

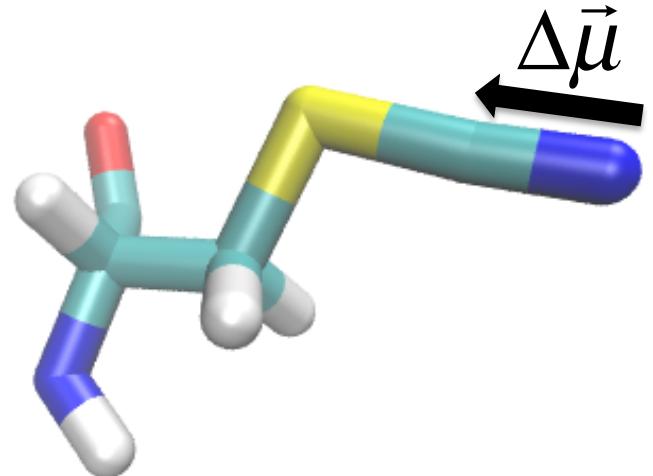
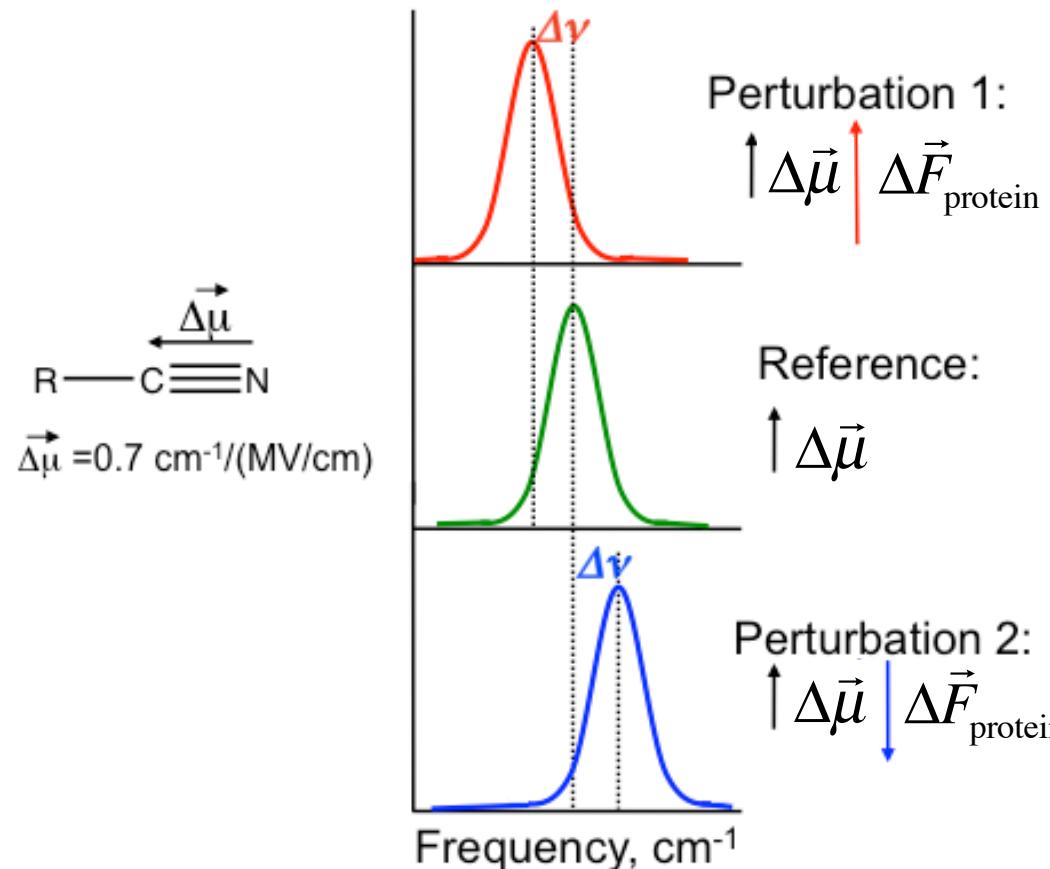
Current State of AMOEBA- Protein Stark Effect Project

Andrew Ritchie

June 16, 2015

Vibrational Stark Effect (VSE)

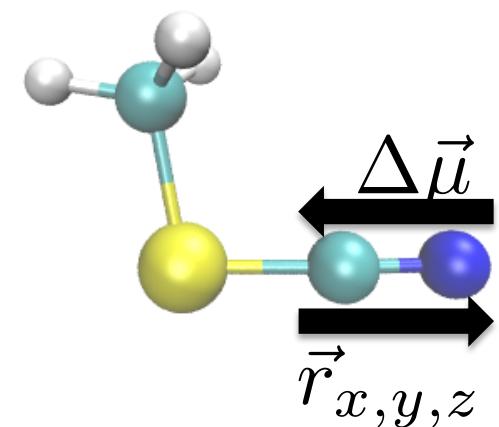
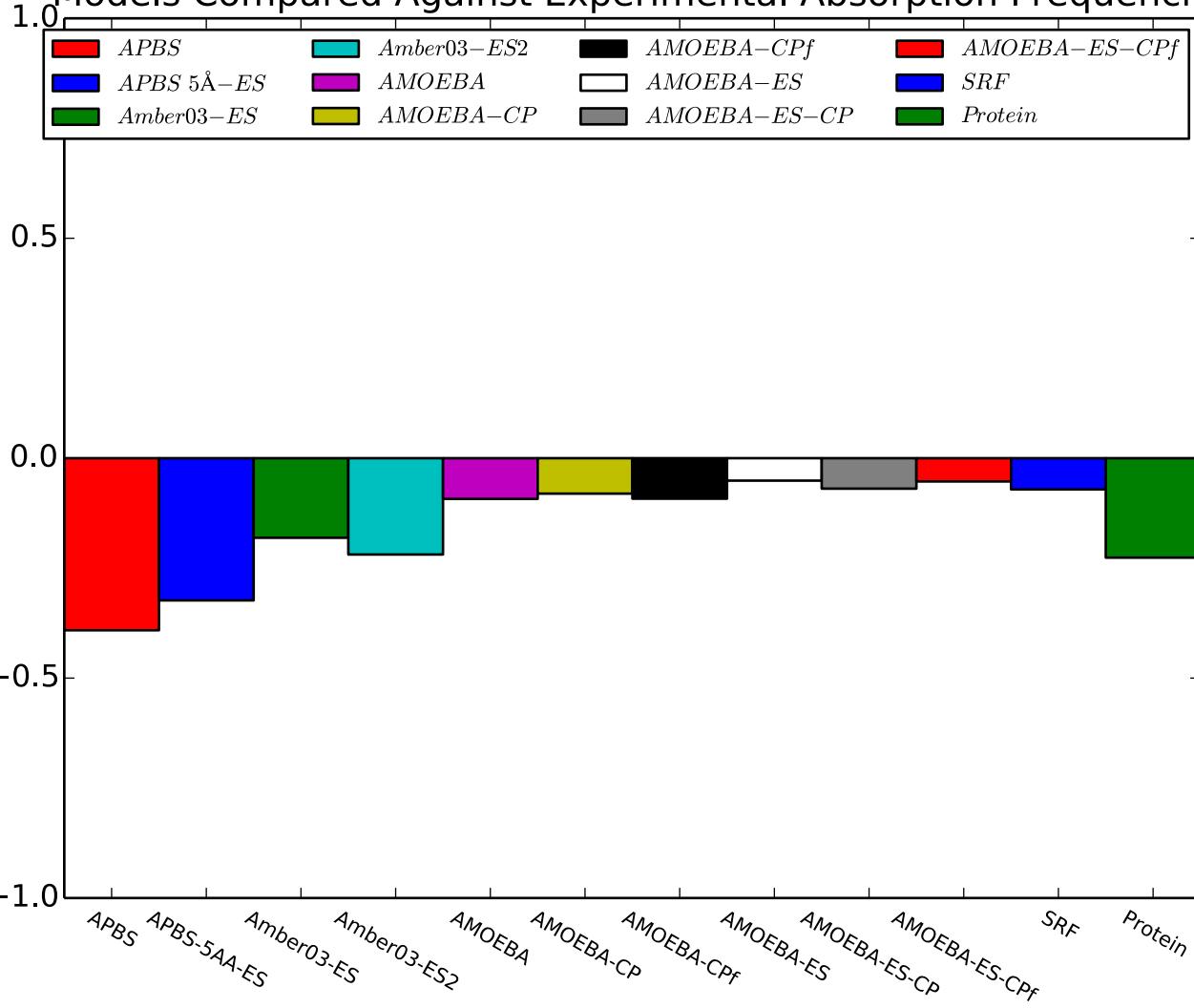
$$\Delta E_{\text{protein}} = hc\Delta\tilde{\nu} = -\Delta\vec{\mu} \cdot \Delta\vec{F}_{\text{protein}}$$



$$\begin{aligned}\Delta\vec{\mu} &= 0.77 \text{ cm}^{-1} / (\text{MV cm}^{-1}) \\ &= 1.99 \text{ cm}^{-1} / (k_b T / e\text{\AA})\end{aligned}$$

Rap & Ras docked to Ral in Amber03 with tip3p water (54 data points)

Correlation Coefficients using Various Electrostatics
Models Compared Against Experimental Absorption Frequencies



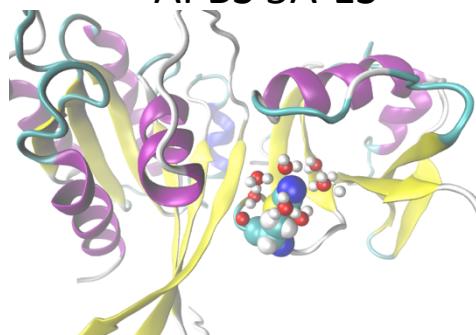
$$\begin{aligned}\Delta E_{\text{protein}} &= hc \Delta \tilde{\nu} \\ &= +\Delta \vec{\mu} \cdot \Delta \vec{F}\end{aligned}$$

Electrostatic Models

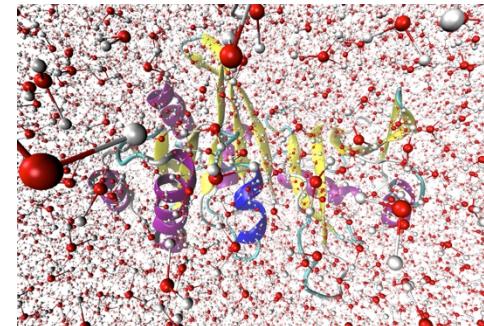
APBS

$$\nabla \cdot \epsilon(\vec{r}) \nabla \phi(\vec{r}) = \epsilon(\vec{r}) \bar{\kappa}^2 \phi(\vec{r}) - 4\pi \rho(\vec{r})$$

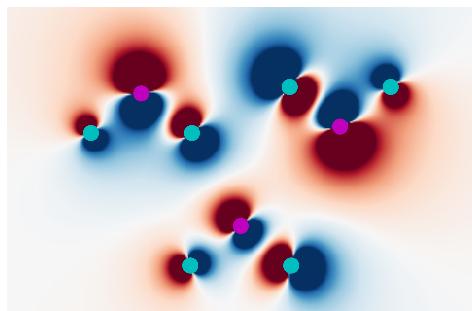
APBS 5Å-ES



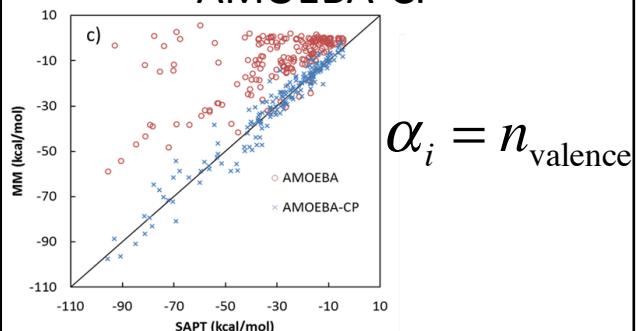
Amber03-ES



AMOEBA



AMOEBA-CP



AMOEBA-CPf

$$V_q(r) = \left[\frac{Z_1 - (Z_1 - q_1)}{\cdot (1 - \exp(-\alpha_1 r))} \right] / r$$

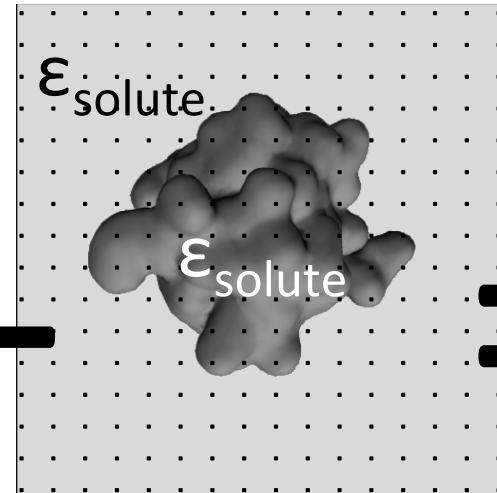
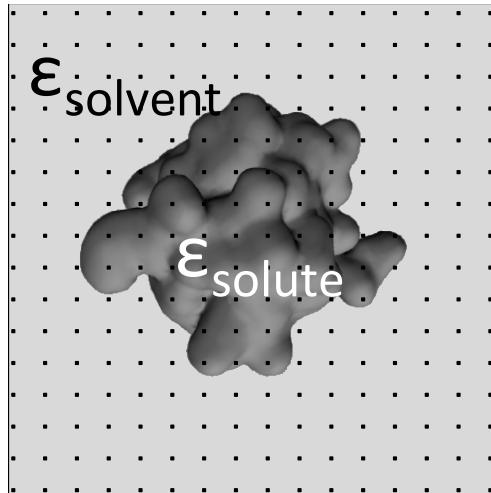
AMOEBA-ES

AMOEBA-ES-CP

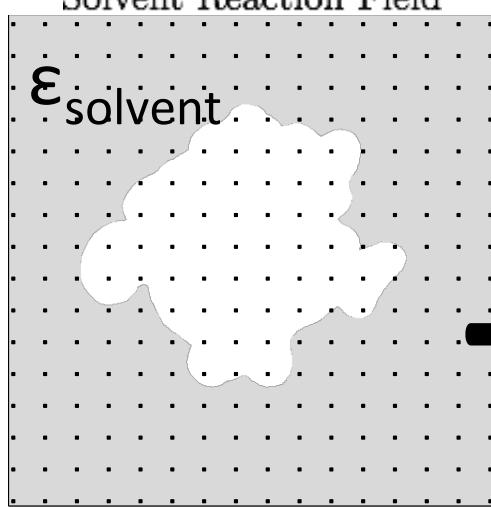
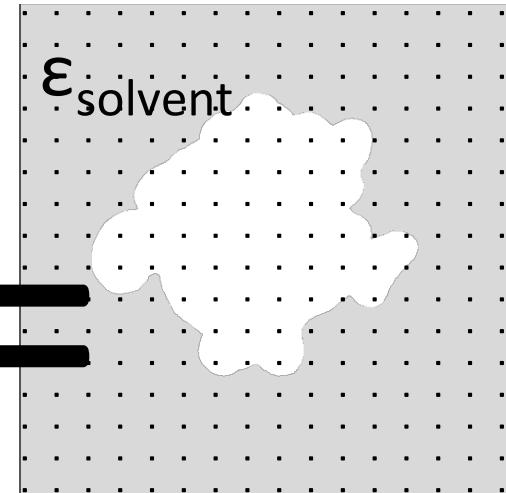
AMOEBA-ES-CPf

APBS and Reaction Field Method

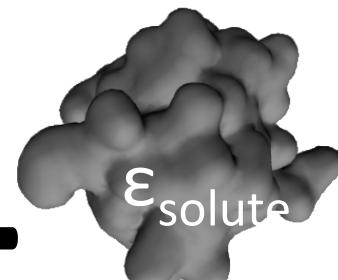
$$\nabla \cdot \epsilon(\vec{r}) \nabla \phi(\vec{r}) = \epsilon(\vec{r}) \bar{\kappa}^2 \phi(\vec{r}) - 4\pi\rho(\vec{r})$$



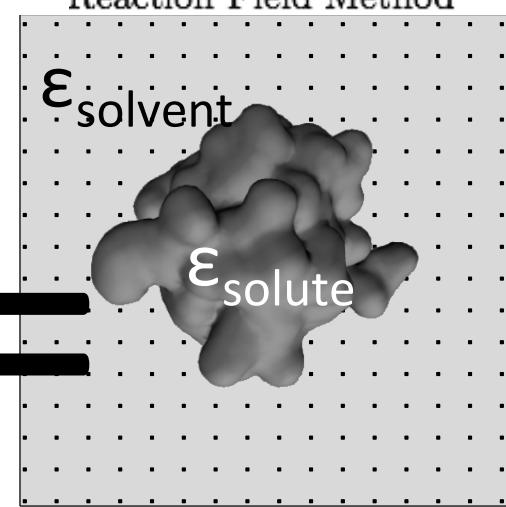
Solvent Reaction Field



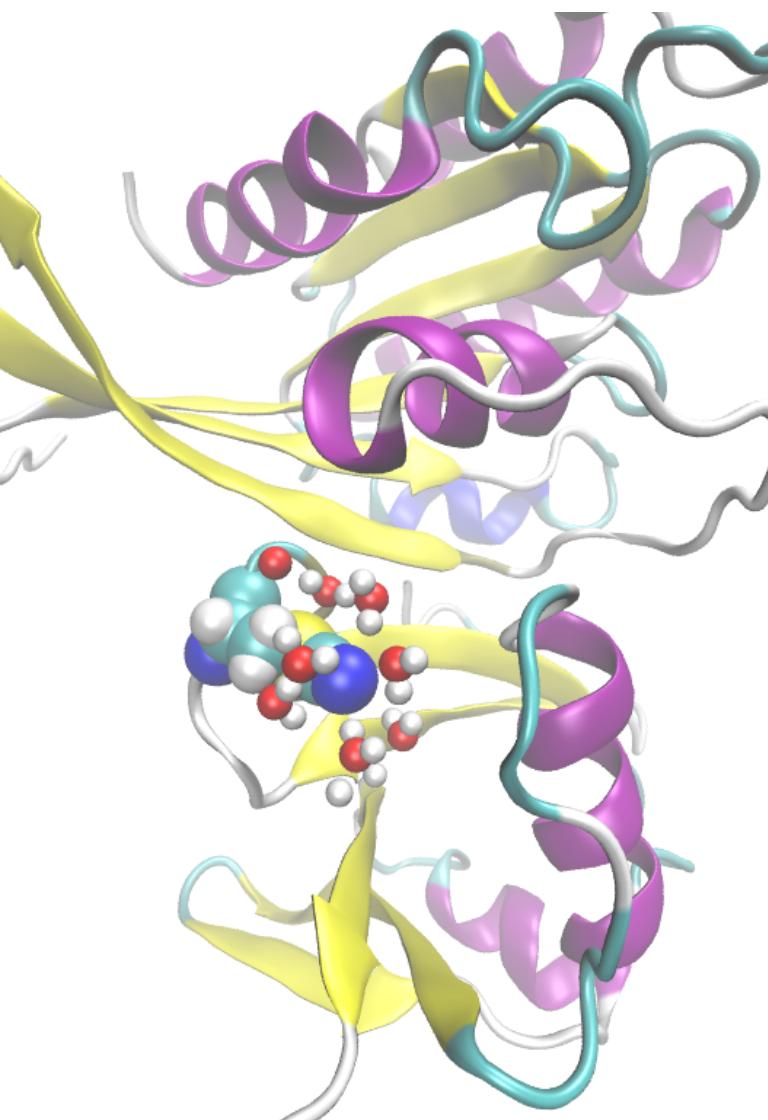
$$\vec{F}_i(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{1}{\epsilon_{\text{solute}}} \frac{q_j}{\|\vec{r}_{ij}\|^2}$$



