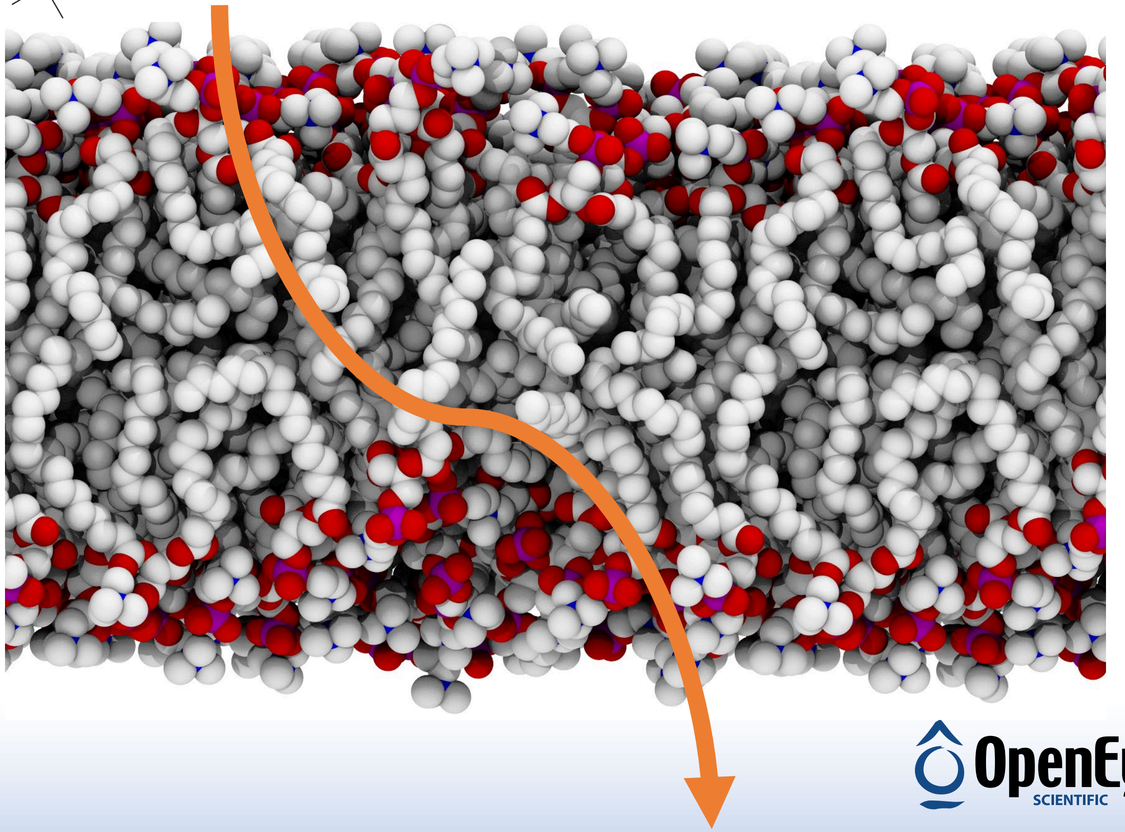
Paul D. Dobson and Douglas B. Kell

Abstract | It is generally thought that many drug molecules are transported across biological membranes via passive diffusion at a rate related to their lipophilicity. However, the types of biophysical forces involved in the interaction of drugs with lipid membranes are no different from those involved in their interaction with proteins, and so arguments based on lipophilicity could also be applied to drug uptake by membrane transporters or carriers. In this article, we discuss the evidence supporting the idea that rather than being an exception, carrier-mediated and active uptake of drugs may be more common than is usually assumed — including a summary of specific cases in which drugs are known to be taken up into cells via defined carriers — and consider the implications for drug discovery and development.

Nat. Rev. Drug. Disc., 2008

Passive transport





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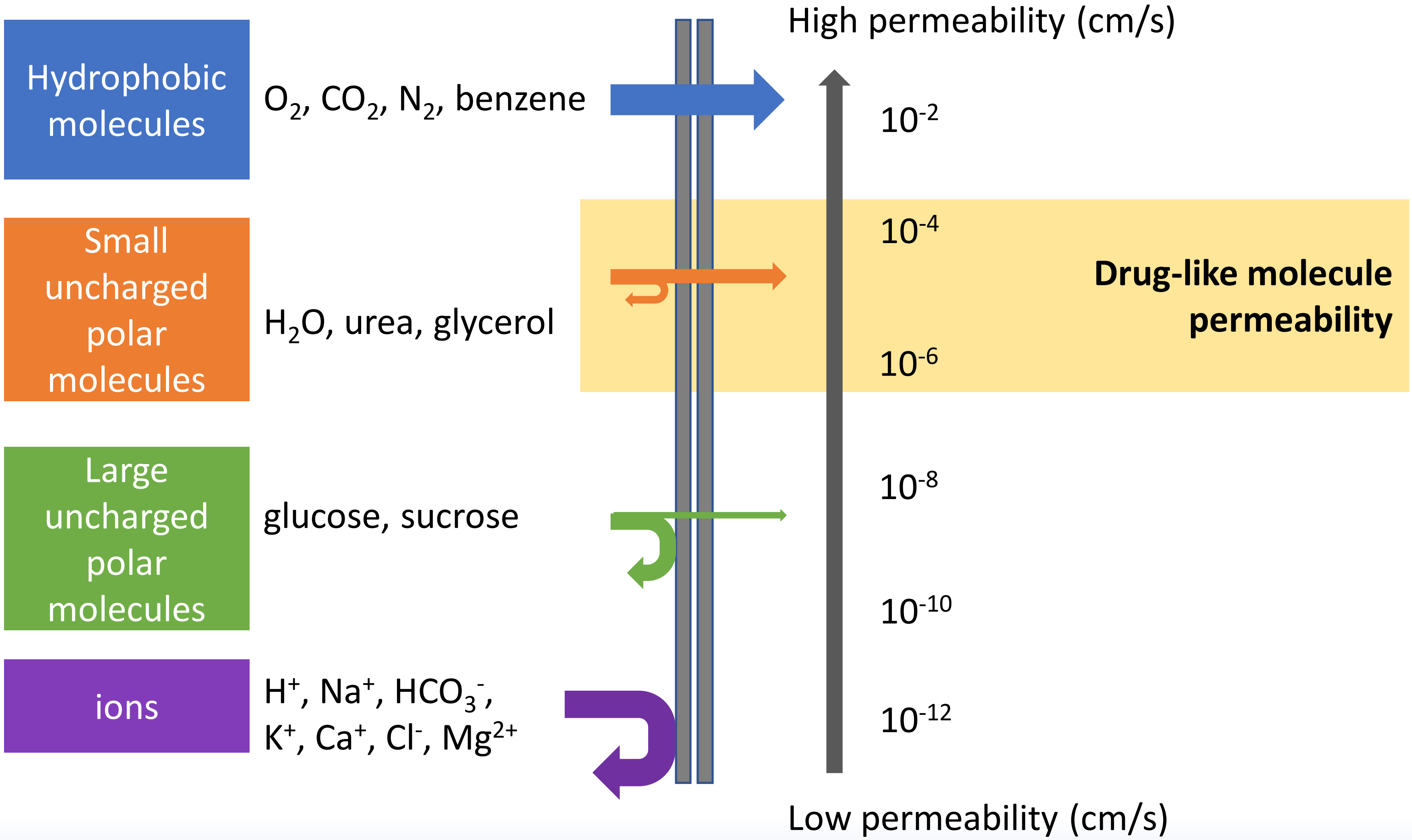
Permeation of various small biomolecules

