A Universal Law of Sensory Adaptation

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Abstract

Sensory adaptation is the gradual decline in response as recorded from sensory neurons to a constant stimulus. Measuring adaptation involves counting the time-varying rate of action potentials generated by the sensory neuron. A typical adaptation curve will involve spontaneous activity prior to the introduction of the stimulus, a peak level of activity soon after the stimulus is presented, and a gradual fall to a new steady-state value. *In this study, the steady-state activity is shown to be equal to the geometric mean of the spontaneous and peak activities.* This remarkably simple equation holds across different sensory modalities and in different animal species. It is obeyed in both modern measurements of neural adaptation as well as the original recordings of Lord Adrian in his seminal work on the discovery of the all-or-nothing principle of nerves. It is likely a universal relationship governing the peripheral response of sensory neurons.

Introduction

Nearly a century ago, Edgar Douglas Adrian discovered the all-or-nothing principle of action potentials of nerves thereby uncovering the language of the nervous system. Along the way, he introduced new techniques in the study of sensory systems by measuring systematically the response of single unit activity to stimulation in various modalities. Collaborating with his assistant Yngve Zotterman, Adrian conducted one of his most celebrated experiments: the measurement of the rate of impulses from the frog muscle spindle to the stretch of a muscle. What Adrian found was that the neural activity rises immediately upon initiation of the stretch and falls monotonically over time [1] (see Fig. 1A reproducing the graph for Experiment 12). This is now known as sensory adaptation and is observed nearly universally in all of the senses across many different organisms. The rate of impulse generation, or firing rate, has an important conceptual role in helping understand how information is coded in the nervous system [2].

Adrian's discovery has been repeated numerous times by other investigators in other modalities utilizing more modern methodologies and technologies [3, 4]. The basic finding of adaptation, however, remains unchanged from the basic shapes uncovered by Adrian. Could there be something, however, in Adrian's original findings that escaped his attention? Fig. 1B shows a schematic representation of a generic adaptation curve similar to what Adrian found for the frog muscle. Three fixed points in the curve stand out: the spontaneous activity prior to the application of the stimulus SR, the peak activity that occurs at or soon after the presentation of the stimulus PR, and the

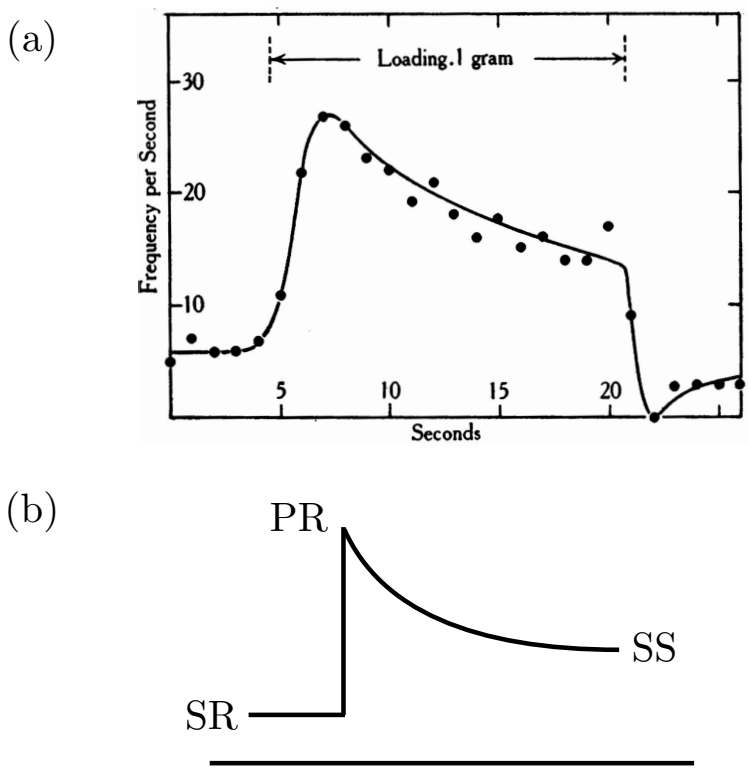

Fig 1. Sensory adaptation curves. (a) Original measurements of impulse generation during frog muscle stretch and figure reproduced from Adrian and Zotterman's original 1926 paper [1]. (b) An idealized sensory adaptation response showing steady-state spontaneous response (SR) prior to introduction of stimulus, the peak response to the stimulus (PR), and the subsequent new steady-state response (SS).

