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A Generalized Theory for the Structural and Spatial Mapping of Energy, Entropy, and Free Energy

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Abstract

Keywords

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Abstract

Systems in which the free energy density is nonuniform in space are familiar; the surface tension of a water droplet and the surface energy of a solid are good examples. Some such cases can be treated with prior theory, notably inhomogeneous solvation theory (IST), but IST is applicable only to liquids. Despite this limitation, IST has proven useful as a guide to the design of ligands to bind a targeted protein, based on the idea that ligands which displace high free energy water will tend to bind more tightly, other things being equal. Here, we present Generalized Thermodynamic Mapping Theory (GTMT), a more general theory that is applicable to the entirety of a biomolecular or other chemical system, and which thus may provide additional guidance for molecular design. For example, it might highlight parts of a ligand whose local free energy rises on binding, thus suggesting where modifications could improve affinity. Starting from classical statistical thermodynamics, we derive structural decompositions that assign energy and entropy to individual atoms or to larger chemical components, such as amino acid residues, and spatial decompositions that define continuously varying thermodynamic densities throughout the system. The potential energy is decomposed via the multibody expansion, and the entropy via the mutual information expansion. The resulting thermodynamic densities satisfy key desiderata: their spatial integrals yield the correct total thermodynamic quantities, the densities vanish where the atomic number density is zero, and all entropy terms above first order go to zero in the absence of correlation. The entropy decomposition in GTMT is closely related to that of IST, but it is simpler, largely because it expresses the entropy in terms of normalized probability density functions instead of non-normalized correlation functions. We show that, while GTMT is formally exact for any number of particles, N, IST is not. The unified framework presented here enables thermodynamic mapping of solute and solvent alike and is expected to support a range of applications, including in structure-based drug design, protein design, the analysis of allostery, and materials science.

1 Introduction

A chemical system at equilibrium need not have a uniform spatial distribution of free energy, energy, or entropy. For example, the surface tension of a water droplet, which is defined as the free energy per unit area of the surface, corresponds at the microscopic level to an elevated free energy per unit volume in the region of space where the mass density grades from its bulk liquid value to its vapor value. In addition, given that the free energy comprises an energetic component and an entropy component, there must be corresponding position-dependent energy and entropy densities. Solids also can have spatially varying thermodynamics, such as grain boundary energies that deviate from the bulk energy [1], and spatially varying elastic energy densities in objects under nonuniform mechanical stress.

Inhomogeneous solvation theory (IST) provides expressions for such position-dependent thermodynamic densities for a liquid in the context of a rigid solute molecule. These expressions can be numerically evaluated through analysis of molecular simulations, and software implementing IST analysis of simulations is used for structure-based drug design [2–6]. The rationale for this application is that a ligand may gain affinity for a protein by displacing binding site water that has a high free energy density and hence is thermodynamically unfavorable [7–10]. Binding of a ligand returns this water to the bulk, leading to an increment in binding affinity.

IST applies to fluids composed of rigid solvent molecules interacting via a pairwise additive potential. We have recently lifted these restrictions with a more general fluid theory that accommodates flexible solvent molecules interacting with an arbitrary multibody potential [11]. However, there has been no analogous formulation that is applicable to solids or to the entirety of a biomolecular system, such as a protein or lipid bilayer in aqueous solution, and we anticipate that such a formulation would be informative. For example, explicit solvent free energy methods [12–17] are widely used to predict protein-ligand binding free energies in the pharmaceutical and biotechnology industries, but are not readily interpretable: they neither explain why one ligand binds better than another nor tell how to modify an initial ligand to generate a new ligand with greater affinity. We conjecture that a comprehensive decomposition of the change in free energy on binding could provide information on which parts of a ligand contribute favorably to the computed binding affinity and therefore should be retained; which parts oppose binding and therefore should be modified; and which parts of the binding pocket could be used to generate new interactions that favor binding. Even an approximate method along these lines could accelerate the discovery of new potent ligands for targeted proteins by replacing guesswork with guided steps toward improved binders. Note that some applications may be best served by a *spatial* mapping of thermodynamic densities, like that provided by IST, though now extended to the protein and ligand themselves; but others may benefit instead from a *structural* decomposition, in which thermodynamic contributions are assigned to atoms or other molecular components. In this paper, we develop general spatial and structural thermodynamic decompositions, or mappings, that we hope will be useful in such applications.

The ability to compute position-dependent thermodynamic densities or structural decompositions of thermodynamics also promises to be useful in understanding and predicting allostery, which is of critical biomedical importance in phenomena ranging from activation of GPCRs, to regulation of metabolic enzymes, to the transduction of chemical energy into mechanical energy by molecular motors. We conjecture that the binding of an allosteric effector generates a rise in local free energy around the binding site, and that this, in turn, drives a distal allosteric change, which relaxes this initial, local, free energy rise. This view fits intuitive explanations common in the literature based on concepts of mechanical stress and strain and local energy storage and release [18–21]. However, our explorations of mechanical stress in proteins [22], including unpublished work, have made it clear that a formal accounting of stress is not particularly informative for proteins. This is because the free energy stored in a protein structure does not vary linearly with stress, as in a simple elastic solid. Instead, the energy landscape has many local energy wells at various energy levels, so a protein can be under little mean stress while in a high-lying local energy minimum. We anticipate that a thermodynamic mapping which accounts for this complexity will be informative regarding energy storage and relaxation in complex molecular systems with nonlinear stress/strain relationships.

Building on prior contributions [11, 23–26], the present paper derives thermodynamic mappings that can be applied to a range of systems, including flexible biomolecules in solution, thus filling a gap in the literature and enabling a range of practical applications. The mappings are derived from the basic equations of classical statistical thermodynamics, and their sums over atoms (for structural mappings) and spatial integrals (for spatial mappings) converge asymptotically to the correct system properties in the appropriate multibody limits. In particular, the densities satisfy basic desiderata [11] that the spatial integral of the free energy density over the entire system should give the correct system free energy, that the free energy density should go to zero where the spatial number density of atoms goes to zero, and that all entropy terms above first order should go to zero in the absence of correlation (i.e., in the limit of an ideal gas).

The remainder of the paper is organized as follows. Section 2 starts with an overview of the approach and a detailed definition of the physical system and coordinate system. It then presents derivations of atom-based structural and spatial mappings of the mean potential energy and entropy, followed by mappings based on molecules and more general chemical components, such as protein residues. Section 3 details the relationship of the present mappings to the solvent energy and entropy densities provided by IST. Finally, the Discussion considers implications and outlines future research directions based on this new theoretical foundation.

2 General Thermodynamic Mapping Theory (GTMT)

2.1 Overview of General Thermodynamic Mapping Theory

We use the fact that both the potential energy and the entropy of a chemical system can be written without approximation as series expansions. Thus, any potential energy function can be expressed as a multibody expansion [11], and the entropy of a multivariable system can be expressed in terms of the mutual information expansion (MIE) [23, 25, 27]. We may therefore, as diagrammed in Figure 1, decompose the potential energy across bodies – typically atoms – by assigning to atom i its full one-body energy, half of its two-body energy, etc. Analogously, atom i may be assigned its entire marginal entropy, minus one half of its pairwise mutual information with all other atoms, etc. We use these expansions to derive expressions for structural decompositions, which assign energy and entropy contributions to individual atoms or larger structural elements, and for spatial mappings, which define position-dependent energy and entropy densities. In practice, the entropy expansion must typically be truncated at low order (e.g. second or third), because converging higher order terms can become computationally intractable. However, the potential energy expansion for a typical pairwise additive force field terminates at second order without truncation, and its decompositions can be evaluated in full.

2.2 System Definition

We consider a flexible solute, such as an organic compound or a protein, immersed in a pure solvent, such as hexane or water, where the entire system of N atoms is contained in a volume V at temperature T and pressure P. The thermodynamic properties to be

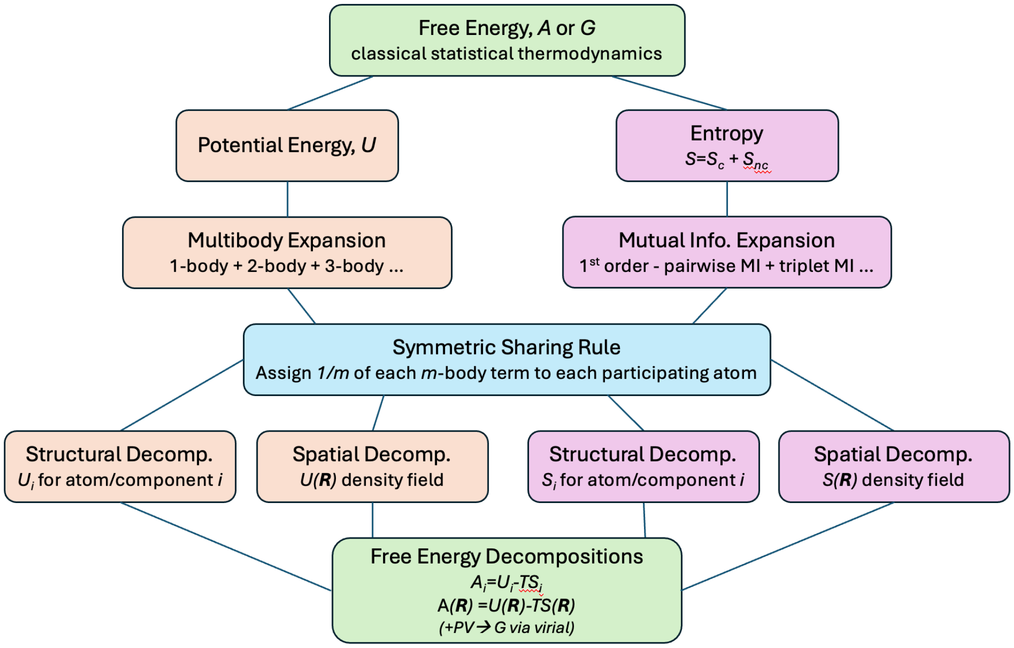

Figure 1: Structure of GTMT theory. Within classical thermodynamics, the free energy is split into the mean potential energy and the entropy (configurational and non-configurational) contributions. Expression of energy in terms of a multibody expansion and entropy in terms of the mutual information expansion allows each contribution to be decomposed structurally (i.e., by atom or chemical component) and spatially (i.e., as thermodynamic densities). The decomposed energy and entropy can then be reassembled to provide structural and spatial decompositions of the free energy. The bottom rectangle lists the Helmholtz free energy, A, while noting that the pressure-volume product, PV, when expressed in terms of the virial, can also be decomposed, allowing full decomposition of the Gibbs free energy as well. Symbols used here are defined in Table 1 and the text.

mapped are the mean potential energy, U, the entropy, S, the Helmholtz free energy, A, and the Gibbs free energy, G. Note that we remain within the classical approximation of statistical thermodynamics [28].

