SSIPTools: Software and Methodology for Surface Site Interaction Point (SSIP) Approach and Applications

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Abstract

We present the SSIPTools suite of programs. SSIPTools is a collection of software modules enabling the use of the Surface Site Interaction Point (SSIP) molecular descriptors, used for the modelling of non-covalent interactions in neutral organic molecules. It contains an implementation of the workflow for the generation of the SSIP descriptors, as well as the Functional Group Interaction Profiles (FGIPs) and Solvent Similarity Indexes (SSIs) applications, based on the SSIMPLE (Surface Site Interaction model for the Properties of Liquids at Equilibria) approach.

Introduction

A wide range of condensed phase phenomena are influenced by the formation of non-covalent interactions, which dominate many solvation effects. These interactions govern physical properties such as solubility, miscibility and vapour pressure,[1–4] as well as chemical properties

such as molecular recognition, supramolecular self-assembly and the rates of chemical reactions.[5–9] The complexity of the network of coupled equilibria involved in solvation of molecular mixtures in different solvent environments has been a substantial issue in the challenge for the theoretical prediction of solubility. Empirical solvent descriptors have proved valuable in extrapolating experimental data,[5,10–13] and computational methods have been developed for including solvent effects in *ab initio* simulations of molecular properties.[14–18]

The Surface Site Interaction Point (SSIP) approach was previously developed for understanding the contribution of individual non-covalent interactions in solvation, which is based on experimental studies of pairwise interactions between hydrogen bonded solutes.[19] The application of the SSIP approach to the calculation of solvent properties uses the Surface Site Interaction for the Properties of Molecules at Equilibrium (SSIMPLE).[20] With SSIMPLE, the population of free and bound SSIPs can be computed, providing insight into the interactions present at equilibrium, allowing calculation of solvation free energies and prediction of partition coefficients. From the population information the energy of solute-solute interactions can be computed, as displayed in functional group interaction profiles (FGIPs).[21] The computed solvation energy of an idealised solute SSIP has also previously been used to develop the Solvent Similarity Index (SSI), a quantitative comparison metric for the assessment of the similarity between two solvent systems.[22]

In this work we describe the software suite created to automate SSIP description generation[23] for a molecule. We then describe how this can be applied to the automated calculation, in the SSIMPLE framework, of FGIPs[21] and SSIs[22] of neutral organic molecules.

The Footprinting process: generating SSIP descriptions

Within the SSIP approach a molecule is described by a set of discrete interaction sites. An interaction parameter, ϵ_i, is assigned to each SSIP (referred to as an SSIP value in this work), which is equivalent to the experimentally measured hydrogen bond donor parameter

(α) for positive sites or the hydrogen bond acceptor parameter ($-\beta$) for negative sites.[19] The dimensionality of SSIP values is such that ϵ^2 is a molar energy.

Generation of the SSIP description, as shown in Figure 1, can be decomposed into three discrete units, promoting the development of a modular code base for the workflow. Generation of a 3D structure for the molecule of interest is followed by calculation of molecular electrostatic potential surface (MEPS) of the molecule. Footprinting converts the MEPS data to the SSIP description in the final step (a coarse graining approach described by Calero *et al*[23]).

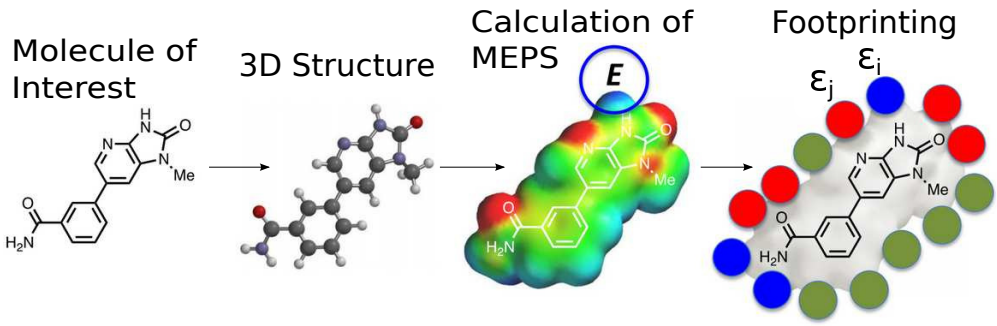


Figure 1: SSIP footprinting. The process starts with a molecule of interest, for which a 3D structure is generated. The MEPS data is then calculated for the molecule, before this is coarse grained to produce a collection of SSIPs which describe the surface interaction sites.

The output of the SSIP footprinting process is an eXtensible Markup Language (XML) file (see ESI for details), making the CML format[24] the appropriate 3D representational format for the structures in this workflow. The molecular electrostatic potential surface (MEPS) data are stored in unformatted cube files.[25]

Each SSIP is associated with a position on the 0.002 e bohr^{-3} electron density isosurface[23] of a molecule. Figure 2 shows the modular construction of the computational framework developed to undertake this work. The process uses the aforementioned data format specifications to be used in input/output operations at the interfaces between different computational modules.

