# Autocatalytic replicators embedded in metabolic networks

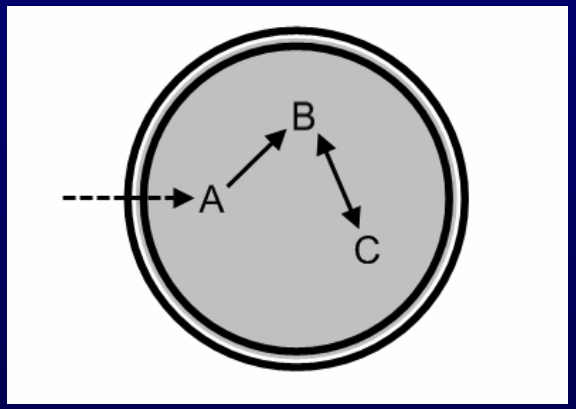
**Balázs Papp**

www.brc.hu/~sysbiol

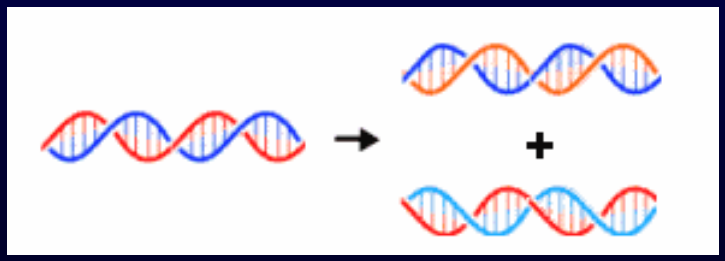
Biological Research Center
Szeged, Hungary

# Two fundamental features of life:

- Metabolism




- Replication (heredity)



# What replicates at the molecular level?

- Template based replication is well established (DNA, RNA)

- But other replicators also exist:
  - Epigenetic chromatin markings
  - Membranes

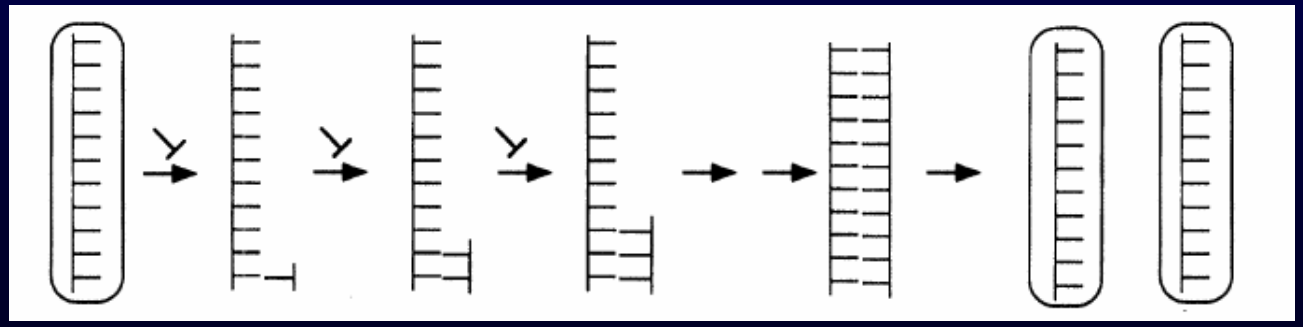
→ The essence of replication is **autocatalysis**

# Autocatalysis

A compound (A) catalyses its own formation:

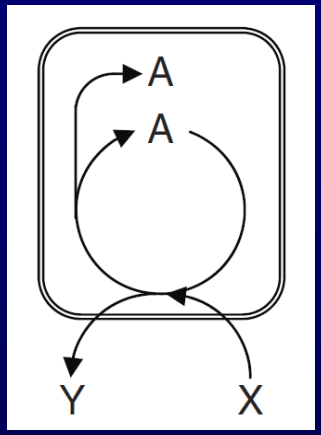
$$A + X \rightarrow 2A + Y$$

Autocatalysis in nucleic acid replication:



