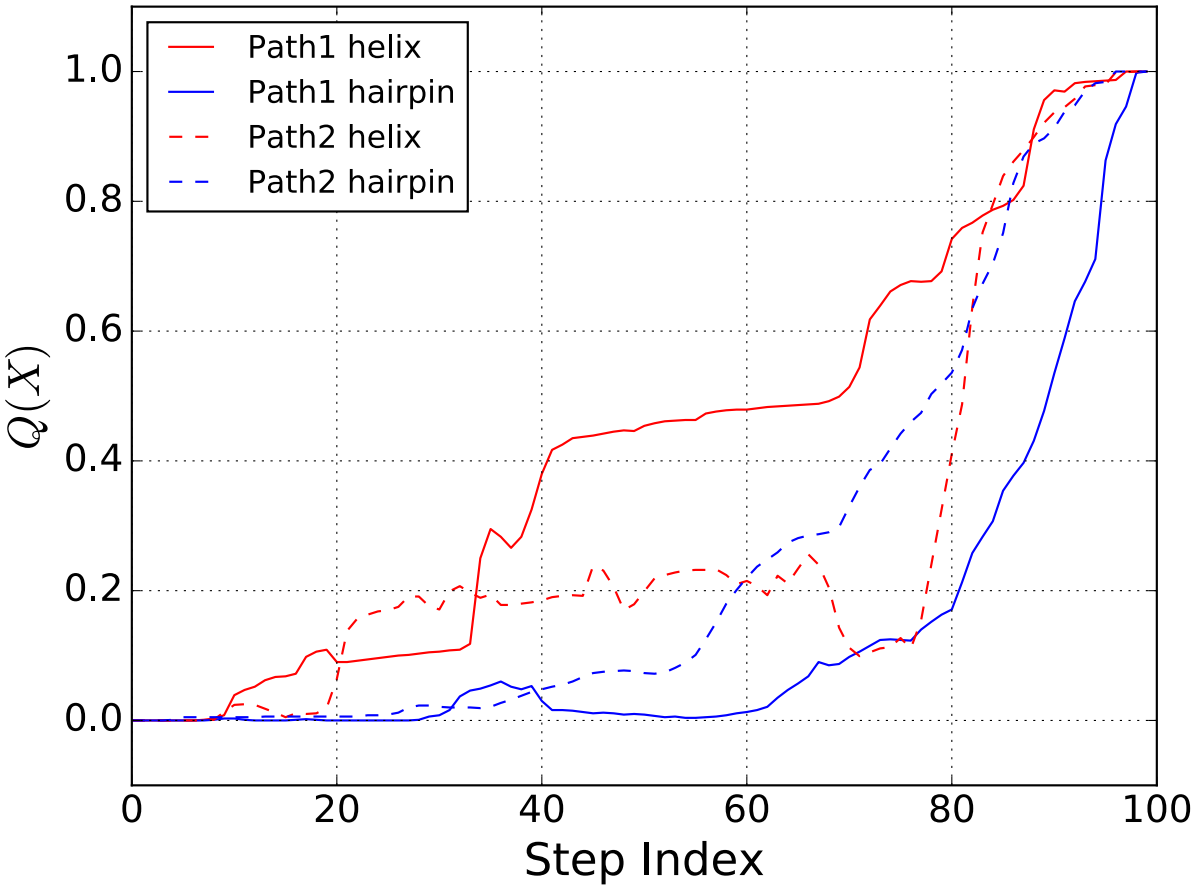
Supplementary Table 1. Parameters for Action-CSA calculations

INDEX	DESCRIPTION OF PARAMETER
1	Total transition time
2	Number of pathway steps
3	Number of pathways retained in bank at each iteration
4	Number of crossover and mutation operations
5	Temperature
6	Friction coefficient
7	Weight of total energy conservation term
8	Annealing schedule of pathway separation distance
9	Solvation model
10	Protein force field

Supplementary Table 2. List of 14 unique pathway types and 44 non-redundant pathways for conformational change of hexane from g-g-g- to g+g+g+

