Principles and Practice of Clinical Electrophysiology of Vision

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Kernel Analysis

J. Vernon Odom

The preceding chapter dealt with linear systems and stated that there is no general method of describing nonlinearities. Nevertheless, these are so common and important in the visual system that methods of description are important and none more so than *kernel analysis*. The aims of this chapter are, first, to give a nonrigorous account of this method that will enable the clinical electrophysiologist to use the method and interpret the results and, second, to briefly indicate the rationale for using kernel analysis and the choice of strategy to fit particular situations. Finally, some clinical and experimental results of this method will be given. For a more mathematically rigorous treatment of many of these same points the reader is referred to other sources. [7, 9, 12–14, 16, 17, 20, 23, 26, 27]

The definitions of a linear system are given in the previous chapter. It will be recalled that if the response to a brief impulse is known, the response of a linear system to any other stimulus can be predicted. This is not true of a nonlinear system. Figure 30–1 shows an example. Part A is a diagram of two stimulus pulses—the stimulus readily obtained from Grass stroboscopes, for example; part B shows the response. The early part of the response is shown as a full line. In the absence of a stimulus, the record would continue according to the dotted line, but in the presence of a second flash the record corresponding to the lower full line is obtained. If the responses to the first and second of the paired flashes were equal (a linear system), the upper of the two lines would be followed. Part C shows the difference between the actual response and the larger response expected from a linear system. Note that the waveform (for ease look at the peak times) of the residual "real" second response and also the waveform of the deficit bear a complex relationship to the impulse response. Many systems that are nearly linear have thresholds and saturation points, and stimuli of appropriate intensity can evoke nonlinear behavior. Such nonlinearities can be modeled by electronic components, e.g., rectifiers, amplifiers, filters. In the case of Figure 30–1, which behaves in a way very similar to the electroretinogram (ERG), the nonlinearity occurs at various voltage levels and is time dependent.

Several strategies exist to characterize a system so that its response to an arbitrary stimulus can be predicted. In the time domain these strategies are based on computing cross-correlations between the stimulus and the response.[7, 9, 11, 13, 14, 16, 20, 23, 27] Stimuli used to determine kernels are presented in Figure 30–2. Typical stimuli are (1) "white" noise or (2) pseudorandom sequences (PRS) such as m-sequences. In the frequency domain, the system's responses to a set of sine waves are described by Fourier analysis, and the responses of appropriate order (e.g., second order, etc.) are summed.[11, 12, 17, 26]

When using these input signals, it is possible to calculate a series of integrals that fully characterize the system's response to any arbitrary stimulus. Kernels are the weights of these integrals; as such they are analogous to the coefficients of a polynomial. The zero-order kernel represents the bias or mean response of a system. The first-order kernel, analogous to the polynomial's first-order coefficient, represents the best linear approximation (in a least mean square error sense) of the response elicited by the stimulus and estimates the impulse response. The second-order kernel is analogous to the second-

