Towards the Simulation of Bulk Properties via Molecular Dynamics

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Biomolecular Simulations under Realistic Macroscopic Salt Conditions

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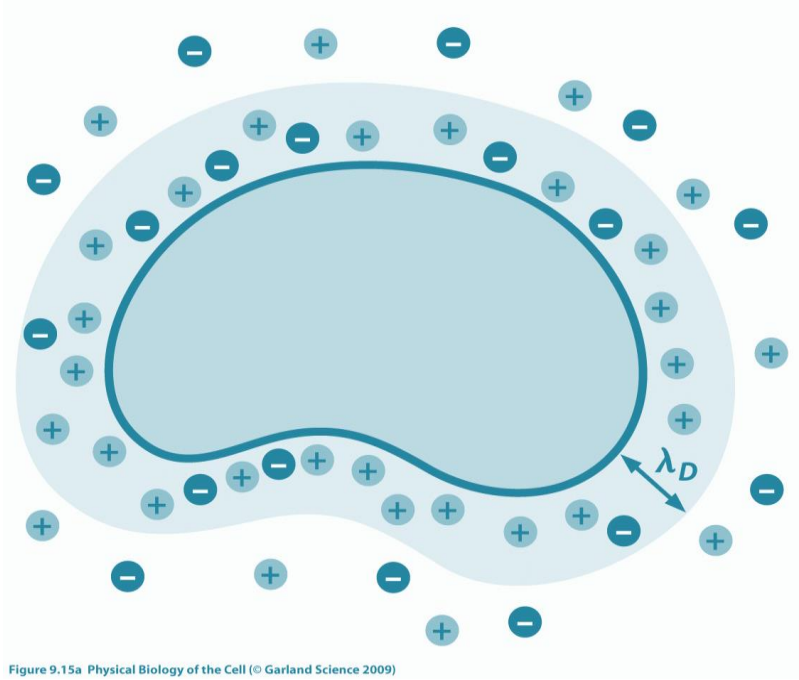
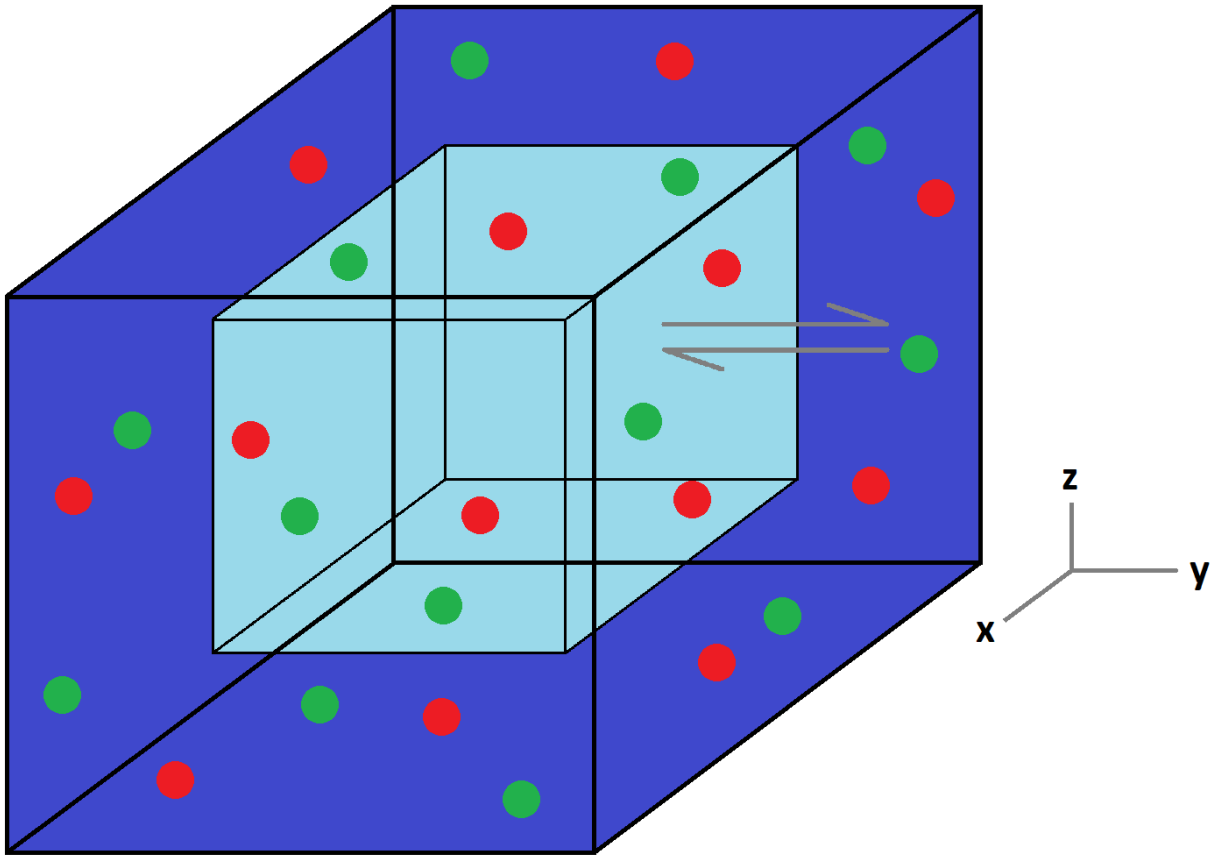


Figure 9.15a Physical Biology of the Cell (© Garland Science 2009)

- Conformations, functions, binding of biomolecules are sensitive to ion content
  - Relevant to pharmacological design
- Simulations fix salt content and so may not accurately represent actual local environment

Ross, Gregory A., et al. "Biomolecular Simulations under Realistic Macroscopic Salt Conditions." *Preprint Ahead of Submission*, 2017, doi:10.1101/226001.;
OpenStax, Biology. OpenStax CNX. May 13, 2015 http://cnx.org/contents/185cbf87-c72e-48f5-b51e-f14f21b5eabd@9.85



