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Applications Note

Structural bioinformatics

PRODIGY: a web server for predicting the binding affinity of protein–protein complexes

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Abstract

Summary: Gaining insights into the structural determinants of protein–protein interactions holds the key for a deeper understanding of biological functions, diseases and development of therapeutics. An important aspect of this is the ability to accurately predict the binding strength for a given protein–protein complex. Here we present PROtein binDIng enerGY prediction (PRODIGY), a web server to predict the binding affinity of protein–protein complexes from their 3D structure. The PRODIGY server implements our simple but highly effective predictive model based on intermolecular contacts and properties derived from non-interface surface.

Availability and Implementation: PRODIGY is freely available at: http://milou.science.uu.nl/services/PRODIGY.

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1 Introduction

Biomolecular interactions between proteins are involved in regulation and control of almost every biological process in the cell. Alterations in such interactions are responsible for many diseases, making protein–protein complexes crucial targets for therapeutics development (Petta *et al.*, 2015). In this scenario, identifying the structural determinants of these interactions and their binding energetics is an important step for a better understanding and controlling of such systems. In particular, the binding affinity (or binding free energy), which defines whether complex formation occurs or not in specific conditions, holds the key to control interactions (e.g. engineering high affinity interactions), design new therapeutics (e.g. guiding rational drug design) or predict the impact of mutations at protein interfaces. The prediction of binding affinity has been investigated for decades (Chothia and Janin, 1975; Horton and Lewis, 1992) yielding approaches ranging from exact methods (e.g. free energy perturbation), which are accurate but computationally costly, to empirical approaches (e.g. scoring functions in docking, various regression models), which are fast but less accurate (Kastritis and Bonvin, 2010). Several valuable web servers have been made available to the scientific community, providing a series of different descriptors (energetics, structural features, etc.) of protein–protein interfaces (Moal *et al.*, 2015; Reynolds *et al.*, 2009; Tina *et al.*, 2007; Saha, *et al.*, 2006; Tuncbag *et al.*, 2009; Vangone *et al.*, 2011). Some of these have also been tested as binding affinity predictors. There is, however, a lack of specific online tools for the prediction of binding affinity (Su *et al.*, 2009).

Recently, we introduced a simple and robust descriptor of binding affinity based only on structural properties of a protein–protein complex. Using the protein–protein binding affinity benchmark in Kastritis *et al.* (2011), we demonstrated that the number of interfacial contacts at the interface of a protein–protein complex correlates with its experimental binding affinity. This information, combined with properties of the non-interacting surface (Kastritis *et al.*, 2014;

