

MLP Tools: a PyMOL plugin for using the molecular lipophilicity potential in computer-aided drug design

Nils Oberhauser · Alessandra Nurisso ·
Pierre-Alain Carrupt

Received: 23 January 2014 / Accepted: 15 April 2014 / Published online: 29 April 2014
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Abstract The molecular lipophilicity potential (MLP) is a well-established method to calculate and visualize lipophilicity on molecules. We are here introducing a new computational tool named *MLP Tools*, written in the programming language Python, and conceived as a free plugin for the popular open source molecular viewer PyMOL. The plugin is divided into several sub-programs which allow the visualization of the MLP on molecular surfaces, as well as in three-dimensional space in order to analyze lipophilic properties of binding pockets. The sub-program *Log MLP* also implements the virtual $\log P$ which allows the prediction of the octanol/water partition coefficients on multiple three-dimensional conformations of the same molecule. An implementation on the recently introduced *MLP GOLD* procedure, improving the GOLD docking performance in hydrophobic pockets, is also part of the plugin. In this article, all functions of the MLP Tools will be described through a few chosen examples.

Keywords Molecular lipophilicity potential · PyMOL · Virtual $\log P$ · Molecular docking · Hydrophobicity

Introduction

Lipophilicity is a physicochemical property which sums up the entirety of all intermolecular effects and intramolecular recognition forces [1]. According to its intrinsic definition, lipophilicity can be sub-divided into two major contributors: hydrophobicity and polarity [2]. The first one describes hydrophobic and dispersive solute–solvent interactions while the latter describes polar interactions such as dipole–dipole and hydrogen bonds. As a molecular property, lipophilicity is commonly expressed by the partition coefficient P of a solute between two immiscible solvent phases under equilibrium conditions. The logarithm of the partition coefficient between octanol and water phases ($\log P_{o/w}$) has emerged to be the most commonly used parameter in pharmaceutical science since it sufficiently models the difference between the polar blood plasma (water) and lipophilic cell membranes (octanol) [3, 4]. In the past decades a wide range of experimental methods able to determine $\log P$ has been described [5, 6]. Since most of the experimental methods are highly time and/or material consuming and thus not applicable for large scale high throughput screenings (HTS), computational methods predicting $\log P$ have also been developed [7, 8]. As a consequence, $\log P$ can nowadays be calculated on an ordinary personal computer within fractions of a second. While most of these predictive methods deliver fairly good results on small molecules, their accuracy decreases with the size and flexibility of a compound [7]. This might be explained by the fact that most common methods do not take three-dimensional or conformational information into account. Testa and co-workers tried to fill this gap by setting up a protocol coupling the molecular lipophilicity potential (MLP) estimated by using fragment-based lipophilicity factors [9, 10], and distance-dependent functions

Electronic supplementary material The online version of this article (doi:10.1007/s10822-014-9744-0) contains supplementary material, which is available to authorized users.

N. Oberhauser · A. Nurisso (✉) · P.-A. Carrupt
School of Pharmaceutical Sciences, University of Geneva,
University of Lausanne, Quai Ernest-Ansermet 30,
1211 Geneva 4, Switzerland
e-mail: alessandra.nurisso@unige.ch

calculated on the solvent accessible surface area of molecules [2, 11]. This strategy has been demonstrated to be useful not only for evaluating lipophilic properties on molecular surfaces [12], but also for estimating conformation-dependent $\log P$ values, also known as virtual $\log P$ [13], lipophilic descriptors in 3D-QSAR studies [14] and in structure-based drug design projects [15–17]. Whereas nowadays a broad variety of commercial software employs this method for describing lipophilicity [18–20], the free software VEGA is the only one, to our knowledge, using the MLP to predict virtual $\log P$ values, to display lipophilic surfaces of small compounds and to estimate molecular interactions strength [21].

In this work we present a free software suite that we named *MLP Tools* which combines all the MLP applications in computer-aided drug design collected from the literature into a user-friendly Graphical User Interface (GUI) written in the object-orientated programming language Python [22]. MLP Tools were developed as a plugin for the three-dimensional molecular viewer PyMOL [23], a widely-used software capable of rendering and ray-tracing high resolution molecular representations in publication quality. An open-source version of this molecular viewer is available, which makes PyMOL especially attractive for academic and educational use. Besides predicting MLP-based virtual $\log P$, MLP Tools can also be used to map lipophilic properties on solvent accessible surfaces of both small molecules and proteins. Three-dimensional distribution of lipophilicity in binding sites can be also visualized and quantitatively evaluated, in order to obtain better insight in the lipophilic nature of protein pockets [15]. MLP Tools further include the recently published MLP GOLD method which alternates the hydrophobic fitting points generated by the widely used molecular docking program GOLD [24] to MLP-based points able to improve docking results on hydrophobic targets [15]. In order to understand and quantify molecular interactions, a MLP-based score has been also implemented in the past [2]. Therefore, MLP Tools, whose features are summarized in Fig. 1, can be considered a complementary free instrument in computer-aided drug design for evaluating and displaying molecular properties and interactions in a high graphic quality environment.

