Spike Train Analysis and Modelling 1

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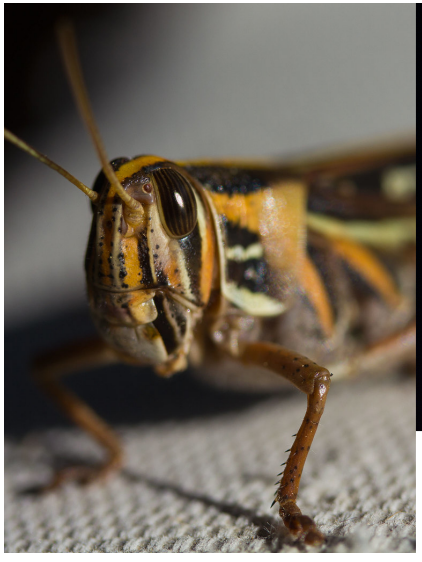
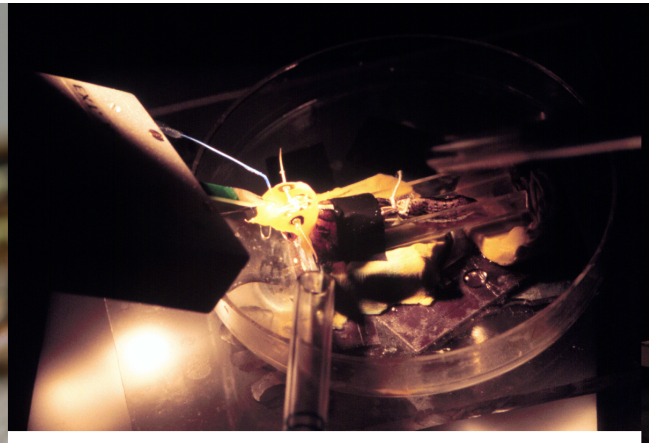
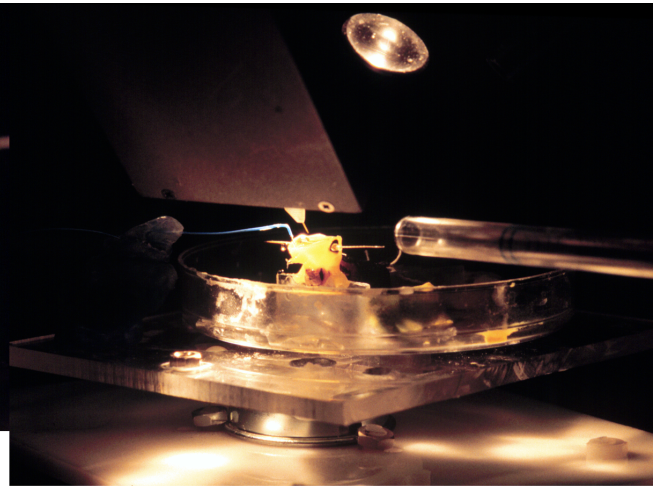
LASCON, January 16 2020

Outline

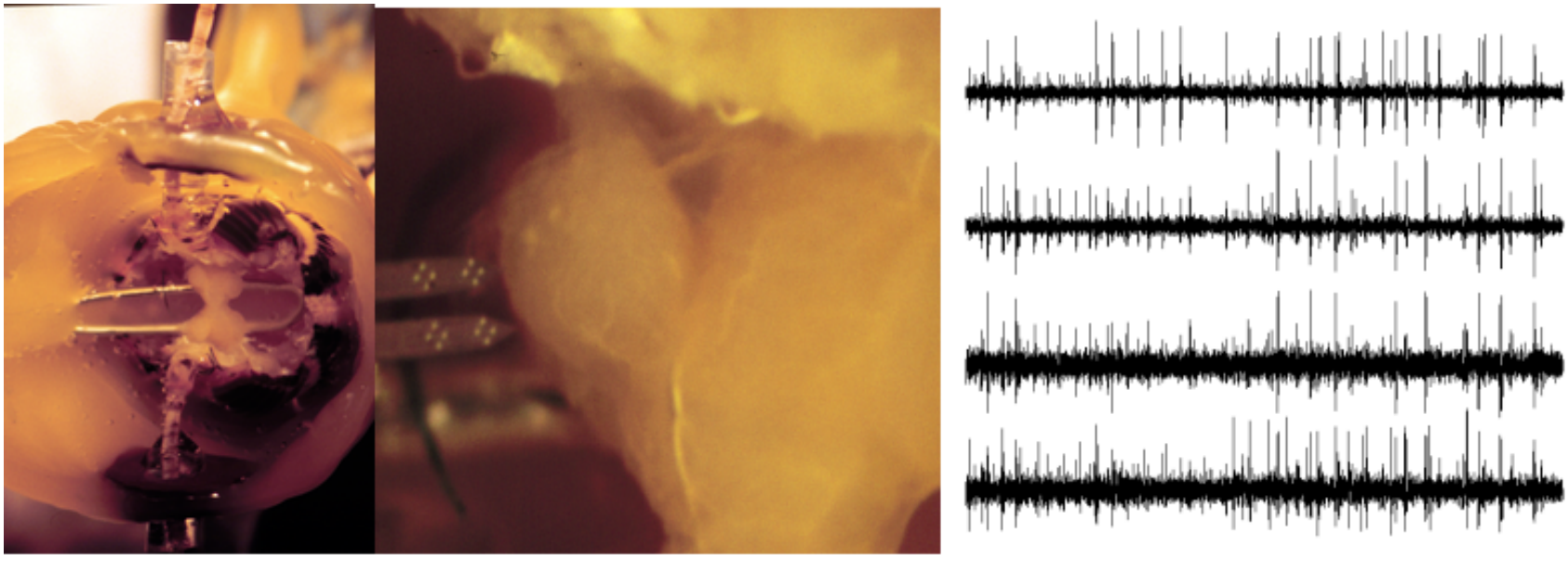
Where are we ?

What are spike trains? Data origin example

Although it's far from being the most common data source, insects like the locust, *Schistocerca americana*, constitute a very attractive preparation.

