

Reliable Prediction of Viral RNA Structures

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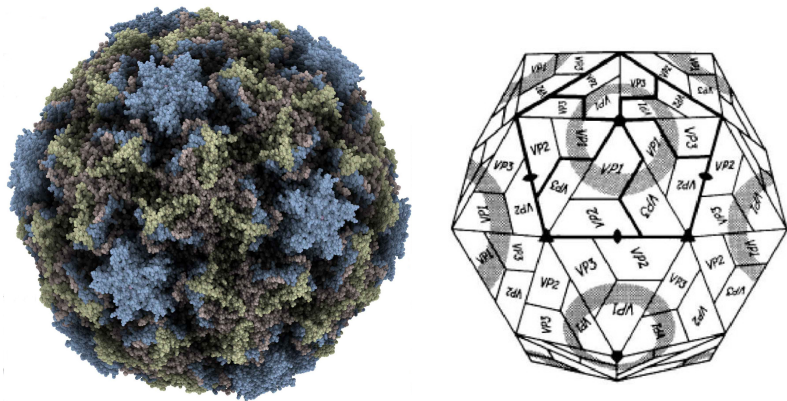


Figure: Crystal Structure and Schematic of Rhinovirus A ¹

Genome size (nt): Human: 3.2×10^9 Rhinovirus: 7×10^3

¹Zhao et al. 1996

Viruses and RNA Structure

- Viruses have little space (small genomes) for information storage
- Specific Functions are often provided by RNA Structures

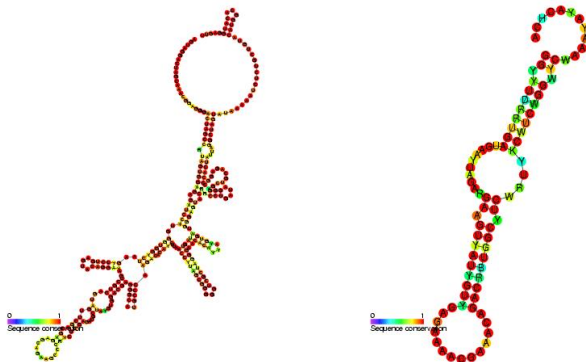


Figure: Pestivirus IRES¹, Rhinovirus CRE-Element

¹Rfam IDs: RF00209, RF00220

Tools for prediction of RNA Secondary Structure:

Structure Prediction Tools

- RNAfold** Prediction of MFE structures/Structure Ensembles
- RNAalifold** RNA folding with evolutionary constraints
- RNAplfold** Local structure Prediction
- AliDot** Heuristic - predicts plausible Structures from alignments
- RNAz** Uses machine learning for conserved structure detection

- How do they perform on Viruses?
- Can we use our tools to find annotated structures?
- What is the optimal approach?

