The RNA world

Definitions of life

Evidence for RNA world

Problems with RNA world

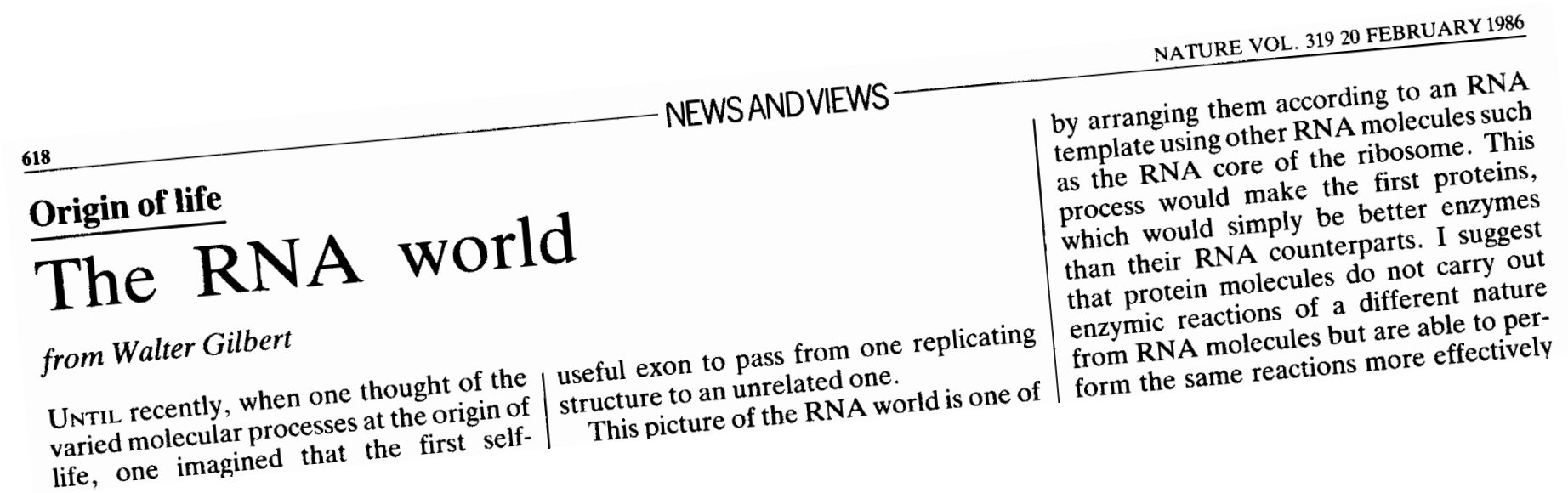
Alternatives (maybe there was no RNA world)

Andrew Torda, April 2018

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

nature COMMUNICATIONS

Received 2 Aug 2015 | Accepted 16 Mar 2016 | Published 25 Apr 2016

DOI: 10.1038/ncomms11328

Spontaneous formation and base pairing of plausible prebiotic nucleotides in water

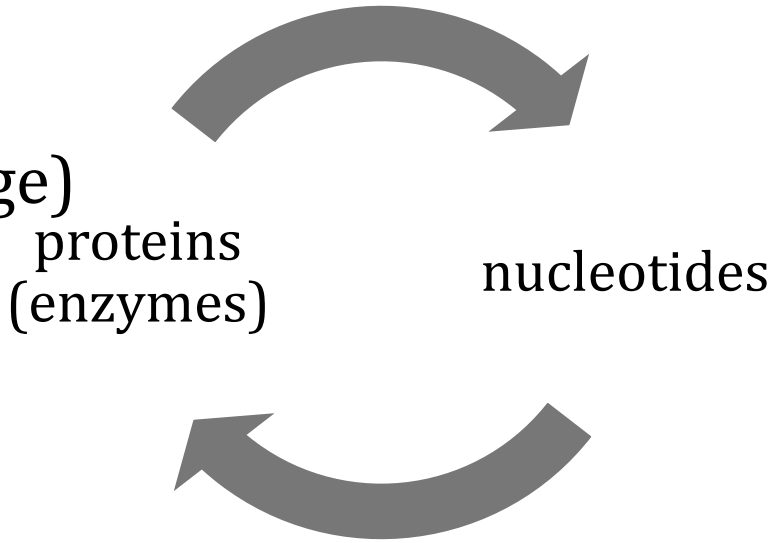
Brian J. Cafferty[1,2], David M. Fialho[1,2], Jaheda Khanam[1,2], Ramanarayanan Krishnamurthy[2,3] & Nicholas V. Hud[1,2]

NATURE COMMUNICATIONS | 7:11328 | DOI: 10.1038/ncomms11328 | www.nature.com/naturecommunications

Life today

Today

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



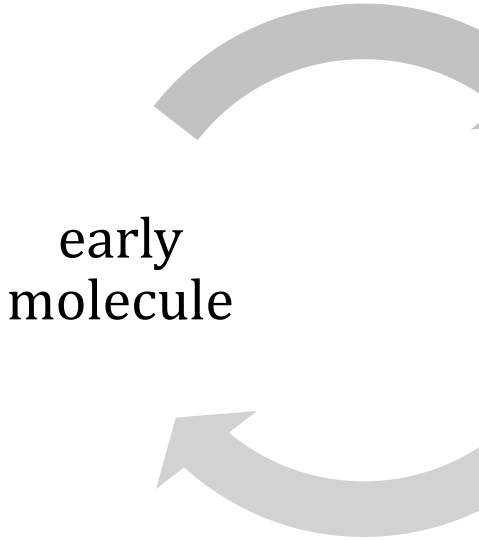
This is templated

- One DNA strand is a template for the other
- DNA is the code for the catalyst/protein

life without proteins

Earlier

- one molecule (phenotype+genotype)
  - self copying
    - possibilities
    1. protein like
    2. nucleotide like
    3. something else



This is also templated

- molecule codes for itself or complement
- remove this requirement later (last few slides)

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

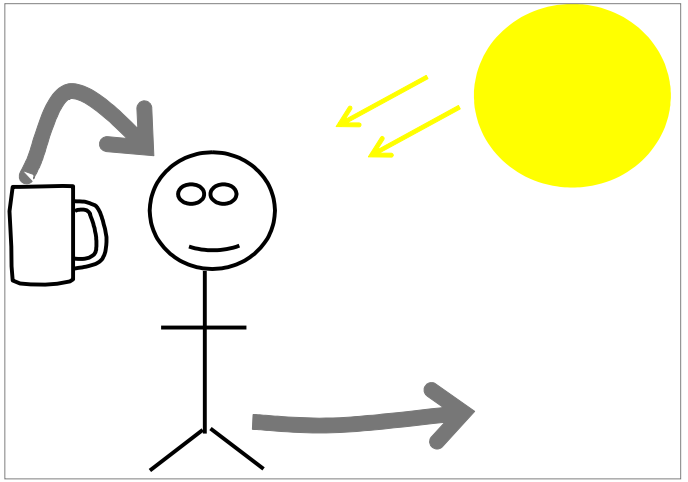
Decay A ↔ B + C, then $\quad \Delta G = RT \ln \frac{[\mathrm{B}][\mathrm{C}]}{[\mathrm{A}]}$

