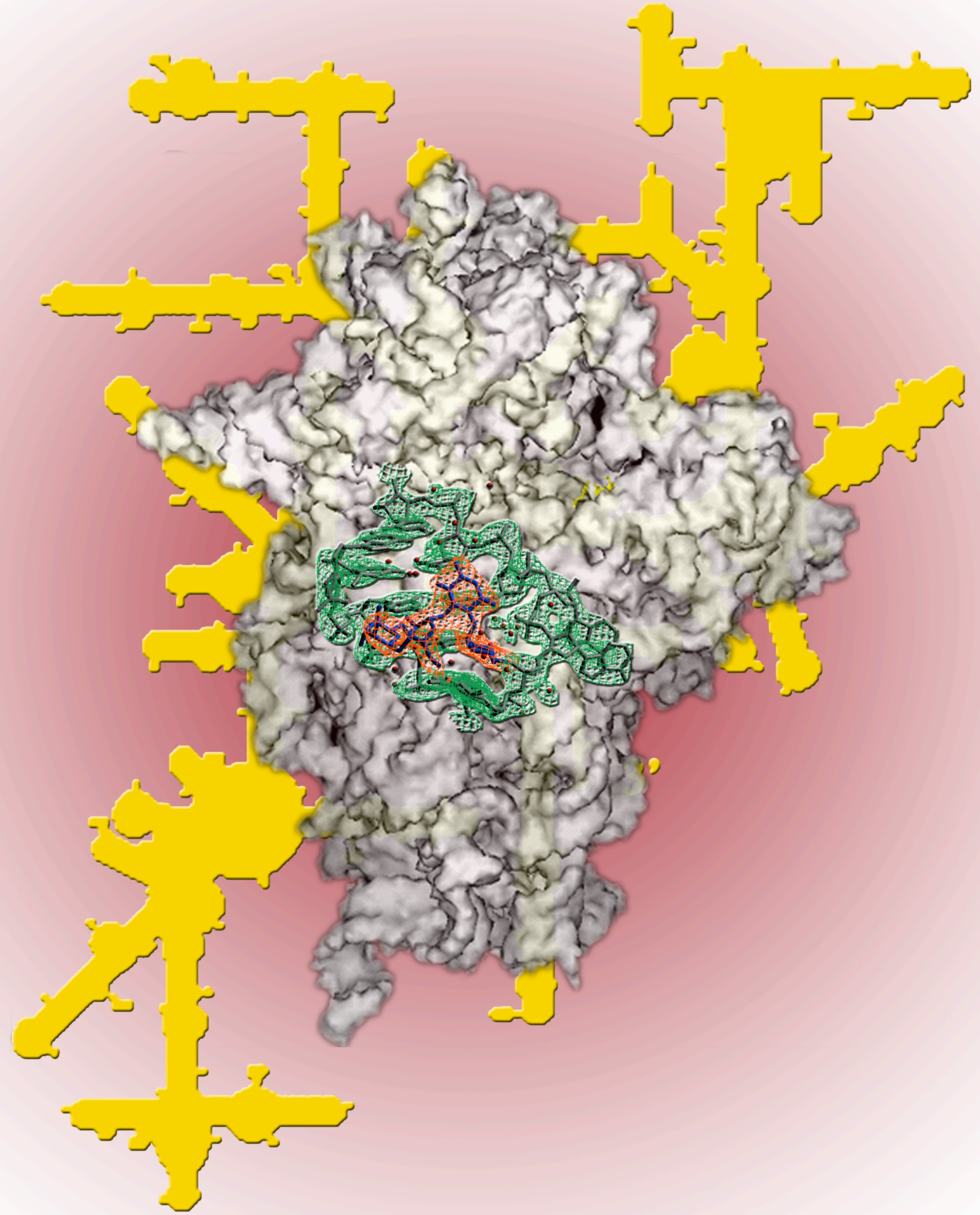
The

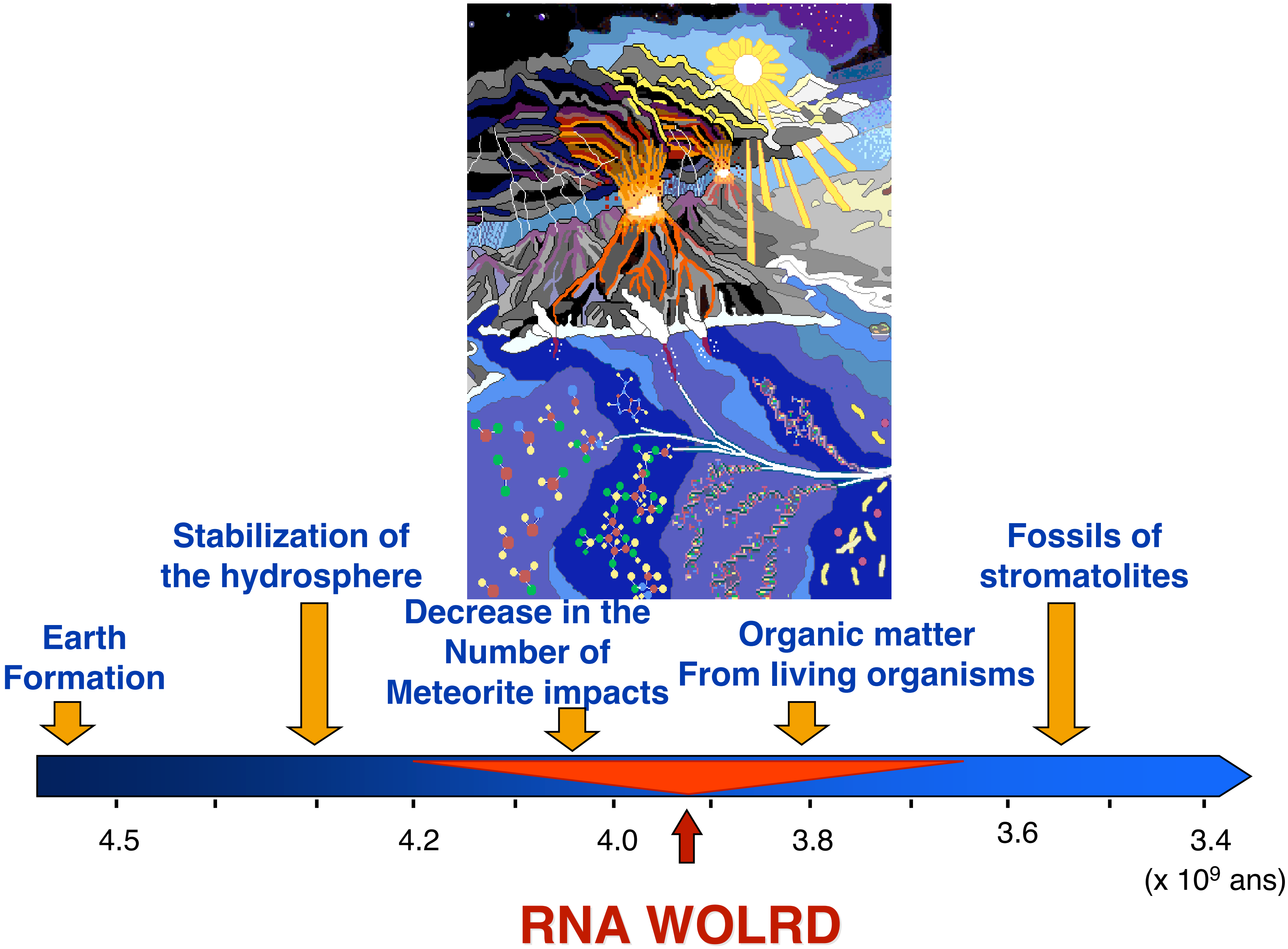
RNA

World

E. Westhof

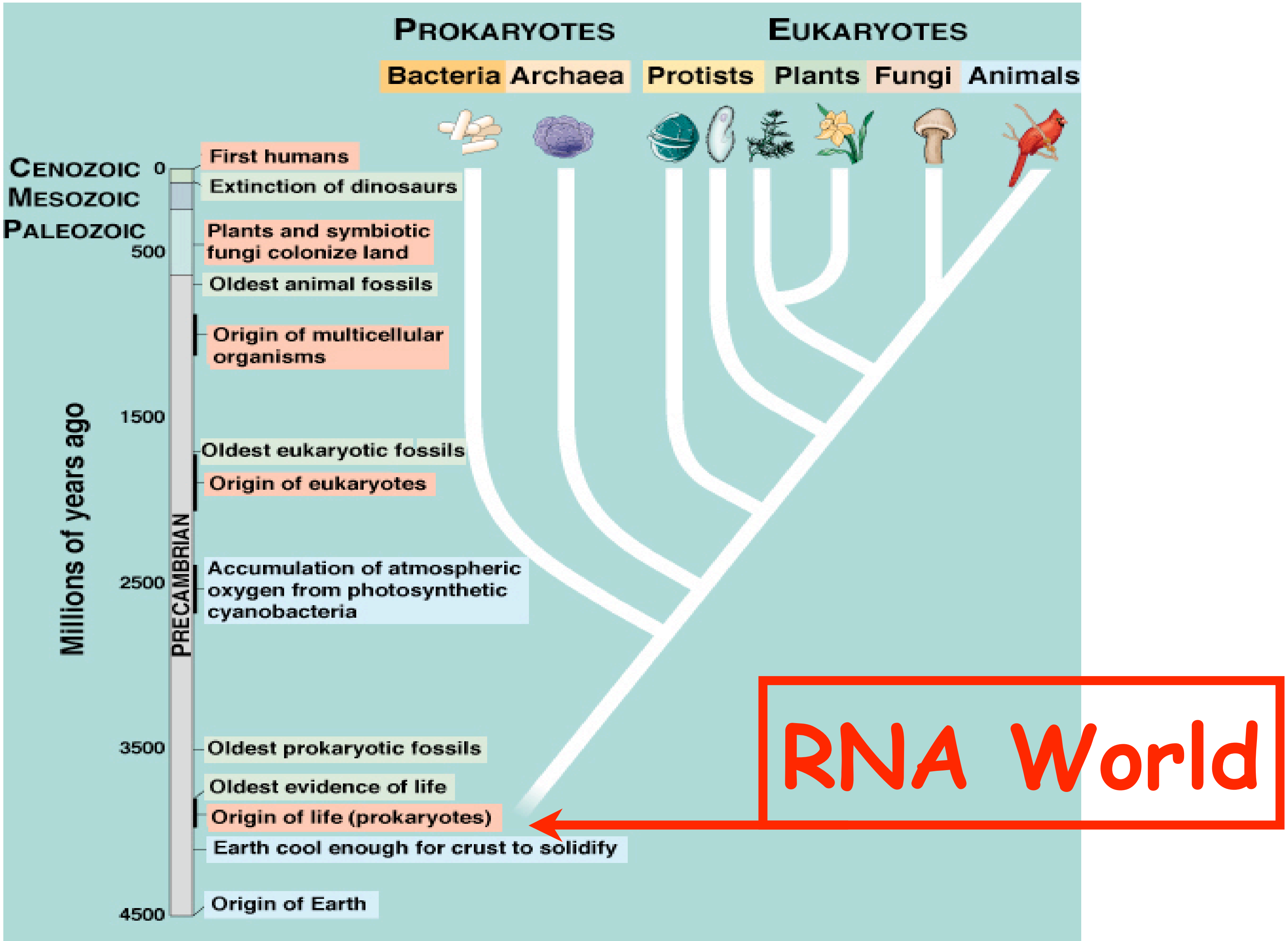


http://www-ibmc.u-strasbg.fr/upr9002/westhof/



Earth Formation
Stabilization of the hydrosphere
Decrease in the Number of Meteorite impacts
Organic matter From living organisms
Fossils of stromatolites
4.5
4.2
4.0
3.8
3.6
3.4
(x 10^9 ans)
RNA WOLRD