-- local environment (simulation volume)

-- nonlocal environment (bulk)

-- positive ion

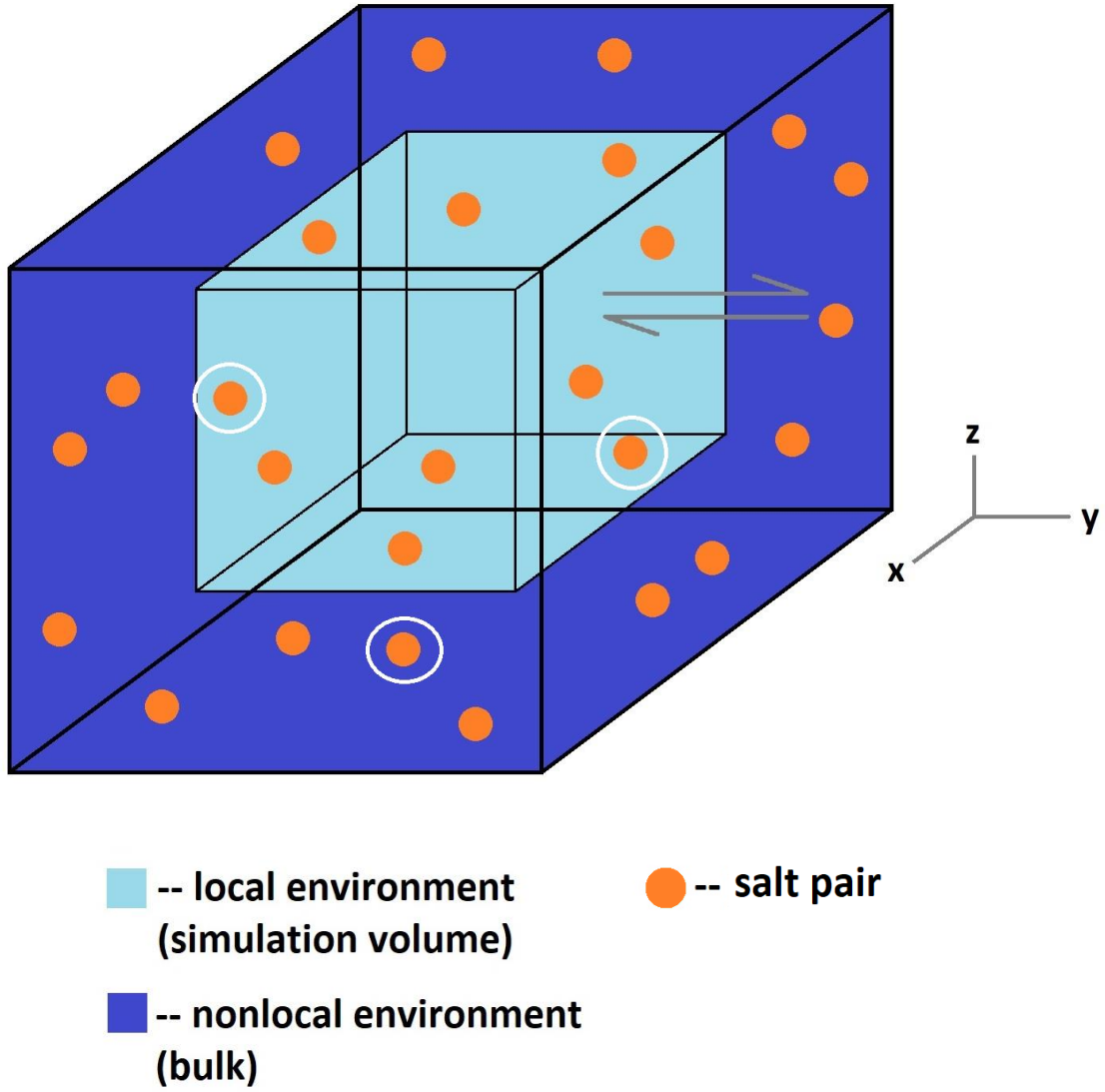
-- negative ion

Fluctuations in Local Environment

- How do fluctuations affect processes like folding, screening layer interactions, and binding?
- How do fluctuations affect free energy?

