The law of mass action: ready to be replaced?
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Scientific theories, like many other things, have a lifetime. Science, like life, evolves. It is important to discard theories when they are no longer useful, no matter how important they have been in history [18]. It is particularly important to replace theories that can be stretched to fit so much data that they are hard to prove wrong [26].

The ólaw of mass actionôis like that. The law of mass action with variable rate constants can stretch a long way. The law of mass action defines a chemical reaction in the minds of chemistry students. We learn the law so young in our careers that we usually forget the crucial question. Are the constants of the law constant? If not, why do the constants vary?

In fact, the rate constants of the law of mass action are hardly ever constants when measured over a range of experimental conditions, specifically, as the concentration of reactants change or concentrations of other species in the system (not reactants and products) are changed.

In fact, if the reactions involve ions in water, the rate constants can hardly ever be constant because of the electrical interactions of an ion with its ionic atmosphere. Nearly all chemical reactions in biology involve ions in water, and a large number of reactions in classical chemistry do as well. The free energy of reactants is changed when background ions (that are not reactants or products) are changed (in concentration or type) because the screening of the reactants is changed. The atmosphere of (counter) ions surrounding a reactant changes the (free) energy and thus the effective concentration of the reactants. In simple solutions like dilute NaCl (less than 50 mM, for example), Debye-Hückel theory describes the ionic atmosphere. In the mixtures of ions in seawater or in the solutions inside and outside biological cells, divalents and interactions are beyond what Debye-Hückel can describe [7, 8].

These effects are not small in the special conditions in which most chemical reactions occur in biology. Biochemical reactions occur mostly in enzymes where the density of ionizable side chains is very large indeed (more than 10 M) because of the abundance of acid and base amino acids in enzyme active sites [16]. In these conditions, reactants and products, and ions, are very crowded and nothing like ideal. Rate constants must vary because the free energies of nonideal reactants depends on every species present. Everything interacts with everything else and rate constants vary importantly with almost everything. Rate constants measured in one condition cannot be transferred to another because they change too much and in a way theory does not predict.

These ideas have been developed and presented (and refereed) elsewhere [5-7, 9, 10] and are in fact not new at all. Physical chemists have known óforeverôthat rate constants are

not constants. What is not so well known are the consequences and possible remedies for the dysfunction of the law of mass action.

The consequences of variable rate constants include theories that cannot be used very well for design. Designs usually have to work in a range of conditions. If rate constants measured under one set of conditions cannot be transferred to another, designs in the one condition will not work as expected in the other.

If the rate constants of a chemical reaction vary with conditions, the (free) energies driving that reaction also vary, almost by definition, as described in most textbooks of physical or biochemistry. If we do not understand how the energies of a chemical reaction vary with conditions, or why they vary, we cannot use those energies to control the reaction. More precisely, we cannot use those energies in a planned and calculated way. We cannot transfer our wisdom learned in one set of conditions to another set of conditions, with any confidence. Rather, we must investigate all conditions separately, learning by trial and error.

Not all of science is like that. Not all of science depends so strongly on trial and error. Some scientific laws are ótransferableô(to use the jargon of chemical simulations). The laws of some sciences are valid with little or no adjustment of parameters under a wide range of conditions producing a tremendous range of behaviors. The water flow out of a shower can be calculated from Navier Stokes equations developed and checked under very different conditions.

We can argue that the fantastic development of semiconductor technology is possible only because the PNP (i.e., drift diffusion) equations do a good job of describing the properties of transistors [21, 22, 30], whether they are working as amplifiers, limiters, switches, exponentiators, or multipliers. We know that modern airplanes are possible because computational fluid dynamics [1, 2] can integrate the Navier-Stokes equations to predict incredibly complicated flows and forces of complex systems [19] including air flow over wings.

In my view biological systems would be far easier to understand and control if the law of mass action were replaced with something that actually fits data. In my view, chemical and biochemical devices would be far easier to design and use if the law of mass action were replaced with something that actually works.

