Clinical trials of orthopaedic implants substitution: computational models from cell attachment to tissue regeneration

computational modelling of cells-implant interactions as a tool for predicting in vivo performance of implants

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Abstract

To get an optimal product of orthopaedic implant or regenerative medicine needs to follow trial-and-error analyses to investigate suitable product's material, structure, mechianical properites etc. The whole process from *in vivo* tests to clinical trials is expensive and time-consuming. To make the product development more efficient and cheaper, computer simulation of clinical trials is seen as a useful analyze tool to evaluate and optimize biomedical devices and implant designs. Computational model is able to build a mathematical system to mimic a real or approximate real situation of the human bodies (orthopaedic biological systems). In this paper, a series of models for simulating whole tissue engineering process from cell attachment to tissue regeneration will be introduced. The numerical models are able to set up suitable relationships between the final performance and product parameters. It not only able to provide opportunities to help researchers to fully understand the entire tissue engineering process, but also enable optimization of the parameters and material types of the tissue engineering products.

1 Introduction

Computational modeling is a method of using computer science, mathematics, physics, and other disciplines to simulate and study complex systems, which contains many variables that characterize the system under study. Computational modeling has been used in all aspects of bioengineering, namely biology[1,2] and clinical trial research, such as heart disease[3–5], cardiovascular disease[6], brain disease[7], epilepsy[8], Alzheimer's disease[9], wound healing[10], etc.

Among them, Kohl et al.[11] developed a heterogeneous cell model composed of a fibroblast and a sinoatrial node muscle cell. The electronic interaction model of these cells predicted the coupling function between fibroblasts and muscle cells. Stergiou et al.[12] used a finite element model method to consider how hematocrit affects the growth of abdominal aortic aneurysms, and concluded that hematocrit does not affect von mises stress, but it does affect wall shear stress. Rubin and Terman[13] created a computational network model to prove how the deep brain stimulation of subthalamic nucleus leads to the destruction of pathological thalamic commandments in the middle and lower reaches of Parkinson's disease. Based on the excitatory and inhibitory Hodgkin–Huxley neuron general miniature neuron network model, Ullah et al.[14] modeled and analyzed the influence of the surrounding environment (such as the concentration of extracellular potassium) on the excitability of the neuron network at the microscopic scale. Anastasio[15] developed a computational model of Alzheimer's disease based on the amyloid hypothesis. This model explains the destruction of amyloid β regulation through the interconnection of various diseases and pathological processes (such as cerebrovascular diseases, inflammation, etc.). That is, cerebrovascular disease will aggravate the progression of Alzheimer's disease. Sherratt and Murray[16] proposed a reaction diffusion model of epidermal wound healing to study the interaction between mitotic growth factors (activators or

inhibitors) and epidermal cell functions. It is concluded that cell mutation is caused by migration, mitosis and cell apoptosis regulated by the chemical factors it produces. Miocinovic et al.[17] developed a computational model for Parkinson's macaques. This model predicted the axon activation mode under subthalamic nucleus electrode stimulation.It also proved that the activation energy of subthalamic nucleus neurons of both activated subthalamic nucleus and globus pallidus interna fibers has an impact on clinical treatment. Suffczynski et al.[18] established a macroscopic model of the effect of multiple areas of the brain in the mechanism of epilepsy, in which a neurological quality model was constructed for the cortex and thalamus. The model shows that applying the same intensity of counter-stimulus during a specific phase of the spike wave can disrupt this activity and return to a normal sleep spindle state.

As a major category in regenerative medicine, tissue engineering provides a new approach with broad application prospects for clinical repair and reconstruction of injured tissues. For example, tissue engineering such as skin, cartilage, and bone has achieved varying degrees of success in the process of in vitro reconstruction[19]. Due to the low-cost and high-efficiency characteristics of computer-aided technology, computational modeling has been widely used in tissue engineering, especially for the modeling of patient-specific characteristics of the injury.

