

A Sequence-to-Function Map for Ribozyme-catalyzed Metabolisms

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Motivation

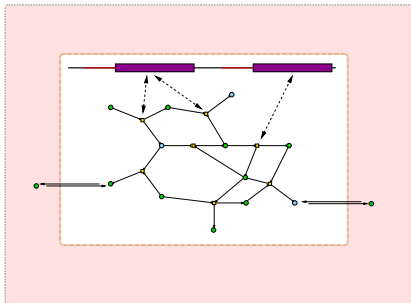
Sequence-to-Function Map

- Observation of the evolution of RNA structure under functional constraints
- Using known statistical properties of the RNA sequence-to-structure map

Ribozyme-catalyzed Metabolisms

- Explaining the evolution of metabolic pathways
- Investigating the emergence of network properties
- Screening for reaction networks with particular dynamic behavior

Schema of Reaction Network Model



- Bag of ribozymes.
- Algebraic chemistry model.
- Exchange of molecules with the environment.

Algebraic Chemistry Model

Molecules are abstracted to vertex and edge labeled graphs.

- Neighborhood relations are preserved by this abstraction.
- Spatial properties (e.g. Chirality, E/Z isomery) can be handled by extending the label set.

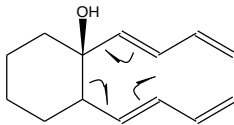
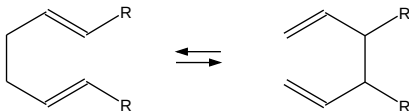
Reactions are abstracted to Graph Rewrite Rules. The grammar ensures **mass conservation**:

- vertex labels are preserved.
- total degrees of corresponding vertices are preserved.

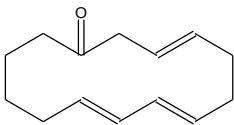
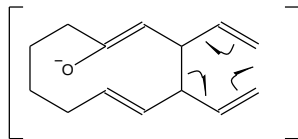
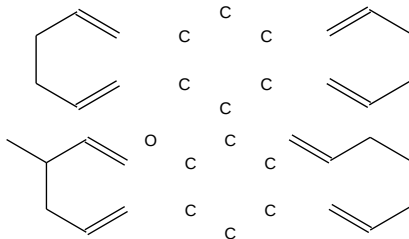
Use graph-indices and QM to calculate physical properties.

