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COMMENT

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Comment on "Simulations of ionization equilibria in weak polyelectrolyte solutions and gels" by J. Landsgesell, L. Nová, O. Rud, F. Uhlík, D. Sean, P. Hebbeker, C. Holm and P. Košovan, *Soft Matter*, 2019, 15, 1155–1185

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In a recent review Landsgesell *et al.*, *Soft Matter* 2019, **15**, 1155 stated that pH – pK_a is a "universal parameter" for titrating systems. We show that this is not the case. This broken symmetry has important implications for constant pH (cpH) simulations. In particular, we show that for concentrated suspensions the error resulting from the use of cpH algorithm described by Landsgesell *et al.* is very significant, even for suspension containing 1 : 1 electrolyte. We show how to modify the cpH algorithm to account for the grand-canonical nature of the cpH simulations and for the charge neutrality requirement.

In a recent review article[1] Landsgesell *et al.* stated that pH – pK_a is a "universal parameter" for titrating systems, in other words one will obtain the same number of protonated groups in different systems as long as they have the same value of pH – pK_a, "provided that all other conditions are the same". This implies the existence of an underlying symmetry

$$\begin{aligned} \mathrm{pH} &\rightarrow \mathrm{pH} + \alpha \\ \mathrm{p}K_a &\rightarrow \mathrm{p}K_a + \alpha, \end{aligned} \tag{1}$$

where α is a real number. The only theoretical motivation for this curious result appears to be the behavior of an ideal non-interacting system, Fig. 1 of the ref. 1. Indeed a simple Langmuir adsorption isotherm for the number of deprotonated groups of a macromolecule can be written as

$$Z_{\mathrm{eff}} = \frac{Z}{1 + \frac{c_a}{K_a}}, \tag{2}$$

where Z is the total number of acid groups, c_a is the concentration of hydronium ions inside the solution, and K_a is the intrinsic equilibrium constant of a group undergoing protonation/deprotonation reaction HA $\rightleftharpoons$ $H^+ + A^-$. The solution pH is defined as $\mathrm{pH} = -\log_{10}\left[\frac{a_H}{c^\ominus}\right]$, where a_H is the activity of hydronium ions and $c^\ominus = 1$ M is the reference concentration. In the absence of salt, and not too low pH, a_H is approximately equal to the concentration of acid $a_H \approx c_H$. The pK_a is defined as p$K_a = -\log_{10}[K_a/c^\ominus]$, so that ideal Langmuir isotherm can be expressed as:

$$Z_{\mathrm{eff}} = \frac{Z}{1 + 10^{-\mathrm{pH}+\mathrm{p}K_a}}, \tag{3}$$

which indeed has the symmetry described using eqn (1). Landsgesell *et al.* then argued that titration simulations can alternatively be done using the "K sweeping" method in which pK_a of surface groups is varied instead of pH. They also suggested that the correct way to present the titration data is by plotting the number of titrated groups as a function of pH – pK_a, instead of the usual pH, since according to the authors this is the "relevant" invariant parameter. In spite of its appeal, one can see that the symmetry described using eqn (1) is not exact for real interacting systems. This already manifests itself at the mean-field level. For example, consider a salt free colloidal suspension in contact with an acid reservoir of concentration c_a. Following R. A. Marcus[2] this can be modeled as a spherical particle of radius a with Z uniformly distributed surface groups, confined inside a spherical cell of radius R. The radius of the cell is determined by the volume fraction of colloidal particles inside the suspension, $\eta = a^3/R^3$. According to Ninham and Parsegian[3] (NP) the number of deprotonated groups is still given by the Langmuir isotherm, but with the bulk concentration of hydronium ions replaced by the local concentration at the surface of the nanoparticle,

$$Z_{\mathrm{eff}} = \frac{Z}{1 + 10^{-\mathrm{pH}+\mathrm{p}K_a} e^{-\beta\phi(a)}}, \tag{4}$$

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where $\phi(a)$ is the surface electrostatic potential which can be obtained from the solution of the Poisson–Boltzmann equation

$$\nabla^2\phi(r) = \frac{8\pi q c^{\ominus} 10^{-\mathrm{pH}}}{\varepsilon_0}\sinh[\beta\phi(r)], \qquad (5)$$

where $\beta = 1/k_BT$ and q is the proton charge. Clearly the surface potential does not satisfy the symmetry described using eqn (1). To make this even clearer, we have numerically solved the NP equations for a nonoparticle of radius a = 100 Å with Z = 600 surface groups inside a spherical cell of R = 200 Å. In the first case we fix pH = 1, pK_a = 2.5 and in the second pH = 6, pK_a = 7.5, in both cases pH − pK_a = −1.5. For the first system we obtain particles with surface charge density $\sigma = -qZ_{\mathrm{eff}}/4\pi a^2$ = −2.65 mC m^{-2} and for the second −0.07 mC m^{-2}. Clearly, there is no "universality".

