Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary Information of "Structural Diversity in Membrane-bound hIAPP Dimer Correlated with Distinct Membrane Disruption Mechanisms"

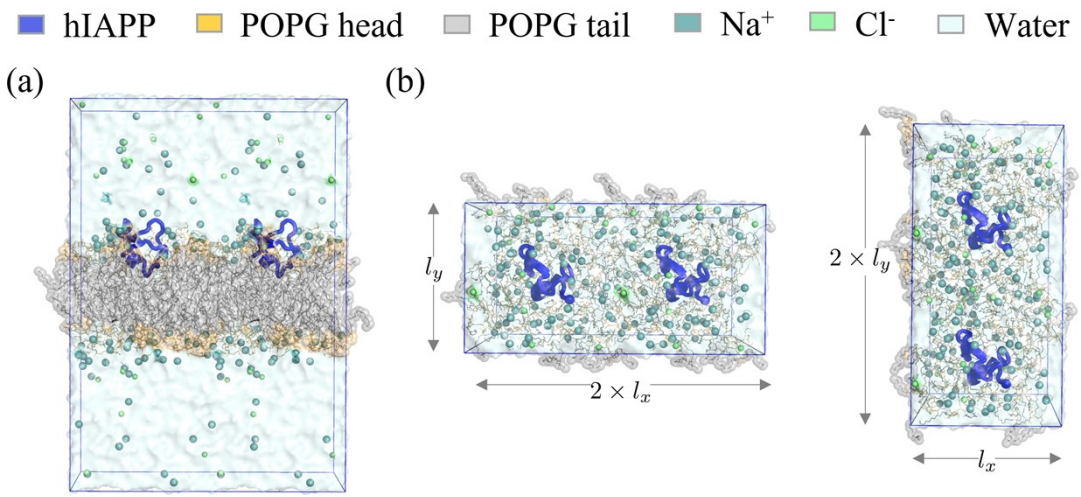
Qin Qiao[1,2*], Guanghong Wei[3], and Zhijian Song[1,2]

[1]Digital Medical Research Center, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China

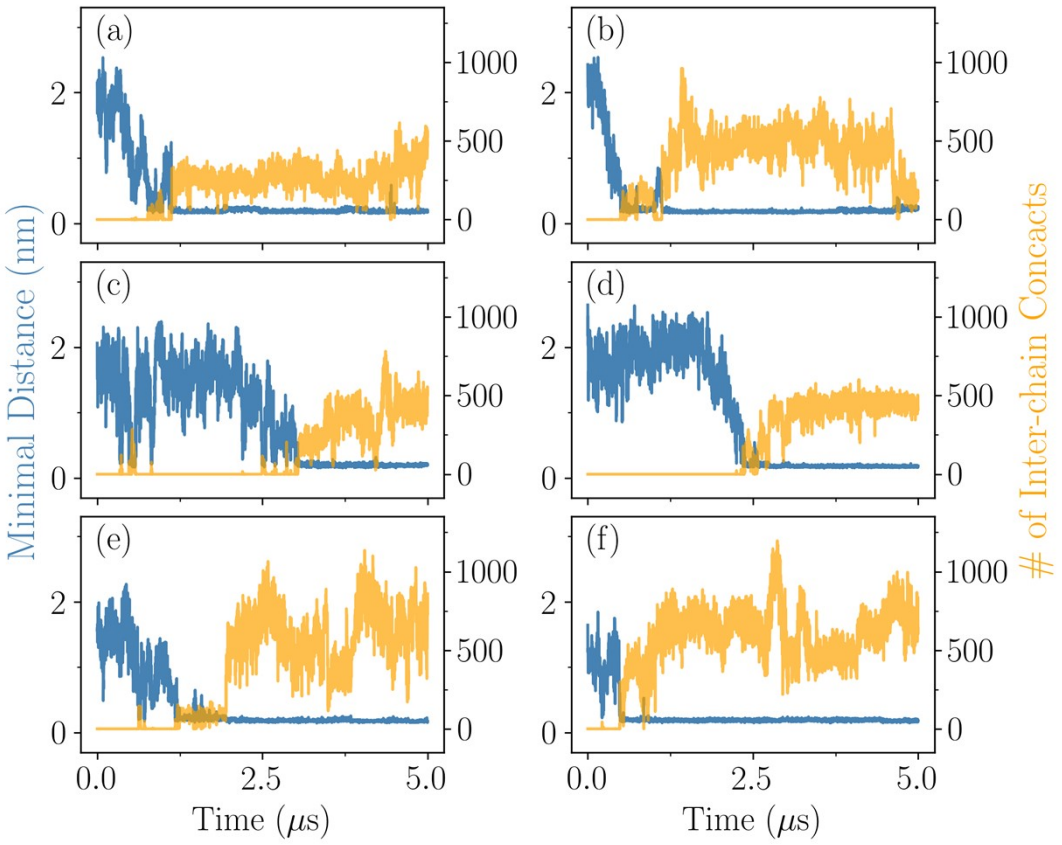
[2]Shanghai Key Laboratory of Medical Imaging Computing and Computer Assisted Intervention, Shanghai 200032, China

