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# Ionic Pulses along Cytoskeletal Protofilaments

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**Abstract.** The experimental evidences regarding ionic waves generation and propagation along both microtubules ( $MT_s$ ) and actin filaments ( $AF_s$ ) motivated us to develop the physical models that provide the framework for the explanation and analysis of these interesting biophysical phenomena.

In pertaining analysis we partly relied on some experimental as well as numerical data, but also on theoretical estimations enabling us to establish the concept of nonlinear transmission lines which could lead to reasonable clearing up of experimental facts.

We are convinced that these ionic currents actually exist and serve to sustain some important biological cellular mechanisms.

## 1. Introduction

The cytoskeleton is basic ingredient of all living cells. It is composed of three major types of filamental structures, including tubulin-protein based  $MT_s$ , actin-protein based  $AF_s$  and intermediate filaments. All of them are organized into networks which are interconnected through different auxiliary proteins [1].

There are at least three well-studied mechanical functions of the cytoskeleton in vivo; providing mechanical strength of the cell, segregating the chromosomes in cell division and active participation in the transport of macromolecules via motor proteins, primarily kinesin, dynein and myosin [2,3,4].

Here we pay the particular attention on the roles of  $MT_s$  and  $AF_s$  in facilitating intra cellular ionic currents which participate in some fundamental biological processes.

First experimental evidences for ionic waves propagating along  $AF_s$  are found out by the group led by H Cantiello [5,6]. These assays had clearly shown that the input ionic signals are being localized and propagate along  $AF_s$  in the forms resembling solitonic pulses. The theoretical explanations of these features were done by J Tuszynski et al [7] and later by M Satarić et al [8].

On the other hand, the experiment of measurement of ionic current along a single  $MT$  was performed within the same group [9]. Theoretical considerations of ionic currents along  $MT_s$  were performed by J Tuszynski et al [10] and in many stages by M Satarić et al [11,12,13,14].

In the following we will first present the outlines of polyelectrolytic concept of cytoskeleton and then briefly consider the main results concerning localized ionic pulses along  $AF_s$  and  $MT_s$ .

## 2. Manning-Oosava counterion condensation

Manning showed [15] that a highly charged cylinderlike polymers exert strong attraction on their counterions that a certain fraction condenses onto the polymer forming the so called ionic cloud (*IC*). Typical representative of this class of biopolymers is *DNA*. This condensation is triggered when the Manning parameter  $M = \frac{l_B}{l_0}$  is greater than unity. Here the Bjerrum length is defined as follows

$$l_B = \frac{e^2}{\varepsilon k_B T} \quad , \quad (1)$$

where  $e$  is the electron charge,  $\varepsilon$  is the dielectric constant of cytosol and  $k_B T$  is the thermal energy ( $k_B = 1,38 \times 10^{-23} J$ ).

Taking the physiological temperature  $T = 310K$  and  $\varepsilon = 80 \times 8,85 \times 10^{-12} F/m$ , we get

$$l_B = 0,67nm. \quad (2)$$

On the other hand,  $l_0$  follows from cylindrical polymer's linear charge density  $q_0$ :

$$q_0 = \frac{e}{l_0} = \frac{q}{L} \quad , \quad (3)$$

where  $L$  is the cylinder's total length and  $q$  its total surface charge.

This charge causes counterion condensation around polymer in the cases where the concentration of counterions ( $n$ ) is small enough that the inequality  $\xi_D \gg a$  holds ( $a$  is the radius of the cylinder).

Here the Debye length  $\xi_D$  is defined as follows

$$\xi_D = (8\pi n l_B)^{-1/2}. \quad (4)$$

Relying on the above conditions we found out that both  $AF_s$  and  $MT_s$  in physiological conditions could be safely considered as polyelectrolites of Manning's class.