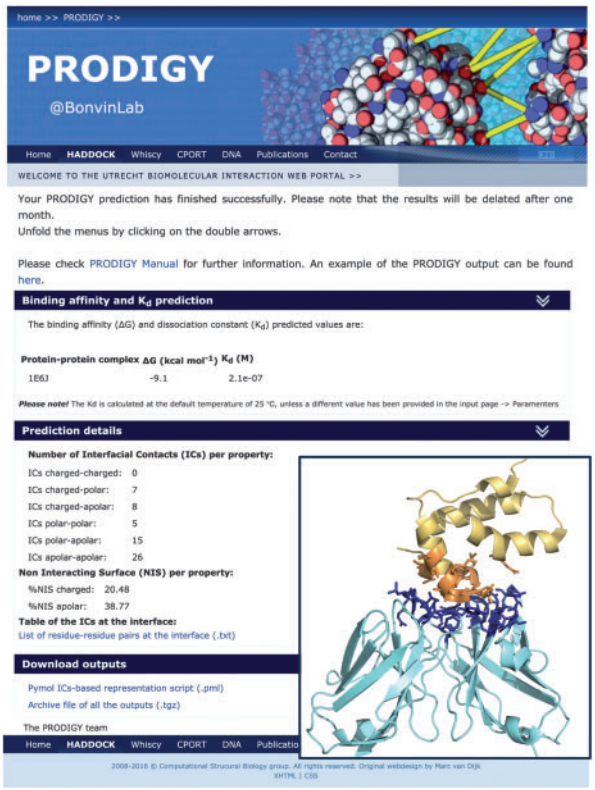

Fig. 1. Example output of PRODIGY for the complex between the FAB and the HIV-1 capsid protein p24 (PDB code: 1E6J). A 3D representation of the complex interface is shown in the inset figure with the color coding of the PRODIGY script (.pml) for Pymol: aquamarine and yellow for Interactor 1 (chains L and H in this example) and Interactor 2 (chain P), respectively. The interacting residues are represented in darker colors with their side-chains showed in sticks (Color version of this figure is available at *Bioinformatics* online.)

Marillet *et al.*, 2016), has led to one of the best performing predictors reported so far. In terms of accuracy, our method showed a Pearson's Correlation coefficient of 0.73 between the predicted and measured binding affinity on the benchmark (P-value <0.0001) and Root Mean Square Error (RMSE) of 1.89 kcal mol^{-1} (Vangone and Bonvin, 2015). While our method performs well on average, errors in particular cases may be expected; for instance, some natural ultra-high-affinity complexes have average or below-average buried surface area, and our method may underestimate their affinity. Alternative physical models of entropy, solvent effects and electrostatics could be taken into consideration to address such cases, although, to date, no such model performs better on average than our simple contact-based approach (see Fig. 4 in Vangone and Bonvin, 2015).

We have implemented our contact-based method as a web server, PRODIGY (PROtein binDIng enerGY prediction), a user-friendly online tool for the prediction of binding affinity in protein–protein complexes.

2 The web server

The PRODIGY server requires as input the 3D structure of a protein–protein complex, which can be provided in three different manners:

- upload of the 3D structure in PDB or mmCIF format;
- automatic download from the protein databank;
- upload as an archive file (.tar, .tgz, .zip, .bz2, .tar.gz) for analyzing multiple structures at the same time (with a limit of 50 MB).

The user is required to specify the chain identifiers for the molecules involved in the interaction. It is also possible to specify the temperature, at which once can calculate the dissociation constant (25 °C by default) and an email address, where a link to the results page will be sent. When an ensemble of models of a NMR-determined complex is submitted as a single input PDB file, only the first model will be used for the prediction. The results (downloadable for 2 weeks) include:

1. the predicted value of the binding free energy (ΔG) in kcal mol^{-1};
2. the predicted value of the dissociation constant (K_d) in M calculated from $\Delta G = RT\ \ln(K_d)$ where R is the idea gas constant (kcal K^{-1} mol^{-1}), T the temperature (K).
3. the number and type of intermolecular contacts within the 5.5 Å distance cutoff (for details see Vangone and Bonvin, 2015);
4. the percentages of charged and polar amino-acids on the non-interacting surface;
5. a downloadable table (.txt) of all residues occurring at the interface and a ready-to-run Pymol script (.pml) (www.pymol.org);
6. a compressed file with all the result files.

Information about the predictive model and the training dataset can be found online in the 'Method' and 'Dataset' page of PRODIGY, respectively, accessible through the main page. PRODIGY has been written in Python and Perl. The solvent accessible surface area is calculated with open-source tool freeSASA (Mitternacht, 2015) using the default NACCESS (Hubbard and Thornton, 1993) parameters for atomic radii. The server is fast, performing the prediction in few seconds for the largest complex examined in the benchmark (1DE4). An example output page of PRODIGY is shown in Figure 1.

In conclusion, the PRODIGY server should contribute to speeding-up development of new predictive approaches and facilitate its use within various fields of biology. PRODIGY is freely accessible at http://milou.science.uu.nl/services/PRODIGY. A standalone version to run locally is freely available from our GitHub repository (see http://www.bonvinlab.org/software).

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