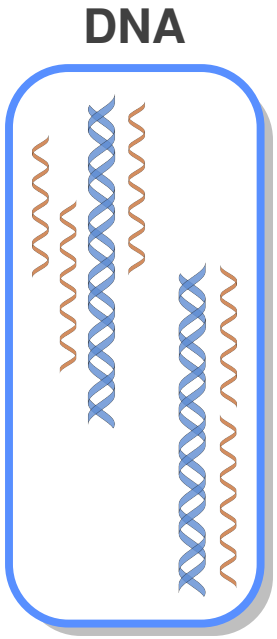



AMIB(io): **A**lgorithms and **M**odels for **I**ntegrative **Bio**logy

Team AMIBio
Inria Saclay IdF
CNRS UMR 7161 LIX

November 17, 2017

Biological context and history



Algorithms and **M**odels for **I**ntegrative **B**iology

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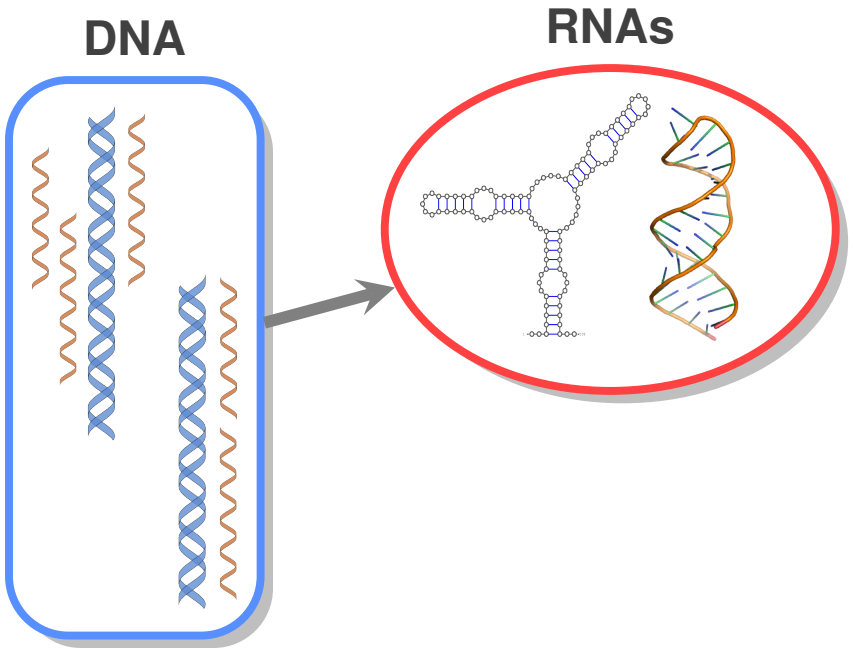

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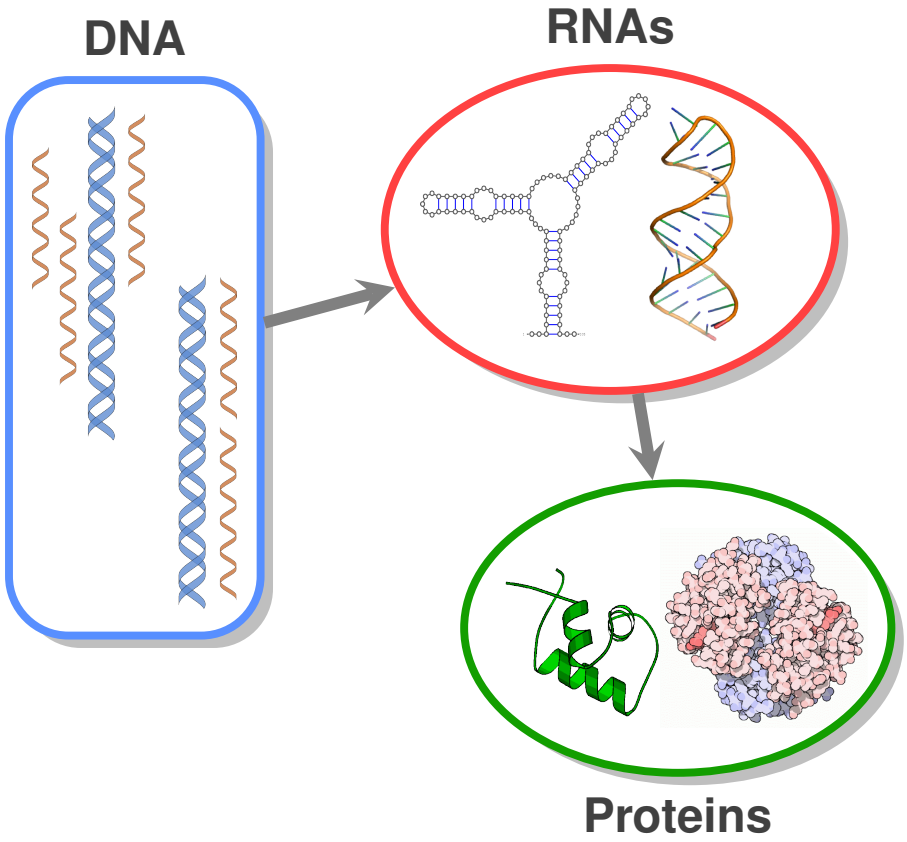

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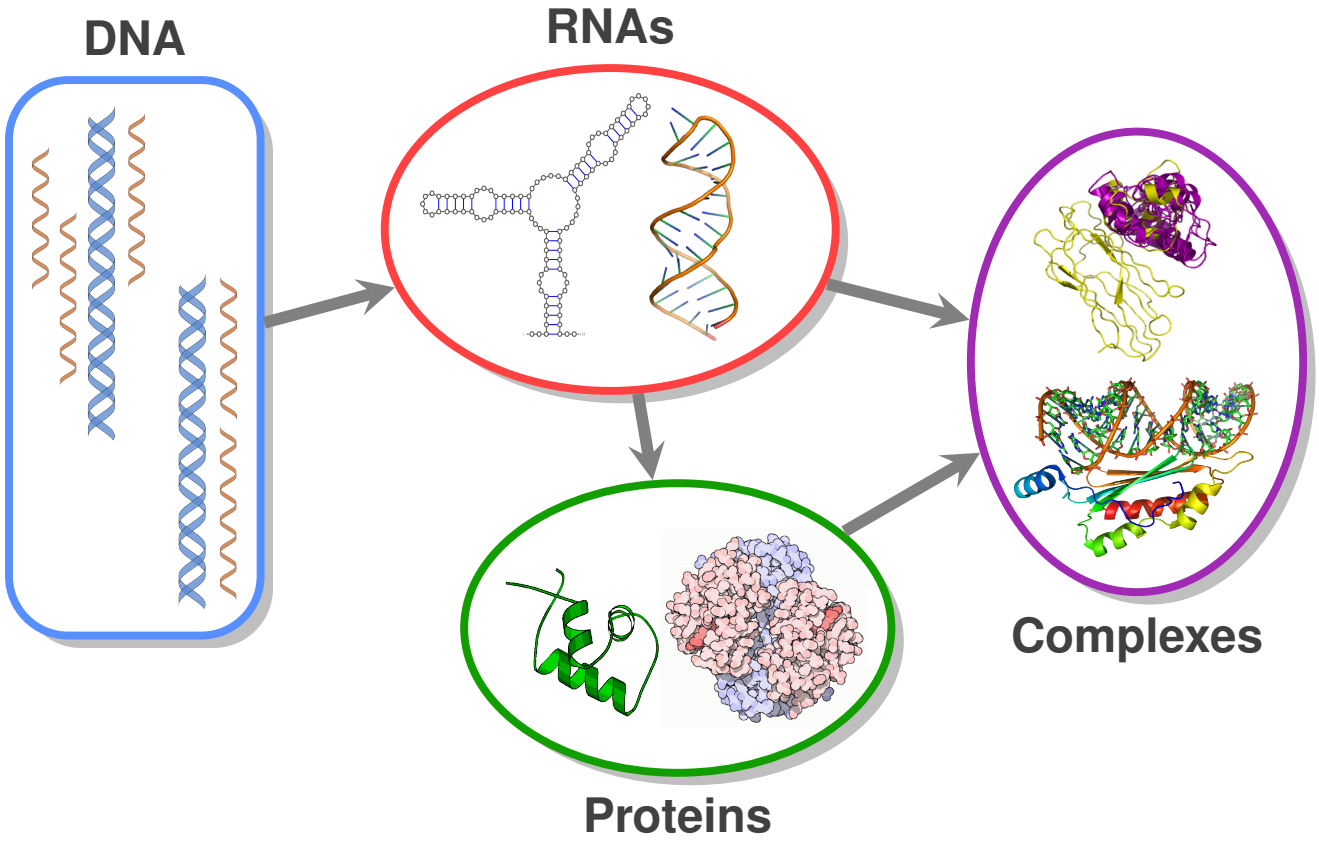

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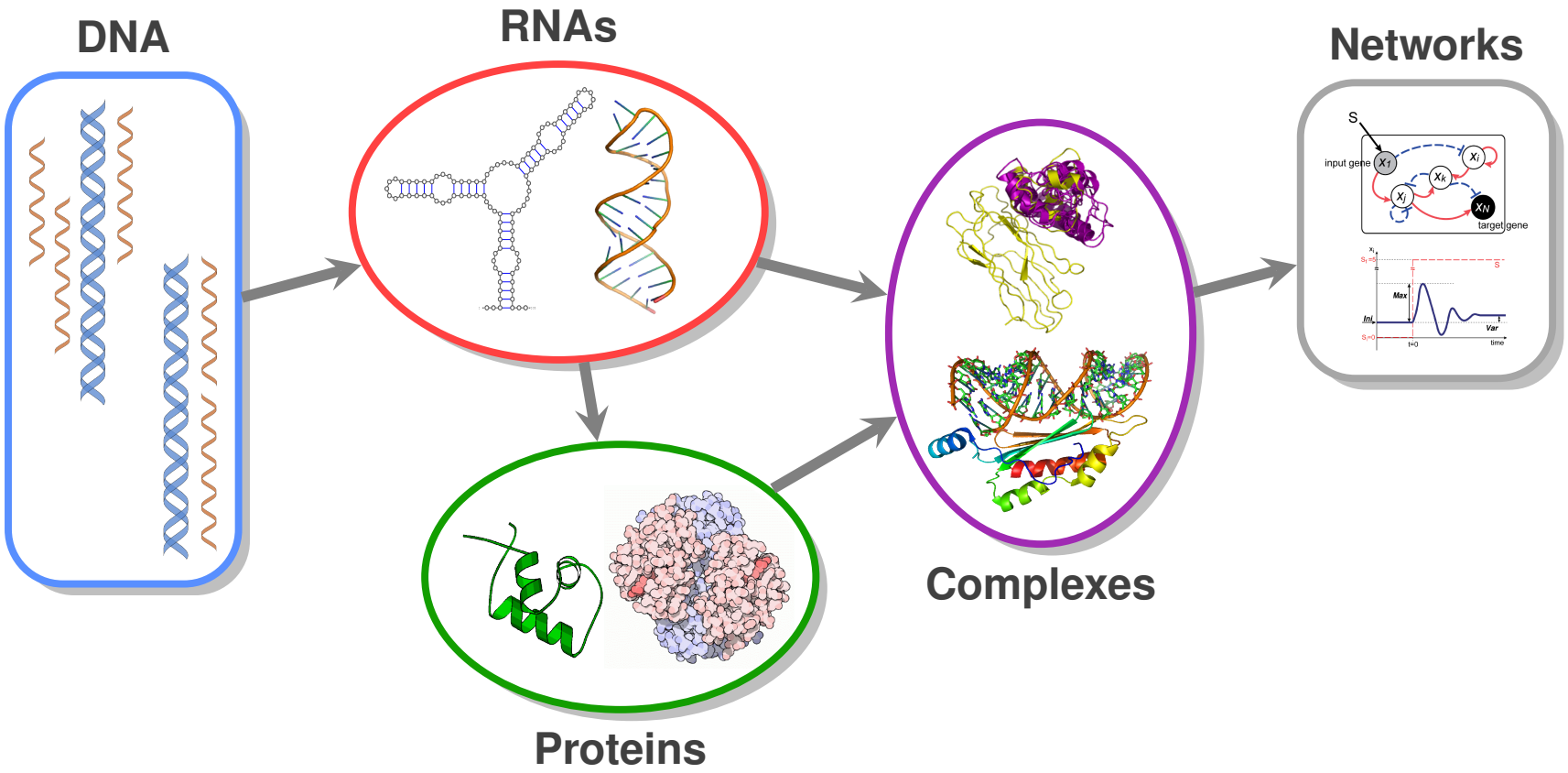

