# Molecular dynamics in physiological solutions: Force fields, alkali metal ions and ionic strength

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## 1. Introduction

Alkali ions are presented in virtually all biological processes. Their energetic properties have been so far predicted mostly by MD or MC calculations based on effective potentials derived for infinite diluted conditions (i.e. a single ion surrounding solely by water molecules) [1].However, in physiological conditions, the concentration of $K^+$ is sub-molar in the cytoplasm, and it may be by one, or even two, orders of magnitude larger near protein or nucleic acids and in active sites of enzymes or channels.
Empirical potential functions are largely employed in atomistic simulations to study non-ideal regimes, for instance to estimate free-energy changes accompanying biological processes such as ion translocation in ion channels or transporters. Even the bulk properties like the "mean chemical potential difference" (or mean activity coefficients) can be reproduced well [2, 3], however, it is not clear how well force fields can reproduce the thermodynamics of single ionic species at finite concentration **I**.
Here we calculated the "excess chemical potential difference" (or activity coefficient) of individual ion for NaCl and KCl aqueous solution at finite **I**. The tested parameter sets are AMBER, CHARMM, Dang95 and OPLS with TIP3P or SPC/E water models.
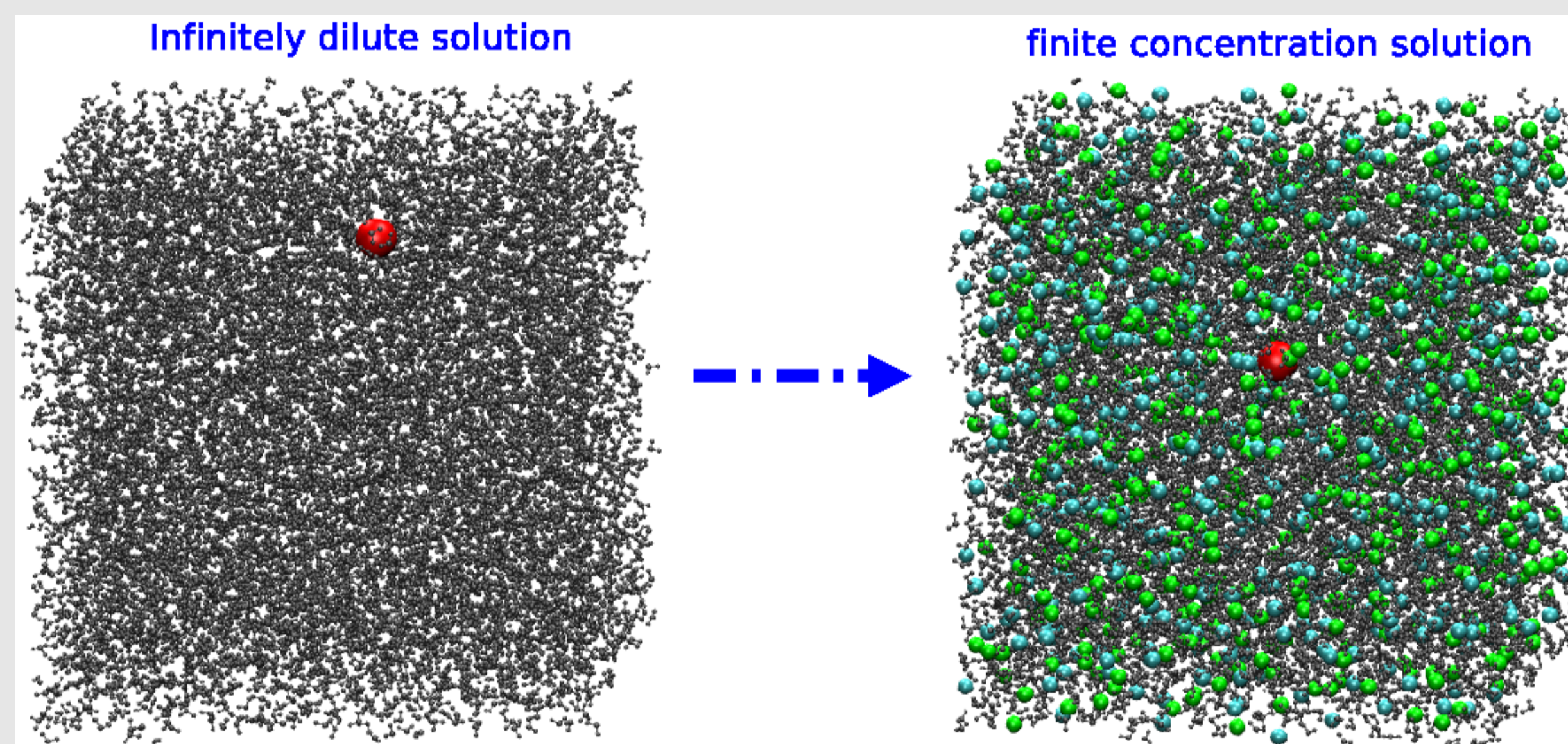


