J Comput Aided Mol Des (2012) 26:81–86
DOI 10.1007/s10822-011-9506-1

PERSPECTIVE

Molecular simulation methods in drug discovery: a prospective outlook

Xavier Barril · F. Javier Luque

Received: 14 November 2011 / Accepted: 30 November 2011 / Published online: 8 December 2011

Abstract Over the last decades, molecular simulations have spread through the drug discovery arena. This trend is expected to continue in the foreseeable future thanks to increased performance and the positive impact they can exert on productivity. In this article we highlight three aspects of molecular modelling for which we expect significant improvements over the next 25 years. Increased computational resources, faster algorithms and novel methods to sample rare events will provide a better handle on target flexibility and its relation with ligand binding. More accurate target druggability predictions will improve the success, but also broaden the scope of target-based drug discovery strategies. Finally, the use of higher levels of theory will increase the accuracy of protein–ligand binding affinity predictions, resulting in better hit identification success rates as well as more efficient lead optimization processes.

Keywords Molecular simulation · Drug discovery · Target flexibility · Target druggability · Binding affinity

Making predictions is always difficult, specially when one has to envisage the progress experienced by computational methods in drug discovery for a vast period covering the next 25 years. If someone asked us for the evolution of computer-assisted drug design 25 years ago, it would have been extremely challenging to give a precise description about the current impact of computational chemistry in drug discovery. At this point, let us simply recall that the formalism of 3D QSAR techniques established in the cornerstone paper about Comparative Molecular Field Analysis (CoMFA) by Cramer, Patterson and Bunce dates back to 1988 [1]. These techniques have played a tremendous influence in pharmaceutical research, as it is pinpointed by the large number of scientific articles (>2,000) that contain the words '3D QSAR' or '3D-QSAR' in the title of the manuscript since 1988. This example suffices to demonstrate the vitality and profound impact that computational methods have acquired in the last decades.

Nowadays computational methods pervade near all aspects of drug discovery [2]. Computer-assisted tools contribute to the decision making process along the whole pipeline leading from the identification and validation of suitable biomolecular targets to the end of the preclinical stage, including assessments about target druggability, high-throughput screening of molecular libraries to find hits promising for development, optimization of lead compounds within a complex cycle that involves design, synthesis and pharmacological assays, and the fine adjustment between pharmacological potency and physico-chemical properties that ensures an adequate biodistribution, efficiency and lack of toxicity upon administration. The penetration of computational tools in drug discovery has been facilitated by the continued increase in computer power in the last decades, and the elaboration of sophisticated algorithms developed to capture the complexity of physico-chemical principles that underlie the activity of drugs. This tendency can be expected to be reinforced in the next years,

X. Barril · F. Javier Luque (✉)
Departament de Fisicoquímica and Institut de Biomedicina (IBUB), Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, 08028 Barcelona, Spain
e-mail: fjluque@ub.edu

X. Barril
e-mail: xbarril@ub.edu

X. Barril
Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys 23, 08010 Barcelona, Spain

as noted for instance in the computational advances afforded by the development of computer applications adapted to graphical processing units (GPU) [3, 4].

Computer-assisted drug design is nevertheless just one of the components that contributes to developing and marketing a new drug. In fact, this process requires an integrative multidisciplinary effort that, besides computational methods, involves the assemblage of diverse technological advances in molecular biology, X-ray crystallography, combinatorial chemistry, high-throughput screening and genomics. However, this complexity likely explains the paradoxical situation experienced by Pharma industry, as the number of chemical entities released along the last years has risen only slightly in spite of the substantial increase in research and development (R&D) investment [5]. In fact, there is no guaranteed way to successfully discover marketable drugs and, as noted by Maryanoff [6, 7], 'drug discovery still depends heavily on one key factor: good luck!'.

How should then computational methods evolve to ameliorate the success of drug discovery? The answer to this question is related to the identification of the current limitations faced by computational algorithms to provide a precise understanding of the delicate balance between factors that determine both potency and ADMET properties of drug candidates. A complete analysis of the current challenges in computer-assisted drug research is beyond the scope of this Perspective, and therefore we limit ourselves to the discussion of three issues, which are the subject of an increasingly more intense research effort in the last years: protein flexibility, target druggability and prediction of binding affinity.

