Constraint Network Analysis - Allostery

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Tags: *1_Drylab 3_CNA*
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<Section | Constraint Network Analysis>

{Rigidity analyses|operation} were performed using the {CNA|:software package:} {3.0|version} (10.1021/ci400044m). We applied CNA on ensembles of {network topologies generated from conformational ensembles provided as input|applied topologies}. Ensembles of {2000|number of frames} conformations were generated from {MD|ensemble generation program} simulation. {Average stability characteristics|calculated measure} were calculated by {constraint counting on each topology in the ensemble|calculation method}.

The {FIRST|:software:} {6.2|version} (10.1002/prot.1081) was used to construct each network of covalent and non-covalent (hydrophobic tethers, hydrogen bonds, and salt bridges) constraints. The hydrogen bond energy E_{HB} is determined from an {empirical energy function|hydrogen bond energy calculation method}. (10.1002/pro.5560060622) Hydrophobic tethers between carbon and sulfur atoms were considered if the distance between these atoms was less than the sum of their van der Waals radii (C: 1.7 Å, S: 1.8 Å) plus {0.25 Å | minimum distance between two vdW radii of carbon and/or sulfur atoms for placing a hydrophobic tether} (D_{cut}). (10.1073/pnas.062492699)

Biomolecules generally display a hierarchy of structural stability, reflecting the modularity of their structure. (10.1002/elsc.200800043) To identify this hierarchy, a {constraint dilution trajectory|network states analysis} of network states {□} is analyzed by {successively removing non-covalent constraints|analysis method} from an initial network topology. (10.1073/pnas.062492699)(10.1002/elsc.200800043) (10.1088/1478-3975/7/1/016002) (10.1002/prot.22946) (10.1016/S1093-3263(02)00146-8) Here, {hydrogen bond constraints (including salt bridges)|removal target} are removed by their increasing strength. That way, for network state □, only {hydrogen bonds|retained bonds} are retained that have an energy { E_{HB} lte E_{cut}(□)|retaining criteria}. Hydrogen bonds constraints were removed in the range of {-0.1 kcal mol^{-1}|E_{start}} to {-6.0 kcal mol^{-1}| E_{stop}} with a step size of {0.1 kcal mol^{-1}|E_{step}}.

<Section | Allosteric signaling through constraint networks>

We used a {per-residue decomposition|:scheme:} for {the extent of single residues contribution to the allosteric signaling |:identification:}. First, {neighbor stability maps ($rc_{ij,neighbor}$) |derived value} are derived from the {constraint dilution trajectory |derivation method}; they contain information accumulated over all network states □ along the trajectory. (10.1021/acs.jctc.7b00529) (10.1002/jcc.23122)

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More precisely, stability maps monitor the persistence of rigid contacts for pairs of residues during a bond dilution process; a rigid contact is present as long as two residues belong to the same rigid cluster *c* of the set of rigid clusters C^{Ecut}. As our focus is on short-range rigid contacts, only pairs of heavy atoms of the residue pair $R_{\{i,j\}}$, $A_{\{k\in i,\, l\in j\}}$, separated by a distance d ≤ {4.5 Å | distance cutoff for identifying native contacts} are considered. The resulting neighbor stability map (Eq. 1) (10.1021/acs.jctc.7b00529) relates to the local stability in the network.

$$rc_{ij,neighbor} = min(E_{cut} | \exists c \in C^{E_{cut}} : (R_i \wedge R_j \in c) \wedge (d(A_{\{\exists k \in i, \exists l \in j\}}) \leq 4.5\text{Å}))$$ - Eq. 1

A chemical potential energy $E_{i,CNA}$ of residue *i* is obtained by summation over all *n* short-range rigid contacts in which the residue is involved (Eq. 2).

$$E_{i.CNA} = \frac{1}{2} \sum_{i \neq j}^{n} rc_{ij,neighbor}$$ - Eq. 2

which is then used in a linear response approximation to obtain the per-residue decomposition (Eq. 3).

$$\Delta G_{i,CNA} = \alpha \left(\left\langle \mathrm{E}_{i,CNA}^{perturbed} \right\rangle - \left\langle \mathrm{E}_{i,CNA}^{ground} \right\rangle \right)$$ - Eq. 3

with α being 0.5. (10.1021/acs.jctc.7b00529).