Modeling Acid–Base by Minimizing Charge-Balance

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Supporting Information

ABSTRACT: In this study, we show that equilibrium pH can be obtained for any specified fluid with any number of buffers and dissociations. This is done by root finding in the equation for charge balance. We demonstrate that this equation is monotonic in proton concentration for conceivable buffers. We show that the total charge on any buffer is a function of only the total buffer concentration and pH, given the thermodynamic dissociation constants. Using the Davies’ equation as a placeholder for single-ion activity coefficients as a function of charge and ionic strength, we develop an iterative algorithm, whereby the apparent dissociation constants are updated from the thermodynamic dissociation constants, and from this, the equilibrium is also identified in the nonideal state. We show how this algebra leads to guaranteed conservation of both thermodynamic dissociation constants and total buffer concentrations because the distribution of buffer species is fixed by the updated dissociation constants, actual pH, and total buffer concentration. Strong ions are assumed to contribute fixed charges. In order to concentrate on the process of modeling the equilibrium pH alone, this algorithm is examined against a series of theoretical results in which the Davies’ equation was given the same status. However, a large sample of clinical pH measurements is also examined. To enhance the practical utility, CO₂ and albumin are present as the default condition. We developed “ABCCharge”, a package in R, an open source language. The main function returns pH, activity coefficients, buffer species distribution, ionic strength, and charge balance for both the ideal and nonideal cases, for any mixture of any buffers with any number of known thermodynamic dissociation constants. Our algorithm can be updated if a more reliable and practical assessment of single-ion activities becomes available. Can Stock Photo/mickeying

INTRODUCTION

Understanding of acid–base physiology can be obtained through deriving rules that allow prediction of pH from elementary measurements. The possibility of achieving this is equivalent with the ability to calculate pH from the chemical constituents of a given fluid. The underpinnings for these calculations are the thermodynamic principles for dissociation and mass conservation and the requirement for balance between moieties with positive and negative charges. At the bedside, understanding acid–base disorders amounts to explaining the current status from known determinants, thereby, suggesting mechanisms for explaining deviations and examining specific hypotheses.

The calculations of equilibrium pH have been technically difficult but methods to automate identification have been developed as advanced numerical solutions became available. Ganesh et al. separate two mathematical approaches, an algebraic and a dynamic. The algebraic approach may result in polynomial equations in which the proper root identifies the equilibrium condition. The dynamic method solves together a series of differential equations and may address the development over time and not only the equilibrium situation.

In this paper, we propose that it is possible to find a unique expression of the net equilibrium charge in any specified fluid. Because the charges are derived either from strong ions with pH-independent fixed charge or from buffers, for which the total charge and distribution of each charged species is a function of pH and total concentration and the dissociation constants, root finding in this expression of charge balance is tantamount to identification of both pH and the distribution of buffer species. We show in the Supporting Information ("Derivation of charge-balance expression") that charge balance is always monotonic in [H⁺], which guarantees a single root. Crucially, from the algebraic formulation of the model, it is ensured that the fitting procedure enforces the conservation of thermodynamic dissociation constants and total buffer concentrations.

An important problem is how to account for ionic strength and apply activity coefficients for nonideal and not very dilute solutions. A recent series of publications attest to the perceived importance of this subject. They all used Davies’ equation as an approximation to the Debye–Hückel theory, and implicitly assumed that, hereby, a useful single-ion activity coefficient was at hand. In reality, the Davies’ equation delivers the mean ionic activity coefficient for prevalent cations and anions. Therefore, assuming that this value can be used as an estimate of single-ion activity coefficient is certainly problematic.

Over the years, it has even been an enigma if single-ion activities can at all be defined, measured, or calculated. As
our aim here is to explore the utility of charge-balance in the modeling of acid–base equilibrium, it is worthwhile to present in brief one argument in favor of the reality of single-ion activity as given by Valiskó and Bodá. The impossibility (according to Valiskó and Bodá) of operating with a single-ion activity roots in the perceived impossibility of adding positive or negative charge without also adding the respective counterions. However, as stressed by these authors, the requirement of charge-balance is relevant in the macroscopic realm, whereas in the microscopic world and over short periods of time, charge imbalance is frequent and important—for instance, in physiology. On the other hand, Kontogeorgis et al. in a recent review on Debye–Hückel modeling conclude that the status of single-ion activity coefficients is uncertain, while also acknowledging that progress in theoretical and practical construction of these takes place by Poisson–Fermi modeling and otherwise. Recently, it has been suggested that single-ion activity coefficients can be obtained from the theoretically well-established single-ion conductivity, lending some support to the reality of the former and probably also, eventually, means for the estimation.

