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EDITORIAL

ACTA PHYSIOLOGICA

Strong ion difference: "ὃ οὐ κινούμενον κινεῖ"[a] or the unmoved physico-chemical mover

After carefully studying Prof. Bie's commentary,[1] one realizes that from the scientific debate—which stemmed from our published article[2] presenting an interpretive approach to urine [SID] according to Stewart's view and extended to a broader critique of his approach on the overall regulation of acid-base balance in the body—remains but a single point of divergence, which does not truly make it so difficult to accept Stewart's view, as it seems to justify the persistent adherence to what is called the classical view of acid-base disorders. This is the *active proton transfer*. Indeed, the central point of the classical approaches to the interpretation of acid-base disorders is the transfer of protons (H^+) between the various compartments of the organism. Although we have already mentioned this topic in our previous papers, we will provide more details here, especially regarding the transport of H^+ through proton pumps/transporters.

As to whether or not [SID] is an independent variable, it will be made clear that, although it has to do with the way one conceives the phenomena, physico-chemical properties of the interacting substances prevail at the end. For the rest of the issues, minor, though necessary, comments are provided.

1 | ACTIVE PROTON TRANSFER

Protons, in whatever way we might symbolize them (let us just look at them as positive elementary charges), being elements of all aqueous solutions, are, in a way, the link between all biomolecules in the body. It has been argued that cells are not very likely to respond quickly when conditions are altered, sensing concentration changes that result simply from diffusive processes. The presence of water seems to be able to serve this purpose sufficiently, by releasing H^+ from a biomolecule, which then acts through the hydrogen-bonded network on other non-touching biomolecules (communication at a distance).[3]

The diffusion of H^+ into aqueous solutions occurs rapidly, owing to the hydrogen-bonded nature of water. Proton transport takes place through the Grotthuss mechanism, in which the proton that enters the chain of hydrogen-bonded water molecules is different from the proton that exits the chain. Aside from details and clarifications, this mechanism is the commonly accepted view of proton transport today. By the Grotthuss mechanism, proton migration occurs in the timescale of hydrogen-bond breaking and making (reorientation motion of water molecules), which is of the order of a picosecond.[4]

This type of proton transport is also described along hydrogen-bonded chains in proteins (proton pumps/proton-coupled transporters), where the hydrogen-bonded network, which facilitates proton transfer through the hydrophobic interior of proteins, includes, in addition to water molecules, protonable amino acid residues (eg their terminal carboxylic groups). A schematic representation of a transmembrane proton transporter (pump) is shown in Figure 1. According to a simplified but quite informative description of the involved mechanism,[5] for the transport of H^+ from inside a cell to the extracellular space, H^+ from the intracellular fluid comes in contact with protein surface acceptor groups and finally with the initial proton donor (Δ_1), at the inner end of the proton transport pathway. Proton transfer then takes place via a series of molecules of water and/or protonable amino acid residues (which form a hydrogen-bonded chain or "proton wire") and terminates in an internal proton acceptor (E_1), which undergoes a conformational change and comes in contact with the outer side of the membrane (E_2), leading to proton transfer along a second hydrogen-bonded chain, until the final release of H^+ in the bulk solution of the extracellular space from the final protein acceptor/donor (Δ_2).

What needs to be understood is that, it is *a topological defect* in the hydrogen-bonded network and not an individual H^+ (or any molecular structure carrying an excess proton) that is transported through the network chains.[4]

It should also be noted that, since the pKa of the groups involved in hydrogen-bonded chains determines the direction and the rate of proton transport, electrostatic interactions, induced, for example, by changing [SID] are of particular importance to this transport. Most particularly, in P-type ATPases (eg animal H^+-K^+-ATPase), each proton transport cycle includes two enzyme conformational states that

[a]Ancient Greek: *ho ou kinoúmenon kineî*, lit. "that which moves without being moved" (Aristotle).