Materials and methods

The molecular interaction field (MIF) known as molecular lipophilicity potential (MLP) [11] was herein re-implemented in the object-oriented programming language Python and the numeric Python library NumPy [22, 25].

MLP Surf: lipophilic surfaces generation

MLP allows a local measurement of lipophilicity on any point in space k by applying the following equation:

$$MLP_k = \sum_{i=1}^N F_i \cdot f(d_{ik})$$

where N is the number of fragments, F_i is the lipophilic contribution of fragment i of the molecule and $f(d_{ik})$ is a distance function based on the distance of the measured point in space k to fragment i . The MLP used in the presented software is characterized by an extended fragmental system [9, 10] as well as a Fermi type distance function [11]. First, a solvent accessible point-surface is created around a molecule by a 1.4 Å probe [26]. Then, on each point of the surface, the MLP is calculated. The point is represented as a colored sphere whereas the color ranges from blue (hydrophobic) to red (polar).

Log MLP: virtual $\log P$ prediction

The overall sum of polar and hydrophobic points of a MLP Surface allows a back-calculation of its experimental parameter of origin, the $\log P$:

$$\log P_{MLP} = \sum MLP^+ \cdot w^+ + \sum MLP^- \cdot w^- + C$$

where MLP^- and MLP^+ are the polar and hydrophobic parts of the MLP respectively. The weighting factors w^+ and w^- as well as the correction constant C had been optimized on a set of compound structures and their experimentally determined $\log P$ [11].

MLP Pocket: estimation of protein pocket lipophilicity

The three-dimensional distribution of lipophilicity within the binding pocket of a protein can provide valuable information for understanding the recognition processes and for explaining the conformations adopted by a candidate drug [1]. The MLP Pocket utility allows the user to visualize a MLP-based lipophilicity within a defined pocket area. A three-dimensional grid of points is generated in the defined binding site. The binding site can be manually defined by Cartesian coordinates or by a reference ligand. On each point in the grid the MLP towards the pocket is calculated. The points are represented as color-coded spheres ranging from blue (hydrophobic) to red (polar).

MLP GOLD: improvement of docking results for hydrophobic targets

The widely used docking program GOLD [27, 28] creates a list of points, the so-called *hydrophobic fitting points*,

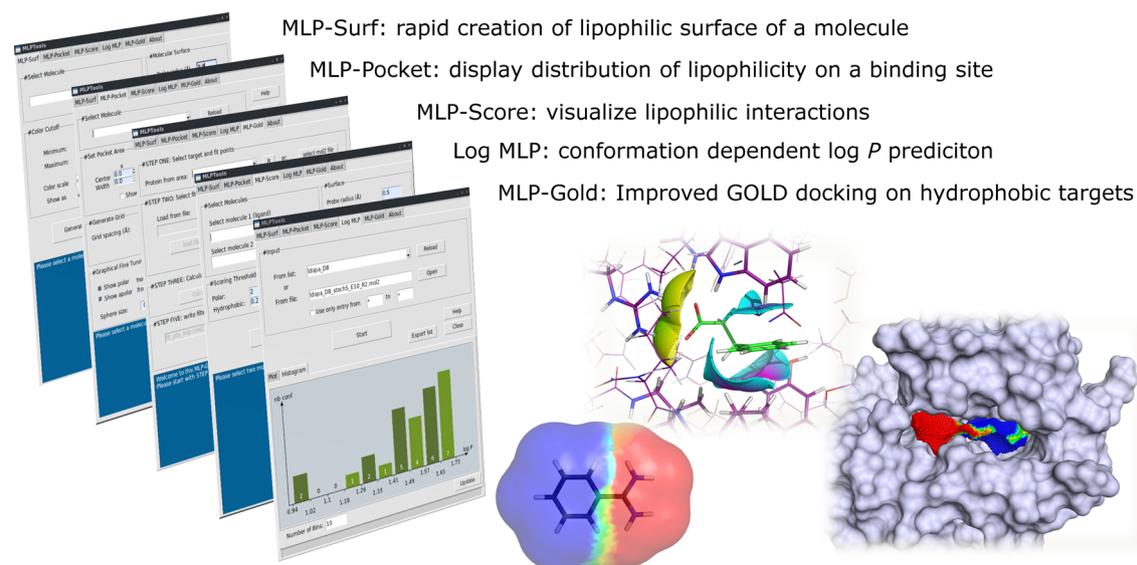


Fig. 1 Summary of the sub-programs and features implemented in the MLP Tools plugin

