Inequalities governing the peripheral spike activity

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A fundamental inequality governing the spike activity of peripheral neurons is derived and tested against auditory data. This inequality states that the steady-state firing rate below saturation lies between the arithmetic and geometric means of the spontaneous and peak activities during adaptation. Implications towards the development of computational auditory models are explored.

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I. INTRODUCTION

Rate coding of auditory neurons is the first step in the processing of sound by the nervous system (Heil and Peterson, 2015; Kiang, 1965). The mechanism of transduction from sound to neural response is an important but unsolved problem, e.g. Meddis et al. (2010); Rudnicki et al. (2015).

A recent paper showed that intensity coding in many modalities and animal species follows a simple equation (Wong, 2021). This equation governs the three fixed points in a typical adaptation curve: The steady-state activity after long term stimulation (SS) equals the geometric mean of the spontaneous activity (SR) and the peak activity (PR) just after stimulus onset. That is,

$$SS = \sqrt{PR \times SR}$$

(1)

This relationship was tested against 250 measurements of adaptation across many sensory modalities (hearing, vision, taste, smell, touch, etc.), animals of different phyla, and in data spanning nearly 100 years since the original recordings of Edgar Adrian (Adrian and Zotterman, 1926a,b). This suggests that (1) is a fundamental equation of neurophysiology.

While (1) was found to work in different modalities, hearing is where the testing of adaptation can be carried out most rigorously. There are a number of reasons for this. Adaptation involves repeated measurements from stimuli held constant. The signal can be controlled to a high degree of accuracy unlike in other modalities like temperature, taste and smell, e.g. Baylin (1979). Secondly, measurements of visual ganglion cells often involve lateral contributions from other units making it difficult to probe single unit responses to
light (Enroth-Cugell and Shapley, 1973). Thus, in many respects, the auditory system is ideal for systematic studies in adaptation.

There are a number of auditory studies that have explored how adaptation changes as a function of stimulus parameters. When (1) is obeyed across different stimulus intensities, the predicted relationship between SS and PR is a straight-line on a double-log plot with slope of 1/2. Several studies were found to obey this relationship, e.g. Fay (1978); Sumner and Palmer (2012); Westerman and Smith (1984); Yates et al. (1985). See Wong (2021) for more details.

II. VIOLATIONS TO THE GEOMETRIC LAW

Consilience can be used to prove the generality of (1) (Wilson, 2000). When scores of unrelated measurements obey the same law under vastly different conditions, this constitutes strong evidence that the law is obeyed widely. However, consilience is less useful in the determination of precise mathematical relationships.

One example would be the adaptation measurements reported in Smith and Zwislocki (1975). Virtually all of the data show a strong linear relationship between peak versus steady-state activity (see panels a-g in Fig. 1). This indicates a violation of (1). The paper goes one step further to propose a remarkably simple equation governing the peak and steady-states: $SS = \frac{PR}{2.5}$. While this equation appears to fit the data well, it cannot be the correct functional relationship between the steady-state and peak activity for the following reason: A unit that undergoes adaptation to a stimulus level of zero intensity must satisfy the condition that both PR and SS equal the spontaneous activity or SR. A
more sensible expression relating SS to PR that can account for the straight line dependence will be derived later.

The geometric law was first predicted theoretically in Wong (2020). We will quickly review this theory before deriving a new inequality which will encompass both the geometric law as well violations to this law. Implications of the inequality to the development of computational auditory models are also discussed.

III. A THEORETICAL BASIS OF THE PERIPHERAL ACTIVITY

An approach to understanding the rate coding of sensory peripheral neurons in terms of measurement uncertainty or entropy was most recently expounded in Wong (2020) following developments in Norwich (1977, 1993); Norwich and Wong (1995); Wong (1997, 2013). The idea behind the theory is straightforward: The sensory receptor samples the stimulus repeatedly and averages these samples. By the central limit theorem, the uncertainty in the sample mean is normally distributed when sample size is large. Calculating the Shannon entropy under finite resolution yields an equation relating entropy to the variance of the measurements and the sample size. Three final steps are required to obtain an equation governing the rate response. First, the association of the variance with the mean of the stimulus (i.e. the strength of stimulation) via a power function; second, the sample size approaches its optimal value by a first-order relaxation process; third, the association of firing rate with the measurement uncertainty or entropy. This last equation in particular seeks to change the very nature of how we understand the sensory coding of intensity (Norwich, 1993).
Written out in full, the equations are

\[ F = kH \]  \hspace{1cm} (2)

\[ H = \frac{1}{2} \log \left( 1 + \frac{\beta (I + \delta I)^p}{m} \right) \]  \hspace{1cm} (3)

\[ \frac{dm}{dt} = -a(m - m_{eq}) \]  \hspace{1cm} (4)

\[ m_{eq} = (I + \delta I)^{p/2} \]  \hspace{1cm} (5)

where \( F \) is the firing rate of the peripheral neuron, \( H \) the entropy, \( I \) the stimulus magnitude and \( t \) the duration of the stimulation. \( m \) is the sample size and \( m_{eq} \) its optimal or equilibrium value. The other terms are parameters which are assumed to be positive and constant for a given unit. These equations were developed without consideration of underlying mechanism, derived in full in Wong (2020) and tested successfully against a number of experimental paradigms including experiments conducted on auditory units. The evaluation of (2-5) requires knowledge of the five parameters \( k, \beta, p, \delta I, a \) which are obtained by fitting the equations to data. But their precise determination can be difficult as the equations are prone to overfitting.

