A Graph Grammar for Modeling RNA Folding

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GaM 2016 Eindhoven, Netherlands

April 3, 2016

Outline

Graph for Modelling Complex Biological Systems

Complex biological systems are made of a number of components that interact with each other in a nonlinear fashion.

It is necessary to understand the interaction between components and pathways.

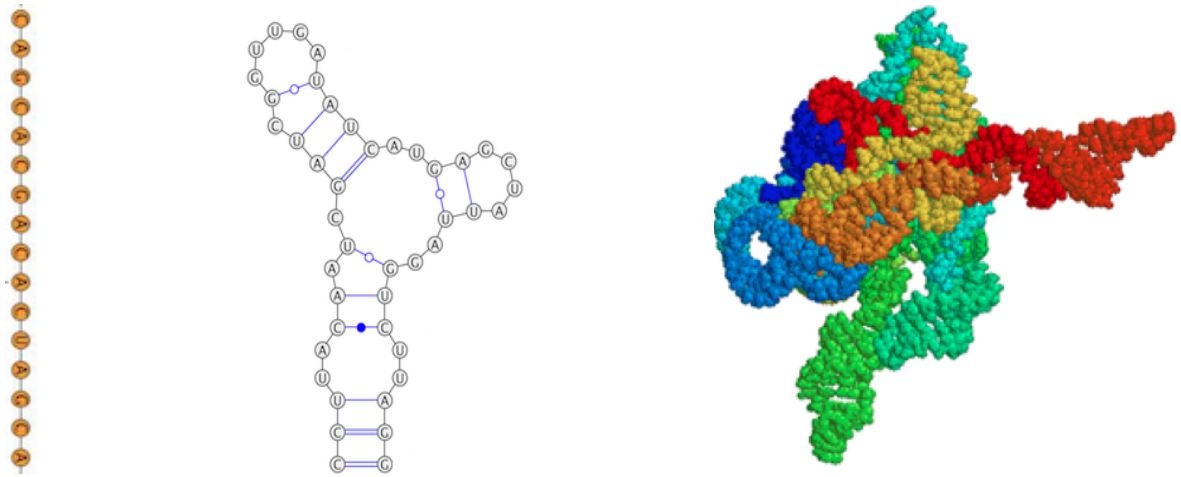
Graph can be applied to modeling complex biological systems.

The elements of a system are represented as vertices of a graph and the interactions between them are represented as edges.

Graph algorithm can be used to analyze, simulate and visualize the system.

RNA: as a Graph

RNA naturally exhibits auto-regulative mechanism that continuously triggers sequences of foldings until stable folding is attained.