In tissue engineering, biomaterials with specific structures are often used to be implanted to promote the self-repair of damaged tissues. The structural configurations of the biological material are called scaffolds, the design of which is the focus on tissue engineering. Tissue engineering research can be divided into bone tissue engineering, skin tissue engineering, cartilage tissue engineering, heart and other complex organ tissue engineering, tooth tissue engineering and so on. In tissue engineering, material properties require a certain degree of biocompatibility and mechanical durability [20]. Titanium metal and its alloys have low density, high mechanical properties, and brilliant biocompatibility. In addition, titanium metal also has osteoconductivity, which can induce the formation of new bones and bind them tightly. Therefore, titanium is widely used in bone tissue engineering [21]. Taking into account the biodegradability and mechanical properties [22–27], some ceramic materials and composite materials composed of polymer materials have also been used to manufacture bone tissue engineering scaffolds [28–30].

Bone tissue engineering is the most active field in the world, and computer-based work mainly focuses on the design of various structural parameters of the scaffold, such as pore size, porosity, and permeability. The above-mentioned multiple parameters affect the cell-scaffold interaction effect and thus the efficiency of bone regeneration. Therefore, it is very important to further analyze the influence of the various parameters of the scaffold on the cell response. In fact, a large number of researchers have focused on studying how to use different mechanochemical conditions to regulate this scaffold-cell response. They have established a large number of simulation models to simulate the real bone regeneration process, the purpose of which is to predict the intermediate process and final results of cells in a specific scaffold design and for a specific patient. However, because each model itself is too simplified or not perfect, the actual effect of most models is far-fetched.

Therefore, this article aims to review some new developments in modeling at various time scales of tissue engineering. Next, for the division of tissue repair stages in tissue engineering, the modeling methods of cell adhesion including blood injection and cell adhesion are described in detail. Then it describes the modeling methods of blood coagulation and nutrient transport, as well as the modeling of cell proliferation, differentiation, and migration.

2 Cell adhesion

Tissue growth is a complex process, and its rate and mode are affected by many factors, such as cell phenotype, density and spatial distribution of seed cells, and culture conditions. These factors directly or indirectly regulate basic cell functions (such as adhesion, Migration, proliferation and differentiation) to affect tissue growth. Cell seeding process, is the initial process of tissue engineering and the results of the cell distribution is strongly related to final tissue formation [31,32]. Lack information has been provided by researchers about cell adhesion and cell spatial distribution because cell distribution on 3D structure especially for complex structures is hard to observe and investigate. Although this is one of the determinants of the final bio-performance of a scaffold, few researchers put much effort on this issue because it is really complicated.

2.1 Blood filling

Bone tissue contains blood vessels. When it is broken, the blood vessels at the fracture site will be destroyed. Subsequently, blood flows from the ruptured blood vessel to the bone tissue at both ends. Similarly, after the scaffold is implanted in the bone, blood will also flow into the voids of the scaffold.

Compared with experimental research, computational simulation of biomaterials reduces the cost and improves the efficiency of scaffold design. In order to optimize various parameters of the scaffold, such as scaffold permeability and wall shear stress, researchers have done a lot of computational fluid dynamics analysis.

When analyzing the blood flow in tissue engineering process, the blood characteristics need to be well considered. Researchers usually assume that blood as a Newtonian fluid with a constant viscosity to simplify the model. In fact, the tiny particles in the blood such as cells, proteins and other components will invalidate this assumption. Because blood contains tiny particles and cannot be completely used as a Newtonian fluid, it is widely regarded as a shear thinning fluid[33].

In order to accurately build the model, researchers began to treat blood as a non-Newtonian fluid. For example, Reymond et al.[34] used standard CFD(computational fluid dynamics) codes for Newtonian and non-Newtonian blood characteristics to simulate the steady flow in a patient-specific model of the entire system circulation.