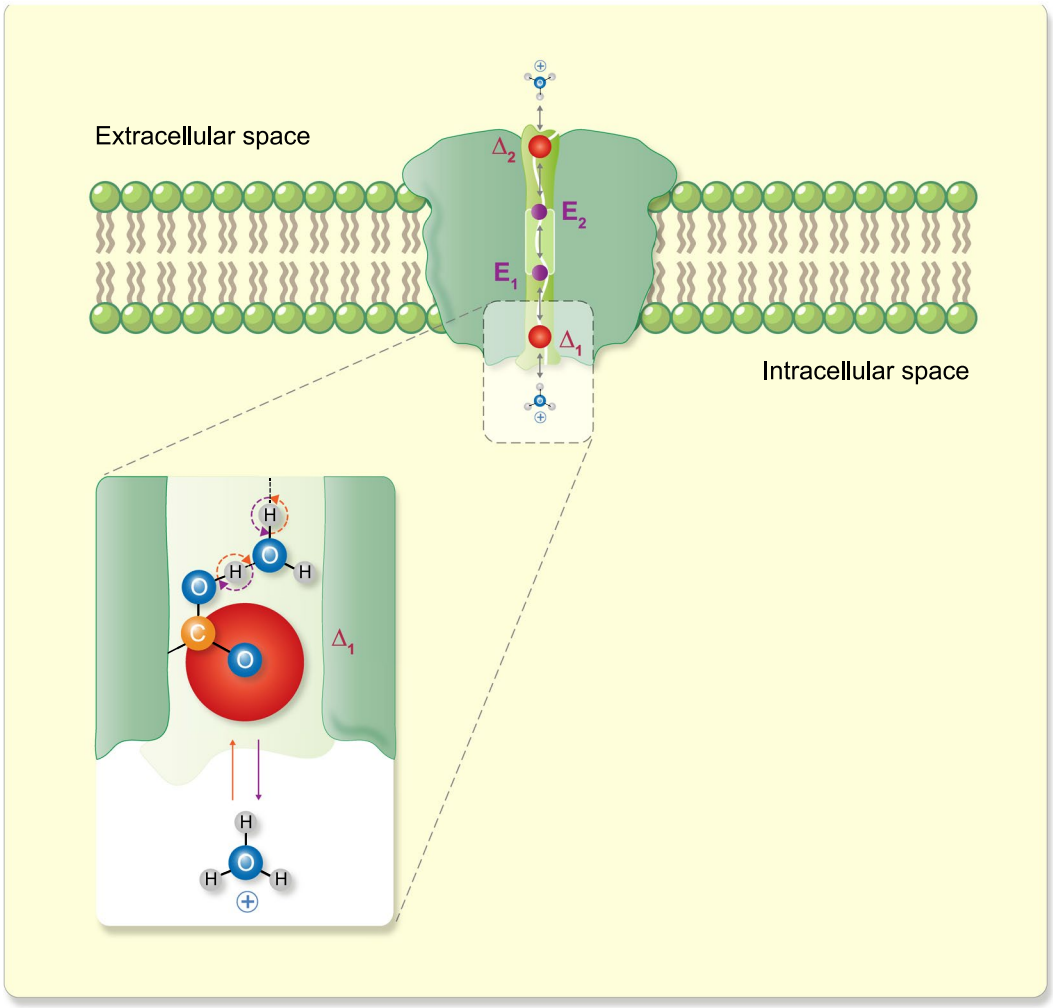

FIGURE 1 Schematic representation of proton transport from inside a cell to the extracellular space, according to the Grotthuss mechanism. Protons from the intracellular fluid, come in contact with the initial proton donor (Δ_1), at the inner end of the proton transport pathway. Proton transfer then takes place via a series of molecules of water and/or protonable amino acid residues (eg their terminal carboxylic groups) and terminates in an internal proton acceptor (E_1), which undergoes a conformational change (E_2), leading to proton transfer along a second hydrogen-bonded chain, until the final release of the protons in the bulk solution of the extracellular space from the final protein acceptor/donor (Δ_2)

alternate, E_1 and E_2, as described above. In the E_1 state, the binding region has high affinity for the exported ions (H^+), while in the E_2 state, the same binding region has low affinity for the exported ions and a high affinity for the ions (counter ions) which are transported within the cell (eg K^+). In H^+-ATPases, the main proton acceptor/donor is a protonable aspartic acid residue (Asp684), which undergoes a regulated proton loading and unloading during the enzyme conformational transitions. A positively charged residue (Arg655) is believed to control pKa changes of Asp684 (proton acceptor/donor), while the transport pathway of protons to and from Asp684 probably consists of charged amino acid residues as well as water molecules.[6]

It is true that the molecular structure of proton pumps/transporters has been described in detail, but tracking the pathway of individual protons is another thing. The same also applies, for example, to gastric H^+-K^+-ATPases; regarding the mode of action of proton pump inhibitors, their reaction with cysteine 813 arrests the H^+-K^+-ATPase in the E_2 configuration,[7] terminating a proton transport mechanism, most likely, as the one described above. Furthermore, on the subject of the acidity of the gastric lumen, we would pose a question: if the transfer of H^+ to the gastric lumen may (and does) occur in exchange for K^+, electroneutrality is not violated; if H^+ that are exported constitute an acidic load that can, by itself, account for the increased acidity (low pH) of gastric fluid, what is the need for the increased concentration of Cl^- in it?

