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A more accurate model of dark-adapted ERG kinetics

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Abstract

Accurate models of the electroretinogram are important both for understanding the multifold processes of light transduction to ecologically useful signals by the retina, but also its diagnostic capabilities for the identification of the array of retinal diseases. The present neuroanalytic model of the human rod ERG is elaborated from the same general principles as that of Hood & Birch (1992), but incorporates the more recent understanding of the early stages of ERG generation by Robson & Frishman (2014). As a result, it provides a significantly better match in six different waveform features of the canonical ERG flash intensity series than previous models of rod responses.

Introduction

The ERG is a powerful non-invasive assay of the layer-by-layer functionality of the human retina. In order to fully comprehend the underlying retinal functions, however, it is important to have a comprehensive model of the ERG dynamics that can quantify the changes in their properties beyond the basic measures of a-wave and b-wave amplitudes and peak times. The approach taken here is neuroanalytic, modeling based on known properties of the underlying neural circuitry, rather than purely mathematical components. All the modeling papers referenced in the present analysis have taken this approach.

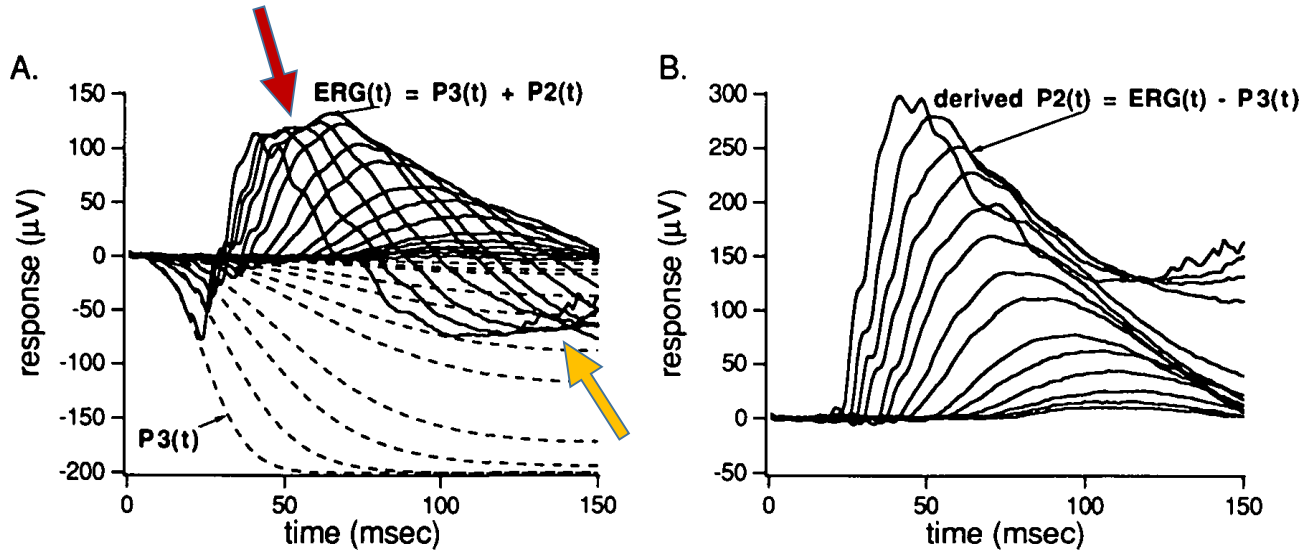

Fig. 1. Empirical derivation of the ERG P2 component underlying the b-wave for canonical dark-adapted flash ERG series (from Hood & Birch, 1992, their Fig. 6).

A relatively complete model of dark-adapted rod ERG kinetics as a function of flash intensity was developed by Hood & Birch (1992, 1993), whose data for the dark-adapted flash response as a function of intensity are depicted as the solid curves in Fig. 1A. Both the initial negative a-wave and the larger positive b-wave increase gradually in amplitude and have progressively decreasing peak times, with the b-wave amplitude tending to saturate at the higher intensities (red arrow). It is noteworthy that the data cross over the baseline to become negative at long durations, even more negative for the smaller flash intensities than the a-wave peaks (yellow arrow).