**Figure 1:** *Non-ideal solution arises from finite salt concentration.*

Chemical potential of cation(+) or anion(-) in electrolyte aqueous solution is defined as:

$$\mu_{+/-} = \mu^o_{+/-} + RT \ln \gamma_{+/-} \cdot x_{+/-} \tag{1}$$

The reference state $\mu^o_{+/-}$ is the infinitely dilute aqueous solution, in which the activity coefficient $\gamma_{+/-}$ goes to unity.
The resulting chemical potential in thermodynamic integration is[4]:

$$\mu_{+/-} = -\frac{1}{\beta} \ln(k_b T/\langle P \rangle \Lambda^3_{+/-})$$
$$-\frac{1}{\beta} \ln \int_0^1 d\lambda \langle U_1 \rangle_\lambda$$
$$= \mu^{id}_{Na+} + \mu^{I,ex}_{Na+} \tag{2}$$

Where $U_1$ is the binding energy of testing ion with the rest ions and water.
The "excess chemical potential difference" of individual ion is:

$$\Delta \mu^{ex} = RT \ln \gamma_{+/-} = \mu^{I,ex}_{+/-} - \mu^{0,ex}_{+/-} \tag{3}$$

## 2. Replica-exchange Thermodynamic Integration

The testing ion can be trapped in local chemical environment due to close packing and strong electrostatic interaction, therefore, replica-exchange thermodynamic integration(RETI) [5] was used to check the convergence of the results. The Metropolis-type criteria for the transition probability between subsystems $Q_{\lambda_i}$ is:

$$acc(Q_{\lambda_i} \to Q_{\lambda_j}) = min\{\exp(-\beta\Delta), 1\} \tag{4}$$

where

$$\Delta = \lambda_i[U_1(\mathbf{x}_j, \lambda_i) - U_1(\mathbf{x}_i, \lambda_i)] - \lambda_j[U_1(\mathbf{x}_j, \lambda_j) - U_1(\mathbf{x}_i, \lambda_j)] \tag{5}$$
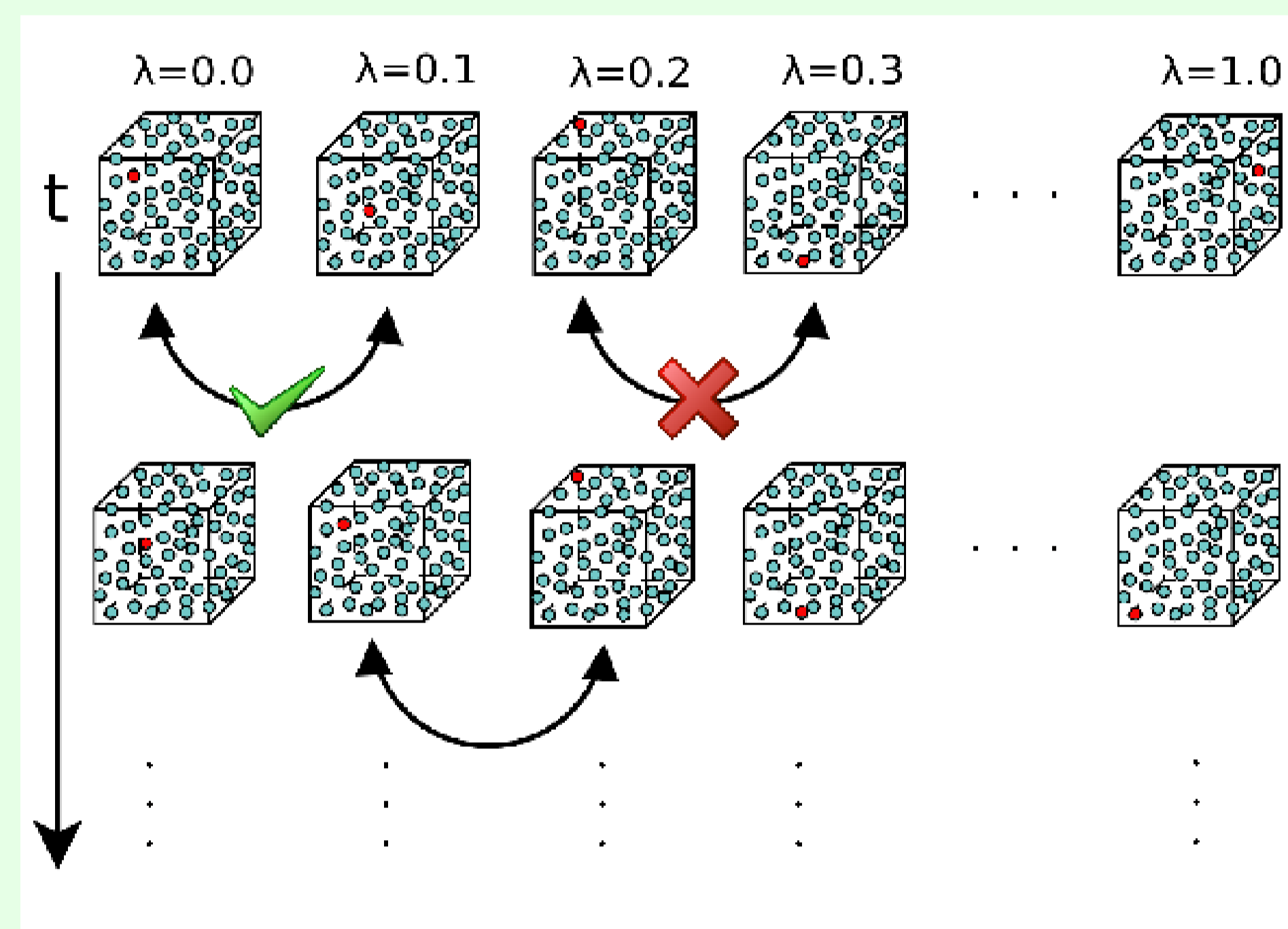


