PCCP

PERSPECTIVE

View Article Online
View Journal | View Issue

Cite this: *Phys. Chem. Chem. Phys.*, 2024, **26**, 9848

Art, fact and artifact: reflections on the cross-talk between theory and experiment

Judith Herzfeld

Received 1st January 2024,
Accepted 13th March 2024

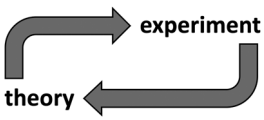
DOI: 10.1039/d4cp00005f

rsc.li/pccp

With the increasing sophistication of each, theory and experiment have become highly specialized endeavors conducted by separate research groups. A result has been a weakening of the coupling between them and occasional hostility. Examples are given and suggestions are offered for strengthening the traditional synergy between theory and experiment.

Introduction

As taught already in grade school, the "scientific method" is predicated on a tight coupling between theory and experiment, in a cycle



Ideally, theory generates predictions that inspire experimental tests, and experimental observations call for theoretical interpretation or generalization that generates new hypotheses. Where distance or energy scales are difficult to access, the cycle may start with a theoretical advance that suggests where and how to look for new phenomena. Where phenomena are relatively easy to observe, the cycle may start with novel experimental observations that suggest challenges to prevailing principles. In either case, incremental progress then follows the canonical cycle. Both theory and experiment lose meaning unmoored from each other. Experimental observations without theory are isolated snapshots, and theory without experimental data is speculative. Ideally, through close and frequent interaction, theory and experiment each guide and discipline the other.

During the scientific revolution, the empiricism of the scientific method distinguished the new discipline of science from the old disciplines of philosophy and technology. Individual practitioners joined observation and reason, obtaining and interpreting their own data. The successful scientist was both an experimentalist and a theoretician. There was specialization, but it was by focus on different phenomena (*e.g.*, astronomy *vs.* electricity *vs.* optics), rather than between experiment and theory. If theory and experiment didn't agree, the issue had to be in one's own observations or one's own reasoning, and being intimately familiar with both could help to resolve the matter.

The situation is very different today: with experimental and theoretical methods sufficiently sophisticated that it can be demanding to master and implement even one, principal investigators generally identify as either experimentalists or theoreticians and train protégées in one or the other. Moreover, the fragmentation can be expected to grow with the rise of big data and scientists who specialize in organizing it.[1] There are a variety of vulnerabilities in this specialization and the example in the next section illustrates some of them with a case that went spectacularly sideways. This is followed by sections considering some roots of the vulnerabilities and some practical suggestions for mitigating them.

The surface charge of water

This is a stand-out example because relevant experimental data were already available well over a century ago and current papers suggest that the issue remains unresolved.[2] It is also important for numerous phenomena including weather, on-water chemistry, and green energy harvesting.

I was introduced to the debate at a 2012 Gordon Research Conference at which a theoretician and an experimentalist reprised a dispute that was, by then, at least three years old.[3,4] In a heated session, the theoretician argued that the experimental observations reflected contamination and the experimentalist argued that the theoretical calculations were naïve. The experimentalist defended his results by describing ever more stringent purification procedures and the theoretician defended his results by citing interpretations of other

Brandeis University, Waltham, Massachusetts, USA. E-mail: herzfeld@brandeis.edu

Table 1 Representative reports of the surface charge of water

Excess surface charge	Experiment	Theory
−	Shredding the surface[5,6]	LEWIS[17]
	Shearing the surface[7–9]	FPMD[18,19]
	Surface proton transfer[10]	
	Surface-selective spectroscopy[11–16]	
+	Shredding the surface[20,21]	MM[14,22–24]
	Surface proton transfer[10]	MS-EVB/MS-RMD[25]
	Surface-selective spectroscopy[13]	

experimental data. So how did such smart scientists, each at the top of their own game, get into such a muddle?

Table 1 groups representative reports of the surface charge of water, from 1861 to the present, by approach and result. (Restricted to the gas–water interface, the table omits studies on electrophoresis of oil droplets and streaming currents on solid surfaces.) As shown, there is qualitative disagreement within theory and within experiment, as well as between the two.