We estimated, on the basis of Manning's theory [15], that the thickness of *IC* in physiological conditions is for  $AF$  and  $MT$  respectively

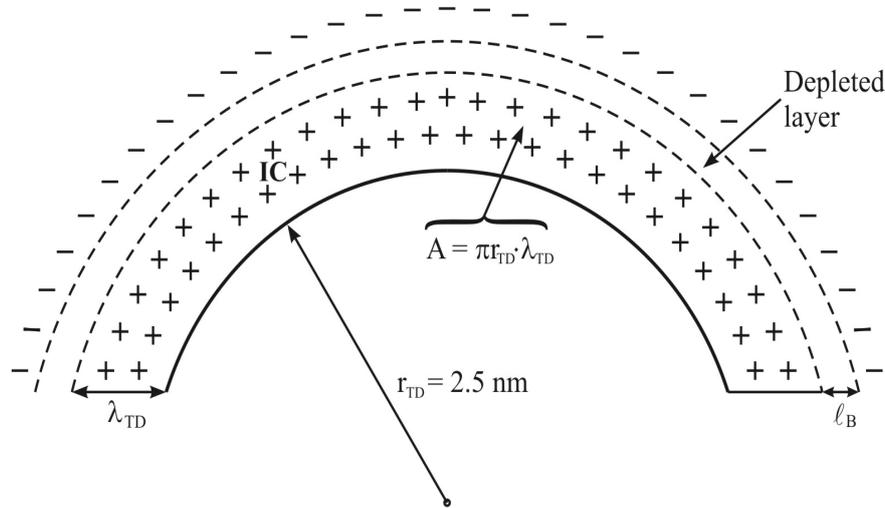
$$\lambda_{AF} = 5nm \quad \text{and} \quad \lambda_{TD} = 2,5nm.$$

On the basis of such concept we established the models where these cytoskeletal cylindrical polymers can be viewed as "coaxial cables" having the features of nonlinear transmission lines. These lines in general could be sequenced in ladders of repeated identical electric elementary units (*EEU*) which posses specific values of capacity, resistivity and conductivity. We estimated that corresponding inductivities of *EEU*<sub>s</sub> are small enough that can be safely ignored [12].

Between *IC* of condensed counterions around *EEU* and repelled rest of bulk ions there exists the depleted layer (with no ions present) with the thickness equal to  $l_B$ , Fig. 1. Thus we consider the *IC* around cylinder as one conductive plate and the depleted layer as the dielectric corroborating the validity of analogy with coaxial cable.

The important point of developed models is the presence of nonlinearity in this concept of "transmission lines".

In both cases, for  $AF_s$  and  $MT_s$ , the nonlinearity is attributed to capacitance of *EEU*<sub>s</sub>. For  $AF_s$  this nonlinearity originates from local pockets between actin proteins arranged helically, while in  $MT_s$  the main contribution arises from so called tubulin tails (*TT*<sub>s</sub>) which are very flexible. These *TT*<sub>s</sub> can shrink or stretch and oscillate, thus changing capacity of *IC* around *MT*.



**Figure 1.** Cytoskeletal cylindrical polymers viewed as "coaxial cables".

### 3. The case of $AF_s$

The detailed consideration of  $AF_s$  in the context of nonlinear transmission lines is presented in Ref [8].

The equation which describes the time-space voltage of ionic pulse reads ( $x$  is the orientation of  $AF$ )

$$l^2 \frac{\partial^2 V}{\partial x^2} - R_1 C_0 \frac{\partial V}{\partial t} + 2bR_1 C_0 V \frac{\partial V}{\partial t} = 0. \quad (5)$$

The length  $l = 5,4nm$  is the dimension of an  $EEU$ , ie. the diameter of one actin protein molecule;  $C_0$  is the leading constant term of  $EEU$  capacitance and  $R_1$  is its longitudinal resistance in direction of  $x$ -axis;  $b$  stands for the parameter of nonlinear term of  $EEU$ 's capacitance. The solution of Eq (5) reads [8]:

$$V(x, t) = W_1 [1 - \exp(\alpha\xi)] \cdot [1 - \frac{W_1}{W_2} \exp(\alpha\varsigma)]^{-1} \quad (6)$$

with following abbreviations

$$W_{1/2} = (2bV_0)^{-1} \left[ 1 \pm \left( 1 + 4 \frac{AbV_0}{v_0} \right)^{1/2} \right]$$