Target flexibility and ligand binding

One of the most relevant challenges in biomolecular simulations is linked to the prevailing view that biomolecular targets are dynamical entities, and that the recognition between a given ligand (metabolites, peptides, drugs,…) and its macromolecular target cannot be properly accounted for by the static description provided by a single structure of the ligand-target complex. Thus, beyond the rigid 'lock-and-key' model, binding events are now recognized to include a broader range of potential scenarios such as the popular 'induced fit' mechanism, the alternative 'conformational selection' process, or even more complex models that combine the selection of specific conformations with the induction of structural readjustments by the binding partner [8]. From a structural viewpoint, the inherent plasticity of biomolecular systems translates into a variety of conformational rearrangements triggered in binding events, which can range from local adjustments in side chains or even the protein backbone to large-scale motions of structural fragments, domains or even subunits [9].

Reproducing the inherent flexibility of biomolecules has thus become one of the most challenging issues in molecular modeling and simulation studies, as it has direct implications not only in fundamental understanding of structure–function relationships, but also for practical applications in areas such as virtual screening and structure-based drug discovery. As an example, let us simply quote a study about the structural adaptability in the ligand-binding pocket of the ecdysone hormone receptor published few years ago [10], where X-ray structures revealed radically different and only partially overlapping binding sites for steroidal and non-steroidal ligands. Remarkably, the ability to adopt different binding cavities highlighted the extreme flexibility of this protein, which allows the moulding of the receptor around its ligand and the formation of the proper ligand-binding pocket. The authors also recognized that the adaptability of the protein to the ligand and the ability to configure the ligand-dependent binding pocket 'could not be predicted by molecular modelling and docking studies'.

Given the intrinsic limitation of conventional simulation tools for sampling the configurational space of biomolecular complexes, only events occurring in short time scales can be reproduced at a high accuracy level through all-atom techniques such as Molecular Dynamics (MD) simulations. Accordingly, full atomistic MD calculations can be used to examine the flexibility of amino acid residues present in the binding site, to explore the binding complementarity between ligand and target, and eventually to extract suitable models for docking [11, 12]. However, larger structural rearrangements demand the use of enhanced sampling methods relying on modified descriptions of the biomolecular system (i.e., coarse-grained models) or the potential surface, leading to elaborate algorithms such as accelerated MD, replica exchange or metadynamics [13–20]. Undoubtedly, the development of multiscale simulation tools and enhanced samplings algorithms will disclose the crucial role of structural plasticity by facilitating the study of rare conformational events implicated in drug binding. Hopefully, in conjunction with the expected increase in computing power, the development of these techniques will permit to overcome the limitations currently posed by the intrinsic flexibility of biomolecular systems in elucidating the interaction between ligands and targets.

Target druggability

In early stages of drug discovery setting up the druggability of a given target represents a formidable challenge, as the success of this decision will have a direct impact on the

economical reward at the end of the highly demanding R&D process of delivering a marketable drug. Target-based drug discovery starts with the selection of a suitable receptor relevant for the modulation of a given pathological disorder. Since around 50% of drug discovery programs fail to produce viable leads even for a privileged target class such as enzymes [21], druggability prediction methods can make a major economical impact, directing the use of resources towards the most promising targets. Target druggability is then a key ingredient in the decision process, specially in the context of the human genome projects, which are expected to yield a sizable enhancement in the number of druggable targets [22, 23].

The ability of target sites to interact very favourably with small organic compounds has been associated to the presence of 'hot spots', while the rest of residues in the binding site conform the right shape and solvent exclusion properties for accommodation of the ligand, thus leading to the consensus that closed and lipophilic binding sites are more likely to be druggable [24–26]. However, polar groups in druggable binding sites have properties that enable them to play a decisive role in ligand recognition. Thus, polar groups act as anchoring points, as they are less solvent exposed due to the embedding in a predominantly hydrophobic environment, resulting in a lower dielectric environment that strengthens electrostatic interactions [27]. Then, a decrease in the polar surface ratio can have the paradoxical effect of increasing the electrostatic interaction energy of the binding site. On the other hand, the solvent exposure of polar atoms in druggable binding sites is a critical factor for their availability to interact with incoming ligands, enabling them to act as kinetic traps [28].

A precise knowledge of the chemical features of druggable binding sites, such as the balance between polar and apolar areas, the role of hydrophobicity in mediating the desolvation of the binding site and the incoming ligand, and the strength of the electrostatic interactions created by polar sites is fundamental to gain an accurate understanding of the thermodynamics and kinetics of ligand binding. In turn, this knowledge will be valuable to set up the definition of target "druggability", which nevertheless should not only include the notion of *chemical tractability*, but also the relationships of the target with other proteins and the role of the target in the pathogenesis of a given disease [29].