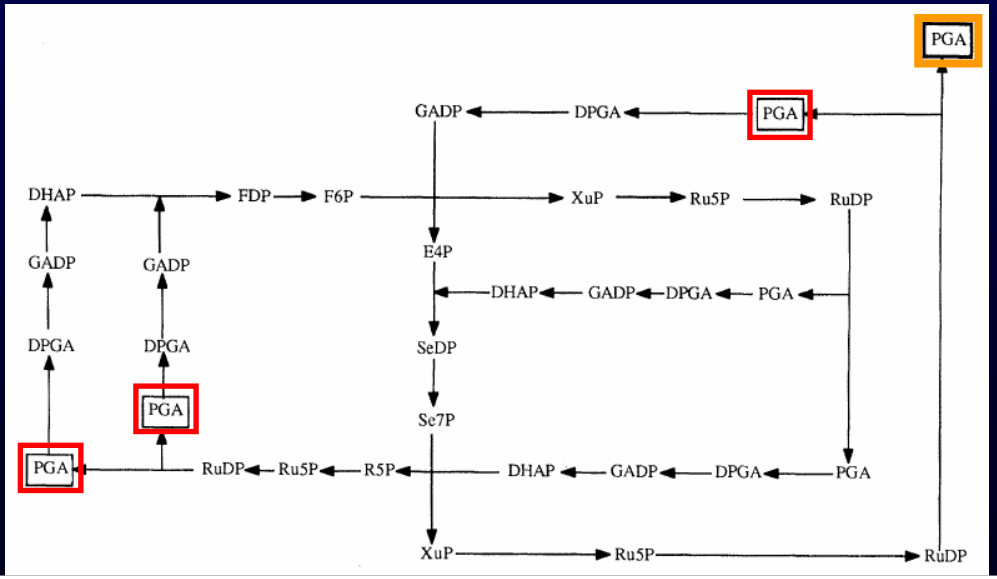
# Autocatalytic cycles in metabolism

- Small molecule metabolism itself can be autocatalytic if it contains at least one autocatalytic cycle