[3]Department of Physics, State Key Laboratory of Surface Physics, Key Laboratory for Computational Physical Science (Ministry of Education), Fudan University, Shanghai 200438, China

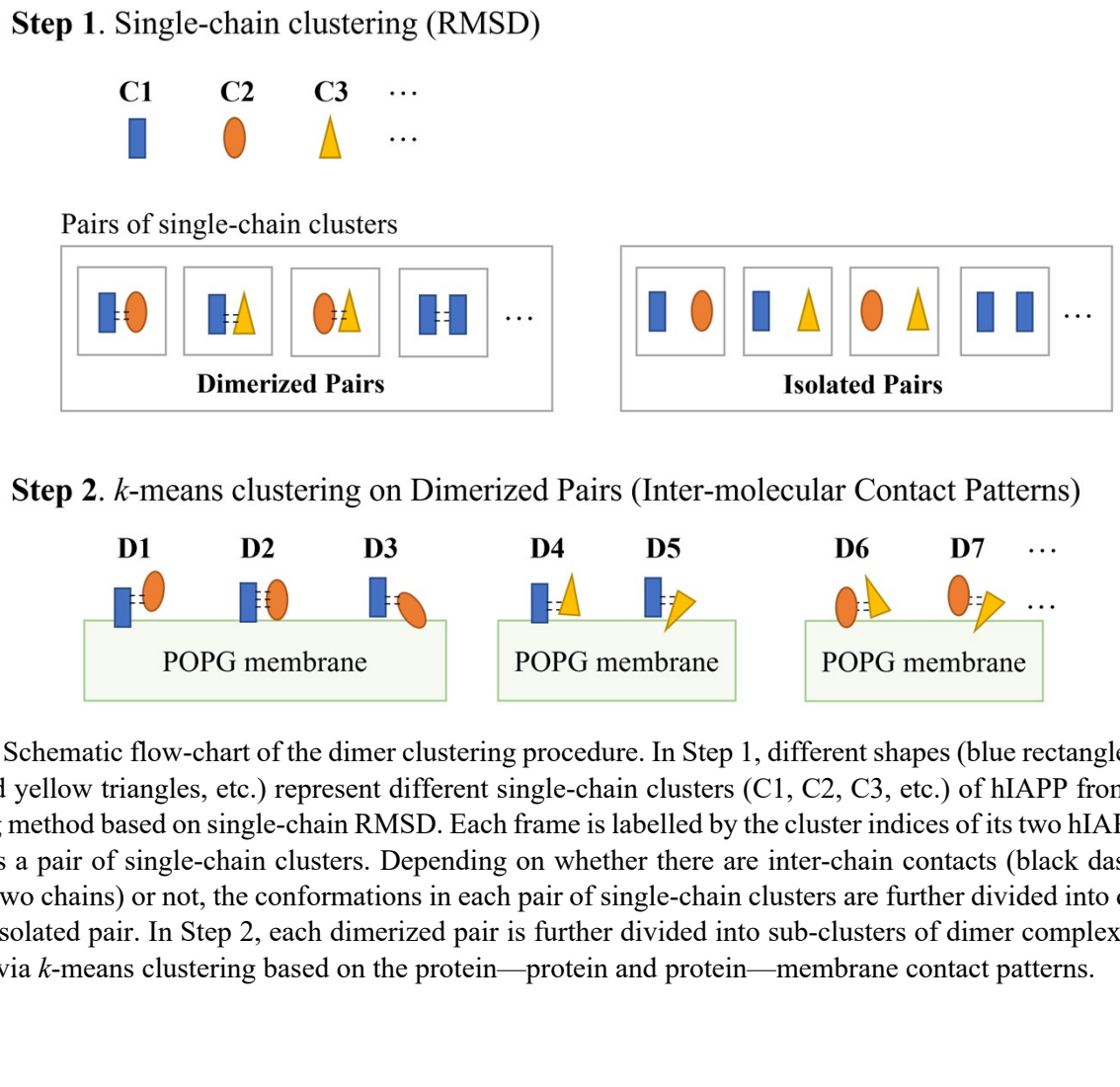
qinqiao@fudan.edu.cn



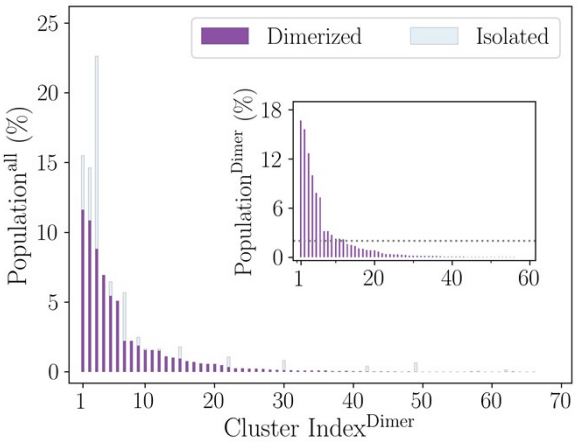
SI Fig. 1. Simulation box of the initial conformations. Side view (a) and top view (b). In each plot, hIAPP chains are in blue cartoon, POPG head groups are in orange, POPG tail groups are in gray, cations Na^+ in teal sphere, anions Cl^- in lime sphere, and water in cyan surface. Subplots in (b) are monomer duplicates along either *x* direction or *y* direction.



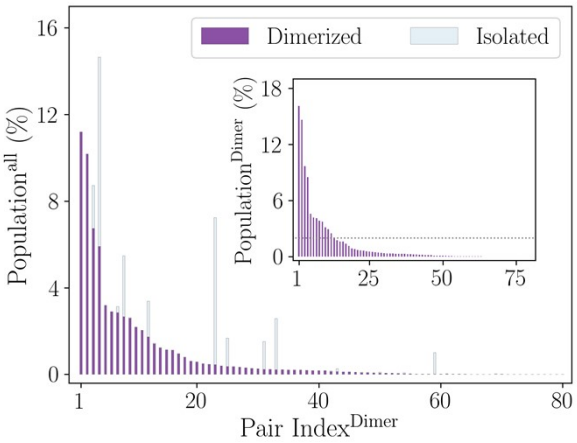
SI Fig. 2. Time evolution of minimal distance between two chains (blue) and inter-chain contact number (orange). Each of subplots (a) to (f) corresponds to one of the six 5-μs-long trajectories.



