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Should medicinal chemists do molecular modelling?

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In this article we discuss the pros and cons of medicinal chemists undertaking three-dimensional (3D) computer-aided drug design (CADD) activities for themselves, from the viewpoint of both medicinal chemists and computational chemists. We describe how best this can be implemented, the potential benefits that can be obtained and the pitfalls that are often encountered.

It is not common practice for a computational chemist or molecular modeller to leave his or her workstation, don a white coat and perform organic chemistry experiments in a medicinal chemistry lab. Indeed many people would consider this to be rather reckless behaviour. Conversely there has always been a school of thought that medicinal chemists should carry out, to a greater or lesser extent, some elements of computer-aided drug design (CADD) for themselves, but is this suggestion just as reckless? In this article we discuss the reasoning behind this approach, how it could be implemented and the potential advantages and pitfalls that can accompany this endeavour.

Medicinal chemists use computer programs on a daily basis during the course of their work, for example to generate experiments in an electronic laboratory notebook, perform database searches, retrieve biological test results, calculate physicochemical properties and generate plots to examine structure–activity relationships. When chemical structures are involved, they are usually considered in two dimensions.

For the purposes of this article, the definition of CADD will not cover such activities, but rather focus on computational approaches using three-dimensional (3D) molecular structures, such as conformational analysis, molecular overlays, pharmacophore modelling and searching, ligand–protein docking, among others. A comprehensive review of CADD-related software and resources has recently been published [1] in addition to an editorial about whether medicinal chemists should get more involved in informatics and computation in general [2].

Do medicinal chemists want to do CADD?

The extent to which medicinal chemists want to do CADD for themselves varies considerably. Usually three groups can be identified:

(i) Enthusiastic: this group proactively seeks ways to get involved in CADD-related activities, often becoming local 'experts' in their laboratories or departments.

(ii) Curious: this group is not performing such tasks but appear to be interested in doing so; often they are not clear about what options are available or who to approach to initiate the interaction. This group is likely to need help and encouragement from CADD experts to become comfortable with using CADD approaches.

(iii) Sceptical: this group tends to be uninterested in or even dismissive of CADD and prefer to rely on traditional medicinal chemistry approaches. It is debatable whether this group should be 'coerced' into performing CADD, but a powerful stimulus perhaps would be observing their contemporaries using CADD approaches successfully in their discovery projects.

Do computational chemists want medicinal chemists to do CADD?

Typically, computational chemists fall into four distinct groupings when this topic is discussed:

(i) Enthusiastic: they believe CADD techniques can be a significant aid to the creativity of the medicinal chemist and that everything possible should be conducted to get robust techniques into their hands.

(ii) Luke warm: they have the opinion that if a medicinal chemist wants to 'play' with CADD techniques they can be assisted, but it would be best not to encourage them.

(iii) Hostile: they consider modelling performed by medicinal chemists to be generally worthless and also dangerous as it can

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generate time-consuming synthetic work based on misunderstandings of how CADD techniques should be used and how results should be interpreted.

(iv) Scared: if medicinal chemists know how to perform CADD techniques they will no longer need professional computational chemists.

Do software vendors want medicinal chemists to do CADD?

It is perhaps obvious that companies selling CADD-related software applications would like medicinal chemists to use their products to increase sales and their user base. In recent years many molecular modelling software companies have moved significantly into areas, such as chemical information and data management (often through mergers), but they retain a strong interest in expanding usage among the medicinal chemists. To this end, many companies including Accelrys (http://accelrys.com), Chemical Computing Group (http://www.chemcomp.com), Schrodinger (http://www.schrodinger.com), OpenEye (http://www.eyesopen.com) and Tripos (http://www.tripos.com) actively promote applications that are specifically designed to target the medicinal chemistry end-user, often using terms, such as 'streamlined', 'simplified', and 'user-friendly', to entice medicinal chemists who might be put off by full-featured CADD applications. Software companies have even been known to attempt to bypass the CADD department completely, appealing directly to the medicinal chemists as potential customers. If the interfaces to these tools are well designed (ideally with input from real medicinal chemists) this approach can be useful and indeed has been implemented successfully in many companies. It is important, however, that the underlying computational methodologies should not also be 'streamlined' to the point where the computational chemist views them as inferior to those available in the fully featured versions. Perhaps the best approach is to enable medicinal chemists to use a simplified interface to applications that are also used by computational chemists.

In addition to software suppliers, there are other groups that produce CADD-related applications aimed at the medicinal chemist, suggesting that there is a perceived need for such tools: Molecular Conceptor™ is a set of e-learning modules that aim to educate the medicinal chemist in aspects of drug design [3]; a recent publication by an academic group describes a PyMOL-based CADD platform for medicinal chemists [4]. Furthermore, review articles on CADD-related topics that target medicinal chemists have been published, such as one covering molecular interactions [5].

