History of my life and work

A.A. Verveen

I
Fluctuation in excitability

■ Born in Indonesia in 1930, as a small child I already exhibited an interest in animals, perhaps stimulated by my first conscious observation. When I was 3 or 4 years old our gardener unearthed a nest of young black snakes, then told me to leave. So at my 6th birthday my parents presented me with Huey's book De dierenwereld in een notedop 1935. This book became my bible and determined my future. Between the ages of 8 to 12 years, I kept many animals in a large box in our garden among which my preference was the harmless brown Indonesian rat snake that my mother allowed me to roam our house under the express condition that I took care of its well-being.

After the Japanese invasion of the Dutch East Indies on March 8, 1942, I missed the final year of primary school (Dutch Chinese School, September 1936 - March 1942). Successively interned in several Japanese prison camps in Ambarawa 2 and 8, and in Bandungan, Central Java since January 1943, I worked as a casual labourer in the prison camps and fields. Since formal education was prohibited by the Japanese (Verveen, 1995), I also missed two years of secondary school.

Once, cleaning a ditch, I found a poisonous snake seemingly hit to death by someone. I took it up to skin and cook and during its transport it fell from my hands to hook itself with one fang in my left knee. I went to the kitchen, heated a needle red-hot in a fire and burned out the thin hole. I was amazed to note that I felt no pain doing this, nor an after burning sensation. Then I cleaned the snake, cooked it and ate it with my even similarly hungry relatives. In later years, I used a similar method to burn away unwanted warts or moles, not experiencing much discomfort with these procedures.

After the end of WW II, I migrated to the Netherlands in June 1946, where I finished my - then compressed - secondary education in September 1949. Still at high school, I once chanced upon several issues of the *Saturday Evening Post* which I studied to better my English. One issue contained an article about the Canadian neurosurgeon and physiologist Wilder Penfield. During his operations on the brain, Penfield discovered the 'homunculus', a mapping of the motor representations of the human body present on a cerebral ridge of the brain, as well as a similar map of the sensory representations of the body on an opposite ridge. (cf. Penfield & Boldrey, 1937, and fig 1 in: Ramachandran & Altschuler, 2009). This event let me to study medicine at the University of Amsterdam, since their preliminary year was taught by the faculty of physics. The course, therefore, contained introductions in physics and in physiology among other subjects. This preparatory year, was filled with lectures by eminent professors like Van Herk (biochemistry), Heijmans (genetics), Ten Cate (neurophysiology), Boeles (physiology) and Ihle (general biology).

On the practical sessions I learned to kill frogs quickly by pitching, destroying their brains in the blink of an eye, followed by the preparation of a set-up of the sciatic nerve to the sural muscle of the freshly killed frog to be mechanical recorded on a drum with a paper covered with a layer of soot.

In 1954 I obtained my M.D. and entered the clinical postgraduate internships and, thus, faced long waiting times in between these internships, generated by the post-war glut of students at the Dutch universities. I finished these internships and received my degree in medicine in October 1957.

Searching for a useful temporary job to fill the gaps in my study for the medical finals, I subscribed to *Intermediair*, a weekly with advertisements for graduates. Among its articles was one by a professor by the name of S.T. Bok [3], since 1952 director of the still mainly anatomically oriented Netherlands Central Institute for Brain Research NCIB who wrote introductions to cybernetics. The field of cybernetics caught my eye because of its interesting implications for physiology and pathology. So I applied to him for a volunteer assistantship. It turned out that Prof. Bok strove to increase the field of anatomy, originally covered by the NCIB, with other fields of study, like pharmacology, and physiology. So he accepted me as a volunteer, to work during my free intervals between the clinical stages, thus to start the then still non-existing physiological branch of the NCIB, from scratch, beginning in 1955, while I continued to work at the NCIB until 1963._

Professor Bok commissioned me to develop a physiological set-up to measure the electrical properties of neurons within the cerebral cortex, hunting for possible sites of memory, then thought by him to be possible candidates for neural memory because of the presence of vacuoles that later on turned out to be fixation artefacts. He agreed with my proposal to begin my stay at the NCIB with the study of electricity, then to set out with the conversion of the mechanical sciatic-nerve-to-striated-muscle preparation into a working electrical set-up, as a foundation for the study of the properties of higher order neurons. A recording device was already available by way of a set of simple cathode ray tubes with its preamplifiers, developed by Bok and his electronic engineer Hans Overdijk. To stimulate the nerve and its fibres Hans Overdijk then built a practically noise-free electrical stimulator, while their constructional fitter Hans de Jong taught me to use the apparatus in their engineering workshop to create the support of the sciatic nerve for the observations of its electrical behaviour.

Sometime in the second half of the 1950-ties I was sufficiently ready for the first test of the electrical set-up of a frog nerve. This test surprised me out of the blue with a strange phenomenon. I had learned that the action potential of a nerve fibre, thus of a nerve, was an all-or-none-event, so I expected stable responses upon repeated stimulation with identical stimuli at a low frequency of one stimulus per 2 seconds, used to avoid the cumulative effects of the restoring afterpotential appearing during the recovery period. The compound action potential, however, behaved in an erratic manner (Fig. 1), showing a varying and unpredictable shape when stimulated with just threshold stimuli.

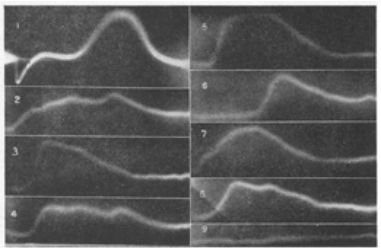

Figure 1. The very first picture of fluctuation in excitability (copy of Figure 2, on page 529, in Blair and Erlanger, 1933).

- Trace 1: Composite action potential at half maximal size.
- Traces 2-8: Repeatedly stimulated at constant stimuli of just threshold intensity. Time base is faster than in 1.
- Trace 9: No stimulation, showing the noise level in 2-8.

My naïve approach turned out to be a boon, since I looked at neurophysiology with a maiden's eye, just relying on what my teachers had told me in their lectures as well as on the limited number of practical sessions that had been available to me during my three years of theoretical studies for my M.D. I am of the opinion that, had I worked in a formal physiological laboratory instead of at the NCIB, then my teachers, being convinced that the variability was caused by ever present minute fluctuations ('noise') in the output of the electrical stimulator, would perhaps have succeeded discouraging me to study the erratic behaviour of the nerve. This serendipitous event led me to study its behaviour in detail, and Professor Bok allowed me to devote much of my time to this subject, but for two exceptions: to proofread his book on cybernetics (1958), and to help with the organization of the Dutch contribution to the Science Pavilion of the 1958 World Exhibition at Brussels. Proofreading his book on Cybernetics appeared to be instrumental in 1964 when I started teaching physiology to medical students. The Expo 58 work also taught me something of value: I learned that I was not a born manager.

