Indicial response functions of growth and remodeling of common bile duct postobstruction

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Dang, Quang, Hans Gregersen, Birgitte Duch, and Ghassan S. Kassab. Indicial response functions of growth and remodeling of common bile duct postobstruction. Am J Physiol Gastrointest Liver Physiol 286: G420–G427, 2004; 10.1152/ajpgi.00306.2003.—Biliary duct obstruction is an important clinical condition that stems from cholelithiasis, the neoplasm in the wall or, most commonly, gallbladder stones. The objective of this study is to understand the structural and mechanical remodeling of the common bile duct (CBD) postobstruction. Porcine CBD was ligated near the duodenum that increased the duct’s pressure from 6.4 to 18.3 cmH2O in the first 12 h and to 30.7 cmH2O after 32 days. The remodeling process was studied after 3 h, 12 h, 2 days, 8 days, and 32 days (n=5 in each group) after obstruction. One additional animal in each group was sham operated. At each scheduled time, the time course of change of morphometry (diameter, length, wall thickness, etc.) and mechanical properties (stress, strain, etc.) was documented. It was found that the diameter increased by about threefold and the wall thickness of the CBD doubled in the 32-day group compared with the sham group (P<0.001). The stress and strain increased initially with increase in pressure but recovered to near the control values by day 32 due to the structural and mechanical adaptations. Hence, the net effect of the structural and mechanical remodeling is to restore the stress and strain to their homeostatic values. Furthermore, the strain recovers more rapidly and more completely than stress. Finally, the remodeling data were expressed mathematically in terms of indicial response functions (IRF), i.e., change of a particular feature of a CBD in response to a unit step change of the pressure. The IRF approach provides a quantitative description of the remodeling process in the CBD.

The biliary duct system serves to transport bile acids and fluid from the liver and gall bladder to the small intestine. Biliary duct obstruction is an important clinical condition that stems from cholelithiasis, the neoplasm in the wall or, most commonly, gallbladder stones. Gallstone disease is an international health problem affecting >20 million people in the United States alone (14). Biliary obstruction is a painful condition that affects liver function and the enterohepatic circulation of bile acids. Obstruction induces an increase in bile pressure and consequent growth and remodeling of the common bile duct (CBD). We (3) recently studied this process in relation to the changes in the morphometry and mechanical properties of the CBD with pressure. The aim of this study was to describe the time course of changes of morphometry and mechanical properties of the CBD postobstruction. Various quantities (diameter, length, stress, strain, collagen content, etc.) are computed at in vivo loading, and the time course of changes is examined over the 32-day duration of the study.

Remodeling of tissue in response to physical stress is a very complex process. Changes in the tissues must be measured, and the results must be organized into mathematical forms suitable for predictions and applications. In the present study, we obtained an approximate step change of pressure (a step plus a perturbation) and then analyzed the results by using the indicial response functions (IRFs). The IRF is the ratio of the change of a particular feature of CBD, e.g., wall thickness, diameter, strain, stress, etc., in response to a unit step change of pressure. Analysis of IRFs is presented, and the implications and limitations are discussed.

METHODS

Available data. Duch et al. (3) recently described the methods of preparation, measurements, and morphometric and mechanical analysis of normal and obstructed porcine CBD. Briefly, 30 female pigs were randomly divided into five groups (n=6 in each group). Five of the pigs in each group were then subjected to CBD obstruction for 3 h, 12 h, 2 days, 8 days, or 32 days, respectively, whereas the sixth pig was sham operated. Before obstruction, a blood sample was taken for the analysis of bilirubin, alanine transaminase, and alkaline phosphatase to detect any occult illnesses of the liver and biliary system. The values for bilirubin, alanine transaminase, and alkaline phosphatase were deemed normal, and all pigs were included in the study. The CBD was ligated (complete obstruction) ~1 mm from the duodenal wall. Pressure in the CBD was measured with a needle inside the duct before and after ligation. A scintigraphy was performed to verify complete obstruction. The study complied with the Danish regulations for care and use of laboratory animals.

