Functional Evolution of Ribozyme-catalyzed Metabolisms in a graph-based Toy-Universe

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Why Metabolic Networks?

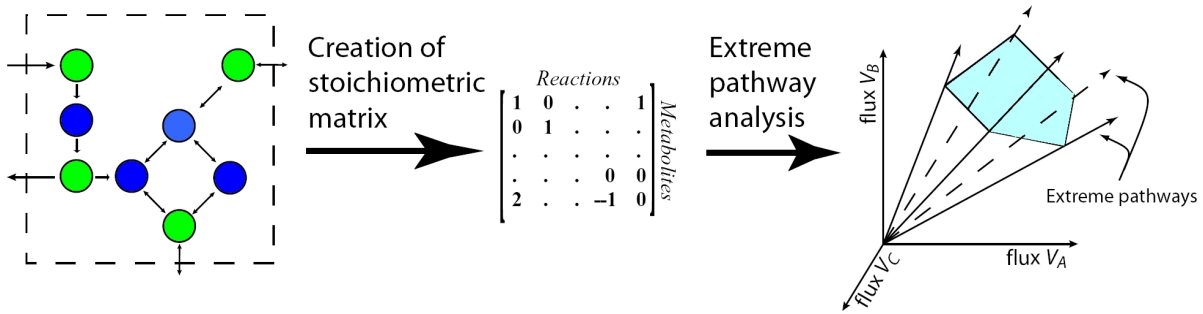
- Available Data
  - complete annotated genomes
  - pathway databases
- Amount of Research
  - Systems biology
  - Flux Analysis
  - Simulations
- Application
  - metabolic engineering
  - functional genomics
  - determination of pharmaceutical targets
  - understanding complex systems

What do we want to find out?

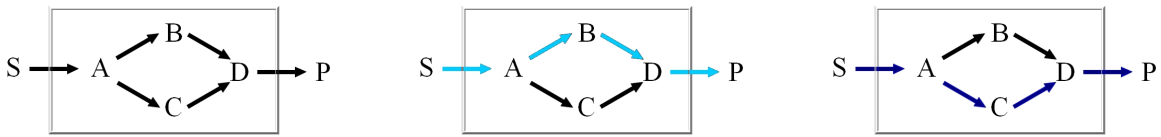
- Evolution of catalytic molecules
  - stepwise or patchwork or ... ?
  - preferred properties
- Evolution of complex biological networks
  - necessary conditions
  - knockout criteria
- Emergence of system-level properties
  - influences
  - dependency