In order to analyse erratic axonal behaviour I then followed a course in medical statistics, developed and given by Prof. H. de Jonge (1963, 1964). To investigate the phenomenon of fluctuations in excitability myself, I needed to study the behaviour of single action potentials. For this I prepared the sciatic nerve from the spinal cord to the thin branches reaching to the very tips of the toes. Stimulation at just subthreshold intensities at the sciatic origin revealed the occurrence of one or at most two action potentials in the thin branches of the sciatic nerve near the tips of the toes.

Application of the run test on continuous series of responses for 18 nerve fibres of the green frog, applied with intervals of 2 seconds, showed that these successions of positive (an action potential) and negative (zero) responses are in each case distributed at random (Verveen, 1960, page 283, and 1961, page 15).

When two action potentials A and B were visible, Pecher (1936, 1937, see next page) measured the probabilities of their occurrence upon a fixed stimulus, repeated more than 100 times at intervals of 2 seconds. In 9 experiments simultaneous occurrences occurred at a chance of PA times PB, thus showing their mutual independence (Pecher, 1939, Table 1 on page 137).

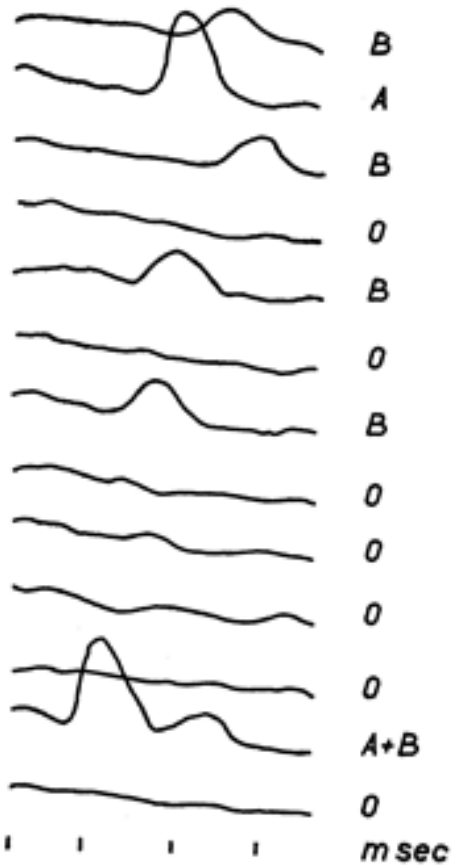

Figure 2. Independent responses of two different fibres with different thresholds in the same nerve to identical stimuli, repeated at a low frequency. Redrawn after figure 1f on page 133 in Pecher, 1939.

This independent behaviour, first noted by Blair and Erlanger, 1933, page 530), is clearly visible on the historical picture of Charles Pecher, redrawn in Fig. 2.

This result, repeated by me on the unmyelinated axons of another species (crayfish, Astacus leptodactylus, Verveen, 1961, page 41), showed that fluctuations in excitability of different nerve fibres (myelinated and unmyelinated), and for different species (the green frog), and the crayfish), were not caused by stimulus variability or 'noise'. However, the majority of my peers then believed stimulus variability to be the cause of the fluctuations and still believed so for many years, during which I often received the remark that I studied the effects of an unstable stimulus, thus of an uninteresting non-physiological process!

Apart from the exact sciences, such as physics and astronomy, noise was considered a bothersome phenomenon in physiology and communication sciences. This is exemplified by the term SNR (signal to noise ratio) that is defined by the power of the signal (meaningful information) and the power of the background noise (unwanted noise corrupting the signal) (cf. https://en.wikipedia.org/wiki/Noise).

Each physiologist looking at axonal behaviour upon electrical stimulation must have observed the fluctuation in excitability, and believed it to be due to variability of the stimulus. Thus, they avoided stimulations within the threshold range (McCulloch, 1958, page 214 of the 1965 reprint). But at least some may have thought otherwise, so in between my experiments I sear-

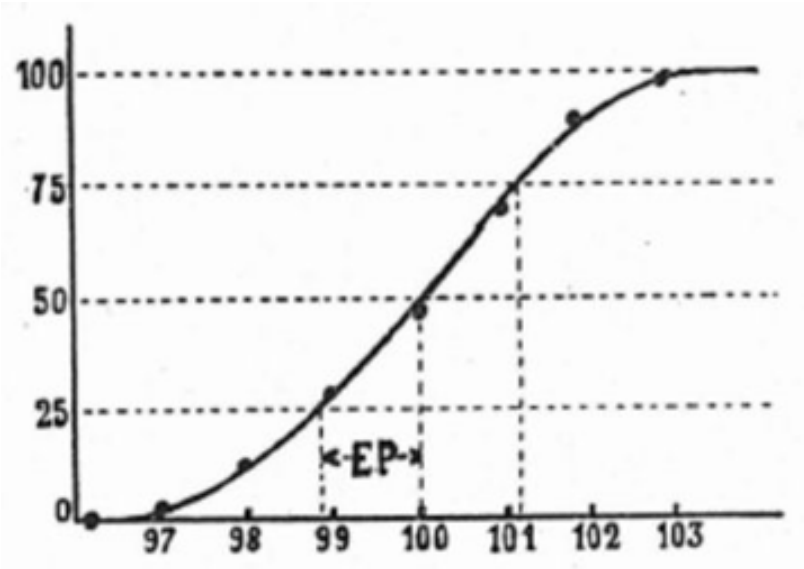

Figure 3. Probability of response of a single nerve fibre. Pecher's picture of the Gaussian distribution function. Reproduction of figure 2, in Pecher, 1939, page 138.

ched the literature for reports on these fluctuations, starting with English language physiological journals, followed by the German journals and finally with the French physiological ones. It took me several painstaking months to hit gold, finally. In several French language journals the Belgian Charles Pecher described the results of his beautiful studies on fluctuation in excitability (Pecher, 1936, 1937 and 1939). Apart from a study by Erlanger, et al., (1941) and by van Lier (1955), the process was forgotten until I encountered it by accident in about 1955/56, as I described already above.

Pecher noted that the process causing the fluctuations was a Gaussian random process (Pecher, 1939, his fig. 2, on page 138) and could be characterised by its mean μ (the threshold) and percentile spread ('écart probable' EP, later called by me the relative spread RS). The RS equals σ/μ, where σ is the standard deviation (the intrinsic spread) of the Gaussian distribution function (Figure 4), being the effective noise component of the fibre. Pecher also noted that that the interval of time between the application of the stimulus and the appearance of the action potential (the latency) showed random variations.