In any case, in the papers considered here, nonideal conditions are handled by correcting for ionic strength and charge by the use of activity coefficients obtained from the Davies’ equation. Our intention here is, therefore, to explore how identification of equilibrium in the nonideal state can be obtained by a charge-balance approach given that the Davies’ equation is understood to deliver single-ion activities. It is acknowledged that this modeling of the nonideal state is provisional and must be improved if and when a more established notion of single-ion activity coefficient becomes available. Therefore, the mean activities obtained by the Davies’ equation are interpreted as placeholders for single-ion activities. Alternatively, we may choose to consider the single-ion activities that results from the disputed activity coefficients as conventional rather than physical entities. The modeling and theoretical comparisons presented here will be insensitive to this choice.

The studies selected for consideration here were chosen because they deliver theoretical calculated pH values, and our intention is to present an algorithm for obtaining such estimates in the equilibrium state in a robust and conceptually simple way. Tessman and Ivanov described a general procedure for finding equilibrium including activity coefficients based on Debye–Hückel via Davies equation. This involved solving polynomials and fitted available measurements well. Similarly, Glaser et al. obtained dynamic results for multiequilibria by writing up all possible chemical reactions in the fluid as differential equations. Both equilibrium and off-equilibrium situations were thereby characterized. It was shown that the algebraic approach yielded a single solution, which was identical to the dynamic approach in the equilibrium situation. Schell et al. augmented this dynamic approach to take ionic strength into account, again using the Davies’ equation. Also, Baeza-Baeza and García-Álvarez-Coque used the Davies’ equation to find activity coefficients and found the equilibrium pH through minimizing a composite criterion. This consisted of the squared difference of the sum of buffer concentrations from known total values, the squared difference of charge balance from zero, and the squared final change in ionic strength after an iterative procedure.

A straightforward and reliable method to model pH may also lead to further improvements in the techniques for measuring the pH. It may seem an unproblematic statement that no matter how the pH is modeled from chemical variables, the final criterion for evaluating putative models will be how well the actual pH measurements are predicted. In contrast, the measurement of pH itself is a highly contentious subject. Central to this problem is just the relationship between ion activities and electric potentials which impact pH measurement as classically defined. Therefore, in the current study, we will mainly examine results which have been obtained by theoretical arguments to avoid the possible problems in measuring pH. However, we will also use a clinical sample of more than 2000 measurements for validation.

Finally, we have placed our methods into a package in R, with which it is possible to estimate equilibrium characteristics for arbitrary fluids with any number of buffers with any number of dissociations, with and without CO2 and albumin. The default option includes, for lack of better options at present, single-ion activity coefficients obtained from the Davies’ equation, but this can be omitted, assuming ideal circumstances. The algorithm proposed to update the estimate of activity coefficients is sensitive to only absolute ionic charge and ionic strength and will therefore require augmentation if other details are taken into account to describe the activity coefficient. Likewise, the algorithm can be modified to include any number of mono- or multivalent bases.

### METHODS

We will first present the charge-balance model with single-ion activity coefficients based on Debye–Hückel/Davies for a very simple system and describe the algorithm for deriving the system characteristics in equilibrium. In the Supporting Information (see: “Derivation of the charge-balance expression”), we present a complete derivation of a more extensive and clinically useful model together with a demonstration of the fact that for any conceivable buffer mixture, the charge-balance expression is monotone in proton concentration. Then, theoretical data from the recent literature will be applied, and the results from the model will be compared to the results from the original publications. Finally, we will analyze a series of clinical data to examine the correspondence with actually measured quantities.

#### Charge-Balance in an Acetate-Buffered System

To explain the model, we present a system consisting of acetate in a solution of NaOH and HCl. For acetate, we have the thermodynamic dissociation coefficient as defined by eq 1, with $f_i$ indicating activity coefficient for monovalent ions, so $aH^+ = f_i[H^+]$, and $[H^+] \approx H^+$ for simplicity. Furthermore, $AC_{tot} = HAc + Ac^-$. It is assumed that the activity of uncharged moieties (e.g., $aHAc$) is equal to the concentration.

$$\frac{aH^+-aAc^-}{aHAc} = K_{Ac} = \frac{f_i^2 \cdot H^+ \cdot Ac^-}{Ac_{tot} - Ac^-}$$

(1)

From this, we have

$$Ac^- = \frac{K_{Ac} \cdot Ac_{tot}}{K_{Ac} + H^+ \cdot f_i^2}$$

(2)

Furthermore, we have from water autodissociation that

$$aH^+ \cdot aOH^- = kw = f_i^2 \cdot H^+ \cdot OH^-$$

(3)
From this, we obtain

$$\text{OH}^- = \frac{kw}{f_2^2} \cdot H^+ \tag{4}$$

Thereby the charge-balance equation is

$$Na^+ - Cl^- + H^+ - \frac{kw}{f_2^2} \cdot H^+ - \frac{K_{Ac} \cdot Ac_{tot}}{K_{Ac} + H^+ \cdot f_2^2} = 0 \tag{5}$$

The ionic strength and activity coefficients from Debye–Hückel/Davies are calculated as

$$I = 0.5 \sum_i z_i^2 \cdot C_i \tag{6}$$

where $Z$ is the charge, and $C$ is the molar concentration of all charged ionic species.