In this context, the ability to develop specific methods for druggability prediction, linked to the availability of curated datasets of systems encompassing various degrees of druggability, will be a fundamental tool not only in assisting target selection, but even more importantly in disclosing novel opportunities for therapeutic intervention associated to unpursued mechanisms of action, such as allosteric modulation, protein–protein inhibitors or pharmacological chaperones.

Protein–ligand binding affinity

Whereas target druggability demands a qualitative understanding of the physico-chemical features that contribute to drug binding, a quantitatively accurate estimate of binding affinity is required in other instances, such as the discrimination between different poses of a ligand in docking studies or the prediction of changes in the binding free energy associated to chemical modifications introduced in a drug candidate during lead optimization.

The binding affinity between a ligand and its macromolecular target stems from a subtle balance between enthalpic and entropic contributions [30]. The chemical complementarity between the functional groups present in the ligand and the residues in the binding pocket modulates the binding affinity through a variety of intermolecular interactions [31, 32]. This stabilizing term compensates for unfavorable contributions to the binding, such as desolvation of ligand and receptor, as well as the entropic loss upon formation of the ligand-receptor complex. In addition, this process can be accompanied by conformational changes in the interacting partners. The difficulty in predicting the binding affinity stems from the fact that the relatively narrow range of binding free energies stems from the compensation between generally large enthalpic and entropic terms, so that small changes in the binding free energy mask sizable and mutually compensating changes in both enthalpy and entropy.

The accuracy in predicting the binding free energy depends on the ultimate goal of the study. For instance, in high-throughput screening scoring functions must combine speed and accuracy in order to explore chemical libraries and identify the most promising hits [33, 34]. Therefore, the main purpose is not to rank potential binders according to binding free energy, but to predict the likelihood for a molecule to bind to the target. Accordingly, scoring functions have intrinsic limitations that prevent them to provide an accurate estimate of the binding free energy. In this context, it is not surprising to find poor correlations between scores and binding free energies [35–37]. However, post-docking processing of the best ligand poses or lead optimization require computationally more demanding methods in order to improve the accuracy in predicting the binding affinity.

In the last years the MM/PB(GB)SA method has been widely used as an alternative method for re-ranking compounds [38–43]. Nevertheless, the accuracy of this technique for predicting binding free energies for structurally diverse compounds is affected by the specific details of the computational setup, including the simulation protocol, the definition of the dielectric constants for the interior of the protein, the atomic radii used to built up the solvent-accessible surface, the treatment of structural water

molecules or the calculation of the entropy term [44–48]. Caution is therefore required for routine applications of these techniques to lead optimization. Nevertheless, it is worth noting recent efforts made to improve the overall accuracy of these calculations by careful parametrization against known binding affinities for diverse protein–ligand complexes [49, 50].

In contrast to continuum-based techniques, the use of classical simulations in conjunction with free energy calculations (i.e., free energy perturbation, thermodynamic integration) have proved to be very valuable for predicting relative binding affinities arising from small chemical differences between structurally related compounds [51–53]. These techniques rely on a rigorous formalism that permits to convert one ligand to another by means of a coupling parameter. They also allow for an extensive sampling of the protein–ligand complex in a realistic environment. However, their accuracy is also affected by several factors. In particular, in the absence of large conformational changes that mediate ligand binding, which would require a very exhaustive sampling unaffordable by these techniques, the accuracy of the results is mainly limited by the quality of the force fields, which generally rely on a pairwise description of intermolecular interactions, thus neglecting the effect of specific terms such as polarization and charge transfer.

Current efforts are being conducted toward the improvement of biomolecular force fields. A significant example of this effort is the development of the AMOEBA polarizable force field, which includes elaborate expressions for intramolecular energy terms (such as accounting of the coupling between stretching and bending, and the inclusion of an harmonicity effects), a buffered 14-7 functional for van der Waals interactions, a multipolar expansion of the permanent electrostatic distribution at each atomic center (up to quadrupole moments), and the treatment of polarization effects via inducible point dipole moments, together with validation against quantum mechanical (QM) data [54]. Other examples are the sum of interactions between fragments ab initio (SIBFA) and the quantum mechanical polarizable force field (QMPFF) [55], where an extensive calibration of the different terms is performed by fitting to high-level QM data [56, 57].

