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Do Endothelial Cells Dream of Eclectic Shape?

Katie Bentley

Computational Biology Laboratory
Center for Vascular Biology Research, BIDMC, Harvard Medical School
99 Brookline Avenue, Boston, MA 02215, USA
E-mail: kbentley@bidmc.harvard.edu

Abstract

Endothelial cells (ECs) line blood vessels and exhibit dramatic plasticity and diversity of form/behavior at the individual and collective cell levels. ECs coordinate in space and time to extend new blood vessel networks into tissues low in oxygen. Using examples from our integrated research program, we will describe how the Artificial Life perspective and approaches can be utilized to drive entirely new experimental biology based discoveries by capitalizing on the emergent behavior, predictive capacity and testable nature of agent-based models in close combination with *in vitro* and *in vivo* experiments.

Introduction

We can learn a great deal about real endothelial cells (ECs) by watching the interaction of simulated ECs in the "Virtual Lab" as they collectively generate new and unexpected tissue-level dynamics. This is detailed in our recent perspectives article (Bentley et al 2014a) and can be illustrated by drawing parallels with the thought-provoking robotic humans (androids) in Philip K. Dick's novel "Do Androids Dream of Electric Sheep?". In both the book and the film adaptation (Ridley Scott's "Bladerunner") android behavior serves as a mirror to view, question and understand human behavior. Taking the Electric sheep/Bladerunner analogy further, we aspire to study ''rogue simulant cells", instantiated with mutations and/or let loose within untested pathological environments. Their unexpected aberrant behavior, we will show, can provide solid predictions, for new *in vitro* and *in vivo* experiments, providing insight into mechanisms behind maladapted behavior of real ECs and therapeutic strategies.

Results

Understanding how, when, and why individual ECs coordinate their decisions to change shape, move and interact in order to grow functional blood vessel networks ("angiogenesis") in relation to the myriad of dynamic environmental signals around them, is key to understanding normal and pathological blood vessel behavior. This is a complex, spatial and temporal problem, however. Each cell's individual autonomy in determining its own, time-variable behavior is not easy to extrapolate from everyday experimental techniques, which often provide instead averaged or static, population-level data. Here, we will show, using several examples from our published and unpublished research, that agent-based models of endothelial cell dyamics integrated with *in vitro* and *in vivo* experimentation, can lead to new mechanistic insight into normal and abnormal cancerous/retinopathy blood vessel growth. We explictly consider the role of individual EC embodiment, active perception, heterogeneous vs homogeneous collective dynamics, pattern formation processes and counter-intuitive emergence from feedback in controller networks (Bentley et al 2008, 2014b, 2014c).

We no longer see the big challenge ahead as whether or not simulations that capture aspects of cellular systems can be built. This has been achieved. The challenge we set ourselves is: can we gain novel, experimentally relevant insight with simulations, that when tested will generate new insights for the experimental biology community as well as for theoretical biologists and the ALife community. We will discuss the practical approaches and guidelines we employ to meet this challenge (detailed in Bentley et al 2014a).

Conclusions

Alife is a perfect mindset and perspective with which to understand spatial autonomous adaptive behavior of cells in biological systems such as the vasculature. If we take care to be rigorous in how we callibrate our models to biological data and make clear experimentally testable predictions, we can drive experimental biology forward. Learning from the insightful, but segregated Androids in Philip K Dick's novel, if we can overcome our cultural differences and integrate our knowledge better between artifical and natural systems, we can together tackle the full and complex array of mechanisms driving coordinated cell behaviors in living systems.

References

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