Approaches used to encourage medicinal chemists to undertake CADD activities

If a decision is made to encourage medicinal chemists to undertake CADD for themselves, there are various strategies that can be used to try to achieve this goal (Fig. 1):

(i) Put workstations into every chemistry laboratory, and send all chemists on a training course for modelling software; many pharmaceutical companies have tried this. The approach could fail if it is not thought through carefully enough: who will monitor the work that is subsequently carried out? And will CADD hypotheses that are formulated be actually tested by synthesising the suggested target molecules? If the medicinal chemists do not use the CADD software regularly enough or if there is insufficient on-going support from CADD experts, the workstation might not be maintained and will eventually fall into disuse, leaving an expensive piece of equipment gathering dust at an empty desk. The approach is more successful if a medicinal chemist is instructed to dedicate a proportion of the working day to such work with end of year targets set for modelling activities. If this is not done the medicinal chemist inevitably will be sucked towards the fume hood to prepare compounds that will satisfy end of year synthesis targets.

(ii) Create simple, web-based interfaces to CADD tools, to increase user-friendliness and also control what functionality the medicinal chemist is exposed to. This is an attractive approach and many companies including Novartis (http://www.novartis.co.uk/index.shtml) [6], GlaxoSmithKline (http://www.gsk.com/) [7], Abbott (http://www.abbott.com/index.htm) [8] and Pfizer (http://www.pfizer.co.uk/default.aspx) [modelling on the web: enabling chemists to pursue drug design calculations: http://www.ukqsar.org/slides/Dan_Ortwine.pdf] have implemented such tools with considerable success: medicinal chemists are able to get meaningful results quickly in a few simple steps without needing to know in detail what is going on in the background. It is important that such applications have a well-thought-out interface, adequate documentation and are neither too simplistic nor too complicated.

(iii) Extract information from more complex CADD experiments and generate static databases that can be accessed by medicinal chemists. This is related to the point above and enables chemists to access computational results that have been previously validated by experts. Typically these would be tools to provide access to protein–ligand crystal structures, docking results or molecular alignment results. The default views would be agreed by each

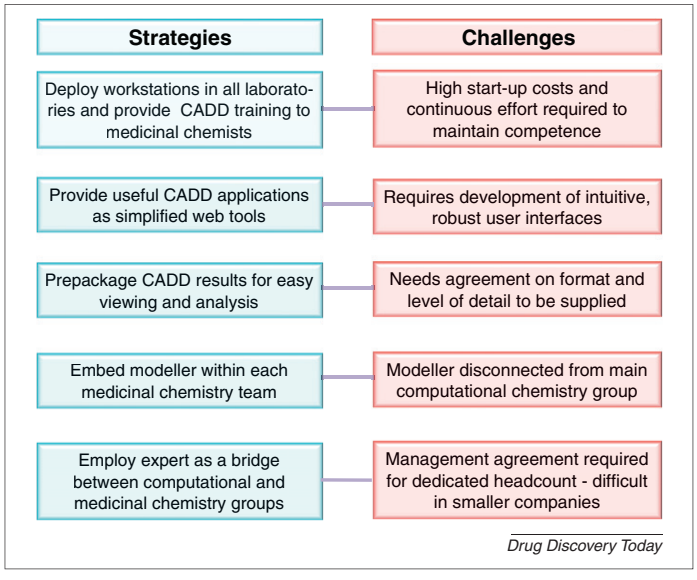

FIGURE 1

Approaches to encourage medicinal chemists to undertake computer-aided drug design (CADD): strategies and challenges.

project team and the medicinal chemist would be presented with tools to enable simple exploration of the ligand–protein interactions and the measurement of geometric properties, among others.

(iv) Embed a computational chemist (full- or part-time) in each medicinal chemistry laboratory. This approach has the advantage of having a CADD expert sitting alongside medicinal chemists, who can offer advice on a day-to-day basis, give instruction on using CADD tools and discuss results and possible next steps in a timely way. This approach fits neatly with the current trend of creating within the research divisions of big Pharma, small groupings of researchers operating in a 'biotech environment'.

(v) Employ a specific expert or experts to work at the interface between the medicinal and computational chemistry groups to champion CADD approaches and facilitate interactions between the two groups. The aim of this approach is to integrate the medicinal and computational chemistry communities by an expert who understands both groups well and can more closely align the wishes of the medicinal chemists with what is offered by the computational chemists. The downside of this approach is that permanent headcount is required to fill this role.

What types of CADD experiments can realistically be carried out by medicinal chemists?

This question is difficult to answer definitively and medicinal chemists and computational chemists would probably disagree on what is possible. Clearly the goal is for medicinal chemists to be able to run CADD experiments that will routinely produce robust, timely results that can be used with confidence in their drug discovery projects that complement the more complex experiments and analyses performed by expert computational chemists. As stated above, CADD tools for chemists that (i) employ 3D information that has been precalculated using validated methods or (ii) are accessed through simplified interfaces with predefined functionality should be relatively 'non-toxic' for general use. The incorporation of 'mouse hover over' help information is useful as a refresher for infrequent users.

