# AN IMPROVED NANOSCALE TRANSMISSION LINE MODEL OF MICROTUBULE: THE EFFECT OF NONLINEARITY ON THE PROPAGATION OF ELECTRICAL SIGNALS

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**Abstract**. *In what manner the microtubules, cytoskeletal nanotubes, handle and process electrical signals is still uncompleted puzzle. These bio–macromolecules have highly charged surfaces that enable them to conduct electric signals. In the context of electrodynamic properties of microtubule, the paper proposes an improved electrical model for divalent ions (Ca$^{2+}$ and Mg$^{2+}$) based on the cylindrical structure of microtubule with nano–pores in its wall. Relying on our earlier ideas, we represent this protein–based nanotube with the surrounding ions as biomolecular nonlinear transmission line with corresponding nanoscale electric elements in it. One of the key aspects is the nonlinearity of associated capacitance due to the effect of shrinking/stretching and oscillation of C– terminal tails. Accordingly, a characteristic voltage equation of electrical model of microtubule and influence of capacitance nonlinearity on the propagation of electrical pulses are numerically analyzed here.*

**Key words**: *microtubule, electrodynamic properties, nonlinear transmission line, voltage equation, soliton wave*

## 1. INTRODUCTION

Biological systems at the nanoscale are rich in electrical activity. Besides the well–known pathways of biochemical regulation, there exist additional pathways of biological communication governed by electrical signals [1]. Recently, *in silico* demonstration has shown that the microtubules (MTs), essential cellular biopolymers, are the source of electromagnetic fields in the form of the electric pulses, playing an important role in the intracellular signaling and information processing [2]. MTs are self–assembling protein mesostructures made up of electrically polar tubulin heterodimer subunits, α– and β–tubulin monomers. Each dimer, 8 nm in length, possesses two highly flexible C–terminal tail regions, by one of each monomer, which can extend up to 4.5 nm from the surface, see Fig. 1a. *In vivo* MT is generally made up of 13 parallel, loosely connected chains, or

protofilaments, formed by polymerization of the tubulin heterodimer molecules so as to result in a helical structure. Cryo–electron microscopic analyses indicate that the single MT resembles a hollow tube with its external and internal diameters of 25 nm and 15nm, respectively, see Fig. 1b, while its length typically varies in the range of few tens of nanometers to several micrometers. Due to the shape and spacing of the tubulin heterodimers, the MT possesses small, nanometer size pores between the outer environment and the inner MT's lumen. Two different types of these nano–pores exist within MT's wall.
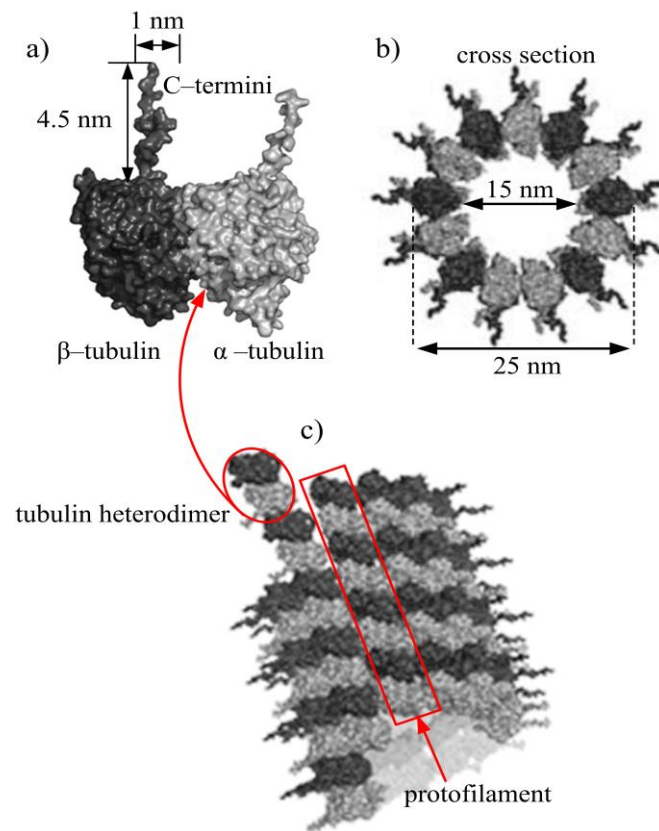


