A Universal Law of Sensory Adaptation

Willy Wong[1,2],

1 Edward S. Rogers Sr. Dept. of Electrical and Computer Engineering, University of Toronto, Toronto, Ontario, Canada
2 Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

* willy.wong@utoronto.ca

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 of Experiment 12 from their original publication). 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 e.g. [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 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].

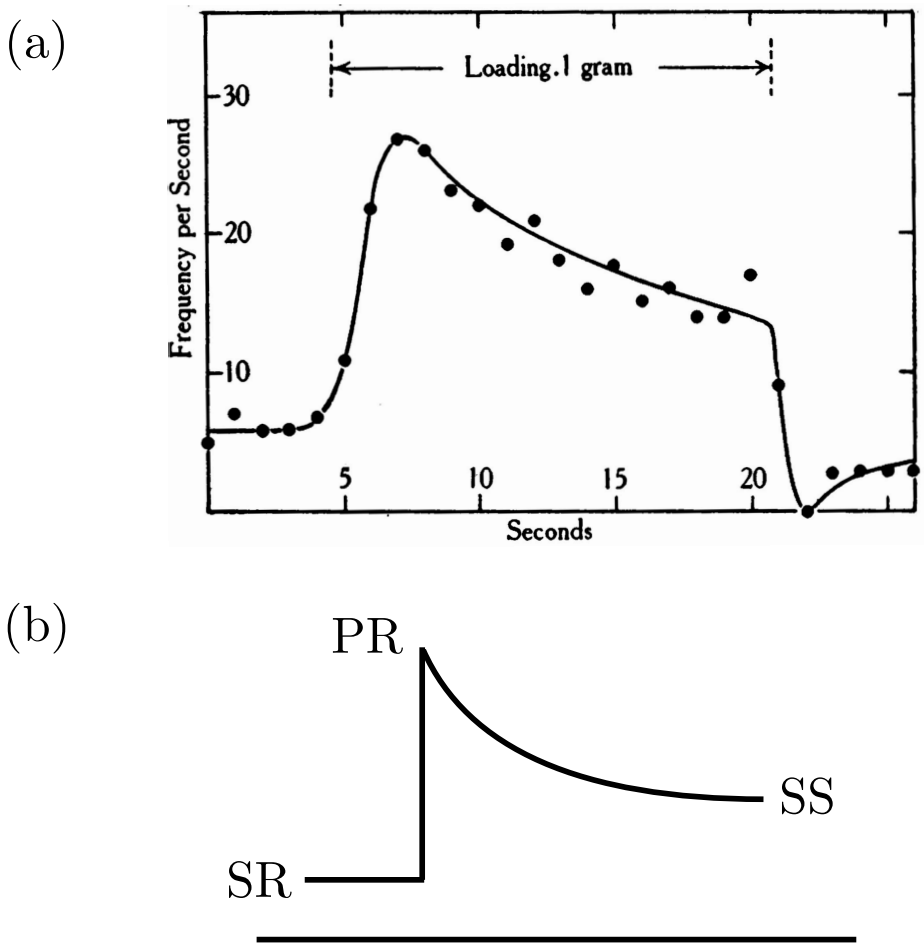

Figure 1: **Sensory adaptation curves.** (a) Original measurements of impulse generation during frog muscle stretch and figure reproduced from Adrian and Zotterman's original 1926 paper [1]. (b) An idealized sensory adaptation response showing steady-state spontaneous response (SR) prior to introduction 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]

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 sensory 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 equals the reciprocal of inter-spike interval (ISI), an equivalent expression can be written in terms of the spontaneous, peak and steady-state inter-spike intervals. 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.

The rate of spontaneous activity is constant for any given sensory unit. Given constant SS, Eq 1 shows that the steady-state activity SR will vary with peak activity PR by a square root relationship. This is explored in Fig. 2 where the data from a number of studies conducted at different intensities are shown. On a double logarithmic plot, PR vs SS will form straight lines with slope equalling one-half. The intercept will of course depend on the specific value of spontaneous activity. Of all single-unit studies, the most thoroughly

explored modality is hearing through the measurement of peri-stimulus or post-stimulus time histograms (PSTH). Fig. 2a shows the results of one adaptation study conducted on guinea pigs (unit GP-17-4 from Fig. 1 of [13]); 2b shows the measurements from a study conducted on gerbils (unit E8F2 from Fig. 1 of [14]); shown in 2c are measurements from four different guinea pig fibres of both high and low spontaneous activity (units GL31/13, GL31/08, GP27/04 and GP27/18 from Figs. 1 and 2 of [15]); 2d shows a further study on ferrets (averaged response from many fibres across a range of input intensities from Fig. 6 of [16]); 2e illustrates a similar study of the response of saccular nerve fibres of a gold fish to noises of varying intensities (Fig. 3 from [17]). The data show a remarkable consistency with the predictions of Eq 1 across sounds of different input intensities, fibres of different spontaneous activity, as well as animals of different species and classes. Of particular importance is the last data set shown in Fig. 2f taken from the results of an experiment conducted on an ON-centre cat ganglion cell to different adapting luminances (Fig. 7A-C of original publication [18]). 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.

