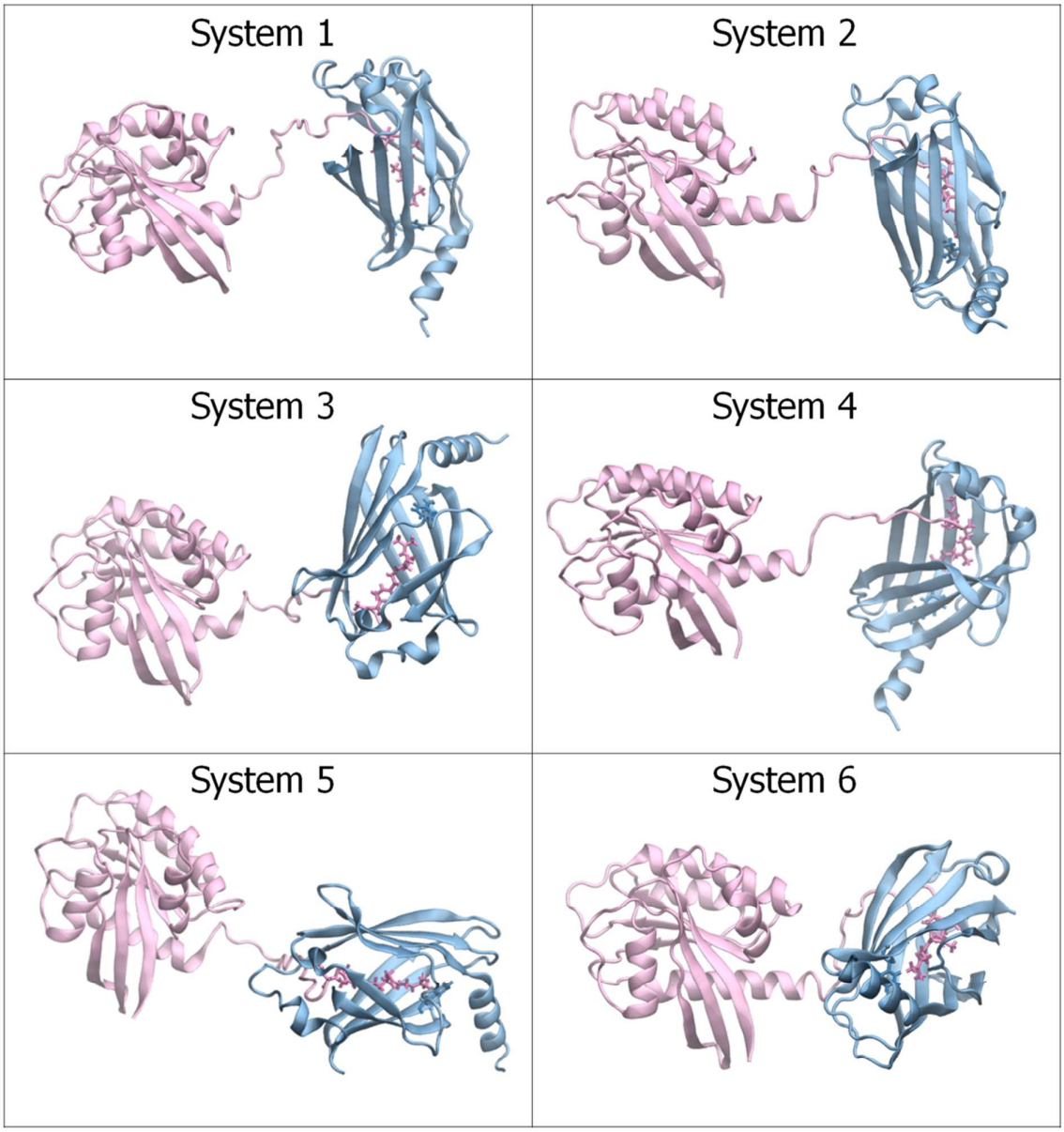

Figure S1. Stating points of the K-Ras4B-GTP/PDEδ systems for the atomistic molecular dynamics (MD) simulations in a water environment. The details of each system are shown in Table 1.