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

Consequence

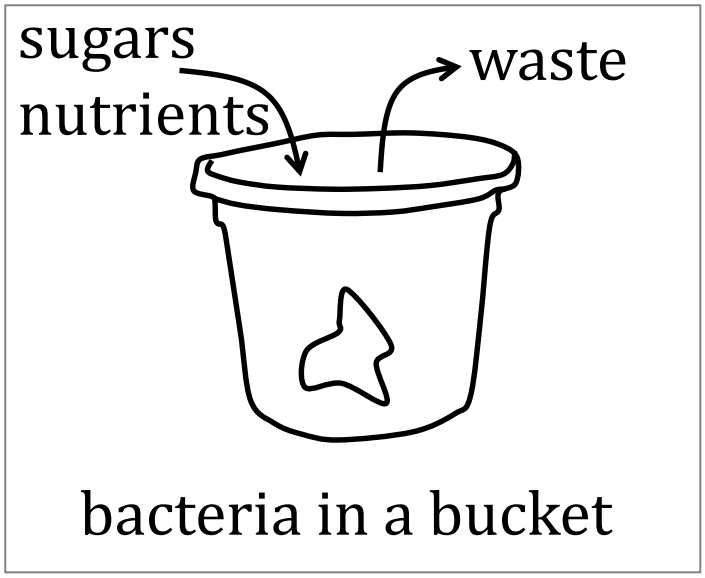
- life looks like "steady state" (stationärer Zustand)
- not equilibrium (Gleichgewicht)

Steady state systems

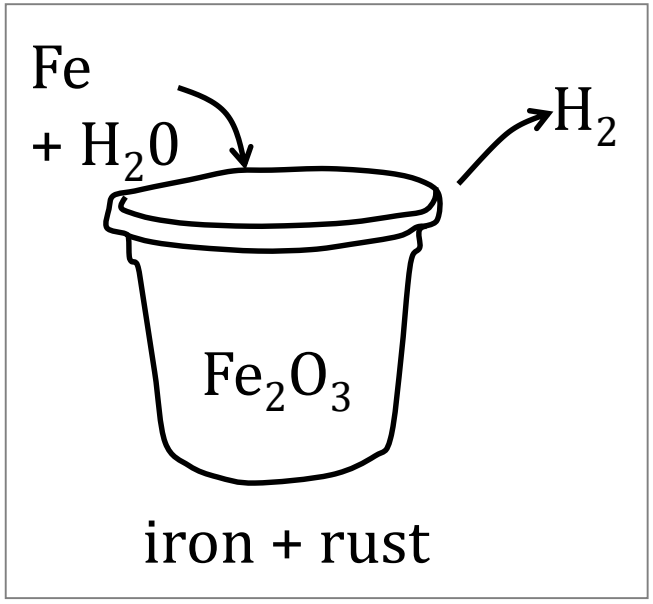


Input of energy

- 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

What else do we have ?

Information / Order

How much information does rust have ? Not much

People and bacteria ? Can we quantify it ?

- consider DNA sequences
  - my DNA 10^9 bases
    - 4^{10^9} possible sequences
  - even dumb virus
    - 6000 bases
    - 4^{6000} sequences

Whatever the details, we have more information than rust

life vs non-life

bacteria	**bucket + rust**
not at equilibrium	
catalytic activity	
variation / selection = evolution	
template copying (A for U, G for C)	maybe
general copying (can copy AAA or ACGU or ..)	

Who cares ?

- the Ursuppe should have the properties from left hand side

Life as we know it or life ?

Are we trying to explain life today ?

- In RNA Biochemie, yes

Is our form of life likely ? Inevitable ? Probably not

Is some self-reproducing system likely ? Much more likely

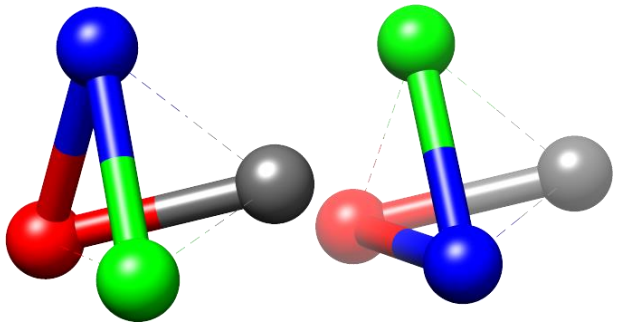
Do we have to have all the properties of bacteria ?

some yes, some not

life on earth	general
C, O, N, H, P, S	
Proteins, lipids, carbohydrates, nucleotides	
enzyme catalysis	
	order
	replication/copying/repair
templated	
one chirality	
variation / selection (evolution)	

- maybe chirality is not clear

Why is one chirality helpful ?



D and L

- both versions are rather similar

Imagine a polymer built from all D or all L

- works well

Imagine a mixed polymer D+L

- sometimes left, right….
- poorly defined structure

To build a polymer of defined structure needs monomers with defined chirality

Why are enzymes so useful ?

Do not say speed (obvious)

Selectivity of products and pathways - examples

- isomers – enzymes give you D or L
- product selection – example:
  - condensation to make..
    - enzymes give you specific sugars
    - esterification at specific sites

Hard to imagine life without some specific catalysts

RNA world definition

Until now

- life in general, life as we know it
- from here, focus on RNA world as precursor to life as we know it

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

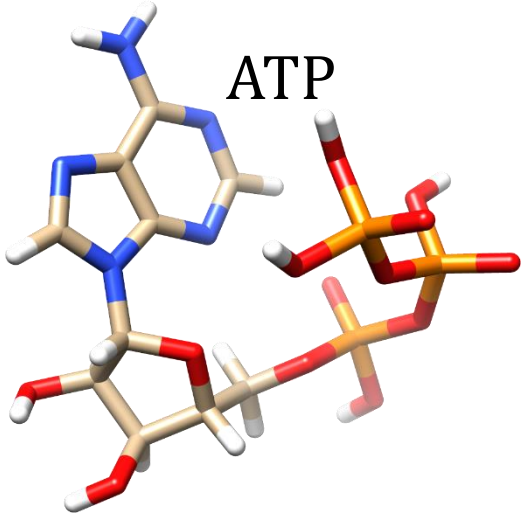
RNA

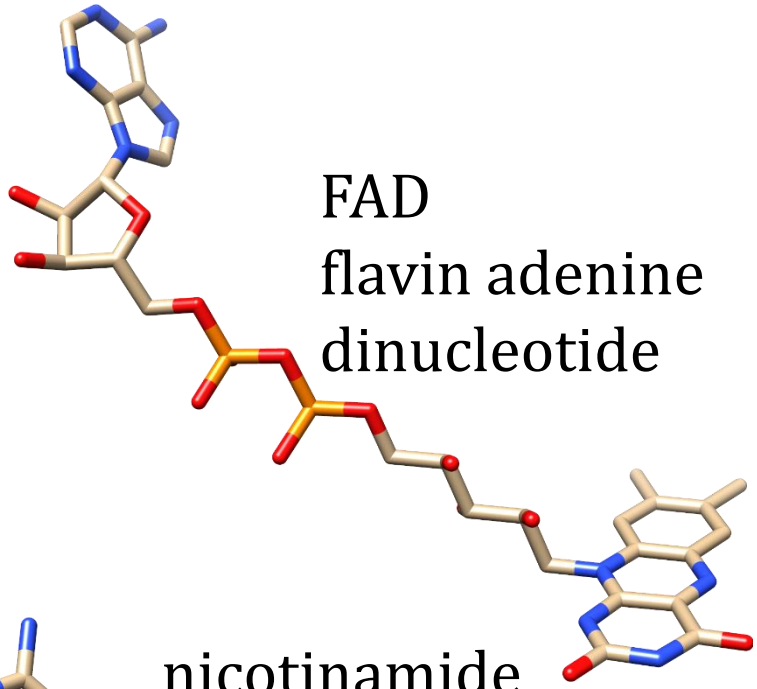
- catalysts
- does encode other DNA / RNA molecules

