General Model of Translation Elongation
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1 Model Description

Translation is one of the most important processes in the cells. Features of translation process may affect the throughput of protein synthesis and also the quality (folding efficiency) of the protein. One cycle of translation elongation comprises of 4 processes:

1. Free tRNA is aminoacylated with the correct amino acid (AA).
2. Formation of ternary complex (TC)
3. TC diffuses to a translating ribosome which need this tRNA and delivers the AA
4. EF-GDP is regenerated into EF-GTP

In prokaryotes, the processes 2 and 4 are very fast. The main rate-limiting step is the process 3 (diffusion). In eukaryotes, the rate limiting step is the process 4 (EF-GTP regeneration).

We intend to develop a model for translation elongation, which allows the prediction of how different conditions and parameters affect the rate and throughput of translation. We are also interested in the fate of individual ribosome, which is also affected by the stochasticity.

2 Assumptions and Equations

To simplify the modeling, we took the following assumptions:
1. The model represents only the situation in prokaryotes.
2. All amino acids are very abundant.
3. The processes 2 and 4 are so fast that we neglect them.
2.1 Deterministic model

All the equations here are using CAG codon (encoding Glutamine) as an example. The same equations can be used for any codon.

\[
\frac{df}{dt} = \frac{k_{\text{cat}}(1-f)}{K_M + (1-f)[tRNA]}[\text{GlnRS}] - k_t[f][m]
\]

\([tRNA] = \) tRNA concentration of CAG-tRNA.
\(f = \) fraction of charged CAG-tRNA.
\(k_{\text{cat}}, K_M = \) kinetic parameters of GlnRS.
\([\text{GlnRS}] = \) concentration of cellular GlnRS.
\(k_t = \) rate constant of delivery of TC on ribosomes.
\([m] = \) concentration of ribosomes which are translating CAG codon.

When a specific tRNA is extensively requested because of expression of some proteins (e.g. poly-glutamine proteins), the concentration of charged tRNA (ternary complex) will decrease, resulting in a prolonged average waiting time of these ribosomes.

When a ribosome translates a stretch consist of continuous codon repeats (e.g. CAG repeats poly-glutamine stretch), the diffusion of ternary complex may additionally hinder the translation.

The diffusion is calculated with the Fick’s law:

\[
\frac{dc}{dt} = D\nabla^2 c , \quad \nabla^2 c = \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}
\]

With the decreased diffusion coefficient (as in the case of osmotic stress), the gradient will increase, resulting in a decreased effective ternary complex concentration and decreased translation rate.

2.2 Stochastic model

The limited number of tRNA and ribosome particles in a cell causes stochasticity. Every ribosome waits different time until the next cognate ternary complex collides with it and delivers the amino acid. Every point of the deterministic model is an average value of a stochastic distribution.

We assume that the ternary complex diffuse in a Brownian manner [1, 2]. When a ternary complex collides successfully with a ribosome (with a given collision efficiency), the amino acid is delivered and the tRNA is released immediately. Simulating a virtual volume with certain number of ternary complex and ribosome particles provides the information of waiting time of individual ribosomes.
3 Numerical Methods

For differential equations, the solutions are found by Runge-Kutta method.
For stochastic model, the simulation is performed with our Visual Basic.NET program based on typical Brownian motion simulation and collision detection.

4 Computational Tools

The deterministic model is implemented in MATLAB on an AMD Dual-Core CPU computer with 4GB RAM running Windows Server 2008 x64 version.
The Brownian motion simulation is implemented in VB.NET 2008 on 8 computers with Dual-Core or Quad-Core CPUs running Windows XP or Windows Server 2008 x64 version. The statistic analysis is performed in MATLAB.

5 Parameter Estimation Techniques

The parameter estimation for the stochastic distribution is performed in MATLAB using the Statistic Toolbox.

6 Applications and Limitations of the Model

Applications: We focus on CAG codons in *E.coli* at the current stage, since most of the parameters are already available. However, this model is applicable to all codons. Considering the process 4, this model is basically also valid for eukaryotes. It provides a general view for the translation elongation. With this model, we can predict how the tRNA concentration, charging features, cellular environment (diffusion) and protein expression profile affect the translation process in a quantitative way. With the deterministic model we can predict the average behavior of the translation. The stochastic model provides a more detailed view, allowing us to investigate the fate of individual ribosomes under various conditions, since prolonged waiting time leads often to frameshifting and pre-mature termination. Direct motion simulations allow also accurate simulations in the cases that the ribosomes are not evenly distributed in the cytoplasm, which is highly possible in the eukaryotes.

Limitations: At the current stage, we only considered the stochasticity of the rate-limiting step (diffusion) in the stochastic model. However, the other processes also contribute to the total stochasticity due to the limited number of particles participated in the reaction. Additionally, the Brownian motion simulation is extremely CPU-intensive and the accurate simulation depends highly on the computational power.
References
