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# REVIEW OF BONE SCAFFOLD DESIGN CONCEPTS AND DESIGN METHODS

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**Abstract**. *The paper brings out a review of existing, state-of-the-art approaches to designing the geometry of the scaffolds that are used for tissue engineering with a special emphasis on the macro scaffolds aimed for bone tissue recovery. Similar concepts of different authors are organized into groups. The focus of the paper is on determining the existing concepts as well as their advantages and disadvantages. Besides the review of scaffolds' geometry solutions, the analysis of the existing designs points to some serious misconceptions regarding the scaffold role within the (bone) tissue recovery. In the last section of the paper, the main requirements regarding geometry, that is, architecture and corresponding mechanical properties and permeability are reconsidered.*

**Key Words**: *Tissue Engineering, Bone Tissue Scaffolds, Design Concepts, Design Methods*

## 1. INTRODUCTION

Tissue Engineering (TE) is an interdisciplinary field that applies the principles of engineering and life sciences to the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ [1]. The tissue is a biological formation built of numerous different but similar types of cells that are of the same origin. Except for the cells, tissue is built of extra-cellular matrix (ECM), which is made of specific proteins and enzymes. The ECM has a role of spatial frame (honeycomb or armature) that provides primarily mechanical support to the cells as well as biochemical communication network among the tissue cells. In tissue engineering the term of *tissue engineering scaffold* (further in text *TE scaffold* or just *scaffold*) is usually used to indicate the artificial ECM, that is, the ECM which is built artificially by the (human-developed) technology, which has or should have the same role as natural ECM: to

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provide for mechanical and biochemical support for the cells that should grow-out through the space of the scaffold, building a new piece of the tissue.

However, the *TE scaffold* should not always be interpreted as an artificially made ECM. Actually, the design of the scaffold architecture should not necessarily mimic the natural ECM. There are several cases [2, 3] of real application of scaffold, especially in the field of bone tissue engineering where the scaffold design is significantly different from the ECM design. These application cases helped to clarify and firm the term of TE scaffold as **a kind of structure** that provides mechanical support (and biochemical connection network) to the tissue cells, and which should not be necessarily equivalent to the ECM.

### 1.1 Classification of the Bone TE Scaffolds Architecture

In terms of so-called architecture or conceptual design, the bone scaffold may be classified into two main different types: the first, porous, that is similar to the geometry of spongy bone tissue (Fig. 1) unlike the second, which may be described as a lattice-like scaffold (Fig. 2). In the first design concept, the main distinctive design characteristic is pore, i.e. void, its shape and size. The junction elements in this scaffold design concept are "in the function" of building the voids, that is, pores. Usually, the junction elements are very complex shell-like (husk-like) shapes that fill the space in-between the pores.

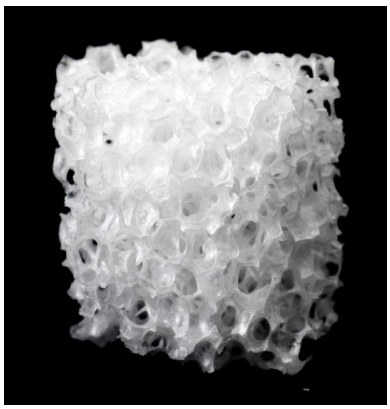

**Fig. 1** Porous scaffold [4]

The scaffold design concept that does not follow a spongy bone tissue as a sort of design template shifts the focus from the pore's design towards the design of scaffold junction elements. The design parameters are related to the shape of the junction elements, i.e. struts, its cross-section profile and the guiding curves. Often, this type of scaffolds resembles a three-dimensional lattice more than a porous structure. Of course, the whole volume of space through which this kind of scaffold is being stretched is the void except for the struts, so the airiness and connection between the voids of this kind of scaffold is (or may be) even greater than in the *porous* scaffolds. However, the contact surface of the junction elements of this type of scaffold is far smaller than in the case of a porous scaffold.

**Fig. 2 L**attice-like scaffolds

There is a third type of architecture of the bone scaffold, which resembles fabric [5]. It is usually made of layers placed one over another. Layers are made of tiny fibers which are oriented randomly or according to some 2D pattern. Considering the design of junction elements (fibers), however, these scaffolds more look like lattice-like scaffolds. In fact, this kind of scaffold design may be categorized as a specific sort of lattice-like scaffold.

Thus, the taxonomy of the bone tissue scaffolds regarding their architecture, i.e. design concept, may be proposed through a following tree (Fig. 3):

- **Porous scaffold**, (tissue-like), where the *focus is on the design of pores*
  - 3D pattern of pore units (pore-cells)
    (the generic units of pores are designed, and the pattern of their 3D disposition is parametrically controlled)
    - where the design of generic units of pores and their 3D pattern are predefined,
    - topologically optimized regarding
      - pores size (ratio of voids/junction elements volume)
      - voids connectivity
      - maximum or minimum of junction shell-like elements contact surface
      - required mechanical properties
      - multi-criteria
- **Lattice-like scaffold** where the *focus is on design of lattice struts*
  - Fabric-like scaffold (layers of fibers disposed in a different 2D patterns); this sub-type of the scaffold architecture is usually made by FDM additive manufacturing technology
    - Optimized regarding
      - ratio of voids/junction elements volume
  - Lattice-like scaffold as a 3D pattern structure made of lattice struts units
    (the generic units of lattice are designed, and the pattern of their 3D disposition is parametrically controlled)
    - where the design of generic units of lattice and the 3D pattern are predefined

- topologically optimized regarding
  - required mechanical properties
  - ratio of voids/junction elements volume
  - multi-criteria

- **Lattice-like scaffold** as 3D non-patterned structure made of fully designed lattice struts
  - topologically optimized regarding
    - required mechanical properties
    - ratio of voids/junction elements volume
    - multi-criteria