Adaptation responses measured from ascending and descending staircases allow for further testing of Eq 1 to pre-adapted levels. An ascending/descending staircase involves constant levels of stimulation held long enough for the neural response to reach steady-state before a further increase/decrease in intensity is introduced. Several studies have explored such stimulus paradigms including; the response of warm units of bats to an ascending staircase of increasingly warmer temperatures (Fig. 2 of [19]); 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 [20]); olfactory sensory neurons of fruit flies to an ascending and descending staircase of acetone concentrations (Fig. 2c of [21]). Taken together, the following law governing transient activity in sensory adaptation can be formulated:

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

This equation includes Eq 1 as a special case. 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 [22, 23]. 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 [24–26]. This approach is based on the entropy or uncertainty of the sensory signal and not on any modality-specific mechanism. It was through entirely theoretical considerations [26] that led to the prediction and discovery of Eqs 1-2. The derivation Eqs 1-2 of will be the subject of a later publication.

There are also circumstances where these equations fail to hold. In the visual system, for example, the adaptation data obtained from ganglion cells do not always follow Eq 1, 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 [18] is an exception as only a narrow region of the centre was excited thereby minimizing the effects of the inhibitory surround. Moreover the intrinsic light response of the M1 ipRGCs follow a simpler pathway [27]. Taken together this provides a possible explanation for why there is agreement between the predicted and measured steady-state values for vision in both Figs. 2 and 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 e.g. [28] 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.