Truscello et al.[35] regarded the culture medium as an incompressible homogeneous Newtonian fluid, which has the characteristics of water, and based on this assumption, established a computational fluid dynamics model to predict the permeability of the scaffold. Subsequently, the pressure drop between the different units of all models is obtained through experiments, which is used to calculate the permeability coefficient of the scaffold and compare it with the predicted value of the model. The relative difference between the measured value and the predicted value in the final result is between 2% to 27%.

Rahbari et al.[36] also used the method of comparing the predicted value of the model with the measured value of the experiment to study the effectiveness of the CFD method in predicting the permeability of the scaffold. They set the characteristics of the inlet fluid of the scaffold to be the same as water, with a density of 1000 kg/m3, a dynamic viscosity of 0.001 kg/m s, and incompressible. Finally, the effective permeability of the porous scaffold was calculated according to Darcy's law. Compared with the experimental results, it was found that the relationship between the experimental permeability and the calculated permeability showed a linear trend of y=1.297x.

Lesman et al.[37] used ANSYS as the CFD solver for the prediction of scaffold shear stress. The nature of the fluid also uses the liquid water built in the solver, which is defined as an incompressible homogeneous Newtonian liquid. The CFD model can predict the velocity and shear stress distribution in the porous scaffold perfused by the medium. During the verification experiment, since the shear stress could not be measured, the penetration experiment measurement was carried out. The ratios of the predicted value to the experimental value were 31%, 1150%, and 2602%, respectively, showing large errors.

In addition to the above hypothesis that the researchers used Newtonian fluid properties, many people have also used this hypothesis for modeling analysis. However, in summary, the modeling and simulation results based on the Newtonian fluid hypothesis have large errors, and the prediction results need to be optimized.

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At present, computational fluid dynamics (CFD) simulations of intracranial aneurysm hemodynamics usually use simplified Newtonian hemorheology models. Xiang et al.[38] used the Newtonian viscosity model to compare with two non-Newtonian models (Casson and Herschel-Bulkley) and found that the Newtonian fluid hypothesis may underestimate the viscosity and overestimate the shear rate in the stagnant or slowly recirculating secondary vortex region.

In addition, Jiang et al.[39] used CFD based on the finite volume method to perform numerical studies on the hemodynamics of blood models with Newtonian and non-Newtonian characteristics, and found that the area of low wall shear stress(WSS) of blood models with non-Newtonian characteristics was smaller , which shows that the blood model is very important for accurately predicting hemodynamics.

In tissue engineering process, Liu et al. used volume of fluid (VOF) model to calculate the blood filling process and set blood as non-Newtonian fluid carrying cells [40]. The filling process is well considered because the blood filling and air coming out is fully governed by VOF model. This model give researchers an opportunity to well investigate following tissue engineering process which no one has done before.

2.2 Cell attachment

Cell attachment to the scaffold is an important step in tissue engineering, and cell seeding is the first stage of cell attachment, the efficiency and distribution of which will affect the final bioperformance of the scaffold, and the design of various parameters of the scaffold can affect the efficiency of cell seeding and cell attachment. For example, geometry (porosity, pore size, tortuosity and connectivity) will affect the transportation of nutrients and cell growth. However, there are some contradictory parameters in the scaffold design, such as pore size and surface area, porosity and strength, fatigue life, etc., which lead to complex evaluation of scaffold design and high cost on in vivo tests for optimizing the design. Since in vitro, in vivo, and clinical trials usually require a large amount of investment, numerical models provide a more ethical, economical, and controllable option for studying the attachment of cells to the scaffold. Numerical methods for predicting cell seeding efficiency should consider cell adhesion and fluid properties (velocity and viscosity). Researchers have different views on fluid assumptions.

2.2.1 Normal CFD model (see cells as pure water)

In the early model analysis, in order to simplify the model to the greatest extent, the researchers regarded the medium (including cells) in the scaffold as pure water, although this caused a certain deviation in the analysis results.