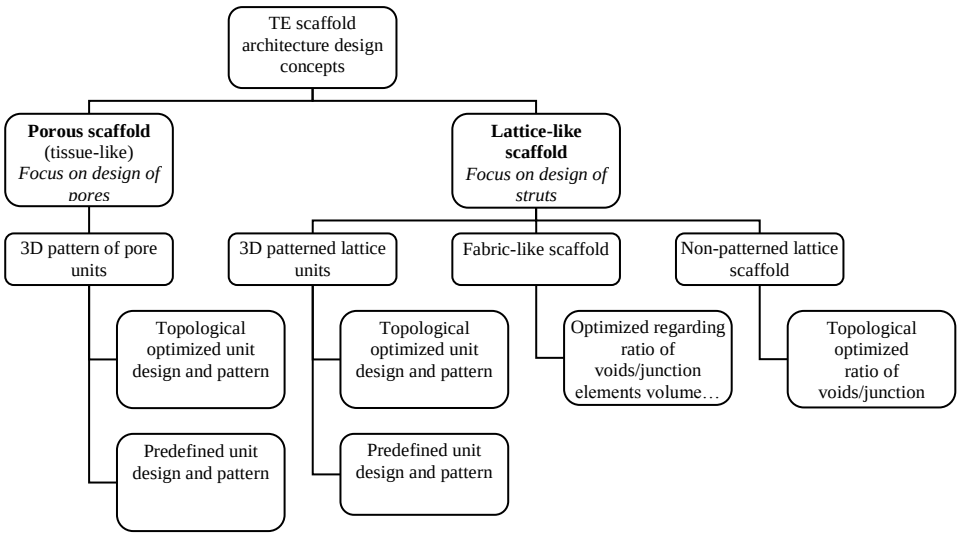


**Fig. 3** Bone TE scaffold design concepts tree

The most often scaffold design solutions in practice are a fabric-like scaffold or a simple porous scaffold, since they are the easiest to produce. For such type of scaffolds, the "fused deposition modeling" is the golden standard as the fabrication method. It is a cheap method which enables application of different materials including various bio-compounds, bio-inks and gels. Complex porous or lattice-like scaffolds are more difficult to produce by FDM due to the necessity for deposition of support structure along with deposition of the main materials. The post-processing can be very pernickety and time-consuming. However, fabric-like and simple porous scaffolds are inapplicable for detailed topological optimization, especially regarding mechanical properties. This is an important shortcoming for the case of the scaffolds aimed for recovery of bone tissue that is usually (and considerably) affected by the mechanical loads.

In addition, having on mind the limitations of the current manufacturing technologies (especially the AMT) the authors of the paper consider that there is a need to propose the scaffold classification regarding scaffold size, too. The scaffolds, whose overall dimensions (height, width, length) are larger than 1 mm should be classified as macro scaffolds. The scaffolds, whose overall dimensions are less than 1 mm should be

classified as micro scaffolds. The similar sub-classification may be done regarding the size of the scaffold design details such as junction elements dimensions or pore size. The scaffolds whose design details are smaller than 0.25 mm like diameter of a pore or a strut or thickness of a junction element should be classified as micro-detail scaffolds (e.g. pore volume is less than 0.01 mm3 and area of the junction element's cross-section is 0.196 $mm^2$). So, regarding sizes, we propose the following taxonomy:

- Macro scaffolds featured by
  - macro-details
  - micro-details
- Micro scaffolds featured by
  - macro-details
  - micro-details

According to the widely accepted requirements for the achievement of successful scaffolds for TE application [6, 7], the scaffold should:

1) possess appropriately sized interconnecting voids (pores) to favor tissue integration, reinnervation and vascularization,
2) be made from material with controlled biodegradability or bio-resorbability so that tissue will eventually replace the scaffold,
3) have appropriate surface chemistry to favor cellular attachment, cell differentiation and proliferation,
4) possess adequate mechanical properties to match the intended site of implantation and handling,
5) not induce any adverse response, and
6) be easily fabricated into a variety of shapes and sizes.

Traditional conventional fabrication techniques [8] generate random architecture and provide minimal control over the internal architecture of the scaffolds, meaning that they are incapable to precisely and repeatably control the structure of the scaffold in terms of pore size, geometry interconnectivity and spatial distribution of pores. Most scaffolds fabricated with these techniques suffer from a lack of mechanical strength and/or uniformity in pore disposition and size.

On the other side, the advent of additive manufacturing technologies (AMT or AT) enabled production of complex three-dimensional structures of scaffolds of controlled internal architecture, that is, fabrication of scaffolds with precisely defined pore's shape and size as well as their spatial disposition. AMT offers major advantages regarding fabrication of TE scaffolds: customized design, computer-controlled fabrication, anisotropic scaffold structures, and application of various biomaterials. To fabricate a TE scaffold by AMT, it is first necessary to model the geometry of the scaffold in CAD software. Considering the importance of internal architecture of scaffolds and lack of adequate review in this field, the focus of this paper is to review the most important published designing approaches for scaffold internal architecture and corresponding design concepts.

For the sake of terminological precision, it seems necessary to clarify the term "internal architecture" of the scaffold. Actually, if one introduces this term, then it should be clarified what the term "external architecture" would refer to. The term *internal architecture of the scaffold* is usual, and it refers to the geometry of the scaffold junction elements that are located in the volume of the scaffold. However, it is possible to design and create specific junction elements of the scaffold that would be located in the so-called

boundary surface (layer) of the scaffold. The boundary surface (layer) of the scaffold is the imaginary surface that wraps the volume of the scaffold and usually imitates the shape of the boundary surface of the tissue region that should be replaced by the scaffold. Thus, the term "external architecture" of the scaffold may refer to the geometry of these junction elements.

## 2. Design Concepts of Scaffolds for Bone Tissue Recovery

As already stated hereinbefore, the design of TE scaffolds usually attempts to mimic both the internal architecture of replaced tissue and the external shape (boundary surface, or "contour geometry"). The internal architecture is complex and consists of numerous pores (voids) interconnected by channels, which facilitate cell proliferation and nutrient flow, and consequently tissue regeneration [9].

There are many attempts to create scaffold design with controlled internal architecture by the application of different design concepts. The most characteristic approaches are presented in this (following) review.

### 2.1 Unit Cells-Based Design

With this kind of design approach, the scaffold internal architecture is created by arranging junction elements as a sort of building blocks or so-called unit-cells in the space which is shrouded by the boundary (contour) surface of the bone region, substituted by the scaffold.

The unit cells are designed in a CAD application and have parametrically controlled geometry. The boundary surface of the scaffold is designed through the process of reverse modeling of the bone based on medical images data (MRI, CT scans or X-ray images). This approach also allows creation of the heterogeneous scaffold internal architectures, by collocating the unit cells of various geometries (already predesigned and stored in the unit cells library) in the space occupied by scaffold.

Advances in computer technology and its use to aid tissue engineering have led to creation of a new field called Computer-Aided Tissue Engineering (CATE). Sun et al. [10] were among the first researchers to review advances in this field. CATE encompasses the following three major applications in tissue engineering:

1) computer-aided tissue modeling,
2) computer-aided tissue informatics, and
3) computer-aided tissue scaffold design and manufacturing [10].

The same authors also discussed the application of CATE to ***so-called*** biomimetic modeling and design of tissue scaffolds [11, 12]. Considering that the biological tissue is inherently a heterogeneous structure regarding its porosity and mechanical features, to model TE scaffold with such features it is required to apply, i.e. to embed the appropriate unit cells from the unit cell library (Fig. 4), which meet required porosity, interconnectivity and mechanical properties.