Reaction Field Method

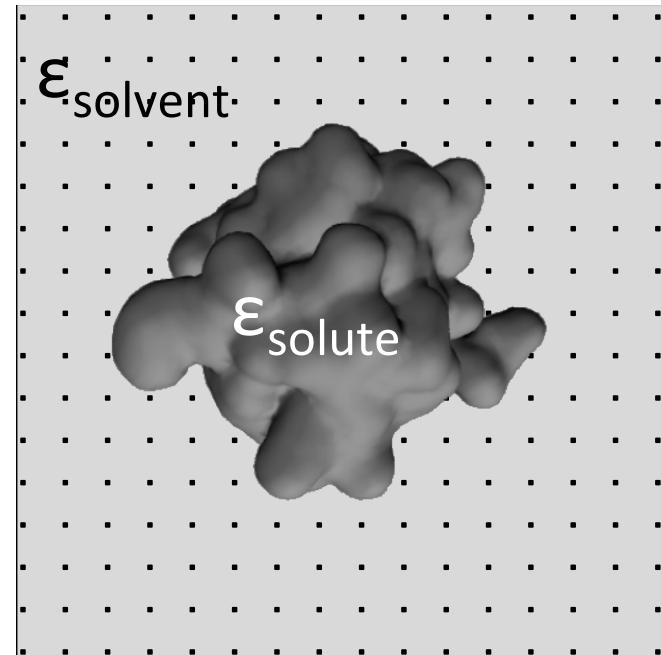


APBS 5Å-ES

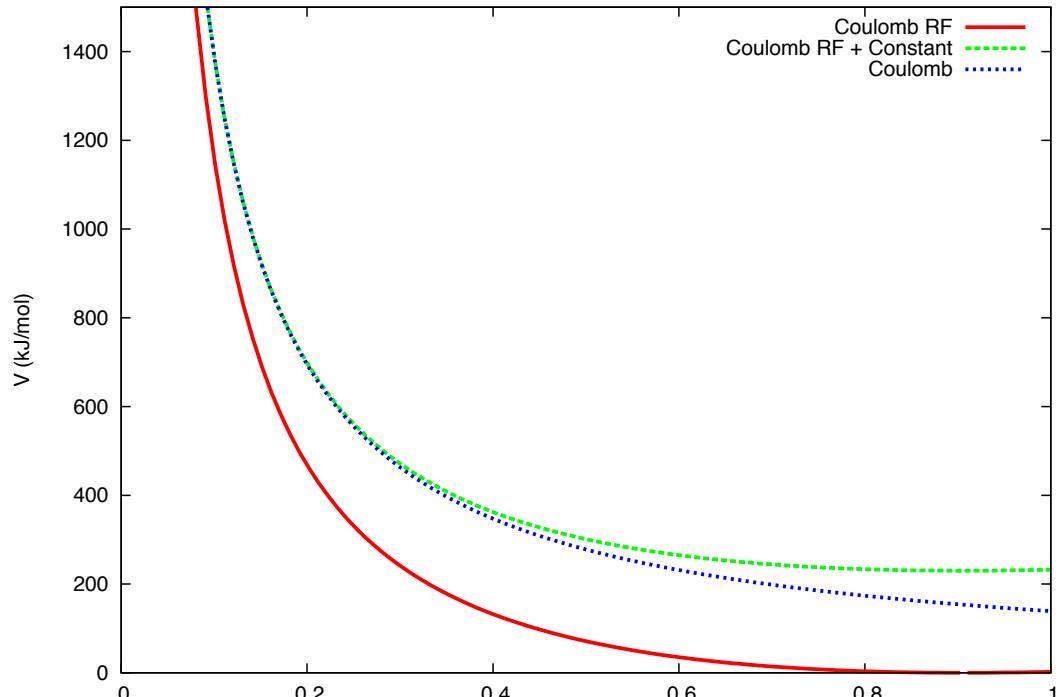
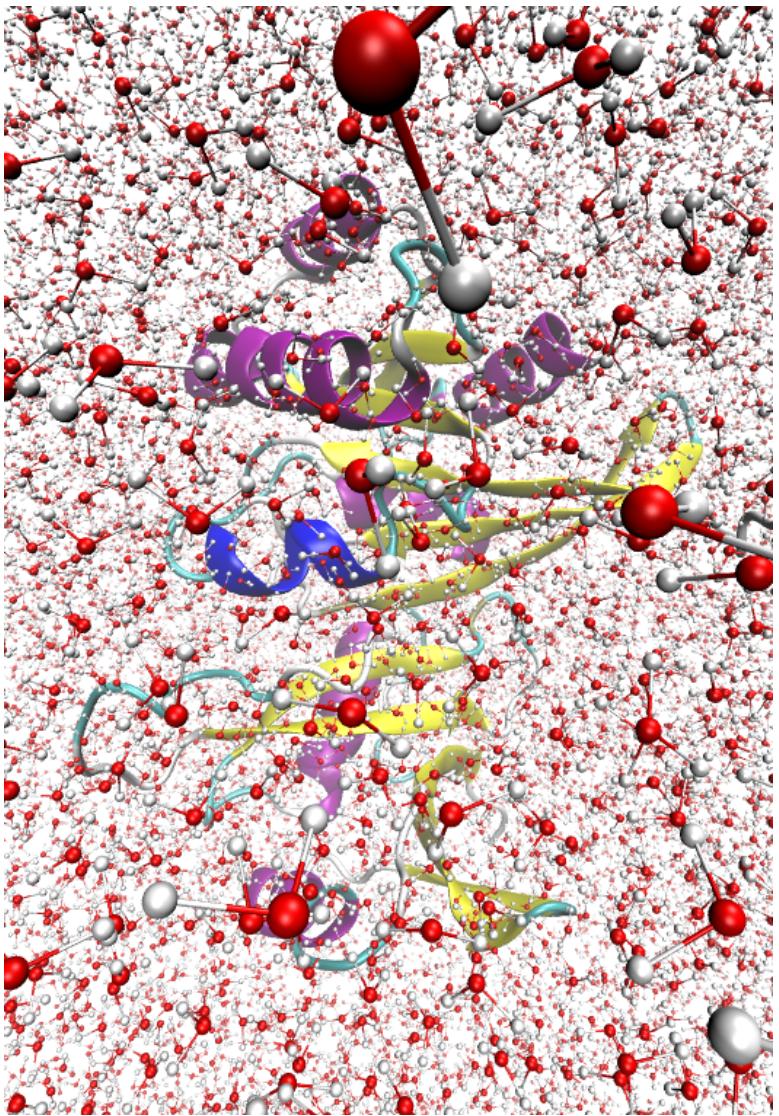


$$\nabla \cdot \epsilon(\vec{r}) \nabla V(\vec{r}) = \epsilon(\vec{r}) \bar{\kappa}^2 V(\vec{r}) - 4\pi\rho(\vec{r})$$
$$\vec{F}_i(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0\epsilon_r} \frac{q_j}{|\vec{r}_{ij}|^3} \vec{r}$$

Reaction Field Method



Amber03-ES



$$\vec{F}_i(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{\epsilon_r} \left[\frac{1}{r_{ij}^2} - 2 \frac{r_{ij}}{r_c^3} \frac{(\epsilon_{rf} - \epsilon_r)}{(\epsilon_{rf} + \epsilon_r)} \right] \frac{\vec{r}_{ij}}{r_{ij}}$$

r_c = short-range cut-off

ϵ_r = short-range dielectric

ϵ_{rf} = long-range dielectric

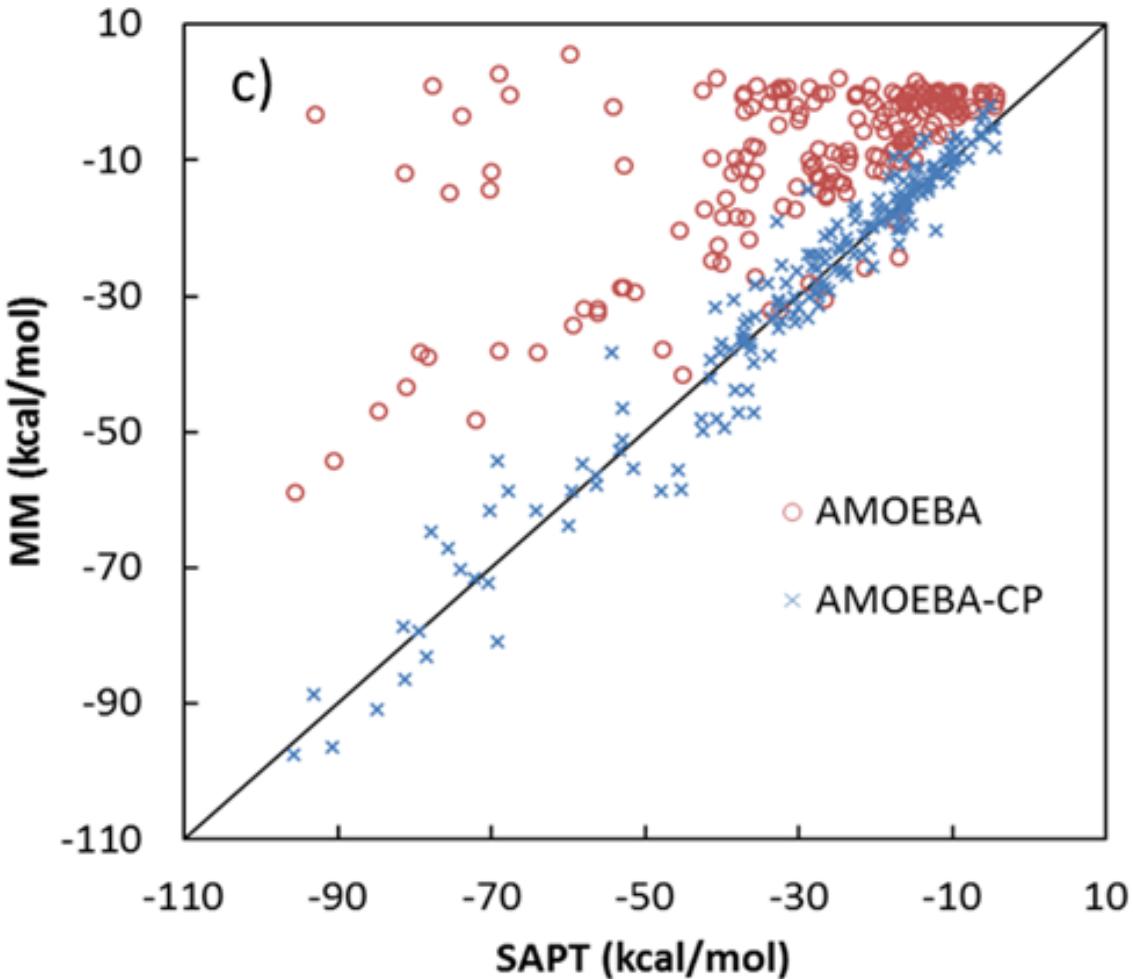
AMOEBA



- Implicit Solvent with Poisson-Boltzmann
- Dielectric handled using SCF induced dipole moments

$$\vec{\mu}_{i, \text{induced}} = \alpha_i (\vec{F}_i^{\text{Solvent}} + \vec{F}_i^{\text{Solute}})$$

AMOEBA-CP & AMOEBA-CPf



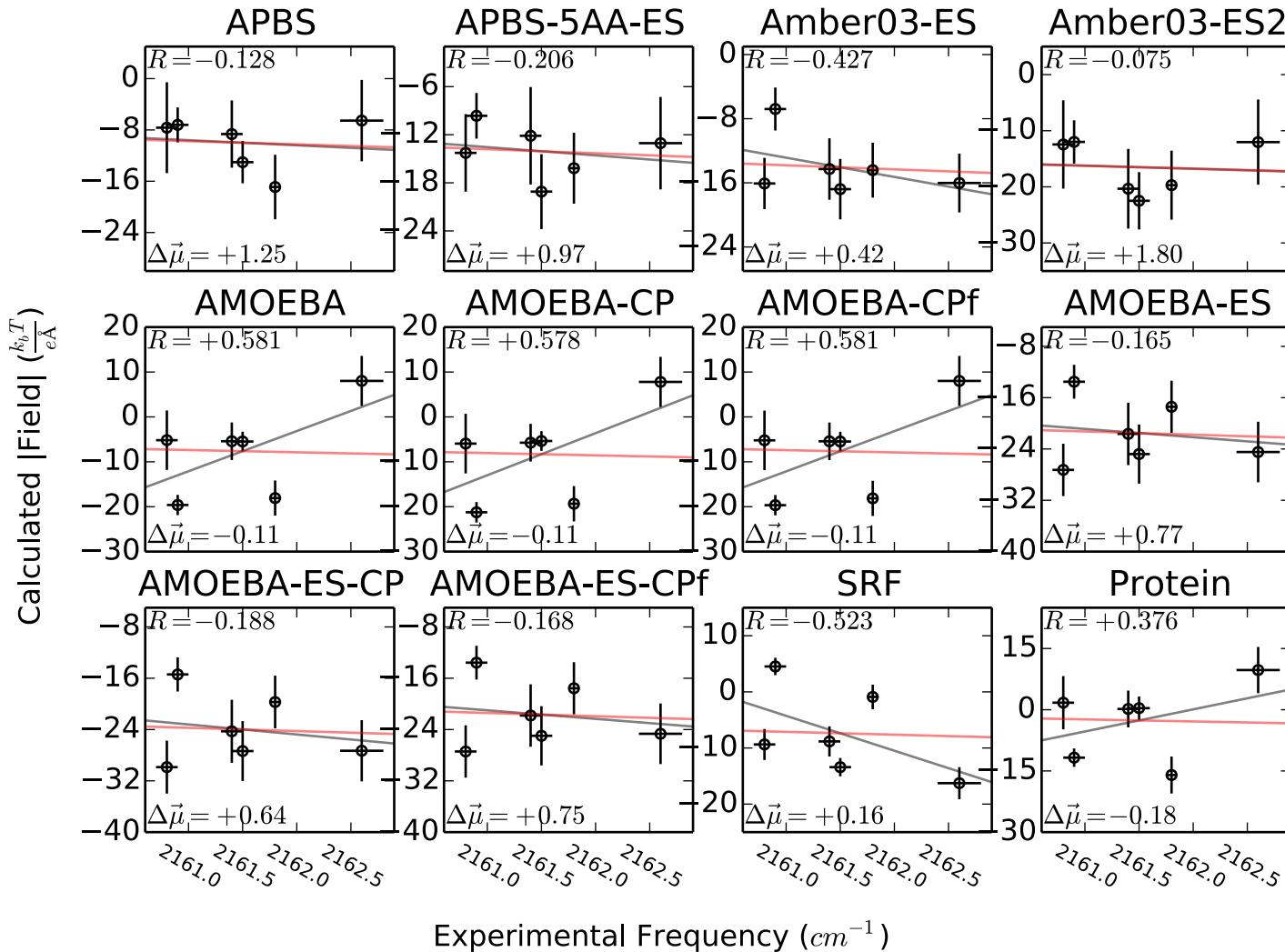
Interactions Include:

- Core-Core
- Core-Electron
- Electron-Electron

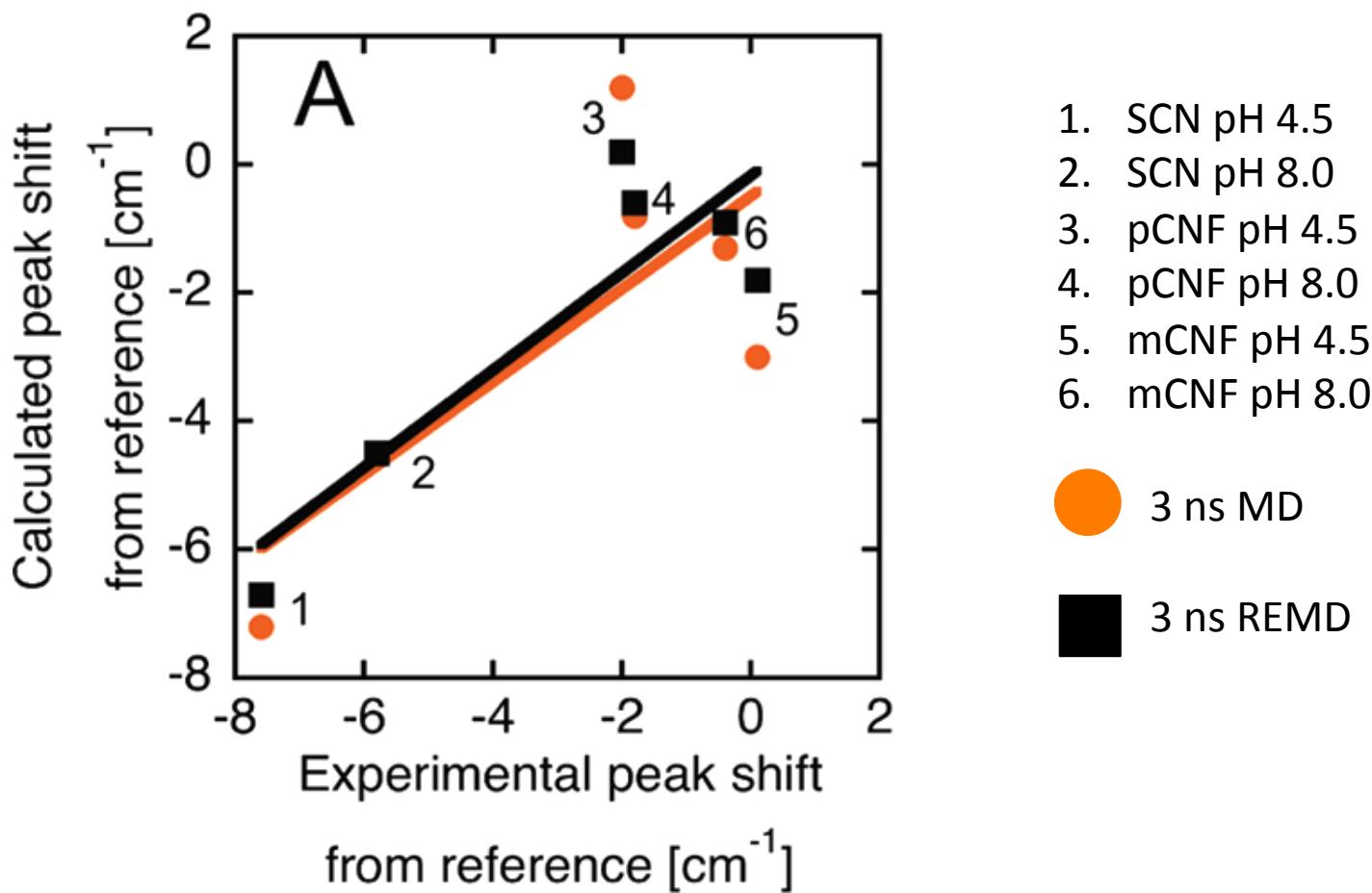
Parameters either implied by atom identity (CP) or fitted from QM potentials (CPf)