Chemical Reaction as Graph Rewrite Rule

Cope Rearrangement

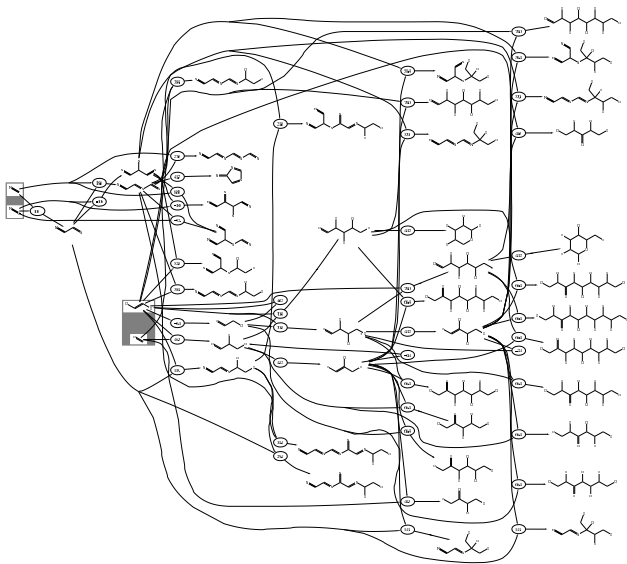


Rewrite Rules



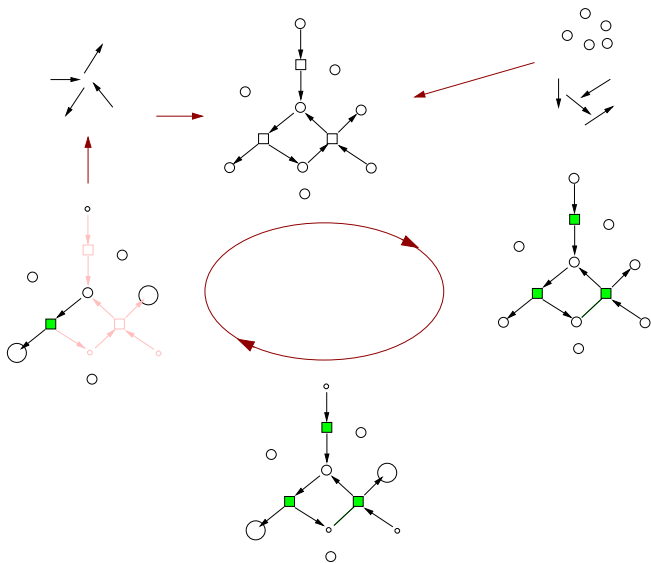
Graph-grammars are a context sensitive language!