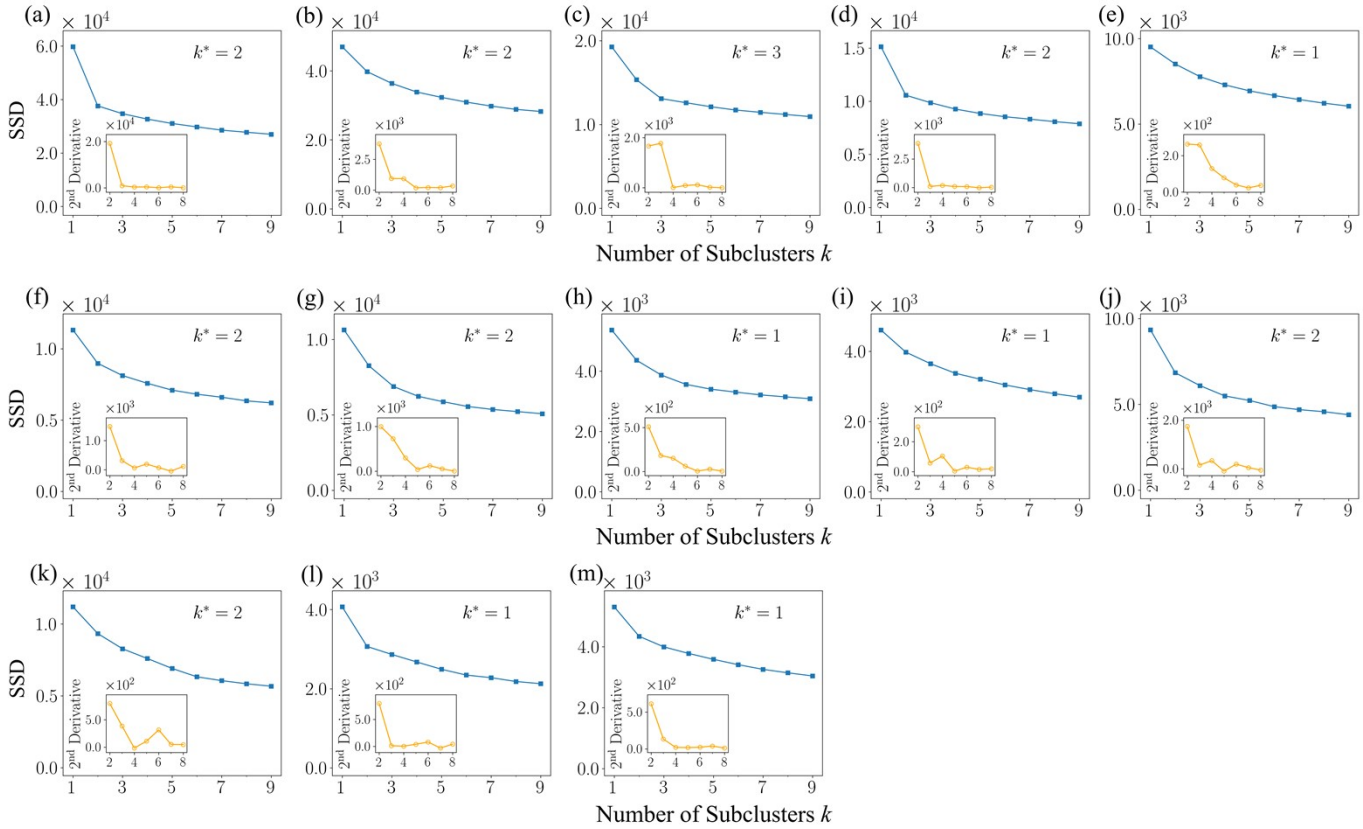
SI Fig. 3. Schematic flow-chart of the dimer clustering procedure. In Step 1, different shapes (blue rectangles, orange ovals, and yellow triangles, etc.) represent different single-chain clusters (C1, C2, C3, etc.) of hIAPP from Daura's clustering method based on single-chain RMSD. Each frame is labelled by the cluster indices of its two hIAPP chains, and forms a pair of single-chain clusters. Depending on whether there are inter-chain contacts (black dashed lines between two chains) or not, the conformations in each pair of single-chain clusters are further divided into dimerized pair and isolated pair. In Step 2, each dimerized pair is further divided into sub-clusters of dimer complex (D1, D2, D3, etc.) via *k*-means clustering based on the protein—protein and protein—membrane contact patterns.



