RNA Chemistry & Structure

00.939 RNA
Andrew Torda, April 2008

- Roles of molecules

	RNA	DNA	proteins
genetic information	yes	yes	
catalysis	yes		yes
regulation / interactions	yes	yes	yes
structure	usually single stranded	usually duplex	lots

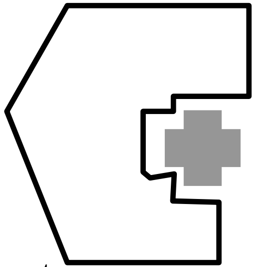
Catalysis

- proteins
  - everywhere
  - classic enzymes
- RNA
  - less common / well established
  - ribosome, hammerhead, …

Regulation

- Proteins
  - bind substrates, ligands, DNA, RNA
- DNA
  - sequence specific binding – to proteins, RNA, DNA
- RNA
  - same as DNA +
  - specific catalysis implies specific recognition

Recognition / binding specificity



- protein view – via evolution
  - protein scaffold / framework positions groups
  - in binding / reactive region specific groups interact
  - lots of chemical groups to choose from (20 amino acids)
- DNA – not thought of in these terms
  - some specificity
    - regulatory binding proteins are sequence specific
- RNA
  - sequence specificity for binding proteins
  - RNAzymes suggest some protein-like abilities
  - experimental
    - selection of specifically binding RNA

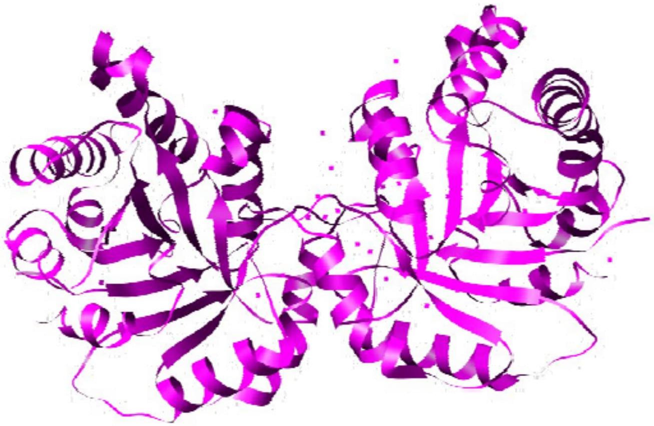
Structure

- DNA
  - mostly thought of as double helix
- Protein (simple dogma)
  - from a specific sequence to a well defined structure
  - less often – floppy, unstructured, mobile, alternative folds
- RNA
  - does an RNA sequence fold up to a well defined structure ?
    - all possible RNA's ?
    - biological RNA's ?
    - some RNA's ?

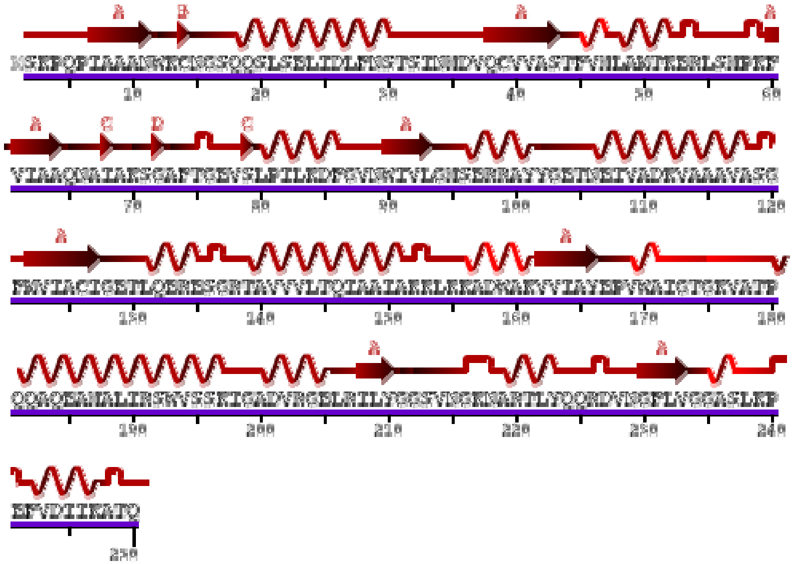
Structure Expectations

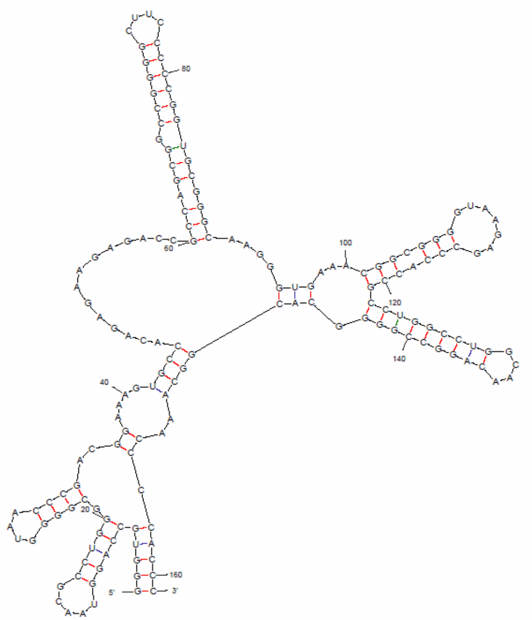
Protein
- usually 3D
- rarely secondary structure

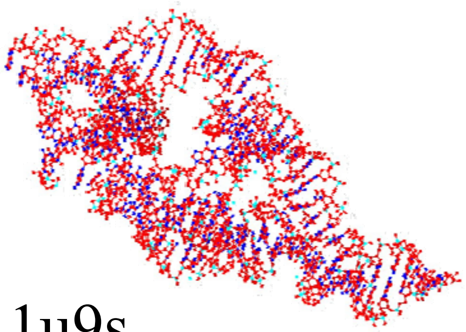
RNA
- usually secondary structure
- rarely 3D



3tim







1u9s

Structural Data

Proteins

- 5.0×10^5 or about 1.7×10^5 interesting ones

RNA

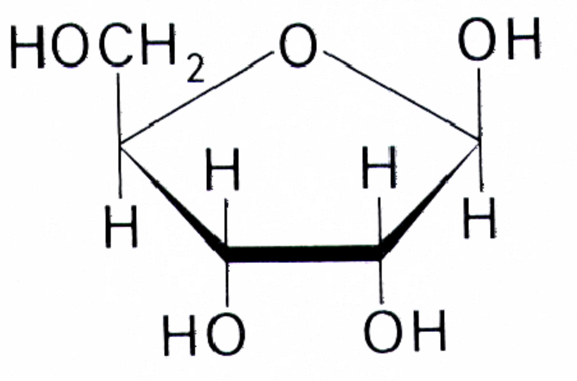
- 1.4×10^3 structures with some RNA
- $< 10^2$ with RNA + DNA (no protein)
- $\approx 6\times10^2$ with pure RNA