Table 1. A summary of different adaptation results highlighting the relationship between spontaneous, peak and steady-state activities for different modalities and organisms.

Spontaneous activity (SR, Hz)	Peak activity (PR, Hz)	Steady-state activity (SS, Hz)	Prediction	Modality	Organism	Source
6.1	26.8	13.2	12.8	Proprioception	Frog	Fig. 10B (exp. 12) [1]
3.7	99.7	19.3	19.2	Touch	Cat	Fig. 8 (exp. 6) [6]
23.4	43.4	32.3	31.9	Proprioception	Cat	Fig. 8 (initial adapt.) [7]
13.6	81.0	29.5	33.2	Taste	Rat	Fig. 2 (initial adapt.) [8]
60.1	179	100	104	Hearing	Cat	Fig. 6.7 (unit 299-22) [3]
4.9	27.5	11.6	12.4	Proprioception	Crayfish	Fig. 1 [9]
4.8	69.9	18.7	18.3	Smell	Fish	Fig. 1c (initial adapt.) [10]
62.2	121	80.3	87.0	Head movement	Monkey	Fig. 7c (unit 213-28) [11]
12.9	31.1	18.9	20.0	Proprioception	Cat	Fig. 4 (initial adapt., prep. 54) [12]

steady-state activity after adaptation has stopped SS. Spontaneous activity is spike activity observed even in the absence of external stimulation. Its origin and role within neural coding is debated to this day [5].

Results

In Adrian's recording the stimulus was terminated prior to the response reaching steady-state. However, one can estimate the steady-state value by extrapolating from his data in Fig. 1A. Fitting the data from peak onset to termination of input with an exponential decay with offset, the steady-state activity can be estimated to be approximately 13 spikes per second (SS = 13.2 Hz). This is close in value to the square root of the product of spontaneous activity times the peak value. That is, $\sqrt{6.1 \times 26.8} = 12.8$ Hz. Is this a coincidence, or is it also a property of their other experimental results? In the third instalment of their celebrated 1926 papers [6], Adrian and Zotterman measured adaptation in Merkel units in the footpad of a cat to pressure stimuli. This time, the stimulus was held long enough to reach steady-state. From Fig. 8 of their paper detailing the results of Experiment 6, the three extracted values are: SR = 3.7 Hz, PR = 99.7 Hz and SS = 19.3 Hz. The predicted value is $\sqrt{3.7 \times 99.7} = 19.2$ Hz, which is close to the measured steady-state activity.

Next we ask if this relationship is obeyed in more modern studies across other modalities. In Table 1 (upper values), data extracted from a number of published studies for both a wide range of modalities and organisms support this observation. The equation works as well in proprioception and touch as it does for taste and hearing. The results can be checked against an even wider range of experiments (Table 1, lower values). However, not all of these experiments were conducted in the manner required to attain the "ideal response" in Fig. 1B which requires a sudden onset of a stimulus to be held constant and applied long enough for the response to reach steady-state. As such we look to these results as a check of consistency. Nevertheless, the agreement to the equation is striking.

These studies point to a universal relationship which can be written in the following manner

$$\mathrm{SS} = \sqrt{\mathrm{PR} \times \mathrm{SR}} \tag{1}$$

Such a relationship is called a *geometric mean*; that is, the steady-state firing rate equals the geometric mean of the peak and spontaneous activities. Since the firing rate is equal to the reciprocal of the inter-spike interval (ISI), there is an equivalent expression which can be written for the inter-spike interval. The geometric mean appears in nature through a variety of situations and circumstances: the mutual inductance between two coils in an electric circuit is bounded by the geometric mean of the individual inductances of each coil. The golden ratio of proportionality $\phi = 1.618...$ comes from a

geometric mean derived from two rectangles for which the sides differ in length by one. Another way to understand Eq 1 is to observe that the ratio of peak activity to steady-state activity equals the ratio of steady-state activity to spontaneous activity.