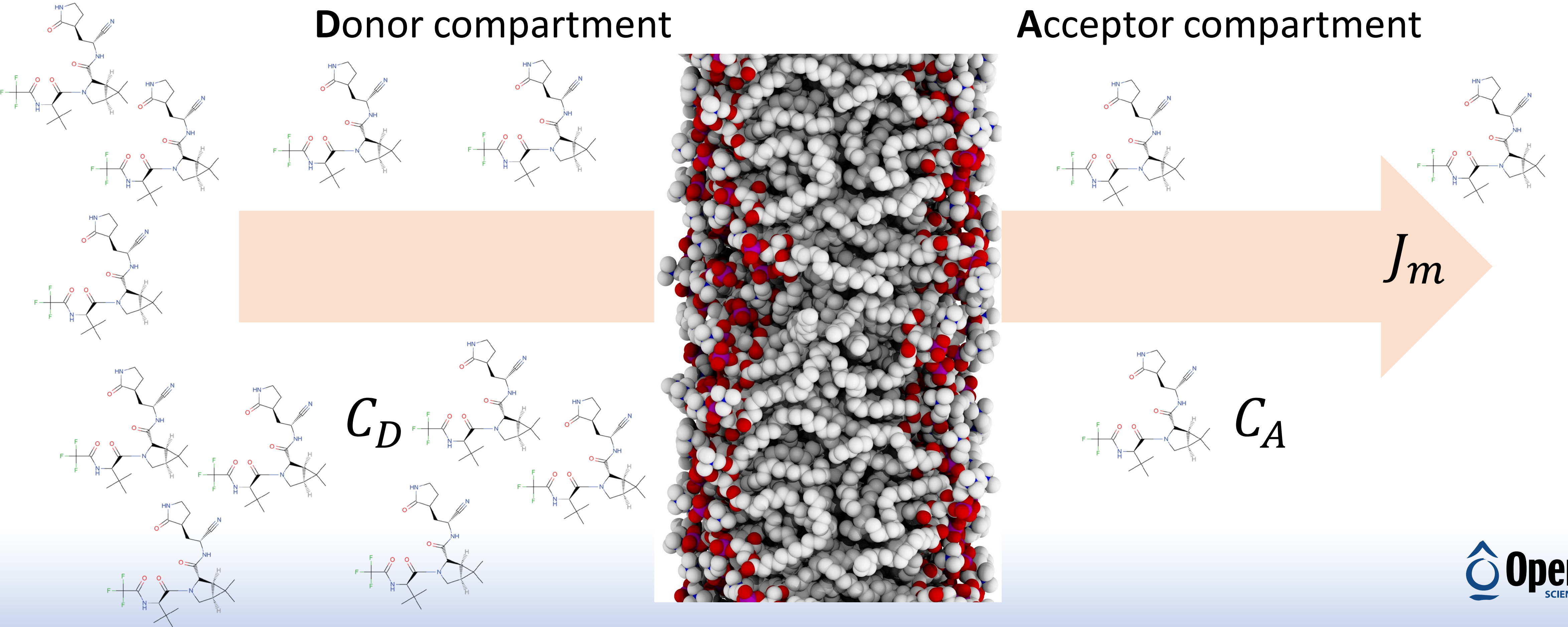


Adapted from *Molecular Biology of the Cell*, B. Alberts et al, 4th ed.

How can one describe membrane permeation?

