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The many faces of “evidence” for dependent and independent variables in the ‘Stewart approach’: reply to Lang

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Dear Editor,

Based on our article [1], Dr. Lang presents in his letter [2] a detailed re-evaluation of the mechanism of dilutional acidosis. His recalculation of our simulations reproduces the same quantitative results, whereas the suggested chemical mechanisms differ. Furthermore, he calculates the Gibbs energy to determine the spontaneous chemical reactions and uses the phase rule as a new justification for the separation into dependent and independent variables. However, for the most part we disagree with the interpretations and conclusions involved in his analysis. In particular, the application of the phase rule is flawed. Due to the limited space we only summarize the conclusions of our reply in the following; further details can be requested from the authors.

The phase rule and the independent variables

The way Dr. Lang applies the phase rule to his example is inappropriate for several reasons: (1) The phase rule is only of interest in a system where changes of state occur and, moreover,

it applies to a closed system in thermodynamic equilibrium, whereas out-of-equilibrium phenomena and metastability are not bound. Both conditions are not fulfilled in the considered example. When blood passes the lungs, with loss of/supply of gases to/from the environment, the system is open and out of thermodynamic equilibrium. (2) A component is a chemical substance, e.g. NaCl or NaHCO₃, but not a single ion such as Na⁺. It is true that the number of components can be derived from the individual ions (species), as done by Dr. Lang. However, the consequential assumptions on the real chemical processes must be obeyed. (3) The choice of intensive variables to which the degrees of freedom are related can be made arbitrarily. Variables can be pressure, temperature, [CO₂] and [NaCl], but can also be pressure, temperature, [H⁺] and [NaHCO₃]. It is not appropriate to derive independent variables from the phase rule. Na⁺, Cl⁻ or the strong ion difference (SID) cannot be independently considered in the phase rule.

Mechanism of dilutional acidosis

By recalculating our simulations, Dr. Lang uses a common procedure in pH calculations, where our master equation is simplified according to each specific simulation; this simplification is not necessary because mathematical software can easily solve the general quartic master equation. The results are exactly the same. However, we fully disagree with the mechanism suggested by Dr. Lang. The main difference is the two-step design of the process: dilution and subsequent chemical reactions. The way simulation 1 is described even seems to include a three-step process: (1) halving of the initial concentrations, (2) consumption of H⁺ by the excess OH⁻ (formation of water), and then (3) the

chemical reaction according to the equilibrium condition (increased water dissociation). It is not appropriate to consider sequential mechanistic steps because the kinetic of neutralisation reactions is very fast (10⁻¹² s) and all reactions take place simultaneously and immediately. The mechanistic consideration is a thought experiment in which the chemical equilibrium state is disturbed and then restored. Of interest are the predominant (net) chemical reactions occurring during this restoration of the chemical equilibrium state. Distinguishing water formation and water dissociation steps does not make sense because chemical equilibria always include continuously ongoing back and forward reactions. In simulation 1, the net reaction is the formation of water, as Dr. Lang himself shows by calculating the Gibbs energy for simulation 1.

Gibbs energy and driving force

As mentioned in the ESM of our paper [1], calculation of the change in Gibbs energy can be used to determine whether a chemical reaction takes place spontaneously. In acid–base solutions, these spontaneous reactions are the driving forces for the restoration of a chemical equilibrium state. Dr. Lang presents the calculation of the Gibbs energy for simulations 1 and 5 and confirms that the spontaneous reactions are exactly those we have suggested: in simulation 1, it is the formation of water (H⁺ + OH⁻ ↔ H₂O), whereas in simulation 5, the two HCO₃⁻-generating reactions are CO₃²⁻ + H⁺ ↔ HCO₃⁻ and A⁻ + H₂CO₃ ↔ HA + HCO₃⁻.

Conclusions

Any attempt to find a physicochemical basis for the mechanistic

importance of SID or strong ions in acid–base reactions must fail. SID is not a chemical substance or entity that can be regulated or changed independently; it is a mathematical value needed to solve equations for pH calculation. Deriving conclusions from arrangements of a mathematical formula (phase rule) without considering the real physicochemical processes that the variables represent must fail. The same mistake occurred in the attempt to derive mechanistic conclusions from the Stewart formula.

2. Lang W (2010) Comment on: “A critique of Stewart’s approach: the chemical mechanism of dilutional acidosis”. *Intensive Care Med.* doi:[10.1007/s00134-010-1897-2](https://doi.org/10.1007/s00134-010-1897-2)

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