At a scheduled time, the pigs were anesthetized again and body weight and bilirubin were measured. The CBD was harvested for in vivo mechanical distension, and the animal was killed. The CBD was transferred to an organ bath containing oxygenated (95% O2-5% CO2) calcium-free Krebs-Ringer solution with 95 mg/l EGTA and 60 g/l dextran at pH = 7.40. EGTA was added to abolish muscle contractions.

The proximal end of the segment was tied over a tube and was connected to an infusion system and a pressure transducer (Baxter). The other end was ligated as close to the sphincter of Oddi as possible as shown in Fig. 1. The bile duct was preconditioned by six cycles of volume infusions and withdrawals with physiological Krebs solution up to 5 kPa pressure. Six cycles were sufficient to obtain reproducible results (5, 6). After preconditioning, the distension experiment was executed. A Sony charge-coupled device camera and a videocassette recorder provided simultaneous recordings of outer.

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dimension (diameter and length) of the CBD at the various imposed pressures.

After the distension protocol, the CBD segment was removed from the organ bath and two rings (2 mm wide) were cut from each of four locations along the length of the segment. One ring from each of the four locations was immersed in buffered formaldehyde and used for histological measurements. The other ring was used for no-load and zero-stress-state studies (7). Photographs were taken with the ring in a horizontal position to evaluate the no-load state. The ring was then cut radially and opened into a sector. A photograph of the sector at the zero-stress state was also obtained. Images were used for measurements of inner and outer circumferences, wall thickness, wall area, and opening angle (3).

Rings cut for histological examination were dehydrated and embedded in paraffin. Sections (6 μm thick) were cut and stained with hematoxylin and eosin and picrosirius red. The sections stained with picrosirius red were evaluated by a point count method under a microscope. Point counts were made at four evenly spaced locations along each CBD segment. The fraction of collagen was defined as points intersecting the collagen area divided by points intersecting the wall area. To estimate the total collagen area in the different groups, the fraction of collagen was multiplied by the total wall area measured at the no-load state.

Length and outer diameter were measured from the digitized images. The internal diameter and wall thickness were calculated according to Kirchhoff stress and Green strain (3, 6).

Determination of various parameters at the in vivo condition. In vivo CBD pressures were measured in all experimental and sham animals before euthanasia. The relationship among diameter, length, wall thickness, stress and strain, and pressure were then determined in vitro through inflation experiments (3). In the present study, we extrapolated the values of the various quantities (diameter, wall thickness, length, stress, and strain) at the in vivo pressures for the different time intervals postobstruction. In vivo volume was calculated on the basis of a cylindrical geometry; i.e., V = πDhL, where D, h, and L are the in vivo inner diameter, wall thickness, and length of the CBD, respectively.

Mathematical analysis of IRF. The basic hypothesis of the IRF analysis is linearity between cause and effect. In the present study, the cause is an increase in pressure due to CBD obstruction. The effect is change in various morphological or mechanical parameters (e.g., diameter, wall thickness, length, stress, strain, etc.). Let ΔP(t) represent the cause as a function of time t, whereas ΔL(t) is the effect. Let the cause ΔP(t) be a step function, ΔP(t) = ΔP(0)H(t − τ), of amplitude ΔP(0), beginning at time τ, and constant after time τ. H is known as the Heaviside step function and is equal to 1 for time t ≥ τ and 0 for time t < τ. The response measured is ΔL(t) = ΔP(0)IRF(t − τ), proportional to ΔP(0) and of a magnitude equal to ΔP(0) × IRF(t − τ). IRF(t − τ) is referred to as the response indexed with respect to ΔP(0); hence the word indicial, which is a term used in circuit theory. An arbitrary function ΔP(t) can be regarded as a superposition of infinitely many step functions [ΔΔP(τ)/dτ]H(t − τ), so that

\[ ΔP(t) = ΔP(0) + \int_0^t \frac{ΔP(τ)}{dτ} dτ \]  

Then the response due to ΔP(t) is the sum of each of the small step functions

\[ ΔL(t) = IRF(t)ΔP(0) + \int_0^t IRF(t − τ) \frac{ΔP(τ)}{dτ} dτ \]

The integral embodies the hypothesis of linearity between cause and effect. Here IRF(t − τ) characterizes the system. Equation 2 is called a Duhamel integral that represents the effect in response to the cause. A more detailed description of the Duhamel or convolution integral is given in Appendix A.