[SID] *is* independent variable under physiological control

According to Stewart, [SID] is a physiological variable, that is, a variable that is subject to physiological control, whose physico-chemical properties make it a "useful tool" for performing normal functions/regulating other dependent variables. The thesis that [SID] is an independent

variable (introduced by Stewart) has a *physico-chemical basis*, that is, it relates to its chemical interaction with other solutes (ie weak acids) in body fluids and the values of the dissociation constants of strong ions (that make up [SID]) compared to those of weak electrolytes. Briefly, strong ions, being fully dissociated, do not participate in acid-base reactions (spectator ions), but form the specific pathophysiological framework that determines the dissociation of weak electrolytes (that are involved in net proton exchange).

At this point, we make a short generic note about the dependence/causative relation between the variables of a mathematical model. We do so, because of a footnote (!) in Prof. Bie's response, which is indicative of the mistreatment of the concept. In this footnote (the purpose of a footnote is to remind already known results, or to present further already known details on a subject; a footnote should not be used as a way to strengthen an argument), it is stated that "mathematical isolation does not show physical directionality," in an attempt to refute Stewart's proposition concerning the dependence of $[H^+]$ on [SID]. A failed attempt of giving a counterexample then follows. We note that every exact science, like physics, is built on mathematics. A mathematical expression of the relation between physical quantities denoted by variables is the quintessence of a physical/natural/exact theory. An exact theory fully described by a mathematical model (eg electromagnetism which is described by the deterministic model of the Maxwell equations) does not reveal a single causal link between the quantities appeared (eg the electric and the magnetic field), but it describes the way the nature distributes their changes. A causative relation is utilized by us, when we know the values of some quantities and we want to calculate the values of the rest. In our case, the mathematical statement "$[H^+]$ is a certain function of [SID]" is equivalent with the physical interpretation that "the concentration of H^+ depends on that specific manner on the concentration of SID." Hence, we can calculate $[H^+]$ by knowing the value of [SID]. This does not contradict with the fact that, if the function is invertible, then we can calculate [SID] by knowing the value of $[H^+]$. As far as the counterexample proposed by Prof. Bie is concerned, body mass index (BMI) is defined as $\mathrm{MI} = m/h^2$. This means that BMI is a certain function of h; thus, height determines BMI with this specific manner (considering, of course, m to be constant). By inverting the function, which is a rigorous mathematical process based on the inverse function theorem, we can write $h = \sqrt{m/\mathrm{BMI}}$, which also means that BMI determines height with this specific manner (considering again that m is constant). The process of inverting a function helps us to switch roles between dependent and independent variables, and does not contradict at all to the interpretation of the physical phenomena. Another trivial example follows. Knowing the displacement x of a moving object of constant velocity v over time t, velocity is determined (is calculated) by time as the expression $v = x/t$ indicates, as well as time is determined by velocity with $t = x/v$ being the corresponding expression. Yet another example is presented in the Appendix A. For the sake of completeness, we also refer to the application of the implicit function theorem in a mathematical equation that implicitly binds several variables, as an alternative way of expressing some of them as a function of the rest.

In the light of the above discussion, there is no ambiguity in the expression that [SID] acts as an independent variable for the determination of $[H^+]$. [SID], "a non-neutral sum of (strong) ion concentration," is what it is, in order to serve the physiological function of the organism in any specific compartment while, under standard conditions ($[A_{TOT}]$, PCO_2), the $[H^+]$/pH have the specific, considered normal, values. Abnormal [SID] values may indicate a functional disorder or a compensatory response, for example, in diabetic ketoacidosis, an anion gap (AG) metabolic acidosis, where apparent [SID] does not change and the strong ion gap ([SIG]) becomes positive, is progressively complicated by non-AG (hyperchloremic) metabolic acidosis,[8] where apparent and effective [SID] decreases equally and [SIG] remains at or near zero; also, during a metabolic acidosis disorder, a positive urine [SID] indicates inefficient renal response/impaired urine acidification (renal tubular acidosis) while a negative urine [SID] signifies a proper renal compensation.[9] Finally, abnormal [SID] values may occur as a result of a medical intervention (increased NS 0.9% solution administration).[10] From what has been said, it cannot be deduced that [SID], in relation to the other acid-base variables, is a dependent variable, in physico-chemical terms. One could, however, in promoting the pathophysiological priority of regulating $[H^+]$ in the organism, refer to [SID] as a *physiologically dependent* variable, which is mobilized each time as a control mechanism, to serve this priority. In our previous paper,[11] we have also referred to the regulation of [Na]/[Cl] on either side of a semipermeable membrane, under the physico-chemical constraints acting on the Donnan equilibrium, created by the distinct *physiological composition* of the separated fluids. It does not matter how one approaches this issue. What matters is to make clear what we are referring to and be consistent with the basics/fundamental principles of the theory throughout our "story." Indeed, the specific value of [SID] in a body fluid compartment, no matter how it is formed, is, from a physico-chemical point of view, an independent determinant of $[H^+]$ in it.

