Roles of the Amino Acids, and mutations to replace them (ref Wrksht2_handedAAroles2008)

• Assignment: WrkSht7–mutations2008
  Graphics: All-atom contacts : (recall howdostwork3KiNG.kin)
  • Mutation check: 1mb6_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 ↑↓ β;  3.5 period favors α helix; a run of “P” favors turns;
  long run of “H” favors transmembrane; short run of “H” favors ↑↑ β

Size, shape, & flexibility of sidechain

  Mainchain flexibility: Gly > Ala (and others) > branched Cβ > Pro > SS
    Entropy mutants (native vs unfolded): SS, A → P , G → A
  Sidechain degrees of freedom: Hydrophobics <= 2 chi’s (χ) (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 Cγ
    ring constrains φ near -60°; good at turns;
    good in N-term end of α helix
    can do α 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; Cτetr near staggered
  Sidechain angles: χ1, χ2 , etc. dihedrals (χ4 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 χ angles and no branches]
Secondary-structure preferences

Loop, turn, coil: Gly, Ser, Asn, Pro, & charges best; Hydrophobics poor
Beta: branched Cβ’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 +φ 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 β-sheet

Asn backbone mimic, best non-Gly for +φ conf.; strong pref.s;
   amide constrained
   vs Gln “plain vanilla” residue: good α, 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); +φ 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)