So my work agreed with his results and, I thus, confirmed his conclusions. Pecher had located two predecessors who noted the irregularity of the fluctuations and ascribed it to be due

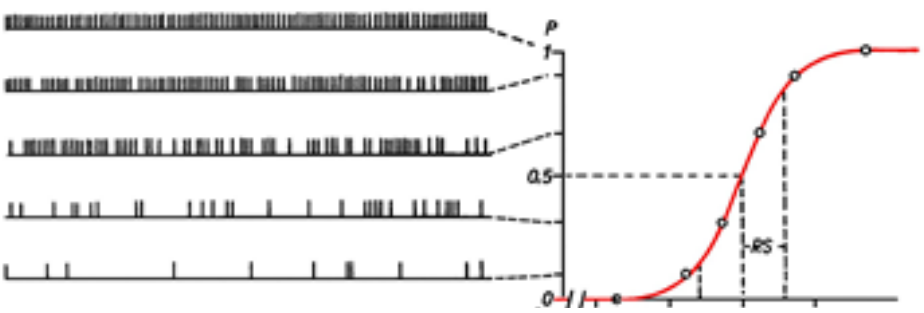

Figure 4. Plots of response probabilities at a range of stimulus intensities showing the S-shape of the cumulative normal or Gaussian distribution, a random process. From Verveen, 1960, Fig. 1 on page 282.

to the influence of an innate random process: Blair and Erlanger 1932, page 548, and 1933, page 530 (see Figure 1), and Monnier and Jasper, 1932, page 548. A corresponding random variation in latency, the interval of time between stimulation and the occurrence of the action potential was noted by Blair and Erlanger (1933, 1935, pages 530-533) and studied by Pecher (1939, page 141-145). The fluctuation of the latency could be explained by the interplay of the Gaussian random process (the 'noise') and the local activation response, generated by the rectangular stimulus, crossing the threshold of the nerve (Ten Hoopen and Verveen, 1963, pages 9 and 12).

Then, I studied the probability of response, for preparations showing only one action potential, over a wider range of stimulus intensities in steps of about 0.5 per cent of the threshold potential; which I defined as the stimulus intensity at which the nerve fibre responded to a longer series of identical stimuli given at 2 second intervals, with a probability of 50 percent (Fig. 4).

I now wanted to contact Charles Pecher, to talk about his work and my confirmation of it, as well as about possible future investigations. But nobody knew of Pecher's whereabouts, not even at the laboratory in Brussels.

At this stage of my investigations, the Netherlands Centre for Brain Research organised from 22 to 25 September, 1959, the Second International Meeting of Neurobiologists, held in the Trippenhuis (the seat of the Netherlands Royal Academy of Sciences at Amsterdam) where some 90 scientists from 15 countries participated in the symposium on Structure and Function of the Cerebral Cortex. This meeting was attended by Warren S. McCulloch, one of the very few who did know Pecher's work (McCulloch 1958. page 215). Here, I presented a synopsis of my work up to that time (Verveen, 1960). It must have been at this meeting that I heard a rumour about Pecher's death at a young age, but no particulars (Verveen, 1961, page 51), so it remained a mystery.

McCulloch, knew about the existing doubts caused by the still present and persistent belief of stimulus variability being the source of the fluctuations, despite the proofs both Pecher and I had presented about the fluctuations being due to an intrinsic neural process. To aid me he asked Professor van der Tweel, head of the medical physics department of the University of Amsterdam to investigate my stimulator for its stability. Van der Tweel did so and he concluded that its output was stable enough and could not generate fluctuations of the size of the fluctuations in excitability. Both McCulloch and van der Tweel supported me and my work during many years, and so kept me going.

McCulloch's work centred on the still open question, how nets of unreliable neurons could lead to reliable results (McCulloch, 1958, page 214). Therein, McCulloch stated that 'Now we must measure the intrinsic jitter' (l.c.). Then I was still busy to just use the two parameters (threshold and RS of this 'jitter'). To investigate neuronal 'noise' in detail, I lacked a solid background in physics, so I mentioned that I searched for a researcher with a comprehensive background in physics, with me to tackle the measurement of the intrinsic jitter (i.e. noise) of neurons. So I had to resort to the RS as a parameter of this process.

Another prejudice I had to deal with, follows from statistical practise. People use statistics to search for the behaviour of the average value or function, i.e. to rid the data from the ac-

companying variability. Once these are obtained, then the spread of the data is not of interest anymore. So they asked me why I was interested in spread and RS, instead of averages? My answer to this question was and is, that the fluctuations are a property of the neurons themselves so I had to investigate the actual random process, thus not only its threshold but the spread, and, if possible, its behaviour in time as such, beginning with spread and RS.

Aided by A.R. Bloemena*, T Harkema and H. Arwert of the Mathematical Centre at Amsterdam, I investigated the sigmoid response curves with the so-called probit analysis (a linear transformation of the cumulative Gaussian S-shape) on their Electrologica X2 computer, to determine for each nerve fibre the threshold and relative spread (RS) for each Gaussian curve (RS = standard deviation / threshold). Threshold and RS appeared to be independent parameters characterising the behaviour of all kinds of axons, since they did not change when stimuli of different intensities and durations were presented, also when fluctuations were studied for stimuli given during the recovery period of the nerve (Verveen, 1961, pages 24-27). Knowing this I studied threshold and RS for the properties of the fluctuations (noise) in different conditions (solutions of the narcotic urethane, and of the rat poison strychnine (Verveen, 1961), as well as of CO_2 since it was in former times used as a narcotic. Urethane (Verveen, 1961), as well as CO_2 (Verveen and Hickey, 1963) increased the threshold and decreased the RS, but did not change their product, which indicated that the intensity of the intrinsic noise process was unaffected. Strychnine (Verveen, 1961) increased the RS but not the threshold, indicating that the intrinsic noise process was raised. The thinner unmyelinated parts ('Ranvier nodes') of the nerve fibres of the green frog (then R*ana esculenta*) exhibited larger values for the RS, than the thicker unmyelinated fibres of the crayfish *Astacus leptodactylus* (Verveen, 1961).

Most of my researches performed up to this point in time, were gathered together in my thesis *Fluctuation in Excitability*, which was published in 1961.

I wanted to engage in a model study to investigate whether noise could reproduce all the properties of the neuronal fluctuations. For this McCulloch advised me to contact M. ten Hoopen at Utrecht, a former pupil of him. I did so and Ten Hoopen built an electrical neuron analogue (Ten Hoopen and Verveen, 1963) in which the square stimulus was transformed into its 'excitability cycle' consisting of the difference between two exponential functions. Upon the injection of electrical noise, the model not only reproduced all the recorded properties of the nerve fi-

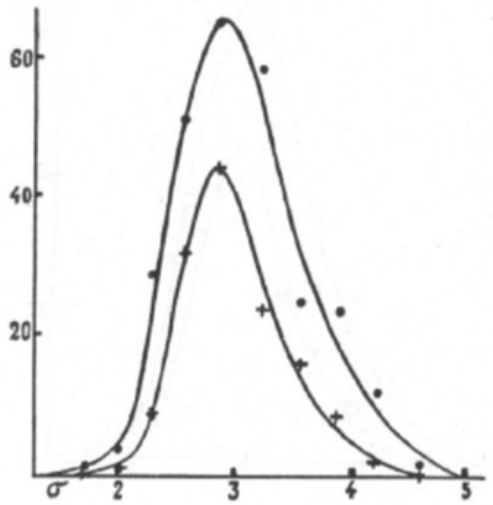

Figure 5. Latency fluctuation histograms of two nerve fibres. Number of responses vs. time σ in milliseconds. After Pecher, 1939 Fig. 3 on page 142.

