3rd grade: Oscillation of transcription factor NF-κB

Summary: In a non-activated state, NF-κB resides in the cytoplasm because of the binding of inhibitor protein IκB. IκB is phosphorylated in a stimulus-dependent manner being subjected to proteasomal degradation. This causes NF-κB free from IκB resulting in its translocation to the nucleus, where it promotes gene expression. Interestingly, IκB is a target gene of NF-κB, and de novo synthesized IκB enters the nucleus deactivating NF-κB. This causes export of nuclear NF-κB back to the cytoplasm again. If the stimulus continues, IκB in the IκB:NF-κB complex is phosphorylated, and NF-κB translocates to the nucleus again. Thus the oscillation of NF-κB emerges.

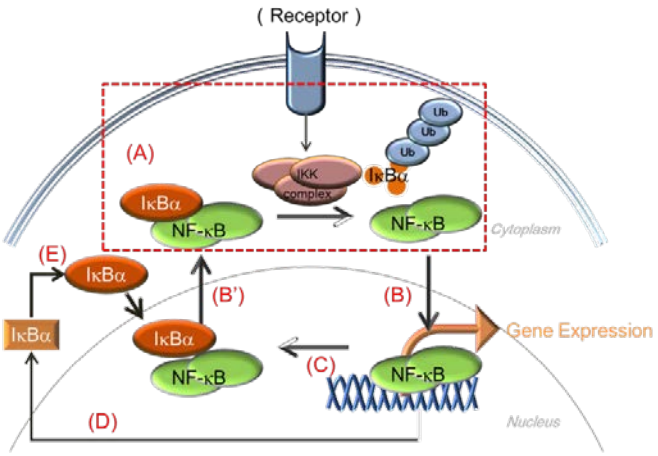

Fig.1 Signal transduction of NF-κB

Cartoon and A-Cell model: Fig.1 is a simplified cartoon for signal transduction of NF-κB. A-Cell models from (A) to (E) in Fig.1 are described below:

When IKK is not active in the absence of stimulus, IκB and NF-κB form a complex IκB:NF-κB, and the translocation of NF-kB is blocked. This is an equilibrium reaction, and a small amount of free NF-κB exists (Fig.2 (1)). When IKK is activated by a stimulus, a complex IKK:IκB:NF-κB is formed, and subsequently, IκB is degraded generating free NF-κB (2). Free NF-κB translocates to the nucleus, where transcription of IκB gene proceeds (3). Gene expression is modeled by am equation. This leads to the translation of IκB protein, while $mRNA_{I_{\kappa B\alpha}}$ (t_IkB in the model) is degraded by a 1st order reaction (4). Newly synthesized IκB protein translocates to the nucleus (5), where it binds with nuclear NF-κB (6), leading to the export of IκB:NF-κB complex from the nucleus (7). In the absence of stimulus, all reactions should be in an equilibrium state. To this purpose, transcription of

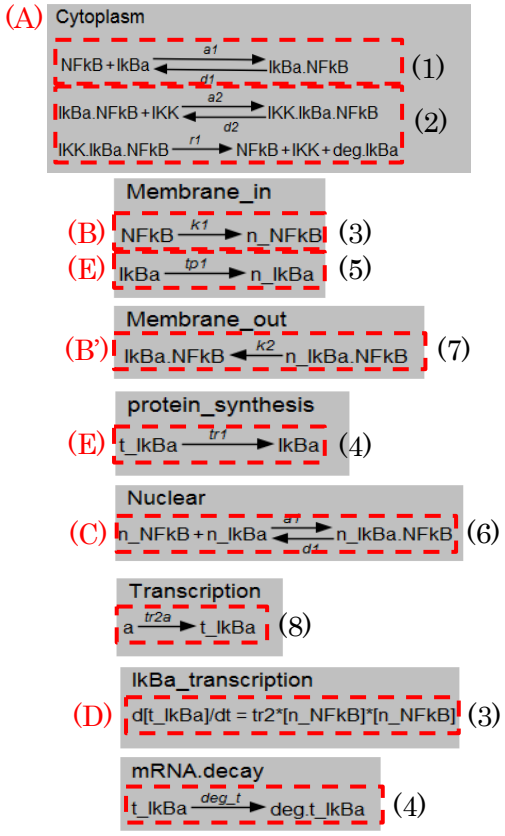

Fig.2 A-Cell model.