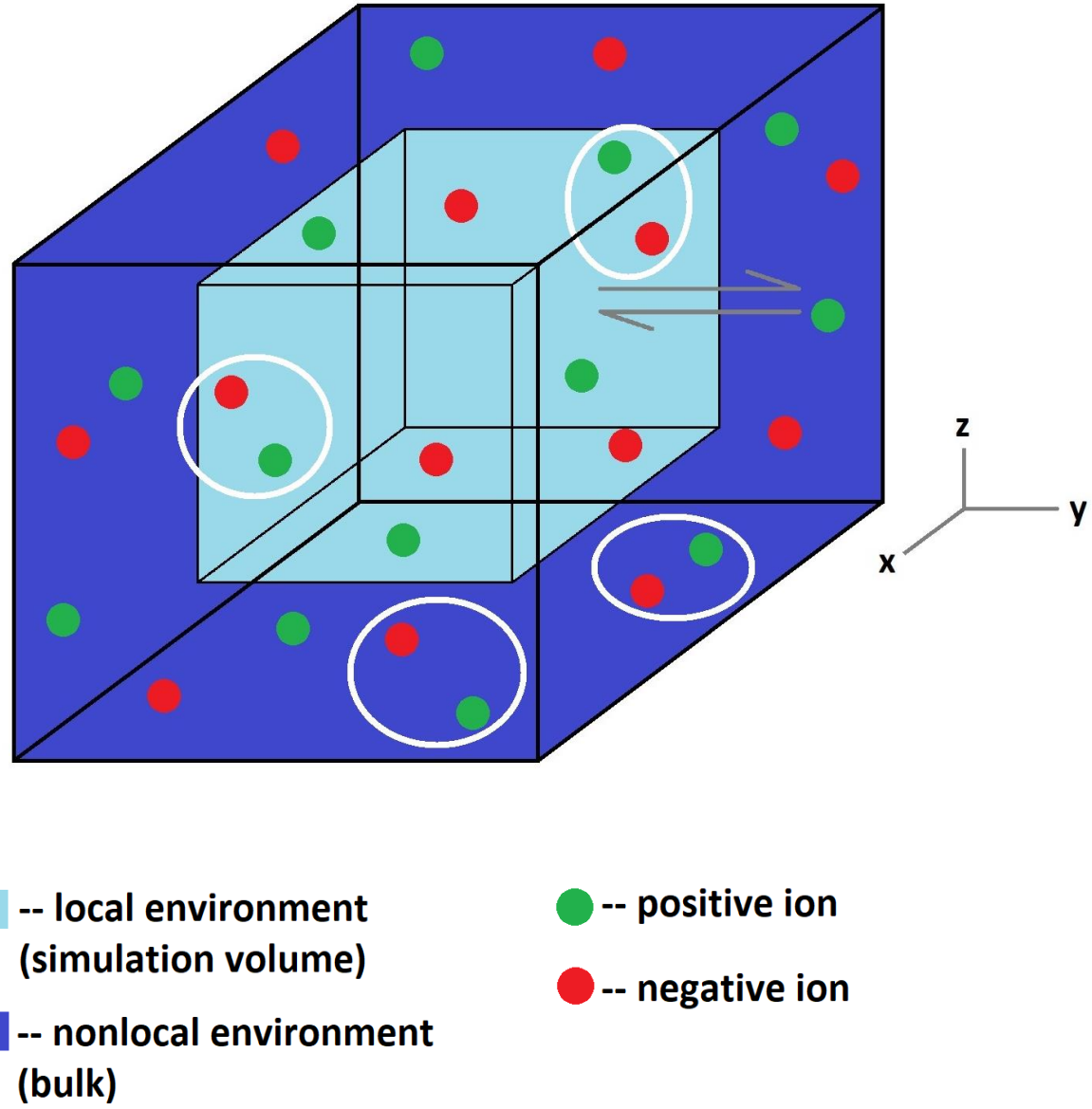
Single particle model

- One degree of freedom
- Anions and cations fluctuate together
- Simplest but least physical



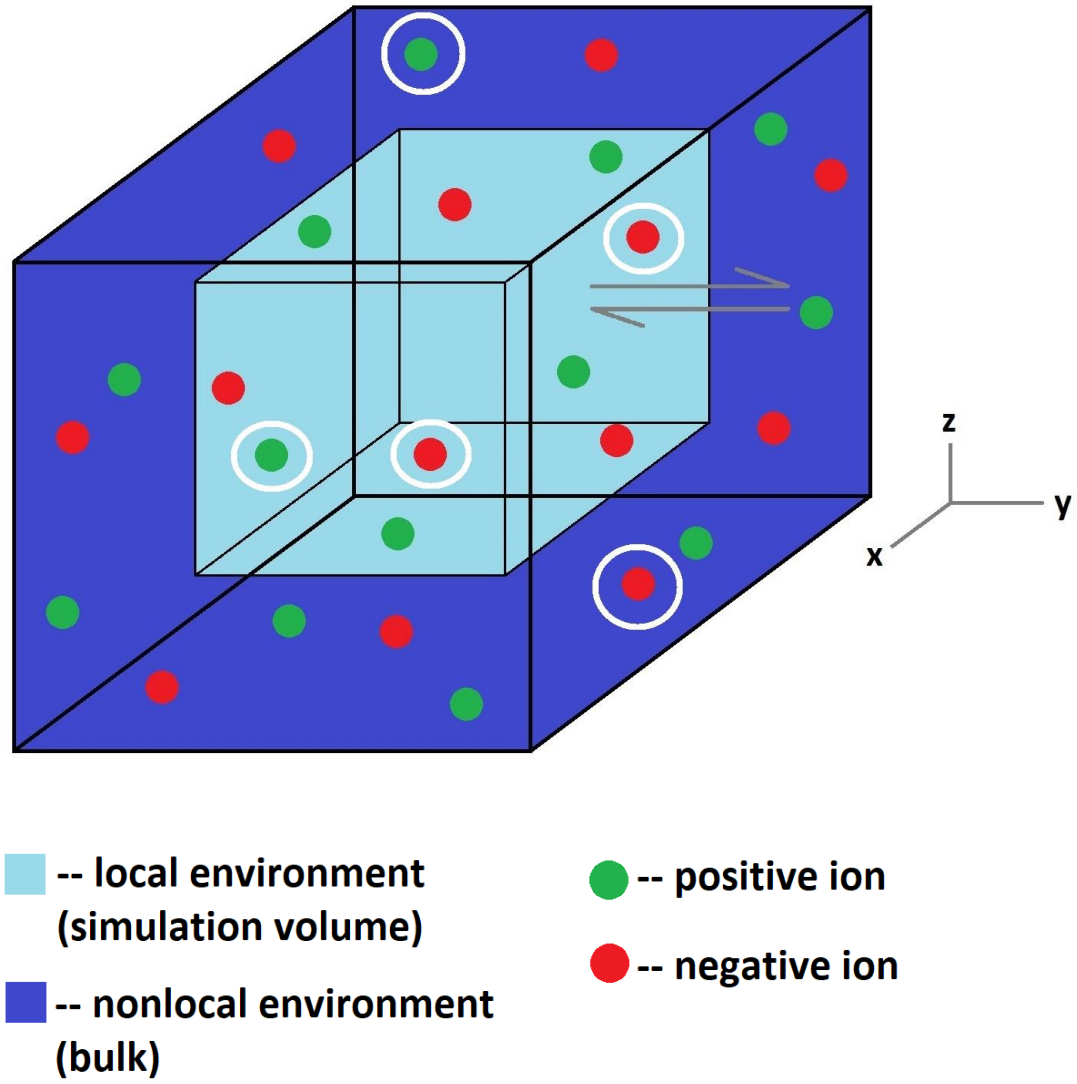
Salt pair model

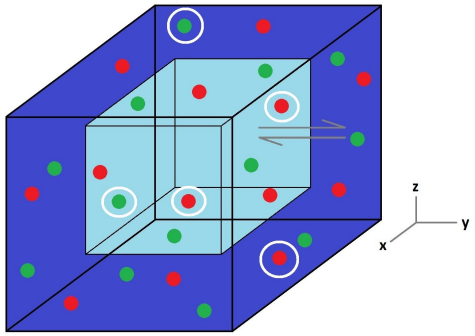
- Two degree of freedom
- Anions and cations fluctuate together
- No electrostatic contribution
- Commonly used for computations