By collocating the unit cells, similar in size, but of different design (and, consequently, of different characteristics), in the space of tissue region that the scaffold should substitute, the designer can create the scaffold of the required characteristics (porosity, structural strength, elasticity, etc.).

The authors identified this approach as the characterization of tissue structural heterogeneity through a homogenization technique. In situations when the "characterization" of bone tissue has to be defined per layers, the designer can build the scaffold by deposing layer by layer, where each layer consists of 2D array of one kind of unit-cell.

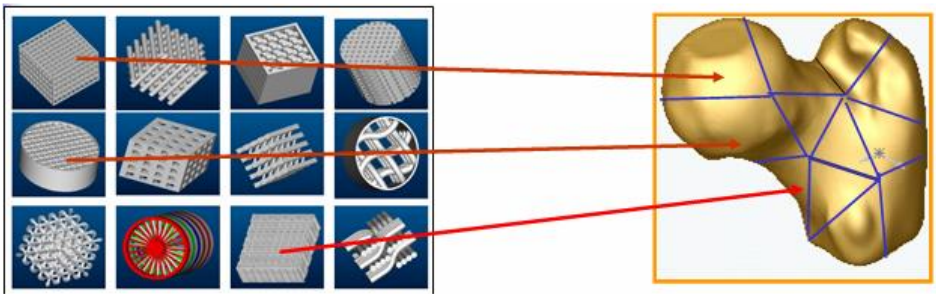

**Fig. 4** Samples of the designed scaffold unit cells [13]

The geometry of the boundary surface of the scaffold model is usually formed by applying Boolean operations of subtraction, where the raw block of scaffold is being pruned (trimmed) by the model of boundary surface of the bone.

Overall procedure of modeling and designing biomimetic bone scaffold is presented in Fig. 5.

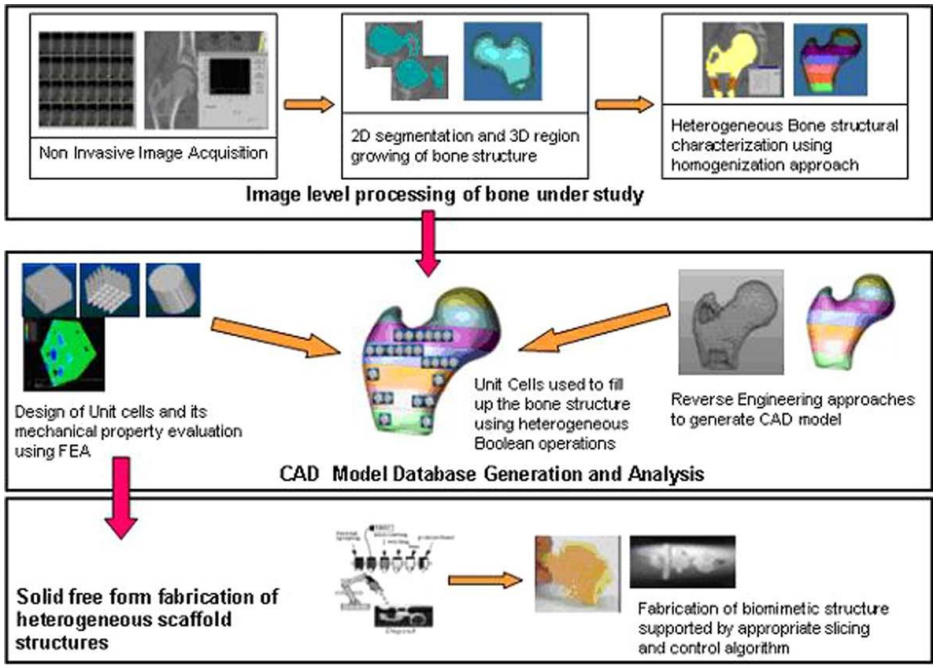


**Fig. 5** Biomimetic bone scaffold design procedure [13]

Sun, Starly and other authors [12, 13, 14], proposed the Internal Architecture Design (IAD) approach to overcome the issues encountered by the designers in CAD software during recurrent emplacing of unit-cells featured by heterogeneous complex geometry in three dimensions. This issue becomes even more difficult to cope with when one should manufacture such intricate structures.

Keeping in mind that this kind of structures is possible to fabricate using AMT, i.e. using the principle of solidification of material layer over layer, the IAD approach offers to generate a kind of biomimetic designed tissue scaffolds through 2D (layered) interior pattern. This pattern is used to generate a processing tool path (Fig. 6).

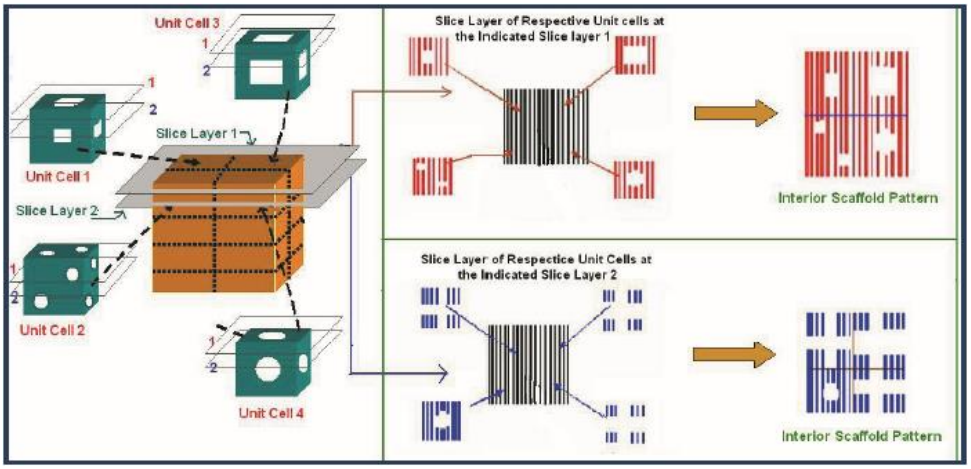


**Fig. 6** Methodology for Internal Architecture Design [13, 14]

Authors designed cylindrically shaped bone scaffolds using the IAD methodology and fabricated them using the TheriForm machine (Fig. 7).

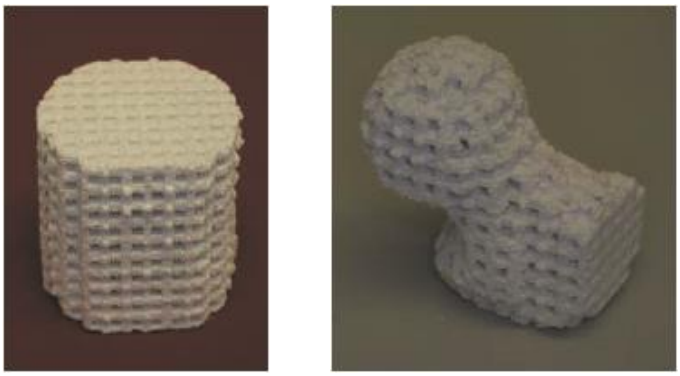

**Fig. 7** Cylindrical shaped and a bone scaffold designed using the IAD [13]

The scaffolds were fabricated of alumina. The main disadvantage of this design approach is the inability to represent (visualize) the final design of the scaffold as a

whole, considering that this approach implies an implicit representation of unit cells geometry of different shapes.