The dependence of the degree of a weak acid dissociation on the [SID] value is illustrated in Figure 2 (concerning a solution that contains strong ions and weak acids). It should be noted that when [SID] has negative value, $[H^+] = -[\mathrm{SID}]$ and (almost) all the amount of the weak acid is in the bound (undissociated) form, whereas when [SID] has a positive sign

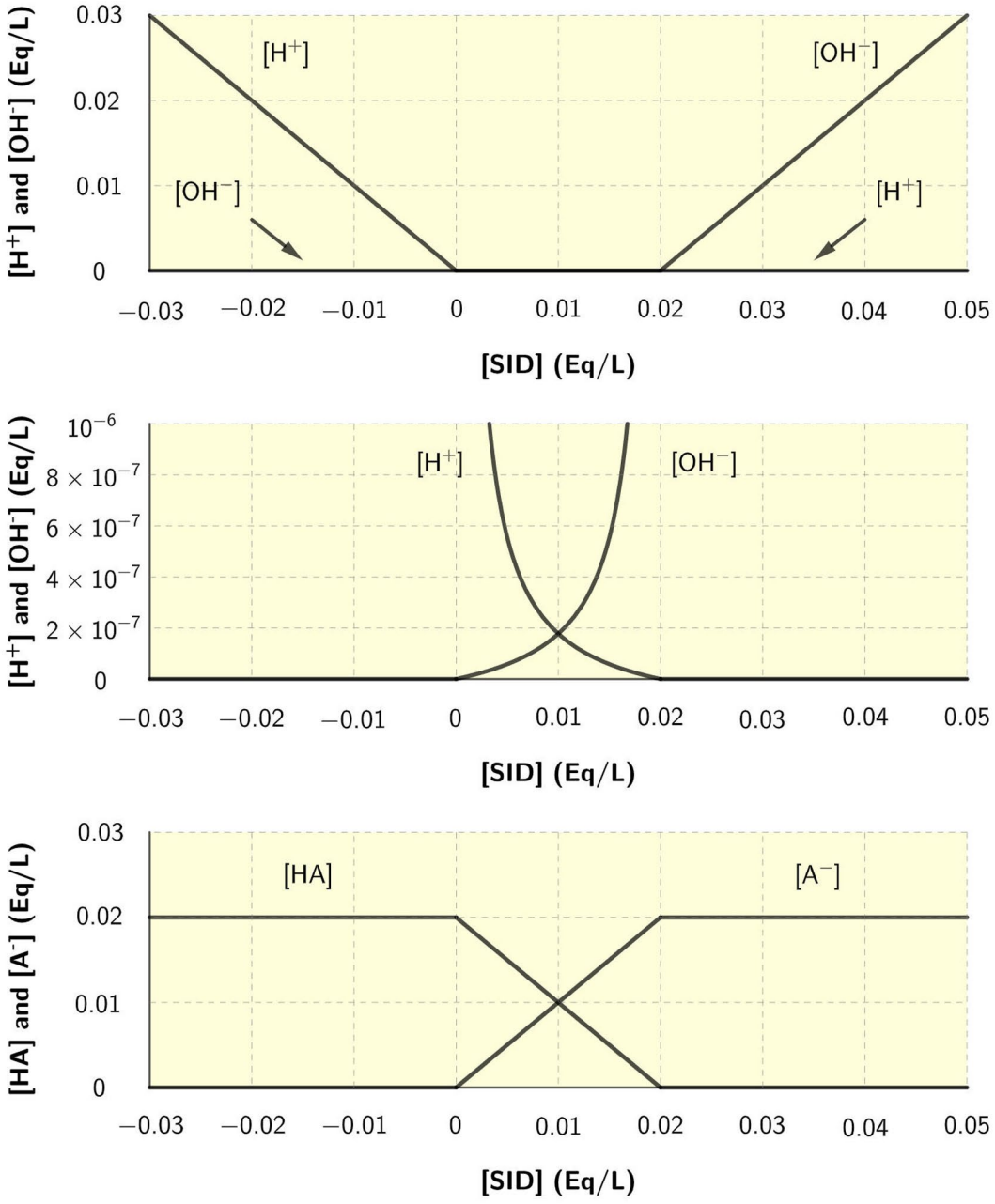

FIGURE 2 $[H^+]$, $[OH^-]$, $[A^-]$, [HA] plotted against [SID] for a weak acid solution. $[A_{TOT}] = 0.02$ mEq/L, $K_A = 2 \times 10^{-7}$ Eq/L, $Kw' = 4.4 \times 10^{-14}$ $(Eq/L)^2$ at 37°C. When beyond the zero to $[A_{TOT}]$ range for [SID], H^+ and OH^- behave as they would in a purely strong ion solution. When [SID] is negative, $[H^+] = -[SID]$ and (almost) all the amount of the weak acid is in the bound (undissociated) form; when [SID] is positive (and $>[A_{TOT}]$), $[OH^-] = [SID]$, $[H^+]$ is negligible and (almost) all of the weak acid is in the dissociated form. The middle graph shows how $[OH^-]$ and $[H^+]$ behave over the [SID] = 0 to [SID] = $[A_{TOT}]$ range. The concentration of $[H^+]$ is on the order of K_A (10^{-7} Eq/L). Adapted with permission. Copyright© 2009 by AcidBase.org

and its value is greater than $[A_{TOT}]$, $[OH^-] = [SID]$, $[H^+]$ is negligible and (almost) all of the weak acid is in the dissociated form (ie it behaves as a strong acid)![12]

> "Charge differences between body fluid compartments represent concentration differences which chemically are infinitesimal"

No matter how "chemically infinitesimal" the "strong ion concentration differences between the body fluid compartments" may be, they certainly cannot be considered insignificant. In fact their maintenance, their regulatory change and/or their spatio-temporal transmission (in the form, respectively, of a transmembrane potential, an ion regulatory mechanism for intracellular pH regulation[13] or a propagating

action potential) are indispensable for the maintenance of the life itself, constituting part of the dissipative structures in biological systems, the dynamical bases of their selforganization, being far from equilibrium.[14]

> The formula that calculates $[H^+]$ by [SID] applies specifically for water solutions that contain only strong ions. It cannot be used for the calculation of $[H^+]$ in plasma, where a much more complicated formula ensues.[15]

