2nd grade: Spatio-temporal model of ECM degradation by MT1-MMP

Summary: Here A-Cell model described in "1st grade: Degradation of extracellular matrix (ECM) protein byMT1-MMP" is expanded to spatio-temporal model. Invadopodia, small protrusions from the surface of cancer cells, are taken into account (Fig.1), because MT1-MMP is highly expressed in invadopodial membrane. Bottom view of an invadopodium is shown in Fig.2 indicating that an invadopodium is a localized structure within a wide spatial extent.

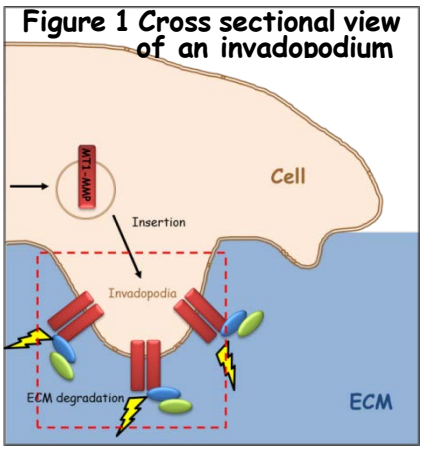

Figure 1 Cross sectional view of an invadopodium

Cartoon and A-Cell model: Reaction model is the same as in "1st grade: Degradation of extracellular matrix (ECM) protein byMT1-MMP". Here we focus on the 3D spatial model as follows:

1) Since an invadopodium is a small structure in a wide space as shown in Fig.2, 3D space is divided into narrow invadopodial and wide other regions (red compartments in Fig.3),
2) Embed MT1-MMP to narrow center compartments. MT1-MMP lacks at other compartments (Fig.4). TIMP-2, MMP-2, and ECM are embedded to all compartments (Fig.5). TIMP-2 and MMP-2 diffuse in 3D space.

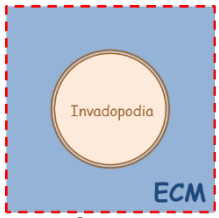

Figure 2 Top view of an invadopodium

A simulation can be run by following conditions: simulation time = 0-3,600 s; calculation step = 100 μs; output step = 10 s. Calculation step of 1 μs is better for an accurate simulation. However this leads to a quite long simulation time (depending on a PC). Parallelization of the simulation program can reduce this to 1/10 with processor having many cores.

The simulation result is shown in Fig.6.

