



## The Kirkwood Superposition Approximation, Revisited and reexamined

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### Abstract

The Kirkwood superposition approximation (KSA) was originally suggested to obtain a closure to an integral equation for the pair correlation function. It states that the potential of mean force of say, three particles may be approximated by sum of potential of mean forces of pairs of particles. Nowadays, this approximation is widely used, explicitly or implicitly, in many fields unrelated to the problem for which it was suggested.

It is argued that the KSA is neither a good approximation nor a bad approximation; it is simply not an approximation at all.

**Key words:** Kirkwood superposition approximation, potential of mean force, pair correlation function.



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## 1. Introduction

In 1935, Kirkwood proposed the so-called superposition approximation.<sup>1</sup> It states that the potential of mean force (PMF) for three (or more) particles may be approximated by the sum of pair-wise PMF.

The PMF is defined as the change in the Helmholtz energy (in the T, V, N ensemble), or the Gibbs energy (in the T, P, N ensemble) associated with the process of bringing the three particles from infinite separation to the final configuration.<sup>1-4</sup> Thus, in the T, P, N ensemble

$$W(\vec{R}_1, \vec{R}_2, \vec{R}_3) = G(T, P, N; \vec{R}_1, \vec{R}_2, \vec{R}_3) - G(T, P, N; R_{ij} = \infty) \quad (1.1)$$

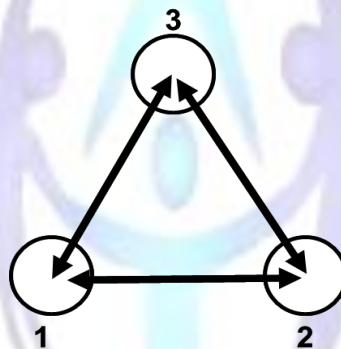
The question we pose here is under what conditions, if any, one can approximate  $W(\vec{R}_1, \vec{R}_2, \vec{R}_3)$  as a sum over pairs of PMFs?

$$W(\vec{R}_1, \vec{R}_2, \vec{R}_3) = W(\vec{R}_1, \vec{R}_2) + W(\vec{R}_1, \vec{R}_3) + W(\vec{R}_2, \vec{R}_3) \quad (1.2)$$

This is known as the Kirkwood supervision approximation (KSA). It was originally introduced by Kirkwood in the theory of liquids to achieve a closure to an integral equation for the pair correlation function. This approximation is intuitively very appealing. The reason is that such a pair-wise additive assumption is a good approximation for the *potential energy function*, (Figure 1), i.e.

$$U(\vec{R}_1, \vec{R}_2, \vec{R}_3) \approx U(\vec{R}_1, \vec{R}_2) + U(\vec{R}_1, \vec{R}_3) + U(\vec{R}_2, \vec{R}_3) \quad (1.3)$$

In fact, the pair-wise additivity of the potential function is exact for some systems; e.g. hard spheres, point charges, point dipoles, etc. It is also a good approximation for the total interaction energy among three (or more) simple, non-polar molecules.



**Figure 1. The energy change for bringing the three particles to a configuration**

$\vec{R}_1, \vec{R}_2, \vec{R}_3$  is the sum of the three energy changes for the process of bringing two particles to a distance as indicated by the double arrows.

Perhaps, Kirkwood was inspired by the additivity of the potential energy (1.3) to suggest the additivity of the PMF (1.2). During the years many authors attempted to improve upon this approximation.<sup>3,5-8</sup> Most of these attempts were aimed at improving the closure relation for the integral equation for the pair correlation function. Recently, an interesting new approach was suggested by Singer.<sup>9</sup> Singer showed that the KSA may be obtained by applying the principle of maximum entropy.<sup>10,11</sup> The question still remains: to what extent the KSA is a good approximation? In other words, is the KSA good approximation, in itself, without any reference to a closure to an integral equation?