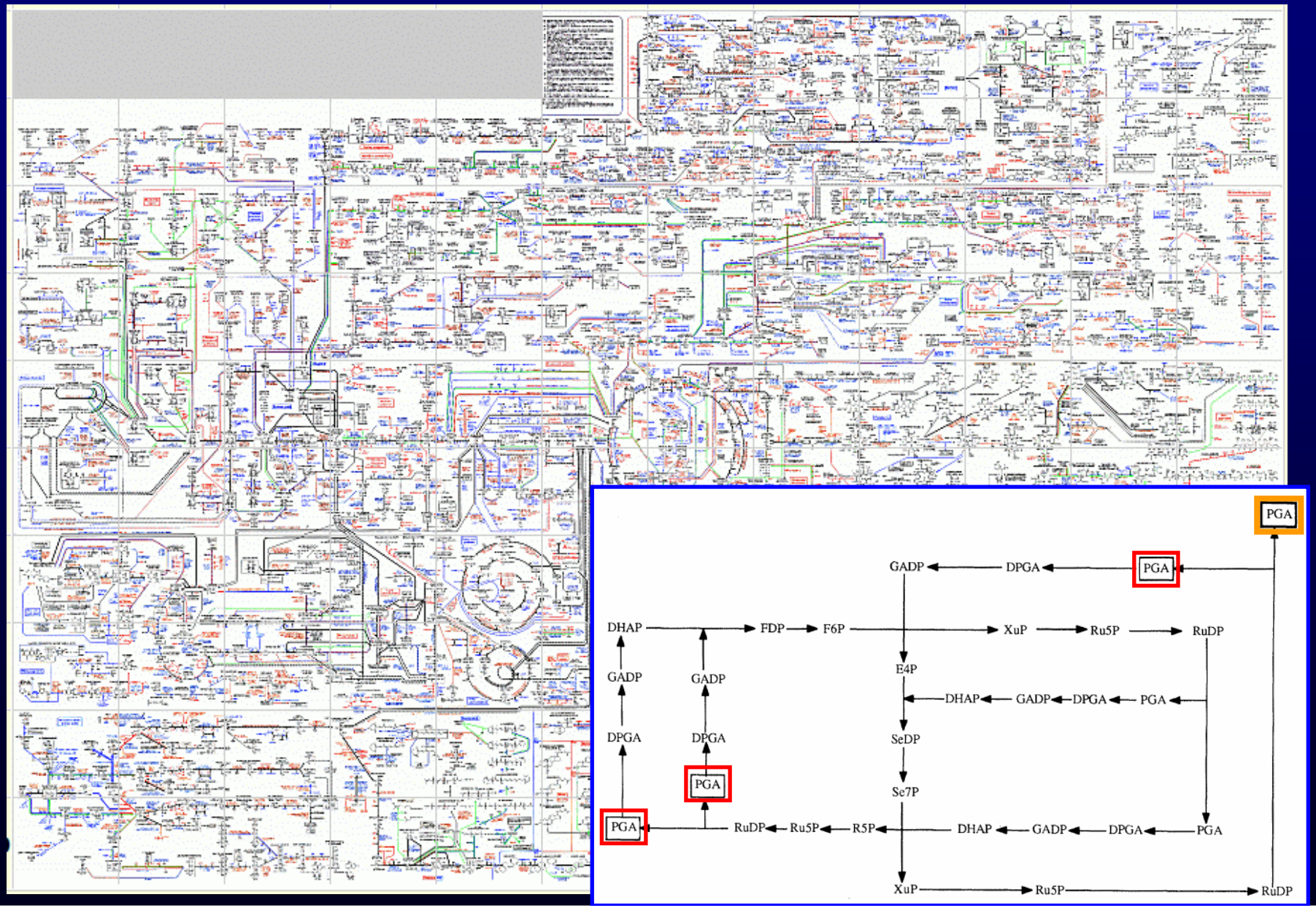



*A* is needed for its own synthesis

- Calvin cycle is an autocatalytic pathway in photosynthetic organisms that fixes $CO_2$



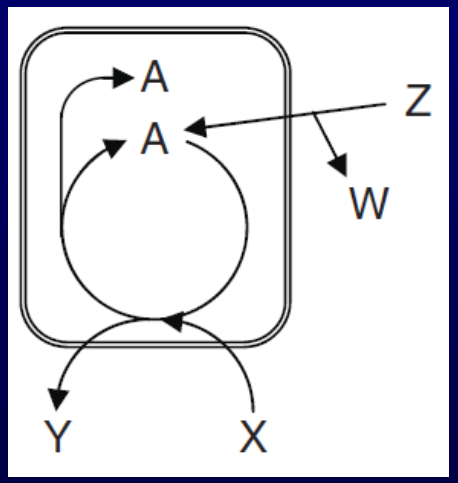
# Autocatalytic cycles are embedded in large networks



# Is the whole metabolic network necessarily autocatalytic?

• Not, if the cycle intermediates can be reconstructed via other routes

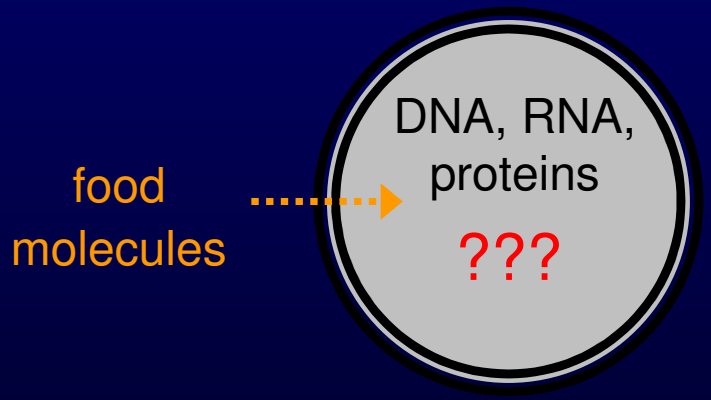
*A* can be also synthesized from *Z*




• How about heterotrophic organisms? Do they also contain autocatalytic cycles?

# Research questions

Are the metabolites of a network accessible just from the food molecules or do we need to add compounds from the network itself to bootstrap the metabolism?




Do ‘bootstrapping’ compounds differ between different species?

