

The Teorell Membrane Oscillator—a Complete Nerve Model

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ABSTRACT

The membrane oscillator discovered by T. Teorell in 1954 (10) is one of the most remarkable kinetic systems exhibiting spontaneous periodic behaviour under constant environmental conditions. It can be shown and demonstrated experimentally that the intrinsic reason for the occurrence of oscillations in the Teorell oscillator, like in other physicochemical and biological oscillatory systems, is an appropriate antagonistic action of a stabilizing positive and a recovering stabilizing negative feedback. Each kind of feedback causes a group of characteristic temporal phenomena, which are observed in all oscillatory systems including the living excitable nerve such as: instability, bistability, excitability, propagation of excitation and recovery, refractoriness, abolition, accommodation etc. .

Introduction:

In Göttingen in 1951 Torsten Teorell presented at the 50th Hauptversammlung of the Deutsche Bunsen-Gesellschaft a most memorable lecture: "On the quantitative treatment of membrane permeability". This lecture and its publication (9) initiated a strong new development in membrane science, and it was quite a convincing confirmation of the rightness and fruitfulness of these new conceptions when in 1954 his discovery of spontaneous membrane flux oscillations in a ion-exchange membrane system became known.

Though 26 years have passed since that event, the Teorell membrane oscillator has thoroughly retained its importance and actuality not only as an exceptional ion-exchange membrane system but also as a general kinetic model for all physicochemical and biological oscillatory systems due to its remarkable transparent kinetics.

1) Nonlinear Properties of Ion-exchange Membranes

As is well-known, in the Teorell membrane oscillator three forces are effective simultaneously (differing potential, pressure and salt concentration on both sides of the membrane) causing three kinds of fluxes across the membrane (electric current, volume flux of fluid and salt flux), which are mutually coupled to a high degree.

The essential kinetic feature of the Teorell oscillator is its pressure dependent non-monotonic current-voltage characteristic⁽¹²⁾ (Fig. 1), giving rise to its instability property, which is one of the necessary prerequisites for the occurrence of oscillations.

With respect to the directions of the driving forces and the sign of the membrane charge formally eight cases of combination are possible. Because, however, nonlinear current-voltage characteristics only occur in the Teorell system under conditions of opposing effects of voltage and hydrostatic pressure, only the four cases shown in Fig. 2 remain to be considered here.

The pronounced voltage dependence of the membrane resistance is caused by the electroosmotic volume flux, which carries either conducting salt into or out of the porous ion-exchange membrane.

In the four cases in question typical nonlinear current-voltage characteristics arise as a consequence of resistance transitions occurring in the voltage range where a reversal of the volume flux takes place exhibiting either non-monotonic N-shaped or monotonic \int -shaped curves. Fig. 3 gives typical experimental measurements of such nonlinear characteristics concerning coarse-grained cation- and anion-exchange membranes whose high porosity allows strong convectional fluxes.

It may be mentioned here, that also in non-convectional membranes nonlinear characteristics of N- and \int -type are to be expected namely under conditions where voltage determining properties of the membrane depend upon the voltage itself. This is the case for instance when the membrane charge (\bar{X}) or its sign (ω) or the selectivity change strongly within a sufficiently narrow range of the membrane potential (Fig. 4).

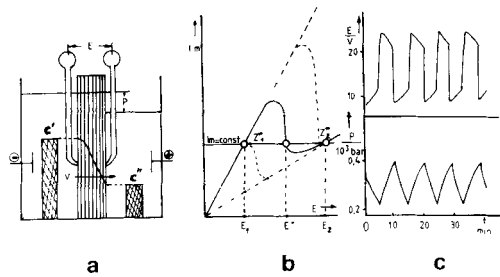


Fig. 1 The Teorell membrane oscillator
 a) set-up; b) current-voltage characteristics (parameter: P);
 c) oscillations of membrane potential and hydrostatic pressure difference P (12, 1, 5).

