The RNA world

Definitions of life

Evidence for RNA world

Before RNA world

Problems with RNA world

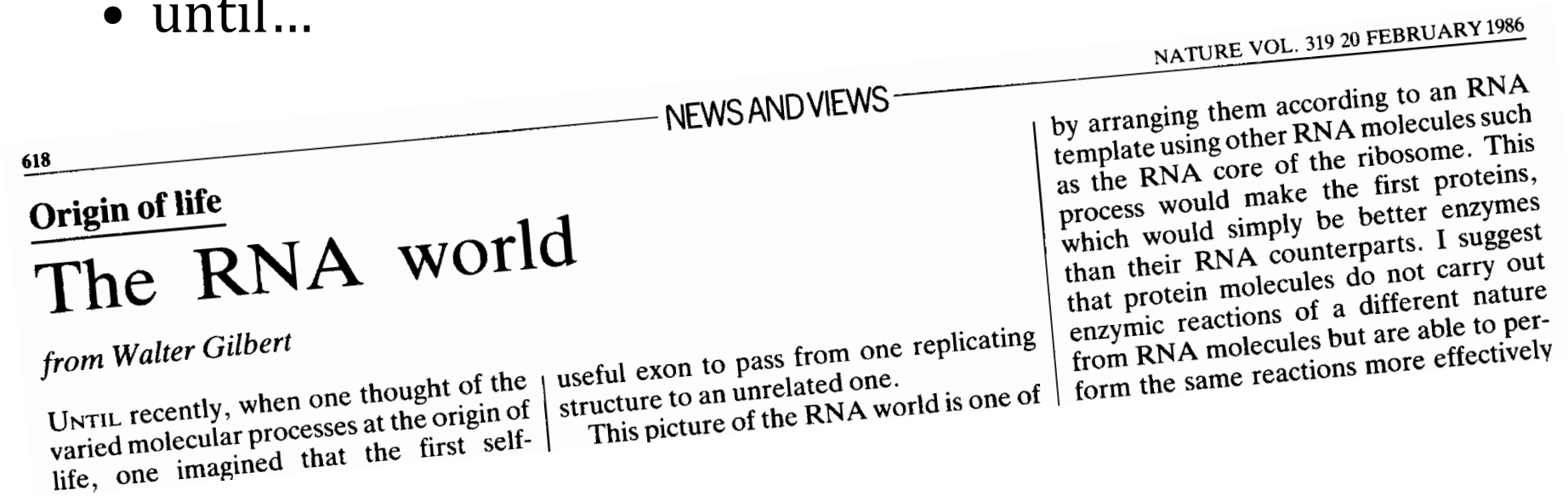
Alternatives (maybe there was no RNA world)

Andrew Torda, April 2015

History

Start of life

- proteins are catalysts –necessary to copy DNA..
  - until…



618 NEWS AND VIEWS NATURE VOL. 319 20 FEBRUARY 1986

Origin of life

The RNA world

from Walter Gilbert

UNTIL recently, when one thought of the varied molecular processes at the origin of life, one imagined that the first self-useful exon to pass from one replicating structure to an unrelated one.

This picture of the RNA world is one of by arranging them according to an RNA template using other RNA molecules such as the RNA core of the ribosome. This process would make the first proteins, which would simply be better enzymes than their RNA counterparts. I suggest that protein molecules do not carry out enzymic reactions of a different nature from RNA molecules but are able to perform the same reactions more effectively

- 1986: first RNAzymes found
- start of RNA world story
  - today …

NATURE CHEMISTRY | NEWS AND VIE

Origin of life: Primordial soup that cooks itself

Paul J. Bracher

Nature Chemistry 7, 273–274 (2015) | doi:10.1038/nchem.2219
Published online 24 March 2015

AAAS

Science

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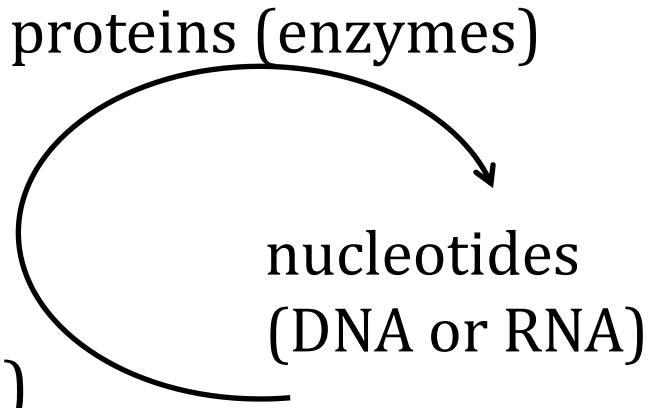
Researchers may have solved origin-of-life conundrum

Today versus history



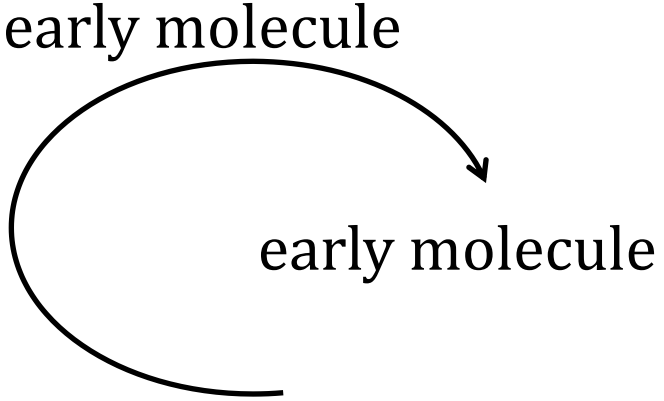
Picture today

- simultaneous development of
  - proteins (copying)
  - nucleotides (information storage)

Suggestion

- one molecule (phenotype+genotype)
  - self copying
    - possibilities

    1. protein like
    2. nucleotide like
    3. something else



This is templated

- later remove this requirement

What is life ? Practical – not philosphical

Practical – not philosophical

- people, trees, …
- bacteria
- viruses ?
- infectious DNA / RNA ?

Some concepts

- life consumes energy – better formulated
- life avoids equilibrium, needs energy, consumes entropy
- evolution

Equilibrium

Reaction A + B ↔ C + D $\Delta G = RT \ln \frac{[\mathrm{C}][\mathrm{D}]}{[\mathrm{A}][\mathrm{B}]}$

Decay A ↔ B + C, then $\Delta G = RT \ln \frac{[\mathrm{B}][\mathrm{C}]}{[\mathrm{A}]}$

In a closed system, if $\ln \frac{[\mathrm{B}][\mathrm{C}]}{[\mathrm{A}]} = 0$ you are dead

Consequence

- life looks like "steady state" (stationärer Zustand)
- not equilibrium (Gleichgewicht)

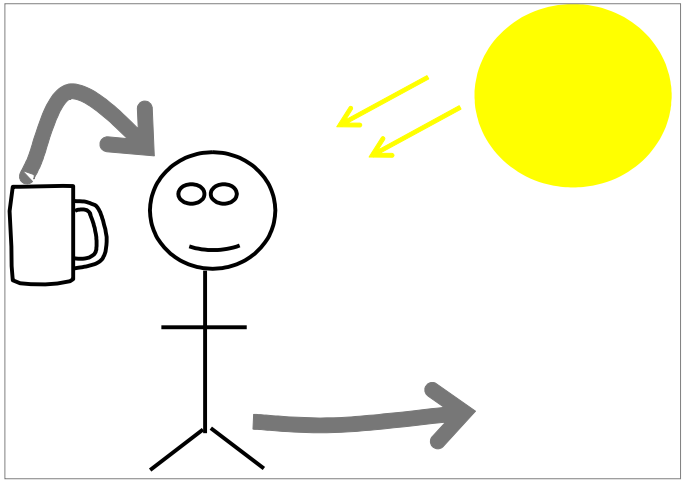
Where we were

- What was the first molecule
- RNA can be phenotype and genotype
- Life is not at equilibrium

Now

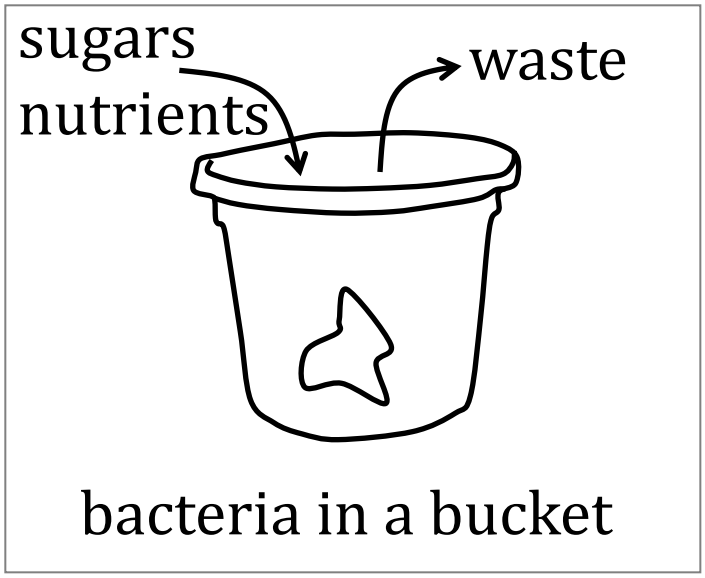
- What are some minimum requirements for life ?