**Fig. 1** a) The topology of tubulin heterodimer with dimensions of the C– terminal tail regions b) Cross–sectional view of microtubule c) Microtubule tube–like structure with marked protofilament

MT functionalization plays a critical role in making the jump from *in vivo* intracellular transport to *in vitro* nanoscale device applications [3]. The potential of this protein structure for application in novel bio–inspired nanoelectronic components was recently demonstrated [4]. In addition, the process of formation of MTs by polymerization of αβ– tubulin heterodimers, which can be controlled by physical (temperature) and chemical (pH, concentration of protein and ions), can result to the production of closely or widely spaced MTs, centers, sheets, rings and other structures [5], thus facilitating fabrication of

nanowires, nodes and networks in the future for bionanotechnological applications. Interestingly, MTs are self–assembling protein–based nanotubes with mechanical behavior similar to carbon nanotubes despite their very different chemical composition: proteins and non–covalent interactions in the case of MTs; carbon and covalent bonds in the case of carbon nanotubes [6].

In view of the key role of MTs in intracellular electrodynamic signaling and information processing, the objective of this study is to provide a framework for the analysis of propagation of electric pulses along this biological transmission line. More specifically, for this purpose we improve our previous electrical model [7] based on polyelectrolyte concept applied to the molecular structure and geometry of these nanotubes. The initial motivation for the model of MT as electrical transmission line was the experimental evidence [8], which revealed that these biopolymers are good conductors of electrical signals at nano–level. Here, we will focus on the specific importance of this mechanism for intracellular transportation of divalent ions, in the first place $Ca^{2+}$ and $Mg^{2+}$ as the most important ions in human body. The particular attention will be paid to the role of nonlinearity parameter that arises from structure and dynamics of C– terminal tails.

## 2. ELECTRODYNAMIC PROPERTIES AND CHARACTERIZATION OF MT

The conductance of MTs is the result of their electrostatic and structural properties. On the basis of detailed molecular dynamics computations, it was recently demonstrated that the outer surface of tubulin heterodimer is mostly electrostatically negative charged, whereby a specifically large negative charge is located on the C–terminal tail regions [9]. As a result, overall surface of MT is predominantly negative charged, as one can see from Fig. 2, while the ends of this nanotube possess a different amount of net charge. Accordingly, it can be readily concluded that the MT supports an intrinsic electric field [5]. The average linear charge density of single MT is estimated to be 52.2 electronic charges ($e$) per dimer or approximately 85 $e$/nm [10]. Also, recent experimental observation was showed that the MT conductivity in a solution is on the order of 10 nS [8], indicating a high level of ionic conductivity along this biopolymer.
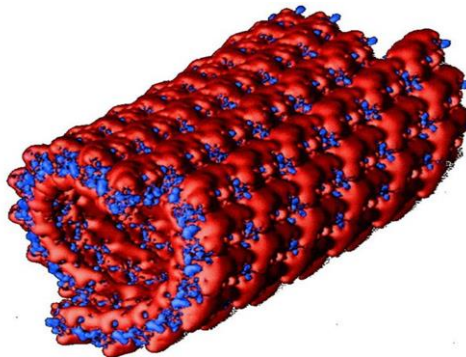


**Fig. 2** Charge distribution on the surface of microtubule (color red indicates negative charges, blue positive charges and white neutral regions) [9]