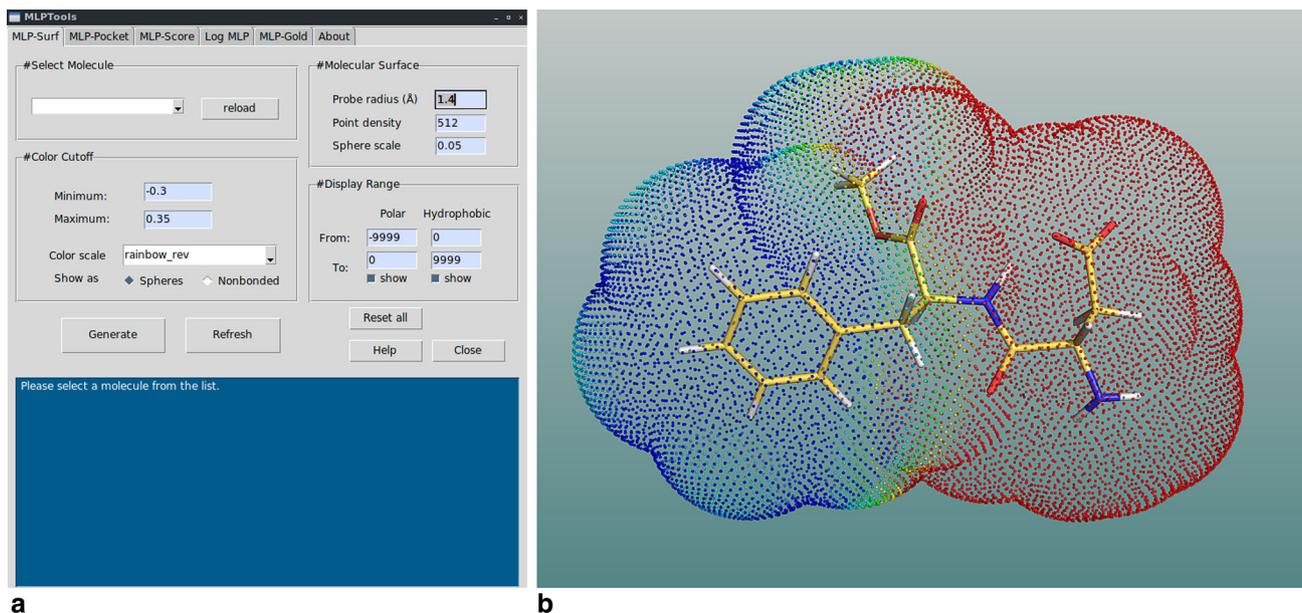


Fig. 2 MLP Surface of Aspartame: polar points are *red*, hydrophobic points *blue* (a). GUI window of the MLP Surf tool (b)

which are used to define hydrophobic regions in the binding site during docking. These points are created by calculating the Lennard–Jones interaction potential at each point of a grid lattice between a carbon sp^3 probe and the atoms of the binding site. Nurisso et al. [15] recently demonstrated that a simple MLP-based filter technique, applied on the fitting points, can help to weed out fitting points that are falsely classified as hydrophobic by GOLD and thus improve the docking outcome on hydrophobic targets. MLP Tools plugin provides an easy-to-use user interface to make the MLP filter available to the public.

The user only needs to provide a three-dimensional structure of the target in mol2 format and a file containing the hydrophobic fitting points automatically created by GOLD (usually named *fit_pts.mol2*). MLP Tools will calculate then the MLP on those points and will generate a new file containing the coordinates of the filtered points. The user will be also able to display those points, color-coded according to the MLP rules. Based on the sum of all positive and the sum of all negative MLP values associated to each point, the so called lipophilic index (LI) can be calculated:

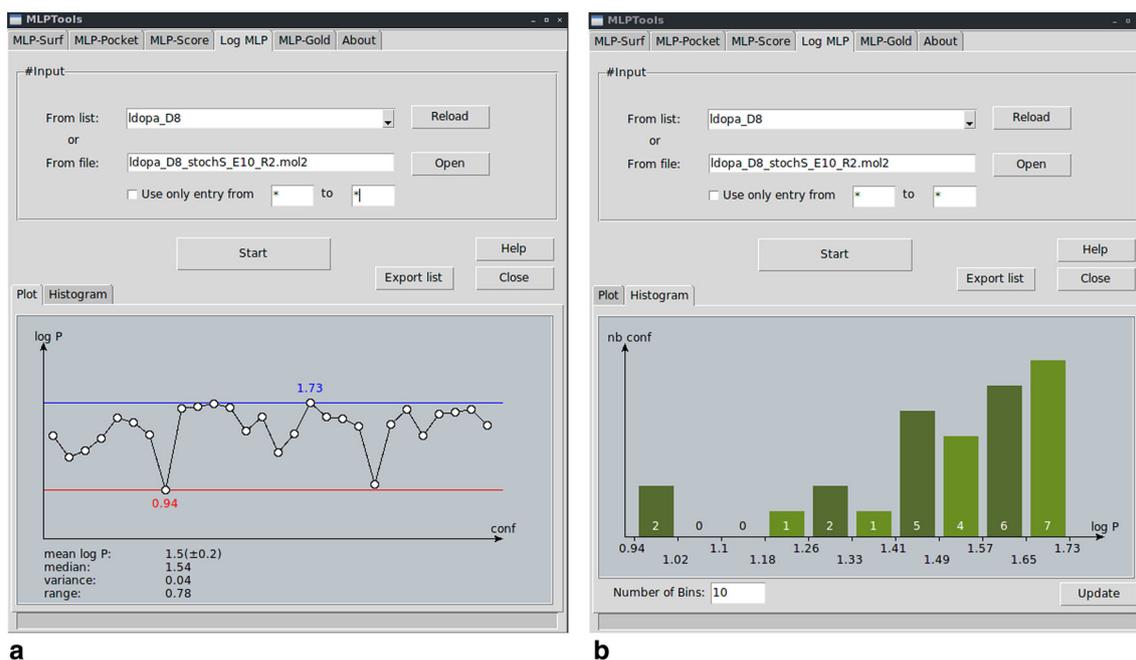


Fig. 3 GUI window of the Log MLP tool, showing the plot of the multiple calculated log P values (**a**) and the histogram tab displaying the log P distribution of the calculated log P s (**b**)

$$LI = \frac{\sum MLP^+}{\sum MLP^+ + |\sum MLP^-|} \cdot 100$$

It had been assessed that the use of the MLP filter is appropriate only for protein pockets with a LI > 10 % [15]. MLP Tools calculates the LI and suggests to the user if the use of the filtered points is appropriate in the particular case or not.

MLP Score: evaluation of molecular interactions

To help gaining a better understanding of ligand–protein or protein–protein interactions, an *intrinsic* MLP can be calculated on the points characterizing the solvent accessible surface of a biotarget. A second *perceived* MLP can be also calculated on these points, but this time evaluating the MLP atomic contributions of the other biotarget. Finally, a function can quantify the similarity between the two MLPs into a global score [2]:

$$SCORE_{MLP} = \sum_{k=1}^{Nb_{dots}} (MLP_k)^{intrinsic} \cdot (MLP_k)^{perceived}$$

where MLP_k -intrinsic and MLP_k -perceived are the intrinsic/perceived MLP values at surface point k . Thus, the MLP Tools implementation of Score MLP gives the user a straight-forward interface to visualize lipophilic interactions and calculates the resulting score for quantifying the strength of interaction between two molecular partners.

Results and discussion

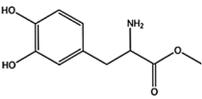
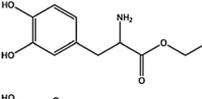
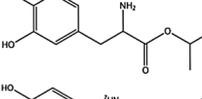
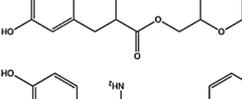
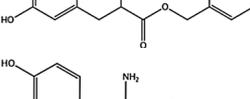
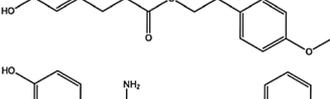
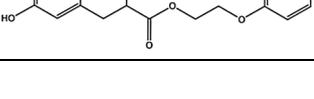
System requirements and installation

In order to install MLP Tools, a working installation of PyMOL version ≥ 1.4 is required. Plugin support must also be available, which should be the case for standard Linux and Windows installations. On a Mac OSX system, only the X-Server-based version of PyMOL supports plugins. Python version $\geq 2.6 / < 3.0$ is required. Numpy libraries ($\geq 1.4.1$) have to be available to the Python installation. If all system requirements are fulfilled, MLP Tools can be installed by running an installation script enclosed in the installation files or manually copied in the PyMOL plugin directory. Do not use the PyMOL plugin manager since it cannot handle multiple installation files. After the successful installation, MLP Tools are accessible by the common PyMOL plugin menu.

Input format

In the current version of MLP Tools, input molecules must be placed in the working directory as Tripos mol2 files. It is assumed that all atom-typing has been assigned correctly and all hydrogen atoms added. An atomic partial charges assignment is not required. If the mol2 file contains more than one molecule, the index corresponding to the current PyMOL state will be taken. For the *Log MLP* program, a multi-mol2 file containing at least two conformations of the

Table 1 Experimental and calculated log *P* values of L-Dopa esters

	2D Structure	log <i>P</i> _{exp}	log <i>P</i> _{MLPmin}	log <i>P</i> _{MLPmax}	log <i>P</i> _{MLPmean}
E1		-0.07	0.02	0.22	0.12 (± 0.08)
E2		0.37	0.39	0.68	0.55 (± 0.08)
E3		0.80	0.88	1.25	1.09 (± 0.11)
E4		0.56	0.60	1.37	1.13 (± 0.19)
E5		1.55	0.98	1.58	1.32 (± 0.20)
E6		1.82	1.60	2.22	1.95 (± 0.19)
E7		1.69	0.94	1.73	1.50 (± 0.20)

same molecule is mandatory. For virtual log *P* calculations on single conformations, the *MLP Surf* utility can be considered.