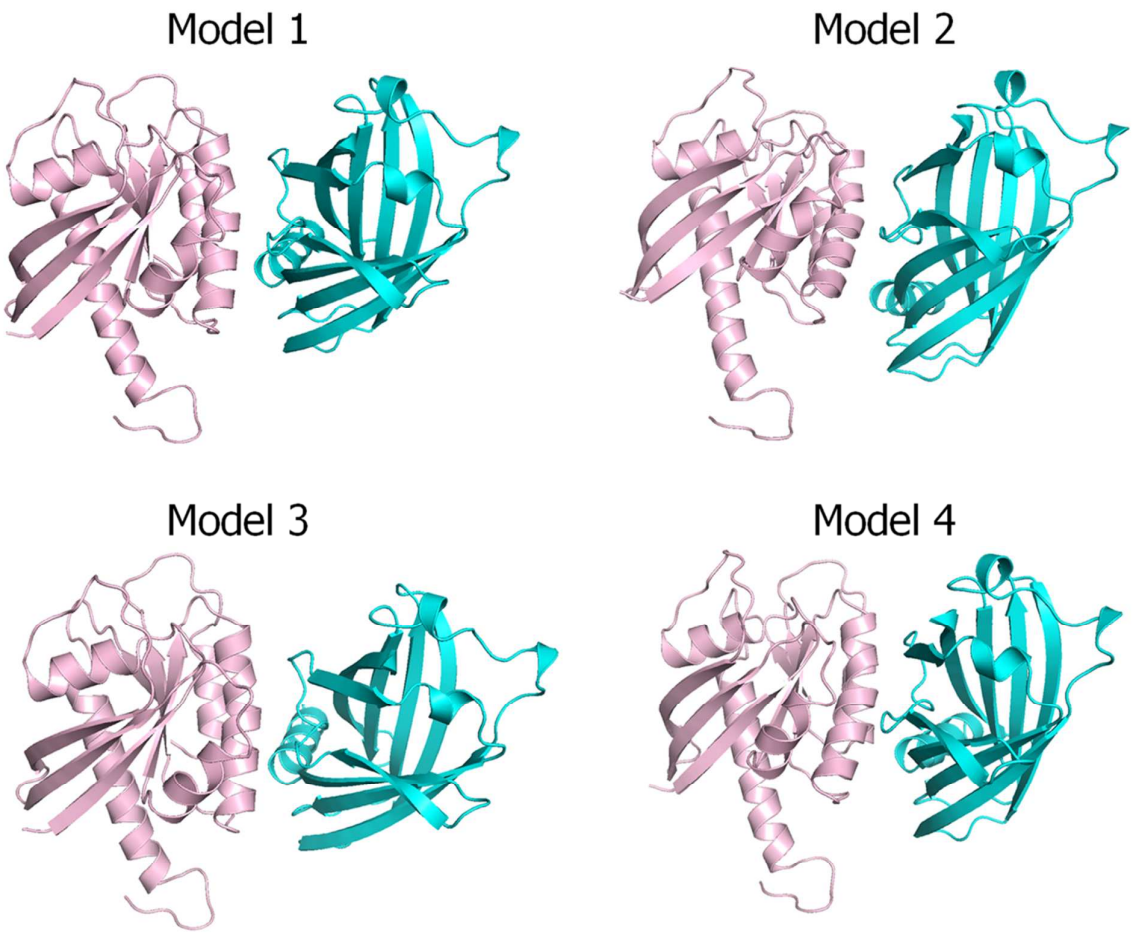

Figure S2. Predicted models of the K-Ras4B catalytic domain interacting with PDEδ by using the standard Rosetta global docking method.