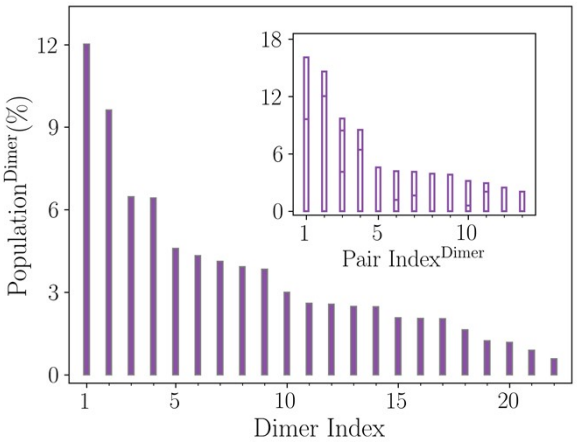
SI Fig. 4. Population distribution of single-chain conformational clusters. In each bar, the dark purple part corresponds to the fraction of dimerized state in the cluster, and the light gray part corresponds to the fraction of isolated state. The inset is the normalized population distribution in the dimerized states, with the gray dotted line indicating the population cut-off at 2%. The *x*-axes of both overall and inset figures are the cluster index sorted by the populations of dimerized states.



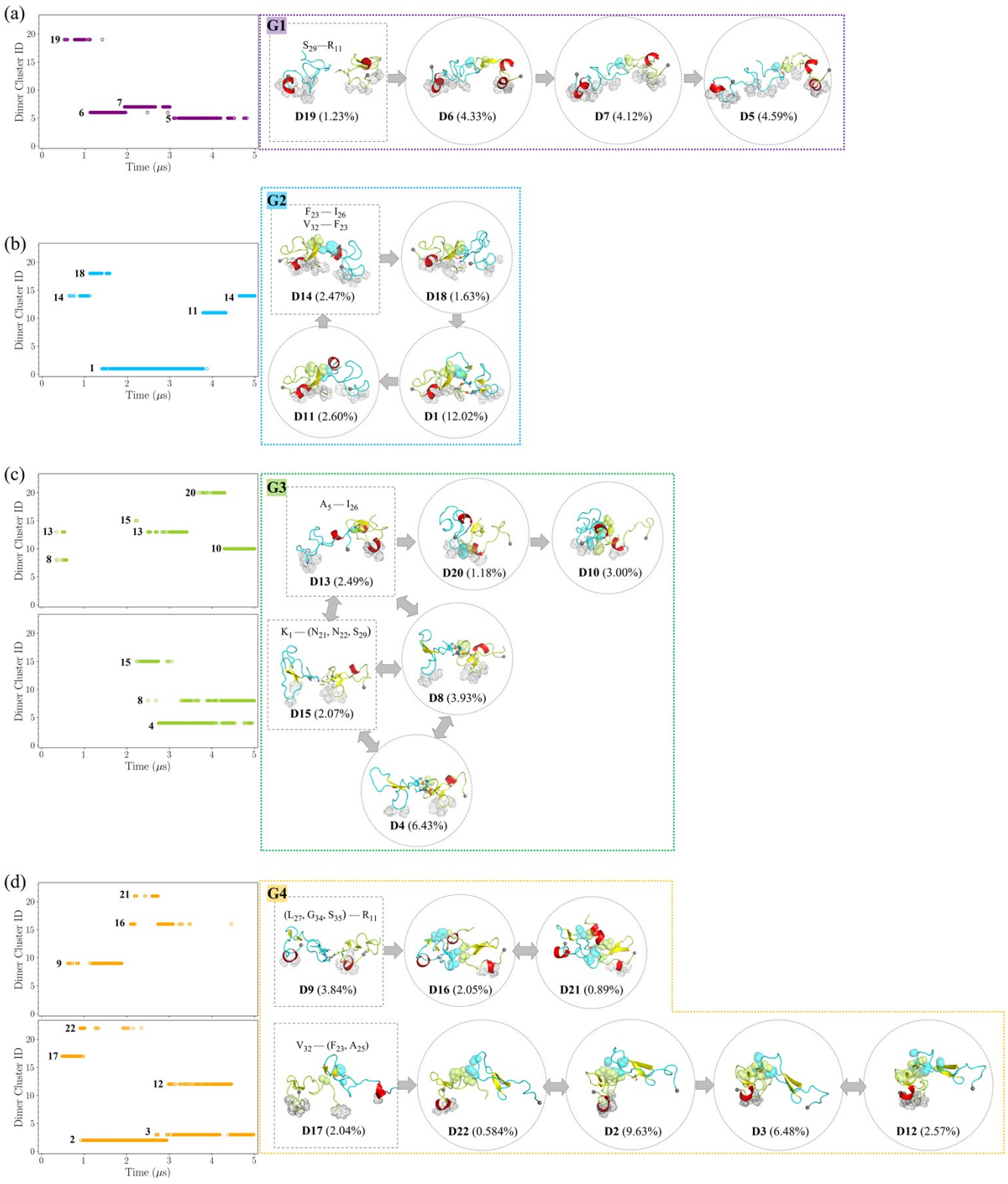
SI Fig. 5. Population distribution of pairs of single-chain conformational clusters. In each bar, the dark purple part corresponds to the fraction of dimerized pair of clusters, and the light gray part corresponds to the fraction of isolated pair. The inset is the normalized population distribution in the dimerized pairs of clusters, and the gray dotted line indicates the population cut-off at 2%. The *x*-axes of both the overall and inset figures are the indices sorted by the populations of the dimerized pairs.



