Autocatalytic replicators embedded in metabolic networks

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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.

<table>
<thead>
<tr>
<th></th>
<th>Total number of metabolites</th>
<th>Number of food molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>761</td>
<td>143</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>485</td>
<td>74</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
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<td>83</td>
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<tr>
<td>Saccharomyces cerevisiae</td>
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<tr>
<td>Lactococcus lactis</td>
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</tr>
<tr>
<td>Streptomyces coelicolor</td>
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<td>104</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td>830</td>
<td>87</td>
</tr>
<tr>
<td>Methanosarcina barkeri</td>
<td>628</td>
<td>70</td>
</tr>
<tr>
<td>Geobacter sulfurreducens</td>
<td>541</td>
<td>41</td>
</tr>
<tr>
<td>Synechocystis †</td>
<td>879</td>
<td>18</td>
</tr>
<tr>
<td>Minimal metabolism</td>
<td>68</td>
<td>11</td>
</tr>
</tbody>
</table>
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

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**

  ![Glycolysis diagram](image)

  **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

Ádám Kun (Eötvös University)

Eörs Szathmáry (Eötvös University, Collegium Budapest)

Open postdoctoral positions

www.brc.hu/~sysbiol
Hypothetical minimal metabolism based on endosymbiont genomes (Gil et al. 2004)