Scaffold biomaterials for tissue engineering can be produced in many different ways depending on the applications and the materials used. Most research into new biomaterials is based on an experimental trial-and-error approach that limits the possibility of making many variations to a single material and studying its interaction with its surroundings. Instead, computer simulation applied to tissue engineering can offer a more exhaustive approach to test and screen out biomaterials. In this paper, a review of the current approach in biomaterials designed through computer-aided design (CAD) and through finite-element modelling is given. First we review the approach used in tissue engineering in the development of scaffolds and the interactions existing between biomaterials, cells and mechanical stimuli. Then, scaffold fabrication through CAD is presented and characterization of existing scaffolds through computed images is reviewed. Several case studies of finite-element studies in tissue engineering show the usefulness of computer simulations in determining the mechanical environment of cells when seeded into a scaffold and the proper design of the geometry and stiffness of the scaffold. This creates a need for more advanced studies that include aspects of mechanobiology in tissue engineering in order to be able to predict over time the growth and differentiation of tissues within scaffolds. Finally, current perspectives indicate that more efforts need to be put into the development of such advanced studies, with the removal of technical limitations such as computer power and the inclusion of more accurate biological and genetic processes into the developed algorithms.

**Keywords:** biomechanics; tissue engineering; biomaterials; finite-element modelling
1. Biomaterial scaffolds for tissue engineering

Biomaterials development has evolved from first- and second-generation biomaterials, which sought primarily, respectively, biocompatibility and bioactivity with the surrounding tissues, to third-generation biomaterials, where biomaterials are designed to elicit a favourable and controlled bioactive response from the surrounding tissues (Hench & Polak 2002). The control of the host tissue response has led biomaterials researchers to focus on the development of new materials compositions, and to study the biomaterials’ physico-chemical surface properties, topographical properties and drug encapsulation capability to favour one response or another depending on the type of interaction required between the engineered and the biological entities (Mikos et al. 2006). Although the inflammation reaction due to the presence of a foreign body is a natural process, with the formation of a fibrous layer encapsulating the foreign body (Castner & Ratner 2002), the aim of biomaterials science is to deceive the receiving body by sending signals eliciting the acceptance of the foreign body.

Within biomaterials, tissue engineering is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physico-chemical factors, to improve or replace biological functions. Traditionally, tissue engineering consists of harvesting cells from a patient, expanding them in vitro and culturing them into a biomaterial (also called a scaffold) that serves as a structural framework to allow cell attachment, proliferation and differentiation into a controlled phenotype (Langer & Vacanti 1993). Chemical and topographic substrate patternings are recognized as powerful tools for regulating cell functions (Lim & Donahue 2007). These committed cells can form an extracellular matrix to produce the desired tissue within the biomaterial scaffold. Tissue engineering has led to great expectations for clinical surgery or various diseases that cannot be solved with traditional devices, such as materials for osteochondral ossification (Martin et al. 2007). The total market for the regeneration and repair of tissues and organs was estimated to be $25 billion worldwide in 2001 and is expected to rise steadily (D&MD 2001). However, the harvesting and culture of cells in a controlled manner remain a challenge (Kalyanaraman & Boyce 2007). Moreover, cost versus health gain is still high compared with existing technologies, which makes its industrialization difficult. Thus, research in tissue engineering still remains very active but it has failed to realize viable commercial products. The challenges facing industrialization have led the scientific community to focus on the development of cell-free biomaterials capable of eliciting the appropriate cell response without the need for seeding cells within the biomaterials prior to their implantation. Instead, the concept of tissue engineering is used to study cell–biomaterial interactions in vitro, with the goal of developing ‘smart’ biomaterials.