More complex tools, such as those for conformational analysis, molecular alignment and ligand–target docking should perhaps be used with more caution and restricted to medicinal chemists who have undergone sufficient training to interpret the results correctly and recognise the limitations of such approaches.

Finally, the use of full-featured CADD packages to access advanced tools, such as pharmacophore generation, 3D database creation and searching and 3D quantitative structure-activity relationships (QSAR) should be limited to those medicinal chemists who are highly motivated CADD enthusiasts and prepared to undergo extensive training and work closely with the CADD group.

What are the benefits that can be obtained?

For medicinal chemists that get involved in CADD, there are several benefits that can assist them in the drug discovery process:

(i) Chemists understand more about the probable 3D conformations of their chemical series. For example, identifying the most probable conformation or preferred binding mode of particular molecular fragments by searching small molecule and protein crystal structures can help in drug design even in projects where crystal structures of ligand–target complexes are not available [9].

(ii) The synthesis of new analogues can be streamlined by eliminating compounds that are unlikely to fit into the binding site, for example by docking virtual analogues with new, as yet unsynthesised substituents.

(iii) Chemists appreciate more about how molecules interact with their biological targets by being aware of commonly observed H-bonding patterns and typical non-polar interactions, thus assisting them in the selection of novel templates.

(iv) As medicinal chemists become familiar with performing the more straightforward experiments themselves, computational chemists have more time to focus on more complex problems.

(v) In addition to scientific and technical benefits, it is important to add that as medicinal chemists and computational chemists begin to understand each other's roles better, this facilitates increased engagement and discussions between these two groups that historically have not always interacted optimally. This can lead to more fruitful collaborations that could benefit everyone in terms of productivity, job satisfaction and team building.

What are the pitfalls to avoid?

Because of the sometimes imprecise nature of computational chemistry and the subsequent interpretation that is required, it is important for medicinal chemists to be aware of the limitations and possible shortcomings in any CADD activities that they undertake. Also misunderstandings can arise about what medicinal chemists want to be able to do in terms of CADD and what computational chemists and software vendors provide. This often arises as a result of insufficient communication between the medicinal chemistry and computational chemistry functions. Finding a 'common language' that is understood by both parties is an important step to bridge the gap between these groups [10]:

(i) Not every result that is generated *in silico* is true. Computational experiments usually produce hard results, such as a pharmacophoric alignment or a docking pose, and it is not necessarily obvious how correct they are. One of the greatest dangers is that a medicinal chemist could operate in a vacuum without computational chemist input. This can enable simple errors to completely undermine the work of the medicinal chemist and can lead to lengthy syntheses being embarked upon for inappropriate compounds.

(ii) Employing software programs that are too complicated for occasional use by medicinal chemists. It is unrealistic to expect medicinal chemists in general to become expert users on advanced CADD software. It is one thing to attend a training course to use a fully featured CADD program and to run through some tutorials, but what happens if the chemist does not use the system again for a month? Owing to time constraints a medicinal chemist might not be able to allocate a lot of time towards CADD activities, and the barrier to getting back up to speed might be too high in this case.

(iii) Employing software programs that are too simple. This is the opposite of the point above: the software enables for simple tasks to be performed but it is not possible to go further, causing frustration when a chemist cannot ask 'what if?' questions.

(iv) If web tools have been implemented, it is important to ensure that they are continuously maintained and updated: if a tool is unavailable or returns errors, medicinal chemists will soon lose interest in trying it again.

What is the ideal situation?

On the basis of our experiences within the pharmaceutical industry, we propose the following arrangement to facilitate the safe and productive use of CADD tools by medicinal chemists:

(i) The computational chemistry team should make available to the medicinal chemists an agreed set of well designed, well maintained web tools.

(ii) An 'enthusiastic' computational chemist, with excellent communication skills, should be resident in each medicinal chemistry laboratory for a good proportion of his or her time. In addition to supporting therapeutic projects, they should provide training and quality control for all computational work performed by the medicinal chemists in the laboratory.

(iii) A medicinal chemist should be assigned to act as an interface between the two groups: championing and participating in the development and usage of new tools. It would not be unreasonable for this to be made a full-time role.

(iv) Successful results from CADD experiments conducted by medicinal chemists should be widely publicised to encourage others to get involved.

Conclusions

Medicinal chemistry and computational chemistry are integral, overlapping parts of the drug discovery process [11]. In answer to the question posed at the beginning of this article, there is no reason why medicinal chemists cannot undertake CADD activities as part of their routine work. In doing so they will understand more about the molecules they are synthesising and obtain new insights into the drug design process. It has been proposed that in the future, medicinal chemists will require greater computational and cheminformatics acumen than in previous years [12]. Perhaps the most 'reckless' behaviour would be to not encourage medicinal chemists to get more involved with CADD! It is crucial; however, that the tools that are available to them are well-thought-out, suitable for their needs, able to generate useful, timely and valid results and be supported by computational chemists. It is also important that the outcomes of any resulting CADD hypotheses that are actively pursued should be analysed regularly to determine which approaches are having a positive benefit in driving drug discovery projects forward [13].

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