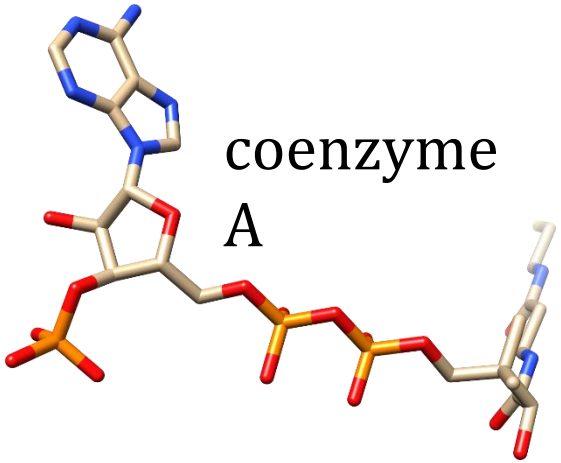
Simplicity - life started with one kind of molecule

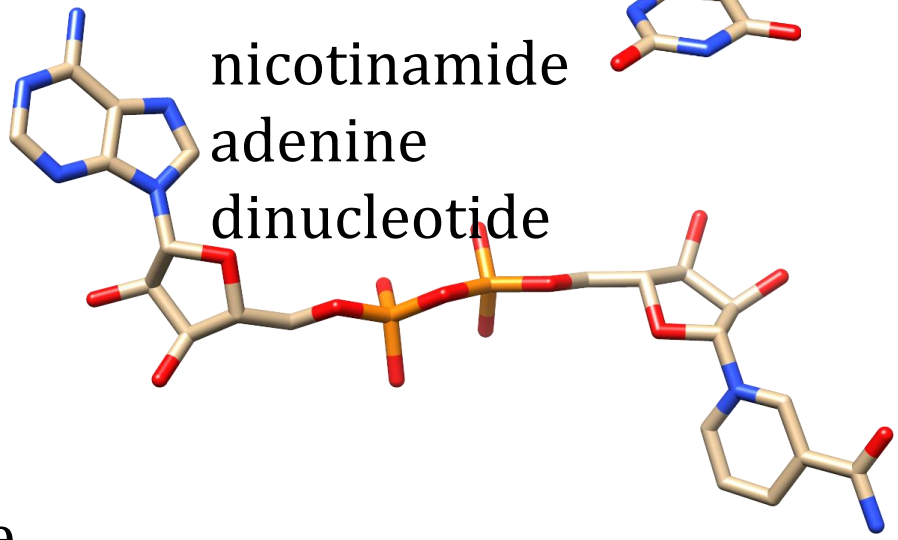
- should be RNA (RNA-like)

