

PREDDIMER: a web server for prediction of transmembrane helical dimers

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Associate Editor: Anna Tramontano

ABSTRACT

Summary: Here we present PREDDIMER, a web tool for prediction of dimer structure of transmembrane (TM) helices. PREDDIMER allows (i) reconstruction of a number of dimer structures for given sequence(s) of TM protein fragments, (ii) ranking and filtering of predicted structures according to respective values of a scoring function, (iii) visualization of predicted 3D dimer structures and (iv) visualization of surface hydrophobicity of TM helices and their contacting (interface) regions represented as 2D maps.

Results: We implemented online the original PREDDIMER algorithm and benchmarked the server on 11 TM sequences, whose 3D dimer conformations were obtained previously by nuclear magnetic resonance spectroscopy. In the most of tested cases backbone root-mean-square deviations of closest predicted conformations from the experimental reference are below 3 Å. A randomization test displays good anticorrelation (−0.82) between values of the scoring function and statistical significance of the prediction ‘by chance’. Going beyond a single dimer conformation, our web tool predicts an ensemble of possible conformations, which may be useful for explanation of a functioning of bitopic membrane proteins, e.g. receptor tyrosine kinases.

Availability and implementation: PREDDIMER can be accessed for free on the web at <http://model.nmr.ru/preddimer/>

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

Received on September 2, 2013; revised on October 21, 2013; accepted on November 3, 2013

1 INTRODUCTION

Transmembrane (TM) domains of bitopic proteins comprise just a single helix. For particular class of such proteins with high biological importance—receptor tyrosine kinases (RTKs)—it has been shown that TM fragments play a crucial role in dimerization and activation of these receptors by controlling orientation of their intracellular kinase domains (Cymer and Schneider, 2010). The knowledge of spatial structures of dimers of TM fragments of bitopic proteins is important for understanding the functioning of these molecules upon their oligomerization in the cell membrane. Being reasonable alternative to experimental

techniques of TM dimer structures determination (Bocharov *et al.*, 2010), the existing modeling approaches vary a lot in their complexity, prediction power and computational efficiency: starting from simple sequence motif-based algorithms to laborious force-field techniques like Monte Carlo conformational search in implicit membranes, coarse-grained or atomic molecular dynamics simulations in lipid bilayers or different combinations of them (Polyansky *et al.*, 2011). Here, we present PREDDIMER web server for prediction of ensembles of possible spatial structures of TM helical dimers based just on respective TM sequence(s). Our web server uses original PREDDIMER algorithm described elsewhere (Polyansky *et al.*, 2012). To our knowledge up-to-date, this is the only online tool, which allows fast and efficient prediction of TM dimers structure as well as visualization of predicted results both in 3D and 2D (2D maps of surface hydrophobicity of interacting helices with outlined contacting interfaces). Although the server does not address a question whether two given TM fragments dimerize or not, which is still far from being fully reachable for solely *in silico* techniques, it provides their putative dimer conformations along with estimation of their reliability.

2 WORKFLOW AND IMPLEMENTATION

The PREDDIMER server has two modes: (i) prediction of TM-dimer structures from sequences and (ii) analysis of hydrophobic properties and contacting regions for an existing dimer structure (separate Protein Data Bank (PDB) files for each of interacting helices have to be uploaded by user). In the first case, user should input one or two TM sequences (single for homo- and two for heterodimers, respectively) with a length 20–35 amino acid residues, optionally specify their name(s) and indicate orientation of helices in a dimer (parallel/antiparallel) and pH, which determines ionization state of amino acid sidechains. On submitting a prediction task, the server sends an e-mail notification with unique link to a result page, which will be created on calculations completion. On average, the prediction takes ~20 min depending on the server workload. The server is implemented using Python and PHP programming languages, and also Zend and Bootstrap frameworks. The algorithm details are available in online manual (<http://model.nmr.ru/preddimer/manual>). Parameters of predicted dimer conformations such as rank of a structure, F_{SCOR} value, helix–helix crossing angle (χ) and rotation angles around helical axes (α_1 , α_2) are presented in an interactive table, where selection of a certain row results in output of respective 2D maps for both helices and interactive 3D conformation of the dimer. Predicted PDB structures, 2D maps (PNG and PDF) and resulting table (text format) are available for download as

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separate files or combined ZIP archive. Similar result page can be created for an existing dimer structure using analyzing mode (mode 2) of the server.

