SUPPORTING MATERIAL

Model potential function

Applying the procedure in Theory section for the identification of non-zero terms in the bivariate polynomial form (Eq. 17 of the main text), the model potential for the histidine titration and tautomer interconversion is determined as

$$U^{\mathrm{mod}}(\lambda_i, x_i) = \lambda_i^2(a_0 x_i^2 + a_1 x_i + a_2) + \lambda_i(a_3 x_i + a_4) \tag{1}$$

and the coefficients in the polynomial function can be derived as

$$\begin{aligned} a_0 &= A_{10} \\ a_1 &= -2A_{10}B_{10} + 2(A_1B_1 - A_0B_0) \\ a_2 &= A_0 \\ a_3 &= -2A_1B_1 + 2A_0B_0 \\ a_4 &= -2A_0B_0 \end{aligned} \tag{2}$$

where $A_0, B_0, A_1, B_1, A_{10}, B_{10}$ are the coefficients in the quadratic functions for the one-dimensional model potential functions as given in Eq. 15 of the main text. Notice that $U^{\mathrm{mod}}(\lambda_i, x_i)$ satisfies all the boundary conditions given in Eq. 15 and Eq. 16 of the main text.

Analogously, for the titration and tautomer interconversion pathway of carboxylic acid, the model potential function can be derived as,

$$U^{\mathrm{mod}}(\lambda_i, x_i) = (a_0\lambda_i^2 + a_1\lambda_i + a_2)(x_i + a_3)^2 + a_4\lambda_i^2 + a_5\lambda_i \tag{3}$$

where the coefficients are given as

$$\begin{aligned} a_2 &= A_{10} \\ a_3 &= -B_{10} \\ a_0 &= (A_1 - A_0)/(1 + 2a_3) \\ a_1 &= 2(A_0 - B_0)/(1 + 2a_3) \\ a_4 &= A_0 - a_0 a_3^2 \\ a_5 &= -2A_0B_0 - a_1 a_3^2 \end{aligned} \tag{4}$$

A numerical problem arises in the determination of a_0 via the above the formula since the values of the numerator and denominator are close to zero. This occurs because the one-dimensional model potential functions for the titration at OD1 and OD2 sites are almost identical. Consequently, a_0, a_1, a_2, a_3 can be determined by following step 3 and 4 of the procedure mentioned in the Theory section. a_4, a_5 can be determined in a similar fashion using step 1 and 2 of the same procedure.