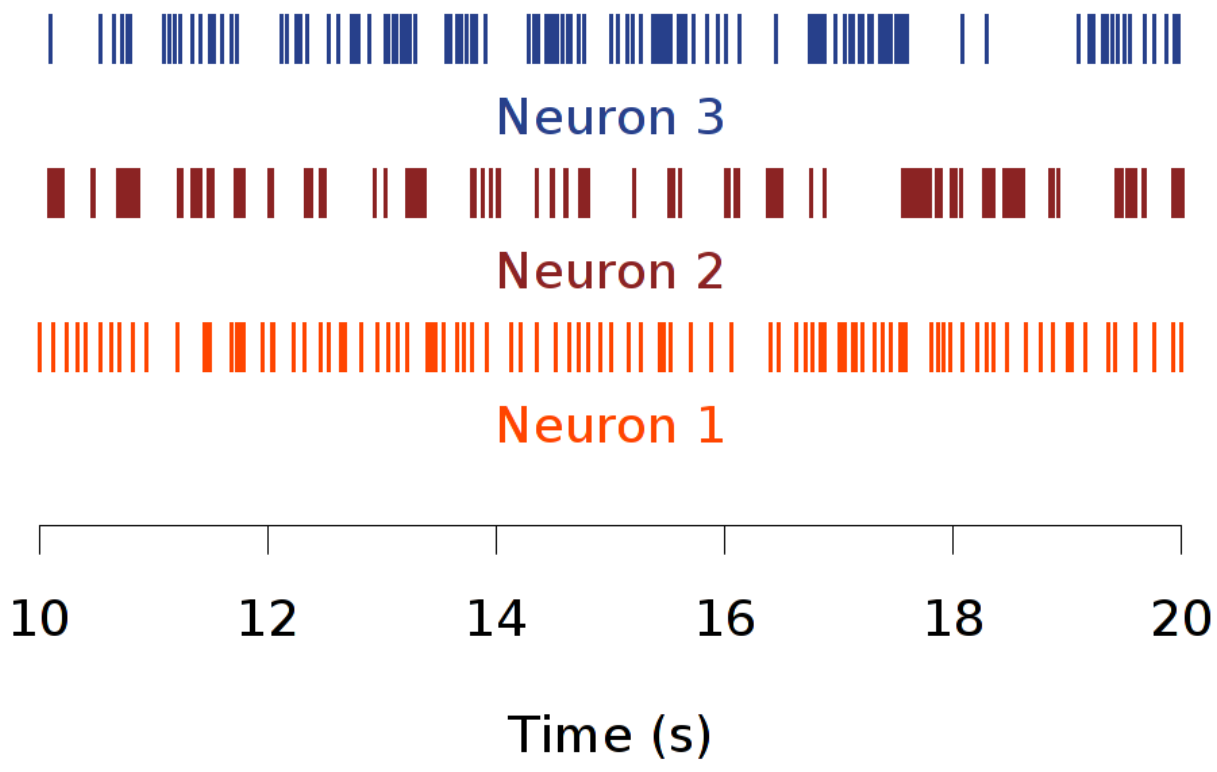
When we 'carefully' insert electrodes into a neuronal tissue containing not too densely packed neurons that fire fast action potentials or spikes, our electrodes can catch the neuronal output.



Left: opened head and brain; center: *antennal lobe* and recording probe (the two shanks with 8 bright spots on each); right: 1 sec recorded from a single *tetrode*, a group of 4 closely spaced recording sites; the data were filtered between 300 Hz and 15 kHz.

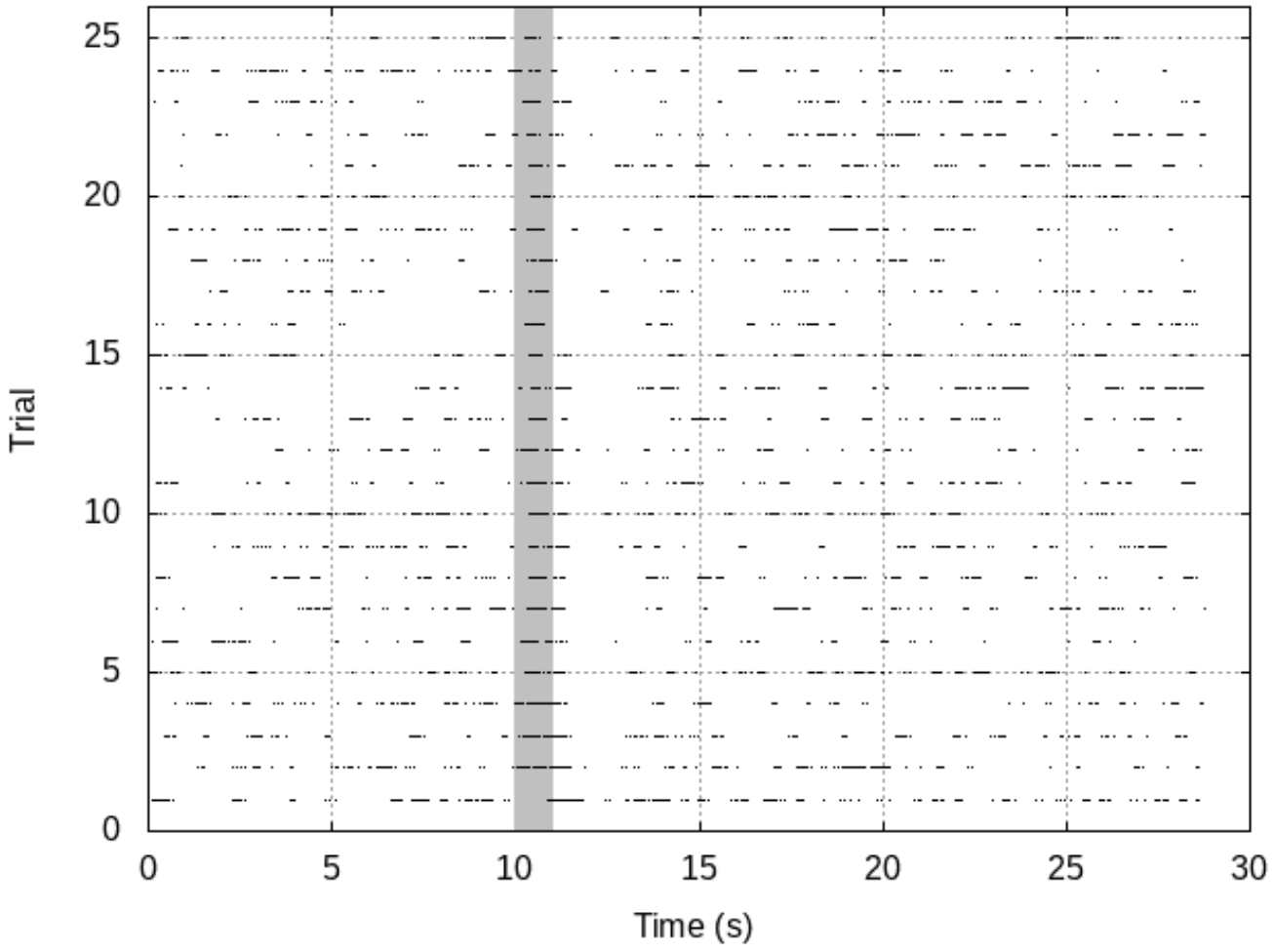
Examples of spike trains: Spontaneous activity