For example, Jungreuthmayer et al.[41] established a continuous three-dimensional CFD deformation model through CT scanning in order to quantify the deformation of cells on the collagen-GAG scaffold, and used CFD simulation to calculate the wall shear stress and hydrostatic wall pressure acting on the cells. It was input into the linear elastostatic model, and the deformation of the cell was calculated. In the CFD model, they assumed: laminar fluid, incompressible Newtonian fluid with a viscosity of 37°C water, no-slip boundary condition on the wall, constant velocity inlet, zero pressure outlet, and cell and scaffold wall is impermeable.

In order to quantitatively compare the wall shear stress of two types of bone tissue engineering scaffolds (collagen-glycosaminoglycan (CG) and calcium phosphate) exposed to fluid flow in a perfusion bioreactor, Jungreuthmayer et al.[42] established a three-dimensional numerical CFD model of two types of scaffolds through micro-CT images. For the two types of scaffolds, the assumptions of the CFD model are basically the same as those of Jungreuthmayer.

In addition to the above two studies, many scholars' CFD models assume that the medium is also treated as pure water, although this assumption ignores the movement of each cell[43–45].

2.2.2 Trap model

Compared with those models that treat the medium as pure water, Olivares et al.[46] introduced the movement factor of the cell itself and proposed a new CFD model, in which the medium is still assumed to be a 37° homogeneous fluid medium, and the cells of the fluid are further assumed to be governed by the translational motion determined by Newton's second law (**Fig. 1.**). Olivares et al. innovatively introduced the theory of wall film used to simulate the deposition of fuel particles in the combustion state to simulate the adhesion state of cells when they hit the scaffold wall. The simulation results are quantitatively compared with the experimental results. The cell density values of the two show a consistent distribution trend in the radial direction of the scaffold. The cell density of one type of scaffold is 11%~31% in the experiment and 6.5% ~14% in the model. There is a big difference in absolute value between the two.

In the above model, the interaction between cells and materials is simplified. For example, the wall of the bioreactor adopts non-slip and non-adhesive conditions, without considering the spread, splashing and rebound of the cells. The above simplifications may cause the deviation between the predicted value and the experimental value, but in general, considering the movement of the cell itself is a big improvement.

2.2.3 Stanton-Rutland model (cell impinge model)

Compared with the model of Olivares et al., Liu et al.[47] proposed a further model (**Fig. 2.**). In addition to the "absorption/capture" situation of cell impact, their model also includes more impact types, such as bounce and splash. Liu et al. assumed that when cells hit the stent, they would bounce back from the scaffold wall, and sometimes split into several smaller particles. This type of impact is similar to the interaction between droplets and the inner wall of an internal combustion engine, so they introduced Stanton- Rutland model[48,49].

The biggest advantage of this model is that it can consider four mechanisms when cells hit the scaffold wall, including stick, rebound, diffusion and splashing. In addition, it can also interact with the discrete phase model(DPM) and the Eulerian multiphase model. In addition, the model can also predict the transport of nutrients such as oxygen and glucose. In comparison with the actual experimental results, the simulation results also show the same trend.

Of course, this CFD model method also has certain limitations. In the model assumption, cells are regarded as droplets and when the cell seeding speed is very slow, there will be no splash phenomenon. In addition, this model is suitable for the prediction of low-velocity cell attachment status, and further research is needed for more complex situations.

3 Blood coagulation

After cell adhesion, the next step in tissue engineering is blood coagulation. Obviously, blood coagulation process control has a greater impact on the biomechanical properties of the final biological tissue formed by tissue engineering. However, we found that there are only a handful of literatures on modeling research of blood coagulation in this field, but fortunately, there have been systematic developments in modeling research on blood coagulation in other fields.