Determining structures

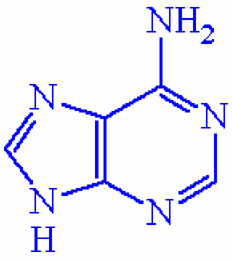
- general – RNA hard to handle (RNases)
- crystallogrophy
- NMR
  - assignments very difficult (only 4 kinds of base)

RNA structure

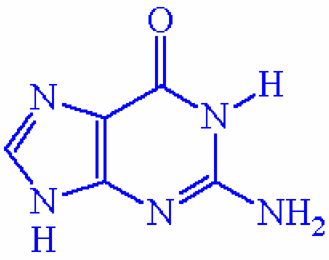
- 3 components
  - ribose (sugar)
  - phosphate (PO_4)
  - base (nucleotide)



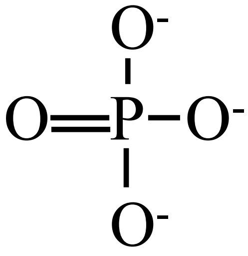
β-D-Ribose



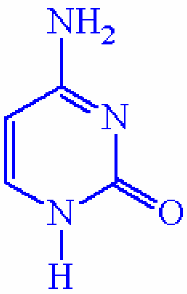
Adenine



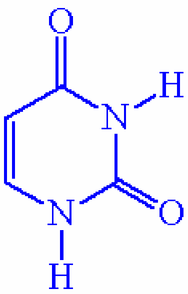
Guanine



$$O=P(O^-)_3$$



Cytosine



Uracil

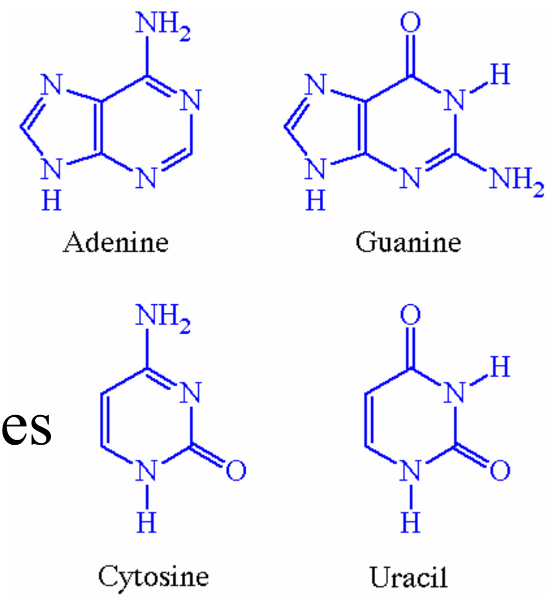
pictures from Stryer, Biochemistry, WH Freeman and Company, New York, 1981

RNA Bases

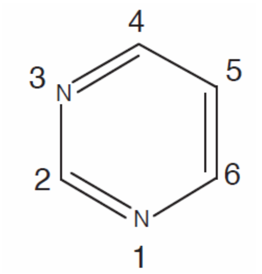
- Are they like protein residues ?
  - not classified by chemistry
  - do they have interactions ?
    - yes, but not discussed

purines

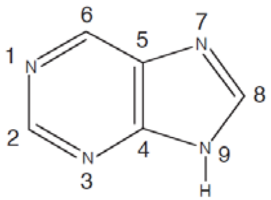
pyrimidines



- mother shapes



pyrimidine



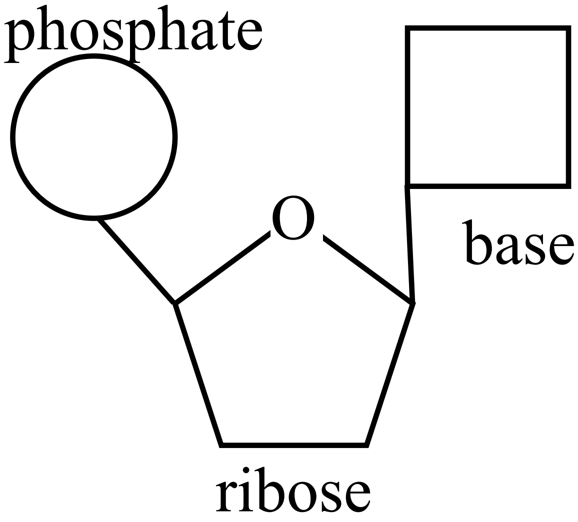
purine

- numbering not used much
- putting pieces together…

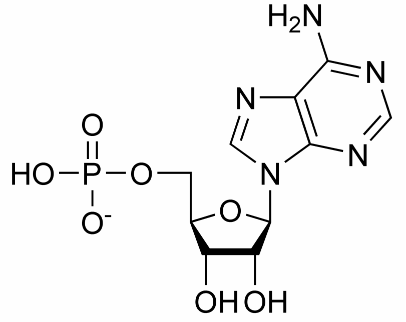
pictures from Stryer, Biochemistry, WH Freeman and Company, New York, 1981