This inability gains the importance especially for the case of applying complex internal scaffold architecture.

The same group of authors (Gomez et al. [15, 16]) presented scaffold designing process that is based on applying unit geometric shapes in three scales (multi-scale: micro-, meso- and macro- scale, Fig. 8).

At the micro-scale the geometry of unit building blocks (cells), their porosity grade, voids connectivity and mechanical properties are considered, that is, their geometric and mechanical congruency with the tissue these unit-cells should substitute.

At the meso-scale, the scaffold design, featured by heterogeneous properties of the real bone tissue, begins to be considered as a whole. Within the meso-scale, designing the heterogeneous scaffold involves the morphological, structural, and mechanical properties of the tissue, which are defined in the micro-scale, but also, the loading conditions for the tissue that are defined in macro-scale [16].

In the macro-scale, the design process is focused on scaffold boundary surfaces and implanting conditions, mechanical constraints and loads, and connections with neighboring tissue.

Thus, the meso-scale model may be perceived as the model which connects and integrates the data sets which come from the models built in micro- and in macro-scale. The changes that are being made in design of the model built in either micro- or macro-scale are reflected in models design in two other scales, thereby integrating the scaffold design process between the scales. The data set inherent to each unit-cell, consisting of parameters relevant to its mechanical, biological and geometric properties as well as to its connectivity and manufacturability, makes an information chunk used for unit cell selection and assembling in a heterogeneous tissue scaffold.

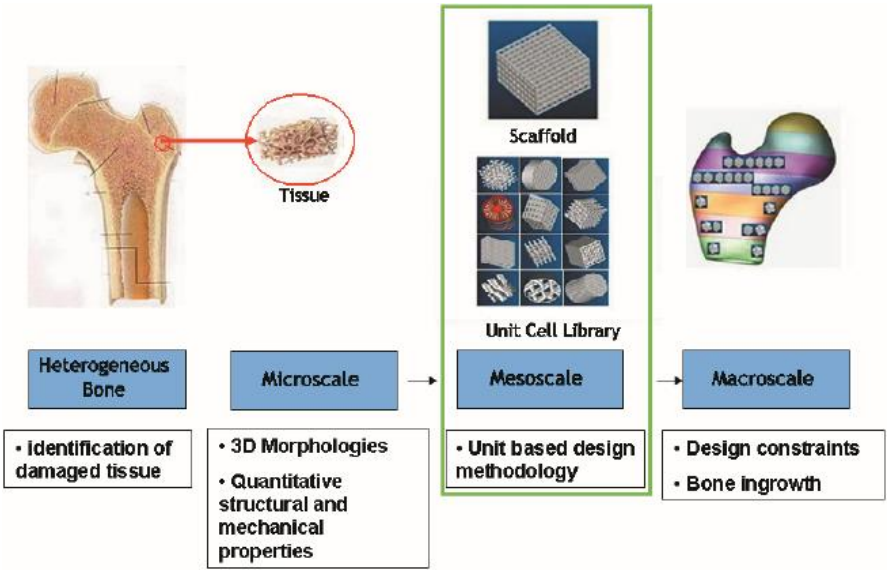


**Fig. 8** Multi-scale modeling of a bone [16]

Wettergreen et al. [16] recognized the lack of a generic geometric connection feature between unit-cells as one of the issues in the other approaches based on unit cells, which may result in emergence of critical stress lines and border fractures.

To overcome this issue, the authors developed the library of unit-cells with generic interface in the form of a torus, capable to be merged seamlessly ensuring the required mechanical properties (like elasticity, stiffness, strength), porosity and perfusion of the scaffold.

Additionally, a series of structural analyses (using finite element method) has been conducted for different geometries of unit-cells to determine their stress and strain state under regular loads/constraints cases for a wide range of material and porosity grades.

The approach was demonstrated on the example of computer-aided design of the scaffold that should substitute the human vertebra body tissue [18]. The scaffold is designed as a layered structure by arranging the unit cells of determined material in series or parallel, trying to provide the similar mechanical properties of the scaffold as the corresponding bone tissue material.

Chua et al. analyzed suitability of different polyhedral shapes for use as a scaffold unit cell [19, 20]. Only open cellular (the cell is made just of cell edges and the cells connect through open faces) were accepted for porous scaffold constructions. Total of 11 polyhedral shapes were selected and subsequently divided into two categories – cells that: 1) can fill space without leaving gaps, and 2) can fill space with leaving gaps.

Selected polyhedral shapes were modeled in CAD software (Creo, former Pro/ENGINEER) in a way that enables scaling to the appropriate pore size in accordance with the application of the scaffold). The geometry of the scaffold unit-cells is parametrically controlled.

The scaffold model is generated by choosing an appropriate unit-cell from the library (depending on porosity grade, ratio between the unit-cell boundary area to its volume and strength requirements), sizing it and assembling automatically following the surface profile of the actual tissue/organ. To verify the concept and developed algorithm for automated scaffold assembling, scaled models of unit cells and scaffolds with different strut thickness were made from commercialized polyamide (PA) material using Selective Laser Sintering (SLS) technology (Sinterstation 2500 machine). All the necessary actions are implemented through the system called CASTS (Computer Aided System for Tissue Scaffolds) [20]. The algorithm of CASTS is able to automatically generate a tissue-like (bio-mimetic) structure that is suitable for the specific application. To validate the system, a patient specific femur scaffold was generated and fabricated from Duraform Polyamide material via.

Automated Scaffold Design (ASD) is another method for designing a 3D bone tissue scaffold introduced by Mahmoud et al. [22]. ASD covers segmentation, registration and 3D rendering visualization of the scaffold and defected bone. Segmentation is performed on Computed Tomography (CT) images using k-means algorithm. Registration is done in three stages and requires CT images of both legs of the patient (where only one is defected) (Fig. 9). 3D visualization is obtained using the MatLab function isosurface, implementing Lorensen's „Marching Cubes" algorithm.

**Fig. 9** For the same slice: healthy bone image (left), defected bone image (middle), and difference between healthy and defected bone image (right) [22]

After remodeling of external architecture of the scaffold, ASD is applied to design the scaffold internal architecture, i.e. unit-cell geometry of appropriate pores size for the desired bone tissue (Fig. 10). The final scaffold model is made by intersecting scaffold structure made of unit-cells with scaffold outer shape, that is, the boundary surface of the bone (Fig. 11).