Permeability coefficient, P_m, from Fick's 1st law of diffusion

$$J_m = P_m(C_D - C_A)$$



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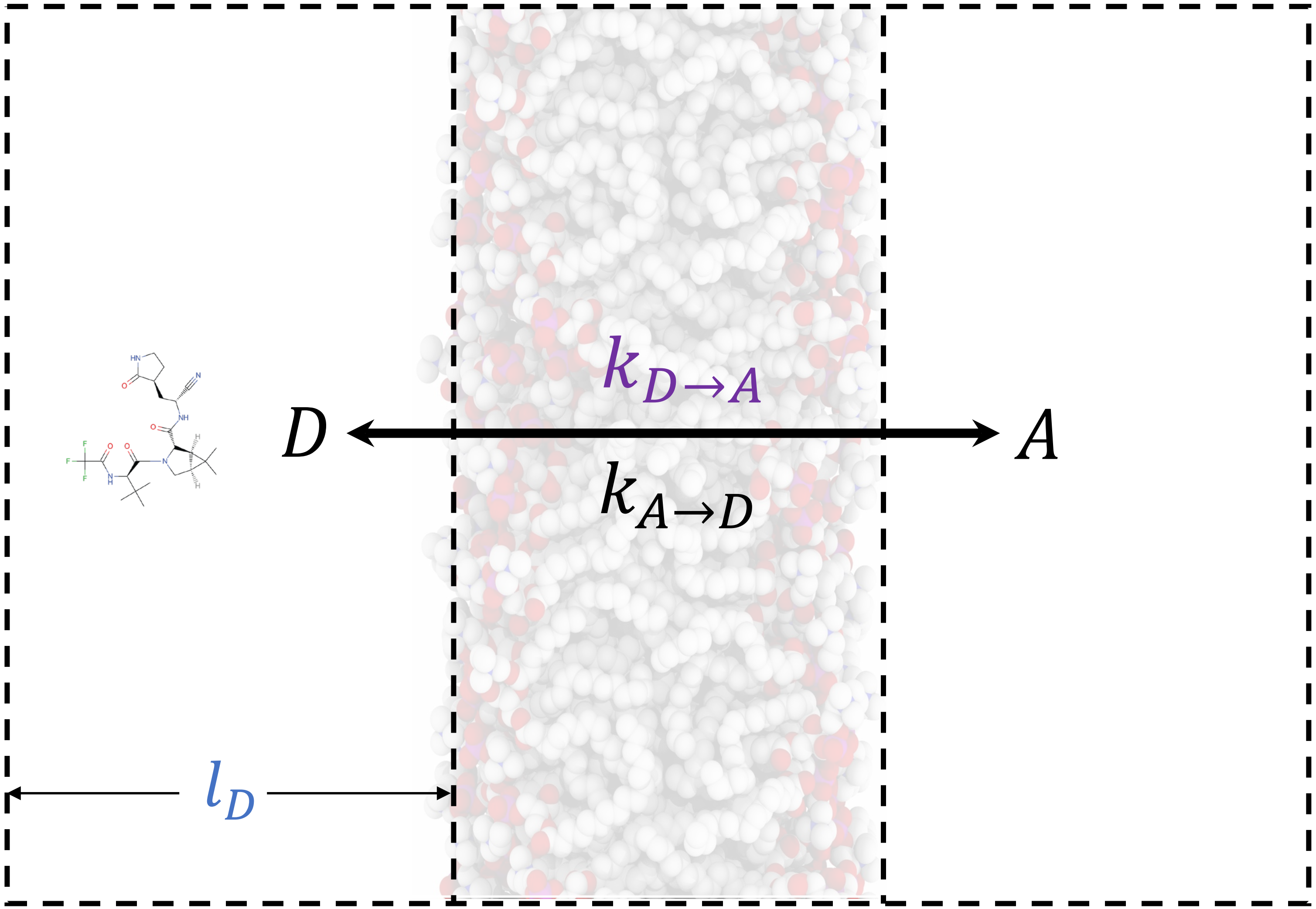
Our permeability model: a kinetic approach



$$P_m = k_{D \to A} l_D$$

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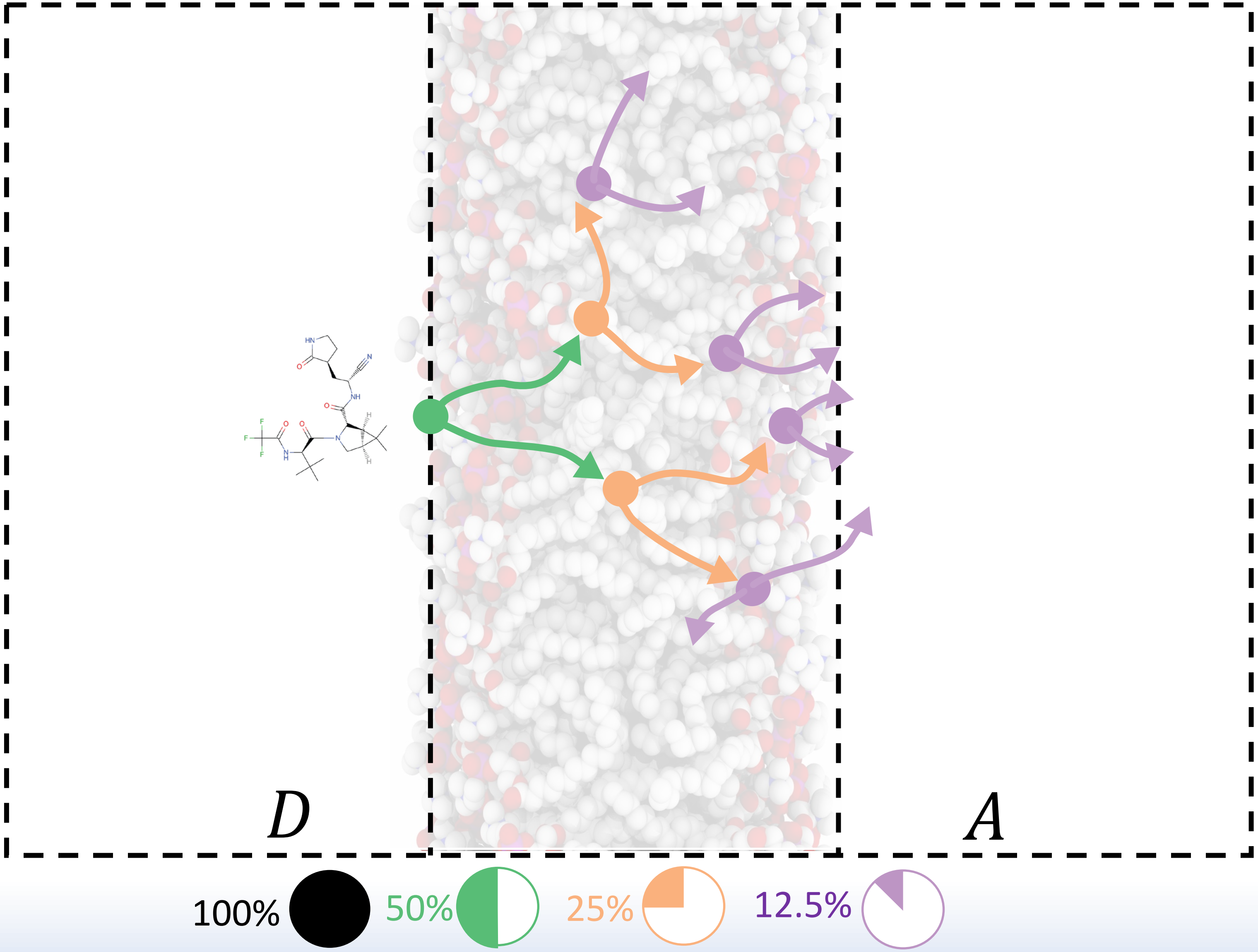
Estimating $k_{D \to A}$ from Weighted Ensemble MD



