Computer-Aided Design 45 (2013) 1507–1523

Contents lists available at ScienceDirect

Computer-Aided Design

journal homepage: www.elsevier.com/locate/cad

Designing heterogeneous porous tissue scaffolds for additive manufacturing processes☆

A.K.M. Khoda [a], Ibrahim T. Ozbolat [b], Bahattin Koc [c,*]

[a] North Dakota State University, United States
[b] The University of Iowa, United States
[c] Sabanci University, Istanbul, Turkey

HIGHLIGHTS

- Heterogeneous porous architecture of tissue scaffolds is designed.
- To improve cell survivability, radial channels are optimally generated.
- Iso-porous curves are optimally determined to generate the spatial porosity.
- A continuous deposition path planning is developed for additive processes.

ARTICLE INFO

Article history:
Received 16 November 2012
Accepted 10 July 2013

Keywords:
Scaffold architecture
Gradient porosity
Medial axis
Biarc fitting
Continuous path planning
Additive manufacturing

ABSTRACT

A novel tissue scaffold design technique has been proposed with controllable heterogeneous architecture design suitable for additive manufacturing processes. The proposed layer-based design uses a bi-layer pattern of radial and spiral layers consecutively to generate functionally gradient porosity, which follows the geometry of the scaffold. The proposed approach constructs the medial region from the medial axis of each corresponding layer, which represents the geometric internal feature or the spine. The radial layers of the scaffold are then generated by connecting the boundaries of the medial region and the layer's outer contour. To avoid the twisting of the internal channels, reorientation and relaxation techniques are introduced to establish the point matching of ruling lines. An optimization algorithm is developed to construct sub-regions from these ruling lines. Gradient porosity is changed between the medial region and the layer's outer contour. Iso-porosity regions are determined by dividing the sub-regions peripherally into pore cells and consecutive iso-porosity curves are generated using the iso-points from those pore cells. The combination of consecutive layers generates the pore cells with desired pore sizes. To ensure the fabrication of the designed scaffolds, the generated contours are optimized for a continuous, interconnected, and smooth deposition path-planning. A continuous zig–zag pattern deposition path crossing through the medial region is used for the initial layer and a biarc fitted iso-porosity curve is generated for the consecutive layer with C^1 continuity. The proposed methodologies can generate the structure with gradient (linear or non-linear), variational or constant porosity that can provide localized control of variational porosity along the scaffold architecture. The designed porous structures can be fabricated using additive manufacturing processes.

1. Introduction

In tissue engineering, porous scaffold structures are used as a guiding substrate for three-dimensional (3D) tissue regeneration processes. The interaction between the cells and the scaffold constitutes a dynamic regulatory system for directing tissue formation, as well as regeneration in response to injury [1]. A successful interaction must facilitate the cell survival rate by cell migration, proliferation and differentiation, waste removal, and vascularization while regulating bulk degradation, inflammatory response, pH level, denaturization of proteins, and carcinogenesis affect. Inducing an amenable bio-reactor and stimulating the tissue regeneration processes while minimally upsetting the delicate equilibrium of the cellular microenvironment is the fundamental expectation of a functional scaffold. Achieving the desired functionality can be facilitated by scaffold design factors such as pore size, porosity, internal architecture, bio-compatibility, degradability, permeability, mechano-biological properties, and fabrication technology [2,3]. For example, cells seeded on the scaffold structure need nutrients,

☆ This paper has been recommended for acceptance by Anath Fischer.

* Corresponding author. Tel.: +90 216 4839557; fax: +90 216 4839550.
E-mail addresses: akm32@buffalo.edu (A.K.M. Khoda), ibrahim-ozbolat@uiowa.edu (I.T. Ozbolat), bahattinkoc@sabanciuniv.edu (B. Koc).