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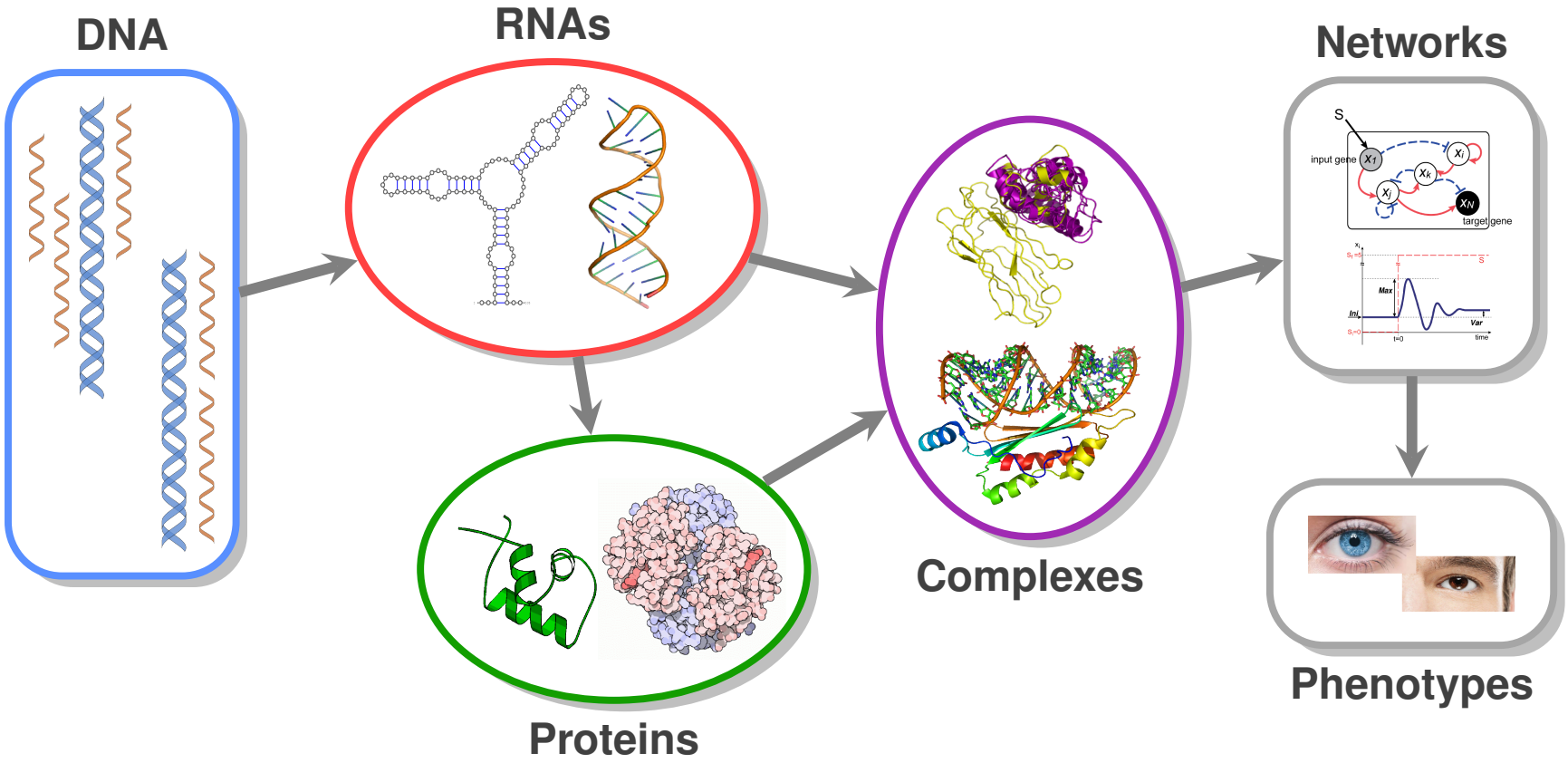

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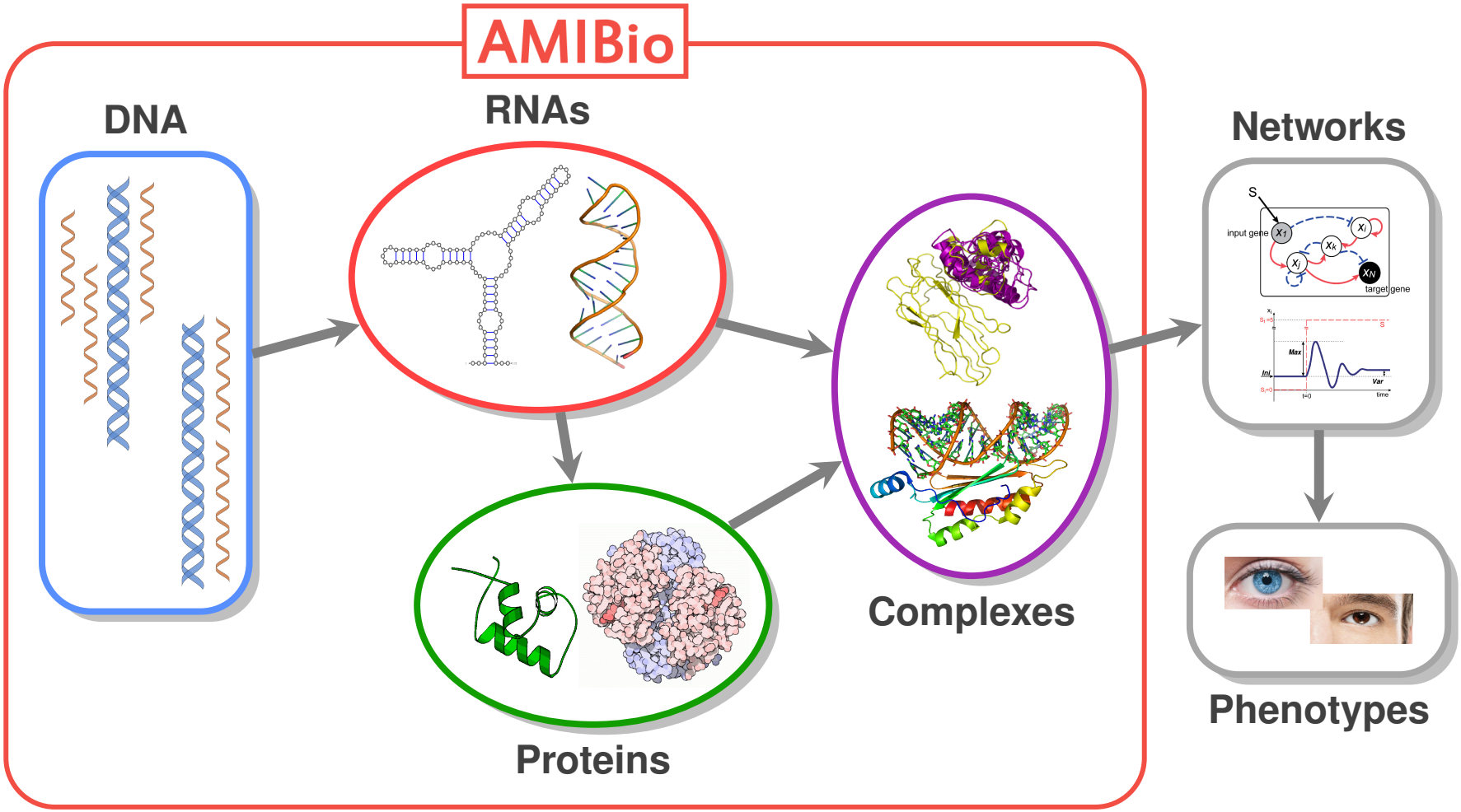

Algorithms and **M**odels for **I**ntegrative **B**iology

Team Members

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(Aemeritus)

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Evelyne Rayssac
(Admin. staff)

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Associate

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Amélie Héliou – 2014
Wei Wang – 2014
Juraj Michalik – 2016

Afaf Saaidi – 2015
Antoine Soulé – 2014
Ha Nguyen Ngoc – 2017
Pauline Pommeret – 2017

Computational Challenges and Methods

AMIBio's Methods:

- Stringology
- Dynamic Programming
- Formal Languages
- Random Generation
- Graph Theory
- Probabilistic models
- Analytic Combinatorics
- Clustering
- Complexity Theory
- Game Theory
- Kinematics
- Computational Geometry

Some challenges:

- What are the active conformation(s) (2D&3D) of a molecule?
- What is the impact of genomic mutations at a structural level?
- Are there structured transcripts within an HTS dataset?
- Can we characterize the kinetics of biopolymers?
- How to predict the geometry of complexes?
- How to design functional molecules using *rational* principles?

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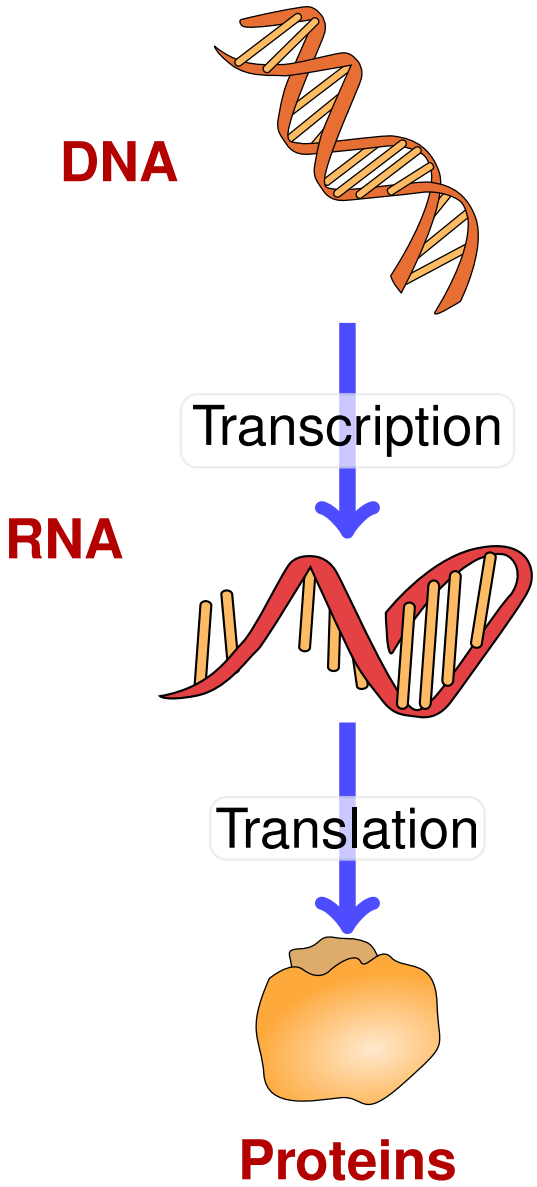
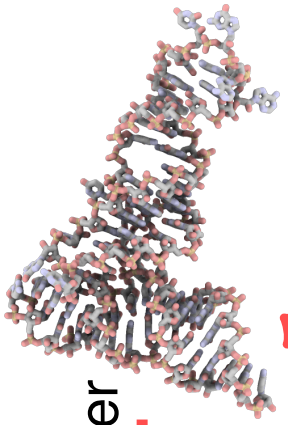
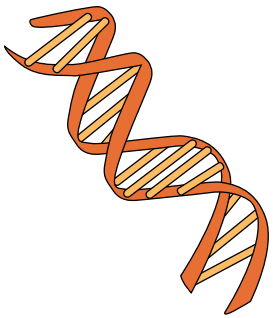
Fundamental *dogma* of molecular biology



Fundamental *dogma* of molecular biology (v2.0)



DNA



Carrier

Transfer

Transcription

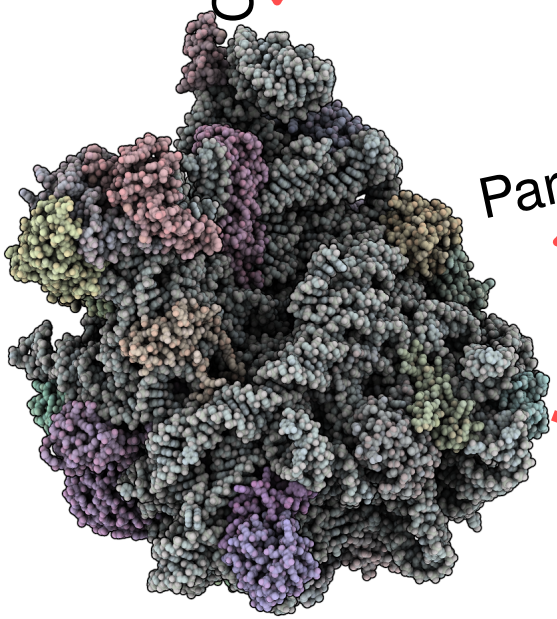
Maturation

RNA

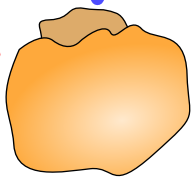
Participates

Regulation

Translation



Synthesis

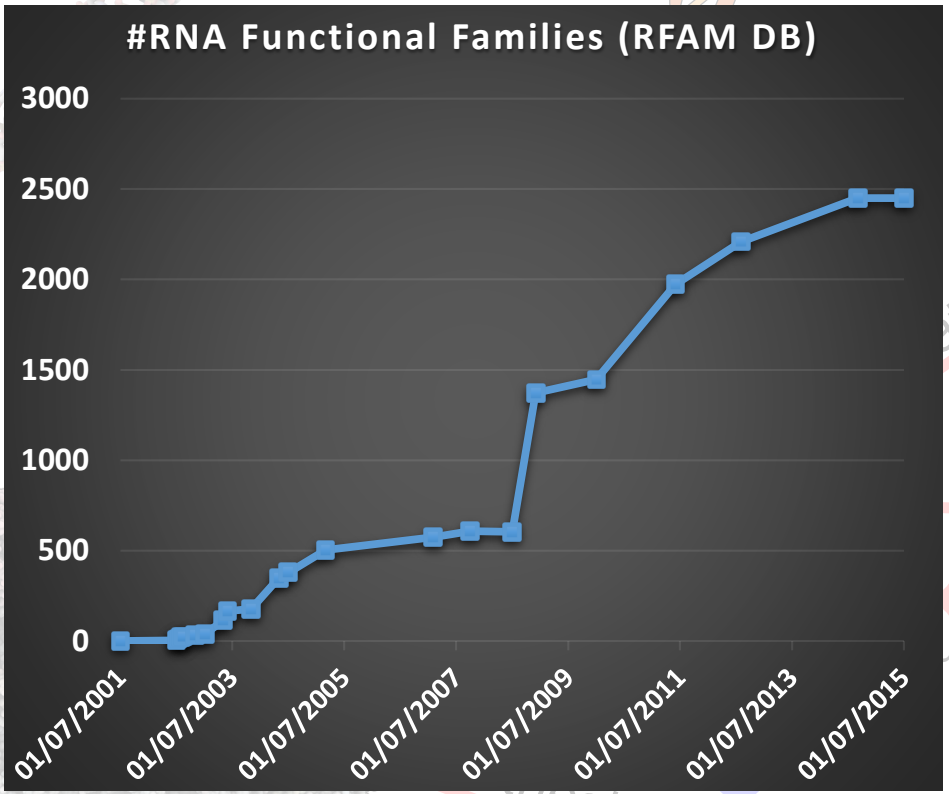


Proteins

RNA functions

- Messenger
- Translation
- Regulation
- Enzyme
- Catalytic
- . . .