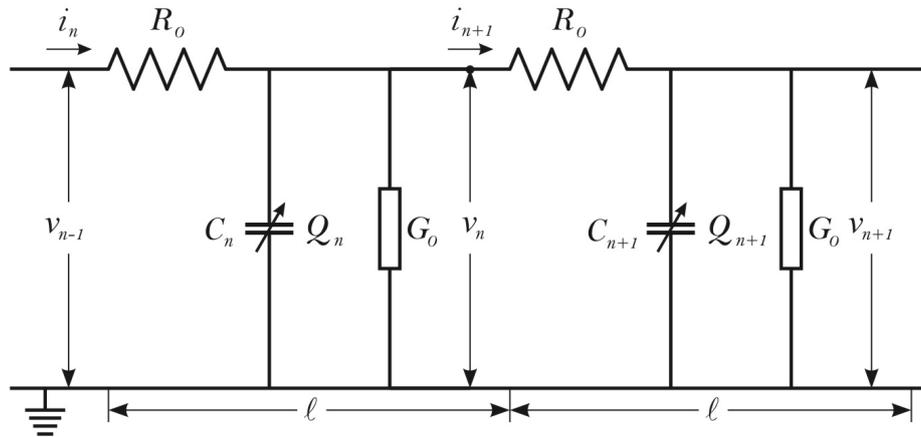
$$\alpha = (W_1 - W_2)bV_0v_0; \quad \varsigma = \left( \frac{x}{l} - v_0 \frac{t}{R_1 C_0} \right). \quad (7)$$

The characteristic wave velocity is

$$v_0 = \frac{l}{R_1 C_0} = \frac{5,4 \times 10^{-9}}{2 \times 10^8 \times 2 \times 10^{-16}} \left( \frac{m}{s} \right) = 13 \frac{cm}{s}.$$

$V_0$  is the voltage amplitude defined by the influx of ions directed along  $AF$ ; At last,

$$A = \left( \frac{dW}{d\xi} \right)_{W=0} < 0.$$



**Figure 2.** An effective circuit diagram for the  $n$ -th  $EEU$  with characteristic elements involved in Kirchoff's laws.

The solution Eq (6) is a typical anti-kink wave propagating with the velocity of the order of ( $cm/s$ ), which has very reasonable order of magnitude.

#### 4. The case of $MT_s$

Microtubules are hollow cylinders of 13 parallel protofilaments consisting of  $\alpha - \beta$  tubulin heterodimers [1].

The experimental evidences regarding ionic currents along  $MT_s$  revealed that  $MT_s$  exhibit some kind of amplifying roles which resemble the "biotransistors" [9].

Our theoretical modeling of these currents was developed in three stages [11,12,13,14].

The first stage [11,12] is similar to that one applied for  $AF_s$  [8] in the way that the roles of nano-pores ( $NP_s$ ) existing between protofilaments of  $MT$  were ignored.

Second version [13] is more complete, where the roles of  $NP_s$  are modeled in the context of an approach developed by Siwy et al [16]. This model involves the nonlinear negative incremental resistance of  $NP_s$  in parallel with nonlinear capacitance of  $EEU_s$  caused by mentioned property of  $TT_s$ . The important point of this stage is that the ohmic loss of transmission line should be balanced by the fresh ions injected into  $IC$  from  $NP_s$  since these act as ionic pumps in suitable voltage regime along  $MT$ . As the result, the solution of Kirchoff's equations of nonlinear circuit is the stable bell-shaped soliton voltage pulse which propagates along  $MT$  with the velocity of the order of  $mm/s$ .

