**Intensive nature of fluctuations: Reconceptualizing Kirkwood-Buff theory via elementary algebra**

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**Abstract**

Quantifying the role of solvation in soft matter and complex solutions has been made challenging by the fluctuational nature of solvation, as well as by the tedious calculus associated with it in converting thermodynamic variables. A new algebraic approach to fluctuation proposed here eliminates the tedious calculus, demonstrated by a simple rederivation of the Kirkwood-Buff theory of solutions, as well as by the calculation of higher-order fluctuations in inhomogeneous solutions. This new approach is based on a new physical insight into fluctuation in solution; concentration fluctuation, since it is independent of system size, is an invariant under transformation between ensembles, with different expressions depending on the choice of extensive variables. This is because a full set of intensive thermodynamic quantities can be represented in multiple yet equivalent ways.

**1. Introduction**

Solvation is one of the driving forces behind self-assemblies of soft matter as well as their conformational and phase behaviours [1,2]. However, quantifying how much solvation contributes to these processes has often been difficult [3]. In fact, the early theories of polymers, colloids and surfaces only implicitly incorporated solvents, either as a parameter, charge, or dielectric constant [4,5]. Yet a slight change of solvent, such as the addition of salts or cosolvents, influences conformations and assemblies in a significant manner [6–8]. Quantifying solvation changes in mixtures requires a rigorous treatment of solvation, which is statistical in nature, requiring particle number fluctuations and particle number correlations [9,10].

Indeed, statistical thermodynamics approach to fluctuation, pioneered by von Smoluchowski [11] and Einstein [12], found its early application to critical opalescence in solution [13,14]. Fluctuation occupies an important place in statistical thermodynamics, whose foundation has been gone through refinement [15–22]. A form of fluctuation theory, particularly useful for the study of solution mixtures, was pioneered by Kirkwood and Buff in 1951 [23], yet applying their theory to quantify interactions in solutions started decades later [24,25], before it became an essential tool for the understanding of solution structure [26–30]. More recently, classical concepts in biomolecular solvation (such as preferential solvation [31,32], pressure [33] and volumetric [34] analyses), based originally on a purely phenomenological basis (such as stoichiometric binding or exchange models [35–37]), have been reformulated rigorously via fluctuation [3,38]. This has led to a universal clarification of preferential solvation phenomena for a number of processes, including biomolecular stability [3,38,39] and hydrotropic solubilization [9,40–43], applicable to small molecules and macromolecular assemblies alike [44,45].

Such an explanatory and clarifying power of the fluctuation solution theory, i.e., KB theory [23] and its subsequent development [3,9,24–30] comes from its foundation, namely its ability to provide (a) a measure of intermolecular interactions in terms of particle number correlations [3,9,24–30], (b) a set of relationships to calculate (a) directly from experimentally measurable quantities, such as solubility [9,40–43], heat and temperature of protein denaturation [3,38,39], binding constants [3], density and osmotic data [24–30], and (c) a link between a particle number correlation and a molecular distribution function [23,24], paving a way towards a molecular-based interpretation of thermodynamic phenomena.

The long, gradual development of the fluctuation solution theory, since its inception by Kirkwood and Buff [23], is due to a significant gap between

1. experimental ensembles, such as NPT (volume and density measurements) or partially open (osmotic and solubility measurements), and
2. the grand canonical ensemble, suitable for quantifying particle number fluctuations.

Indeed, conversion from (a) to (b) requires cumbersome series of conversions of thermodynamic variables, which had long prevented the initial proposal of Kirkwood and Buff [23] from being inverted to be applicable to experiments [24,25]. The link between (a) and (b) has been made clearer and more accessible recently via a systematic approach to inversion [25,46] and inhomogeneous solution theory [42,47,48], as well as via a unified theoretical framework for solvation and adsorption [42,48–50]. Yet, the incessant conversion of thermodynamic variables is still at the core even of the latest development [48,51,52].

