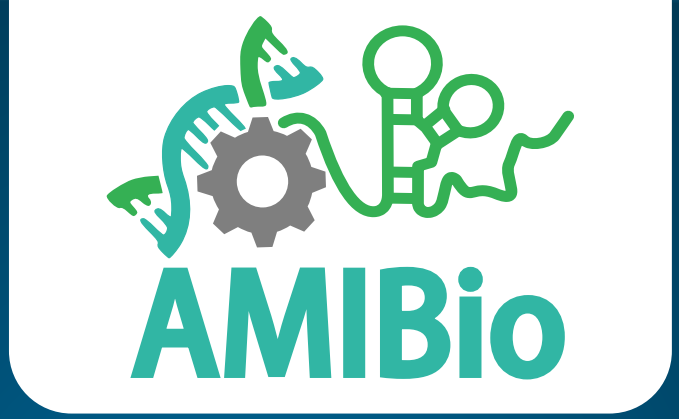


Rational design and structure modeling of functional RNAs

Discrete algorithms for RNA Bioinformatics

AMIBio team
LIX, UMR 7161

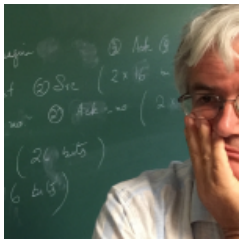
Yann Ponty (DR CNRS)

The AMIBio team

Yann Ponty
Research Director

Sebastian Will
Full Professor

Sarah Berkemer
Asst Professor



Philippe Chassignet
Asst Professor

Jean-Marc Steyaert
Full Prof (Aemeritus)

Hélène Thibault
Admin assistant

PhD Students

Hua-Ting Yao – 2018/??

Taher Yacoub – 2020/??

Bertrand Marchand – 2020/??

Ha Nguyen Ngoc – 2017/21

RNA in Human biology and health: Friend **and** Foe!

RiboNucleic Acids (RNAs)

Encodes proteins
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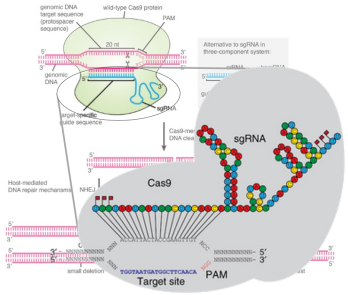

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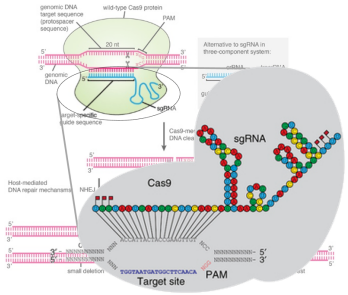

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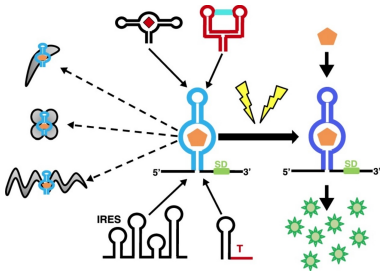

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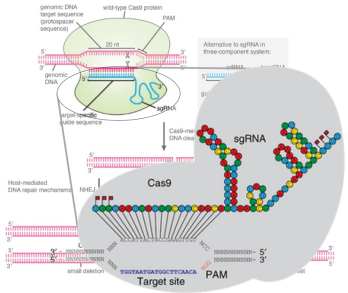

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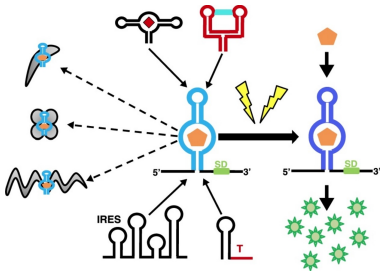

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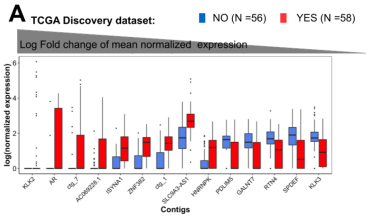

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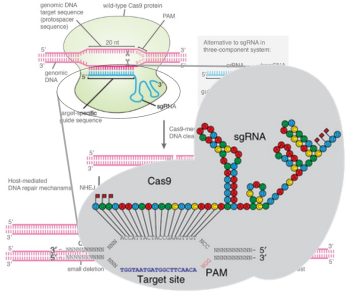

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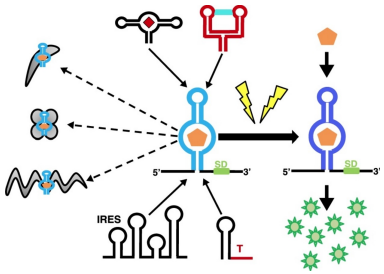

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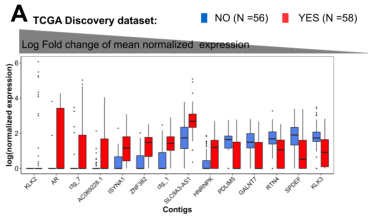

