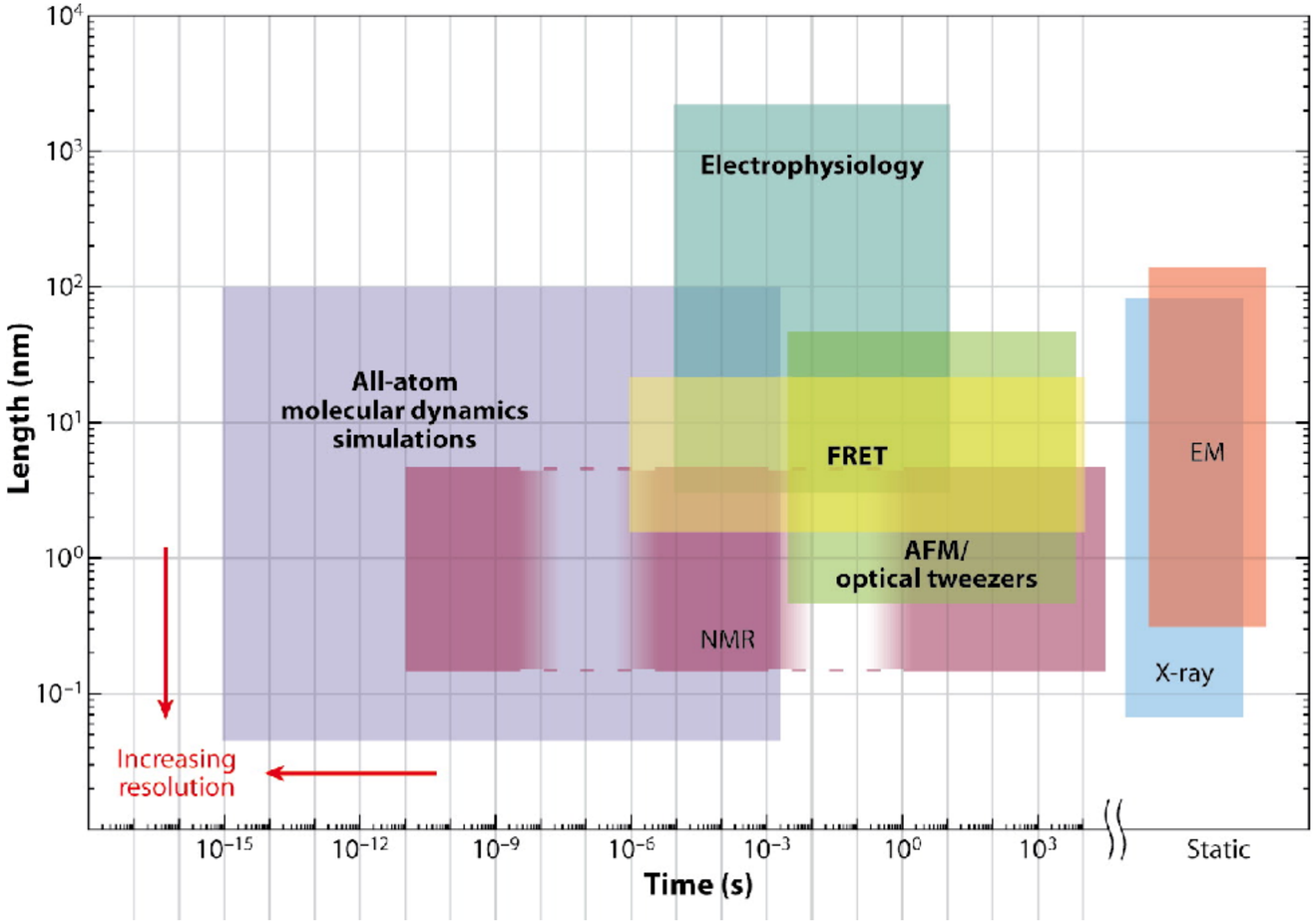
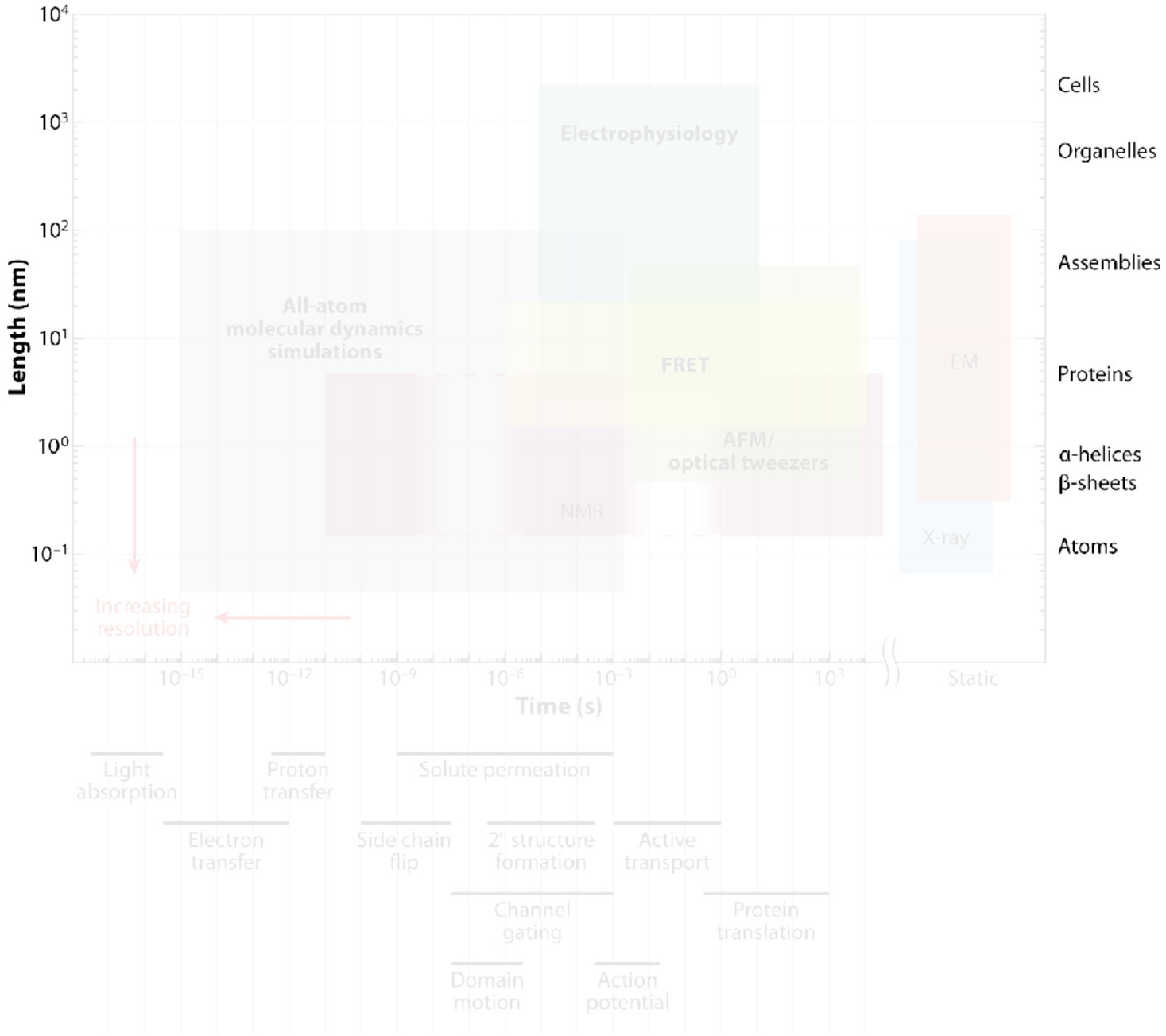
Improving and applying atomistic simulation to study biophysical conformational dynamics

Keri A. McKiernan
March 9, 2018

biophysical toolbox



Dror et al, doi.org/10.1146/annurev-biophys-042910-155245



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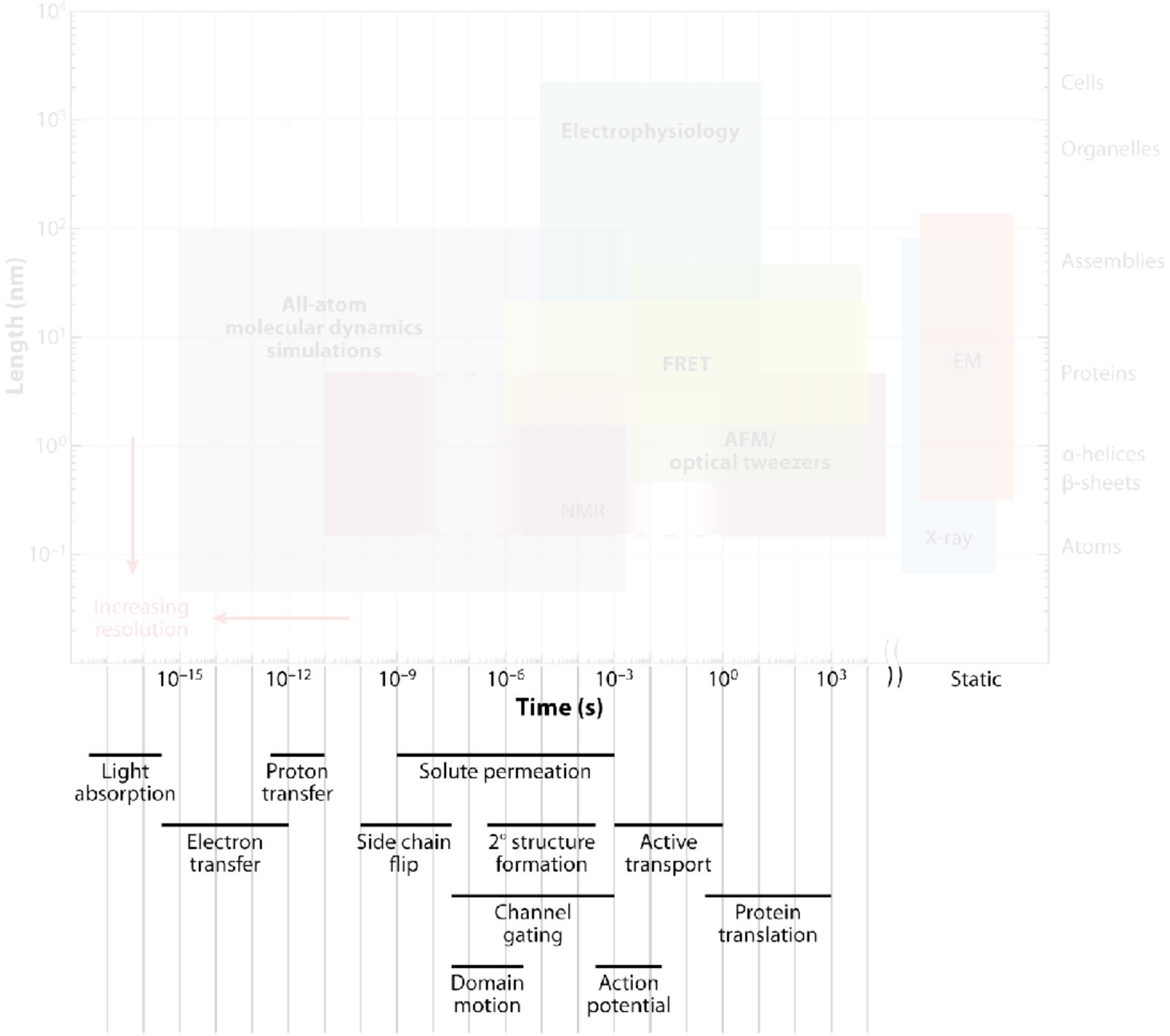

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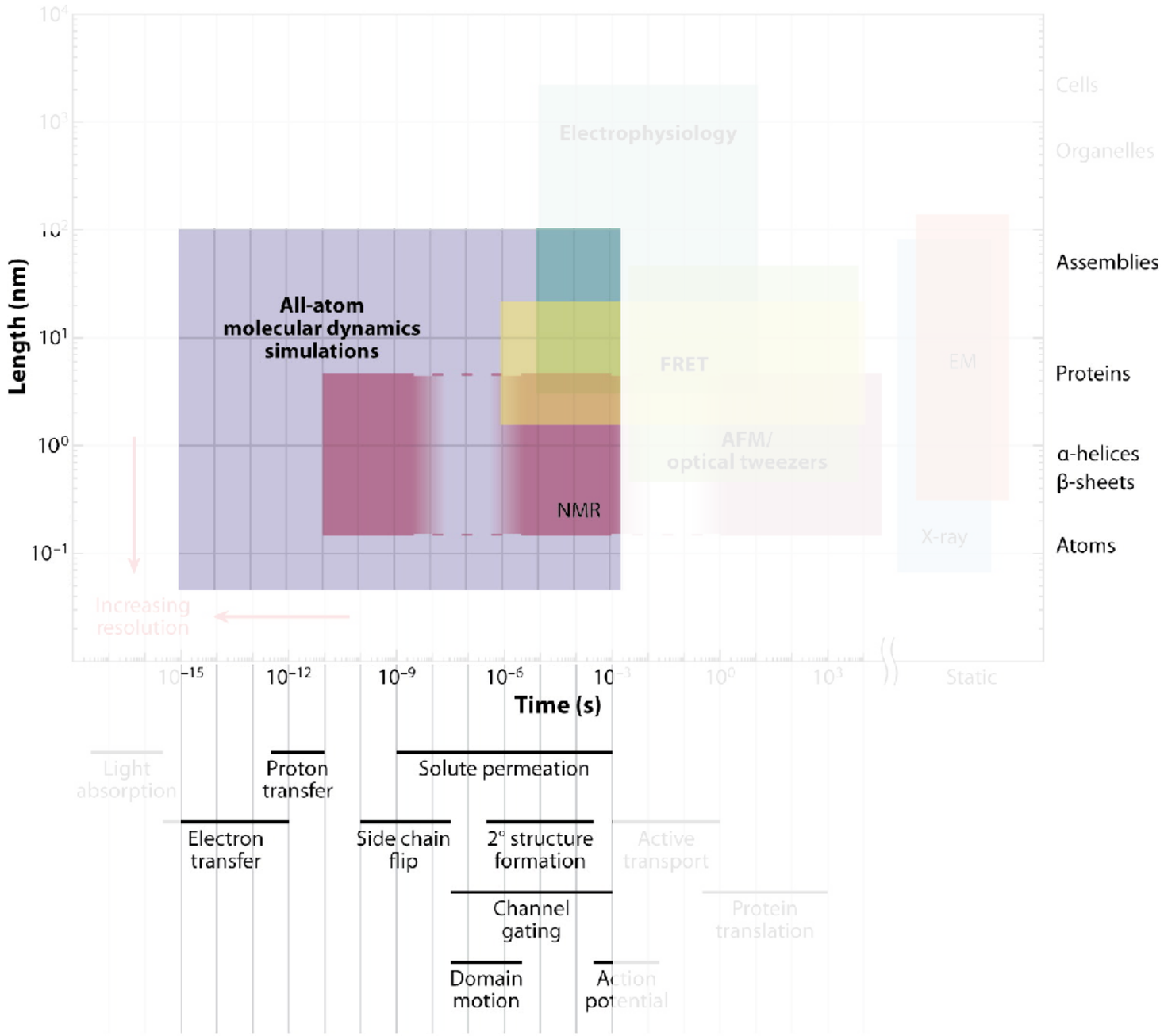

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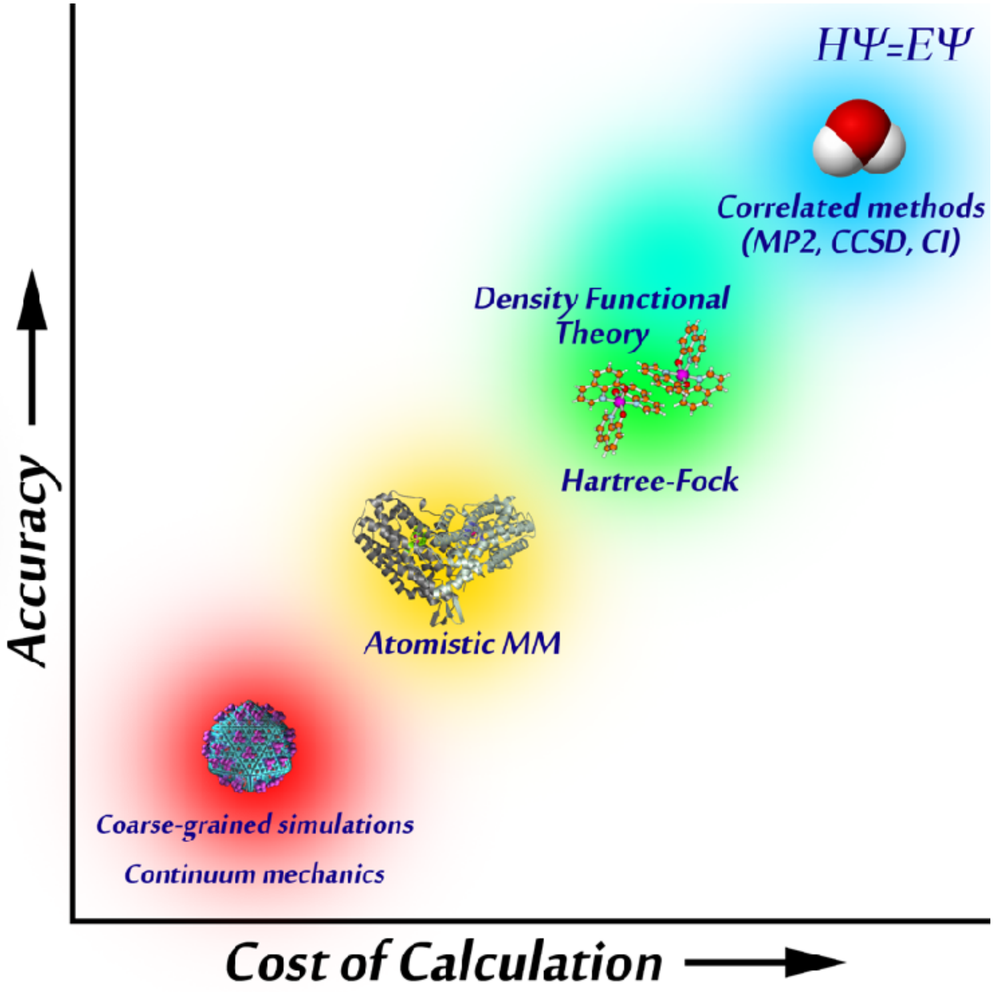
simulation relies on an underlying theoretical description



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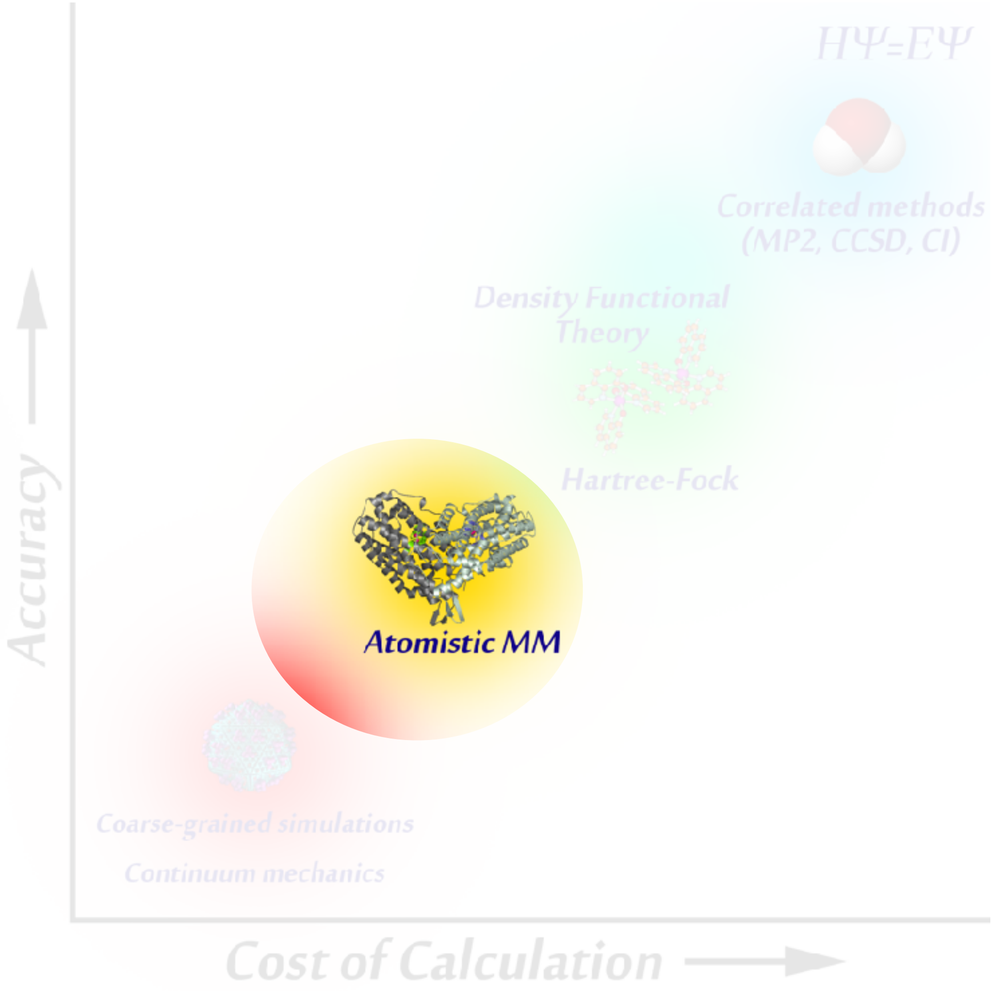

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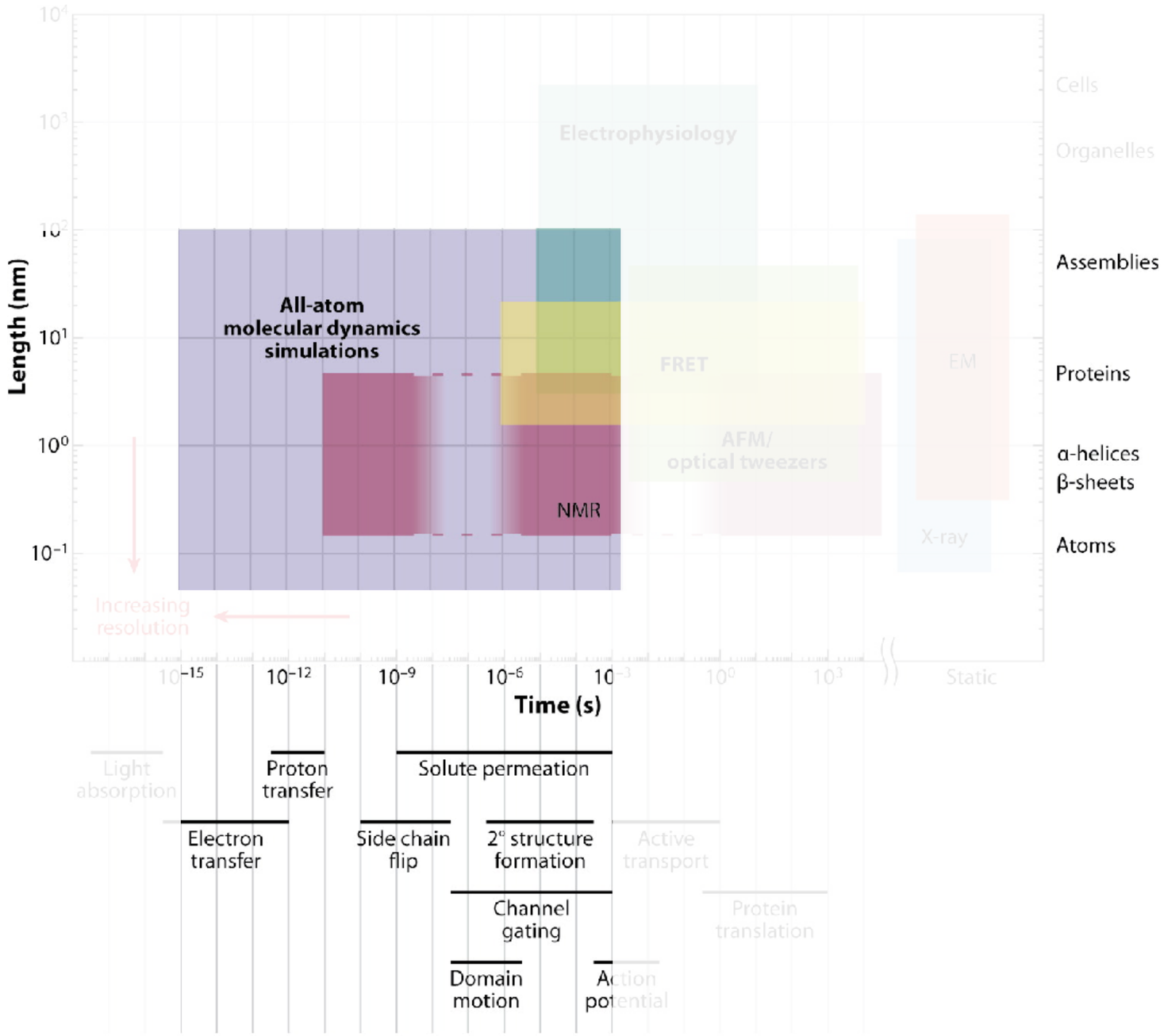

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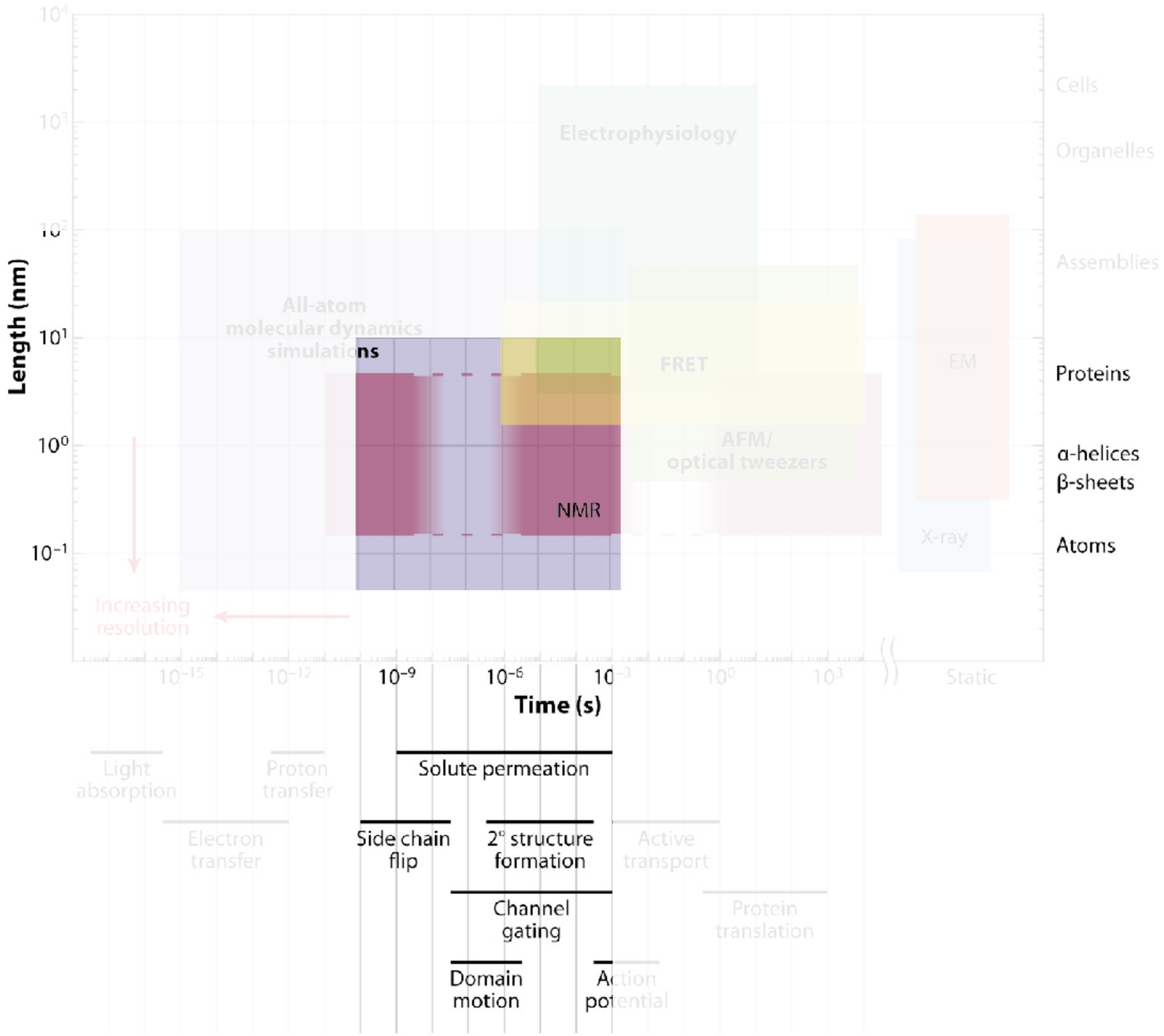

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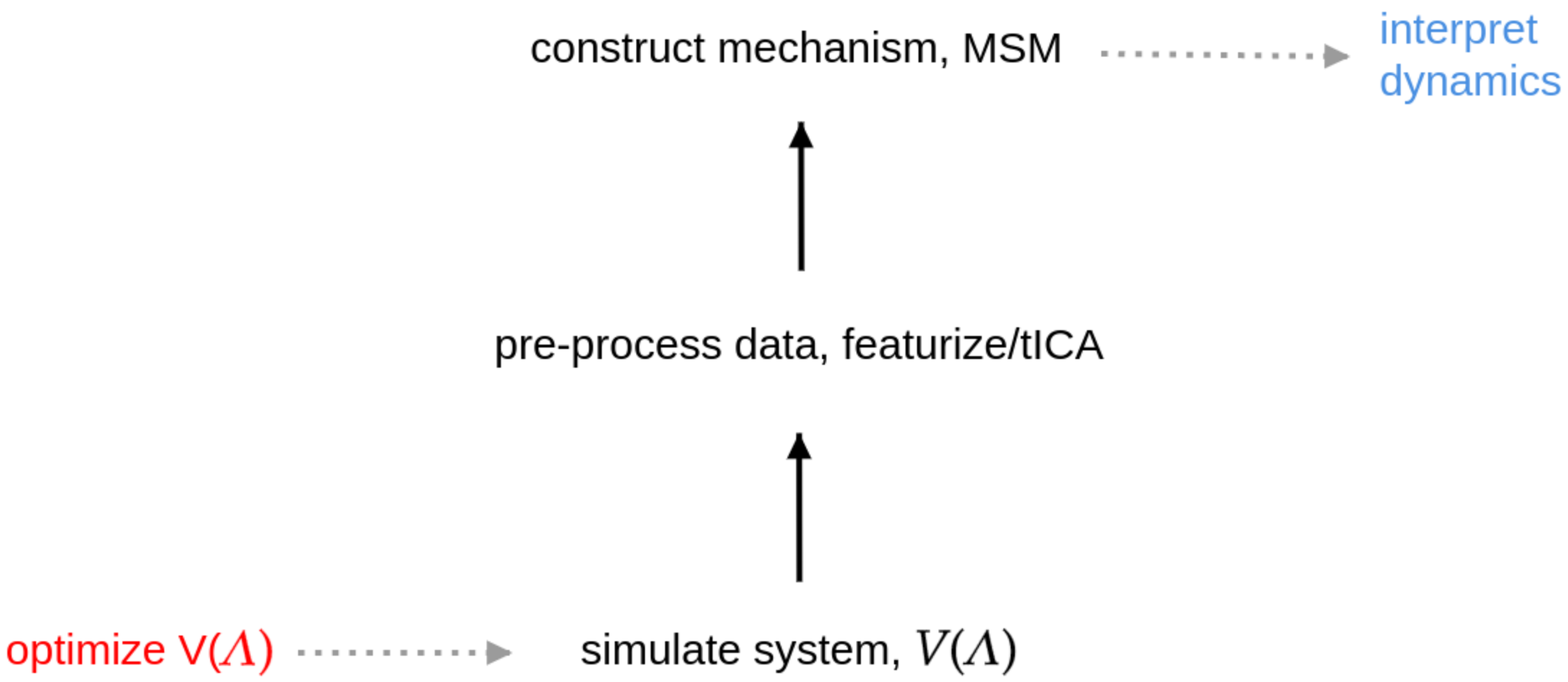
simulation pipeline



simulation pipeline

simulate system, $V(\Lambda)$

simulation pipeline

pre-process data, featurize/tICA

↑

simulate system, $V(\Lambda)$

simulation pipeline

construct mechanism, MSM

↑

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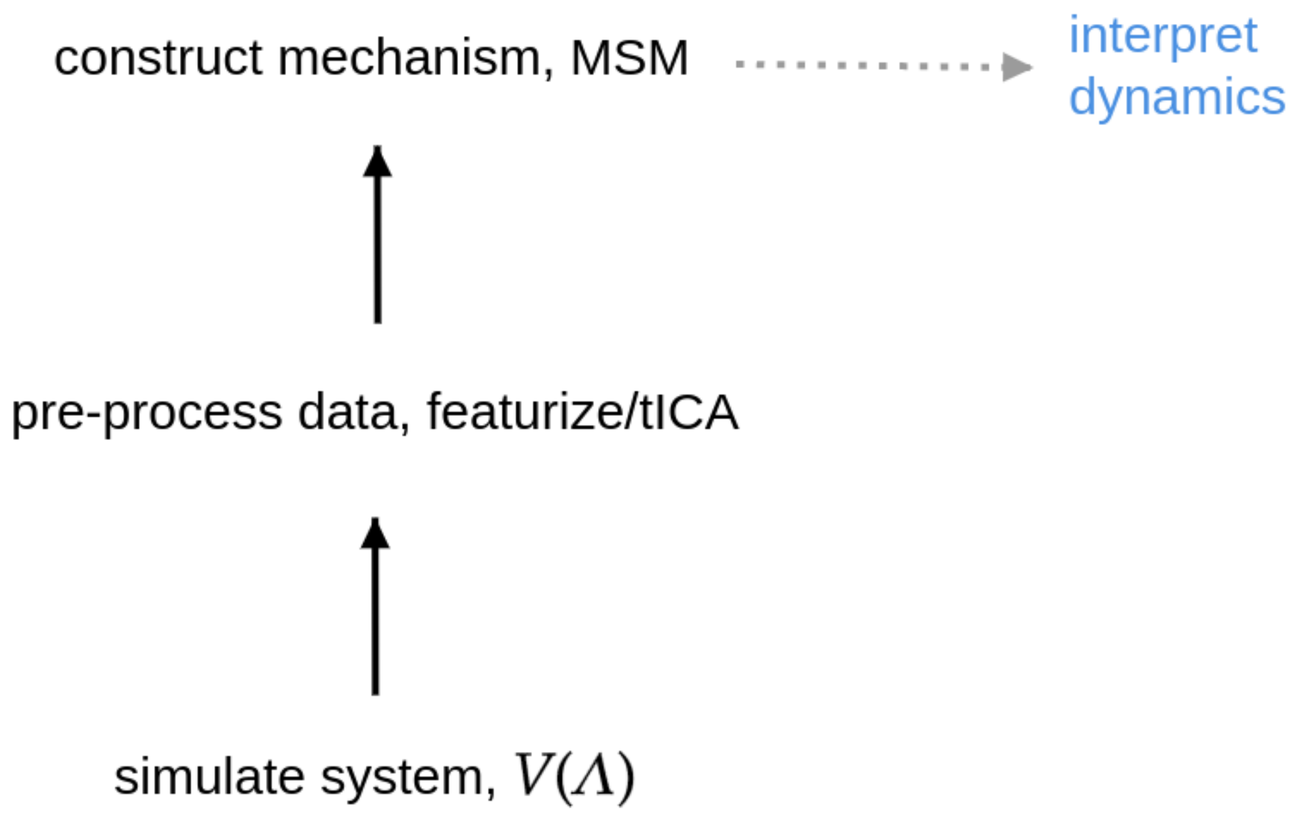

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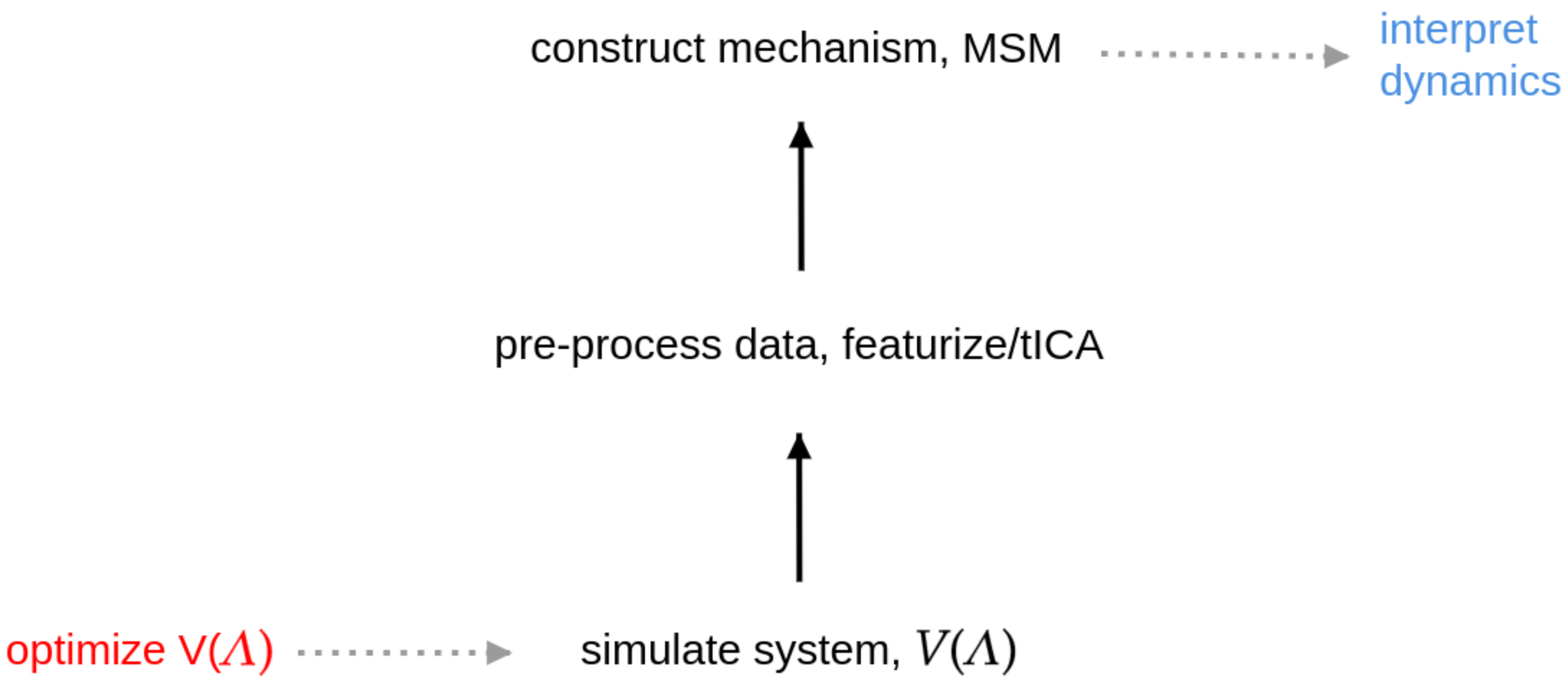
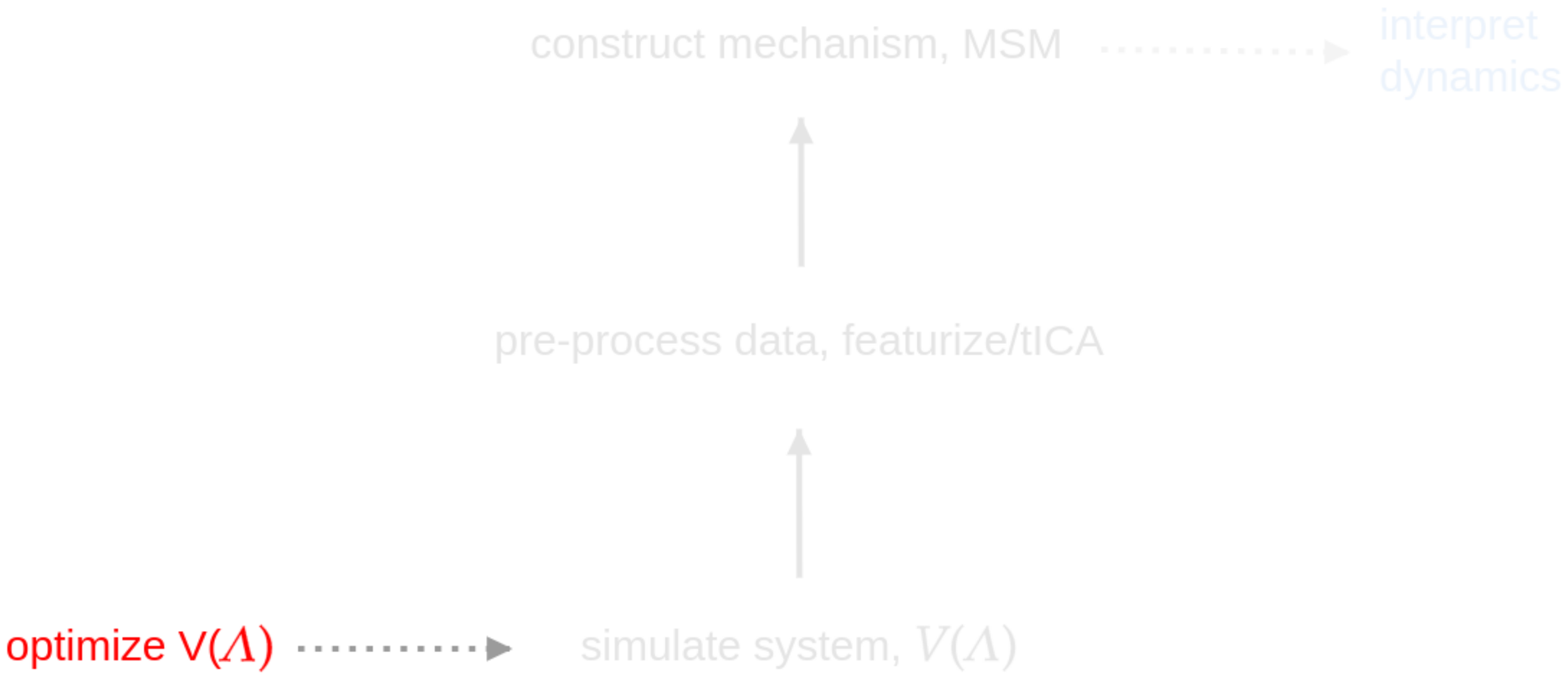


project 1: improving the accuracy of MD force fields



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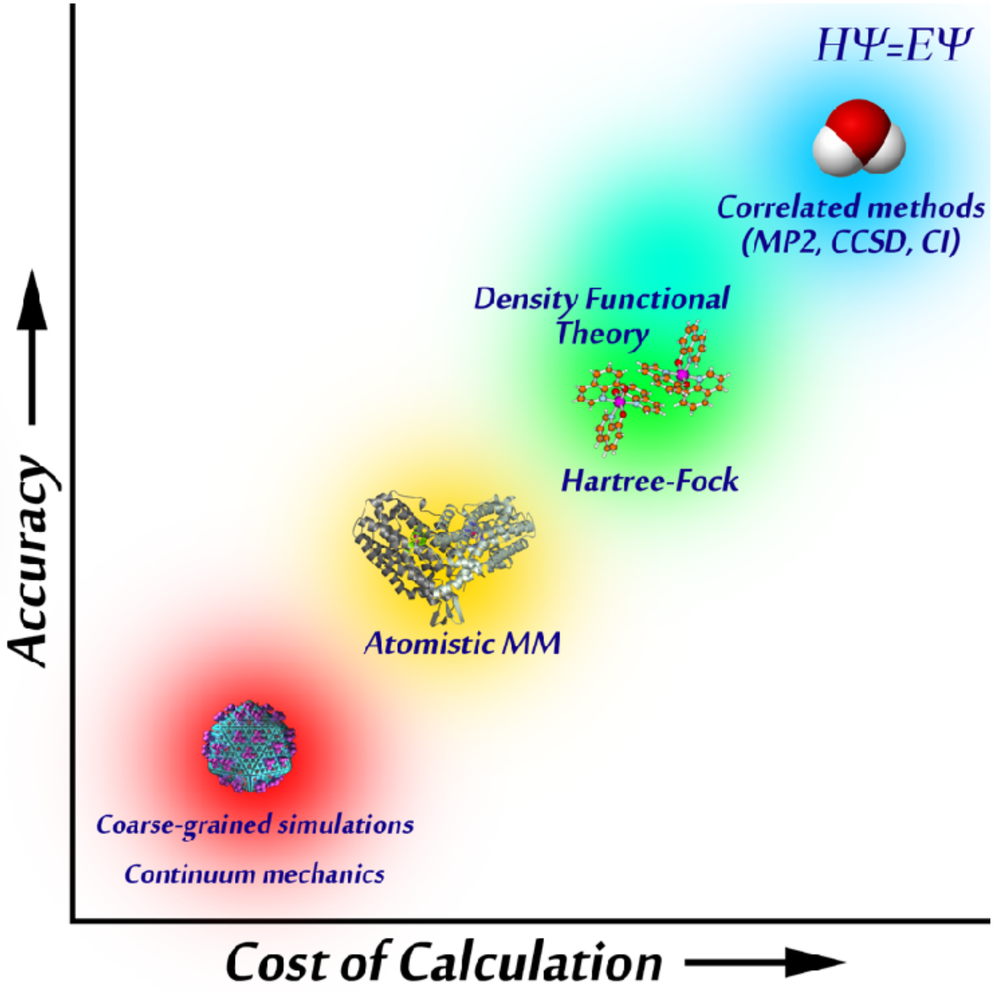

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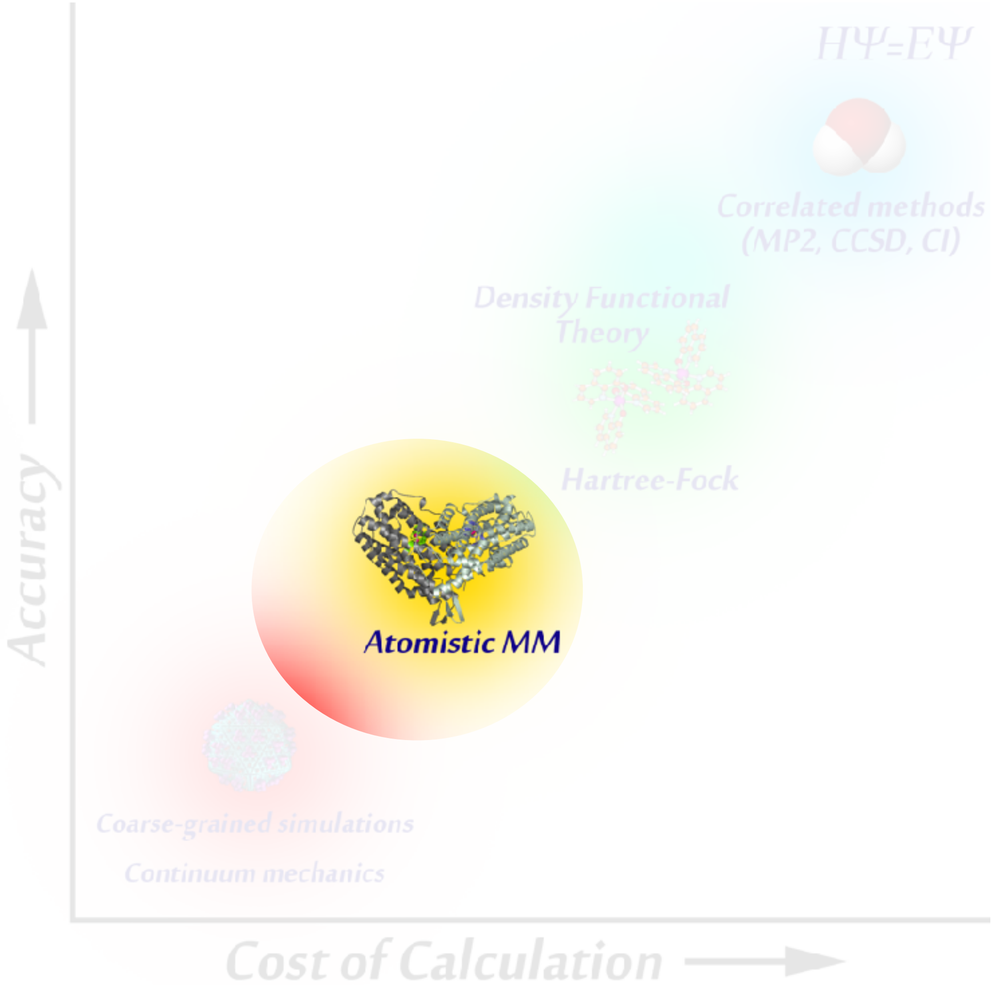

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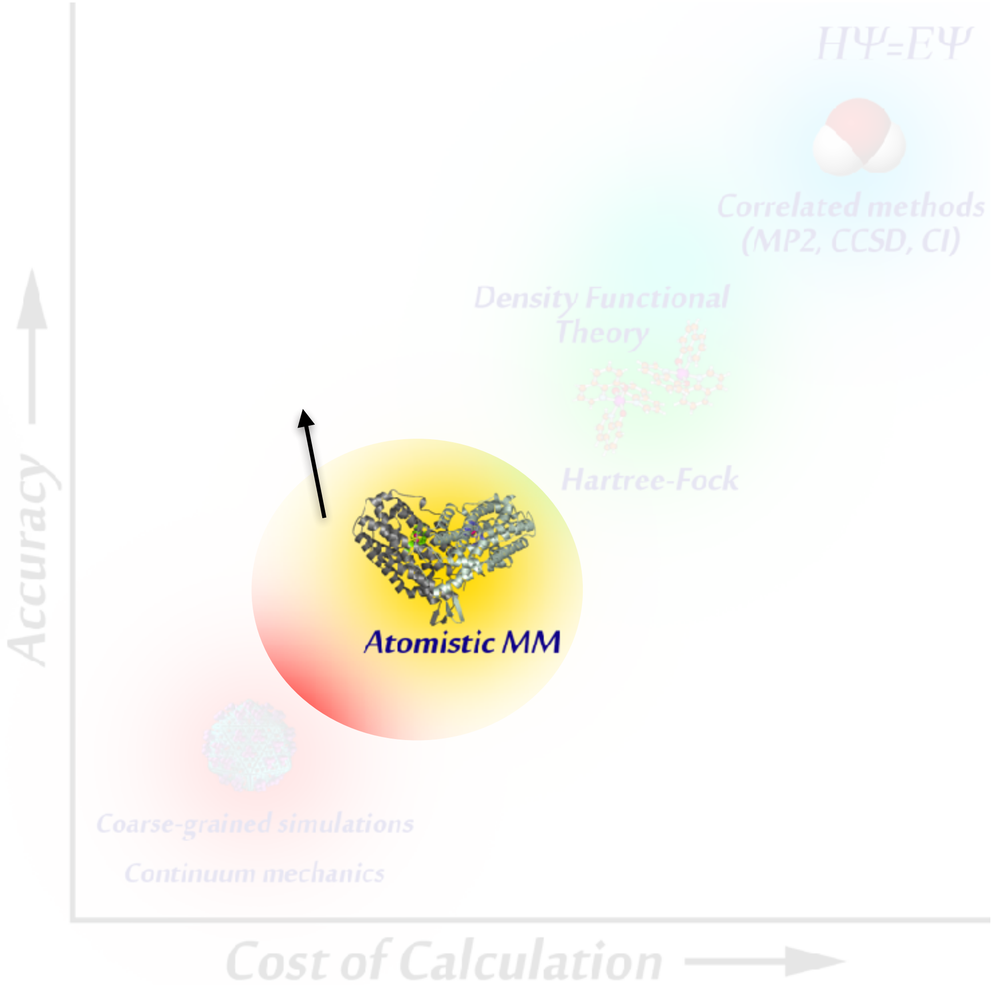

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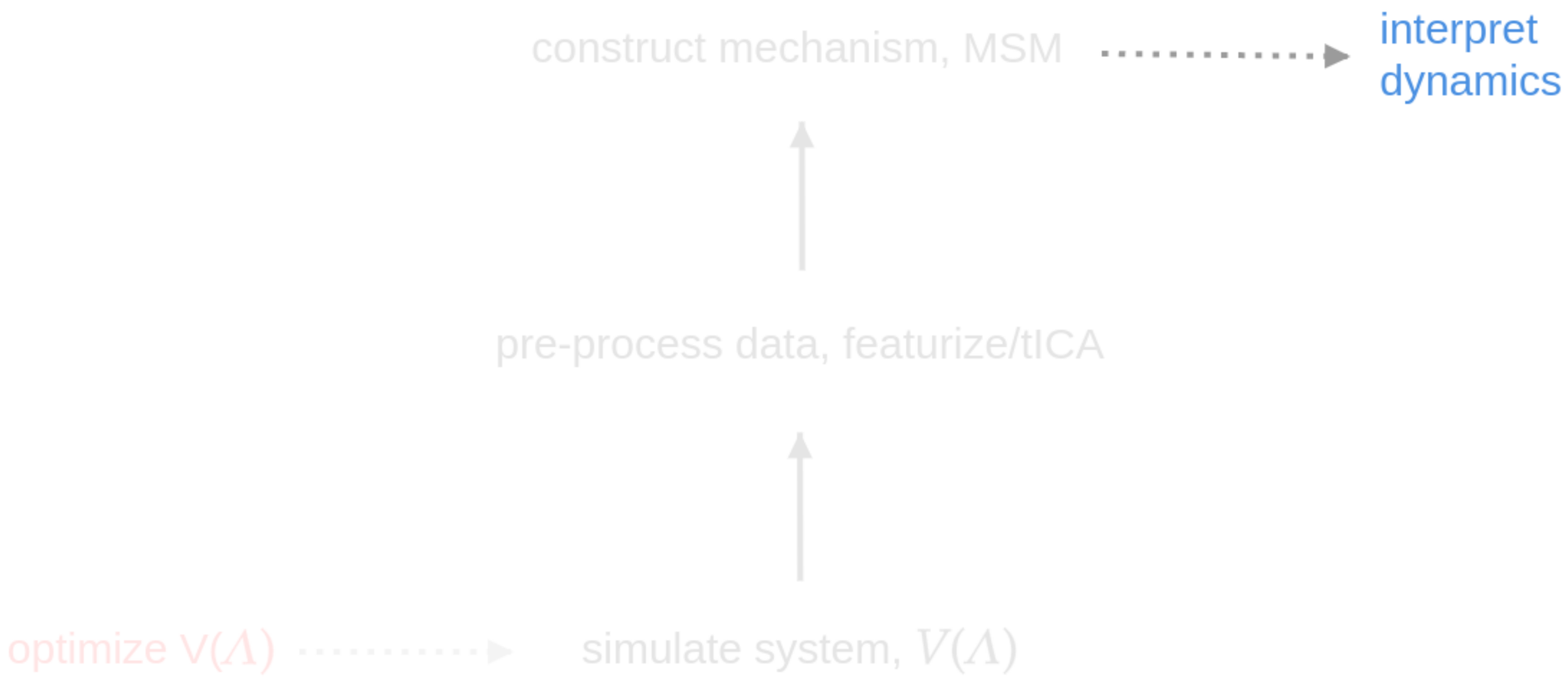
project 2: applying MD to study ion channel gating



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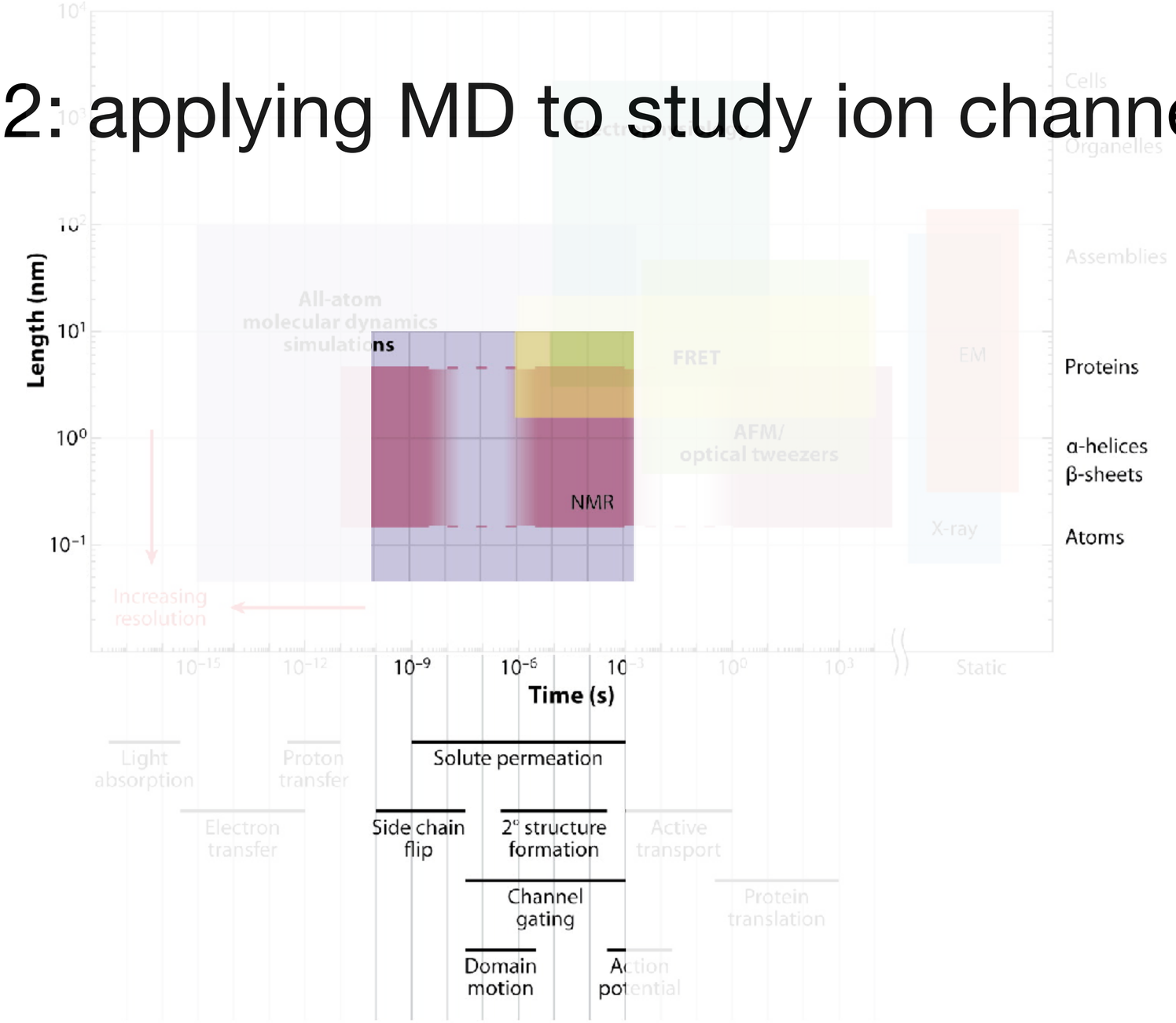

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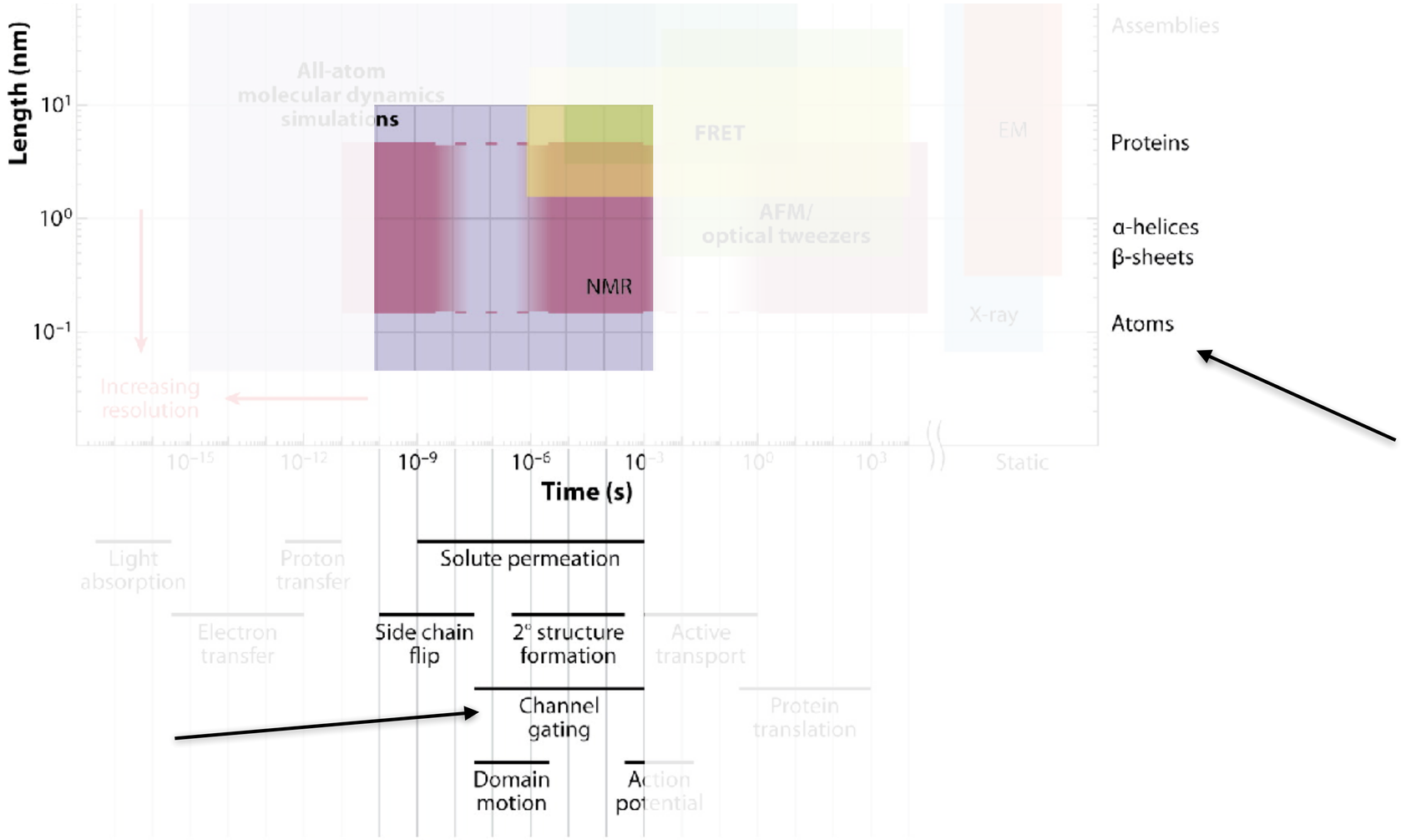

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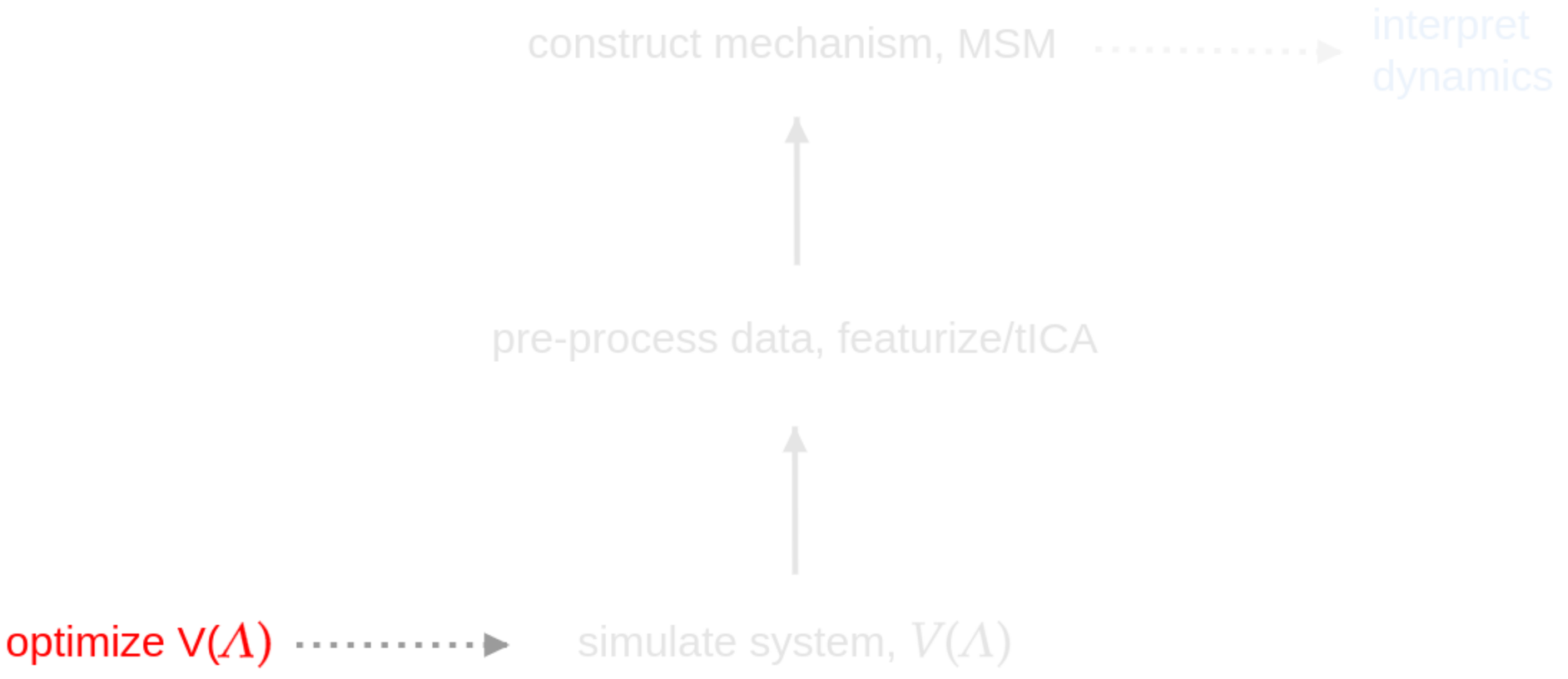
Improving simulation: training a phospholipid force field


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
optimize V(Λ)
simulate system, $V(\Lambda)$

MOLECULAR POTENTIAL ENERGY

$$V = \sum_{\text{All}} \tfrac{1}{2} K_b (b - b_0)^2 + \sum_{\text{All}} \tfrac{1}{2} K_\theta (\theta - \theta_0)^2$$

Hooke 1635

$$+ \sum_{\text{All Torsion}} K_\phi [1 - \cos(n\phi + \delta)]$$

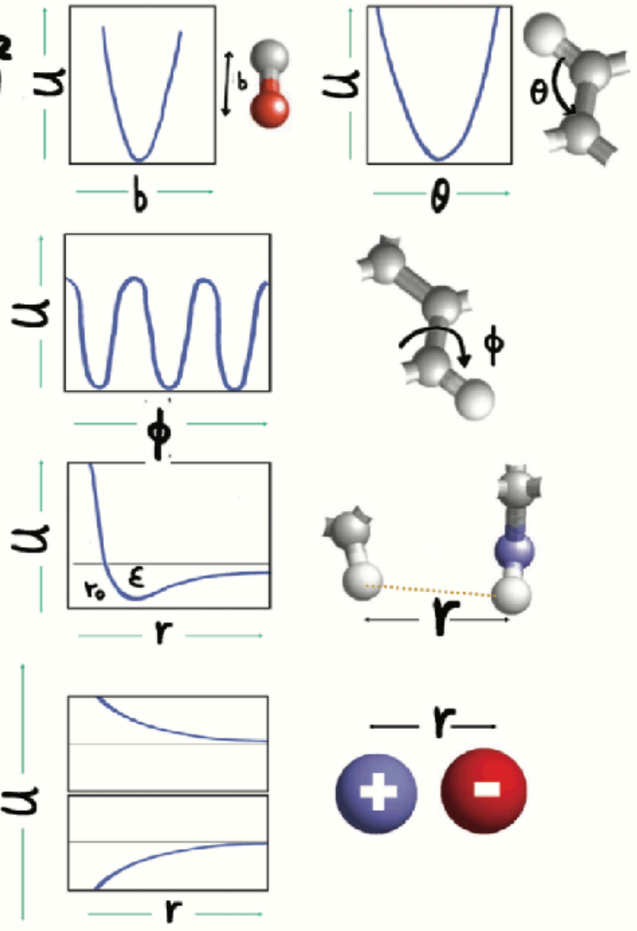
Fourier 1768

$$+ \sum_{\text{All Nonbonded}} \epsilon \left[\left(r_0/r\right)^{12} - 2\left(r_0/r\right)^{6} \right]$$

Van der Waals 1837

$$+ \sum_{\text{All partial}} 332 q_i q_j / r$$

Coulomb 1736



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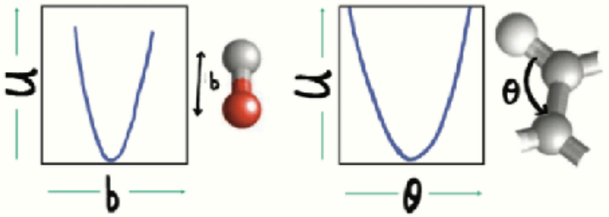

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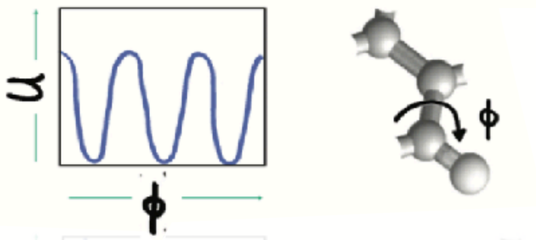

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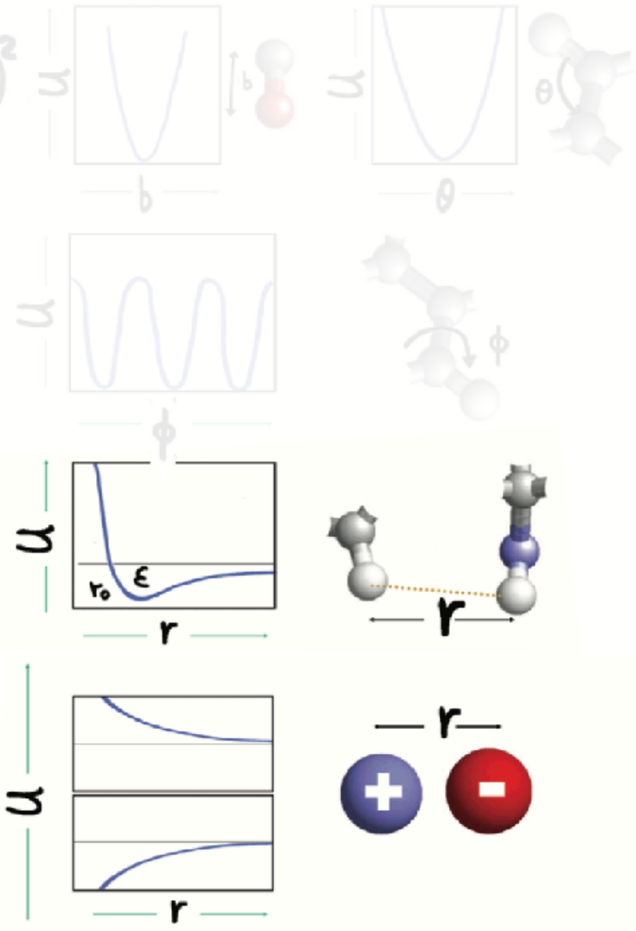

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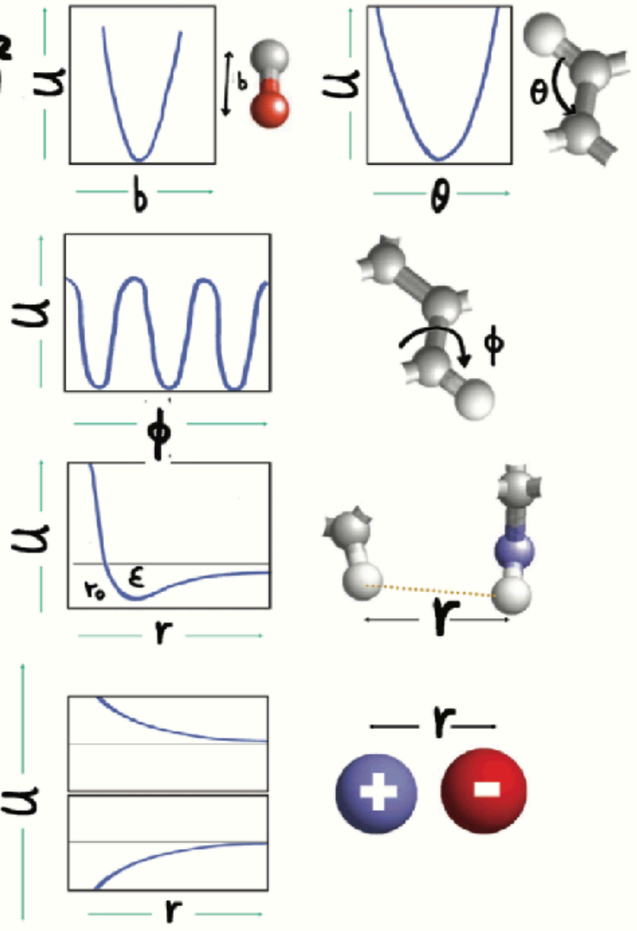