MLP Surf and Log MLP: two tools for studying the lipophilic properties and conformation-dependent behavior of molecules

The user can visualize the MLP-based lipophilic properties of molecules by using the *MLP Surf* option of the MLP Tools. MLP Surf allows a quick calculation a lipophilic molecular surface giving the user complete control over parameters such as radius number of points to calculate together with color-cutoff values. The default setting displays polar areas in red, hydrophobic areas in blue, but these settings may be changed by the user (Fig. 2). A virtual log *P* can be then calculated as stated in the *MLP Surf* window.

In order to demonstrate the capabilities and the importance of these utilities implemented in MLP Tools, the virtual log *P* was calculated for a series of minimal energy conformations of seven esters of the non-proteogenic amino acid L-3,4-dihydroxyphenylalanine (L-Dopa) [29]. To perform a virtual log *P* calculation of a series of conformers, the user has to first generate multiple conformers of a specific compound and save them in one multimol2 file. In MLP Tools the user can either open the multimol2

file (“from file” option) or choose a molecule that is already present in the PyMOL window. In this case, the stochastic search method from the molecular operating environment (MOE) was used to obtain multiple L-Dopa derivatives conformations [20]. The virtual log *P* calculation can be submitted by clicking the *Start* button. Once the calculation has finished, a plot is created, showing the range of the calculated virtual log *P* values. If a specific point of the plot is selected, the corresponding conformation is loaded into the PyMOL viewer. Statistical information, such as minimum, maximum and mean virtual log *P* values (Fig. 3a) is also displayed in the same MLP Tools window. A list containing the calculated log *P* values can be exported as text file by selecting the *Export List* option. Further, a histogram representing the distribution of log *P* values is created by default. It can be visualized by clicking on the histogram panel. The virtual log *P* values are here clustered in bins, whose number can be directly chosen by the user and displayed after clicking the *update* button (Fig. 3b). Table 1 shows minimum, maximum and mean log *P* values calculated on the different conformations of a series of L-Dopa esters, as well as their experimentally measured log *P* values. It is noticeable that the difference between the highest and the lowest virtual log *P* values, calculated for one structure, i.e. the range of virtual log *P*, increases with the number of free rotatable bonds. Figure 4 a, b show the two conformations of

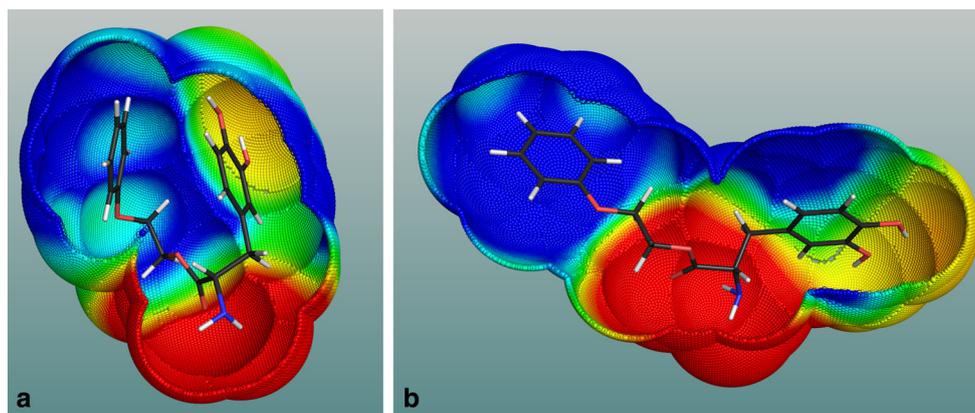


Fig. 4 A compact (a) and an extended (b) conformation of compound E7, an aryl ester L-Dopa derivative. The compact conformation is predicted to be more polar ($\log P_{MLP} = 0.94$) than the extended one ($\log P_{MLP} = 1.73$). c Variations of the calculated

$\log P$ of seven different esters of L-Dopa within the conformational space (vertical lines). The horizontal lines mark the experimental $\log P$ value