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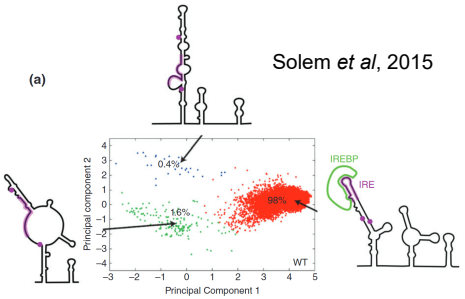

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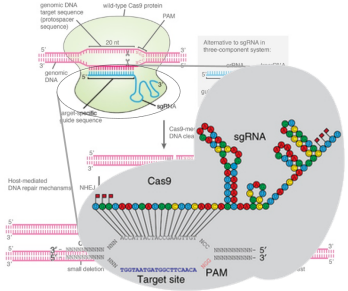

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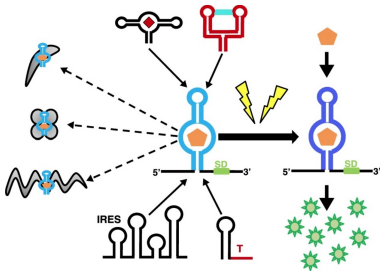

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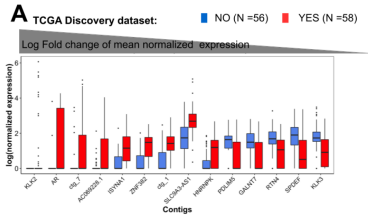

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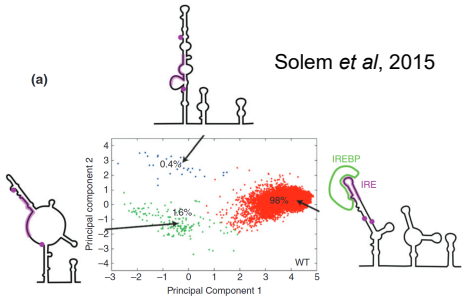

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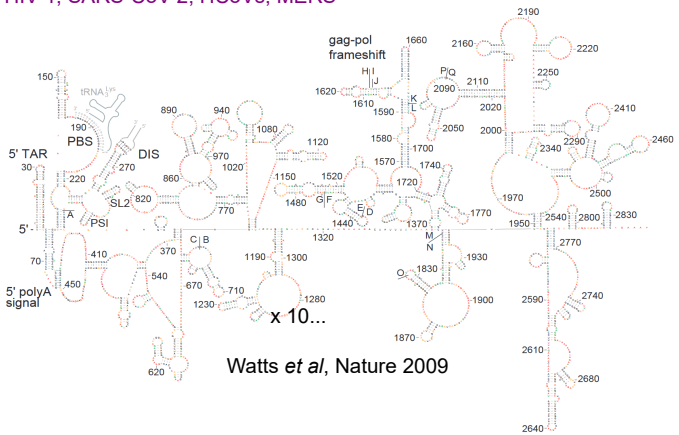

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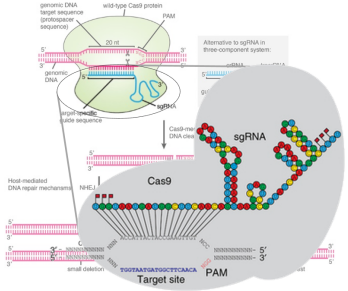

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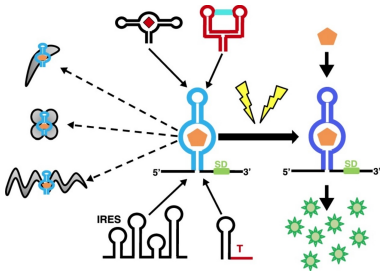

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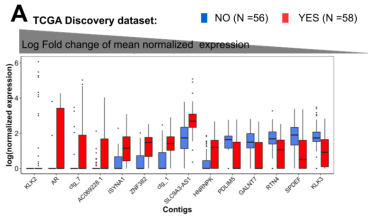

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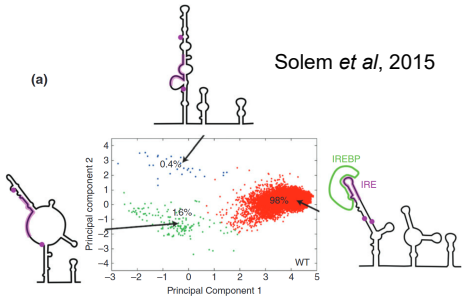

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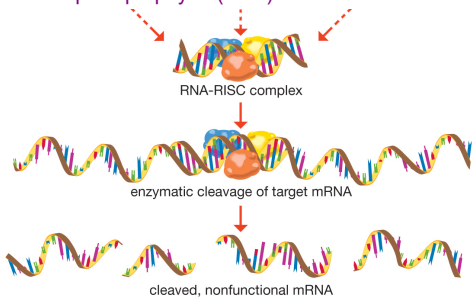

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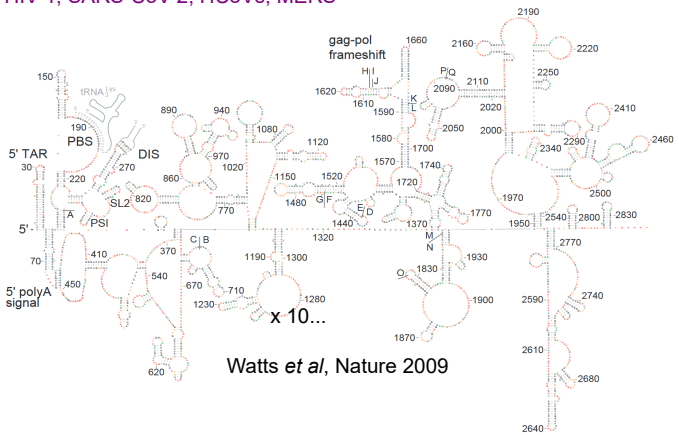