Before proceeding further, we switch from a lab-frame coordinate system to an internal Cartesian coordinate system, i.e., one rooted in the frame of reference of the solute. If we used a laboratory frame of reference, local variations in thermodynamic densities around the solute would be averaged over the entire system volume due to translation of the solute in the lab frame, and thus would be uniform over the volume. Lab-frame rotations on their own would similarly smear variations in thermodynamic density and lead to relatively uninteresting radially symmetric densities. Such results would not be wrong, but they would be uninformative. One way to set up such a coordinate system is to choose one solute atom, i, as the origin of coordinates; choose a second solute atom, j, and define the x-axis in terms of the unit vector from atom i to atom j; choose a third atom, k, and define the y-axis in terms of the unit vector starting at atom i, in the plane defined by atoms i, j, and k, and orthogonal to the new x-axis; and define the z axis as vector starting at atom i and extending orthogonally to both the x- and y-axes. With this definition, the coordinates of atom i are always $\mathbf{r}_i = (0, 0, 0)$, those of atom j are always $\mathbf{r}_j = (x_j, 0, 0)$, and those of atom k are always

$\mathbf{r}_k = (x_k, y_k, 0)$, where the six zeroes associated with the three root atoms correspond to the eliminated degrees of freedom (or, more properly, to the external degrees of freedom of the solute). For convenience, we still write the coordinates of all N atoms as $\mathbf{r}^N = (\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$. Note that, to avoid a situation where the internal coordinates become numerically unstable because atoms i, j, k are nearly collinear, it is helpful to choose i, j, k as three sp3 or sp2 hybridized atoms in bonding sequence, so that the i, j, k angle remains far from zero. (The condition of exact collinearity does not pose a substantive theoretical problem because the phase space volume associated with this singularity is infinitesimal.) Details of this coordinate change are available in the "Anchored Coordinates" part of the Appendix of a prior publication [29]). Note that, in order to reduce the sensitivity of the entropy decomposition for a protein to the choice of root atoms, one may, alternatively, use bond-angle-torsion coordinates [27] or "chained Cartesian coordinates", where the position and orientation of each residue is defined in the frame of the prior residue, and the Cartesian coordinates of each atom are defined in the frame of reference of their own residue.

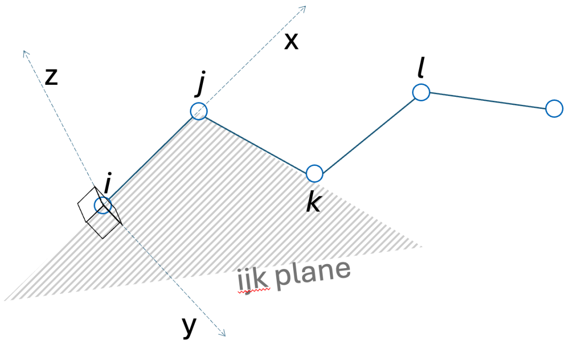

Figure 2: Diagram of one way to define a Cartesian coordinate system in the frame of reference of the solute. Atoms indexed i, j, k define the coordinate system, with the origin at atom i, x-axis lying along the $i - j$ bond, the y-axis orthogonal to the x-axis and in the i, j, k plane, and the z-axis orthogonal to both the x- and y-axes.

We now summarize important aspects of the notation used here, while Table 1 defines additional symbols used in this paper. The total mean potential energy U and configurational entropy S of the system are decomposed into atomic contributions, U_i and S_i for atom i, and spatial densities, $U(\mathbf{R})$ and $S(\mathbf{R})$, at location $\mathbf{R}$ in the solute-based reference frame. In Section 2.6, we distinguish between the positional (i.e., translational) coordinates $\mathbf{r}_a$ and the combined internal and orientational coordinates $\mathbf{q}_a$ of a given molecule (e.g., a water molecule) or chemical component (e.g., a protein residue) a.

The probability density function (PDF) over all atomic coordinates is $p(\mathbf{r}^N)$, and marginal probability density functions for e.g. single atoms and pairs of atoms, are given by:

$$
\begin{aligned}
p(\mathbf{r}_i) &= \int p(\mathbf{r}^N) \prod_{k \neq i}^{N} d\mathbf{r}_k \\
p(\mathbf{r}_i, \mathbf{r}_j) &= \int p(\mathbf{r}^N) \prod_{k \neq i,j}^{N} d\mathbf{r}_k
\end{aligned} \tag{1}
$$

In constructing GTMT, we build on the Irving-Kirkwood formalism [30], which uses delta functions to define continuously varying spatial densities. For example, the mass density in space, $M(\mathbf{R})$, would be written as follows in terms of atomic masses m_i, PDFs $p(\mathbf{r}_i)$, and positions, $\mathbf{r}_i$:

$$
M(\mathbf{R}) = \int \sum_{i=1}^{N} \left[\delta(\mathbf{R} - \mathbf{r}_i)\, m_i\, p(\mathbf{r}_i) \right] d\mathbf{r}_i \tag{2}
$$

The delta functions pick out the contribution of each atom, i, at location $\mathbf{R}$. However, when comparing GTMT with IST in Section 3, we revert to the simpler but less general formalism typically used to express IST.

Coordinates and Counts	
$\mathbf{r}_i$	Cartesian coordinates (x, y, z) of atom i
$\mathbf{r}^N$	$(\mathbf{r}_1, \mathbf{r}_2, \ldots, \mathbf{r}_N)$, all N sets of atomic coordinates in a given system configuration.
$\mathbf{R}$	Cartesian coordinates (x, y, z); used for thermodynamic densities
$\mathbf{q}$	combined orientational and internal coordinates of a molecule or other chemical component
$\mathbf{p}^N$	Momenta of all N atoms
$\mathbf{p}_i$	Momentum of atom i
N_{perm}	Number of permutations among all indistinguishable atoms
n_l	Number of indistinguishable atoms in group l
Distribution and Correlation Functions	
$p(\mathbf{r}^N, \mathbf{p}^N)$	Normalized probability distribution function (PDF) over all spatial and momentum coordinates
$P(\mathbf{r}^N, \mathbf{p}^N)$	Non-normalized distribution function defined in Eq 12
$p(\mathbf{r}^N)$	Normalized PDF over Cartesian coordinates of all N atoms
$p(\mathbf{r}_i)$	Normalized marginal PDF of atom i as a function of its atomic coordinates, $\mathbf{r}_i$
$p(\mathbf{r}, \mathbf{r}')$	Normalized joint PDF of atoms i, j as a function of their respective positions, $\mathbf{r}, \mathbf{r}'$
$p(\mathbf{q}_a \mid \mathbf{r}_a)$	PDF of orientational and internal coordinates $\mathbf{q}$ of chemical component a conditioned on its being located at $\mathbf{r}$
$g(\mathbf{r})$	One-body solvent correlation function, as used in IST
$g(\mathbf{r}, \mathbf{r}')$	Two-body solvent correlation function, as used in IST
ρ	Number density
Energy	
U	Mean potential energy of the system
U($\mathbf{R}$)	Potential energy density at $\mathbf{R}$
$U(\mathbf{r}^N)$	Instantaneous potential energy of configuration $\mathbf{r}^N$
$u_i(\mathbf{r}_i)$	One-body potential energy term for atom i as a function of $\mathbf{r}_i$
$u_{ij}(\mathbf{r}_i, \mathbf{r}_j)$	Two-body potential energy term for atoms i, j as a function of $\mathbf{r}_i, \mathbf{r}_j$
$U_i(\mathbf{r}^N)$	Potential energy assigned to atom i for a given system configuration, $\mathbf{r}^N$
U_i	Mean potential energy assigned to atom i
$U_i(\mathbf{R})$	Mean potential energy density at $\mathbf{R}$ contributed by atom i
U_a	Mean potential energy associated with chemical component a
$U_a(\mathbf{R})$	Mean potential energy density at $\mathbf{R}$ contributed by chemical component a
Entropy	
S	Entropy of the system
S_c	Configurational entropy of the system
$S_c(\mathbf{R})$	Configurational entropy density at $\mathbf{R}$
$S_{c,i}(\mathbf{R})$	Configurational entropy density of atom i at $\mathbf{R}$
$S_{c,i}$	Configurational entropy of atom i
S_{nc}	Nonconfigurational entropy of the system
$S_{nc,i}$	Nonconfigurational entropy of atom i
$S_{nc}(\mathbf{R})$	Nonconfigurational entropy density at $\mathbf{R}$
$S_{nc,i}(\mathbf{R})$	Nonconfigurational entropy density of atom i at $\mathbf{R}$
S($\mathbf{R}$)	Entropy density at $\mathbf{R}$
$S_c^{(1)}$	First order contribution to (and first-order estimate of) the configurational entropy
$S_{c,i}^{(1)}$	First order contribution to (and first-order estimate of) the configurational entropy associated with atom i
$S_c^{(2)}$	Second order estimate of the configurational entropy
I_{ij}	Mutual information between atoms i and j
$I_i^{(2)}$	Pairwise mutual information associated with atom i
$I_{\bar{i}j}(\mathbf{R})$	Density of mutual information between atoms i and j and associated with atom i, at $\mathbf{R}$.
$S^{(1)}(\mathbf{R})$	First order contribution to (and estimate of) configurational entropy at $\mathbf{R}$
$I^{(2)}(\mathbf{R})$	Pairwise mutual information density at $\mathbf{R}$
$S_a^q(\mathbf{R})$	Density of the orientational/internal entropy of component a conditioned on component a being located at $\mathbf{R}$
S_{ig}	Entropy of an ideal gas
$S_{IST}^{(2)}$	Second order estimate of entropy from IST
$S_{IST}^{(1)}(\mathbf{r})$	First order estimate of entropy density from IST at $\mathbf{r}$
$S_{IST}^{(2)}(\mathbf{r})$	Second order estimate of entropy density from IST at $\mathbf{r}$
Free Energy	
A	Helmholtz free energy of the system
A_i	Helmholtz free energy assigned to atom i
$A(\mathbf{R})$	Helmholtz free energy density as a function of position
G	Gibbs free energy of the system
G_i	Gibbs free energy assigned to atom i
$G(\mathbf{R})$	Gibbs free energy density as a function of position
$\mathcal{W}(\mathbf{r}^N)$	Virial of the system in configuration $\mathbf{r}^N$
$\mathcal{W}_i(\mathbf{r}^N)$	Contribution of atom i to the virial, for system configuration $\mathbf{r}^N$
$(PV)_i$	Contribution of atom i to the pressure-volume product

Table 1: Definitions of selected symbols used in this paper.

2.3 Mapping the Potential Energy

The mean potential energy of the entire system is given by

$$U = \int p(\mathbf{r}^N) U(\mathbf{r}^N) d\mathbf{r}^N \tag{3}$$

For example, in the canonical ensemble,

$$p(\mathbf{r}^N) = \frac{e^{-\beta U(\mathbf{r}^N)}}{Z} \tag{4}$$

$$Z = \int e^{-\beta U(\mathbf{r}^N)} d\mathbf{r}^N \tag{5}$$

where $U(\mathbf{r}^N)$ is the potential energy as a function of the atomic coordinates, $\mathbf{r}^N$; $p(\mathbf{r}^N)$ is the PDF over all atomic coordinates and is given by the Boltzmann distribution defined in Equations 4 and 5; Z is the configuration integral, and $\beta = 1/k_B T$, with k_B the Boltzmann constant and T the absolute temperature.

2.3.1 Structural Mapping of the Potential Energy

Here, we derive a decomposition, or mapping, of the mean potential energy, U, to individual atoms, while Section 2.6 provides a decomposition by chemical components comprising multiple atoms, such as entire solvent molecules or the separate residues of a protein. We begin with the multibody expansion of the instantaneous potential energy, where a "body" is an atom,

$$U(\mathbf{r}^N) = \sum_{i=1}^{N} u_i(\mathbf{r}_i) + \sum_{i=1}^{N}\sum_{j>i}^{N} u_{ij}(\mathbf{r}_i, \mathbf{r}_j) + \sum_{i=1}^{N}\sum_{j>i}^{N}\sum_{k>j}^{N} u_{ijk}(\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k) + \ldots \tag{6}$$

where i, j, k index atoms; $u_i(\mathbf{r}_i)$, $u_{ij}(\mathbf{r}_i, \mathbf{r}_j)$, and $u_{ijk}(\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k)$ are the 1-body, 2-body, and 3-body energy contributions associated with atom i, atom pair i, j, and atomic triplet i, j, k, respectively; and the ellipsis indicates the possibility of 4-body and higher terms. In a prior paper [11], we used ϕ rather than u in the multibody expansion; we change notation here for simplicity and for consistency with the broader literature. Note that these sums run over all atoms of both the solute and solvent, so they include the interactions of the solute atoms with the solvent. Therefore, the one-body term is expected to be nonzero only in the presence of an external field, whereas in IST, which focuses on the solvent, the first order term reflects the interactions of the solvent with the solute.