# Method

- We searched for autocatalytic compounds in various species and in an inferred minimal metabolism
- Only high-quality network reconstructions were used → with information on food molecules that can be imported

| | Total number of metabolites | Number of food molecules |
|---|---|---|
| *Escherichia coli* | 761 | 143 |
| *Heliobacter pylori* | 485 | 74 |
| *Staphylococcus aureus* | 644 | 83 |
| *Saccharomyces cerevisiae* | 672 | 101 |
| *Lactococcus lactis* | 508 | 92 |
| *Streptomyces coelicolor* | 601 | 104 |
| *Mycobacterium tuberculosis* | 830 | 87 |
| *Methanosarcina barkeri* | 628 | 70 |
| *Geobacter sulfurreducens* | 541 | 41 |
| *Synechocystis*† | 879 | 18 |
| Minimal metabolism | 68 | 11 |

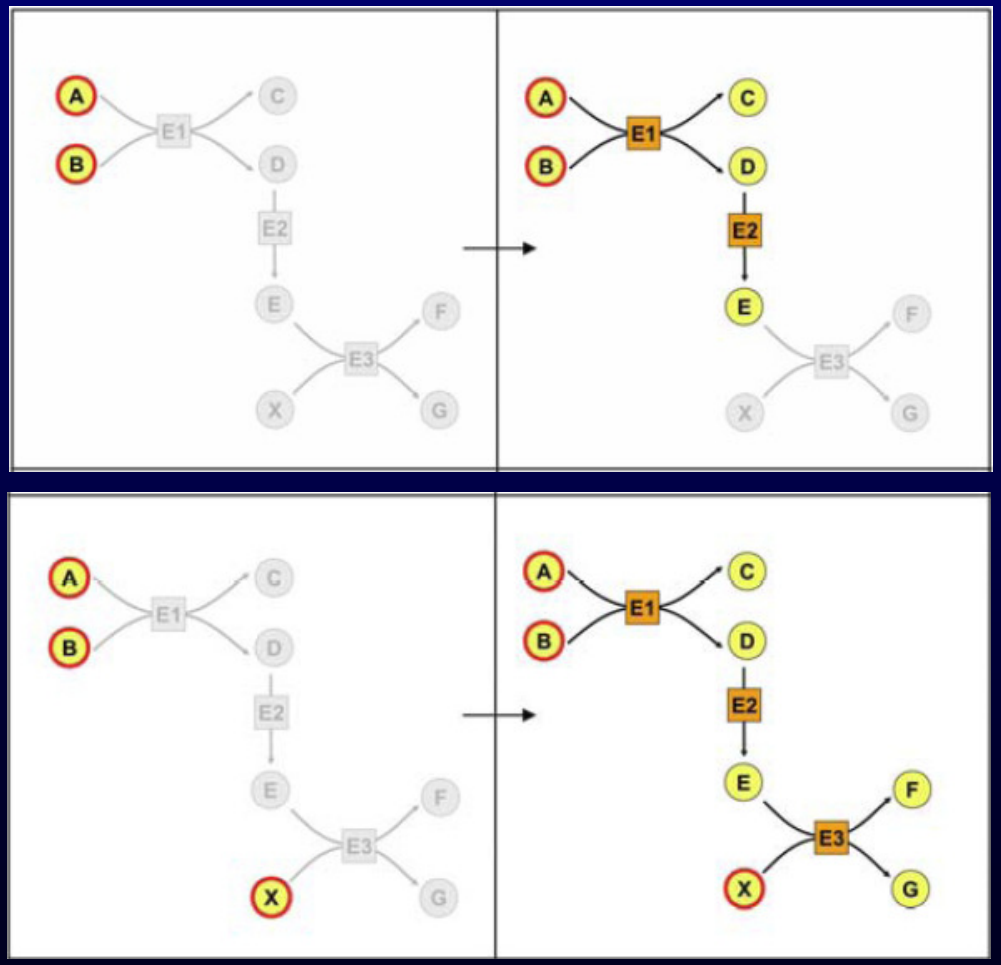
# Method

Scope analysis*: identifying compounds that are not accessible from food molecules

A, B: food molecules

X, F and G are not accessible!