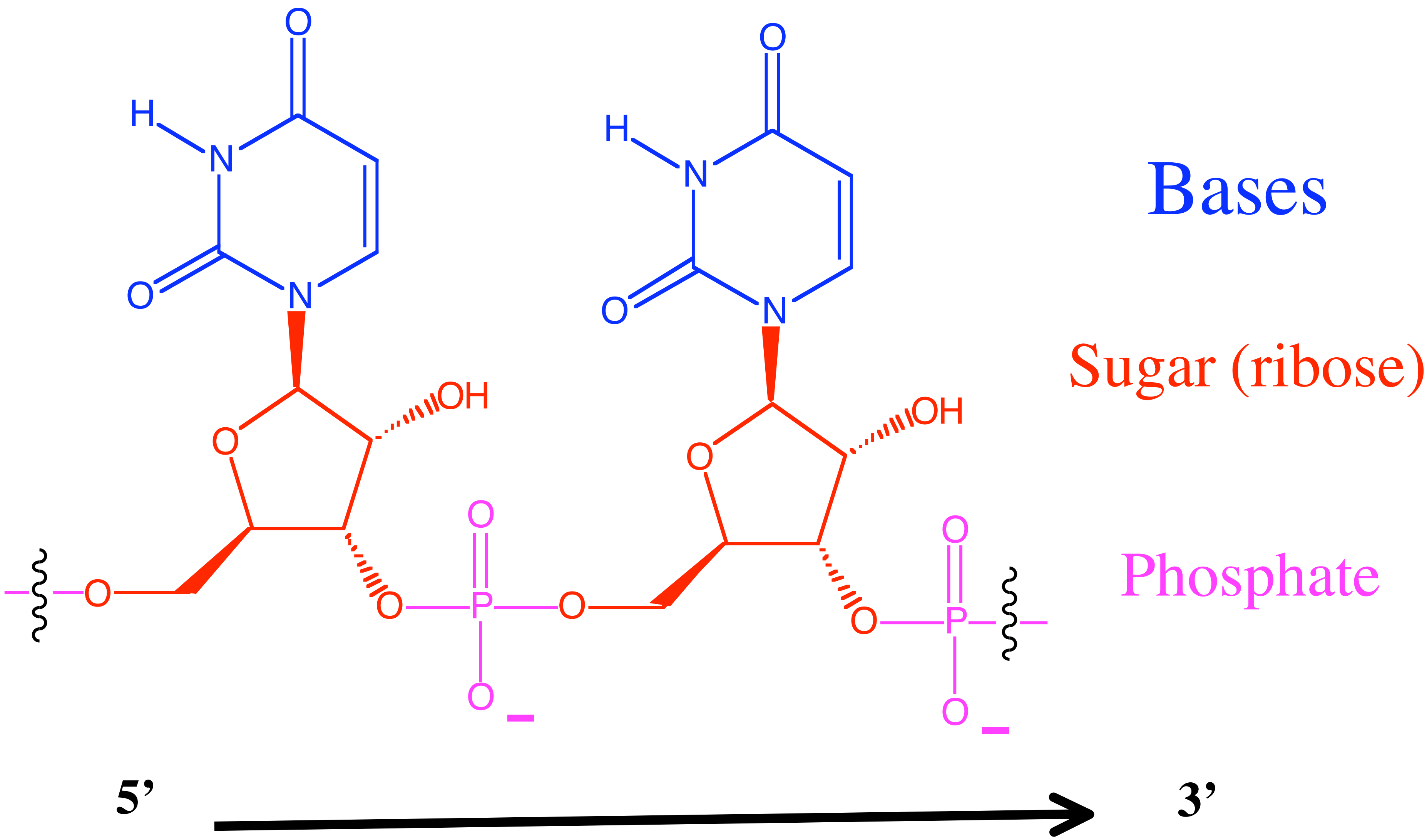
Global overview of all life



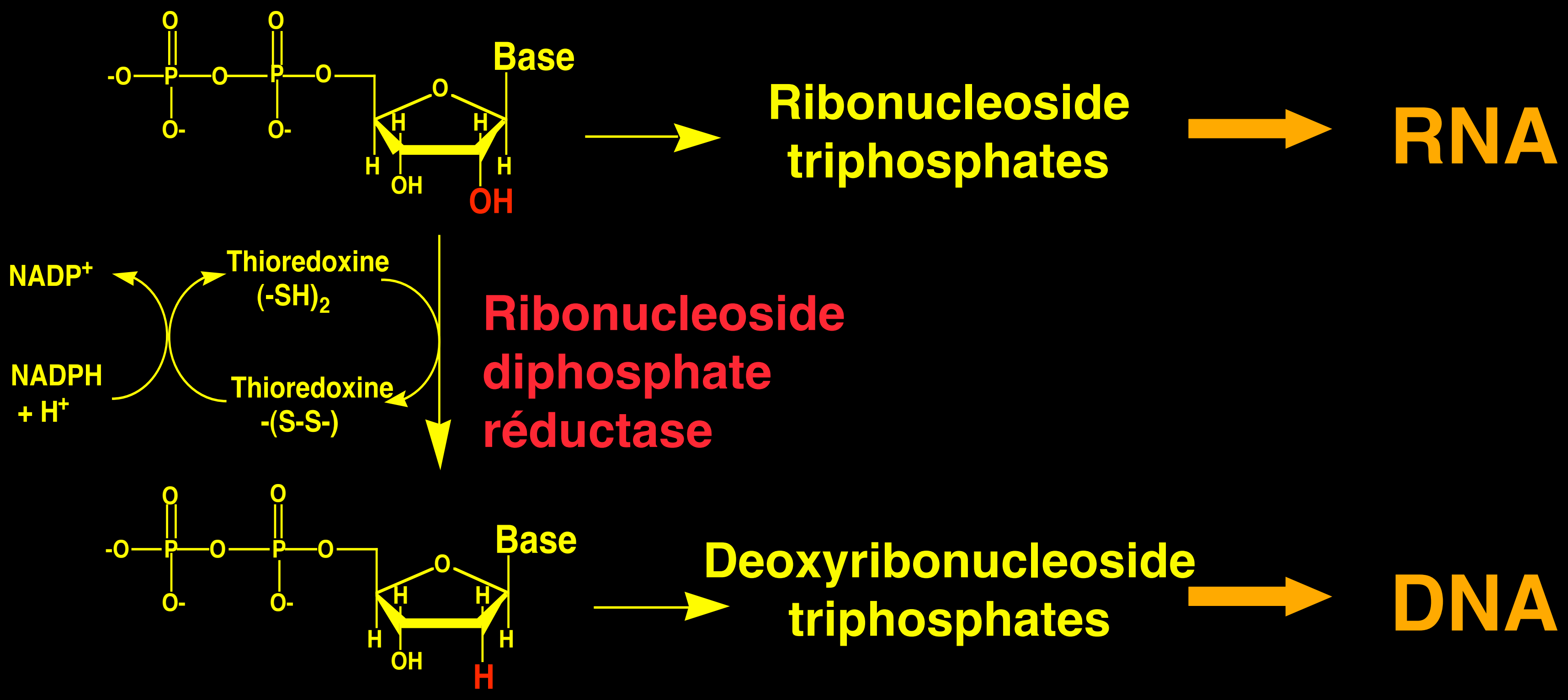
The RNA World

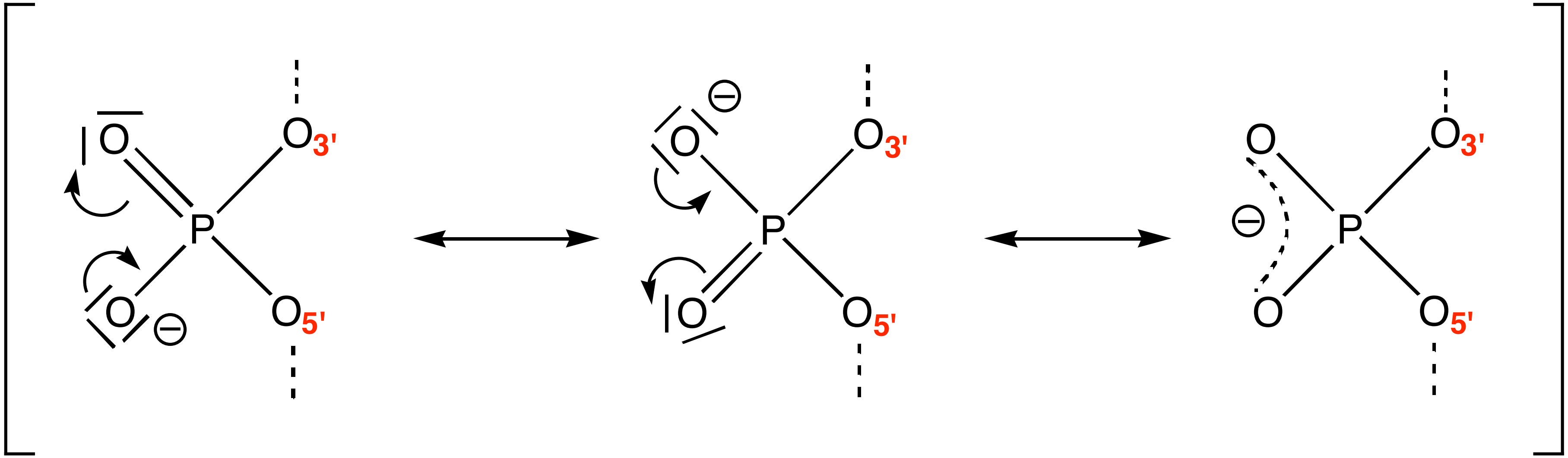
- Origin of life / central dogma paradox
    - DNA needs proteins to replicate
    - Proteins coded for by DNA
- RNA can be code and machinery
    - Selex, aptamers
- RNAs are remnants
    - Ancient and Essential

RNA, Parts



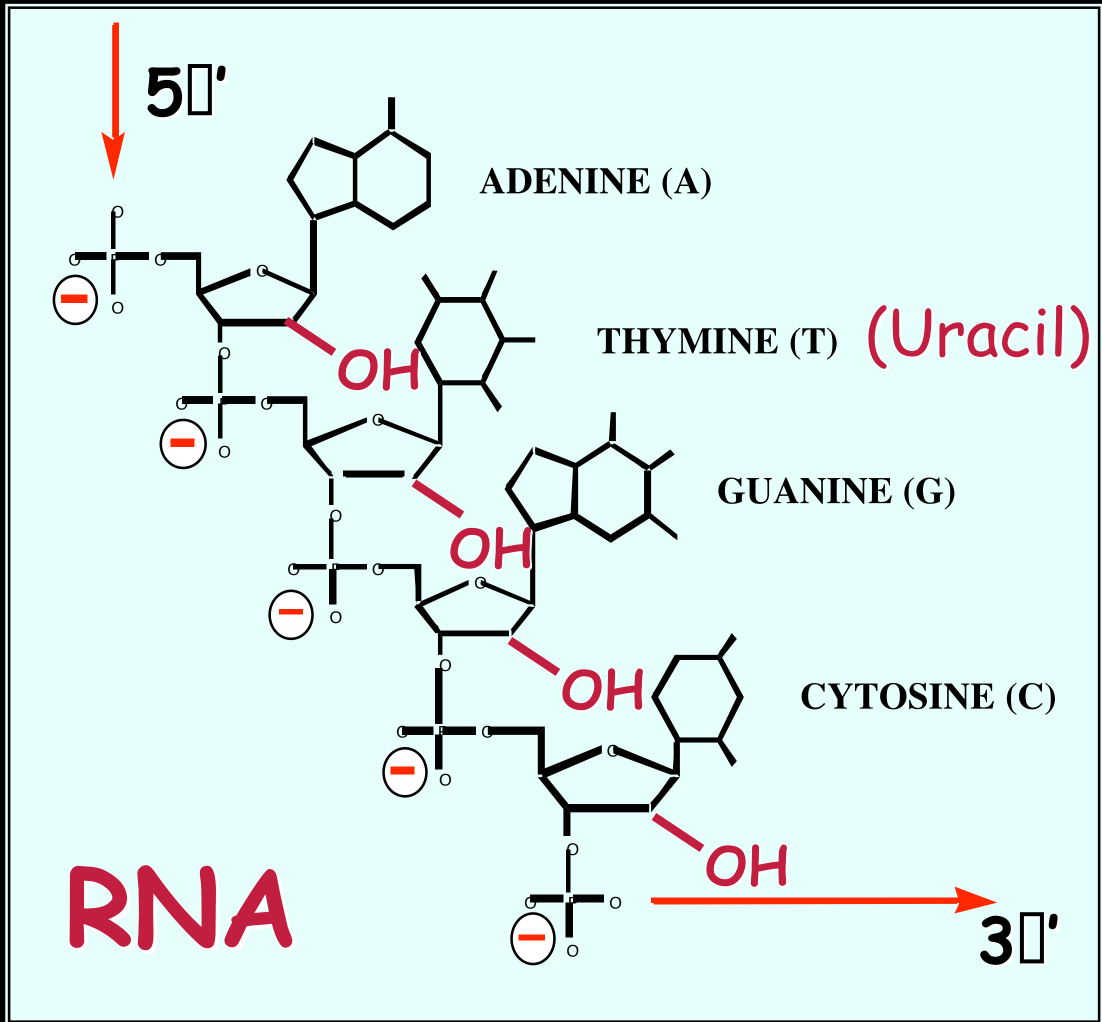
DNA = modified RNA





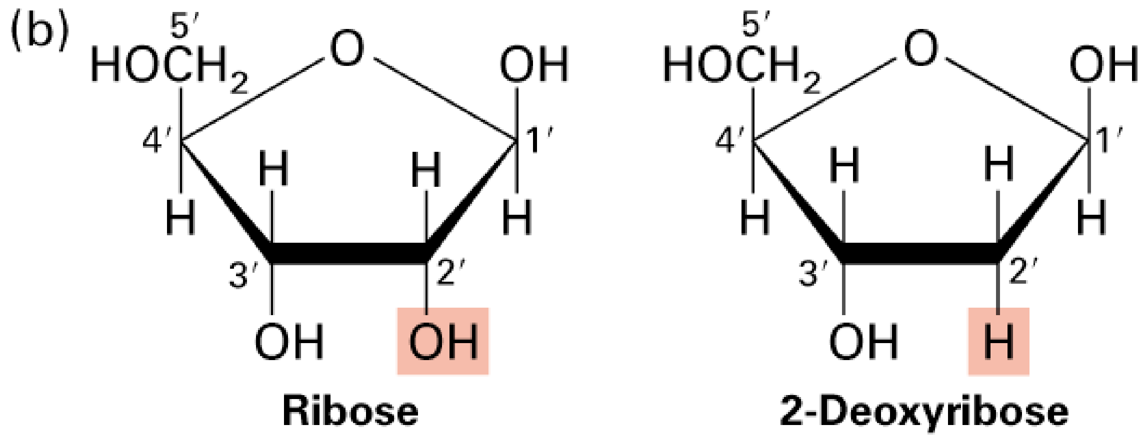
O
P
O3'
O5'

Nucleic acids are negatively charged biopolymers ...

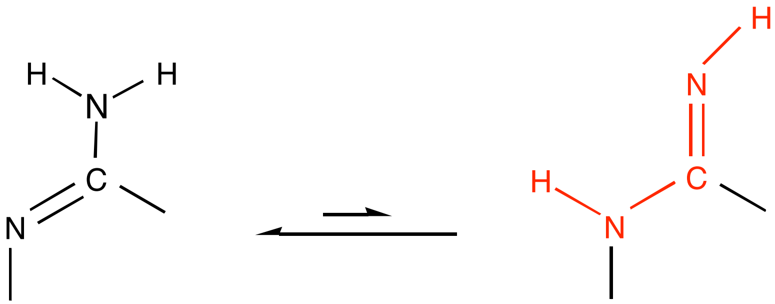


Conformations of RNA

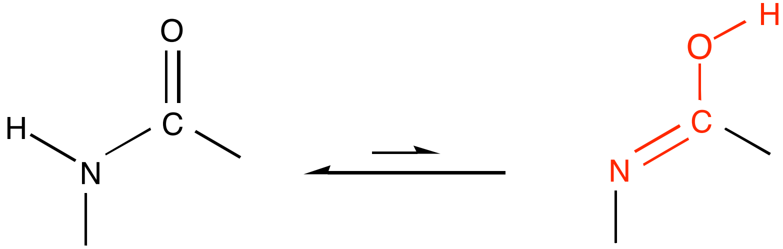
•Primary structure of RNA similar to DNA



•RNA, like DNA, can be single or double stranded, linear or circular.
•Unlike DNA, RNA can exhibit different foldings
•Different folds permit the RNAs to carry out specific functions in the cell



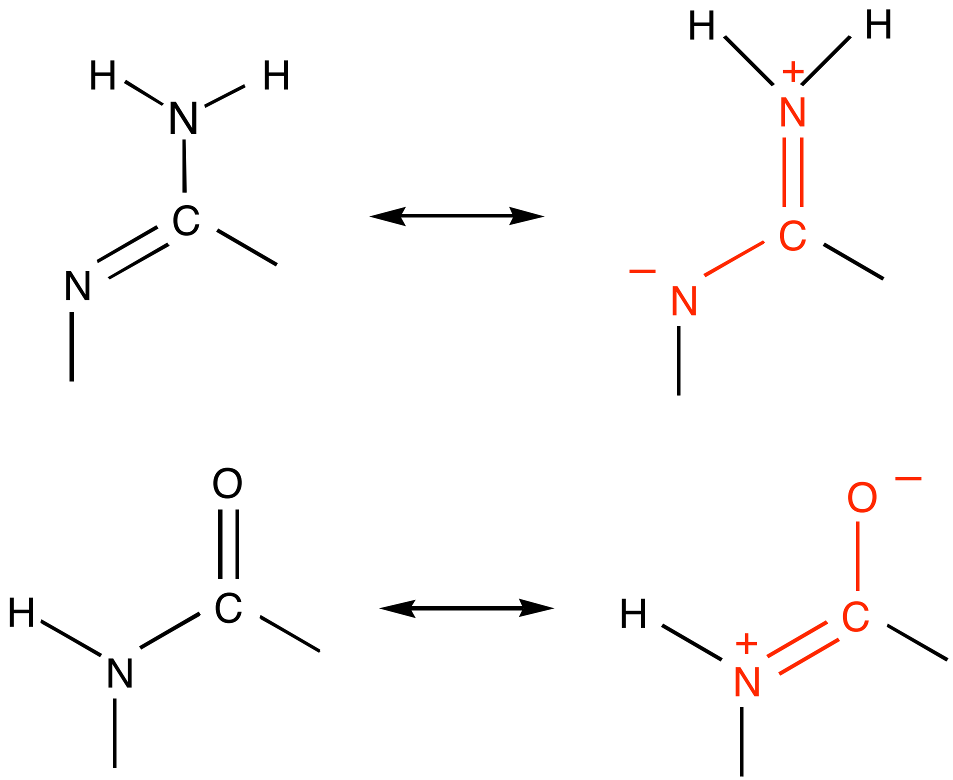
énamine imine



lactame (forme céto) lactime (forme énol)

