Tweaking structures: working on the fiddly bits

Kevin Karplus

karplus@soe.ucsc.edu

Biomolecular Engineering Department

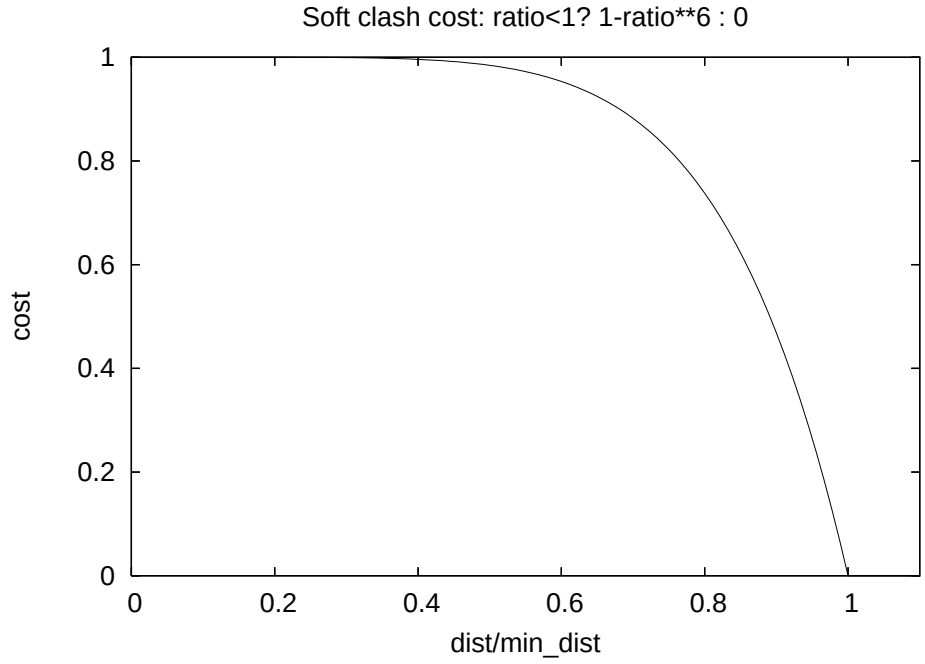
University of California, Santa Cruz

Outline of Talk

- Cost functions
  - Clash detection
  - Sidechain quality
  - H bond quality
  - Predicted backbone structure
- Conformation change operators
  - JiggleSegment JiggleSubtree
  - TweakHbond
  - TweakPsiSegment TweakPsiSubtree
  - TweakPhiSegment TweakPhiSubtree
  - TweakPeptide
  - TweakPsiPhiSegment TweakPsiPhiSubtree
  - BackRub BigBackRub