$$k_{D \to A} = \langle \hat{f}_{D \to A} \rangle$$

Average instantaneous probability flux from D to A

P_m estimate ✓

P_m mechanism ✓

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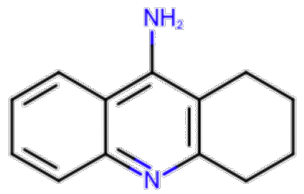
Four WESTPA protocols were tested

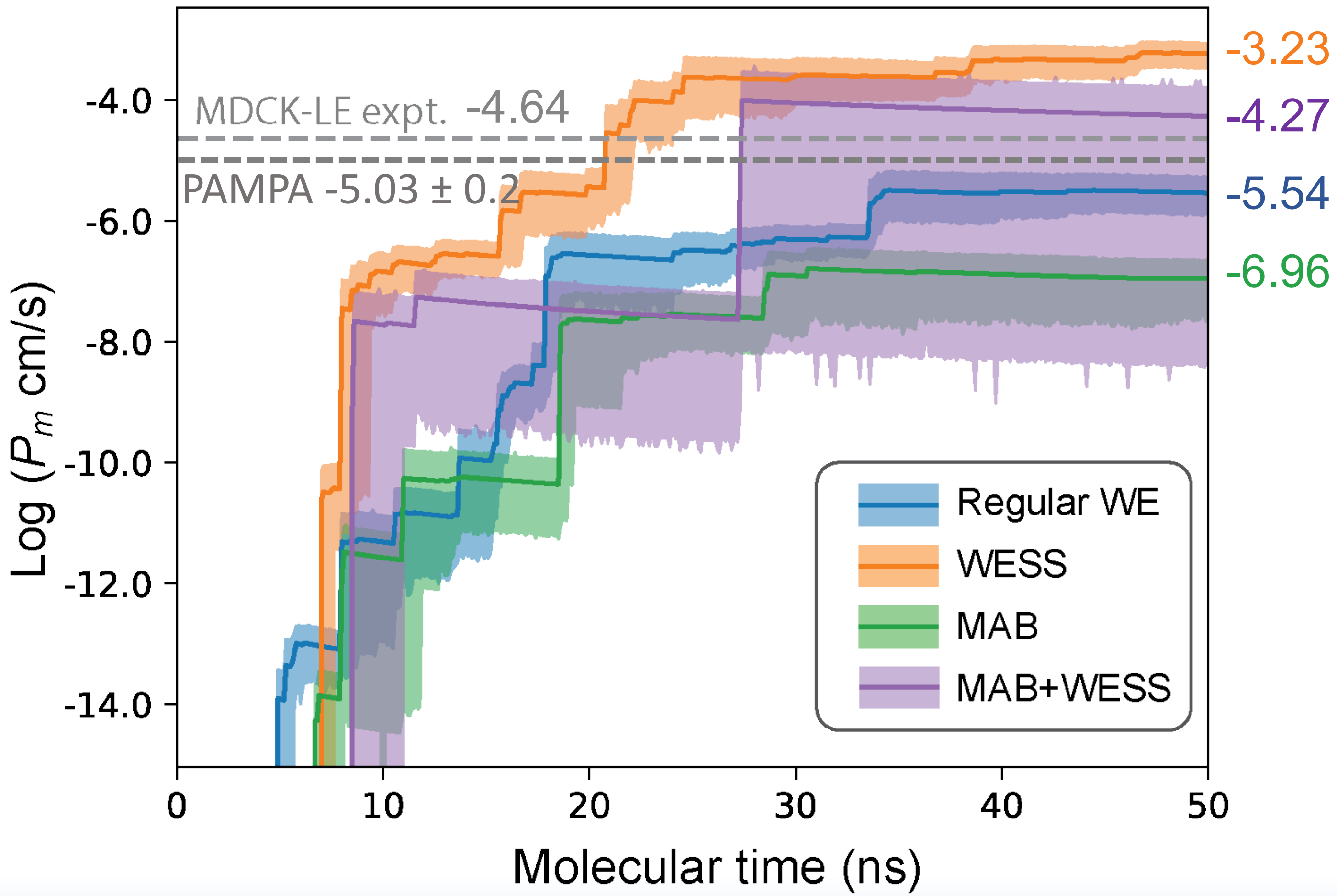
	Regular WE	WESS	MAB	MAB+WESS
Pro	Greatly enhanced sampling with respect to brute force MD	Enhanced convergence to equilibrium. Can be applied to any WE setup.	Focused sampling of WE bins allows for reduced total simulation (**8 μs**)	Focused sampling of WE bins allows for reduced total simulation (**8 μs**) and convergence to equilibrium
Con	**25 μs** of total simulation needed	**25 μs** of total simulation needed	Estimates for rate constants may be far from equilibrium	Multiple runs may be needed for full convergence