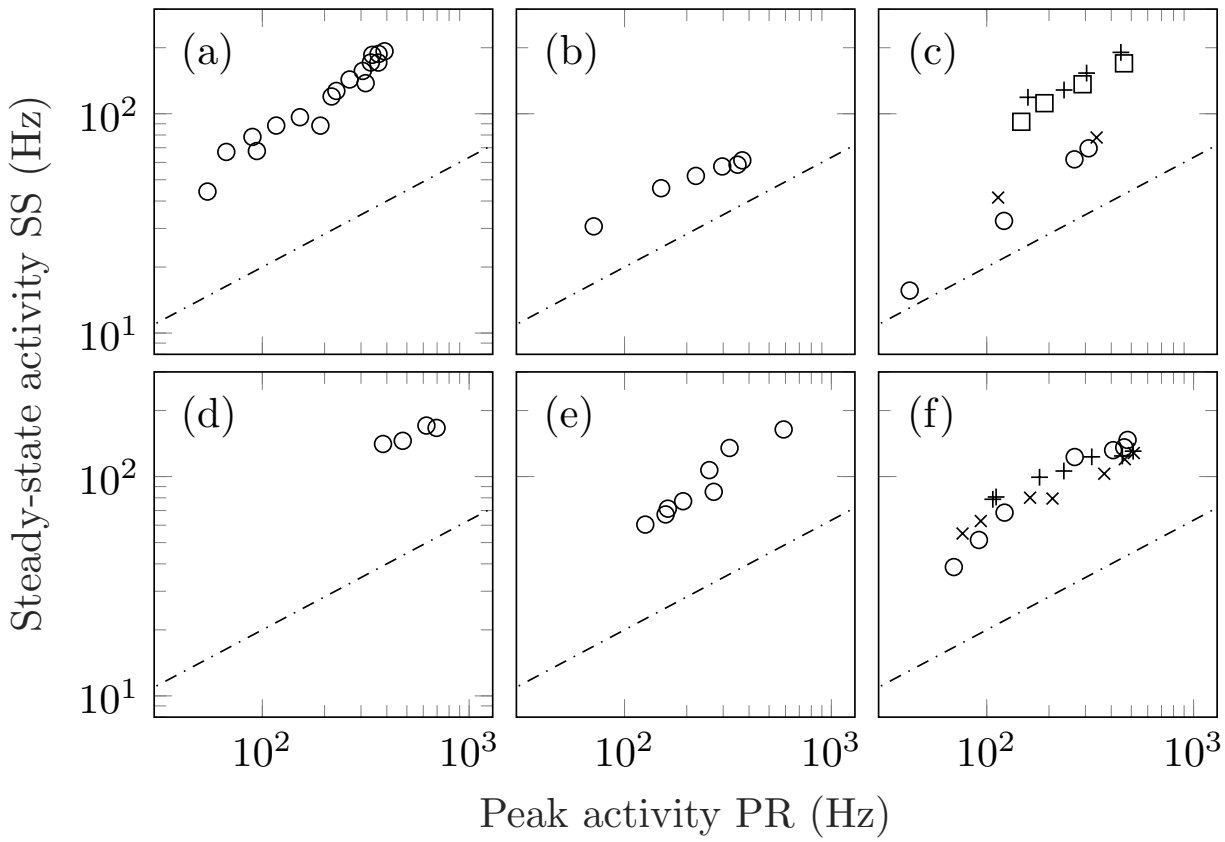

Figure 2: **Steady-state activity (SS) plotted as a function of peak activity (PR) for different stimulus intensities.** (a) Plot of SS vs PR for auditory data taken from a single guinea pig fibre [13]; (b) the same for auditory data from a single gerbil fibre [14]; (c) results for four separate guinea pig auditory fibres of both high and low spontaneous activity (squares and plus signs, high SR; circles and crosses, low SR) [15]; (d) the averaged auditory data from ferrets [16]; (e) auditory responses obtained from the saccular nerve fibres of a gold fish [17]; and (f) vision data from a single ON-centre ganglion cell in the cat [18]. The vision data differ from the other auditory data in that they are derived from pre-adapted luminance values (circle: $1 \times 10^{-5}\,\mathrm{cd\,m^{-2}}$; plus: $1 \times 10^{-3}\,\mathrm{cd\,m^{-2}}$; cross: $1 \times 10^{-1}\,\mathrm{cd\,m^{-2}}$). In all subfigures, the dashed line shows the predictions of Eq 1 which is a line with slope one-half on a log-log plot. The value of the intercept depends on the precise value of spontaneous activity. Please see text for more details.