We now define the potential energy associated with any atom, i, for a given configuration, $\mathbf{r}^N$, as:

$$U_i(\mathbf{r}^N) = u_i(\mathbf{r}_i) + \frac{1}{2}\sum_{j\neq i}^{N} u_{ij}(\mathbf{r}_i, \mathbf{r}_j) + \frac{1}{3}\sum_{j\neq i}^{N}\sum_{\substack{k\neq i\\ k>j}}^{N} u_{ijk}(\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k) + \ldots \tag{7}$$

This expression assigns all of atom i's interaction with any external field to atom i alone; it assigns one half of all of atom i's interactions with other atoms j to atom i, leaving the other half to be assigned to atoms j, and it assigns one third of the three-body interactions that involve atom i to atom i. For example, for a four-atom system, atom 1 is assigned the following energy, to third order:

$$\begin{aligned}U_1(\mathbf{r}^N) = u_1(\mathbf{r}_1) &+ \frac{1}{2}\left[u_{12}(\mathbf{r}_1,\mathbf{r}_2) + u_{13}(\mathbf{r}_1,\mathbf{r}_3) + u_{14}(\mathbf{r}_1,\mathbf{r}_4)\right] \\ &+ \frac{1}{3}\left[\, u_{123}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_3) + u_{134}(\mathbf{r}_1,\mathbf{r}_3,\mathbf{r}_4) + \right. \\ &+ \left. u_{124}(\mathbf{r}_1,\mathbf{r}_2,\mathbf{r}_4)\,\right]\end{aligned}$$

The elided higher order terms of the multibody potential make analogous contributions to atom i's potential energy. The total system potential energy, $U(\mathbf{r}^N)$, is, by construction, the sum of the atomistic potential energies over all solute and solvent atoms:

$$U(\mathbf{r}^N) = \sum_{i=1}^{N} U_i(\mathbf{r}^N) \tag{8}$$

Therefore, Equation 7 provides a well-defined mapping of the total potential energy to individual atoms for a given configuration, and averaging over configurations gives the contribution, U_i, of each atom to the mean potential energy of the system:

$$\begin{aligned}U &= \sum_{i=1}^{N} U_i \\ U_i &= \int p(\mathbf{r}^N) U_i(\mathbf{r}^N) d\mathbf{r}^N \\ &= \int p(\mathbf{r}_i) u_i(\mathbf{r}_i) d\mathbf{r}_i + \frac{1}{2}\sum_{j\neq i}^{N} \int p(\mathbf{r}_i,\mathbf{r}_j) u_{ij}(\mathbf{r}_i,\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \\ &+ \frac{1}{3}\sum_{j\neq i}^{N}\sum_{\substack{k\neq i\\ k>j}}^{N} \int p(\mathbf{r}_i,\mathbf{r}_j,\mathbf{r}_k) u_{ijk}(\mathbf{r}_i,\mathbf{r}_j,\mathbf{r}_k) d\mathbf{r}_i d\mathbf{r}_j d\mathbf{r}_k + \ldots\end{aligned} \tag{9}$$

where we have used the fact that $\int p(\mathbf{r}^N) \prod_{k\neq i}^{N} d\mathbf{r}_k = p(\mathbf{r}_i)$ to write $\int p(\mathbf{r}^N) u_i(\mathbf{r}_i) d\mathbf{r}^N = \int p(\mathbf{r}_i) u_i(\mathbf{r}_i) d\mathbf{r}_i$, and similarly for the higher order terms.

2.3.2 Spatial Mapping of the Potential Energy Density

This structural decomposition of the energy is expected to be useful for the solute, where chemically distinct atoms make distinct, interpretable, contributions to U. In contrast, because the solvent molecules are all indistinguishable from each other, they will be assigned identical mean energies. For example, if the solvent is water, then every water oxygen will be assigned the same mean energy, U_O, and every hydrogen atom will be assigned the same mean energy, U_H, so the total mean energy of each water, $U_w = U_O + 2U_H$, will be the same for every water molecule in the system, making such an analysis relatively uninformative. A spatial mapping of the potential energy is more useful in this setting [26, 31]. In GTMT, a spatial mapping of mean potential energy is constructed by inserting the delta-function $\delta(\mathbf{R} - \mathbf{r}_i)$ into the integrals of Equation 9 to pick out the mean energy of each atom when it is at $\mathbf{R}$, yielding $U_i(\mathbf{R})$, and summing $U_i(\mathbf{R})$ over atoms i to obtain $U(\mathbf{R})$:

$$
\begin{aligned}
U(\mathbf{R}) &= \sum_{i=1}^{N} U_i(\mathbf{R}) \\
U_i(\mathbf{R}) &= \int \delta(\mathbf{R}-\mathbf{r}_i) p(\mathbf{r}^N) U_i(\mathbf{r}^N) d\mathbf{r}^N \\
&= \int \delta(\mathbf{R}-\mathbf{r}_i) p(\mathbf{r}_i) u_i(\mathbf{r}_i) d\mathbf{r}_i + \frac{1}{2}\sum_{j\neq i}^{N} \int \delta(\mathbf{R}-\mathbf{r}_i) p(\mathbf{r}_i,\mathbf{r}_j) u_{ij}(\mathbf{r}_i,\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \\
&+ \frac{1}{3}\sum_{j\neq i}^{N} \sum_{\substack{k\neq i \\ k>j}}^{N} \int \delta(\mathbf{R}-\mathbf{r}_i) p(\mathbf{r}_i,\mathbf{r}_j,\mathbf{r}_k) u_{ijk}(\mathbf{r}_i,\mathbf{r}_j,\mathbf{r}_k) d\mathbf{r}_i d\mathbf{r}_j d\mathbf{r}_k \ + \ \ldots \qquad (10)
\end{aligned}
$$

With these definitions, it is clear that

$$
\begin{aligned}
U_i &= \int U_i(\mathbf{R}) d\mathbf{R} \\
U &= \int U(\mathbf{R}) d\mathbf{R} \qquad (11)
\end{aligned}
$$

Thus, our definition of the potential energy density satisfies the desideratum that its integral over the system volume equals the mean potential energy.

2.4 Mapping the Entropy

We start with Wallace's expression for the total entropy [32] in terms of the following non-normalized distribution function

$$P(\mathbf{r}^N,\mathbf{p}^N) = \frac{e^{-\beta H(\mathbf{r}^N,\mathbf{p}^N)}}{\frac{1}{h^{3N} N_{perm}} \int e^{-\beta H(\mathbf{r}^N,\mathbf{p}^N)} d\mathbf{r}^N d\mathbf{p}^N} \qquad (12)$$

which should be distinguished from the normalized PDF

$$p(\mathbf{r}^N,\mathbf{p}^N) = \frac{e^{-\beta H(\mathbf{r}^N,\mathbf{p}^N)}}{\int e^{-\beta H(\mathbf{r}^N,\mathbf{p}^N)} d\mathbf{r}^N d\mathbf{p}^N} \qquad (13)$$

where $H(\mathbf{r}^N,\mathbf{p}^N)$ is the total energy (kinetic and potential) as a function of spatial coordinates $\mathbf{r}^N$ and momenta $\mathbf{p}^N$, and h is Planck's constant. Because i ranges over both solute and solvent atoms, only certain subsets of particles are indistinguishable, so we have replaced $N!$ by N_{perm}, the number of possible permutations of all indistinguishable atoms. If there are n groups l of indistinguishable atoms, each with n_l atoms, such that $\sum_{l=1}^{n} n_l = N$, then $N_{perm} = \prod_{l=1}^{n} n_l!$, so, for example, $N_{perm} = 1$ if all atoms are distinct, and $N_{perm} = N!$ if all atoms are identical.

Following Wallace, we write the entropy as

$$\begin{aligned}
S &= -\frac{k_B}{h^{3N} N_{perm}} \int P(\mathbf{r}^N, \mathbf{p}^N) \ln P(\mathbf{r}^N, \mathbf{p}^N) d\mathbf{r}^N d\mathbf{p}^N \\
&= -k_B \int p(\mathbf{r}^N, \mathbf{p}^N) \left[\ln p(\mathbf{r}^N, \mathbf{p}^N) + \ln(h^{3N} N_{perm})\right] d\mathbf{r}^N d\mathbf{p}^N \\
&= S_c + S_{nc} \\
S_c &= -k_B \int p(\mathbf{r}^N) \ln p(\mathbf{r}^N) d\mathbf{r}^N \\
S_{nc} &= -k_B \sum_{i=1}^{N} \left[\int p(\mathbf{p}_i) \ln p(\mathbf{p}_i) d\mathbf{p}_i\right] - k_B \ln(h^{3N} N_{perm}) \qquad (14)
\end{aligned}$$

where we have factorized the integral by using the fact that, in the classical approximation and at equilibrium, momenta are statistically independent of position and of each other, so $p(\mathbf{r}^N, \mathbf{p}^N) = p(\mathbf{r}^N) \prod_i p(\mathbf{p}_i)$.

Here S_c is the Gibbs-Shannon configurational entropy, and S_{nc}, the non-configurational entropy, contains the momentum entropy, the indistinguishability correction, and a term involving Planck's constant which cancels the units of the probability density functions over position and momentum in the other logarithmic terms. The non-configurational entropy is unaffected by changes in $p(\mathbf{r}^N)$ at constant T and N, and hence is of little interest in many applications, so it is often set aside [26, 31, 33]. We include S_{nc} nonetheless, as it depends on temperature and composition, and there are cases where these are not constant. Including it also facilitates comparisons with prior papers that used comparisons with the Sackur-Tetrode equation as a test of validity [32, 34].

