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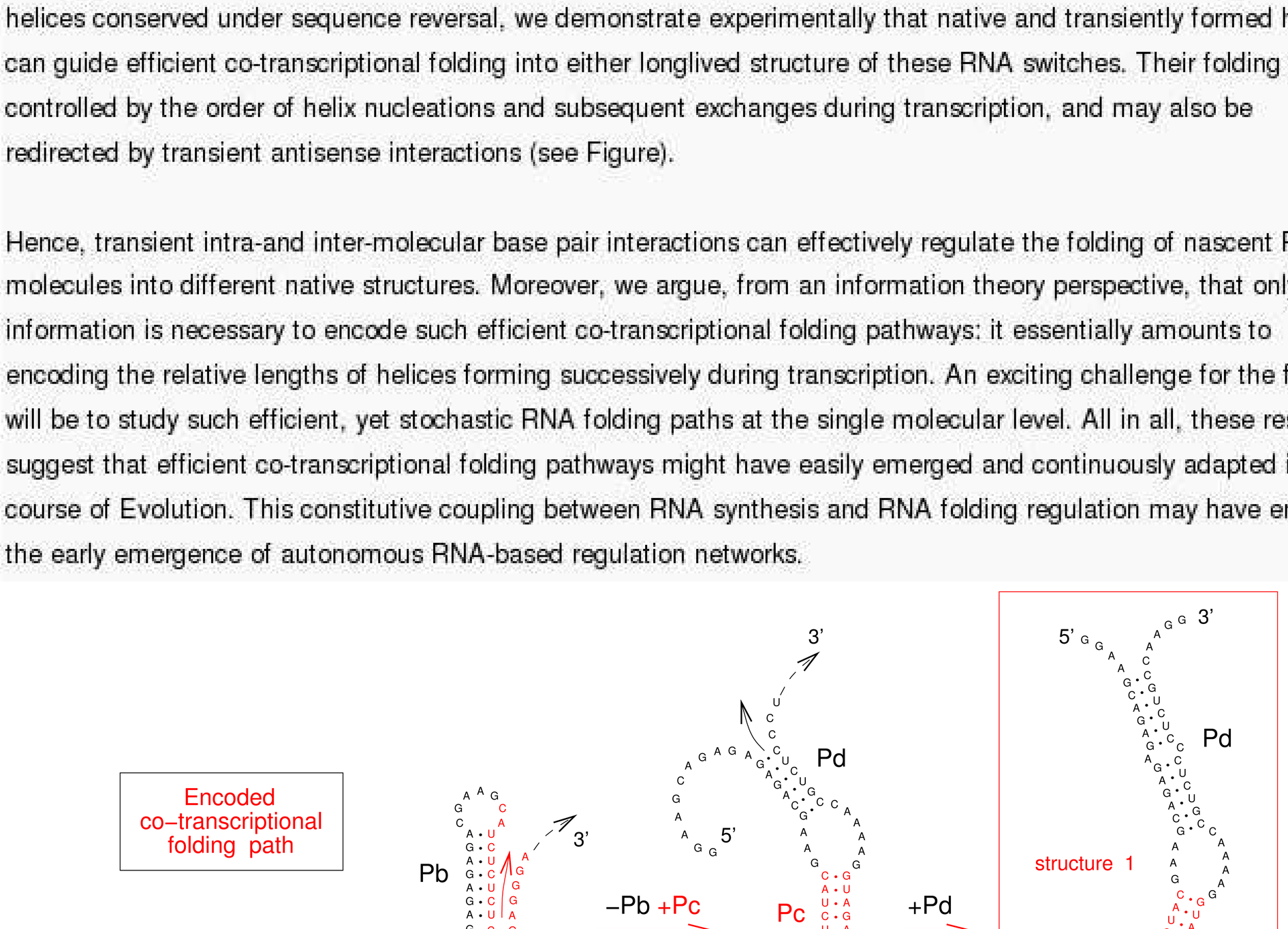
Encoding folding paths of RNA switches

HFSP Program Grant holder Herve Isambert and colleagues

RNA molecules exhibit a wide range of functions from essential components of the transcription/translation machinery to natural ribozymes, in vitro selected aptamers, and gene expression regulators. In particular, recently discovered non-coding RNAs participate in a variety of gene expression controls from metabolic pathways (riboswitches) to various stress responses in bacteria, or developmental timing (miRNA), gene silencing (siRNA) and epigenetic remodeling of chromatin in some multicellular eukaryotes. Yet, because of their limited four-letter alphabet and strong base pair stacking energies, RNAs are also prone to adopt long-lived misfolded structures, as observed for instance upon heat renaturation. Hence, efficient RNA folding paths leading to properly folded structures bear an important role in the regulatory function of non-coding RNAs and mRNA untranslated regions (UTRs). Indeed, RNA co-transcriptional folding has long been suspected to play an active role in helping proper native folding of ribozymes and regulatory structural motifs in mRNA UTRs. Yet, the underlying mechanisms and coding requirements for efficient co-transcriptional folding has remained unclear.

Traditional approaches have intrinsic limitations to dissect RNA folding paths, as they rely on sequence mutations or circular permutations that typically perturb both RNA folding paths and equilibrium structures. In this paper, we show that exploiting sequence symmetries instead of mutations can circumvent this problem by essentially decoupling folding paths from equilibrium structures of designed RNA sequences. Using bistable RNA switches with symmetrical helices conserved under sequence reversal, we demonstrate experimentally that native and transiently formed helices can guide efficient co-transcriptional folding into either longlived structure of these RNA switches. Their folding path is controlled by the order of helix nucleations and subsequent exchanges during transcription, and may also be redirected by transient antisense interactions (see Figure).

Hence, transient intra-and inter-molecular base pair interactions can effectively regulate the folding of nascent RNA molecules into different native structures. Moreover, we argue, from an information theory perspective, that only little information is necessary to encode such efficient co-transcriptional folding pathways: it essentially amounts to encoding the relative lengths of helices forming successively during transcription. An exciting challenge for the future will be to study such efficient, yet stochastic RNA folding paths at the single molecular level. All in all, these result suggest that efficient co-transcriptional folding pathways might have easily emerged and continuously adapted in the course of Evolution. This constitutive coupling between RNA synthesis and RNA folding regulation may have enabled the early emergence of autonomous RNA-based regulation networks.



PubMed link

Reference:

Encoding folding paths of RNA switches, A. Xayaphoummine, V. Viasnoff, S. Harlepp and H. Isambert, Nucleic Acid Res. 2007, 35(2), 614-622. Epub 2006 Dec 18