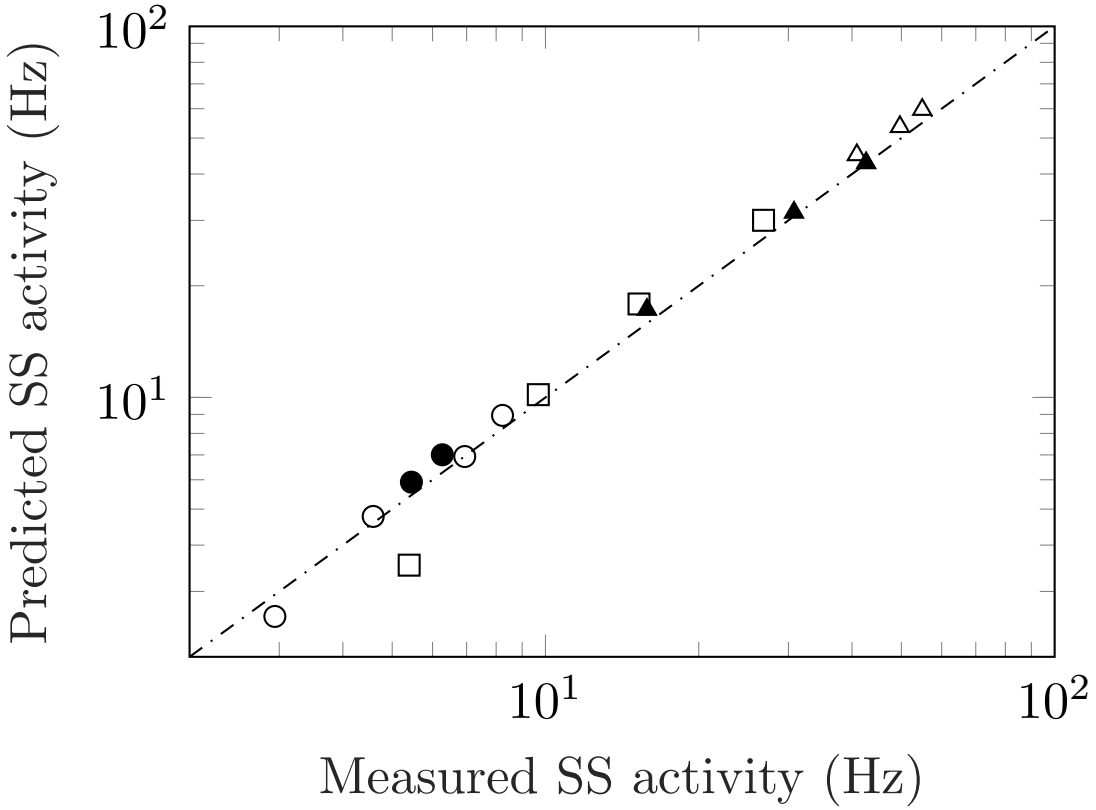

Figure 3: **Measured versus predicted steady-state activity for ascending and descending staircases.** Squares show the measured steady-state values versus predictions from Eq 2 to an ascending staircase of temperatures in warm units of bats [19]; circles (filled and open) show the same for two M1 ipRGCs in mice to an ascending luminance staircase [20]; open/filled triangles are for ascending/descending staircases of acetone concentrations from olfactory sensory neurons in fruit flies [21]. Line shows the case of perfect agreement between measurement and prediction.

These equations can be used to study how the neural response is transformed by the later stages of sensory processing.

Moreover, there are also specific classes of sensory units for which the adaptation response does not conform to the general pattern illustrated in Fig. 1. 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. [19]. 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) [29]. This may be a reason for the difference in adaptation behaviour, although the role of thermal TRP channels in mediating temperature sensing is still being debated. In touch, only the tonic or slow-adapting (SA) units show the sustained response illustrated in Fig 1b. 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, including both vertebrates and invertebrates. There is also preliminary evidence that the equation is satisfied in cnidarians. Recordings from the pacemaker cells in the visual sensory structures (rhopalia) of jellyfish not only show responses which mirror the adaptation curves found in Fig. 1b but also satisfy the geometric mean relationship [30].

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 an integral part of normal sensory function [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. 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 nerve fibres despite sizeable changes to the spontaneous, peak and steady-state rates [38]. This may be a reason for the universality of this equation among the different animal species. These equations will be useful in exploring the mechanisms underlying sensory transduction and the evolution of the senses in the different animal species.

Of the various equations in physiology, few have the simplicity of Eqs 1 and 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] and ultimately the rate is reduced to a lower, steady level. The constancy in activity ratio may in fact be due to the discriminability of the peripheral response. An equality of ratios ensures that the peak response will be as easily differentiated from steady-state activity as steady-state is from spontaneous activity.

Material 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 [40]. 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 [15], 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 (which was noted by the study authors themselves). For the M1 ipRGCs study [20], 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.

Acknowledgments

The author acknowledges a Discovery Grant from the Natural Sciences and Engineering Research Council of Canada.

References

1. Adrian ED, Zotterman Y. The impulses produced by sensory nerve-endings: Part 2. The response of a Single End-Organ. Journal of Physiology. 1926;61(2):151–171.

2. Stein RB, Gossen ER, Jones KE. Neuronal variability: Noise or part of the signal? Nature Reviews Neuroscience. 2005;6(5):389.

3. Kiang NYS. Discharge Patterns of Single Fibers in the Cat's Auditory Nerve. MIT Press, Cambridge; 1965.

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

5. Imaizumi K, Ruthazer ES, MacLean JN, Lee CC, editors. Spontaneous Activity in the Sensory System. Frontiers Media, Laussane; 2018.

6. Adrian ED, Zotterman Y. The impulses produced by sensory nerve endings: Part 3. Impulses set up by Touch and Pressure. Journal of Physiology. 1926;61(4):465–483.

7. Matthews P, Stein R. The sensitivity of muscle spindle afferents to small sinusoidal changes of length. Journal of Physiology. 1969;200(3):723–743.

8. Smith DV, Bealer SL, Van Buskirk RL. Adaptation and recovery of the rat chorda tympani response to NaCl. Physiology & Behavior. 1978;20(5):629–636.

9. Barrio L, Buño W, Segundo J. Sensory-synaptic interactions in crayfish stretch receptor neurones. Biological Cybernetics. 1988;59(6):385–394.

10. Friedrich RW, Laurent G. Dynamics of olfactory bulb input and output activity during odor stimulation in zebrafish. Journal of Neurophysiology. 2004;91(6):2658–2669.

11. Fernández C, Goldberg JM. Physiology of peripheral neurons innervating otolith organs of the squirrel monkey. I. Response to static tilts and to long-duration centrifugal force. Journal of Neurophysiology. 1976;39(5):970–984.

12. Boyd I, Roberts T. Proprioceptive discharges from stretch-receptors in the knee-joint of the cat. Journal of Physiology. 1953;122(1):38–58.

