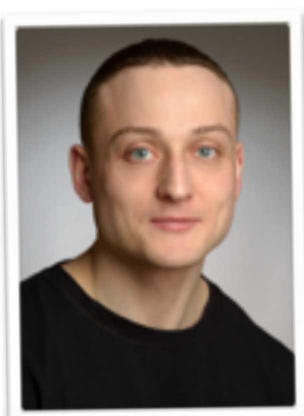
Molecular Dynamics at Constant pH

Gerrit Groenhof

Department of Chemistry & Nanoscience center
University of Jyväskylä
Finland

Computational
Biomolecular
Chemistry

Plamen Dobrev



Thomas Ullmann

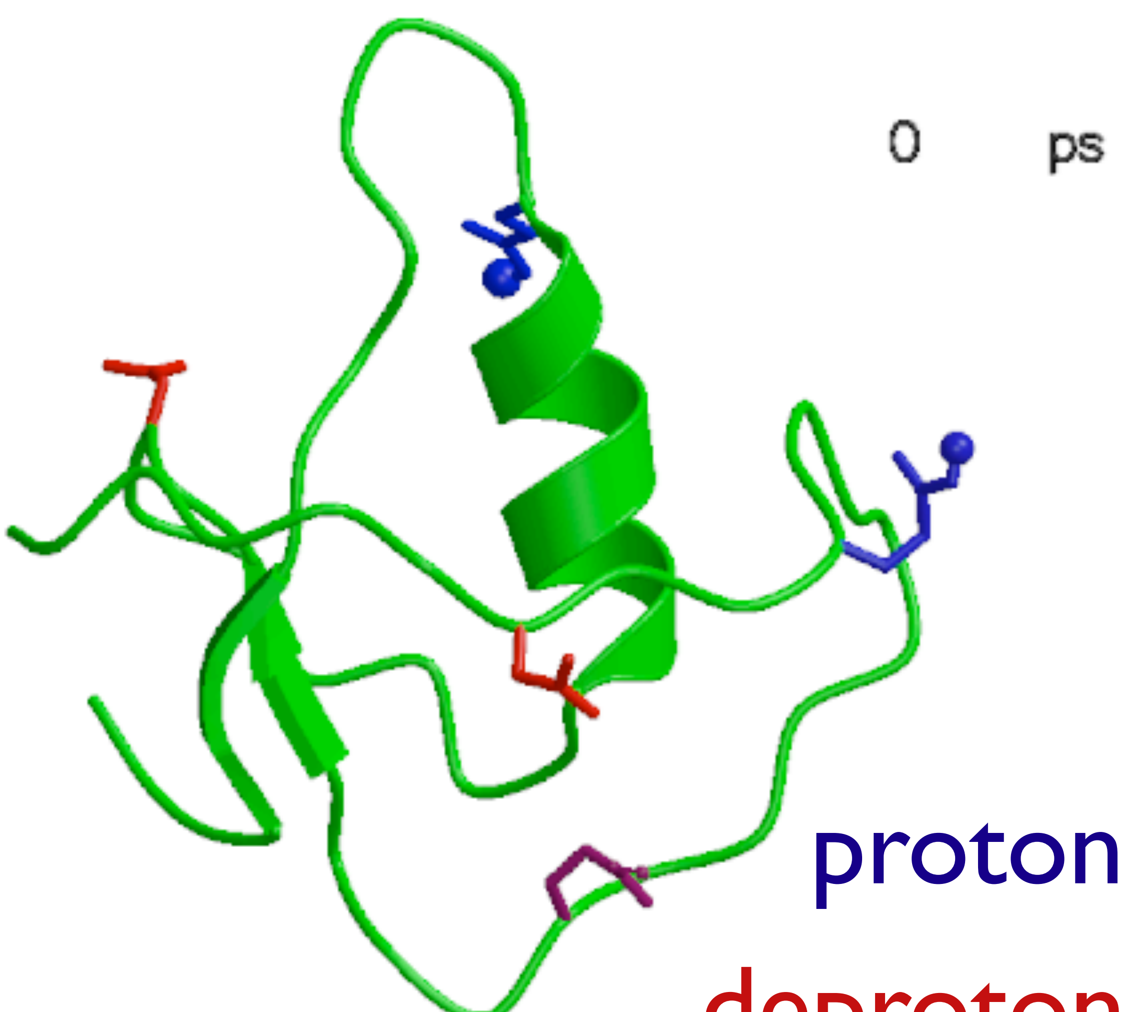
Serena Donnini

Helmut Grubmüller

Why molecular dynamics at constant pH?

protonation states are variable

third domain of turkey ovomucoid inhibitor at pH = 4



protonated

deprotonated

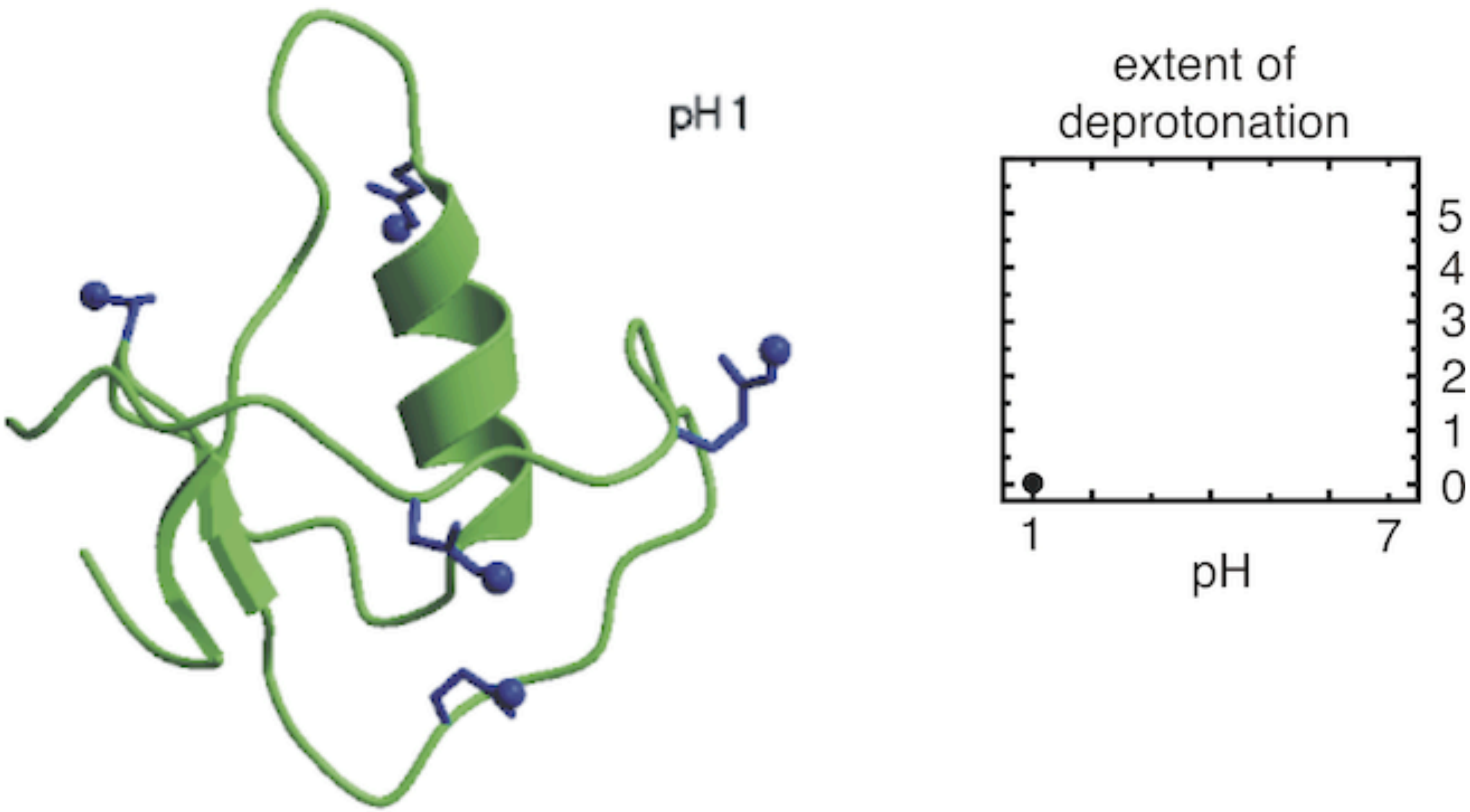
Why molecular dynamics at constant pH?

in silico titration experiment

MD simulations at different solvent pH values

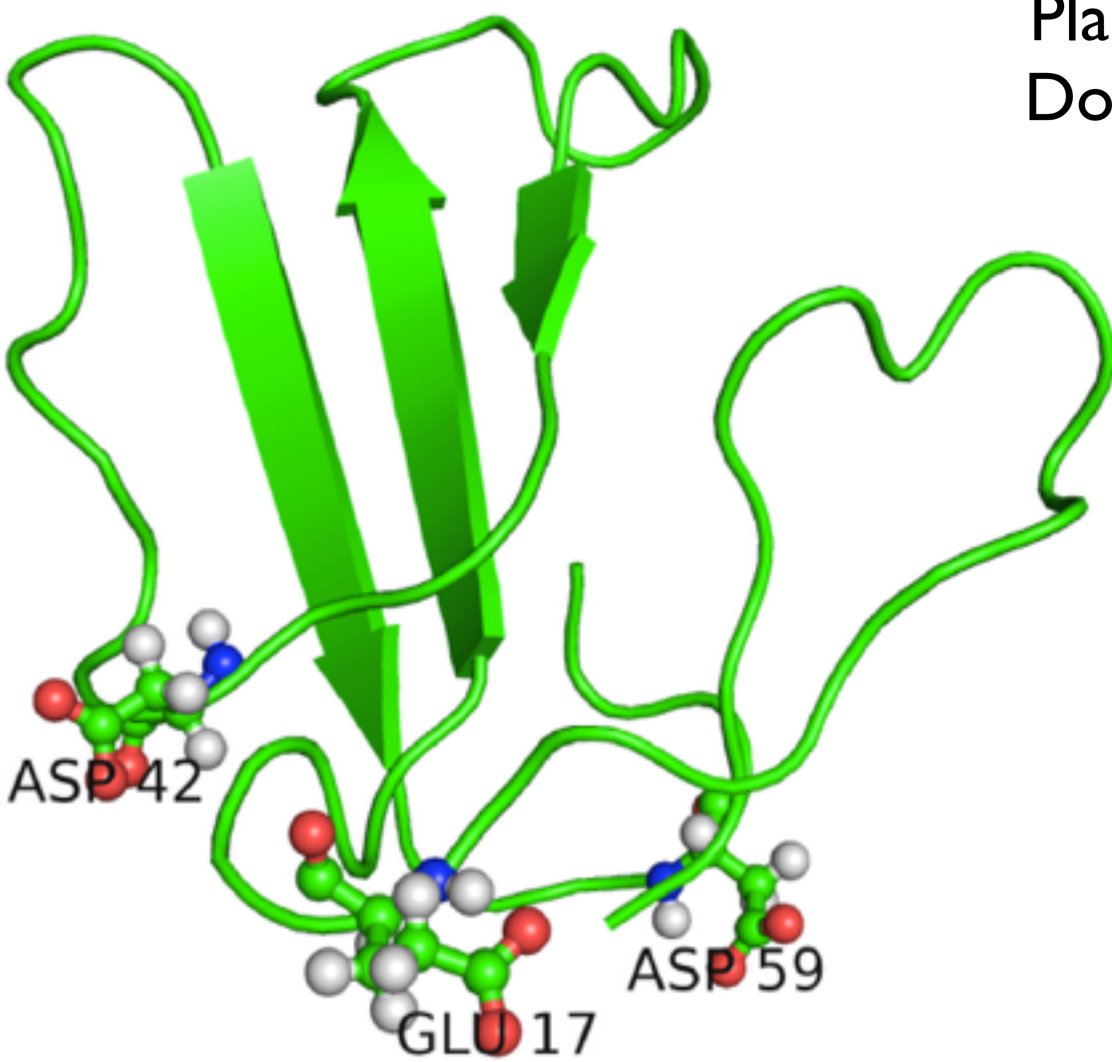
Henderson-Hasselbalch

$$\frac{[\mathrm{A}^-]}{[\mathrm{A}^-]+[\mathrm{AH}]} = \frac{1}{10^{n(\mathrm{pK_a}-\mathrm{pH})}+1}$$