RNA structure

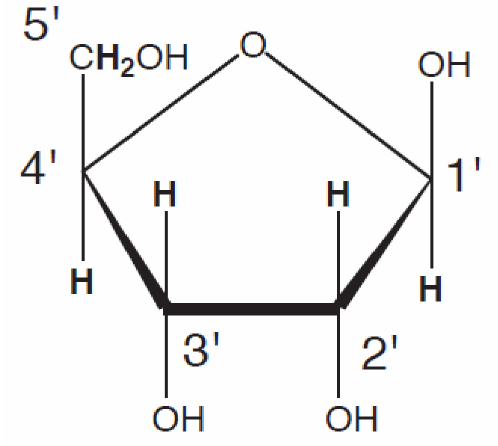
- joining the components



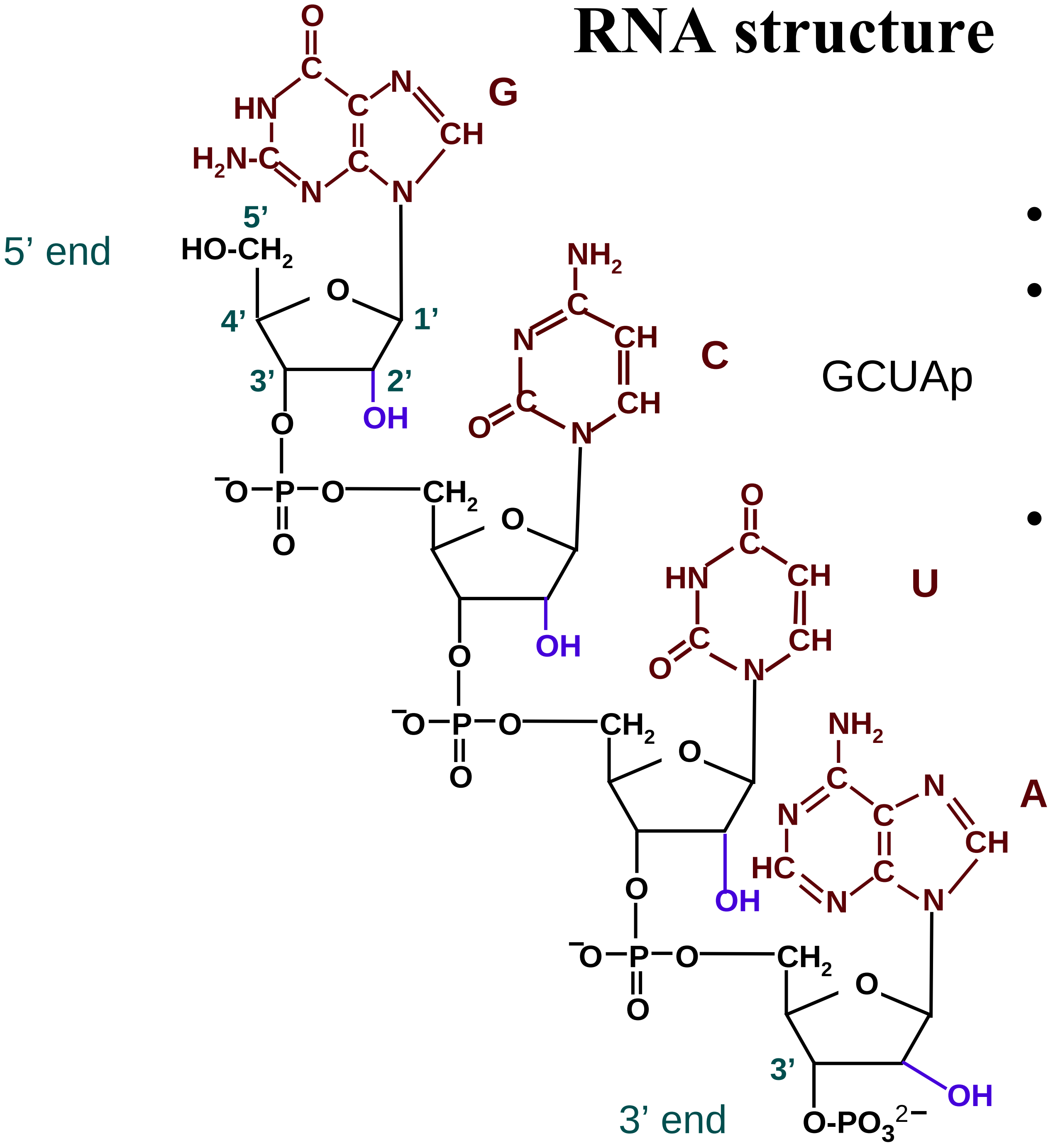
- adenosine 5'-monophosphate
  - not adenine, adenosine, …



- note numbering on sugar ring



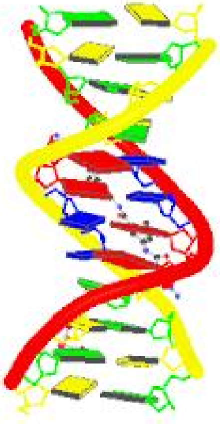
RNA structure



- negative charges
- directional
  - 5' to 3'
- notation
  - always 5' to 3'

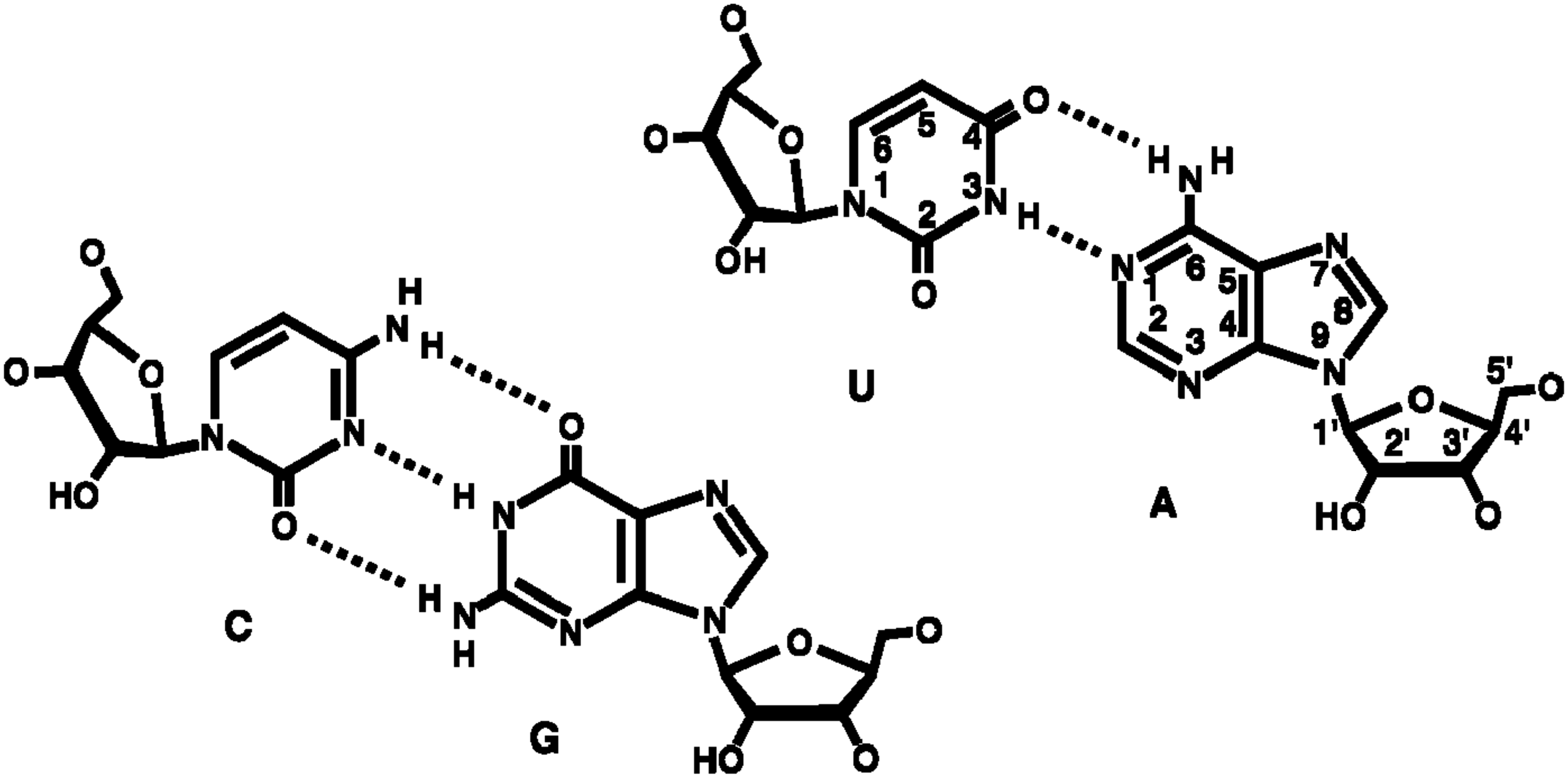
from Parson, W, http://courses.washington.edu/bioc441/lectures/ppt/13.DNA&RNA.ppt