3 PERFORMANCE

We calculated possible conformations for 10 homodimers and 1 heterodimer, whose structures were obtained previously by nuclear magnetic resonance (NMR) spectroscopy (Fig. 1A). In most cases, NMR-like conformations are among three top-scoring models for a given dimer (total number of models is shown in parentheses) and display backbone root-mean-square deviations (RMSD) from the references below 3 Å. The only exceptions are ErbB3 homodimer, whose published structure displays anomalous packing compared with other RTKs (Li *et al.*, 2012), and FGFR3, whose NMR structure is characterized by the presence of distorted conformations of TM helices (Volynsky *et al.*, 2013). For the most well-known TM dimer structure of glycophorin A (GpA, PDB: 1AFO), the server gives a top-ranked model with RMSD of 1.56 Å from the reference. We performed also randomization test, where probability to form a dimer between a given TM fragment and random ones were estimated over 1000 shuffles of interacting sequence. *P*-values obtained for the studied dimer models display good anticorrelation (-0.82) with the respective F_{SCOR} values (Supplementary Figure S1), suggesting the scoring function as reasonable and fast estimate of the reliability of predicted conformations.

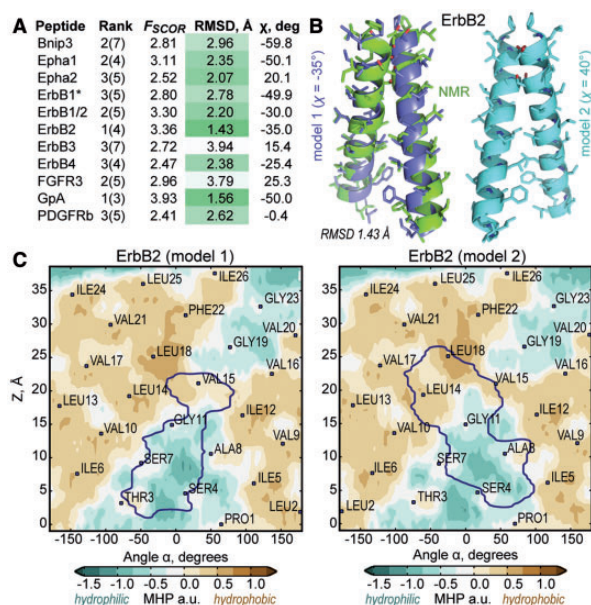


Fig. 1. Prediction results for TM helical dimers obtained using PREDDIMER server. (A) Parameters of dimer conformations compared with the experimental references (see Supplementary Material for details). (B) Spatial structures of NMR-like (left) and alternative (right) models for ErbB2. Peptides are shown in cartoon-and-sticks representation. (C) 2D maps of the molecular hydrophobicity potential (MHP) (Efremov *et al.*, 2007) on the peptide surfaces in two ErbB2 models generated by the server. Dimerization interfaces are outlined. Axis values correspond to the rotation angle around the helical axis (α) and the distance along the latter (Z), respectively. 2D maps are colored according to MHP arbitrary units

Because the algorithm operates with ideal helices, it outputs rather ‘coarse-grained’ initial dimer configurations, whereas the membrane environment is not accounted explicitly. At the same time, the predicted conformations represent a reliable starting point for further molecular dynamics optimization in explicit membranes, which usually increases their similarity to the experimental structures (Polyansky *et al.*, 2012). Noteworthy, the algorithm predicts a number of possible dimer configurations, which is not a case of NMR techniques usually giving a set of similar models optimally suited for the particular membrane mimic (micelles, bicelles). The calculated dimer conformations can correspond to different intermediate states of TM domains, thus shedding light on the mechanism of protein functioning. We illustrate this on the example of RTK ErbB2 (Fig. 1B and C). The first predicted right-handed model (Fig. 1B, left) corresponds well to the experimental structure (2JWA, RMSD of 1.43 Å), whereas the second one (Fig. 1B, right) is similar to alternative left-handed state suggested by modeling for this dimer (Fleishman *et al.*, 2002). Switching between possible interaction interfaces (Fig. 1C) results in different helices orientation with respect to intracellular kinase domains and may contribute to activation of ErbB2 (Fleishman *et al.*, 2002) and other RTKs (Endres *et al.*, 2013; Volynsky *et al.*, 2013). In this context, PREDDIMER web tool goes beyond common concept of just a single structure of TM helical dimer usually available experimentally in specific conditions of NMR setup.

ACKNOWLEDGEMENTS

The authors thank Sergey Goncharuk for the help with server setup.

Funding: Ministry of Education and Science of the Russian Federation (14.514.11.4069), the Russian Foundation for Basic Research and the RAS Programmes ‘Basic fundamental research for nanotechnologies and nanomaterials’ and ‘Molecular and Cellular Biology’.

Conflict of Interest: none declared.

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