In the context of the above–mentioned findings, it is possible to consider MT like one–dimensional polymer that behaves as highly charged polyelectrolyte [7, 10]. In a solution, positive ions are attracted to the negative charged surface of the MT, while negative ions are repelled, creating a positive condensed ionic cloud (CIC) localized around the MT's landscape. In the presence of an applied voltage, the loosely held CIC is free to migrate along MT, creating an ionic flow and an associated electrical current [11]. In accordance with Manning's condensation theory of polyelectrolytes [12], negative ions in solution are repelled at the distance called the Bjerrum length ($l_B$), which is defined by the balance between electrostatic attraction energy of the ions and the pertaining thermal energy:

$$l_B = \frac{ze^2}{4\pi\,\varepsilon_r\varepsilon_0 k_B T}. \tag{1}$$

The particular emphasis is paid on the divalent ions ($z = 2$) such as $Ca^{2+}$ and $Mg^{2+}$, which are primary attracted by the MT's surface. Their flows around MTs play fundamental roles in auditory processes as well as in the cardiac muscles action. For these important ions in human body, the width of such "depleted layer" sandwiched between two charged regions is $l_B = 1.34$ nm at physiological temperature $T = 310$ K. Other parameters used in the estimation of Bjerrum length are the elementary electric charge $e = 1.6\times10^{-19}$ C, the dielectric constant of cytosol $\varepsilon_r = 80$, the permittivity of vacuum $\varepsilon_0 = 8.85\times10^{-12}$ F/m and Boltzmann's constant $k_B = 1.38\times10^{-23}$ J/K.

Based on Manning's approach, the thickness of CIC $\lambda$ around the rod–like filamentous polyon of radius $r$ is given by the following expression:

$$\lambda = \mathcal{A}(rl_{Db})^{1/2}; \quad \mathcal{A} < 1, \quad l_{Db}^{-1} = (8\pi\,nl_B)^{1/2}. \tag{2}$$
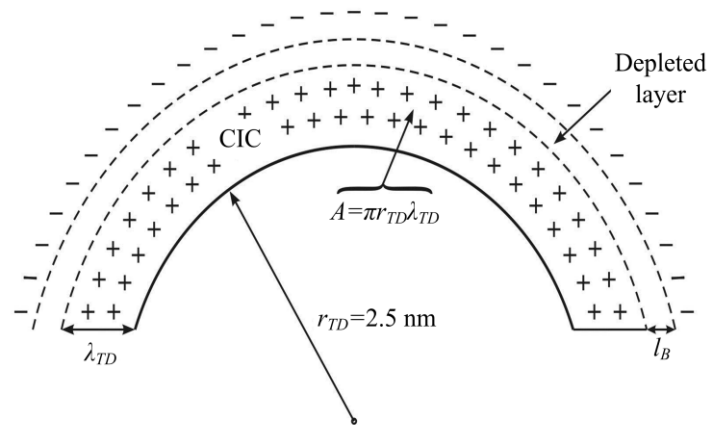


**Fig. 3** Schematic illustration of a tubulin dimer with its condensed ionic cloud (CIC), depleted layer and the geometry of "coaxial cable" with the dimensions. $A$ is the cross section area of a CIC around tubulin dimer.

Using the above equation, the corresponding values for tubulin heterodimer (TD) and C– terminal tails (CT) are $\lambda_{TD}$ = 2.96 nm and $\lambda_{CT}$ = 0.92 nm, respectively, for equilibrium ionic concentration $n$ = 1.5×10$^{23}$ m$^{-3}$ and parameter $\mathcal{A}$ = 0.5. The estimated depleted layer between CIC and repelled negative ions (anions) plays the role of a dielectric medium between charged plates in "coaxial cable", see Fig. 3. It provides resistive and capacitive components for the behavior of the tubulin heterodimer that make up the MT.

## 2.1. Electrical parameters of the MT model

Bearing in mind the CIC around the MT's cylinder, this protein–based nanotube may act as biological "electrical wire" which can be modeled as nonlinear transmission line [7, 11]. In this section, we describe the nature and estimate the value of electrical components at nanoscale that make up transmission line model that mimics the behavior of MT in solution. Due to symmetry of this biopolymer, it is plausible to consider just one of thirteen MT's protofilaments and to introduce the so called elementary electric unit, which is a single tubulin dimer with its two C–terminal tails and two different types of nano– pores in MT's wall.