The accuracy achieved by QM methods justifies not only the increasing tendency for constructing and refining the separate energy components of classical force fields [58–60], but also the exploration of these methods for the evaluation of the binding affinity. In fact, Raha and Merz reported in 2005 a large-scale validation of a QM-based scoring function for predicting the binding affinity of a diverse set of ligands, where the protein–ligand interaction was determined using the divide-and-conquer method and the semiempirical AM1 or PM3 hamiltonians in conjunction with the classical attractive component of the Lennard–Jones interaction potential [61]. More recently, Merz and coworkers used a mixed quantum mechanics/molecular mechanics (QM/MM) approach as scoring function for a set of 23 metalloprotein–ligand complexes [62]. QM/MM calculations have been used by other authors to explore the protein-ligand interaction in a variety of molecular complexes. For instance, Hensen et al. found that the explicit treatment of polarization effect via QM/MM calculations was crucial for discriminating the interactions of high affinity inhibitors of HIV-1 protease [63], and Zhou et al. [64] reported that a QM description was necessary when the inhibitor/protein complexes have highly variable charge–charge interactions. A successful application to metalloproteins was also presented by Khandewal et al. [65]. A QM-based end-point method for calculating the binding free energy in ligand–protein complexes termed MM/QM-COSMO has been reported by Cavasotto and coworkers as an efficient strategy to improve the accuracy of electrostatic interactions [66]. Similarly, Hobza and coworkers have examined the reliability of the PM6 hamiltonian supplemented with dispersion and hydrogen bonding corrections for the interaction of diverses classes of inhibitors [67–69].

Based on the preceding discussion, it can be concluded that QM methods will have a profound impact not only as a tool to calibrate and refine force fields designed for biomolecular simulations, but also to develop novel computational strategies designed to provide accurate estimates of binding affinities. At present stage, it is clear that intense research efforts are still required to further calibrate the computational framework of QM-based strategies to develop reliable tools for the study of protein–ligand complexes. This requirement not only concerns the level of theory required for a reliable description of molecular interactions, but also the implementation of electronic structure codes in order to ensure an efficient evaluation of QM calculations. In this context, the efforts made for the redesign of quantum chemistry codes to GPUs appears very promising for the successful application to drug discovery [70–74].

Conclusions

Predicting the status of computational tools in 25 years time is an unattainable goal, especially when one keeps in mind the extraordinary progress of computational chemistry seen in the past 25 years. However, it is quite simple to predict what will be demanded from them in the field of drug discovery; the same as today: to accurately predict properties of biological systems that are too complex, too expensive or plainly impossible to measure experimentally. We have highlighted three areas that we believe are of

fundamental importance and will experience major progress in the next couple of decades. Understanding target flexibility is a necessary step towards correct predictions in all structure-based methods. This will be achieved thanks to longer simulation times, but also by combining unbiased all-atom simulations with coarse-grain and biasing potentials. Accurate detection of druggable binding sites will be necessary to extend the application of rational target-based drug discovery to underexploited targets (e.g. nucleic acids) and mechanism of action (e.g. allosterism). This will likely be achieved through a combination of better understanding of the unique properties of binding sites and the use of empirical methods. Finally, accurate predictions of receptor-ligand binding free energies is the highest goal, as it would significantly reduce the amount of required experimental testing and the time needed to develop new bioactive compounds. For methods based on first principles, the path is fairly obvious: increase the level of theory to reduce the errors due to the underlying approximations in simpler approaches. However, as the computational cost usually escalates with increased levels of theory, striking the right balance between computational feasibility and accuracy will be complicated. Not least because the optimal solution is going to differ depending on the application type (e.g. virtual screening vs. lead optimization) and is likely to evolve over time. All in all, we expect that molecular simulation methods will continue to increase their role in drug discovery becoming an ever more fundamental component of this multidisciplinary endeavour.

Acknowledgments This work was supported by the Spanish Ministerio de Innovación y Ciencia (SAF2008-05595, SAF2009-08811) and the Generalitat de Catalunya (2009-SGR00298).