In the original article,<sup>1</sup> Kirkwood used a probabilistic argument to justify the superposition approximation, namely that the probability of observing, say three particles at a configuration  $\vec{R}_1, \vec{R}_2, \vec{R}_3$  is the product of the three pair-wise probabilities. Equivalently, the superposition approximation may be formulated in terms of triplet and pair-correlation functions.<sup>1-4</sup>

$$g^{(3)}(\vec{R}_1, \vec{R}_2, \vec{R}_3) \approx g^{(2)}(\vec{R}_1, \vec{R}_2)g^{(2)}(\vec{R}_1, \vec{R}_3)g^{(2)}(\vec{R}_2, \vec{R}_3) \quad (1.4)$$

The equivalency between (1.2) and (1.4) follows from the definition of the PMF and the corresponding correlation function<sup>1-4</sup> for any number of particles

$$W^{(n)}(\vec{R}_1, \dots, \vec{R}_n) = -k_B \ln g^{(n)}(\vec{R}_1, \dots, \vec{R}_n) \quad (1.5)$$

Nowadays, it is not uncommon to encounter especially in the biochemical literature, reference to the PMF as a *potential energy function*. As a "potential energy," one is inclined to apply the additivity assumption (1.3), without examining its

validity. This nomenclature, though common, is unfortunate. The PMF is different from a *potential energy* in some fundamental properties. One is that the PMF is temperature dependent, whereas the potential energy is approximately independent of temperature. The second is the non-additivity of the PMF, even when there is an exact additivity of the potential energy.

In the rest of this article, we shall present arguments showing the source of the non-additivity of the PMF. We shall show that the superposition approximation cannot be theoretically justified even when the potential energy of interactions are strictly additive. Therefore we conclude that the KSA is not an approximation at all.

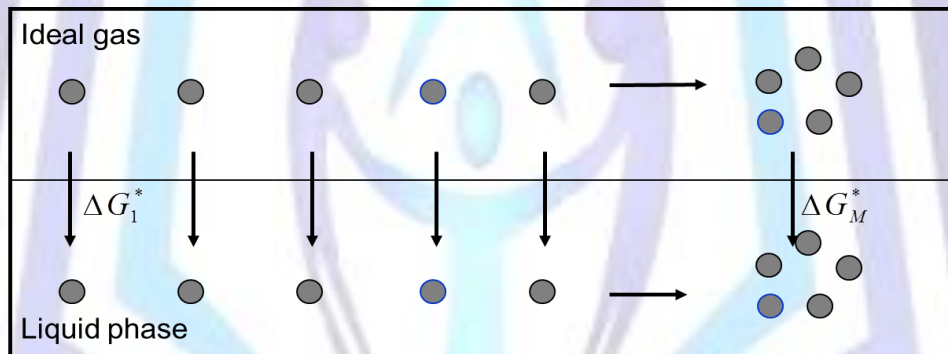
## 2.The source of the non-additivity of the PMF

The starting point of our argument is the following: For a classical system we can write the triplet PMF as:

$$\begin{aligned} W(\vec{R}_1, \vec{R}_2, \vec{R}_3) &= U(\vec{R}_1, \vec{R}_2, \vec{R}_3) + \delta G(\vec{R}_1, \vec{R}_2, \vec{R}_3) \\ &= U(\vec{R}_1, \vec{R}_2, \vec{R}_3) + \Delta G^*(\vec{R}_1, \vec{R}_2, \vec{R}_3) - 3\Delta G_s^* \end{aligned} \quad (2.1)$$

Equation (2.1) states that the work (here at  $T, P, N$  constants) of bringing three particles 1,2,3 from infinite separations to the final configuration  $\vec{R}_1, \vec{R}_2, \vec{R}_3$  can be written in two terms, a *direct interaction energy*  $U(\vec{R}_1, \vec{R}_2, \vec{R}_3)$ , and a solvent induced part  $\delta G(\vec{R}_1, \vec{R}_2, \vec{R}_3)$ . The latter can be rewritten as the difference in the solvation Gibbs energy of the triplet of particles at the configuration  $\vec{R}_1, \vec{R}_2, \vec{R}_3$ , Figure 2, and three times the solvation Gibbs energy of one particle in the same solvent.<sup>4,12</sup> Here, by “solvent” we mean all other particles in the system excluding the three particles 1, 2 and 3.

To highlight the source of the non-additivity of the PMF, we shall assume that the potential energy in (2.1) is pair-wise additive (approximately or exactly). We shall show below that the non-additivity of the PMF originates from the *solvation* Gibbs energy  $\Delta G^*(\vec{R}_1, \vec{R}_2, \vec{R}_3)$ .