After a 'rather heavy' and *not neutral* pre-processing stage called *spike sorting*, the *raster plot*, one way of representing *spike trains*, can be built:



Examples of spike trains: Odor responses

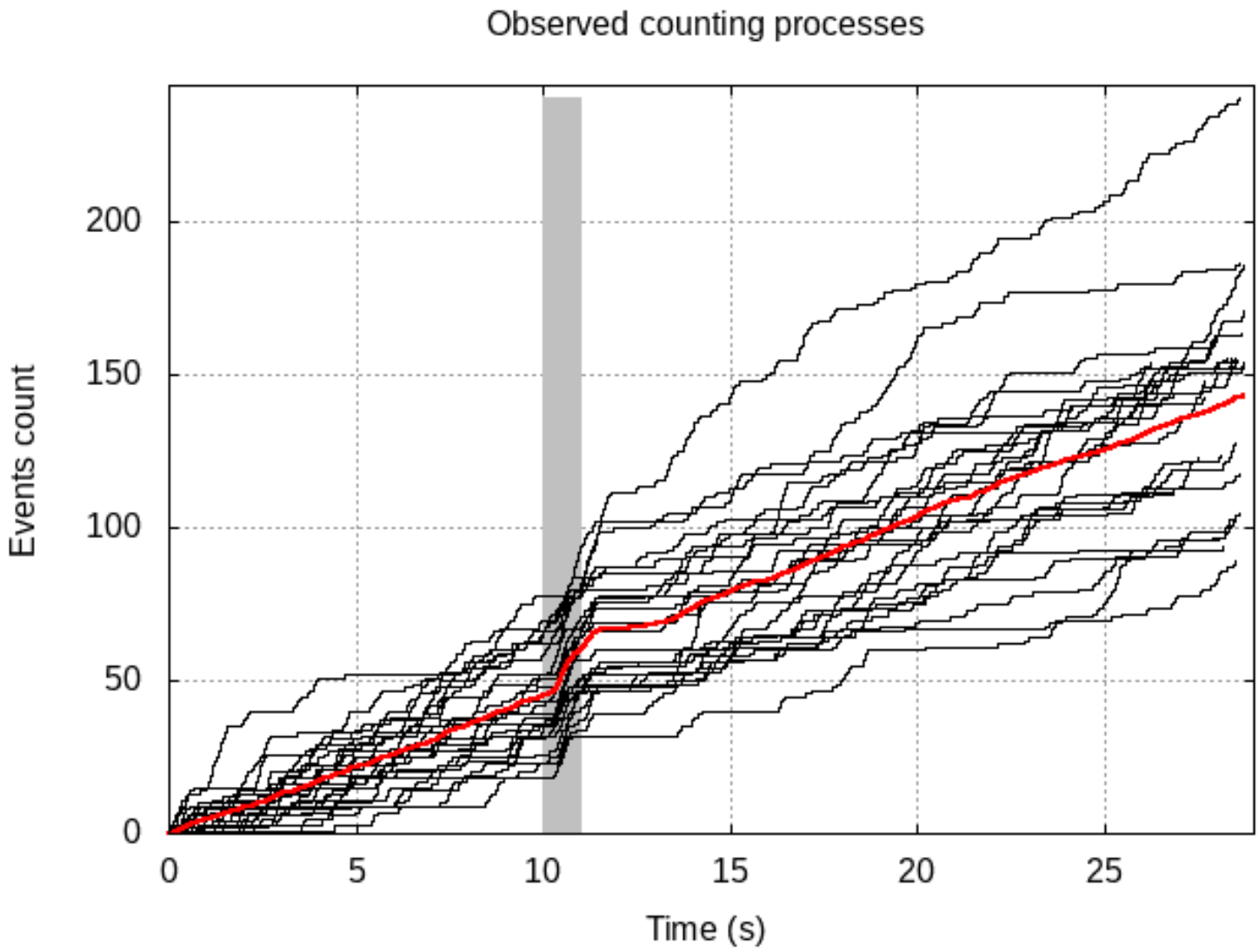
Since the brain region that is here recorded is the first olfactory relay, we usually look not only at the 'spontaneous' activity but also at *odor responses*:



Remarks

- Spike train representation by *raster plots* is omnipresent in neurophysiology even though it quickly becomes hard to read.
- In fact, the first figure of the 'classical book' of Cox and Lewis *The statistical analysis of series of events* displays the *sample path* of the *counting process* (or the *observed counting process*) instead.
- Formally, a stochastic process $\{N(t), t \geq 0\}$ is said to be a *counting process* if $N(t)$ represents the total number of 'events' that have occurred up to time t.

Counting process sample paths of Odor responses



The sample paths of the counting processes associated with the 25 spike trains just shown. In red, the empirical mean of the 25.

Why should we bother with spike trains?

- A key working hypothesis in Neurosciences states that the spikes' occurrence times (Adrian and Zotterman, 1926), as opposed to their waveform are the only information carriers between brain regions.
- This hypothesis legitimates and leads to the study of spike trains *per se*.
- It also encourages the development of models whose goal is to predict the probability of occurrence of a spike at a given time, without necessarily considering the biophysical spike generation mechanisms.

Remark

- Everything *is not* mediated by spikes in the brain!
- In the retina, the output cells, the *ganglion cells* apart, most of the other neurons: *receptors*, *bipolar cells*, *horizontal cells* and *amacrine cells*, *do not spike*.
- The function of the action potential is to propagate 'reliably' a signal over 'long' ($> 100 - 200\ \mu m$) distances.
- The retina is very thin, the neurites there are 'short' and essentially passive transmission does the job.
- It also allows an 'analog signal encoding'.

The 'messy' aspect of spike trains

- The last figures do not lead one to think that spike trains are very regular objects.
- This suggests, if we want to model them directly, that using stochastic models might be a sound idea.
- Before presenting actual spike train models, we will briefly review neurophysiological facts that, independently of our interest for spike trains, make clear that neurons (at least most of them) *are not deterministic machines*.

