

What is faster, transcription or translation?

Transcription, the synthesis of mRNA from DNA, and translation, the synthesis of protein from mRNA, are the main pillars of the central dogma of molecular biology. How do the speeds of these two processes compare? This question is made all the more interesting as a result of the existence of the “Christmas tree” structures (see Fig. 1) observed in prokaryotes which reflect the simultaneous transcription and translation of the same gene and which suggest a synchrony between the two processes.

Transcription of RNA by RNA polymerase in *E. coli* cells proceeds at a maximal speed of about 40-80 bp/sec (Dennis & Bremer 1974, *E. coli* and salmonella 1996). Translation by the ribosome in *E. coli* proceeds at a maximal speed of about 20 aa/sec (Young & Bremer 1976, Dennis & Bremer, *EcoSal* 1996). Interestingly, since every 3 base pairs code for one amino acid, the rates of the two processes are quite similar and as noted above, this is probably not accidental. Translation that is faster than transcription would cause the ribosome to “collide” with the RNA polymerase. Is there some biological reason why transcription is not significantly faster than translation? There are probably multiple explanations, and one of them centers on the ability of the cell to be able to have viable feedback. Arguments from control theory demand that to have stable regulation there needs to be time to respond to the feedback signal itself. If transcription was much faster than translation the response to a signal for a change in gene expression could overshoot the required response; the cell will produce a lot of mRNA and the signal that enough proteins are now present will come too late.

How does one know the rates of these key processes of the central dogma? This is an interesting challenge even with today’s advanced techniques. Let’s consider how we might attack this problem. If you’re thinking: “let’s express a GFP and measure the time until it appears”, you should check out the section on maturation time (minutes to an hour) of a fluorescent protein, which demonstrates a mismatch of time scales between the processes of interest and that of the putative readout.

This question was even more challenging given the more limited experimental arsenal available in the 1970’s when the answers were first convincingly obtained. Yet, in a series of clever experiments, Miller *et al.* using electron microscopy and Bremer and colleagues, at the University of Texas but formerly from the Copenhagen School were able to come up with ingenious techniques based on using radioactive labeling to achieve exactly that. They relied on a subtle quantitative analysis in order to tease out the rates.

Measurements on transcription rates were based upon a special trick in which transcription initiation was shut down by using the drug rifampin. Though no new transcription events can begin, those that are already proceeding continue unabated. As a result, this drug treatment effectively begins the running of a stopwatch which times how long since the last transcription process began. Amazingly, in these experiments, by then stopping the transcription process completely at different times after the drug treatment and then performing electron microscopy (resulting in images like that shown

in fig. 1) it was possible to measure the length of RNA polymerase-free DNA and from this to back out the rate at which these polymerases are moving.

As with the transcription measurements, the measurement of translation rates similarly depended upon finding an appropriate stopwatch, but this time for the protein synthesis process. The crux of the method is the following: add a labeled amino acid at time zero and follow the fraction of labeled products of mass m comparing it to the overall fraction that is labeled (the equation used by Young *et al.*, 1976, was: $F(m, t) = (\text{label in polypeptides of mass } m \text{ at time } t) / (\text{label incorporated into total protein at time } t) = (3\text{H in mol.wt. class } m \text{ at time } t) / (3\text{H in total protein at } t)$). What would you expect to see? Immediately after the pulse of labeled amino acids one starts to see labeled proteins of mass m ; these are the nascent chains that were almost complete at time zero and which then had radioactive labeling incorporated only onto their unfinished ends. These newly synthesized proteins contain only a small fraction of radioactive labeling since only in the final stages of their translation were there labeled amino acids available. With time the fraction will increase as the newly synthesized chains have a larger proportion of their length labeled. After a time τ_m , depending on the transcript length, the whole chain will be labeled, as these are proteins that began their translation at time zero when the label was added. At this time one observes a peak in the relative fraction of labeled proteins of mass m . Given the time that elapsed, τ_m , and by knowing how many amino acids are in a polypeptide chain of mass m it is possible to derive an estimate for the translation rate. For rigorous understanding of the experimental details, it is useful to refer to the original reference (Young & Bremer 1976). The values achieved of 10-20 aa/sec were in line with earlier observations (Jacobsen 1974) that were based on a more narrow range of observations in which the enzyme beta galactosidase (LacZ) was abruptly expressed and the time at which initial enzymatic activity was observed was measured. From knowledge of the length of the protein a similar value was derived.

What happens in eukaryotes? In yeast the rate of translation is about 2 fold slower, but one should note that the “physiological” temperature at which it is measured is 30°C whereas for *E. coli* measurements are at 37°C. The slower rate is what one would expect based on the general tendency of about a factor of 2-3 per 10 deg (Q10 value, BNID 100919). Transcription in monkey and human cells was shown to consist of elongation at rates that are similar to those measured in *E. coli* (50-100 nts/sec, BNID 105113, 100662) interspersed with pauses leading to an average rate that is about an order of magnitude slower (~6 nts/sec, 100661). It should be kept in mind that in eukaryotes, transcription and translation are not as intimately coupled as in bacteria due to the fact that they are actually geometrically segregated with transcription taking place in the nucleus and translation in the cytoplasm. Further, as introns are excised from transcripts prior to translation the correspondence between the rates is trickier. Finally, we note that a key process is the initiation of transcription that can sometimes be the rate limiting step.

Fig. 1 – Christmas tree structure exhibiting simultaneous transcription and translation of the same gene. (Miller, Science, 169, 392 (1970))

