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Dynamics of +1 ribosomal frameshifting

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ABSTRACT

It has been well characterized that the amino acid starvation can induce +1 frameshifting. However, how the +1 frameshifting occurs has not been fully understood. Here, taking *Escherichia coli* RF2 programmed frameshifting as an example we present systematical analysis of the +1 frameshifting that could occur during every state-transition step in elongation phase of protein synthesis, showing that the +1 frameshifting can occur only during the period after deacylated tRNA dissociation from the posttranslocation state and before the recognition of the next "hungry" codon. The +1 frameshifting efficiency is theoretically studied, with the simple analytical solutions showing that the high efficiency is almost solely due to the occurrence of ribosome pausing which in turn results from the insufficient RF2. The analytical solutions also provide a consistent explanation of a lot of independent experimental data.

1. Introduction

The protein elongation by the ribosome is a precise process, with an error frequency estimated to be less than 3×10^{-5} per codon [1,2]. However, programmed ribosomal frameshifting, i.e., translating ribosomes slipping by one base in either the 5′ (−1) or the 3′ (+1) direction, is the most widely used translational regulation mechanism employed by many viruses to express defined ratios of structural and enzymatic proteins [3–11]. It was shown that −1 frameshifting can occur at the slippery sequence on the presence of a downstream mRNA pseudoknot [6,11–15]. It was also well characterized that the amino acid starvation, i.e., the limitation for particular amino acids, can induce +1 frameshifting [6,11,16–22]. For example, in Ty1 retrotransposable element of yeast *Saccharomyces cerevisiae*, the "hungry" AGG codon induces the translating ribosome to pause over sequence CUU_AGG_C (shown as codons in the initiation reading frame and the dashes separate in-frame triplets), awaiting delivery of the rare aminoacyl-tRNA^{Arg} to the A-site codon AGG [18]. Shifting reading frames of peptidyl tRNA +1 from CUU to UUA makes the new A-site codon GGC, which corresponds to a highly abundant aminoacyl-tRNA^{Gly}. Another well-studied example is the ribosomal +1 frameshifting occurring in the *prfB* gene of *Escherichia coli* [17]. The *prfB* gene encodes the peptide release factor 2 (RF2) that could bind to the ribosome and promote recognition of the UGA terminator, prematurely terminating translation of *prfB*.

In the literature, several models have been proposed to explain +1 frameshifting [16,23–25]. For example, Harger et al. [16] proposed an "integrated model" to explain different effects of mutations that affect selection of aminoacyl-tRNA in the A site, accommodation of the 3′-end of the aminoacyl-tRNA into the peptidyltransferase center, peptidyl transfer and translocation on the +1 and −1 frameshifts. Baranov et al. [24] proposed that the +1 frameshifting efficiency depends on the stability of the P-site interaction and the concentration of incoming aminoacyl-tRNA available for the zero and +1 frames. However, the above two models cannot explain the experimental data showing that the E site also plays a crucial role in the efficiency of +1 frameshifting in *E. coli* [26]. Thus, to include the effect of the E-site tRNA release on +1 frameshifting, Liao et al. [25] proposed a complicated mathematical model, which is in fact composed of three models, called Model 1, Model 2, and Model 3. In Model 1, simultaneous slippage of the E- and P-site tRNAs is hypothesized to occur before aminoacyl-tRNA selection. In Model 2, the E-site tRNA dissociation occurs during the codon recognition step, while in Model 3, the E-site tRNA dissociates after codon recognition. Both Models 2 and 3 result in the formation of ribosomes with only P-site tRNA, which can slip to the +1 frame. It is noted that the kinetic model of Liao et al. [25] supposed that the E-site tRNA dissociation occurs during the codon recognition step and/or after the codon recognition. However, recent single-molecule experimental data showed that the E-site tRNA dissociation occurs mainly during the period after the posttranslocation but before the binding of the aminoacyl-tRNA.EF-Tu.GTP ternary complex [27,28]. Thus, the kinetic model of Liao et al. [25] should be modified to include the effect of tRNA dissociation before the codon recognition.

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In this work, we present a new model for +1 frameshfiting, in which we consider that the E-site tRNA dissociation can occur at any moment after the posttranslocation. Based on our analysis, we propose that +1 frameshifting can occur only during the period after the E-site tRNA dissociation from the posttranslocation state and before the recognition of the next "hungry" codon. The simple analytical solutions show that the occurrence of +1 frameshifting is almost solely due to the occurrence of pausing which in turn results from the insufficient RF2 for *E. coli* RF2 frameshifting or the rare CCU-tRNA^{Arg} for Ty1-mediated frameshifting. The analytical solutions also provide a consistent explanation of a lot of independent experimental data.

For convenience of writing, in this work we take *E. coli* RF2 programmed frameshift as an example to study the dynamics of +1 frameshifting.

2. Methods

2.1. Model of ribosome translation elongation

To study +1 frameshifting, we should analyze the frameshifting that could occur at any state-transition step in the elongation phase of protein synthesis, as done in the previous work to study −1 frameshifting [29]. We use the translation elongation model, which has been presented before to study dynamic tRNA occupancy and dynamics of −1 frameshifting [29,30], to analyze +1 frameshifting. For convenience of reading, we re-describe the translation elongation model as follows.