Fundamental *dogma* of molecular biology



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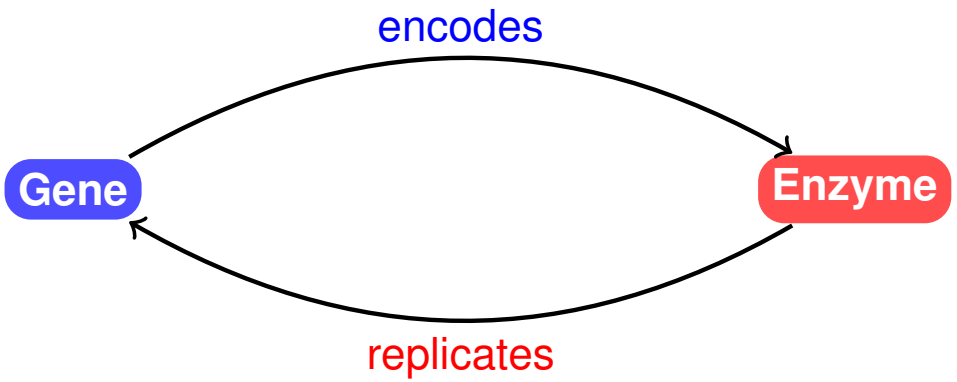
Proteins

RNA world: Solving the *chicken vs egg* paradox at the origin of life. . .

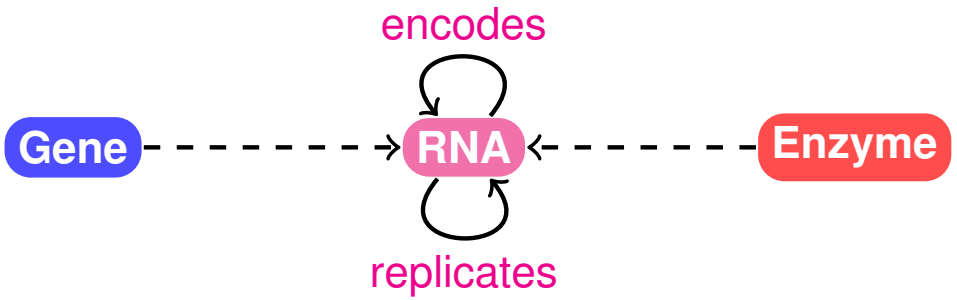


A gene big enough to specify an enzyme would be too big to replicate accurately without the aid of an enzyme of the very kind that it is trying to specify. So the system *apparently cannot get started*.

[. . .] This is the RNA World. To see how plausible it is, we need to look at why proteins are good at being enzymes but bad at being replicators; at why DNA is good at replicating but bad at being an enzyme; and finally why *RNA might just be good enough at both roles to break out of the Catch-22.*

R. Dawkins. *The Ancestor's Tale: A Pilgrimage to the Dawn of Evolution*

RNA world: Solving the *chicken vs egg* paradox at the origin of life. . .



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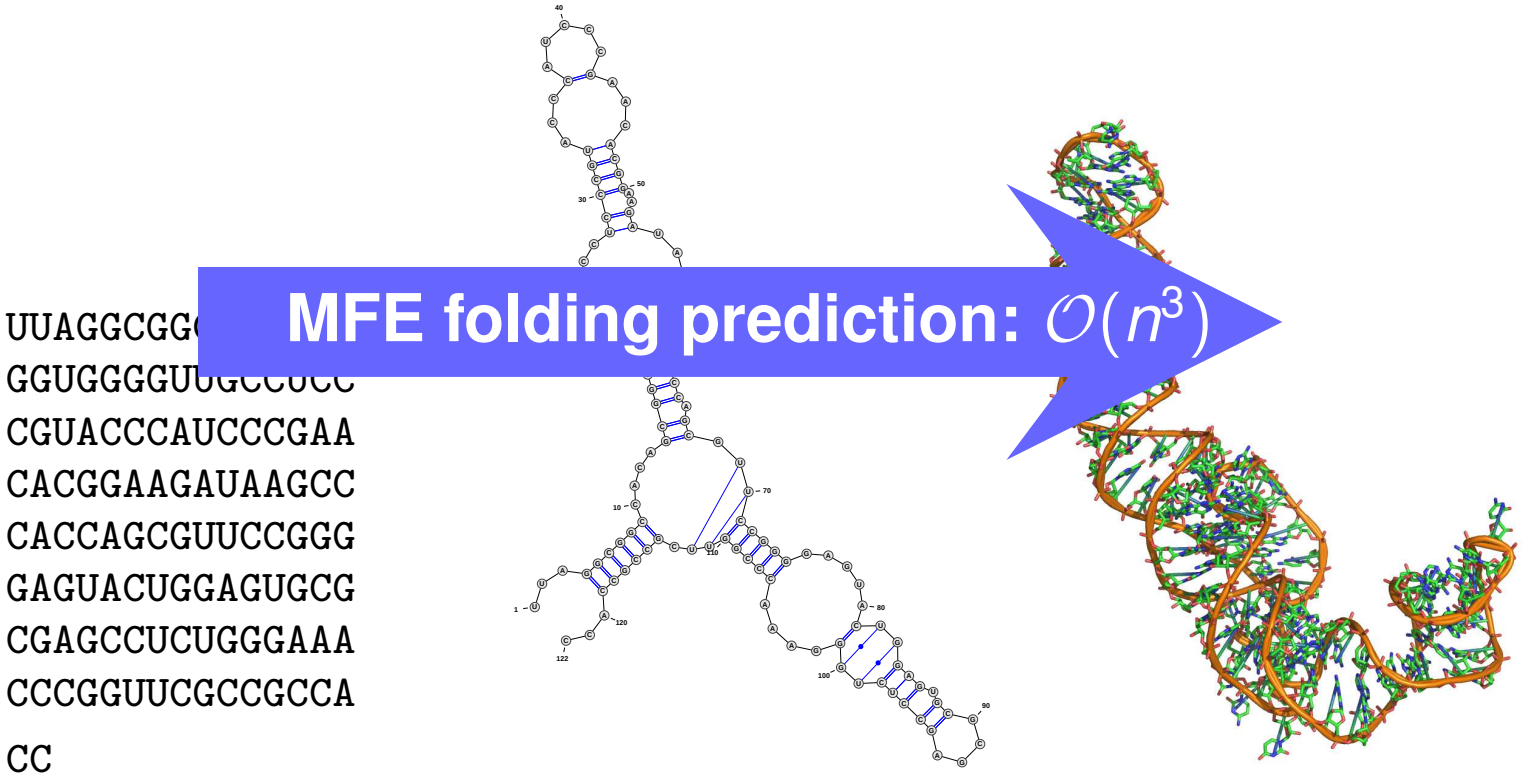
RNA sequence and structure(s)

RNA = Linear Polymer = Sequence in $\{A,C,G,U\}^\star$



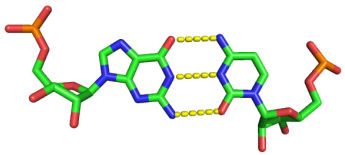
Primary Structure Secondary Structure Tertiary Structure

5s rRNA (PDBID: 1K73:B)

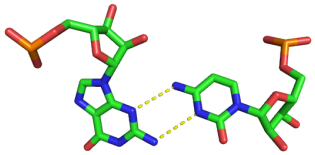
Crossing interactions

Excluded from the secondary structure:

- Non-canonical base-pairs:
  Any base-pair other than {(A-U), (C-G), (G-U)}
  OR interacting in a non-standard way (WC/WC-Cis) [Leontis Westhof, RNA 2001].

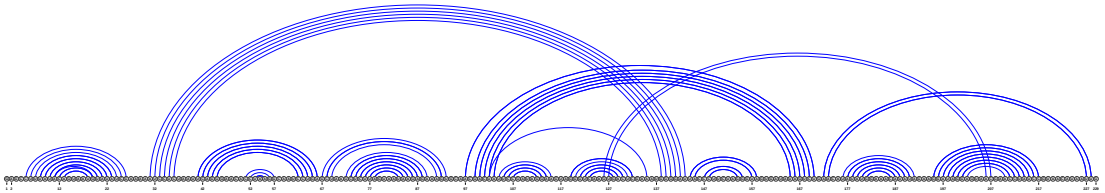


Canonical CG base-pair (WC/WC-Cis)



Non-canonical base-pair (Sugar/WC-Trans)

- (Pseudo?)knots: Crossing sets of nested stable base-pairs



Group I Intron (PDBID: 1Y0Q:A)

Crossing interactions

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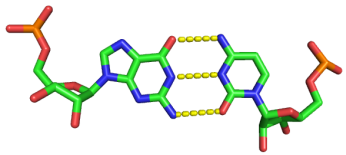
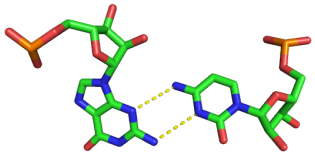


Canonical CG base-pair (WC/WC-Cis)



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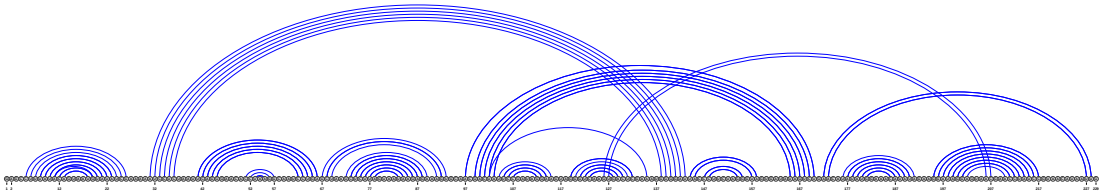
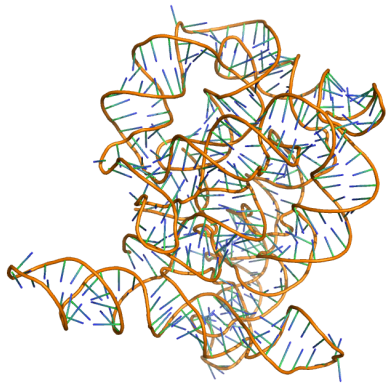


Group I Intron (PDBID: 1Y0Q:A)

Crossing interactions

Excluded from the secondary structure:

- Non-c
  Any b
  OR in



Crossing interactions do exist!