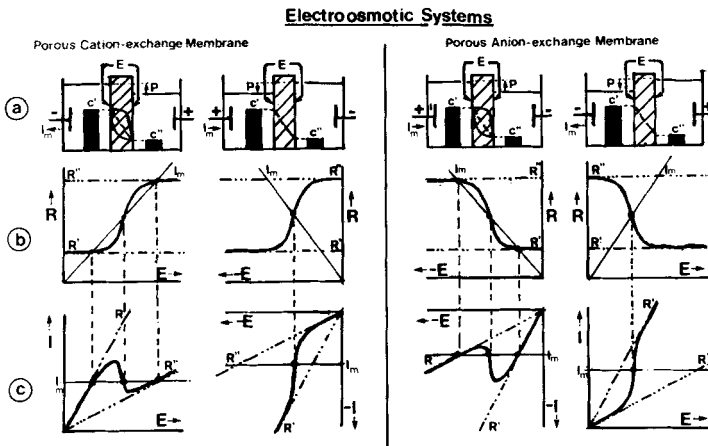


Fig. 2 Nonlinear electroosmotic membrane systems
 a) set-up; b) membrane resistance R as a function of the membrane potential E; c) current-voltage characteristics;

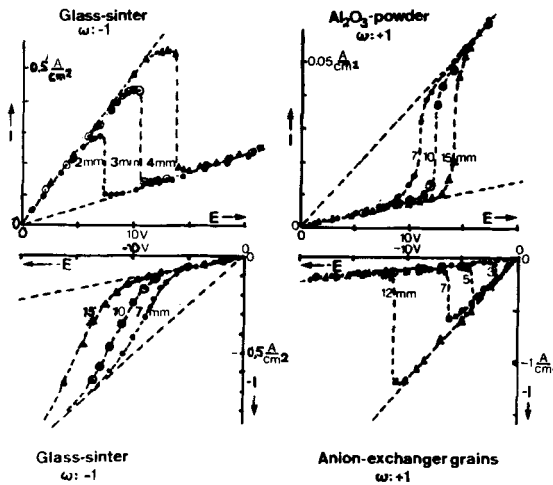


Fig. 3 Examples of nonlinear current-voltage characteristics of porous ion-exchange membranes (parameter: P hydrostatic pressure - mm column of water) (1).

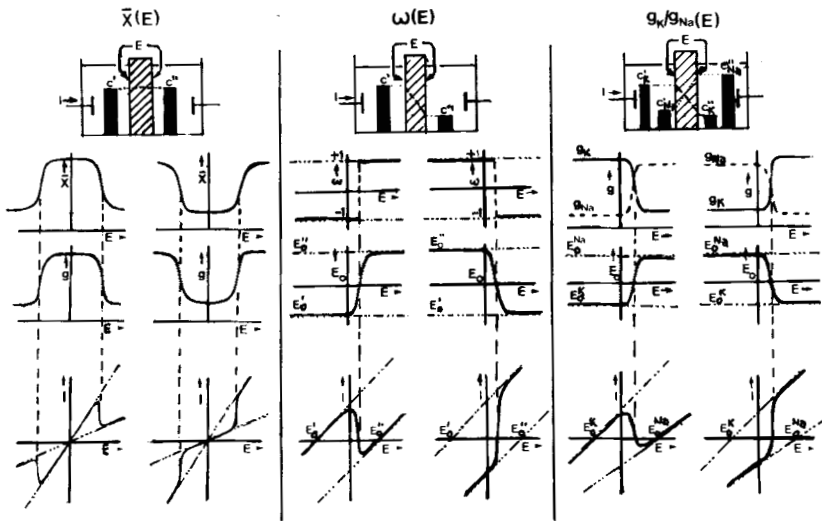


Fig. 4 Non-convictional membrane systems (X̄: membrane charge; ω: sign of membrane charge; g: conductivity)

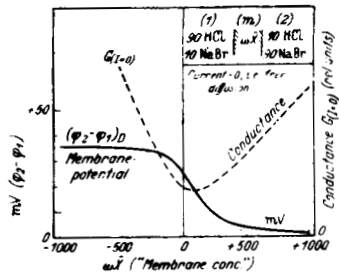


Fig. 5 Membrane conductance as a function of membrane charge (T. Teorell 1951) (9).

In 1951 T. Teorell has shown that the conductivity of an ion-exchange membrane depends on the concentration of its fixed ion charge \bar{X} (Fig. 5). Hence the conductivity of a membrane exhibiting voltage dependence of \bar{X} is a function of the membrane voltage too.

The third case of Fig. 4 (voltage depending selectivity) corresponds to the well-known concept of the Hodgkin-Huxley theory of excitable biological tissues.

2) The Feedback Concept of Nonlinear Physicochemical Systems

The main concern of this text is to show that all kinetical phenomena resulting from nonlinear flux-force characteristics are brought forth in actual fact by feedback mechanisms which all physicochemical oscillatory systems including the Teorell oscillator and the excitable nerve have in common (3, 6).

Before doing so, we have to look a little closer into feedback processes occurring in physicochemical systems.

As well known feedback arises when a process acts kinetically upon itself. It consists therefore basically in a closed chain of action causing the known effects of "self-enhancement" in case of positive feedback or "self-inhibition" in case of negative feedback.