Various Nitrile Probes on Rap E30/K31

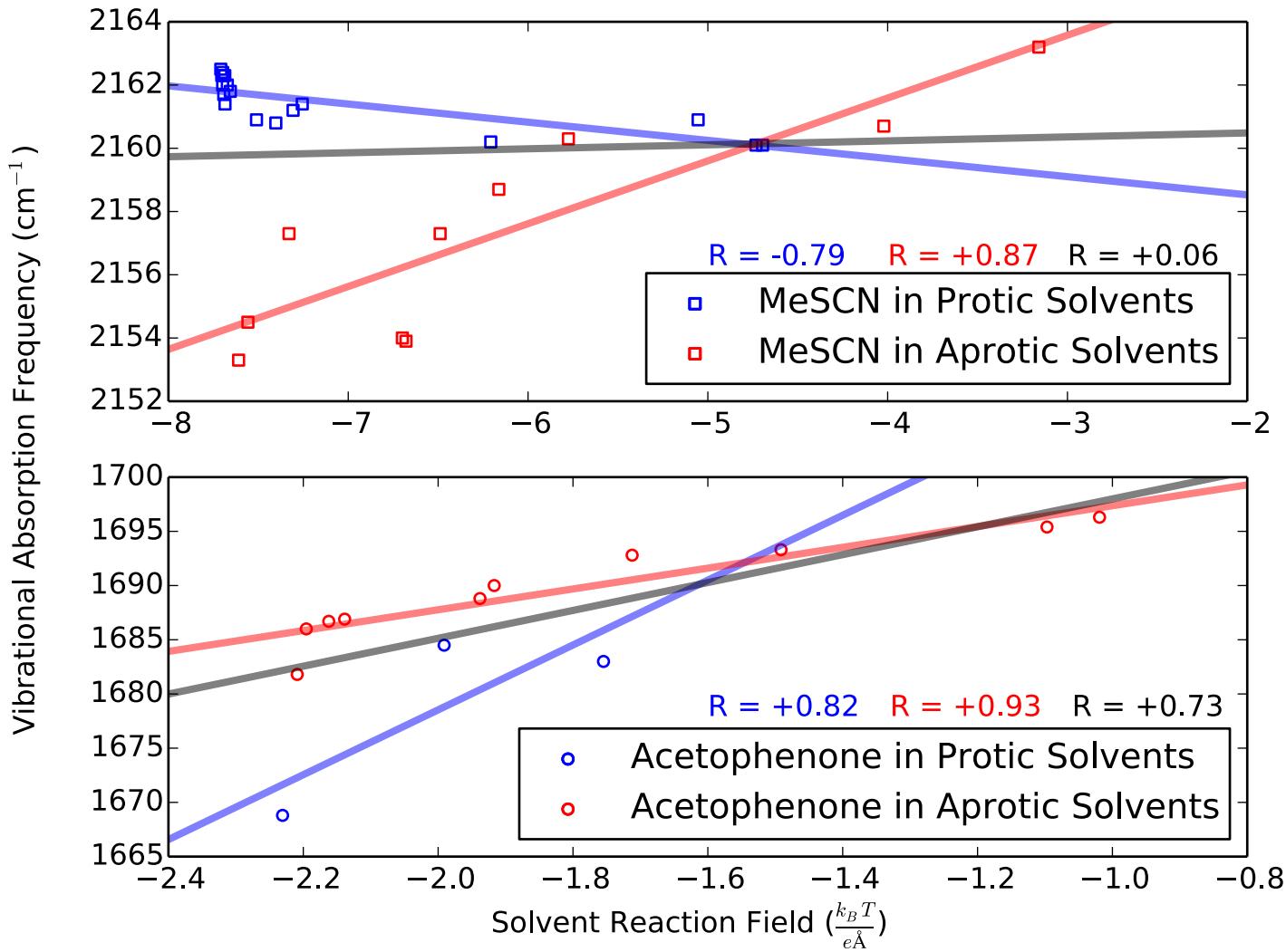
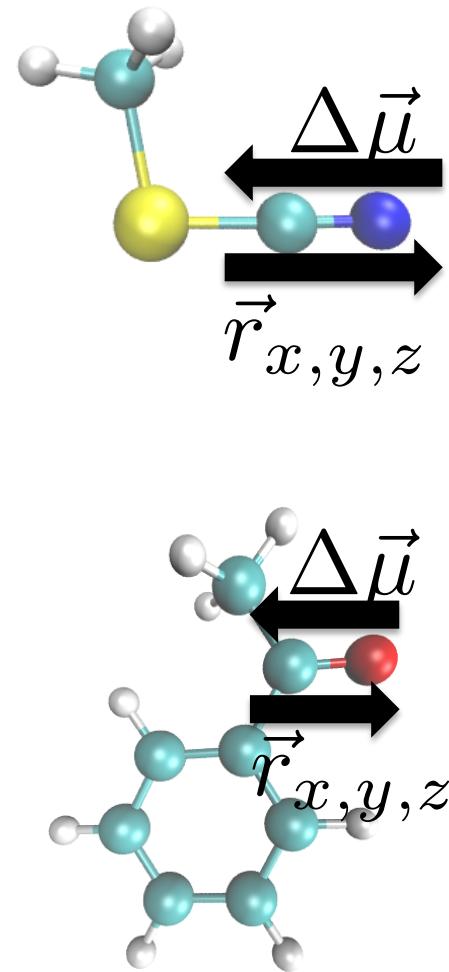
$$\Delta\vec{\mu} = 0.77 \text{ cm}^{-1} / (\text{MV cm}^{-1}) \\ = 1.99 \text{ cm}^{-1} / (k_b T / e\text{\AA})$$



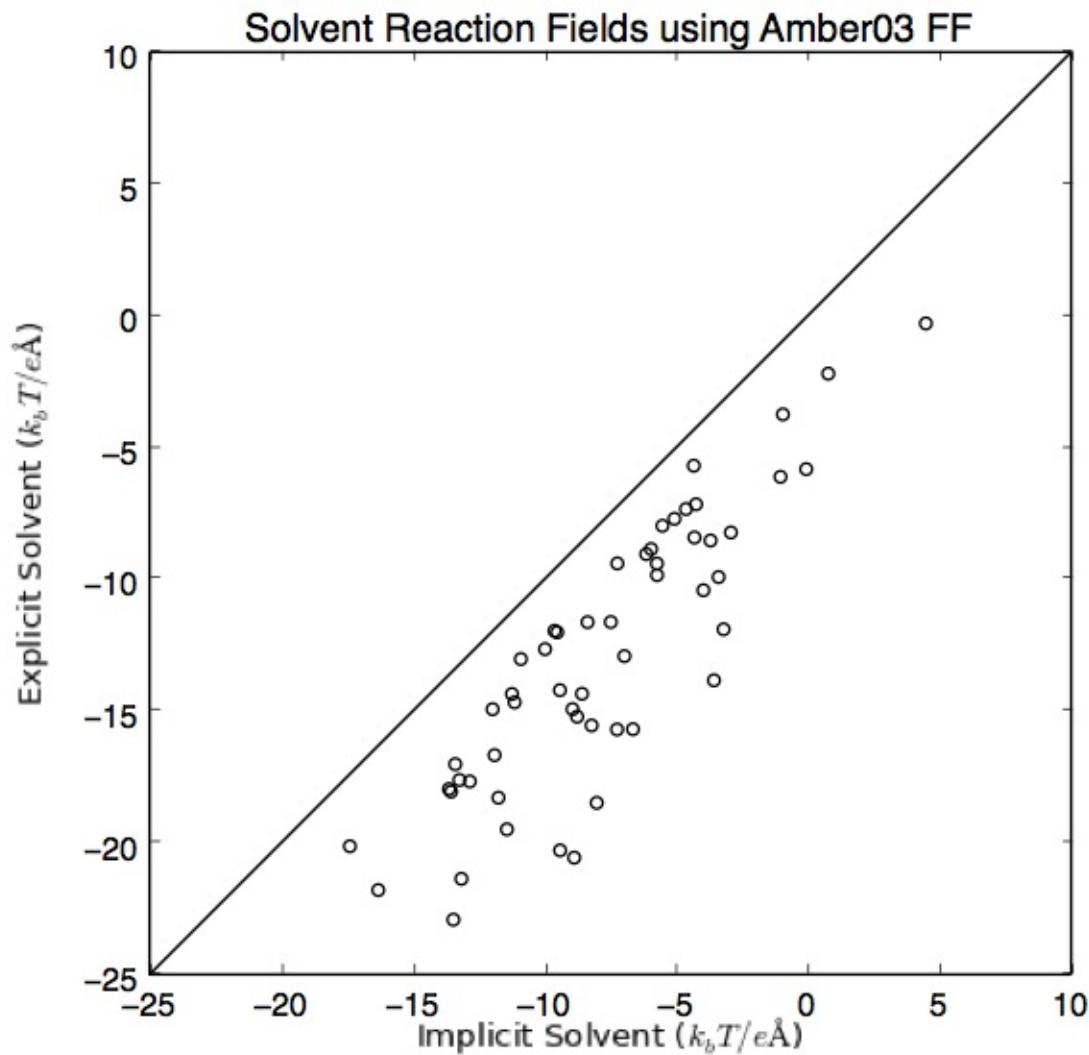
Fields in Ribonuclease S



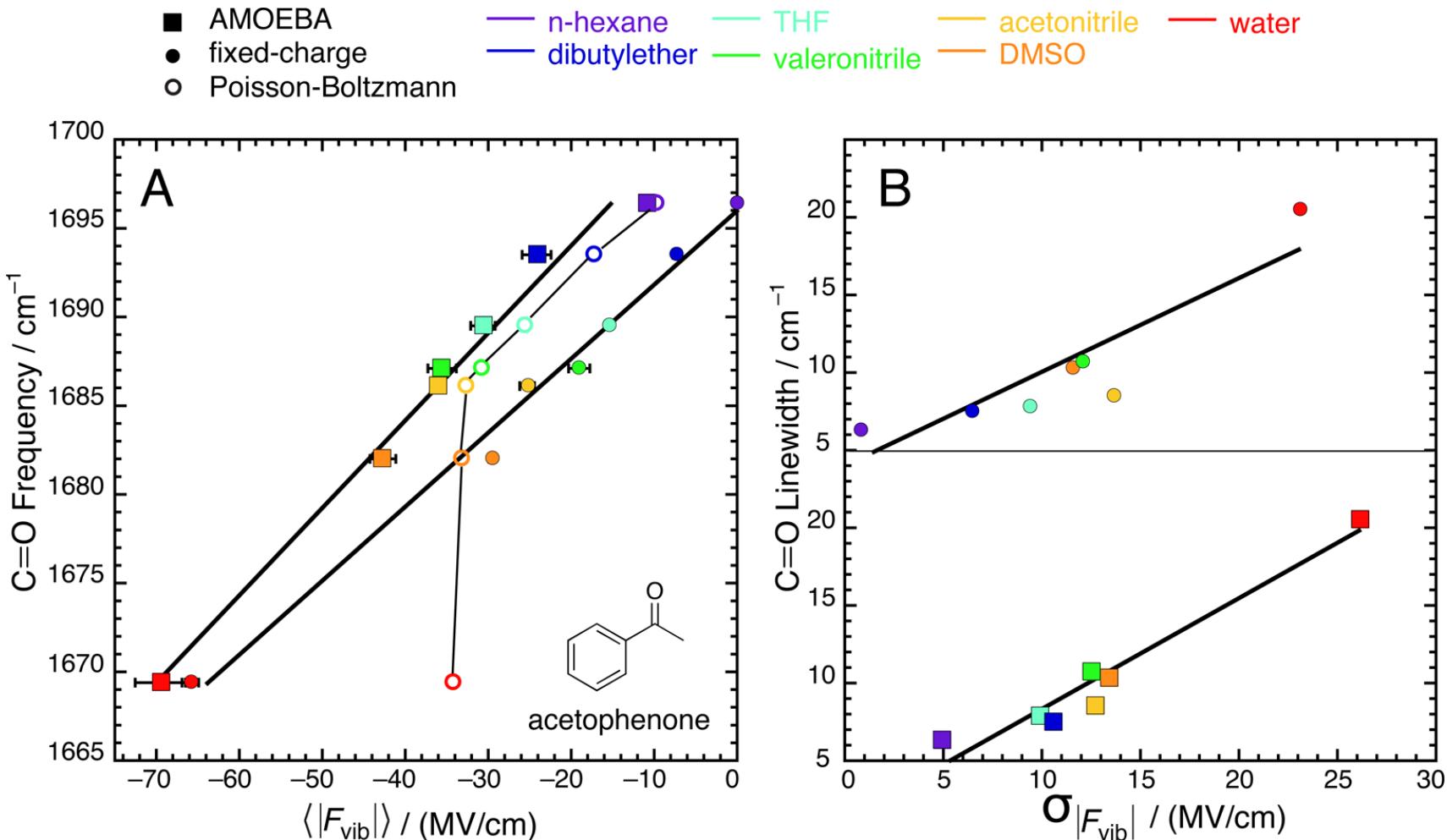
PB on small molecules in various solvents