Iterating the Graph Grammar

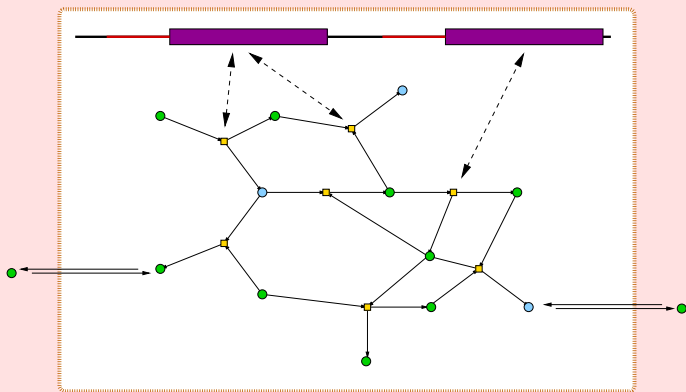


cyanide, formaldehyde glycol; aldolcondensation, tautomerization

Way to avoid the Combinatorial Explosion

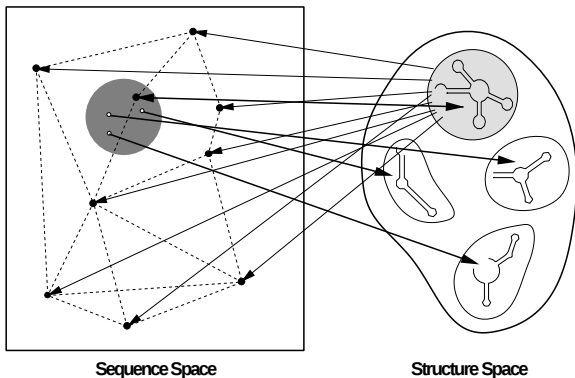


We need a model for the genetic system

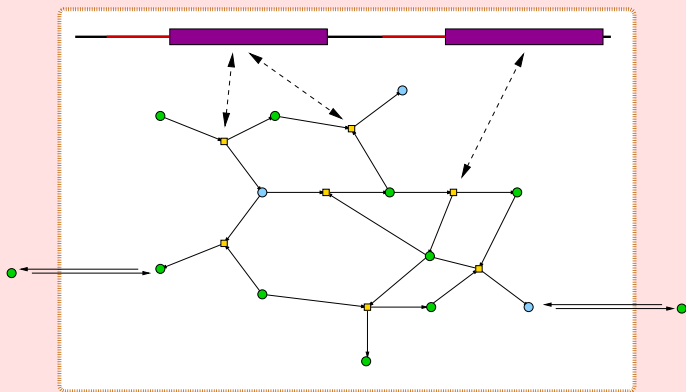


RNA sequence-to-structure map in 2 minutes

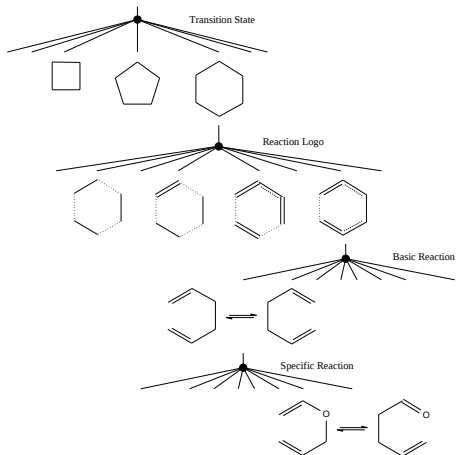
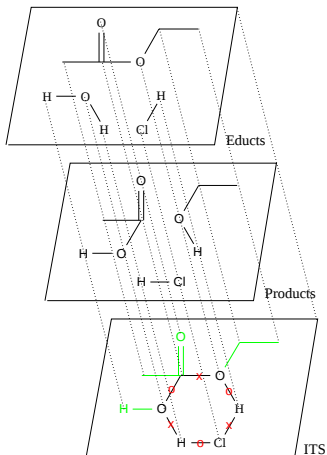
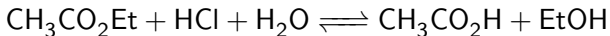
- **Redundancy:** Many more sequences than structures.
- **Sensitivity:** Small changes in the sequences may lead to large changes in the structure.
- **Neutrality:** A substantial fraction of mutations does not alter the structure.



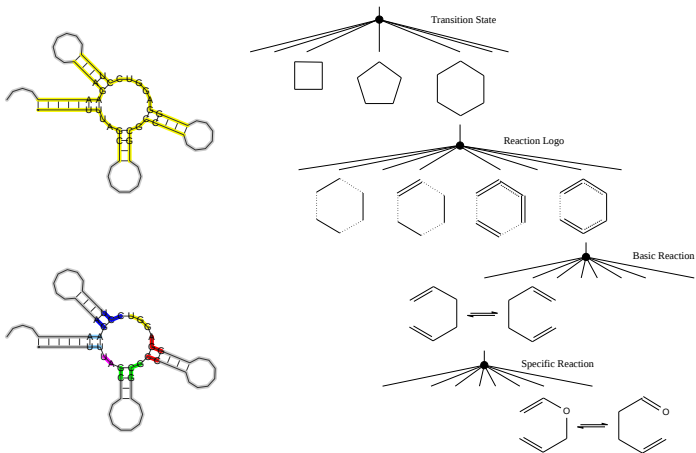
We need a model for the structure-to-function map



Reaction Classification



The structure-to-function map



Neutrality is higher than in the RNA sequence-to-structure map.

Results

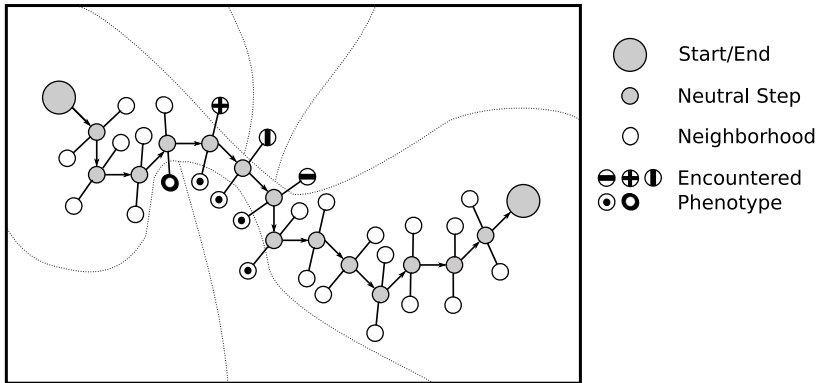
Genotype-phenotype-map

- Random neutral walk
- Neutral networks
- Network properties $\rightarrow$ Map properties