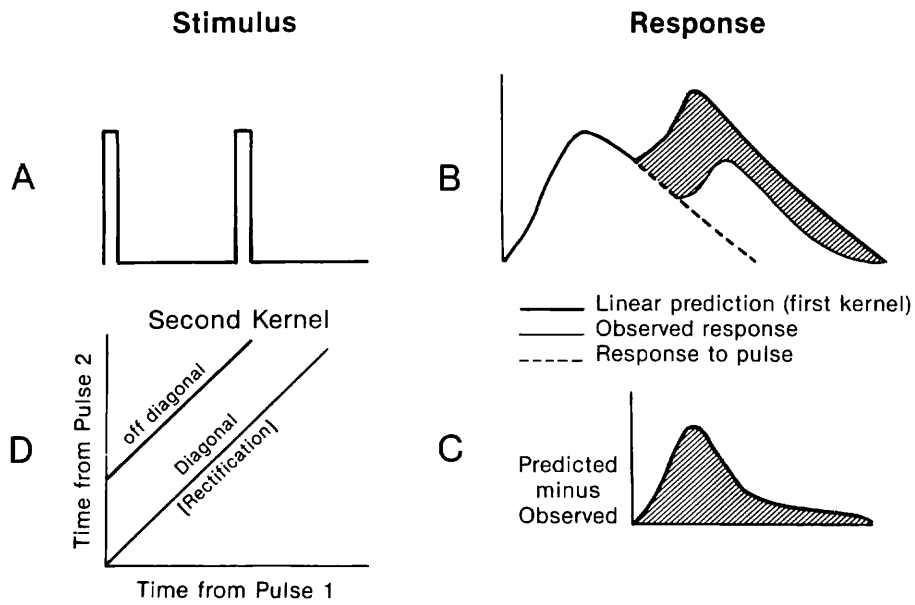

FIG 30–1.
First- and second-order kernels. The four panels illustrate several of the major points of first- and second-order kernels. Panel **A** illustrates two impulses with a fixed separation. Panel **B** illustrates (1) the response to a single pulse, (2) the linear prediction of the response to two pulses with the delay illustrated in panel **A** (the response of two single flashes added together with the appropriate delay), and (3) the obtained response. Panel **C** indicates the difference between the predicted response and the response obtained in panel **B.** Panel **D** illustrates one way of presenting the second-order kernel. The second-order kernel has three dimensions. Time from pulse 1 is on the abscissa, and time from pulse 2 is on the ordinate. The difference between linear predictions and obtained results (e.g., panel **C**) would be plotted either on the z-axis (not displayed) or as contour lines on the xy-coordinates. The main diagonal represents the response when the two pulses were at the same time and reflects second-order nonlinearities related to amplitude differences in the pulses. One physical system with second-order amplitude-dependent nonlinearities is a rectifier. Off diagonals represent the differences between predicted and obtained responses for a specific difference in time between the two pulses. Panel **C** would represent an off diagonal, with the time between pulses illustrated in **A.**

order coefficient in a polynomial equation; it represents the interactions of two stimulus pulses or variations in stimulus pulse amplitude on the response. It is difficult to record enough response samples to characterize higher-order kernels accurately. Consequently, it is uncommon to calculate kernels beyond the second order. Figure 30–3 illustrates some of the difficulties of linear approximations of nonlinear systems. A linear approximation of a nonlinear system varies with the range of stimulus conditions over which the estimate is made.

FIRST-ORDER KERNELS AND SYSTEMS

If a system were linear, the first-order kernel would completely characterize the system and would be exactly equivalent to the normalized impulse response. In a nonlinear system, the first-order kernel represents a linear approximation to the system's impulse response. Because higher-order odd nonlinearities (e.g., third, fifth, etc.) can influence the estimate of the first-order kernel, it does not represent or estimate the system's linear elements or processes directly. However, given a model of the visual system, e.g., a sandwich model, one can evaluate the appropriateness of the models.[7, 14, 16, 17, 26]

The visual system is highly nonlinear. The visual system's nonlinearity is indicated by its response to pattern stimulation, expecially as recorded by visual evoked potentials (VEPs). Figure 30–4 illustrates that a linear system's response to either pattern appearance or reversal as recorded by scalp electrodes cannot be observed if (1) there is no change in the mean luminance with pattern appearance or change and (2) the receptor elements are homogeneously spaced and one assumes that the elements responds symmetrically to light increase and decrease.[16, 30] Despite the visual system's essential