Steady state systems

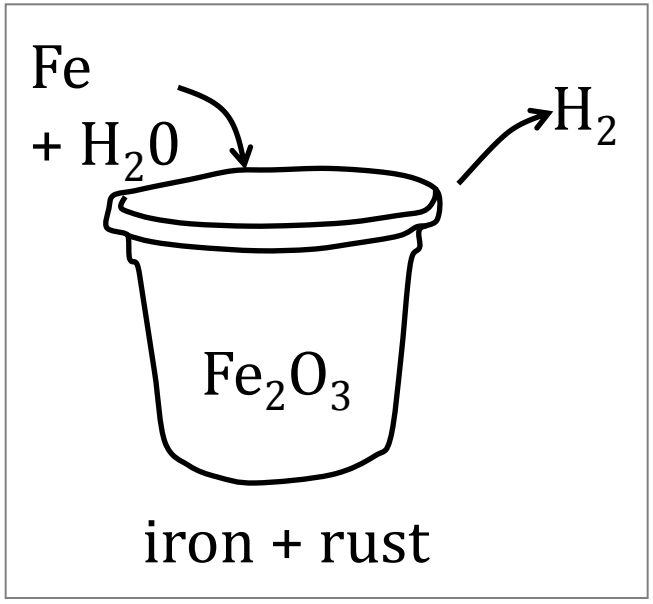


Input of energy

- maintenance of order
- grows
- catalytic and specific



bacteria in a bucket



iron + rust

Bacteria and bucket+rust

- grow, eat nutrients, catalyse their own copying

Why is bucket+rust not alive ?

Rust can catalyse production of rust, but

- does not adapt / evolve – no selection

Arguments on

- information (low in rust)
- no general copying machinery

Contrast with life…

Summary of life

bacteria	**bucket + rust**
not at equilibrium	
catalytic activity	
copying with changes / selection = evolution	
template copying (AAA template for UUU)	maybe
general copying (can copy AAA or ACGU or ..)	

Who cares ?

- the Ursuppe should do this as well

RNA world definition

What does "RNA World" mean ?

- genetic continuity via RNA
- Watson-Crick base pairing
- no genetically-coded proteins

    - did it exist ?

Why believe in an RNA world ?

1. both phenotype and genotype
2. roles of nucleotides
3. Selex
4. biosynthesis
5. ribosome

In turn..

Phenotype and Genotype

Proteins

- catalysts
- rarely code for other proteins

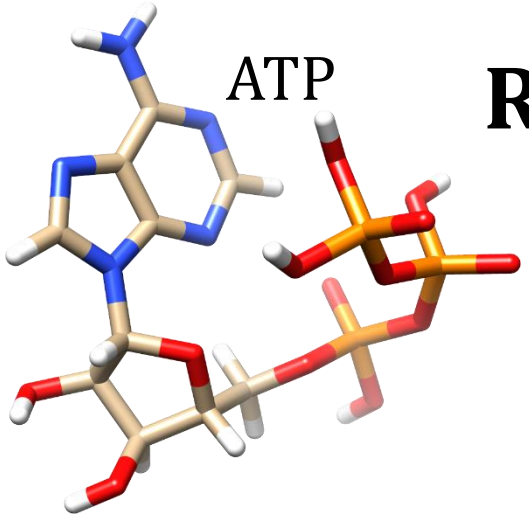
RNA

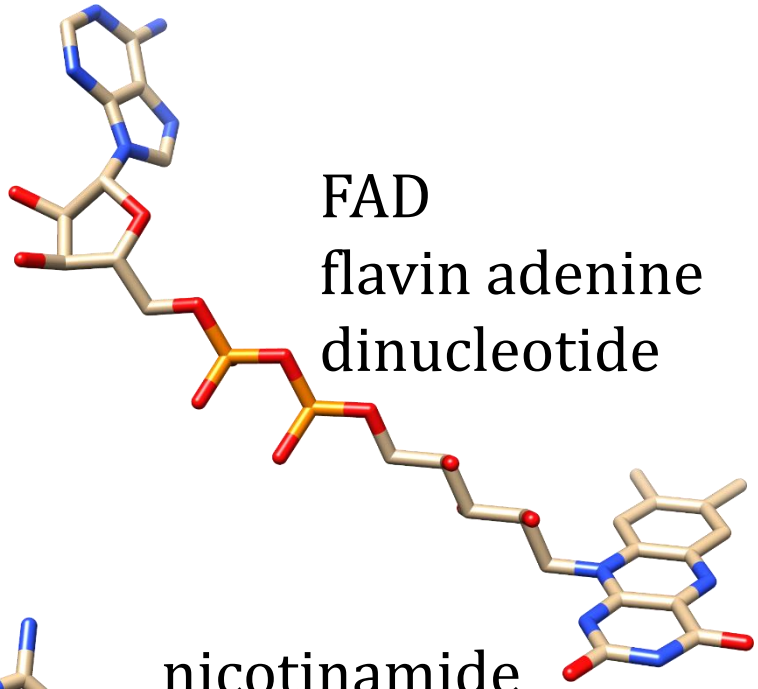
- catalysts
- does encode other DNA / RNA molecules

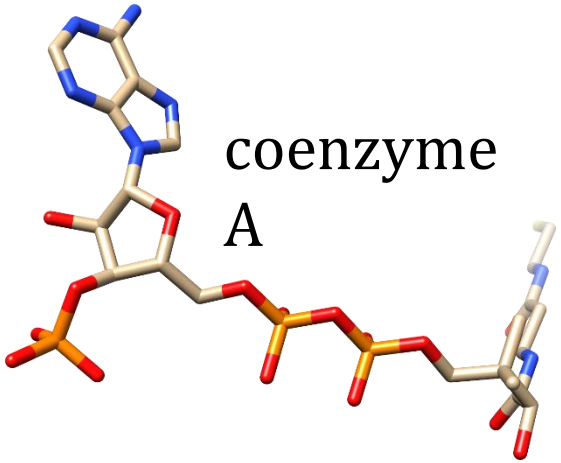
Simplicity - life started with one kind of molecule

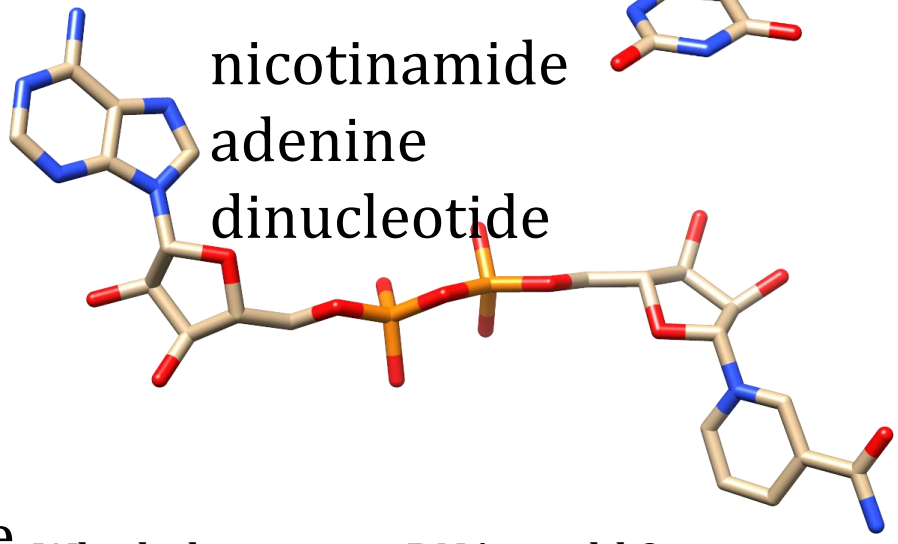
- should be RNA (RNA-like)

