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A Fixed Charge System as a Formal Model for the Behaviour of Smooth Muscles and the Heart

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ABSTRACT

An extension of the theory of the "fixed charge" controlled "membrane oscillator" is used for simulation of a variety of excitability phenomena in nerves, presso-receptors,smooth muscle and the heart. A central issue is the prediction of water movements across the cell membrane resulting in "swelling" and "shrinkage". The presented "electrohydraulic excitability analog" (EHEA) deals particularly with the generation of action potentials, volume-pressure changes and contractility in response to externally applied mechanical stimuli, i.e. the EHEA is applied as a pressoreceptor analog. The agreement between the theoretical model results and some experimental physiological observations cited from the literature is quite satisfactory.

INTRODUCTION

The history of membrane transport processes is long and fascinating(Sollner (4) ,Teorell (18)) and there were many attempts to demonstrate applications in bioelectricity. New efforts were made in the fifties when the "membrane oscillator" (MO) was introduced (6)-(9). This device displayed oscillatory membrane events which showed obvious similarities to physiological action potentials as occur in nerves and other "excitable tissues" (mechano-receptors ,smooth muscles and the heart). The salient feature of the MO is the presence of a membrane loaded with "fixed charges" in the water permeable pores. The membrane separates two compartments (simulating the "cell interior" and the "cell environment") containing electrolytes. The "driving forces" eliciting the oscillations (electric potentials, conductance changes and water flows) are a steady electric current and a salt concentration gradient across the membrane. It should be remarked that an intra-membrane salt gradient could arise from the current flow alone, even if the salt composition in the surrounding compartments was identical, see (10). The oscillations are essentially an electro-osmotic phenomenon, goverend by the laws of electro-kinetics (see (9-14)).

THE DEVELOPMENTS OF THE "ELECTROHYDRAULIC EXCITABILITY ANALOG".

1. The rigid MO-system.— The first version of the MO was a rigid "Lucite" chamber system (ref. 6-10). It gave oscillatory responses to electric and/or mechanical perturbations ("stimuli") and thus acted as a primitive "mechano--electrical transducer" with a constant frequency of the oscillations. However, it is well-known that the main "signal code" of the nervous elements is a varying "spike" frequency,i.e. "frequency modulation" (FM). This implies that the spike (=action potential) frequency varies with the strength of the stimulus.

2. Heterogeneous (leaky) membranes and visco-elasticity. — In the second version of the MO improvements were added to achieve FM (ref 10,13,14). These were a/ introduction of non-charged, "leaky" pores in the membrane (=membrane heterogeneity) and b/ introduction of a non-rigid membrane, displaying visco--elasticity (without "creep") by assumption of a non-linear relation between cell pressure, P, and the cell volume change,M. The P=f(M) relation is of a decisive importance for the bandwidth of the FM, it was chosen to be hyperbolic so that it approached a P-maximum with increasing M ("swelling").This means that the excitable "cell" has a certain "turgor" pressure P which varies with the cell volume and keeps it distended.

It should be observed that the "visco-elasticity" is located entirely within the structure of the cell membrane. The results obtained by this more refined model were so satisfactory when compared with actual experimental results published by many authors in receptor physiology that a new designation of the original MO-model became justified. Under the new name of the "electro-hydraulic excitability analog" (EHEA) new comparisons were published (13,14). The paper (14) of 1971 in the Handbook of Sensory Physiology gives a thorough account of the EHEA both as regards the underlying theories and its capacity to simulate widely scattered observations in the field of physiological pressoreceptors.