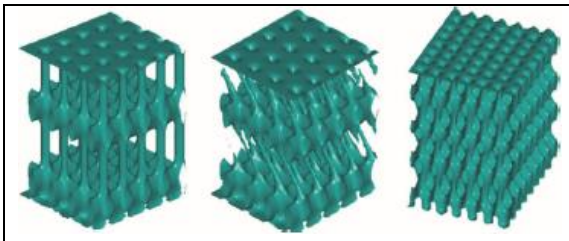

**Fig. 10** Differently designed internal architecture of the scaffold, i.e. differently designed unit-cells and their 3D arrangement [22]

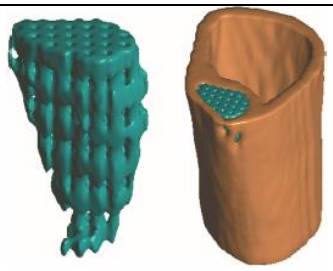

**Fig. 11** Final scaffold model (left), and its positioning in the volume of the defective bone (right) [22]

Chantarapanich et al. evaluated library of 119 polyhedrons for modeling of so-called open-cellular and closed-cellular scaffolds [23]. Each polyhedron was evaluated according to the criteria related to geometry, mechanical strength and manufacturability. The result of evaluation revealed that only four polyhedrons were suitable to be used for the creation of the closed-cellular scaffold, while six polyhedrons were suitable for open-cellular scaffold creation.

### 2.2Image-Based Design

Image-based design approach is also focused on creating the biomimetic scaffold architecture featured by irregular or regular porous structure. It relies on radiographic images analysis, usually CT and μCT. This approach was initially proposed by Hollister et al. [24]. Their design method (called Image Based Engineering (IBE)) begins with creation of defect image (contour design of the implant) by inverting the contrast of the CT or Magnetic Resonance Imaging (MRI) image. Scaffold internal architecture (3D array of structure units) is created by so-called image-based topology design method, which implies setting voxels within an image design cube to either "0" (void voxel) for no material or "1" (solid voxel) for material. The structure units may be created of entities which can be expressed by a geometric mathematical formula, such as cylinders

or spheres. The porous structure, that is, internal channels of these units, can have regular or random spatial disposition. Random porous structure can be created by random setting voxels to 0 or 1.

The image pore size is defined by the image resolution as mm/voxel. Scaffold is created by combining defect image with architecture image.

Scaffolds made of epoxy using stereolithography (SLA 250 machine) were created for orbital floor, and Yucatan mini-pig temporomandibular joint condyle reconstruction. In vivo testing was conducted with scaffolds manufactured from hydroxyapatite (HA) (with different internal architectures) implanted in a Yucatan mini-pig mandible.

Drawing on aforementioned work of Hollister, Taboas et al. developed methods for creating scaffolds that contain locally porous and globally porous internal architectures [25]. Global porous architecture and scaffold exterior are created using IBE method [24]. Local porous architecture is created using conventional techniques. Scaffolds are produced by using *indirect* Solid Free Form (SFF) manufacturing technique developed by the authors. This technique is compatible with IBE method and combines the benefits of local pore manufacturing and direct SFF fabrication. The main characteristic of indirect SFF is that a mold is used to cast the final product.

Poly(L)lactide (PLA) scaffolds were made with porogen leaching and emulsion-solvent diffusion casting of polymer into SFF global pore molds. Molds were created on a SolidScape ModelMaker II 3D printer. Porous discrete composites, including regions of pure sintered ceramic (HA), pure polymer (PLA, polyglycolide (PGA)), and combinations of the two in the same scaffold, were also fabricated. Biomimetic PLA scaffold, replicating human distal femoral trabecular bone structure, was produced with solvent casting. In accordance to the proposed taxonomy this kind of scaffold is a *porous scaffold* featured by random architecture.

Multi-scale voxel modeling approach presented by Fung et al. [26] uses patient specific digital images as the basis for modeling the bone structure both at the macroscopic and microscopic levels.

Macroscopic geometry is acquired from low resolution digital images of the patient bone by traditional reverse engineering techniques.

A high resolution image is used for microscopic geometry construction (Fig. 12 (left)). Randomness of the trabecular network was described by using correlation function, which can be thought of as the probability of finding randomly selected points that are both in the pore phase (Fig. 12 (right)).


**Fig. 12** Scanning electron photomicrograph of transverse slab of vertebral trabecular bone (left). The sample image after thresholding (middle). 2-point correlation function of pore (R represents the distance of two randomly selected points) (right). [26]

The basic idea of the authors was to reconstruct a target (micro)structure (starting from the initial regular structure) which would be statistically equivalent to the original (micro)structure (Fig. 13).

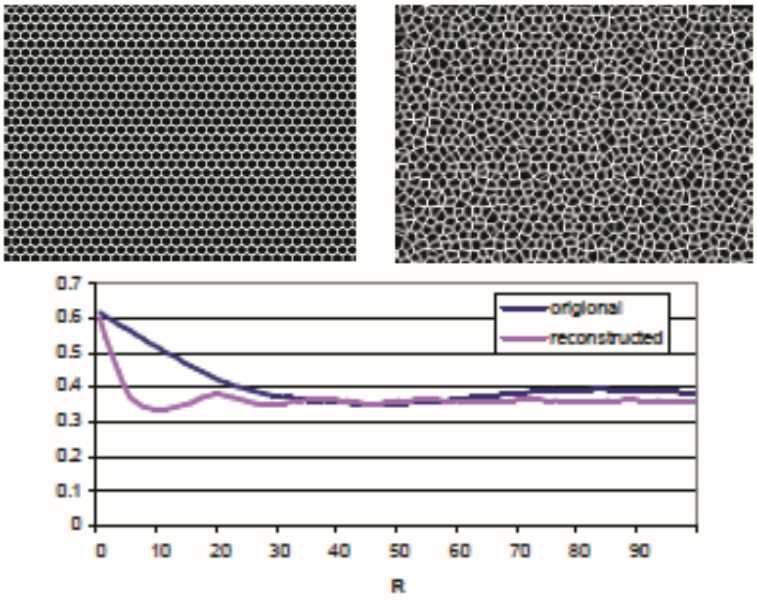


**Fig. 13** The initial regular cell structure (left). The final random cell structure (right). The comparison of correlation functions (down) [26]

Na-Alginate sample, based on voxel model, was fabricated on an in-house built direct fabrication system (Fig. 14).