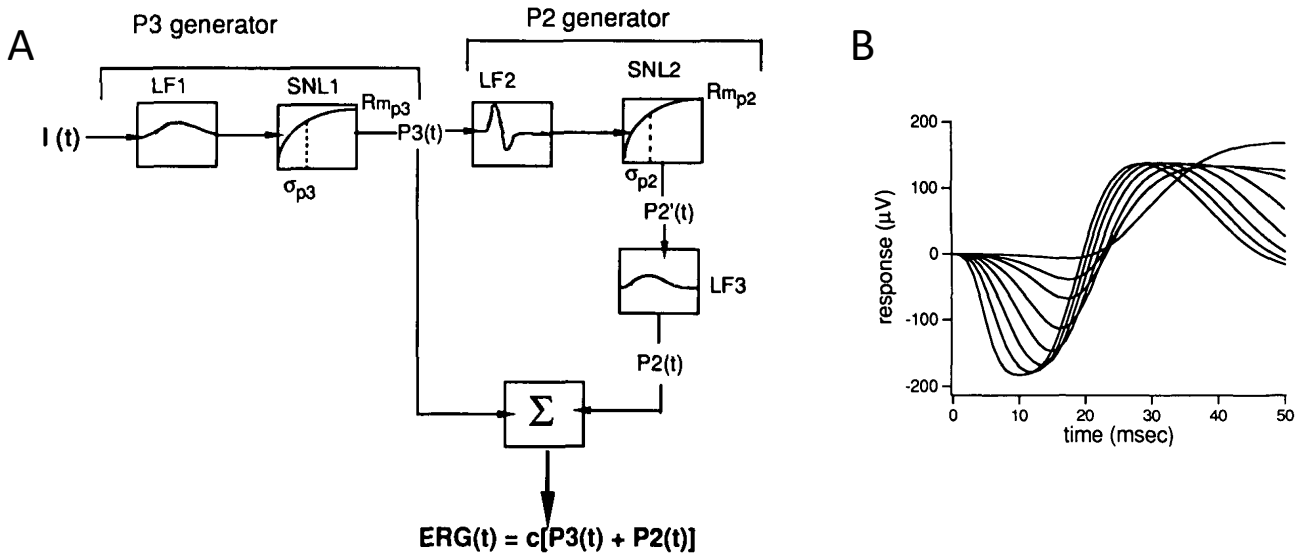

Fig. 2. Theoretical model of the a/b-wave complex (from Hood & Birch, 1992, their Figs. 8 & 9).

The initial approach to neuroanalytic modeling of these ERG functions is depicted in Fig. 1, where Hood & Birch fitted the initial a-wave portion of their stack of flash responses with a set of model step responses (Fig. 1A). The resulting fits were subtracted from the whole ERG to provide an estimate of the prevailing b-waves at each intensity (Fig. 1B). Notice that this derivation suggests that the non-monotonic variation of the b-wave peak amplitude with intensity (data in Fig. 1A, red arrow) derives from a monotonic increase of the derived P2 wave (Fig. 1B) summing with the saturating receptor potential (P3; dashed lines). Thus, the results imply that both the inferred receptor potential and bipolar -cell response (P2) are non-linear, though in different ways.

A key feature of their analysis is that the underlying model P3 component (the receptor potential from cat retina derived by Granit, 1933, as the PIII component) is much slower than the ERG b-wave, effectively operating as a graded step response for the early time period of the ERG analyzed here, especially when it runs into the saturation range at the higher intensities. A notable aspect of their flash ERG data is the late crossover of the waveforms after about 70 ms (Fig. 1A) to a negative-going response comparable in amplitude with the early negative peak of the a-wave. Notice also that these late-phase responses show a roll-back towards the baseline for higher-intensity flashes (Fig. 1A, orange arrow). These will prove to be discriminative features for the present ERG model (see discussion of Fig. 3).