Spontaneous activity takes on a value which is constant for a given unit. As such, the mathematical form of Eq 1 implies that the steady-state activity SR will vary with peak activity PR by a square root relationship. This is explored in Fig. 2 where a number of adaptation studies conducted at different stimulus intensities are shown. On a double logarithmic plot, the prediction is that the data will form straight lines with slope equal to 1/2. Of all single-unit adaptation studies, the most thoroughly explored modality is hearing through the measurement of peri-stimulus or post-stimulus time histograms (PSTH). Fig. 2 shows the results from two separate auditory adaptation studies conducted on guinea pigs with both high and low spontaneous activity (unit GP-17-4 from Fig. 1 of original publication [13]; units GL31/13, GL31/08, GP27/04 and GP27/18 from Figs. 1 and 2 of original publication [14]), one study conducted on gerbils (unit E8F2 from Fig. 1 of original publication) [15] and a further study on ferrets (averaged response from many fibres across a range of input intensities from Fig. 6 of original publication) [16]. The data show a remarkable consistency across sounds of different input intensities and fibres of different spontaneous activities. Of particular importance is the last data set taken from the adaptation results from an experiment conducted on an ON-centre cat ganglion cell to different adapting luminances (Fig. 7A-C of original publication) [17]. This is the only systematic study of its kind that allows for the generalization of Eq 1 to cases where the unit is already adapted to an existing level and responds to a further increment. This agreement suggests that Eq 1 can be generalized to the steady-state activity of any increment equalling the geometric average of the peak and the steady-state activity prior to the increment.

Additionally, adaptation measured from ascending and descending staircases from a number of modalities allows for further testing of Eq 1 to pre-adapted levels: warm units of bats to an ascending staircase of increasingly warmer temperatures (Fig. 2 of original publication [18]); two M1 cells specializing in non-image-based vision (intrinsically photosensitive retinal ganglion cells or ipRGCs) from mice to light of increasing levels (Figs. 1b/c of original publication [19]); olfactory sensory neurons of fruit flies to an ascending and descending staircase of acetone concentrations (Fig. 2c of original publication [20]). Taken together, the following fundamental law governing the behaviour of transient activity in the sensory neuron can be formulated:

$$\mathrm{SS}_{\mathrm{final}} = \sqrt{\mathrm{PR} \times \mathrm{SS}_{\mathrm{initial}}} \tag{2}$$

The data from the three studies together with the predicted values from Eq 2 are shown in Fig. 3.

Discussion

The ubiquity of Eqs 1-2 across different modalities and organisms, across different adapting intensities and unit types, suggests that they are in fact universal equations. It also raises a number of further questions. The first question is what model of adaptation would be compatible with such a relationship. There are a number of models, particularly in hearing, that provide good compatibility to experimental data recorded from single unit activity [21, 22]. However, Eq 2 is an equation that works across different modalities and it is not reasonable to expect a modality-specific model to be easily extended to work with other modalities without additional, possibly ad hoc, assumptions. Instead, Eq 2 can be derived from a theory of sensory processing that has been under development for the past forty years [23–25]. This approach is based on the entropy or uncertainty of the sensory signal and not on any modality-specific

