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Agent-based modeling of porous scaffold degradation and vascularization: Optimal scaffold design based on architecture and degradation dynamics

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ABSTRACT

A multi-layer agent-based model (ABM) of biomaterial scaffold vascularization is extended to consider the effects of scaffold degradation kinetics on blood vessel formation. A degradation model describing the bulk disintegration of porous hydrogels is incorporated into the ABM. The combined degradation-angiogenesis model is used to investigate growing blood vessel networks in the presence of a degradable scaffold structure. Simulation results indicate that higher porosity, larger mean pore size, and rapid degradation allow faster vascularization when not considering the structural support of the scaffold. However, premature loss of structural support results in failure for the material. A strategy using multi-layer scaffold with different degradation rates in each layer was investigated as a way to address this issue. Vascularization was improved with the multi-layered scaffold model compared to the single-layer model. The ABM developed provides insight into the characteristics that influence the selection of optimal geometric parameters and degradation behavior of scaffolds, and enables easy refinement of the model as new knowledge about the underlying biological phenomena becomes available.

Statement of significance

This paper proposes a multi-layer agent-based model (ABM) of biomaterial scaffold vascularization integrated with a structural-kinetic model describing bulk degradation of porous hydrogels to consider the effects of scaffold degradation kinetics on blood vessel formation.
This enables the assessment of scaffold characteristics and in particular the disintegration characteristics of the scaffold on angiognesis. Simulation results indicate that higher porosity, larger mean pore size, and rapid degradation allow faster vascularization when not considering the structural support of the scaffold. However, premature loss of structural support by scaffold disintegration results in failure of the material and disruption of angiogenesis. A strategy using multi-layer scaffold with different degradation rates in each layer was investigated as away to address this issue. Vascularization was improved with the multi-layered scaffold model compared to the single-layer model.
The ABM developed provides insight into the characteristics that influence the selection of optimal geometric and degradation characteristics of tissue engineering scaffolds.

1. Introduction

Biomaterial scaffolds are an important component of tissue engineering and regenerative medicine practices, as they provide a three-dimensional (3D) support structure for vascularization and tissue growth, and serve as a delivery vehicle for different bioactive molecules and signal cues that enhance specific cell

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function [1–3]. The scaffold should have a balanced set of properties that provide both structural support and biofactors necessary to promote vascularization and tissue growth. In addition, the scaffolds provide temporary support for the physical volume of the defect while tissue development occurs. The complex interactions among scaffold, cells, and biological signals in tightly controlled conditions lead to formation of replacement tissues and organs [4].

Tissue engineers have had clinical success primarily in the development of thin or less metabolically demanding tissues. Vascularization of porous scaffolds has critical importance for tissue growth in 3D [5]. Angiogenesis, the formation of new blood vessels via sprouting from host vasculature, is the primary mechanism for vascularization of tissue engineering scaffolds [6,7]. Porous scaffolds with well-designed architecture and controlled porosity and interconnectivity can be manufactured using a variety of fabrication methods [8–10]. The scaffold pore architecture is a critical design variable [11–14], as it influences the rate and depth of blood vessel invasion [15], the diffusion properties of growth factors, nutrients, and oxygen [10,16,17], and scaffold mechanical properties [18,19]. Kinetics of scaffold degradation is also important for optimizing the process of tissue development [20]. However, the porous structure of the scaffolds is strongly affected by degradation, changing dynamically over time [21,22].

Taking into account the effect of numerous design parameters and optimizing them at the same time is a difficult task using experiments only, as it requires a large number of animal samples that often need to be sacrificed to collect data, resulting in consecutive measurements being from different animals [23–25]. Conflicting factors, interrelated requirements and complex interactions increase system complexity to levels far beyond what can be observed using experimental studies alone [26].

