True Cell Simulations Inc.
cell blog
Aug/6/2025, Kazuhisa Ichikawa

15. Pathway Simulation and Cell Simulation

The use of the terms 'pathway simulation' and 'cell simulation' is ambiguous. Here, we distinguish these two explicitly: pathway simulation with no explicit spatial modeling and cell simulation with spatial modeling*1. Why do we need clear discrimination? Pathway simulation assumes all molecules reside in a point (zero-volume space) or are homogeneously distributed. While cell simulation assumes molecules are inhomogeneously distributed. This difference is well known, but it yields unexpected simulation results of large discrepancies, even in such a small cell. This is the reason why we distinguish 'pathway simulation' and 'cell simulation'. Two examples below show these differences.

*1 Simulations with realistic organella distributions in a cell might be called true cell simulations, which have not yet been achieved.

What are the differences? : In cell simulations, a cellular space is divided into small compartments, to each of which pathways are embedded (Fig.1). This enables us to model 1) diffusion, 2) spatially distinct reactions, and 3) molecular amount in addition to concentration*2. Among these three, 2) is easily understood. 1) can also be understood, but its effect is not easy to presume. 3) is a simple effect, but it is not readily understood. Although these can be conceptually modeled in a pathway simulation, such approaches can be misleading. Here, the consequences arising from these three are shown in the following.

*2 A combined system of reaction and diffusion is called a reaction-diffusion system. Cell simulation is a reaction-diffusion simulation. Pathway simulation is a reaction simulation.

Two examples: We show the differences by MT1-MMP, an ECM-degrading protein, and NF-κB, a transcription factor activated by cytokines. MT1-MMP is expressed on cancer cell membranes, triggering invasion (Fig.1A). NF-κB, a transcription factor, resides in the cytoplasm when in an inactive state, but is translocated to the nucleus upon activation, resulting in the expression of many genes, including IκB, an inhibitor of NF-κB. This causes NF-κB return to the cytoplasm, generating an anti-phase oscillation in the cytoplasm and the nucleus (Fig.1B).

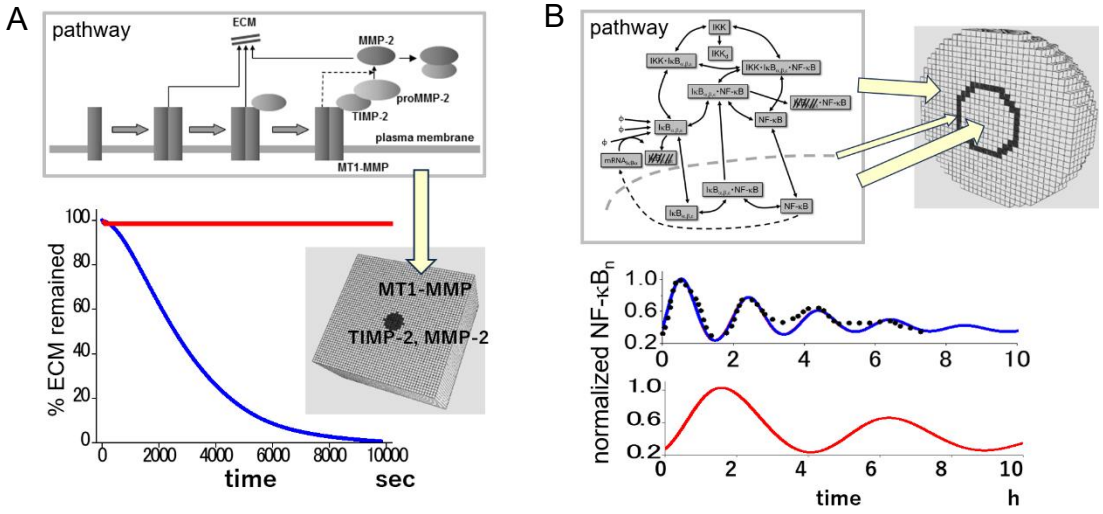

Fig.1 Results of pathway (blue lines) and cell simulation (red lines) for MT1-MMP (A) and NF-κB (B).

In cell simulations, spatial models in the real size of a cell for MT1-MMP (Hoshino, D., et al., PLoS.Comp.Biol., 2012) and NF-κB (Ohshima, D., et al., PLoS ONE, 2012) were constructed, and spaces were divided into many small cuboid compartments, to each of which pathway models were embedded (yellow arrows in Fig.1), and diffusion was specified (A-Cell software was used). Note that pathways, rate constants, and molecular concentrations were the same as in the pathway simulation. MT1-MMP was embedded only in a dark circular region according to the experiments.

The results of pathway simulations (blue lines) both for MT1-MMP and NF-κB coincided well with experiments. Black dots in Fig.1B were redrawn from experiments (Sung, M.L. et al., PLoS ONE, 2009). In contrast, cell simulations for both (red lines) were largely different from experiments: ECM was not degraded by MT1-MMP, and the oscillation frequency of NF-κB was much lower. We were very confused by these big differences. In the course of the analyses, however, we found the reasons that could not be reached by pathway simulations as follows.

Undoubtedly, cell simulations are much closer to real cells than pathway simulations, because cell simulations model the cellular space in addition to pathways. Thus, the results shown in Fig.1 indicate that pathway simulations can lead to false conclusions. Importantly, we reached the novel phenomena together with their mechanism in the course of analyzing the difference between pathway and cell simulations. In MT1-MMP, for example, our prediction by cell simulation and the mechanism were validated experimentally by another group (Hagedorn, E.J., et al., J.Cell Biol, 2014). In addition, we found novel therapeutic targets by cell simulation of MT1-MMP[*3].

*3 Detailed analysis can be found in our report (Hoshino, D., et al., PLoS.Comp.Biol., 2012). Briefly, the difference was due to the bulk amount of proteins, but not the concentration. In NF-κB, the spatial storage of proteins was found to make a big difference (Ohshima, D., et al., PLoS ONE, 2012). The analyses for NF-κB were not easy. But in the course of the analyses, transport via nuclear pores and location of translation were found unexpectedly to alter the oscillation of NF-κB.

Cell simulations have given unexpected consequences, as shown above. In addition, unexpected phenomena and mechanisms were also found. These are not specific to the examples shown here. We may find such spatial effects in other cellular systems. Here, a question arises. As discussed in Blogs No.7 and No.10, intracellular structure is not static but is dynamically altered by environmental change. This can lead to an altered signal transduction as shown here. However, the cell autonomous circadian clock is preserved by the change in environmental temperature. Is it also preserved by the change in the intracellular structures? The oscillation of NF-κB was altered by the change in intracellular structure (Ohshima, D., et al., PLoS ONE, 2012, 2014, 2015). If the circadian clock is kept constant, what is the mechanism behind it? If a cell possesses both changing and robust responses to intracellular structural changes, what is the mechanism for robustness? Is there any common mechanism or principle for robustness?