Whichever of the two approaches is used in tissue engineering, there has been a clear need for a more controlled environment for in vitro cell culture (Kirkpatrick et al. 2007). Better control of the culture conditions can lead to (i) more reproducible methods and therefore a more feasible industrialization of tissue engineering, (ii) the application of physical and chemical cues mimicking the ones perceived by the cells in vivo, and therefore allowing a more realistic in vitro study of cell–biomaterial interactions, and (iii) the application of controlled physical and chemical stimuli in order to improve cell response in
reaction to the biomaterial. Thus, there has been a plethora of bioreactors developed mainly in-house to improve cell seeding, cell attachment, cell proliferation and cell differentiation (Freed et al. 2006). Cell seeding in three-dimensional scaffolds is particularly difficult but essential for the following cellular steps of proliferation and differentiation. Diffusion through culture medium and tissue typically limits oxygen transport in vitro, leading to hypoxic regions and limiting the viable tissue thickness (Malda et al. 2007). For this reason, one of the most common bioreactors nowadays is the perfusion bioreactor, where a fluid flow (FF) is forced through the scaffold to give a very high seeding efficiency (Holtorf et al. 2007). This initial step is critical not only to enhance proliferation and differentiation but also to avoid cell apoptosis by bringing nutrients to the cells. Perfusion has been shown to enhance proliferation for a highly porous critical-size β-tricalcium phosphate (TCP) scaffold with dimensions of 14 mm diameter and 30 mm length, for which static culture leads to hypoxic conditions (Xie et al. 2006). The perfusion bioreactor, in addition to its simplicity, also has the advantage of being able to control the FF profile and magnitude within the tubes and, to a lesser extent, within the scaffold. Other types of bioreactors have also been developed and can be used complementarily with the perfusion bioreactor (Martin et al. 2004). These can apply other types of mechanical stimuli such as compression, tension, bending or shearing. Overall, a large range of bioreactors have been developed to apply a wide range of stimuli depending on the biomaterial used and the tissues to engineer. It has been shown, for example, that a 10 per cent uniaxial cyclic tensile strain can increase osteogenic differentiation of human mesenchymal stem cells (MSCs) through bone morphogenetic protein (BMP-2) mRNA expression without the addition of osteogenic supplements (Sumanasinghe et al. 2006).

The objectives of this paper are to present a review of the scaffold designs currently used and of their characterization using imaging techniques, and to present the finite-element analyses and mechanobiological concepts used to study the mechanical stimuli in biomaterial scaffolds applied to bone tissue engineering. We address the issues confronting researchers when modelling scaffolds for tissue engineering. In particular, we review current concepts to generate accurate computational models of scaffolds using finite-element analysis, and how this may impact on tissue engineering research in the future.

2. Scaffold designs

The design of a scaffold is essential for its correct interaction with cells as indicated above. Moreover, it is essential that it fulfils its in vivo function. Biomaterials science has mainly adopted a ‘trial-and-error’ approach, with modifications being made to an existing design based on experimental in vitro or in vivo results. Improvements in cell culture conditions and the development of bioreactors have greatly improved the reliability of in vitro experiments. Nonetheless, computer-aided design (CAD) can also contribute to the reduction of experimental tests and to shortening the design process of scaffolds (Sun & Lal 2002; Sun et al. 2004a,b). CAD consists of the design of engineering components through computer techniques based on mechanical design. This technique can be used to design any kind of component or material and could be very useful for the
design of scaffolds for tissue engineering. Previous work on scaffold design was done by Hollister and colleagues, who showed that scaffolds of a defined material (with a given Young’s modulus and Poisson’s ratio) and a certain volume could match the stiffness or strength of natural tissues under many different kinds of design architecture (Hollister et al. 2002; Hollister 2005; Adachi et al. 2006). This technique is powerful, since it allows calculation of the mechanical response of a scaffold, and versatile, since a scaffold with different pore sizes or pore types can be modelled. However, this approach of assuming that growth morphologies would present the best or ‘optimal’ scaffold geometries might no longer be true. Instead, it might be better to define scaffolds with geometries and mechanical properties similar to those found initially in the embryonic state or to those found in a regeneration state as a transition between the current and the targeted morphologies.