Tip3p water looks like PB continuum solvent



Fields on small molecules in various solvents

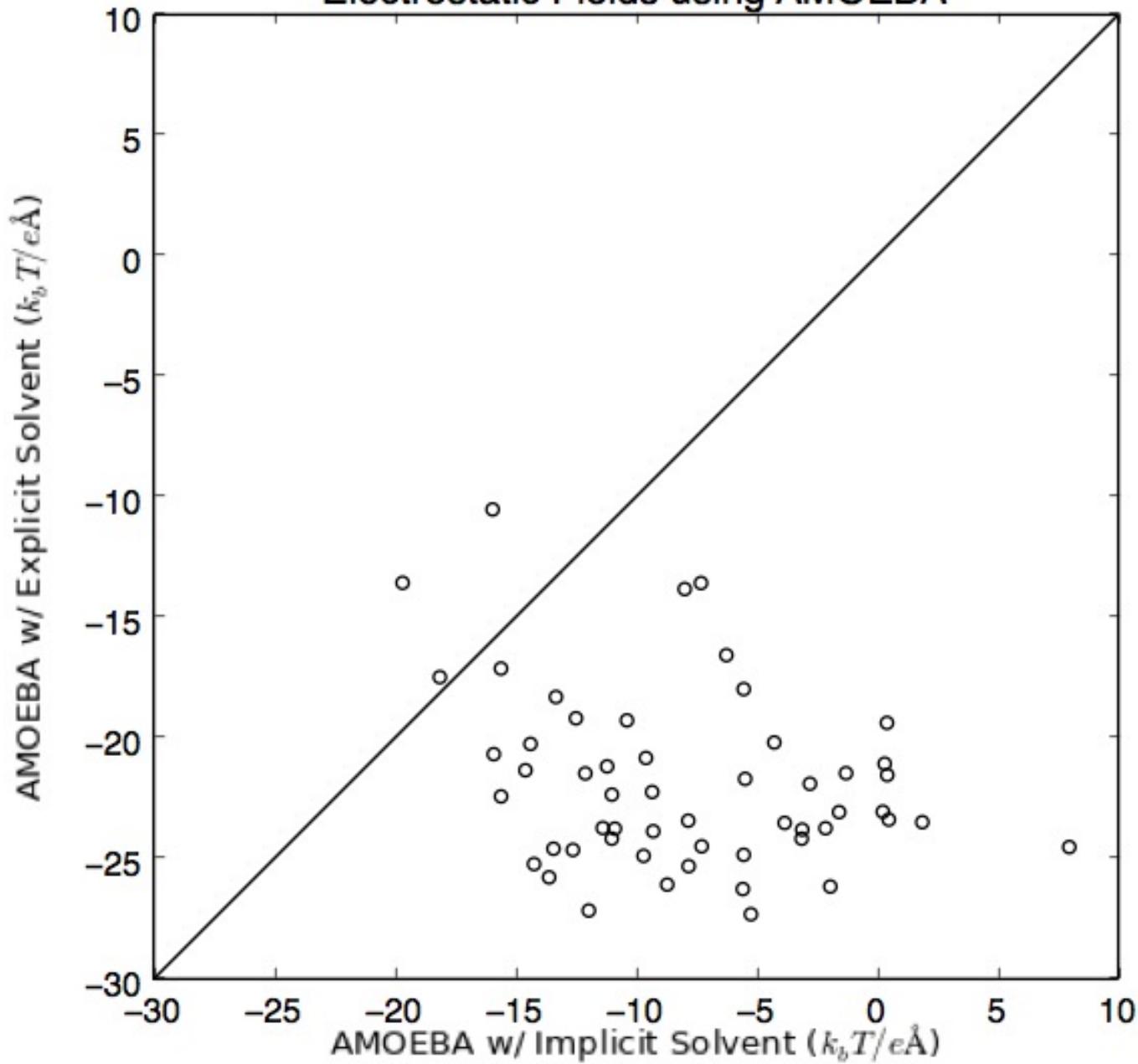


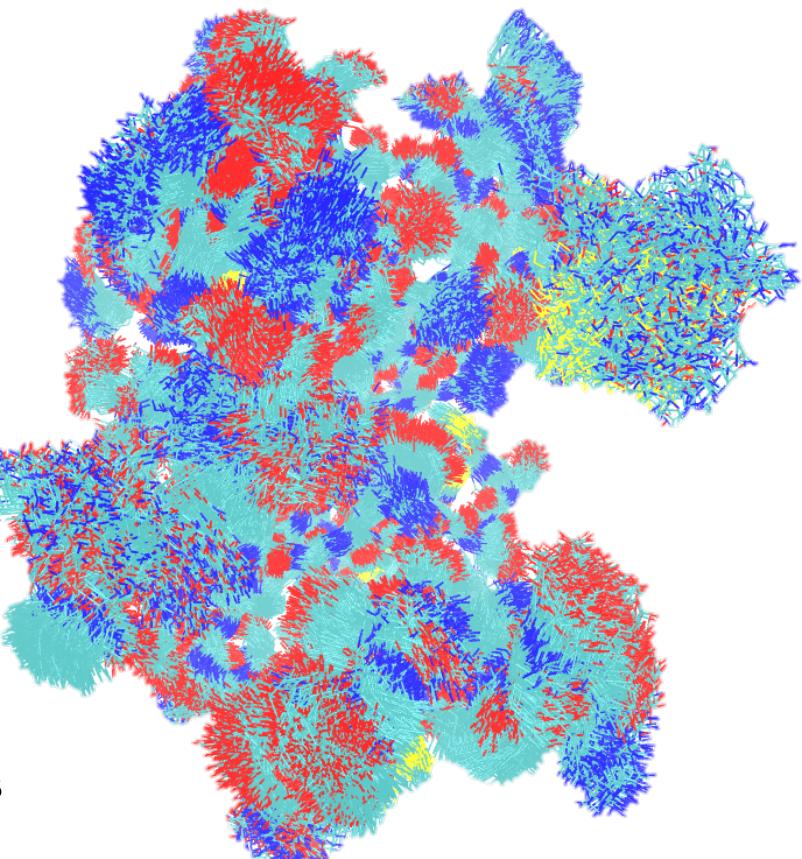
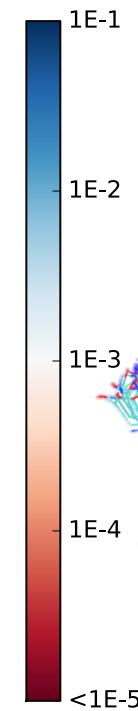
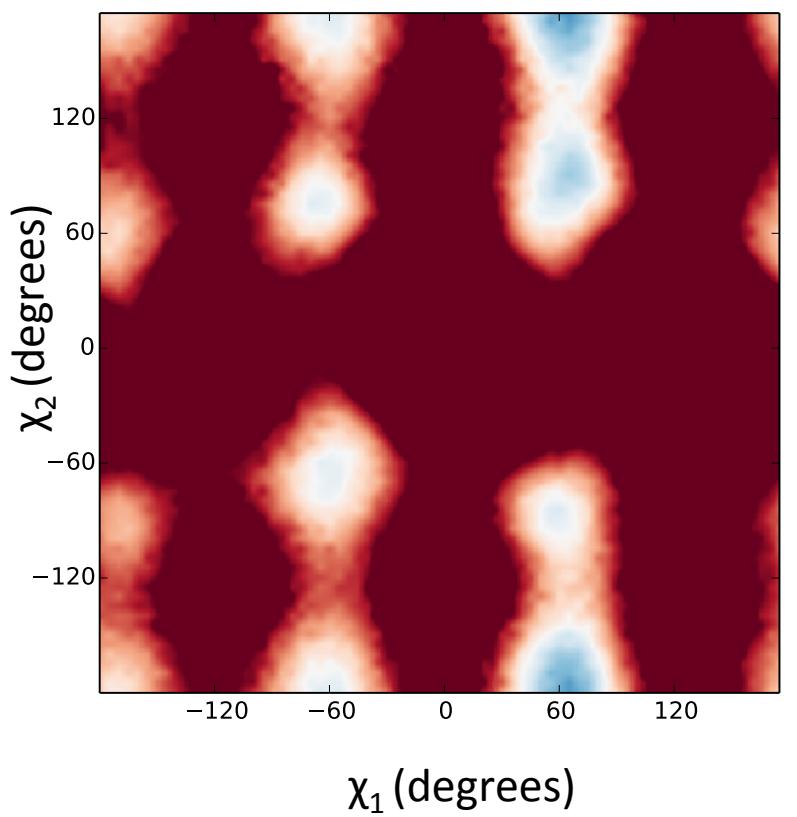
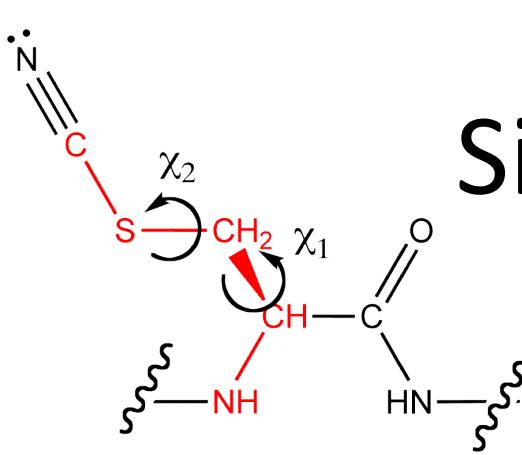
Fields on small molecules in various solvents

- “short” ~150 ps runs
 - SCDipoles to 10^{-5} D
 - Beeman integrator
 - Bussi Thermostat
 - Monte Carlo barostat
 - 1 fs timestep
- “long” ~1500 ps runs
 - SCDipoles to 10^{-3} D
 - RESPA integrator
 - Berendsen Barostat
 - 2 fs timestep
- Snapshots every 10 fs
- Field averaged from induced dipoles
- ≥ 2000 ps
 - SCDipoles to 10^{-4} D
 - Heavy Hydrogen
 - 4 fs timestep
 - Normal Hydrogen
 - 2.5 fs timestep
 - Bussi barostat
- Snapshots every 1000 fs
- Field averaged from induced dipoles
- Field at point in space

*Note: The Fried paper does not allow the solute to polarize the solvent

Electrostatic Fields using AMOEBA

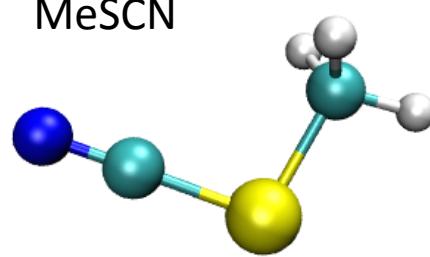




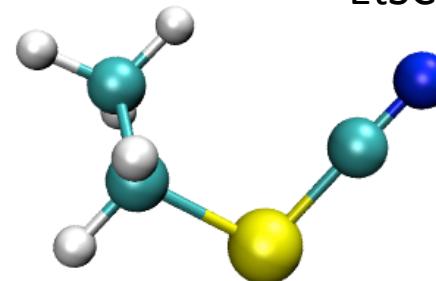
Simulating in AMOEBA

Simulating in AMOEBA

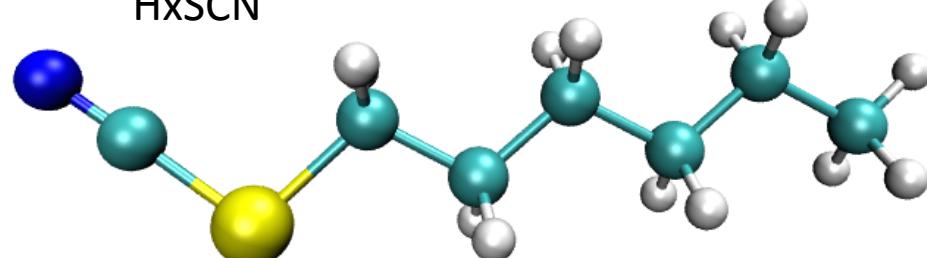
MeSCN



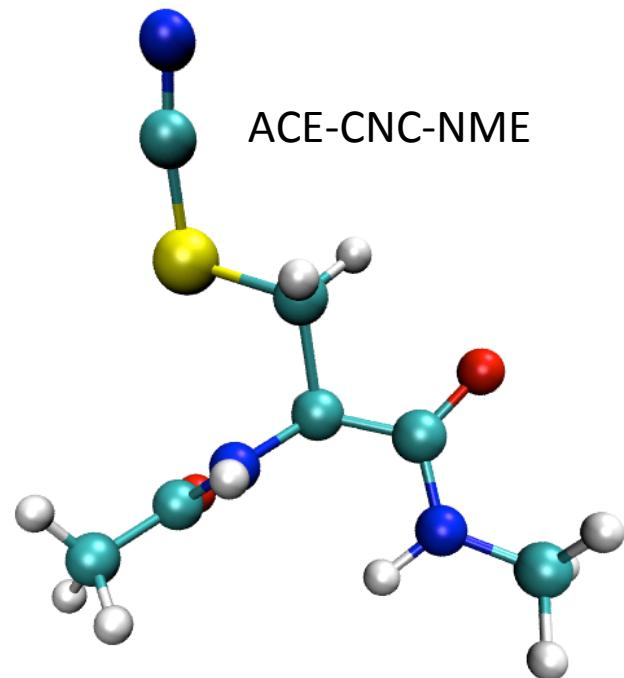
EtSCN



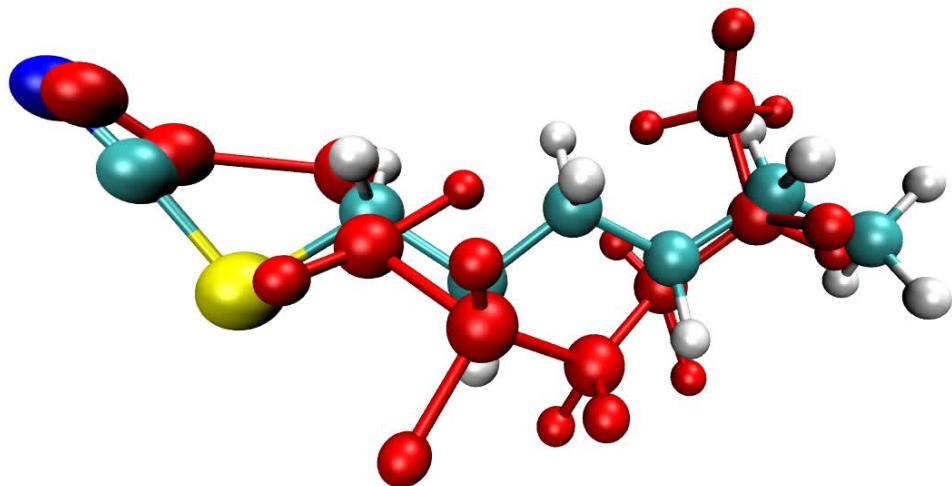
HxSCN



ACE-CNC-NME



Crashing in AMOEBA



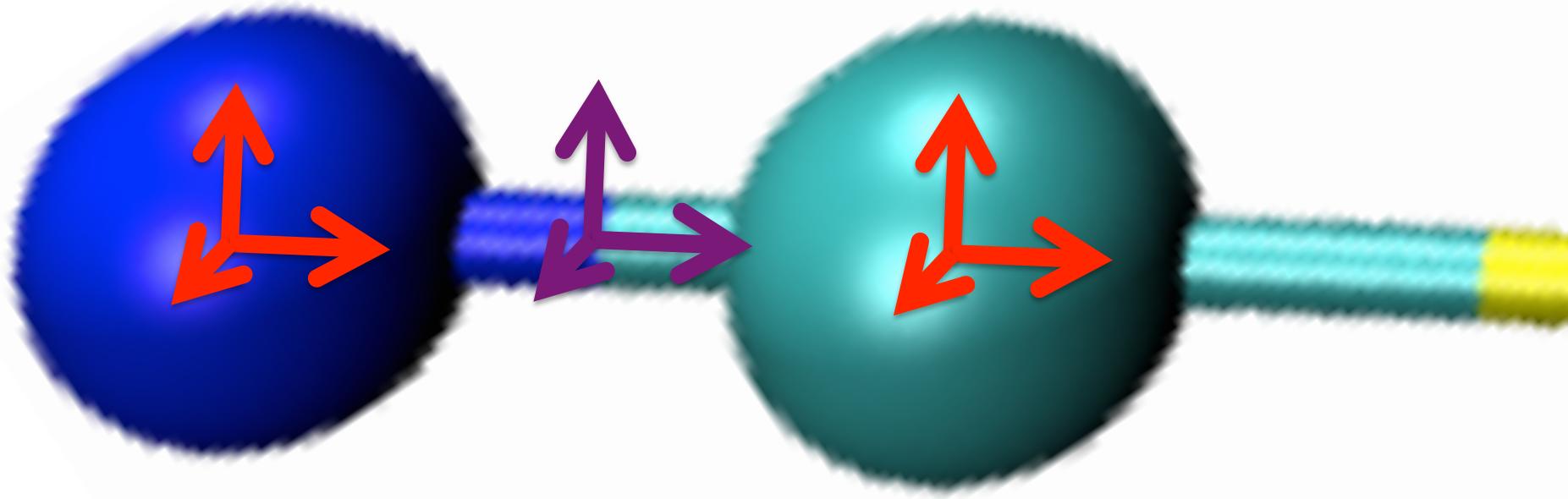
- RESPA with Bussi Thermostat
- Heavy Hydrogen
 - 4 ps stepsize
 - Took a long time to crash
- Normal Hydrogen
 - 2.5 ps stepsize
 - Took a long time to crash

Crashing in AMOEBA

- Parameters webb_amoebapro13.prm
- randomseed 123456789
- save-induced
- save-force
- archive
- octahedron
- vdw-cutoff 12.0
- neighbor-list
- ewald
- ewald-cutoff 7.0
- neighbor-list
- integrator respa
- thermostat bussi
- polar-eps 0.0001
- polar-predict
- FFT-PACKAGE fftw
- OPENMP-THREADS 16

Calculated fields thus far

$$\vec{F} = 0.5 \cdot \left(\left\langle \frac{\vec{\mu}_{\text{induced}}^C}{\alpha^C} \right\rangle + \left\langle \frac{\vec{\mu}_{\text{induced}}^N}{\alpha^N} \right\rangle \right)$$



$$\vec{F} = \sum_{i=0}^{N \text{ atoms}} \vec{F}_i^{\text{monopole}} + \vec{F}_i^{\text{dipole}} + \vec{F}_i^{\text{quadrupole}}$$

AMOEBA

$$V_{i,\text{m}}(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{q_j}{|\vec{r}_{ij}|}$$

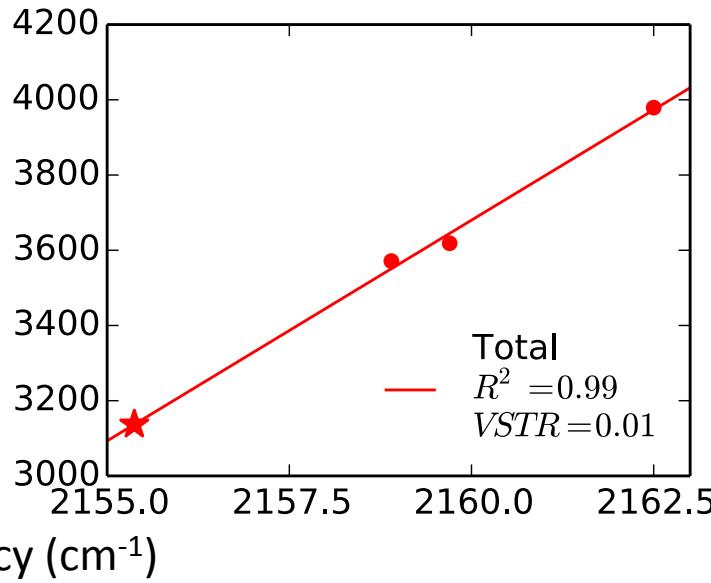
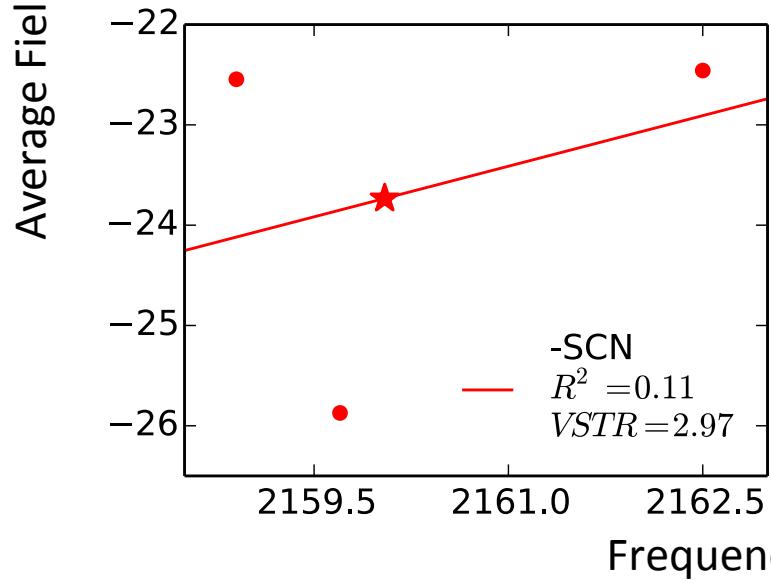
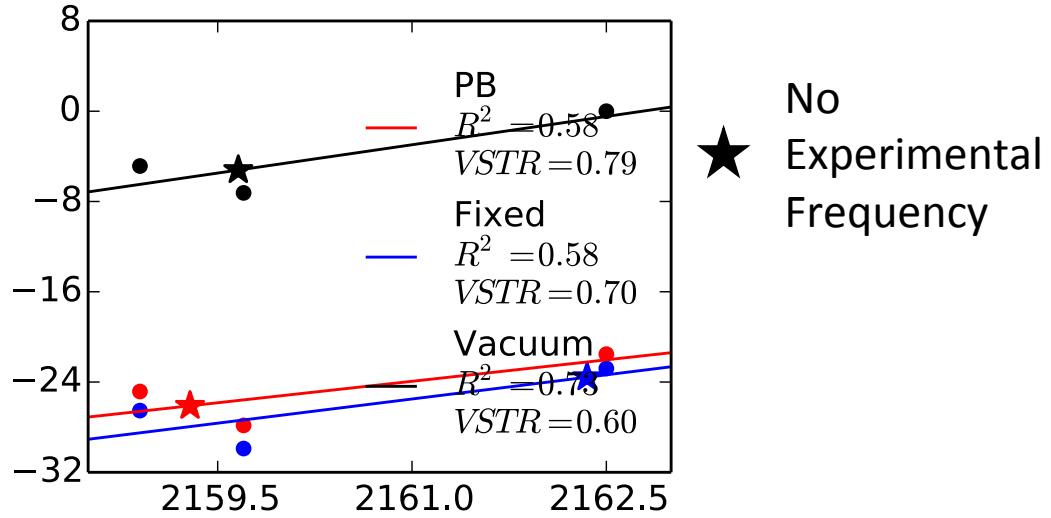
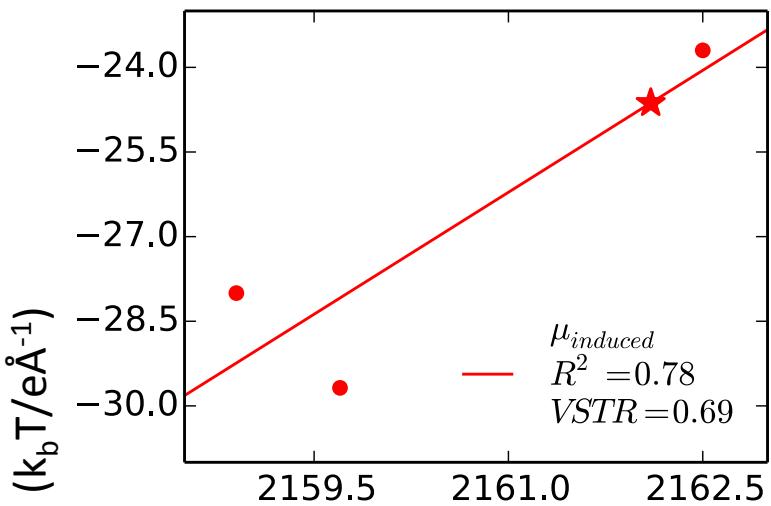
$$V_{i,\text{d}}(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{\vec{p}_j \cdot \hat{r}_{ij}}{|\vec{r}_{ij}|^2}$$

$$V_{i,\text{q}}(\vec{r}_{ij}) = \frac{1}{4\pi\epsilon_0} \sum_{k=1}^3 \frac{\hat{r}_j \hat{r}_k Q_{jk}}{2|\vec{r}_{jk}|^3}$$

$$\vec{F}_i = -\nabla(V_{ii,\text{m}} + V_{i,\text{d}} + V_{i,\text{q}} + \dots)$$

