

DEVELOPMENT OF A SCALABLE BIOREACTOR FOR INTRAVASCULAR TISSUE ENGINEERED MEDICAL PRODUCTS (ITEMPS) PROVIDING MECHANICAL STIMULATION AND EVALUATION CAPABILITIES

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GOALS

The specific goal of this paper is to discuss a bioreactor for mechanically stimulating Intravascular Tissue Engineered Medical Products (ITEMPS). This paper addresses deficiencies of previous bioreactor designs, and outlines the ability of the new bioreactor to apply a wide range of mechanical stimulation conditions to the ITEMPS and to record the ITEMPS response. The prototype system will be further refined and the long-term aim is to provide a versatile bioreactor system that can be used either for academic and industrial research or in producing ITEMPS within a commercial setting.

BACKGROUND AND SIGNIFICANCE

The replacement or repair of diseased vessels with natural synthetic vascular grafts has become a routine treatment for certain types of intravascular disease. For coronary bypass surgery, the autologous saphenous vein remains the graft of choice for its non-thrombogenic flow surface, ability to be healed by the host as well as its strength and elasticity. Efforts to create a suitable synthetic small diameter vascular graft have been largely unsuccessful.

Similarly, man-made medical devices have been used to replace heart valves and repair other intravascular complications. The devices are fixed form and do not conform to the body as the patient grows from childhood to adulthood thus necessitating multiple surgeries.

There are some areas (ie: venous valves) where medical device designs offer low patency and the only means of repair is through reconstructive surgery or transplantation.

In recent years, researchers have sought to develop living alternatives to the traditional "man-made" medical devices. These intravascular tissue engineered medical products (ITEMPS) use the patient's own cells to create a replacement device that can be further nurtured and adapted once implanted. Through design, specification, and fabrication of cells, biomaterials, or biomolecules, it is hoped that ITEMPS will play a major role in future heart valve replacement,

cardiovascular bypass surgery, venous valve repair and other intravascular surgeries.

PREVIOUS BIOREACTOR DESIGNS

ITEMPS are typically comprised of a collagen/elastin matrix or scaffold that is populated with multiple layers of cells including endothelial, smooth muscle and fibroblasts. The scaffold provides a structure that the cells can grow on. In order for the cells to grow, they must be exposed to a nutrient environment. Much of the early work in bioreactor development focused on creating an environment where the cells could grow and multiply rapidly.

Most bioreactors that are design specifically for stimulating ITEMPS have been built by the researchers themselves. The bioreactor designs that have been investigated have common areas where improvement is needed....

Instrumentation: Most research bioreactors do not have transducers for measuring the applied stress, pressure, flows, motion, temperature or chemistry within the vicinity of the ITEMPS. This means the researcher is unable to measure the effect the mechanical conditioning is having on the ITEMPS.

Control: The existing bioreactors rely on fixed volume pumps and timers and external pumps to provide the pulsatile flows. This means the control of the applied variables is not accurate and usually limited to approximated physiological conditions. Better control is desired as it would be useful to explore many different mechanical stimulation conditions.

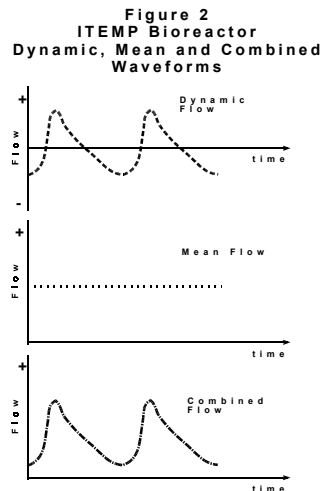
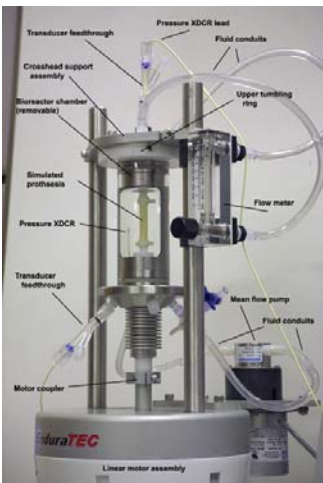
Measurement of ITEMPS Material Properties: In addition to reduced cell growth times, a major desired outcome of mechanical stimulation is to create enhanced material properties of the ITEMPS. These include modulus of elasticity and ultimate pressure. It is also believed that desirable material properties include the storage and loss modulus of elasticity as a function of applied strain rate or frequency.