Such processes of self-influence may arise in two ways (Fig. 6):

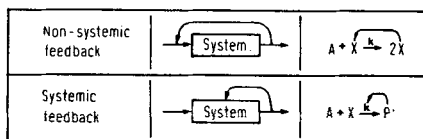


Fig. 6 "Non-systemic" and "systemic" feedback in physicochemical systems.

If the output of a transmission system (that may be an electronic amplifier, a chemical reaction, an electrode or a membrane system etc.) acts kinetically upon its own input, then a feedback situation arises in which the output-"effect" influences its own "cause". This mode of feedback has no effect upon the properties of the transmission system. For this reason it shall be designated here as "non-systemic " feedback (4).

In physicochemical and biological systems, however, most feedback mechanisms act not upon the input but instead upon the properties of the transmission system. This kind of feedback correspondingly shall be designated as "systemic"feedback.

Feedback loops in open systems may concern the formation or the consumption of the kinetic species X and may be - as already mentioned - of positive or negative nature. In this way four different feedback situations are possible being called: backward activation, forward inhibition, backward inhibition and forward activation (Fig. 7) (7).

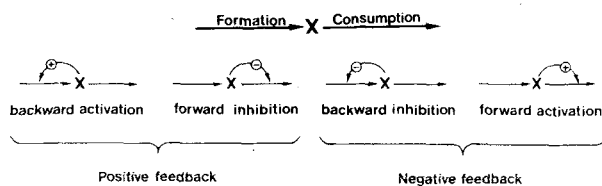


Fig. 7 Positive and negative feedback in open systems.

Oscillatory systems contain at least two simultaneous processes. By mutual (cross-) coupling between these processes 16 different possibilities have to be taken into consideration (Fig. 8). In their over-all effects they lead to four cases each for backward activation, forward inhibition, backward inhibition and forward activation (6).

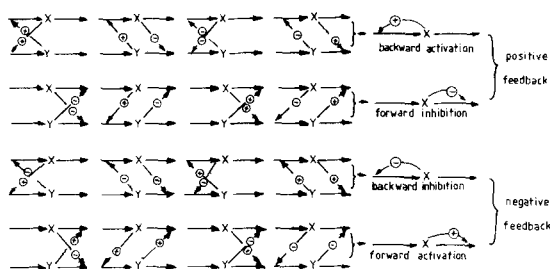


Fig. 8 Feedback by coupling of two simultaneous processes (6).

In most realistic feedback systems the types of effective feedback processes can be found out directly by experimental methods.

Because all coupling or feedback mechanisms are represented by real reactions or transportation processes of defined rates, all feedback processes necessarily need time for their proceeding. The time delay in physicochemical feedback loops varies in a large scale of magnitude. In the case of the Teorell system it ranges in minutes, in the case of the nerve membrane in milliseconds.

3) The Temporal Behaviour of Feedback systems

The temporal behaviour of positive and negative feedback systems is of essential importance for the occurrence and the temporal pattern of physicochemical oscillations.

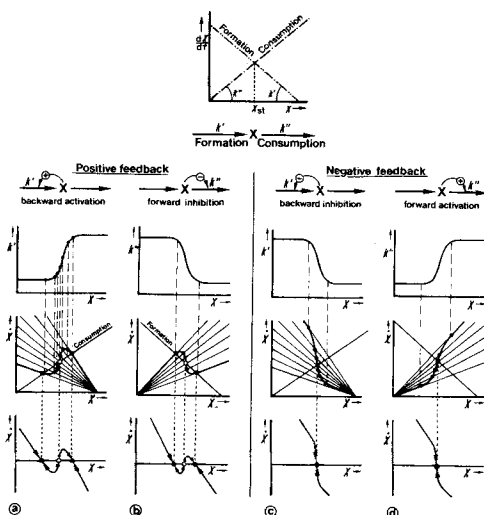


Fig. 9 Nonlinear flux-force characteristics as a result of feedback action (4).

Fig. 9 illustrates the general temporal behaviour of the four modes of coupling leading to positive or negative feedback.

Assuming for the sake of simplicity that the formation and consumption of the kinetical species X are processes of first order, a plot of $\frac{dX}{dt}$ versus X gives two straight lines which intersect at the steady state value X_{st} . Their slopes correspond directly to the relevant rate constant k or the conductance g .

Self-coupling alters the slope of the kinetic characteristic belonging to the feedback process in question. In case of forward positive feedback it is getting flatter with increasing X and it is getting steeper in case of negative feedback.