3. Hysteresis effects. — In the Handbook article (14) it was often noted that the relation between mechanical "displacement" (stretch) of a tissue and the ensuing "tension" was dependant on the time history, - i.e. the relation could exhibit "hysteresis" and "creep". Such phenomena were not directly incorporated in the EHEA equations (which were solved by an analog machine technique), although they were included,in some instances, by additional "soft ware". This situation has prompted the question of how to formalize a time-dependant visco-elasticity. In the first place the whole problem of the actual nature of this property remains obscure as regards the actual anatomical structures involved. Nevertheless a "symbolic" mathematical treatment may be justified for

want of better information. Many useful expressions are available in the literature (springs,dashpots, etc.). Such devices symbolically depicted, can be discerned in a diagram in an earlier publication,fig. 9 (14) .They could be incorporated in the non-linear P=f(M) equation referred to earlier. However, such an operation might involve volume changes within the cell membrane proper.In fact, this was the kind of notion which was sketched already in 1962 in Fig 18 in the paper (11), (referred to by Dr Tasaki in his paper in this volume). To circumvent the arising mathematical dilemma another approach was chosen. When dealing with tissues, not single cells, it might be conceivable that the extra-cellular compartments participate in controlling P,the cell transmembrane pressure difference. The extracellular volume space could also be thought of as bounded by a distensible membrane or casing with a non-linear volume-pressure relation somewhat like P = f(M) for the single cell. There will be a different effect of a mechanical stimulus: in the single cell case a mechanical "poking" will squeeze out water from the cell to the external medium in one stage with an immediate effect on the transmembrane P. In the two-compartment case the poking will affect first the extracellular volume (which now is the connecting link to the medium). The extracellular pressure level (referred to the medium as zero) will now change and P reacts with some time delay ("hysteresis").

Qualitatively, these concepts can be described: The excitable tissue as a whole can be symbolized as two concentric water filled ballons, the inner one representing the excitable cell proper, the outer one the extracellular tissue space. Both may leak to some extent, but both are kept inflated by the operation of membrane "water pumps". The cell pump is electroosmotic, the extracellular pump may be similar, or rather of the colloid osmotic type assumed to exist between blood capillaries and the extracellular space. The operation of this two-compartment, or series coupled,system is briefly described in (15,17). This extended EHEA remains "hydraulic" in the sense that the central changes are internal shifts of water volumes. In these papers of 1974-76 excellent simulations were achieved of the experimental findings of Almqvist (1) from isolated heart strips of the Helix pomatia. Further examples will be given later in this paper.

4. A formalism for contractility. — For long it has been known that a muscle contraction follows an electric stimulus, but it was first about 1950 that the exact time relations between monophasic action potentials (AP) and contractile force (CF) ("twitch") were described. Already in the first works on the MO our attention was brought to the close similarity between the pressure excursions (P) and physiological CF, both with regard to time relations and shape. In fact, a decrease of P could be "read" as a contraction. Also in the EHEA models this ad hoc assumption has been maintained. Useful as it may be,

this P-CF relationship has entirely lacked a physiological or physical foundation. In order to get a more "clean" physical formulation one can reason that a contractile force is equivalent to a work term. The pressure-volume changes in the MO can represent external work according to the wellknown formula: Work = (Pressure)·(volume change). The variables P and dM/dt are available as instantaneous quantities in the MO mathematics. Adding a further assumption from muscle physiology that the CF = (passive tension) + (active state),one can derive the following formalism

$$CF = \text{passive tension } (T) + T \cdot (dM/dt)$$

This expression has been used in the diagrams of this paper and has superseded a more empirical equation in (15,17). The "tension" T is still used instead of P. The difference between the two versions is not very large, nor does the introduction of a "surface expansion work" (Laplace) change much.

METHODS

The mathematic equations are basically the same as given in the Appendix of (14) and supplemented by an expression for visco-elasticity:$(dT/dt) = K(f'(t) - zT)$ where T = tension,z = a "resilience" coefficient,t = time and f' (t) = the time derivative of the length displacement (step,ramp or sinusoidal in shape), K=a given non-linear function f(T),cf (15,17).A new independant expression for contractile force has been referred to above.- The solution of the equations was performed on a Hewlett-Packard 9810 digital computer with the aid of a Runge-Kutta-Gill program for simultaneous differential equations. The numerical assignments of the main variables were sligthly modified from those given in (14).

SOME TYPICAL RESULTS OF THE EHEA-MODEL

Only a few simulation examples should be presented here, obtained from a larger material.