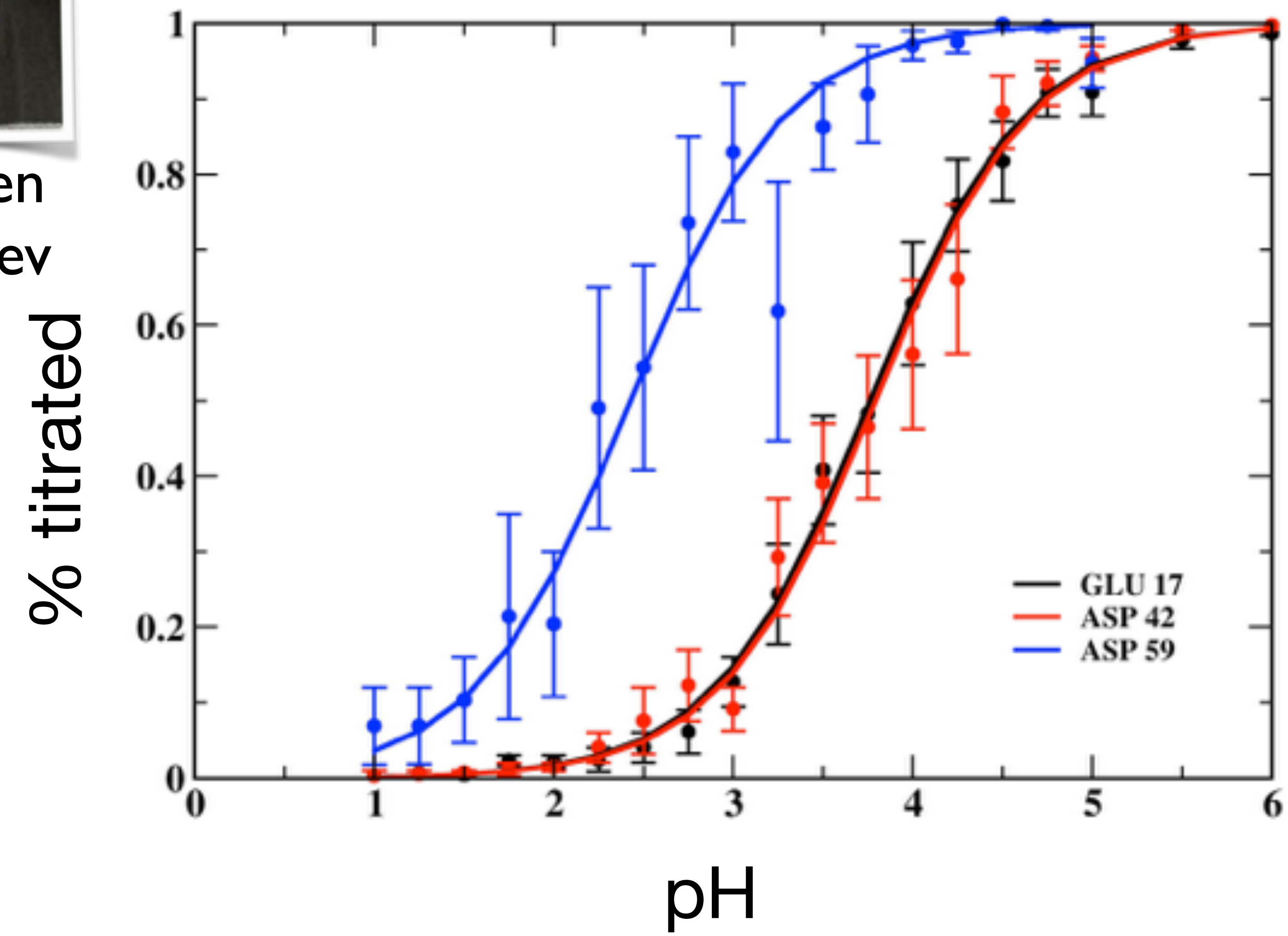


pK_a's of proteins

cardiotoxin V



Plamen Dobrev

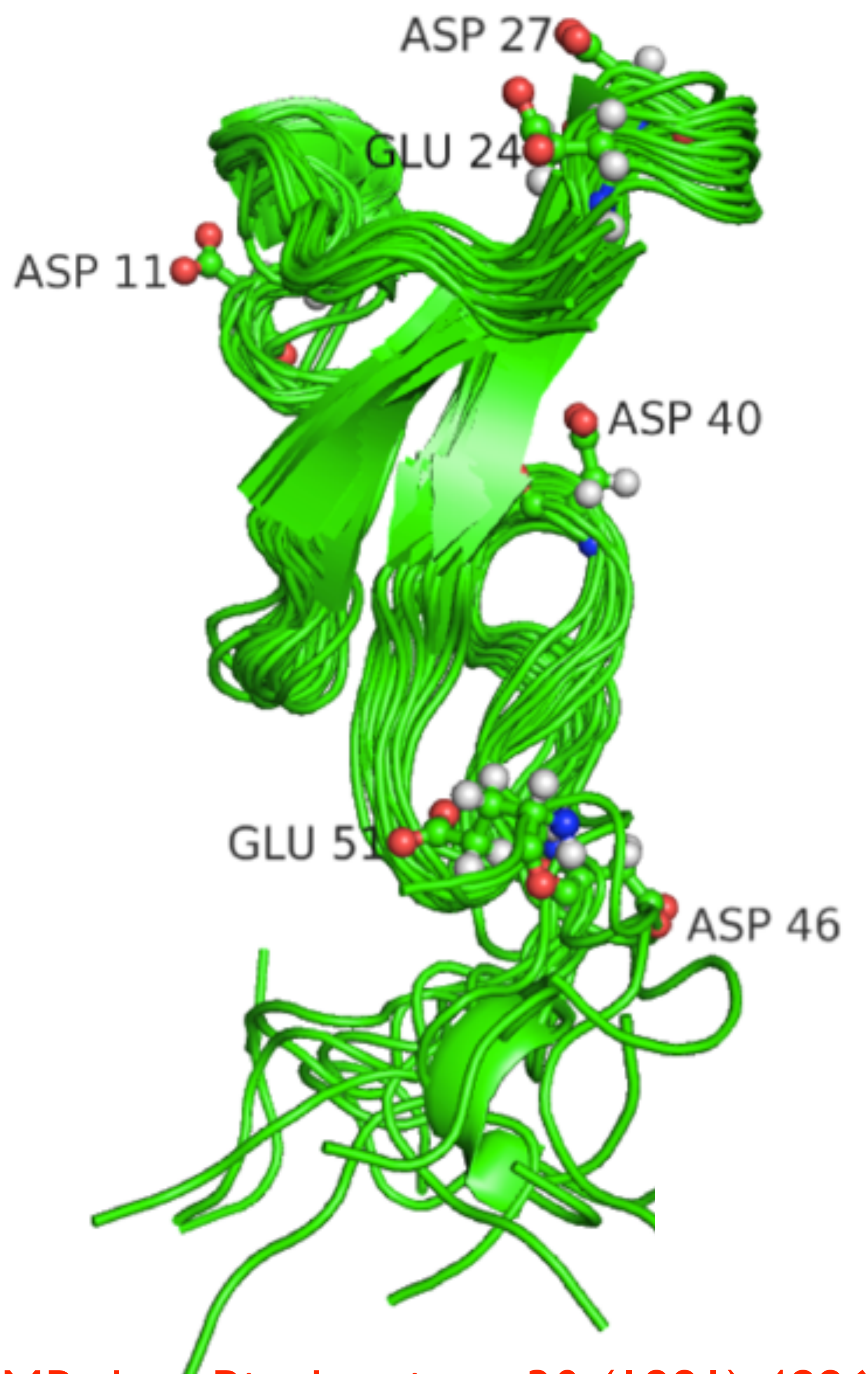


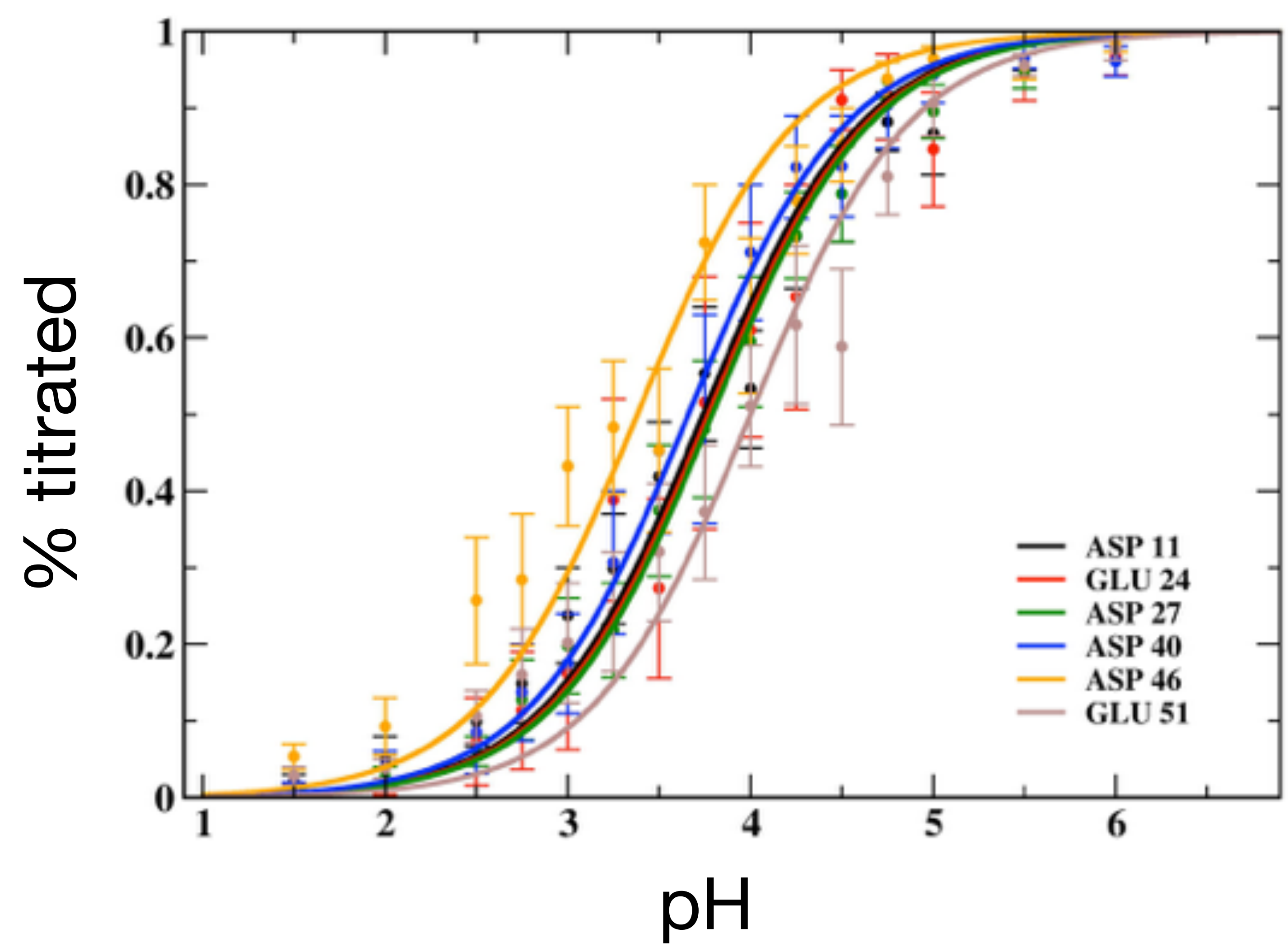
residue	CPHMD	PB	NMR
Glu17	3.77 (0.06)	3.73	4
Asp42	3.8 (0.07)	3.64	3.2
Asp59	2.44 (0.12)	2.84	< 2.3

NMR data: Biochemistry 35 (1996) 9167

pK_a's of proteins

epidermal growth factor





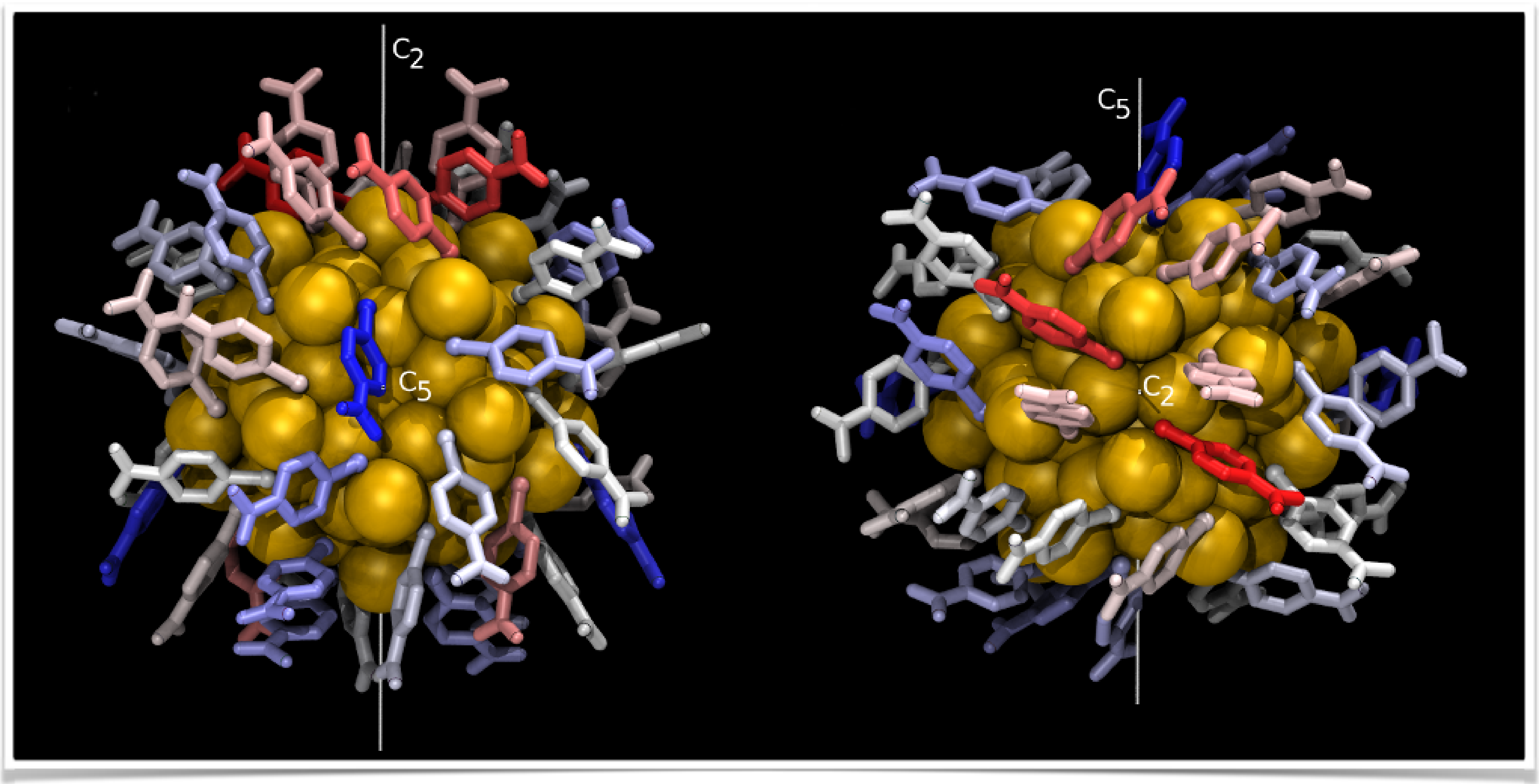
residue	CPHMD	PB	NMR
Asp11	3.74 (0.07)	4.2 (0.13)	3.9
Glu24	3.77 (0.12)	3.78 (0.15)	4.1
Asp27	3.79 (0.07)	3.8 (0.08)	4
Asp40	3.66 (0.09)	5.33 (0.28)	3.6
Asp46	3.38 (0.09)	4.1 (0.34)	3.8
Glu51	4.0 (0.09)	4.1 (0.24)	4

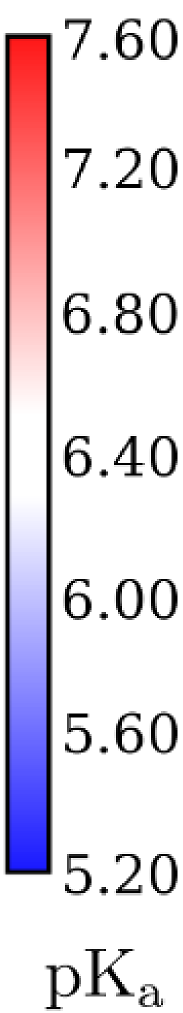
NMR data: Biochemistry 30 (1991) 4896

pK_a's of other stuff

monolayer protected gold nano-clusters

surface pK_a & charge distribution

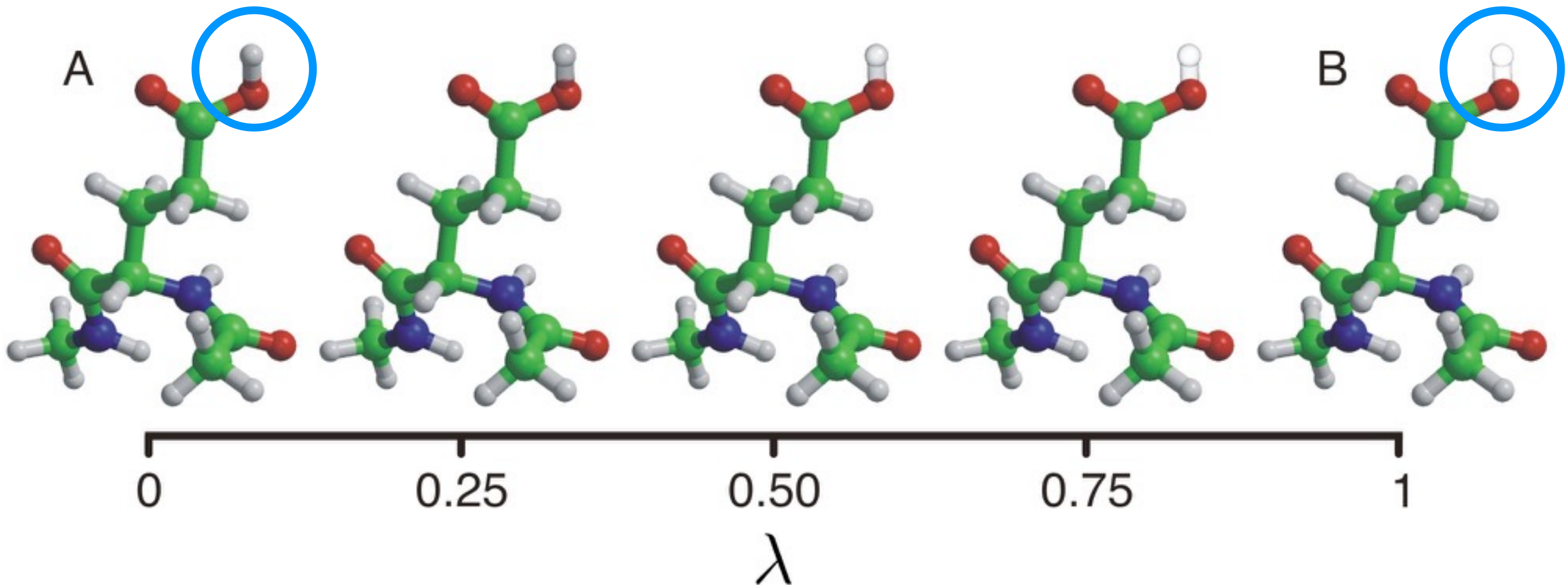




J. Koivisto, X. Chen, S. Donnini, T. Lahtinen, H. Häkkinen, G. Groenhof. M. Pettersson *J. Phys. Chem. C* 120 (2016) 10041