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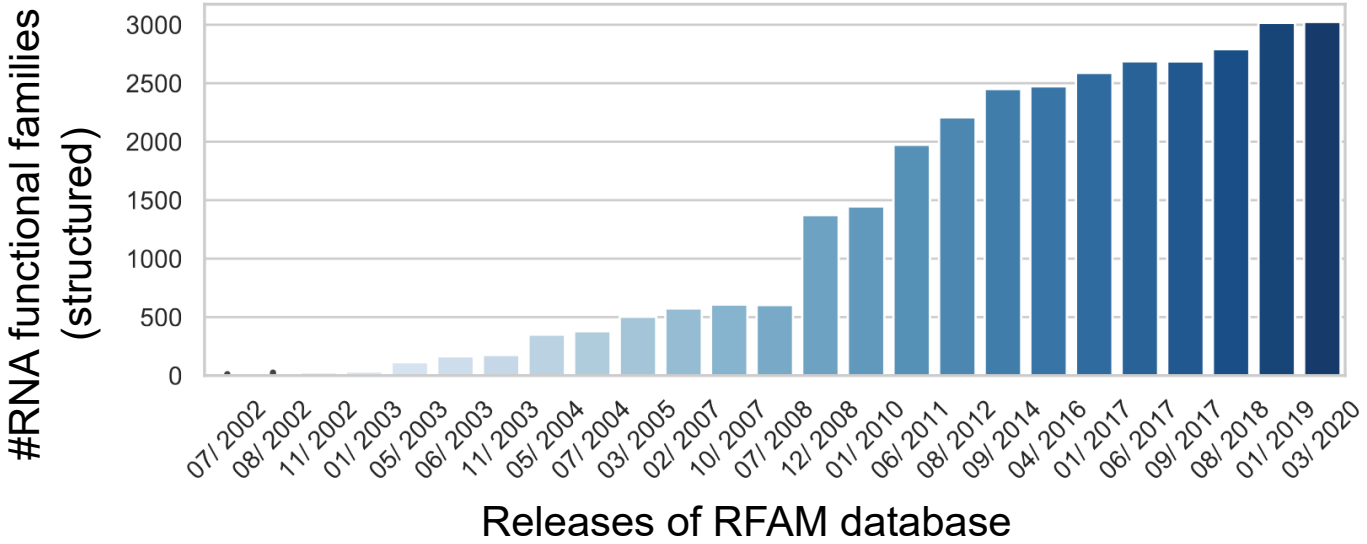

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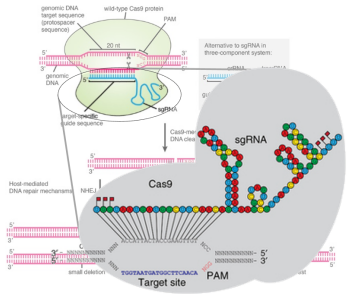

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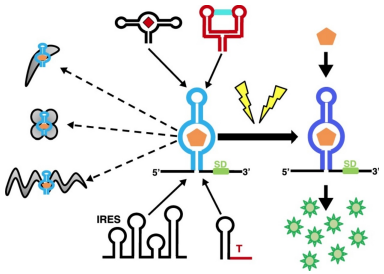

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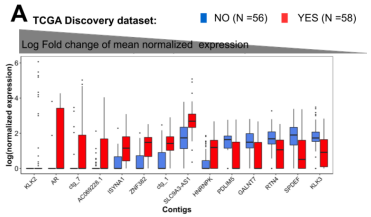

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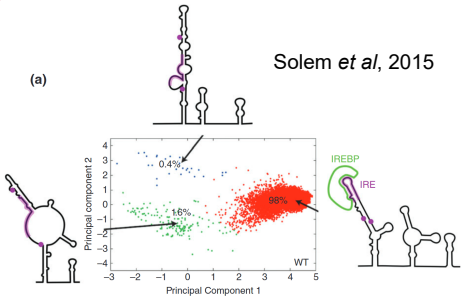

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RNA Design

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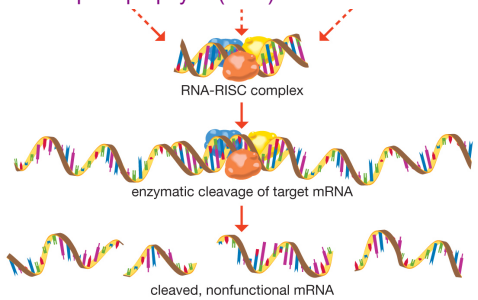

