2.1 Introduction to the Method of Quantum Pharmacology

This chapter describes the methodology of 'Quantum Pharmacology' that utilizes modern quantum mechanical methods to efficiently study pharmacological problems of interest and extract pharmacological features and other important aspects that can be related to the potency and activity of the drug. The application of modern quantum mechanical techniques to study a drug's activity, potency and mechanism is termed as quantum pharmacology [1]. The main features of such a study are:

a. Select prototypes from chemically and structurally different high potency clinically tested drugs

b. Find out common conformational features responsible for drug's activity. These are termed as pharmacophore.

c. Receptor mapping by calculating molecular electrostatic potentials.
d. Build receptor model based on site directed mutagenesis studies and active site information for residues within 5 Å radius.

e. Drug-receptor interaction studies based on supermolecule type approach.

f. Analysis of drug receptor interaction and correlation with the drug’s potency.

g. Simulation of drug’s mechanism of action.

h. Suggest modifications for improving drug’s quality and potency.

Quantum pharmacology leads to a better understanding of the key factors (drug-receptor interactions) responsible for a drug’s activity and can thus be of greater importance in designing newer and more potent drugs.

A flow chart on the following page describes the so-called “Quantum Pharmacological Procedure”[2]. The following sections and subsections of this chapter describe each step of the procedure in detail.

2.2 Selection of compounds to be studied

We select some chemically & structurally different, high potency, clinically tested drugs. Chemically & structurally different drugs are chosen with the idea that they must possess certain common conformational
features, which help them to bind to the same receptor, and we wish to pick out these important geometrical parameters referred to as the pharmacophoric features. Selected drugs must be of high potency and clinically tested to ensure that they bind well with the receptor and do show antiarrhythmic activity. If we can understand how these high potency drugs act then we can suggest refinements for better selectivity drugs.

2.3 Conformational analysis of selected drugs

For each selected drug we follow the ab initio Hartree Fock self-consistent field (HF SCF) molecular orbital (MO) calculations [3] followed by the Davidon's optimally conditioned (OC) optimization method [4]. Each step of SCF and geometry optimization procedure is shown in the flow chart. Since the drugs are often chemically large systems having conformational flexibility the initial geometry is chosen according to the bioactive conformation. The subsections listed below explain, in detail, the general HF SCF MO procedure and the OC optimization procedure used.

2.3.1 Ab initio Hartree Fock Molecular Orbital Calculations
The essence of the Hartree Fock approximation is to replace the complicated many electron problem by a one electron problem in which electron-electron repulsion is treated in an average way. The ground state of a N-electron system can be written as a single slater determinant.

\[ | \Psi_o \rangle = | \psi_1 \psi_1 \cdots \psi_i \psi_i \cdots \psi_{N/2} \psi_{N/2} \rangle \]

Where each spatial molecular orbital \((\psi_i | i = 1, 2, ..., N/2)\) is doubly occupied. According to the variation principle the best wave function is the one that gives the lowest possible energy

\[ E_o = \langle \Psi_o | H | \Psi_o \rangle \]

\(H\) is full electronic Hamiltonian. The variational flexibility of wave function is in the choice of orbitals. By minimizing \(E_o\) with respect to the choice of orbitals one can derive the HF equations, which determine the optimal orbitals. HF equations are eigenvalue equations of the form

\[ f(1) \psi_i(1) = \varepsilon_i \psi_i(1) \]

Where \(f(1)\) is an effective one electron operator, called the Fock operator.

\[ f(1) = - \frac{1}{2} \nabla_i^2 - \sum_{A=1}^{M} \frac{Z_A}{r_{1A}} + V_{HF}(1) = h(1) + V_{HF}(1) \]
The Fock operator \( f(I) \) is the sum of a core Hamiltonian operator \( h(I) \) and an effective one electron potential operator called the Hartree Fock potential \( v^{\text{HF}}(I) \). \( v^{\text{HF}}(I) \) is the average potential experienced by the electron \( I \) due to the presence of other electrons. Therefore, \( v^{\text{HF}}(I) \) depends on the orbitals of other electrons. The HF equations are non-linear and must be solved iteratively. The procedure for solving the HF equations is called the self-consistent field (SCF) method and is shown in the flow chart.

### 2.3.2 Choice of basis set

Molecular orbitals are expressed as a linear combination of set of functions

\[
\psi_I = \sum_{\mu=1}^{K} C_{\mu \iota} \phi_{\mu} 
\]

A linear combination of Gaussian type orbitals (GTO) (contraction) is made. A 6-31G basis set has been used throughout. The contraction of GTO'S has the form.

\[
\phi_{\mu}(r - R_A) = \sum_{p=1}^{L} d_{p \mu} g_p (\alpha_{p \mu}, r - R_A) 
\]
QUANTUM PHARMACOLOGICAL PROCEDURE

Select chemically & structurally different, high potency clinically proven drugs

Conformational analysis of all selected drugs

Initial geometry according to bioactive conformation. Basis set and initial guess at density matrix.