To confirm the "universality" of pH − pK_a, authors of ref. 1 performed canonical reactive MC (RMC) and constant pH (cpH) simulations. RMC simulations allow for the protonation and deprotonation moves between hydronium ions and polyelectrolyte groups. The difficulty is that RMC simulations do not provide a direct access to the pH inside the solution, which must be obtained using a separate Widom insertion simulation method. This makes such simulations inaccurate for large pH when very few hydronium ions are present inside the simulation cell. On the other hand cpH simulations, which use acceptance probabilities:

$$P = \min[1, \exp(-\beta\Delta U + \zeta(\mathrm{pH} - \mathrm{p}K_a)\ln(10))] \qquad (6)$$

with $\zeta = \pm 1$ for deprotonation/protonation moves respectively can, in principle, be easily implemented for any pH. Indeed this equation satisfies the symmetry given by eqn (1). Clearly this contradicts our simple mean-field argument, which shows that eqn (1) is not an exact symmetry of titrating systems and, therefore, eqn (6) can not be correct. To understand the underlying problem, it is important to realize that constant pH simulations are intrinsically grand-canonical. This can be clearly seen from the weight for a protonation move which has $e^{-\ln(10)\mathrm{pH}} \sim e^{\beta\mu_{\mathrm{H}}}$, where μ_{H} is the chemical potential of hydronium. This is exactly the grand-canonical weight corresponding to the removal of a hydronium ion from the reservoir. When performing grand-canonical MC (GCMC) simulations of Coulomb systems, it is essential to preserve the charge neutrality inside the simulation cell. Therefore, a grand-canonical protonation move must be combined with a corresponding grand-canonical insertion move for an anion, and a deprotonation move with a GCMC removal of an anion. The acceptance probabilities for deprotonation and protonation moves can then be written as:[4]

$$P_{\mathrm{d}} = \min\left[1, \frac{N_{\mathrm{Cl}} e^{-\beta(\Delta U + \mu_{\mathrm{Cl}}^{\mathrm{ex}}) + \ln(10)[\mathrm{pH} - \mathrm{p}K_a]}}{c_{\mathrm{Cl}} V}\right],$$

$$P_{\mathrm{p}} = \min\left[1, \frac{c_{\mathrm{Cl}} V e^{-\beta(\Delta U - \mu_{\mathrm{Cl}}^{\mathrm{ex}}) - \ln(10)[\mathrm{pH} - \mathrm{p}K_a]}}{N_{\mathrm{Cl}} + 1}\right], \qquad (7)$$

where N_{Cl} is the number of chloride ions inside the simulation box of volume V and c_{Cl} is the concentration of chloride in the reservoir and $\mu_{\mathrm{Cl}}^{\mathrm{ex}}$ is its excess chemical potential. It is instructive to define $\mathrm{pCl} = -\log_{10}(a_{\mathrm{Cl}}/c^{\ominus})$, where a_{Cl} is the activity of Cl$^-$. Recalling that activity is $a_{Cl} = c_{Cl}e^{\beta\mu_{\mathrm{Cl}}^{\mathrm{ex}}}$, the correct acceptance probabilities of titration moves for a constant pH simulation are:

$$P_{\mathrm{d}} = \min\left[1, \frac{N_{\mathrm{Cl}}}{c^{\ominus} V} e^{-\beta\Delta U + \ln(10)[\mathrm{pH} - \mathrm{p}K_a + \mathrm{pCl}]}\right],$$

$$\mathrm{P}_p = \min\left[1, \frac{c^{\ominus} V}{N_{Cl} + 1} e^{-\beta\Delta U - \ln(10)[\mathrm{pH} - \mathrm{pK}_a + \mathrm{pCl}]}\right]. \qquad (8)$$