2.4.1 Structural Mapping of the Entropy

We consider S_{nc} and then S_c. To decompose S_{nc}, we use the well-known fact that, in classical statistical thermodynamics, the PDFs of the three momentum components of each atom are statistically independent. This allows us to factorize $p(\mathbf{p}_i)$ into three identical Gaussian distributions, for which the entropy can be written analytically:

$$\begin{aligned}
p(\mathbf{p}_i) &= p(\mathbf{p}_{ix}) p(\mathbf{p}_{iy}) p(\mathbf{p}_{iz}) = \left[\frac{e^{-\frac{p_x^2}{2mk_BT}}}{\int e^{-\frac{p_x^2}{2mk_BT}} dp_x}\right]^3 \\
-k_B \int p(\mathbf{p}_i) \ln p(\mathbf{p}_i) d\mathbf{p}_i &= 3\frac{k_B}{2}\left[1 + \ln(2\pi m k_B T)\right] = 3k_B\left[\frac{1}{2} - \ln\Lambda_i + \ln h\right] \qquad (15)
\end{aligned}$$

where $\mathbf{p}_{ix}, \mathbf{p}_{iy}, \mathbf{p}_{iz}$ are the three momentum components of atom i, and $\Lambda_i = \frac{h}{\sqrt{2\pi m_i k_B T}}$ is the de Broglie wavelength of atom i with mass m_i. Thus, we may write the non-configurational entropy as

$$\begin{aligned}
S_{nc} &= \frac{3Nk_B}{2} - k_B \sum_{i=1}^{N} \ln \Lambda_i^3 + 3Nk_B \ln h - 3Nk_B \ln h - k_B \ln N_{perm} \\
&= \frac{3Nk_B}{2} - k_B \sum_{i=1}^{N} \ln \Lambda_i^3 - k_B \ln N_{perm} \qquad (16)
\end{aligned}$$

This allows a natural decomposition of the non-configurational entropy given in Equation 16 by atoms, i:

$$
\begin{aligned}
S_{nc} &= \sum_{i=1}^{N} S_{nc,i} \\
S_{nc,i} &= k_B \left[\frac{3}{2} - \ln \Lambda_i^3 - \frac{\ln n_{l(i)}!}{n_{l(i)}} \right]
\end{aligned}
\tag{17}
$$

where we have introduced $l(i)$, a function which returns the index l of the indistinguishability group that i belongs to. In the limit of large N and hence n_l, application of Stirling's approximation gives

$$
S_{nc,i} = k_B \left[\frac{5}{2} - \ln \Lambda_i^3 - \ln n_{l(i)} \right] \tag{18}
$$

The MIE allows the configurational entropy to be written as a sum of 1-atom, 2-atom, 3-atom, etc, terms:

$$
S_c = \sum_{i=1}^{N} S_{c,i}^{(1)} - \sum_{i=1}^{N} \sum_{j>i}^{N} I_{ij} + \sum_{i=1}^{N} \sum_{j>i}^{N} \sum_{k>j}^{N} I_{ijk} \dots \tag{19}
$$

where, for simplicity, and since there are no non-configurational mutual information terms, we have omitted a "c" subscript from the mutual information contributions. The 1-body (i.e., one-atom) configurational entropies are

$$
S_{c,i}^{(1)} = -k_B \int p(\mathbf{r}_i) \ln p(\mathbf{r}_i) d\mathbf{r}_i \tag{20}
$$

the 2-body mutual information terms have the general form $I_{ij} = S_i + S_j - S_{ij}$ and are given here by

$$
\begin{aligned}
I_{ij} &= -k_B \int p(\mathbf{r}_i) \ln p(\mathbf{r}_i) d\mathbf{r}_i - k_B \int p(\mathbf{r}_j) \ln p(\mathbf{r}_j) d\mathbf{r}_j \\
&+ k_B \int p(\mathbf{r}_i, \mathbf{r}_j) \ln p(\mathbf{r}_i, \mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j
\end{aligned}
\tag{21}
$$

and the 3-atom terms are available elsewhere [23, 25, 27]. Accordingly, one may write successive approximations of the configurational entropy as, e.g.,

$$
\begin{aligned}
S_c^{(1)} &= \sum_{i=1}^{N} S_{c,i}^{(1)} \\
S_c^{(2)} &= S_c^{(1)} - \sum_{i=1}^{N} \sum_{j>i}^{N} I_{ij} \\
S_c^{(3)} &= S_c^{(2)} + \sum_{i=1}^{N} \sum_{j>i}^{N} \sum_{k>j}^{N} I_{ijk}
\end{aligned}
\tag{22}
$$

The configurational entropy associated with atom i, S_i, then follows from the same logic used above to associate a potential energy with a given atom; i.e., S_i is the 1-body entropy of atom i plus half of atom i's 2-body terms with all other atoms, plus a third of its 3-body terms, etc.:

$$\begin{aligned}
S_c &= \sum_{i=1}^{N} S_{c,i} \\
S_{c,i} &= S_{c,i}^{(1)} - I_i^{(2)} + I_i^{(3)} + \ldots \\
I_i^{(2)} &= \frac{1}{2}\sum_{j\neq i}^{N} I_{ij} \\
I_i^{(3)} &= \frac{1}{3}\sum_{j\neq i}^{N}\sum_{\substack{k\neq i\\ k>j}}^{N} I_{ijk}
\end{aligned} \tag{23}$$

Here $I_i^{(m)}$ denotes the sum of all mth order mutual information terms involving atom i, and we note that individual mutual information terms are not changed by permuting their indices; e.g., $I_{ijk} = I_{ikj}$. The alternation of signs of successive mutual information contributions merely reflects the sign convention used in defining these terms. Finally, we obtain a decomposition of the full entropy by combining Equations 17 and 23:

$$\begin{aligned}
S &= \sum_{i=1}^{N} S_i \\
S_i &= S_{c,i} + S_{nc,i}
\end{aligned} \tag{24}$$

Note that $S_{nc,i}$ is perhaps best regarded as a contribution to the one-body entropy, because it is unaffected by statistical dependencies among atoms, so

$$S_i^{(1)} = S_{c,i}^{(1)} + S_{nc,i}^{(1)} \tag{25}$$

As done in prior work on entropy expansions [32, 34], we now check whether this formulation gives the correct entropy for an ideal gas of indistinguishable atoms in the absence of an external field. In this case, all mutual information terms are identically zero, because the atomic PDFs are statistically independent so, for example, $p(\mathbf{r}_i, \mathbf{r}_j) = p(\mathbf{r}_i)p(\mathbf{r}_j)$, and we are left with the following expression for the entropy of the ideal gas:

$$S_{ig} = S_{nc} - Nk_B \int p(\mathbf{r}_i) \ln p(\mathbf{r}_i) d\mathbf{r}_i \tag{26}$$

Due to the absence of an external field, $p(\mathbf{r}_i) = \frac{1}{V}$, and the fact that all atoms are indistinguishable means that $\Lambda_i = \Lambda_j = \Lambda$ for all i, j, and that $N_{perm} = N!$, so

$$S_{ig} = Nk_B \left(\frac{3}{2} + \ln \frac{V}{\Lambda^3}\right) - k_B \ln N! \tag{27}$$

which is the correct result for finite N. Finally, taking the limit of large N via Stirling's approximation, which says that $\lim_{N\to\infty} \ln N! = N \ln N - N$, we obtain:

$$\begin{aligned}
\lim_{N\to\infty} S_{ig} &= Nk_B\left(\frac{3}{2} + \ln\frac{V}{\Lambda^3}\right) - (Nk_B \ln N - Nk_B) \\
&= Nk_B\left(\frac{5}{2} + \ln\frac{V}{N\Lambda^3}\right) \qquad (28)
\end{aligned}$$

which is, as hoped, the Sackur-Tetrode equation.

2.4.2 Spatial Mapping of the Entropy Density

Just as we were interested in a spatial mapping of the potential energy density (Section 2.3.2), so we are interested in a spatial mapping of the entropy density. The entropy density has two parts, configurational and non-configurational:

$$S(\mathbf{R}) = S_c(\mathbf{R}) + S_{nc}(\mathbf{R}) \qquad (29)$$

where

$$\begin{aligned}
S_{nc}(\mathbf{R}) &= \sum_{i=1}^{N} S_{nc,i}(\mathbf{R}) \\
S_{nc,i}(\mathbf{R}) &= \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i) S_{nc,i}\, d\mathbf{r}_i \qquad (30)
\end{aligned}$$

and $S_{nc,i}$ is given by Equation 18.

The configurational entropy density as a function of position, $S_c(\mathbf{R})$, is constructed as follows for terms to second order:

$$\begin{aligned}
S_c(\mathbf{R}) &= \sum_{i=1}^{N} S_{c,i}(\mathbf{R}) \\
S_{c,i}(\mathbf{R}) &= S_{c,i}^{(1)}(\mathbf{R}) - I_i^{(2)}(\mathbf{R}) + \ldots \\
S_{c,i}^{(1)}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i) \ln p(\mathbf{r}_i) d\mathbf{r}_i \\
I_i^{(2)}(\mathbf{R}) &= \frac{1}{2} \sum_{j\neq i}^{N} I_{\bar{i}j}(\mathbf{R}) \\
I_{\bar{i}j}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i, \mathbf{r}_j) \ln \frac{p(\mathbf{r}_i)p(\mathbf{r}_j)}{p(\mathbf{r}_i, \mathbf{r}_j)} d\mathbf{r}_i d\mathbf{r}_j \\
&= -k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i, \mathbf{r}_j) \Big[\ln p(\mathbf{r}_i) + \ln p(\mathbf{r}_j) - \ln p(\mathbf{r}_i, \mathbf{r}_j)\Big] d\mathbf{r}_i d\mathbf{r}_j \\
&= -k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i) \ln p(\mathbf{r}_i) d\mathbf{r}_i \\
&- k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i, \mathbf{r}_j) \ln p(\mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \\
&+ k_B \int \delta(\mathbf{R} - \mathbf{r}_i) p(\mathbf{r}_i, \mathbf{r}_j) \ln p(\mathbf{r}_i, \mathbf{r}_j) d\mathbf{r}_i d\mathbf{r}_j \qquad (31)
\end{aligned}$$

Here, the overline on i in $I_{\bar{i}j}(\mathbf{R})$ indicates that this is the atom where the ij mutual information is considered to be localized; we have, again, used delta functions to pick out the contribution of atom i at location $\mathbf{R}$ as detailed in Section 2.2; and we have made use of the fact that

$$\int p(r,r')\ln p(r)dr' = \ln p(r)\int p(r,r')dr' = p(r)\ln p(r) \tag{32}$$

The second term in the final expression may be interpreted by writing

$$\delta(\mathbf{R}-\mathbf{r}_i)p(\mathbf{r}_i,\mathbf{r}_j)\ln p(\mathbf{r}_j) = \delta(\mathbf{R}-\mathbf{r}_i)p(\mathbf{r}_i|\mathbf{r}_j)p(\mathbf{r}_j)\ln p(\mathbf{r}_j) \tag{33}$$

Thus, we are integrating the entropy contribution of atom j at $\mathbf{r}_j$, weighted by the probability of finding atom i at $\mathbf{r}_i$ given that j is at $\mathbf{r}_j$.

The integral of $I_{\bar{i}j}(\mathbf{R})$ over space gives the total mutual information between atoms i and j; i.e.,

$$\int I_{\bar{i}j}(\mathbf{R})\,d\mathbf{R} = I_{ij} \tag{34}$$

because, for any function $f(\mathbf{r})$,

$$\int\left[\int \delta(\mathbf{R}-\mathbf{r})f(\mathbf{r})d\mathbf{r}\right]d\mathbf{R} = \int f(\mathbf{r})d\mathbf{r} \tag{35}$$

The factor of $\frac{1}{2}$ in Equation 31 prevents double-counting of the ij mutual information densities associated with atoms i and j.

