

An Introduction to Scaffold Design Using Topology Optimization Methods

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Abstract. In this text, the fundamentals of topology optimization (TO) are applied to trabecular bone's topology design, with the goal of then extrapolating their uses to bio-scaffold design for regenerative therapy.

Total fragility bone fractures in the EU are estimated to increase from 2.7 million in 2017 to 3.3 million in 2030; a 23% increase. The resulting annual fracture-related costs (€37.5 billion in 2017) are expected to increase by 27%. An estimated 1.0 million quality-adjusted life years were lost in 2017 due to fragility fractures. The current disability-adjusted life years per 1000 individuals age 50 years or more were estimated at 21 years, which is higher than the estimates for stroke or chronic obstructive pulmonary disease (see [1]).

Healing of bone fractures and reconstruction of critical-sized bone defects represent a significant challenge. With bone graft and synthetic material reconstruction techniques having their unfortunate limitations, bio-scaffolds came into play to get the best of both. Since scaffolds require very high porosity levels for osteoconductivity and must simultaneously bear a great amount of force occurring from the daily loads a patient experiences, structural analysis is indispensable to optimize their mechanical properties. Also, materials used for scaffold design are not as nearly as stiff as native bone, making optimization even more crucial.

The Solid Isotropic Material with Penalization (SIMP) method for TO is quickly discussed and a perimeter constraint is introduced to impose porous-like structures in the design.

Then, a topology optimization analysis is performed to mimic the trabecular architecture of a human's proximal femur. The femur's boundary conditions when it's subjected to daily gait are talked through. Lastly, an application to scaffold design is discussed.

INTRODUCTION

Conventional medicine therapies for large bone defects use techniques such as bone grafting and synthetic material reconstruction.

Bone grafts have the advantage that biological tissue is implanted and thus the native tissue can adapt to the graft and functionally remodel. A disadvantage is that it may require a second surgical intervention on the patient's body (if it is an autograft), which leads to site morbidity and a longer recovery time. It may even require a donor (allograft)

and the foreign graft implant has a longer adaptation time on the patient's tissue. Other shortcomings are that there is a limit on tissue available and difficulty in obtaining/modifying the shape for the defect site.

On the other hand, synthetic material reconstruction offers the advantages that it does not have a limit on material usage (when costs are neglected) and that the shape can be specifically manufactured for a particular defect. Despite not needing a second surgical site, it is known that the synthetic material's integration in the host's tissue is not optimal, which leads to problems such as mechanical loosening in the site. These reconstructions do not allow bone remodeling in the defect site since the material is occupying all the volume and shielding all stresses, preventing bone stimulation/formation.

To circumvent drawbacks of both techniques, a third approach was motivated.

Bio-scaffolds show a promising future in the rising field of Tissue Engineering (TE). These 3D, bio-degradable and bio-compatible structures are implanted into the region of defect and allow tissue regeneration whilst degrading so as not to remain in the patient's body after the regenerative process is complete. During this period of degradation it is important that the scaffold can withstand outer stresses in a similar manner to its surrounding tissue. Porosity is one of the main positive properties for cell adhesion and differentiation in the scaffold, whilst being reciprocally proportional to stiffness. For this reason, it is important that the topology of the structure is optimized, so as to be as stiff as possible while maintaining its desirable bio-mechanical properties such as porosity. As the field of TE grows, so does in parallel the field of Additive Manufacturing (AM), allowing us to print or manufacture highly complex optimized nano-structures.

Many studies have by now noted that pore-size and material of the scaffold have a key influence on the bone and cartilage regeneration process. Degradability-rate, bio-compatibility and viscosity are examples of such important material properties.

Although these points are crucial, the topology of the scaffold's internal structure is just as important. For the regenerated bone to carry mechanical load, the scaffold's internal structure must be mechanically optimized for the daily loads the patient experiences and give the bone formation process a temporary structural support till bone restores complete function. This is vital, because

- An over-stressed state of the bone results in tissue resorption (see [2]), so that bone cannot reform during the patient's bone daily loads.
- Recent remodeled bone tissue is less mineralized than older tissue (about 20 – 25% less [2]), thus it needs extra structural support during the first weeks/months of remodeling.