Where are we ?

Introduction

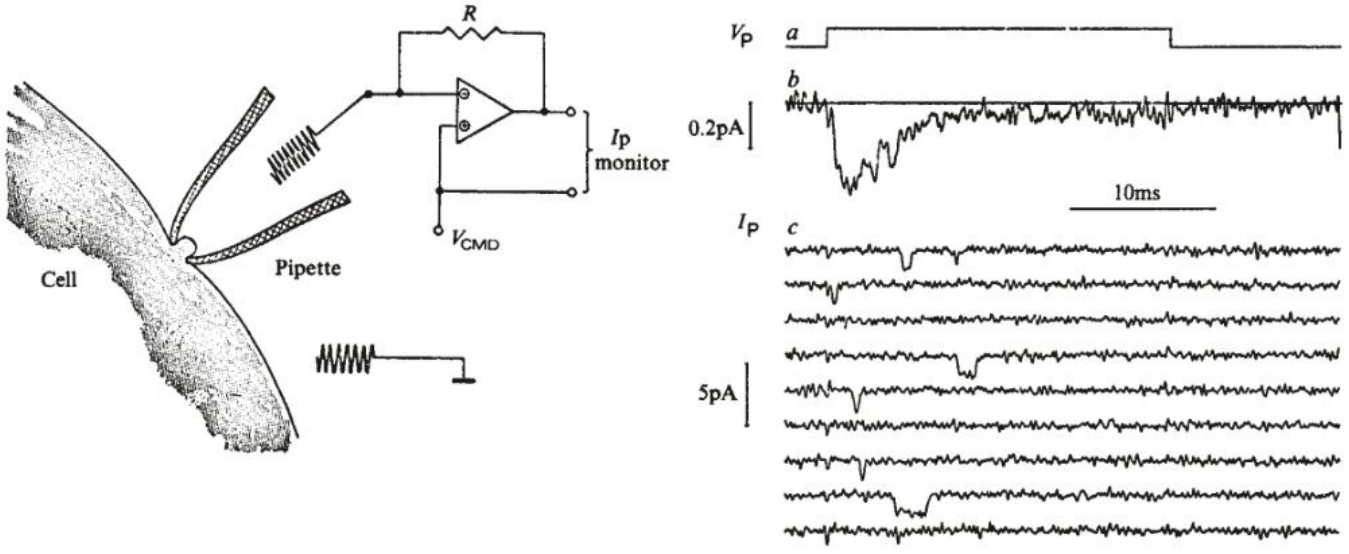
Why a modeling approach with a strong stochastic element?
Membrane noise can lead to output fluctuations

Why a modeling approach with a strong stochastic element?
Synaptic noise is ubiquitous

Other sources of variability

Membrane noise can lead to output fluctuations

- We now know something that Hodgkin and Huxley did not know when they introduced their famous model: the sodium and potassium conductances responsible for the action potential are due to voltage-gated ion channels that are pore forming transmembrane proteins.
- As most macromolecules, ion channels can be found in several transient states and will switch spontaneously between those states.
- A change in membrane voltage will change the proportion of time they spent in the different states.
- In the case of voltage-gated sodium channels spontaneous transitions are observed between 'closed' and 'open' states.



Figures 1 and 2 of Sigworth and Neher (1980). The first single channel recordings from sodium channels. Left, experimental setting. Right, single channel currents during 10 mV depolarizations: a, imposed patch membrane potential (40 mV pulse amplitude), one pulse was applied every second; b, average of a set of 300 responses; c, nine successive individual records.

- Voltage-gated sodium channels have a small conductance (5-10 pS) and cases where the spontaneous opening of a single channel can give rise to a full action potential are rare.
- It can only occur in very tiny neurons that have therefore an input resistance large enough to enable a tiny current (through a tiny conductance) to bring a membrane potential change large enough to reach threshold.

Action potentials initiated by single channels opening in a small neuron (rat olfactory receptor)

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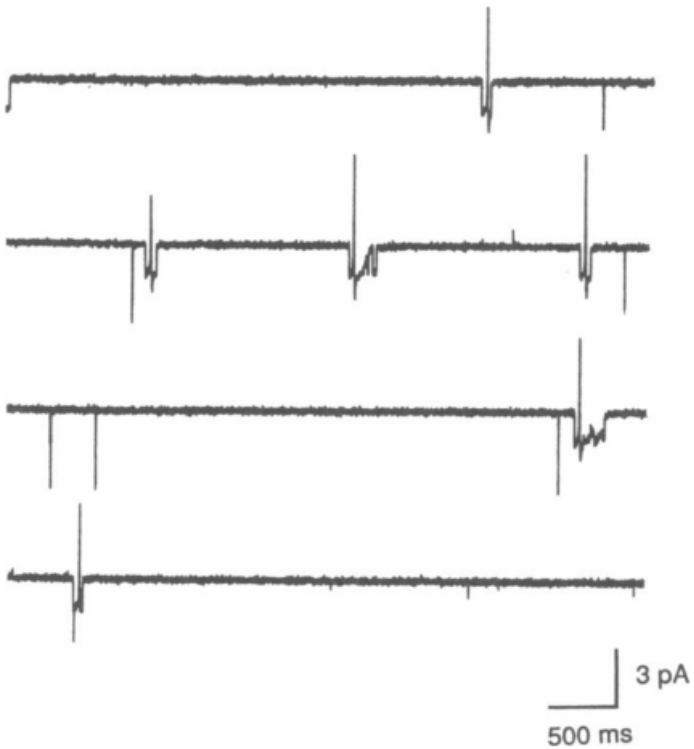


FIGURE 1 Action potential patch-current waveforms initiated by the opening of single channels. In all figures, downward current deflections represent channel openings and currents flowing into the cell. Action potential patch currents (*upward spikes*) in the remainder of the cell were initiated by current injected into the cell by the opening of single channels in the patch. The large downward spikes were large-conductance "bursting" channels with openings too brief to initiate action potentials. The four current records are continuous and were made at a pipette potential of +70 mV. All displayed records were filtered at 1 kHz.