The design of a scaffold through CAD is particularly well suited when used in conjunction with a rapid prototyping technique to produce physical scaffolds. Rapid prototyping is the general term used to define a manufacturing technique that consists of the construction of a structure layer by layer to form a totally controllable structure. Rapid prototyping techniques include selective laser sintering, fused deposition modelling, stereolithography, electron beam melting and three-dimensional printing (see Yeong et al. 2004 for details). This method is particularly useful for tissue engineering since it allows a very good reproducibility and the production of almost any kind of structure within the limitations of each technique used. Using this technique, it is possible to design a structure that mimics the natural structure to be replaced (Van Cleynenbreugel et al. 2002; Hutchmacher & Cool 2007; Smith et al. 2007).

3. Scaffold characterization through computed tomography images

It is not always possible or necessary to construct a scaffold using rapid prototyping, and therefore scaffolds for tissue engineering can have inhomogeneous structure. In such cases, it is particularly important to characterize the scaffold geometry to relate the architecture with cell response and tissue formation. Traditionally, scanning electron microscopy or transmission electron microscopy has been used with great success to give very accurate details of the surface of a scaffold (e.g. Kellomäki et al. 2000; Charles-Harris et al. 2008). However, the use of three-dimensional scaffolds with an internal pore structure has favoured the use of non-destructive characterization techniques such as microcomputed tomography (microCT) or synchrotron tomography (Ho & Hutmacher 2006; Cancedda et al. 2007). These techniques are based on the biomaterial being scanned through X-rays crossing the material as the sample rotates within the X-ray beam. A three-dimensional volume is reconstructed from this set of data using filtered back projection (Feldkamp et al. 1989). The resolution that can be obtained using such techniques depends on the X-ray source and detector, in combination with the field of view chosen.

Imaging techniques from microCT data have allowed characterization of scaffolds and have been reviewed by van Lenthe et al. (2007). In particular, the overall porosity can be calculated along the distribution of the number of pores as a function of its size. Other parameters such as pore anisotropy and scaffold
permeability can also be calculated. Thus, microCT is a very useful tool to characterize scaffolds in a non-destructive manner. However, owing to the limiting resolution, only pores above a few micrometres are detected and therefore the microporosity in a scaffold cannot be obtained that way. The microCT technique has also been used to monitor three-dimensional mineralization over time in a perfusion bioreactor (Porter et al. 2007). High-resolution magnetic resonance imaging (MRI) could also be useful to determine axial fluid velocity within the pores of a scaffold (Swider et al. 2007).

MicroCT in tissue engineering is also used for in vivo scaffold and tissue characterization. When used on small animals, in vivo microCT can be used to evaluate scaffold/tissue integration, tissue formation and scaffold degradation (Komlev et al. 2006). In vivo microCT scanning has been shown to be both repeatable and reproducible (Voor et al. 2008). This can be obtained with a lower resolution than for in vitro experiments but has the advantage of characterizing the same scaffold at different time points. Bone tissue formation was characterized within a single scaffold in an in vitro experiment by Cartmell et al. (2004).

Porous and biodegradable calcium phosphate (CaP)-based bone cement and glass ceramic materials have been characterized by Lacroix et al. (2006) using microCT with a resolution of up to 7.8 μm. Cross sections were superimposed using the software MIMICS (Materialise, Leuven, Belgium) to form a three-dimensional reconstruction of the sample. Lower and upper thresholds were used to separate the material from the pores. The samples were then divided into smaller cylinders, 1.15 mm in height and 1.5 mm in diameter. The overall porosity of the samples and the average porosity of each small cylinder were calculated using MIMICS. Porosity calculations indicate that the overall macroporosity of non-injected CaP bone cement, injected CaP bone cement and porous glass are, respectively, 32.2, 30.2 and 30.7 per cent. The porosity of porous glass is more homogeneously distributed than that of CaP bone cement (figure 1). The variability of macropores is also higher in CaP bone cement than in porous glass.
However, no significant differences could be seen between injected and non-injected CaP bone cements, which confirms quantitatively the similarity of the final product independent of the preparation technique.

A study combining synchrotron X-ray microtomography with simultaneous in situ mechanical tests to analyse the microstructure and the deformation of completely degradable composite polylactic acid (PLA)/CaP glass scaffolds was performed by Charles-Harris et al. (2007). In this study, internal movement (and therefore strain) within the scaffold could be observed through the imaging technique (figure 2). It can be observed that the ‘trabeculae’ of the scaffold can undergo displacement with or without strain depending on the architecture of the scaffold. Thus, this technique brings a deeper insight into the internal mode of deformation of this scaffold.

