The nuts and bolts of translational efficiency and the "closed-loop" model

Do you remember that clear image in your biology text book showing an extended eukaryotic mRNA circularized by protein-RNA and protein-protein interactions? Yes, that's right: the "closed-loop" model. It is a simple yet elegant theory for how bringing the 5' and 3' ends of an mRNA together protects the mRNA from degradation. At the same time the model allows ribosomes to circulate around the message thereby boosting translational efficiency.

In the classical model the 5' cap of an mRNA is bound by the cap-binding protein eIF4E, this interacts with the translation initiation factor eIF4G which then sticks to poly-(A) binding protein that is bound to the mRNA poly-(A) tail. But did you know that the wonderful atomic force microscopy image that appears in all the text books has a major caveat? In this work the mRNA was hybridized to a complementary DNA molecule which artificially held the mRNA in a looped out and unstructured state...

The time may be ripe to start re-thinking the "closed-loop" model. This is not an easy task given that knockout of eIF4E, eIF4G and PABP proteins is lethal in yeast and mammals… An interesting new possibility that Vicens et al (Mol Cell 72, 2018, 805-812) have recently highlighted is that there are lots of reasons why eukaryotic mRNAs might have 5' and 3' ends which are in close proximity

independent of interactions between the 5’ cap and poly-(A) tail precisely because mRNAs are not unstructured like the pictures in the text books. In a given mRNA every nucleobase can interact with every other nucleobase, the RNA backbone is very flexible, bases can stack together and many tertiary interactions are possible. So maybe most eukaryotic mRNAs have good 5’ to 3’ end communication even in the absence of external factors?

Benefits of a 5' cap and poly-(A) tail for translational efficiency

What can’t be ignored though is that there is support for the “closed-loop” model which is relevant to anyone who wants to translate mRNA into their favourite protein: lengthening the 3’ poly-(A) tail is associated with an increase in cap-dependent translation; shortening the poly-(A) tail not only decreases translation efficiency but also reduces mRNA stability. Don't forget that there is also no doubt that the presence of a 5' cap strongly stabilises eukaryotic mRNAs, so even if you are unsure about the "closed-loop" model, having a 5' cap on your mRNA will surely increase translational efficiency too...

If you want to take advantage of these benefits we recommend the excellent 5’-capping and poly-(A) tailing kits available from Cellscript through Cambio.

See here for 5’ capping
See here for poly-(A) tailing

Tech tip:

To prepare synthetic mRNA with both 5’ cap and poly-(A) tail we recommend transcribing the body of the mRNA first and then dressing with 5’ cap and poly-(A) tail later.