Example: Group II Intron (PDB ID: 3IGI)

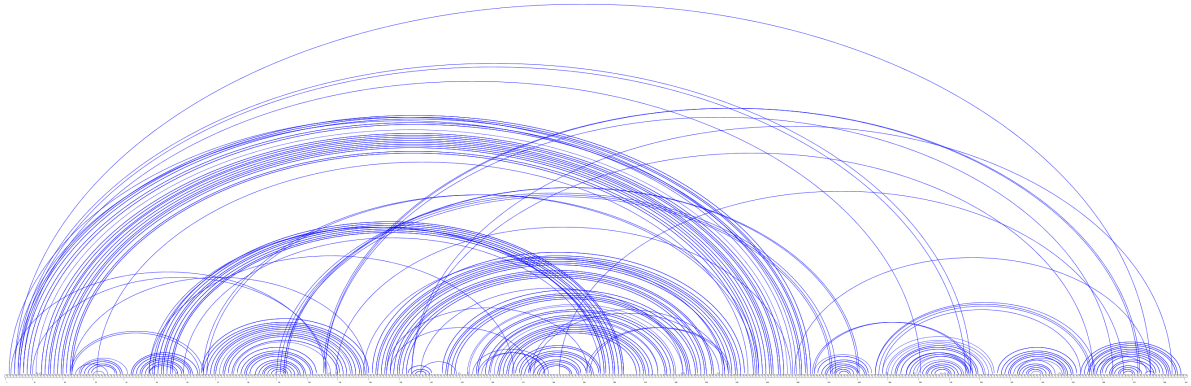
But are hard to predict

[Lyngsoe-ICALP'04]

[Sheikh Backofen Ponty, CPM'12]

Can /WC-Trans)

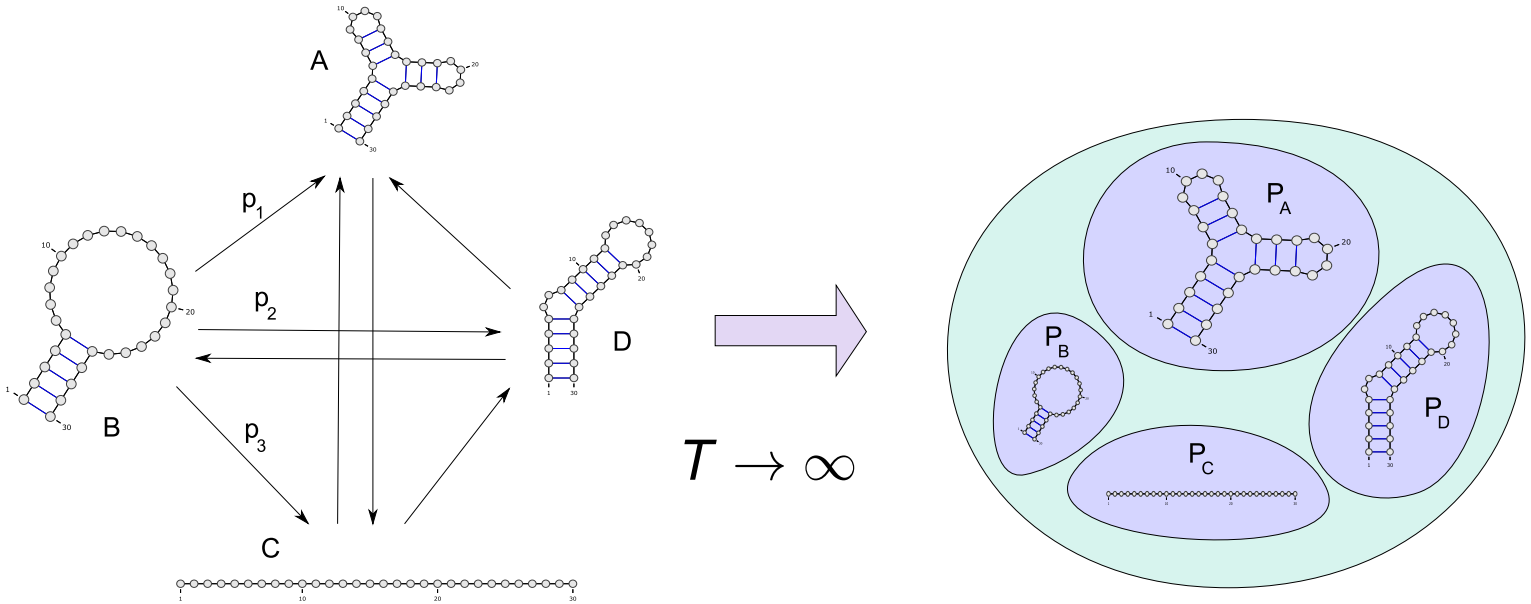
- (Pseu



Group I Intron (PDBID: 1Y0Q:A)

Thermodynamics view

RNA folding can be adequately abstracted as a (continuous) Markov process, whose stationary distribution is the Boltzmann distribution.



Definition (Thermodynamic equilibrium)

Each structure S *compatible* with an RNA w observed with probability:

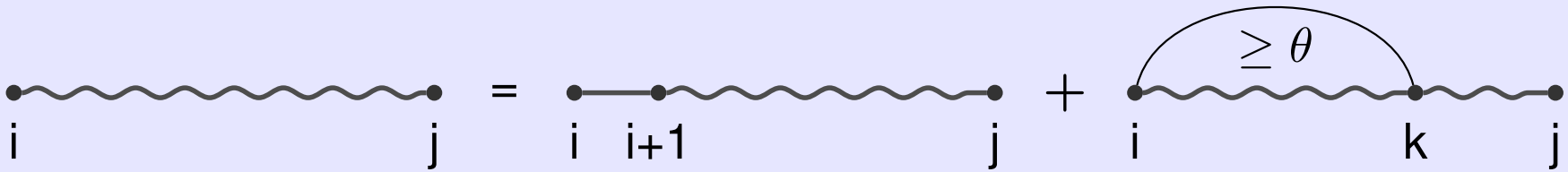
$$\mathbb{P}(S \mid w) = \frac{e^{\frac{-E_w(S)}{kT}}}{\mathcal{Z}_w} \quad \text{and} \quad \mathcal{Z}_w \equiv \sum_{S'} e^{\frac{-E_w(S')}{RT}} \quad \{\text{Partition function}\}$$

$E_w(S)$: **free-energy** of S over w; R: Boltzmann constant; and T: temperature.

Dynamic programming (DP) for RNA folding

Theorem (Exact solution – BP models [Nussinov1980])

Most stable structure computable in $\mathcal{O}(n^3)/\mathcal{O}(n^2)$ time/memory



$E_{i,k}$: Free-energy contribution of base-pair (i,k).

$\boldsymbol{N}_{i,j}$: Max #base-pairs over interval $[i,j]$

$$\boldsymbol{N}_{i,t} = 0, \quad \forall t \in [i, i+\theta]$$

$$\boldsymbol{N}_{i,j} = \min \begin{cases} \boldsymbol{N}_{i+1,j} & \{i \text{ unpaired}\} \\ \min\limits_{k=i+\theta+1}^{j} E_{i,k} + \boldsymbol{N}_{i+1,k-1} + \boldsymbol{N}_{k+1,j} & \{i \text{ paired to } k\} \end{cases}$$

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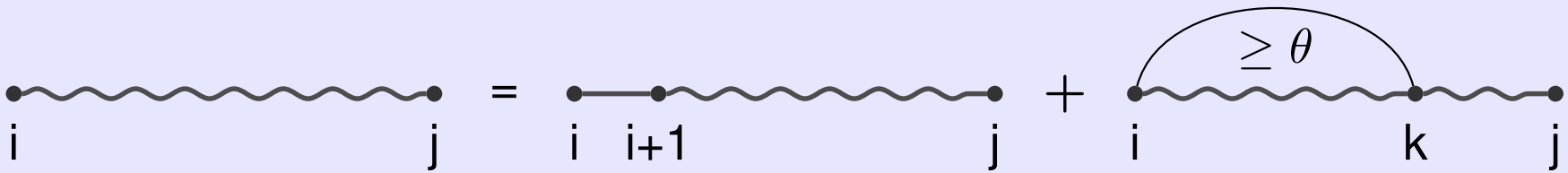

$E_{i,k}$: Free-energy contribution of base-pair (i,k).

$\boldsymbol{C}_{i,j}$: Number of secondary structures restricted to $[i,j]$

$$\boldsymbol{C}_{i,t} = \mathbf{1}, \quad \forall t \in [i, i+\theta]$$

$$\boldsymbol{C}_{i,j} = \sum \begin{cases} \boldsymbol{C}_{i+1,j} & \{i \text{ unpaired}\} \\ \sum_{k=i+\theta+1}^{j} \mathbb{1}_{\text{comp.}(i,k)} \times \boldsymbol{C}_{i+1,k-1} \times \boldsymbol{C}_{k+1,j} & \{i \text{ paired to } k\} \end{cases}$$

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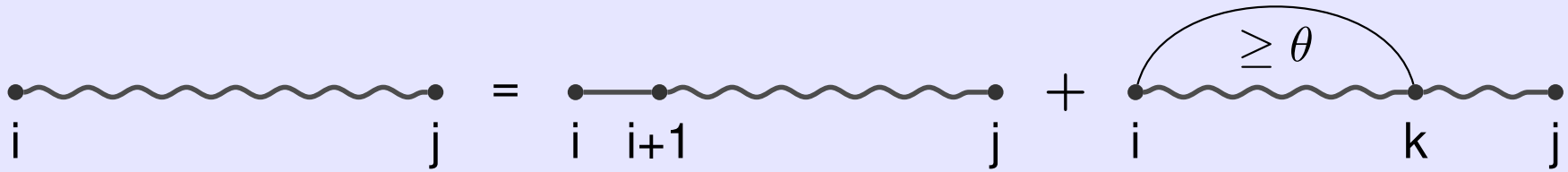

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$$\mathcal{Z}_{i,j} = \sum_{\substack{S \text{ comp.} \\ \text{with } w_{[i,j]}}} e^{\frac{-E_W(S)}{RT}} = \text{Partition function of structures over } [i,j]$$

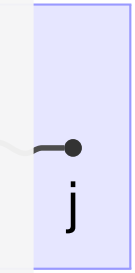
$$\mathcal{Z}_{i,t} = \mathbf{1}, \quad \forall t \in [i, i+\theta]$$

$$\mathcal{Z}_{i,j} = \sum \begin{cases} \mathcal{Z}_{i+1,j} & \{i \text{ unpaired}\} \\ \sum_{k=i+\theta+1}^{j} e^{\frac{-E_{i,k}}{RT}} \times \mathcal{Z}_{i+1,k-1} \times \mathcal{Z}_{k+1,j} & \{i \text{ paired to } k\} \end{cases}$$

Dynamic programming (DP) for RNA folding

Many extensions:

- Nearest-neighbor/Turner energy model [Zuker1981]
- Comparative folding [Sankoff1985]
- Equilibrium base-pairing probabilities [McCaskill1990]
- Moments of additive features [Miklos2005,Ponty2011]
- Δ kcal.mol^{-1} suboptimal structures of MFE [Wuchty1999]
- Basic crossing structures [Rivas1999]...
- Exact sampling in Boltzmann distr. [Ding2003,Ponty2008]
- Moments of additive features [Miklos2005,Ponty2011]
- Maximum expected accuracy structure [Do2006]
- Distance-classified partitioning of Boltzmann ens. [E.Freyhult2007a]



Made possible by:

- Completeness/Unambiguity of decomposition
- Objective function additive with respect to DP scheme

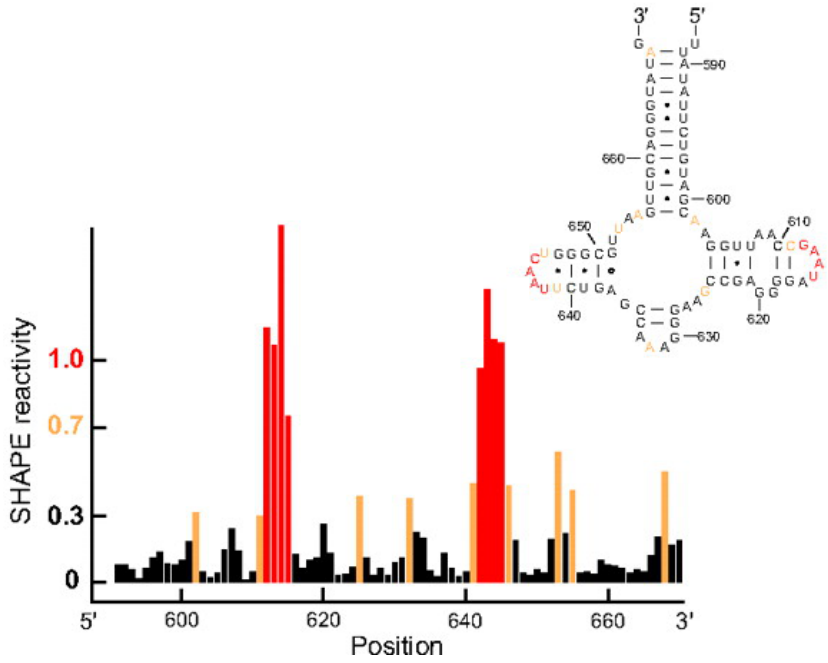
$\Rightarrow$ Combinatorial Dynamic Programming

SHAPE probing

SHAPE = Selective 2'-Hydroxyl Acylation by Primer Extension

Produces accessibility profiles, i.e. *projections* of RNA structure.

in silico analysis of SHAPE data remains complex and misleading.



Our goal: To develop *hybrid* modeling approaches with experimentalists (Paris V) and bioinformaticians (McGill)

- Massively parallel derivation of profiles (PCR/NGS/EM);
- Clustering to model structure of viruses (HIV, Ebola);
- Joint analysis of multiple SHAPE profiles.