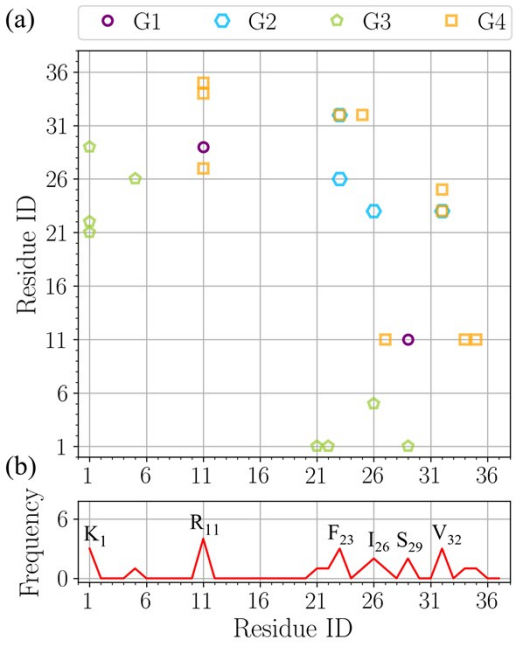
SI Fig. 6. Sum of squared distances (SSD) changing with the number of subclusters (k) based on the hIAPP inter-chain and hIAPP-membrane contact patterns in each pair. Insets are the 2nd derivates of SSD. In each plot, we labelled the optimal number of subclusters (k^*). Plots from (a) to (m) correspond to the top 1 to top 13 dimerized pairs.



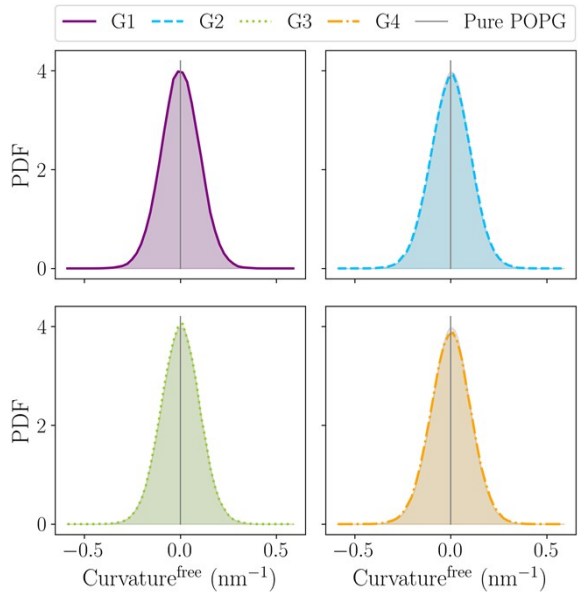
SI Fig. 7. Population distribution of dimer clusters after the additional *k*-means clustering on the dimerized pairs. Inset is the cluster partition in the top 13 dimerized pairs after the *k*-means clustering, i.e., each pair is further divided into the optimal number of clusters based on inter-molecular contact patterns.



