Introduction to
lipid bilayer MD simulations
and applications

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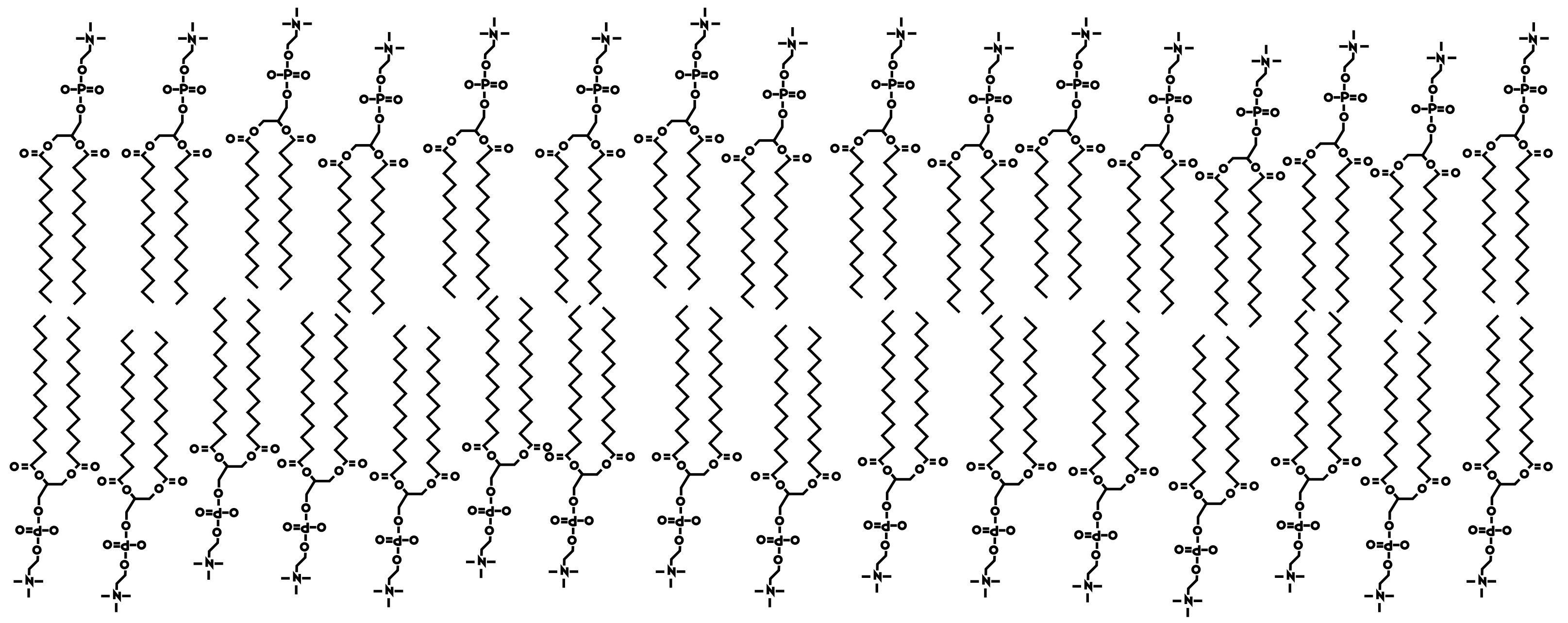
NMRlipids summer school
Helsinki, June 1st 2022

Simulating biomolecular systems



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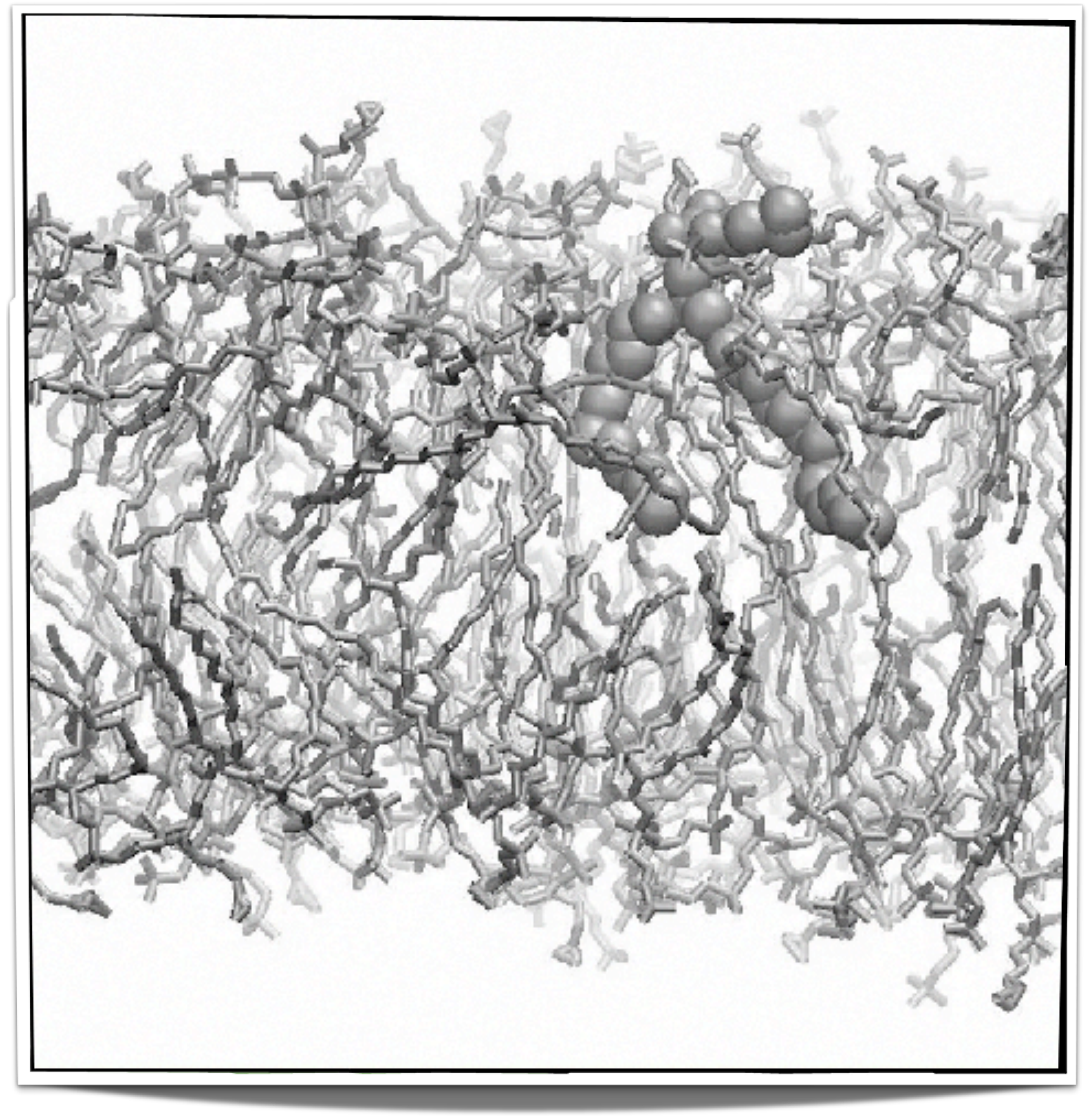

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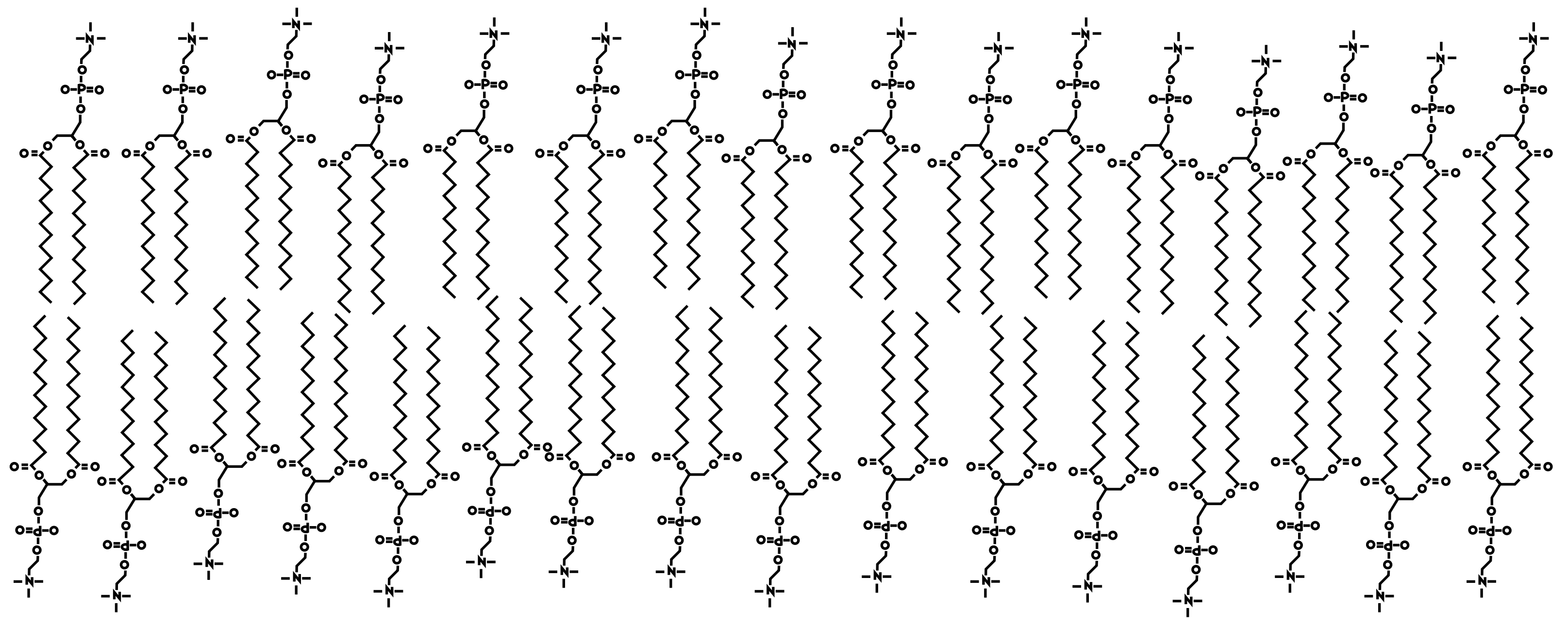

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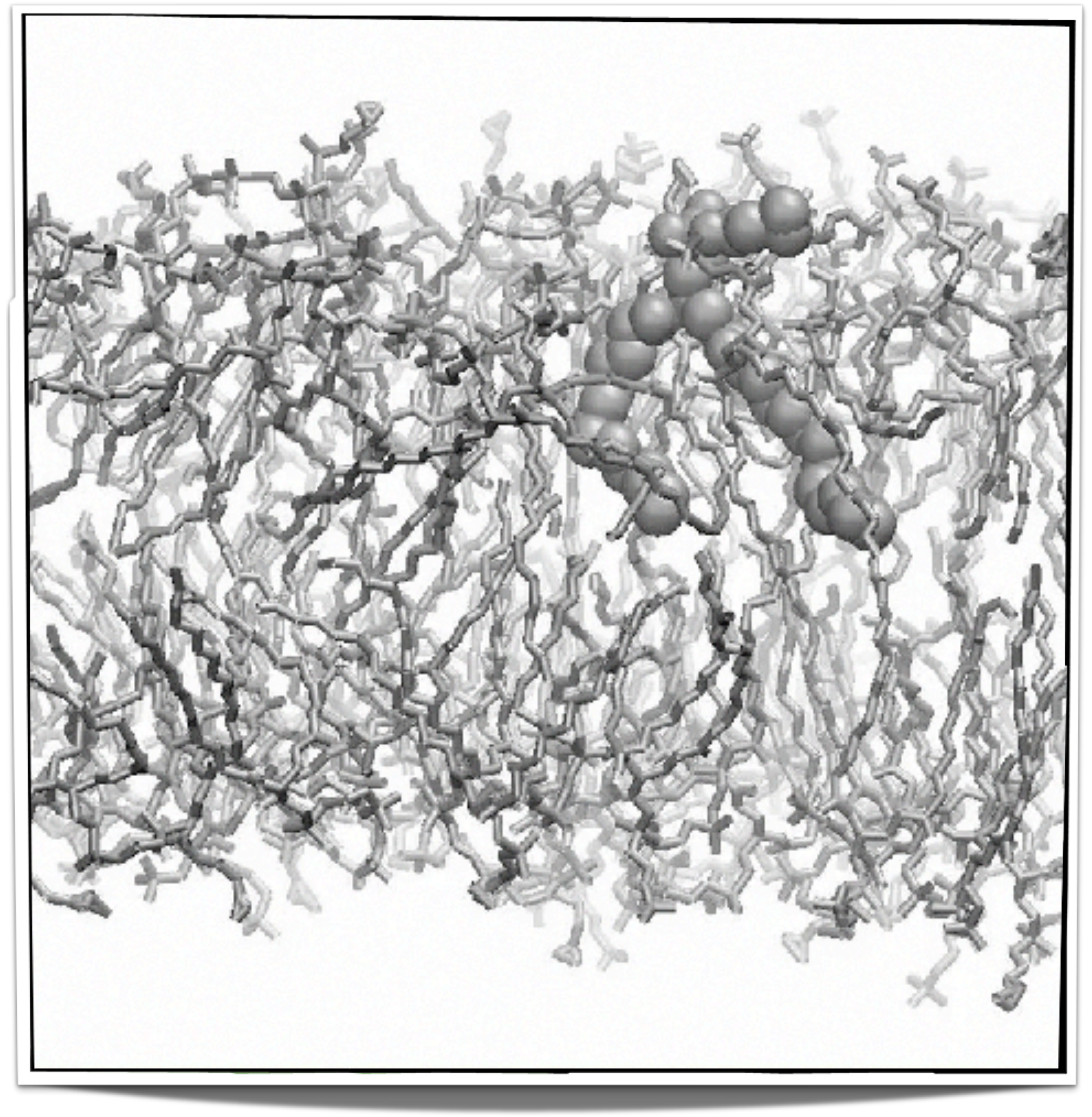

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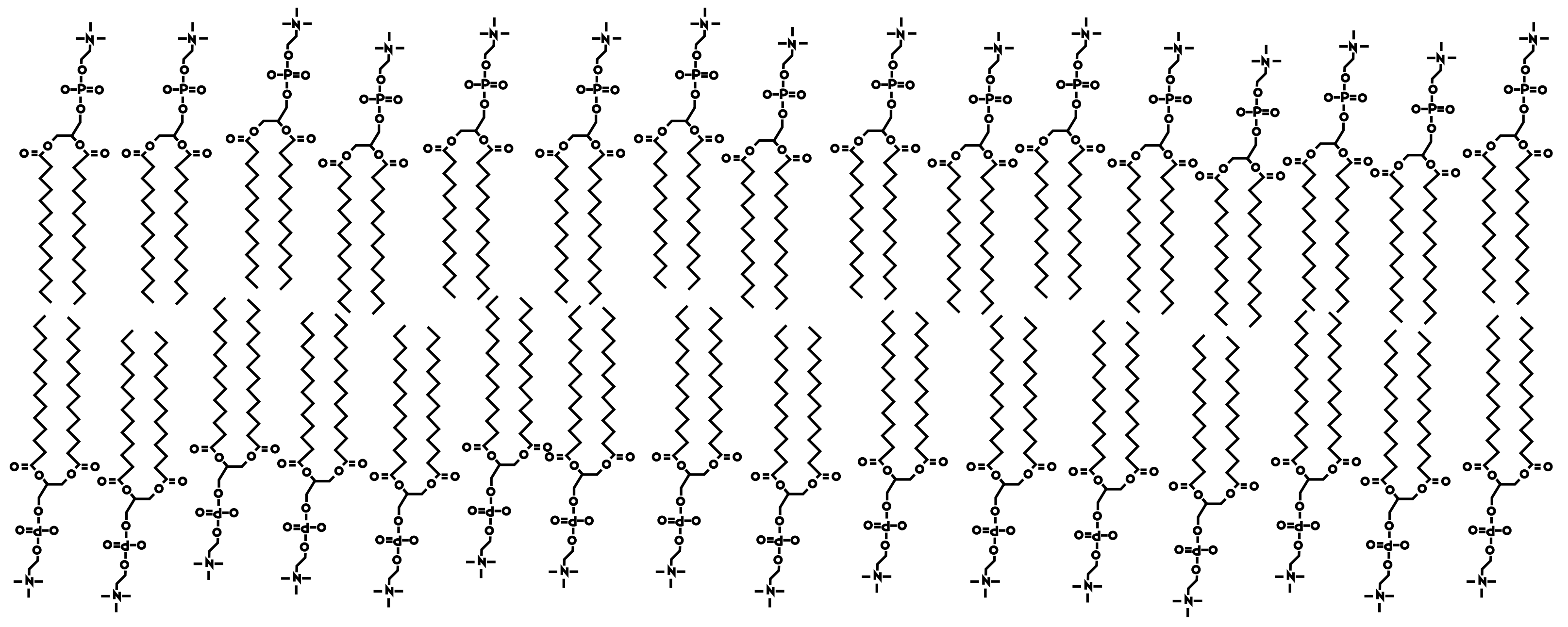
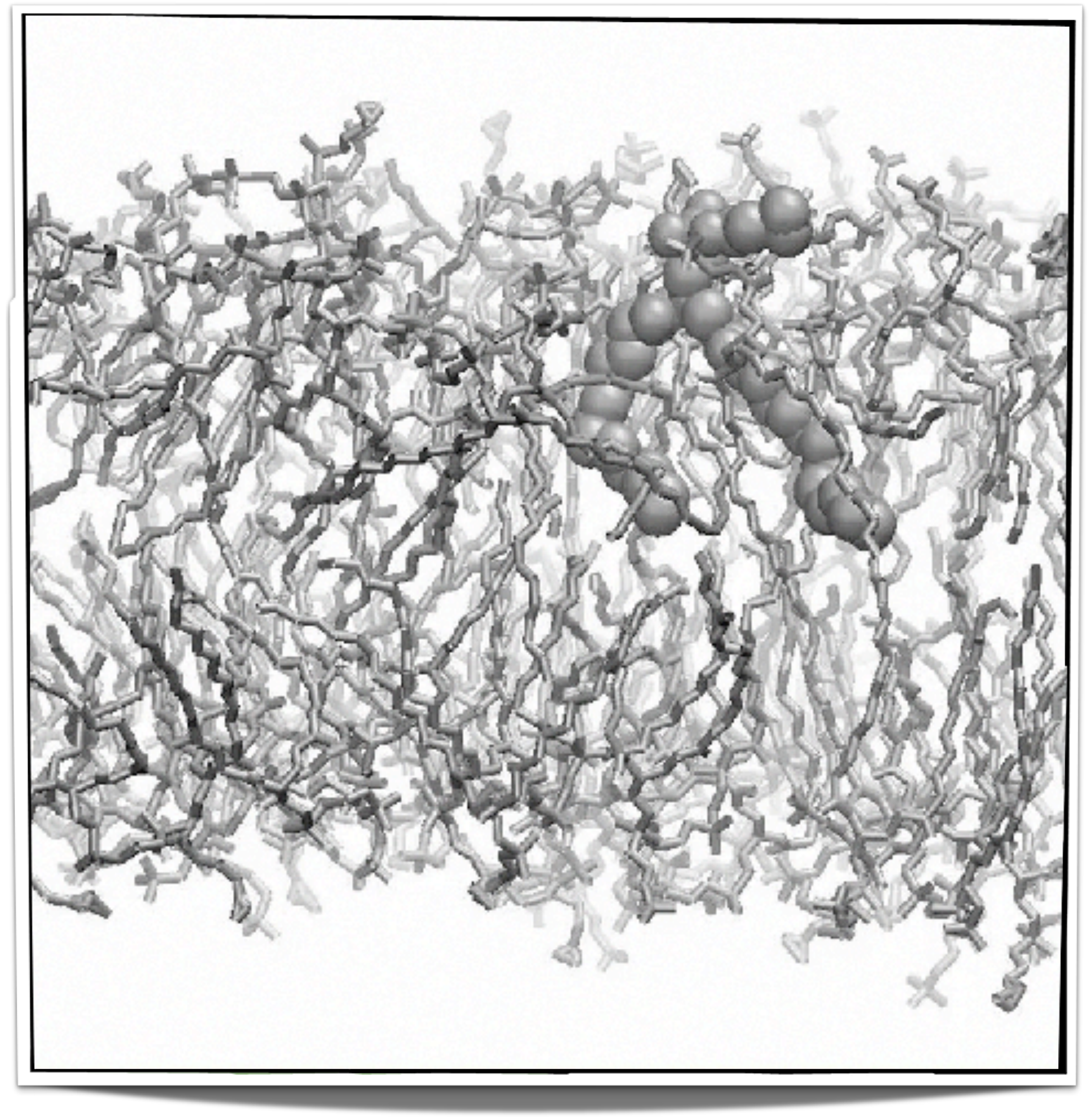


QM ?



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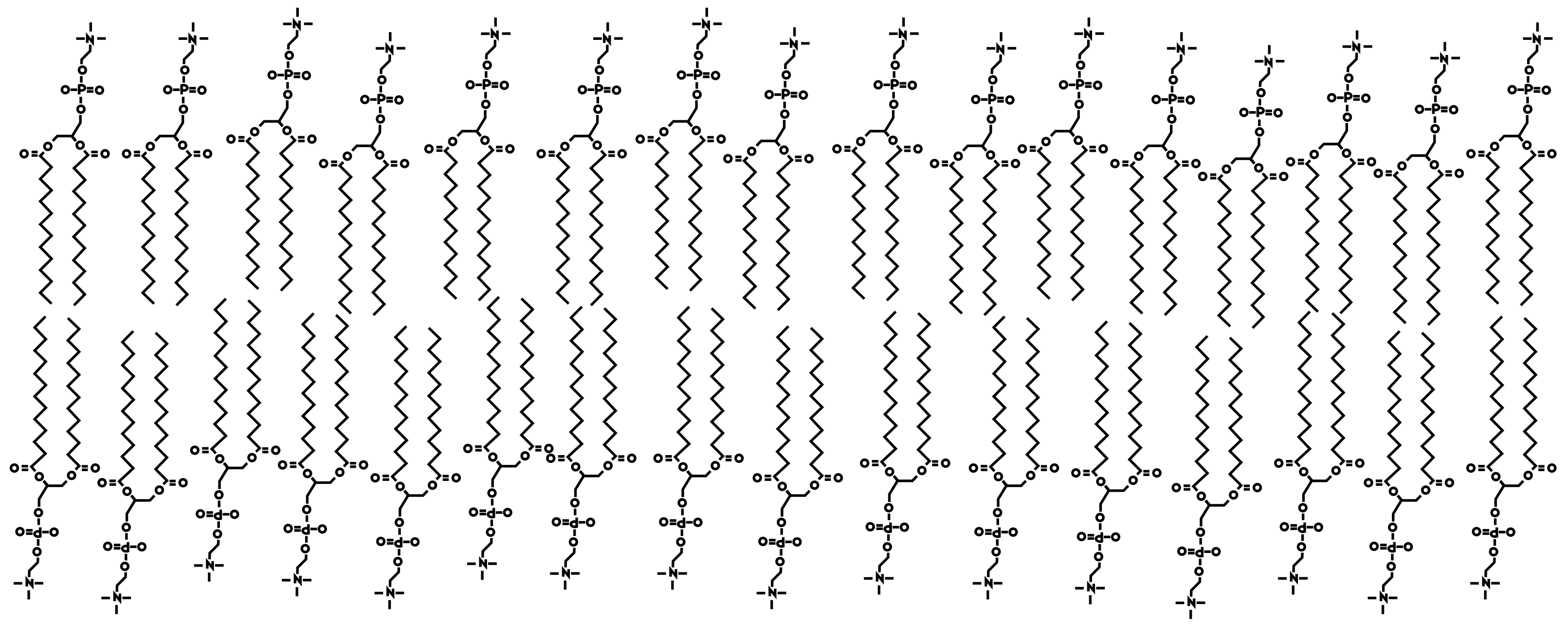

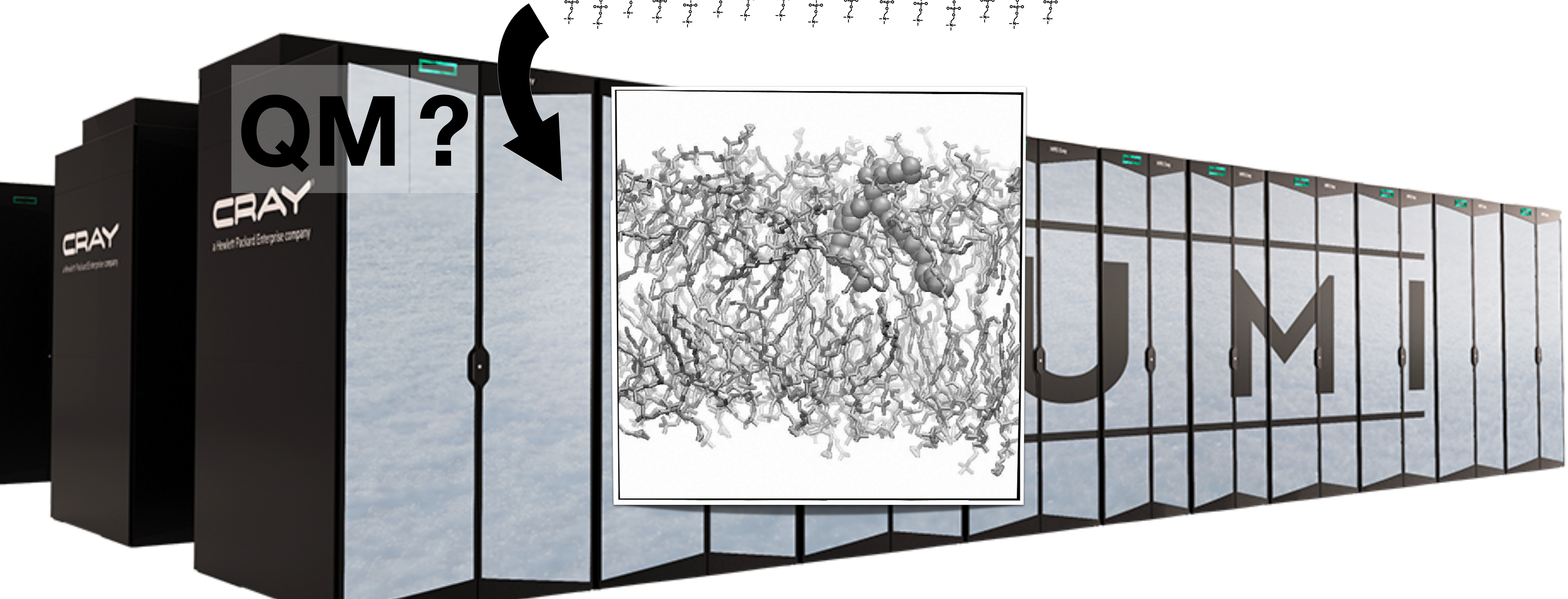

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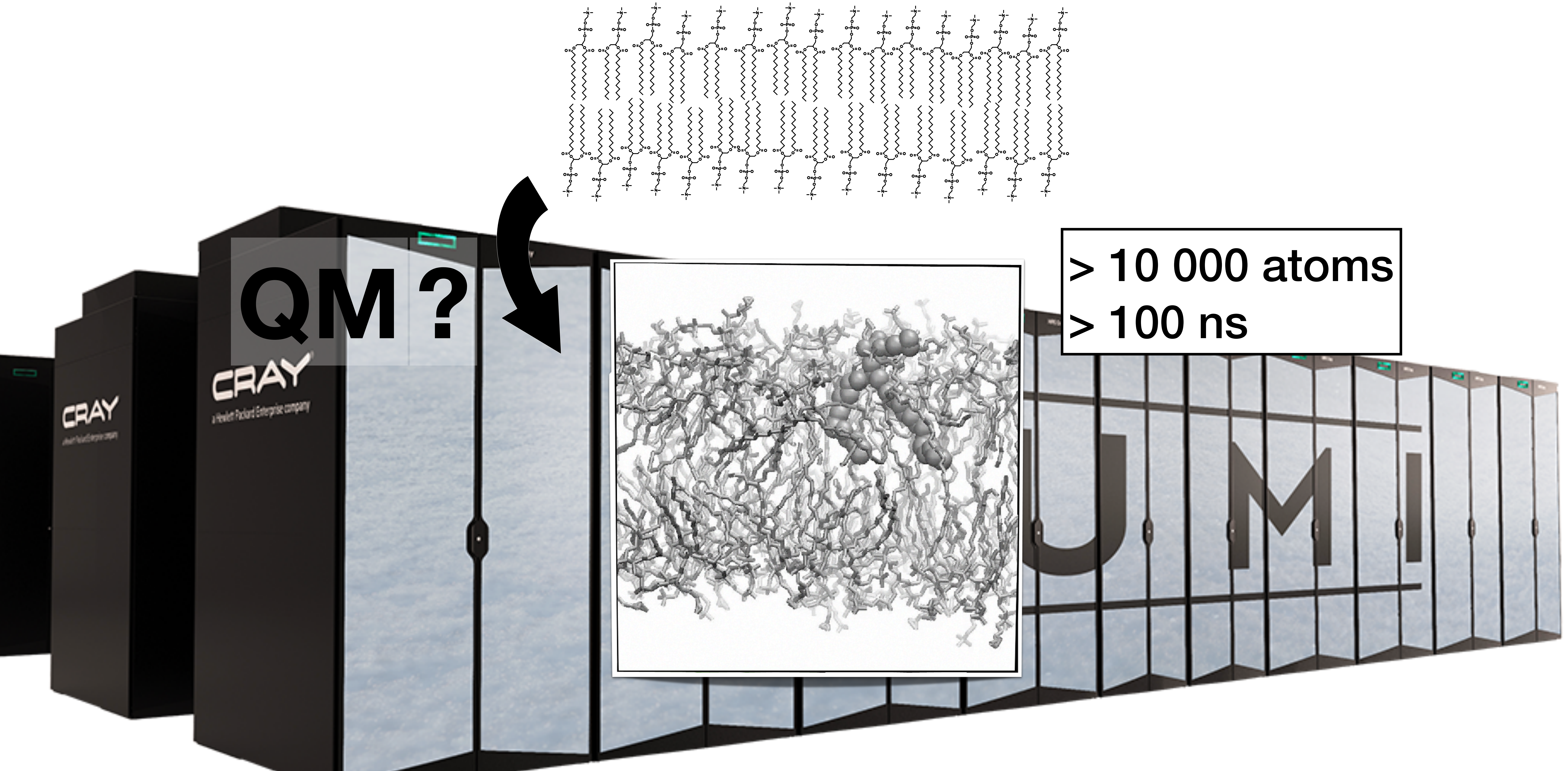

