

Fluctuation in excitability
A personal account in honour of Charles Pecher
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www.verveen.eu

For Evelyn Pecher and her mother Jacqueline, for Carla Webbles and Janine Pecher-Webbles

General introduction

The nervous system receives, processes and sends signals throughout the body. The basic signal processing units of the nervous system are the nerve cells or neurones (Figure 1).

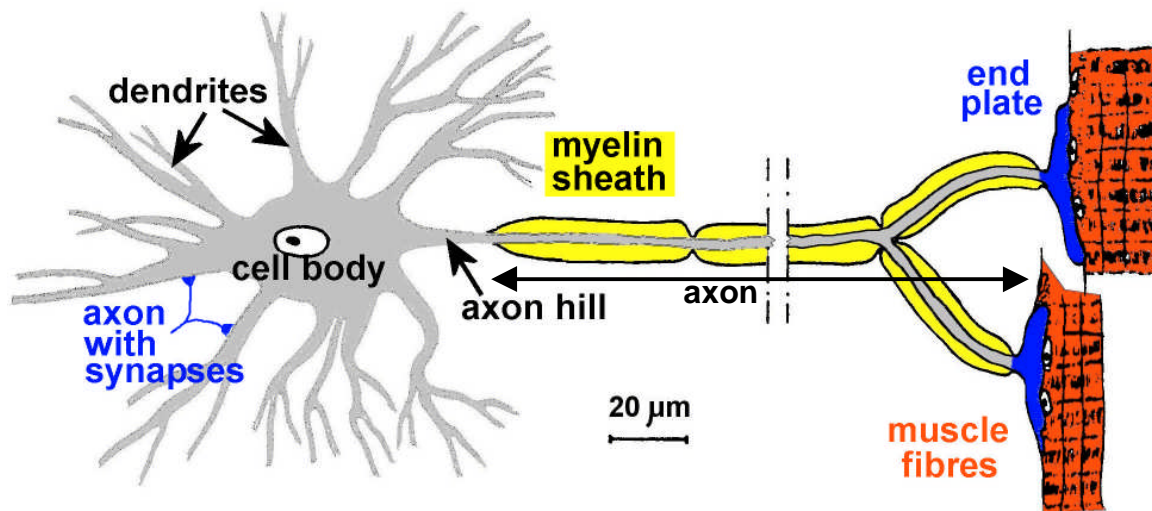


Figure 1. Diagram of a neurone controlling a muscle fibre (motoneuron or motor neurone).
The isolating myelin sheath is missing in some types of neurones

Neurones receive input from other neurones (or from specialised sensors) through transmission spots (called synapses) located on small receptive extensions (so-called dendrites) of the neurone. The resulting variations in electrical potential over the cell membrane (the outer coat of the neurone) are integrated at the axon hillock, the place where the nerve fibre (also called axon) originates. When the electrical variation at this point transcends a given value (called “threshold”) a unitary (digital) electrical signal, the action potential, is generated and transported over the nerve fibre towards its destination, which is either another neurone, or a muscle fibre or some other specialised structure. For a muscle fibre, the end plate is a giant synapse.

A nerve contains many nerve fibres. Each nerve fibre is a microscopically thin cable that transports action potentials into, within or out of the nervous system. Each nerve fibre consists of a hollow tube (the nerve membrane). It contains an ion-containing solution rich in potassium ions and lies in another ion-containing solution rich in sodium ions. A nerve fibre responds with an action potential to an electrical stimulus of sufficient intensity. An action potential consists of a transient change in electrical voltage over the nerve membrane (Figure 2).

The action potential has a fixed shape (thus its digital nature, the triangular shape in Fig. 2). It travels along the axon like a fire over a fuse. In contrast with a fuse, however, a nerve fibre restores to its original condition. This occurs within the time span of a second. In our

mentioned investigations, we had, therefore, to wait for restoration to be completed before we could apply the following stimulus. Otherwise, contamination of our measurements with effects of partial restorations of the foregoing action potentials would occur.

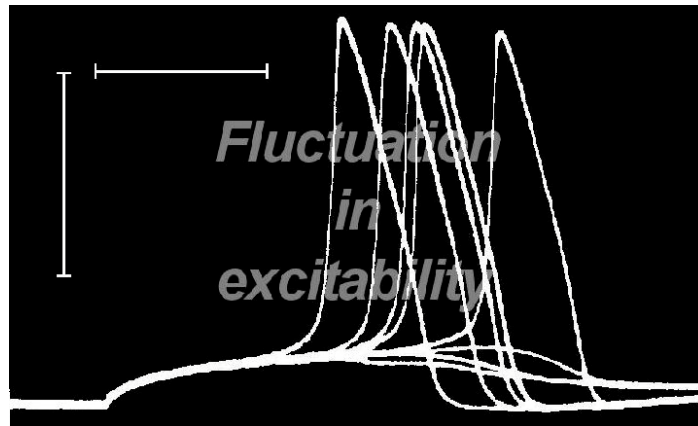


Figure 2. Eight stimuli of about threshold intensity resulting in five action potentials. Bars: millisecond (horizontal) and 50 milliVolt (vertical). Stimulus frequency: one per two seconds.

(Verveen & Derksen, 1968, also reproduced in www.verveen.eu/Figuur_01.html)

Information is contained in the action potential pattern travelling over a given axon towards another neuron or an effector cell such as a muscle fibre, much like the pattern of the digital pulses flowing over wires into, within and out of processors within computers, or like the frequency modulation of TV or radio waves beamed to their receivers.

The action potential is an all-or-none event. It occurs when the electrical stimulus “exceeds a critical value called threshold and it does not appear when stimulus strength lies below the threshold”.

Personal account

I joined the staff of the Netherlands Central Institute of Brain Research at Amsterdam, at first during the waiting times between the clinical stages of the study in medicine. There, I had to teach myself neurophysiology. Early in 1958, I started with the preparation of the sciatic nerve (hind leg nerve) of pre-killed (pithed and brain destructed) frogs. The nerve preparation was kept alive in a suitable solution (so-called Ringer’s solution).