Thus, the application of the fundamental, physico-chemical principles for a solution with the plasma composition leads to the following system of equations: (1) law of mass action for the water dissociation reaction: $[H^+] \times [OH^-] = Kw'$, (2) law of mass action for the dissociation of the weak, non-volatile acids: $[HA] \times KA = [H^+] \times [A^-]$, (3) law of conservation of mass for the total amount of the weak acid (anion), that is, in bound and ionized form: $[HA] + [A^-] = [A_{TOT}] = \text{constant}$, (4) law of mass action for the dissociation reaction of H_2CO_3: $[H^+] \times [HCO_3^-] = K_2 \times PCO_2$, (5) law of mass action for the HCO_3^- dissociation reaction: $[H^+] \times [CO_3^{-2}] = K_3 \times [HCO_3^-]$ and (6) law of electrical neutrality: $[SID] + [H^+] - [OH^-] - [A^-] - [HCO_3^-] - [CO_3^{-2}] = 0$. In this system consisting of six equations, there are three independent variables ([SID], PCO_2, $[A_{TOT}]$) that regulate $[H^+]$ and the values of the other dependent variables. It can be solved with respect to $[H^+]$:

$$[SID] + [H^+] - \frac{K_2 \times PCO_2}{[H^+]} - \frac{K_A \times [A_{TOT}]}{(K_A + [H^+])} - \frac{K_3 \times K_2 \times PCO_2}{[H^+]^2} - \frac{K'_w}{[H^+]} = 0$$

However, one should not worry, the calculations can be done by the computers!

2 | GROSS METABOLISM

Although we have referred to this issue in our previous paper,[11] it would be appropriate to point out something: according to Prof. Bie, the food and the metabolic substrates present in it (the processing of which provides the energy as well as the structural elements that the organism needs) are treated as bearing (or creating during their catabolism) a specific proton load, which, as an independent variable, affects the acid-base status of the organism. We will simply refer to the relevant Figure,[1] noting that in the case of "H^+ generating metabolism," the final metabolic product appears to be a strong anion (Cl^-, derived from the HCl dissociation, eventually excreted by the kidneys; we presume that the increased Cl^- in urine might, most probably, lessen the urine [SID]), while in the case of "H^+ consuming metabolism" (ie alkalinizing effect), the final metabolic product appears to be a strong cation (K^+, resulting from the dissociation of KOH, also excreted by the kidneys)!