Molecular dynamics at constant pH: how?

protons as extra degrees of freedom



dynamics of λ-particle (protonation)

$$m_\lambda d^2\lambda/dt^2 = -\partial V(\mathbf{x},\lambda)/\partial\lambda$$

X. Kong & C.L. Brooks *J. Chem. Phys.* 105 (1996) 2414

M.S. Lee, J.F.R. Salsbury, C.L. Brooks *Proteins* 56 (2004) 738

S. Donnini, F. Tegeler, G. Groenhof. H Grubmüller *JCTC* 7 (2011) 1962

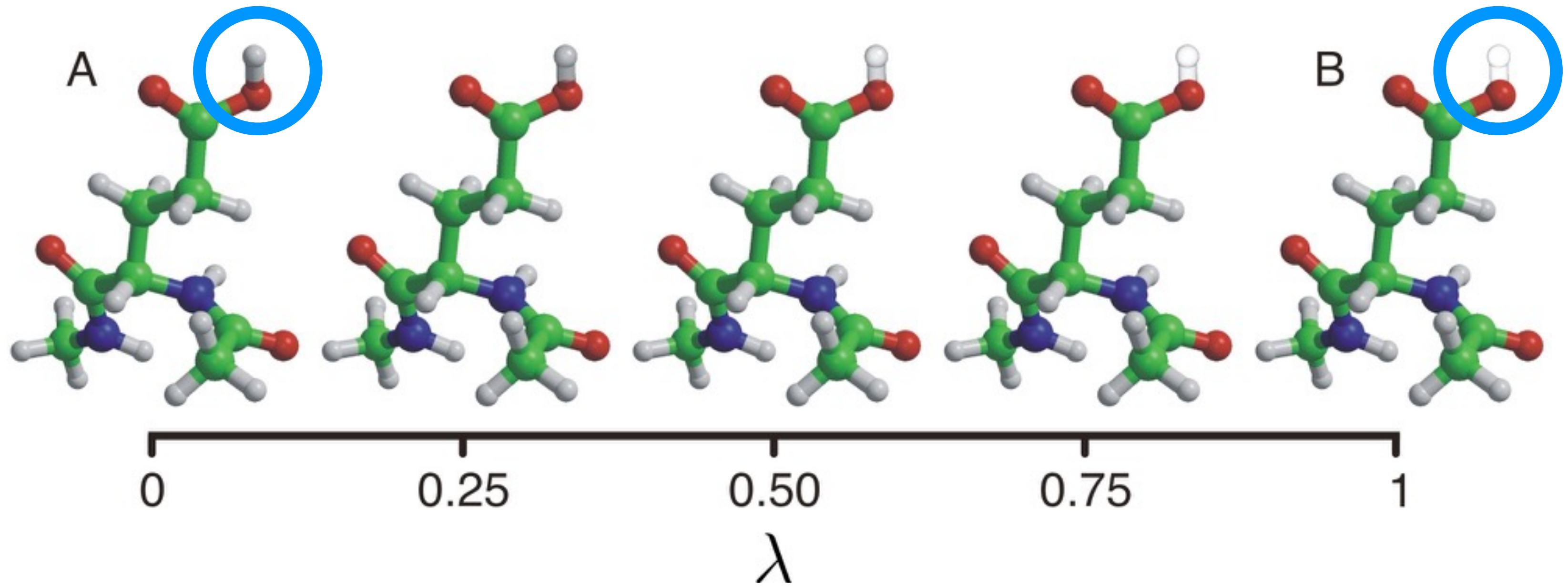
Why interpolate between the Hamiltonians?

partition function

$$Q(\lambda) = \sum \exp - \frac{H(\lambda)}{k_B T}$$

with masses untouched

$$H(\lambda) = T_{\text{kin}} + V(\lambda)$$



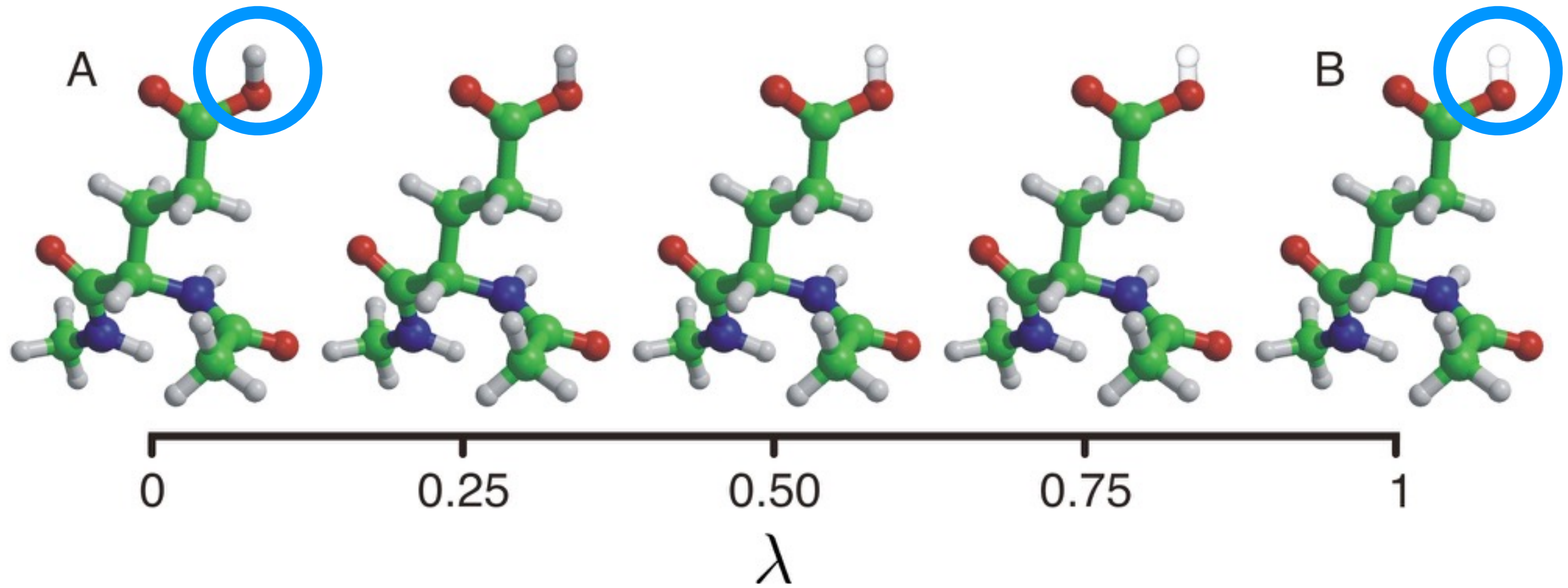
Why interpolate between the Hamiltonians?

partition function

$$Q(\lambda) = \sum \exp -\frac{H(\lambda)}{k_\mathrm{B}T}$$

with masses untouched

$$H(\lambda) = T_\mathrm{kin} + V(\lambda)$$



free energy

$$G(\lambda) = -kT_\mathrm{B} \ln Q(\lambda)$$

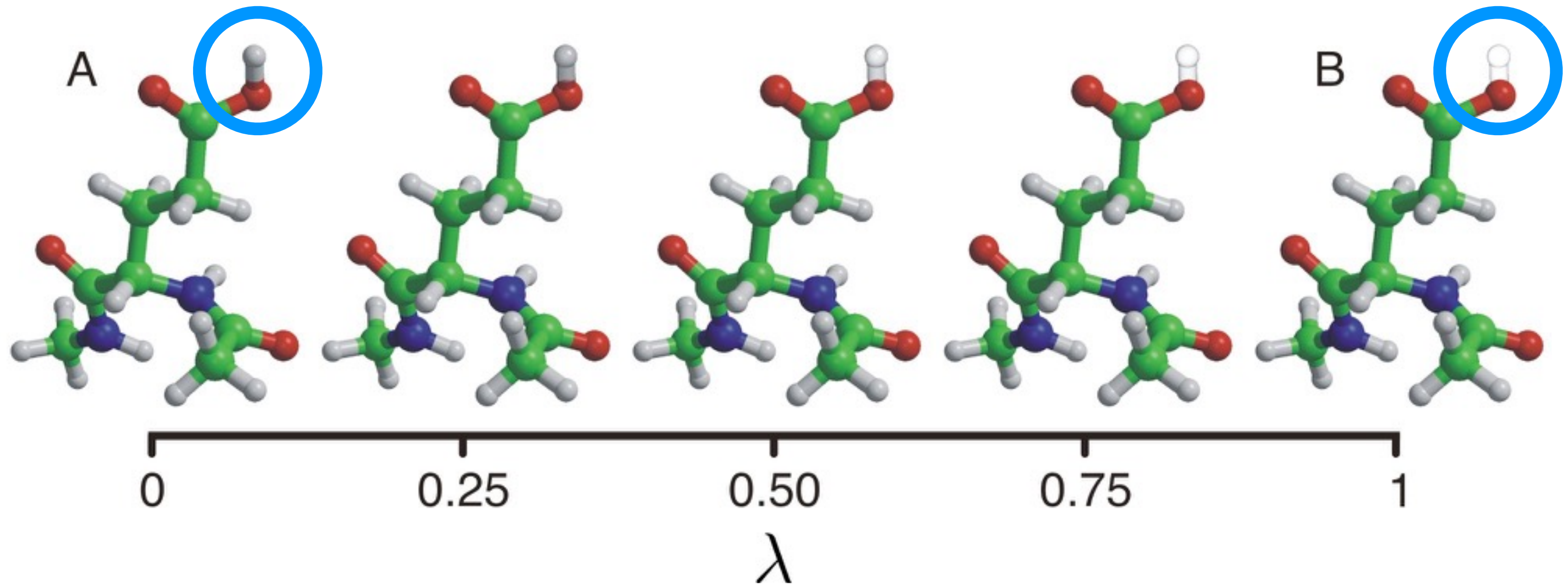
Why interpolate between the Hamiltonians?

partition function

$$Q(\lambda) = \sum \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}$$

with masses untouched

$$H(\lambda) = T_{\mathrm{kin}} + V(\lambda)$$



free energy

$$G(\lambda) = -kT_{\mathrm{B}} \ln Q(\lambda)$$

derivative

$$\frac{\partial G}{\partial \lambda} = \frac{\sum \frac{\partial H}{\partial \lambda} \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}}{\sum \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}} = \left\langle \frac{\partial H}{\partial \lambda} \right\rangle = \left\langle \frac{\partial V}{\partial \lambda} \right\rangle$$

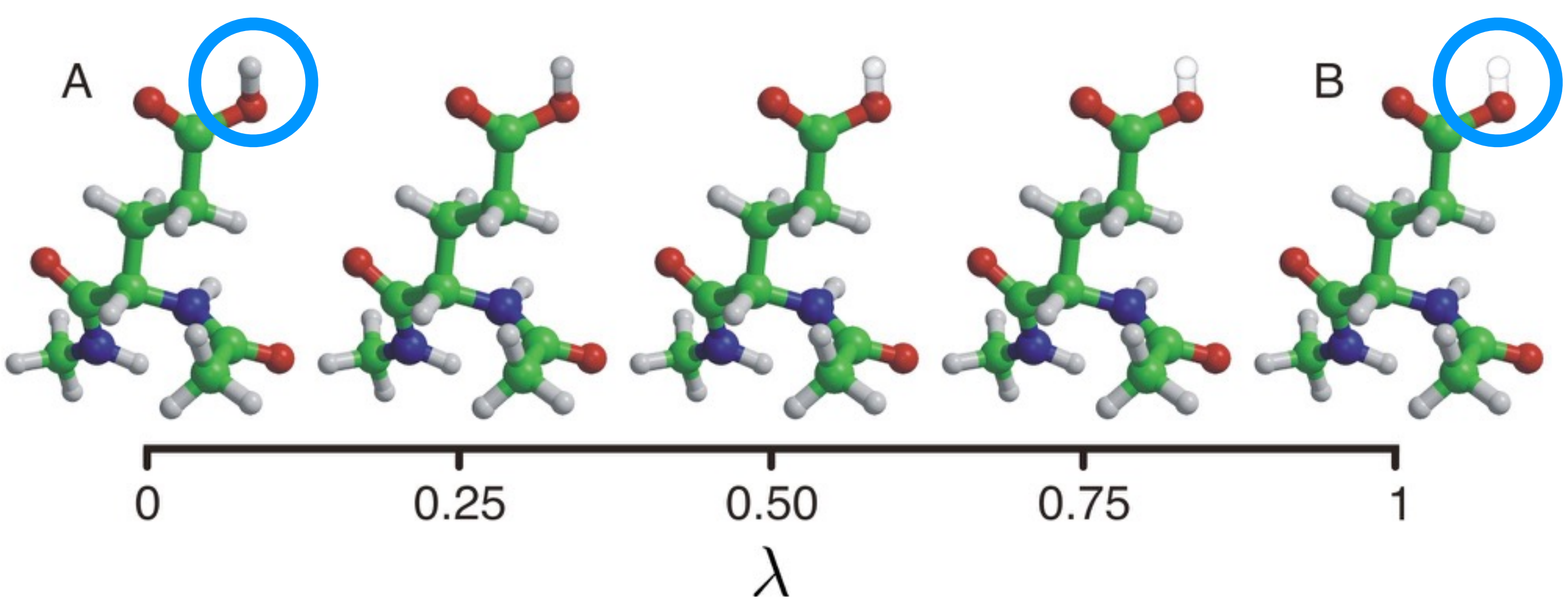
Why interpolate between the Hamiltonians?