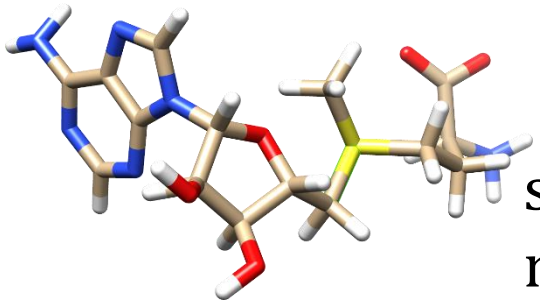
Roles of nucleotides









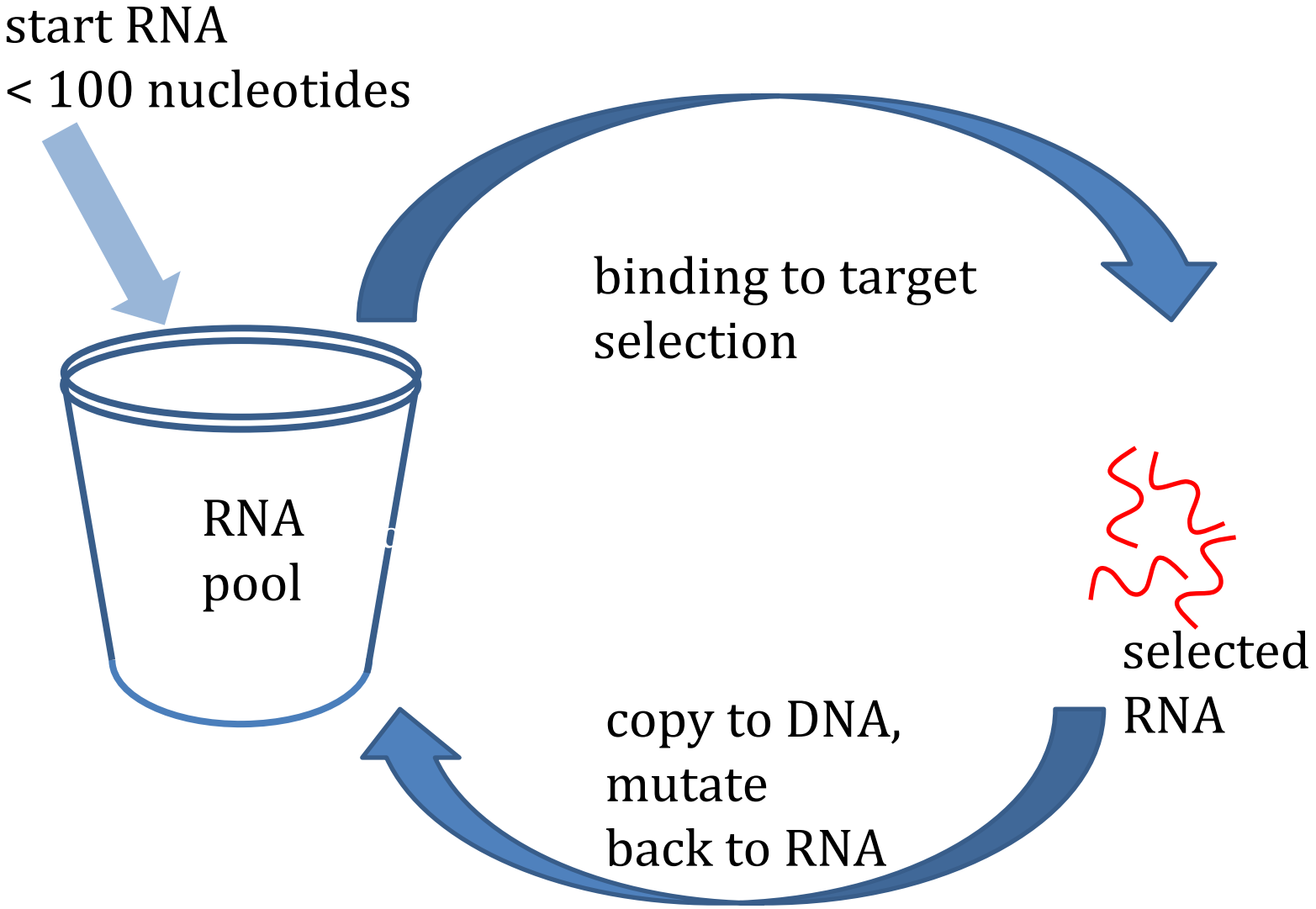


Roles of nucleotides

Cofactors, nucleotides, energy

- basically nucleotides
  - ATP, FAD, NAD, TPP, …

SELEX in 90 seconds



SELEX

Empirical

- fishing in an RNA soup, one can find all kinds of activities / binding abilities
- can one find binding / stabilization of transition states ?

Interpretation

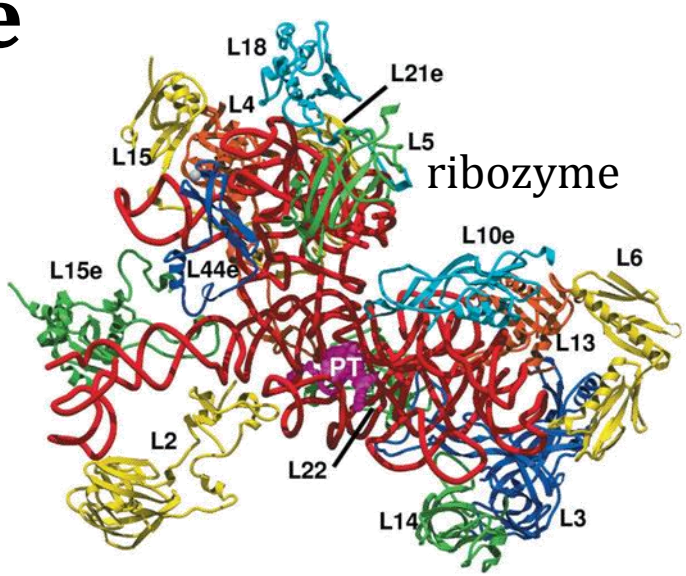
- activities are present in random soup waiting to be found
- start of life was just a big selection experiment

Biosynthesis

- much machinery devoted to RNA biosynthesis many enzymatic steps
- DNA is just a modification afterwards
- looks as if RNA is the older molecule

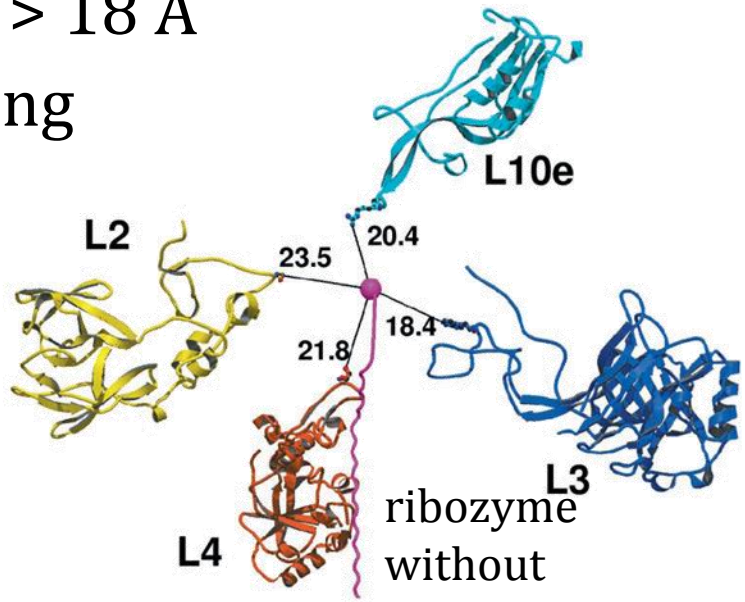
The ribosome

- incredibly conserved
- part of ribosome near active site



ribozyme

- remove all the RNA
- the nearest protein to active site is > 18 Å
- the fundamental operation of making proteins from a template
  - carried out by a ribozyme



ribozyme without RNA

Nissen P, Hansen J, Ban N, Moore PB, Steitz TA., Science 289, 920-930 (2000)

Why believe in an RNA world ?

RNA World – requirements

Source of basic requirements

- ribose
- bases (A, C, G, U + more T, I, X, …)

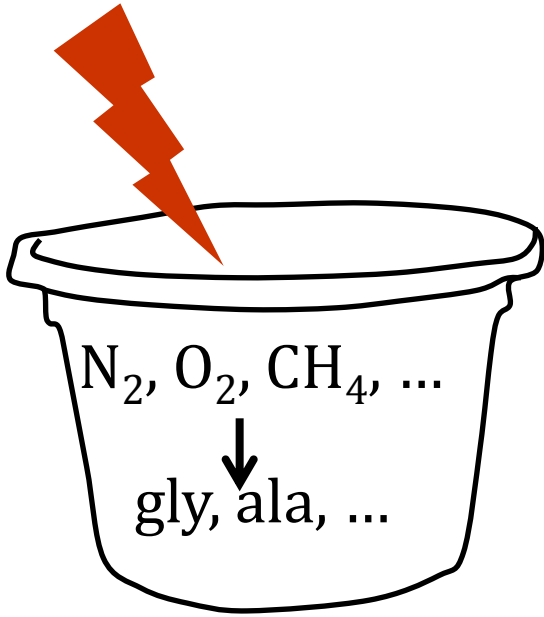
Vague source

- Miller experiments from 1950's

More modern ideas

- minerals, inorganic catalysts

Very active area



Requirements - RNA replicase

One model – we have one replicase

- basic requirement – replicase should
  - act on itself (or similar copies)
  - should produce
    - itself or
    - complementary copies