Fig. 9 shows in particular how non-monotonic N-shaped curves result from positive feedback and monotonic S-shaped curves from negative feedback.

Provided that the positive feedback is sufficiently strong three intersection - representing steady states - may occur between the curves of consumption of X exhibiting bistability and instability resp. .

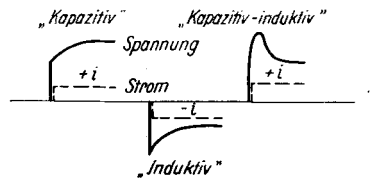
Positive feedback labilizes the system, and it is the intrinsic reason for all instability phenomena of autocatalytic and other self-enhancing systems.

In contrast negative feedback has a stabilizing effect. It generates always one stable state only.

The bottom row of graphs shows the "dynamic diagrams" which describe the over-all temporal variation of X as a function of X itself. The inserted arrows indicate the directions of the resulting temporal variations, and which illustrate how stability and instability arise from the variations in the immediate neighbourhood of a particular steady state.

For positive as well as for negative feedback characteristic modes of temporal behaviour result as a direct consequence of the feedback delay.

Concerning ionic membranes, already in 1951 T. Teorell pointed out in the paper already mentioned that in such membranes "pseudo-capacitance" and "pseudo-inductance" behaviour are observed (Fig.10).



Zeitlicher Spannungsverlauf verschiedener Systeme Elektrolyten-Membran (nach Einschalten eines konstanten Stromes). Das System zeigt scheinbare Kapazität, Induktivität bzw. Kapazität + Induktivität

Fig. 10 Pseudo-capacitive and pseudo-inductance behaviour of ion-exchange membranes (T. Teorell 1951)(9).

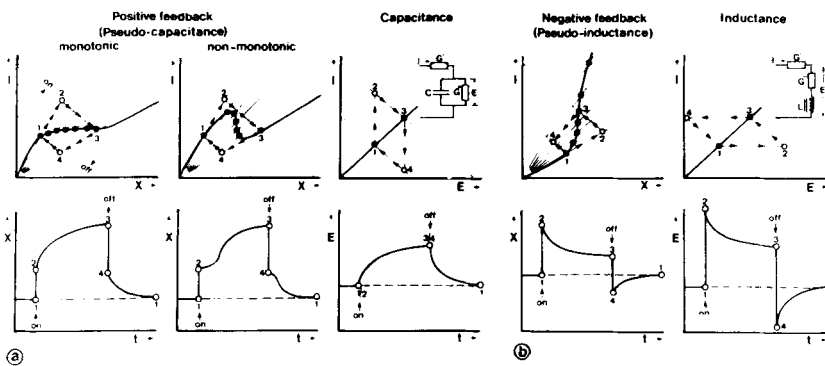


Fig. 11 Temporal behaviour of feedback systems compared with electric capacitance and inductance circuits (6).

Fig. 11 illustrates that positive feedback actually leads to temporal pattern resembling that of a capacity. Systems containing negative feedback behave correspondingly like inductances exhibiting overshoot phenomena which in fact are recovery phenomena as a consequence of the stabilizing activity of the negative feedback. Now we are in a position to identify the nature of feedback loops existing in a particular system by studying its temporal behaviour.

In this context it might be stated that from the feedback point of view it is evident that the temporal behaviour of physicochemical systems is quite the same as it is well-known from feedback in electric circuits or technical control systems, and in actual fact the occurrence of oscillations in physicochemical and biological systems obviously is based on the same dynamical principles as it is the case in electrical systems whose oscillatory behaviour as a result of feedback action is quite self-evident for us.

4) The Principle of Antagonistic Feedback.

It is a highly interesting fact that all physicochemical oscillatory systems found so far clearly exhibit positive and negative feedback simultaneously.

It is most likely that oscillations in such systems are the result of a general kinetic principle which is represented in Fig. 12 in form of a general feedback pattern. It may be designated here as the "Principle of antagonistic feedback of physicochemical oscillators" (3).

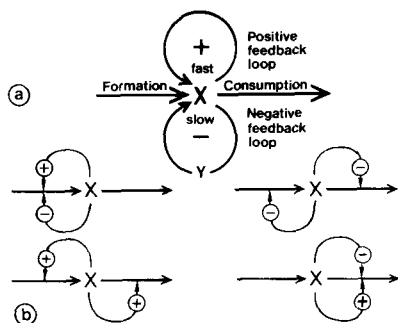


Fig. 12 Antagonistic feedback in oscillatory open systems containing two simultaneous processes (3).