Adaptation is defined as the condition where a unit is initially in silence and in steady-state; a stimulus is turned on and held constant for \( t \geq 0 \) (Benda and Tabak, 2014). We can solve for the adaptation response as follows. The process is first described conceptually. A change in the stimulus level brings about measurement uncertainty and the sample size is increased as a consequence. The optimal sample size is calculated from (5) which is dependent on intensity, and solving the differential equation in (4) gives the change in sample size as a function of time. Since the numerator of the argument inside the logarithm
in (3) is constant, increasing the value of \( m \) results in a monotonic fall in uncertainty \( H \) (and therefore \( F \)) giving rise to the decay in spike activity observed in adaptation. Next we proceed to a mathematical description.

A constant level of stimulus implies that \( m_{eq} \) in (5) is constant, i.e. \( m_{eq} = (I + \delta I)^{p/2} \) where \( I \) is the level of stimulation. From this, we solve for the sample size \( m \) as a function of time from (4) to obtain

\[
m(t) = m(0) e^{-at} + m_{eq} (1 - e^{-at})
\]  

(6)

Due to the continuity condition of (4), \( m(0) \) equals the value of \( m \) just prior to the stimulus being turned on. For \( t \leq 0 \), we have \( I = 0 \) and the unit is in steady-state. Therefore, \( m(0) = \delta I^{p/2} \). Substituting \( m \) into (3) and (2) is all that is needed to solve the neuronal response to a constant stimulus.

The solutions of these equations to a step function as well as to many other input types (square wave, sinusoidal, ramp, etc) compare well to experimental measurements and are detailed in Wong (2020). The response can also be carried out numerically using just a few simple lines of computer code (see Appendix A). There are, however, several drawbacks to this approach. The predicted response falls short in two key aspects: (a) There is no saturation of response at high intensities; (b) The predictions are purely deterministic and do not account for the stochastic nature of the response.

Next we turn to the derivation of several inequalities governing the predicted response of adaptation activity.
IV. INEQUALITIES CONCERNING PERIPHERAL ACTIVITY

We begin by defining $x = \beta \delta I^{p/2}$ and $y = \beta (I + \delta I)^p / \delta I^{p/2}$. Note that $0 \leq x \leq y$ due to the fact that all of the parameters are positive and $I \geq 0$. We also set $k/2 = 1$ as it has no bearing on the results.

From this, the spike activity $F$ at arbitrary time $t \geq 0$ is obtained by substituting (6) into (3) and (2) to obtain

$$F = \frac{1}{2} k \log \left( 1 + \frac{\beta (I + \delta I)^p}{\delta I^{p/2} e^{-at} + (I + \delta I)^p / (1 - e^{-at})} \right)$$

$$= \log \left( 1 + \frac{xy}{\alpha x + (1 - \alpha) \sqrt{xy}} \right)$$

where $\alpha = e^{-at}$. Since $t \geq 0$, both $\alpha$ and $1 - \alpha$ are non-negative numbers. Observe that

$$F \geq \log \left( 1 + \frac{xy}{\alpha \sqrt{xy} + (1 - \alpha) \sqrt{xy}} \right) = \log (1 + \sqrt{xy})$$

and

$$F \leq \log \left( 1 + \frac{xy}{\alpha x + (1 - \alpha) x} \right) = \log (1 + y)$$

where $x \leq \sqrt{xy} \leq y$ was used. We recognize the lower bound in (9) to be the activity as $t \to \infty$ in (8) and the upper bound in (10) to be the activity as $t \to 0$. Moreover, since $\log (1 + y)$ is the largest attainable value of (8), we formally define this as the peak activity $PR = \log (1 + y)$ and the steady-state activity $SS = \log (1 + \sqrt{xy})$. Thus, the equations show that $F$ is bounded by both the peak and steady-state activities during adaptation.

Next we show that the steady-state activity obeys the inequality

$$\sqrt{PR \times SR} \leq SS \leq \frac{PR + SR}{2}$$
where \( SR = \log (1 + x) \) is the spontaneous activity obtained by substituting \( \lim_{I \to 0} y = x \) into the definition of SS. That is, the steady-state activity is bounded by the geometric and arithmetic mean of the spontaneous and peak activities. This remarkable result is independent of intensity or the choice of any of the parameters in the equation \( k, \beta, p, \delta I, a \).

First, we establish the upper bound for SS:

\[
\frac{PR + SR}{2} = \frac{\log (1 + x + y + xy)}{2} \geq \frac{\log (1 + 2\sqrt{xy} + xy)}{2} = \log (1 + \sqrt{xy}) = SS
\]

where we have used \( \sqrt{xy} \leq (x + y) / 2 \) for \( x, y \geq 0 \). The lower bound requires the observation that if \( \log f(z) \) is a twice differentiable function that is concave with respect to \( u = \log z \) then

\[
\log f \left( e^{u_1} \right) \geq \log \left( \frac{f(e^{u_1}) + f(e^{u_2})}{2} \right) \geq \log \sqrt{f(e^{u_1}) f(e^{u_2})}
\]

or, in terms of \( z \), we have

\[
f \left( \sqrt{z_1 z_2} \right) \geq \sqrt{f(z_1) f(z_2)}
\]

Choosing \( f(z) = \log (1 + z) \) provides the inequality needed for (11). That is,

\[
SS = \log (1 + \sqrt{xy}) \geq \sqrt{\log (1 + x) \log (1 + y)} = \sqrt{PR \times SR}
\]
We check for concavity of $f(z)$ by evaluating the second derivative of $\log f(e^u) = \log \log (1 + e^u)$ with respect to $u$:

$$
\frac{d^2 \log f(e^u)}{du^2} = \frac{e^u [\log (1 + e^u) - e^u]}{(1 + e^u)^2 \log^2 (1 + e^u)} < 0 \quad (20)
$$

where the second line is due to the inequality $\log(1+z) < z$ for $z = e^u \geq 0$. Thus $\log \log(1+z)$ is concave with respect to $\log z$, and both the lower and upper bounds are now proved in full.