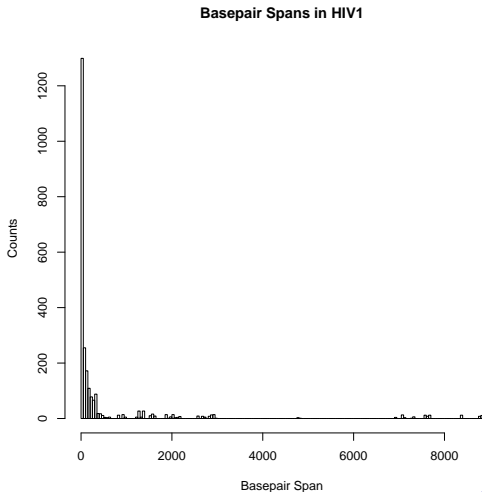
HIV1 Structure - The Gold Standard



Figure: HIV1 genome, folded with SHAPE-Data¹

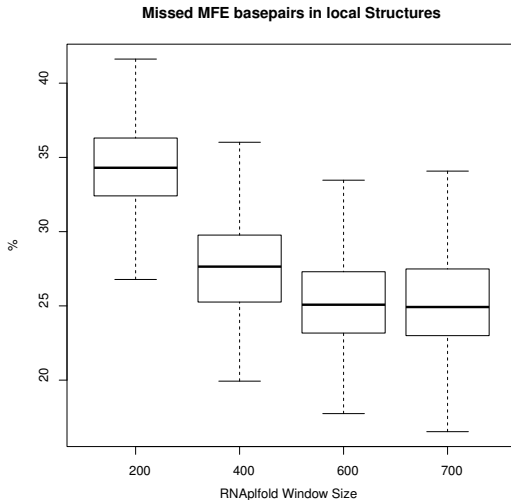
¹Watts et al. 2009

How far reaching are base-pairings in HIV1?



Local vs. Global Folding

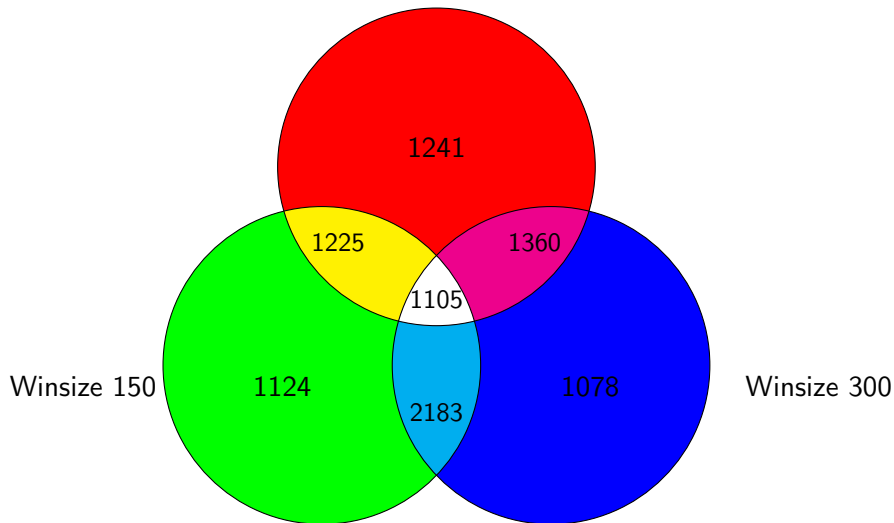
How many HIV1-MFE basepairs do we miss by folding locally?



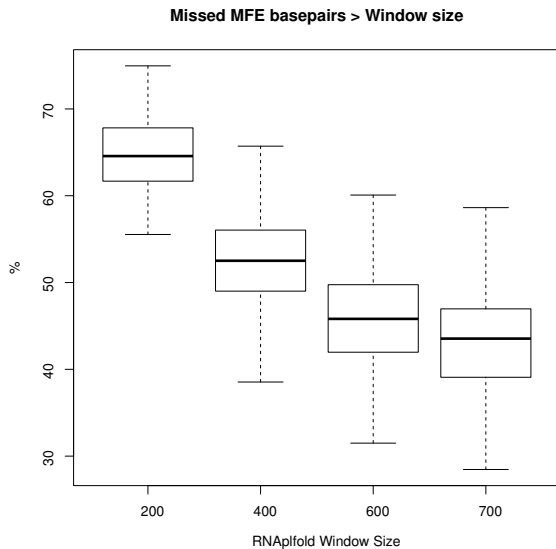
Global vs. Local Folding

RNAfold vs RNAlfold - Shared Basepairs

RNAfold - with SHAPE constraints



Local vs. Global Folding



Annotated viral RNA Structures

Name	Hits	Length
RRE	200	336
HIV_GSL3	200	83
HIV_POL-1_SL	200	112
HIV_FE	186	51
HIV-1_SL4	175	19
HIV-1_DIS	148	39
mir-TAR	139	60
HIV-1_SL3	129	22
HIV-1_SD	121	18
HIV_PBS	90	96
astro_FSE	3	51
mir-224	1	96