To distinguish this from the cpH simulations of Landsgesell *et al.*, we shall call this the "grand canonical pH simulation" (GCpH).[4] If in addition to acid the reservoir contains salt, additional grand canonical insertion/deletion moves of ions must be included in the simulation.[5] For pH < 7, hydrolysis of water can be neglected, so that pCl ≈ pH. Using this in eqn (8), it is clear that the symmetry of eqn (1) is broken. It is actually possible to forgo the pairing of hydronium and of anions during the titration moves, but at the cost of introducing the Donnan potential between the system and the reservoir into the exponential of eqn (6). This will also break the symmetry of eqn (1). The Donnan potential is a Lagrange multiplier[6] that forces the net charge neutrality inside the system, while making titration and GCMC moves independent. It is possible to show that both methods result in the same number of protonated groups.[5,7] Implementation of the Donnan method, however, is more involved, since the Donnan potential must be adjusted throughout the simulation to keep the simulation cell charge neutral. We have performed the constant pH simulations using the correct acceptance ratios, eqn (8), for the same nanoparticle system studied above with the NP mean-field theory. The simulation uses explicit ions all of radius 2 Å, and implicit water of dielectric constant ε_w = 78. For the case of pH= 1 and pK_a= 2.5, we obtain the surface charge density −3.24 mC m^{-2}; and for the case of pH = 6 and pK_a = 7.5 we obtain −0.08 mC m^{-2}, in a reasonable agreement with the mean-field theory. Clearly pH − pK_a is not universal. To our knowledge Labbez and Jönsson[4] where the first to point out that eqn (6) has a problem and that it can result in significant errors. In the present Comment, we were led to the same conclusion by the fact that that the mean-field theory does not possess the "universal" symmetry advocated by the authors of ref. 1

Finally, it is important to note that simply combining protonation move with a random deletion of a hydronium from the simulation cell, and a deptrotonation move with a random creation of hydronium inside the cell does not resolve the fundamental problem of eqn (6). Since the total number of protons/hydroniums in such simulation is conserved, the correct acceptance probabilities for the deprotonation/protonation moves in such canonical reactive MC simulations are:[8,9]

$$P_{\mathrm{d}} = \min\left[1, \frac{VK_a}{N_{\mathrm{H}} + 1} e^{-\beta\Delta U}\right],$$

$$P_{\mathrm{p}} = \min\left[1, \frac{N_{\mathrm{H}}}{VK_a} e^{-\beta\Delta U}\right]. \qquad (9)$$

Table 1 Average number of deprotonated groups (Z_{eff}) calculated using: canonical, cpH, and GCpH simulation methods. Suspension of volume fraction η in contact with a reservoir of salt (NaCl) at a concentration of 100 mM and pH indicated in the Table. Colloidal particles of Z = 600, a = 80 Å, and pK_a = 5.4

	η = 29.6%			η = 6.4%		
pH	Canonical	cpH	GCpH	Canonical	cpH	GCpH
5.1	124.2	168.3	124.0	124.1	143.9	124.2
5.6	205.0	284.1	205.3	205.0	235.3	205.0
6.1	305.0	411.4	305.1	305.0	344.4	305.1
6.6	412.0	512.9	412.3	412.0	453.0	412.5

where, N_H is the number of hydronium ions inside the simulation cell. The canonical acceptance probabilities, eqn (9), do not depend on pH of solution and are not invariant under the transformation described by eqn (1). On the other hand, such canonical simulation provides an excellent test for the cpH and GCpH simulation methods. We can run the GCpH simulation for a system in contact with a reservoir containing both acid and NaCl salt. After the system has equilibrated, we can obtain the average number of Na^+, Cl^-, and protons (both bound and free) inside the simulation cell. We can then run a *canonical* reactive MC simulation, eqn (9), starting from an initial state in which colloidal particle is fully deprotanated, and the same numbers of Na^+, Cl^-, and hydroniums obtained from GCpH simulation are randomly distributed inside the simulation cell. Based on the ensemble equivalence of statistical mechanics, both simulation methods must converge to the same number of protonated groups. In Table 1, we see that this is exactly what we find for colloidal suspensions of various volume fractions, pH, and salt concentration. On the other hand the charge neutral cpH simulations (with hydroniums and salt inside the simulation cell) only become reasonably accurate for dilute suspensions of a very low volume fraction, even in the presence of 100 mM salt.

Conclusions

To conclude: pH – pK_a is not a universal parameter for titrating systems. For dilute suspensions containing large concentrations of 1 : 1 electrolyte, it is an approximate symmetry. The fact that in general the pH – pK_a symmetry is broken, implies that the cpH simulations based on eqn (6) are flawed and should be replaced by GCpH simulations based on eqn (8). The GCpH algorithm takes into account the underlying grand-canonical structure of cpH simulations and the requirement of charge neutrality. The precise conditions for which the difference between cpH and GCpH algorithms will be significant *i.e.* the volume fraction of a polyelectrolyte, ionic strength of solution, the presence of multivalent ions, intrinsic pK_a, *etc.* – has to be explored in more details in the future. The examples presented in this Comment, however, clearly demonstrate that for suspensions of a finite volume fraction, the errors resulting from the use of the cpH algorithm are significant, even for suspensions with large concentrations of 1 : 1 electrolyte.

Conflicts of interest

There are no conflicts to declare.

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