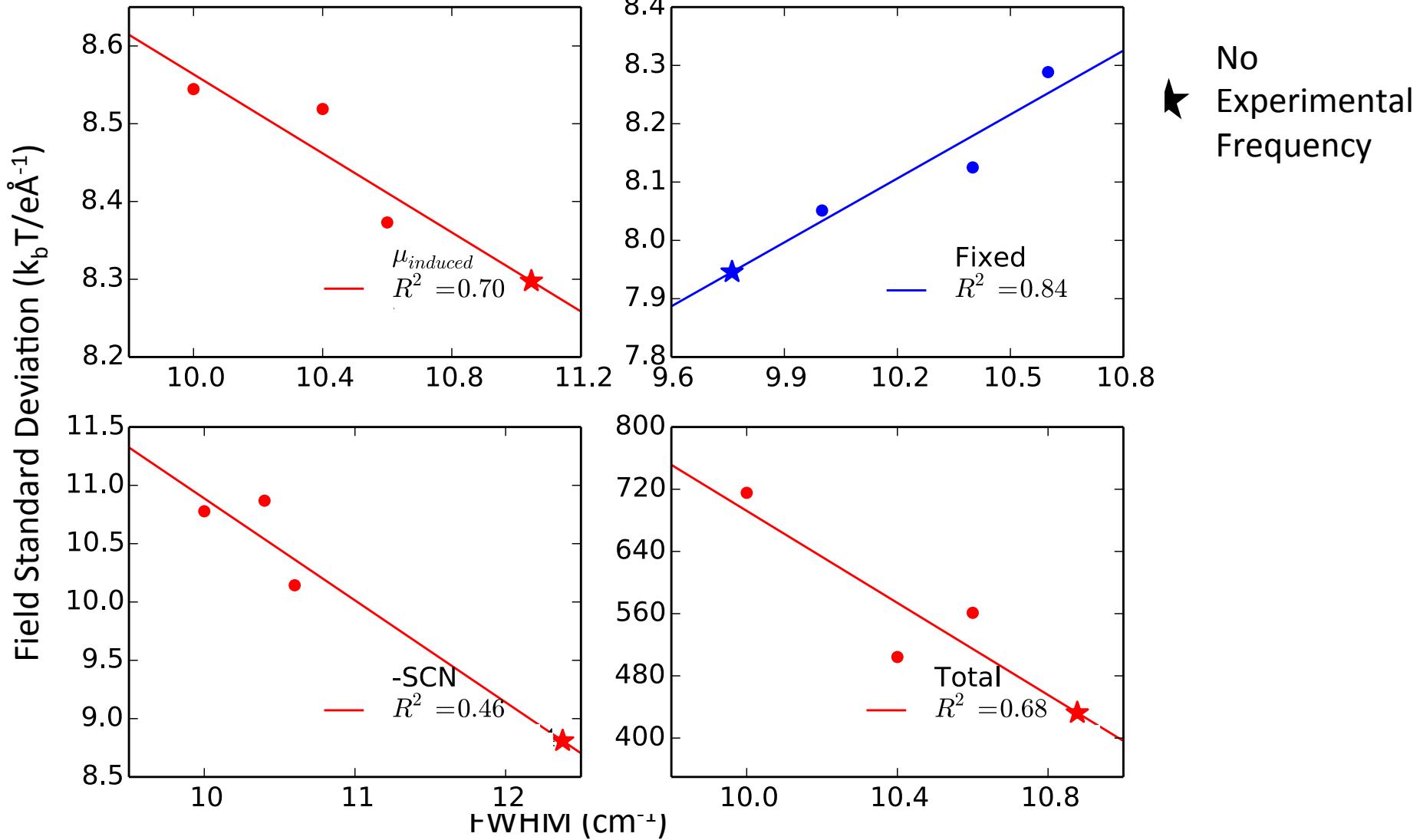
$$\mu_i = \alpha \left(\vec{F}_i^{\text{Solvent}} + \vec{F}_i^{\text{Solute}} \right)$$

