

Discrete and solitons-like modes as nonlinear dynamics in microtubules based on an improved longitudinal u -model

R. J. Noumana Issokolo,^{1, 2, a)} S. E. Mkam Tchouobiap,^{2, b)} and F. Naha Nzoupe^{3, c)}

¹⁾*National Advanced School of Engineering of Yaounde, University of Yaounde I, P.O. Box 8390, Yaounde, Cameroon*

²⁾*Laboratory of Research on Advanced Materials and Nonlinear Science (LaRAMaNS), Department of Physics, Faculty of Science, University of Buea, P.O. Box 63, Buea, Cameroon.*

³⁾*Laboratory of Mechanics, Department of Physics, Faculty of Science, University of Yaounde I, P.O. Box 812, Yaounde, Cameroon.*

(Dated: 21 February 2023)

In the present work, we focus on the longitudinal model of microtubules (MTs) proposed by Satařić *et al.* [Phy. Rev. E 48, 89 (1993)], that consider cell MTs to have ferroelectric properties, i.e., a displacive ferro-distortive system of dimers and usually referred to as u -model of MTs. It has been shown that during the hydrolysis of GTP into GDP, the energy released is transferred along the MTs through kink-like solitons. Substantially, we propose to theoretically investigate the dynamic of MTs by intrinsically taking into account the effect of the oriented molecules of polarized cytoplasmic water and enzymes surrounding the MT. In this regards, we introduce a cubic nonlinear term in the electric potential characterizing the polyelectrolyte features of MTs and show that in addition to the kink and antikink solitons, asymmetrical bright and dark solitons, and discrete modes can also propagate along the MTs. These results are supported by numerical analysis. The investigation shows us that the nonlinear dynamics of MTs is strongly impacted by the intrinsic electric field, the polyelectrolyte and the viscosity effects. Moreover, new solitons and discrete solitary modes may help to find new phenomena occurring in the microtubulin systems.

Keywords: Microtubules, modified longitudinal u -model, polyelectrolyte and viscosity effects, ordinary differential equation, solitons, discrete modes

^{a)}Electronic mail: remi.issokolo@univ-yaounde1.cm

^{b)}Electronic mail: mkam.tchouobiap@ubuea.cm (Corresponding author)

^{c)}Electronic mail: fernand.naha.nz@gmail.com

I. INTRODUCTION

Microtubules (MTs) that are intensively described in the literature¹⁻³⁰ are ubiquitous in all eukaryotic cells; and their association with microfilaments and actin filaments form the cell's cytoskeleton which is a network of long protein fibers that compose the structural framework of the cell. MTs are cylindrical-like assembly of a set of tubulin proteins through the formation of 13 longitudinal protofilaments (PFs) covering its cylindrical wall, that has an outer and inner radii of 25 nm and 15 nm, respectively, and each PF is a string of proteins composed of α - β tubulin heterodimers¹⁻⁷. During the mechanism of formation of MTs, there is a continuous binding of molecules of tubulin which is made possible by the guanosine triphosphate (GTP) hydrolysis molecule to the guanosine diphosphate (GDP) molecule and accompanied by a continuous high consumption of energy, making this process dissipative as their self-organization is energy-intensive⁸⁻¹⁰. Therefore, from the structural and functional characterization, MTs can be regarded as reaction-diffusion systems, and as such they are very dynamic tubulin dimers' polymers associated in a chain-like manner^{4,7-12}.

Also, MTs appear as a good candidates for dynamic information processing as it was demonstrated that neuronal MTs are fundamentally responsible for storage, processing, and transduction of biological information in a brain^{2,13-15}. More particularly, there are evidences that the cytoskeleton polymers could store and process information through their dynamic coupling mediated by mechanical energy, and mechanical properties of MTs involving bending or buckling MTs are largely responsible of most of their biological functions¹⁶⁻²¹. Beside their mechanical role as a part of the cytoskeleton, MTs serve as roads for multiple motor proteins (dynein and kinesin) moving along MTs for microtubule-based transport in the form of cargo in-vivo molecules to specific synapses and locations^{2,22-26}.

On the other hand, MTs are known to undergo a tread-milling phenomenon^{5,11-17}. In this regards, as far as their structure polarities are concerned with positive and negative ends, they undergo various activities of rapid polymerization due to their assembly in the positive (+) end, and depolymerization due to their disassembly in the negative (-) end^{5,16,17}. Moreover, MTs control the internal organization of the cells and their shapes. They also undergo various activities such as the intracellular transport of biological materials, cellular mobility, cytoplasmic transport and mitosis^{18,27}. Hence, it is still crucial to have a panoramic understanding of their mechanisms.

Indeed, taking into account the strong intrinsic nonlinear complex interactions in MTs such as their non-equilibrium dynamic has led to the development of mathematical models supported by theoretical analysis to understand the intrinsic properties and behaviors of the PFs. In this regards, following various purposes associated with the excitability and the propagation of nonlinear ionic waves in MTs, some theoretical studies have considered electrophysiological features of MTs, and modeled the MTs as an electric circuit with nonlinear resistance^{28–30}. For example, an existing electrical model was upgraded to study the ionic currents propagating in narrow layer along MTs²⁹, while another electrical model was proposed and applied for the investigation of the amplification, infratrasmission and supra-transmission of electrical signal in MTs³⁰. For the later model, the system was found to increase significantly the amplitude of the input signal, thus confirming some known experimental results. In addition, considering the capability of the PFs to behave like an excitable structure, another electrical model was also proposed that encapsulate various excitability features of PFs, and it conjectures that the study could be of great interest in the description of the developmental and informative processes occurring on the subcellular scale²⁸.

On the other hand, in various studies regarding the nonlinear dynamics of a PF associated with nearest neighbors interactions, the generalized mathematical model used for the longitudinal displacement of MTs namely the u -model, first proposed by Satarić *et al*¹¹ and later on used in various works^{10,22–24,31}, is mainly associated with the longitudinal displacement of a dimer at a given position n , u_n , the kinetic energy of the dimer, an harmonic nearest-neighbor interaction potential, a site potential composed with a double-well potential of ϕ^4 -type, a linear electric potential, and a viscous force¹⁰. The given equation takes into account substantially the effect of dispersion, viscous dissipation and nonlinearity to study the energy propagation in the interesting assembly and disassembly behavior of MTs. Using some existing mathematical tools, various authors have proposed different solutions describing the dynamics of MTs in terms of tanh- and cotanh-functions^{22,23}, sech-function^{10,19}, and exp-function²⁵. However, Zeković *et al*²⁶ showed the possibility of using Jacobi elliptic function to obtain analytical solutions for the given model, by presenting the link between Jacobi elliptic functions and hyperbolic functions^{32,33}.

In the present work, we consider the polyelectrolyte features of MTs to propose a modified u -model describing the nonlinear dynamics of MTs. It as been shown that many external factors such as gravity, temperature, magnetic field and electromagnetic field, influence the

assembly and disassembly of PFs. In the same vein, considering the intrinsic electric field, as well as the ferroelectric properties of the dimer that play a crucial role in the propagation direction of the energy excitation from the hydrolysis¹¹, we propose to include a cubic term in the electric potential that account for the nonlinear intrinsic electric interactions in the cell. In order to proceed to the analyses of the given mathematical model, we apply a method proposed by Samsonov³⁴ to study some features associated with the energy propagations in MTs. Through that method, we observe the propensity of MT's assembly to favor the emergence of various localized patterns including localized discrete modes, and asymmetrical bright and dark solitons, whose generation and evolution are influenced by the cooperative nonlinear interaction of the intrinsic electric field, the polarized solvent (water) and the viscous force. These solutions were obtained using exp-function, Jacobi elliptic functions, and Weierstrass \wp -function associated with Jacobi elliptic functions, through various transformations that can be found in various documents and textbooks³²⁻³⁹.

The present paper is organized as follows. In section II, we introduce the improved longitudinal u -model for MTs and present the theoretical framework or mathematical procedures necessary to obtain the relevant equation of motion, the crucial differential equation, and the solutions of the nonlinear dynamical model. Section III focuses on the analyses and discussions of the obtained solutions. Finally, section IV is devoted to concluding remarks.