Length constraints

- define fidelity q = probability that one residue is correctly added
- probability of copying chain length n correctly = q^n
- no mistakes – no evolution

q	n	perfect copies
0.9	4	0.66
0.9	10	0.35
0.95	10	0.65
0.95	20	0.36

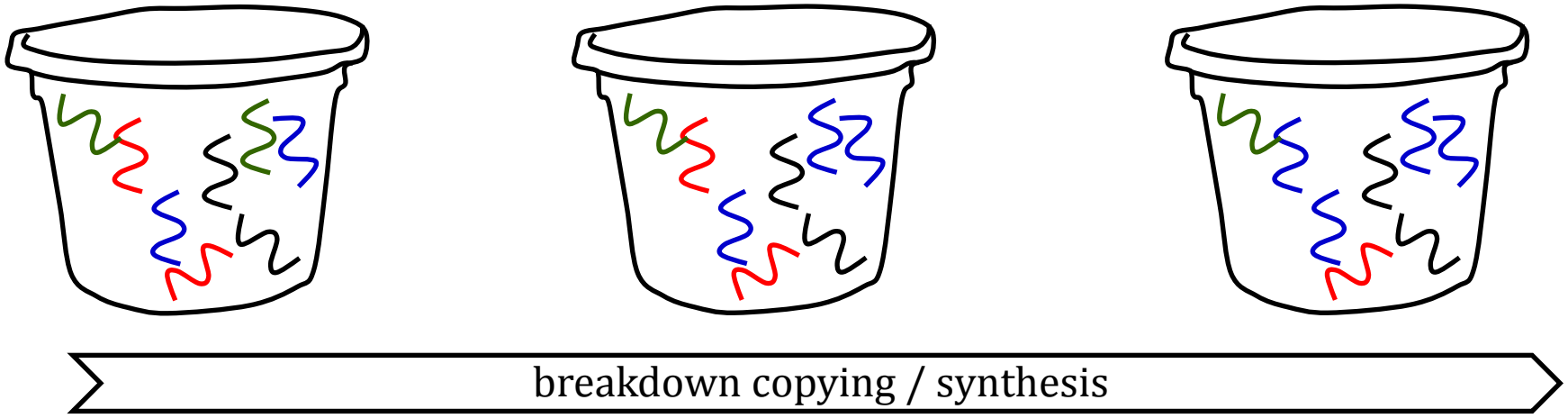
Replicase Quality

- Is there are magic q ?
- Must we wait for some chemicals with correct q ?

- No ! Evolution helps

evolution without cells (primordial slime)

What do we need for evolution ? Not much



If the blue molecule and related variants

- copies itself better
- is copied by other molecules
- resistant to breakdown

It will eventually dominate

First replicase

How likely are we to take a random soup of nucleotides

- ribozyme of 40 bases
- $q = 0.9$
  - not very likely, but if
- a replicase starts
  - copies related molecules better than unrelated

If it copies better / faster it will be selected for and evolve

Problems

Not everybody believes in the RNA World

- …

ribosome (problems)

Usually believed to be a ribozyme.. Is it ?

Now many ribosome structures

- better resolution
- with substrates bound

Strong evidence of L27 + L16 interacting with tRNA

The point

- not everybody believes that the ribosome is a ribozyme

Other RNAzymes may not be RNAzymes (problems)

Rnase P

- maturation of mRNA
- recent RNA-free variant found (seminar topic ?)

- Are there more RNAzymes which are not RNAzymes ?

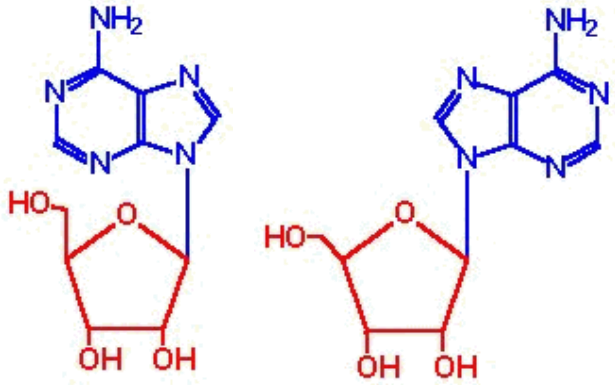
Specificity – sugars (problems)

Make sugar in lab

- condensation from smaller molecules
- result ?
  - mixture of 5 member sugars (ribose, pyranose, …)
  - ribose is not dominant

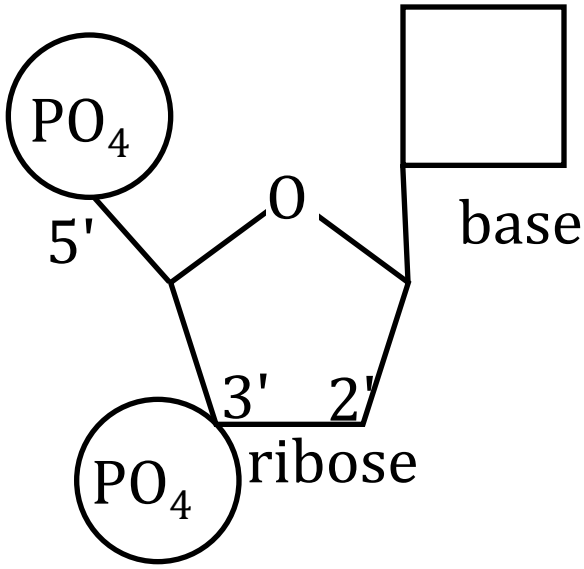
Enantiomers, isomers, ..

- details of linkages different, but only one is used in modern world
  - syn / anti, L / D



syn / anti

Joining monomers (problems)



Modern chemistry always 5' to 3'

Nucleotide mono phosphates (NMP)

- 3 reactive groups
  - 5' PO_4, 3' OH, 2' OH

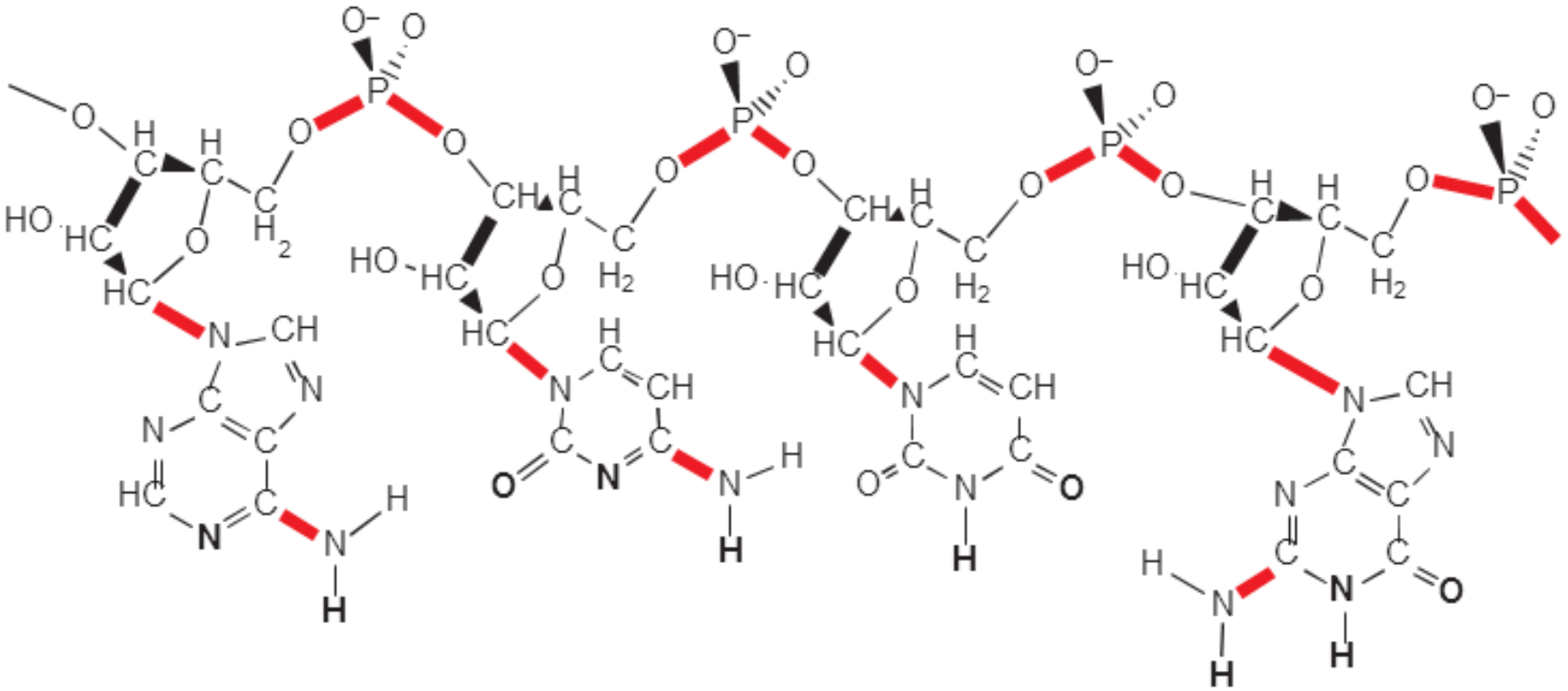
Soup of 5' NMPs and condense

- mixture of
  - 5', 5' pyrophosphate
  - 2', 5' PO_4 diester
  - 3', 5' desired diester

Primitive chemistry will be a mess

RNA is not very stable (problems)