Funded by *Fondation pour la Recherche Médicale* (2015-2018)

[Desforges, . . . , **Saaidi**, **Ponty**, Ohlmann, Sargueil, NAR 2017]

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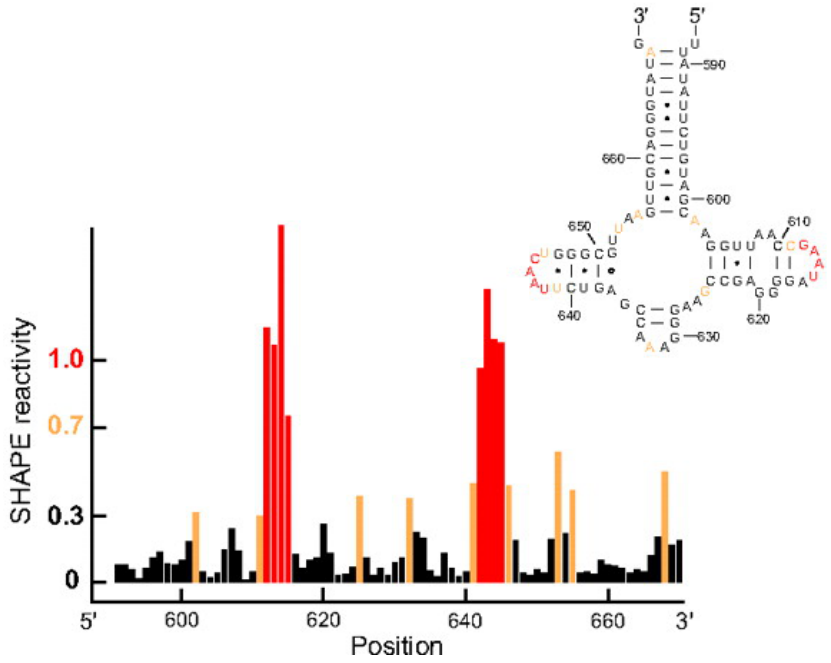

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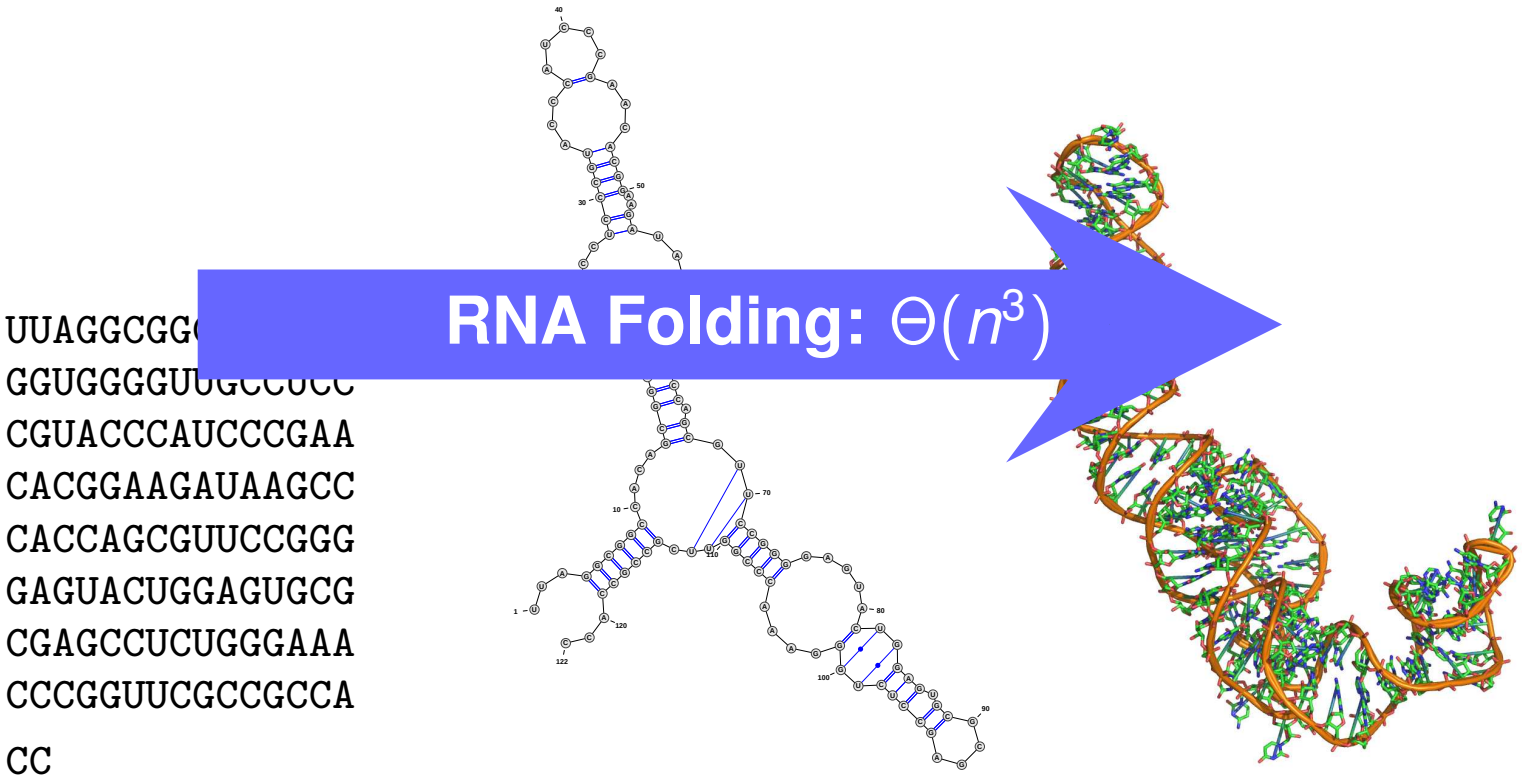
[Desforges, . . . , **Saaidi**, **Ponty**, Ohlmann, Sargueil, NAR 2017]

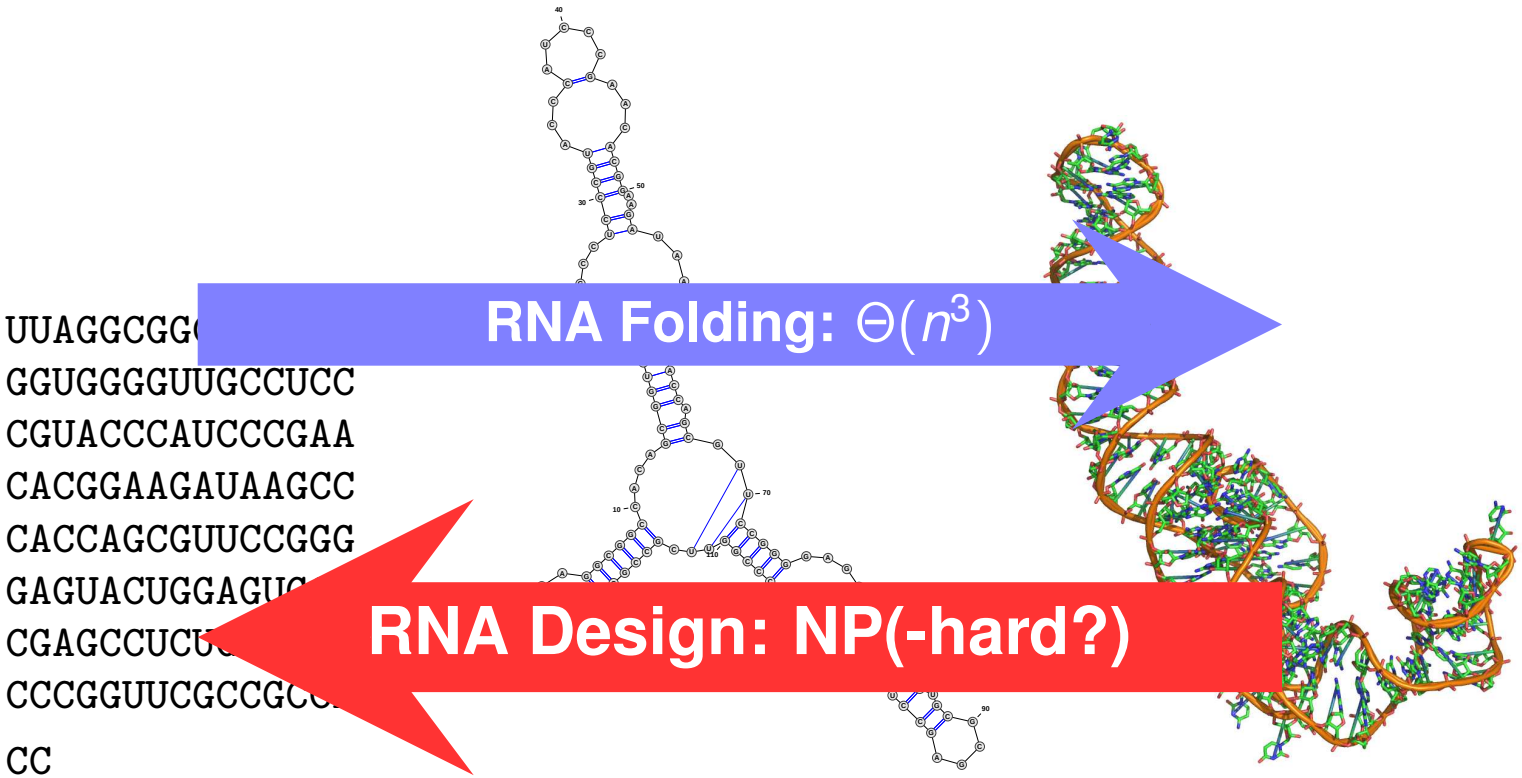
Interface: Dyn. Prog./Rand. Gen. (RNA Design) 1/3



Primary structure Secondary structure Tertiary structure

5s rRNA (PDBID: 1K73:B)

Interface: Dyn. Prog./Rand. Gen. (RNA Design) 1/3



Primary structure Secondary structure Tertiary structure

5s rRNA (PDBID: 1K73:B)

Dyn. Prog./Rand. Gen. (RNA Design) 2/3

Input: Set of constraints

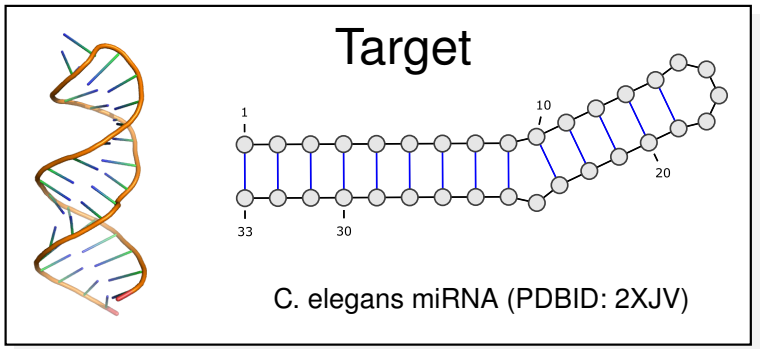
- Secondary structure
- Pattern avoid-ance/occurrence
- Energy/robustness
- Putative interactions
- ...

Goal:

Design of active RNAs

Method:

Generation + Selection



Generation

Candidates

Sequence	GC	Ener.	Prob.	mfe?
CUGUUCUGUACGUUGGCGAACGUGGCGGAGCAG	61	-15.7	0.38	Y
GGUCGGGCUGUAUUACAUGAUACAAGCCUGACU	48	-17.6	0.27	Y
AUACUGGGUGCGGGUGCCCCUGUGACUUAGUAU	55	-13.9	0.35	Y
GGGUGCCGUAAUGGUCACUCAUUCGUGGCAUUC	55	-9.8	0.11	Y
GGAGUACCUCAGCGUCCAUGCUGCGGGUGCUCC	67	-20.3	0.63	Y
GAAAUGGCCUGGAGUGAGUUCUGUGGUCAUUUU	45	-11	0.45	Y
CGAUAGGUGGCGAAGUGCUUUGUACAUUUAUCG	45	-11.2	0.53	Y
UAAACUAGGUGAUACUAGUGUCAACCUAGUUUA	33	-14.8	0.29	N
GAGGAGAUGUUACCCAGGGGUAGUUGUUUCCUU	48	-11.2	0.05	N
AAAUUAUUUCUUUGAUAUUAAAGAAGGUGGUUU	21	-4.9	0.07	N

Selection	$\leq$60	$\leq$-13	$\geq$0.3	=Y

Dyn. Prog./Rand. Gen. (RNA Design) 3/3

Fact #1: Selection is expensive

$\Rightarrow$ Capture constraints during generation stage

Fact #2: Goals of synthetic biology are evolving

$\Rightarrow$ Need for modular approaches

Our approach: Non-uniform *Boltzmann* random generation

Easy targets:
Language models

Sec. str. compatibility [4]

Ex.:

$$
\begin{aligned}
S_0 &\to AS_1U \mid US_1A \mid GS_1C \mid CS_1G \\
S_1 &\to AS_2U \mid US_2A \mid GS_2C \mid CS_2G \\
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S_4 &\to AS_5 \mid US_5 \mid GS_5 \mid CS_5 \\
S_5 &\to AS_6 \mid US_6 \mid GS_6 \mid CS_6 \\
S_7 &\to A \mid U \mid G \mid C
\end{aligned}
$$

Pattern avoidance/occurrence
(FDA$\times$CFG $\subseteq$ CFG)

$\Rightarrow$ Context-free grammars

Hard constraints

Additional feature distributions
Typically Gaussian

$\Rightarrow$ Weighted random generation [1]

$$\mathbb{P}(w) = \frac{\pi_a^{n_a}\pi_b^{n_b}\cdots}{\mathcal{Z}_\pi} \qquad \mathcal{Z}_\pi := \sum_{w\in S} \pi_a^{n_a}\pi_b^{n_b}\cdots$$

+ Low variances

$\Rightarrow$ **Efficient rejection**

Boltzmann principle [2,3]

Soft constraints

Complex features

Robustness

Predicted folding
(2D/MFold, 3D/MCFold...)

