Evaluating molecular dynamics force fields using computed NMR chemical shifts

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8.5

9.0



Experiment







Regions of Interest (ROI)



- Identify all nearby polar and aromatic atoms
- Separate analysis for O and NH









ROI Conformer



- Extend target residue to capped 4-residue peptide
- Extend nearby polar/aromatic atoms to 3-residue peptide
- Include nearby waters







HartreeFocker @edsherer · 4h #compchem when you tell someone you're using B3LYP #acsdc





HartreeFocker @edsherer · 4h #compchem when you tell someone you're using B3LYP #acsdc



Calculate Chemical Shifts







Pattern Templates



O:R:R|3.512|3.408|3.131|3.295|4.399|2.129|4.802|3.906|4.912|5.907|4.884|5.752|5.908|6.788|8. **O**|3.361|2.866|3.072|3.337|4.310|1.945|4.619|3.614|4.312|5.528 **Z**|3.652|3.518|3.071|3.151|4.390





Matching Parameter









ROI Selection



foreach pattern
create_graph G_{pattern}
foreach frame in simulation
foreach ROI with pattern
create_node n in G_{pattern}
foreach m in G_{pattern}
if MP(n,m) < threshold
add_edge (n,m) to G_{pattern}

Solve dominating set problem Smallest subset of nodes D such that every node of G is either in D or is adjacent to a node in D

NP-hard, but good approximation algorithm













Sources of Error

Level of Quantum Theory Size of ROI Reduction to Pattern Closeness of Match

> Sampling of MD Accuracy of MD

Molecular Dynamics Evaluation

Sampling

- 30 x 10ns simulations
- independent equilibration, random velocities

Amber Force Fields

- ff94
- ff96
- ff99SB
- ff14SB
- ff14ipq
- ff15ipq

Proteins (BMRB)

| 1enh | 2a3d |
|------|------|
| 1ubq | 3obl |
| 1qzm | 1hik |
| 1igd | 1l2y |

¹³C^α RMS Error

| | | | (| | | | |
|------------|------|------|-----------------|-----------------|---------|---------|---------------|
| 1enh | 1.85 | 1.93 | 1.94 | 1.92 | 1.97 | 2.02 | 2.25 |
| 1hik | 1.76 | 1.71 | 1.80 | 1.77 | 1.76 | 1.87 | 2 10 \ |
| .⊆ 1igd | 2.19 | 2.08 | 2.31 | 2.19 | 2.21 | 2.15 | |
| Hora 1 dzm | 2.05 | 2.01 | 2.11 | 2.18 | 2.01 | 2.03 | <u>1.95</u> Ш |
| ດ້ 1ubq | 1.94 | 2.08 | 2.13 | 2.04 | 2.13 | 2.31 | 1.80 ≥ |
| 2a3d | 2.14 | 2.03 | 1.92 | 2.01 | 2.23 | 2.07 | 1 65 |
| 3obl | 1.88 | 1.98 | 1.78 | 1.91 | 2.00 | 2.03 | 1.00 |
| Mean | 1.97 | 1.97 | 2.00 | 2.00 | 2.04 | 2.07 | |
| Std | 0.16 | 0.13 | 0.19 | 0.15 | 0.16 | 0.14 | |
| AbsErr% | 2.78 | 2.77 | 2.87 | 2.85 | 2.90 | 2.93 | |
| • | ff94 | ff96 | ff99SB Force | ff14SB Field | ff14ipq | ff15ipq | |

¹⁵N RMS Error

| | | | 1 | N | | | |
|---------|------|------|-----------------|-----------------|---------|---------|------------------|
| 1enh | 6.66 | 6.64 | 6.41 | 6.43 | 6.03 | 5.78 | 7 2 |
| 1hik | 5.55 | 5.44 | 5.34 | 5.42 | 5.28 | 4.97 | |
| .⊆ 1igd | 7.42 | 7.36 | 7.66 | 7.51 | 7.13 | 7.30 | 6.6 9 |
| g 1qzm | 6.42 | 6.36 | 6.24 | 6.24 | 6.32 | 5.89 | 6.0 ^Ш |
| Lubq | 6.23 | 6.25 | 6.14 | 5.99 | 5.81 | 5.57 | $54 \sum$ |
| 2a3d | 5.02 | 4.95 | 4.88 | 5.06 | 5.10 | 4.55 | |
| 3obl | 5.65 | 5.73 | 5.75 | 5.70 | 5.10 | 5.23 | 4.8 |
| Mean | 6.14 | 6.11 | 6.06 | 6.05 | 5.82 | 5.61 | |
| Std | 0.80 | 0.80 | 0.89 | 0.80 | 0.74 | 0.88 | |
| AbsErr% | 4.25 | 4.17 | 4.20 | 4.16 | 3.98 | 3.85 | |
| | ff94 | ff96 | ff99SB Force | ff14SB Field | ff14ipq | ff15ipq | |

