**Chemistry, Fluctuations and Consistency**

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Chemistry is about chemical reactions. A reactant in a chemical reaction has been described by a single concentration—independent of spatial location—for what seems centuries, indeed from before physicists believed that molecules existed. The law of mass action has been used (nearly) universally to describe chemical reactions for all that time. The concentrations and rate constants of mass action equations are independent of spatial location in most cases. Spatial locations were not dealt with explicitly because the necessary mathematics was not known and not computable in those days. Chemists ignored spatial dependence so they could make progress even without the necessary mathematics. The spectacular success of chemistry would not have been possible (in my opinion) if chemists of the last centuries had to deal with the spatial dependence of reactants as well as the atomic details of the reactions themselves.

Chemical reactions are today resolved on an attosecond 10-18 sec time scale, faster by some eighteen orders of magnitude than the time resolution available when the law of mass action was introduced. The question we deal with is a modern one: can the law of mass action deal with reactions on such a fast scale?

The difficulty with fast time scales is seen clearly in reactions in liquids, for example in reactions in water of the type that make the chemistry of life. These are of particular interest to me, because almost all of life occurs in liquids, actually in ionic solutions derived from sea water in which life presumably started. When the solutions of life are viewed with sufficient resolution, fluctuations in concentration are obvious in both experiments and simulations . Roughly speaking such fluctuations occur in ionic solutions in times nanosecond 10-9 sec and shorter. Fluctuations of concentrations like these cannot be removed by stirring because they are too fast.

Fluctuations produce regions of high concentration that persist for a long time compared to the attosecond 10-18 sec time scale of electron flow in a chemical reaction. Chemical reactions depend steeply on concentration so reactions occur at a very fast rate in the regions that happen to fluctuate to a higher concentration. Where concentrations are near their average value, reactions will occur much more slowly. One imagines that an attosecond 10-18 sec reaction quickly starts and reaches completion when a local concentration fluctuates to a value much larger (say 10×) than the spatial average.

In my imagination, chemical reactions in solutions occur mostly at concentrations very different from the (spatial) average concentration. Most chemical reactions in solutions occur at concentrations very different from the spatially uniform concentrations of classical descriptions.

In my mind, chemical reactions occur mostly in local regions of high concentration, that have lifetimes long compared to attosecond 10-18 sec but short compared to nanoseconds 10-9 sec because local concentrations fluctuate to values very much larger than the spatial mean for very long times indeed compared to the time scale of attosecond 10-18 sec reactions. That is where most chemical reactions occur (I suspect) because reactions proceed much more quickly when concentrations are high. In such a system what is actually happening the has only a faint resemblance to the classical image of a chemical reaction in a spatially uniform system.

What actually happens in a fluctuating coupled system like this can be horribly complex, because it depends on the interactions of the chemical reaction itself and the concentrations of reactants fluctuating because of thermal motion. The fluctuations in concentrations have a direct effect through the law of mass action but they also have an electrical effect that may be just as important. Most reactants have significant electrical charge; many have net charge. Most reactions occur in ionic solutions. All reactions important for biology occur in ionic mixtures (like extracellular ‘Ringer’ solutions) derived from seawater. In ionic solutions, fluctuations in the number density of reactants and ions produce fluctuations in electric forces. These interact directly with the electrons moving in the chemical reaction itself. ‘Everything’ electrical interacts with ‘everything else’ because of the long range of electric forces. (Electric forces extend to the boundaries at times faster than say nanoseconds 10-9 sec, because screening takes longer than that to occur.) The flow of electrons in the reactants (as they change into products) is coupled to the electrodiffusion of the surrounding solutes. Analysis and simulation involve a coupled system that deals together with the quantum chemistry of the chemical reaction and also the electrodiffusion in the ionic solution.

All flows and forces must be dealt with consistently if a simulation or theory is to deal with what is happening in a chemical reaction as it actually occurs in an ionic solution. (‘Consistently’ means that the each of the types of forces must satisfy know physical laws, e.g., electrical potential must be consistent with the charges present, according to Maxwell’s equations or their appropriate simplifications. Hydrodynamic flows must be consistent with Navier-Stokes equations. The influence of charge flows on hydrodynamic flows must satisfy Newton’s laws. Classical Brownian motion theory cannot be used, unfortunately, because it does not allow electrical forces to fluctuate as concentrations of ions fluctuate.)

I write to say that chemical reactions in solution need to be analyzed with theories and simulations that allow spatial fluctuations in concentration. Assuming spatial uniformity has been highly productive and appropriate in our history but is inappropriate (in my opinion) as we seek understanding on atomic scales of space and time.

Reactions in ionic solutions are likely to occur in small spatial domains with concentrations of reactants very different from the spatial average. Analysis will require theory and simulations that couple the electron flows that make a chemical reaction to fluctuations in the concentration of charges in the surrounding solution, as the charges move in incessant thermal motion, so very slow compared to the attosecond 10-18 sec time scale of the electron flows themselves. A consistent fully coupled variational treatment seems to be needed to couple these fields, although surely the problem of coupling the wildly different scales in the resulting Euler Lagrange equations will be very hard to solve. The Schrödinger equation (or whatever) description of electron flow in the reacting molecules will need to be coupled to the Maxwell equations of the electric field in the solution (pun intended) itself (on the time scale of attosecond 10-18 sec) and then to the simulation or field equations of electrodiffusion. It is natural to couple the various flows with a variational treatment so the resulting (integro) differential equations are automatically consistent. For example, Schrödinger equation (or whatever) description of electron flow in the reacting molecules could be coupled to an Energetic Variational description of an ionic solution of bio-ions. Consistency must be enforced by the mathematics, in my view. Ad hoc treatments will almost certainly fail in some conditions, for example, in the (very) crowded conditions of ions in and near channels and active sites of enzymes.

Consistent treatments of reactions and ionic solutions are not well developed. Almost everything remains to be done before we can understand when the classical description of chemical reactions is appropriate for reactions in solution.