stimulus-independent transcription of IκB gene is included in the model (8). The translation process is quite complex including many mRNA binding proteins and polysome formation. It is desirable to describe these complex processes in detail. However, we are focusing on the spatio-temporal dynamics of NF-κB in the model. Therefore, the transcription of IκB protein is modeled in a simple 1st order reaction (Fig.2 (4)). This is a technique for model construction, and at the same time, this simplification might be a limitation of the model. It is important to realize the limitation of a model in the analysis of simulation results.

The model shown in Fig.2 can be simulated by "in situ calculation" method of A-Cell without generating simulation program. As shown in Fig.3, an oscillation of nuclear NF-κB was observed as in experiments. Simulation time, calculation step, and output step were 10 hours (36,000 s), 0.1 s, and 36 s, respectively. Calculation step of 0.1 s is large in comparison to many simulations of this sort. However there is no fast reaction in the model, this parameter setting generates appreciable results with small simulation errors. Phases of the oscillations in Fig.3 differ in three species. By finding reasons for this will lead to the better understanding of the mechanisms of the oscillation.

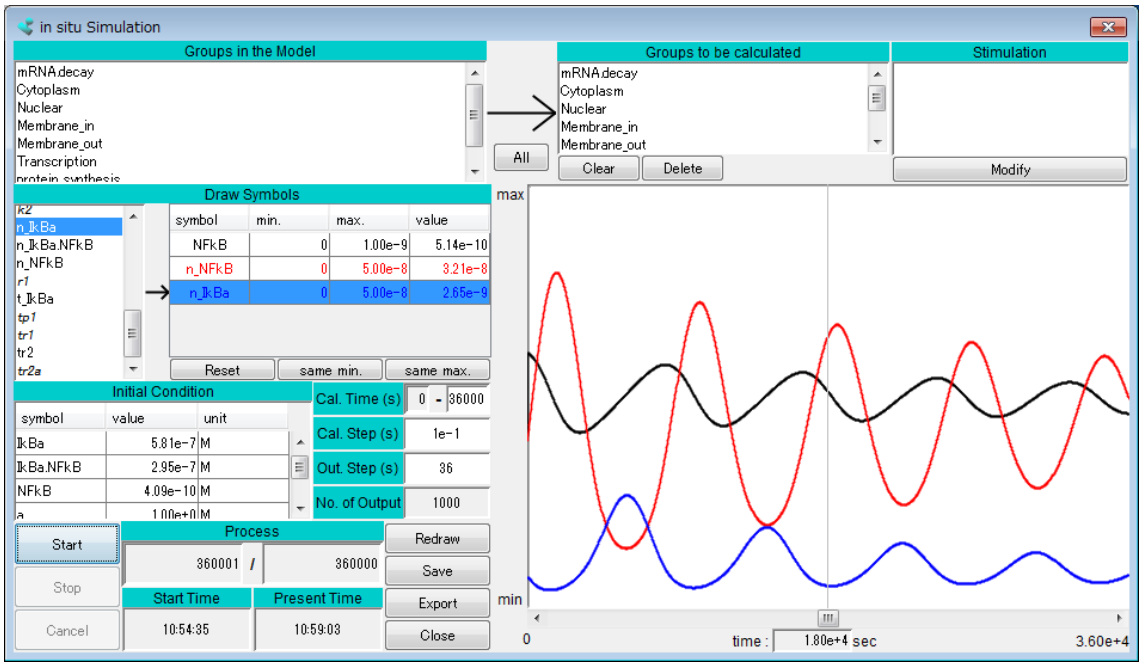

Fig.3 An "in situ simulation" result.

References: Hoffmann, A., et al., Science, 2002, 298, 1241.

Ohshima, D., et al., PLoS ONE., 7(10): e46911.