Because blood coagulation model research is closely related to deep vein thrombosis, diabetes-related stroke, cerebral artery tumor, pulmonary embolism and other related diseases, researchers have always been enthusiastic about the study of blood coagulation mechanism models. In this article, we review the various basic assumptions and the numerical simulation models used by researchers when conducting numerical simulation modeling. In terms of computational strategies, this article categorizes them into macroscopic models, mesoscopic models, microscopic models, and multi-scale models, and hopes that the field of tissue engineering can use these strategies as a reference.

3.1 Macroscopic model

As the name implies, the macroscopic model considers the modeling of the blood flow and coagulation process from a large-scale perspective, and the model constants are usually determined by actual experiments. The macro model usually adopts the convection diffusion reaction (CDR) equation[50,51], which is used to define the transmission behavior of chemical substances, electric current or temperature, and its general form is:

$$\partial c/\partial t = D\nabla^2 c - u\nabla c + R$$

Among them, c can be expressed as the concentration of chemical substance transport or the temperature of heat transport. D is the thermal diffusivity or mass, u is the velocity vector of the medium, and R is the chemical reaction of the substance that produces c. The solution of the CDR equation is the change value of c with time and space. This equation is very suitable for simulating the fibrin polymerization reaction.

In the macroscopic model of blood coagulation, the research of Hockin et al.[52] is widely cited. They constructed an in vitro coagulation system model through multiple ordinary differential equations similar to the CDR equation, and the predicted values of the model were consistent with the experimental data.

Similar to the former, Panteleev et al.[53] developed a macroscopic heterogeneous coagulation model, and studied the spatial regulation mechanism of coagulation through in vitro experimental models and computer simulation models.

Anand et al.[54] used 23 equations similar to CDR to simulate the biochemical changes and transport processes during coagulation and fibrinolysis in resting plasma, and compared the model prediction results with published experimental data, and finally verified the the validity of the model under static conditions.

Weisel et al.[55] developed a kinetic model that can simulate the formation of a fibrin clot by a single monomer, and used a simple rate equation to simulate the mechanism of fibrin polymerization. In order to fit the lag time in the actual experiment, they modified the relevant parameters in the model. Weisel et al. also pointed out in the article that many of the reaction equations they proposed require experiments to determine the precise rate constants.In practice, however, most of these rate constants are randomly selected.

Ravanshadi et al.[56] also used a similar method, that is, the Michaelis-Menten equation system to model the blood factors of the coagulation cascade, substituting the actual observed concentration and rate constant, and the kinetics of the reaction

can be simulated by the model. The shortcomings of these methods are obvious. The model must rely on empirical models and experimentally observed rate constants, so this method may indicate that it uses inaccurate dynamic assumptions.

In addition to the above studies, many scholars[57–59] have used macroscopic models to study various mechanisms of blood coagulation, and the results show that the macroscopic model methods are practical to a certain extent.

3.2 Mesoscopic model

Although the macroscopic model can simulate and predict the rate of coagulation or other specific mechanisms on a large scale, it cannot simulate coagulation on special geometric shapes, and this shortcoming may be unacceptable in the field of tissue engineering.

Most of the mesoscopic models assume that blood vessels or attachments are rigid walls and blood components are massless particles. Under these basic assumptions, we can use NS equations (Navier-Stokes equations) and CDR equations for modeling.

Aaron L. Fogelson[60] conducted a modeling study on the blood clotting mechanism in small blood vessels, in which the model assumed that blood is a viscous incompressible fluid with discrete massless platelets suspended in the blood. Platelets are initially non-adhesive, but become adhesive when stimulated by ADP (adenosine diphosphate), and release more ADP components into the blood. Aaron L. Fogelson conducted a two-dimensional numerical study on the equations of the model, and estimated the influence of the media flow rate on the blood coagulation mechanism by solving the NS equation and the CDR equation.