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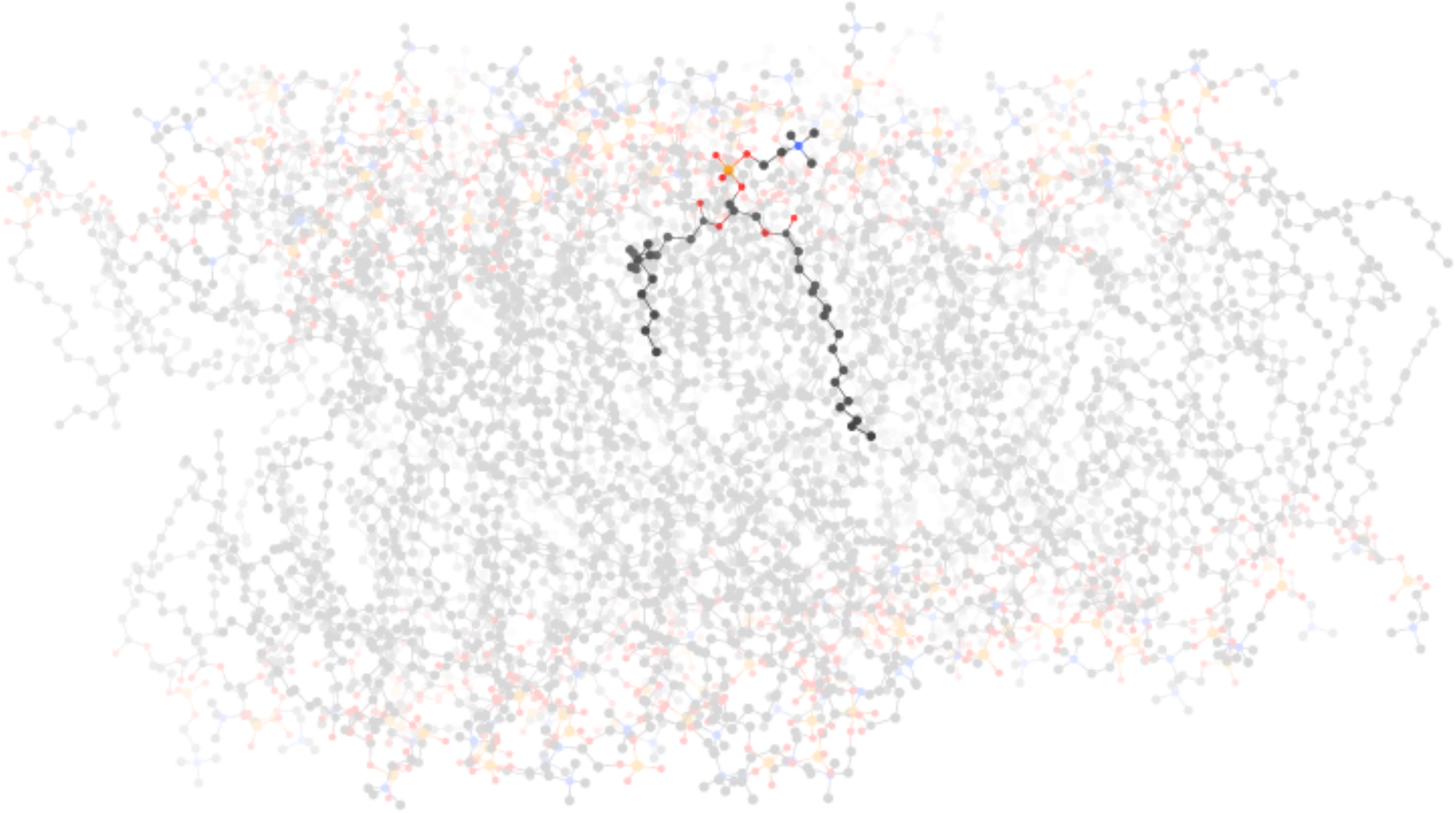
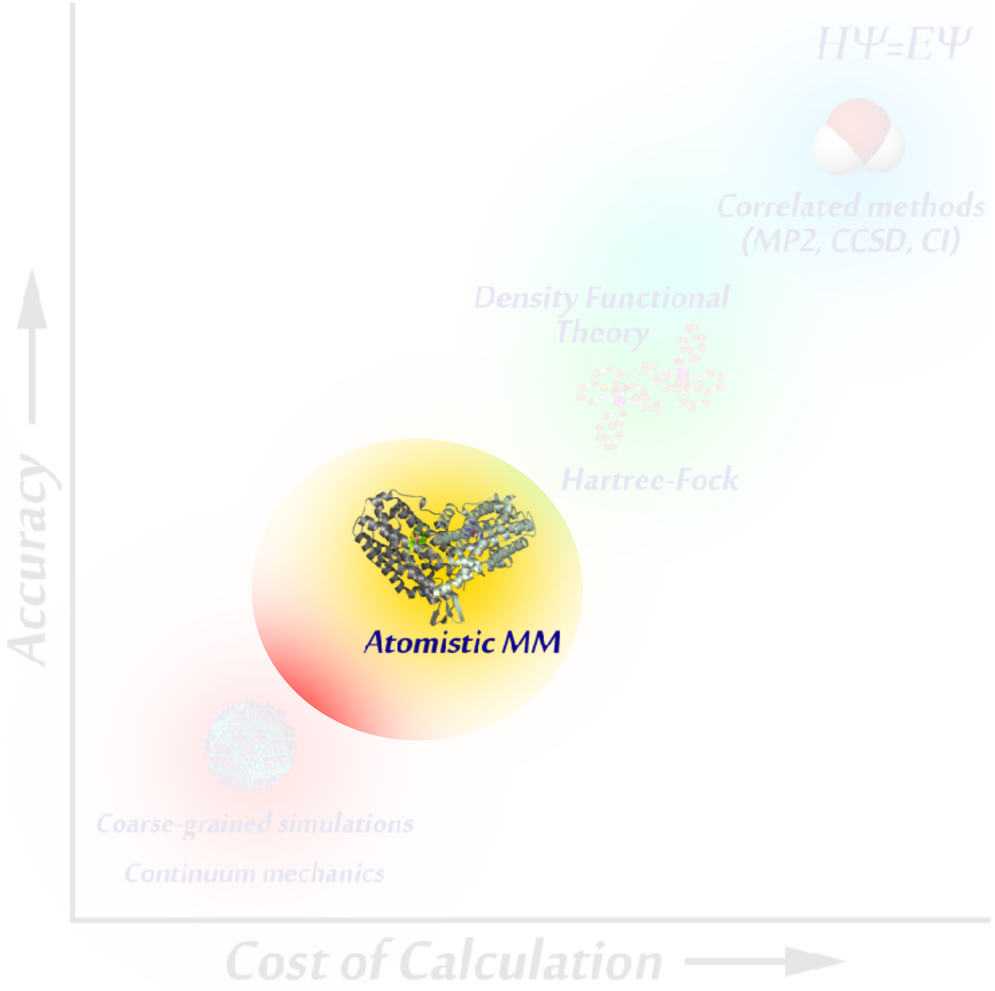


project 1: improving the accuracy of MD (MM) force fields



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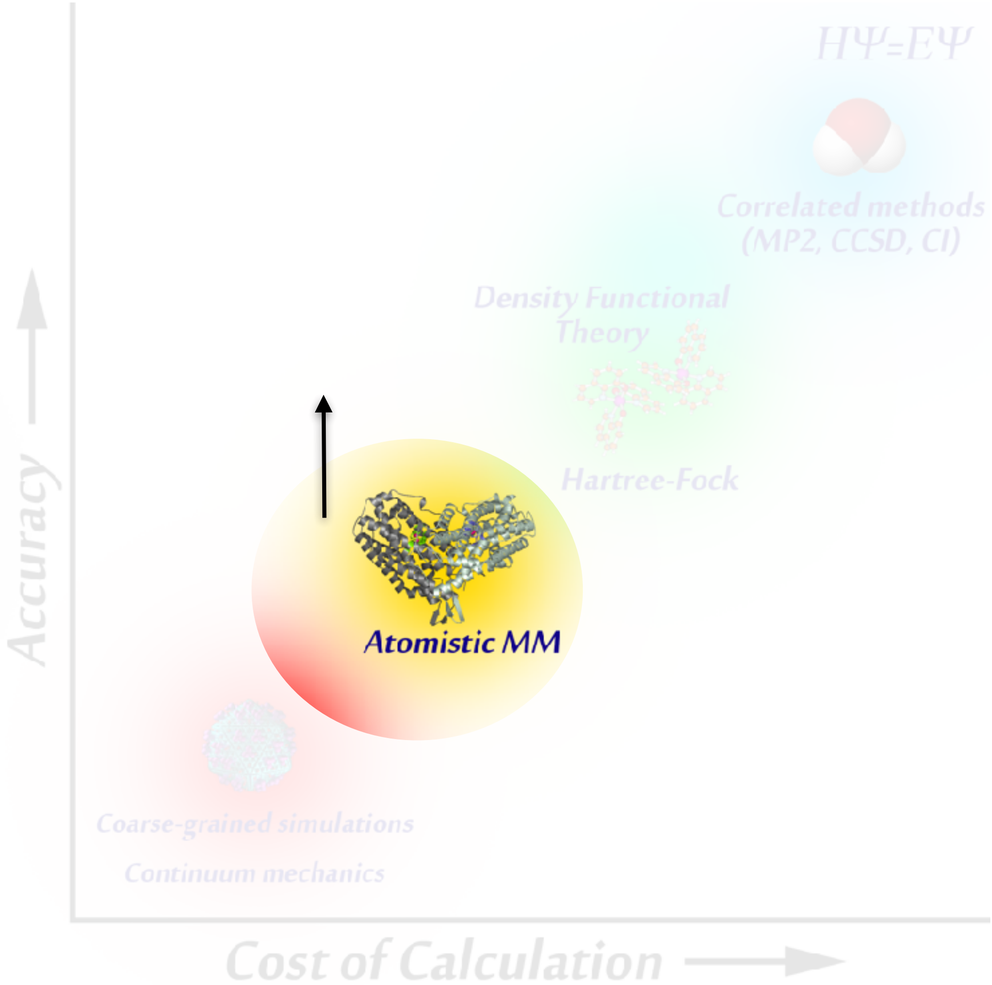

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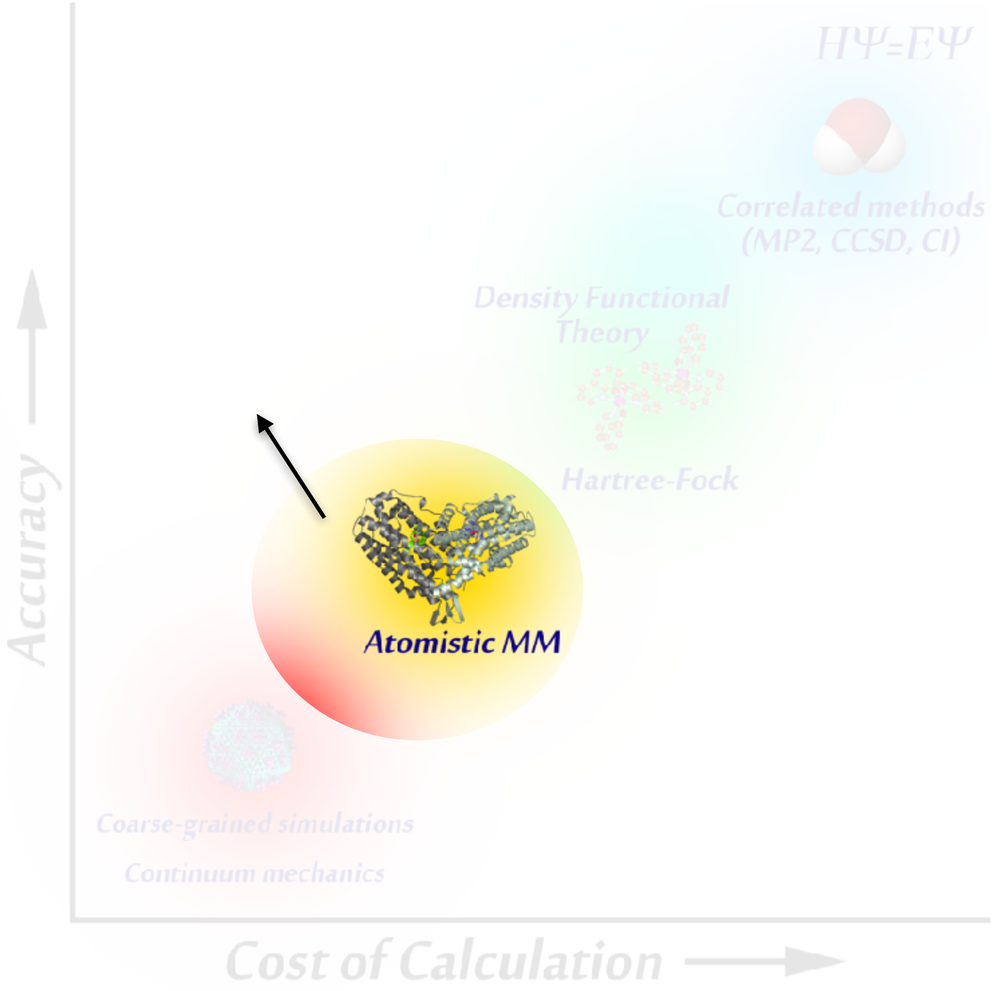

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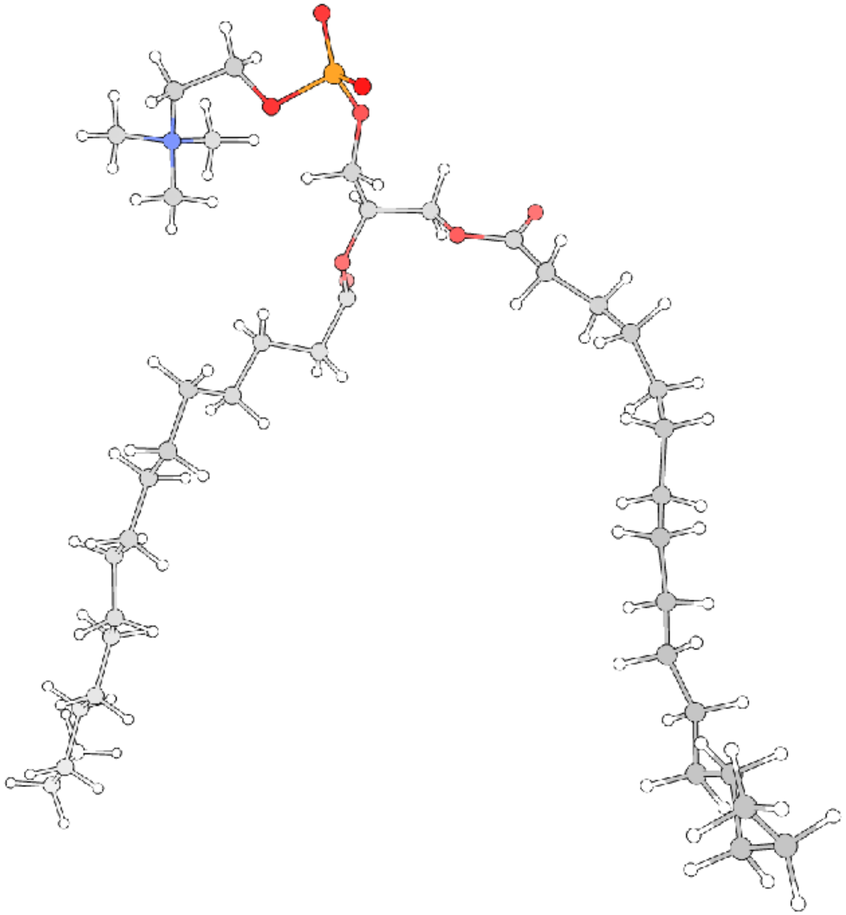

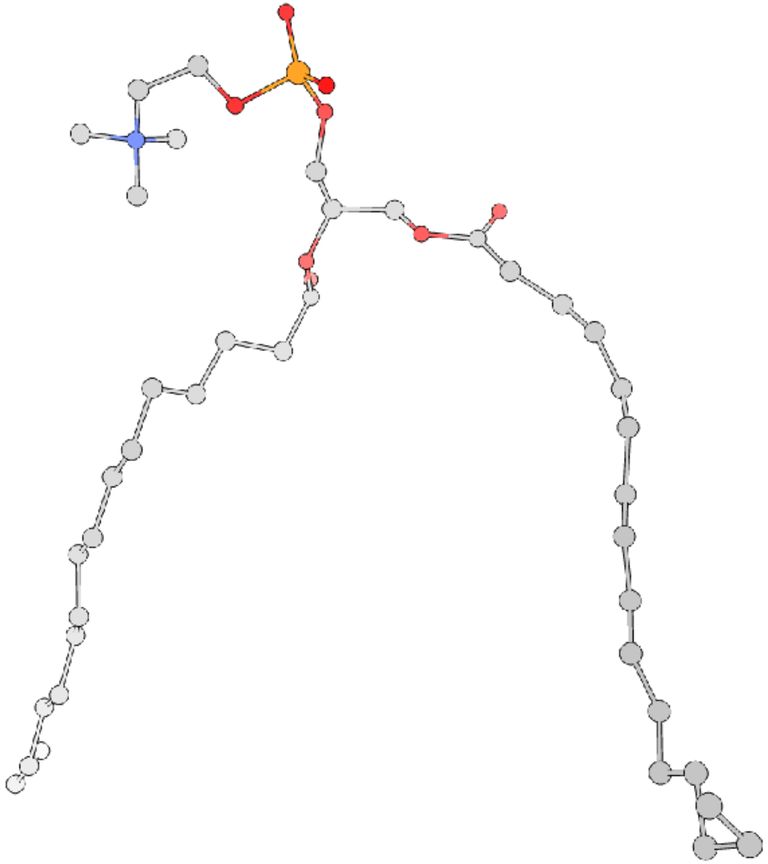

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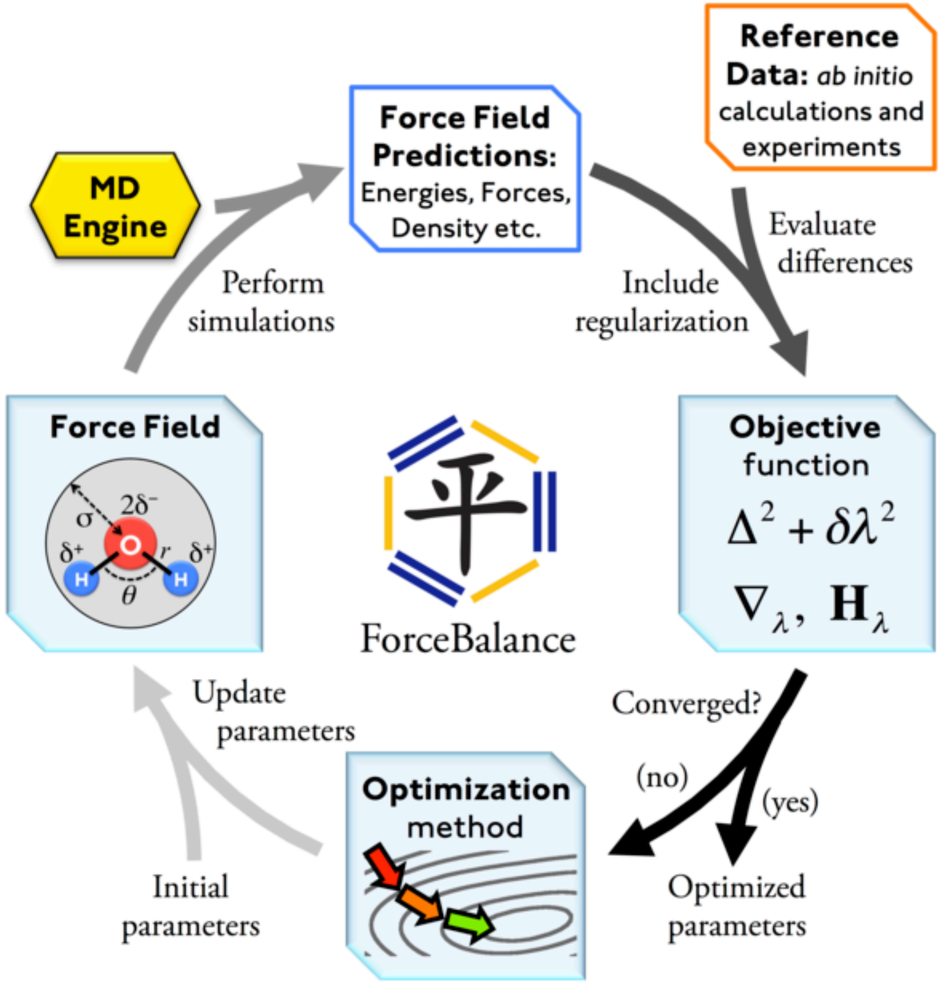

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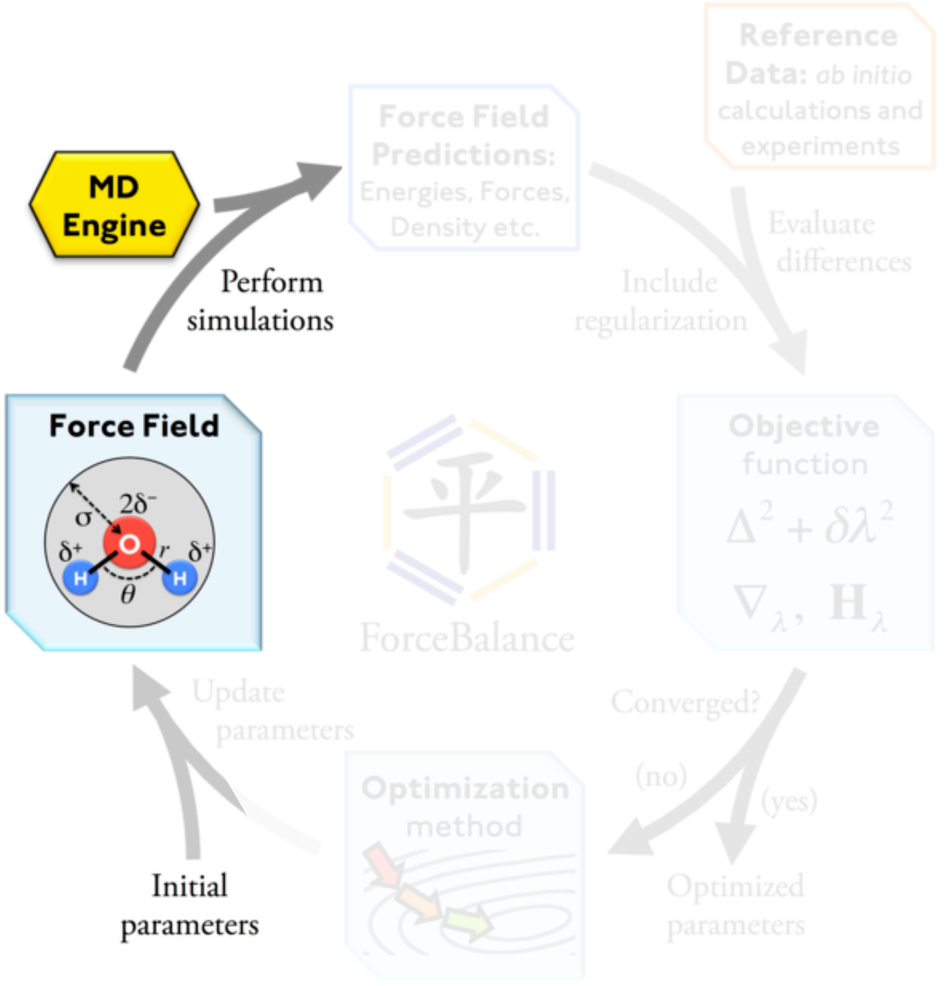

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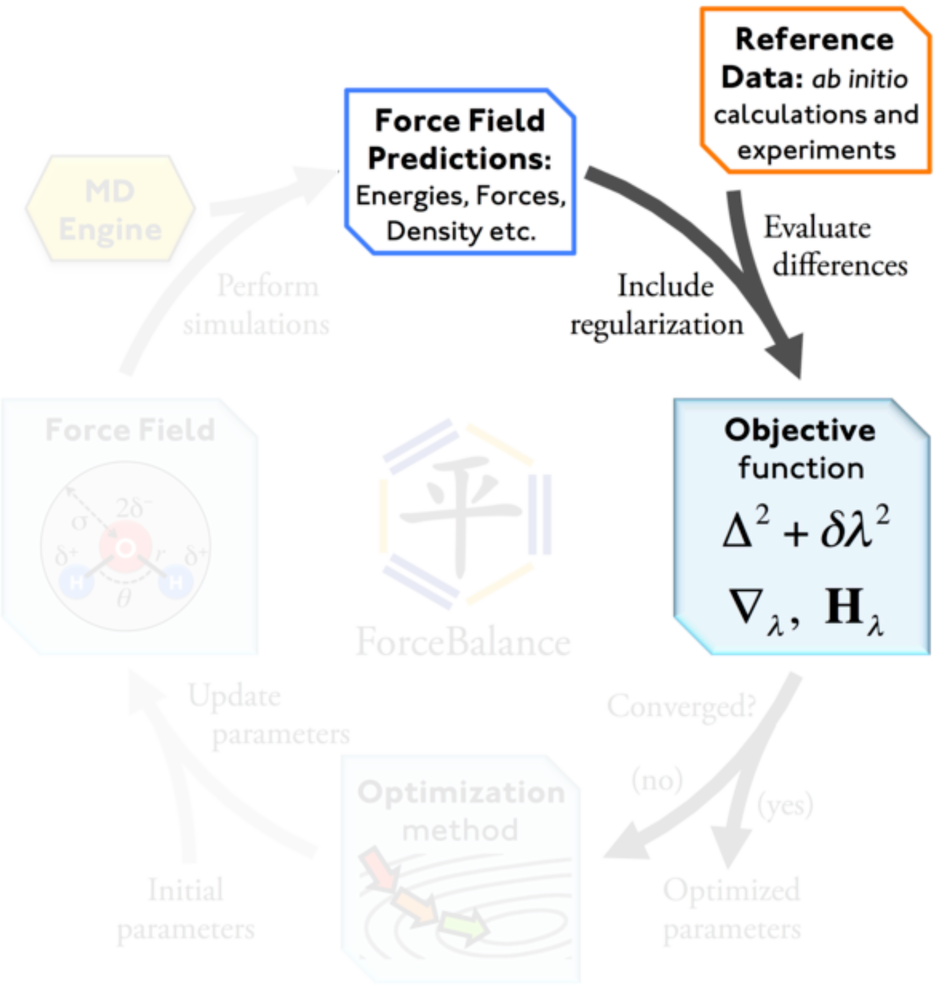

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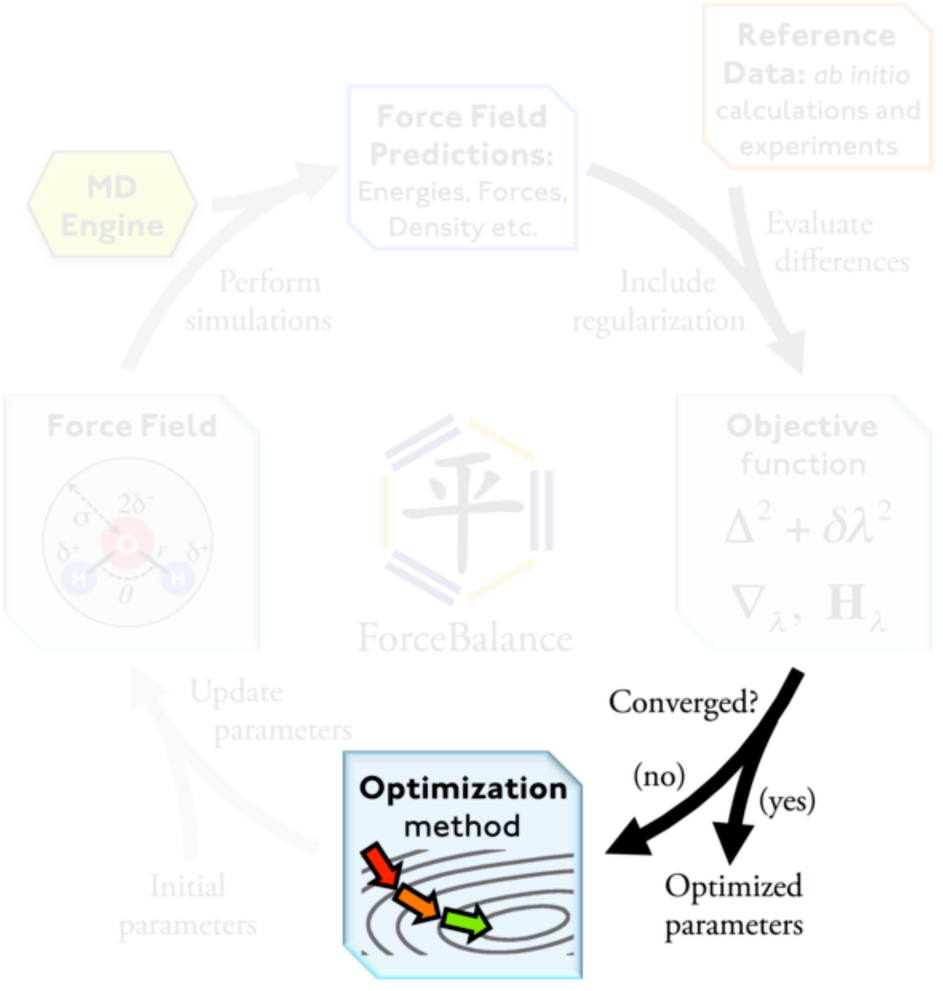

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Accuracy limit of rigid 3-point water models

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[1]*Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, Virginia 24060, USA*
[2]*Departments of Computer Science and Physics, Center for Soft Matter and Biological Physics, Virginia Tech, Blacksburg, Virginia 24060, USA*

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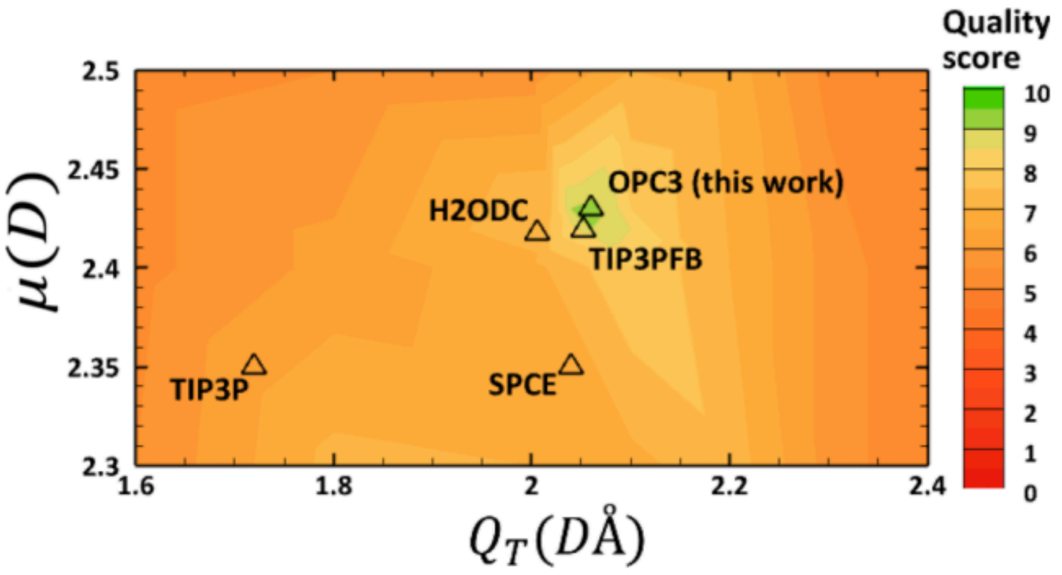

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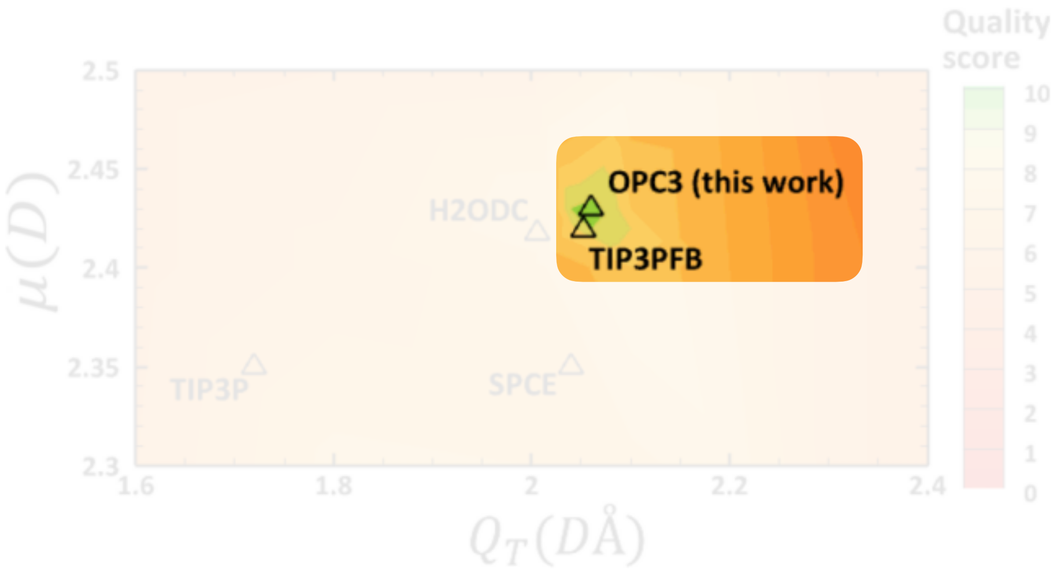

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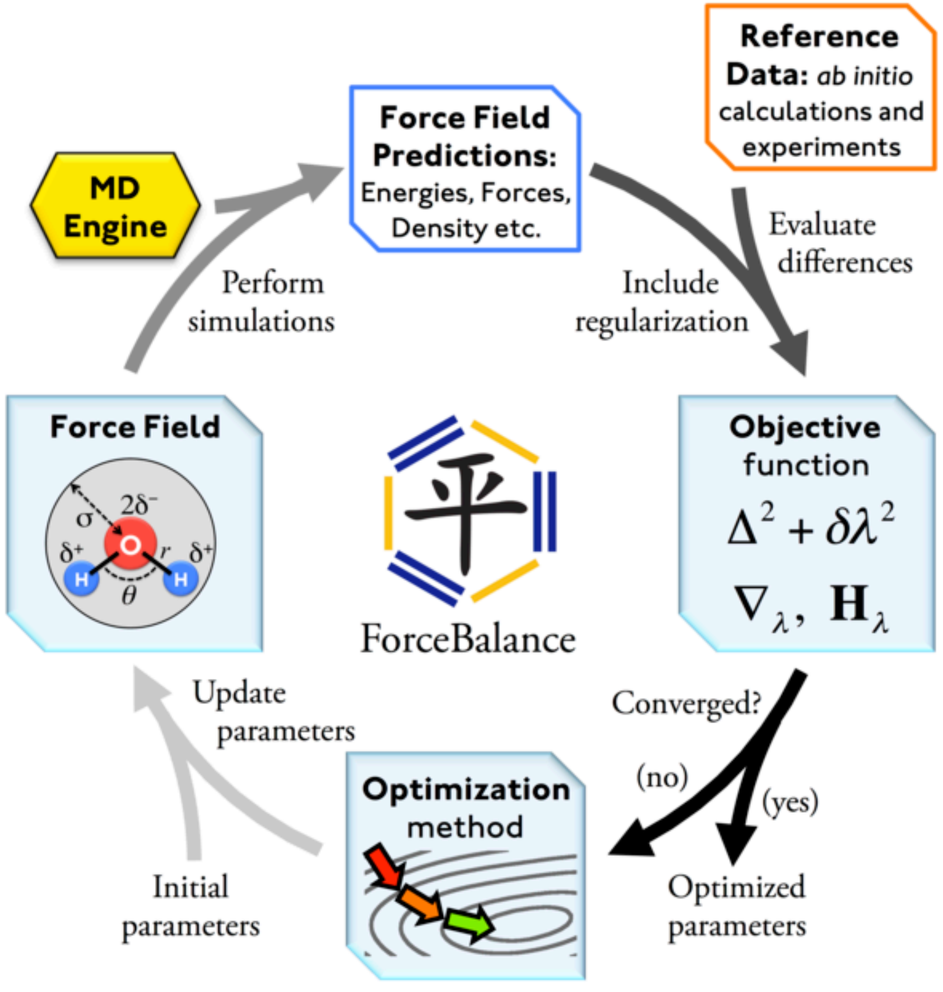

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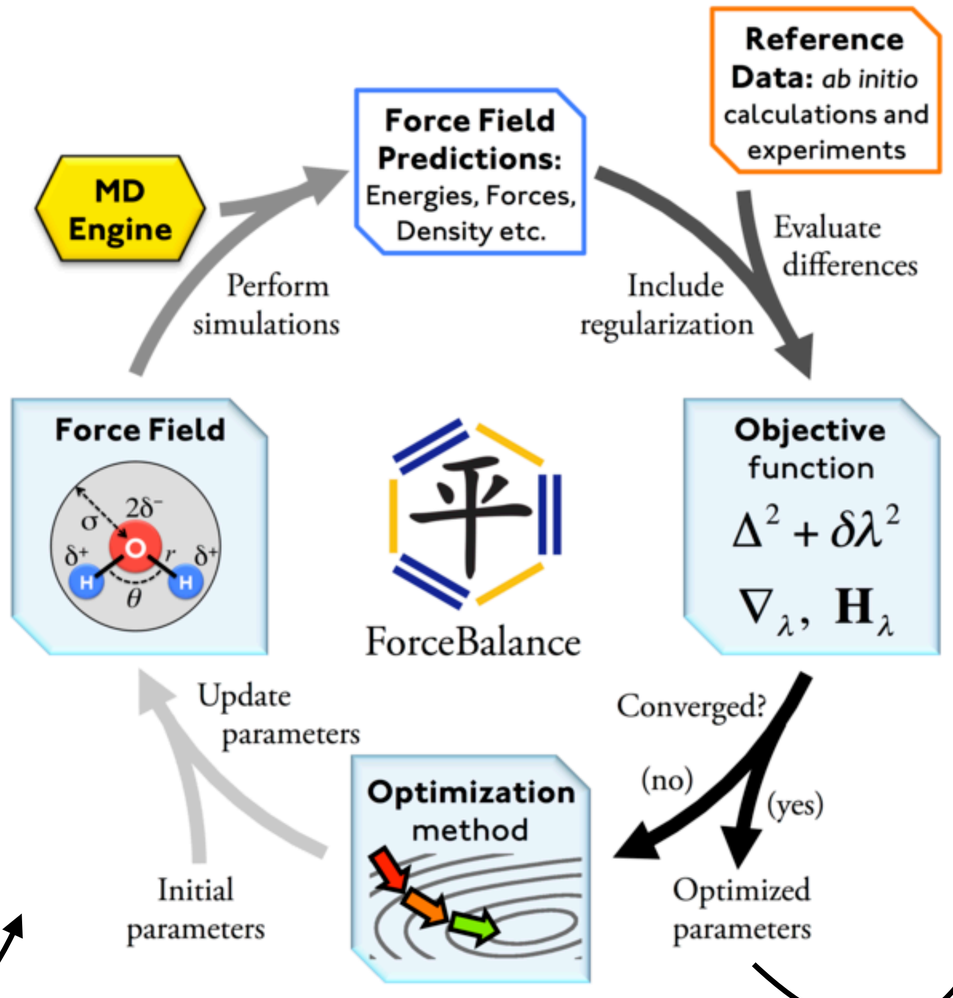
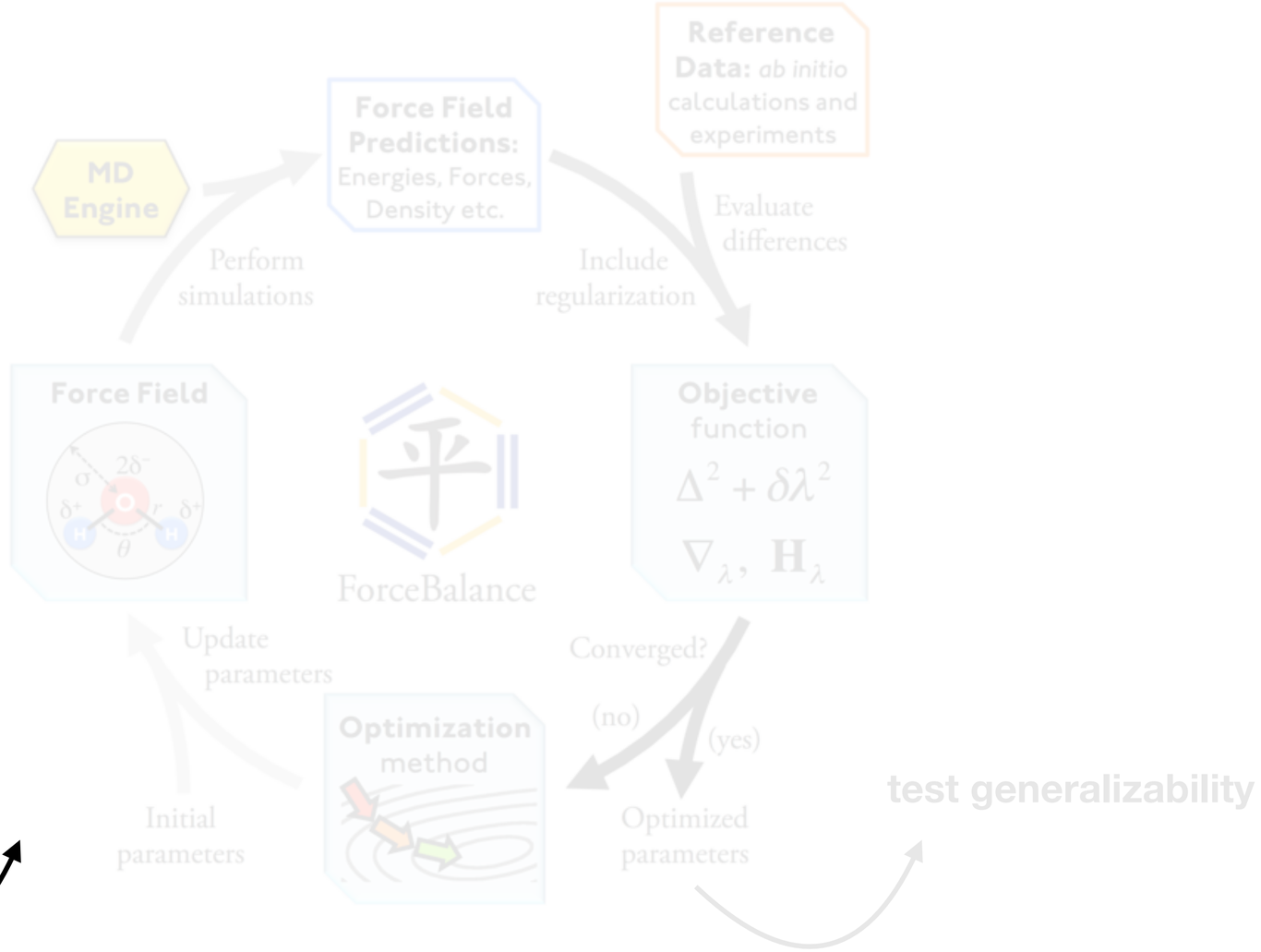


curate training dataset

test generalizability



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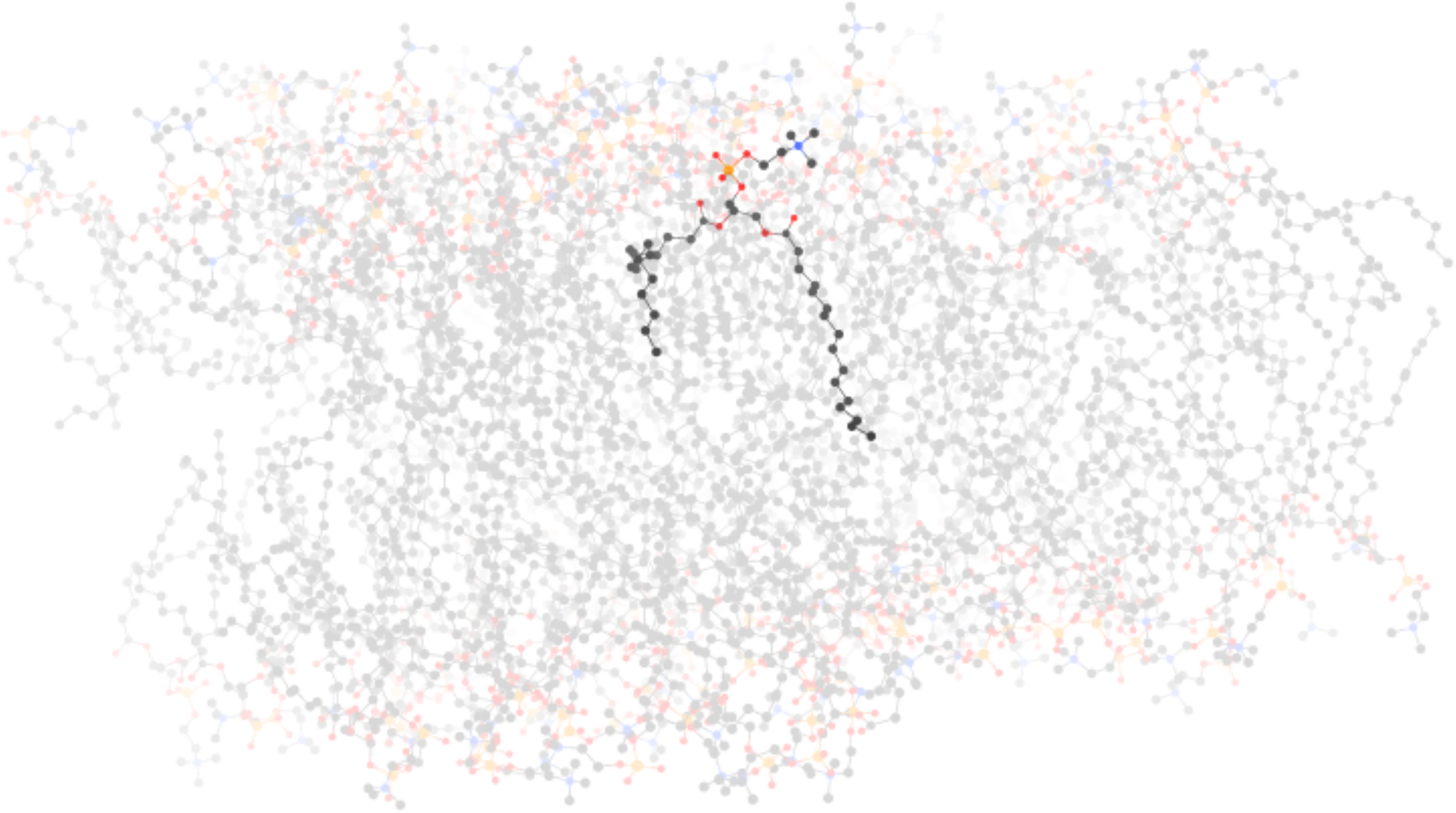
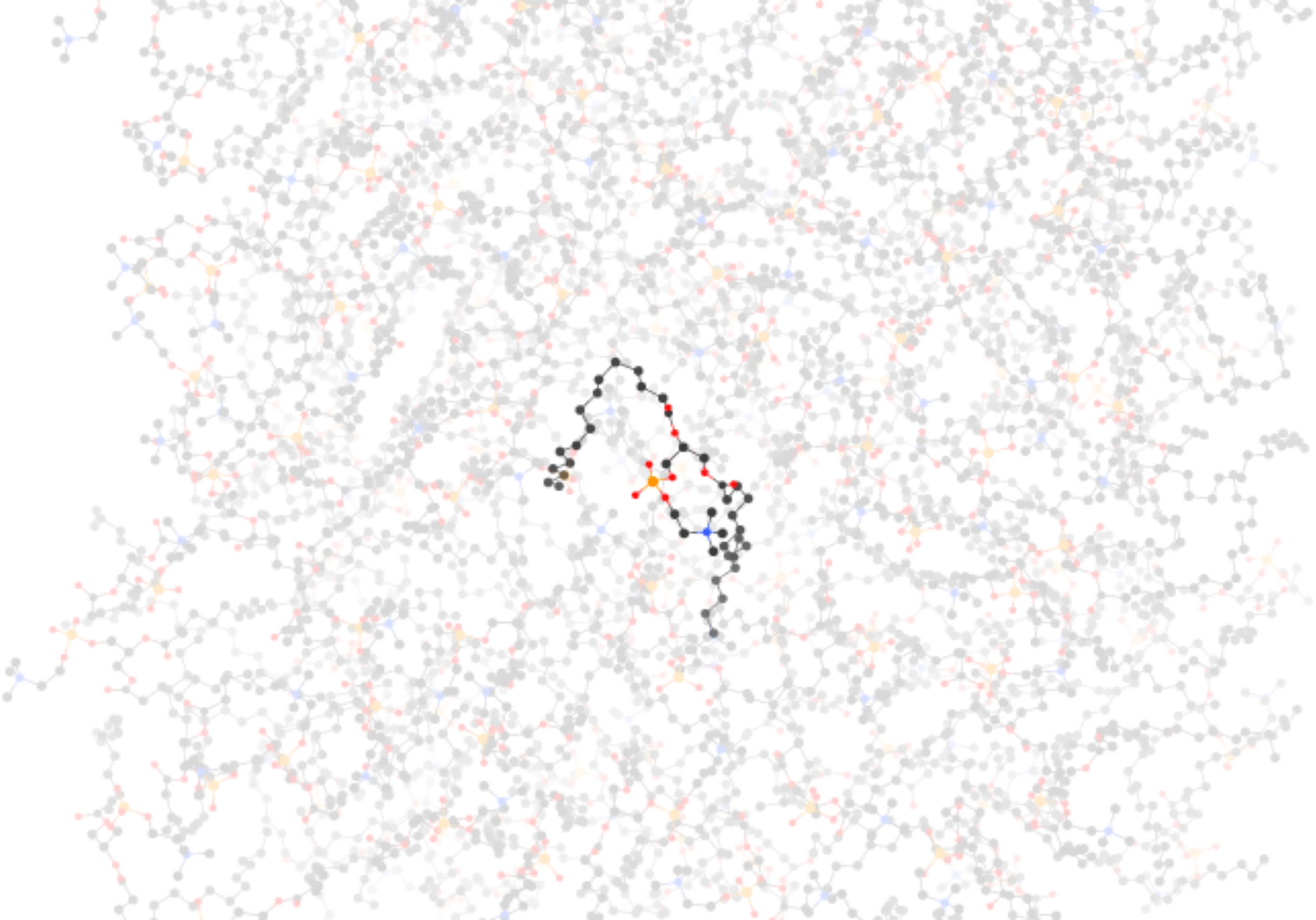
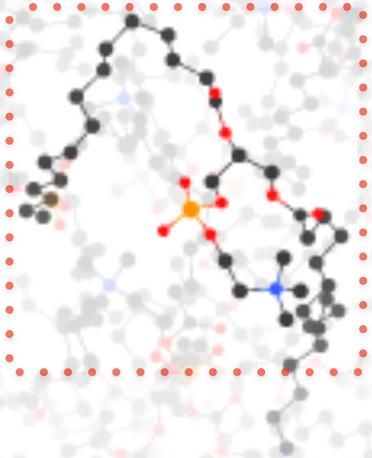
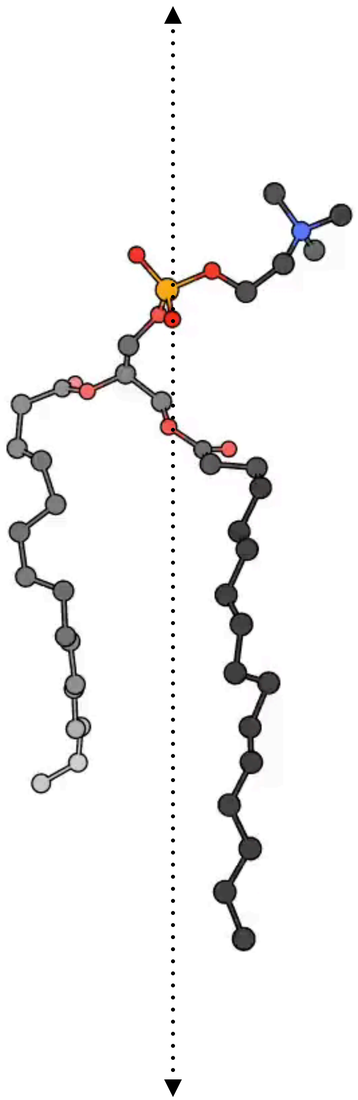






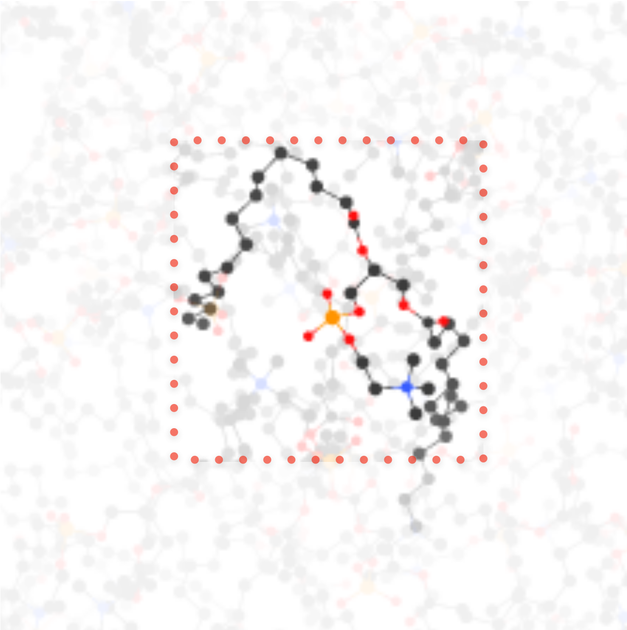
A_L / nm^2

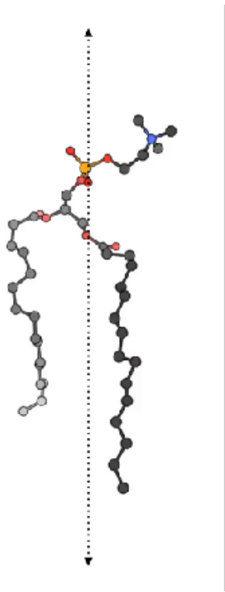


S_{CD} /

define system through available data

$$t_i \in T$$

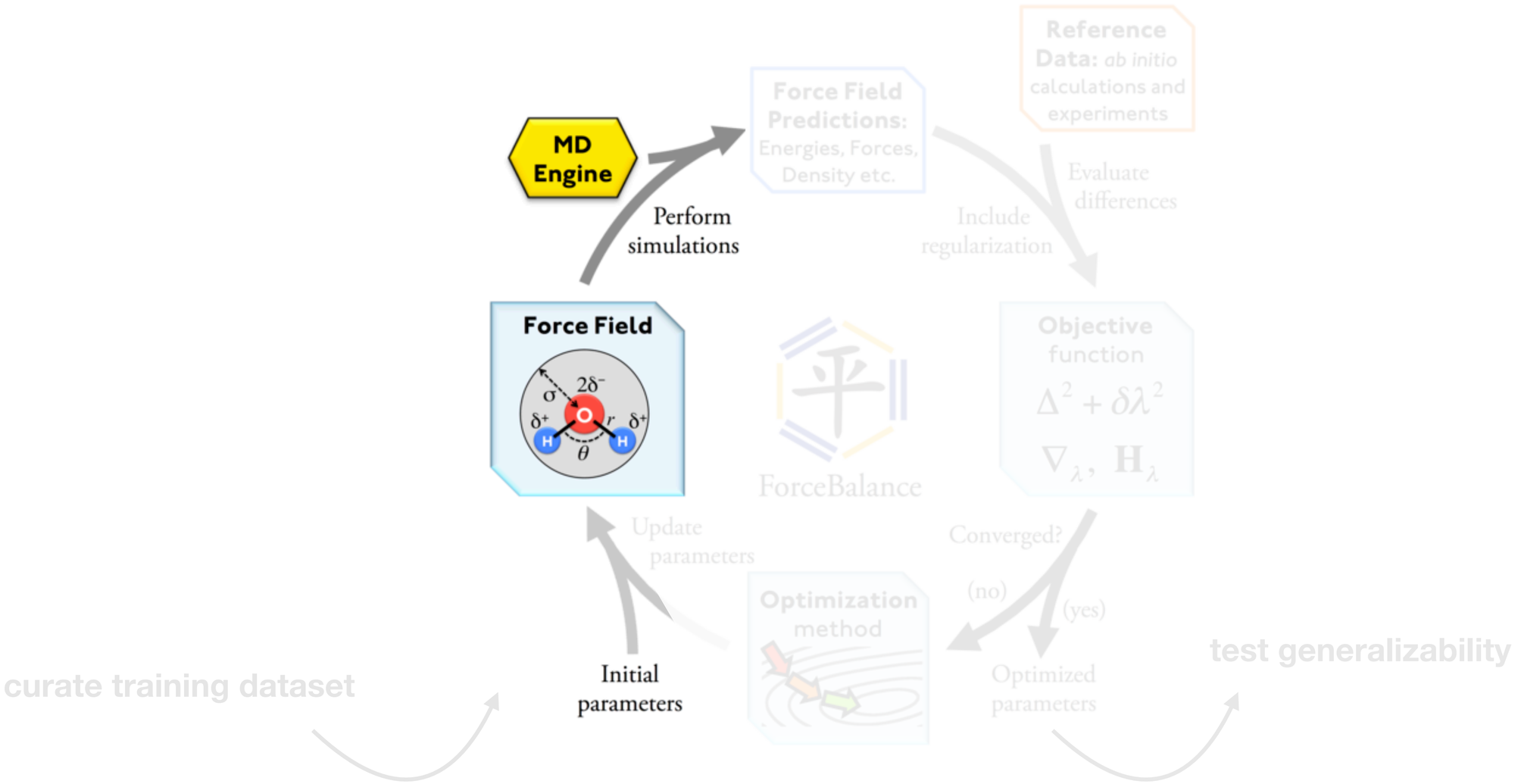




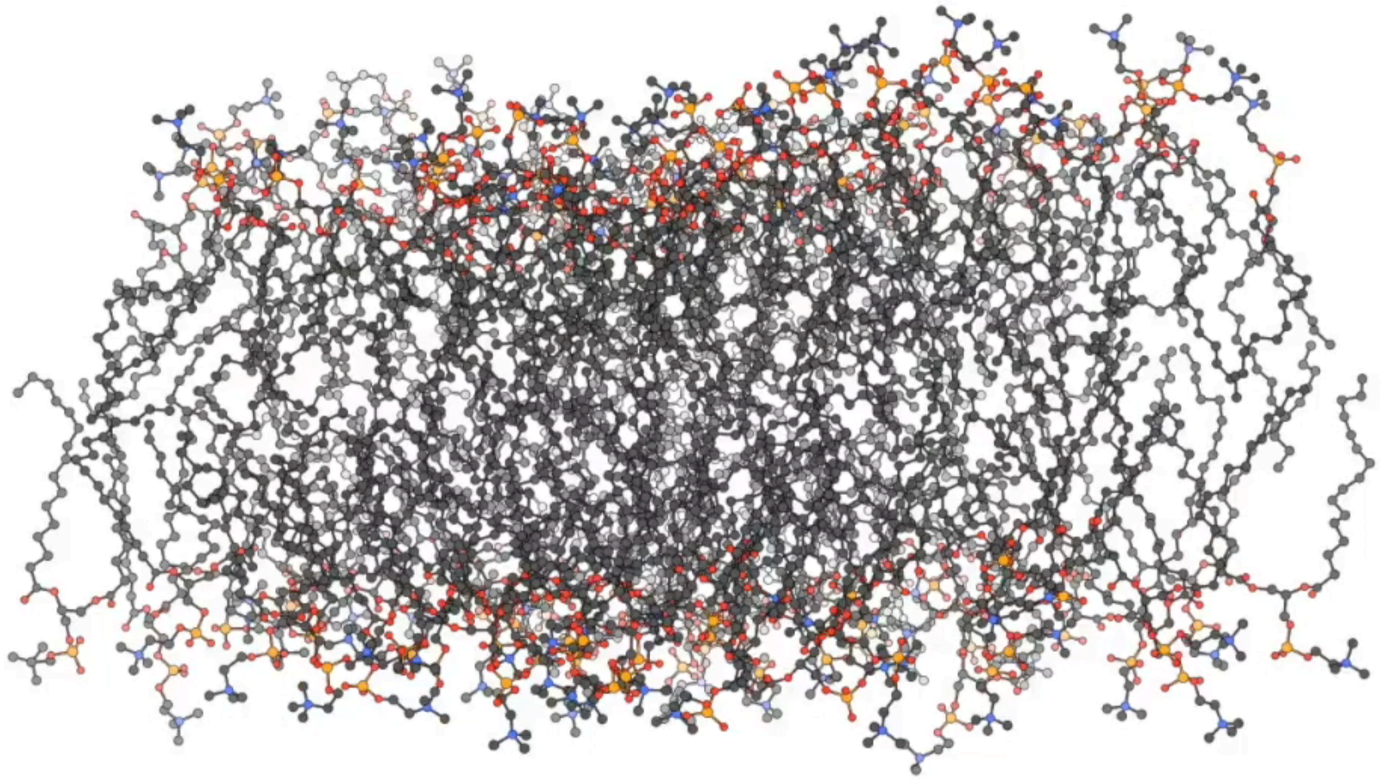
A_L / nm^2

S_{CD} /

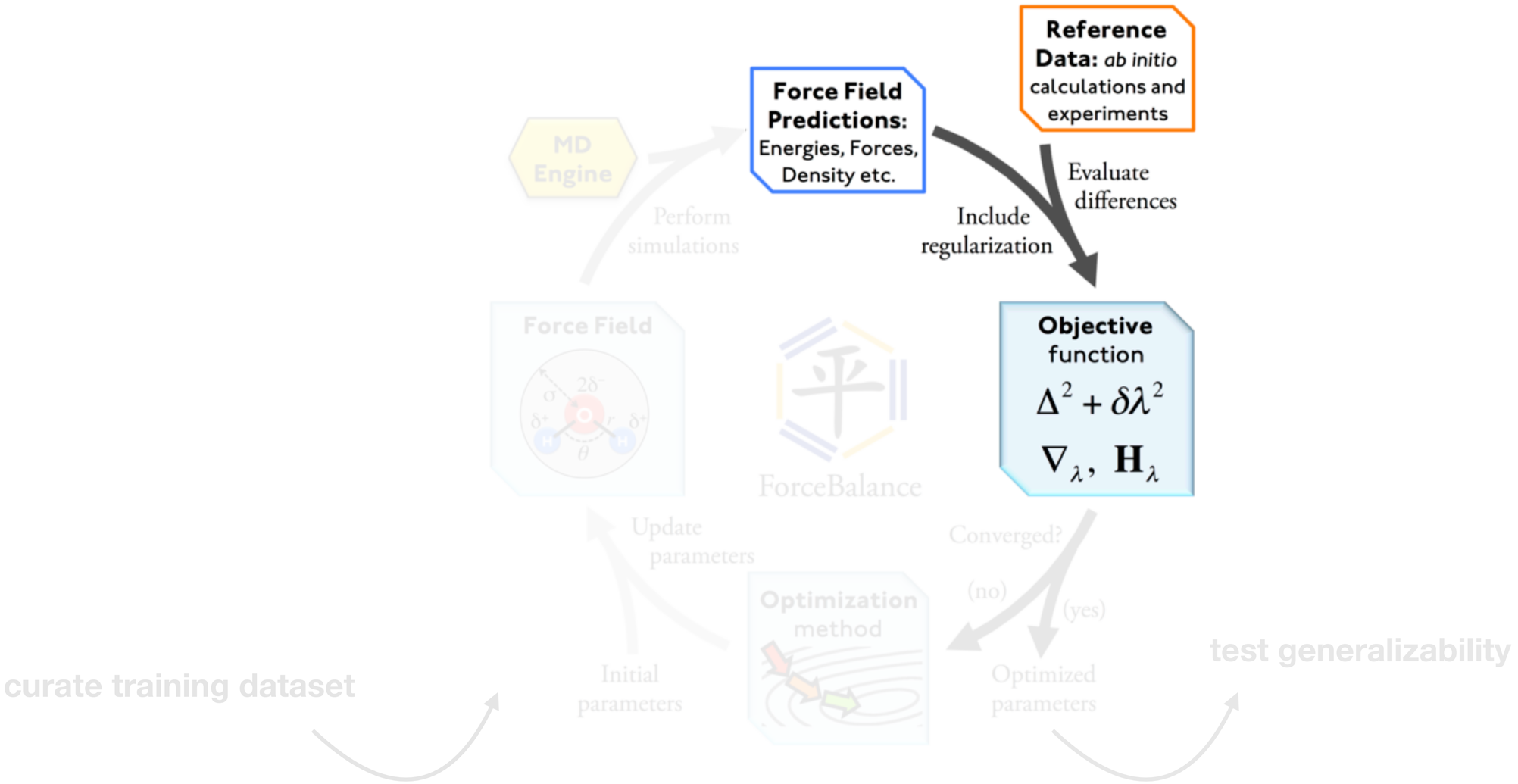
run initial simulation



run initial simulation

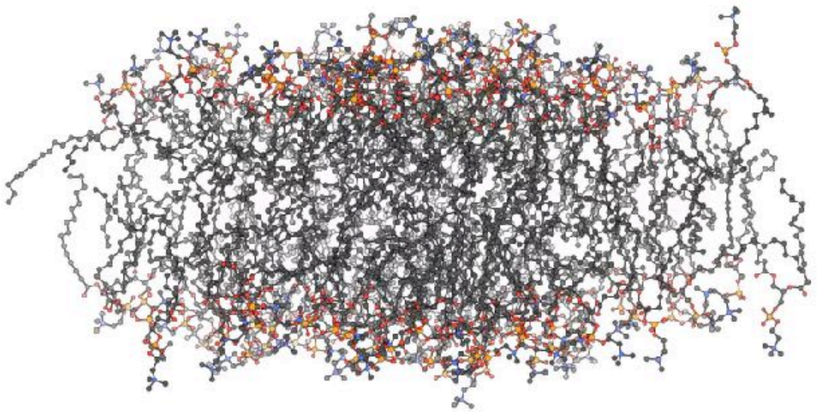


compute objective function using training data



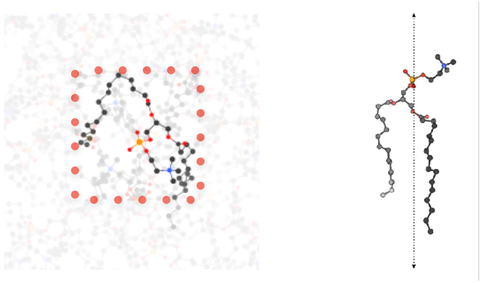
compute objective function using training data

$$V(q|\Lambda)$$



$$L(\Lambda|T, \alpha, \beta)$$

compute objective function using training data

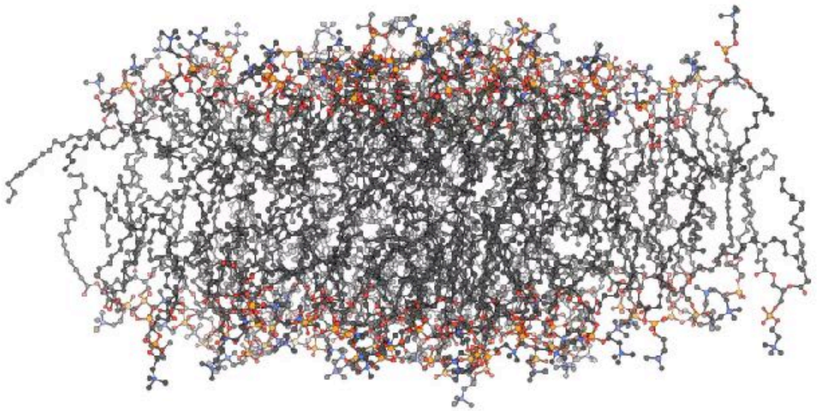


$\widetilde{t}_i(\Lambda)$

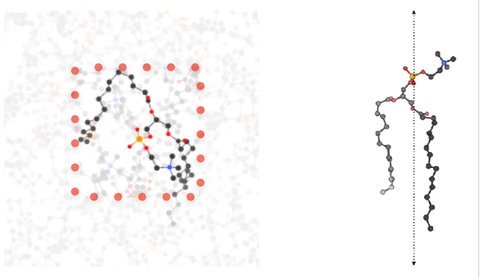
$t_i \in T$

$V(q|\Lambda)$

$L(\Lambda|T, \alpha, \beta)$



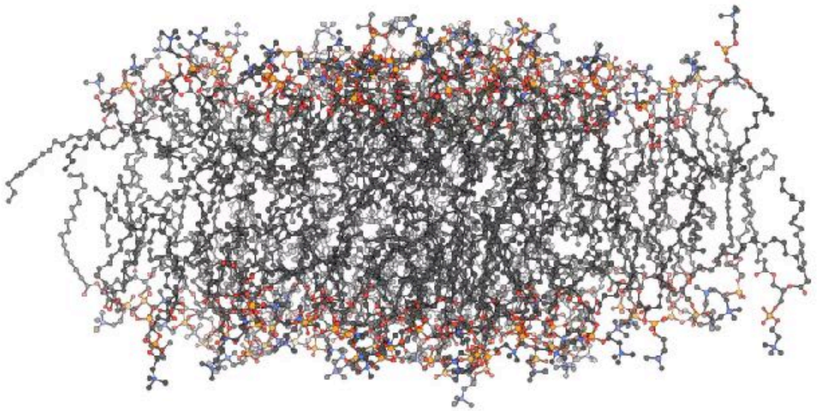
compute objective function using training data



$\widetilde{t}_i(\Lambda)$

$t_i \in T$

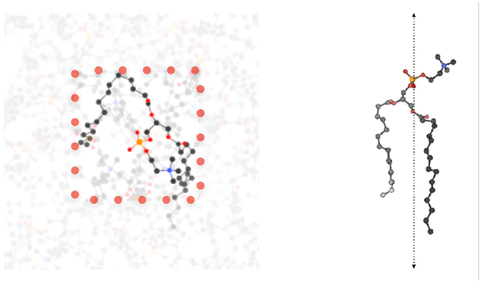
$V(q|\Lambda)$



$$L(\Lambda|T,\alpha,\beta)$$

$$= \sum_i^{|T|} \alpha_i \left(t_i - \widetilde{t}_i(\Lambda)\right)^2 + \sum_i^{|\Lambda|} \beta_i ||\lambda_i||^2$$

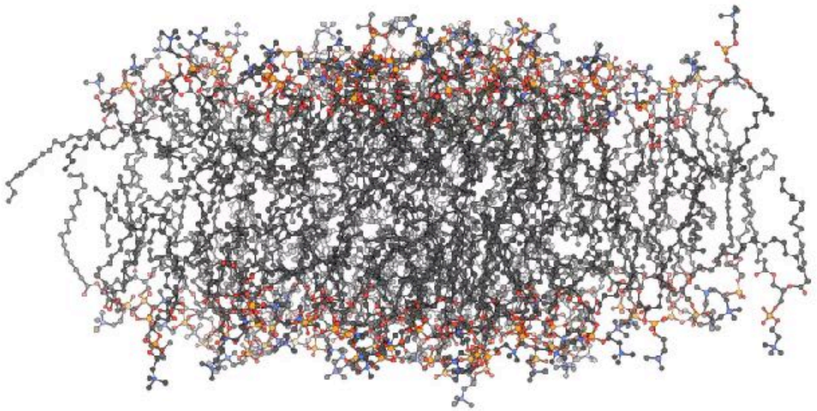
compute objective function using training data



$\widetilde{t}_i(\Lambda)$

$t_i \in T$

$V(q|\Lambda)$



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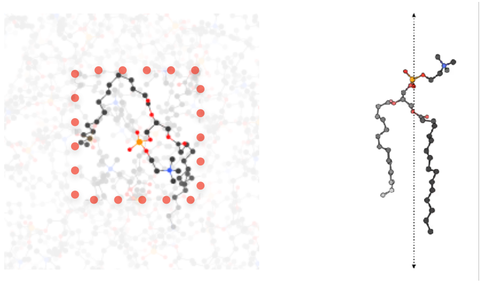
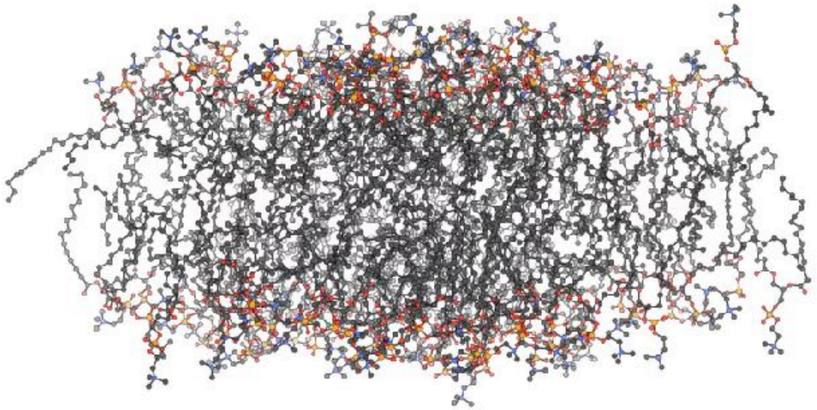


$$\widetilde{t}_i(\Lambda)$$

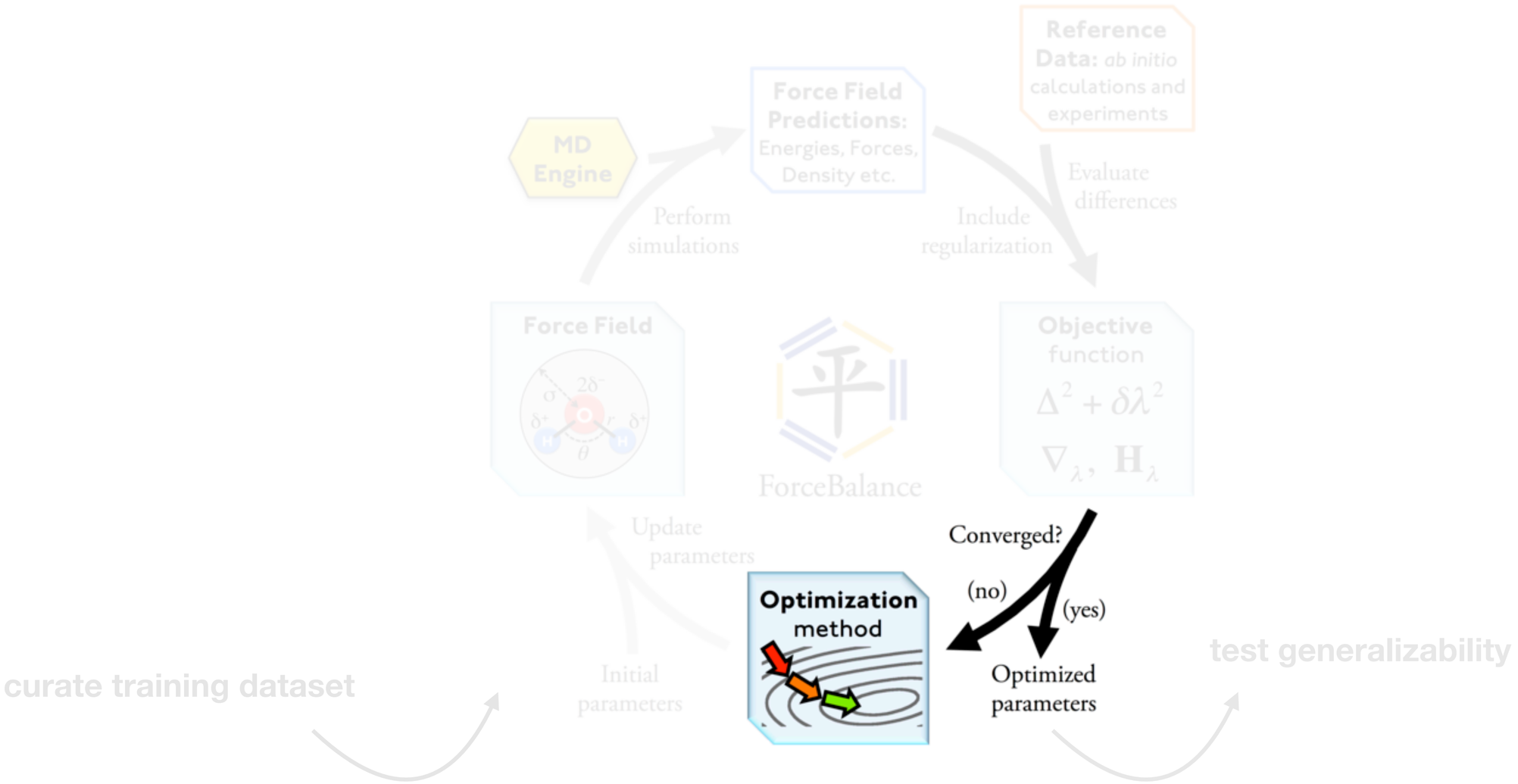
$$V(q|\Lambda)$$



$$L(\Lambda|T,\alpha,\beta)$$

$$= \sum_i^{|T|} \alpha_i \left(t_i - \widetilde{t}_i(\Lambda)\right)^2 + \sum_i^{|\Lambda|} \beta_i ||\lambda_i||^2$$

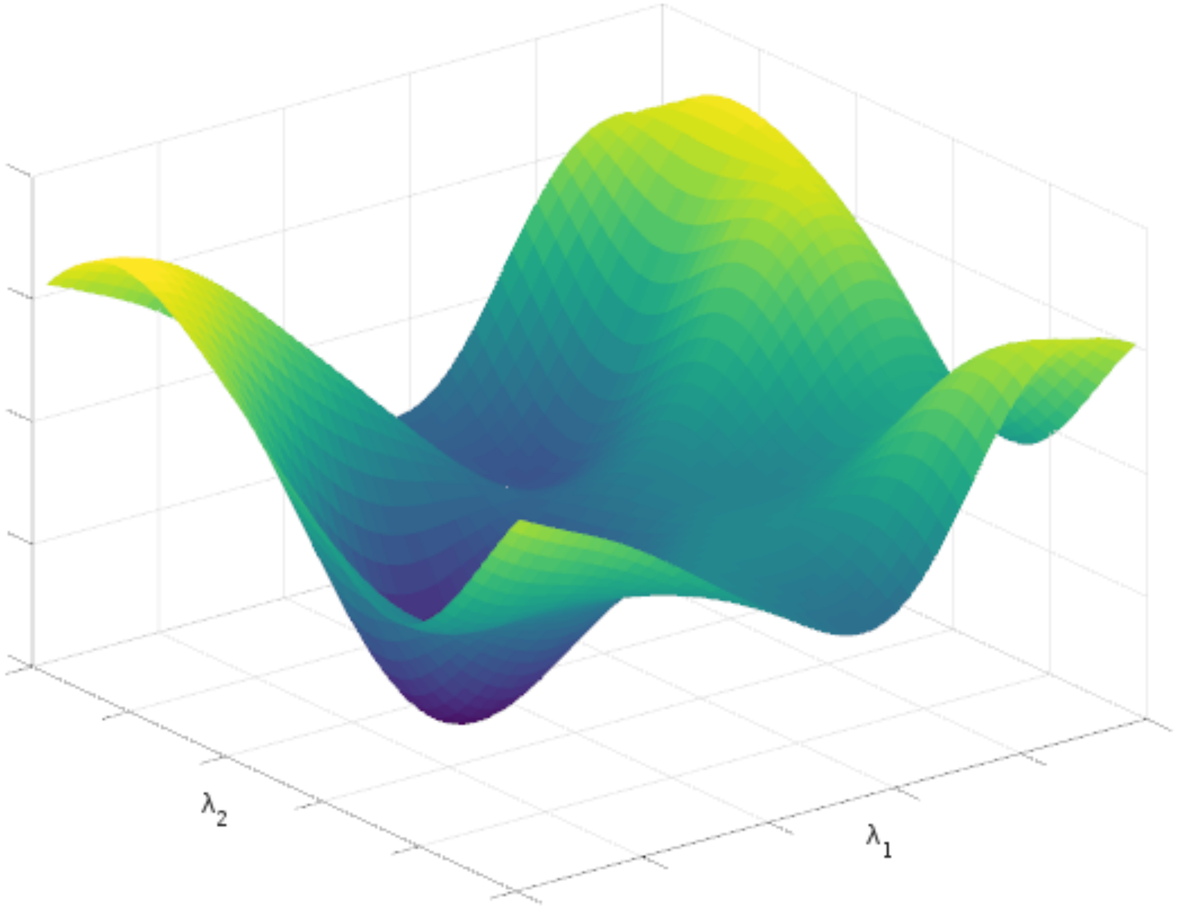
minimize objective (loss) function



minimize objective function using Levenberg–Marquardt

OBJECTIVE FUNCTION:

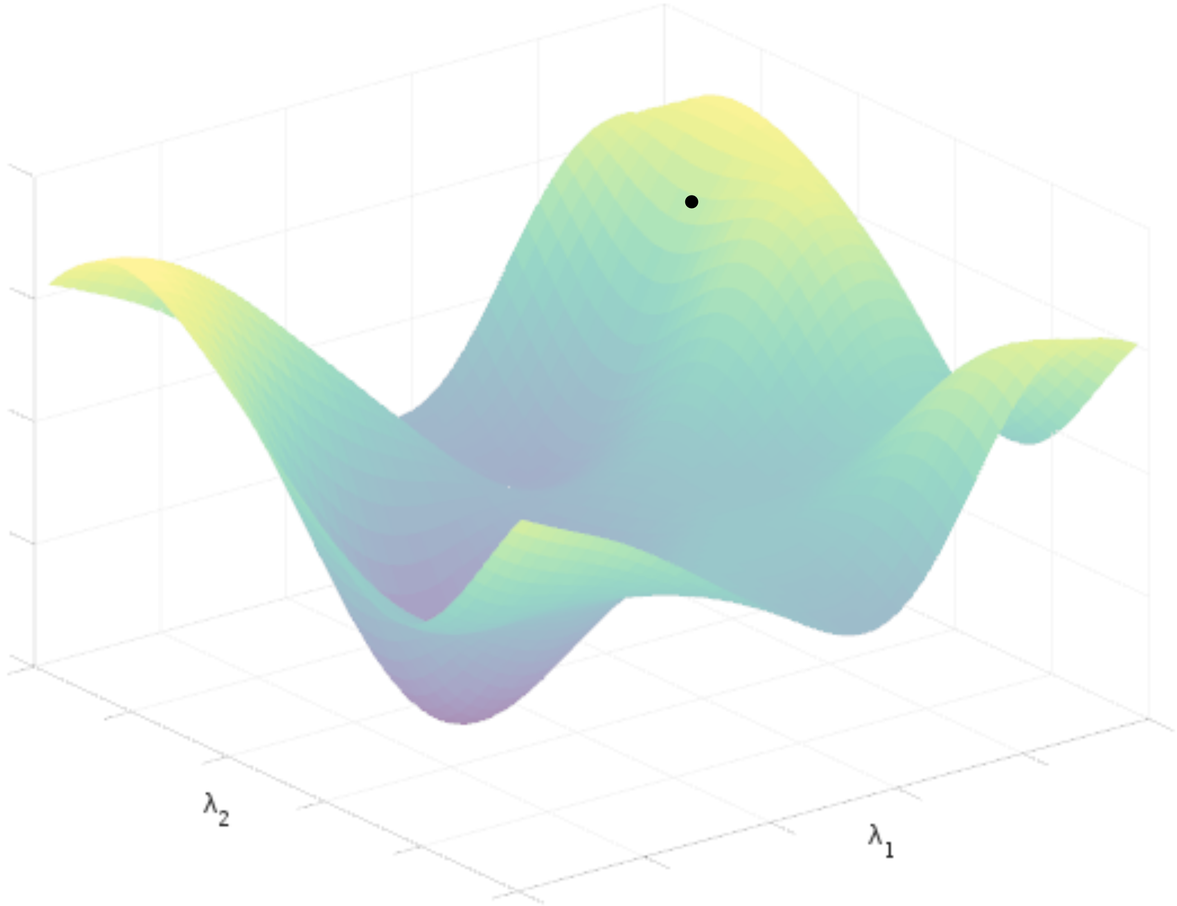
$$L(\Lambda|T, \alpha, \beta)$$



minimize objective function using Levenberg–Marquardt

OBJECTIVE FUNCTION:

$$L(\Lambda|T, \alpha, \beta)$$



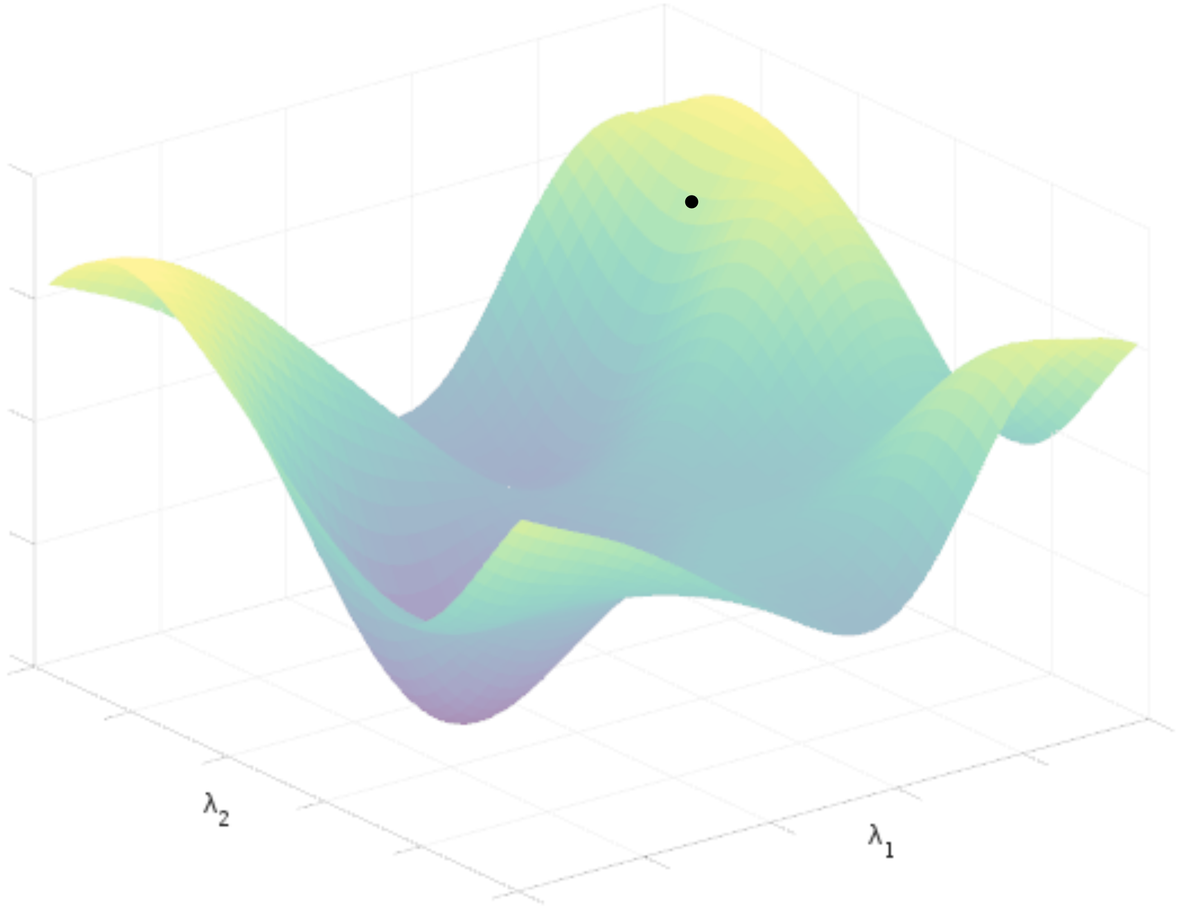
minimize objective function using Levenberg–Marquardt

OBJECTIVE FUNCTION:

$$L(\Lambda|T, \alpha, \beta)$$

GOAL:

$$\underset{\lambda}{\operatorname{argmin}}\, L(\Lambda|T, \alpha, \beta)$$



minimize objective function using Levenberg–Marquardt

OBJECTIVE FUNCTION:

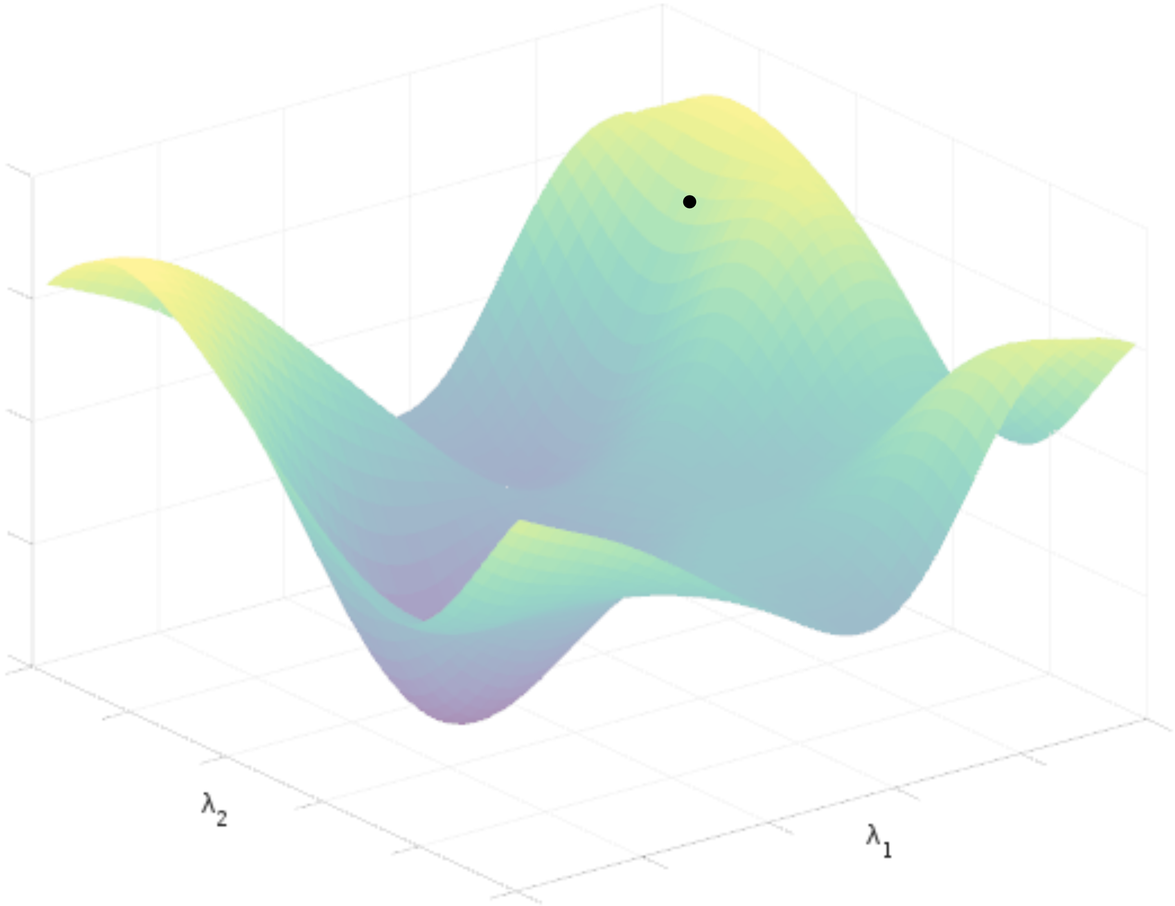
$$L(\Lambda|T,\alpha,\beta)$$

GOAL:

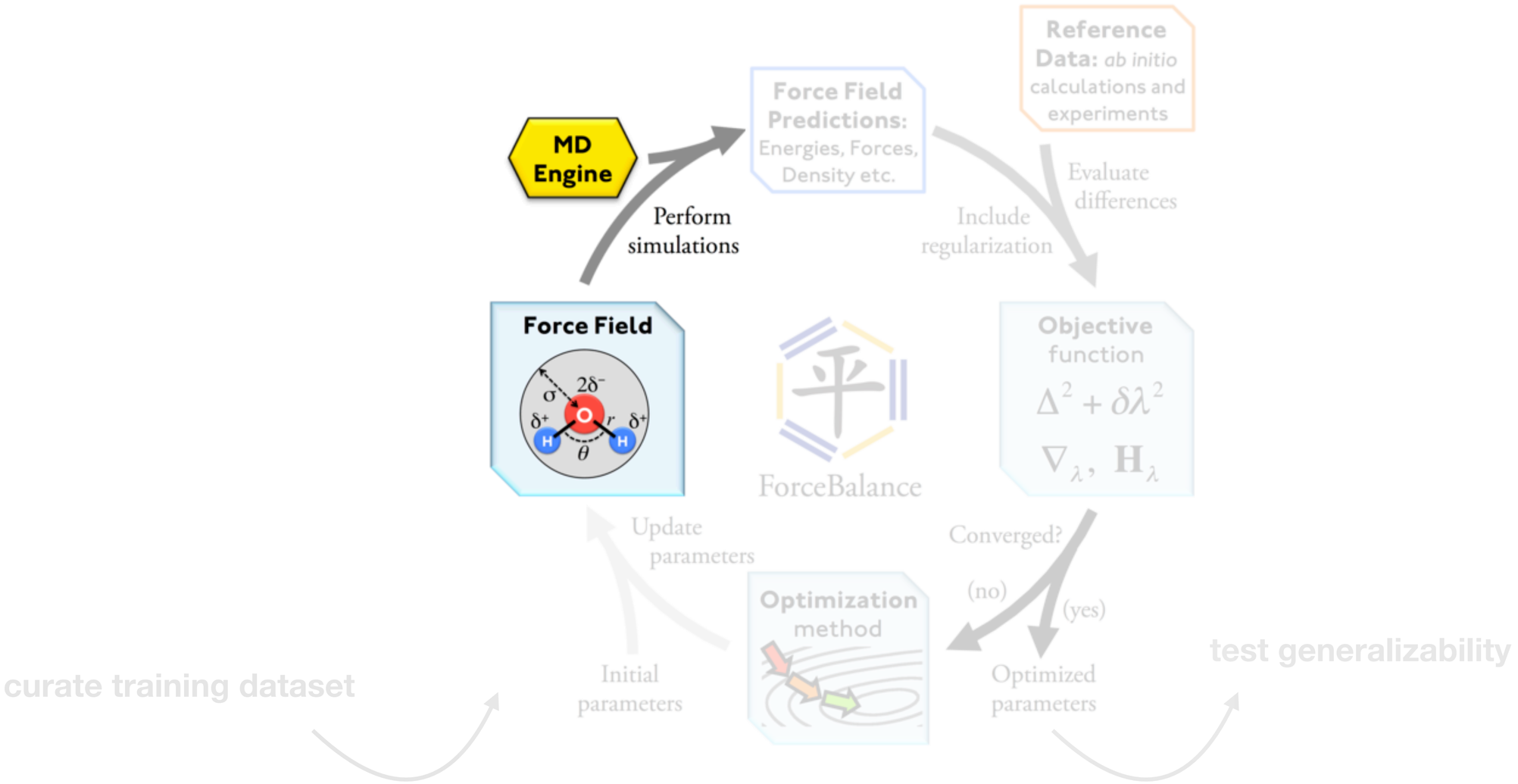
$$\underset{\lambda}{\operatorname{argmin}}\, L(\Lambda|T,\alpha,\beta)$$

OPTIMIZER:

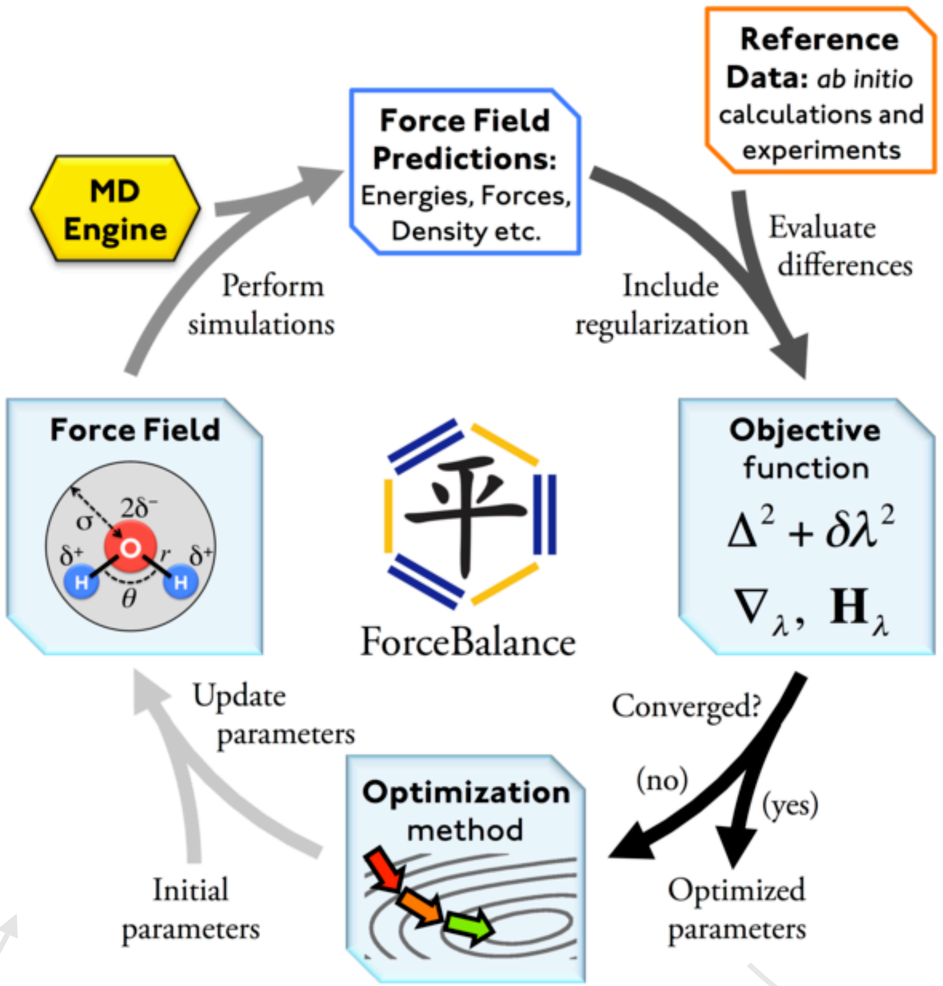
$$\lambda_{i+1} = \lambda_i + \mu \frac{\nabla L(\Lambda|T,\alpha,\beta)}{\nabla^2 L(\Lambda|T,\alpha,\beta) + bI}$$



iterate


MD Engine
Perform simulations
Force Field Predictions: Energies, Forces, Density etc.
Reference Data: ab initio calculations and experiments
Evaluate differences
Include regularization
Force Field
Objective function
$\Delta^2 + \delta\lambda^2$
$\nabla_\lambda, \mathbf{H}_\lambda$
ForceBalance
Update parameters
Converged?
(no)
(yes)
Optimization method
Initial parameters
Optimized parameters
curate training dataset
test generalizability

iterate



curate training dataset

test generalizability

iterate

OBJECTIVE FUNCTION:

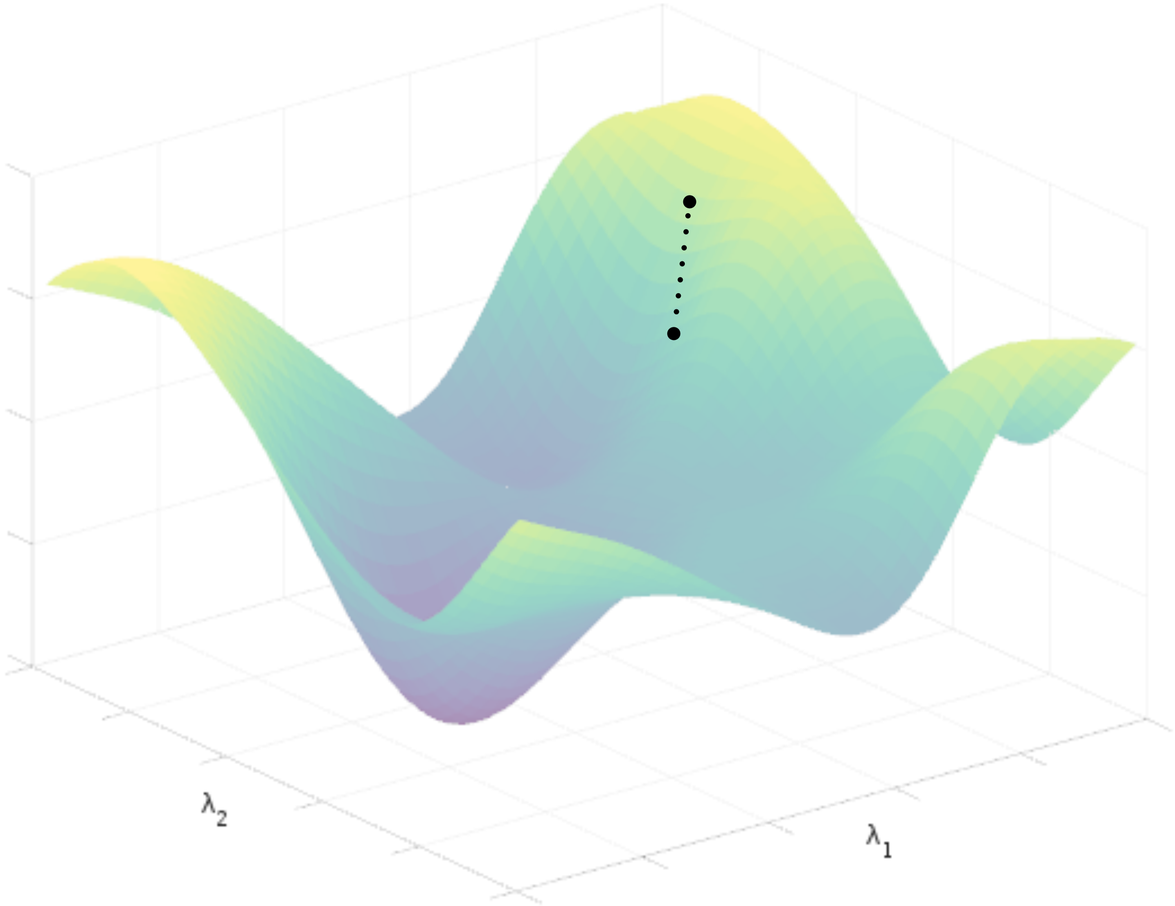
$$L(\Lambda|T, \alpha, \beta)$$

GOAL:

$$\underset{\lambda}{\operatorname{argmin}}\, L(\Lambda|T, \alpha, \beta)$$

OPTIMIZER:

$$\lambda_{i+1} = \lambda_i + \mu \frac{\nabla L(\Lambda|T, \alpha, \beta)}{\nabla^2 L(\Lambda|T, \alpha, \beta) + bI}$$



iterate

OBJECTIVE FUNCTION:

$$L(\Lambda|T, \alpha, \beta)$$

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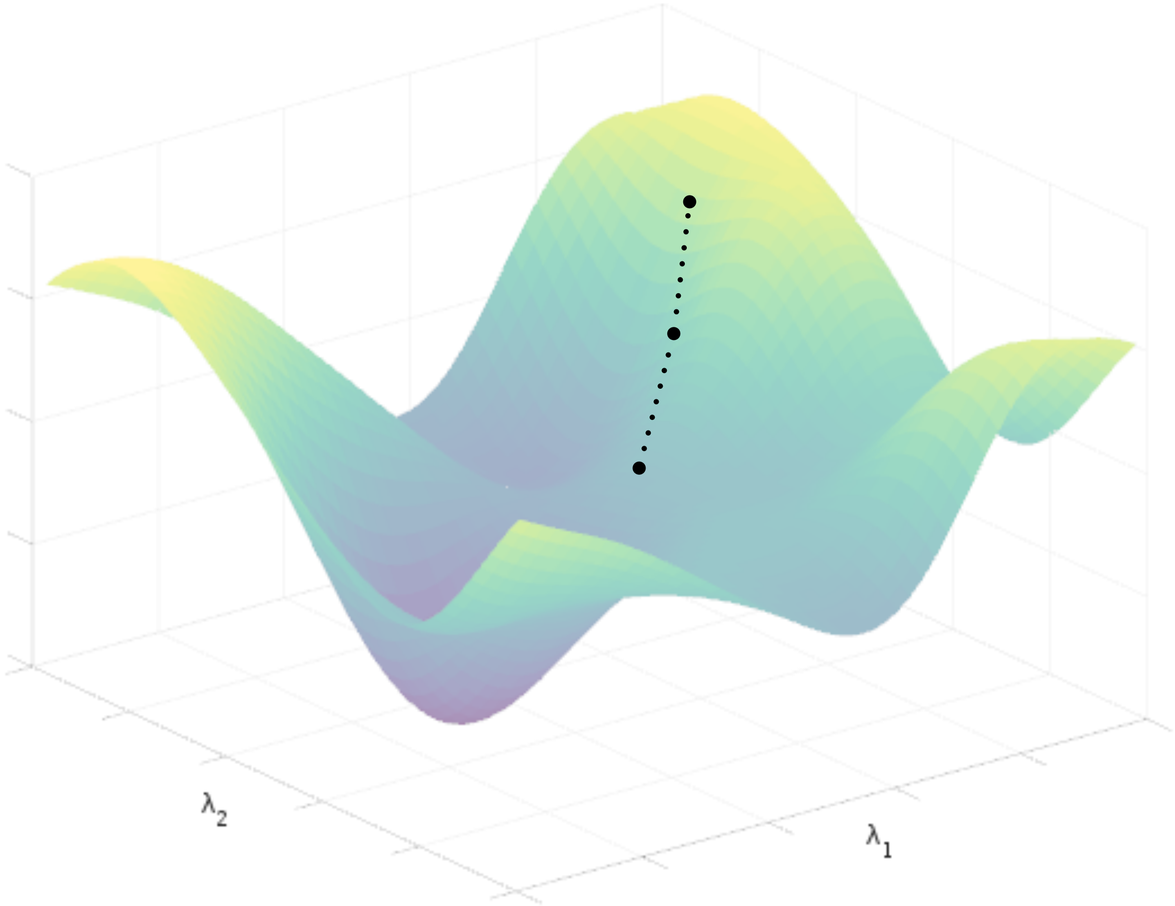

iterate

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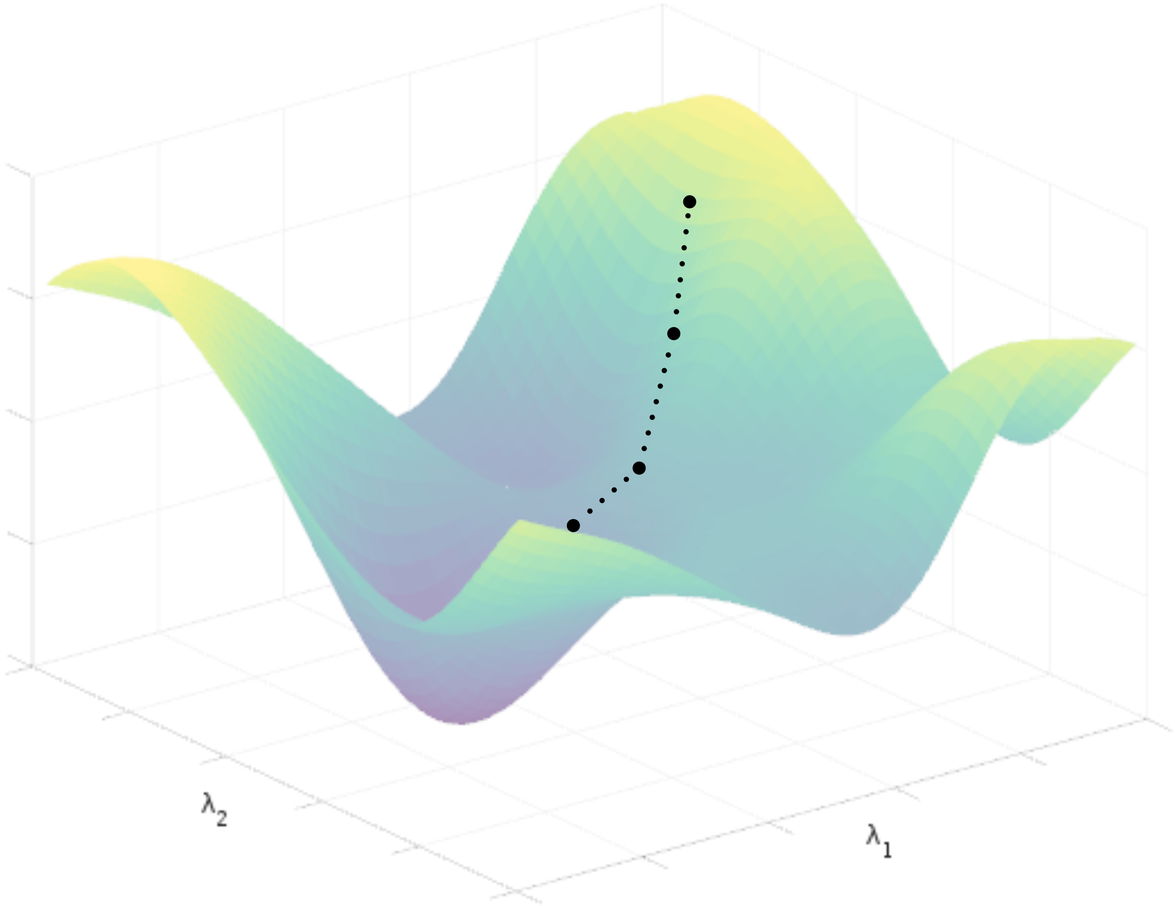

iterate

OBJECTIVE FUNCTION:

$$L(\Lambda|T, \alpha, \beta)$$

GOAL:

$$\underset{\lambda}{\operatorname{argmin}}\, L(\Lambda|T, \alpha, \beta)$$

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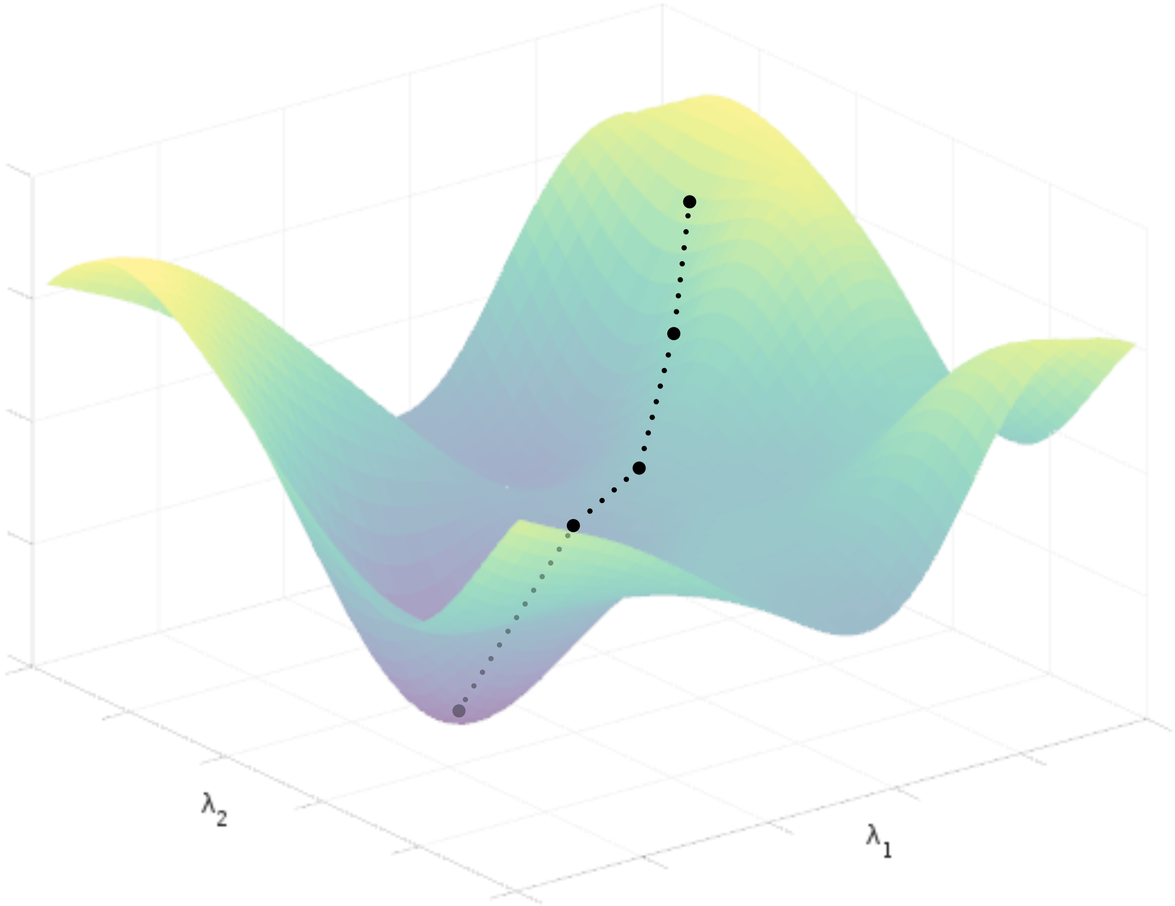
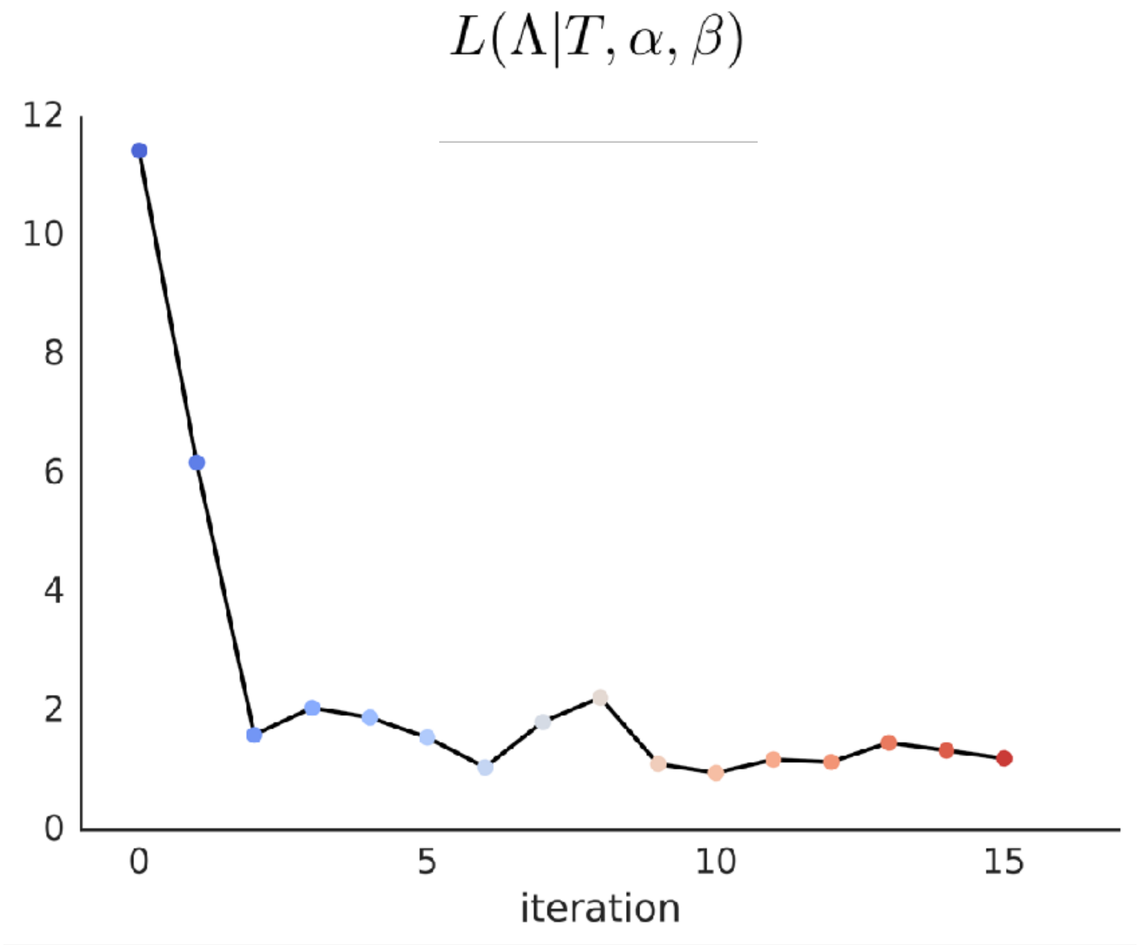


monitor convergence using objective function



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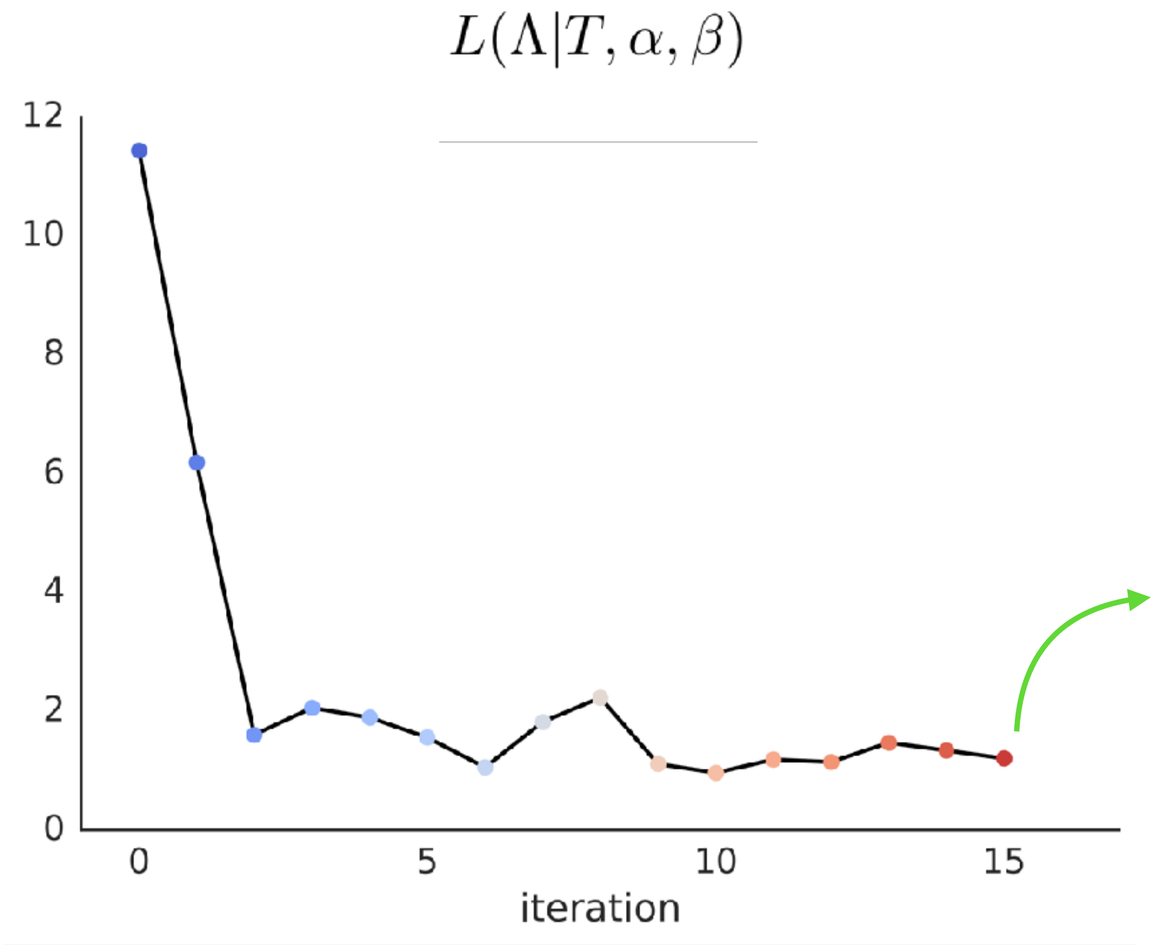
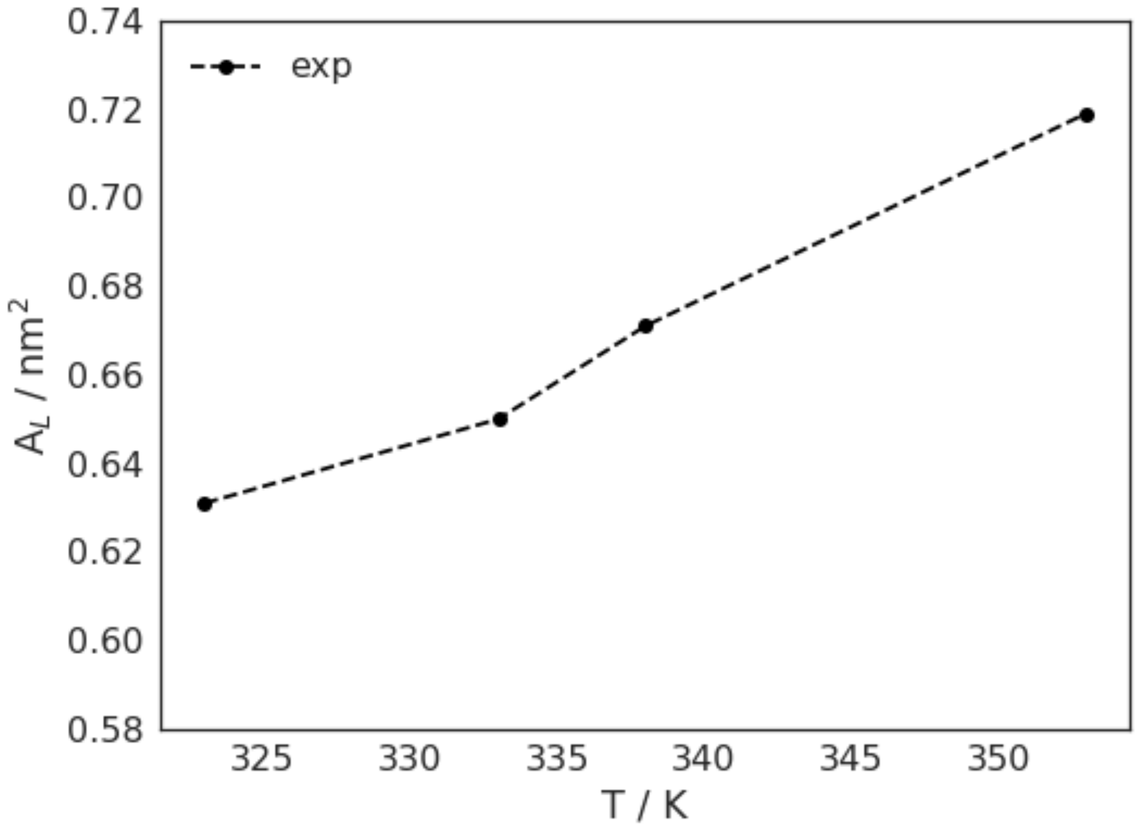
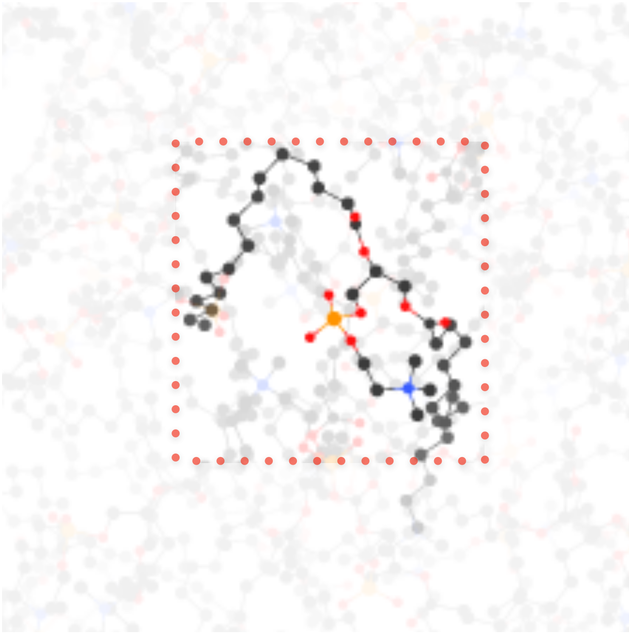
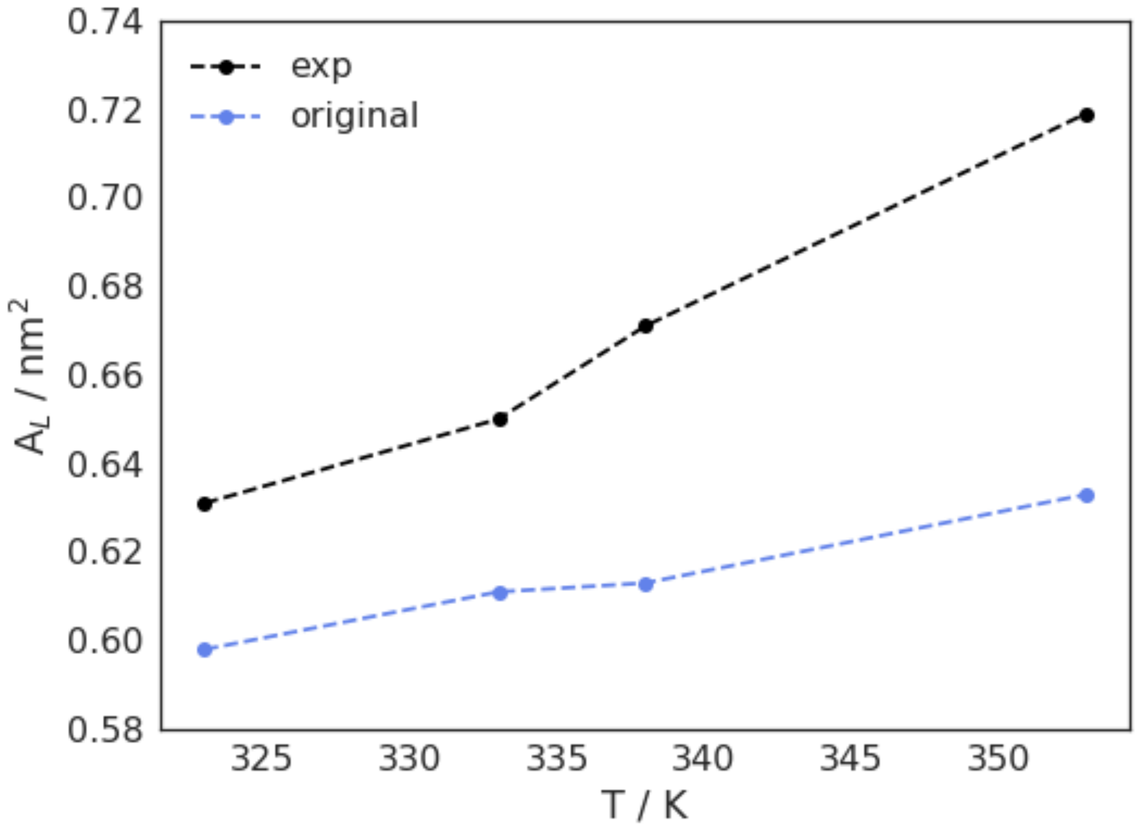


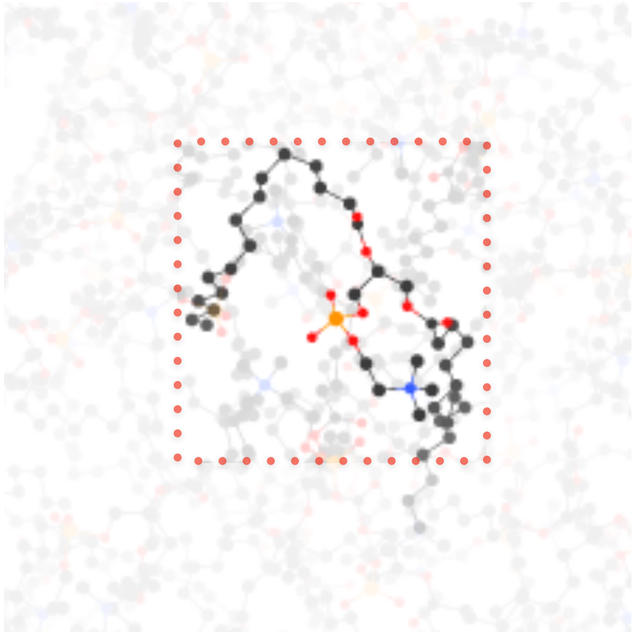
training accuracy



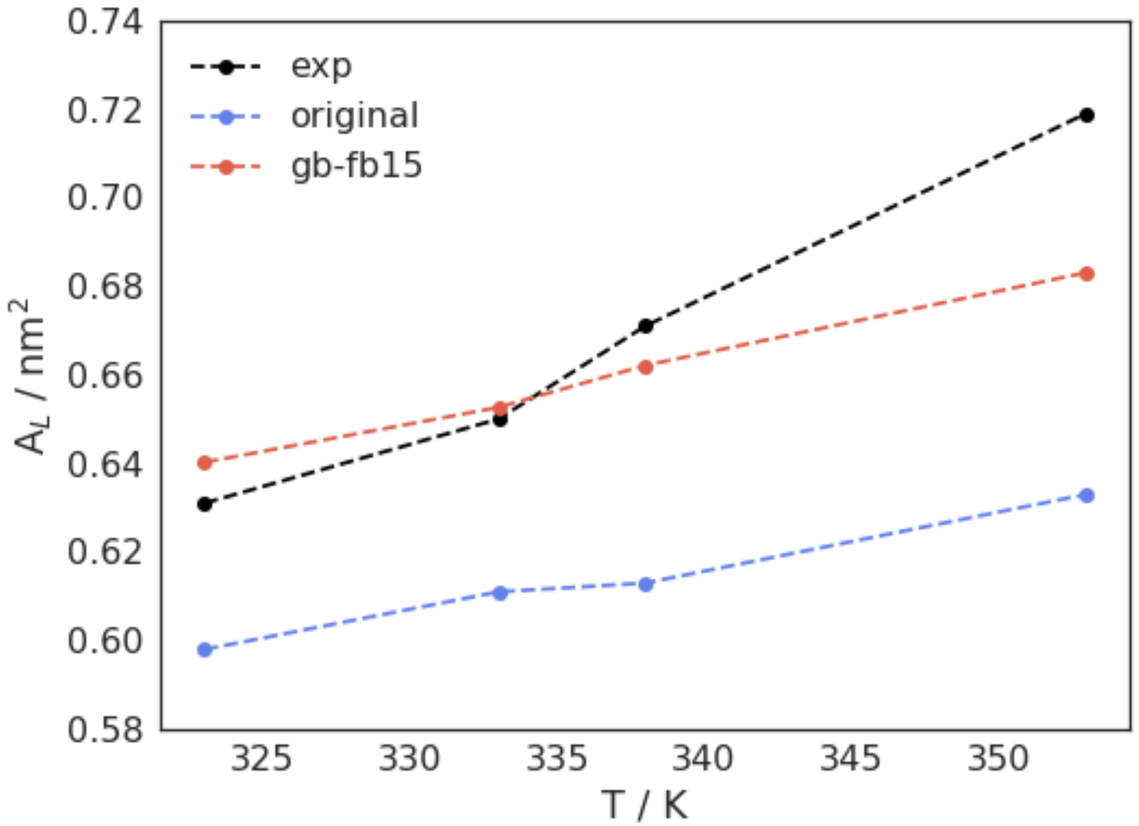


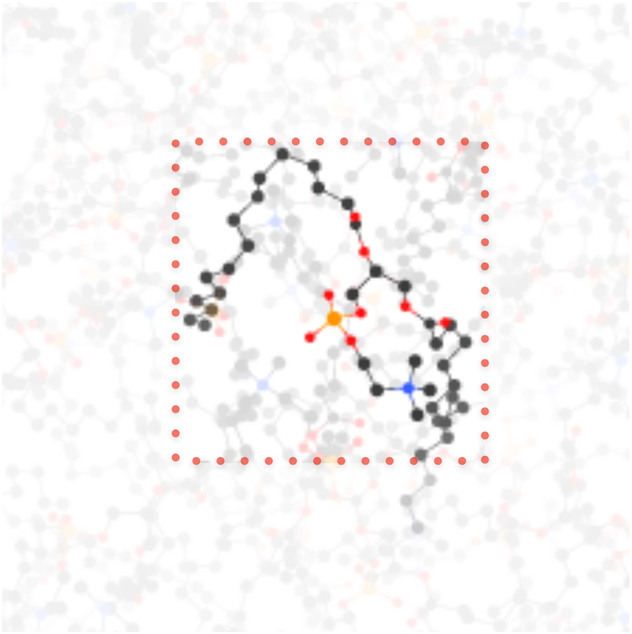
training accuracy



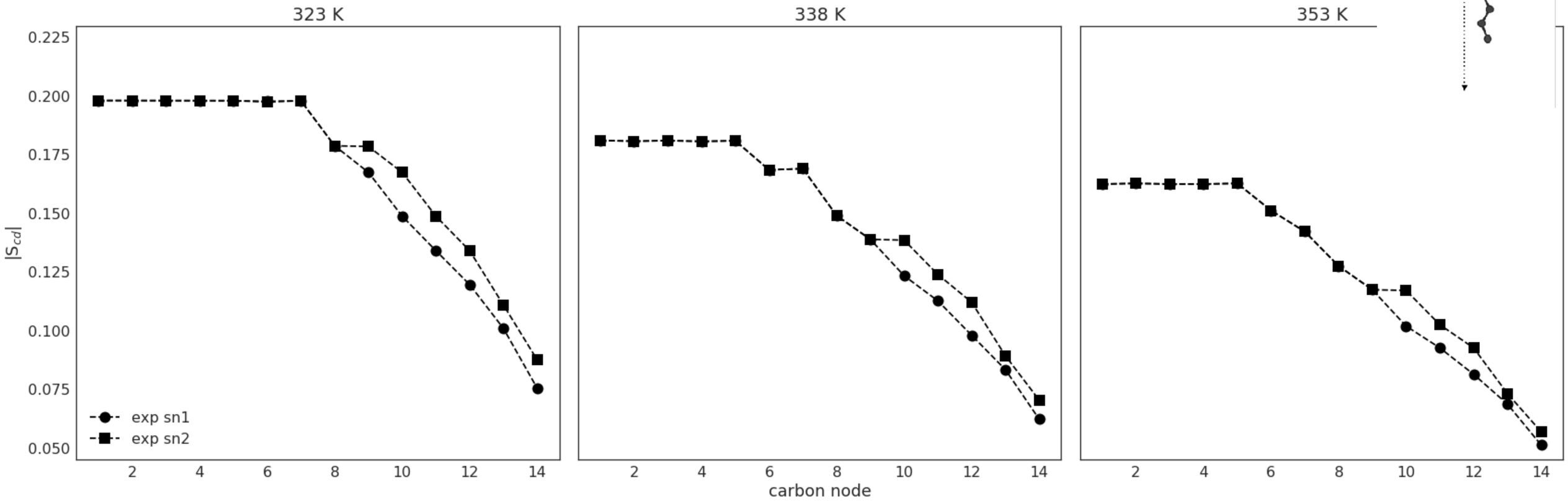


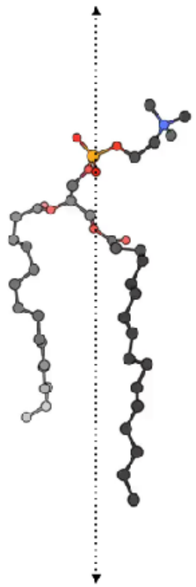
training accuracy



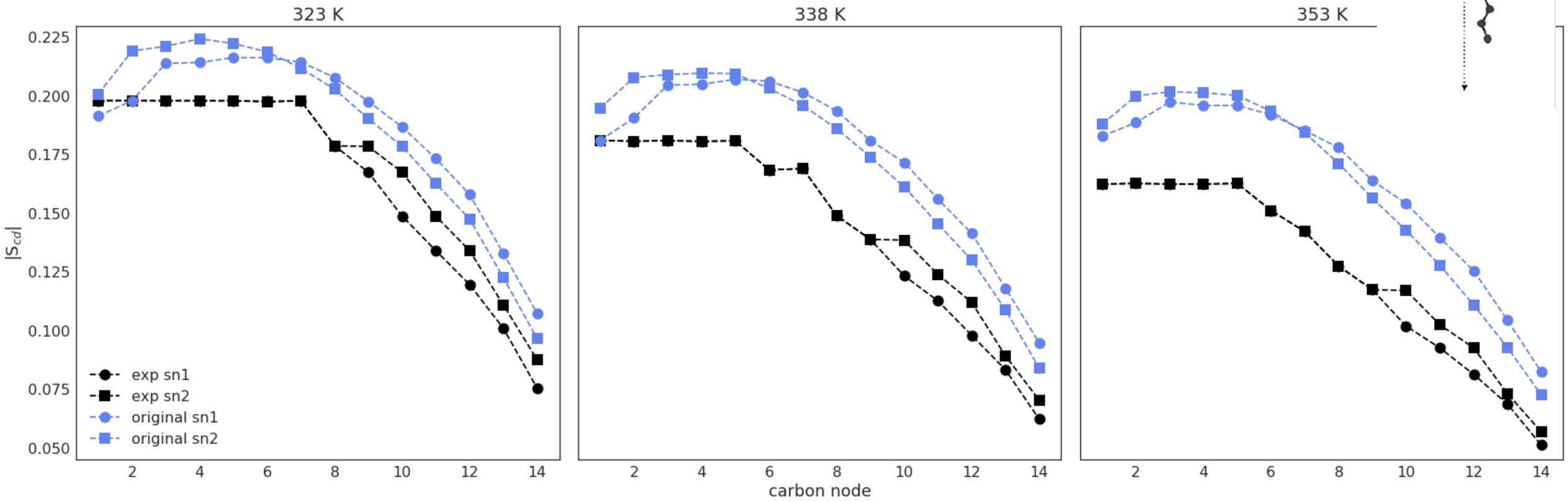


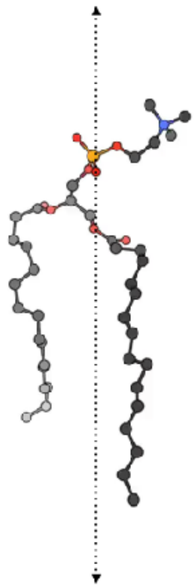
training accuracy



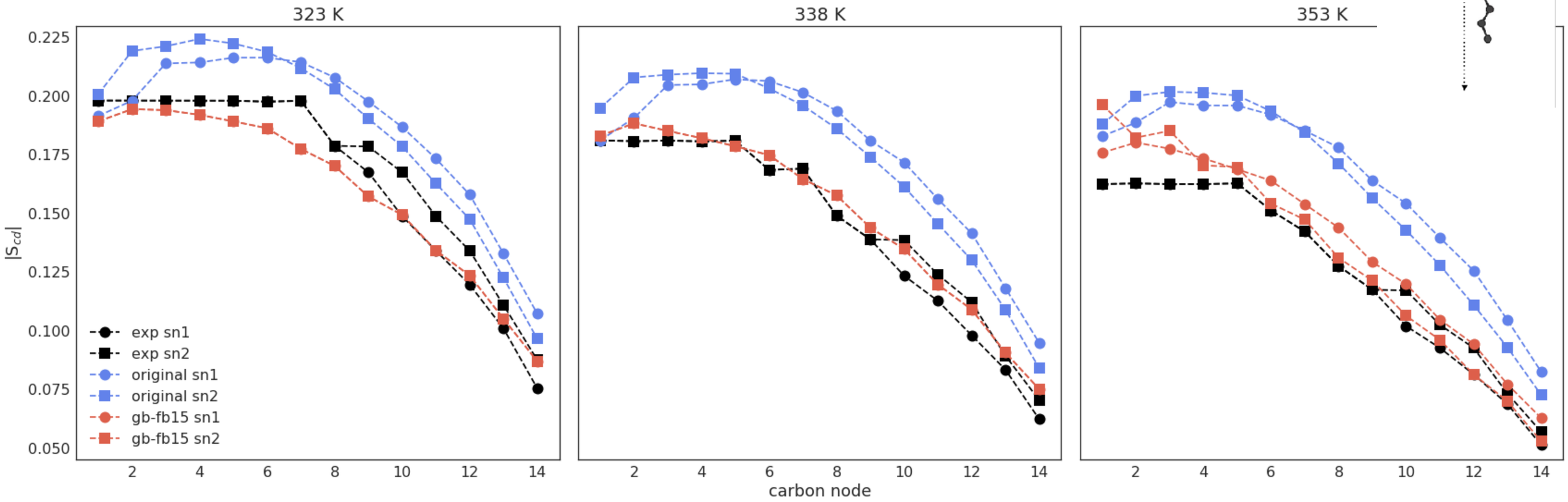


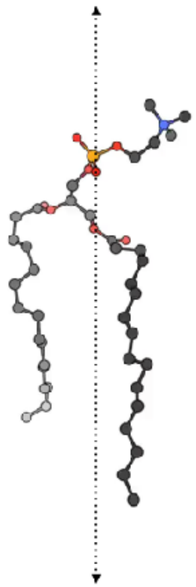
training accuracy



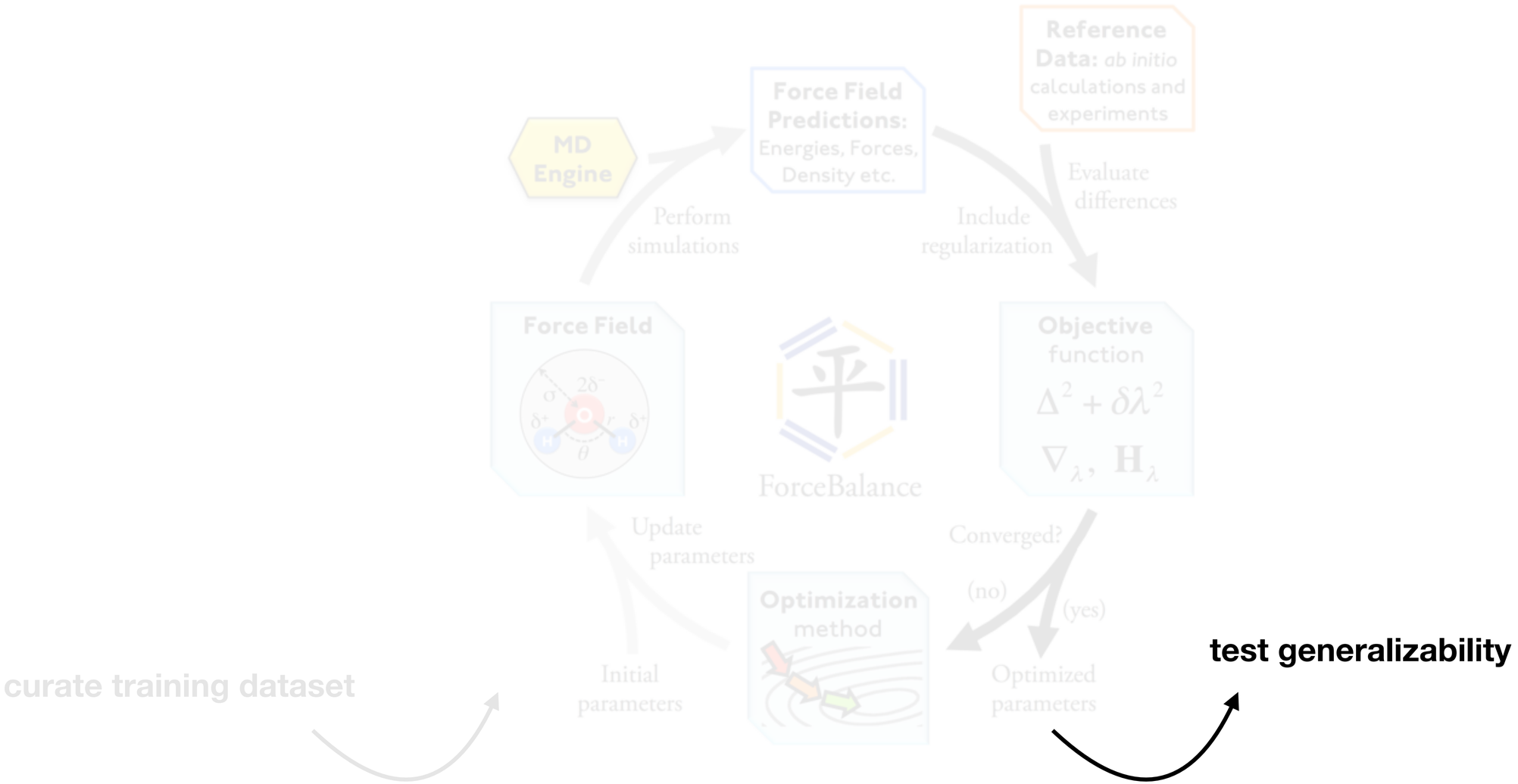


training accuracy



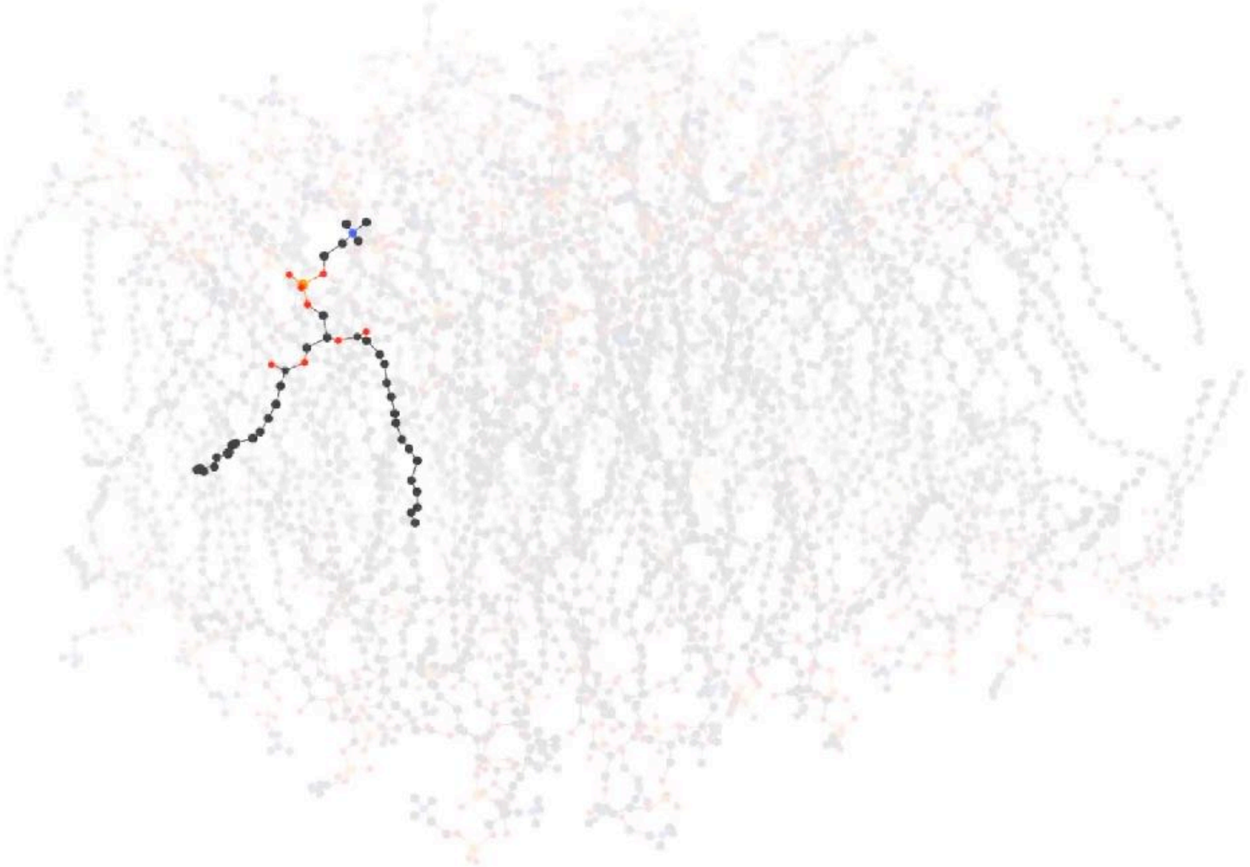


test generalizability



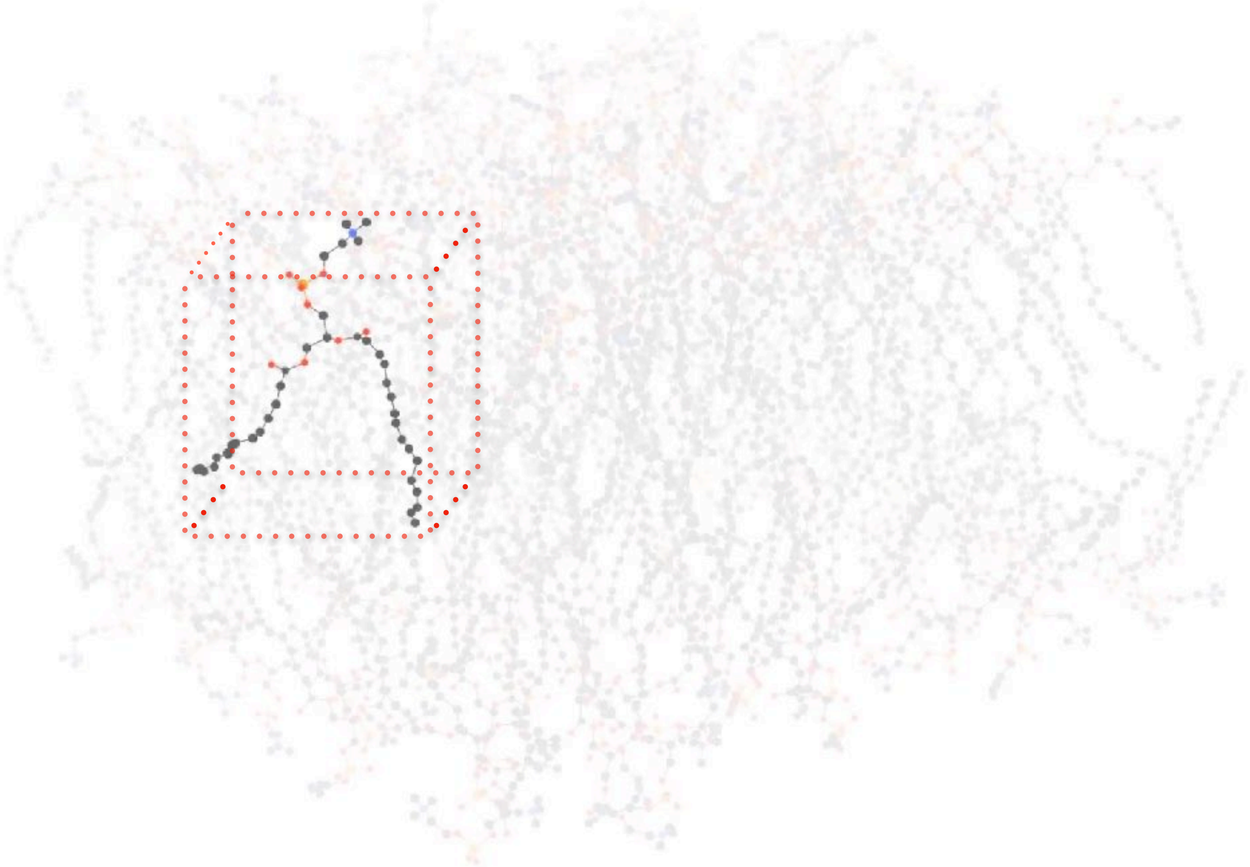
test generalizability

V_L (Å^3)

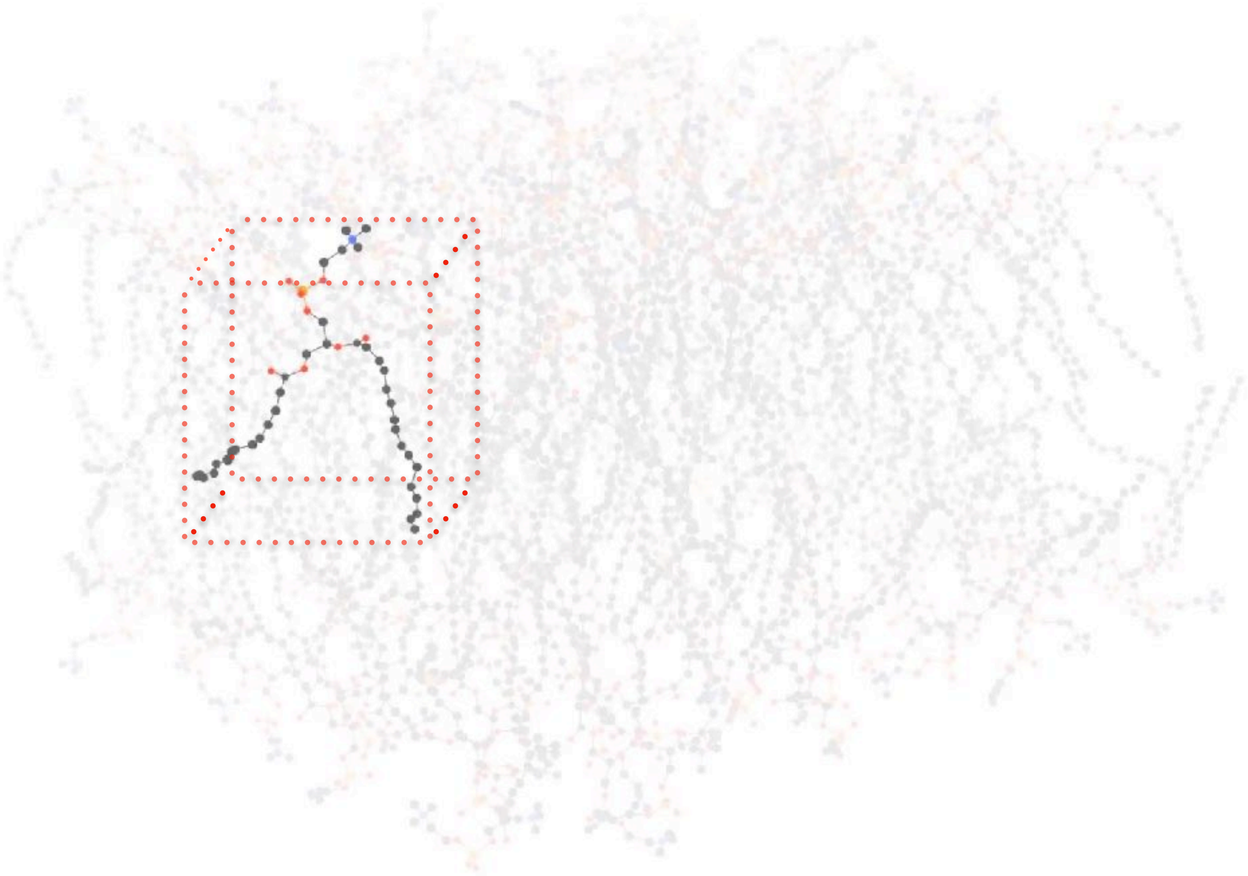


test generalizability

V_L (Å^3)



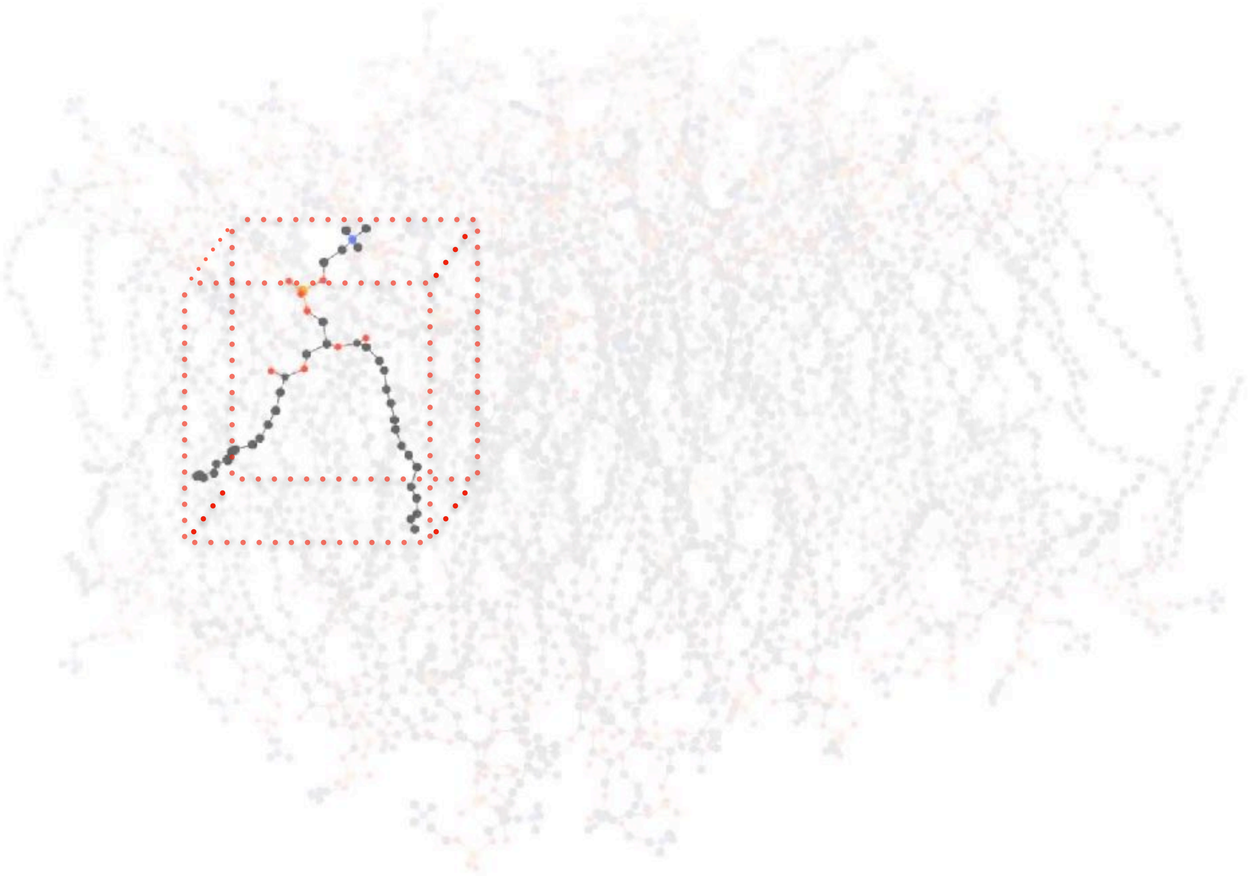
test generalizability



V_L (Å^3)

