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A Systems Approach to Tissue Remodeling

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Abstract

Remodeling of tissue in response to physical stress is a very complex process. The changes of stimulus (cause) and response (effect) must be measured and the results must be organized into mathematical forms that are suitable for predictions and applications. An experiment where the stimulus (pressure, flow, shear stress, etc.) can be changed approximately as a step function (a step plus a perturbation) and the response (structure, material properties, function, etc.) can be measured over time can be simulated by indicial response functions (IRF). The IRF is a mathematical expression of the ratio of the change of a particular feature of the system in response to a unit step change of stimulus. The IRF approach provides a quantitative description of the remodeling process and simplifies the interpretation of data and greatly increases the potential of using the experimental data for prediction of the outcome of future experiments. The objective of this review is to provide an overview of the IRF approach including some exemplary systems. The goal is to illustrate how the indicial expressions make it possible to integrate biological complexity by convolution. The time courses of stimuli represent half of the convolution while the time course of changes in response represents the second half of the convolution. The IRF approach provides an understanding of physiological problems with mathematical accuracy and may be conducive to new findings.

There is no doubt that knowledge of the adaptation mechanisms in structure and function in response to physical stress is important in health and disease. A systematic approach to describe the remodeling process is to record the course of changes that take place in various features of the tissue following a step change of input variable. Response to a step function is called the indicial response function (IRF); i.e., change of a particular feature of a blood vessel; e.g., wall thickness, opening angle, strain, stress, etc., in response to a unit step change of input variable; e.g., pressure, flow, shear stress. If the system is linear, then a convolution of the IRF yields the response to any arbitrary input function within the same limits. This approach was first proposed by Fung (personal communication) and was later used by Fung and colleagues (1–3) to obtain the IRF of arterial remodeling in response to changes in blood pressure. The IRF approach was subsequently used to understand the effect of flow-overload in an artery by Lu et al (4) and the effect of pressure-overload on the common bile duct (CBD) by Dang et al(5). Below, we shall review the basic premise of the IRF and provide some exemplary illustrations of the approach. We will also discuss advantages and potential utility of the approach.

Mathematical Analysis of IRF

The basic hypothesis of the indicial response function (IRF) analysis is linearity between cause and effect. The cause may be a change in pressure or flow. The effect may be change in various molecular, morphological or mechanical parameters. Let $\Delta I(t)$ represent the cause

(or Input) as a function of time t , whereas $\Delta O(t)$ is the effect (or Output). Let the cause $\Delta I(t)$ be a step function, $\Delta I(t) = \Delta I(0)\mathbf{H}(t-\tau)$, of amplitude $\Delta I(0)$, beginning at time τ , and constant after time τ . $\mathbf{H}$ is known as the Heaviside step function and is equal to 1 for time $t \geq \tau$, and 0 for time $t < \tau$. The response measured is $\Delta O(t) = \Delta I(0)\text{IRF}(t-\tau)$, proportional to $\Delta I(0)$, and of magnitude equal to $\Delta I(0)$ times $\text{IRF}(t-\tau)$. $\text{IRF}(t-\tau)$ is referred to as the response indexed with respect to $\Delta I(0)$. An arbitrary function $\Delta I(t)$ can be regarded as a superposition of an infinitely many small step functions $[d\Delta I(\tau)/d\tau]d\tau \mathbf{H}(t-\tau)$, such that

$$\Delta I(t) = \Delta I(0) + \int_0^t \frac{d\Delta I(\tau)}{d\tau} d\tau \quad [1]$$

Then the response due to $\Delta I(t)$ is the sum of each of the small step functions:

$$\Delta O(t) = \text{IRF}(t) \Delta I(0) + \int_0^t \text{IRF}(t-\tau) \frac{d\Delta I(\tau)}{d\tau} d\tau \quad [2]$$

The integral embodies the hypothesis of linearity between cause and effect; and the indicial response function, $\text{IRF}(t-\tau)$, characterizes the system. Equation [2] is called a Duhamel integral which represents the effect in response to the cause. To establish a concrete mathematical link between the cause and effect, $I(t)$ and $O(t)$ must be determined mathematically as functions of time. To calculate the indicial response function, the method of Laplace transformation can be used.