H bonding



- What holds the pairs of a helix together ? H-bonds
  - applies to RNA
  - rules from proteins
    - H-bond donors are NH, OH
    - acceptors – anything with partial –'ve
- Historic H-bonding pairs…

Historic H-bonding pairs



from Batey, BT, Rambo, RP, Doudna, JA, Angew. Chem. Int. Ed. (1999), 38, 2326-2343

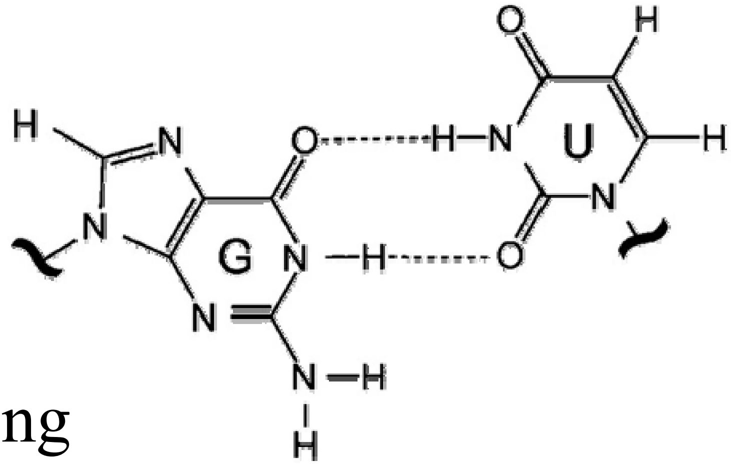
Historical point

- RNA has 4 bases + GC, AU base pairs
- H-bond pairs look flat

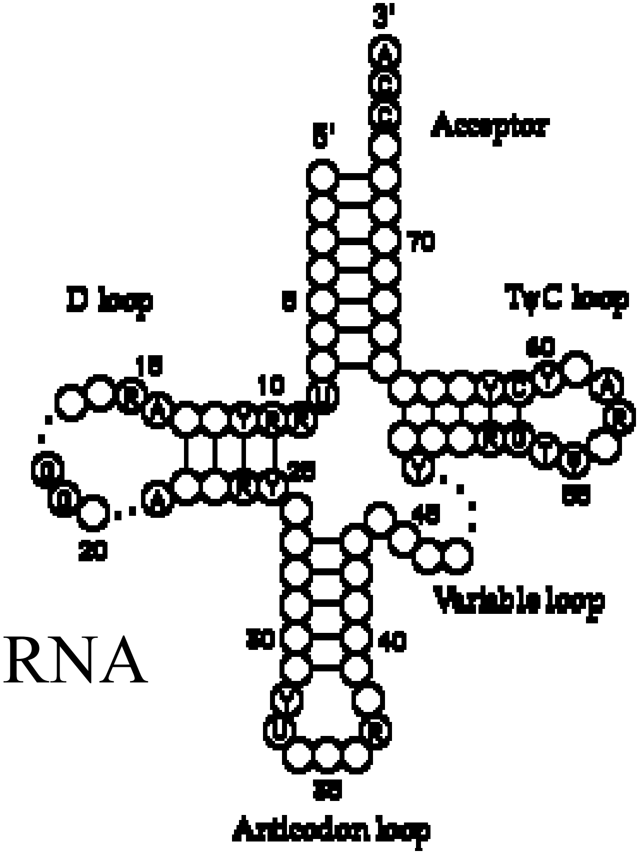
  BORING
- other kinds of H-bonds and bases
- base pairs are not perfectly flat

Other common H-bond partner

- Contrast with DNA (GC and AT)
  - rarely violated (mismatch)
- Interesting base pairing
  - RNA (GC, AU) much more interesting
    - third base pair GU (rather common)
    - lots of weaker pairs possible



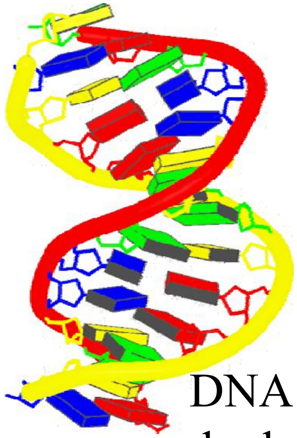
More bases



- standard machinery for copying DNA→RNA (standard base pairs)
- every tRNA has a modified base

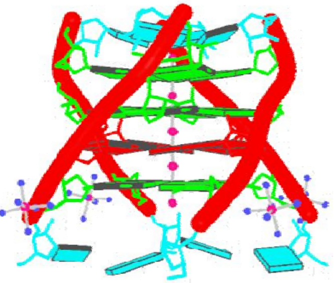
Possible RNA structures

- DNA ? nearly always similar helix
  - some debate about A, B, Z, ..
- RNA
  - lots of varieties known
  - nomenclature..

