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Web Server Issue

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Abstract

The sense of smell is a biological process involving volatile molecules that interact with proteins called olfactory receptors to transmit a nervous message that allows the recognition of a perceived odor. However, the relationships between odorant molecules, olfactory receptors and odors (O3) are far from being well understood due to the combinatorial olfactory codes and large family of olfactory receptors. This is the reason why, based on 5802 odorant molecules and their annotations to 863 olfactory receptors (human) and 7029 odors and flavors annotations, a web server called Pred-O3 has been designed to provide insights into olfaction. Predictive models based on Artificial Intelligence have been developed allowing to suggest olfactory receptors and odors associated with a new molecule. In addition, based on the encoding of the odorant molecule's structure, physicochemical features related to odors and/or olfactory receptors are proposed. Finally, based on the structural models of the 98 olfactory receptors a systematic docking protocol can be applied and suggest if a molecule can bind or not to an olfactory receptor. Therefore, Pred-O3 is well suited to aid in the design of new odorant molecules and assist in fragrance research and sensory neuroscience. Pred-O3 is accessible at ' https://odor.rpbs.univ-paris-diderot.fr/'.

Graphical abstract

Introduction

The sense of smell is a biological process that allows to human to perceive odors in our environment. Smell plays a major role in the perception of a large number of volatile environmental chemicals and can influence our health and well-being (1,2). Smell is mediated by the detection of odorant molecules by olfactory receptors (ORs) that are transmembrane G-protein coupled receptors (GPCRs) present at the surface of the nasal olfactory epithelium and that transform them into pattern of neuronal activity that are recognized in the brain (3–5).

The relation between odorant molecules and odors is a complex phenomenon where chemicals can interact as agonist, antagonist, or even by allosteric modulation (6) with one or several ORs, while OR can be activated or deactivated by several odorants. Odorants mixture can result in the recognition of several odors (heterogeneous percepts) or the recognition of one unique odor (homogeneous percepts) (7–10). The olfactory systems use a combinatorial olfactory receptor code which is converted into an odor. Therefore, the fact that millions of odorant molecules can be recognized by around 400

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different human olfactory receptors make it quite challenging to investigate all combinations and to have a clear understanding of the relationships between OR codes and the perceived odor quality (11–13).

To encompass this limitation, a variety of databases related to olfaction are available. Some databases focus on molecules and their odors and flavors (14–19). Others focus on ORs (20,21) and OR—odorant information (22,23). For example, OlfactionBase is a repository database that collects a lot of information reported in the literature (24). Although these resources give significant insight into olfaction there is no freely available web server that allows to analyze and predict odorant-odor, OR-odor and odorant-OR relationships.

With the PredO3 web server, we aim to gather accessible information related to OR-Odorant-Odor (O3) interactions, along with dedicated computational software's to enrich the knowledge on all the olfactory actors, to facilitate their visualization and to predict their intrinsic links when it is not known. Globally, three programs and several visualization applets have been implemented. For example, it is possible to search for chemical substructures to study functional groups connected to particular odors, as well as using similarity structural search methods to look for similar odorant molecules for a query chemical of interest. A prediction tool, recently developed internally, based on a deep learning approach (Graphical Neural Network) was implemented in the aim to predict the odors or olfactory receptors associated for a query compound (25). Finally, we precomputed 3D protein models for 1572 olfactory receptors and integrated them in the SeamDock server giving the possibility to dock any odorant molecules and to provide the potential mode of binding of an odorant to an olfactory receptor (26,27). More details about the programs implemented in the Pred-O3 web server and their applications are presented in the next sections.

Materials and methods

Data sources

Odorant molecules, ORs and odors were retrieved from multiple sources. Odorant molecules with their associated odor tags were retrieved from OlfactionBase (27), Flavor-Base (http://www.leffingwell.com/flavbase.htm) and TGSC (http://www.thegoodscentscompany.com/). OlfactionBase is a curated database of odorant molecules with tags carefully classified in odors and subodors compiling information from multiple related odor databases. Flavor-Base (10th version) is the last version to date of a database of flavor & regulatory data relevant to the Flavor, Food, Beverage & Tobacco industry. TGSC is a database of flavor, fragrance, food and cosmetic industries odors.