Recent techniques for the fabrication of bio-scaffolds include salt-leaching and unit cell based design. In the former technique, salts (usually NaCl) are mixed with polymer (usually PCL), molded and heated in an oven. Then, the scaffold is soaked in water so that the salts leach out of the scaffold, which results in a porous medium design. Unit cell based design techniques can be handy, because the effective properties of the whole scaffold (assembled from a repetition of unit cells whose properties are known) are easily computed.

Nonetheless, design with uncontrolled pore connectivity and orientation does not favor a stiff internal structure and hence results in a scaffold with poor mechanical assets. It was only very recently that efforts have been made to optimize the scaffold's internal structure. Structural multi-objective constrained optimization for scaffold design is starting to gain attention (see [3] for an overview).

MATHEMATICAL MODEL

SIMP Model

Let $\Omega^{mat} \subset \Omega$ be the domain of a mechanical body and $\partial\Omega = S \cup S_u \cup S_l$ its boundary, where S_u and S_l are the boundaries where displacements $u = \hat{u}$ and the boundary traction forces $\sigma_{ij}(x)n_j(x) = g_i(x)$ are specified, respectively. n_j is the outward normal of the surface at $x \in \Omega^{mat}$ and σ_{ij} is the stress tensor. Let $(u, \bar{u}) \in \mathbb{U}^2$ be real and virtual displacements mapped from Ω^{mat} to $\mathbb{U}$, where $\mathbb{U}$ is the set of admissible displacement functions¹. Associated with a displacement one has the strain tensor

$$\epsilon : u \mapsto \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right). \quad (1)$$

¹Displacements must be at least C^1 and virtual displacements must satisfy $\bar{u} = 0$ at S_u

where $x \in \Omega^{mat}$ is a first rank tensor defining position. Define the external work of applied loads in the linear form

$$l : u \mapsto \int_{\Omega} f_i u_i d\Omega + \int_{S_l} g_i u_i dS_l. \quad (2)$$

where f_i are the body forces (inside Ω^{mat}).

Now define the internal virtual work at the equilibrium displacement u and for an arbitrary virtual displacement $\bar{u}$ in the bilinear form

$$a : (u, \bar{u}) \mapsto \int_{\Omega} \mathcal{E}_{ijkl} \epsilon_{ij}(u) \epsilon_{kl}(\bar{u}) d\Omega \quad (u, \bar{u}) \in \mathbb{U}^2 \quad (3)$$

where $\mathcal{E}_{ijkl} \in \mathbb{E}$ is a fourth rank tensor defining stiffness properties, known as stiffness tensor, and $\mathbb{E}$ is the space of admissible stiffness tensors.

Taking into account the principle of virtual work, which states that the internal and external virtual work must be equal for any virtual displacement, the penalized, proportional stiffness model (or SIMP, an acronym for Solid Isotropic Material with Penalization) for TO is stated as the following optimization problem ([4]):

$$\min_{u \in \mathbb{U}, \mathcal{E} \in \mathbb{E}} l(u) \quad (4a)$$

$$\text{subject to} \quad a_{\mathcal{E}}(u, \bar{u}) = l(\bar{u}), \quad \forall \bar{u} \in \mathbb{U} \quad (4b)$$

$$\mathcal{E}_{ijkl}(x) = \rho^p \mathcal{E}_{ijkl}^0(x) \quad (4c)$$

$$\int_{\Omega} \rho d\Omega = V^{mat} \quad (4d)$$

$$0 < \rho_{min} \leq \rho(x) \leq 1 \quad (4e)$$

where $\rho(x)$ is the density of material at point x (because the volume of the structure is evaluated as $\int_{\Omega} \rho d\Omega$), $\mathcal{E}_{ijkl}^0(x)$ is the constant stiffness tensor with the materials properties, $\mathcal{E}_{ijkl}(x)$ is an interpolation of $\mathcal{E}_{ijkl}^0(x)$ and $\rho(x)$, also called effective stiffness tensor, and the exponent p (typically $p \geq 3$) is intended to steer the density values towards 0 or 1 (notice that since $\rho \in [\rho_{min}, 1]$ intermediate values are penalized if ρ has an exponent greater than 1). We still refer to ρ as a density of material because the volume of the structure is evaluated as $\int_{\Omega} \rho d\Omega$.