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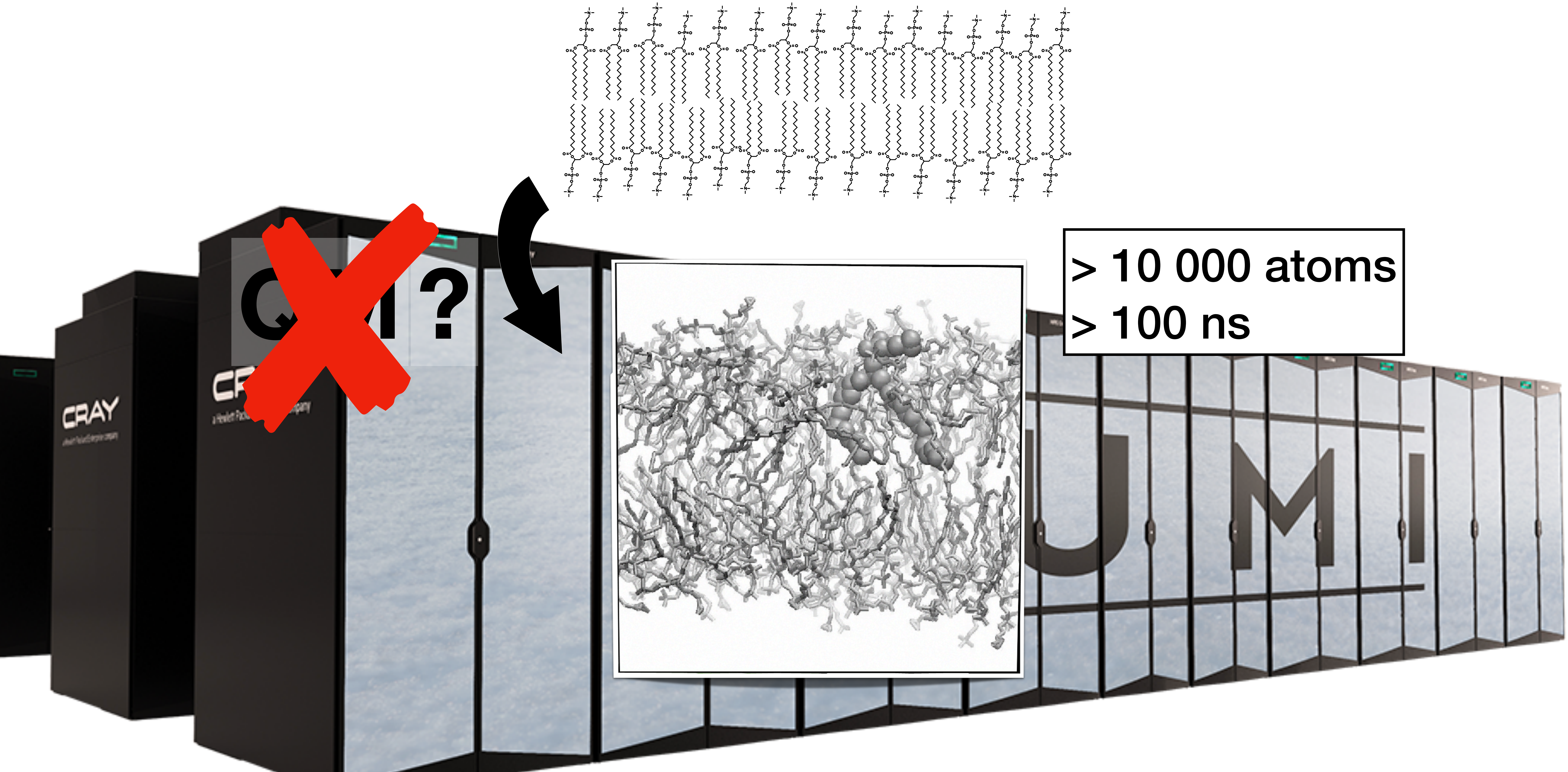

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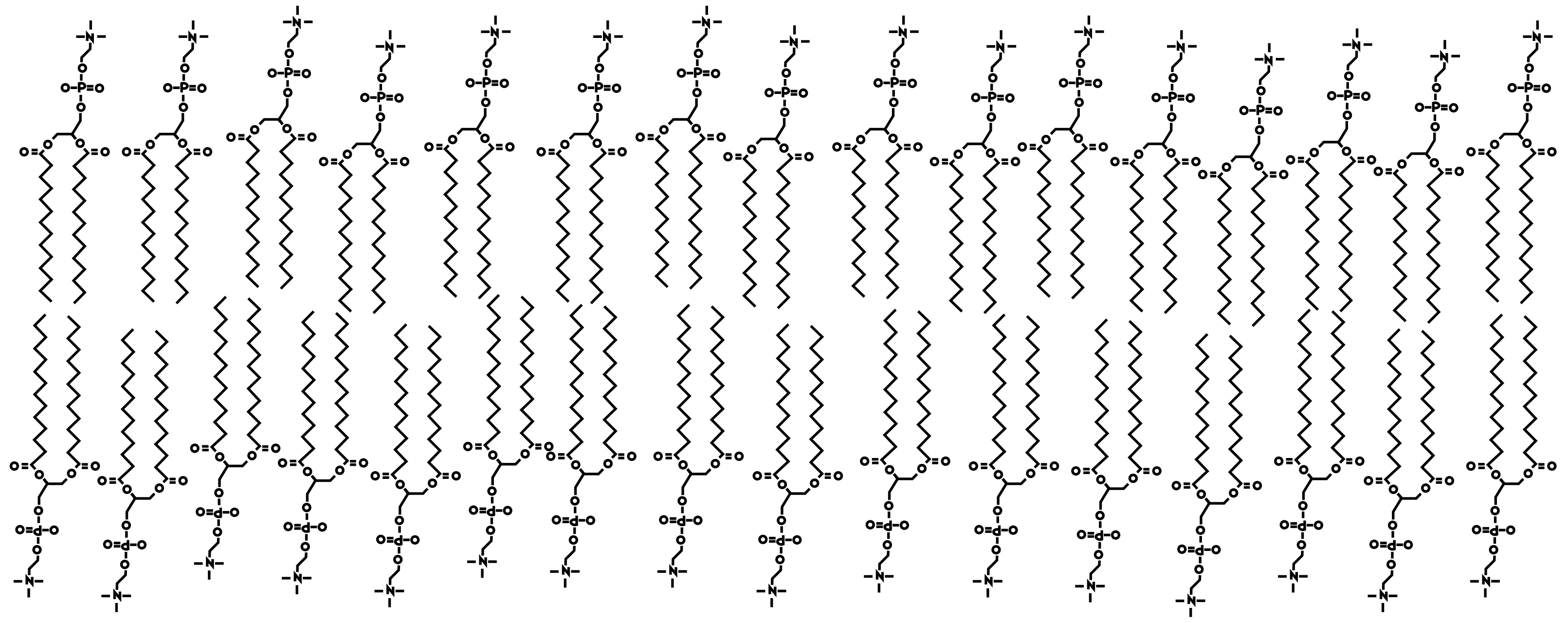
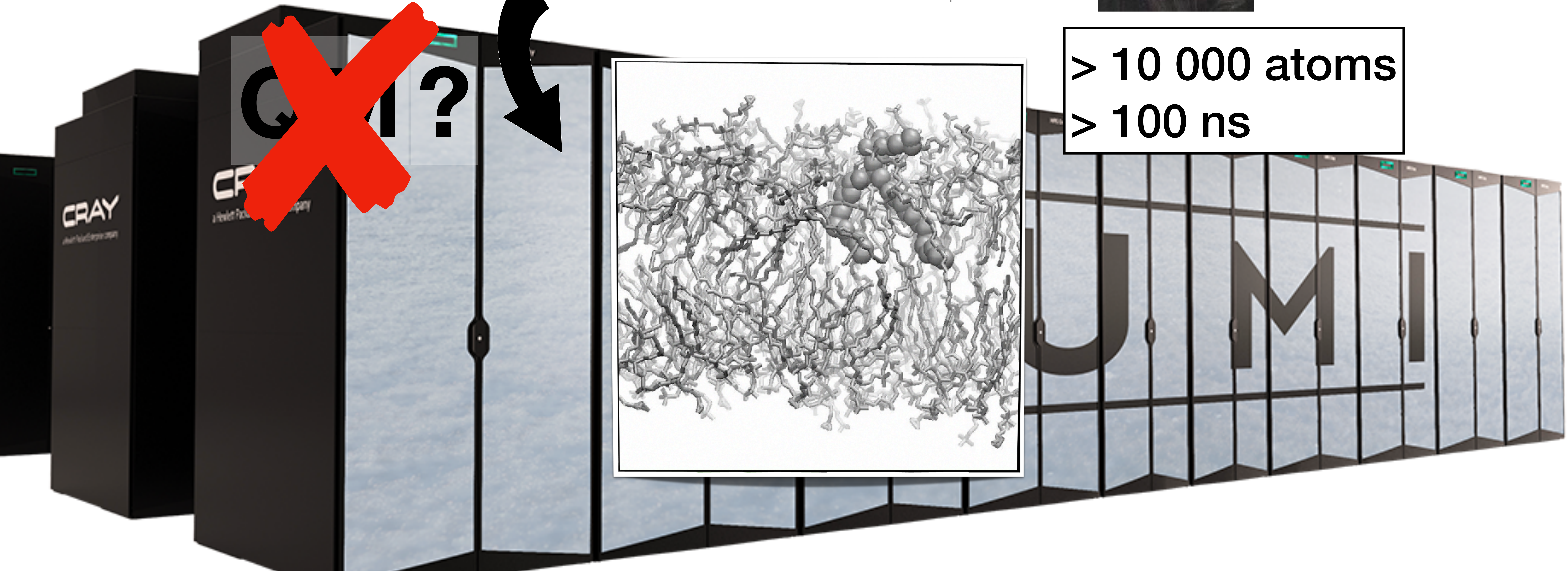


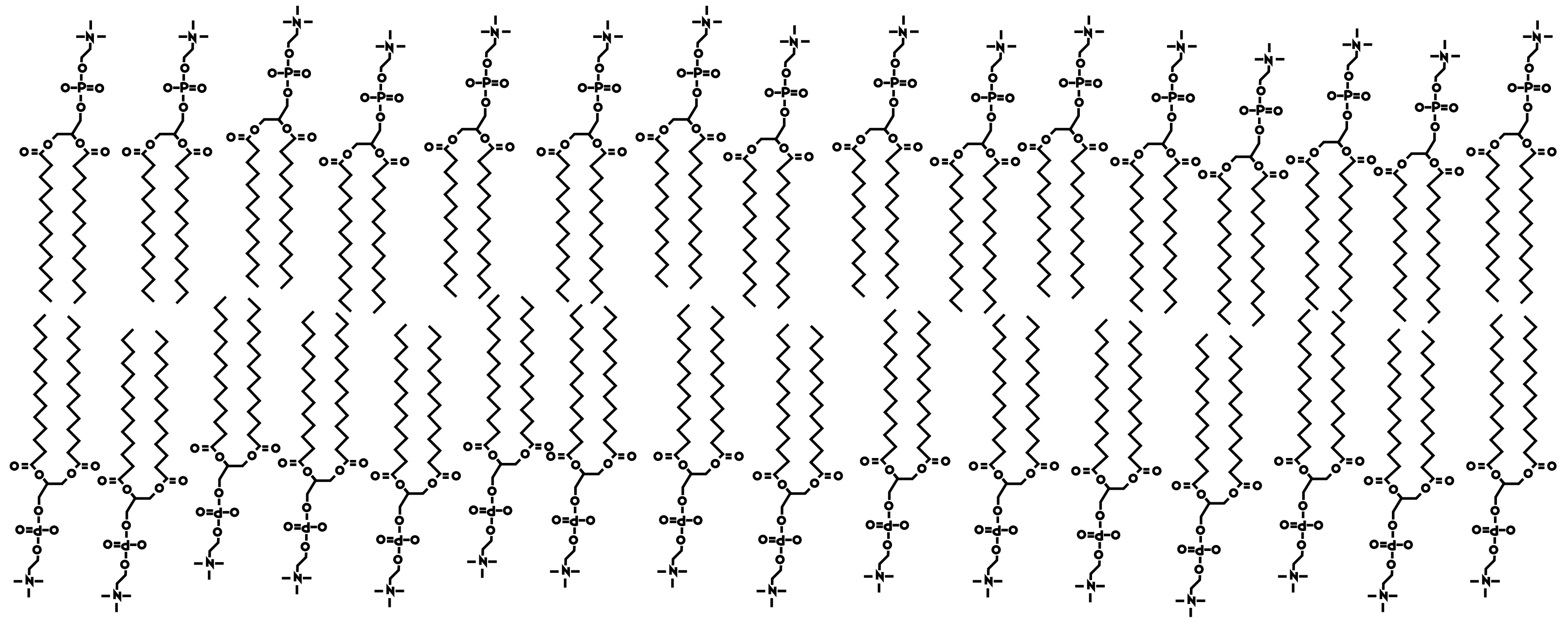
F=*ma*

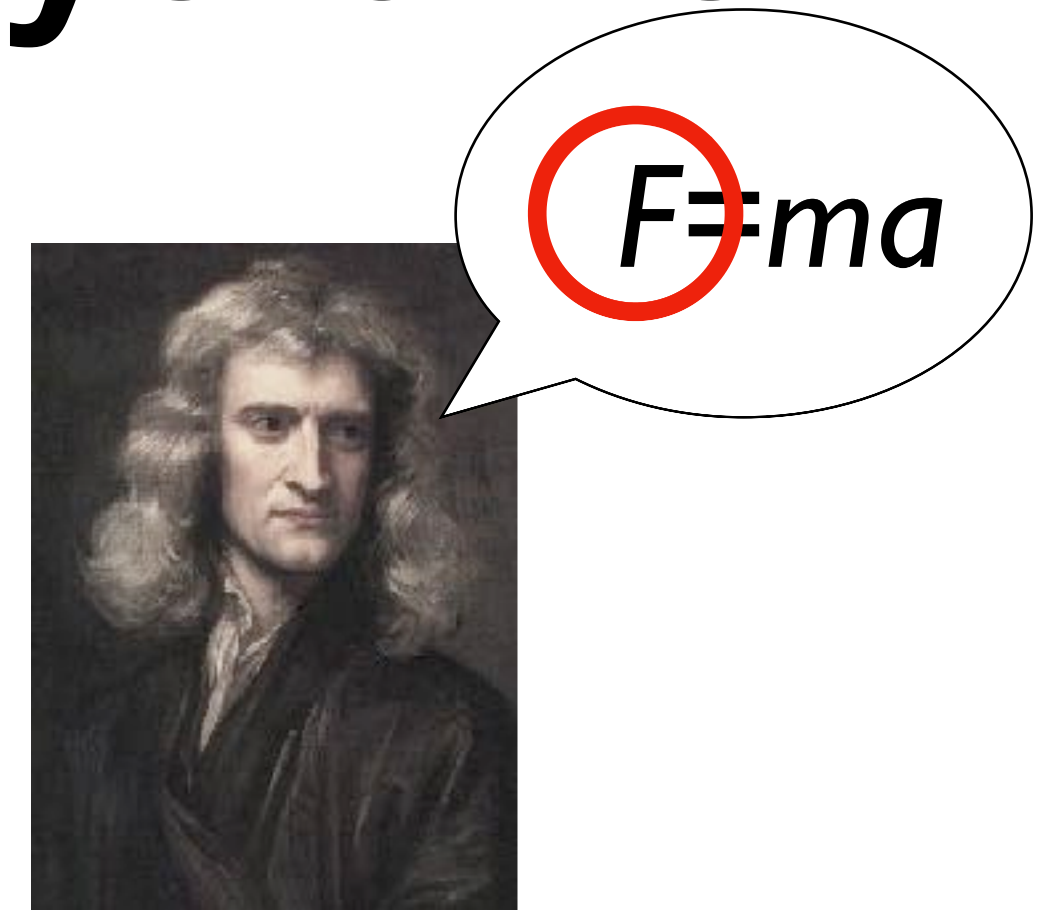
~~QM~~?

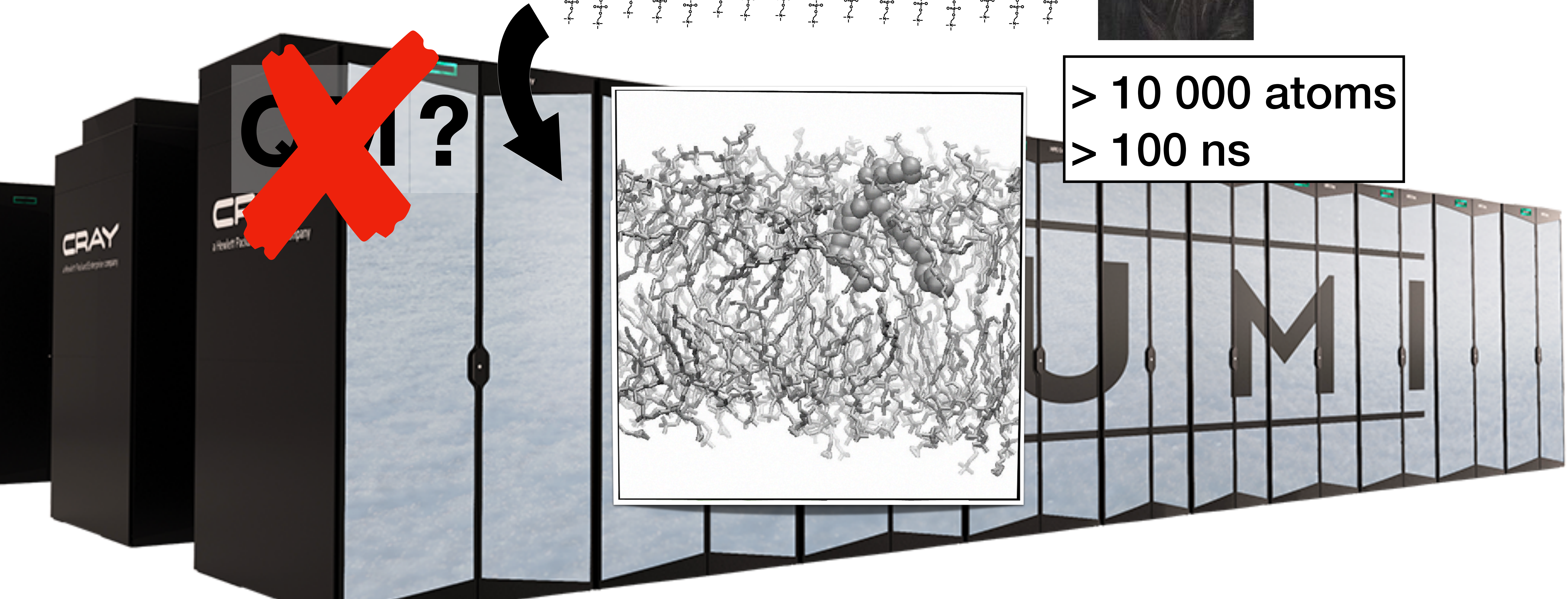


> 10 000 atoms
> 100 ns

Simulating biomolecular systems







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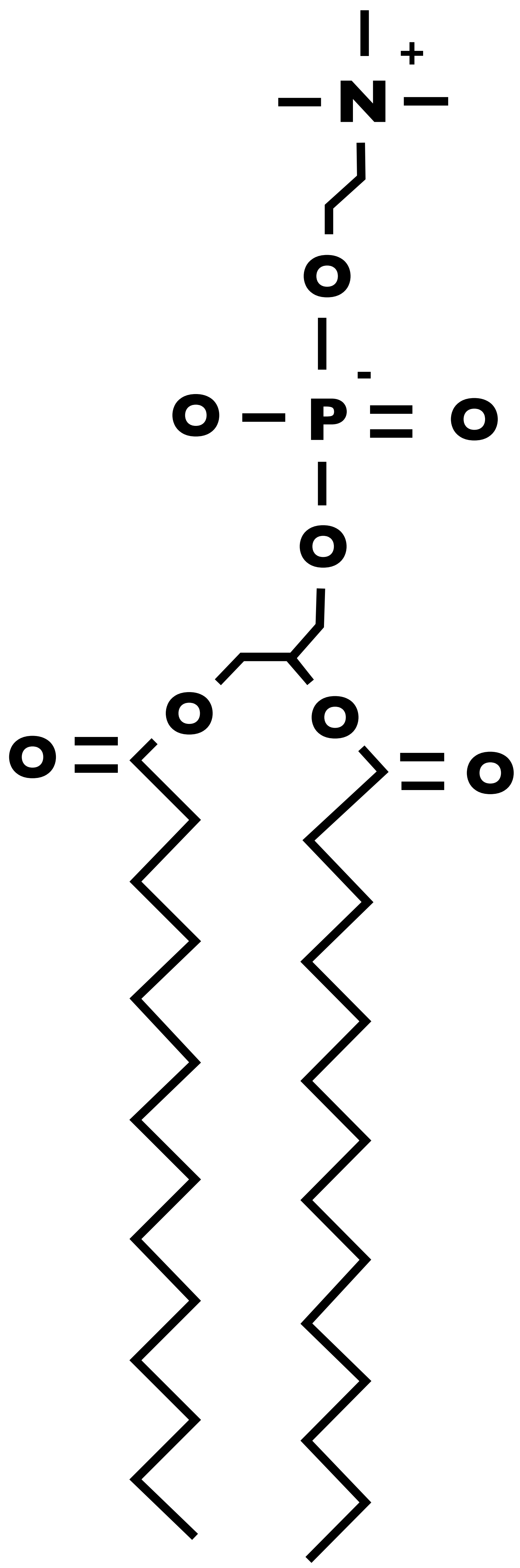
Molecular Dynamics simulations

The (inherently quantum mechanical) interactions of atoms are approximated by classical position-dependent potentials:

Molecular Dynamics simulations



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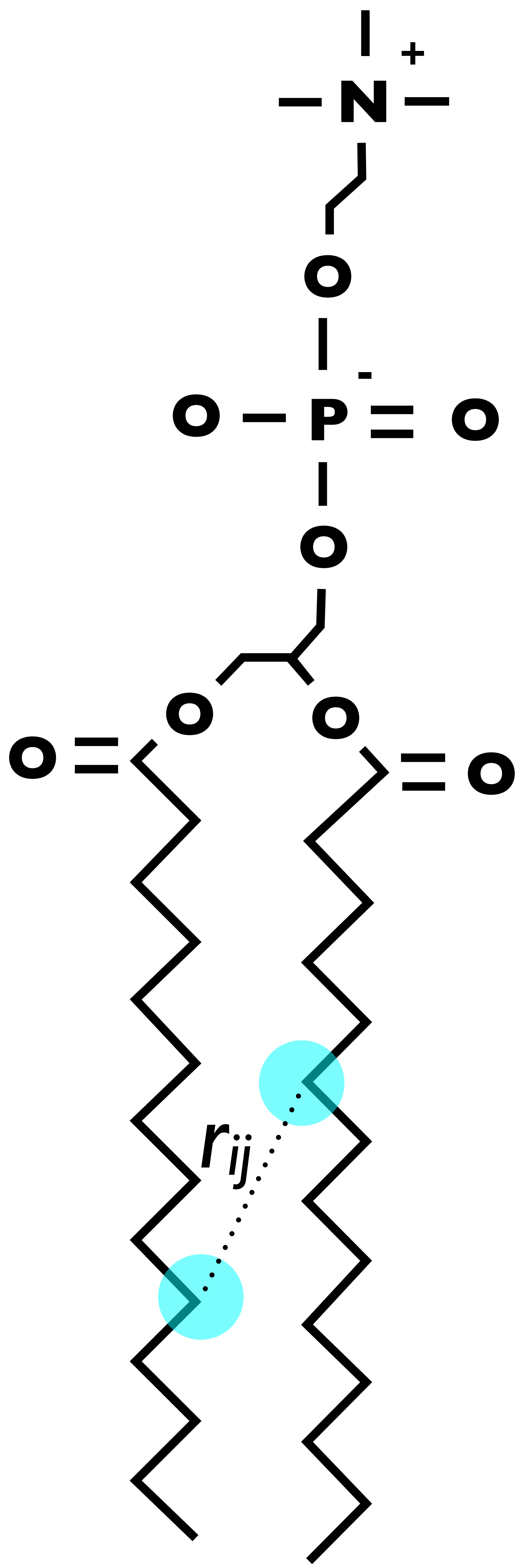

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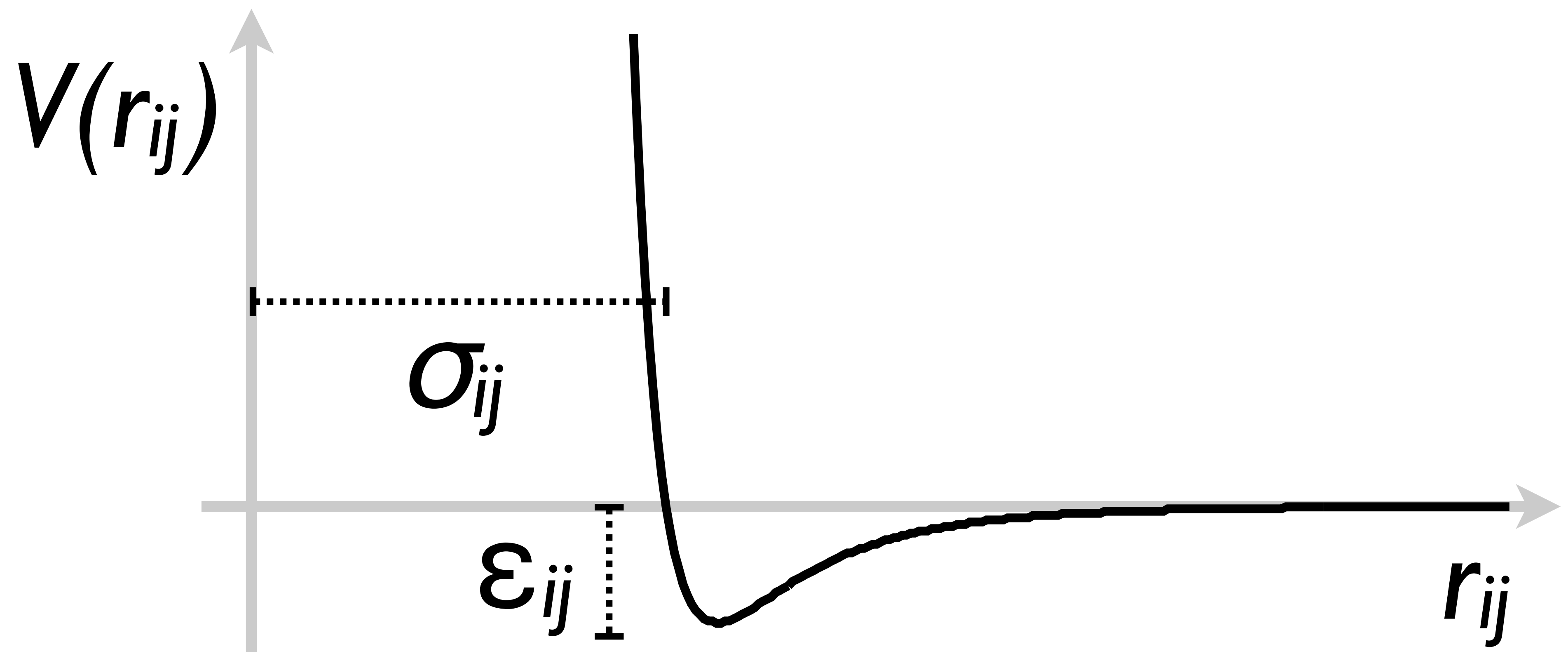
1) non-bonded interactions



