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Applications Note

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HMI-PRED 2.0: a biologist-oriented web application for prediction of host–microbe protein–protein interaction by interface mimicry

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Abstract

Summary: HMI-PRED 2.0 is a publicly available web service for the prediction of host–microbe protein–protein interaction by interface mimicry that is intended to be used without extensive computational experience. A microbial protein structure is screened against a database covering the entire available structural space of complexes of known human proteins.

Availability and implementation: HMI-PRED 2.0 provides user-friendly graphic interfaces for predicting, visualizing and analyzing host–microbe interactions. HMI-PRED 2.0 is available at https://hmipred.org/.

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1 Introduction

Microbes alter host cell signaling and modulate immune responses to maximize their survival. They induce diverse physiological conditions including immune-mediated diseases and cancers (Ruff *et al.*, 2020; Sepich-Poore *et al.*, 2021). Though the importance of microbial effects on human health is now well-accepted, in most cases the detailed mechanisms through which they induce the conditions are yet to be determined (Zhou *et al.*, 2022). Microbial species interact with their hosts by exploiting diverse strategies, including host–microbe protein–protein interactions at multiple stages of the cell's life cycle with many different, albeit partially shared interactors (Gupta *et al.*, 2012; Guven-Maiorov *et al.*, 2017; Schneider and Hoffmann, 2022; Tyl *et al.*, 2022; Walch *et al.*, 2021).

As observed broadly across the eukaryotes, for microbes, mimicry of favored interface motifs is an important and efficient strategy, where a microbial protein can interact with a host protein if the microbial protein has a surface patch similar to the binding surface of a known interactor of the host protein (Franzosa and Xia, 2011; Guven-Maiorov *et al.*, 2019; Lasso *et al.*, 2021). That is, the microbial protein postures as an intrinsic interactor of the host protein and masquerades it, by mimicking the interaction interface, without needing high sequence identity or global structural homology. Interface mimicry studies suggest pathogenic mechanisms of cancers, and neuropsychiatric symptoms associated with the recent coronavirus disease 2019 (COVID-19) pandemic (Guven-Maiorov *et al.*, 2017, 2019; Ovek *et al.*, 2022; Yapici-Eser *et al.*, 2021).

Computational methods have been developed to predict, integrate and analyze general or virus–human protein–protein interactions at a large scale, where the use of non-structural features is incentivized due to the limited structural coverage (Andrighetti *et al.*, 2020; Ding and Kihara, 2018; Dong *et al.*, 2021; Karabulut *et al.*, 2021; Mahajan and Mande, 2017; Wu *et al.*, 2020). On the other hand, it was suggested that the structural space is sufficient for protein complex modeling (Kundrotas *et al.*, 2012). Recent advances in deep learning enabled computational modeling of unsolved protein structures from primary sequences with unprecedented quality, providing ways to reveal atomic details of protein–protein interactions for the structural dark space (Baek *et al.*, 2021; Jumper *et al.*, 2021). Exploiting the protein structural information across the entire available space to accurately and efficiently model protein–protein interactions on a large scale is thus possible and vital.

To date, HMI-PRED (version 1) is the only method that screens the whole structural space to predict host–microbe interactions based on interface mimicry (Guven-Maiorov *et al.*, 2020). That version of HMI-PRED was a more conceptual study that provides the predicted host–microbe interactions with limited microbial protein coverage, search functionalities and outdated structural visualizations; thus, users need to perform filtering, analysis and visualization for their individual proteins of interest. HMI-PRED 2.0 is therefore

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a completely rebuilt automated tool with the same core concept of interface mimicry. HMI-PRED 2.0 is equipped with new interface templates as well as computationally modeled microbial proteins to cover broader interactions, enabling more potential host–microbe interactions to be scanned. Visualization of templates and predicted interactions are improved for publication-ready images. More importantly, HMI-PRED 2.0 Library allows users to find host–microbe interactions of interest from the pre-computed interactions in our database with enrichment analysis and network visualization options. We also provide bulk download for predicted interactions as well as the microbial protein structures modeled using AlphaFold 2 (Jumper *et al.*, 2021). Using HMI-PRED 2.0, users can predict, search, analyze visualize and download the predicted host–microbe protein–protein interactions. HMI-PRED 2.0 is freely available at https://hmipred.org/.

