

# BCH 258 lecture notes Fri. Sept 12, 2008

Reports: Instructions, demo.

Roles of the Amino Acids, and mutations to replace them (ref Wrksht2\_handedAAroles2008)

• Assignment: WrkSht7-mutations2008

Graphics: All-atom contacts : (recall howdotswork3KiNG.kin)

• Mutation check: 1lmb6\_85aH.kin : in class: show Thr 8 → Val does NOT work!

(WorkSheet homework: show Tyr 22 → Trp does work!)

Thr 8 → Asn NOT work, Asn 58 → Gln NOT work, (Gly 43 → Ser NOT work)

Good N-cap residues, 2 sets: Ser, Thr vs. Asn, Asp

## BACKGROUND

Hydrophobic “H” vs polar “P” : is the most important parameter

“HP” pattern in sequence determines approx. 3D fold, puttin most H in, P out

“H” : function of Hydrophobic surface area (but Cys also strongly buried)

“P” : function of charge, H-bonding, polarizability (but Pro out, forming corners)

alternating “HP” favors  $\uparrow\downarrow\beta$ ; 3.5 period favors  $\alpha$  helix; a run of “P” favors turns;

long run of “H” favors transmembrane; short run of “H” favors  $\uparrow\uparrow\beta$

Size, shape, & flexibility of sidechain

Mainchain flexibility: Gly > Ala (and others) > branched C $\beta$  > Pro > SS

Entropy mutants (native vs unfolded): SS, A → P, G → A

Sidechain degrees of freedom: Hydrophobics  $\leq 2$  chi's ( $\chi$ ) (except Met 3))

many Polars have more, esp/ Lys & Gln very loose

Aromatics (FYWH): big & flat, help constrain packing

slightly + on edge, - on face,

more often perpendicular than stacked

Pro: not aromatic, not flat; puckers up or down at C $\gamma$

ring constrains  $\phi$  near  $-60^\circ$ ; good at turns;

good in N-term end of  $\alpha$  helix

can do  $\alpha$  middle, but bends helix

Ile, Thr sidechains handed: long arm, or Og, on “left” side (arms in front of body)

Sidechains “rotameric”, i.e. few preferred conformations; Ctetr near staggered

Sidechain angles:  $\chi_1, \chi_2$ , etc. dihedrals ( $\chi_4$  max, for Lys & Arg)

for bonds between tetrahedral carbons, staggered >> eclipsed

overall, a few well-defined sidechain conformations are good: rotamers

[only 2 good ( 4 more OK) for Leu; 13 for Met with 3  $\chi$  angles and no branches]



## Secondary-structure preferences

Loop, turn, coil : Gly, Ser, Asn, Pro, & charges best; Hydrophobics poor

Beta : branched C $\beta$ 's best (Val, Ile, Thr); Pro, Asn worst

Helix : in middle: Ala, Leu, Met, Gln best; Pro worst

near beginning – charge good (Asp, Glu); near end + charge good (Lys, Arg, His)

N-cap : Asp, Asn, Ser, Thr best (sc H-bond to mc NH of N-cap +3 or +2)

N-cap +1 : Pro best

C-cap : Gly best (usually has + $\phi$  value)

pair of touching Hydrophobics often bracket N or C caps

## Pair comparisons (What is a conservative replacement?)

**Arg** ordered, H-bonded (5-planar O's),

vs **Lys** often disordered, helps solubility

**Leu** one of best for helix,

vs **Ile** one of best for  $\beta$ -sheet

**Asn** backbone mimic, best non-Gly for + $\phi$  conf.; strong pref.s;  
amide constrained

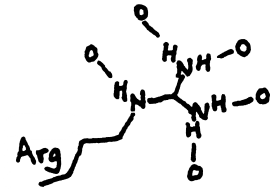
vs **Gln** “plain vanilla” residue: good  $\alpha$ , OK most places;

amide very free

Asn one of best N-caps, Gln is worst

Gln one of best at specific DNA base H-bonds,

Asn too short & wrong angles



## Multiple roles: distinguish by substitution pattern in aligned sequences

**Arg:** +charge (sub=Lys); oriented H-bonds (sub=Gln); Hydrophobic (sub=Tyr, Leu, Ile)

**Gly:** flexibility (sub=Ser); small size (sub=Ala or none); + $\phi$  conf. (sub=Asn)

**His:** titrates near pH 7 (no sub); +charge (sub=Lys, Arg); H-bonds (sub=Gln, Asn);  
metal ligand (sub= Cys, Asp, Glu)

**Cys:** buried SH (sub=Hydrophobics); SS (sub=Hydrophobics, rarely);  
metal ligand (sub=His, Asp, Glu, rarely)