2.5 Mapping the Helmholtz and Gibbs Free Energies

We can now write the Helmholtz free energy, A as the sum of the Helmholtz free energies of atoms i,

$$\begin{aligned} A &= \sum_{i=1}^{N} A_i \\ A_i &= U_i - TS_i \end{aligned} \tag{36}$$

or as the integral of the Helmholtz free energy density as a function of position,

$$\begin{aligned} A &= \int A(\mathbf{R})d\mathbf{R} \\ A(\mathbf{R}) &= U(\mathbf{R}) - TS(\mathbf{R}) \end{aligned} \tag{37}$$

The Gibbs free energy differs from the Helmholtz free energy by addition of PV, the product of the system pressure and volume. This quantity may be mapped to individual atoms by using the virial expression for the pressure [35, 36]:

$$PV = Nk_BT + \frac{1}{3}\langle \mathcal{W}(\mathbf{r}^N)\rangle \tag{38}$$

where:

$$\mathcal{W}(\mathbf{r}^N) = \frac{1}{2}\sum_{i=1}^{N}\sum_{j\neq i}^{N}\mathbf{r}_{ij}\cdot\mathbf{f}_{ij}(\mathbf{r}^N)$$
$$\langle\mathcal{W}(\mathbf{r}^N)\rangle = \int \mathcal{W}(\mathbf{r}^N)p(\mathbf{r}^N)d\mathbf{r}^N \tag{39}$$

where $\mathbf{r}_{ij}$ is the vector from atom j to atom i, and $\mathbf{f}_{ij}(\mathbf{r}^N)$ is the central force on atom i due to the presence of atom j, with the understanding that a potential function with 3-body or higher order terms must be re-expressed in terms of central forces in order for this expression to be applied [37]. Note that $\mathbf{r}_{ij}$ is a function of $\mathbf{r}^N$, although we have not written this explicitly.

We now decompose the virial on an atomic basis as

$$\mathcal{W}_i(\mathbf{r}^N) = \frac{1}{2}\sum_{j\neq i}^{N}\mathbf{r}_{ij}\cdot\mathbf{f}_{ij}(\mathbf{r}^N) \tag{40}$$

so that $\mathcal{W}(\mathbf{r}^N) = \sum_i^N \mathcal{W}_i(\mathbf{r}^N)$ We can now decompose PV across atoms i as

$$(PV)_i = k_BT + \frac{1}{3}\langle\mathcal{W}_i\rangle \tag{41}$$

and accordingly write the atomic decomposition of the Gibbs free energy as

$$G = \sum_{i=1}^{N} G_i$$
$$G_i = A_i + k_BT + \frac{1}{3}\langle\mathcal{W}_i\rangle \tag{42}$$

The corresponding spatial decomposition is

$$G(\mathbf{R}) = A(\mathbf{R}) + \rho(\mathbf{R})k_BT + \frac{1}{3}\langle\mathcal{W}(\mathbf{R})\rangle$$
$$\langle\mathcal{W}(\mathbf{R})\rangle = \sum_{i=1}^{N}\int \delta(\mathbf{R}-\mathbf{r}_i)p(\mathbf{r}^N)\mathcal{W}_i(\mathbf{r}^N)d\mathbf{r}^N \tag{43}$$

where $\rho(\mathbf{R})$ is the number density of atoms at $\mathbf{R}$.

2.6 Mapping Energy and Entropy by Chemical Components

We have so far focused on atom-based mappings. In contrast, IST groups the atoms of each rigid solvent molecule into a single component, whose coordinates are fully defined by the location and orientation of the molecule. This approach has advantages over the atomistic treatment because it automatically accounts for strong, intramolecular correlations (due in the case of IST to the molecule's rigidity) instead of pushing the effects of these correlations into pairwise and higher order interatomic terms in the MIE, which can be difficult to evaluate. We expect there will also be value in assigning energy and entropy to other type of chemical components, such as to each of the amino acid residues that make up a protein, or to each molecule in a molecular crystal. Here, therefore, we develop thermodynamic decompositions in terms of chemical components, where in general a component may be a single atom or a collection of atoms.

We index chemical components with subscripts $a, b, c\ldots$, the number of components is N_{comp}, and the number of atoms in component a is N_a. Every atom in the system belongs to one and only one component, and a given component may have only one atom. The location of component a, $\mathbf{r}_a(\mathbf{r}^N) = (x_a, y_a, z_a)$, may be defined, for example, as the coordinates of component a's center of mass or the coordinates of a particular atom in component a. (We have taken the liberty of overloading the symbol $\mathbf{r}$, as well as other symbols below, to avoid the need for yet additional symbols) The full coordinates of component a are $(\mathbf{r}_a, \mathbf{q}_a)$, where $\mathbf{q}_a$ represents its orientational and internal coordinates. If a has N_a atoms, then $\mathbf{q}_a$ has dimensionality $3N_a - 3$.

2.6.1 Mapping Potential Energy by Chemical Components

The mean potential energy of component a may now be defined as the sum of the mean potential energies of its atoms:

$$U_a = \sum_{i \in a}^{N_a} U_i \tag{44}$$

where U_i is defined in Equation 9, and the summation is over atoms i belonging to component a. Because the components are non-overlapping, $U = \sum_{a=1}^{N_{comp}} U_a$.

The potential energy density, in terms of components, is

$$U(\mathbf{R}) = \sum_{a=1}^{N_{comp}} U_a(\mathbf{R}) \tag{45}$$

where the contribution of component a to the spatial energy density at $\mathbf{R}$ is

$$U_a(\mathbf{R}) = \int \left[\delta(\mathbf{R} - \mathbf{r}_a(\mathbf{r}^N))\, p(\mathbf{r}^N) \sum_{i \in a}^{N_a} U_i(\mathbf{r}^N) \right] d\mathbf{r}^N \tag{46}$$

2.6.2 Mapping Entropy by Chemical Components

The entropy of component a is given by the sum of its nonconfigurational and configurational components:

$$S_a = S_{nc,a} + S_{c,a} \tag{47}$$

and the entropy density in terms of components is given by the corresponding terms:

$$S(\mathbf{R}) = S_{nc}(\mathbf{R}) + S_c(\mathbf{R}) \tag{48}$$

Note that this $S(\mathbf{R})$ is, in general, different from that provided by the purely atomistic decomposition.

The nonconfigurational part of the entropy of chemical component a is written simply as:

$$S_{nc,a} = \sum_{i \in a}^{N_a} S_{nc,i} \tag{49}$$

where $S_{nc,i}$ is defined in Eq 17, and the spatial density of the nonconfigurational entropy is

$$\begin{aligned} S_{nc}(\mathbf{R}) &= \sum_{a=1}^{N_{comp}} S_{nc,a}(\mathbf{R}) \\ S_{nc,a}(\mathbf{R}) &= \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a) S_{nc,a}\, d\mathbf{r}_a \end{aligned} \tag{50}$$

where $p(\mathbf{r}_a)$ is the PDF of the location of component a.

We now develop the configurational part of the entropy of chemical component a. To do this, we consider the distributions over $\mathbf{q}_a$ to be conditional on $\mathbf{r}_a$: $p(\mathbf{r}_a, \mathbf{q}_a) = p(\mathbf{q}_a|\mathbf{r}_a)p(\mathbf{r}_a)$, just as prior work considers the orientational distribution of a rigid solvent molecule to be conditional on the molecule's position [26, 38]. By analogy with the atomistic entropy mappings in Sections 2.4.1 and 2.4.2, we write the first order configurational entropy contribution of component a as

$$\begin{aligned} S_{c,a}^{(1)} &= -k_B \int p(\mathbf{q}_a|\mathbf{r}_a)p(\mathbf{r}_a) \ln\left[p(\mathbf{q}_a|\mathbf{r}_a) + \ln p(\mathbf{r}_a)\right] d\mathbf{r}_a d\mathbf{q}_a \\ &= -k_B \int p(\mathbf{r}_a) \ln p(\mathbf{r}_a) d\mathbf{r}_a + \int p(\mathbf{r}_a) S_a^q(\mathbf{r}_a) d\mathbf{r}_a \\ S_a^q(\mathbf{r}_a) &= -k_B \int p(\mathbf{q}_a|\mathbf{r}_a) \ln p(\mathbf{q}_a|\mathbf{r}_a) d\mathbf{q}_a \end{aligned} \tag{51}$$

and the contribution of a to the first order entropy density at $\mathbf{R}$ is again picked out with a delta function at $\mathbf{r}_a$:

$$S_{c,a}^{(1)}(\mathbf{R}) = -k_B \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a) \ln p(\mathbf{r}_a) d\mathbf{r}_a + \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a) S_a^q(\mathbf{r}_a) d\mathbf{r}_a \tag{52}$$

The first term on the right is the first-order translational entropy density of component a, and the second term is the probability-weighted orientational+internal entropy of a as a function of location.

Summing over components then gives the total first order estimate of the configurational entropy density:

$$S_c^{(1)}(\mathbf{R}) = \sum_{a=1}^{N_{comp}} S_{c,a}^{(1)}(\mathbf{R}) \tag{53}$$

The second-order estimate of the configurational entropy of component a is

$$S_{c,a}^{(2)} = S_{c,a}^{(1)} - \frac{1}{2} \sum_{b \neq a}^{N_{comp}} I_{ab} \tag{54}$$

where I_{ab}, the mutual information between components a and b, may be written as

$$\begin{aligned}
I_{ab} &= S_{c,a}^{(1)} + S_{c,b}^{(1)} + k_B \int p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) \ln p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= S_{c,a}^{(1)} + S_{c,b}^{(1)} + k_B \int p(\mathbf{q}_a, \mathbf{q}_b | \mathbf{r}_a, \mathbf{r}_b) p(\mathbf{r}_a, \mathbf{r}_b) \big[\ln p(\mathbf{q}_a, \mathbf{q}_b | \mathbf{r}_a, \mathbf{r}_b) + \ln p(\mathbf{r}_a, \mathbf{r}_b)\big] d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= S_{c,a}^{(1)} + S_{c,b}^{(1)} + k_B \int p(\mathbf{r}_a, \mathbf{r}_b) \ln p(\mathbf{r}_a, \mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b - \int p(\mathbf{r}_a, \mathbf{r}_b) S_{ab}^q(\mathbf{r}_a, \mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b \\
S_{ab}^q(\mathbf{r}_a, \mathbf{r}_b) &= -k_B \int p(\mathbf{q}_a, \mathbf{q}_b | \mathbf{r}_a, \mathbf{r}_b) \ln p(\mathbf{q}_a, \mathbf{q}_b | \mathbf{r}_a, \mathbf{r}_b) d\mathbf{q}_a d\mathbf{q}_b \qquad (55)
\end{aligned}$$

Here $S_{ab}^q(\mathbf{r}_a, \mathbf{r}_b)$ is the joint entropy of the internal and orientational coordinates, $\mathbf{q}_a$ and $\mathbf{q}_b$, of components a and b conditioned on these components being located at $\mathbf{r}_a$ and $\mathbf{r}_b$.

