STRUCTURALLY RESOLVED STOCHASTIC SIMULATION MODEL OF ACTIN POLYMERIZATION

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Abstract

Actin polymerization in cell is a basic biological process relevant to health and disease. We have developed the efficient stochastic simulation algorithm for modelling actin dynamics regulated by actin-associated proteins. As opposed to other existing actin-cytoskeleton mathematical models, our approach is based on the advanced Monte Carlo simulation schemes and associates the main biochemical actin-related reactions, including multistep spontaneous actin nucleation, random and stress-induced filament fragmentation, with structural properties of protein filaments. Created algorithms were integrated into a freely available software package with user-friendly interface.

1 Introduction

The process of actin polymerisation is required for many crucial physiological functions like morphogenesis, cell migration and division. Thorough understanding of how actin polymerization is regulated to generate forces and cell movement will lead to a better understanding of its contribution to these psychopathological processes. Though several mathematical models have been published recently for investigation of filament structures and dynamics [1], there is still a need in a powerful computer approach predicting the major actinpolymerization processes in the presence of actin regulatory proteins.One of the efficient modelling methods for simulation of cytoskeleton dynamics and actin filament structures is the Monte Carlo simulation method.
In this work we have developed the efficient stochastic model algorithm, based on the advanced Monte Carlo simulation schemes, for modeling actin polymerization and actin filaments. In addition to simulating the main actin polymerization processes the developed model integrates algorithms for modelling the multistep spontaneous actin nucleation, filament annealing, random and stress-induced filament fragmentations.

2 Simulation model

To describe the simulation model we introduce the following notation for the types of molecules and reactions (the values in brackets are used in the simulations):
Reagents: ATM-globular actin (monomeric form) with incorporated ATP ($6\mu M$); ATD-actin in dimer form with incorporated ATP($0\mu M$); ATF -filamentous actin

protomer with incorporated ATP ($0\mu M$); *APF*-filamentous actin protomer with incorporated ADP-Pi ($0\mu M$); *ADF*-filamentous actin protomer with incorporated ADP ($0\mu M$).
Reactions: k_{SNUC}-spontaneous nucleation of the filament ($2.16{*}10^{-8}\mu M^{-2}s^{-1}$[2]);$k_{SNMD}$-monomer to dimer association (the first stage in the multistep or staged nucleation) ($2.18\mu M^{-1}s^{-1}$[3]); k_{SNDT}-dimer to trimer association (the second stage in the staged nucleation) ($35.7\mu M^{-1}s^{-1}$[3]); k_{FRGM}-random fragmentation($1.1{*}10^{-8}subunits^{-1}s^{-1}$[2]); k_{FRST} -stress-induced fragmentation($1.8*10^{-8}subunits^{-2}s^{-1}$[2]); k_{ANNL} annealing($1*10^{-8}\mu M^{-1}s^{-1}$[2]); k_{DIDM}- dissociation of actin from dimer to monomer(staged nucleation) (1. 3* s^{-1} [3]); k_{DITD}- dissociation of actin from trimer to dimer (staged nucleation) (1.63* s^{-1} [3]); k_{TTOP}-ATP-hydrolysis(0.3 s^{-1} [2]), k_{PTOD}-phosphate release(0.0026 s^{-1} [2]); k_{DTOT}-recharge of monomer actins in the pool (20 (pro) s^{-1}[3]).The reactions of association and dissociation of ATP/ADP-Pi/ADP terminated actins at the both ends of actin filaments were also taken into account. For the simulations we used their typical reaction rate constants reported in literature [2].
To simulate the reactions in the structurally resolved actin system the Gillespie first reaction algorithm and the advanced Monte Carlo simulation schems were used [1]. Standard Gillespie algorithm is defined for simple molecular species and is limited for the simulation of polymeric structures. In our formalism filament is represented by the bidirectional list, which stores mutual positions of actin protomers in different states (ATP/ADP-Pi/ADP) and bound regulatory proteins regarding to the filament ends. The reaction events are determined based on the required descriptive statistics of filament compositions. For example, the probability of random filament fragmentation event is proportional to the number of possible positions between protomers in filament. After identification of the reaction type the model modifies the filament structures.

3 Results

The developed simulation model and computational algorithms were integrated in the software package ActinSimChem. The program has a user-friendly interface and is realized as an object-oriented software package programmed in C++. In order to extensively validate the source code, the debug procedure was launched after simulation of each simulated reaction. The code was verified for a wide range of reaction rate constants, typically covering ± 2 orders of magnitudes from the values presented in the previous section and validated for simulated volumes higher than $30\mu m^3$.