All of the red bonds are subject to hydrolysis



Benner, SA, Kim, HJ, Yang, Z (2012) Cold Spring Harb Perspect Biol, 4, a003541

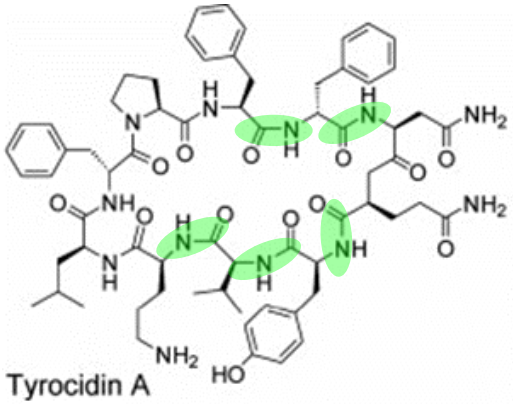
Do we need RNA for proteins ? (problems)

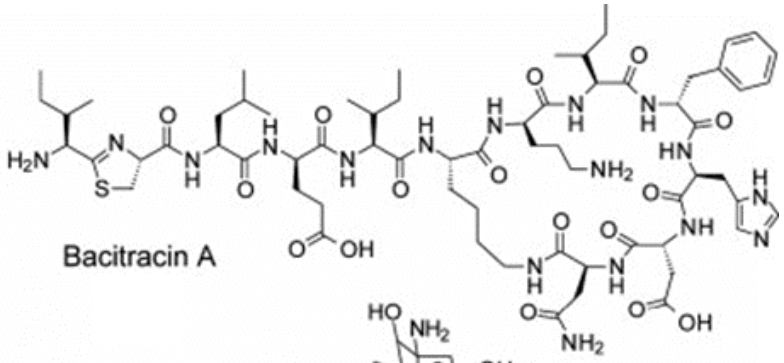
You think we need nucleotides to code for proteins, but..

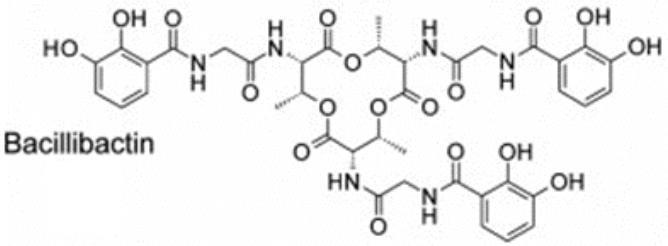
- there are many peptidyl transferases
- antamanide, glutathione ..

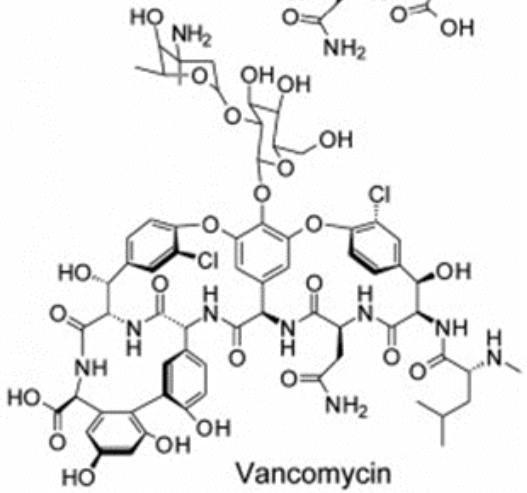
  lots of products, examples …

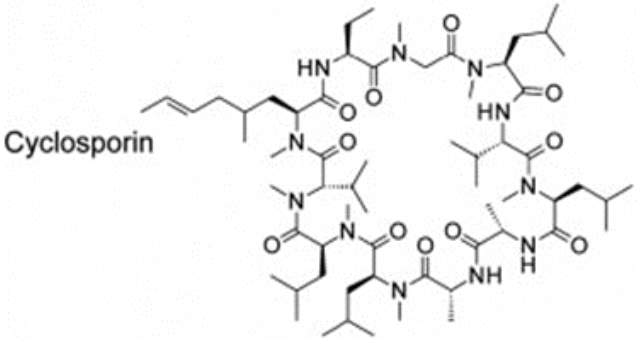
peptides – not genetically encoded

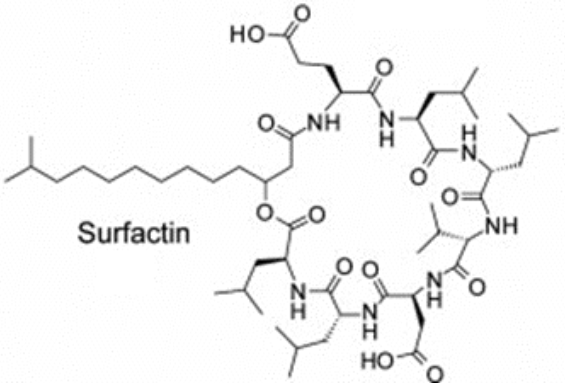












Marahiel, M.A. (2009), J. Pept. Sci. 15, 799-807

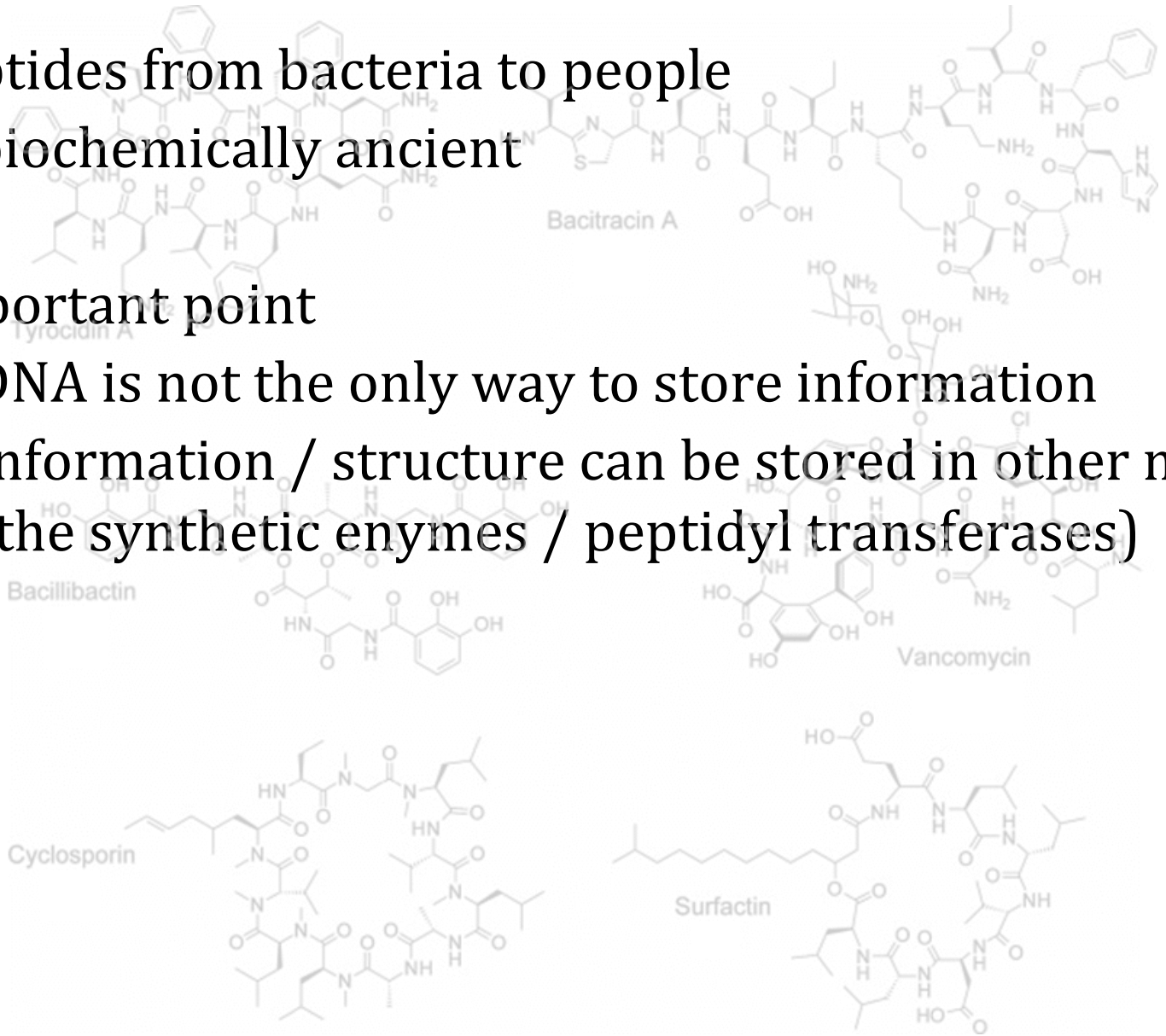
peptides – not genetically encoded

Peptides from bacteria to people

- biochemically ancient

Important point

- DNA is not the only way to store information
- Information / structure can be stored in other molecules (the synthetic enymes / peptidyl transferases)



RNA first ? Protein first ? (problems)

