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Stochastic Transcription Elongation via Rule Based Modelling

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Abstract

Transcription elongation is the mechanism by which RNA polymerase (RNAP) moves along template unzipped DNA and synthesizes a complementary single-stranded RNA. During the elongation, RNAP forms a stable transcription elongation complex (TEC) with the template DNA and the nascent RNA. The mechanism involves back-tracked and forward-tracked modes of TEC and the polymerisation and depolymerisation of RNA. To capture the stochasticity of the elongation, we describe the mechanism in terms of rule-based modelling through the TEC's local window frame of adjacent active sites. In this way, we can uniformly derive the variations of known kinetic pathways for various interaction combinations of TEC's active sites. From the compact interactions at local sites, we find abstracted rules for the elongation. As the semantic counterpart, we derive quasi-steady state approximations to the chemical master equations. The stochastic models are thermodynamically interpreted as the free energy distributions of agents with variant configurations.

Keywords: RNA polymerase, Transcription Elongation Complex, Master Equation, Rule-Based Modelling, Brownian Ratchet Model, Equilibrium Kinetics, Chemical Equilibrium, Steady State Dynamics, Quasi-Steady State, Michaelis-Menten Kinetics, Free Energy, Boltzmann Distribution

1 Introduction

The stochasticity of gene regulation and expression, which is intrinsic to discreteness and small numbers of molecules partaking in and regulating biological events [19], has been successfully modelled by stochastic process calculi such as stochastic π [22] and rule based κ [7,11]. Such models represent each constituent of the biochemical process by stochastic interactions among agents. Agents interact at biochemical sites through channels at rates modelled by exponential time distributions. As a syntactical rule, this description yields a semantic counterpart of a Markov process, such that each single-step interaction has a Poisson waiting time. Similar modelling has been applied in queue theory [10] and more generally in the theory of stochastic petri nets [9].

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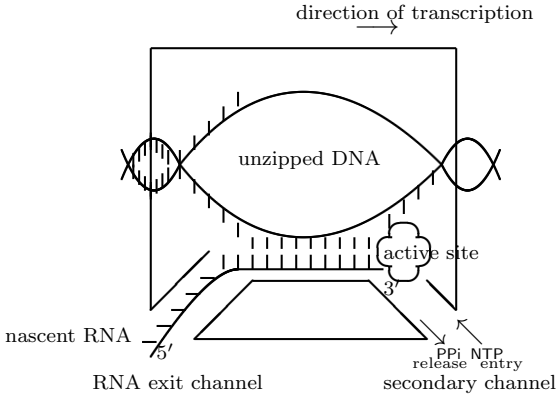

Fig. 1. Structure of TEC

In this paper, we examine whether stochastic rule-based modelling captures multi-step molecular interactions. As biochemical interactions are non-uniform and occur at different rates, they are characterized by stochastic fluctuations, non-Poisson time dynamics and decay of particular biological events. For this purpose, we model *transcription*, which is a typical molecular multi-step interaction. As the first phase of gene expression, transcription involves a tiny minority of the molecules reacting in cells. Thus, for modelling transcription, a rule-based stochastic method is preferred over the deterministic method of mass action laws. Rule-based modelling directly describes the stochastic and discrete nature of chemical reactions in transcriptional elongation. The primitive agents are the hundreds (or thousands) of base pairs contained in a single gene, and a similar number of nucleoside triphosphates (NTPs) that join the transcript via RNA polymerase. The present author applied a similar nucleotide-based modelling concept to multiple branching processes in RNA interference [15].

Transcription (mRNA synthesis) from the corresponding unzipped single-stranded DNA template proceeds in three sequential stages: *Initiation*, *Elongation* and *Termination*. The main stage is elongation. RNAP is a mechano-chemical coupling mechanism that converts the chemical energy derived from NTP hydrolysis into mechanical work, together with random Brownian motion involving back-tracked and forward-tracked modes. The RNAP kinetics and mechano-chemical motions are mediated by the *Transcription Elongation Complex* (TEC) [18], formed by the combination of RNAP, the template DNA and the nascent RNA (cf. Fig 1). The principal kinetic feature is the mechano-chemical cycle of NTP binding: Nucleotide incorporation induces the pre-translocation state of TEC. The TEC advances by 1 bp along the DNA, thereby returning to post-translocation. Initiation is much faster than elongation; moreover, during the elongation phase, the mRNA synthesis is often disrupted by transcriptional pauses, which are linked to the reverse translocation of RNA along the DNA. Therefore, stochastic fluctuations and time delays are characteristic of transcriptional regulation.

Based on recent single-molecule experiments (such as magnetic and optical tweezers and single-molecule fluorescence), researchers have proposed theoretical biochemical models to explain the elongation kinetics in terms of the individual