At my very first experiment with electrical stimulation of a living frog nerve, I was utterly surprised when I saw its responses to these stimuli. The compound action potential, which is the sum of the individual electric responses of its many nerve fibres, did not show the textbook-expected all-or-none behaviour mentioned above. Instead, the composite response fluctuated significantly and unpredictably in the presence of a constant stimulus (that was repeatedly applied, but at a low frequency, such to avoid the occurrence of the successive influences mentioned above). The word “constant” refers to stimulus duration (fixed) as well as stimulus intensity (strength, amplitude).

I then modified the set-up, to record the responses of only one or two axons. The one-axon set-up showed the non-existence of a sharp threshold. In between the “all-behaviour” and the “none-behaviour” each axon showed an S-shaped threshold range (Fig. 3). Within this threshold range, the occurrence, yes or no, of an action potential upon a given and constant stimulus, can not be predicted: it is due to chance. The nerve fibre turned out to bet. This

betting behaviour could be investigated only by repeated application of the same stimulus. Its outcome (as given by each single row of fixed stimulus intensities in the left part of Fig. 2) follows after dividing the number of action potentials by the number of stimuli. This number lies within the range from zero to one. It describes the probability for a positive betting-result by that nerve fibre (namely the occurrence of an action potential) for that stimulus and is called the “probability of response” (response probability, probability of occurrence, symbol: p). It depends on the intensity (size, amplitude) of the stimulus. For each stimulus, only a probability of response could be defined. “Certainty” (in a loose sense) applies only to those parts of the range where the probability is about zero (so no response is to be expected at low stimulus intensities) or about one (always a response to a high intensity stimulus).

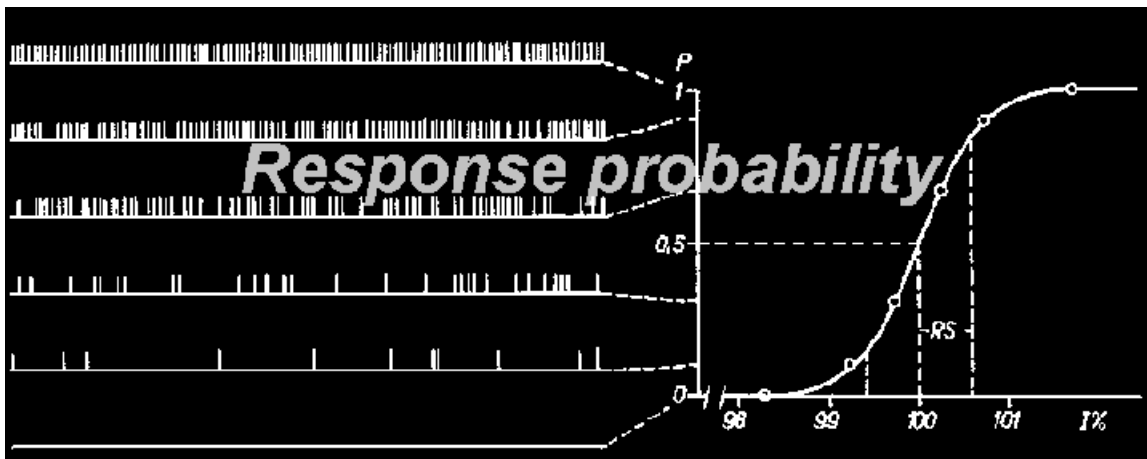


Figure 3. The occasional responses of a nerve fibre to repeated low-frequency stimulation with a constant stimulus. Response series for six different stimulus intensities (Verveen, 1960, also reproduced in Verveen & Derksen, 1968 and www.verveen.eu/Figuur_02.html)

Although I knew my stimuli to be stable (their own variability was sufficiently small with respect to nerve fibre variability), this could as such not be considered a valid argument. However, in a preparation with two nerve fibres one sometimes encounters a situation in which their response ranges overlap. One fibre responds only rarely to a given constant stimulus (the low-probability responder) while the other responds more often to it (the high probability responder). One then notes that each axon responds independent of the other for the low-probability responder sometimes produces an action potential in the absence of a response of the higher probability responder. This proves that the phenomenon can not be caused by stimulus fluctuations and is, therefore, due to fluctuating processes located within each individual axon.

Charles Pecher

I then set out to investigate fluctuation in excitability in quantitative detail. A search of the literature was needed first, for textbooks did not mention this phenomenon at all. The textbook writers had most probably assumed the quite evident response variability to be caused by shortcomings of stimulus amplitude stability. This possibility forms a common pitfall indeed, in our case called “stimulus artefact”. Recent reports in the literature about this probability phenomenon, which must have been obvious to every physiologist who recorded from electrically stimulated nerve or nerve-muscle preparations, were of no help either since they did not exist, probably because it was still considered a stimulus artefact.

Retrieval aids were lacking in those days. So I set out to visit the university libraries regularly, to leaf through the main English, German and French physiological journals. For each year of publication, I studied all physiological journals in that order of languages, thoroughly, while I worked backwards in time to detect the most recent paper on the subject, with the intent to save time by the use of its references for a more detailed search. Several unsuccessful months passed in this way for I investigated all fifth decade physiological journals in vain. The journals published in the fourth decade bore no fruit either. I hit gold at last in the publications of 1939, within the last consulted, therefore, French volume. It contained an article that was both a report, as well as a review (6) on the subject, written by a Belgian by the name of Charles Pecher.

This paper also provided me with the data on his two earlier papers (4 and 5) as well as with references to his predecessors (1 – 3) (here numbered according to the sequence of publication, see the references for details):

(1). Monnier, A. –M. & H. H. Jasper, 1932. (A new demonstration of the “all-or-none” behaviour of the nerve fibre).