For the study of coagulation mechanism under blood flow in three-dimensional space, Govindarajan et al.[61] developed and applied a model of thrombosis under blood flow, described platelet deposition and the formation mechanism of complex thrombus, and can predict the basic dynamics of thrombus in blood flow chamber experiment feature. In the model, Govindarajan et al. also used the NS equation to simulate the flow of the medium, and the CDR equation was used to predict the temporal and spatial concentration of platelets. In addition, an additional porous media item was added to the model to simulate the effect of thrombus itself on blood flow, and this change affects the viscosity of the high fibrin concentration area.

In general, the numerical simulation of the mesoscopic model in the complex geometric environment has good practical value for specific thrombosis cases, such as aortic dissection[62] and cerebral aneurysm[63]. The simulation in these scenarios can be through the two-way coupling of the NS equation and the CDR equation to realize.

3.3 Microscopic model

The aforementioned model greatly simplifies the composition of the medium and analyzes the mechanism of the coagulation process in a relatively macroscopic manner, while the micro model considers a more microscopic and comprehensive approach, using dissipative particle dynamics to simulate complex fluid systems, such as nanometers composite materials, surfactants, and fibers in viscous media[64,65]. The DPD (Dissipative Particle Dynamics) method regards the fluid system as a set of particles, and the force on each particle is expressed as the sum of internal and external forces:. The external force is gravity or other types of force, and the internal force is composed of soft repulsive conservative force F_{ij}^{C} , dissipative force F_{ij}^{D}, and random force F_{ij}^{R}:

$$f_i^{\text{int}} = \sum_{j \neq i} (F_{ij}^{C} + F_{ij}^{D} + F_{ij}^{R})$$

Filipovic et al.[66] conducted research on arterial obstruction that caused cardiovascular disease, focusing on the mechanical aspects of platelet-mediated thrombosis, including platelet movement, collision, adhesion and aggregation in the blood. The mechanical model of platelet aggregation on the blood vessel wall is established by DPD method. The blood is also a collection of a group of particles according to the hypothesis of DPD. The final model simulation data basically matches the experimental data of Karino et al.[67], so it provides a promising method for the microscopic model method of blood vessels.

Tosenberger et al.[68] further expanded the DPD model and added the consideration of time span, that is, the model considers the different stages of the platelet adhesion process, and they believe that the core of the clot is composed of platelets. Then the platelets can no longer adsorb new platelets because they are activated by thrombin or are wrapped in

fibrin, and then the blood clot stops growing. The final simulation result is in good agreement with the experimental value[69].

Later, Tosenberger et al.[70–72] further considered other components in the blood, such as fibrinogen and other important coagulation factors, and used the CDR equation method to optimize and improve the model.

In addition to the DPD method, the microscopic model method also includes the Cellular Potts Model (CPM), which can simulate the collective behavior of cell structures, such as cell migration, aggregation, and growth[73–75].

3.4 Multi-scale model

The multi-scale model method introduced at the end of this section is actually a mixed model of the above methods, that is, two or more multi-scale coupled models are used. Most multi-scale models often use the CDR method to model the substance concentration, use the NS equation to model the blood flow, and then use the microscopic method to model the movement of the tiny particles. In this way, the macroscopic law of coagulation can be captured without losing the micro-scale characteristics.

As mentioned above, Xu et al.[76] used a multi-scale model for the plane, used the NS equation to describe the macroscopic dynamics of the blood, and used the CPM model to simulate the movement of platelets. The simulation results show that the inside of the thrombus is uneven, and preliminary experimental data also proved this. In subsequent research, Xu et al.[77–79] further improved this model by adding the CDR equation method and other methods.

For multi-scale models, many scholars have done related research on blood coagulation mechanism[80–82]. The modeling research of blood coagulation mechanism has been reviewed before, but there are few existing literatures about blood coagulation mechanism research in the field of bone tissue engineering[83–85]. However, this is an area that should be paid attention to.

4 Nutrient transport

To achieve success in tissue engineering, nutrient transport into the interior of a scaffold should be well investigated as it is one the most significant factors for its success [86]. Although nutrient transportation plays a vital role in tissue regeneration, it is hard to experimentally investigate this dynamic process. Two of the main mechanisms governing nutrient transportation are convection and diffusion [46].