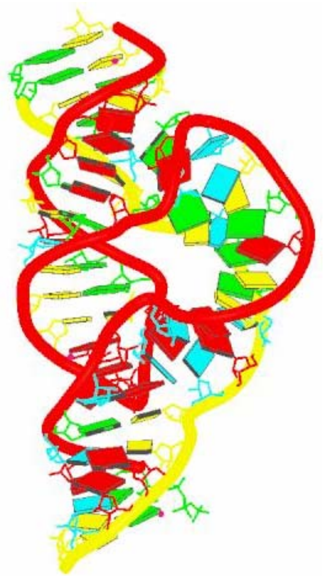


DNA
duplex
140D

group I intron
1hr2



tetraplex
1mdg



hammerhead
2oeu

tRNA
1evv

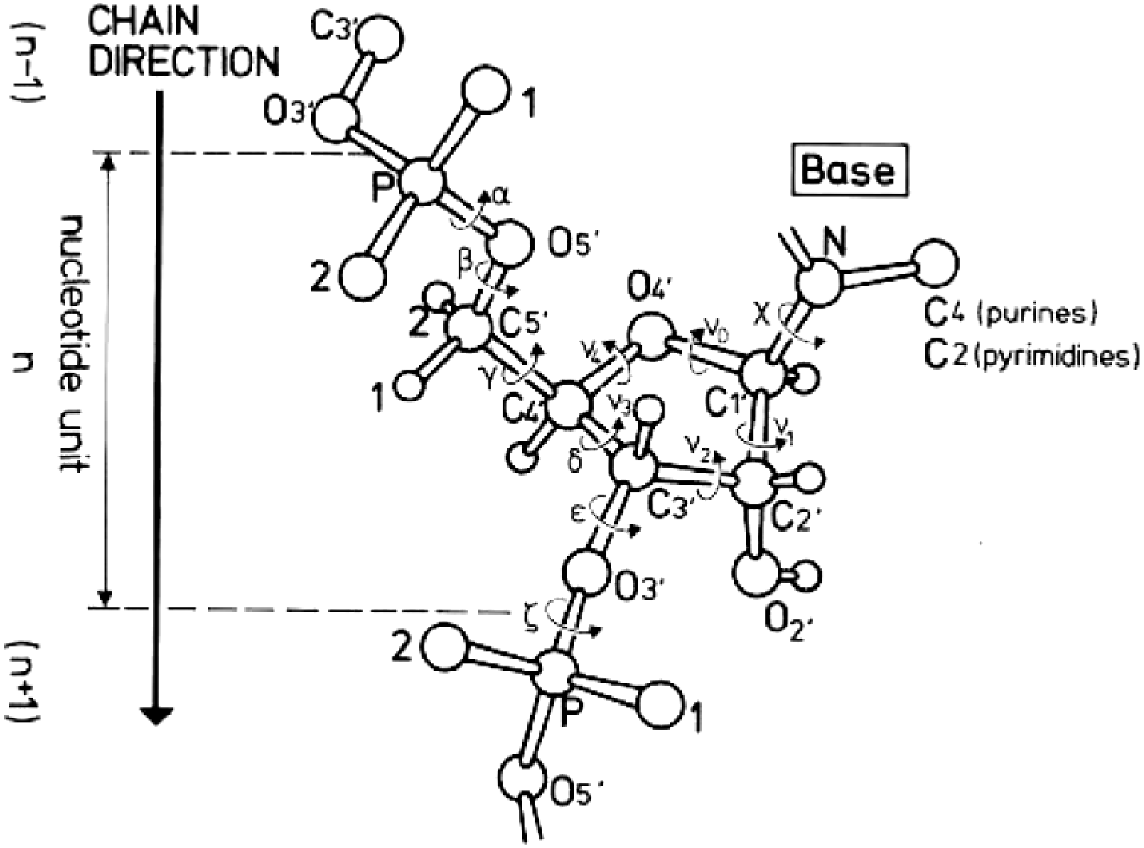
RNA coordinates / nomenclature

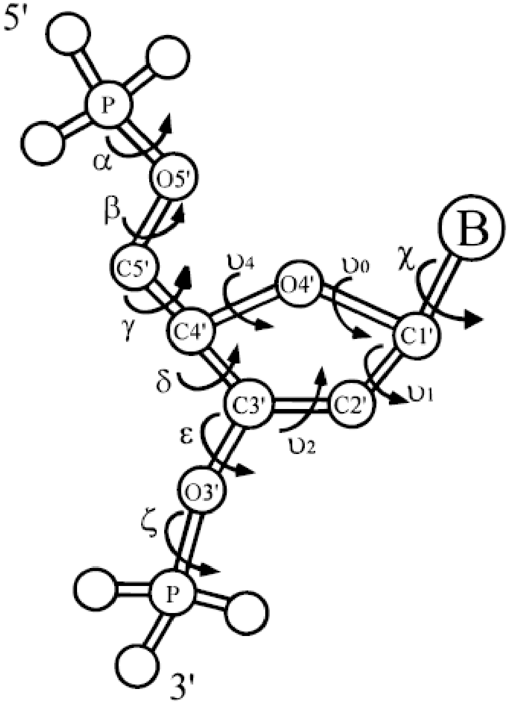
- As for proteins: PDB format

```
ATOM      1  O5*   G A 103      58.355  47.332  91.116  1.00175.32
ATOM      2  C5*   G A 103      57.373  48.210  90.636  1.00175.32
ATOM      3  C4*   G A 103      56.962  47.802  89.224  1.00175.19
ATOM      4  O4*   G A 103      58.148  47.463  88.474  1.00175.34
ATOM      5  C3*   G A 103      56.096  46.543  89.152  1.00175.03
```

- As for proteins
  - dihedral angles are useful
- Unlike proteins (φ,ψ) there are 8 (α, β, γ...)

dihedral angle nomenclature





from Marino, JP, Schwalbe, H., Griesinger, C, Acc. Chem. Res. 32, 614-623 (1999)

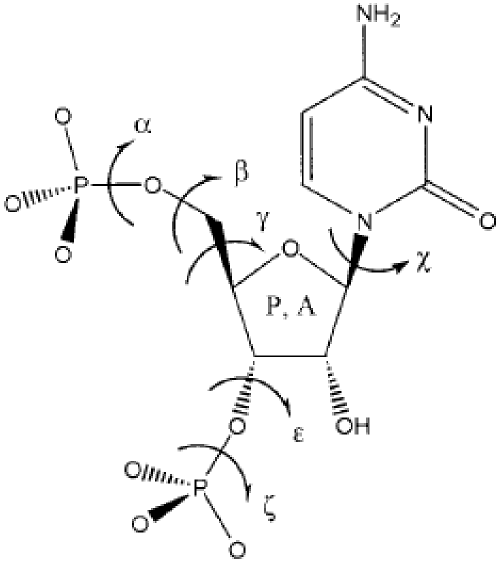
from Saenger, W. Principles of Nucleic Acid Structure, Springer, N.Y. 1984

dihedral angle nomenclature

- 8 angles
  - α, β, γ, ε, ζ, χ
  - 2 for sugar (P, A)
- too many for me – how to simplify ?