Stability
(Molecular dynamics)

Interactions
(RNACofold, Docking)

Non-redundant generation [5]

Posterior selection

References: [1] TCS 2010, [2] AOFA'10, RECOMB'11, [4] NAR'12, [5] TCS'13

+ Recent theoretical developments@CPM'15 & Algorithmica'17

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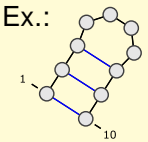

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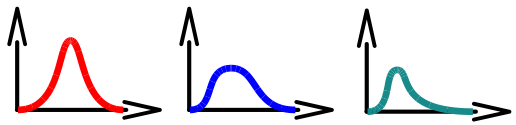

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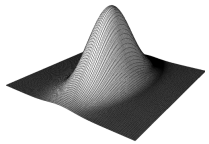

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RNA kinetics

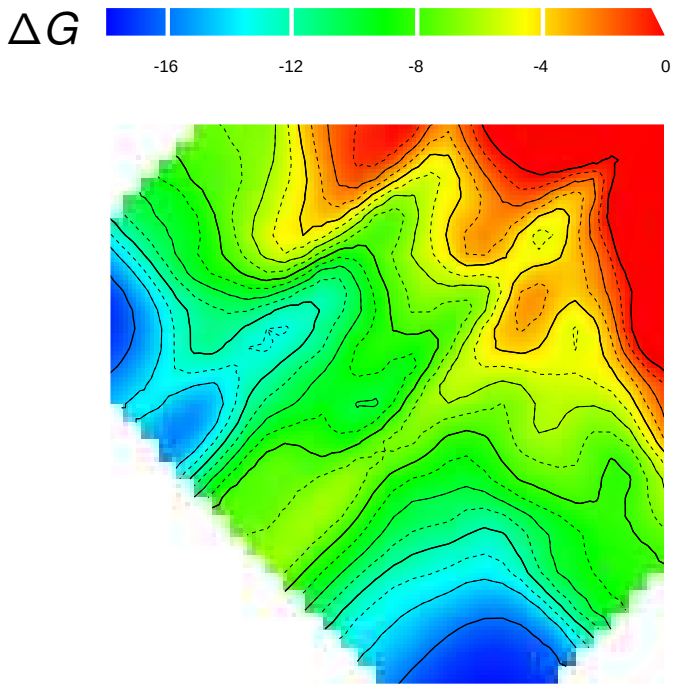
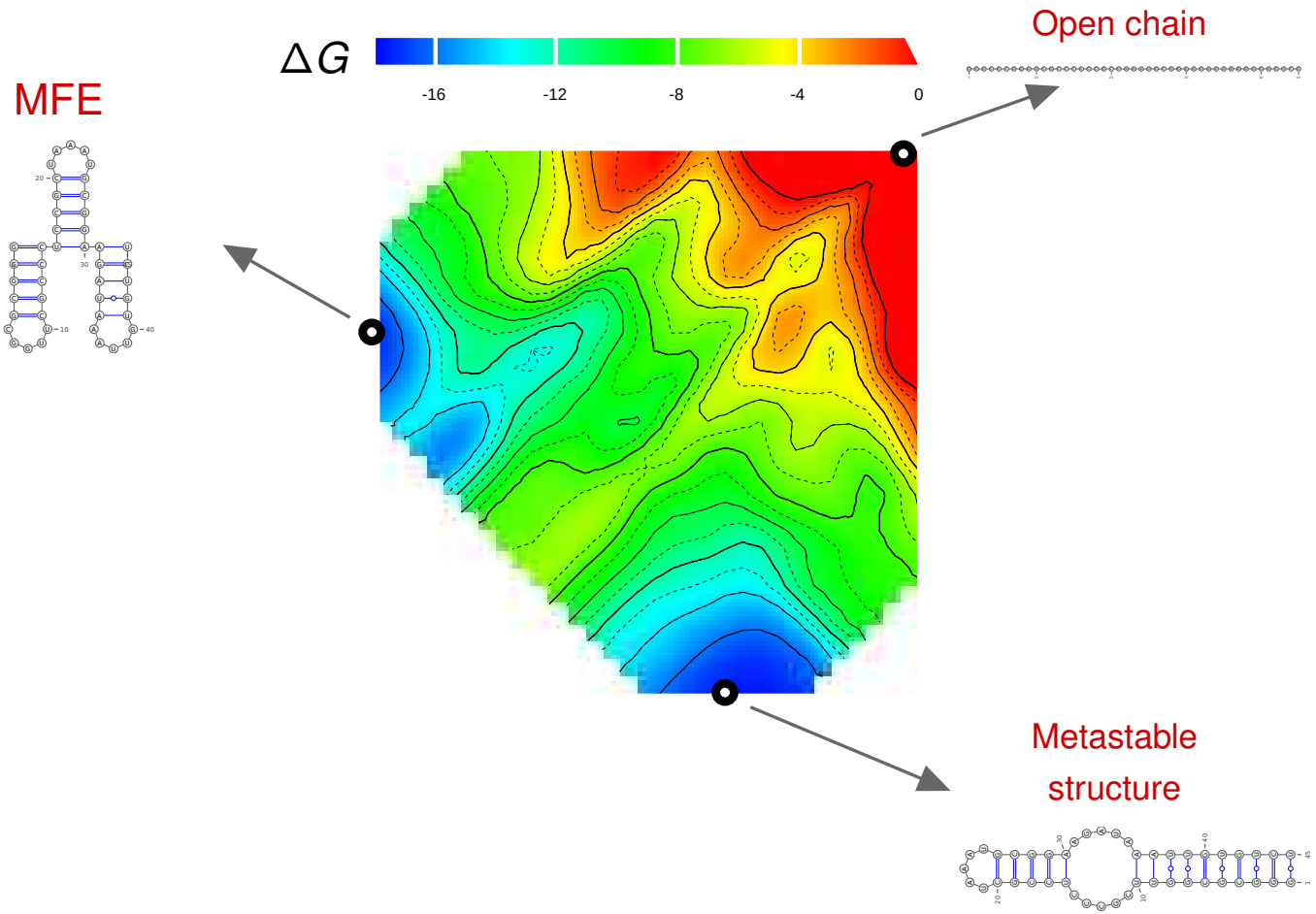


Image : Lorenz *et al*, GCB'09

Assuming a thermodynamic equilibrium sometimes misrepresents the reality of RNA folding in finite time $\rightarrow$ RNA kinetics!

RNA kinetics



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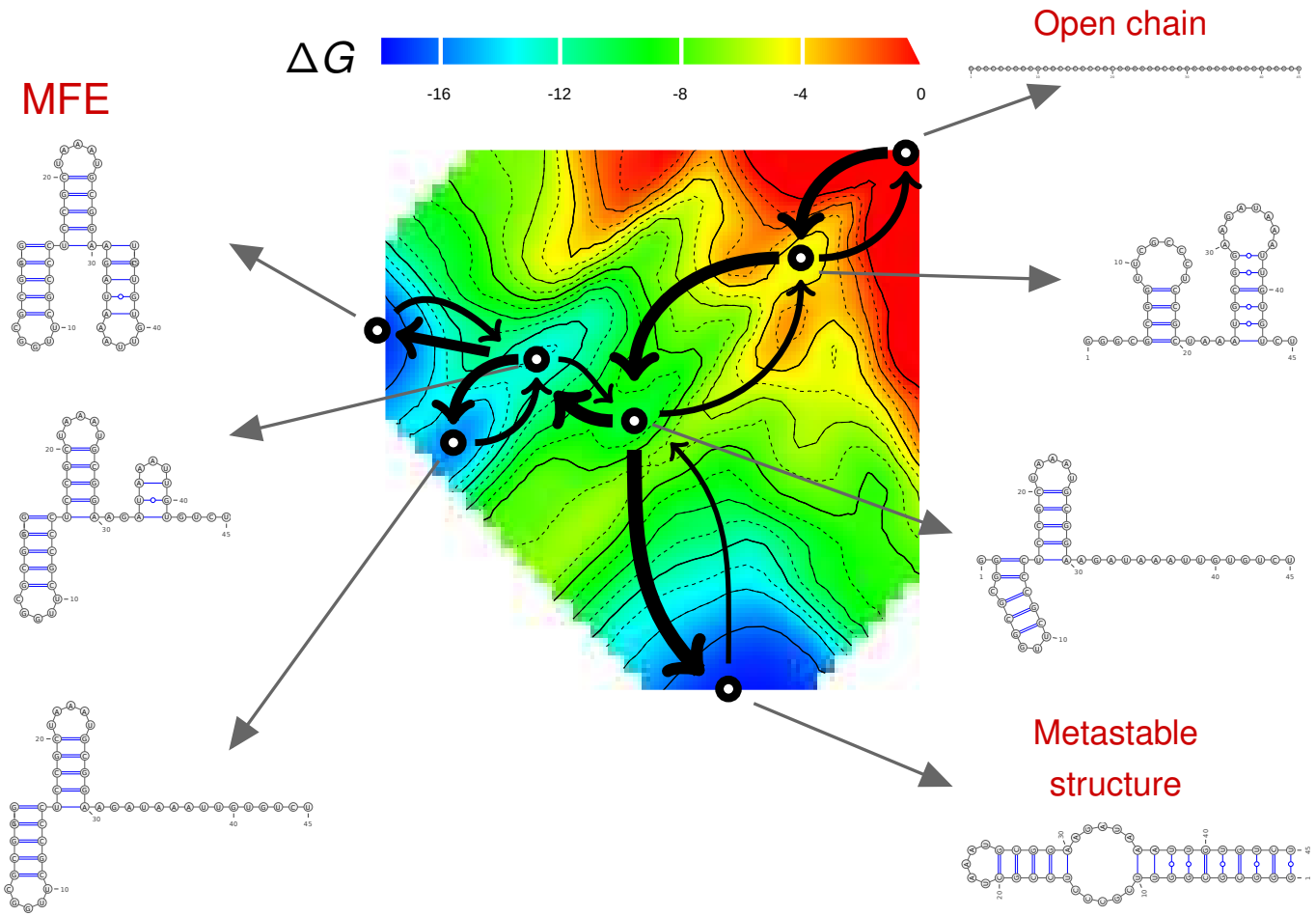

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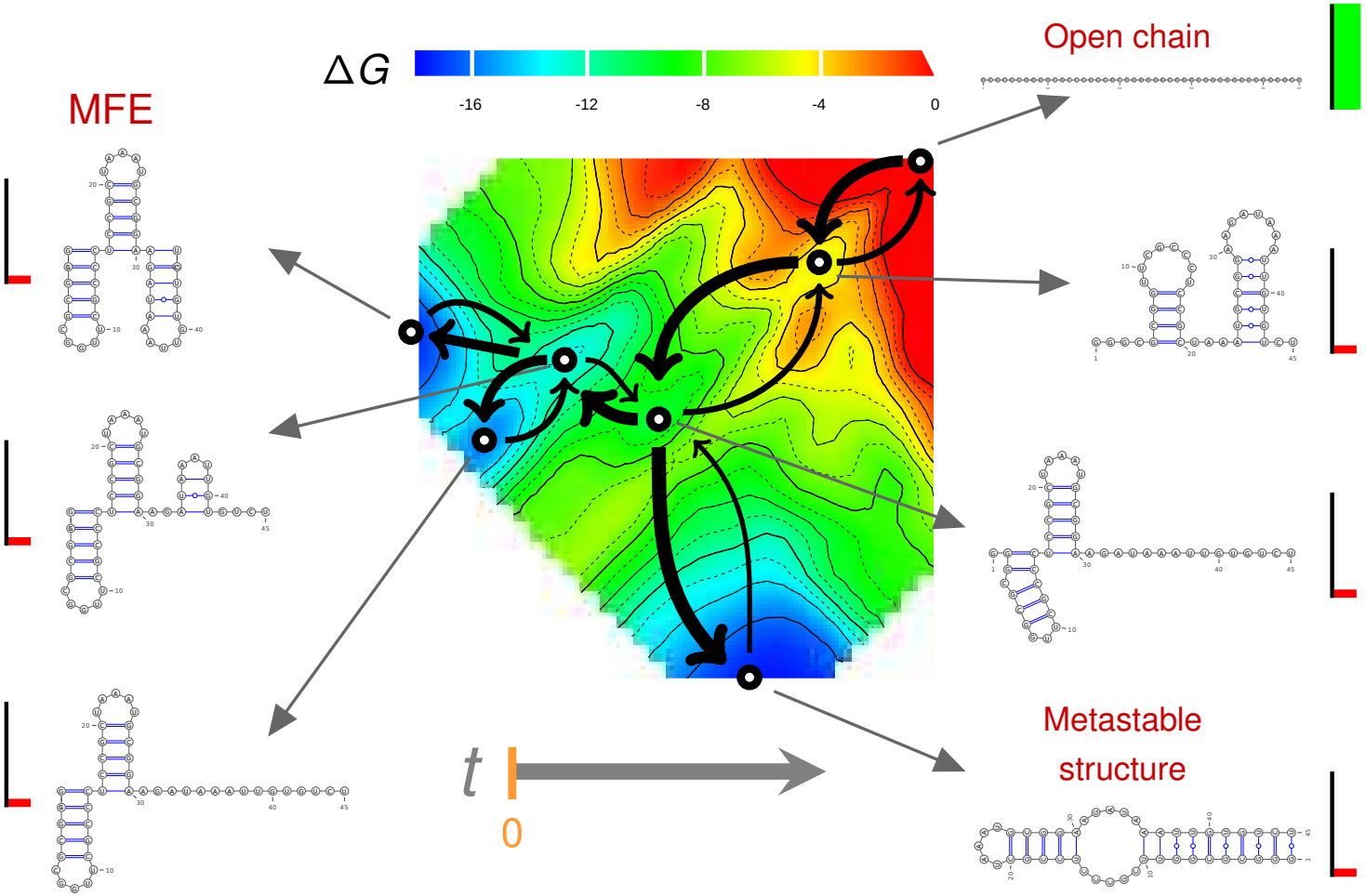