OR-odorant interactions information were retrieved from ODORactor (22), OlfactionDB (23) and through a bibliographic review (28). Only known OR-odorant interactions in human, mouse and rat were included in our study. For each OR we searched their corresponding UniProt id and sequence by querying the UniProt server (29) with their name and their species source.

Each molecule was mapped to a PubChem CID to remove duplicates and redundant information (30). This mapping made it possible to preserve some odor specificity for certain isomeric form of a molecule when the information is available (like for example the carvone (31–35). At the same time, we retrieved from PubChem, relevant information on molecules like the name, CAS, synonyms and their corresponding smile representation.

The 3D structure of chemicals was computed using RDKIt (https://github.com/rdkit/rdkit) with the ETDKG (v3) (36) forcefield. The 3D structure of ORs was retrieved and computed with AlphaFold (37) as no 3D structures of ORs have been crystalized and reported in the protein data bank so far (38).

Overall, PredO3 encompasses an extensive dataset comprising 5802 distinct odorant molecules, alongside 863 human olfactory receptors, 1407 mouse olfactory receptors and 10 rat olfactory receptors, culminating in a total of 2280 receptors across all species. Within this dataset, 5605 odor tags are meticulously classified into 933 distinct odor notes, facilitating comprehensive analysis and categorization of olfactory stimuli. Specifically focusing on chemical-odors, the dataset encompasses 36 016 chemical-odor tags, with 234 compounds identified as odorless. Moreover, PredO3 elucidates the intricate relationships between chemical and olfactory receptors with 2732 unique interactions between odorants and olfactory receptors, thereby advancing our understanding of olfactory signal transduction mechanisms.

All the retrieved information was gathered in a relational model and stored in a MySQL database as shown in Supplementary Information (Supplementary Figure S1).

Data Visualization

UMAP

The structural similarity between odorant molecules can be visualized through a Uniform Manifold Approximation and Projection (UMAP) representation (39). Basically, each molecule is encoded into an Extended-connectivity fingerprints (ECFP) (40), i.e. presence/absence of a given function/substructure in the compound and projected in a 2D map. So, the user can visualize molecules that share the same odors or the same interactions with specific olfactory receptors.

Radar plot

Difference in occurrence of functional groups among a subset of molecules related to a specific odor or olfactory receptor against all odorant molecules is visualized through a radar plot. It highlights overrepresented or underrepresented functional groups for an odor or an olfactory receptor of interest.

Prediction methods

Structural search

Structural similarity search for a query odorant molecule can be performed by either searching for overall similar structure though a Tanimoto score or by searching for sub-structures. The similarity search based on a Tanimoto score for a query molecule returns a score between 0 (dissimilar) and 1 (similar) for all the molecules in the database. The molecule encodes MACCS fingerprint which is a bit vector of 120 bit counting the presence (1) or absence (0) of a specific functional group in the structure of the molecule. Molecules are then sorted from most similar to the lowest.

Machine learning model

Two deep learning models based on graphical neural network (GNN) have been implemented. One to predict odors asso-

ciated with a chemical and a second one to predict olfactory receptors. Models were implemented for 160 odors and 109 human olfactory receptors. Details about the model's development have been reported in Achebouche *et al.* (28). The outcome of the prediction is a probability score between 0 and 1. Only ORs and odors with a probability over 0.5 are shown.