(2). Blair, E. A. & J. Erlanger, 1932. Responses of axons to brief shocks.

(3). Blair, E. A. & J. Erlanger, 1933. A comparison of the characteristics of axons through their individual electrical responses

(4). Pecher, Ch., 1936. (Statistical study of the spontaneous variations in excitability of a nerve fibre).

(5). Pecher, Ch., 1937. (Independent fluctuations in excitability of two fibres in the same nerve).

(6). Pecher, Ch., 1939. (Fluctuation in excitability of the nerve fibre).

Note that Charles Pecher’s papers (written in French) can be retrieved from my website.

I realised that the work of these authors on the subject of fluctuation in excitability, seemed to be utterly forgotten, judging from the lack of papers on the subject of fluctuation in excitability of axons or neurones in all subsequent volumes up to my first publication (Verveen, 1960). However, I discovered later on that, at about the end of the fifth decade, two other people had also discovered Pecher’s work, and that they had used his results in the interpretation of their own investigations: Lawrence S. Frishkopf (1956) and Warren S. McCulloch (1958) at the Massachusetts Institute of Technology (MIT), Cambridge, USA. Frishkopf used Pecher’s results in the interpretation of the stochastic (chance) nature of sensory (auditory) receptor output. Warren McCulloch’s work is particularly interesting, because he posed the question “how a network of unreliable neurones still produces reliable results.” Note that they did not try to investigate fluctuation in excitability as such.

I wondered why Pecher had not continued his promising investigations after World War II. So I tried to learn more about him but in vain. Upon a letter, to the Brussels’ Institute Solvay mentioned in his publications I obtained the answer that they did not have any information about him. I assumed, therefore, that he must have died at a young age.

This was a pity for, in my search for clues about his motivation, I could only examine his work as such. His papers were, of course, written following scientific practice, so they did not contain his ideas on the possible function(s) of this interesting phenomenon, apart from a paragraph near the end of his 1939 publication (see below).

That his work was forgotten, is not too surprising, for the number of people interested in positive and, therefore, useful, effects of random processes existing within us (such as

fluctuations and noise) is extremely small. In the context of our “fight against uncertainty”, we by and large play the ostrich. So we deny the existence of uncertainty and chance (³), albeit inconsistently given the popularity of gambling to try to better one’s life. The denial of the existence of uncertainty and its possible functions appeared within neurophysiology as well, as will become clear below.

Excitability fluctuations in nerve fibres, could only be noted after the introduction of the oscilloscope in physiology by Gasser and Erlanger in 1932, and after the development of sufficiently powerful and reliable methods of amplification. As a result, the individual responses of nerve fibres became detectable in 1932. Only then could their kaleidoscopic appearance be noted. The random nature of the appearance of these “elementary action potentials” was immediately recognised, both by Monnier and Jasper (1932, p. 549) and Blair and Erlanger (1932, p. 530). The latter found that “The irritability of axons [. . .] varies spontaneously through a narrow range”. They concluded: “presumably this and the latency variations are an expression of spontaneous alterations in reactivity.” (p. 562), for when “two fibres are stimulated with threshold shocks all possible response variations are seen” from which they concluded that “they must be due to spontaneous and independent variations in the irritabilities of the two fibres.” (p. 530).

The term “latency” applies to the duration of the interval between the beginning of the stimulus and the beginning of the response, here the action potential, cf. Figure 2.

Pecher must have been stricken by the random nature of the responses of axons, so he started a thorough, quantitative statistical investigation of this phenomenon. In his first publication (Pecher, 1936, recounted in Pecher, 1939), Pecher reported the results of his statistical study of the distribution of sequences of positive (action potential) and negative (none) responses to repeated stimulation. This was done at low frequencies, to avoid modification of the response by restoration effects. He showed that these sequences could be described as following the laws of chance: “L’examen des tracés montre que la répartition des ripostes est parfaitement compatible avec les lois du hasard, aussi longtemps que la fréquence d’excitation est de l’ordre de 1 par seconde.” (The examination of the sequences shows that the distribution of responses is perfectly compatible with the laws of chance, as long as the excitation frequency remains of the order of one per second). In his second paper (Pecher, 1937), Pecher wrote that:

“Le rapport du nombre des réactions obtenues au nombre d’excitations provoquées définit la probabilité de réaction.”

(The quotient of the number of positive responses divided by the number of stimuli defines the probability of response.)

Here, this quotient, the probability of response for a given nerve fibre (here to be called fibre c) at a fixed stimulus intensity, is written as $p(c)$ and reads as “the (response) probability p of nerve fibre”. For preparations in which each of two almost equally excitable nerve fibres within the same nerve showed a fluctuating response to the same stimulus Pecher confirmed Blair and Erlanger’s observation that all possible response combinations occur (Figure 4).

The action potential, of the axon with the lowest number of responses, so with the highest threshold, does occasionally appear without the response of the other, more sensitive, fibre. A similar phenomenon occurs for the fluctuations in latency: when both responses appear then their mutual positions in time fluctuate independently of each other. These phenomena indicate that the sources of the fluctuations are located within the nerve fibres, and are not due

to small random variations in stimulus intensity. Both phenomena are evident in Pecher's 1937 picture, here reproduced in Figure 4.

Pecher, however, set out to investigate this in statistical detail. For a given fixed stimulus intensity, Pecher measured the response probability $p(a)$ of fibre a and $p(b)$ of fibre b, as well as the probability of their simultaneous occurrence, the combined response probability $p(a+b)$. A well-known law states that when two mutually independent random all-or-none events occur then the probability of their combined occurrence is equal to the product of their individual probabilities: $p(a+b) = p(a) \times p(b)$. Pecher showed this to be indeed the case, thus:

“Les fluctuations d’excitabilité de deux fibres d’un même nerf sont donc complètement indépendantes l’une de l’autre.”

(The fluctuations in excitability of each of the two fibres of the same nerve are, therefore, completely independent of each other.)