The purpose of the mathematical analysis is to link the changes in the luminal pressure of the CBD to changes in its morphology or mechanical properties. We recorded the pressure and various morphological parameters such as wall thickness and outer diameter at several time periods. To establish a concrete mathematical link between the pressure and the morphological parameters, we must obtain the pressure, P(t), and the morphologic parameters, L(t), as functions of time.

CBD was ligated to generate a relatively abrupt increase in pressure. Ideally, we wish to generate a step increase; however, no known method exists to create the step increase in vivo. Pressure at t = 0 was taken as the control value. After ligation of the CBD, the pressure initially rose quickly and then gradually over time. Pressure at any time t, P(t), can then be modeled as the sum of the control pressure plus the step increase and a perturbation

\[ P(t) = P(0) + A_1 H(t) + A_2 e^{-at} \]

where P(0) is the control value of the pressure, A_1 H(t) represents the step increase, and A_2 e^{-at} represents the perturbation. Because we are interested in linking the change in geometric and mechanical properties of the CBD to a change in pressure rather than to the absolute change in pressure due to CBD obstruction, the effect is an increase in pressure due to CBD obstruction. The effect is change in various morphological or mechanical parameters (e.g., diameter, wall thickness, length, stress, strain, etc.). Let ΔP(t) represent the cause as a function of time t, whereas ΔL(t) is the effect. Let the cause ΔP(t) be a step function, ΔP(t) = ΔP(0)H(t − τ), of amplitude ΔP(0), beginning at time τ, and constant after time τ. H is known as the Heaviside step function and is equal to 1 for time t ≥ τ and 0 for time t < τ. The response measured is ΔL(t) = ΔP(0)IRF(t − τ), proportional to ΔP(0) and of a magnitude equal to ΔP(0) × IRF(t − τ). IRF(t − τ) is referred to as the response indexed with respect to ΔP(0); hence the word indicial, which is a term used in circuit theory. An arbitrary function ΔP(t) can be regarded as a superposition of infinitely many step functions [ΔΔP(τ)/dτ]H(t − τ), so that

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Then the response due to ΔP(t) is the sum of each of the small step functions

\[ ΔL(t) = IRF(t)ΔP(0) + \int_0^t IRF(t − τ) \frac{ΔP(τ)}{dτ} dτ \]
The quantity \( K_1 + K_2 \) approximates the initial step change. \( L(0) \), experimental control value \( b \) and \( c \) are curve-fit constants.

![Fig. 2](https://via.placeholder.com/150)

**Table 1. Coefficients of nonlinear regression fit for the equation** \( \Delta L = K_1 + K_2 e^{-bt} + K_3 t + K_4 te^{-ct} \)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>( L(0) )</th>
<th>( K_1 )</th>
<th>( K_2 )</th>
<th>( b ), day</th>
<th>( K_3 )</th>
<th>( K_4 )</th>
<th>( c ), day</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length, mm</td>
<td>34.4 mm</td>
<td>16.9 mm</td>
<td>–9.79 mm</td>
<td>0.091</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.973</td>
</tr>
<tr>
<td>Outer diameter, mm</td>
<td>9.07 mm</td>
<td>19.9 mm</td>
<td>–16.8 mm</td>
<td>0.277</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.972</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>0.467 mm</td>
<td>–0.133 mm</td>
<td>0</td>
<td>0</td>
<td>0.0168 mm/day</td>
<td>0</td>
<td>0</td>
<td>0.989</td>
</tr>
<tr>
<td>Wall volume, mm(^3)</td>
<td>433 mm(^3)</td>
<td>4027 mm(^3)</td>
<td>–3955 mm(^3)</td>
<td>0.052</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.999</td>
</tr>
<tr>
<td>Bilirubin concentration, ( \mu M )</td>
<td>3.0 ( \mu M )</td>
<td>72.1 ( \mu M )</td>
<td>–32.3 ( \mu M )</td>
<td>0.173</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.863</td>
</tr>
<tr>
<td>Collagen area, mm(^2)</td>
<td>8.4 ( \mu M )</td>
<td>0.185 ( \mu M )</td>
<td>0</td>
<td>0</td>
<td>1.13 mm(^3)/day</td>
<td>0</td>
<td>0</td>
<td>0.991</td>
</tr>
<tr>
<td>Circumferential stress, kPa</td>
<td>3.46 kPa</td>
<td>86.3 kPa</td>
<td>–80.8 kPa</td>
<td>0.078</td>
<td>–1.88 kPa/day</td>
<td>0</td>
<td>0</td>
<td>0.980</td>
</tr>
<tr>
<td>Axial stress, kPa</td>
<td>2.65 kPa</td>
<td>42.6 kPa</td>
<td>–32.9 kPa</td>
<td>0.126</td>
<td>–0.918 kPa/day</td>
<td>0</td>
<td>0</td>
<td>0.927</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>0.873</td>
<td>0.30</td>
<td>0</td>
<td>0</td>
<td>–0.020 day</td>
<td>1.53 day</td>
<td>0.803</td>
<td>0.991</td>
</tr>
</tbody>
</table>