The stochastic opening of channels can lead, in some cases at least, to fluctuating / jittering spike times as was demonstrated (before channels were known) by Verveen and Derksen (1968)

Fluctuation Phenomena in Nerve Membrane

A. A. VERVEEN AND H. E. DERKSEN

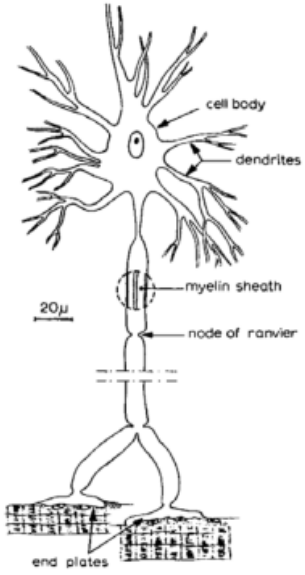


Fig. 1. Schematic representation of neuron

ulus per two seconds. Both the mean of the distribution function (defined as the threshold) and the standard deviation show an approximately hyperbolic relation to stimulus duration. The coefficient of variation (the normalized standard deviation) is constant for a given fiber. The latency distributions exhibit a rather complex dependence on duration and amplitude of the stimulus (Pecher,[8] Horvath *et al.*,[9] ten Hoopen and Verveen [10]).

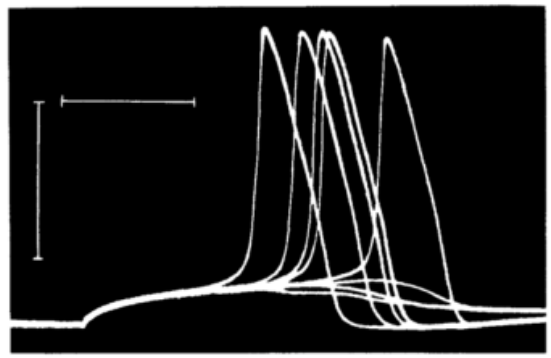


Fig. 2. Response of a Ranvier node to repeated stimulation at threshold intensity. Stimulus duration: 5 ms. Interval between successive stimuli: 2 seconds. Superposition of eight successive sweeps.

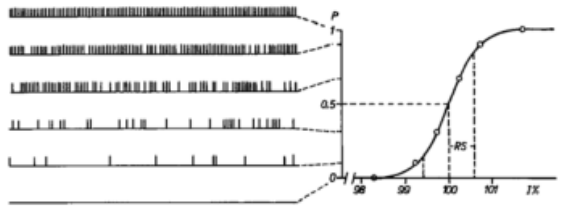


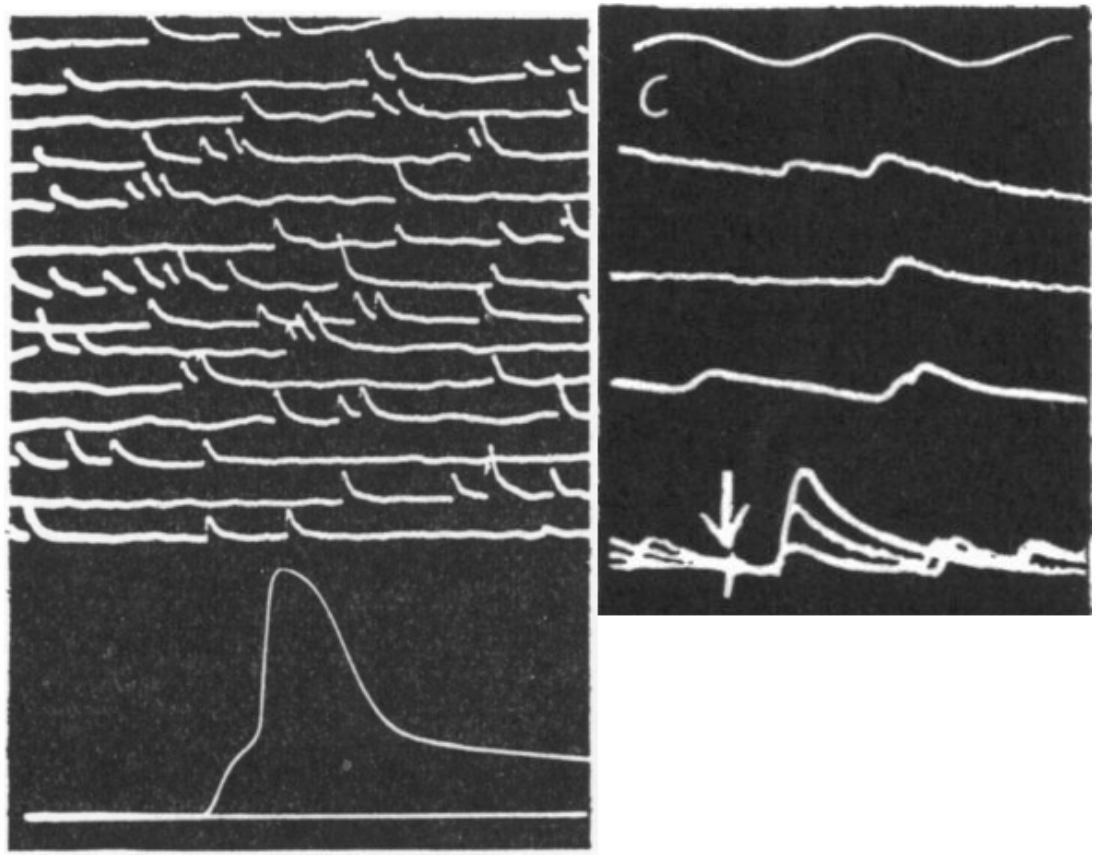
Fig. 3. Relation between stimulus intensity and probability of response. Frequency of stimulation: 0.5 Hz. (From Verveen[4].)

Montage of Figures 1, 2 and 3 of Verveen and Derksen

Where are we ?

