Towards Kinetic Modeling of DNA Replication Using the E-CELL System

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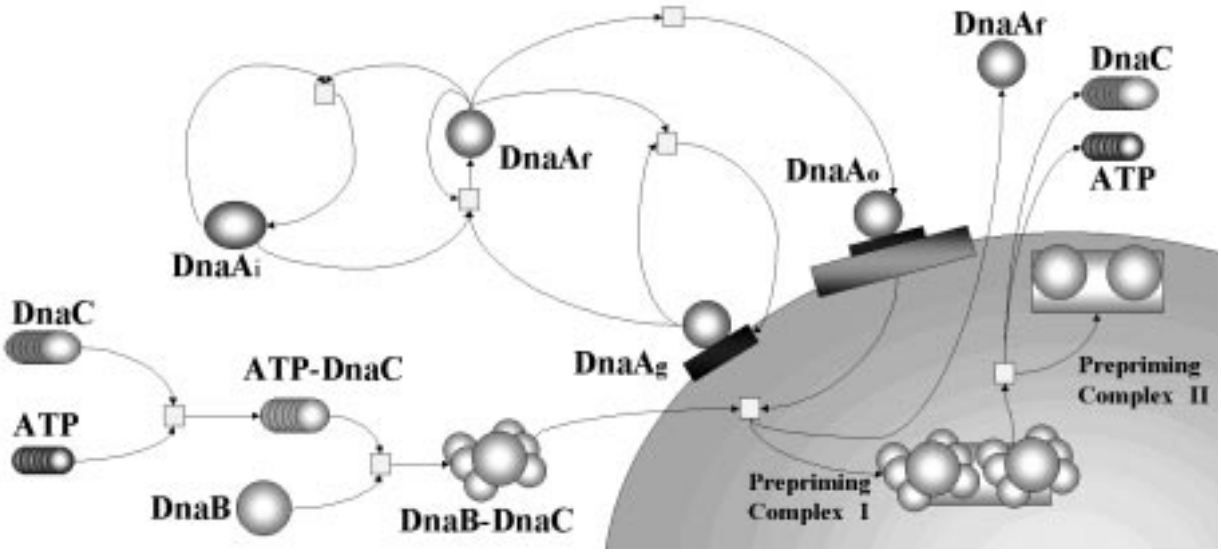
1 Introduction

We have been developing a computer model of *E. coli* 's DNA replication system using the E-CELL System, a generic software for simulation of cellular processes. In this paper, we present kinetic models for initiation and elongation of the DNA replication.

2 Initiation



The figure above illustrates the initiation process of *E. coli* DNA replication. *E. coli* initiates DNA replication when ATP-binding DnaA protein binds to each of the four DnaA-boxes in oriC. States of the DnaA protein can be classified as follows: (i) Non-active DnaA ($DnaA_i$), (ii) ATP-bound DnaA (DnaA-ATP) which freely exists in cytoplasm ($DnaA_f$), (iii) DnaA-ATP which is bound to a DnaA-box in oriC($DnaA_o$), (iv) DnaA-ATP which is bound to a non-oriC consensus sequence($DnaA_g$). The kinetics used in the simulation is based on the following four formulas [1].

Kinetic equations:

$$\begin{aligned}
\frac{d[DnaA_o]}{dt} &= 4(k_0[DnaA_f] - k_d) \\
\frac{d[DnaA_g]}{dt} &= k_{g1}[DnaA_f]([GS] - [DnaA_g]) - (k_{g2} + \mu)[DnaA_g] \\
\frac{d[DnaA_f]}{dt} &= \frac{k_{r1}}{1 + K_{r2}([DnaA_f] + \gamma[DnaA_i])} - k_{g1}[DnaA_f]([GS] - [DnaA_g]) \\
&\quad + k_{g2}[DnaA_g] - (k_{r3} + \mu)[DnaA_f] \\
\frac{d[DnaA_i]}{dt} &= k_{r3}[DnaA_f] - \mu[DnaA_i]
\end{aligned}$$

where $k_0 = 0.13$ ($\times 10^{-9}$OD$_{450}$/molecule·min), $k_d \cong 0.35$ (min^{-1}), $k_{g1} \cong 0.0186$ ($\times 10^{-9}$OD$_{450}$/molecule·min), $k_{r1} \cong 46.7$ ($\times 10^9$ molecules / OD$_{450}$·min), $K_{r2} = 2$ ($\times 10^{-9}$OD$_{450}$/molecules), $k_{r3} \cong 0.58$ (min^{-1}), $\gamma = 0.01$, $[GS] = 123.8$ ($\times 10^9$molecules/OD$_{450}$), $\mu = 0.0156$ and $k_d = 0.35$(min^{-1}).

3 Elongation

The kinetics of the DNA chain elongation reaction is expressed with the E-Cell System using the following formula [2]. This formula takes into consideration the length of the replicated DNA chain, the activity of DNA polymeraseIII, and the time required for a NTP to bind to the DNA chain.

Kinetics equations:

$$v = \frac{K_T[E_0][S_0]}{K_M + [S_0](1 + K_H[I])}$$

where K_T=turnover number, K_M=Michaelis constant, K_H = inhibition parameter,
I=free template concentration, E_0 = DNA polymeraseIII concentration, and S_0 = NTP concentration.

4 Future work

Work is being done for the modeling of cell division [3]. Simulation of a full cell cycle would ultimately be made possible by connecting the DNA replication model with the new cell division model.

Acknowledgements

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