**Figure 2. A process of bringing  $M$  particles, or groups from infinite separation ( $R_{ij} = \infty$ ) to the final configuration ( $\vec{R}^M$ ) in an ideal gas phase and in the liquid phase.**

Note that when the solvent density tends to zero, then all the solvation Gibbs energies on the right-hand side of (2.1) will tend to zero. At this limit the PMF becomes identical with the potential energy. It is perhaps this limiting example that inspired Kirkwood as well as many others to adopt the supposition approximation for the PMF. Unfortunately, whenever a solvent is present, even a solvent consisting of a single molecule, the additivity assumption of the PMF becomes invalid.

We first show the source of the non-additive for the simplest solvent; a single water molecule.<sup>13</sup> We also use the  $T, V, N$  ensemble simply for convenience. The conclusions are valid also for the  $T, P, N$  ensemble.

The solvation Helmholtz energy  $\Delta A^*$  of  $M$  particles at any specific configuration  $\vec{R}^M$  is defined as<sup>4,12</sup>

$$\Delta A^*(\vec{R}^M) = -k_B T \ln \langle \exp[-\beta B(\vec{R}^M)] \rangle_0 \quad (2.2)$$

where  $k_B$  is the Boltzmann constant,  $T$  the absolute temperature,  $\beta = (k_B T)^{-1}$ , and  $B(\vec{R}^M)$  is the *binding energy* defined by

$$B(\vec{R}^M) = \sum_{k=1}^M U(\vec{R}_k, \vec{X}_w) \quad (2.3)$$

The average in eq. (2.2) is over all configurations of the water molecule in the  $T, V, N$  ensemble with the probability distribution

$$P(\vec{X}_w) = \frac{1}{V(8\pi^2)} \quad (2.4)$$

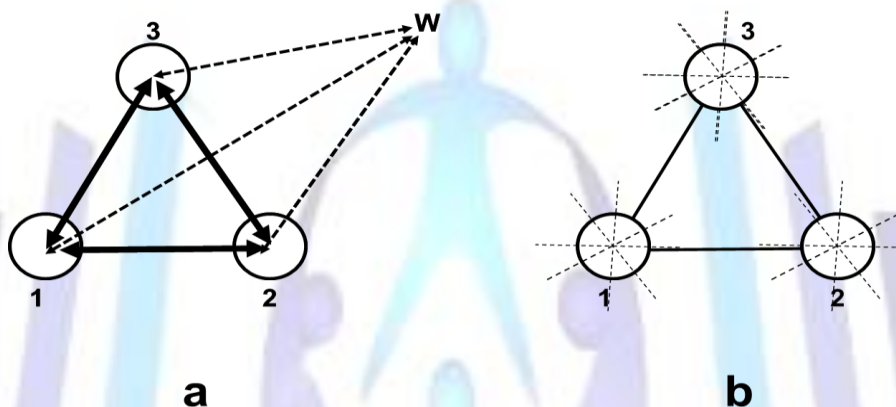
Assuming that the total interaction energy in the system is pair-wise additive, we can write the Helmholtz energy function as

$$A(\vec{R}^M) = \sum_{i<j} U(\vec{R}_i, \vec{R}_j) - k_B T \ln \int \prod_{k=1}^M \exp[-\beta U(\vec{R}_k, \vec{X}_w)] P(\vec{X}_w) d\vec{X}_w - M\Delta A_s^* \quad (2.5)$$

The integration in (2.5) is over all possible configurations of the water molecule. We can now see the main difference between the potential energy function  $U(\vec{R}^M)$  and the Helmholtz energy function,  $A(\vec{R}^M)$ .

Figure 3. The total interaction energy in a system of  $M$  particles (here  $M = 3$ ) is the sum of the interaction energies of all pairs of atoms. These are indicated by bold double arrows. The interactions between the  $M$  particles and the water molecule are indicated by the dashed double arrows (a), and for the more general case in (b).

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The assumption of pair-wise additivity of the potential function (whether exact or approximate) is indicated in Figure 3a as bold double arrows connecting all the  $M$  particles. On the other hand, the second term on the rhs of (2.5) contains only “lines of interactions” between the  $M$  particles and the water molecule. These are shown as dashed double arrows in Figure 3a.