All metabolites become accessible when X is provided

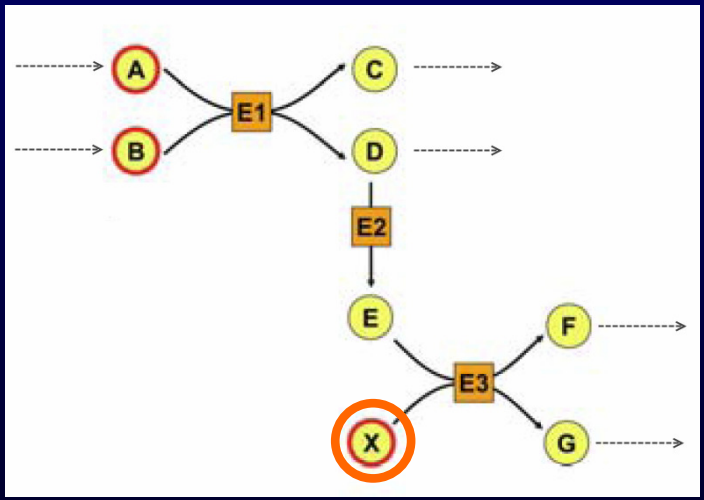



* J Mol Evol (2005) 61: 498-512

# Method

- We identified the smallest set of compounds that have to be added to the network to make all metabolites accessible

- Not all these compounds are autocatalytic, some are simply dead-end

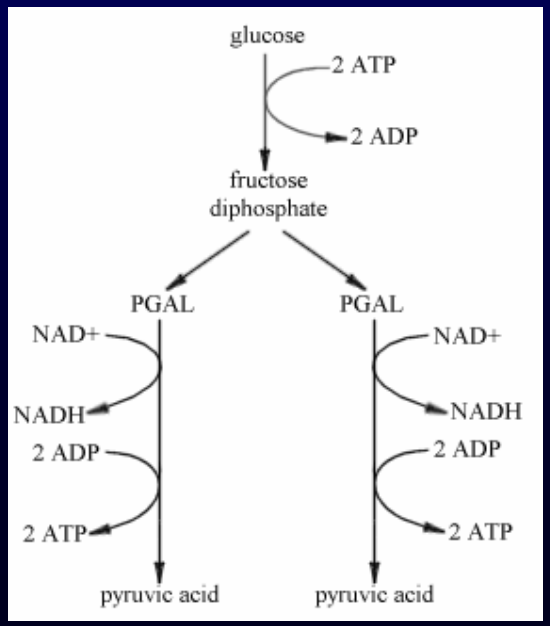



*X* is a dead-end metabolite

# Results

- All analysed metabolic networks show autocatalytic behaviour, even the minimal metabolism
- At least one molecule has to be always added to kick-start the metabolism:

**ATP** synthesis is universally autocatalytic




E.g.: glycolysis

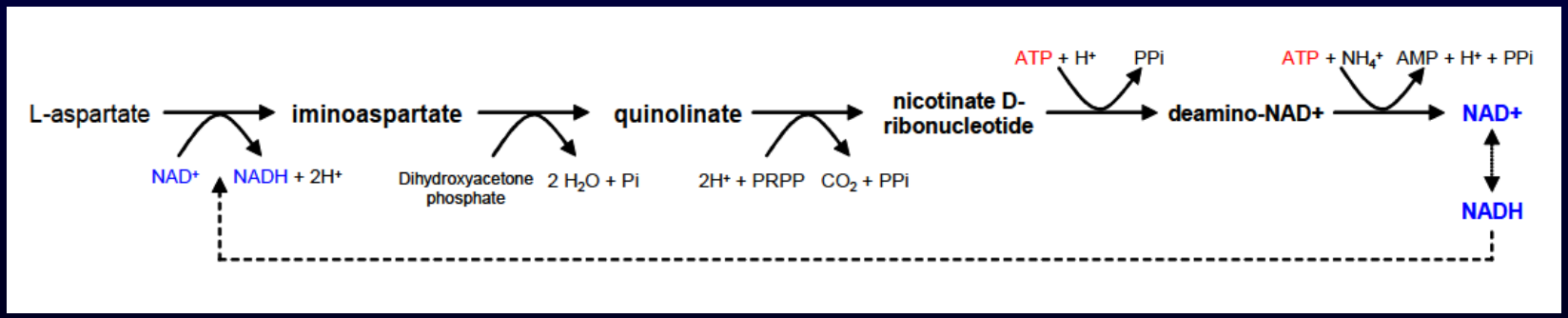
# Results

- Sugar synthesis is autocatalytic in *Synechocystis* when growth is photosynthetic (→ Calvin cycle), but not when the food set includes organic compounds