Table: Rfam - Annotated RNA structures in 200 Reference HIV1 genomes

Reproduction of Rfam-annotated Structures

Element 1: HIV-1_DIS (Retroviral Psi packaging element)

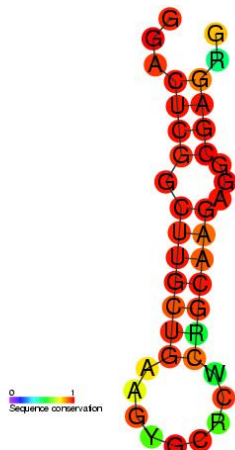


Figure: HIV Retroviral Psi packaging Element

Reproduction of Rfam-annotated Structures

Reference (Rfam)	...(((.((((((((.....)))))))))...))...)
RNAfold (global))..))(((((((.(((((.....((.....
RNAfold (local)	..(((.((((((((.....).)))))))))...))...)

Table: HIV1 Psi Packaging Element, Alignment Size: 200, MPI = 86.91

Reproduction of Rfam-annotated Structures

Reference (Rfam)	...(((.(((((((.....))))))....)))... <hr/>
RNAfold (global)))..))(((((((.((((.....((.....)
RNAfold (local)	..(((.(((((((.....).))))))....)))... <hr/>
Alifold (local, clustal)	..(((.(((((((.....))))))....)))... <hr/>
Alifold (local, mlocarna)(((((((.....))))))....))....
Alifold (global))).(((.(((((((.....))))))....)))... <hr/>

Table: HIV1 Psi Packaging Element, Alignment Size: 200, MPI = 86.91

Reproduction of Rfam-annotated Structures

Reference (Rfam)	...(((.((((((.....))))))...)))...
RNAfold (global)))..))(((((((.((((.....((....))
RNAfold (local)	..(((.((((((.....)))))...)))...
Alifold (local, clustal)	..(((.((((((.....))))))...)))...
Alifold (local, mlocarna)(((((((.....)))))).....
Alifold (global))).(((.(((((((.....))))))...)))...
mlocarna	..(((.(((((((...(...).))))))...)))..
AliDot	..(((...(((.....))))...)))..
RNAz	..(((.((((((.....))))))...)))...

Table: HIV1 Psi Packaging Element, Alignment Size: 200, MPI = 86.91

Reproduction of Rfam-annotated Structures

Element 2: HIV_POL-1_SL (HIV pol-1 Stem Loop)

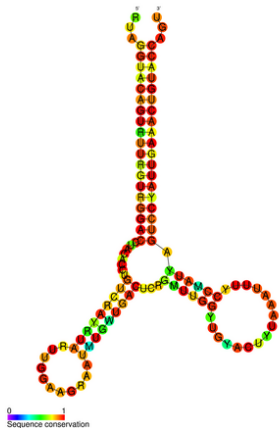


Figure: HIV pol-1 stem loop

Reproducibility of HIV_POL-1_SL

Reference (Rfam)((((((((((((((((((((.....(((((((.....))))))))).....((((.....))))))..)))))))))))))).....
RNAfold (global)))((((.....(((.....(((((((.....))))))))).....))))..))..(((((((.....((((.....))))))..))..))..
RNAfold (local)(((((((.....(((((((.....))))))))).....))))..))))..))))..))))..))))..))))..))..
Alifold (local, clustal)((((.....)))).....
Alifold (local, mlocarna)(((((((.....(((((((.....))))))))).....))))..))..))))..))))..))))..))))..))..
Alifold (global)(((((((.....(((((((.....))))))))).....))))..))))..))))..))))..))))..))))..))..

Table: HIV1 Polymerase 1 stem loop, Alignment Size: 200, MPI=87.99

- Even though long range interactions are found, the HIV1 genome is dominated by short-range base pairings
- Unconstrained, global Folding fails to reproduce known structures
- Sequence - based alignments can bias consensus-structure based folding of viral structures

Acknowledgements

- Ivo Hofacker
- Christoph Flamm
- TBI colleagues
- ..and you!



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wien

FWF

Der Wissenschaftsfonds.