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Abstract
Phyre is a widely-used web server for tertiary protein structure prediction and modelling with over 80,000 distinct users per year and is part of the ELIXIR tools resource. We are developing 3D models for predicted complexes by integrating tertiary models, the experimental structure of complexes and protein-protein interaction data. A new resource, PhyreRisk, is being developed which will enable users to map protein missense variants onto experimental and predicted tertiary structures and complexes. See www.sbg.bio.ic.ac.uk/~phyre2 and phyrerisk.bc.ic.ac.uk

1. Introduction

Knowledge of the 3D structure of protein and their complexes is central to understanding biological behaviour and to the development of strategies to exploit this fundamental knowledge. In particular, the rapid decreasing cost of genome and exome sequencing is yielding a wealth of data about genetic variation including missense (non-synonymous) variants. The prediction the probable phenotypic effect of such variants, particular if they are associated with a diseased state, can be markedly enhanced via structural information. We report PhyreRisk which integrates variant and structural data.

2. Phyre2 and Phyre3

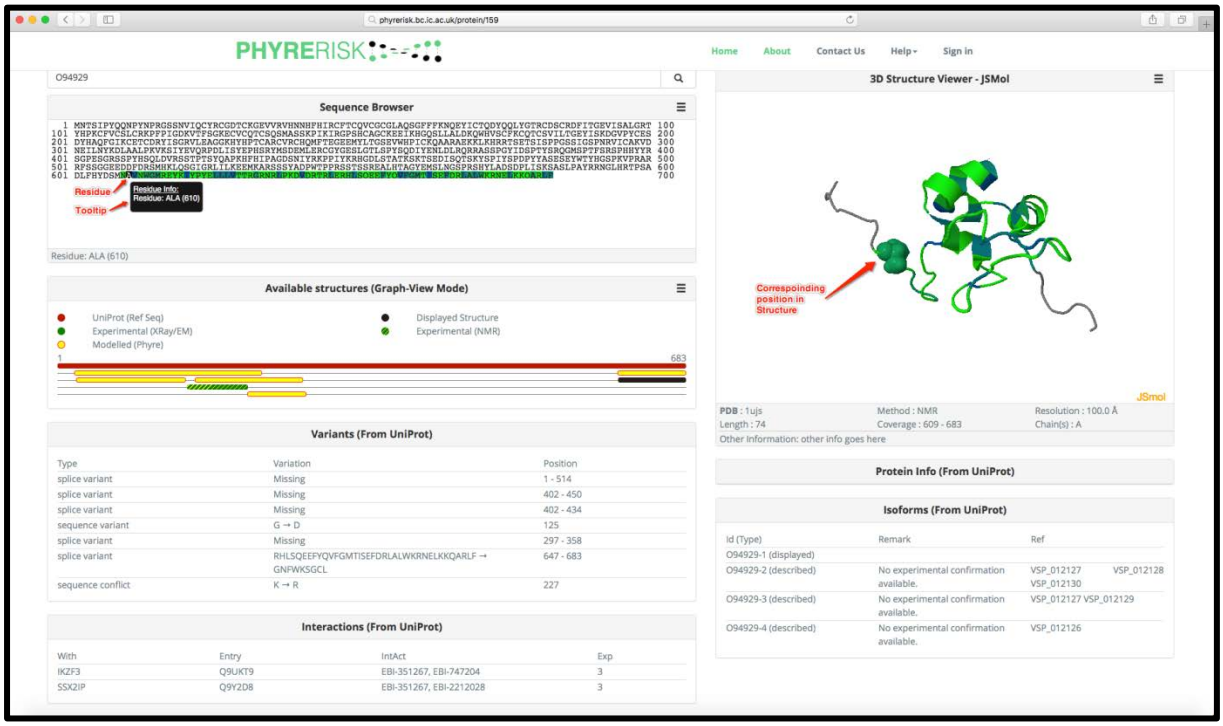
Phyre2 (1) provides a web-based resource for the community to obtain predicted 3D structures based on the known structure of a template. Predicted models typically are returned via an e-mail link within a few hours and the user can examine alternate models with their multiple sequence alignments. There are facilities for users to examine the accuracy of the model along the sequence (Phyre Investigator), to request weekly re-runs of their query against updates databases (PhyreAlarm), and to see if a 3D structure occurs in other genomes (BackPhyre). Users can also submit batch files with numerous sequences to process. Phyre2 is now a resource with the UK node of ELIXIR, a European distributed infrastructure for life-science information. There are over 80,000 distinct users of Phyre2 per year. We are launching Phyre3 which will have an enhanced interface with more information in different, toggable windows.

3. Prediction of complexes

With the increase in the number of experimentally-determined structures of complexes, a powerful and widely applicable approach is to use these as templates to predict the structure of other complexes. The Kansas group has been following this approach and based on identified protein-protein interactions in Intact and BioGrid has provided the community with the GWIDD (2) database of predicted complexes. We are now providing the Kansas group with predicted Phyre models, which together with experimental structures, are the inputs for the prediction of binary complexes.

4. PhyreRisk

PhyreRisk, which we plan to release in summer 2018, will provide a resource for a user with human variant data, either at the genomic or the protein level, to map any missense, nonsense or stop gain variant onto the structure of an individual protein and its complex. PhyreRisk has an interactive sequence/structure viewer to provide user-driven mapping. Moreover we have developed an approach to predict the structural consequences of a missense mutation (such as loss of a salt bridge) and have parameterised this to be effective in both experimental and predicted structures. Our plan is to integrate databases of variation, such as ClinVar and gnomAD, into PhyreRisk.



A screenshot of PhyreRisk (taken 5 March 2018). The display show which experimental and Phyre-predicted structures that map to the sequence. Selection of one of these structures generates the molecular graphics display. There is an interactive mapping of a residue from the sequence onto the structure.

5. Discussion

One challenge we address is to develop a method to present users with a representative subset of predicted structures (e.g. open and closed forms) whilst not overburdening them with trivial different structures (which can be inspected if required). We aim to provide a measure of confidence given that complexes can be based on one or two predicted tertiary structures and then modelled into a predicted model for their association. Despite major advances in linking database, as we work on these resources we are need to resolve many technical issues to deliver a resource that meets the needs of the ever-increasing number of users who are not bioinformaticians. This work was funded by the BBSRC (BB/M011526/1 & BB/P011705/1), the Wellcome Trust (104955/Z/14/Z), the NSF and the Thai Government (SI).

References

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