4. Finite-element analysis in tissue engineering

Finite-element analysis was first used in tissue engineering for the design of the scaffold to optimize stiffness/geometry as described in §2. More recently, a stress–strain analysis of complete scaffolds has been performed to investigate the state of stress and strain within the scaffolds and its interaction with the surrounding tissues (Jaecques et al. 2004). Such an analysis can be used to vary several geometrical or material parameters at the same time and to choose the most suitable ones for the replacement of natural tissues (Van Cleynenbreugel et al. 2006).

Finite-element analyses of cylinders of 1.15 mm height and 1.5 mm diameter were carried out on CaP-based scaffolds to calculate the stress–strain distribution throughout larger scaffolds (Lacroix et al. 2006). The dimensions chosen were restricted owing to computational limitations but were large enough to fully characterize the scaffold. This resulted in models of approximately 600 000 elements of element length approximately 10–25 μm. This method allowed comparison of the evaluation of microstructure and stiffness with a larger sample (6 mm in diameter and 12 mm in height) from the same material but...
prepared using two different techniques: moulded manually or injected with a syringe. It was found that there was hardly any difference in the relationship between stiffness and porosity when comparing the method of preparation of the two cements (figure 3). In this study, a linear correlation was used to fit the data points, whereas the stiffness of an open porous material is usually represented as a function of the square of the porosity (Gibson 2005). This discrepancy may be due to the relatively low porosity used for this bone cement (from 5 to 55%), where a linear fit is sufficient to represent correctly the results, given the dispersion of the data. Similar results were obtained by Boger et al. (2008) on polymethylmethacrylate bone cement.

Very few studies have performed a finite-element analysis of FF within a scaffold. So far, only simulations of a perfusion bioreactor have been investigated (Cioffi et al. 2006; Sandino et al. 2008). An FF finite-element analysis has been performed by Sandino et al. (2008) on CaP cement cylinders of 1 mm diameter and 2 mm height. For the simulation of the interstitial FF (fluid models), an inlet fluid velocity of 10 μm s$^{-1}$ was fixed on the nodes of the entrance side of the meshes, a fluid velocity of zero was fixed on the nodes of the walls of the outer diameter, simulating a confined perfusion system, and the outlet fluid pressure was set as zero on the nodes of the exit side of the meshes. Steady-state Newtonian fluid analyses were performed with a non-slip condition on the walls of the scaffold. Fluid density and viscosity were similar to those of the cell culture medium. The fluid velocity distribution into the pores showed that the FF did not reach all interconnected pores of the samples (figure 4). Moreover, high changes of fluid velocity were observed; there were regions where the fluid velocity was almost zero, and other parts with high-velocity FF. Each pore of the samples had different values of fluid velocity, fluid pressure and fluid shear stress, depending mainly on its position within the scaffold, its size and its

![Figure 3. Relationship between effective Young’s modulus and scaffold porosity for a CaP bone cement using a manual preparation and an injected preparation. The effective Young’s modulus was defined as the axial stress (reaction force divided by area) over the axial strain (0.5%) (black diamonds, non-injected CaP bone cement; grey squares, injected CaP bone cement). Adapted from Lacroix et al. (2006).](http://rsta.royalsocietypublishing.org/)

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interconnectivity with other pores. When simulating a physiological FF within the scaffold, it was found that maximum FF could increase 1000 times inside the scaffold (Sandino et al. 2008). This result therefore shows that the mechanical stimuli through FF sensed by the cells can be much higher than the one applied macroscopically on the scaffold.