According to this principle the oscillations are understood as a consequence of an antagonistic interaction of a relatively fast acting positive feedback of labilizing tendency and a slower acting negative feedback of stabilizing recovering tendency.

This concept of oscillatory systems consisting of two distinct loops of positive and negative feedback requires at least two kinetical variables, one for each feedback mechanism. Each loop, however, may contain several variables in series. All these variables participate in the over-all oscillatory process. In most real cases of oscillations it is possible to find out from the recordings to which class of feedback loop a particular oscillating variable belongs (Fig. 13). Also a general classification of the temporal phenomena of feedback systems can be given now with respect to the nature of the feedback being responsible for a particular phenomenon (Fig. 14).

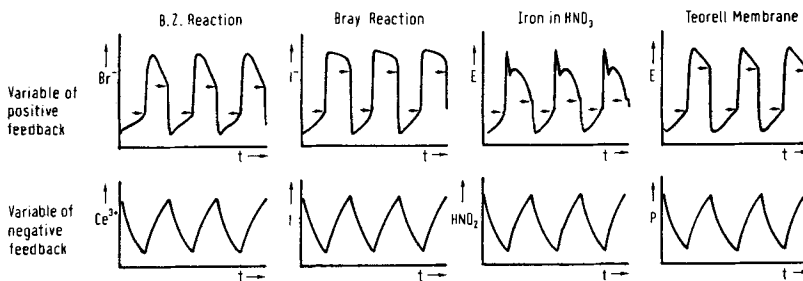


Fig. 13 Simultaneous oscillograms of variables belonging to different feedback loops. Variables involved in positive feedback loops exhibit flip-flop-type oscillograms showing instability features (\rightarrow). Oscillograms of variables belonging to negative feedback loops usually have simple saw-tooth shape without marks of instability (B.Z.: Belousov -Zhabotinsky reaction)(6).

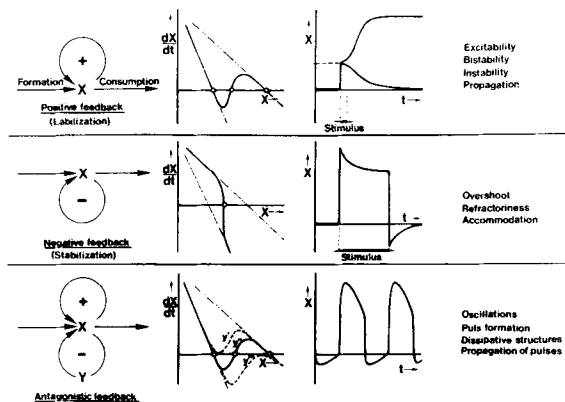


Fig. 14 Classification of temporal phenomena of feedback systems (4).