¹⁵N RMS Error



¹H RMS Error

| | | | F | -1 | | | |
|---------|-------|-------|-----------------|-----------------|---------|---------|-------------|
| 1enh | 1.86 | 1.75 | 1.87 | 1.82 | 1.70 | 1.73 | |
| 1hik | 1.61 | 1.52 | 1.62 | 1.58 | 1.48 | 1.57 | 1.95 |
| ligd _ | 1.70 | 1.62 | 1.73 | 1.69 | 1.60 | 1.63 | |
| | 1.91 | 1.84 | 1.90 | 1.83 | 1.76 | 1.73 | 工.0U ⊆ Ш |
| 2 1qzm | 1.76 | 1.74 | 1.79 | 1.74 | 1.62 | 1.64 | 1 65 S |
| 🗅 1ubq | 1.66 | 1.62 | 1.61 | 1.56 | 1.40 | 1.52 | N N |
| 2a3d | 1.66 | 1.51 | 1.70 | 1.66 | 1.50 | 1.57 | 1.50 |
| 3obl | 1.59 | 1.55 | 1.54 | 1.48 | 1.38 | 1.42 | |
| Mean | 1.72 | 1.64 | 1.72 | 1.67 | 1.55 | 1.60 | |
| Std | 0.11 | 0.12 | 0.13 | 0.13 | 0.14 | 0.11 | |
| AbsErr% | 19.41 | 18.26 | 19.41 | 18.85 | 17.17 | 18.03 | |
| | ff94 | ff96 | ff99SB Force | ff14SB Field | ff14ipq | ff15ipq | |

¹H RMS Error



Secondary Structure

| Н | | | | | | | | | | | |
|-------|------|------|-----------------|-----------------|---------|---------|---|-----------------------------|--|--|--|
| All | 1.68 | 1.61 | 1.68 | 1.63 | 1.51 | 1.57 | | 2.0 _ | | | |
| Coil | 1.79 | 1.73 | 1.74 | 1.69 | 1.58 | 1.59 | | 1.8 U U | | | |
| Helix | 1.73 | 1.64 | 1.80 | 1.74 | 1.61 | 1.71 | | 1.6 ഗ ≥ | | | |
| Sheet | 1.37 | 1.30 | 1.31 | 1.27 | 1.18 | 1.23 | | 1.4 CC | | | |
| | ff94 | ff96 | ff99SB | ff14SB | ff14ipq | ff15ipq | | • 1.2 | | | |
| | | | ľ | N | | | | | | | |
| All | 6.02 | 5.99 | 5.95 | 5.94 | 5.71 | 5.52 | | 6.2 | | | |
| Coil | 5.95 | 5.74 | 5.91 | 6.00 | 5.66 | 5.59 | | 6.0 H | | | |
| Helix | 6.09 | 6.18 | 5.92 | 5.92 | 5.83 | 5.42 | | 5.8 S | | | |
| Sheet | 6.16 | 6.14 | 6.28 | 6.11 | 5.73 | 5.79 | | 5.6 ℃ | | | |
| I | ff94 | ff96 | ff99SB | ff14SB | ff14ipq | ff15ipq | | 1 | | | |
| | | | (| | | | | | | | |
| All | 1.94 | 1.95 | 1.97 | 1.99 | 2.02 | 2.05 | | 2.10 _ | | | |
| Coil | 1.85 | 1.89 | 1.83 | 1.93 | 1.98 | 1.95 | | 2.04 은 1 00 Ш | | | |
| Helix | 1.99 | 1.97 | 2.03 | 1.99 | 1.98 | 2.04 | | ^{1.98} ທ 1.92 ≥ | | | |
| Sheet | 1.98 | 2.02 | 2.00 | 2.01 | 2.07 | 2.15 | | 1.86 œ | | | |
| | ff94 | ff96 | ff99SB Force | ff14SB Field | ff14ipq | ff15ipq | - | | | | |

Correlation





ff15ipq Correlation







ff94 vs ff14ipq



Drilling Down: 30BL TYR52



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ff14ipq 3OBL:TYR52



ff15ipq 3OBL:TYR52



Water Models



Conclusions



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John Vries



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Questions?