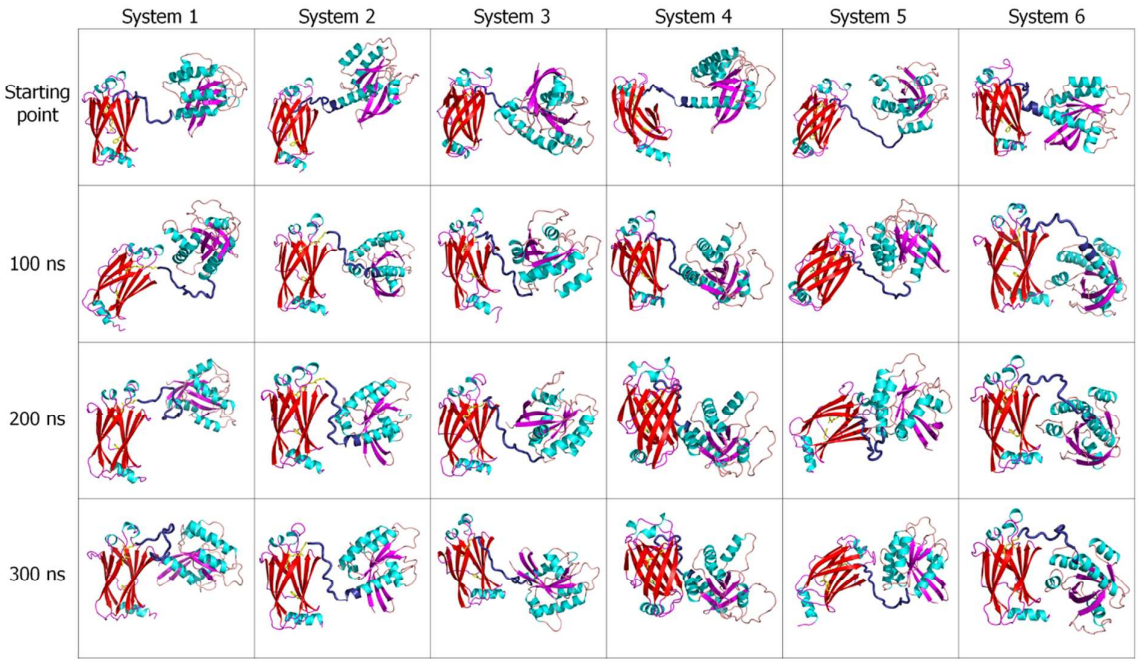

Figure S3. The snapshots of K-Ras4B-GTP/PDEδ complex (System 1 – System 6) at the start point, 100 ns, 200 ns, and 300 ns run points.