References

1. Cramer RD III, Patterson DE, Bunce JD (1988) J Am Chem Soc 110:5959–5967
2. Jorgensen WL (2004) Science 303:1813–1818
3. Stone JE, Philips JC, Freddolino PL, Hardy DJ, Trabuco LG, Schulten K (2007) J Comput Chem 28:2618–2640
4. Schmid N, Bötschi M, van Gunsteren WF (2010) J Comput Chem 31:1636–1643
5. Service RF (2004) Science 303:1796–1799
6. Maryanoff BE (2004) J Med Chem 47:769–787
7. Maryanoff BE (2009) J Med Chem 52:3431–3440
8. Csermely P, Palotai R, Nussinov R (2010) Trends Biochem Sci 35:539–546
9. Spyrakis F, Bidon-Chanal A, Barril X, Luque FJ (2011) Curr Topics Med Chem 11:192–210
10. Billas IML, Iwema T, Garnier J-M, Mitschler A, Rochel N, Moras D (2003) Nature 426:91–96
11. Kua J, Zhang Y, McCammon JA (2002) J Am Chem Soc 124: 8260–8267
12. Alonso H, Bliznyuk AA, Gready JE (2006) Med Res Rev 26: 531–568
13. Hamelberg D, Mongan J, McCammon JA (2004) J Chem Phys 120:11919–11929
14. Liu P, Kim B, Friesner RA, Berne BJ (2005) Proc Natl Acad Sci USA 102:13749–13754
15. Cheng X, Cui G, Hornak V, Simmerling C (2005) J Phys Chem B 109:8220–8230
16. Tozzini V (2005) Curr Opin Struct Biol 15:144–150
17. Lei H, Duan Y (2007) Curr Opin Struct Biol 17:187–191
18. Gervasio FL, Laio A, Parrinello M (2005) J Am Chem Soc 127:2600–2607
19. Colizzi F, Perozzo R, Scapozza L, Recanatini M, Cavalli A (2010) J Am Chem Soc 132:7361–7371
20. Biarnés X, Bongarzone S, Vargiu AV, Carloni P, Ruggerone P (2011) J Comput Aided Mol Des 25:395–402
21. Macarron R (2006) Drug Discov Today 11:277–279
22. Russ AP, Lampel S (2005) Drug Discov Today 10:1607–1610
23. Overington JP, Al-Lazikani B, Hopkins AL (2006) Nat Rev Drug Discov 5:993–996
24. Hajduk PJ, Huth JR, Fesik SW (2005) J Med Chem 48: 2518–2525
25. Cheng AC, Coleman RG, Smyth KT, Cao Q, Soulard P, Caffrey DR, Salzberg AC, Huang ES (2007) Nat Biotechnol 25:71–75
26. Schmidtke P, Barril X (2010) J Med Chem 53:5858–5867
27. Gao J, Bosco DA, Powers ET, Kelly JW (2009) Nat Struct Mol Biol 16:684–690
28. Schmidtke P, Luque FJ, Murray JB, Barril X (2011) J Am Chem Soc 133 (in press)
29. Sheridan RP, Maiorov VN, Holloway MK, Cornell WD, Gao YD (2010) J Chem Inf Model 50:2029–2040
30. Gohlke H, Klebe G (2002) Angew Chem 41:2644–2676
31. Bissantz C, Kuhn B, Stahl M (2010) J Med Chem 53:5061–5084
32. Hunter CA (2004) Ang. Chem Int Ed 43:5310–5324
33. Taylor RD, Jewsbury PJ, Essex JW (2002) J Comput Aided Mol Des 3:151–166
34. Cavasotto CN, Orry AJ (2007) Curr Top Med Chem 7:1006–1014
35. Warren GL, Andrews CW, Capelli AM, Clarke B, LaLonde J, Lambert MH, Lindvall M, Nevins N, Semus SF, Senger S, Tedesco G, Wall ID, Woolven JM, Peishoff CE, Head MS (2006) J Med Chem 49:5912–5931
36. Sándor M, Jiss R, Keseru GM (2010) J Chem Inf Model 50:1165–1172
37. Plewczynski D, Lazniewski M, Augustyniak R, Ginalski K (2011) J Comput Chem 32:742–755
38. Lyne PD, Lamb ML, Saeh JC (2006) J Med Chem 49:4805–4808
39. Brown SP, Muchmore SW (2007) J Chem Inf Model 47: 1493–1503
40. Stoica I, Sadiq K, Coveney PV (2008) J Am Chem Soc 130: 2639–2648
41. Thompson DC, Humblet C, Joseph-McCarthy D (2008) J Chem Inf Model 48:1081–1091
42. Camps P, Formosa X, Galdeano C, Muñoz-Torrero D, Ramírez L, Gómez E, Isambert N, Lavilla R, Badia A, Clos MV, Bartolini M, Mancini F, Andrisano V, Arce MP, Rodríguez-Franco MI, Huertas O, Dafni T, Luque FJ (2009) J Med Chem 52:5365–5379
43. Tzoupis H, Leonis G, Durdagi S, Mouchlis V, Mavromoustakos T, Papadopoulos MG (2011) J Comput Aided Mol Des 10:959–976
44. Swanson JMJ, Adcock SA, McCammon JA (2005) J Chem Theory Comput 1:484–493
45. Weis A, Katenzadeh K, Söderhjelm P, Nilsson I, Ryde U (2006) J Med Chem 49:6596–6606
46. Wong S, Amaro RE, McCammon JA (2009) J Chem theory Comput 5:422–429
47. Jacob K, Ryde U (2009) J Comput Aided Mol Des 23:63–71
48. Genhenden S, Ryde U (2011) J Chem Theory Comput 7: 3768–3778