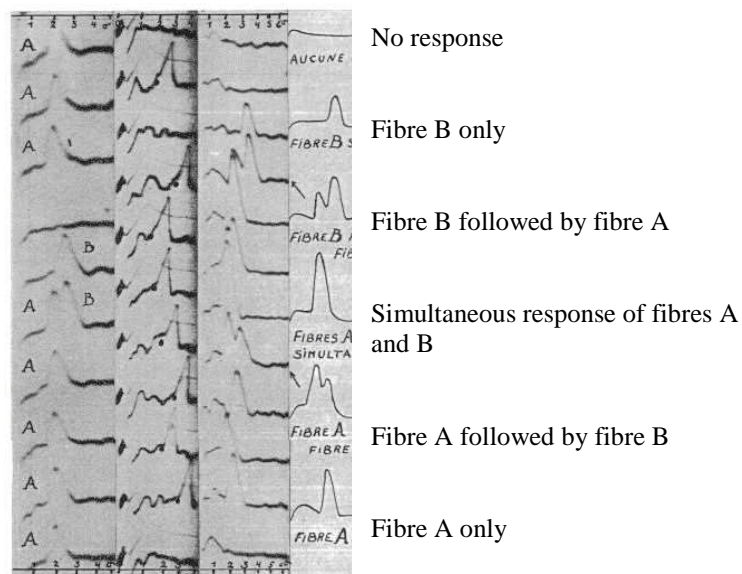


Figure 4. External recording of the action potentials of two nerve fibres in a single nerve, responding to the same stimulus (Pecher, 1937)

He amplified this conclusion in his third paper (Pecher, 1939), where he tabulated the results of nine two-fibre observations (“Tableau I. – Fluctuations d’excitabilité de deux fibres”) where he showed the close correspondence between the calculated probability of each combined response and its observed probability (Pecher, 1939 p. 137). He concluded that these fluctuations were a property of the nerve fibre itself, thus should be called “fluctuations of excitability” (or “fluctuation in excitability”):

“Ces fluctuations apparaissent au sein du nerf et nous pouvons donc les qualifier de fluctuations de l’excitabilité.”

(The fluctuations are situated in the heart of the nerve, and we may, therefore, qualify them as excitability fluctuations).

He continued :

“Elles se manifestent entre autres, selon deux aspects: fluctuation du seuil d’excitation et fluctuation du temps de latence.”

(The fluctuations manifest themselves in two ways: a fluctuation of the threshold of excitation and a fluctuation in latency, the interval of time between stimulus and response.)

He then investigated these two aspects in detail.

He noted that the S-shaped curve relating response probability to stimulus intensity resembled the integral of the Galton curve (¹) (Pecher, 1939, Fig. 2 on p. 138) (Figure 5).

Pecher then defined the average threshold (“seuil moyen” p. 139) as the stimulus intensity corresponding with the halfway point, i.e. the intensity that elicits 50 responses to 100 stimuli (Pecher, 1939, Fig. 2 on p. 138), thus with a response probability of 0.5 or 50 percent. The average threshold varies widely because of the changes in distance thus resistance between stimulus electrode and the nerve fibre under investigation. To compare different fibres he used relative stimulus intensities. This sets the intensity of the stimulus at the threshold to 100 percent (Pecher, 1939, Table 2 on p. 139).

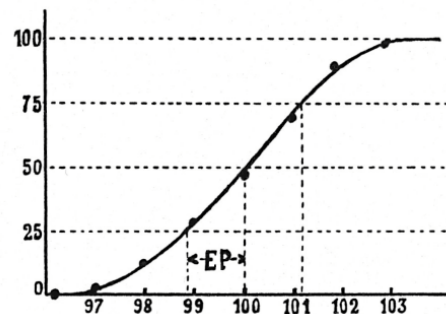


Figure 5. Integral of the Galton curve. (Pecher, 1939).

EP: “écart probable” (probable spread, i.e. the interquartile range) (here relative).

Horizontal axis: Stimulus intensity plotted *relative* to threshold intensity (set at 100%).

Threshold intensity is defined as the intensity at which the response probability is 50 %.

Vertical axis: response probability in percent

From drawings of the S-shaped graphs of stimulus intensities and response probabilities (the cumulative distribution function, Figure 5), he derived a measure for the spread of each distribution. The equally sized differences between each of the two quartiles (relative stimulus intensities for which the probabilities are 25 percent and 75 percent respectively) and the average threshold was called by him the “écart probable”, abbreviated to EP (probable spread, i.e. the interquartile range, also called the midspread or middle fifty) (Figure 5). Their values varied between 0.7 and 2 percent of the average threshold, corresponding with “maximal” values for the spread of the whole range of between 2 and 5 percent (Pecher, 1939 Table II p. 139).

For the fluctuation in latency, Pecher noted the asymmetrical shape of the curves describing the occurrence probability with time after the initiation of the stimulus (Pecher, 1939, Fig. 3 p. 142) and he also started an inquiry into the effects of stimulus duration and variation in stimulus frequency.

In the discussion, Pecher investigated probable causes for the phenomenon. He rejected degradations of the preparations as well as macroscopic temperature fluctuations. He also noted that thermal noise, called by him the effects of electrical resistivity (“les caractéristiques électriques de la membrane polarisée de la fibre nerveuse” Pecher, 1939, p. 148) is too small to explain the size of the fluctuations. He then set out to show that a statistical variation in ion number could indeed explain the phenomenon, probably together with other local sources of fluctuations. He believed that fluctuations due to the discontinuity

of matter should necessarily play an important role. He stated this rather cautiously (Pecher, 1939, p. 149/150):

“... la fluctuation d’excitabilité due à la discontinuité de la matière, intervient pour une part certainement non négligeable dans la fluctuation que nous avons observée expérimentalement.”

(the fluctuation in excitability due to the discontinuity of matter interferes with a certainly non-negligible part in our experimentally observed fluctuations.)