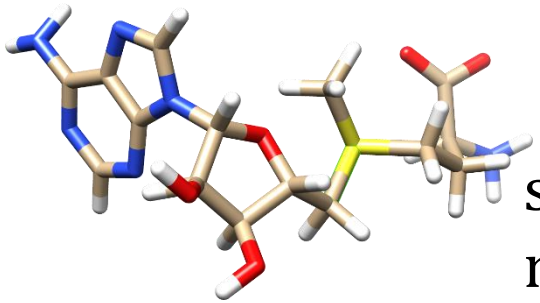
Roles of nucleotides











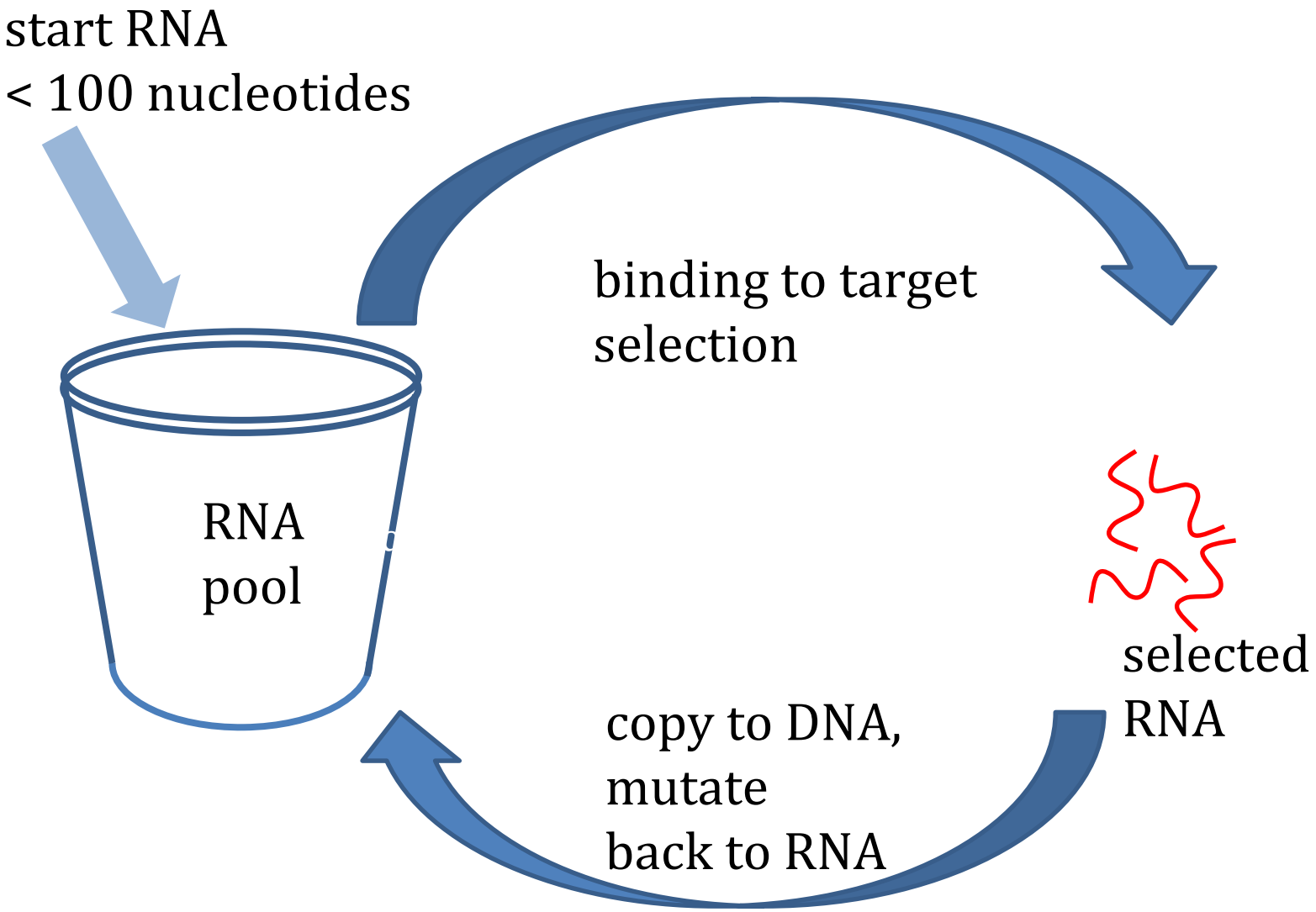
Roles of nucleotides

Cofactors, nucleotides, energy

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

RNA-like molecules are in much universal biochemistry

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

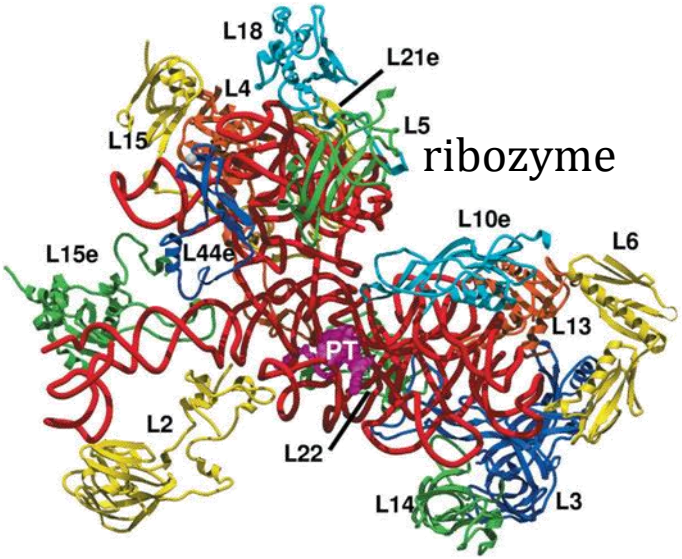
- activities are present in random soup waiting to be found
- start of life was just a big selection experiment

Biosynthesis

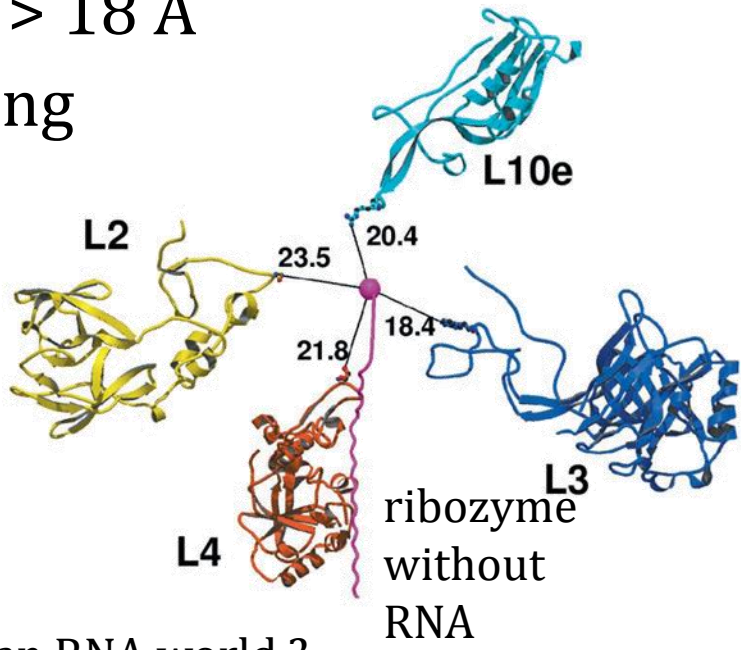
- much machinery devoted to RNA biosynthesis - many enzymatic steps
- DNA is just a modification afterwards
- looks as if RNA is the older molecule

The ribosome

- very conserved
- part of ribosome near active site



- 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



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, …)

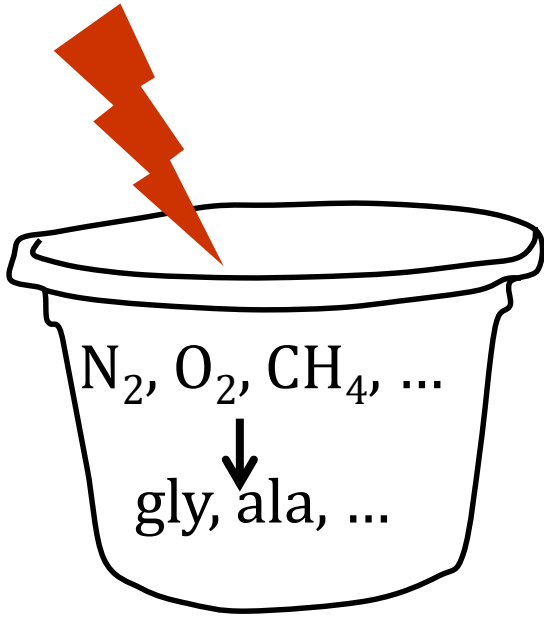
Vague source

- 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 or templates)
  - 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

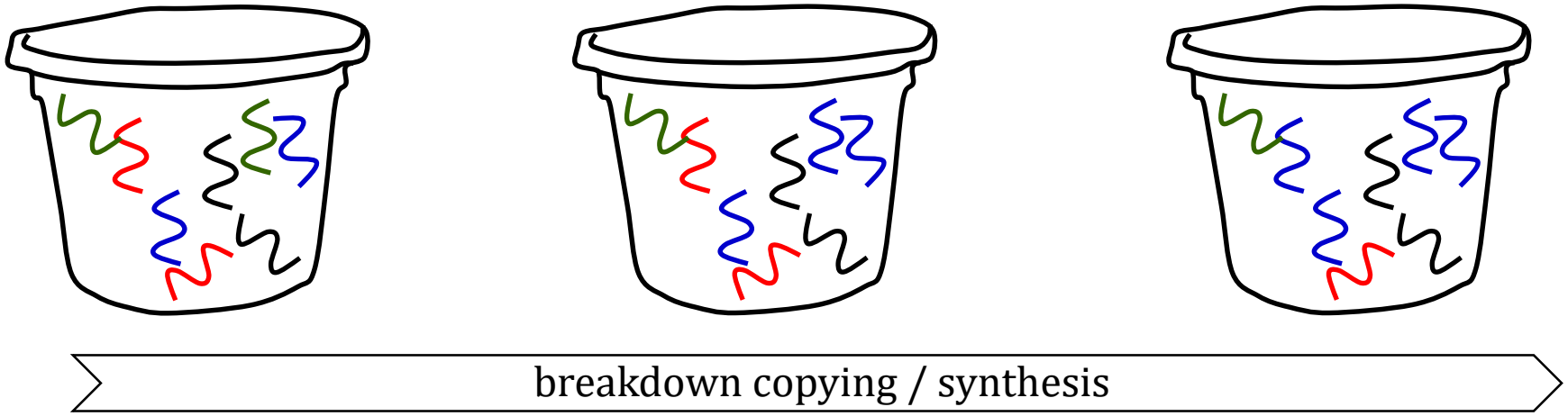
Replicase Quality

- 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

Are there more RNAzymes which are not RNAzymes ?