Calculated fields thus far

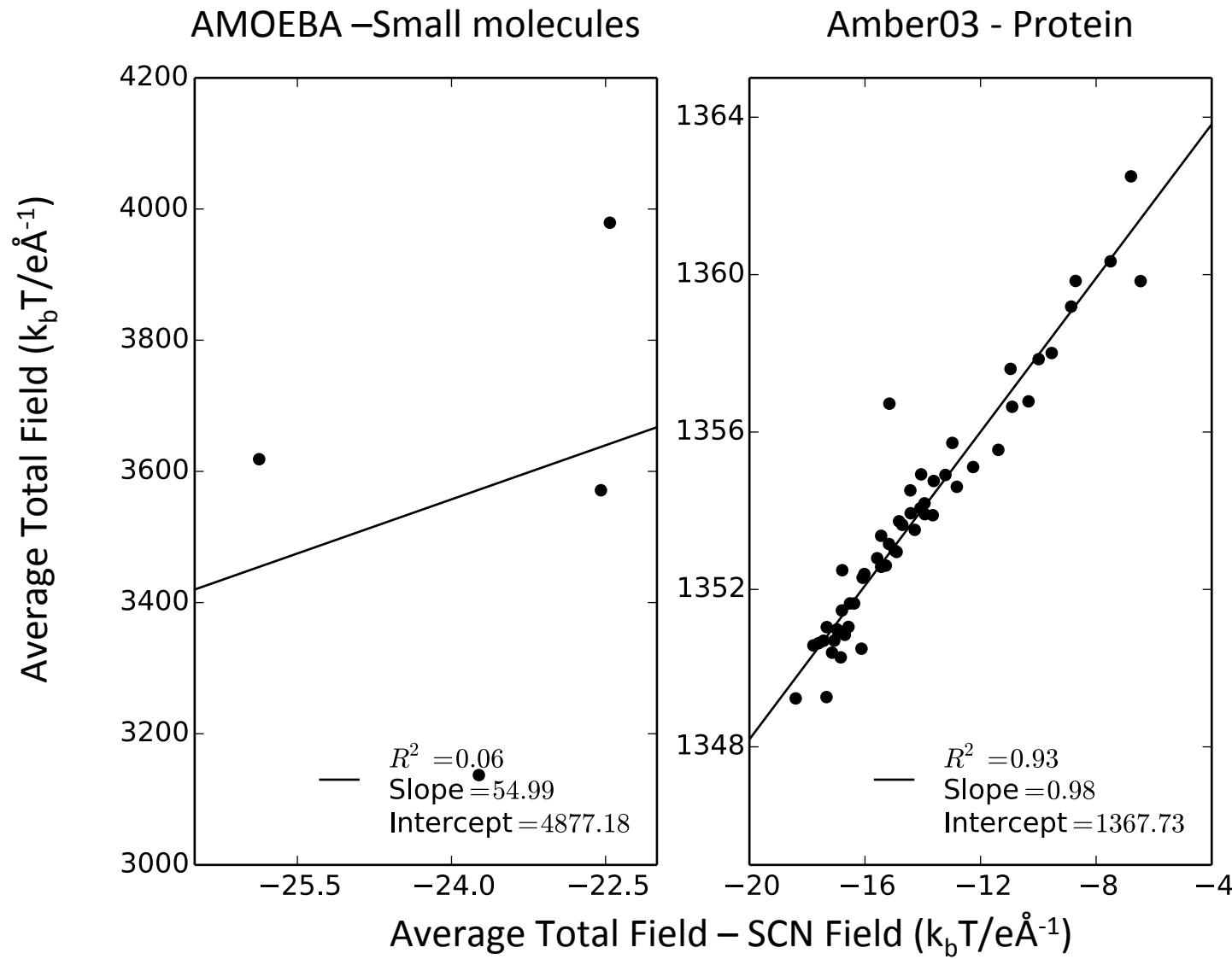


★ No Experimental Frequency

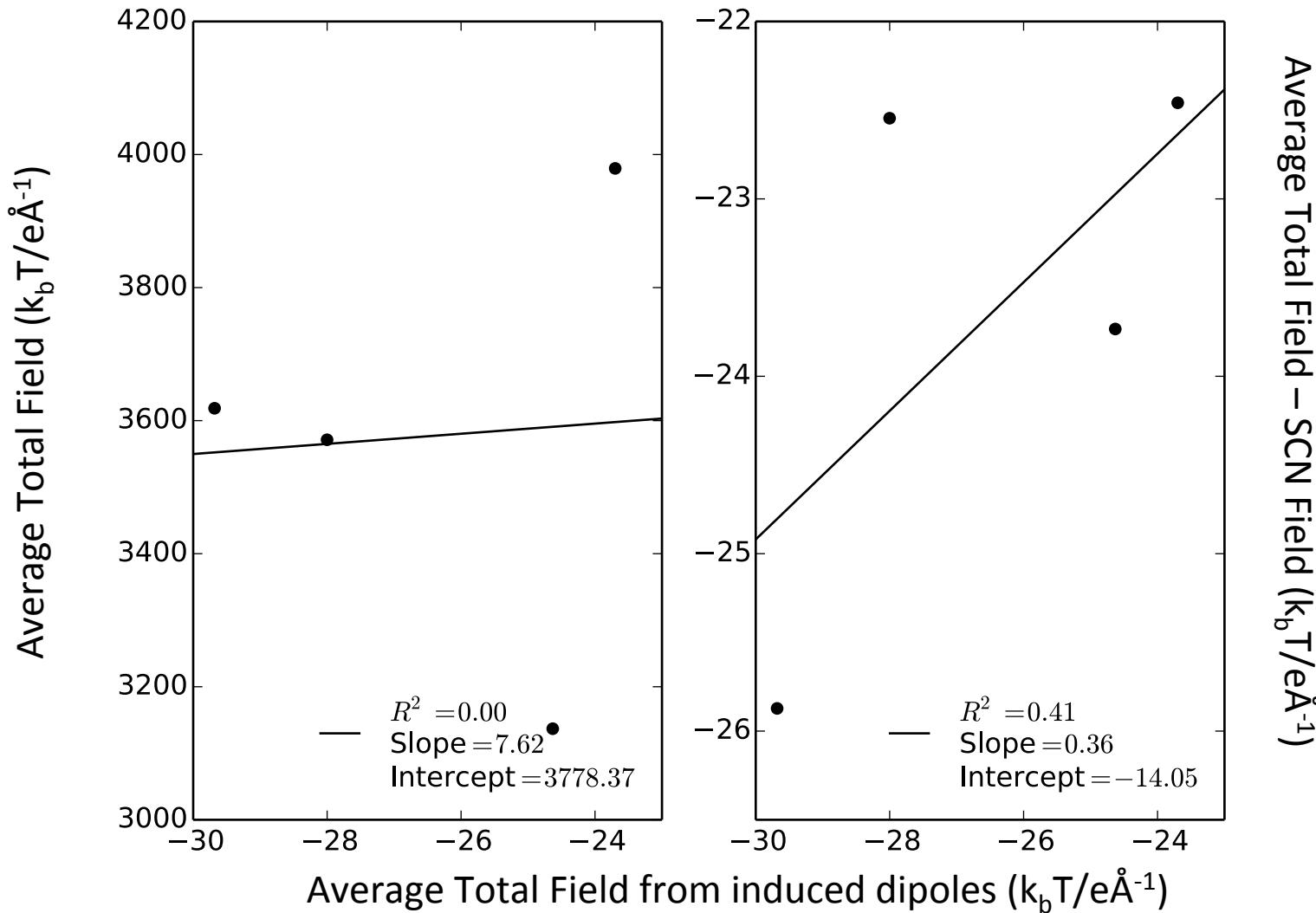
Standard deviations



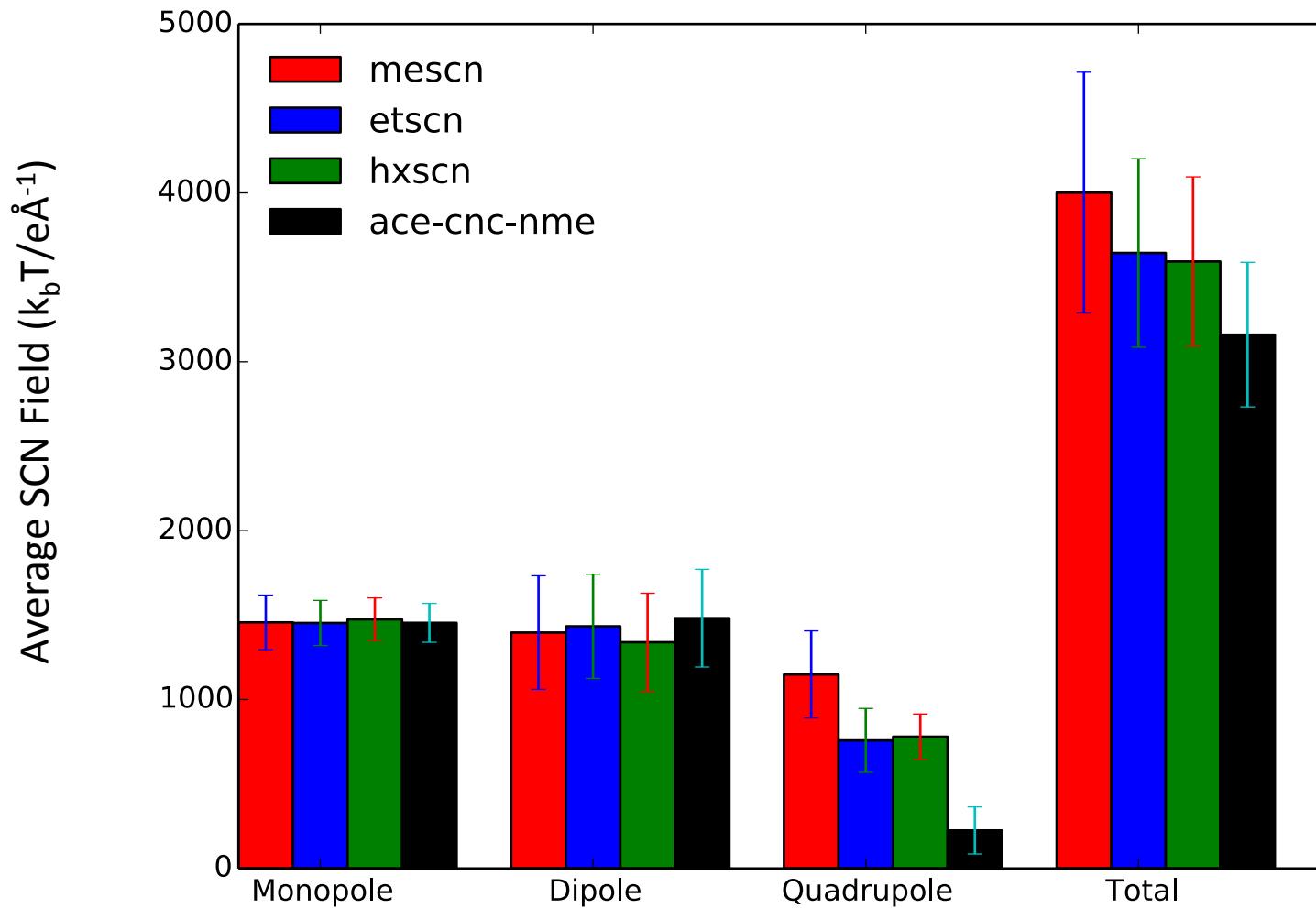
SCN field contribution is not constant



SCN field contribution is not constant



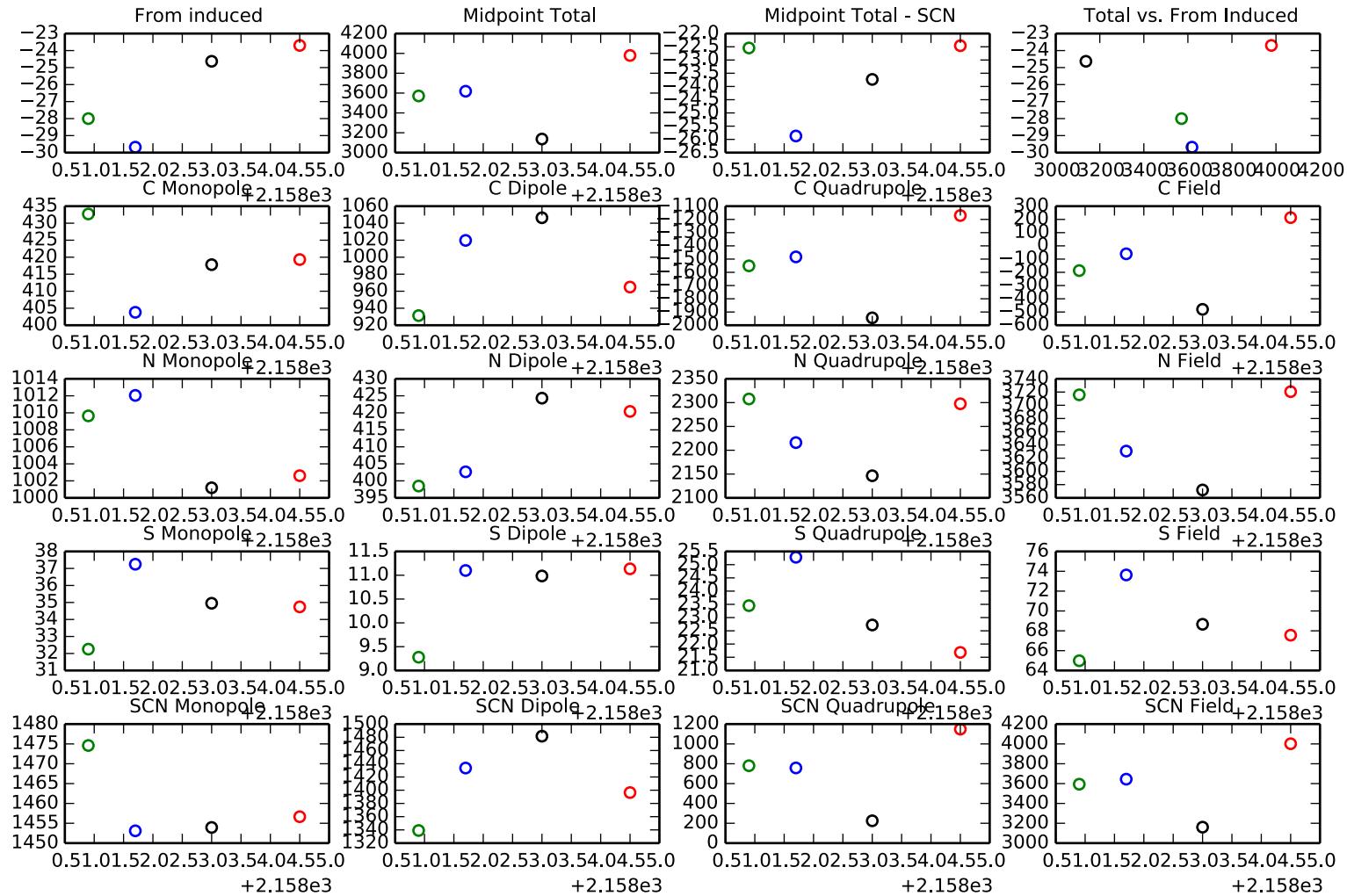
SCN field contribution is not constant



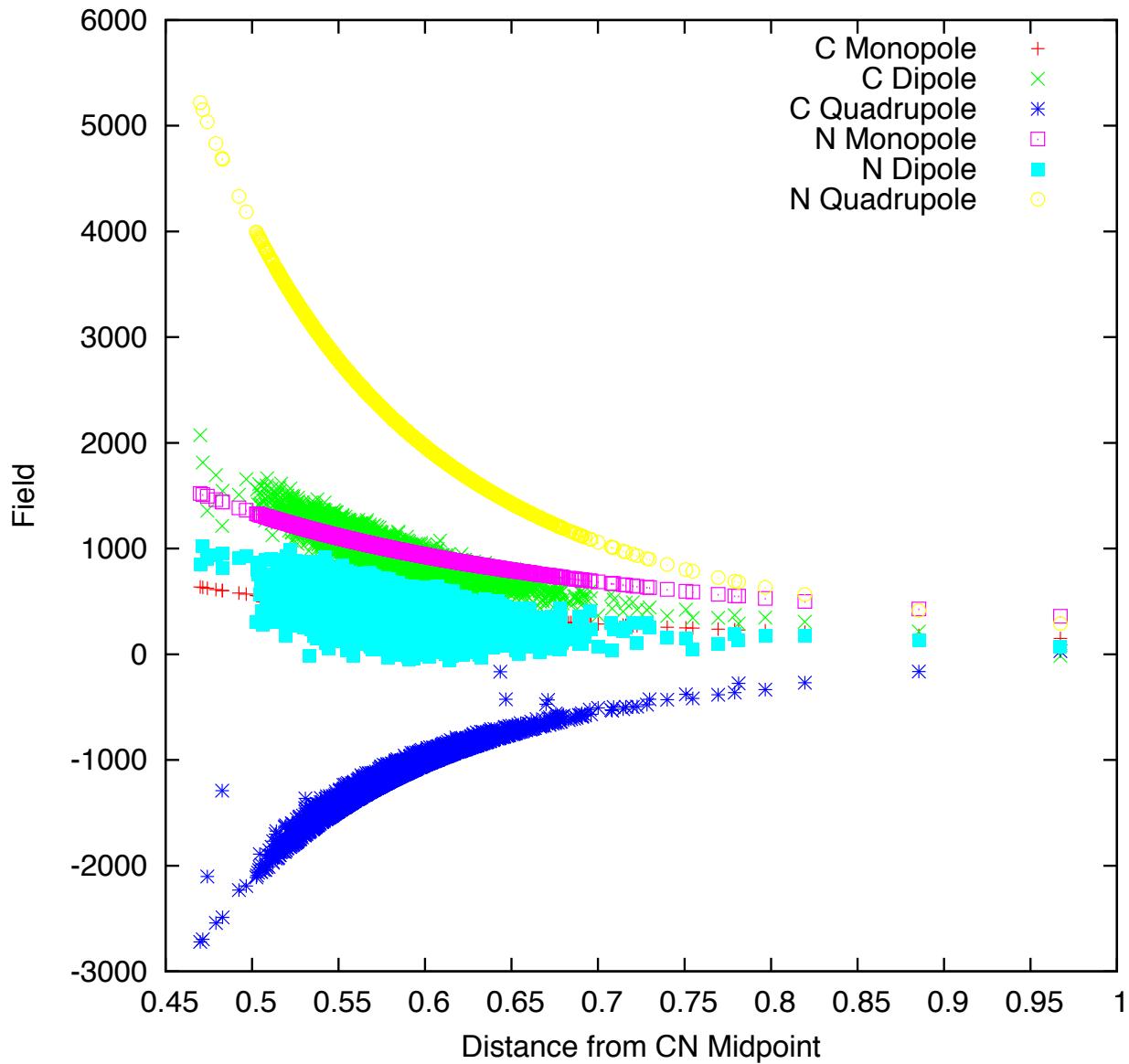
-SCN contribution is not constant

	mescn (k _b T/eÅ)	etscn (k _b T/eÅ)	hxscn (k _b T/eÅ)	ace-cnc-nme (k _b T/eÅ)
From induced	-23.70 (8.54)	-29.68 (8.37)	-28.00 (8.52)	-24.63 (8.30)
Midpoint Total	3979.15 (715.37)	3618.58 (561.05)	3571.21 (504.22)	3136.93 (432.50)
Midpoint Total - SCN	-22.46 (10.78)	-25.87 (10.14)	-22.55 (10.87)	-23.73 (8.81)
C Monopole	419.31 (47.40)	403.80 (37.82)	432.71 (37.92)	417.81 (33.76)
C Dipole	964.87 (195.12)	1019.75 (179.22)	931.32 (159.98)	1046.39 (162.46)
C Quadrupole	-1170.71 (266.15)	-1483.44 (303.87)	-1551.01 (275.86)	-1944.12 (332.09)
C Field	213.47 (99.06)	-59.89 (168.72)	-186.99 (131.43)	-479.92 (195.50)
N Monopole	1002.61 (113.35)	1012.05 (94.80)	1009.64 (88.47)	1001.18 (80.89)
N Dipole	420.41 (167.82)	402.65 (158.41)	398.47 (158.76)	424.31 (155.50)
N Quadrupole	2297.57 (513.36)	2216.01 (411.62)	2307.65 (395.78)	2146.43 (340.55)
N Field	3720.59 (730.61)	3630.71 (596.44)	3715.76 (567.72)	3571.93 (508.07)
S Monopole	34.74 (2.59)	37.25 (2.37)	32.25 (1.86)	34.95 (1.90)
S Dipole	11.13 (4.59)	11.10 (4.48)	9.28 (4.45)	10.98 (4.19)
S Quadrupole	21.68 (3.66)	25.28 (3.58)	23.45 (2.91)	22.72 (2.34)
S Field	67.56 (7.80)	73.63 (7.46)	64.98 (6.34)	68.66 (6.20)
SCN Monopole	1456.65 (161.58)	1453.10 (133.32)	1474.60 (127.03)	1453.95 (115.14)
SCN Dipole	1396.41 (336.26)	1433.50 (308.66)	1339.08 (289.92)	1481.68 (289.25)
SCN Quadrupole	1148.54 (257.93)	757.85 (189.12)	780.08 (134.01)	225.03 (139.45)
SCN Field	4001.61 (712.99)	3644.45 (558.15)	3593.76 (500.92)	3160.66 (428.16)