Independent fluctuations

- Two degree of freedom
- Anions and cations fluctuate independently
- Electrostatic contribution





Describing independent fluctuations

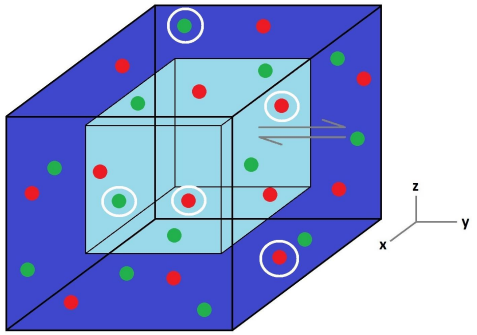
Electrostatic component

Two chemical components

$$Z = \sum_{N_+,N_-} \frac{V^{N_+}}{N_+!} * \frac{V^{N_-}}{N_-!} * e^{\frac{e^2}{8\pi\epsilon RkT}(Q+N_+-N_-)^2} * e^{(N_++N_-)\frac{\mu}{kT}}$$

Two translational components

$\boldsymbol{N_\pm} = number\ of\ \pm\ ions$
$\boldsymbol{V} = volume\ of\ local\ environment$
$\boldsymbol{Q} = charge\ of\ macromolecule$
$\boldsymbol{R} = radius\ of\ local\ environment$
$\boldsymbol{\mu} = chemical\ potential$
$\boldsymbol{e} = charge\ of\ electron$



Evaluating Free Energy using SLTCAP

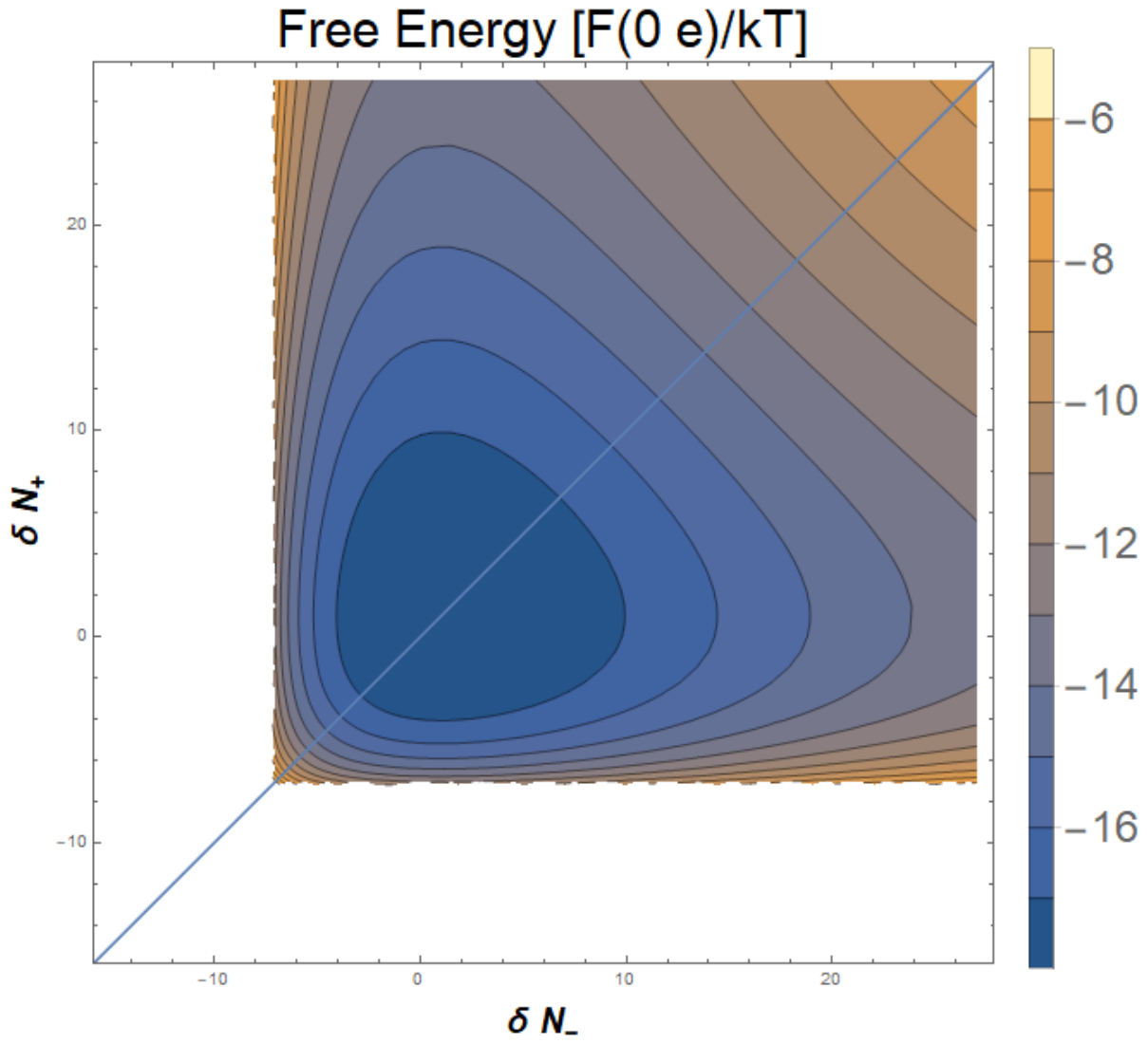
$$F(N_+, \delta N_+, N_-, \delta N_-, Q, V, \mu) = -kT \ln Z$$