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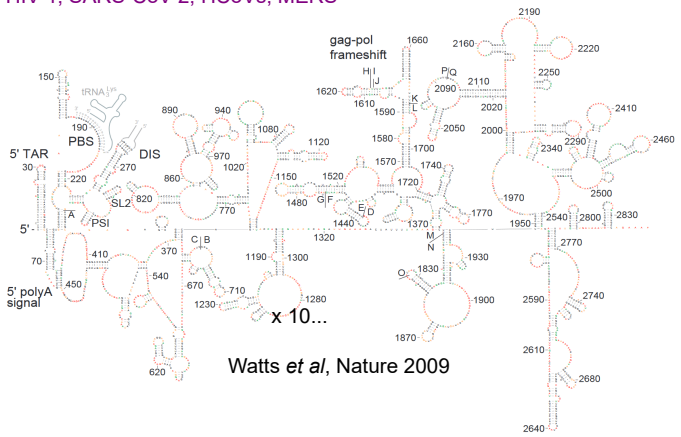

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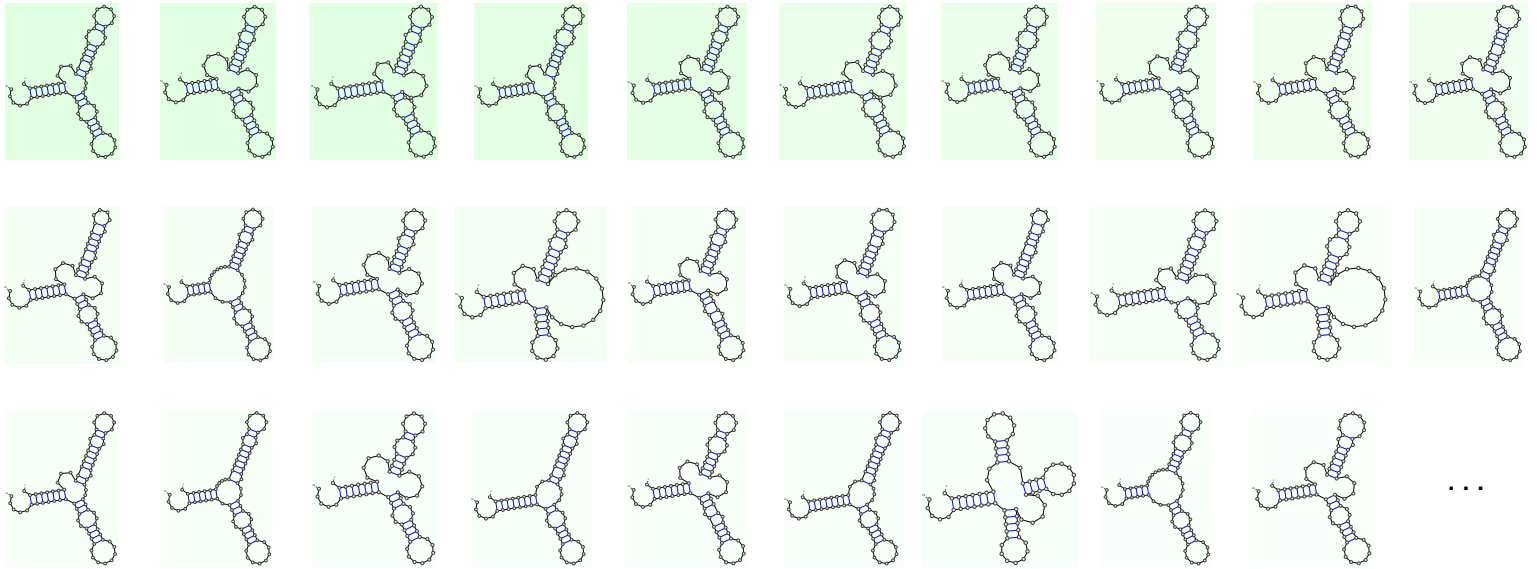
RNA: A combinatorial biopolymer

GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA



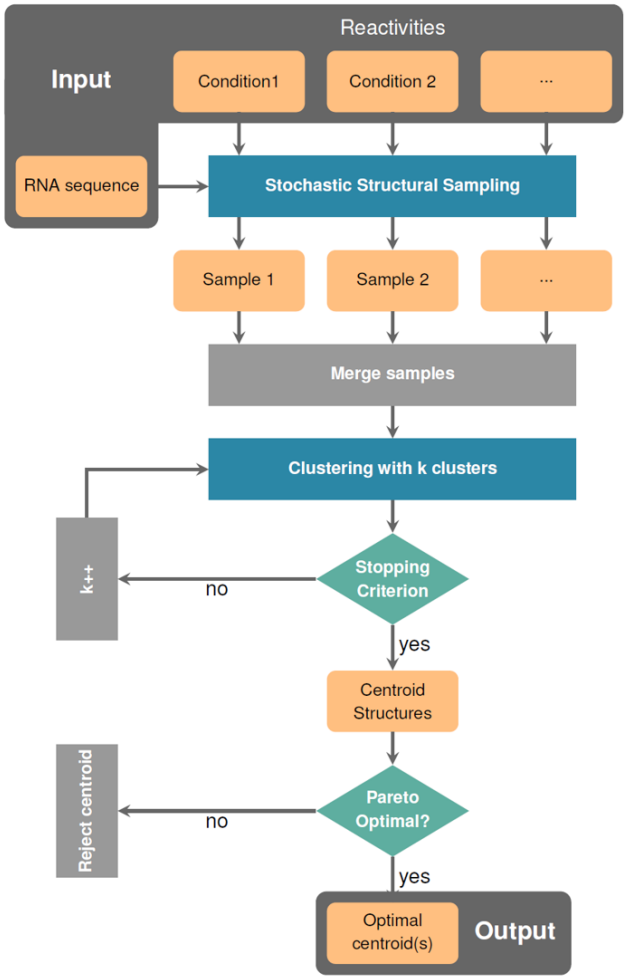
Free-energy minimization $\rightarrow$ Finding a needle in a haystack:

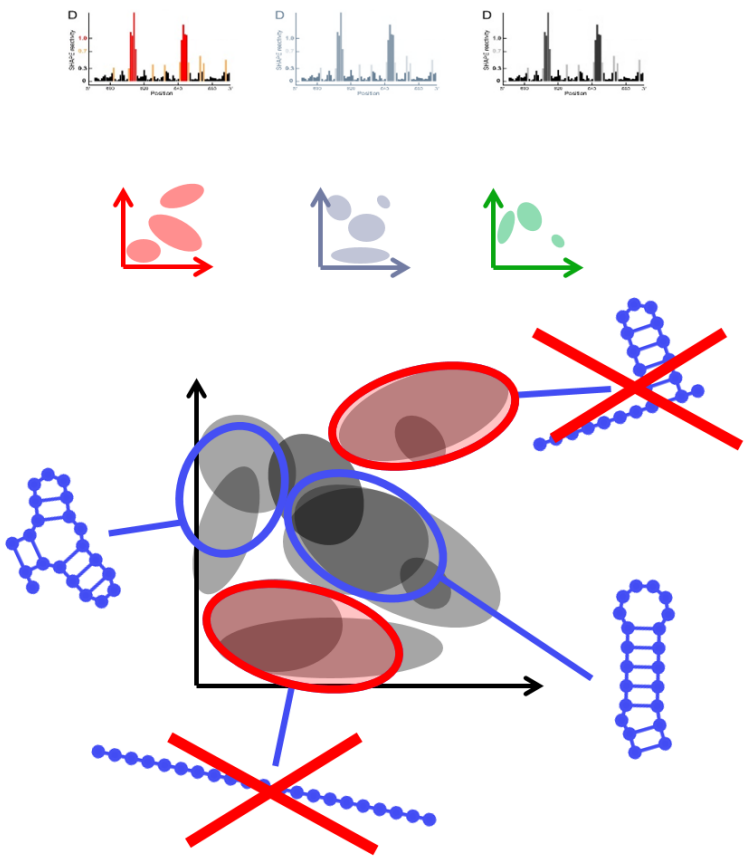
$$\#\text{2D structures} \approx \frac{1.8^n}{n\sqrt{n}} \rightarrow 37,974,319,446,212,728 \text{ 2D structures}$$

Yet efficient/polytime ($\mathcal{O}(n^3)$) dynamic programming algorithms:

- Exact energy minimization + exp. evidences (chemical probing)
- Simultaneous folding/alignment [Will *et al*, Bioinformatics 2015]
- Perfect Boltzmann-Gibbs sampling...

Integrating multiple sources of probing data





IPANEMAP Method

[Saaidi *et al*, Nucleic Acids Research 2020]