T (K)	original	gb-fb15	exp
323.15	1171.7 (1)	1191.7 (3)	1232
333.15	1179.6 (1)	1199.0 (3)	
338.15	1183.7 (1)	1203.3 (2)	
353.15	1194.5 (1)	1214.3 (1)	

test generalizability

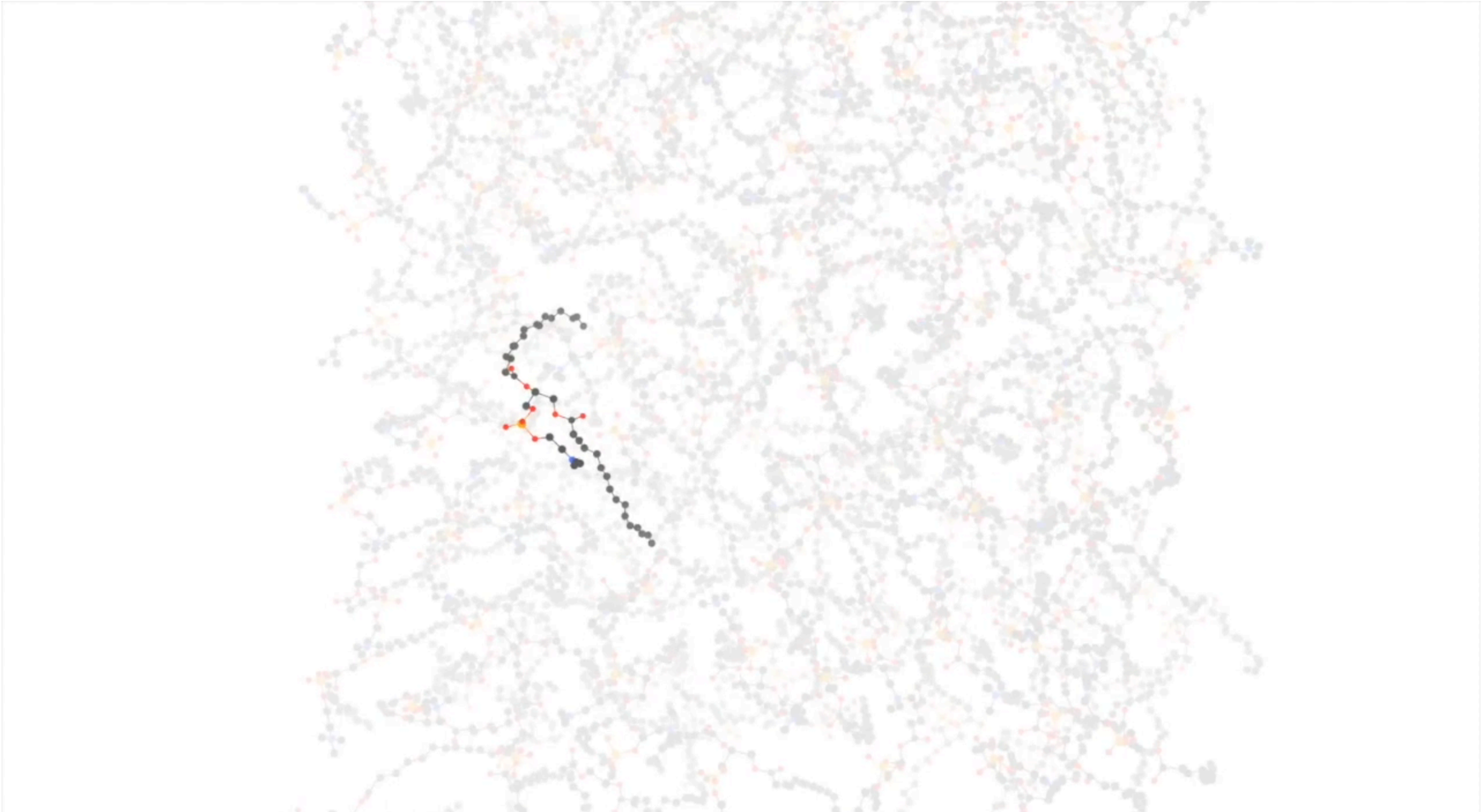


V_L (Å^3)

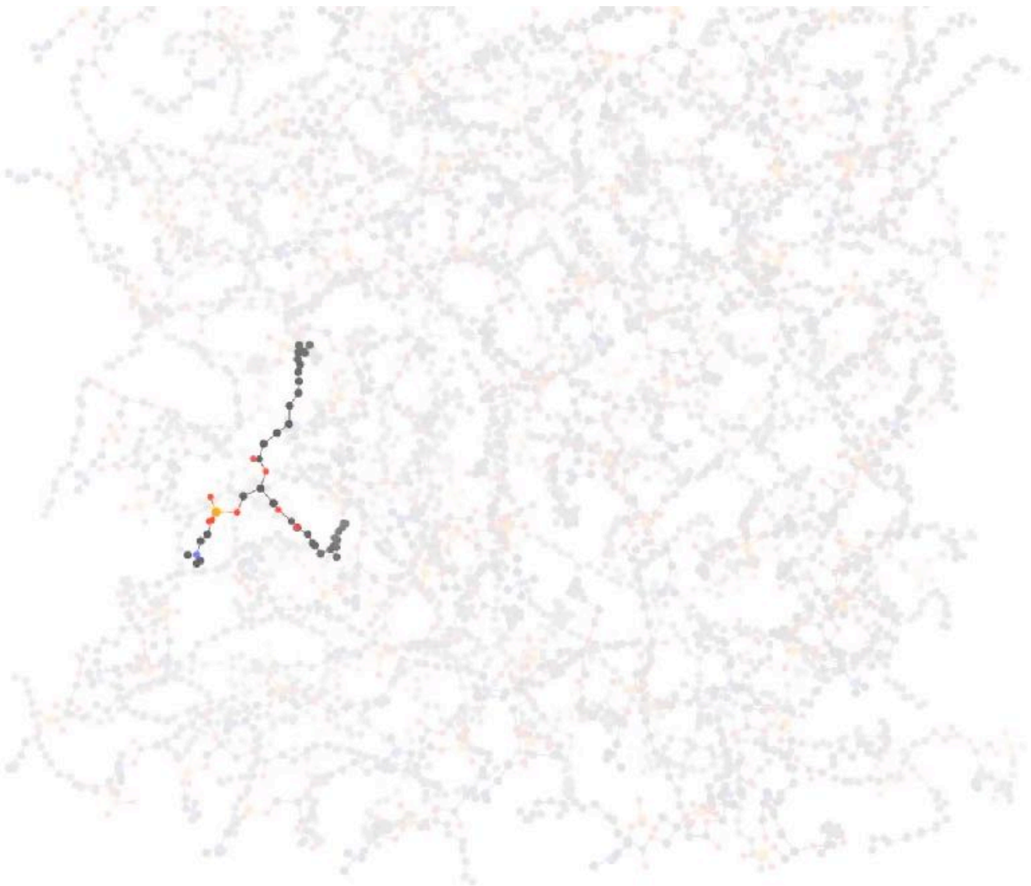
T (K)	original	gb-fb15	exp
323.15	1171.7 (1)	1191.7 (3)	1232
333.15	1179.6 (1)	1199.0 (3)	
338.15	1183.7 (1)	1203.3 (2)	
353.15	1194.5 (1)	1214.3 (1)	

test generalizability

D_l $(10^{-8}$ cm^2 s$^{-1})$

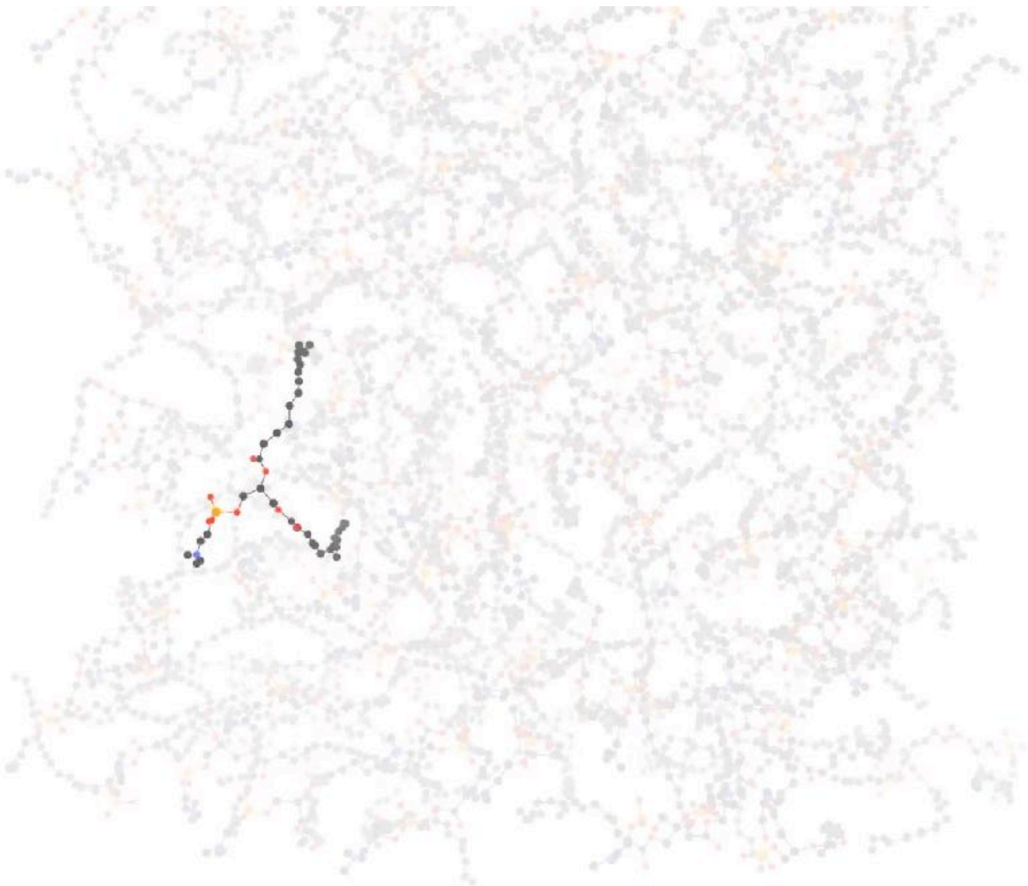


test generalizability



	D_l (10^{-8} cm^2 s^{-1})		
T (K)	original	gb-fb15	exp
323.15	8.8 (5)	12.8 (5)	12.5
333.15	10.6 (8)	14.4 (5)	
338.15	11.9 (7)	15.1 (5)	
353.15	16.5 (8)	19.8 (8)	

test generalizability



	D_l (10^{-8} cm^2 s^{-1})		
T (K)	original	gb-fb15	exp
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333.15	10.6 (8)	14.4 (5)	
338.15	11.9 (7)	15.1 (5)	
353.15	16.5 (8)	19.8 (8)	

https://github.com/kmckiern/gb-fb15

https://github.com/kmckiern/gb-fb15

Branch: master ▾ gb-fb15 / gromacs /

Create new file | Upload files | Find file | History

This branch is even with pandegroup:master. Pull request Compare

kmckiern gromacs parameter, topology, and initial state files — Latest commit 1b9102f on Aug 17, 2016

..		
DPPC.itp	gromacs parameter, topology, and initial state files	2 years ago
ic.gro	gromacs parameter, topology, and initial state files	2 years ago
lipid.top	gromacs parameter, topology, and initial state files	2 years ago
npt.mdp	gromacs parameter, topology, and initial state files	2 years ago
nve.mdp	gromacs parameter, topology, and initial state files	2 years ago

https://github.com/kmckiern/gb-fb15

GMX simulation

1 ns of NPT dynamics, assuming you are in the root of this repository and GMX is in your PATH

```
cd gromacs
grompp -f npt.mdp -c ic.gro -p lipid.top -o ic_npt.tpr
mdrun -deffnm ic_npt
```