When the only ions present are the self-ions of water, there is actually broad experimental agreement about surface charge. The earliest measurements were of negative charges on droplets torn from the water surface by mechanical forces.[6,26] This ''waterfall effect'' has even been reproduced in American bathrooms where splashing from sink height produces less charge than splashing from shower height and more charge than the swirl of a toilet flush.[27] In more controlled experiments, electrophoresis of gas bubbles consistently indicates that the charge is negative on the bubble side of the slip plane in the sheared the water surface[8] and that the isoelectric point, arrived at by adding minimal amounts of acid to the system, occurs at a bulk pH $\sim$3.5.[7]

The same picture is revealed by monitoring proton transfer reactions on- *vs.* in-water droplets prepared at different bulk pH's. For the protonation of trimethylamine, the equivalence point for the on-water reaction occurs for droplets with a bulk pH of 3.8, *vs.* 9.8 for the in-water reaction. In particular, the surface of a neutral droplet is no better able to protonate triethylamine than either the interior or the surface of a droplet prepared at bulk pH 12.[10] Other on-water protonation studies show that the change in the surface as the bulk is titrated through pH 3–4 is very dramatic. Although *n*-hexanoic acid is an extremely weak base, it is protonated on the surface of droplets with bulk pH as high as 3.[28] Similarly, isoprene, another weak base, is protonated and polymerizes on the surface of droplets with bulk pH as high as 4.[29] On the other hand, whereas deprotonation of hexanoic acid occurs in the bulk with an equivalence point of 4.8, it occurs on the surface of droplets with an equivalence point of 2.8.[30]

Surface-selective spectroscopy tells a comparable, though ill-recognized, story. While, UV second harmonic generation spectra show no detectable change in surface hydroxide signals from bulk pH 7 to 13,[15] vibrational sum-frequency spectroscopy has covered a wider pH range.[11–14,16] Consistent with the UV results, the vibrational spectrum from the surface of neutral water is very similar to that from the surface of aqueous base. However, the features of the vibrational spectra are sensitive to titration of the bulk through pH 3–4 such that the spectrum from the surface of aqueous acid becomes markedly different from that from the surface of neutral water or aqueous base. Unfortunately, except for the distinctive signals of dangling OH groups, there are no assignments of specific vibrational features as these are likely shifted for semi-dehydrated surface species *vs.* their bulk counterparts.

So, what about the contrary experimental results? What they have in common is salinity. Already in 1892, Lenard reported that, in simulating the ''waterfall effect'' by splashing water against hard surfaces, the charge on ejected droplets became less negative, and eventually reversed sign, as salt was added to the water.[6] This is consistent with subsequent studies establishing that small droplets ejected from seawater are positively charged.[20,21,31–33] The effect of salt is also evident in proton transfer reactions on- *vs.* in-water droplets: with the addition of less than 1 mM NaCl or LiCl in the preparation of neutral water droplets, the surface becomes abruptly capable of protonating trimethylamine (declining a bit at much higher salt concentrations, but not to the total absence of protonation seen without salt).[10] In addition, vibrational SFG spectra at OH stretch frequencies show changes in surface structure on addition of sodium halides that are similar to those seen on acidification.[13]

In other words, the presence of salt alters the partitioning of the self-ions of water between the bulk and the surface. This should not be surprising because the preference between the two environments depends on conditions in both. A particularly salient feature of neat bulk water is its three-dimensional hydrogen bonding network, a feature reflected in the remarkable heat capacity of bulk water, which at 3k per atom is as expected for a network solid rather than for a liquid of small molecules (in which contributions from rotational and translational modes are expected to dominate over those from vibrational modes). As is well-known, this hydrogen bonding network is disturbed by salt, as water molecules are rearranged into solvation shells around the solute ions.

It follows that a theory that does not do a good job of describing the H-bonding of water and its self-ions will predict the correct surface charge of water only by accident. For first principles methods, this will depend on the choice of basis set. For density functional theory, it will also depend on the choice of functional. And for molecular mechanics, it will depend on the choice of force field. In addition, spurious results may arise from simulations with periodicities that are too tight or sampling that is too brief. (Avoiding this source of artifacts is particularly difficult for *ab initio* methods, still challenging for density functional methods, and least difficult for molecular mechanics.) All things considered, off-the-shelf simulation packages should be expected to be inadequate for the task unless shown otherwise. In fact, correctly predicting the observed surface charge of water should have been considered

a test of the theory, a view that would have conformed to the traditional relationship between theory and experiment.

As it happened, it wasn't until this century that theoretical simulations were able to begin addressing the surface charge of bulk water and it is fair to say that much of what drove repeated and diverse experimental probes thereafter was a response to repeated theoretical predictions by diverse conventional methods that the surface of neat water was positively charged. Ultimately, only a radically new approach to molecular modeling produced results consistent with experiment, uniquely predicting a robust preference of hydroxide for the surface and of hydronium for the bulk.[17] The LEWIS force field achieved this by modeling valence electron pairs as semi-classical particles with mobility independent of kernels. This intrinsically affords molecules not just flexibility, but also anisotropic polarizability and reactivity. Furthermore, with strictly pairwise interactions of the electron pairs with each other and with kernels, the model has an efficiency that allows large (1000 molecules) and long (500 ps) simulations of water.[17] In this construct, an excellent description of hydrogen bonding is achieved by training the particle pair potentials on the structures and energies of water monomers and dimers in all their common protonation states,[34] resulting in a force field that does an excellent job of describing acid–base dynamics in bulk water.[35] At the surface, the predicted propensities of the self-ions are consistent not only with the experimentally observed negative surface charge of neutral water, but also with the observed need to increase the bulk hydronium ion concentration and decrease the bulk hydroxide concentration by several orders of magnitude in order to reorganize the surface.

