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# COCOMAPS: a web application to analyze and visualize contacts at the interface of biomolecular complexes

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## ABSTRACT

**Summary:** Herein we present COCOMAPS, a novel tool for analyzing, visualizing and comparing the interface in protein–protein and protein–nucleic acids complexes. COCOMAPS combines traditional analyses and 3D visualization of the interface with the effectiveness of intermolecular contact maps.

**Availability:** COCOMAPS is accessible as a public web tool at http://www.molnac.unisa.it/BioTools/cocomaps

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Interaction between biomolecules is at the basis of many of the most important molecular processes in the cell. Protein–protein interactions underlie for instance signaling, regulation, immunogenic recognition, whereas protein–nucleic acid interactions underlie processes such as DNA transcription, repair, replication, as well as post-transcriptional events, including RNA splicing and editing.

Availability of a 3D structure for a complex allows detailed analysis of the interaction at atomic level between the molecular partners, which is a fundamental step for possible biomedical and biotechnological applications. Moreover, the recent development of well-performing docking softwares to predict the 3D structure of macromolecular complexes (Janin, 2010) requires, in the analysis step, the accurate and tedious screening of all the best solutions. It is indeed well accepted that the correct solution, if any, can be found within the 10–20 best ranked ones (e.g. the CAPRI assessment accepts 10 different models per target from each predictor).

It is therefore of timely interest, both for bioinformaticians and wet biologists, to have programs and tools able to automatically analyze features of a complex interface, and to easily and intuitively discriminate between similar and different binding solutions. Several valuable web tools have been indeed made available (Cavallo *et al.*, 2003; Fischer *et al.*, 2006; Gabdoulline *et al.*, 2003; Kleinjung and Fraternali, 2005; Krissinel and Henrick, 2007; Negi *et al.*, 2007; Reynolds *et al.*, 2009; Salerno *et al.*, 2004; Tina *et al.*, 2007), most of them being specialized in the analysis of the interface in protein–protein complexes.

However, no available web tool has been implemented to provide interactive contact maps from the 3D structure of a biomolecular complex. Introduced to provide a reduced representation of a protein structure, contact maps have been successfully exploited for describing similarity between protein structures (Holm and Sander, 1996). Analogously, an intermolecular contact map between two or more interacting molecules could identify uniquely and intuitively the surface of interaction, representing a sort of fingerprint of the complex and reporting the crucial information in a ready-to-read form. Interesting work has indeed been done to demonstrate the advantages of using contact map representations for the alignment of protein–protein interfaces (Pulim *et al.*, 2008).

For these reasons, herein we present COCOMAPS (bioCOmplexes COntact MAPS), a novel web tool to easily and effectively analyze and visualize the interface in biological complexes, such as protein–protein, protein–DNA and protein–RNA complexes, by making use of intermolecular contact maps. COCOMAPS is available at the URL: http://www.molnac.unisa.it/BioTools/cocomaps. A user-friendly interface allows to download input files directly from the wwPDB (Berman *et al.*, 2000) or to upload locally stored PDB formatted files. The user is requested to specify the chain identifiers for the molecules involved in the interaction to be analyzed. More chains can be selected for each interacting partner, which overcomes a limitation of the other available tools that either work on all the chains present in a PDB file or on one pair of them at a time. Therefore, COCOMAPS can be used to analyze the interface between two molecules, between one molecule and an ensemble (made by two or more molecular chains) or between two ensembles, depending on how many chains are specified.

COCOMAPS outputs are displayed on the results HTML page for 1 month and archived as downloadable compressed files. A link to the online resource is also emailed to the user, if requested. COCOMAPS provides three graphical contact maps defining the interface of the complex. The first one is a classical intermolecular contact map, where a black dot is present at the cross-over of residues $i$ and $j$, belonging to molecule/ensemble 1 and molecule/ensemble 2, respectively, if any pair of atoms belonging to the two residues is closer than a cut-off distance chosen by the user (default value being 8 Å). The second map, named 'distance range contact map', reports in different colors interresidue contacts at increasing distances (7, 10, 13 and 16 Å). The third contact map, named 'property contact map', is similar to the first one, but each contact is colored according to the physicochemical nature of the two interacting residues: i.e. hydrophobic–hydrophobic, hydrophilic–hydrophilic and hydrophobic–hydrophilic. By mousing over the maps, it is possible to visualize the identity of the residue pairs corresponding to the dots.

