Supporting Information

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In this supplementary document the covariance overlaps, z-scores and spring parameters obtained in our study are reported. We also outline the spring function naming convention in detail. The following is a complete list of spring functions presented in this study. The functional forms replace $k(R^{\circ}_{ij})$ in Eq. (1), restated here for convenience:

$$U_{ij} = k(R^{\circ}_{ij}) \left(|R_{ij}| - |R^{\circ}_{ij}| \right)^2 \tag{S1}$$

The Heaviside step function is defined by:

$$k(R^{\circ}_{ij}) = \begin{cases} 1 & : R^{\circ}_{ij} < R_c \\ 0 & : R^{\circ}_{ij} \geq R_c \end{cases} \tag{S2}$$

In figures referring to an "exponential" spring function the following form is used:

$$k(R^{\circ}_{ij}) = \exp(-aR^{\circ}_{ij}) \tag{S3}$$

The spring can also vary with a power function:

$$k(R^{\circ}_{ij}) = (R^{\circ}_{ij})^{-a} \tag{S4}$$

The functional form developed by Hinsen et al.[24] and referred to as HCA in our text takes the following form:

$$k(R^{\circ}_{ij}) = \begin{cases} a(R^{\circ}_{ij}) + b & : R^{\circ}_{ij} < R_c \\ c(R^{\circ}_{ij})^{-d} & : R^{\circ}_{ij} \geq R_c \end{cases} \tag{S5}$$

The following functional forms rely on chemical information, connecting bonded residues (those neighboring in sequence) and non-bonded residues (all other beads in the system) with separate spring types. In the following functions we label springs with the bonded term followed by the non-bonded term, separated by a colon. A constant stiffness, k_1, for bonded terms and an

exponentially decaying stiffness for non-bonded terms would be labelled - Constant:Exponential. That function takes the following form:

$$k(R_{ij}^{\circ}) = \begin{cases} k_1 & : \text{Bonded} \\ c \times \exp(-dR_{ij}^{\circ}) & : \text{Non} - \text{bonded} \end{cases} \tag{S6}$$

In addition a power function could be used instead of the exponential function. The following form would be labelled Constant:Power:

$$k(R_{ij}^{\circ}) = \begin{cases} k_1 & : \text{Bonded} \\ c(R_{ij}^{\circ})^{-d} & : \text{Non} - \text{bonded} \end{cases} \tag{S7}$$

The following functional forms rely on chemical information, connecting bonded residues (those neighboring in sequence), angle residues (second-nearest neighboring in sequence) and non-bonded terms (all others) with three separate spring types. The nomenclature used for these functions is the bonded term, followed by the angle term, followed by the non-bonded term, all separated by colons. The function below is labelled Constant:Constant:Exponential when reported in figures and tables:

$$k(R_{ij}^{\circ}) = \begin{cases} k_1 & : \text{Bonds} \\ k_2 & : \text{Angles} \\ c \times \exp(-dR_{ij}^{\circ}) & : \text{Non} - \text{bonded} \end{cases} \tag{S8}$$

Similarly, the function Constant:Constant:Power takes the form:

$$k(R_{ij}^{\circ}) = \begin{cases} k_1 & : \text{Bonds} \\ k_2 & : \text{Angles} \\ c(R_{ij}^{\circ})^{-d} & : \text{Non} - \text{bonded} \end{cases} \tag{S9}$$

Opsin Simulation Details

The opsin data has not been published elsewhere. The starting structure used coordinates obtained from an x-ray crystallographic structure (PDB ID: 3CAP).[1] All waters and fatty acids were removed. Opsin was then embedded in a membrane made of 123 1-stearoyl-2-docosahexaenoyl-phosphatidylethanolamine (SDPE) molecules. The system was hydrated with 8,200 water molecules. We added 15 Na^+ and 19 Cl^- atoms to neutralize the system and obtain an $\approx$100 mM sodium chloride concentration.

This simulation was performed in NAMD 2.8[2] using the NPγT ensemble, where γ is a 30 dyn/cm surface tension applied laterally to the bilayer. The CHARRM22 forcefield[3,4] was used for the protein and the CHARMM36 forcefield[5] was used for lipids.

The resulting system was then simulated for 472 ns on the University of Rochester's Blue Gene/P using a 2 fs timestep with the RATTLE applied to constrain hydrogen containing bonds to their equilibrium length.[6] The temperature was held at 310K using Langevin dynamics. Electrostatic interactions were computed using the Particle Mesh Ewald method[7–9] with a 75x75x96 grid. Van der Waals interactions were smoothly truncated by force switching from 9 to 10 Å.

Supplementary Tables

Table S1: β_2AR covariance overlaps and Z-scores (n = 10,000) after individual parametrization.