In a finite element setting with n elements and where $\Omega = \bigcup_{e=1}^n \Omega_e$ with m independent load cases $(F_i)_{i=1, \dots, m}$, one must solve for m global displacements $(U_i)_{i=1, \dots, m}$ and compute m compliance values $(c_i)_{i=1, \dots, m}$. The problem can be restated

$$\min_{\rho} \quad c(\rho) = \frac{1}{l} \sum_{i=1}^m c_i \quad (5a)$$

$$\text{subject to} \quad KU_i = F_i, \quad i = 1, \dots, m \quad (5b)$$

$$\sum_e \rho_e |\Omega_e| = V^{mat} \quad (5c)$$

$$0 \leq \rho \leq 1 \quad (5d)$$

where $c_i = U_i^T K U_i$.

Pore and Member Size Control

If we are willing that the end result topology of our optimization problem mimics trabecular bone's structure, we need a means to impose a porous topology to it during the optimization. One way to do this is to define a perimeter function for the topology ([5]), given by

$$P : \rho \mapsto \sum_{k=1}^n \sum_{\substack{l=1 \\ l \neq k}}^n |\langle \rho \rangle_{kl}| \gamma_{kl} \quad (6)$$

with $\langle \rho \rangle_{kl} = \rho_l - \rho_k$ and γ_{kl} is the interface length of neighboring elements k and l . At every iteration, the perimeter can be computed and constrained to a prescribed value $\bar{P}$. It is obvious that more pores in the topology of the body imply

a greater perimeter, but the reciprocal is not true. Since it is not necessarily true that a greater perimeter imposes more pores, it is key that the initial topology already is porous, with a perimeter value close to the prescribed one. Doing this also ensures a steadier convergence to the solution of the optimization problem.

Furthermore, to ensure finite element mesh-independence, the linear filter operator

$$H(\rho_e, r_{\min}) := \frac{\sum_{i \in \mathcal{N}_e} h_{e,i} \rho_i}{\sum_{i \in \mathcal{N}_e} h_{e,i}} \quad (7)$$

is employed, where $\mathcal{N}_e = \{i | \text{dist}(\Omega_e, \Omega_i) \leq r_{\min}\}$, $h_{e,i} = \max(0, r_{\min} - \text{dist}(\Omega_e, \Omega_i))$. Evidently, tuning the $r_{\min}$ value results in different mean structure member size thicknesses. Filtering and perimeter control are techniques originally thought to avoid mesh-dependence (see [6] for further details on the filtering and projection schemes). In this context, the filter is used to control the member thickness of the lattice like structures of bones (in particular trabecular thickness) or scaffolds: The greater the filtering radius, the larger the structural members.

Simulation

It is well known by now that a specimen's bone topology functionally adapts to outer stimulus (for example particular ground reaction forces during gait and other frequent activities). This phenomenon is usually denominated "Wolff's Law" named after Julius Wolff or "Roux's Functional Adaptation" a concept developed by Wilhelm Roux, a contemporary of Wolff. The crux of all this is that bone's topological adaptation to outer stimuli (which is in essence the same as topology optimization) can be seen as a main subset activity of bone's functional adaptation. Hence, we can expect to see a topology optimization algorithm return similar topologies as those of trabecular bone. There have been many attempts to simulate bone remodeling. Some articles suggested a rate equation for stress uniformity over a body ([7]). There have even been recent attempts to do the same using topology optimization algorithms ([8]).

Two-Dimensional Femur Trabecular Topology Optimization

For the sake of simplicity, a longitudinal cross-section of a human femur CT-Scan was considered. The first goal was to approximate the topology of its lattice-like interconnected structure, using the optimization process. The physical domain Ω has dimensions $100\text{mm} \times 100\text{mm}$ (see figure 1a) and was discretized into a 800×800 square Q4 element regular mesh. This resulted in a $0.125\text{mm} \times 0.125\text{mm}$ element size. A mean trabecular separation/pore radius of 1mm (8 elements) and a thickness of 0.5mm (4 elements, thus $r_{\min} = 4$) was assumed. The initial topology consists of random circular patterns containing these properties (figure 1b).