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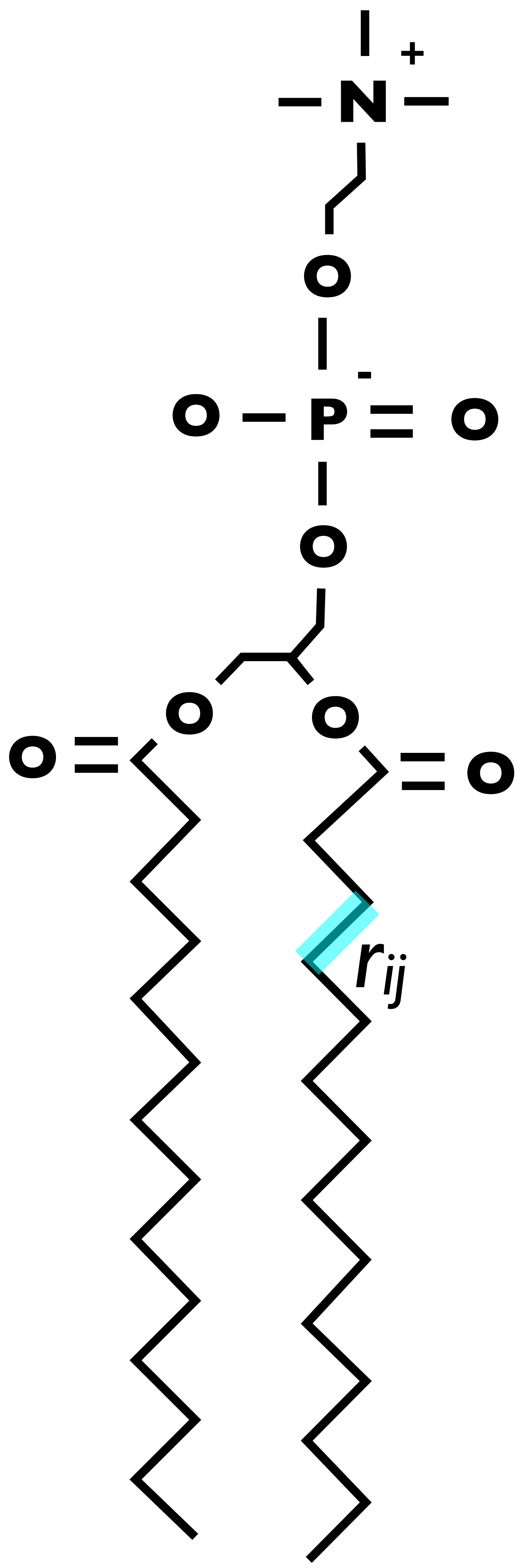
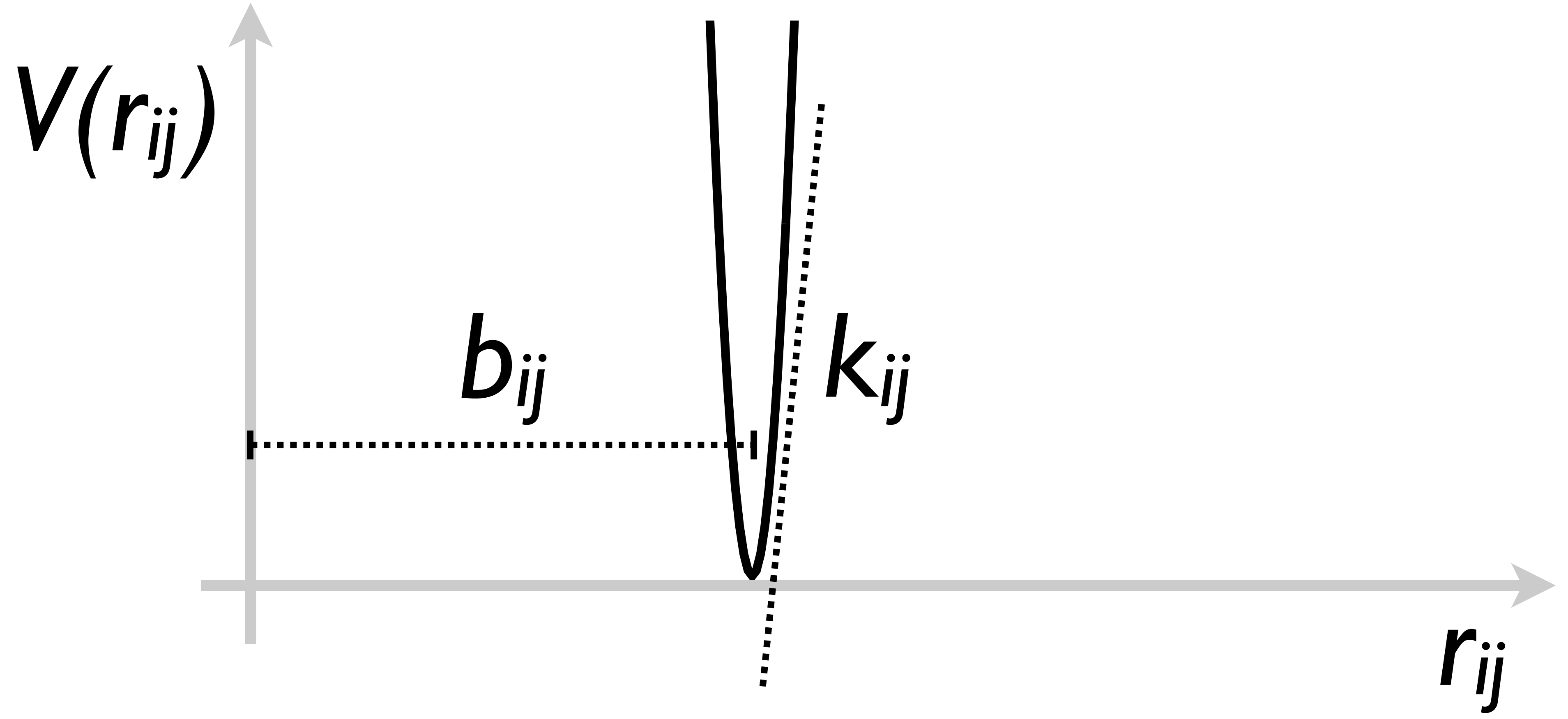


The (inherently <u>quantum mechanical</u>) interactions of atoms are approximated by <u>classical</u> position-dependent potentials:

1) non-bonded interactions

2) bonds



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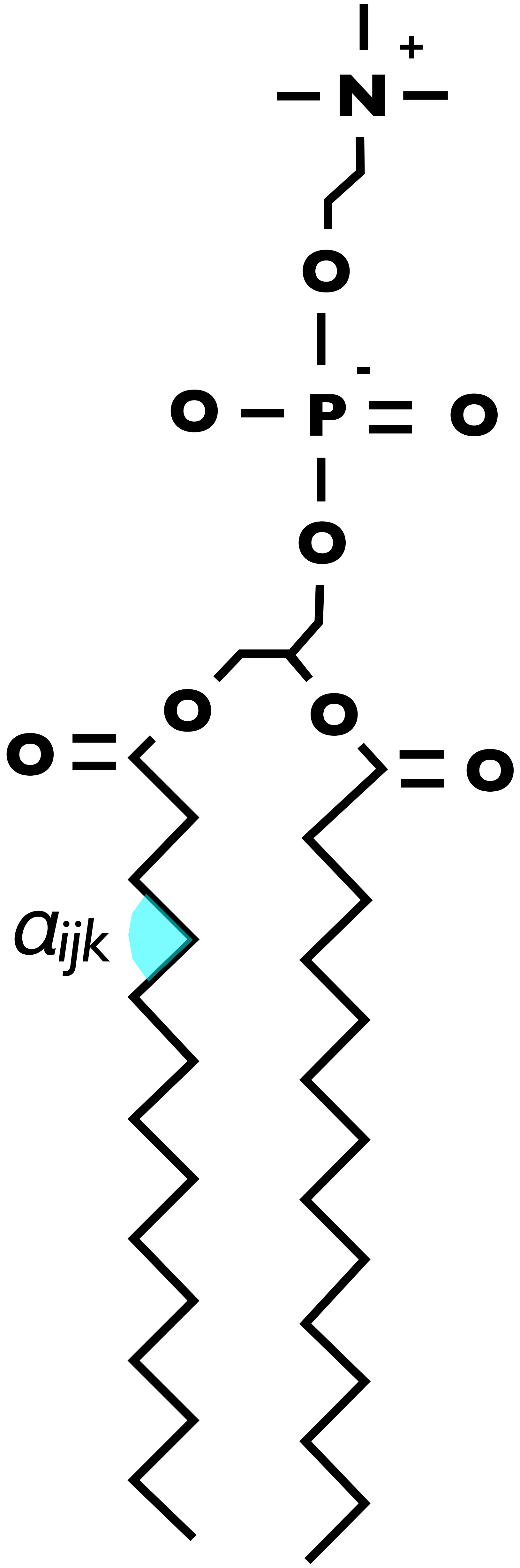

The (inherently quantum mechanical) interactions of atoms are approximated by classical position-dependent potentials:

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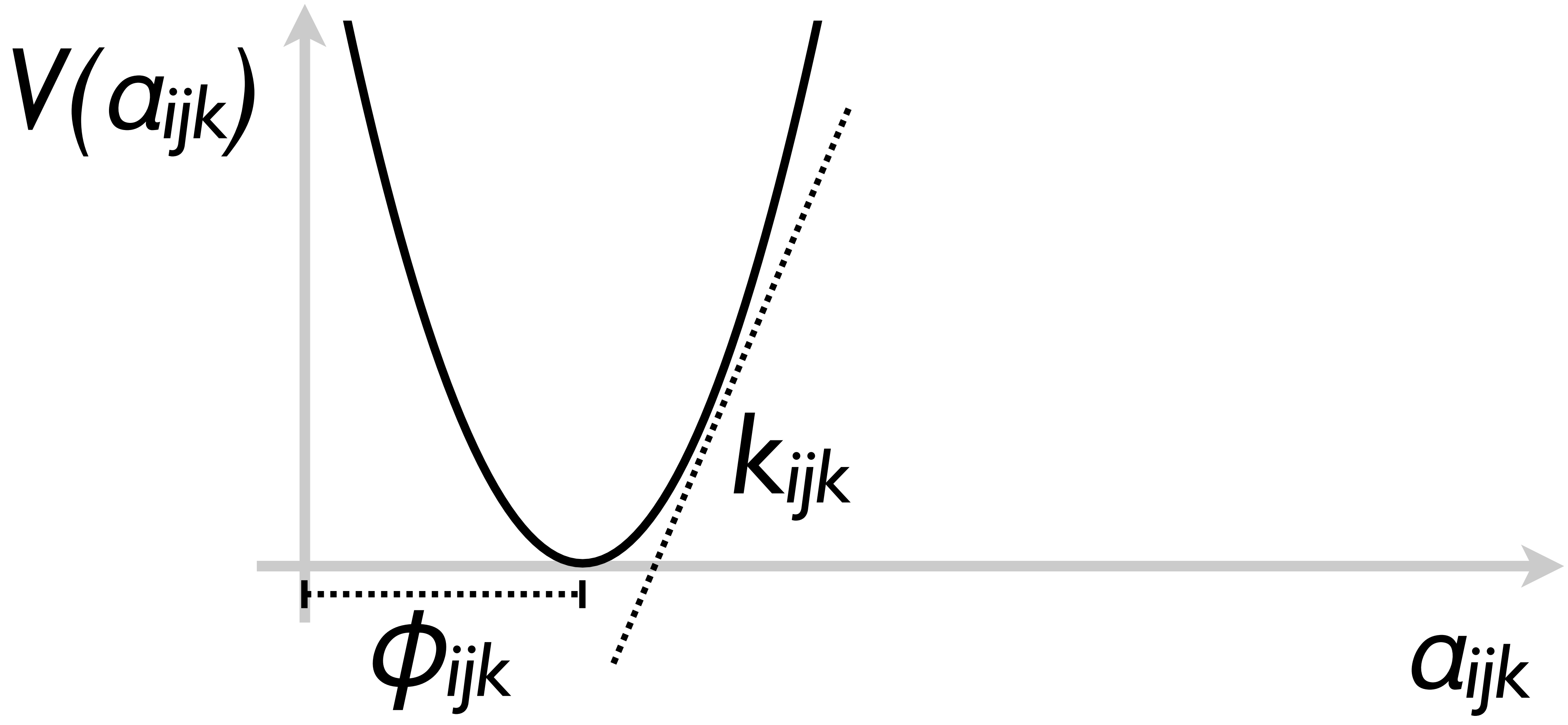
3) angles



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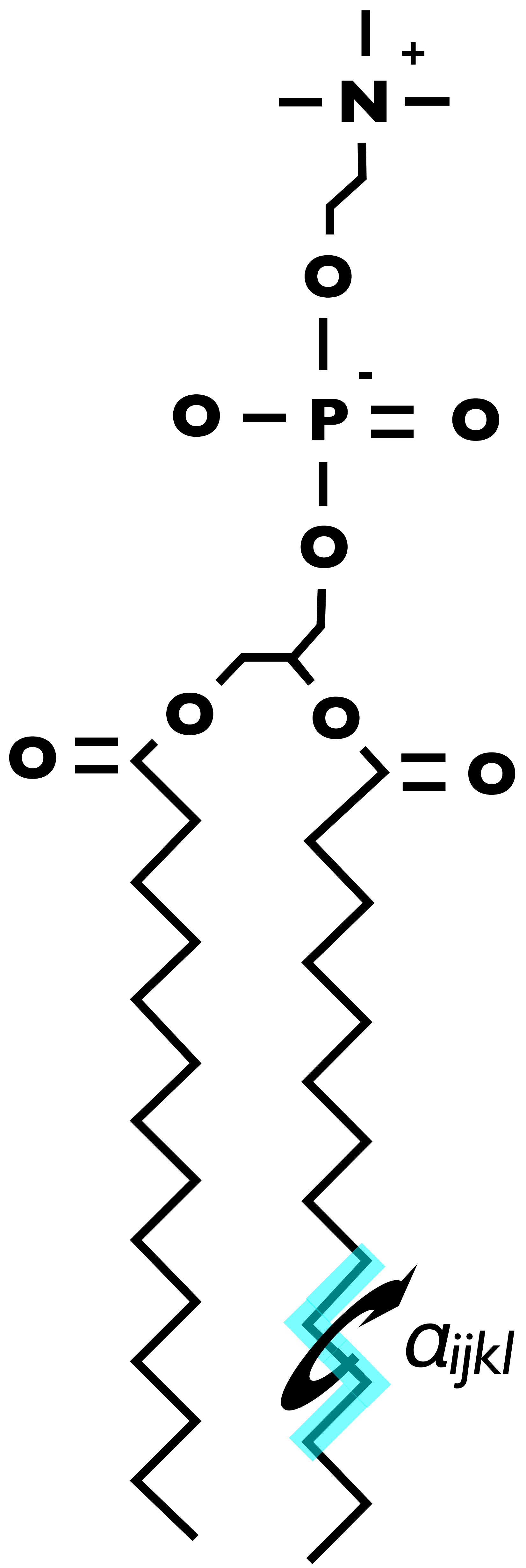
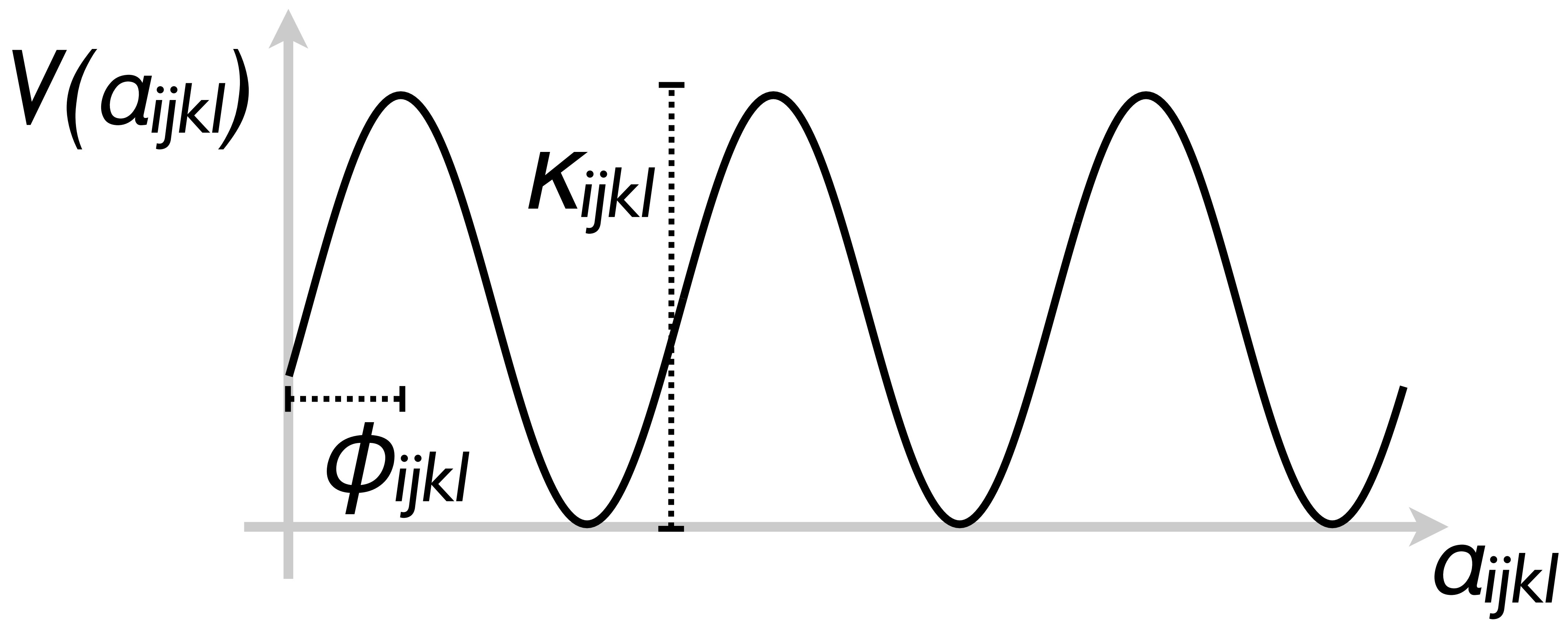


The (inherently quantum mechanical) interactions of atoms are approximated by classical position-dependent potentials:

1) non-bonded interactions
2) bonds
3) angles
4) torsions (dihedrals)



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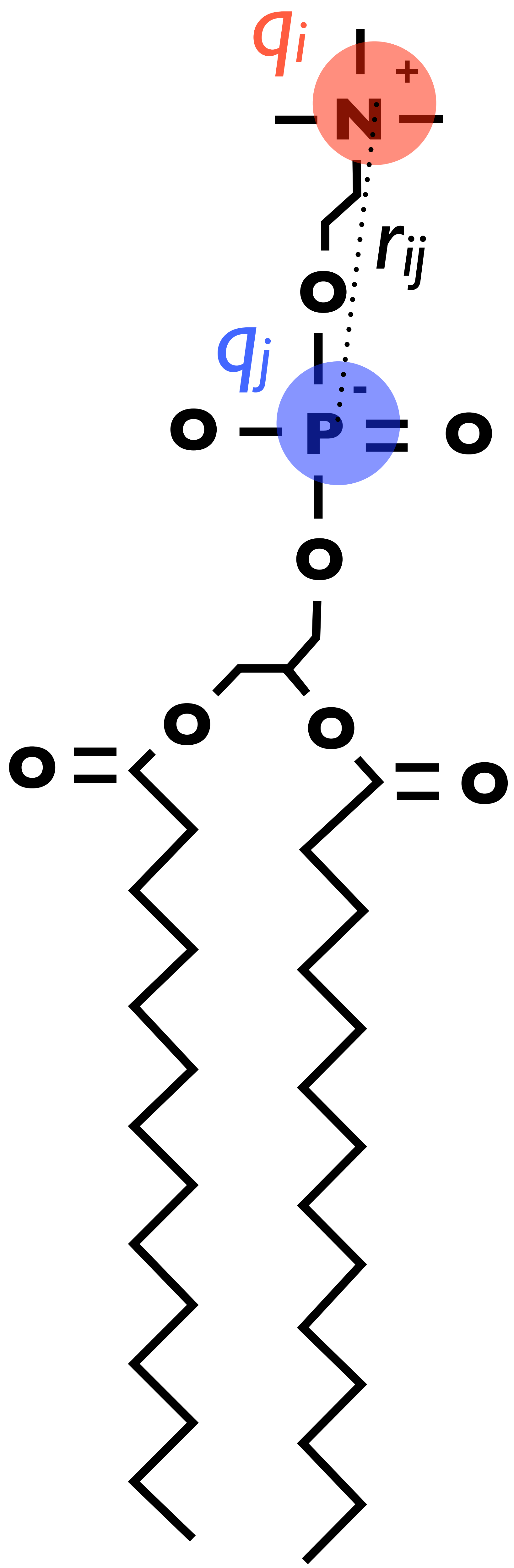

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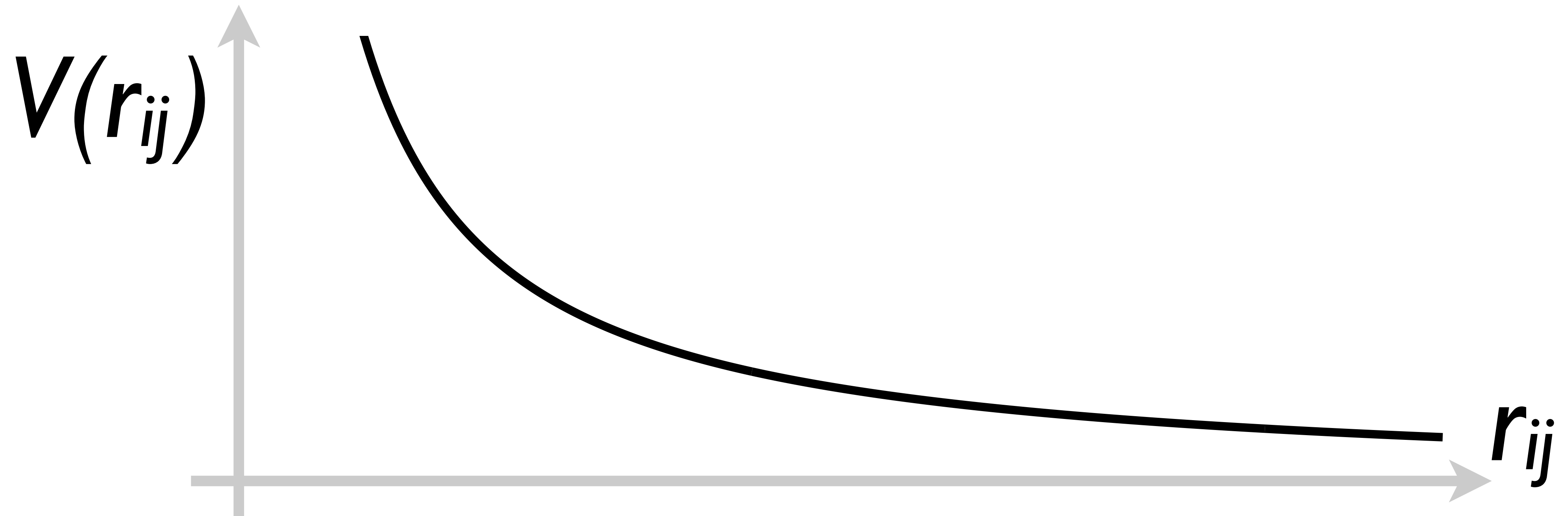

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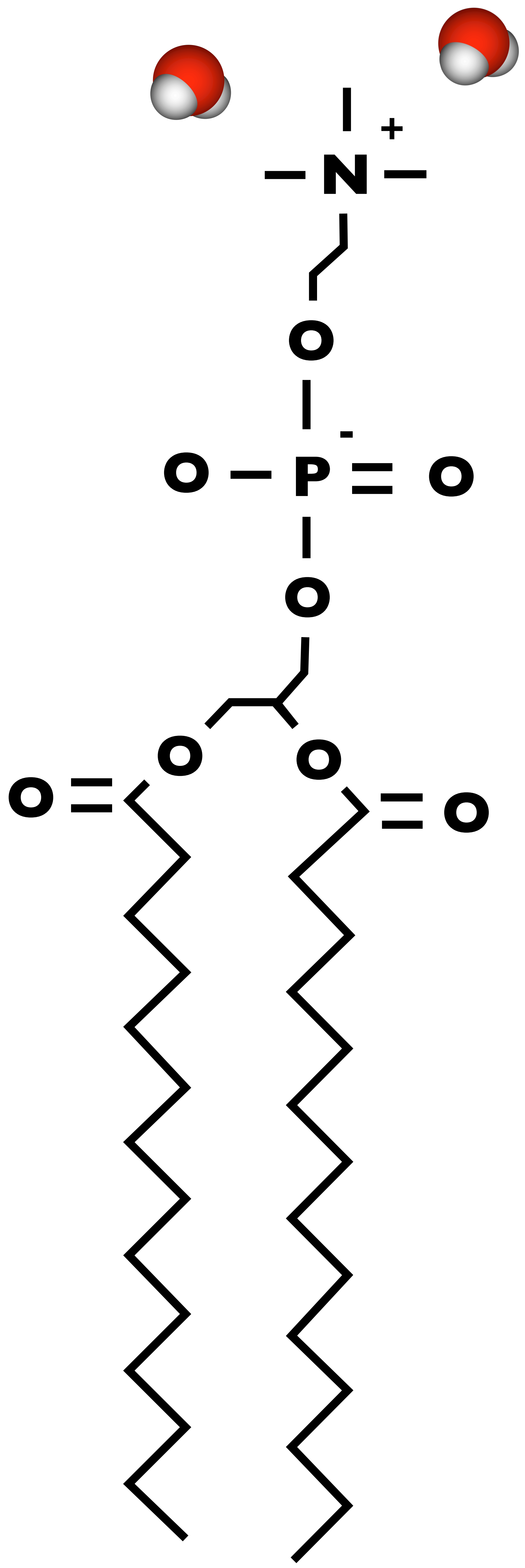

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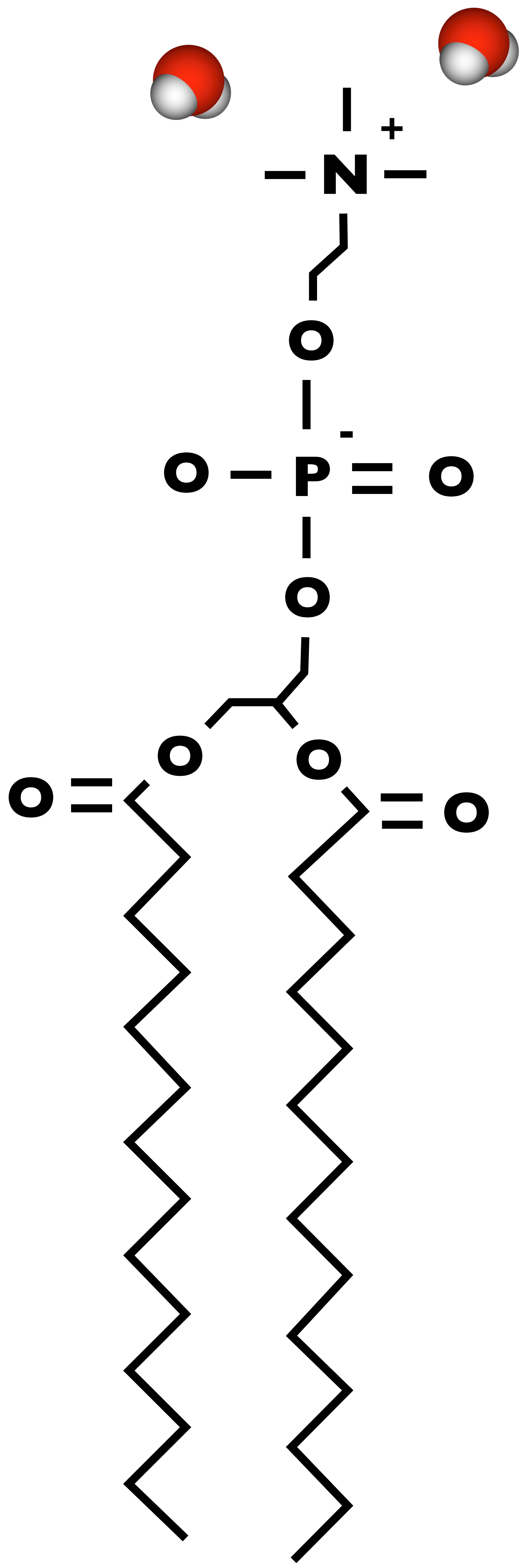

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'Force field'

(> 100 parameters)

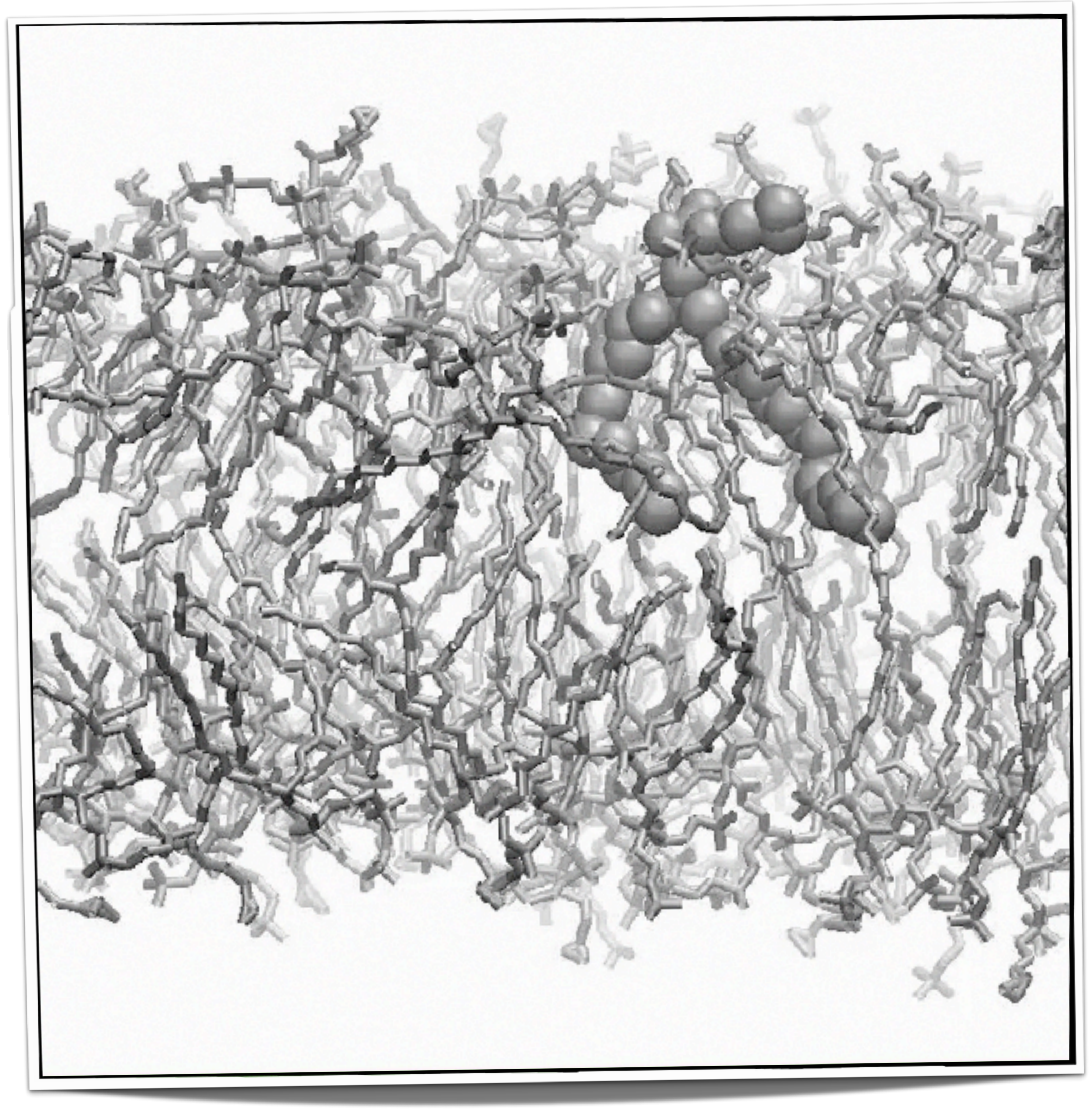
Three commonly known facts about **force fields**:

1. They determine all the molecular detail.

2. None of them is perfect.

3. Testing and developing them is hard work — and hard to fund.

So you do get this:



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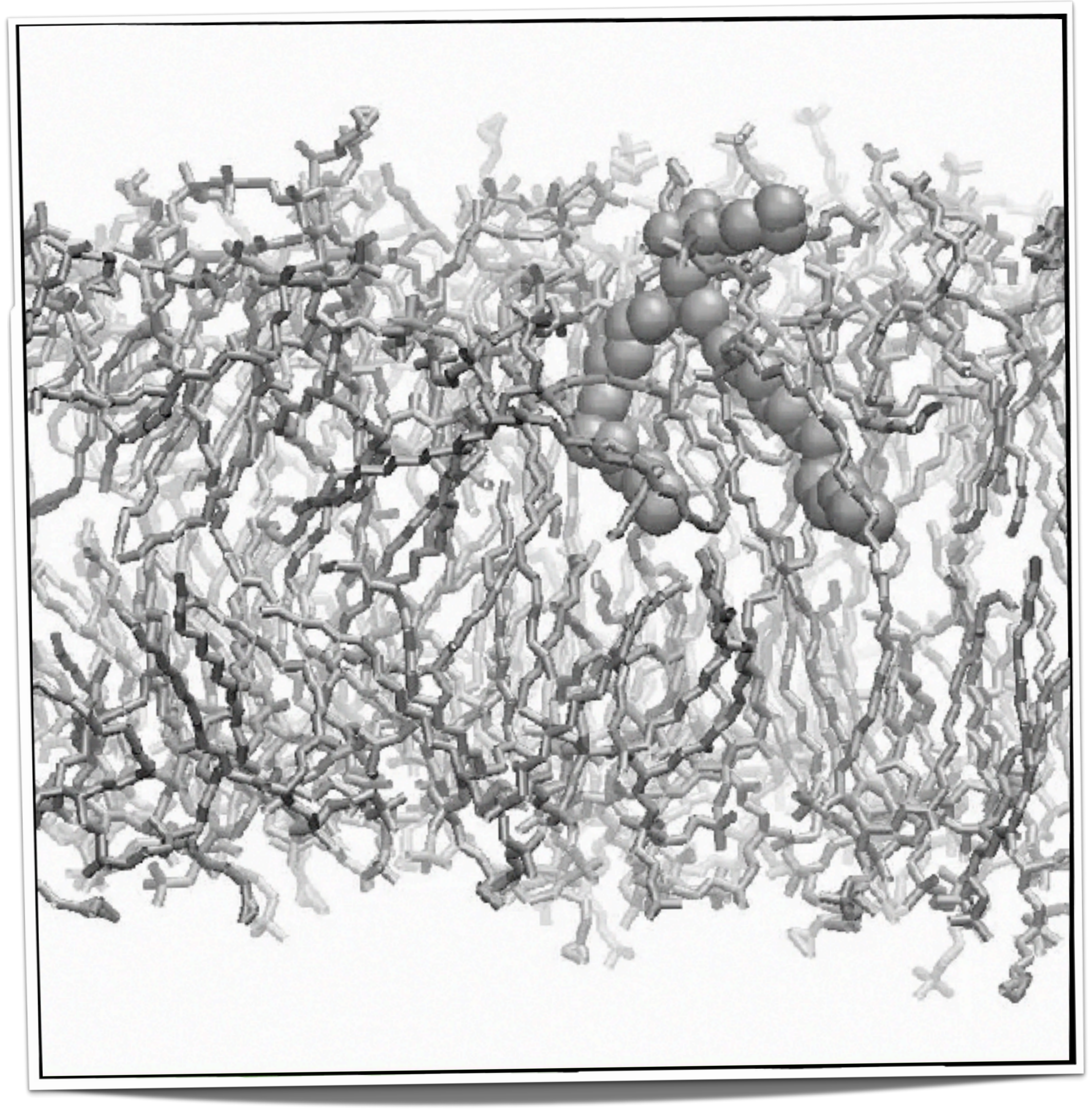

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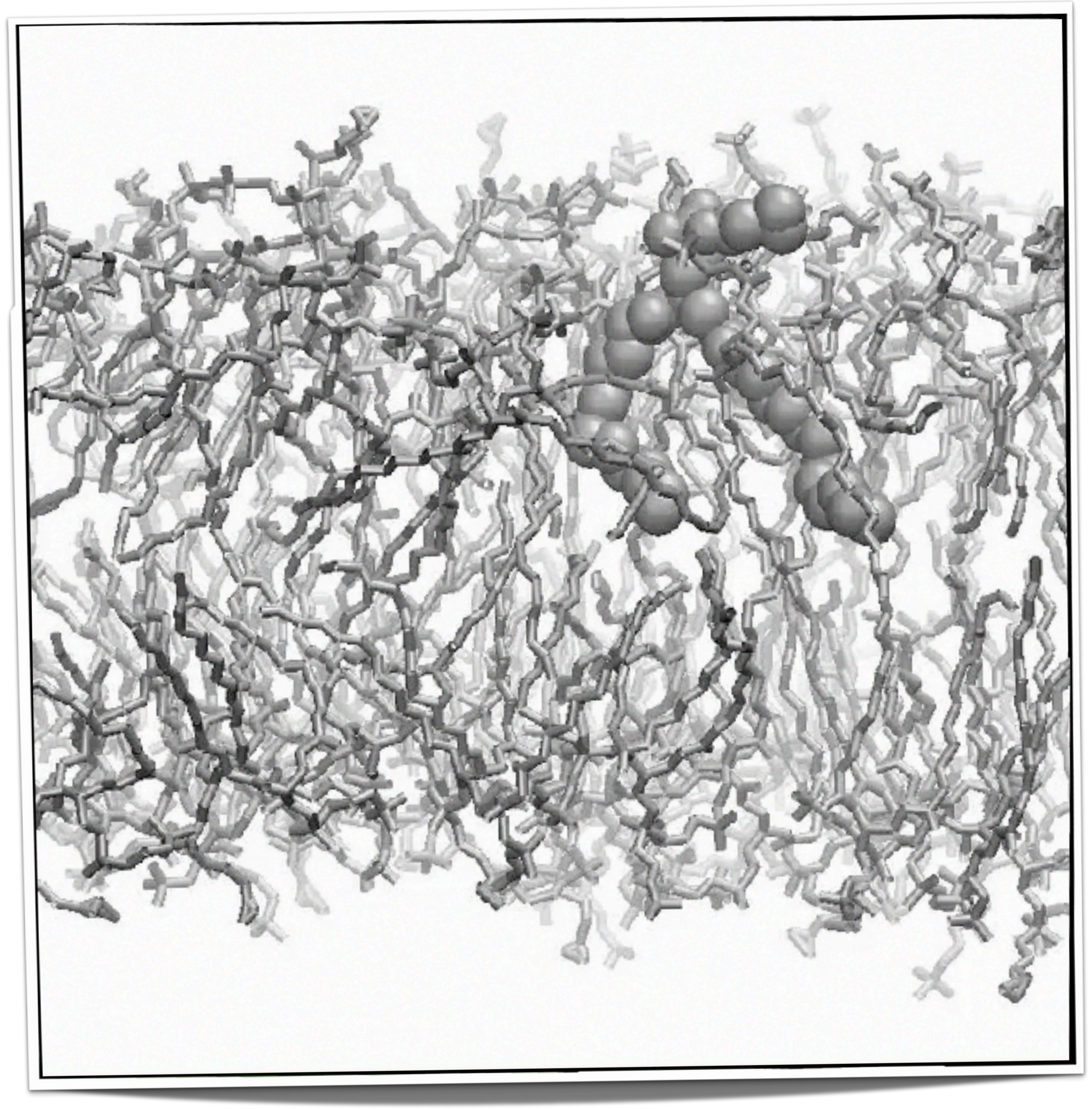

But is it what actually happens?

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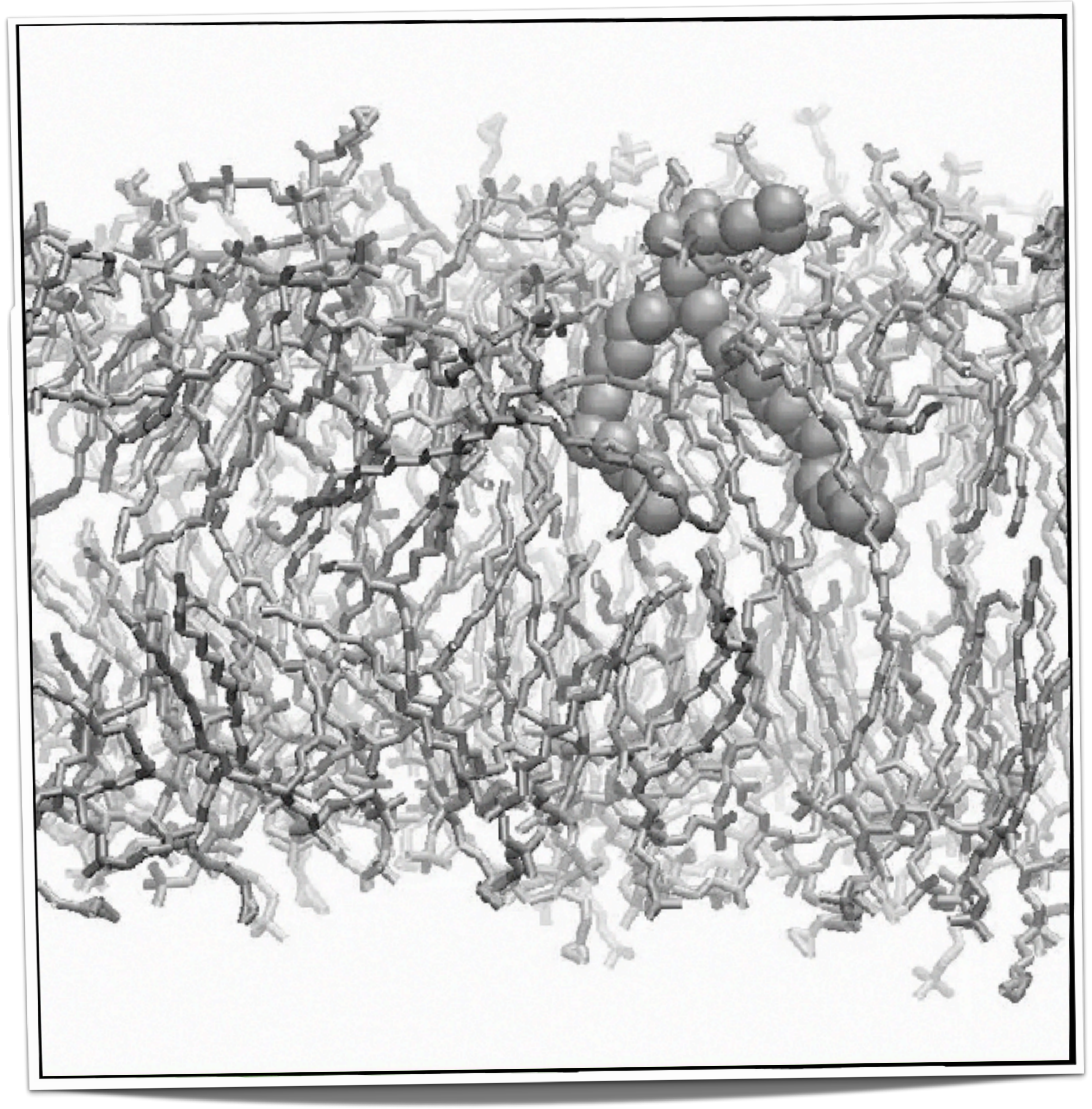

But is it what actually happens?

No, not quite. But more on this at 16:30.

Time integration, or
“How do you make them move?”

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First guess: Would just a Taylor expansion in time work?

$$x(t+\Delta) = x(t) + x'(t)\Delta + (x''(t)/2)\Delta^2$$

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$$x(t+\Delta) = x(t) + x'(t)\Delta + (x''(t)/2)\Delta^2$$
$$= x(t) + v(t)\Delta + (F(t)/2m)\Delta^2$$

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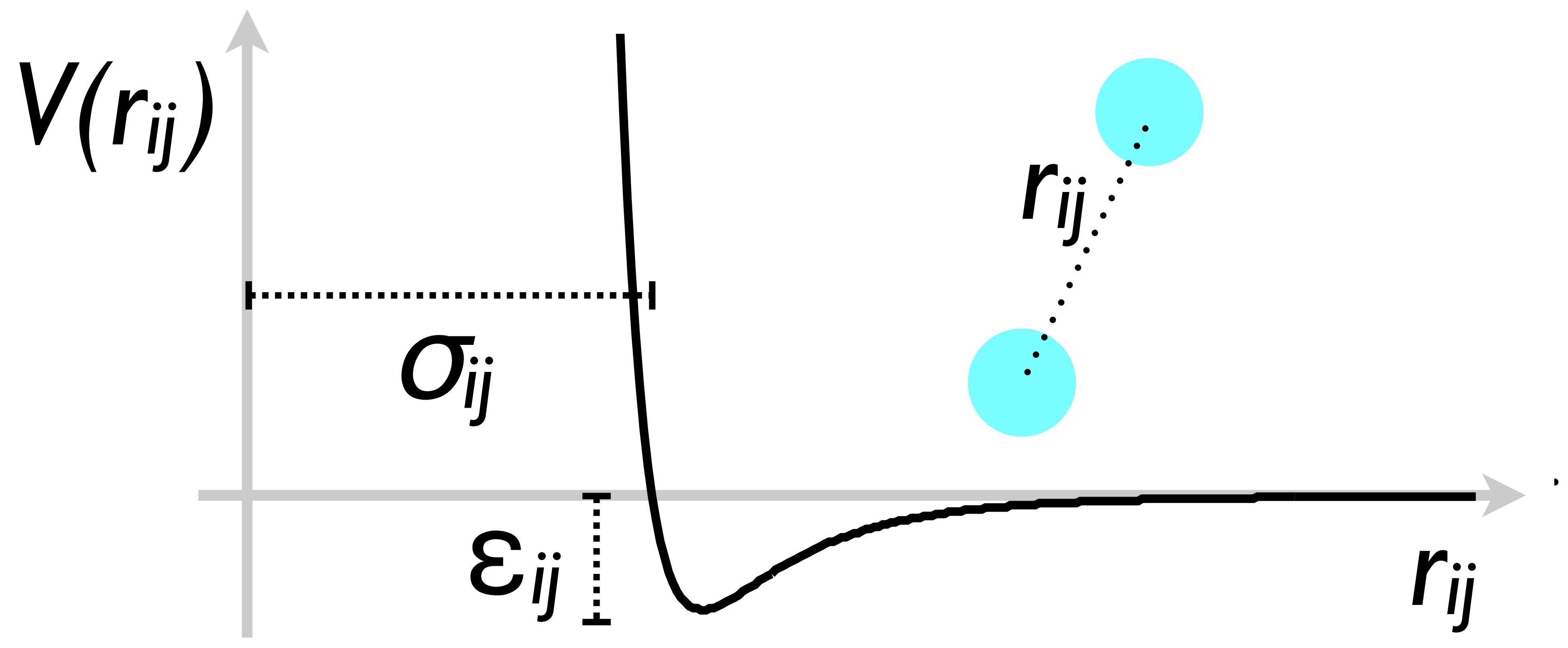

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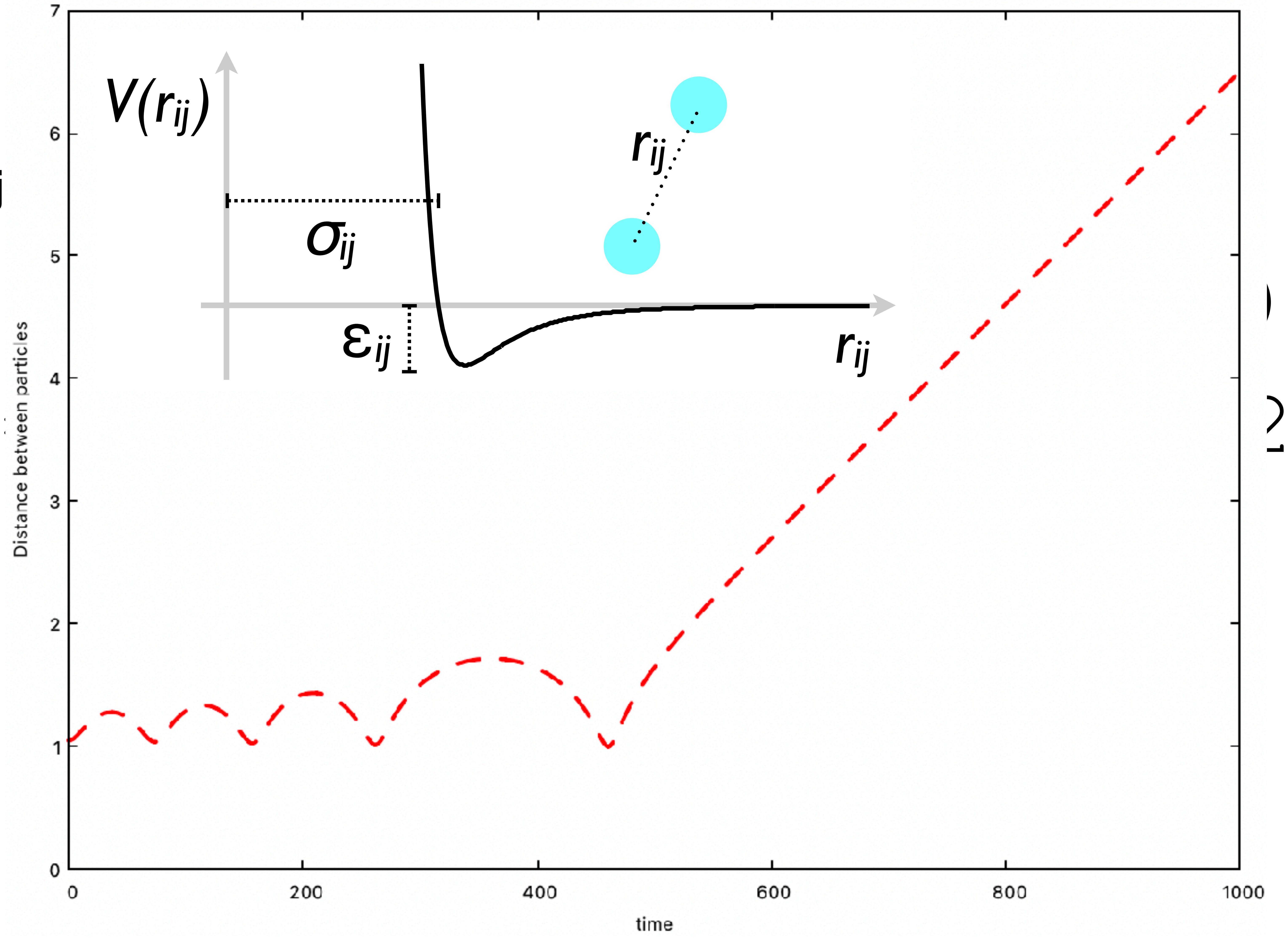
x(t+Δ)

) /2) Δ^2

2m) Δ^2



Time integration, or "How do you make them move?"

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$$x(t+\Delta) = x(t) + \cancel{x'(t)\Delta} + (x''(t)/2)\Delta^2$$

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Second guess:

$$x(t+\Delta) = x(t) + v(t)\Delta + (F(t)/2m)\Delta^2$$
$$x(t-\Delta) = x(t) - v(t)\Delta + (F(t)/2m)\Delta^2$$

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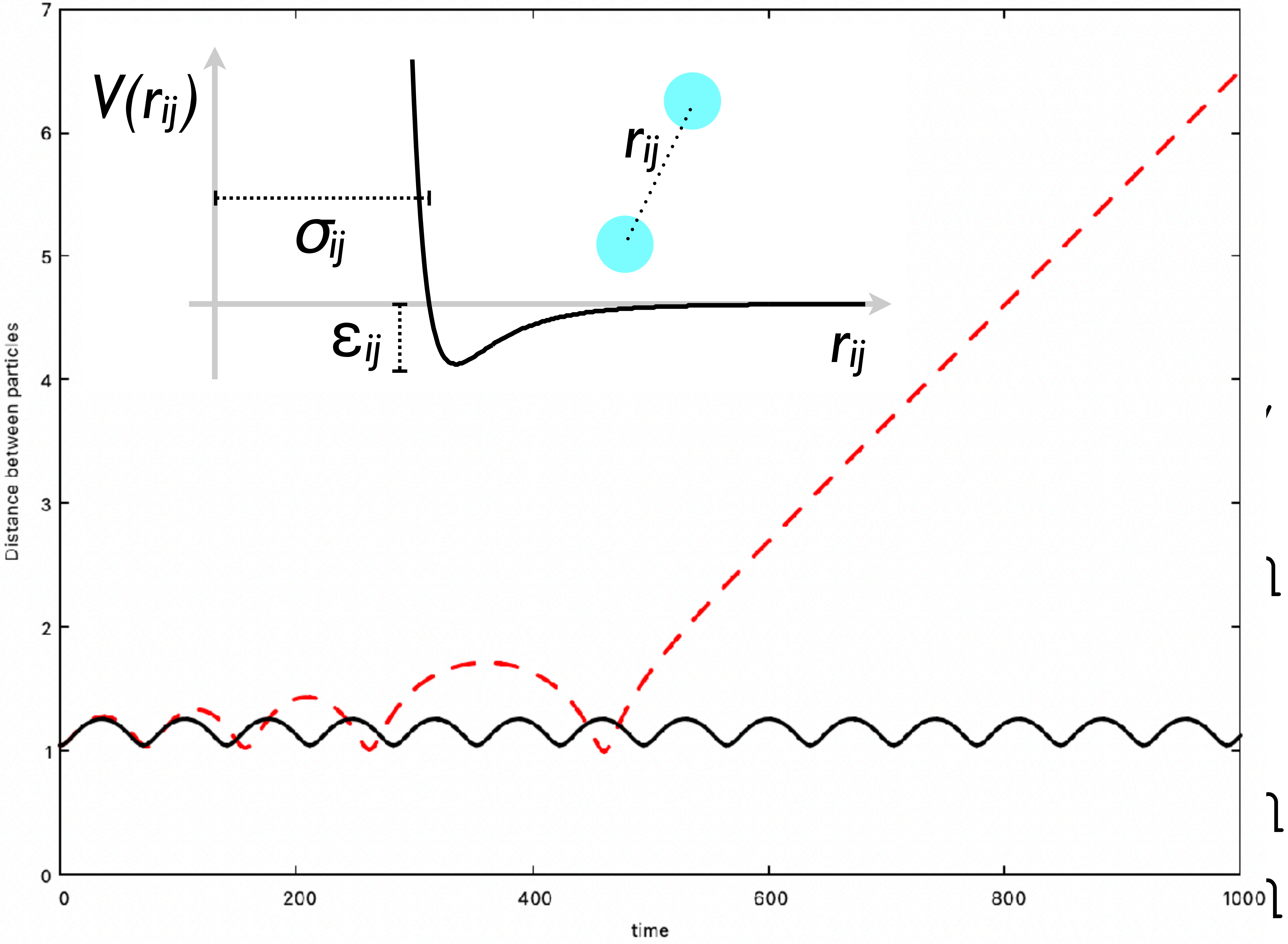
Second guess:

$$x(t+\Delta) = x(t) + v(t)\Delta + (F(t)/2m)\Delta^2$$

$$+\; x(t-\Delta) = x(t) - v(t)\Delta + (F(t)/2m)\Delta^2$$

$$x(t+\Delta) = 2x(t) - x(t-\Delta) + (F(t)/m)\Delta^2$$

Time integration, or "How



First guess: Would just

$x(t+\Delta) =$ … $'2)\Delta^2$

$=$ … $)\Delta^2$

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$+\ x(t-\Delta) =$ … $)\Delta^2$

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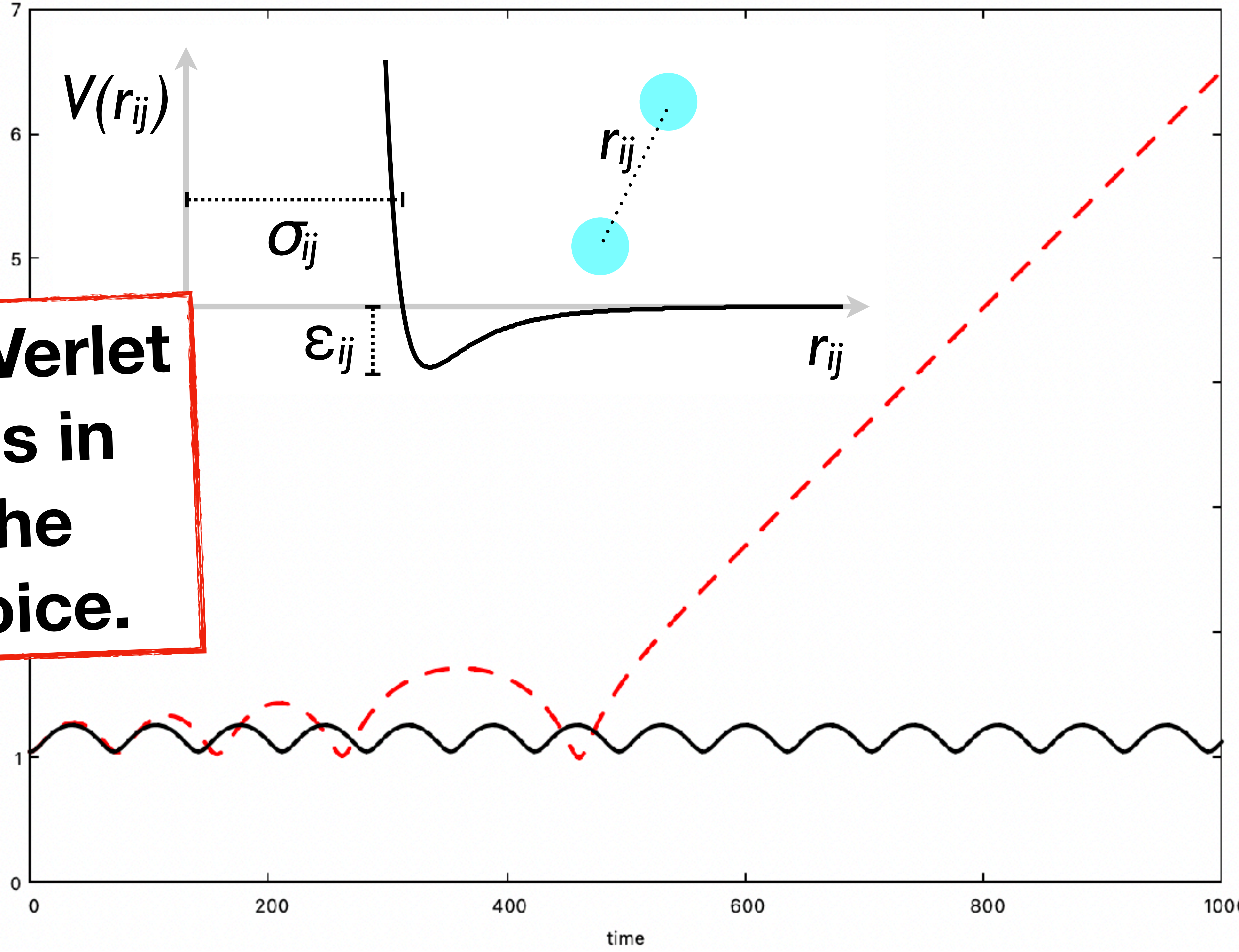

First

This simple ‘Verlet algorithm’ is in practice the optimal choice.