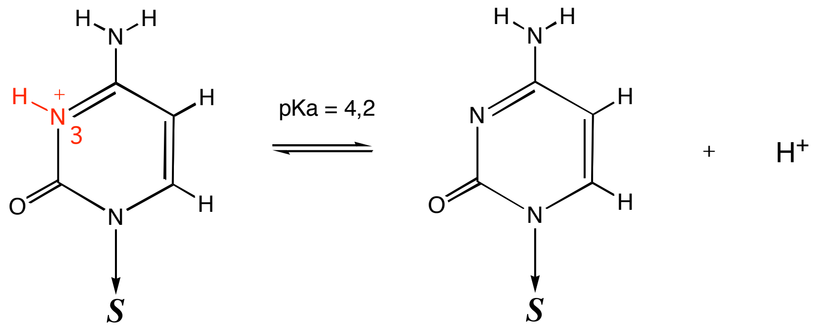
Tautomeric forms

Charge delocalization

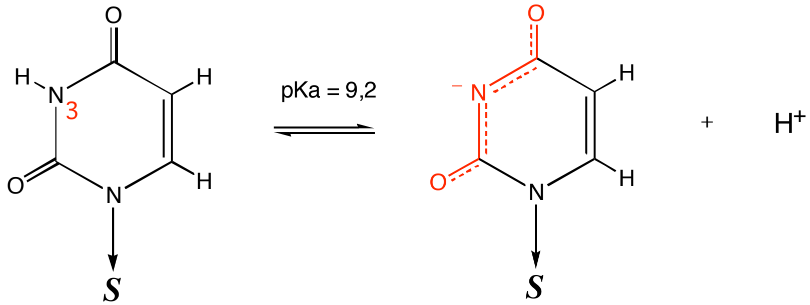


Protonation possibilities

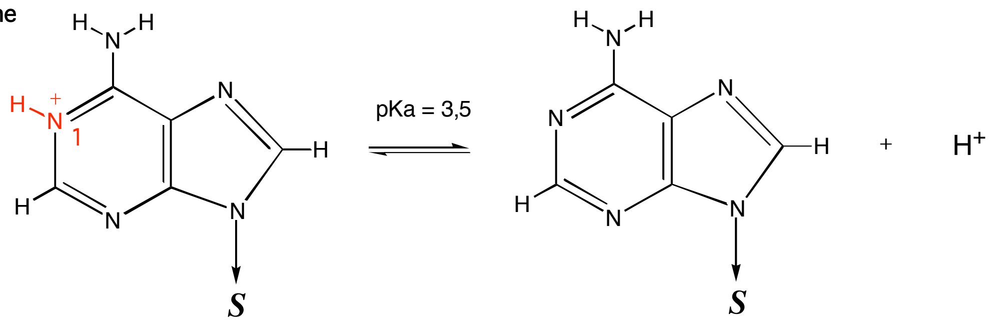
Cytidine



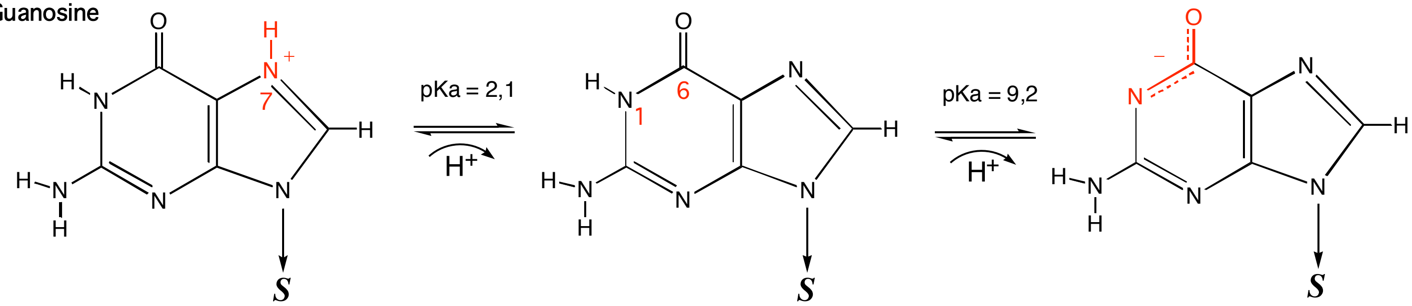
Uridine



Adénosine



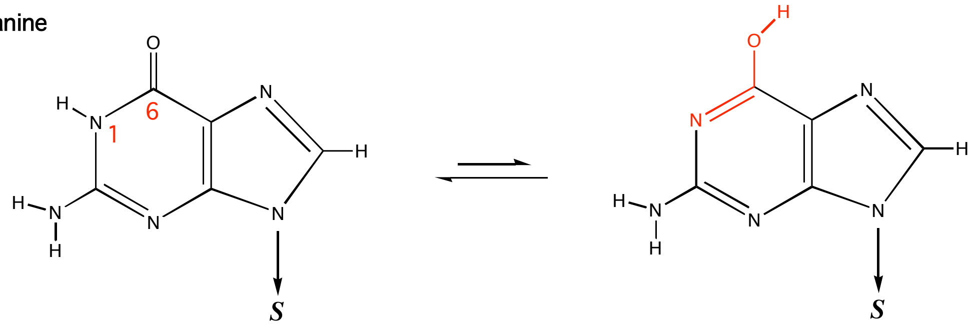
Guanosine



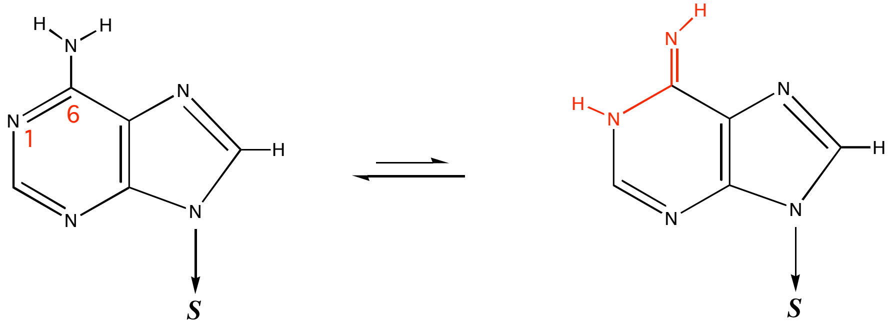
Always seen

Never seen

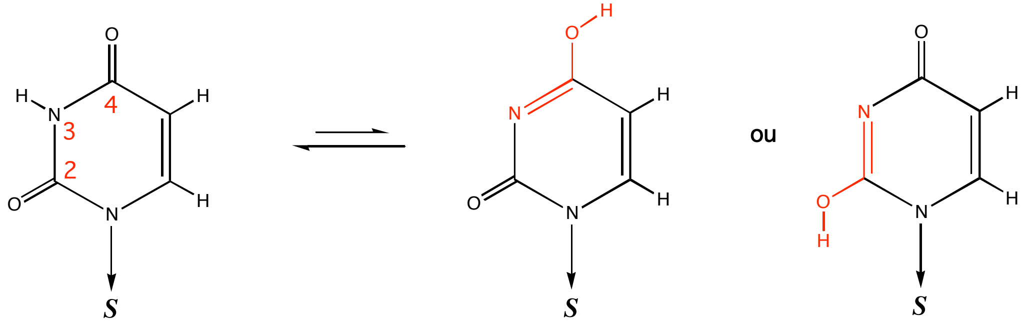
Guanine



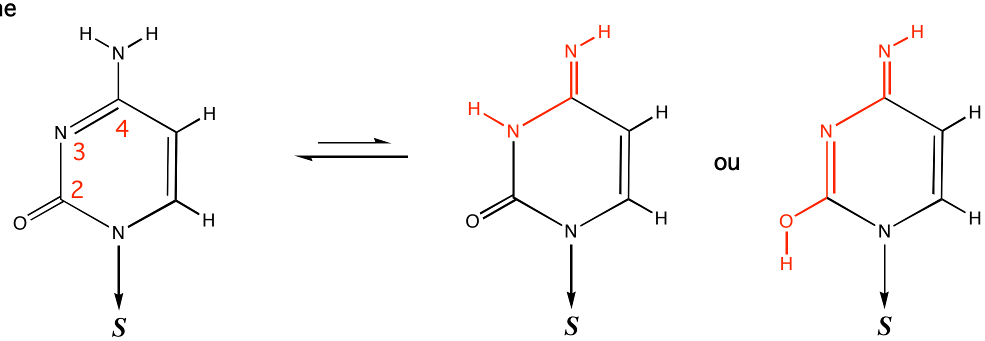
Adénine



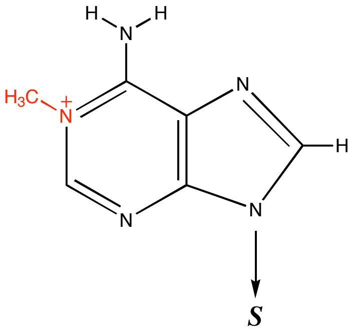
Uracile



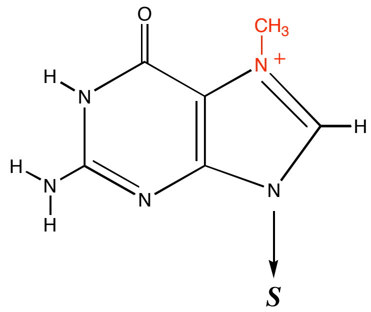
Cytosine



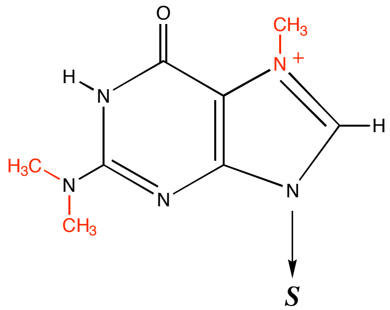
Modified bases have different …



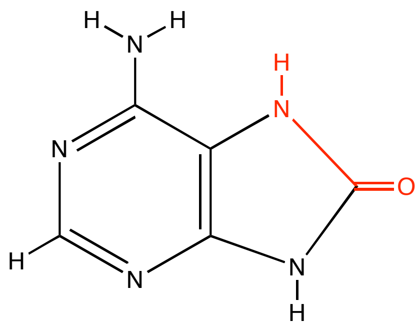
1-méthyladénine



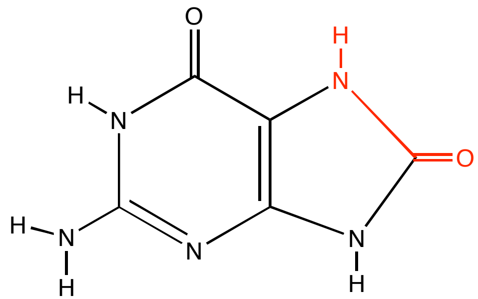
7-méthylguanine



2,2,7-triméthylguanine

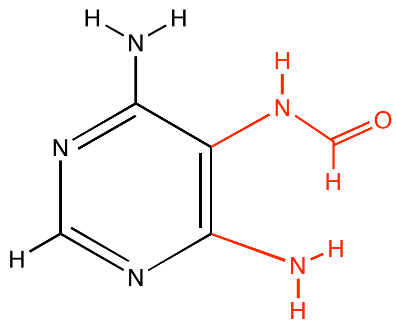


8-oxoadénine

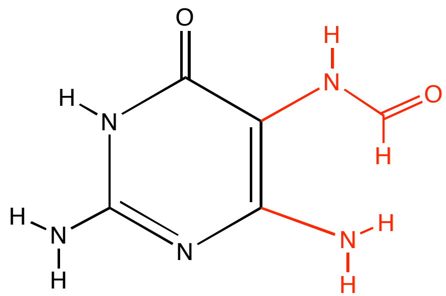


8-oxoguanine

… electronic properties

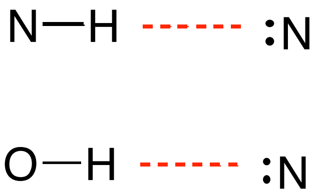


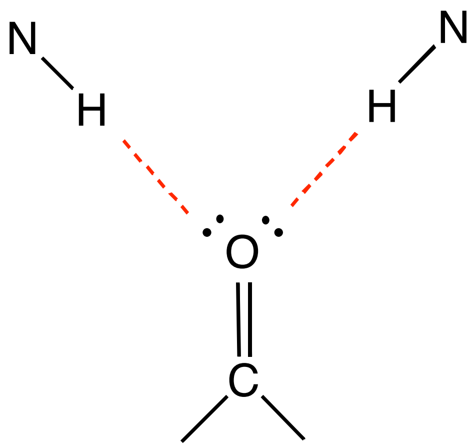
Fapy-adénine

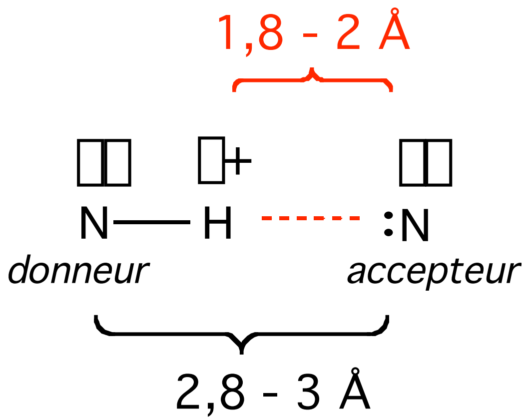


Fapy-guanine

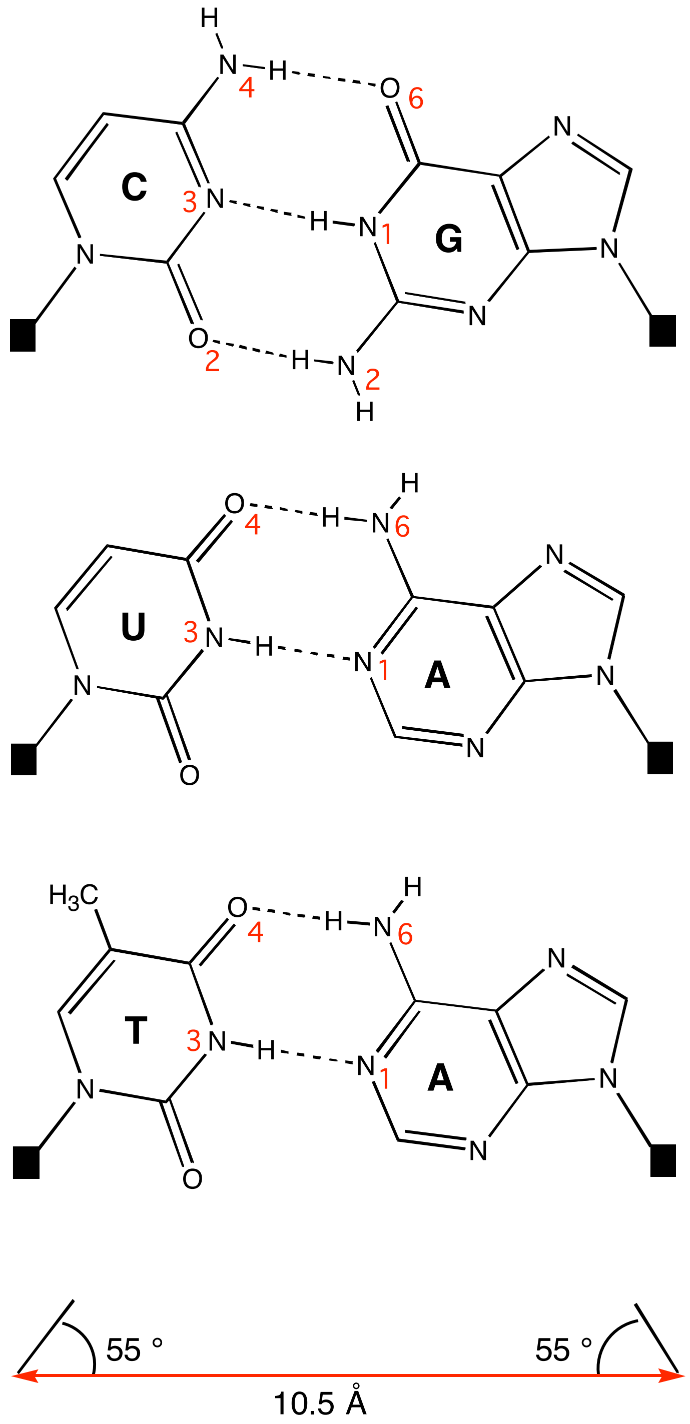
H-bond characteristics



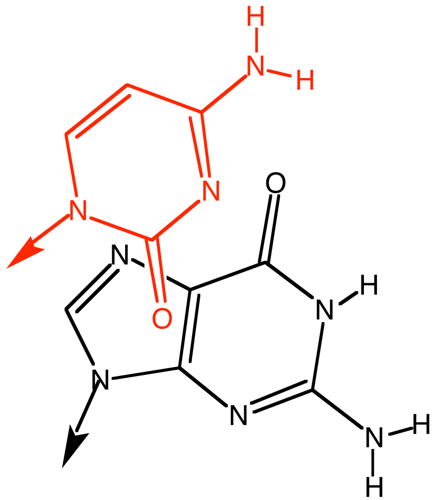


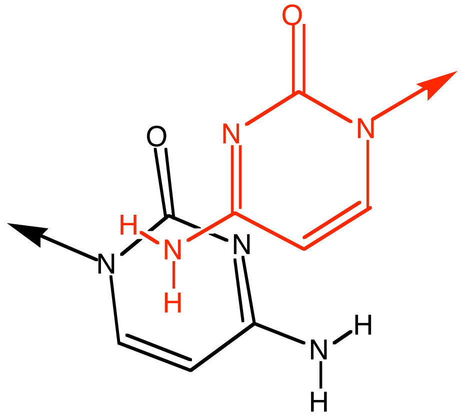


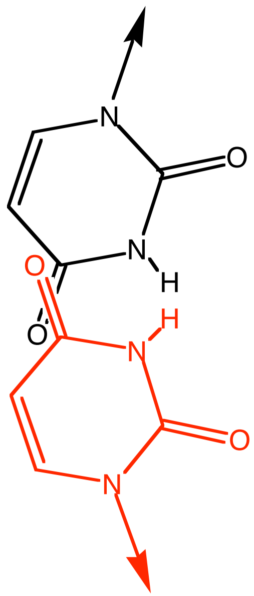
Horizontal
Interactions
Base pairing.
In helices
Complementary
Watson-Crick

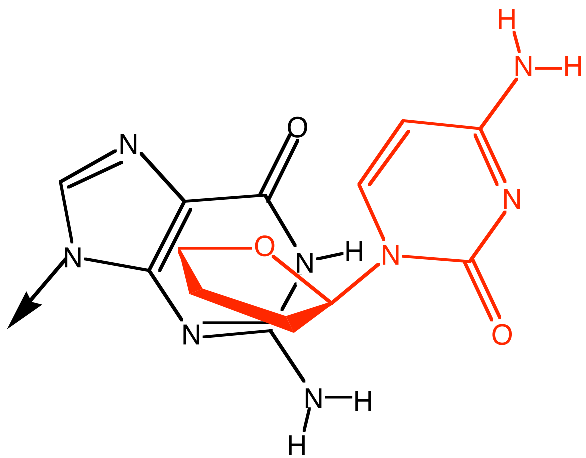


Vertical interactions : stacking









Stacking forces

- Driving Force : hydrophobic effect.
- Not very specific

- Partition in

very polar regions (phosphates) &
less polar ones (exocyclic groups of bases)

History of the many roles of RNA

Central dogma

The flow of genetic information

$$\text{DNA} \xrightarrow{\text{transcription}} \text{RNA} \xrightarrow{\text{translation}} \text{Protein}$$

DNA notoriety

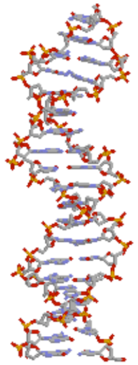
Rosalind Franklin: Dark Lady of DNA

Book Sheds New Light on a Scientific Landmark

Rosalind Franklin
Photo: courtesy HarperCollins

Oct. 6, 2002 -- Early next year, scientific institutions in the United States and Great Britain will mark the 50th anniversary of one of the greatest discoveries in science. In April of 1953, James Watson, Francis Crick and Maurice Wilkins identified the substance of life -- the structure of DNA.

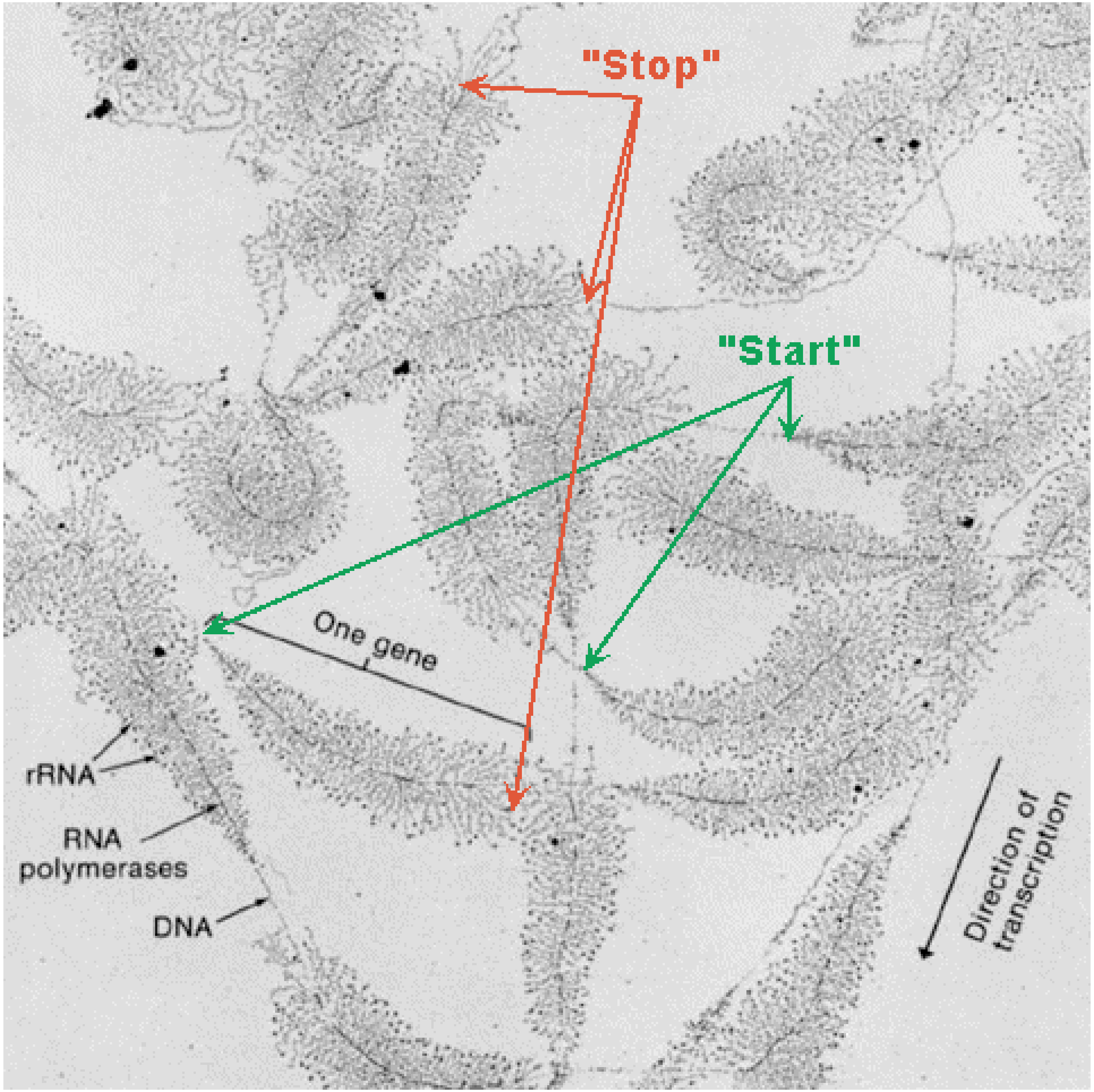
They later shared a Nobel Prize. Their discovery depended heavily on the work of a woman, chemist Rosalind Franklin, whose research was used without her knowledge or permission. Watson's memoir of the discovery dismisses Franklin as frumpy, hostile and unimaginative. A later work by a friend casts Franklin as a feminist icon, cheated of recognition.



