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EDITORIAL

Coming to peace with protein complexes? 5th CAPRI evaluation meeting, April 17–19th 2013 – Utrecht

Interactomes are large, intricate and highly dynamic molecular networks that determine the fate of the cell. They rely on thousands of protein complexes that form the executive machinery underlying biological processes, from DNA replication to protein degradation through metabolism. Understanding the function of these macromolecular assemblies and designing new drugs that target them requires taking the step towards solving their three-dimensional structures. This is, however, not a trivial task and there is a large gap between the number of complexes identified by large-scale proteomics efforts and those for which high-resolution 3D experimental structures are available. For this reason complementary computational approaches are welcome additions to the structural biology toolbox. Being able to predict, model and understand biomolecular assemblies requires tackling the challenges of predicting large conformational changes potentially occurring upon binding, dealing with heterogeneous multi-component assemblies and predicting their binding affinity. The molecular docking community, catalyzed by CAPRI (Critical Assessment of PRedicted Interaction), is tackling those challenges.

CAPRI is a community-wide blind experiment aimed at objectively assessing the performance of computational methods for modeling protein interactions by inviting developers to test their algorithms on the same target system and quantitatively evaluating the results (http://www.ebi.ac.uk/msd-srv/capri/). This involves sampling putative association modes and modeling their atomic structure (the docking problem), and identifying those likely to be stable out of a very large pool of decoys (the scoring problem). In CAPRI, groups can tackle the different categories of problems (as 'dockers' and/or 'scorers').

This issue describes the state of the art of these computational methods as presented at the 5th CAPRI evaluation meeting that took place in Utrecht, the Netherlands on April 17–19, 2013 (http://www.isgtw.org/feature/protein-power-capri-2013). The Utrecht meeting follows four very successful CAPRI meetings - 2002 (La Londe-des-Maures, France), 2004 (Gaeta, Italy), 2007 (Toronto, Canada) and 2009 (Barcelona, Spain), which were all the subject of a special issue of Proteins (Proteins 2003:52(1), 2005:60(2), 2007:69(4) and 2010:78(15)). Moving from Spain to Utrecht, the Netherlands, was very timely and symbolic: Indeed, Utrecht celebrates this year the 300th anniversary of the Treaty of Utrecht, which established the Peace of Utrecht, a series of individual treaties signed by the belligerents in the War of the Spanish Succession. Does this hint that the docking community has finally come to peace with protein complexes and solved all the challenges? This latest CAPRI special issue provides some answers.

The 5th evaluation meeting covered eight rounds of CAPRI, which took place in the years 2010–2012, corresponding to a total of 15 targets. Of these only 5 were "classical" protein assemblies, the others consisting of designed systems, of an intra-molecular assembly for a multi-domain protein and of a protein-oligosaccharide complex. For the first time, for one of the complexes, low-resolution experimental information was made available to the predictors in the form of SAXS data. These rounds also introduced new challenges involving the prediction of the hydration structure at a protein-protein interface and of the binding affinity of designed complexes and various single point mutants thereof. Defining objective criteria to assess these new categories of predictions is also non-trivial.

In this special issue, all targets and their challenges are described in Janin's article, while the prediction and scoring results are presented by Lensink and Wodak. The results of the binding-affinity and water prediction challenges are only shortly summarized as they have already been published elsewhere in papers that bear the signature of all the participants and describe the collective effort of the CAPRI community (Fleishman *et al. J. Mol. Biol.*, **414**, 289–302 (2011); Moretti *et al. Proteins*, ePub (2013); Lensink *et al. Proteins*, in press). It is clear that

predicting the binding affinity of biomolecular assemblies, and even of point mutations in designed systems will remain a major challenge for the years to come. In order to address it, it will be crucial to have quantitative and high quality affinity data at hand. As to the "classical" docking targets, in general, the present results indicate a sustained and robust performance of docking and scoring methods with some groups reaching for the first time >80% success rate. The trend observed in previous evaluations, of complementing docking calculations with external information is still strong, with bioinformatics predictions or structural homologues providing for some targets the key to successfully guide the docking and/or identify near-native models. The overall good success rate is encouraging considering the new challenges and the fact that all targets were provided either in the unbound form, or had to be modeled by homology. Particularly noteworthy is the improved performance of automatic docking servers, with some demonstrating an excellent performance close to that of the best predictor groups. All these aspects are discussed in the various contributions to this special issue.