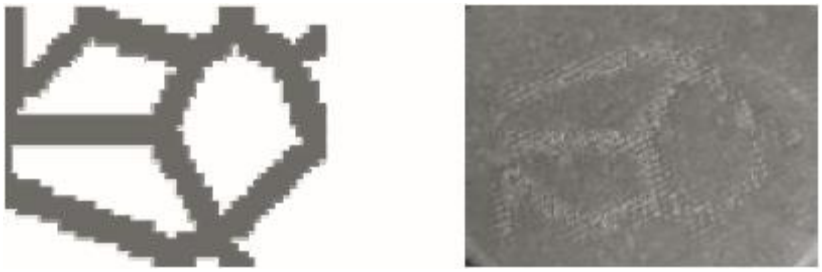

**Fig. 14** Designed simple voxel model (left). Fabricated Na-Alginate sample based on voxel model (right) [26]

One of the possible approaches is direct reconstruction of 3D volumetric model from μCT images, as presented by Podshivalov et al [27]. In accordance to the proposed taxonomy this kind of scaffold may be categorized as a *porous*, featured by random architecture. They presented micro-scale structure scaffolds made from a polymeric

biocompatible material manufactured at different levels of resolution (24 μm and 48 μm) [27]

*Voronoi tessellation* method was used by Gomez et al. [28] for the design of 3D trabecular bone-like structures.

In accordance to the proposed taxonomy this kind of scaffold may be categorized as a *lattice-like* scaffold whose struts are topologically optimized.

The core of the *method* is in disposition of the points within the volume-of-interest (VOI) in accordance to the certain distribution, and subsequent creation of irregular polyhedral unit cells from these points.

Distribution of points is defined by using the μCT images of the L3 human vertebra. Images were split by Voronoi tessellation method, which results in formation of Voronoi cells.

For every image, distribution of points in 2D is defined by creating center points of Voronoi cells.

3D distribution of points is the result of summarizing successive 2D slides at a distance equal to the bone index "mean trabecular separation".

3D Voronoi cell structure is obtained by processing these points. Polyhedral unit cells separated from each other at an equivalent distance to the bone trabecular thickness are created next. Boolean operations give the final 3D porous interconnected structure. Smoothing is being performed at the end.

### 2.3 Implicit Surfaces Modeling

Implicit surfaces modeling is a highly flexible approach which allows complex scaffold internal architecture to be easily described using a single mathematical equation.

Application of Triply Periodic Minimal Surfaces (TPMS) for the construction of scaffold internal architecture is a dominant approach among researchers nowadays [29, 30, 31, 32]. Minimal surfaces may be characterized as surfaces of minimal surface area for given boundary conditions. TPMS are minimal surfaces that are periodic in three independent directions, extending infinitely.

The most important advantages of TPMS in the field of scaffold internal architecture design are the following [29, 30, 31, 32]:

1) precise and easy controllability of internal pore architecture,
2) design process can be fully automated, and
3) a high Surface Area to Volume (SA/V) ratio.

TPMS also appears in the natural and man-made worlds (silicates, bi-continuous composites, lyotropic colloids, detergent films, and lipid bilayers).

Starting from the TPMS mesh surface (composed of simple trigonometric functions), through the offsetting procedure, Yoo generated various types of thickened solids, suitable for representing scaffold internal architecture [29]. The scaffold architecture may be characterized as a porous, topologically optimized.

He also presented a new method which uses TPMS as the basic pore-making element and generates human bone scaffold models. This was the first attempt to use TPMS for scaffold design.

The same author proposed a new approach based on the multi-void TPMS pore architectures [30].

The main advantage of multi-void TPMS-based scaffolds is a dramatic increase of SA/V ratio compared to conventional TPMS scaffolds.

Another contribution of Yoo is a hierarchical porous scaffold design based on TPMS [33]. This time the author used Boolean operation of intersection to generate scaffold with controlled internal architecture. Talus bone scaffold model was designed and fabricated using the SysOpt Eden 330 RP machine. Scaffold was made of UV-curable polymer.

Like Yoo, Yang and Zhou presented an effective method for multiple substructures combination [34]. The proposed method enables easy construction and direct fabrication of Functional Gradient Porous Scaffold (FGPS).

### 2.4 Specific Approaches

Lal and Sun [35] presented a computer modeling approach for constructing 3D microsphere-packed bone graft structure. Basic microspheres packing model was created from Scanning Electron Microscopy (SEM) images of synthesized cylindrical bone grafts. Two extreme cases of microspheres packing were examined: maximum packing density (minimum porosity and open-cell bone structure) and minimum packaging density (maximum porosity and closed-cell bone structure). For these cases, number of microspheres was determined. Since bone is composed of open and closed-cell structures, the number of microspheres in synthetic bone graft (a combination of both packing cases) was calculated using a statistical approach. Microsphere-packed 3D bone graft is formed by stacking randomly packed microsphere layers (randomly combined open/closed cell packing situations). Parametric study on the impact of the microsphere's diameter on pore size and number of packed microspheres was conducted. Comparison between the CAD model of bone graft showing bone ingrowth and histological image of in vitro bone ingrowth showed that the CAD model resembles a histological image. This scaffold may be categorized as a pattern porous scaffold.

Lian et al. [36] discussed 3D concentric microstructure construction in artificial bone. 3D concentric architecture with gradient porosity is constructed by arranging 2D concentric structures which have the same mathematical model. 2D structures can have different structural patterns that are obtained by changing the model parameters. Among the input parameters there are porosity, height and radius of the artificial bone. Special software for design of concentric architecture (fiber structures) was developed. In accordance with the proposed taxonomy, this kind of scaffold is a *fiber-liked lattice scaffold*. These structures were incorporated into the Calcium Phosphate Cement (CPC) matrix to form a fiber reinforced CPC composite artificial bone with controlled internal architecture and the desired porosity. It was also confirmed that these resorbable fibers incorporated in the artificial bone may provide short-term strength and can be degraded significantly faster than the HA leaving macro-pores suitable for bone ingrowth.

Cylindrical CPC-fiber scaffold with a height of 23 mm and a diameter of 10 mm was fabricated by indirect AMT.

Ramin and Harris [37, 38] developed a dedicated library of routines in order to interact with CAD software and perform the automatic design of geometric elements representing scaffold internal architecture. They used multi-section solid as the basic element. Developed routines were used for defining the pore shape and size, 3D path for each multi-section solid and designing the multi-section solids. This methodology allows

rapid design and integration of a complex network of channels within scaffold, determined by the set of variable parameters that can be changed within the software, to match the desired characteristics defined by internal architecture of tissue. Five cubic scaffolds with interconnected pore channels that range from 200 to 800 μm in diameter were made using this methodology. This kind of scaffold is a porous scaffold with predefined 3D pattern of voids.