Short history of RNA

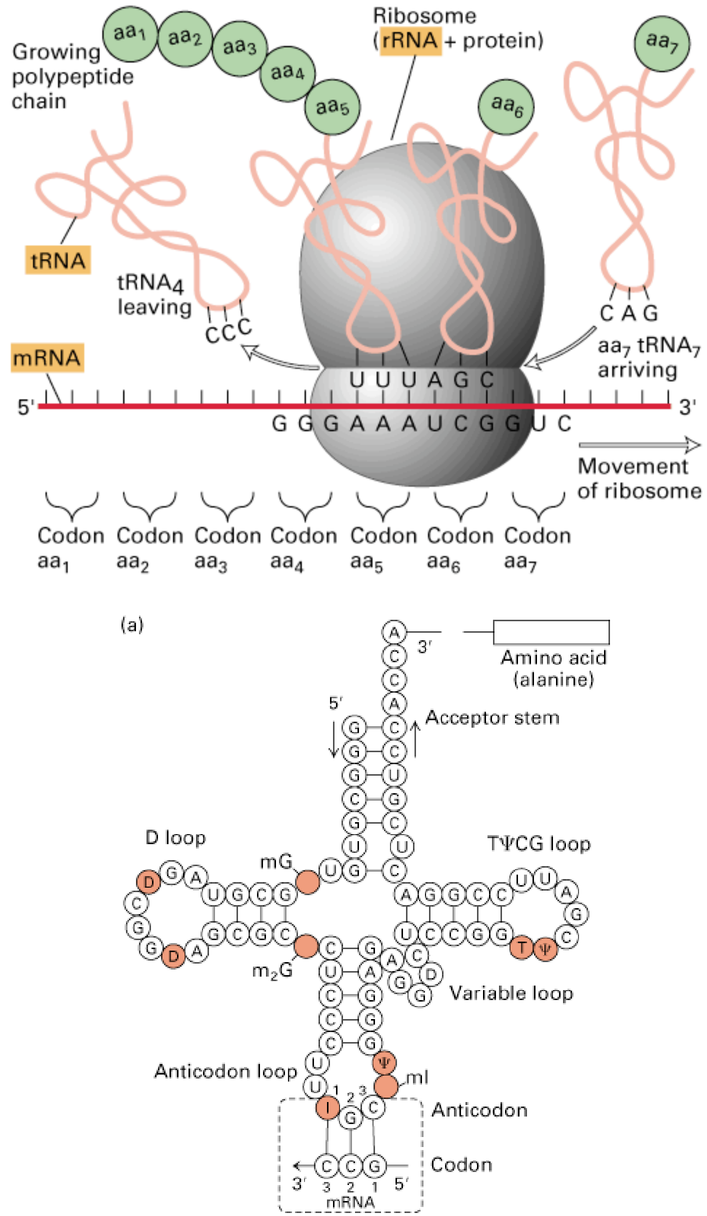
- Late 1800's - 2nd kind of nucleic acid not in the nucleus (rRNA)
- 1920's - sugar for DNA vs RNA
- 1958 - tRNA (Hoagland)
- 1960's - mRNA

Relative Amount of RNA in E. coli
rRNA 80%
tRNA 15%
mRNA 5%

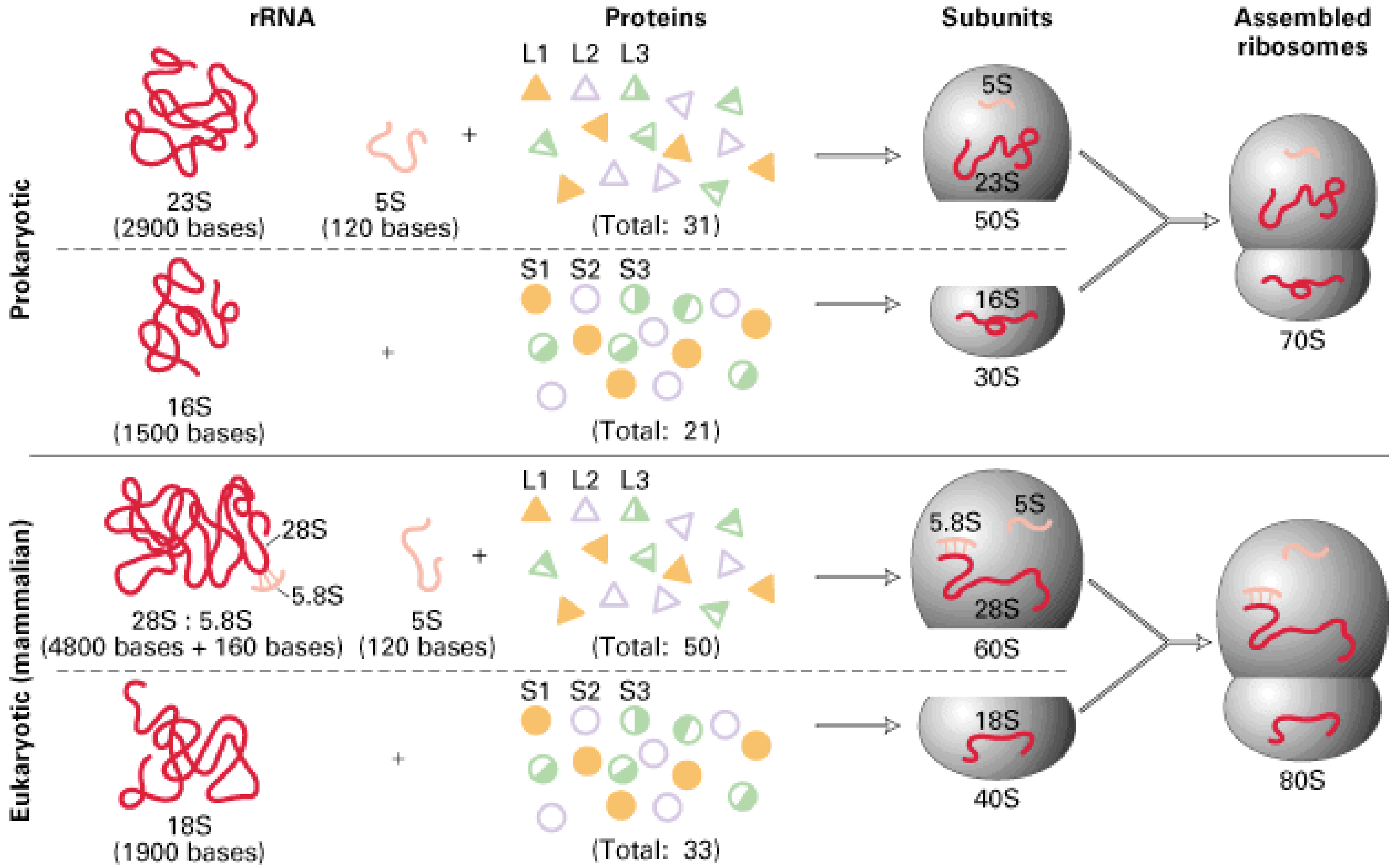

"Stop"
"Start"
One gene
rRNA
RNA polymerases
DNA
Direction of transcription

RNA

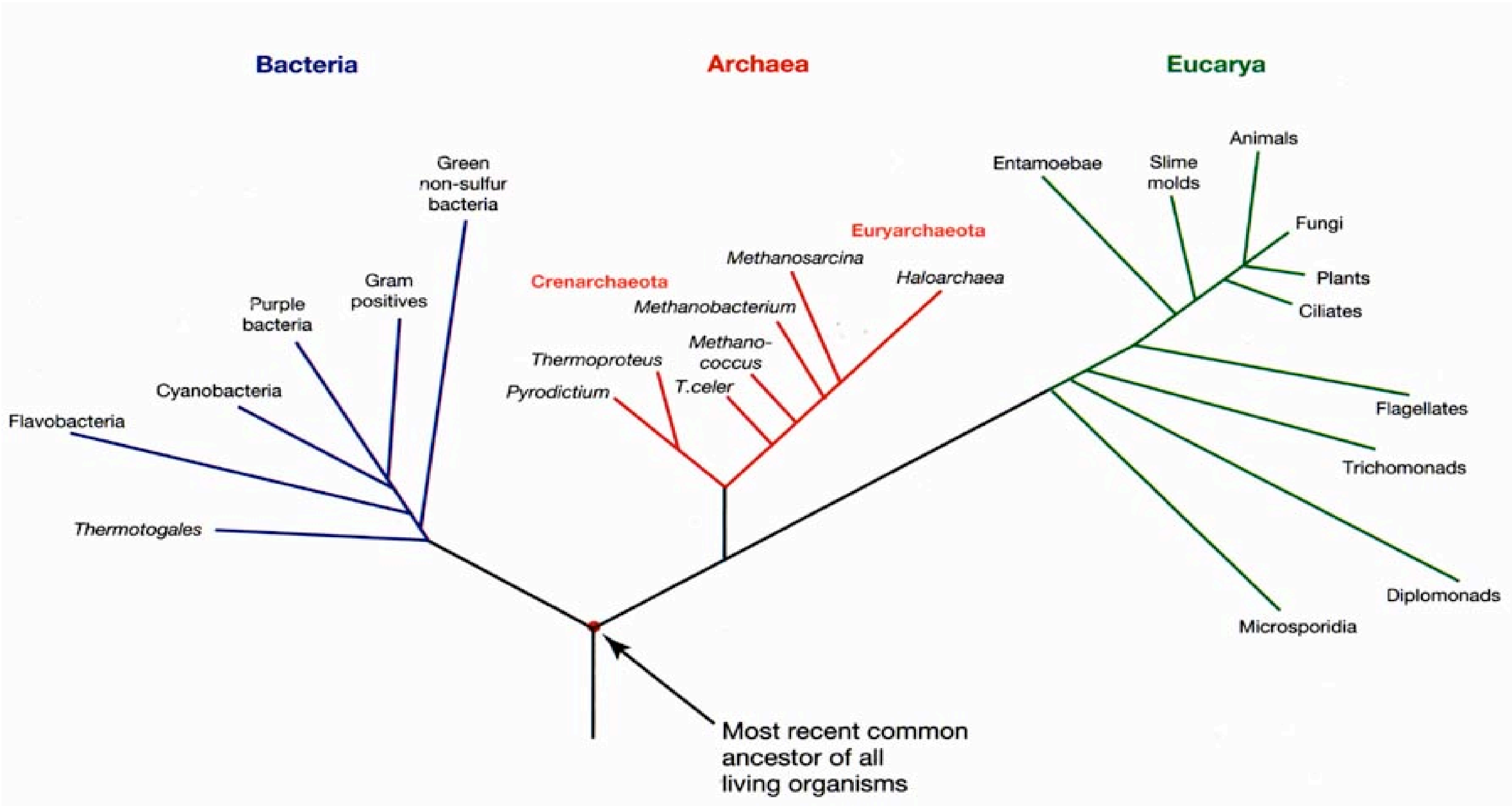
- "Three" different types of RNA
  - mRNA - messenger RNA, specifies order of amino acids during protein synthesis
  - tRNA - transfer RNA, during translation mRNA information is interpreted by tRNA
  - rRNA – ribosomal RNA, combined with proteins aids tRNA in translation



Ribosomal RNA (rRNA)

