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REVIEW

Application of computational fluid dynamics in tissue engineering

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The process of tissue regeneration consists of a set of complex phenomena such as hydrodynamics, nutrient transfer, cell growth, and matrix deposition. Traditional cell culture and bioreactor design procedure follow trial-and-error analyses to understand the effects of varying physical, chemical, and mechanical parameters that govern the process of tissue regeneration. This trend has been changing as computational fluid dynamics (CFD) analysis can now be used to understand the effects of flow, cell proliferation, and consumption kinetics on the dynamics involved with *in vitro* tissue regeneration. Furthermore, CFD analyses enable understanding the influence of nutrient transport on cell growth and the effect of cell proliferation as the tissue regenerates. This is especially advantageous in improving and optimizing the design of bioreactors and tissue culture. Influence of parameters such as velocity, oxygen tension, stress, and strain on tissue growth can be effectively studied throughout the bioreactor using CFD as it becomes impractical and cumbersome to install probes at several locations in the bioreactor. Hence, CFD offers several advantages for the advancement of tissue engineering.

[**Key words:** Tissue engineering; Computational fluid dynamics; Bioreactors; Permeability; Mesh size; Scaffold; Cell growth; Nutrients; Glucose; Transient profile]

Engineering tissues using biodegradable porous scaffolds is an attractive solution for generating functionally replaceable tissue parts, synthetic surrogates to test disease progression, and drug development. Porous scaffolds guide and support the in-growth of cells during tissue regeneration (1). Furthermore, extracellular matrix (ECM) elements such as collagen, proteoglycans, and elastin are secreted by the colonizing cells which undergo enzymatic processes and aggregate into native fibers. The material constituting the scaffold degrades gradually during tissue regeneration, ultimately leaving the necessary functional tissue (2). To grow tissues, some initial concentration of cells are seeded on to a porous scaffold and grown in a system where the nutrients supply is replenished and optimum conditions are maintained similar to that in the body. Since a significant number of cells are required to colonize porous scaffolds, bioreactors are used to provide a continuous supply of essential nutrients (i.e., amino acids, glucose, oxygen) and regulate the pH and temperature as the cell seeded matrix matures. Furthermore, many parts of the body are exposed to stresses either due to the weight they carry (bone), the function they perform (bladder and cartilage), or due to the flow of fluid (lung and blood vessels). It is therefore important to grow cells outside the body by exposing them to the same physiological conditions. Since appropriate bioreactor design is important in obtaining tissues with desired shape and quality, several types have been explored (3–7). However, the selection of bioreactor configurations is mainly random assuming the system as a "black box". This trend has been changing as computational fluid dynamics (CFD) analysis can now be used to understand the effects of flow, cell proliferation, and consumption kinetics, on the dynamics involved with *in vitro* tissue regeneration approach. This review summarizes recent CFD advancements relevant to tissue regeneration and tissue culture.

USES OF CFD IN TISSUE ENGINEERING

CFD computations are now extensively used to analyze biological systems and to study flow patterns through bioreactors (8–11). Computations are carried out to provide an insight into the hydrodynamic environment of a bioreactor and the factors affecting it. Furthermore, CFD computations also enable understanding the influence of nutrient transport on cell growth and the effect of cell proliferation as the tissue regenerates. One could also understand the effect of mechanical loading on scaffolds using CFD (12). These are especially advantageous in selecting and optimizing the design of bioreactors. CFD modeling helps characterize fluid flow, provides initial estimates, and more importantly supplements experimental results. Influence of parameters such as velocity, oxygen tension, stress, and strain on tissue growth can be effectively studied throughout the reactor using CFD. The direct benefits of such virtual design capabilities include: integrating mass and momentum transfer calculations in a single system, analyzing problems that might accompany scaling-up the reactors, and identifying novel bioreactor configurations (Fig. 1) while reducing the number of expensive and time-consuming experiments. For example, bioreactors can be investigated for various factors: (i) bioreactor shapes (rectangular, circular and spherical), (ii) flow rate,

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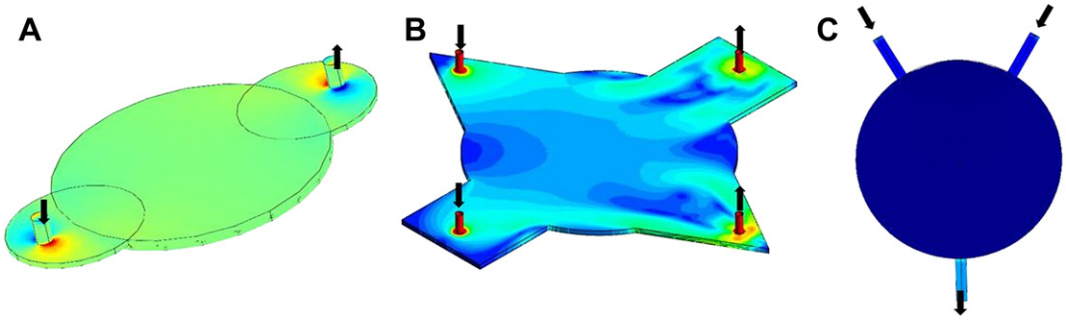

FIG. 1. Different bioreactor configurations tested using CFD computations. (A) Circular bioreactor containing a 2 mm thick and 100 mm diameter scaffold optimized for uniform shear stress distribution. (B) Circular bioreactor containing a 2 mm thick and 100 mm diameter scaffold with two inlets and two outlets. Also inlet and outlet shapes are different. (C) Spherical bioreactor with features resembling human bladder.