Finally, there is a weaker inequality that can be obtained from (11), but one that does not require knowledge of SR. Since $SR \geq 0$, we conclude trivially that $SS \leq PR/2$. That is, the steady-state activity cannot exceed one half of the peak activity.

V. RESULTS AND DISCUSSION

Fig. 1 shows auditory adaptation data from multiple studies plotting steady-state (SS) versus peak activity (PR) together with the theoretical bounds predicted by (11). It is important to remember that there are no fitted parameters required to plot these bounds. All that is needed is knowledge of SR which can be obtained directly from data measurements. Fig. 1 includes all studies of peripheral measurements of auditory adaptation measured across different intensities known to the author. These studies encompass measurements from a number of animal species including guinea pigs (a-g) Smith and Zwislocki (1975) and (m-p) Yates et al. (1985), gerbils (h-l) Westerman and Smith (1984), ferrets (q) Sumner and Palmer (2012) and fish (r) Fay (1978). Overall, the agreement between data and theory
is good. One should be mindful that the bounds are not statistical in nature as they are derived from deterministic equations and are only expected to be satisfied on average. Panel (f) (among others) is worth highlighting. In this case, the spontaneous activity is low enough to take $SR \approx 0$. As such, (11) simplifies to $SS \leq PR/2$, and SS is restricted to lie below the diagonal of the plot. Finally, it should be mentioned that while the number of detailed adaptation studies carried out in hearing is limited, since the lower bound (geometric mean law) is also obeyed to good approximation in other modalities (Wong, 2021), it is likely that (11) is observed widely in all of sensory peripheral activity.

The inequality also explains the origins of the geometric mean law as well as a new arithmetic mean law. Consider (3) which is in the form of $\log(1 + z)$. The lower bound occurs when $z = \beta (I + \delta I)^p / m \ll 1$ is satisfied for all three quantities: $SR$, $PR$ and $SS$. Taking $\log(1 + z) \approx z$ allows for us to derive the lower bound $SS = \sqrt{PR \times SR}$ which is the geometric mean. Alternatively if $z = \beta (I + \delta I)^p / m \gg 1$, taking $\log(1 + z) \approx \log z$ gives the upper bound $SS = (PR + SR) / 2$ which is the arithmetic mean. For small $SR$, the arithmetic mean relationship also provides a way to understand the empirical equation proposed in Smith and Zwislocki (1975): $SS = PR/2.5$. While the theoretical slope overestimates the value found empirically ($1/2.5$), this is easily explained: Data falling below the upper bound can be force-fitted to a straight line but with slope less than $1/2$. The arithmetic mean law also satisfies the correct limiting case for $I = 0$ (adaptation in the limit of zero stimulus) unlike $SS = PR/2.5$.

Finally, since the form of the equations (2-5) remain unchanged for all values of intensities, the derivation in the previous section can be generalized to any arbitrary transient response,
FIG. 1. Steady-state activity plotted versus peak activity for a number of studies. In all panels, the dashed lines show the theoretical upper and lower bounds of (11). No fitted parameters were required to plot these bounds. SS vs PR from (a-g) single or averaged guinea pig fibre recordings (figs. 11a-d, 12, 17a and 4a) Smith and Zwislocki (1975); (h-l) single fibre gerbil recordings (figs. 4 and 5) Westerman and Smith (1984); (m-p) single guinea pig fibre recordings (figs. 1 and 2) Yates et al. (1985); (q) averaged ferret data (fig. 6) Sumner and Palmer (2012); (r) saccular nerve fibres of goldfish (fig. 3) Fay (1978).

not just that of adaptation from silence. Given a unit with steady-state level of activity adapted to a particular stimulus level, if the unit is perturbed by a sustained change in the stimulus level, the resulting new steady-state activity will satisfy the same inequality with the geometric and arithmetic means calculated from the original steady-state and the peak value. Therefore, (11) is expected to be obeyed for the termination of a signal (i.e. a recovery response), as well as for any type of stimulus staircase. Some preliminary evidence can be found in Table 1 and Fig. 2 of Wong (2021).