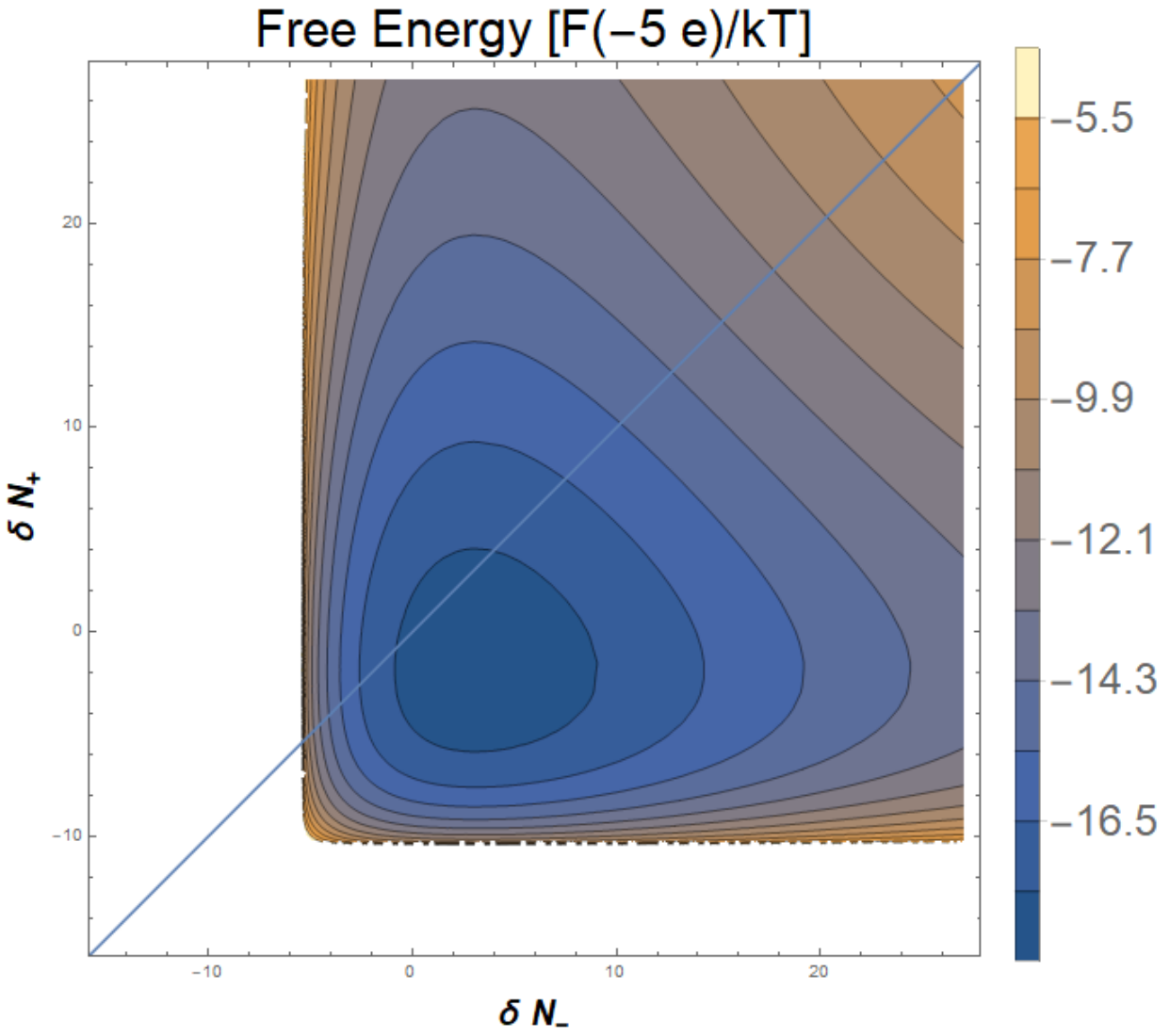
$$N_\pm = Vc_0 * e^{\mp \operatorname{arcsinh}\left(\frac{Q}{2\,e\,V c_0}\right)}$$

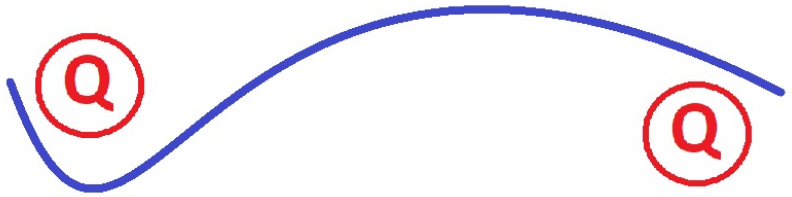
$\boldsymbol{N_\pm} = number\ of \pm ions$
$\boldsymbol{\delta N_\pm} = number\ of\ fluctuations$
$\boldsymbol{V} = volume\ of\ local\ environment$
$\boldsymbol{Q} = charge\ of\ macromolecule$
$\boldsymbol{R} = radius\ of\ local\ environment$
$\boldsymbol{\mu} = chemical\ potential$
$\boldsymbol{e} = charge\ of\ electron$

