Is it Biologically Relevant?
An Evolutionary Method for Distinguishing Biological Interfaces from Crystal Contacts

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Motivation
Thanks to a series of technical and conceptual advances, macromolecular crystallography is nowadays a very powerful technique that can achieve the crystallization and structure determination of very complex molecular objects. Such complexity makes it increasingly difficult to distinguish by visual inspection the two different types of interfaces found in protein crystals: biologically relevant ones and non-specific ones, corresponding to crystal lattice contacts. A need thus exists for computational tools capable of assigning a given interface as either 'biological' or as 'crystal contact'. To this end we devised a novel indicator called CRK (1) and a software tool to compute it.

Methods
The CRK indicator compares the selection pressure acting, on average, on interface residues that are fully buried upon protein-protein interface formation (the core residues) and on those that are only partially buried upon interface formation (the rim residues). For a biologically relevant interface, the average selection pressure should be stronger on the core residues than on the rim residues, while in a crystal contact interface it is assumed not to differ significantly between the rim and core set. The CRK software evaluates selection pressure at the single residue level by calculating Ka/Ks ratios with SELECTON (2), or also by sequence entropy.

Results
The CRK indicator distinguishes the two types of interfaces very effectively. It can also be used for validating structures of oligomeric proteins and of protein complexes. A new version of the CRK software is being written, with the goal of being user-friendly and easy to install. The method is being further developed; the current status of the project and an outlook will be presented.

References

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