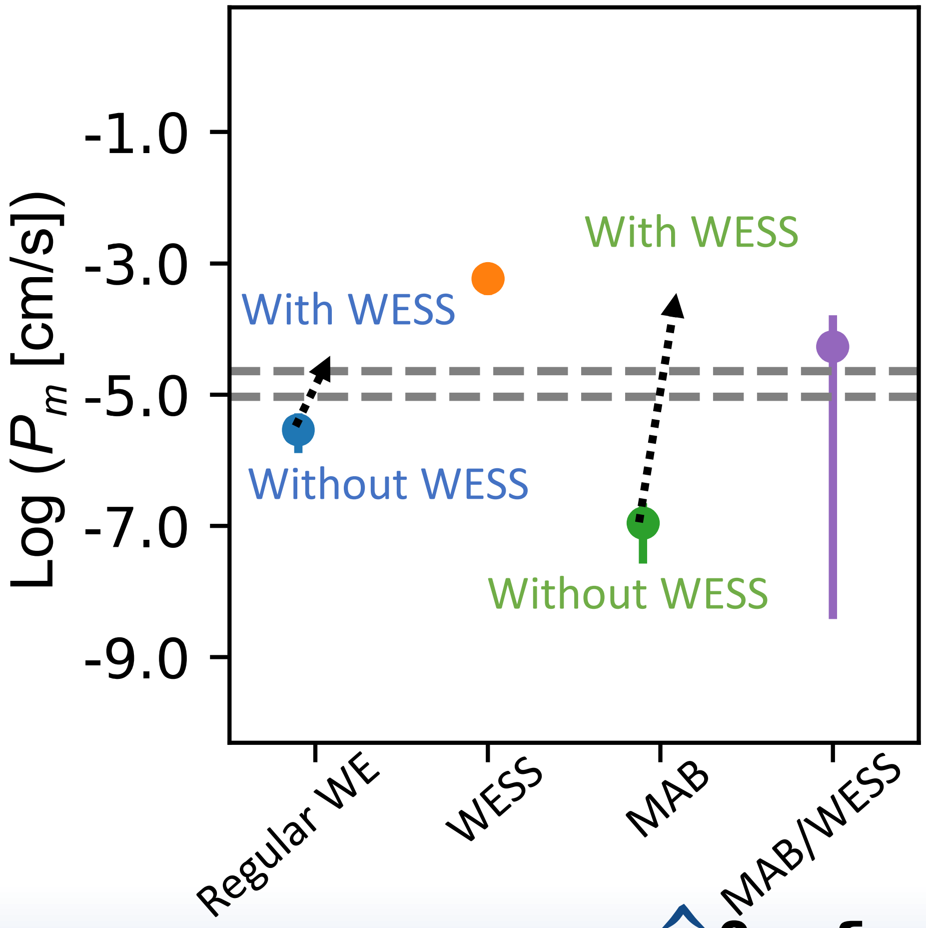
Evaluation of Weighted Ensemble protocols:



tacrine

MDCK-LE expt.: Dickson et al.. JCIM 2019; PAMPA expt: Katt et al. PloSOne 2016





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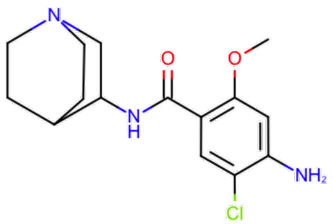
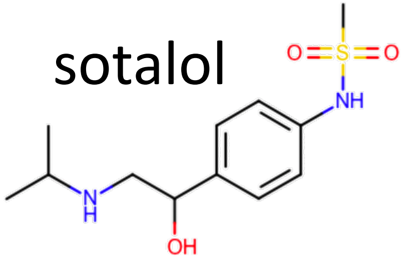
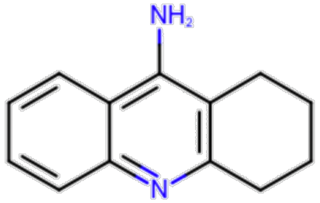
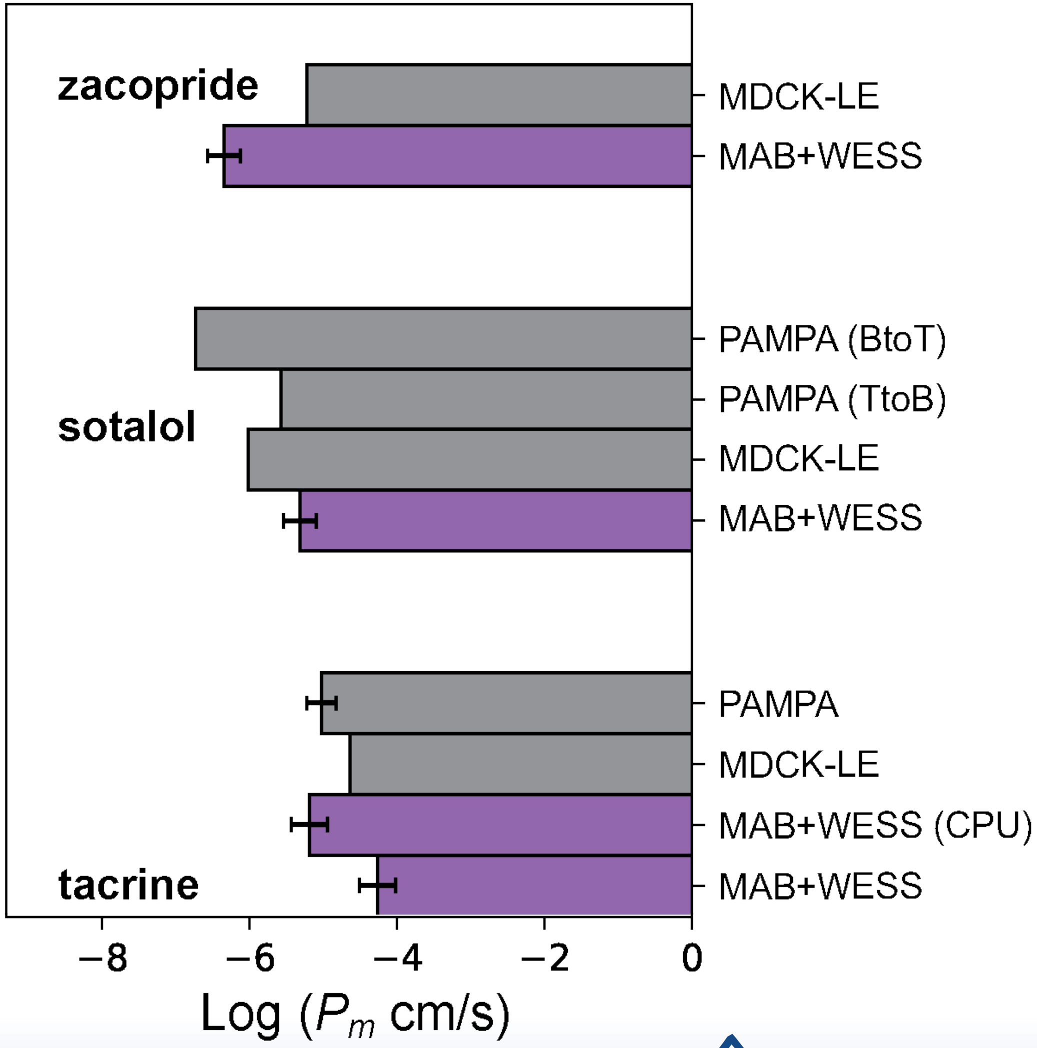
Permeability estimates for three Ro5 molecules