- what if two angles are highly correlated ?
  - if we know *x*, then *y* is probably known

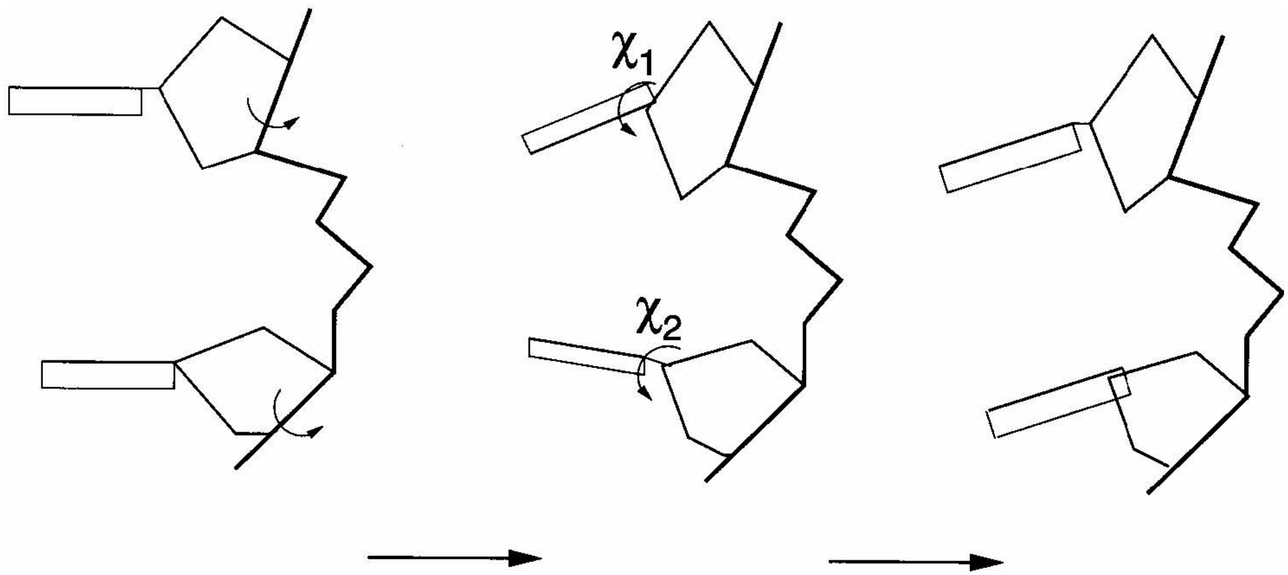
- ideas for classification (not textbook)…



Murthy, V.L., Srinivasan, R, Draper, D.E., Rose, G.D. J. Mol. Biol. 291, 313-327 (1999)

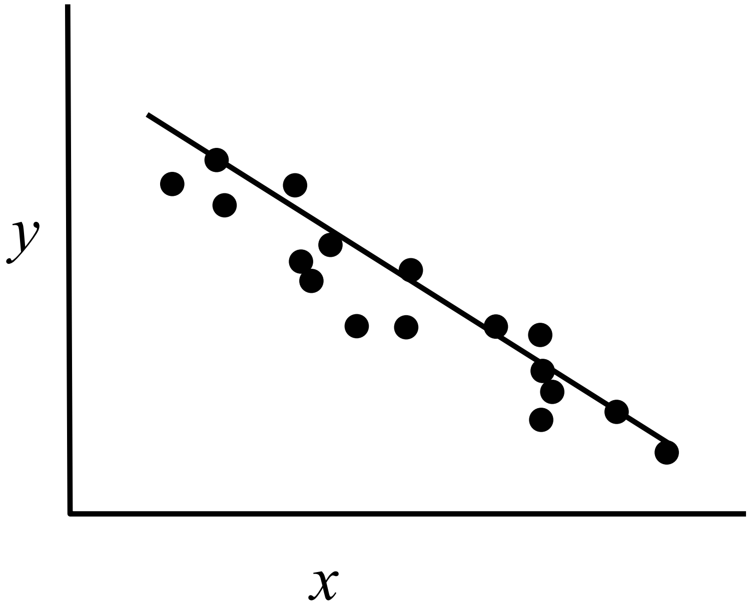
Describing RNA conformation

- Example approach – look for correlations
  - principle component analysis (quick detour if necessary)
- what if sugars move in two residues ?
  - energetically, would like to maintain base pairing…
  - P, A move, χ will compensate
    - χ will be correlated with sugar angles



Beckers, MLM & Buydens, MC, (1998), J. Comput. Chem. 19, 695-715.

PCA reminder



I have two dimensional data

- could well be described by a first (component) and
- maybe second component

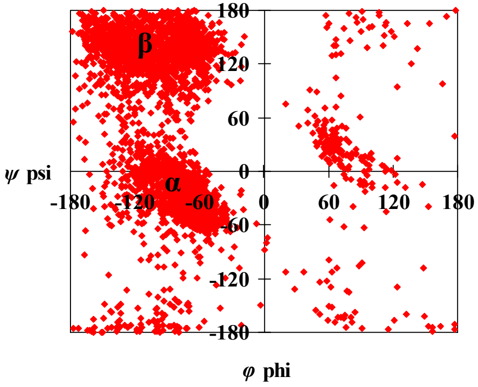
n-dimensional data

- how much of variance is described by 1st, 2nd, … components

Describing RNA conformation

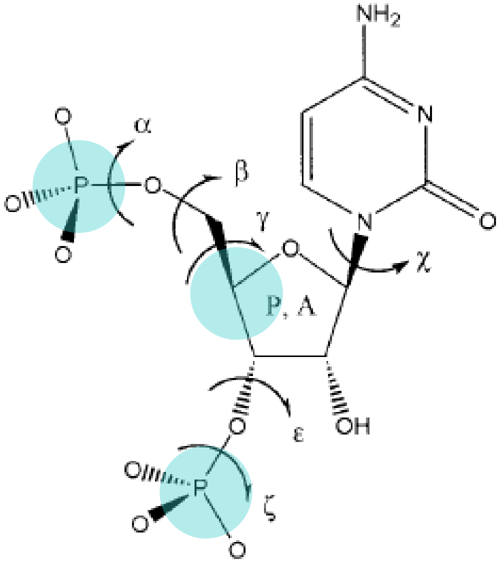
- Claim – from one DNA paper
  - most conformations are well described by 3 variables
- alternative…
  - do not work in terms of real dihedral angles
  - invent reference points
  - example study…
    - Duarte, CM & Pyle, AM, (1998) 284, 1465-1478

- remember ramachandran plots in proteins
  - can one do something similar in RNA ?