3 | RENAL PHYSIOLOGY

Prof. Bie in his editorial argues that there is no known renal mechanism regulating chloride excretion against sodium excretion, deeming SID as physiologically irrelevant. Indeed, while the kidney is largely responsible for keeping the concentration of all strong ions in the plasma within a strict range, there is, yet, no knowing mechanism specifically regulating their concentration difference. Thus, presenting [SID] as the forefront determinant of $[H^+]$, while also lacking an established, direct, regulatory mechanism is problematic.

Nevertheless, we would argue that the potential for an, at least, indirect [SID] regulation does exist as a large number of ionic channels have been described in the kidney, controlling the reabsorption/excretion of strong ions (*which make up SID*), both individually and in combination and serving, finally, diverse objectives, as salt reabsorption, acid-base control and cell volume management.[16-18]

Moreover, fine and coordinated adjustments are made according to the existing conditions in order to maintain homeostasis in the body. Thus, in aqueous solutions, the almost identical biophysical characteristics of K^+ and NH_4^+enable renal epithelial transport of NH_4^+, that competes with K^+ for binding to the K^+-transport site of essentially all K^+ transporters; also, specific isoforms of the Na^+/H^+ antiporter operate in an Na^+/NH_4^+ exchange mode, for example, NH_4^+ competes with luminal Na^+ for reabsorption by NHE-3.[19] In case of an acidosis disorder—during which ammoniagenesis increases in the kidney—these procedures are likely to prevent strong cation loss in urine, which, combined with increased Cl^- excretion, decreases [SID] in urine and increases, in a compensatory way, plasma [SID].

The proposed view, made on the basis of existing evidence, would therefore pose an interesting research question, a starting point for further investigation.

It should be noted that NH_3 (which at pH 7.4 is about 98.3% in the form of NH_4^+) is produced in the kidney: ammonia in the urine and the renal vein far exceeds ammonia in the renal artery.[19] Apparently, NH_4^+ plays a leveraging role locally, being an operational part of the renal mechanism that regulates acid-base balance. However, Stewart does not consider NH_3/NH_4^+ *quantitative changes* per se important for the overall regulation of acid-base balance in the body: its concentration in plasma is very low and its change cannot affect the values of the independent variables which determine $[H^+]$. Based on the explanatory view mentioned above, it can really be argued that NH_4^+ major importance lies in its functional role, that is, its mediation for the regulation of [SID] in

urine and plasma (sparing strong cations) and not in being a "carrier" of the excreted H^+ load.

Stewart's approach may be thought of, largely, as a matter of perspective, rather than a matter of practicality. The described regulation does not require the discovery of new mechanisms in the kidney, as it depends on those already known. What changes are merely our perspective of how these mechanisms affect $[H^+]$ in the plasma.

> Common sense: Indeed, the sunny sky is blue to the human eye, thanks to the Rayleigh scattering!

Prof. Bie seems to misinterpret the way we used the concept of "common sense," in order "a theory's falseness or hollowness to be exposed," and not "to validate, at least partly (!), a scientific theory" as he states. Initially, we note that the confirmation/proof of the invalidity of a theory follows a different mental process from the corresponding confirmation/proof of its validity, since we refer to two different (opposite) things. Prof. Bie clearly identifies the exposure (let alone the proof) of the inaccuracy of a theory with its validation. Of course, a theory that contradicts common sense is dubious, still not yet an invalid one. Of course, a theory is not validated just because it is in agreement with the common sense. However, these last two sentences do not coincide. No further comments are provided on Prof. Bie's "examples of physical theories" that allegedly circumvent common sense.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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REFERENCES