In order to estimate the total static capacitance of elementary electric unit for the case of divalent ions, we firstly consider the contribution of a tubulin heterodimer as half– cylindrical capacitor which has the value

$$C_{TD} = \frac{\pi \varepsilon_r \varepsilon_0 l}{\ln\left(1 + \dfrac{l_B}{R}\right)} = 0.75 \times 10^{-16} \text{ F.} \tag{3}$$

Here $l$ = 8 nm is the length of tubulin dimer, and the parameter $R = r_{TD} + \lambda_{TD}$ = 5.46 nm represents the outer radius of respective CIC, see Fig. 3, while the other parameters are already mentioned and used. In a similar way, viewing an extended C–terminal tail as a smaller cylinder with $r = r_{CT} + \lambda_{CT}$ = 1.42 nm, one obtains its capacitance as follows

$$C_{CT} = \frac{2\pi \varepsilon_r \varepsilon_0 l^{eff}}{\ln\left(1 + \dfrac{l_B}{r}\right)} = 0.14 \times 10^{-16} \text{ F,} \tag{4}$$

where $l^{eff} = l_{CT} - \lambda_{TD}$ = 1.54 nm is the corresponding effective length of the part of C– terminal not plunged in $\lambda_{TD}$. Since each tubulin heterodimer has two C–terminal tails, and keeping in mind that the capacitances of tubulin dimer and C–terminal tails are in parallel arrangement [13], it implies that total maximal static capacitance of the elementary electric unit is readily estimated as the simple sum of above determined components:

$$C_0 = C_{TD} + 2 \times C_{CT} = 1.03 \times 10^{-16} \text{ F.} \tag{5}$$

It is evident that the capacitance in our model represents the charge distribution in the region from CIC to approximately one $l_B$ away perpendicularly to the surface of the MT. Since the ions in this layer are assumed to be condensed, the charge of this capacitor will vary in a nonlinear way with voltage as follows:

$$Q_n = C_0[1 - \Gamma\Omega(t - t_0) - bv_n]v_n \ .$$  (6)

The non–stationary term $\Gamma\Omega(t–t_0)$ reflects the fact that the presence of extra ions injected within the ionic cloud affects the local concentration during the time compared with the characteristic charging time of localized C–terminal's capacitor. The nonlinear parameter $b$ represents the change of capacitance of elementary electric unit with an increasing concentration of condensed cations due to the flexibility of the C–terminal tails (their shrinking/stretching). This expression (6) was derived and explained in detail in the previous version of electrical model of MT [7].

In order to estimate the conductance of nano–pores, we rely on the detailed atomic–scale *in silico* calculations using 3D Brownian dynamics [14]. In accordance with these numerical results, the conductance of both nano–pores is estimated to be $G = 10.7$ nS, which is determined as a sum of pretty different components reflecting difference in two types of nano–pores [7, 13]. Using the same numerical calculation, the resistance of the parallel flow of ions along elementary electric unit is $R = 6.2 \times 10^7$ Ω, neglecting the ionic current which leaks through the depleted layer. Finally, in the earlier simplified version of the electrical model of MT [11], we found that corresponding inductance of elementary electric unit is small enough that its role can be safely ignored in this improved model.