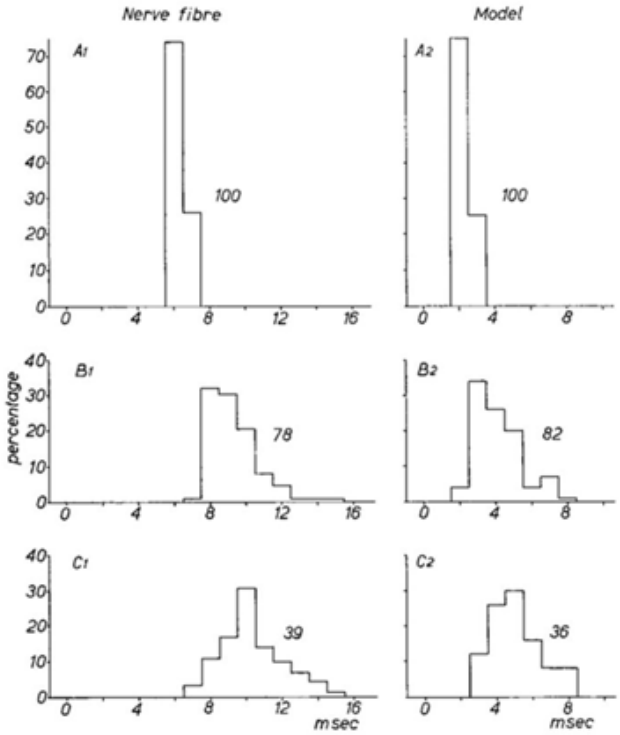

Figure 6. Latency histograms for a nerve fibre and the electronic model at three different stimulus intensities. Response percentage besides the histograms. From fig. 4 on page 12 in Ten Hoopen and Verveen, 1962.

bres, but even more: the transform function generated a fluctuation of the response time. This latency fluctuation was already observed and investigated by Pecher (1939 pages 142-145) to be a monophasic and asymmetrical function of time (Fig. 5). This was then investigated and confirmed by me on the frog nerve fibre, for the histograms of nerve fibre and neuron model had similar shapes and behaviour (Figure 6).

Model experiments with noise injections with different high cut-off rates showed that the RS was a function of the frequency content of the noise, decreasing in size with the decrease of the higher cut-off frequency.

In 1952, Fatt and Katz (p. 126) suggested that membrane noise might depend on axon diameter (supposing a threshold level of about 15 mV), then

$$\log C = -2.38 - 0.75 \log d$$

where C is the quotient of the effective noise voltage of the fluctuations and the threshold. This relationship is represented by line a in Figure 7.

Also in 1961, my wife and I went to Napoli for several months, to complete my observations on the RS of different species, this time on the giant unmyelinated nerve fibre of the cuttlefish Sepia officinalis, besides the already finished RS measurements on the green frog and the crayfish.

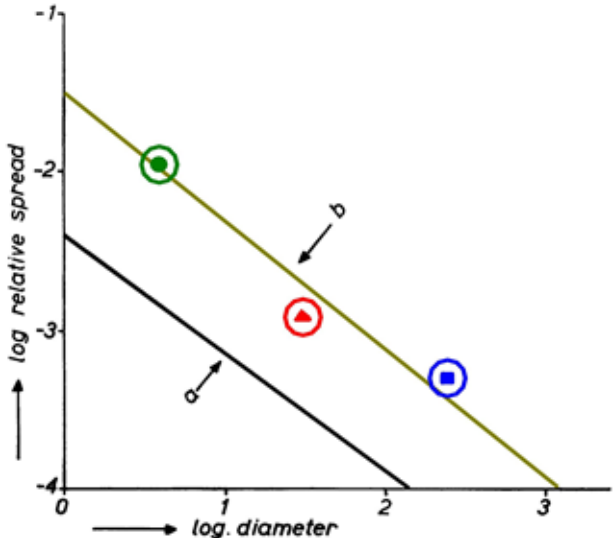

Figure 7. Double logarithmic plot of the RS against diameter of the unmyelinated (parts) for the largest nerve fibres of frog (filled green circle), crayfish (red triangle) and cuttlefish (blue square). After figure 2 in Verveen, 1962, page 83.

It follows that the RS increases with the inverse of the diameter d of the nerve. These data support the hypothesis that fluctuation in excitability might be due to the thermal agitation of ions within the nerve membrane.

II
Electrical membrane (channel) noise

■ In the meantime, McCulloch had received my thesis and he invited me and my wife Nel to join him and his wife Rook in Cambridge, Massachusetts, in January 1962 me as a staff member at M.I.T. and my wife as a volunteer at the Child Health Department of Harvard Medical School, both for a period of six months. Since I wanted to travel and visit the neurophysiologic centres in the USA in search of a physicist to tackle the nerve fibre by direct measurement of the supposed electrical membrane noise, and to visit Hiroshi Ooyama, 1961 at Florida University, a pupil of Ichiji Tasaki, to learn to prepare an isolated and living nerve fibre of the green frog, a technique developed by Tasaki. So we did, and I saw Ooyama who was so kind to show me into detail how to perform the operation. On this grand tour through the USA, I did not encounter a physicist with a special interest in biological noise, however. But I did all this, just in time to return to the Netherlands to attend the 22d International Congress of the International Union of Physiological Sciences at Leiden in September 9-17, 1962.

As luck would have it, two papers dealing with neuronal noise were presented at the Congress: one by me (Verveen, 1962: on neural fluctuations and the behaviour of its parameters), and the other by Derksen and Van der Mark (1962: on the difference between real neural networks consisting of receptor and neurone, and a model of these, where the model appeared to need injections of electrical noise to reproduce the original responses). So, here we listened to and met each other.

Mirabile dictu, after I had searched the new world's universities in vain for a physicist interes-

ted in my problem, I found one who worked in the Physiological Laboratory at Leiden, so, close to the NCIB at Amsterdam: Hans Edi Derksen.

The following year (1963) we regularly met each other and discussed how to tackle the direct measurement of membrane noise. We concluded that the problem, although rather difficult, yet could be tackled. This required the development of a sophisticated set-up (Verveen, aided by the constructer 'Pa' ter Keurs, Figure 8) and of extremely low noise preamplifiers to extend measurement resolution from the millivolt range into that of the microvolt (Derksen). In the mean time I also trained myself with the operation to isolate a living single nerve fibre, while Derksen developed a computing system for Fourier analysis of noise voltage tracks.