Fluctuations at the neuromuscular junction

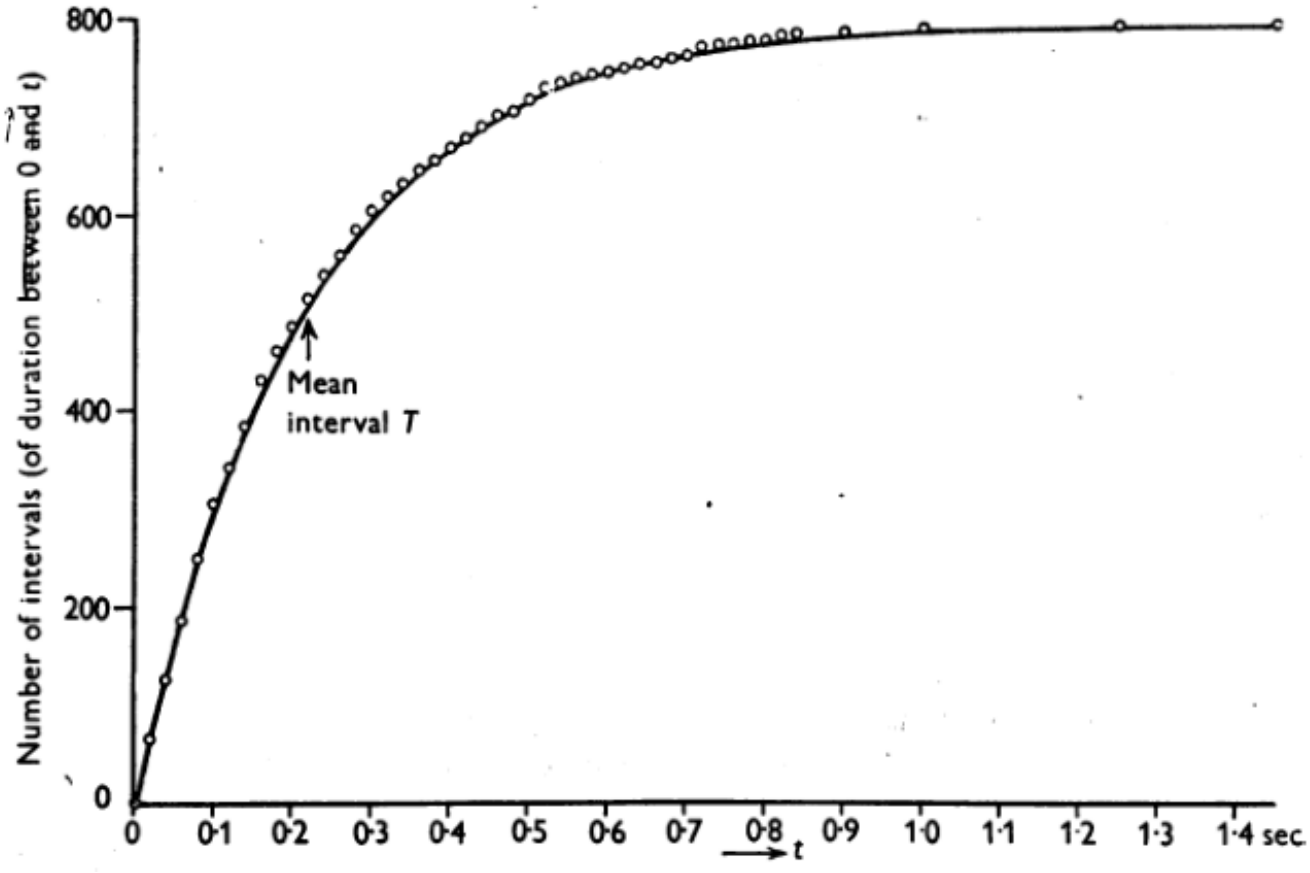
- In 1952, Fatt and Katz reported the observation of small spontaneous potentials from the end-plate region of the frog neuromuscular junction.
- They named those miniature end-plate potentials (*mepp*).
- They argued that these potentials originate from the *spontaneous release of transmitter from the nerve terminal*.
- They then studied the response of the same muscle fiber to presynaptic nerve stimulation in a low extracellular calcium condition.
- They saw that these reduced evoked responses fluctuate in steps whose amplitudes matched the ones of spontaneous potentials.



Top left: spontaneous activity recorded intracellularly from a frog muscle fiber close to the end-plate. Bottom left: response to a presynaptic nerve stimulation recorded from the same location (lower magnification on the y scale). Top right trace: 50 Hz oscillation giving a time reference. Middle right 3 traces: spontaneous potentials. Bottom right trace: superposed evoked responses recorded in low calcium; the presynaptic stimulation time is indicated by the arrow.

- In the same paper, Fatt and Katz studied the distribution of the intervals between successive *mepp* and showed it to be compatible with an exponential distribution.
- This is a first indication that these miniature events follow a homogeneous Poisson process.
- These inter *mepp* interval data can be found in the Appendix of Cox and Lewis' book where they are wrongly described as *inter spike interval* data.

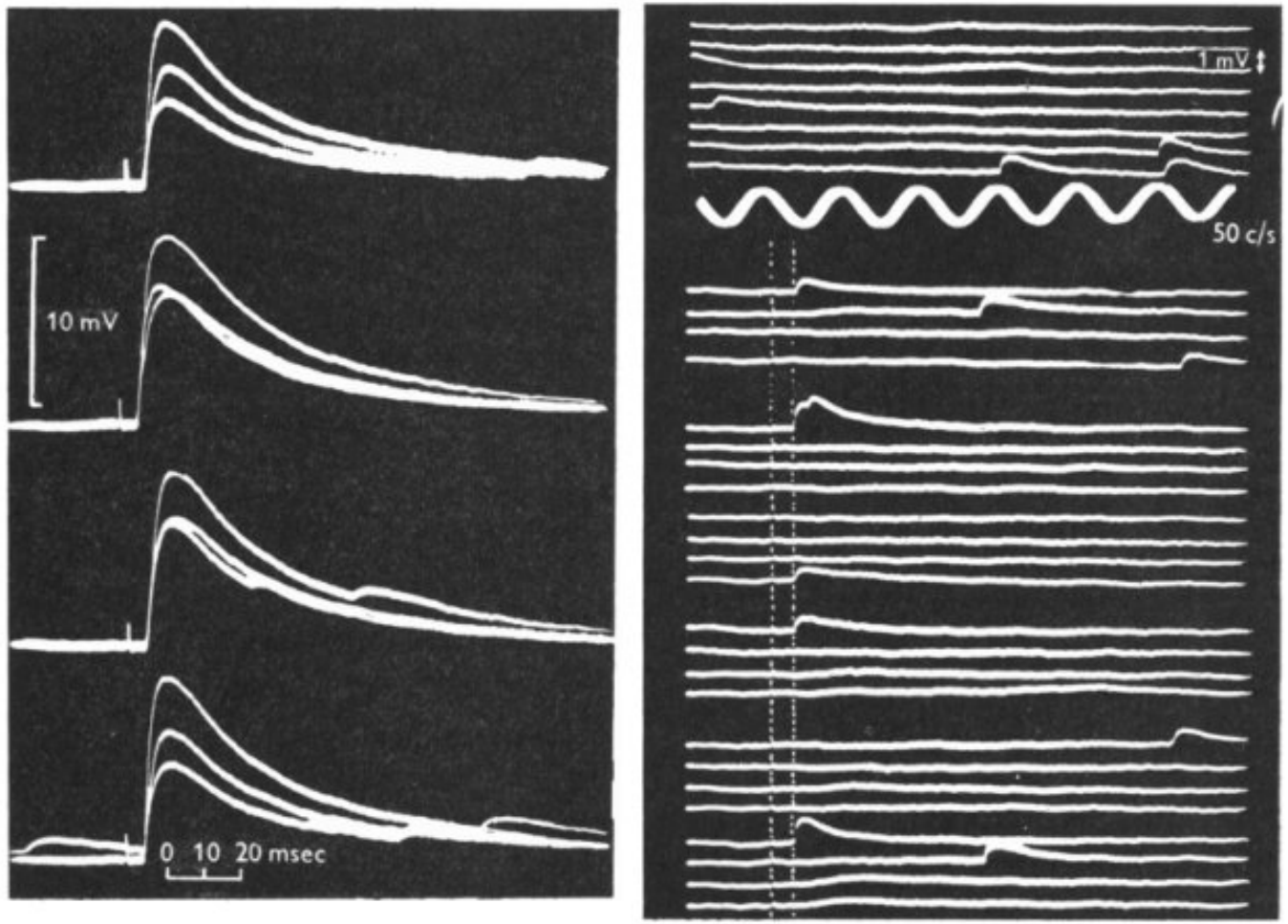
- It should be noted that this observation of the *mepp* and the suggestion that 'normal' evoked end-plate potentials are made of a bunch of *mepp* predates the observation, using electron-microscopy, of what we now call *synaptic vesicles* in the presynaptic terminal.
- De Robertis and Bennett in 1955 and Palay in 1956, describing the synaptic vesicles, were the first to suggest that a *mepp* is due to the fusion of a single vesicle.