VI. IMPLICATIONS FOR MODELS OF AUDITORY TRANSDUCTION

The inequalities considered above are derived from a theory that is free from the consideration of mechanism. However, non-mechanistic theories work hand-in-hand with mechanistic models to help further the understanding of sensory transduction. This section is devoted to bridging between these two approaches.
A. The inequality and computational auditory systems

A number of mechanistic models have been proposed describing the process of generating the peripheral auditory spike response, e.g. Eggermont (1973); Meddis (1986); Schroeder and Hall (1974); Smith and Brachman (1982); Westerman and Smith (1988). For an extensive review of past models see Hewitt and Meddis (1991); Zhang and Carney (2005). There are also more extensive end-to-end computational systems which attempt to model the entire process from sound to spike response. Such examples include the MATLAB Model of Auditory Periphery (MAP) (Meddis, 2011) and its earlier version, the Development System for Auditory Modelling (DSAM) (O’Mard, 2021), as well as the series of developments that comprise the Zilany-Bruce-Carney model (henceforth referred to as ZBC) (Bruce et al., 2018; Carney, 1993; Heinz et al., 2001; Zilany et al., 2014). They take sound inputs and generate the associated animal-specific spike rate response from auditory neurons. Both are computational auditory systems: a collections of models from various contributors which can account for the outer, middle and inner ear characteristics as well as the inner hair cell-auditory nerve synapse to model the process of neurotransmitter release determining spike activity. A first step is to use these computational systems to see how the predictions compare with the inequality derived earlier. Using default parameter settings in each of the models (see Methods), a comparison is made between MAP, DSAM and the two latest version of ZBC in Fig. 2. Each simulator was used to calculate the adaptation response to constant sinusoidal pure tones of length 200 ms of varying intensities up to 40 dB and the responses were averaged before extracting SR, PR and SS. Interestingly, the results track
both the upper and lower bounds, but most importantly they fall within the inequality. Indeed, this should not come as a surprise: The systems were developed and evaluated with many of the same data sets from Fig. 1. Further investigation is needed to better understand how these responses are generated.

FIG. 2. Steady-state (SS) versus peak activity (PR) simulated with the (a) MATLAB model of the auditory periphery (MAP) (Meddis, 2011), (b) Development System for Auditory Modelling (DSAM) (O’Mard, 2021), (c) Zilany-Bruce-Carney 2018 model (Bruce et al., 2018) and (d) Zilany-Bruce-Carney 2014 model (Zilany et al., 2014). The dotted lines show the predictions of the upper and lower bounds of (11).

At the heart of each computational system is a process which governs the transduction between physical stimulation and spike generation. In the auditory system, this thought to be determined primarily at the inner hair cell/synapse interface (Heil and Peterson, 2015). We
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will examine three such phenomenological models based on considerations of mechanisms, two of which form the core of the MAP/DSAM and the ZBC systems. Coverage of these models is superficial. There is no detailed analysis beyond a simple cursory explanation, nor are definitions provided for the many of the parameters or variables. The interested reader is referred to the original publications. The goal is simply to get to the underlying equations which can be solved for the adaptation response and to highlight the role of how the inequality (11) can be used to further the development of these models.

B. Implications for models without mechanism of intensity coding

The first model is one proposed by Westerman and Smith (1984) (hereby referred to as the Westerman model) which forms a core part of the ZBC computational system. The Westerman approach involves a two-compartmental model of transmitter release in the inner hair cell synapse of the auditory nerve fibre. The use of the model within ZBC was later modified to include fractional noise and power-law adaptation dynamics (Zilany et al., 2014, 2009), and most recently included a synaptic vesicle docking model (Bruce et al., 2018). However, the core idea lies with the original Westerman model. The two compartment model includes both a local and immediate compartment:

\[ V_I c_I (t) = -p_I c_I (t) + [c_L (t) - c_I (t)] \] (22)

\[ V_L c_L (t) = -p_L (c_L (t) - c_I (t)) + p_G [c_G (t) - c_L (t)] \] (23)
where the dot signifies a time derivative. Combining the two differential equations we obtain

\[ \alpha \ddot{c}_I (t) + \beta \dot{c}_I (t) + \gamma c_I (t) = \delta \]  

(24)

where \( \alpha, \beta, \gamma, \delta \) are constants obtained from parameters of the model. The general solution of this equation is

\[ c_I (t) = C_1 e^{-\kappa_1 t} + C_2 e^{-\kappa_2 t} + C_3 \]  

(25)

with the constants to be determined from the system parameters of the original equations. \( c_I \) is then taken to be proportional to firing rate. This equation allows adaptation to be modelled as a sum of two exponentials with different time constants. The constants \( C_1, C_2, C_3 \), are fitted parametrically to adaptation data at different intensities (Westerman and Smith, 1984, 1988). For the ZBC model, the parameterization is more complicated but the idea remains the same (Heinz et al., 2001; Zhang et al., 2001).

The second example is a “universal” phenomenological model based on the idea that mechanisms of adaptation can be reduced to a single current gated by another variable obeying a first order differential equation (Benda and Herz, 2003). This model has been applied to auditory neurons (Hildebrandt et al., 2009). The equations governing the firing frequency are given by

\[ f = f_0 (I - A) \]  

(26)

\[ \tau_a \dot{A} = -A + A_\infty (f) \]  

(27)
where $f$ is the firing rate, $A$ the gating variable and $f_0$ a function of $I - A$. If $f_0$ is a linear function of its arguments then $f$ can be solved for constant $I$ to be

$$f(t) = (f_0 - f_\infty) e^{-t/\tau_{\text{eff}}} + f_\infty$$

(28)

Use of this equation requires empirical determination of both the peak growth curve $f_0$ and the steady-state growth curve $f_\infty$ as a function of stimulus intensity. Both are fitted to the equation

$$\frac{f_{\text{max}} - f_{\text{min}}}{1 + \exp[-k(I - I^0)]} + f_{\text{min}}$$

(29)

where $f_{\text{min}}, f_{\text{max}}, k, I^0$ are parameters to be determined from data fitting. Equations (28) and (29) allow for the firing rate to be calculated as a function of intensity of stimulation and duration.