He then states that more precise investigations are needed to be able to explain the excitability fluctuations (Pecher, 1939, p. 150). At this moment, his investigations halted and could, alas, never be taken up by him again.

Pecher then asked whether similar phenomena played a role elsewhere in the nervous system. He mentioned two likely spots, namely sensors and synapses. He proved to be prophetic in both instances (Pecher, 1939, p. 150):

- Several types of sensors produce irregular sequences of action potentials that must have been generated by irregular fluctuations and that may act as information carriers (cf. Verveen and Derksen, 1965).
- In the 1950’s B. Katz and co-workers (starting with Fatt & Katz, 1952) showed that synapses (cf. Figure 1) produce irregularly occurring miniature synaptic potentials of which the probability of occurrence increases much upon the arrival of its action potential.

As regards possible functions of the fluctuations, Pecher notes that their effects will cancel in large systems, thus are non-notable, but (Pecher, 1939, p. 150):

“Il n’en est peut-être plus ainsi, si l’on considère des processus nerveux plus subtils, mettant en jeu seulement quelques influx dans quelques neurones.”

(But this is probably not the situation in case of more subtle neural processes, especially when processing just some input into a few neurones.)

He did not speculate further on the subject, which is a pity, but speculation does not belong in a scientific report as such (neither did I in my official publications). However, I do think that, in his concluding paragraphs, Pecher lifted a corner of the veil that covers the question why he chose to study precisely this phenomenon.

Extension of the quest

On the basis of Pecher’s work, I now continued my own quest, as well as Pecher’s, had he lived, to further the quantitative analysis of fluctuation in excitability. Despite earlier work, people were still considering the irregular fluctuations to be an artefact caused by stimulus variability. So I had to examine the statistical nature of the response sequences again, though with a different method (the run test). I analysed my data on response probability versus stimulus intensity with a method - 'probit analysis' - with the use of one of the early computers (Electrologica X1 at the Mathematical Centre in Amsterdam, with ALGOL 60 as its programming language).

The size of the relative spread (RS: standard deviation divided by mean intensity; instead of the interquartile range EP as such) was calculated for sequences of constant stimuli applied to the same nerve fibre.

From experiments with variation of stimulus duration between the different sequences, followed that the size of the RS does not depend on stimulus properties, so the RS appeared to be a real parameter of the fluctuation in excitability (Verveen, 1960), expressing the size (amplitude) of the fluctuations.

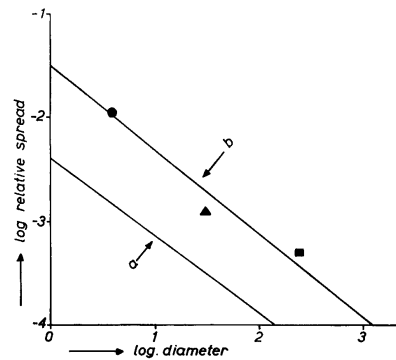


Figure 6. Relationship between nerve fibre diameter and relative spread.

Line a. Fluctuation size expected from intrinsic thermal noise.

Line b: Line expressing actual noise level, about 10 times that of the thermal noise level (Verveen, 1962)

In order to try to understand the nature of the phenomenon or phenomena behind it, the effect of some chemicals was investigated (Verveen, 1961), as well as that of nerve fibre diameter (1962).

A clear inverse relationship was found between RS and fibre diameter (Figure 6, Verveen, 1962), with a much larger size of the RS than could be expected from white electrical noise (thermal noise). From these experiments followed that *the size of the fluctuations is larger, the smaller the diameter of the excitable element is.*

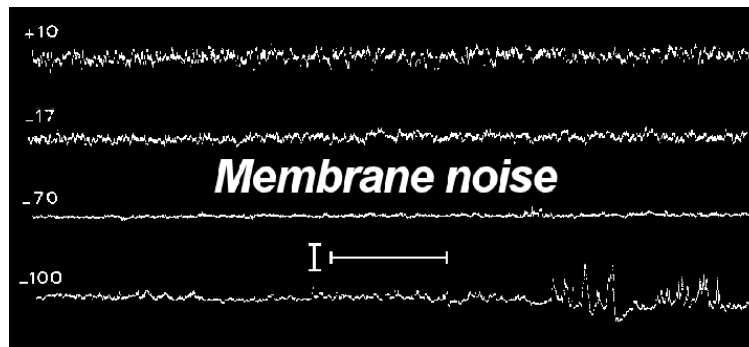


Figure 7. Electrical membrane noise

Its intensity and "shape" depends on membrane potential (in mV, at left, inside of the nerve fibre with respect to outside).

Units: 5 mV (vertical) and 1 ms (horizontal).

(Verveen and Derksen, 1968)

Injections of electrical noise (figure 7), in an electrical model for the nerve fibre, showed that noise as such could reproduce all known properties of the excitability fluctuations (Ten Hoopen and Verveen, 1963). It also followed, that noise sensitised the nerve (model) to weak stimuli (see also Figure 8 C).

A multineurone model, made by Derksen, showed that the introduction of mutually independent noise sources into the neurones smoothed and linearised the output of the neurone network model with respect to its input (Derksen, 1964) (Figure 8).

Late in the year 1962, Derksen and I learned of each other's interests, so we decided to join forces to try to investigate the underlying physiological process. We developed a set-up for

the direct measurement of the voltage over the nerve membrane at the microvolt level, instead of the millivolt level then in use. With this set-up, our measurements did indeed show the random pattern of voltage fluctuations (Figure 7. So-called “membrane noise”, also visible as the tiny fluctuations of each of the traces in figure 2), which led to Derksen’s PhD thesis, in 1965. Since the discovery of membrane noise was the result of the combined work of the two of us, we intended to publish this at about the same instant of time in *Science*, but the appearance in this journal was delayed by the familiar question posed by the referees who thought the reported noise pattern to be a stimulation artefact. However, it was finally and belatedly accepted for publication (Derksen and Verveen, 1966)⁽²⁾.