**Figure 2:** *Schematic diagram of replica-exchange thermodynamic integration.*

We found that Replica-exchange TI is much faster to converge than straightforward TI in non-ideal electrolyte aqueous solutions. The thermodynamic forces due to the Lennard-Jones potential converge after 1.8ns with replica-exchange TI, whereas no convergence is reached after 2 ns with straightforward TI (Fig.3 left) The electrostatic free energy calculated with replica-exchange TI is much smoother than straightforward TI (Fig. 3 right). Even the number of windows are doubled, the results from replica-exchange TI do not deviate from each other significantly. These indicate the sufficient sampling with replica-exchange TI.
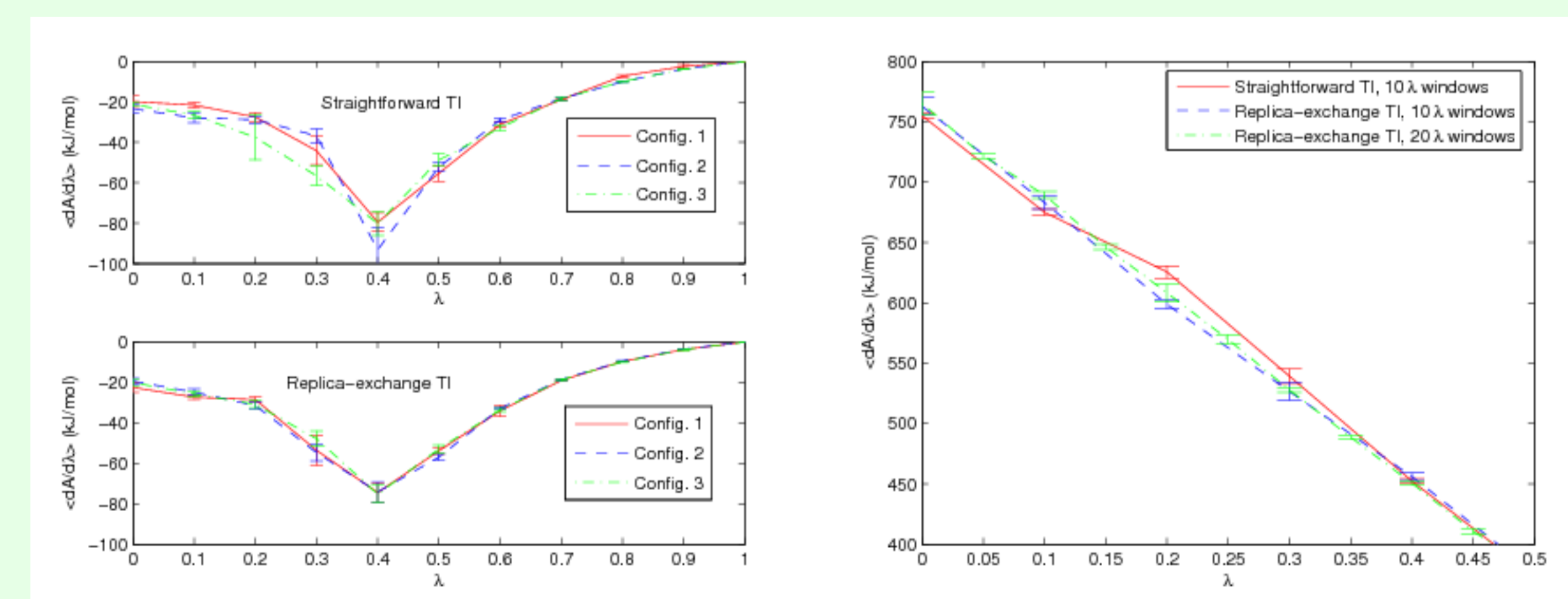