If the world began with RNA

- the oldest proteins should be involved in nucleotide synthesis / copying

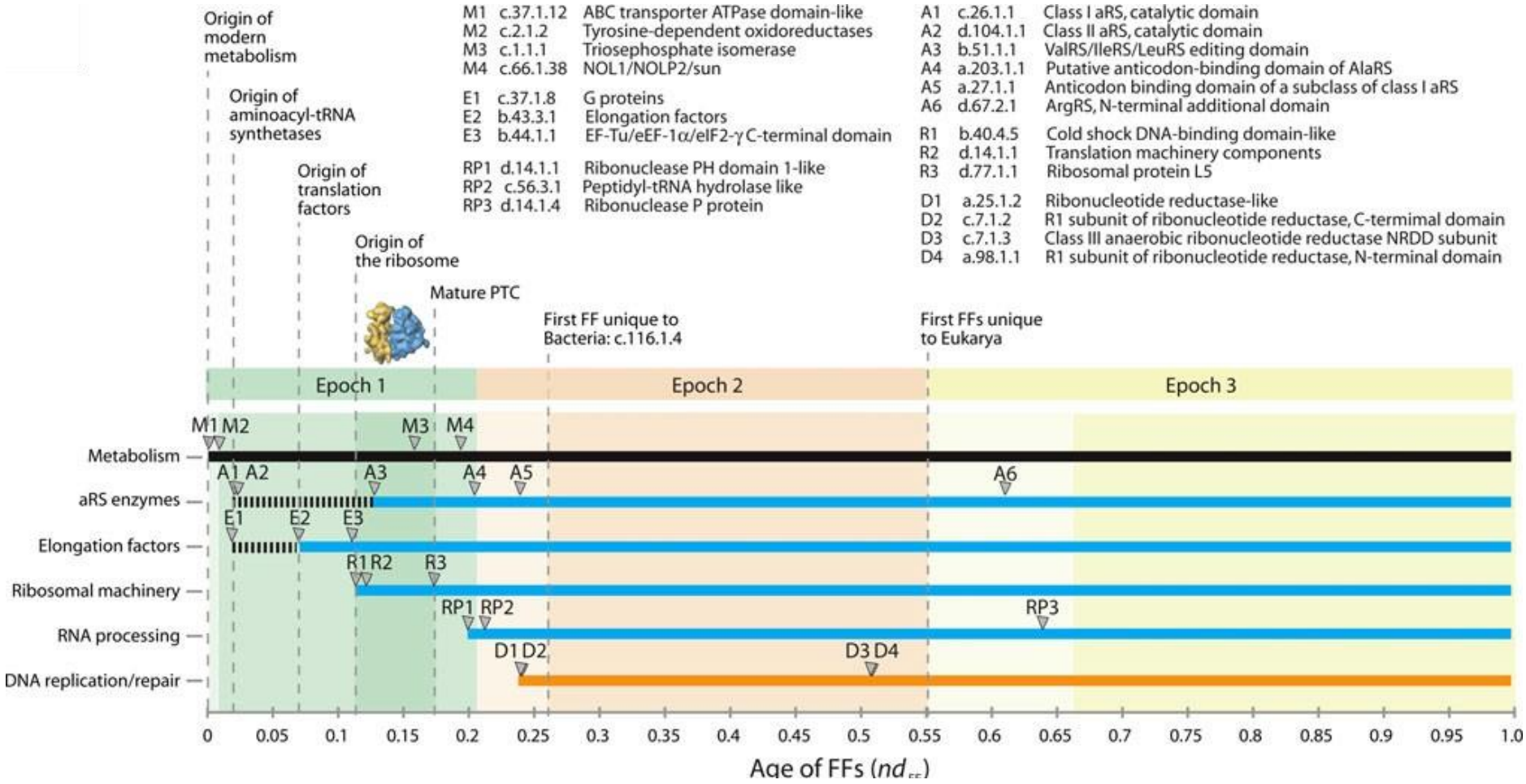
  Are they ?

Take lots of genomes

- Phylogenies (Baum des Lebens)
- trace history of proteins
- attempt to find the age of each protein

  (how far back in tree)
- …

RNA first ? Protein first ? (problems)



Caetano-Anollés, D, Kim, MK, Mittenthal, JE, Caetano-Anollés, G; J Mol Evol (2011) 72, 14-13

RNA first ? Protein first ? (problems)

Strong claim

- conventional metabolism precedes
  - RNA synthesis
  - amino-acyl tRNA synthesis

  - really all nucleotide biochemistry

General worries (problems)

Take

- several decades
- good organic chemistry labs
- lots of PhDs
- modern simulations
- modern laboratory equipment

Try to create

- a self replicating system out of abiotic components

Never really successful

Complete change of philosophy

maybe we do not need an RNA world

Do we need this general templating ?

So far – search for general replicase, polymerase

- Can one build a living system from less general components ? (nucleotides are very general)

- Examples earlier (antamanide, tyrocidin, many more)
  - what if tyrocidin catalysed the formation of antamanide which catalysed .. tyrocidin ?

What might we need for a self copying system ?

Basic ingredients

Easy to explain / imagine

- prebiotic monomers
- condensation / hydrolysis..