The model is built up based mainly on the following lines of experimental evidence. (i) The occupation of the P site by peptidyl-tRNA (in the P/P state) "locks" the ribosome, accelerating EF-G.GDP release and prohibiting the binding of EF-G.GTP [31,32]. (ii) The peptidyl transfer or removal from the P-site tRNA results in the ribosome in a "labile" state, allowing the relative rotation between the two ribosomal subunits, with the two conformations called non-ratcheted and ratcheted (or hybrid) [31,33–36]. The labile ribosome also allows the binding of EF-G.GTP and the binding facilitates transition to and stabilizes the ratcheted conformation [31,36]. (iii) GTP hydrolysis to GDP.Pi in hybrid state "unlocks" the ribosome, detaching the mRNA–tRNA complex from the decoding center in the 30S subunit and stimulating reverse relative rotation between the two ribosomal subunits, i.e., the transition from the ratcheted to non-ratcheted conformations [37–39]. Moreover, after transition to the non-ratcheted conformation, the mRNA channel in the 30S subunit is tight again, as suggested by Frank and Agrawal [32]. (iv) The 50S P site has a specific affinity for the peptidyl moiety and the 50S E site has a high affinity for deacylated tRNA [40–42].

Based on the above lines of evidence, the proposed model to describe a translation elongation cycle is described as follows. We begin with deacylated tRNA bound to the E site and the peptidyl-tRNA to the P site (State 1, Fig. 1a). It is noted that the deacylated tRNA could now be either dissociated from or still bound to the E site. Since the ribosome is in the "locking" state, which prohibits the binding of EF-G.GTP, only the aminoacyl-tRNA.EF-Tu.GTP ternary complex can bind to the ribosome in the A/T state (State 2, Fig. 1b). The subsequent codon recognition (State 3, Fig. 1c) promotes the E-site deacylated tRNA dissociation if it is still bound to the ribosome [43]. The binding of the ternary complex triggers GTPase activation, GTP hydrolysis and Pi release [44], inducing a large-scale conformational change of EF-Tu to the GDP-bound form [45–47], which is followed by the release of EF-Tu.GDP and the

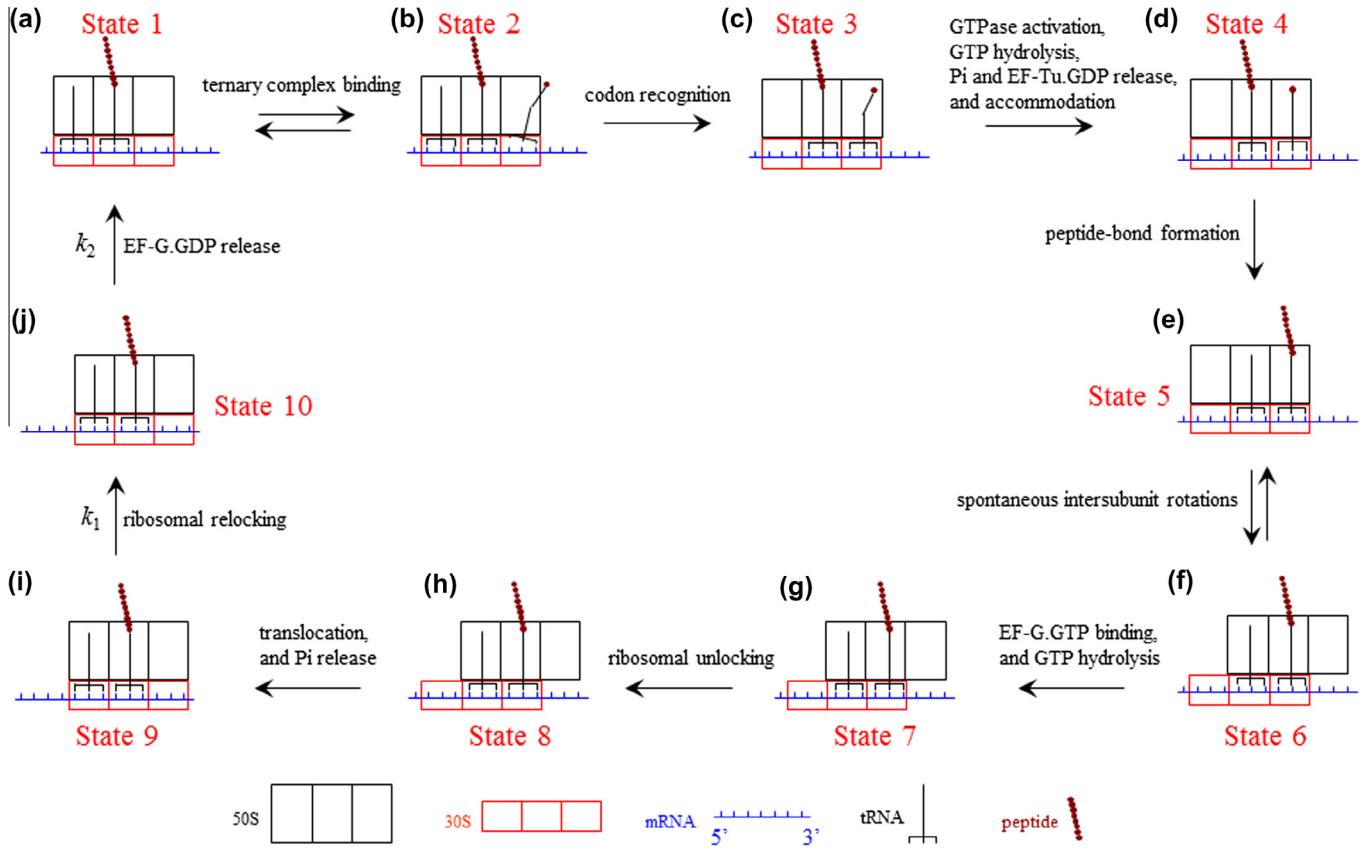

Fig. 1. Schematic illustrations of the model for ribosome translation elongation (see text for detailed description). We draw here that deacylated tRNA dissociation occurs after codon recognition although the dissociation could occur at any state after the posttranslocation.