The activity coefficient is, then, obtained from the Davies’ equation

$$\log_{10}(f_z) = -A \cdot z^2 \cdot \left(\frac{\sqrt{I}}{1 + \sqrt{I}} - b \cdot I\right) \tag{7}$$

Here, $A$ is a temperature-dependent constant, and $b$ is a constant.

As described in the Supporting Information ("Derivation of charge-balance expression"), we model albumin using the model of Watson, which assigns 21 fixed and 16 variable charges to each mol albumin. The mobility of these charges in the fluid is difficult to know, and because the molar concentration of albumin is likely to be less than 0.001, we have decided to ignore albumin in the calculation of ionic strength.

The procedure to find pH and distribution of ionized species on the basis of charge balance, then, is as follows:

1. Find $H^+$ as the single root of the charge expression.
2. Knowing $H^+$ and total buffer concentration, the partition among the buffer species is fixed at current estimates of activity coefficients.
3. Based on the identified concentrations of buffer species plus the known concentrations of strong ions, the ionic strength is calculated.
4. From the ionic strength, using Davies’ adaptation of Debye–Hückel, the activity coefficients are found.
5. $H^+$ is found again from the charge expression at the updated activity coefficients.
6. Steps 1–5 are repeated until the difference between the $H^+$ estimates in steps 1 and 5 vanishes.

For more complex solutions including multivalent buffers, for example, carbonic acid, a generalization of Henderson–Hasselbalch as employed implicitly in eq 1 is used. This is described in the Supporting Information (see: “Derivation of the charge-balance expression”).

When extending the charge balance to be dependent on ionic strength, the thermodynamic dissociation constants for the buffers are expressed as based on activities as shown in eq 1 above. From this, corrected concentrations of the buffer species are calculated to update the charge-balance expression. The only unknown in the charge balance equation then is the $H^+$ concentration. It is crucial, as detailed in the Supporting Information (see: “Derivation of the charge-balance expression”), that all considered buffer species can be shown to contribute with increasing charge as $[H^+]$ increases. Therefore, root finding in the charge-balance equation is very efficient. When comparing this root to measured pH values based on the IUPAC convention, the activity coefficient obtained for a single charge is then multiplied by the $H^+$ concentrations.

**Practical Implementation.** We used open-source, R, for specifying the models and fitting and plotting the results. All results are documented in the Supporting Information and on ACS figshare as R markdown files. The functions are given as an extensively commented and freely available package in R, “ABCcharge”. Thereby, the user will be able to analyze any conceivable fluid by specifying total concentrations of any number of individual buffers, each with any number of known thermodynamic dissociation constants. A range of strong ions are included as default but set to zero concentration, if not present. Likewise, $pCO_2$ and albumin are handled, if needed. The derivation is presented as Supporting Information (see: “Derivation of the charge-balance equation”). The functions will deliver pH, ionic strength, distribution of buffer species, and charge balance at equilibrium for the ideal case (assuming all activity coefficients are equal to 1), and also, the same quantities plus activity coefficients at equilibrium for the data corrected for ionic strength. The functions, we sought publications in which the resulting pH was theoretically derived. Thereby, we could in a first step concentrate on the principles of the modeling in the competing formulations without concern for the validity of the pH measurements.

Here, we focused primarily on a recent publication by Schell et al. that identifies the equilibrium condition in mixtures of dihydrogen phosphate and citric acid with and without correction for ionic strength employing Davies’ equation. This analysis is presented in detail. Also, some of the results from Tessman and Ivanov* are presented and analyzed to further expose the consequences of disagreement in assessing the equilibrium conditions. Furthermore, we modeled a set of previously examined clinically obtained pH values on the basis of electrolyte, albumin, phosphate, lactate, and $pCO_2$ values. Finally, analyses of the papers by Glaser et al.* and Baeza-Baeza and García-Alvarez-Coque are presented in brief.

To assess our methods in comparison with those from the literature, the estimated pH values were compared, but also, if possible, we tried to evaluate if charge balance approached zero in equilibrium. Likewise, the recovery of thermodynamic dissociation constants in equilibrium was appraised. Clearly, agreement in these respects is required for the methods to be consistent. This means that at the estimated equilibrium, the distribution of buffer concentrations together with strong ions must result in a charge balance close to zero. The sum of the buffer species (including uncharged items) must be the known starting total concentrations, and, with the calculated activity coefficients, recovery of thermodynamic dissociation constants must be verified. Although, as shown below, our methods guarantee fulfillment of these requirements in principle, in
actual applications, the finite accuracy in numeric calculations may result in minor deviations.

