

SI Text

1 Double-G \bar{o} Model

The united-residue “double-G \bar{o} ” model [1] consists of alpha-carbon interaction centers with pairwise contact interactions as described below.

For a molecule with N residues, the total potential is the sum of $N(N-1)/2$ two-body potentials,

$$u^{\text{tot}} = \sum_{i=1}^N \sum_{j>i}^N u_{i,j}, \quad (1)$$

where i and j label residues. The two-body potential is given by

$$u_{i,j} = \begin{cases} u_{i,j}^{\text{bond}} & \text{if } j = i + 1 \\ u_{i,j}^{\text{non-bond}} & \text{if } j > i + 1 \end{cases} \quad (2)$$

When the i th and j th residues are sequential ($j = i + 1$), $u_{i,j}^{\text{bond}}$ accounts for the chain connectivity. An infinite well potential is constructed with reference to interresidue distance in the Apo (calcium-free) structure $r_{i,i+1}^{\text{Apo}}$, as shown in SI Fig.6.

When the i th and j th residues are *not* sequential, their interaction potential $u_{i,j}^{\text{non-bond}}$ is further classified into “non-native”, “single-native” and “double-native” depending on the distances found in the two native structures (1CFD and 1CLL). First we define a cut-off distance R_{cut} ; standard square-well (contact) interactions occur only below it, vanishing for $r_{i,j} > R_{\text{cut}}$.

(i) If $r_{i,j}^{\text{Apo}} > R_{\text{cut}}$ and $r_{i,j}^{\text{Holo}} > R_{\text{cut}}$, the i th and j th residues are considered *non-native*. The interaction potential is taken to consist of a forbidden region defined by a hard-core radius found in the Apo (calcium-free) structure and a shoulder for the remaining part for $r_{i,j} < R_{\text{cut}}$. See SI Fig.7a.

(ii) If $\min(r_{i,j}^{\text{Apo}}, r_{i,j}^{\text{Holo}}) < R_{\text{cut}}$ and $\max(r_{i,j}^{\text{Apo}}, r_{i,j}^{\text{Holo}}) > R_{\text{cut}}$, the pair is termed *single-native* - i.e., the pair of residues is sufficiently close in one of the two native structure. Their interaction is described by a square-well pair potential. The single well is centered near $\min(r_{i,j}^{\text{Apo}}, r_{i,j}^{\text{Holo}})$. See SI Fig.7b.

(iii) If $r_{i,j}^{\text{Apo}} < R_{\text{cut}}$ and $r_{i,j}^{\text{Holo}} < R_{\text{cut}}$, the pair is considered *double-native*. Their interaction is described by two square wells centered near $r_{i,j}^{\text{Apo}}$ and $r_{i,j}^{\text{Holo}}$ respectively with a barrier between them. See SI Fig.7c.

In summary, the double-native G \bar{o} potential stabilizes two native structures and creates a barrier between them. This is accomplished by the pairwise potentials shown in SI Fig.7. The key double-well interactions occur between residues exhibiting two distinct distances in the two reference structures, as in SI Fig.7c. The potential guarantees that the two native structures (1CFD and 1CLL) have

low total energies and that the transition between the two is possible. The potential is, of course, constructed using empirical information and can be used with care in specific applications.

See ref. [1] for full details and for the parameters used in the simulation.

2 DRMSD

Like the standard RMSD, the distance-RMSD (DRMSD) quantifies molecular distance measurement. Letting d_{ij} and d'_{ij} be the distances between residue i and j in two structures of the same molecule, which has N residues, then

$$\text{DRMSD} \equiv \sqrt{\frac{2}{N \times (N - 1)} \sum_{i < j} (d_{ij} - d'_{ij})^2}. \quad (3)$$

(Sometimes the constant factor $\sqrt{2}$ is removed in the definition.) DRMSD does not require alignment of two structures. For our united-residue model of calmodulin, it is faster to compute than RMSD and provides qualitatively similar information.

3 Probability Evolution

The text of the paper refers to the evolution of the probability distribution in our WE “production” run, which is given in SI Fig.5.

References

- [1] Zuckerman D M (2004) *J. Phys. Chem. B* 108:5127–5137.