Analysis of metabolic networks

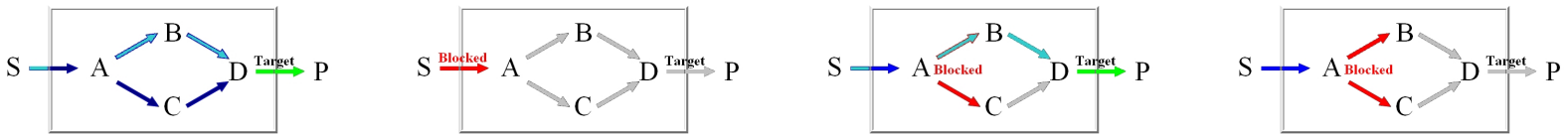
- Metabolic Pathway Analysis



- Pathway Distribution using extreme pathways



- Knockout Analysis using minimal knockout sets

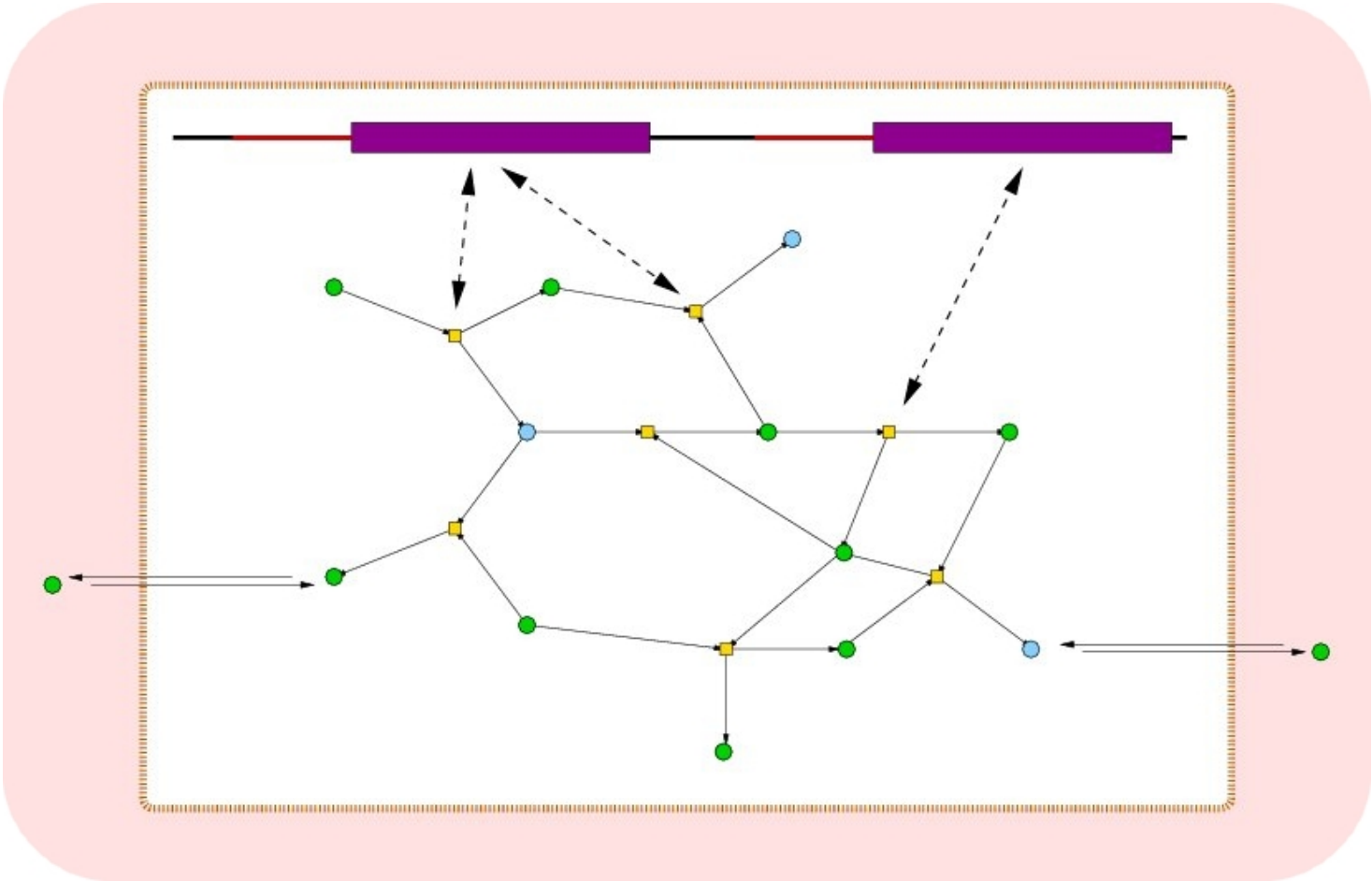


- Viable Conditions using the notion of biological organizations

Simulation of metabolic networks

- Limitation of a static-image approach
  - Knowledge horizon: common ancestor of modern cells
  - No Data before the emergence of a property
- Achievements of simulation approaches
  - Bonhoeffer: Evolution of connectivity; Cooperation vs Competition
  - Segovia: Preferential biochemical coupling of reactions vs Patchwork and stepwise evolution

Simulation - Overview



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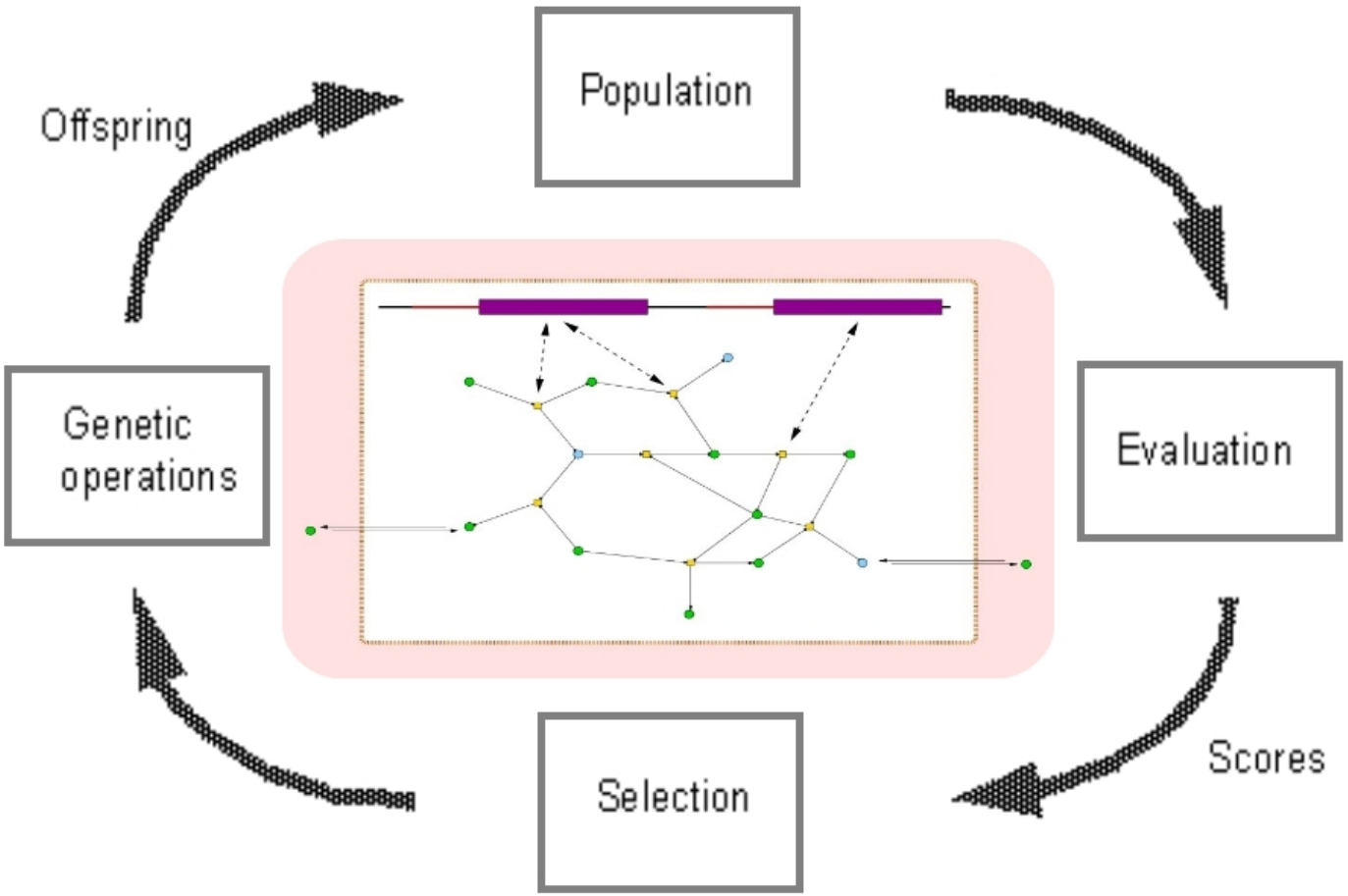
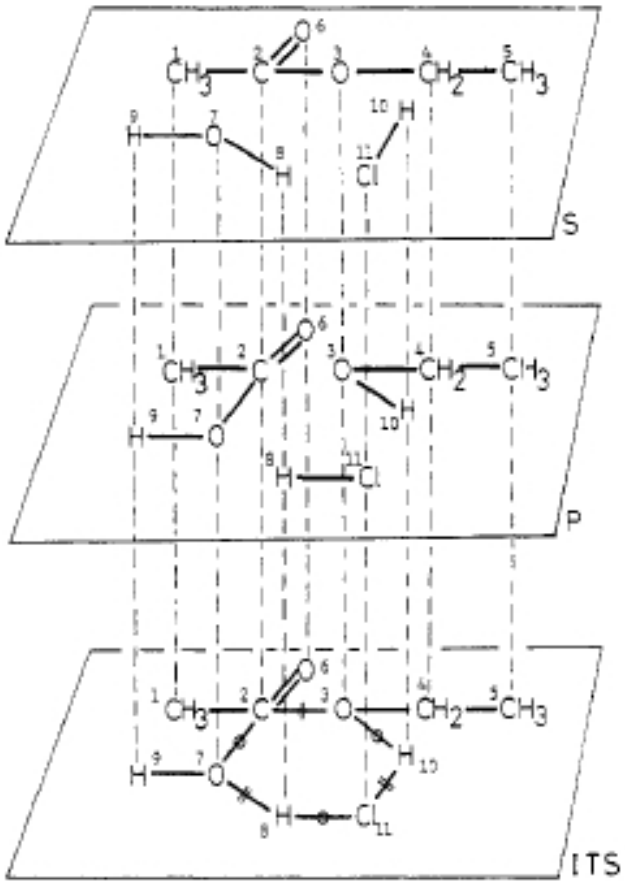