Main point

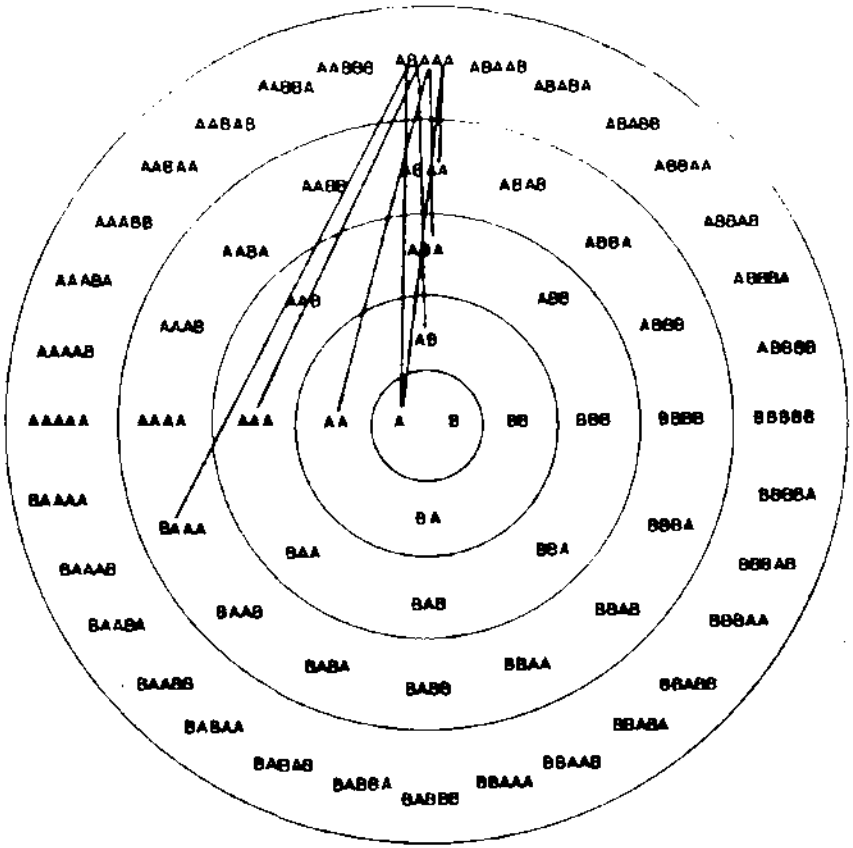
- catalytic closure

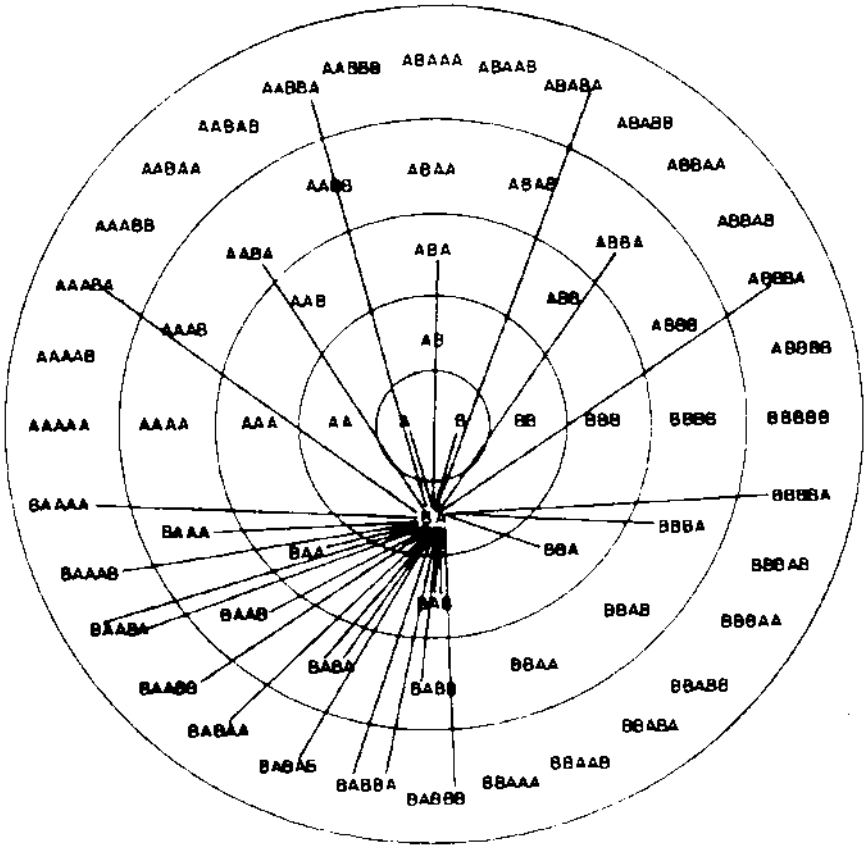
Catalytic closure

Imagine a soup of polymers with conversions

- ABCDE↔ ABC + DE

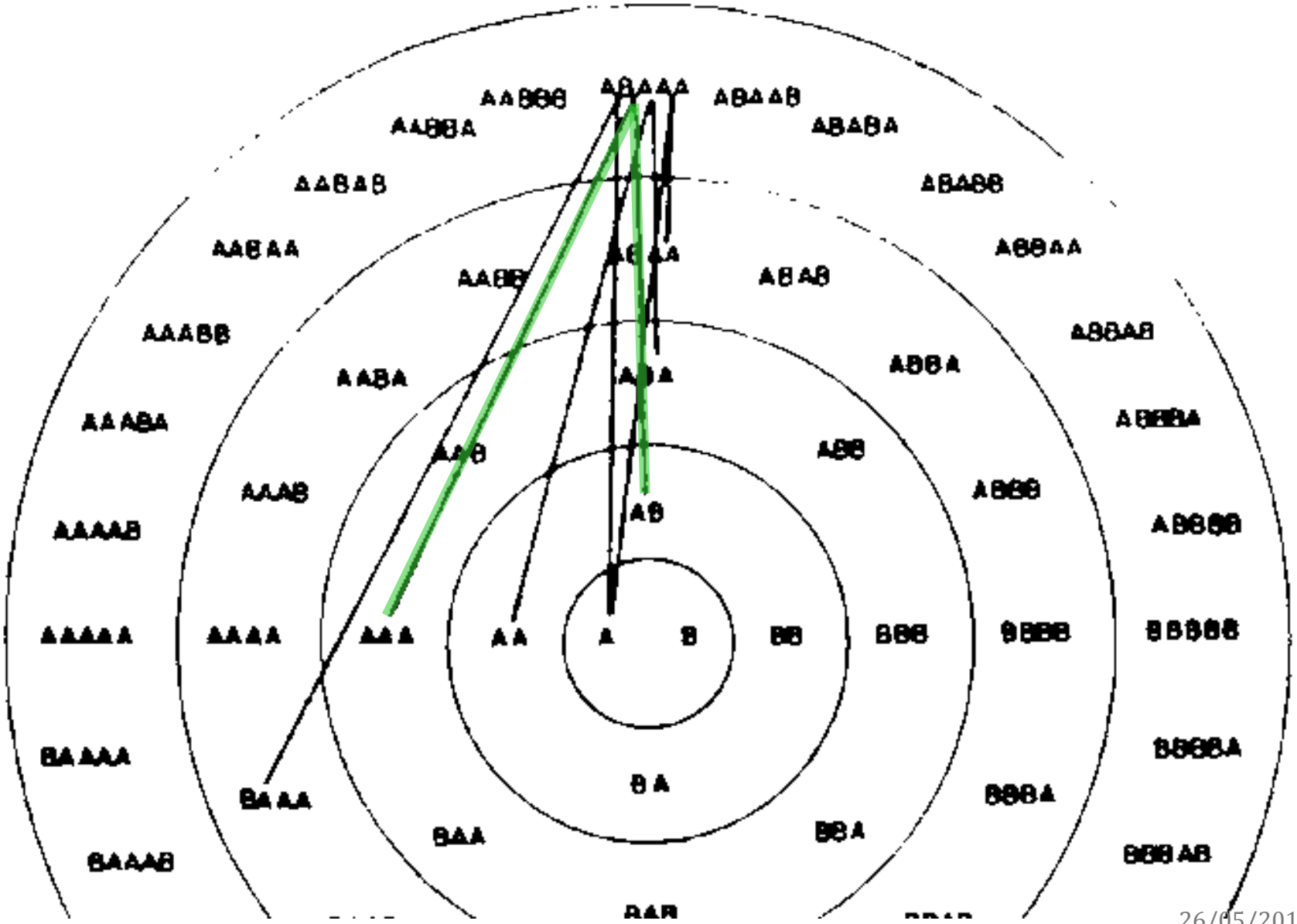
How many ways can we form a 5-mer ? or 2-mer ?





Kauffman, SA, The Origins of Order, Oxford University Press, NY 1993

AB + AAA form ABAAA just an example



Catalytic cycle

The system

- some products catalyse other reactions

$$X + Y \underset{QR}{\rightleftharpoons} XY$$

$$Q + R \underset{XY}{\rightleftharpoons} QR$$

What is the chance of finding cycles ?

- not so bad …

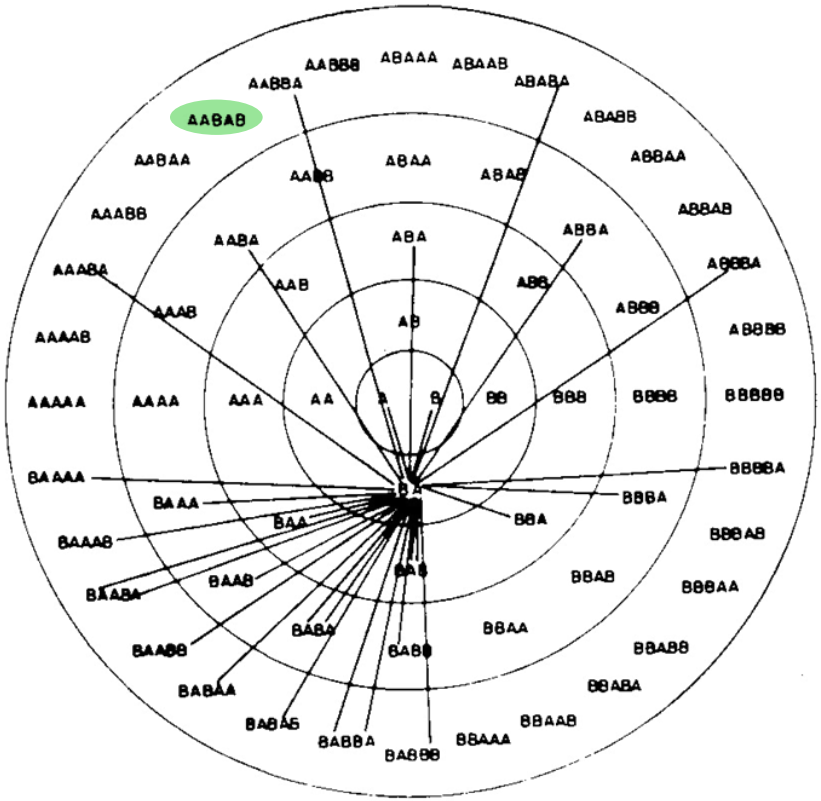
Argumentation

- Consider some random polymers
- some are catalysts for other reactions

Catalytic subset

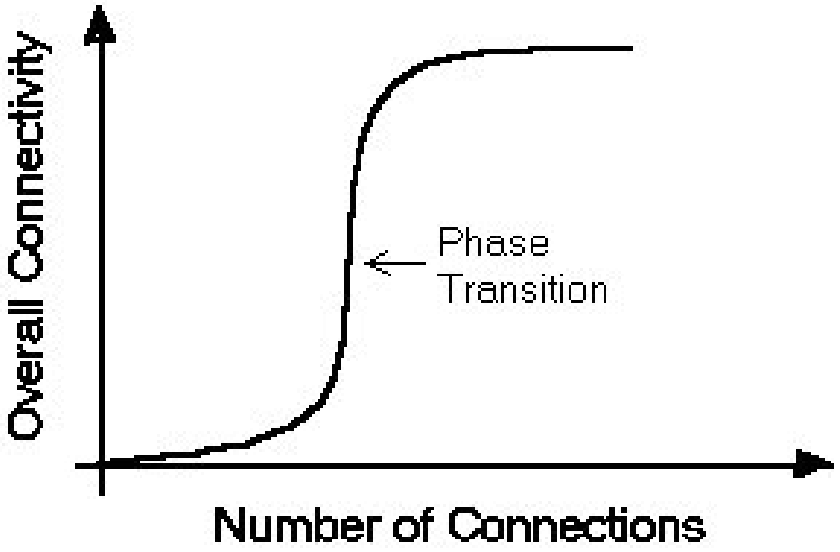
- for RNA 4×4=16 X-Y types
- imagine green sequence catalyses formation of AB bonds
  - leads to huge number of edges
- go to next sequence,
  maybe he catalyses some other reaction