Resolution	Connectivity	Spring Function	Z-score	Overlap
one-bead/ two-residues	Distance	Heaviside	96.26	0.459
		Exponential	94.81	0.481
		Power	87.33	0.477
		HCA	89.31	0.477
	Bonds: Non-bonded	Constant:Exponential	95.80	0.481
		Constant:Power	84.49	0.46
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	95.83	0.481
		Constant:Constant:Power	84.39	0.464
one-bead/ residue	Distance	Heaviside	238.50	0.503
		Exponential	205.82	0.545
		Power	206.05	0.552
		HCA	205.32	0.552
	Bonds: Non-bonded	Constant:Exponential	204.24	0.545
		Constant:Power	206.95	0.552
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	199.57	0.548
		Constant:Constant:Power	206.38	0.524
two-beads/ residue	Distance	Heaviside	145.27	0.251
		Exponential	179.17	0.275
		Power	183.75	0.275
		HCA	321.85	0.350
	Bonds: Non-bonded	Constant:Exponential	181.92	0.276
		Constant:Power	188.95	0.275
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	216.98	0.273
		Constant:Constant:Power	225.66	0.269

Table S2: rhodopsin covariance overlaps and Z-scores (n = 10,000) after individual parametrization.

Resolution	Connectivity	Spring Function	Z-score	Overlap
one-bead/ two-residues	Distance	Heaviside	73.46	0.381
		Exponential	77.30	0.406
		Power	70.60	0.412
		HCA	71.72	0.414
	Bonds: Non-bonded	Constant:Exponential	72.79	0.409
		Constant:Power	69.59	0.400
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	75.11	0.409
		Constant:Constant:Power	69.85	0.400
one-bead/ residue	Distance	Heaviside	192.94	0.414
		Exponential	168.60	0.457
		Power	165.15	0.467
		HCA	163.83	0.468
	Bonds: Non-bonded	Constant:Exponential	158.02	0.457
		Constant:Power	162.12	0.465
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	157.27	0.459
		Constant:Constant:Power	158.53	0.445
two-beads/ residue	Distance	Heaviside	345.15	0.367
		Exponential	319.74	0.394
		Power	312.13	0.394
		HCA	315.39	0.394
	Bonds: Non-bonded	Constant:Exponential	312.12	0.394
		Constant:Power	307.45	0.393
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	338.12	0.383
		Constant:Constant:Power	320.09	0.385

Table S3: CB2 covariance overlaps and Z-scores (n = 10,000) after individual parametrization.

Resolution	Connectivity	Spring Function	Z-score	Overlap
one-bead/ two-residues	Distance	Heaviside	87.69	0.414
		Exponential	91.71	0.449
		Power	83.47	0.450
		HCA	89.31	0.436
	Bonds: Non-bonded	Constant:Exponential	88.61	0.451
		Constant:Power	81.97	0.438
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	84.17	0.442
		Constant:Constant:Power	82.23	0.438
one-bead/ residue	Distance	Heaviside	194.58	0.407
		Exponential	182.01	0.472
		Power	168.17	0.490
		HCA	169.95	0.490
	Bonds: Non-bonded	Constant:Exponential	182.91	0.472
		Constant:Power	167.41	0.490
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	175.79	0.480
		Constant:Constant:Power	172.43	0.469
two-beads/ residue	Distance	Heaviside	355.10	0.377
		Exponential	327.10	0.408
		Power	325.17	0.416
		HCA	319.13	0.417
	Bonds: Non-bonded	Constant:Exponential	327.95	0.414
		Constant:Power	326.84	0.416
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	375.64	0.415
		Constant:Constant:Power	351.09	0.423

Table S4: Optimized spring parameters after fitting to all three trajectories simultaneously. All distance-based parameters are in angstroms and all other quantities are unitless.

Resolution	Connectivity	Spring Function	Parameters
one-bead/ two-residues	Distance	Heaviside	13.93
		Exponential	-0.60
		Power	-6.54
		HCA (R_c, a, b, c, d)	3.68, 1944.5, 2675.36, 5.84296e+06, 6.60
	Bonds: Non-bonded	Constant:Exponential	11.77 : -5.15
		Constant:Power	1.60 : -6.59
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	106.7 : 59.7 : -0.52
		Constant:Constant:Power	30.84 : 8.68 : -6.48
one-bead/ residue	Distance	Heaviside	8.64
		Exponential	-1.06
		Power	-8.48
		HCA (R_c, a, b, c, d)	2.91, 2089, 3076, 4.173e+06, 8.60
	Bonds: Non-bonded	Constant:Exponential	9.77:-1.06
		Constant:Power	2.72:-8.56
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	9.41 : 0.053 : -0.87
		Constant:Constant:Power	15.99 : 2.83 : -7.93
two-beads/ residue	Distance	Heaviside	8.63
		Exponential	-1.32
		Power	-9.01
		HCA (R_c, a, b, c, d)	8.63, 3154.45, -1313.51, 5.87623e+06, 5.38
	Bonds: Non-bonded	Constant:Exponential	0.30 : -1.19
		Constant:Power	8.52 : -8.84
	Bonds:Angles: Non-bonded	Constant:Constant:Exponential	0.51 : 30.79 : -0.76
		Constant:Constant:Power	5.927e-04 : 4.47e-04 : -6.43

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