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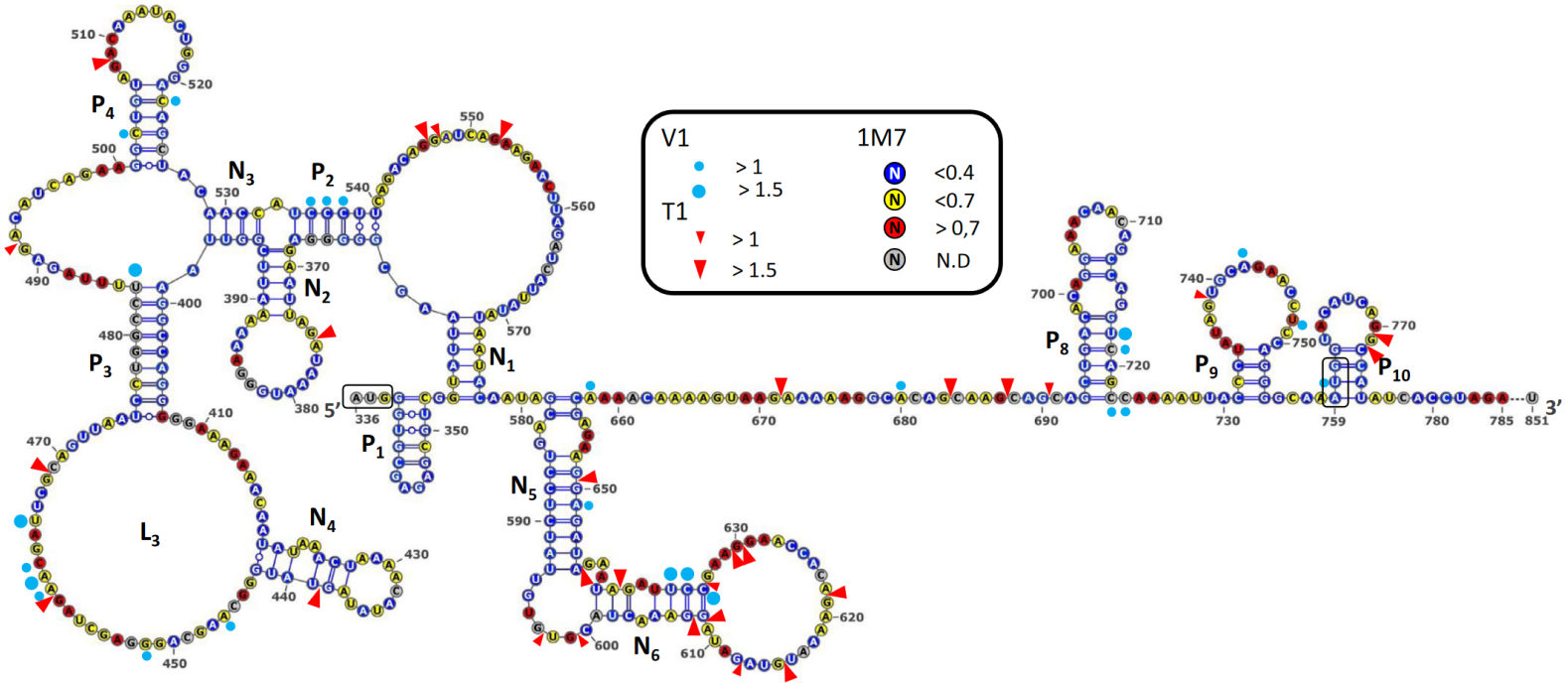
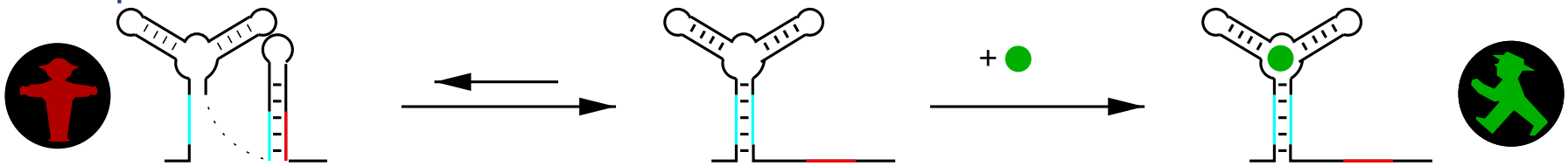


Structure modeling of HIV-1 Gag-IRES
→ Discovery of new recruitment sites for 40S ribosome
[Deforges *et al*, Nucleic Acids Research 2017]

Similar algorithms to predict RNA-RNA interactions
→ Discovery of alternative template switching mechanisms in SARS-CoV 2
[Wang *et al*, Molecular Cell 2021]

Multiple flavors of RNA Design

Example: *Riboswitch* for translation control



Multiple target structures → *Multiple design of RNAs*

```
abcdefghijklmnopqrstuv
(((((.)).(((..))).))).
((.))((...))..(((..)))
....((((..))...))...
```

Associated algorithmic problems much harder (NP-hard, #P-hard)!

Parameterized complexity algorithms [Hammer *et al*, BMC Bioinfo 2019]
+ Efficient implementations (RNARedprint, InfraRed)

Amenable to efficient negative design [Yao *et al*, RECOMB 2021]

Towards a fully declarative, highly flexible and efficient framework for RNA design

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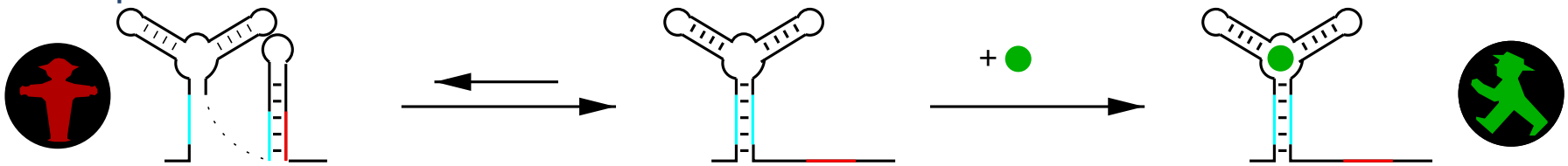

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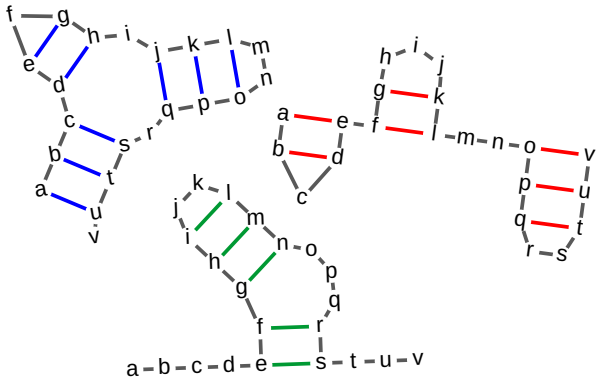