Here we propose an alternative approach ‒ a simpler link between solvation thermodynamics and fluctuation. We will replace the incessant and tedious changes of variables in thermodynamic partial derivatives [23,24] by elementary algebra from statistics. Such a simplification comes from a novel approach to fluctuation. It is based on the two suppositions: (a) relative fluctuation can be calculated from subsystems and (b) a full set of intensive thermodynamic quantities can be represented in multiple, equivalent ways. The use of subsystems to clarify the physical basis of the Kirkwood-Buff theory goes back to Hall [53]. However, this approach becomes cumbersome when applied to a simple and homogeneous binary mixture, even though it can be applied elegantly to a ternary mixture around a solute [53]. Such a caveat can also be overcome in our new approach to fluctuation. In fact, the two suppositions ((a) and (b)) in combination will lead to a powerful insight: a relative fluctuation of extensive quantities, since it is independent of system size, can be converted under transformations between ensembles, because of the ensemble-invariance of concentration and its fluctuation. We will demonstrate that this insight can circumvent tedious thermodynamic variable conversions that have hampered the fluctuation theory.

**2. Fluctuation theory for pure liquids**

As a first step, the fluctuation theory for a pure solvent will be reformulated in a rigorous manner, starting from the textbook relationship [15,54] between solvent number fluctuation and the chemical potential derivative of solvent number

(1)

where , , and express the Boltzmann constant, volume, and temperature, respectively. Note that the ensemble average was taken in the grand canonical ensemble. For clarity, throughout this paper, we denote the fixed parameters in . Obviously, the ensemble average depend on which parameters are fixed. Classical textbooks [15,54] present a rather acrobatic approach to link Eq. (1) to isothermal compressibility ,

(2)

where is the pressure. Our goal is to establish a general principle and rigorous methodology, applicable to any thermodynamic quantities in multiple-component mixtures. Linking to *methodically* serves as a first step.

Since compressibility is an intensive property, the rightmost side of Eq. (2) is intensive, depending only on and . Hence the right-hand side of Eq. (2) no longer depends on *N*, meaning that the relative fluctuation of , , is independent of system size. Therefore, a *macroscopic subsystem* [15,20] with a constant particle number can be used for the calculation of volume fluctuation, namely

(3)

where is the volume of the subsystem. Note that the lower-case quantities (such as and ) are used to signify quantities pertaining to a subsystem. The intensive parameters, and *,* remain the same for the subsystem.

Using macroscopic subsystems is the key to ensemble conversion. The Gibbs phase rule states that the number of intensive parameters is 2 for a single component system in a single phase [15,55]. Hence, converting to is facilitated by noting that the intensive parameters in these ensembles, and , are merely the two different representations of the same thermodynamic state, interlinked via or . Hence, we can focus exclusively on the extensive quantities. This realization leads to a simplification in carrying out the ensemble conversion. Namely, our goal is now simplified as: how to convert (the change of under constant ) to (the change of under constant ). Such a conversion requires the use of density . All we need to realize is that the same density change can be expressed in the isochoric and isobaric ensembles. The change of density under constant is due to volume change,. Taking up to the first order of the Maclaurin expansion, the density change can be expressed as

(4)

The change of density can also be expressed under constant . In this case, particle number change, , is responsible for the change of density. This can be expressed as

(5)

Here we postulate that the two different representations via and ensembles, Eqs. (4) and (5), are equivalent, which yields

(6)

where, for clarity, the intensive parameters were written explicitly again. Substituting Eq. (6) into Eq. (3), we obtain

(7)

which is the well-known relationship between number fluctuation and compressibility [15,54]. Note that the Landau symbol signifies “the same order of magnitude as ” and that means “infinitesimal in comparison to ”.

The equivalence of density changes expressed in two different ensembles can be started equivalently as the density and its fluctuation being the invariant under ensemble transformation, as has been shown in Appendix A. This can be generalized straightforwardly to multiple component solutions.

Thus, macroscopic subsystems facilitate ensemble conversion. Intensive parameters are merely different representations of the same thermodynamic state. The change of concentration, arising from volume expansion or particle influx, should be equivalent. These two principles underlie a facile conversion between number and volume fluctuations. So far, our approach was equivalent to the well-known derivations [15,54]. However, what we have identified here (the Gibbs phase rule, the density and its fluctuations as invariants under ensemble transformation, and the order of magnitude analysis) will be demonstrated to be the key tools for the algebraic reconceptualization of the fluctuation solution theory.

**3. Fluctuations in binary and multiple-component mixtures**

**3.1. Isothermal compressibility**

Here we generalize the approach in Section 2 to binary and multiple-component solutions. As a first step, consider and molecules that form a single phase. The composition defined by is a useful parameter. As before, the intensive parameters can be expressed in multiple different yet equivalent manner, which enables us to focus our attention on the conversion between extensive quantities.

