

MODELING THE GROWTH OF THREE-DIMENSIONAL TISSUES

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ABSTRACT

We report the development of a model that describes the dynamic behavior of a population of cells that migrate and proliferate to fill a three-dimensional scaffold. This model is then applied to study how cell migration and the density or spatial distribution of seed cells affect the tissue growth rates.

INTRODUCTION

The growth of three-dimensional tissues with proper structure and function is the main goal of tissue engineering. Since bioartificial constructs must reproduce the architecture of the tissues they replace, they are always built on highly porous, three-dimensional scaffolds made from suitable biomaterials (e.g. purified extracellular matrix proteins, or synthetic materials like polymers). The scaffolds are built in the right shape, "seeded" with cells harvested from the patient and implanted in the wound site. To populate all regions of the construct, cells migrate in all directions using the three-dimensional architecture of the scaffold and proliferate. As the cells populate the scaffold, they produce their own extracellular matrix and may degrade the scaffold biomaterial to form a new tissue with the proper function. Clearly, the growth rate of tissues is affected by many factors: scaffold properties, cell adhesion and migration and external stimuli (growth factors, nutrients) that modulate cellular functions. For this reason, the development of bioartificial tissues involves extensive and time-consuming experimentation. Progress in this area, however, can be greatly sped up by computational models with predictive capabilities [1]. The development of such a model is described in this study.

MODEL DEVELOPMENT

The growth of three-dimensional tissues is modeled using cellular automata and discrete iterations. Simulations are carried out in a three-dimensional array of cubic computational sites that span a highly-porous and fully connected scaffold. Each computational site consists of scaffold substrate (e.g. ECM matrix) and a void big enough to contain a single cell at confluence. At any time, a site is *occupied* if it contains the nucleus of a migrating cell. The computational array is seeded with cells that are then allowed to execute persistent random walks [1,2] in the three-dimensional scaffold. The migration speed, the persistence of movement and other locomotory parameters are obtained by independent measurements [2]. Migrating cells change their direction of movement at time intervals equal to their measured persistence [1] or when they collide with other cells. When a cell reaches the end of its cycle, it divides and the two daughter cells continue their persistent random walk. This process is repeated until confluence is reached and all the computational sites are occupied.

SIMULATION RESULTS

Figures 1 and 2 show how the initial seed density and the

migration speed affect the tissue growth rate. Note that increasing speeds of cell migration have a diminishing effect on the time required to reach confluence (Fig. 2). The model also allows us to compute the population-average speed of migration that decreases as the cell density increases. It can also be used to describe the effects of cell death, nutrient limitations due to diffusion and scaffold heterogeneities.

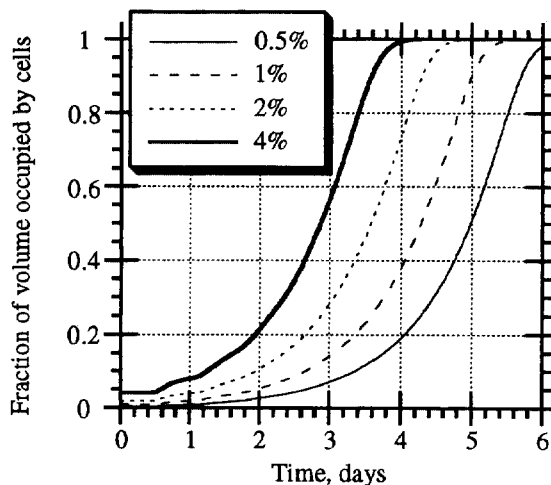


Figure 1: Effect of seed density on tissue growth rate. (Cell migration speed = 50 $\mu\text{m/hr}$ - 128x128x128 grid)

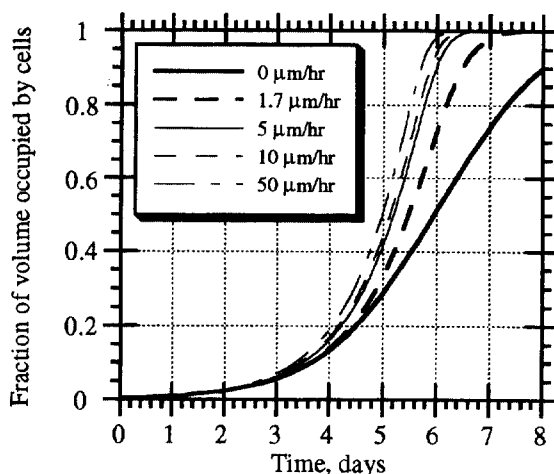


Figure 2: Effect of cell migration speed on tissue growth rate. (Seed cell density = 0.5% - 128x128x128 grid)

REFERENCES

- [1] Y. Lee, S. Kouvroukoglou, L.V. McIntire and K. Zygourakis, *Biophysical Journal*, **69**, 1284-94 (1995).
- [2] Y. Lee, P. Markenscoff, L.V. McIntire and K. Zygourakis, *Biochem. Cell Biol.*, **73**, 461-472 (1995).