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**MASARYK UNIVERSITY**  
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Ph.D. Thesis

Partial Atomic Charges and Their  
Chemoinformatics Application

Brno 2021

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To my grandma.

## **Acknowledgements**

## Declaration

I hereby declare that this dissertation thesis is my original authorial work, which I have worked on alone. All sources, references and literature used or excerpted during the elaboration of this work are properly cited and listed in a complete reference with regard to the source.

Brno, xxth xxxxxxxx 2021 ..... Stanislav Geidl

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# **Part I**

## **Introduction**

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# Introduction

In recent years, a vast amount of data about various types of molecules became available. For example, we can obtain the complete human genome of a selected individual in a few days, and about 150 thousand biomacromolecular structures have been determined and published (Protein Data Bank [1]). Furthermore, more than 100 million various small molecules are described in freely accessible databases (e.g., Pubchem [2], ZINC [3], ChEMBL [4]). This richness of data caused the formation of novel modern life-science research fields focused on the utilization of this data. The best-known modern life sciences are bioinformatics, structural bioinformatics, systems biology, genomics, proteomics, and also chemoinformatics. These current research specializations have provided many key results in basic and applied research (e.g. [5–11]).

One fascinating and beneficial field utilizing and processing newly available data about small molecules (i.e., drug-like compounds) is chemoinformatics. This discipline offers methodologies for comparing molecular similarity, molecular database search, virtual screening, and the prediction of molecules' properties and activities. This prediction is based on the idea that molecular structures' similarity has a consequence – a similarity in molecular properties. In chemoinformatics, the structure is first described using mathematical characteristics (so-called descriptors) – numbers containing 3D (or 2D or 1D) structure information and applicable as inputs of mathematical models. Then, these models are constructed based on a relation between descriptors and known values of the property or the activity. Such models are called Quantitative Structure-Property Relationship (QSPR) models or Quantitative Structure-Activity Relationship (QSAR) models.

A property, which is strongly required and is therefore often a target of chemoinformatics prediction models is the acid dissociation constant,  $K_a$ , and its negative logarithm  $pK_a$ . Those  $pK_a$  values are of interest in chemical, biological, environmental, and pharmaceutical research [12–14].  $pK_a$  values have found applications in many areas, such as evaluating and optimizing drug candidate molecules, pharmacokinetics, ADME profiling, understanding protein-ligand interactions, etc. Moreover, the critical physicochemical properties such as permeability, lipophilicity, solubility, etc., are  $pK_a$  dependent. Unfortunately, experimental  $pK_a$  values are available only for a limited set of molecules. In addition to that, obtaining experimental  $pK_a$  values for newly designed molecules is very time-consuming because they must be synthesized first. Chemoinformatics approaches for  $pK_a$  prediction are therefore currently intensively examined.

For this reason, I also focused on the chemoinformatics way of  $pK_a$  prediction in my work. Very promising descriptors for  $pK_a$  prediction are partial atomic charges [] because they hold



information about the distribution of electron density within the molecule. Specifically, electron densities on atoms close to the dissociating hydrogen provide a clue about its dissociation ability. The most common and accurate method for calculating partial atomic charges is an application of quantum mechanics (QM). QM calculation can be performed via various approaches, introducing different approximation levels (i.e., approximating a wave function by different sets of mathematical equations, which are called basis sets). QM outputs electron distribution in orbitals and this distribution can be divided into individual atoms using several charge calculation schemes (e.g., MPA, NPA, AIM, Hirshfeld, MK, etc.). Therefore, the correlation between  $pK_a$  and relevant atomic charges calculated by different QM approaches has been analyzed []. I also focused on this file in my bachelor thesis, developed a workflow for calculation of  $pK_a$  using QM partial atomic charges and examined, which types of QM are the most suitable [].

QM charges are accurate, but their calculation is very time-consuming. A faster Alternative to QM charges is empirical charge calculation approaches. Furthermore, if we would like to apply chemoinformatics  $pK_a$  prediction models practically – for example, in pre-screening large sets of drug candidates – we need a fast approach. Therefore, in my master thesis, I developed a  $pK_a$  prediction workflow based on charges (including Electronegativity Equalization Method).

However, several pieces of the puzzle were still missing. For example, the developed  $pK_a$  prediction workflows [] were strongly dependent on 3D structure source, and also, the quality of available EEM charges was low.

Therefore, my dissertation’s goal was to develop a workflow that predicts  $pK_a$  for molecules not synthesized yet and without available experimental 3D structures.

Specifically, the thesis examined how to improve the process of  $pK_a$  prediction via providing suitable inputs. First, the influence of 3D structure source on  $pK_a$  prediction accuracy was analyzed. Afterward, the work focused on obtaining high-quality partial atomic charges, which served as descriptors for  $pK_a$  calculation. In the end, the authors also support the development of methodology and software tools for obtaining these high-quality charges.