Other large and long simulations use classical molecular dynamics in which electrons are represented only implicitly. Employing rigid models of water and various models of the self-ions, a scheme that is not expected to adequately represent the flexibility and lability of the hydrogen bonding network, this approach predicted that hydronium prefers the surface and hydroxide weakly avoids it.[14,22,23]

While *ab initio* simulations are only practical for systems that are too small for periodic boundary conditions to reasonably describe bulk properties, they are suitable for water clusters and find that an excess proton prefers the surface.[22,36] However, clusters have no bulk region and LEWIS also predicts that the energy of a protonated 21-mer is lowest with the excess proton located on the tightly curved surface of the distorted H-bond network.[37]

Kohn–Sham density functional theory has afforded sizeable simulations either directly, through on-the-fly calculation of forces in FPMD,[18,19] or indirectly, by informing barrier heights between sets of MS-EVB basis states.[25] In both cases, a limitation has been in the weaknesses of the chosen functional, BLYP, which is relatively practicable, but is known to have problems with hydrogen bonds[38–41] (even though it, like LEWIS, does predict the correct order of the self-diffusion constants of the water self-ions *vs.* each other and water[42]). The most recent MS-EVB studies predicted that hydronium is weakly attracted to the surface while hydroxide is repelled.[25] Meanwhile, the FPMD simulations are the only ones besides LEWIS to find hydroxide attracted to the surface, although only weakly so[19] and with hydronium indifferent between the surface and the bulk.[18] It seems likely that the disagreement between FPMD and MS-EVB results owes to the artificial restriction in MS-EVB to a set of basis states and that the divergence of both from the LEWIS results owes to the limitations of the BLYP functional. LEWIS and BLYP DFT also disagree on the dominant H-bonding of hydroxide in bulk water, with LEWIS predicting traditional coordination[43] and BLYP predicting hypercoordination.[44,45] The latter can be expected to penalize transfer to the surface.

The twists and turns in the long saga of the surface charge of neat water, which are relatively clear in retrospect, exemplify some real-time issues in modern science more generally. Two of these are discussed in the following two sections.

Black boxes

Scientists cheerfully and gratefully acknowledge standing on the shoulders of giants. This includes making use of established ideas and rubrics in interpreting experimental data. But, in choosing among these schemes, we need to be aware not only of what they do, but also how they do it, *i.e.*, what assumptions are baked in. This becomes ever more difficult the further removed we are from their origins.

For example, Langmuir absorption theory was used to analyze UV intensities on the surface of water.[15] However, that theory assumes that absorption events occur independently at a uniform set of sites in the surface from a uniform set of sites in the bulk. In contrast, the surface adsorption of hydroxide is a cooperative process that involves separation of charge and large multiplicities of states in both the surface and the bulk due to the flexibility of H-bonding. Misapplication of the theory was manifest by theoretical curves with shapes that could not be fit to the experimental data.

As another example, the simulations of slabs of water described above employed a variety of approaches, each with their own sets of underlying assumptions. Although these were generally acknowledged, they were not always associated with commensurate skepticism about the results, especially in interpretations of vibrational spectra.[14]

More generally, it is tempting to take at face value the software packages that have proliferated for both processing and interpreting data. Choices, not only among packages, but also among the input options afforded the user, may be made by custom without much consideration of their impact. It is a tall order to be familiar with the details of these complex packages, but it can make a big difference.

In the case of data processing, it is important to understand, for example, how and why NMR spectra depend on the details of the conversion of data from the time domain to the frequency domain, especially for multi-dimensional experiments with non-linear sampling. Similarly, it is important to understand how the translation of electron diffraction data into macromolecular structures may be biased by the force field that is chosen to make the process of fitting the electron densities

more manageable by constraining the structures. This is especially so for studies of higher energy structures that occur in cryogenically trapped functional intermediates.