Empirical and fitted distribution functions of the inter mepp intervals. The dots are the data and the continuous line the fitted exponential distribution function. A series of 800 mepp was used, the shortest interval that could be resolved was 5 ms, the mean interval was 221 ms (Fatt & Katz, 1952).

Quantal neurotransmitter release

- In 1954, Del Castillo and Katz investigated systematically the 'composite nature' of evoked end-plate potentials.
- Their conclusion are best summarized by the title they chose for their paper: *Quantal components of the end-plate potential*.
- In high magnesium conditions–that reduces release since, as we now know, it blocks calcium channels–, not only could they reproduce Fatt and Katz observation of fluctuating evoked potentials but they could also observe *transmission failures*.

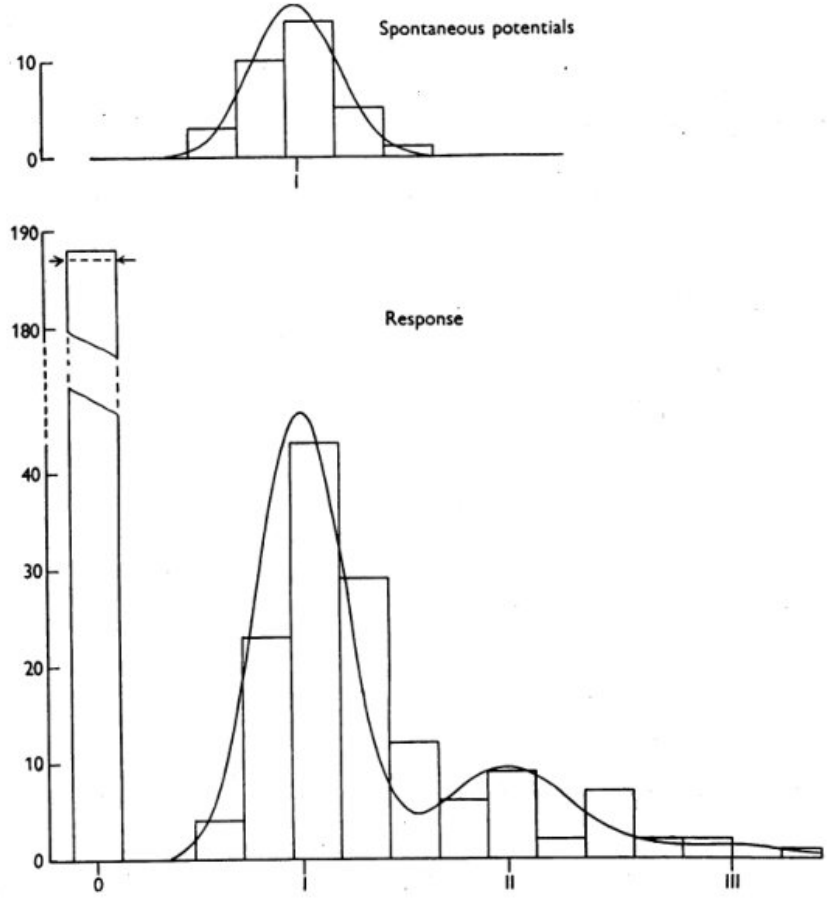


Left, Fluctuating evoked end-plate potentials in high magnesium (note the scattered *mepp*). Right (high magnesium *and* low calcium conditions): top, *mepp*; middle, 50 Hz cycles for time reference; bottom, evoked responses with many 'failures'; stimulus artifact and response latency are indicated by a pair of dotted vertical lines.