$'2)\Delta^2$

$\iota)\Delta^2$

Second guess:

$x(t+\Delta) = \ldots \iota)\Delta^2$

$+ \; x(t-\Delta) = \ldots \iota)\Delta^2$

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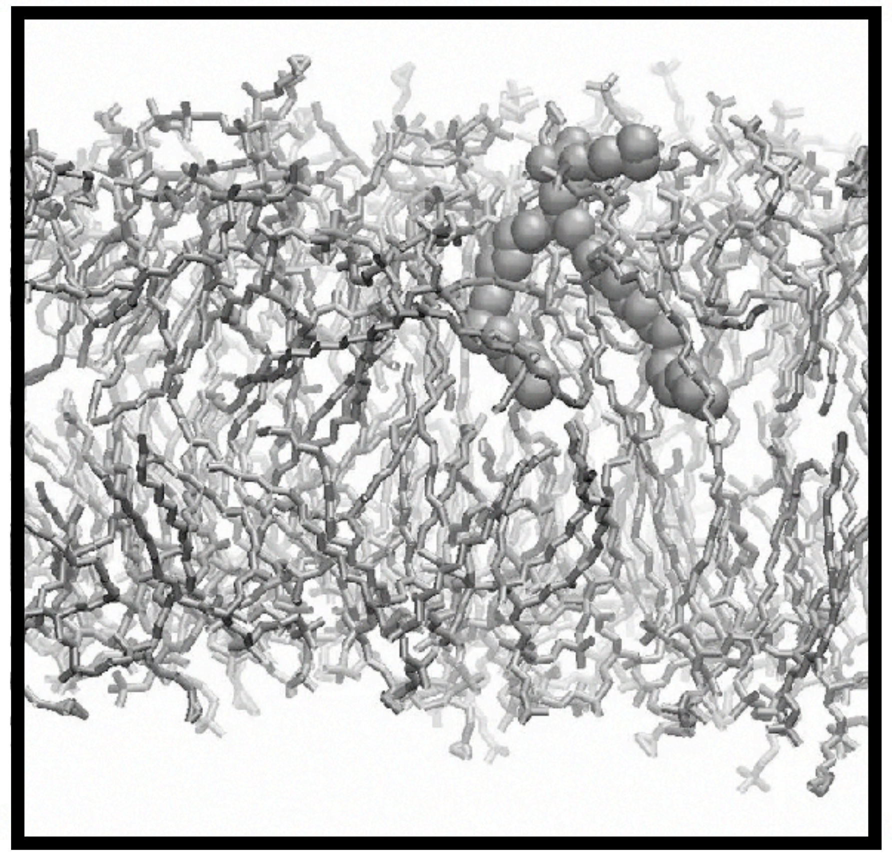
Periodic Boundary Conditions



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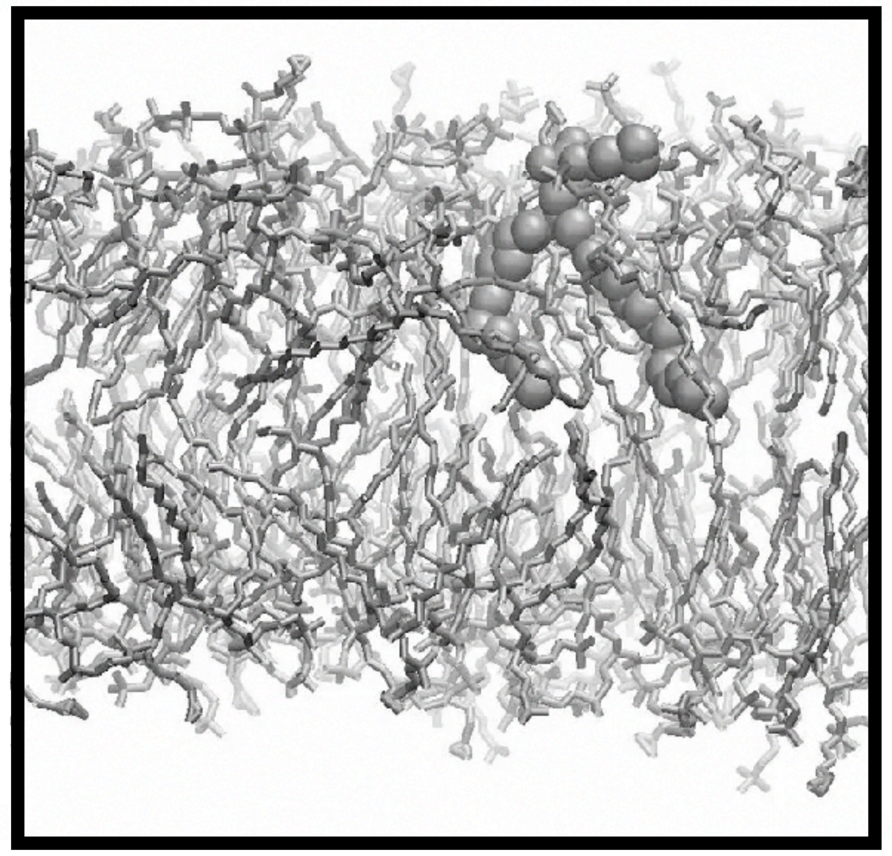

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Advantages

- no surface effects
- no tracking of ‘escaped’ particles
- long-range interactions through Fourier space

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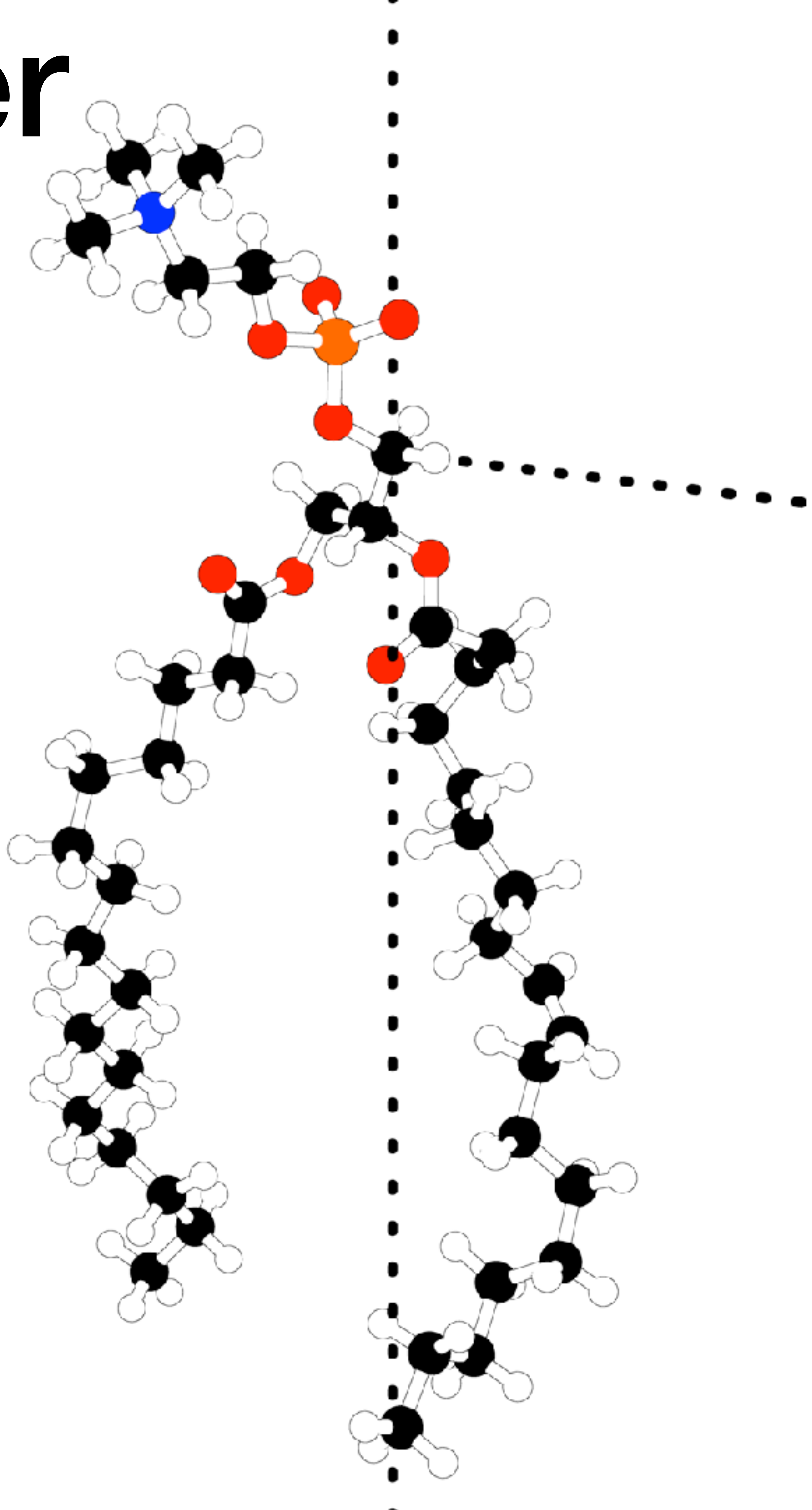
Note: Location of the 'central box' has no physical meaning.

Applications: How one measures from MD:

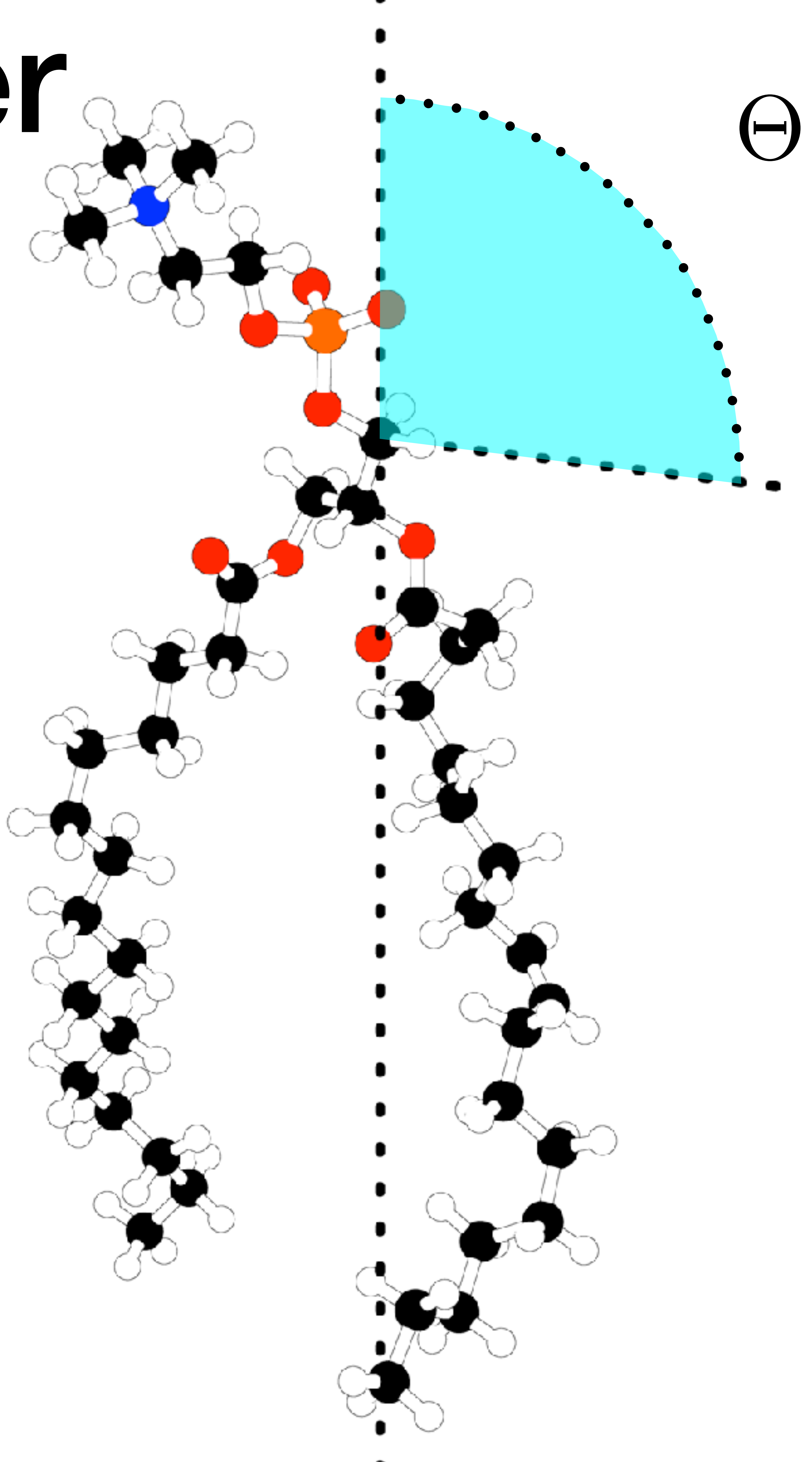
1) **C-H bond order parameters S_{CH}**
2) **C-H bond effective correlation times τ_e**
3) **X-ray scattering form factors $F(q)$**

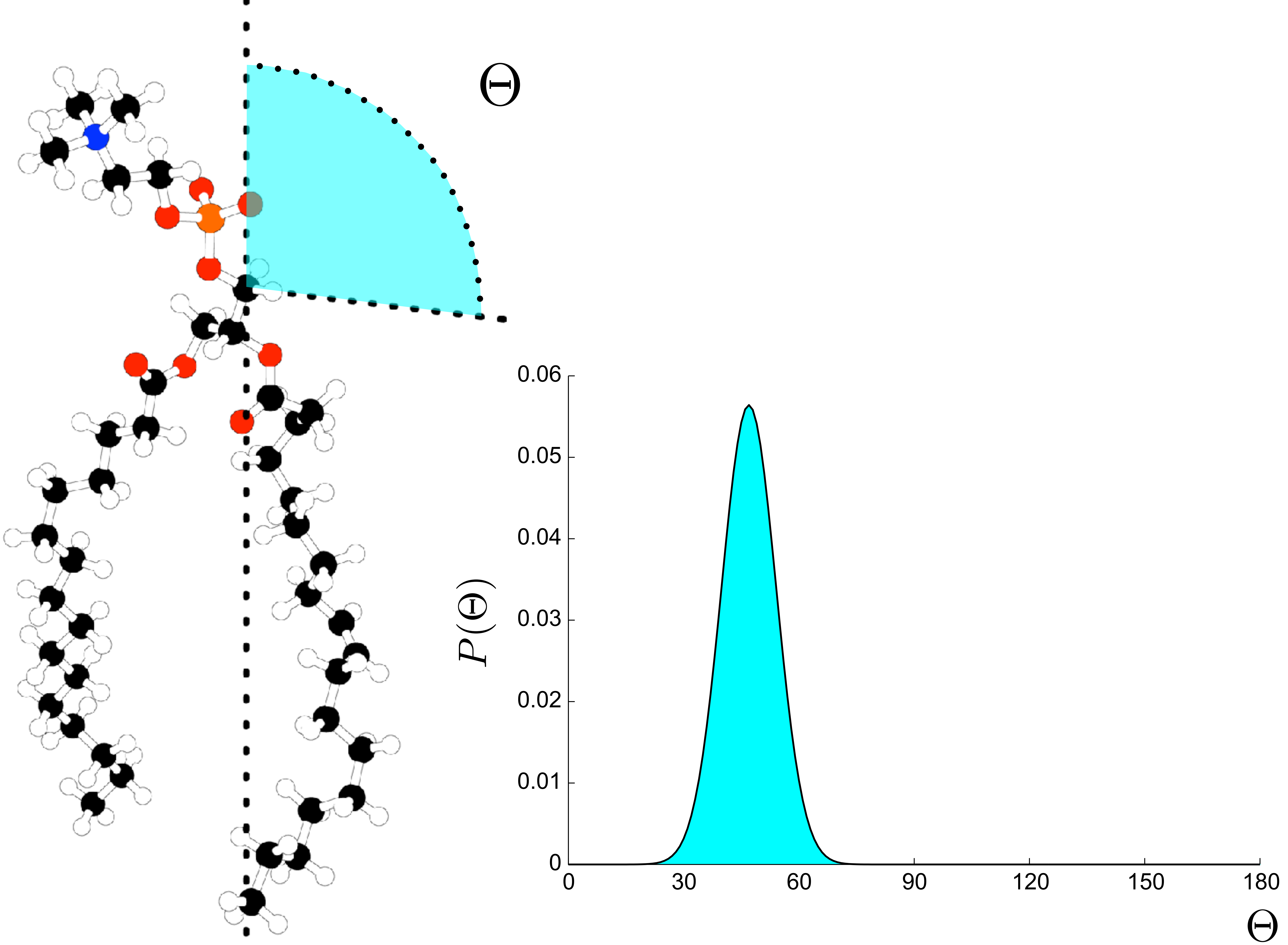
Order parameter
S_{CH}

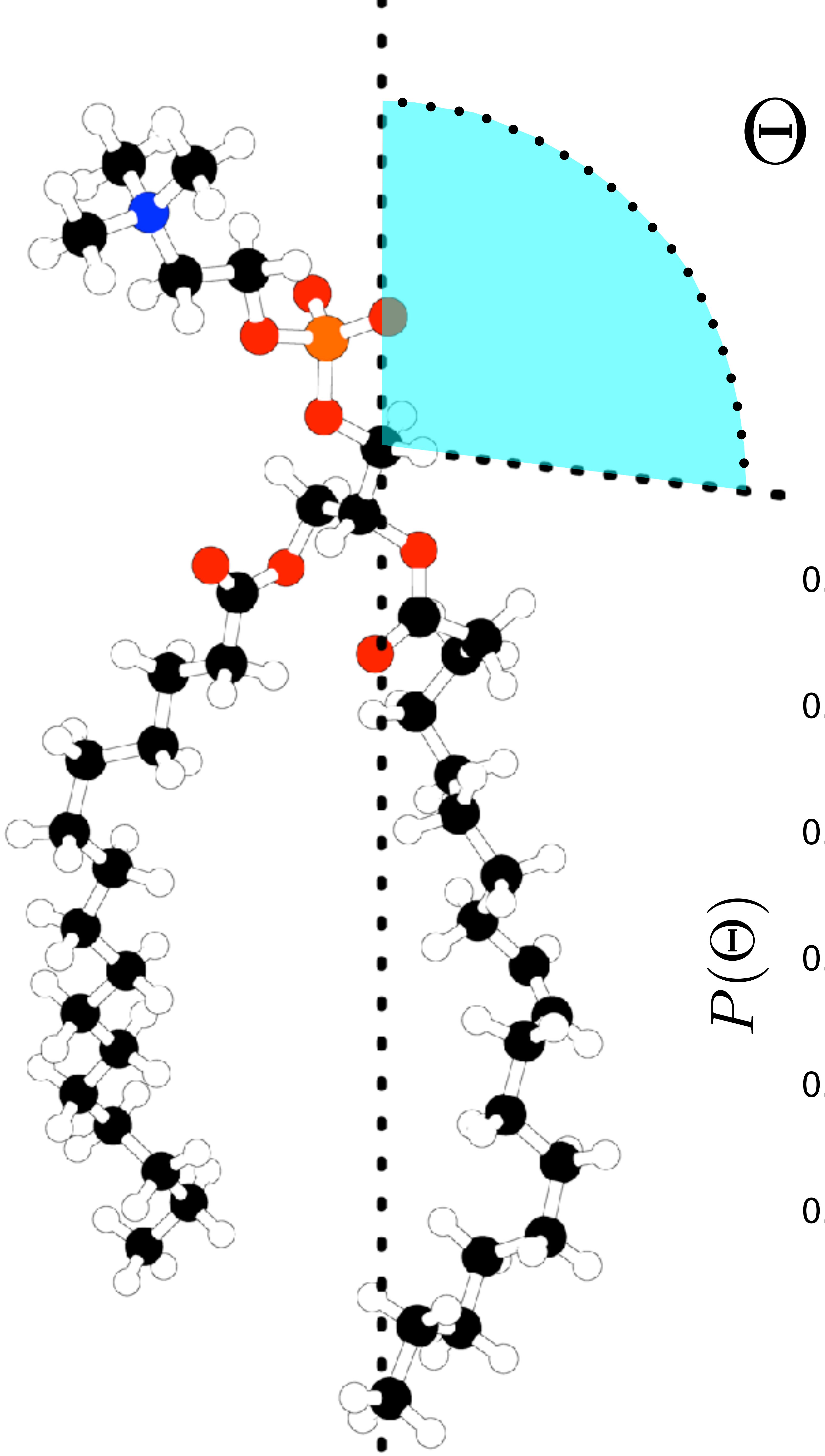
Order parameter S_{CH}



Order parameter S_{CH}



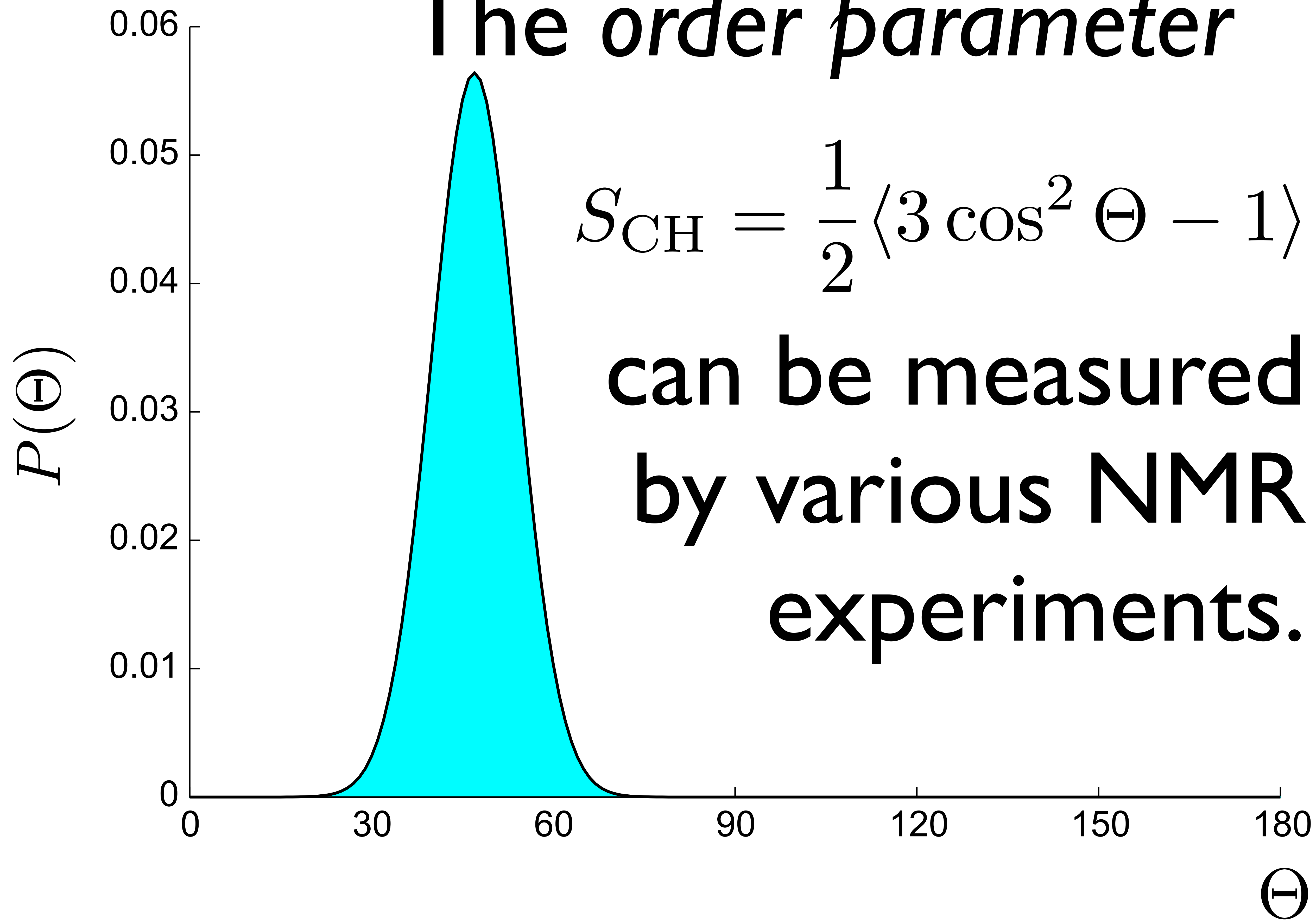

Θ
0.06
0.05
0.04
0.03
0.02
0.01
0
$P(\Theta)$
0
30
60
90
120
150
180
Θ

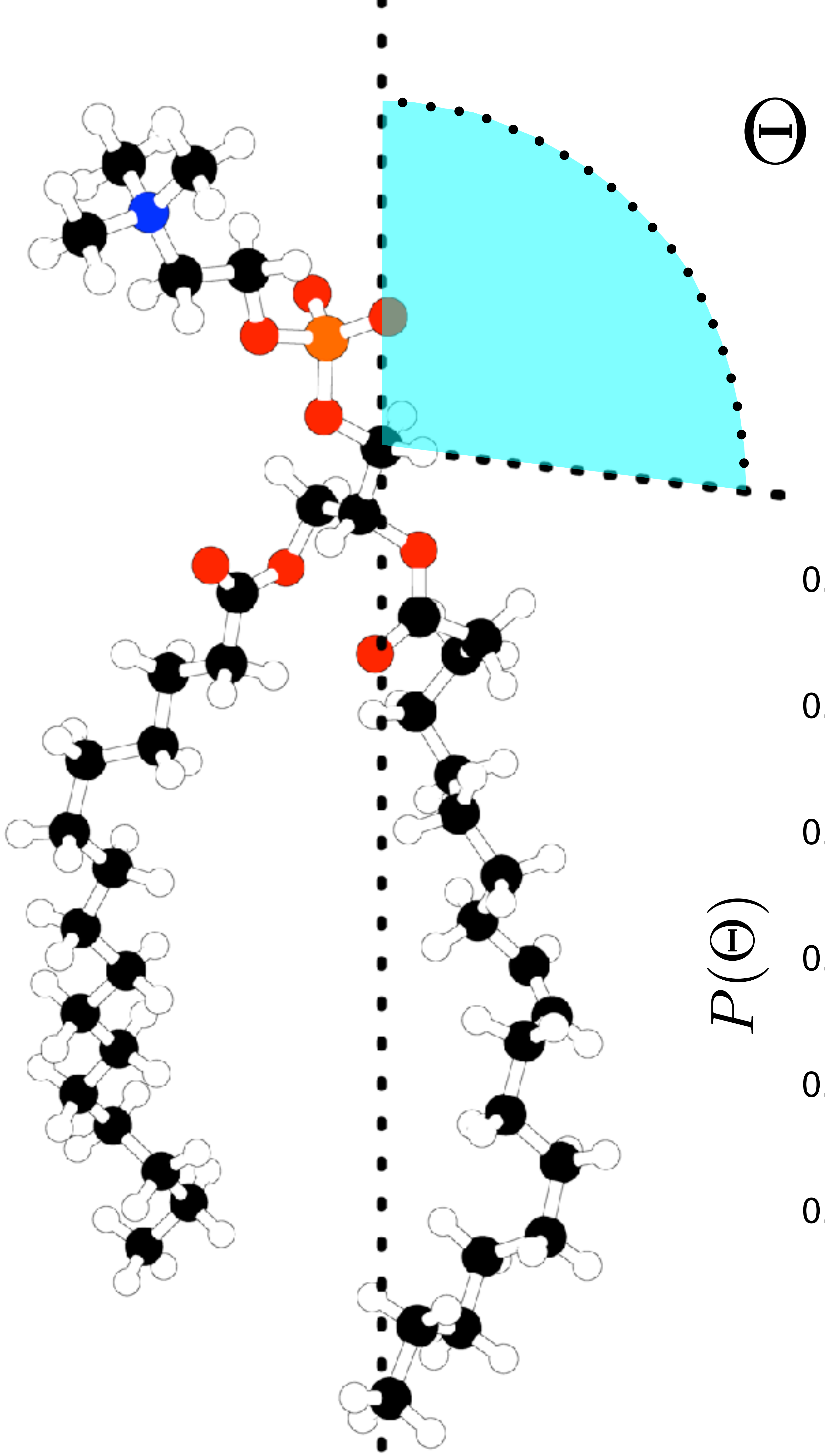


The *order parameter*

$$S_{\mathrm{CH}} = \frac{1}{2}\langle 3\cos^2\Theta - 1\rangle$$

can be measured by various NMR experiments.





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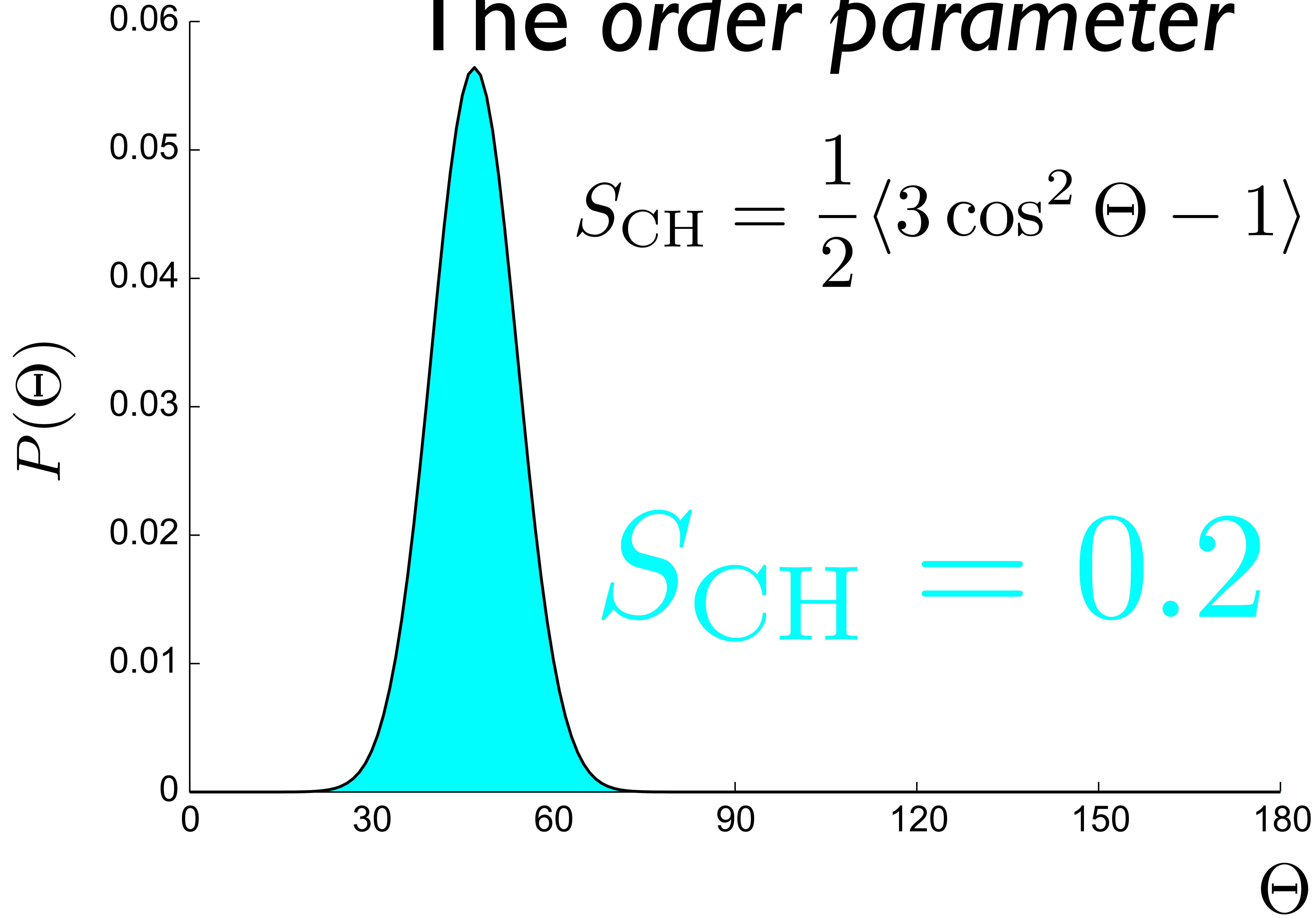
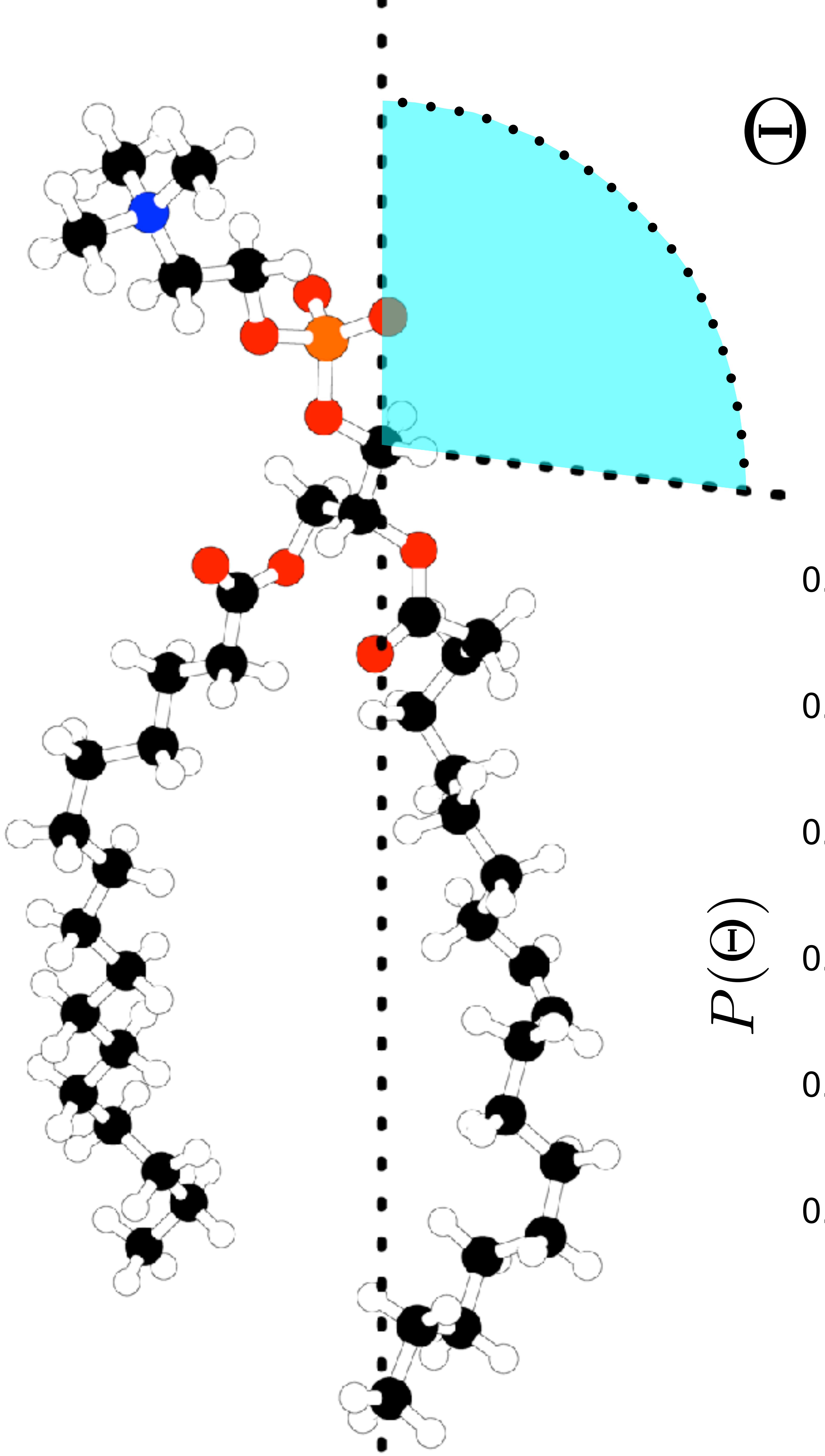


$$S_{\mathrm{CH}} = 0.2$$



The *order parameter*

$$S_{\mathrm{CH}} = \frac{1}{2}\langle 3\cos^2\Theta - 1\rangle$$

is degenerate.