Indicial Response Experiments

Ideally, indicial responses should be measured in one vessel. This is not possible, however, if histological or molecular measurements have to be made at different stages of tissue remodeling in different animals. Furthermore, there is no method to change the hemodynamic stimulus (pressure or flow) as a strictly mathematical step function. In practice, one has to use many animals with approximate steps of flow and then analyze the results by statistical means. Finally, one should change one variable at a time and evaluate the separate effect in turn; e.g., change pressure at constant flow or flow at constant pressure.

Since the experiments are done by approximate step change of blood flow, we have to transform the results to those of exact steps by computation. This can be done if the system is linear with respect to the amplitude of the disturbance about a homeostatic state. Assuming linearity, this can be done through a convolution integral (Eq. 2).

Indicial Response Functions

The physiological significance of IRF analysis is three fold: 1) It allows the reduction of complicated and interwoven sets of experimental data into simple, definitive statements in terms of mathematical functions; 2) Under the linearity assumption, it allows the prediction of 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 $O(t)$ with respect to the amplitude of the stimulus. A system is linear if O is proportional to $\Delta I(0)$ in equation [2]. Otherwise, the system is nonlinear. If a system is nonlinear, but a small change in $\Delta I(0)$

results in a small change in $O(t)$, then Eq. [2] can still be used. If a small change in $\Delta I(0)$ produces a large change in $O(t)$, 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 $\Delta I(0)$ 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 I . 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.

Mathematical Expression of Cause Functions

Blood pressure and flow are a complex function of time and space as is the shear stress acting on the endothelium surface of the vessel. In order to invoke the IRF approach, one must mathematically capture the essential details of the hemodynamic stimuli. The well-known Fourier spectral analysis works well only for strictly periodic or stationary random functions of time (6–8). In the 1950's, McDonald and Womersley and their colleagues demonstrated that the arterial system could be viewed as being in a steady state of oscillation to enable analysis in the frequency domain by Fourier analysis (9). To deal with non-stationary stochastic functions, a number of methods have been introduced, such as the Spectrogram (10), the Wavelet's analysis (11–14), the Wigner-Ville distribution (15,16), the Evolutionary Spectrum (17), the Modal analysis (18), and others; all designed to modify the global representation of the Fourier analysis. They all have some weaknesses as discussed by Huang et al (19,20) who developed the intrinsic mode function (IMF) method. The IMF method minimizes the artifact of the hypothesis of strict periodicity and brings out subharmonic oscillations and other nonlinear mechanics features.

Recently, we obtained continuous data on flow and pressure in a chronically instrumented animal using the first fully implantable telemetry system (21). It was found that the popular methods of Fourier analysis, and wavelets introduce confusing artifacts because they require the hypothesis of stationary random oscillations, and usually miss out on the nonlinear sub harmonic oscillations (22). We found Huang's IMF method invented for study of ocean waves fits the need. This method was first applied to blood pressure in the rat by Fung's group (23). It was illustrated by the change of the pulmonary blood pressure in response to a step change of the oxygen level in the gas that a rat breathes. The pressure signal was treated with the IMF method, and resolved into the mean trends and oscillations about each mean trend. A later study was carried out for blood flow which was analyzed by the IMF-Hilbert Spectrum method and compared with popular methods such as wavelet analysis and principal component analysis (22). A set of "mean trends" was obtained, each of which represents a "mean" value in a definitive sense, and together they represent the mean trend systematically with different degrees of oscillatory content. Correspondingly, the oscillatory content of the signal about any mean trend was represented by a set of partial sums of IMFs. These IMF provide the basis for the mathematical characterization of the cause or stimulus function in the IRF analysis as demonstrated by Fung and colleagues (23,24).