II. MATHEMATICAL MODEL AND THEORETICAL FRAMEWORK

Considering the dynamics of the dimers in the longitudinal direction expressed by the u -model, the nonlinear dynamical equation to describe the oscillations of MTs is presented in the system Hamiltonian that has the form¹⁰

$$H = \sum_n \frac{m}{2} \dot{u}_n^2 + \frac{K}{2} (u_{n+1} - u_n)^2 + V_1(u_n) + V_2(u_n), \quad (1)$$

where the dot represents the first derivative with respect to time, m is the mass of the dimer, k stands for an effective intra-dimer stiffness parameter or dimer-dimer bonding interaction parameter within the same PF, and the integer n denotes the position of the considered dimer in the PF^{11,19,23}. Hence, it is obvious that the first term represents the kinetic energy of the dimer at position n , while the second one characterizes the potential energy due to the chemical interactions between the neighbouring dimers belonging to the same PF and

where, obviously, the nearest neighbour approximation is considered. However, as an important part of the Hamiltonian here and a source of nonlinearity, the last two terms represent the potential energies associated with each dipole and due to the overall effects (chemical influences) of all surrounding dipole dimers and of the polarized cytoplasmic water molecules and enzymes surrounding the MT, in one hand, and to the nearly uniform intrinsic electric field at the site n generated by all other tubulin dimers including the dimers belonging to the neighbouring PFs and polarized cytoplasmic water, on the other hand; as dimers are electric dipoles existing in the field of all other dipoles. Indeed, the presence of the oriented molecules of cytoplasmic water and enzymes surrounding the MT was experimentally observed using electron microscopy technique⁴⁰, which imply their plausible participation or responsibility in the nonlinear dynamics and stability of MTs which are crucial for biological systems, in numerous cellular activities such as growth and division known to be of essential for the living state of MTs, and in a number of mechanisms such as information processing (information transfer and storage in brain microtubules) which is the fundamental issue for understanding MTs^{2,13,41,42}. Therefore, we also assume here that a MT together with the polarized cytoplasmic water surrounding it, induces a nearly uniform intrinsic electric field parallel to its axis and that the additional potential due to internal electric field and surrounding polarized water, which is associated to each dipole is nonlinear in nature. Moreover, $V_1(u_n)$ is a generalized symmetrical double-well potential of ϕ^4 -type that displays the overall effect of the surrounding dimers on a dipole at a chosen site n , and $V_2(u_n)$ is the additional potential associated with each dipole dimer and due to the intrinsic electric field, and the surrounding polarized water and motor proteins in microtubulin systems. Therefore, in the present analysis the energy potentials $V_1(u_n)$ and $V_2(u_n)$ are expressed as

$$V_1(u_n) = -\frac{1}{2}A u_n^2 + \frac{1}{4}B u_n^4, \quad \text{and} \quad V_2(u_n) = -C u_n - \epsilon u_n^3, \quad C = qE, \quad (2)$$

where A , B and ϵ are positive model parameters that should be determined or, at least, estimated¹⁴, although A is typically a linear function of the temperature¹¹ that may change sign at an instability temperature T_c ; q represents the excess charge within the dipole while E denotes the intrinsic electric field strength directed along the longitudinal axis of the MT cylinder, with $q > 0$, and $E > 0$. It is important to precise that E is induced by all dimers including the dimers from the neighboring PFs. Figure 1 displays the potentials $V_1(u_n)$ (upper graph) and $V_2(u_n)$ with and without the added term (lower graphs). As the potential

$V_1(u_n)$ takes into account the quantum chemistry considerations through the chemical effect of all other dimers^{11,19}, its shape for an isolated single-dimer is shown in figure 1 (upper graph), where it appears that the potential actually has two degenerated minima separated by a potential barrier. Figure 1 (lower graphs) shows that $V_2(u_n)$ with $\epsilon \neq 0$ possesses a local extrema and, to the best of our knowledge, the association of both potentials results in the lifting of the degeneracy (breaking of symmetry), leading to an asymmetric double-well potential. The nonlinear character of $V_2(u_n)$ suggests beyond expectations that various excitability phenomena can be generated regarding the energy propagation within MTs, as can be seen in figure 1 (lower graph (b)). By introducing generalized coordinates q_n

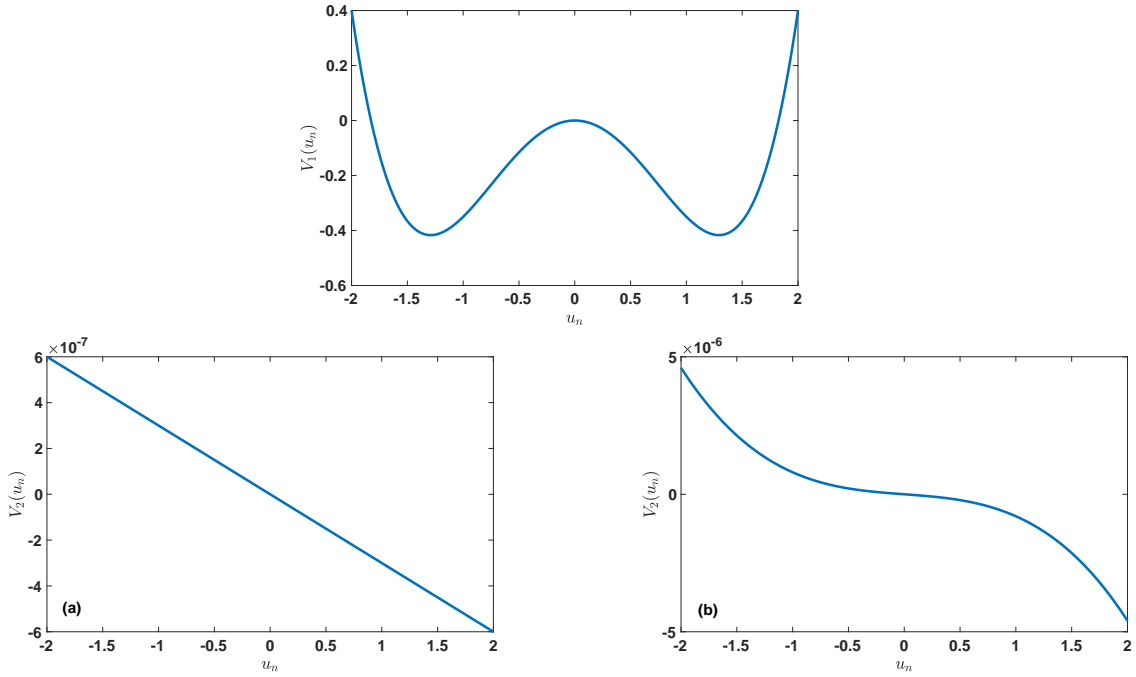


FIG. 1. Profiles of the symmetrical double-well potential of ϕ^4 -type $V_1(u_n)$ (upper graph) and of the additional potential $V_2(u_n)$ without (a) and with (b) additional term (lower graphs), associated with each dipole dimer as a function of the longitudinal displacement of a dimer at a given position n , u_n . The model parameters are selected as follows: $A = 1.0 \text{ N}[u_n]^{-1}$, $B = 0.6 \text{ N}[u_n]^{-3}$, $qE = 3 \times 10^{-7} \text{ N}$, $\epsilon = 0$ (a) and $\epsilon = 5 \times 10^{-7} \text{ N}[u_n]^{-2}$ (b). The unit of x -axis graduated by u_n is $[u_n]$ while the unit of y -axis is one $\text{N}[u_n]$.