In the case of molecular interpretation, valid use of theoretical packages often requires expertise well beyond what an experimental group can be expected to cultivate or sustain in-house. In particular, for molecular dynamics, it is necessary not only to choose a suitable model for the system of interest (about which more below), but also to adopt adequate system dimensions and boundaries, an appropriate ensemble with effective controls, a suitable step size, a sufficiently long trajectory, and a satisfactory sampling scheme.

The lamppost and the Peter Principle

Just as the old joke has a drunkard looking under a lamppost for his lost keys because that is where the light is, we face limitations in the resources available for interpreting or predicting experimental data. Moreover, existing tools can be extended only so far, and, under a Peter Principle that says that methods rise to their level of incompetence, one should be cautious with novel applications of old methods. Except for systems so small that they are rarely of interest, all theories have to make approximations that will eventually fail. Of course, it is not necessarily obvious where a model will fail and it can be interesting to find out. It can even be somewhat illuminating if one can isolate specific assumptions that are inconsistent with describing a given phenomenon. However, that should then be an explicit part of the discussion.

In the computational chemistry landscape, there are three general types of lampposts: the first principles ones based on the description of electrons by wave mechanics; the molecular mechanics ones that treat electrons implicitly, modeling only their effects; and the fledgling sub-atomistic force fields that treat the valence electrons as semi-classical particles. Across the board, these involve various clever approaches to avoiding the prohibitive computational cost of *ab initio* calculations. However, whereas *ab initio* theory has a known path to greater accuracy (*i.e.*, larger basis sets and more configurations), the other methods don't.

—In the first principles group, density functional theory has explored scores of functionals, finding that different ones are more reliable for different applications.

—Also in the first principles group, semi-empirical methods provide great gains in efficiency by obviating evaluation of demanding integrals. However, this entails careful parameterization for specific applications.

—Parameterization is a growing headache in the molecular mechanics camp where, not only are the traditional parameters required for each type of atom, bond, bond angle, and dihedral angle, but new parameters have been increasingly required for patches to add polarizability and reactivity, features that were not contemplated in the original conception of molecular mechanics.

—The sub-atomistic force fields need far fewer parameters because, based only on valence electrons and kernels[34,46–48] (or all electrons and nuclei[49,50]), polarizability and reactivity are built in with no need for distinction between different types of bonding. However, these force fields are still in early stages of development.

In the process of parameterization, one has to be concerned about the choice of functional forms and the content of the training set. Machine learning can help avoid restrictive functional forms. However, to the extent that this approach relies on very large training sets populated by properties calculated from density functional theory, the results will reproduce the idiosyncrasies of the functional used in those calculations.

Synergy

This perspective opened with an example of theory and experiment talking past each other over an extended period of time. Happily, however, there are times when theory and experiment still work well together, despite specialization that can require effort to overcome. Here I will recall two examples (one in which I was on the theory side and one in which I was on the experimental side), before outlining propitious practices in the following section.

Regulation of oxygen delivery by hemoglobin

Efficient delivery of oxygen from the lungs to other tissues depends on hemoglobin's sigmoid oxygenation curve, with the steep part allowing oxygen binding and release at only moderately different partial pressures. This feature owes to cooperative interactions among the four heme-bearing subunits of the protein. In addition, adaptation requires the ability to shift the steep part of the oxygenation curved to higher and lower pressures. Extensive experimental work, under carefully controlled conditions, showed that rapid accommodation to metabolism is afforded by sensitivity of the protein to pH and slow accommodation to altitude owes to the effect of polyphosphates. On the theory side, three mechanisms were proposed to explain the cooperativity of oxygen binding. To examine a wide range of experimental data in quantitative detail, these three mechanisms were combined in a general, yet tractable, model that also included polyphosphate binding.[51] The result, with just a few adjustable parameters, was a close fit of oxygenation curves over a range of polyphosphate concentrations. While that supported the efficacy of the model and revealed the contributions of different cooperative mechanisms, it also predicted the occurrence of biphasic oxygenation curves. As it turned out, experimentalists had seen such curves, but not published them on the supposition that they were artifacts. The theory showed that they weren't and accurately predicted the conditions under which they would occur. Without close communication between theorists and experimentalists, each would have had reason to doubt their results.

Enforcement of vectoriality in a light-driven ion pump

Bacteriorhodopsin is an integral membrane protein comprising a bundle of seven transmembrane helices enveloping a retinal chromophore Schiff base linked to a buried lysine residue.