Other material properties might include strength, density, chemistry, temperature and more. Measurement of the material properties of the ITEMp while within the bioreactor would be beneficial in determining the “right” conditioning sequence.

Use of Material Measurements as Feedback in Determining Applied Conditions: Once the material properties are measured and understood. It is believed that the researcher can develop control algorithms for optimizing the applied conditions. The use of a computerized monitoring and control system would enable the researcher to program these algorithms into the bioreactor conditioning system so that the computer can make changes to the conditioning sequence on a real-time basis.

ITEMPS BIOREACTOR

This new bioreactor concept is based on a Stent/Graft Test Instrument (SGT) currently produced by EnduraTEC Systems Corporation. That system was designed to test vascular prostheses and features a method for measuring the prostheses material properties while the test is running. That device also features a microcomputer control system, linear motor driven dynamic pump assemblies and transducer feedback systems.



The system is comprised of a bioreactor chamber assembly and a computer controlled linear motor and frame for holding the reactor. During the ITEMp installation and seeding process, the bioreactor chamber is uncoupled from the linear motor and removed from the frame. The chamber is designed so that it is easily disassembled for installation and removal of the ITEMp construct.

The bioreactor includes ports for replenishing nutrients and maintaining the CO₂ level of the fluid. This can be done using a circulation system although it also can be treated as a closed system.

The mechanical stimulating flow is comprised of two components: First, the linear motor, frame and bellows on the bioreactor provide a dynamic pumping action. Secondly, the mean flow pump provides a mean or steady state flow. Use of a linear drive motor for the dynamic pumping action enables the researcher to vary the frequency and shape of the applied pulse. A Windows based computer operates the dynamic pump under closed loop control. Figure 2 shows an example of what the dynamic waveform output might look like. It's flow is centered about zero flow. Figure 2 also shows how the mean flow pump output

is combined with the dynamic pulse to provide a physiologic-like combined flow.

Once the bioreactor chamber is installed and plumbed and the conditioning sequence is ready to begin, transducers are inserted into the reactor chamber. Many transducers can be inserted including catheter pressure transducers, flow, and temperature. The flow device may either be a Doppler based flow sensor or a catheter based (differential pressure) transducer. Additionally provisions have been made for measuring the diametric displacement of the ITEMp inside and outside diameters as this can be useful for measuring the ITEMp material properties. By measuring both the applied pressure and diametric displacement, one can determine the material properties in real-time.

The transducers are monitored and recorded using a Windows based computer. This computer also controls the dynamic and mean flow pumps. Figure 3 shows a proposed system functional showing the possible transducer connections.

The ITEMp bioreactor design is modularized and can be scaled to condition multiple ITEMps simultaneously. Figure 4 shows a proposed second generation multiple chamber design. The advantages of this approach include increased sample sizes and reduced cost. A study has been undertaken in collaboration with Georgia Tech to determine the effectiveness of this bioreactor design as compared to several “home-made” bioreactor designs. Preliminary results should be available for the June 2003 ASME meeting.

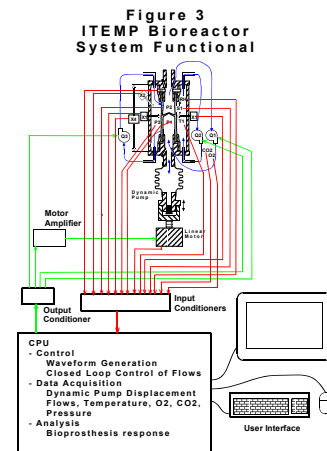


Figure 4
2G Bioreactor