partition function

$$Q(\lambda) = \sum \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}$$

with masses untouched

$$H(\lambda) = T_{\mathrm{kin}} + V(\lambda)$$



free energy

$$G(\lambda) = -kT_{\mathrm{B}} \ln Q(\lambda)$$

derivative

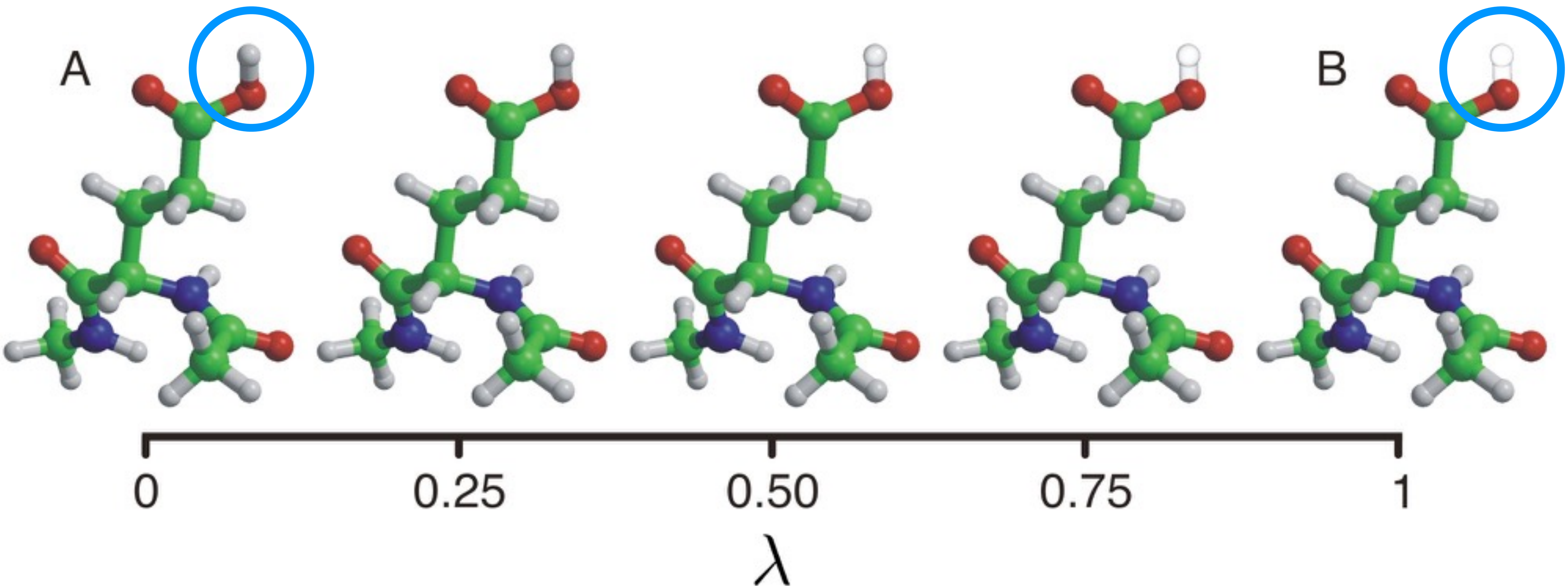
$$\frac{\partial G}{\partial \lambda} = \frac{\sum \frac{\partial H}{\partial \lambda} \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}}{\sum \exp -\frac{H(\lambda)}{k_{\mathrm{B}}T}} = \left\langle \frac{\partial H}{\partial \lambda} \right\rangle = \left\langle \frac{\partial V}{\partial \lambda} \right\rangle$$

free energy difference (work along λ): thermodynamic integration

$$\Delta G = \int_0^1 \frac{\partial G}{\partial \lambda} d\lambda = \int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

Molecular dynamics at constant pH: how?

protons as extra degrees of freedom



dynamics of λ-particle (protonation)

$$m_\lambda d^2\lambda/dt^2 = -\partial V(\mathbf{x},\lambda)/\partial\lambda$$

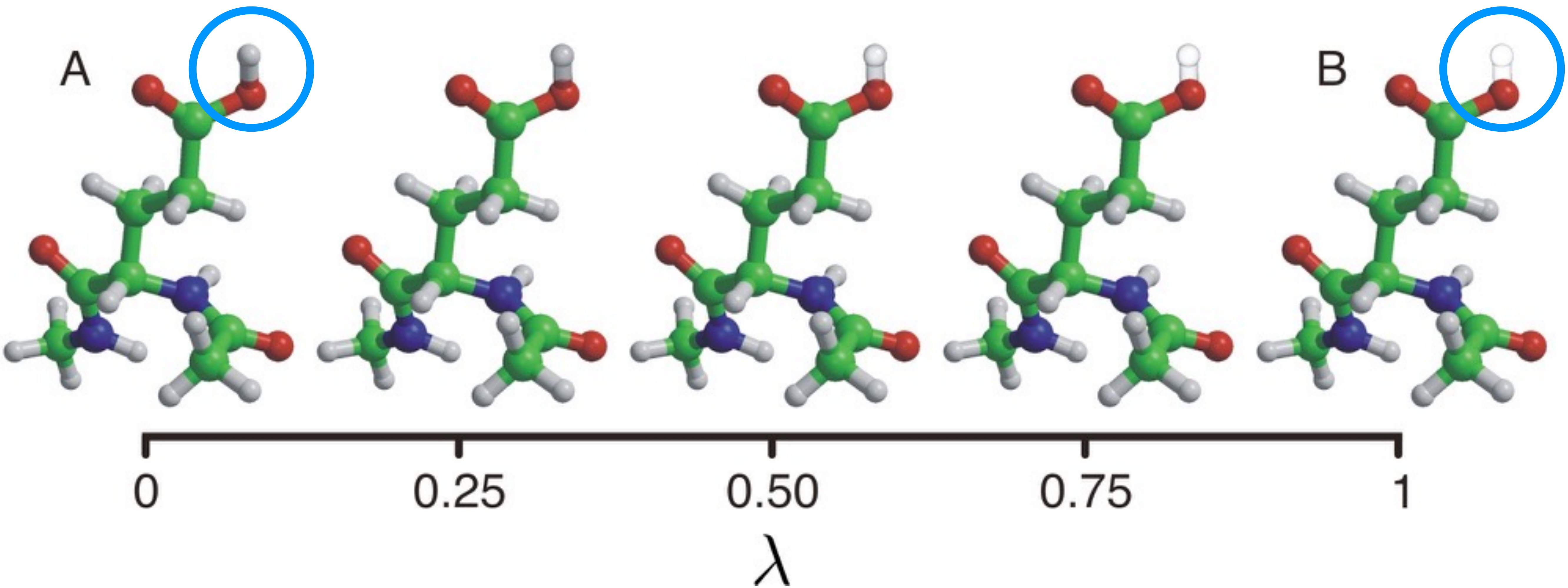
X. Kong & C.L. Brooks *J. Chem. Phys.* 105 (1996) 2414

M.S. Lee, J.F.R. Salsbury, C.L. Brooks *Proteins* 56 (2004) 738

S. Donnini, F. Tegeler, G. Groenhof. H Grubmüller *JCTC* 7 (2011) 1962

Molecular dynamics at constant pH: how?

protons as extra degrees of freedom



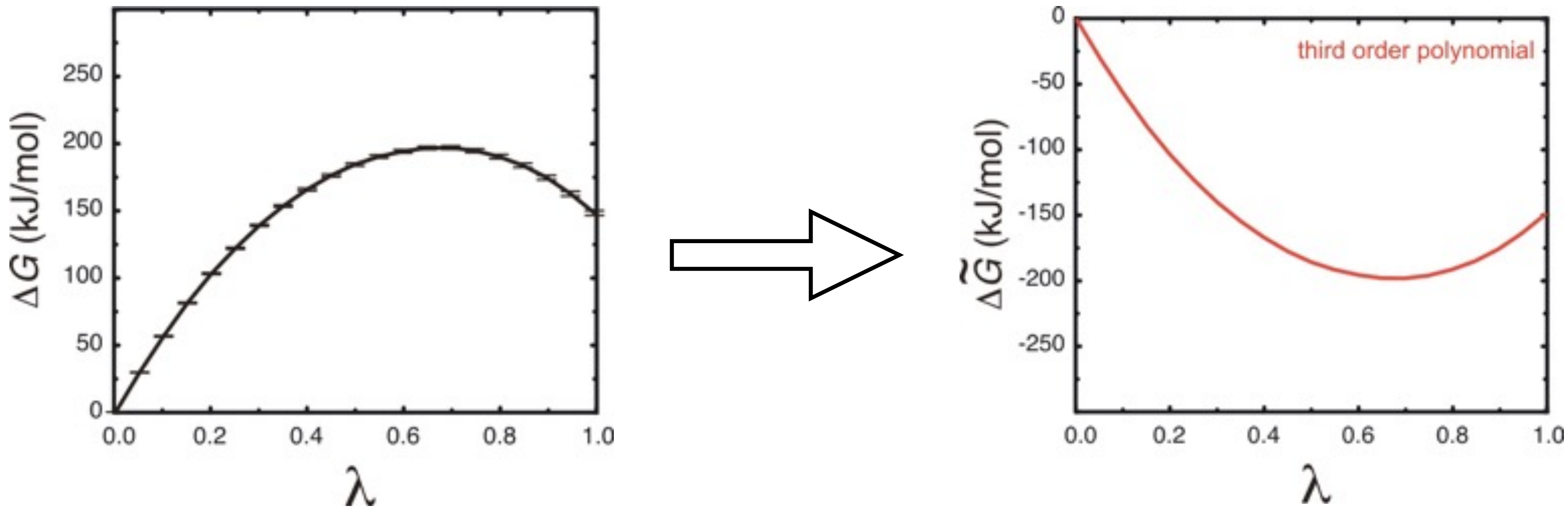
dynamics of λ-particle (protonation)

$$m_\lambda d^2\lambda/dt^2 = -\partial V(\mathbf{x},\lambda)/\partial\lambda$$

$$V(\mathbf{x},\lambda) = (1-\lambda)V^{\mathrm{A}}(\mathbf{x}) + \lambda V^{\mathrm{B}}(\mathbf{x}) + U(\lambda) + \lambda RT\ln(10)[pK_{\mathrm{a,\ ref}}^{\mathrm{exp}} - pH] + \Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$$

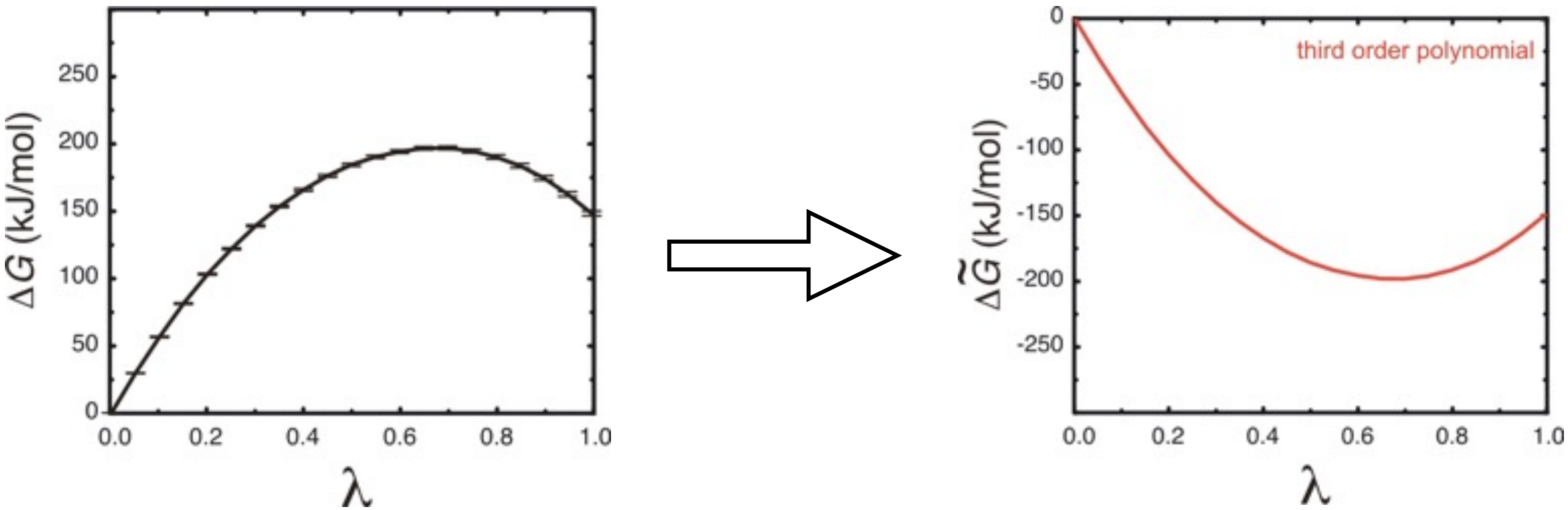
$$V(\mathbf{x},\lambda) = (1-\lambda)V^{\mathrm{A}}(\mathbf{x}) + \lambda V^{\mathrm{B}}(\mathbf{x}) + U(\lambda) + \lambda RT\ln(10)[pK_{\mathrm{a,\ ref}}^{\mathrm{exp}} - pH] + \boxed{\Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)}$$

$\Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$ obtained by thermodynamic integration (pH = pK_a)

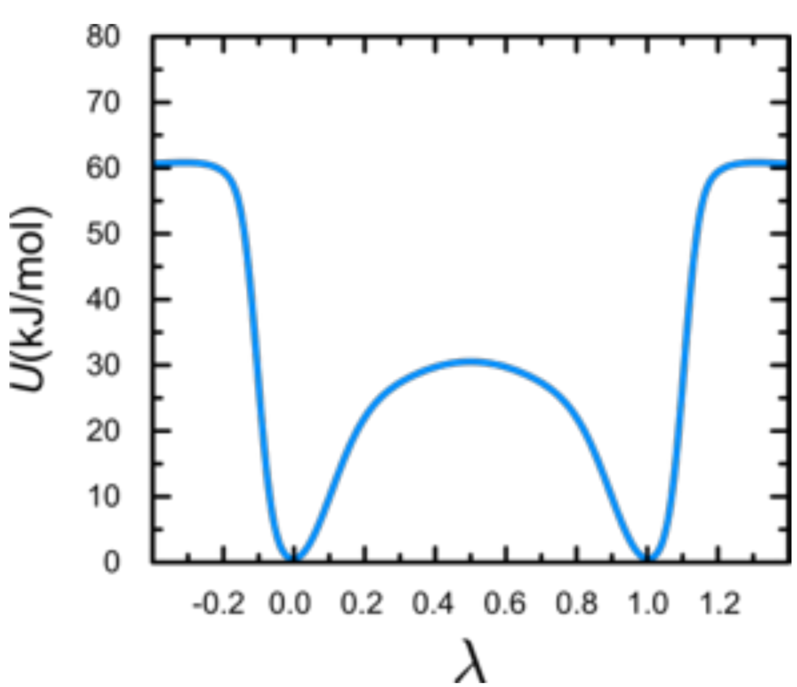


$$V(\mathbf{x},\lambda) = (1-\lambda)V^{\mathrm{A}}(\mathbf{x}) + \lambda V^{\mathrm{B}}(\mathbf{x}) + U(\lambda) + \lambda RT\ln(10)[pK_{\mathrm{a,\ ref}}^{\mathrm{exp}} - pH] + \Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$$

$\Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$ obtained by thermodynamic integration (pH = pK_a)