**RESULTS**

**Analysis of the Data from Schell et al.** The material consisting of 30 mixtures of disodium hydrogen phosphate and citric acid is reproduced (see associated content) as "S1.dat". This file also contains the equilibrium pH as identified by Schell et al. for ideal solutions and after accounting for ionic strength using $b = 0.1$ or 0.2 in eq 7. We will restrict analysis to only $b = 0.1$, and as the authors use A in eq 7 with a value of 0.5108. Furthermore, we will use from the results in Schell et al., their calculated species concentrations of citrates at equilibrium (reproduced as "Citrate.dat" in the Supporting Information) and their calculated distribution at equilibrium of phosphate species (reproduced as "Phosphate.dat" in the Supporting Information). Our analysis is presented as "Schell.rmd" on ACS.figshare and the results as "Schell2018.pdf" in the Supporting Information. Also, after installing R package "ABCharge", the entire analysis is reproduced by "example(Schell)".

The charge-balance equation for this system, as derived in the Supporting Information (see: "Derivation of the charge-balance expression"), is given as [concentration markers ([ ] ) are omitted for brevity]

$$\text{Charge} = \text{Na}^+ + \text{H}^+ - kw/(f_1^2 \cdot \text{H}^+) - P_{\text{tot}}$$

$$= \frac{K_a}{f_1^2 \cdot \text{H}^+} + 2 \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + 3 \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1 - C_{\text{tot}}$$

$$= 0$$

(8)

In eq 8, $P_{\text{tot}}$ is the total concentration of all phosphate species, and $C_{\text{tot}}$ is the total concentration of all citrates. $K_a$ are the thermodynamic dissociation constants for phosphoric acid and $K_a$ is like for citric acid.

A crucial step in the algorithm above is the second step: knowing $[\text{H}^+]$ and total buffer concentration, the partition among the buffer species is fixed at current estimates of activity coefficients, and this partition maintains the thermodynamic dissociation constants at prespecified values. This is explained with a pseudocode below because it is essential for demonstrating the strength of the proposed method for finding equilibrium characteristics.

For phosphoric acid:

Given $[\text{H}^+]$, $P_{\text{tot}}$, $K_a$, and $f_1 - f_3$, we find the individual four components (derivation is shown in the Supporting Information "Derivation of the charge-balance expression")

$$\text{H}_3\text{PO}_4^- = \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

(9)

$$\text{H}_2\text{PO}_4^- = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

(10)

$$\text{PO}_4^{3-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

(11)

$$\text{HPO}_4^{2-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

(12)

Therefore, it is evident that given $[\text{H}^+]$, $P_{\text{tot}}$, $K_a$, and $f_1 - f_3$, the concentrations of all species are fixed. Furthermore, by summing all four species it is clear that $P_{\text{tot}}$ is maintained. Finally, we can see that for any value of $[\text{H}^+]$, $P_{\text{tot}}$, $K_a$, and $f_1 - f_3$, and $f_1 - f_3$ by division of eq 10 by eq 9 that $\frac{K_a}{f_1^2 \cdot \text{H}^+} = \frac{H_3\text{PO}_4^-}{\text{H}_2\text{PO}_4^-}$

from which

$$K_a = \frac{f_1^2 \cdot \text{H}^+ \cdot \text{H}_2\text{PO}_4^-}{\text{H}_3\text{PO}_4^-}$$

(13)

Eq 13 is the definition of the thermodynamic dissociation constant for the first dissociation of phosphoric acid, again assuming the activity coefficient for uncharged moieties is 1. Likewise, by division of eq 11 by eq 10, we have

$$\text{HPO}_4^{2-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

$$\text{PO}_4^{3-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

Here, eq 14 is the thermodynamic dissociation constant for the second dissociation of phosphoric acid. Finally, by division of eq 12 by eq 11, we get

$$\text{PO}_4^{3-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

$$\text{HPO}_4^{2-} = \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{P_{\text{tot}}}{1 + \frac{K_a}{f_1^2 \cdot \text{H}^+} + \frac{K_a K_a}{f_1 \cdot f_2 \cdot (\text{H}^+)^2} + \frac{K_a K_a K_a}{(\text{H}^+)^4 f_1^2} f_1}$$

which is the definition of the thermodynamic dissociation constant for the third dissociation of phosphoric acid.

Therefore, we can see that there is a guarantee that the algorithm delivers estimates of concentrations of the buffer species that algebraically align with the requirements of preserved dissociation constants. Again, in actual applications, due to imperfections in computer representation of floating-point numbers, minor deviations are possible.

