Exploration of Pockets on Protein Surfaces

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Motivation
Recent technological advances in drug discovery such as high throughput and fragment-based screenings, either in vitro or in silico, make feasible the development of small chemicals also for curing rare diseases. An example is offered by pharmacological chaperones which are currently in clinical trial for the treatment of some genetic diseases. They are small molecules, usually reversible inhibitors or antagonist, which are used at sub-inhibitory concentration to stabilize mutant enzymes or receptors. Allosteric ligands might act as pharmacological chaperones, and in this case they might prove to be more effective than reversible inhibitors or antagonists, since they would play their stabilizing action without competing with the natural substrate. In order to make the research of new drugs as economic as possible, it is necessary to exploit in silico techniques at most, and, in particular, it is very advantageous to explore surface pockets of proteins, active sites or not, which might be the targets of low molecular weight drugs.

Methods
We detected surface pockets and cavities of human proteins with known 3D structure using CastP. We obtained homologs for each protein running Blast and we developed a tool to associate the probability of enrichment of conserved aminoacids to each pocket or cavity under a Poisson background model. Druggability of pockets is assessed by structure based virtual screening with GOLD

Results
Our method optimize the choice of the input sequences to be used to distinguish evolutionary conserved from non conserved pockets on protein surfaces. By so doing we are able to detect the active site with high accuracy because, in general, it coincides with the most conserved pocket. We extended our analysis to all the pockets found on the surface of human proteins and divided them in three groups: conserved and coinciding with the active site, conserved but not coinciding with active site and non conserved. Several features were compared among which volume, amino-acid composition or hydrogen bond donors and acceptors occurrence. For special cases of medical interest, druggability of the pockets was also assessed computationally mapping solvent molecules as well as the common frameworks, also known as privileged compounds, used
for fragment based drug design.

**Availability**

http://www.sbcentrostorico.unina.it/cammisa

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