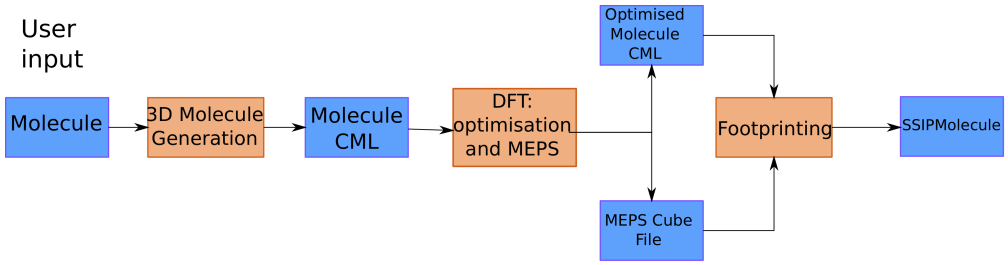


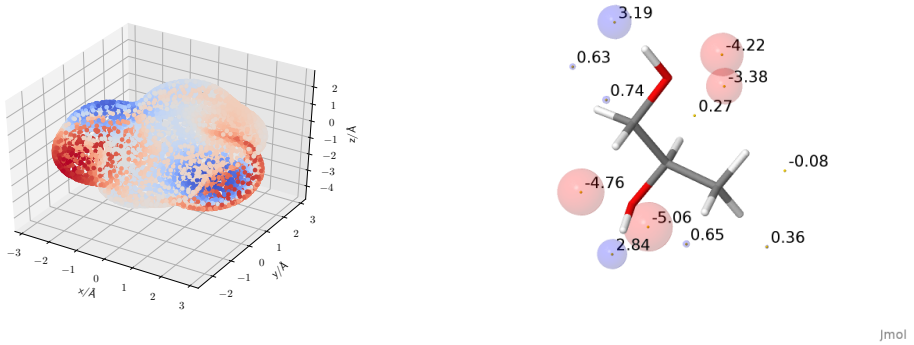
Figure 2: Workflow showing the process of generating a SSIP description for a molecule from input structure to the final XML output. Blue rectangles represent input/output information, Orange rectangles represent computational processes.

The Python library cmlgenerator (see ESI for details) created for this work provides the functionality required to generate schema conforming CML input files for the MEPS calculation. Existing 3D structures of target molecules in other input formats (e.g. PDB, mol2, SDF) are converted by cmlgenerator using Open Babel[26] as a backend. It is also possible to input structures as a 2D SMILES[27] string representation. To generate a suitable 3D structure the RDKit[28] package is used with the ETDKG2[29] conformer generation and the UFF[30] force field to select a suitably optimised starting point to be used in the MEPS generation step if no structure is given (a full geometry optimisation is carried out in the next step).

Density functional theory (DFT) is used to optimise the molecule geometry and to generate the MEPS on the 0.002 e bohr^{-3} electron density isosurface.[23] The calculation employs the B3LYP functional[31–34] and a 6-31G*[35,36] basis set for all atoms, except Bromine, Selenium and Iodine, for which 6-311G**[37] is used, based on work in.[23] Calculations were run using NWChem[38,39] and forms the rate limiting step in the workflow. The Python library nwchemcmlutils (see ESI for details) was created to provide a simple CLI for the generation of MEPS information (see ESI for further details).

The computed MEPS and 3D structure are then combined during the footprinting process (originally detailed in[23]) to produce the SSIP description using the SSIP Java package. Figure 3 contains example output of the footprinting process for 1,2-propandiol. The details of the Java package used for this work, and our previous studies,[21,22] including algorithmic

improvements, is described in the ESI.



(a) 1,2-propandiol MEPS (b) 1,2-propandiol with SSIPs

Figure 3: The conversion of the MEPS (left, with no atoms shown) to the SSIPs (right, with atoms shown) for 1,2-propandiol. A colour map is used for the MEPS, going from blue (for positive MEPS points) to red (negative electrostatic potentials), with the colour intensity representing the magnitude of the MEPS (darker is stronger). (b) blue is used for positive SSIPs and red for negative SSIPs, the size of each sphere representing its magnitude.

Surface Site Interaction Model for the Properties of Liquids at Equilbrium (SSIMPLE) and applications

Interactions between SSIPs are treated in a pairwise manner to describe a liquid or gas phase using SSIMPLE.[20] The association constant for the interaction of the ith and jth SSIP, K_{ij}, is given by Equation (1).

$$K_{ij} = \frac{1}{2} e^{-\frac{\epsilon_i \epsilon_j + E_{vdW}}{RT}} \tag{1}$$

Where $E_{vdW} = -5.6$ kJ mol^{-1}.