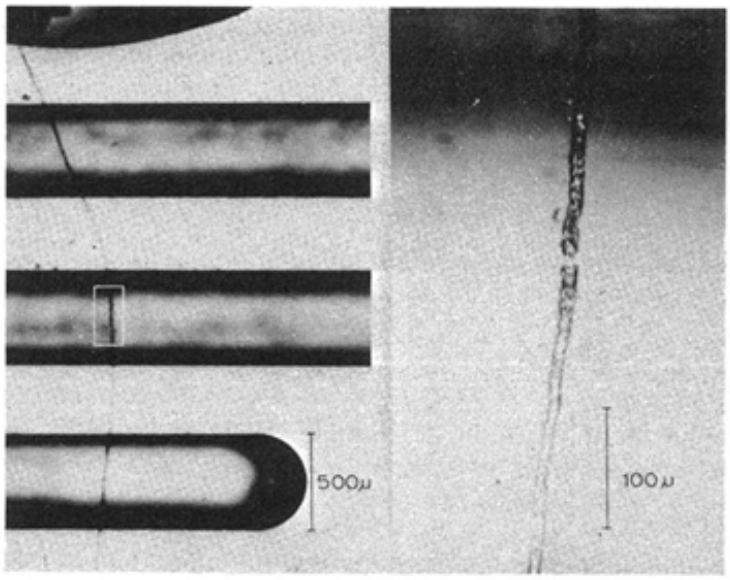

Figure 8. Top view of the nerve chamber with its pools (left) and with the isolated living nerve fiber in situ (right, detail). From Verveen and Derksen, 1968, figure 3 on page 909.

In the same year (1963), two full professors in physiology, Prof. Ties van Hoff from the Erasmus University at Rotterdam, and Prof. Paul Voorhoeve from the University of Amsterdam visited me at the NCIB. They studied my set-up in detail, as well as the random behaviour of the living frog sciatic nerve fibres. Later on, I learned that these two former pupils of Prof. Duyff, the director of the Laboratory of Physiology of the medical faculty at the University of Leiden, were instructed by him to decide whether I was a Don Quichot fighting windmills or was investigating a real phenomenon.

In the meantime Derksen and I concluded that we needed a then very rare as well as quite expensive instrument at our fingertips, a general purpose computer and that one of us would then move to the institution that could provide us with it: either the NCBR or the medical faculty at Leiden. The NCIB did not have one, though there were vague plans to install one in the future, while the Leiden medical faculty was installing a faculty computer right in their Physiological Laboratory. I was welcomed to join the staff of the Physiological Laboratory, so the decision was not very difficult: Derksen should stay in Leiden, while I was moving to the IBM 1800 computer in the said laboratory.

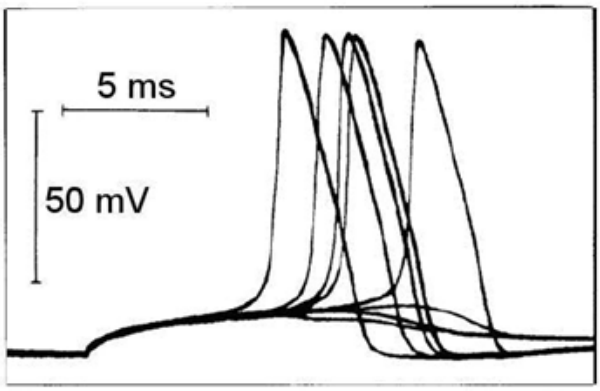

Figure 9. High resolution picture of the responses of an isolated frog nerve fibre to repeated stimulation with identical pulses at a low frequency. From Verveen and Derksen, 1968, figure 2 on page 907.

In 1964 we could test the set-up. At first we looked at the action potential itself in high resolution. Figure 9 shows the responses of an isolated nerve fibre, upon repeated stimulation with identical longer duration pulse at about threshold intensity. The photo shows the fluctuation in excitability as well as in latency.

So we then looked at the membrane potential itself, pictured at different levels of the membrane potential. Its noise was quite well visible now, showing different patterns at different membrane potentials (figure 10),

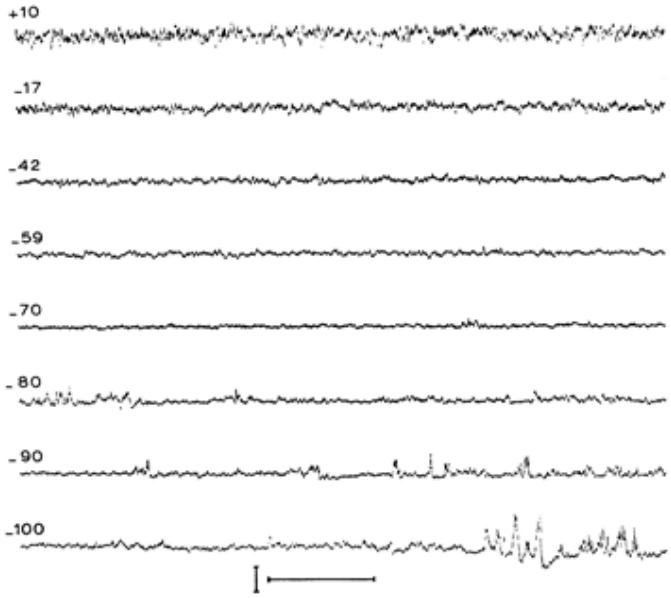

Figure 10. Noise patterns at different membrane potentials. Units: 5 mV and 1 second. From Verveen and Derksen, 1968, figure 19 on page 913.

The standard deviations (spreads, i.e. wide-band rms values) of the noises are minimal at the resting membrane potential (figure 11). The amplitude distributions are Gaussian at this potential and more positive ones. These distributions become skewed to the right at lower levels caused by the presence of (still mysterious) depolarizing noise bursts.

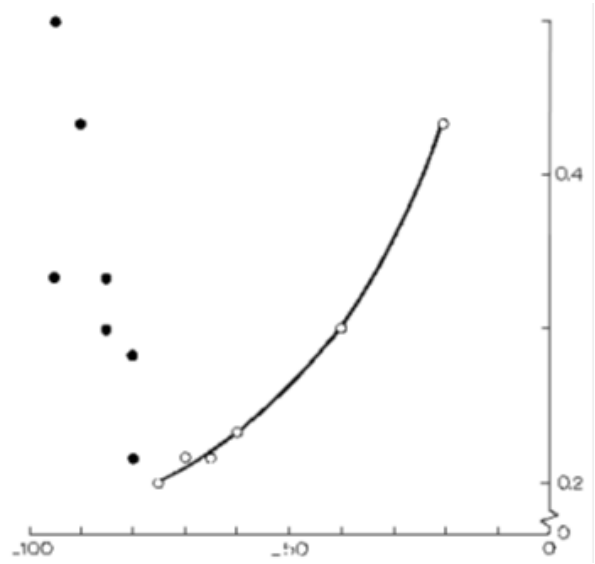

Figure 11. Standard deviations (ordinate in mV) of membrane noises at different membrane potentials (abscissa in mV). Open circles: Gaussian distributions. Filled circles: positively skewed distributions. From Verveen and Derksen, 1968, figure 17 on page 912.

In 1965, we published a paper showing that neural noise could explain sensor behaviour (Verveen and Derksen, 1965, pages 156-159).