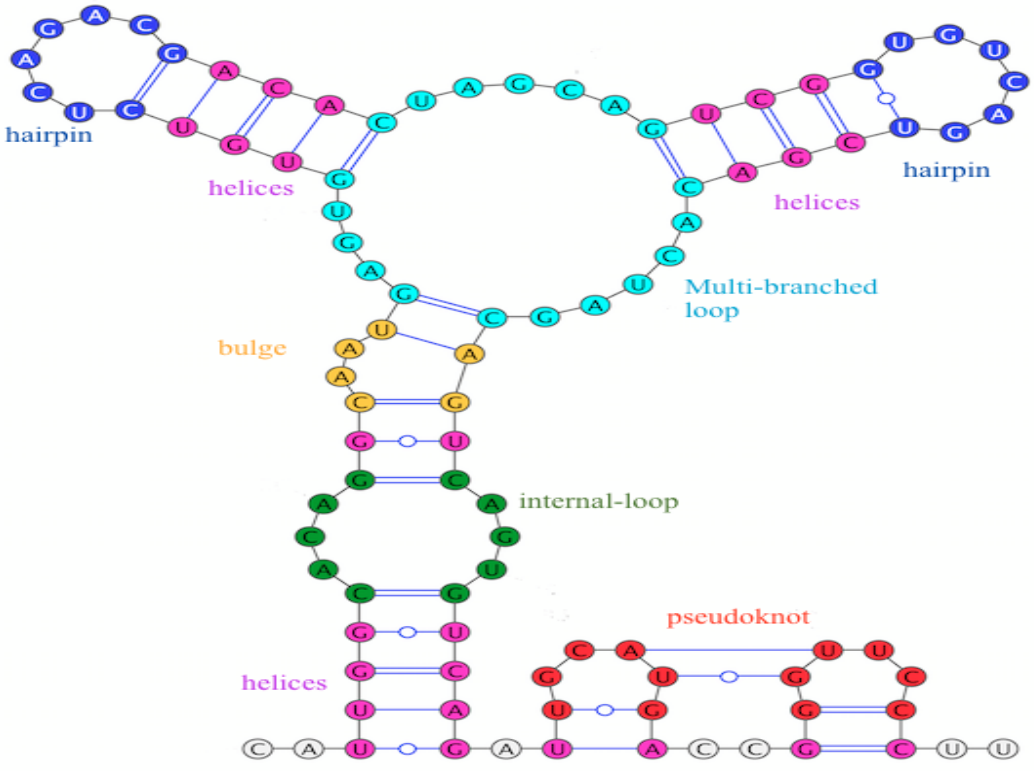


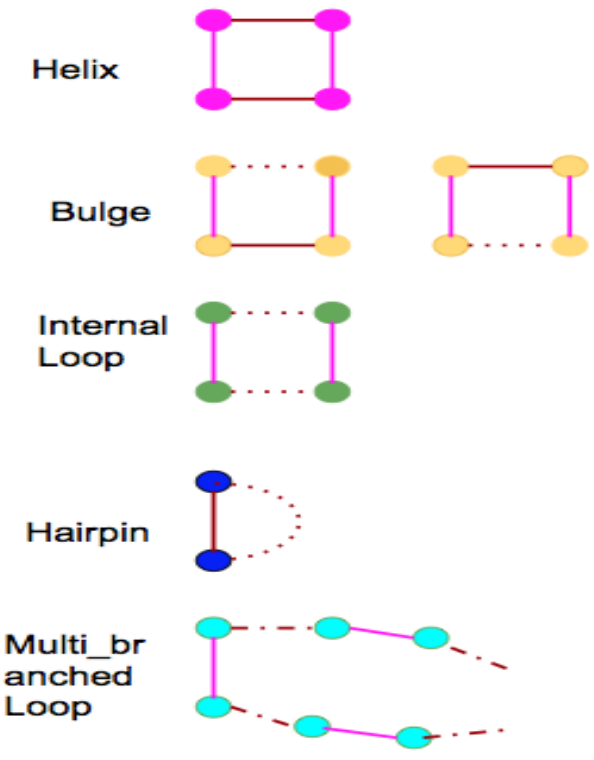
RNA folding can be regarded as a hierarchical process in which secondary structure (SS) forms before tertiary structure.

SS formation is due to nucleotide base pairings, namely Watson-Crick (C-G and A-U) and Wobble (G-U).

RNA SS Sub-Graphs

The structure of RNA can be regarded as a conformation with various local elements (sub-graphs), called structural elements.





SSs can be distinguished as pseudoknot free and pseudonotted.

Why RNA Prediciton

RNA plays a central role in:

- Protein synthesis
- Enzymatic catalysis
- Genome organization

Predicting RNA SSs is important for inferring structure-function relationship of RNA molecules.

Approaches Used

The optimal (minimum free energy) RNA secondary structure can be determined

- Experimental techniques: X-ray, crystallography and NMR
- Computational methods: dynamic programming and comparative sequence analysis

Predicting pseudoknot free structure is inaccurate [Lorenz et. al., 2016] and predicting pseudoknotted structure is NP-complete [Lyngsø et. al., 2000].

Moreover, it is still an open question to what extent the functional structures of natural RNAs are determined by folding kinetic than by the optimal one [Flamm et. al., 2008].

Study Aim

RNA molecule exhibits:

- Dynamical behaviour
- self-adaptability behaviour

We devise a new approach based on:

- Graph transformation
- S[B]-paradigm

Graph Transformation

It has been used in computational biology in different contexts:

- Employed to model the evolution of developmental pathways [Benk et. al., 2004]
- Used to encode RNA tertiary structure motifs [St-Onge et. al., 2007]
- Gene expression was simulated using a general purpose graph rewriting system [Schimmel et. al., 2009]

An RNA primary structure is represented as a graph and its folding evolution as a graph transformation in the folding space.