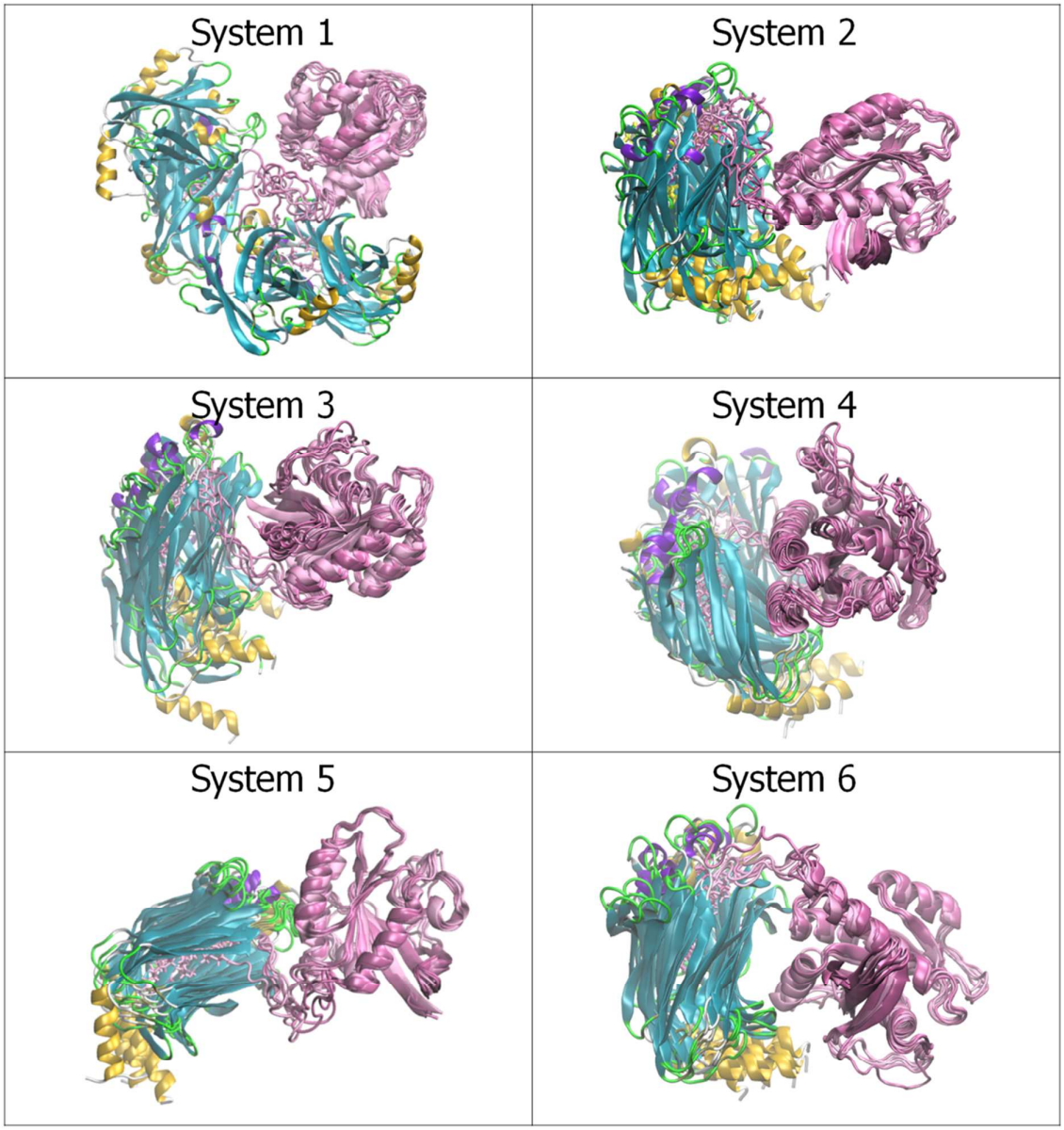

Figure S4. The superimposed snapshots taken every 50 ns simulations of these six K-Ras4B-GTP/PDEδ systems.

