Quantum Mechanical Justification for Invariant Binding Affinity in Coordinate Transformations

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Abstract

Molecular docking, pharmacological modeling, and quantum chemistry calculations frequently involve coordinate transformations, like the conversion between PDB (Protein Data Bank) and SMILES (Simplified Molecular Input Line Entry System) formats. This paper presents a rigorous quantum mechanical justification for why the binding affinity and molecular interaction properties of a ligand remain invariant under such transformations. Using the Quantum Mechanics, including the invariance of the Schrödinger equation under translation, the Born-Oppenheimer approximation, molecular orbital theory, and electrostatic potential analysis, we demonstrate a mathematical framework that makes sure the conservation of molecular interactions.

1 Introduction

Molecular docking studies and ligand-receptor interactions play an important role in computer aided drug discovery. Often, molecular structures undergo coordinate transformations such as PDB to SMILES and back to PDB during computational workflows. However, the concern arises whether such transformations alter the molecular properties that govern binding affinity. Here, we provide a quantum mechanical justification to confirm that these transformations do not affect binding affinity.

2 Mathematical Framework of Molecular Invariance

2.1 Schrödinger Equation and Translation Invariance

The electronic structure of a molecule is determined by the time-independent Schrödinger equation:

$$\hat{H}\Psi = E\Psi, \tag{1}$$

where $\hat{H}$ is the molecular Hamiltonian, Ψ is the wavefunction, and E is the total energy. The molecular Hamiltonian is given by:

$$\hat{H} = \sum_i \left(-\frac{\hbar^2}{2m_i} \nabla_i^2 \right) + \sum_{A<B} \frac{Z_A Z_B e^2}{|\mathbf{R}_A - \mathbf{R}_B|} + \sum_{i,A} \frac{-Z_A e^2}{|\mathbf{r}_i - \mathbf{R}_A|} + \sum_{i<j} \frac{e^2}{|\mathbf{r}_i - \mathbf{r}_j|}, \quad (2)$$

where:

- $\mathbf{R}_A$ are nuclear coordinates,
- $\mathbf{r}_i$ are electronic coordinates,
- Z_A are nuclear charges.

Since the Hamiltonian depends only on relative distances, translating the entire system by a vector $\mathbf{T}$ results in:

$$\mathbf{r}_i \to \mathbf{r}_i + \mathbf{T}, \quad \mathbf{R}_A \to \mathbf{R}_A + \mathbf{T}. \quad (3)$$

Because the energy levels are eigenvalues of $\hat{H}$, they remain unchanged under translation, proving that the molecular properties are invariant.

2.2 Born-Oppenheimer Approximation and Potential Energy Surface (PES) Stability

Under the Born-Oppenheimer approximation, the molecular energy is expressed as:

$$E(\mathbf{R}) = E_{\text{elec}}(\mathbf{R}) + E_{\text{nuc}}(\mathbf{R}). \quad (4)$$

Since only relative nuclear coordinates determine molecular interactions, a rigid-body translation does not alter the PES. Thus, molecular docking scores, binding affinities, and ligand interactions remain unchanged.

2.3 Molecular Orbitals and Electron Density Preservation

Molecular interactions depend on electron density $\rho(\mathbf{r})$:

$$\rho(\mathbf{r}) = \sum_i |\psi_i(\mathbf{r})|^2. \quad (5)$$

Since electronic wavefunctions $\psi_i(\mathbf{r})$ are functions of interatomic potentials, translating coordinates does not affect orbital overlap or molecular recognition.

2.4 Electrostatic Potential (ESP) and Binding Affinity

The electrostatic potential (ESP) governs non-covalent interactions and is defined as:

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r}'. \quad (6)$$

Since nuclear and electronic charge distributions are simply shifted under a coordinate transformation, the ESP remains invariant, making sure that binding affinity is conserved.

3 Conclusion

The quantum mechanical framework shown here demonstrates that coordinate transformations such as PDB-SMILES-PDB do not alter molecular binding affinity. The invariance of the Schrödinger equation under translation, the stability of the potential energy surface, the conservation of molecular orbitals, and the invariance of electrostatic potential collectively supports this result.

4 References

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