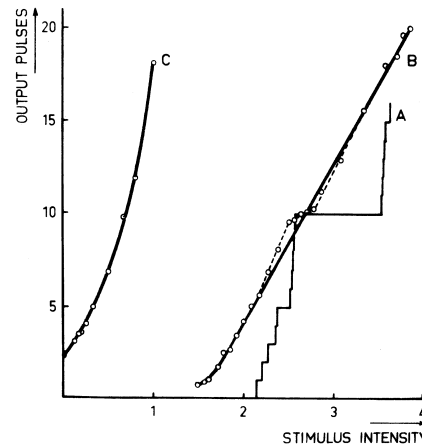


Figure 8. Response of a model, that consisted of several model neurones, to stimulation with a 100 ms series of 10 pulses. Each pulse lasted 1 ms (millisecond). Their intensity was changed:

A. as such (without noise), B. with noise added, C. like B but with decreased neurone thresholds

(Adapted after Derksen (1964), also reproduced in www.verveen.eu/Figure_05.html)

We measured the frequency spectrum of the membrane noise: the plot of the intensity of each frequency component versus its frequency. This spectrum, appeared to belong to the so-called one-over-f type, at which noise intensity at each frequency component f equals a constant times $1/f$. In this paper, we also showed that the noise was associated with potassium ion transport.

In 1965, we published a paper showing that neural noise could explain sensor behaviour (Verveen and Derksen, 1965).

Membrane potential and action potential were, at that time, theorised to be generated by the action of potassium channels and sodium channels situated within the nerve (neurone) membrane (Hodgkin and Huxley, 1952).

Theorists showed that kinetics of the then still theoretical membrane channels could generate electrical membrane noises of the one-over-f-squared noise or $1/f^2$ noise pattern (figure 9). From this pattern, electrical channel resistance as well as the number of channels involved could be derived (Hill and Chen, 1972; Stevens, 1972). To our disappointment no generally applicable theory existed (nor exists) to describe the $1/f$ kind of noise spectrum.

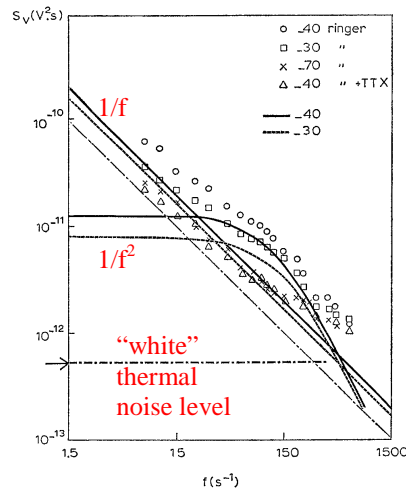


Figure 9. Different kinds of noise present in a nerve fibre.
Open symbols: measured noise spectrum, lines: 1/f, 1/f-squared and white noise components.

Vertical axis: log noise intensity, horizontal axis: log frequency component.
(After Van den Berg, de Goede and Verveen, 1975)

In a series of publications published between 1972 and 1975 with Siebenga, Meyer, de Goede and van den Berg, we showed that different ionic membrane-channel systems did indeed generate their own membrane noise pattern (cf. Siebenga and Verveen, 1972), as was also shown by Fishman and co-workers from 1972 onward.

From the analysis of the noise pattern, the number of channels involved in such a system could then be calculated as well as single channel resistance. For sodium channels is referred to the papers by Siebenga et al. (1972, 1973 and 1974) and by Van den Berg et al. (1975); and for potassium channels to the papers by Van den Berg et al. (1977 and 1984). For membrane noise and membrane channels in general, I refer to the work of DeFelice with whom I wrote a - - for me final - review paper on membrane noise in 1974. Since 1974/75, Van den Berg and DeFelice carried on with and extended upon these investigations.

These results, as well as the work on synaptic noise by Katz and co-workers (1951 and later), induced other investigators, to search for and develop innovative methods to investigated these channels, especially the patch clamp technique (Neher and Sakmann, late 1970's and their co-workers).

A chance discovery of an elongated hourglass inspired me to investigated the flow of particles through its long stem. Its pattern suggested a comparison with the flow of ions through a membrane channel (Schick and Verveen, 1974).

In a well-executed set of investigations, Van den Berg, in coöperation with De Goede and De Vos (1981 – 1989), showed that the spectrum of the noise of ions flowing through a well-defined channel shows no 1/f noise at all. The noise existing in such a system can be explained by fluctuations in the number of the ions present within the fluid flowing through the channel. 1/f noise appears when the complexity of the system increases, for instance by the presence of larger particles tending to obstruct the pore. One may conclude that the 1/f noise types may be an indication of system complexity.

Possible functions of the noise and some practical applications

- Neurons are noisy elements, where noise sources are present at the input sites (the synapses, Figure 1) as well as at its output site (the axon hillock, Figure 1). They are, therefore, modulating randomness. This aspect of their function is especially pronounced when the decision level is critical (Figure 3).

- The inverse relationship between the amplitude of membrane noise and the diameter of the triggerable neural unit (Verveen, 1962), implies that for extremely small neurones, as well as for the thin nerve fibre “endings” situated in receptors (Verveen and Derksen, 1965), irregular sequences of action potentials are generated by the noise (Ten Hoopen and Verveen, 1963). Such stochastic (i.e. random) series may be useful in multiunit parallel network systems:
 - They may function as carrier waves for signalling small variations in receptor inputs.
 - The irregular spacing between the action potentials in such sequences, in nerve fibres, avoids accidental crosstalk between the fibres as may otherwise occur because of their dense packing within nerves and within other nervous tissues, thus conserves the original information content transported by the individual nerve fibres.