First, the results from Schell et al. assuming ideal conditions that is with all activity coefficients fixed at 1 were compared to the results from the proposed charge-balance algorithm. The agreement between the calculated results by our charge-balance method and the results from Schell et al. is good with a correlation coefficient of 0.99996. The difference between the pH reported by Schell et al. and our calculated pH values has a median of 0.002 with a range of −0.027 to 0.036 (Point 1 in supplementary "Schell2018.pdf"). Equally, for the results after imposing correction for ionic strength, the correlation coefficient is similar at 0.9996 and the differences in pH values by our method and the reported method has a median of 0.004 and a range of −0.031 to 0.044; (point 2 in the Supporting Information "Schell2018.pdf").
Differences between results obtained from our method and those employed in Schell et al.\textsuperscript{6} do exist, however, if we consider the reported distribution at equilibrium of citric acid and phosphoric acid species using the results with correction for ionic strength. The distribution of the buffer species allows reconstruction of thermodynamic dissociation constants from the results of Schell et al.\textsuperscript{6} because the activity coefficients can be calculated from the reported ionic strength using eq 7. As described, the dissociation constants for triprotic acids are given in eq 13/eq 15, so with the reported distribution of buffer species and the reported ionic strength, based on the results reported by Schell et al.\textsuperscript{6} we have the following results (see: point 3 in the Supporting Information “Schell2018.pdf”). (A number of the concentrations reported by Schell et al.\textsuperscript{6} are given as zero, and these are obviously not used as basis for estimation).

For citric acid, the results are reported in Figure 1 which shows some variability from the known thermodynamic constant, and in Table 1 for the three known pK_a values for citric acid.

Similarly, Figure 2 shows the somewhat greater deviation for phosphoric acid. The last pK_a build on only one measurement. The results are also shown in Table 2.

In contrast, with the results from our estimation, the thermodynamic dissociation constants are closely conserved. The calculated pK_a values are shown in Table 3.

Apparently, these problems are not the consequence of the fact that concentrations of the buffer species are rounded to 0.1 mM in the results of Schell et al.\textsuperscript{6} because the maximal charge imbalance (see below) is more than 10 times higher than the cutoff value. Furthermore, plotting the difference between the known thermodynamic dissociation constant and the one estimated on the basis of the given data yields a clear regression with the ionic strength. This is demonstrated in the Supporting Information (“Schell2018.pdf”) and with example (Schell) from R package ABCharge.

The net charge at equilibrium for the results reported by Schell et al.\textsuperscript{6} can be calculated from data in the Supporting Information (reproduced here in Associated content as S1.dat, S2a.dat and S2b.dat) and median charge is 0.1 mEq/L with a range from −0.9 to 1.2 mEq/L (see: point 4 in “Schell2018.pdf”). In contrast, with our method, median net charge is $1 \times 10^{-7}$ mEq/L with a range from 0 to $3.5 \times 10^{-5}$ mEq/L (see point 4a in the Supporting Information “Schell2018.pdf”).

Analysis of Results from Tessman and Ivanov.\textsuperscript{5} We restrict attention to the results in Table 1 of Tessman and Ivanov\textsuperscript{5} of two mixtures of boric acid, phosphoric acid, acetic acid, and NaOH. Concentrations were: 0.0267, 0.0267, 0.0267, and 0.0667 for the first sample, and 0.02, 0.02, 0.02, and 0.1 for the second sample, all in M.

Several details from the modeling by Tessman and Ivanov\textsuperscript{5} were not available, for instance, the exact form of the Davies’ equation employed or the assigned value of the water autodissociation constant. The entire analysis is available from package ABCharge using “example(Tessman)”. As reported also in “Tessman.rmd” on ACS figshare and as “Tessman2002.pdf” in the Supporting Information, for the first example, the reported pH was 6.812 at an ionic strength of 0.0798, whereas our charge balance application gave pH of 6.771 and ionic strength of 0.0799. However, it is observed that our first ionic strength calculated before assignment of activity coefficients is 0.079806. This is available from step 3 in the first iteration of our algorithm.

Table 1. Calculated pK_a Values for Citric Acid Based on Data from Schell et al.\textsuperscript{6}

| min  | median | max  | input |
|------|--------|------|-------|
| 3.025 | 3.131  | 3.172| 3.13  |
| 4.275 | 4.711  | 5.572| 4.76  |
| 4.573 | 5.882  | 7.346| 6.40  |

Table 2. Calculated pK_a Values for Phosphoric Acid Based on Data from Schell et al.\textsuperscript{6}

| min  | median | max  | input |
|------|--------|------|-------|
| 2.02 | 2.158  | 2.409| 2.16  |
| 6.313 | 6.913  | 7.613| 7.21  |
| 8.848 | 8.848  | 8.848| 12.32 |

Table 3. Calculated pK_a Values for Phosphoric Acid and Citric Acid Based on Our Charge Balance Algorithm

| median pK_a | lowest pK_a | highest pK_a | input pK_a |
|-------------|-------------|--------------|------------|
| 2.159999563 | 2.159995387 | 2.160001260 | 2.16 (phosphoric acid) |
| 7.210000000 | 7.209998425 | 7.210007498 | 7.21 (citric acid) |
| 12.32000106 | 12.32000000 | 12.32001500 | 12.32 (citric acid) |
| 3.129999653 | 3.129995387 | 3.130001260 | 3.13 (citric acid) |
| 4.760000000 | 4.759998425 | 4.760007498 | 4.76 |
| 6.400001061 | 6.400000000 | 6.400014997 | 6.40 |