and p_n , defined as $q_n = u_n$, and $p_n = m \dot{u}_n$, and assuming the validity of the continuum approximation (long wavelength limit) $u_n(t) \rightarrow u(x, t)$ ¹⁰, which eventually allow the Taylor

series expansion of terms $u_{n\pm 1}$, i.e.,

$$u_{n\pm 1} \rightarrow u \pm \frac{\partial u}{\partial x} l + \frac{1}{2} \frac{\partial^2 u}{\partial x^2} l^2, \quad (3)$$

the following appropriate continuum dynamical equation of motion can be obtained:

$$m \frac{\partial^2 u}{\partial t^2} - K l^2 \frac{\partial^2 u}{\partial x^2} + B u^3 - \epsilon u^2 - A u - qE + \gamma \frac{\partial u}{\partial t} = 0, \quad (4)$$

which is a nonlinear partial differential equation, and where in order to derive a realistic equation, we have further adequately take into consideration damping (viscosity) effects, through the introduction of a viscosity force $F_\nu = -\gamma \frac{\partial u}{\partial t}$, with γ denoting the viscosity (damping) coefficient, into the equation of motion^{11,23}. As well-known, Eq. (4) can be transformed into an ordinary differential equation (ODE) by introducing a unified variable along with a dimensionless function. Accordingly, by setting the following suitable transformations

$$z = kx - \omega t \quad \text{and} \quad u = \sqrt{\frac{A}{B}} \psi, \quad (5)$$

where k and w are constants representing the wave number and the frequency, respectively, with z denoting a unified variable; the function $u \equiv u(x, t) = u(kx - \omega t) \equiv u(z)$ is a traveling wave, while ψ is a dimensionless function representing an elongation of the oscillating dimer at position x and at time t . More interesting, Eq. (4) can be transformed into the following ODE

$$\alpha \psi'' - \rho \psi' - \psi - \beta \psi^2 + \psi^3 - \sigma = 0, \quad (6)$$

where the prime sign denotes the first derivative with respect to the unified variable z (i.e., $\psi' \equiv \frac{\partial \psi}{\partial z}$), and which contains the following four dimensionless new parameters α , ρ , β and σ underpinning the physics of the relevant model as follows:

$$\alpha = \frac{mw^2 - Kl^2k^2}{A}, \quad \rho = \frac{\gamma w}{A}, \quad \beta = \frac{\epsilon}{A\sqrt{\frac{A}{B}}}, \quad \text{and} \quad \sigma = \frac{qE}{A\sqrt{\frac{A}{B}}}. \quad (7)$$

Indeed, it is noteworthy that as expressed in Eq. (7), the parameter α accounts for the competitive interaction between the kinetic energy of the dimers and the relevant chemical bounds, while the parameter β accounts for the polyelectrolyte features of MTs. Likewise, the parameters ρ and σ are proportional to viscosity and electric field strength, respectively. All of these effects are very important as they are crucial for nonlinear dynamics and stability of MTs, and for understanding mechanisms such as dynamical information processing, and

cellular activities including cell growth and division in MTS^{2,11–19,43,44}. Moreover, Eq. (6) is a nonlinear dispersive (even order term) and dissipative (odd order term) wave propagation ordinary differential equation (ODE) and in the present, we will use a mathematical approach proposed Samsonov³⁴ to find explicit solutions of this ODE. This method has the advantage to use simple transformations that transform Eq. (6) to an equation solvable using Jacobi elliptic and Weierstrass \wp -functions, without considering the Painleve properties⁴⁵ of Eq. (4). In this regards and for the sake of simplicity, we first rewrite Eq. (6) as follows:

$$\psi'' - a_0\psi' - b_1\psi - b_2\psi^2 + b_3\psi^3 - b_0 = 0, \quad (8)$$

where the coefficients a_0 , b_1 , b_2 and b_3 are defined as

$$a_0 = \frac{\rho}{\alpha}, \quad b_0 = \frac{\sigma}{\alpha}, \quad b_1 = \frac{1}{\alpha}, \quad b_2 = \frac{\beta}{\alpha}, \quad \text{and} \quad b_3 = \frac{1}{\alpha}, \quad (9)$$

assuming that $\alpha \neq 0$. Also, according to the mathematical basis for our theoretical framework procedures and in order to practically address Eq. (8), it is convenient to introduce new dimensionless functions. Hence, by considering and performing the following transformations

$$\phi(\psi) = \frac{1}{\psi'(z)}, \quad (10)$$

and

$$\eta' = \frac{1}{\xi\phi(\eta)}, \quad (11)$$

into Eq. (8), and after applying appropriate derivations and computations while keeping in mind that: $\psi = \psi(z)$ such that $\psi' \equiv \frac{\partial\psi}{\partial z}$, $\phi = \phi(\psi)$ such that $\phi' \equiv \frac{\partial\phi}{\partial\psi}$ and $\eta = \eta(\xi)$ such that $\eta' \equiv \frac{\partial\eta}{\partial\xi}$, we can straightforwardly obtain the following convenient equation

$$\xi^2\eta'' + \gamma_3\eta^3 - \gamma_2\eta^2 - \gamma_1\eta - \gamma_0 = 0, \quad (12)$$

where the coefficients are defined as

$$\gamma_0 = \frac{\sigma}{\rho}, \quad \gamma_1 = \frac{\alpha}{\rho^2}, \quad \gamma_2 = \frac{\beta\alpha^2}{\rho^3}, \quad \gamma_3 = \frac{\alpha^3}{\rho^4}, \quad (13)$$

provided that $\rho \neq 0$, and where the functions $\psi(z)$ and $\xi(z)$ have to be determined. Before we proceed, let us mention that as important point in our treatment, one of the main transformation used to obtain Eq. (12) is given by the relation

$$\eta = \int a_0 d\psi, \quad (14)$$

where the parameter a_0 is given by Eq. (9). However, one of the major difficulties of this mathematical method lies in the choice of the appropriated ansatz, since the ansatz varies with the equation form. At this point, a solution of Eq.(12) for η can be constructed by assuming it to be in the form

$$\eta(\xi) = C\xi^p F(y) + D, \quad y = \xi^q, \quad (15)$$

where the parameters C , p , D and q , and the unknown functions $\xi = \xi(z)$ and $F = F(y)$ should also be determined. In addition, it should be emphasized here that we should plug the expression of the trial function $\eta = \eta(\xi)$ given in Eq. (15) into Eq. (12), which brings about the following equation:

$$\begin{aligned} & q^2 C\xi^{p+2q} F'' + \gamma_3 C^3 \xi^{3p} F^3 - \gamma_0 - \gamma_1 D - \gamma_2 D^2 + \gamma_3 D^3 \\ & + [2pq + q(q-1)] C\xi^{p+q} F' + (-\gamma_2 + 3\gamma_3 D) C^2 \xi^{2p} F^2 \\ & + [p(p-1) - \gamma_1 - 2\gamma_2 D + 3\gamma_3 D^2] C\xi^p F = 0. \end{aligned} \quad (16)$$

Thence and according to the theoretical method, the ansatz for the solution η must be consistent with the series expansion of the above equation in powers of the function $F = F(y)$, adopted in Eq.(15), and its derivatives^{34,35,45}. Accordingly, by eliminating F' and excluding the lower degrees of F up-to the second order, which is satisfied if all the corresponding coefficients are simultaneously equal to zero. This annihilation of terms brings about the following system of four equations:

$$\text{Order } F^0 : \quad -\gamma_0 - \gamma_1 D - \gamma_2 D^2 + \gamma_3 D^3 = 0, \quad (17)$$

$$\text{Order } F^1 : \quad p(p-1) - \gamma_1 - 2\gamma_2 D + 3\gamma_3 D^2 = 0, \quad (18)$$

$$\text{Order } F^2 : \quad -\gamma_2 + \gamma_3 D = 0, \quad (19)$$

$$\text{Order } F' : \quad 2pq + q(q-1) = 0. \quad (20)$$

Let us notice that the above system of equations induces only implicit relations between the parameters. Therefore, in order to proceed further in our investigation, and for the sake of convenience we assume that $q \neq 0$, and for autonomy³⁵ we set the following condition

$$p = \frac{2}{n+3} = \frac{1}{3}, \quad (21)$$

where n is the highest degree of the polynomial ($n = 3$). Accordingly, by using Eqs. (19) and (20) and the value of p obtained previously (21), we obtain the expressions of parameters D

and q given by

$$D = \frac{\gamma_2}{\gamma_3}, \quad (22)$$

and

$$q = 1 - 2p = \frac{1}{3}. \quad (23)$$

Therefore, Eq. (15) can finally be transformed in the following simplest form

$$F'' + 9 C^2 \gamma_3 F^3 = 0. \quad (24)$$

In addition, by setting $C^2 = -\frac{2}{9\gamma_3}$, Eq. (24) can now takes the form of a simplified ordinary differential equation given by:

$$F'' - 2F^3 = 0. \quad (25)$$

In this order of ideas, we note here that by using Eq. (17), we can derive the crucial condition $\gamma_1 \gamma_2 = -\gamma_0 \gamma_3$ that will helps us to express C^2 without the minus sign. Of course, this does not affect the final result. Moreover, by multiplying Eq. (25) by F' and integrating we obtain the following relation

$$F'^2 = F^4 + R_0, \quad (26)$$

where R_0 is an arbitrary constant of integration. This is a crucial equation whose solution will explain nonlinear dynamics of MTs. As far as Eq. (26) is concerned, the divergence of the solution F can only be prevented by finding the exact solution to Eq. (26) in z . In this regards, we can derive corresponding expressions for the functions ξ , y and η . Alternatively, according to Eqs. (10) and (11), we can finally obtain the equality $a_0 \xi(z) \frac{\partial \psi}{\partial \xi} = \frac{\partial \psi}{\partial z}$, and then by solving the resulting set of equations recursively and by using Eq. (15), it results to the final expressions of the functions $\xi(z)$ and $y(z)$ given, respectively, by

$$\xi(z) = \exp(a_0 z), \quad (27)$$

and

$$y(z) = \exp\left(\frac{1}{3}a_0 z\right). \quad (28)$$

Finally, the solution of Eq. (26) must be obtained by integrating Eqs. (27) and (28) into the said solution, and different solutions may be obtained from different conditions on R_0 . By contrast, from Eq. (15), we obtain a general solution of the function $\eta(z)$ given by

$$\eta(z) = \sqrt{\frac{2\gamma_1\gamma_2}{9\gamma_0}} \exp\left(\frac{1}{3}a_0 z\right) F(z) + \frac{\gamma_2}{\gamma_3}, \quad (29)$$

provided the expression of the continuous function F will be obtained, and where γ_3 has been replaced in C^2 by a new expression obtained above. In the same vain, using Eq. (14), we have after integration that $\eta = a_0 \psi$. Hence, following the procedure explained above and after some simple algebra with Eqs. (27), (28), and (29), we straightforwardly obtain the final expression for ψ as:

$$\psi(z) = \frac{\alpha}{\rho} \left[\sqrt{\frac{2\beta\alpha^3}{9\sigma\rho^4}} \exp\left(\frac{\rho}{3\alpha} z\right) F(z) + \frac{\beta\rho}{\alpha} \right], \quad (30)$$

provided an expression of α as a function of ρ and β , obtained by solving Eq. (18), is given by

$$\alpha = \frac{2\rho^2}{9\chi}, \quad \chi = \beta^2 - 1 \neq 0. \quad (31)$$

It is relevant to stress that this expression of α that depends on ρ and β must be positive ($\beta > 1$), as imposed by the presence of the expression of its square root in Eq.(30). Obviously, this interesting solution Eq. (30) is derived in terms of the original parameters for more clarity.

III. RESULTS AND DISCUSSION

As generally known, solving Eq.(26) can provide a richness of wave solutions depending on the mathematical tools explored. A part of the difficulty stems from the fact that resolution of such equation requires specific considerations or conditions which involves various technical difficulties coming from the fact Eq.(26) is an ordinary differential equation ODE. Then, the possible solutions of Eq.(26) can be obtained in terms of exponential functions, Jacobi and Weierstrass elliptic functions^{32–39}. In this regards and to overcome the technical difficulty, we shall not be so much concerned with technical details and all the tedious derivations. Instead, two sets of solutions are considered, depending on the condition on arbitrary constant of integration R_0 , i.e., the conditions $R_0 = 0$ and $R_0 \neq 0$, respectively, that we will concretely analyze hereafter.

Moreover, Eq. (6) has been analytically addressed using the mathematical method mentioned above with a couple of conditions, and completely different solutions have been derived. Therefore, in what follows and in order to proceed further, we will investigate and analyze the obtained solutions and perform numerical analysis using the Runge Kutta 4

scheme, followed by a numerical simulation of their time evolution, taking into account the expression of α given by Eq. (31).

Now, by setting the constant of integration $R_0 = 0$ and after appropriated calculations, one can write down the explicit form of one soliton solutions in terms of exponential function³⁶, as:

$$\psi_1(z) = \frac{\alpha}{\rho} \left[-\frac{\sqrt{\frac{2\beta\alpha^3}{9\sigma\rho^4}} \exp\left(\frac{\rho}{3\alpha} z\right)}{\exp\left(\frac{\rho}{3\alpha} z\right) + z_0} + \frac{\sigma\rho}{\alpha} \right]. \quad (32)$$

More precisely, this solution is reminiscent to a tanh-function solution^{24,46–49}.

Figure 2 presents the evolution of the solution $\psi_1(z)$ predicted by Eq. (32) as function of the unified variable z , in the form of a localized antikink-solitons, for a fixed value of parameter σ ($\sigma = 0.3$), and for different values of parameters β , ρ and the initial shift z_0 . Following the antikink profiles, figure 2 suggests that the initial location of the antikink-soliton depends strongly on the initial shift z_0 . Otherwise, depending of the values of the other parameters σ , β and ρ , the antikink-soliton profiles manifest amplitude and waveform variations, and also present the important influence of the damping effect.

Accordingly, as we can see in figure 2 (a) where the solution is shown for four arbitrary values of the parameter z_0 , the antikink-soliton location depends on the value of z_0 which is the initial shift that defines a position of the center of the antikink. Also, it is obvious that the intensity of the antikink-soliton increases with increasing β , as clearly seen in figure 2 (b) in comparison with figure 2 (a) where $\beta = 1.7$ and 1.5 , respectively. On the other hand, we see that the damping effect on the antikink's amplitude and profile is highlighted with increasing ρ as shown in figures 2 (c) and (d) for $\rho = 0.5$ and $\rho = 1.5$, respectively. Among other things, it appears that the parameter β is an important factor in the rapid propagation of solitonic waves and in the very interesting assembly and disassembly behaviour in MTs, as can be seen from figure 2 (b). Therefore, all these aspects noticed and illustrated in Fig. 2, sufficiently demonstrate that in addition to kink-like domain walls, the antikink dynamics can be viewed as bits of information propagating along MTs^{11,24}. This form of dynamics governed by antikink type soliton solutions is known as anterograde mechanism for the movement of motor proteins^{12,50–52}.

On the other hand, by considering the constant of integration $R_0 \neq 0$, a careful integration