49. Traian S, Corbeil CR, Purisima EO (2010) J Chem Theory Comput 6:1608–1621
50. Traian S, Qizhi C, Purisima EO (2011) J Chem Inf Model 51: 2066–2081
51. Kollman PA (1993) Chem Rev 93:2395–2417
52. Free energy calculations. Theory and applications in chemistry and biology (2007) Chipot C, Pohorille A (eds) Springer series in chemical physics, vol 86. Springer, Berlin
53. Jorgensen WL (2009) Acc Chem Res 42:724–733
54. Poner JW, Wu C, Ren P, Pande VS, Chodera JD, Schnieders MJ, Haque I, Mobley DL, Lambrecht DS, DiStasio RA Jr, Head-Gordon M, Clark GNI, Johnson ME, Head-Gordon T (2010) J Phys Chem B 114:2549–2564
55. Piquemal JP, Chevreau H, Gresh N (2007) J Chem Theory Comput 3:824–837
56. Donchev AG, Ozrin VD, Subbotin MV, Tarasov OV, Tarasov VI (2005) Proc Natl Acad Sci USA 102:7829–7834
57. Donchev AG, Galkin NG, Pereyaslavets LB, Tarasov VI (2007) J Chem Phys 125:244107–244119
58. Misquitta AJ, Stone AJ (2008) J Chem Theory Comput 4:7–18
59. Söderhjelm P, Kongsted J, Ryde U (2010) J Chem Theory Comput 6:1726–1737
60. Luque FJ, Dehez F, Chipot C, Orozco M (2011) WIRES Comput Mol Sci 1:844–854
61. Raha K, Merz KM Jr (2005) J Med Chem 48:4558–4575
62. Hayik SA, Dunbrack R Jr, Merz KM Jr (2010) J Chem Theory Comput 6:3079–3091
63. Hensen C, Hermann JC, Nam K, Ma S, Gao J, Höltje H-D (2004) J Med Chem 47:6673–6680
64. Zhou T, Huang D, Caflisch A (2008) J Med Chem 51:4280–4288
65. Khandelwal A, Lukacova V, Comez D, Kroll DM, Raha S, Balaz S (2005) J Med Chem 48:5437–5447
66. Anisimov VM, Cavasotto CN (2011) J Comput Chem 32:2254–2263
67. Fanfrlik J, Bronowska AK, Rezac J, Preenosil O, Kovalinka J, Hobza P (2010) J Phys Chem B 114:12666–12678
68. Dobes P, Rezac J, Fanfrlik J, Otyepka M, Hobza P (2011) J Phys Chem B 115:8581–8589
69. Dobes P, Fanfrlik J, Rezac J, Otypeka M, Hobza P (2011) J Comput Aided Mol Des 25:223–235
70. Ufimtsev IS, Martínez TJ (2008) J Chem Theory Comput 4: 222–231
71. Ufimtsev IS, Martínez TJ (2009) J Chem Theory Comput 5: 1004–1015
72. Ufimtsev IS, Martínez TJ (2009) J Chem Theory Comput 5: 2619–2628
73. Luehr N, Ufimtsev IS, Martínez TJ (2011) J Chem Theory Comput 7:949–954
74. Uejima Y, Terashima T, Maezono R (2011) J Comput Chem 32:2264–2272