Figure 1. Citrate pK_a values based on reported species distribution in Schell et al.\textsuperscript{6}

Figure 2. Phosphate pK_a values based on reported species distribution in Schell et al.\textsuperscript{6}
The next example demonstrates a wider difference as the reported pH is 12.005, whereas we find 11.5244 at the ionic strength of 0.1428 compared to the reported ionic strength of 0.1367. Again, it is observed that our initial ionic strength before the application of Davies’ equation is very similar at 0.13669, and likewise it is observed that the first pH in the iterations, that is before going beyond all activity coefficients being equal to 1, is 12.00455, that is quite similar to the reported value.

Although for the reasons mentioned above, we are unable to compare these methods directly, we can examine the characteristics of the results in Tessman and Ivanov\(^5\) in their equilibrium, that is pH 12.005 and ionic strength 0.1367. This requires finding the activity coefficients via the Davies’ equation,\(^8\) and from these and the known total concentrations of buffer species, the known thermodynamic dissociation constants, and the found pH (12.005), we can find the concentration of individual buffer species and hence, the charge balance. As shown in the Supporting Information (“Tessman2002.pdf”) and demonstrated in code (“Tessman.rmd” on ACS figshare), this charge balance is rounded to ±22 mM. This is found using the form of Davies’ equation in Schell et al.\(^6\) with \(b = 0.1\) but using \(b = 0.2\) and the \(A\) of 0.509 in eq 7 as used by Baeza-Baeza and Garcia-Alvarez-Coque’ does not change that significantly (results not shown). This will inevitably generate a very huge potential. With the uncertainty resulting from the fact that the methods in Tessman and Ivanov\(^5\) are not wholly specified, this must still leave some doubt as to the validity of the estimate in the paper.\(^5\) In contrast, we should be able to closely inspect the results obtained by our charge balance approach for validity.

Hence, if the distribution of buffer species identified at equilibrium is examined, a proper identification of equilibrium is verified if: (a) the total concentrations of buffer species are maintained, (b) the thermodynamic dissociation constants after taking account of the found activity coefficients are all conserved, and (c) the charge balance at equilibrium approaches zero. These are, we believe, the necessary and sufficient conditions for identifying equilibrium. As shown in the Supporting Information (“Tessman2002.pdf”), these three points are all confirmed, with buffer concentrations and dissociations closely recovered, and with a charge balance of 68 × 10\(^{-6}\) mM, which is approximately half a million times better compared to the charge imbalance inferred for the results reported in the paper.\(^5\)

Furthermore, as the system described by Tessman and Ivanov\(^5\) is quite complicated with eight different dissociation constants (including water autodissociation), it would be of interest to inspect charge-balance as a function of pH to get an impression that the expression of charge-balance could contain sufficient information for close identification of pH. The curves are generated by finding the charge balance as a function of pH and the found activity coefficients, first over the entire pH range (Figure 3) and next as a close-up near the identified equilibrium (Figure 4).

**Analysis of Clinical Data from Critically Ill Patients.** Modeling pH was accomplished based on a set of 2437 values found in Ring\(^2\) by way of the thermodynamic dissociations corrected for ion strength and taking the measured pH to be $-\log(aH^+)$.\(^{24}\) This was a sample from critically ill but very heterogenous patients, and the modeling was based on all of the nine measured moieties, corresponding to 13 different charges (see “Derivation of the charge-balance model” in the

**Supporting Information**). Problems with measurements of every item including pH were expected, and the presence of unmeasured anions and cations were considered likely.\(^2\) The ionic strength was, as typical for clinical samples, high around 0.15, and correspondingly, the single-charge activity coefficients about 0.733, that is far from 1.

Hence, it was expected that the pH corrected for ionic strength would be different from the estimate obtained assuming ideal conditions. As shown in Figure 5, assuming ideal conditions caused the modeled pH to overestimate the measured pH (green curve). In contrast, taking the H\(^+\) values from the estimation including activity coefficients directly as

**Figure 3.** Charge balance plotted over pH grid based on Tessman and Ivanov.\(^5\)

**Figure 4.** Close up of charge vs pH from Tessman data.

**Figure 5.** Modeled minus observed pH for clinical data.
the basis for pH resulted in the modeled pH underestimating the measured pH (blue curve). However, correcting this last H⁺ for the found activity coefficient for single charges resulted in the difference between modeled and measured pH to be approximately centered on zero.