https://github.com/dkoes/MD2NMR

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SHIFT X2 Comparison

| | | | | | | | Н | | | | | | | |
|--|---|---|--|--|---|---|---|--|---|--|--|--|--|--|
| | | | ab i | nitio | | | | | | SHIF | TX2 | | | |
| ff94 | 1.000 | 0.949 | 0.965 | 0.951 | 0.875 | 0.878 | | 1.000 | 0.962 | 0.973 | 0.970 | 0.951 | 0.949 | ff94 |
| ff96 | 0.949 | 1.000 | 0.943 | 0.927 | 0.851 | 0.848 | | 0.962 | 1.000 | 0.969 | 0.967 | 0.944 | 0.943 | ff96 |
| ff99SB | 0.965 | 0.943 | 1.000 | 0.956 | 0.888 | 0.902 | | 0.973 | 0.969 | 1.000 | 0.980 | 0.955 | 0.964 | ff99SB |
| ff14SB | 0.951 | 0.927 | 0.956 | 1.000 | 0.916 | 0.932 | | 0.970 | 0.967 | 0.980 | 1.000 | 0.966 | 0.969 | ff14SB |
| ff14ipq | 0.875 | 0.851 | 0.888 | 0.916 | 1.000 | 0.936 | | 0.951 | 0.944 | 0.955 | 0.966 | 1.000 | 0.972 | ff14ipq |
| ff15ipq | 0.878 | 0.848 | 0.902 | 0.932 | 0.936 | 1.000 | | 0.949 | 0.943 | 0.964 | 0.969 | 0.972 | 1.000 | ff15ipq |
| | ff94 | ff96 | ff99SB | ff14SB | ff14ipq | ff15ipq | | ff94 | ff96 | ff99SB | ff14SB | ff14ipq | ff15ipq | |
| | | | ah i | nitio | | | Ν | | | СПІ | | | | |
| ((0.4 | | | | iiiio | | | _ | | | JIII | | | | |
| ff94 | 1.000 | 0.964 | 0.977 | 0.968 | 0.949 | 0.957 | | 1.000 | 0.982 | 0.992 | 0.986 | 0.975 | 0.980 | ff94 |
| ff94 ff96 | 1.000 0.964 | 0.964 1.000 | 0.977 0.961 | 0.968 | 0.949 0.938 | 0.957 0.938 | | 1.000 0.982 | 0.982 1.000 | 0.992 | 0.986 | 0.975 0.972 | 0.980 0.971 | ff94 ff96 |
| ff94 ff96 ff99SB | 1.000 0.964 0.977 | 0.964 1.000 0.961 | 0.977 0.961 1.000 | 0.968 0.950 0.980 | 0.949 0.938 0.954 | 0.957 0.938 0.967 | | 1.000 0.982 0.992 | 0.982 1.000 0.982 | 0.992 0.982 1.000 | 0.986 0.975 0.988 | 0.975 0.972 0.975 | 0.980 0.971 0.983 | ff94 ff96 ff99SB |
| ff94 ff96 ff99SB ff14SB | 1.000 0.964 0.977 0.968 | 0.964 1.000 0.961 0.950 | 0.977 0.961 1.000 0.980 | 0.968 0.950 0.980 1.000 | 0.949 0.938 0.954 0.963 | 0.957 0.938 0.967 0.975 | | 1.000 0.982 0.992 0.986 | 0.982 1.000 0.982 0.975 | 0.992 0.982 1.000 0.988 | 0.986 0.975 0.988 1.000 | 0.975 0.972 0.975 0.981 | 0.980 0.971 0.983 0.988 | ff94 ff96 ff99SB ff14SB |
| ff94 ff96 ff99SB ff14SB ff14ipq | 1.000 0.964 0.977 0.968 0.949 | 0.964 1.000 0.961 0.950 0.938 | 0.977 0.961 1.000 0.980 0.954 | 0.968 0.950 0.980 1.000 0.963 | 0.949 0.938 0.954 0.963 1.000 | 0.957 0.938 0.967 0.975 | | 1.000 0.982 0.992 0.986 0.975 | 0.982 1.000 0.982 0.975 | 0.992 0.982 1.000 0.988 0.975 | 0.986 0.975 0.988 1.000 0.981 | 0.975 0.972 0.975 0.981 1.000 | 0.980 0.971 0.983 0.988 0.986 | ff94 ff96 ff99SB ff14SB ff14ipq |
| ff94 ff96 ff99SB ff14SB ff14ipq ff15ipq | 1.000 0.964 0.977 0.968 0.949 | 0.964 1.000 0.961 0.938 0.938 | 0.977 0.961 1.000 0.980 0.954 0.967 | 0.968 0.950 0.980 1.000 0.963 0.975 | 0.949 0.938 0.954 0.963 1.000 | 0.957 0.938 0.967 0.975 0.974 | | 1.000 0.982 0.992 0.986 0.975 0.980 | 0.982 1.000 0.982 0.975 0.972 | 0.992 0.982 1.000 0.988 0.975 0.983 | 0.986 0.975 0.988 1.000 0.981 0.988 | 0.975 0.972 0.975 0.981 1.000 0.986 | 0.980 0.971 0.983 0.988 0.986 1.000 | ff94 ff96 ff99SB ff14SB ff14ipq ff15ipq |

