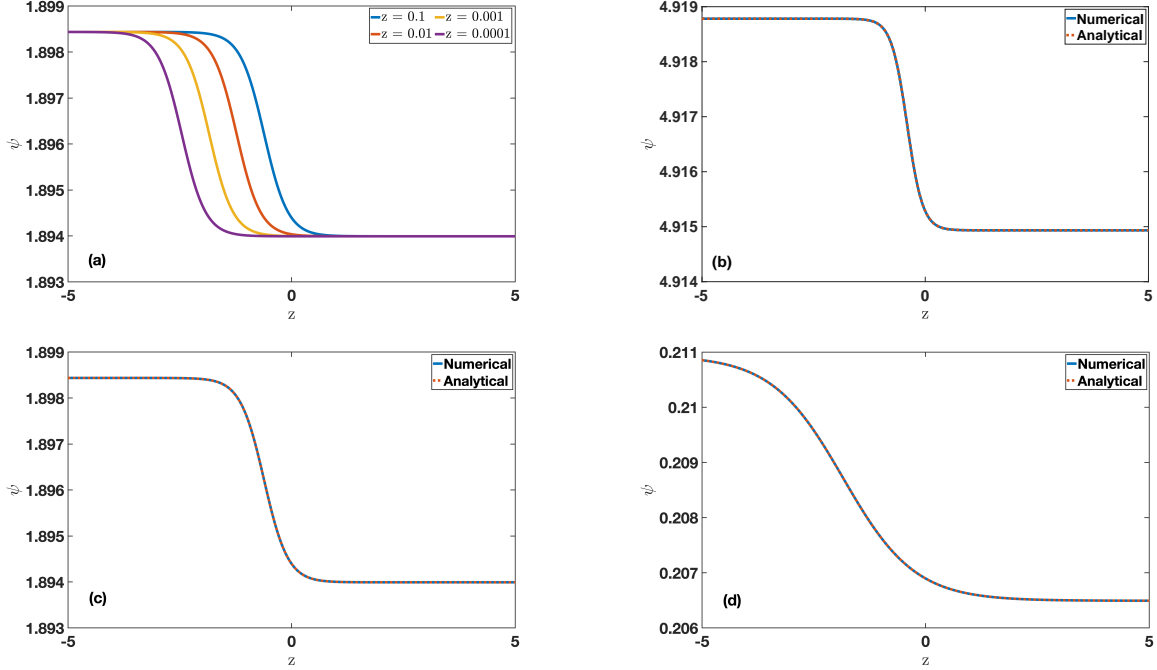


FIG. 2. Waveform profiles of traveling antikink-soliton solution $\psi_1(z)$ predicted by Eq. (32) as function of the unified variable z for $\sigma = 0.3$, and different values of parameters ρ , β and z_0 . (a) $\rho = 0.5$, $\beta = 1.5$ and the initial shift $z_0 = 0.1, 0.01, 0.001, 0.0001$, respectively; (b) $\rho = 0.5$, $\beta = 1.7$ and $z_0 = 0.1$; (c) $\rho = 0.5$, $\beta = 1.5$, and $z_0 = 0.1$; and (d) $\rho = 1.5$, $\beta = 1.5$, and $z_0 = 0.1$.

of Eq. (26) can lead to a solution ψ in terms of the Jacobi elliptic functions^{32–35,37}, viz,

$$\psi_2(z) = \frac{\alpha}{\rho} \left[\sqrt{\frac{2\beta\alpha^3}{9\sigma\rho^4}} \exp\left(\frac{1}{3}\frac{\rho}{\alpha}z\right) \frac{\lambda \left[1 + \sqrt{\delta} \operatorname{tn}\left(\exp\left[\frac{1}{3}\frac{\rho}{\alpha}z\right], \kappa\right)\right]}{1 - \sqrt{\delta} \operatorname{tn}\left(\exp\left[\frac{1}{3}\frac{\rho}{\alpha}z\right], \kappa\right)} + \frac{\sigma\rho}{\alpha} \right], \quad (33)$$

where $\operatorname{tn}()$ is the Jacobi elliptic function with modulus κ , and the new parameters λ , κ , and δ can be expressed as

$$\lambda = \sqrt[4]{R_0} = R_0^{1/4}, \quad \kappa^2 = \frac{8\sqrt{2}}{(2 + \sqrt{2})^2}, \quad \delta = \frac{2 - \sqrt{2}}{2 + \sqrt{2}}. \quad (34)$$

Quite remarkably here, the quantities κ and δ turn out to be non arbitrary constants, i.e., fixed. In fact they depend on the defined physical parameters of the model^{26,32,33}. Before we proceed, we want to give some additional remarks regarding the above obtained solution given by Eqs.(33) and (34). Of course, let us notice that for the sake of simplicity the free parameter λ is assumed to be non negative, provided that the constant of integration R_0 is undeniably a positive constant, and the Jacobi elliptic function $\operatorname{tn} \equiv \operatorname{sn}/\operatorname{cn}$, with sn and cn representing standard Jacobian elliptic functions with modulus κ ^{32,33}.

Figures 3 and 4 display the analytical (dots) and numerical (solid lines) localized patterns of discrete modes as function of the unified variable z , and their evolution in the $x - t$ plane for four different values of the parameter β . Accordingly, the discrete modes are spatially localized and their lifetime depends on the cooperative interactions between the parameters β and ρ , as can be seen in Figs. 3 and 4. More precisely, the 2-D representation of these discrete modes (left graphs) and their propagations with time (right graphs) for different values of β indicate that the initial localized discrete patterns persist as time evolves, illustrating the fact that the behavior of the localized discrete modes in MTs is acceptable as the soliton's, as depicted in Figs. 3 (a)-(d) and 4(a)-(d). Also, the study provides strong evidence of the influence of the parameter β on the discrete pattern behavior through the mode profiles, although it is apparent that the amplitudes of the discrete modes seem not altered as the waves are propagating, demonstrating the stability of the localized discrete modes, as shown in Figs. 3(a)-(d) and 4(a)-(d). Among other things, from the results it is evident that recurrence is observed as time passes and such discrete modes are intrinsically generated as a response to the combined effects of spatial discreteness and nonlinearity⁴⁶. However, from solution (33), these localized discrete modes are generated in complex cooperative interaction incorporating ferroelectric processes, dispersion, dissipation, discreteness and nonlinearity, and it appears that these modes are structurally and symmetrically non uniform, as during their generation, their spatial profile and symmetry change with β in the course of propagation through the tubulin-heterodimers lattice.

Most interestingly, taking the initial value of β in the analysis to be $\beta = 1.10$, it is shown that a slight variation of its value, i.e., $\beta = 1.10, 1.11, 1.12$ and 1.13 , respectively, has a direct incidence on the modes symmetries and a relative impact on their amplitudes (see figures Figs. 3(a), 3(c), 4(a) and 4(c)).

On the other hand, and from another perspective, by considering Weierstrass \wp -function and taking $R_0 \neq 0$, an integration of Eq. (26) can yield to another general solution ψ expressed as follows:^{38,39,45}

$$\psi_3(z) = \frac{\alpha}{\rho} \left[\sqrt{\frac{2\beta\alpha^3}{9\sigma\rho^4}} y \frac{\wp'(y, g_2, 0)}{\wp(y, g_2, 0)} + \frac{\sigma\rho}{\alpha} \right], \quad (35)$$

where g_2 is a free parameter, y is a function defined by Eq. (28) and \wp' denotes the first derivative with respect to y . The Weierstrass \wp -function can be associated to Jacobi elliptic function considering different values of g_2 ⁴⁵, which will lead to soliton-like solutions. In order

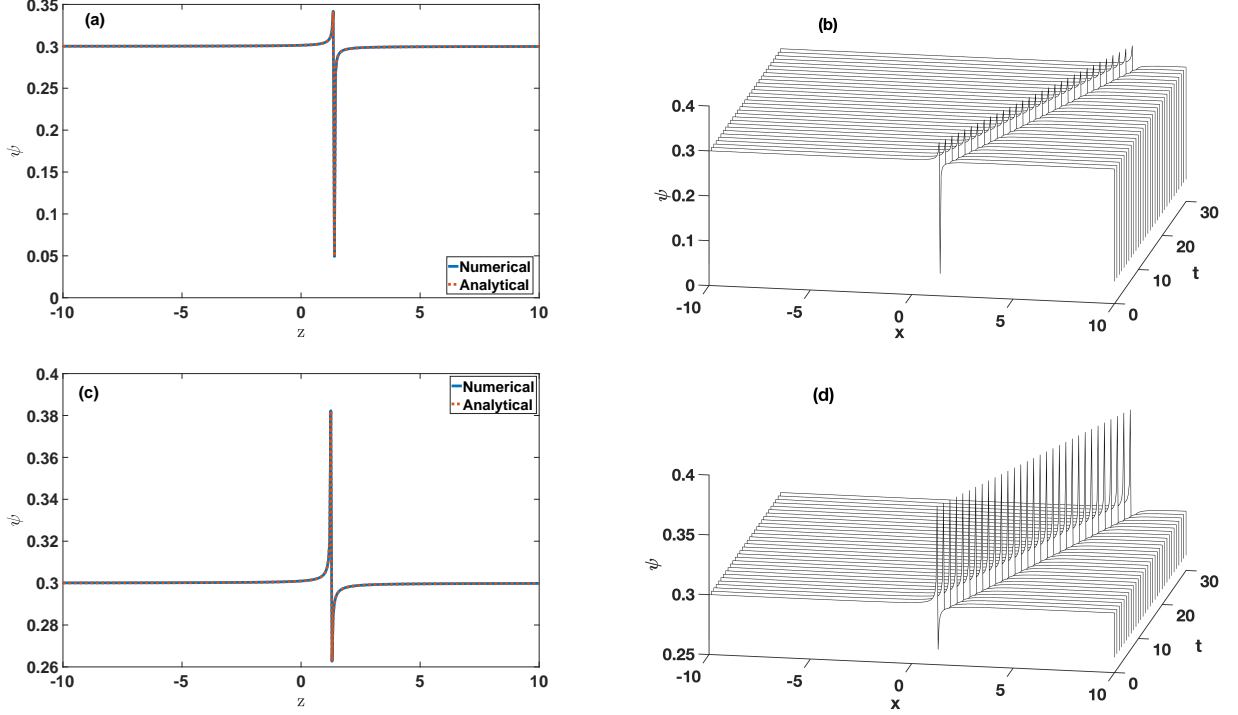


FIG. 3. The analytical (dots) and numerical (solid lines) generation of localized discrete modes in the MTs, solutions of Eq. (6), as function of the unified variable z (left graphs) and their propagation (right graphs) for $\beta = 1.10$ (a) and (b), respectively, and $\beta = 1.11$ (c) and (d), respectively. The analytical solution is predicted by $\psi_2(z)$ (Eqs. (33) and (34)). The other parameters are $\sigma = 0.3$, $\lambda = 0.1$, $\rho = 0.5$ and $\kappa = 0.98$.