To write the second order component-based entropy density, we need an expression for the component-based pairwise mutual information density. This involves three terms: a standard one-body entropy density for component a; a "cross-entropy" term that maps the first order entropy of component b to the location of a; and a joint entropy term, also mapped to the location of a. Thus,

$$\begin{aligned}
S_c^{(2)}(\mathbf{R}) &= S_c^{(1)}(\mathbf{R}) - \sum_{a=1}^{N_{comp}} I_a^{(2)}(\mathbf{R}) \\
I_a^{(2)}(\mathbf{R}) &= \frac{1}{2} \sum_{b \neq a}^{N_{comp}} I_{\overline{a}b}(\mathbf{R}) \qquad (56)
\end{aligned}$$

where $I_{\overline{a}b}(\mathbf{R})$ is the mutual information density for component a located at $\mathbf{R}$:

$$\begin{aligned}
I_{\overline{a}b}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) \Big[\ln p(\mathbf{r}_a, \mathbf{q}_a) + \ln p(\mathbf{r}_b, \mathbf{q}_b) \\
&\quad - \ln p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b)\Big] d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= S_{c,a}^{(1)}(\mathbf{R}) \\
&\quad - k_B \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) \ln p(\mathbf{r}_b, \mathbf{q}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&\quad + k_B \int \delta(\mathbf{R} - \mathbf{r}_a) p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) \ln p(\mathbf{r}_a, \mathbf{q}_a, \mathbf{r}_b, \mathbf{q}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= S_{c,a}^{(1)}(\mathbf{R}) + T_2(\mathbf{R}) - T_3(\mathbf{R}) \qquad (57)
\end{aligned}$$

We thus have three terms, one of which, $S_{c,a}^{(1)}(\mathbf{R})$, has already been developed and two others which may be developed as follows. We have, first:

$$\begin{aligned}
T_2(\mathbf{R}) &= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{q}_a,\mathbf{r}_b,\mathbf{q}_b) \ln p(\mathbf{r}_b,\mathbf{q}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) p(\mathbf{r}_a,\mathbf{r}_b) \left[\ln p(\mathbf{r}_b) + \ln p(\mathbf{q}_b|\mathbf{r}_b)\right] d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&- k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{q}_b|\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) S_{ab}^{cross}(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b \\
S_{ab}^{cross}(\mathbf{r}_a,\mathbf{r}_b) &= -k_B \int p(\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{q}_b|\mathbf{r}_b) d\mathbf{q}_b \qquad (58)
\end{aligned}$$

Here, $S_{ab}^{cross}(\mathbf{r}_a,\mathbf{r}_b)$ is the internal and orientational entropy of component b when components a and b are at $\mathbf{r}_a$ and $\mathbf{r}_b$, respectively, and we have used the fact that

$$\int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{q}_b|\mathbf{r}_b) d\mathbf{q}_a = \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{q}_b|\mathbf{r}_b) \qquad (59)$$

For the third term, we write:

$$\begin{aligned}
T_3(\mathbf{R}) &= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{q}_a,\mathbf{r}_b,\mathbf{q}_b) \ln p(\mathbf{r}_a,\mathbf{q}_a,\mathbf{r}_b,\mathbf{q}_b) d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) p(\mathbf{r}_a,\mathbf{r}_b) \left[\ln p(\mathbf{r}_a,\mathbf{r}_b) + \ln p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b)\right] d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) S_{ab}^{q}(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b \\
S_{ab}^{q}(\mathbf{r}_a,\mathbf{r}_b) &= -k_B \int p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) d\mathbf{q}_a d\mathbf{q}_b \qquad (60)
\end{aligned}$$

Here, $S_{ab}^{q}(\mathbf{r}_a,\mathbf{r}_b)$ is the joint internal and orientational entropy of components a and b when components a and b are at $\mathbf{r}_a$ and $\mathbf{r}_b$, respectively.

The total mutual information density associated with component a at $\mathbf{R}$ thus may be written as

$$\begin{aligned}
I_{\overline{a}b}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a) \ln p(\mathbf{r}_a) d\mathbf{r}_a + \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a) S_a^q(\mathbf{r}_a) d\mathbf{r}_a \\
&- k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) S_{ab}^{cross}(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b \\
&- k_B \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) \ln p(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_a) p(\mathbf{r}_a,\mathbf{r}_b) S_{ab}^{q}(\mathbf{r}_a,\mathbf{r}_b) d\mathbf{r}_a d\mathbf{r}_b
\end{aligned} \qquad (61)$$

Comparison with the corresponding atomistic mutual information density shows that the first term in each line of Equation 61 has the same form as a corresponding line at the end of Equation 31, with $\mathbf{r}_a$ and $\mathbf{r}_b$ substituted for i, and j, respectively. These three terms define the translational mutual information density associated with component a, while the second term in each line of Equation 61 is a probability-weighted contribution from the internal+orientational coordinates of components a and b.

Just as for the atomistic entropy density in Eq 31, and for the same mathematical reason, the spatial integral of this mutual information density recovers the total mutual information between components a and b; i.e.,

$$\int I_{\overline{a}b}(\mathbf{R})\,d\mathbf{R} = I_{ab} \tag{62}$$

The present approach to defining the mutual information aligns with the treatment in IST (Section 3), but it is rather complex. The Appendix provides a simpler alternative formulation that may be of interest.

3 Relationship of GTMT to IST

IST and its theoretical antecedents have been enormously productive, providing practical computational tools for drug design and contributing to the conceptual foundation on which the present work builds. It is thus of particular interest to analyze how GTMT relates to IST. Because IST was derived for the special case of a solvent composed of N identical molecules interacting with a pair potential, we compare GTMT with IST in this simplified, yet still informative, setting, and we further simplify by making the solvent monatomic and by considering entropy terms to only second order. The first appearance of an IST free energy density seems to be Eq 41 of a 2003 paper by Lazaridis and Karplus [31]; this was obtained by simply omitting the integrations over $\mathbf{r}'$ from the corresponding equations for solvation energy and entropy (see their Eqs 35-38). An apparently equivalent formulation can also be inferred from a 2006 paper [39]; see local integrals in their Equations 9 and 10 and the sum in their Equation 20.

3.1 Relationship to Energy Density in IST

For the case of interest, our first order instantaneous energy term, $u_i(\mathbf{r}_i)$, corresponds to IST's $u_{sw}(\mathbf{r})$, while our $u_{ij}(\mathbf{r}_i, \mathbf{r}_j)$ corresponds to IST's $u_{ww}(\mathbf{r}, \mathbf{r}')$. Here, as prefigured in Section 2.2, we adopt the notation of IST by moving away from the use of delta functions to map from atomic positions to coordinates of the density fields and instead allow $\mathbf{r}$ to represent both an atomic position in a PDF and the argument of a potential energy or entropy density, while $\mathbf{r}'$ is the position of a second atom in a PDF. Thus,

$$\begin{aligned}
U(\mathbf{r}) &= NU_i(\mathbf{r}) \\
U_i(\mathbf{r}) &= p(\mathbf{r})u_{sw}(\mathbf{r}) + \frac{1}{2}(N-1)\int p(\mathbf{r}, \mathbf{r}')u_{ww}(\mathbf{r}, \mathbf{r}')d\mathbf{r}' \\
U(\mathbf{r}) &= \rho(\mathbf{r})u_{sw}(\mathbf{r}) + \frac{1}{2}\int \rho(\mathbf{r}, \mathbf{r}')u_{ww}(\mathbf{r}, \mathbf{r}')d\mathbf{r}'
\end{aligned} \tag{63}$$

where i is the index of any solvent atom, all being equivalent, $\rho(\mathbf{r})$ is the number density of solvent at $\mathbf{r}$, $\rho(\mathbf{r}, \mathbf{r}')$ is the density of solvent pairs across locations $\mathbf{r}$ and $\mathbf{r}'$, and we have used the facts that $\rho(\mathbf{r}) = Np(\mathbf{r})$ and $\rho(\mathbf{r}, \mathbf{r}') = N(N-1)p(\mathbf{r}, \mathbf{r}')$. The corresponding IST expression from Lazaridis and Karplus is:

$$U(\mathbf{r}) = \rho g(\mathbf{r}) u_{sw}(\mathbf{r}) + \frac{1}{2}\rho^2 g(\mathbf{r}) \int g(\mathbf{r}') g(\mathbf{r}, \mathbf{r}') u_{ww}(\mathbf{r}, \mathbf{r}') d\mathbf{r}' \tag{64}$$

where we have omitted the subtraction of the pure solvent energy, because we are interested in the mean potential energy, rather than the solvation energy. Here, as stated immediately below their Eq 38, $\rho = \frac{N}{V}$ is the solvent number density, $\rho g(\mathbf{r}) = \rho(\mathbf{r})$, and $g(\mathbf{r}, \mathbf{r}') = \frac{\rho(\mathbf{r}, \mathbf{r}')}{\rho(\mathbf{r})\rho(\mathbf{r}')}$. It is readily verified that this IST expression is identical to the GTMT one in Equation 63.

3.2 Relationship to Entropy Density in IST

We now compare the entropy density expressions provided by GTMT with those of IST. In order to elucidate the relationship between the treatments of entropy in GTMT and IST, we consider not only the entropy density for a general monatomic fluid (Section 3.2.2) but also the total entropy in the ideal gas limit (Section 3.2.3), where the atomic distributions become statistically independent of each other.

Some expectations for the outcome of this comparison may be set by noting that GTMT is composed of entropy density contributions having the general form $S(r) = -k_B \rho(r) \ln p(r)$, where $\rho(r)$ is the number density, and $p(r)$ is a PDF and hence is normalized to 1, as expected for the standard Gibbs-Shannon entropy [33]; whereas IST expresses the entropy in an analogous series expansion, but its terms have the general form $S'(r) = -k_B \rho(r) \ln g(r)$, where $g(r)$ is proportional to $p(r)$ but is not normalized to unity. As a consequence, the IST expressions generate extraneous terms: if the constant of proportionality is a, we have $g(r) = ap(r)$, so $S'(r) = S(r) - k_B \rho(r) \ln a$. For example, as detailed below, the first order IST entropy density is $-k_B \rho(\mathbf{r}) \ln g(\mathbf{r}) = -k_B \rho(\mathbf{r})[\ln p(\mathbf{r}) - \ln V]$, rather than $-k_B \rho(\mathbf{r}) \ln p(\mathbf{r})$. These extra $\ln a$ terms lead to complications not encountered in GTMT.

3.2.1 Second Order GTMT Entropy Density for Monatomic Solvent

We start with the GTMT configurational entropy density (Section 2.4), rewritten, for the sake of comparison with IST, by using $\mathbf{r}$ both for the location of an atom and for the location where the density is to be determined, and using $\mathbf{r}'$ for the position of a second, indistinguishable, atom. We also dispense with the delta function formulation, again in keeping with the notation of IST, and use the facts that all Λ_i are the same and so may be substituted by Λ; and that all N atoms are indistinguishable so the summations over atoms may be replaced by simple factors of N. Making the second order approximation, we have:

$$
\begin{aligned}
S(\mathbf{r}) &\approx S_c^{(2)}(\mathbf{r}) + S_{nc}(\mathbf{r}) \\
S_c^{(2)}(\mathbf{r}) &= S_c^{(1)}(\mathbf{r}) - I^{(2)}(\mathbf{r}) \\
S_c^{(1)}(\mathbf{r}) &= -k_B N p(\mathbf{r}) \ln p(\mathbf{r}) \\
I^{(2)}(\mathbf{r}) &= -\frac{k_B\, N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \big[\ln p(\mathbf{r}) + \ln p(\mathbf{r}') - \ln p(\mathbf{r},\mathbf{r}')\big] d\mathbf{r}' \\
S_{nc}(\mathbf{r}) &= N k_B \left[\frac{3}{2} - \ln \Lambda^3 - \frac{\ln N!}{N}\right] p(\mathbf{r})
\end{aligned}
\tag{65}
$$

We have used the facts that all $\Lambda_i = \Lambda$ are the same, $N_{perm} = N!$, and $p(\mathbf{r}) = \frac{1}{V}$, but we have not taken the limit of large N.

3.2.2 Second Order IST Entropy Density for a Monatomic Solvent

The original papers leading to and defining IST [32, 34, 38] provide the *total* entropy of the system but not the entropy *density*; it is the last three lines of Eq 41 of Lazaridis and Karplus 2003 [31] that appear to be the most explicit original definition of the second order solvation entropy density in IST. This particular expression also is helpfully simplified because it omits any orientational or conformational entropy contributions, so the entropic contribution to the free energy is interpretable as the solvation entropy density of a monatomic fluid around a rigid solute. In using this expression, we do not subtract the pure solvent entropy because we are interested in the absolute entropy, not the solvation entropy. Note, too, that the entropy densities provided for IST omit the non-configurational entropy contribution, but IST expressions for total entropy [24, 38] do include this contribution, as further detailed in the subsections below.