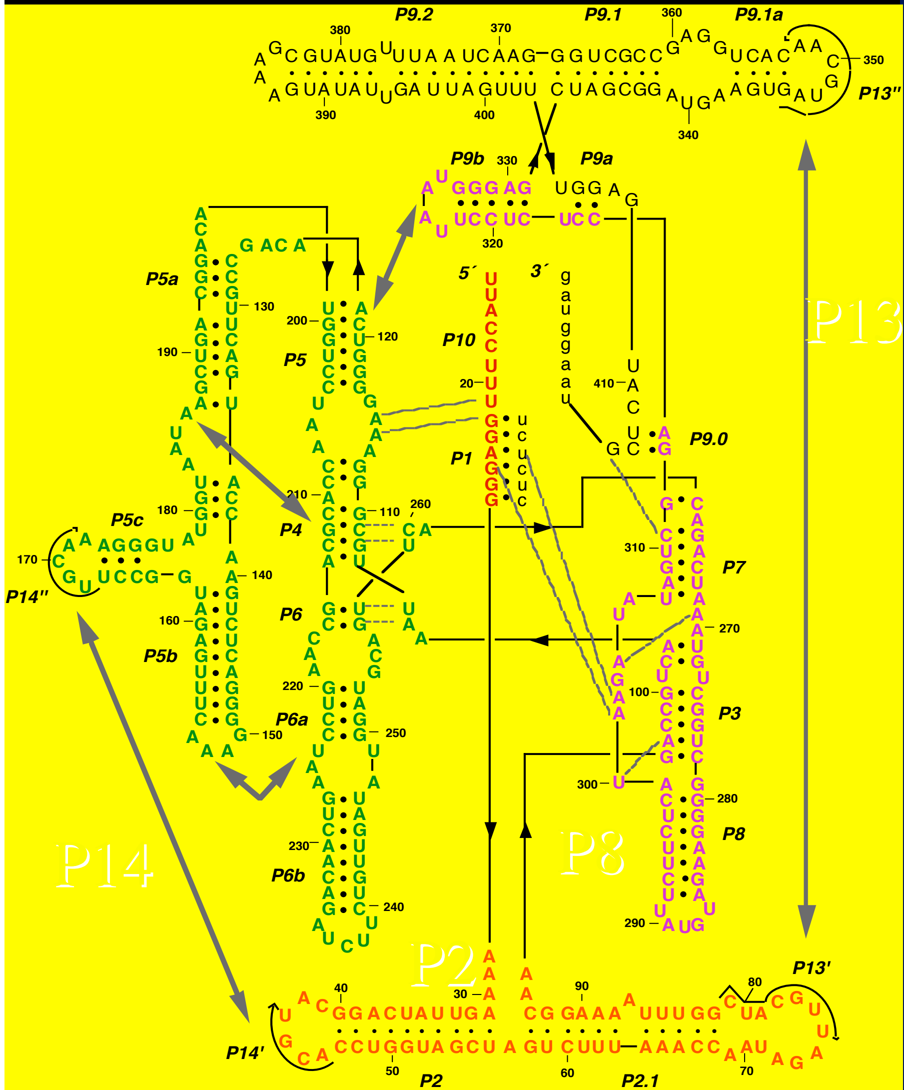


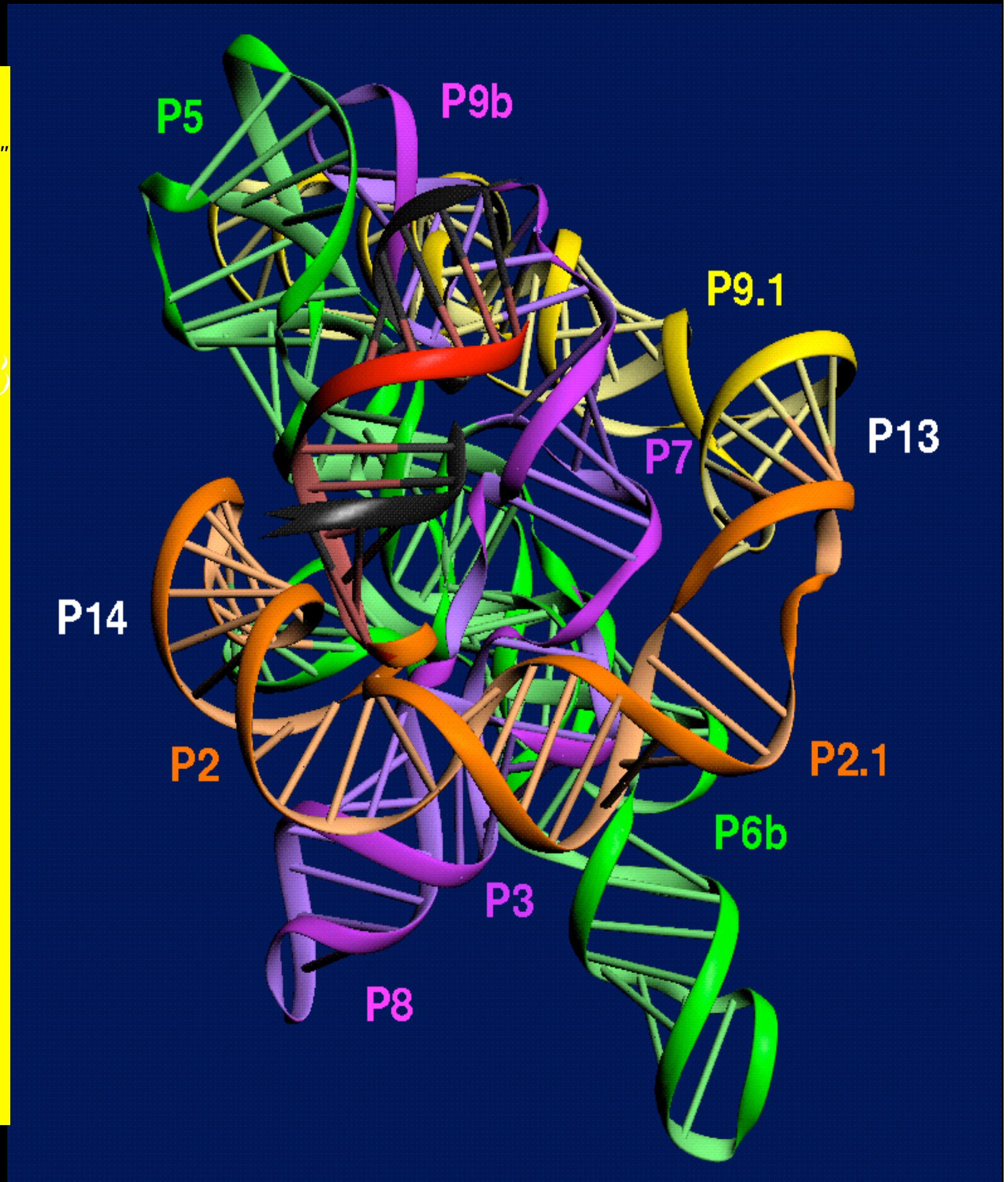
Phylogeny of Life using SSU rRNA



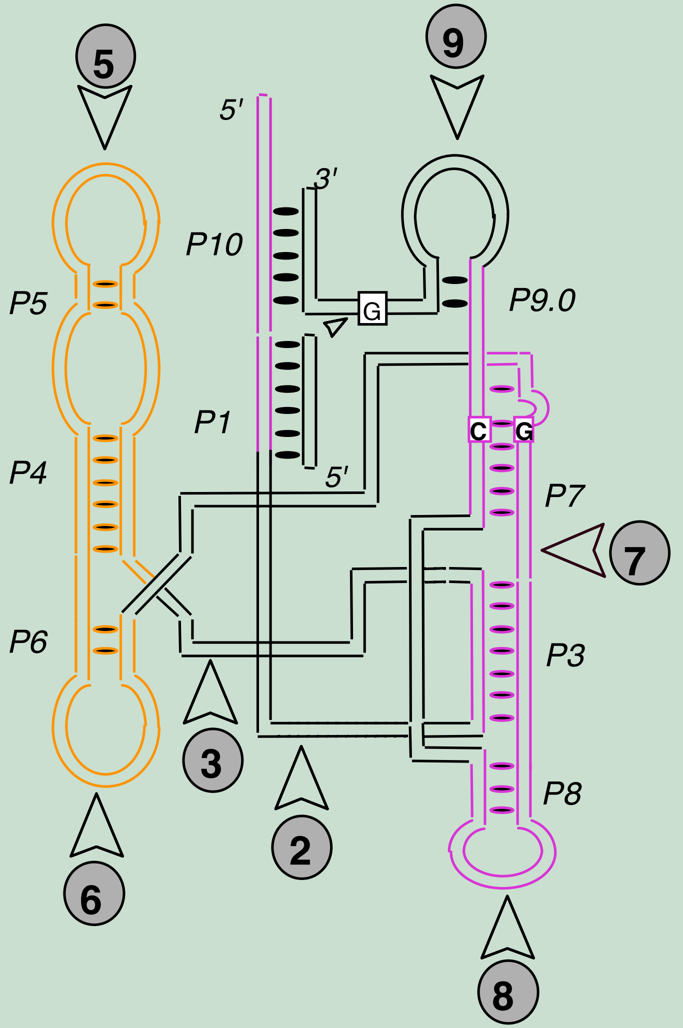
Discovery of catalytic RNA

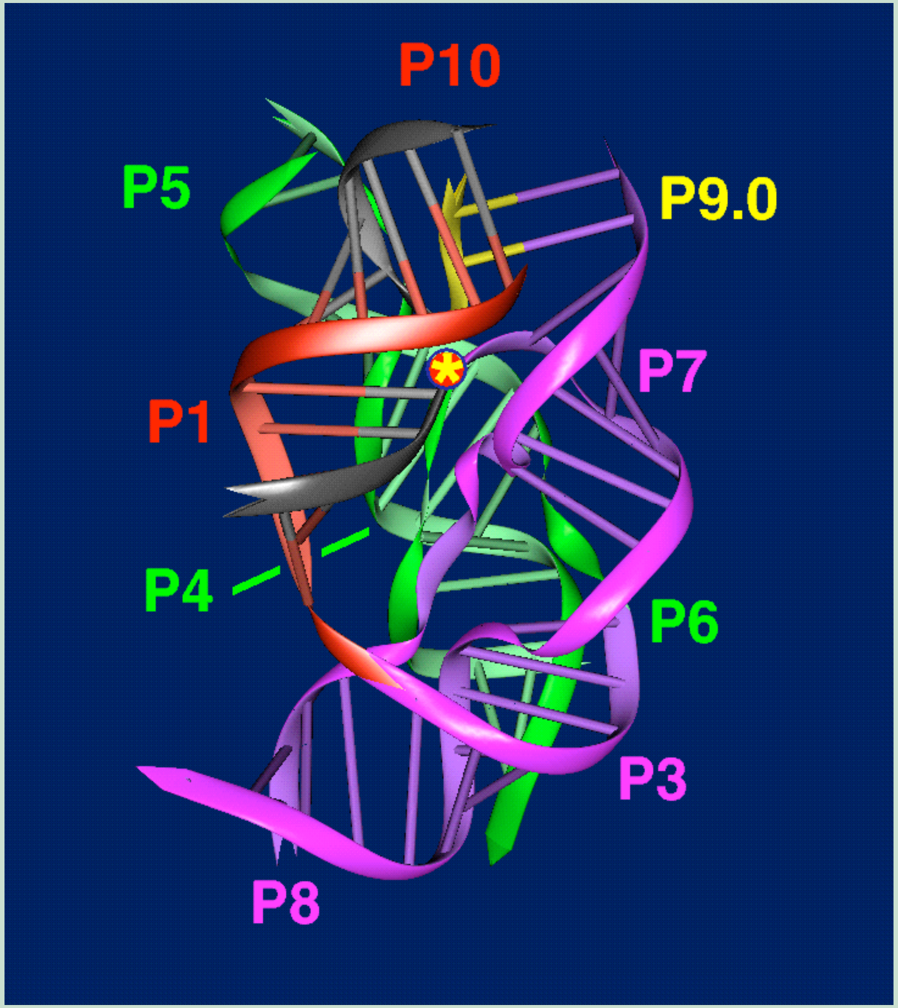
- Early 1980’s :
- Tom Cech & Sidney Altman
- Self-splicing group I introns and
- Ribonuclease P


P9.2
P9.1
P9.1a
P13''
P9b
P9a
P5a
P5
P10
5´
3´
P1
P9.0
P5c
P4
P14''
P7
P6
P5b
P6a
P3
P8
P6b
P14
P13
P2
P13'
P14'
P2.1

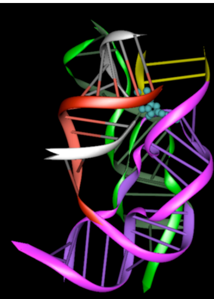

P5
P9b
P9.1
P7
P13
P14
P2
P2.1
P6b
P3
P8

Group I self-splicing introns
Core structure

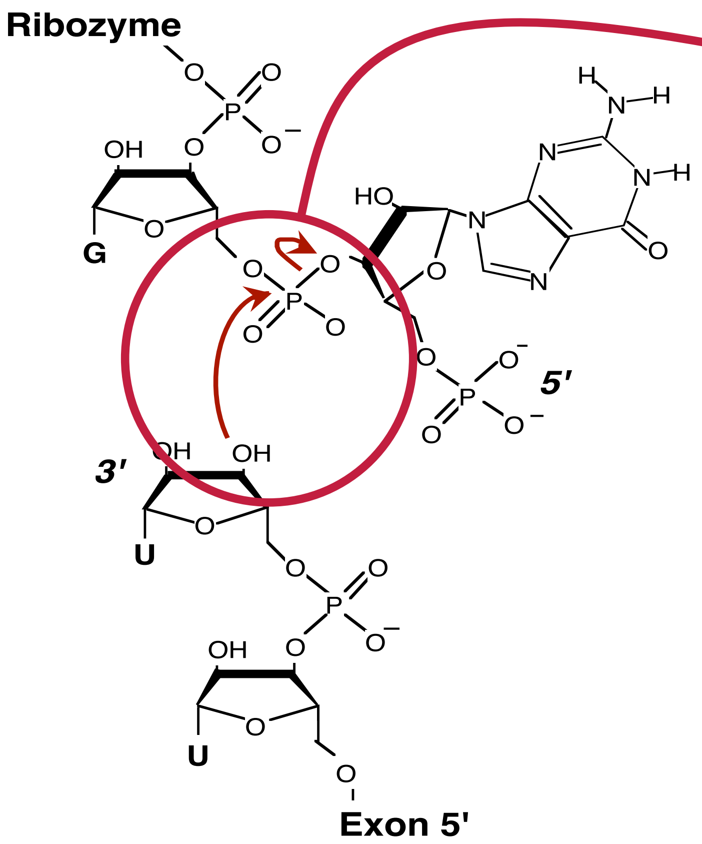


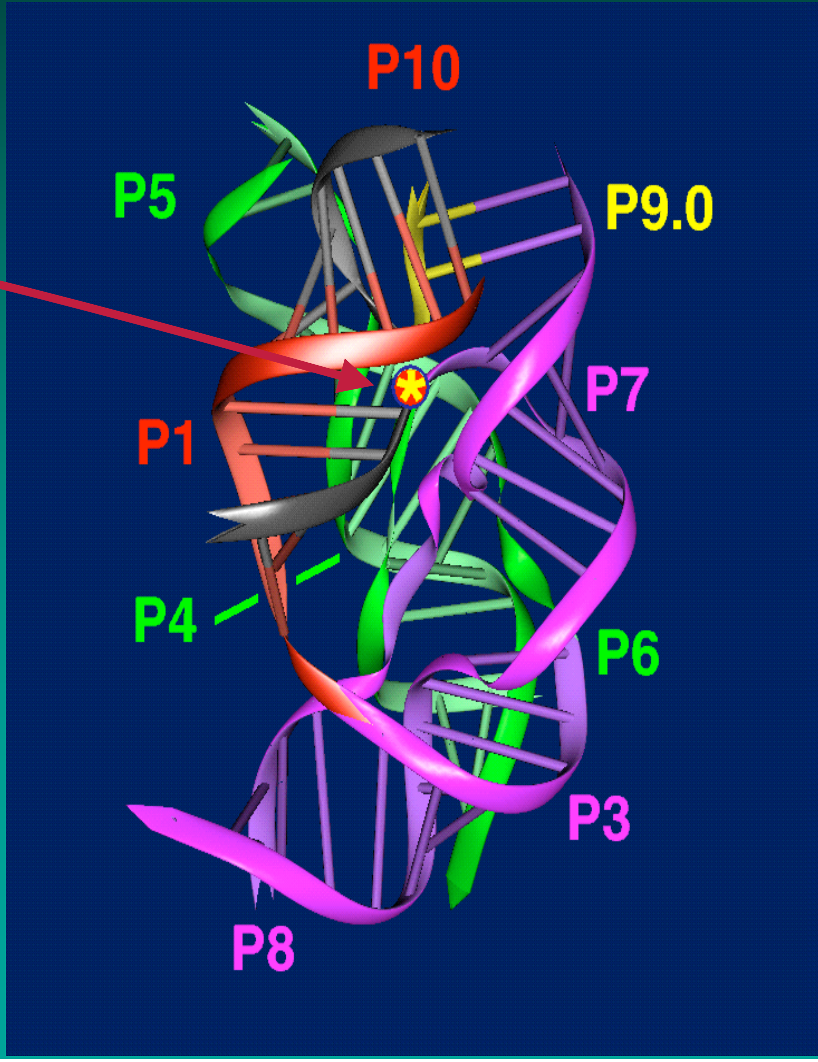


Catalytic Core of Group I introns



Transesterification





Second discovery of RNA

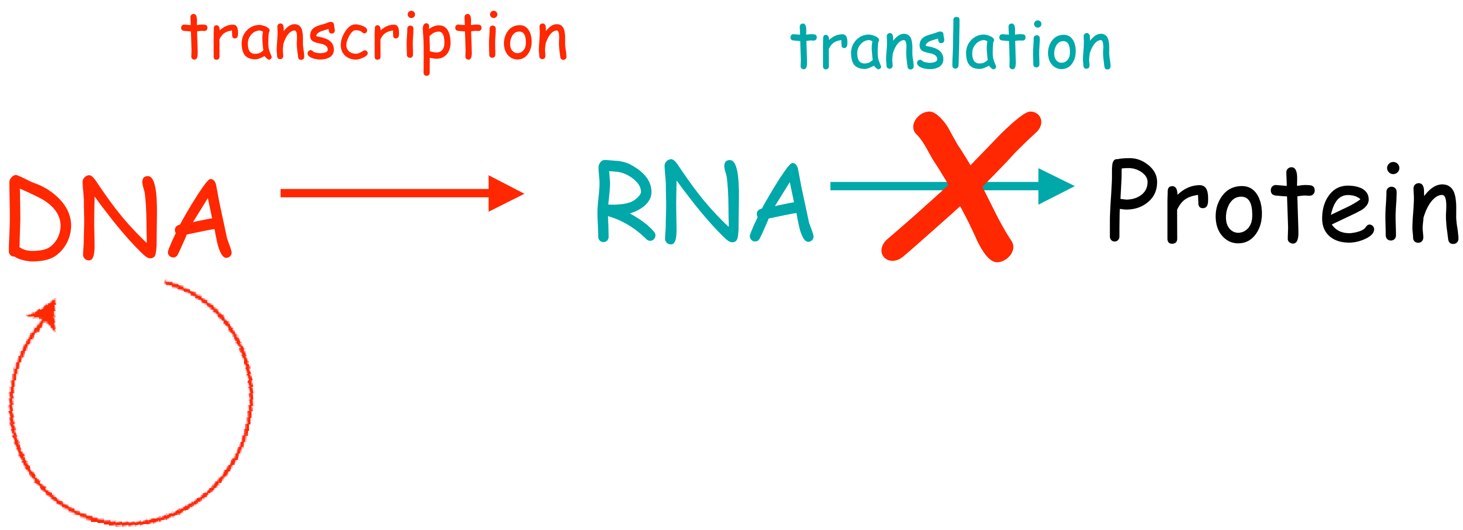
- ncRNAs - functional RNA molecules rather than proteins; RNA other than mRNA (ex.XIST)
- RNAi - RNA interference
- siRNA- active molecules in RNA interference; degrades mRNA (act where they originate)
- miRNAs - tiny 21–24-nucleotide RNAs; probably acting as translational regulators of protein-coding mRNAs (regulate elsewhere)

Other Roles of RNA

- stRNA - Small temporal RNA; (ex. lin-4 and let-7 in *Caenorhabditis elegans* : development
- snRNA - Small nuclear RNA; includes spliceosomal RNAs
- snoRNA - Small nucleolar RNA; most known snoRNAs are involved in rRNA modification
- RNA world - RNA as catalyst