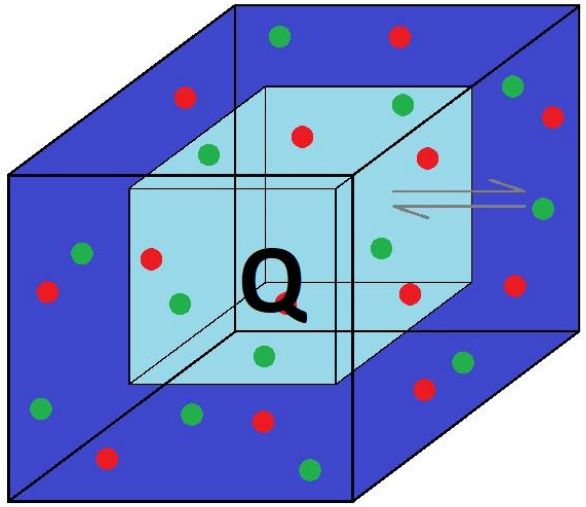
$$F(\delta N_+, \delta N_-, Q, V, c_0)$$

Schmit, Jeremy D., et al. “SLTCAP: A Simple Method for Calculating the Number of Ions Needed for MD Simulation.” Journal of Chemical Theory and Computation, vol. 14, no. 4, 2018, pp. 1823–1827., doi:10.1021/acs.jctc.7b01254.


Free Energy [F(0 e)/kT]
δ N+
δ N_
20
10
0
−10
−10
0
10
20
−6
−8
−10
−12
−14
−16


Free Energy [F(−5 e)/kT]
δ N+
δ N_
20
10
0
−10
−10
0
10
20
−5.5
−7.7
−9.9
−12.1
−14.3
−16.5





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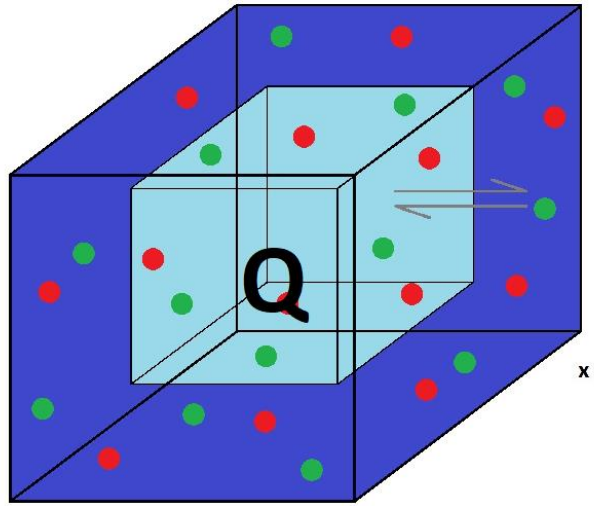

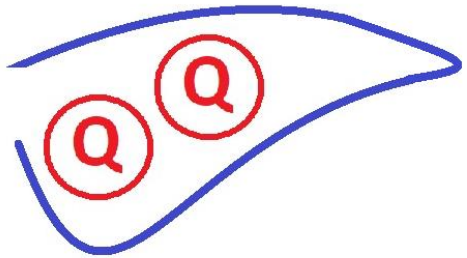

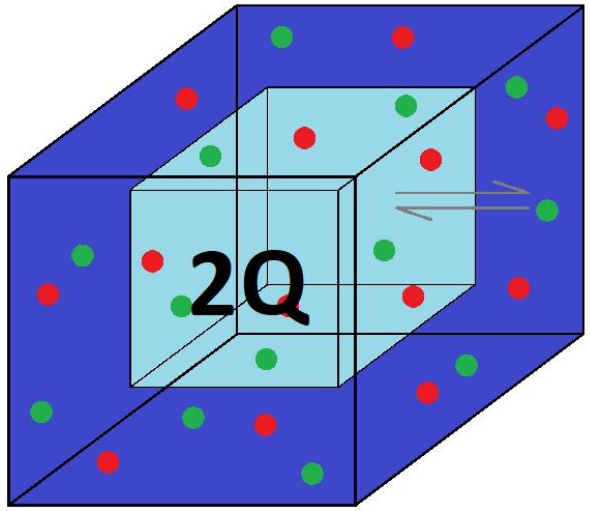

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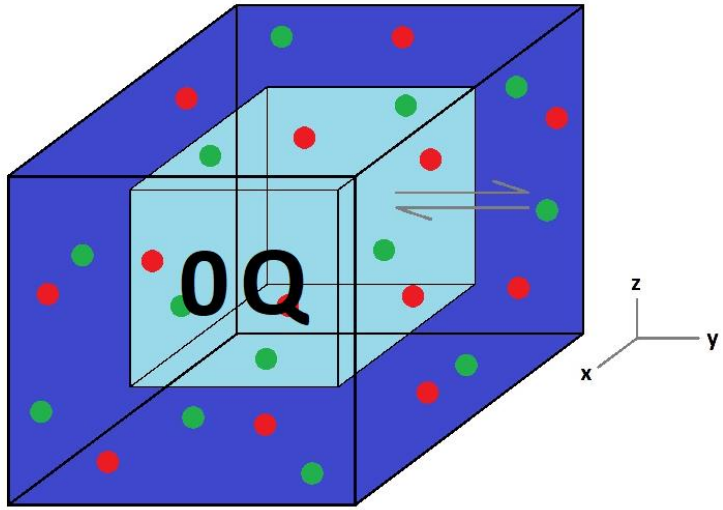