The authors followed up the analysis of Fig. 1 in the same paper with a full model of the a/b-wave complex within the first 50 ms, as depicted in Fig. 2. The basic concept is of an impulse response generator following by a static compressive nonlinearity for the receptor potential (P3), summing with the output of a second stage that takes the temporal derivative of the resulting P3 and puts it through a second static nonlinear following by a second-stage filter, giving this second stage the appropriate dynamic nonlinearity. The resulting dynamic model expresses many of the features of the dark-adapted ERG flash series, but has the following shortcomings:

1. The a-waves are too broad, with much larger amplitudes than the empirical data.
2. The b-wave peaks do not decrease as intensity is reduced.
3. The model response does not account for the negative crossover seen in the empirical responses at long durations, which is comparable in magnitude to the negative peak of the a-wave (See Fig. 1).
4. Other issues addressed in Results.

A more recent modeling effort focused on the rod outer segment contribution to the transretinal macaque ERG (Robson & Frishman, 2014, their Fig. 5). They used a Hodgkin-Huxley style electronic ladder-network model to capture the photoreceptor current and voltage dynamics (Fig. 3). Their simulations reproduced the well-known behavior from single-cell recordings that the rod photocurrent has an impulse response peaking at about 100 ms, limited by an instantaneous saturating nonlinearity of the form derived empirically by Granit (1933) for the P3 ERG component.

Methods

The present simulations were programmed in Matlab. the receptor potential is modeled as the simple Granit (1933) form of the cat receptor potential. The P2 generator is modeled as a transient generated by the derivative of the P3 wave, such as in the transmission dynamics of the rod-bipolar synapse, as in the Hood & Birch (1992) model. The model P2 wave is then generated as aa filtered version of the generator transient, and the ERG is obtained as the sum of the model receptor potential (P3) and bipolar response (P2).

Results

Figure 3 contrasts the Hood & Birch simulation (Fig. 3B) of their flash intensity ERG series (Fig. 3A) with the results of the present simulation (Fig. 3 C-F) for the receptor potential (Fig. 3C). The resulting ERG waveform predictions (Fig. 3F) have a late crossover to a negative signal beginning at about 70-140 ms, depending on flash intensity, and remain strongly negative thereafter, as do the empirical ERGs over this 150 ms timecourse (Fig. 3A). Note that the full model replicates the feature in the data that, for the smaller flash intensities, the late crossovers become far more negative than the small a-waves at those intensities.