The isothermal compressibility of a binary mixture is linked to volume fluctuation as [23,24]

(8)

where the right-most expression with conforms to the number of intensive parameters (i.e., 3) according to the Gibbs phase rule. (, instead of , may be chosen as the extensive parameter.) Because Eq. (8) is independent of system size, the relative volume fluctuation is the same in a macroscopic subsystem , hence

(9)

Thus, the consideration based on the Gibbs phase rule has led us to a subsystem, which is pertinent to the experimentally observable isothermal compressibility parameter. Such a subsystem, under constant , is realizable by the variation of system volume while keeping constant. Note that can be a fluctuating quantity for certain subsystems such as upon which the KB theory is founded.

Our goal is to link Eq. (9) to the subsystem, because it is employed by the KB theory. Noting that the intensive parameters, and , are merely the two different representations of the same thermodynamic state, we can focus on how to convert (the change of under constant ) to (the change of and under constant ). Note that is automatically constant in because and are constants. The change of density can be induced by volume expansion under constant

(10)

by the influx of particles under constant

(11)

Since the two expressions for the density change is the same, Eqs. (10) and (11) in combination yield

(12)

which is the generalization of Eq. (6). Through the Gibbs-Duhem equation, with the partial molar volume, ,

(13)

the following relationship follows from Eq. (12) for and :

(14)

Combining Eq. (14) with Eq. (12) for , Eqs. (8) and (9) can be rewritten as

(15)

Choosing instead for Eq. (12), we also obtain

(16)

Using the Kirkwood-Buff integral (KBI), defined as [42]

(17)

(where is Kronecker’s delta), Eqs. (15) and (16) can be expressed as

(18)

(19)

which are indeed the well-known KB relationship on isothermal compressibility [53,56]. It is easy to generalize Eq. (17) into -component solutions, as a set of equations () as

(20)

Thus, the KB relationships on compressibility were derived through simple algebra without any thermodynamic variable conversion. Is this merely a convenient calculation technique based around several recipes? On the contrary, as we have shown above, that the relative fluctuation , being intensive, can be converted from one ensemble from another, as long as the different sets of intensive variables, or , represent the same thermodynamic state. As shown in Appendix A, the ensemble-independence of the concentration changes (Eqs. (10) and (11)) can be stated equivalently as the ensemble invariance of molar concentration and its fluctuation.

**3.2. Composition fluctuation**

Here we aim to express the following relationship on particle number fluctuation,

(21)

in terms of KBIs. Eq. (21) has occupied an important position in small angle scattering through its relationship to the fluctuation of the composition [51,52,57–59]. We will demonstrate that our subsystem-based approach can provide a facile route, without any need for thermodynamic variable conversions. We first note that the right-hand side of Eq. (21) is in fact independent of the system size, , and the relative fluctuation remains the same in a macroscopic subsystem, i.e.,

(22)

Rewriting Eq. (21) in terms of KBIs requires a conversion of fluctuation from to . As before, the two different sets of intensive parameters, and , are the two different representation of the same thermodynamic condition. Here, the invariance of mole-ratio concentration () and its fluctuation under ensemble transformation enables a facile conversion of relative fluctuation. Hence we can focus on converting (the change of under constant ) to and (the changes of and under constant , respectively) , which can be executed via .

Note that the change of solution composition, , can be expressed either by the increment of , while keeping constant, as

(23)

or by the increments both of and under constant volume, as

(24)

Since Eq. (23) and (24) are merely the same phenomenon viewed from two different subsystems,

(25)

Combining Eqs. (21), (22) and (25), we obtain

(26)

Using the definition of KBI (Eq. (17)), Eq. (26) can be rewritten into a well-known form

(27)

where

(28)

Converting into and , we obtain other familiar expressions [23,24,53]:

(29a)

(29b)

It is straightforward to generalize our approach to a -component solution. The following relationship, derivable straightforwardly using the partially open ensemble, is our starting point:

(30)

where is a set of chemical potentials () except for specifically excluded components. Repeating our previous discussion (Eqs. (23)-(25)), Eq. (30) holds true for macroscopic subsystems (the rightmost term). We can generalize Eq. (25) for the equivalence of composition changes, as

(31)

Eq. (31) leads straightforwardly to

(32)

which is the key tool for the conversion between the partially open ensemble and the grand canonical, through which Eq. (30) can be rewritten as

(33)

which is a generalization of Eq. (26) to a component solution.

