Cooperative behavior on gene expression: a stochastic sequence-dependent model for transcription on E. coli

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INTRODUCTION

The transcription of the information encoded within the DNA to an RNA molecule has as the protagonist the RNA polymerase enzyme (RNAP). Theoretical models have been proposed to explain and predict the RNAP kinematics during the polymerization. However, experiments showed that if more than one RNAP molecule initiates from the same promoter, their behavior slightly change and new phenomena are observed. We proposed and implemented a theoretical model that considers collisions between RNAP and predict their cooperative behavior during multi-round transcription. The model generalizes Bai et al. stochastic sequence-dependent model. In our approach, collisions between elongating enzymes modify their transcription rate values.

The Transcription Elongation Complex (TEC), composed by the RNAP, DNA open strand and nascent RNA, could assume three different modes, as we can see in Figure 1.

METHODS

We performed simulations of the kinetics for 1 to 10 RNAP on the same DNA strand; 4800 simulations for each case. The nucleotide sequence considered corresponds to the first 150 nucleotides of the T7 A1 D167 and D387 sequences.

RESULTS

The sequence-dependent parameters are shown on Table 1. $\Delta G$ is the Gibbs free energy for the transcription bubble. $F$ represents an external force on the RNAP and $d$ is the distance of 1bp (approx. 0.34nm).

Using Michaelis-Menten kinetics, the main rate of Eq. 1 is given by

$$k_{max}(n) = \frac{k_{max}[NTP]}{K_{m}[NTP]}$$

The RNAP could also backtracking. Its rate is given by

$$k_{back} = k_0 \exp[(\Delta G' + G_{mol}) + Fd/k_BT]$$

We simulated the elongation using the Gillespie algorithm in Mathematica®.

Collisions between the RNAP molecules modify their transcription rate values, changing the $F$ value in Eq. 2 and 4. During the simulation, both the trailing RNAP molecule (T) and the leader one (L) could be in normal elongation, or in backtracking. Basically, if we have a collision and T is in normal elongation, it applies 25pN on L. As the result, L applies 25pN on T in the opposite direction. If L is backtracking and after the collision T moves forwards, T pushes the other forwards. If they both are backtracking, we treat the collision as being perfectly elastic.

CONCLUSIONS

- Our results are in accordance with the literature, showing that the multi-round transcription could enhance transcription, by reducing pauses duration and suppressing RNAP backtracking.
- These may be interpreted as an intrinsic regulation: multi-round transcription could be an efficient way to attenuate pauses in highly transcribed genes, for example.
- The contribution of the interaction of the nascent RNA with the RNAP have to be consider in order to improve the results.

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