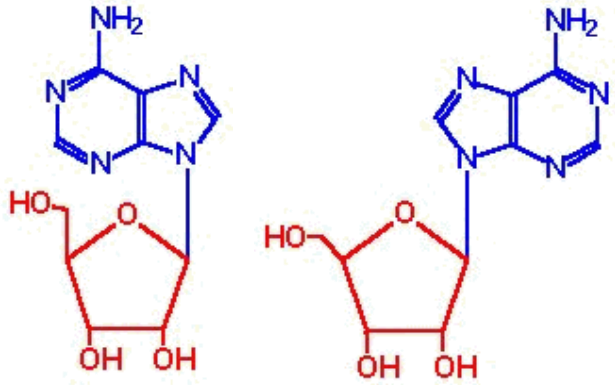
Specificity – sugars (problems)

Make sugar in lab

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

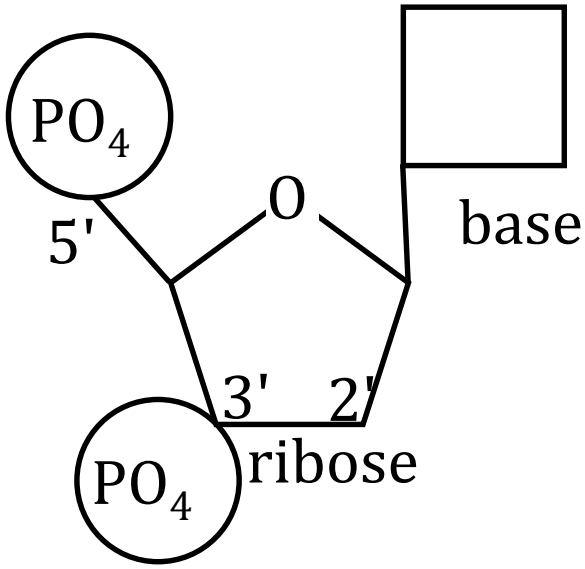
Enantiomers, isomers, ..

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



syn / anti

Joining monomers (problems)



Biology always 5' to 3'

Nucleotide mono phosphates (NMP)

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

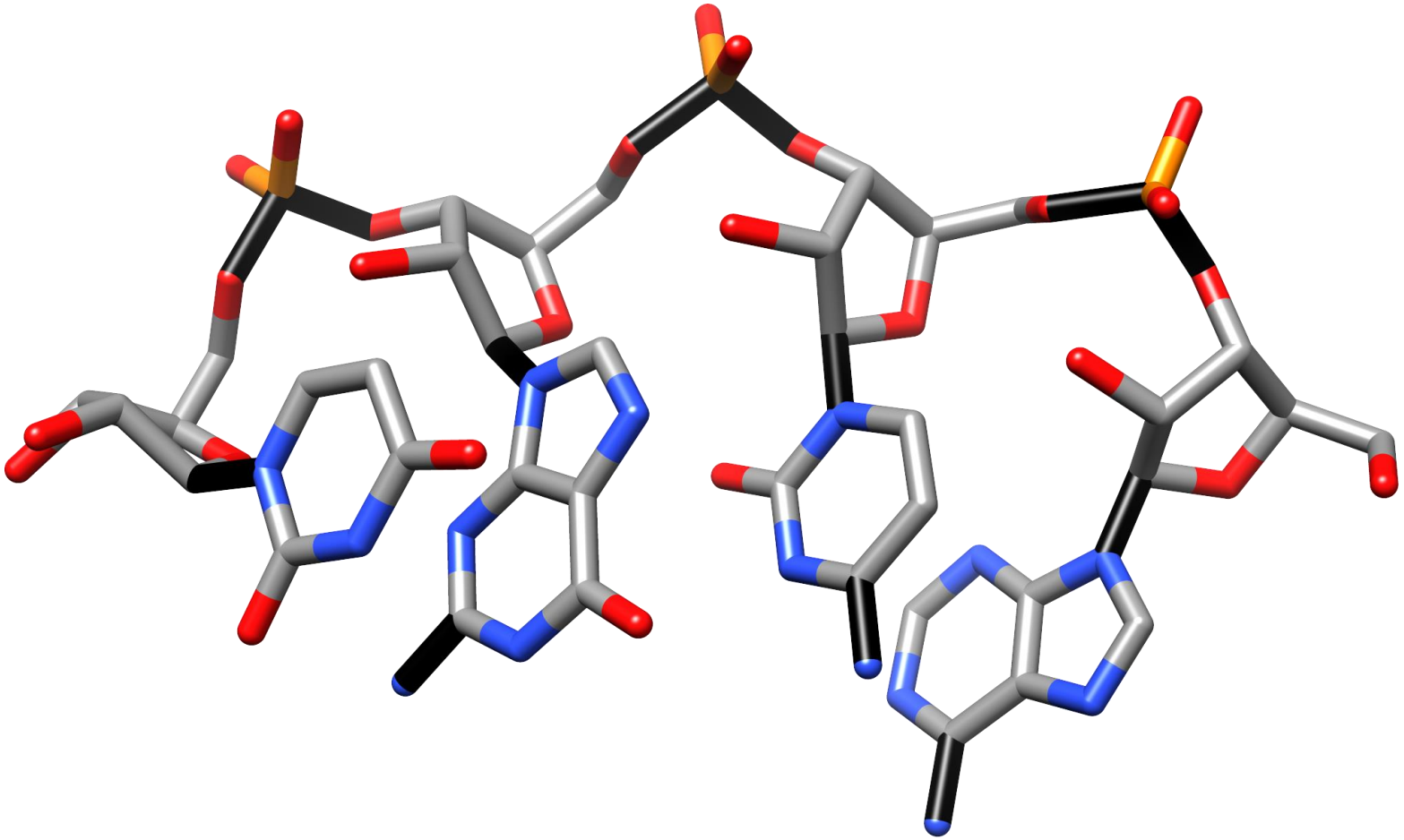
Soup of 5' NMPs and condense

- 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 black bonds are subject to hydrolysis



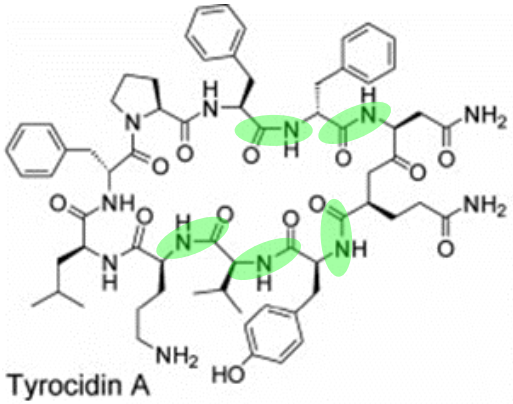
Do we need RNA for proteins ? (problems)

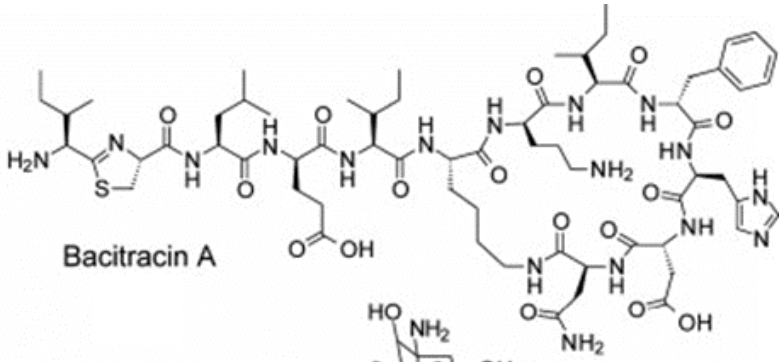
You think we need nucleotides to code for proteins, but..