Using this corrected pH to regress the modeled on measured pH yielded Figure 6. There was a highly significant correlation of 0.796 (P < 2.2 × 10⁻¹⁶). Compared to the in vitro experimental situations described previously, the agreement between measured and modeled pH was less convincing. On the other hand, given the circumstances of a clinical study as described, and given the uncertain status of the employed Davies’ correction, we believe the charge-balance model to be potentially useful, also in the clinical context. Again, the entire analysis is presented with “example(Pittsburgh)”.

Results from Glaser et al. Glaser and coworkers first reported finding pH in mixtures of malate, malic acids alone, and combinations of these using a dynamic approach resulting in a polynomial model, for which they show that exactly one root corresponds to the equilibrium situation. As shown in our analysis (see “Glaser2014.rmd” on ACS figshare for the entire analysis, and the results as “Glaser2014.pdf” in the Supporting Information), we can confirm these pH values with a correlation greater than 0.99999 in one single run, that is taking the three cases together, because all we need for estimation is total buffer concentration, the two pKₐ values for diprotic malic acid, and strong ion concentration (assuming complete dissociation of the malate salt). As shown (see “Glaser2014.pdf” in the Supporting Information), given the quite high ionic strength in these experiments, we can also assess the importance of taking ionic strength into account. These analyses also are shown with “example(malate)”. Next, Glaser et al. analyzed the dissociation of bromic acid (HBrO₃) in mixtures of sulfuric acid and bromate salts over a grid of assumed pKₐ values for bromic acid. Assuming the ideal situation (all activity coefficients 1), we can again, with correlation 0.9999, confirm the resulting pH values, and we can reproduce the distribution of bromate and bromic acid species. Taking ionic strength into account, we can again show the shifts in results as shown by the distribution of species concentrations over the grid of pKₐ values. Finally (see, “Glaser2014.pdf” in the Supporting Information), using the reported species concentrations (Table S4 in Glaser et al., reproduced here as “brom.dat” in the Supporting Information), we can calculate a charge balance for the uncorrected case with a maximal value of 0.3 mM, whereas with our methods, the maximal charge balance is 4.8 × 10⁻¹⁶ M. These analyses are also reproduced with example(brom).

Results from Baeza-Baeza and García-Álvarez-Coque. Baeza-Baeza and García-Álvarez-Coque developed a method in Excel to take ionic strength into account using a composite criterion for optimization, consisting of the sum of the squared deviations of total concentrations of buffers, charge balance, and change in ionic strength during iterations. We only look at their first example, where potassium hydrogen phthalate is mixed with hydrochloric acid. Our results are reproduced in “Baeza-Baeza2012.rmd” on ACS figshare and shown in “Baeza-Baeza2012.pdf” in the Supporting Information. We get a corrected pH of 3.1003, which is in good agreement with the reported 3.100. However, their charge balance (calculated from column F in Figure 1) is −2.61 × 10⁻⁶ M, whereas we find a balance of 0. We recover the total phthalate concentration closely and obtain 2.9500001 and 5.4100025 for the 2pKₐ values, whereas from the results reported by Baeza-Baeza and García-Álvarez-Coque, 2.9491 and 5.4096 can be recovered. Again, example(Baeza) shows the code and results.

## DISCUSSION

We have demonstrated that the charge-balance model effectively estimates pH for specified fluids, including clinical samples. Most of our results demonstrate excellent concordance between the results obtained with the charge-balance method as implemented and the original methods described in the literature. However, there are a few deviations which require consideration. First, the second example from Tessman and Ivanov yields a distinctly different pH value. We cannot be absolutely sure why this difference occurs, but the reported equilibrium value that is identified with our charge-balance model evidently has better characteristics in terms of charge balance, which we know must be close to zero. Apparently, the requirement of charge balance at equilibrium is better enforced by the explicit formulation in the charge-balance expression. This is also manifest in examining the results from Schell et al. and Baeza-Baeza and García-Álvarez-Coque, as a second deviation. The algorithm is attractive because the requirement for conserved total buffer concentrations, minimization of charge balance, and the stability of thermodynamic dissociation constants are directly enforced in the formulation of the charge balance equation. Hence, we do not need to optimize separately for these items as, for example, Baeza-Baeza and García-Álvarez-Coque have. As shown in the Supporting Information (see: “Derivation of the charge-balance expression”), the step to find the equilibrium [H⁺] is effective because the charge balance is monotonic in [H⁺] for all of the cases considered up to trivalent acids and bases and their mixtures. We are working to prove that this has to be so in general and so far, have managed to prove the monotonicity for any multivalent buffer.

It may appear surprising that it is possible to confidently identify the equilibrium pH from the calculated charge. As demonstrated for the single example reported by Tessman and Ivanov in Figures 3 and 4, the identification of the equilibrium pH from the charge balance is apparently quite feasible, at least in these examples.

