Use of Lagrange multipliers to determine normalization.

$$\mathcal{L} = \left\{ \prod_{ij} \frac{1}{\sigma_j} e^{-\left\{[c_j^0 + \Delta c_j f_i] - \alpha_i D_{ij}\right\}^2 / 2\sigma_j^2} \right\} e^{-s^2/2\sigma^2} \, e^{\left[\sum_{i=1}^{N} \alpha_i - N\right]\lambda}$$

std. dev. at each residue

Forces "minimum" σ_j^2

Lagrange multiplier

$$\ell = -\sum_j N_{conc} \log \sigma_j - \frac{1}{2} \sum_{ij} \frac{1}{\sigma_j^2} \Big\{ \underbrace{[c_j^0 + \Delta c_j f_i]}_{D_{ij}^{pred}} - \alpha_i D_{ij} \Big\}^2 - \frac{s^2}{2\sigma^2} + \lambda \left[\sum_{i=1}^{N} \alpha_i - N \right]$$

$$\frac{\partial \ell}{\partial \sigma_j} = -\frac{N_{conc}}{\sigma_j} + \sum_i \frac{1}{\sigma_j^3} \left[D_{ij}^{pred} - \alpha_i D_{ij} \right]^2 + \frac{s^2}{\sigma_j^3} = 0$$

$$\Rightarrow \quad \sigma_j = \left[\frac{1}{N_{conc}} \sum_i \left[D_{ij}^{pred} - \alpha_i D_{ij} \right]^2 + s^2 \right]^{1/2}$$

$$0 = \frac{\partial \ell}{\partial \alpha_i} = -\sum_j \frac{1}{\sigma_j^2} \left[D_{ij}^{pred} - \alpha_i D_{ij} \right] D_{ij} + \lambda$$

$$\Rightarrow \quad \lambda = \sum_j \frac{1}{\sigma_j^2} \left[D_{ij}^{pred} - \alpha_i D_{ij} \right] D_{ij}$$

or

$$\alpha_i = \frac{\sum_j D_{ij}^2/\sigma_j^2 - \lambda}{\sum_j \frac{D_{ij}^{pred} \cdot D_{ij}}{\sigma_j^2}}$$

Now enforce constraint:

$$N = \sum_i \alpha_i = \sum_i \left[\frac{\sum_j D_{ij}^2/\sigma_j^2}{\sum_j \frac{D_{ij}^{pred} \cdot D_{ij}}{\sigma_j^2}} \right] - \sum_i \frac{\lambda}{\sum_j \frac{D_{ij}^{pred} \cdot D_{ij}}{\sigma_j^2}}$$

$$\lambda = \left[\sum_i \left\{ \left[\sum_j \frac{D_{ij}^{pred} \cdot D_{ij}}{\sigma_j^2} \right]^{-1} \right\} \right]^{-1} \left[\sum_i \frac{\sum_j D_{ij}^2/\sigma_j^2}{\left(\sum_j \frac{D_{ij}^{pred} \cdot D_{ij}}{\sigma_j^2} \right)} - N \right]$$

$$= \frac{\left\{ \sum_i \beta_i \left(\sum_j D_{ij}^2/\sigma_j^2 \right) \right\} - N}{\sum_i \beta_i}$$

where $\beta_i = \left\{ \sum_j \left[D_{ij}^{pred} \cdot D_{ij} \right] / \sigma_j^2 \right\}^{-1}$