Guest Editorial Preface

Comments on the IJQSPR Perspectives

Jorge Galvez, Molecular Topology and Drug Design Research Unit, Department of Physical Chemistry, University of Valencia, Valencia, Spain

Even in the almost overcrowded field of chemical journals, especially in applied chemistry, IJQSPR can play a key role. During the years, the journal has gathered editors and authors among the most renowned names in the area of QSPR contributing to guarantee high standards in publications as well as new creative insights. Until very recently, the QSAR / QSPR methods were considered as simple complements to other methods with a more solid theoretical basis. They were classified within the semi-empirical methods, even if descriptors were derived from quantum chemistry, molecular mechanics or molecular dynamics, just to mention a few examples. Some scientists consider QSPR based on mathematical descriptors (usually topological descriptors) like a sort of black box, from which useful information may be extracted without a solid theoretical basis behind. This way of thinking is reflected in the quite common assert: "rational drug design." One would think that any design is rational and therefore that the sentence is redundant. However, the idea lying behind such statement, whether implicit or explicit, is that any design not based on a detailed knowledge of the receptor, as well as its interaction with the potential drug, is irrational. Moreover, following the same logic, such knowledge should be based on physical and / or geometric chemical descriptors, since those are the only interpretable by physics. This is far from being true. Many drugs have been discovered using QSPR based on molecular topology, without specific knowledge of the underlying mechanism of action (MOA). Furthermore, in many cases, the MOA was inferred from the mathematical models. So, instead of defining the topological description of a molecule like a black box, it may be adequate to talk about a valid alternative to the physical and geometrical description. In 2016, both Physics and Chemistry Nobel Prizes were awarded to researchers who have used topology in describing and interpreting their experiments. This can be considered a key factor in establishing the topological paradigm. The Nobel Prize in Chemistry was awarded to Sauvage, Stoddart and Feringa for the design and synthesis of molecular machines in which molecular topology (as for instance in rotaxanes) is essential. While, the Nobel Prize in Physics was awarded to Thouless, Duncan, Haldane and Kosterlitz, for their theoretical discoveries on topological phase transitions and topological phases of matter. This is important because for the very first time in experimental Physics, energy is considered to be dependent on topology - and not the contrary, as commonly assumed so far.

Another notable contribution of IJQSPR is linked to the development of new statistical techniques, big data analysis and artificial intelligence; just to mention a few examples, artificial neural networks and machine learning. All these techniques have enabled substantial improvement in the development of predictive QSPR mathematical models and have been in the spotlight, thanks to the IJQSPR publications. In this regard, our group has recently discovered new chitin deacetylase (CDA) inhibitors developing a QSPR study based on just one single active molecule described in literature. CDA catalyzes the formation of chitin in three different parasites: fungi, nematodes and arthropods, therefore it can be used in controlling pathogenic strains or vectors of these species (including mosquitoes, nematodes or fungi). In fungi the process is interesting because the inhibition of CDA triggers the plant's immune system and thus eliminates the parasite. As far as we know this is a new mechanism of action and very unlikely to generate resistances (Pérez-García, Martínez

Cruz, Zanni et al., 2019). The possibility to perform a successful QSAR/QSPR study starting from a database comprised of only one active molecule is groundbreaking and is in contrast with up to date supposed irrefutable principle that at least several active compounds are required to create an efficient training set and develop a reliable QSAR/QSPR model.

We cannot talk about QSAR/QSPR without mentioning 3D-QSAR. Here, the basic idea is that the properties related to biological activity (ligand-receptor interaction) depend on 3D molecular characteristics. Many different ways exist for taking into account such a feature. One consists of the Cramer analysis (CoMFA). Here changes in shapes and intensities of non-covalent calculated interaction surrounding the molecules (also called molecular interaction fields, MIFs) are considered. This also works in other cases. For example, for chiral molecules it is possible to follow very simple algorithms, such as the introduction of a weight into the adjacency matrix just in the corresponding entry, depending on the R or S character of the chiral center (for example a chiral carbon) to distinguish between enantiomers or diasteroisomers's behavior. For example, it allowed our group to distinguish between active and inactive chiral analgesics (de Julián-Ortiz, de Gregorio Alapont, Ríos-Santamarina, García-Doménech & Gálvez, 1998).

Finally, during the last decade, multi-target QSAR (mt-QSAR) models have been developed, showing significant advantages with respect to conventional approaches. The main improvement is the possibility to predict the activity over different biological targets, including macromolecules, cell lines, bacteria, etc. (Speck-Planche & Cordeiro, 2015) simultaneously. A special mention goes to mt-QSAR for the prediction of drug interactions with specific gram negative proteins. This is a powerful tool to exploit in the near future for the design and development of new molecules against Gram-negative bacterial resistances, which are responsible of the death of up to 700 thousand people yearly worldwide (O'Neill, 2016).

In summary, it seems clear that all these arguments and topics support the idea that QSPR methods will continue to be of great importance and that IJQSPR is a journal that has come to stay for many years and to spread a branch of knowledge considered until recently as the poor relative of computational chemistry.

Jorge Galvez
Guest Editor
IJQSPR

REFERENCES

de Julián-Ortiz, J. V., de Gregorio Alapont, C., Ríos-Santamarina, I., García-Doménech, R., & Gálvez, J. (1998). Prediction of properties of chiral compounds by molecular topology. *Journal of Molecular Graphics & Modelling*, *16*(1), 14–18. doi:10.1016/S1093-3263(98)00013-8 PMID:9783256

O'Neill, J. (2016). Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. *The Review on Antimicrobial Resistance*. Retrieved from https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

Pérez García, A., Martinez Cruz, J., Zanni, R., Romero Hinojosa, D., Fernández Ortuño, D., Gálvez Llompart, M., García Domenech, R., & Gálvez Álvarez, J. (2019). Chitin deacetylase inhibitors and their use as agricultural fungicides, arthropocides and nematicides (p201930440). Patent pending.

Speck-Planche, A., & Cordeiro, M. N. (2015). Simultaneous Prediction of Activities against Biomacromolecules Present in Gram-Negative Bacteria. *Current Topics in Medicinal Chemistry*, *15*(18), 1801–1813. doi:10.2174/1568026615666150506144814 PMID:25961517