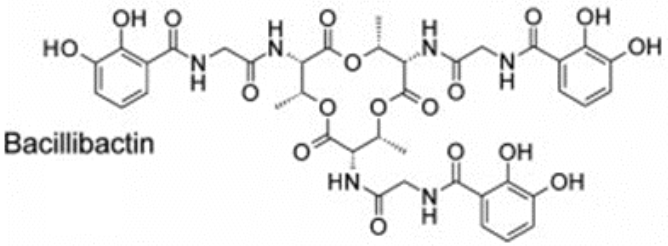
- there are many peptidyl transferases
- antamanide, glutathione ..

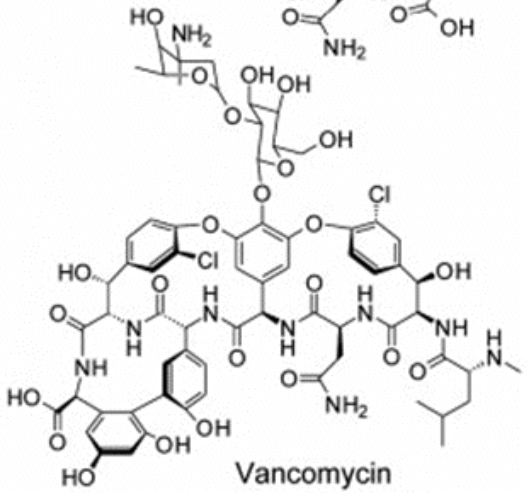
  lots of products, examples …

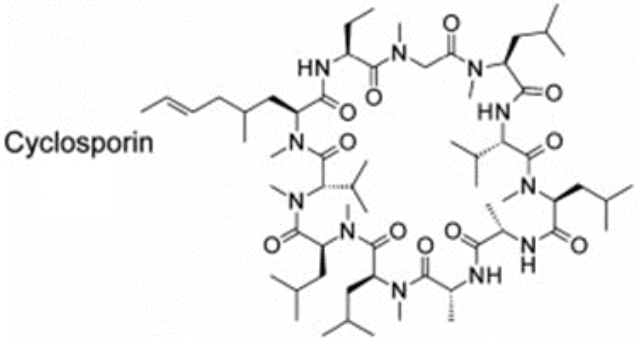
peptides – not genetically encoded (problems)

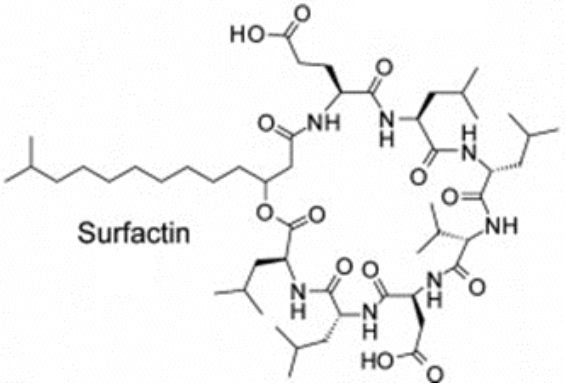












Marahiel, M.A. (2009), J. Pept. Sci. 15, 799-807

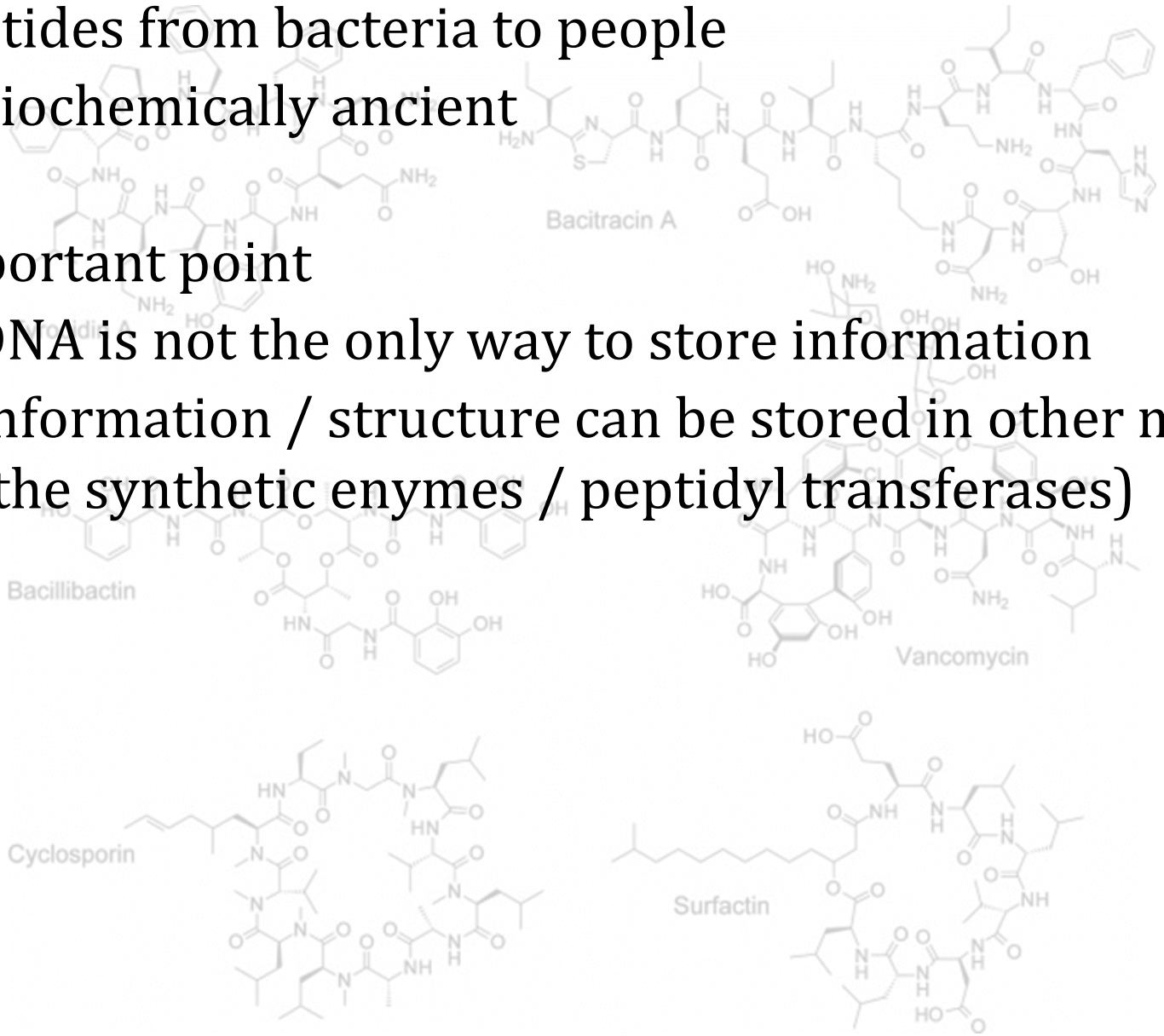
peptides – not genetically encoded (problems)