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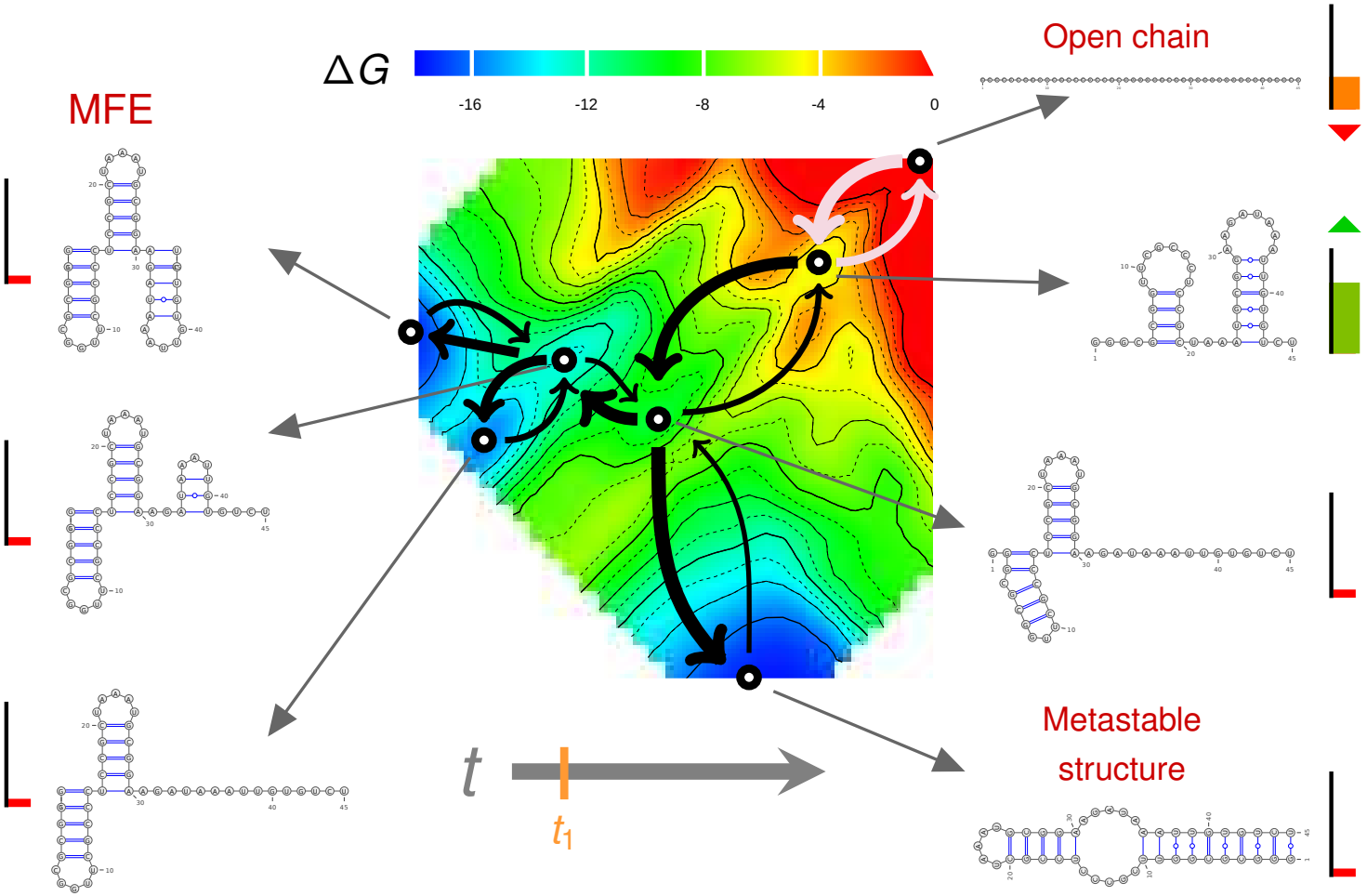

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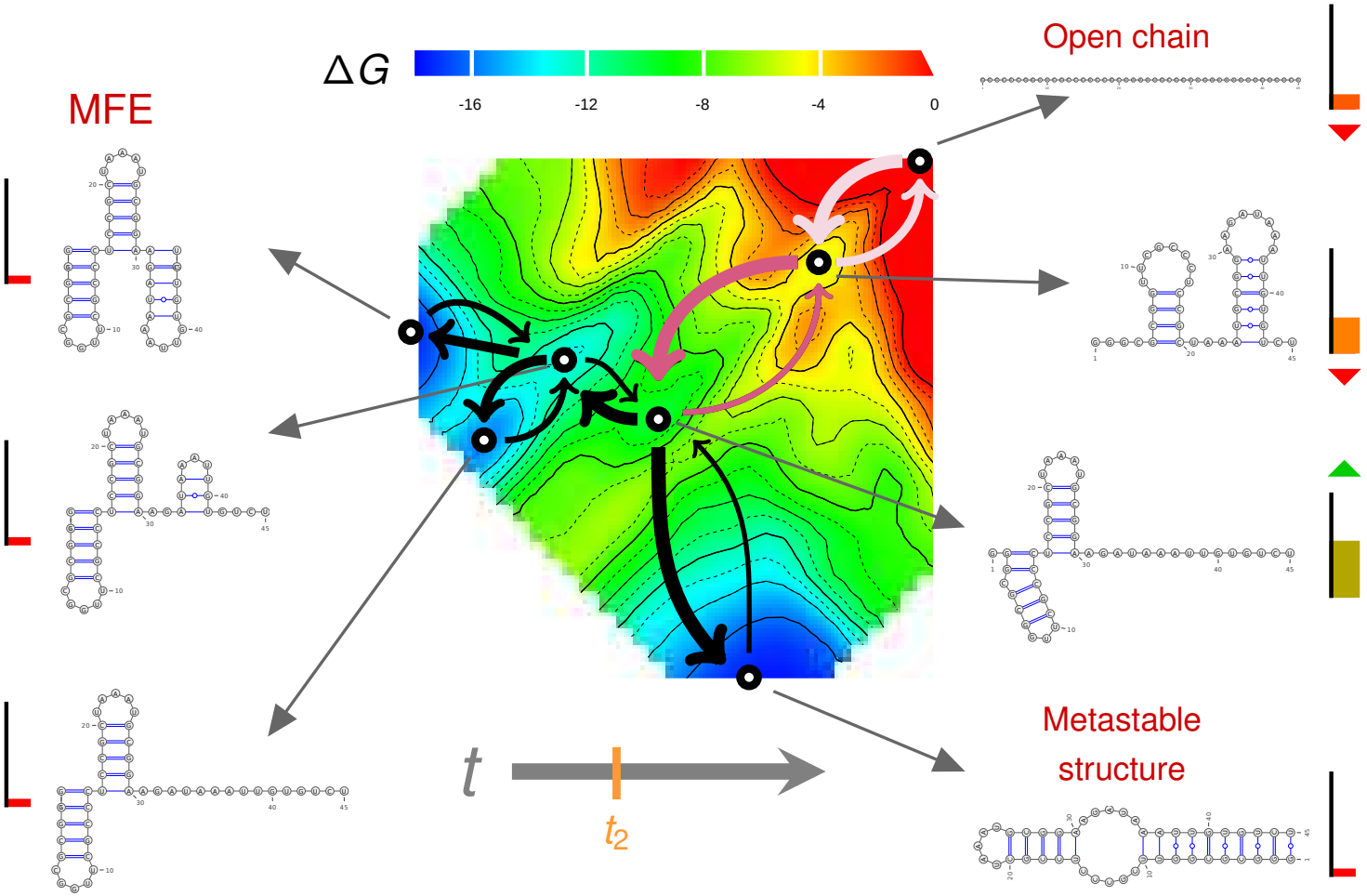

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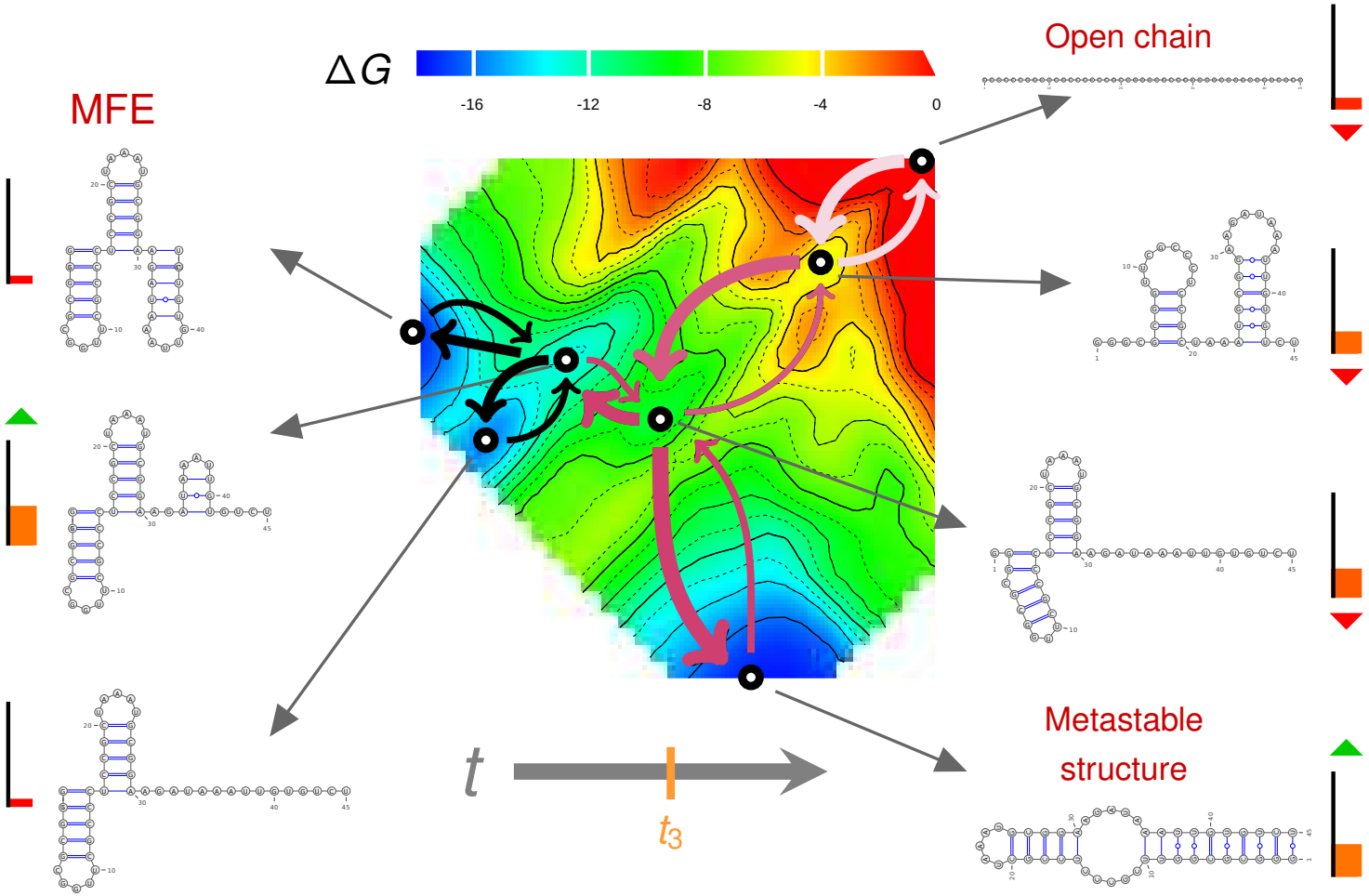