Docking analysis

Based on the structural model of each OR, we connected Pred-O3 to the SeamDock web server developed in our team (30). SeamDock is a web server that facilitate the access to small molecule docking for non-specialists. In order to standardize docking parameters for all docking of the ORs that are G-protein coupled receptors, we aligned all the structures against Olfr17 (Uniprot id Q7TRM9) on the Z axis with a reference center set at 0.0.0 with PyMOL (https://pymol.org). The grid box size has been set to X: 43 Å, Y: 24 Å, Z: 38 Å in order to be sufficiently large and restricted to target the core of all the ORs. So, local docking of any odorant molecule can be performed given the possibility to observe mode of interaction with the OR studied.

Webserver development

The webserver has been implemented using the django framework (https://www.djangoproject.com/foundation/). This web framework is coded in python and follows the model template view architectural pattern facilitating the implementation and ergonomics of the website. Information related to chemicals, odors, and olfactory receptors are displayed in dedicated templates as well as implemented tools of the website such as the structural search method, the prediction models and the docking tool.

The home page gives an overview of the different tools and information accessible in the website. It also provides the possibility to perform a fast search in the database for odors, chemicals and ORs. The 'help' page gives an overview on how to use the website, the different tools accessible and how to read the output of the different queries.

An overview of the different tools is depicted in Figure 1.

Case study

Webserver search

At the home page, the user can make a search for a chemical, an olfactory receptor or an odor. For example, searching for the acetaldehyde chemical, the user will obtain information about the chemical structure, some physicochemical properties, the list of odors (13 for acetaldehyde) and the list of olfactory receptors (Or2b4, Or10a48, Or2a25) collected in different databases. Also, a visualization of the acetaldehyde location in the chemical space of odorant molecules is depicted, given the possibility to observe the distribution of odorant chemicals around the selected molecule and thus sharing a similar structure. Finally, a phylogenic tree of olfactory receptors is depicted. It is based on the work from Glusman *et al.* who classified the ORs into 31 families (based on their sequence similarity) (41). So, in our case, acetaldehyde interacts with 2 ORs from the same class (Or2b4 and Or2a25) and a third OR quite different (Or10a48).

The user can do a similar query for an olfactory receptor or an odor. He will get in return a similar card with all the odorant molecules annotated to them and the visualization of them in the chemical space. This last option can be of interest to see groups of chemicals distributed in the same area in the 2D UMAP. It means that they share a similar structural pattern that could be specific to an olfactory receptor or an odor. Also, a radar plot with functional groups of odorant molecules that are over or under -represented are depicted. For example, for the OR1D2 olfactory receptor, 137 compounds have been detected. From the radar plot, benzene and aldehyde function have more represented and susceptible to be important features to bind to OR1D2. A similar exercise for the coffee odor shows that 145 odorant molecules are annotated to coffee with a majority of them having a sulfide group, Aromatic nitrogen (Ar_NH), a furan or a NHO group. It is important to notice that all the results can be downloaded as a csv file and so the user can use this information for others analyses.

Web server tools

On the home page, three computational tools are proposed for the user. The 'Structure search', 'Prediction' and 'Docking' tools. An overview of the available information accessible in Pred-O3 webserver with a compilation of snapshots from (A) chemical template page, (B) odor template page, (C) olfactory receptors page, is depicted in Supplementary Information (Supplementary Figure S2).

Structure search

On the 'structure search', from a chemical structure, it is possible to collect all the odorant molecules that shared a similar structure based on the Tanimoto similarity score (launch similarity search). For example, with the phenol compound (with the smiles code [OH]c1ccccc1), similarity with all the odorant molecules in our database is provided. Two compounds (4-methylphenol and 3-methyphenol) have a Tanimoto score over 0.85. Substructure search can also be performed by 'launching substructure search'. Here, the user can search for a substructure pattern matching by searching via a smart pattern or any molecule identifier available in the searching method. It returns all the molecules of the database with the query substructure in its structure. In the example with the phenol compound, we can observe that tyramine and sodium salicylate, among others, share the same structural pattern.

