The Reference Interaction Site Model Integrated Calculator (RISMiCal) program package for nano- and biomaterials design

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Abstract. Solvent molecules play an essential role in various chemical, physical, and biological processes in solution phase. The reference interaction site model (RISM) and its three-dimensional extension (3D-RISM) are powerful tools for considering the solvation effect on chemical reactions, biological functions, and structure formation upon coupling with the quantum chemistry electronic structure theory and/or molecular dynamics simulation technique. We recently developed the reference interaction site model integrated calculator (RISMiCal) program package based on the RISM and 3D-RISM theories, which has interfaces for external programs such as GAMESS and Tinker. The features of the RISMiCal package are reviewed here.

1. Introduction
Modeling a solvent environment is crucial for nano- and biomaterials design because the solvent plays an essential role in determining the structures, properties, and functions of the materials existing in solution.[1] The solvent models can be classified into several categories. The most popular model is the dielectric continuum model, which treats the solvent environment as a continuum medium characterized by the dielectric constant.[2, 3] Molecular mechanics (MM) is also a widely used approach. In MM, the solvent molecules are explicitly placed around the solute molecule and the coordinates are generated by the molecular dynamics (MD) or Monte Carlo techniques.[4] The integral equation theory (IET) of molecular liquids is another candidate to handle the solvent environment and is based on the statistical mechanics theory of liquids.[5-7] To date, several IETs have been proposed, including the reference interaction site model (RISM).[8-11] and its three-dimensional extension, the 3D-RISM theory.[12-14] The RISM and 3D-RISM theories have been used in a number of studies due to their high applicability involving low computational cost and high accuracy. Based on the RISM and 3D-RISM theories, many theoretical and computational developments have been carried out. We recently developed the reference interaction site model integrated calculator (RISMiCal) program package, which has interfaces for external programs such as GAMESS (the quantum chemistry software) and Tinker (the MD software). In this paper, we review the features and specifications of the RISMiCal package.

2. RISM and 3D-RISM Theories
The RISM equation is given by
\[ h_{\alpha}\gamma}(r) = \omega_{\alpha\alpha'} c_{\gamma\gamma'} (\omega_{\gamma\gamma} + \rho_{\gamma\gamma} h_{\gamma\gamma}) \] (1)
and the Kovalenko–Hirata (KH) closure relation is given by[15]
\[ g_{\alpha}\gamma}(r) = \begin{cases} \exp[d_{\alpha\gamma}(r)] & \text{for } d_{\alpha\gamma}(r) < 1 \\ d_{\alpha\gamma}(r) + 1 & \text{for } d_{\alpha\gamma}(r) \geq 1 \end{cases} \] (2a)
\[ d_{\alpha\gamma}(r) = -\beta u_{\alpha\gamma}(r) + h_{\alpha\gamma}(r) - c_{\alpha\gamma}(r) \] (2b)
where \( g_{\alpha\gamma}(r) = h_{\alpha\gamma}(r) + 1 \) is a radial distribution function between interaction sites \( \alpha \) and \( \gamma \); \( \omega_{\alpha\alpha'}, c_{\alpha\gamma}, \beta, \) and \( \rho \) denote intramolecular correlation function, direct correlation function, inverse temperature, and number density, respectively, and \( u_{\alpha\gamma} \) is a pair interaction potential between sites \( \alpha \) and \( \gamma \). The symbol * indicates that a convolution integral and the summation should be taken for repeated indices. By solving the RISM equation and KH closure under a given \( u_{\alpha\gamma} \) iteratively, one can obtain the distribution and direct correlation functions.

Similarly, the 3D-RISM equation and the 3D-KH closure are given by
\[ h_{\alpha}(r) = c_{\gamma} \left[ \omega_{\gamma\alpha} + \rho_{\gamma\alpha} h_{\gamma\alpha} \right] \] (3)
\[ g_{\alpha}(r) = \begin{cases} \exp[d_{\alpha}(r)] & \text{for } d_{\alpha}(r) < 1 \\ d_{\alpha}(r) + 1 & \text{for } d_{\alpha}(r) \geq 1 \end{cases} \] (4a)
\[ d_{\alpha}(r) = -\beta u_{\alpha}(r) + h_{\alpha}(r) - c_{\alpha}(r) \] (4b)
In the 3D-RISM case, one can obtain the spatial distribution function, which is suitable for describing the solvation structure of complex systems such as nano- and biomaterials.