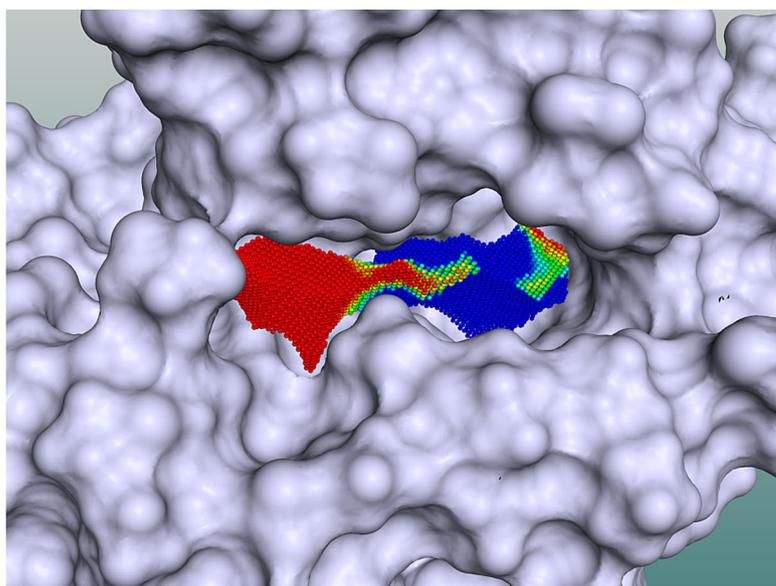
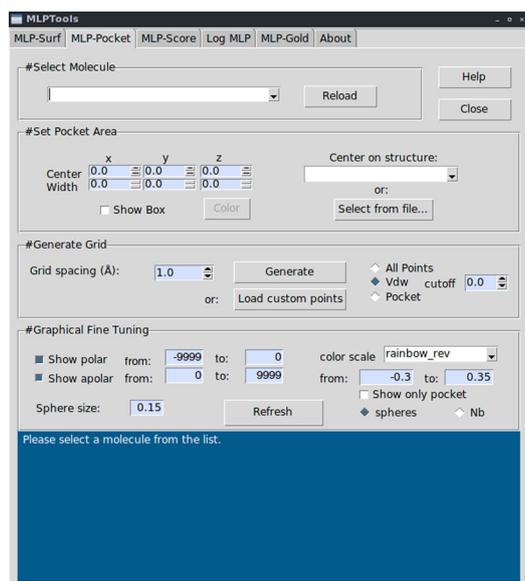


Fig. 5 GUI window of the MLP Pocket tool (a). Distribution of the lipophilicity in the binding pocket of the human thyroid hormone receptor α (PDB code: 1nav) from red (polar regions) to blue (hydrophobic regions) (b)

compound E7 (Table 1) associated to the highest and the lowest virtual $\log P$ value. Due to internal hydrophobic interactions, the hydrophobic surface of the conformation in Fig. 4a is reduced, which results in a lower $\log P$ (virtual $\log P = 0.94$). On the contrary, the hydrophobic surface of the conformer in Fig. 4b is fully exposed, what may explain the increased $\log P$ value (virtual $\log P = 1.73$) towards this unfolded conformation. One can see that in the cases of alkyl esters (structures E1–E4, Table 1) the lowest (most polar) virtual $\log P$ is always closer to the

experimental partition coefficient whereas for aryl esters (structures E5–E7, Table 1) the opposite case is observed. These observations suggest a different conformational behavior of the two groups of esters in solution. The alkyl esters hence exist mostly as folded conformers while the aryl esters prefer the extended conformation. The effect on the accessibility of the conformational changes could be partially responsible for different rates of hydrolysis exhibited by alkyl and esters, which had been observed experimentally [29].