## 3. ELECTRICAL MODEL OF MT AS BIOMOLECULAR NONLINEAR TRANSMISSION LINE

On the basis of above estimations for the components of elementary electric unit of the MT, we are now in the position to establish the corresponding electrical model. Electric circuit that simulates single MT's protofilament is presented in Fig. 4.
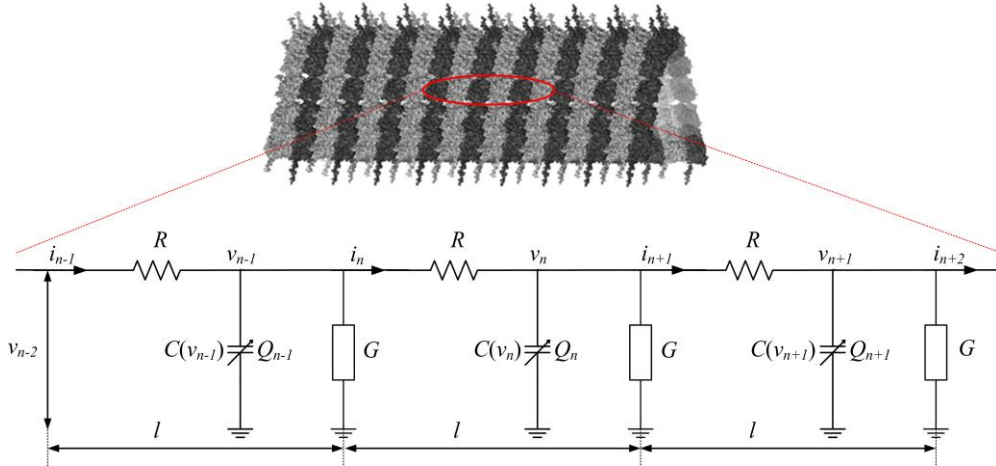


**Fig. 4** A scheme describing the corresponding electrical model of MT

In order to derive the characteristic voltage equation of model, we begin by introducing the discrete potential in one section of the MT where Kirchhoff's laws for the currents and voltages read as follows

$$i_n - i_{n+1} = \frac{\partial Q_n}{\partial t} + Gv_n, \qquad v_{n-1} - v_n = Ri_n.$$ (7)

We then introduce new function $u_n(x, t)$ unifying voltage and its accompanying current along a MT as follows

$$u_n(x,t) = Z^{1/2}i_n = Z^{-1/2}v_n,$$ (8)

where $Z$ is characteristic impedance of the elementary electric unit corresponding to characteristic frequency $\omega = 2\pi/(RC_0)$

$$Z = R + \left(\frac{G^{-1}}{C_0^2\omega^2 G^{-2} + 1}\right)\left(1 + \frac{C_0^2\omega^2}{G^2}\right)^{1/2}.$$ (9)

This expression for $Z$ is much more accurate compared to the previous that was used in [7]. Assuming that a large number of tubulin heterodimer along the protofilament of MT, the next step is to go over to the continuum approximation with respect to space variable $x$ and as a result we get the following voltage equation of established model of MT

$$\frac{\partial^3 u}{\partial \xi^3} + 3\left(\frac{ZC_0 s}{T} - 2\right)\frac{\partial u}{\partial \tau} + 3ZC_0\Gamma\Omega(\xi - \xi_0)\frac{\partial u}{\partial \xi} + 6\frac{Z^{3/2}bC_0 s}{T}\left(u\frac{\partial u}{\partial \xi}\right) +$$ (10)
$$3(ZG + Z^{-1}R - ZC_0\Gamma\Omega)u = 0.$$

Here, the first term is dispersive one arising from diffusive spreading of ions within the pulse. The second one with negative sign ($ZC_0 s < 2$) resembles the corresponding time dependent term in Fick's diffusion law. Third term reflects the non–stationary change of capacity due to the ratchet mechanism. Fourth term represents nonlinearity that competes with dispersion. The key point here is that the last term accounts the competition between energy expenditure due to ohmic losses and energy supply by non–local ratchet mechanism. This term can be discarded as being very small due to the balance of above competition. In characteristic voltage equation (10), the characteristic charging (discharging) time of the elementary capacitor through the elementary resistance is given by $T = RC_0$, while the dimensionless variables of space $\xi$, time $\tau$ and velocity $s$ are defined as follows:

$$\xi = \frac{x}{l} - \tau, \quad \tau = s\frac{t}{T}, \quad s = \frac{v}{v_0}, \quad v_0 = \frac{l}{T},$$ (11)

where parameter $v_0 = l/T$ represents the characteristic cut–off velocity, and $l$ is the length of one tubulin heterodimer.

