Molecular dynamics: New advances in drug discovery Preface

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Editorial

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1. Preface

Over the past years, a myriad of new biologically active molecules have been synthesized or isolated from natural sources. But, in the last decade, despite the intense research efforts devoted to the discovery of new effective drugs, out of 10,000 new drug candidates proposed per year only one has been selected for clinical treatments. Why medicinal chemistry makes such low progression?

Plainly, there is a crying need to find ways to design (and screen) an increasingly large number of promising drug candidates at the lowest possible cost. Moreover, the entire drug discovery process has to be streamlined in such a way that compounds that pass the screening move quickly along the development pipeline. The majority of the significant successes in the medicinal chemistry area have been mostly achieved after the discovery of novel targets – e.g. metabolic pathways and enzymes. But now it is fair to state that, while chemists have been successful in providing new medicines that have significantly improved our capacity to treat some diseases (e.g. the discovery of protease inhibitors for the treatment of virus infections including HIV and kinase inhibitors used in the therapy of several tumors to mention a few), we are still far away from being able to tackle new challenging targets, such as amyloid aggregation and protein–protein interaction as well [1]. The most relevant progresses have been made in the investigation of 3D structures of ligand–receptor complexes by NMR or X-rays crystallography. Both these two experimental techniques provide a powerful tool to scrutinize the binding of a biologically active substance to its target. Drug–target interactions can thus be investigated with high precision and displayed in three dimensions – a key preliminary step for the development of new active molecules. However X-rays crystallography provides only “frozen” protein structures and NMR methods may not be applied to large biomacromolecules.

Computational chemistry has effectively complemented these experimental techniques providing a valuable contribution in the field of drug discovery [1]. The term “virtual screening” was used for the first time in the late 90s. It describes the use of in silico methods for the identification of new molecules with potential employment in therapy. Since those early attempts, many software tools have been developed and applied for the discovery of new lead compounds [2–8]. Nevertheless, although a large number of virtual screening methods have proved to be successful in many circumstances [9] their real potential in driving a particular drug discovery project to the market has been questioned. It would seem that the major success of virtual screening methods so far has been the identification/elimination of the mass of inactive molecules for a certain target rather than the selection of active drug candidates [8]. Moreover, the development of virtual screening software with higher accuracy and reliability has been stagnating in the last years, also probably because many academic groups have focused on the application of virtual screening in the industrial R & D. Significant advances in virtual screening campaigns are expected to occur only after that a deeper understanding of the motions that regulate protein folding and/or ligand–target dynamics has been reached. Automated docking has made much progress in obtaining reliable ligand poses but the scoring functions used to rank the different binding modes are still rather coarse [10–12]. Flexible binding modes, the role of water molecules and protonation states should lie at the root of a new thinking of the use of computational chemistry in drug design where a dynamic description of the ligand–target complexes has to replace the traditional – static – vision of the investigated systems. Molecular dynamics (MD) simulations, due to the impetuous advances in computing power and in simulation models, have recently evolved into a potent tool for investigating the dynamics and the structures of biomolecular complexes [13]. MD simulations treat biomolecules and solvation water as particles interacting one another through a classical potential energy function named “forcefield”. Integration of Newton's law of motions versus time provides information, at an atomistic level, of the conformational transitions of the investigated system. Of course, this wealth of information needs to be interpreted and complemented, if possible, by experiments. Well established experimental approaches are certainly available but offer a limited degree of characterization of the mechanical properties within large databases of target–drugs complexes at a reasonable cost. On the other hand the analytical capabilities of computational methods are evolving rapidly in their ability to accurately define the subtle and concerted structural dynamics that comprise target–drug assemblies. Towards this goal, the challenge of this special issue is to bring together a collection of different computational investigations required to link molecular mechanisms with cellular pathways and potential drug development.

Within this issue, H. Zhao and A. Caflisch, present several examples of in silico discoveries of tyrosine kinase inhibitors and bromodomain antagonists whose binding modes were predicted by automated docking and further corroborated by MD simulations. Final validation by X-ray crystallography of the outcome of computational data offers compelling evidence of the quality and reliability of these state-of-art molecular simulations.