Simulation - Objectives

- Flexible
  - observation of different phenomenas
  - $\Rightarrow$ user-defined environment and chemistry
- Realistic
  - representations close to the real world
  - $\Rightarrow$ graph representations, RNA sequence to structure map
- Unbiased
  - existence of options for alternative solutions
  - $\Rightarrow$ different reactions, molecules, genetic operations
- Open-ended
  - emergence of new adaptive traits
  - increase in complexity
  - $\Rightarrow$ pushing the borders further (Outlook)

Model - Parts

- Genome
  - circular (random) RNA-sequence
  - Genes of fixed length
  - TATA-box
- Metabolism
  - bidirectional and bipartite graph
  - Nodes = Metabolite or Enzymes
  - Edges = Reactions
- Metabolites
  - Molecular-, Orbital Graph, SMILES or ID
  - Environment can be defined by user
- Enzymes
  - Transition State, Graph-rewrite Rule
  - Reaction-set can be refined by user



Model - Parts

- Evaluation
  - Metabolic Pathway Analysis
- Scores
  - Optimal metabolic yield
- Selection
  - Now: Yield
- Genetic Operations
  - Now: Mutation, Duplication
- Reproduction
  - asexual
- Protocol
  - Mutations, Phylogeny, MPA statistics, Network

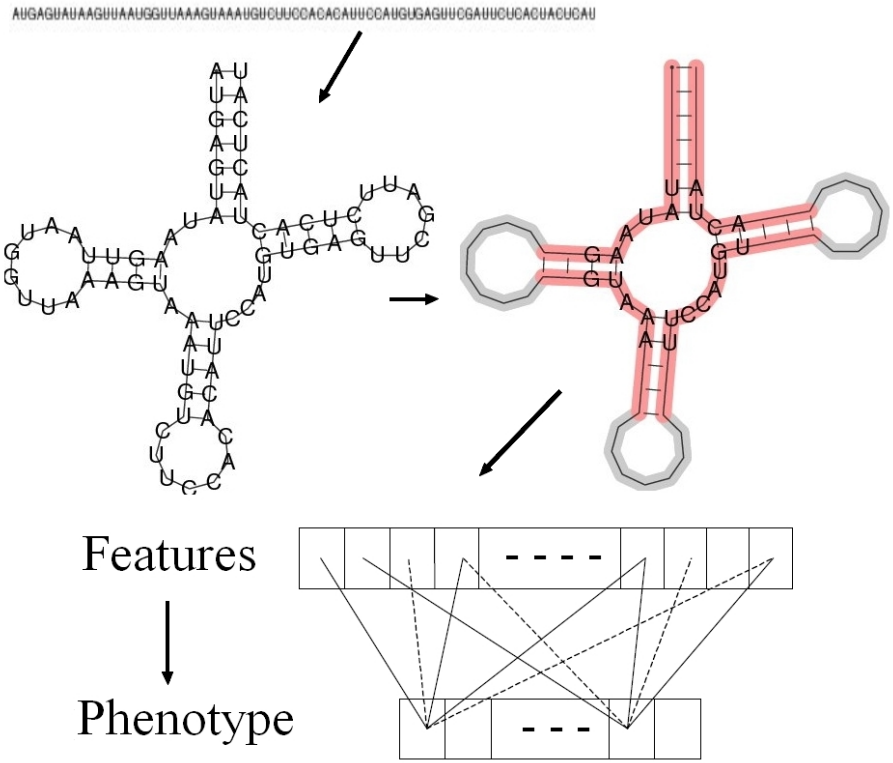
Mapping from Gene to Enzyme - Why?

- Evolution of catalytic elements
  - comparable to RNA or Protein folding
  - evolutionary steps (and influences) are traceable
- Redundancy
  - is abundant in real world systems
  - allows for evolvability AND robustness

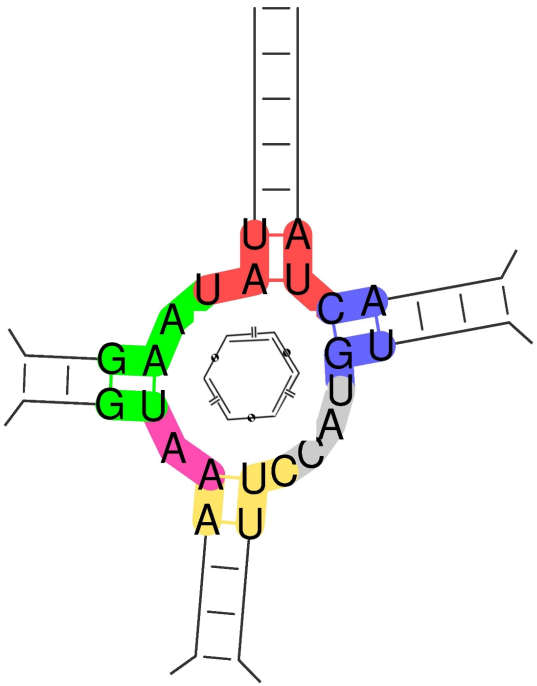
Mapping from Gene to Enzyme - How?