	molecular weight	# rotatable bonds	# hydrogen bond donor/acceptor
zacopride 	310	3	2/4
sotalol 	272	6	3/5
tacrine 	198	0	1/2



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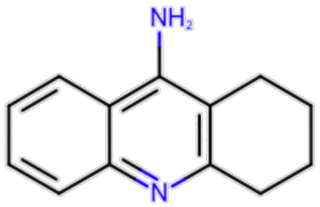
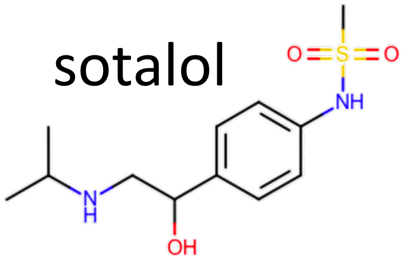
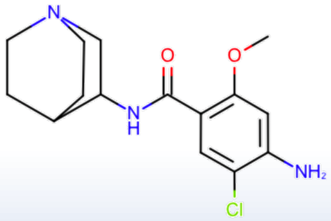
How does WE compare to brute force MD?

	Physical time	Wall clock time (single event)	
	MFPT (ms)	**Anton3 (years)**	**WE in Orion (days)**
tacrine 	5	0.1	1.1
sotalol 	52	0.7	10.7
zacopride 	559	7.7	7.5

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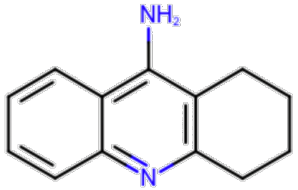
Top-weighted permeation pathway:



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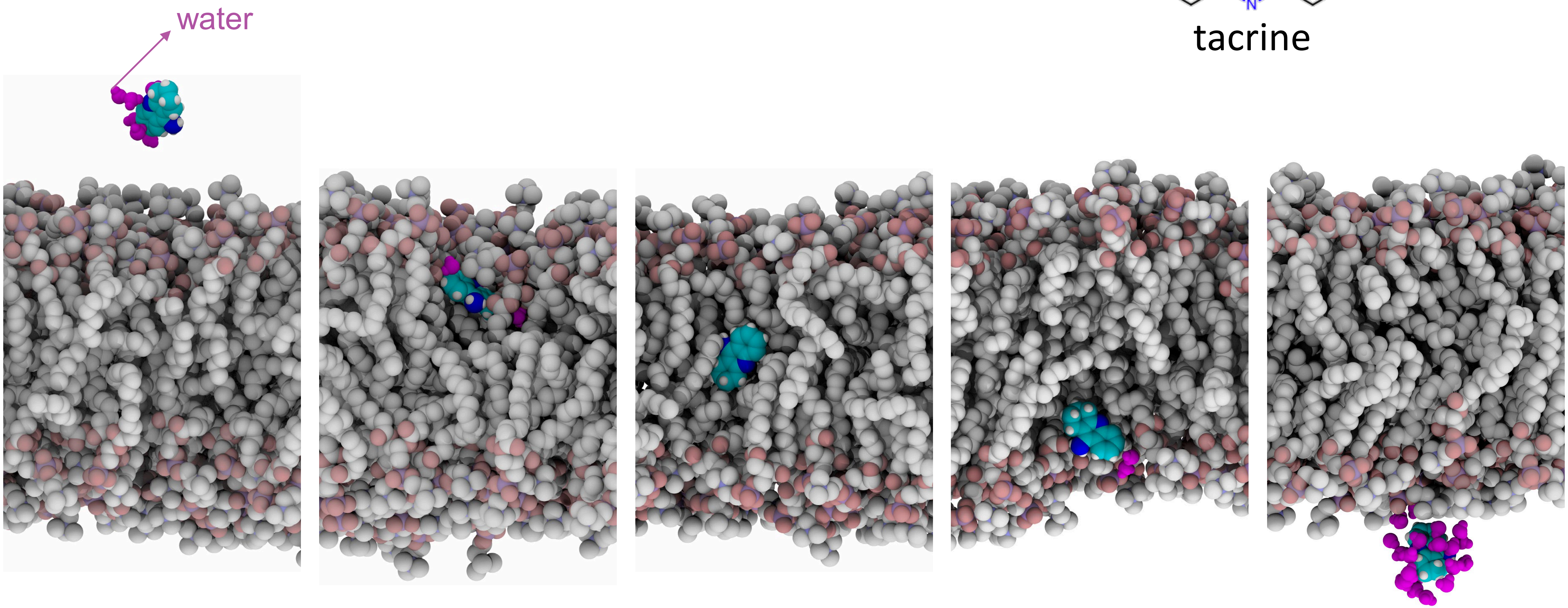