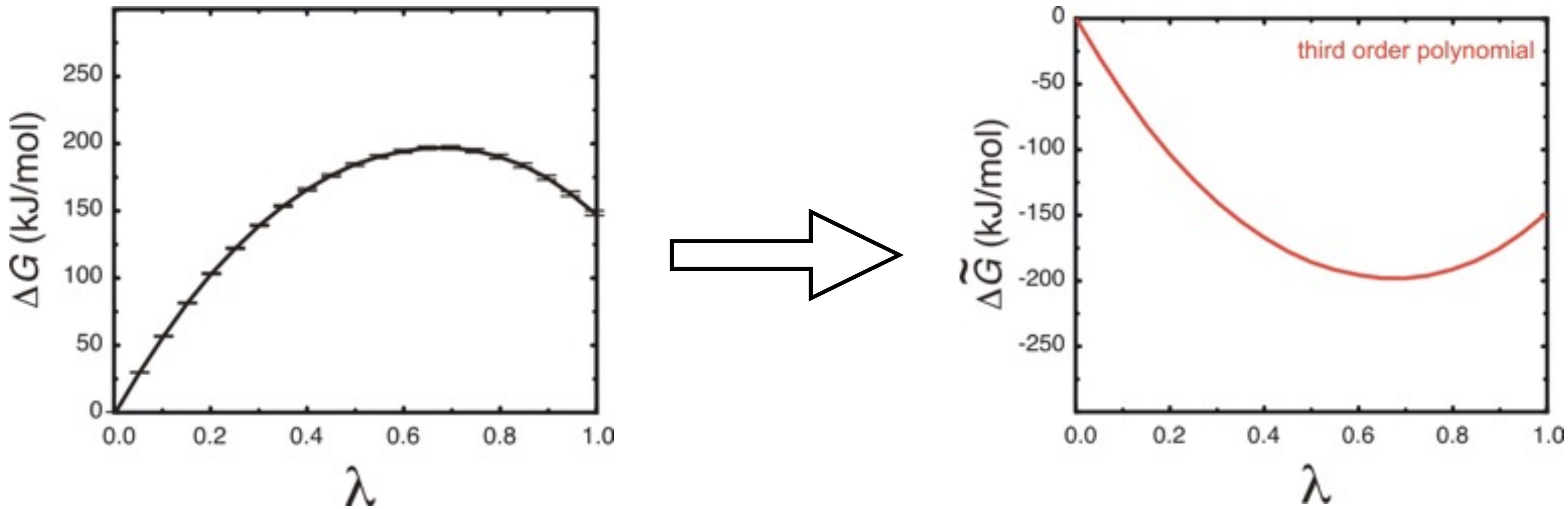
barrier potential



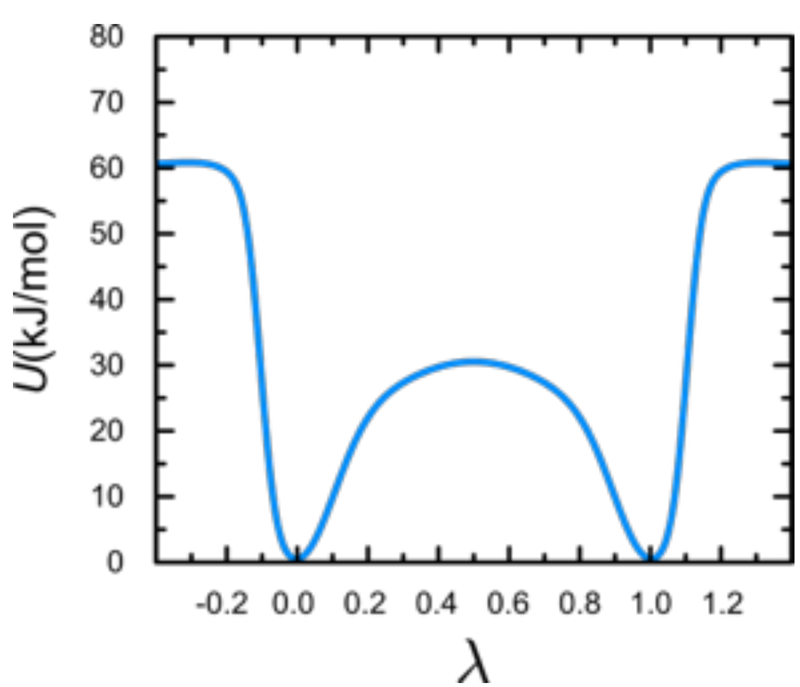
S. Donnini, R. T. Ullman, G. Groenhof. H Grubmüller *JCTC* 12 (2016) 1040

$$V(\mathbf{x},\lambda) = (1-\lambda)V^{A}(\mathbf{x}) + \lambda V^{B}(\mathbf{x}) + U(\lambda) + \lambda RT\ln(10)[pK_{a,\,\mathrm{ref}}^{\mathrm{exp}} - pH] + \Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$$

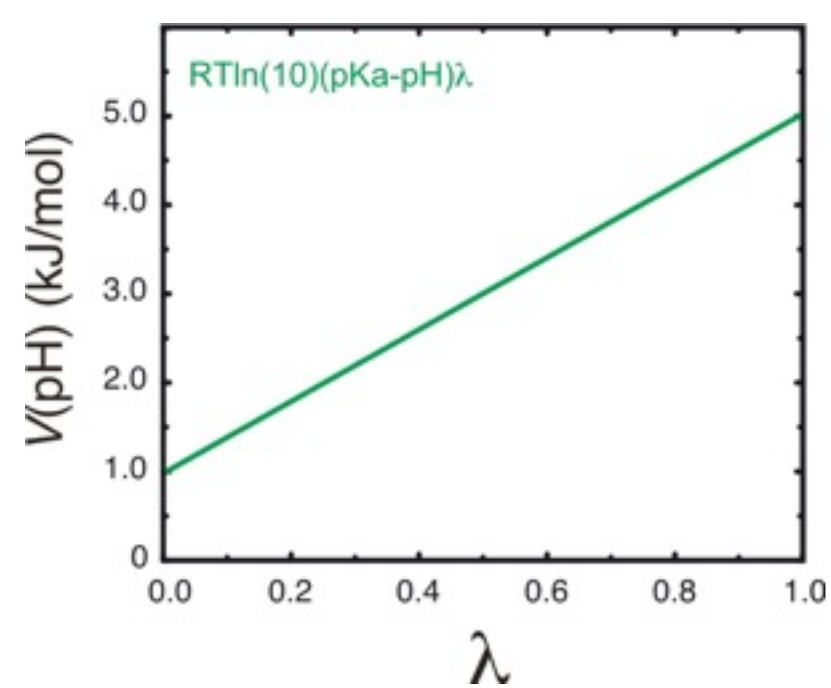
$\Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda)$ obtained by thermodynamic integration (pH = pK_a)



barrier potential

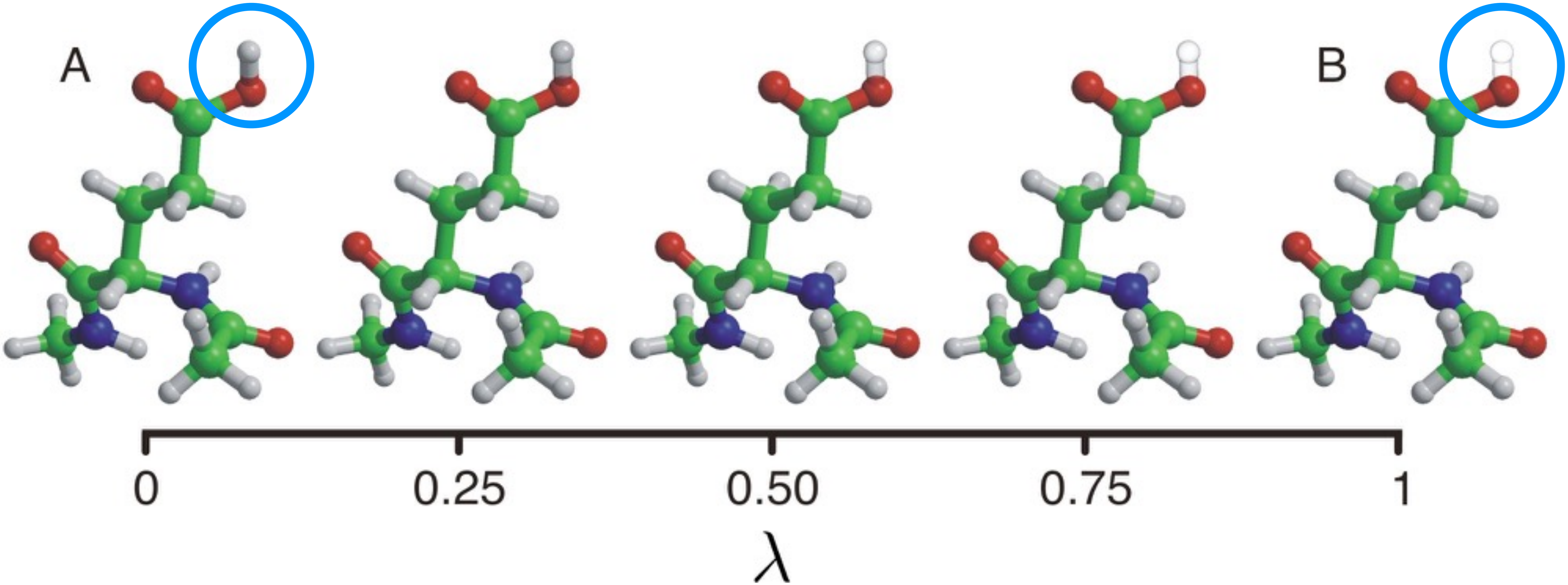


pH dependence



Molecular dynamics at constant pH: how?

protons as extra degrees of freedom



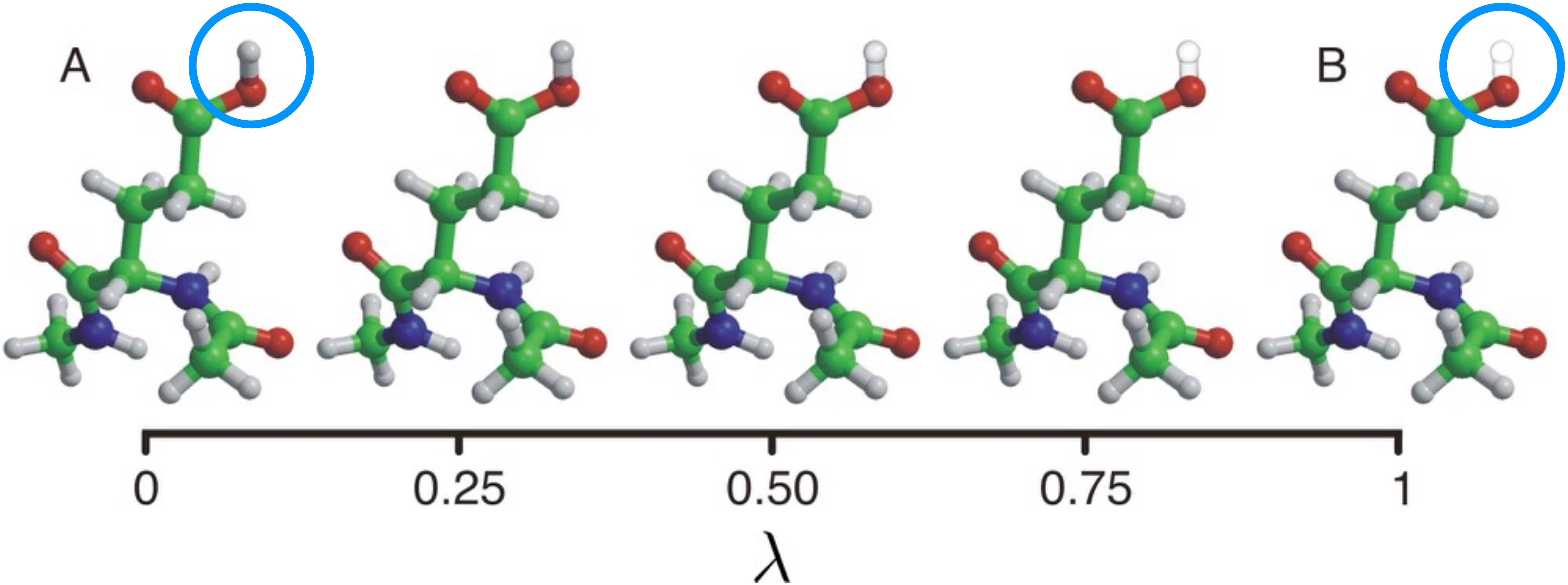
dynamics of multiple λ-particles (protonation states)

$$m_{\lambda_i} d^2\lambda_i/dt^2 = -\partial V(\mathbf{x},\boldsymbol{\lambda})/\partial\lambda_i$$

$$V(\mathbf{x},\boldsymbol{\lambda}) = H(\boldsymbol{\lambda}) + \textstyle\sum_i [U(\lambda_i) + \lambda_i RT\ln(10)[pK_{\mathrm{a,ref}_i}^{\mathrm{exp}} - pH] + \Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda_i,\boldsymbol{\lambda})]$$

Molecular dynamics at constant pH: how?

protons as extra degrees of freedom



dynamics of multiple λ-particles (protonation states)

$$m_{\lambda_i} d^2\lambda_i/dt^2 = -\partial V(\mathbf{x},\boldsymbol{\lambda})/\partial\lambda_i$$

$$V(\mathbf{x},\boldsymbol{\lambda}) = \boxed{H(\boldsymbol{\lambda})} + \sum_i [U(\lambda_i) +$$

$$\lambda_i RT\ln(10)[pK^{\mathrm{exp}}_{\mathrm{a,ref}_i} - pH] + \Delta\tilde{G}^{\mathrm{corr}}_{\mathrm{MM}}(\lambda_i,\boldsymbol{\lambda})]$$

Interpolation schemes

linear interpolation of Hamiltonians for one λ-group

$$H(\lambda) = (1 - \lambda)H^0 + \lambda H^1$$

Interpolation schemes

linear interpolation of Hamiltonians for one λ-group

$$H(\lambda) = (1-\lambda)H^0 + \lambda H^1$$

protonated

$$\begin{aligned} H^0 \quad = \quad &+ \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^A q_j \\ &+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^A q_j^A \\ &+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

deprotonated

$$\begin{aligned} H^1 \quad = \quad &+ \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^B q_j \\ &+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^B q_j^B \\ &+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

Interpolation schemes

linear interpolation of Hamiltonians for one λ-group

$$H(\lambda) = (1-\lambda)H^0 + \lambda H^1$$

protonated

$$\begin{aligned} H^0 &= +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^A q_j \\ &+ \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^A q_j^A \\ &+ \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

deprotonated

$$\begin{aligned} H^1 &= +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^B q_j \\ &+ \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^B q_j^B \\ &+ \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

derivative

$$\begin{aligned} \frac{\partial H}{\partial \lambda} &= H^1 - H^0 \\ &= +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^B q_j + \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^B q_j^B \\ &\quad -\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i^A q_j - \tfrac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} q_i^A q_j^A \end{aligned}$$

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1, \lambda_2) &= (1-\lambda_1)[(1-\lambda_2)H^{00} + \lambda_2 H^{01}] + \lambda_1((1-\lambda_2)H^{10} + \lambda_2 H^{11}) \\
&= +H^{00} - \lambda_2 H^{00} - \lambda_1 H^{00} + \lambda_1 \lambda_2 H^{00} \\
& \quad +\lambda_2 H^{01} - \lambda_1 \lambda_2 H^{01} \\
& \quad +\lambda_1 H^{10} - \lambda_1 \lambda_2 H^{10} + \lambda_1 \lambda_2 H^{11}
\end{aligned}
$$