(iii) inlet and outlet location, (iv) inlet and outlet size, (vi) oxygen and glucose consumption kinetics, (vii) location of the scaffold within the bioreactor, (viii) thickness of the scaffold, and (ix) types of cells (13–15). In static cultures, one can understand the effect of elevation on the nutrient distribution (Fig. 2). However, caution should be exercised when interpreting the results, as they depend on multiple factors such as the suitability of the governing equations used, meshing structures employed, and grid independence results.

Simulation studies can be used as a guide to building scaffolds and bioreactors. For example, flow characterization studies were performed using CFD to test the effect of geometric shape of micro pillars on microfluidic channels (16). The CFD studies showed the elliptical micro pillar design to be the best configuration over other semi-circular micro pillar designs; these results were later validated experimentally by performing tests on various micro pillar designs. A study on flow characterization in a spinner flask with cartilage tissue engineering also took advantage of CFD along with experimental studies to understand flow regime (17). Other CFD studies have also modeled perfusion effects in 3D cultures to investigate shear stresses due to fluid flow (10,18).

SIGNIFICANCE OF SPATIAL AND PERIODIC DISCRETIZATION

Investigations related to three-dimensional transport involve solving partial differential equations simultaneously. Not all such equations have analytical solutions or require complicated techniques to obtain analytical solutions. Numerical techniques are much more straightforward and allow quick estimation of the solutions; however, these solutions are approximations to the actual solution. All CFD simulations require proper completion of four steps in order to be accurate; these include: (i) setting up the correct geometry; (ii) dividing the system in suitable and viable number of elements, at which the numerical calculations are carried out; (iii) selecting mathematical models that best represent the system; and (iv) applying suitable boundary conditions.

Application of numerical method requires the system domain to be divided into smaller elements. This process of discretizing the solution domain into a collection of smaller nodes is termed as meshing or grid generation in numerical computations and CFD. The governing equations in their discretized form are then used to solve for the unknown parameters at each node in the system, based on the conditions in the surrounding nodes. Fig. 3 depicts the cross-sectional view of a disc-shaped porous scaffold from unmeshed to meshed states (using triangular elements). One could vary the shape of the mesh based on the object shape.

Selecting mesh sizes and asymmetric meshing CFD involves dividing the solution domain into smaller elements (or steps) and solving each element separately based on the conditions in the adjacent elements. The accuracy of any CFD simulation therefore depends on the extent of discretization of the solution

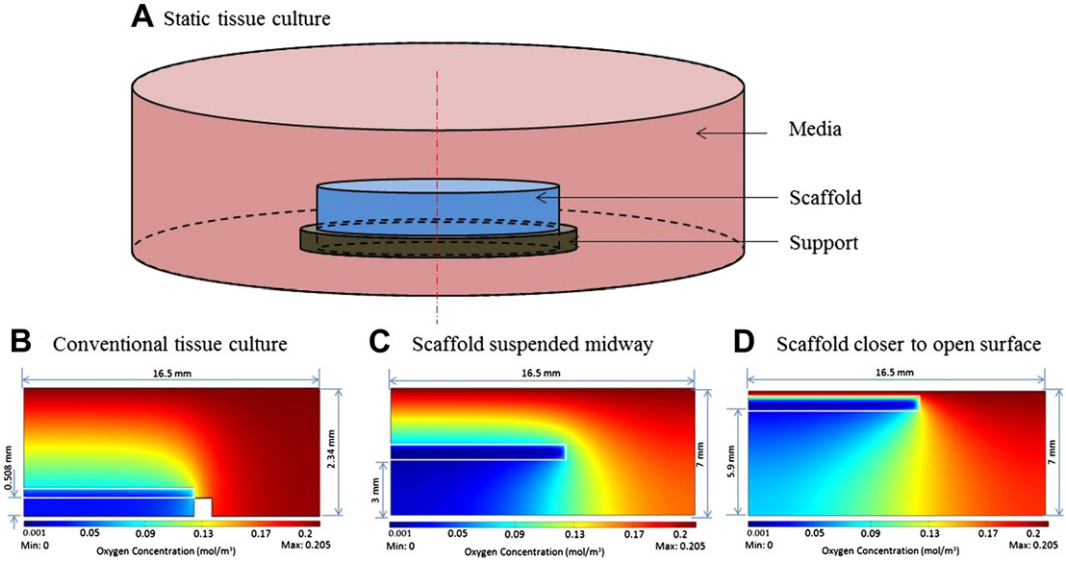

FIG. 2. CFD simulations in static tissue culture of 33 mm diameter containing 19 mm porous scaffold. (A) Schematic description of the setup. (B–D) Distribution of oxygen for different configurations.