Recently the more advanced version of the same concept was presented [14] in which the  $NP_s$  are treated according to within the numerical simulations performed the group led by Tuszynski [17].

We established simple periodic ladder network composed of the lumped sections equal to identical  $EEU_s$  (every tubulin dimer of one protofilament is an  $EEU$ ) as represented in Fig.2

According to Kirchoff's laws from Fig.2 we have

$$\begin{aligned} i_n - i_{n+1} &= \frac{\partial Q_n}{\partial t} + G_0 v_n, \\ v_{n-1} - v_n &= R_0 i_n, \end{aligned} \quad (8)$$

where  $Q_n$  represents the charge of  $EEU$  capacitor as nonlinear function of voltage  $v$ ;

$$Q_n = C_0[1 - \Gamma_0\Omega(t - t_0) - b_0v]v \quad (9)$$

which is deeply elaborated in Ref (14).

Introducing the characteristic impedance  $Z$  of an  $EEU$  corresponding to characteristic frequency  $\omega$

$$Z = \frac{1}{\omega C_0}, \quad (10)$$

and the function  $u(x, t)$  unifying the voltage and ionic current along a  $MT$

$$u_n = Z^{1/2}i_n = Z^{-1/2}v_n, \quad (11)$$

and going over to the continuum approximation with respect to space variable  $x$ , we get from Eqs (8), in terms of Eqs (9,10),

$$\begin{aligned} \frac{\partial^3 u}{\partial \xi^3} + 3 \left( \frac{ZC_0s}{T_0} - 2 \right) \frac{\partial u}{\partial \tau} + 3ZC_0\Gamma_0\Omega(\xi - \xi_0) \frac{\partial u}{\partial \xi} + 6 \frac{Z^{3/2}b_0C_0s}{T_0} \left( u \frac{\partial u}{\partial \xi} \right) \\ + 3(ZG_0 + Z^{-1}R - ZC_0\Gamma_0\Omega)u = 0. \end{aligned} \quad (12)$$

Here the characteristic charging (discharging) time of an  $EEU$  capacitor  $C_0$  through the resistance  $R_0$  is  $T_0 = R_0C_0 = 6, 2 \times 10^7 \Omega \times 1, 92 \times 10^{-16} F = 1, 2 \times 10^{-8} s$ .

The dimensionless space and time variables are

$$\xi = \frac{x}{l} - \tau; \quad \tau = s \frac{t}{t_0}; \quad s = \frac{v}{v_0}.$$

The characteristic speed is  $v_0 = \frac{l}{T_0} = \frac{8 \times 10^{-9} m}{1, 2 \times 10^{-8} s} = 0, 67 \frac{m}{s}$ ;  $l = 8 \times 10^{-9} m$  is the length of one tubulin dimer ( $EEU$ ).

$G_0$  is the conductance of a  $NP$  and  $\Omega$  the frequency of thermal oscillations of a  $TT$ ;  $b_0$  is the parameter of nonlinear capacity of a  $TT$ .

After a tedious procedure the solution of Eq (11) reads

$$u(\xi, \tau) = \frac{u_0 \exp(-2\gamma_0\tau)}{\cos h^2 \left\{ \left[ \frac{\alpha u_0}{4\beta} \exp(-2\gamma_0\tau) \right]^{1/2} \left[ \xi - \xi_0(1 - \exp(\gamma_0\tau)) + \frac{\alpha u_0}{3\beta} (1 - \exp(3\gamma_0\tau)) \exp(-2\gamma_0\tau) \right] \right\}}, \quad (13)$$

