Proceedings of the ASME 2012 Summer Bioengineering Conference
SBC 2012
June 20-23, 2012, El Conquistador Resort, Fajardo, Puerto Rico

SBC2012-80437

ISOLATED LYMPHATIC VESSEL PERFUSION SYSTEM DESIGN FOR INDEPENDENTLY CONTROLLING HOOP STRESS AND SHEAR STRESS

Jeffrey A. Kornuta† **and J. Brandon Dixon**†‡
† Department of Mechanical Engineering, ‡ Department of Biomedical Engineering
Georgia Institute of Technology
Atlanta, GA 30332

INTRODUCTION

Most tissues in the body are supported by the lymphatic system for a variety of functions, including the regulation of fluid balance, the removal of particulate matter from the interstitium, as well as the transport of fat from the intestine to the blood, among others. Lymphedema, a chronic disease characterized by an inability of the lymphatics to maintain tissue homeostasis and estimated to affect over 130 million people worldwide, can result in serious clinical problems for which there are very few beneficial cures or therapies [1]. However, despite the importance of lymphatics and the prevalence of lymphatic disease, very little is known about the particular mechanisms through which the lymphatics fulfill its primary functions.

Lymphatic vessels contract much like the heart to promote flow, pumping in response to changes in lymph fluid shear stress. While it is known that the shear-induced inhibition of lymphatic contraction is important in regulating function, whether the magnitude or the rate of fluid shear stress is more important remains unknown. Additionally, little is certain regarding the coupled effects of fluid shear stress and hoop stress due to transmural pressure. Moreover, understanding the mechanisms which regulate lymphatic function is critical to developing effective treatments for ailments such as lymphedema.

In order to study both the independent and coupled effects of shear stress and hoop stress on lymphatic pump function, the authors propose a novel *ex vivo* perfusion system [Fig. 1] capable of controlling the biomechanical state of an isolated rat lymphatic vessel. Such a system would be critical for studying the physiological effects of biomechanical stresses on lymphatic contractility and would allow single-factor studies to be performed that would be nearly impossible with *in vivo* models. The device and compensator designs for the proposed system are summarized henceforth.

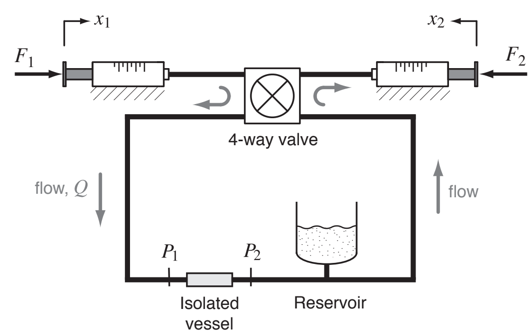

FIGURE 1. Two independently-actuated syringes control the flow rate, Q, and average transmural pressure, $P_{avg} = (P_1 + P_2)/2$, across the isolated vessel.

DEVICE DESIGN AND CONTROL

In order to control the desired biomechanical state (shear and hoop stresses) of the excised rat lymphatic vessel, the flow rate, Q, and transmural pressure, P_{avg}, must be precisely controlled. The device uses two independently-actuated glass syringes in a closed-loop configuration connected with a four-way solenoid valve, which can maintain the directionality of flow with respect to the vessel for an indefinite period of time [2]. The two glass syringes permit the precise generation of completely arbitrary flow rate and transmural pressure waveforms, which are capabilities that no other *ex vivo* perfusion systems are known to have [3,4].

The authors made several assumptions regarding the system modeling. First, the actuator dynamics are assumed to be much faster than the dynamics of the system and thus are ignored (the Parker MX80L linear stages have a rate-limiting acceleration of 4 g's). Next, because the P_{avg} experienced within rat lymphatics are very low (< 20 cmH_2O) [5], the tubing is assumed to be completely rigid with the only source of compliance being the reservoir downstream of the isolated vessel. Lastly, the system is assumed to behave linearly, with all possible nonlinear effects ignored except for the saturation properties of the actuators.

The general state-space equations for the device were modeled using a bond-graph approach:

$$\begin{aligned}\dot{\mathbf{x}}(t) &= \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t)\\ \mathbf{y}(t) &= \begin{bmatrix} Q(t) \\ P_{\text{avg}}(t) \end{bmatrix} = \mathbf{C}\mathbf{x}(t)\end{aligned} \quad (1)$$

where $\mathbf{x}(t) \in \mathbb{R}^{3\times1}$, $\mathbf{A} \in \mathbb{R}^{3\times3}$, and $\mathbf{u}(t) \in \mathbb{R}^{2\times1}$. Due to the implementation of a state transformation, the state variables were chosen to be quantities that can be measured from the system, $\mathbf{x}(t) = \begin{bmatrix} v_1 & P_{\text{avg}} & v_2 \end{bmatrix}^{\mathsf{T}}$, where v_1, v_2 are the velocities of the linear stages and P_{avg} is the average (transmural) pressure across the vessel. In this way, full-state feedback may be implemented in the compensator design since the system is fully controllable.