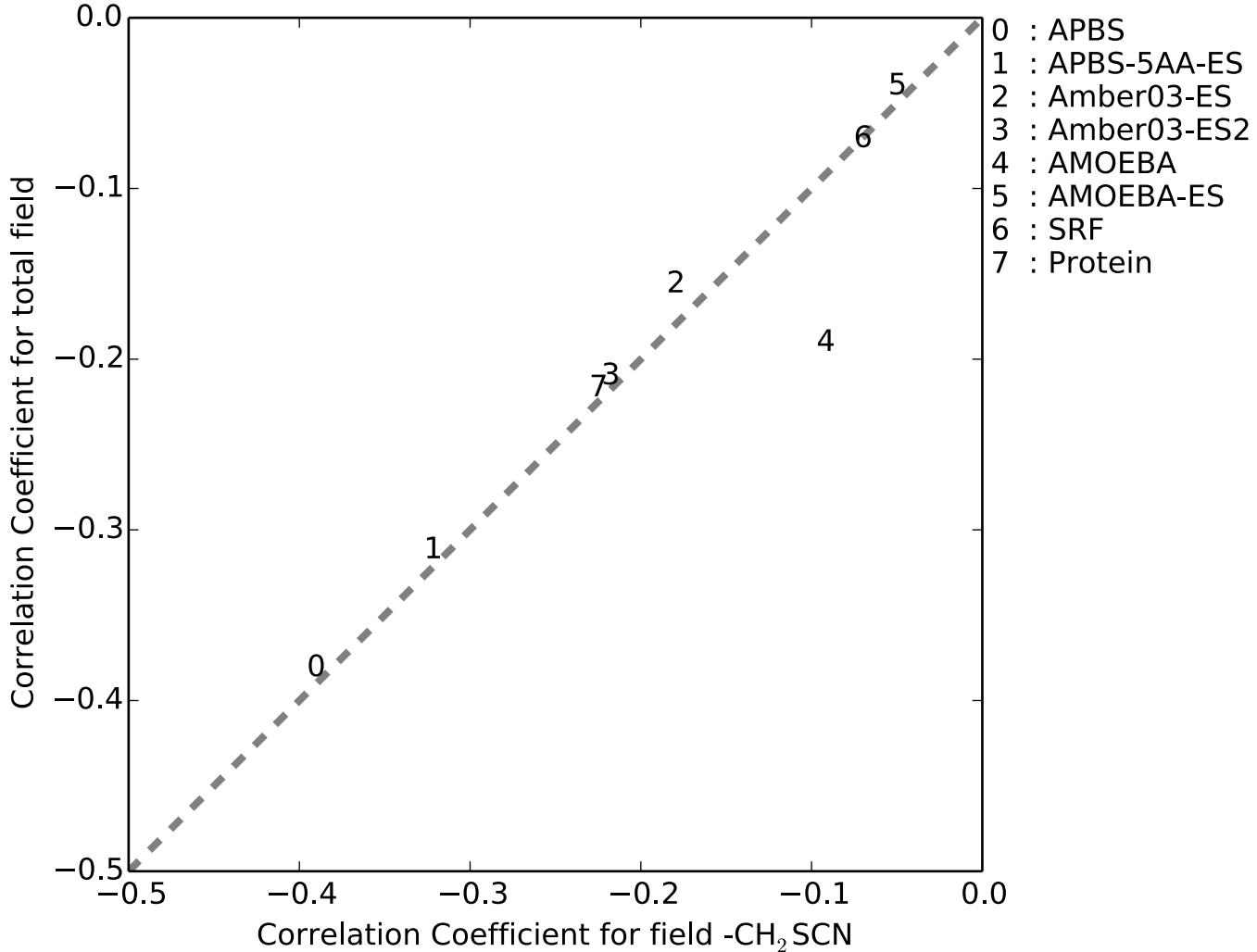
Calculated fields thus far



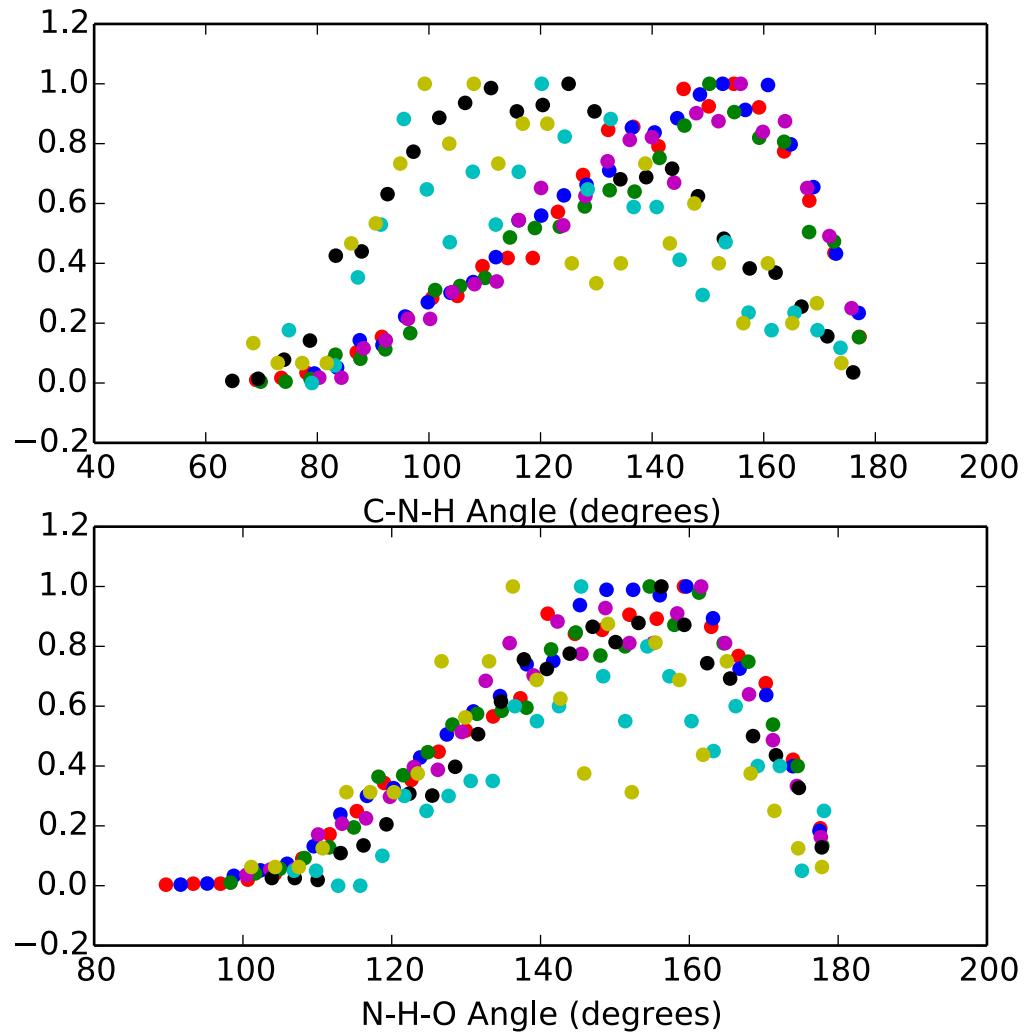
Calculated fields thus far



This does not significantly alter
previous studies sampled in in
Amber03

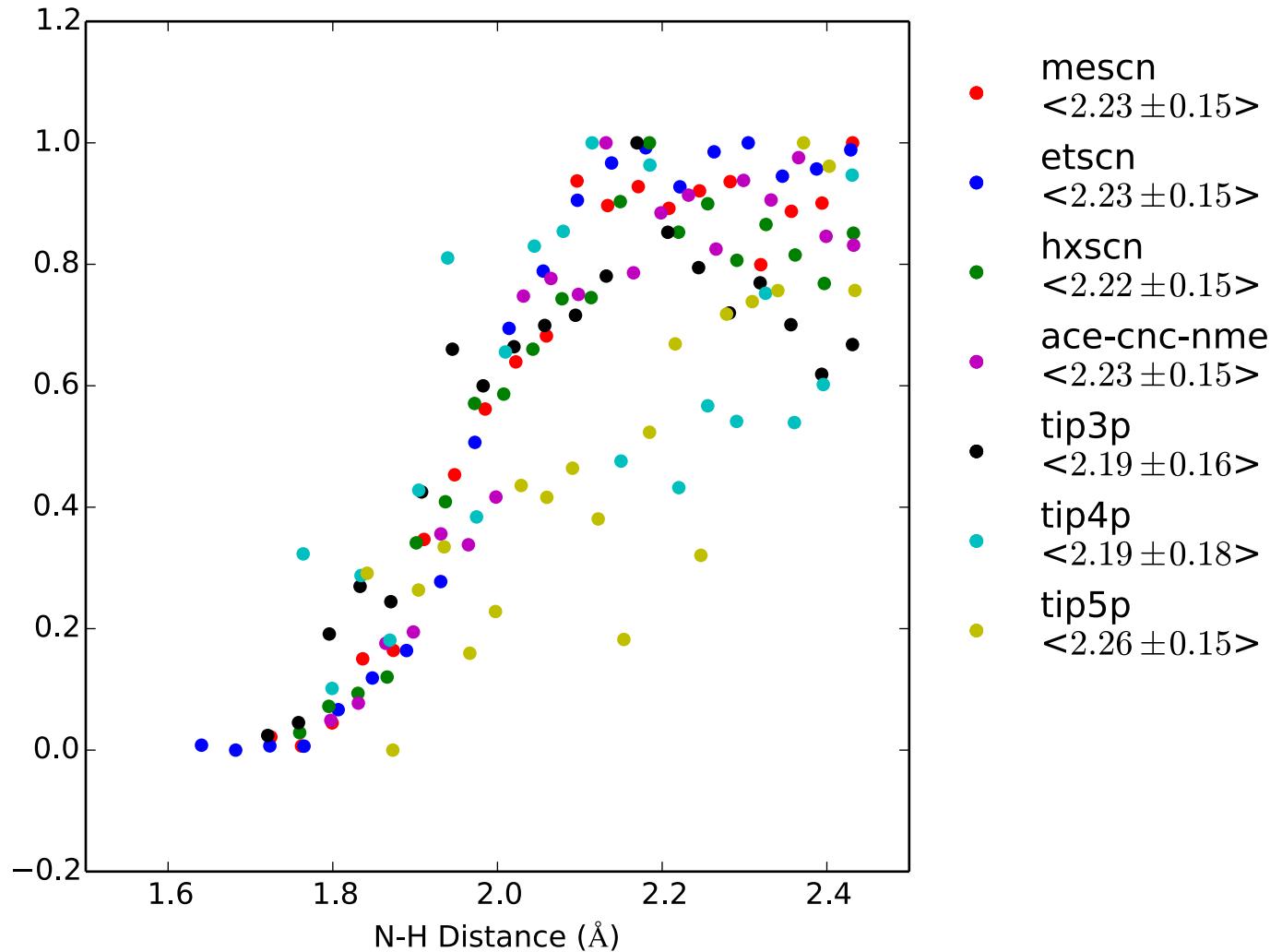


Comparing Water



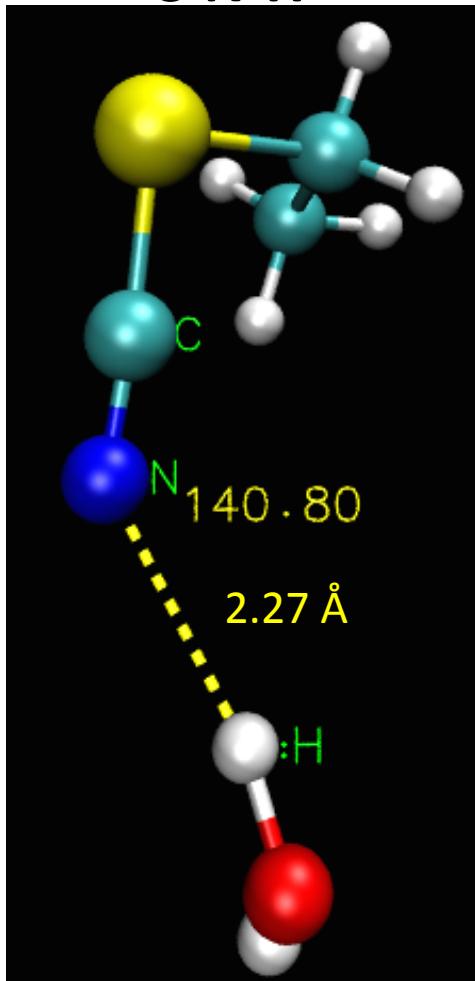
- mescn
• $\langle 139.33 \pm 22.01 \rangle$
• $\langle 147.76 \pm 16.93 \rangle$
 - etscn
• $\langle 139.96 \pm 21.87 \rangle$
• $\langle 147.10 \pm 17.08 \rangle$
 - hxscn
• $\langle 139.72 \pm 21.93 \rangle$
• $\langle 147.56 \pm 16.95 \rangle$
 - ace-cnc-nme
• $\langle 140.17 \pm 21.40 \rangle$
• $\langle 146.97 \pm 16.73 \rangle$
 - tip3p
• $\langle 121.69 \pm 22.93 \rangle$
• $\langle 148.60 \pm 15.16 \rangle$
 - tip4p
• $\langle 122.02 \pm 22.25 \rangle$
• $\langle 149.03 \pm 14.91 \rangle$
 - tip5p
• $\langle 119.69 \pm 23.92 \rangle$
• $\langle 142.81 \pm 16.75 \rangle$
- Stdev: 0.31, 0.32
- Stdev: 9.26, 1.89

Comparing Water

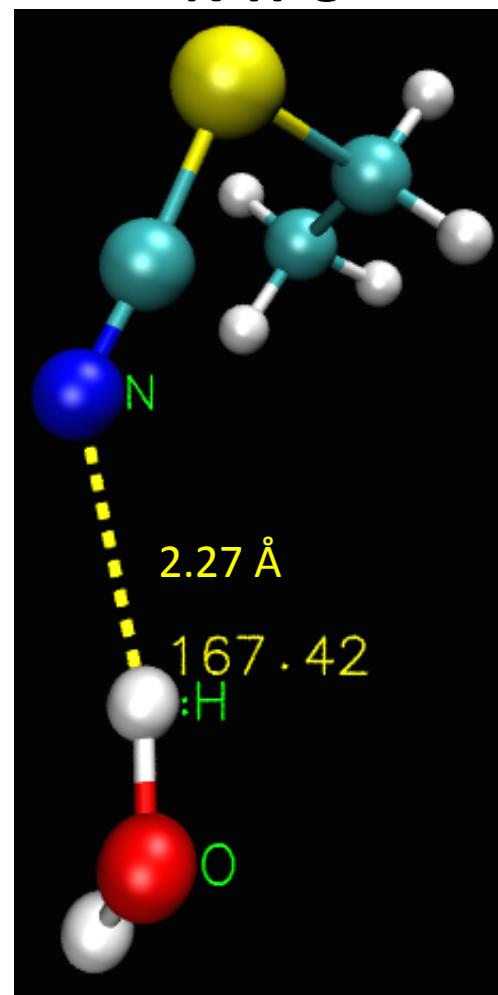


Comparing Water

C-N-H



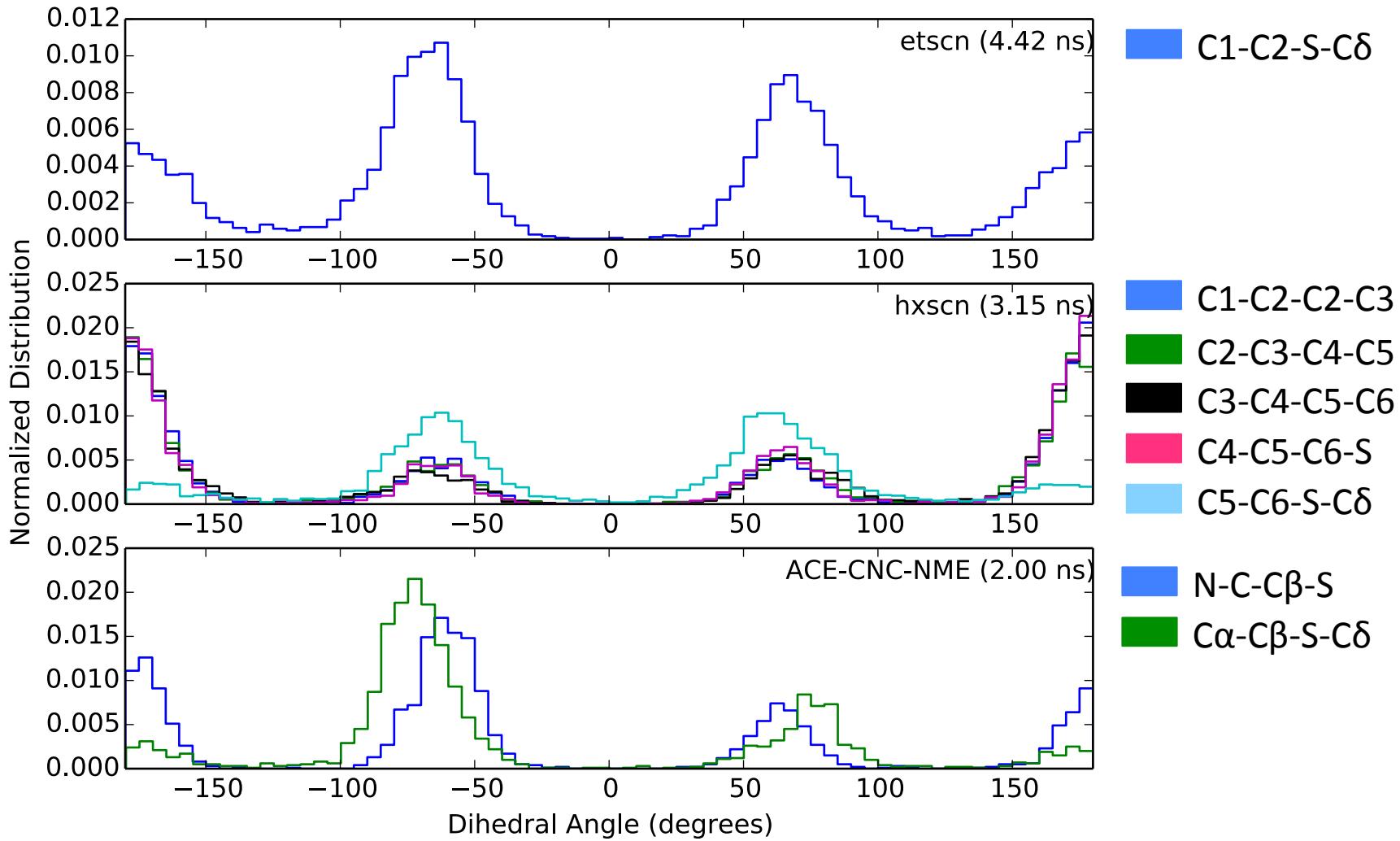
N-H-O



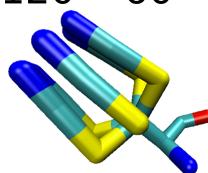
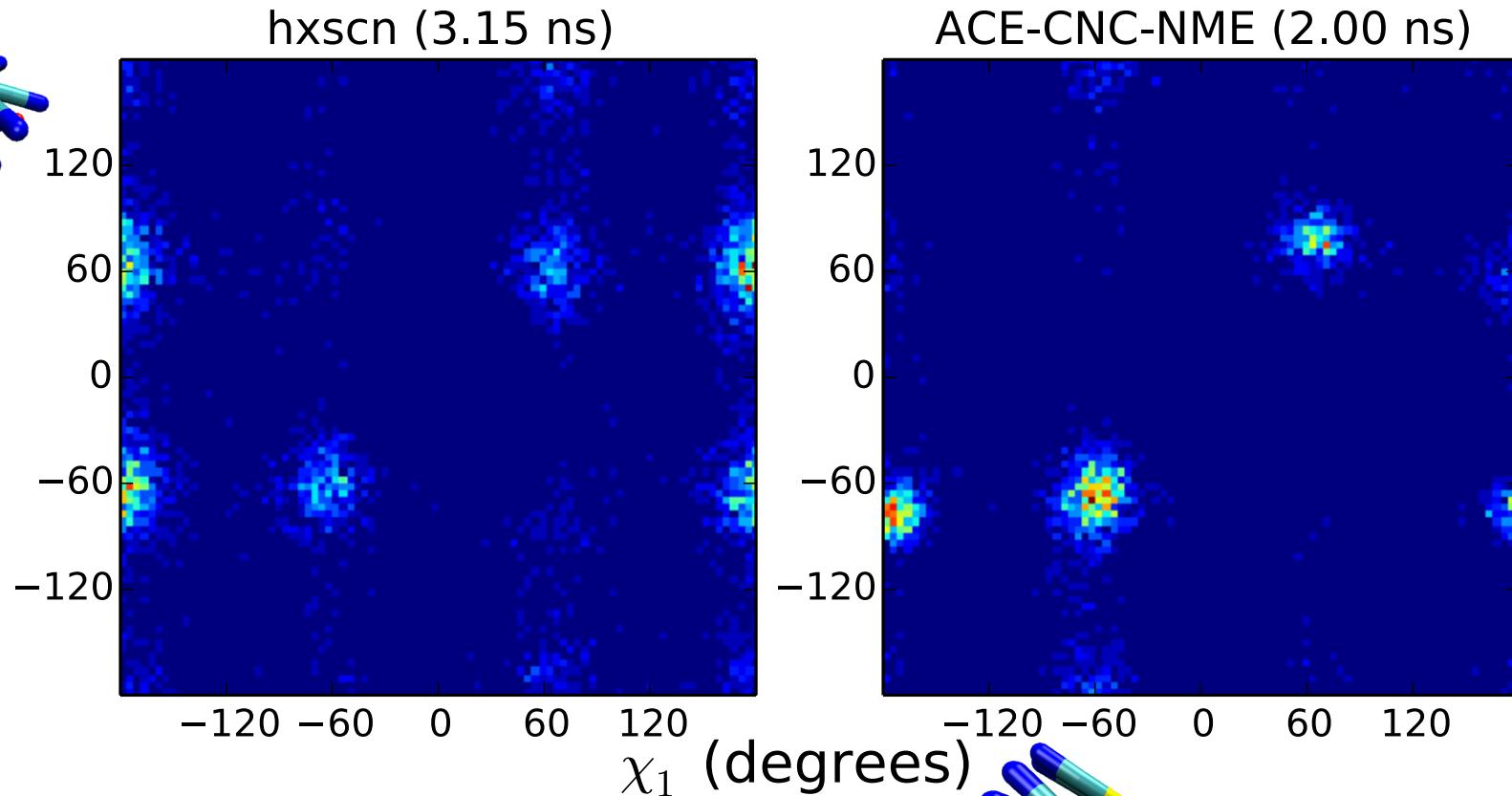
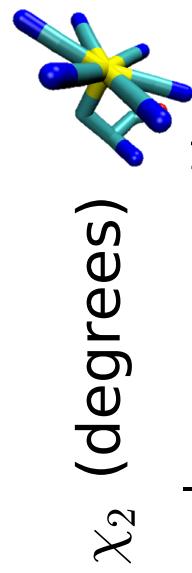
In Progress: Comparing Water

- Santiago currently working on production simulations of small molecules in tip3p, tip4p, and tip5p water
- Calculate the fields in the different point-charge water models and comparing to AMOEBA and experiment

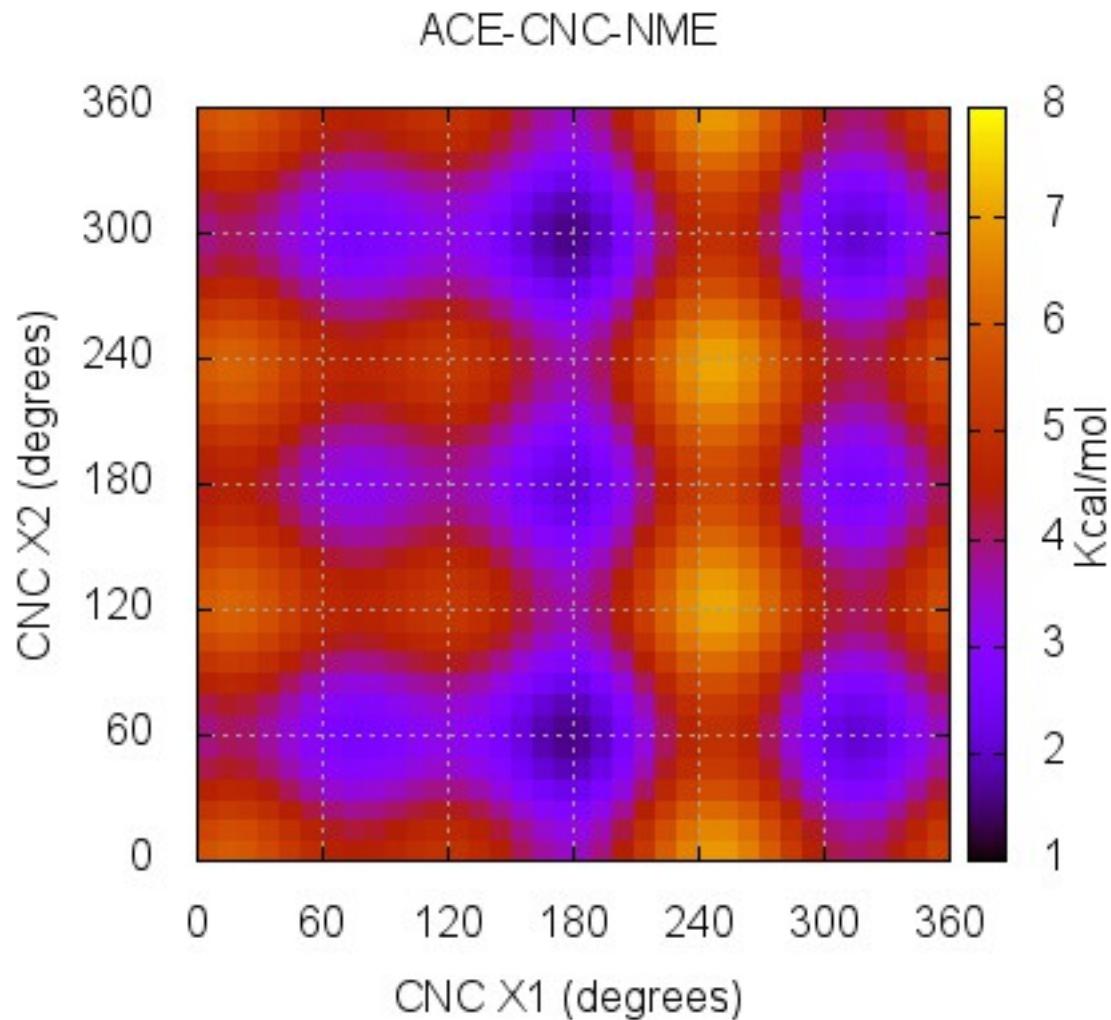
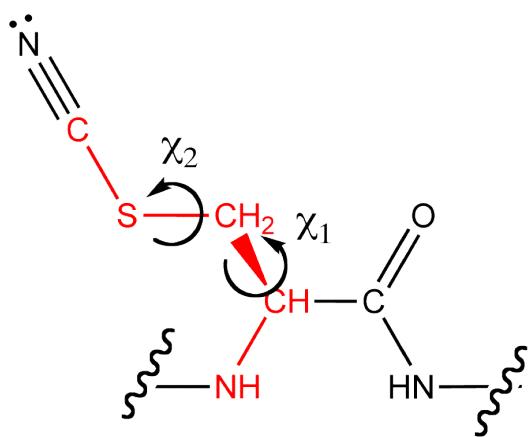
Sampling dihedral space, umbrella sampling required?