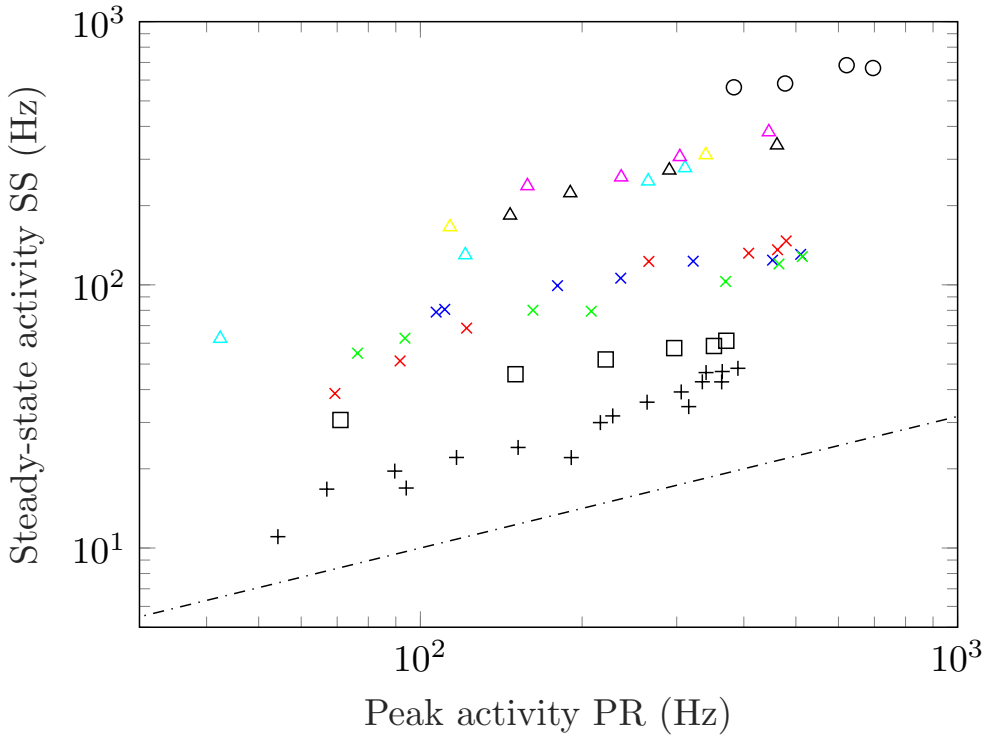

Fig 2. Steady-state activity (SS) plotted as a function of peak activity (PR) for different stimulus intensities. Circles show averaged auditory data from ferrets [16]; triangles show auditory data from four separate guinea pig fibres of both high and low spontaneous activity [14]; squares are auditory data from a single gerbil fibre [15]; plus signs are auditory data from a single guinea pig fibre [13]. Crosses show vision data from a single ON-centre ganglion cell in the cat [17]. The vision data are different as they are derived from pre-adapted luminance values (red: $1 \times 10^{-5}\,\mathrm{cd\,m^{-2}}$; blue: $1 \times 10^{-3}\,\mathrm{cd\,m^{-2}}$; green: $1 \times 10^{-1}\,\mathrm{cd\,m^{-2}}$). Line shows a power function with 1/2 exponent. Data are translated with multiplicative factors to avoid overlap (circles, 4x; cyan and yellow triangles, 4x; black and magenta triangles, 2x; crosses, 1x; squares, 1x; plus signs, 1/4x).