Note that the second term on the rhs of (2.5) has no component which is pair-wise additive in the sense that the  $U(\vec{R}^M)$  has. Therefore, one cannot assume that the Helmholtz energy function is pair-wise additive, unless the second term on the rhs of (2.5) is negligible, which means that the Helmholtz energy function reduces to the potential energy function.

The conclusion reached above is valid for any solvent, not necessarily the simplest “solvent” discussed above. In the more general case the Helmholtz energy function is written as

$$A(\vec{R}^M) = U(\vec{R}^M) + \Delta A^*(\vec{R}^M) - M\Delta A_s^* \\ = U(\vec{R}^M) - k_B T \ln \int \dots \int \exp[-\beta B(\vec{R}^M)] P(\vec{X}^N) d\vec{X}^N - M\Delta A_s^* \quad (2.6)$$

where  $P(\vec{X}^N)$  is the configurational distribution of the solvent molecules.<sup>4,12</sup>

Again, we see that the function  $U(\vec{R}^M)$  has “lines of interactions” between all pairs of particles. On the other hand, the solvation Gibbs energy has only “lines of interactions” connecting the solute particles to water molecules Figure 3b. The averaging over all the configurations of the solvent molecules has no effect on this conclusion.<sup>12</sup>

Thus the general argument is that although the process of bringing the three particles in vacuum and in the liquid are the same processes, Figure 2, the works associated with these two processes are very different. The very rewriting of the PMF in the form (2.1), or the more general form (2.6) reveals the inadequacy of the Kirkwood superposition approximation. In the limit of low solvent density,  $\Delta G^*(\vec{R}^M)$  may be shown to be factorizable into a product of solvation Gibbs energies of the  $M$  *single* particles. In this limit the last two terms on the rhs of eq. (2.6) cancel out, and we are left with the potential energy, which to a good approximation may be assumed to be pair-wise additive. In the next section we shall present a few exact examples demonstrating the non-additivity of the potential of mean force. We also present one experimental data

showing that the extent of non-additivity of the solvation Gibbs energy is of the same order of magnitude as the solvation Gibbs energy itself.<sup>12,14</sup>

### 3. Some specific examples demonstrating the non-additivity of the Helmholtz (or Gibbs) energy of solvation

We have seen that the culprit for the non-additivity of the PMF is the solvation Gibbs energy of the cluster of  $M$  particles. In this section, we present a few examples for which the PMF may be calculated exactly for both triplets and pairs of particle.

#### (i) Three hard spheres (HS) at $\vec{R}_1, \vec{R}_2, \vec{R}_3$ , and a solvent consisting of a single hard sphere

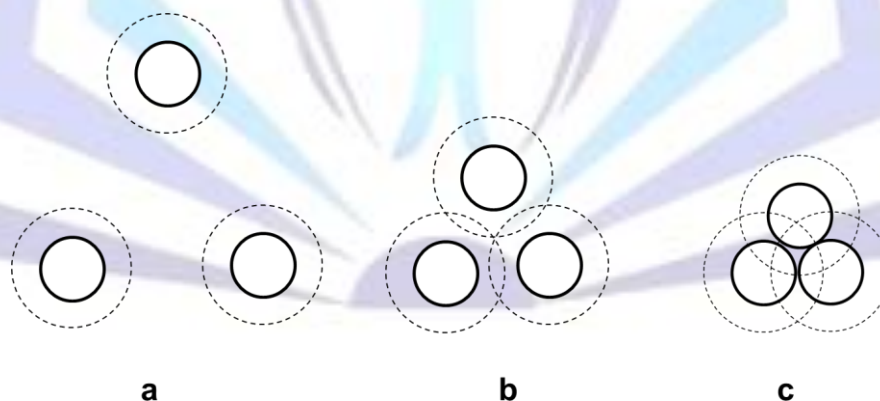
This is the simplest case of solvation of the triplet of HS particles in a one-hard-sphere “solvent” denoted  $w$ . The solvation Helmholtz energy in this case is

$$\begin{aligned} \exp[-\beta\Delta A^*(\vec{R}_1, \vec{R}_2, \vec{R}_3)] &= \langle \exp[-\beta B(\vec{R}_1, \vec{R}_2, \vec{R}_3)] \rangle \\ &= \int \frac{d\vec{R}_w}{V} \exp[-\beta B(\vec{R}_1) - \beta B(\vec{R}_2) - \beta B(\vec{R}_3)] \\ &= \frac{1}{V} \int d\vec{R}_w \exp[-\beta U(R_{1w}) - \beta U(R_{2w}) - \beta U(R_{3w})] \\ &= \frac{V - V^{EX}(\vec{R}_1, \vec{R}_2, \vec{R}_3)}{V} \end{aligned} \quad (3.1)$$