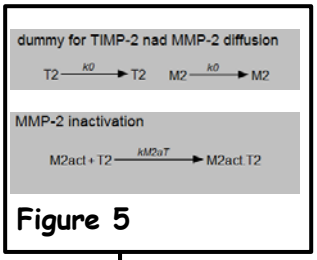

Figure 5

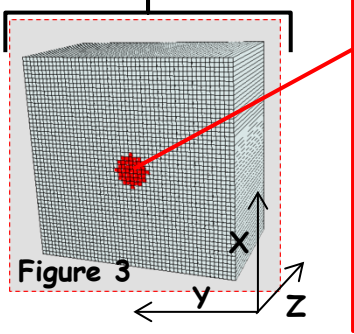

Figure 3

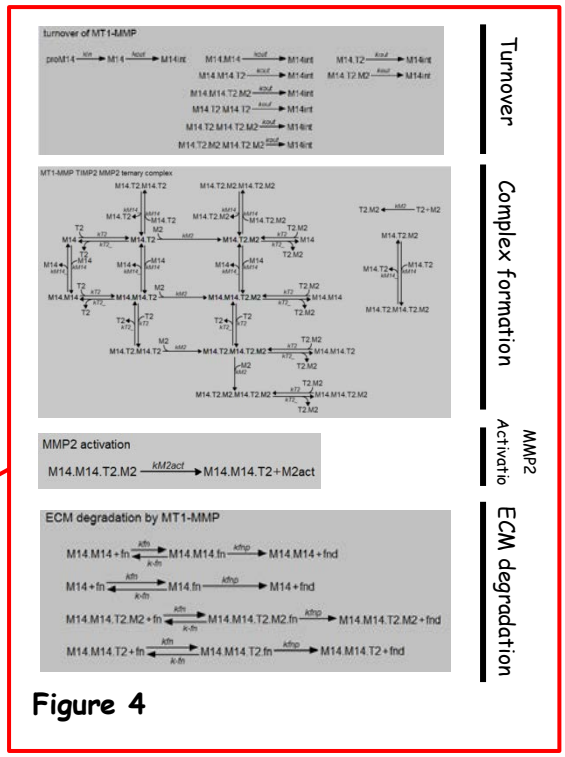

Figure 4

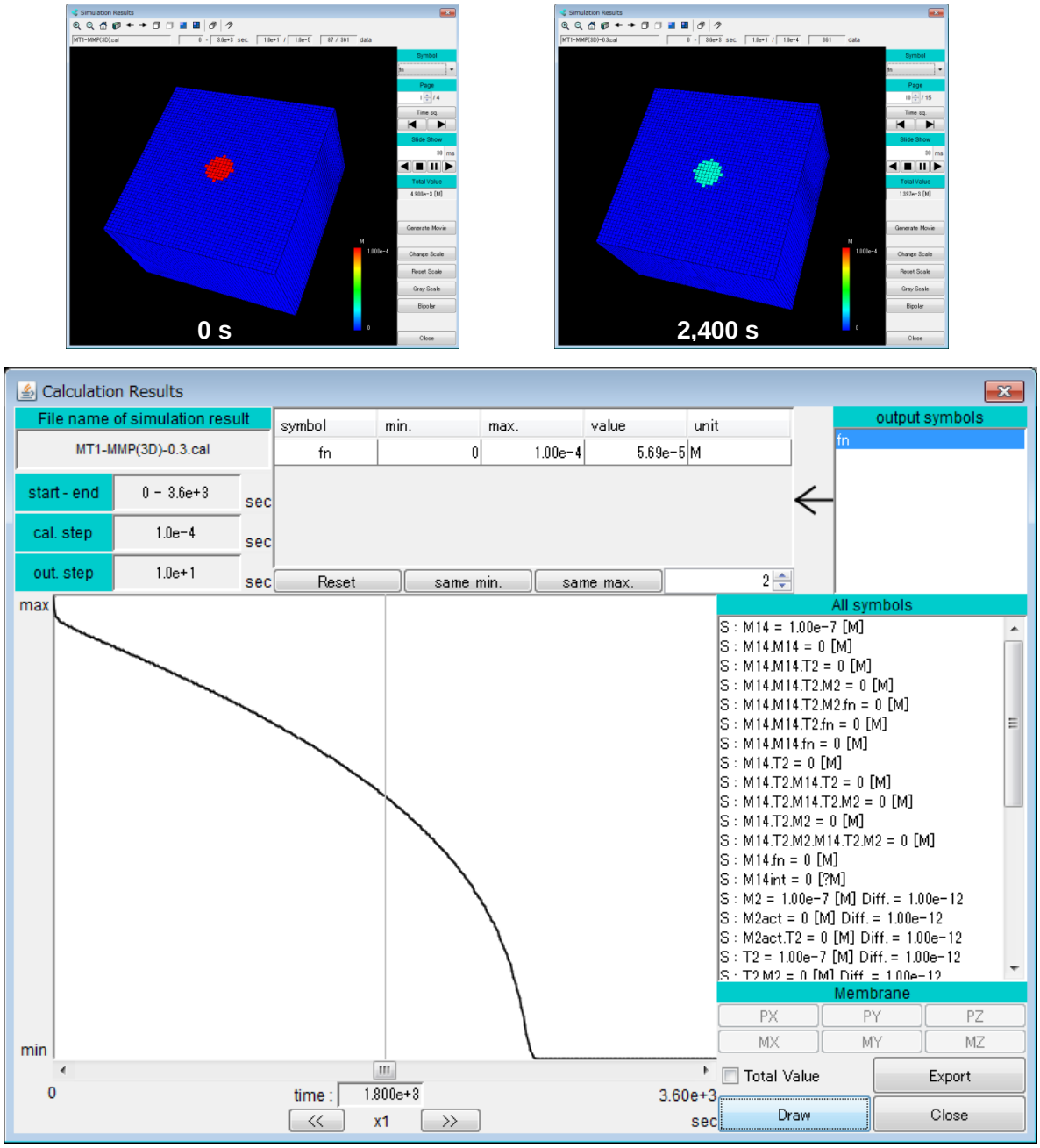

Fig.6 Simulation results. 3D view of ECM degradation at t=0 and 2,400 (upper panels) and a time course of ECM degradation at the center compartment (lower panel).

By simulations deleting turnover reactions from the model or stopping the diffusion of TIMP-2, the essential role of the turnover of MT1-MMP will be clearly shown.

References: Hoshino D., et al., PLos Comput Biol., Vol.8(2012), e1002479.

Watanabe, A., et al., PLoS Comp.Biol., Vol.9(2013), e1003086.