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| **Supplementary file 1** **Summary table of simulations** | | | | | | |
| simulation ID | bilayer composition | duration | initial position (nm) / orientation1) | time fraction (%) showing PD-bilayer binding2) | time fraction (%) showing C2-bilayer binding2) | time fraction (%) showing the productive orientation2),3) |
| *coarse-grained* | | | | | | |
| cg\_po\_1a, b, c | 212 POPC | 3 × 2s | -3.5 / C2K558 | 0.0, 0.0, 0.8 | 10.8, 0.0, 0.0 | 0.0, 0.0, 0.0 |
| cg\_po\_2a, b, c | 212 POPC | 3 × 2s | -4.1 / LDR246 | 0.4, 0.0, 0.0 | 0.0, 0.0, 0.0 | 0.0, 0.0, 0.0 |
| cg\_po\_3a, b, c | 212 POPC | 3 × 2s | -3.5 / PDK364, C2Y522 | 0.0, 0.0, 0.0 | 0.0, 0.0, 0.8 | 0.0, 0.0, 0.0 |
| cg\_po\_4a, b, c | 212 POPC | 3 × 2s | -3.5 / PDK427, PDY429 | 0.0, 0.0, 0.0 | 0.0, 0.2, 0.0 | 0.0, 0.0, 0.0 |
| cg\_po\_5a to h | 212 POPC | 8 × 1s | -1.6 / LDR246, C2K558  (prebound) | 4.4, 8.4 4) | 45.8, 99.6 4) | 2.8, 3.6 4) |
| cg\_po\_pi\_1a, b, c | 208 POPC/4 PIP3 | 3 × 2s | -4.0 / C2K558 | 95.8, 86.6, 93,4 | 95.2, 12.8, 44.7 | 71.7, 0.4, 34.7 |
| cg\_po\_pi\_2a, b, c | 208 POPC/4 PIP3 | 3 × 2s | -4.0 / LDR246 | 99.6, 93.6, 97.6 | 5.0, 57.1, 38.7 | 3.8, 33.3, 3.2 |
| cg\_po\_pi\_3a, b, c | 208 POPC/4 PIP3 | 3 × 2s | -4.0 / PDK364, C2Y522 | 78.8, 86.6, 72.9 | 50.7, 48.7, 98.8 | 30.7, 27.3, 34.7 |
| cg\_po\_pi\_4a, b, c | 208 POPC/4 PIP3 | 3 × 2s | -3.5 / PDK427, PDY429 | 83.2, 89.8, 90.6 | 13.0, 4.6, 28.9 | 0.0, 3.4, 7.4 |
| *Atomistic* | | | | | | |
| at\_po\_1 | 212 POPC | 100ns | -2.6 / LDR246, C2K558 | 42.2 | 97.1 | 42.2 |
| at\_po\_2 | 212 POPC | 100ns | -2.6 / LDR246, C2K558 | 92.5 | 99.0 | 51.0 |
| at\_po\_3 | 212 POPC | 100ns | -2.6 / LDR246, C2K558 | 97.2 | 98.2 | 97.2 |
| at\_po\_4 | 212 POPC | 100ns | -3.2 / LDR246, C2K558 | 98.5 | 99.5 | 97.5 |
| at\_po\_5 | 212 POPC | 100ns | -3.2 / LDR246, C2K558 | 10.4 | 85.1 | 0.0 |
| at\_po\_6 | 212 POPC | 100ns | -3.2 / LDR246, C2K558 | 0.5 | 90.7 | 0.0 |
| at\_po\_pi\_0 5) | 208 POPC/4 PIP3 | 100ns | -2.5 / PDR281, C2K558 | 97.9 | 39.1 | 39.1 |
| at\_po\_pi\_1 | 208 POPC/4 PIP3 | 100ns | -3.1 / LDR246, C2K558 | 86.1 | 81.2 | 60.9 |
| at\_po\_pi\_2 | 208 POPC/4 PIP3 | 100ns | -3.1 / LDR246, C2K558 | 91.1 | 31.2 | 28.2 |
| at\_po\_pi\_3 | 208 POPC/4 PIP3 | 100ns | -3.4 / LDR246, C2K558 | 79.7 | 89.1 | 77.2 |
| at\_po\_pi\_4 | 208 POPC/4 PIP3 | 100ns | -3.4/ LDR246, C2K558 | 0.0 | 80.0 | 0.0 |
| at\_po\_pi\_5 | 208 POPC/4 PIP3 | 100ns | -3.1 / PDR281, C2K516 | 94.5 | 19.9 | 17.9 |
| at\_po\_pi\_6 | 208 POPC/4 PIP3 | 100ns | -3.4 / PDR281, C2K516 | 84.1 | 95.5 | 83.6 |
| at\_po\_pi\_7 | 208 POPC/4 PIP3 | 100ns | -3.4 / PDR281, C2K516 | 85.1 | 98.1 | 84.6 |
| at\_steered | 208 POPC/4 PIP3, 212 POPC, | Two runs named POPC/PIP3\_1 and 2 were started with structures sampled from at\_po\_pi\_5 and POPC\_1 and 2) were with two structures from at\_po\_4.6) | | | | |

1) Position is represented by the z-position (i.e., the positions along the z-axis, which is parallel to the membrane normal) of the center of mass of the protein relative to the phosphorus layer. Orientation is represented by the domain name (C2, PD or VSD-PD linker (LD)) along with, in superscript, the residue initially located the nearest to the bilayer. 'PDK364, C2Y522' for example, represents that both Tyr-522 of the C2 domain and Lys-364 of the PD were equally close to the bilayer. 2) For CG sets, three values correspond to the three independent runs (a,b and c). 3) The fraction of time period showing not only the productive orientation but also the binding of the both the PD and C2 domain is shown. 4) The results of two representative runs are shown. 5) Initial structure was prepared mimicking the structure sampled from cg\_po\_pi\_1a. In this run, the both domains were initially set bound to the POPC/PIP3 bilayer, but the C2 domain detached from and the PD remained bound to the bilayer. 6) The legend for Figure 2-figure supplement 6 has more detail.