3.1 Staged nucleation

We compared the staged actin spontaneous nucleation against approximative three-monomer actin nucleation [2]. The simulated ATF concentrations over time are shown in Fig.1. An excellent agreement have been obtained for simulations of the actin systems with the initial concentration of $ATM > 1\mu M$ and the reaction rate $k_{SNUC} = 2.16 * 10^{-8}\mu M^{-2}s^{-1}$. (see in Fig. 1A). Decreasing the initial concentrations of the ATM molecules has resulted in slowing down the simulation process and significant

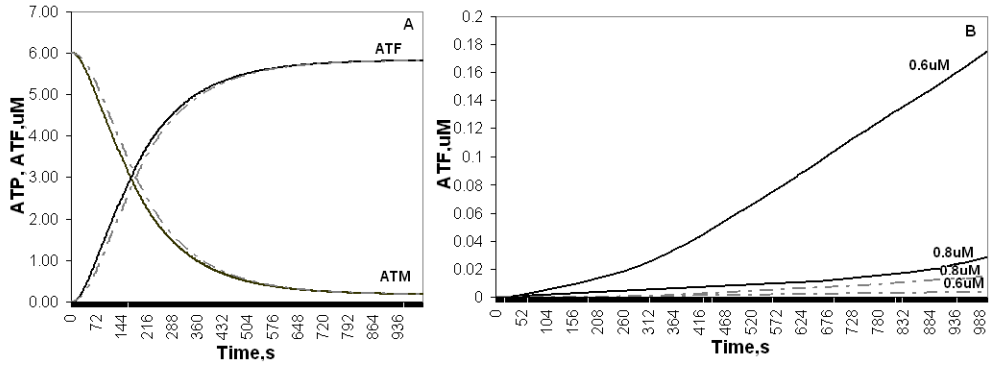

Figure 1: Simulation of the staged (dash-dot lines) and three-actin (solid lines) nucleation for the initial concentration of ATP -6uM (A) and 0.6, 0.8 uM (B). For simplicity, in the simulation we assume that that all F-actins are in the ATP state.

difference of the results of two modelling methods(Fig. 1B).

3.2 Annealing and fragmentation

We investigated the role of filament annealing, random and stress-induces fragmentation in the filament turnover.Our simulations provided: i) the filament length distribution in a steady state and ii) the average filament length in time (Fig. 2). The reactions of annealing, random fragmentation, stress-induced fragmentation have an obvious influence on both the filament length distribution and the average filament length (Fig. 2A). The actin filaments becomes shorter, less then 6300 actins, if compared with the filaments in the so-called pure actin systems , having the length about 20 000-40 000 subunits per filament. This tendency is confirmed by the average filament length in time. Fig. 2B shows that in the presence of annealing and fragmentation processes in 2 hours after the start of polymerisation the system reaches the maximum value of the average filament length. Then it starts to decrease until the system comes to an equilibrium or steady state (12 hours). It suggests that the stress-induced fragmentation reduces the number of long filaments resulting first in a Poisson-like length distribution then, as the G-actin concentration reaches the critical concentration, in a stationary exponential distribution. This is in a principal agreement with [2]. However, the effect of the stressed-induced fragmentation is not determinative.

4 Conclusions

We have designed the stochastic simulation algorithm for modelling the actin cytoskeleton dymamics including the staged spontaneous actin nucleation, filament annealing, filament random and stress-induced fragmentation. The results of this work let make the following conclusions:
(1) for high initial ATM concentrations($>$ 1uM) the staged nucleation can be well approximated by three-monomer actin nucleation in accordance with [2, 3]. The best fit

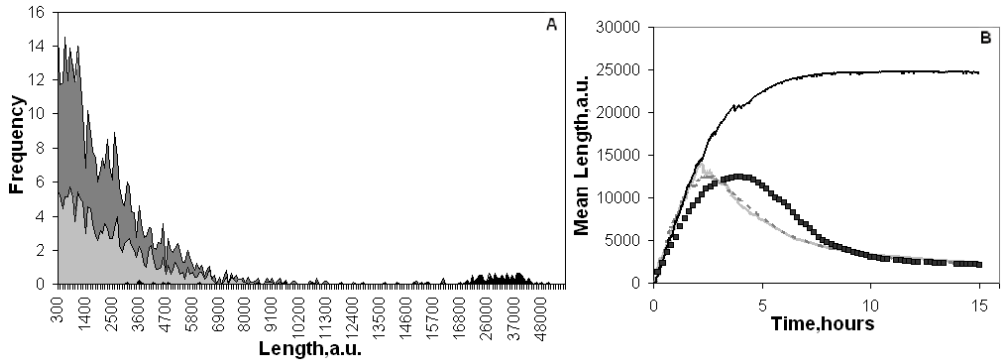

Figure 2: Simulation of (1) the pure actin sytem- black line, (2) the actin system with annealing and random fragmentation-light gray line, (3) the actin system with annealing, random fragmentation and stress-induced fragmentation-dark gray line: A) the filament length distribution in steady state, B) the average filament length in time (squares- the comparative simulated carve taken from [2]). The initial ATM concentration -0.5 uM.

has been obtained for the parameters of the staged actin nucleation taken from [2] and the rate constant $2.16 * 10^{-8} \mu M^{-2} s^{-1}$ of the three-monomer actin nucleation, that is similar to that reported in [3]. When the initial ATM concentrations $ATM < 1\mu M$,the difference between two models becomes significant and the simulation process slows down dramatically.High-throughput computational resources are needed in order to simulate and to explore the actin systems with low initial ATM concentrations.
(2) annealing, random and stress-induced fragmentation influence on both the filament length distribution in steady state and the average filament length - the actin filaments become shorter by a factor of 5-10 times.
(3) according to the results we have obtained the effect of stress-induced fragmentation should be taken into account in simulations, however, its influence is minor as compared to the random fragmentation.

References

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