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

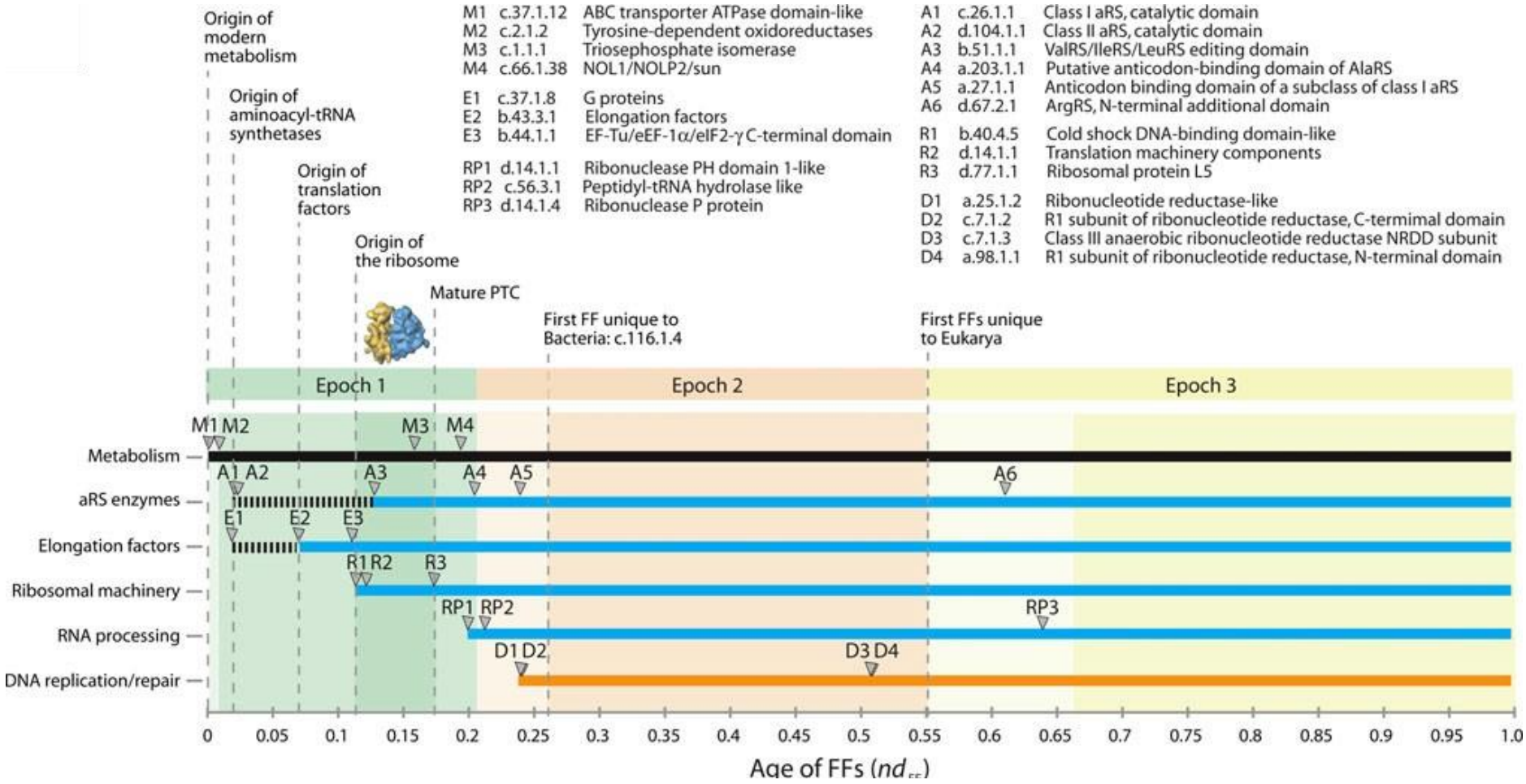
  Are they ?

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

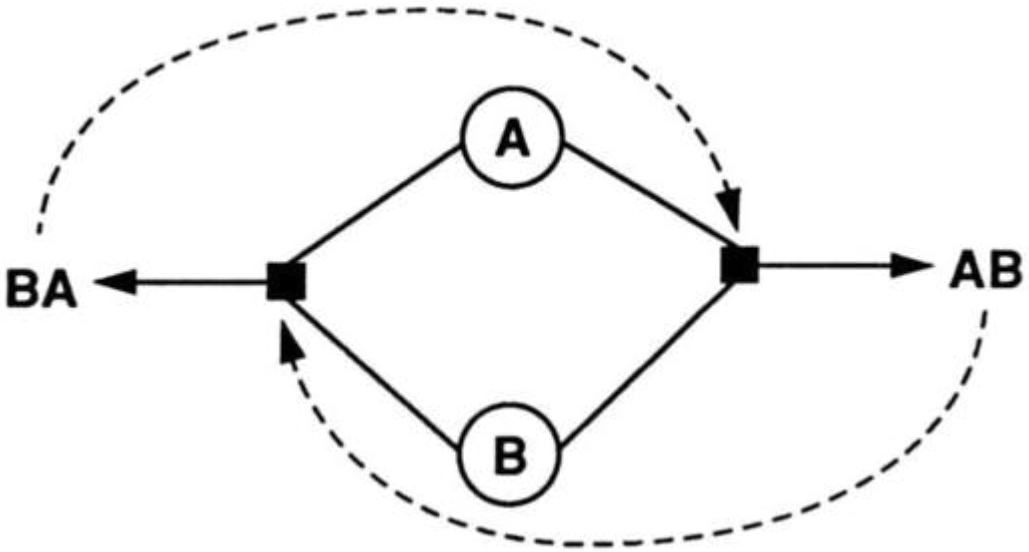
- prebiotic monomers
- condensation / hydrolysis..

Main point

- catalytic closure

autocatalytic cycles

$$A + B \underset{}{\overset{BA}{\rightleftharpoons}} AB \quad \text{and} \quad A + B \overset{AB}{\rightleftharpoons} BA$$



with a source of monomers (A, B) we have everything to keep making AB and BA

- more complicated..

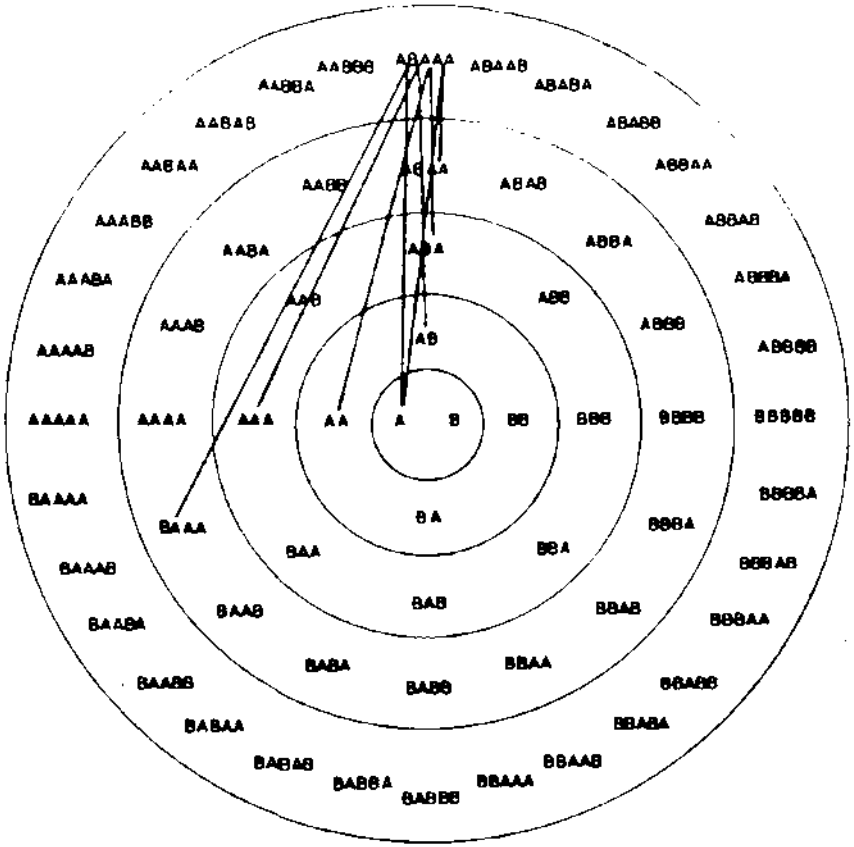
Kauffman, SA, At Home In the Universe, Oxford University Press, NY 1995

