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Editorial Open Access

The Need for an Integrated Computational/Experimental Approach in the Discovery and Design of New Drugs

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Among all the main problems of haemostasis, we can cite the discovery of novel anticoagulants without side effects. Ever since the discovery of the anticoagulant properties of hirudin from the leech saliva, the increasing relevance of thromboembolic diseases has encouraged a continuous search for new compounds with anticoagulant activity, which has led to the development of the new commercially available anticoagulants [1]. One of the targets for prophylaxis and treatment of thromboembolic diseases is the plasma anticoagulant antithrombin. This protein circulates in blood in a metastable conformation, in which the reactive centre loop is partially inserted and is only activated by heparin and heparan sulfate glycosaminoglycans on the injured subendothelium [2]. Accordingly sulfated polysaccharide heparin chains with different size, from unfractionated to the essential pentasaccharide, have been used with more or less success in anticoagulant therapy and thromboprophilaxis [3]. In the last decades new molecules able to bind antithrombin have been identified. The strategies used in this search have been based mainly on the synthesis or chemical modification of existing drugs, or in the application of natural compounds with similar properties to those currently used [2]. Examples for such compounds are lignins and flavonoids [1,4], highly sulfated small organic ligands that seem to have similar properties to heparins.

Therefore, the discovery of novel or improved drugs for given diseases or special groups of patients, is a very slow and expensive process. Nevertheless, recent results demonstrate the discovery using Virtual Screening (VS) of a novel molecular scaffold [5], different to the previous ones based on heparin. Using this alternate approach, a large database of millions of chemical compounds is screened in-silico and affinity-ranking is used to identify some at least weakly-binding molecules for further refinement. Aided by ever-increasing computational power [3,6,7], VS is an appealing and cost-effective approach to tap into the wealth of available structural information [8,9]. Consequently, novel and enhanced VS methodologies, conveniently exploited in innovative drug discovery strategies can lead to significant and quantifiable developments.

An example of research group that performs drug design and discovery in this direction is the "Bioinformatics and High Performance Computing Research Group (BIO- HPC)", as stated on their website (http://bio-hpc.eu). This research group works in many different but completely related research areas such as:

a) High Performance computing: their research interest includes massively parallel architectures such as Graphics Processing Units, Intel Xeon Phi and Heterogenous processors, as well as bio-inspired algorithms such as Ant Colony Optimization [10], to evaluate the newest frontiers of computing. We are also working in applying these techniques to challenging problems in the fields of Science and Engineering [11,12].

b) Prediction studies of the biological activity of chemical substances by QSAR methods: their work is mainly focused on the search for structural alerts [13,14] for mutagenicity especially less studied for two trials (trials in mammalian cells and in vivo micronucleus studies) but also accepted by the OECD (Organization for Economic Cooperation and Development) for classification of mutagenicity of chemicals. They are also working with several universities to develop predictive QSAR models for different activities (study of antioxidant activity [15] and inhibition of human monoamine oxidase [16]). During this work they also make their contribution to the development of QSAR methodology [17].

c) Advanced Data Clustering Methods: Among the most relevant techniques used for pattern recognition, they develop and apply fuzzy clustering algorithms. These algorithms do not rely on assumptions common to conventional statistical methods, using the theory of fuzzy set. In the literature of fuzzy clustering, the fuzzy c-means (FCM) clustering algorithms defined by Dunn [18] and generated by Bezdek [19] are the well-known methods in cluster analysis. Recently Antonio et al. [20] and Soto et al. [21,22] showed modifications of FCM that improving probabilities in a fuzzy clustering partition. Currently, they are developing their own algorithms for applications in drug discovery, and big data, using HPC.

d) Development and application of Computational Intelligence Methods: Virtual Screening (VS) methods can considerably aid clinical research, predicting how ligands interact with drug targets. However, the accuracy of most VS methods is constrained by limitations in the scoring function that describes biomolecular interactions, and even nowadays these uncertainties are not completely understood. In order to improve accuracy of scoring functions used in most VS methods they propose [23-25] a hybrid novel approach where neural networks (NNET) and support vector machines (SVM) methods are trained with databases of known active (drugs) and inactive compounds, this information being exploited afterwards to improve VS predictions.

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e) Biophysics of Ion Channels: Many physiological properties of undifferentiated mouse embryonic stem cells (mESCs), such as ion channel function, are not fully understood. Ion channels are thought to be involved in cell proliferation and to play an important role in mESCs differentiation. The aim of their study is to characterize functional ion channels [26,27] in cultured undifferentiated mESCs and their role in cell proliferation and differentiation, and apply obtained results to applied projects in drug discovery.

Thus, we consider that in order to make efficient progress in drug discovery areas, a multidisciplinary research group, such as the one described in the previous paragraphs is necessary, and that research groups whose research line(s) are strictly focused on much concreted research areas cannot efficiently contribute to the development of the drug research field.

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