M. Persico, L. Petrella, N. Orteca, A. Di Dato, M. Mariani, M. Andreoli, M. De Donato, G. Scambia, E. Novellino, C. Ferlini and C. Fattorusso have investigated, by using computational and biological studies, the interactions of guanylate-binding protein 1 (GBP1) with Proviral Integration of Moloney virus kinase (PIM1). GBP1 is a GTP-binding protein and an important component of the innate

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immune response because it mediates cellular responses to interferon gamma in infection and inflammation. Not surprisingly, over-expression of GBP1 is associated with different types of tumors. GBP1 and PIM1 interact at a molar ratio 1:1 and it is known that this protein–protein interaction initiates a signaling cascade that induces resistance to common chemotherapeutics such as paclitaxel. It turned out that GTP decreases the formation of the GBP1:PIM1 complex through an allosteric mechanism, paving the way to the identification of new compounds able to revert resistance to paclitaxel.

G. Palermo, U. Rothlisberger, A. Cavalli and M. De Vivo review how computational studies based on classical molecular dynamics, full quantum mechanics, and hybrid QM/MM methods have shed light on the binding and biological activity of some substrates and inhibitors of the Fatty Acid Amide Hydrolase (FAAH). FAAH plays an important role in the regulation of the endocannabinoid system and its inhibition is a promising strategy to cure a variety of diseases including pain, and inflammation. The authors discuss how computations have been helpful for building structure–activity relationships of FAAH inhibitors.

One of the hallmarks of Alzheimer's disease (AD) is the aggregation of the amyloid β (Aβ) peptide. P. Derreumaux, B. Tarus, P. H. Nguyen, O. Berthoumieu, P. Faller and A. J. Doig, have employed replica exchange molecular dynamics to simulate the self-assembly of the amyloid β (Aβ) peptide in the presence of 1,4-naphthoquinon-2-yl-L-tryptophan (NQTrp), a small molecule with a known capacity to inhibit amyloid aggregation. The authors show that the population of β-hairpin is reduced by a factor of 1.5 and the population of α-helix in the region 17–24 is increased by a factor of two upon NQTrp binding to Aβ. The results of this study point to these two evidences as key factors to reduce the pathogenic formation of peptide dimers and may suggest routes to the design of novel amyloid inhibitors with improved potency.

M. Cronin, M. J. Coolbaugh, D. Nellis, J. Zhu, D. W. Wood, R. Nussinov and Ma Buyong have combined computations and experiments to examine the impact of the V67L mutation on the stability and conformational dynamics of the *Mycobacterium tuberculosis* RecA (Mtu recA) mini-intein splicing domain. Inteins catalyze the ligation of flanking host exteins while excising themselves. Inteins may have interesting applications in drug design, as they are capable of undergoing selective activation of a protein, drug, or drug encapsulation in a viral coat. However, it is still a challenge to tightly control intein function within mammalian cells. The authors evidence that the V67L mutation stabilizes the global structure and that cooperative dynamics of all intein regions appear more important for intein function than high stability. These studies suggest that quenching the structural dynamics of inteins through engineered allosteric interactions may deactivate their splicing.

J. O. S. Giacoppo, D. T. Mancini, A. P. Guimaraes, A. S. Gonclaves, E. F. F. da Cunha, T. C. C. França, A. S. Gonçalves, and T. C. Ramalho have applied a mix of Molecular Dynamics, Docking calculation and experimental methods to predict new therapies against *Bacillus anthracis* (BaDHFR). The relevance of this study is quite evident in order to prevent health issue in case of biological war. In particular they proposed new molecules with potential activities against BaDHFR.

A. P. Guimarães, F. R. de Souza, A. A. Oliveira, A. S. Gonçalves, R. B. de Alencastro, T. C. Ramalho, T. C. C. França have constructed a homology model of the enzyme thymidylate kinase from Variola virus (VarTMPK). Next, they used the antivirals cidofovir and acyclovir as reference compounds to choose eleven compounds as lead to the drug design of inhibitors for VarTMPK. Docking and molecular dynamics (MD) studies of the interactions of these compounds inside VarTMPK and human TMPK (HssTMPK) have evidenced that they compete for the binding region of the substrate and were used to propose the structures of ten new inhibitors for VarTMPK. Further MD refinement simulations suggest that nine among ten are potential selective inhibitors of VarTMPK.