The resting structure was determined by cryo-electron microscopy and various forms of time-resolved spectroscopy identified a series of photocycle intermediates with changes in the protonation of the Schiff base and various acidic residues along the central channel. To prevent ion back flow, the initially protonated Schiff base has to change connectivity immediately after deprotonation. Since the Schiff base is H-bonded to the extracellular network in the resting state and also deprotonates to the extracellular side after photoisomerization, the connectivity sequence in between remained mysterious. Solid-state NMR of cryo-trapped photocycle intermediates showed that, while the protonated Schiff base loses its H-bond to its resting state counterion after photoisomerization, it then establishes a new, stronger H-bond before deprotonation. The NMR spectra also showed that, in the process, the photoisomerized retinylidene chain becomes twisted, consistent with reestablishing a Schiff base connection to the extracellular channel. Spontaneous unwinding of this twist could cause the connectivity to switch as soon as the Schiff base becomes electrically neutral by losing its proton.[52] In the meantime, Bondar *et al.* were carrying out very carefully designed QM/MM studies of this portion of the photocycle and found three pathways to the primary proton transfer step with feasible activation barriers, one of which resulted in the Schiff base H-bonded to a threonine residue connected by other H-bonds to the extracellular channel.[53] Eventually, 2D NMR correlation spectra showed that the new Schiff base H-bond involved an alcohol group.[54] Thus, theory and experiment converged: the NMR result showed which of the three QM/MM pathways is operative and the QM/MM simulations identified the specific alcohol group that captures the Schiff base after photoisomerization and lets it go as soon as it is deprotonated.

The blind men and the elephant

Just as the blind men in the parable had different ideas of what an elephant is, based on the part that each one touched, experimentalists and theorists can have different views of how their system works based on their differing approaches. Of course, a single blind man traveling around to different parts of the elephant would gain a more complete picture of what an elephant is. That would be analogous to the practice of science in earlier times, when the same scientist carried out measurements, analysis and interpretation. The next best thing would be for the various blind men to compare notes and come up with a composite, self-consistent idea. That version of the parable is analogous to what happened in the two synergistic examples above. On the other hand, other versions of the parable have the blind men coming to blows instead.

Clearly the central requirement of synergistic relationships is regular, open, constructive communication, with thoughtful and detailed reading and listening. This is non-trivial, and conducive formats for conferences, schools and journal articles become ever more critical. Among other things communication needs to include attention to the ills mentioned above. Too often, presentations make only brief mention of the methods used, while emphasizing the results obtained. However, even conventional methods require a thoughtful appraisal of strengths and weaknesses for a particular application.

Blackboxes

Science funding increasingly emphasizes the dissemination of new data and tools to the general community. For adopters to use these data and tools correctly they need to be as informed of their limitations as they are of their capabilities. This requires that authors forthrightly pair pride in advancement with humility regarding remaining issues. Adopters also need to understand the implications of different modes of implementation. Generally, manuals should feature substantial context and critical discussion, as well as operating tutorials. Preparing thoughtful manuals takes time, but the benefit can be wider and more productive adoption. The process can also point to future efforts to extend the range of capability. Downstream, journals can help promote sound practices by making sure that articles containing both theory and experiment are reviewed by at least one referee with each expertise.

Lampposts and the Peter Principle

For lampposts to shed useful light, they need to be pointing in the right direction. In other words, for theory to be useful, the model needs to incorporate essential features of the system in a way that is both tractable and insightful (or, as attributed to Einstein, ''as simple as possible, but not simpler''). This requires what Evelyn Fox called ''a feeling for the organism'',[55] attained by extensive and careful reading of the literature and thoughtful exploratory studies. For example, in the above work on bacteriorhodopsin, the leading theoretician examined the experimental reports in such detail and asked such penetrating questions about the work that she seemed to understand those papers better than anyone beside the authors themselves. That understanding allowed her to design simulations that would be most relevant to the outstanding questions. On the other hand, a renowned experimentalist told me that she had stopped seeking insight from theory papers about her enzyme of interest because there was no way to tell which were reliable.

In fact, theoretical calculations operate in multiple modes. The first is validation, *i.e.*, to show that the theory reproduces experimental results at a relevant level. Only once appropriately validated, can theory offer explanations and make potentially reliable predictions. Where no experimental data are available for relevant validation, theory can offer no more than suggestions as to what might be expected. In the above example of cooperativity in hemoglobin, the model was validated on abundant sigmoidal data and then used to (accurately) predict biphasic saturation under intermediate conditions. In the above example of the bacteriorhodopsin photocycle, there was no opportunity for direct validation of the theory and the results were presented as suggestions of possible trajectories. In the above example of the surface charge of water, there was abundant experimental data (the left side of Table 1) and the theoretical work (the right side of Table 1) should have been regarded as attempts at validation of different models in the

regime of extensive intermolecular H-bonding. While most of the water models clearly bumped up against the Peter Principle, LEWIS was validated for the surface charge of water (as well as for the acid–base behavior of bulk water more generally[37]) and therefore able to offer explanations for experimental observations (in particular that there is a net gain (loss) of H-bonds when hydroxide (hydronium) ions displace water molecules from the surface of neat water).