The time course of pressure is shown in Fig. 2. The data suggest that the pressure initially changes as a step function (within the first 12 h) and subsequently increases in a slow exponential manner reaching an asymptotic value. Consequently, a nonlinear least-squares fit for the pressure time course is represented by Eq. 2.

\[
\Delta P(t) = A_1 H(t) + A_2 e^{-at} 
\]

\( A = 25.1, A_2 = -15.7, \) and \( a = 0.102 (R^2 = 0.985) \). The mathematical form of time course of pressure is used in the IRF analysis as shown in Appendix B.
correlation coefficient ($R^2$) of the least-squares fit. Figure 3, A–D depicts the time course of change of the length, outer diameter, wall thickness, and wall volume, respectively, in the CBD postobstruction. Baseline or control values of the various morphometric parameters are listed in Table 1. The ensuing changes can be seen to be quite significant. The chronic changes of length and outer diameter have a functional form that is similar to that of the change of pressure, whereas the increase in wall thickness is linear. The length and wall volume changes show a strong positive correlation with the change of pressure ($R^2 = 0.988$ and $0.961$, respectively). Figure 4 shows the change of collagen area in the CBD wall and the change in blood bilirubin concentration. The time course of change in the collagen area is linear, whereas the shape of the bilirubin curve resembles that of pressure.

Data for the change in axial and circumferential stresses along with their curve fits are shown in Fig. 5, A and B, respectively. The data show an acute mechanical response followed by a remodeling course that tends toward the control value after 10 days. The circumferential strain (Fig. 5C) shows a sharp initial increase followed by an exponential decay toward the control value. The control or homeostatic values are listed in Table 1. A negative correlation was found between the change in circumferential strain and the change in time course of pressure ($R^2 = -0.969$).

IRFs are shown graphically in Fig. 6, A, B, C, and D for the length, outer diameter, wall thickness, and wall volume, respectively. Similarly, Fig. 7, A and B shows the variation of IRF for the bilirubin concentration and collagen area, respectively. Finally, the IRF of axial and circumferential stresses as well as the circumferential strain are shown in Fig. 8, A–C, respectively. These plots show the change of a quantity (effect) per change of pressure (cause). To assess the magnitude and time constant of stimulus, the IRF of the axial and circumferential stress and strain are normalized to their respective values as shown in Fig. 9.

**DISCUSSION**

**Obstruction of CBD.** Obstruction of the CBD leads to an accumulation of bile and hence an increase in the pressure of the hepatic ducts. The bile production stops when the pressure in the bile duct increases to $30 \text{ cmH}_2\text{O}$ (16). Increase in pressure has both acute and chronic consequences. In relation to the 32-day duration of the experiment, the first 12 h can be considered as the acute phase. Acutely, pressurization of a vessel will lead to circumferential and longitudinal stresses and strains (6). Specifically, it is expected that the diameter and length will increase, whereas the wall thickness will decrease in response to an increase in pressure. This is precisely what is observed acutely where $\Delta L(0)$ and $\Delta D(0) > 0$ and $\Delta WT < 0$.
for the change of length, diameter, and wall thickness, respectively, as shown in Fig. 3, A, B, and C. This response is due purely to the viscoelastic deformation of the tissue in response to increase in pressure. Volume of the tissue is not expected to change acutely, however, because the tissue is incompressible. Again this is confirmed by Fig. 3D where the change in volume at \( t = 0 \) is zero. Because no growth or remodeling occurs in the acute phase, the change in collagen area is zero, whereas there is an acute response in blood bilirubin concentration in response to absence of bile as shown in Fig. 4.