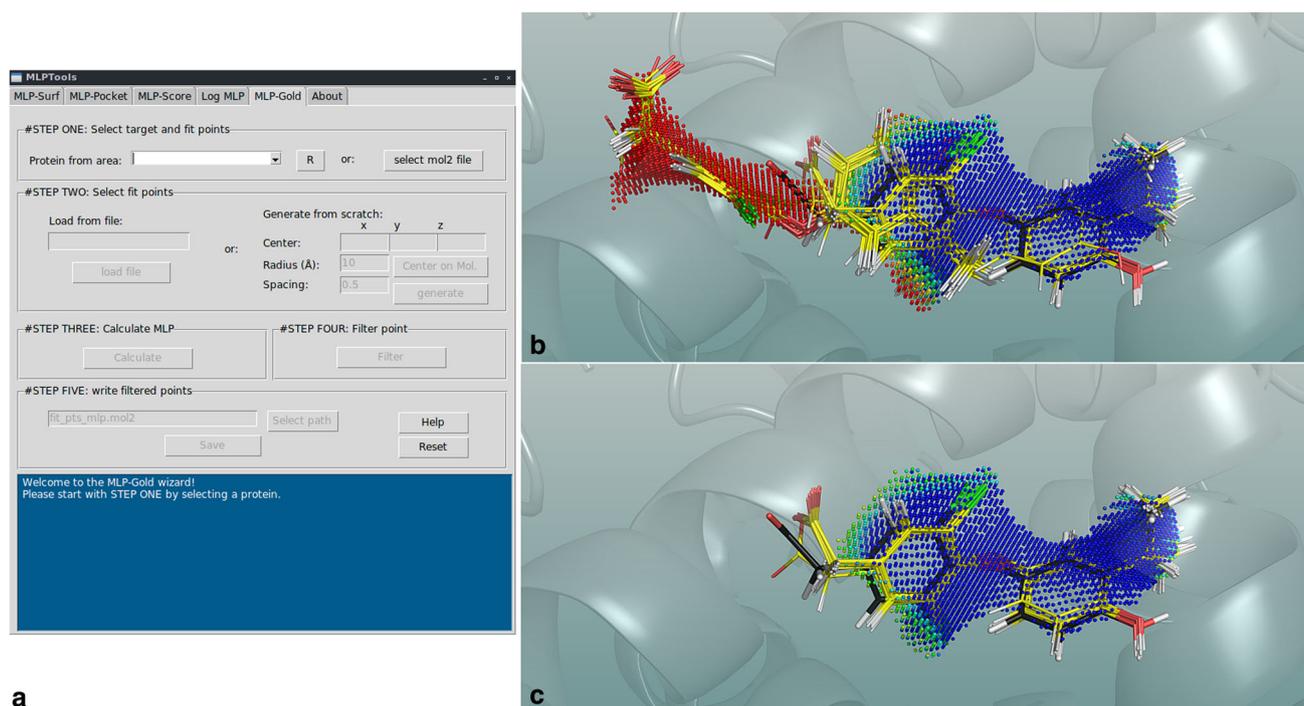


Fig. 6 GUI window of the MLP-GOLD tool (a). 20 docked conformations of the endogenous thyroid hormone in the human thyroid hormone receptor α without (b) and with (c) the application of the MLP filter tool. The *black* conformation corresponds to the x-ray conformation

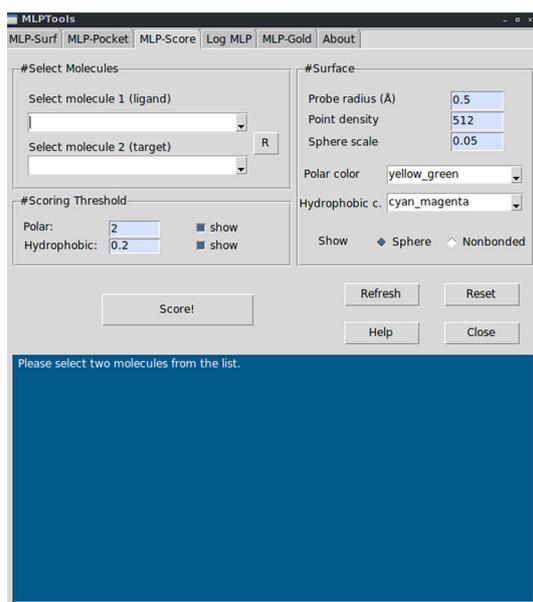
MLP Pocket, MLP GOLD and MLP Score: evaluation of lipophilic properties, interactions and improvement of molecular docking results

The docking of the endogenous thyroid hormone into the human thyroid hormone receptor α (PDB code: 1nav) will be used here as a case study to demonstrate how to use and combine the *MLP Pocket* and *MLP GOLD* utilities in order to characterize lipophilic properties of binding sites and enhance GOLD docking results.

To use *MLP Pocket*, the user needs to provide a protein structure in mol2 format and the location of the binding site. The binding site can be manually defined by Cartesian coordinates or by a reference ligand. Figure 5 shows a screenshot of the MLP Pocket GUI (a) and the distribution of the lipophilicity in the pocket of the human thyroid hormone receptor α (b). The pocket shows a clear separation of polar (red spheres) and hydrophobic (blue spheres) properties of the pocket.

In the first steps of the *MLP GOLD* procedure, the user is asked to provide the mol2 file containing the protein structure used for running the standard GOLD docking run and the mol2 file containing the GOLD hydrophobic fitting points (HFP), by default named *fit_pts.mol2* by the docking software. To obtain the HFP file, it is necessary to run a standard GOLD docking run. By using the *generate from scratch* option, the user may choose to generate points that are simply based on Lennard–Jones potential values

calculated between a carbon Sp3 probe and the residues of the binding pocket, retaining only points with a negative energy. The spacing and the spherical size of the grid may be set by user. The fitting points are now loaded into the PyMOL window as shown in Fig. S1a. After clicking the *Calculate* button, the MLP is calculated on all hydrophobic fitting points that are colored according to the standard MLP color code, i.e., blue meaning hydrophobic and positive MLP values and red meaning polar and negative MLP values (Fig. S1b). Successively, the user can filter and remove all points that have MLP values lower than zero, thus polar according to the MLP system (Fig. S1c–d). It has been demonstrated that the use of this methodology can be beneficial for improving GOLD results in all cases with the exception of truly hydrophilic pockets [15]. In order to quantify the lipophilic properties of the pockets, *MLP GOLD* calculates the Lipophilic Index LI value. Protein pockets with a LI lower than 10 are considered purely hydrophilic [15]. The *MLP GOLD* window gives the user a suggestion whether to use or not the MLP-based procedure for docking. Filtered points can be saved in a mol2 format ready to be used in GOLD through the activation of the *read hydrophobic fitting points* option in the GOLD configuration file. For the case study of the docking of the endogenous thyroid hormone in its receptor α , 100 docking runs were performed by the GOLD program using preset options for the genetic algorithm and the empirical scoring function GoldScore [15]. The docking was done once with