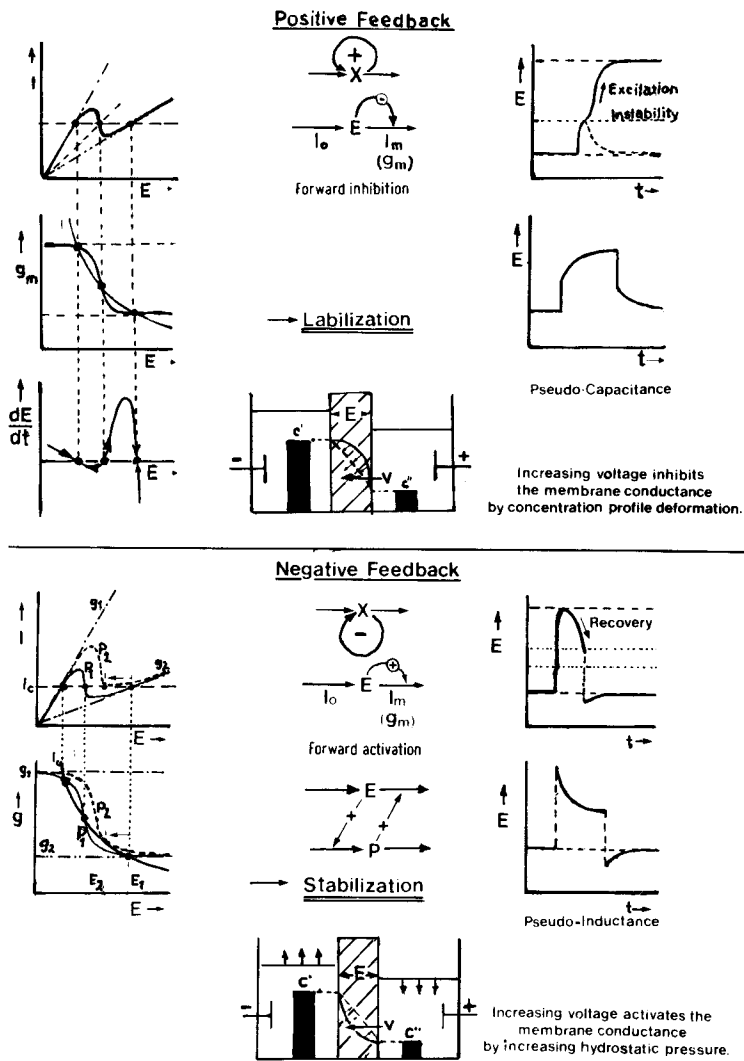


Fig. 15 Positive and negative feedback arising in the Teorell system.

5) The Feedback Situation in the Teorell Membrane Oscillator

Let us now look at the Teorell membrane system from the feedback point of view. There is clearly a positive feedback loop provable with respect to the transmembrane potential, and which manifests itself in the voltage dependence of the membrane resistance (Fig. 15). The "formation" and "consumption" of the kinetical species X concerns primarily the salt content inside the membrane as a result of the volume flux driven by the electroosmotic effect of the membrane potential inside the ion-exchange membrane.

Because the salt content of the membrane determines the membrane resistance, there exist under current clamp conditions a direct relationship between the salt content and the membrane potential. Therefore we may replace X directly by the voltage E as the characteristic kinetical variable of the positive feedback loop. It is easy to show that in the Teorell membrane system this loop is realized by a forward inhibition constellation. Here, an increasing voltage inhibits the membrane conductance by a corresponding deformation of the concentration profile. The positive feedback leads to pseudo-capacitive behaviour, to a non-monotonic current-voltage characteristic and to a corresponding dynamic relationship between $\frac{dE}{dt}$ and E.

The negative feedback of the Teorell oscillator (Fig. 15) comes about as a result of the volume flux dependence of the hydrostatic pressure, which is - besides the membrane potential - the other driving force of the volume flux.

The negative feedback loop represents here a typical example of mutual coupling of two simultaneous processes whose over-all effect concerns a forward activation. Increasing voltage activates here the membrane conductance by increasing hydrostatic pressure.

6) The Teorell Membrane Oscillator as a "Complete Nerve Analogue".

Surveying the list of feedback phenomena of Fig. 14 we are strongly reminded of the phenomenology of the excitable nerve and other biological excitable tissues. Tab. 1 sums up the properties which are considered as fundamental phenomena of the nerve membrane.

Physicochemical systems exhibiting these properties are designated as "complete nerve models" or "nerve analogues".

Table 1.

Fundamental Electrophysiological Properties of Excitable Tissues

Instability:	Bistability Excitability (Triggerability) Threshold Phenomena Abolition
Impulse Response:	Excitable Actionpotential Spontaneous Recovery of Excitation Refractoriness Accommodation Overshoot Phenomena
Propagation:	Two-way Propagation of Excitation Propagation of Actionpotential Triggerability of Propagation Phenomena Saltatoric Propagation
Rhythmical Activity:	Oscillatory Phenomena

Obviously the nerve represents kinetically a system of antagonistic feedback too. Hence we may define a complete nerve analogue briefly as a system exhibiting antagonistic feedback as outlined here.

There are several articles published by T. Teorell twenty years ago which clearly show that already in the fifties he was quite aware and convinced that his membrane oscillator in actual fact represents a complete nerve analogue (11 - 13).

In particular by aid of an analogue computation program derived from the set-up and the data of the membrane oscillator Teorell demonstrated convincingly a great deal of these excitability phenomena. But also under suitable conditions these phenomena can be demonstrated in the real Teorell membrane system.

Because the author does not know exactly which of these experiments have already been carried out by T. Teorell himself, some of the author's results may be given here in order to show the efficiency and the completeness of the nerve analogue properties of Teorell's membrane system.

Tab. 2 gives a list of materials suitable for membranes in the Teorell oscillator. Most of the experiments shown in the following pictures have been carried out by means of Duran-sinter glass

membranes of a thickness of .7 mm and an area of .3 cm² (\bar{X} : 10⁻⁸ mol/l, width of pores: ~9 μ).

Table 2.