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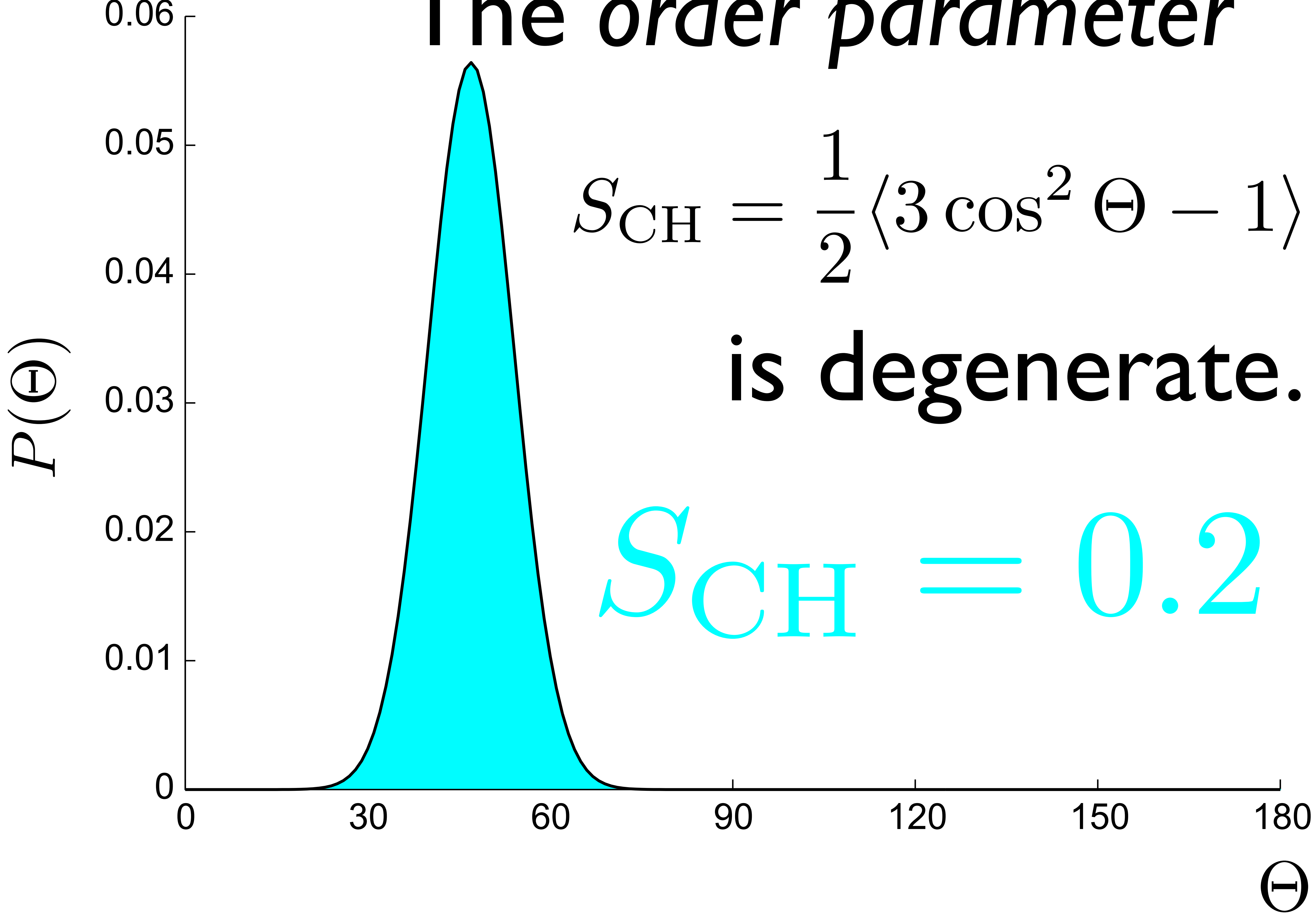

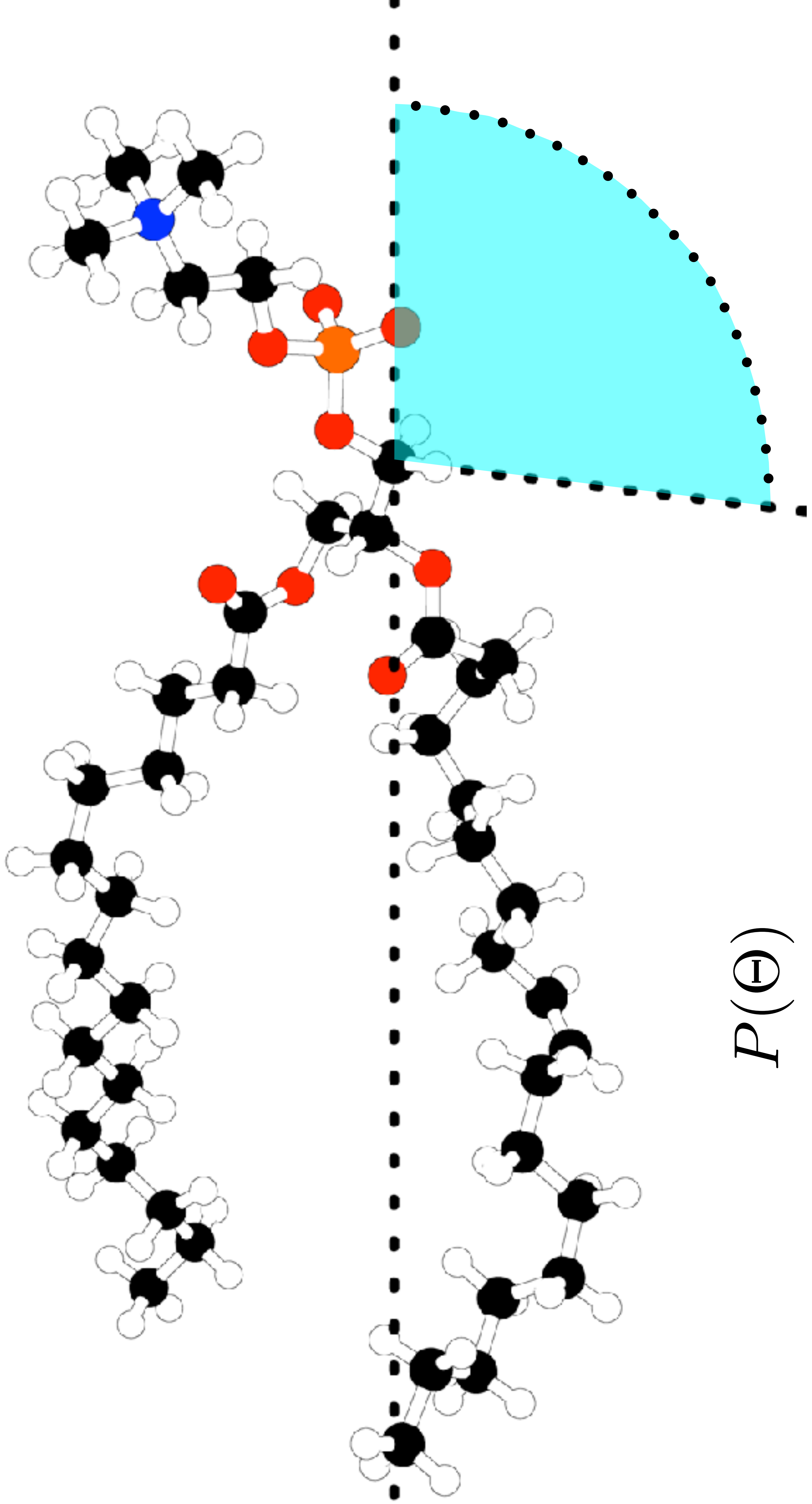

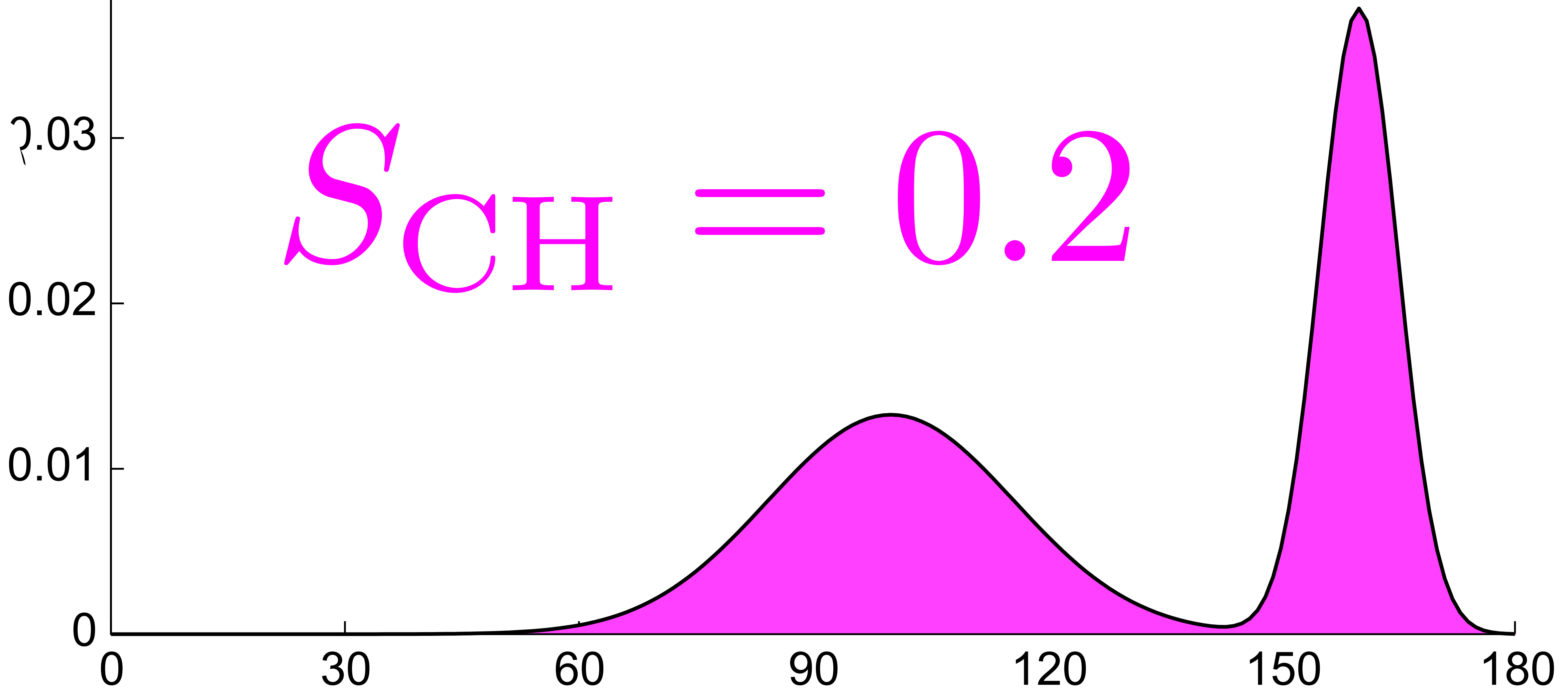

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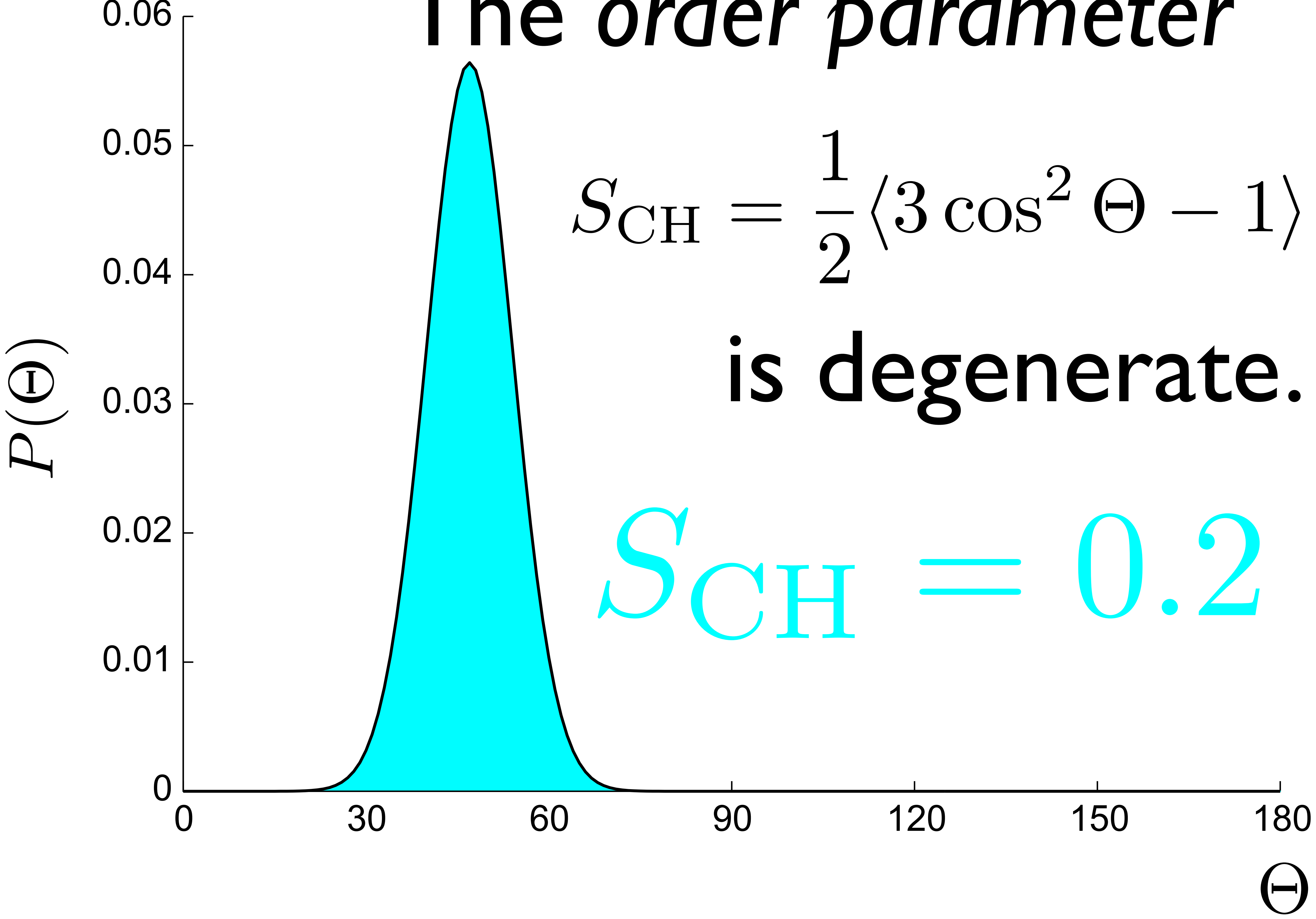
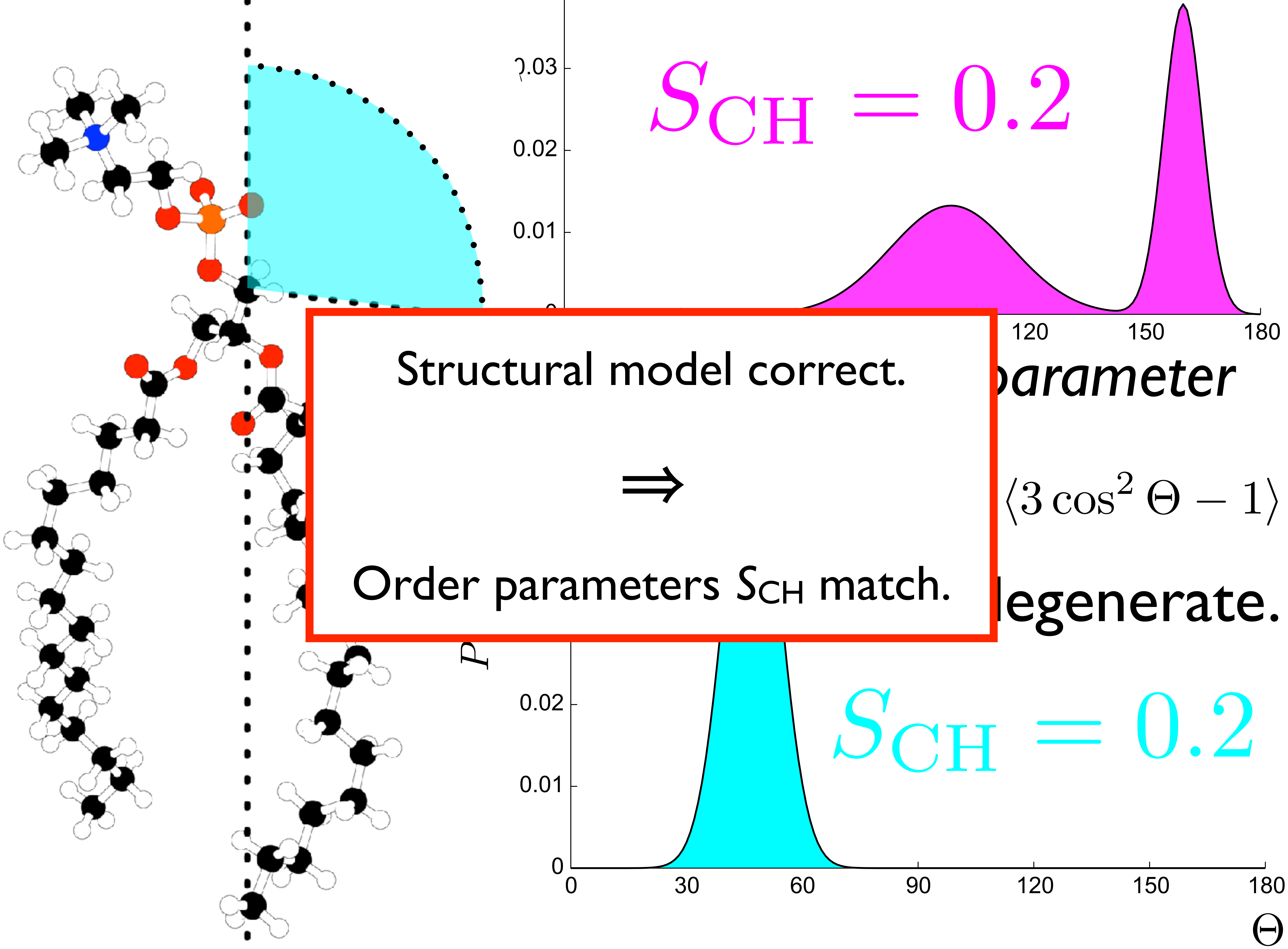
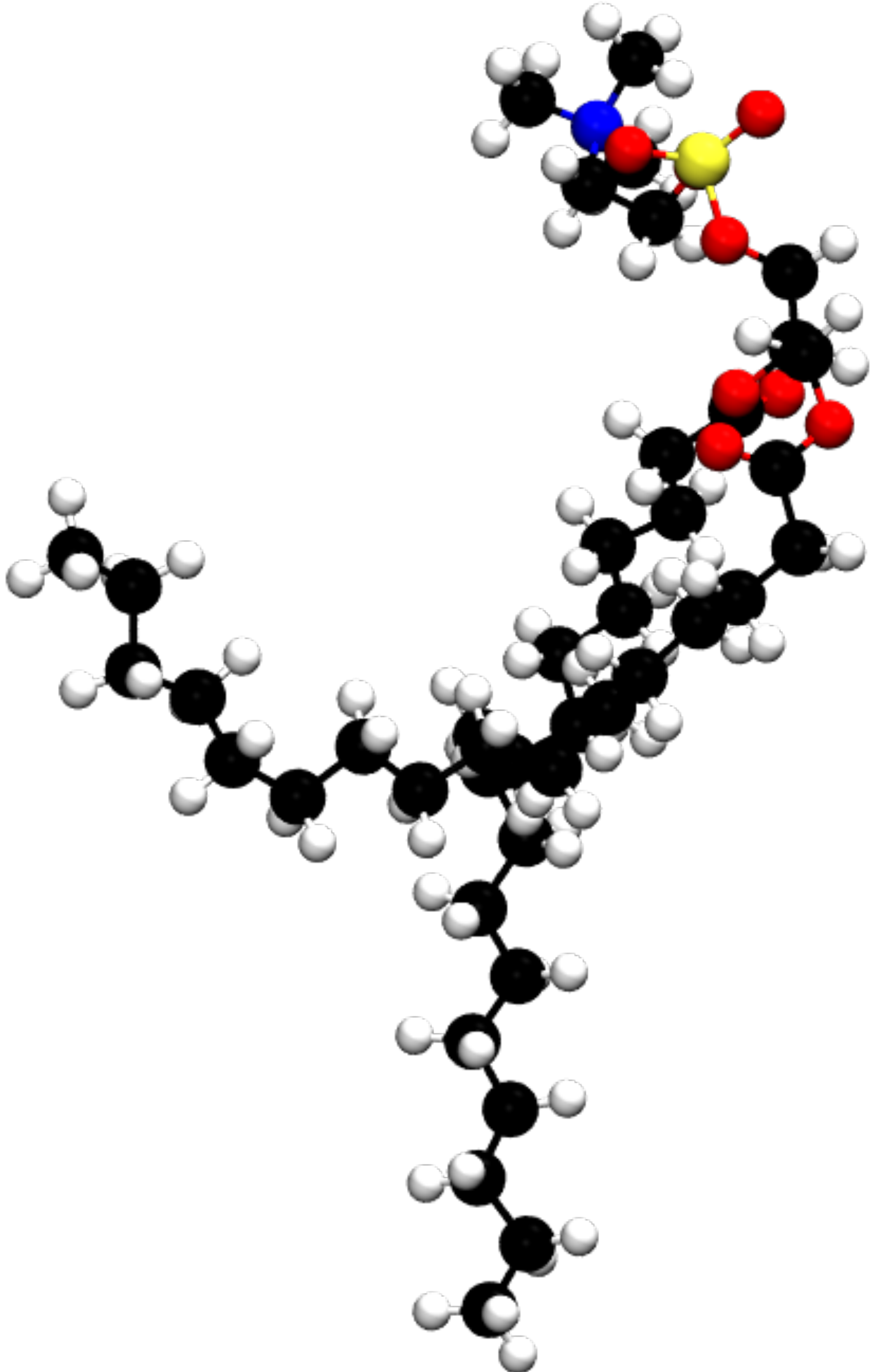


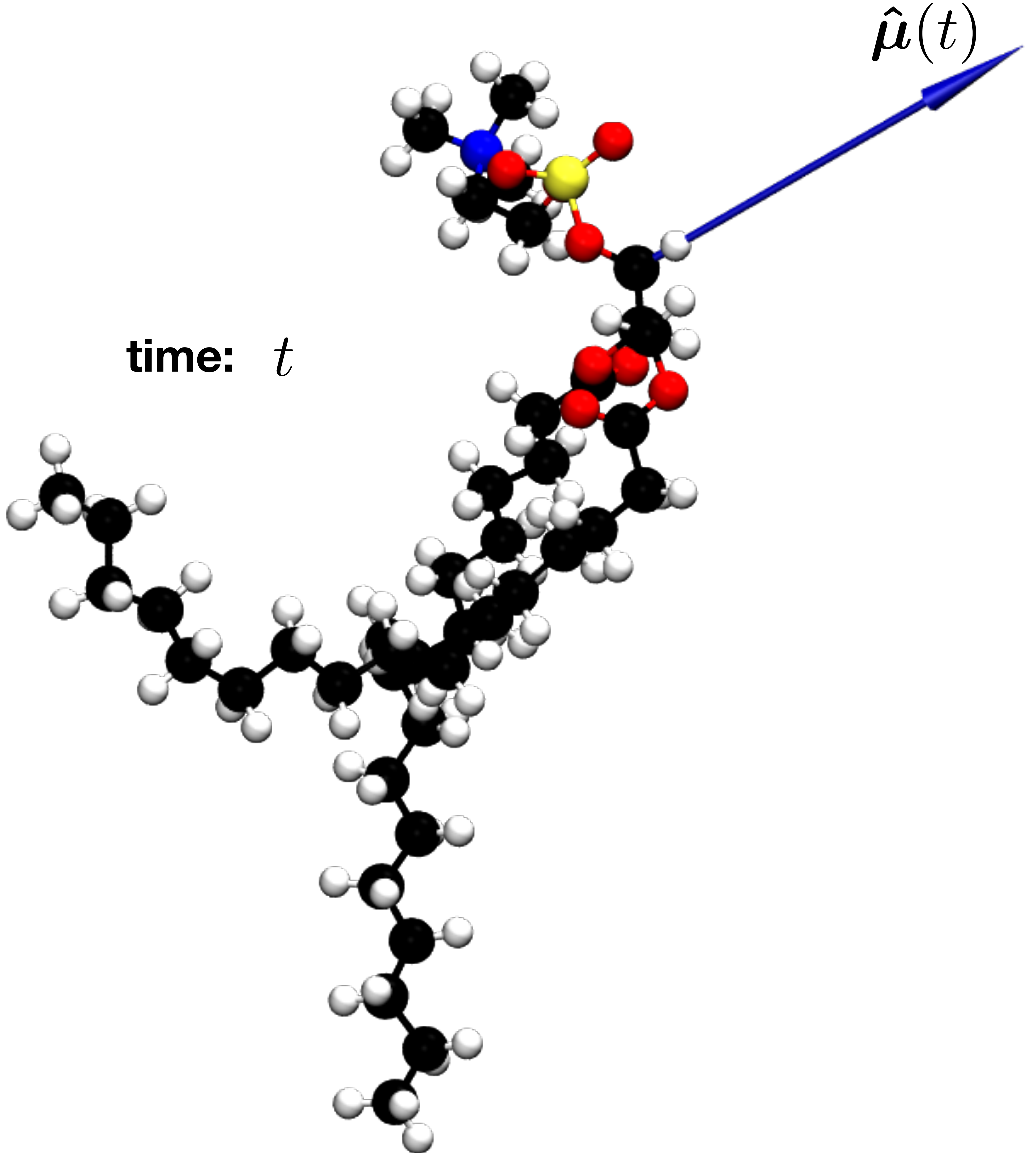


$S_{\mathrm{CH}} = 0.2$
0.03
0.02
0.01
120
150
180
parameter
$\langle 3\cos^2\Theta - 1\rangle$
degenerate.
Structural model correct.
$\Rightarrow$
Order parameters S_{CH} match.
$S_{\mathrm{CH}} = 0.2$
0.02
0.01
0
0
30
60
90
120
150
180
Θ