Central dogma

The flow of genetic information

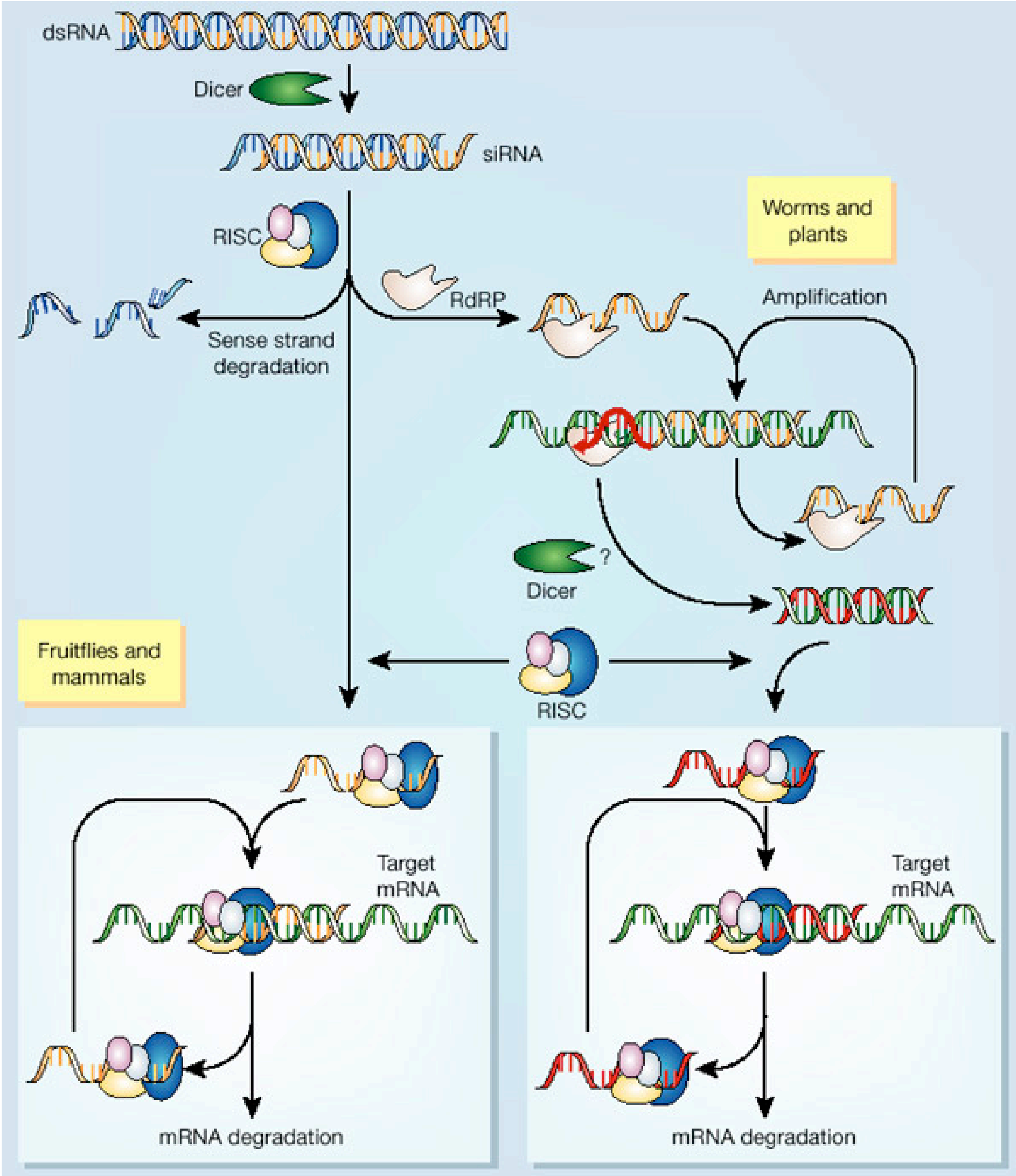


ncRNA genes

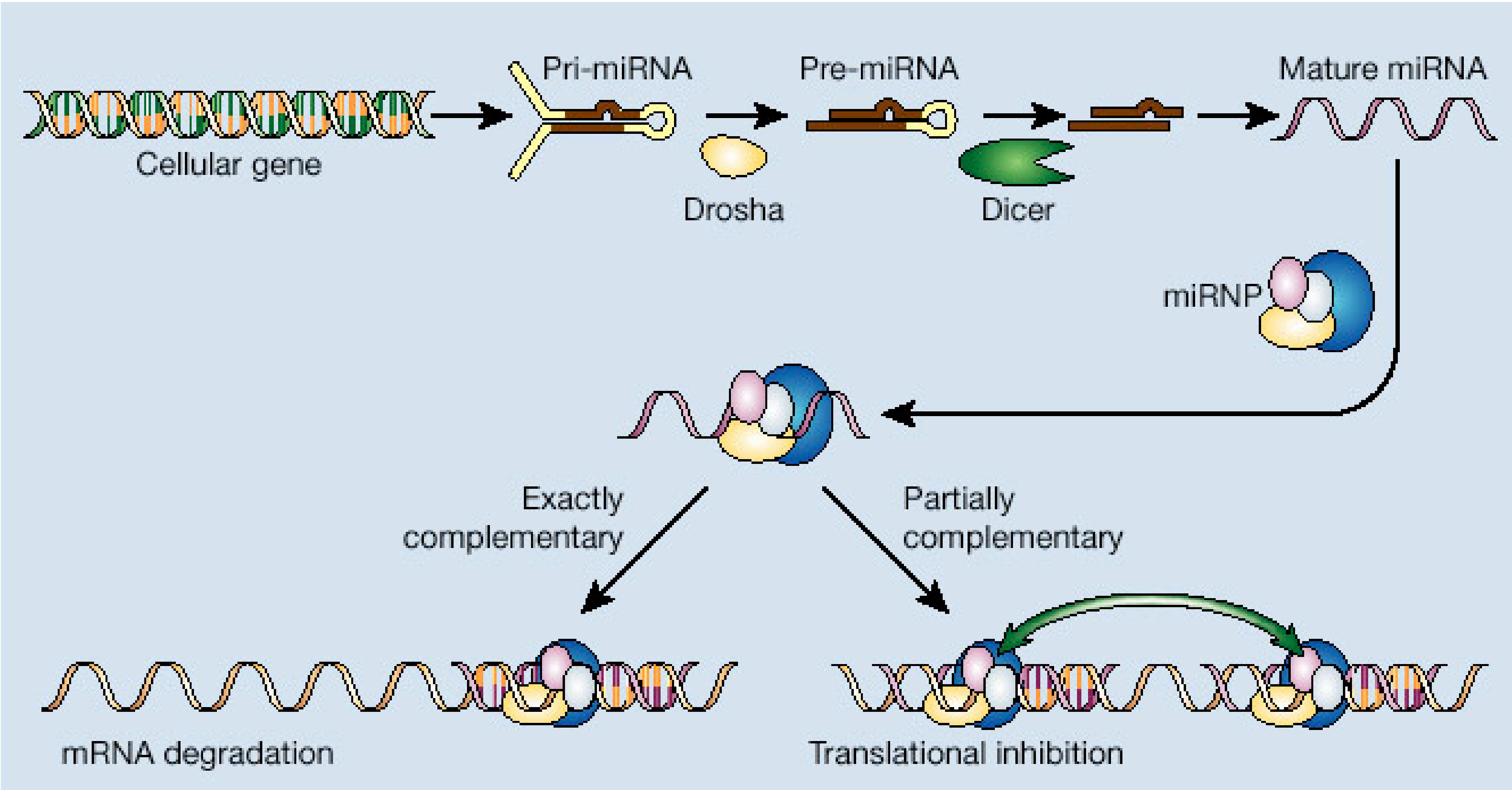
- Genomic dark matter
  - Ignored by gene prediction methods
  - Not in EnsEMBL
  - Computational complexity
- ~10% of human gene count?

RNA interference

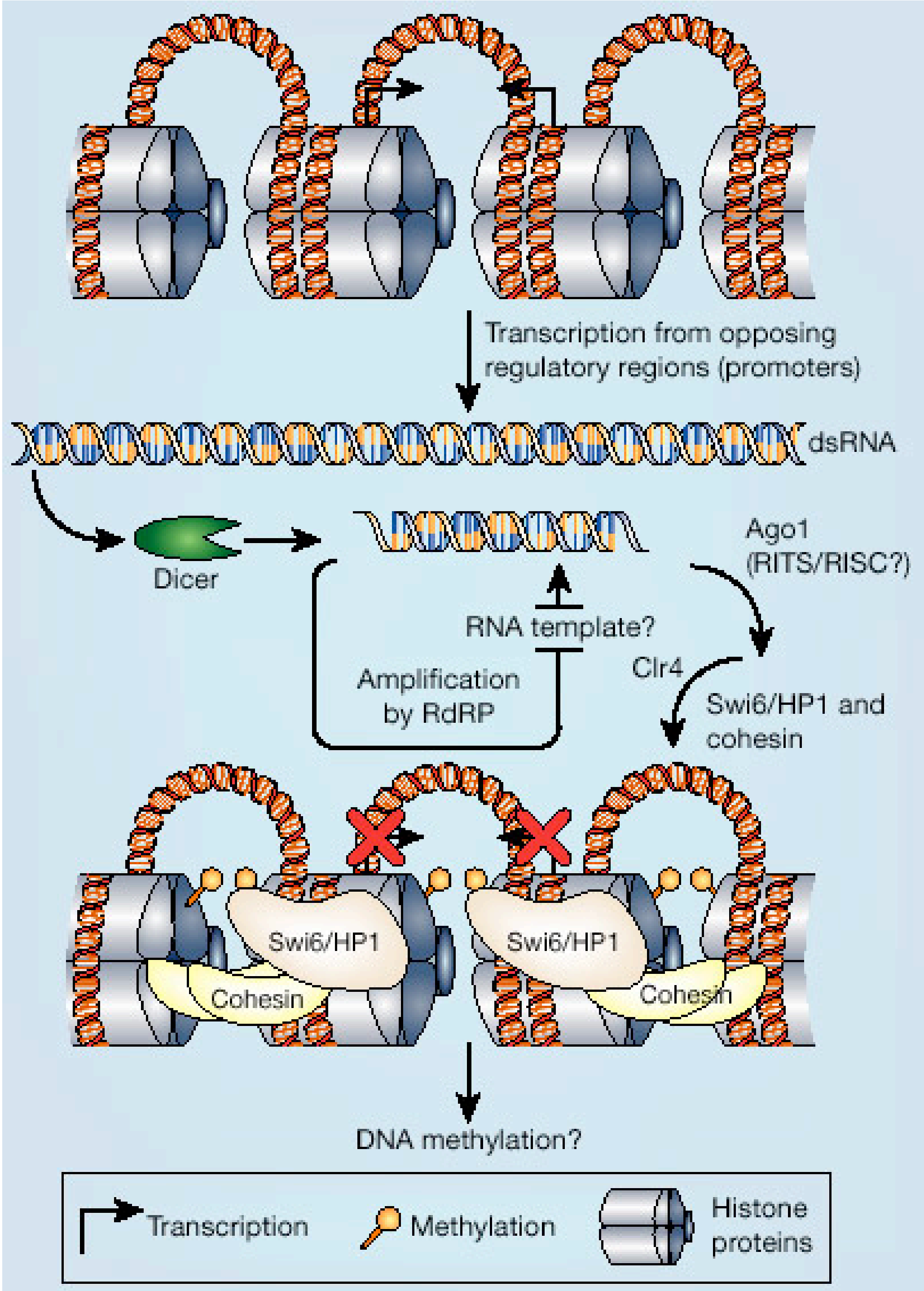
Short interfering RNAs (siRNAs)	A class of double-stranded RNAs of 21–22 nucleotides in length, generated from dsRNAs. siRNAs silence genes by promoting the cleavage of mRNAs with exactly complementary sequences, or recruiting inhibitory proteins to, or directing the modification of, DNAs with exactly complementary sequences.
MicroRNAs (miRNAs)	A class of 19–25-nucleotide, single-stranded RNAs that are encoded in the genomes of most multicellular organisms studied. Some are evolutionarily conserved and are developmentally regulated. They silence certain cellular genes at the stage of protein synthesis.
Tiny non-coding RNAs (tncRNAs)	A newly discovered class of short, 20–22-nucleotide RNAs that are encoded in the genome of *C. elegans*. They are not evolutionarily conserved, but some are developmentally regulated. Their function is still unknown.
Small modulatory RNA (smRNA)	A short, dsRNA, identified earlier this year in mice, that allows the expression of neuron-specific genes only in adult neurons.


dsRNA
Dicer
siRNA
RISC
Worms and plants
RdRP
Amplification
Sense strand degradation
Dicer
?
Fruitflies and mammals
RISC
Target mRNA
mRNA degradation
Target mRNA
mRNA degradation

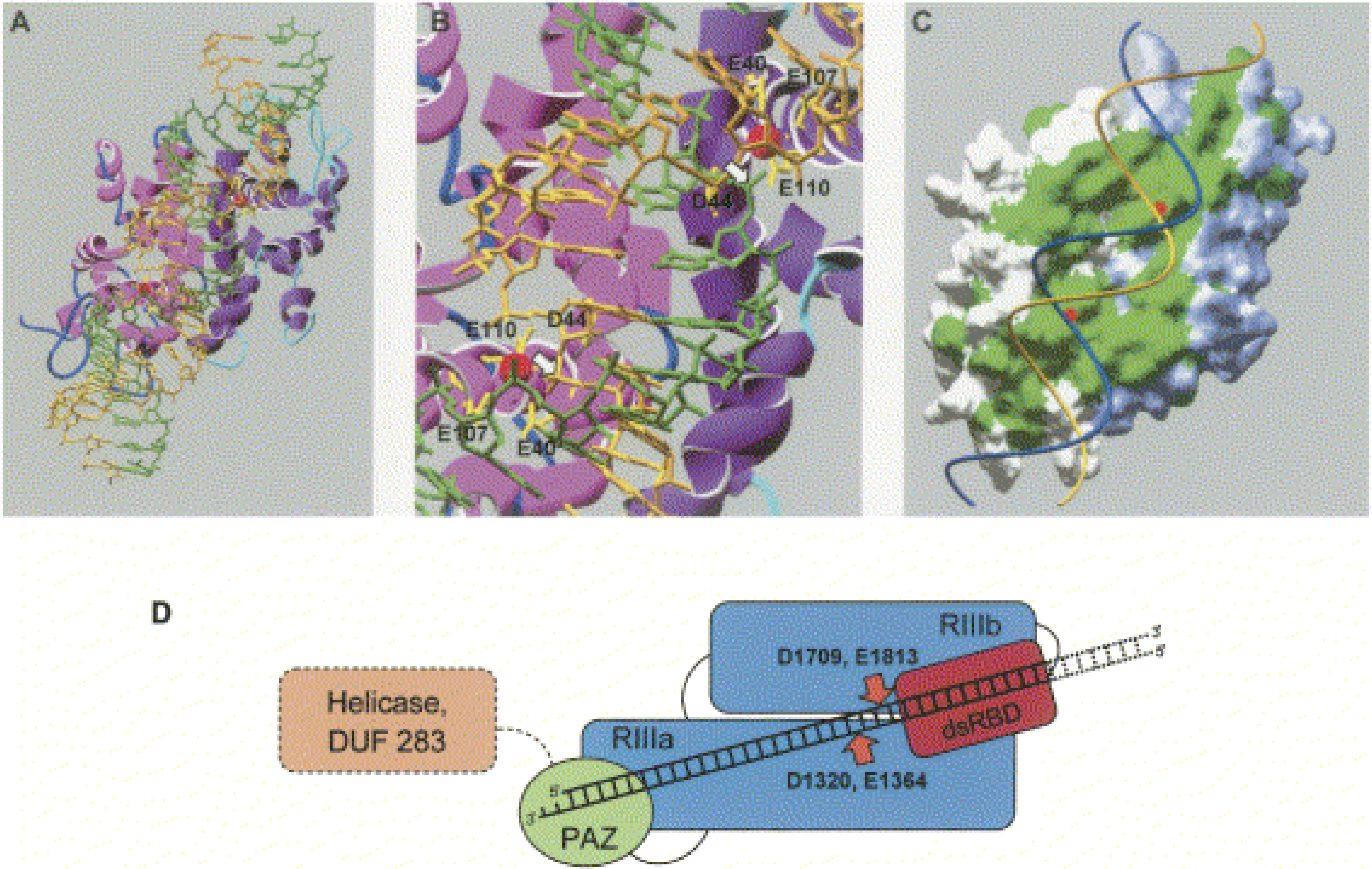
Intricate maturation pathways



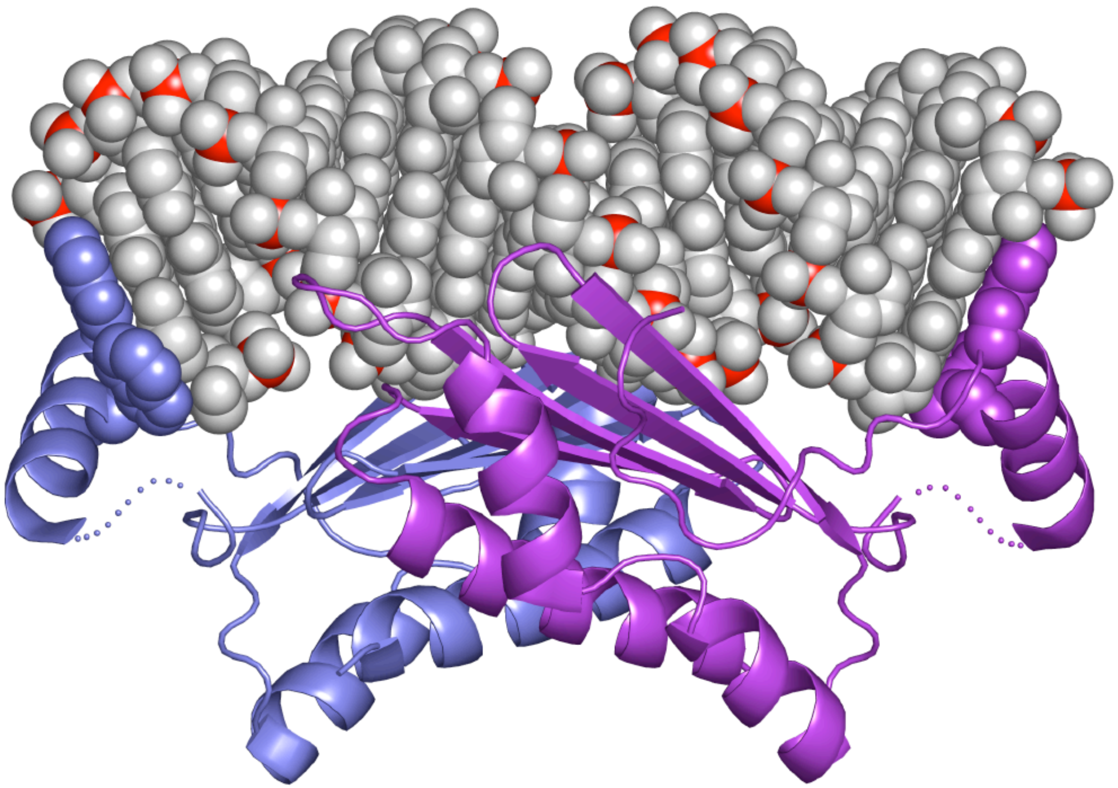
Implicated in chromatine remodelling



Cleavage part of DICER



Measuring device for 21 nt



ONE Role of RNA in cells

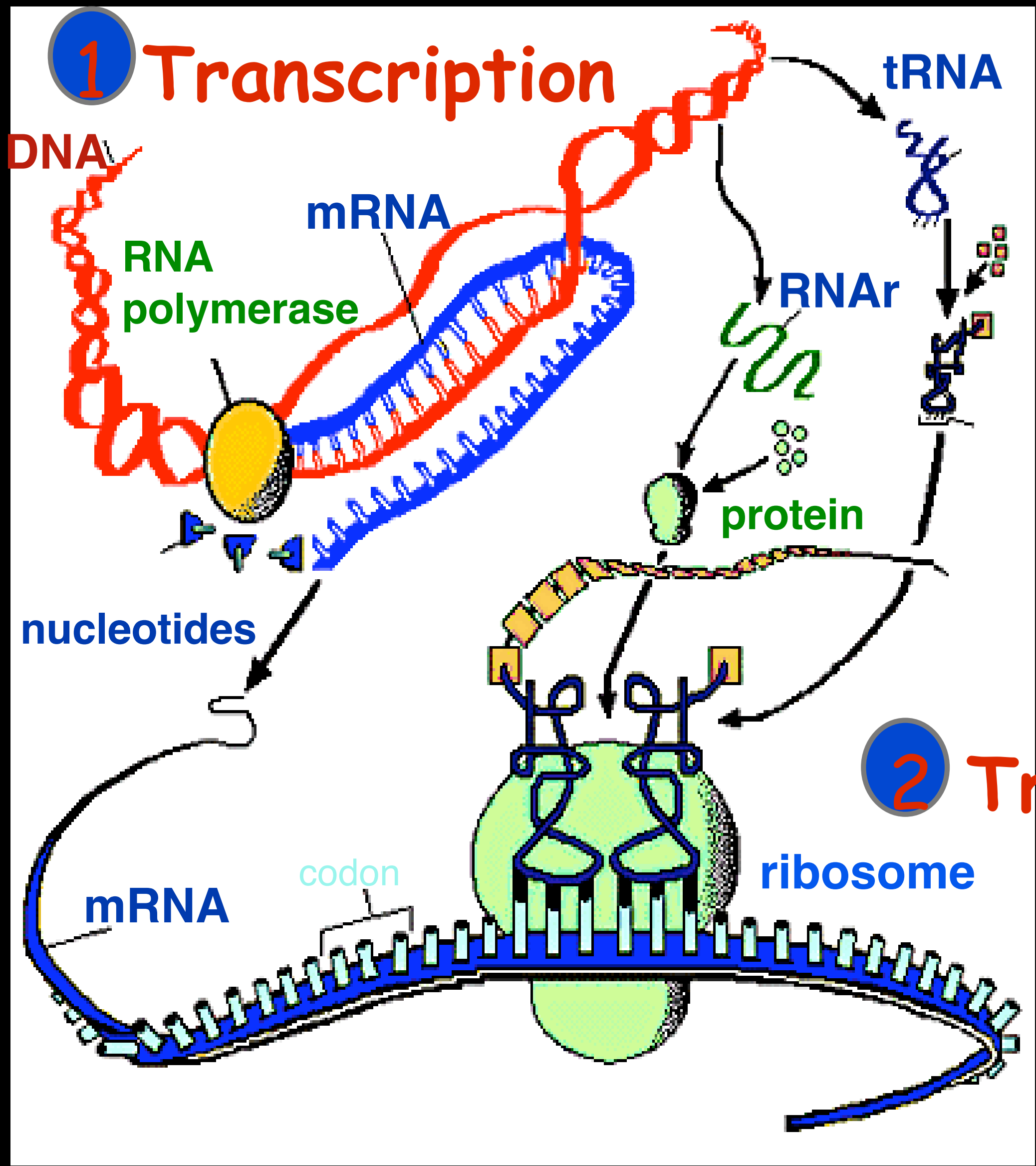
DNA

1

RNA

2

Proteins



Versatility of RNA functions

- Not only messenger RNAs (alternative splicing)
- Number & variety of non-coding RNAs : ribosomal RNAs, snRNAs, snoRNAs,and numerous regulator RNAs..
- Cofactor RNAs : telomerase,
- …… to be discovered