1. Bie P. Strong ion difference: questionable stewardship. *Acta Physiol*. 2021;26:e13667.
2. Alevrakis E, Gialelis N, Vasileiadis I. Strong ion difference in urine: a measure of proton excretion or of the net plasma charge alteration? *Acta Physiol*. 2020;230(3):e13559.
3. Chaplin M. Do we underestimate the importance of water in cell biology? *Nat Rev Mol Cell Biol*. 2006;7(11):861-866.
4. Marx D. Proton transfer 200 years after von Grotthuss: insights from ab initio simulations. *ChemPhysChem*. 2006;7(9):1848-1870.
5. Adelroth P. Special issue on proton transfer in biological systems. *Biochim Biophys Acta*. 2006;1757(8):867-870.
6. Buch-Pedersen MJ, Pedersen BP, Veierskov B, Nissen P, Palmgren MG. Protons and how they are transported by proton pumps. *Pflugers Arch*. 2009;457(3):573-579.
7. Engevik AC, Kaji I, Goldenring JR. The physiology of the gastric parietal cell. *Physiol Rev*. 2020;100(2):573-602.
8. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. *N Engl J Med*. 2015;372(6):546-554.
9. Batlle D, Ba Aqeel SH, Marquez A. The urine anion gap in context. *Clin J Am Soc Nephrol*. 2018;13(2):195-197.
10. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology*. 1999;90(5):1265-1270.
11. Vasileiadis I, Alevrakis E, Gialelis N. Stewart's approach: just a heresy or another lens into acid-base physiology? *Acta Physiol*. 2021;232:e13622.
12. Stewart PA. Weak electrolytes and buffers. In: Kellum JA, Elbers PWG, eds. *Stewart's Textbook of Acid-Base*, 2nd edn. Egham, UK: Lulu Enterprises; 2009:74.
13. Aickin CC, Thomas RC. An investigation of the ionic mechanism of intracellular pH regulation in mouse soleus muscle fibres. *J Physiol*. 1977;273(1):295-316.
14. Goldbeter A. Dissipative structures in biological systems: bistability, oscillations, spatial patterns and waves. *Philos Trans A Math Phys Eng Sci*. 2018;376(2124):20170376.
15. Stewart PA. Strong ions plus carbon dioxide plus weak acid (isolated blood plasma and isolated intracellular fluid). In: Kellum JA, Elbers PWG, eds. *Stewart's Textbook of Acid-Base*, 2nd edn. Egham, UK: Lulu Enterprises; 2009:165.
16. Devuyst O, Guggino WB. Chloride channels in the kidney: lessons learned from knockout animals. *Am J Physiol Renal Physiol*. 2002;283(6):F1176-F1191.
17. Patel-Chamberlin M, Varasteh Kia M, Xu J, Barone S, Zahedi K, Soleimani M. The role of epithelial sodium channel ENaC and the apical Cl^-/HCO_3^- exchanger pendrin in compensatory salt reabsorption in the setting of Na-Cl cotransporter (NCC) inactivation. *PLoS One*. 11(3):e0150918.
18. Felder RA, Jose PA, Xu P, Gildea JJ. The renal sodium bicarbonate cotransporter NBCe2: is it a major contributor to sodium and pH homeostasis? *Curr Hypertens Rep*. 2016;18(9):71.
19. Weiner DI, Verlander JW. Role of NH_3 and NH_4^+ transporters in renal acid-base transport. *Am J Physiol Renal Physiol*. 2011;300(1):F11-F23.
20. Iannelli M, Pugliese A. *An Introduction to Mathematical Population Dynamics, Along the Trail of Volterra and Lotka*. Cham, Heidelberg, New York, Dordrecht, London: Springer; 2014.
21. Maloney JV Jr, DeHaven JC, DeLand EC, Bradham GB. Example of a large-model simulation of the blood biochemical system. *J Chronic Dis*. 1966;19(4):411-425.

APPENDIX A

Here, we present the dependence relation between the dissociation of two or more acids in aqueous solutions, as another example of the process of switching roles between dependent and independent variables in a physical model.

Consider a system that comprises an aqueous solution containing amounts of n acids, each of one of which to be denoted as HA_i, for $i = 1, \ldots, n$, (following Arrhenius's definition of acids), with corresponding dissociation constant K_{A_i}. We then have the system of the following chemical reactions

$$H_{A_i} \rightleftarrows H^+ + A_i^-, \quad \forall\, i = 1, \cdots, n.$$

According to the isohydric principle, when more than one acids are present in an aqueous solution, all are exposed/are in equilibrium with the same $[H^+]$. Hence, applying the Guldberg-Waage mass action law for the acid dissociation reactions, we deduce the corresponding system of equations

$$\left[H^+\right] = K_{A_i} \times \frac{\left[HA_i\right]}{\left[A_i^-\right]}, \quad \forall\, i = 1, \cdots, n.$$

We denote by $\lambda_{A_i} = [A_i^-]/[HA_i]$, for $i = 1, \ldots, n$. Every λ_{A_i} measures the dissociation of H_{A_i}: the increase of λ_{A_i} indicates greater dissociation of H_{A_i}. We note that in case of a strong acid H_{A_i} we have $K_{A_i} = \lambda_{A_i} = \infty$. The above system of equations then gets the following form

$$\left[H^+\right] = \frac{K_{A_i}}{\lambda_{A_i}}, \quad \forall\, i = 1, \cdots, n,$$

from which we derive that

$$\frac{K_{A_i}}{K_{A_j}} = \frac{\lambda_{A_i}}{\lambda_{A_j}}, \quad \forall\, i, j = 1, \cdots, n.$$

Hence, given a specific quantitative correlation between a pair K_{A_i} and K_{A_j}, for $i, j = 1, \ldots, n$, we can derive the relation between the measures of dissociation λ_{A_i} and λ_{A_j}. For example, $\lambda_{A_i} = 10^3 \lambda_{A_j}$ is equivalent to $\lambda_{A_j} = 10^{-3} \lambda_{A_i}$, when K_{A_i} is thousand times as much as K_{A_j}.