All things considered, it would be most helpful to readers for theorists to be very clear in their papers about distinctions between validation, explanation, prediction and suggestion. In this context, it behooves theorists to give readers an idea of what they think their approach gets right and what it sidesteps. As long as some progress has been made, whether in testing or applying theory, thoughtful caveats should be seen as a strength of a paper, rather than a deficiency.

When existing approaches have reached their limits, there are two possibilities. One is to apply patches that address the perceived gap (such as polarizability and reactivity in atomistic force fields). However, at some point thought also needs to be given to starting from scratch (as in the pursuit of sub-atomistic force fields) to address applications that were not foreseen in previous methods design. Innovation has always been the answer to the proverbial young scientist's nightmare that if an experiment or calculation is interesting it either has already been done or can't be done. In fact, science keeps progressing because methodological advances make studies possible that were not before. New experimental methods may reach new length/time scales or disentangle signals that are of different types or from different parts of a sample. New theoretical methods may rethink assumptions made/avoided, the organization of data, or the method and means of analysis. Stepping out in a new direction can seem daunting, and may be discouraged by grant reviewers as too blue-sky, but it is also important for the long-term health of the community that it be wary of falling into the ''sunk cost fallacy''.

Conclusions

As science practice becomes ever more sophisticated, automated and specialized, it behooves us to become ever more aware of increased opportunities for misapplications, misinterpretations and misunderstandings. While it is a growing burden for each new generation to be critically versed in the workings of various methods applied to their systems, the alternative is worse. The antidote is clear, constructive and insightful communication across specialties. In addition to private discussion, conferences, schools, journals and granting agencies have a major role to play.

Conflicts of interest

There are no conflicts to declare.

References

1 B. Nachman, Opinion: The Rise of the Data Physicist, *APS News*, 2023, vol. 32, **https://www.aps.org/publications/apsnews/202311/backpage.cfm**.
2 Y. Uematsu, Electrification of water interface, *J. Phys.: Condens. Matter*, 2021, **33**(42), 423001.
3 J. K. Beattie, A. M. Djerdjev and G. G. Warr, The surface of neat water is basic, *Faraday Discuss.*, 2009, **141**, 31–39.
4 P. Jungwirth, Spiers memorial lecture ions at aqueous interfaces, *Faraday Discuss.*, 2009, **141**, 9–30.
5 L. Laakso, A. Hirsikko, T. Grönholm, M. Kulmala, A. Luts and T.-E. Parts, Waterfalls as sources of small charged aerosol particles, *Atmos. Chem. Phys.*, 2007, **7**(9), 2271–2275.
6 P. Lenard, Ueber die Electricität der Wasserfälle, *Ann. Phys.*, 1892, **46**, 584–636.
7 P. Creux, J. Lachaise, A. Graciaa, J. K. Beattie and A. M. Djerdjev, Strong specific hydroxide ion binding at the pristine oil/water and air/water interfaces, *J. Phys. Chem. B*, 2009, **113**(43), 14146–14150.
8 G. Quinke, Ueber die Fortführung materieller Theilchen durch strömende Elektricität, *Ann. Phys. Chem.*, 1861, **113**, 513–598.
9 H. McTaggart, XXXIII. The electrification at liquid–gas surfaces, *London, Edinburgh Dublin Philos. Mag. J. Sci.*, 1914, **27**(158), 297–314.
10 S. Enami, M. R. Hoffmann and A. J. Colussi, Proton availability at the air/water interface, *J. Phys. Chem. Lett.*, 2010, **1**(10), 1599–1604.
11 K.-Y. Chiang, L. Dalstein and Y.-C. Wen, Affinity of hydrated protons at intrinsic water/vapor interface revealed by ion-induced water alignment, *J. Phys. Chem. Lett.*, 2020, **11**(3), 696–701.
12 S. Das, M. Bonn and E. H. Backus, The surface activity of the hydrated proton is substantially higher than that of the hydroxide ion, *Angew. Chem., Int. Ed.*, 2019, **58**(44), 15636–15639.
13 L. M. Levering, M. R. Sierra-Hernandez and H. C. Allen, Observation of Hydronium Ions at the air−aqueous acid Interface: vibrational spectroscopic studies of aqueous HCl, HBr, and HI, *J. Phys. Chem. C*, 2007, **111**(25), 8814–8826.
14 M. Mucha, T. Frigato, L. M. Levering, H. C. Allen, D. J. Tobias, L. X. Dang and P. Jungwirth, Unified molecular picture of the surfaces of aqueous acid, base, and salt solutions, *J. Phys. Chem. B*, 2005, **109**(16), 7617–7623.
15 P. B. Petersen and R. J. Saykally, Is the liquid water surface basic or acidic? Macroscopic vs. molecular-scale investigations, *Chem. Phys. Lett.*, 2008, **458**(4–6), 255–261.
16 T. L. Tarbuck, S. T. Ota and G. L. Richmond, Spectroscopic studies of solvated hydrogen and hydroxide ions at aqueous surfaces, *J. Am. Chem. Soc.*, 2006, **128**(45), 14519–14527.
17 C. Bai and J. Herzfeld, Surface propensities of the self-ions of water, *ACS Cent. Sci.*, 2016, **2**(4), 225–231.
18 M. D. Baer, I.-F. W. Kuo, D. J. Tobias and C. J. Mundy, Toward a unified picture of the water self-ions at the air–water interface: A density functional theory perspective, *J. Phys. Chem. B*, 2014, **118**(28), 8364–8372.