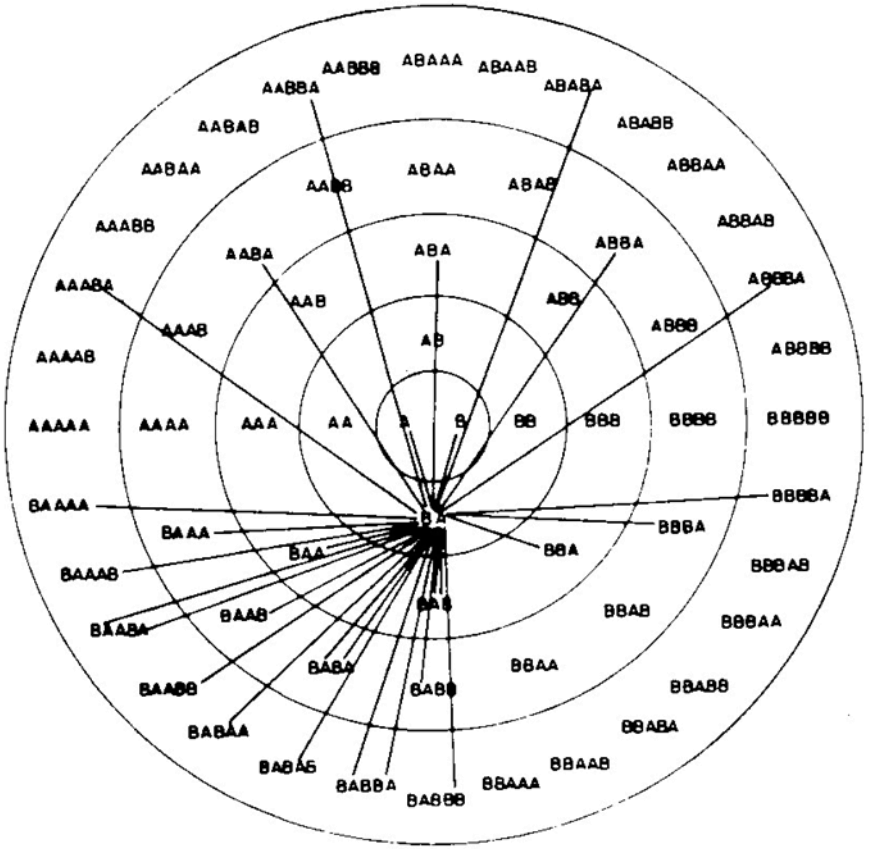
How many reactions / catalysts do I need ?



Formation of cycles

Behaviour with random graphs ?

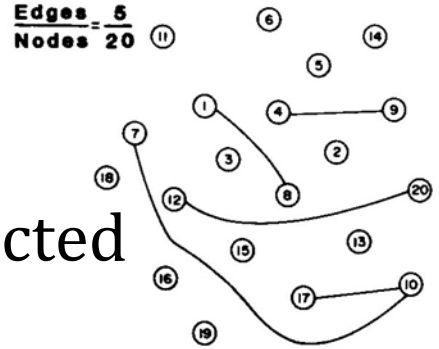


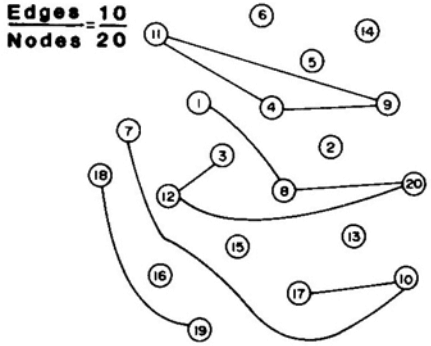


edges and connectivity

As $n_{\text{edges}} \approx \frac{n_{\text{nodes}}}{2}$

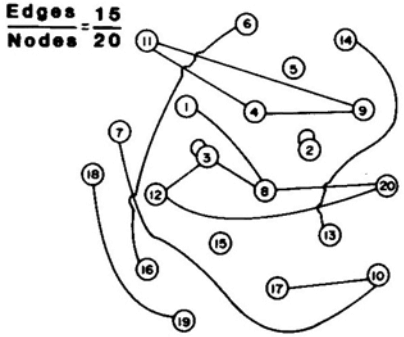
- most components are connected

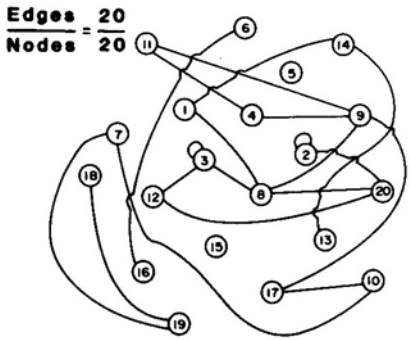


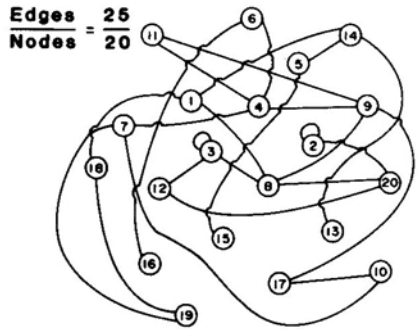


If $n_{\text{edges}} \approx n_{\text{nodes}}$

- cycles appear







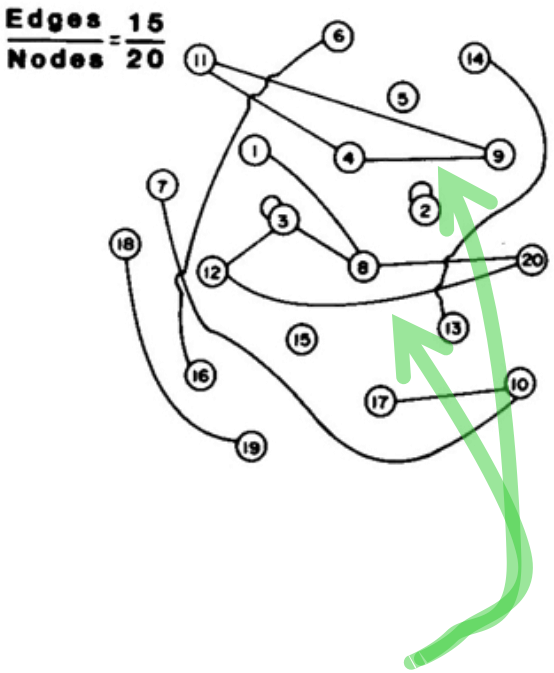
Those nodes in cycles

- can be synthesised using only other components in the cycle
- probability of cycles is near 1

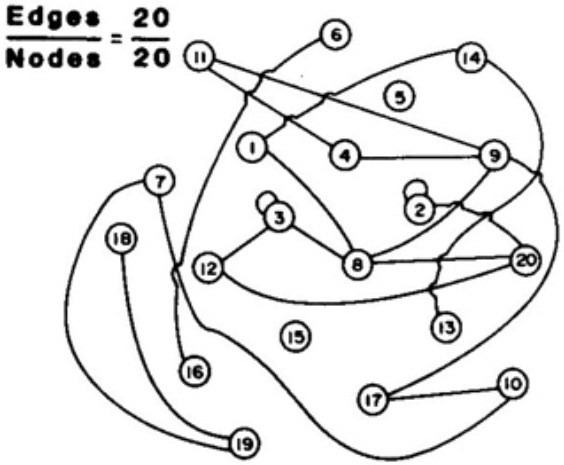
Connectivity

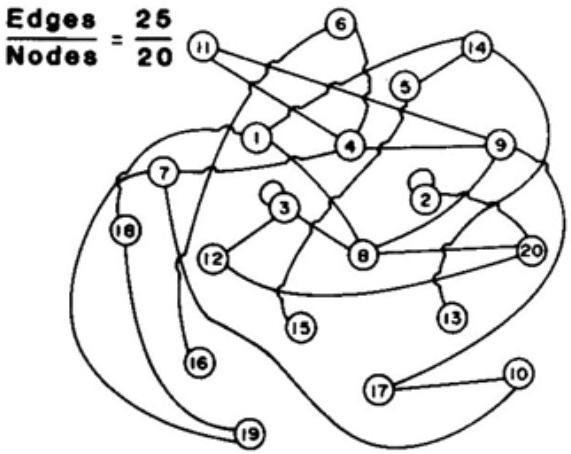
As soon as I have a cycle..

- Self-reproducing system… Life ?



here ?





Why is life likely ?

You ask

- What is the probability of forming a RNA reproducing system ?
    - low

Now ask

- From the Ursuppe (random small, monomeric soup)

- what is the probability of finding some catalytic cycles ?
    - not so low

RNA might just be the winner – or some other biopolymer

Auto-catalytic model

Without real "information" system

- self reproducing
- may have errors, tolerance of errors = evolution

- life may emerge suddenly
- order appears suddenly (Entropy disappears ..OK ?)

This is life

- grows, selection, evolution, but..
- not templated

For an Exam

- characteristics of life
- evidence for RNA world
- problems with RNA world
- auto-catalytic model

Summary

- life
- evolution, errors and tolerance of errors
- RNA world
  - ribosome – strong evidence
  - search for template directed replication
  - difficult to specify exact reactions producing
    - activated monomers
    - polymers
- search for simple template-directed replication may not be necessary
- self reproducing system may spontaneously form