Effective correlation time τ_e

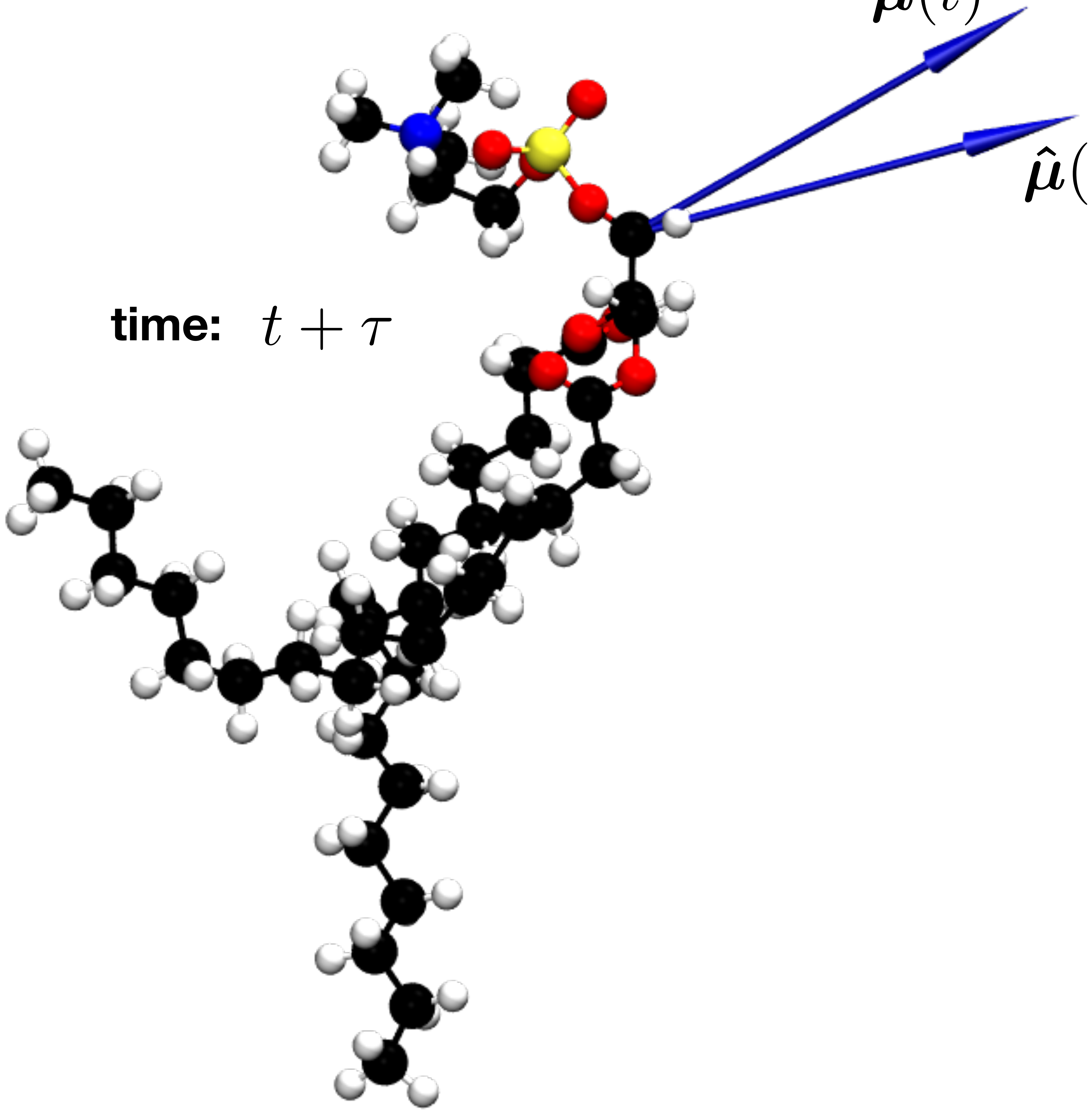


Effective correlation time τ_e



Effective correlation time τ_e

$\hat{\boldsymbol{\mu}}(t)$

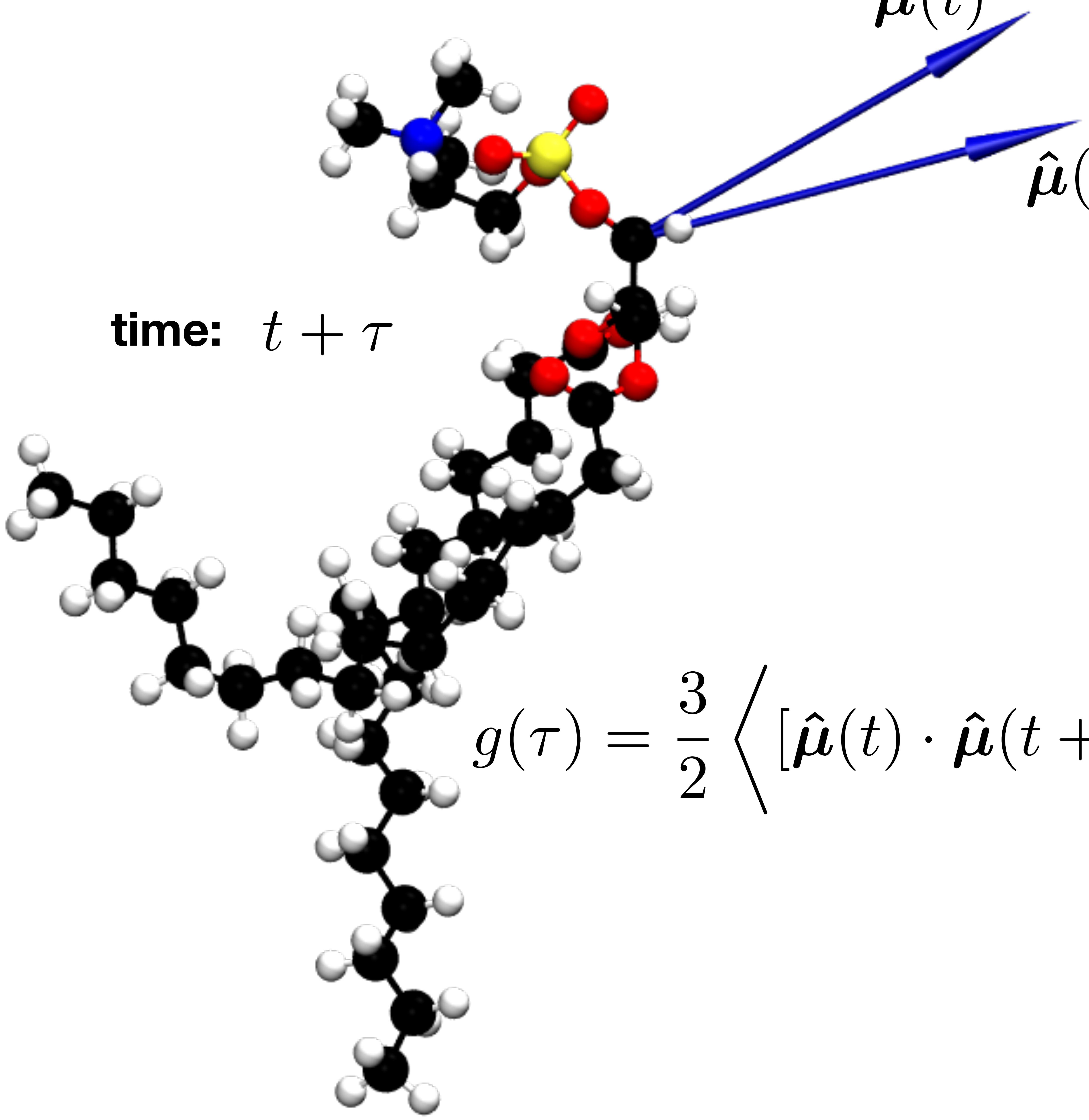


$\hat{\boldsymbol{\mu}}(t+\tau)$

time: $t+\tau$

Effective correlation time τ_e

$\hat{\boldsymbol{\mu}}(t)$

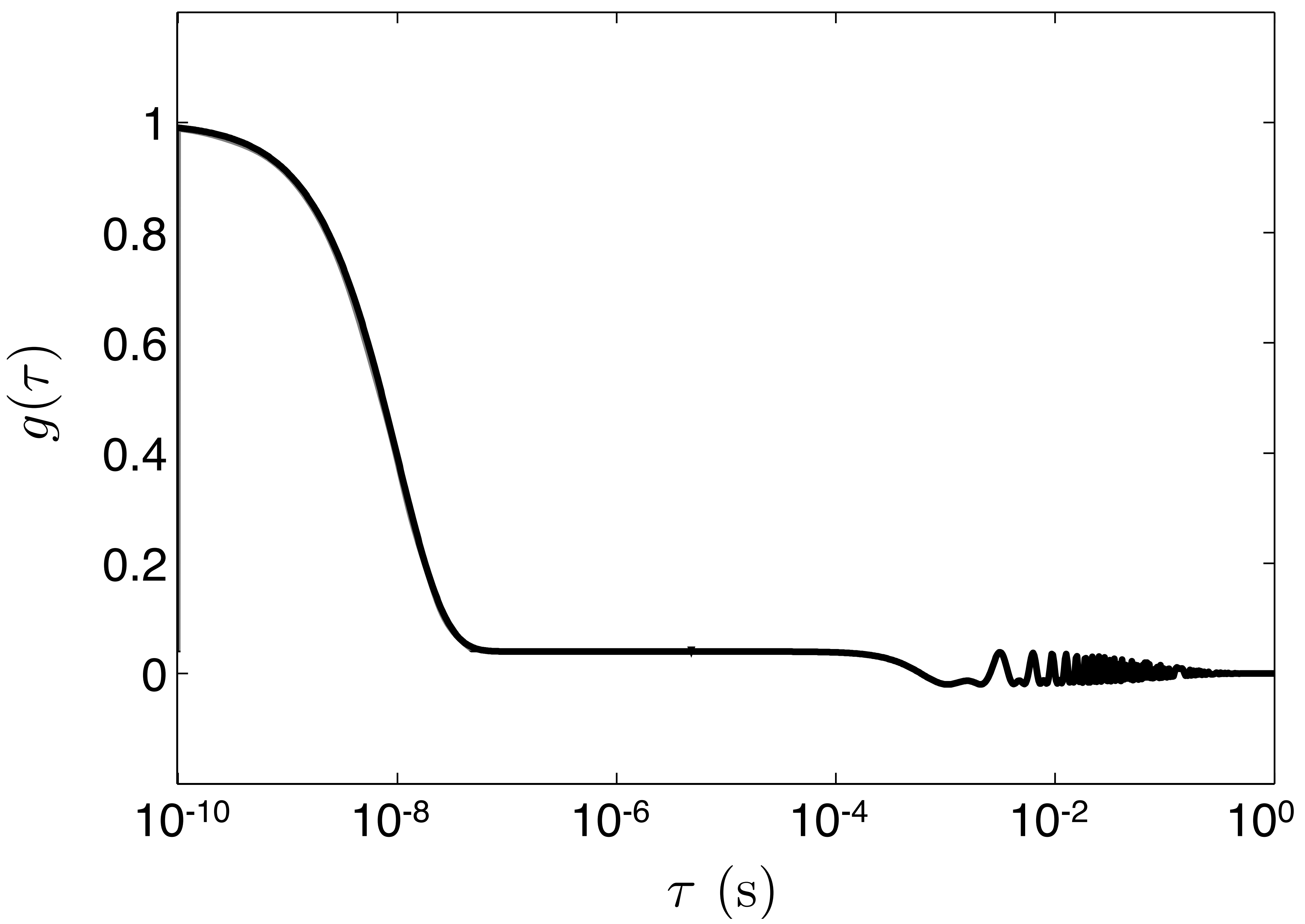


$\hat{\boldsymbol{\mu}}(t+\tau)$

time: $t+\tau$

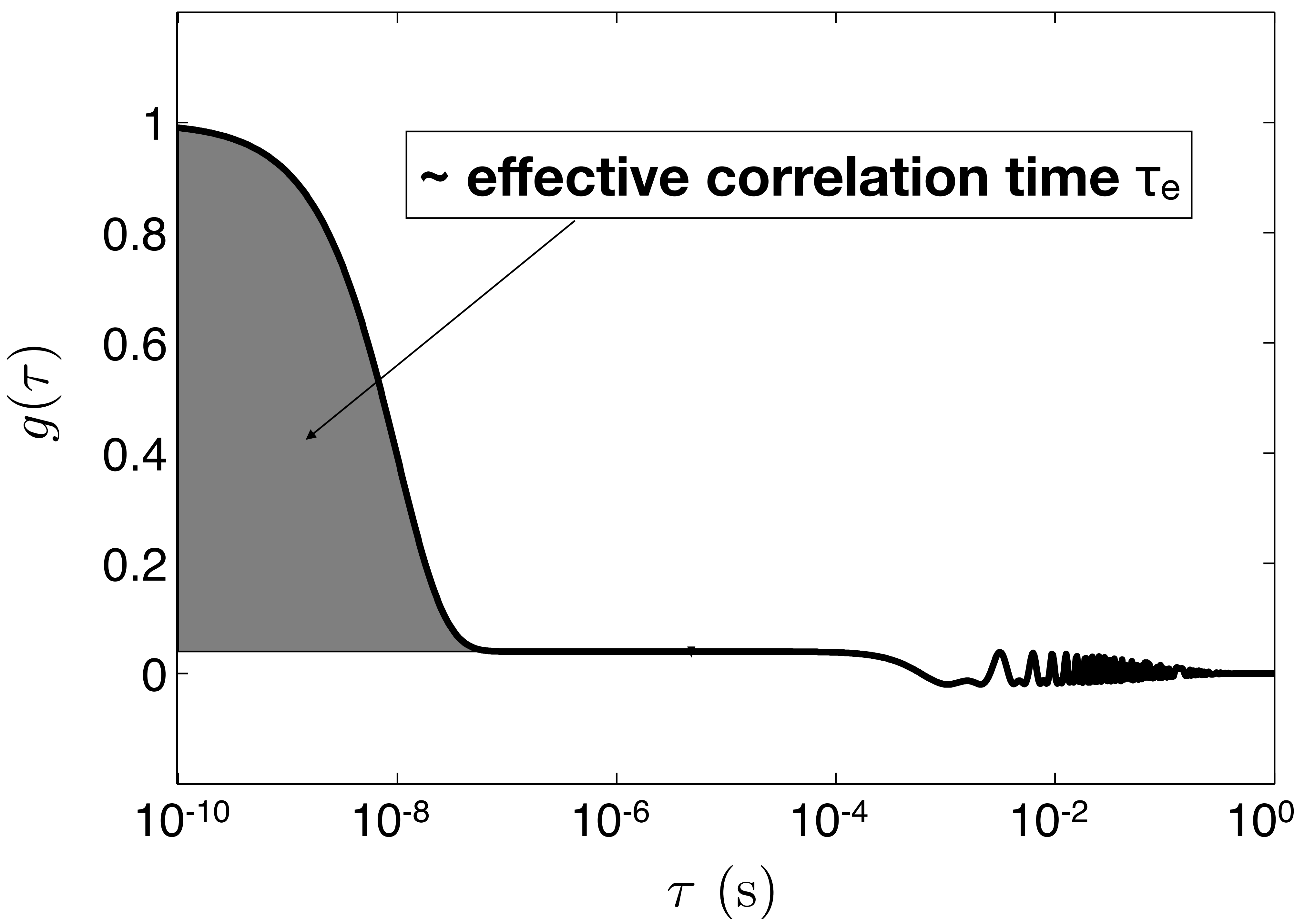
$$g(\tau) = \frac{3}{2}\left\langle \left[\hat{\boldsymbol{\mu}}(t)\cdot\hat{\boldsymbol{\mu}}(t+\tau)\right]^2 - \frac{1}{3}\right\rangle$$

Effective correlation time τ_e



$$g(\tau) = \frac{3}{2}\left\langle \left[\hat{\boldsymbol{\mu}}(t)\cdot\hat{\boldsymbol{\mu}}(t+\tau)\right]^2 - \frac{1}{3}\right\rangle$$

Effective correlation time τ_e



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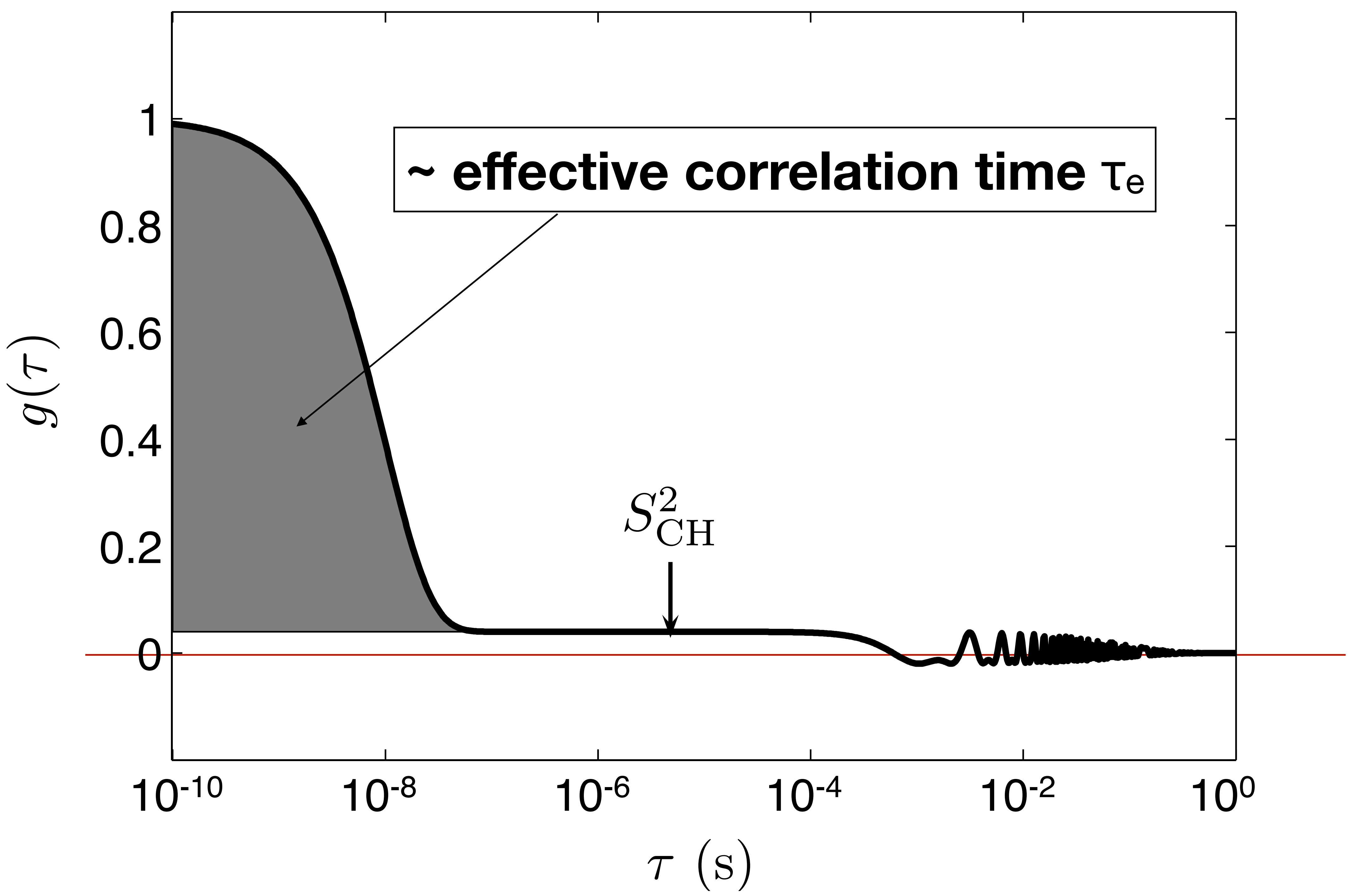
Effective correlation time τ_e



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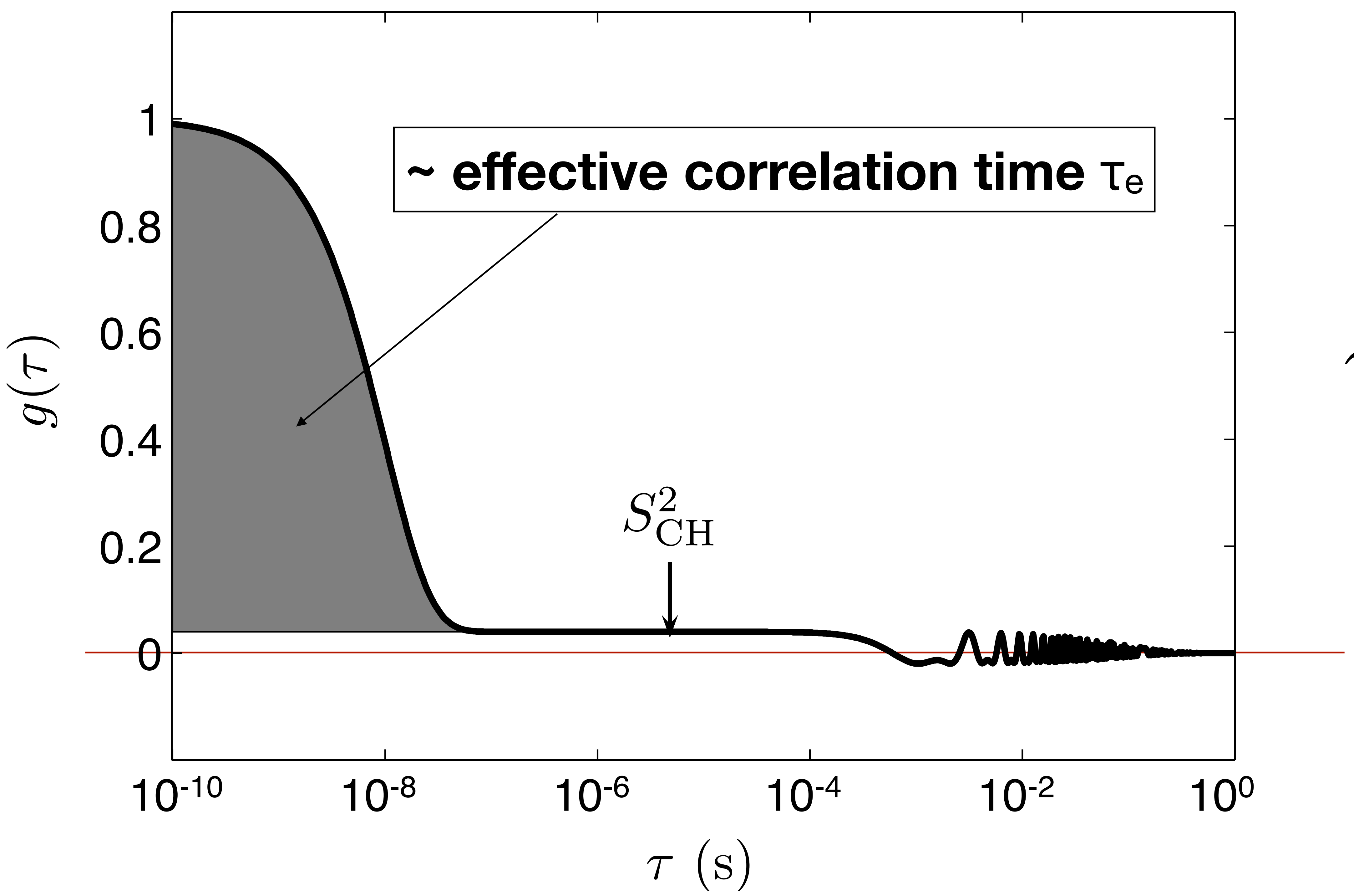
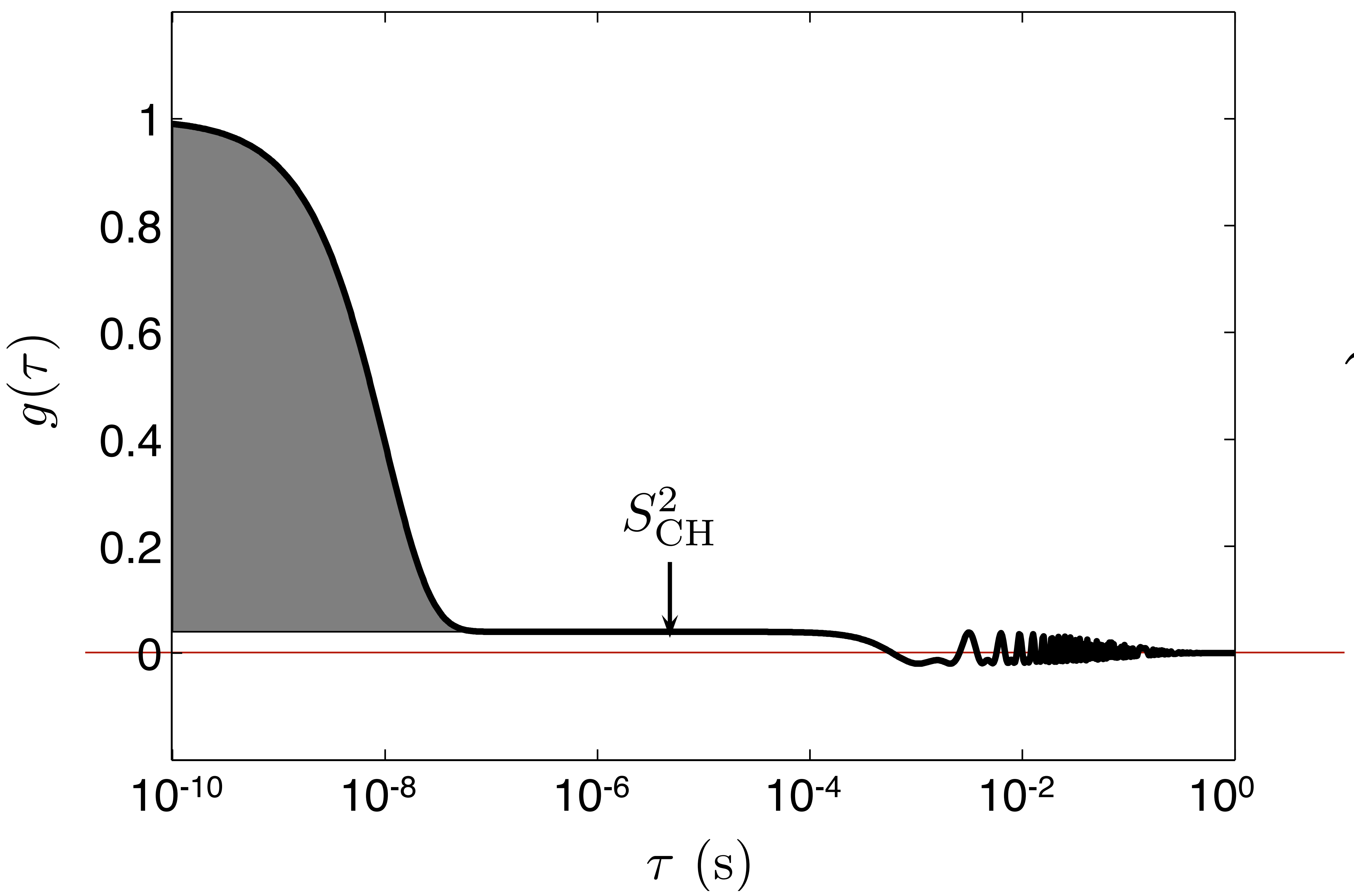
Effective correlation time τ_e



$$\tau_{\mathrm{e}} = \int_0^{10^{-6}\mathrm{s}} \frac{g(\tau) - S^2_{\mathrm{CH}}}{1 - S^2_{\mathrm{CH}}}\,\mathrm{d}\tau$$

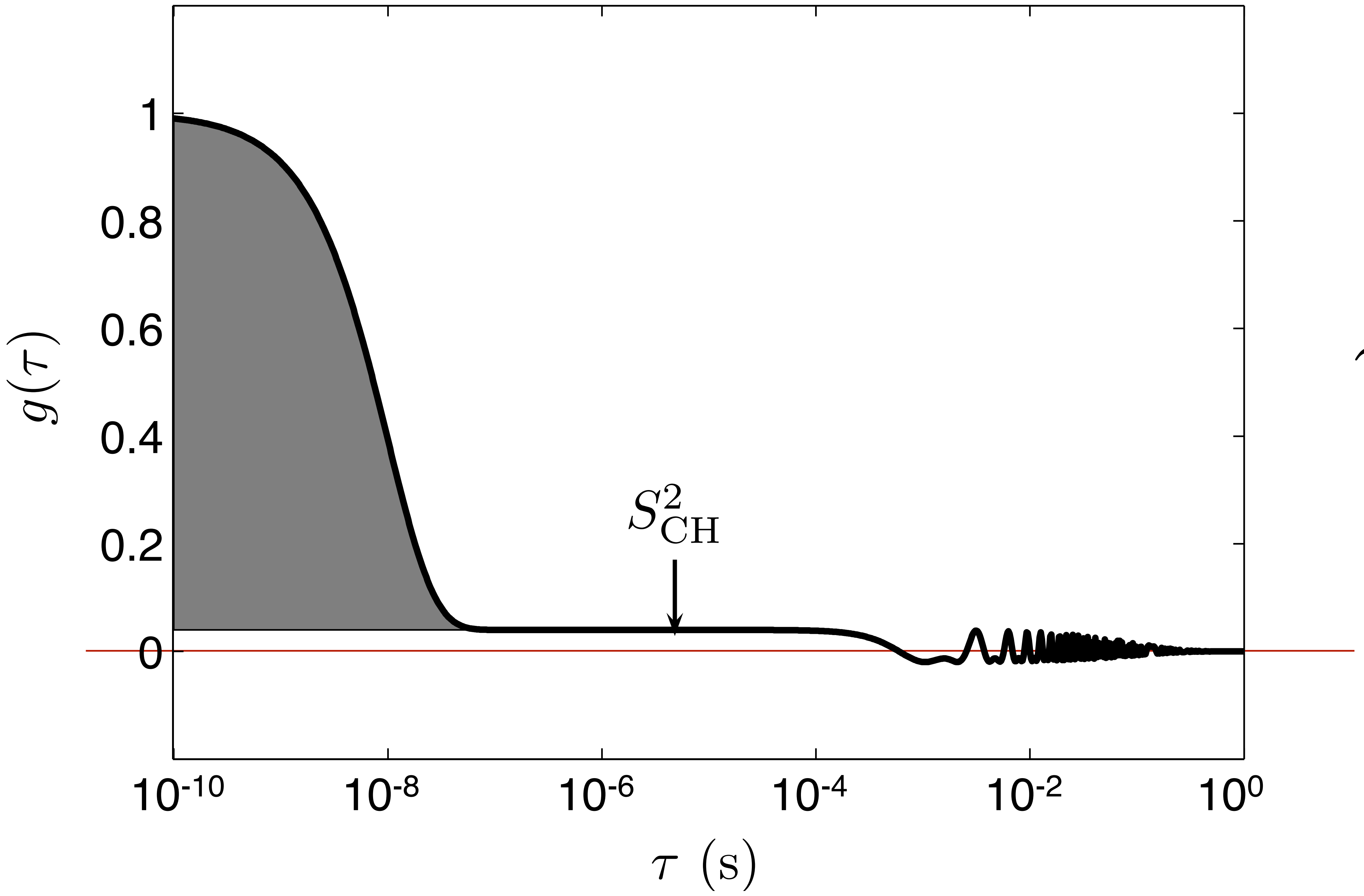
$$g(\tau) = \frac{3}{2}\left\langle \left[\hat{\boldsymbol{\mu}}(t)\cdot\hat{\boldsymbol{\mu}}(t+\tau)\right]^2 - \frac{1}{3}\right\rangle$$

MD gives only a lower bound for τ_e!