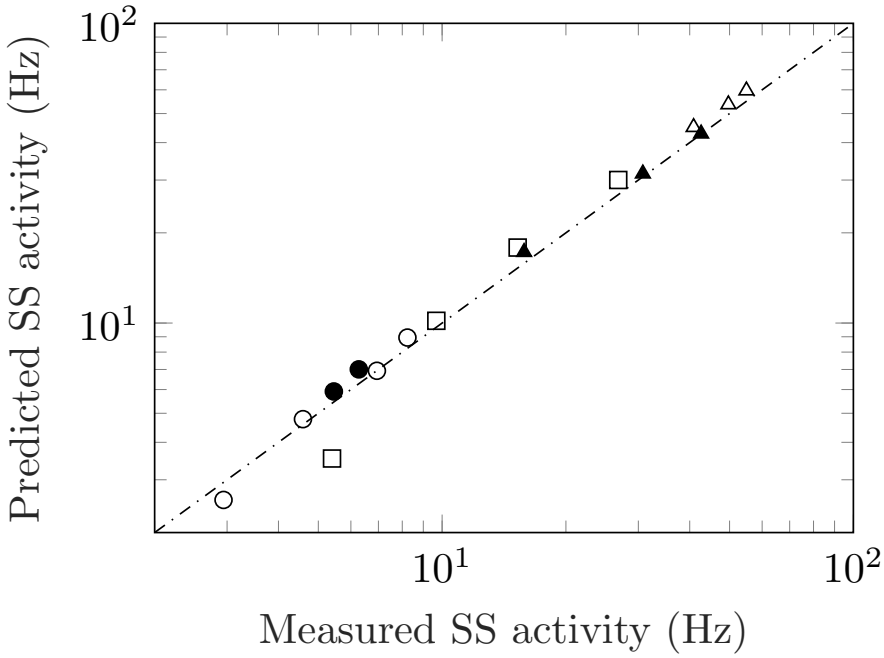

Fig 3. Measured versus predicted steady-state activity for ascending and descending staircases. Squares show the measured steady-state values versus predictions from Eq 2 to an ascending staircase of temperatures in warm units of bats [18]; circles (filled and open) show the same for two M1 ipRGCs in mice to an ascending luminance staircase [19]; open/filled triangles are for ascending/descending staircases of acetone concentrations from olfactory sensory neurons in fruit flies [20]. Line shows the case of perfect agreement between measurement and prediction.

mechanism. It was through entirely theoretical considerations [25] that led to the prediction and discovery of Eqs 1-2.

There are also circumstances where these equations fail to hold. In the visual system, for example, adaptation data obtained from ganglion cells do not always follow this relationship, e.g. [4]. The visual system is complex and the ganglion cells receive inputs from other cells in the descending pathway. The study of Sakmann and Creutzfeldt [17] is an exception as only a narrow region of the centre was excited thereby minimizing the effects of the inhibitory surround. Similarly the intrinsic light response of the M1 ipRGCs follow a simpler pathway [26] which may be the reason for the agreement observed in Fig. 3. Additionally, the equations are not always obeyed in activity recorded in the descending auditory pathway. For example, certain patterns of adaptation activity in the cochlear nucleus [27] do not follow the geometric average relationship. Thus Eqs 1-2 appear to govern neural activity in the absence of interaction from other cells in the neural circuitry. These equations may be useful in future studies on how the neural response is transformed by the later stages of sensory processing.

Moreover, there are also specific classes of sensory neurons for which the adaptation response does not conform to Eqs 1-2. The somatosensory system encompasses many types of temperature receptors for which mainly only the warm units appear to respond in the manner associated with typical adaptation curves e.g. [18]. Molecular studies have revealed that different thermal stimuli activate different classes of temperature-gated ion channels in the neuronal plasma membrane (transient receptor potential or TRP channels) [28]. This may be a reason for why there is a difference in adaptation behaviour, although the role of TRP channels in mediating temperature sensing is still being debated. In touch, only the tonic or slow-adapting (SA) units follow the type of adaptation behaviour illustrated in Fig 1B [29]. Similarly, in the vestibular system, not all units show adaptation to the extent predicted by Eqs 1-2 [11]. Whether these units respond to other types of head movement outside of acceleration, or this is an indication of deviation from general behaviour, requires further study. However, these exceptions do not take away from the universal nature of Eqs 1-2. This relationship is observed to hold robustly in many modalities and many different animal species, from vertebrates to invertebrates. There is even preliminary evidence that the relationship is satisfied in cnidarians. Recordings from the pacemaker cells found in the visual sensory structures rhopalia of jellyfish show responses which mirror adaptation curves found in Fig. 1b, satisfying the geometric mean relationship [30] (see particularly the response of the upper lens eye).

Second, there is considerable debate over the origins and role of spontaneous activity [5, 31]. Spontaneous activity is often thought of as noise within the nervous system [32, 33] when in fact it is clear from Eq 1 that it is likely an integral part of normal sensory function. It conveys information just as the peak and steady-state levels convey sensory information about the environment [34]. There has been much recent effort in investigating the cellular mechanisms of spontaneous activity [35, 36]. Although the mechanism of generation may differ, it is likely that its functional role is the same across the modalities [31]. Certain conditions can also lead to elevated levels of spontaneous activity. In hearing for example, noise-induced hearing loss can result in higher than usual spontaneous rates leading possibly to tinnitus [37]. Eq 1 opens up new avenues for the study of sensory mechanisms and disorders by tying together changes in spontaneous activity with other variables associated with the neural response. For example, the geometric mean relationship appears to be preserved under changes in temperature to auditory neurons despite sizeable changes to the spontaneous, peak and steady-state rates [38]. This may be a reason for the universality of this equation in the different animal species. Eq 2 is likely a useful tool for exploring the mechanisms underlying sensory transduction as well as the evolution of the senses.