Evaluate one & two e' integrals

Form fock matrix

Diagonalize to obtain eigen values and M.O. coefficients.

Form density matrix.

Calculate energy (E)

New geom. q',s

Not converged

OC optimization (gradient method.)

Calculating (i.e. $\frac{\partial E}{\partial q_i} = 0$ for all i (stationary point)

Calculate complete molecular electrostatic potential

Use MOLDEN

Generate MESP contours

Predict complementary receptor charge environment & extract common conformational features.

Model for active site based on site directed mutagenesis studies.

Inter molecular interaction calculations

Correlate interaction energy with potency
\[ \psi_i = \sum_{\mu=1}^{K} C_{\mu;i} \phi_{\mu} \]

\( \alpha_{\mu} \) and \( \delta_{\mu} \) are exponents and contraction coefficients respectively. \( L \) is the length of contraction. For 6-31G basis set \( L = 6 \) for core and 3 and 1 for valence orbitals which are split into two [5]. 3-21 G basis set has also been used for intermolecular interaction calculations as higher basis set is not available for calcium. For 3-21 G basis set \( L = 3 \) for core and 2 and 1 for valence orbitals.

### 2.2.3 Closed shell Hartree Fock: The Roothan Equations

The Hartree Fock hamiltonian is defined as

\[ H_0 = \sum_{i=1}^{N} f(i) \]

Where \( f(i) \) is the fock operator for the \( i^{th} \) electron.

The closed shell restricted (\( \alpha \) and \( \beta \) spin orbitals are constrained to have the same spatial function) ground state for an \( N \)-electron system can be described as
Each of the occupied spatial molecular orbitals ($\psi_a | a = 1, 2, \ldots, N/2$) is doubly occupied. As described before the Fock operator is a sum of a core Hamiltonian operator and an effective one electron potential operator called the Hartree Fock potential $v^{HF}(1)$.

$$F(1) = h(1) + v^{HF}(1) = h(1) + \sum_{a}^{N/2} 2J_a(1) - K_a(1)$$

$J_a$ and $K_a$ are the coulomb and exchange operators respectively, which are defined as follows:

$$J_a(1) = \int_{r_{12}} dr_2 \psi_a^* (2) \frac{1}{r_{12}} \psi_a (2)$$

$$K_a(1) \psi_a (1) = [\int_{r_{12}} dr_2 \psi_a^* (2) \frac{1}{r_{12}} \psi_1 (2)] \psi_a (1)$$

The coulomb term represents the average local potential at $r_1$ arising from an electron in $\psi_a$. The exchange term arises from the antisymmetric
nature of the single determinant and does not have a simple classical interpretation.

The closed shell HF energy is given by

$$E_0 = \langle \Psi_0 | H | \Psi_0 \rangle$$

The calculation of molecular orbitals now becomes equivalent to the problem of solving the spatial integro-differential equations.

$$f(1) \psi_i(1) = \varepsilon_i \psi_i(1) \quad (1)$$

Roothan showed that by introducing a set of known spatial basis functions the differential equation could be converted to a set of algebraic equations and solved by standard matrix techniques. Introducing a set of \(K\) known basis functions \(\{\phi_{\mu}(r) \mid \mu = 1, 2, \ldots, K\}\) and expanding the unknown molecular orbitals in the linear expansion

$$\psi_i = \sum_{\mu=1}^{K} C_{\mu i} \phi_{\mu} \quad i = 1, 2, \ldots, K \quad (2)$$

Substituting the linear expansion (2) into the Hartree Fock equation (1) we get
\[ f(1) \sum_{v} C_{vi} \phi_{v}(1) = \varepsilon_{i} \sum_{v} C_{vi} \phi_{v}(1) \]

Multiplying by \( \phi_{\mu}^\ast(1) \) on the left and integrating

\[ \sum_{v} C_{vi} \int dr_{1} \phi_{\mu}^\ast(1) f(1) \phi_{v}(1) = \varepsilon_{i} \sum_{v} C_{vi} \int dr_{1} \phi_{\mu}^\ast(1) \phi_{v}(1) \quad (3) \]

One can define an overlap matrix \( S \), a \( K \times K \) hermitian matrix, which has elements

\[ S_{\mu v} = \int dr_{1} \phi_{\mu}^\ast(1) \phi_{v}(1) \]

Also defining the fock matrix \( F \) that has the elements

\[ F_{\mu v} = \int dr_{1} \phi_{\mu}^\ast(1) f(1) \phi_{v}(1) \]

