RankViaContact: ranking and visualization of amino acid contacts

Bairong Shen¹ and Mauno Vihinen¹,²,*

¹Institute of Medical Technology, University of Tampere, FIN-33014 and
²Research Unit, Tampere University Hospital, FIN-33520 Tampere, Finland

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ABSTRACT

Summary: RankViaContact is a web service for calculation of residue–residue contact energies in proteins based on a coarse-grained model, and for visualization of interactions. The service provides information about ranked contact energies of residues, coordination numbers and the relative solvent accessibility of selected residues, as well as sequence and structure information. The program can be used to design stabilizing mutations, to analyze residue–residue contacts and to study the consequences of mutations.

Availability: http://bioinf.uta.fi/Rank.htm

Contact: mauno.vihinen@uta.fi

Stability is a desirable property, e.g. for proteins used in biotechnology. Flexibility and stabilizing contacts are crucial for stability and activity. However, stability, flexibility and functional properties often have opposed and competing structural requirement (Vihinen, 1987; Beadle and Shoichet, 2002). Strong contacts between residues are favorable for stability, while weaker contacts between residues may point to functional regions (Beadle and Shoichet, 2002). Detailed analysis of residue contact energies can be used to locate functionally or structurally important residues, to determine and classify consequences of mutations, to identify residues for site-directed mutagenesis, as well as to de novo design of proteins.

Several methods are available for the estimation of residue contact energies in proteins, including, e.g. quantum mechanical (QM) calculations, potential-based molecular mechanics (MM) methods and coarse-grained models. For large proteins, QM calculations are impractical, because of very time-consuming high-level calculations for the non-bonded and non-specific residue–residue contacts. MM methods may be computationally less intensive, but the accuracy and reliability can be relatively low. Both these techniques are very sensitive even for minor structural deviations.

Coarse-grained models need only limited computational time and geometric deviations have only small effects on the end result. RankViaContact program is based on the coarse-grained model, which has been shown to outperform potential-based methods in a number of applications (Zhang and Kim, 2000). Residues are treated as united interacting particles, and the parameters for calculation of contact energies are environment-dependent, secondary structure-specific. The method is less sensitive for local structural deviations thus allowing also the use of computer-aided molecular models.

RankViaContact is fast, interactive service for the determination of contacting residues, for the evaluation of effects of mutations and for the evaluation of protein models. RankViaContact is also useful for the design of point mutations affecting protein stability.

We have here expanded the use of the parameters of Zhang and Kim to new applications.

RankViaContact is implemented by combining Perl and C++ programming. Secondary structures and relative solvent accessibility of residues are derived by a locally installed DSSP program (Kabsch and Sander, 1983). For the visualization of three-dimensional (3D) structures Chime (Sayle and Milner-White, 1995) is used. All the features are combined into a user-friendly and interactive service at http://bioinf.uta.fi/Rank.htm (Fig. 1). The program requires a PDB format file as input.

RankViaContact HAS SEVERAL MODES OF ANALYSIS

Ranking residues

Generally, residues with lower contact energies, i.e. stronger contacts are important for the stability of protein structure, and those with higher contact energies often locate at or near the surface and may relate to protein function. RankViaContact routine calculates residue contact energies for all residues, and obtains the secondary structure and relative solvent accessibility information from DSSP. Coordination numbers can be obtained for query residues. Analysis at this level provides a global view of the contacts in a protein structure. The regions for strong or weak contacts can be located and visualized. The number of displayed residues can be chosen freely, e.g. by selecting residues within 10% lowest or highest contact energies.
energies. The ranked residues can be visualized in sequence and 3D structure windows.

Contact analysis
At this level, RankViaContact analyzes the contacts of one residue in detail. The environment of the query residue is inspected in respect to sequence and 3D structure. Contact energies and contacting residues are listed. In Figure 1, the residue L32 of Bruton tyrosine kinase (Btk) pleckstrin homology (PH) domain is investigated. The X-linked agammaglobulinemia-causing mutation to serine has been previously classified as structural (Baraldi et al., 1999).

RankViaContact analysis shows that this residue is among those with the 5% strongest contact energies. All the contact energies for L32 are negative, indicating that the leucine is essential for the stability of Btk PH domain.

With the options of Chime plug-in, the solvent accessible surface can be colored according to the electrostatic potential to facilitate identification of the most exposed or the most charged regions. RankViaContact, compared with the previous work of protein contact analysis (Sobolev et al., 1999), provides both the quantitative results and structural visualization.

Total contact energy calculation
Total contact energies calculated by RankViaContact can be used for distinguishing native structure among a set of models (Zhang and Kim, 2000). Structurally feasible structures can be detected with these calculations.

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REFERENCES