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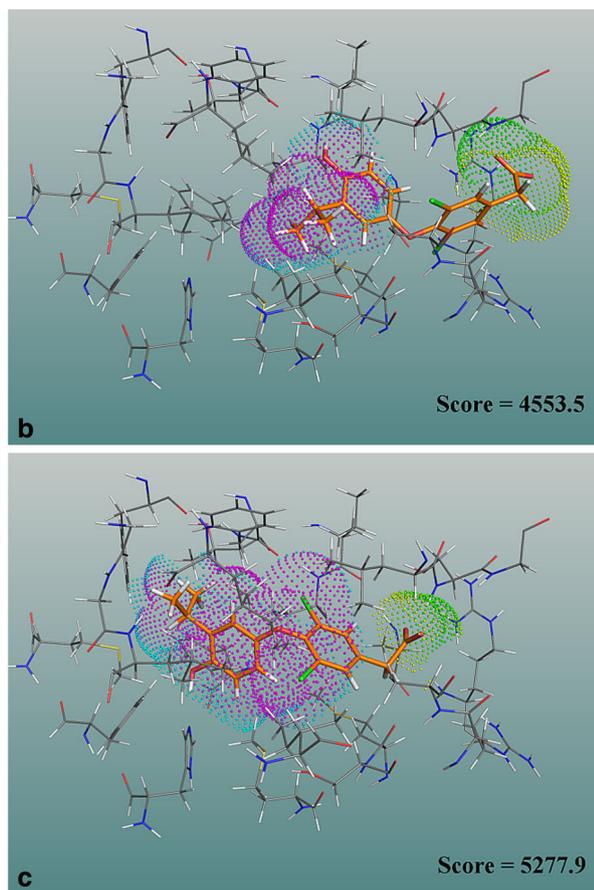


Fig. 7 GUI window of the MLP Score tool (**a**). One of the wrong docked conformations of the endogenous thyroid hormone in the human thyroid hormone receptor α obtained with the standard GOLD docking tool (**b**) and one docked conformation obtained by applying

MLP GOLD (**c**). The magenta/cyan spheres mark areas on the ligand's surface where both the intrinsic and the perceived MLP are positive. The green/yellow areas mark areas where both MLP values are negative

the standard unmodified HFPs produced by GOLD and once under the use of the MLP-filtered fitting points. Among the 100 docking solutions retrieved by the standard GOLD approach, 48.0 % were characterized by root mean square deviation (RMSD) values higher than 2 Å with respect to the crystallographic binding pose (Fig. 6a). GOLD predicts these solutions to be shifted into a zone that is rich in polar residues in which the carboxylate functional group is accommodated by creating a stable salt bridge with the residue Arg228. The reason for this failure is related to a misleading definition of hydrophobicity in the binding site. The HFPs generated at the beginning of the docking simulation covered an extended area of the cavity, including a clearly polar region (Fig. S1b). The MLP filter was able to recognize that polar region and remove points that guided the ligand in the wrong direction into the pocket. Thus, 100 % of the docking solutions were able to reproduce the experimental binding mode with the MLP GOLD procedure (Fig. b) with RMSD values lower than

2 Å, demonstrating a strong improvement in the quality of docking.

The use of the *MLP Score* tool can further substantiate these findings. In *MLP Score* the user must select two molecules in the user interface. In the present case, the first molecule is the ligand (endogenous thyroid hormone) and the second molecule is the thyroid hormone receptor α . The intrinsic MLP on the ligand and perceived MLP on the receptor are determined and a global MLP-score is calculated by clicking on *Score*. To visualize lipophilic interactions, the surface points associated to a positive MLP score are shown in the PyMOL window (Fig. 7a). Points on which both MLP points are positive are colored in a magenta/cyan and points on which both MLP points are negative are colored in green/yellow. For better visual inspection, the number of points can be limited by a score threshold in the *MLP Score* window. Figure 7 shows two examples of docked conformations of the endogenous thyroid hormone into its receptor: one docked conformation obtained without MLP

filter (Fig. 7b) and one docked conformation using the filter (Fig. 7c). With a MLP score of 4,553.5, the non-MLP filtered solution obtained a significantly lower score than the one obtained when the filter was applied (MLP score = 5,277.9). This result further confirms that the MLP can aid to predict and to discriminate correct binding conformations. Indeed, the MLP Score tool can be used to aid in visual inspection of docking results or to re-score docked conformations in order to determine the right bound ones.

Conclusions

The MLP has previously been proven to be a useful descriptor in computational drug design. We have herein introduced the PyMOL MLP Tools plugin which is a comprehensive collection of useful programs in a high graphic quality environment that apply the MLP to quickly visualize color-coded lipophilicity around molecules or in binding pockets and to quantify this lipophilicity by predicting, respectively, conformational dependent log *P* or lipophilic index LI values. MLP GOLD also provides a good user interface for using the MLP filter method which has proven to enhance GOLD docking performance on hydrophobic binding sites. Finally, the determination of a MLP-based score can further help to evaluate and choose a right docked conformation by describing and scoring lipophilic interactions between biomolecules. The MLP Tools PyMOL plugin is freely available for download (<http://mlp-tools.tk/>).

Acknowledgments The authors thank Dr. Antoine Daina for helpful preliminary discussion and the Excellence scholarship of the University of Geneva, Switzerland, for financial support.

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