$$V = V(x_0, x_0) + \sum_{s=1}^{M} \sum_{i=1}^{N_s} \lambda_{si} (V(x_0, x_{si}) + V(x_{si}, x_{si})) + \sum_{s=1}^{M} \sum_{i=1}^{N_s} \sum_{t=s+1}^{M} \sum_{j=1}^{N_t} \lambda_{si} \lambda_{tj} V(x_{si}, x_{tj}) + V_{bias}(\{\lambda\})$$

$$V_{bias}(\{\lambda\}) = V_{fixed}(\{\lambda\}) + V_{quadratic}(\{\lambda\}) + V_{end}(\{\lambda\}) + V_{skew}(\{\lambda\})$$

$$V_{fixed}(\{\lambda\}) = \begin{cases} 0 & \text{if reference state} \\ \lambda(\Delta G_{model} + 2.303RT(pK_a - pH)) & \text{otherwise} \end{cases}$$