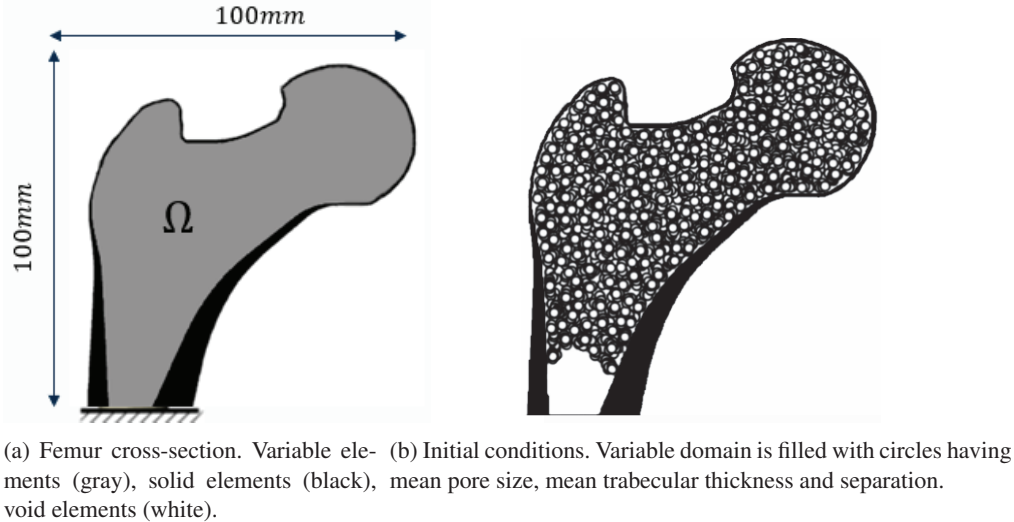


FIGURE 1: Femur cross-section domain and initial configuration.

A chunk of trabecular bone, viewed from a big representative volume (mm^3) is highly anisotropic. Though, when viewed at a tissue level (μm^3), this anisotropy decreases. The homogenized mechanical properties of collagen fiber matrix and hydroxy-apatite crystals at a tissue level are not fully isotropic, but one makes this approximation since their anisotropy is minimal and not yet fully understood ([2]). For this reason, an isotropic model was used and the element's modulus was chosen to be $E_0 = 12.7 \text{ GPa}$, the poisson ratio $\nu = 0.28$, values which are often reported in bone mechanics books (see for instance [2]). The loads considered were the joint reaction and muscular tension forces in the proximal femur during a human's gait. One-legged stance, leg abduction and adduction are the main actors (figure 2). The femoral head suffers an orthogonal reaction force coming from the contact with the acetabulum and the greater trochanter is pulled by the piriformis and gluteus muscles in all cases.

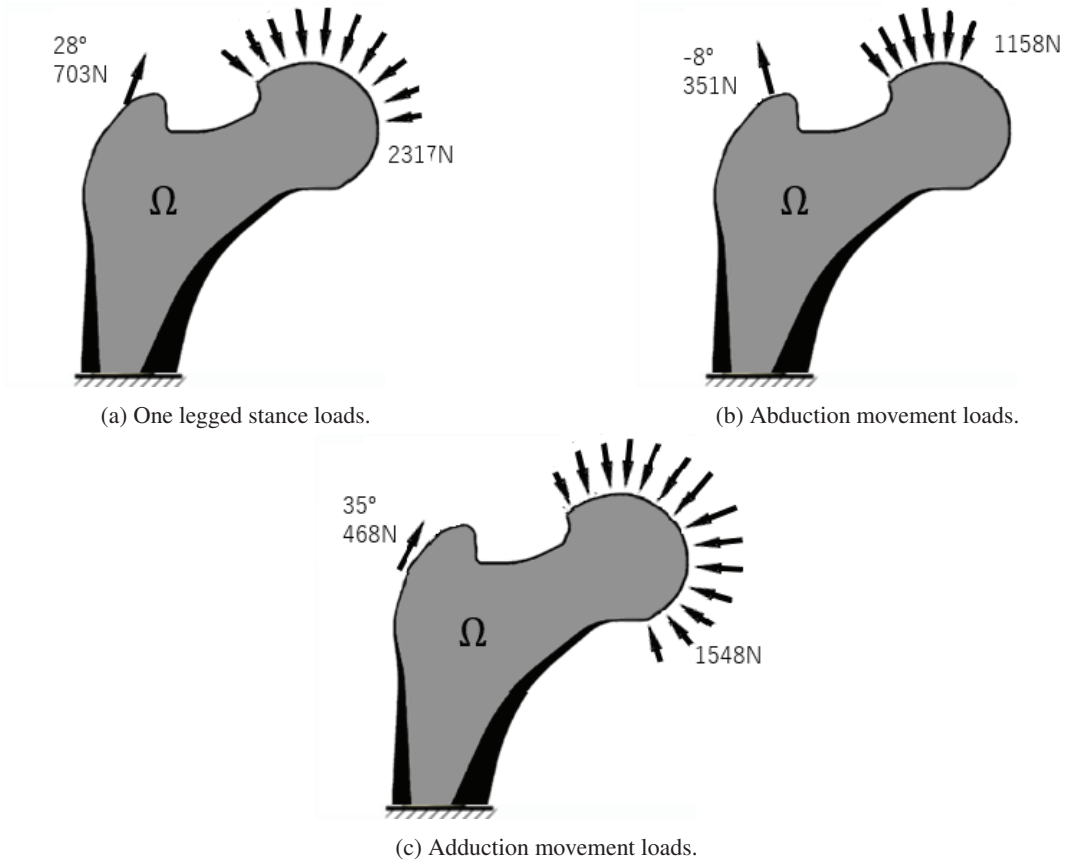
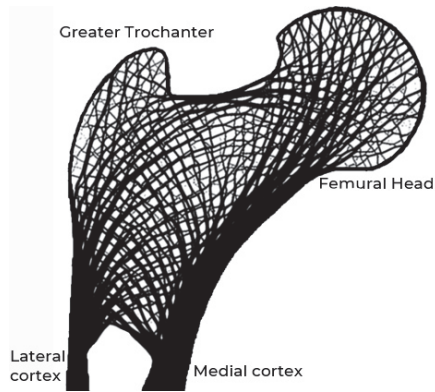