The task of parameterizing and fitting (25) or (28) to adaptation data of different intensities becomes an exercise in curve-fitting a surface over time and intensity. With a large number of fitting parameters, overfitting can occur easily. The inequality derived earlier offers two distinct advantages. The first is to help find initial values for the curve-fitting process. Often it is difficult to set parameter values to their correct approximate values. If the optimization is run on poorly chosen starting points, the algorithm may converge to suboptimal choices. Either the lower or the upper bound in (11) can be used to help identify initial values. The second is to use the inequality to reduce the total number of fitting parameters. By knowing the value of spontaneous activity, the dimensionality of the fit can be reduced. For example, if we have determined empirically that the data of a particular fibre follows either the geometric or the arithmetic law there is now an additional constraint
of \( \sqrt{(C_1 + C_2 + C_3) SR} = C_1 \) or \((C_1 + C_2 + C_3 + SR)/2 = C_1 \) which can be used to reduce the number of fitting parameters from five to four in (25).

For the universal phenomenological model, the determination of \( f_0 \) and \( f_\infty \) requires a total of eight free parameters to fit both the peak and steady-state growth curves. By choosing \( f_0 = (k/2) \log [1 + \beta (I + \delta I)^p] \) and \( f_\infty = (k/2) \log \left[1 + \beta (I + \delta I)^{p/2}\right] \) from (2-5), this ensures compatibility with the inequality. Moreover, the choice of \( f_0 \) and \( f_\infty \) requires only four fitting parameters. To include the saturation of activity, we need only two further parameters making it a total of six, which is still less than the eight parameters required for (29).

C. Implications for the Meddis model

Neither of the two earlier models provide a mechanism for deriving the dependency of firing rate on intensity. In the final example, we consider the model of Meddis (Meddis, 1986, 1988; Meddis et al., 1990) which provides one method of deriving this dependency by modelling the process of transduction through a set of non-linear compartmental equations governing the release of neurotransmitter in the auditory synapse (Meddis, 1986). The Meddis model forms the heart of the approach in both the MAP and DSAM computational systems. In this case, the dependency on the various concentrations is given by

\[
\dot{q}(t) = y [M - q(t)] + x w(t) - k(t)q(t) \quad (30)
\]

\[
\dot{c}(t) = k(t)q(t) - (l + r)c(t) \quad (31)
\]

\[
\dot{w}(t) = r c(t) - x w(t) \quad (32)
\]
where $c(t)$ is the cleft concentration of transmitter, which is proportional to the firing rate, and the permeability $k(t)$ is a monotonic function of the sound pressure level $s(t)$. In later versions of this model, the concentrations were quantized and the process made stochastic (Sumner et al., 2002, 2003). However, this does not change the overall dynamics of the model.

In the original model, the relationship between $k(t)$ and $s(t)$ was modelled via a simple mathematical rectification (Meddis, 1986). In later models, the relationship between $k(t)$ and $s(t)$ requires evaluation of a biophysical model of the inner hair cell and the signal filtering that precedes it (Sumner et al., 2002). However, since the inequality (11) is not dependent on the value of intensity itself, all that matters here is that the average value of $k$ is a monotonic increasing function of stimulus intensity.

Under certain conditions, these equations can be solved analytically. For choices of $l, r$ which are large, (31) mimics the properties of a low-pass filter. As such, if the system is driven at high frequencies the equations can be approximated with $k(t)$ being constant. The equations can now be solved in the s-domain using the Laplace transform (Zhang and Carney, 2005). Zhang et al went further by approximating these equations under the condition of $l, r \to \infty$. This means that the time-constant $1/(l + r)$ in (31) governing the transient behaviour between $c$ and $q$ is effectively zero. From here, we can now decouple $c$ from (32) and replace it instead with the equivalent expression for $q$. This then gives rise to
the simplified model

\[
\dot{q}(t) = y[M - q(t)] + x w(t) - \bar{k} q(t) \quad (33)
\]

\[
\dot{c}(t) = \bar{k} q(t) - (l + r)c(t) \quad (34)
\]

\[
\dot{w}(t) = \bar{k} u q(t) - x w(t) \quad (35)
\]

where \( u = r/(l + r) \) and \( \bar{k} \) replaces \( k(t) \) with the average permeability (Zhang and Carney, 2005). These equations can now be solved with the Laplace transform to obtain

\[
Q(s) = \frac{\left[q(0)s + yM\right](s + x) + sxw(0)}{s(s + x)(s + \bar{k} + y) - \bar{k}ux} \quad (36)
\]

\[
C(s) = \frac{\bar{k}Q(s) + c(0)}{s + l + r} \quad (37)
\]

where \( q(0) \), \( c(0) \) and \( w(0) \) are the initial values. If the system is initially in quiet and steady-state prior to stimulus onset, the initial values can be solved by setting the derivatives in (30-32) equal to zero to obtain

\[
c(0) = \frac{\bar{k}_{sp}My}{\bar{k}_{sp}l + (l + r)y}, \quad q(0) = \frac{c(0)(l + r)}{\bar{k}_{sp}} \quad \text{and} \quad w(0) = \frac{c(0)r}{x}
\]

where \( \bar{k}_{sp} \) is the permeability/rate of transmitter leakage in silence. Finally, \( c(t) \) is obtained by taking the inverse Laplace transform of (37). \( c(t) \) is taken to be proportional to the spike activity of the adaptation response.