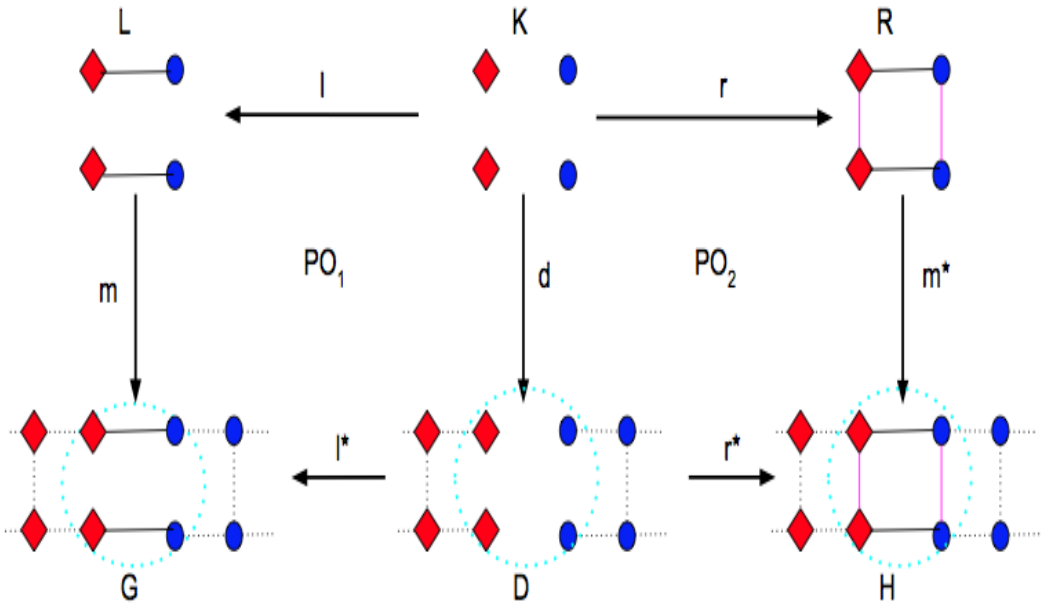
RNA Graph Grammar and Transformation

DPO is used to model RNA folding evolution.

RNA graph grammar:

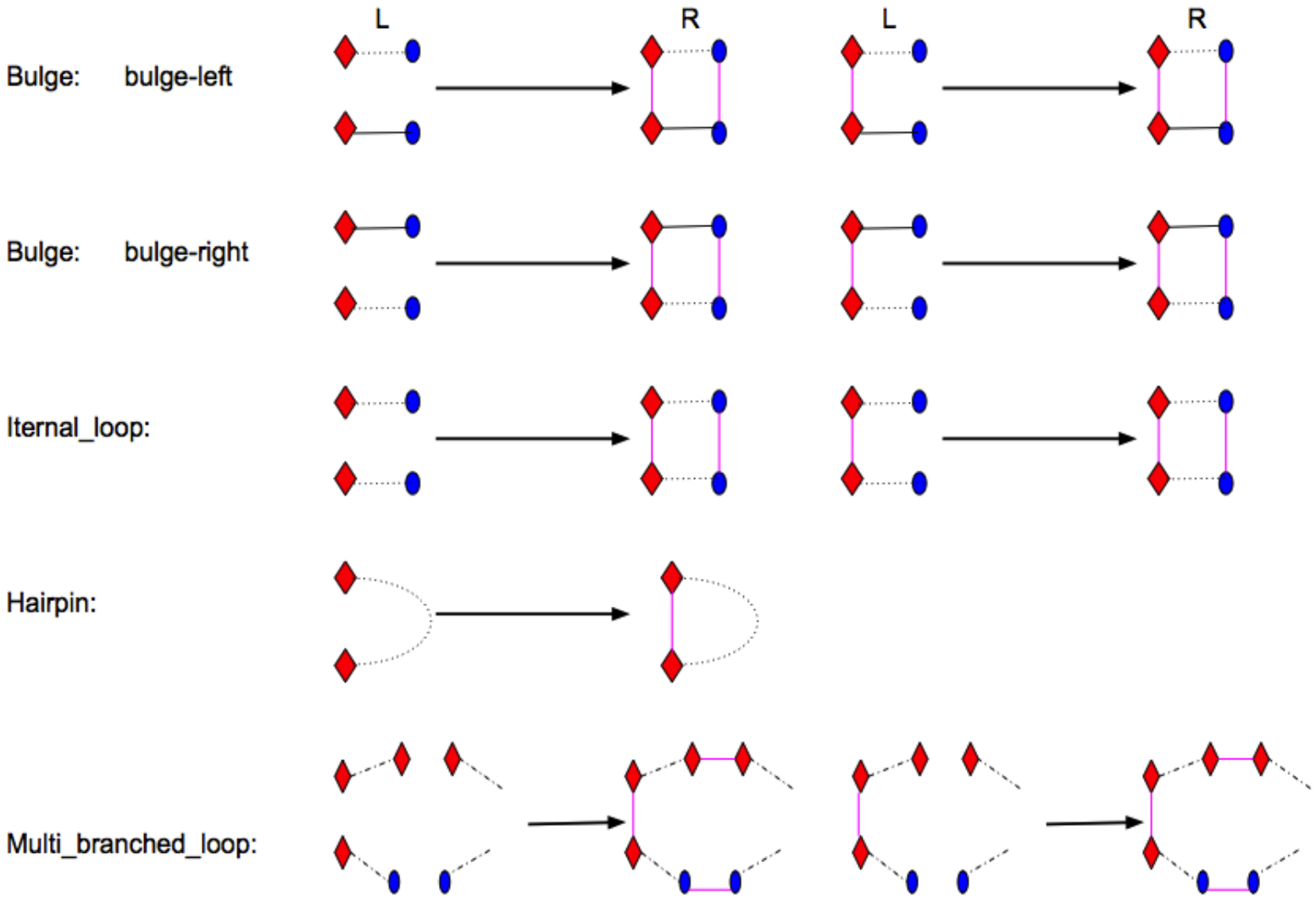
$$G_{RNA} = (\{p : L \leftarrow K \rightarrow R\}_{p \in P}, G_0)$$

p $(Helix - 1)$:



RNA Graph Grammar...

Production rules:



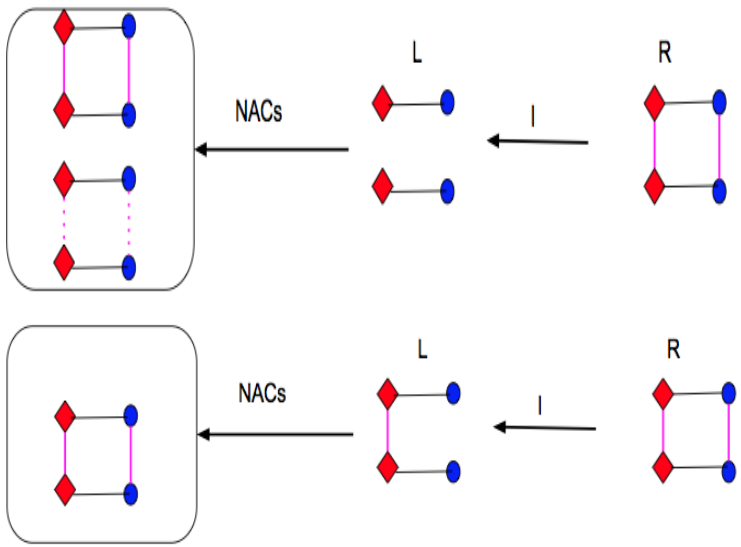
Negative Application Conditions

DPO rules are applicable whenever there are a valid matches for their LHS.

Only G-C and A-U (Watson-Crick) and G-U (wobble).