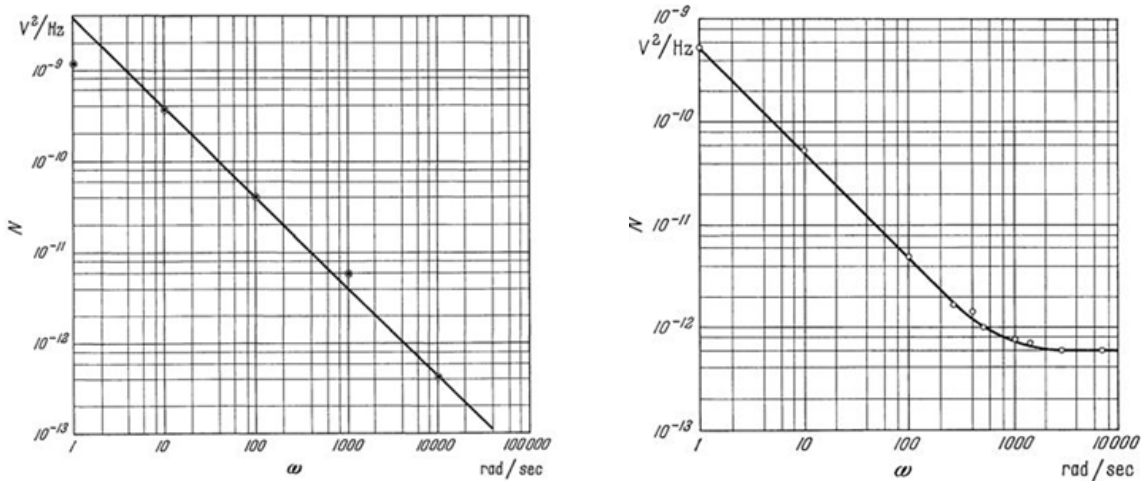

Figure 12. Two frequency spectra from the very first set of 15, measured for the frog node of Ranvier. From Verveen and Derksen, 1965, figures 3 and 4 on page 154.

Figure 12 shows the very first frequency spectra of the noise of the frog node, a choice from the measurements of 15 nodes. These were presented at the June 1964 meeting of the International Organization of pure and applied Biophysics in Paris and published on February 1965 (Verveen and Derksen, 1965, page 154), and was published in 1965 for Hans Derksen to receive his PhD on November 10, 1965.

Since the rules of the university forbade PhD promotions with more than one writer I renounced my right to join in the formal publication of our work, which was officially published in 1965.

So from now on the power spectra of membrane noise could be measured and investigated.

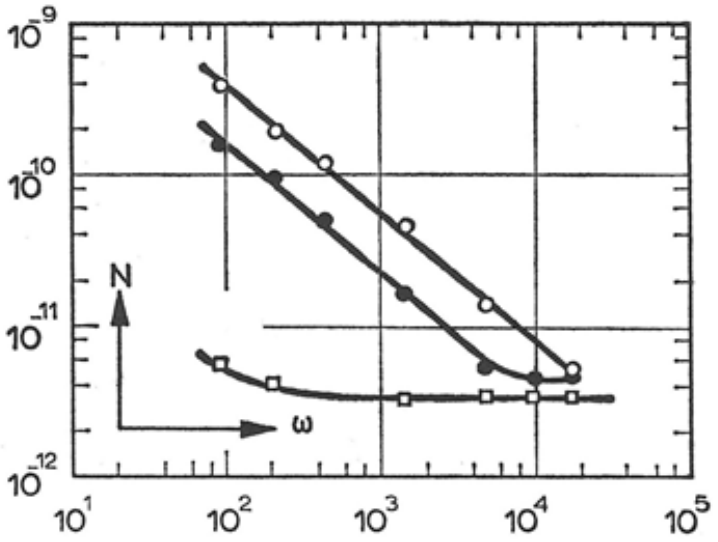

Figure 13. Power spectrum of a single frog node of Ranvier. In normal Ringer solution (open circles); after replacement of sodium chloride by potassium chloride (squares); and back to normal Ringer solution. Noise power N in volt2sec, angular frequency ω in radians/sec. From Derksen and Verveen, 1966, fig. 1 on page 1389, and Derksen, 1965, page 447.

We showed that shape of the power spectrum of the frog node of Ranvier depended on the concentration of potassium chloride in the fluid bathing the node (Figure 13). Its shape is 1/f, but changes into white noise (straight line) when transport of K+ ions is abolished by replacement of the sodium chloride in the bathing fluid by potassium chloride, or when the node is 20 mV hyperpolarized. This change into white noise does not occur upon further hyper- or depolarization, but for its absolute size, nor when sodium inflow is abolished by replacement of the sodium chloride with choline chloride, nor by the addition of urethane or by blocking active sodium transport by 2,4-dinitrophenol or ouabain.

The synopsis of our results was sent to the Science journal, where it was received at 25 October 1965. We received comments from two referees. One advised against publication because he thought that instability of our set-up came into play. The other referee stated quite frankly that he had some doubts, but that the paper had a ring of truth, so he gave us the benefit of the doubt, to not disgrace the journal by an unwarranted rejection. So he advised for publication. The paper appeared in Science on March 18, 1966. It became clear, quickly, that we now had passed a watershed, as followed from:

- an invitation from the Institute of Electrical and Electronic Engineers, IEEE, to write a review of fluctuation phenomena in nerve fibres, to be published in their proceedings (Verveen and Derksen, June 1968).
- Invited lectures at conferences in Oxford 1966, Ravenna 1968, Koblenz 1975, Erice 1977, Tokio 1977.
- Visits to our laboratory for a year or longer by several scientists: Kenneth L. Schick (Verveen, Derksen and Schick, 1967; Schick and Verveen, 1974). This paper, on the flow of particles in an hourglass, 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 flow through hoppers, in avalanches, or sand piles, and of pedestrians when many people try to move through narrow doorways.
- Louis J. DeFelice, (Verveen and DeFelice, 1974) who wrote several books on membrane noise

- Denis M. Poussart, who recorded 1/f noise in crayfish and in the giant nerve fibre of squid (1971)
- Chuck F. Stevens who calculated noise patterns for Hodgkin Huxley ion channels (1972), and - Christoffel.R. Anderson.

Derksen and I had hoped to find noise frequency patterns like that of shot noise, to enable to search for models of the noise process. The pattern we discovered was, however, of the one over f (1/f) type. This was unlucky, for we could not relate the spectrum to some known model. Yet today this pattern is still unsolved. There is no true explanation available and it remains a problem in physics (Strauch, 2011; Ward and Greenwood, 2007) [4].

In the meantime two promising students, Elias Siebenga (1969) and Ruud van den Berg (1972), learned how to prepare single nerve fibres of frog and of the African clawed frog (*Xenopus laevis*) and to perform the measurements of frequency spectra. This happened just in time, since disaster struck around 1968 for the two senior scientists of the lab, Prof. dr. J.W. Duyff and associate professor H.E. Derksen then became seriously ill, and both died in 1969. So I had to assume the responsibility for running the lab and taking care of the lectures in physiology for the students, leaving me no time anymore for executing experimental work, but for taking formal care of my own research group besides. Siebenga and van den Berg as well as our guests mentioned before continued and expanded on the membrane noise research.

– Cited from the Homage to Pecher paper –
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/f2 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). Note that this does not apply to 1/f noise producing ion systems.