### 3.1. Numerical analysis of the voltage equation

Since one of the key aspects of electrical model of MT as transmission line is the nonlinearity of capacitance of elementary electric unit, the characteristic voltage equation and effect of capacitance nonlinearity on the propagation of ionic pulses along MT are numerically analyzed. Numerical simulations are based on a finite–difference time–domain method applied to the differential equation (10) governing the voltages of proposed nonlinear circuit [15]. A circuit simulator is implemented in *Matlab* software package.

In Fig. 6 is shown the numerical results of voltage equation $u(\xi, \tau)$ for estimated values of electric components of the established model and different values of capacitance nonlinearity.
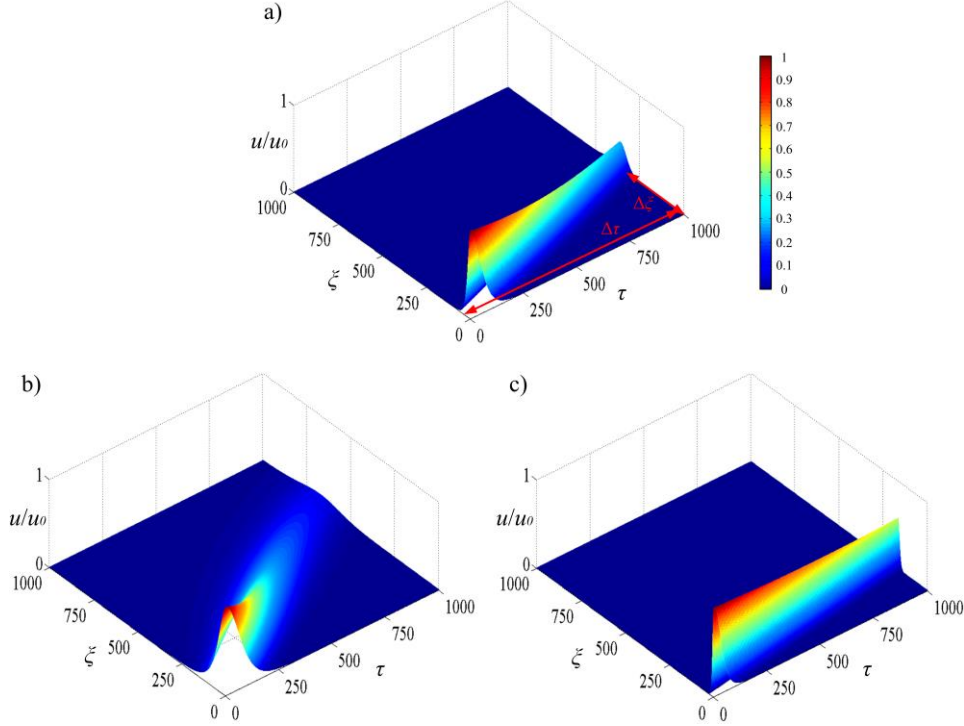


**Fig. 5** Numerical solution of the voltage equation $u(\xi, \tau)$ for the set of estimated electric components of the established model and a) capacitance nonlinearity of 0.05 V$^{-1}$, b) lower value of capacitance nonlinearity of 0.01 V$^{-1}$ and c) higher value of capacitance nonlinearity of 0.1 V$^{-1}$