3. Hybrid Multiscale Implementation

3.1. GAMESS
The RISMicCal package has an interface for the GAMESS quantum chemistry electronic structure program package.[16, 17] RISMicCal with GAMESS realizes the RISM self-consistent field (RISM-SCF).[18] 3D-RISM-SCF.[19] and DFT/3D-RISM computation.[12] An analytical free energy gradient for efficient geometry optimization of solvated molecules is also incremented.[20]

In the RISM/3D-RISM-SCF, the solvated Hamiltonian, \( \hat{H}_{\text{solv}} \), is given by
\[ \hat{H}_{\text{solv}} = \hat{H}_{\text{iso}} + \hat{V}_{\text{solv}} \] (5)
where \( \hat{H}_{\text{iso}} \) and \( \hat{V}_{\text{solv}} \) are the Hamiltonian for isolated molecules and an electrostatic potential due to the solvents, respectively. In the 3D-RISM case, \( \hat{V}_{\text{solv}} \) is given by
\[ \hat{V}_{\text{solv}}(r') = \sum_{\alpha} \rho_{\alpha} \int g_{\alpha}(r) \frac{q_{\alpha} |\Psi(r')|^2}{|r - r'|} \, dr \] (6)
where \( g_{\alpha}(r) \) is obtained by solving the 3D-RISM equation. The wave function of solute molecules is obtained by solving the Schrödinger equation for the solvated Hamiltonian. The interaction potential for solving the 3D-RISM is
\[ u_{\alpha}(r) = \sum_{i} 4\varepsilon_{i\alpha} \left\{ \left( \frac{\sigma_{i\alpha}}{|r - r_{i}|} \right)^{12} + \left( \frac{\sigma_{i\alpha}}{|r - r_{i}|} \right)^{6} \right\} + \int \frac{q_{\alpha} |\Psi(r')|^2}{|r - r'|} \, dr' \] (7).

Therefore, by solving the Schrödinger equation and the 3D-RISM equation through \( \hat{V}_{\text{solv}} \) and \( u_{\alpha}(r) \), iteratively, one can obtain the electronic structure \( \Psi \) and solvation structure \( \{g_{\alpha}\} \), simultaneously.
3.2. Tinker
The RISMiCal package has an interface for the Tinker molecular modeling package.[21] RISMiCal/Tinker can perform the MD simulation and structure optimization based on the MM.[22, 23] The solute molecules are treated by Tinker in the usual manner, immersed in solvent, where the solvent distribution is evaluated by 3D-RISM. The force acting on solute atoms due to the solvent is given by

\[ F_{\text{solv},i} = \sum_{\alpha} \rho_{\alpha} \int \frac{\partial u_{\alpha}(r)}{\partial R_{i}} g_{\alpha}(r) dr \]  

(8)

where \( R_{i} \) is a coordinate of solute atom \( i \). The computation of this additional force term to the solute atoms is implemented in the “gradient” module in Tinker.

4. Miscellaneous Implemented Features
The RISMiCal package includes many functions for analyzing solvation thermodynamics based on the RISM and 3D-RISM theories. The implemented functions in the RISMiCal package are summarized in Table 1.

| Function                          | Description                                                                 | Ref.   |
|-----------------------------------|-----------------------------------------------------------------------------|--------|
| QM / MM / RISM                    | Hybrid method of QM / MM and RISM / 3D-RISM                                   | [24]   |
| FMO / RISM                        | Hybrid method of the fragment molecular orbital and 3D-RISM                  | [25]   |
| MOZ-SCF                           | Hybrid method of the molecular Ornstein–Zernike and electronic structure theory | [26]   |
| RismPath / SM                     | Method for finding the minimum free energy pathway of ions through protein based on 3D-RISM and the string method | [27]   |
| Solvent placement                 | Solvent placement algorithms based on the distribution function evaluated by 3D-RISM | [28, 29] |
| Dielectric consistent RISM / D-Stell dielectric correction | Correction methods to reproduce the dielectric constant of solvent | [30, 31] |
| Pressure correction / universal correction / Repulsive bridge correction / Partial wave expansion | Correction schemes of solvation free energy | [32-35] |

5. Summary
We have developed the RISM/3D-RISM program package, RISMiCal, for use in the design of nano- and biomaterials. RISMiCal has interfaces for the GAMESS and Tinker packages. In addition, it has various functions for analyzing the solvation thermodynamics of nano- and biomaterials based on the RISM and 3D-RISM theories. We are currently preparing this program for public release.
6. References

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