Cai and Xi [39] introduced morphology-controllable modeling approach for constructing TE bone scaffolds. The main advantage of this approach is the possibility to create scaffolds with various irregular pores by using finite element shape function. The pore shape is controlled by subdivided units. The volume (solid model) of the bone that should be substituted by the scaffold is being discretized into the 3D mesh of hexahedral elements (units). The vertices and edges of every hexahedral element (unit) are being used as vertices and edges of the control polyhedron of the surface subdivision sphere primitive. This primitive is introduced as a basic pore making unit, which can be mapped into various irregular pore units. The iso-parametric transformation was used for mapping the basic unit into an arbitrary unit (irregular pore).

At the last step, the scaffold model is being created by Boolean operation of subtraction. One bone scaffold model was fabricated by ink-jet printing.

The scaffold made in this way obviously belongs to the porous kind of scaffolds with predefined void's geometry and predefined 3D pattern disposition.

### 2.4 Lattice-Like Scaffold as 3D Non-Patterned Structure Made of Fully Designed Lattice Struts

The so-called *anatomically shaped lattice scaffold* (ASLS) that was developed by the research group from the University of Niš [2, 40, 41,] is a kind of 3D lattice scaffold whose struts do not follow some 3D pattern. It is a design concept that aims to ensure high geometrical congruency to the particular anatomy, to provide maximal permeability as well as the simple and efficient fixation. The proposed lattice design concept is featured by two groups of struts (Fig. 15). The *enveloping struts* are densely interlaced following the geometry of outer wrapping surface of the bone tissue. Still the lattice of enveloping struts is designed sparse enough to enable easy penetration of vascular and nerve structures to the interior of the scaffold volume. The second group of struts (cross-linking struts) is stretched through the interior space of the scaffold volume, the space which should be taken by the spongy bone tissue.

The cross-linking struts connect the struts in the enveloping lattice, providing the required strength and stiffness to the cage of the scaffold. Low density of the inner structure is designed to assure profound vascularization and innervation of the bone graft.

Several scaffolds of this kind are applied for the in-vivo experiment, which is performed in order to explore their applicability for the real cases of missing large pieces of the bone. The scaffolds are designed for large trauma of proximal diaphysis of rabbit's tibia (Fig. 16). They are made of Ti-alloys by application of AMT (in particular for the experiment, by using EBM and DMLS). The newest research regarding this kind of scaffold is focused on making the whole implant assembly of bone graft and biodegradable scaffold at once by using bio-3D-printer.

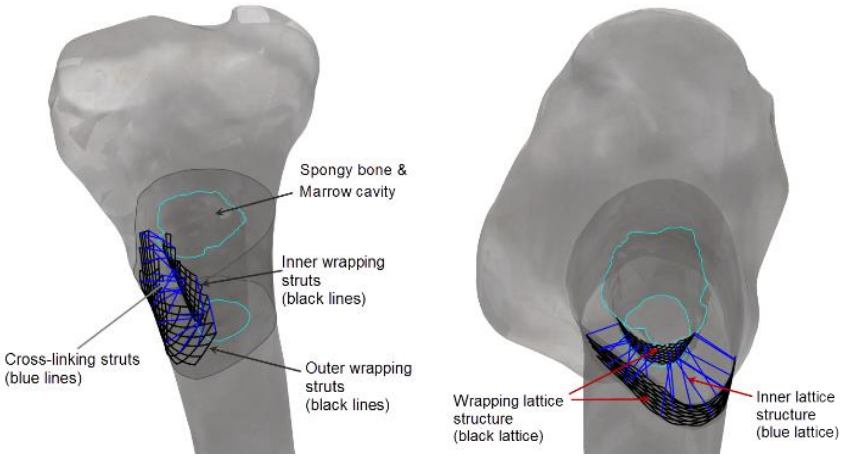


**Fig. 15** Concept solution of ASLS developed for human tibia [2]

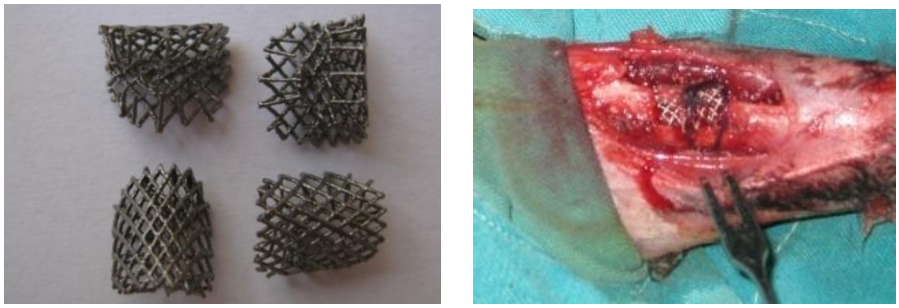

**Fig. 16** Scaffold designed and fabricated for large trauma of proximal diaphysis of rabbit's tibia (left), scaffold implantation into the defect area in a rabbit model (right) [42]

### 2.5 Topology Optimization

In the last ten years, with the significant increase of the computer capabilities, and the emerging new algorithms for the so-called topological shape optimization [43, 44, 45, 46], 3D modeling of bone tissue scaffolds becomes an ideal field for applying topological optimization of scaffold architecture in order to provide the desired characteristics regarding the expected mechanical stresses and deformations. Material distribution method has demonstrated its potential in a large number of case studies in this field [43].

In terms of scaffold design, one of main and unavoidable optimization goals should be minimal volume of the material of the scaffold, which leads TO algorithm [47] to generate lattice like structures.

At the same time, this goal ensures the lattice-like structure to be as much airy as possible. In case of this optimization goal, TO algorithm should not consider the structures featured by “closed” pores, keeping in mind that the scaffold should enable maximal communication through its volume.

Another optimization goal should be related to the minimization of strain in the structure. This optimization goal would direct TO algorithm to generate a kind of

anisotropic lattice-like structure optimal to bear the load typical for that bone region. However, for engaging this optimization goal into TO algorithm, it is necessary to model the equivalent load case, which should approximately emulate the usual and real load cases [48].

In the field of scaffold design topology optimization techniques were used also by Hollister [49, 50, 51, 52, 53], Challis et al. [54] and many others. They considered stiffness and diffusive transport properties in their works. Using topology optimization, Hollister and co-workers also created an interbody fusion cage with porous architecture to help improve arthrodesis [55]. In this study a topology optimization algorithm is proposed as a technique to design scaffolds that meet specific requirements for mass transport and mechanical load bearing.