For reasonable value of the nonlinearity parameter of 0.05 V$^{-1}$, the pulse appears in the form of soliton–like wave exhibiting the slowly decaying amplitude and an almost constant velocity of propagation. This wave possesses the energy losses due to ohmic resistance, but it preserves the stable localized form. Using the values of time and space units, the average velocity of localized voltage pulse can be estimated from the obtained graphic shown in Fig. 5a as follows:

$$\langle \text{v} \rangle = \frac{\Delta \xi}{\Delta \tau} = \frac{280l}{1000T_{\text{CT}}} \cong 3 \frac{\text{cm}}{\text{s}}, \tag{12}$$

where $l$ is length of elementary electric unit that is one tubulin heterodimer. The parameter $T_{\text{CT}}$ represents a swing period of C–terminal tail which is given by the following expression [10]

$$T_{CT} = 6\pi \frac{ZC_0}{ZG + Z^{-1}R} \cong 0.72 \times 10^{-7}\,\text{s}. \tag{13}$$

The obtained propagation velocity of voltage pulse is the order of several cm/s that is close to experimental findings [8] and it depends on the electrical papameters of established circuit model of MT. It is also possible to estimate that the pulse width is of the order of 10 elementary units. This fact supports the validity of continuum approximation. The range of this soliton–like localized pulse is about $280 \times l \approx 2.24\ \mu\text{m}$, which is of the order of cell's diameter.

In the case of lower value of nonlinearity parameter of 0.01 $V^{-1}$ presented in Fig. 9b, the amplitude of pulse decreases significantly faster so that over about 350 elementary units it becomes negligible. The graphic shows the deceleration of the soliton–like pulse along its path. For higher value of capacitance nonlinearity of 0.1 $V^{-1}$, the voltage pulse exhibits not only a higher localization, but also a slower decay of its amplitude and greater robustness compared to the previous two cases. Also, Fig. 5c indicates that the propagation velocity is lower than the average velocity of 3 cm/s for the case of nonlinearity parameter of 0.05 $V^{-1}$. Overall, the performed numerical analysis of the voltage equation demonstrates that the role of capacitance nonlinearity is of decisive importance for the stability and localized character of $Ca^{2+}$ and $Mg^{2+}$ pulses along MTs.

## 4. DISCUSSION AND CONCLUSION

In this paper, we have developed an improved electrical model of MT that provides qualitative framework for the observations of propagation of $Ca^{2+}$ and $Mg^{2+}$ signals along this charged polar biopolymer. In summary, the geometric symmetry of MT provided the opportunity that one MT's protofilament can be approximately seen as a "coaxial cable" with the "charged plates" composed of counterions of solution with a depleted layer of water molecules in between. It enabled that the series of tubulin heterodimers with pertaining C– terminal tails could be observed as series of identical elementary electric units with estimated capacitance and resistance, including the conductance of two different types of nano–pores existing in MT's wall. The background for the proposed model is the molecular structure of MT and its polyelectrolyte properties.

Numerical analysis of characteristic voltage equation of model showed that the nonlinearity of capacitance, arising from structure and dynamics of C– terminal tails, is essential important parameter for the character propagation of $Ca^{2+}$ and $Mg^{2+}$ signals along MT. For reasonable value of the nonlinearity parameter of 0.05 $V^{-1}$, numerical results indicated stable and localized soliton–like pulses which propagate with a velocity value close to experimental findings and cross the distance of cell's size despite ohmic dissipation. Velocities of these pulses are of the order of several cm/s, depending on the amount of the injected ions and valence of the ions. Under physiological conditions, this effect is much faster than the process of propagation of the ions by pure diffusion (a few $\mu$m/s). Interestingly, if we compare the estimated velocity with the drift velocity of electrons in a typical semiconductor, we get the same order of magnitude at current density of order of $A/mm^2$. However, the velocity of establishing a local field around the protein biopolymers is much lower due to heaviness of the ions, which are much more massive than electrons.

Finally, we believe that our predictions may have important consequences for understanding of MT's ability to conduct electrical signals, which may affect the neuronal computational capabilities, among other known functions. Also, our findings could encourage experimentalists to conduct more subtle assays in an attempt to elucidate this important aspect of cellular activities. On the other hand, the much–needed experimental validation of presented results would undoubtedly lead to exciting new opportunities in the development of biological nanoscale electronic applications.

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