A sensible objection to the validity of the approach could be that strong ions and buffer species are reported typically with error margins in a millimolar range. Hence, it might appear...
unreasonable to expect the charge balance expression to yield distinctive information on the proton concentration at a magnitude several orders lower. However, as it appears from the charge-balance expression, for example in eq 8, protons appear mainly in the denominator and simulations show that 10% shift in proton concentration has a similar effect on the charge as 10% shift in strong ions. However, strong ions obviously have a major influence on the charge balance. Amazingly, the fact that there could be an impact of the strong ions on the pH has been controversial in the literature. In contrast, from a charge-balance perspective, charges in a fluid can be divided between those that are independent of pH (strong ions) and those that are dependent on pH. Because the balance must still be zero, if we change the net charge on those moieties that are charged independently of pH, we only have the possibility to balance by those that change their charge dependent on pH. And this cannot happen unless pH changes.

In comparison with the original reports, our methods may be better in defining the equilibrium conditions. As mentioned, a reasonable criterion for consistent identification of equilibrium could be that charge balance is close to zero, total buffer concentrations conserved at input values, and thermodynamic dissociation constants maintained. As shown, this is true theoretically for the charge balance model and also approximately in praxis. In contrast, the results from Schell et al. and Glaser et al. may have issues in these respects. We cannot be sure about what causes these minor problems in the reported studies. In the case of Baeza-Baeza and Garcia-Álvarez-Coque, it is possible that the combined criterion, on which the optimization occurs, results in opaque trade-offs among the three items (square difference in total buffer concentrations over sum of calculated species, squared differences in charge balance, and squared last difference between results for ionic strength). For the studies by Schell et al. and Glaser et al., we have no access to the complete code used, and therefore are unable to comment further. It is crucial to realize that, for instance, with regard to the results from Schell et al., the recovery of the thermodynamic dissociation constants shown in Figures 1 and 2 was carried out entirely on their own reported results. Hence, their ionic strength (from "S1.dat") gives the activity coefficients using their version of the Davies’ equation, and the equilibrium concentrations of buffer species (their Table S2a,b, given here as “Citrate.dat” and “Phosphate.dat”) together with the definitions of the thermodynamic dissociation constants (eq 13/eq 15).

Finally, the validation using clinical samples, extending the model to cover the CO2 buffer system and albumin, may indicate that the model may be useful in clinical research and perhaps even in clinical practice. The versatility of the charge balance model must be stressed. For instance, patients may have a significantly lower pH than that calculated from measured standard quantities and instead of just accepting a diagnosis of anion-gap acidosis, an anion with specific concentration and Kc could be added to the charge balance expression, such as AC = \frac{AC_{measured}Kc}{Kc + H+^f}, which could be verified, for instance, with NMR spectrometry. We have used this to confirm the diagnosis of pyroglutamate intoxication.

However, this implementation is certainly not free of conundrums or loose ends. The central problem is how to account for nonideal circumstances. It is evident from the derivations that the specification of thermodynamic dissociation constants builds heavily on single-ion activity coefficients. In the introduction, we have alluded to the ongoing debate about their status and to the fact that the Davies’ equation specifies a mean and not single-ion activity coefficient. However, the papers from which we took the material for testing our modeling use just this specification of single-ion activity coefficients and other have done likewise. First and foremost, however, we saw no other opportunity if we wanted to use the mentioned material to test our modeling approach. Also, even if the specification of the nonideal situation as employed here is indeed wanting from a theoretical point of view, it may nonetheless have some value as indicated by the assessment of a large clinical material.

Furthermore, we may regard the current specification of single-ion activity coefficient as a placeholder for a true value, if this true value is mainly determined by ionic strength and charge because then, our updating algorithm will also be appropriate for the true value.

We hope eventually that our modeling can be used to test better specifications of nonideality so that, for instance, activity coefficients for positive and negative ions with the same absolute charge are not identical as in the current implementation of the Davies’ equation. Also, eventually, we might add a correction for uncharged species by way of the Scehnev equation, but this does not deviate far from 1, and therefore has little effect on the results and so was omitted.

Finally, in contrast to the dynamic systems used by Glaser et al. and Schell et al., our methods are unable to clarify the situation outside equilibrium.

### CONCLUSIONS

It has been shown that the charge balance approach allows a simple direct modeling of pH in situations where no correction for ionic strength is performed. If activity coefficients are applied by way of Debye–Hückel/Davies to the buffer species, an excellent reproduction of the equilibrium pH values obtained with previously reported tools are obtained. Crucially, the mathematical elegance of the charge-balance approach results in improved characteristics of the results in terms of conservation of thermodynamic constants and charge difference. Finally, the implementation is provided as an R package and all methods are totally transparent and can be scrutinized, modified, and extended as desired.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00270.

Comprehensive explanation for the derivation of the model and proofs of the characteristics and results from the analyses of Schell et al. 2018, Tessman and Ivanov 2002, Pittsburgh ICU data, Glaser et al, and Baeza-Baeza et al. (PDF)

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