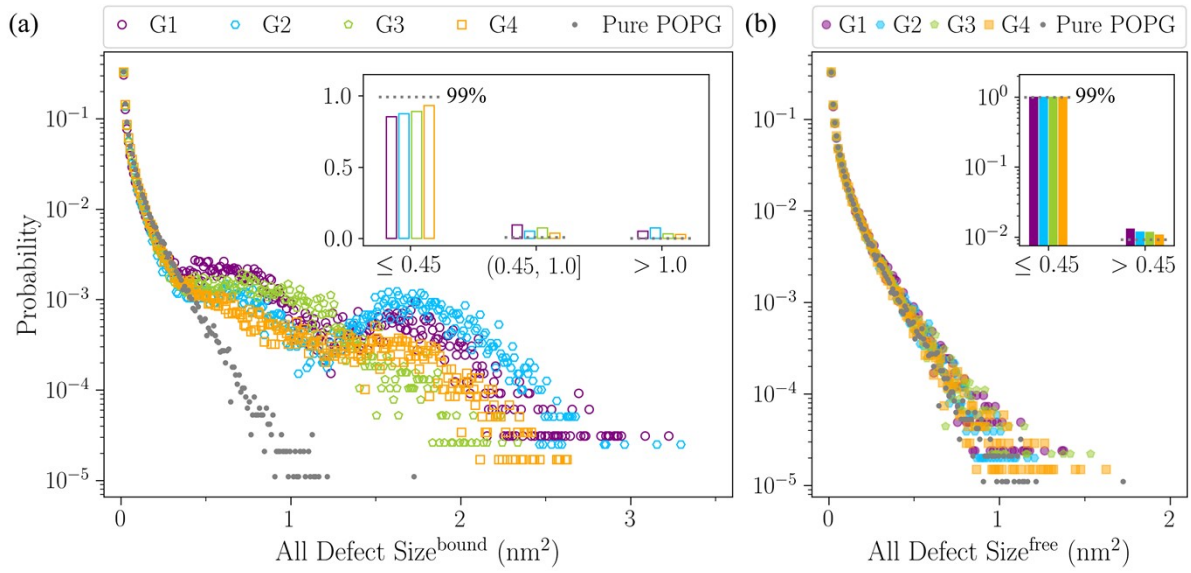
SI Fig. 8. Time evolution of dimer clusters (left column) and their conformational transitions (right column) of hIAPP dimer in POPG membrane. Subplots (a) to (d) correspond to Group 1 (G1) to G4 respectively. In each group, we labelled the dimer cluster IDs in the time evolution plot (left column). The plot scheme of dimer conformations (right column) is the same as that in the main-text Fig. 2(d-g), and the population of each dimer cluster is also labelled at the bottom. In each initially collapsed dimer clusters (in dashed square outlines), the residues forming the initial inter-chain contacts are also labelled.



SI Fig. 9. (a) Residue-based contact map in initially collapsed dimer clusters, with purple circles for G1, blue hexagons for G2, green pentagons for G3, and orange squares for G4. (b) Frequency of each residue participating in inter-chain contacts of initially collapsed dimer clusters.



SI Fig. 10. Distribution of mean curvature in the hIAPP-free leaflet. The distribution in Group1 (G1) is in purple solid line, G2 in blue dashed line, G3 in green dotted line, and G4 in orange dash-dotted line. The vertical gray lines indicate the average values of pure POPG membrane, and the gray shaded areas indicate the distributions of pure POPG.



SI Fig. 11. Size distribution of overall POPG hydrophobic defects. The left subplot is for the hIAPP-bound leaflet and the right one is for the hIAPP-free leaflet. In each subplot, the distribution in Group1 (G1) are in purple, G2 in blue, G3 in green, G4 in orange, and pure POPG in gray. The inset plots indicate the probability of defect sizes in different ranges, with the gray dotted lines indicating the corresponding probability distribution of pure POPG as the reference.