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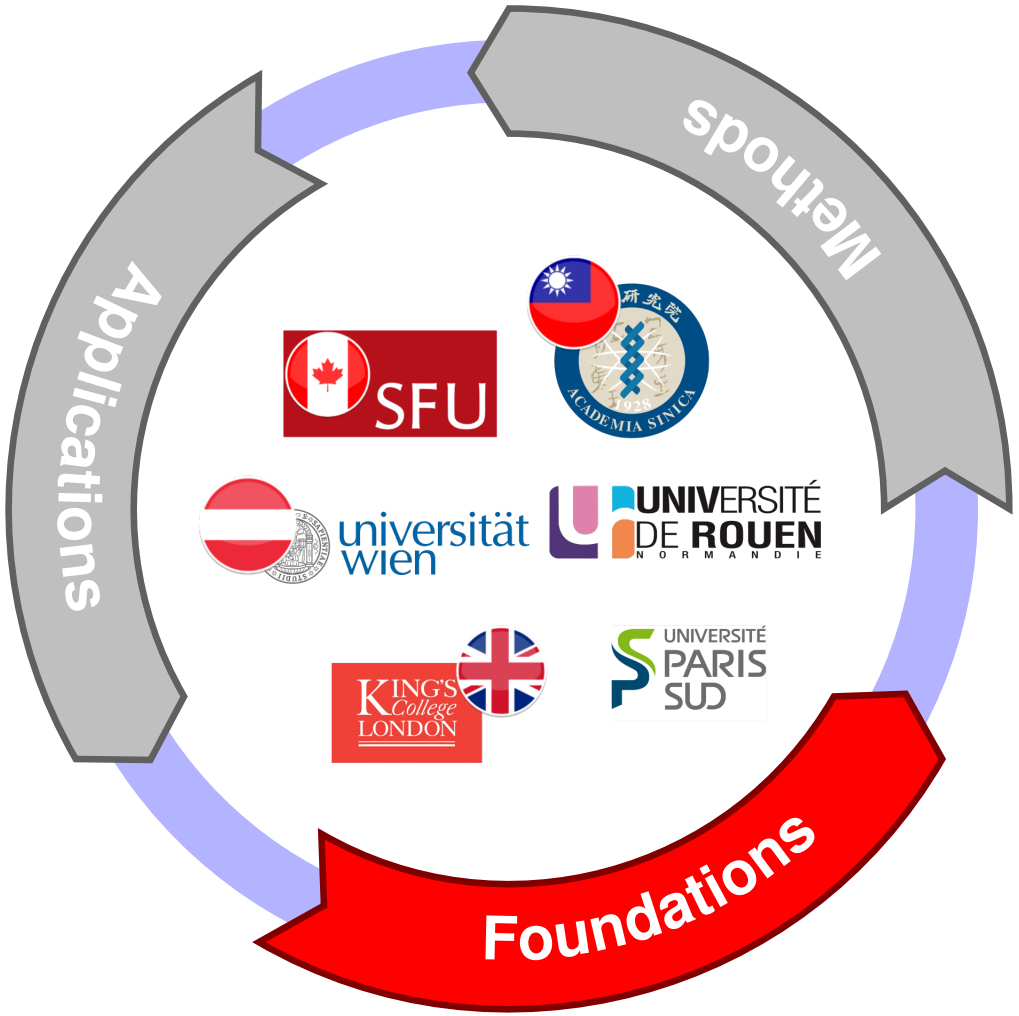

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Discrete Mathematics

- Constraints Satisfaction
- Enumerative/Analytic Combinatorics
- Discrete Algorithms (FPT, approx)
- (Algebraic) Dynamic Programming
- Machine Learning

(Exact) Methods for Molecular Biology

- Structure modeling
- Rational design
- Predicting interactions
- Visualization

Applications

- Structure modeling for RNA viruses
- Cancer transcriptomics
- Aptamer/drug design (Alzheimer)
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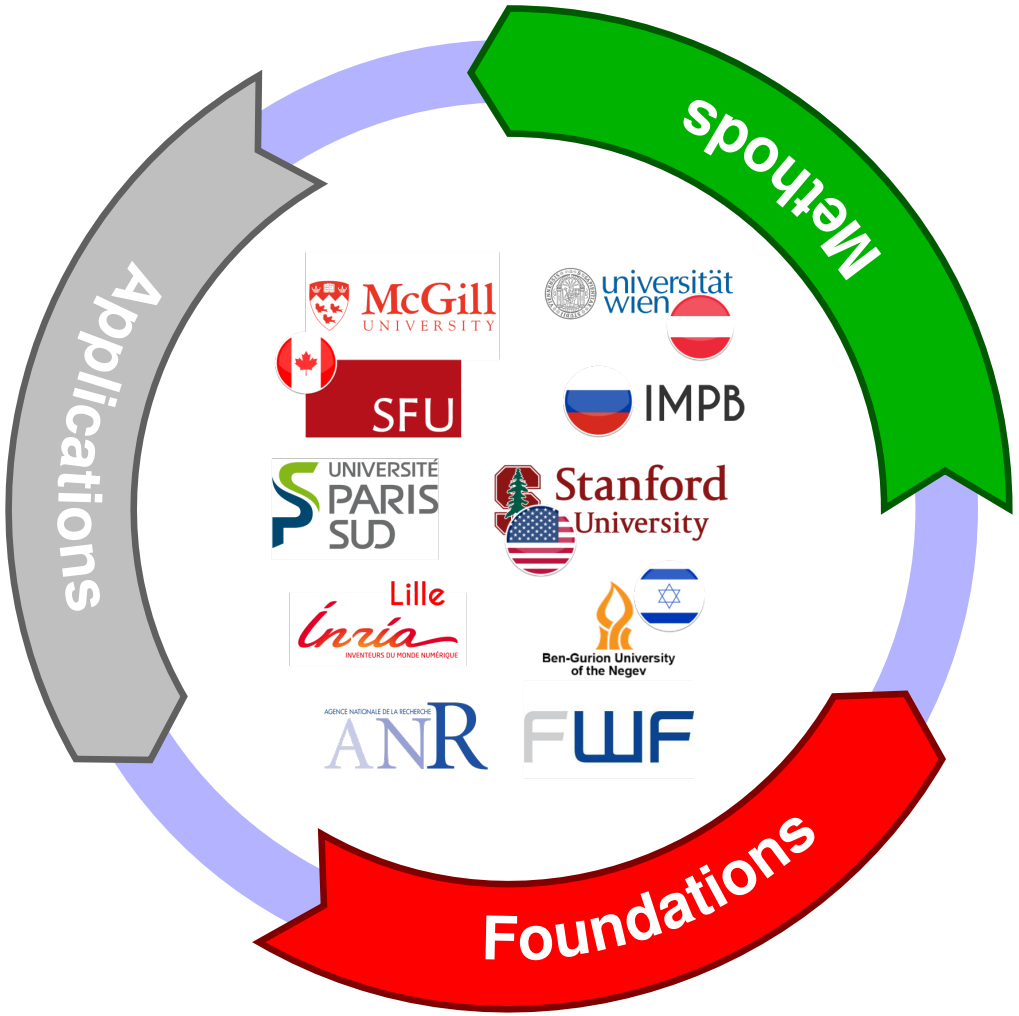