Making the required adjustments and re-rendering the equation in terms that better match our notation, we obtain:

$$
\begin{aligned}
S_{IST}^{(1)}(\mathbf{r}) &= -k_B \rho g(\mathbf{r}) \ln g(\mathbf{r}) \\
S_{IST}^{(2)}(\mathbf{r}) &= S_{IST}^{(1)}(\mathbf{r}) - I_{IST}^{(2)}(\mathbf{r}) \\
\\
I_{IST}^{(2)}(\mathbf{r}) &= \frac{1}{2} k_B \rho^2 g(\mathbf{r}) \int g(\mathbf{r}') \left[g(\mathbf{r},\mathbf{r}') \ln g(\mathbf{r},\mathbf{r}') - g(\mathbf{r},\mathbf{r}') + 1\right] d\mathbf{r}' \\
&= I_{IST,1}^{(2)}(\mathbf{r}) + I_{IST,2}^{(2)}(\mathbf{r}) \\
\\
I_{IST,1}^{(2)}(\mathbf{r}) &= \frac{1}{2} k_B \rho^2 g(\mathbf{r}) \int g(\mathbf{r}') g(\mathbf{r},\mathbf{r}') \ln g(\mathbf{r},\mathbf{r}') d\mathbf{r}' \\
I_{IST,2}^{(2)}(\mathbf{r}) &= -\frac{1}{2} k_B \rho^2 g(\mathbf{r}) \int g(\mathbf{r}') \left[g(\mathbf{r},\mathbf{r}') - 1\right] d\mathbf{r}'
\end{aligned}
\tag{66}
$$

We have broken $I_{IST}^{(2)}(\mathbf{r})$ into two parts, $I_{IST,1}^{(2)}(\mathbf{r})$ and $I_{IST,2}^{(2)}(\mathbf{r})$, for separate analysis. Note, too, that the IST expressions for entropy density omit the non-configurational entropy, S_{nc}, as further discussed below. We now rewrite these expressions in term of PDFs, to enable direct comparison with the corresponding expressions from GTMT, above, by using the identities provided immediately following Equation 64, above. The first order term gives

$$S^{(1)}_{IST}(\mathbf{r}) = -k_B N p(\mathbf{r}) \ln p(\mathbf{r}) - k_B N p(\mathbf{r}) \ln V \tag{67}$$

The second term here corresponds to the $\ln a$ term mentioned in the second paragraph of Section 3.2.

We consider the two parts of the second order term separately: The first integral in the second order term gives:

$$\begin{aligned}
I^{(2)}_{IST,1}(\mathbf{r}) &= \frac{1}{2} k_B \rho(\mathbf{r}) \int \rho(\mathbf{r}') \frac{\rho(\mathbf{r},\mathbf{r}')}{\rho(\mathbf{r})\rho(\mathbf{r}')} \ln \frac{\rho(\mathbf{r},\mathbf{r}')}{\rho(\mathbf{r})\rho(\mathbf{r}')} d\mathbf{r}' \\
&= \frac{1}{2} k_B \int \rho(\mathbf{r},\mathbf{r}') \ln \frac{\rho(\mathbf{r},\mathbf{r}')}{\rho(\mathbf{r})\rho(\mathbf{r}')} d\mathbf{r}' \\
&= \frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \ln \frac{(N-1)p(\mathbf{r},\mathbf{r}')}{N p(\mathbf{r}) p(\mathbf{r}')} d\mathbf{r}' \\
&= \frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}') + \ln \frac{N-1}{N} \right] d\mathbf{r}' \\
&= \frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}') \right] d\mathbf{r}' \\
&+ \frac{k_B N(N-1)}{2} p(\mathbf{r}) \ln \frac{N-1}{N}
\end{aligned} \tag{68}$$

Thus, we have an initial term identical to $I^{(2)}(\mathbf{r})$ from GTMT (see Equation 64) and an additional term resulting in part from the fact that $\rho(\mathbf{r},\mathbf{r}')$ is not normalized. The second integral in the second order term gives:

$$\begin{aligned}
I^{(2)}_{IST,2}(\mathbf{r}) &= -\frac{k_B}{2} \int \left[\rho(\mathbf{r},\mathbf{r}') - \rho(\mathbf{r})\rho(\mathbf{r}') \right] d\mathbf{r}' \\
&= -\frac{k_B}{2} \left[N(N-1) p(\mathbf{r}) - N^2 p(\mathbf{r}) \right] \\
&= \frac{N k_B}{2} p(\mathbf{r})
\end{aligned} \tag{69}$$

Assembling the results gives the second order term in IST,

$$\begin{aligned}
I^{(2)}_{IST}(\mathbf{r}) &= I^{(2)}_{IST,1}(\mathbf{r}) + I^{(2)}_{IST,2}(\mathbf{r}) \\
&= \frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}') \right] d\mathbf{r}' \\
&+ \frac{k_B N(N-1)}{2} p(\mathbf{r}) \ln \frac{N-1}{N} + \frac{N k_B}{2} p(\mathbf{r})
\end{aligned} \tag{70}$$

and the IST estimate of the entropy density to second order is:

$$\begin{aligned}
S^{(2)}_{IST}(\mathbf{r}) &= S^{(1)}_{IST}(\mathbf{r}) - I^{(2)}_{IST,1}(\mathbf{r}) - I^{(2)}_{IST,2}(\mathbf{r}) \\
&= -k_B N p(\mathbf{r}) \ln p(\mathbf{r}) - k_B N p(\mathbf{r}) \ln V \\
&- \frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}')\right] d\mathbf{r}' \\
&- \frac{k_B N p(\mathbf{r})}{2} \left[(N-1) \ln \frac{N-1}{N} + 1\right]
\end{aligned} \tag{71}$$

We are now in a position to compare the full second-order entropy estimate from GTMT, $S^{(2)}(\mathbf{r})$ in Eq 65, with the corresponding IST quantity, $S^{(2)}_{IST}(\mathbf{r})$ in Eq 71:

$$S^{(2)}_{IST}(\mathbf{r}) = S^{(2)}(\mathbf{r}) + D_1(\mathbf{r}) + D_2(\mathbf{r})$$

$$\begin{aligned}
D_1(\mathbf{r}) &= -k_B \rho(\mathbf{r}) \ln V - S_{nc}(\mathbf{r}) \\
D_2(\mathbf{r}) &= -\frac{k_B N p(\mathbf{r})}{2} \left[(N-1) \ln \frac{N-1}{N} + 1\right]
\end{aligned} \tag{72}$$

where we have kept the extra first-order term, $D_1(\mathbf{r})$, separate from the extra second order term, $D_2(\mathbf{r})$. For convenience, Table 2 provides direct comparisons of the first- and second-order entropy densities provided by GTMT, and by IST in terms of correlation functions and of PDFs. If we set aside $S_{nc}(\mathbf{r})$, which seems to have been deliberately excluded from the IST density, we are left with a difference between first-order IST and GTMT of $D'_1(\mathbf{r}) = -k_B \rho(\mathbf{r}) \ln V$. As noted above, the deviations of IST from GTMT, $D'_1(\mathbf{r})$ and $D_2(\mathbf{r})$, derive in part from the $\ln a$ terms mentioned in the second paragraph of Section 3.2.

The additional IST terms do not have an obvious physical interpretation, and as we show below, they prevent the second- and higher-order terms from vanishing for an ideal gas, despite the absence of particle-particle correlations in this setting. By contrast, entropy terms above first order vanish identically for GTMT, as they should. Differences between IST and GTMT are explored further in Section 3.2.3.

3.2.3 Comparing GTMT with IST for an Ideal Gas

Here we further characterize the differences between IST and GTMT for the case of an ideal gas of identical atoms, as done before in a similar setting [34]. Because there is no solute, and hence no solute reference frame, the coordinates here are referenced to a lab frame.

For GTMT at second order, using Eq 65 and the facts that, for the ideal gas, $p(\mathbf{r}) = \frac{1}{V}$ and $p(\mathbf{r},\mathbf{r}') = p(\mathbf{r})p(\mathbf{r}')$, due to the statistical independence of the atomic motions, and we obtain the following entropy density:

$$S^{(2)}(\mathbf{r}) = S^{(1)}(\mathbf{r}) = \frac{3k_B\rho}{2} + k_B\rho \ln \frac{V}{\Lambda^3} - \frac{k_B}{V} \ln N! \tag{73}$$

Integrating over volume to get the system entropy gives

$$S^{(2)} = \frac{3}{2} N k_B + N k_B \ln \frac{V}{\Lambda^3} - k_B \ln N! \tag{74}$$

Theory	**Order**	**Entropy density term**
GTMT	1	$-k_B N p(\mathbf{r}) \ln p(\mathbf{r}) + N k_B \left[\frac{3}{2} - \ln \Lambda^3 - \frac{\ln N!}{N}\right] p(\mathbf{r})$
IST (g)	1	$-k_B \rho g(\mathbf{r}) \ln g(\mathbf{r})$
IST (p)	1	$-k_B N p(\mathbf{r}) \ln p(\mathbf{r}) - k_B N p(\mathbf{r}) \ln V$
GTMT	2	$\frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}')\right]$
IST (g)	2	$\frac{1}{2} k_B \rho^2 g(\mathbf{r}) \int g(\mathbf{r}') \left[g(\mathbf{r},\mathbf{r}') \ln g(\mathbf{r},\mathbf{r}') - g(\mathbf{r},\mathbf{r}') + 1\right] d\mathbf{r}'$
IST (p)	2	$\frac{k_B N(N-1)}{2} \int p(\mathbf{r},\mathbf{r}') \left[\ln p(\mathbf{r},\mathbf{r}') - \ln p(\mathbf{r}) - \ln p(\mathbf{r}')\right] d\mathbf{r}'$ $+ \frac{k_B N p(\mathbf{r})}{2} \left[(N-1) \ln \frac{N-1}{N} + 1\right]$

Table 2: Comparison of the first order contribution (Order 1) and the second order contribution (Order 2) to the pairwise estimate of the entropy density in GTMT, in IST expressed in terms of correlation functions g, and in IST expressed in terms of PDFs p. Note that the first order GTMT expression includes the non-configurational entropy density, $N k_B \left[\frac{3}{2} - \ln \Lambda^3 - \frac{\ln N!}{N}\right] p(\mathbf{r})$, whereas IST includes a non-configurational component only in its expressions for the total entropy of the system, not in its density expressions.

which is the correct expression for finite N. Taking the limit of large N by using Stirling's approximation, $\ln N! \to N \ln N - N$, gives the standard Sackur-Tetrode equation:

$$S^{(2)} = N k_B \left[\frac{5}{2} - \ln(\rho \Lambda^3)\right] \tag{75}$$

Thus, the GTMT entropy density gives the exact ideal gas entropy for both finite and infinite N, consistent with our conclusion for the structural decomposition of entropy in Section 2.4.1. Because mutual information terms above second order also go to zero for the case of the ideal gas, GTMT gives the correct ideal gas entropy for all orders of the MIE.