2.9 ns 9.0 ns 23.0 ns 32.0 ns 34.0 ns

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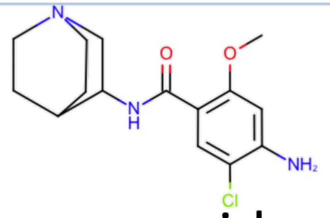
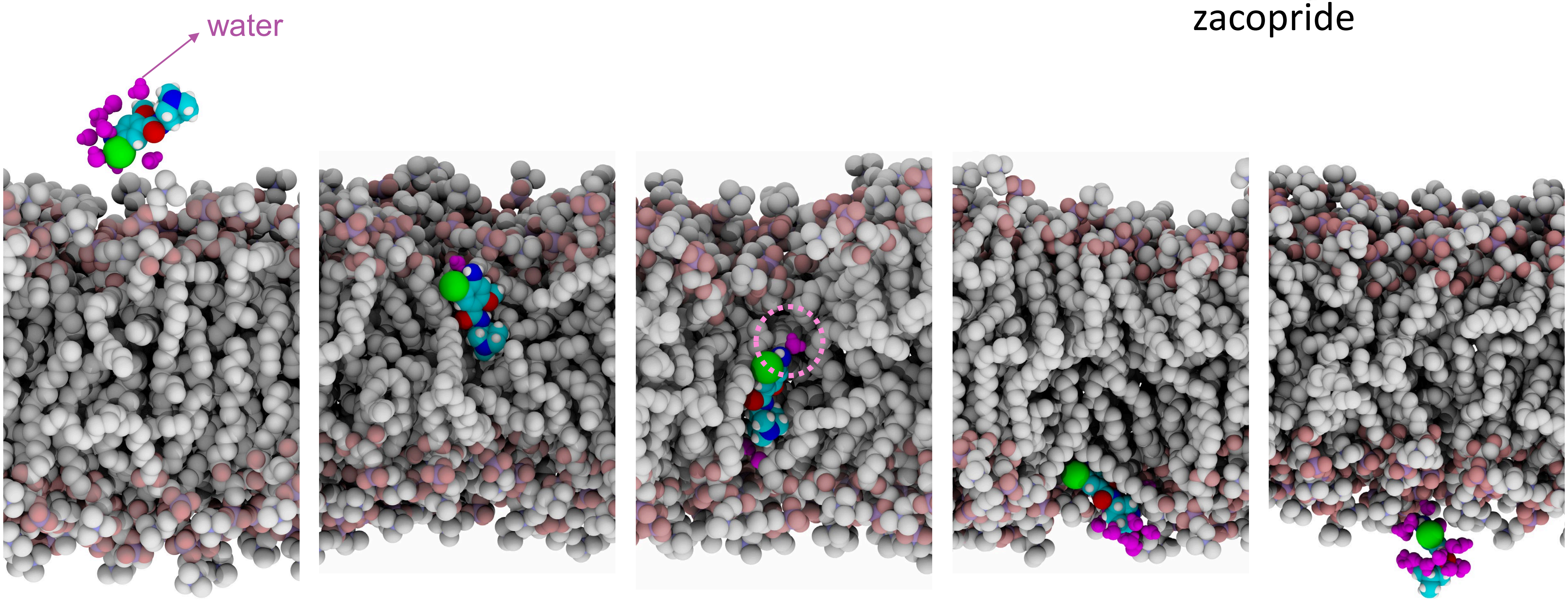
Top-weighted permeation pathway:



zacopride



1.3 ns　9.1 ns　13.0 ns　23.0 ns　46.0 ns

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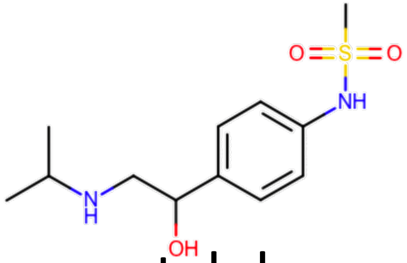
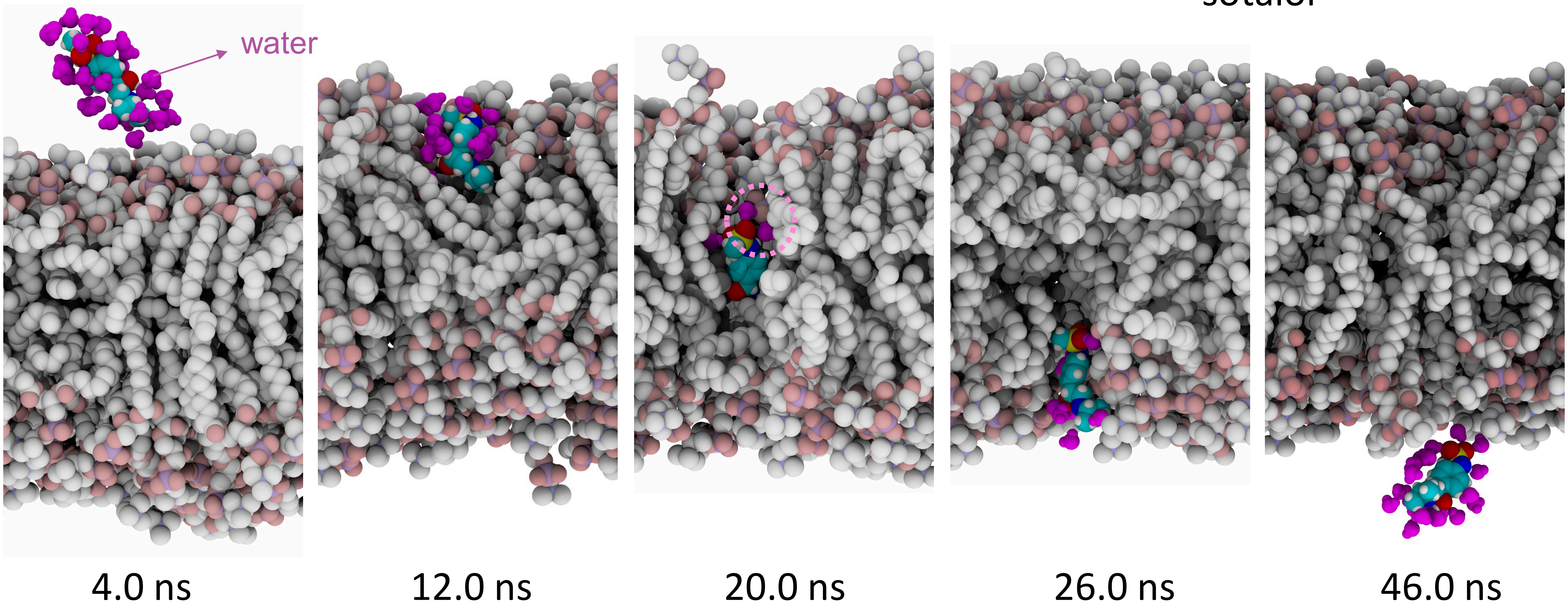
Top-weighted permeation pathway:



sotalol



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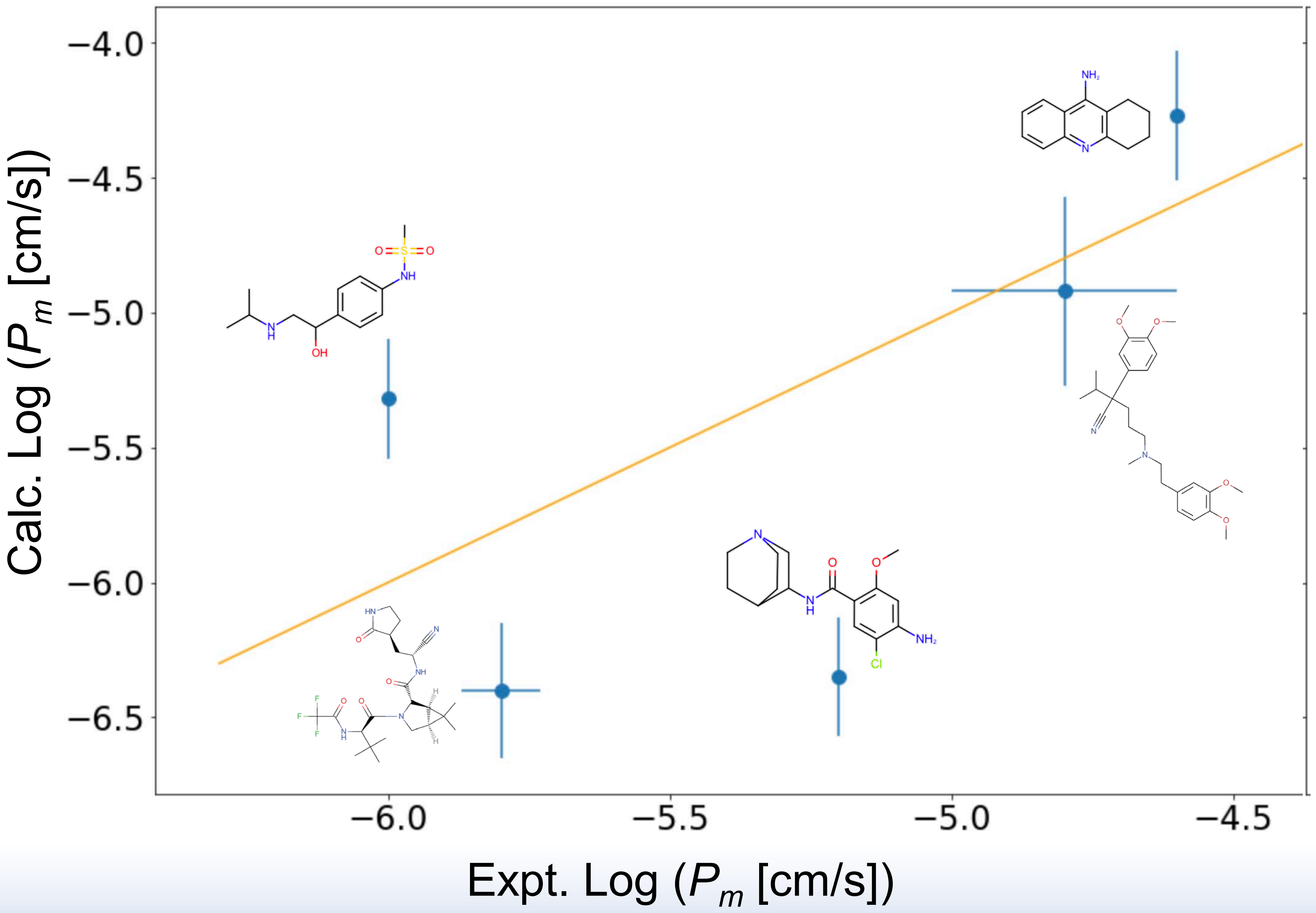
Statistical analysis of 5 drug-like compounds



R^2	MAE
0.38	0.57

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Conclusions and future outlook

Permeability coefficients can be estimated from models, experiments, and MD methods. However:

P_m estimate ✓ P_m mechanism 🚫

We developed a floe using a kinetic model for permeability based on WE path sampling that relies on the kinetic rate constant for membrane permeation:

P_m estimate ✓ P_m mechanism ✓

Our method works well for a few Ro5 molecules; we would like to expand to bRo5 molecules and the BBB as well.

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MD Orion Developers

Gaetano Calabro
Christopher Bayly

Orion Frontend Developers

WESTPA Developers

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Thank You

The End

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