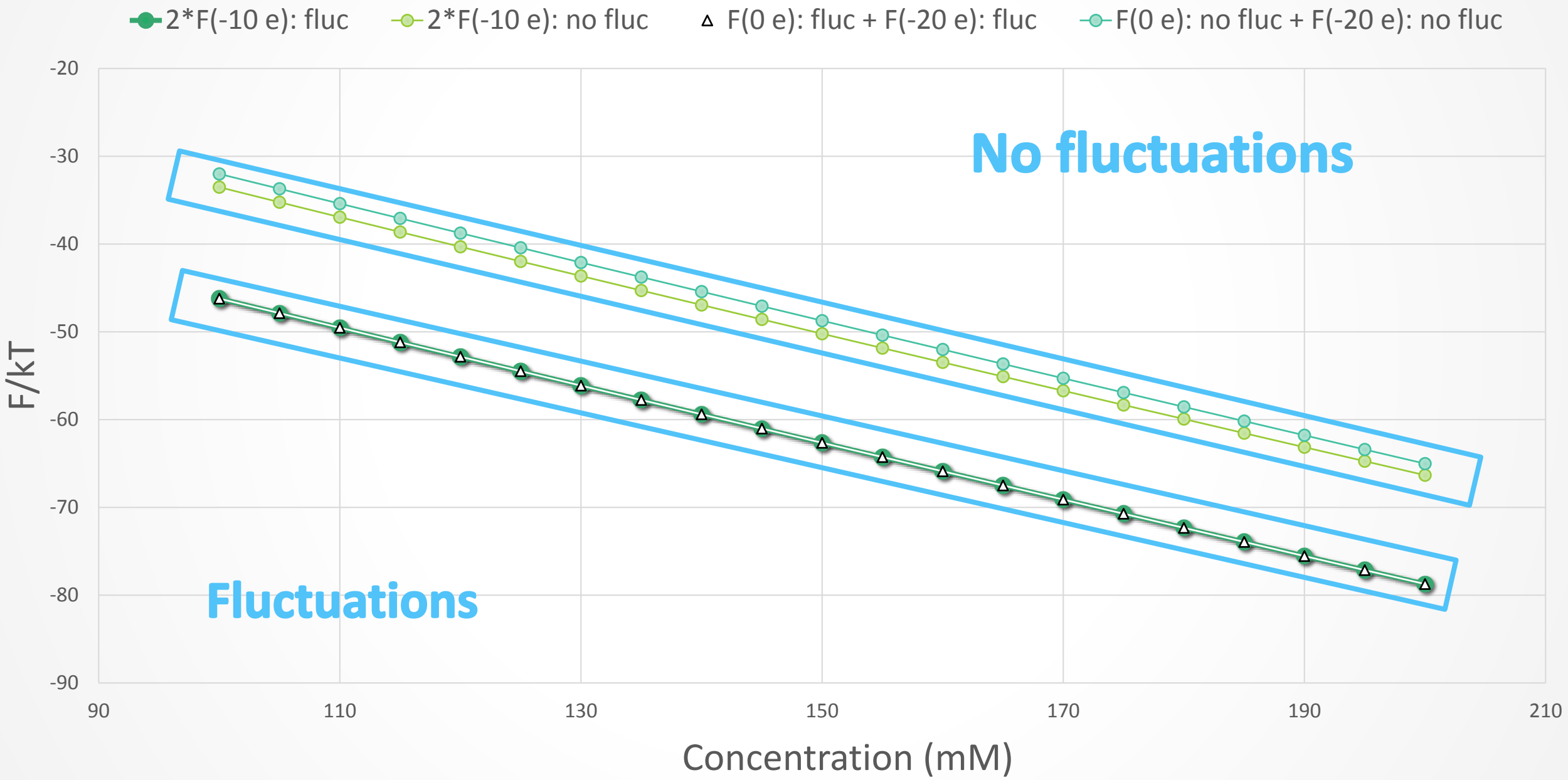
-- local environment (simulation volume)

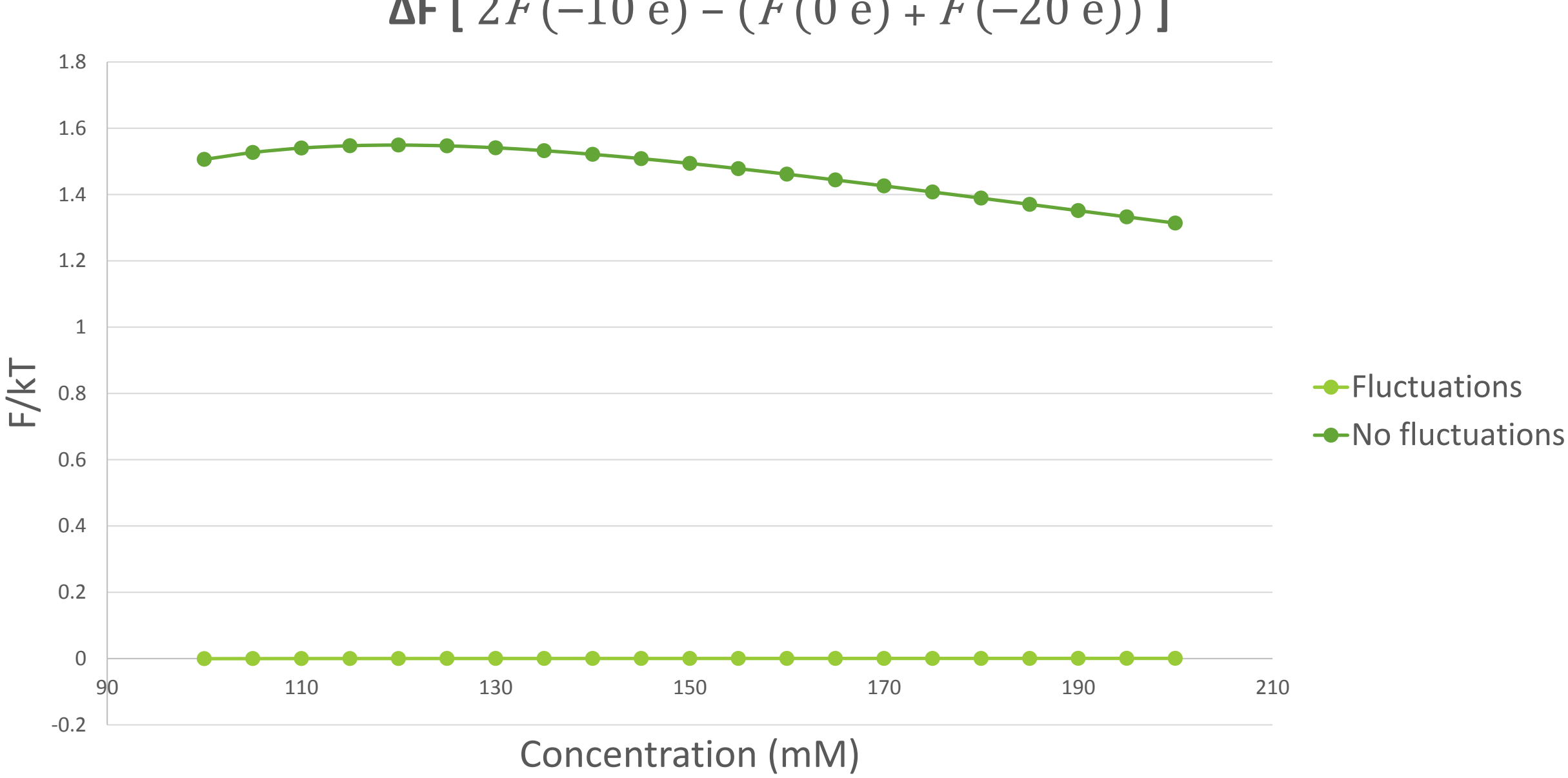
-- nonlocal environment (bulk)