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$\begin{aligned}
H(\lambda_1,\lambda_2) &= (1-\lambda_1)[(1-\lambda_2)H^{00}+\lambda_2 H^{01}] + \lambda_1((1-\lambda_2)H^{10}+\lambda_2 H^{11}) \\
&= +H^{00} - \lambda_2 H^{00} - \lambda_1 H^{00} + \lambda_1\lambda_2 H^{00} \\
& \quad +\lambda_2 H^{01} - \lambda_1\lambda_2 H^{01} \\
& \quad +\lambda_1 H^{10} - \lambda_1\lambda_2 H^{10} + \lambda_1\lambda_2 H^{11}
\end{aligned}$$

protonated, protonated

$$\begin{aligned}
H^{00} = &+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}q_i^A q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^A q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^A q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^A q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^A q_j
\end{aligned}$$

protonated, deprotonated

$$\begin{aligned}
H^{01} = &+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}q_i^A q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^A q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^A q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^B q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^B q_j
\end{aligned}$$

deprotonated, protonated

$$\begin{aligned}
H^{10} = &+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}q_i^B q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^B q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^B q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^A q_j^A \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^A q_j
\end{aligned}$$

deprotonated, deprotonated

$$\begin{aligned}
H^{11} = &+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}q_i^B q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^B q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^B q_j \\
&+\tfrac{1}{2}\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}q_i^B q_j^B \\
&+\textstyle\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i^B q_j
\end{aligned}$$

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1, \lambda_2) \quad = \quad & +\tfrac{1}{2} \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{n} \sum_j^{n} \tfrac{1}{r_{ij,kl}} q_i q_j \\
& +\tfrac{1}{2} \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g_1} \sum_j^{g_1} \tfrac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A q_j^A + \lambda_1 q_i^B q_j^B] \\
& + \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g_1} \sum_j^{g_2} \tfrac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B][(1-\lambda_2) q_j^A + \lambda_2 q_j^B] \\
& + \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g_1} \sum_j^{n} \tfrac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B] q_j \\
& +\tfrac{1}{2} \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g_2} \sum_j^{g_2} \tfrac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A q_j^A + \lambda_2 q_i^B q_j^B] \\
& + \textstyle\sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g_2} \sum_j^{n} \tfrac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A + \lambda_2 q_i^B] q_j
\end{aligned}
$$

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1,\lambda_2) \quad = \quad & +\tfrac{1}{2}\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
& +\tfrac{1}{2}\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A q_j^A + \lambda_1 q_i^B q_j^B] \\
& +\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A + \lambda_1 q_i^B][(1-\lambda_2)q_j^A + \lambda_2 q_j^B] \\
& +\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A + \lambda_1 q_i^B]q_j \\
& +\tfrac{1}{2}\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A q_j^A + \lambda_2 q_i^B q_j^B] \\
& +\sum_k^{n_\text{box}}\sum_l^{n_\text{box}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A + \lambda_2 q_i^B]q_j
\end{aligned}
$$

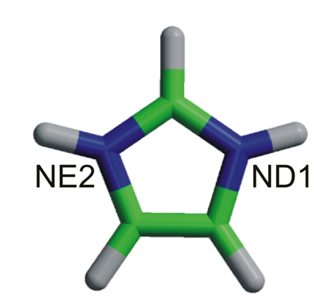
Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1,\lambda_2) \quad = \quad & +\tfrac{1}{2}\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{n}\sum_j^{n}\frac{1}{r_{ij,kl}}q_i q_j \\
& +\tfrac{1}{2}\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A q_j^A+\lambda_1 q_i^B q_j^B] \\
& +\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1 q_i^B][(1-\lambda_2)q_j^A+\lambda_2 q_j^B] \\
& +\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1 q_i^B]q_j \\
& +\tfrac{1}{2}\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_2}\sum_j^{g_2}\frac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A q_j^A+\lambda_2 q_i^B q_j^B] \\
& +\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_2}\sum_j^{n}\frac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A+\lambda_2 q_i^B]q_j
\end{aligned}
$$

three-step evaluation

calculate Coulomb energy for a system with interpolated charges



Interpolation schemes

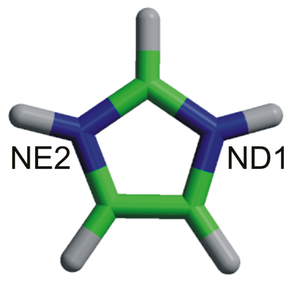
linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1, \lambda_2) \quad = \quad & +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_1} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A q_j^A + \lambda_1 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B][(1-\lambda_2) q_j^A + \lambda_2 q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B] q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A q_j^A + \lambda_2 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A + \lambda_2 q_i^B] q_j
\end{aligned}
$$

three-step evaluation

calculate Coulomb energy for a system with interpolated charges

subtract internal interactions of λ-groups 1 and 2 with interpolated charges



Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

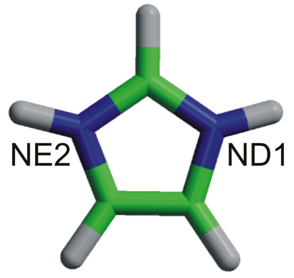
$$
\begin{aligned}
H(\lambda_1, \lambda_2) \quad = \quad & +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_1} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A q_j^A + \lambda_1 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B][(1-\lambda_2) q_j^A + \lambda_2 q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B] q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A q_j^A + \lambda_2 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A + \lambda_2 q_i^B] q_j
\end{aligned}
$$

three-step evaluation

calculate Coulomb energy for a system with interpolated charges

subtract internal interactions of λ-groups 1 and 2 with interpolated charges

add internal interactions of λ-groups 1 and 2 with A and B charges



Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1, \lambda_2) \quad = \quad & +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_1} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A q_j^A + \lambda_1 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B][(1-\lambda_2) q_j^A + \lambda_2 q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_1} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B] q_j \\
& +\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A q_j^A + \lambda_2 q_i^B q_j^B] \\
& + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g_2} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_i^A + \lambda_2 q_i^B] q_j
\end{aligned}
$$

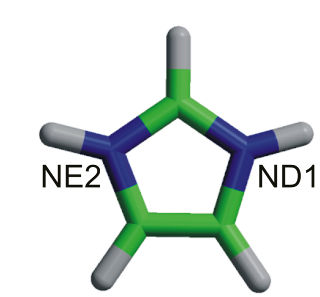
three-step evaluation

calculate Coulomb energy for a system with interpolated charges

subtract internal interactions of λ-groups 1 and 2 with interpolated charges

add internal interactions of λ-groups 1 and 2 with A and B charges

+



5 PME calls & corrections to cartesian gradients

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1,\lambda_2) &= (1-\lambda_1)[(1-\lambda_2)H^{00}+\lambda_2 H^{01}]+\lambda_1((1-\lambda_2)H^{10}+\lambda_2 H^{11}) \\
&= +H^{00}-\lambda_2 H^{00}-\lambda_1 H^{00}+\lambda_1\lambda_2 H^{00} \\
& \quad +\lambda_2 H^{01}-\lambda_1\lambda_2 H^{01} \\
& \quad +\lambda_1 H^{10}-\lambda_1\lambda_2 H^{10}+\lambda_1\lambda_2 H^{11}
\end{aligned}
$$

derivatives

$$
\begin{aligned}
\frac{\partial H}{\partial \lambda_1} &= +\tfrac{1}{2}\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{g_1}\frac{1}{r_{ij,kl}}(q_i^B q_j^B - q_i^A q_j^A) \\
& \quad +\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{g_2}\frac{1}{r_{ij,kl}}(q_i^B - q_i^A)[(1-\lambda_2)q_j^A+\lambda_2 q_j^B] \\
& \quad +\sum_k^{n_{\mathrm{box}}}\sum_l^{n_{\mathrm{box}}}\sum_i^{g_1}\sum_j^{n}\frac{1}{r_{ij,kl}}(q_i^B - q_i^A)q_j
\end{aligned}
$$

Interpolation schemes

linear interpolation of Hamiltonians for two λ-groups

$$
\begin{aligned}
H(\lambda_1, \lambda_2) &= (1-\lambda_1)[(1-\lambda_2)H^{00} + \lambda_2 H^{01}] + \lambda_1((1-\lambda_2)H^{10} + \lambda_2 H^{11}) \\
&= +H^{00} - \lambda_2 H^{00} - \lambda_1 H^{00} + \lambda_1 \lambda_2 H^{00} \\
& \quad +\lambda_2 H^{01} - \lambda_1 \lambda_2 H^{01} \\
& \quad +\lambda_1 H^{10} - \lambda_1 \lambda_2 H^{10} + \lambda_1 \lambda_2 H^{11}
\end{aligned}
$$

derivatives

$$
\begin{aligned}
\frac{\partial H}{\partial \lambda_2} &= +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_1} \sum_j^{g_2} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_i^A + \lambda_1 q_i^B](q_j^B - q_j^A) \\
& \quad +\frac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_2} \sum_j^{g_2} \frac{1}{r_{ij,kl}} (q_i^B q_j^B - q_i^A q_j^A) \\
& \quad +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_2} \sum_j^{n} \frac{1}{r_{ij,kl}} (q_i^B - q_i^A) q_j
\end{aligned}
$$

Interpolation schemes

linear interpolation of Hamiltonians for 3 λ-groups

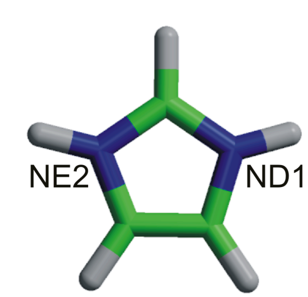
$$
\begin{aligned}
H(\lambda_1,\lambda_2,\lambda_3) \;=\; & (1-\lambda_1)((1-\lambda_2)((1-\lambda_3)H^{000}+\lambda_3 H^{001}) \\
& +\lambda_2((1-\lambda_3)H^{010}+\lambda_3 H^{011})) \\
& +\lambda_1((1-\lambda_2)((1-\lambda_3)H^{100} \\
& +\lambda_3 H^{101})+\lambda_2((1-\lambda_3)H^{110} \\
& +\lambda_3 H^{111}))
\end{aligned}
$$

three-step evaluation

calculate Coulomb energy for a system with interpolated charges

subtract internal interactions of λ-groups 1, 2 and 3 with interpolated charges

add internal interactions of λ-groups 1, 2 and 3 with A and B charges

+ 

---

7 PME calls & corrections to cartesian gradients

Interpolation schemes

linear interpolation of Hamiltonians for *N* λ-groups

$$H(\lambda_1, \lambda_2, ..\lambda_N) = (1 - \lambda_1)...$$

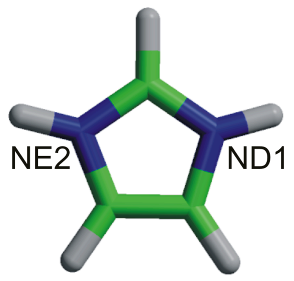
2^N terms in the Hamiltonian

three-step evaluation

calculate Coulomb energy for a system with interpolated charges

subtract internal interactions of λ-groups 1 - *N* with interpolated charges

add internal interactions of λ-groups 1 - *N* with A and B charges

+ 

2 *N* + 1 PME calls & corrections to cartesian gradients

Interpolation schemes

linear interpolation of charges for one λ-group

$$
\begin{aligned}
H'(\lambda) &= +\sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda)q_i^A + \lambda q_i^B] q_j \\
&+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda)q_i^A + \lambda q_i^B][(1-\lambda)q_j^A + \lambda q_j^B] \\
&+ \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j
\end{aligned}
$$

Interpolation schemes

linear interpolation of charges for one λ-group

$$\begin{aligned} H'(\lambda) \quad = \quad & + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] q_j \\ & + \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B][(1-\lambda) q_j^A + \lambda q_j^B] \\ & + \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

after some hopefully correct algebra

$$H'(\lambda) = H(\lambda) + \frac{1}{2} \lambda (\lambda - 1) \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (q_i^A - q_i^B)(q_j^A - q_j^B)$$

Interpolation schemes

linear interpolation of charges for one λ-group

$$\begin{aligned} H'(\lambda) \quad = \quad & + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^g \sum_j^n \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] q_j \\ & + \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^g \sum_j^g \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B][(1-\lambda) q_j^A + \lambda q_j^B] \\ & + \frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^n \sum_j^n \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

after some hopefully correct algebra

$$H'(\lambda) = H(\lambda) + \frac{1}{2} \lambda (\lambda - 1) \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^g \sum_j^g \frac{1}{r_{ij,kl}} (q_i^A - q_i^B)(q_j^A - q_j^B)$$

important for parameterisation with Hamiltonian interpolation

$$\Delta \tilde{G}_{\text{MM}}^{\text{corr}'}(\lambda) \leftrightarrow \Delta \tilde{G}_{\text{MM}}^{\text{corr}}(\lambda)$$

Interpolation schemes

linear interpolation of charges for one λ-group

$$\begin{aligned} H'(\lambda) \quad = \quad & + \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] q_j \\ & + \frac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B][(1-\lambda) q_j^A + \lambda q_j^B] \\ & + \frac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j \end{aligned}$$

derivative

$$\frac{\partial H'}{\partial \lambda} = \frac{\partial H}{\partial \lambda} + (\lambda - \frac{1}{2}) \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (q_i^A - q_i^B)(q_j^A - q_j^B)$$

important for parameterisation with linear interpolation

$$\Delta \tilde{G}_{\mathrm{MM}}^{\mathrm{corr}}(\lambda) = \int_0^{\lambda} \langle \frac{\partial H}{\partial \lambda'} \rangle_{\lambda'} d\lambda' = \int_0^{\lambda} \langle H^1(\mathbf{x}) - H^0(\mathbf{x}) \rangle_{\lambda'} d\lambda'$$

Interpolation schemes

linear interpolation of charges for one λ-group

$$
\begin{aligned}
H'(\lambda) \quad = \quad & +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] q_j \\
& + \frac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B][(1-\lambda) q_j^A + \lambda q_j^B] \\
& + \frac{1}{2} \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{n} \sum_j^{n} \frac{1}{r_{ij,kl}} q_i q_j
\end{aligned}
$$

derivative

$$
\frac{\partial H'}{\partial \lambda} = \frac{\partial H}{\partial \lambda} + (\lambda - \frac{1}{2}) \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (q_i^A - q_i^B)(q_j^A - q_j^B)
$$

important for parameterisation with linear interpolation

$$
\Delta \tilde{G}^{\mathrm{corr}'}(\lambda) = \Delta \tilde{G}^{\mathrm{corr}}(\lambda) + \int_0^{\lambda} + \langle (\lambda' - \frac{1}{2}) \sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (q_i^A - q_i^B)(q_j^A - q_j^B) \rangle_{\lambda_i'} d\lambda_i'
$$

Interpolation schemes

linear interpolation of charges for one λ-group

derivative

$$\begin{aligned}\frac{\partial H'}{\partial \lambda} &= +\sum_k^{n_\mathrm{box}} \sum_l^{n_\mathrm{box}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) q_j \\ &\quad + \frac{1}{2} \sum_k^{n_\mathrm{box}} \sum_l^{n_\mathrm{box}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) [(1-\lambda) q_j^A + \lambda q_j^B] \\ &\quad + \frac{1}{2} \sum_k^{n_\mathrm{box}} \sum_l^{n_\mathrm{box}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] (-q_j^A + q_j^B) \\ &= \sum_i^{g} \Phi'(\lambda, \mathbf{r}_i) \Delta q_i\end{aligned}$$

$$\Delta q_i = q_i^B - q_i A$$

Interpolation schemes

linear interpolation of charges for one λ-group

derivative

$$\frac{\partial H'}{\partial \lambda} = +\sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) q_j$$

$$+\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) [(1-\lambda) q_j^A + \lambda q_j^B]$$

$$+\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] (-q_j^A + q_j^B)$$

$$= \sum_i^{g} \Phi'(\lambda, \mathbf{r}_i) \Delta q_i$$

$$\Delta q_i = q_i^B - q_i A$$

Interpolation schemes


Berk Hess

linear interpolation of charges for one λ-group

derivative

$$\begin{aligned}\frac{\partial H'}{\partial \lambda} \quad = \quad & + \sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) q_j \\ & + \frac{1}{2} \sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) [(1-\lambda) q_j^A + \lambda q_j^B] \\ & + \frac{1}{2} \sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] (-q_j^A + q_j^B) \\ & = \sum_i^{g} \Phi'(\lambda, \mathbf{r}_i) \Delta q_i \end{aligned}$$

electrostatic potential of system with interpolated charges

$$\Phi'(\lambda, \mathbf{r}_i) = \sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_j^{n} \frac{1}{r_{ij,kl}} q_j + \sum_k^{n_{\rm box}} \sum_l^{n_{\rm box}} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_j^A + \lambda q_j^B]$$

