Dead End Elimination in side chain modeling

Desmet et al. Nature 356,539-542(1992)

We consider the problem of side chain placement using rotamer library. The backbone of the protein is fixed and we consider model energy of the type:

$$E = \sum_i E(i_r) + \sum_i \sum_j E(i_r, j_s)$$

where the r and s denote rotamer states, and the i and j are the indices of the side chains.

Consider now two rotamers of the same amino acid -- i_r and i_t. We wish to determine if the following inequality hold for any i_t:

$$E(i_r) + \sum_j \min_s E(i_r, j_s) > E(i_t) + \sum_j \max_s E(i_r, j_s) \qquad i \neq j$$

This inequality means the following:
Consider the left hand side of the inequality. It is the best possible local energy of the i_r rotamer. That is, for any other amino acid j that interacts with amino acid i find the best possible rotamer j_s. This is relatively easy in the present model in which only pairs of interactions are considered (for any j pass over the few j_s and find the one with the lowest interaction energy $E(i_r, j_s)$).
Now consider the right hand side of the inequality. It is the worse arrangement of an alternate rotamer i_t. That is we consider the j_s rotamers that will yield the worse possible energies when interacting with i_t.

If the best we could do with the rotamer i_r is still not good enough to be better (lower energy) than rotamer i_t, then this rotamer is declared as “dead-end”. There is no way that this rotamer will be part of a global energy structure. The “dead-end” rotamers can be removed immediately from the list and therefore reduce the number of rotamers that are required detailed evaluation. Another way of saying it is that the interaction energy of the i_r rotamer with the backbone ($E(i_r)$) is so bad that it cannot be corrected by adding the interactions of the same rotamer with other side chains.

This kind of argument can be extended also to pairs. If a pair of interacting rotamers is so bad that it cannot be corrected and made sufficiently low compared to others (by adding the interaction of each of the rotamers with other side chains), then this pair is also a dead end and can be eliminated.

Define an energy of a pair as: $\varepsilon([i_r, j_s]) = E(i_r) + E(j_s) + E(i_r, j_s) \quad i \neq j$

The interaction energy of this paper with any other monomer is defined as
$\varepsilon([i_r, j_s]k_t) = E(i_r, k_t) + E(j_s, k_t) \quad i, j \neq k$

Then a rotamer pair $[i_r, j_s]$ is a dead end if there exists a pair $[i_u, j_v]$ such that
$\varepsilon([i_r, j_s]) + \sum_k \min_t \varepsilon([i_r j_s]k_t) > \varepsilon([i_u, j_v]) + \sum_k \max_t \varepsilon([i_u j_v]k_t)$

Hence we can exclude quite a few pairs based on the above formula in further consideration and of course reduce significantly the combinatoric explosions of possible combination.

The number of conformations can also be reduced significantly by initial filtering. Removing rotamers that collide with the protein own backbone (i.e. $E(i_r) > 30$). In the original paper the DEE was applied to insulin dimer as a test case. There are 76 residues to model with 2.7×10^{76} possible rotamers to consider. After completion of the elimination only seven residues remain with more than one rotamer. Hence the problem became essentially trivial. The whole process took a few minutes on a workstation.