Supercomputer-based Quantum Chemical Analysis of Frontier Orbitals in the Determination of Molecular Hardness of Neurotransmitters and Antidepressants

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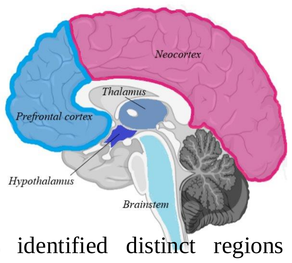
Abstract

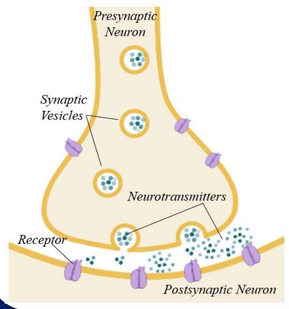
In this study, we utilized high-performance computing (HPC) to explore the electronic properties of neurotransmitters and antidepressants and understand their chemical actions in the brain. We employed quantum chemistry methods using QCHEM calculations to identify the lowest energy state geometry of various neurotransmitters and antidepressants. Utilizing this optimized geometry, we calculated the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) energies. From these orbital energies, we derived chemical properties such as ionization potential and electron affinity. Ionization potential is the energy required to remove an electron from the molecule and the electron affinities indicate the energy change when an electron is added to the molecules. After being computed, these parameters were used to evaluate chemical hardness, a measure of the molecule's resistance to changes in its electron cloud and provide information about molecular reactivity and selectivity. Our findings provide an insight into the stability and reactivity of brain chemicals, potentially contributing to the development of new pharmaceuticals. This research demonstrates the potential of HPC in rapidly finding detailed characteristics of biologically relevant molecules, which is crucial in accelerating drug development.

Background

Neurotransmitters act as chemical messengers. Their job is to carry chemical signals from one neuron to the next target cell (1). It's not known exactly how antidepressants work, but it is thought they work by increasing levels of neurotransmitters (2). Certain neurotransmitters, such as serotonin and noradrenaline, are linked to mood and emotion.



Research has identified distinct regions in the brain characterized by chemical hardness, which affects how neurotransmitters interact with their receptors (3); chemical hardness (η) is defined as a measure of the tendency of a chemical species to localize charge density. In the above figure, pink regions indicate the release of chemically hard neurotransmitters, while blue regions represent neurons that release chemically soft neurotransmitters.



Molecules with similar hardness are more likely to interact favorably. In this research, we utilize super-computing to compute the molecular hardness of various neurochemicals, enabling the exploration of potential new drugs.

Methods

Q-Chem was utilized to optimize the molecules geometry and determine their energies and molecular structures. Q-Chem is a sophisticated ab initio quantum chemistry software package designed for electronic structure calculations of molecules.

The chosen method for calculation was **B3LYP**. The B3LYP approach predicts repulsive long-range interactions between molecules that are attracted to each other by dispersion forces (4).

B3LYP is a Density **Functional Theory** (DFT), which is a quantum-mechanical method used in chemistry and physics to calculate the electronic structure of atoms, molecules, and solids (5). The equation below shows the Kohn-Sham equation: the framework DFT uses for solving the electronic structure of matter.

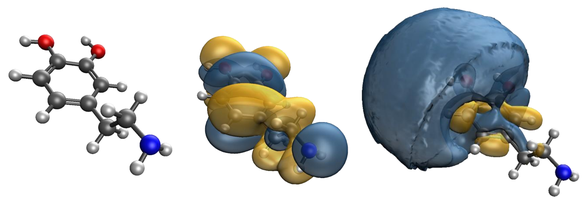
The partition of electron energy according to Kohn-Sham equation:

$$E = E^T + E^V + E^J + E^{XC}$$

E^T = kinetic energy of electrons
E^V = nuclear-electron and nuclear-nuclear interactions
E^J = electron-electron repulsion
E^{XC} = electron correlation represented by the *quantum mechanical exchange-correlation energy*.