RNA-Sequence

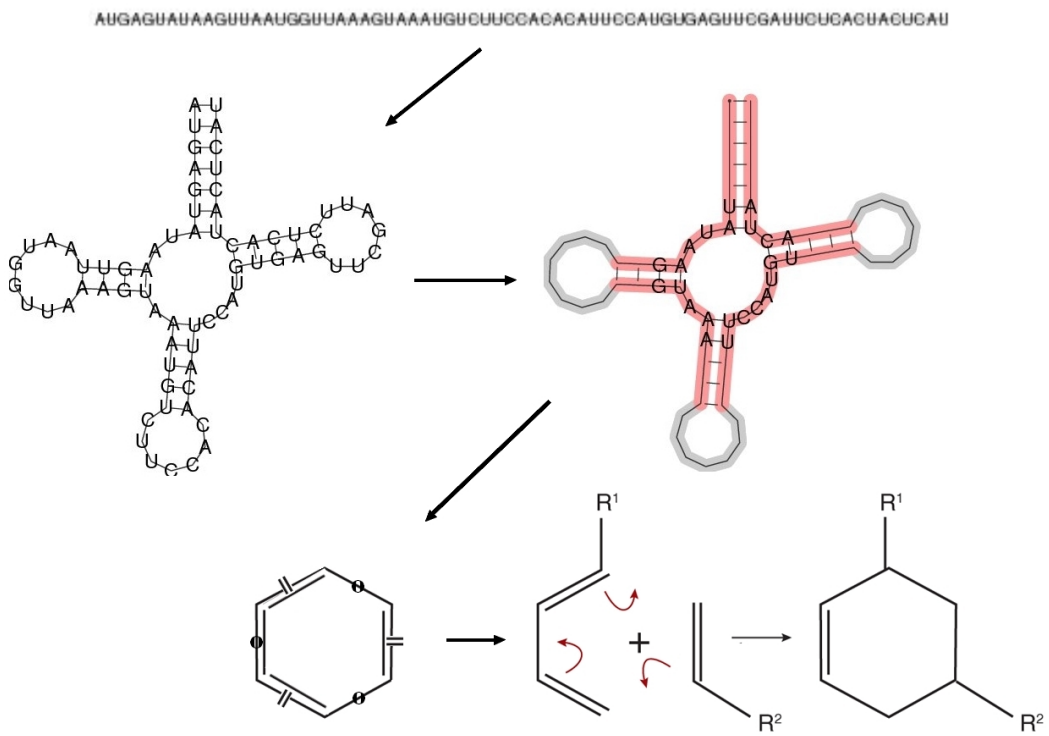
- RNA-Structure
- reduced Structure
- Features
- ITS ID
- ITS
- Graph-rewriting Rule



Mapping from Gene to Enzyme - Example

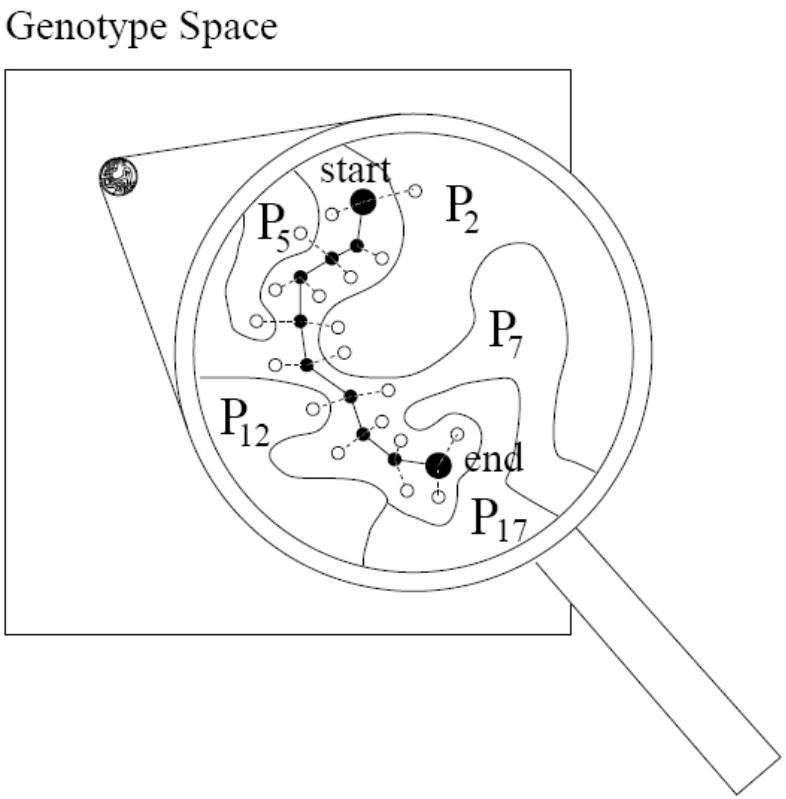


Section	Loop	C-G pair	Neighbor > 5 bp	**Bond**	Valence	Seq. (loop)	**Sequence**
1 (red)	yes	0	yes (+1)	**1** "–"	2	4	**4 = C**
2 (blue)	yes	1	no	**1** "–"	3	1	**3 = N**
3 (gray)	no	-	yes (+1)	**1** "–"	3	4	**4 = C**
4 (yellow)	yes	0	no	**0** " "	2	4	**4 = C**
5 (pink)	no	-	yes (+1)	**1** "–"	2	2	**2 = O**
6 (green)	yes	0	no	**0** " "	2	3	**3 = N**



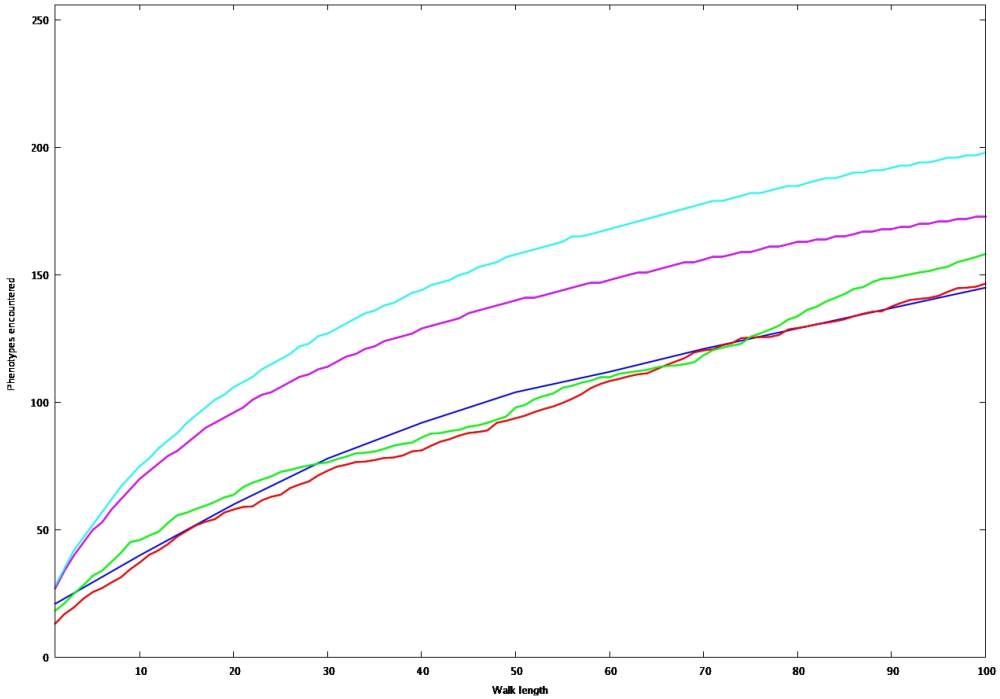
Mapping from Gene to Enzyme - Comparison