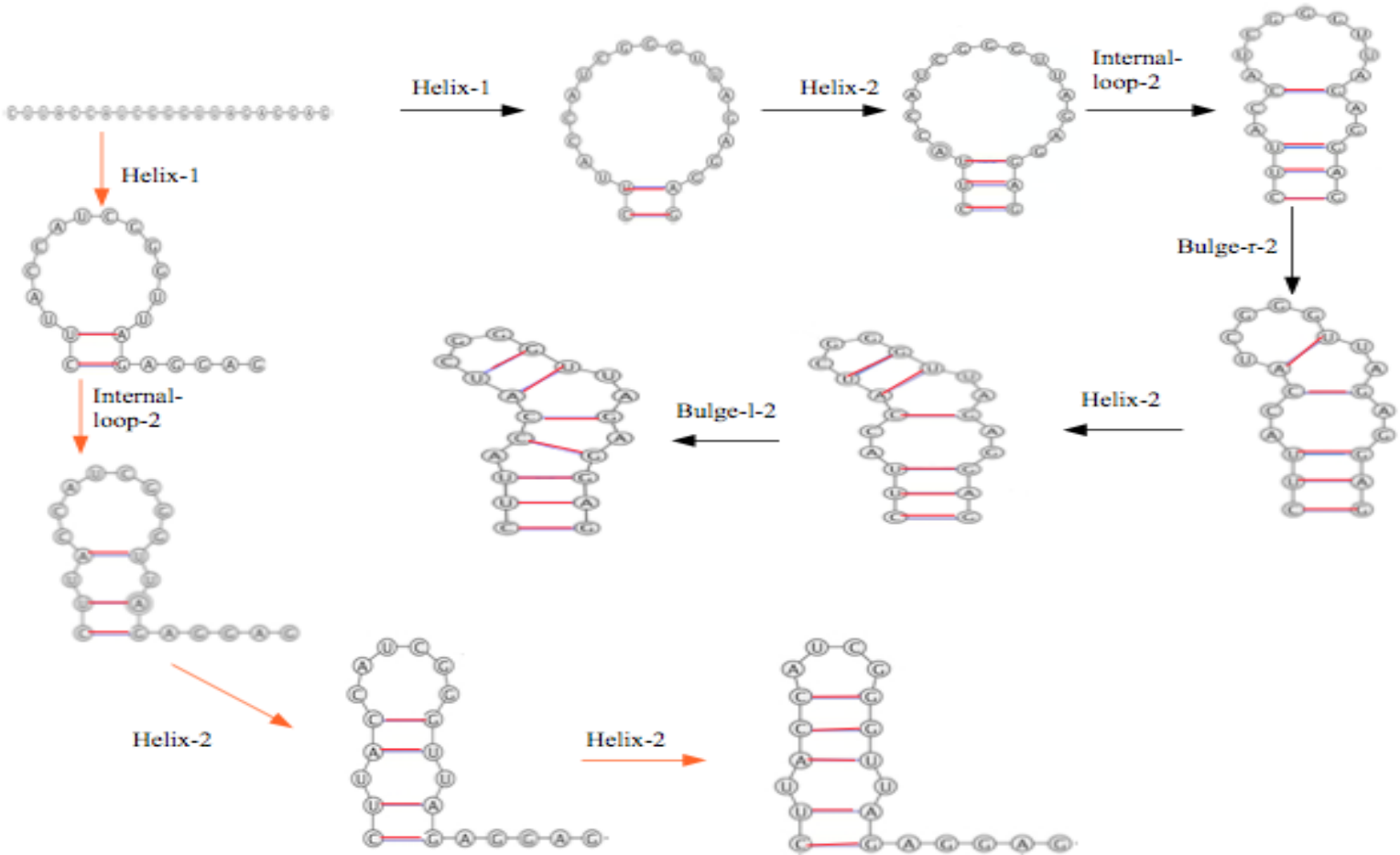
The application of the rewriting rules must take into account a NAC:

- Each nucleotide can form a base pair by interacting with at most one other nucleotide.



