# A PHYSICAL BASIS FOR A TWO TIME CONSTANT CONSTITUTIVE MODEL FOR LIVER

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## INTRODUCTION

Soft biological tissues are complex materials whose heterogeneous makeup contributes to their viscoelastic nonlinear mechanical behavior. Developing a constitutive law for soft tissues to characterize their behavior under large deformations typical of medical manipulations is an area of active research [1-4]. Although these groups have developed nonlinear constitutive laws for the liver, none have taken the fluid flow into account. We recently made large strain creep indentation measurements on porcine liver to determine the effects of perfusion on the viscoelastic response [5]. The results not only indicate that perfusion greatly effects the creep response of the organ but also suggest that a constitutive model containing two time constants is required. A summary of these findings and a physiological basis behind the two time constant model are presented.

## METHODS

To determine the effects of perfusion on the liver, we developed a perfusion system for *ex vivo* experimentation [5]. We conducted large strain creep tests on porcine livers by applying a 100 g load to the surface while displacement was recorded over 5 minutes. We did this on livers in the *in vivo*, *ex vivo* perfused, *ex vivo* post perfused, and *ex vivo* excised sectioned states. Empirical models were fit to the responses to quantitatively compare the differences between the conditions. A second order lumped element model was required to describe the behavior of the large strain creep response (Figure 1, Equation 1),

$$x_0(t) = A_0 - A_1 e^{-t/\tau_1} - A_2 e^{-t/\tau_2} \quad (1)$$

where $A_0$ is the amplitude of the steady state displacement and $A_1$ and $A_2$ are the amplitude contributions due to the creep time constants $\tau_1$ and $\tau_2$.

The liver is one of the largest organs in the body and receives 30% of the cardiac output resulting in a total blood flow of 1.5 L/min [6]. The portal system is unique in that it receives 75% of its blood volume from the portal vein, which drains deoxygenated blood from the gut at a low pressure of 8-10 mmHg. The remaining 25% is oxygenated blood from the hepatic artery (95-100 mmHg). The

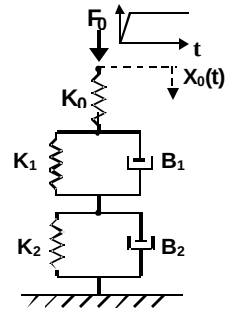



**Figure 1: Second order lumped element model for creep indentation of liver.**

intricate structure of the liver's vasculature is comprised of lobular units: a parallel branching organization of the portal triad (portal veins, hepatic arteries and bile ducts) connects to a central vein via a dense microstructure. Specifically, the portal vein and the hepatic artery drain into low-pressure (5 mmHg) fenestrated discontinuous capillaries (sinusoids). These sinusoids act as a filter where the blood is slowly carried past the parenchymal cells (hepatocytes) to perform the various functions of the liver (synthesis, storage, waste removal, detoxification, etc.) before draining into the central veins (2 mmHg). Over 1 billion sinusoids (1,500 km) work in parallel to slow the flow of the blood, thus providing a large pressure gradient (resistance) between the portal and central veins.

Resistance to flow is a function of vessel geometry (length and radius), vessel organization (series or parallel arrangements), the fluid (perfusate viscosity and type of flow), and the existence of extravascular mechanical forces. To conceptualize how the liver's physiology contributes to changes in flow induced by a large strain creep indentation we turn to Poiseuille's law for laminar, non-pulsatile fluid flow through a uniform straight pipe.