- Random neutral walk
  - 100 steps, 256 phenotypes
  - neutral mutations ⇒ robustness
  - encountered phenotypes ⇒ evolvability
  - neighboring phenotypes ⇒ innovation



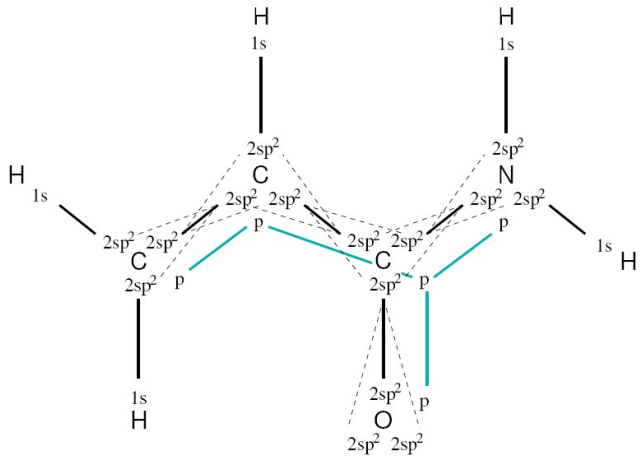
Mapping from Gene to Enzyme - Comparison

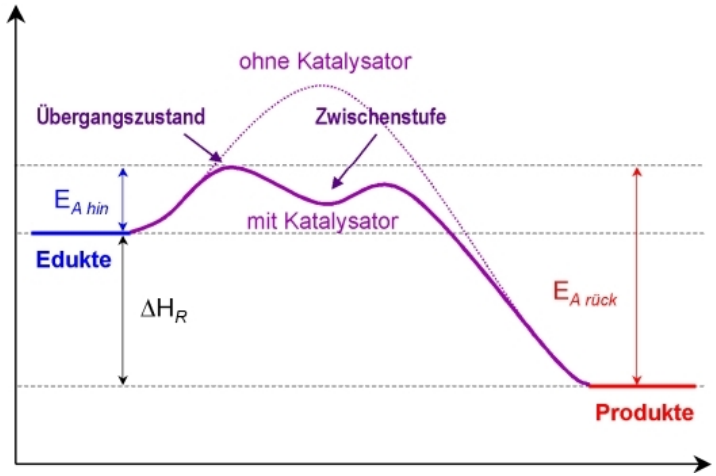
- Robustness
  - RNA:50% RBN:58% CA:42%
- Evolvability
  - RNA:198/256 RBN:149/256 CA:99/256
- Innovation
  - RNA:28 RBN:21 CA:14



Artificial Chemistry

- Now: Toy Chemistry
- In Process: Quantum Chemistry
- Task: Reaction Rate Calculation
  - Determination of Transition State Geometry
  - Energy Calculation for all three molecules
  - Calculation of Activion Energy





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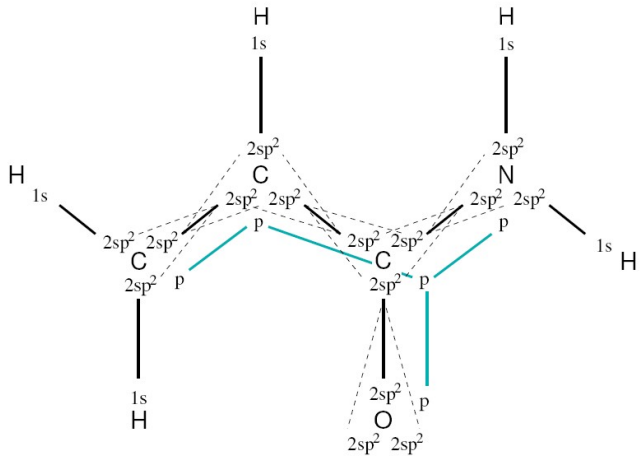