19 C. J. Mundy, I.-F. W. Kuo, M. E. Tuckerman, H.-S. Lee and D. J. Tobias, Hydroxide anion at the air–water interface, *Chem. Phys. Lett.*, 2009, **481**(1–3), 2–8.
20 D. C. Blanchard, Electrically charged drops from bubbles in sea water and their meteorological significance, *J. Atmos. Sci.*, 1958, **15**(4), 383–396.
21 R. Reiter, Charges on particles of different size from bubbles of Mediterranean Sea surf and from waterfalls, *J. Geophys. Res.: Atmos.*, 1994, **99**(D5), 10807–10812.
22 V. Buch, A. Milet, R. Vácha, P. Jungwirth and J. P. Devlin, Water surface is acidic, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**(18), 7342–7347.
23 B. Jagoda-Cwiklik, L. Cwiklik and P. Jungwirth, Behavior of the Eigen form of hydronium at the air/water interface, *J. Phys. Chem. A*, 2011, **115**(23), 5881–5886.
24 B. Winter, M. Faubel, R. Vácha and P. Jungwirth, Behavior of hydroxide at the water/vapor interface, *Chem. Phys. Lett.*, 2009, **474**(4–6), 241–247.
25 Y.-L. S. Tse, C. Chen, G. E. Lindberg, R. Kumar and G. A. Voth, Propensity of hydrated excess protons and hydroxide anions for the air–water interface, *J. Am. Chem. Soc.*, 2015, **137**(39), 12610–12616.
26 E. Pierce and A. Whitson, Atmospheric electricity and the waterfalls of Yosemite Valley, *J. Atmos. Sci.*, 1965, **22**(3), 314–319.
27 E. Pierce and A. Whitson, Atmospheric Electricity in a Typical American Bathroom, *Weather*, 1966, **21**(12), 449–455.
28 S. Enami, L. A. Stewart, M. R. Hoffmann and A. J. Colussi, Superacid chemistry on mildly acidic water, *J. Phys. Chem. Lett.*, 2010, **1**(24), 3488–3493.
29 S. Enami, H. Mishra, M. R. Hoffmann and A. J. Colussi, Protonation and oligomerization of gaseous isoprene on mildly acidic surfaces: Implications for atmospheric chemistry, *J. Phys. Chem. A*, 2012, **116**(24), 6027–6032.
30 H. Mishra, S. Enami, R. J. Nielsen, L. A. Stewart, M. R. Hoffmann, W. A. Goddard III and A. J. Colussi, Brønsted basicity of the air–water interface, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**(46), 18679–18683.
31 D. C. Blanchard, Electrified droplets from the bursting of bubbles at an air–sea water interface, *Nature*, 1955, **175**(4451), 334–336.
32 D. C. Blanchard, The electrification of the atmosphere by particles from bubbles in the sea, *Prog. Oceanogr.*, 1963, **1**, 73–202.
33 S. Gathman and E. M. Trent, Space charge over the open ocean, *J. Atmos. Sci.*, 1968, **25**(6), 1075–1079.
34 S. Kale and J. Herzfeld, Natural polarizability and flexibility via explicit valency: The case of water, *J. Chem. Phys.*, 2012, **136**, 084109.
35 C. Bai and J. Herzfeld, Special pairs are decisive in the autoionization and recombination of water, *J. Phys. Chem. B*, 2017, **121**(16), 4213–4219.
36 S. S. Xantheas, Low-lying energy isomers and global minima of aqueous nanoclusters: Structures and spectroscopic features of the pentagonal dodecahedron (H_2O) 20 and (H_3O) + (H_2O) 20, *Can. J. Chem. Eng.*, 2012, **90**(4), 843–851.
37 C. Bai, S. Kale and J. Herzfeld, Chemistry with semi-classical electrons: reaction trajectories auto-generated by sub-atomistic force fields, *Chem. Sci.*, 2017, **8**(6), 4203–4210.
38 C. K. Egan and F. Paesani, Assessing many-body effects of water self-ions. I: OH–(H_2O) n clusters, *J. Chem. Theory Comput.*, 2018, **14**(4), 1982–1997.