5. Mechanobiology in bone tissue engineering

Mechanobiological concepts have been proposed to relate mechanical stimuli to cell differentiation and tissue formation. Pauwels (1960) first proposed a concept based on hydrostatic pressure and octahedral shear strain (SS) to relate fibrous tissue formation and cartilage formation in fracture healing. This concept was developed in a mathematical formulation by Carter et al. (1988) and extended to include bone formation as a function of the same mechanical stimuli. Further study by Claes & Heigele (1999) has refined this concept to quantify it with validated finite-element analyses. Another mechanobiological concept was proposed by Prendergast et al. (1997) based on shearing stimuli produced by the biphasic nature of tissues: solid phase of collagen and liquid phase of interstitial fluid. Both phases are assumed saturated and the continuity equation for the mixture holds, i.e.

\[ \sum_{\alpha=1}^{n} \nabla \cdot (\phi^\alpha v^\alpha) = 0, \quad (5.1) \]

where \( n \) is the number of constituents \( \alpha \); \( \nabla \) is the gradient operator; \( \phi^\alpha \) is the volume fraction of the \( \alpha \)th constituent; and \( v^\alpha \) is the local velocity component of the \( \alpha \)th constituent. Conservation of linear momentum gives the equation of motion for the \( \alpha \)th constituent as

\[ \nabla \cdot \sigma^\alpha + \rho^\alpha q^\alpha + \pi^\alpha + \rho^\alpha c^\alpha v^\alpha = \rho^\alpha \frac{Dv^\alpha}{Dt}, \quad (5.2) \]

where \( \sigma^\alpha \) is the partial stress; \( q^\alpha \) is the body force per unit mass; \( \pi^\alpha \) is the rate of momentum supply to the \( \alpha \)th constituent; and \( \rho^\alpha c^\alpha v^\alpha \) is the momentum supply from biochemical reactions, neglected here (Kelly 1964). The constitutive relationships must satisfy thermodynamic constraints (i.e. energy balance and entropy inequality), as described by Mow et al. (1980). For a biphasic material in...
which the fluid is inviscid and each constituent is isotropic, and where the
infinitesimal strain–displacement relationship is assumed, we can write, following
Mow et al. (1980),
\[
\sigma^s = \phi^s p I + \lambda \varepsilon^I + 2\mu \varepsilon^s, \quad \sigma^f = -\phi^f p I,
\]
(5.3)
where \(\varepsilon\) denotes the strain and \(\varepsilon\) denotes the dilatational strain; \((-)^s\) and \((-)^f\)
denote solid-phase and fluid-phase quantities; \(p\) is the apparent pressure; \(\lambda\) and \(\mu\)
are Lamé constants; and \(I\) is the unit matrix. A finite-element formulation is
applied using the soil analysis capabilities of commercial software programs
(MSC MARC (MSC Software, Santa Ana, CA, USA) or ABAQUS (Simulia, Providence,
RI, USA)) through an implicit integration based on the full Newton–Raphson
algorithm with the relative residual force tolerance convergence set by default to 0.1.

The stimuli investigated are octahedral SS and FF velocity in the sense that
both stimuli can produce some distortion of the cell to affect its differentiative
activity. Threshold stimuli \(S\) were defined by Prendergast et al. (1997) by
\[
S = \frac{SS}{a} + \frac{FF}{b},
\]
(5.4)
where \(a = 0.0375\) and \(b = 3 \mu m s^{-1}\). If \(S > 3\), then fibrous tissue differentiation occurs;
if \(3 > S > 1\), then cartilage differentiation occurs; if \(1 > S > 0.267\), then immature
bone differentiation occurs; and if \(0.267 > S > 0.01\), then resorption occurs.

This concept builds on the one proposed by Pauwels since it includes the
deviatoric deformation tensor but does not include the hydrostatic tensor and is
applied to both phases of tissues. Although the biological processes and mechanical
environment can be quite different, this concept was tested with success as a
predictive model on various applications such as implant–bone interface (Huiskes
et al. 1997), fracture healing (Lacroix & Prendergast 2002), osteochondral defect
(Kelly & Prendergast 2006), bone chambers (Geris et al. 2008a,b) and bone
distraction (Isaksson et al. 2007). These predictive models establish some initial
conditions such as loading and material properties that vary over time in an
iterative manner depending on the values of the calculated mechanical stimuli of
the mechanobiological concept. Moreover, recent studies on fracture healing have
shown that the FF stimuli seemed to be the most determinant in tissue
differentiation (Isaksson et al. 2006). These concepts are useful to better understand
the processes of mechanotransduction and mechanoregulation.