Membrane Materials Suitable for Teorell-Oscillations

Porcelain (Teorell)	.7 μ
Porous Glass-sinter (Teorell)	1 μ
Porous Duranglass-sinter	9 μ
Porous Polyvinylchloride ('Porvic')	4 μ
Porous Polystyrol ('Flexolith')	2.5 μ
Nuclepor Filter (Meares & Page)	1 μ
Quartz Powder	5 μ
Al ₂ O ₃ -Powder	2 μ
Cation-exchanger Grains (Teorell)	
Anion-exchanger Grains	

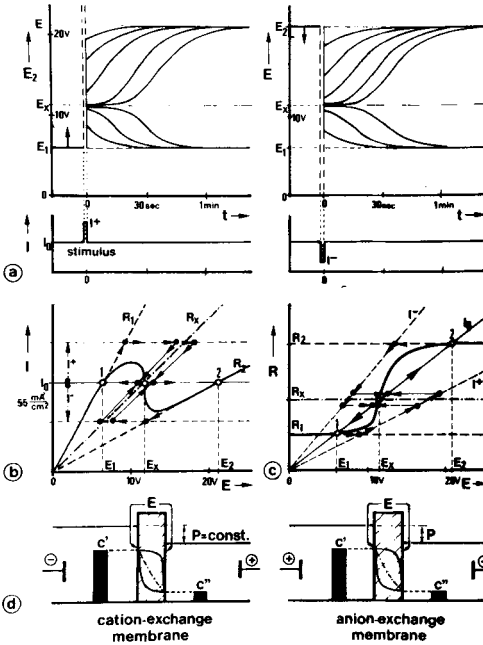


Fig. 16 Threshold behaviour of the TNA (Teorell Nerve Analogue).

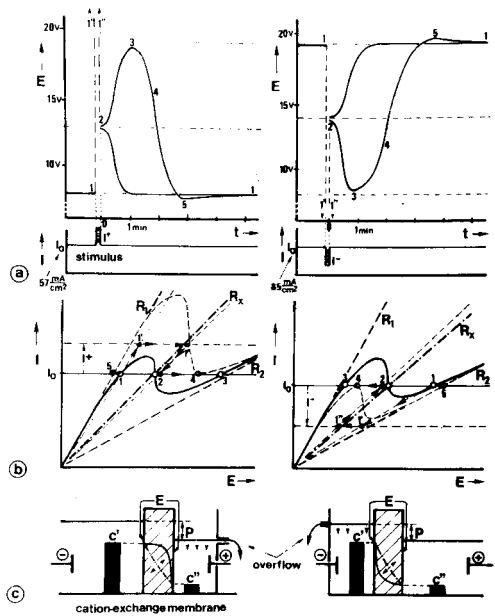


Fig. 17 Action potential response of the TNA.

Fig. 16 shows the well-known temporal pattern of the threshold behaviour of such an excitable Duran-glass membrane. In this case the compartments are virtually unlimited so that no oscillations can occur.

Excitability in such a bistable system is, as well-known, a two-sided phenomenon with respect to both stable states, which are completely equivalent in the kinetical sense. Super-threshold stimuli shift the membrane resistance beyond the value of the unstable concentration profile, subthreshold stimuli don't reach it. Simply by limitation of one compartment fitted with an overflow the Teorell system exhibits triggerable action potentials (Fig.17). It depends upon on which side of the set-up this compartment limitation is made whether an upward or a downward action potential occurs. The recovery is the result of the variation of the hydrostatic pressure caused by the volume flux during the period of excitation. The overflow prevents repetitive excitation.

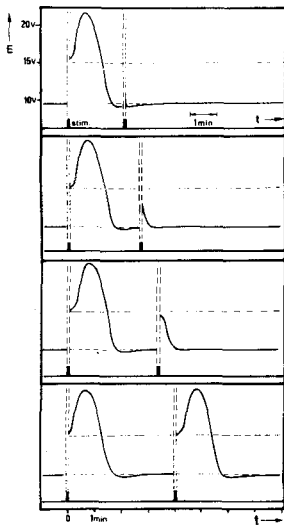


Fig. 18 Refractoriness of the TNA.

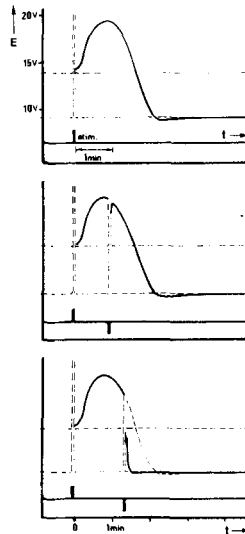


Fig. 19 Abolition of action potential of the TNA.

Fig. 18 demonstrates at the same membrane system the phenomenon of refractoriness by applying of two stimuli of the same strength with increasing temporal distances. With decaying refractoriness - realized by decaying hydrostatic pressure, the system regains its excitability.

