**Supporting Material**

**Title: Stable and metastable states of human amylin in solution**

Authors: Allam S Reddy, Lu Wang, Sadanand Singh, Yun L. Ling, Lauren Buchanan, Martin T. Zanni, James L. Skinner, and Juan J. De Pablo

**REFEREE 1:**

I found the observation that the human IAPP ensemble can be separated into macrostates, one involving a helical conformation plus short beta strand, a second with a full beta-hairpin conformation, and a third defined as random coil, quite interesting . The thermodynamic integration indicates that the "aggregation competent" beta-hairpin is a more stable  conformation.  Related to this point, the authors refer to the lowest free energy state as the "misfolded" state (explaining this as an extension of terminology used for CGRP).  However, as the beta-hairpin is identified as the lowest free energy conformation, I find the terminology

# Supplemetal Material: Stable and metastable states of human amylin in solution

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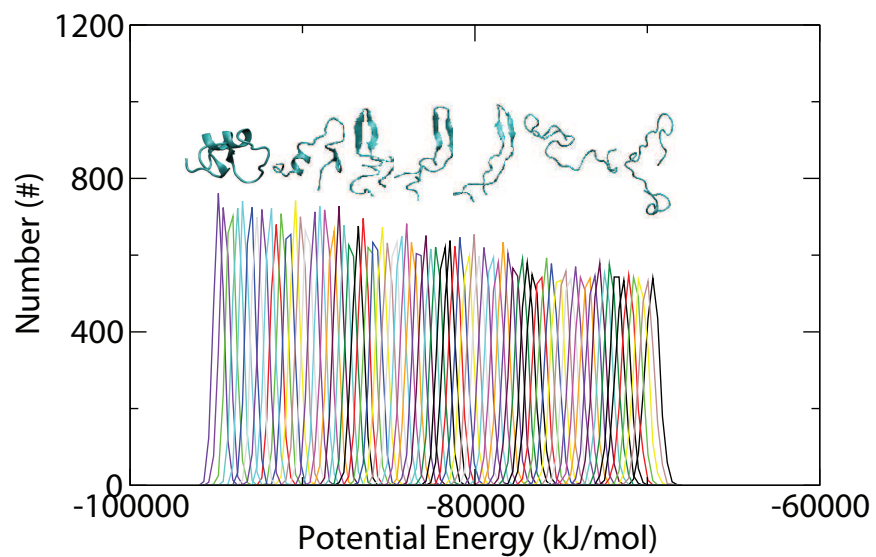*Corresponding author. E-mail: depablo@engr.wisc.edu.

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Figure S1: Probability distribution curves of potential energy, at the 74 different temperatures (between 273–578 K) used in REMD simulations.
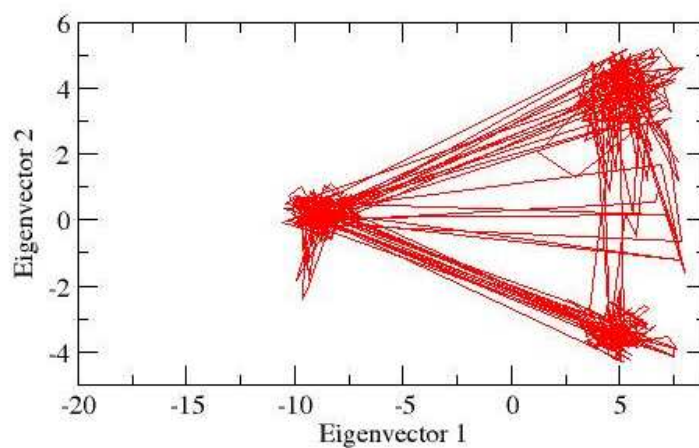


Figure S2: Principal component analysis revealing the presence of 3 major clusters corresponding to the three conformations discussed in this manuscript.
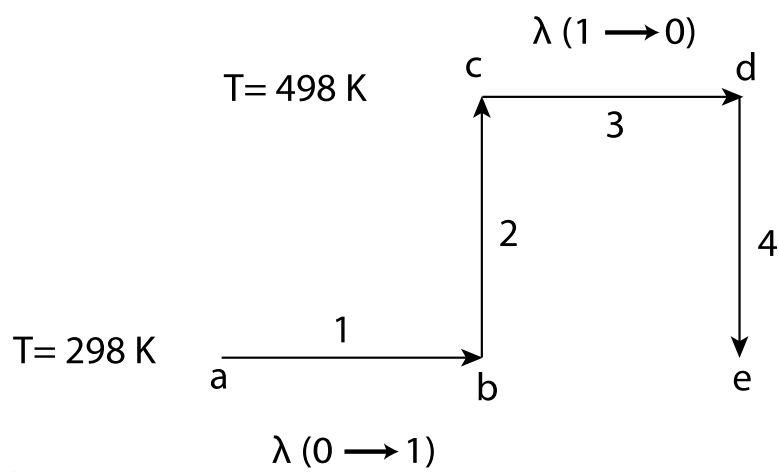
Figure S3: Schematic representation of the path used in Thermodynamic Integration as explained in the text.