The thesis structure is the following: First, an overview of key fields is provided (Part II), i.e. – 3D structure and approaches for its prediction, charge calculation methods, and  $pK_a$  prediction approaches. Next, the achieved results, which we published in three research papers, are briefly described (Part III), and full-texts of the respective published papers are attached in Appendix: Main papers. During the elaboration of this thesis, I was also involved in other projects. Most of them were not related to  $pK_a$  prediction but tightly connected to the field of chemoinformatics or structural bioinformatics. The outcome of these projects consists of several papers and a book I have co-authored. Their title pages are attached in Appendix: All My Publications.

# **Part II**

## **Theory and Methods**

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## Structure

### 2.1 Molecular Structure in Computer

The chemical structure is the essential information for chemoinformatics and computational chemistry calculations. We recognize different types of chemical structures according to the complexity of information [15].

The empirical or chemical formula provides information about molecule composition – elements and their count. The structural formula (2D structure) extends this information about topology – bonds between atoms. The three-dimensional structure also provides the conformation of a molecule – the relative placement of atoms in space. We try to provide conformation with the lowest energy representing the most probable conformation of molecule in reality. For some applications, there can even be an assembly of these 3D structures.

In chemoinformatics, two-dimensional structures are often used, but the three-dimensional structure can often bring new information into the *in silico* calculations or models. On the other hand, this 3D structure can be obtained experimentally for a limited number of small molecules. What with other molecules, including those which were not synthesized yet?

### 2.2 3D Structure Calculation

We apply more computationally efficient methods for 3D structure computation because we use them as input for high-throughput methods. For this reason, many resources were devoted to the development of fast and accurate 3D structure prediction methods [?]. These can be classified into the following groups []: rule-based and data-based, fragment-based, numerical methods, and conformational analysis. These rule-based and data-based, fragment-based methods are partially overlying.

#### 2.2.1 Rule-Based and Data-Based Methods

These methods [] use chemical knowledge of geometric and energetic rules known from experiments and theoretical calculations. In these methods, we use rules explicitly to describe, e.g., bond lengths and angles; we use data implicitly to describe, e.g., ring conformation.

### 2.2.2 Fragment-Based Method

The fragment-based method [] is the incremental method using rules in the first step to fragment a structure into parts. According to the following rules, the parts are assembled by linking fragment templates from a library (database). Predicted structures are created from the most similar and largest fragments in a database as possible.

### 2.2.3 Numerical Method

These numerical methods [] consist of three methods: molecular mechanics (MM), quantum mechanics, and distance geometry (DG). Distance geometry is a great tool to prepare a reasonable initial structure, which is very close to some low-energy conformation. For this structure, we can use the optimization process from MM or/and QM.

### 2.2.4 Conformational Analysis

This method [] generates a set of conformations for one molecule using different approaches - genetic algorithms, systematic methods, random techniques, Monte Carlo or MD simulation. The one or more different structures are selected based on criteria such as the number of conformers, minimum RMSD [], only conformations with the lowest MM energy (low-energy conformers).

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## Partial Atomic Charges

### 3.1 The Concept of Atomic Charges

Atomic charges are a theoretical concept for the quantitative description of electron density around every atom in a molecule. The first basic concept came from early chemistry, where an integer expressed these charges (e.g. -1, +2). Later, they were a real number (partial charge) in organic chemistry and physical chemistry [16]. It is a great approach to explain the mechanism of a lot of chemical reactions. Recently, partial atomic charges also became popular in chemoinformatics, as they proved to be informative descriptors for QSAR and QSPR modeling [17, 18] and for other applications [19–21]; they can be utilized in virtual screening [22, 23] and similarity searches [24, 25]. In reality, we are not able to measure these numbers, only calculate or estimate them. For such reasons, many different approaches for the calculation of partial atomic charges were developed.

### 3.2 Overview of Charge Calculation Methods

#### 3.2.1 QM Charge Methods

These methods use a wave function as a starting point and then apply subsequent population analysis, charge calculation scheme, or fit to some physical observation [?].

Mulliken population analysis (MPA) [26, 27] simply calculates a charge of an atom as a sum of an electron density from its molecular orbitals and a half of an electron density from its bonding orbitals. Natural population analysis (NPA) [28, 29] sophisticatedly improves the MPA method by orthogonalization of specific atoms and after this, NPA performs charge assignment from electron density the same way as in MPA. NPA atomic charges are more stable and independent of the size of basis sets. Other possible population analyses are Löwdin population analysis [30], Hirshfeld population analysis [31].

AIM (atoms-in-molecules) charge calculation scheme is based on the idea that electron density measured by X-ray can help with the calculation of partial charges. Bader and his coworkers [32, 33] defined an atomic volume that is used for charge calculation. Other well-known approaches are electrostatic potential fitting methods (ESP) like CHELPG [34] or MK (Merz-Singh-Kollman) [35] and their extension – RESP methods [?].

Cramer and at [36] also developed semiempirical methods – charge model 5 (CM5), which extends Hirshfeld population analysis by empirical parameters to reproduce charge-dependent observables.

### 3.2.2 Empirical Methods

Empirical approaches use only empirical parameters, and some of these can calculate charges from the 3D structure or only from the topology (2D structure) of a molecule. Therefore, they are distinctly faster than QM approaches.