## 3. DISCUSSION

Almost all (except TO) methods presented for modeling the geometry of bone tissue scaffolds are intended to mimic the complex geometry of the trabecular structure of spongy bone tissue. Comparing to the spongy bone tissue, the geometry of the *cortical bone* structure is not in the focus of current research, probably for two reasons: the first relates to its density - the structure of the cortical bone is too dense and it is not likely that the artificially created structure could allow required extent of communication of surrounding tissue to the bone interior, necessary for profound innervation and vascularization of proto-tissue within the volume of the scaffold; another reason is the limitations of the current additive manufacturing technologies to produce such a dense and, in the same time, geometrically complex structure. The resolution of solidification and/or deposition of materials that can be achieved by existing additive manufacturing technologies are insufficient for such fine details.

### 3.1 Design of Scaffold and its Real Implantation Purpose

Regardless the type of bone tissue for which scaffold design methods are being developed - spongy or cortical, it is important to emphasize, once again, that the vast majority of these design methods are aimed to mimic the geometry of the structure of natural bone tissue to a greater or lesser extent. However, the question is - is it necessary at all to create a bone scaffold geometry which resembles the structures of natural bone tissue? Such an approach could be justified if the goal is to produce a kind of tissue endoprosthesis that should completely and permanently replace the missing bone.

In that case, the goal would be to model the geometry of both the outer, wrapping surface of the bone and the internal structure of the spongy bone, which matches as closely as possible the geometry of the natural tissue. It would not, however, be a scaffold, but rather an endoprosthesis with all the geometric details of the complete bone volume However, with bone scaffold implantation, the intent is substantially different from implantation of a bone endoprosthesis. First of all, the bone scaffold is aimed to reinforce the proto tissue in early stage of recovery, that is, to provide required temporary mechanical properties to the growing bone tissue.

Keeping that in mind, the scaffolds that are aimed for bone tissue recovery, but whose design imitates neither spongy bone tissue nor the ECM, are usually designed as a kind of three-dimensional lattice structure that resembles a cage. The cage holds the proto-tissue

that should transform into true bone tissue with all its natural features including geometry during recovery.

The early proto-tissue is a mixture of a crushed natural or artificial bone with the addition of fat tissue, blood plasma, progenitor cells and growth factors. Due to its mushy consistence, that is, very low structural strength, the proto-tissue cannot be exposed to higher mechanical loads. On the other hand, the research and practice [56, 57] indicate the necessity of mechanical loads application to a portion of the traumatized bone as one of the main stimuli for the ossification process, first at the interface of the proto-tissue and surrounding healthy tissue, and later, at the depth of the proto-tissue itself. Also, the scaffold geometry should enable smooth penetration of nutrients into the volume of proto-tissue without which it is not possible to expect the transformation of proto-tissue into genuine bone tissue. In fact, the scaffold geometry should not obstruct the proliferation of blood vessels and nerves into the proto-tissue volume. This scaffolding function indicates the maximum porosity or transparency of the lattice structure. Scaffolds whose geometry mimics spongy bones, however, do not facilitate but hinder the sprouting of native tissue into the space of scaffolds. This function calls for maximum porosity or airiness of the lattice structure of the scaffold. Another important feature of the scaffold geometry in the macro and micro scale is suitable adhesiveness of the scaffold strut surfaces that will help the proto-tissue particles to attach to the scaffold firmly. Finally, the last, but no less important feature of the bone scaffold, which, however, is not directly related to its geometry is its biodegradability. Since the proto tissue is expected to transform into a genuine bone tissue during the recovery process, growing up through the volume of the scaffold cage, it is necessary for the artificial structure of the scaffold to degrade and resorb over time, and the volume of degraded scaffold structures to be replaced with the real bone tissue. It is the most desirable scenario of recovery that would allow any artifactual structure, which could possibly be the source of infections and necrotic processes in the future, to disappear from the tissue. If the time-controlled biodegradability of the scaffolds could be achieved in near future, this would be indirectly related to the scaffold geometry. Certain elements of the scaffold cage structure would degrade faster while the others would degrade slower, so the mechanical properties of the scaffold cage structure could change according to a predefined time plan. The initial load taken over by the scaffold at the beginning of recovery process could be transferred to the newly formed bone tissue during the recovery time gradually.

Having in mind the primary function of bone scaffold to reinforce the proto- bone tissue during the recovery, scaffold geometry (i.e. lattice structure of the scaffold) should match the required anisotropy of the mechanical properties. This is needed in order to ensure proper deformability according to the load conditions and bone characteristics specific for the particular patient. The scaffold models created as a three-dimensional pattern of shape units, i.e. unit cells (voids or struts) have small potential to adjust the anisotropy precisely, that is, to be personalized for the particular patient. In contrast, the algorithms of topological optimization coupled with modern CAE software bring momentous advantage in designing of personalized lattice-like bone scaffolds that match the required anisotropy of mechanical properties.

## 4. CONCLUSION

Here are the concluding remarks regarding the presented methods for designing of scaffolds aimed for bone tissue recovery in four aspects:

Regarding geometry: The presented review of realized bone scaffolds concepts shows that there are many different approaches to the geometric modeling of bone scaffolds. Also, the most of existing methods are focused on designing the scaffolds whose geometry mimic spongy bone tissue. The modern CAD applications enable modeling of such shapes in an efficient manner, by recurrent laying of the three-dimensional shape units in the space, simultaneously controlling the size of pores (voids). Even though numerous methods for bone scaffold designing are developed, it is important to notice that complex and multi-lateral requirements which a bone scaffold should meet are still not clearly defined and agreed. Within the discussion section a thesis about an important misconception that seems to exist regarding the current scaffold design concepts is brought out: the determination to design the scaffold geometry congruently to the spongy bone tissue geometry is in contrast to the basic functions of scaffold.

Mechanics: A significant drawback of most of the design concepts of bone scaffolds, especially those that are unit-cell based (3D pattern), is their inability of adaptation to the required anisotropic mechanical properties.

Fabrication: Considering the geometric complexity of the structures, additive manufacturing technologies seem as an optimal choice for the scaffold fabrication method (FDM, SLS, DMLS). However, in order to produce geometry details that can exist in the bone scaffolds as it is introduced in this paper, a significant improvement in hardware as well as the speed and resolution of RP machines are required. Also, according to many authors, the future scaffold design concepts that should be personalized in terms of geometry, mechanics and time-controlling biodegradability, will require to be fabricated of multiple materials, which will also call for a significant improvement of fabrication process. Very probably, we should expect to witness a new additive manufacturing technology which will be able to create the multi-material scaffold simultaneously infiltrated by personalized bio-material of bone graft.

Testing and application: Regarding the experimental research of the bone scaffold design, it is worth mentioning that there were just a few research studies where the scaffolds of complex design (TMPS, TO) were applied in in-vivo experiments. Mostly, the experimental research was done with simple three-dimensional pattern unit-cell design concepts of scaffolds in in-vitro experiments. As far as we have found out, there is lack of data on possible research cases of clinic application of biodegradable scaffolds for bone tissue regeneration.

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