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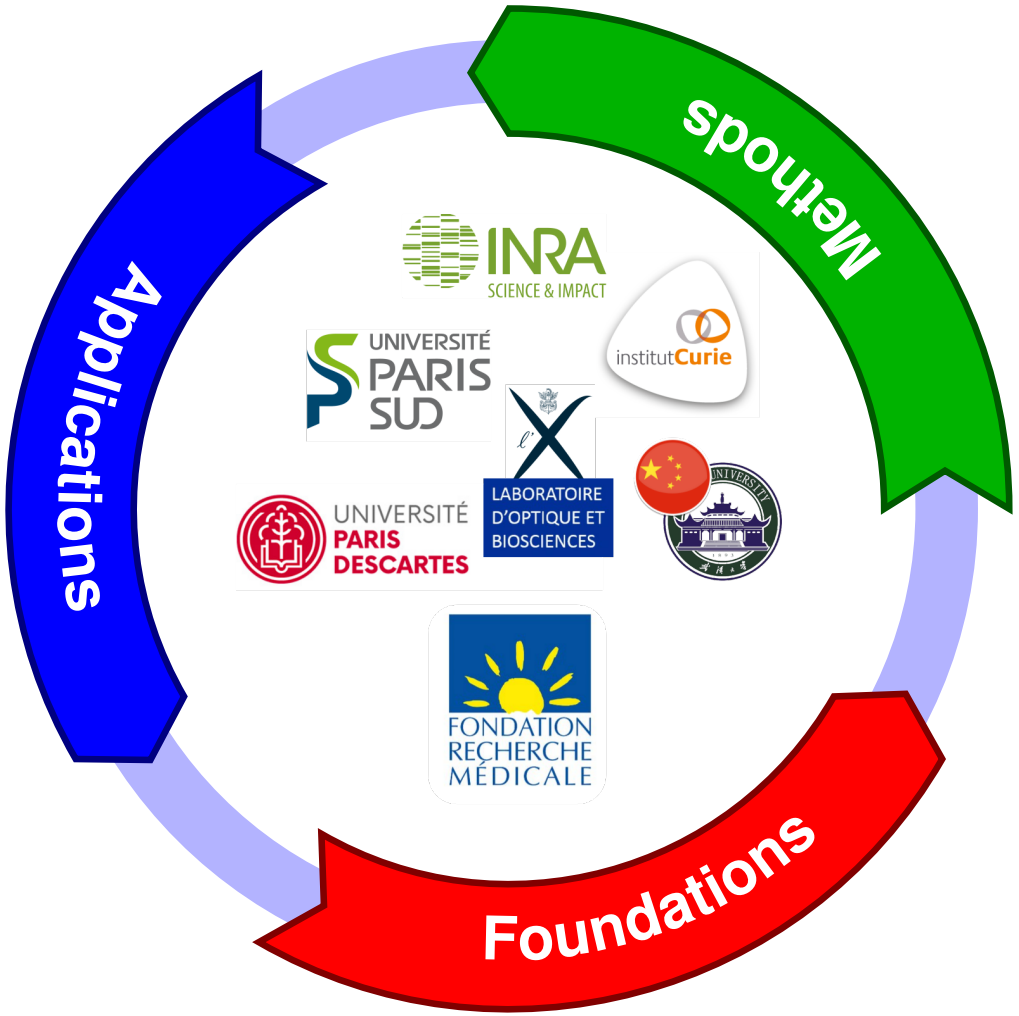

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- Machine Learning

(Exact) Methods for Molecular Biology

- Structure modeling
- Rational design
- Predicting interactions
- Visualization

Applications

- Structure modeling for RNA viruses
- Cancer transcriptomics
- Aptamer/drug design (Alzheimer)
- Evolution

Thanks