https://github.com/kmckiern/gb-fb15

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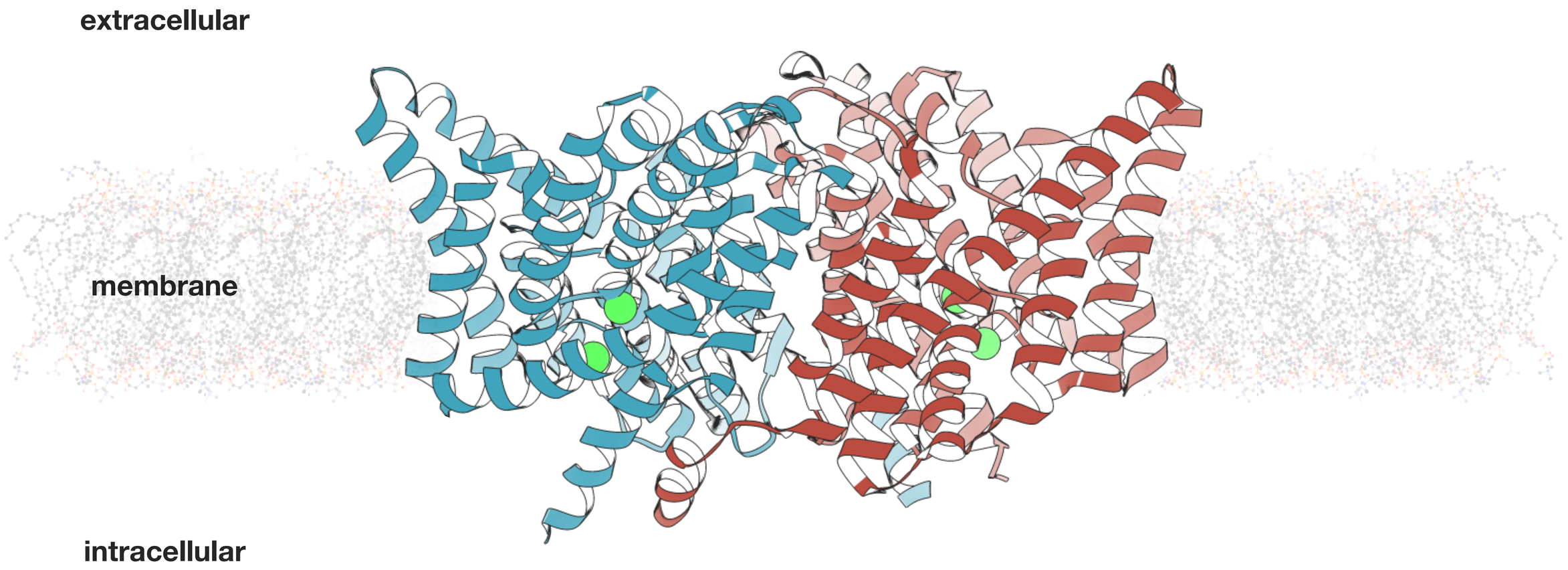
mdrun -deffnm ic_npt
```

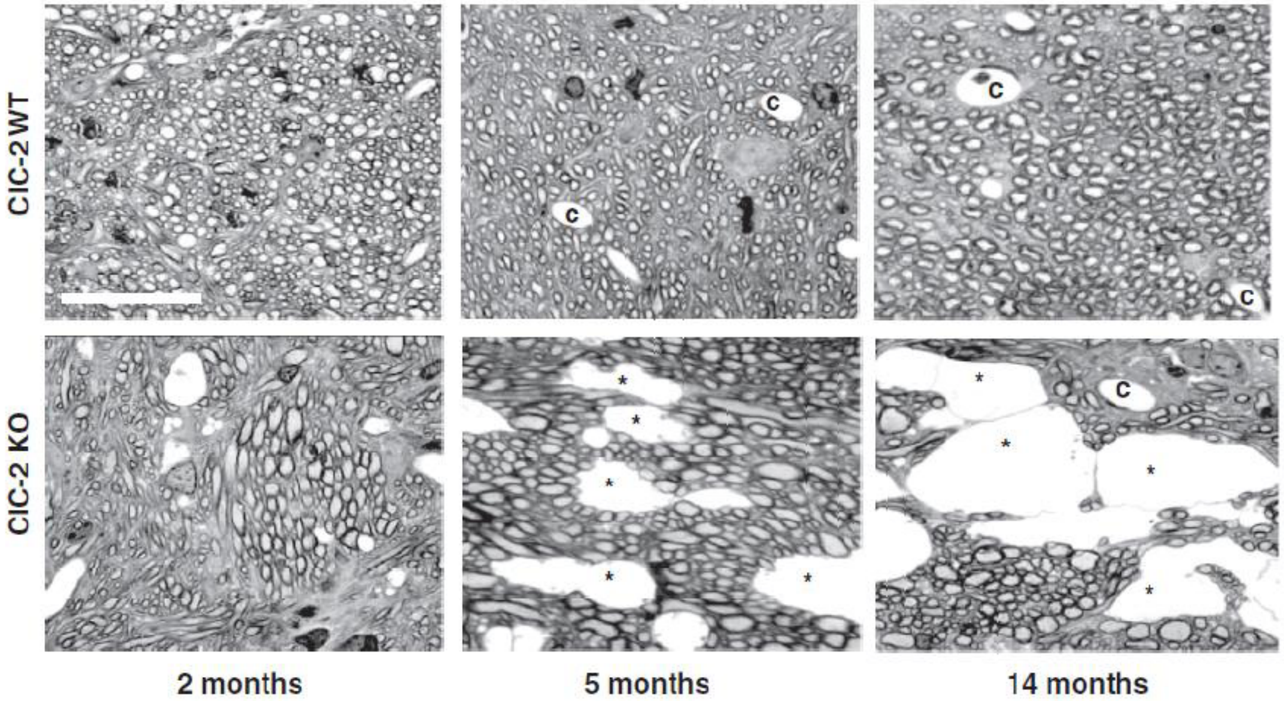
Details

10.1021/acs.jctc.6b00801

Applying simulation:
Markov modeling of CLC-2 ion channel conformational dynamics

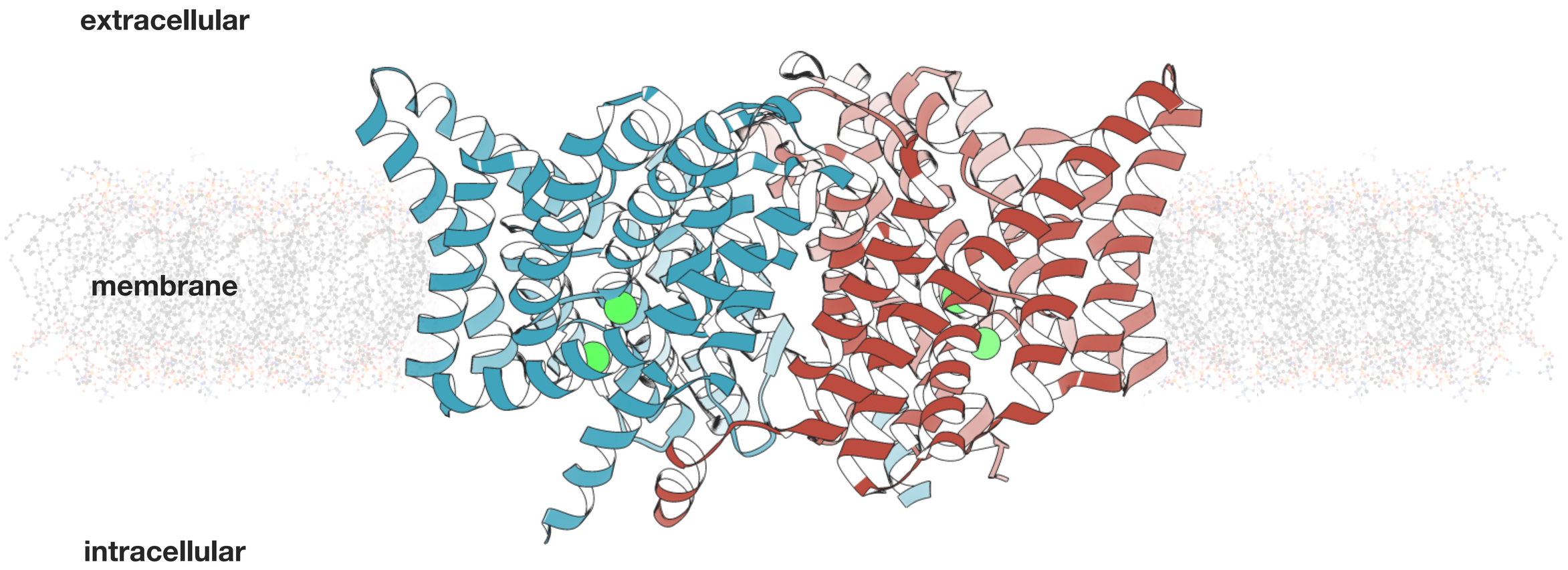

extracellular
membrane
intracellular

white matter degeneration

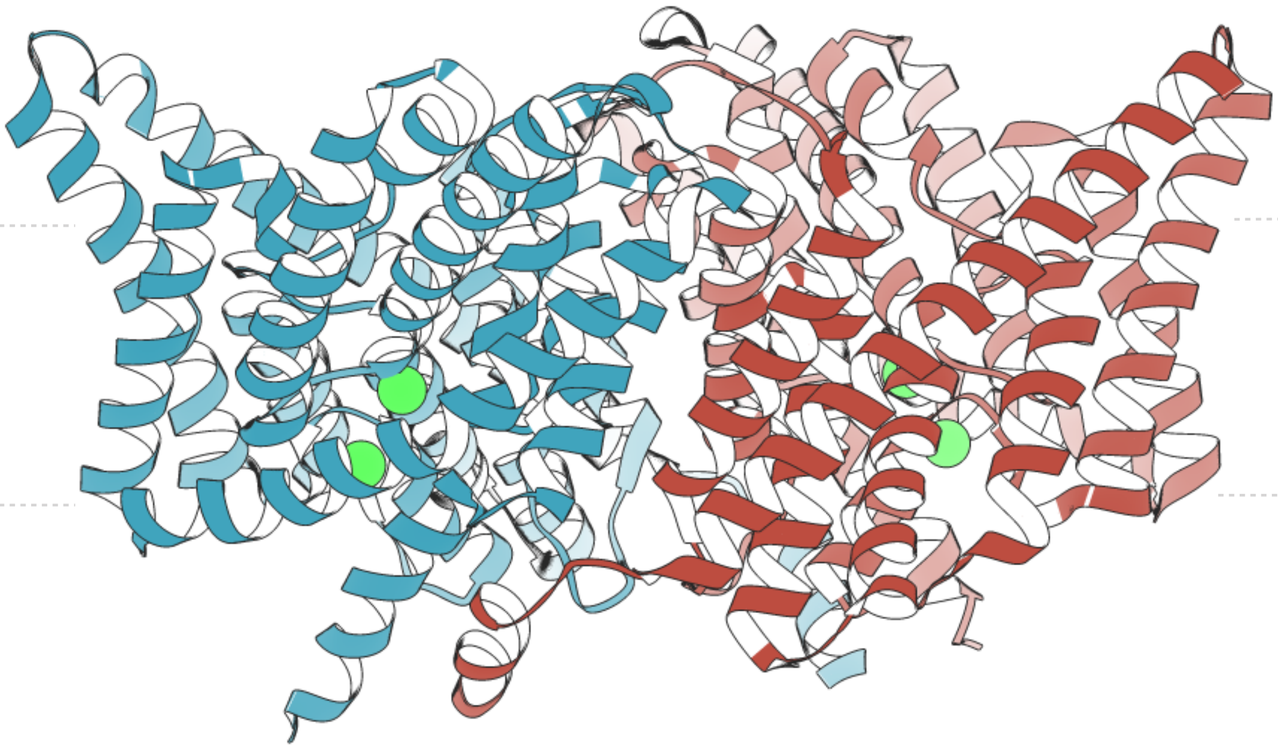


C = Capillaries
* = Vacuoles

Blanz, Judith, et al. The Journal of neuroscience 27.24 (2007): 6581-6589

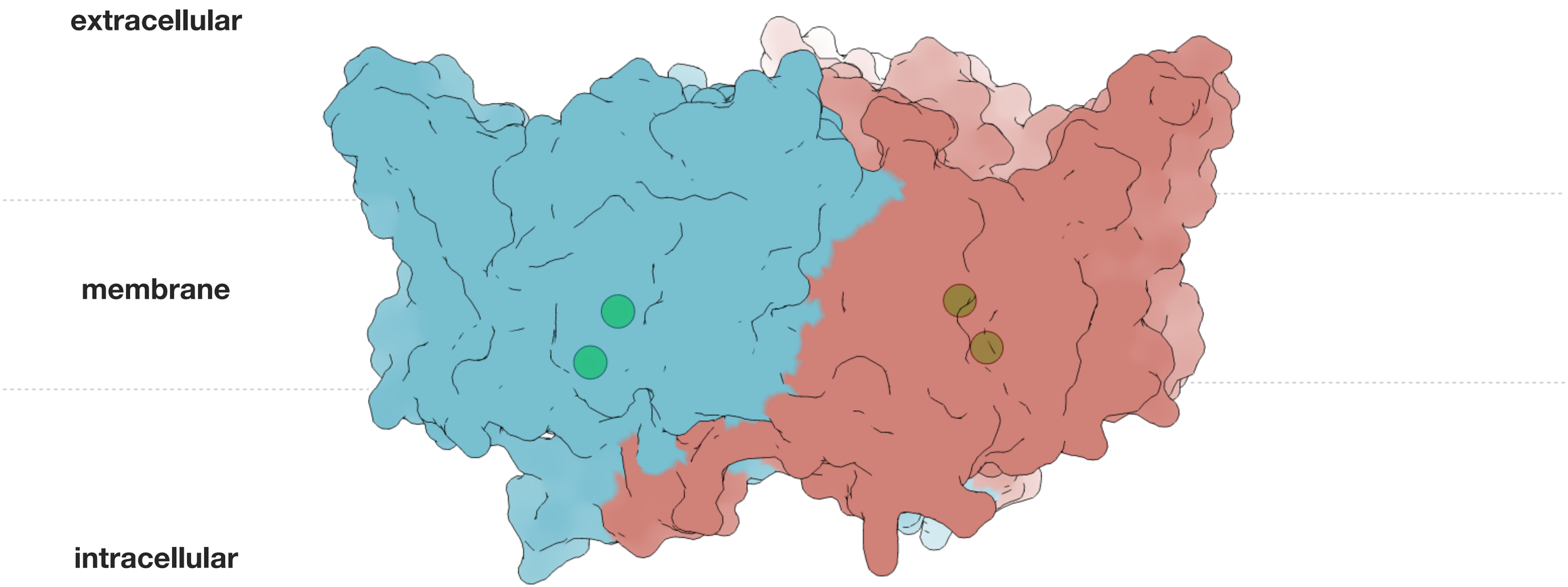

extracellular
membrane
intracellular

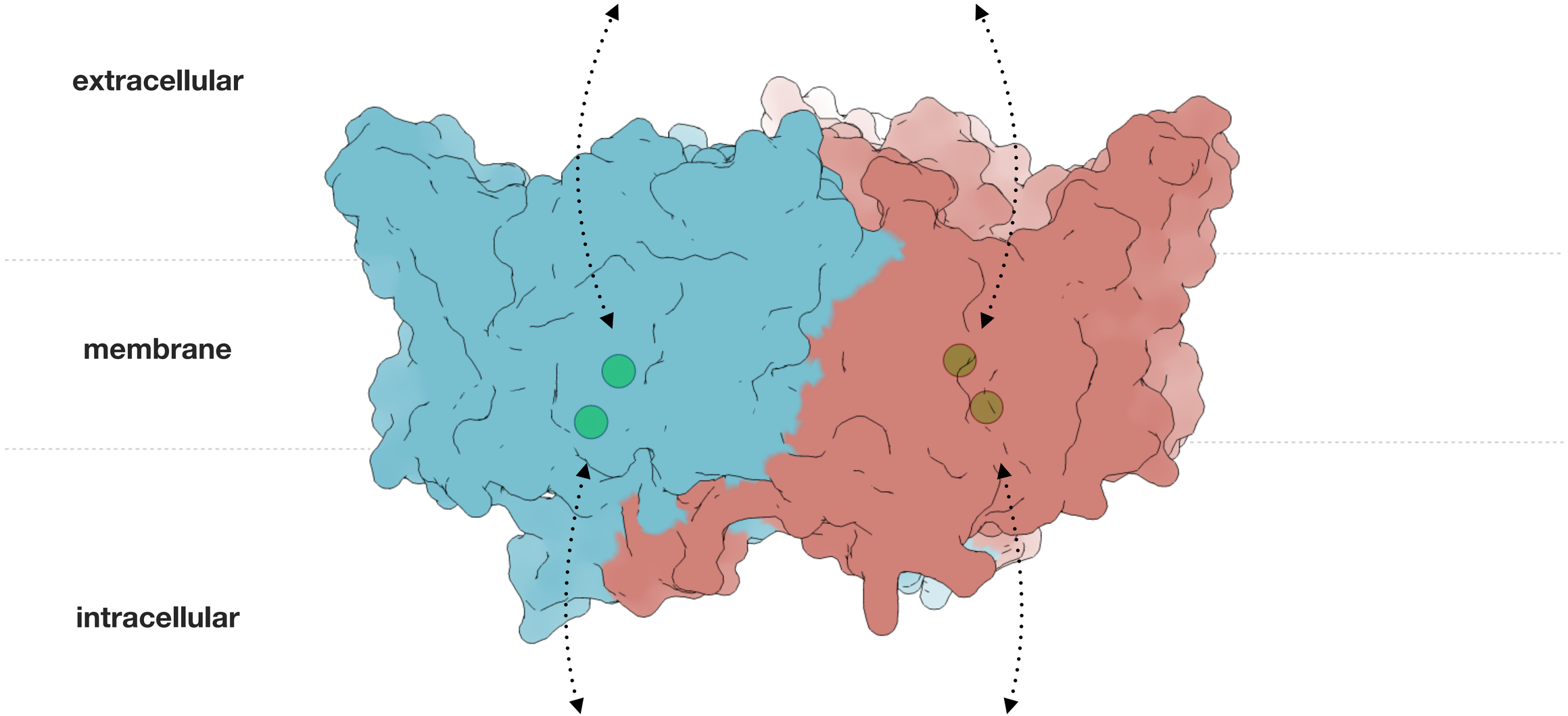
extracellular

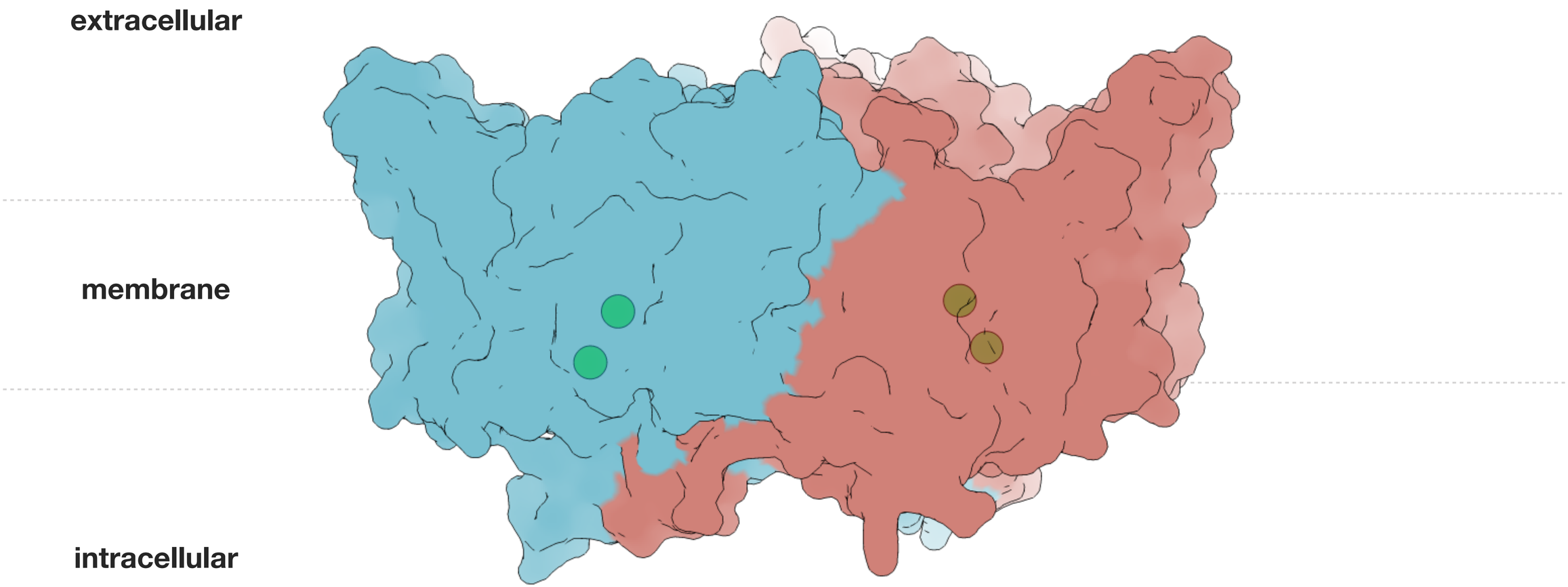


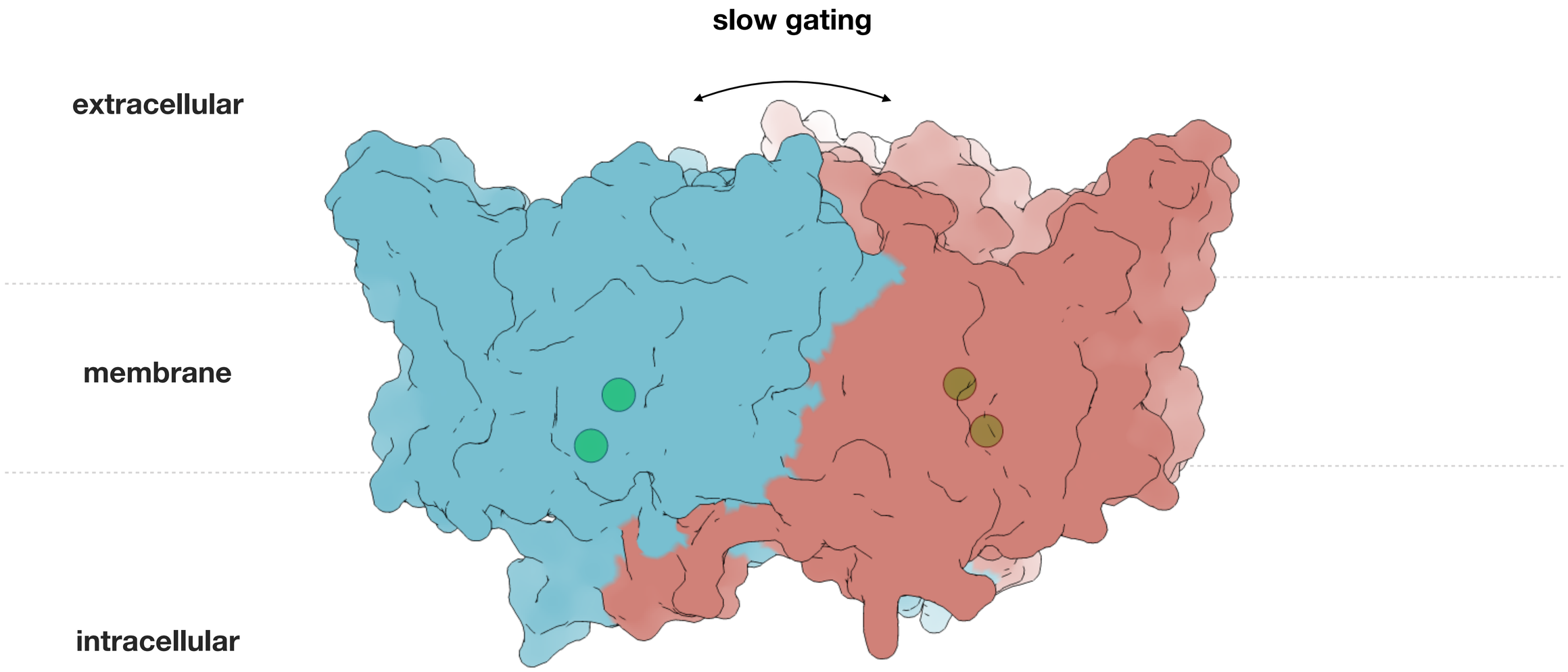
membrane

intracellular


extracellular
membrane
intracellular


extracellular
membrane
intracellular

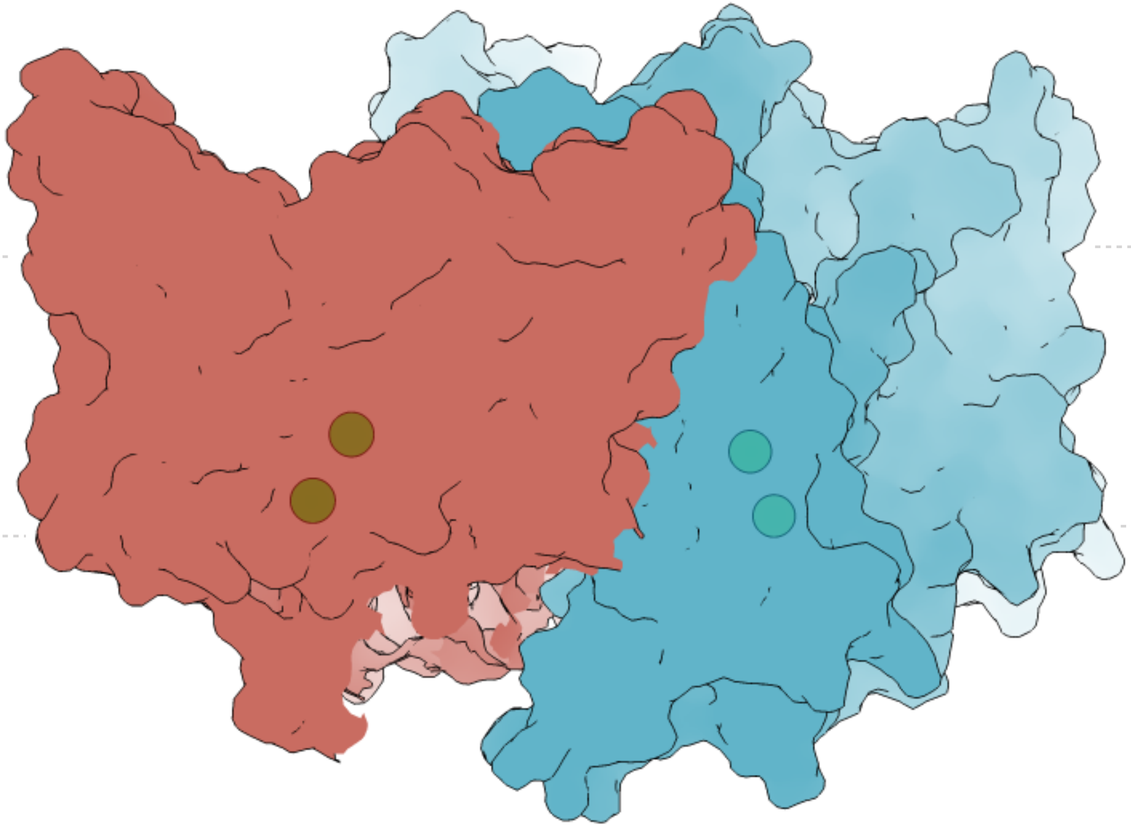

extracellular
membrane
intracellular


slow gating
extracellular
membrane
intracellular

extracellular

membrane

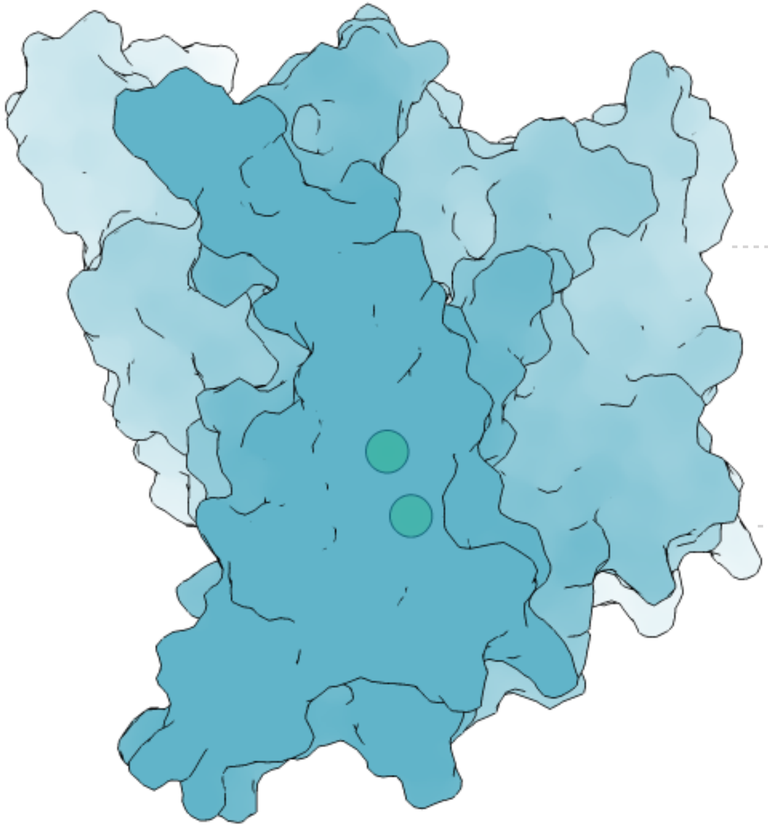
intracellular



extracellular

membrane

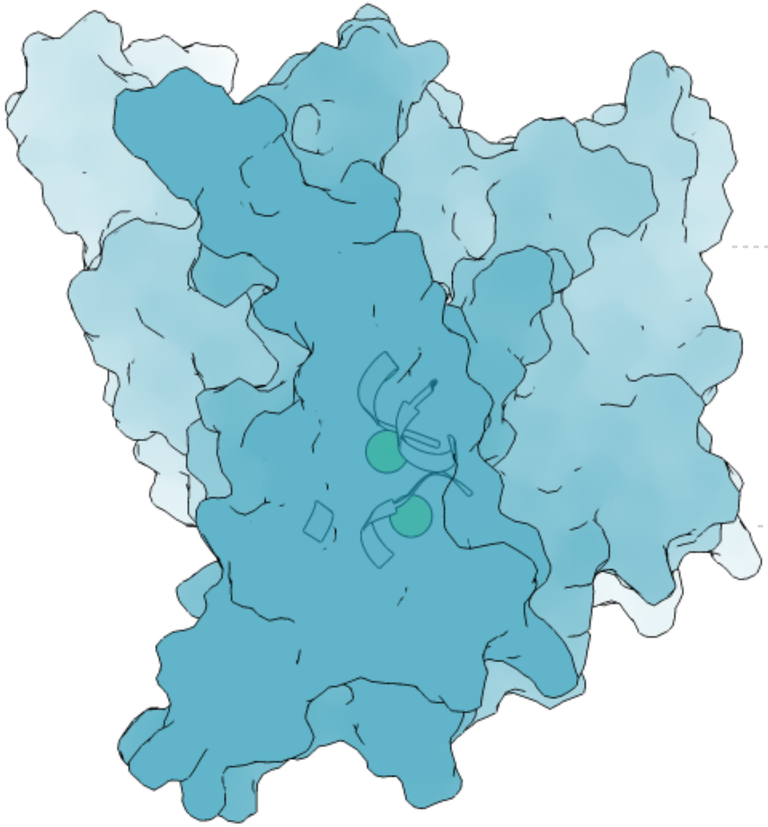
intracellular

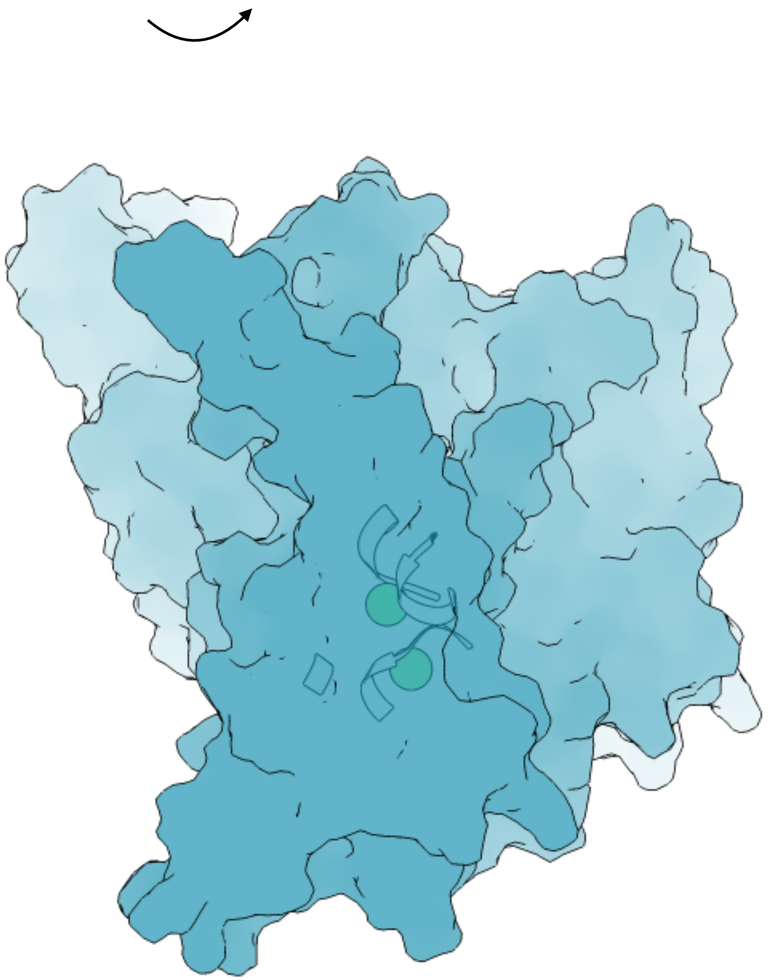


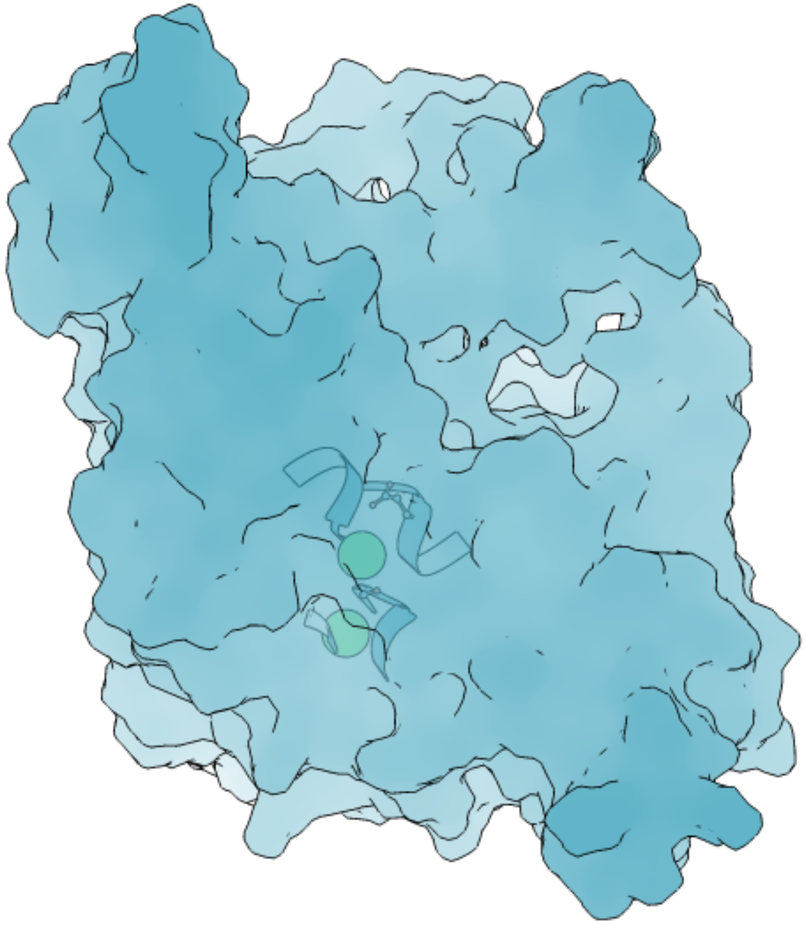
extracellular

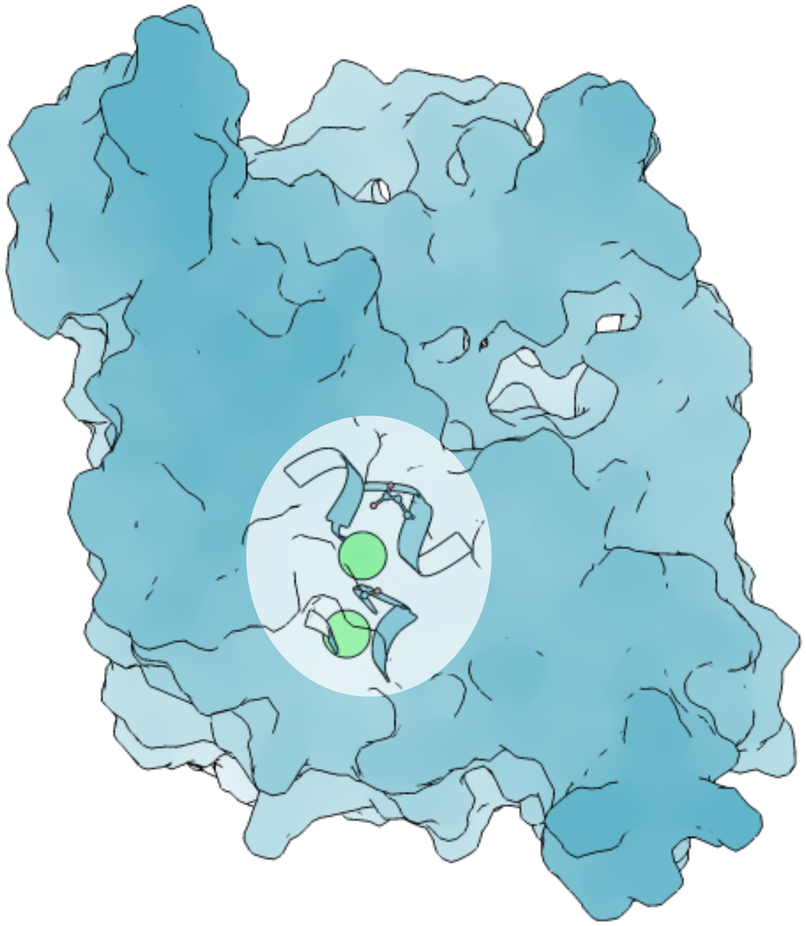
membrane

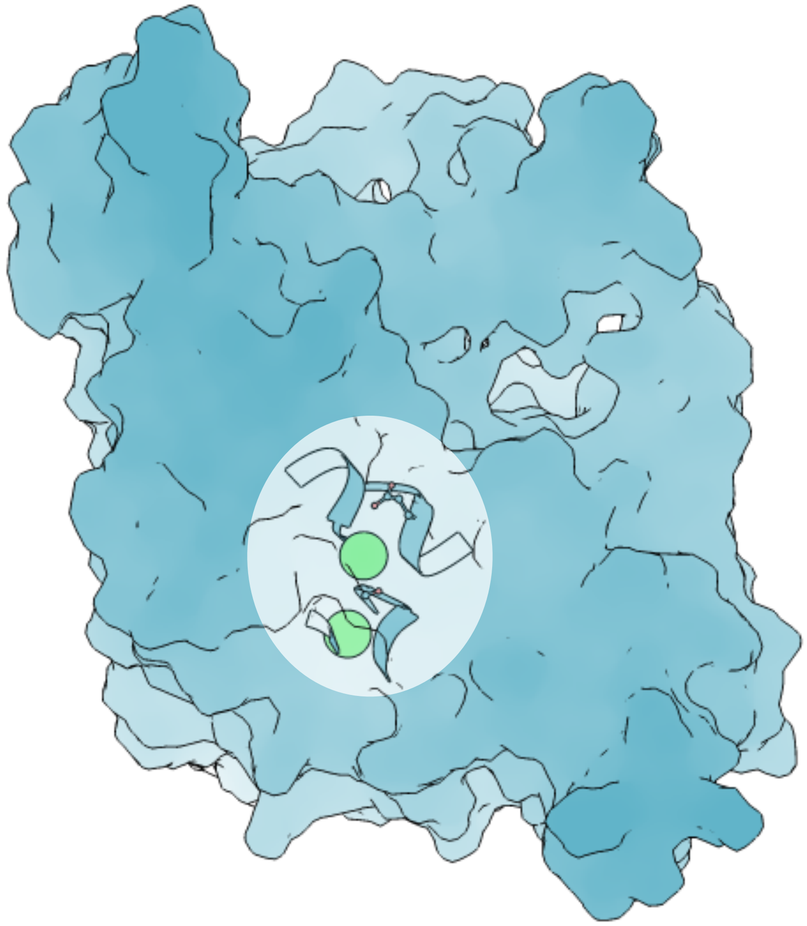
intracellular



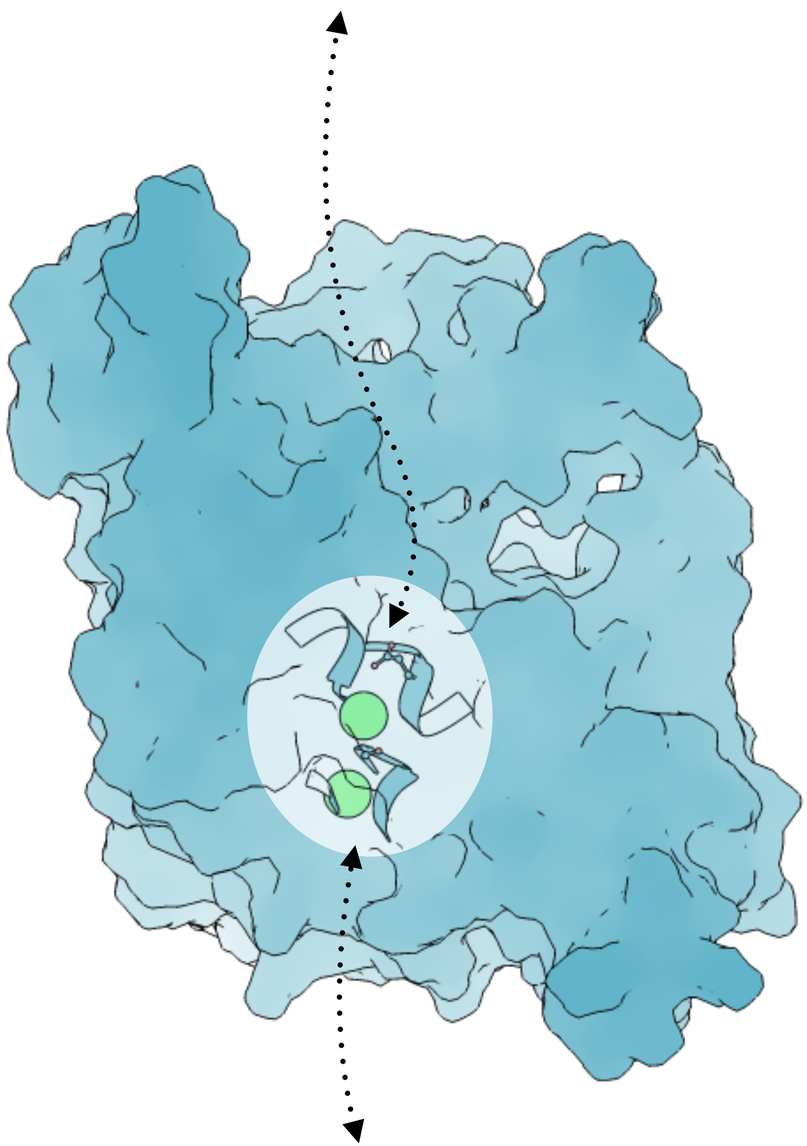






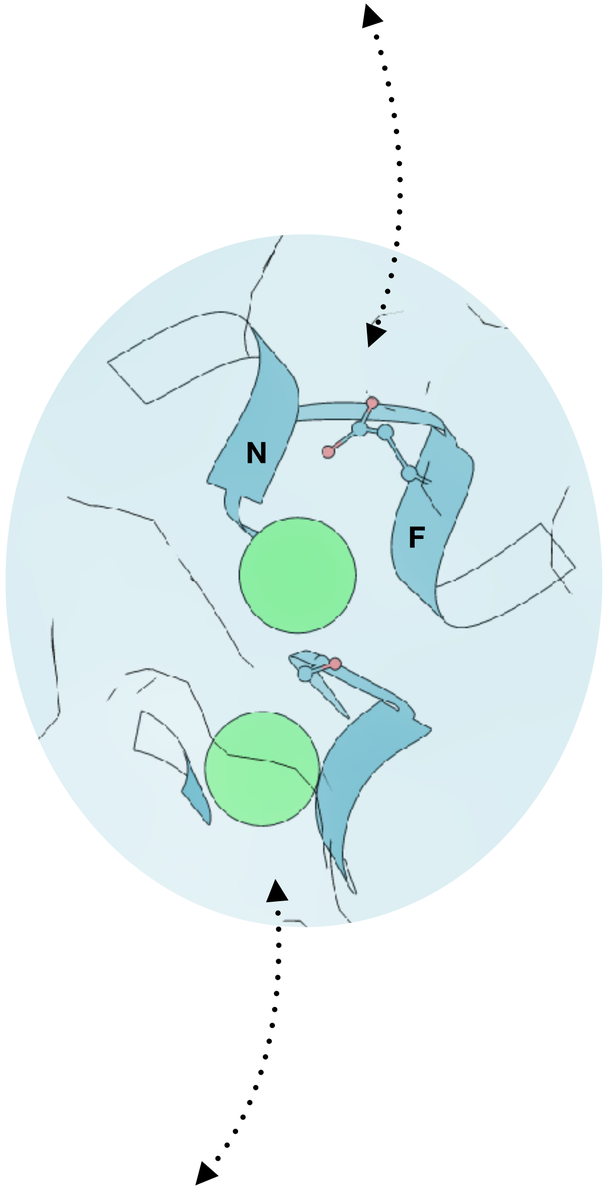


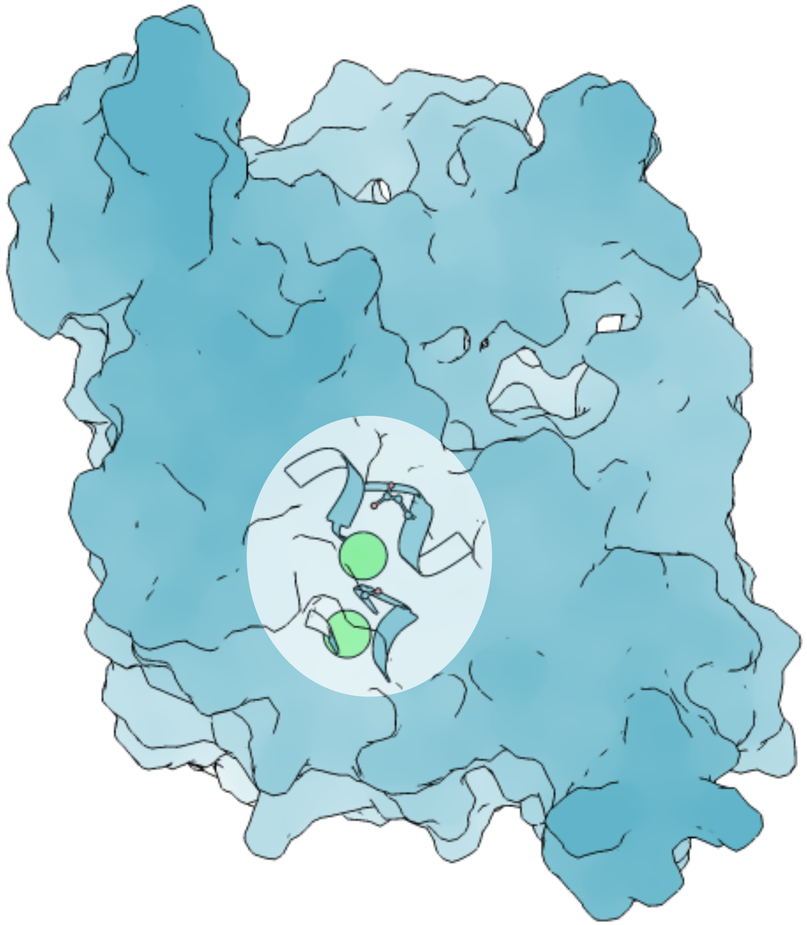
selectivity filter, SF



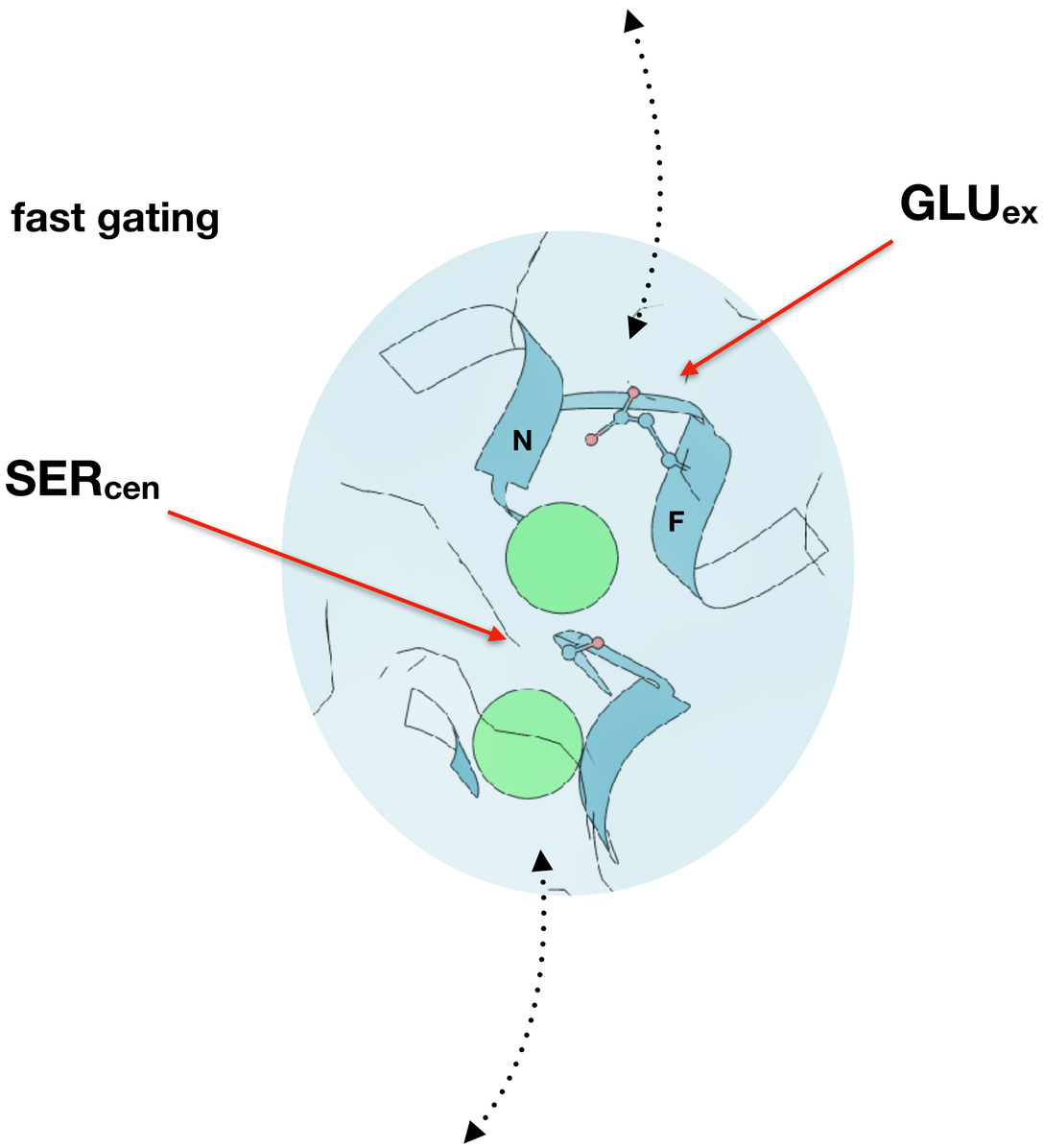
selectivity filter, SF

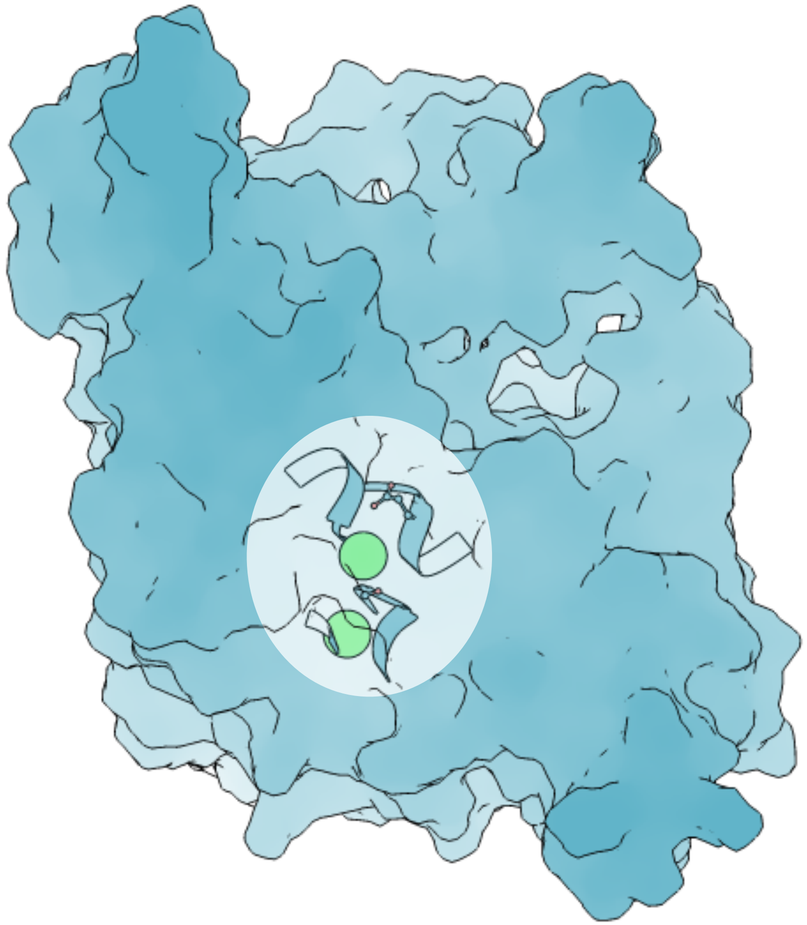
fast gating





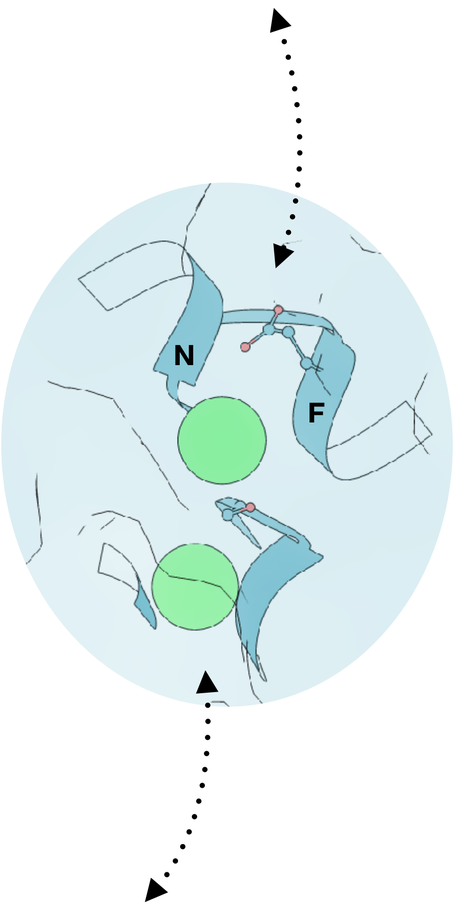
selectivity filter, SF



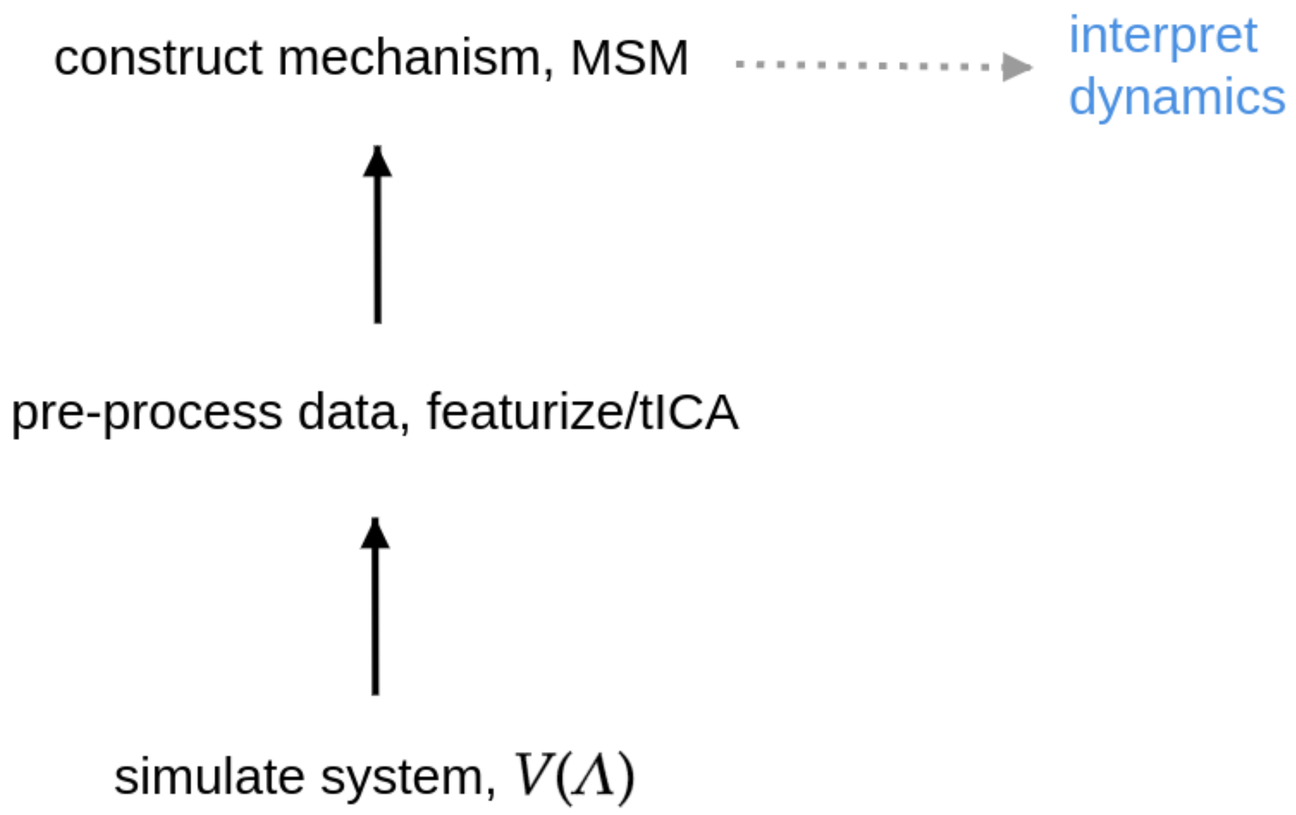


selectivity filter, SF

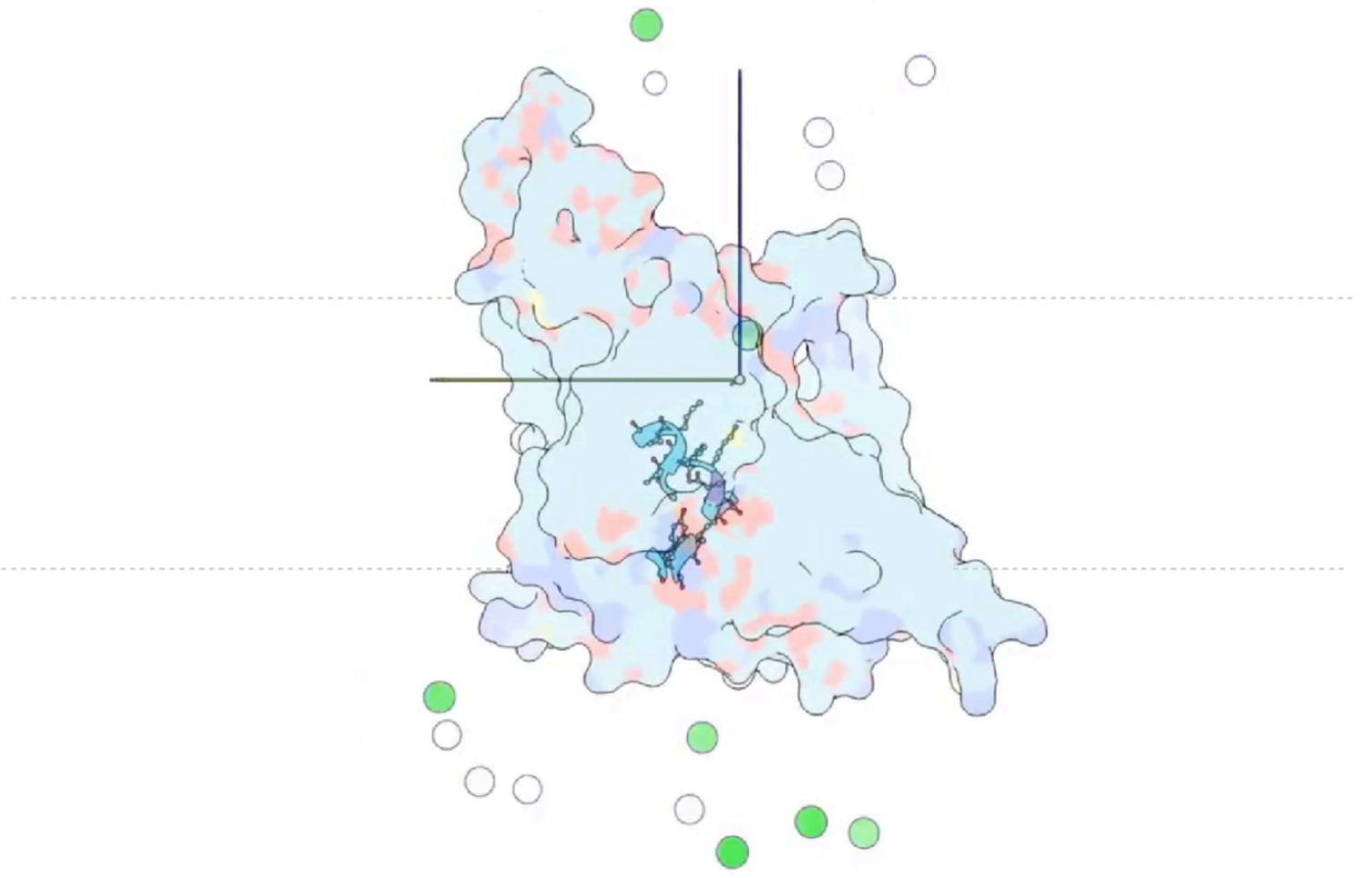
what are the conformational dynamics of fast gating?



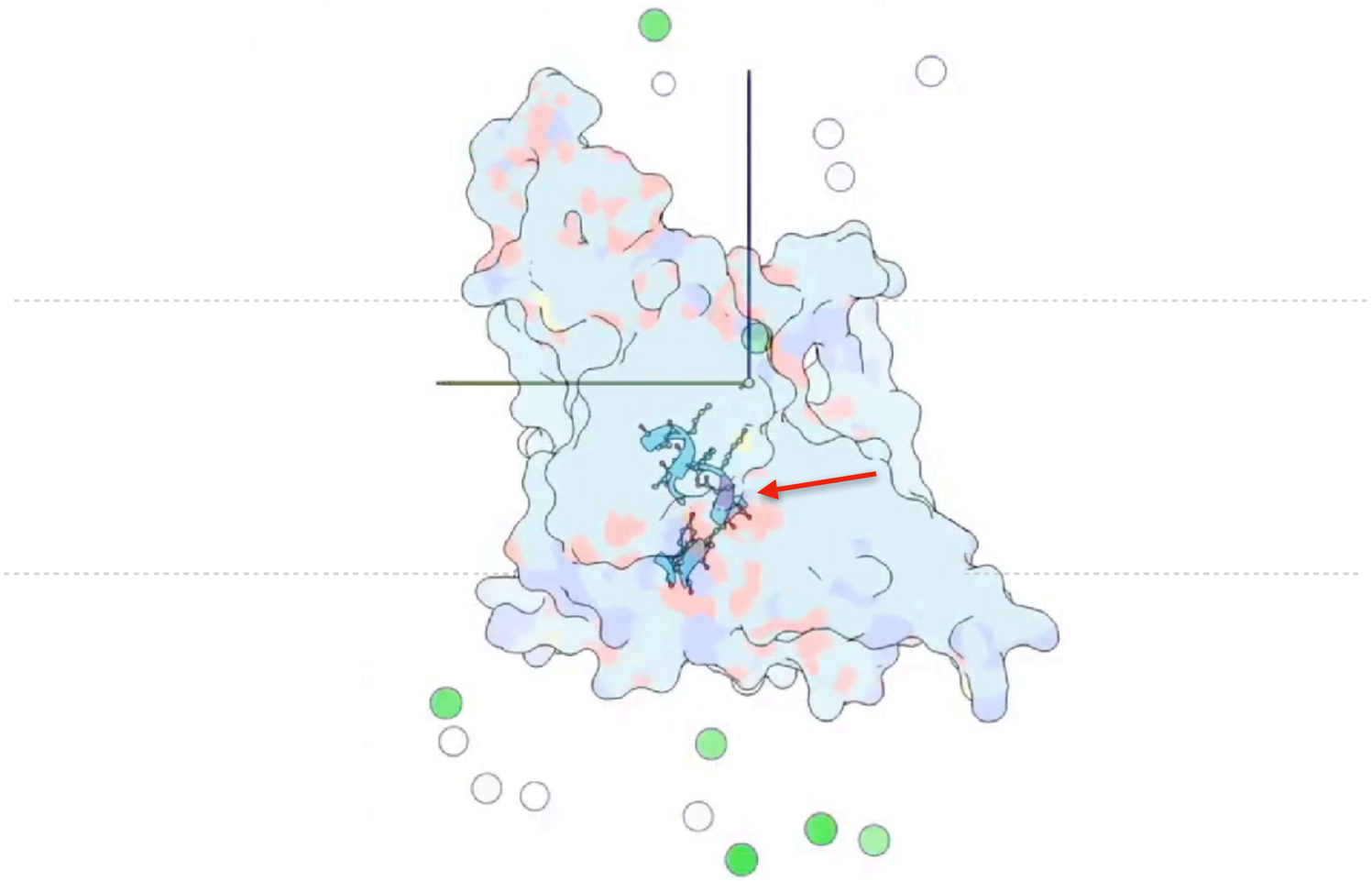
what are the conformational dynamics of fast gating?



simulate system, $V(\Lambda)$



simulate system, $V(\Lambda)$



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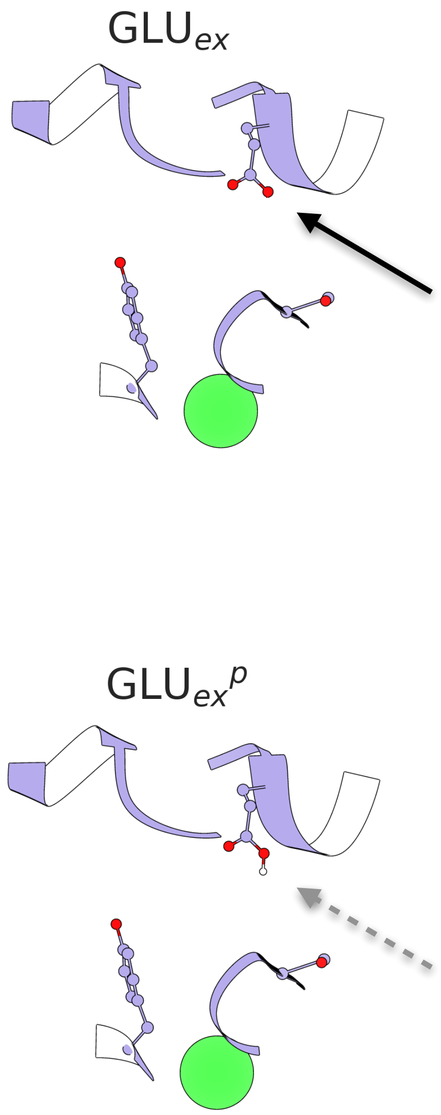
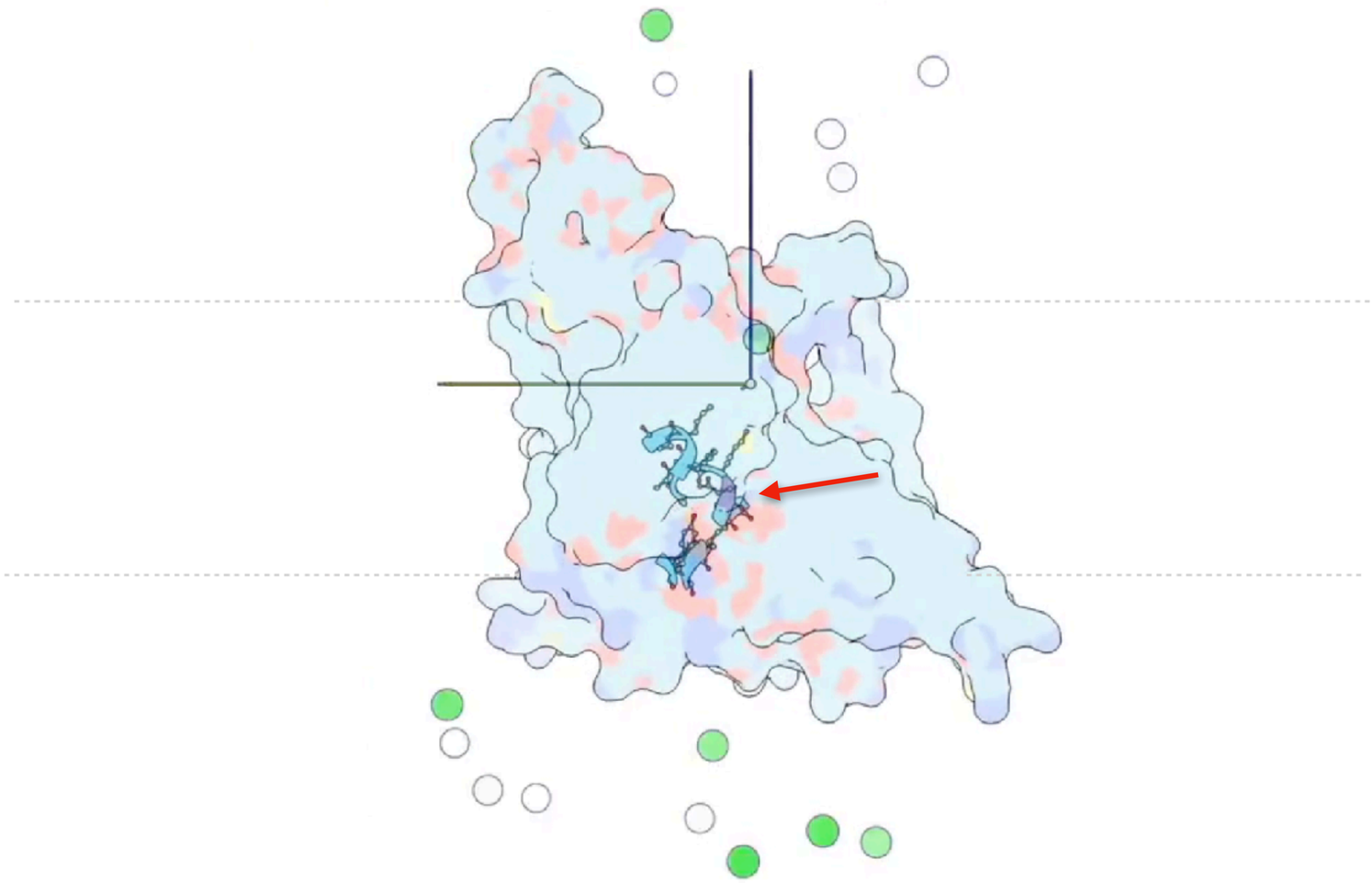
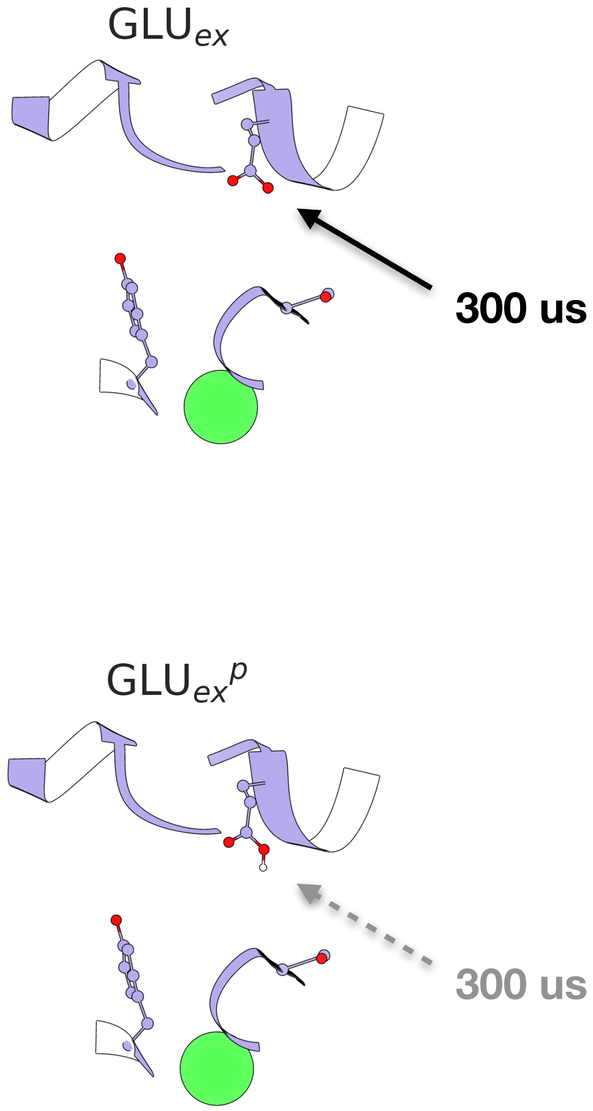
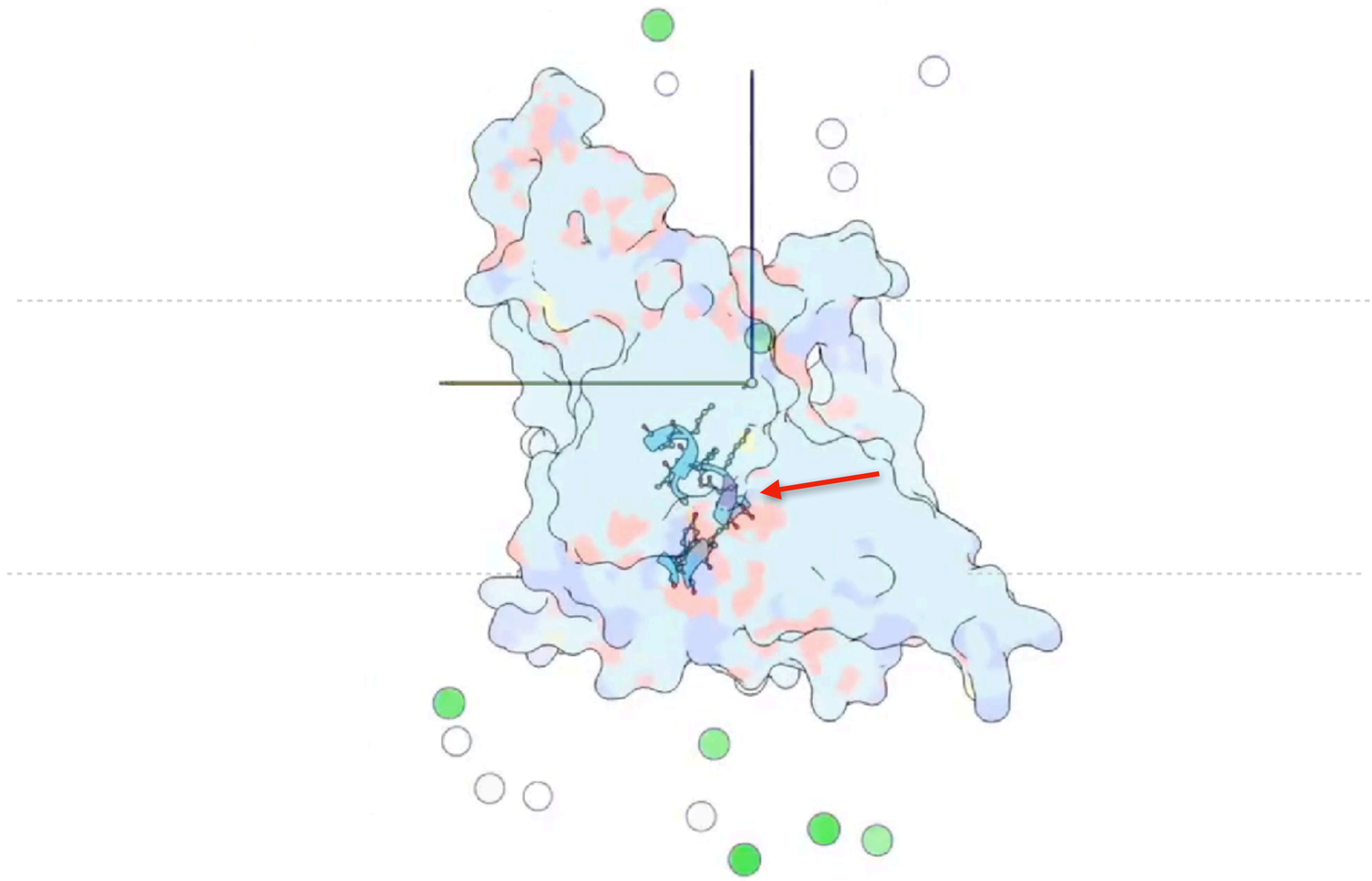


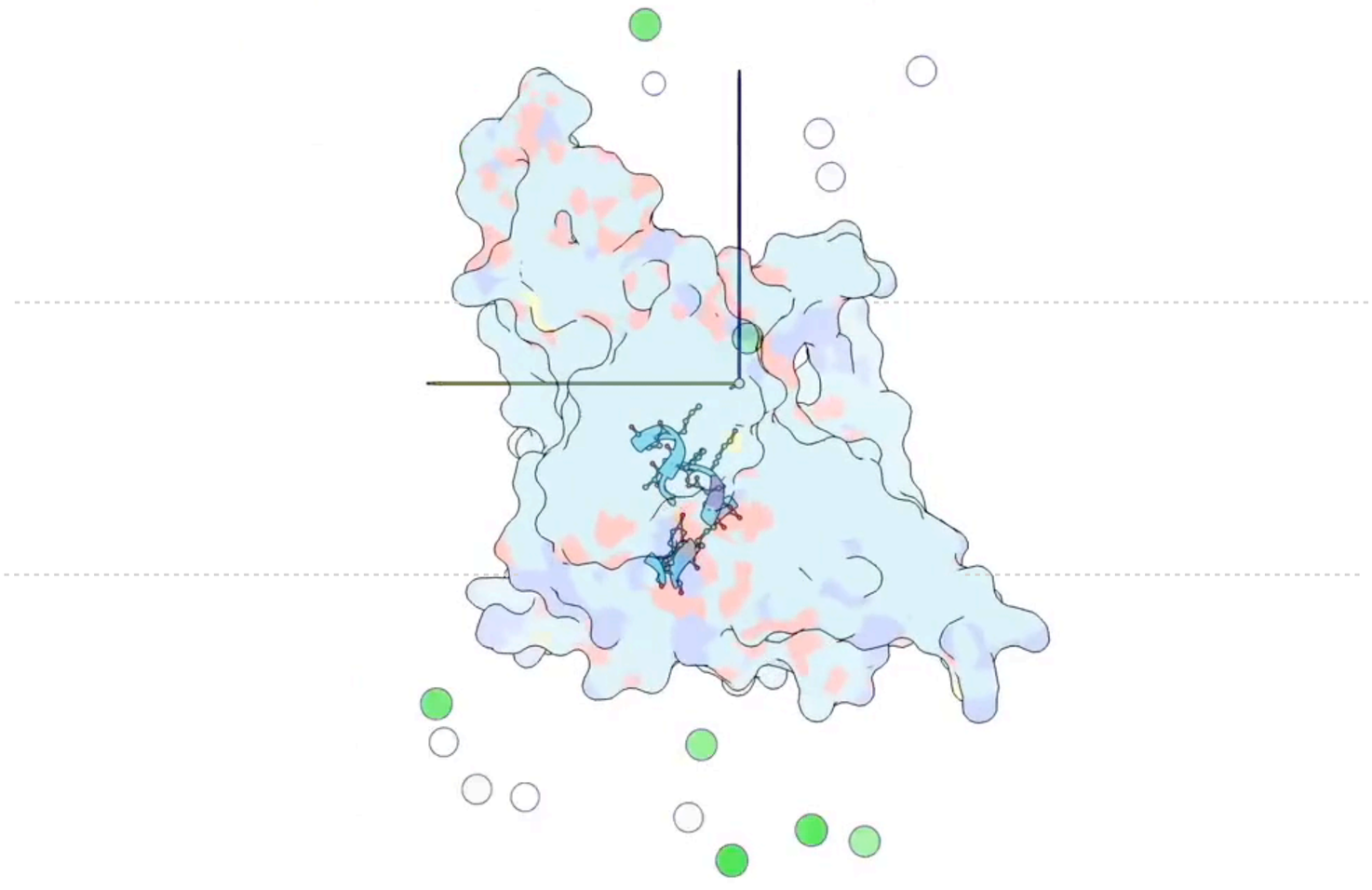


simulate system, $V(\Lambda)$





simulate system, $V(\Lambda)$



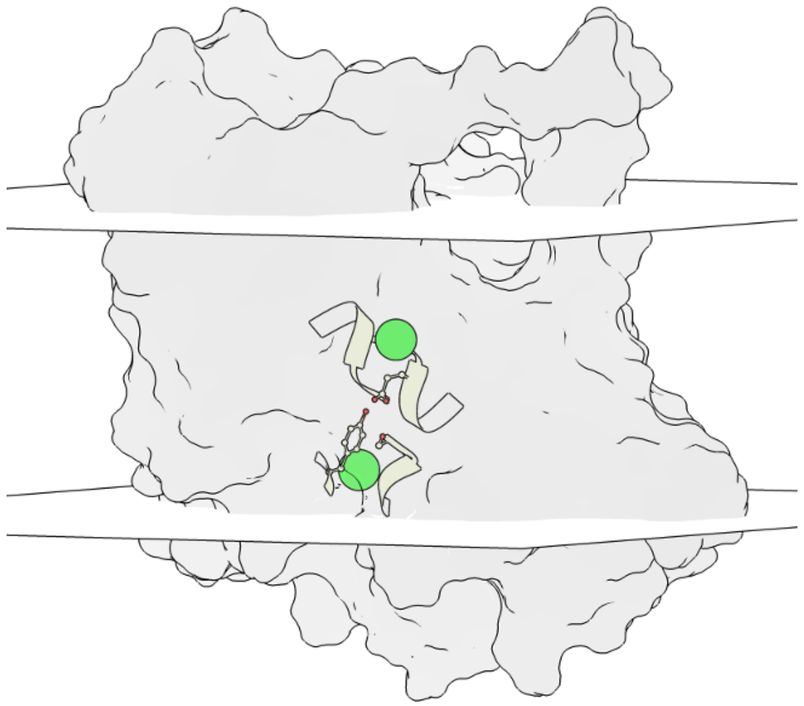
simulate system, $V(\Lambda)$

pre-process data, featurize/tICA

↑

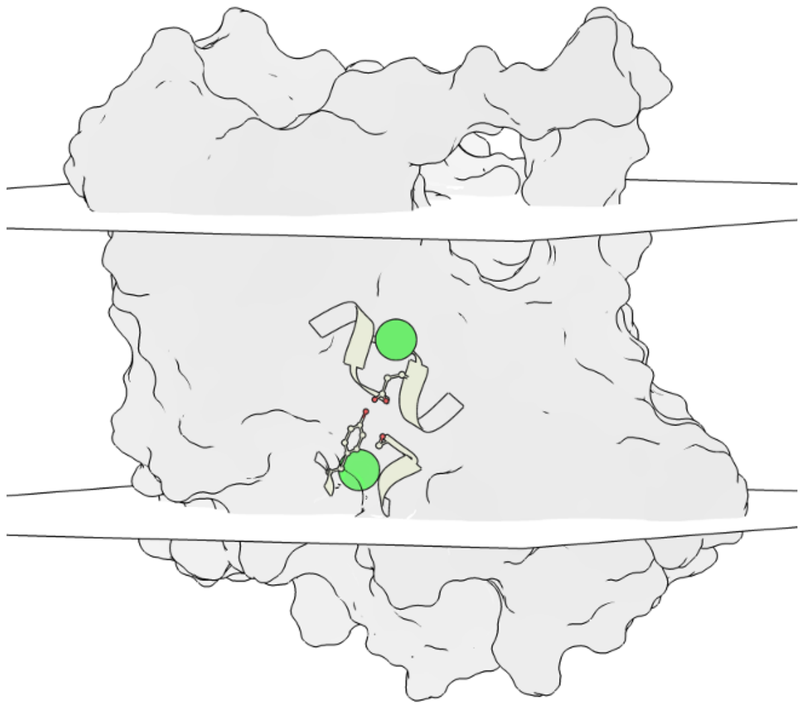
simulate system, $V(\Lambda)$

pre-process data, featurize/tICA



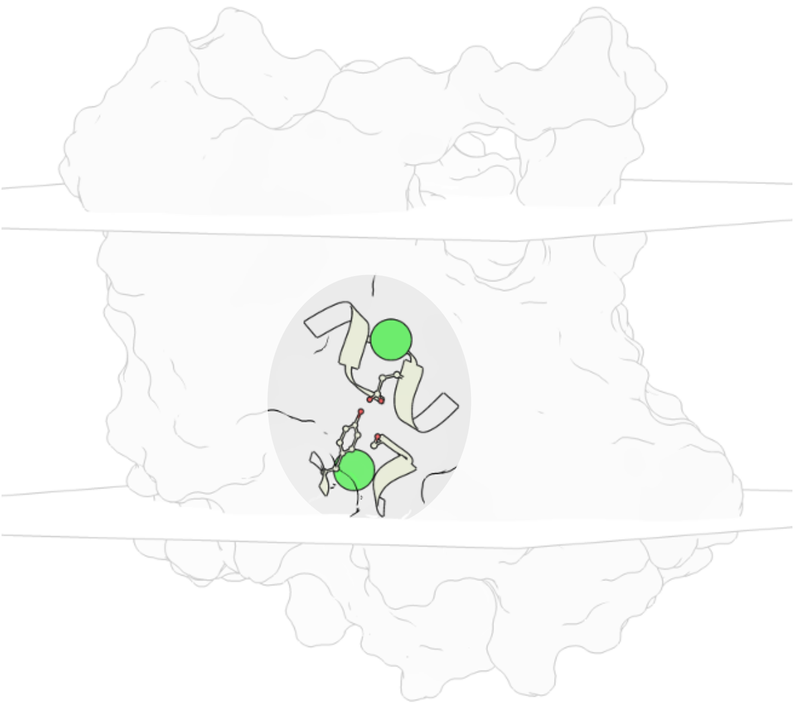
pre-process data, featurize/tICA

[atom x position x time]



pre-process data, featurize/tICA

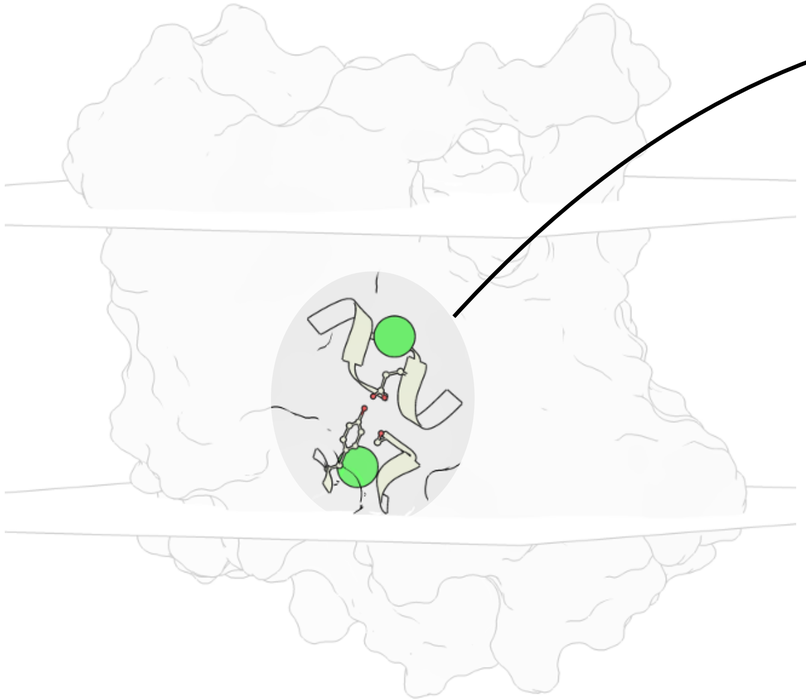
[atom x position x time]



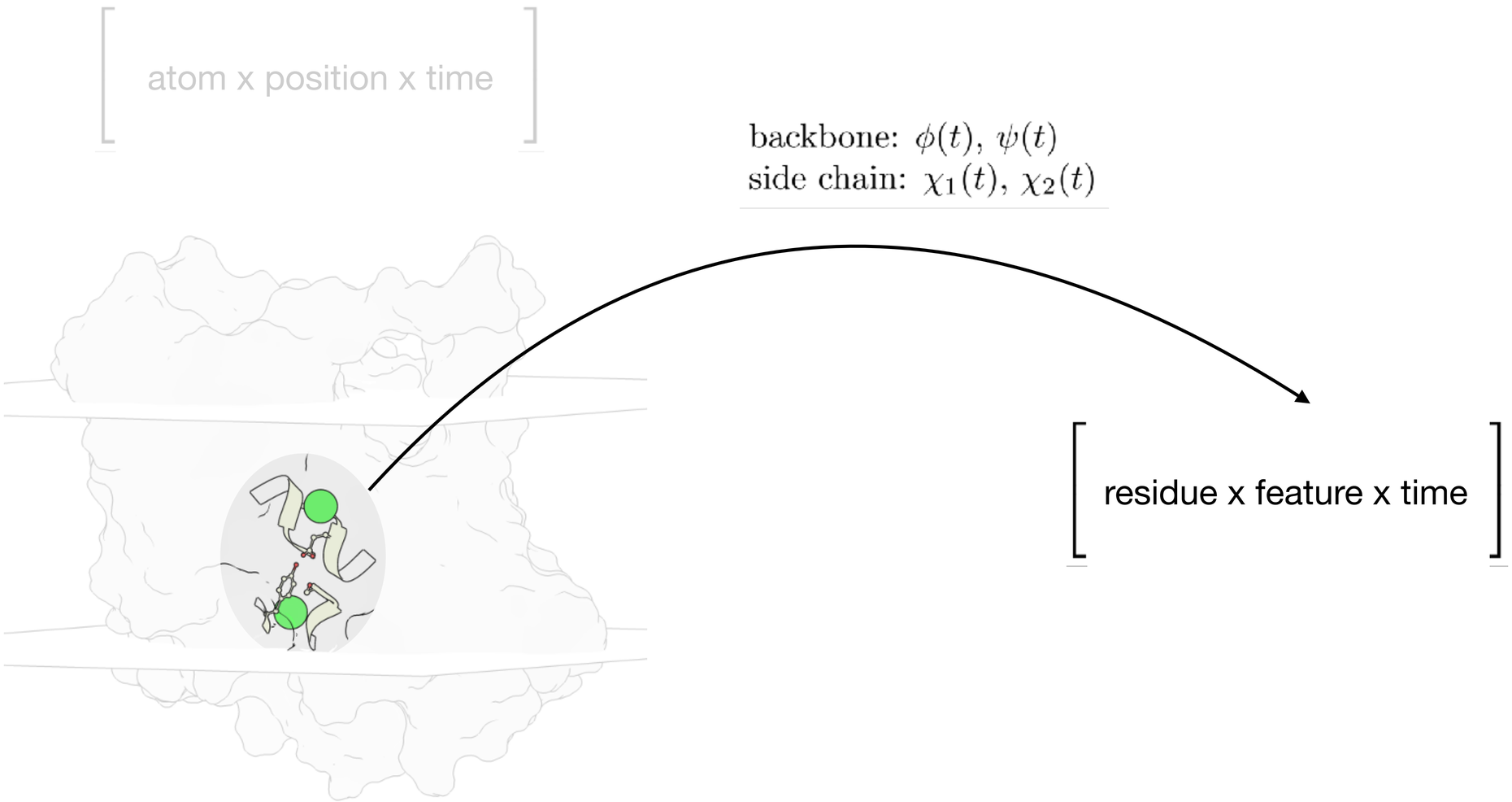
pre-process data, featurize/tICA

[atom x position x time]

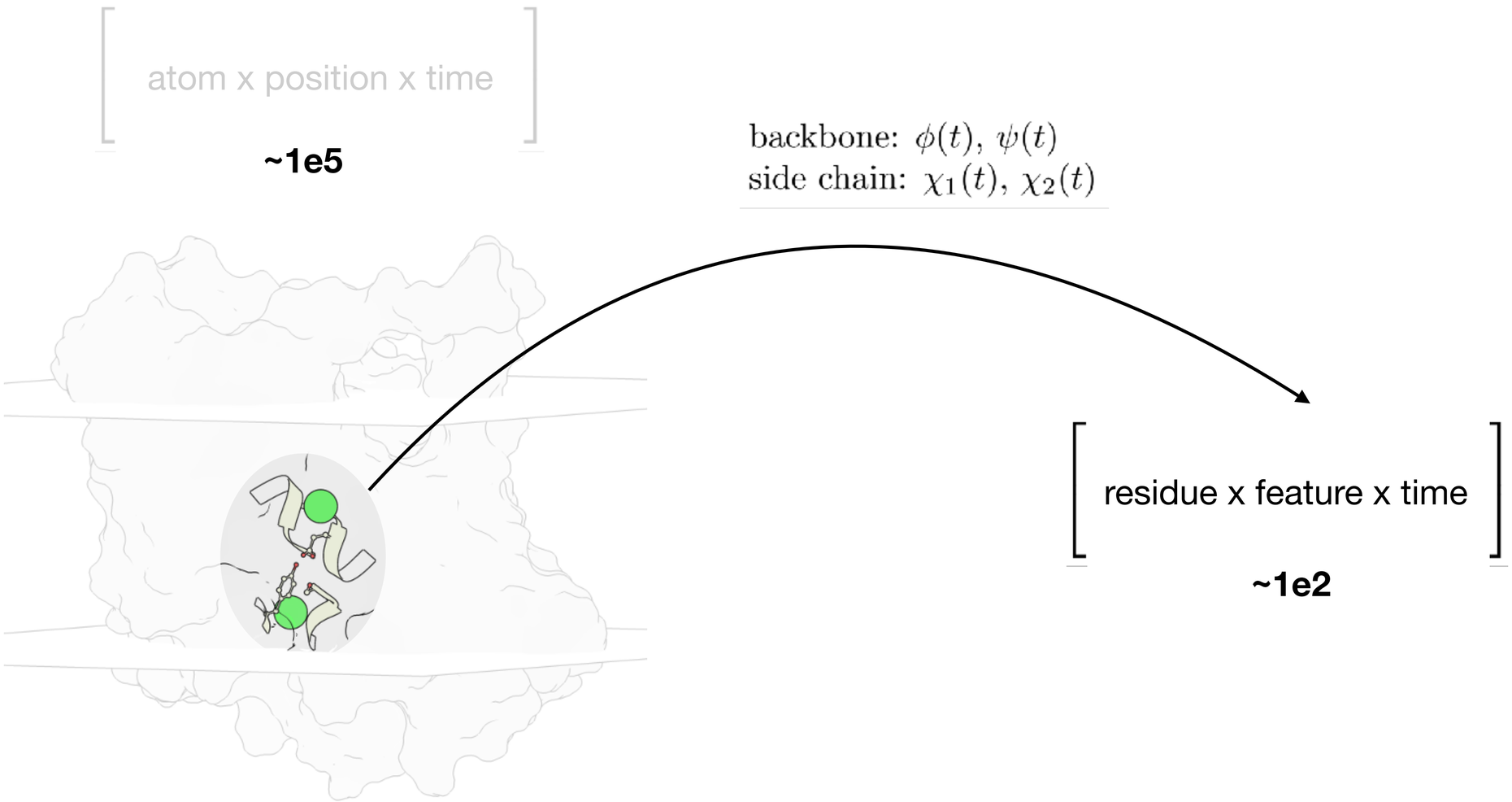
backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$



pre-process data, featurize/tICA

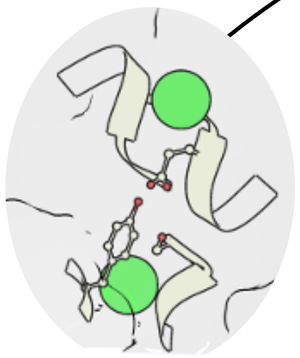


pre-process data, featurize/tICA



pre-process data, featurize/tICA

backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$



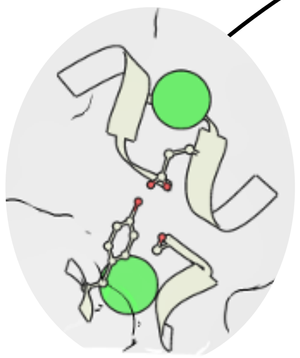
$$\left[\ \text{residue x feature x time}\ \right]$$

pre-process data, featurize/tICA

$$X = \{\phi_j(t), \psi_j(t), \chi_{1_j}(t), \chi_{2_j}(t) : j \in R\}$$

backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$

$j \in R$



residue x feature x time

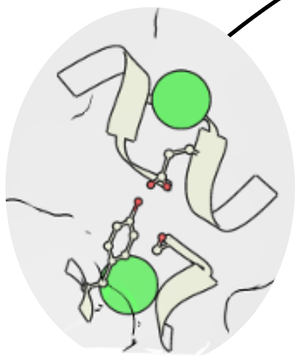
pre-process data, featurize/tICA

$$X = \{\phi_j(t), \psi_j(t), \chi_{1_j}(t), \chi_{2_j}(t) : j \in R\}$$

backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$

$$A_i(\tau) = \frac{\mathbb{E}[(x_i(t) - \mu)(x_i(t+\tau) - \mu)]}{\sigma^2}$$

$j \in R$



[residue x feature x time]

[$A_i(\tau)$ for $x_i \in X$]

pre-process data, featurize/tICA

$$X = \{\phi_j(t), \psi_j(t), \chi_{1_j}(t), \chi_{2_j}(t) : j \in R\}$$

backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$

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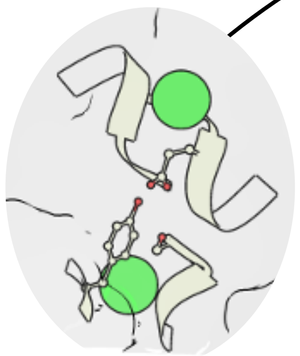
$j \in R$



[residue x feature x time]

[$A_i(\tau)$ for $x_i \in X$]

eigendecomposition

tICs

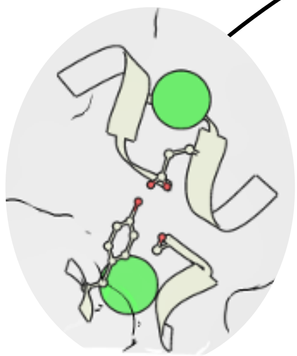
pre-process data, featurize/tICA

$$X = \{\phi_j(t), \psi_j(t), \chi_{1_j}(t), \chi_{2_j}(t) : j \in R\}$$

backbone: $\phi(t)$, $\psi(t)$
side chain: $\chi_1(t)$, $\chi_2(t)$

$$A_i(\tau) = \frac{\mathbb{E}[(x_i(t) - \mu)(x_i(t+\tau) - \mu)]}{\sigma^2}$$

$j \in R$



[residue x feature x time]

~1e2

[$A_i(\tau)$ for $x_i \in X$]

eigendecomposition

tICs

~1

pre-process data, featurize/tICA

tICs: long timescale dynamical processes

dynamical mode	conformational change	top residue features
tIC 0	SER_{cen} backbone rotation	ψ(I170,G169), ψ(G169,S168)
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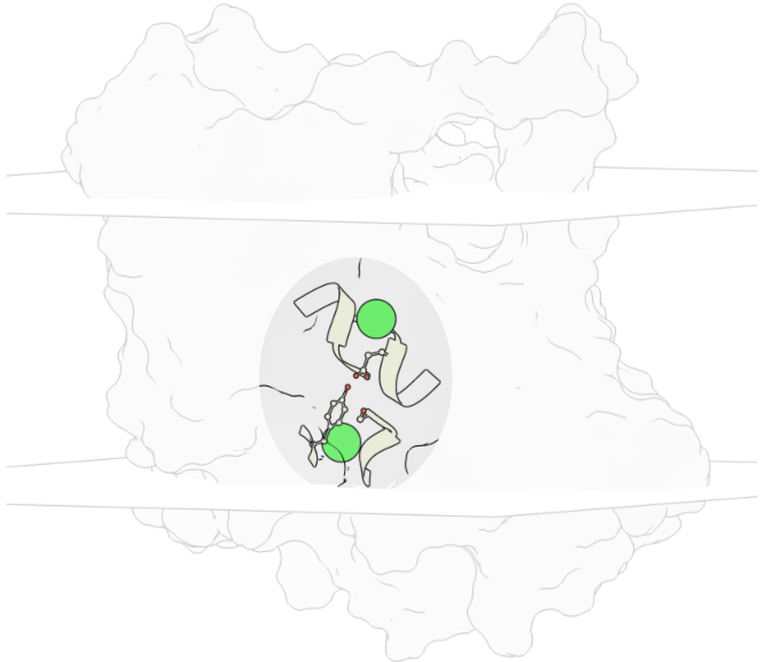

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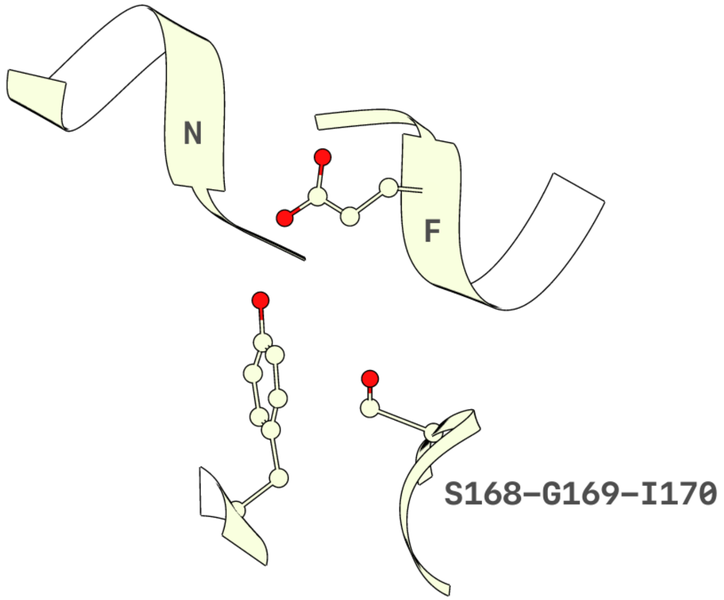

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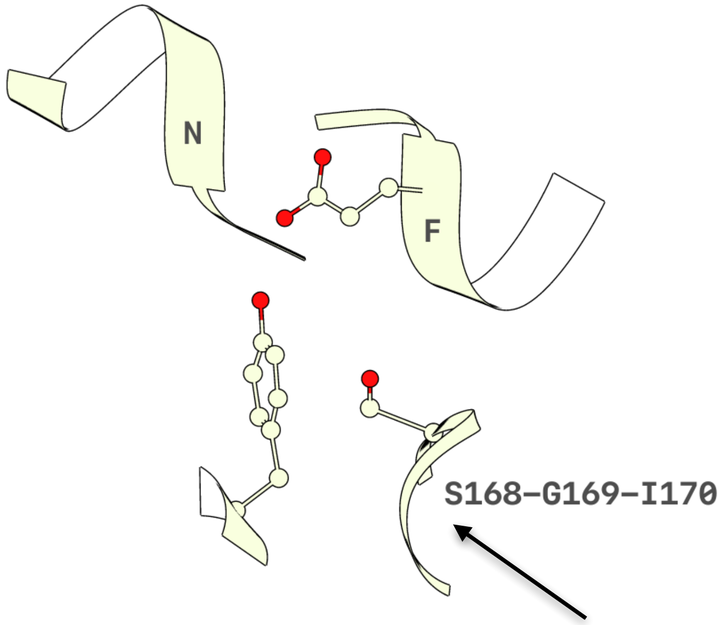

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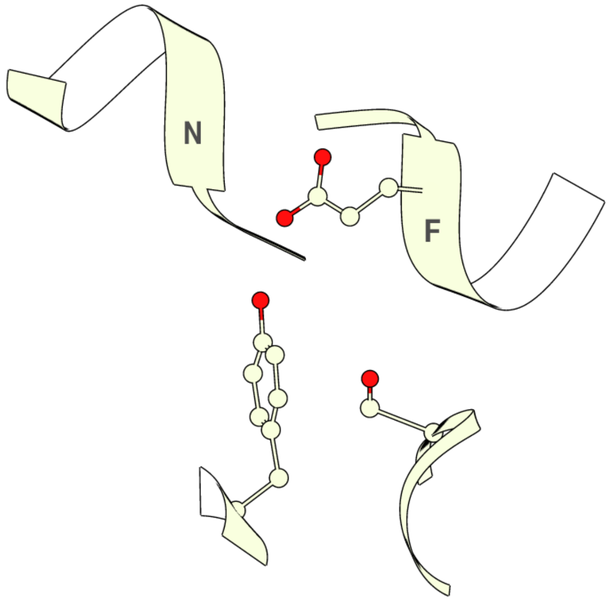

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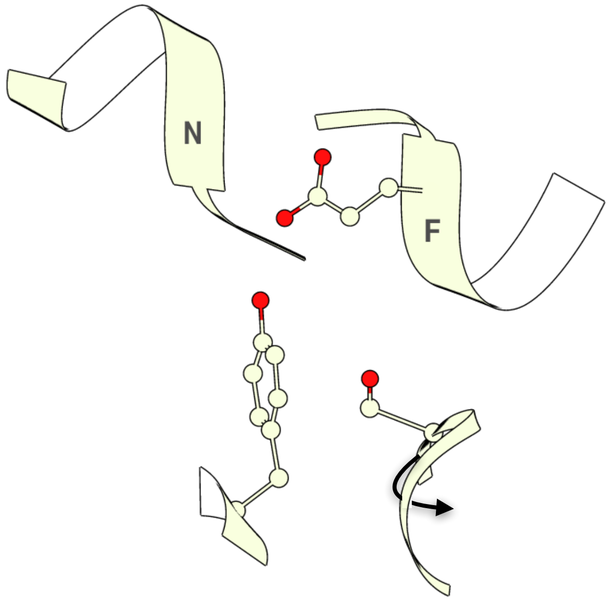

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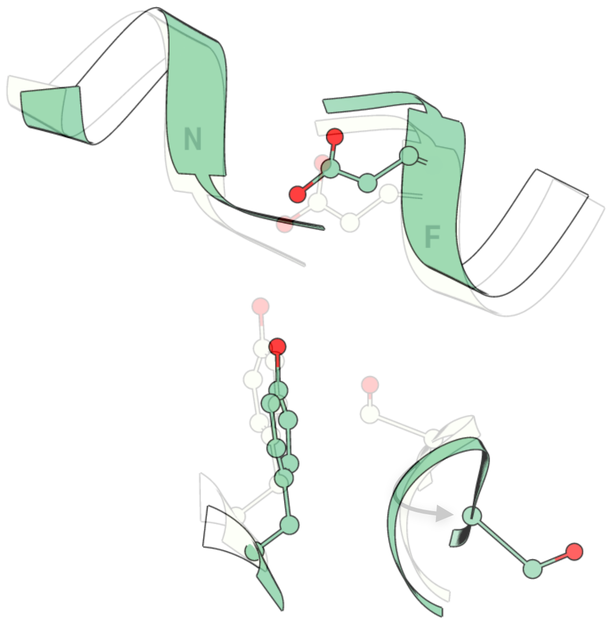