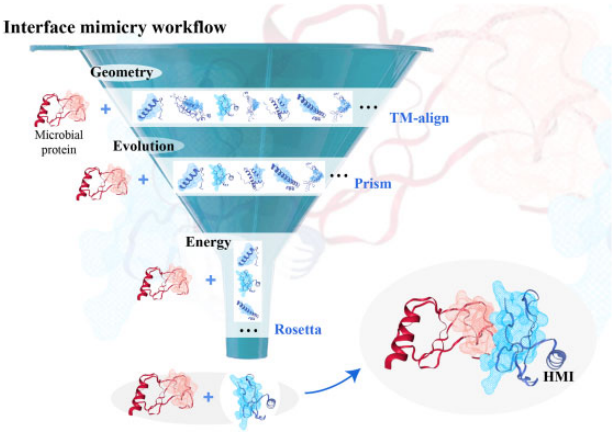


Fig. 1. Interface mimicry workflow, the core prediction mechanism of HMI-PRED 2.0. The input microbial protein (red chain) is scanned through the host protein template database (blue box) to predict host–microbial protein–protein interaction (HMI at the bottom). The prediction process is composed of three main steps. The 3D geometry of the microbial protein is compared against templates, evolutionarily conserved interaction hot spots are checked, and the protein–protein binding energy is estimated. Therefore, HMI-PRED 2.0 predicts host–microbe protein–protein interactions that are geometrically, evolutionarily and energetically favorable, which can be used for downstream analyses (A color version of this figure appears in the online version of this article)

2 Implementations

2.1 Workflow

The core concept of HMI-PRED 2.0 resembles HMI-PRED version 1 and PRISM (Fig. 1) (Baspinar *et al.*, 2014; Guven-Maiorov *et al.*, 2020). First, the extracted surfaces from the microbe protein structures are structurally compared to the interfaces in our template database using TM-Align, with an optional evolutionary hot spot filtering (Tuncbag *et al.*, 2009; Zhang and Skolnick, 2005). The filtered microbe proteins are docked to the complementary proteins (known interactors of mimicked ones) using Rosetta (Gray *et al.*, 2003). Thus, the predicted host–microbe interactions are structurally well-aligned, evolutionarily conserved and energetically favorable. More details about the prediction algorithm, including the estimated false positive rate of 18%, can be found in Guven-Maiorov *et al.* (2020).

2.2 Implementation

HMI-PRED 2.0 is built on top of the Django framework, which is suitable for database-centric web services (Django Software Foundation, 2020). First, our new template database covers 60 868 protein complexes deposited on RCSB PDB (Burley *et al.*, 2020) by January 2021. Users can submit mmCIF-formatted files as input for large structures. Our web service accumulated more than 1.6 million predicted host–microbe interactions for over 20 000 microbial proteins, among which 8520 are modeled using AlphaFold 2 (Jumper *et al.*, 2021). The modeled protein structures as well as predicted interactions can be searched, viewed, analyzed and downloaded via our web service. Proteins are visualized using NGL viewer, which provides publication-quality structure views and interactive options (Rose *et al.*, 2018). We also provide options to visualize the interactions as a network using Cytoscape (Franz *et al.*, 2016) and perform enrichment analysis via String (Szklarczyk *et al.*, 2019) (Fig. 2).

