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# Revisiting replication-induced transcription in *Escherichia coli*

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Bacterial transcription is highly complex. Producing a single RNA molecule requires thousands of molecular steps, each subject to cellular regulation. It is therefore peculiar that, for a long time, the kinetics of RNA production in *E. coli* were imagined to be extremely simple, frequently described as a Poisson process where the probability of making RNA from the gene is constant in time. However, as single-cell measurements have enabled the experimental interrogation of transcription, assumptions of simplicity have begun to fail. Thus, the Poissonian picture was upended by the observation that transcription from multiple *E. coli* promoters takes place in a pulsatile, bursty manner, a behavior later found in eukaryotes as well[1].

Another simplifying assumption commonly made concerning *E. coli* transcription was that it is independent of the bacterial cell cycle. But, in fact, cell-cycle progression involves many changes that could conceivably modulate transcription; for example, the continuous decrease in the concentrations of RNA polymerase and transcription factors as the cell volume increases. The cell cycle also involves discrete events that may have a dramatic effect on transcription, such as cell division (which randomizes the numbers of molecules in the cell) and the replication of the transcribed gene. With regard to the latter event, in particular, it was hypothesized long ago that transcription of some genes (those encoding low-copy proteins) would take place at the time of gene replication, rather than throughout the cell cycle[2]. The idea of replication-induced transcription was motivated by experiments in the 1960s, which found that populations of synchronized bacteria exhibited a step-like increase in protein production at a single time during the cell cycle. Multiple mechanisms were put forward as potentially enabling the coupling of transcription to replication, including the changes in DNA supercoiling and methylation surrounding the replication fork, the movement of the replicated gene to the surface of the nucleoid, and the transient de-repression of the newly replicated gene copy. The latter idea, that a bound repressor will be removed by the moving replication fork, is consistent with recent single-molecule measurements[3].

However, until now, direct observation of the coupling between gene replication and transcription has not been reported. This is because commonly used genomic and single-cell measurements of mRNA in bacteria are oblivious to the cell-cycle phase of the interrogated cells. To overcome this limitation, we recently combined single-molecule quantification of mRNA and its encoding gene locus, to measure the transcriptional activity of an endogenous

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gene in individual *E. coli*[4]. Tracking this activity along the bacterial cell cycle, we found that, just as predicted by Guptasarma [2], a weakly expressed gene exhibited a transient increase in transcription around the time of gene replication. In contrast, the activity of a strong consecutive promoter appeared constant throughout the cell cycle, with the amount of cellular mRNA closely following the gene dosage[4].

While our results demonstrate that transcription is correlated with gene replication, elucidating the mechanistic origins of this effect will require the measurement of additional cellular observables, which are currently still inaccessible at the single-cell level: the supercoiling and methylation state, transcription-factor binding, and spatial position, at and around the moving replication fork. Just as intriguing, but similarly unknown, are the physiological consequences of replication-induced transcription. Most notably, whether it serves to abrogate the cell's risk of losing the complete pool of a critical protein present at low numbers, as would occur frequently under the scenario of stochastic Poissonian transcription[5]. Thus, as always in biology, new findings may settle one question but beget many others.

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