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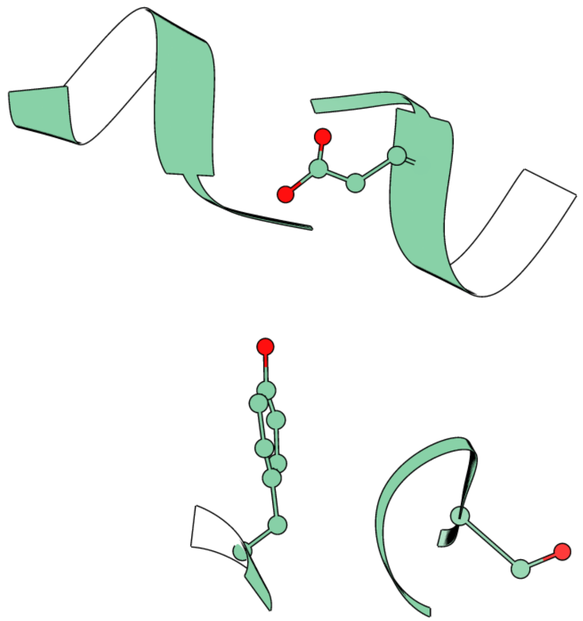

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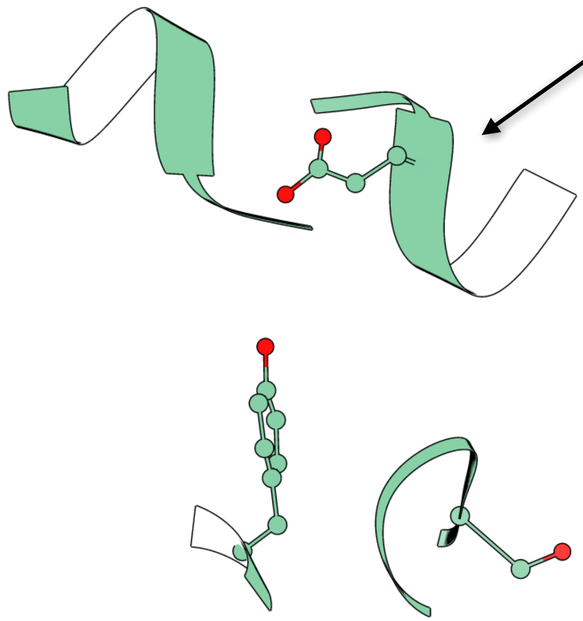

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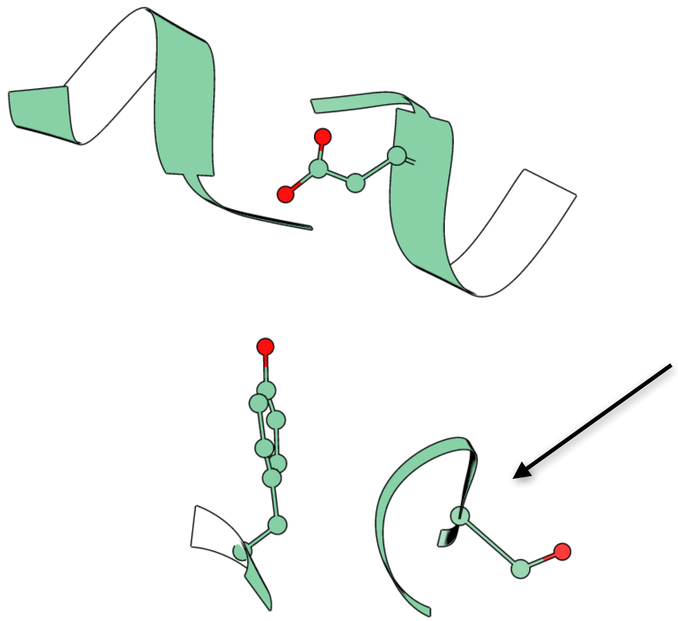

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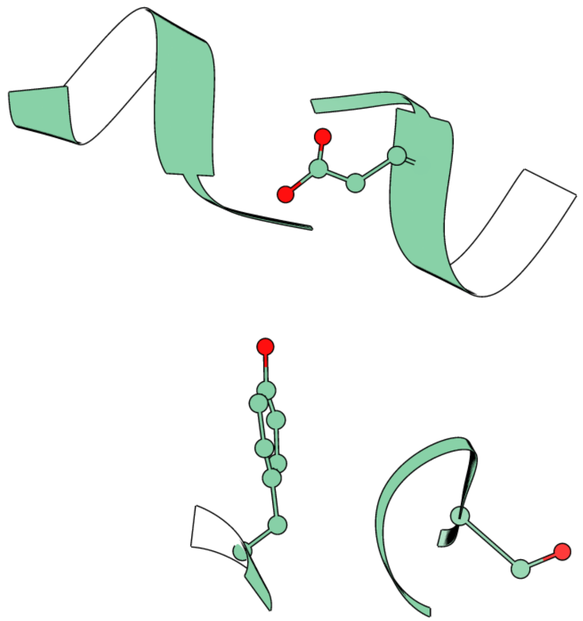

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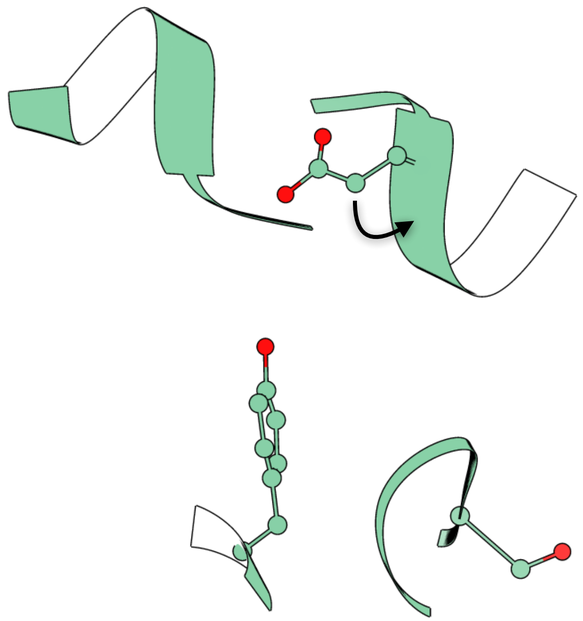

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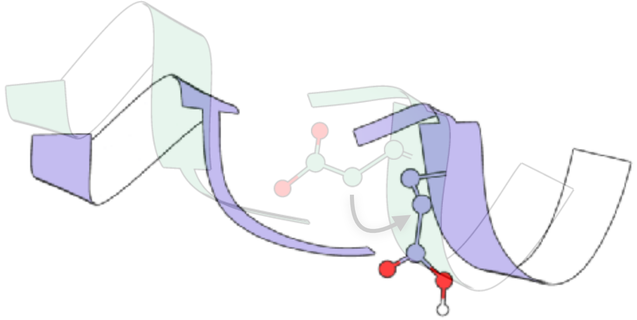

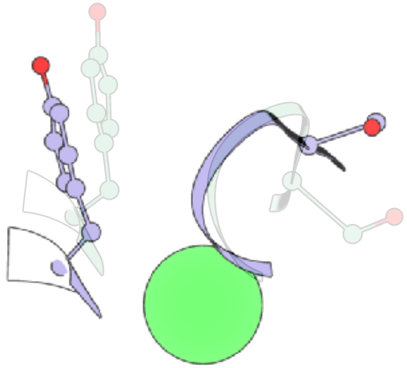

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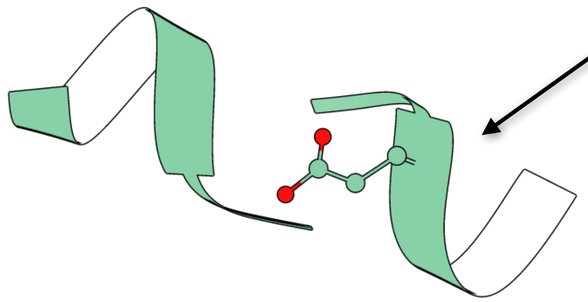

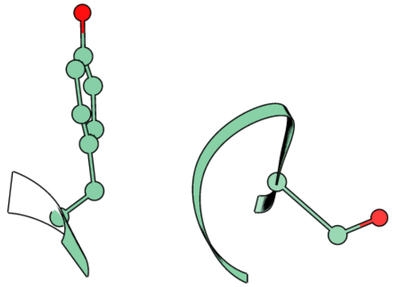

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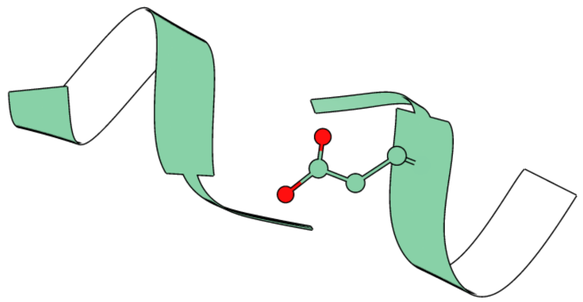

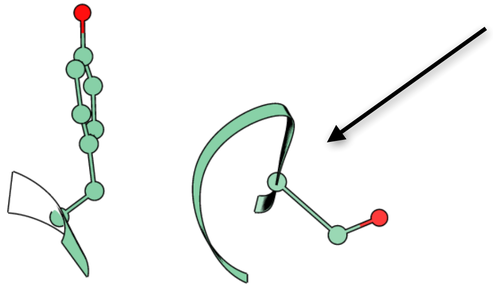

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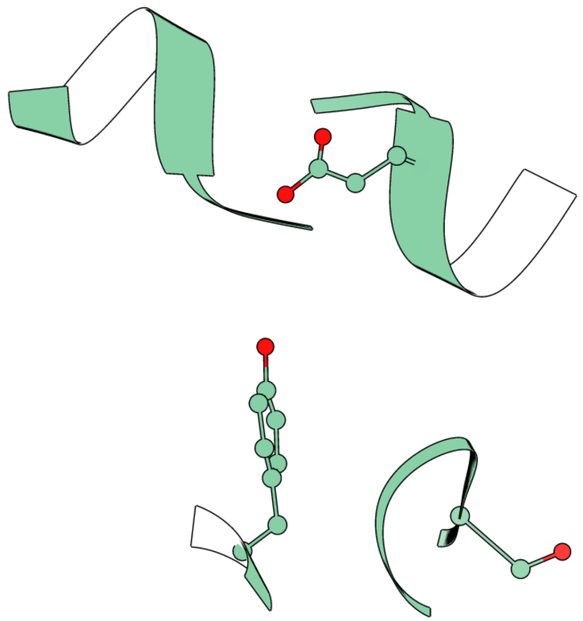

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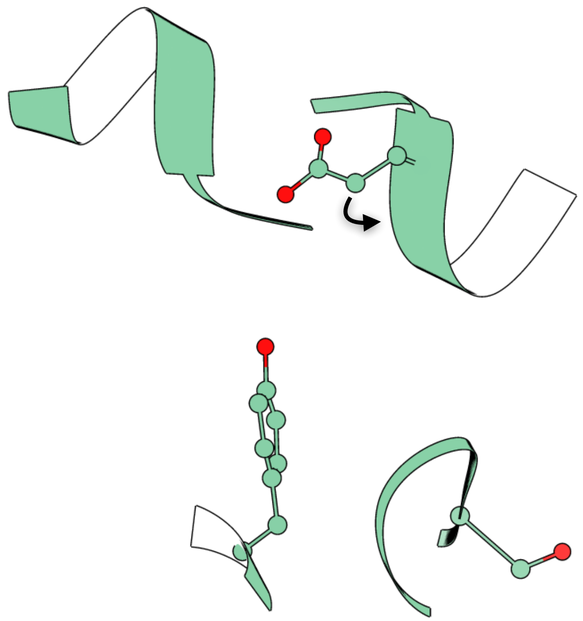

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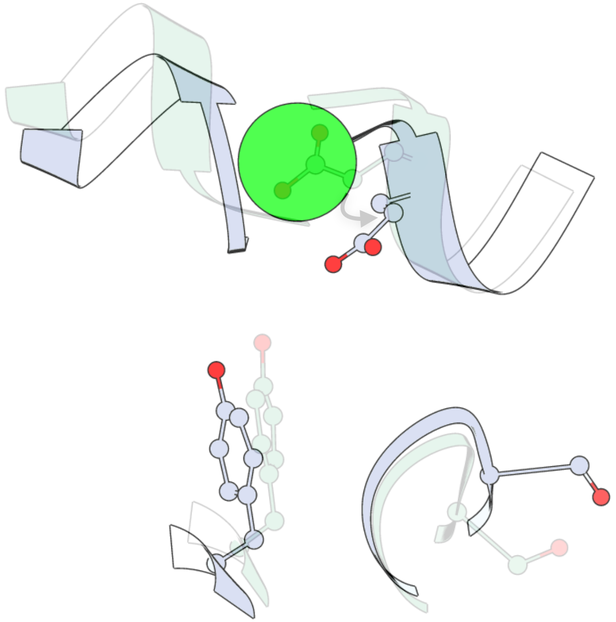

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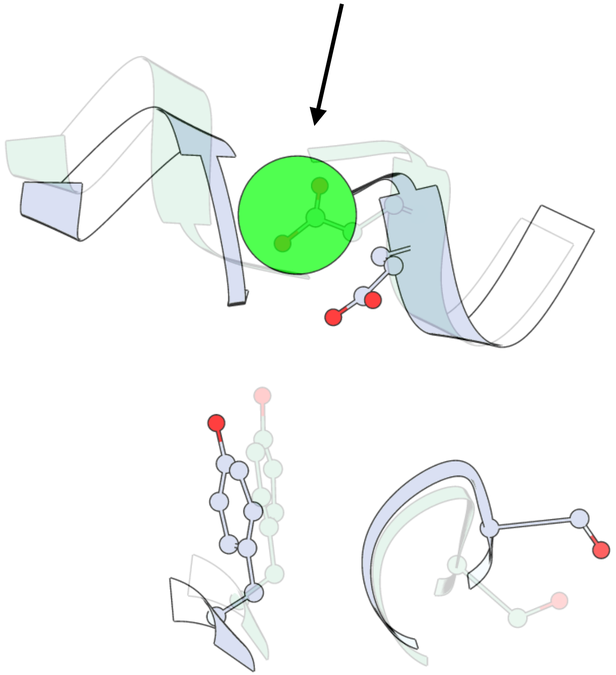

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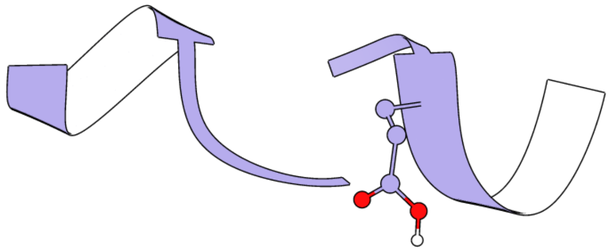

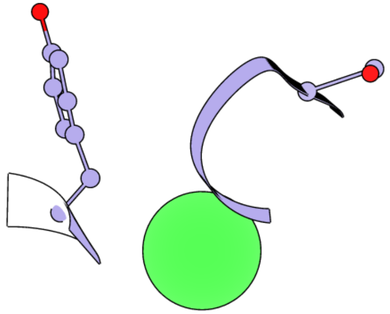

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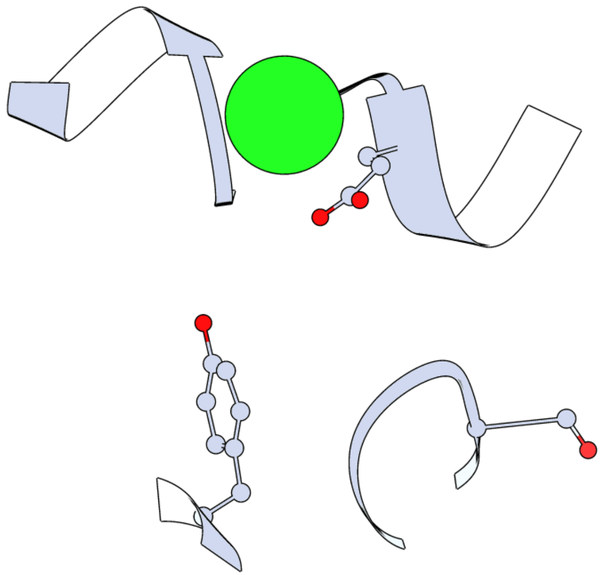

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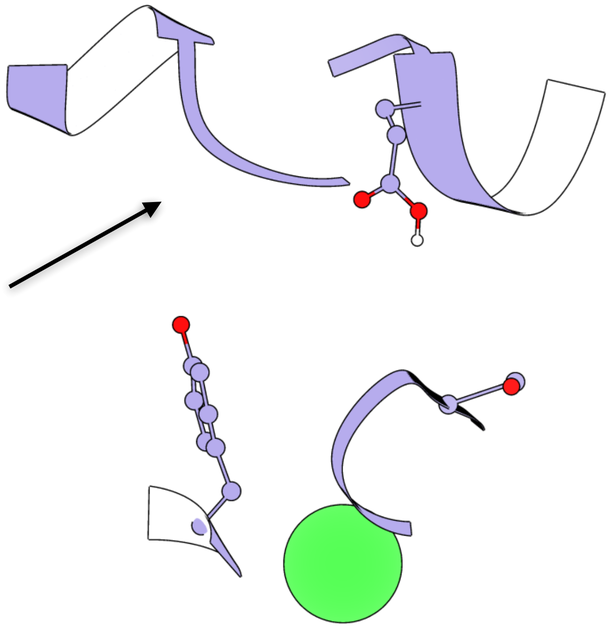

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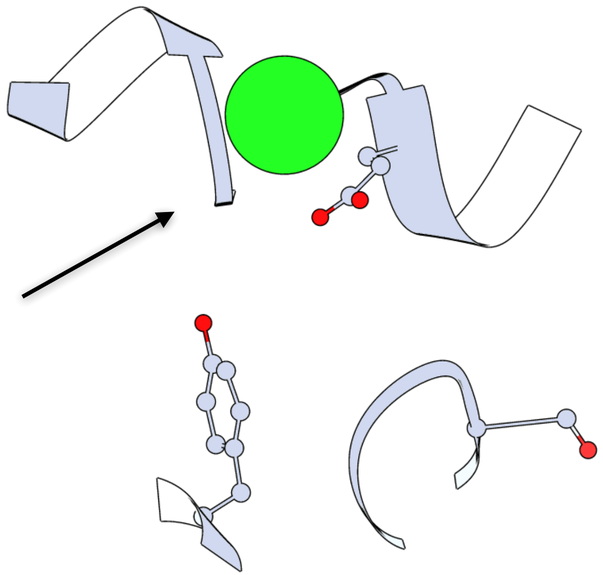


construct mechanism, MSM

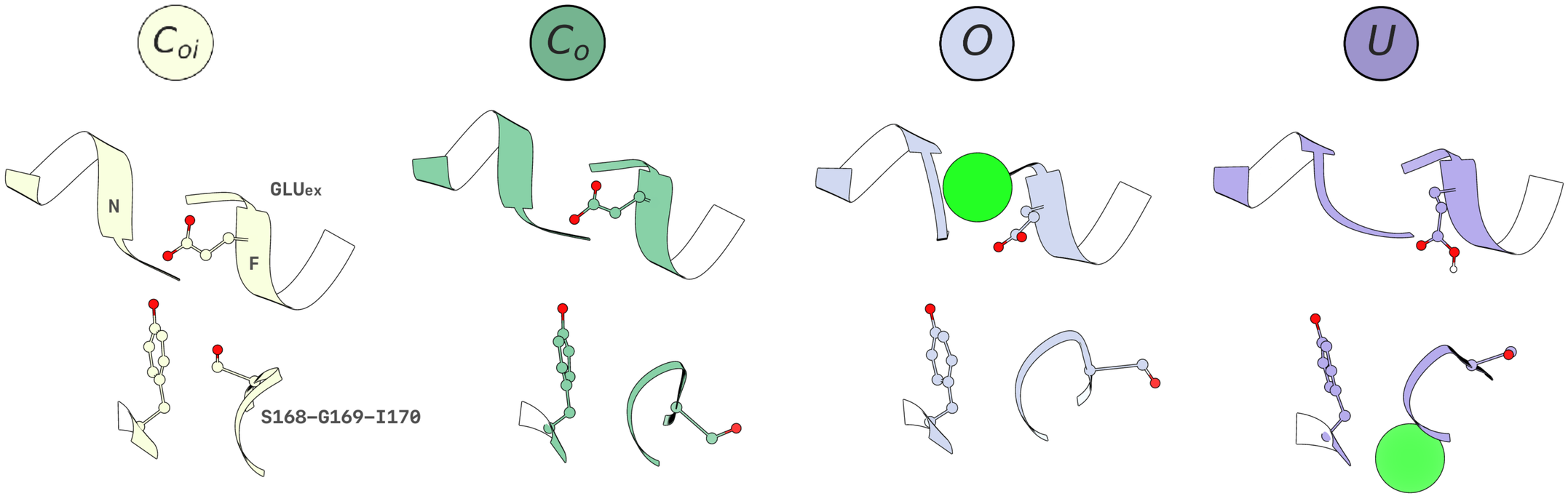
↑

pre-process data, featurize/tICA

↑

simulate system, $V(\Lambda)$

construct mechanism, MSM



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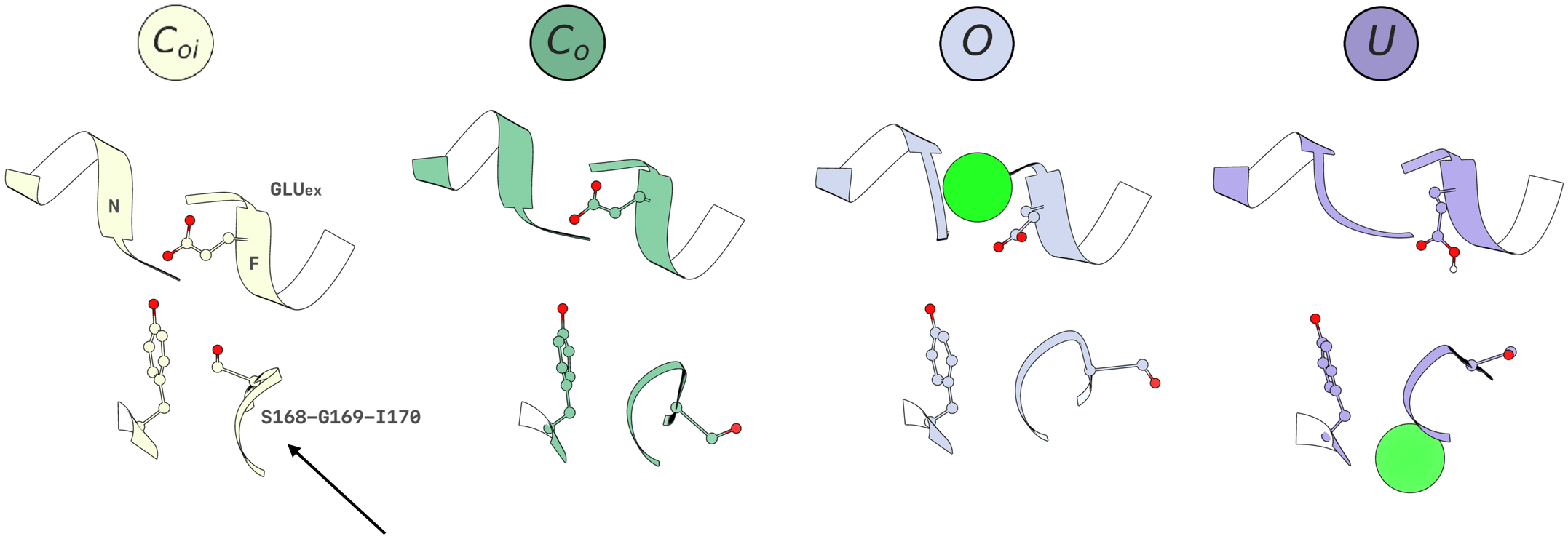

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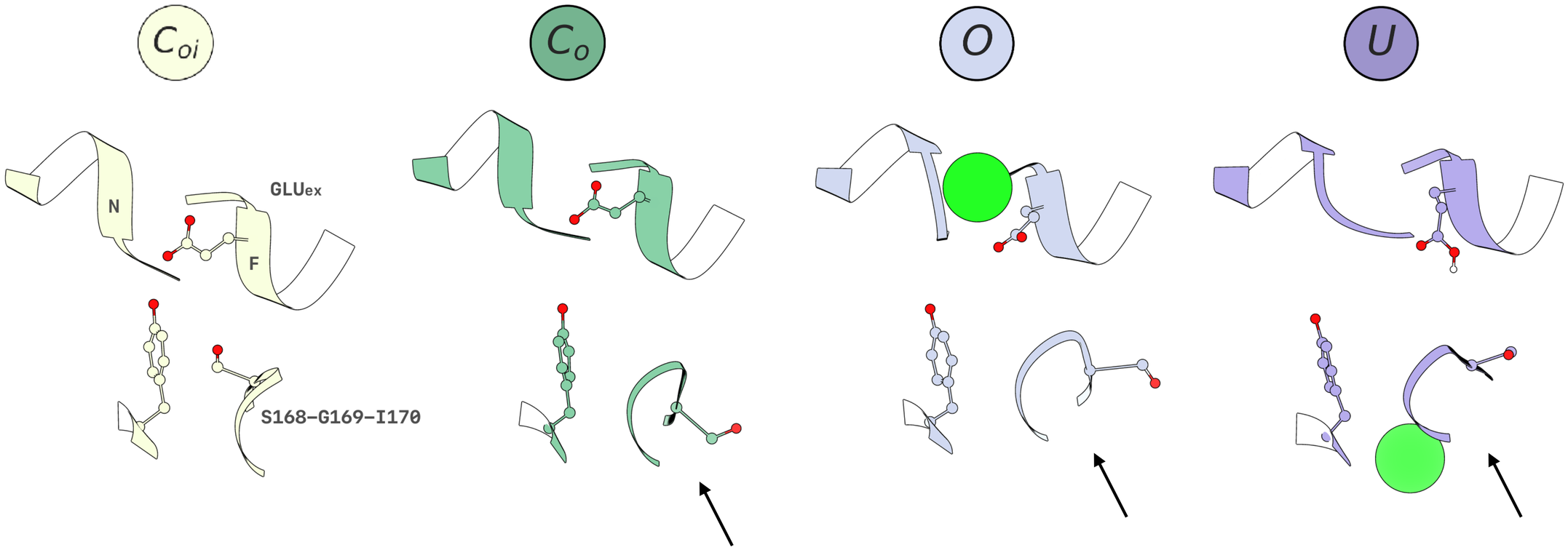

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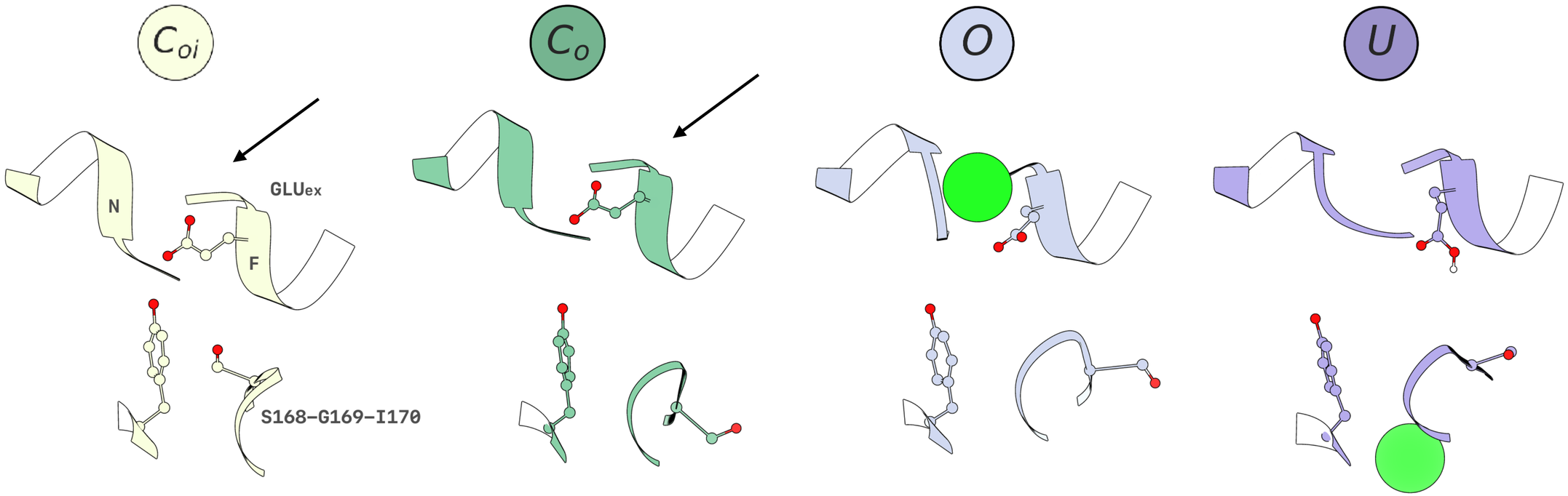

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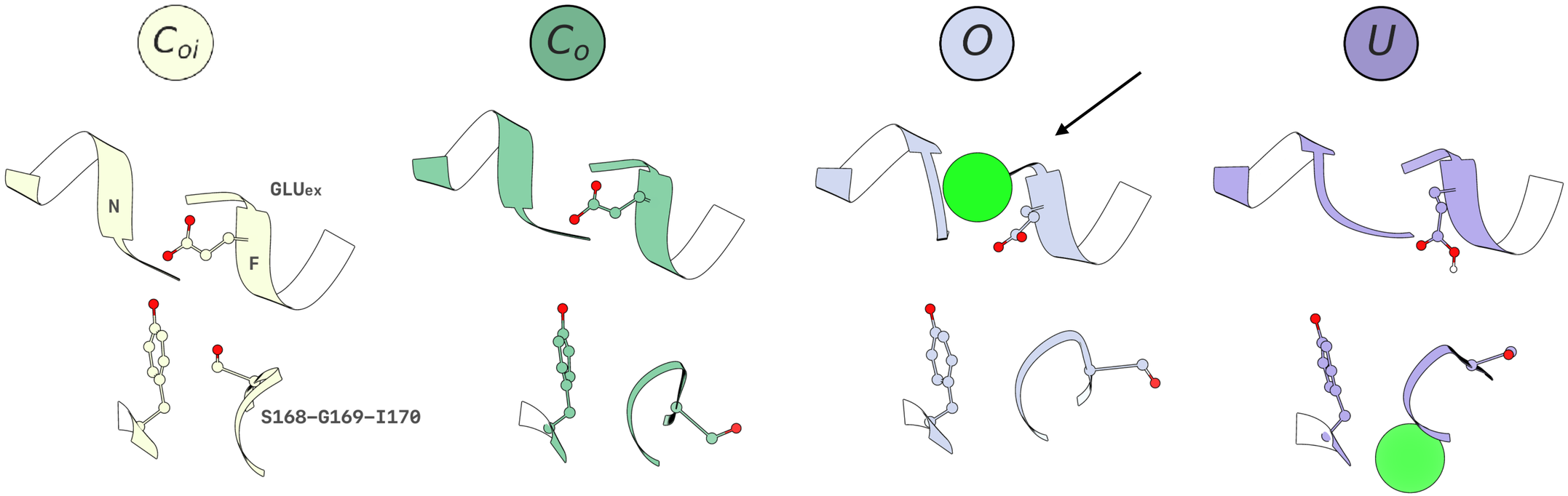

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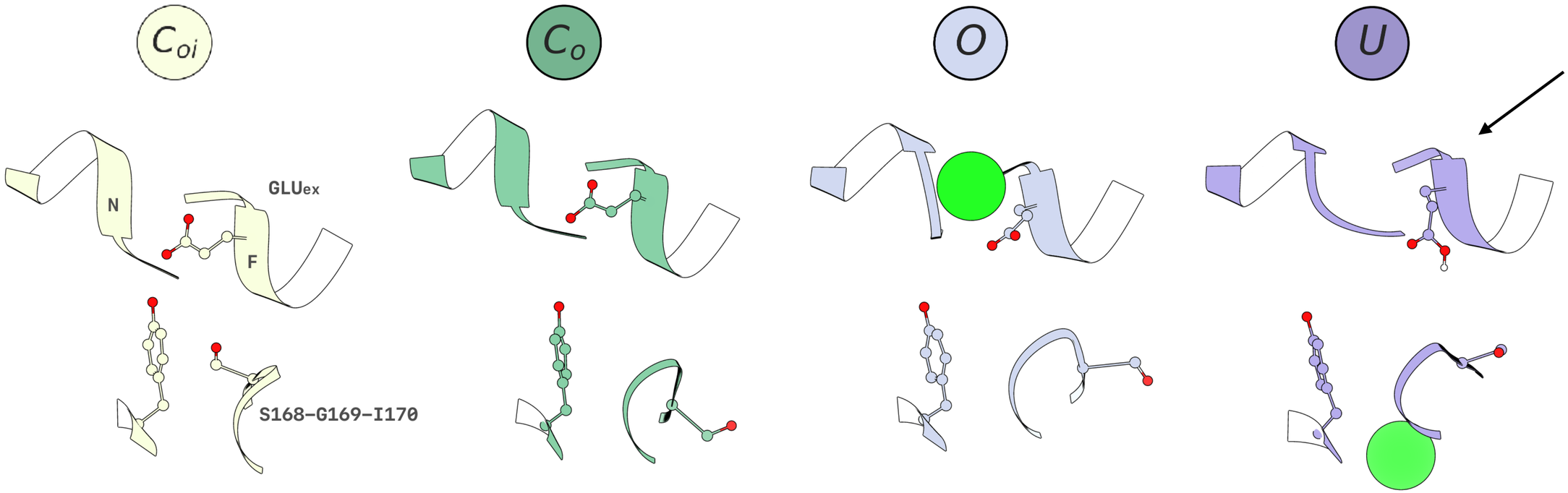

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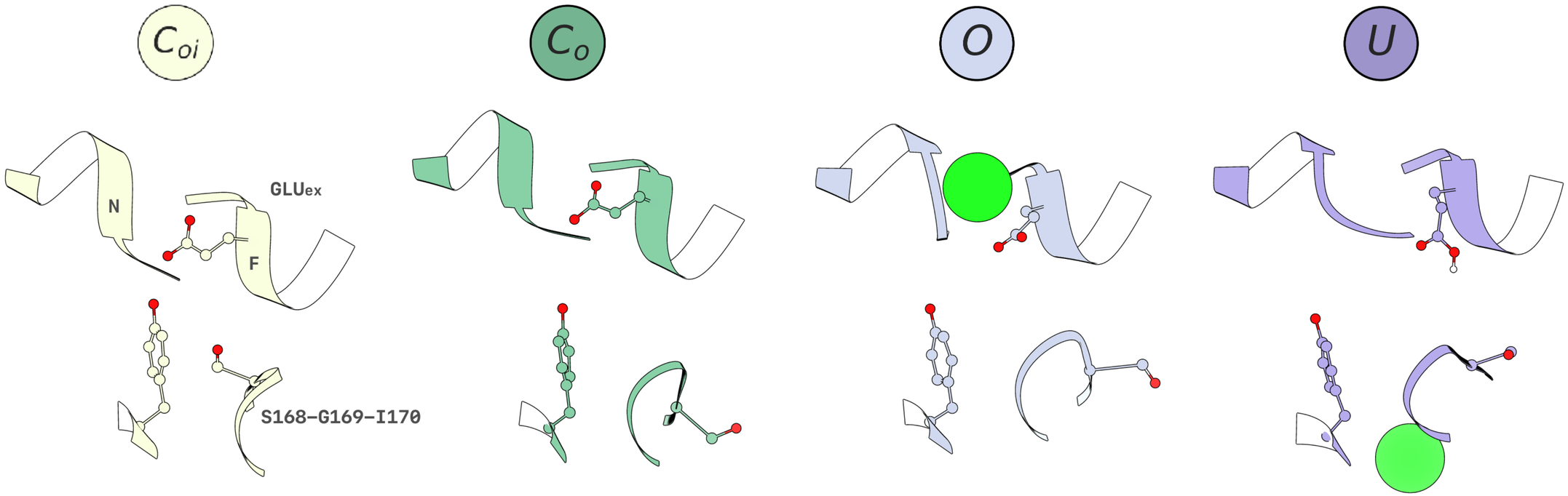
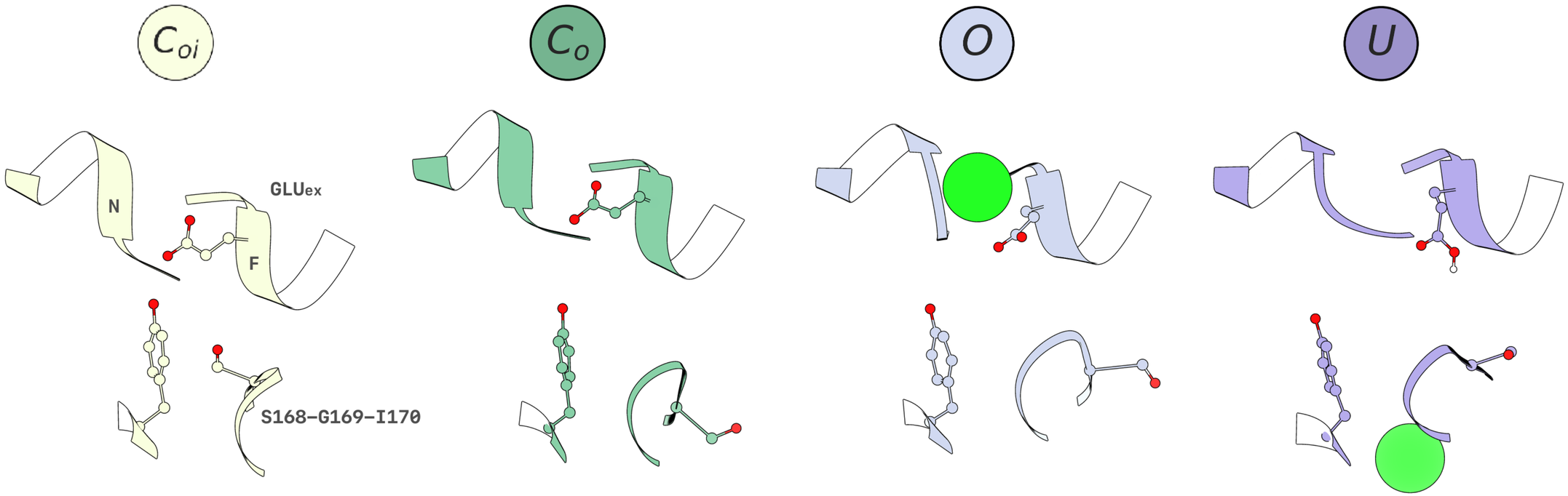


$$\vec{p}^{t+1} = \vec{p}^{t}\mathbf{T}$$

construct mechanism, MSM

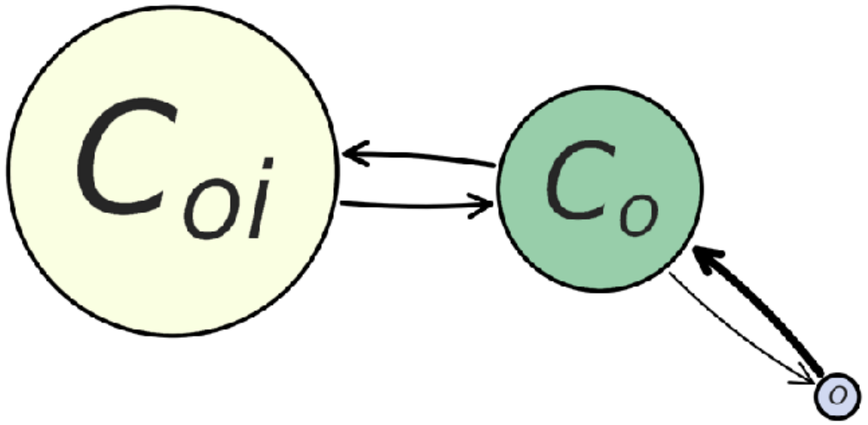


$$\vec{p}^{t+1} = \vec{p}^{t}\mathbf{T}$$

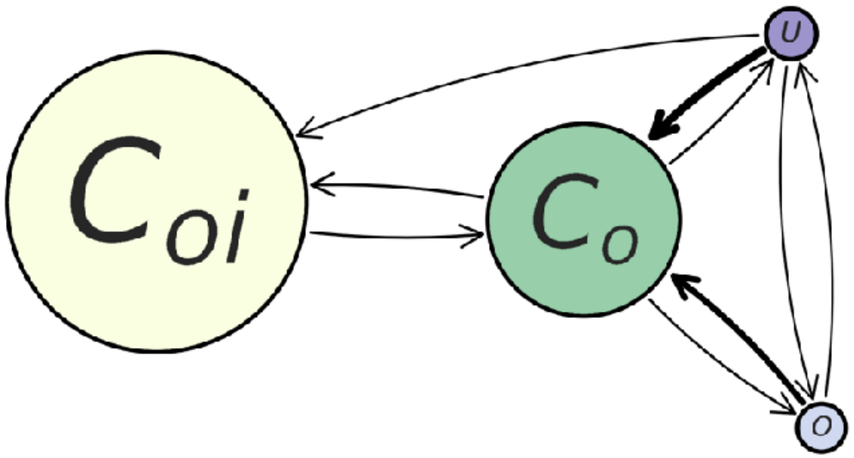
$$\vec{\pi} = \vec{\pi}\mathbf{T}$$

construct mechanism, MSM

GLU$_{ex}$



GLU$_{ex}{}^{p}$

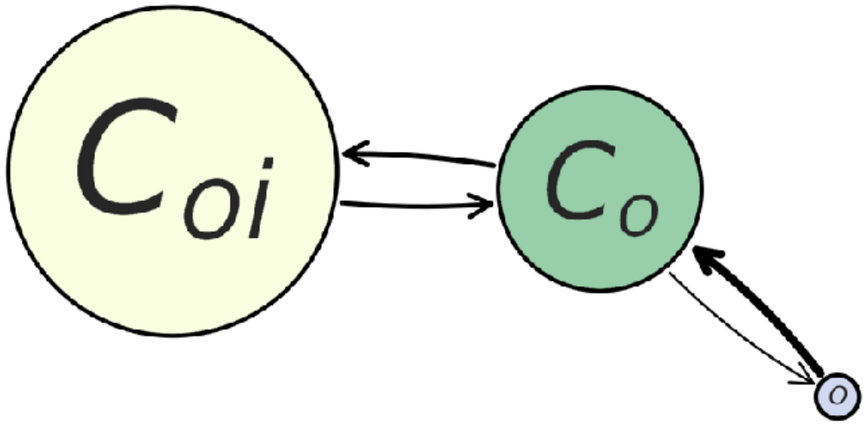


$$\vec{p}^{t+1} = \vec{p}^{t}\mathbf{T}$$

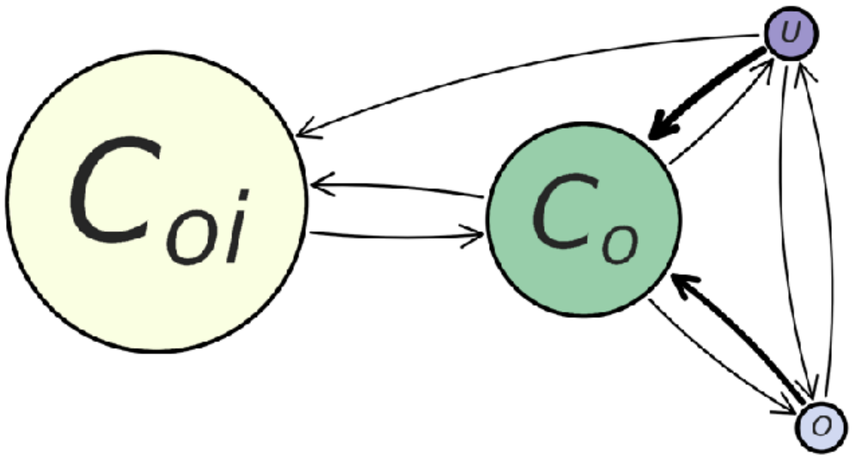
$$\vec{\pi} = \vec{\pi}\mathbf{T}$$

construct mechanism, MSM

GLU$_{ex}$



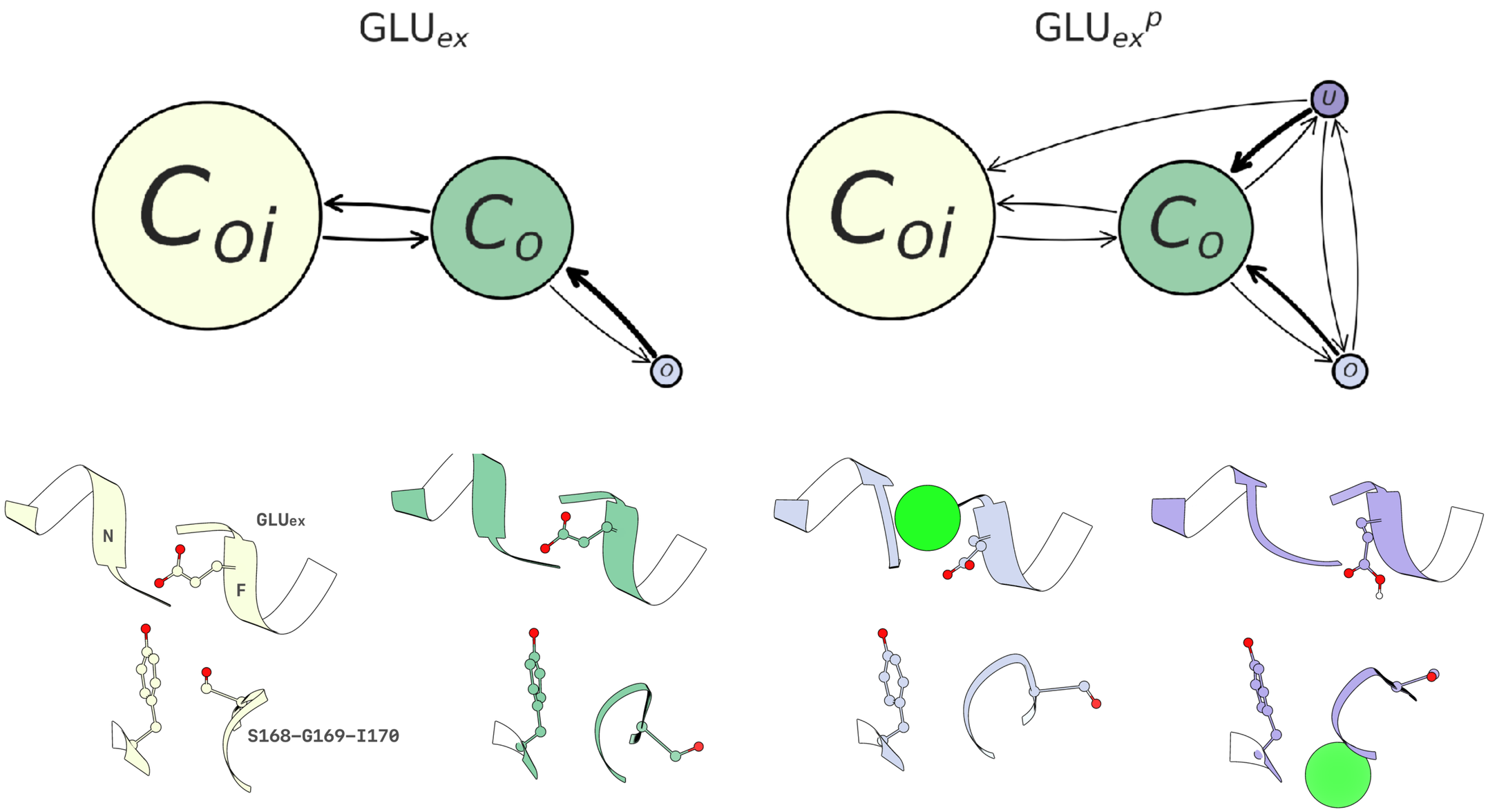
GLU$_{ex}{}^{p}$



$$\vec{p}^{t+1} = \vec{p}^{t}\mathbf{T}$$

$$\vec{\pi} = \vec{\pi}\mathbf{T}$$

construct mechanism, MSM ⇢ interpret dynamics


GLUex
GLUex^p
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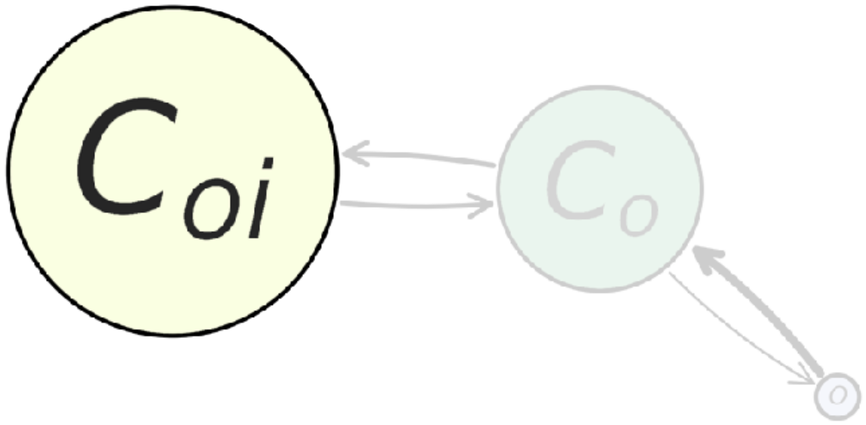
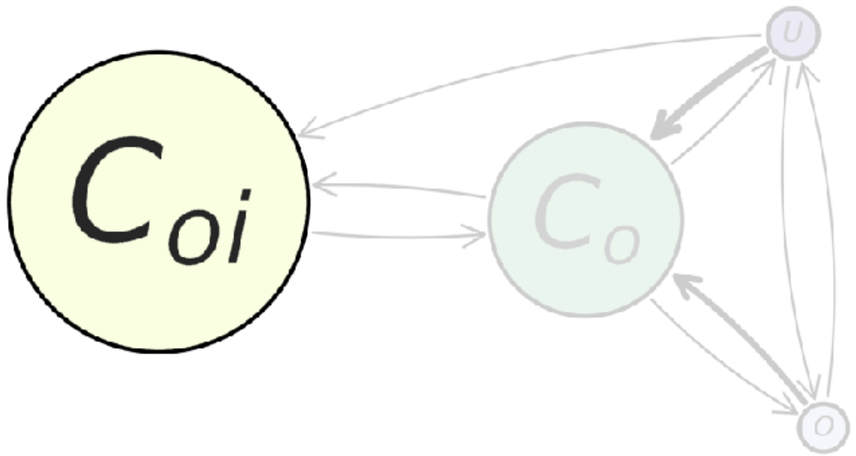
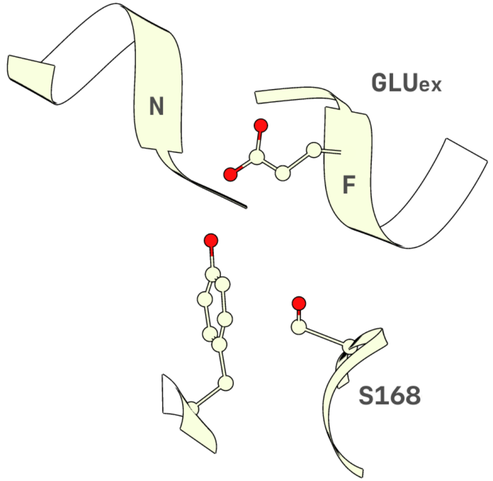
GLUex
S168-G169-I170

GLU_{ex}

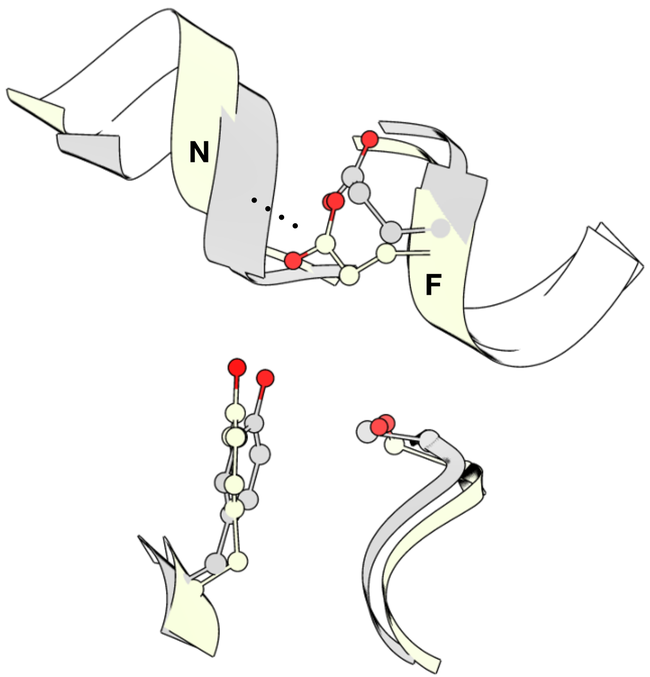


$GLU_{ex}{}^{p}$

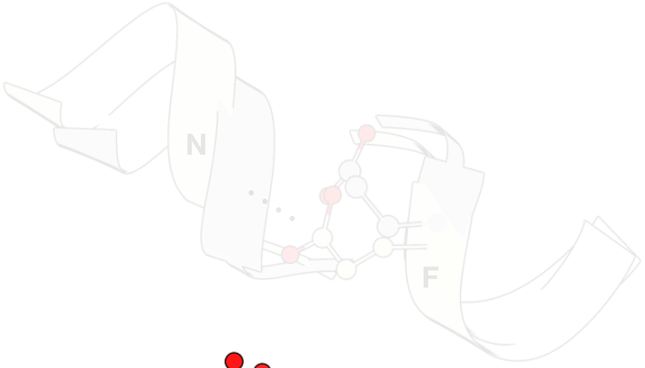


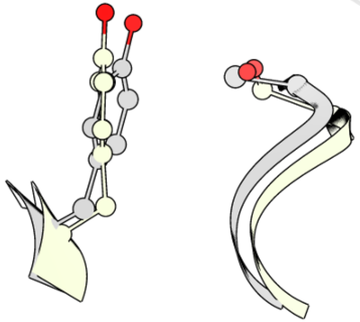


C_{oi} 1OTS (WT CLC-ec1)

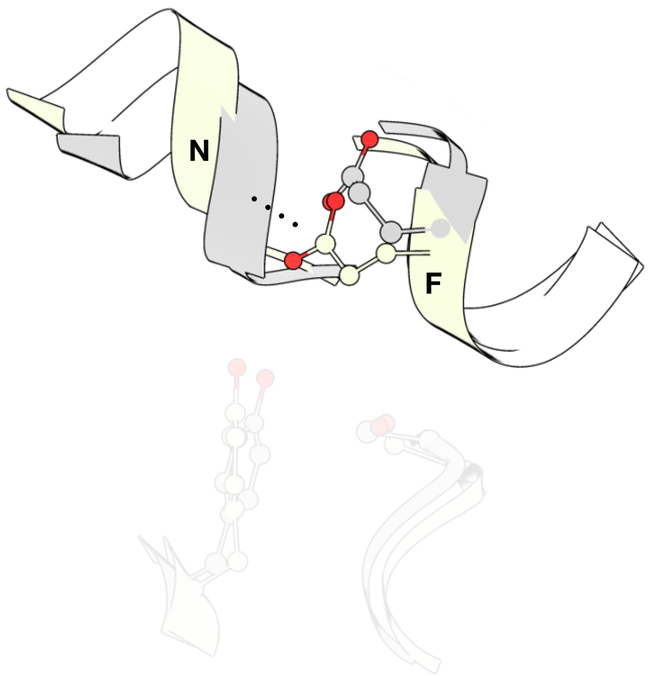


C_{oi} 1OTS (WT CLC-ec1)

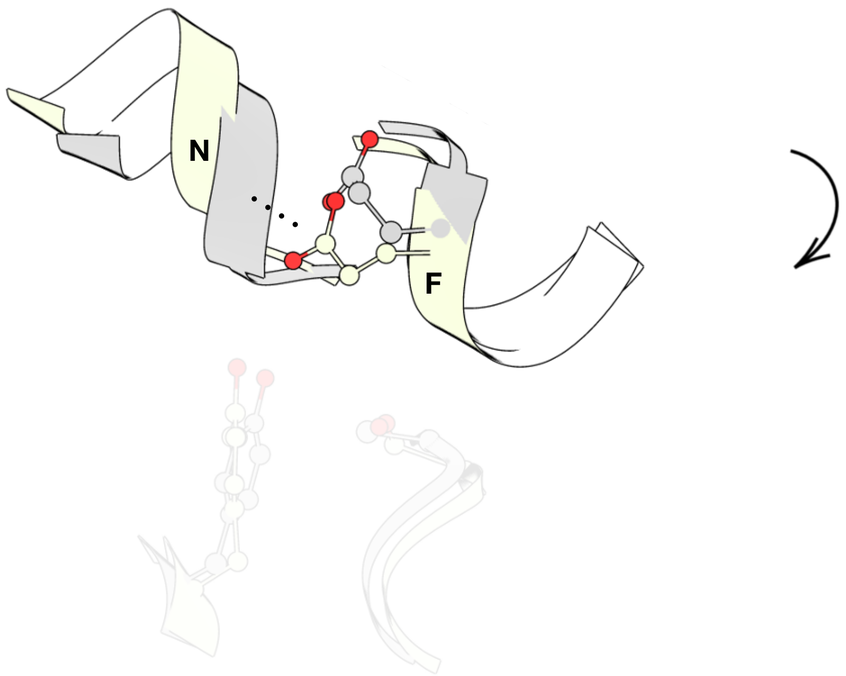




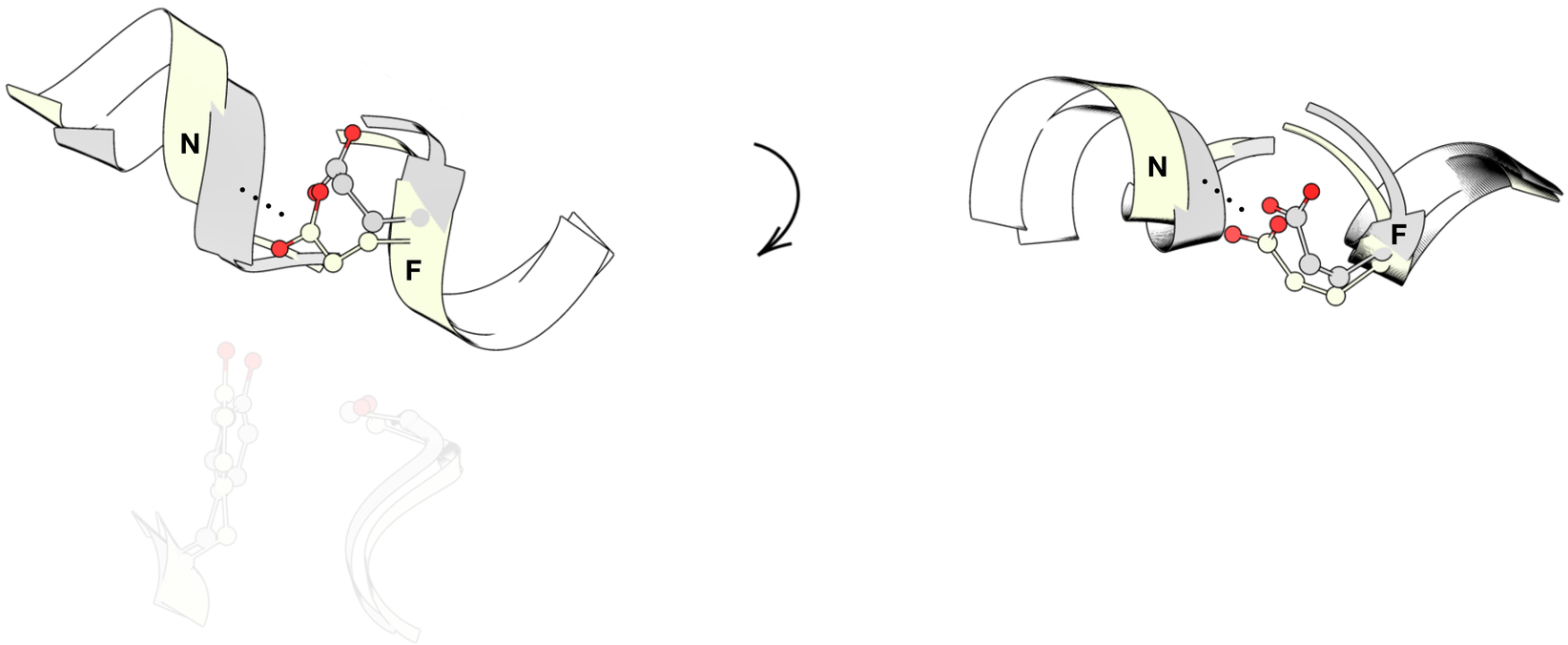
C_{oi} 1OTS (WT CLC-ec1)



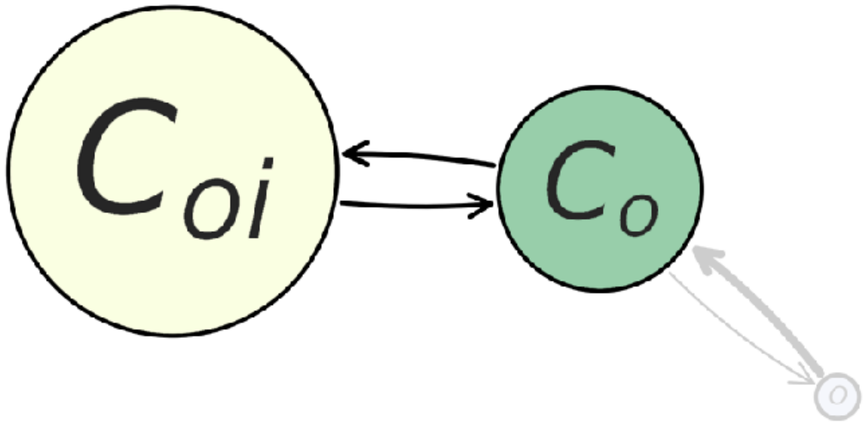
C_{oi} 1OTS (WT CLC-ec1)



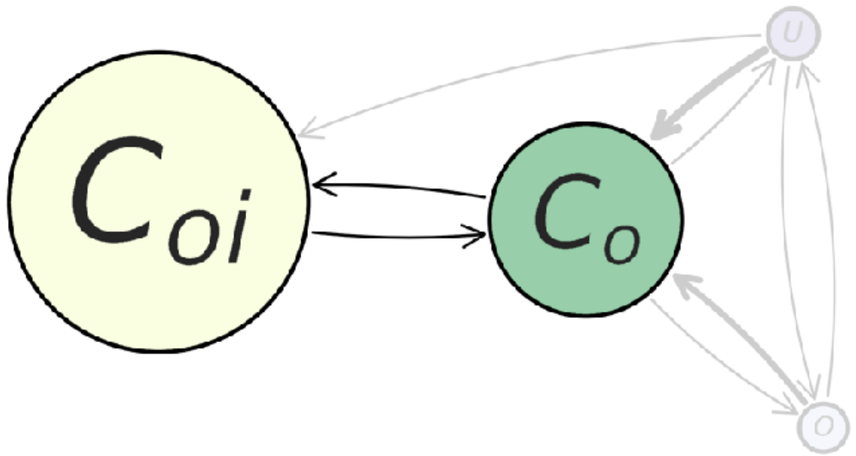
C_{oi} 1OTS (WT CLC-ec1)



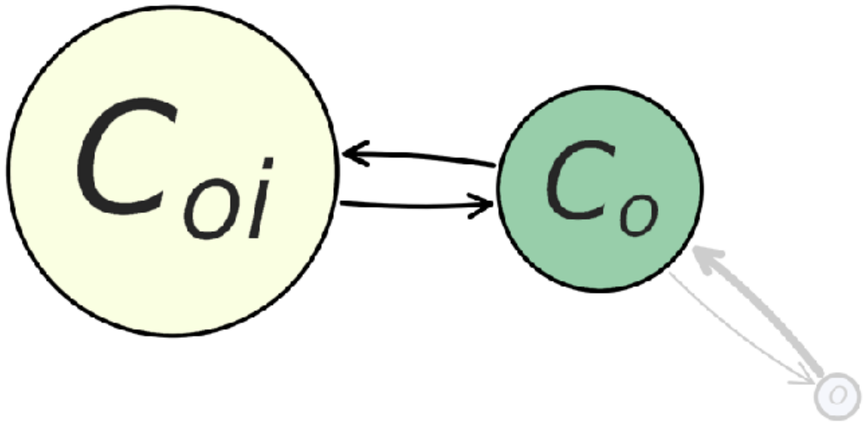
GLU_{ex}



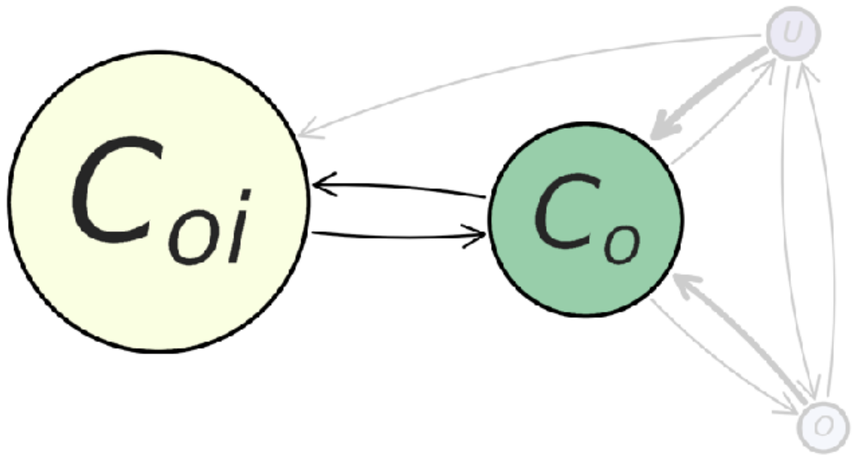
$GLU_{ex}{}^{p}$

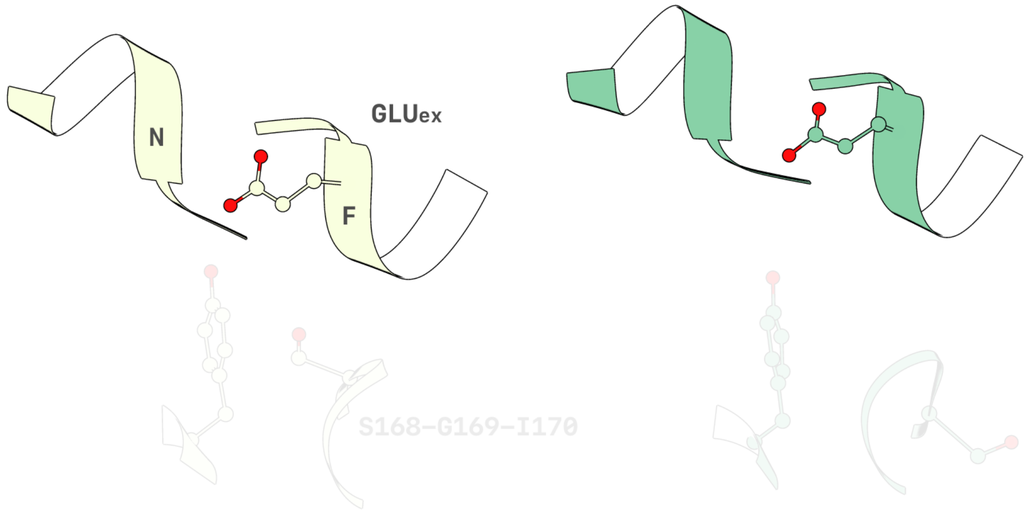


GLU_{ex}

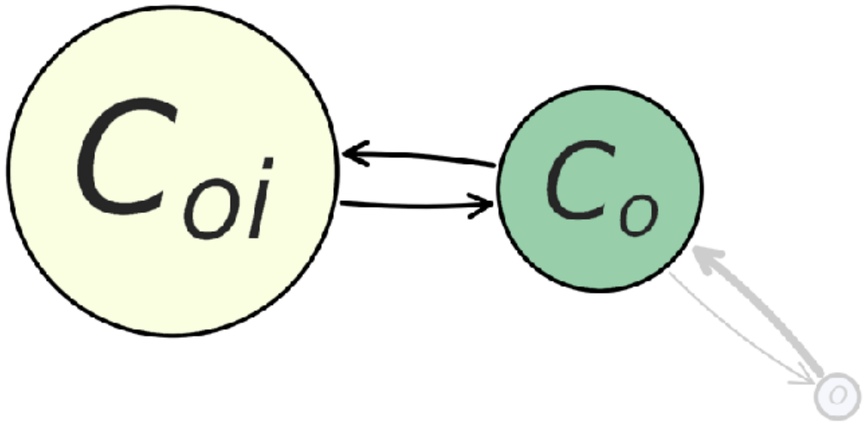


$GLU_{ex}{}^{p}$

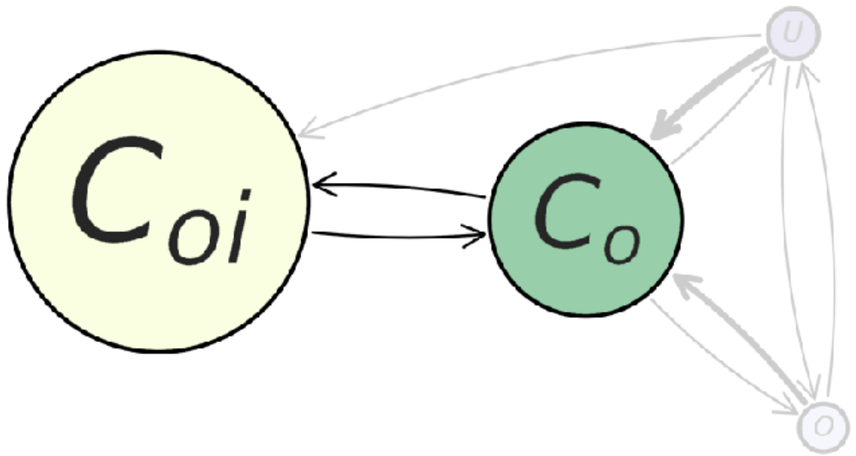


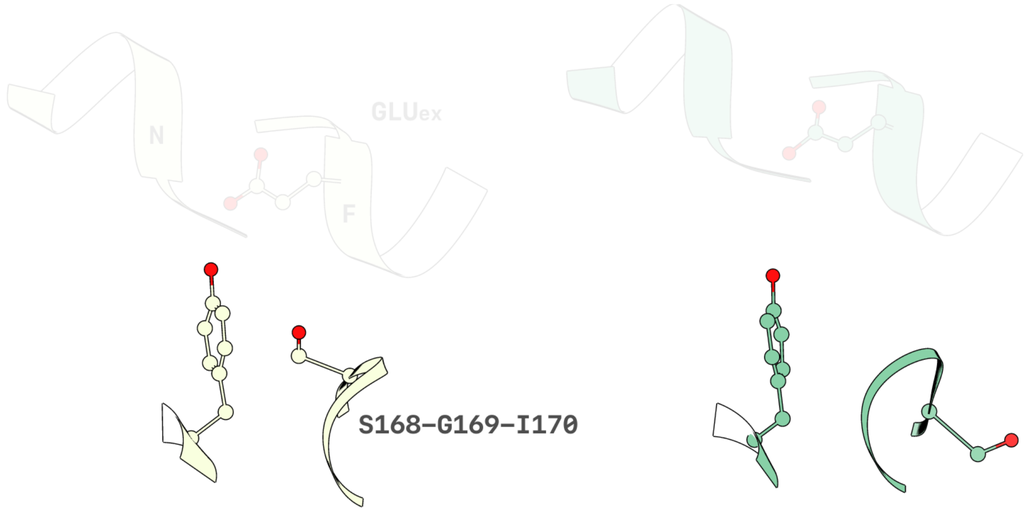


GLU_{ex}

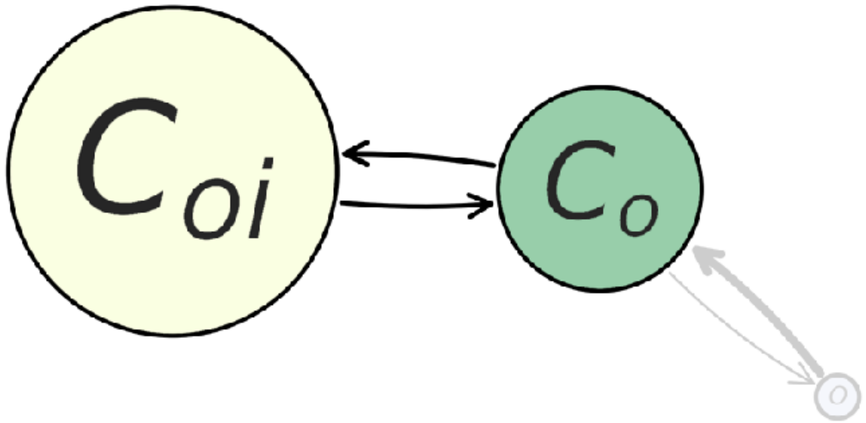


$GLU_{ex}{}^{p}$

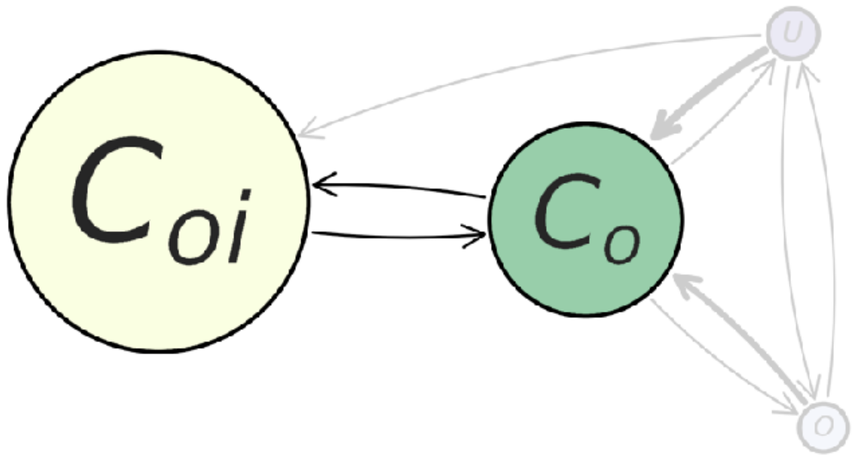


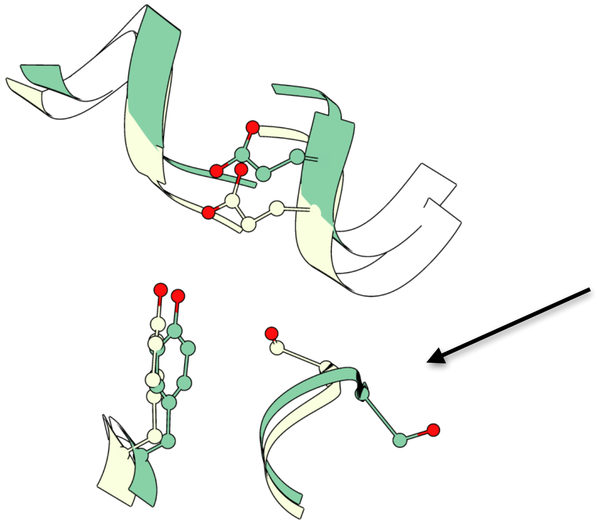


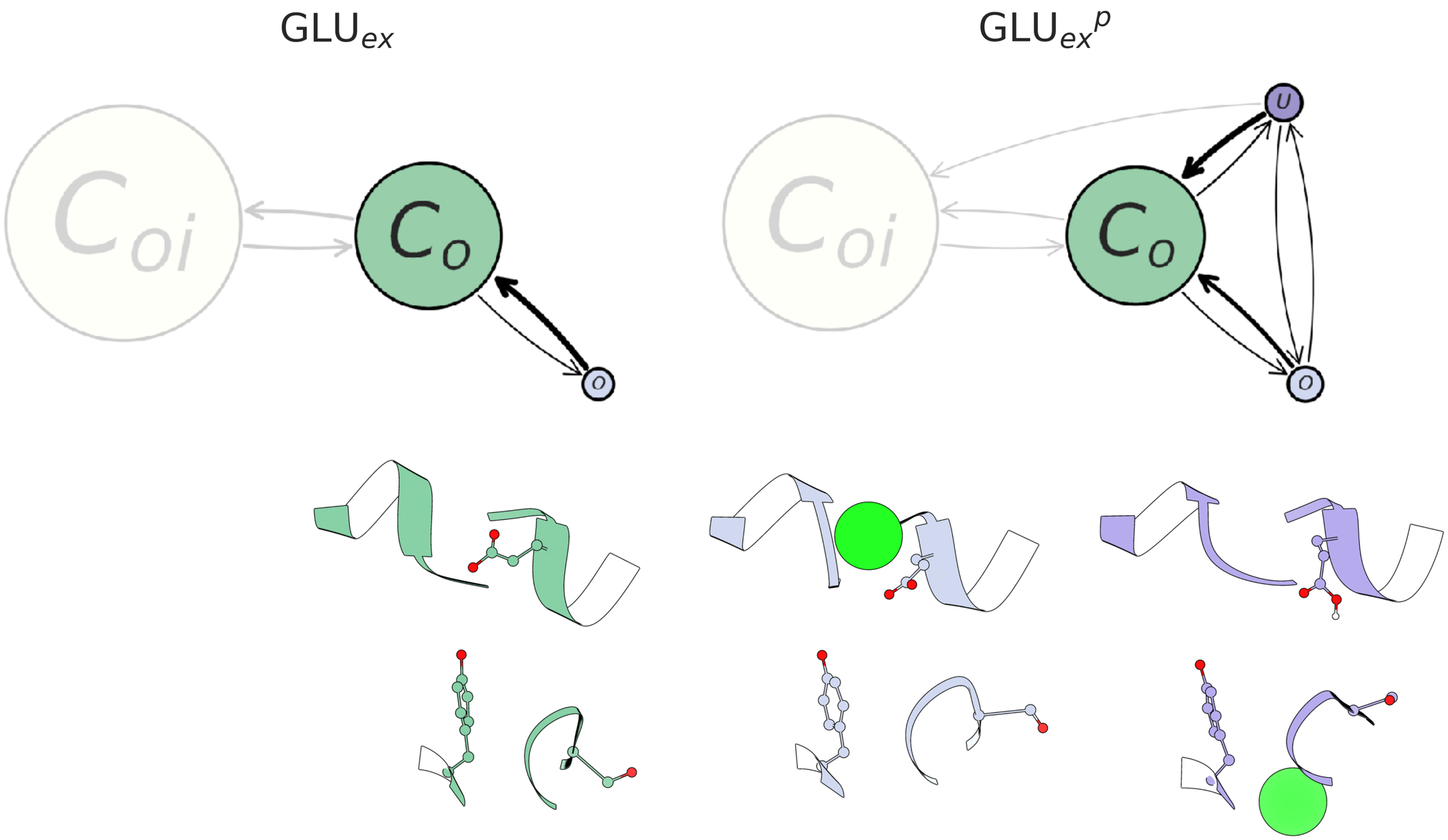
GLU_{ex}



$GLU_{ex}{}^{p}$






GLU$_{ex}$
GLU$_{ex}^{p}$
C_{oi}
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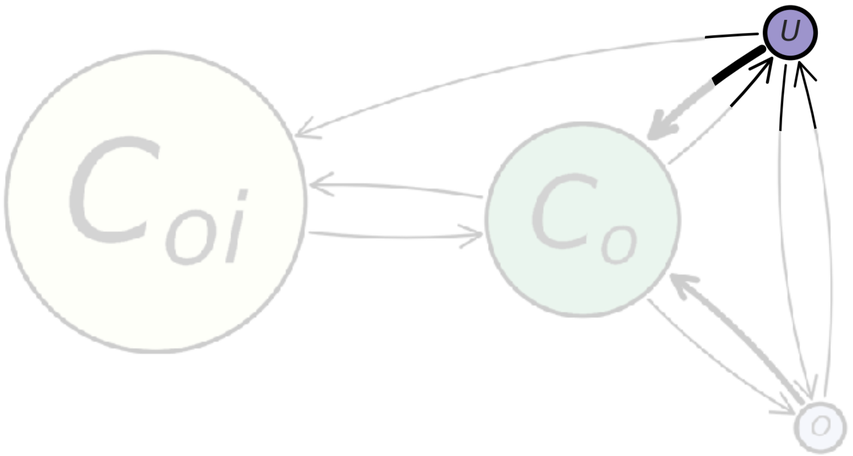
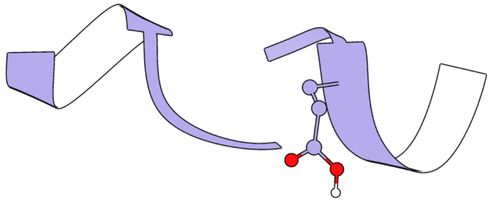
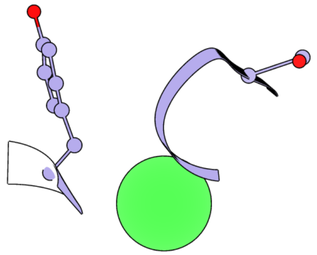
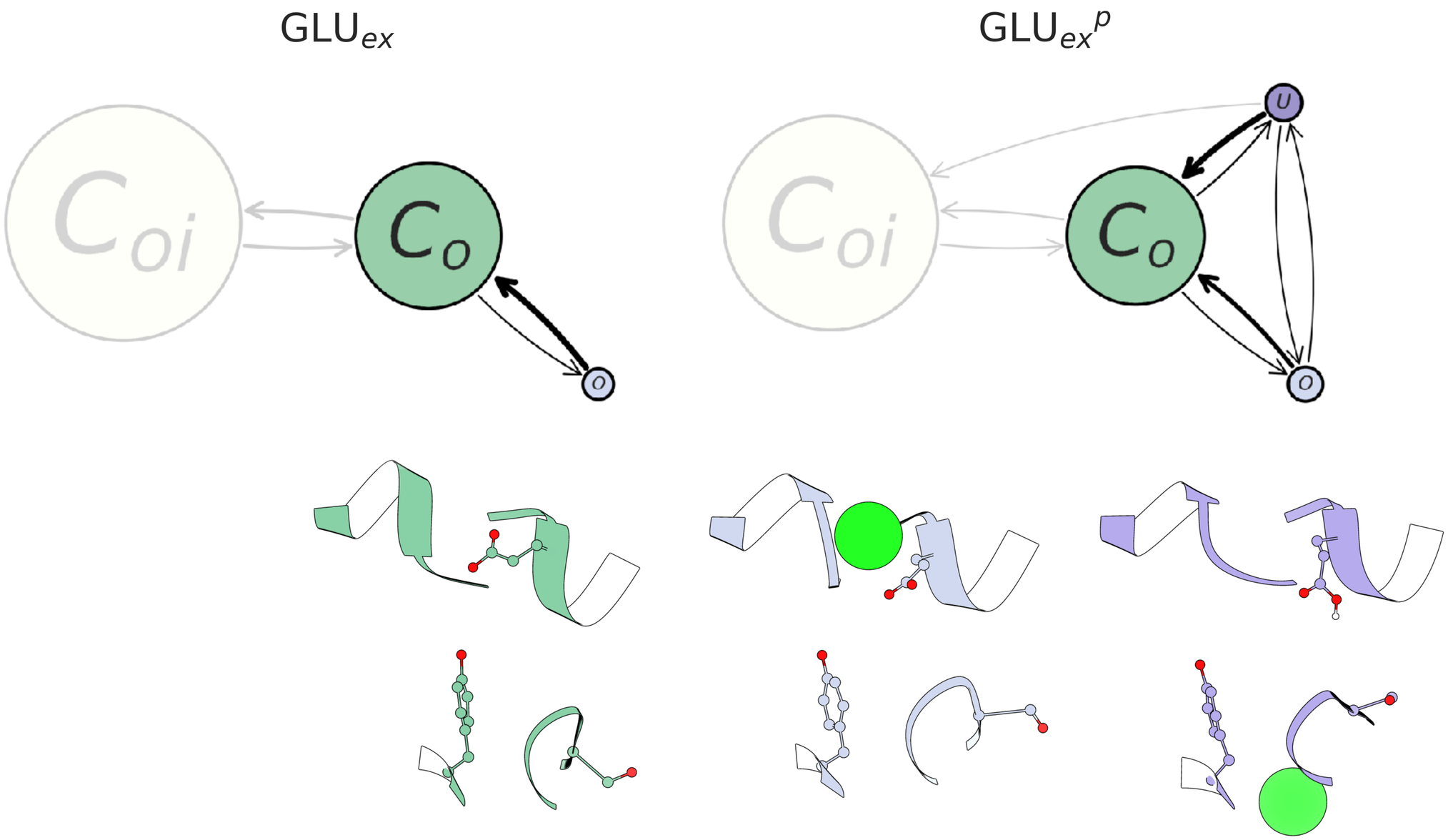
GLU$_{ex}$

GLU$_{ex}{}^{p}$








GLU$_{ex}$
GLU$_{ex}^{p}$
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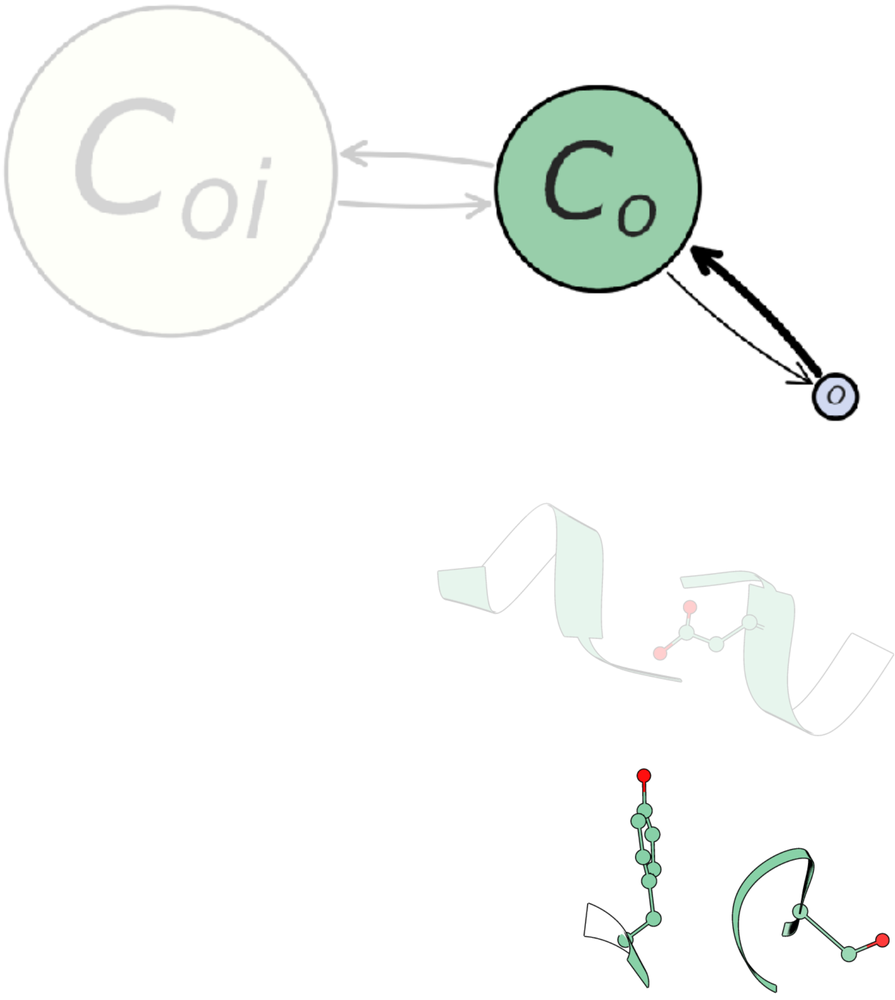
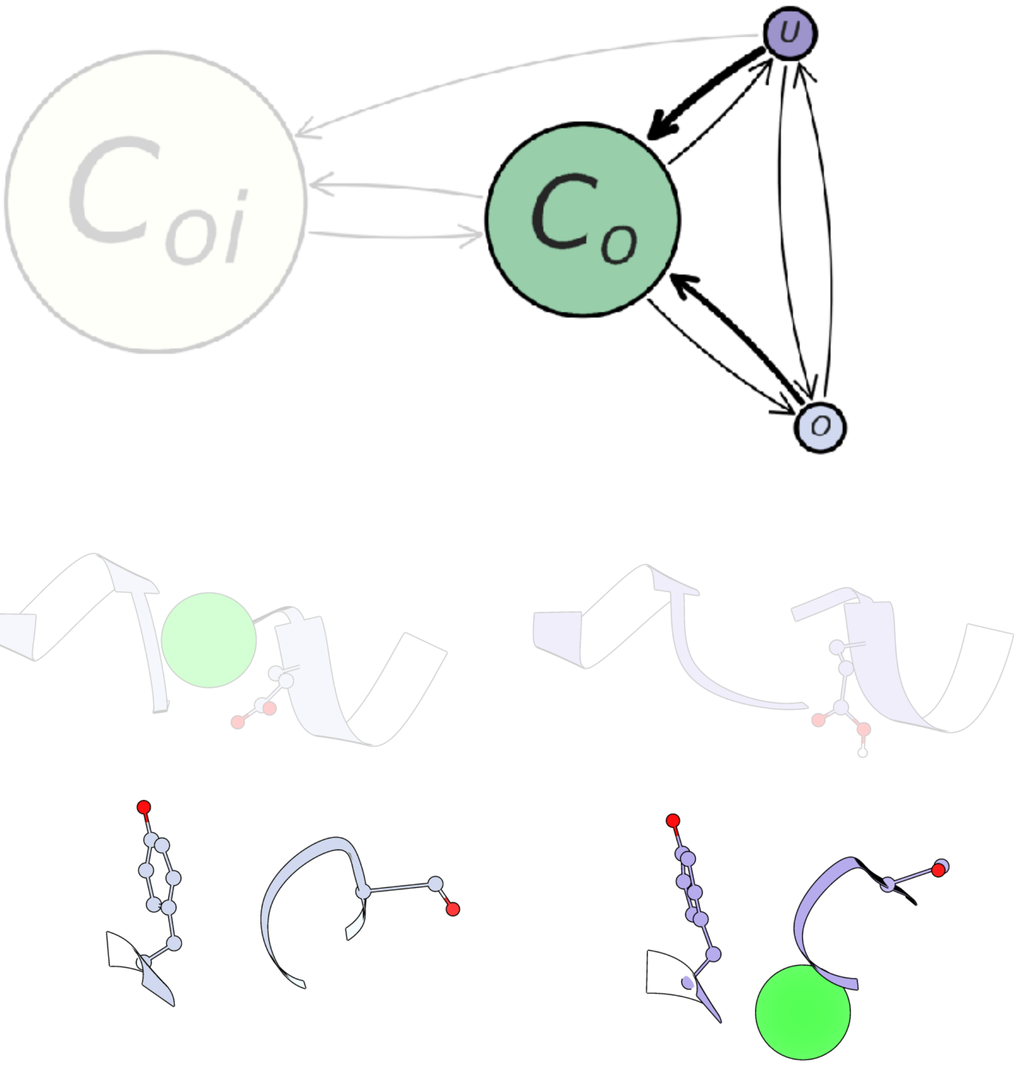
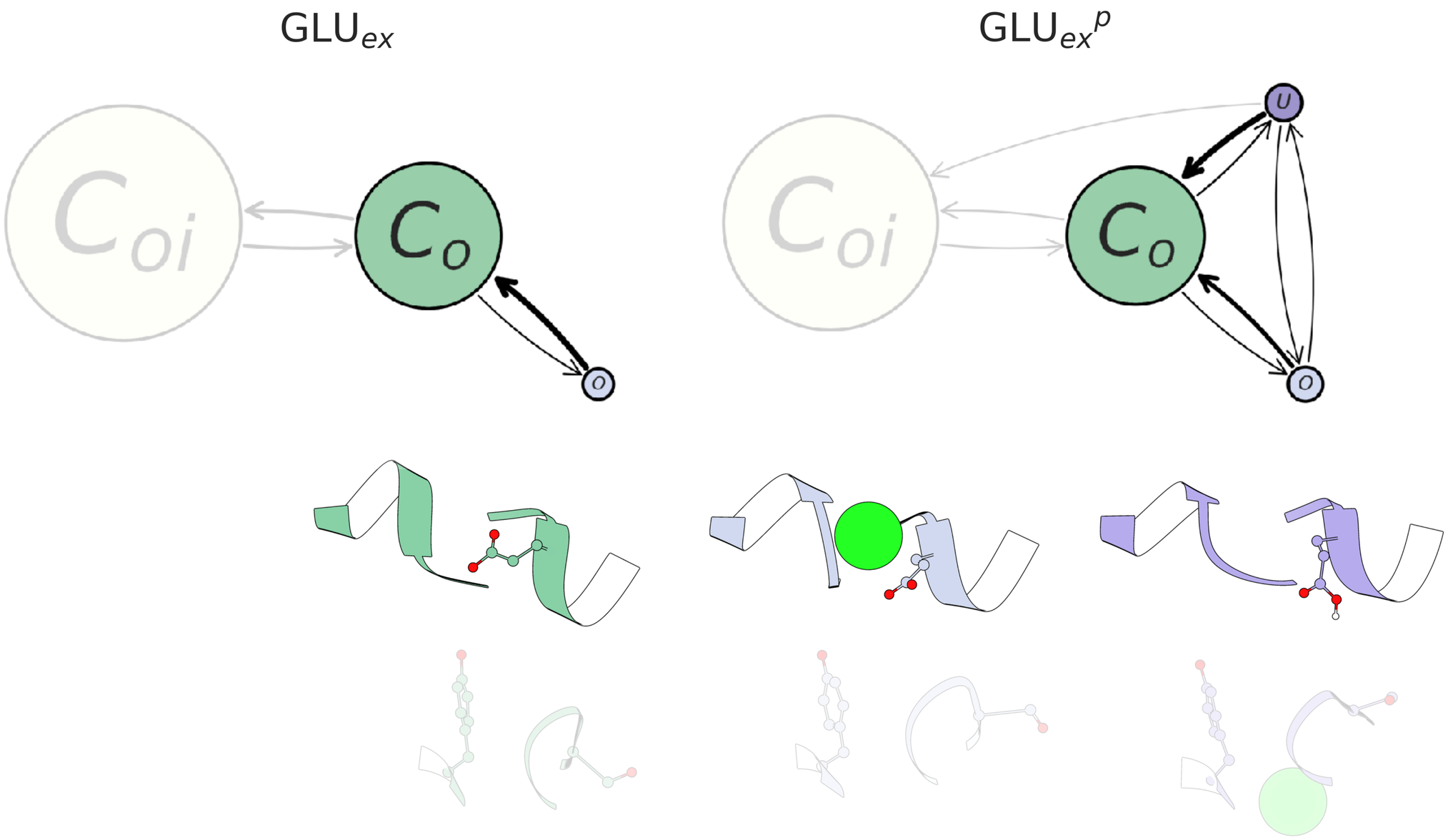
GLU_{ex}



$GLU_{ex}{}^{p}$




GLU$_{ex}$
GLU$_{ex}^{p}$
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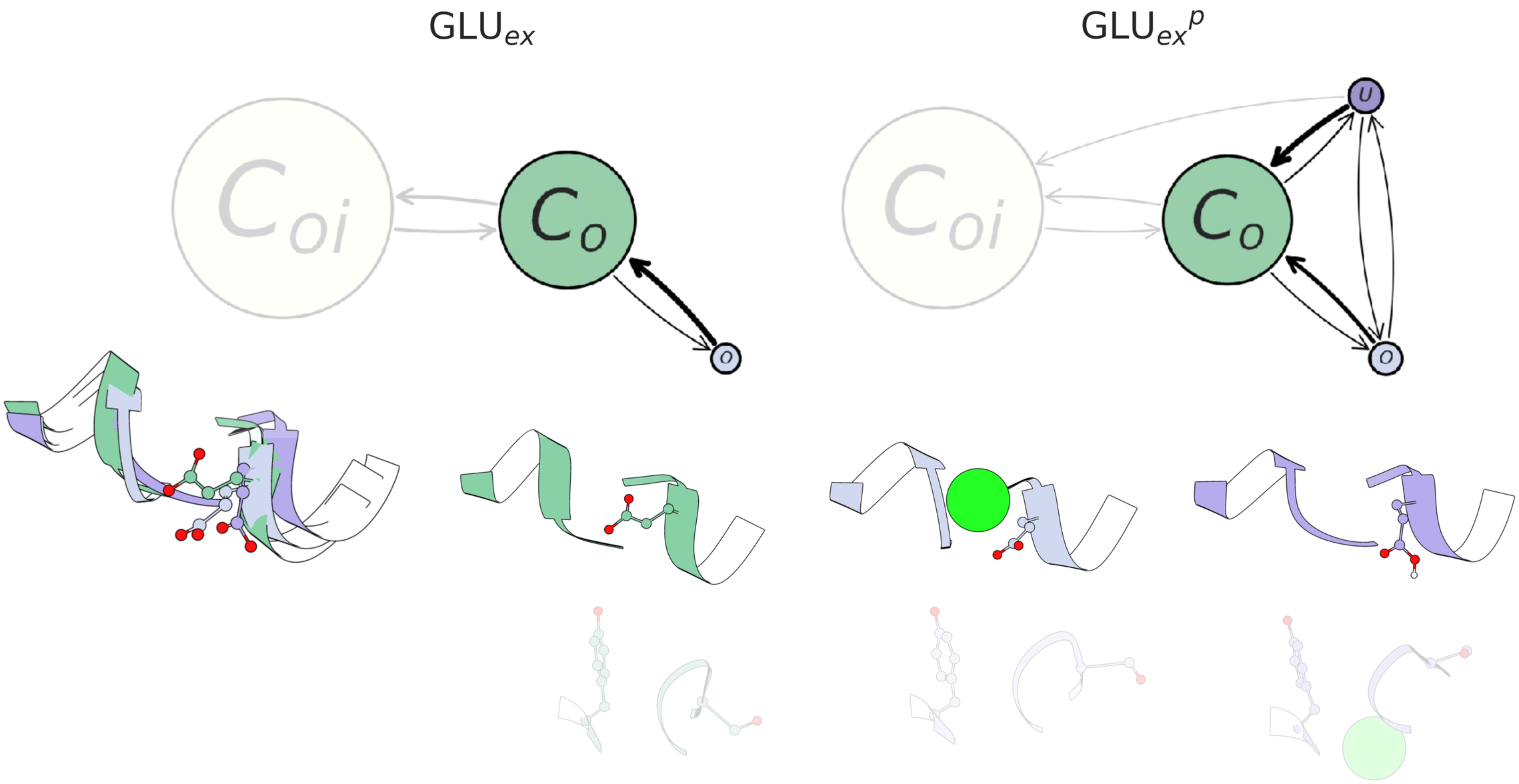
GLU$_{ex}$
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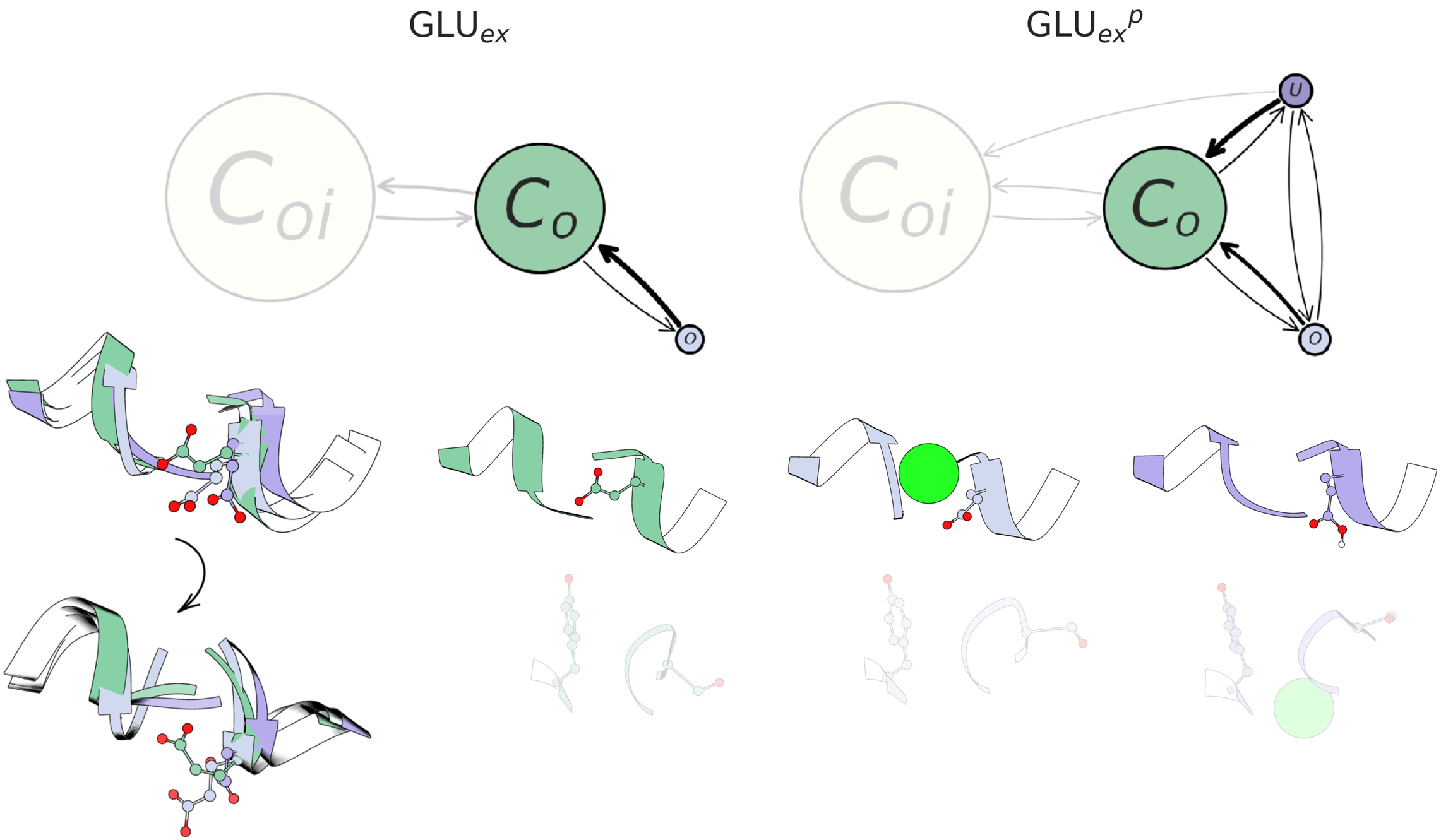
GLU$_{ex}$
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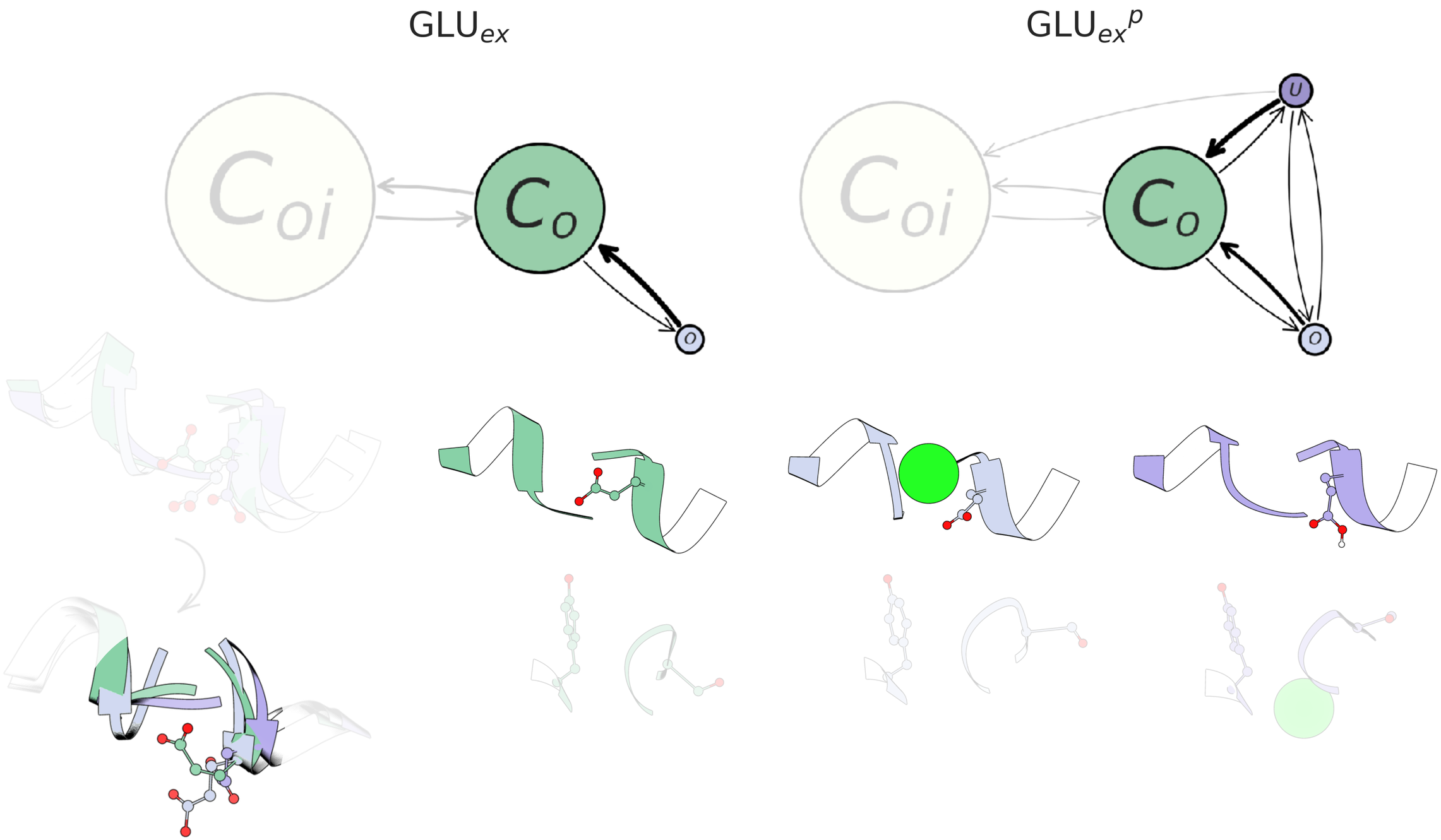
GLU$_{ex}$
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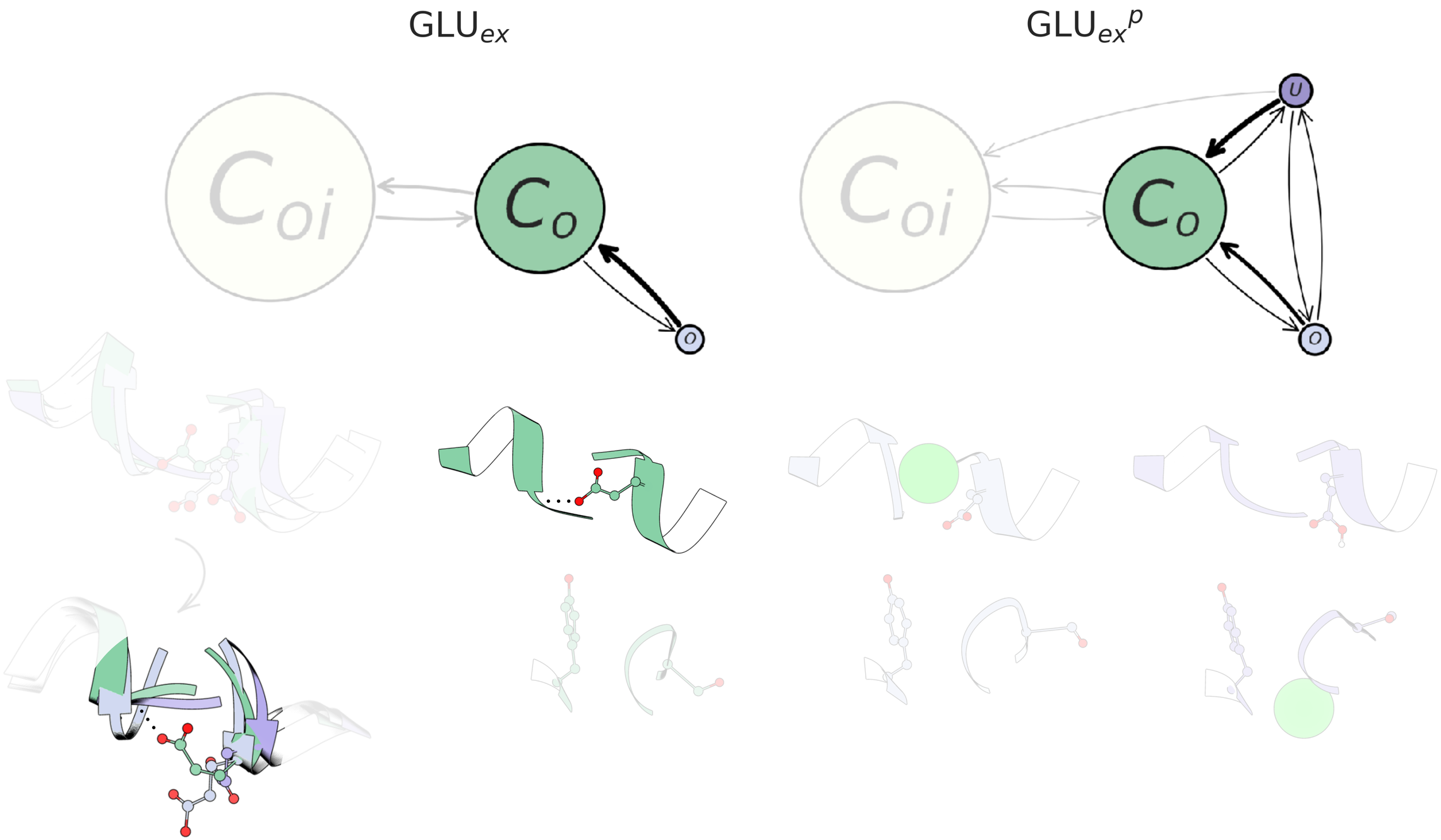