Of the various equations in physiology, few have the simplicity of Eq 2, and certainly not within the equations governing the nervous system. It might be reasonably asked *why* the peak activity is related to the two other steady-state values. One answer may lie with the consumption of metabolic energy and how the response is decoded in the descending pathway. When there is a change in the environment (through the introduction of a stimulus), it is reasonable to assume that the nervous system brings salience to this signal through a higher level of impulse generation. However, the metabolic cost of maintaining a rapid rate of spike generation is high [39, 40] and ultimately the rate is reduced to a lower, steady level. The constancy in activity ratio may be related to the discriminability of the peripheral response. An equality of ratios implies that the peak response will be as easily differentiated from steady-state activity as steady-state is from spontaneous activity.

Materials and Methods

The data used in the analyses were obtained from previously published adaptation studies available in the literature. Since many of the studies were conducted some time in the past, no attempt was made to contact the investigators to obtain the raw data. The data were extracted from publications in the following manner. When the electronic form of the journal from the publishers' websites were of poor quality, original scans were made from the print format of the journal. All attempts were made to scan pages as flat as possible despite the presence of the book binding. The images were scanned at 400 dpi and kept in portable document format (PDF). The images (from either the electronic format, or scanned from original sources) were then converted to portable network graphics format (PNG), cropped and imported into photo editing software to correct for distortions (typically rotations). The graphs were also enlarged through magnification before being brought into a tablet for mark-up. Lines were drawn electronically at three locations indicating the level of activity for the spontaneous, peak and steady-state levels. The spontaneous and peak levels were often easiest to estimate. The spontaneous activity sometimes appears twice, once before the introduction of the stimulus and at the recovery after the stimulus is removed, allowing for a cross-check of the value. The peak activity showed less variability than either the spontaneous or steady-state activity, consistent with what has been found elsewhere [41]. In all cases the largest value of the firing rate was taken to be the peak activity.

The more challenging step was finding the steady-state activity. Not only does adaptation show time-varying changes in firing rate, but the variability makes it difficult to know exactly which value to choose. Averaging of the data is not feasible without extracting a large number of data points, and this was not possible from noisy images. As such, with the exception of two studies, one where the mean activity was already provided in the graph [16] and the other where the peak and steady-state values were plotted as functions of sound intensity [13], a visual estimation of the average activity in the final portion of the adaptation curve was used. The marked-up images were imported into custom software where the coordinates were then converted into actual firing rates.

For the two experiments by Adrian and Zotterman [1, 6], a slightly different methodology was used. All of the data points from the two adaptation graphs were extracted. For the frog muscle adaptation curve, the data from $t = 5.6193$ (when peak occurred) until the removal of stimulus were fitted to the equation $c_1 \exp\left[-c_2\left(t - 5.6193\right)\right] + c_3$ where c_1, c_2 and c_3 are fitting parameters. The fit was carried out in MATLAB R2019b (MathWorks) using the function `nlinfit`. The value of c_3 was taken to be the steady-state activity. For the pressure/touch experiment, the steady-state value was estimated using another experiment conducted on the same unit,

but with a slower stimulus ramp (crosses from Fig. 8 of Exp. 6). The spontaneous activity for both curves was estimated by averaging the data prior to the rise in the curve.

In the study on guinea pig auditory fibres [14], only the adaptation values conducted at 5 dB and 10 dB were extracted for unit GP27/04 as both the 15 dB and 20 dB experiments show peak responses exceeding the limit of the graph (noted by the study authors themselves). For the M1 ipRGCs study [19], values were extracted only where there was a clear steady-state level of activity attained, and that the input levels lie within the sensitivity range of the unit. This included the third to seventh levels of the luminance staircase in Fig. 1b and the fourth to sixth levels in Fig. 1c.

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