**Figure 3:** *Thermodynamics force profile using standard TI and replica-exchange TI.*

## 3. $\Delta\mu^{ex}$ of single ion

First, the free energy calculations predict different non-ideal behavior for the two alkali metal cations reminiscent of that found experimentally. Importantly, the excess chemical potential difference clearly depends on contributions beyond the simple ion-ion interactions in the Debye approximation.
Second, the calculated $\Delta\mu^{ex}$ differs quantitatively from experimental data, except for the calibrated case of **I** =0. Such discrepancy is large (about 10 kJ/mol at the largest measured **I**), and is more for $K^+$ than $Na^+$.
Finally, the corresponding plot for $Cl^-$ ion (Fig. 4 bottom) shows that, at **I** =0, (i) quantitative agreement with experiment can be achieved, as it was for the cations; (ii) the calculated $\Delta\mu^{ex}$ turns out to depend on the counter-ion much more in the calculation than in experiment. The large deviation of $\Delta\mu^{ex}$ for $Cl^-$ in KCl solution is coincident with that for $K^+$, which suggests that $K^+$ models might be at fault.
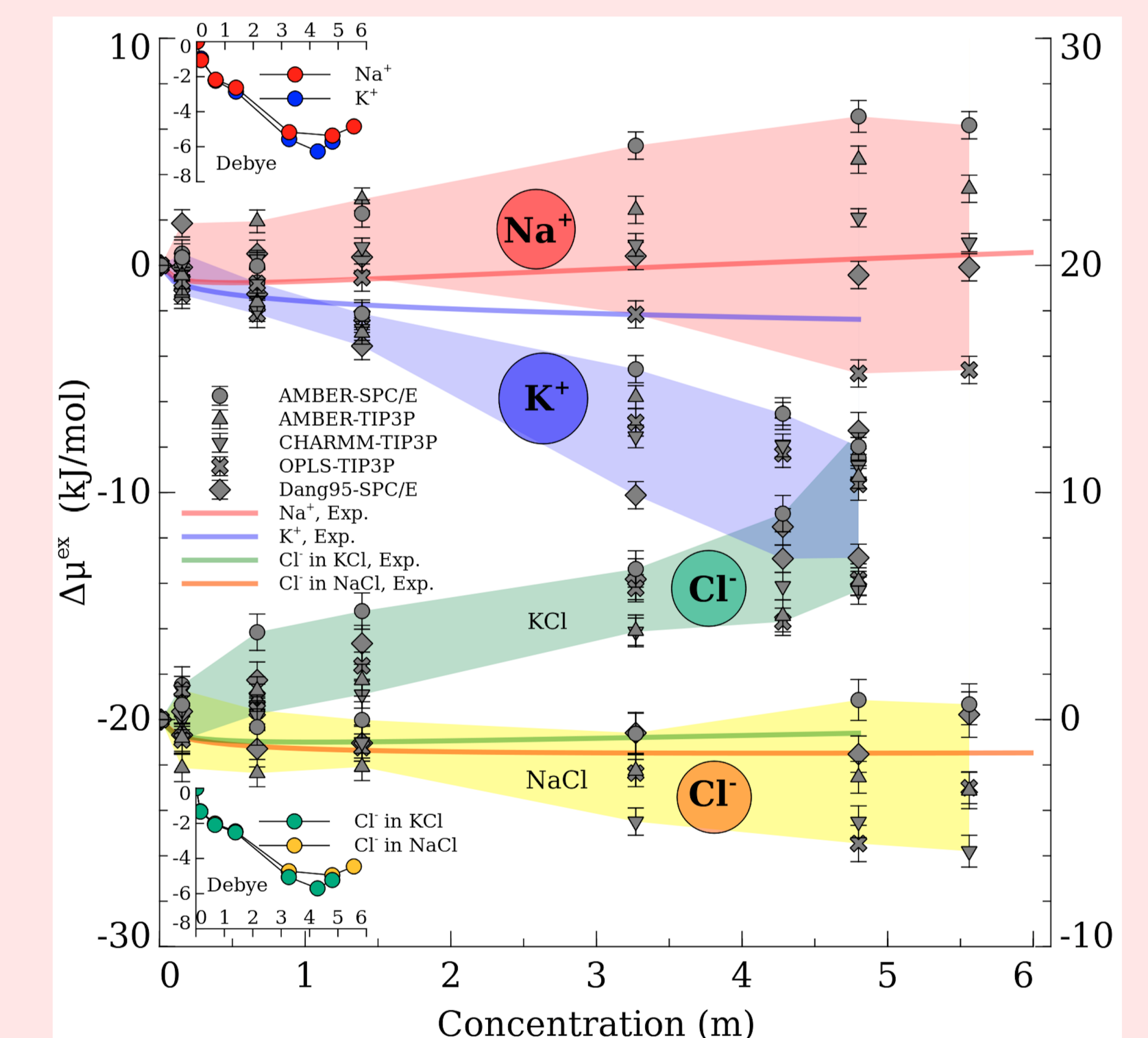


**Figure 4:** *Calculated and experimental[6] excess chemical potential difference $\Delta\mu^{ex}$ of $Na^+$ and $K^+$ ions (top) and $Cl^-$ ions (bottom) in NaCl and KCl aqueous solutions. Insects: $\Delta\mu^{ex}$ of $Na^+$ and $K^+$ (top left) and $Cl^-$ (bottom left) as obtained using Debye approximation, based on AMBER-SPC/E recipe.*

## References

[1] Patra, M.; Karttunen, M. *J. Comput. Chem* 25: 678-689, 2004

[2] Hess, B.; van der Vegt, F. A. *Proc. Natl. Acad. Sci. USA* 106: 13296-13300, 2009

[3] Joung, I. S.; Cheatham, III, T. E. *J. Phys. Chem. B* 113: 13279-13290, 2009

[4] Ferrario, M.; Ciccotti, G.; Spohr, E.; Cartailler, T.; Turq, P. *J. Chem. Phys.* 117: 4947-4953, 2002

[5] Fukunishi, H.; Watanabe, O.; Takada, S. *J. Chem. Phys.* 116:9058-9067, 2002

[6] Wilczek-Vera, G.; Rodil, E. and Vera, J. H. *AIChE J.* 50: 445-462, 2004