The replacement for the law of mass action would need to deal with flows. In biology in particular, flows are an essential feature of the living. Flows cease, and thermodynamic equilibrium occurs only at death (in cadavers and crystals). In technology, flows are nearly as important as in biology. Most of technology depends on devices and machines that require power supplies and flow. An amplifier at equilibrium without a power supply and current flow does not amplify.

The replacement for the law of mass action needs to involve location explicitly. Flows

go from one place to another. Devices always have inputs and outputs. The descriptions of devices must have different boundary conditions at different locations because inputs and outputs have different properties. And the replacement of the law of mass action must deal with interactions in crowded conditions in which everything interacts with everything else, because these special conditions are so important in biology and devices. Biological systems like enzymes, ion channels, and nucleic acids have enormous number densities of ions near and in their ćactive sites.ôOur electrochemical technology has enormous densities of reactants where they are important, near electrodes.

The law of mass action has not been replaced up to now, in my view, because a suitable replacement was not available. A promising candidate is now at hand, and its promise needs to be tested by extensive application, throughout the areas of science where the law of mass action has been used, throughout the areas of science where the law of mass action fits data only when its constants are varied.

My candidate to replace the law of mass action was developed to deal with complex fluids of many components, like oil droplets in water, or the liquid crystals of LED technology. The replacement method extends classical variational principles of mechanics to systems with dissipation. Navier Stokes equations can now be derived from an energetic variational approach we call EnVarA. EnVarA combines Hamiltonians of classical mechanics with the dissipation functions of Rayleigh [27, 28]. The derivations are a matter of mathematics, with existence and uniqueness theorems available, as well as many numerical results.

Attempts to include dissipation in mechanics are hardly new. Onsager and followers tried heroically to develop such methods, but did not succeed. Their methods could not deal with the properties of ionic mixtures, or even concentrated NaCl solutions, in equilibrium let alone when they flow. But now a variational treatment of ions in water (really a treatment of the primitive model of charged spheres in a frictional dielectric) has been developed [11]. Tis paper and its successors can serve as a tutorial introduction to the energetic variational approach but they are not more than that. Certainly other treatments of the physics are possible and perhaps superior [3, 4, 12-15, 17, 20, 29, 32-34].

The best replacement for the law of mass action is not known, and may not be unique, because it depends on the physical nature of the energies and dissipations. These are a matter of physics, chemistry, and biology. It is not likely that one model of energy and dissipation will be enough to deal with the tremendous range of properties of ionic solutions. The law of mass action probably needs to be replaced by a set of models of solutions and reactions, not just one model. I believe the models will use variational methods so they can accommodate boundary conditions and flows, multiple components, and many types of forces and fields.

I certainly do not know how to choose or design models in most of these cases. Each profession dealing with chemical reactions and ionic solutions has a wisdom and experience

published in thousands of papers dealing with model design. The wisdom of each profession will be needed to design the appropriate variational model for its use. But few of those professions have had available a mathematics that allows transfer of rate constants from one set of conditions to another. Few of those professions have a theory that allows flows, or interactions. The law of mass action needs to be replaced in those cases.

In a few special cases, the variational approach has been developed and is known to be feasible and not particularly difficult. The selectivity of some types of (open) ionic channels has been treated with a variational approach. In this application, EnVarA can replace dysfunctional equilibrium theories (that always used variable constants to describe (un)constant fields) with variational theories [12-14, 25] that allow flow and interactions and design of new channels [23, 24, 31].

I write to suggest that a similar approach might be useful in many other fields. I write to suggest that the law of mass action needs in general to be repealed and replaced with an energetic variational approach able to deal with location, boundary conditions, and flows in a mathematically consistent and defined way.

The variational mathematics that can replace the law of mass action is not very different from that used by a wide range of physicists, but chemists and biologist are not used to this approach, in my experience. Mathematicians and physicists, familiar with variational methods, will be needed to help us replace the law of mass action with something more useful, something powerful enough to deal with the flows found in everything alive, something powerful enough to allow useful design of devices.

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