to proceed further with our investigation, we can distinguish the following two cases: $g_2 < 0$ and $g_2 > 0$. Accordingly, when $g_2 < 0$, the Weierstrass elliptic function $\wp(y, g_2, 0)$ can be expressed as follows^{38,39}

$$\wp(y, g_2, 0) = \wp(y) = a + 2asn^{-2}\left(\sqrt{2a}y, \kappa\right), \quad (36)$$

where κ is the modulus of the Jacobi elliptic function sn , with $0 \leq \kappa \leq 1$, and a is an appropriate fundamental function of g_2 ³².

In Fig. 5, we display in this case the profile of the associated soliton-like solution obtained numerically and analytically using $\psi_3(z)$ and the solution (36) as function of the unified variable z , and achieve its evolution (propagation) in the $x - t$ plane for chosen values of model parameters defined above, i.e., $\rho = 0.5$, $\sigma = 0.3$, $\beta = 1.15$, $\kappa = 1$ and $a = 0.5$. Here, we observe that the solution is a space-localized pattern of soliton-like profile emerging as an asymmetric bright solitary wave, as depicted in Fig. 5(a). Also, its evolution in the $x - t$

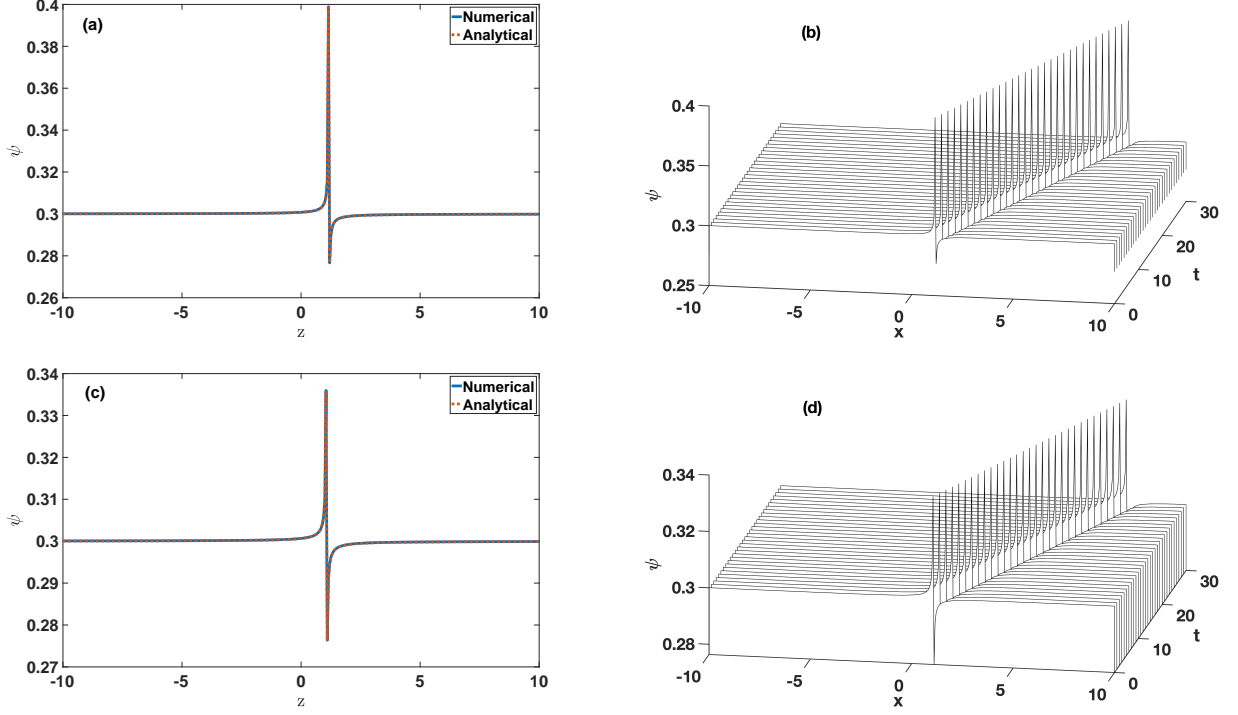


FIG. 4. The analytical (dots) and numerical (solid lines) generation of localized discrete modes in the MTs, solutions of Eq. (6), as function of the unified variable z (left graphs) and their evolution in the $x - t$ plane (right graphs) for $\beta = 1.12$ (a) and (b), respectively, and $\beta = 1.13$ (c) and (d), respectively. The analytical solution is given by $\psi_2(z)$ (Eqs. (33) and (34)). The other parameters are $\sigma = 0.3$, $\lambda = 0.1$, $\rho = 0.5$ and $\kappa = 0.98$.

plane illustrates the persistence of the initial bright solitonic pattern as time evolves, which demonstrate the stability of the solution, as can be seen in Fig. 5(b).

In the same order, when $g_2 > 0$, the Weierstrass elliptic function \wp can now be expressed as^{38,39}

$$\wp(y, g_2, 0) = \wp(y) = \frac{1 + cn(y, \kappa)}{1 - cn(y, \kappa)}, \quad (37)$$

where cn is a well-known Jacobi elliptic function with modulus κ ($0 \leq \kappa \leq 1$) and y is still defined by Eq. (28).

Fig. (6) presents the profile of the associated soliton-like solution obtained numerically and analytically using the solution (37) as function of the unified variable z , and its propagation in the $x - t$ plane for the same chosen values of model parameters defined above, i.e., $\rho = 0.5$, $\sigma = 0.3$, $\beta = 1.15$, $\kappa = 1$ and $a = 0.5$. Accordingly, for the same chosen values of model parameters, it appears that the solution is a space-localized pattern of soliton-like

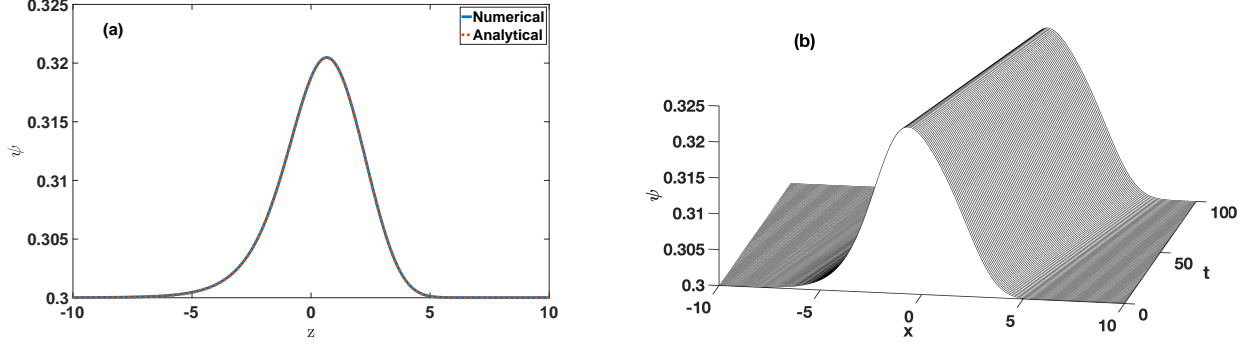


FIG. 5. The analytical (dots) and numerical (solid lines) generation of a localized asymmetrical bright soliton in the MTs, solutions of Eq. (6), as function of the unified variable z (left graph) and its evolution in the $x-t$ plane (right graph) for $\rho = 0.5$, $\sigma = 0.3$, $\beta = 1.15$, $\kappa = 1$ and $a = 0.5$. The analytical solution is given by $\psi_3(z)$ [Eq. (35)] and Eq. (36).