Some Illustratory Examples

To change either flow or pressure separately, we considered two different experimental models. An arterial venous (a-v) fistula creates a sudden increase in flow (step change) followed by a gradual change (with little change in pressure). Obstruction of the CBD causes an analogous increase in pressure with little change in bile flow. The two models are discussed below.

The a-v fistula was created in the right leg of six groups (2 days, 1, 2, 4, 8 and 12 weeks after the fistula) and the vessels in the left leg were used as sham controls (4). The *in vivo*

blood pressure, flow, and femoral outer diameter, and the *in vitro* zero-stress state geometry were measured. The *in vivo* shear rate at the endothelial surface increased approximately as a step function by about 83%, after two days, when compared to the control artery. The arterial luminal and wall area significantly increased post-surgically after 12 weeks. The physical factors (wall shear rate, circumferential stress and midwall strain) that stimulate vascular remodeling were expressed in terms of the IRFs for the three biomechanical parameters (4). In order to compare the relative magnitude of the three biomechanical IRFs, the quantities were normalized with respect to their initial values as shown in Fig. 1. It can be seen that the two major biomechanical stimuli for remodeling are wall shear strain and midwall strain. The midwall circumferential strain has a shorter rise time and a shorter decay time than the wall shear rate. This suggests that the circumferential strain may be an important initial stimulus for remodeling.

The porcine CBD was ligated near the duodenum which increased the duct pressure from 6.4 to 18.3 cmH₂O in the first 12 hours and to 30.7 cmH₂O after 32 days. The remodeling process was studied after 3 hours, 12 hours, 2 days, 8 days and 32 days after obstruction. The time course of change of morphometry (diameter, length, wall thickness, etc.) and mechanical properties (stress, strain, etc.) was documented. 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. When comparing axial and circumferential stress and circumferential strain, it was found that strain recovers more rapidly and more completely than stress as shown in Figure 2.

Strain Homeostasis Hypothesis

The synthesis of the two cited examples supports the well known principle of mechanical homeostasis; i.e., the variation in vessel wall stresses and strains are relatively small under physiological conditions (25). A novel direct finding of this analysis highlights strain as an important stimulus. Any perturbation of mechanical homeostasis leads to growth and remodeling. In this sense, tissue dysfunction may be viewed as an adaptation process gone awry.

In search of further evidence for existence of strain homeostasis in the CV system, we determined the distribution of circumferential stress and strain along the aorta and throughout the coronary arterial tree. We found the stretch ratio and stress vary between 1.2 to 1.6 and 10 to 150 kPa, respectively, along the aorta and LAD arterial tree (26). The relative uniformity of strain (50% variation) from the proximal aorta to a 10 μ m arteriole implies that the vascular system closely regulates the degree of deformation. This homeostasis of strain in the CV system has important implications for mechanotransduction and for vascular growth and remodeling (25,27).

Concluding Remarks

Tissue remodeling is important to physiology and pathophysiology. It is involved in hypertrophy, hypertension, ischemia, atherosclerosis, the success or failure of angioplasty, as well as healing and improvement of health. Tissue remodeling is a very complex phenomenon. The changes in stimulus and response must be measured and the results must be organized into mathematical forms which are suitable for applications. The data must be analyzed with the best computational method, the results must be condensed into concise yet comprehensive mathematical formulas, the constants that characterize these formulas must be determined, and the application of these results to the modeling of growth and remodeling of tissue must be illustrated. Then, with mathematical models, the effects of pressure or flow on the dynamics of growth and remodeling can be channeled into a computational program.

This is a step in the direction of dynamic modeling; i.e., the prediction of the course of change of the tissue in response to a non-stationary blood flow and pressure; and vice versa. Modeling provides guidance to experiments and to the synthesis of novel hypotheses. When successful, the outcome can become predictable and the program may become a clinical routine that benefit healthcare.

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Figure 1. Normalized IRF of shear stress, circumferential stress and midwall strain for femoral artery in flow-overload.

Figure 2. Normalized IRF of circumferential strain, axial stress and circumferential stress for CBD in pressure-overload.