- Deterministic patterns may have the effect of wearing blinkers (blinders) and random processes may, therefore, play a valuable role in our brain for it to let us generate new ideas (“creativity”) and to allow us to gain an original attitude (“free will”):
 - Extremely small neurones, present within the nervous system, may produce spontaneous activity, i.e. activity generated in the absence of input into such neurones. Such activity may enable unusual combinations to occur. Like in evolution, most combinations will not lead to meaningful activity and will be filtered away, but useful new activity may occur once in a while. Such activity may, therefore, be involved in creative processes. Think for instance of the spontaneous occurrence of an entirely new solution to a problem one has been carrying around for some time.
 - Since larger neurons are less noisy, they may be involved in functions that require high accuracy. The anatomical structure of neurons as visible in cortical slices may as such be indicative of the degree of randomness allowed or even used within the system involved. The large size of, for instance, many motoneurons, thus implies high accuracy requiring activities.
 - A related result of such spontaneous activity may be the resolution of a mental block of some sort, comparable with the application of a random hit to a mechanical or analog electrical apparatus that “refuses” to function at some moment in time.
 - Neuronal “betting” at critical decision levels will lead to similar results.

- Neural noise increases the quality of the statistical stimulus response relationship within networks of neurones since it increases as well as linearises the range over which information is gathered and transmitted (Derksen, 1964) (Figure 6).
This possibility has been used in the construction of a functional hearing implantation (Bruce et al. 1999).

- The mentioned 1974 hourglass paper became popular around the turn of this century in theoretical and applied studies of systems with flows of macroscopic particles, such as heavy road traffic, in the transshipment of grain and other particles and of many people trying to move through narrow doorways.

This discussion shows again that science is a continuous process carried out by individuals in relation to what other individuals did before, much like Google Scholar coins in its motto: "Stand on the shoulders of giants", although we have to keep in mind that giant size is quite variable and waxes and wanes during the course of time" (<http://scholar.google.com/>).

Note added in January 2012

Charles Pecher's fate remained a mystery for an extraordinarily long time. About five decades later, early in 2009, I received out of the blue an e-mail from Carla Webbles, a cousin of Charles Pecher, who had just heard that her uncle had died in 1941, under highly questionable circumstances. Searching the internet she had discovered references to me in relation to Charles Pecher's work and, therefore, mailed me to obtain more information. I was flabbergasted by it, and wrote the first version of this very article to tell her, her mother and Charles Pecher's daughter Evelyne Cerf-Pecher, born after her father's death, how much I admired him.

By that time, Evelyne had already set course on an admirable path of discovery of her father's work and destiny. She uncovered an extraordinary though sad story, published in 2011, about this brilliant and resourceful man who had embarked on another fascinating field of science, for which he moved from Belgium to the USA in September 1939. There, his investigations concerned the pioneering use of radioactive substances in medicine. This work falls outside the scope of my discussion, here, but for the notion that it is remarkable that both fields contain a common denominator given by the role of chance within nerve fibres as well as - indirectly - by the use of radioactive isotopes! This happened in 1941, early during World War 2, and radioactivity became a subject of basic military importance. As a result, not only his work was declared a military secret but, because of his knowledge of radio isotopes, he was a secret himself in a sense! He became tragically entangled in its consequences as a result, for the different interests of his own country, and his new one mangled him and led to his untimely death at the end of August 1941.

His work on radioactivity and medicine remained a military secret for an extraordinarily long time, but it has recently been rediscovered. His pioneering work in nuclear medicine is, therefore, now fully recognized, as one can see using Google Scholar.

Notes

==> 1966 ¹ The 1965 publication in *Science* marked a breakthrough. Despite proof to the contrary peer reviewers considered the fluctuations to be due to instrumental noise. This was the first instance of acceptance of our work for publication in a high-rating journal. I think that people are still extremely reluctant to consider that our brain may function on a probability basis. Even more so when we consider the fact that any neuron, "facing" a critical decision, resorts to betting, using an input weighted probability of response.

² cf. http://www.galtoninstitute.org.uk/Newsletters/GINL9909/francis_galton.htm.

It is sometimes called "relation of de Moivre"

(<http://www.nature.com/nature/journal/v132/n3340/abs/132713a0.html>).

Nowadays this relation (the Law of Error) is called the normal or Gaussian (density) distribution, sometimes going by the name of frequency curve or Bell curve. The S-shaped integral or 'cumulative distribution function'.

³ Recently, I coined the term "*horror incerto*", fear of uncertainty, for this phenomenon. (March 13th, 2012, www.verveen.eu/index).

References

- Blair, E. A. & J. Erlanger, 1932. Responses of axons to brief shocks. Proc. Soc. Exp. Biol. and Med., 29: 926-927.
- Blair, E. A. & J. Erlanger, 1933. A comparison of the characteristics of axons through their individual electrical responses. Am. J. Physiol., 106: 524-564.
- Bruce, I.C. , M.W. White, L.S. Irlicht, S.J. O'Leary, G.M. Clark, 1999. The effects of stochastic neural activity in a model predicting intensity perception with cochlear implants: low-rate stimulation IEEE Transactions on Biomedical Engineering, 46(6):617-629.
- Bruin, G. de, I. Guy and R.J. Van den Berg, 1984. Single potassium channel conductance in the frog node of Ranvier. Biophys. J. 45: 855-858.
- Cerf-Pecher, Evelyne, 2011. Mon père Charles Pecher, l'homme de sciences, 1913-1941 avec en annexe "The story in English" ... the scientist, World War 2, the forgotten pioneer ... Didier Devilled Éditeur, Bruxelles
- Derksen, H.E., 1964. Discussion. In: Information processing in the nervous system. R.W. Gerard and J.W. Dwyff, eds. Proceedings of the International Union of Physiological Sciences, 22d International Congress, Leiden, vol. 3: 384-394.
- Derksen, H.E., 1965. Axon membrane voltage fluctuations. Acta Physiol. Pharmacol., Neerlandica 13: 373-466
- Derksen, H.E. and A.A. Verveen, 1966. Fluctuations of resting neural membrane potential. Science 151: 1388-1389.
- Fatt, P. and B. Katz (1951) An analysis of the end-plate potential recorded with an intra-cellular electrode. J.Physiol.115, 320-370.
- Fishman, H.M., 1972. Excess noise from small patches of squid axon membrane. Biophys. Soc. Abstr, 1972
- Frishkopf, Lawrence S., 1956. A probability approach to certain neuroelectric phenomena. Reserach Laboratory of Electronics, M.I.T., Technical Report nr. 307.
Link:
<http://dspace.mit.edu/bitstream/handle/1721.1/4775/RLE-TR-307-04734586.pdf?sequence=1>
- Hill, T.L. and Yi-Der Chen, 1972. On the Theory of Ion Transport across the Nerve Membrane. Biophysical Journal, 12 (8): 948-959.
- Hodgkin, A., and A. Huxley, (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117:500–544.
- McCulloch, Warren S., 1958/59. Agatha Tyche: Of nervous nets –the lucky reckoners. Reprinted in W.S. McCulloch, 1965. Embodiments of mind. The MIT Press, Cambridge, Massachusetts