Properties of RNA molecules

Assemble in double-starnded helices like DNA

➡ Carry GENETIC INFORMATION like DNA

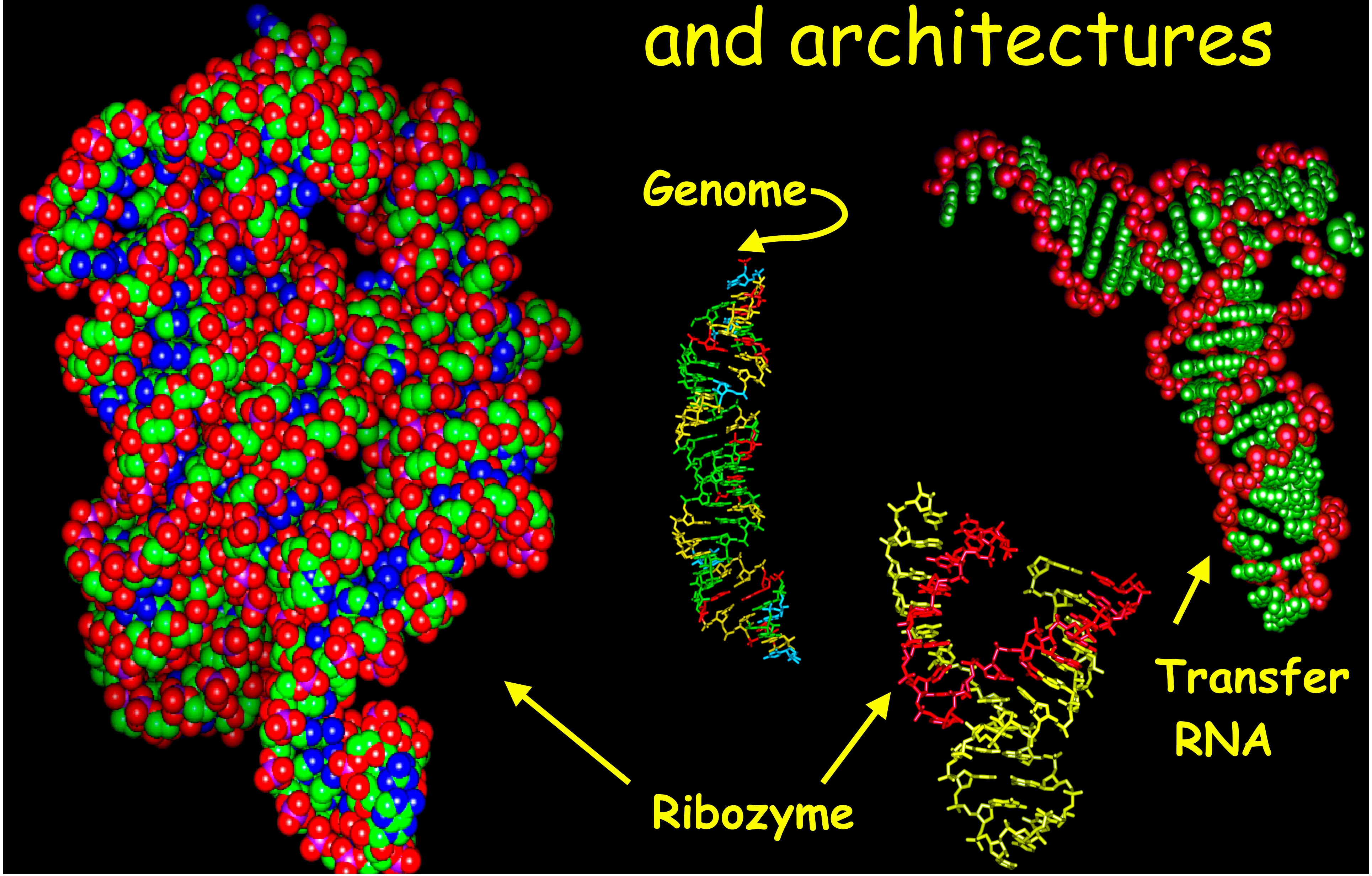
Fold in complex tertiary architectures like proteins

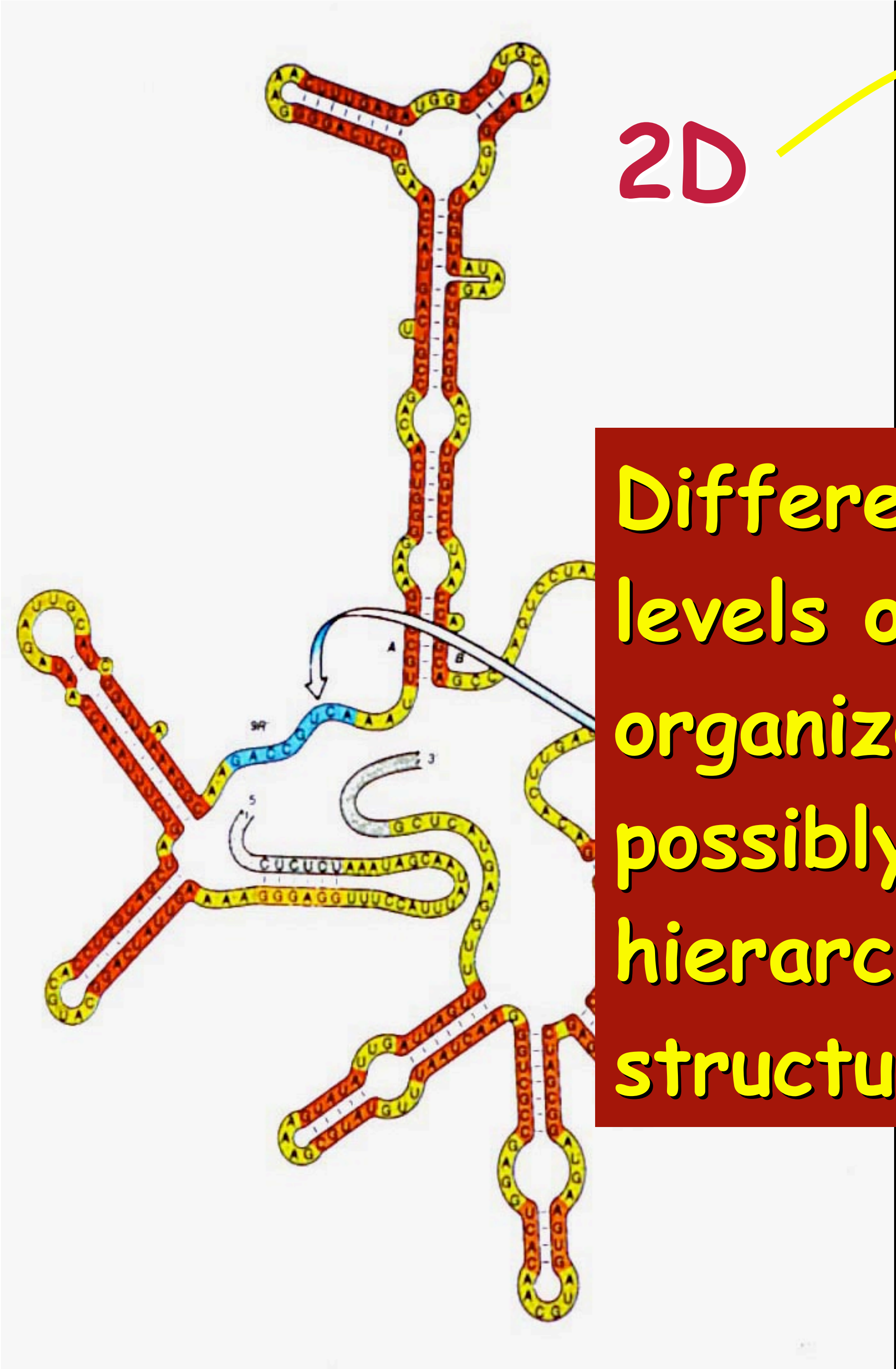
➡ Perform CHEMICAL CATALYSIS like proteins

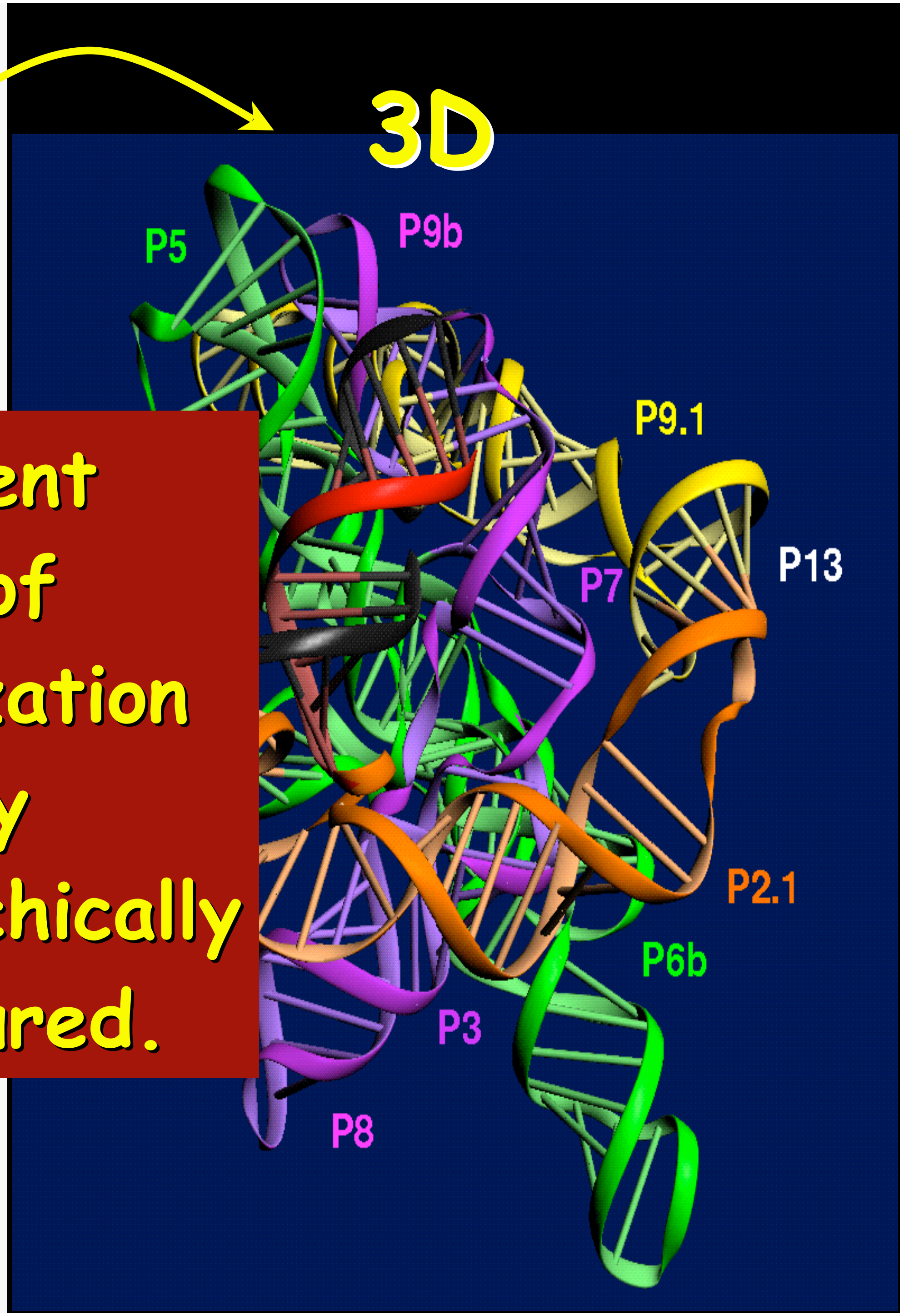
Catalytic RNAs

- Ribonuclease P
- Self-splicing introns
- Hepatitis delta virus
- The ribosome and peptide bond formation
- The spliceosome (not fully proven yet)
- and ...

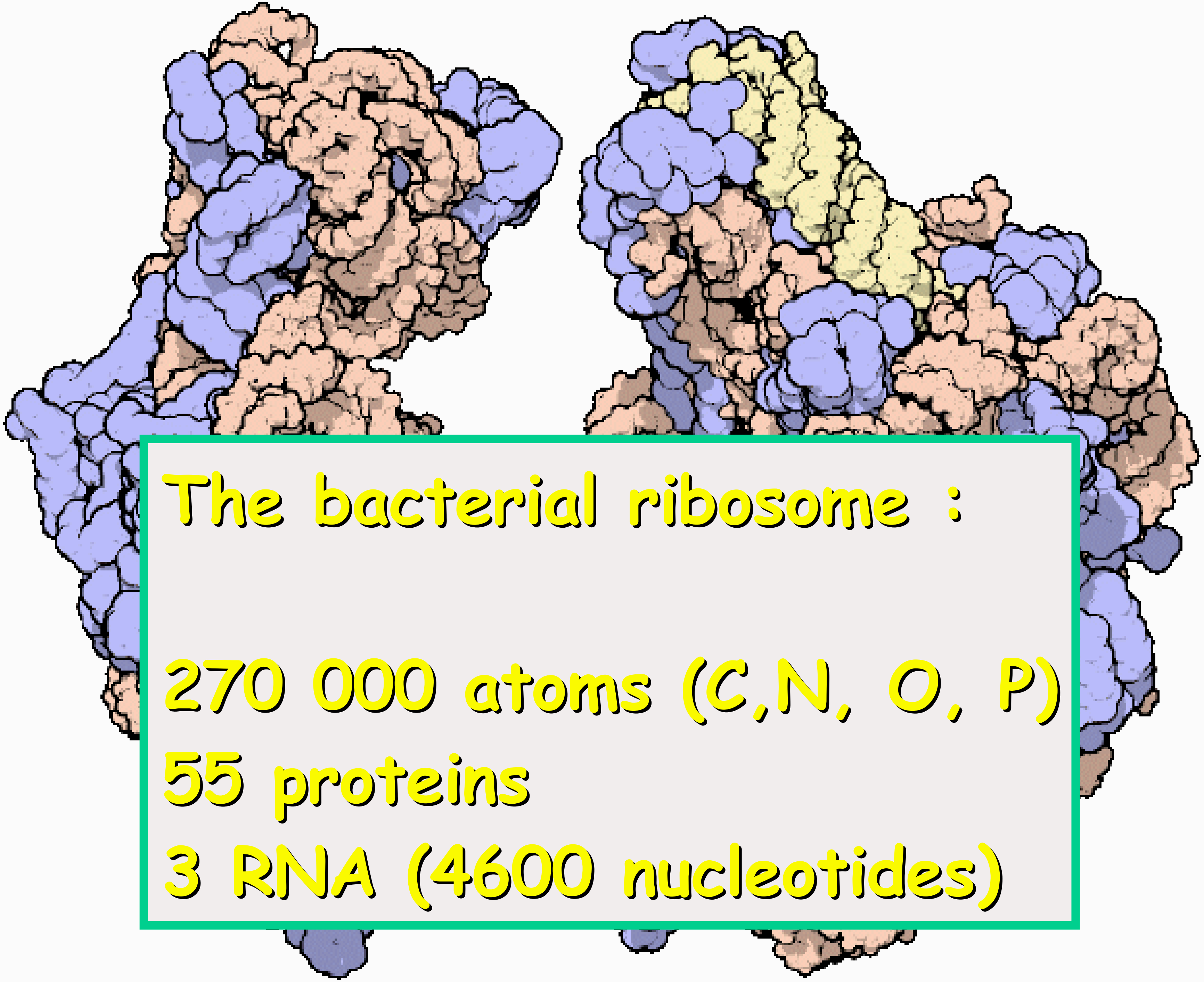
Great diversity of RNA functions and architectures







Different levels of organization possibly hierarchically structured.