As we have shown previously,[20,40] Van der Waals interactions between non-polar molecules are, to a first approximation, a linear function of surface area, so by choosing a description that gives all SSIPs the same area footprint on the Van der Waals surface of a molecule, a constant value can be used for E_{vdW}. The interaction energy is made up of a polar term, $\epsilon_i \epsilon_j$,

and a non-polar term, E_{vdW}, which is the energy of the van der Waals interaction between two SSIPs. For repulsive interactions (i.e. ϵ_i and ϵ_j have the same sign), it is assumed that a state can be found where the polar sites are misaligned such that only non-directional van der Waals interactions are made, and the polar interaction term, $\epsilon_i\epsilon_j$, is set to zero.

The standard state used to ensure K_{ij} is dimensionless is the maximum theoretical density of SSIPs, $c_{max} = 300$ M. The value of c_{max} is based on the reference volume associated with a SSIP, 5 Å^3, that was defined using the volume enclosed by the van der Waals surface of a water molecule, which is represented by 4 SSIPs.[20] The speciation of all SSIP contacts in the liquid phase can then be calculated.

From this speciation data, the phasetransfer energies,[20] FGIPs[21] and SSI[22] information have previously been derived.

The workflow in Figure 4 is entirely encompassed by the phasecalculator module (see ESI for details), so that only a description of the solvent mixture (the phase composition) is required as an input when all solvents were previously explored. For instance, only two command line calls of the phasecalculator were required to generate the FGIP for water at 298K, whose representation is reported in Figure 5, allowing reproduction of the results from.[21]

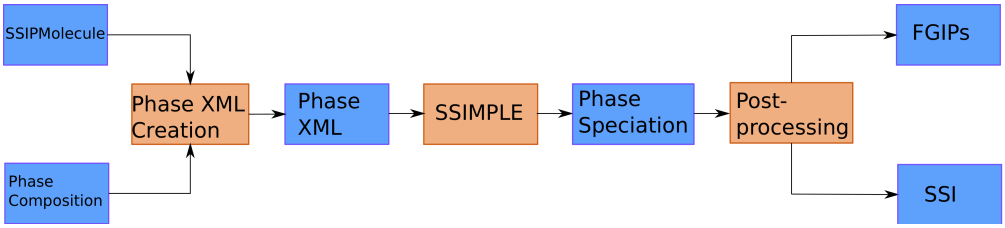


Figure 4: Workflow showing the process of preparing SSIMPLE calculations for application to FGIP and SSI generation. The phasecalculator interface provides a convenient interface wrapping to automate of the processing involved.

The phase compositions for mixtures to be explored is specified using a tab-separated values (.tsv) file. One phase specification is included per line, with temperature reported in the first column, and each subsequent pair of columns representing a component name and mole fraction. An example of this input file is found in Figure 6, containing two different