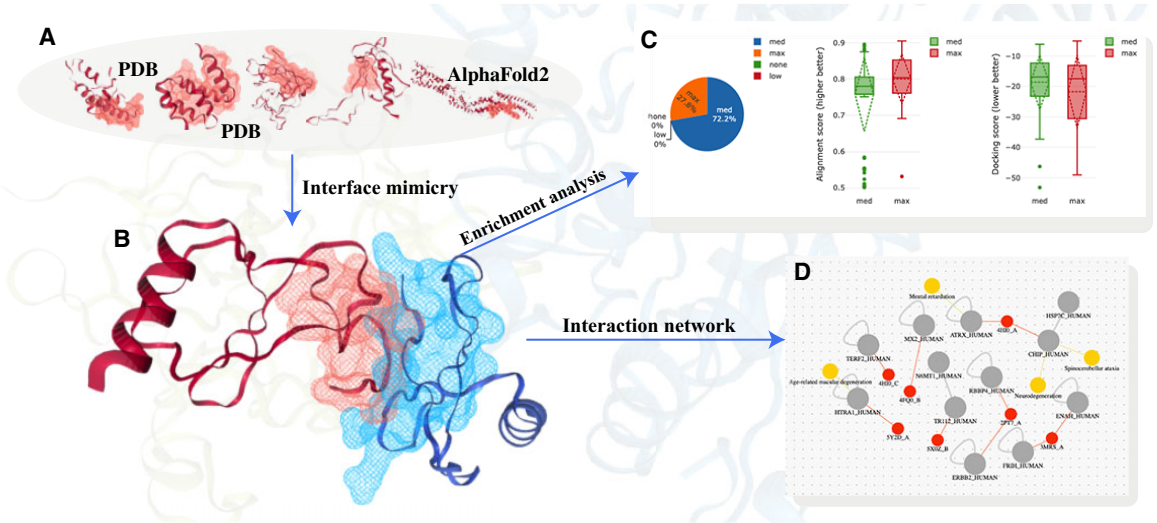


Fig. 2. Illustration of HMI-PRED 2.0 workflow. (**A**) Users can submit input protein structures or search for pre-computed interactions, which include experimentally solved or AlphaFold 2-modeled microbial proteins. (**B**) HMI-PRED 2.0 predicts potential host–microbe protein–protein interactions based on interface mimicry concept. The interface mimicry-based prediction process includes three main stages as shown in Figure 1. At the end of a prediction task, there may be multiple predicted interactions for a microbial input protein. The false positive rate is approximately 18% based on our previous study. (**C** and **D**) HMI-PRED 2.0 web server provides two analysis/visualization functions: human pathway enrichment analysis when multiple human proteins are targeted (C), and interaction network visualization showing diseases associated with targeted human proteins (D). The charts in (C) are conceptual; the actual analysis output is a table with texts

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In the section below, we demonstrate the basic usage of our web service. For more detailed usage, users are referred to the tutorials page on our web service.

2.3 Basic usage

Users can either search for pre-computed host–microbe interactions in our database or submit a new prediction task. HMI-PRED 2.0 Library allows users to find host–microbe interactions by several different filter options. One example is shown in the next paragraph.

Users can search predicted host–microbe interactions for all organisms whose name contains 'Epstein–Barr' (case insensitive) and moderate-to-high level of hot spot conservation. Under 'Library—ALL HMI' page, write 'Epstein–Barr' in the 'Microbe organism' box on the filter menu column. Also choose 'med' and 'max' in the 'Hotspot conservation' on the filter menu, and hit 'Apply' (leave the default Max. Rosetta score of −5.0 as is for this example). It returns 90 interactions on the Host–Microbe Interactions table. Click 'Enrichment Analysis' button once the table is shown with results, which will redirect to String with 20 nodes (human proteins predicted to interact with Epstein–Barr viral proteins) and 12 edges. Under 'Analysis' tab, a few important pathways and diseases appear. For example, the associations between the virus and 'MicroRNAs in cancer', 'Ras signaling pathway', 'Kaposi sarcoma-associated herpesvirus infection' and 'non-Hodgkin lymphoma' are supported by literature evidence (Caetano *et al.*, 2021; Fukuda and Longnecker, 2007; Pinzone *et al.*, 2015). Please note that the thorough validation or individual investigation of these associations is out of the scope of this manuscript. Users can apply filters according to their scientific questions and perform analysis accordingly.

In case the microbial protein of interest is not found, users can submit a new prediction task under 'RUN HMI-PRED' page by providing either a valid PDB ID with chain ID or a protein structure file in mmCIF or PDB format. More details can be found on the tutorial pages of our web service.

3 Conclusions

We developed HMI-PRED 2.0, a web service for structure-based host–microbe protein–protein interaction prediction. HMI-PRED 2.0 provides user-friendly interfaces with analysis tools for users without programming experiences. HMI-PRED 2.0 is freely available at https://hmipred.org/.

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Conflict of Interest: none declared.

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