Acute increase in stresses and strains in response to the increased pressure is evident in Fig. 5. Growth is clearly observed in this model beyond the acute phase where length, diameter, and wall thickness increase by 48, 210, and 88%, respectively, after 32 days. Furthermore, increase in volume shown in Fig. 3D is proportional to increase in mass (for a constant density) and reflects the growth law for the CBD. The total increase in wall volume is 760% after 32 days.

**Physical principles that dictate the growth and remodeling process.** It is unlikely that pressure increase is the direct stimulus for growth and remodeling. Instead, stress (a measure of intensity of force per unit area) and strain (a measure of deformation) are more intrinsic quantities, and the increase in those parameters is more likely to be the stimulus of growth and remodeling. Stress and strain increase in response to the pressure overload is shown in Fig. 5. Our data show that circumferential and axial stress and circumferential strain increase initially and tend to decrease toward initial homeostatic values after 32 days. Hence, the growth and remodeling process occur in such a way as to return the values of stress and strain to the homeostatic levels. The circumferential strain peaks sooner and normalizes more rapidly than the stresses as shown in Fig. 9. Hence, wall deformation may be an earlier stimulus of growth and remodeling. After recovery of strain to a homeostatic value, the CBD continues to grow and remodel because of the elevated stress.

**Analogy with vascular hypertension.** Laplace’s equation states that the mean circumferential stress in a cylinder is directly proportional to the pressure and is inversely proportional to the vessel thickness-to-radius ratio. Hence, an increase in pressure causes an increase in the mean circumferential stress. In the cardiovascular literature, it is reported that the vessel wall remodels itself both morphologically and mechanically in response to the elevated stress. Morphologically, it appears that the blood vessel wall thickness-to-radius ratio increases in proportion to the increase in blood pressure such that the mean circumferential stress remains constant (8, 12, 17–19). These conclusions are consistent with results of the present study. Hence, the adaptation to pressure overload in blood vessels and CBD is very similar.
The physiological significance of IRF analysis is threefold: 1) it allows us to reduce complicated and interwoven sets of experimental data into simple, definitive statements in terms of mathematical functions; 2) under the linearity assumption, it allows us to predict the tissue remodeling process quantitatively under an arbitrary course of stimulation (not necessarily a step change); and 3) it presents a definitive, quantitative way to verify whether the basic assumption of linearity or superposability is valid or not.

Equation 2 is based on the linearity assumption of the response function \( L(t) \) with respect to the amplitude of pressure. A system is linear if \( L \) is proportional to \( \Delta P(0) \) in Eq. 2. Otherwise, the system is nonlinear. We rely on the experimental results to tell us whether the system is linear or not. If a system is nonlinear but a small change in \( \Delta P(0) \) results in a small change in \( L(t) \), then Eq. 2 can still be used. If a small change in \( \Delta P(0) \) produced a large change in \( L(t) \), then the system is highly nonlinear and Eq. 2 cannot be used. In this case, a record of the way the indicial function depends on \( \Delta P(0) \) is an ideal way to quantitatively express the nonlinearity; i.e., IRF is not only a function of \( t \), but also a function of the magnitude of \( P \). Modifying the IRF in this way, one can still use Eq. 2, which now becomes nonlinear. The range of agreement between theory and experiment will correspond to the range of linearity. The goal of future experiments is the verification of the superposability hypothesis.

Previous studies on IRF. The IRF approach was first proposed by Y. C. Fung (personal communication) and was later used by Liu and Fung (10) to obtain the IRF of mesenteric arteries in response to changes in blood pressure. Subsequently, Lu et al. (11) obtained the IRF of femoral artery in response to flow overload. Finally, Li et al. (9) used the IRF approach to understand the remodeling process in the aorta and its branches in response to lowering of blood pressure. The present study represents the first application of the IRF analysis to tissue outside of the cardiovascular system.

