1 SUPPLEMENTARY DATA

1.1 Benchmark other softwares

To evaluate the performances of IncaRNAtion, we benchmark a set of classical softwares lacking GC-content control. Those are RNAinverse, INFO-RNA, NUPACK:Design and Frnakenstein. We present in Fig. 1 the average sequence identity and frequency for the sequences that generated them.

1.2 Benchmark IncaRNAtion +RNAinverse

To emphasize the usefulness of processing IncaRNAtion sequences with RNAinverse, we present the number of structures for which at least one sequence was generated with the desired MFE in Figure. 2

1.3 Limited impact on GC of local-search postprocessing of IncaRNAtion output

Since local search approaches tend to experience a bias towards GC-rich regions, it could be expected that our glocal approach, by postprocessing unpaired regions using a local search algorithm, would suffer from such a drift. However, as summarized in Table 1, we observed that the local search heuristic used to design nucleotides in loop regions has a very limited impact on the GC-content. For each class of GC-content, we reported the observed GC-content in the sequence initially generated by IncaRNAtion, and the observed GC-content after the RNAinverse postprocessing (as defined in Section **??**). Our results show that the GC-content is relatively well conserved (less than 6% variation), with a general tendency of the postprocessing step to bring the GC-content back to 50%.

Target GC-content (%)	GC-content (%) of designed sequences	
	IncaRNAtion (Global)	IncaRNAtion + RNAinverse (Glocal)
10%	15%	21% ↗ 6%
30%	30%	33% ↗ 3%
50%	48%	49% ↗ 1%
70%	71%	69% ↘ 2%
90%	83%	78% ↘ 5%

Table 1. Observed GC-content of solutions returned by IncaRNAtion (2nd column) and after the application of the local search postprocessing (3rd column).

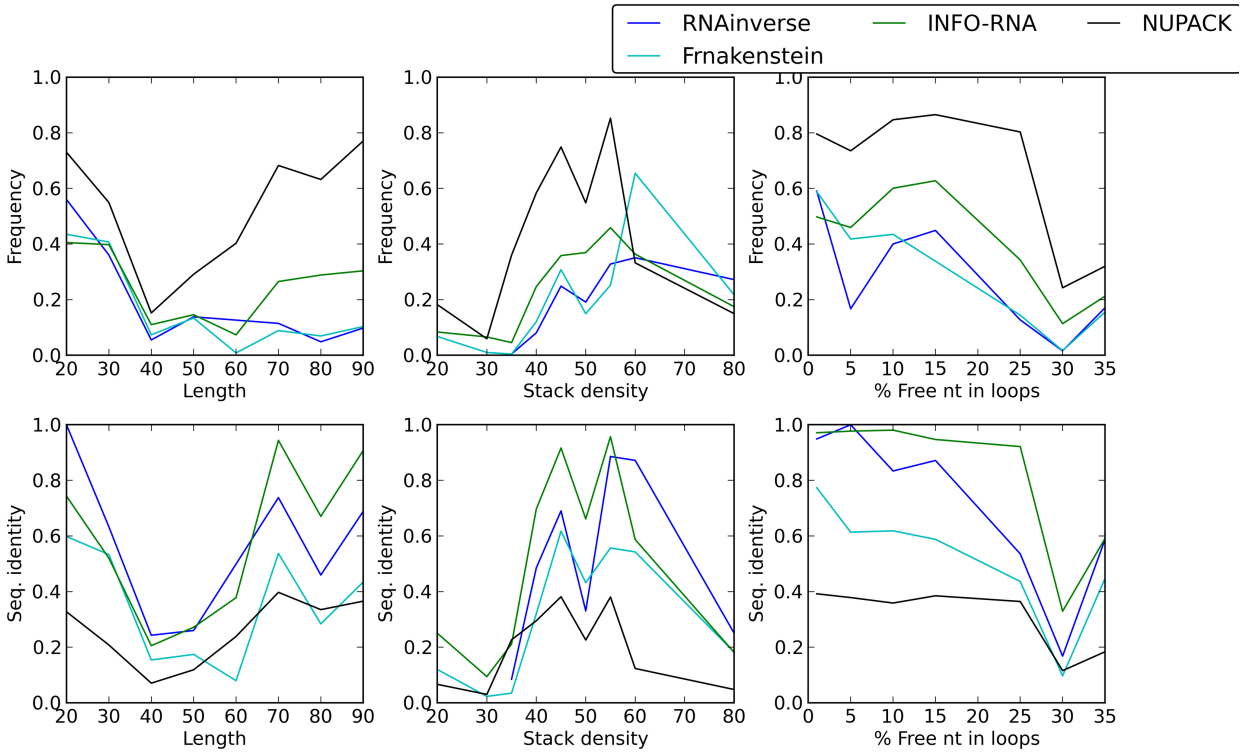

Fig. 1: The average sequence identity and frequency for softwares without GC-content control.

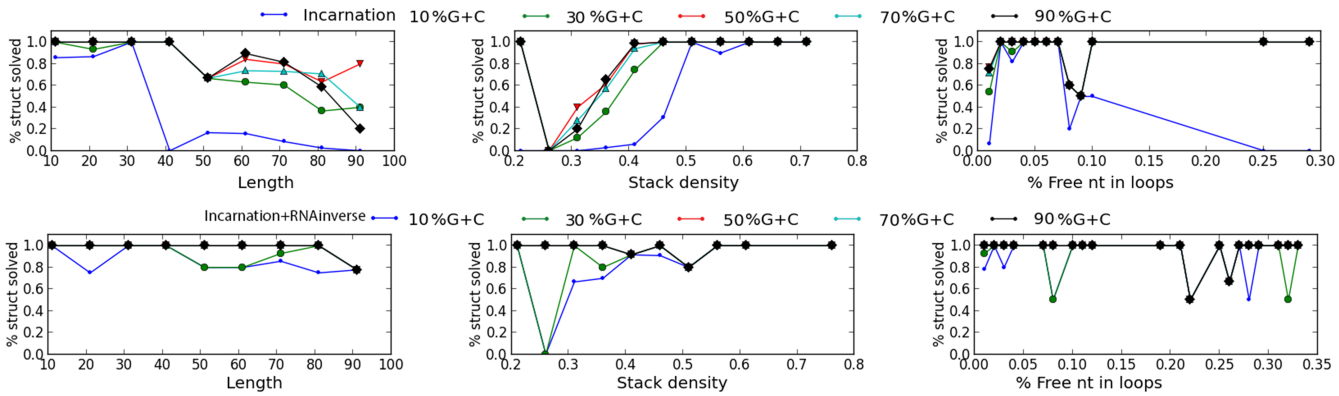

Fig. 2: The first row shows the number of structures for which one generated sequence has the structure as MFE when only using `IncaRNAtion`. The second row shows when we process `IncaRNAtion` results with `RNAinverse`.