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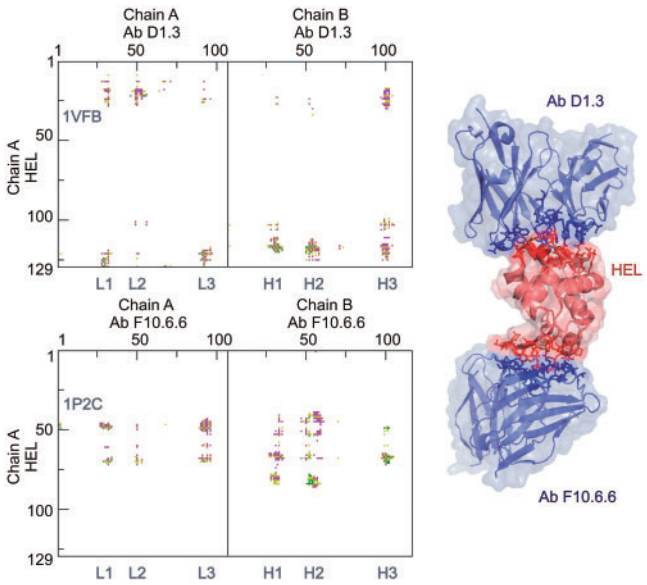


**Fig. 1.** Comparison of the complexes of HEL with the two antibodies: D1.3 (PDBcode: 1VFB) and F10.6.6 (PDBcode: 1P2C). Left: COCOMAPS 'property contact maps'. Labels have been added for the antibody hypervariable loops L1–L3 and H1–H3. Magenta, green and yellow dots indicate hydrophilic–hydrophilic, hydrophobic–hydrophobic and hydrophobic–hydrophilic contacts, respectively. The cut-off distance is set to 10 Å. Right: A Pymol visualization of the complexes based on the automatic COCOMAPS script .pml; residues at the interface are shown as 'sticks'.

COCOMAPS also provides detailed information, organized in tables, about: (i) interacting residues, defined on the basis of a cut-off distance that can be customized by the user (see above); (ii) residues at the interface, defined on the basis of the buried surface upon complex formation; and (iii) intermolecular H-bonds, with specification of the acceptor and donor atoms. A 3D visualization of the complex in JMol (http://www.jmol.org) is also provided online, with the interacting residues highlighted. Finally, a ready-to-run Pymol script (http://www.pymol.org), which generates a visualization of the interface in the corresponding 3D structure, is downloadable. All the programs under the COCOMAPS web tool have been written in python, taking advantage of python libraries such as SciPy and Matplotlib. Accessible surfaces and H-bonds are calculated by NACCESS (Hubbard and Thornton, 1993) and HBPLUS (Mcdonald and Thornton, 1994), respectively.

Although COCOMAPS provides a complete characterization of the interfaces in biological complexes, the real novelty that it introduces is the generation of intermolecular contact maps. Contact maps give an immediate view of which regions of the two partners are in contact. From the property map, it is also possible to immediately appreciate the physicochemical nature of the interaction. As an example, in Figure 1 property contact maps are reported for the complexes of hen egg lysozyme (HEL) with two different antibodies, namely D1.3 [(Bhat *et al.*, 1994), PDBcode: 1VFB] and F10.6.6 [(Cauerhff *et al.*, 2004), PDBcode: 1P2C], together with the corresponding Pymol 3D representation of the complexes, as generated by COCOMAPS. The 2D contact maps of the HEL–antibody complexes reported in Figure 1 show at a glance that the two binding solutions are completely alternative, and the corresponding epitopes present no overlap. In addition, contact maps specify which regions of the antibodies and of the antigen are in contact. As expected, both antibodies contact HEL with their six hypervariable loops (L1, L2, L3, H1, H2 and H3, also labeled in the figure, for the sake of clarity). As for the HEL antigen, it contacts the D1.3 antibody with ∼30 N- and 30 C-terminal residues and the F10.6.6 antibody with its central region (residues 40–85). The same information could of course be extracted either from lists of interacting residues or from the 3D view of the complexes (such as that in Figure 1). However, differently from the contact map view, which is immediate, in both of the above cases, manual intervention by the user would be required to extract the needed information. Further, the contact maps in Figure 1 immediately indicate that the H3 loop of the D1.3 antibody is more involved in the interaction with HEL than the F10.6.6 H3 loop, and that it mostly gives hydrophilic–hydrophilic contacts (magenta dots). This is a consequence of the D1.3 H3 loop sequence, ERDYRLDY, which is longer than the F10.6.6 one, GDGFYVY, and much more hydrophilic, containing five charged residues.

In conclusion, COCOMAPS combines in a single tool the traditional analysis and 3D visualization of interfaces in biomolecular complexes with the effectiveness of the contact map view. It can straightforwardly be applied to the analysis of interfaces both in experimental and predicted 3D structures of biological complexes.

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