Interpolation schemes


Berk Hess

linear interpolation of charges for one λ-group

derivative

$$\frac{\partial H'}{\partial \lambda} = +\sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{n} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) q_j$$

$$+\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} (-q_i^A + q_i^B) [(1-\lambda) q_j^A + \lambda q_j^B]$$

$$+\frac{1}{2} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_i^{g} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_i^A + \lambda q_i^B] (-q_j^A + q_j^B)$$

$$= \sum_i^{g} \Phi'(\lambda, \mathbf{r}_i) \Delta q_i$$

electrostatic potential of system with interpolated charges

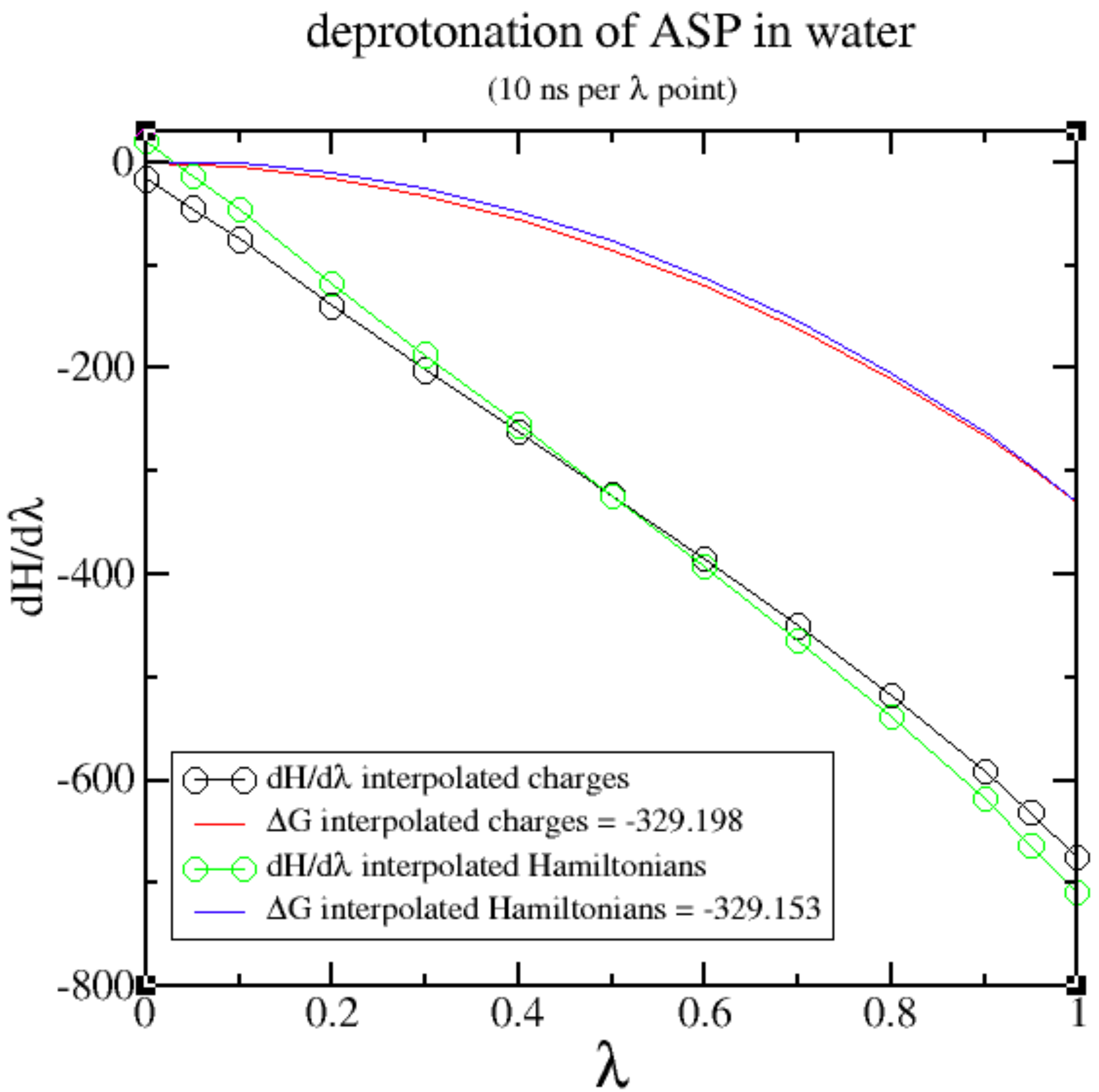
$$\Phi'(\lambda, \mathbf{r}_i) = \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n} \frac{1}{r_{ij,kl}} q_j + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{g} \frac{1}{r_{ij,kl}} [(1-\lambda) q_j^A + \lambda q_j^B]$$

one PME call to get cartesian and λ gradients

Interpolation schemes

charge interpolation versus Hamiltonian interpolation

example:



Interpolation schemes

linear interpolation of charges for two λ-groups

$$
\begin{aligned}
H'(\lambda_1,\lambda_2) \quad = \quad & +\tfrac{1}{2}\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{n}\sum_j^{n}\tfrac{1}{r_{ij,kl}}q_i q_j \\
& +\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{g_1}\sum_j^{n}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1 q_i^B]q_j \\
& +\tfrac{1}{2}\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{g_1}\sum_j^{g_1}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1 q_i^B][(1-\lambda_1)q_j^A+\lambda_1 q_j^B] \\
& +\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{g_1}\sum_j^{g_2}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1 q_i^B][(1-\lambda_2)q_j^A+\lambda_2 q_j^B] \\
& +\tfrac{1}{2}\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{g_2}\sum_j^{g_2}\tfrac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A+\lambda_2 q_i^B][(1-\lambda_2)q_j^A+\lambda_2 q_j^B] \\
& +\sum_k^{n_{\text{box}}}\sum_l^{n_{\text{box}}}\sum_i^{g_2}\sum_j^{n}\tfrac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A+\lambda_2 q_i^A]q_j
\end{aligned}
$$

Interpolation schemes

linear interpolation of charges for two λ-groups

$$
\begin{aligned}
H'(\lambda_1,\lambda_2) \quad = \quad & +\tfrac{1}{2}\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{n}\sum_j^{n}\tfrac{1}{r_{ij,kl}}q_iq_j \\
& +\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{n}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1q_i^B]q_j \\
& +\tfrac{1}{2}\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1q_i^B][(1-\lambda_1)q_j^A+\lambda_1q_j^B] \\
& +\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_2}\tfrac{1}{r_{ij,kl}}[(1-\lambda_1)q_i^A+\lambda_1q_i^B][(1-\lambda_2)q_j^A+\lambda_2q_j^B] \\
& +\tfrac{1}{2}\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\tfrac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A+\lambda_2q_i^B][(1-\lambda_2)q_j^A+\lambda_2q_j^B] \\
& +\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{n}\tfrac{1}{r_{ij,kl}}[(1-\lambda_2)q_i^A+\lambda_2q_i^A]q_j
\end{aligned}
$$

after some hopefully correct algebra

$$
\begin{aligned}
H'(\lambda_1,\lambda_2) \quad = \quad & H(\lambda_1,\lambda_2) \\
& +\tfrac{1}{2}\lambda_1(\lambda_1-1)\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_1}\sum_j^{g_1}\tfrac{1}{r_{ij,kl}}(q_i^A-q_i^B)(q_j^A-q_j^B) \\
& +\tfrac{1}{2}\lambda_2(\lambda_2-1)\sum_k^{n_{\rm box}}\sum_l^{n_{\rm box}}\sum_i^{g_2}\sum_j^{g_2}\tfrac{1}{r_{ij,kl}}(q_i^A-q_i^B)(q_j^A-q_j^B)
\end{aligned}
$$

Interpolation schemes

linear interpolation of charges for two λ-groups

derivatives

$$\frac{\partial H'}{\partial \lambda_1} = +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_1} \sum_j^{n} \frac{1}{r_{ij,kl}} (q_i^B - q_i^A) q_j$$

$$+\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_1} \sum_j^{g_1} \frac{1}{r_{ij,kls}} (q_i^B - q_i^A)[(1-\lambda_1)q_j^A + \lambda_1 q_j^B]$$

$$+\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_1} \sum_j^{g_2} \frac{1}{r_{ij,kl}} (q_i^B - q_i^A)[(1-\lambda_2)q_j^A + \lambda_2 q_j^B]$$

$$\frac{\partial H'}{\partial \lambda_2} = +\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_2} \sum_j^{n} \frac{1}{r_{ij,kl}} (q_i^B - q_i^A) q_j$$

$$+\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_2} \sum_j^{g_2} \frac{1}{r_{ij,kls}} (q_i^B - q_i^A)[(1-\lambda_2)q_j^A + \lambda_2 q_j^B]$$

$$+\sum_k^{n_{\mathrm{box}}} \sum_l^{n_{\mathrm{box}}} \sum_i^{g_2} \sum_j^{g_1} \frac{1}{r_{ij,kl}} (q_i^B - q_i^A)[(1-\lambda_1)q_j^A + \lambda_1 q_j^B]$$

Interpolation schemes

linear interpolation of charges for two λ-groups

derivatives

$$\frac{\partial H'}{\partial \lambda_1} = \sum_i^{g_1} \Phi'(\lambda_1, \lambda_2, \mathbf{r}_i)\Delta q_i$$

$$\frac{\partial H'}{\partial \lambda_2} = \sum_i^{g_2} \Phi'(\lambda_1, \lambda_2, \mathbf{r}_i)\Delta q_i$$

electrostatic potential of system with interpolated charges

$$\begin{aligned}\Phi'(\lambda_1, \lambda_2, \mathbf{r}_i) \quad = \quad & + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n} \frac{1}{r_{ij,kl}} q_j \\ & + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n_1} \frac{1}{r_{ij,kl}} [(1-\lambda_1) q_j^A + \lambda_1 q_j^B] \\ & + \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n_2} \frac{1}{r_{ij,kl}} [(1-\lambda_2) q_j^A + \lambda_2 q_j^B]\end{aligned}$$

Interpolation schemes

linear interpolation of charges for *N* λ-groups

derivatives

$$\frac{\partial H'}{\partial \lambda_m} = \sum_i^{g_m} \Phi'(\boldsymbol{\lambda}, \mathbf{r}_i) \Delta q_i$$

electrostatic potential of system with interpolated charges

$$\begin{aligned}\Phi'(\boldsymbol{\lambda}, \mathbf{r}_i) \quad = \quad & \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n} \frac{1}{r_{ij,kl}} q_j \\ & + \sum_m^{N_\lambda} \sum_k^{n_{\text{box}}} \sum_l^{n_{\text{box}}} \sum_j^{n_m} \frac{1}{r_{ij,kl}} [(1-\lambda_m) q_j^A + \lambda_m q_j^B]\end{aligned}$$

one PME call to get cartesian and λ gradients

modular constant pH code in Gromacs

few modifications to do_force()

return electrostatic potential on atoms of λ groups

local λ-dynamics routine

md.cpp

```
rvec *phi=NULL;
snew[phi,md->nr];
init_lambda_dynamics(inputrec,cr,
                     mdatoms, top, ..);

do_force(fplog, cr, ir, step, nrnb, wcycle, top, groups,
        state->box, state->x, &state->hist,
        f, force_vir, mdatoms, enerd, fcd,
       state->lambda, graph,fr, vsite, mu_tot, t,
       mdoutf_get_fp_field(outf), ed, bBornRadii,
        (bNS ? GMX_FORCE_NS : 0) | force_flags, phi);

do_lambda_dynamics(inputrec,cr,
                 mdatoms, top, phi, ..);
```

modular constant pH code in Gromacs

few modifications to do_force()

do_lambda_dynamics()

calculate the gradients with the electrostatic potential

$$\frac{\partial H'}{\partial \lambda_i} = \sum_j^{g_i} \Phi'(\boldsymbol{\lambda}, \mathbf{r}_j)\Delta q_j \qquad \Delta q_j = q_j^B - q_j^A \qquad j \in \lambda_i$$

$$F_{\lambda_i} = -\frac{\partial H'}{\partial \lambda_i} - \frac{dU_i}{d\lambda_i} - RT\ln(10)[pK_{\mathrm{a,ref}_i} - pH] - \frac{d\Delta\tilde{G}_{\mathrm{MM}}^{\mathrm{corr},i}}{d\lambda_i}$$

update the λ_i-coordinates

$$v_{\lambda_i}(t+\frac{1}{2}\Delta t) = v_{\lambda_i}(t-\frac{1}{2}\Delta t) + \frac{\Delta t}{m_\lambda}F_{\lambda_i}$$

$$\lambda_i(t+\Delta t) = \lambda_i(t) + \Delta t v_{\lambda_i}(t+\frac{1}{2}\Delta t)$$