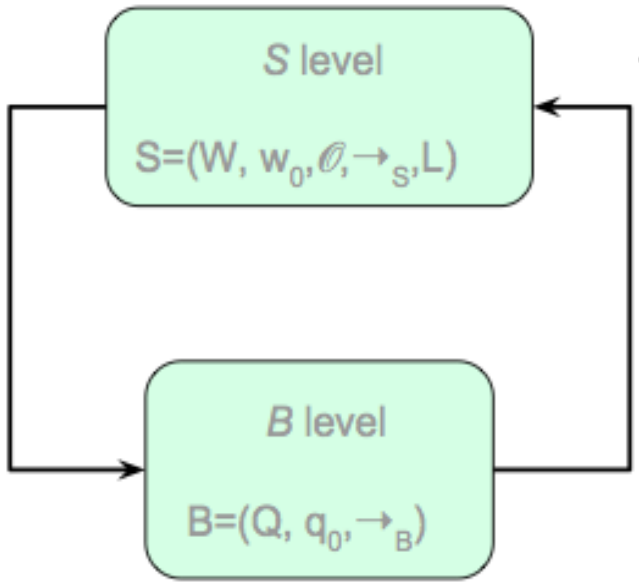
RNA Folding as Graph Transformation: a toy example

Two possible folding transformations of an RNA molecule with 21 nucleotides



S[B] Paradigm: an Overview

A computational model for self-adaptive systems with two coupled levels.

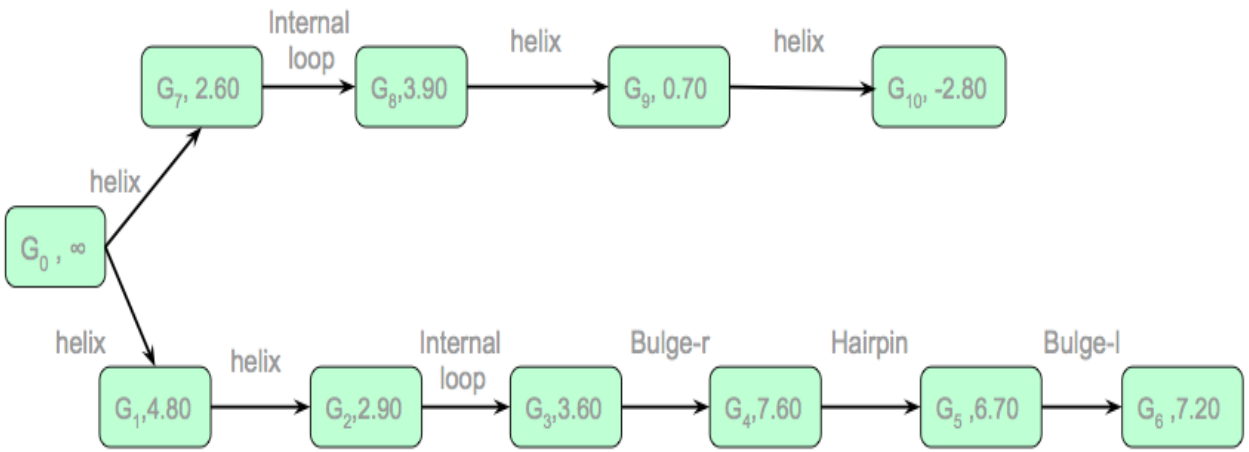


- B (behavioural level): describes the admissible dynamics of the system
- S (structural level): accounts for global and stable features of the system, also regulates B.

RNA Folding Process as a Self-adaptive System

RNA folding is presented as a graph rewriting for which the dynamics is defined by a set of rewriting rules.

A Labelled Transition System (LTS) is constructed with graphs as states and rule application as transitions:



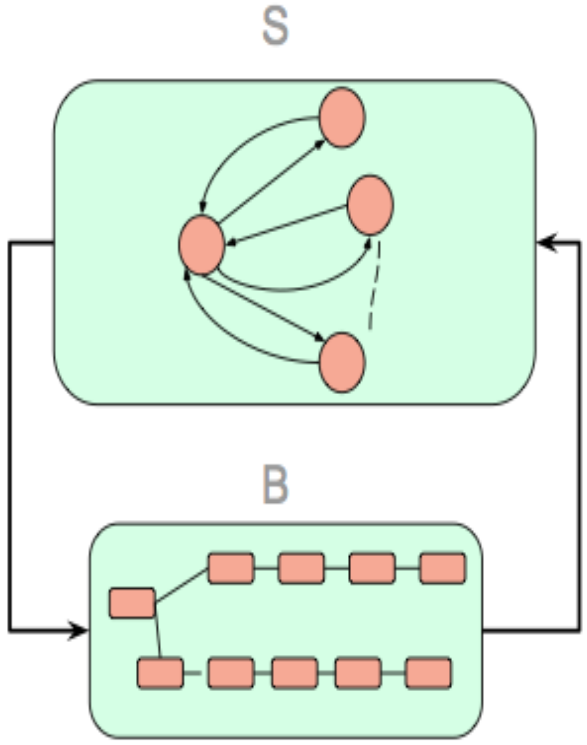
At each state in the LTS the value of the free energy is called the observable value.