Since the Meddis model is the only model capable of independently evaluating the validity of the inequality (11), an attempt is made to solve these equations. The spontaneous rate SR can be obtained from the initial condition and the steady-state activity SS by applying the final value theorem to (36):

\[
c_{SR} = \frac{\bar{k}_{sp}My}{\bar{k}_{sp}l + (l + r)y} \quad (38)
\]

\[
c_{SS} = \frac{\bar{k}My}{kl + (l + r)y} \quad (39)
\]
The main difficulty, however, lies in the evaluation of the peak $c_{PR}$. This involves typically inverting (37) into the time domain and then differentiating to find the location of the maximum activity which can be complicated mathematically. However, under approximation, we can replace (37) by $C(s) \approx \bar{k}Q(s)/(l + r)$ for small values of $\bar{k}$ and obtain by the initial value theorem

$$c_{PR} = \frac{\bar{k}My}{\bar{k}_{sp}l + (l + r)y}$$  

(40)

To test the validity of (40), the peak activity $c_{PR}$ was evaluated by three methods. The first method is to solve Meddis’ original equations (30-32) using a sinusoidal input for $k(t)$ and following the technique outlined in Meddis (1986). Since the location and value of peak activity depends on the exact phase of the signal, the solution of the differential equation was averaged across different values of the input phase, and the maximum value of $c(t)$ extracted. This constitutes a calculation of peak activity most consistent with Meddis’ original model, e.g. Meddis (1986). The second method is to solve for $c(t)$ using the simplified Meddis model (33-35) with constant $k$ and finding the maximum value. Finally, $c_{PR}$ can also be calculated directly from (40). In Fig. 3 we observe that (40) approximates the true value well with deviations observed only for large $\bar{k}$.

We are now in a position to see how the three derived quantities $c_{PR}$, $c_{SR}$ and $c_{SS}$ compare with the inequality (11). For values of $\bar{k}$ which are large, $c_{PR}$ grows unbounded while the value of $c_{SS}$ asymptotes to the value of $My/l$. This violates (11) and we conclude that the Meddis model is likely not compatible with adaptation measurements for large $\bar{k}$. What
FIG. 3. Comparing the value of \( c_{PR} \) evaluated by three methods

about small \( \bar{k} \)? In Appendix B, we show that (11) implies that

\[
\left. \frac{dc_{SS}}{dk} \right|_{k=k_{sp}} = \frac{1}{2} \left. \frac{dc_{PR}}{dk} \right|_{k=k_{sp}}
\]

That is, the slope of \( c_{SS} \) equals one half of the value of \( c_{PR} \) at small sound intensities. From here, a linearization of \( c_{SS} \) from (41) and (40) gives

\[
c_{SS} = \frac{\bar{k}_{sp} M y}{k_{sp} l + (l + r) y} + \frac{m (l + r) y^2}{[k_{sp} l + (l + r) y]^2} (\bar{k} - \bar{k}_{sp})
\]

This is then the predicted value of \( c_{SS} \) from the inequality. On the other hand, a direct linearization of (39) yields

\[
c_{SS} = \frac{\bar{k}_{sp} M y}{k_{sp} l + (l + r) y} + \frac{m y}{2 k_{sp} l + 2 (l + r) y} (\bar{k} - \bar{k}_{sp})
\]

The two expressions are identical if and only if

\[
\bar{k}_{sp} = \left(1 + \frac{r}{l}\right) y
\]

Equation (44) the constraint imposed by the inequality on the model of Meddis.
Equation (44) can be interpreted in the following manner. If recordings of neural activity are to follow (11) then for the model to match these recordings it must too obey a constraint whereby the choice of $y, l, r$ lies close to the value of $\bar{k}_{sp}$ according to (44). An inspection of the parameters reported by Meddis appears to confirm this case. In Meddis (1986) and Meddis (1988), values of $l/r \approx 2.5$ and $y \approx 5$ were chosen as the parameters of best choice. Independently, a value of $\bar{k}_{sp} \approx 33$ was used to give the correct level of spontaneous activity. The two sides of (44) are of the same order of magnitude. These parameters were further refined in Sumner et al. (2002, 2003) where $l/r$ remains 2.5 but $y$ was increased to 10. The two sides are now identical in value demonstrating the utility of the inequality.

VII. METHODS

A. Data extraction

The data from Fig. 1 were digitized and extracted from the original publications. The extracted data is available in the Supplementary Material. For Smith and Zwislocki (1975), peak PR and steady-state SS activities were obtained from fig. 4a, fig. 11a-d, fig. 12 and fig. 17a together with the spontaneous activity SR where available. When SR was not available, its value was set to be equal to the lowest measured value of SS (see panels e-g in Fig. 1). For Westerman and Smith (1984), data was provided in terms of the coefficients $C_1, C_2, C_3$ of (25). See fig. 4 and 5 from their paper. PR and SS were then calculated from the coefficients using the equation. SR was provided for all units. For Yates et al. (1985), PR, SS and SR were extracted from the graphs. For unit GP27/04, only two values are available.
as the peak rate for 15 and 20 dB exceeded the maximum value of the graph. Finally, for
Sumner and Palmer (2012), PR, SS and SR were extracted from fig. 6 and the same was
done for fig. 3 for Fay (1978).