Fig.1. The effect of stretch on a muscle spindle. (From Shephard & Ottoson). In this case the object was to study the effect of two ramp displacements on the action potential pattern. The rapid ramp caused a "firing pause",but in both cases marked frequency changes occurred ("FRQ"). The S & O results (dark insets) have a correspondence in the "AP" patterns. One should note that the FRQ curve (the crosses) run in parallel with the lower envelope of the volume change records ("M"), the volume changes determine the "frequency modulation".

The relationship between the volume change envelope and the (instantaneous) frequency FRQ is approximately linear in the firing ranges.This "law" is also evident in the Fig.2a and Fig.3.

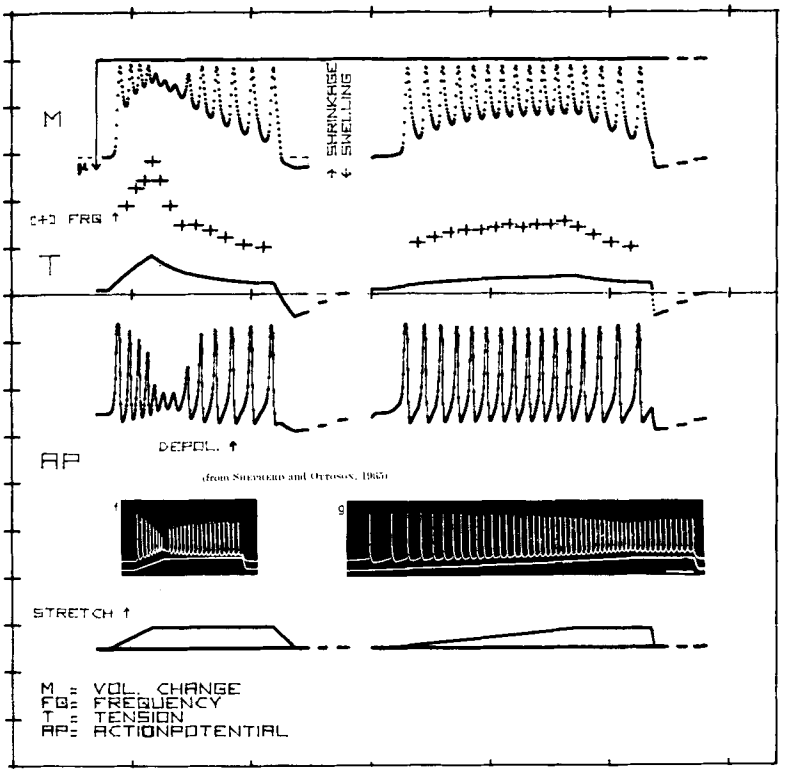


Fig.1.— Stretch effects on the EHEA and a pressoreceptor. (Insets are reproduced from Fig. 9 in (3), with permission)

Fig 2a and 2b. The effect of stretch on an isolated heart strip (Helix pomatia). — In Almqvist's experiment (original record to the right) only the twitches were recorded as response to an almost square shaped length displacement (stretch). The EHEA result is the "CF" graph which simulates remarkably well the Helix result. Noticeable in both cases are the transient inhibition zones (this is also reflected in the theoretical AP pattern). Interesting pictures on heart strips,also with AP,can be found in ref. 15 and 17.

Fig 3. The effect of hypertonic solutions on smooth muscle(rat portal vein) — In a series of experiments Johansson & Jonsson found that osmotic changes in the bathing medium caused variations in contraction heights and frequency which they ascribed to "volume changes". Their picture of the effect of 50 mmol/l sucrose (in the inset of Fig 3) can best be interpreted as an initial "expan-

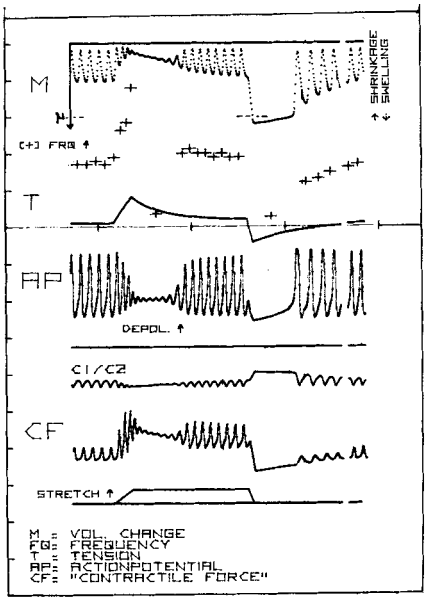
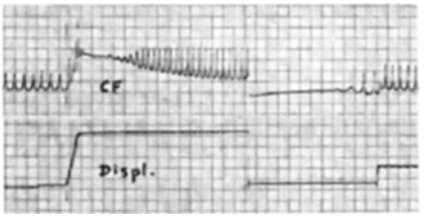


Fig 2a.— Strecth effect on the EHEA.