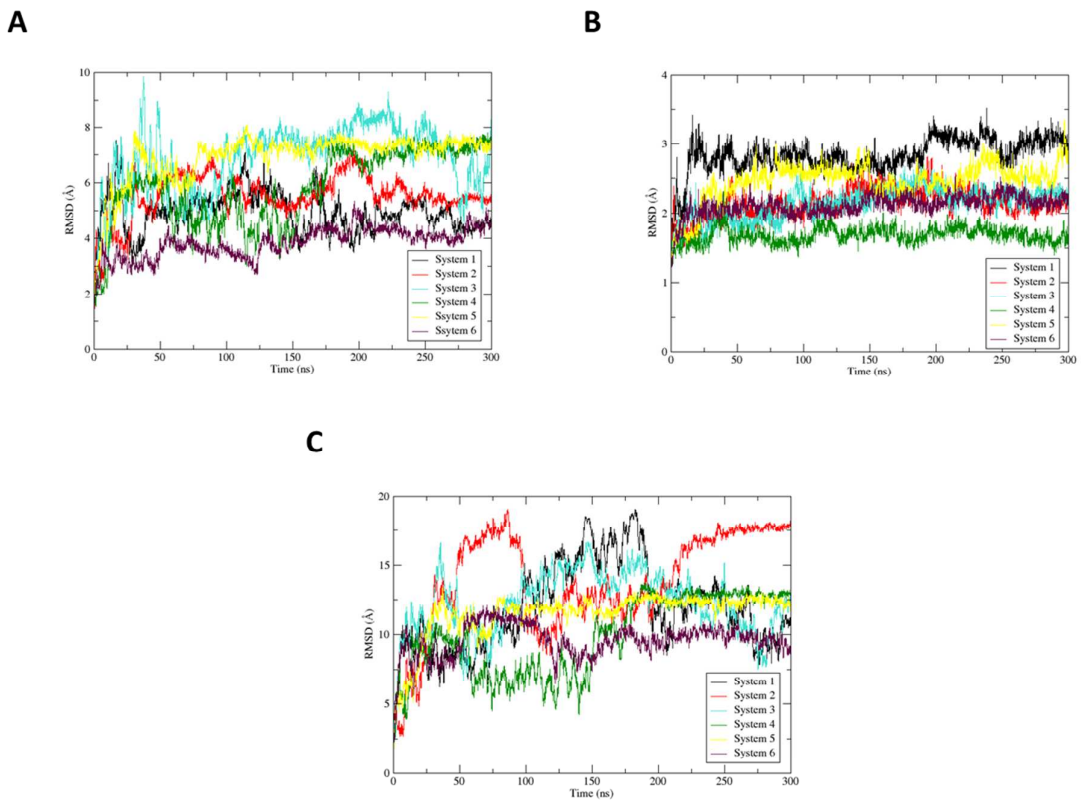

Figure S5. Root-mean-squared deviations (RMSDs) of (A) K-Ras4B, (B) PDEδ, and (C) K-Ras4B/PDEδ complex in the six K-Ras4B/PDEδ systems.

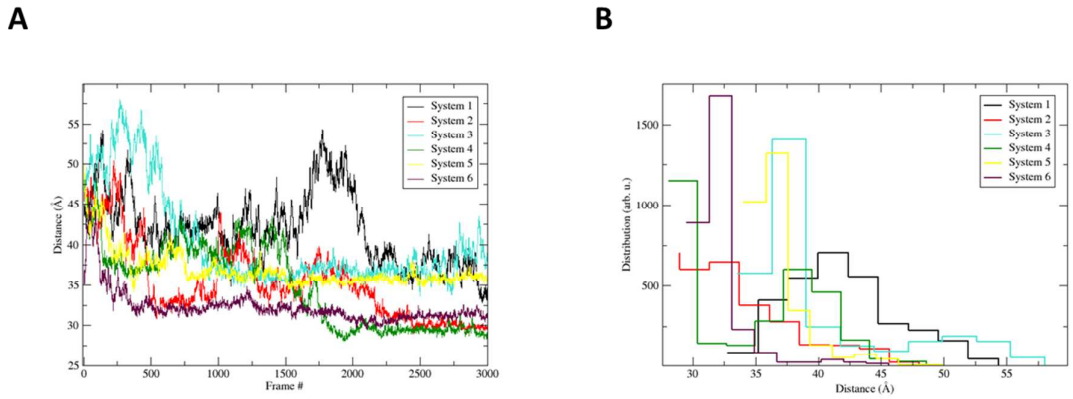

Figure S6. Distance analysis of the six K-Ras4B/PDEδ systems. (A) The center of mass distance between K-Ras4B and PDEδ of the six K-Ras4B/PDEδ systems. (B) Distribution of the center of mass distance of the six simulated K-Ras4B/PDEδ systems.

Table S1. Average RMSD values of the K-Ras4B, PDEδ and K-Ras4B/PDEδ complex

Configuration	Average RMSD (Å)		
	K-Ras4B	**PDEDδ**	**Complex**
System 1	4.9 ± 0.7	2.8 ± 0.3	11.9 ± 3.1
System 2	5.5 ± 0.8	2.1 ± 0.2	13.9 ± 3.6
System 3	6.9 ± 1.2	2.2 ± 0.2	12.3 ± 2.3
System 4	5.8 ± 1.3	1.7 ± 0.1	9.9 ± 2.8
System 5	6.9 ± 0.9	2.5 ± 0.3	11.6 ± 1.7
System 6	3.8 ± 0.5	2.1 ± 0.2	9.6 ± 1.2

Table S2. Types of atomic interactions in the prenylated K-Ras4B-GTP/PDEδ complex. The number in the parenthesis denotes percentage of the atomic pair interaction based on the distance between the paired atoms.