One of the first empirical methods developed, CHARGE [67], performs a breakdown of the charge transmission by polar atoms into single-bond, double-bond, and triple-bond additive contributions. Other empirical methods have been developed on the electronegativity equalization principle. One group of these empirical approaches are using the Laplacian matrix formalism and the product is a redistribution of electronegativity: Gasteiger-Marsili (PEOE, partial equalization of orbital electronegativity) [37,38], GDAC (geometry-dependent atomic charge) [?], KCM (Kirchhoff charge model) [39], DENR (dynamic electronegativity relaxation) [40] or TSEF (topologically symmetric energy function) [40].

The second group of approaches applies the full equalization of orbital electronegativity. For example, this group contains EEM (electronegativity equalization method) [41] and its extensions (ABEEM [?], SFKEEM [17]), QEq (charge equilibration) [39], EQEq (extended QEq) [?], or SQE (split charge equilibration) [40].

Group of conformationally independent methods (based on the 2D structure) contains CHARGE, Gasteiger-Marsili, KCM, DENR, and TSEF. Group of conformationally dependent – geometrical charges (based on the 3D structure) also consider an influence of conformation and includes the following methods: GDAC, EEM, ABEEM, SFKEEM, QEq, EQEq, and SQE.

A typical representative of the topological method is the Gasteiger-Marsili method, which first assigns charges based on atom types and then iteratively updates atomic charges based on the closest partners. The correction is smaller and smaller in every step until the sixth step when these corrections are too small and atomic charges are final. Empirical parameters for this method were calculated from QM.

On the other hand, the EEM method needs a complete 3D structure and more applicable charges for some of the applications.

## 3.3 EEM Calculation

EEM (electronegativity equalization method) [41] is one of the most popular empirical charge calculation methods and was developed more than twenty years ago. This method’s new parameterizations [D17, D56–D62] and extension [D59, D63, D64] are still under development. An advantage of EEM calculation is that it considers the influence of the molecule’s conformation on the atomic charges. For this reason, EEM charges are often used in predictive models as chemoinformatics regressors (descriptors) [D65].

EEM is based on three principles:

The first principle is Sanderson’s electronegativity equalization principle. It assumes that the effective electronegativity of each atom in the molecule is equal to the molecular electronegativity:

$$\chi_1 = \chi_2 = \dots = \chi_x = \bar{\chi} \quad (3.1)$$

where  $\chi_x$  is the effective electronegativity of the atom  $x$  and  $\bar{\chi}$  is the molecular electronegativity.

The second principle is the principle of the charge balance. The sum of all charges is equal to the total charge  $Q$ :

$$\sum_{x=1} q_x = Q \quad (3.2)$$

where  $q_x$  is the charge of the atom  $x$ .

And the last principle is the principle of charge-dependent electronegativity. This principle is the definition of atomic electronegativity, and states that the electronegativity of each atom can be expressed as a function of its charge:

$$\chi_x = A_x + B_x \cdot q_x + \kappa \sum_{y=1, x \neq y}^N \frac{q_y}{R_{x,y}} \quad (3.3)$$

where  $R_{x,y}$  is the distance between atoms  $x$  and  $y$ , and the coefficients  $A_x$ ,  $B_x$  and  $\kappa$  are empirical parameters.

These principles can be summed up to a system of equations with  $N + 1$  unknowns (where  $q_1, q_2, \dots, q_N$  and  $\bar{\chi}$ ):

$$\begin{pmatrix} B_1 & \frac{q_y}{R_{1,2}} & \dots & \frac{q_y}{R_{1,N}} & -1 \\ \frac{q_y}{R_{2,1}} & B_2 & \dots & \frac{q_y}{R_{2,N}} & -1 \\ \dots & \dots & \dots & \dots & \dots \\ \frac{q_y}{R_{N,1}} & \frac{q_y}{R_{N,2}} & \dots & B_N & -1 \\ 1 & 1 & 1 & 1 & 0 \end{pmatrix} \cdot \begin{pmatrix} q_1 \\ q_2 \\ \dots \\ q_N \\ \bar{\chi} \end{pmatrix} = \begin{pmatrix} -A_1 \\ -A_2 \\ \dots \\ -A_N \\ Q \end{pmatrix} \quad (3.4)$$

## 3.4 Quality and Usability of EEM parameters

## 3.5 EEM Parametrization

## 4

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# Acid Dissociation COnstant Prediction

### 4.1 Motivation

### 4.2 Overview of Approaches

#### 4.2.1 LFER (Linear Free Energy Relationships) Methods

#### 4.2.2 Database Methods

#### 4.2.3 Ab Initio Quantum Mechanical Calculations

#### 4.2.4 QSPR Method



## **Part III**

## **Results**

# 5

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## Synopsis of the Results

## 6

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### **Follow-up work and future plans**

## **Part IV**

# **Conclusion**

**7**

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## **Conclusion**

# **Appendix**

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## **Appendix: Main papers**

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## **Appendix: All My Publications**

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# Curriculum Vitae