GLU$_{ex}$
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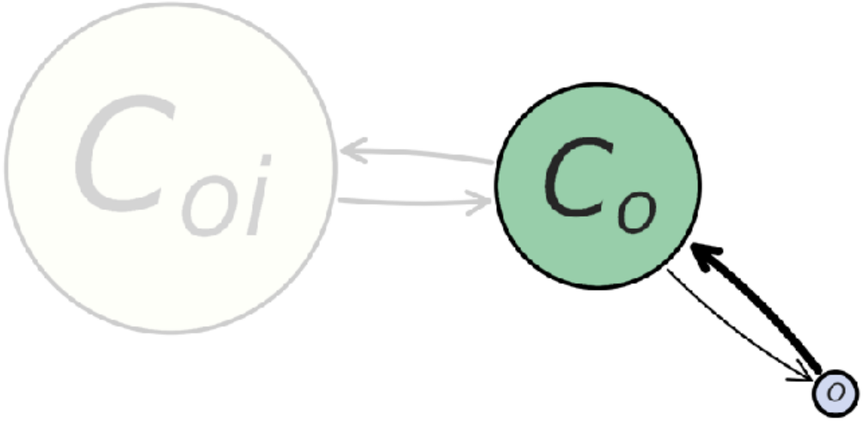
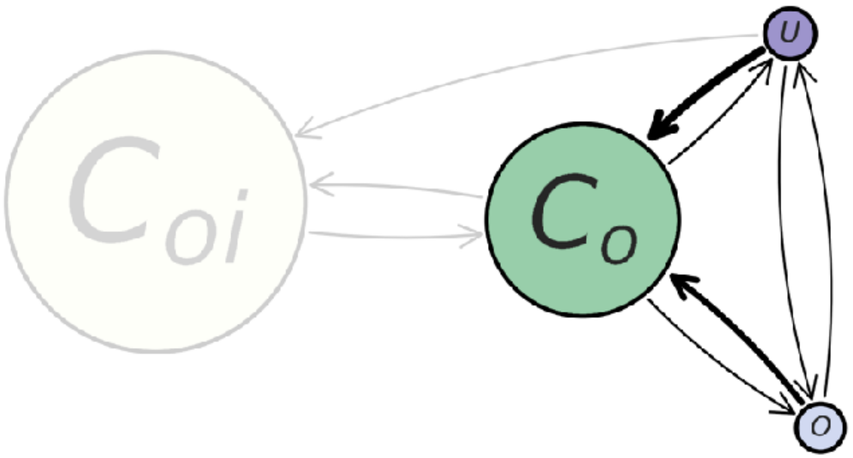
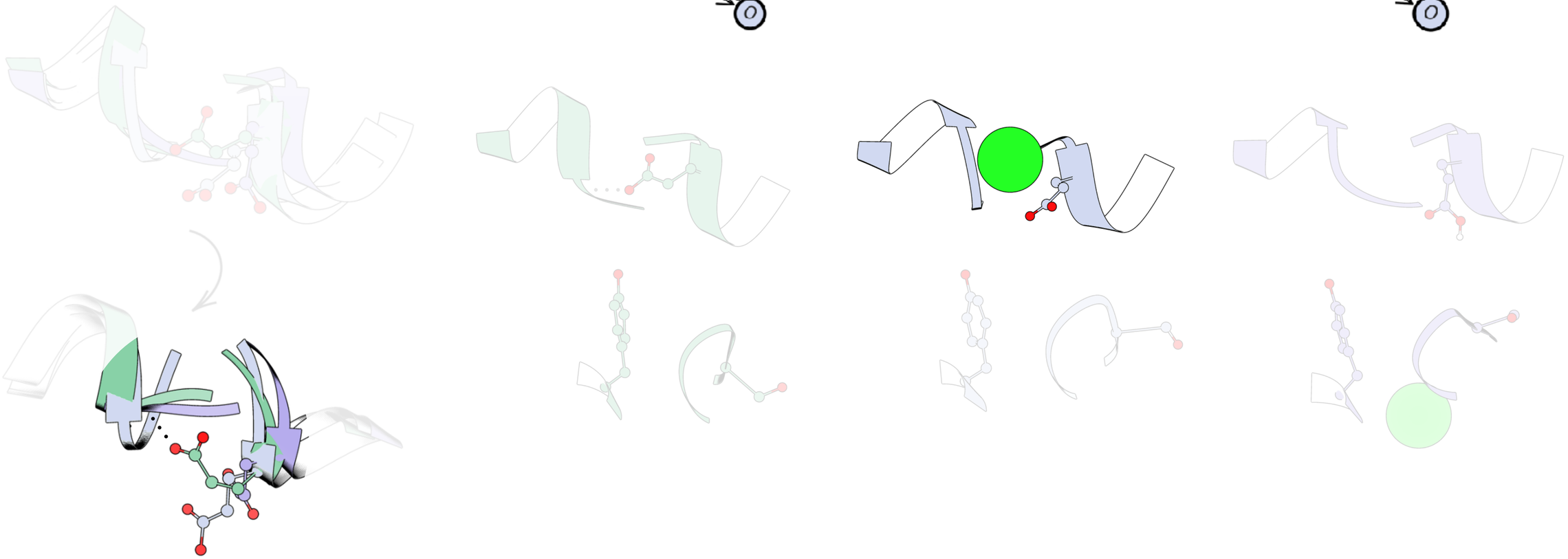
GLU_{ex}

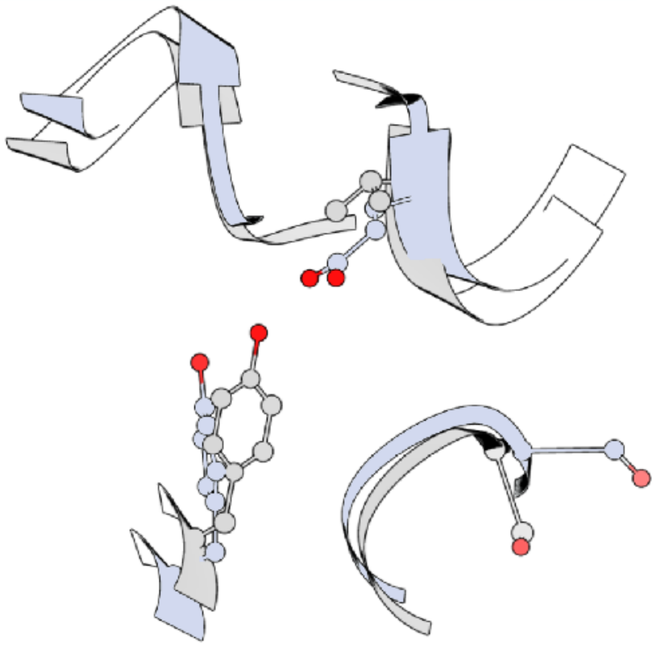


$GLU_{ex}{}^{p}$





O 5TQQ (CLC-K)



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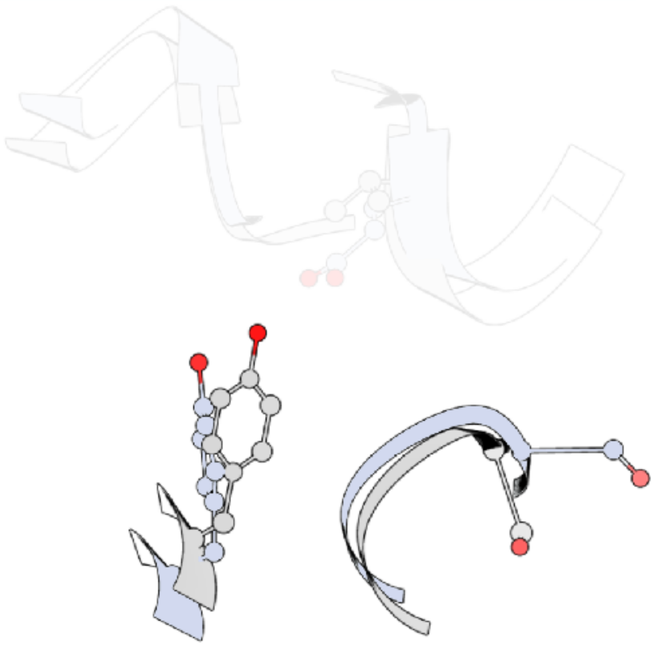

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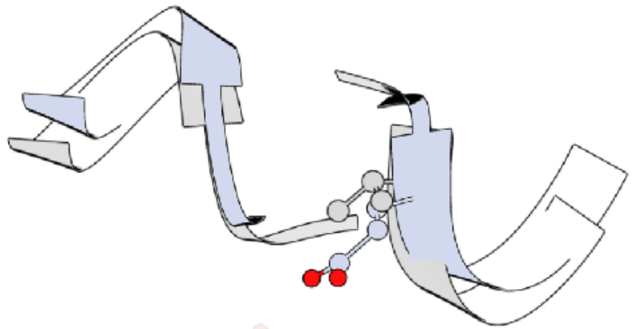

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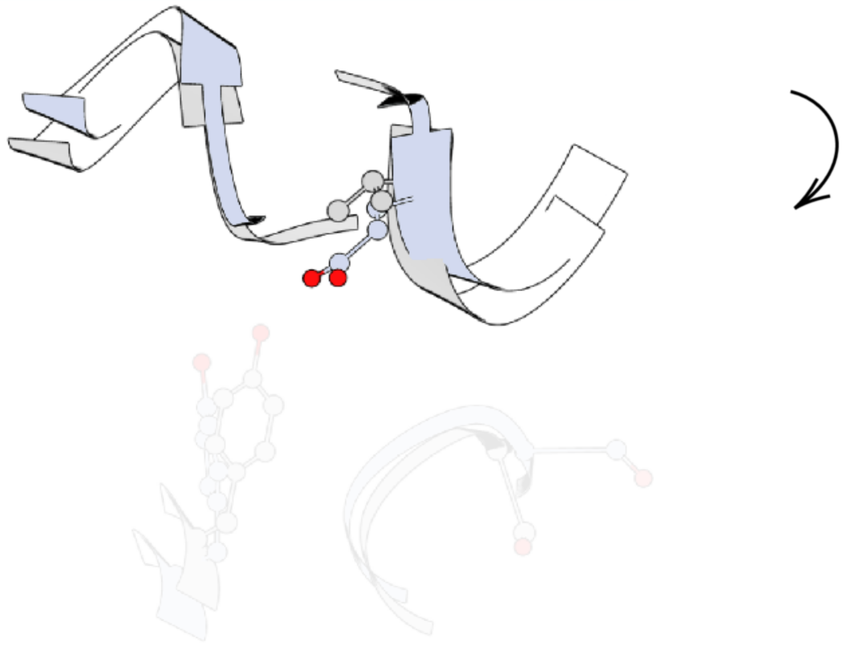
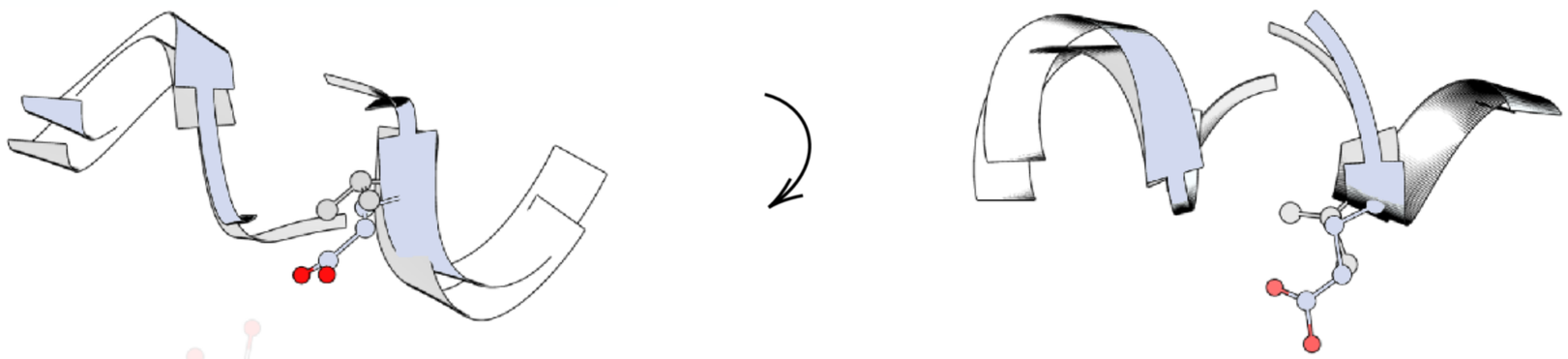
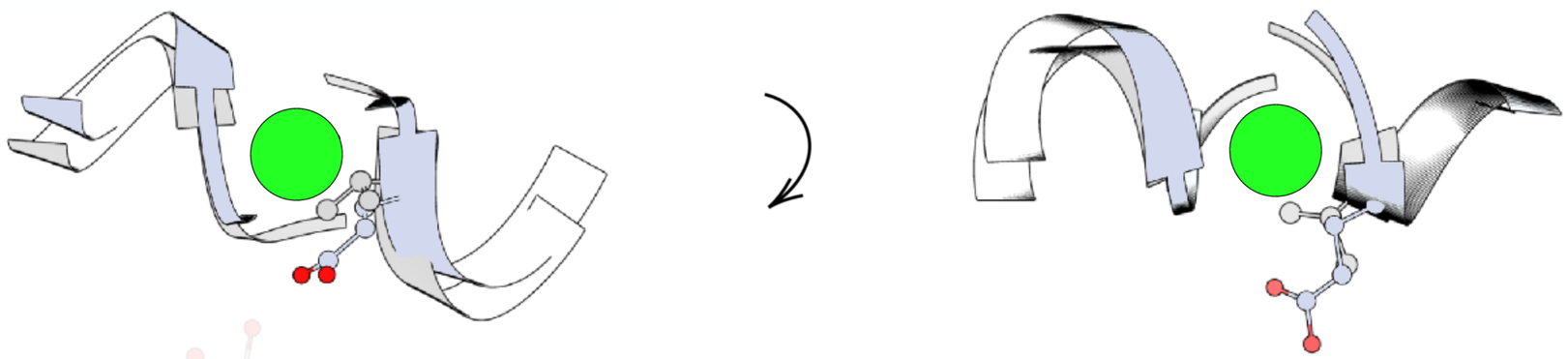


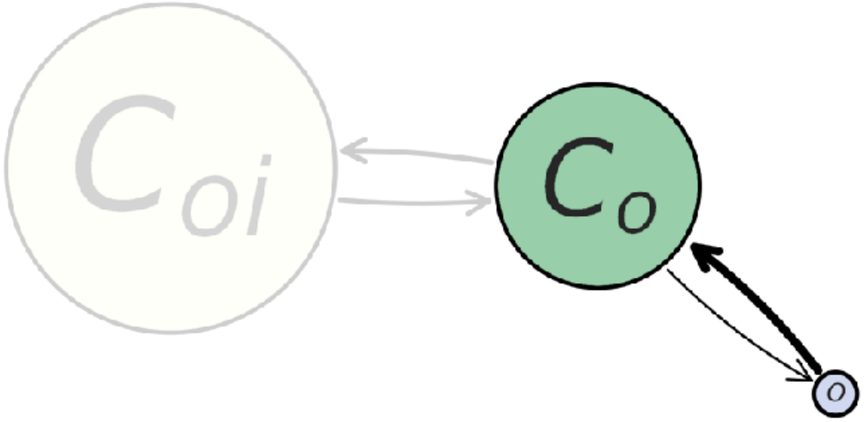
O 5TQQ (CLC-K)



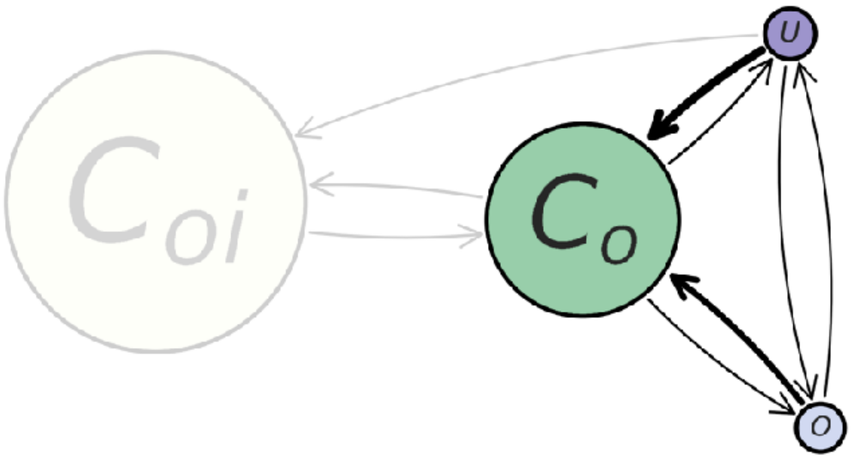
O 5TQQ (CLC-K)

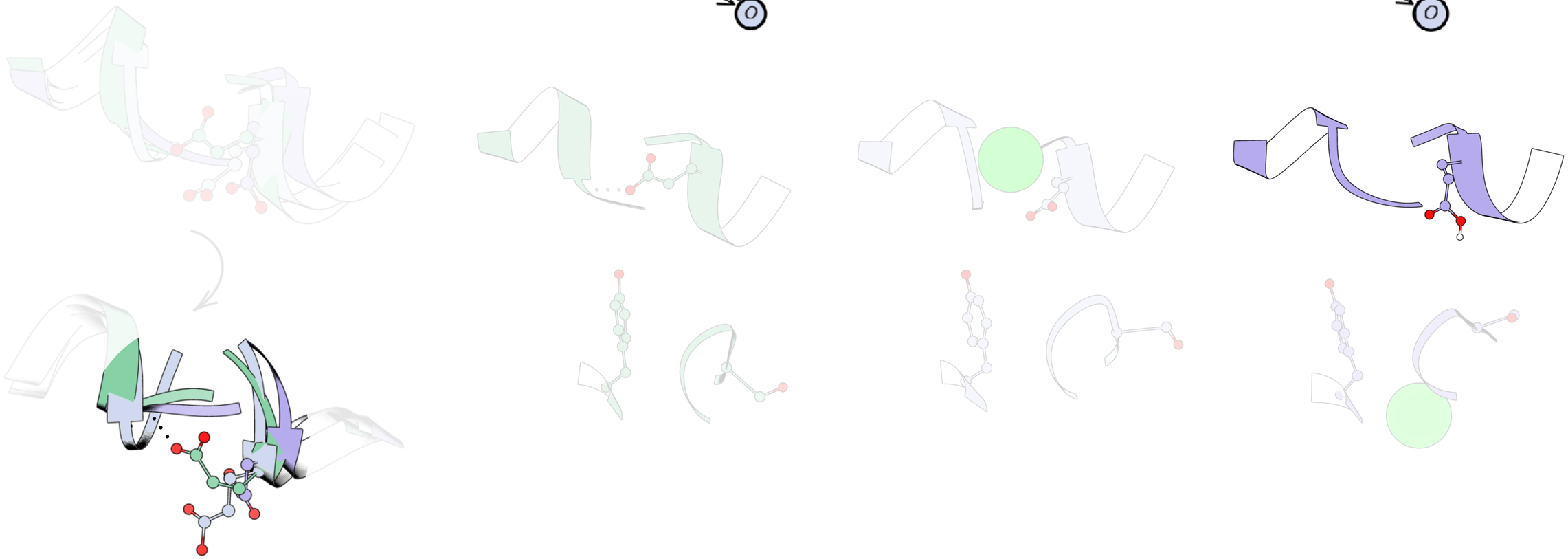


GLU_{ex}

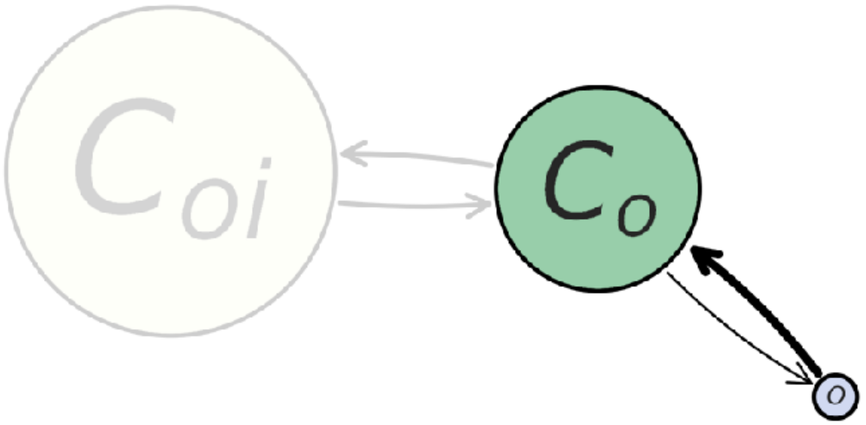


$GLU_{ex}{}^{p}$

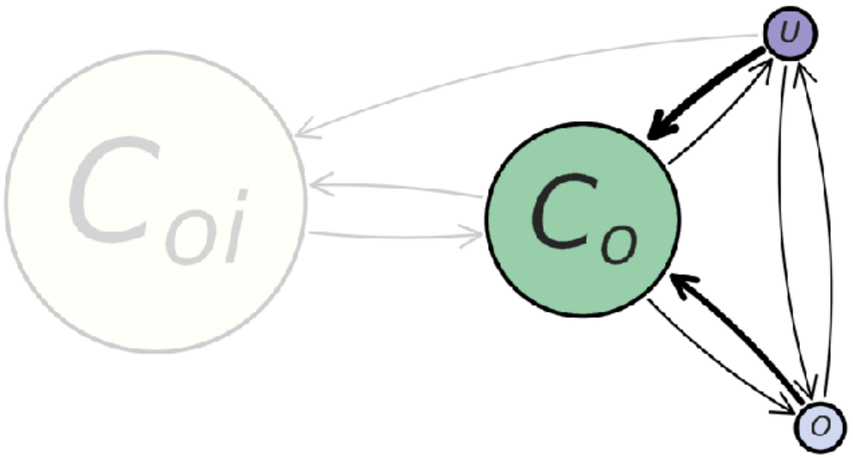


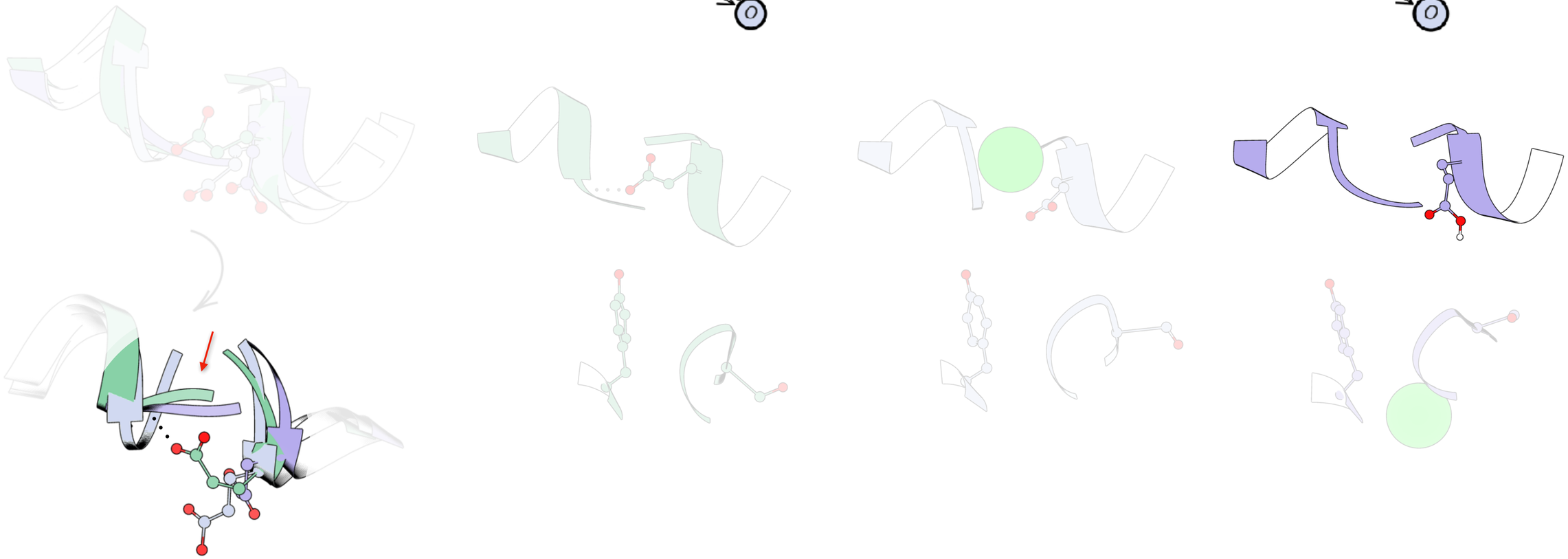


GLU_{ex}

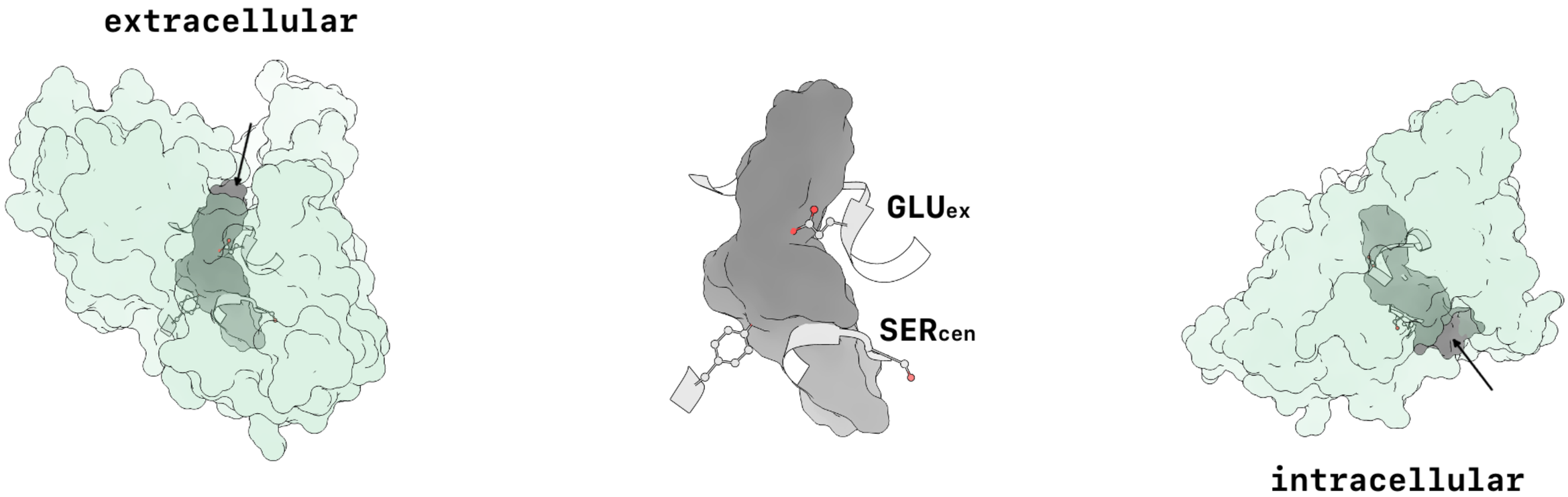


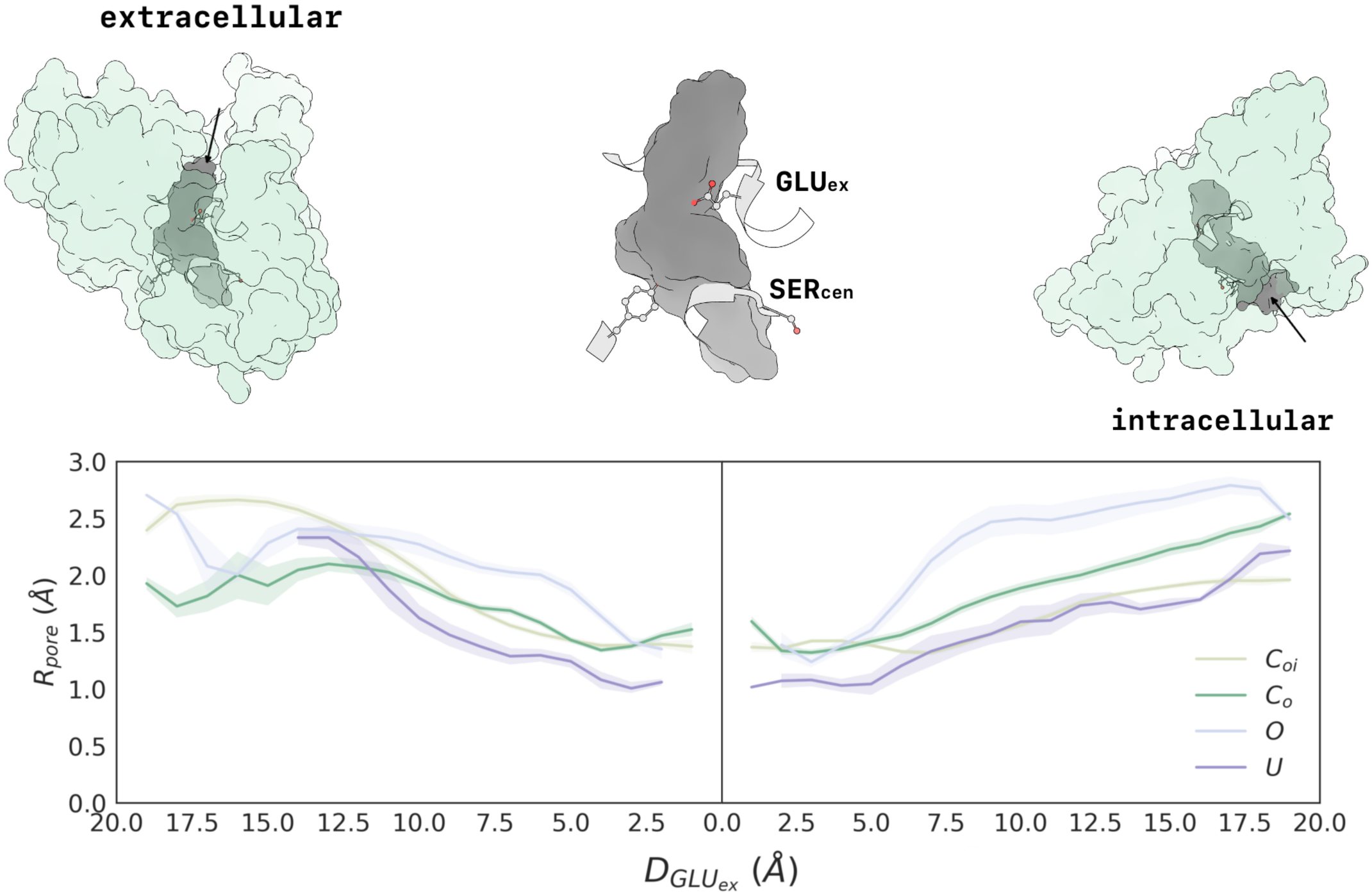
$GLU_{ex}{}^{p}$

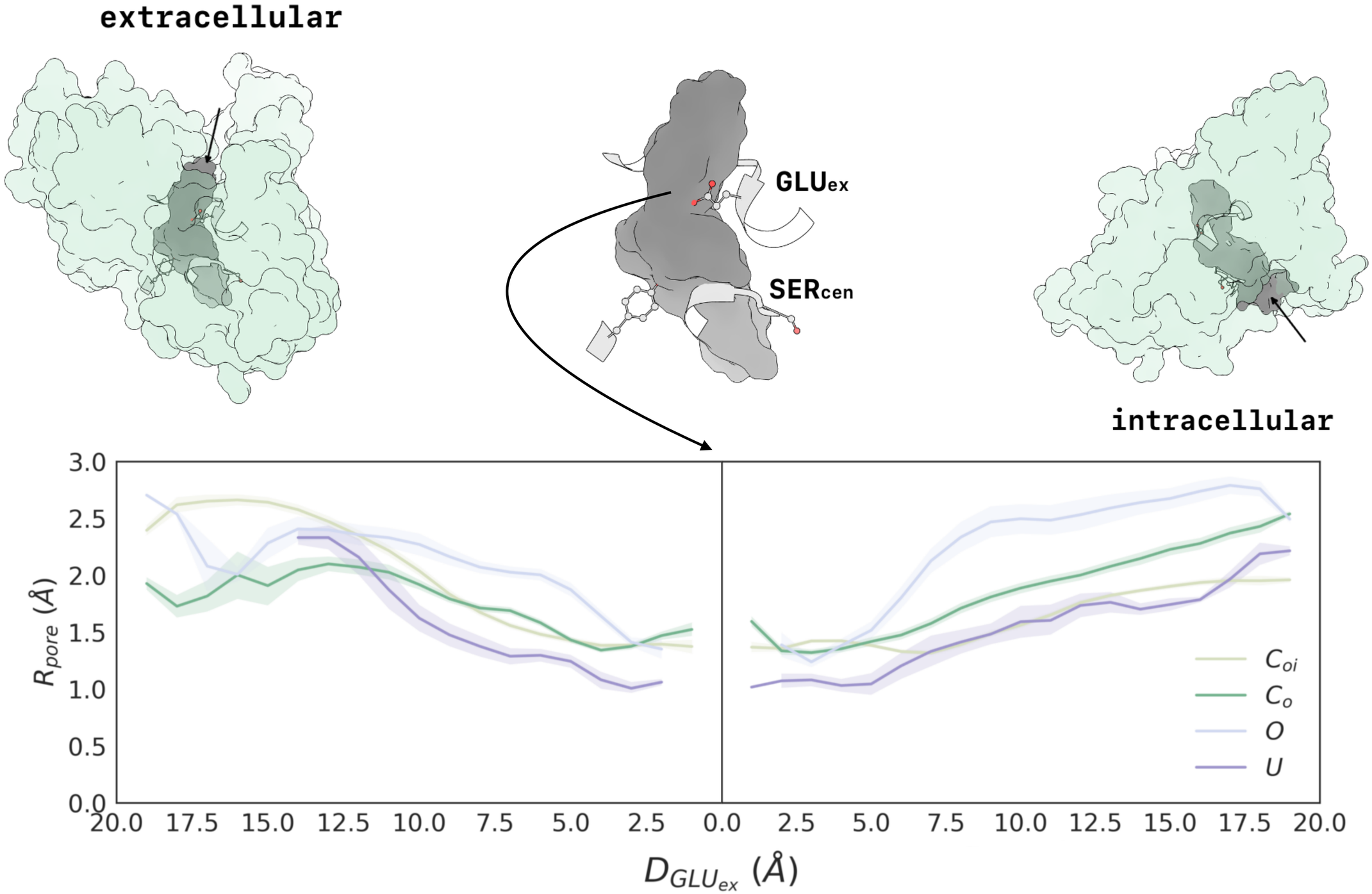


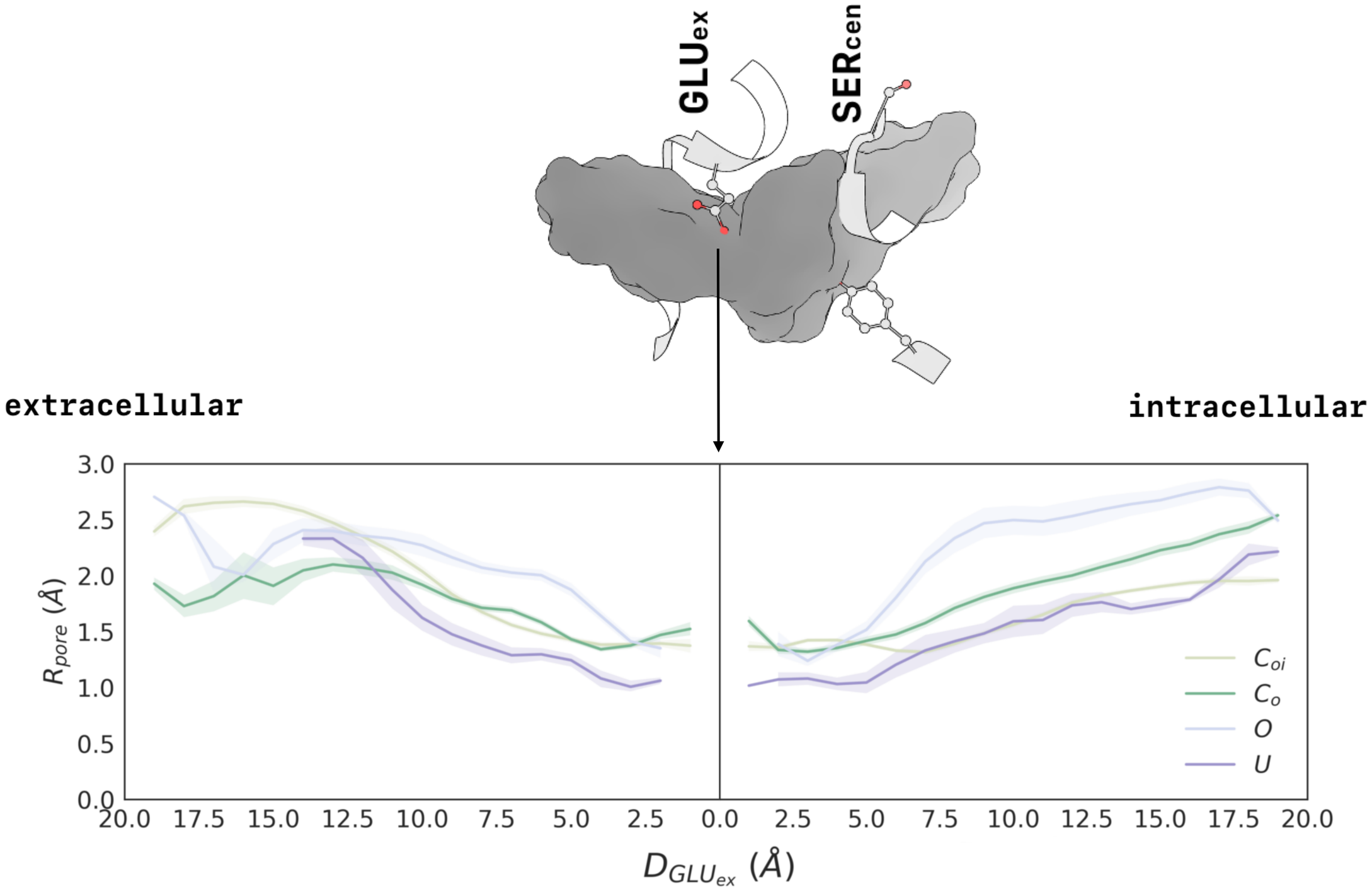


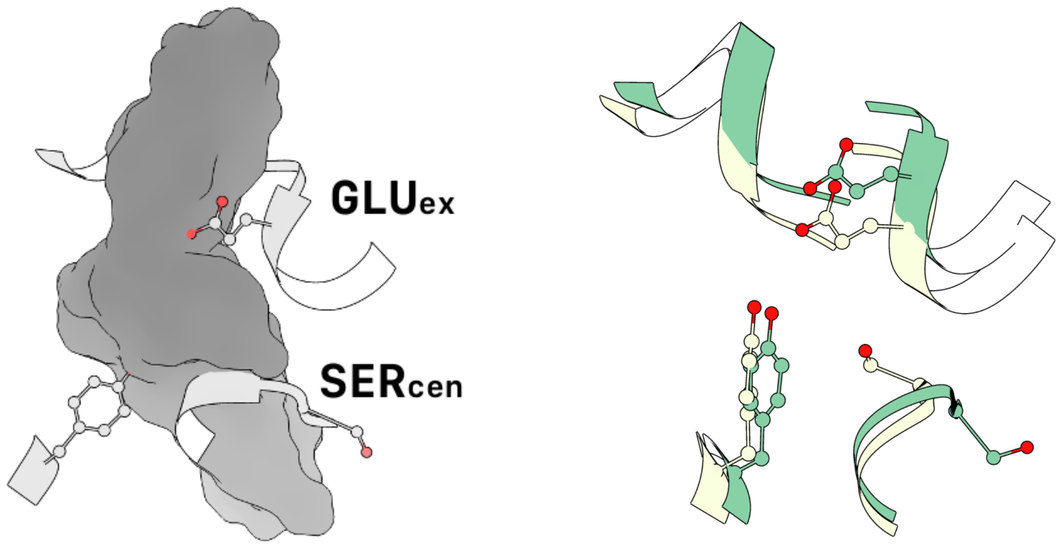
volume of the ion conduction pathway




extracellular
GLUex
SERcen
intracellular
3.0
2.5
2.0
1.5
1.0
0.5
0.0
R_{pore} (Å)
20.0 17.5 15.0 12.5 10.0 7.5 5.0 2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
$D_{GLU_{ex}}$ (Å)
C_{oi}
C_o
O
U

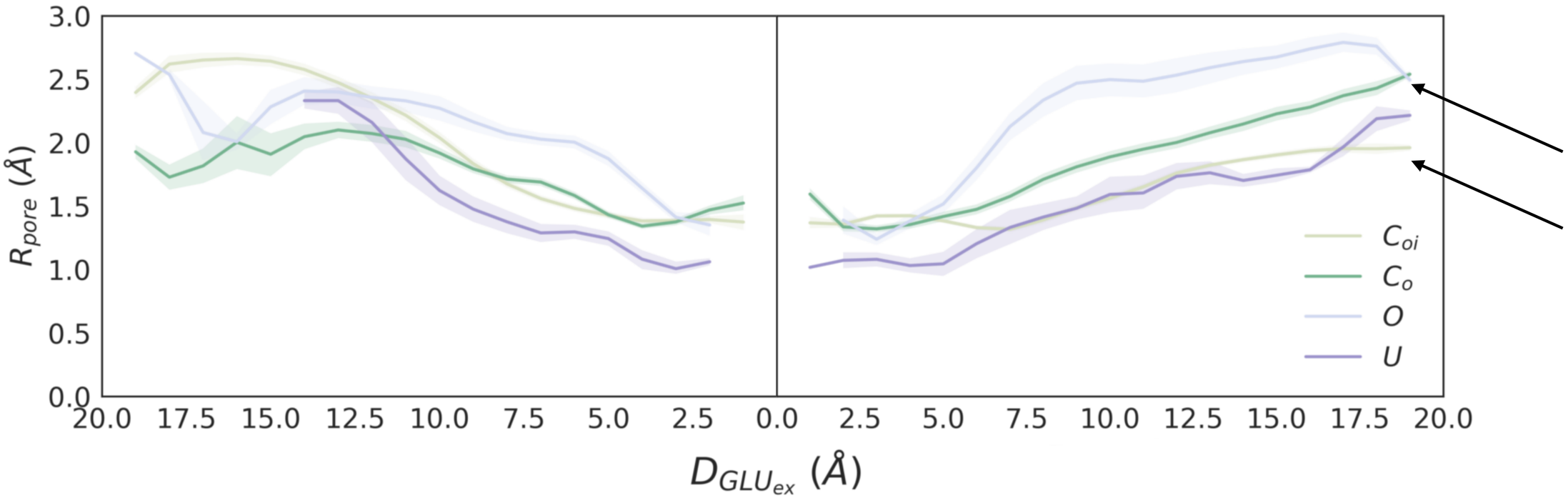

extracellular
GLUex
SERcen
intracellular
3.0
2.5
2.0
1.5
1.0
0.5
0.0
R_{pore} (Å)
20.0 17.5 15.0 12.5 10.0 7.5 5.0 2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
$D_{GLU_{ex}}$ (Å)
C_{oi}
C_o
O
U

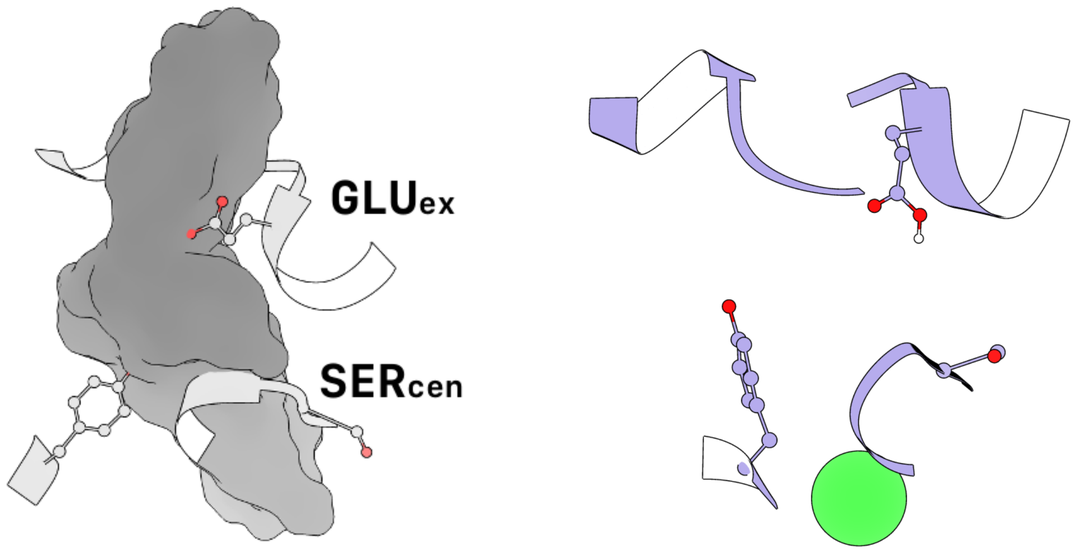

GLUex
SERcen
extracellular
intracellular
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Rpore (Å)
20.0 17.5 15.0 12.5 10.0 7.5 5.0 2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
DGLUex (Å)
Coi
Co
O
U



extracellular

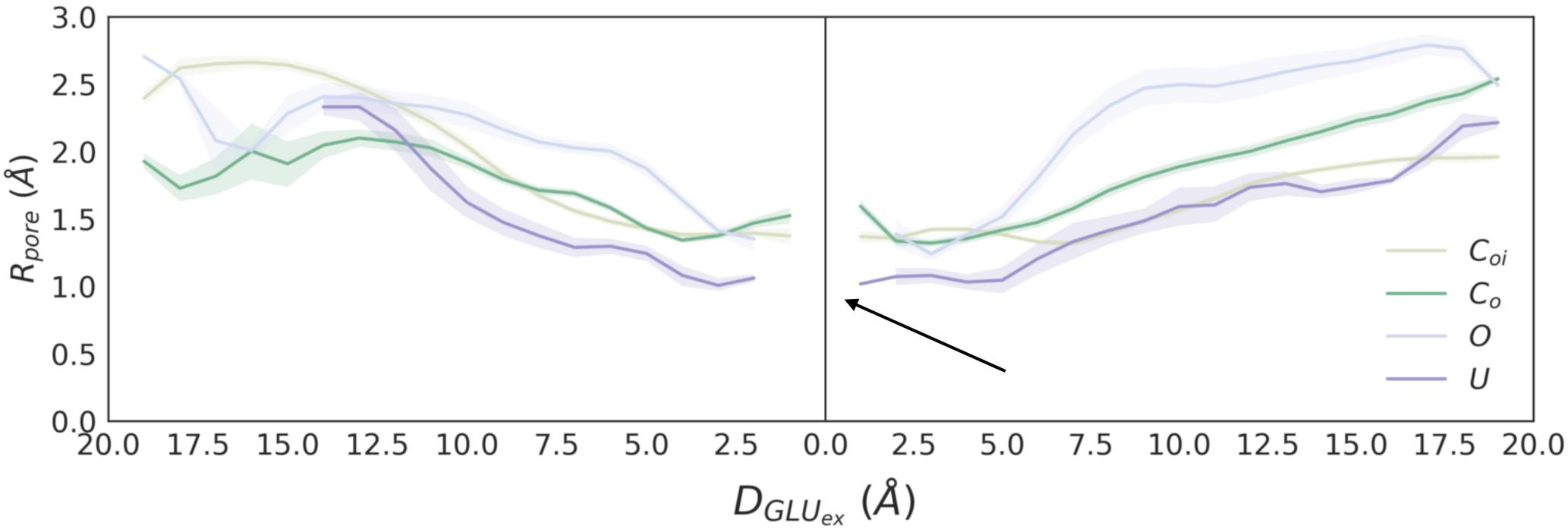
intracellular

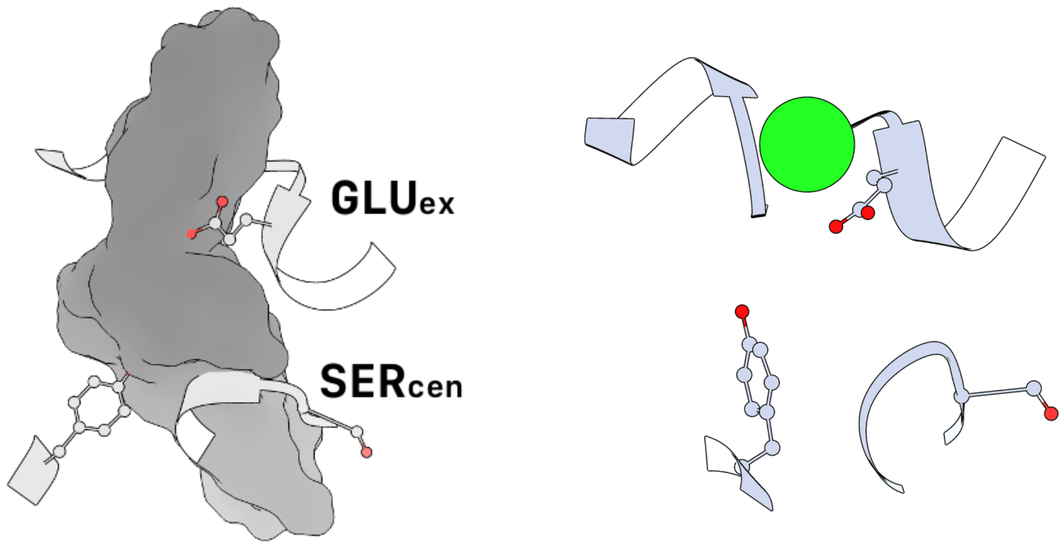


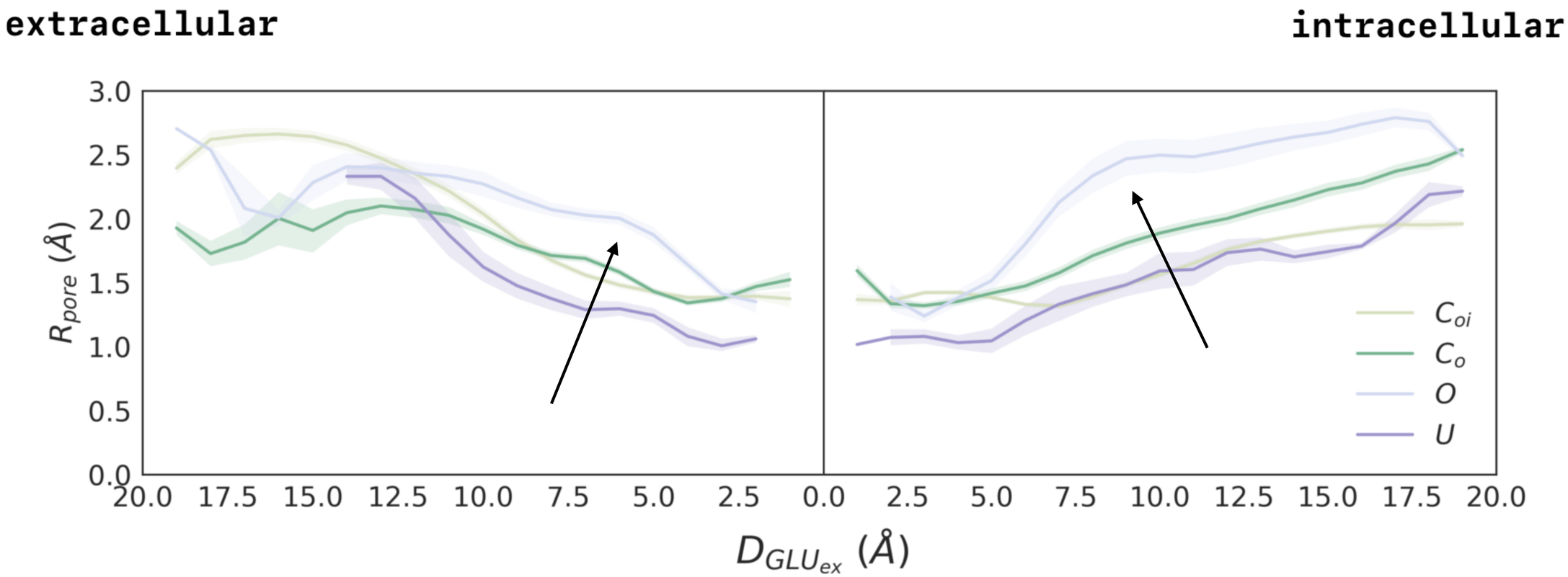


extracellular

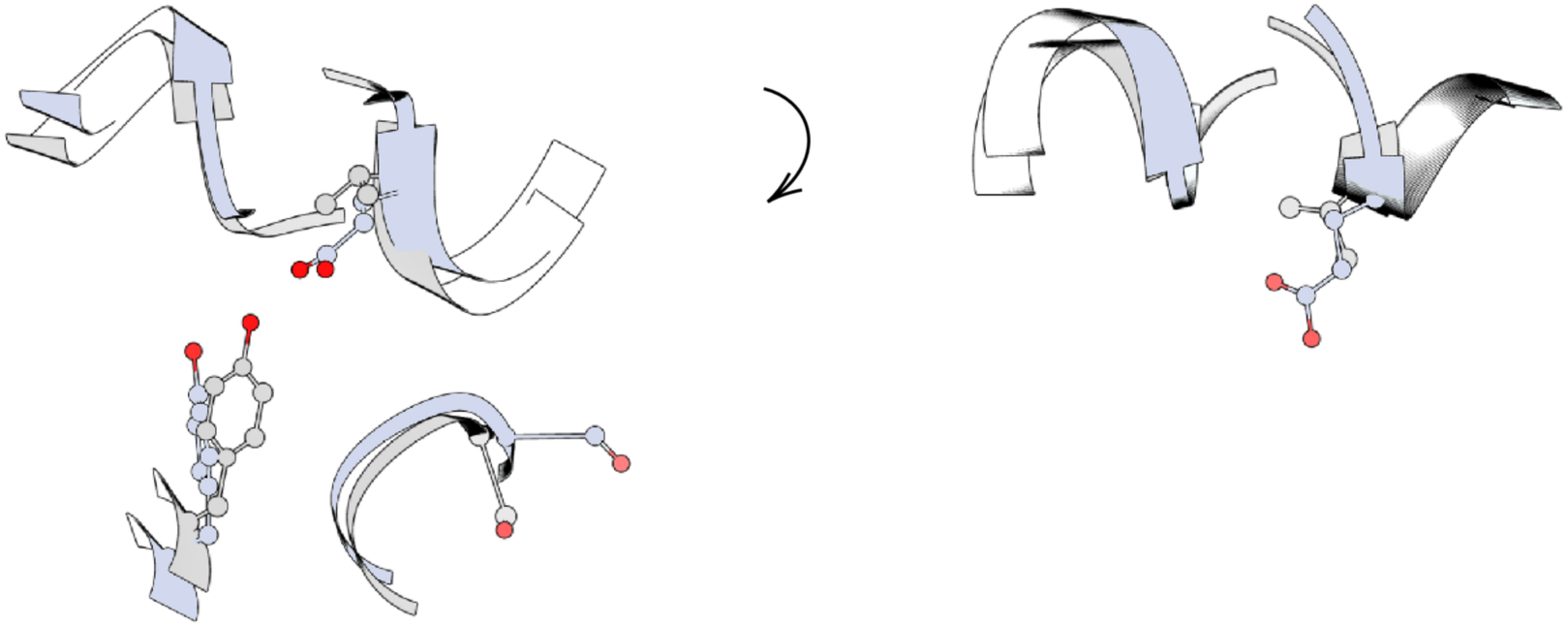
intracellular

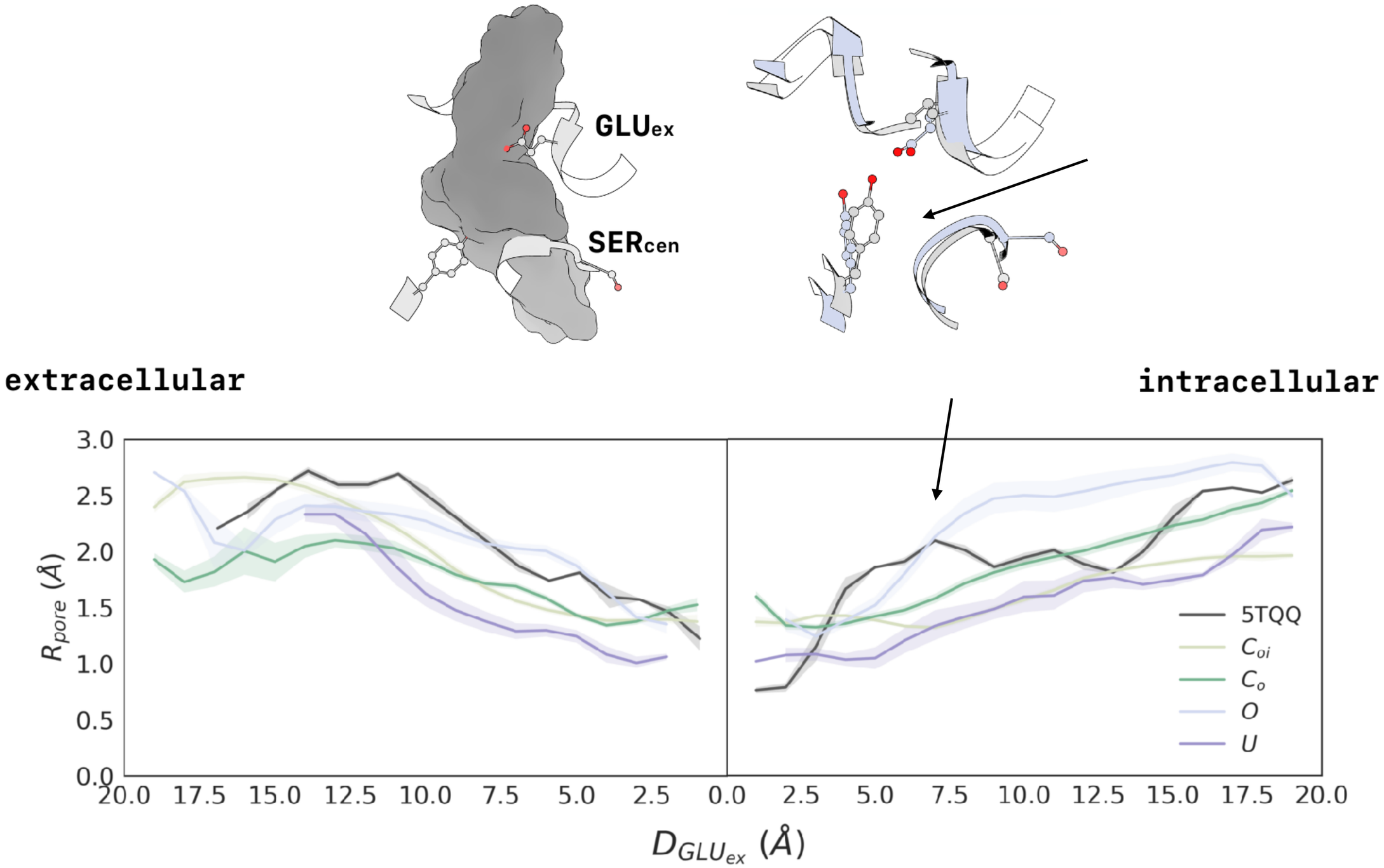


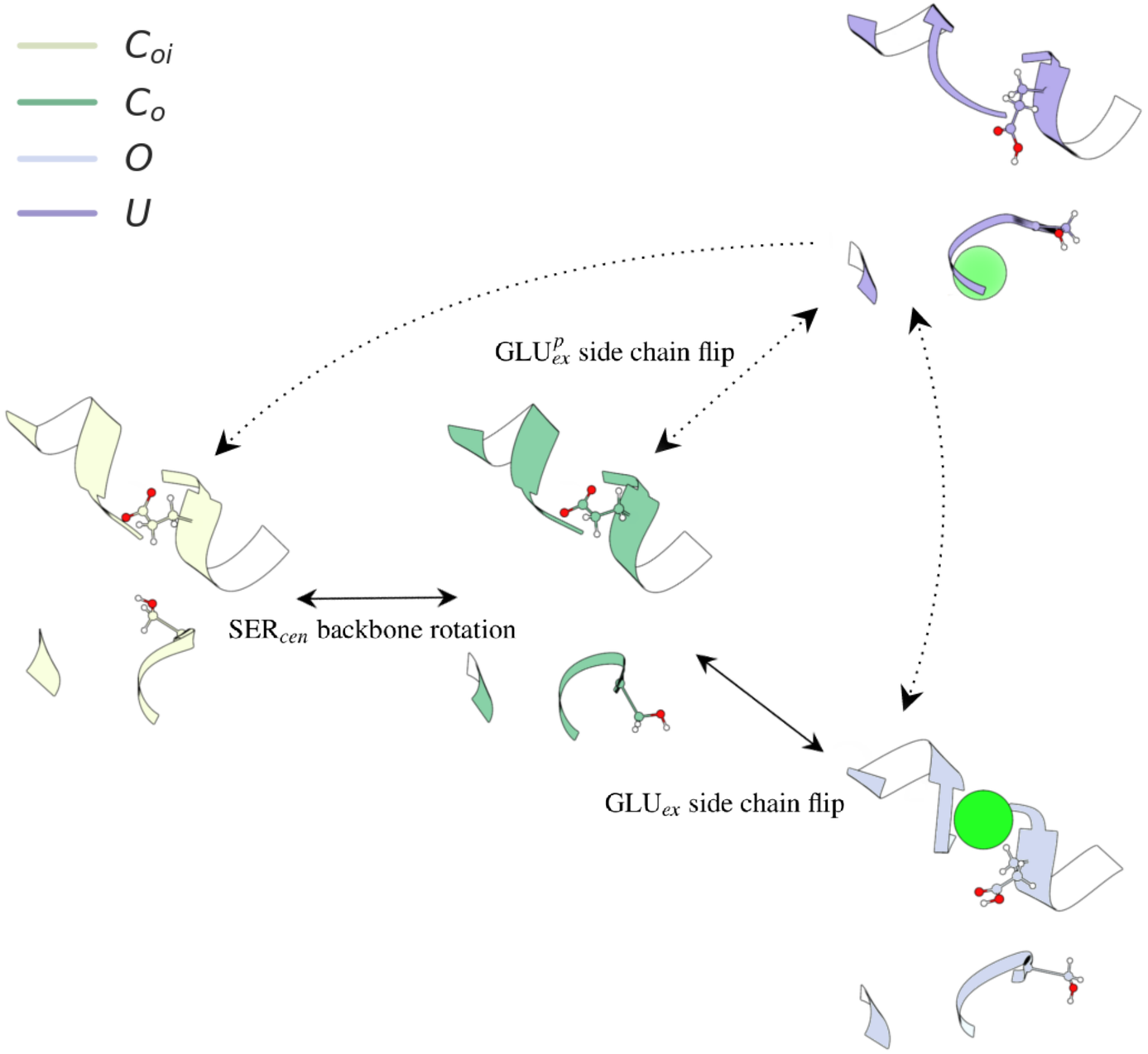

GLUex
SERcen

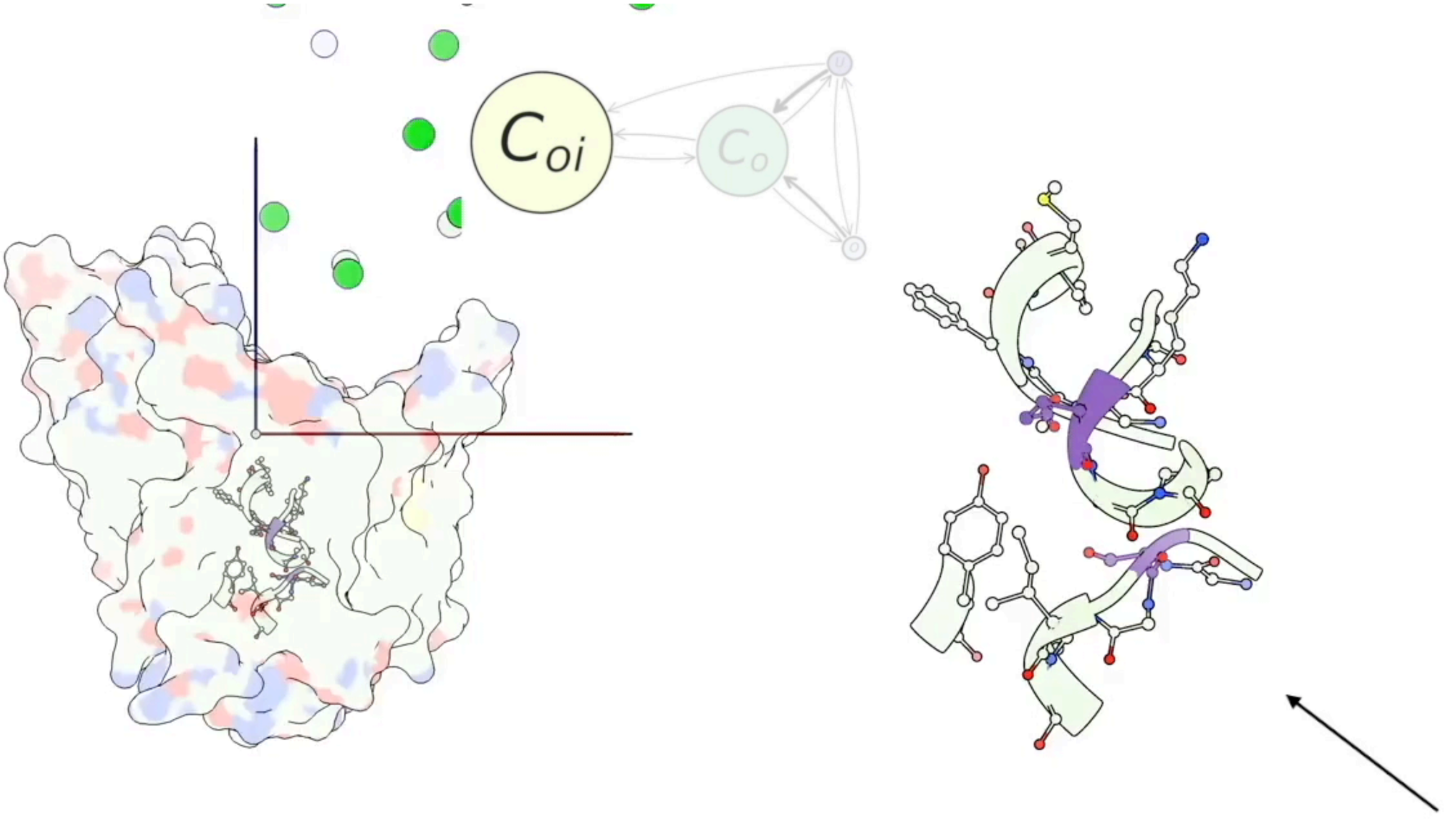

extracellular
intracellular
3.0
2.5
2.0
1.5
1.0
0.5
0.0
R_{pore} (Å)
20.0 17.5 15.0 12.5 10.0 7.5 5.0 2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
$D_{GLU_{ex}}$ (Å)
C_{oi}
C_o
O
U

O 5TQQ (CLC-K)




GLUex
SERcen
extracellular
intracellular
3.0
2.5
2.0
1.5
1.0
0.5
0.0
R_{pore} (Å)
20.0 17.5 15.0 12.5 10.0 7.5 5.0 2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0
$D_{GLU_{ex}}$ (Å)
5TQQ
C_{oi}
C_o
O
U


C_{oi}
C_o
O
U
GLU^p_{ex} side chain flip
SER_{cen} backbone rotation
GLU_{ex} side chain flip

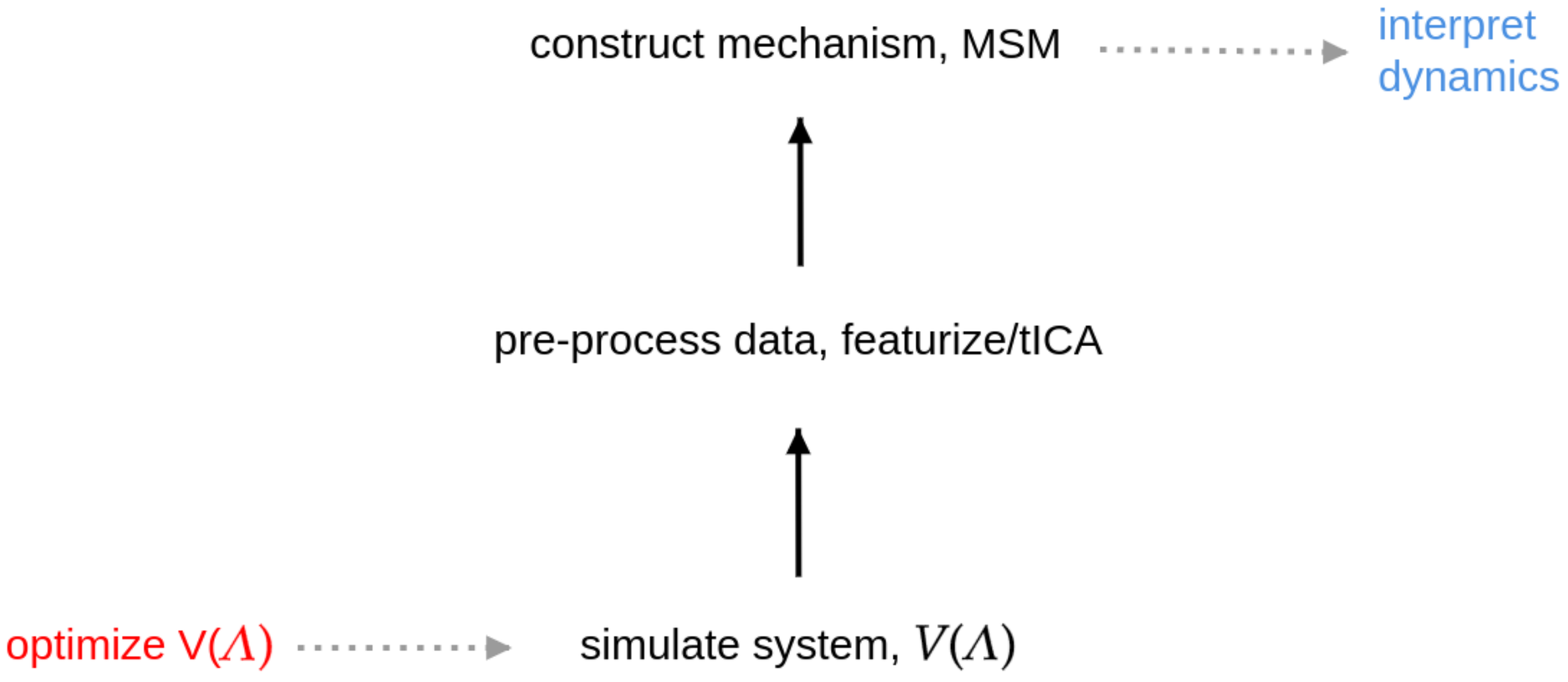

C_{oi}
C_o

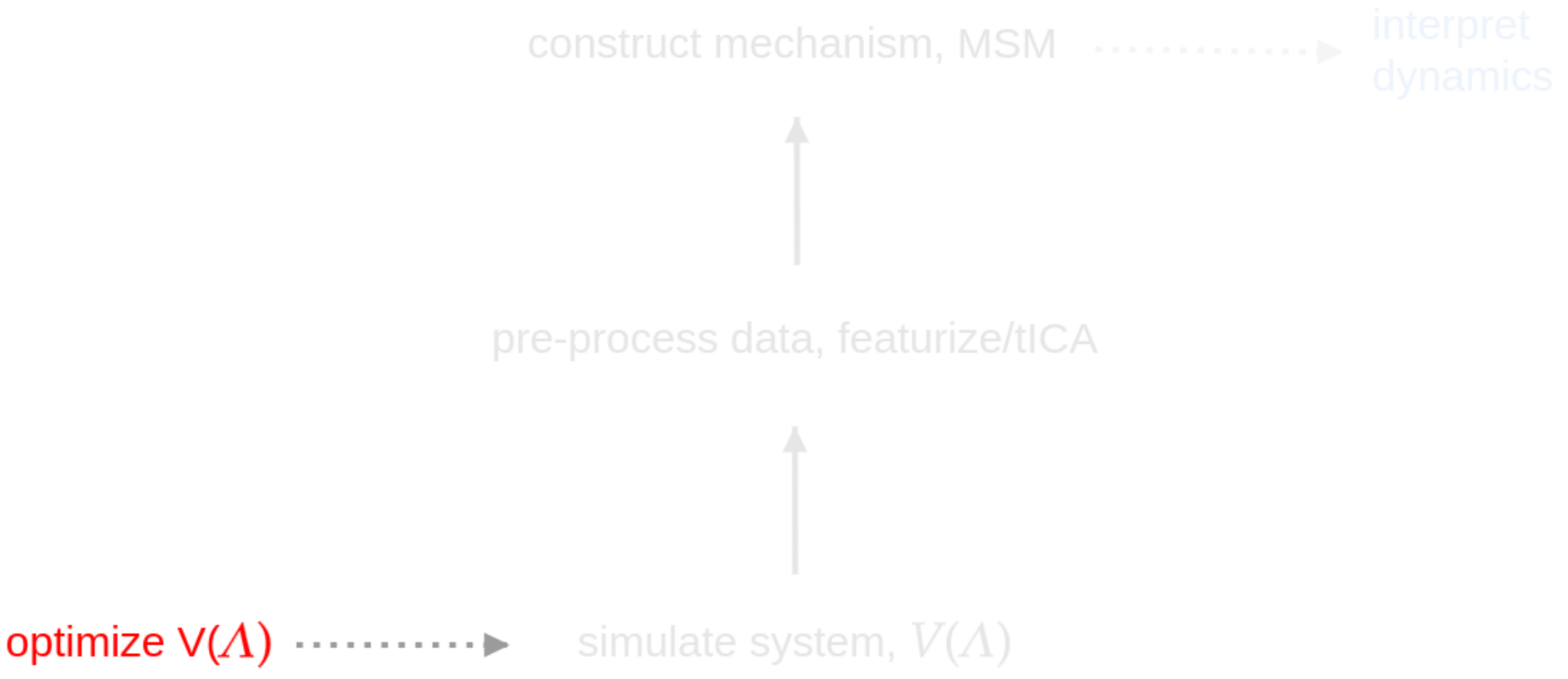
Dynamical model of the CLC-2 ion channel exhibits a two-step gating mechanism

Keri A. McKiernan[1], Anna K. Koster[1,2], Merritt Maduke[2], and Vijay S. Pande[3,*]

10.1101/228163

future directions


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
optimize V(Λ)
simulate system, $V(\Lambda)$


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
optimize V(Λ)
simulate system, $V(\Lambda)$

frontiers for force field development

- More experimental data
- More QM data

$$L(\Lambda|T, \alpha, \beta)$$

frontiers for force field development

- More experimental data
- More QM data
- Global minimization

$$L(\Lambda|T,\alpha,\beta)$$

$$\lambda_{i+1} = \lambda_i + \mu \frac{\nabla L(\Lambda|T,\alpha,\beta)}{\nabla^2 L(\Lambda|T,\alpha,\beta) + bI}$$

frontiers for force field development

- More experimental data
- More QM data

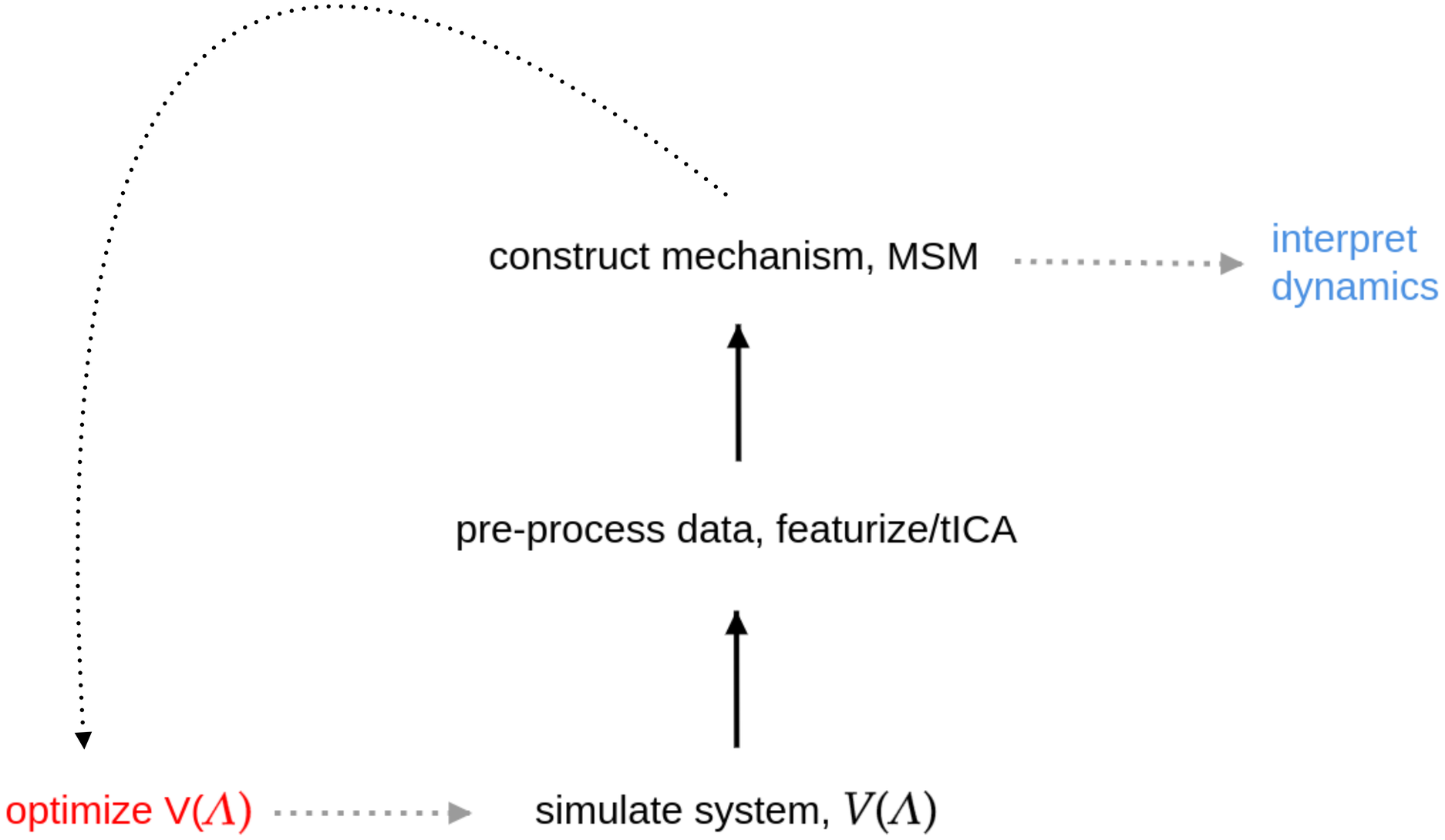
$$L(\Lambda|T, \alpha, \beta)$$

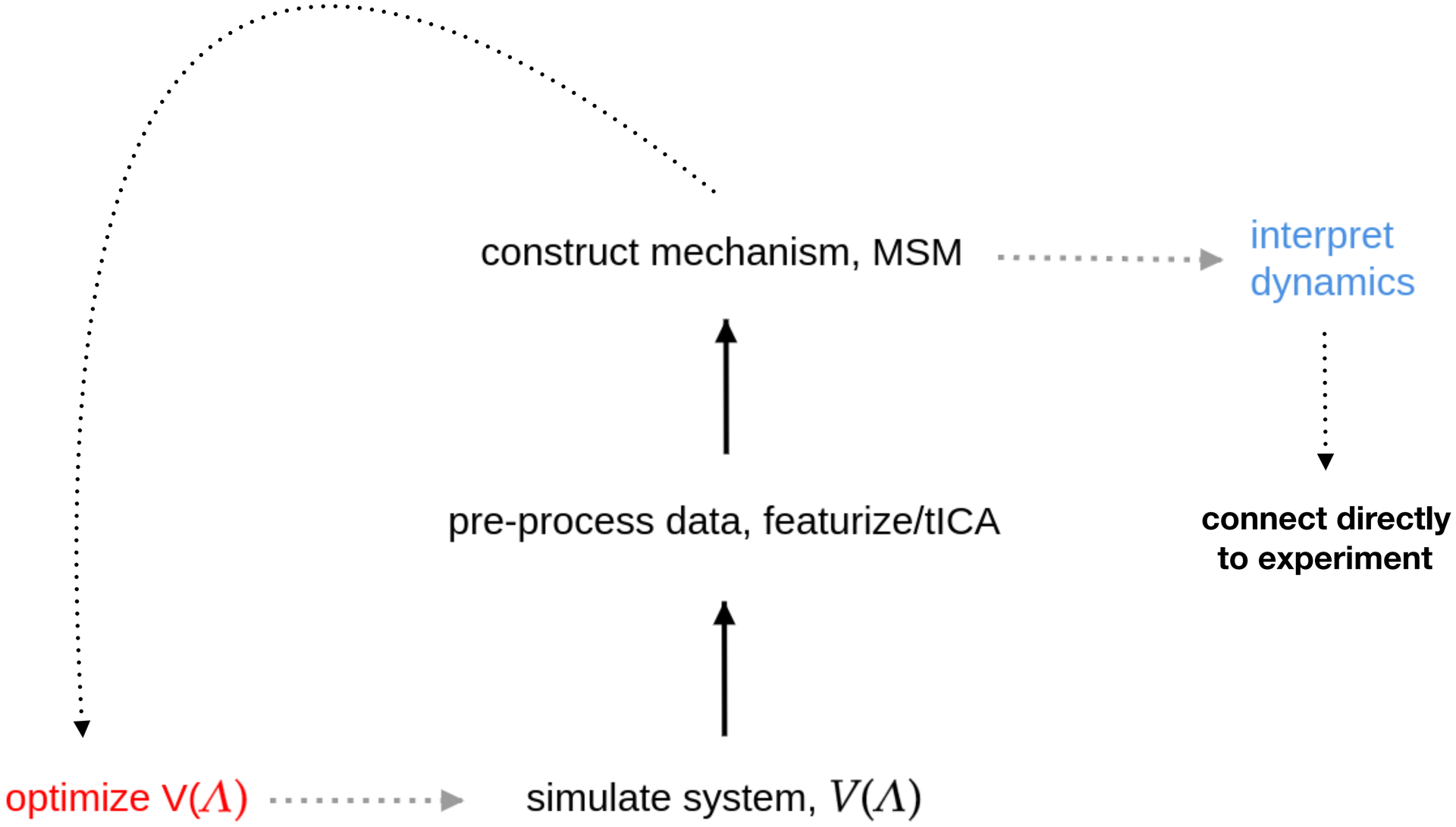
- Global minimization

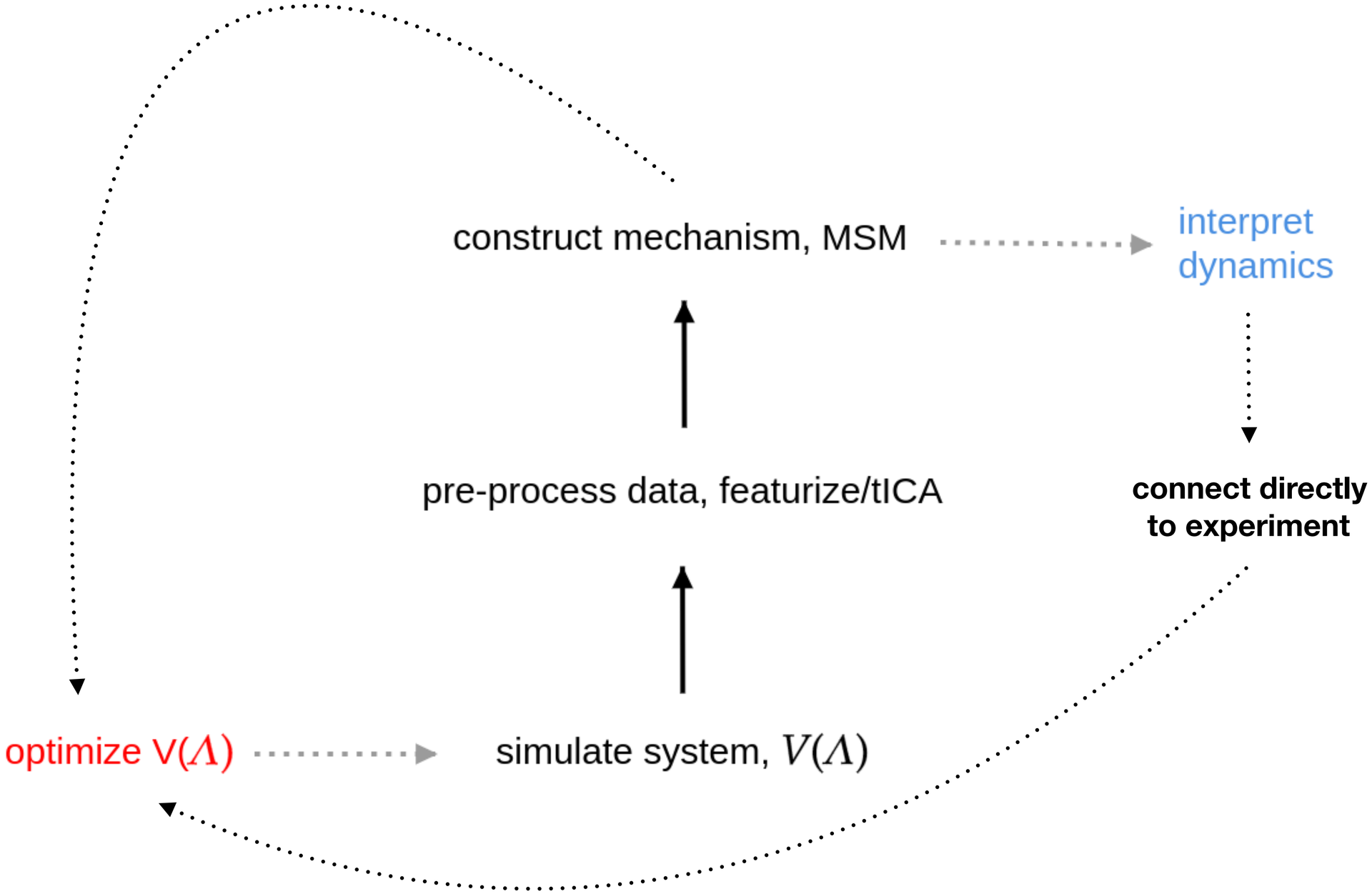
$$\lambda_{i+1} = \lambda_i + \mu \frac{\nabla L(\Lambda|T, \alpha, \beta)}{\nabla^2 L(\Lambda|T, \alpha, \beta) + bI}$$

- Exploration in function space
- Neural network potentials

$$V(q|\Lambda)$$


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
optimize V(Λ)
simulate system, $V(\Lambda)$


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
connect directly to experiment
optimize V(Λ)
simulate system, $V(\Lambda)$


construct mechanism, MSM
interpret dynamics
pre-process data, featurize/tICA
connect directly to experiment
optimize V(Λ)
simulate system, $V(\Lambda)$

acknowledgements

acknowledgements

acknowledgements

acknowledgements

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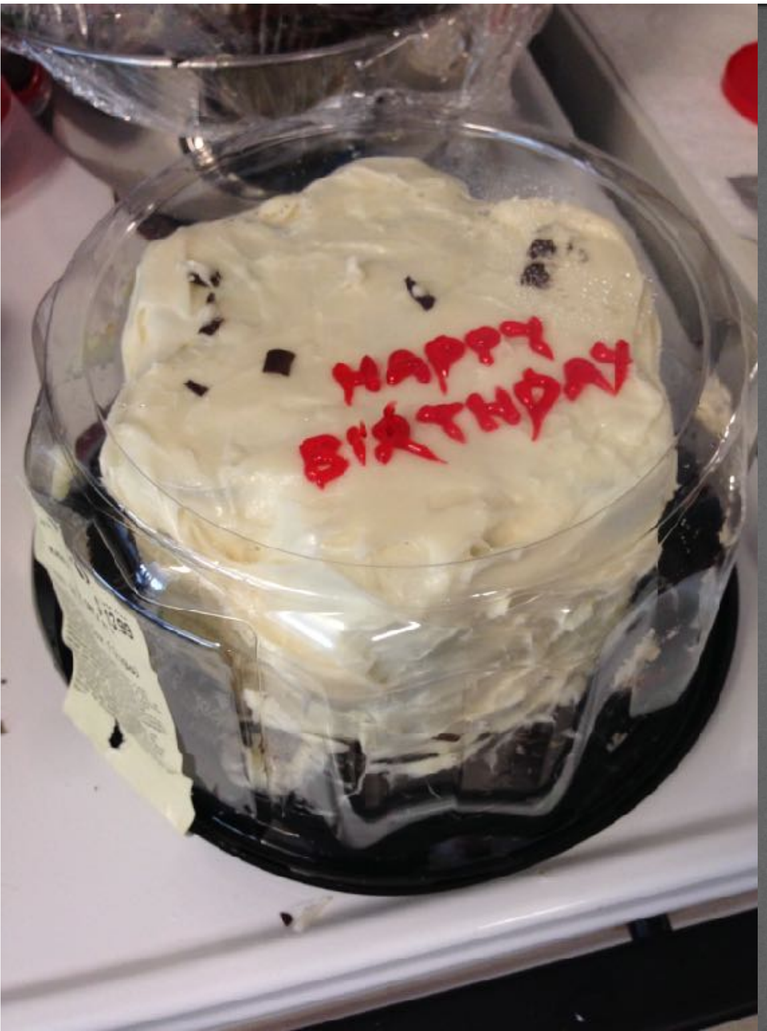
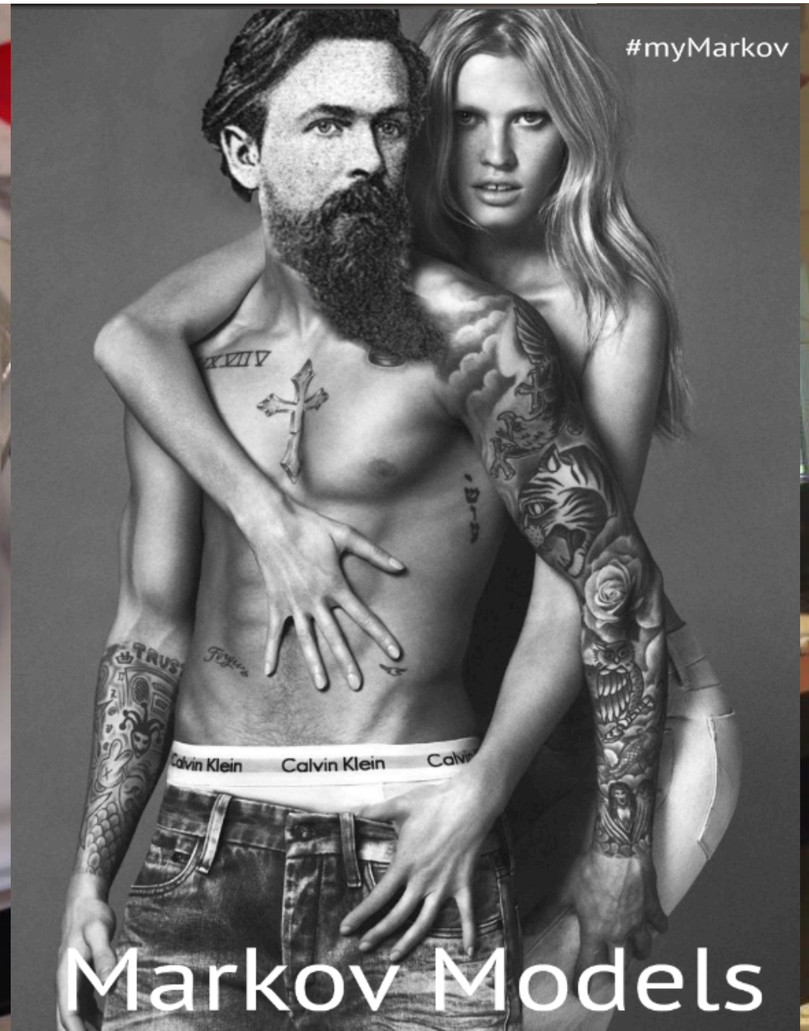
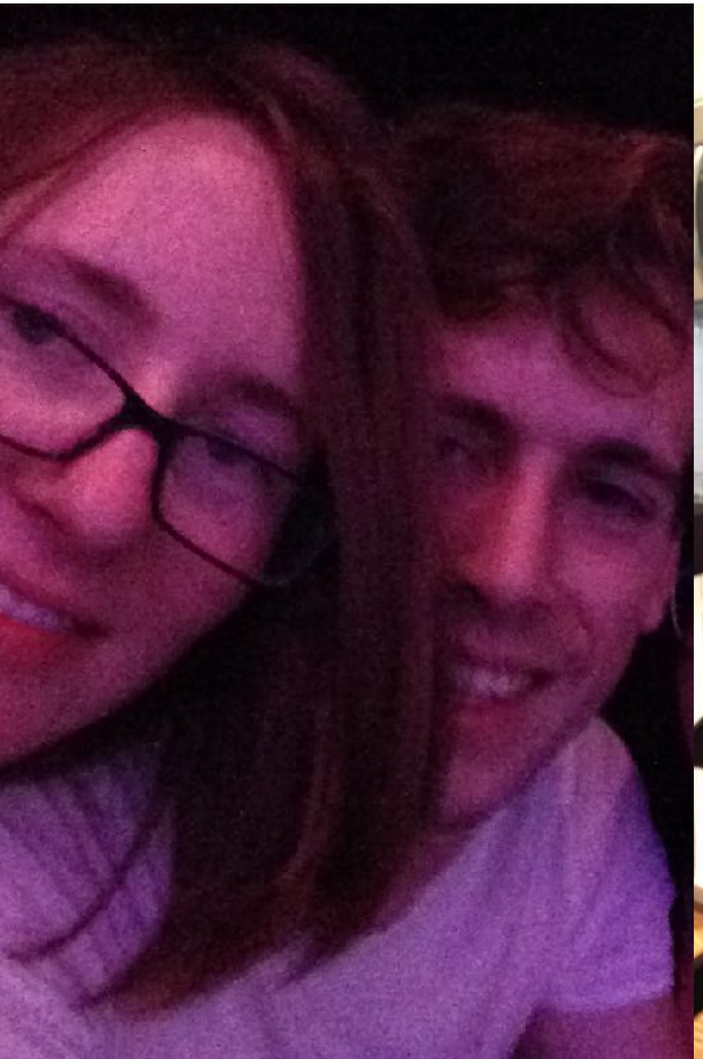




acknowledgements

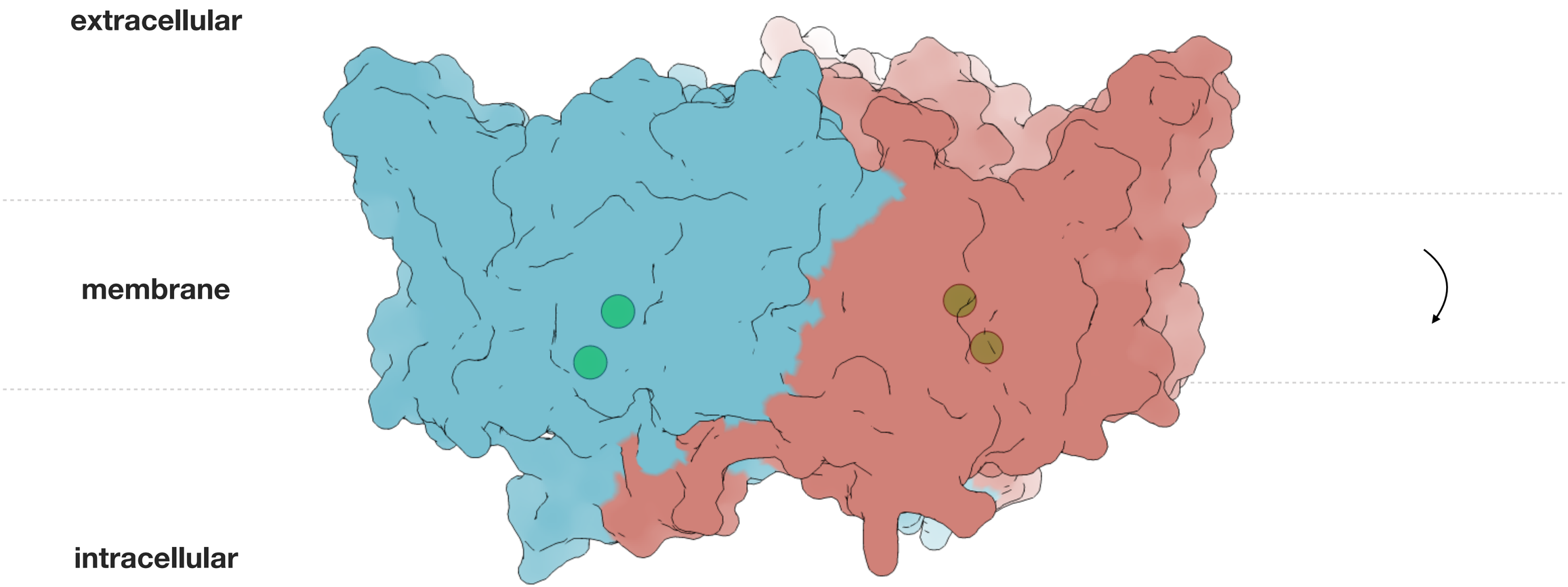
acknowledgements



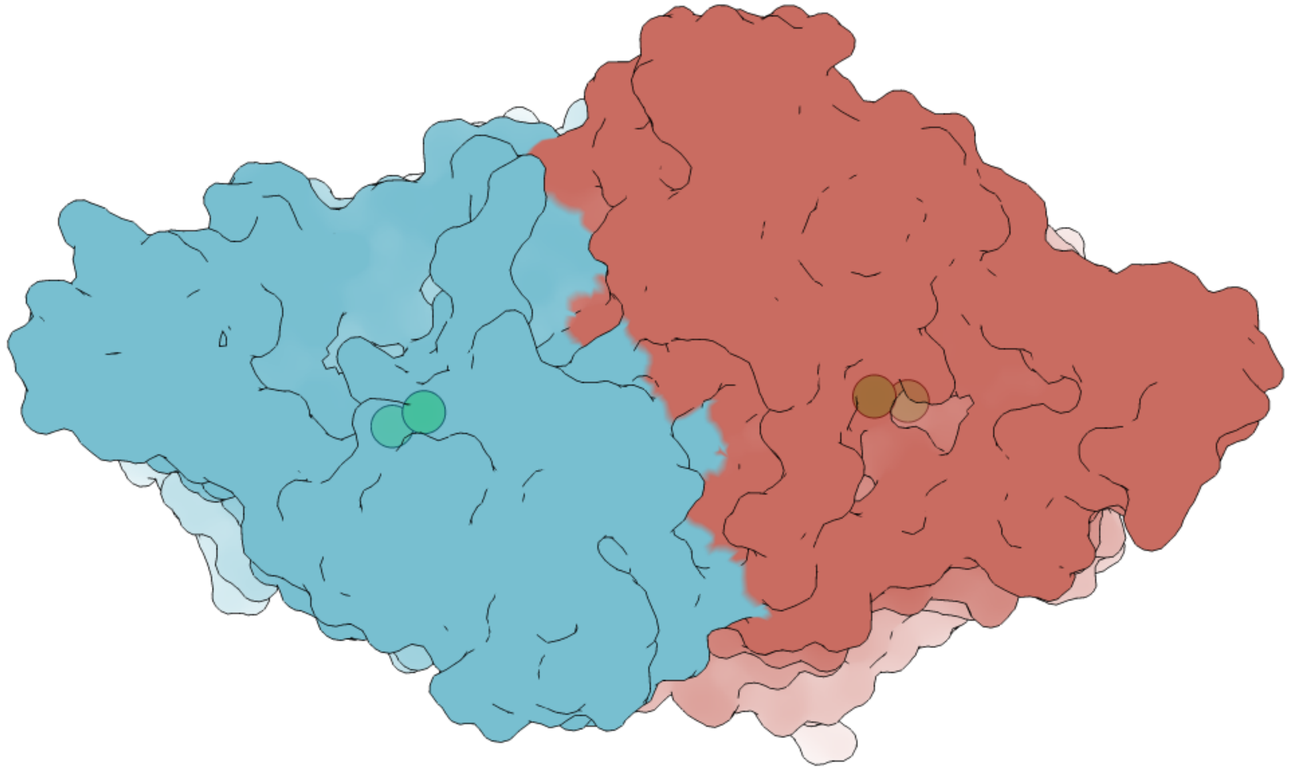
acknowledgements

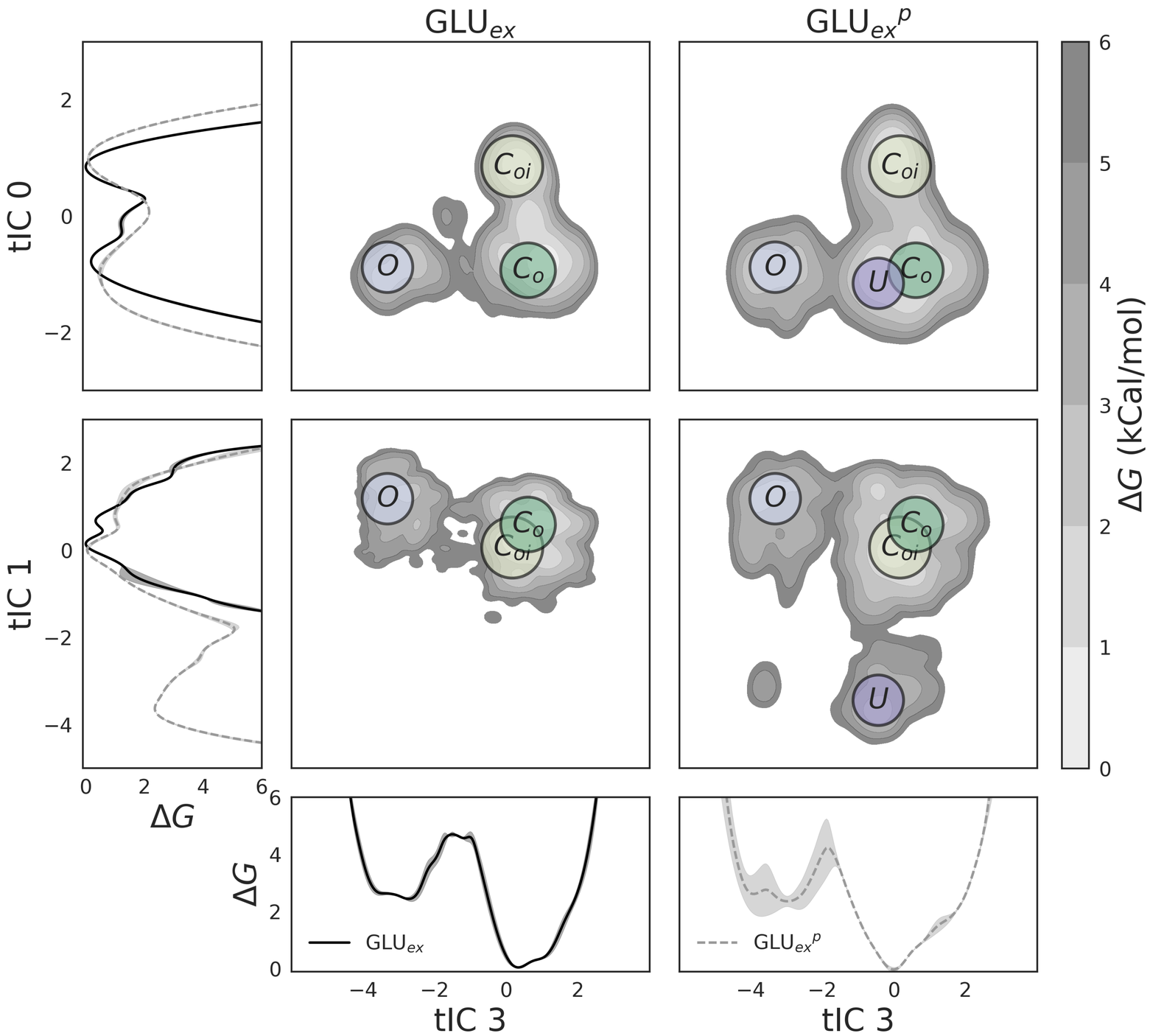
thank you!

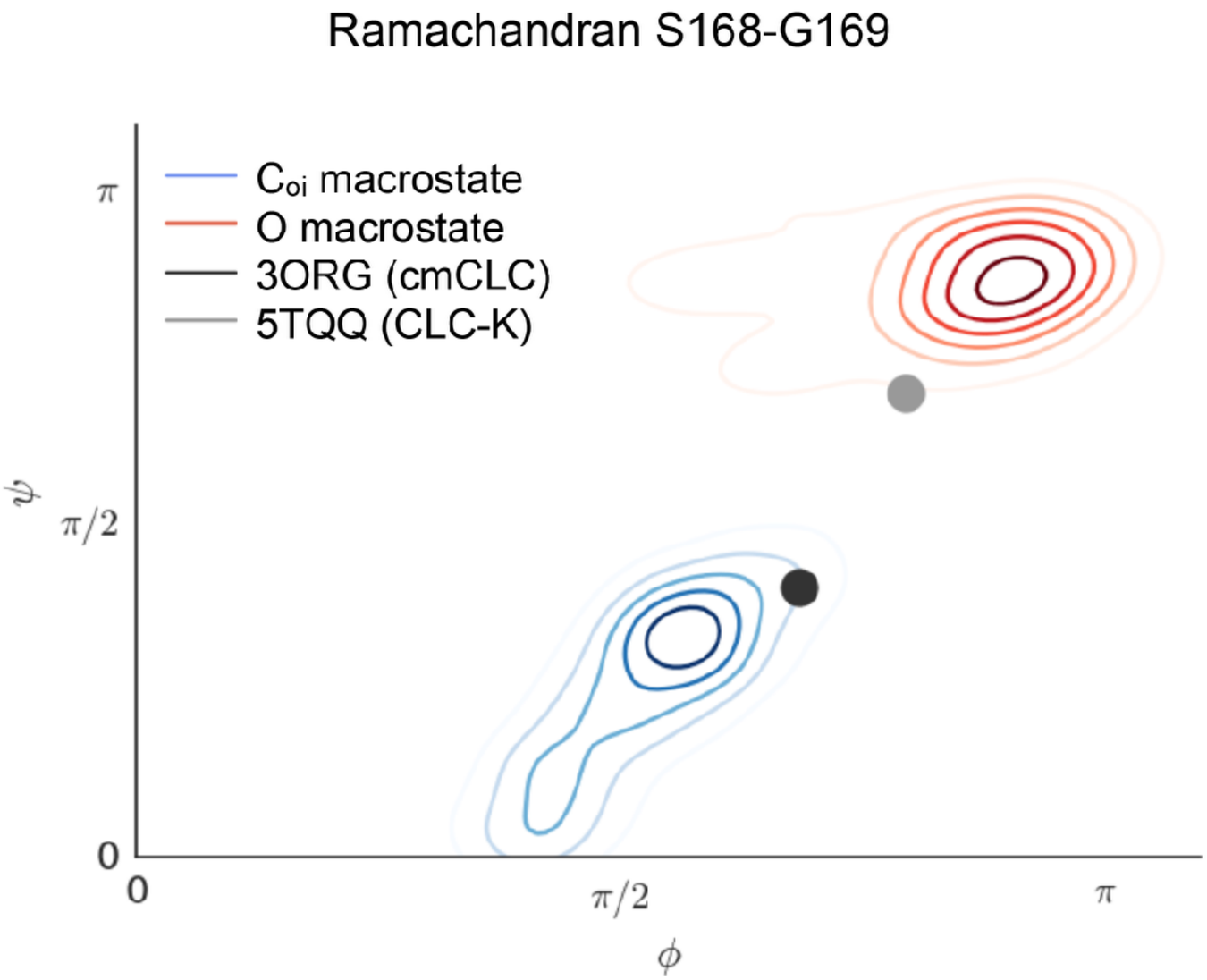
supp clc

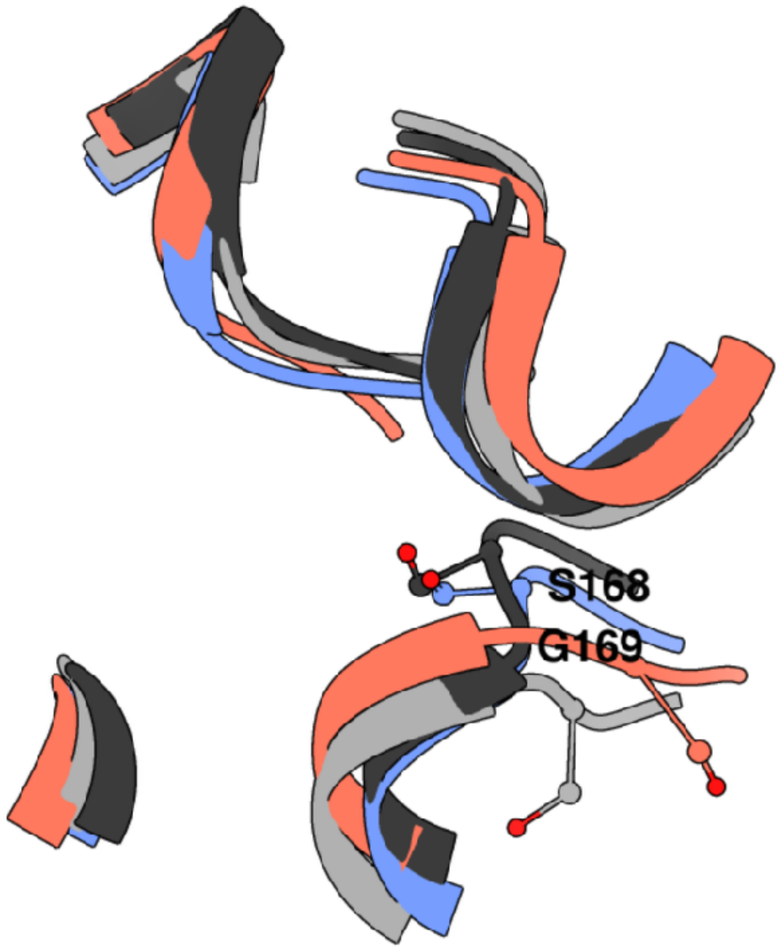

extracellular
membrane
intracellular

membrane




GLU$_{ex}$
GLU$_{ex}^{p}$
tIC 0
tIC 1
ΔG
C_{oi}
C_o
O
U
ΔG (kCal/mol)
GLU$_{ex}$
GLU$_{ex}^{p}$
tIC 3


Ramachandran S168-G169
C_{oi} macrostate
O macrostate
3ORG (cmCLC)
5TQQ (CLC-K)
π
$\pi/2$
0
ψ
0
$\pi/2$
π
ϕ


S168
G169