For each calculation, a **Geometry optimization** in Q-Chem was performed. This involves finding the most stable molecular structure with the lowest possible energy. Q-Chem uses iterative algorithms to adjust the positions of atoms in a molecule until the forces acting on them are minimized. This requires repeated calculations of energies, gradients, and sometimes Hessians at each optimization cycle until convergence is attained (6).

Chemical hardness, a concept in Density Functional theory (DFT), relates to a molecule's resistance to change in electron distribution. It is defined as the difference between the energies of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO). A larger HOMO-LUMO gap indicates a harder, less polarizable (more localized electron density) molecule, while a smaller gap suggests a softer, more polarizable (less localized electron density) molecule. The figure below displays the HOMO and LUMO gap of dopamine.



Dopamine LUMO HOMO

For this project, chemical hardness was calculated using the equation below:

$$\chi = \left(\frac{I_p + E_a}{2}\right)$$

$$\eta = \left(\frac{I_p - E_a}{2}\right)$$

Electronegativity (χ) is the ability of an atom in a molecule to attract the bonding pair of electrons towards itself. The chemical hardness (η) on the other hand is a measure of how easily the valence electron cloud of a chemical species can be deformed (7,8).

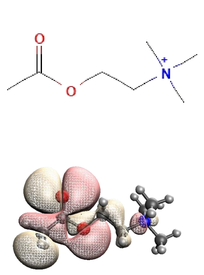
Ionization potential (Ip) is the difference between the ground state energy of the neutral molecule and the ground state energy of the cation molecule. Electron affinity (Ea) is determined by the difference of energy between the anion and the neutral form of a molecule. Another way to calculate electronegativity and hardness is by first determining the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

$$\chi = -\frac{1}{2}(\varepsilon_{HOMO} + \varepsilon_{LUMO})$$

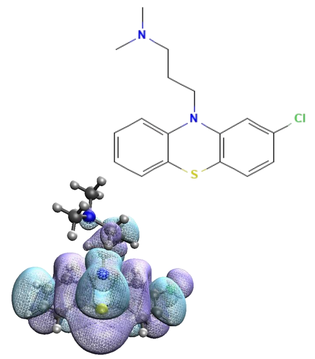
$$\eta = -\frac{1}{2}(\varepsilon_{HOMO} - \varepsilon_{LUMO})$$

Results

Acetylcholine $C_7H_{16}NO_2^+$

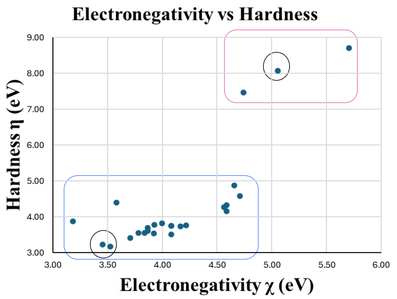


Chlorpromazine $C_{17}H_{19}ClN_2S$



The figure above displays the HOMOs of Acetylcholine on the left and Chlorpromazine on the right. Acetylcholine's calculated hardness was 8.07 eV, while Chlorpromazine had a hardness of 3.22 eV. Generally harder molecules have tighter knit electron shells while softer ones have more "fluffy"/"delocalized" shells. Inspecting the image, we can see the "fluffiness" of the chlorpromazine which agrees with the chemically soft property of this molecule (η = 3.22 eV).

The graph at the top of column four displays a graph of the electronegativity and hardness. The blue rectangle represents the softer regions of molecules, and the pink rectangle represents the harder molecules.



Conclusions

- DFT with B3LYP functional was used to calculate the molecular hardness of twenty-six neurotransmitters.
- Computed hardnesses varied from 3.22 to 8.07 eV.
- Computed electronegativities varied from 3.18 to 5.71 eV.
- The analysis suggests that predominantly 88% of the studied chemicals bind to the soft region of the human brain.

Future Directions

- Studying the binding of these neurotransmitters and commonly used antidepressants to the protein receptors in certain regions of the brain.

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