Monnier, A. -M. & H. H. Jasper, 1932. Recherche de la relation entre les potentiels d'action élémentaires et la chronaxie de subordination. Nouvelle démonstration du fonctionnement par "tout ou rien" de la fibre nerveuse. C. R. Soc. Biol. 110: 547-549.

(Investigation of the relationship between elementary action potentials and the "chronaxie de subordination". A new demonstration of the "all-or-none" behaviour of the nerve fibre).

Neher, E. & Sakmann, B. 1976. Single-channel currents recorded from membrane of denervated frog muscle fibres.

Nature 260, 799-801.

Pecher, Ch., 1936. Étude statistique des variations spontanées de l'excitabilité d'une fibre nerveuse. C. R. Soc. Biol. 122: 87-91.

(Statistical study of the spontaneous variations in excitability of a nerve fibre).

Pecher, Ch., 1937. Fluctuations indépendantes de l'excitabilité de deux fibres d'un même nerf. C. R. Soc. Biol. 124: 839-842.

(Independent fluctuations in excitability of two fibres in the same nerve).

Pecher, Ch., 1939. La fluctuation d'excitabilité de la fibre nerveuse.

Arch. Intern. Physiol. 49 (2): 129-152.

(Fluctuation in excitability of the nerve fibre).

Schick, K. L, and A.A. Verveen, 1974. 1/f noise with a low frequency white noise limit.

Nature 251: 599-601.

Siebenga, E. and A.A. Verveen, 1972. Membrane noise and ion transport in the node of Ranvier.

In: Biomembranes vol. 3: Passive Permeability of Cell Membranes, F. Kreuzer and J.F.G. Slegers, eds., Plenum Press, NY – London: 293-298.

Siebenga, E., A.W.A. Meyer and A.A. Verveen, 1973. Membrane shot-noise in electrically depolarized nodes of Ranvier.

Pflügers Arch. 341: 87-96.

Siebenga, E., J. de Goede, A.A. Verveen, 1974. The influence of TTX, DNP and TEA on membrane flicker noise and shot effect noise of the frog node of Ranvier.

Pflügers Arch. 351: 25-34.

Stevens, C.F., 1972. Inferences about Membrane Properties from Electrical Noise Measurements.

Biophysical Journal, 12 (8): 1028-1047.

Ten Hoopen, M. and A.A. Verveen, 1963. Nerve-Model Experiments on Fluctuation in Excitability.

Progress in Brain Research 2: 8-21.

Van den Berg, R.J., J. de Goede and A.A. Verveen, 1975. Conductance Fluctuations in Ranvier Nodes.

Pflügers Arch. 360: 17-23.

Van den Berg, R.J., E. Siebenga and G. de Bruin, 1977. Potassium ion noise currents and inactivation in voltage clamped node of Ranvier.

Nature 265: 177-179.

R.J. Van den Berg, A. de Vos, P. Van der Boog and J. de Goede, 1986. Resistivity fluctuations in ionic solutions.

In: Proc. 8th Intern. Conf. on Noise in Physical Systems, 213-216. Eds. A. d'Ámico and P. Mazzetti, Rome, Elsevier Science Publishers.

R.J. Van den Berg, A. de Vos and J. de Goede, 1987. Resistivity fluctuations in solutions of hydrochloric acid.

In: Proc. 9th Intern. Conf. on Noise in Physical Systems, 275-278. Ed. C.M. Van Vliet, Montreal, Word Scientific Publishing Co., Singapore

R.J. Van den Berg, A. de Vos and J. de Goede, 1989. Electrical noise in solutions of hydrochloric acid in ethanol.

Physics Letters A 139: 249-252, 1989.

Verveen, A.A., 1960. On the fluctuation of threshold of the nerve fibre.

In: Structure and Function of the Cerebral Cortex. D.B. Tower and J.P. Schadé, eds. Proceedings of the Second International Meeting of Neurobiologists (Amsterdam 1959). Amsterdam, Elsevier: 282-288.

Verveen, A.A., 1961. Fluctuation in Excitability. Research report on signal transmission in nerve fibers.

Amsterdam: Netherlands Central Institute for Brain Research. 76 pages.

Verveen, A.A., 1962. Axon diameter and fluctuation in excitability.

Acta Morphologica Neerlandico-Scandinavica 5 (1): 79-85.

Verveen, A.A. and H.E. Derksen, 1965. Fluctuations in membrane potential of axons and the problem of coding. *Biological Cybernetics*, **2**, 152-160

Verveen, A.A., and H.E. Derksen, 1968. Fluctuation phenomena in nerve membrane. Proc. IEEE 56: 906-916.

Verveen, A.A. and L.J. DeFelice, 1974. Membrane Noise.

Progr. Biophys. Mol. Biol. 28: 189-265.

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www.verveen.eu**