Thus, we have demonstrated the power of our novel approach to fluctuation through a facile derivation of the KB theory without any need for tedious thermodynamic variable conversions.

**3.3. Extension to inhomogeneous solutions**

Our new approach to fluctuation can be extended readily and straightforwardly to inhomogeneous solutions. Despite their importance in the elucidation of dramatic, non-linear (cooperative) solubility enhancement by hydrotropes [42,51,60], calculating fluctuation in inhomogeneous solutions is often tedious and lengthy, despite a significant simplification brought about by the inhomogeneous solution theory, which enables to consider a three-body correlation (such as solute-water-water) effectively as a two-body correlation (water-water) in the presence of a solute [42,48]. The present approach drastically simplifies derivation as will be demonstrated below.

Let us consider a mixture of water (component 1) and cosolvent (component 2), in the presence and absence of a solute (component ) molecule. The cosolvent can be a hydrotrope, because our formalism is applicable to any cosolvent in general. Our starting point is how the solvation free energy of a solute, , depends on the chemical potential of water, . This can be expressed in terms of a pair of partially-open partition functions, (inhomogeneous, in the presence of a solute) and (homogeneous for the bulk solution), as [60]

(34)

where the same is used for both ensembles. The presence of three intensive variables in Eq. (34) is consistent with the Gibbs phase rule [1,2]. Its first order derivative with respect to yields

(35)

where in the subscript signifies the ensemble average taken in an inhomogeneous ensemble. The second-order derivative is particularly important in the understanding of cooperative solubilization, which can be calculated as

(36)

Since the left-hand side of Eq. (36) is intensive for a solute of microscopic size, the dependence on can be dropped. (If *u* becomes a surface, it is impossible to carry out a -derivative under constant *T* and *P*; according to the Gibbs phase rule, there are only two intensive variables allowed for a surface. For a more detailed discussion on the difference between a solute and a surface, refer to our previous papers [48,49].) Note, on the right-hand side, that the number of species 2, , is the same for both ensembles. The left-hand side of Eq. (36), being intensive, is dependent on solution composition but not on system size. Eq. (36) can therefore be written using macroscopic subsystems, as

(37)

where, again, the homogeneous and inhomogeneous subsystems contain the same number of species 2, . We emphasize here that the subsystems are large enough to cover the entire interaction range of the microscopic solute considered here, as has been pointed out in the inhomogeneous solution theory route to fluctuation [3,49,53].

Our goal is to convert the fluctuations in the right-hand side from to . The difference between the and ensembles are:

* For a constant- ensemble, is the same between the inhomogeneous and homogeneous systems. However, the volume is different between the two, due to the solute-cosolvent interaction.
* For a constant- ensemble for KB theory, is the same between inhomogeneous and homogenous systems [3,53]. However, is different between the two, due to the solute-cosolvent interaction.

Because and transform differently in the homogeneous and inhomogeneous systems, and must be converted to the constant ensembles separately. What is crucial here is that and on their own cannot be expressed in terms of the subsystems, because they are extensive quantities. To circumvent this problem, Eq. (37) should be rewritten in terms of the relative fluctuations as

(38)

such that both and are indeed independent of the system size, pertaining to the subsystems. Consequently, they can be converted from constant to constant ensemble, based on the invariance of molar concentration and its fluctuation under ensemble transformation. Following the same procedure as in Section 3.2, the change in bulk solution composition, , can be expressed in different yet equivalent ways by the and ensembles, as

(39)

Therefore,

(40)

Consequently,

(41)

Likewise,

(42)

holds true by repeating the same argument for the homogeneous (bulk) subsystem. Using Eqs. (41) and (42), the relative fluctuations in Eq. (38) can be converted into the grand canonical ensembles as

(43)

(44)

To recapitulate, our goal will be fulfilled by substituting Eqs. (43) and (44) into the combination of Eqs. (36)-(38), namely

(45)

Before carrying out this substitution, let us note that the terms in is . Consequently, because , whether or is to be used for in Eq. (45) leads to the negligible difference, up to (see Eq. (A4) in Appendix A). Hence, we adopt for convenience. Taking up to the zeroth order of yields

(46)

which has been obtained through considerable calculation in our previous papers [42,51]. Appendix A presents a further justification that the remainder of the terms are indeed .

