Individual Cell-Based Simulation of 3D Multicellular Spheroid Self-Assembly

J J Zhu [1], S Coakley[1], M Holcombe[1], S MacNeil[2], R H Smallwood [1]

[1]Department of Computer Science, University of Sheffield, UK.

[2]Department of Engineering Materials, University of Sheffield, UK

INTRODUCTION:

We present a three-dimensional agent-based, biophysical model to study the in vitro self-assembly of multicellular spheroids. We investigate how the collective cell migration and pattern formation originate in the behavior of a collection of individuals, each of which responds to a number of physical forces, such as specific and nonspecific adhesion forces between cells and cell-substrate; repulsive force between cells, resistance force between cell-ECM and cell-substrate.

METHODS:

Computer simulation is implemented by solving over-damping type equations for individual cell. We study, by variation of cell-specific parameters, which of them affect the spatial-temporal organization and self-aggregation.

RESULTS:

Self-aggregation of DU 145 human prostate carcinoma cells in liquid overlay culture are shown in Figure 1 (*t=0)* and figure 2 (*t=13.89* days). Spheroids formed in a short time interval (*t≈3* hours), then reorganized and increased in size. Case study also was carried out for an in vitro LNCaP human prostate cancer cell aggregate. Numerical simulations are compared with experiment results in literature. Main parameters (unit: SI): cell radius $R_0=5\times10^{-6}$, ECM resistance $c_m=1.2$, Young modulus E=1000, adhesion coefficient $\varepsilon_s=6\times10^{-4}$, $\varepsilon_c=3\times10^{-4}$, resistance coefficient $\mu_s = 3\times10^{11}$, $\mu_c= 3\times10^{11}$, activation force $|\mathbf{F}_{A0}|=3\times10^{-9}$. Subscript s/c stands for substrate/cell.

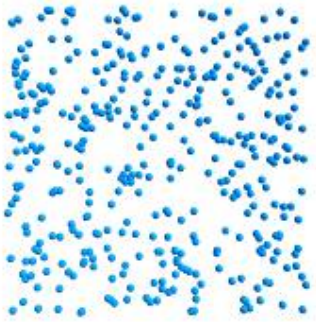

Figure 1. Randomly distributed 400 cells in a square 400μm×400μm

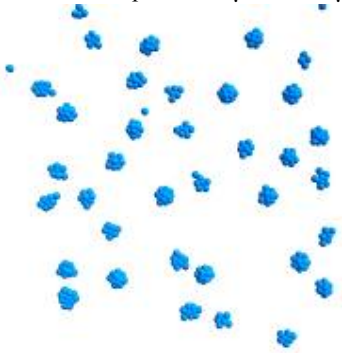

Figure 2. Spheroid formation at *t=13.89* days

DISCUSSION & CONCLUSIONS:

Adhesion forces and cell motility play a predominant role in self-assembly of multicellular spheroids. Self-aggregation could not occur if cell motility is too large or adhesion force between cells is too small. 3D spheroid will not form, if adhesion coefficient between cells is much smaller than adhesion coefficient between cell and substrate.

REFERENCES:

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