Reduced RNA conformation

- Basic idea
  - pick 4 atoms that are not sequential
  - define a simplified backbone
    - P-C_4-P-C_4-P-C_4-…
  - leads to "pseudo-torsion" angles

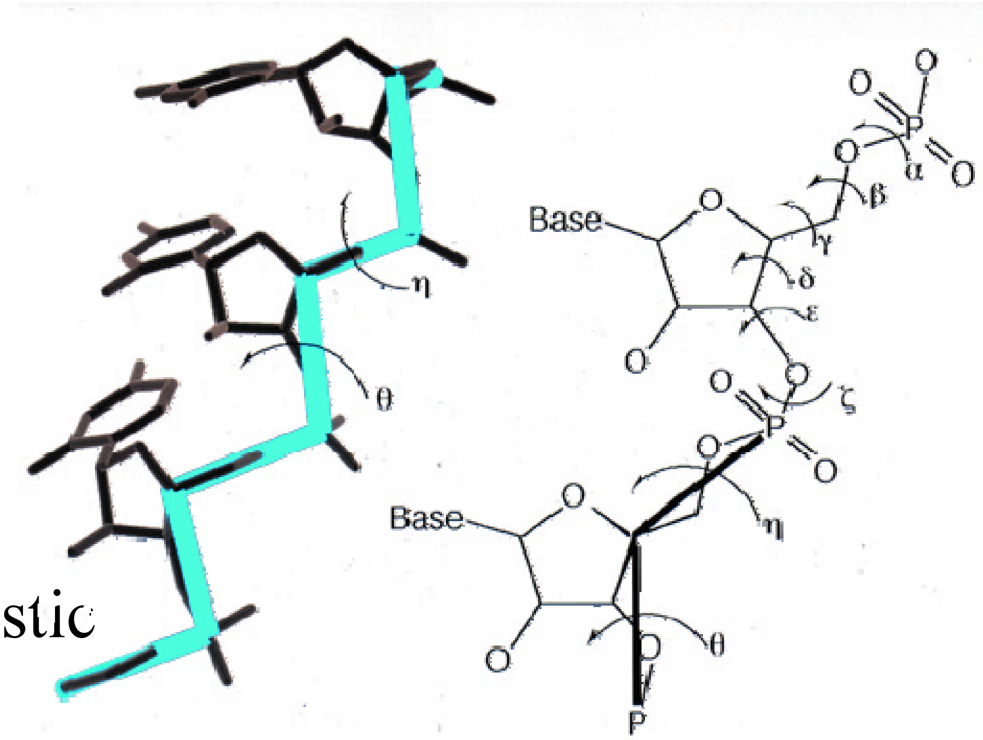


  - η
    - $C4_{n-1}$-P_n-$C4_n$-P_{n+1}
  - θ
    - P_n-$C4_n$-P_{n+1}-$C4_{n+1}$

Reduced RNA conformation

Plan of authors

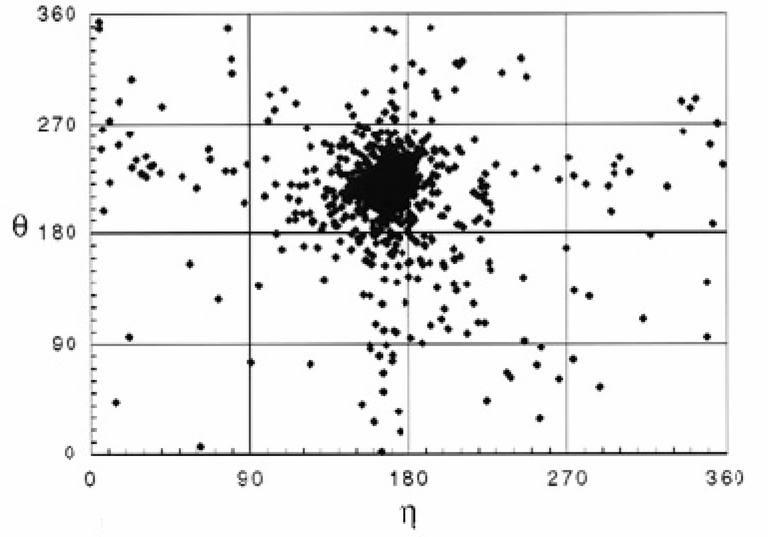
- take 52 structures
    - (≈700 nucleotides)
    - collect η, θ
        - see if there are clusters
        - see if angles are diagnostic