Prediction

Two deep learning prediction models based on a Graphical Neural Network (GNN) have been added to the website to predict the potential odor and/or the potential interacting human ORs of a query compound. These models have been extracted from the article (25). The odor predictor can predict one or multiples odors class among a set of 23 odor note with a prc AUC of 0497 and the human ORs predictor can predict the potential interaction of a molecule with one or multiple human olfactory receptors among a set of 74 human OR with a prc-auc of 0,91. For example, with the phenol chemical, five olfactory receptors (OR9Q2, OR10G4, OR5AN1, OR52D1, OR1G1) and two odors (phenolic, medicinal) have been predicted with these two models.

Also, after the prediction is computed, the user can visualize in a radar plot the most frequent functional groups found in the set of molecules with the same known odor or human olfactory receptor. UMAPs showing close molecules with the same known odor notes or binding to the same olfactory re-

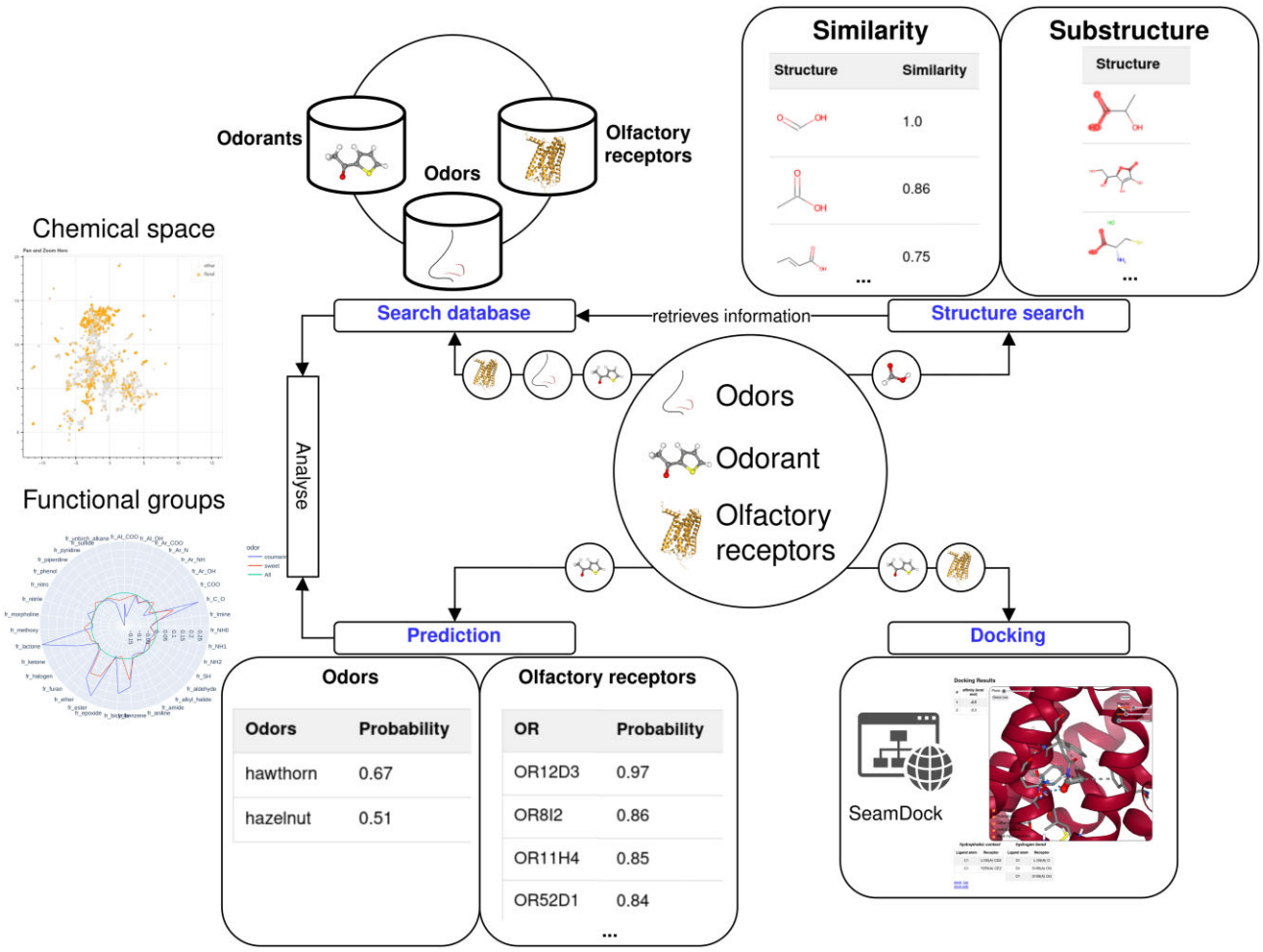

Figure 1. Overview of the available tools in Pred-O3. Users can access information in the database by searching using odorants, odors, and olfactory receptors (Search database). Chemical information can be retrieved by searching the database using similarity, measured by a Tanimoto score, or by searching for substructure (Structure search). For new compounds, the server can predict their potential odors and interacting olfactory receptors using two GNN models in Prediction toolbar. The web server is linked to the SeamDock web server, allowing the transfer of odorants and olfactory receptors from the database for docking simulations (Docking). Users have the capability to analyze the overrepresented or underrepresented functional groups in the database for a particular odor or olfactory receptor through a radar plot (Functional groups). The chemical space of compounds associated with a specific odor or interacting with a specific olfactory receptor can be visualized with an UMAP (Chemical space).

ceptor are also depicted. Additional physicochemical information on the query molecule is computed and shown to the user as the molecular weight, log *P* and name if found in PubChem database. The similarity of the query compound is also computed on all odorant of the database and the 10 most similar odorant are displayed with their odor notes and potential ORs interaction information to strengthen the confidence of the given prediction.

Docking of ligand on specific olfactory receptors