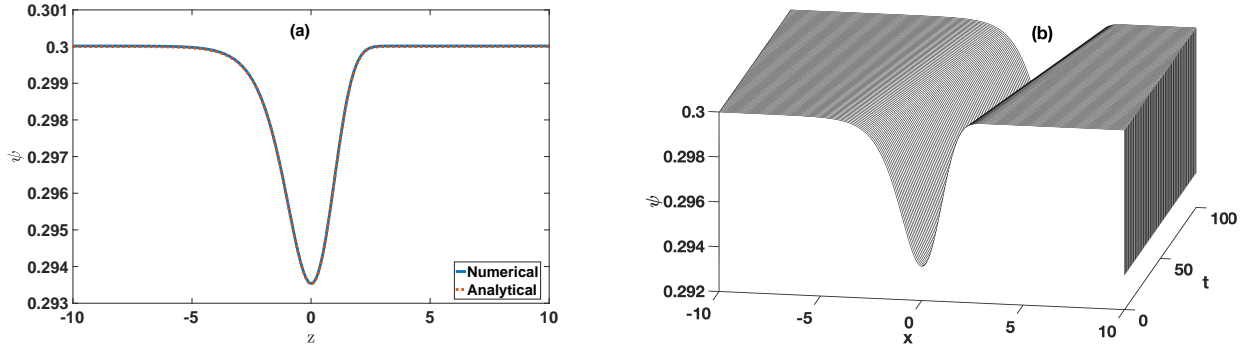


FIG. 6. The analytical (dots) and numerical (solid lines) generation of a localized asymmetrical dark soliton in the MTs, solutions of Eq. (6), as function of the unified variable z (left graph) and its evolution in the $x-t$ plane (right graph) for $\rho = 0.5$, $\sigma = 0.3$, $\beta = 1.15$, and $a = 0.5$. The analytical solution is given by $\psi_3(z)$ [Eq. (35)] and Eq. (37).

profile emerging as an asymmetric dark solitary wave, as seen in Fig. 6(a). Here again, the propagation in the $x-t$ plane lead to a stable solution, as can be clearly seen in Fig. 6(b). From Figs. 5(b) and 6(b), it can be seen from the propagation of the soliton-like solutions that the amplitude and the width of the dark and bright soliton profiles do not vary as time evolves, which is characteristic of the stability of soliton-like solutions. According to the parameters of MT dimers and based on the initial condition, it is apparent that localized discrete and soliton-like modes are accessible as nonlinear dynamical behaviors in MTs provided that the model parameters are fine tuned. It is worth mentioning that Figs. 5

and 6 show the behavior of bright and dark soliton-like modes according to the sign of the free parameter g_2 . Among other things, these stable soliton pulses are obtained without neglecting the viscosity term, but $\beta \gg \rho$. Therefore, following analytical-numerical approach interpreting this behavior, the stability of the soliton-like solutions is achieved due to the balance between the nonlinearities. From the initial expression of α in Eq.(7), it appears that α can be expressed as a sum of the solitonic and linear sound velocities, v_1 and v_2 , respectively, namely

$$\alpha = \frac{mk^2}{A}(v_1^2 - v_2^2); \quad v_1 = \frac{w^2}{k^2}, \quad v_2 = \frac{Kl^2}{m}. \quad (38)$$

Using the expressions of α in Eq.(38) and Eq.(31), we derive a relation between the solitonic and the linear sound velocities as

$$v_1 = \frac{v_2}{\sqrt{1 - \frac{2\gamma^2}{9Am^2\chi}}}. \quad (39)$$

In Eq. (39), we deduce that the velocity of propagation will be supersonic if $v_1 > v_2$, i.e., the condition $9Am^2\chi > 2\gamma^2$ must hold. In both Figs. (5) and (6), an observation of their solutions suggests that the width of the pulse is affected by the value of β , i.e, increasing the value of β will increase the speed of propagation of the soliton as given by the expression of v_1 in Eq. (39).

Moreover, we have performed analytical of Eq. (6) using the obtained solutions and numerical analysis using the Runge Kutta 4 scheme, followed by a numerical simulation of their time evolution, taking into account the expression of α given by Eq. (31), and we observe a good agreement between the analytical and numerical analysis of the localized stationary solutions.

More interestingly, all these various features underlying the nonlinear dynamics of MTs can be relevant to many biological processes such as cell growth and division for which MTs disassemble and re-assemble^{7,11,53,54}, chemical energy transition in the process of hydrolysis of GTP nucleotides and microtubule motor proteins transport such as kinesins and dyneins^{12,50-52}, excitations and inhibition of biomembranes and neurons^{7,13,55}, intracellular transport of biological materials including cytoplasmic transport and transport of both proteins and organelles^{18,27,56}, cellular movements including and separating chromosomes during mitosis and meiosis⁵⁷⁻⁵⁹, respiratory infection⁶⁰, dynamic information processing including processing, propagation, storage and transduction, of biological information in MTs^{2,7,13-16}.

IV. CONCLUSION

In the present paper, we proposed a modified u-model that takes into account the polyelectrolyte features of the tubulin molecules, to study the nonlinear dynamics of MTs. In this regards, we have introduced a cubic nonlinear term in the electric field potential of the u-model, that account for the nonlinear electric interactions in the MT resulting from the combined effects of the intrinsic electric field and the polarized cytoplasmic water and enzymes surrounding the MT. The results have shown the waves responsible for energy transfer within tubulin dimers that are responsible for the mechanisms of assembly and disassembly in MTs, can evolve as kink-like solitons, discrete modes and asymmetrical bright and dark solitons. These solutions arise from the requirements that α must be positive, $\alpha \neq 0$, and $\beta > 1$ from Eq. (30). The condition on α means that the kinetic energy of the dimers is predominant in its competitive interactions with the chemical bounds. An explanation proposed by Zdravković *et al*²² justify this result by the fact that Mts are polymerized without strong covalent bond. Moreover, taking $\beta > 1$ implies from Eq. (7) that $\epsilon > A\sqrt{\frac{A}{B}}$, Thus the value of ϵ should be estimated around the values of A and B .

In spite of nonlinearities in microtubulin systems, the nonlinear dynamics MTs is found to be governed by stable localized discrete and soliton like modes, demonstrating the complex nonlinear dynamics of the microtubules. Also, it is interesting that the description of the dynamics of the microtubulin system depend on applied mathematical procedures. We guesswork that the existence of such nonlinear dynamics or quanta of energy transfer in the form of discrete patterns and solitonic waves would offer a new view of the motor proteins transport mechanism on the stability of MTs in numerous cellular activities such as growth and division in microtubulin systems, and which are essential for living state.

ACKNOWLEDGMENTS

One of the author MTSE gratefully acknowledges the support from The World Academy of Sciences (TWAS), Trieste, Italy, within the framework of the TWAS-UNESCO Associateship with iThemba LABS-National Research Foundation, Somerset West, South Africa.