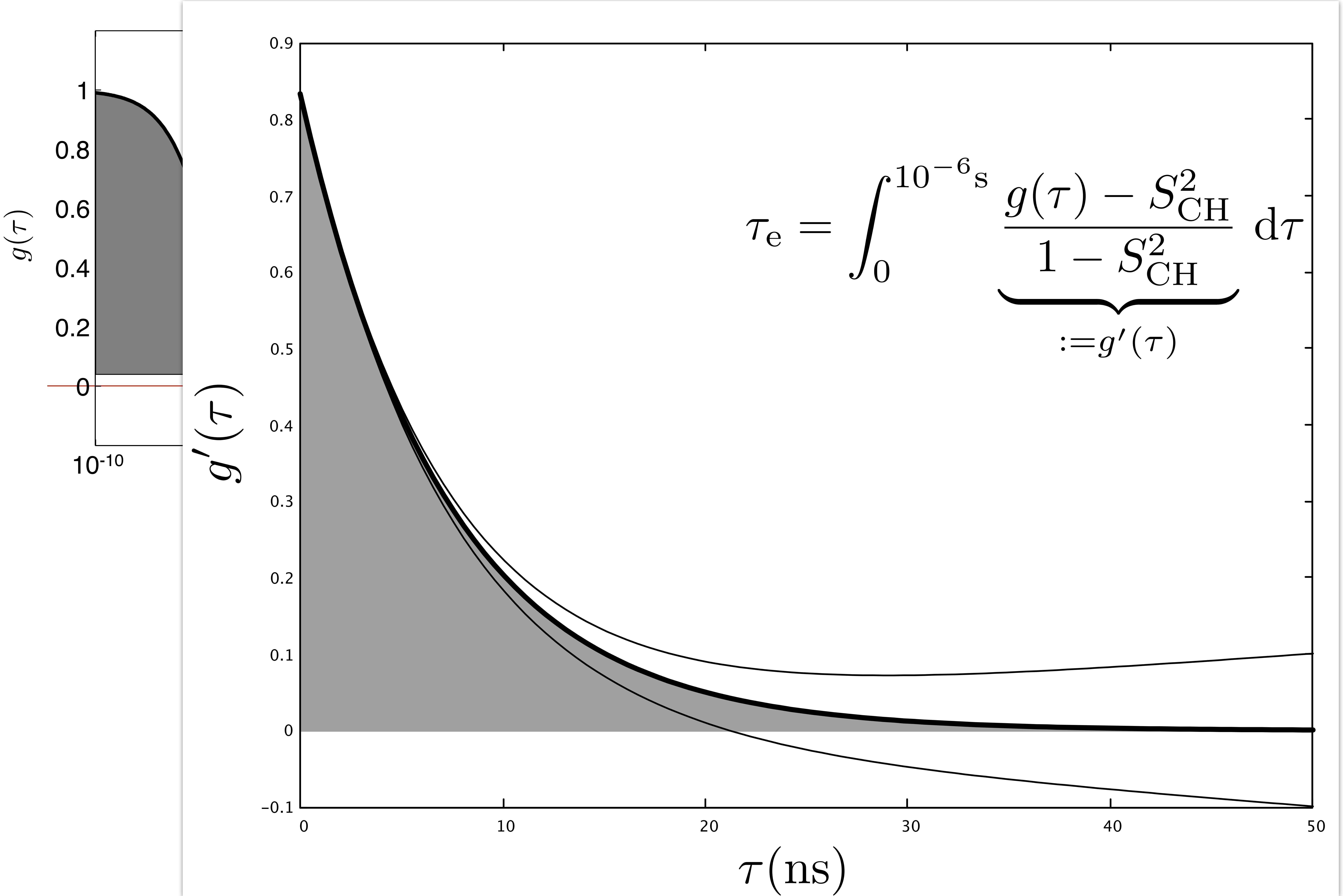
$$\tau_{\mathrm{e}} = \int_0^{10^{-6}\mathrm{s}} \frac{g(\tau) - S^2_{\mathrm{CH}}}{1 - S^2_{\mathrm{CH}}}\,\mathrm{d}\tau$$

MD gives only a <u>lower</u> bound for τ_e !

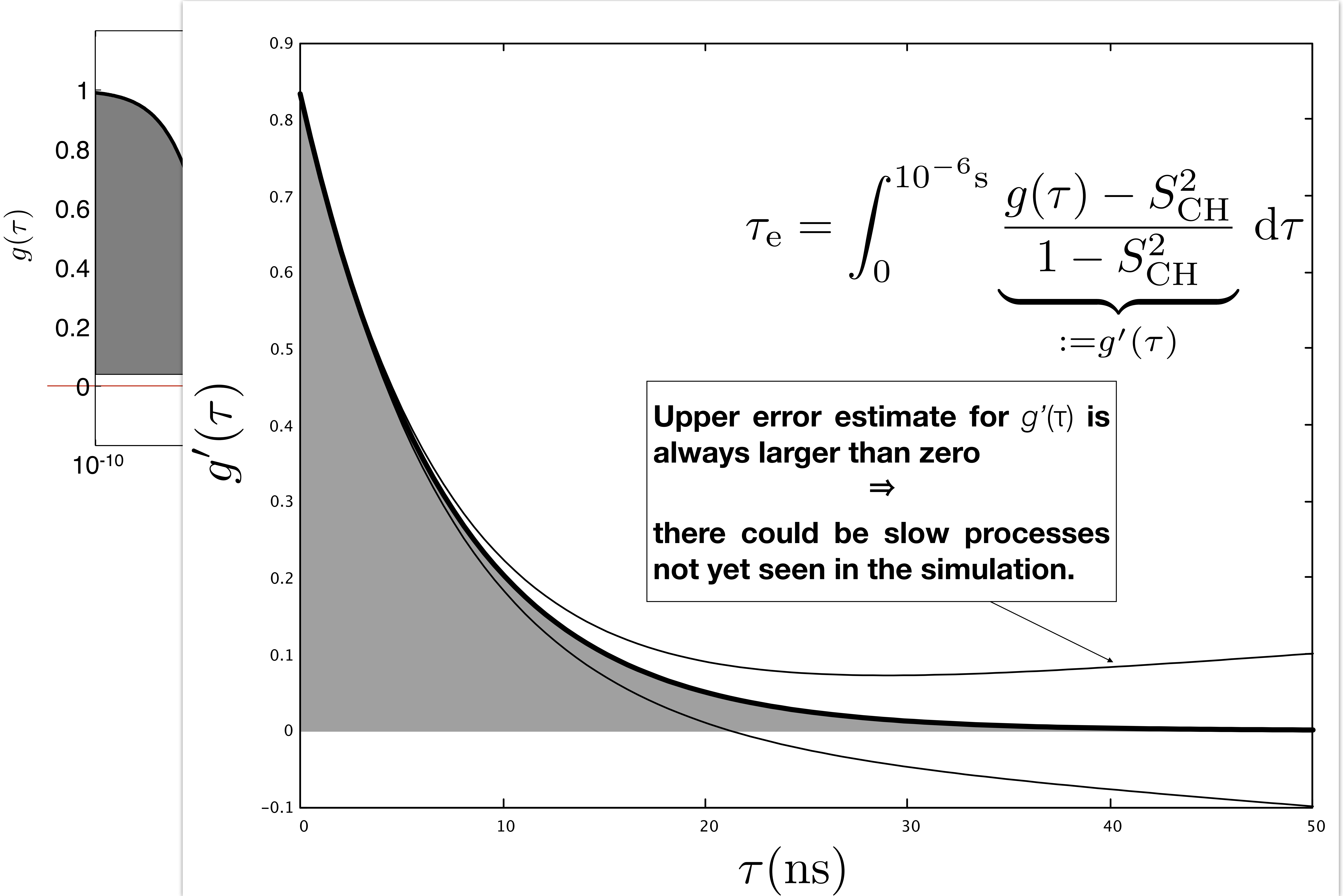


$$\tau_e = \int_0^{10^{-6}\mathrm{s}} \underbrace{\frac{g(\tau) - S^2_{\mathrm{CH}}}{1 - S^2_{\mathrm{CH}}}}_{:=g'(\tau)} \, \mathrm{d}\tau$$

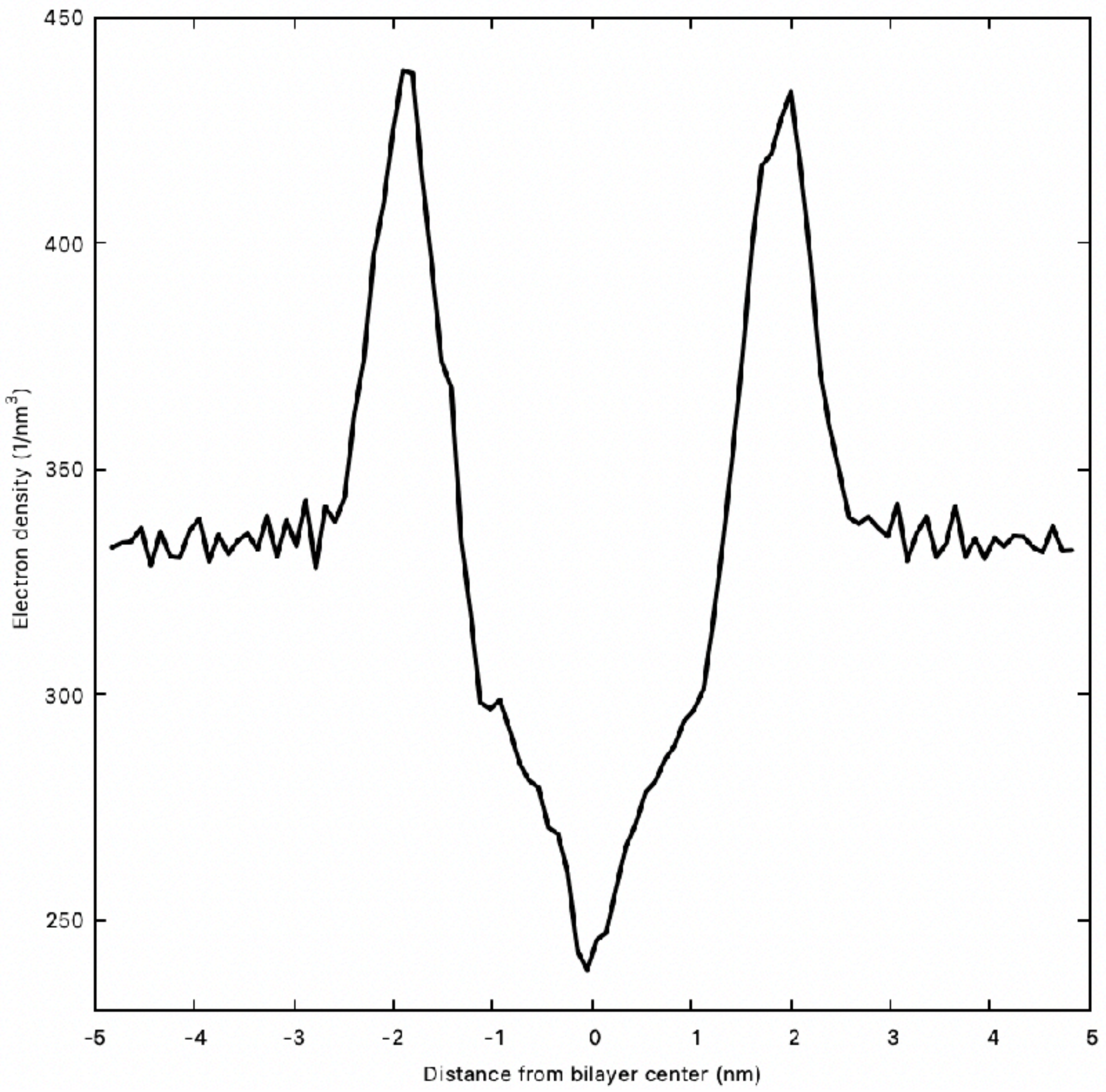
MD gives only a <u>lower</u> bound for τ_e !



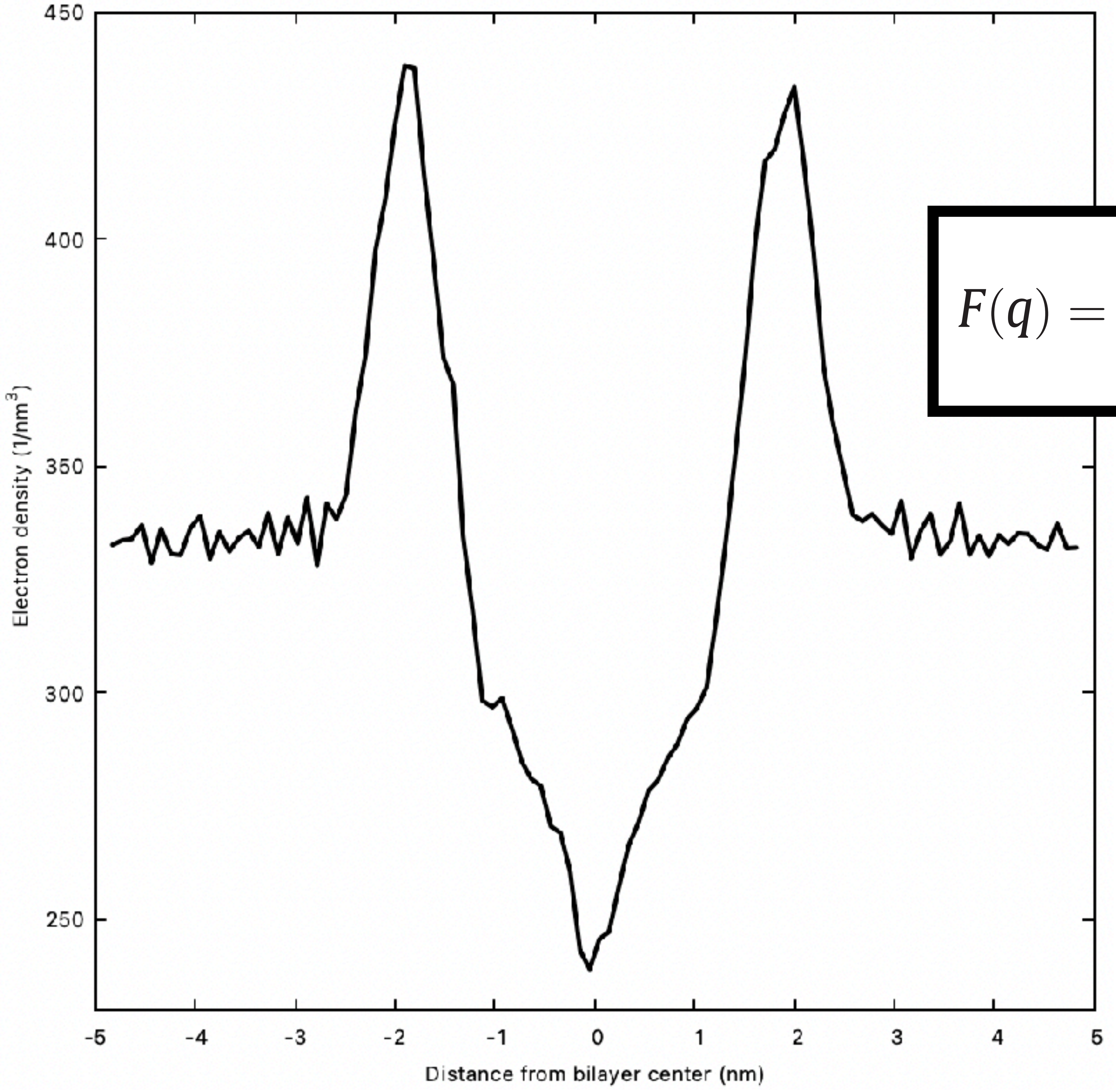
MD gives only a lower bound for τ_e!



Scattering form factor $F(q)$



Scattering form factor *F*(*q*)

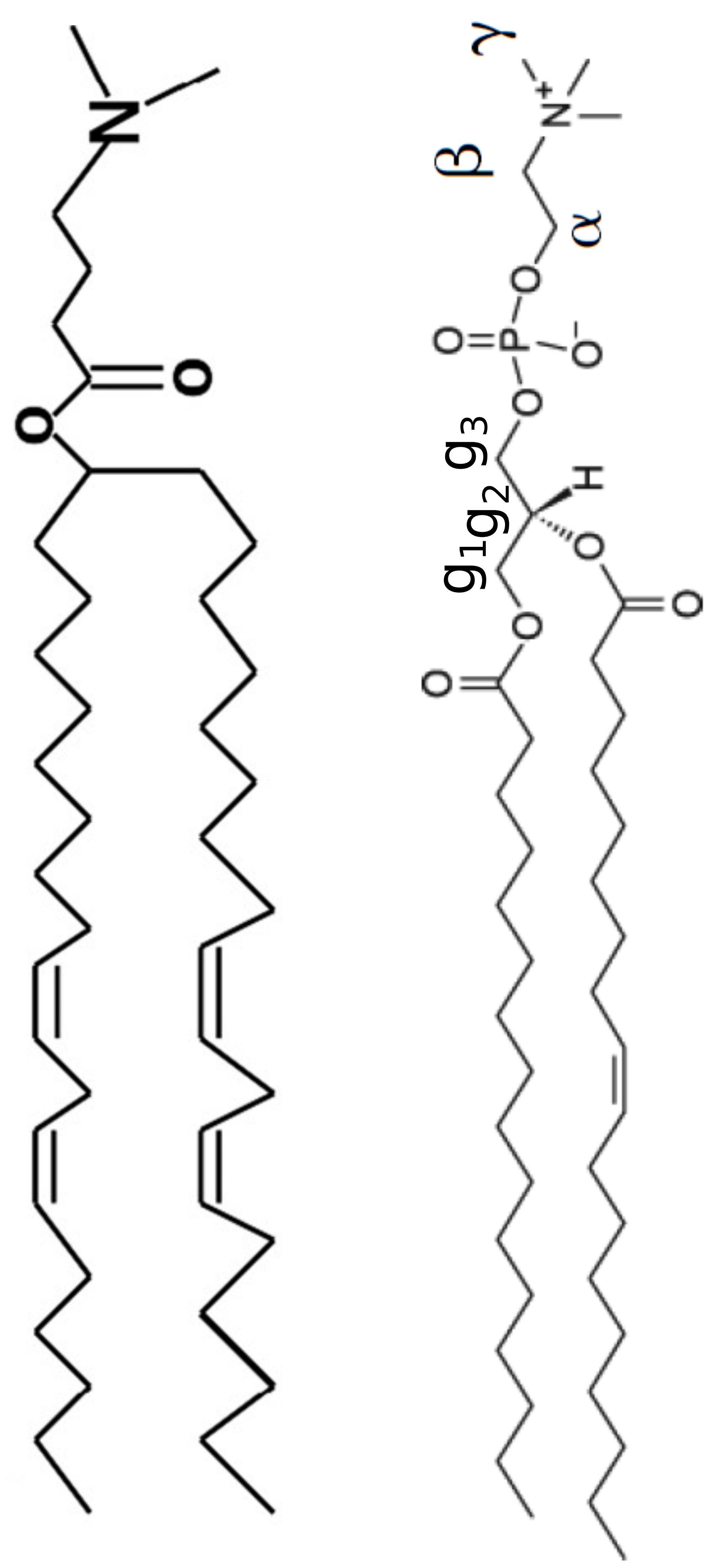


$$F(q) = \int_{-D/2}^{D/2} \Delta\rho_e(z)\cos(zq_z)\mathrm{d}z$$

Scattering form factor *F*(*q*)

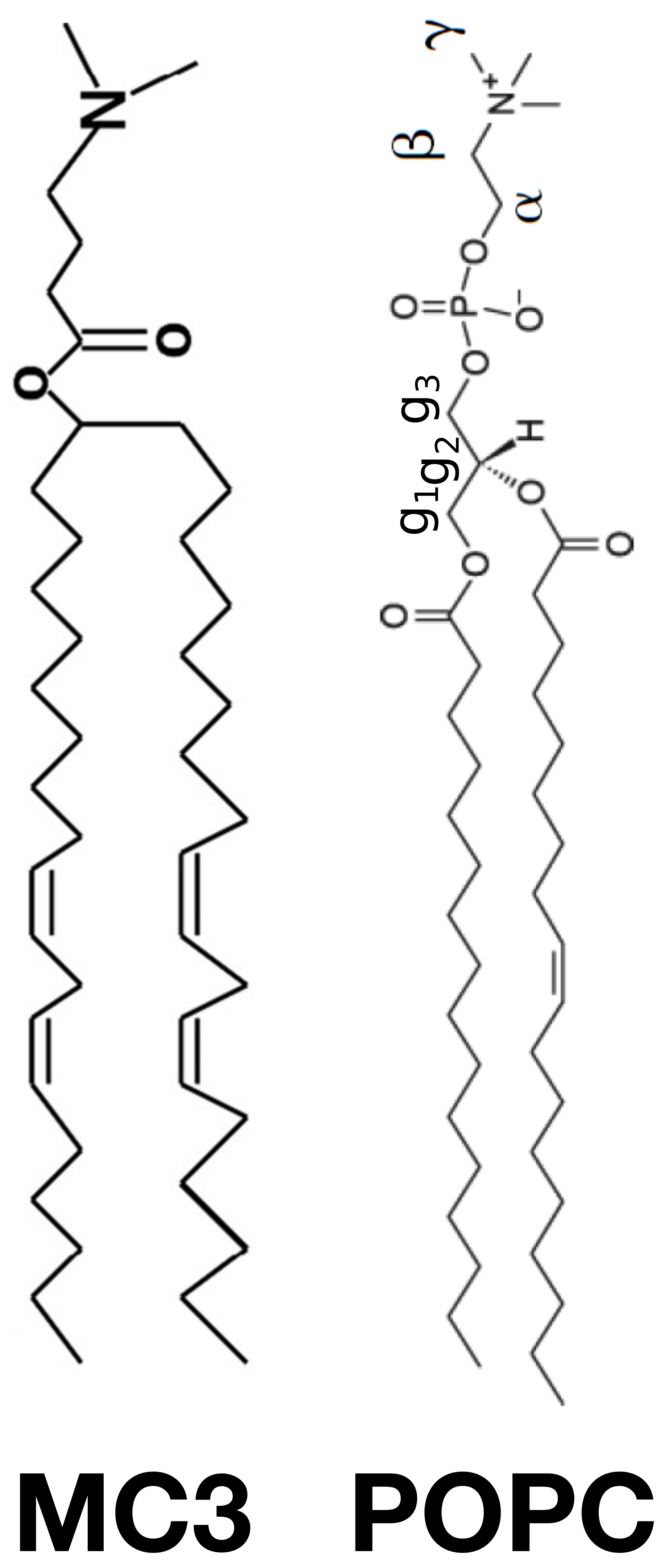
$$F(q) = \int_{-D/2}^{D/2} \Delta\rho_e(z) \cos(z q_z) \mathrm{d}z$$

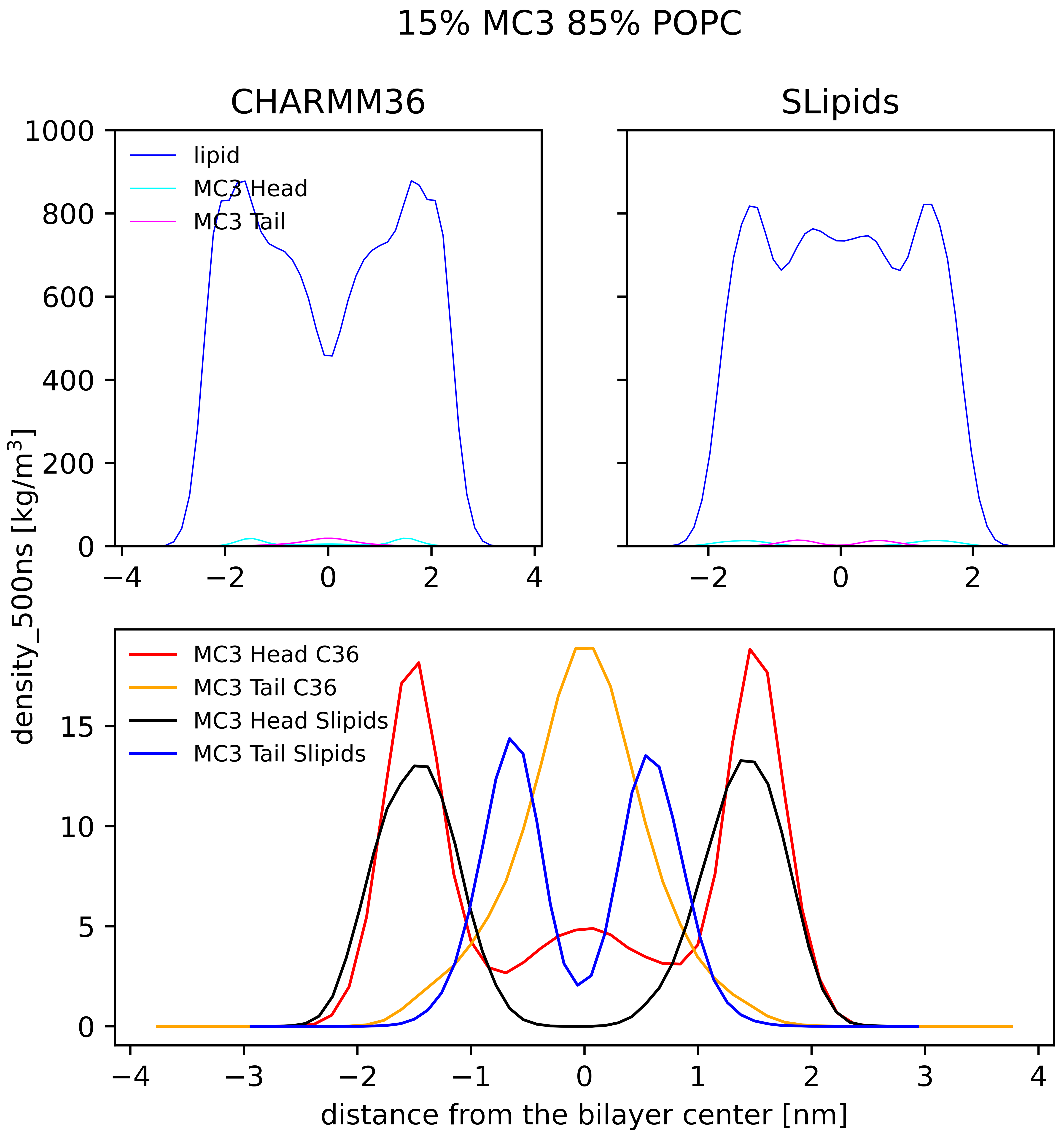
Application: lipid nanoparticle simulations (Batu)



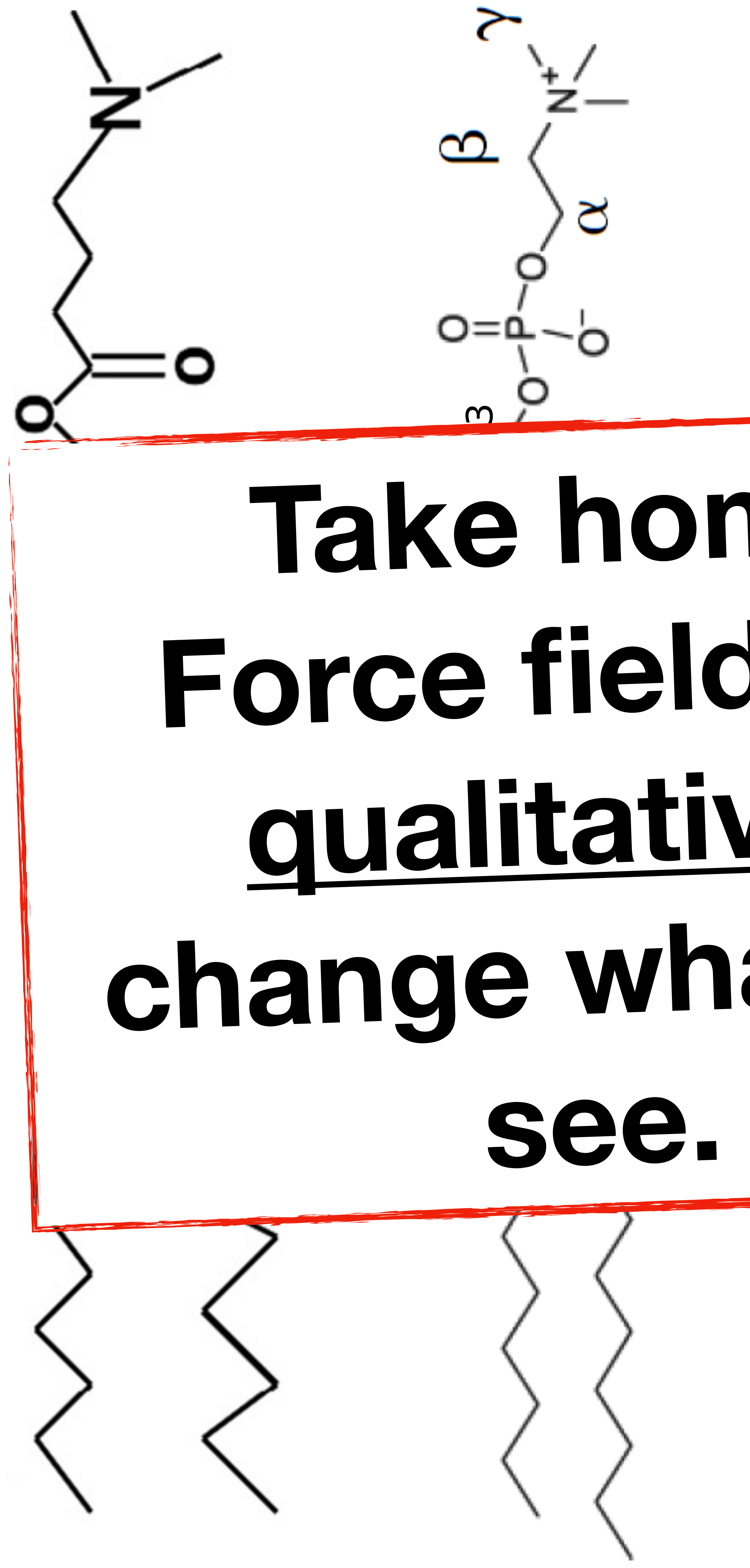
MC3   POPC

Application: lipid nanoparticle simulations (Batu)





Application: lipid nanoparticle simulations (Batu)



Take home:
Force field can **<u>qualitatively</u>** **change what you see.**

MC3 POPC

15% MC3 85% POPC