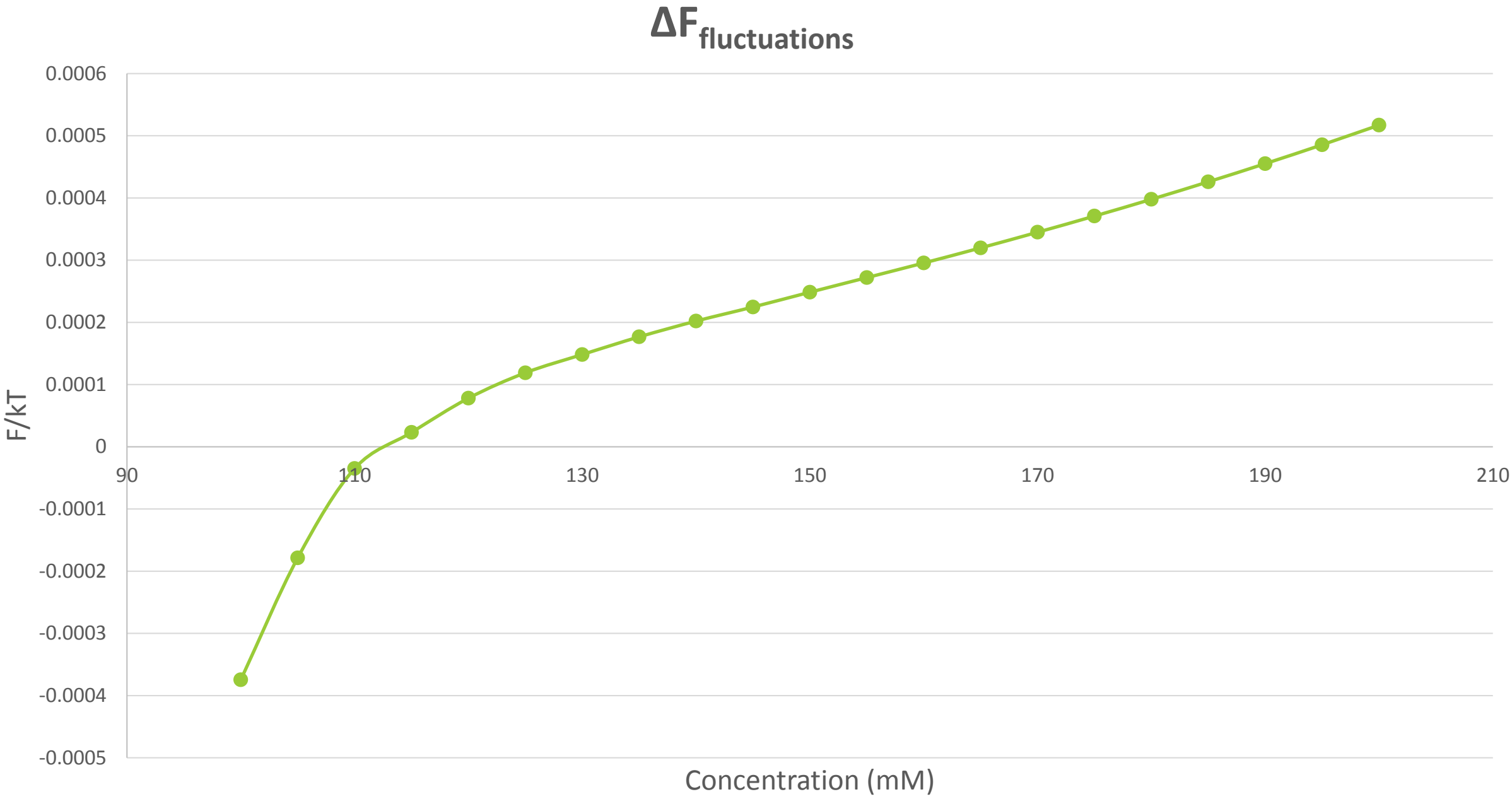
-- positive ion

-- negative ion

Free Energy


2*F(-10 e): fluc
2*F(-10 e): no fluc
F(0 e): fluc + F(-20 e): fluc
F(0 e): no fluc + F(-20 e): no fluc
No fluctuations
Fluctuations
F/kT
-20
-30
-40
-50
-60
-70
-80
-90
90
110
130
150
170
190
210
Concentration (mM)


ΔF [2F(−10 e) − (F(0 e) + F(−20 e))]
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
F/kT
90
110
130
150
170
190
210
Concentration (mM)
Fluctuations
No fluctuations


ΔF fluctuations
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
-0.0001
-0.0002
-0.0003
-0.0004
-0.0005
F/kT
90
110
130
150
170
190
210
Concentration (mM)

Further Research

Explain why $\Delta F_{fluctuations} \ll \Delta F_{no\ fluctuations}$

Collaborate to implement model in simulations

Acknowledgements

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