Significance of the present study. The biliary duct system serves to transport bile acids and fluid from the liver and gall bladder to the small intestine, primarily as a passive low-pressure conduit. Biliary duct obstruction is an important clinical condition affecting a large number of people throughout the world with pain, impaired liver function, and interrupted enterohepatic circulation of bile acids. In most cases, it is possible to release the obstruction by endoscopic procedures, leaving the bile duct intact. In other cases, it may be necessary to perform a Roux-en-Y cholecystojejunostomy or to insert stents into the bile duct to create passage for the bile. The present study clarifies the principles that dictate the growth and remodeling process postobstruction and pressure overload. A reduction in the wall thickness in the first days of obstruction along with an increased duct diameter suggest that operative procedures such as suturing, anastomosis, and procedures related to endoscopic retrograde cholangiopancreatography should be performed with care to avoid damage to the CBD. On the other hand, it is clinically important to perform prompt relief of obstruction of the CBD, because persistent obstruction causes long-term changes to the connective tissue of the organ (1, 2, 13, 15).

Use of IRFs simplifies the interpretation of data and greatly increases the potential of using experimental data for prediction of the outcome of future experiments. This is a new and
exciting approach in physiology that will help us understand physiological problems with a mathematical accuracy.

APPENDIX A: FORMULATION OF DUHAMEL INTEGRAL

The main idea behind Eq. 2 is linearity or the principle of superposition. Let the response of a system \([\Delta P(t)]\) be linearly related to an input function \([f(t)]\). In our analysis, we used the change in pressure \([\Delta P(t)]\) as our input. For every unit of input, there is a response of size \([IRF(t)]\). In general, the step input does not have to be of magnitude 1. Assuming linearity between input and response, a step input of \([f(t)]\) can be broken down into a sum of small steps at different times as shown in Fig. 10, then each small step input will result in a small step response. Region 1 in Fig. 10 or Table 2, for example, is the step input occurring at \(t = 0\). Above it are several horizontal slabs representing subsequent small-step inputs. Region 2 in Fig. 10 is a representative small step input that occurs at \(time t = \tau\) with a magnitude of \(\Delta f(\tau)\). According to Table 2, the response associated with Region 2 is \(\Delta f(\tau) \times IRF(\tau - \tau)\). The principle of superposition ensures that the total response of the system, \(\Delta L(t)\), is the sum of the individual responses. By adding all of the responses, we get

\[
\Delta L(t) = f(0)IRF(t) + \Delta f(\tau)IRF(t - \tau) \quad (A1)
\]

In the limit that \(\Delta \tau \rightarrow \infty\)

\[
\Delta L(t) = f(0)IRF(t) + \int_{0}^{t} \frac{df(\tau)}{d\tau} IRF(t - \tau)\,d\tau \quad (A2)
\]

The integral in Eq. A3 is called the Duhamel integral. Equation A3 is a restatement of Eq. 2 in which the general input function \(f(t)\) becomes \(\Delta f(\tau)\) for the pressure change in the CBD.

APPENDIX B: DETERMINATION OF THE IRF

Equation 2 for \(IRF(t)\) cannot readily be solved by using basic calculus; more advanced techniques are required. One approach is to apply the Laplace transform to Eq. 2, thereby converting Eq. 2 into s-space. The Laplace transform allows us to reduce Eq. 2 from an integral equation into an algebraic equation. We then algebraically solve for the Laplace transform of \(IRF(t)\); i.e., \(IRF(s)\). Finally, by applying the inverse Laplace transform to the expression for \(IRF(s)\), we recover the desired function, \(IRF(t)\).

Laplace transforms of \(\Delta P(t)\) and \(\Delta L(t)\) are defined as

\[
\tilde{\Delta P}(s) = \int_{0}^{s} e^{-st} \Delta P(t)\,dt \quad \Delta L(s) = \int_{0}^{s} e^{-st} \Delta L(t)\,dt \quad (B1)
\]

Laplace transform of \(\Delta P(t)\), as given in Eq. 3, is

\[
\tilde{\Delta P}(s) = \frac{A_1}{s} + \frac{A_2}{s + a} \quad (B2)
\]

As an example, the Laplace transform of \(\Delta L(t)\) as given by Eq. 6b (with \(K_a = 0\)) is

![Graph](http://ajpgi.physiology.org/10.220.33.5 on June 10, 2017)

