

# Chapter 4

## Quantitative Structure–Activity/ Property/Toxicity Relationships through Conceptual Density Functional Theory–Based Reactivity Descriptors

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### ABSTRACT

*Developing effective structure-activity/property/toxicity relationships (QSAR/QSPR/QSTR) is very helpful in predicting biological activity, property, and toxicity of a given set of molecules. Regular change in these properties with the structural alteration is the main reason to obtain QSAR/QSPR/QSTR models. The advancement in making different QSAR/QSPR/QSTR models to describe activity, property, and toxicity of various groups of molecules is reviewed in this chapter. The successful implementation of Conceptual Density Functional Theory (CDFT)-based global as well as local reactivity descriptors in modeling effective QSAR/QSPR/QSTR is highlighted.*

### 1. INTRODUCTION

The properties of molecules mainly depend on the distribution of electron density within the individual molecules. It is, therefore, believed that molecules having similar structures will exhibit similar properties. On this hypothesis, the idea of structure-activity relationship (SAR) exists (Nantasenamat et al., 2009). Accordingly, it is assumed that molecules with similar structures exhibit comparable activities (properties), and, so on the basis of known properties of a set of molecules, prediction of the properties of unknown molecules having similar structures could be made, provided appropriate models are de-

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veloped. Models which are able to predict the properties of an unknown molecule on a qualitative basis are termed as Qualitative Structure-Activity Relationship models (Arning et al., 2008), and, the ones which can quantify such relationship are termed as Quantitative Structure-Activity Relationship (QSAR) models (Gramatica, 2007). Such QSAR models are very useful in the design of molecules which can serve as a better drug or in the manufacturing of materials which could serve as better substance in terms of utility, economy, durability and environmental effects in totality. The quest for such molecules begins with SAR studies. On the basis of activities of a set of molecules of similar structures or parameters, different SAR models are designed. Thereafter, those molecules which are found to have a potential to show a desired characteristic (property/activity) are filtered with the aid of such models, and, then the systematic efforts towards their syntheses begin. Thus, such an approach helps in the reduction of the cost effectively. Since a molecule can have different kinds of properties, a large number of QSAR models could be developed for the same set of molecules depending on their properties. Such properties could be physico-chemical properties, quantum-chemical properties or even toxicity properties. It clearly implies that not only the unknown toxicity parameter of a molecule of whose different parameters are yet to be assessed, could be determined, but its other set of properties could also be determined provided effective QSAR models are generated. When the attempt is to determine the toxicological effect of a molecule based on a model having correlation between structure and toxicity of already determined molecules, then such an approach is defined as Quantitative Structure-Toxicity Relationship (QSTR) model (Roy and Ghosh, 2004). Such models are very effective in the prediction of toxicity of molecules which have potential to act as a toxic substance. Thus, QSTR helps in building up of an effective regression model that helps in predicting the reactivity of an unknown molecule on the basis of behavior of an analogous set of chemically or structurally similar compounds.

QSTR models are proposed based on different parameters. Most often these parameters are defined in terms of descriptors. These descriptors could be based on different experimental and theoretical properties such as physico-chemical and quantum-chemical properties, respectively. One of the most popular and cheap methods in the field of quantum-chemical prediction of the properties of molecules is Density Functional Theory (DFT) (Parr & Yang, 1989). It predicts the properties of a molecule based on its molecular electron density. A closely related method describing the chemical properties such as electronegativity, ionization potential, hardness etc with the aid of DFT method is known as Conceptual Density Functional Theory method (CDFT) (Chattaraj, 2009; Chakraborty et al., 2010; Chattaraj & Giri, 2009; Geerlings et al., 2003). This method has been successfully and exhaustively employed in the generation of different descriptors, which have been able to produce QSAR and QSTR models of very high efficiency. Thus, CDFT has helped in the assessment of activity and toxicity of different molecules within the ambit of QSAR and QSTR respectively. It has been found that CDFT is quite cheaper in comparison to other expensive quantum-chemical methods such as *ab initio* methods. CDFT has been proven to develop effective and efficient QSTR models.

In this chapter, at first we have provided a general introduction highlighting the necessity of structure-activity/toxicity based regression models. Various QSAR/QSPR/QSTR based methods are outlined in section 2. Section 3 describes the conceptual density functional theory and the related global and local reactivity descriptors. Section 4 deals with the utility of electrophilicity index and net electrophilicity index and their local variants in predicting toxicity of various classes of molecules. Section 5 mentions about the importance of the group philicity towards modeling an effective QSAR. Section 6 highlights the effect of studied levels and / or basis sets in constructing QSAR/QSPR/QSTR models. Section 7 concludes the chapter by mentioning the effectiveness of various CDFT based descriptors in building QSAR/QSPR/QSTR models.

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