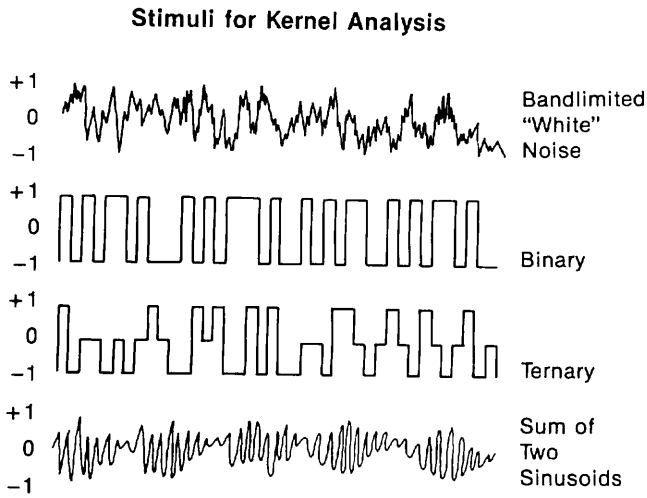

FIG 30–2.
Stimuli for kernel analysis. The values of +1, 0, and −1 represent arbitrary dimensions. They may be thought of as input voltages, logic levels, or intensity levels. **A**, an effort to represent band-limited white noise. It should have a flat frequency spectrum and a gaussian amplitude distribution. White noise may be approximated by using a sum of sinusoids (usually eight or more different frequencies). Binary pseudorandom sequences **(B)**, ternary sequences **(C)**, and sums of two sinusoids **(D)** have useful properties. Deterministic signals such as **B**, **C**, and **D** may have greater contrast, are computationally easier to analyze, and may be averaged.

nonlinearity it is possible to calculate a first-order kernel.

SECOND-ORDER KERNELS

In the time domain, the second-order kernel is a three-dimensional construct that represents the response as a function of time from a first impulse and a second impulse. It indicates the nonlinear effect of the time between two pulses on the response.[7, 9, 14, 27] Usually, the second-order kernel is plotted as a two-dimensional contour map (see Fig 30–1,D) with the x- and y-axes representing time from the first and second pulses, respectively. In the frequency domain, the second-order kernel is the sum of all of the second-order frequencies present in the response.[11, 12, 26]

STIMULI

Theoretically, gaussian white noise is the most appealing stimulus with which to characterize a system. It has equal power at all frequencies and a gaussian amplitude distribution and is equivalent to all frequencies of sine waves, with their phases random with respect to one another. If white noise has a gaussian amplitude distribution, most of the changes in stimulus values are small, and if the stimulus is light, the nonnegative nature of light requires a truncation of range about the mean value.

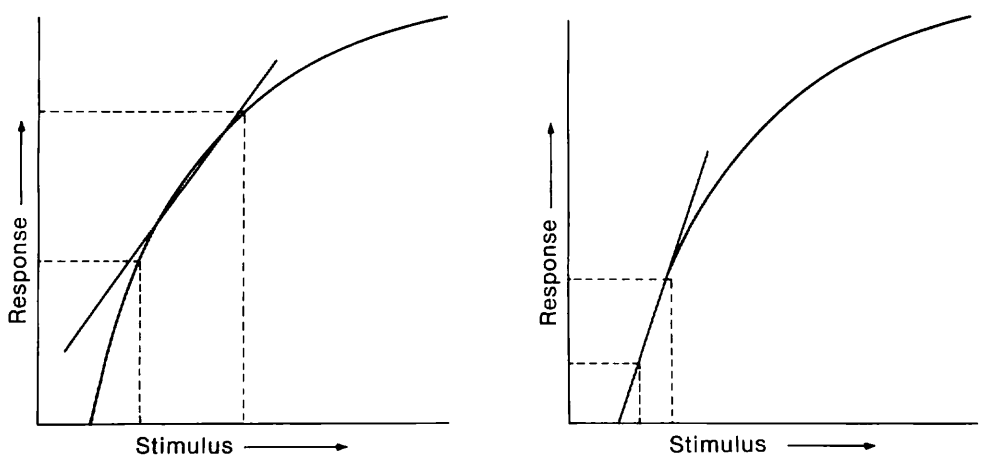

FIG 30–3.
Linear approximations of the response of a nonlinear system. The *dotted lines* extending to the abscissa indicate the limits of the stimulus conditions; those extending to the ordinate indicate the limits of the observed responses. The *straight lines* were best fit through the indicated regions. Linear estimates of a nonlinear process will be different depending on the input conditions, e.g., mean luminance or contrast, and are highly dependent on the stimulus values used. Consequently, different experiments can yield very different estimates of the first-order kernel. The presence of a strong reliable first-order kernel for a particular stimulus range does not mean that the system or the response is linear.