Configuration	H-bond K-Ras4B / PDEδ (%)	Salt-bridge K-Ras4B / PDEδ (%)
System 1	Lys184 / Glu88 (34.92)	Lys184 / Glu88 (28.92)
System 2	Lys184 / Glu88 (45.50) Lys182 / Glu89 (22.17) Glu63 / Arg9 (19.33) Lys178 / Glu88 (16.75) Lys177 / Glu89 (16.50) Asp105 / Lys79 (16.00)	Lys177 / Glu89 (28.58) Lys184 / Glu88 (25.00) Asp105 / Lys79 (17.92) Lys182 / Glu88 (17.75) Asp105 / Lys132 (16.25) Lys178 / Glu88 (15.08)
System 3	Lys184 / Glu88 (30.92) Thr183 / Glu88 (27.92) Lys176 / Glu77 (24.58) Lys178 / Glu93 (20.25)	Lys176 / Glu77 (33.80) Lys175 / Asp136 (28.92)
System 4	Thr183 / Glu88 (68.25) Lys184 / Glu88 (49.75) Lys172 / Asp137 (37.33) Lys172 / Asp136 (30.67) Lys177 / Glu89 (30.17) Lys182 / Ala112 (28.17) Lys169 / Glu93 (18.92) Lys176 / Glu93 (17.75) Lys180 / Glu110 (16.50)	Lys172 / Asp136 (55.80) Lys172 / Asp137 (53.70) Lys169 / Glu93 (36.80) Lys180 / Glu110 (22.30) Lys177 / Glu89 (15.30)
System 5	Thr183 / Glu110 (63.92) Thr183 / Glu88 (55.42) Ser181 / Glu88 (49.42) Lys182 / Glu88 (45.17) His95 / Pro113 (24.58) Tyr64 / Met117 (24.17) Lys180 / Glu88 (21.50) Lys182 / Ala112 (17.42) Lys180 / Glu89 (15.83) Gln99 / Ser115 (15.08)	Lys182 / Glu110 (16.30) Lys178 / Glu89 (15.25)
System 6	Arg73 / Glu77 (71.17) Ser181 / Glu88 (34.42) Asp69 / Lys79 (33.67) Cys185 / Ala112 (31.08) Lys182 / Glu88 (26.25) Lys184 / Met118 (25.50) Lys179 / Glu88 (23.67) Arg73 / Glu89 (20.33)	Lys182 / Glu88 (25.70) Lys179 / Glu88 (22.60) Asp69 / Lys79 (22.50)

Table S3. Types of atomic interactions of the HVRs of both K-Ras4A and N-Ras with PDEδ. The number in the parenthesis denotes percentage of the atomic pair interaction based on the distance between the paired atoms.

Configuration	H-bond HVR/ PDEδ (%)	Salt-bridge HVR / PDEδ (%)
System A1	Lys185 / Glu88 (43.95) Lys182 / Glu88 (27.05) Lys185 / Glu114 (18.15)	Lys185 / Glu88 (97.3)
System A2	Lys185 / Glu88 (53.50) Lys184 / Glu88 (45.75) Lys185 / Glu88 (42.10) Arg167 / Glu93 (31.25) Arg167 / Glu93 (35.45) Cys180 / Glu89 (17.60)	Lys185 / Glu88 (93.5) Lys 173 / Glu89 (16.45)
System N1	Arg167 / Glu110 (35.75) Cys181 / Glu110 (31.40) Met182 / Glu88 (26.95) Gly183 / Glu88 (24.60) Cys181 / Ala112 (16.50)	NA
System N2	Gly183 / Glu88 (17.10) Arg167 / Glu110 (16.75) Pro185 / Tyr149 (15.75)	NA