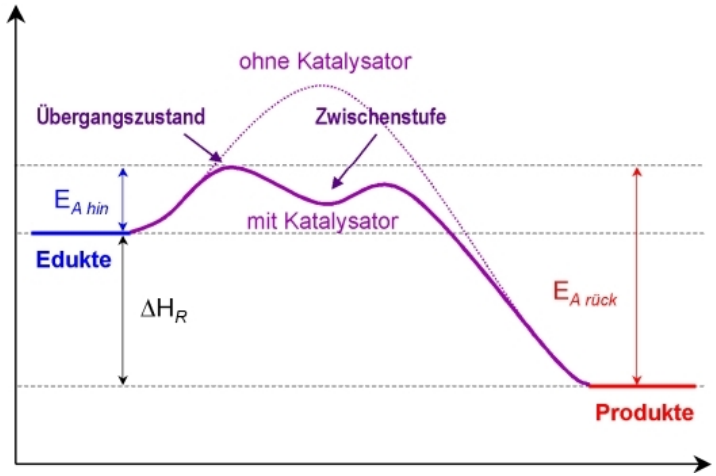

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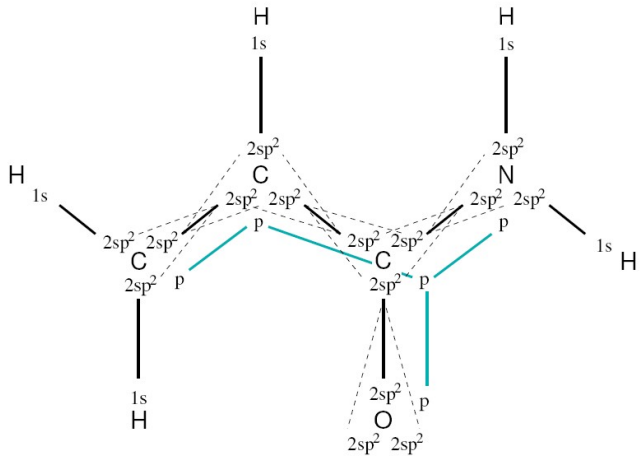
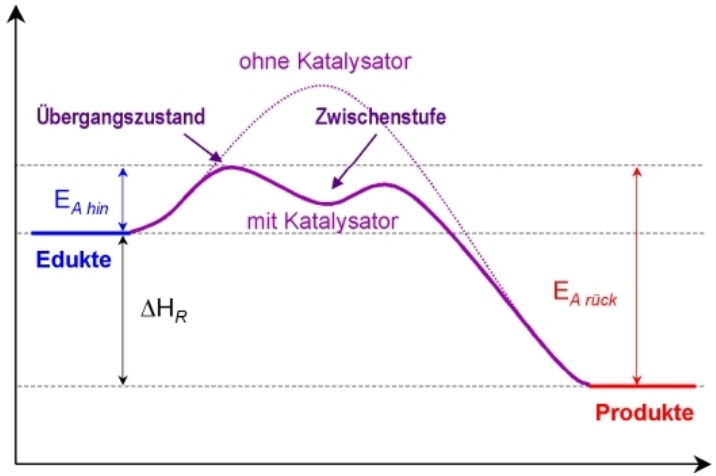
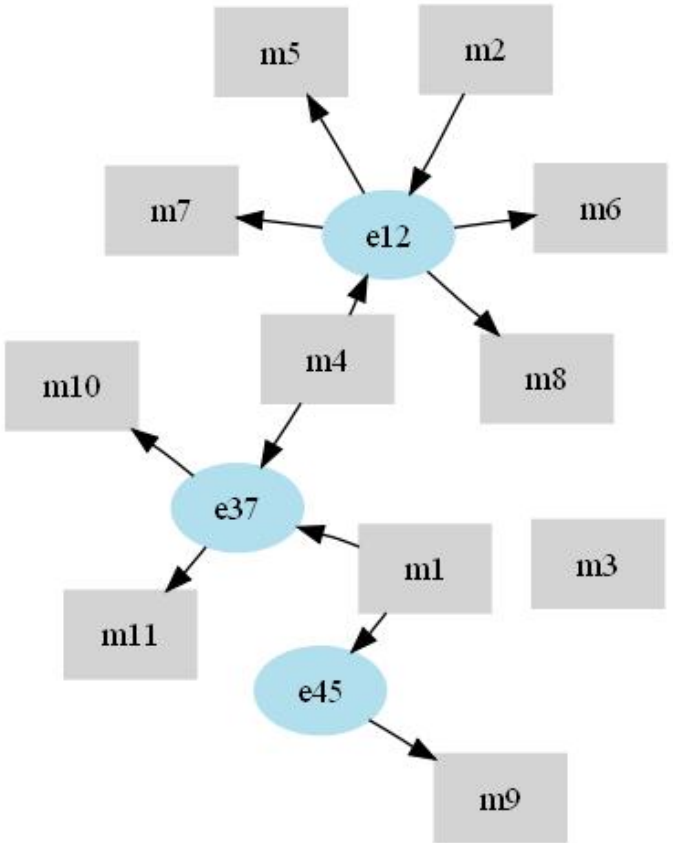




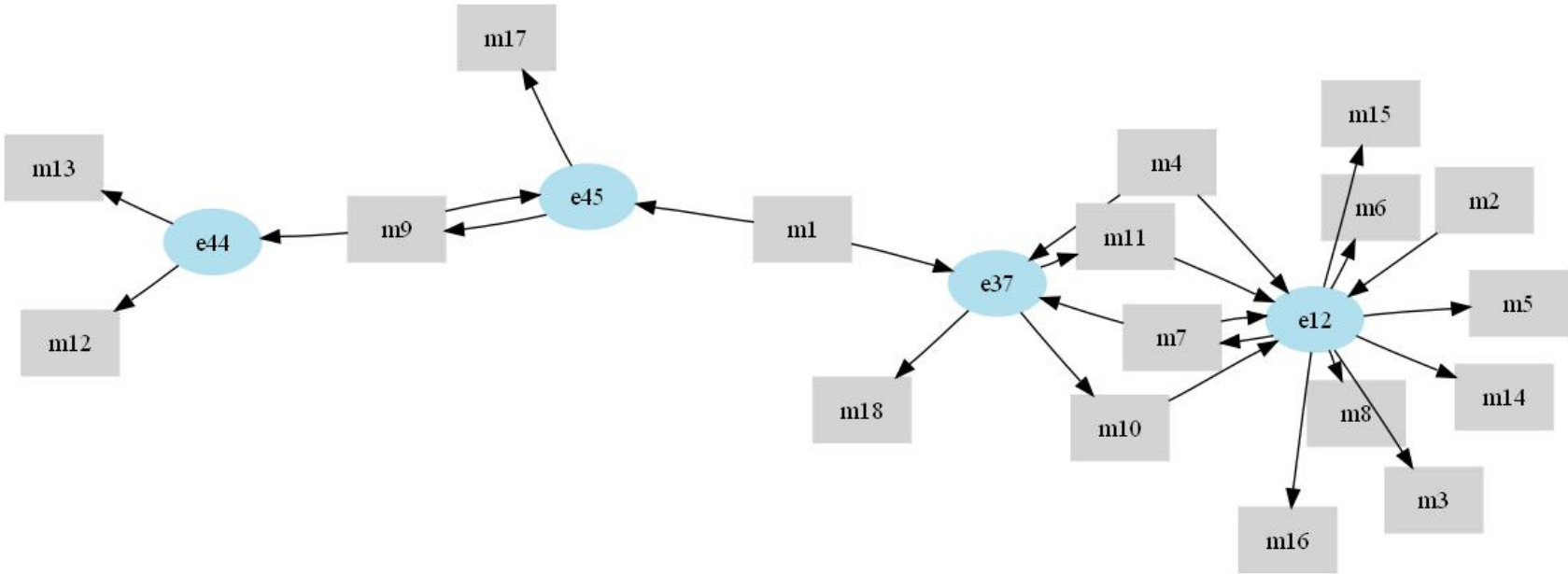
Results

- Metabolite Connectivity follows a power law distribution
- Highly connected Enzymes and Metabolites origin (mostly) from the first generations
- Robustness can emerge/evolve without selecting for it