Clash Detection

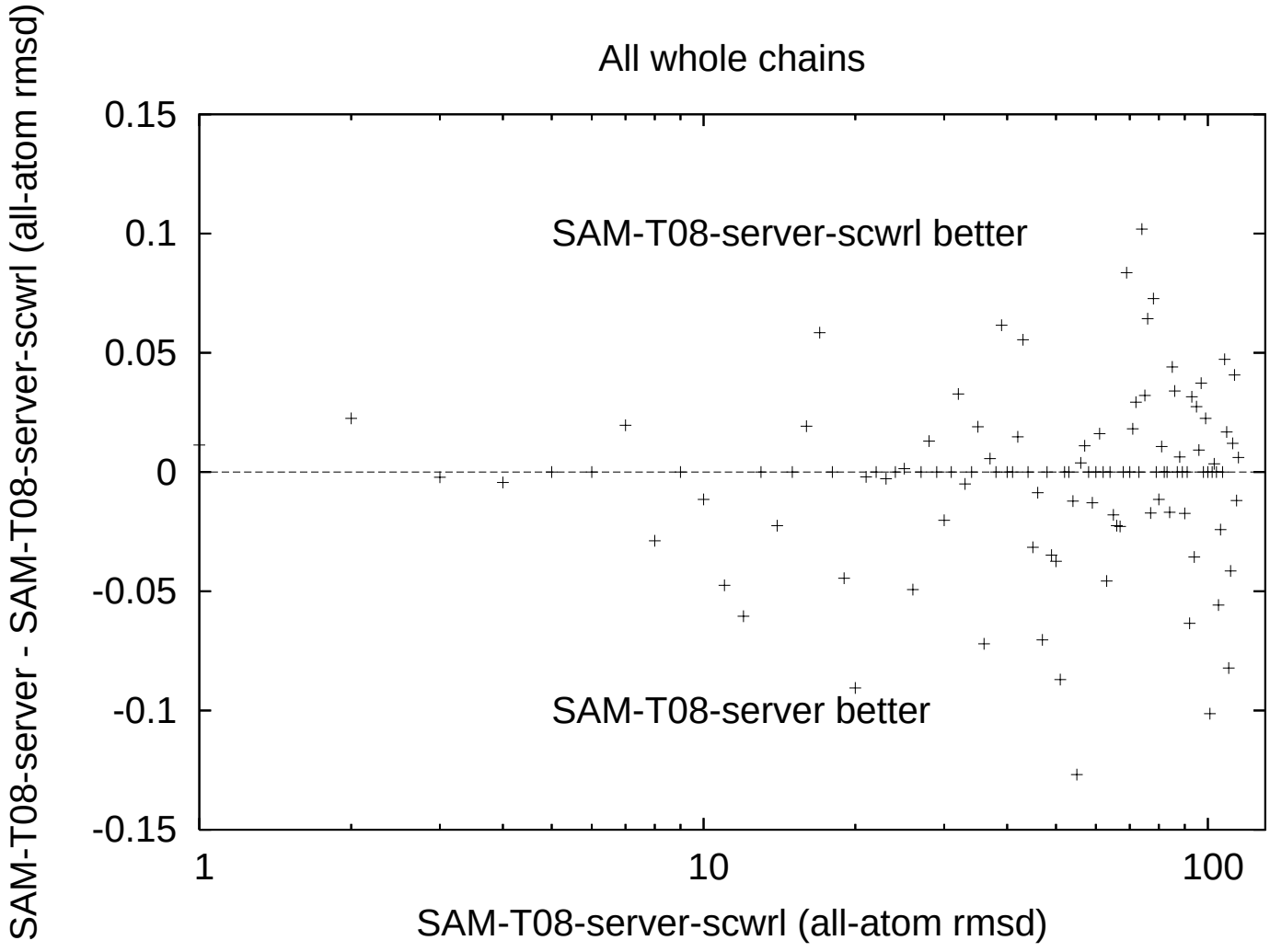
- Simple clash detector with minimum legal distance for each pair of atoms (no attractive term).
- Distances trained (badly) on large set of high-quality structures.



Sidechain quality

- 9-dimensional space (where are CA-1, CA+1, and distal point on sidechain)
- Gaussian mixture for “rotamer library”
- Estimates joint probability of backbone and rotamer, not rotamer conditioned on backbone.
- Redoing our sidechains with SCWRL gives about equal number of better and worse models.

Our sidechains are not supremely good



Hbonds

- Different cost functions for different types of H-bonds.
  - separation=3
  - separation=4
  - other separation
  - 4 non-backbone classes
- Backbone H-bonds most carefully done:
  - distance
  - non-planarity
  - asymmetry
  - donor-acceptor-carbon angle

Predicted backbone structure

- Local structure prediction using neural nets
- Several alphabets:
  - Bystroff's ϕ-ψ classification
  - de Brevern's protein blocks
  - CA-CA-CA-CA α torsion angle
- Cost function uses

$$\log \frac{P(\text{class}|\text{neural net})}{P(\text{class}|\text{amino acid})}$$

Jiggle, TweakHbond

- JiggleSegment JiggleSubtree: make a small rigid transform. Move either
  - the segment (between chain breaks)
  - a subtree consisting of several segments.
- TweakHbondSegment or TweakHbondSubtree
  - same idea, but donor or acceptor has very small change to position.
  - other atoms of segment or subtree may move further

TweakPhi, TweakPsi, TweakPeptide

- TweakPhiSegment, TweakPhiSubtree, TweakPsiSegment, TweakPhiSegment: Make small change to angle.
- TweakPsi generally more productive than TweakPhi.
- TweakPeptide: rotates peptide plane about axis through two CA atoms.

TweakPsiPhi Segment/Subtree

- Make small change to psi angle and opposite change to next phi angle.
- Note: axes of rotations almost parallel on opposite ends of peptide plane.
- Moves rest of segment (or subtree) along circular arc without reorienting it much.

BackRub, BigBackRub

- Rotate chain segment about line between two CA atoms.
- For Backrub, CA are 2 apart on backbone.
- Reposition first and last peptide planes to try to get optimal superposition on new CA positions but old N and O positions (to preserve Hbonds).
- These tweaks tend to have high success rate and so can be done with larger angular changes than other tweaks.

Web sites

CASP8 working files: `http://www.soe.ucsc.edu/~karplus/casp8/`

List of my papers:

`http://www.soe.ucsc.edu/~karplus/papers/paper-list.html`

These slides: `http://www.soe.ucsc.edu/~karplus/papers/`

`tweak-slides-2008-dec.pdf`

UCSC bioinformatics (research and degree programs) info:

`http://www.soe.ucsc.edu/research/compbio/`