In the second step on the right-hand side of (3.1) we wrote the average quantity explicitly. Here, the probability density of the solvent molecule is simply

$$\Pr(\vec{R}_w) = \frac{1}{V} \quad (3.2)$$

Since there is only one solvent-molecule, denoted  $w$ , the binding energy reduces to the solute-solvent interaction energy. We next use the property of the HS interaction potential, which makes the integrand zero whenever the solvent molecule penetrates into the excluded volume ( $V^{EX}$ ) of the triplet of particles, and unity otherwise. The resulting expression is the right-hand side of (3.1).



**Figure 4. Three configurations of three spherical particles (here depicted as three**

**disks). At large distances there is no overlap in the excluded volume about each particle. At closed distances there is some overlap (b), and the maximum overlap is shown in the configuration (c).**

Figure 4 shows three configurations of the three particles and the corresponding excluded volumes. For simplicity we assume that the configuration  $\vec{R}_1, \vec{R}_2, \vec{R}_3$  is an equilateral triangle. Since  $V$  is much larger than  $V^{EX}$  we can expand  $\Delta A^*$ , to first order in  $V^{EX}/V$  to obtain

$$\Delta A^*(\vec{R}_1, \vec{R}_2, \vec{R}_3) = -k_B T \ln \left( 1 - \frac{V^{EX}(\vec{R}_1, \vec{R}_2, \vec{R}_3)}{V} \right)$$



$$\approx \frac{k_B T}{V} V^{EX}(\vec{R}_1, \vec{R}_2, \vec{R}_3) \quad (3.3)$$

and similarly for a pair of particles at  $\vec{R}_1, \vec{R}_2$ .

$$\Delta A^*(\vec{R}_1, \vec{R}_2) \approx \frac{k_B T}{V} V^{EX}(\vec{R}_1, \vec{R}_2) \quad (3.4)$$

The assumption of pair-wise additivity is equivalent to the equality of

$$V^{EX}(\vec{R}_1, \vec{R}_2, \vec{R}_3) = V^{EX}(\vec{R}_1, \vec{R}_2) + V^{EX}(\vec{R}_1, \vec{R}_3) + V^{EX}(\vec{R}_2, \vec{R}_3) \quad (3.5)$$

Clearly, an equality of this kind does not exist, as can be seen from Figure 4. Note that when the particles are sufficiently far apart, such that the excluded volume around the particles is the sum of the excluded volume of each particle, then we have

$$V^{EX}(\vec{R}_1, \vec{R}_2, \vec{R}_3) = 3V^{EX}(\vec{R}_1) \quad (3.6)$$

$$V^{EX}(\vec{R}_1, \vec{R}_2) = 2V^{EX}(\vec{R}_1) \quad (3.7)$$

In this case, the equality (3.5) certainly does not hold. However, the solvent induced contribution  $\delta G$  as well as the interaction energy are zero, and this case is of no interest.

**(ii) “Solvation” on an adsorbent molecule with conformational changes.**

This example is instructive because the “solvation” of the ligand on the adsorbent molecule can be solved exactly. We describe here the model and the results. The details of the calculations are quite lengthy and are available elsewhere.<sup>15</sup>

The solvent in our case is a system of adsorbent molecules. Each can be in two conformational states and each has three adsorption sites, Figure 5. The system is simple enough so that one can write down the partition function of the system and all the relevant thermodynamical properties. Specifically, we shall be interested in the analog of the PMF, or equivalently the Helmholtz energy change for the following two processes<sup>15</sup>

$$2[1,0,0] \rightarrow [1,1,0] + [0,0,0] \quad (3.8)$$

$$3[1,0,0] \rightarrow [1,1,1] + 2[0,0,0] \quad (3.9)$$

In process (3.8) we start with two singly occupied adsorbent molecules, transfer one ligand from one adsorbent molecule to the other to form a doubly occupied adsorbent molecule. In process 3.9, we start with three singly occupied adsorbent molecules and we transfer two ligands to form a triply occupied adsorbent molecule.