- Some organisms contain other autocatalytic cofactors in addition to ATP: $NAD^+$, CoA, THF

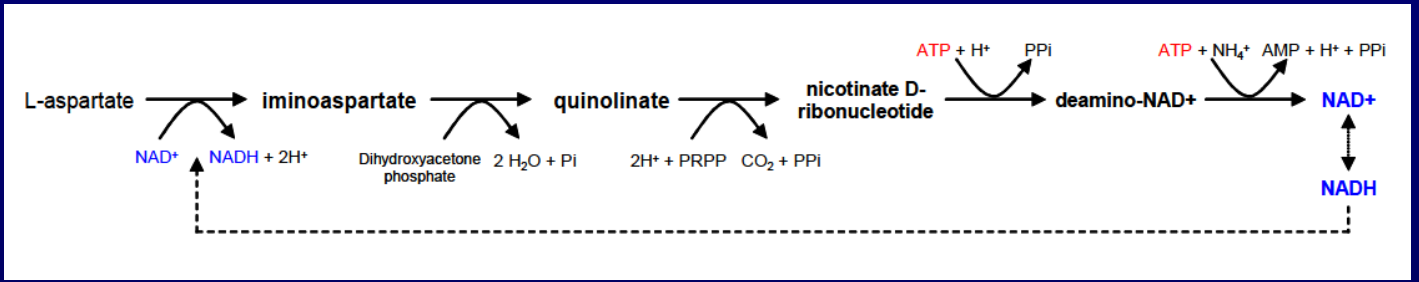
Example:

$NAD^+$ biosynthesis in *Geobacter sulfurreducens*

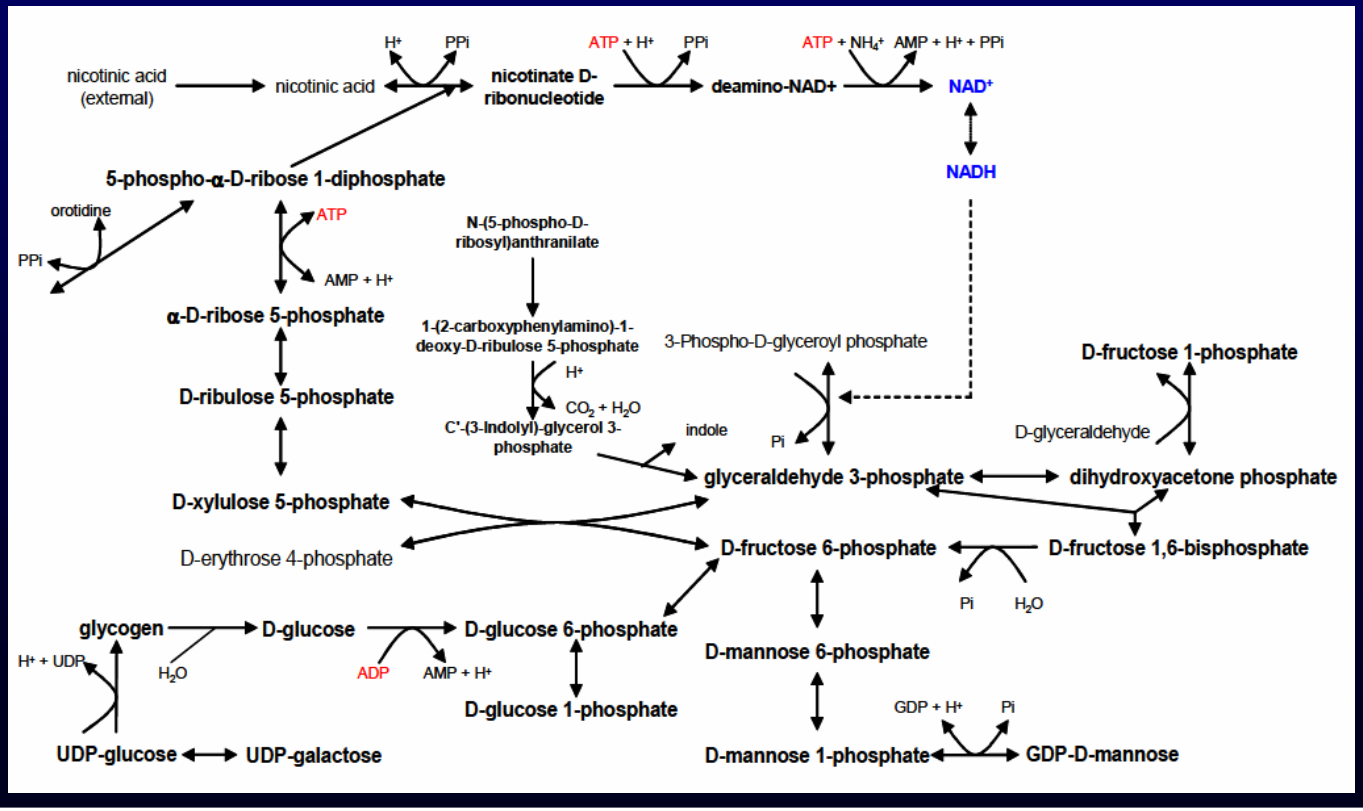


# Evidence for alternative forms of an autocatalytic cycle:

NAD+ biosynthesis in *Geobacter sulfurreducens*




NAD+ biosynthesis in *Methanosarcina barkeri*



# Conclusions

- Metabolism is universally autocatalytic at the level of small molecules, even when organic compounds are available for uptake

- Even a hypothetical minimal network is autocatalytic

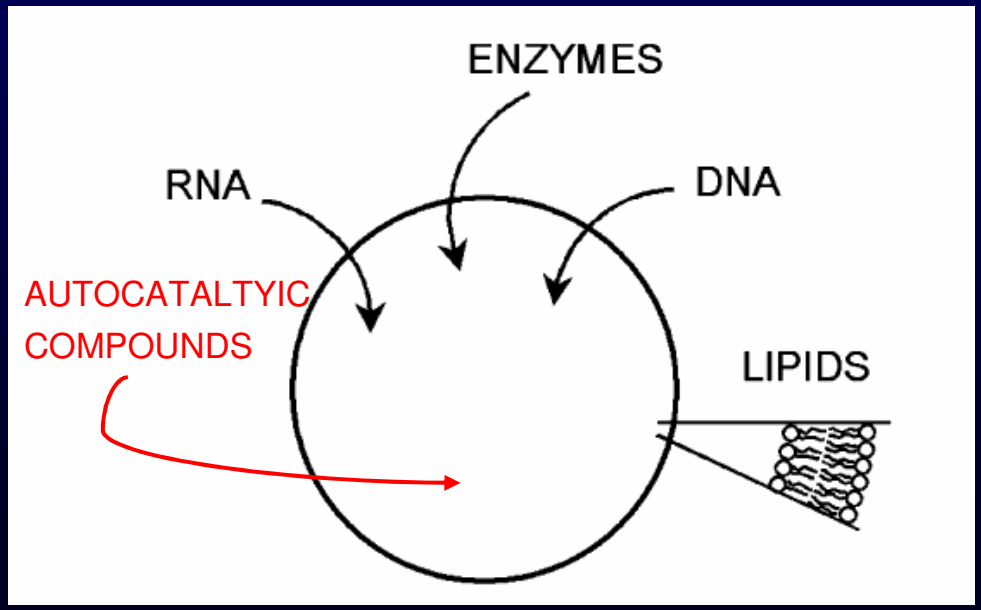
- There are different metabolic replicators: ‘alleles’

Kun, Papp, Szathmáry (2008) *Genome Biol* **9**: R51

# Implications for synthetic biology

- There are projects to synthesize minimal cells from scratch

- ‘bootstrapping’ compounds have to be considered when designing synthetic cells



# Implications for evolutionary biology

- Metabolic replicators provide a limited form of inheritance

  DNA: number of possible types **>>** number of DNA molecules

  metabolic replicators: only few possible types

- The autocatalytic nature of coenzyme biosynthesis might be an ancestral feature

- Origin of life: are non-enzymatic autocatalytic cycles possible (apart from formose reaction)?

# Acknowledgements

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## Open postdoctoral positions

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# Hypothetical minimal metabolism based on endosymbiont genomes (Gil et al. 2004)