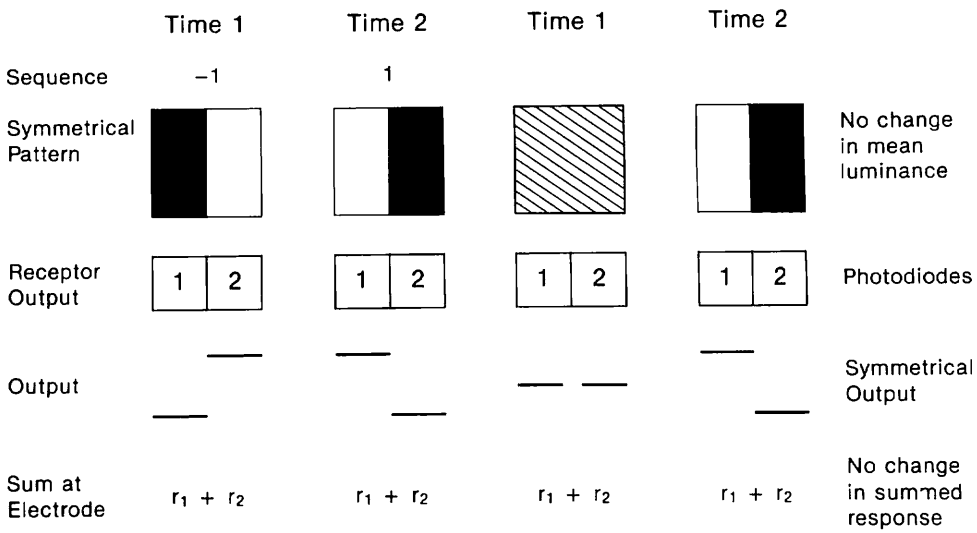

FIG 30–4.
If the visual system were composed of linear elements, the response recorded by ERG and VEP electrodes to pattern reversal and to pattern appearance would be zero. The *top section* of the figure represents the stimuli observed at two time periods, time 1 and time 2. The *second row* indicates the two sensors that detect the light level in the two regions of the figure. The *third row* represents the voltage outputs of the sensors at the two times, low output for dark and higher outputs for light. The *fourth row* indicates that any ERG or VEP electrode sums the output of the two sensors. In each case the sums are the same in time 1 and time 2, and there would be no change in response recorded by the electrode.

Therefore, the signal-to-noise ratio of responses elicited by white noise stimuli is often small and requires longer recording periods to acquire reliable kernel estimates. The same considerations apply to sums of sinusoids. The larger the number of frequencies used, the lower the maximum contrast of individual sine waves because the total contrast of the sum of sinusoids must be 100% or less. For example, if one employed a sum of eight sine waves, the maximum contrast of any one frequency would be about 12%.

If a PRS of two or three stimulus levels or a sum of sinusoids with two or three sine waves is selected as the stimulus, the system characterization will be less complete, but there will be an improved response signal-to-noise ratio because the stimuli can be presented at higher contrasts. Therefore, shorter recording periods may be used to acquire the response. Because the stimulus is deterministic, more efficient analysis procedures may be used to calculate the kernels, and the responses may be signal averaged.

When determining kernels from PRS several constraints are important. First, if a binary PRS controls stimulus polarity, it is impossible to establish the main diagonal of the second-order kernel (Table 30–1). Second, when using PRS, general principles of digital sampling must be observed. The accuracy of the kernels is primarily determined by the total duration of the experiment,[5, 27] and the highest-order kernel that can be calculated is limited by the recording period.