The Helmholtz energy change for this process is

$$\begin{aligned} W[1,1,0] &= U[1,1] + \delta A \text{ (process 3.8)} \\ &= U[1,1] - k_B T \ln \frac{(1 + Kh^2)(1 + K)}{(1 + Kh)^2} \end{aligned} \quad (3.10)$$

In (3.10) we wrote the PMF as a sum of two terms, the *direct interaction* energy between the two ligands occupying two sites on the adsorbent molecule, and the *indirect* part, or the “solvent-induced” part of the Helmholtz energy change. The latter is expressed in terms of the two molecular quantities

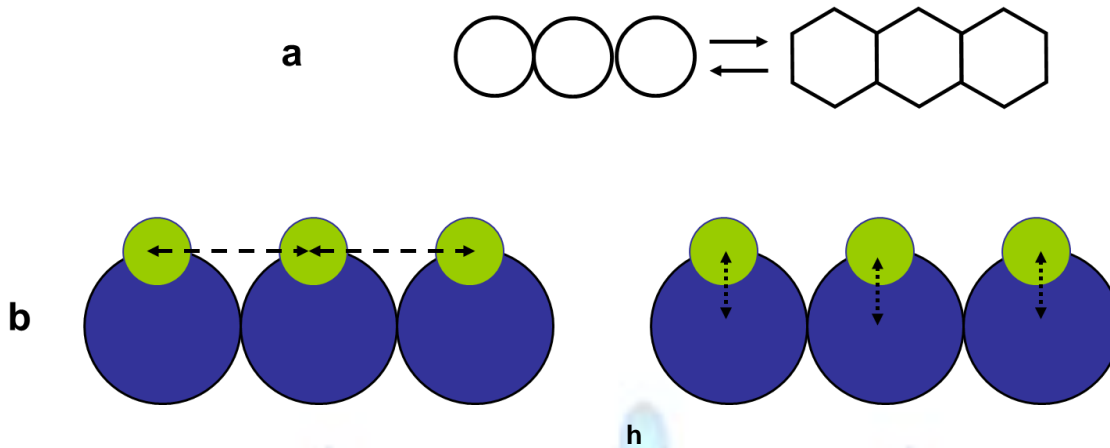
$$K = \exp[-\beta(E_H - E_L)] \quad , \quad h = \exp[-\beta(U_H - U_L)] \quad (3.11)$$

where  $E_H$  and  $E_L$  are the energy levels corresponding to the two conformations H and L, respectively, and  $U_H$  and  $U_L$  are the binding energies to the sites of H and L, respectively.

Similarly, the Helmholtz energy change for the process (3.9) is

$$\begin{aligned} W[1,1,1] &= 3U[1,1] + \delta A \text{ (process 3.9)} \\ &= 3U[1,1] - k_B T \ln \frac{(1 + Kh^3)(1 + K)^2}{(1 + Kh)^3} \end{aligned} \quad (3.12)$$

Where we have assumed pair-wise additivity for the direct interaction energy, i.e.  $U[1,1,1] = 3U(1,1)$ , and  $K$  and  $h$  have the same significance as in (3.11).



Since we have assumed the direct interaction energy between ligands is pair-wise additive, we can focus on the indirect parts of  $W(1,1,1)$  and  $W(1,1)$  and examine the condition under which we might have additivity of the form

$$\delta A \text{ (Process 3.8)} \approx 3\delta A \text{ (Process 3.7)} \quad (3.13)$$

or equivalently

$$\frac{(1 + Kh^3)(1 + K)^2}{(1 + Kh)^3} \stackrel{?}{=} \left[ \frac{(1 + Kh^2)(1 + K)}{(1 + Kh)^2} \right]^3 \quad (3.14)$$

Note that for either  $K = 0$  or  $h = 1$  the quantities on the two sides of (3.14) become equal to unity, hence the corresponding  $\delta A$  are zero. This is the case when there exists no indirect part of the PMF and therefore is of no interest to us. For any other values of  $K \neq 0$  and  $h \neq 1$ , there exists no condition under which the equality sign applies to (3.14). The reader is referred to reference 15 for more details.