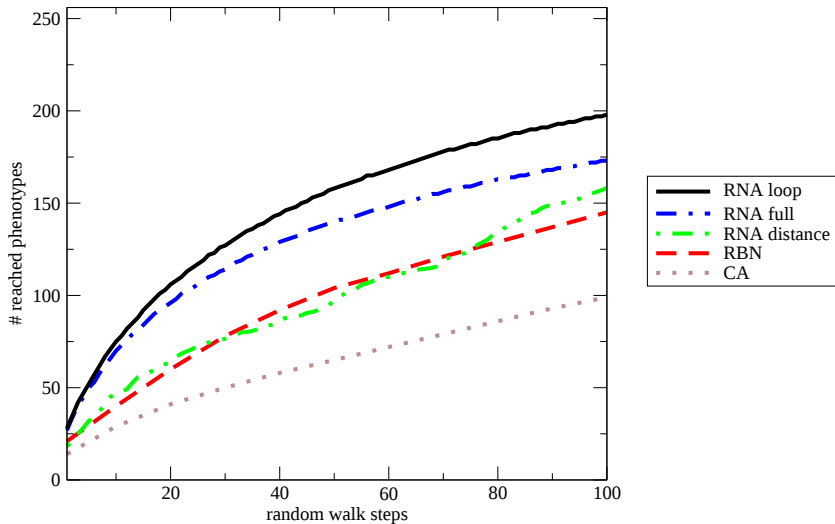
Evolution of metabolism

- Metabolic pathway analysis
- Network properties $\rightarrow$ System properties

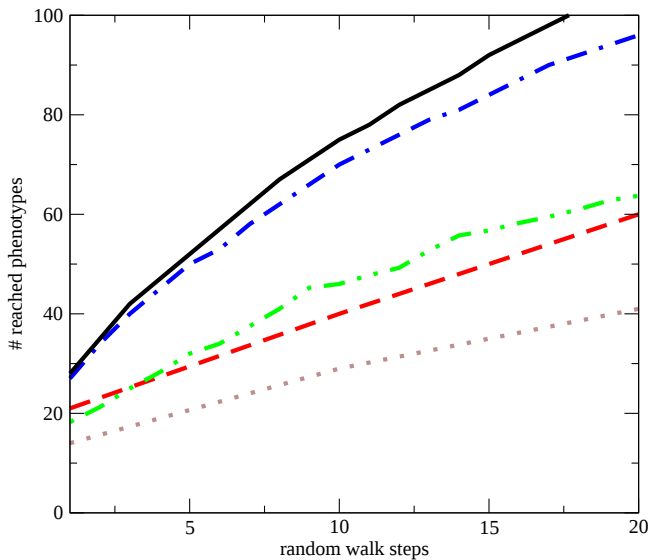
Random neutral walk



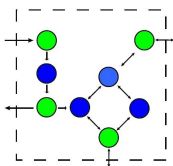
Encountered Phenotypes (length=100)



Encountered Phenotypes (length=20)



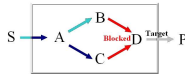
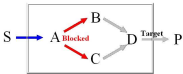
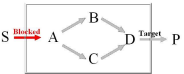
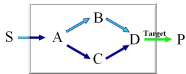
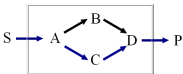
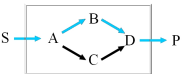
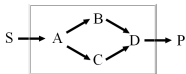
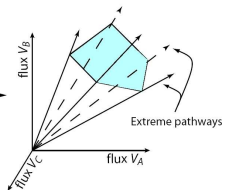
Metabolic Pathway Analysis



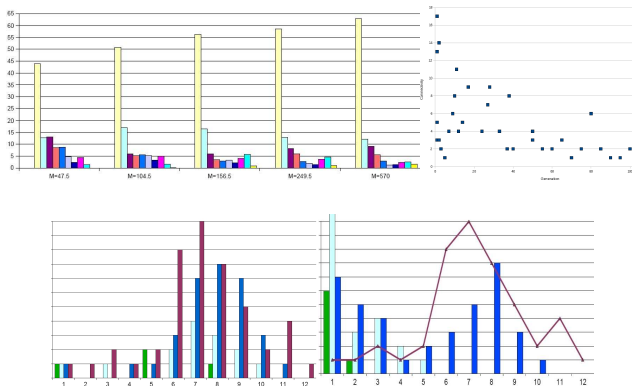
Creation of
stoichiometric
matrix

$$\begin{array}{c} \text{Reactions} \\ \left[\begin{array}{cccc} 1 & 0 & \cdot & 1 \\ 0 & 1 & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & 0 \\ 2 & \cdot & \cdot & -1 \end{array} \right] \end{array} \begin{array}{c} \text{Metabolites} \\ \left[\begin{array}{c} \cdot \\ \cdot \\ 0 \\ 0 \\ 0 \end{array} \right] \end{array}$$

Extreme
pathway
analysis



Robustness, Modularity, ...



robustness and modularity measures based on elementary modes

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