where the abbreviations have the values

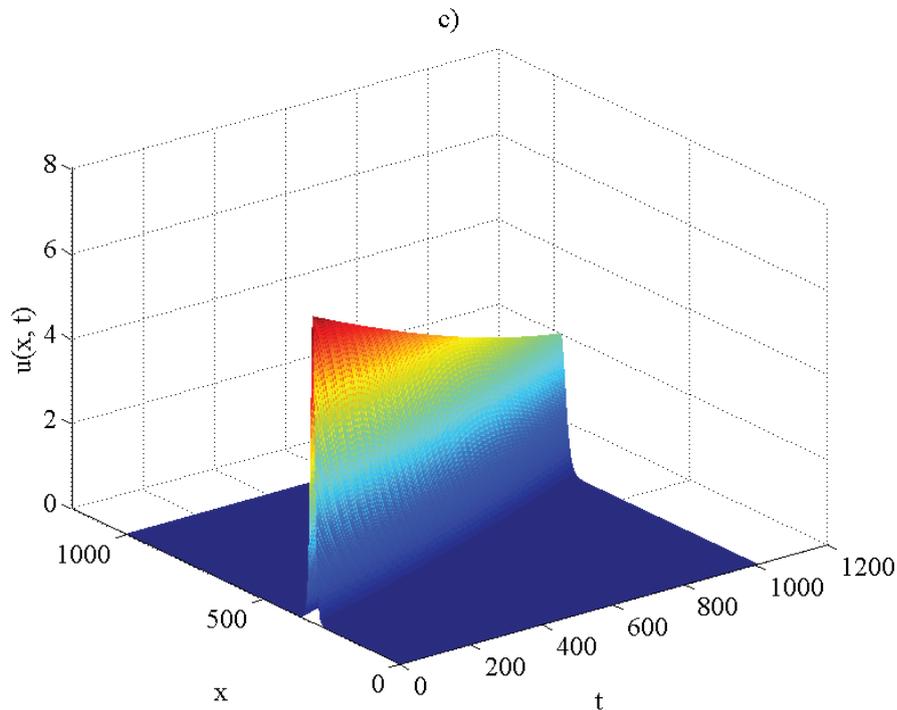
$$\begin{aligned} \alpha &= \frac{2Z^{3/2}b_0C_0s}{T_0 \left( \frac{ZC_0s}{T_0} - 2 \right)}; & \beta &= \left[ 3 \left( \frac{ZC_0s}{T_0} - 2 \right) \right]^{-1} \\ \gamma_0 &= ZC_0\Gamma_0\Omega \left( \frac{ZC_0s}{T_0} - 2 \right)^{-1}. \end{aligned} \quad (14)$$

$u_0$  is the amplitude defined by the initial conditions.

We here mention one of possible numerical solutions of Eq (11) for the specific set of parameters, Fig. 3

$$\alpha = 0, 5; \quad \beta = 0, 1; \quad \gamma_0 = 0, 1; \quad \xi_0 = 0, 1.$$

It is apparent that localized pulse-like wave propagates with slightly decreasing amplitude along distances of hundreds  $EEU_s$  with constant velocity.



**Figure 3.** One of possible numerical solutions of Eq (11).

This velocity can be estimated from Fig. 3 as follows:

$$\begin{aligned} \Delta x &= 400l = 400 \times 8nm = 3,2\mu m \\ \Delta t &= 1000T_0 = 10^3 \times 1,2 \times 10^{-8}s = 1,2 \times 10^{-5}s \\ v &= \frac{\Delta x}{\Delta t} = 0,26 \frac{m}{s}. \end{aligned} \quad (15)$$

The range of this soliton is  $3,2\mu m$  which is of the order of cell's diameter.

## 5. Discussion and conclusion

In this paper we briefly reviewed the recent contributions regarding the role of cytoskeletal filaments ( $AF_s$  and  $MT_s$ ) in ionic propagation within the living cells.

The general feature of all mechanisms is the concept of nonlinear transmission lines. The origin of nonlinear effects is mostly attributed to capacitance of these filaments. The coaxial cable-like geometry of transmission lines relies on their polyelectrolite properties in accordance with Manning's theory.

The order of magnitude of soliton like localized pulses arising within the scope of our theory ranges from  $mm/s$  to a several  $cm/s$  which are very reasonable values.

## Acknowledgements

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