### (iii) Ising model in one dimensional system

We discuss here the simplest 1-D Ising model. Particles occupying lattice points on a 1-D system can be in one of the two states, say “up” or “down”, or A and B. It is well known that the triplet correlation function in this system has the following property:

For any consecutive triplet of particles,  $i, i + 1$  and  $i + 2$ , the triplet correlation function may be written as<sup>15</sup>

$$g(s_i, s_{i+1}, s_{i+2}) = g(s_i, s_{i+1})g(s_{i+1}, s_{i+2}) \quad (3.15)$$

where  $s_i$  is the state (“up” or “down”, or A and B) of the site  $i$ . This property follows from the Markovian character of the 1-D Ising model.<sup>15</sup> Equation (3.15) is equivalent to the following equality of the analog of the PMF

$$W(s_i, s_{i+1}, s_{i+2}) = W(s_i, s_{i+1}) + W(s_{i+1}, s_{i+2}) \quad (3.16)$$

This is sometimes referred to as the “Kirkwood superposition approximation”.<sup>15,16</sup> However, the additivity expressed in (3.16) should be clearly distinguished from the Kirkwood superposition approximation, which, for the Ising model should be written as

$$W(s_i, s_{i+1}, s_{i+2}) = W(s_i, s_{i+1}) + W(s_{i+1}, s_{i+2}) + W(s_i, s_{i+2}) \quad (3.17)$$

One can show that the third term on the right-hand side of (3.17) is not zero.<sup>15</sup> It follows that the Kirkwood superposition approximation does not hold for the 1-D Ising model. Thus, although an additivity of the form (3.16) exists, it is different from the Kirkwood superposition approximation.

### (iv) An experimental evidence for the non additivity of the PMF



The indirect, or solvent induced part, of the PMF is defined in Eq (2.1). Here we calculate this quantity for three methane molecules in water. The indirect part of the Gibbs energy change for the process of bringing three methane molecules to a configuration of cyclo-propane is about :

$$\delta G_3 = -3.49 \text{ kcal/mol}$$

The corresponding value for two methane molecules is:

$$\delta G_2 = -2.16 \text{ kcal/mol}$$

Thus, the extent of nonadditivity is

$$\delta G_3 - 3\delta G_2 = (-3.49 + 3 \times 2.16) = 2.99 \text{ kcal/mol}$$

This is of the same order of magnitude as  $\delta G_2$  and  $\delta G_3$ , therefore one cannot view the pair-wise additivity as an approximation for  $\delta G_3$

#### 4. Some concluding remarks.

We have shown that the KSA cannot be considered either a good or a bad approximation, for the PMF between any number of particles and in any solvent. The reason for that conclusion is that the extent of non-additivity of the solvation Gibbs or Helmholtz energy is, in general, of the same order of magnitude as the Gibbs or Helmholtz energy of solvation itself.

Unfortunately the KSA is used, either explicitly or implicitly, in many studies of aqueous solutions. In particular, in the study of protein folding, and protein-protein association. Here it is more common to refer to the potential energy function as the energy landscape (EL), and to the potential of mean force as the Gibbs energy landscape (GEL).<sup>14</sup>

In processes such as protein folding or protein-protein association it is believed that the solvation Gibbs energy term dominates the GEL. Therefore, we can conclude that even when the EL is strictly pair-wise additive, the GEL can never be assumed, not even approximated as a pair-wise additive function. This conclusion is valid for any solvent, or mixture of solvents of any composition.

Most theories of protein folding which starts from either the EL or the GEL assume some kind of pair-wise additivity. In the older literatures people focused on the EL, in which case the pair-wise additivity assumption is a valid approximation. However, since proteins "live" in solution, and since the solvent effects are dominant in both the dynamics of the protein folding, as well as the stability of the native structure of the protein, the relevant landscape is the GEL, and not the EL. In most cases, even when one acknowledges the relevance of the GEL, one assumes pair-wise additivity for the GEL. In listing the various contributions to the EL or the GEL, one also includes solvent induced contributions, specifically hydrophobic interaction. Once one includes hydrophobic interactions, one is committed to working with the GEL, although quite often one refers to the resulting function as the EL. Unfortunately, the very inclusion of hydrophobic effects as an additive term into the GEL invalidates the basis on which theory is developed.

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