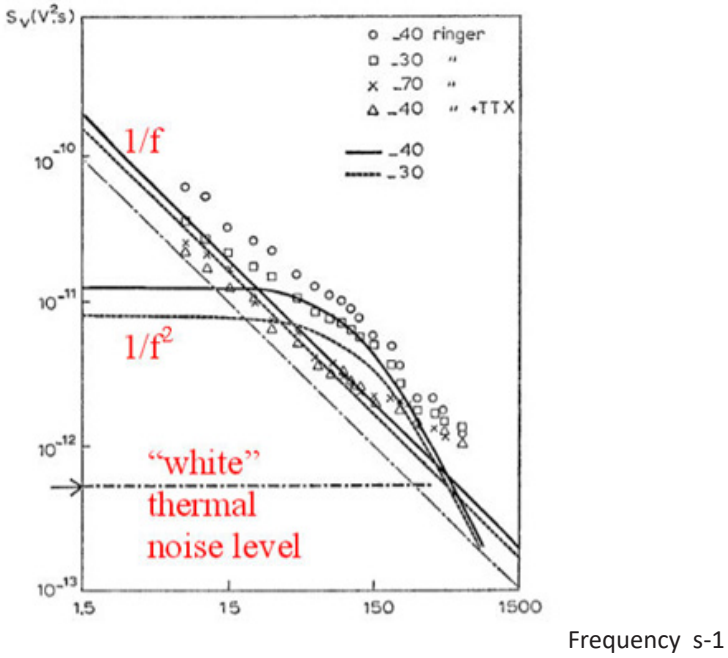

Figure 14. Different kinds of noise present in a nerve fibre. Open symbols: measured noise spectrum, lines: 1/f, 1/f-squared and white noise components. Vertical axis: log noise intensity, horizontal axis: log frequency component. (After Van den Berg, de Goede and Verveen, 1975, p. 19).

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 at 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 investigate these channels, especially the patch clamp technique (Neher and Sakmann, late 1970's and their co-workers). Ypey learned this technique and introduced it in the Netherlands.

A chance discovery of an elongated hourglass inspired me to investigated the flow of particles through its long stem. Its visual pattern suggested a comparison with the flow of ions through a membrane channel. The passage of the particles through the narrow stem turned out to be 1/f noise (Schick and Verveen, 1974).

In a well-executed set of investigations, Van den Berg, in cooperation 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.
– Citation from the 'Homage paper' ends here –

Electrical noises associated with ion fluxes through membranes are probably quite general. Thus, it was found in cells of quite different origins and species like living cancer cells(cultured neuroblastoma cells) and a potassium ion dependent 1/f noise in the protozoon *Paramecium* (Moolenaar, et al., 1976).

Thus we had answered Warren McCulloch's injunction: 'Now we must measure the intrinsic jitter.' (McCulloch, 1965 pages 203-204). But the whole field of probabilistic neuronal activity, nowadays [not quite adequately] called 'stochastic resonance' (SR) or 'stochastic facilitation' (SF) is still very much in the making, for: 'Understanding the dynamics of noisy neurons remains an important challenge in neuroscience' (Bodová, et al., 2015 page 40).

With regard to McCulloch's original quest: 'How nets of unreliable neurons could lead to reliable results' we had contributed only three suggestions, namely, that noise:
- renders a triggerable unit more excitable (Ten Hoopen & Verveen, 1963, page 20),

- linearizes non-linear sensor output (Derksen and van der Mark, 1962, abstract 950; Derksen, 1964, pages 390-393),
- generates a 'carrier wave' for coded sensor output (Verveen & Derksen, 1965, pages 156-159).

Warren McCulloch suggested negative feedback as one of the tools our body uses to generate stability despite elemental unreliability (1958, 1965 reprint page 204).

III
Homeostasis
or physiological feedback systems and their diseases
'Systems pathophysiology'

■ Since my arrival in Leiden in 1964, I have been involved in the teaching of physiology to freshmen in medicine. Remembering my 1958 acquaintance with Prof. Bok's book on Cybernetics, I set out to learn the students the ins and outs of physiological feedback systems. In 1865 the French physiologist Claude Bernard noted that the body's internal environment remained stable despite external challenges. In 1926 Walter Bradford Cannon coined the term 'homeostasis' (homeo = self, stasis = constancy), for this property of the body [5]. I used examples from temperature regulation of our houses as well as our own bodies, and of hormonal regulations such as the control of the blood level of several hormones, especially thyroid hormone, as well as hormones involved in reproduction.

Here, I will dwell on some aspects of our regulating systems, the feedback systems in particular (for details, see Verveen, 1972, 1978, 1979, 1982 and 1983), since it gives you an insight into the ins and outs of some diseases of such systems.

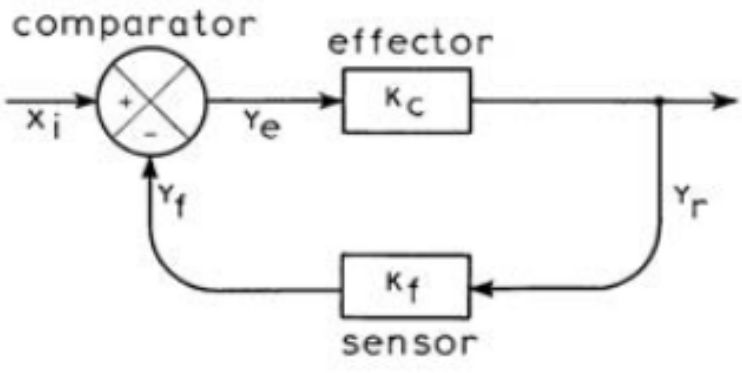

Figure 15. Regulating system diagram. Regulated state yr; feedback signal yf; error signal ye, sensor gain Kf and effector gain Kc. The arrowed lines in this graph symbolise signals or hormone transport by some transport system like the circulation of the blood.

Homeostasis, the regulation of some variable, like room or body temperature, implies that the thermo regulating system always 'knows' the temperature in the room or body. It does so with the use of a sensor (like an electrical thermometer) that senses the temperature and produces an electrical output (voltage or current) of which the size encodes the temperature. In symbols: the temperature of the room or body here will be called the regulated variable $\mathbf{y}_r$, where

y symbols a variable, and the **r** applies to regulation (Figure 15). The sensor output is written here as $\mathbf{y}_f$, where y also indicates that it is a variable, here electrical voltage, dependent on the temperature $\mathbf{y}_r$:, here expressed in centigrade (degrees Celsius).

$$\mathbf{y}_f \equiv \mathbf{K}_f \mathbf{y}_r \qquad (1)$$

The **f** indicates feedback, since this output is sent back into the regulating system (Figure 15). $\mathbf{K}_f$ is called the *transfer function* since it determines size and nature of the output value. The ≡ sign, as well as the **K**, tell us that different dimensions are involved. For example: for an electrical thermometer as sensor at a room temperature of 20 centigrade producing an output of 40 Volts, $\mathbf{K}_f$ encodes 2 centigrade to Volt. Note that this rather complicated business of dimension transformations must always be given attention to, especially in the design of technical regulating systems, but that here we will drop it for ease of reasoning. However the triple equal sign ≡ as well as the capital **K** will remind us that encodings are involved and that the dimensions must be given attention to, when needed. So in this case we will from now on call **K** the *gain* instead of *transfer function* and write $\mathbf{K}_f = 2$ in this example.