Only recently such mechanobiological concepts have also been applied to
tissue engineering. The first application to tissue engineering was done by Kelly &
Prendergast (2006) in which a mechanoregulation algorithm for tissue
differentiation was used to determine the influence of scaffold material properties
on chondrogenesis in a finite-element model of an osteochondral defect. An
optimal design was determined by parametrically varying the mechanical
properties of the scaffold through its depth. More recently, it has been used for
bone tissue engineering in the development of scaffolds based on CaP cement
(Byrne et al. 2007). Tissue engineering of a three-dimensional finite-element
model of a scaffold made of repeated uniform unit cells was simulated with the
modelling of the dispersal of the various cell populations in three dimensions.
Both cell proliferation and cell migration are based on a stochastic process
consisting of a sequence of discrete steps of fixed lengths occurring within
a lattice that covers the finite-element domain (Pérez & Prendergast 2007).

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A lattice point can be occupied by an MSC, a fibroblast, a chondrocyte, an osteoblast or an endothelial cell. A mechanoregulation model is implemented to simulate MSC differentiation and it was assumed that each lattice point was surrounded by appropriate extracellular matrix. Based on Richardson et al. (1992), who observed an exponential increase in stiffness in differentiating tissue, an exponential rate equation is used to better describe the evolution of the Young modulus of the regenerating tissue,

\[ E_i = K_i e^{\beta_i t}, \]

where \( E_i \) represents the Young modulus for tissue phenotype ‘i’ (where ‘i’ is fibrous tissue, cartilage, immature or mature bone); \( t \) is the time; and \( K_i \) and \( \beta_i \) are two parameters regulating the shape of the exponential curve (Boccaccio et al. 2008). The Young modulus of each element is then averaged over the last 10 iterations in order to account for a gradual change of cell differentiation over time. From one iteration to another, there is therefore a change of mechanical properties of the tissues modelled, reflecting the production or resorption of extracellular matrix by cells. From a computational point of view, the poroelastic analysis is started without initial conditions for each iteration. Rules govern the development of capillaries, and osteogenesis is allowed only within a defined distance (100 μm) of a capillary. It was shown that porosity, Young’s modulus and dissolution rate design variables have a critical effect on the amount of bone regeneration. Scaffolds should be produced that depend on the site of implantation. In a low-load environment (1 MPa), high porosities and higher stiffness but a medium dissolution rate give the greatest amount of bone (figure 5). Alternatively, the initial porosity and rate of dissolution should be lower in a high-load environment (2 MPa) in order to maintain the mechanical and structural integrity of the bone–scaffold system.

Owing to the complexity in implementing these algorithms in structures with non-regular porosity distribution, only static finite-element analyses have been performed so far for tissue engineering in these structures. Nonetheless, the static mechanical stimuli are useful to determine the level of stress or strain within the structure and to relate it to the mechanical stimuli that the cells should feel when seeded within the scaffold. For example, a micro-finite-element analysis of a bone cement scaffold was performed by Lacroix et al. (2006), who calculated the mechanical stimuli at the surface of the scaffold. Most nodes have strain stimuli between 1 per cent under compression and 0.5 per cent under tension (figure 6), and fluid shear stress stimuli between 0 and \( 1 \times 10^{-3} \) Pa. In the CaP cement scaffold, there are more nodes under tension than in the glass scaffold, and the fluid shear stress distribution at these nodes is also more spread in the CaP than in the glass sample (Sandino et al. 2008). The CaP scaffold has regions with a high level of fluid shear stress and/or compressive strain, whereas the glass scaffold has regions with a high level of only one of these stimuli. Owing to the difficulty in creating an automatic mesh for scaffolds with non-regular porosity distribution (Viceconti et al. 2004), scaffolds made with rapid prototyping through the repetition of uniform unit cells can be more easily modelled and adapted to multiscale studies. In such studies, as previously discussed, parametric studies can be performed more easily to investigate the effect of pore size, surface-specific area, permeability, etc.
6. Future perspectives