Unique path type	Non-redundant path
C+C+	g-g-g- → tg-g- → tg-t → ttt → tg+t → tg+g+ → g+g+g+
	g-g-g- → g-g-t → tg-t → ttt → tg+t → g+g+t → g+g+g+
C+C-	g-g-g- → g-g-t → tg-t → ttt → tg+t → tg+g+ → g+g+g+
	g-g-g- → tg-g- → tg-t → ttt → tg+t → g+g+t → g+g+g+
T+C+	g-g-g- → tg-g- → tg-t → ttt → ttg+ → tg+g+ → g+g+g+
	g-g-g- → g-g-t → tg-t → ttt → g+tt → g+g+t → g+g+g+
	g-g-g- → g-g-t → g-tt → ttt → tg+t → g+g+t → g+g+g+
	g-g-g- → tg-g- → ttg- → ttt → tg+t → tg+g+ → g+g+g+
T+C-	g-g-g- → g-g-t → tg-t → ttt → ttg+ → tg+g+ → g+g+g+
	g-g-g- → tg-g- → tg-t → ttt → g+tt → g+g+t → g+g+g+
	g-g-g- → g-g-t → g-tt → ttt → tg+t → tg+g+ → g+g+g+
	g-g-g- → tg-g- → ttg- → ttt → tg+t → g+g+t → g+g+g+
C+M+	g-g-g- → tg-g- → tg-t → ttt → ttg+ → g+tg+ → g+g+g+
	g-g-g- → g-g-t → tg-t → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → tg+t → g+g+t → g+g+g+
	g-g-g- → g-tg- → g-tt → ttt → tg+t → tg+g+ → g+g+g+
C+M-	g-g-g- → g-g-t → tg-t → ttt → ttg+ → g+tg+ → g+g+g+
	g-g-g- → tg-g- → tg-t → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-tg- → g-tt → ttt → tg+t → g+g+t → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → tg+t → tg+g+ → g+g+g+
T+T+	g-g-g- → tg-g- → ttg- → ttt → ttg+ → tg+g+ → g+g+g+
	g-g-g- → g-g-t → g-tt → ttt → g+tt → g+g+t → g+g+g+
T+T-	g-g-g- → tg-g- → ttg- → ttt → g+tt → g+g+t → g+g+g+
	g-g-g- → g-g-t → g-tt → ttt → ttg+ → tg+g+ → g+g+g+
T+M+	g-g-g- → g-g-t → g-tt → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → tg-g- → ttg- → ttt → ttg+ → g+tg+ → g+g+g+
	g-g-g- → g-tg- → g-tt → ttt → g+tt → g+g+t → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → ttg+ → tg+g+ → g+g+g+
T+M-	g-g-g- → g-g-t → g-tt → ttt → ttg+ → g+tg+ → g+g+g+
	g-g-g- → tg-g- → ttg- → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-tg- → g-tt → ttt → ttg+ → tg+g+ → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → g+tt → g+g+t → g+g+g+
M+M-	g-g-g- → g-tg- → g-tt → ttt → ttg+ → g+tg+ → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-tg- → g-tt → ttt → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-tg- → ttg- → ttt → ttg+ → g+tg+ → g+g+g+

T+XT-	g-g-g- → g-g-t → g-tt → g-tg+ → ttg+ → tg+g+ → g+g+g+
	g-g-g- → tg-g- → ttg- → g+tg- → g+tt → g+g+t → g+g+g+
TXM	g-g-g- → g-tg- → g-tt → g-tg+ → ttg+ → tg+g+ → g+g+g+
	g-g-g- → tg-g- → ttg- → g+tg- → g+tt → g+tg+ → g+g+g+
	g-g-g- → g-g-t → g-tt → g-tg+ → ttg+ → g+tg+ → g+g+g+
	g-g-g- → g-tg- → ttg- → g+tg- → g+tt → g+g+t → g+g+g+
M+XM-	g-g-g- → g-tg- → g-tt → g-tg+ → ttg+ → g+tg+ → g+g+g+
	g-g-g- → g-tg- → ttg- → g+tg- → g+tt → g+tg+ → g+g+g+



Supplementary Figure 1. A comparison of native contact fractions Q(x) of the helix and hairpin regions of FSD-1 along the lowest OM action pathways. *Red and blue lines represent the helix and the hairpin regions of FSD-1. Solid and dashed lines represent the lowest and second lowest OM action pathways.*