13. Smith RL, Zwislocki J. Short-term adaptation and incremental responses of single auditory-nerve fibers. Biological Cybernetics. 1975;17(3):169–182.

14. Westerman LA, Smith RL. Rapid and short-term adaptation in auditory nerve responses. Hearing Research. 1984;15(3):249–260.

15. Yates GK, Robertson D, Johnstone BM. Very rapid adaptation in the guinea pig auditory nerve. Hearing Research. 1985;17(1):1–12.

16. Sumner CJ, Palmer AR. Auditory nerve fibre responses in the ferret. European Journal of Neuroscience. 2012;36(4):2428–2439.

17. Fay RR. Sound intensity processing by the goldfish. The Journal of the Acoustical Society of America. 1985;78(4):1296–1309.

18. Sakmann B, Creutzfeldt OD. Scotopic and mesopic light adaptation in the cat's retina. Pflügers Archiv. 1969;313(2):168–185.

19. Schäfer K, Braun HA, Kürten L. Analysis of cold and warm receptor activity in vampire bats and mice. Pflügers Archiv. 1988;412(1-2):188–194.

20. Milner ES, Do MTH. A population representation of absolute light intensity in the mammalian retina. Cell. 2017;171(4):865–876.

21. Kim AJ, Lazar AA, Slutskiy YB. System identification of Drosophila olfactory sensory neurons. Journal of Computational Neuroscience. 2011;30(1):143–161.

22. Sumner CJ, Lopez-Poveda EA, O'Mard LP, Meddis R. Adaptation in a revised inner-hair cell model. Journal of the Acoustical Society of America. 2003;113(2):893–901.

23. Zilany MS, Bruce IC, Nelson PC, Carney LH. 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. 2009;126(5):2390–2412.

24. Norwich KH. On the information received by sensory receptors. Bulletin of Mathematical Biology. 1977;39(4):453–461.

25. Norwich KH, Wong W. A universal model of single-unit sensory receptor action. Mathematical Biosciences. 1995;125(1):83–108.

26. Wong W. On the Asymptotic, Near-Equilibrium Sensory Response. arXiv preprint arXiv:13076445. 2013;.

27. Graham DM, Wong KY. Melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs). In: Webvision: The Organization of the Retina and Visual System [Internet]. University of Utah Health Sciences Center; 2016.Available from: `https://www.ncbi.nlm.nih.gov/books/NBK27326/`.

28. Young ED, Robert JM, Shofner WP. Regularity and latency of units in ventral cochlear nucleus: Implications for unit classification and generation of response properties. Journal of Neurophysiology. 1988;60(1):1–29.

29. Bagriantsev SN, Gracheva EO. Molecular mechanisms of temperature adaptation. Journal of Physiology. 2015;593(16):3483–3491.

30. Garm A, Mori S. Multiple photoreceptor systems control the swim pacemaker activity in box jellyfish. Journal of Experimental Biology. 2009;212(24):3951–3960.

31. Blankenship AG, Feller MB. Mechanisms underlying spontaneous patterned activity in developing neural circuits. Nature Reviews Neuroscience. 2010;11(1):18.

32. Fitzhugh R. The statistical detection of threshold signals in the retina. Journal of General Physiology. 1957;40(6):925–948.

33. Faisal AA, Selen LP, Wolpert DM. Noise in the nervous system. Nature Reviews Neuroscience. 2008;9(4):292.

34. Eggermont JJ. Animal models of spontaneous activity in the healthy and impaired auditory system. Frontiers in Neural Circuits. 2015;9:19.

35. Tritsch NX, Yi E, Gale JE, Glowatzki E, Bergles DE. The origin of spontaneous activity in the developing auditory system. Nature. 2007;450(7166):50.

36. Trenholm S, Awatramani GB. Origins of spontaneous activity in the degenerating retina. Frontiers in Cellular Neuroscience. 2015;9:277.

37. Norena A, Eggermont J. Changes in spontaneous neural activity immediately after an acoustic trauma: Implications for neural correlates of tinnitus. Hearing Research. 2003;183(1-2):137–153.

38. Ohlemiller KK, Siegel JH. Temporal aspects of the effects of cooling on responses of single auditory nerve fibers. Hearing Research. 1998;123(1-2):78–86.

39. Laughlin SB, van Steveninck RRdR, Anderson JC. The metabolic cost of neural information. Nature Neuroscience. 1998;1(1):36.

40. Churchland MM, Byron MY, Cunningham JP, Sugrue LP, Cohen MR, Corrado GS, et al. Stimulus onset quenches neural variability: A widespread cortical phenomenon. Nature Neuroscience. 2010;13(3):369.