Supplementary Text S1

In this document we present a proof of Proposition 1. We restate both the iMinDEE criteria, and Proposition 1 for clarity.

The iMinDEE criterion is:

$$E_\circ (i_r) + \sum_{j \neq i} \min_s E_\circ (i_r, j_s) > E_\circ (i_t) + \sum_{j \neq i} \max_s E_\circ (i_t, j_s) + I.$$  \hspace{1cm} (7)

**Proposition 1.** When Eq. (7) holds, rotamer $i_r$ can be provably pruned from the search space because it cannot be part of the minimized global minimum energy conformation (minGMEC).

*Proof.* Let $G$ be the rotamer vector that minimizes into the minimized-GMEC and $E_\circ (G)$ be the energy of the minimized-GMEC. Let $A = G_{i_s \rightarrow i_t}$ be the rotamer vector $G$ where rotamer $i_g$ is replaced with $i_t$. Let $E_\circ (i_r | A)$ be the internal energy of $i_r$ when rotamer vector $A$ is minimized and let $E_\circ (i_r, j_s | A)$ be the pairwise energy of $i_r$ and $j_s$ when $A$ is minimized. Also, let $L$ be the rotamer vector with the lowest minimum bound. Note, $L$ and $G$ are most likely not the same rotamer vector. By definition we know that

$$E_\circ (A) \geq E_\circ (L).$$

Adding $E_\circ (G)$ to both sides gives:

$$E_\circ (A) + E_\circ (G) \geq E_\circ (G) + E_\circ (L).$$

Moving $E_\circ (L)$ to the left side and using the definition, $I \geq E_\circ (G) - E_\circ (L)$:

$$E_\circ (A) + I \geq E_\circ (G).$$

Expanding $E_\circ (A)$ and $E_\circ (G)$:

$$E_\circ (i_t) + \sum_{j \neq i} E_\circ (i_t, j_g) + \sum_{j \neq i} E_\circ (j_g) + \sum_{j \neq i} \sum_{k \neq i} E_\circ (j_g, k_g) + I$$

$$\geq E_\circ (i_g | G) + \sum_{j \neq i} E_\circ (i_g, j_g | G)$$

$$+ \sum_{j \neq i} E_\circ (j_g | G) + \sum_{j \neq i} \sum_{k \neq i} E_\circ (j_g, k_g | G).$$

We can use the fact that

$$\sum_{j \neq i} E_\circ (j_g | G) \geq \sum_{j \neq i} E_\circ (j_g),$$

$$\sum_{j \neq i} \sum_{k \neq i} E_\circ (j_g, k_g | G) \geq \sum_{j \neq i} \sum_{k \neq i} E_\circ (j_g, k_g)$$

and substitute these two equations into Eq. (8) which simplifies to:

$$E_\circ (i_t) + \sum_{j \neq i} E_\circ (i_t, j_g) + I \geq E_\circ (i_g | G) + \sum_{j \neq i} E_\circ (i_g, j_g | G).$$

We can further relax this inequality by using the fact that $E_\circ (i_g | G) \geq E_\circ (i_g)$ and $\sum_{j \neq i} E_\circ (i_g, j_g | G) \geq \sum_{j \neq i} \min_s E_\circ (i_g, j_s)$ and substitute into the above inequality:

$$E_\circ (i_t) + \sum_{j \neq i} E_\circ (i_t, j_g) + I \geq E_\circ (i_g) + \sum_{j \neq i} \min_s E_\circ (i_g, j_s).$$
Since we will not know $G$ during the computational search, and since
\[ \sum_{j \neq i} \max_s E(i_t, j_s) \geq \sum_{j \neq i} E(i_t, j_g), \]
we again relax the inequality:
\begin{equation}
E(i_t) + \sum_{j \neq i} \max_s E(i_t, j_s) + I \geq E(i_g) + \sum_{j \neq i} \min_s E(i_g, j_s).
\end{equation}

(9)

Now, if there exists a rotamer $i_r$ that meets the criterion of Eq. (7) we can substitute the left hand terms of Eq. (7) into Eq. (9):
\[ E(i_r) + \sum_{j \neq i} \min_s E(i_r, j_s) > E(i_g) + \sum_{j \neq i} \min_s E(i_g, j_s). \]

Thus, if the pruning condition holds, rotamer $i_r$ cannot be $i_g$, so $i_r$ can be pruned from the rotamer search. \qed