Fig 2b.— Stretch effect on a Helix heart.



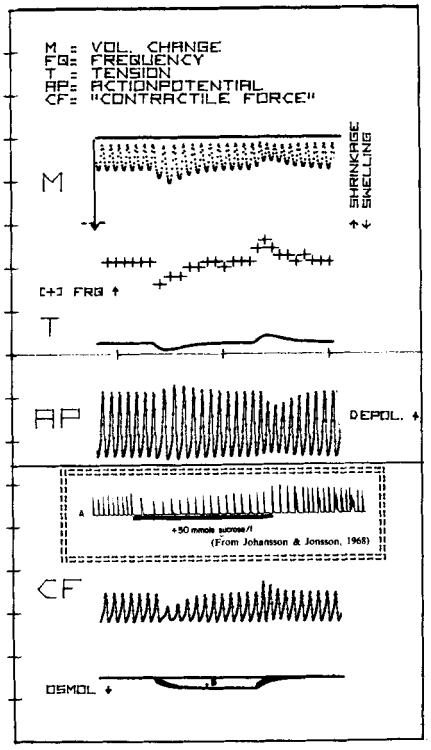


Fig 3. — Osmolarity effects on EHEA, and a smooth muscle.

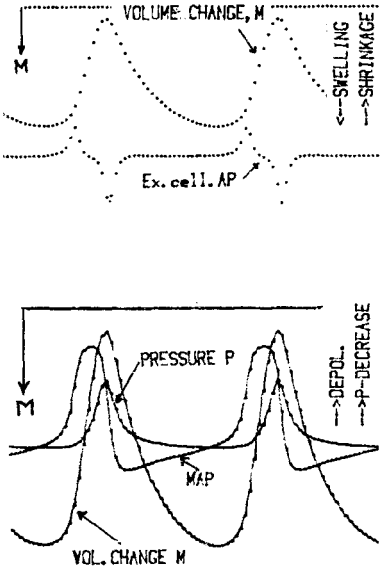


Fig 4. — Theoretical relations: AP (=MAP), volume, pressure, Ex.cell AP (=d(MAP)/dt).

sion" effect of the involved excitable cell groups rather than as a compression. The simulation used a slow "negative" going displacement ramp.This might be an indication of a "two"-compartment system as discussed earlier in this paper.The immediate effect of the sucrose is to suck out water from the extracellular space, which in turn permits the excitable cell to expand. The wash out effect will be the reverse and corresponds to a cell compression (note the increased frequency and diminished volume M).

DISCUSSION

The object of this paper has been to investigate how a theoretical model implying "fixed charges" in cell membranes can simulate selected physiological observations on a presso-receptor,smooth muscle and the heart. The results commented on above show a good agreement between observation and theory. The inferences are

1/ that bilateral water movements are involved in basic excitability phenomena (action potential,conductance change and frequency modulation),

2/ that effects of electrical as well as of mechanical stimulation (stretch and osmotic interventions) can be understood as affecting the water shifts in the excitable cell or tissues (here "viscoelasticity" is of importance),

3/ that the frequency modulation, i.e. the response frequency of action potentials and/or contractions, is a consequence of volume changes,

4/ that the response pattern of potentials and/or contractions of any kind of external stimulus is dependant on both the magnitude and the rate of change of the stimulus. Under certain conditions marked inhibitory events can occur, for example "firing pause" and "overstretch" effect.