4.1 Convection (blood filling, before coagulation)

Convection is a faster method of mass transport due to bulk fluid motion whilst diffusion is a significantly slower transportation movement due to its reliance on a concentration gradient. In a bioreactor system, the solution transportation is usually generated by external sources which are called forced convection[87]. In most cases, the flow speed caused by external sources is far higher than the diffusion speed; therefore the major type of transportation in a bioreactor system relies on convection rather than diffusion. For tissue engineering field, the movement of blood when put scaffold into the targeting area is mainly convection and the nutrient transport before blood coagulation is also mainly depended on convection.

4.2 Diffusion (after blood coagulation)

After blood coagulation, nutrient transport is mainly rely on diffusion which is slower than before. During in vivo and in vitro tests, there are no techniques which are able to monitor the entire biosystem including temperature, cell density, bone marrow speed, nutrients transportation and density. Computational analysis provides a promising method for researchers to understand the tissue regeneration process from the initial cell seeding to tissue regeneration[47].

In consideration of diffusion speed of nutrient (glucose), Edward et al. explored the effects of flow-induced nutrient transport and fluid perfusion for cells on scaffolds in a rotational bioreactor during dynamic bioreactor cultivation[88]. As oxygen is also one of the most important ingredients of nutrients, Alireza et al. developed a numerical model considering both convection and diffusion to understand the relationship between oxygen supplying and cell density in a channeled scaffold[89].

5 Cell proliferation, differentiation and migration

After Mesenchymal Stem Cells (MSCs) attachment, cells would start to proliferate, differentiate and migrate. A random walk method could be used to predict MSCs migration, proliferation and differentiation to predict tissue engineering bioperformance. It is a mathematical object, known as a stochastic or random, which describes a path that consists of a succession of random steps on some mathematical space such as the integers. According to the Pérez's work, cells disperse with a preferential direction of proliferation[90] (**Fig. 3.**). The highest probability positions are the ones in which one daughter cell tends to appear in a preferred direction (downwards) with p1. The corresponding value of p is computed fulfilling$\sum_{i=1}^{n_1} p_1 + \sum_{i=1}^{n_2} p_2 + \sum_{i=1}^{n_3} p_3 = 1$, and the preferred direction is seen as $p_1 = 10p_2 = 60p_3 = p = \frac{4}{13}$. MSCs differentiation can be expressed as [91]

$$S = \frac{\gamma}{a} + \frac{\vartheta}{b}$$

High levels of stimuli (S>3) promotes the differentiation of MSCs into fibroblasts, intermediate levels (1<S<3) stimulate the differentiation into chondrocytes and low levels (S<1) favor the differentiation of osteoblasts from the MSC pool. Cells then synthesize the appropriate extracellular matrix leading to tissue formation and new mechanical properties for the tissue. The values are a=0.0375 and $b = 3\mu m s^{-1}$, based on Søball's experimental results[91]. The geometry of the scaffold will be optimized by 2 parameters getting from this program. Most of osteoblast should grow on bottom and most of chondrocytes should grow on top.

In addition, Damien et al.[92] used a three-dimensional finite element model method to simulate tissue differentiation and bone regeneration (**Fig. 4.**). The model predicts that porosity, Young's modulus, and solubility have a greater impact on bone regeneration.

6 Conclusion

The objective of this paper is to sum up all the tissue engineering process models from cell attachment until tissue regeneration. To develop a tissue regeneration model for tissue engineering, all the above models need to be considered. And most of them still need further experiments to improve the accuracy and efficiency. These models provide platforms for researchers to predict and optimize tissue engineering products geometry and material design.

7 Conflict of Interest

All financial, commercial or other relationships that might be perceived by the academic community as representing a potential conflict of interest must be disclosed. If no such relationship exists, authors will be asked to confirm the following statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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