Fig. 19 demonstrates the phenomenon of abolition of the action potential by counteracting stimuli. In case of the excitable nerve I. Tasaki has demonstrated abolition in 1956 (8).

Also the phenomenon of excitation propagation can be demonstrated by means of Teorell's membrane system (Fig. 20). Propagation is a

direct consequence of the bistability of the system containing strong positive feedback. The propagation may concern the conversion of the upper state into the lower state or the reversed process. Also saltatonic propagation can be realized in Teorell's nerve model (2).

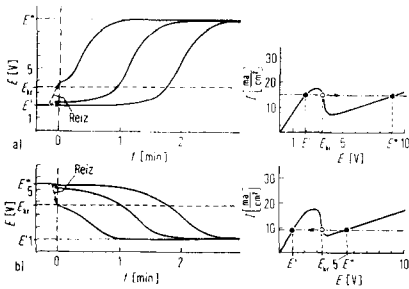


Fig. 20 Propagation of state transitions (2)
 a) from lower to upper state;
 b) from upper to lower state;

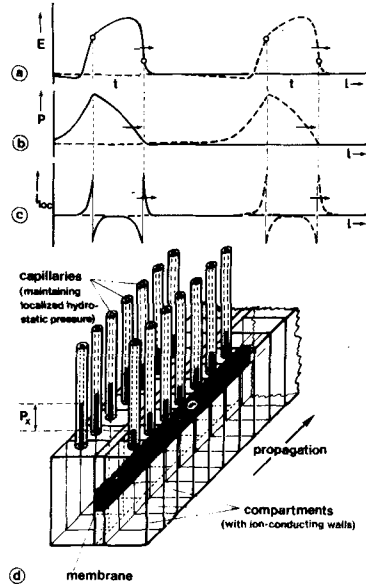


Fig. 21 A project of a TNK exhibiting action potential propagation.

Propagation of action potentials should be demonstratable too by means of the Teorell system. Fig. 21 shows a project of a set-up which should exhibit action potential propagation. It consists of an array of compartments bounded by ionic conducting walls on both sides of the membrane allowing that localized hydrostatic pressure can be maintained.

There is no doubt that this model will work and it can be predicted on the basis of the experiences with the Teorell system that in this nerve analogue a wave of action potential accompanied by a wave of hydrostatic pressure and a double wave of eddy currents would travel along the membrane after a local stimulated excitation.

This project, whose realization would be very laborious, is mentioned here in order to show that the missing of actionpotential

propagation experiments is no disproof of the completeness of the nerve analogue property of Teorell's membrane system.

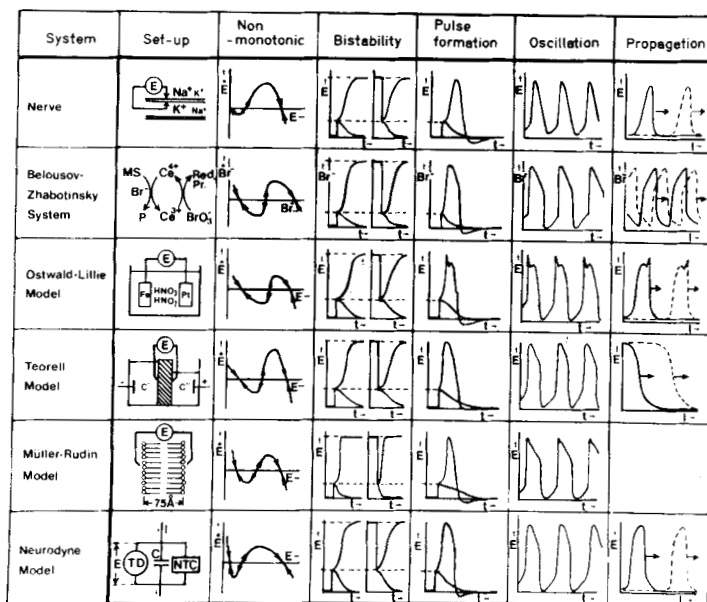


Fig. 22 Synopsis of the general phenomenology of systems containing antagonistic feedback.

Concluding a synopsis of physicochemical oscillations are shown in Fig. 22. These systems which are regarded as nerve models are of extremely different substantial nature, but they have obviously one property in common: the antagonistic feedback. From this point of view it is no more surprising that they exhibit nevertheless an identical phenomenology. Among these systems Teorell's membrane oscillator certainly is the system being best understood now due its simplicity and transparent kinetics.

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