The sensor output $\mathbf{y}_f$ is sent to a *comparator organ* (element, Figure 15) where it is compared with the value of a *reference signal* $\mathbf{x}_i$ received from elsewhere in the body or the vicinity. This signal encodes the 'ideal state' on which the system is set to work, and is, therefore, also called *set point*. The symbol x indicates that it is a system independent signal. Comparison implies subtraction, so the *error signal* $\mathbf{y}_e$ equals

$$\mathbf{y}_e \equiv \mathbf{x}_i - \mathbf{y}_f \qquad (2)$$

Note that the input gains of the comparator are simplified (so, equal to 1), as well as its output gain, a simplification that can be mended when needed. The index **i** in (2) refers to the ideal value of the regulated state $\mathbf{y}_r$.

The error signal is then sent to the *corrector* (or *effector*) *organ* (element) (figure 15). This element generates the regulated state $\mathbf{y}_r$ (index **r** from regulated) with gain $\mathbf{K}_c$ (index **c** from correction):

$$\mathbf{y}_r \equiv \mathbf{K}_c \mathbf{y}_e \qquad (3)$$

So we obtain the value of the regulated state by substitution of (1) into(2) and the result into (3):

$$\mathbf{y}_r \equiv \frac{\mathbf{K}_f \mathbf{K}_c}{1 + \mathbf{K}_f \mathbf{K}_c} \cdot \frac{\mathbf{x}_i}{\mathbf{K}_f} \qquad \mathbf{(4)}$$

where the dot . indicates multiplication and the two horizontal lines ———— and — **or** / are symbols for division.

The product $\mathbf{K} = \mathbf{K}_f \mathbf{K}_c$ is called the **open loop gain** of the system, and **1 + K** the *closed loop gain*. Note that for large values of **K** their quotient **K** / (**1 + K**) is about equal to **1**. Thus, equation (4) is practically equal to

$$y_r \approx x_i / K_f \qquad (5)$$

where the symbol ≈ means *is about equal to*. So, it follows from equation (5) that the regulated state y_r is for high-gain feedback systems equal to the quotient of set point x_i and feedback gain (sensor gain) K_f.

The beauty of feedback is that the effector gain K_c drops out of the equation (4) that describes the regulated state given by equation (5). Therefore, its action does in most cases not influence regulation at all. Only in case the effector is severely affected by some disease, so that it approaches very low values, does the system lose its function.

IV
System theory examples

■ Suppose that for a hormonal regulating system (Fig. 15) some disease is slowly attacking the effector gland, like a tumour attacking this gland, then its loss does not become notable until nearly all of the gland has been destroyed. The disease will, therefore, remain silent for months or years, unless it becomes visible by accident, such as may occur during an operation for different symptoms that are unrelated to the regulating system itself.

Another possibility is that cells of the effector gland are growing pathologically while they still are actively secreting the hormone, and remain sensitive to the error signal that is transported by the blood circulation (Fig. 15). This means that the gain K_c of the effector gland increases. So, the systems regulates quite well all the time this situation exists. This also means that it remains silent for many months or years and may never be discovered, unless it is found by accident upon an operation for a different reason, or after death from another cause is discovered upon autopsy.

For weak feedback systems, with, say, $K_c \approx 1$, like in the regulation of the blood level of thyroid hormone, the system is not silent and the regulated state varies with the state of the disease of **K** (cf. equation (4).

A completely different situation arises when the tumour cells do not listen to the error signal anymore (Fig. 16), but autonomously secrete the hormone. This is indicated by the autonomous tumour output x_a, and comparable with the now obsolete regular intake of thyroid pills to lose weight.

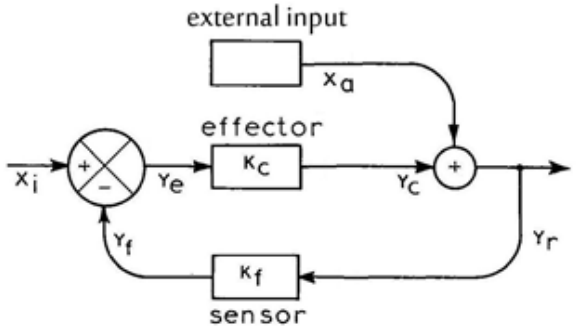

Figure 16. Feedback in the presence of an independent external input x_a

Here, the regulated state $\mathbf{y}_r$ is given by

$$yr \equiv \frac{K_f K_c}{1 + K_f K_c} \cdot \frac{x_i}{K_f} + \frac{x_a}{1 + K_f K_c} \qquad (6)$$

Note that for systems with large open loop gains $\mathbf{K} = \mathbf{K}_f \mathbf{K}_c$, the remaining contribution of the external input xa is reduced very much, so, equation (6) reduces to (5): $\mathbf{y}_r \approx \mathbf{x}_i / \mathbf{K}_f$. This means that feedback regulation reduces the effects of pills or autonomous tumour, so of all independent inputs $\mathbf{x}_a$. It does this by reducing the correcting output $\mathbf{y}_c \approx \mathbf{x}_i / \mathbf{K}_f$ with the about equal amount of input $\mathbf{x}_a$ (its derivation forms an exercise for you, reader):

$$\mathbf{y}_c \approx \mathbf{x}_i / \mathbf{K}_f - \mathbf{x}_a \qquad (7)$$

This has a price. The effector does not need to work at its original intensity. Cells that do not work as hard as they should, then adjust to this situation, so, they reduce their gain and 'hypotrophy' (as their decrease in size is called). If this goes on the effector may even disappear altogether ('atrophy'). When the pills are not available or when the autonomous tumour is removed, then the feedback systems does not work anymore since $\mathbf{K}_c$ is about equal to zero, and so is the gain **K**. The person is now dependent on the pills, addicted to them. This is a dangerous situation that should be counteracted in advance by gradually lowering the ingestion to allow the system to grow back its effector. It is for this reason that treatments with hormones should be carefully monitored, and that has made the 'treatment' of overweight with thyroid hormone pills obsolete.

One may like to visualise what happens during diseases of feedback regulation. A useful tool is the *regulation characteristic*, the graph of the regulated value $\mathbf{y}_r$ as a function of the size of the independent external input $\mathbf{x}_a$. This is also left by way of an exercise, and the answers are available in Verveen (1979). For more details about the theory of feedback diseases see Verveen (1983).

V
Sexology

■ As a student of medicine I often faced unanswerable questions by third parties about sexual problems, and I noted that the study of medicine at that time did not include sexology, not even during my final practical stage in gynaecology and obstetrics. In 1966 Master and Johnson's book *Human sexual response* appeared. This work fitted in the physiology course I was teaching, so I faced this challenge (Verveen, 1979b, 1980). Thus, from then on sexology became a regular part of the medical curriculum. Even so much so, that it warranted the creation of a new chair in the Leiden medical faculty, 'sexology', in 1980.