RNA Folding Process as a Self-adaptive System

We use the LTS defined above as the B level of an S[B] model.

For the S level we use the state machine.

Each state of S level is associated with a constraint over the observable variables (free energy) of the B level.



RNA Folding Process as a Self-adaptive System

The S-level impose constraint on the states of B, i.e., q:

Constriant

$$\phi_0 = \exists q_{\text{next}} \in \text{next}(q) : \mathcal{O}(q_{\text{next}}) \leq \mathcal{O}(q) \wedge (\forall q' \in \text{next}(q) : \mathcal{O}(q_{\text{next}}) \leq \mathcal{O}(q'))$$

Where:

- q is the current state of the B level
- $\mathcal{O}(q)$ is the observable value associated to q
- $\text{next}(q)$ a function giving the successors states of q in B

How the Adaption Works

The adaption is triggered whenever q cannot evolve because there is no next B state that satisfies the current S constraints.

During adaption, the S[B] system attempts to evolve towards a new B state that satisfies a new S state, chosen among the successors of the current one.

Adaption terminates successfully when B ends up in a state that fulfils the new global situation (free energy) represented by one of the admissible S states.

Issue of Scalability

An RNA sequence of n nucleotides has $\approx \quad 1.8^n$ possible SSs [Zuker et. al., 1984].

Attempting to explore the complete folding space of RNA SS is computationally expensive.

Approaches used to handle scalability issues:

- Dynamic programming: explores the RNA SS space to find the lowest free energy structure without explicitly generating all possible structures.
- A stochastic simulation, described as a continuous time Markov process, used to handle the RNA folding kinetics.

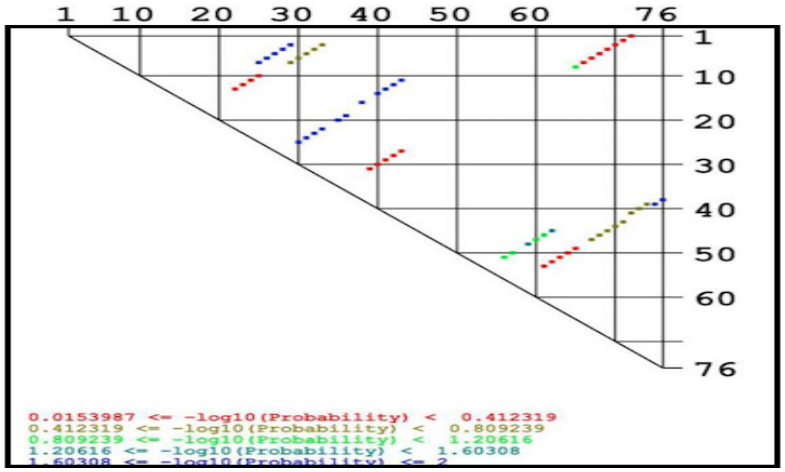
Issue of Scalability

Possible scenarios:

- Graph Transformation:
  - Stochastic graph transformation: a rule with lower energy would be more likely to be applied than a rule with a higher energy
  - Use rules with more probable base pairs.
- State space Exploration:
  - guided greed search algorithm: guided depth first search.

Future Work

- Exploit the partition function of RNA folding space to identify the replacement graph with the more probable base-pairs.



- Check whether parallelism, concurrency and bisimulation theorems are still valid in case of RNA folding.

Acknowledgement

Our study is financed by the European project: TOPology DRIven Methods for complex systems (TOPDRIM) - FP7-ICT/ICT-2011.9.7.
http://www.topdrim.eu

The goal of this project is to provide methods for describing the dynamics of multi-level complex systems based on topological data analysis.

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Thank You!