An increasing number of preclinical assays [27] and theoretical models [28–31] have been developed to study angiogenesis. Experimental and computational approaches have been combined to gain better understanding of the underlying mechanisms and to reveal dominant behaviors [32–35], and such collaborations are argued to be the inevitable future of angiogenesis research [35]. Few theoretical models in the literature specifically address the effects of scaffold architecture on vascularization and/or tissue growth. This is while the state-of-the-art in manufacturing biomaterial scaffolds enables close control of scaffold architecture and production of scaffolds with exact architectural parameters [8,36,37]. A few computational studies have investigated vascularization within porous tissue engineering scaffolds in response to a variety of stimuli. Jabbarzadeh and Abrams modeled growth factor (GF) transport within scaffolds to investigate the effect of various GF concentration profiles, and GF release and degradation rates on angiogenesis [38]. Prendergast et al. developed mechano-biological models to investigate the effect of various mechanical stimuli and different cell seeding strategies of scaffolds with regular [39] and irregular [40] morphologies on vascularization and tissue formation. Lemon et al. developed a model to simulate capillary invasion within one single cylindrical pore, considering blood flow and nutrient delivery during the vascularization process [41]. In a similar study, Das et al. developed an ABM to investigate sprout formation patterns in response to GF and scaffolding matrix and compared their simulation results with microfluidics experiments [42]. Agent-based models [43] use a number of rules that govern the behavior of the individual constituents of a system to reproduce, visualize or predict the emergent system level behavior [44,45]. Long et al. used a state-machine paradigm and combination of experimental observations and computational modeling to identify endothelial cell (EC) decision patterns leading to specific capillary structures, in the presence of GFs [46]. The effect of scaffold degradation on bone formation was investigated in two separate studies [21,47], both assuming constant degradation rates.

Previous research works have investigated scaffold degradation [48–50] and vascularization [40,41,51] separately. However, it is advantageous to study these processes simultaneously to better understand their interactions. The scaffold structure is considered to remain constant over time in reported models, but the degradation behavior of the scaffold is important for predicting the lifetime of biomaterials [52], and the effects on cellular activities and mechanical properties [53]. In most clinical cases, the scaffold is required to degrade at a closely controlled rate while tissue growth and morphogenesis regenerates functional tissue constructs [54]. The availability of models that consider scaffold degradation will contribute to a better understanding of the role played by scaffold degradation.

This study aims at investigating the combined effects of scaffold degradation and architecture on vascularization. A statistical degradation model, developed by Metters et al. [55], was incorporated in a previously developed angiogenesis ABM [51]. Considering the sudden loss of mechanical support of scaffolds due to the reverse gelation behavior [48], a multi-layer scaffold model is proposed to further optimize the vascularization process. We hypothesized that both scaffold architecture and degradation properties impact blood vessel formation.

2. Methods

2.1. Scaffold degradation model

A statistical-kinetic model developed by Metters et al. for predicting the hydrolytic degradation of hydrolysable polymers is used to predict the mass loss of the scaffolds [55]. The degradation model is originally developed to describe mass loss profiles of PLA-b-PEG-b-PLA hydrogels, however it can be extended to describe the degradation behavior of any other bulk-degrading polymeric system where the network cross-links are hydrolyzed [56]. Details of the bulk degradation model are described in Appendix A.

We assumed that scaffold density is constant throughout the simulation run. Hence, mass changes are equal to volume changes, and they are equivalent. In the scaffold layer of the ABM, therefore, scaffold degradation results in volume loss, which is caused by erosion of degraded scaffold parts. In this paper, erosion is assumed to occur instantaneously following degradation and scaffold degradation and erosion are used interchangeably in our model.

The mass loss profiles depend on the hydrolysis reaction kinetic rate constant (k'), the number of cross-links per backbone chain (N), and the mass fraction of network contained in the backbone polymer chains as opposed to the rest of the network (W_{PA}). To take into account the increased rate of mass loss observed in the experimental data at the final stage of hydrogel degradation, a critical reverse gelation point is calculated as well. At the reverse gelation point, enough PLA units are broken, and the scaffold becomes a collection of highly branched, soluble backbone chains, and hence the whole biomaterial can be assumed water-soluble. The critical time at which reverse gelation occurs is a function of hydrogel network properties (N) and kinetic hydrolysis rate constant (k'). The equations and variables used to describe the bulk degradation model are listed in Table 1.

2.2. Multi-layer ABM of vascularization

A multi-layer ABM is developed to simulate vascularization of 3D porous biomaterial scaffolds through sprouting angiogenesis. The ABM includes a software layer describing angiogenesis process, including endothelial cell (EC) agents and the rule base governing their actions and interactions, and another layer for modeling the 3D porous structure of the scaffolds and its degradation