update charges in mdatoms and/or communicate λ_i

$$q_j = (1-\lambda_i)q_j^A + \lambda_i q_j^B \qquad j \in \lambda_i$$

constant pH input

multiple λ states in topology file

sequential entries

redmine issue #1653

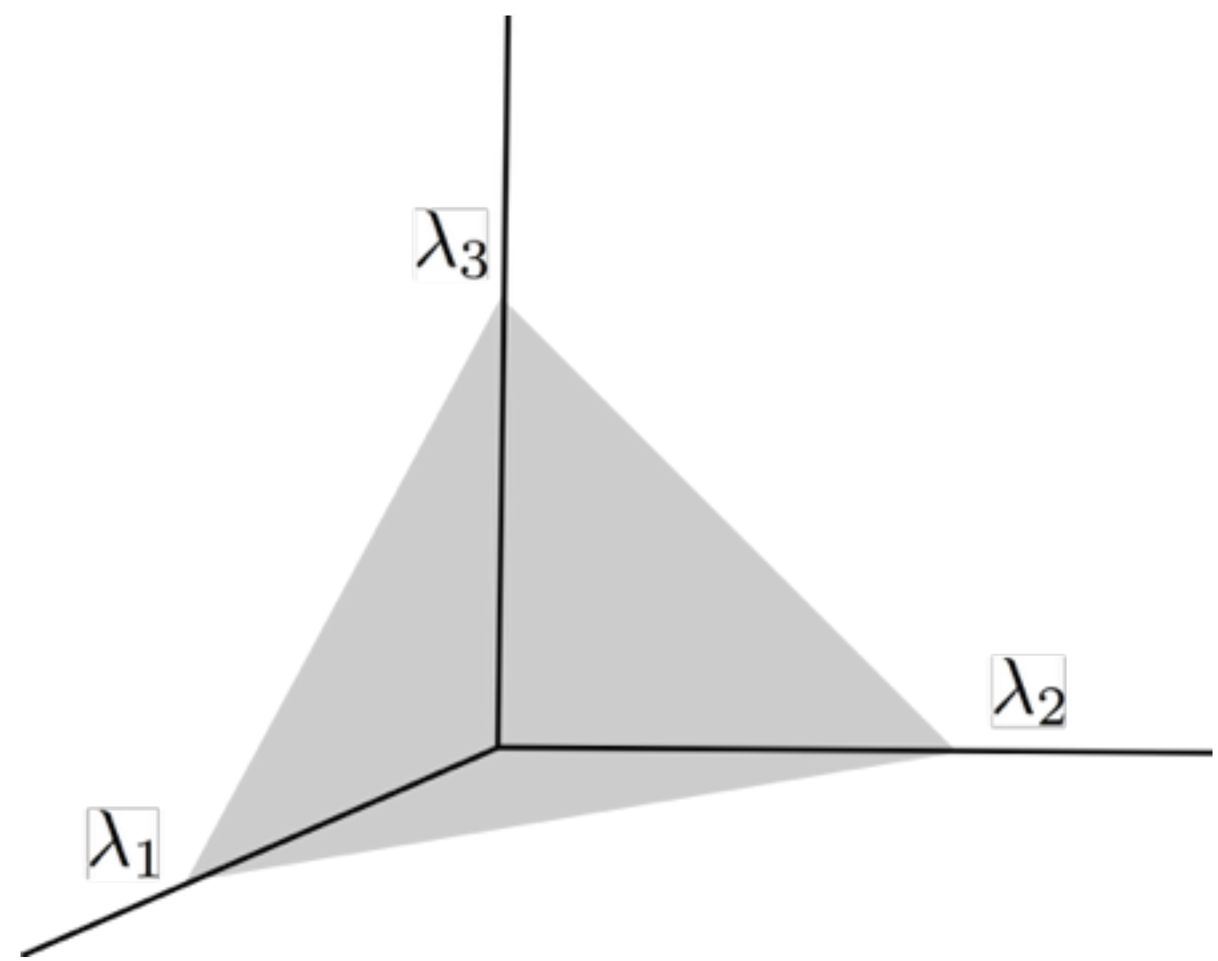
`[ atoms ]`

`;state_A    state_B`

`Resnr N`

`Resnr N`

`Resnr N`



constraint

proton-SHAKE

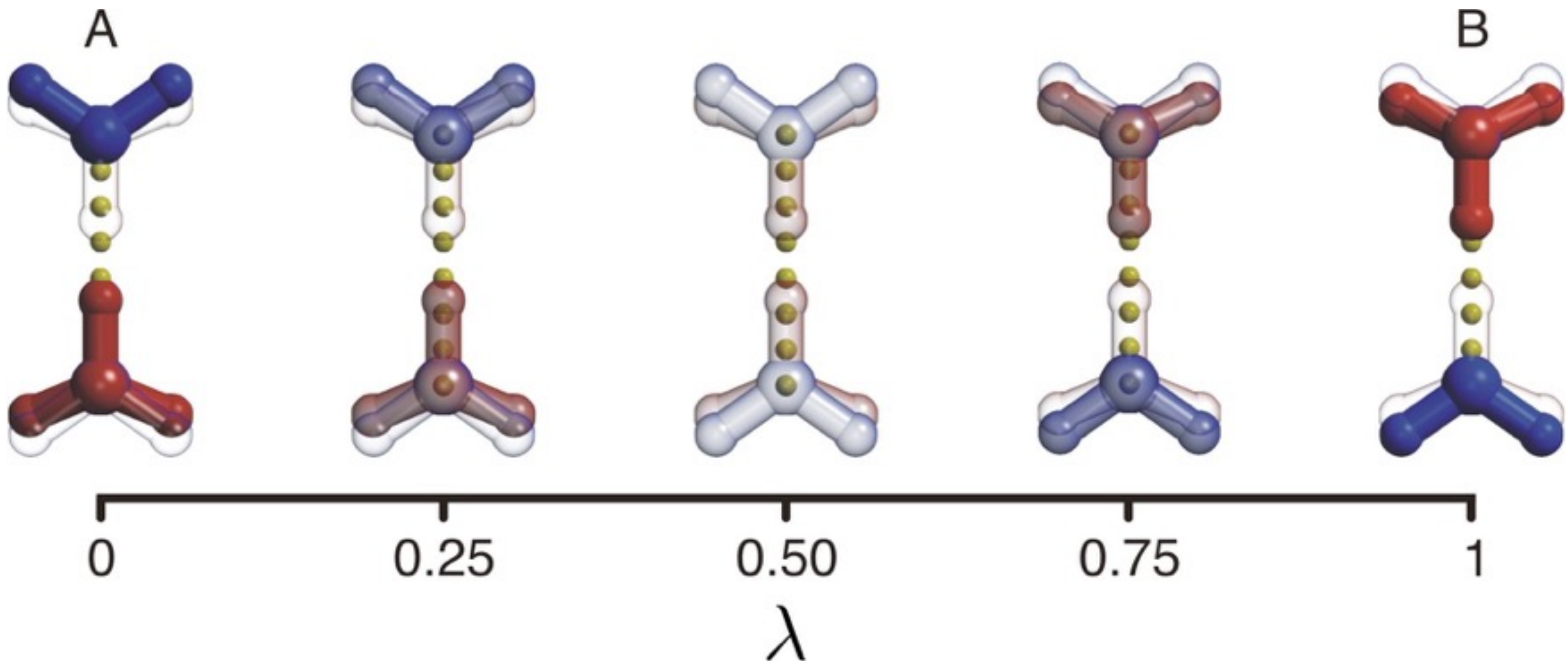
coupled sites

what about postion updates?

S. Donnini, R. T. Ullman, G. Groenhof. H Grubmüller *JCTC* 12 (2016) 1040

Proton transfer in force field simulations

morph between donor and acceptor



dynamics of λ-particle (proton transfer reaction coordinate)

$$m_\lambda d^2\lambda/dt^2 = -\partial V(\mathbf{x},\lambda)/\partial\lambda$$

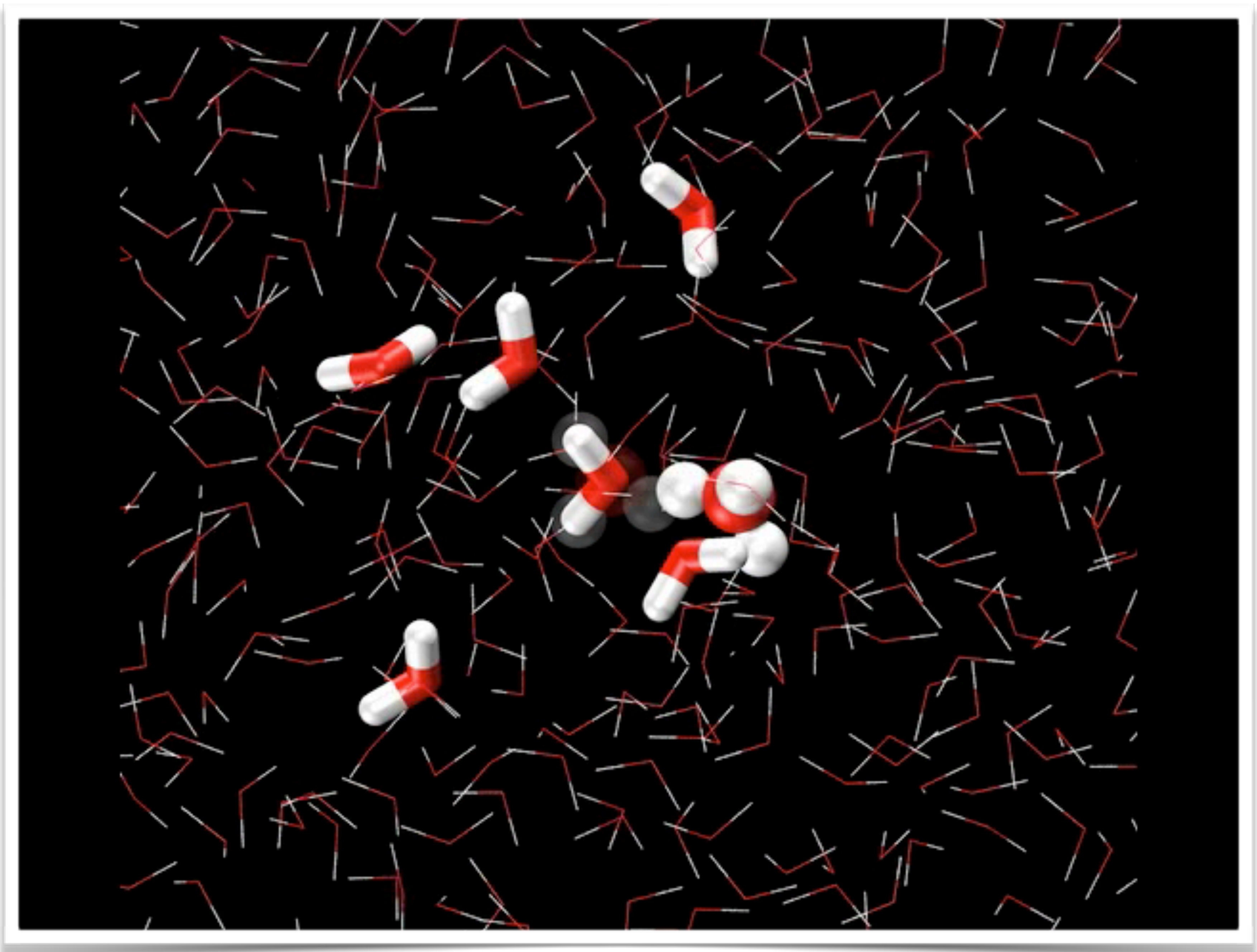
$$V(\mathbf{x},\lambda) = (1-\lambda)V^{\mathrm{A}}(\mathbf{x}) + \lambda V^{\mathrm{B}}(\mathbf{x})$$

Proton transfer in force field simulations

detailed balance

Monte Carlo selection of donor-acceptor pairs

λ-dynamics for proton transfer



Maarten Wolf

J. Comp. Chem. 35 (2014) 657

Proton transfer in force field simulations

incorporating Grotthuss shuttling mechanism

more realistic than classical hydronium

diffusion constant

solvation structure & dynamics

general applicability

straightforward parametrization protocol

force field	Zundel/Eigen	rate (ps^{-1})	$D(H^+)$ $10^{-5}cm^2s^{-1}$	$D(H_3O^+)$ $10^{-5}cm^2s^{-1}$	$D(H_2O)$ $10^{-5}cm^2s^{-1}$
SPCE	0.67/0.33	0.4	4	1	2.5
TIP3P	0.76/0.24	0.24	4.4	4.4	5.3
SWM4-NDP	0.75/0.25	0.49	4.1	4.1	2.3
reference	0.72/0.28	0.6	9.3	9.3	2.3

Acknowledgements

Milko Vesterinen

Berk Hess

funding

MAX-PLANCK-GESELLSCHAFT

SUOMEN AKATEMIA

constant pH input

multiple λ states in topology file

sequential entries

redmine issue #1653

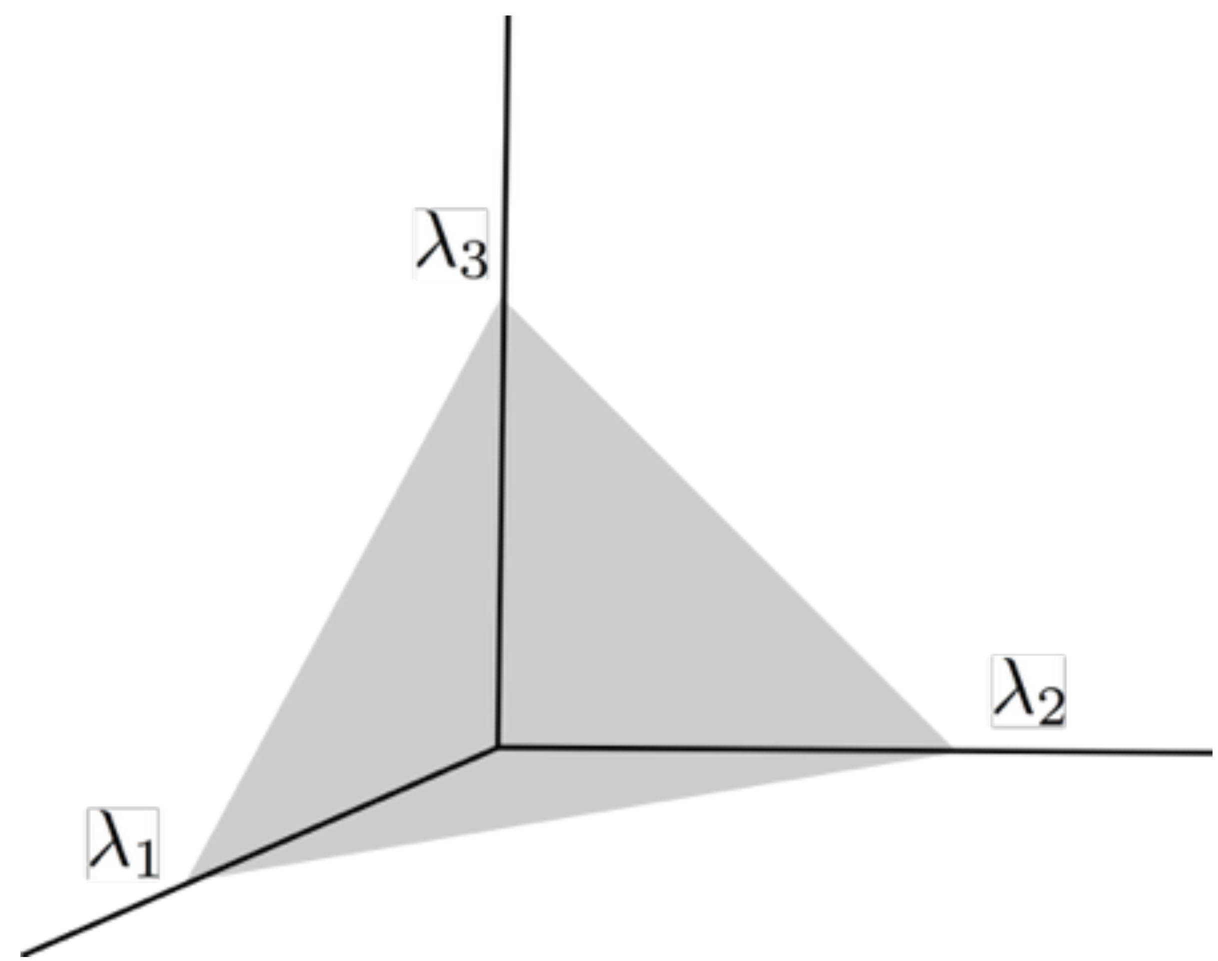
```
[ atoms ]
; id typeA resnr resname atname cgnr chargeA massA typeB chargeB massB
1   AR_dum  1 AR AR 1  0 39.948 AR   -1 39.948
2   AR_dum  2 AR AR 2  0 39.948 AR    0 39.948
3   AR_dum  3 AR AR 3  0 39.948 AR   +1 39.948
```

constraint

proton-SHAKE

coupled sites

what about postion updates?



S. Donnini, R. T. Ullman, G. Groenhof. H Grubmüller *JCTC* 12 (2016) 1040

Internal interaction

approximation

monopole expansion

self-energy of +1 point charge

$$\left|\sum_i (q_i^B - q_i^A)\right| = 1$$

$$\frac{\text{internal energy of Glu}^- \quad \text{PME energy of +1 point charge}}{\text{PME energy of Glu}^-} \; +$$

no additional PME call

PME energy of point charge vs box size