For IST at second order, two steps are required to obtain the total entropy of an ideal gas. First, we evaluate and integrate $S^{(2)}_{IST}(\mathbf{r})$ over volume, as done for the GTMT expression. Using Equation 71 with $p(\mathbf{r}) = \frac{1}{V}$ and $p(\mathbf{r},\mathbf{r}') = p(\mathbf{r})p(\mathbf{r}')$, we obtain:

$$\begin{aligned} S^{(1)}_{IST}(\mathbf{r}) &= 0 \\ S^{(2)}_{IST}(\mathbf{r}) &= D_2(\mathbf{r}) \\ S^{(2)}_{IST} &= \int S^{(2)}_{IST}(\mathbf{r}) d\mathbf{r} = -\frac{k_B N}{2} \left[(N-1) \ln \frac{N-1}{N} + 1\right] \end{aligned} \tag{76}$$

Second, we add in the non-configurational entropy term provided in IST expressions for the total entropy [24,38], i.e., $N k_B \left[\frac{5}{2} - \ln(\rho \Lambda^3)\right]$, which is recognizable as, precisely, the ideal gas entropy provided by the Sackur-Tetrode equation. Thus, the total ideal gas entropy provided by IST is

$$S^{(2)}_{IST} = N k_B \left[\frac{5}{2} - \ln(\rho \Lambda^3)\right] - \frac{k_B N}{2} \left[(N-1) \ln \frac{N-1}{N} + 1\right] \tag{77}$$

This expression appears to be incorrect not only for finite N, but also in the thermodynamic limit of infinite N, where it is straightforward to show that the second term goes not to zero, but to $-\frac{k_B}{4}$.

4 Discussion

We have described a broadly applicable structural and spatial decompositions of the potential energy, entropy, and free energy, derived from fundamental classical statistical thermodynamics. The resulting expressions satisfy desiderata mentioned in the Introduction and previously [11], namely that the spatial integral of the free energy density over the entire system should give the correct system free energy, that the free energy density should go to zero where the spatial number density of atoms goes to zero, and that all entropy terms above first order should go to zero in the absence of correlation. Our application of the MIE in an integrated fashion across both the solute and the solvent unites our prior work applying the MIE to liquids [11], where it essentially takes the place of IST's entropy expansion, and to proteins [27], where we used it to study changes in configurational entropy on protein-peptide binding [40]. Because of this integration, GTMT is applicable to not only the solvent but also the solute in a solute-solvent system. It should also be applicable to other types of system, including solids and lipid membranes.

In the past, the solvent-only theory IST has been used to gain insight into the role of water in protein-ligand binding and thus guide ligand design, via analysis of molecular simulations with tools such as WaterMap [41], GIST [26, 42] SSTMap [43], and STOW [44]. We anticipate that the present generalized theory will provide further insight into the contributions of various parts of the protein and ligand to their binding free energy and thus enable new tools for structure-based drug design. It may also provide a new window into other phenomena, such as how point-mutations affect protein stability, the thermodynamics of grain boundaries and defects in solids, and how energy flows in allosteric proteins and molecular motors. In particular, as noted in the Introduction, allostery and other binding-induced molecular motions may be associated with a localized rise in free energy around the binding site, followed by a structural relaxation that mediates function.

Given the central role that IST and related theory have played in developing this field, it is useful to define the relationship between GTMT and IST. The GTMT treatment of the potential energy density is similar to that of IST, but is generalized to arbitrary potential functions for flexible molecules. The GTMT treatment of the entropy density writes the entropy in terms of normalized PDFs instead of non-normalized n-particle correlation functions, $g_N^{(n)}$, as done in IST. Using PDFs avoids the generation of extraneous terms which make IST inexact. For example, IST yields nonzero second- and higher-order entropy terms for an ideal gas and thus risks giving the incorrect impression that the particles correlate. In contrast, as shown in Section 3.2.3, GTMT gives the exact ideal gas entropy. Expressing entropy in terms of PDFs also simplifies the application of GTMT for different ensembles, makes GTMT simpler conceptually and mathematically, enables a unified treatment of entropy density for an entire solute-solvent system, and makes the theory more accessible to researchers who are familiar with PDFs but not with correlation functions. Thus, we hope that this formulation will facilitate connections to the large body of literature on the significance and calculation of the Gibbs-Shannon entropy [45–51].

The present treatment of entropy density also differs from that of IST by including the non-configurational component, S_{nc}. It is reasonable that this contribution has largely been omitted in the past [26, 31, 33], because the non-configurational entropy changes only for processes that change T or N. Nonetheless, we include its contribution to both the structural and spatial entropy decompositions of GTMT in order to demonstrate the existence of a rigorous decomposition of the total entropy that is consistent with our desiderata (above), to provide a foundation for applications of GTMT to processes where S_{nc} does change, due to changes in T or composition, and also for use with the grand canonical partition function, which is made up of canonical partition functions with different values of N.

Our atomistic decomposition of the potential energy appears to match that used by Kalayan and coworkers, who recently presented an approach to decomposing energy and entropy for a protein-water system [52]. However, although their multiscale cell correlation entropy method appears to have the merit of rapid numerical convergence, it is not derived from the exact configurational entropy and does not reduce to a known exact result in any well-defined limit. In contrast, the MIE-based entropy in GTMT is an exact mathematical identity whose truncation errors are, in principle, systematically improvable.

We plan to use GTMT to extract structural and spatial thermodynamic mappings from molecular simulation data and to explore biophysical and pharmaceutical applications of the results. Achieving adequate numerical convergence of the potential energy maps is likely to be feasible for simulations with widely used non-polarizable force fields [53–56]. Based on our prior work [27, 57, 58], and given recent advances in GPU hardware, we also anticipate achieving adequate numerical convergence of entropy mappings to second order. Going to third order will be considerably more difficult, but progress may be feasible by pruning the number of triplets that are computed, based e.g., on the pairwise mutual information values within the triplet. (It is also encouraging that IST and GIST have proven useful even when applied only at first order [7,9,41].) Additional methods will be needed to account for both solute and solvent entropy, as IST and GIST have to date typically been applied to rigid models of the solute. One possible approach is to group solute conformations into clusters and analyze the solvent for a representative snapshot from each cluster. It is encouraging that computational methods based on accessible levels of convergence for IST and the MIE have already proven insightful and useful [3,7,40,57,59–61], and we anticipate that the same will be true for the generalized thermodynamic mapping theory laid out here.

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6 Author disclosures

MKG has an equity interest in and is a cofounder and scientific advisor of VeraChem LLC. He is also on the scientific advisory boards of Denovicon Therapeutics, In Cerebro, Cold Start Therapeutics, and Beren Therapeutics.

TK is founder and scientific advisor of Deep Waters NYC, LLC; has an equity interest in and is a scientific advisor for Ventus Therapeutics; has an equity interest in and is a director and scientific advisor for InCerebro Inc.; and is an author on U.S. patents 7,756,674; 7,970,580, 7,970,581.

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7 Appendix

Given the complexity of the spatial mapping of mutual information density by chemical components presented in Section 2.6.2, it may be of interest to consider a simpler alternative definition of this density. This alternative can also be applied to the atomistic mapping developed in Section 2.4.2.

Here, we write the density of the total mutual information between components a and b as

$$I_{ab}(\mathbf{R}) = S^{(1)}_{c,a}(\mathbf{R}) + S^{(1)}_{c,b}(\mathbf{R}) - S_{c,ab}(\mathbf{R}) \tag{78}$$

where we omit the overline on a present in the original formulation, i.e., $I_{\overline{a}b}(\mathbf{R})$, because the present definition treats components a and b symmetrically. Here, the first two terms in Equation 78 take their standard form (Equation 51),

$$\begin{aligned}
S^{(1)}_{c,a}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a)p(\mathbf{r}_a)\ln p(\mathbf{r}_a)d\mathbf{r}_a + \int \delta(\mathbf{R}-\mathbf{r}_a)p(\mathbf{r}_a)S^q_a(\mathbf{r}_a)d\mathbf{r}_a \\
S^{(1)}_{c,b}(\mathbf{R}) &= -k_B \int \delta(\mathbf{R}-\mathbf{r}_b)p(\mathbf{r}_b)\ln p(\mathbf{r}_b)d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_b)p(\mathbf{r}_b)S^q_b(\mathbf{r}_b)d\mathbf{r}_b
\end{aligned} \tag{79}$$

while the joint entropy density is constructed as

$$\begin{aligned}
2S_{c,ab}(\mathbf{R}) &= -k_B \int \Big[\delta(\mathbf{R}-\mathbf{r}_a) + \delta(\mathbf{R}-\mathbf{r}_b)\Big] p(\mathbf{r}_a,\mathbf{q}_a,\mathbf{r}_b,\mathbf{q}_b)\ln p(\mathbf{r}_a,\mathbf{q}_a,\mathbf{r}_b,\mathbf{q}_b)d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \Big[\delta(\mathbf{R}-\mathbf{r}_a) + \delta(\mathbf{R}-\mathbf{r}_b)\Big] p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b)p(\mathbf{r}_a,\mathbf{r}_b)\big[\ln p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b) \\
&\quad + \ln p(\mathbf{r}_a,\mathbf{r}_b)\big] d\mathbf{r}_a d\mathbf{r}_b d\mathbf{q}_a d\mathbf{q}_b \\
&= -k_B \int \delta(\mathbf{R}-\mathbf{r}_a)p(\mathbf{r}_a,\mathbf{r}_b)\ln p(\mathbf{r}_a,\mathbf{r}_b)d\mathbf{r}_a d\mathbf{r}_b - k_B \int \delta(\mathbf{R}-\mathbf{r}_b)p(\mathbf{r}_a,\mathbf{r}_b)\ln p(\mathbf{r}_a,\mathbf{r}_b)d\mathbf{r}_a d\mathbf{r}_b \\
&\quad + \int \delta(\mathbf{R}-\mathbf{r}_a)p(\mathbf{r}_a,\mathbf{r}_b)S^q(\mathbf{r}_a,\mathbf{r}_b)d\mathbf{r}_a d\mathbf{r}_b + \int \delta(\mathbf{R}-\mathbf{r}_b)p(\mathbf{r}_a,\mathbf{r}_b)S^q(\mathbf{r}_a,\mathbf{r}_b)d\mathbf{r}_a d\mathbf{r}_b \\
S^q(\mathbf{r}_a,\mathbf{r}_b) &= -k_B \int p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b)\ln p(\mathbf{q}_a,\mathbf{q}_b|\mathbf{r}_a,\mathbf{r}_b)d\mathbf{q}_a d\mathbf{q}_b
\end{aligned} \tag{80}$$

The factor of two corrects what would otherwise be a double-count of the joint entropy.

Much as in Section 2.6.2, the integral of the mutual information density returns the correct mutual information:

$$\int I_{ab}(\mathbf{R})\, d\mathbf{R} = I_{ab} \tag{81}$$

However, whereas in Section 2.6.2,

$$I_{\overline{a}b}(\mathbf{R}) \neq I_{\overline{b}a}(\mathbf{R}) \tag{82}$$

here

$$I_{ab}(\mathbf{R}) = I_{ba}(\mathbf{R}) \tag{83}$$

Thus, the two definitions of the mutual information density may be termed “asymmetric” vs. “symmetric”. The asymmetric formulation aligns with IST, while the symmetric one may be simpler to code and perhaps equally useful. The chief difference lies in where each contribution is localized in space. In the asymmetric version, every term in $I_{\overline{a}b}(\mathbf{R})$, is localized at $\mathbf{r}_a$ via $\delta(\mathbf{R} - \mathbf{r}_a)$. For example, the marginal entropy contribution of component b, in term $T_2(\mathbf{R})$, appears at the location of a, weighted by the conditional probability that a is at $\mathbf{R}$ given that b is at $\mathbf{r}_b$. In the symmetric version, by contrast, the marginal entropy contribution of b is localized at $\mathbf{r}_b$ by its own delta function.