B. Simulations

The results of the simulations in Fig. 2 were carried out using default settings as part of
the demonstrations associated with each simulator. In each case, adaptation was simulated
at the unit’s best frequency to a pure tone stimulation of length 200 ms with short ramps,
and then averaged for 2000 runs. The simulations were carried out over increasing intensities
until saturation of the response was observed at approximately 40 dB. For specific values
of parameters used see the configuration files available for download in the Supplementary
Material.

APPENDIX A: COMPUTER CODE TO SOLVE FOR ADAPTATION RESPONSE

The following code is developed for the MATLAB programming environment (Mathworks
2021) but can be easily adapted to any other language to solve (2-5) numerically using just
a few lines of code. The parameters can be set to just about any value provided that they
are positive. A forward Euler method is used to solve the differential equation in (5).

% Numerical solution of the entropy equations

% Setting parameters and initial values for sample size and intensity
k=1; b=1; p=1; di=1; a=1; m=di^(p/2); i=0;

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dt=0.1; t=0:dt:10; % Time variable and increment
for j=1:length(t)
    if t(j)>2 i=10; end % Stimulus turns on at t = 2
    m=m-dt*a*(m-(i+di)^(p/2)); % Forward Euler method
    f(j)=.5*k*log(1+b*(i+di)^p/m);
end
plot(t,f); % Plot calculations

While the above code was developed to solve for the adaptation response, a simple change to the line governing the stimulus allows for the code to solve for the response to any time-varying input. For the example illustrated in the code, note that SR = 0.35, PR = 1.15 and SS = 0.75 satisfies the upper-bound of the inequality (11).

APPENDIX B: SLOPE OF STEADY-STATE ACTIVITY

As a consequence of (11), we will prove that the slope of the steady-state activity SS with respect to changes in intensity equals one half of the slope of peak activity PR at low intensities (i.e. $\bar{k}$ close to $\bar{k}_{sp}$). Before embarking on this proof, we first explore the problem in the abstract. Consider the functions $f(x)$, $g(x)$ and $h(x)$ defined over the domain $x \geq 0$ satisfying the inequality $f(x) \leq g(x) \leq h(x)$ for all non-negative values of $x$. Moreover, we impose the conditions that $f(0) = g(0) = h(0) = y_0$ and $f'(0) = h'(0)$. $f'$ designates the first derivative of $f$ with respect to $x$, etc. Next we prove that these conditions are equivalent to the statement $g'(0) = f'(0) = h'(0)$. 
Consider a positive increment \( \Delta x \). By the inequality, we have \( f(\Delta x) \leq g(\Delta x) \leq h(\Delta x) \). Subtraction by \( y_0 \) and division by \( \Delta x \) gives \[ \frac{f(\Delta x) - y_0}{\Delta x} \leq \frac{g(\Delta x) - y_0}{\Delta x} \leq \frac{h(\Delta x) - y_0}{\Delta x} \]. Since \( \Delta x \) was arbitrary, we examine the limit as \( \Delta x \to 0 \). This is now the definition of the derivative at \( x = 0 \). But since \( f'(0) = h'(0) \), therefore \( g'(0) = f'(0) = h'(0) \).

We now recast the proof in terms of SS, PR and SR. In this case, intensity replaces \( x \) and \( GM(0) = SS(0) = AM(0) = SR \) where AM and GM refer to the arithmetic and geometric means of SR and PR. That is, at zero intensity both the GM and AM equals SR. Since SR is constant with respect to intensity, both AM'(0) and GM'(0) equals PR'(0)/2. By the same steps as before, we conclude that SS'(0) = AM'(0) = GM'(0) = PR'(0)/2. Therefore, the slope of SS equals one half the value of PR at low intensities. Since permeability \( \bar{k} \) is a monotonic increasing function of stimulus intensity, the above derivation holds also for changes of \( \bar{k} \) near \( \bar{k}_{sp} \).

Adrian, E. D., and Zotterman, Y. (1926a). “The impulses produced by sensory nerve-endings: Part II. the response of a single end-organ,” Journal of Physiology 61(2), 151.

Adrian, E. D., and Zotterman, Y. (1926b). “The impulses produced by sensory nerve endings: Part III. impulses set up by touch and pressure,” Journal of Physiology 61(4), 465.

Baylin, F. (1979). “Temporal patterns and selectivity in the unitary responses of olfactory receptors in the tiger salamander to odor stimulation.,” Journal of General Physiology 74(1), 17–36.
Benda, J., and Herz, A. V. (2003). “A universal model for spike-frequency adaptation,” Neural Computation 15(11), 2523–2564.

Benda, J., and Tabak, J. (2014). “Spike-frequency adaptation,” Encyclopedia of Computational Neuroscience 667, 1–12.

Bruce, I. C., Erfani, Y., and Zilany, M. S. (2018). “A phenomenological model of the synapse between the inner hair cell and auditory nerve: Implications of limited neurotransmitter release sites,” Hearing Research 360, 40–54.

Carney, L. H. (1993). “A model for the responses of low-frequency auditory-nerve fibers in cat,” Journal of the Acoustical Society of America 93(1), 401–417.

Eggermont, J. (1973). “Analog modelling of cochlear adaptation,” Kybernetik 14(2), 117–126.

Enroth-Cugell, C., and Shapley, R. (1973). “Adaptation and dynamics of cat retinal ganglion cells,” Journal of Physiology 233(2), 271–309.