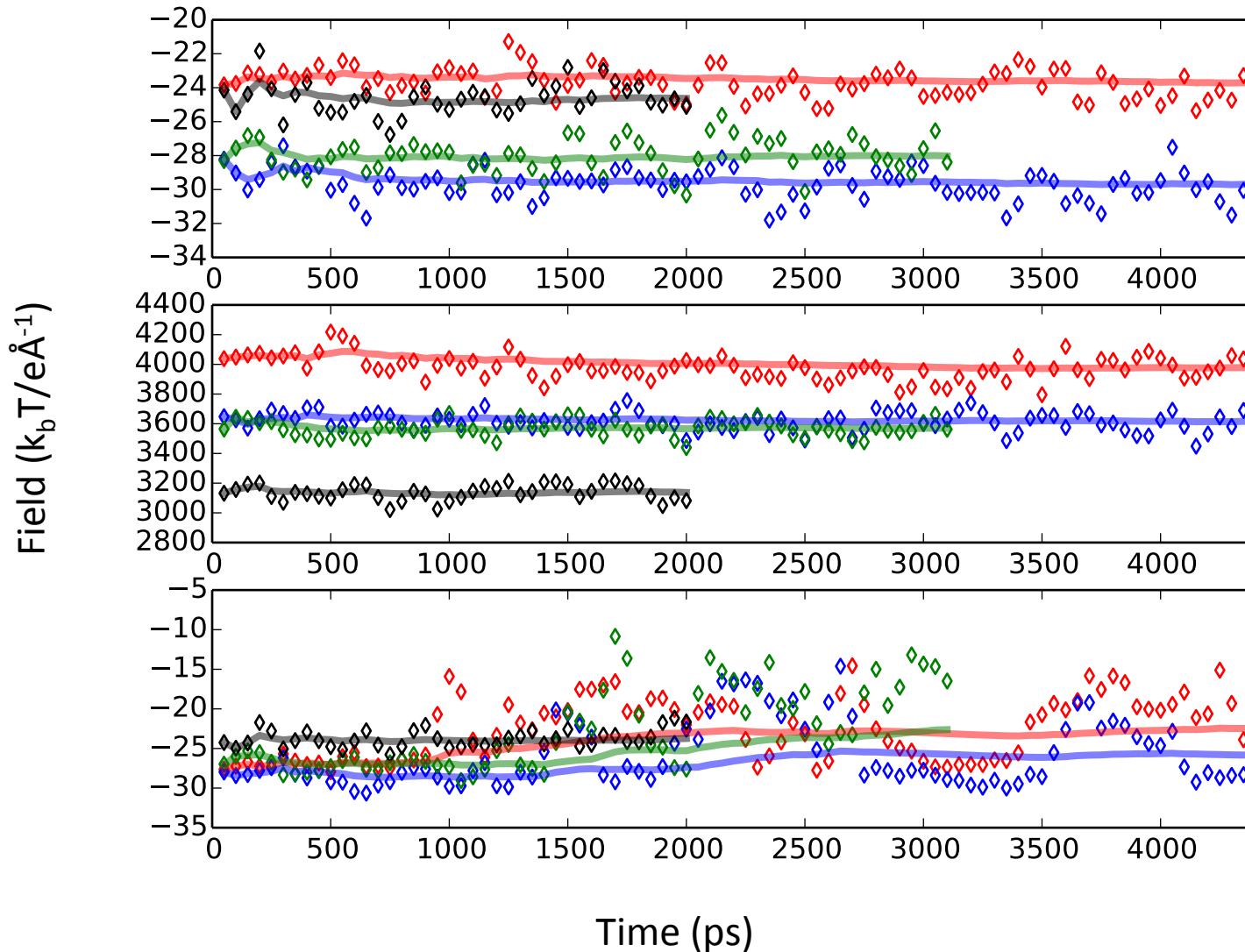
Sampling dihedral space, umbrella sampling required?



Quick Torsional Sanity Check



Convergence



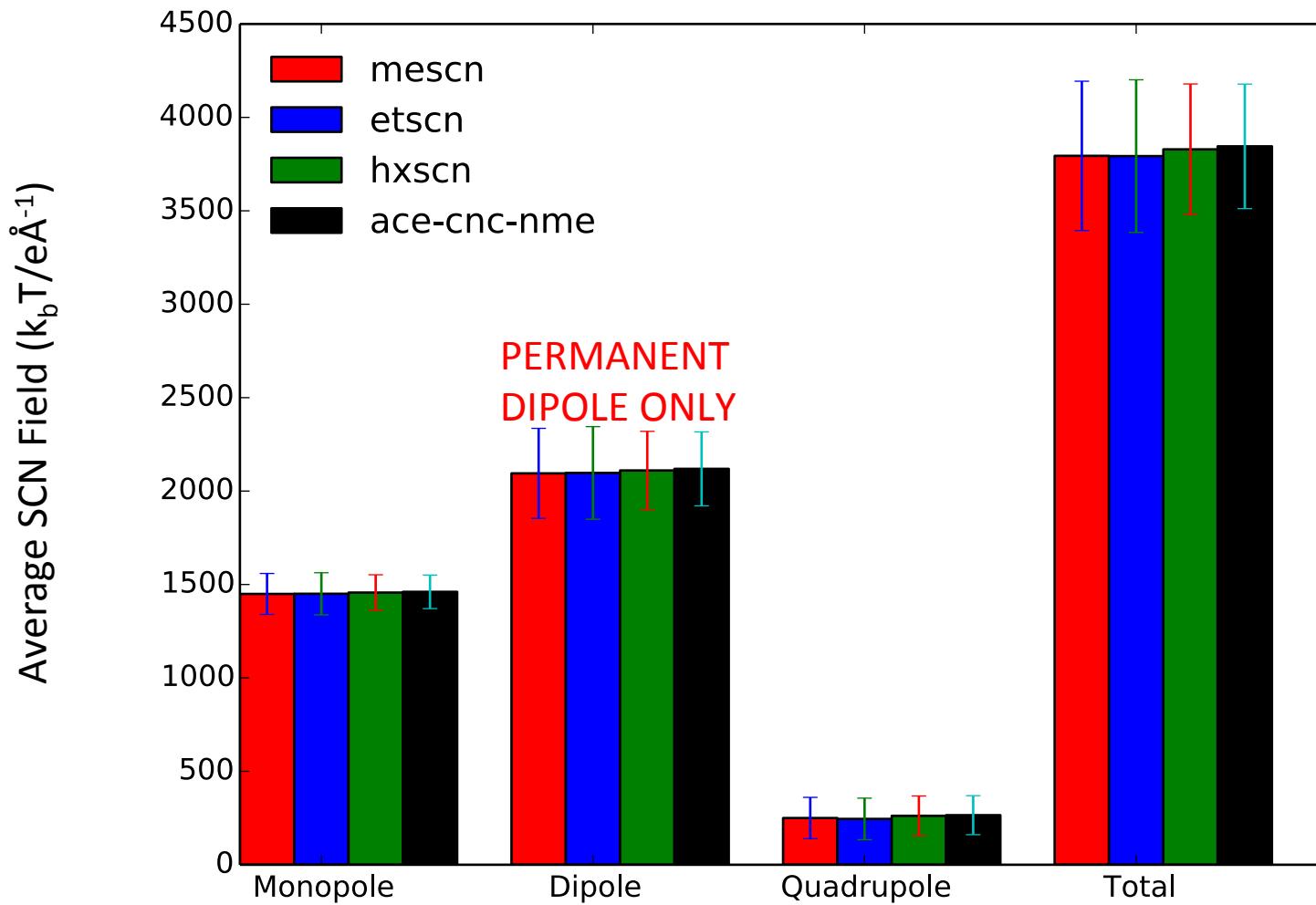
In Progress: Umbrella Sampling

- Work with Jeremy to establish a protocol consistent with previous work
- Determine “good” biasing force constants along dihedral space
- All CNC-containing peptides ACE-CNC-NME

The following slides are new

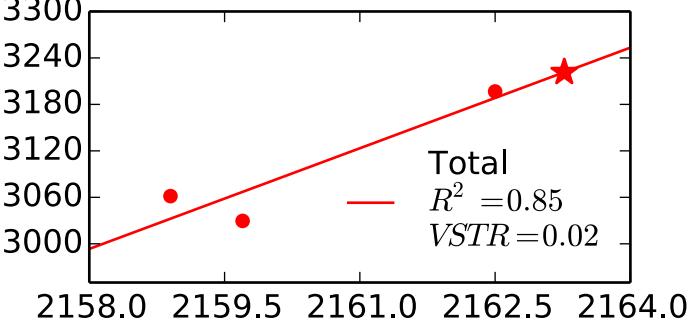
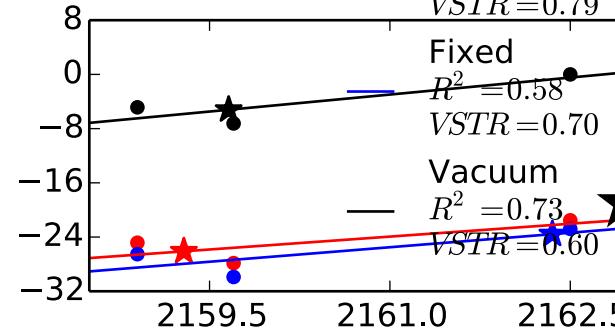
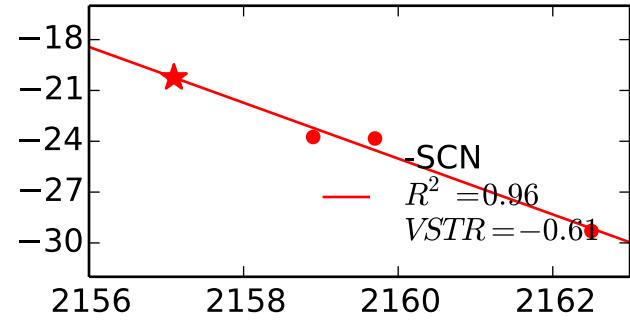
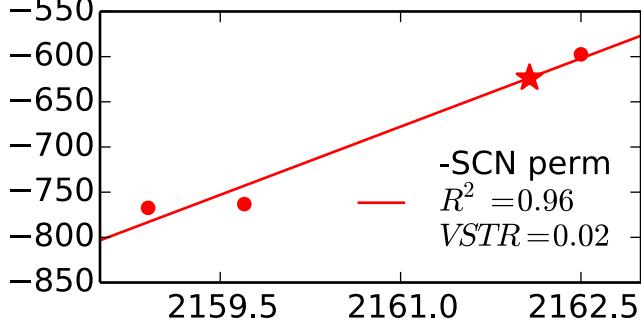
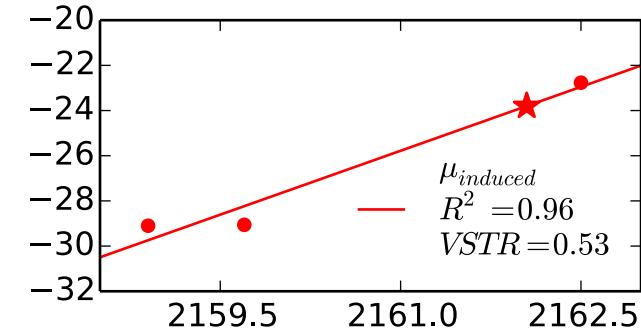
- Dr. Ren suggested I take the multipoles on SCN from one of the parameterizations and fix the SCN multipoles on the other molecules and re-optimize. In this way, MeSCN, EtSCN, HxSCN, and CNC all have the same SCN multipole parameters, and the only thing different is what they are bound to. Here are the results thus far.
- There is another bit of information added. I previously have removed the SCN contribution to the field from the total field. This results in the field being reported only being the part due to the probe environment, and not the probe itself. One of the things we observed was that the SCN field was not constant, hence the re-parameterization previously mentioned. When I looked at the sort of plot on slide 27, the monopole and quadrupole contributions were *very* similar. While the dipole contributions were significantly closer to each other than previously, they were less so than the other monopoles and quadrupoles. The reason for that is the dipole has 2 contributions, the permanent and the induced. The permanent dipole contribution to field is approximately equal for all molecules (slide 42). So now, in addition to showing the (total – SCN) field, I'm also showing the (total - SCN permanent only), where the SCN induced dipole field contribution is included.
- 3 ns MeSCN, EtSCN, HxSCN (2 fs timestep), 4 ns ACE-CNC-NME

SCN field contribution is now relatively constant



Calculated fields

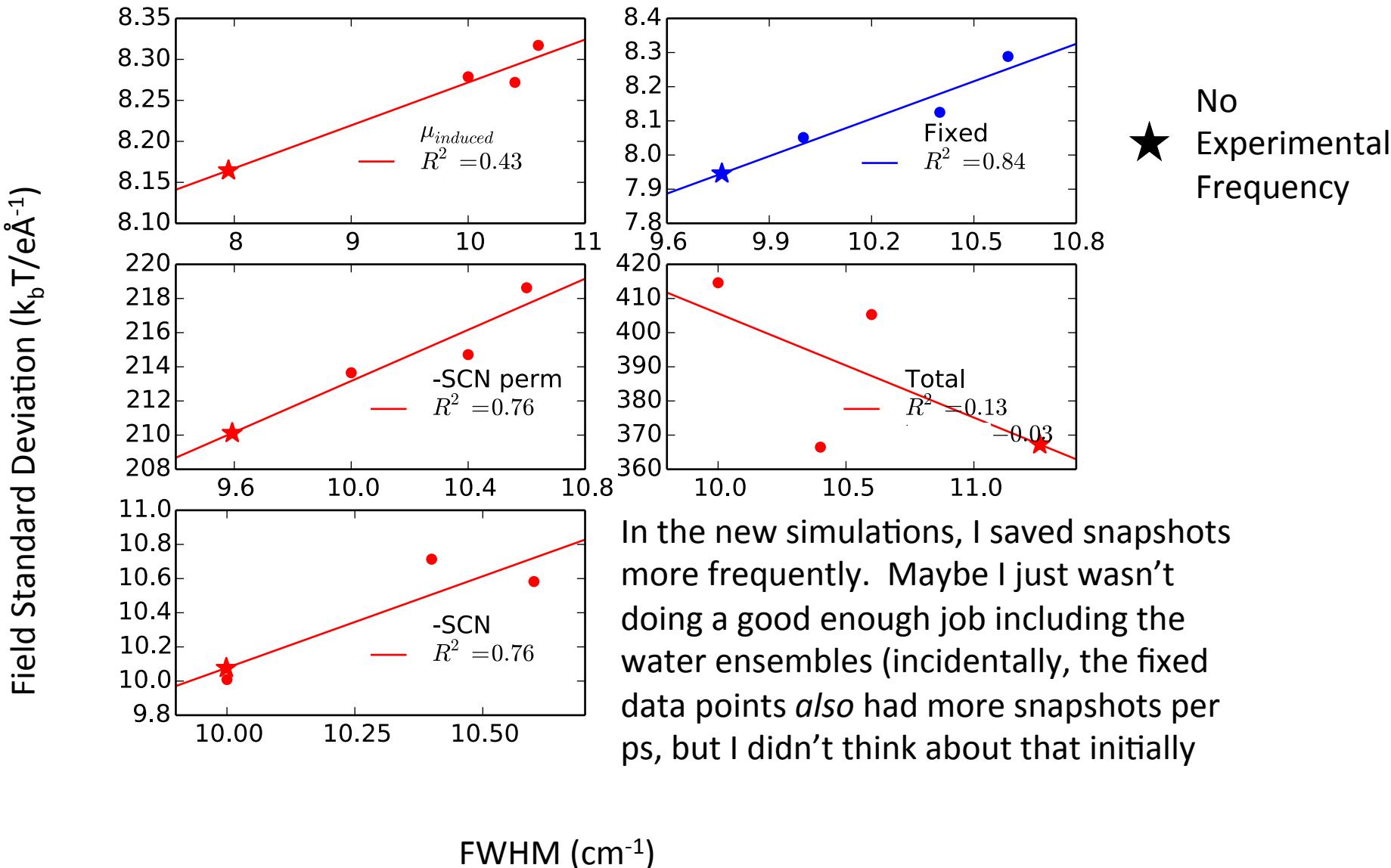
Average Field ($k_b T / e\text{\AA}^{-1}$)



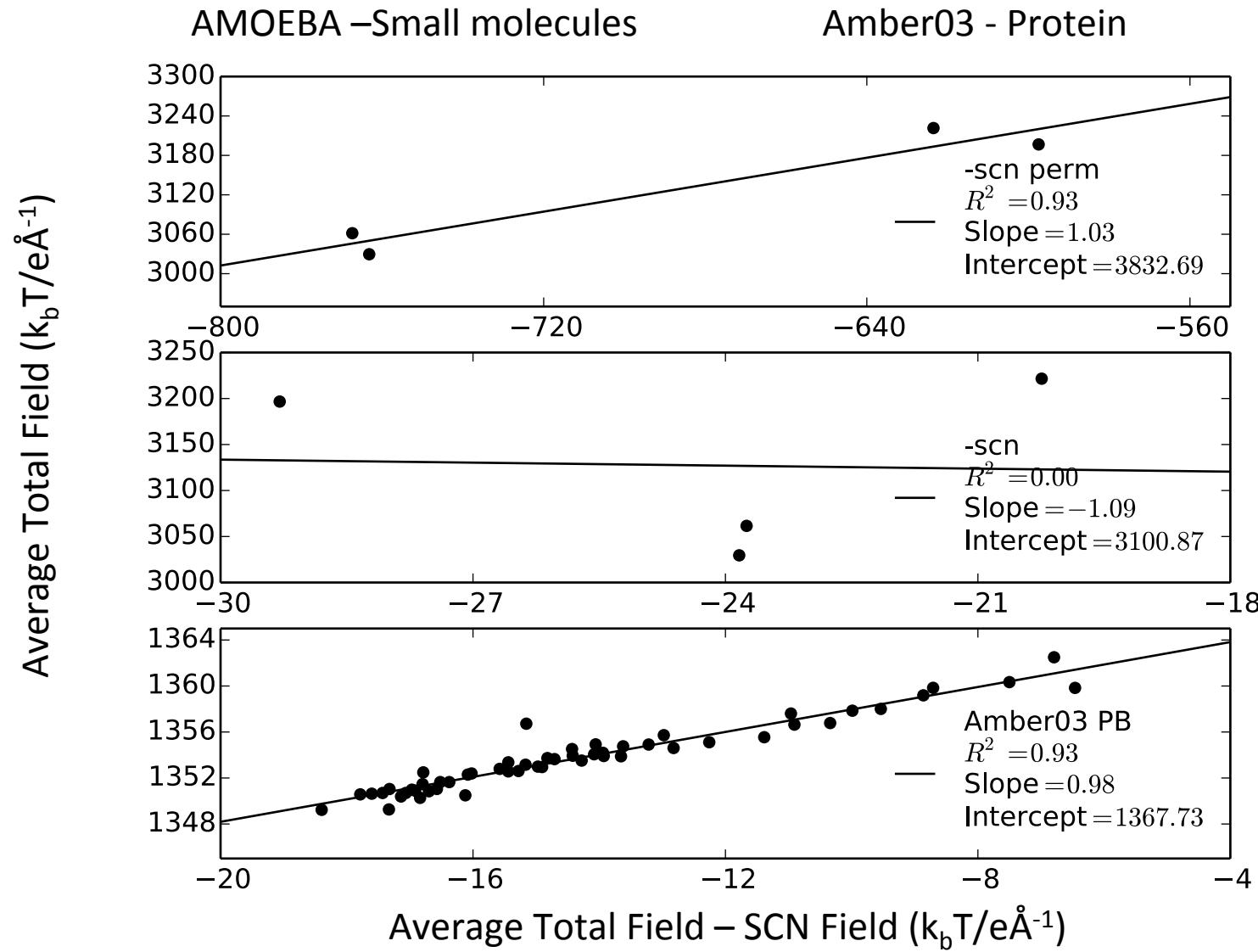
No
Experimental
Frequency

Interestingly, if we remove the SCN contribution to the field, the slope is negative. If we allow the probe to polarize (ie: include the induce dipole SCN part of the field), then we recover the expected positive slope. A possible reason why the Amber03 calculations show the wrong slope?

Standard deviations



Removing the permanent part of the SCN field is approximately removing a constant from the total field



SCN field contribution is not constant