REFERENCES

- ¹H. Lodish, A. Berk, P. Matsudaira, C. A. Kaiser, M. Krieger, M. P. Scott, L. Zipursky, J. Darnell, *Molecular cell biology* Publisher: W. H. Freeman, fifth edition 2008.
- ²P. Dustin, *Microtubules*, 2nd revised edition, (Springer-Verlag, Berlin, 1984).
- ³J. A. Tuszyński, J. A. Brown, E. Crawford, E. J. Carpenter, M. L. A. Nip, J.M. Dixon, M.V. Satarić, *Math. Comput. Model.* **41**, 1055 (2005).
- ⁴M. V. Satarić, R. B. Žakula, J. A. Tuszyński, *Nanobiology* **1**, 445 (1992).
- ⁵J. A. Tuszyński, S. Hameroff, M. V. Satarić, B. Trpisová, M. L. A. Nip, *J. Theor. Biol.* **174**, 371 (1995).
- ⁶M. Cifra, J. Pokorný, D. Havelka, O. Kučera, *BioSystems* **100**, 122 (2010).
- ⁷S. Hameroff and R. Penrose, *Phys. Life Rev.* **11**, 39 (2014).
- ⁸O. Kučera, D. Havelka, *BioSystems* **109**, 346 (2012).
- ⁹J. Tabony and D. Job, *Proc. Natl. Acad. Sci. USA* **89** 6948 (1992).
- ¹⁰S. Zdravković, *J. Serb. Chem. Soc.* **82**, 1 (2017).
- ¹¹M. V. Satarić, J. A. Tuszyński and R. B. Žakula, *Phys Rev E* **48**, 1 (1993).
- ¹²B. Mickey and J. Howard, *J. Cell Biol.* **130**, 909 (1995).
- ¹³S. R. Hameroff and R. C. Watt, *J. Theor. Biol.* **98**, 549 (1982).
- ¹⁴T. Horio and H. Hotani, *Nature* **321**, 605 (1986).
- ¹⁵S. Rasmussen, H. Karamporsala, R. Vaidyanath, K. Jensen, and S. R. Hameroff, *Physica D* **42**, 428 (1990).
- ¹⁶H. Athenstaedt, *Ann. N. Y. Acad. Sci.* **238**, 68 (1974).
- ¹⁷L. Margulis, L. To, and D. Chase, *Science* **200**, 1118 (1978).
- ¹⁸J. Jaber, R. Portugal and L. P. Rosa, *Biosystems* **83**, 1 (2006).
- ¹⁹S. Zdravković, S. Zeković, A. N. Bugay and M.V. Satarić, *Appl. Math. Comput.* **285**, 248 (2016).
- ²⁰A. Vinckier, C. Dumortier, Y. Engelborghs and L. Hellemans, *J. Vac. Sci. Technol. B Microelectron. Nanometer Struct. Process. Meas. Phenom.* **14**, 1427 (1996).
- ²¹A. Marx and E. Mandelkow, *European Biophys. J.* **22**, 405 (1994).
- ²²S. Zdravković, M. V. Satarić, A. Maluckov, A. Balaž, *Appl. Math. Comput.* **237**, 227 (2014).

- ²³S. Zdravković, L. Kavitha, M.V. Satarić, S. Zeković and J. Petrović, *Chaos, Solitons Fractals* **45**, 1378 (2012).
- ²⁴S. Zdravković and G. Gligorić, *Chaos* **26**, 063101 (2016).
- ²⁵S. Zdravković, A. Malukov, M. Dekić, S. Kuzmanović and M. V. Satarić, *Appl. Math. Comput.* **242**, 353 (2014).
- ²⁶S. Zeković, A. Muniyappan, S. Zdravković and L. Kavitha, *Chin. Phys. B* **23**, 020504 (2014)
- ²⁷J. A. Tuszyński, E. J. Carpenter, J. T. Huzil, W. Malinski, T. Luchko and R. F. Ludeña, *Int. J. Dev. Biol.* **50**, 341 (2006).
- ²⁸P. Guemkam Ghomsi, J. T. Tameh Berinyoh and F. M. Moukam Kakmeni, *Chaos* **28**, 023106 (2018).
- ²⁹M. V. Satarić, D. Sekulić, and M. Živanov, *J. Computational and Theoretical Nanoscience* **7**, 2281 (2010).
- ³⁰F. T. Ndjomatchoua, C. Tchawoua, F. M. Moukam Kakmeni, B. P. Le Ru, and H. E. Z. Tonnang, *Chaos* **26**, 053111 (2016).
- ³¹M. D. Fendji, J. Y. Effa, C. G. L. Tiofack, L. Kavitha, A. Mohamadou, and B. Z. Essimbi, *J. Comput. Theor. Nanosci.* **11**, 2297 (2014).
- ³²P. F. Byrd and M. D. Friedman, *Handbook of elliptic integrals for engineers and scientists* (Springer-Verlag, Berlin Heidelberg GMBH, 1954).
- ³³N. I. Akhiezer, *Elements of the Theory of Elliptic Functions, Translations of Mathematical Monographs*, vol. 79 (American Mathematical Society, Providence, 1990).
- ³⁴A. M. Samsonov, *Strains solitons in solids and how to construct them, Monographs and Surveys in Pure and Applied Mathematics*, Vol. 117 (Chapman and Hall/CRC, CRC Press, 2001).
- ³⁵A. M. Samsonov, *On some exact travelling wave solutions for nonlinear hyperbolic equations in Nonlinear waves and dissipative effects*, edited by D. Fusco and A. Jeffrey (Pitman Research Notes in Mathematics Series, 1991).
- ³⁶S. K. Liu and S. D. Liu, *Nonlinear Equations in Physics* (Peking University Press, Beijing, 2000).
- ³⁷Z. X. Wang and D. R. Guo, *Special Functions* (World Scientific, Singapore, 1989).
- ³⁸E. T. Whittaker and G. N. Watson, *A course of Modern Analysis* (Cambridge University Press, Cambridge, 1927) 4th Edition.

- ³⁹R. Beals and R. Wong, *Special Functions* (Cambridge University Press, Cambridge, 2010).
- ⁴⁰H. Stebbins and C. Hunt, Cell Tiss. Res. **227**, 609 (1982).
- ⁴¹H. Fröhlich, *Modern Bioelectrochemistry*, edited by Guttman F. and Keyzer H. (New York, 1996).
- ⁴²M. P. Barnett, *Molecular Systems to Process Analog and Digital Data Associatively*, (DC: Naval Research Laboratory, Washington, 1987).
- ⁴³J. Fabera, R. Portugala, and L. Pinguelli Rosa, BioSystems **83**, 1 (2006).
- ⁴⁴S. Zdravković, M. V. Satarić and S. Zeković, Eur. Phys. Let. **102**, 38002 (2013).
- ⁴⁵P. A. Clarkson, Physics letters A **109**, 205 (1985).
- ⁴⁶S. Flacha and A. V. Gorbach, Physics Reports **467**, 1 (2008).
- ⁴⁷E. Fan, Phys. Lett. A **277**, 212 (2000).
- ⁴⁸L. Kavitha, N. Akila, A. Prabhua, O. Kuzmanovska-Barandovska, D. Gopi, Math. Comput. Model. **53**, 1095 (2011).
- ⁴⁹D. L. Sekulić, M.V. Satarić, M. B. Živanov, Appl. Math. Comput. **218**, 3499 (2011).
- ⁵⁰H. Salman, Y. Gil, R. Granek, and M. Elbaum, Chem. Phys. **284**, 389 (2002).
- ⁵¹M. Cifra, J. Pokorny, D. Havelka, and O. Kučera, BioSystems **100**, 122 (2010).
- ⁵²B. Trpisova and J. A. Tuszyński, Phys. Rev. E **55**, 3288 (1997).
- ⁵³S. Huang and D. E. Ingber, Nat. Cell Biol. **1**, E131 (1999).
- ⁵⁴L. Margulis, L. To and D. Chase, Science **200**, 1118 (1978).
- ⁵⁵K. Kullander, Trends Neurosci. **28**, 239 (2005).
- ⁵⁶M. V. Satarić, L. Budinski-Petković, I. Lončarević, and J. A. Tuszyński, Cell Biochem. Biophys. **52**, 113 (2008).
- ⁵⁷S. P. Gross, M. Vershinin and G. T. Shubeita, Curr. Biol. **17**, R478 (2007).
- ⁵⁸W. O. Hancock, Curr. Biol. **18**, R715 (2008).
- ⁵⁹G. Karp, S. Vogel, S. Kuhlmann-Krieg and K. Beginnen, *Molekulare Zellbiologie* (Springer-Lehrbuch) (2005).
- ⁶⁰B. Estrella, R. Estrella, J. Oviedo, X. Narvaez, M. T. Reyes, M. Gutierrez and E. N. Naumova, Ecuador. Environ. Health Perspect. **113**, 607 (2005).