To avoid what are termed deconvolution errors in kernel estimation, the stimulation frequency should be high relative to the high-frequency limit of the visual system (e.g., the ERG or VEP critical flicker fusion frequency) at the particular mean luminance and contrast selected. To avoid transduction errors

TABLE 30–1.
Effect of Binary Sequence Control

Sequence Value	Popularity		Change/Reversal	
	Light	Pattern	Light	Pattern
−1	off	1	off	1
+1	on	2	on	2
+1	on	2	off	1
−1	off	1	off	1
+1	on	2	on	2
−1	off	1	on	2
+1	off	1	off	1
−1	off	1	off	1
+1	on	2	on	2
−1	on	2	on	2
−1	off	1	on	2
+1	on	2	off	1

the stimulus must be accurately presented, i.e., the stimulus-generating interface must be able to follow a stimulus of at least twice the maximum stimulus frequency. For example, a video display cannot follow stimuli of greater than 30 Hz in the Americas or 25 Hz or so in Europe and Asia. The luminance of xenon flash units often varies with the frequency or interstimulus interval. If a xenon flash is used, it must be stable in these characteristics. A cathode ray tube display, a light-emitting diode display, or a bright light with a shutter or chopper as the stimulus should work well.

To understand the meaning of a kernel, one must know which stimulus events were controlled by the PRS (see Table 30–1). If the stimulus is light and a PRS controls stimulus polarity (light on or light off), the impulse is a rapid change from the minimum light level to the maximum light level employed in the PRS and has a duration of one time period in the PRS. If the stimulus is pattern, the PRS may control stimulus polarity (e.g., pattern phase 1 or 2) or the presence or absence of a reversal. The impulse is a pattern reversal in the second case. In the first case, it is the rapid change from pattern phase 1 to phase 2 and back to phase 1. Only a few VEP or ERG experiments have employed kernel analysis.[1–6, 8, 13, 15, 17–22, 24, 25, 28–30] Determinations of the first- and second-order kernels permit the detection of different frequency regions of VEP activity[13, 14, 17] and isolation of the characteristics of different stages of monocular[5, 11, 30] and binocular[1, 10, 29] visual processing and demonstrate the feasibility of using kernel analysis in clinical situations.[3, 4, 15] The isolation of particular pathways or stages of visual processing open exciting possibilities for clarifying the nature of disease processes or detecting and diagnosing different diseases.

VEP[4] and cone ERG[3, 5, 8] first-order kernels elicited by luminance are reported to be acquired more rapidly and/or to be more reliable than their averaged equivalents. Cone ERG first-order kernels are abnormal in some amblyopes.[6] Rod ERG first-order kernels are considerably smaller than the clinical dark-adapted flash ERG[5] because (1) it is difficult to achieve the same level of dark adaptation in the PRS conditions as in the clinical situation, (2) the flash intensity is usually lower, and (3) the clinical ERG reflects linear and nonlinear processes.

Pattern reversal stimulation has been employed successfully to determine first-order kernels of VEPs[6, 15] and ERGs[6] (see Table 30–1). Patients with multiple sclerosis generally have altered VEP pattern reversal kernels,[15] and amblyopes have smaller VEP and pattern ERG responses in the amblyopic eye.[6]

Recently, arrays of several hundred light sources have been employed to estimate ERG and VEP first- and second-order kernels. From these kernels it is possible to compute ERG[25] or VEP[24] visual fields with finer spatial resolution than automated perimetry can in a recording session of less than 30 minutes for both eyes. ERG fields are abnormal in blind spot syndrome and age-related maculopathy patients.[25]

The physiological substrate of kernels is not well understood. For example, the A- and B-waves of the ERG first-order kernel may have the same retinal origins as the ERG a- and b-waves.[5, 8] The physiological origin of the ERG second-order kernel is unknown but may be largely determined in the inner retina. As understanding of the origin and meaning of kernels advances, they will become more widely used in clinical situations and aid in the more precise identification of the origins of deficits created by ophthalmic diseases.

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