

## A New Model for the Kinetic Folding of RNA

Wilfred Ndifon,<sup>1,2</sup> Dwayne Hill<sup>1</sup>, and Asamoah Nkwanta<sup>2</sup>

**Keywords:** RNA folding, folding trajectories, metastable states, complex adaptive systems

### 1 Introduction

The kinetic folding of RNA at the coarse-grained secondary structure level can be thought of as a time-series of structural rearrangements, involving the successive formation, dissociation, or shifting of a single base pair [1,2]. Here, such kinetic folding is modeled as a complex adaptive system [3] in which the rate of structural rearrangement depends only on the local context of the nascent RNA structure and on an autonomous stochastic process that determines, based on a prescribed fitness criterion, the rearrangements that will occur during a given time interval/step. Using examples from natural RNAs, it is shown that from the (local) structural rearrangements emerge characteristic (global) RNA folding dynamics. The new model offers substantial improvement in computational efficiency over existing RNA folding methods that operate on a similar move-set, e.g., *kinfold* [1,2].

### 2 The model

The kinetic folding of RNA is modeled as a complex adaptive system. The components of the system are the individual bases of an RNA sequence, including their specific local contexts, and inter-component interactions involve bond formation, dissociation and shifting. Only pair-wise accessible<sup>3</sup> and complementary bases are allowed to interact. Each such interaction constitutes a local rearrangement of the nascent RNA structure, i.e., a local move in RNA conformation space. The probability of a given interaction,  $P_i$ , is computed based on the Kawasaki dynamics [4]. During each time step,<sup>4</sup> stochastic universal sampling [5] is applied to determine which interactions can proceed, using  $P_i$  as fitness criterion. The model has been implemented in a C# program that is available from W.N.

### 3 Sample applications

To illustrate the usefulness of the model, we studied the folding kinetics of the yeast tRNA<sup>Phe</sup> and SV11 molecules. We found that stabilizing the hairpin loops of tRNA<sup>Phe</sup>, through base modifications, significantly decreases folding times (see Figure 1a). We also used flux dynamics from a representative folding trajectory to illustrate the ruggedness of the tRNA<sup>Phe</sup>'s folding landscape (see Figure 1b). Furthermore, we determined the rates of formation of both the stable and metastable structures of SV11 (see Figure 2). These results are in agreement with experimental data, as well as with predictions made by *kinfold* [2]. Note that the

---

<sup>1</sup>Department of Biology, Morgan State University, Baltimore, MD 21251

<sup>2</sup>Department of Mathematics, Morgan State University, Baltimore, MD 21251

<sup>3</sup>This condition prevents the formation of pseudo-knots.

<sup>4</sup>Folding times are calibrated using experimentally measured hairpin kinetics [6], as in [2].

greater computational efficiency of our model (see Table 1) allowed us to simulate longer folding times for tRNA<sup>Phe</sup> and SV11 ( $1.5 \times 10^4 \mu s$ ) than was done in [2] (i.e.,  $600 \mu s$ ).

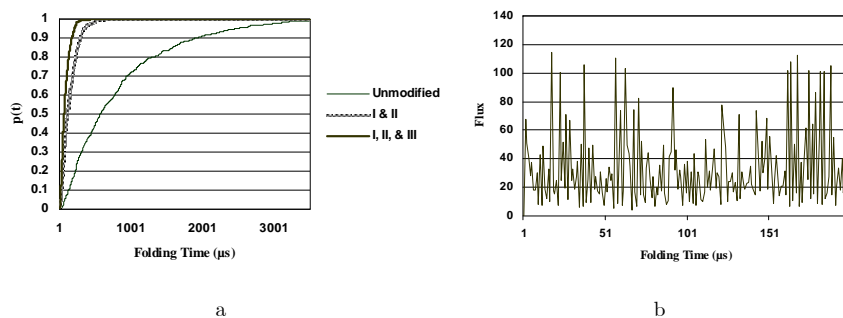


Figure 1. a) Folding kinetics of the modified and unmodified tRNA<sup>Phe</sup>. I, II, and III indicate the modified hairpin loops. (b) Flux dynamics.

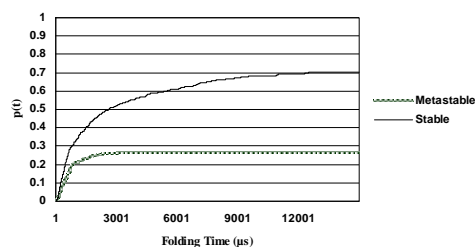


Figure 2. Rates of formation of the stable and metastable structures of the 115nt SV11.

<b>Folding Method</b>	<b>Success Rate (%)</b>	<b>Avg. CPU Time (s)</b>
Kinfold	100	1740
Our model	100	20

Table 1. Average CPU time from 1000 simulations of tRNA<sup>Phe</sup> folding, performed on an Intel Pentium III machine running Windows XP. Success rate refers to the fraction of simulations that found the ground state.

## 4 References

- [1] Flamm, C. et al. 2000. RNA Folding at elementary step resolution. *RNA* 6:325-338.
- [2] Flamm, C. 1998. Kinetic folding of RNA. Doctoral dissertation. University of Vienna, Austria.
- [3] Levin, S. A. 2003. Complex adaptive systems: Exploring the known, the unknown and the unknowable. *Bulletin of the American Mathematical Society* 40:3-19.
- [4] Kawasaki, K. 1966. Diffusion constants near the critical point for time-dependent Ising models. *Physical Review* 145:224-230.
- [5] Baker, J. E. 1987. Reducing bias and inefficiency in the selection algorithm. In Grefenstette, J. (ed.) *Proceedings of the Second International Conference on Genetic Algorithms and their Application*, Hillsdale, NJ, Lawrence Erlbaum Associates, pp. 14-21.
- [6] Pörschke, D. 1974. Thermodynamic and kinetic parameters of an oligonucleotide hairpin helix. *Biophysical Chemistry* 2:283-296