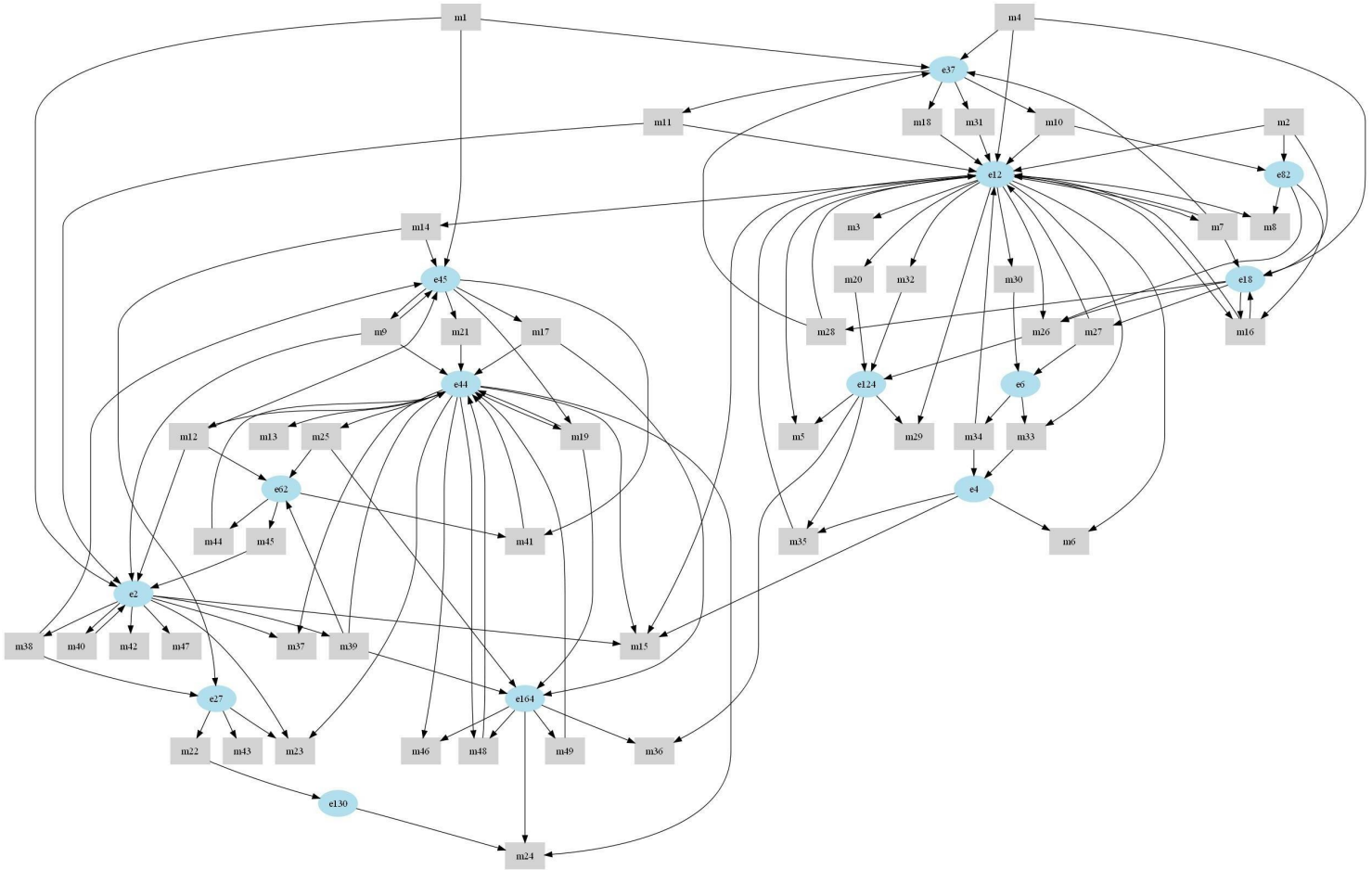
Results



Results


m17
m13
e45
m9
e44
m1
m12
m4
m15
m6
m2
m11
e37
m5
e12
m7
m18
m10
m8
m14
m3
m16

Results


m1
m4
e37
m11
m18
m31
m10
m2
e12
e82
m14
m3
m7
m8
e45
m20
m32
m30
e18
m9
m21
m17
m28
m26
m27
m16
e44
e124
e6
m12
m13
m25
m19
m5
m29
m34
m33
e62
e4
m44
m45
m41
m35
m6
e2
m38
m40
m42
m47
m37
m39
m15
e27
e164
m22
m43
m23
m46
m48
m49
m36
e130
m24

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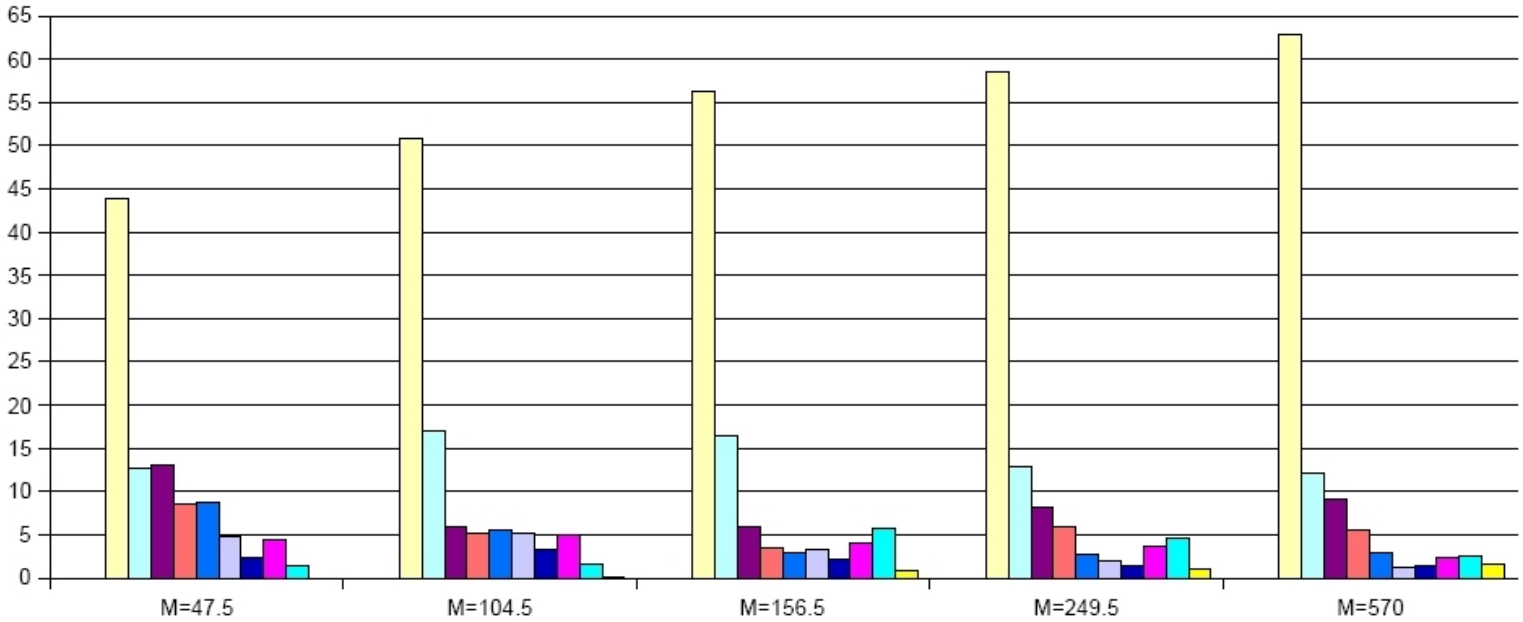