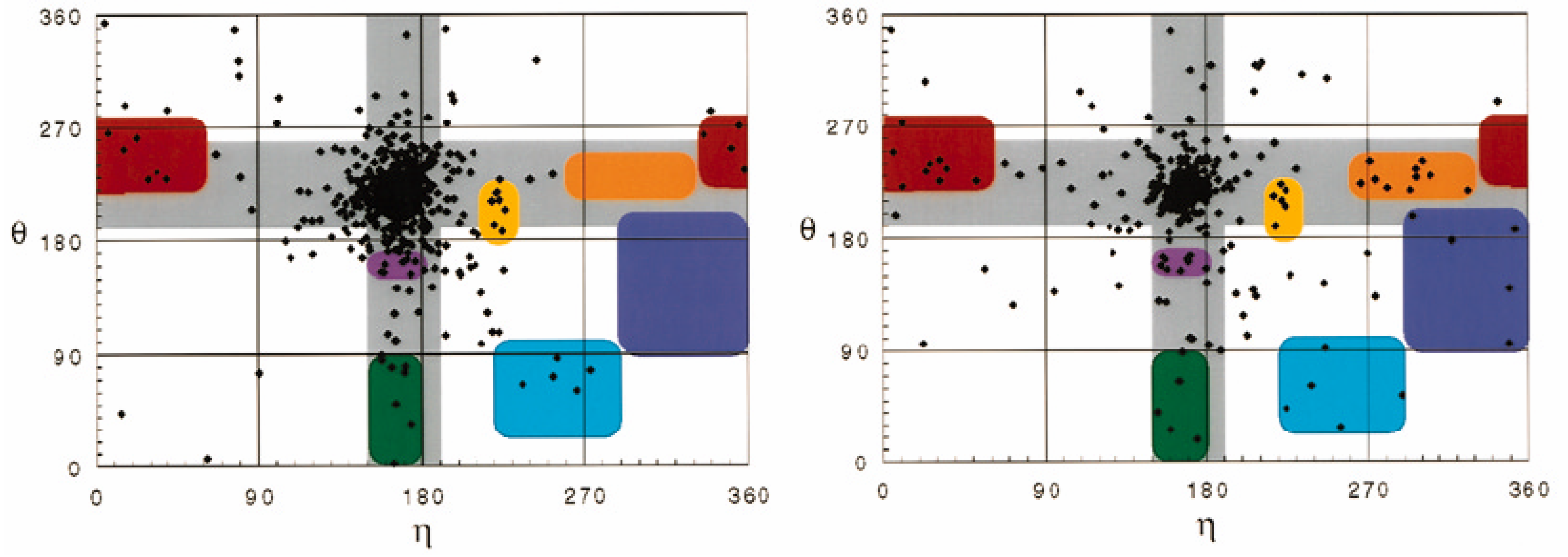
Duarte, CM & Pyle, AM, (1998) 284, 1465-1478

Reduced RNA conformation

- Do you see clusters ?
  - main set of points …
  - boring RNA helix



- a big claim



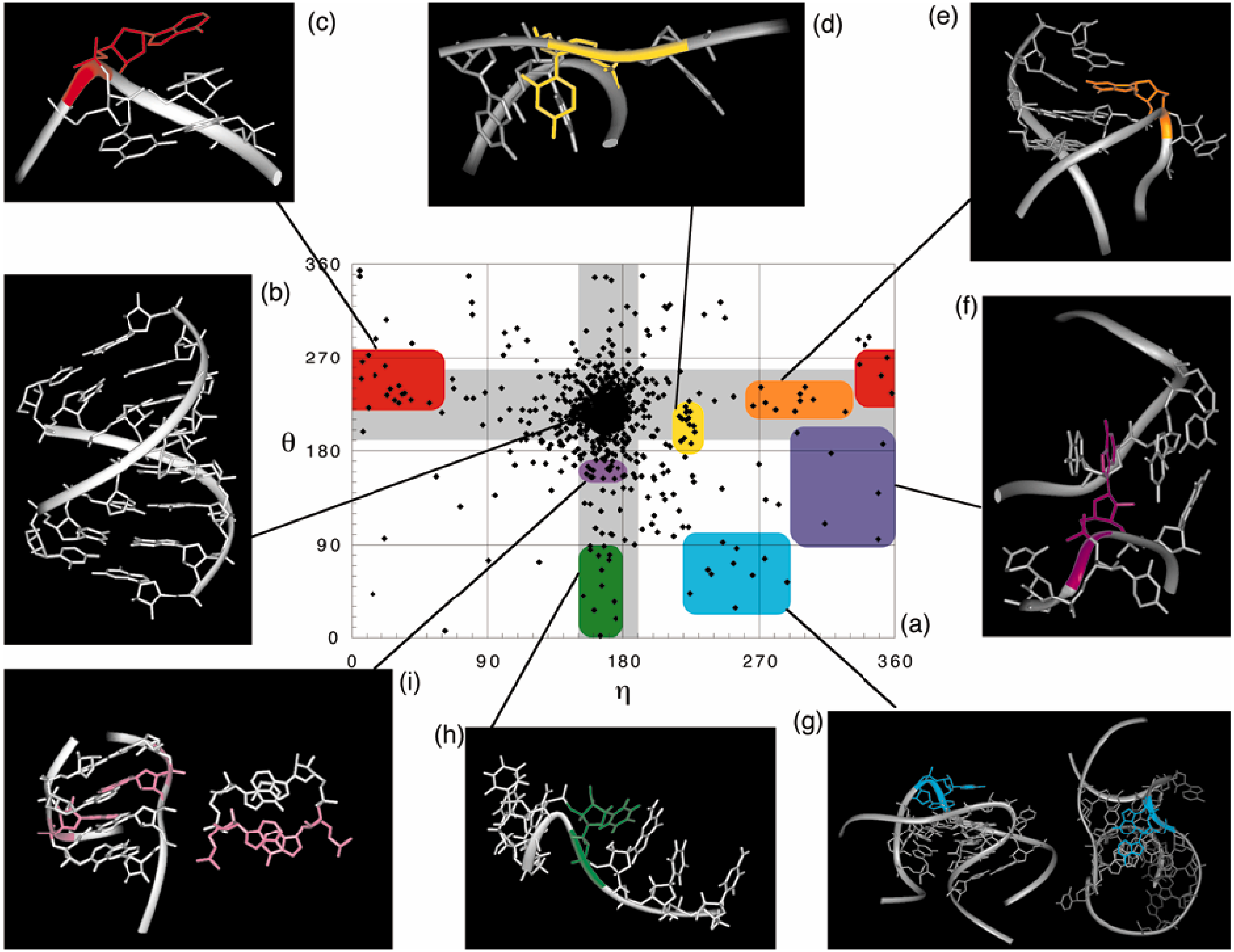
no tertiary interactions

yes tertiary interactions

Duarte, CM & Pyle, AM, (1998) 284, 1465-1478

Reduced RNA conformation

- with a bit more human interpretation



Duarte, CM & Pyle, AM, (1998) 284, 1465-1478

Reduced RNA conformation

We are interested in a critical look at ideas

How to read this…

- if you measure a pair of η, θ pseudo-angles
    - could you guess if something is wrong in structure ?

    - could you use this to categorise the conformation ?

- are there better ways to categorise structure ?

Summary

- RNA structure as per Watson-Crick, old text books
- How are RNA structures different to DNA ?
- What are the biological roles ?
- Can we neatly summarise RNA structures ?
  - see what information (angles) are necessary
  - define alternative angles

- Next time from me
  - nothing less than.. What is life ?