The inferences given above are, of course, tentative and supported only by indirect evidence, using the two common excitability "indicators",action potentials and/or contractions. A more direct "proof" must await experiments where actual volume or pressure changes can be recorded. Hardly any such attempts have been made as yet. Fig 4 depicts an enlarged section of the heart experiment (Fig2a). This shows the theoretically expected time relations between the AP, its time derivative (= external AP record), the volume change M and the pressure term P: There is swelling and shrinkage concomittant with the AP. Dr I Tasaki reports elsewhere in this volume,for the first time, experimental data on simultaneous measurements of volume and pressure changes on spontaneously firing, isolated squid axons.

Concluding remarks. — Although the "fixed charge" models of exitability presented in this paper give a satisfactory formalism for real physiological observations they do all rest on the assumption of an electric "current source", in, or at the membrane. This current source may represent a chemical-electric

conversion, ultimately derived from unknown metabolic processes (a "fuel cell" device). This concept of a "current pump" and the conventional ideas of "ion pumps" belong perhaps to the same realm.

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REFERENCES

1. Almqvist,M.: Mechano-electrical transduction in isolated myocardium of Helix pomatia. Acta Univ Upsal (abstr of Uppsala dissertation,Faculty of Medicine,nr 161,Uppsala 1973).

2. Johansson,B. & Jonsson,O.: Cell volume as a factor influencing electrical and mechanical activity of vascular smooth muscle. Acta Physiol Scand.72: 456-468,1968.

3. Ottoson,D. & Shepard,G.M.: Transducer properties and integrative mechanisms in the frog´s muscle spindle. In "Handbook of sensory physiology,vol.1. Principles of receptor physiology", 442-499, Springer Co.,Berlin,N.Y.1971.

4. Sollner,K.:The early developments of the electrochemistry of polymer membranes. In "Charged gels and membranes,Part I": 3-53,E.Sélégny (edit), Reidel Publ Co, 1976,Dordrecht-Holland, 1976.

5. Tasaki,I.: "Nerve excitation",Charles C Thomas Publ, Springfield, Ill.,USA, 1968.

6. Teorell,T.: A contribution to the knowledge of rhythmical transport processes of water and salts. Exp Cell Res. Suppl 3:339-345,1955.

7. Teorell,T.: Rectification in a plant cell (Nitella). Z physik Chem NF 15: 385-398,1958.

8. Teorell,T.: Electrokinetic membrane processes in relation to properties of excitable tissues. I.J Gen Physiol 42: 831-845,1959.

9. Teorell,T.: Electrokinetic membrane processes in relation to properties of excitable tissues. II. J Gen Physiol 42:847-863,1959.

10. Teorell,T.: Oscillatory electrophoresis in ion exchange membranes. Ark Kemi (Roy Ac Sci,Stockholm) 22: 401-408,1961.

11. Teorell,T.: Excitability phenomena in artificial membranes.Biophys J,2 (No 2, part 2,Suppl): 27-32,1962.

12. Teorell,T.: Some biophysical considerations on presso-receptors. Arch int pharmacodyn 40: 563-576,1962.

13. Teorell,T.: Electrokinetic considerations of mechano-electrical transduction. New York Acad Sci 137,2: 950-966,1966.

14. Teorell,T.: A biophysical analysis of mechano-electrical transduction. In "Handbook of sensory physiology,Vol.1. Principles of receptor physiology", 291-339,Springer Co.,Berlin,N.Y.,1971.

15. Teorell,T.: A biophysical formalism of the electro-mechanical events of the heart. In "Actualités neurophysiologiques",170-185,A.Monnier (edit),Masson et Cie, Paris,1974.

16. Teorell,T.: Elektrische Kräfte an Zellmembranen.Klin Wschr 53:985-996,1975.

17. Teorell,T.: Non-linear transport and oscillations in fixed charge membranes: Some possible biological implications.In "Charged gels and membranes,Part II",205-211,E. Sélégny (edit),Reidel Publ. Co, Dordrecht-Holland,1976.

18. Teorell,T.: The development of the modern membrane concepts and the relations to biological phenomena. In "Charged Gels and Membranes,Part I", 57-69,E.Sélégny (edit), Reidel Publ. Co, Dordrecht-Holland, 1976.

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