tICs: long timescale dynamical processes

featuregroup	featurizer	otherinfo	resnames	resseqs
psi	Dihedral	cos	[GLY, ILE]	[169, 170]
phi	Dihedral	sin	[PHE, ALA]	[464, 465]
psi	Dihedral	sin	[PHE, ALA]	[464, 465]
phi	Dihedral	sin	[GLY, SER]	[168, 169]
psi	Dihedral	cos	[GLY, SER]	[168, 169]
phi	Dihedral	sin	[GLY, SER]	[167, 168]
chi1	Dihedral	cos	[GLU]	[211]

⋮

tICs: long timescale dynamical processes

featuregroup	featurizer	otherinfo	resnames	resseqs	tIC loading
psi	Dihedral	cos	[GLY, ILE]	[169, 170]	-0.529498
phi	Dihedral	sin	[PHE, ALA]	[464, 465]	-0.190180
psi	Dihedral	sin	[PHE, ALA]	[464, 465]	-0.122220
phi	Dihedral	sin	[GLY, SER]	[168, 169]	-0.117311
psi	Dihedral	cos	[GLY, SER]	[168, 169]	0.093205
phi	Dihedral	sin	[GLY, SER]	[167, 168]	0.105494
chi1	Dihedral	cos	[GLU]	[211]	0.179382

⋮

tICs: long timescale dynamical processes

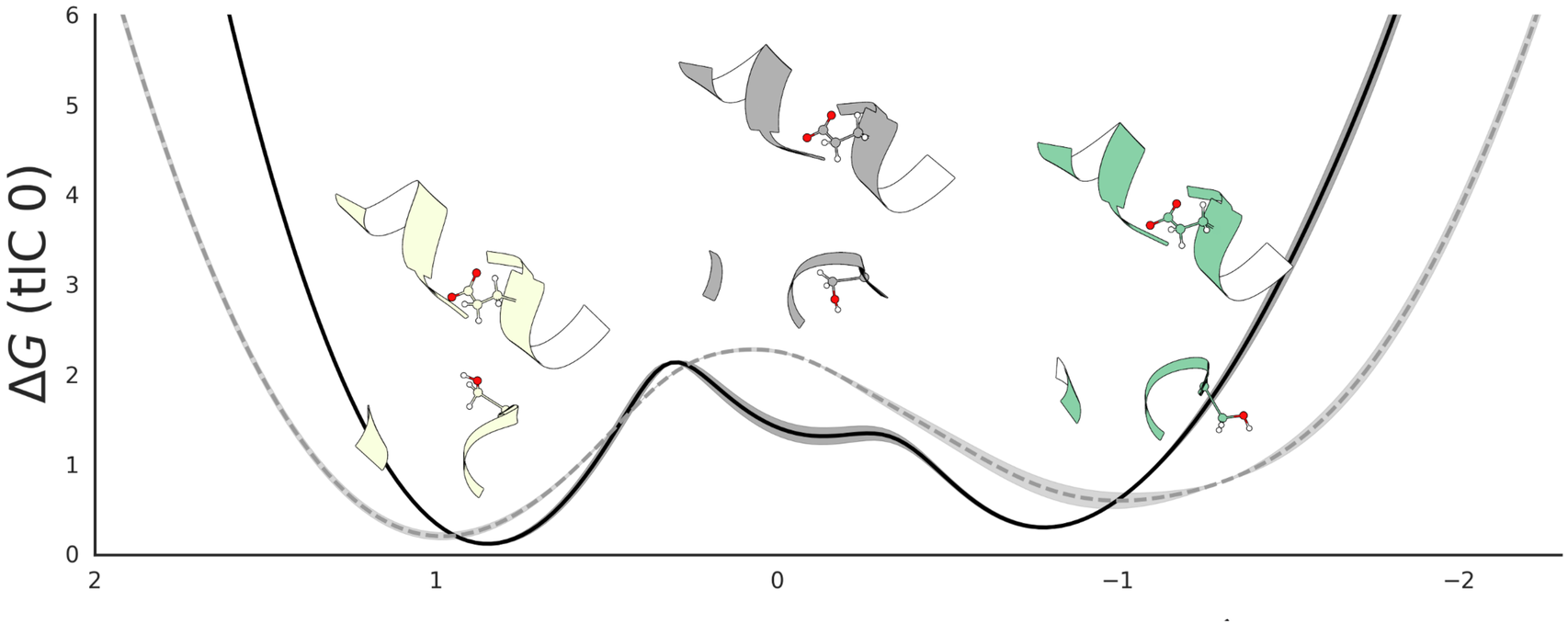
featuregroup	featurizer	otherinfo	resnames	resseqs	tIC loading
psi	Dihedral	cos	[GLY, ILE]	[169, 170]	-0.529498
phi	Dihedral	sin	[PHE, ALA]	[464, 465]	-0.190180
psi	Dihedral	sin	[PHE, ALA]	[464, 465]	-0.122220
phi	Dihedral	sin	[GLY, SER]	[168, 169]	-0.117311
psi	Dihedral	cos	[GLY, SER]	[168, 169]	0.093205
phi	Dihedral	sin	[GLY, SER]	[167, 168]	0.105494
chi1	Dihedral	cos	[GLU]	[211]	0.179382

← top residue feature

⋮

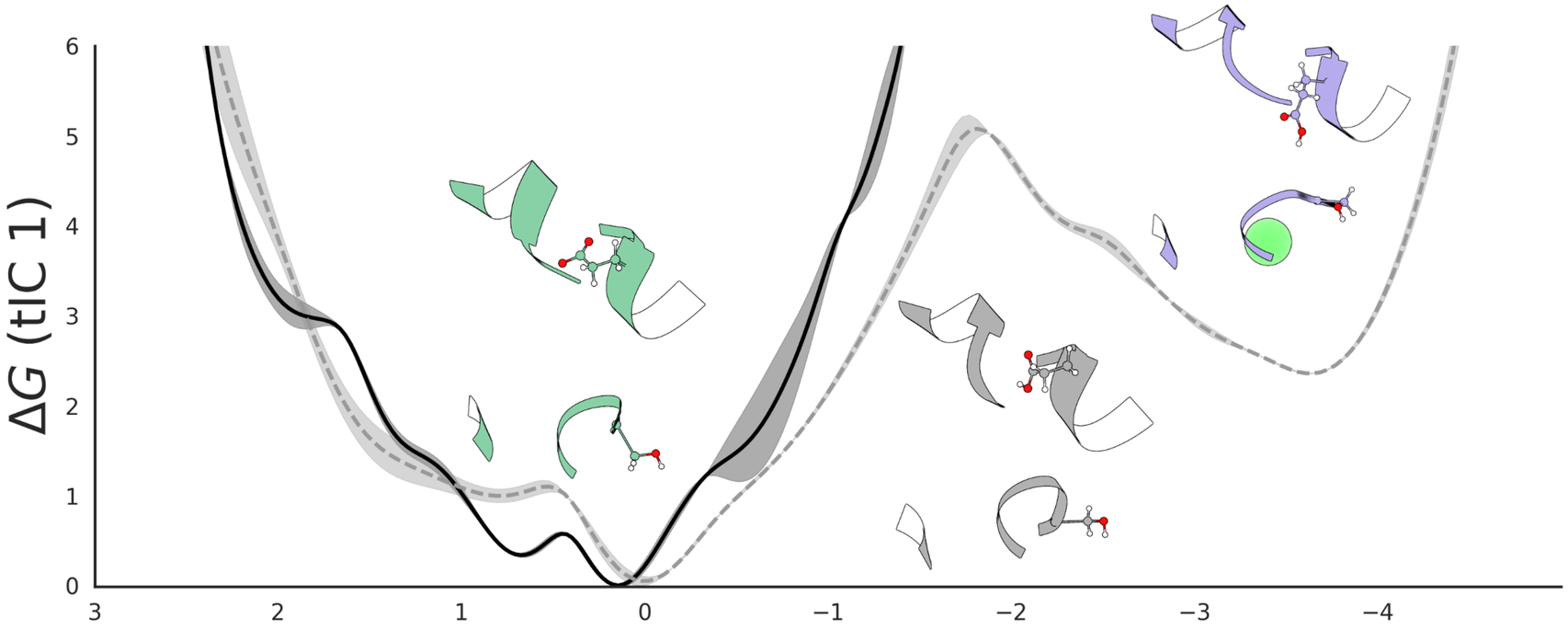
tICs: long timescale dynamical processes

dynamical mode	conformational change	top residue features
tIC 0	SER_{cen} backbone rotation	ψ(I170,G169), ψ(G169,S168)
tIC 1	GLU^{p}_{ex} side chain flip	χ_1(E211), ϕ(S168,G167)
tIC 3	GLU_{ex} side chain flip	χ_1(E211), ϕ(G169,S168)



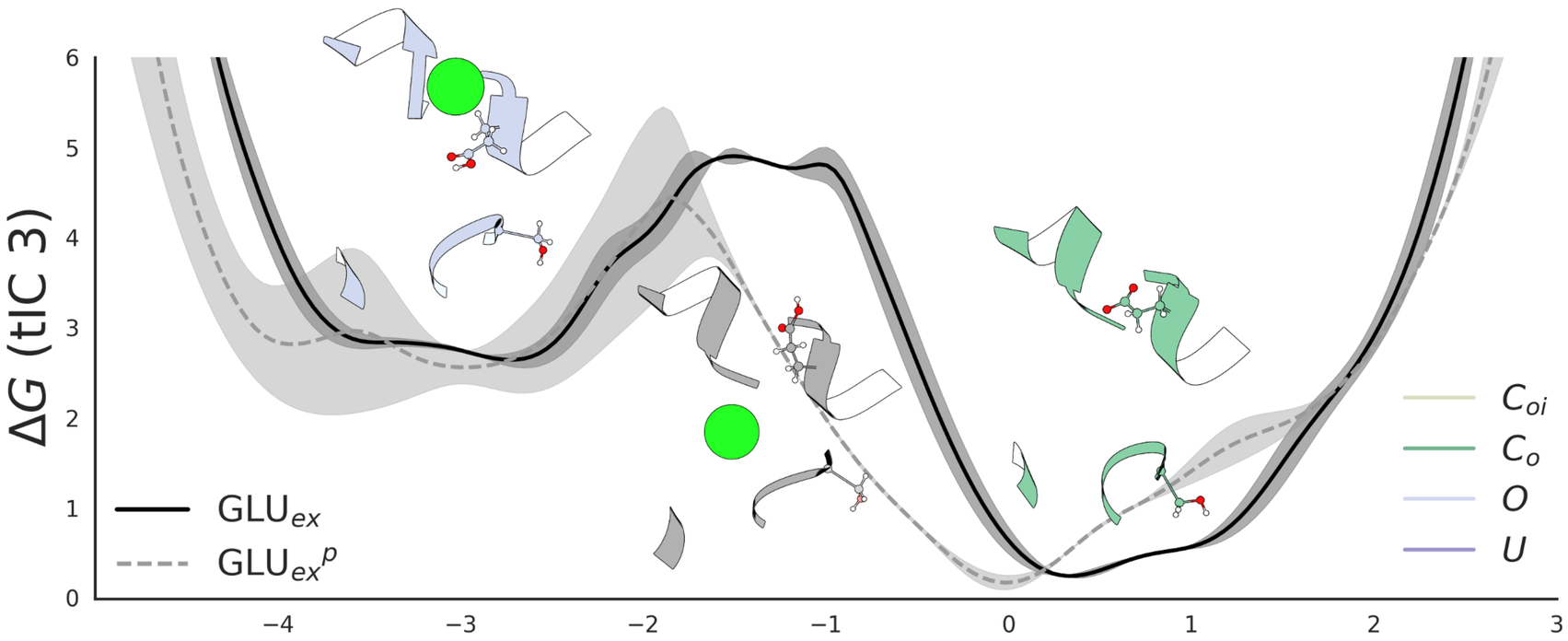
tICs: long timescale dynamical processes

dynamical mode	conformational change	top residue features
tIC 0	SER_{cen} backbone rotation	ψ(I170,G169), ψ(G169,S168)
tIC 1	GLU^{p}_{ex} side chain flip	χ_1(E211), ϕ(S168,G167)
tIC 3	GLU_{ex} side chain flip	χ_1(E211), ϕ(G169,S168)

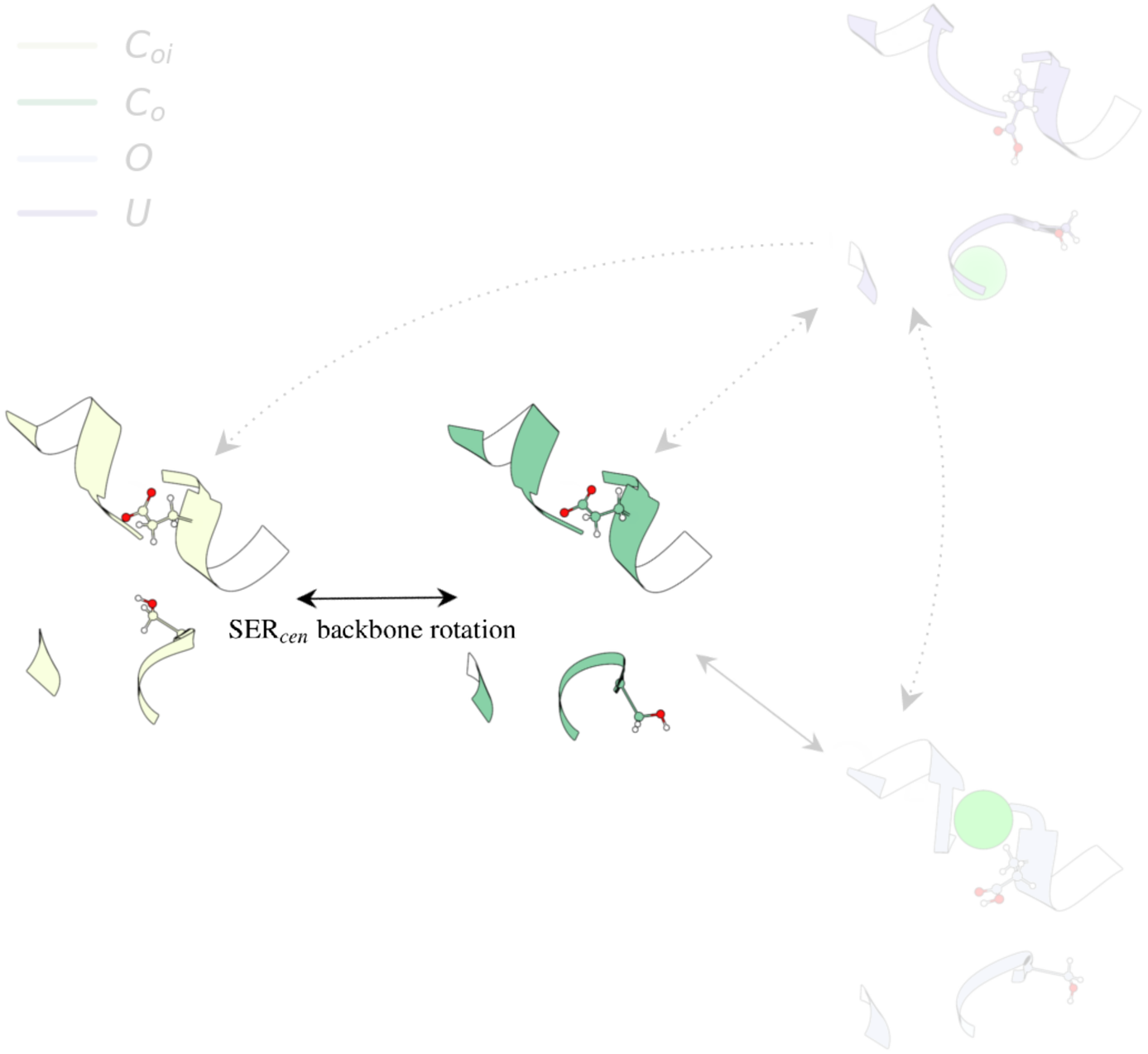


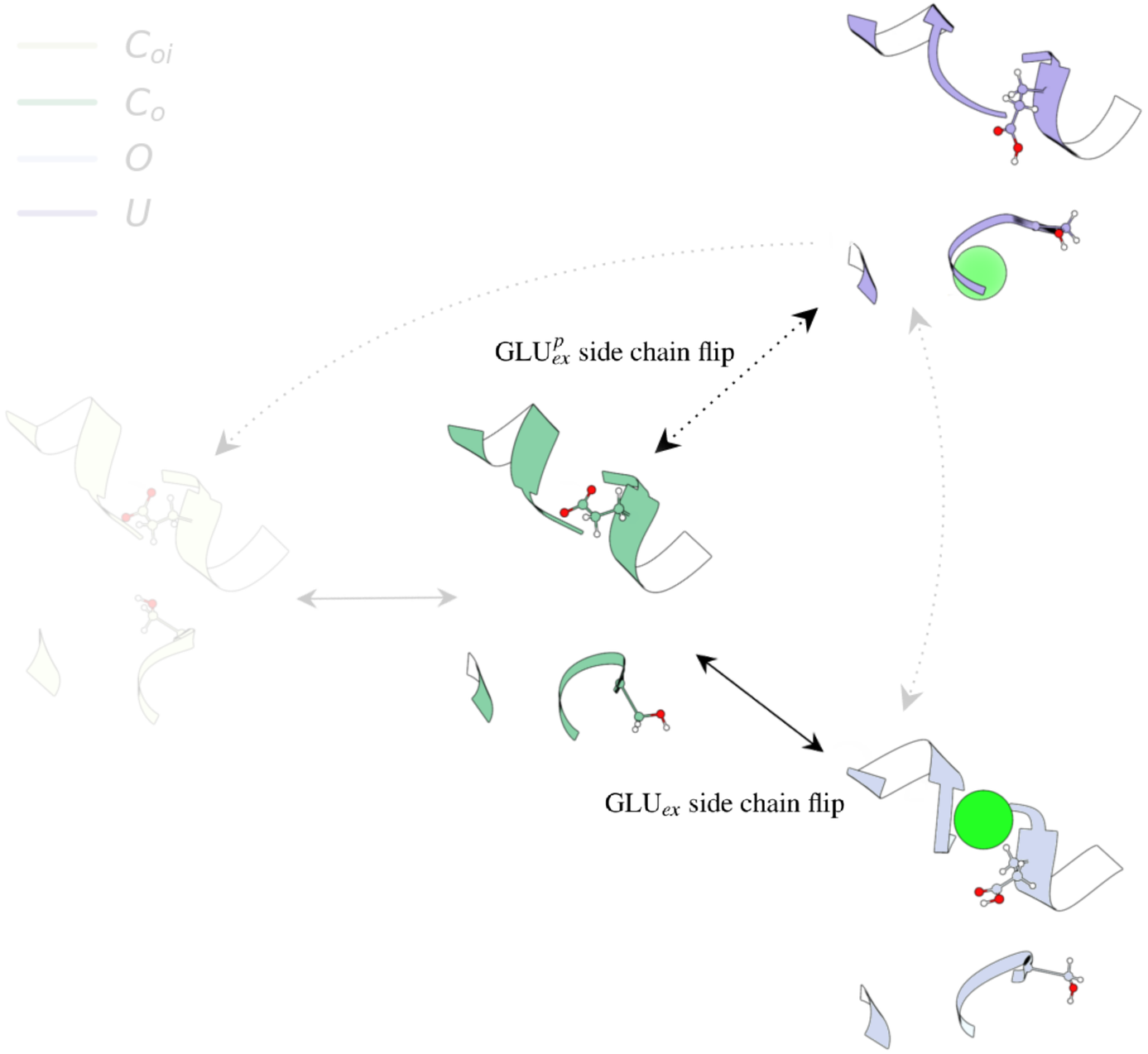
tICs: long timescale dynamical processes

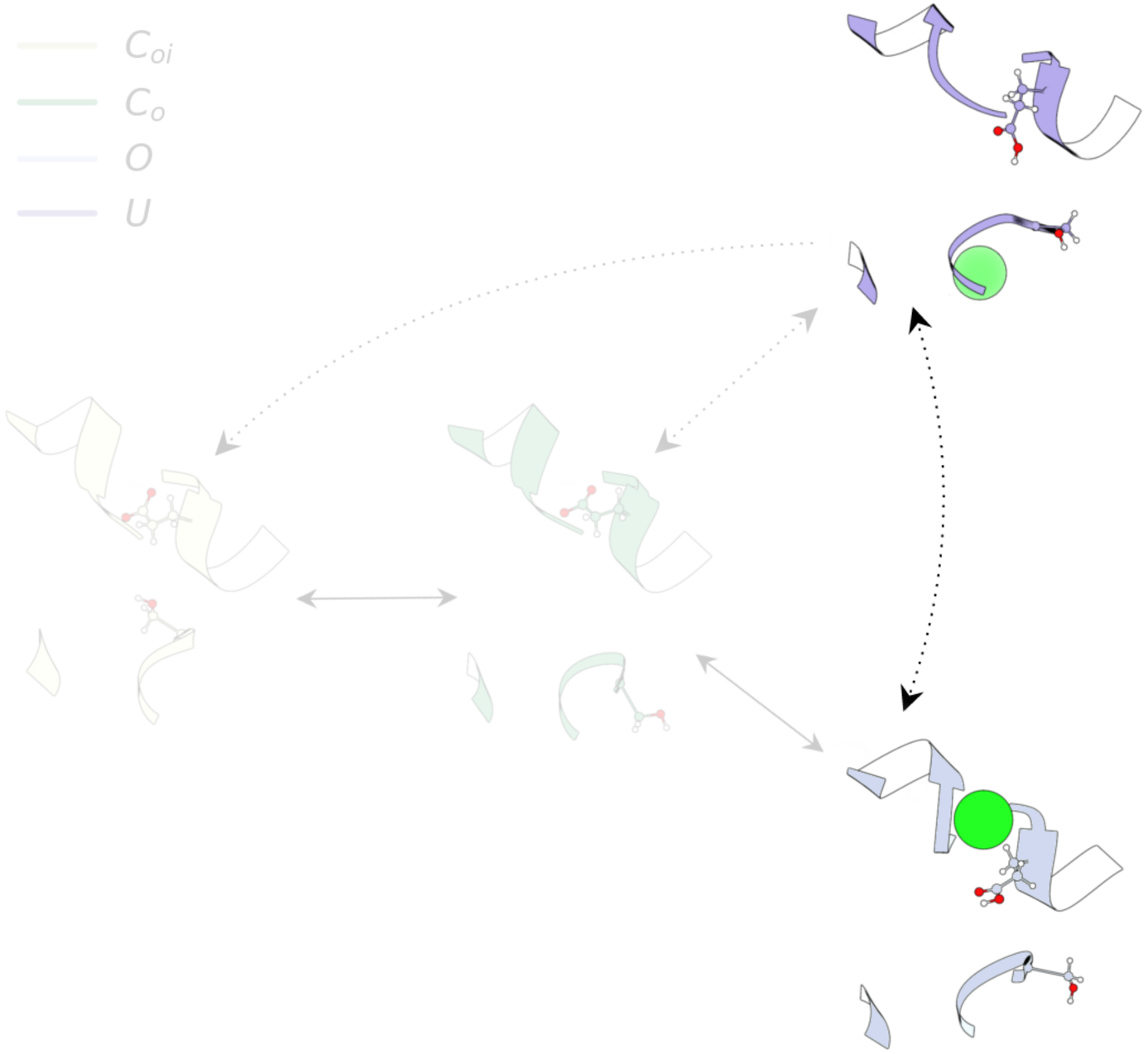
dynamical mode	conformational change	top residue features
tIC 0	SER_{cen} backbone rotation	ψ(I170,G169), ψ(G169,S168)
tIC 1	GLU_{ex}^{p} side chain flip	χ_1(E211), ϕ(S168,G167)
tIC 3	GLU_{ex} side chain flip	χ_1(E211), ϕ(G169,S168)

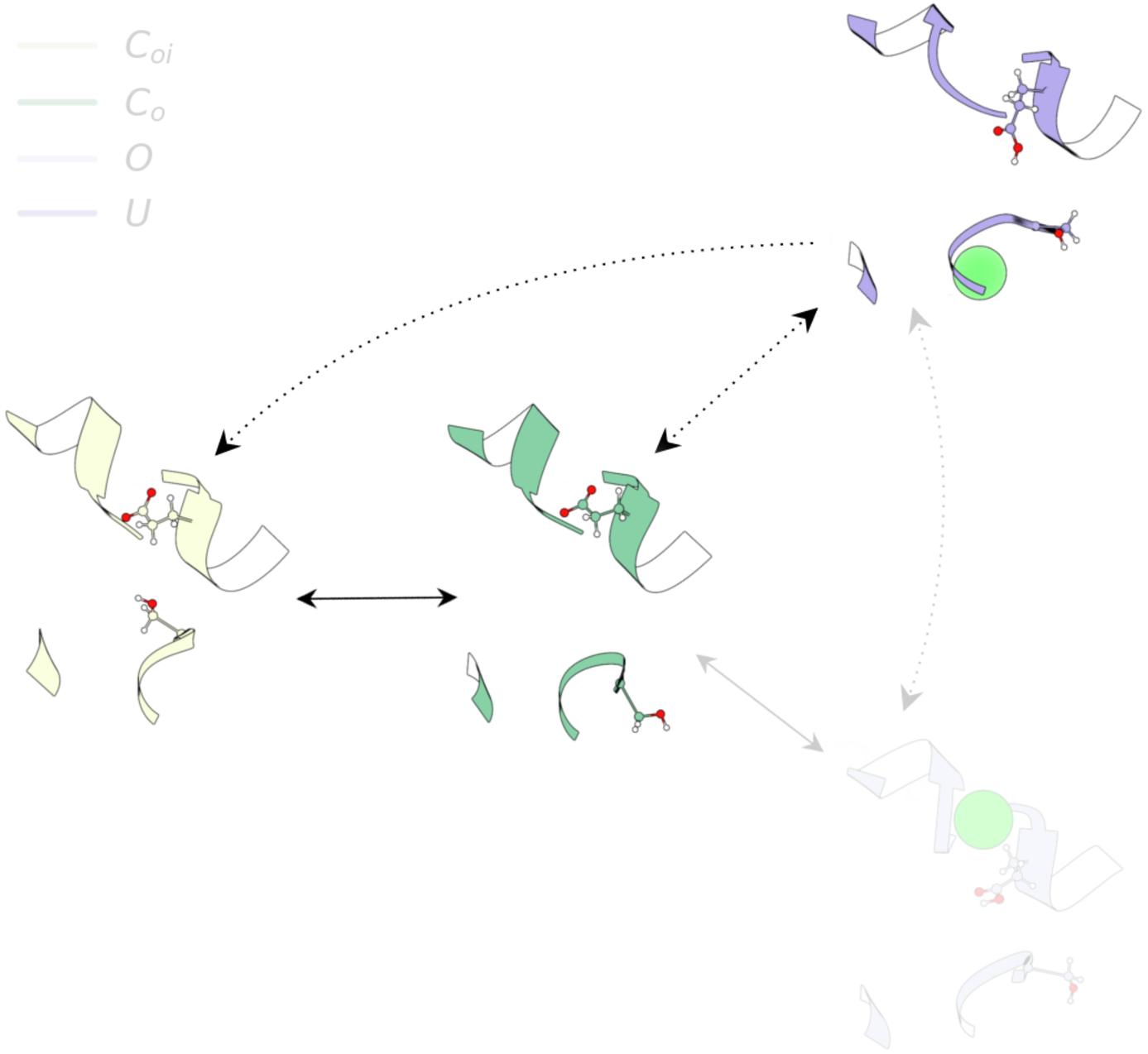


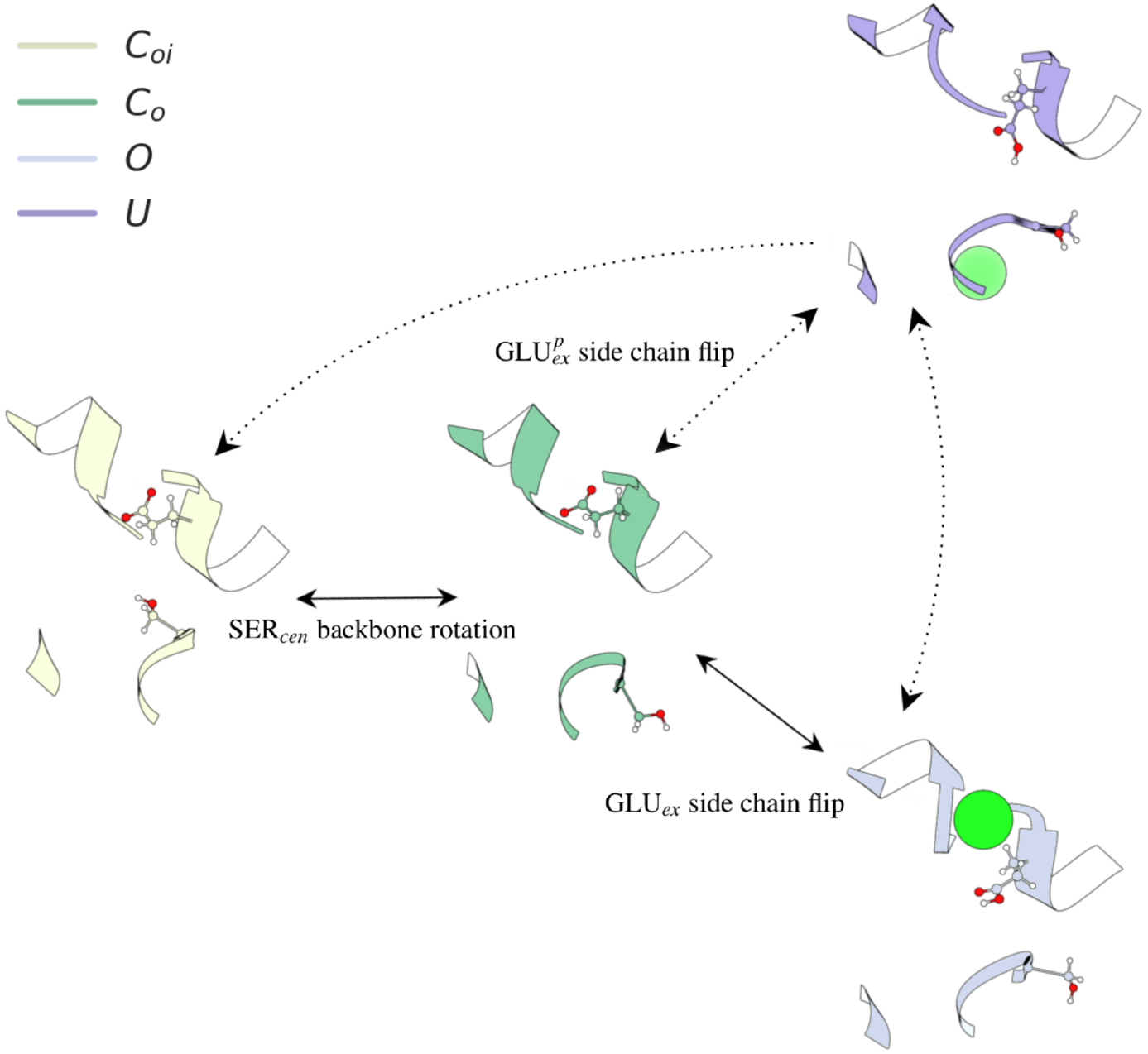
C_{oi}
C_o
O
U

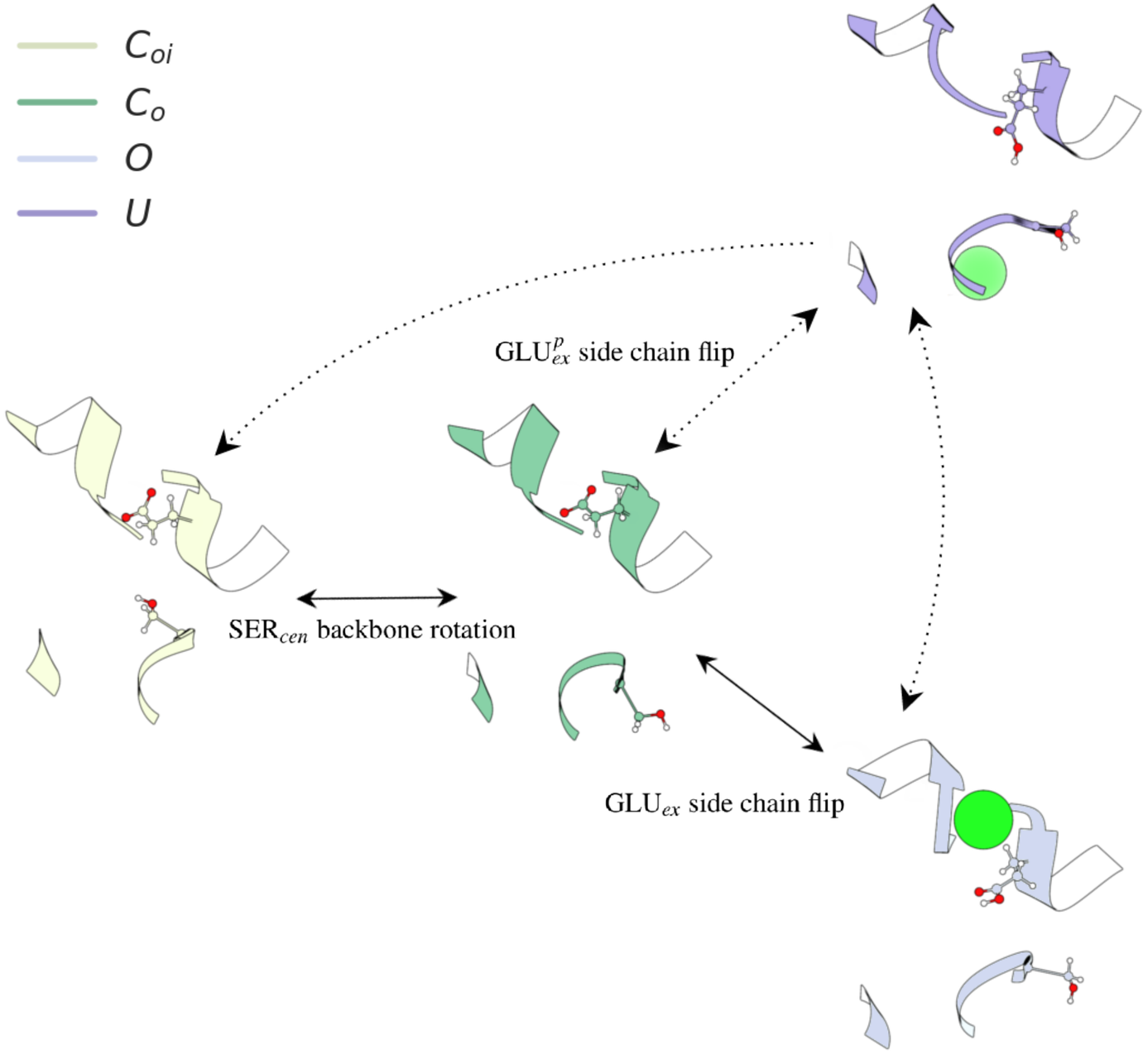

C_{oi}
C_o
O
U
SER$_{cen}$ backbone rotation


C_{oi}
C_o
O
U
GLU^p_{ex} side chain flip
GLU_{ex} side chain flip


C_{oi}
C_o
O
U


C_{oi}
C_o
O
U


C_{oi}
C_o
O
U
GLU^p_{ex} side chain flip
SER_{cen} backbone rotation
GLU_{ex} side chain flip


C_{oi}
C_o
O
U
GLU^p_{ex} side chain flip
SER_{cen} backbone rotation
GLU_{ex} side chain flip

supp lipid

the ensemble average of a generic observable A that does not depend explicitly on the force field parameters (for example, the density or an order parameter) can be expressed as follows:

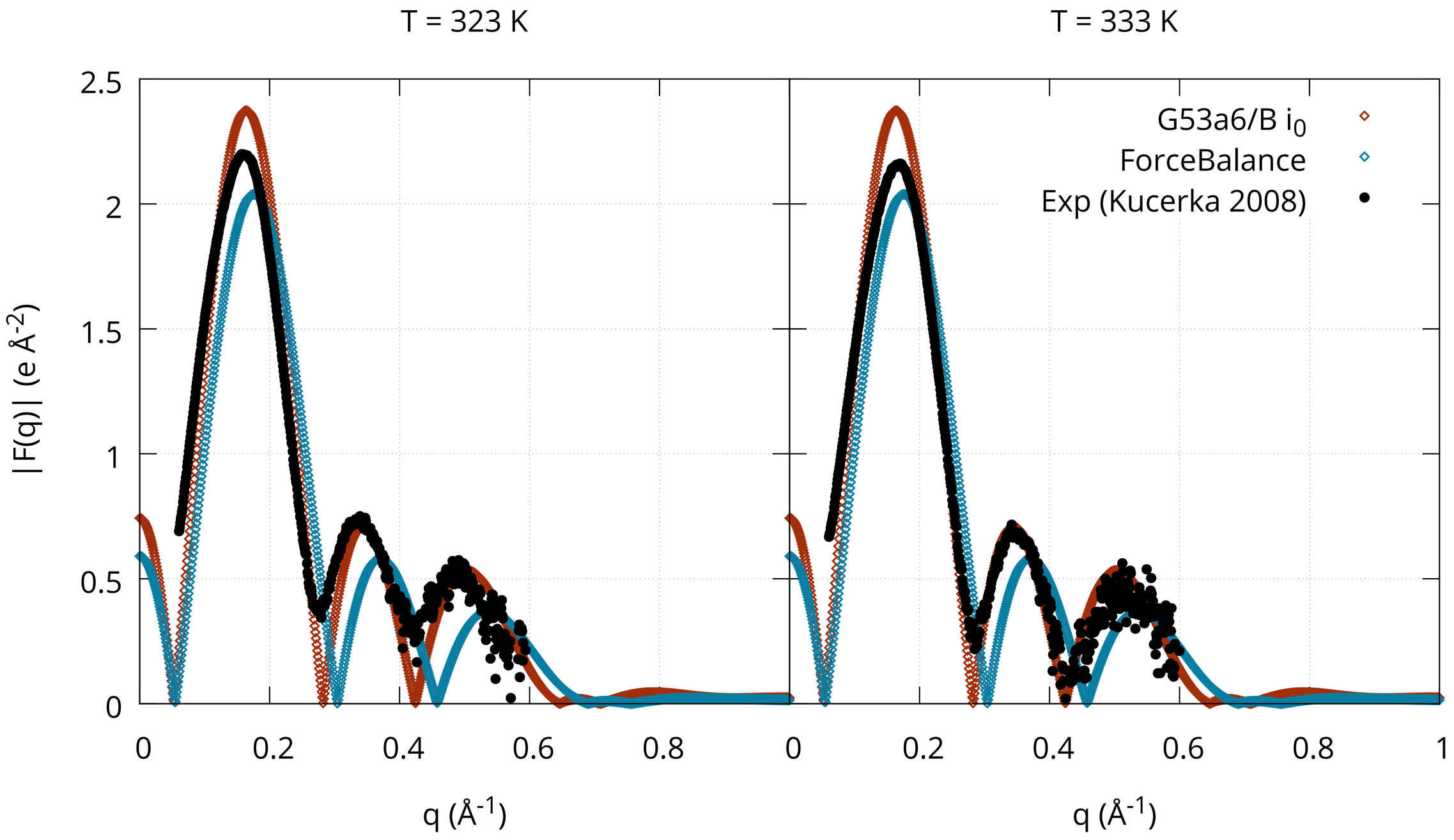
$$\langle A \rangle_\lambda = \frac{1}{Q(\lambda)} \int A(\mathbf{r}, V) \exp(-\beta(E(\mathbf{r}, V; \lambda) + PV))\, \mathrm{d}\mathbf{r}\, \mathrm{d}V$$

$$Q(\lambda) = \int \exp(-\beta(E(\mathbf{r}, V; \lambda) + PV))\, \mathrm{d}\mathbf{r}\, \mathrm{d}V$$

Since the expression for A depends on λ only through the potential energy E, we can differentiate the above expression and obtain the analytic derivative:

$$\frac{\mathrm{d}}{\mathrm{d}\lambda}\langle A \rangle_\lambda = \frac{1}{Q(\lambda)} \int A(\mathbf{r}, V) \exp(-\beta(E(\mathbf{r}, V; \lambda) + PV)) \left(-\beta \frac{\mathrm{d}E(\mathbf{r}, V)}{\mathrm{d}\lambda}\right) \mathrm{d}\mathbf{r}\, \mathrm{d}V - \frac{1}{Q(\lambda)^2} \frac{\mathrm{d}Q}{\mathrm{d}\lambda} \int A(\mathbf{r}, V) \exp(-\beta(E(\mathbf{r}, V; \lambda) + PV))\, \mathrm{d}\mathbf{r}\, \mathrm{d}V$$

$$= -\beta\left(\left\langle A \frac{\mathrm{d}E}{\mathrm{d}\lambda} \right\rangle_\lambda - \langle A \rangle_\lambda \left\langle \frac{\mathrm{d}E}{\mathrm{d}\lambda} \right\rangle_\lambda\right)$$


T = 323 K
T = 333 K
G53a6/B i_0
ForceBalance
Exp (Kucerka 2008)
|F(q)| (e Å^{-2})
q (Å^{-1})
q (Å^{-1})
0
0.5
1
1.5
2
2.5
0
0.2
0.4
0.6
0.8
0
0.2
0.4
0.6
0.8
1

Optimization specifics

Goal: $min_\lambda(\chi^2)$
where $\chi^2 = \sum_i w_i \Delta O_i^2 + R$ and $\Delta O_i = O_{MM} - O_{Ref}$

Need: $\nabla\chi^2$ and $H(\chi^2)$

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$\nabla\chi^2$ found via analytic derivatives of observables.

if $\langle O_i \rangle_\lambda = \frac{1}{Q(\lambda)} \int O_i(r, V) e^{-\beta(E(r,V;\lambda)+PV)} drdV$

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and $\nabla\chi^2 = \frac{\partial}{\partial\lambda_k} \sum_i O_i^2$
$= 2 \sum_i O_i \frac{\partial}{\partial\lambda_k} O_i$

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$H(\chi^2)$ found via Gauss-Newton approximation.

$H_{jk} = \frac{\partial^2}{\partial\lambda_j \partial\lambda_k} \sum_i O_i$

$= 2 \sum_i \left[\frac{\partial^2}{\partial\lambda_j \partial\lambda_k} O_i^2 + O_i \frac{\partial^2}{\partial\lambda_j \lambda_k} O_i \right]$

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Minimization step determined by the Levenberg algorithm.

$(H(\chi^2) + b * I)^{-1} * \nabla\chi^2$

$$F = -\nabla V(q|\Lambda)$$

$$\lambda_i \in \Lambda$$