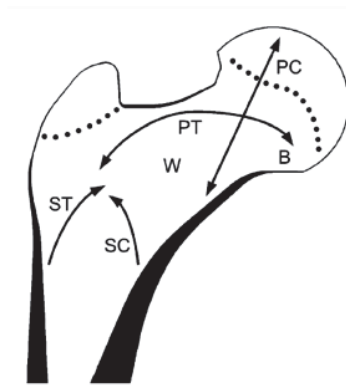
FIGURE 2: Forces acting on the femur during gait. Forces acting on the femoral head are orthogonal to its surface and come from the hip's acetabulum. The angles and magnitudes of the loads were taken from [7]

The results of the simulation are shown in figure 3. The higher density regions show how similar the results 3a are to the nominal groups (figure 3b) in the real trabecula of the femur. Namely, one can see the principle compressive group (PC) run from the medial cortex up the femoral head along the femoral neck. It can also be seen how the secondary tensile group (ST) crosses the secondary compressive group (SC), in an almost orthogonal fashion, coming from the lateral cortex. The low density area between the compressive and tensile groups, denominated Ward's Triangle, is also apparent. Since the algorithm cannot predict the medullary cavity (it exists because of biological demands), it was kept as passive void throughout the optimization.

A plot containing the maximum stresses (in MPa) in every element is shown in figure 4a. Looking at the values, it is noticeable that the most stressed states in the femur occur in the femoral shaft and neck. This observation is coherent with the fact that femoral neck and shaft fractures are the most common types of fracture in the femur. Also, notice that the tensile normal groups happen to have most internal stresses relative to the compressive groups. The information obtained from stress analysis is of great importance when optimizing a scaffold's topology. A scaffold



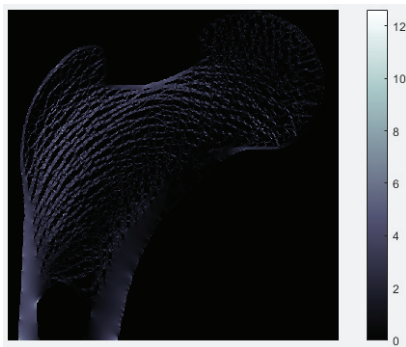
(a) Final topology and real computer tomography scan



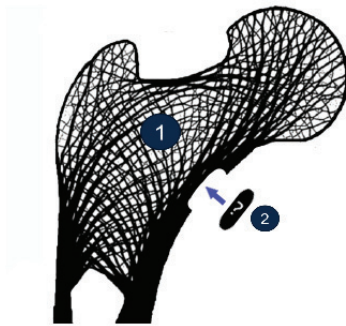
(b) Nominal groups

FIGURE 3: Simulation results

should be optimized against the internal stresses that would occur within the defect site (where it is implanted). For example, the interior design of a scaffold for a defect in the medial cortex (as shown in figure 4b) can be designed specifying porosity, pore size and thickness with the information obtained by now. This can be accomplished by obtaining the internal stresses from the end topology of a first optimization round (mimicking the bone's topology) and using them as boundary conditions for a second optimization round where the scaffold's topology is effectively optimized within a defect region.