It is also a \( K \times K \) hermitian matrix. The basis functions \( \{ \phi_{\mu} \} \) are not in general orthogonal to each other and hence overlap with a magnitude \( 0 \leq |S_{\mu v}| \leq 1 \). The diagonal elements of \( S \) are unity and the off diagonal elements are less then unity. The sign of the off diagonal terms depends on the relative sign of the two basis functions, and their relative orientation and separation.
in space. With these definitions the integrated HF equation (3) can be written as

\[ \sum_{\nu} F_{\mu\nu} C_{\nu i} = \varepsilon_i \sum_{\nu} S_{\mu\nu} C_{\nu i} \quad i = 1, 2, \ldots, K \]

These are Roothaan's equations, which can be written as the single matrix equation.

\[ FC = SC\varepsilon \quad (4) \]

\( C \) is a \( K \times K \) square matrix of the expansion coefficients \( C_{\mu i} \)

\[ C = \begin{pmatrix}
C_{11} & C_{12} & \cdots & C_{1K} \\
C_{21} & C_{22} & \cdots & C_{2K} \\
\vdots & \vdots & \ddots & \vdots \\
C_{K1} & C_{K2} & \cdots & C_{KK}
\end{pmatrix} \]

and \( \varepsilon \) is a diagonal matrix of the orbital energies \( \varepsilon_i \).

\[ \varepsilon = \begin{pmatrix}
\varepsilon_1 \\
\varepsilon_2 \\
\vdots \\
0
\end{pmatrix} \]

As the Fock matrix depends on the expansion coefficients the resulting Roothaan equations are nonlinear.
\[ F(C) \mathbf{C} = \mathbf{S} \epsilon \]

and are solved iteratively (See Appendix Ia for details). For an orthogonal basis set i.e. \( S = 1 \) Roothaan’s equations have the form of the usual matrix eigenvalue problem and the eigenvalues \( \epsilon_i \) are calculated by diagonalizing \( F \) [6]. Therefore the procedures for orthogonalizing the basis functions are considered (Refer to Appendix Ib).

\section*{2.3.4 Geometry optimization using the optimally conditioned (OC) optimization algorithm}

Geometry optimizations have been performed using a variable metric algorithm proposed by Davidon [4]. For convergence the gradient length was required to be \( \leq 5.0 \times 10^{-4} \) where the gradient length is defined as

\[ \left( \sum_{i=1}^{N} g_i^2 \right)^{1/2} \]

Where \( N = \) number of optimizable parameters.

After a stationary point is achieved corresponding to each selected drug molecule, the optimized conformation is analyzed with the help of ORTEP [7] drawings.
2.4 Conformational mapping

The idea of conformational mapping is to understand the variations in the conformation of the drug with respect to a normal substrate (which binds perfectly) or with respect to a clinically tested potent drug (which can again be assumed to bind perfectly).

To achieve this, drugs are mapped (overlapped) one by one over the normal substrate or a highly potent drug. This helps us to understand the conformational changes required to bring the drug to a perfect pharmacophoric conformation.

2.5 Charge distribution and complete molecular electrostatic potential maps

Charge environment has been studied using complete molecular electrostatic potential maps which have been depicted in the form of contours. Electrostatic potential derived charges were also computed using Breneman’s procedure [8] and can be used as a first guess towards predicting complementary receptor environment before modeling the receptor. Complete molecular electrostatic potential over the whole molecule
in the form of grid has been computed and depicted in the form of isopotential contours utilizing the graphics package MOLDEN [9].

2.6 Receptor Mapping

The receptor charge environment is assumed to be complementary to the drugs binding at the receptor. With this concept the common features of drug's charge environment are extracted and the complementary charge environment of the receptor is predicted. This is compared with the experimental information on receptor's charge environment based on the active residues and site directed mutagenesis studies.

2.7 Modeling the active site

To simulate a model of the active site all information about amino acid residues within 10Å radius is collected from mutagenesis and X-ray studies. Selected residues, which are nearest to the drug, are placed as efficiently as possible utilizing all the available information regarding the position and conformation of the residue and thus a model of drug interacting with active site residues is prepared.
2.7.1 Interaction Energy calculations

The interaction energy of the drug with the active site residues is calculated for the above-prepared model using a supermolecule type approach.

\[ \Delta E_{\text{int}} = E_{AB} - (E_A + E_B) \]

Where \( E_{AB} \) is the HF energy of the supermolecule and \( E_A \) and \( E_B \) are the energies of the two fragments.

2.7.2 Correlating interaction energy with potency

The last step of quantum pharmacology is to find out any possible correlation between drug-receptor interaction energies calculated as above and available IC\(_{50}\) data. The correlation clearly indicates the important residues in the active site, which help in binding the drugs and its inhibitory action.

All calculations described in the above sections have been carried out using ab initio M.O. calculations packages Gaussian 98 [10] and MUNGAUSS [11].
References


11. R.A. Poirier, M. R. Peterson and A. Yadav MUNGAUSS, Department of Chemistry, Memorial University of Newfoundland, St. Johns' Newfoundland, Canada.