Electronic Supplementary Information

"A natural missing link between activated and downhill protein folding scenarios"

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Potential surfaces were encoded as a sum of Gaussians dimples of variable depth $A_i(T)$, variable anisotropic width $\sigma_i(T)$ and position $x_i(T)$. For the 1-D three-well surface in figure 8 of the main paper,

$$G(x,T) = -\sum_{i=1}^{3} A_i(T) e^{-(x-x_{0i}(T))^2/\sigma_i(T)^2} \qquad \text{(A1)}$$

The temperature dependence of the parameters P_i in equation A1 was expanded in a Taylor series to first order, with a reference temperature T_0 of 20 ºC:

$$P_i(T) = P_i(T_0) + P_i^{'}(T_0)(T - T_0) \qquad \text{(A2)}$$

Because only the relative well-depths and the barriers between wells are physically significant, we restricted the Gaussian wells to a minimum depth such that the normalized probability density approached zero at the edges of the sampling grid. In Figure 8, the depth is offset so that the native well has a minimum at zero energy. We kept the diffusion coefficient coordinate-independent, but allowed its average value to vary.

Signal functions $S_i(x)$ were chosen to be sigmoids with offset S_0, height h, width σ, slope m, and switching at position x_o.

$$S_i(x) = S_{i0} + m_i x + \frac{h_i}{1 + e^{-(x-x_{i0})/\sigma_i}} \qquad \text{(A3)}$$

Signal functions shown in Figure 8 were normalized to the range 0 to 1 from the fitted values.

Table 1 gives the minimum and maximum values allowed in the genetic algorithm for the final optimization resulting in the fit presented in the main text. Initial guesses were determined using larger ranges by optimizing one set of signal data at a time with double-well potentials. Parameter ranges were alternately constrained to narrow the parameter space until acceptable optimization was realized.

Table 1

	Parameter	Minimum	Maximum	Optimized Value
Well 1	$A(20\ °C)$	50	50	50
	$A'(20\ °C)$	0	0	0
	$\sigma(20\ °C)$	0.352	0.485	0.392
	$\sigma'(20\ °C)$	0	0	0
	$x_0(20\ °C)$	1.42	1.42	1.42
	$x_0'(20\ °C)$	0	0	0
Well 2	$A(20\ °C)$	27	34	29.8
	$A'(20\ °C)$	0.5	0.65	0.56
	$\sigma(20\ °C)$	0.506	0.565	0.564
	$\sigma'(20\ °C)$	0	0	0
	$x_0(20\ °C)$	1.89	2.07	2.01
	$x_0'(20\ °C)$	0	0.0026	0.0010
Well 3	$A(20\ °C)$	42	46	42.8
	$A'(20\ °C)$	0.2	0.6	0.312
	$\sigma(20\ °C)$	0.5286	0.6390	0.6153
	$\sigma'(20\ °C)$	0	0	0
	$x_0(20\ °C)$	3	3.17	3.05
	$x_0'(20\ °C)$	-0.0044	0	-0.0015
Fluorescence Intensity Signal	S_0	15	15	15
	m	0	4.5400	0.6129
	σ	0.00001	0.0440	0.0130
	x_0	1.233	1.762	1.328
	h	-15	0	-12.48
Circular Dichroism Signal	S_0	25	25	25
	m	-13.62	0	-6.156
	σ	0.00001	0.0440	0.0108
	x_0	2.203	3.084	2.819
	h	-25	0	-24.1
Fluorescence Wavelength Signal	S_0	25	25	25
	m	0	22.7	11.7
	σ	0.00001	0.0661	0.0141
	x_0	1.1	1.76	1.39
	h	-25	0	-11.08
Diffusion Coef. (nm^2/ns)	D	8.8×10^{-6}	1.76×10^{-5}	1.23×10^{-5}