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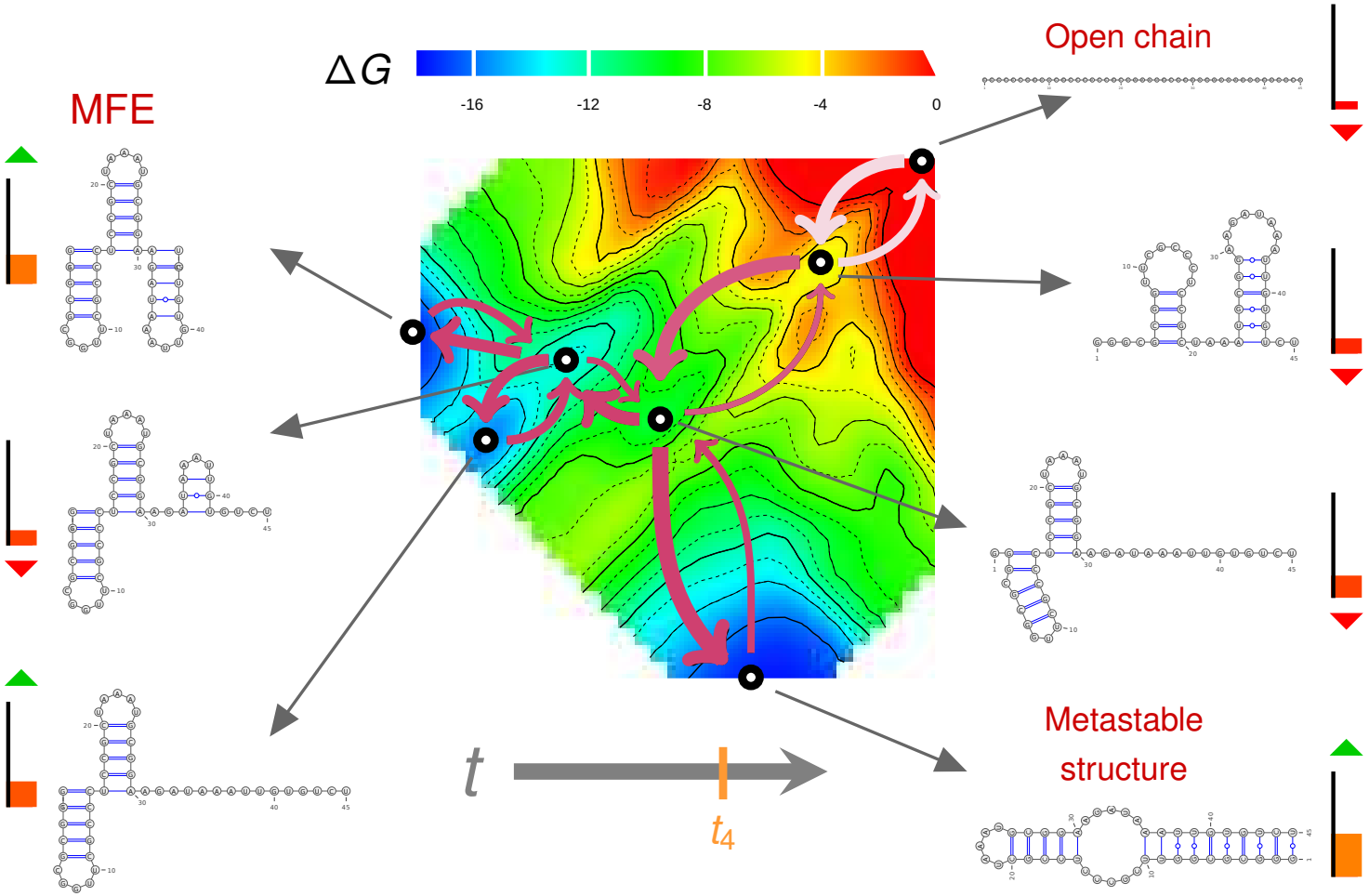

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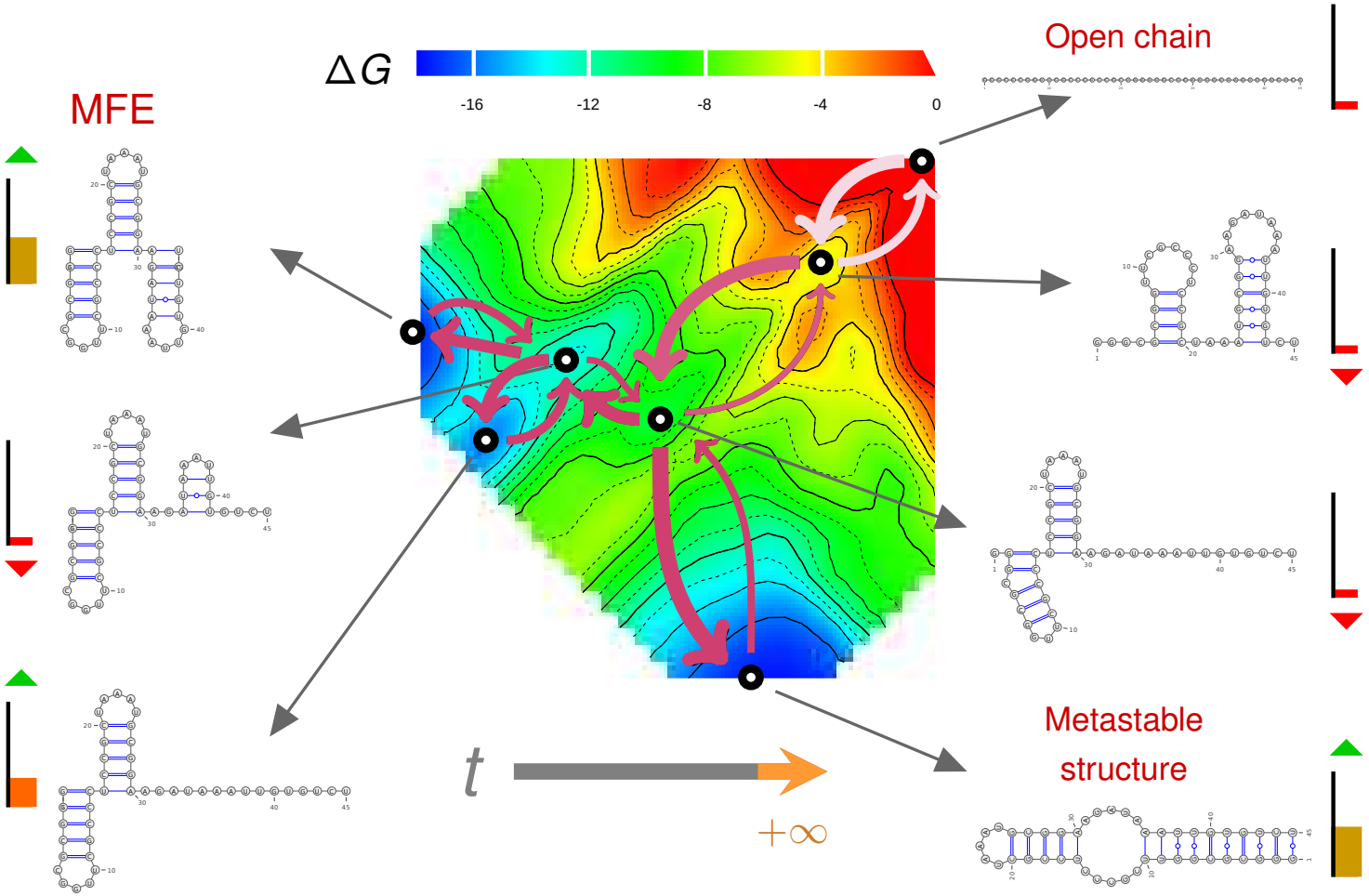

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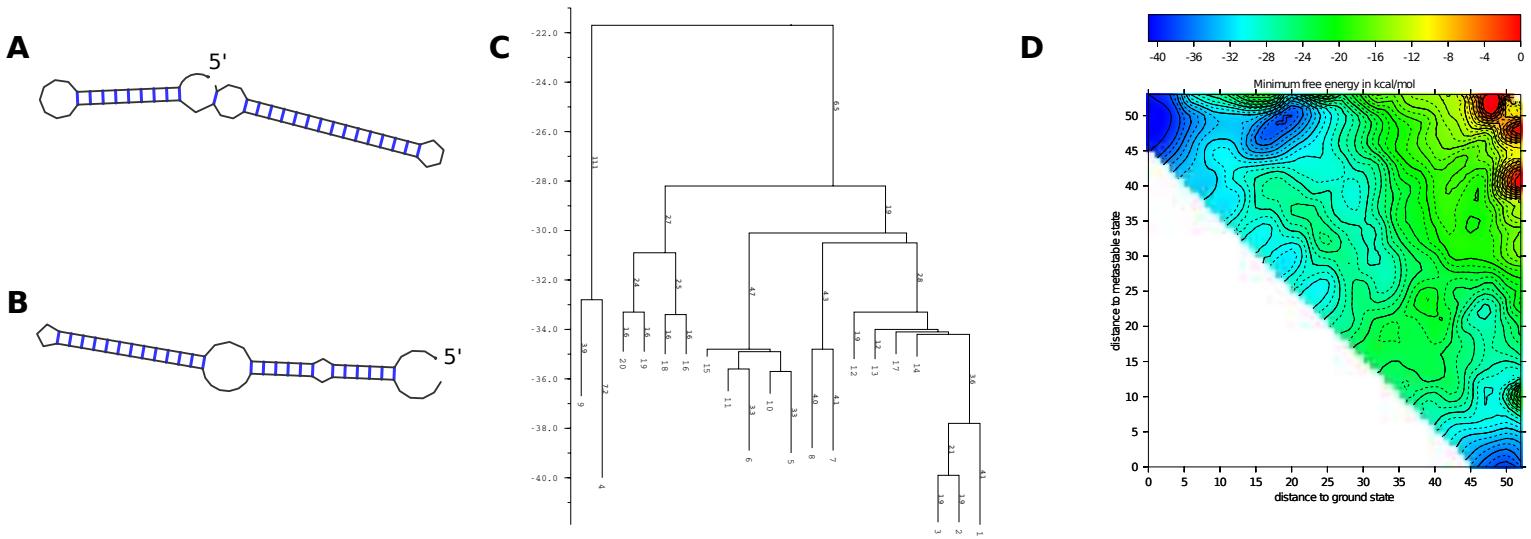

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- Bottleneck: Build kinetic landscape (combinatorial explosion);
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$\Rightarrow$ ANR/FWF-funded RNALands project (2015 – 2019)

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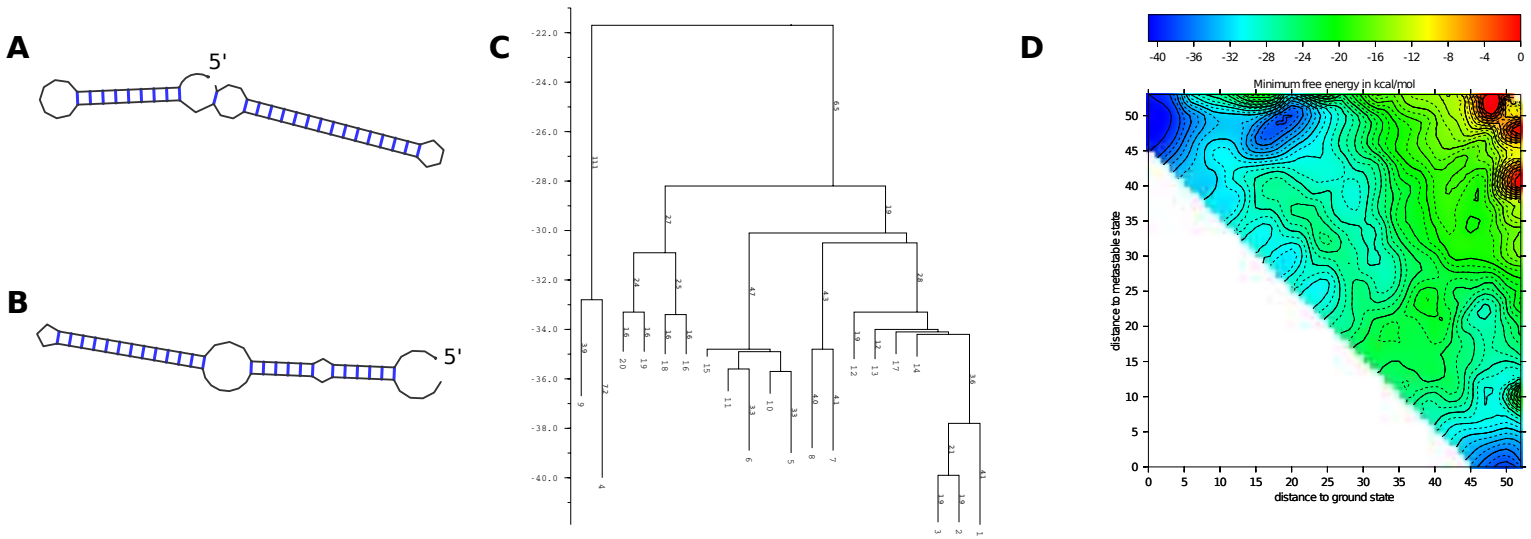

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