Table 2. Input function-response function relationship

<table>
<thead>
<tr>
<th>Region</th>
<th>Input Function</th>
<th>Response Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(H(t))</td>
<td>(IRF(t))</td>
</tr>
<tr>
<td>1</td>
<td>(H(t - \tau))</td>
<td>(IRF(t - \tau))</td>
</tr>
<tr>
<td>2</td>
<td>(f(0)H(t))</td>
<td>(f(0)IRF(t))</td>
</tr>
<tr>
<td>3</td>
<td>(\Delta f(\tau)H(t - \tau))</td>
<td>(\Delta f(\tau)IRF(t - \tau))</td>
</tr>
</tbody>
</table>

*Response due to a step input of magnitude 1, which is the unit step function \(H(t)\), is \(IRF(t)\). The response function \((f)\) was arbitrarily chosen and serves only to illustrate the different responses due to varying input functions. Response due to a unit step increase occurring at \(time \tau\) is \(IRF(t - \tau)\), which is the IRF shifted to \(t = \tau\). Region 1, for a step input of magnitude \(f(0)\), the response is equal to \(f(0) \times IRF(t)\). Region 2, when the step input occurs at \(time \tau\) and the magnitude of that step input is \(\Delta f(\tau)\), then the response is \(\Delta f(\tau) \times IRF(t - \tau)\).*
\[
\Delta L(s) = \frac{K_1}{s} + \frac{K_2}{s+b} + \frac{K_3}{s} \quad (B3)
\]

Laplace transformation of Eq. 2 yields
\[
\Delta L(s) = \Delta P(0) f(s) + \text{IRF}(s) + [s \cdot \Delta P(s) - \Delta P(0)]
\]
(B4)
Cancellation of terms and rearranging Eq. B4 in combination with Eq. B2 gives
\[
\text{IRF}(s) = \frac{\Delta L(s)}{s \cdot \Delta P(s)} = \frac{\frac{K_1}{s} + \frac{K_2}{s+b} + \frac{K_3}{s}}{s \left( \frac{A_1}{s} + \frac{A_2}{s+a} \right)} \quad (B5)
\]

Equation B5 provides the expression of IRF(s) in s-space. An inverse Laplace transform applied to Eq. B5 yields the desired function, IRF(t). We must, however, express the right side of Eq. B5 in terms of partial fractions to facilitate the inverse Laplace transform. Thus IRF(s) can be rewritten as
\[
\text{IRF}(s) = \frac{(s+a)(bK_1 + bK_2 + sK_3 + s'K_1 + s'K_2)}{(A_1 + A_2)r(s+b)(s+r)} \quad (B6a)
\]
where
\[
r = \frac{aA_1}{A_1 + A_2} \quad (B6b)
\]
We observe that Eqs. B6a and B6b can now be readily reduced to partial fractions of the form
\[
\text{IRF}(s) = \frac{\alpha}{s+r} + \frac{\beta}{s+b} + \frac{\gamma}{s} + \frac{\delta}{s} \quad (B7)
\]
We will not show the details of the solution for the constants \(\alpha, \beta, \gamma,\) and \(\delta.\) Suffice it to say that the method to obtain the constants in partial fraction problems can be found in most elementary calculus texts. We present the expressions for the constants as follows:
\[
\alpha = \frac{(a-r)(bK_1 - bK_2 + r - K_3 r + K_3 r^2)}{(A_1 + A_2)r(b-r)}
\]
\[
\beta = \frac{K_3 (b-a)}{(A_1 + A_2)(b-r)}
\]
\[
\delta = \frac{aA_1 K_2 - A_1 K_2}{aA_1}
\]
\[
\gamma = \frac{K_1}{A_1}
\]
Quantities on the right side of Eq. B8 are determined from nonlinear curve fitting of data and are listed in Table 1. Hence, the constants \(\alpha, \beta, \gamma,\) and \(\delta\) can be readily computed. The inverse Laplace transform of Eq. B7 yields the desired result
\[
\text{IRF}(t) = ae^{-rt} + be^{-bt} + a\gamma t + \delta \quad (B9)
\]
For verification, it can be easily shown that Eq. B9 satisfies Eq. 2 exactly.

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**REFERENCES**