CAPRI would not be possible without the continuous efforts over the years of the CAPRI committee consisting of Joël Janin (Prof. Emeritus, Université Paris-Sud, Orsay, France), John Moult (CARB, Rockville, MD, USA), Lynn Ten Eyck (USCD, La Jolla, CA USA), Michael Sternberg (Imperial College London, UK), Sandor Vajda (Boston University, Boston, USA), Ilya Vakser (The University of Kansas, Lawrence KS, USA) and Shoshana Wodak (University of Toronto and Hospital for Sick Children, Canada). Joël Janin, John Moult and Lynn ten Eyck have now stepped down and been replaced after approval by the CAPRI participants by Alexandre Bonvin (Utrecht University), Marc Lensink (CNRS, University of Lille I, France), Sameer Velankar (EBI, Hinxton, UK) and Zhiping Weng (University of Massachusetts Medical School, Worcester MA, USA).

I wish to address here my special thanks and those of the entire CAPRI community to Joël Janin for his key role in making CAPRI a success by overseeing the collection of CAPRI targets and the organization of the prediction experiments. His role will now be taken over by Shoshana Wodak. Special thanks go also to Sameer Velankar, for running the CAPRI web site and dealing with the submissions, and to Marc Lensink, for the herculean task of evaluating the predictions that are still often so diverse in their format.

The 2013 CAPRI meeting could not have taken place without the substantial financial support of the European FP7 e-Infrastructure project WeNMR (www.wenmr.eu). The financial contributions of Utrecht Life Sciences and YASARA Biosciences are also acknowledged. We also thank our media sponsor, e-ScienceTalk (www.e-sciencetalk.org). The entire CAPRI community expresses its gratitude to all structural biologists, and protein "designers" who provided the targets of round 20-17: J.F. Acheson, L.J. Baily and B. Fox (University of Wisconsin), P. Minard and M. Graille (Orsay, France), J.A. Wojdyla and C. Kleanthous (University of York, UK), S. Leysen and S. Strelkov (Leuwen, Belgium), S. Najmudin (Lisbon, Portugal), A. Basle and R. Lewis (Newcastle University, UK) and S. Fleishman and D. Baker (University of Washington, Seattle, WA).

I wish to take here the opportunity, in the name of the CAPRI committee, to call upon the worldwide structural biology community to contribute targets to CAPRI. If you have solved or are about to solve the 3D structure of a protein-protein, protein-DNA, protein-RNA or protein-peptide complex, you may consider submitting your structure as a target to CAPRI**.** By doing so, you will contribute to advancing the methodology. We are now more than 12 years into CAPRI, and the counter only stands at 64 targets, some of which were cancelled (for some of the cancelled targets, the credits have to be given to Google and some smart search strings – this was for example the case in this round for target 53 for which we found both the manuscript and the yet undeposited coordinates while searching for mutagenesis data online!). This clearly indicates that, not only solving the structure of complexes experimentally is still a non-trivial task, but also that every complex is still hot, which might make experimentalists reluctant to provide their coordinates ahead of publication. CAPRI is however designed to maintain strict confidentiality on the target and imposes no delay on its publication, as the experiment is running whenever a new target is submitted, prior to any public release of the coordinates to the PDB and publication. Furthermore, providing targets to CAPRI might increase the visibility of the work since all participants are requested to duly cite the provenance of all targets. To enable this, the coordinates should be made available to the CAPRI assessment team on a confidential basis prior to their release. To find out more about CAPRI target submission see: http://www.ebi.ac.uk/msd-srv/capri/call_for_targets.html

So have we come to peace with protein complexes? Reliably adding the structural dimension to interactomes, or even predicting them (which requires understanding binding affinity) conveys many challenges that still need to be addressed. Nature is clearly working in mysterious ways that current computational models and/or resources cannot yet fully address. So we still have to fight to untangle those challenges and can't speak yet of a "*Utrecht Protein Complexes Peace Treaty*" as a result of the last CAPRI evaluation. The field is however progressing as illustrated in this special issue.

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