Fay, R. R. (1978). “Coding of information in single auditory-nerve fibers of the goldfish,” Journal of the Acoustical Society of America 63(1), 136–146.

Heil, P., and Peterson, A. J. (2015). “Basic response properties of auditory nerve fibers: a review,” Cell and Tissue Research 361(1), 129–158.

Heinz, M. G., Zhang, X., Bruce, I. C., and Carney, L. H. (2001). “Auditory nerve model for predicting performance limits of normal and impaired listeners,” Acoustics Research Letters Online 2(3), 91–96.

Hewitt, M. J., and Meddis, R. (1991). “An evaluation of eight computer models of mammalian inner hair-cell function,” Journal of the Acoustical Society of America 90(2), 904–
Hildebrandt, K. J., Benda, J., and Hennig, R. M. (2009). “The origin of adaptation in the auditory pathway of locusts is specific to cell type and function,” Journal of Neuroscience 29(8), 2626–2636.

Kiang, N. Y.-S. (1965). Discharge Patterns of Single Fibers in the Cat’s Auditory Nerve (MIT Press, Cambridge).

Meddis, R. (1986). “Simulation of mechanical to neural transduction in the auditory receptor,” Journal of the Acoustical Society of America 79(3), 702–711.

Meddis, R. (1988). “Simulation of auditory–neural transduction: Further studies,” Journal of the Acoustical Society of America 83(3), 1056–1063.

Meddis, R. (2011). “Matlab model of auditory periphery (MAP)” muhttps://github.com/rmeddis/MAP, Last accessed on 2022-03-12.

Meddis, R., Hewitt, M. J., and Shackleton, T. M. (1990). “Implementation details of a computation model of the inner hair-cell auditory-nerve synapse,” Journal of the Acoustical Society of America 87(4), 1813–1816.

Meddis, R., Lopez-Poveda, E. A., Fay, R. R., and Popper, A. N. (2010). Computational models of the auditory system (Springer).

Norwich, K. H. (1977). “On the information received by sensory receptors,” Bulletin of Mathematical Biology 39(4), 453–461.

Norwich, K. H. (1993). Information, sensation, and perception (Academic Press San Diego).

Norwich, K. H., and Wong, W. (1995). “A universal model of single-unit sensory receptor action,” Mathematical Biosciences 125(1), 83–108.
O’Mard, L. P. (2021). “Development system for auditory modelling (DSAM)” muhttp://dsam.sourceforge.net/downloads.htm, Last accessed on 2022-03-12.

Rudnicki, M., Schoppe, O., Isik, M., Völk, F., and Hemmert, W. (2015). “Modeling auditory coding: from sound to spikes,” Cell and Tissue Research 361(1), 159–175.

Schroeder, M., and Hall, J. (1974). “Model for mechanical to neural transduction in the auditory receptor,” Journal of the Acoustical Society of America 55(5), 1055–1060.

Smith, R., and Brachman, M. (1982). “Adaptation in auditory-nerve fibers: a revised model,” Biological Cybernetics 44(2), 107–120.

Smith, R. L., and Zwislocki, J. (1975). “Short-term adaptation and incremental responses of single auditory-nerve fibers,” Biological Cybernetics 17(3), 169–182.

Sumner, C. J., Lopez-Poveda, E. A., O’Mard, L. P., and Meddis, R. (2002). “A revised model of the inner-hair cell and auditory-nerve complex,” Journal of the Acoustical Society of America 111(5), 2178–2188.

Sumner, C. J., Lopez-Poveda, E. A., O’Mard, L. P., and Meddis, R. (2003). “Adaptation in a revised inner-hair cell model,” Journal of the Acoustical Society of America 113(2), 893–901.

Sumner, C. J., and Palmer, A. R. (2012). “Auditory nerve fibre responses in the ferret,” European Journal of Neuroscience 36(4), 2428–2439.

Westerman, L. A., and Smith, R. L. (1984). “Rapid and short-term adaptation in auditory nerve responses,” Hearing Research 15(3), 249–260.

Westerman, L. A., and Smith, R. L. (1988). “A diffusion model of the transient response of the cochlear inner hair cell synapse,” Journal of the Acoustical Society of America 83(6),
Wilson, E. O. (2000). “Consilience,” New York: Alfred A Knoff.

Wong, W. (1997). “On the physics of perception,” Ph.D. thesis, University of Toronto.

Wong, W. (2013). “Perceptual arrow of time and the sensory transduction process” arXiv:1307.6445v1.

Wong, W. (2020). “On the rate coding response of peripheral sensory neurons,” Biological Cybernetics 114(6), 609–619.

Wong, W. (2021). “Consilience in the peripheral sensory adaptation response,” Frontiers in Human Neuroscience 526.

Yates, G. K., Robertson, D., and Johnstone, B. M. (1985). “Very rapid adaptation in the guinea pig auditory nerve,” Hearing Research 17(1), 1–12.

Zhang, X., and Carney, L. H. (2005). “Analysis of models for the synapse between the inner hair cell and the auditory nerve,” Journal of the Acoustical Society of America 118(3), 1540–1553.

Zilany, M. S., Bruce, I. C., and Carney, L. H. (2009). “A phenomenological model of the synapse between the inner hair cell and auditory nerve: long-term adaptation
with power-law dynamics,” Journal of the Acoustical Society of America 126(5), 2390–2412.