Comparing the *mepp* amplitude distribution with the one of the evoked potentials in low calcium conditions, they proposed the following scenario, commonly referred to as the quantal neurotransmitter release:

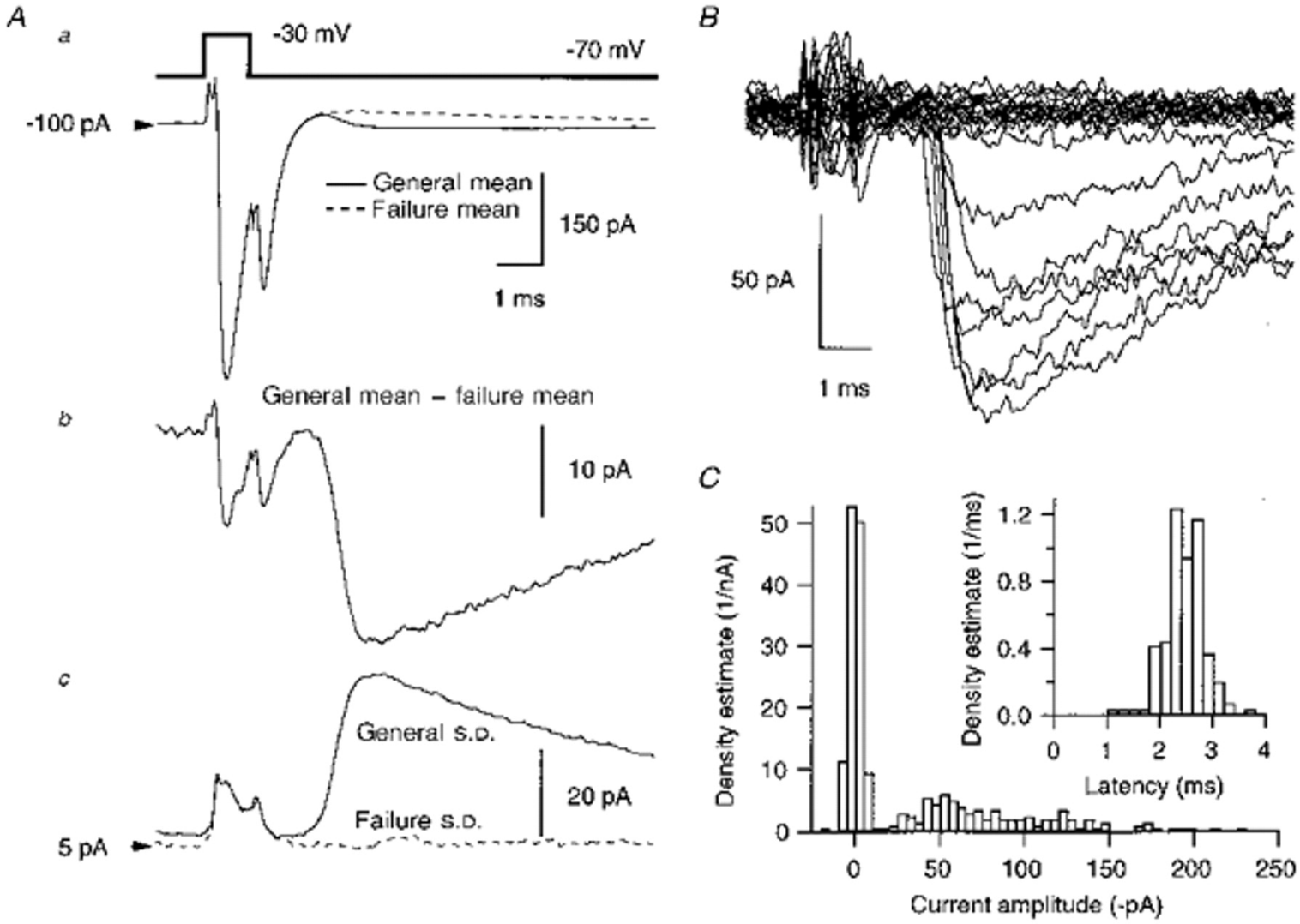
- the presynaptic terminal contains n vesicles;
- when a presynaptic action potential invades the terminal, each of the n vesicle will *independently of the others* release the transmitter it contains with a probability p (p depends on the extracellular calcium and magnesium concentrations);
- each vesicle that releases its content gives rise to an elementary end-plate potential whose distribution is the same as the one of the *mepp*;
- the evoked end-plate potential is the sum of the individual potentials due to each vesicle that released its transmitters.

Under this scenario/hypothesis the evoked potential should follow a binomial distribution–or, if p is small and n is large, a Poisson distribution with parameter np–corrupted by noise (from an increasing number of normally distributed *mepp*) as is indeed observed:



What about the central nervous system?

- These studies carried out at 'the' neuromuscular junction–a synapse designed to be reliable–exhibit marked fluctuations in specific conditions (low calcium or high magnesium) while in normal conditions the fluctuations can be neglected: every time a presynaptic spike arrives, muscle contraction ensues.
- In the *central nervous system*, synapses typically have a small number of vesicles (n) and the *release probability* (p) is rarely close to 1.
- Marked fluctuations are therefore the rule, *even in physiological conditions*.



Synaptic transmission fluctuation observed at an autapse (a synapse made by the neuron onto itself) of a molecular layer interneuron of the cerebellar cortex.

Remark

You should keep in mind that these synaptic transmission studies in the CNS are performed on *brain slices* and that taking a slice out of a brain is artifact prone.

Sources of quantal size fluctuations

The quantal neurotransmitter release we just described exhibits two sources of fluctuations:

i) the number of vesicles released varies from one synaptic activation to the next;

ii) the size of the elementary response due to a single vesicle release (the *quantal size*) is not fixed but described by a *distribution* (formally, it is modeled by a *random variable*).

The quantal size distribution can originate from different sources:

i) the number of transmitter molecules in a given vesicle is probably not absolutely fixed;

ii) the transmitter molecules diffuse in the *synaptic cleft* upon release and bind to postsynaptic receptors, depending on the numbers of transmitter molecules and receptors, as well as on geometrical factors–location of the fusion site above the receptors, receptors location, etc.–fluctuations of the number of receptors bound to transmitter are expected to occur;

iii) like the voltage-gated ion channels, (most of) the postsynaptic receptors are also ion channels and they also go back and forth between close and open states.

Where are we ?

Other sources of variability

- We have briefly described the most thoroughly studied sources of fluctuations in neurons.
- They are not the only ones known, for instance action potential propagation failures at branch points have been observed and could be at least partly random.
- More importantly, in a given experimental setting, we can never record from all the neurons involved.
- That implies that the neurons we observe receive *de facto* most of their inputs from sources we ignore.
- Modeling these unobserved inputs as random inputs, even if they are fully deterministic, makes sense as soon as there are many of them and that they are not too strongly correlated.

Conclusions

- We are facing now a modeling problem: where and how shall we incorporate 'stochastic components' in our neuron models?
- There are clearly several possibilities:
  - one would be to stick to the 'detailed biophysical model' tradition and take a 'usual' model and for instance, replace the Hodgkin and Huxley conductance model by a Markov process one;
  - the somewhat 'opposite' approach would be to 'lump together' the known and unknown sources of variability in a *single component* of the model;
  - this is the way we will pursue in the sequel and we are going to start by reviewing some of the solutions that have been proposed along this line.