Figure 2 shows the control scheme, which consists of a servo loop utilizing full-state feedback from the plant. Due to the system's structure, the combined state-space equations for Fig. 2 may be written using an augmented state vector with the control law $\mathbf{u}(k) = -\begin{bmatrix} \mathbf{K}_x \,\vdots\, \mathbf{K}_I \end{bmatrix} \begin{bmatrix} \mathbf{x}(k) \,\vdots\, \mathbf{x}_I(k) \end{bmatrix}^{\mathsf{T}}$, which includes the integrated error vector, $\mathbf{x}_I(k)$, and allows the poles of the entire system to be placed arbitrarily. To assist in the design of the compensator gains $\mathbf{K}_x$ and $\mathbf{K}_I$, the optimal control solution of the linear-quadratic regulator (LQR) is used. Accordingly, the optimal pole locations are chosen automatically based on qualitative weighting matrices provided by the designer.

SYSTEM PERFORMANCE AND FUTURE WORK

Figure 3 demonstrates the performance of the system using the designed compensator with the desired inputs being an oscillatory flow rate and a constant average transmural pressure. The actual (simulated) outputs track the desired outputs very well, with negligible integral wind-up observed for P_{avg} since the minimum experiment time would be on the order of minutes. The digital hardware for the compensator design is currently being developed using a Microchip 32-bit PIC32 microcontroller running at 80 MHz, which should provide ample computational headroom for this application. The system construction is scheduled to be completed by Summer 2012.

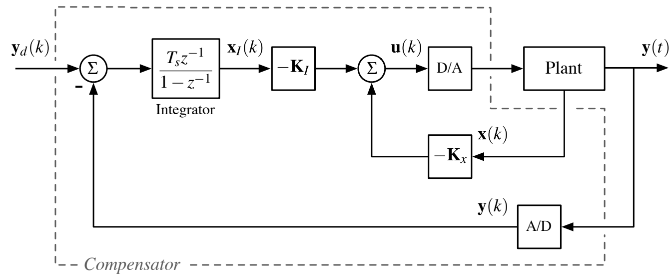

FIGURE 2. The control scheme consists of a servo system utilizing full-state feedback with gains chosen via LQR. The output, $\mathbf{y}(t)$, can be driven to any state since the system is output controllable.

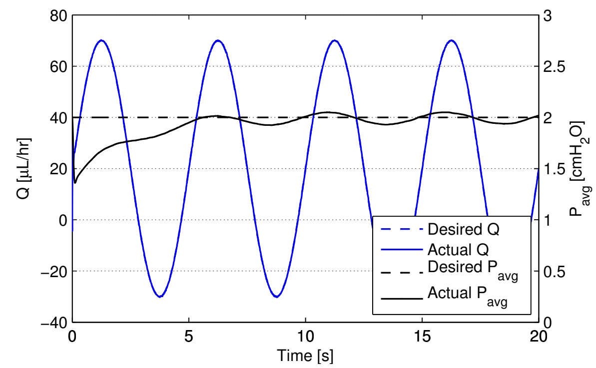

FIGURE 3. Simulation example showing desired outputs vs. actual outputs for the system running at 200 Hz with measurement noise.

ACKNOWLEDGMENT

This material is based upon work supported under a National Science Foundation Graduate Research Fellowship. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the National Science Foundation.

REFERENCES

[1] Rockson, S. G., 2001. "Lymphedema". *Am J Med*.

[2] Holdsworth, D. W., Rickey, D. W., Drangova, M., Miller, D. J., and Fenster, A., 1991. "Computer-controlled positive displacement pump for physiological flow simulation". *Med Biol Eng Comput*.

[3] Conklin, B. S., Surowiec, S. M., Lin, P. H., and Chen, C., 2000. "A simple physiologic pulsatile perfusion system for the study of intact vascular tissue". *Med Eng Phys*.

[4] Rachev, A., Dominguez, Z., and Vito, R., 2009. "System and method for investigating arterial remodeling". *J Biomech Eng*.

[5] Dixon, J. B., Greiner, S. T., Gashev, A. A., Coté, G. L., Moore, J. E., and Zawieja, D. C., 2006. "Lymph flow, shear stress, and lymphocyte velocity in rat mesenteric prenodal lymphatics". *Microcirculation*.