Enzyme	e37	e45	e12	e44	e18	e27	e6	e82	e4	e62	e124	e130	e2
Generation	1	1	1	2	3	3	7	10	14	42	44	51	53
Connectivity	4	5	12	9	4	2	2	2	2	2	3	1	6

Specificity of enzymes in the example network

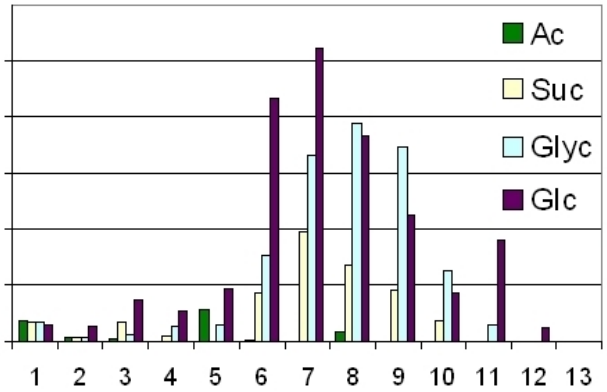
Ongoing Experiments

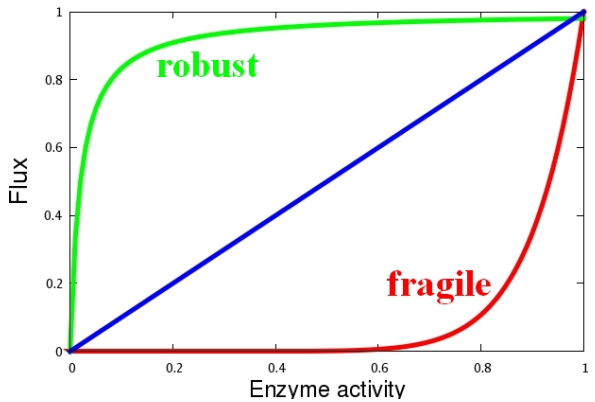
- Calculating different measures for robustness
  - Knockout set size distribution
  - Ratio between enzyme activity and the flux in the network
  - Elementary mode measures

$$R_1 = \frac{\sum_{i=1}^{r} z^{(i)}}{r \cdot z}$$

$$R_2 = \frac{\sum_i R_1^{(i)}}{n}$$

$$R_3 = \min\left\{R_1^{(1)}, R_1^{(2)}, \ldots, R_1^{(n)}\right\}$$

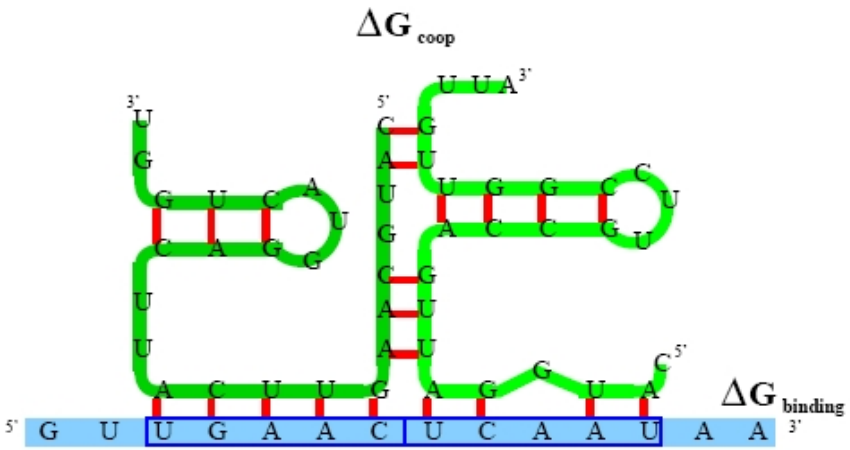


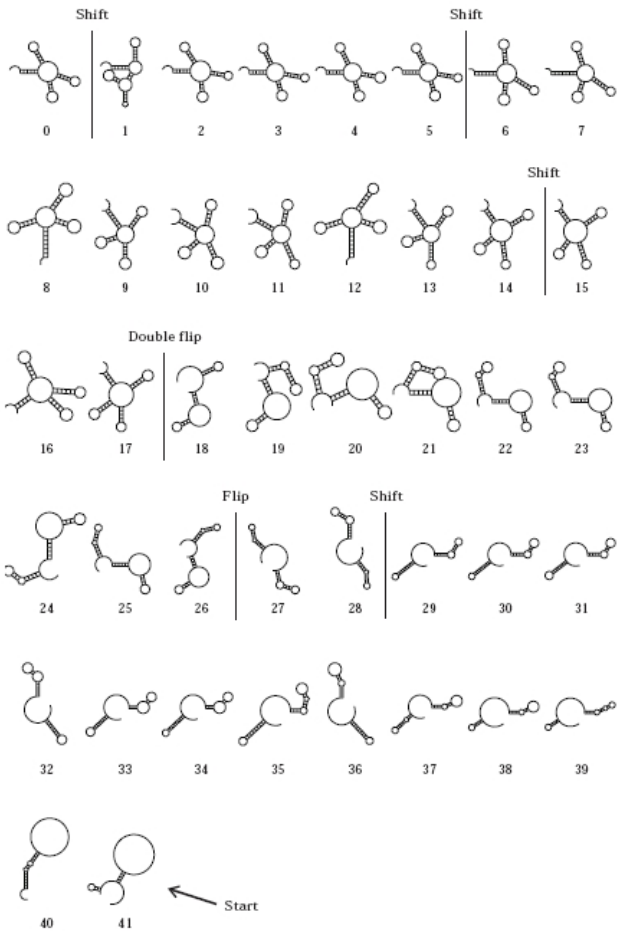


- The Role of ineffective parts of the Genome
- Determining good kinetic parameters (reaction rates)

Future Objectives

- Study of the catalytic molecules
  - major transitions in the evolution
- Regulatory Elements/Network
- Interaction between cells
  - Competition vs Cooperation
  - Additional modes





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You for listening!