Thus, not only can our new algebraic approach to fluctuation be applied straightforwardly to inhomogeneous solutions but also lead to significant simplification.

**4. Concluding remarks**

Solvation and solvent-mediated interactions between particles are one of the universal driving forces in soft-matter phenomena. Yet, elucidating solvation based fully on its fluctuational nature has been hampered by the incessant and tedious conversion of thermodynamic variables, arising from the need to link the experimental ensemble (such as the isothermal isobaric ensemble where the activity and density measurements take place) and the grand-canonical ensemble (in which the KBIs are defined) [23,24].

A novel approach to fluctuation was proposed in this paper, a simple algebraic alternative to tedious thermodynamic variable conversions. The ease comes from a new understanding of solution fluctuation that a concentration (molar or mole ratio) and its fluctuation are invariants over ensemble transformation. Consequently, they can be expressed differently, depending on what the extensive variable is in given ensemble. This understanding was derived from the suppositions that (a) relative fluctuation can be calculated from subsystems and (b) a full set of intensive thermodynamic quantities can be represented in multiple, equivalent ways. The link between different ensembles has been simplified via (a) and (b), applicable even to inhomogeneous solutions, liberating the fluctuation theory from the endless conversion of thermodynamic variables. This paper has focused on deriving previously published results as a form of validation and a demonstration of its simplicity. It can readily be expected that the technique can be applied to novel problems that have previously been difficult to analyze via the previous methodology.

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**Appendix A**

Here we show that the transformation of relative fluctuation between different ensembles is equivalent to the invariance of concentration (such as molar or mole ratio ) and its fluctuation. We take the molar density in the single component solution (see Section 2) as an example, but the argument here can be expanded to straightforwardly to both molarity and mole ratio concentration scales in multiple-component solutions that have been treated in Section 3.

The concentration fluctuation under constant subsystem volume can be expressed as

(A1)

The same fluctuation under constant particle number becomes

(A2)

Postulating the invariance of density fluctuation under ensemble transformation, we obtain

(A3)

Here we simplify Eq. (A3) by noting that

(A4)

Note that . Using Eq. (A4), Eq. (A3) can be simplified as

(A5)

Since the molar concentration is another invariable under ensembles transform, we obtain

(A6)

The argument here can be generalized straightforwardly to molar () or mole ratio () concentrations. Thus, we have shown that the invariance of concentration and concentration fluctuation underlies the transformation of relative fluctuations.

**Appendix B**

Here we demonstrate rigorously that the higher-order terms present in Eq. (46) are indeed . To demonstrate this, let us expand Eqs. (43) and (44) up to the first order of as

(B1)

Likewise,

(B2)

Combining Eqs. (43)-(45), we obtain,

(B3)

where and represent the contributions from Eqs. (B1) and (B2), respectively. The negligibility of the final term will be presented at the end of this Appendix.

The first term in the right-hand side of Eq. (B3) is Eq. (46). Let us show that the rest of the terms are indeed . To do so, from the definition of the KBI in inhomogeneous system,

(B4)

Because , . A factor in the third term of Eq. (B3) can therefore be rewritten as

(B5)

Using Eq. (B5), the last two terms of Eq. (B3) becomes

(B6)

To evaluate the order of magnitude of the first two terms of Eq. (B6), let for simplicity. Our goal is then reduced to the order of magnitude analysis of . Let us consider the intensive quantity , which can be linked to

(B7)

which can be linked to the expression in an inhomogeneous solution using

(B8)

into

(B9)

Note that is an ensemble average in the homogeneous system. This means , even though the solution is dilute. This leads to

(B10)

Since , it follows from Eq. (B10) that . The last term of Eq. (B6) is also , because , and . Thus, the third and fourth terms of Eq. (B3) have been shown to be .

Regarding the final term of Eq. (B3), the only difference between these two terms is the presence of the solute molecule. Therefore, using the same argument that led to Eq. (B10) for , it follows that . Consequently, the final term of Eq. (B3) is and hence negligible.

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