U. S. Sudheendra, V. Dhople, A. Datta, R. K. Kar, C. E. Shelburne, A. Bhunia and A. Ramamoorthy have addressed, by an array of computations and experimental techniques, the capacity of Human beta defensin-3 (HβD-3) to interact with zwitterionic or anionic model membranes. There is considerable interest in the function of this protein due to its antibacterial activity against Gram-positive *Staphylococcus aureus*. The whole of the results have demonstrated the importance of the positively charged residues at the HβD-3 C-terminus in providing selectivity to Gram-negative bacteria.

L. Russo, M. Palmieri, J. V. Caso, G. D'Abrosca, D. Diana, G. Malgieri, I. Baglivo, C. Isernia, P. V. Pedone and R. Fattorusso, have characterized in silico the prokaryotic Cys2His2 zinc finger motif, included in the DNA binding region (Ros87) of Ros protein from *Agrobacterium tumefaciens*. Cys2His2 zinc finger motifs are known to be the most important structural domains playing a major role in driving protein–DNA interactions in eukaryotes. The authors investigated ROS87–DNA interactions using a combination of Nuclear Magnetic Resonance (NMR) and Molecular Dynamics (MD) simulations data. They demonstrated that Ros87–DNA interaction involves the first two residues of the first α-helix of ROS87, and several residues located in the basic regions of the zinc-finger protein. They have also shown that the introduction of the protein flexibility in docking studies is needed to improve, in terms of accuracy, the quality of the obtained models.

S. Decherchi, M. Masetti, I. Vyalov and W. Rocchia have reviewed existing theories and methods to estimate solvent effects in Molecular Dynamics. Solvation plays a fundamental role in many biological processes and especially in molecular binding. Its precise estimation is then of critical importance in MD simulations of biomolecules. In most of the currently adopted models, the solvent is considered as a continuum homogenous medium (implicit models), while the solute can be represented at the atomic detail and at different levels of theory. The authors highlight that, despite their degree of approximation, implicit methods are still widely employed due to their convenient trade-off between accuracy and computational costs.

I. Autiero, M. Saviano and E. Langella have investigated, by means of a molecular dynamics approach, the structural properties that drive the interaction of the chiral D-Lys-PNA (Peptide Nucleic Acid) and the corresponding achiral PNA system with DNA as well as RNA complementary strands. Currently, PNA finds useful applications in various areas of diagnostics and therapeutics including gene induction, for inhibition of translation, and also as probe to identify specific gene sequences or to recognize even a single gene mutation. The results obtained reconcile with experimental data and suggest that PNA/RNA recognition, if compared to DNA, results differently affected by the three D-Lys groups on the PNA backbone. These evidences suggest what modifications should be taken into account for the development of new PNA-based molecules able to discriminate between DNA and RNA.

Transmissible spongiform encephalopathies or prion diseases are characterized by accumulation of an insoluble form of the prion protein in the brain. Therefore, various studies have been directed toward the development of therapeutics for preventing the formation of this pathogenic prion isoform. N. S. Pagadala, R. Perez-Pineiro, D. S. Wishart and J. A. Tuszynski have developed and applied a new predictive 3D quantitative structure–activity relationship to rationalize the antiprion properties of 2-aminothiazoles. Molecular simulations combined with fluorescence studies have evidenced that these compounds bind to pocket-D of SHaPrP

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near Trp145 confirming the importance of this site in targeting prion pathogenesis.

In conclusion, computational methods have become a major focus in the academic and industrial pharmaceutical research, and the expectations of new effective drugs emerging from them are considerable. But, in many cases determining *a priori* whether or not a molecule will exhibit any therapeutical activity is a difficult process and as a matter of fact, of all the molecules designed by computational methods only a few have the planned biological activity. For example, we have still a limited control over the off-target activities of most of the molecules that are designed and synthesized. It is likely that in the very next future, new computational algorithms will routinely assist medicinal chemists in designing their own research thus fully realizing the potential of virtual screening methods. To this aim, this special issue will hopefully constitute a reliable source of information for medicinal chemists and contribute to attract researchers from other disciplines to get involved into this fascinating field.

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