(a) Internal stresses (MPa) at last iteration. The displacements used to compute the strains and stresses are the mean displacements of all load cases.



(b) Femoral head defect and scaffold to be optimized.

FIGURE 4: Stress state, typical femoral and scaffold optimization.

Conclusion

The ultimate goal is to develop a scaffold topology optimization framework that can include multiple objectives and constraints important for scaffold design. One eventually looks at a problem like

$$\min_{u \in \mathbb{U}, \mathcal{E} \in \mathbb{E}} w_1 l(u) + \sum_{d=2}^D w_d f_d \quad (8a)$$

$$\text{subject to} \quad a_{\mathcal{E}}(u, \bar{u}) = l(\bar{u}), \quad \forall \bar{u} \in \mathbb{U} \quad (8b)$$

$$\mathcal{E}_{ijkl} = \rho^p \mathcal{E}_{ijkl}^0 \quad (8c)$$

$$\int_{\Omega} \rho d\Omega = V^{mat} \quad (8d)$$

$$g_d = \hat{g}_d \quad d = 1, \dots, I \quad (8e)$$

$$0 < \rho_{min} \leq \rho \leq 1 \quad (8f)$$

where $(f_d)_{d=2,\dots,D}$ could be objective quantities such as permeability or target tissue strains. Constraints $(g_d)_{d=1,\dots,I}$ could be on quantities like bulk modulus, weight and others. Bone's topological adaptation to outer forces is just a small portion of all the factors that influence bone's topology. So adding more related quantities is essential to approximate reality. Main challenges coming from building such a framework are:

1. Understanding which factors influence the remodeling of bone and their weight of importance.
2. Knowing exactly what constraints lead to an osteoconductive scaffold and their compatibility with other constraints.
3. The computational complexity when more quantities are added to the problem, especially when 3D discretizations are sought after.

It is also necessary to validate the first optimization round (the mimicking of the bones topology) before the scaffold optimization. This could be done in several ways. Here are some of them:

1. Comparing the topology's raster densities pixel by pixel with a real CT scan.
2. Comparing trabecular orientations, using for example fabric tensor analysis (see [2]).
3. Compare volume fractions at certain regions.

Finally, the steps for designing the scaffold would be the ones shown in figure 5.

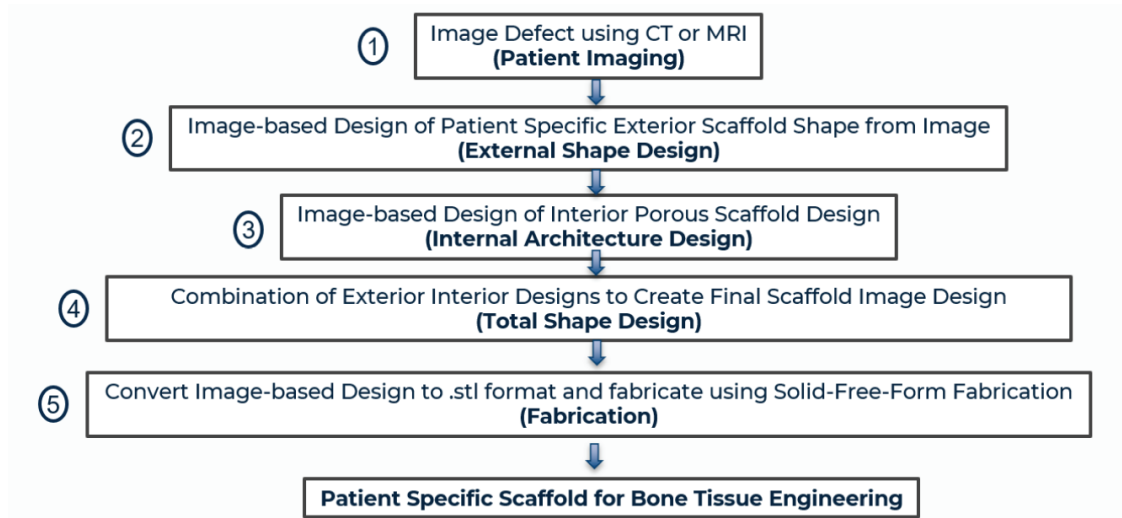


FIGURE 5: Steps in designing a bio-scaffold.

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