In recent years, we have only seen the tip of the iceberg in numerical simulations in tissue engineering. Most studies are still in their infancy, with most of them dealing with static studies of scaffold design or static studies of mechanical analysis. However, more sophisticated analyses are necessary to better understand the effect of mechanical stimuli within the whole body, with its interaction between biological, chemical and other physical cues on the one hand, and

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Figure 5. Predicted cell distribution in a printed-type scaffold (dark grey). Only one-eighth of the scaffold needs to be modelled for symmetry reasons. The sections shown are the face of the one-eighth section described by the white outline box. EC, endothelial cell. Note porosity increasing over time due to dissolution of the scaffold biomaterial, initial porosity 50%. Adapted from Checa & Prendergast (2008). A colour version of figure 5 is available in the electronic supplementary material.
foreign bodies such as biomaterials on the other. For this, future perspectives of numerical simulations of biomaterial scaffolds for tissue engineering, and, in a more general sense, regenerative medicine, rely on the development of new methods to account for the multiscale dimension of the problems, on the increasing power of computing capabilities, and on the integration of predictive models between biology, materials science and physical stimuli. An approach that accounts for all the different scales at play becomes necessary (Wikswo et al. 2006; Sanga et al. 2007). Multiscale modelling has been developed in many disciplines (Stoneham & Harding 2003; Coveney & Fowler 2005; Cohen & Harel 2007; Southern et al. 2008). Already multiscale analyses have been applied to the heart (Noble 2002), cancer (Bellomo et al. 2008), the design of aortic valves (Weinberg & Kaazempur Mofrad 2009), trabecular bone failure (Müller & van Lenthe 2006), teeth (Miura et al. 2009) and the human femur (Cristofolini et al. 2008). It has recently been applied to tissue engineering for bone regeneration (Sanz-Herrera et al. 2009). These approaches will be translated into the clinical side with the development of patient-specific multiscale studies (Kerckhoffs et al. 2008).

Future perspectives include the development of computer power. This should inevitably lead to more complex models of higher size being studied. Nonetheless, the use and development of existing tools by the bioengineering community can be pushed forward. The use of the supercomputing grid within the Distributed European Infrastructure for Supercomputing Applications (DEISA) can allow the development of models with high complexity in their resolution or in the management of databases. This can only be done if the models developed are highly parallel, which is not such an easy task with studies of higher complexity. The bioengineering community has a role to play in this development.

More integration is needed between the interrelations of biology, materials science and physical stimuli. Computational models also have a role to play in this direction (Sengers et al. 2007). Most of the models so far are rather mechanistic and include very little biology or materials science. For example,

Figure 6. Example of the distribution of octahedral SS in a CaP cement scaffold, showing the strain distribution around the pores and the influence of the homogeneity of the pore distribution. Adapted from Lacroix et al. (2006). A colour version of figure 6 is available in the electronic supplementary material.
the effect of angiogenesis is crucial for the processes of tissue engineering, as in other biological processes such as wound healing or fracture healing where it has been included (Bailón-Plaza & van der Meulen 2001; Geris et al. 2008a,b; Peirce 2008). In tissue engineering, this has just been introduced (Checa & Prendergast 2008). Computer models can only be as good as the input data that are fed to them, which need to be correct and sufficient. More experimental tests and biological information are needed to model biological processes more precisely. Most of the interactions between biomaterials and tissues are simulated through the definition of structure parameters, such as scaffold stiffness or pore size, for example. However, physical and chemical surface properties are critical for the development of functional scaffolds for tissue engineering (Castner & Ratner 2002). Therefore, it becomes necessary to include such properties in a computer model to model effectively the integration between biomaterials and surrounding tissues.

As a conclusion, tissue engineering has seen a tremendous expansion through experimental in vitro and in vivo tests, with the development of new biomaterials that try to elicit a controlled reaction from the surrounding tissues. But the future of computational models applied to tissue engineering is very promising, with the establishment of more powerful and more realistic models that can simulate more accurately the biological processes and the design of biomaterial scaffolds.

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