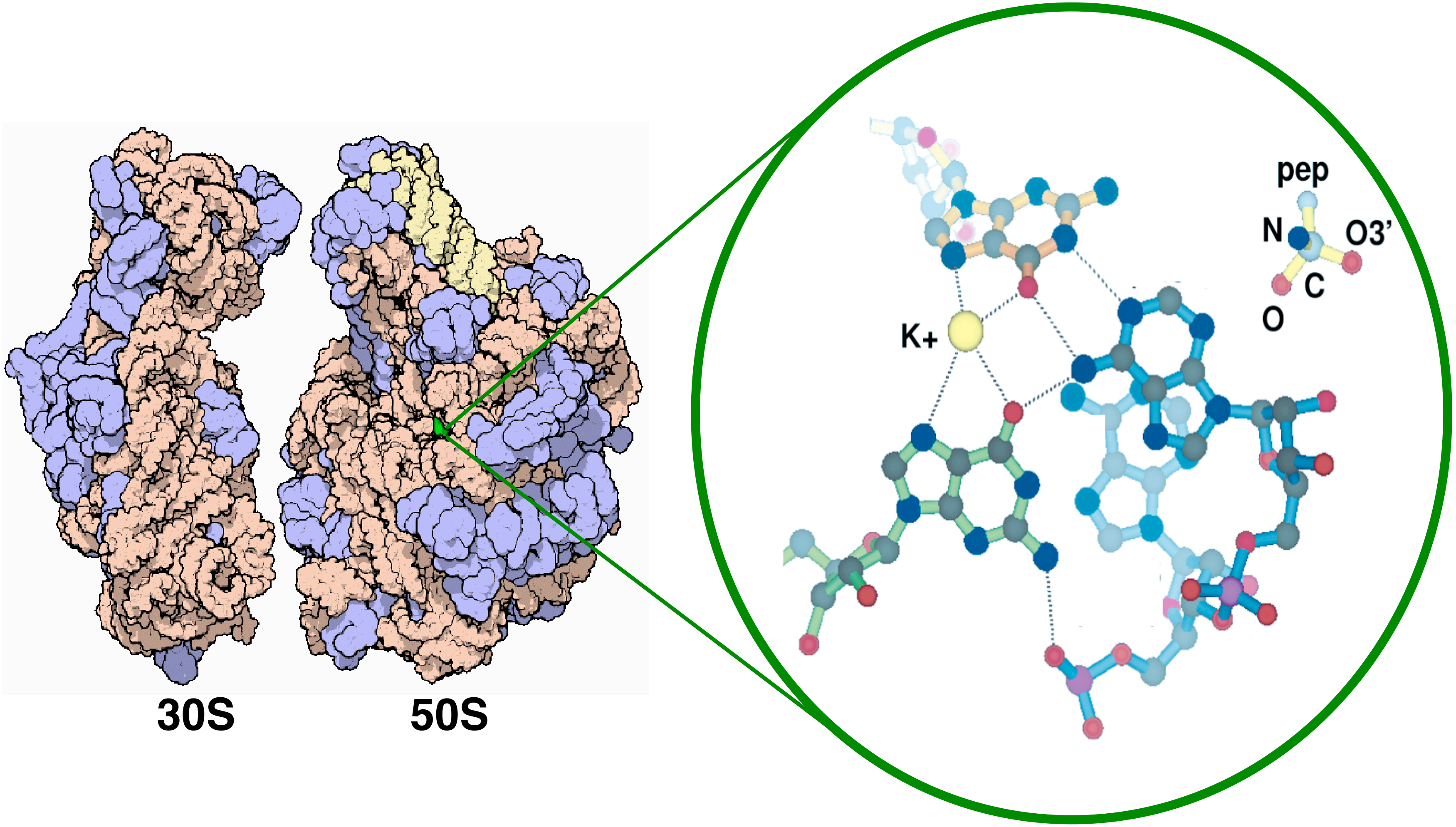
The bacterial ribosome :

270 000 atoms (C,N, O, P)

55 proteins

3 RNA (4600 nucleotides)

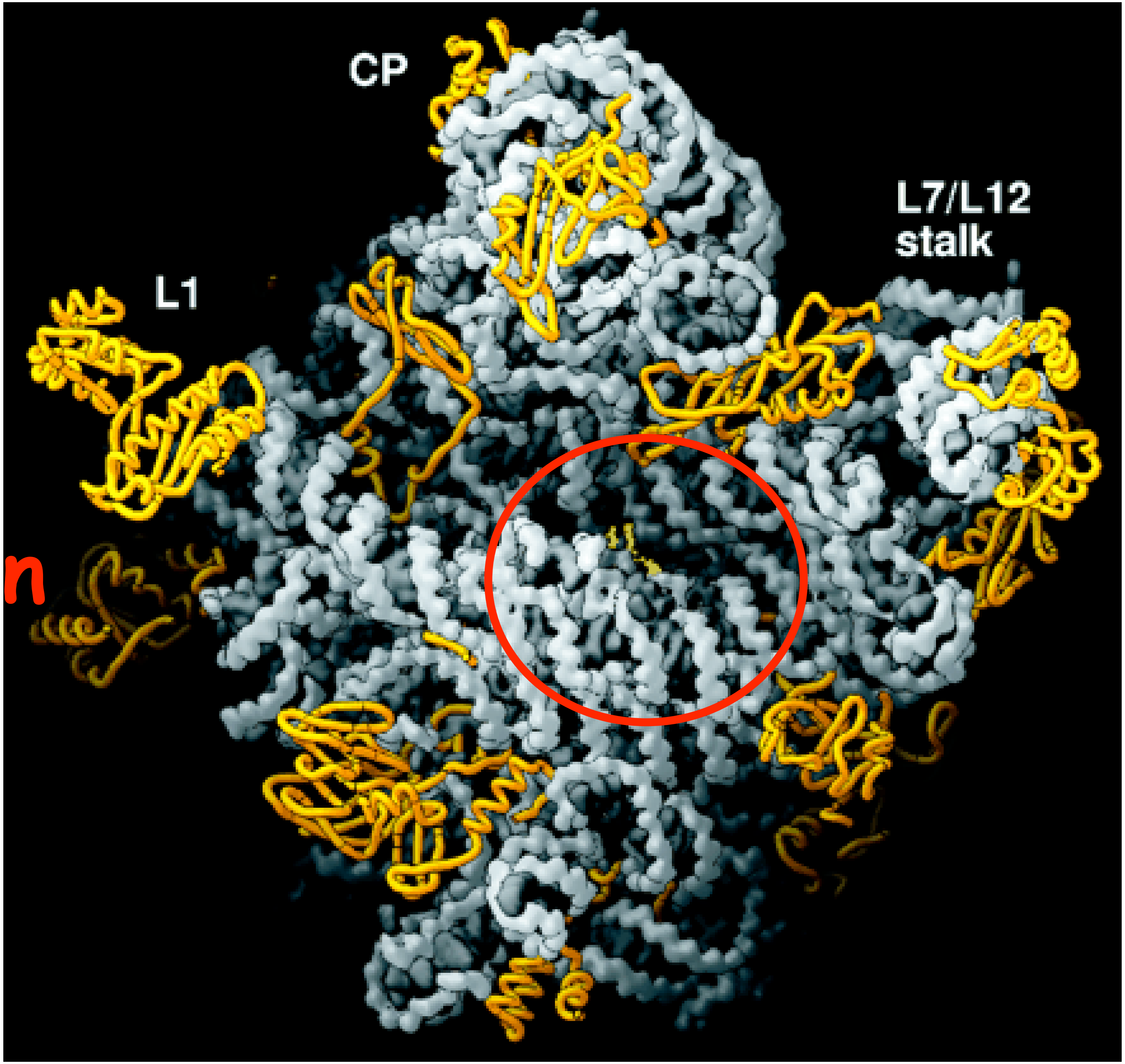
Ribosome active site



Nissen et al. (2000) Science, 289

H. F. Noller, T. A. Steitz, P. B. Moore, A.Yonath, V. Ramakrishnan

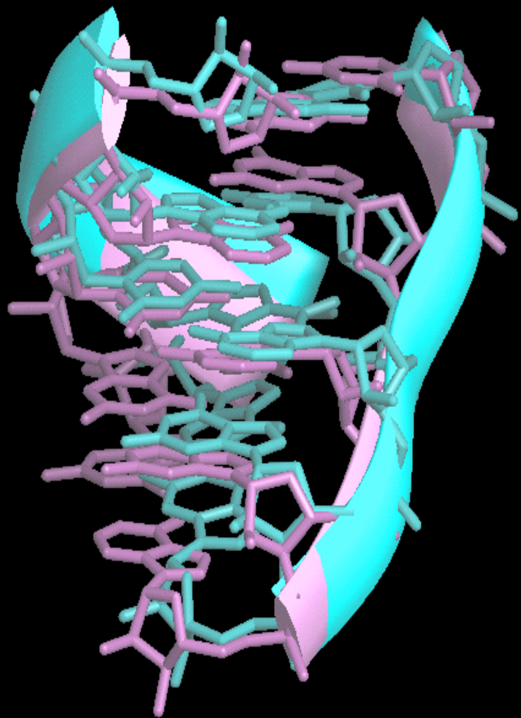
Only RNA in the reaction site



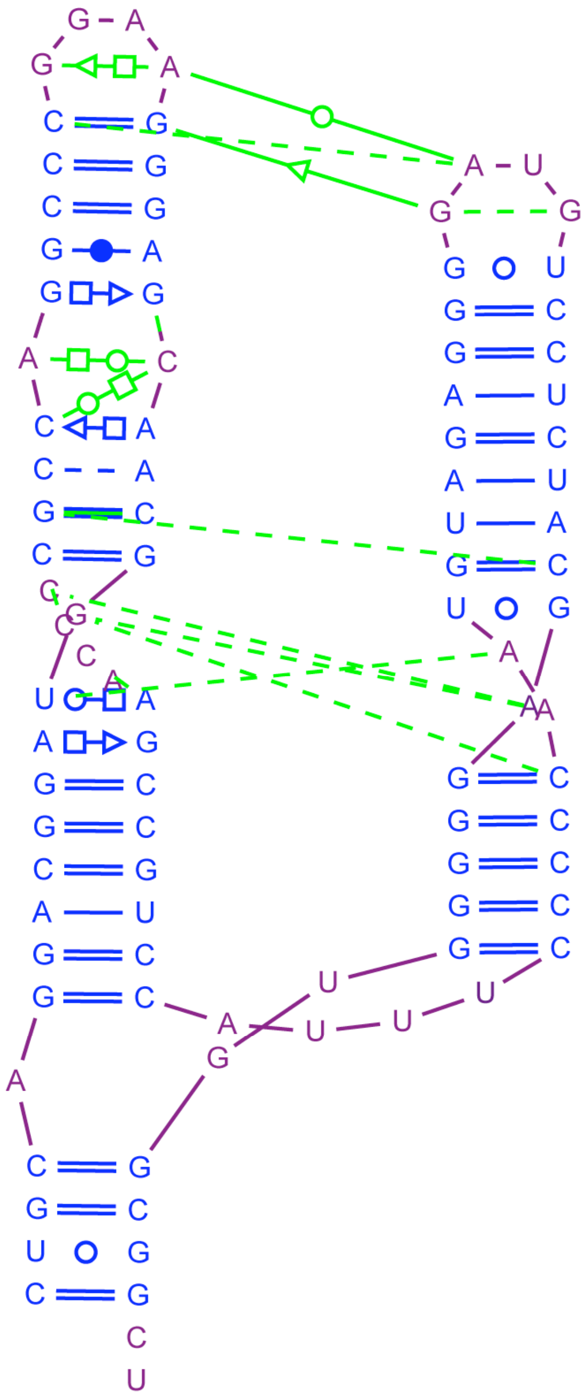
Comparisons of 3D structures

↕

Comparisons of sequences



((((		(((		)))		)))-)
GCUG	UUAGG	GGA	GUUUUA	UCC	AGCGU	CAG-C
GCCG	UUAGG	GGA	GUUUCA	UCC	AGCGA	UGG-C
GUUG	UAGG	GGA	GUCUCA	UCC	AGCA	CAA-C
GCUG	GAGG	GAA	GC AA	UUC	AGCA	CAG-C
ACUU	CAGU	GGA	GC AA	UCC	AGCA	GAGAU
ACUU	CAGU	GGA	GC AA	UCC	AGCA	GAGAU
GAUG	GAGG	UUG	G AAA	CAA	UGCA	CAU-C
GGGC	CAGG	GGU	G AAA	ACC	AGCA	GCC-A
GGCC	UAGG	UCG	G AAA	CGG	AGCA	GGU-C
GGCC	CAGG	UCG	G AAA	CGG	AGCA	GGU-C
GGCC	CAGG	UCG	G AAA	CGG	AGCA	GGU-C
GGCC	CAGG	UCG	G AAA	CGG	AGCA	GGU-C
GGCC	CAGG	UCG	G AAA	CGG	AGCA	GGU-C



Biological sequence analysis

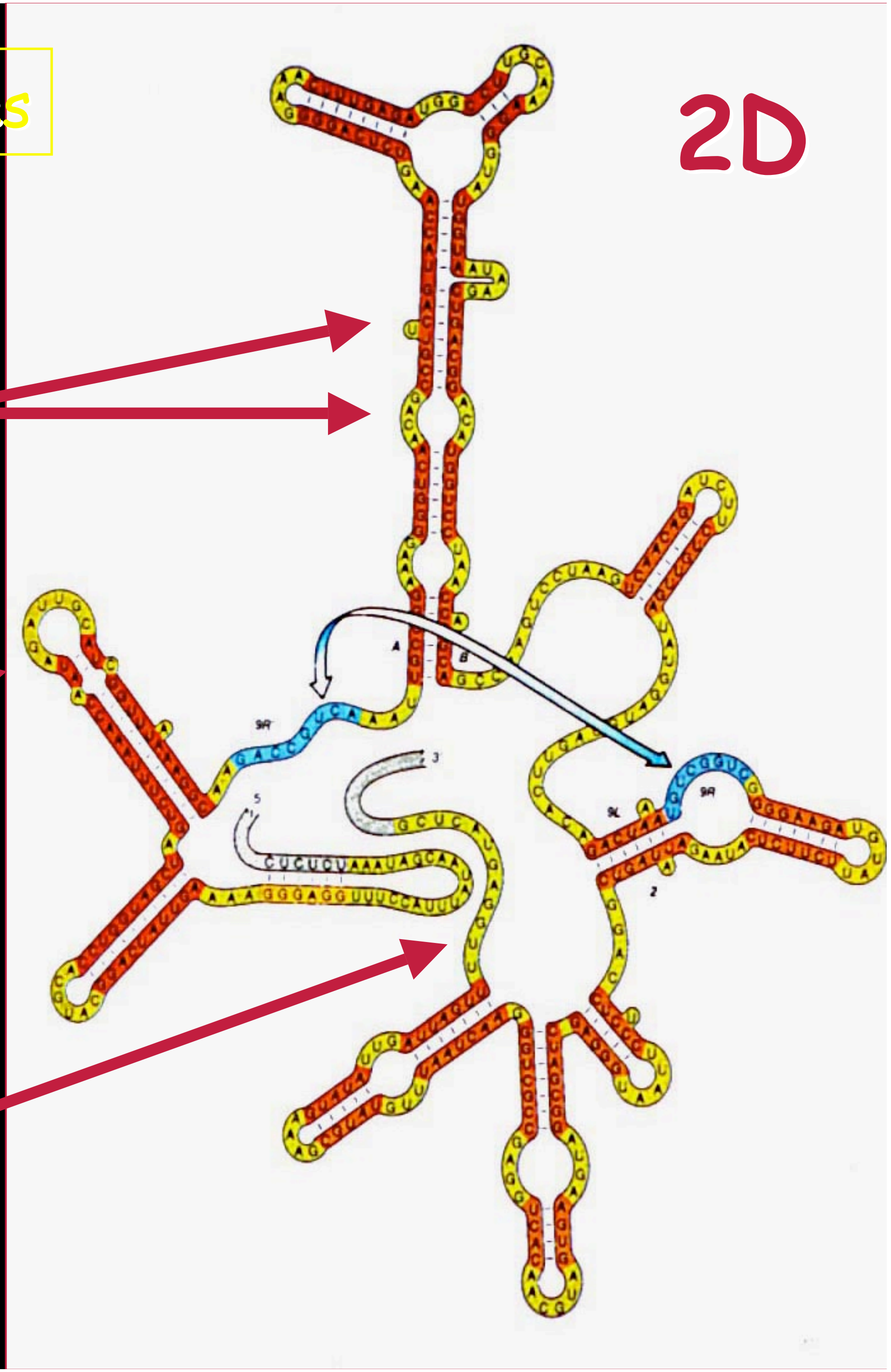
Protein easy
RNA hard

Watson-Crick base paired helices

Internal loops (symmetric, Asymmetric, bulge)

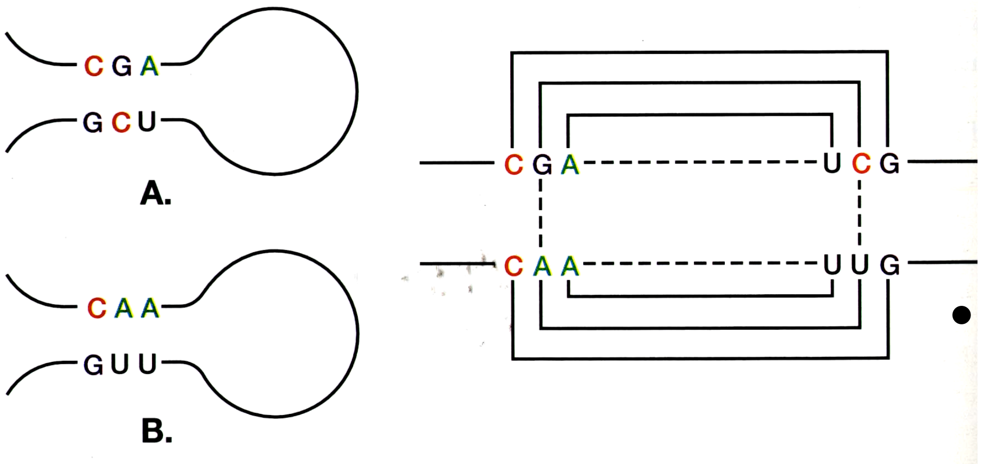
Hairpin loops

Single-strands junctions



RNA alignments

- RNA sequences are aligned/compared differently because sequence variation in RNA maintain base-pairing patterns



- Thus an alignment will exhibit covariation at interacting basepairs

- RNA specifying genes will have conserved regions reflecting common ancestry

Main building block :
the RNA double helix
held together by
Watson-Crick pairs