39 R. Liu, C. Zhang, X. Liang, J. Liu, X. Wu and M. Chen, Structural and dynamic properties of solvated hydroxide and hydronium ions in water from ab initio modeling, *J. Chem. Phys.*, 2022, **157**(2), 024503.
40 T. Ohto, M. Dodia, S. Imoto and Y. Nagata, Structure and dynamics of water at the water–air interface using first-principles molecular dynamics simulations within generalized gradient approximation, *J. Chem. Theory Comput.*, 2018, **15**(1), 595–602.
41 T. Ohto, M. Dodia, J. Xu, S. Imoto, F. Tang, F. Zysk, T. D. Kühne, Y. Shigeta, M. Bonn and X. Wu, Accessing the accuracy of density functional theory through structure and dynamics of the water–air interface, *J. Phys. Chem. Lett.*, 2019, **10**(17), 4914–4919.
42 D. Marx, A. Chandra and M. E. Tuckerman, Aqueous basic solutions: hydroxide solvation, structural diffusion, and comparison to the hydrated proton, *Chem. Rev.*, 2010, **110**(4), 2174–2216.
43 S. Kale and J. Herzfeld, Proton defect solvation and dynamics in aqueous acid and base, *Angew. Chem., Int. Ed.*, 2012, **51**(44), 11029–11032.
44 M. E. Tuckerman, D. Marx and M. Parrinello, The nature and transport mechanism of hydrated hydroxide ions in aqueous solution, *Nature*, 2002, **417**(6892), 925–929.
45 M. Tuckerman, K. Laasonen, M. Sprik and M. Parrinello, Ab initio simulations of water and water ions, *J. Phys.: Condens. Matter*, 1994, **6**(23A), A93.
46 S. Ekesan, S. Kale and J. Herzfeld, Transferable pseudoclassical electrons for aufbau of atomic ions, *J. Comput. Chem.*, 2014, **35**(15), 1159–1164.
47 J. Herzfeld, Emergence of Linnett's ''double quartets'' from a model of ''Lewis dots'', *Phys. Chem. Chem. Phys.*, 2023, **25**(7), 5423–5429.
48 J. Li, X. Song, P. Li and J. Herzfeld, A Carbon Is a Carbon Is a Carbon: Orbital-Free Simulations of Hydrocarbon Chemistry without Resort to Atom Types. *The*, *J. Phys. Chem. A*, 2022, **126**(45), 8468–8475.
49 J. T. Su and W. A. Goddard III, Excited electron dynamics modeling of warm dense matter, *Phys. Rev. Lett.*, 2007, **99**(18), 185003.
50 J. T. Su and W. A. Goddard, The dynamics of highly excited electronic systems: Applications of the electron force field. *The*, *J. Chem. Phys.*, 2009, **131**, 244501.
51 J. Herzfeld and H. E. Stanley, A general approach to co-operativity and its application to the oxygen equilibrium of hemoglobin and its effectors, *J. Mol. Biol.*, 1974, **82**(2), 231–265.
52 J. Herzfeld and B. Tounge, NMR probes of vectoriality in the proton-motive photocycle of bacteriorhodopsin: evidence for an 'electrostatic steering'mechanism, *Biochim. Biophys. Acta, Bioenerg.*, 2000, **1460**(1), 95–105.

53 A.-N. Bondar, M. Elstner, S. Suhai, J. C. Smith and S. Fischer, Mechanism of primary proton transfer in bacteriorhodopsin, *Structure*, 2004, **12**(7), 1281–1288.
54 Q. Z. Ni, T. V. Can, E. Daviso, M. Belenky, R. G. Griffin and J. Herzfeld, Primary transfer step in the light-driven ion pump bacteriorhodopsin: An irreversible U-turn revealed by dynamic nuclear polarization-enhanced magic angle spinning NMR, *J. Am. Chem. Soc.*, 2018, **140**(11), 4085–4091.
55 E. F. Keller, *A Feeling for the Organism: The Life and Work of Barbara McClintock*, W. H. Freeman, 1983.