0010-4485/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cad.2013.07.003

Nomenclature

List of symbols

$C_i(t)$	ith contour curve represented with the parameter t
$\overrightarrow{N}(t)$	Unit normal vector on curve $C_i(t)$ at a parametric location t
d	Offset distance
$ul^{/}$	Upper widths for the biologically allowable pore size for cells in growth
$ll^{/}$	Lower widths for the biologically allowable pore size for cells in growth
δ	Width of the medial region
$MB_i(t)$	Medial boundary of ith contour curve represented with the parameter t
$[a_i, b_i]x$	Range of parameter t for ith contour curve
$[A_i, B_i]$	Range of parameter t for ith medial boundary
P_c	Set of points generated on the external contour curve $C_i(t)$
P_m	Set of points generated on the medial boundary curve $MB_i(t)$
N_1	Number of points generated on $C_i(t)$ with equal cord length sections
N_2	Number of points generated on $MB_i(t)$ with equal cord length sections
$P_c^{/}$	Counterpart point set for P_m on $C_i(t)$
$P_m^{/}$	Counterpart point set for P_c on $MB_i(t)$
p_{cj}	jth point on external contour curve $C_i(t)$
p_{mk}	kth point on medial boundary curve $MB_i(t)$
LR	Set of ruling lines
N	Total number of ruling lines generated
$\overrightarrow{N(p_{cj})}$	Normal direction at point location p_{cj} on external contour curve $C_i(t)$
$\overrightarrow{N(p_{mk})}$	Normal direction at point location p_{mk} on medial boundary curve $MB_i(t)$
$\dot{\mathbf{A}}$	Area between $C_i(t)$ and $MB_i(t)$
LS	Set of segments, which is defined by the area between two adjacent ruling line
SA_n	Area of nth segment
SL_n	Lower width of nth segment
SU_n	Upper width of nth segment
SR	Set of sub-region channels
RA_d	Area of dth sub-region
RS_d	Lower width of dth sub-region
RU_d	Upper width of dth sub-region
RA^*	Expected area of sub-region
RL^*	Expected lower width of sub-region
RU^*	Expected upper width of sub-region
ω_a	Penalty weight for sub-region area deviation
ω_l	Penalty weight for sub-region lower width deviation
ω_u	Penalty weight for sub-region upper width deviation
SRA	Set of sub-region's boundary lines
PCL	Set of pore-cell line segments (iso-porosity)
CS	Set of starting points for pore-cell line segment
CE	Set of ending points for pore-cell line segment
P	Number of pore cells or iso-porosity regions
$PC_{d,p}$	pth pore-cell in dth sub-region
d_s	Deposited filament diameter
AS	Set of starting points for SRA
AE	Set of end points for SRA
M_i	Medial axis for ith contour curve $C_i(t)$
$AE^{/}$	Set of points projected on M_i from point set AE
RK	Refined pore cell point set
$RPCL$	Refined iso-porosity line segment
ζ	Acceptable tolerance for biarc fitting
$\varepsilon_{\max}$	Maximum (Hausdorff) distance between fitted biarc and CS and CE.

proteins, growth factors and waste disposal, which make mass and fluid transport vital to cell survival. However, in traditional homogeneous scaffolds, seeded cells away from the boundary of the scaffold might have limited access to the nutrient and oxygen affecting their survival rate [4]. Thus, controlling the size, geometry, orientation, interconnectivity, and surface chemistry of pores and channels could determine the nature of nutrient flow [5]. Moreover, the size of the pores determines the distance between cells at the initial stages of cultivation and also influences how much space the cells have for 3D self-organization in later stages. Cell seeding on the surface of scaffold and feeding the inner sections are limited when the pores are too small, whereas larger pores affect the stability and its ability to provide physical support for the seeded cells [6].

The porous internal architecture of the scaffold may have significant influence on the cellular microenvironment [7] and tissue re-generation process [8]. Several studies have focused on designing the internal architecture of the porous scaffold and a few have tried to optimize the scaffold's geometric structure [9]. However, functional pore size and porosity for scaffold structure varies with native tissue [10] and their spatial location. Multifunctional hierarchical bone structure and porosity have been analyzed [11] and modeled using synergy between the geometric model and the multi-scale material model. In [12,13], the authors modeled bone tissue using multi-scale finite element analysis, which provides better understanding of the bone tissue. As mentioned in this paper, tissues cannot be represented by homogeneous properties and hence require tissue scaffolds with multi-scale porosity. Karageorgiou [8] in their studies found that larger pores (100–150 and 150–200 μm) showed substantial bone ingrowth while smaller pores (75–100 μm) resulted in ingrowth of unmineralized osteoid tissue. They also determined that the pore sizes of 10–44 and 44–75 μm were penetrated only by fibrous tissue cells and thus recommend the pore sizes greater than 300 μm. Hollister [14] designed the scaffolds with the pore sizes of 300 and 900 μm for bone tissue. Karande [15] also reported that considering the tissue type, scaffold material and fabrication systems, a wide range of pore size (50–400 μm) was found to be acceptable. Thus, there is no consensus regarding the optimal pore size either for bone or soft tissue scaffold.

The development of bio-manufacturing techniques and the improvement in biomaterial properties by synergy provides the leverage for using additive processes to manufacture interconnected porous structures. Additive manufacturing processes can build mass customized 3D object layer-by-layer providing a high level of control over external shape and internal morphology [16] while guarantee its reproducibility [10,17]. A detail review of the bio-manufacturing processes can be found in [16,17]. Despite such a unique freedom to fabricate complex design geometries, additive manufacturing approaches have been very much confined within homogeneous scaffold structures with uniform porosity [3]. But homogeneous scaffolds do not capture the spatial properties and may not represent the bio-mimetic structure of native tissues. A possible solution for performing the diverse functionality would be designing scaffolds with functionally variational porosity. Gradient porosity along the internal scaffold architecture might provide extrinsic and intrinsic properties of multi-functional scaffolds and might perform the guided tissue regeneration. Thus, achieving controllable, continuous and interconnected gradient porosity may lead to a successful tissue engineering approach. Improved cell seeding and distribution efficiency has been reported by Sobral et al. [18] by implementing continuous gradient pore size. Hence, the need for a reproducible and manufacturable porous structure design with controllable gradient porosity is obvious but possibly limited by either available design or fabrication methods or both [9,18].

Variational porosity design has been used by Lal et al. [19] in their proposed microsphere-packed porous scaffold modeling