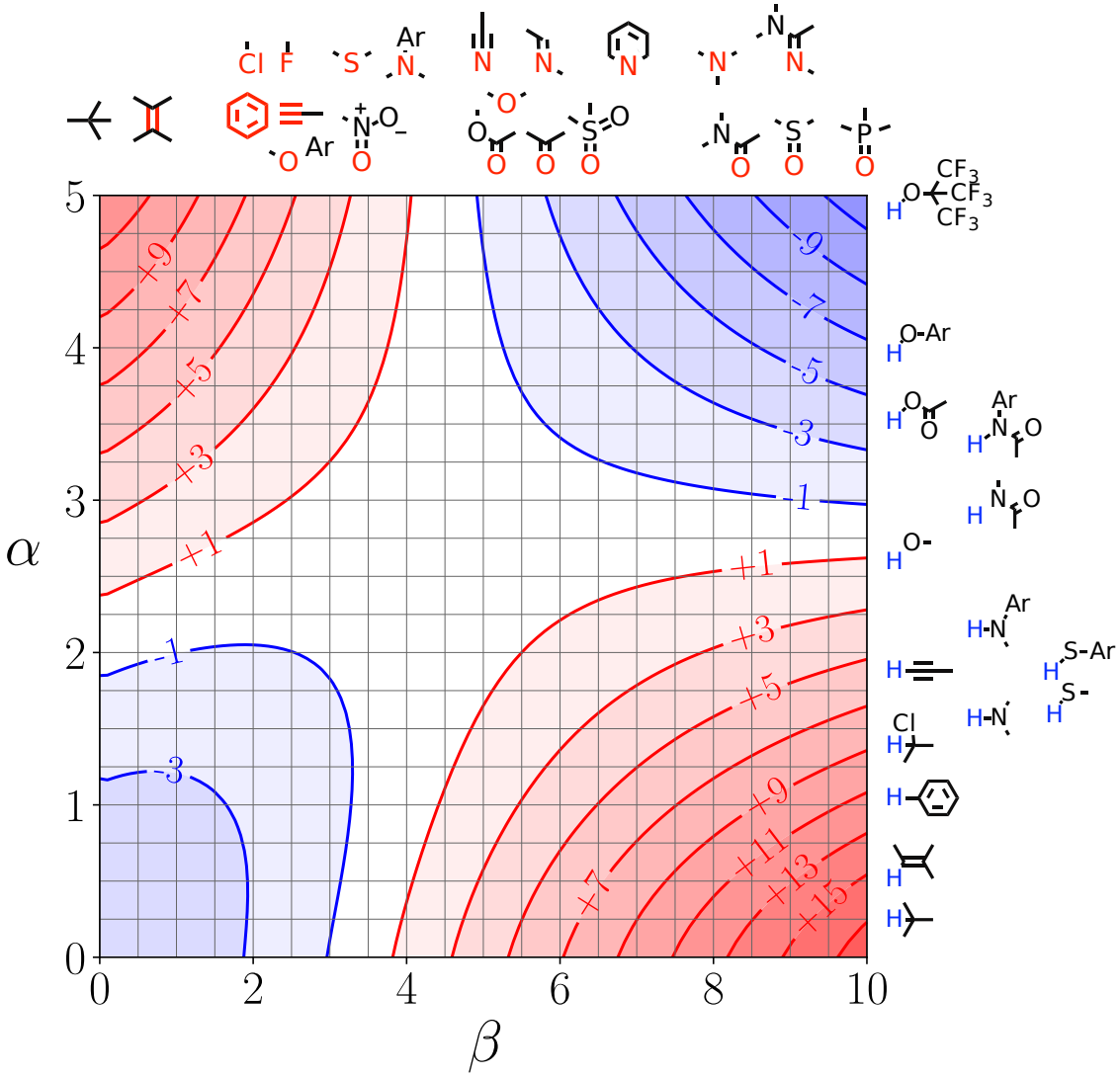


Figure 5: FGIP for the interaction of two solutes in water at 298K ($\Delta\Delta G_{FGI}$ in kJ mol^{-1}). The solute-solute interactions are favourable in the blue region, and unfavourable in the red region. Produced using phasecalculator interface.

phase definitions. The file provides the ability to calculate additional properties using the previously defined solvent SSIP descriptions[21,41] (see ESI for more detail).

```
298.0   water    1.0
298.0   water    0.75  ethanol  0.25
```

Figure 6: Contents of tsv file required to specify creation of two phases. The first line defines a phase of pure water ($\chi_{water} = 1.0$) at 298K. This input was used to generate the FGIP in Figure 5. The second line defines a mixed phase of water ($\chi_{water} = 0.75$) and ethanol ($\chi_{ethanol} = 0.25$) at 298K.

Conclusion

The SSIP approach to molecular description has previously been described along with applications of the SSIMPLE method. The workflow presented here provides a detailed description of the computational tools used to generate the previous work, to allow readers to replicate the results and explore novel solvent systems tailored to individual requirements. The publishing of the accompanying software using popular repositories will allow other researchers to use the tools we have developed to explore systems of interest.

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Conflicts of interest

M.D.D., C.A.H. and T.N. have a financial interest in the commercial use of the software.

Software availability

The software described in the paper is hosted at the University of Cambridge gitlab, located here: `https://gitlab.developers.cam.ac.uk/ch/hunter/ssiptools`. All software in the SSIPTools collection is released under an AGPLv3 license for academic use. Enquiries for any non-academic use of SSIPTools including commercial use should be directed to Cambridge Enterprise:

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Email: software@enterprise.cam.ac.uk

The python packages have also been deployed to conda-forge, enabling installation using the anaconda python distribution. This allows installation by the following command:

```
conda install -c conda-forge {package name}
```

The python packages in SSIPTools are:

- xmlvalidator
- cmlgenerator †

- nwchemcmlutils †
- ssipfootprint †
- phasexmlcreator
- phasexmlparser
- resultsanalysis
- puresolventinformation
- solventmapcreator
- phasecalculator †

Packages marked with † are the main packages users will interact with and install (other packages are dependencies that will be installed automatically by anaconda during dependency resolution).

The Java SSIP project in SSIPTools has three jar targets:

- ssip-footprint (ssip when installed as a deb package), which performs the footprinting process described in.[23]
- ssip-phasetransfer (phasetransfer when installed as a deb package), which performs the SSIMPLE calculation described in.[20]
- ssip-visualisation (ssip-vis when installed as a deb package) which is used for SSIP description visualisation.

Pre-compiled artefacts are available for download from the website. It has also been deployed to maven for inclusion in other Java projects.

ASSOCIATED CONTENT

Supporting Information Available

Detailed algorithm and extended feature descriptions.

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