We can further analyse the above dependence equations by utilizing the properties of the dissociation constants K_{A_i}, for $i = 1, \ldots, n$. A first approach could be by the very definition of those constants. We remind that we define

$$K_{A_i} = \frac{K_{A_i}^+}{K_{A_i}^-}, \quad \forall\, i = 1, \cdots, n,$$

where each $K_{A_i}^+$ corresponds to the respective reaction

$$H_{A_i} \rightarrow H^+ + A_i^-,$$

while each $K_{A_i}^-$ stands for the reaction rate constant of

$$H_{A_i} \leftarrow H^+ + A_i^-.$$

According to the law of mass action, we have the following system of nonlinear ordinary differential equations

$$\frac{d\left[HA_i\right]}{dt} = K_{A_i}^- \left[H^+\right]\left[A_i^-\right], \quad \forall\, i = 1, \cdots, n,$$

as well as

$$\frac{d\left[H^+\right]}{dt} = \frac{d\left[A_i^-\right]}{dt} = K_{A_i}^+ \left[H_{A_i}\right], \quad \forall\, i = 1, \cdots, n.$$

We note that, in the equilibrium, we derive by the law of conservation of mass (mass balance) that

$$\frac{d\left[HA_i\right]}{dt} = \frac{d\left[H^+\right]}{dt} = \frac{d\left[A_i^-\right]}{dt}, \quad \forall\, i = 1, \cdots, n,$$

which gives us the well-known expression

$$K_{A_i} = \frac{\left[H^+\right]\left[A_i^-\right]}{\left[HA_i\right]}, \quad \forall\, i = 1, \cdots, n.$$

We also note that the form of the above system is quite common in applications, like ecology (see, eg the Lotka-Volterra model) and epidemiology (see, eg SIR model), for which we refer to Ref. [20]. In particular, we can write each constant $K_{A_i}^{\pm}$ as

$$K_{A_i}^- = \frac{c_- \times p_-}{\left[H^+\right] + \left[A_i^-\right]}$$

and

$$K_{A_i}^+ = \frac{c_+ \times p_+}{\left[HA_i\right] + \left[H_2O\right]} \times \left[H_2O\right] \simeq \frac{c_+ \times p_+}{\left[HA_i\right] + 55.5} \times 55.5,$$

where

- c_- stands for the number of occasions the ions H^+ and A_i^- get close enough to react with each other,
- p_- stands for the probability a close encounter of the ions H^+ and A_i^- to end up with the formation of the molecule HA_i,
- c_+ stands for the number of occasions the molecules HA_i and H_2O get close enough to react with each other, and
- p_+ stands for the probability a close encounter of the molecules HA_i and H_2O to end up with the formation of the ions H^+ and A_i^-.

At the end of the day, we are able to express every constant K_{A_i} in terms of the above variables. Thus, the same is true for

the aforementioned dependence relation between the dissociation of the acids in the aqueous solutions. For the sake of completeness, we further note that

$$\frac{[H^+]}{[H^+] + [A_i^-]}$$

is the probability for an ion A_i^- to face an ion H^+ in a close encounter with another ion and

$$\frac{[A^-]}{[H^+] + [A_i^-]}$$

is the probability for an ion H^+ to face an ion A_i^- in a close encounter with another ion. Similarly,

$$\frac{[HA_i]}{[HA_i] + [H_2O]}$$

is the probability for a molecule H_2O to face a molecule HA_i in a close encounter with another molecule, and

$$\frac{[H_2O]}{[HA_i] + [H_2O]}$$

is the probability for a molecule HA_i to face an ion H_2O in a close encounter with another molecule.

A second approach could be a straight thermodynamic one. Indeed, every constant K_{A_i} is exponentially related to the (Gibbs) free energy change per mole for the dissociation reaction under standard conditions $\Delta G_i^\circ = -R \times T \times \ln K_{A_i}$, where $R = 8.314 J \times K^{-1} \times mol^{-1}$ (universal gas constant), and T is the thermodynamic (absolute) temperature (Kelvin). Free energy change provides a quantitative measure of the favourability of a given reaction (at constant temperature and pressure). Therefore, the aforementioned dependence relation can be expressed in terms of free energies and comparative thermodynamic favourability (ie which of the two dissociation reactions is thermodynamically/energetically more favourable). In fact, quantitative analyses of body fluid chemistry have been carried out using free energies.[21]