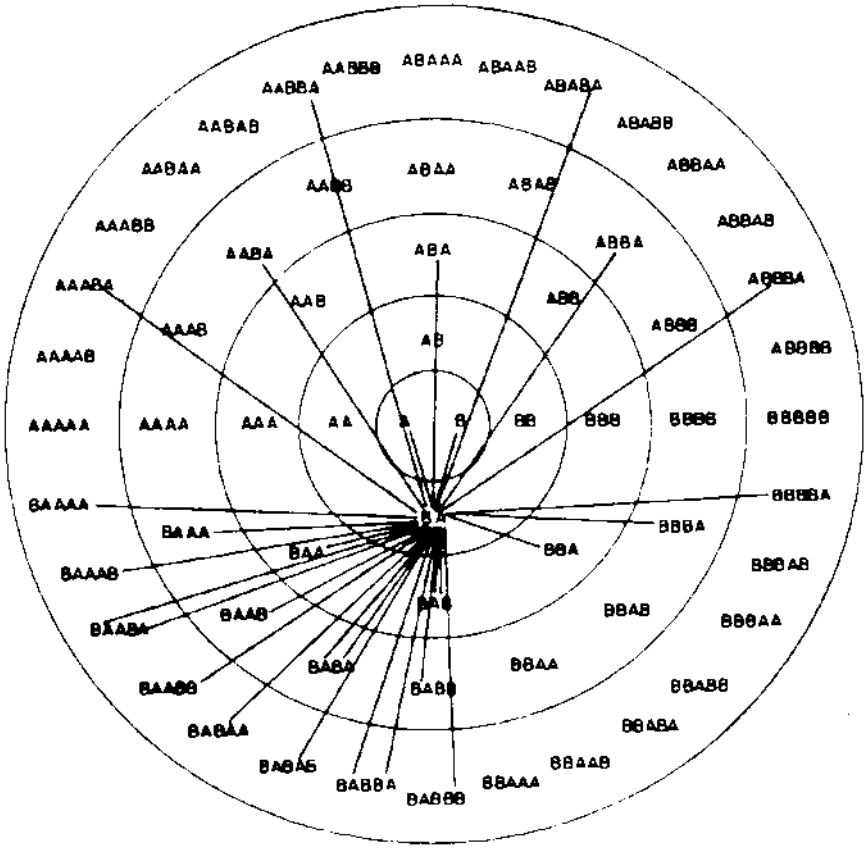
Catalytic closure

Imagine a soup of polymers with conversions

- ABCDE↔ ABC + DE

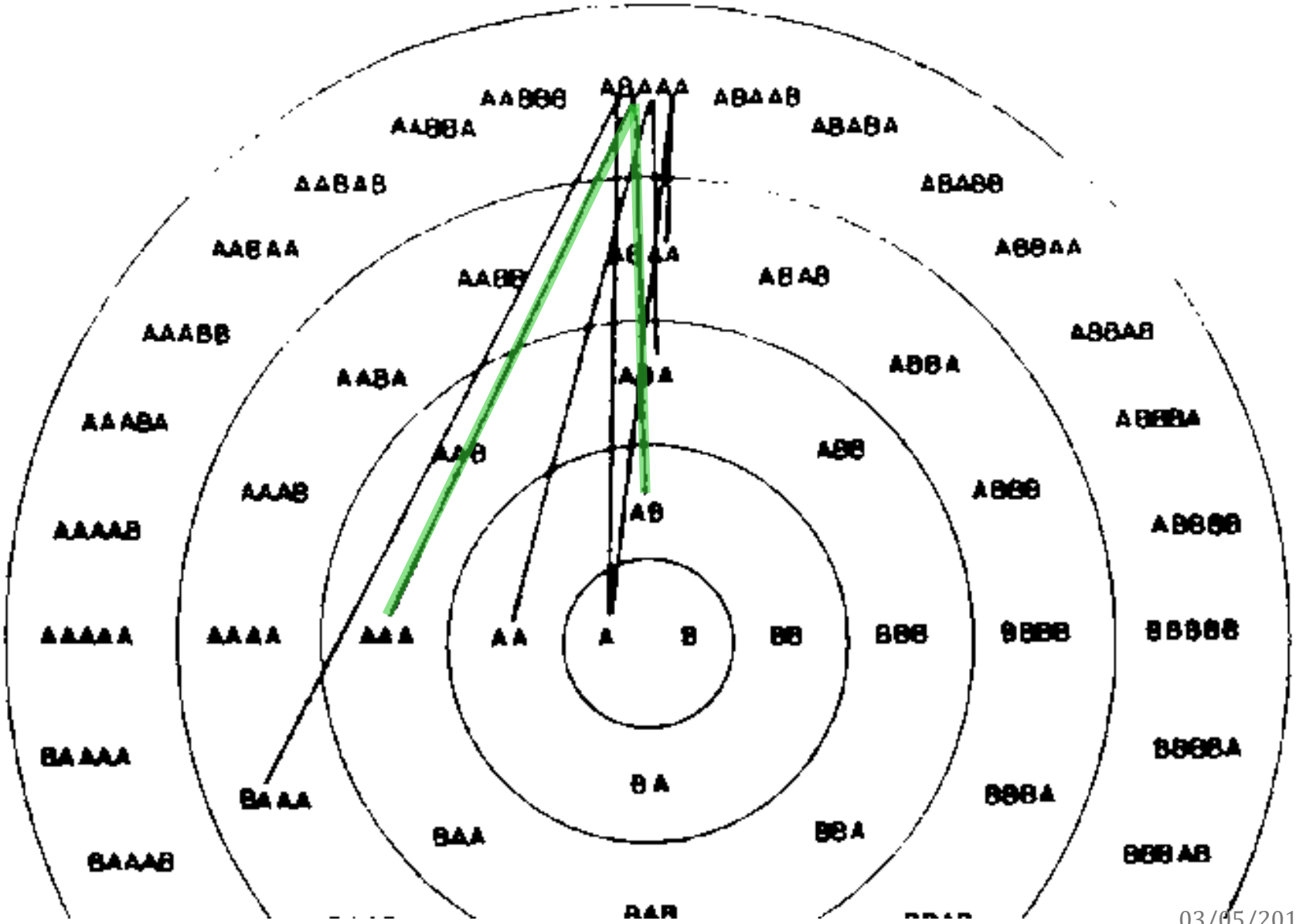
How many ways can we form a 5-mer ? or 2-mer ?





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

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 obvious information, system

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

- life may emerge suddenly

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