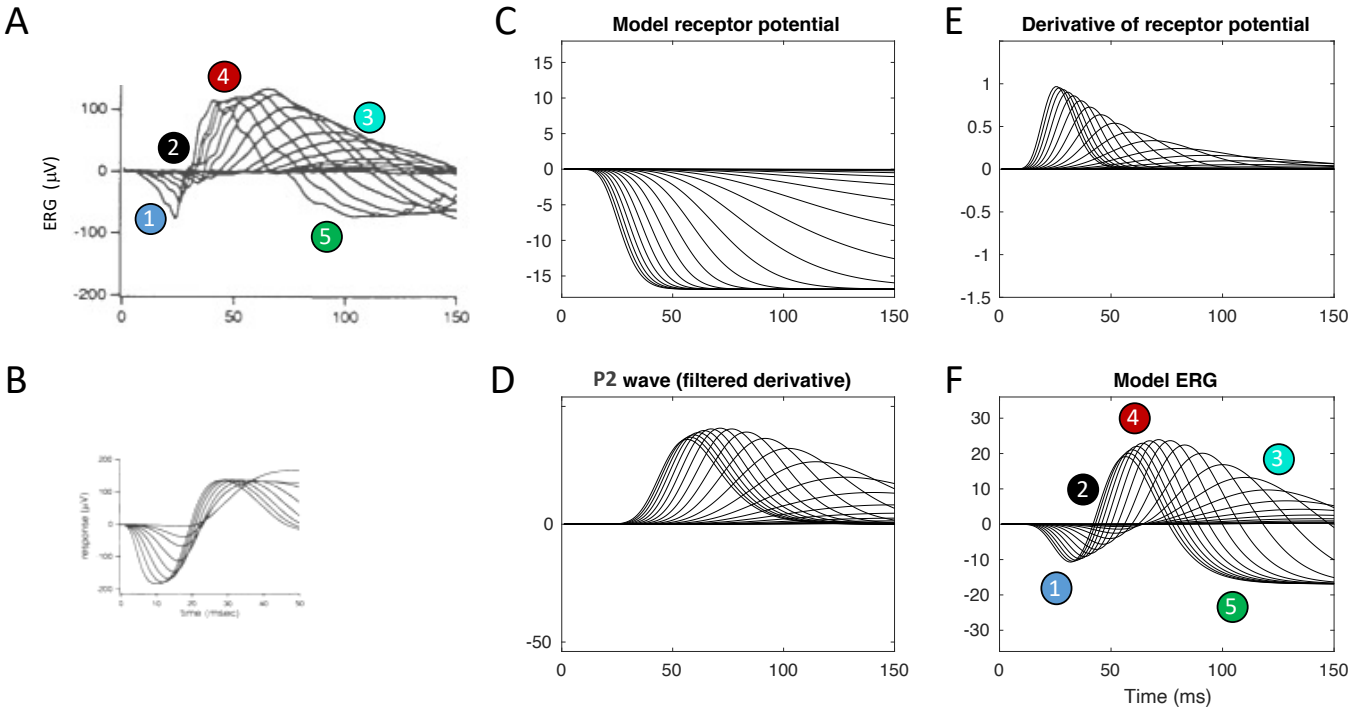

Fig. 3 A. Dark-adapted flash ERG responses from Hood & Birch (1992). The following features are not captured by the Hood & Birch model: 1) sharp a-wave; 2) advance in b-wave peak time with intensity; 3) increase in b-wave amplitude with intensity; 4) reduction in b-wave amplitude at high intensity;and 5) crossover of post b-wave response to negative signal comparable in amplitude with the positive b-wave. B. Model ERGs from Hood & Birch (1992) scaled to the same coordinates as for (A). C-E. Present ERG model stages: simple photoreceptor potential (C), P2 transient pulse generator (E), monophasic P2 wave (D), and predicted overall ERG waveform (F).

Discussion

The present neuroanalytic model, though based on the same general principles as that of Hood & Birch (1992) depicted in Fig. 2, provides a significantly better match to their canonical data than does their own model in relation to the five different features enumerated in Fig. 3A, and is also compatible with the more recent modeling of the early stages of ERG generation by Robson & Frishman (2014).

One of the key improvements in the present model is in the way the intensity nonlinearity of the receptor potential is introduced as a gain control mechanism rather than a static nonlinearity, providing a much better match to the rise in b-wave amplitudes of the empirical waveform with intensity (Fig. 3A,F) than the fixed b-wave amplitude of the Hood & Birch simulation of Fig. 2B.

A second compressive gain-control was required to capture the empirical reduction in b-wave amplitude at the highest intensities (feature 4 in Figs. 3A,F). This compressive function had to be located between the two convolution stages of the model in order to restrict the amplitude reduction to the P2 wave *per se*. Without it, the P2 amplitude would continue to rise in the manner of the P2 generator response of Fig. 3E, rather than saturating.

A third key feature is the crossover of the later response to a strong negativity following the b-wave peak, which is absent in the Hood & Birch model. This is evidently an important aspect of the empirical responses without which the model would be incomplete. Note that this part of the ERG time course is well beyond the temporal range that is addressed by the model of Robson & Frishman (2014).

In several respects, therefore, the present model offers a significant advance over previous models, accounting for the full dark-adapted ERG flash response intensity series, and identifying discriminative features that allow some of the underlying neural contributions to the overall ERG to be quantified.

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