We linked our server to the SeamDock server to perform online docking on olfactory receptors. To perform docking we retrieved 3D structure of olfactory receptors computed with Alpha Fold for the proteins of the rat, mouse and human (1572 proteins). So, the user can select the structure of an OR and a chemical directly from the website and launch a docking. For example, using phenol as a ligand and OR1G1 as an olfactory receptor, SeamDock proposes a visualization of the binding mode of the molecule in OR1G1. It identifies the residues F104, V108 and Y278 in the binding of phenol with a suggested binding affinity of –4.1 kcal/mol. The type of interactions, salt, hydrophobic, cation-pi and hydrogen bond are also depicted.

Conclusion

The Pred-O3 web server is an user-friendly free resource that can provide significant insights into olfaction. It incorporated multiple tools to decipher the underlying structural relationships between odorant-odor and OR-odor. Functional molecular groups in a chemical related to one or multiple odors, or interacting with olfactory receptors can be visualized. Prediction of ORs and odors associated with a new chemical can be performed and mode of binding of a chemical within an OR is also suggested through a docking server.

There are some potential limitations that the user has to keep in mind when using the webserver. First, the information used in our study are categories. Therefore, quantifying the relationship between an odorant and an olfactory receptor or an odor is still relative. Moreover, the stereoisomeric form is

only considered when information is available. It might bias some predictions from the models. Finally, the docking analysis is based on structural models of the olfactory receptors performed in a systematic way. The diverse nature of olfactory receptors, as shown in the phylogenic tree of ORs from Glusman (41), suggest that the binding pocket defined on the seamdock server might be not optimal and further analyses have to be performed to confirm observation from docking.

Nevertheless, ongoing projects on olfactory research should provide new information that will be integrated in the web server in a yearly based (when available). Therefore, we believe that Pred-O3 is well suited to aid in the design of new odorant molecules and assist in fragrance research, sensory neuroscience and many others field of research in cosmetic and food industries.

Data availability

The complete list of odorants, olfactory receptors and odors used in the webserver is accessible in supplementary data (Supplementary Table S1).

Supplementary data

Supplementary Data are available at NAR Online.

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Conflict of interest statement

None declared.

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