Poiseuille's law is applied to determine the flow rates ($Q$) of the various vessels in the lobule when subjected to the large strain creep indentation. We assume that the indenter locally induces a pressure gradient and displaces a volume that is initially absorbed by the elastic elements of the model ($K_0$), and then squeezes fluid through the

vasculature ($K_1$, $B_1$, $K_2$, $B_2$, vessel geometry) until a new equilibrium state is reached. Furthermore, we assume that the same volume of fluid passes through a series of vessels of varying radii, lengths, and pressures. The time to go through a single vessel is related to the change of volume ($DV$) divided by the flow ($Q$),

$$t = \Delta V / Q = \Delta V \left( 8mL / p\Delta PR^4 \right) \quad (2)$$

where $DV$ is the displaced volume from the indenter (0.238 ml for an indenter with a 3 mm radius and 8 mm creep response), μ is the fluid viscosity (6.82E$^{-4}$ Pa-s, for water at 37.8C), $L$ is the length of the vessel, $DP$ is the change of pressure across the $L$, and $R$ is the radius of the vessel. Table 1 gives values for these constants [7, 8].

| Vessel | R [mm] | DP [Pa] | L [mm] |
|---|---|---|---|
| Portal vein | 17.5 | 601.8 | 41.3 |
| Hepatic artery | 6 | 12,203 | 41.3 |
| Sinusoid | 4.5 | 418 | 1 |
| Central vein | 28 | 26.5 | 4 |

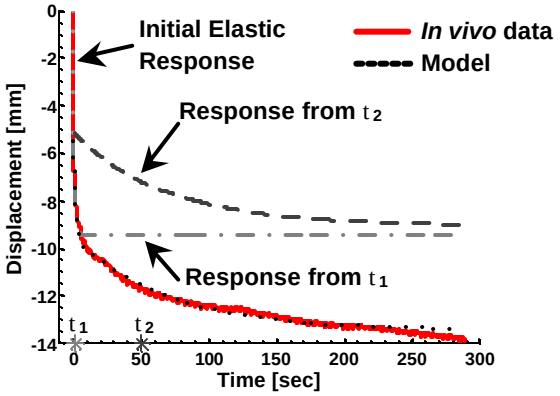
**Table 1. Vessel parameters**

## RESULTS

The results of the large strain creep indentation experiments revealed that the unperfused organs had a different mechanical response as compared to the *in vivo* state, whereas the *ex vivo* perfused condition nearly approximated the *in vivo* state. Although not a constitutive model in itself, the second order lumped element model used to describe the behavior of the creep tests resulted in $\tau_1$= 1.86±1.03 seconds and $\tau_2$= 51.3±18 seconds (Figure 2).

**Figure 2: Representative *in vivo* creep response, the model fit, and the responses due to each time constant.**

Applying equation 2 with the values for the vessels given in table 1 results in time constants on the order of $10^4$-$10^6$ seconds. Our model




was calculated for a single vessel whereas in fact there are thousands of vessels in parallel to redistribute the induced volume displacement. Thus we can look at the ratio of the calculated time constants to compare the physiological flow model to the lumped element model's results. The ratio of the central vein to the sinusoid (23.8) nearly equals the ratio of the two time constants from the creep model (27.6).

## DISCUSSION

This work is part of an ongoing effort to determine the constitutive model of the liver. Results of large strain creep indentation tests suggest that two time constants are needed to describe the viscoelastic behavior of the liver. To determine a physical basis for these time constants we use Poiseuille's law to model the effects of a sudden change in local volume on the flow of fluid through the liver.

The liver is a complex organ with an intricate multifaceted vasculature filled with non-Newtonian blood. We justify using the Poiseuille formulation because the results of the large strain creep indentation experiment across various environmental conditions suggests that the response from an *ex vivo* perfusion system (water-based perfusate, non-pulsatile flow) nearly approximates the *in vivo* response [5]. Similarly, although the sinusoids have a nonlinear pressure-flow response due to a closing pressure and waterfall effect [9], we assume that the vessels are open due to the increased local pressure on the system, and we bring the analysis down to a single vessel scale so that we can assume the flow is through straight "pipes".

The results of this work support that the redistribution of fluid from large strain indentation is initially accounted for by an elastic response, and then is absorbed by flow through the vasculature until equilibrium is achieved. The latter is dominated by two time constants: a fast time constant from the large diameter low-pressure central veins, and a slow one from the resistance in the sinusoid microstructure. This simple physical basis supports the need for two time constants when determining a constitutive law for liver.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