



PAPER

Neuronal firing and DNA dynamics in a neural network

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Abstract

We study the mutual effects of neuronal electrical activity and DNA dynamics in a network of electrically coupled neurons with nearest neighbors communication. For that we develop by means of the coupling function method, a mathematical DNA-neuron model that can be considered as an extension of the simplified Hodgkin-Huxley models. Numerically, we explore the biological properties of the model with emphasis on local phase transitions and synchronous neural activity. Our results suggest that firing and coherent behavior of neural network are controlled by DNA dynamics. Conversely, neuronal activity induces DNA electrochemical denaturation. As a result, we expect that the prominent DNA-neuron model would be worth in controlling gene expression and neurodegenerative diseases in the sensory thalamus.

1. Introduction

The human brain is one of the largest and most complex organs in the body. It is made up of more than 100 billion of neurons that communicate in trillions of connections called synapses. The neuron represents an electrically excitable cell that receives, processes and transmits information through electrical and chemical signals. These unitary cells can connect to each other to form neural network. Eucaryote cells like neurons contain the molecule of desoxyribonucleic acid (DNA) confined in their cores. DNA is a thread-like chain of nucleotides carrying the genetic information used in the growth, development, functioning and reproduction of all known living organisms and many viruses. During the last decades, neuronal activity [1–28] and DNA dynamics [29–48] have received much interest because of their implications in most biological processes governing the behavior of all living cells, animals and plants.

The transmission of genetic information from one generation to another is only possible when the separation of double-stranded DNA (dsDNA) occurs by means of a biological process called thermal denaturation [30, 31]. Besides solvent temperature, environmental factors such as salt concentration [42], *pH* value [43] and external stretching [44] can also influence the local denaturation known as bubble formation in the closed double helix. In [45], authors have demonstrated that voltage bias can excite the base pairs (bp), hence increases the chemical activity of DNA that leads naturally in DNA bubble creation. Interestingly, they have shown that a voltage bias as high as 0.2V is capable of heating the DNA chain up to the melting phase, while for lower biases transient denaturation can occur but can not sustain. All these evidences aim to demonstrate that formation of denaturation bubbles and indirectly, complete denaturation of DNA molecule is a threshold phenomenon which arises from a minimum value of the excitation parameter. Very recently, many authors have shown that neuronal activity is in perfect correlation with the formation of DNA double strand breaks (DSBs) in neural network [27, 28]. For instance, Madabhushi *et al* [27] suggested that activity-dependent stimulation of neurons results in the formation of DNA DSBs at very specific location in the genome, particularly near early-response genes, while an enzyme such as Topoisomerase *IIβ* is necessary for activity-induced DSB formation. Accordingly neuronal activity can be used as an effective tool to excite the base pairs (bp) and enhance their

chemical activity up to the fully denaturation state. However, this new experimental approach remains even less explored theoretically.

External stimuli and inherent noise are known to be the potential precursors of neuronal activity in the brain, not only in the normal [5], but also in pathological brain activity such as epileptic seizures, mental depression, Parkinson's diseases and many others [26]. More remarkably, Xu and its coworkers have found the possibility for which spiking activity is generated and sustained by a small pacemaker in neural network [6]. We understand that neuronal activity also responds to the excitability threshold law. For example, an input current generates sustained neural activity only if it exceeds a threshold dimensionless value $I_s = 1.32$ [18].

The main dynamical behavior of a neural network that has received much attention from neuroscientists is the neuronal synchronization phenomenon [11, 15, 16, 19, 21–25]. In fact, also intrinsic properties of a neuron (its ion channel composition, morphology, capacitance and temperature) change its susceptibility to synchronization in a network [49]. As a threshold phenomenon, neuronal synchronization is known to be very sensitive to the fluctuations of some parameters such as: coupling strength [11, 16, 17], long-range parameter [11], time delay [15], spatial inhomogeneity stimulus [7] and noise [8, 17]. For example by studying the transitions to a synchronized state using a model of coupled bursting neurons, Dhamala *et al* [16] show that the increase of coupling strength increases incoherence first and then induces two different transitions to synchronized states, one associated with bursts at $\epsilon = 0.45$ and the other with spikes at $\epsilon = 0.50$, ϵ being the electrical coupling strength among neurons. The same authors in [15] have also shown that, at low coupling strength, $\epsilon = 0.1$ the value $\tau = 8.0$ of time delay could induce transition from asynchrony to synchrony state in a system of two electrically coupled neurons. In addition, Et  m   *et al* [11] have predicted that, neural network with long-range diffusive interactions displays a synchronous behavior when the electrical coupling strength of interconnected neurons reaches a minimal value $K_1 = 0.6$ for a strong long-range interaction ($g = 1$), where g characterizes the power-law long-range parameter. More recently, Xu *et al* [17] have studied synchronization between neurons coupled by memristor and found that, synchronization can be enhanced under memristor coupling strength and appropriate noise is also helpful for synchronization stability.

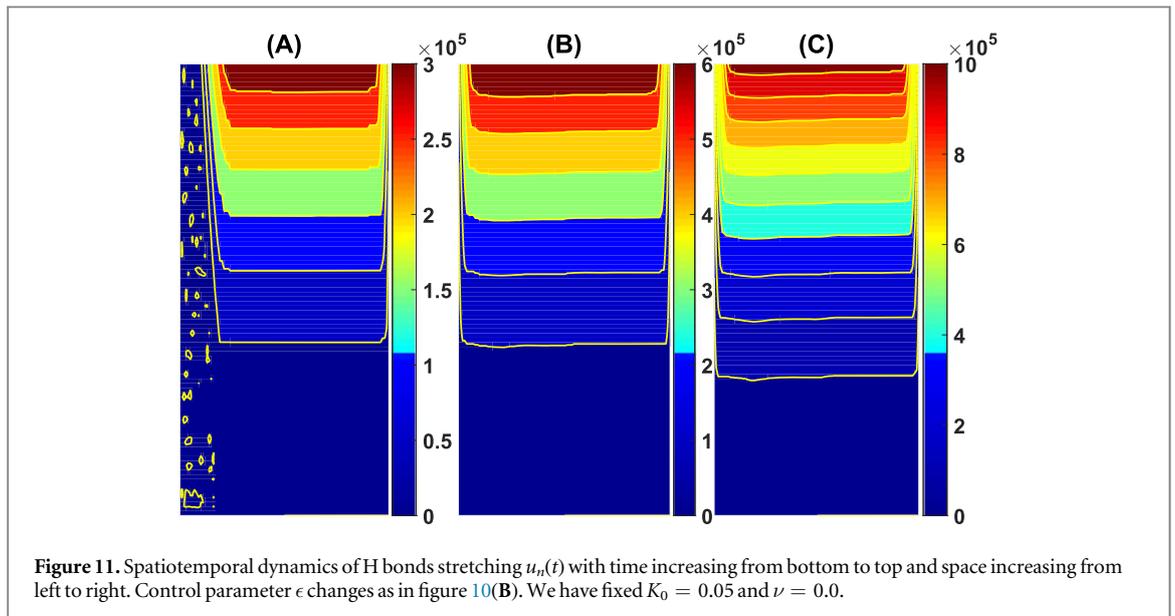
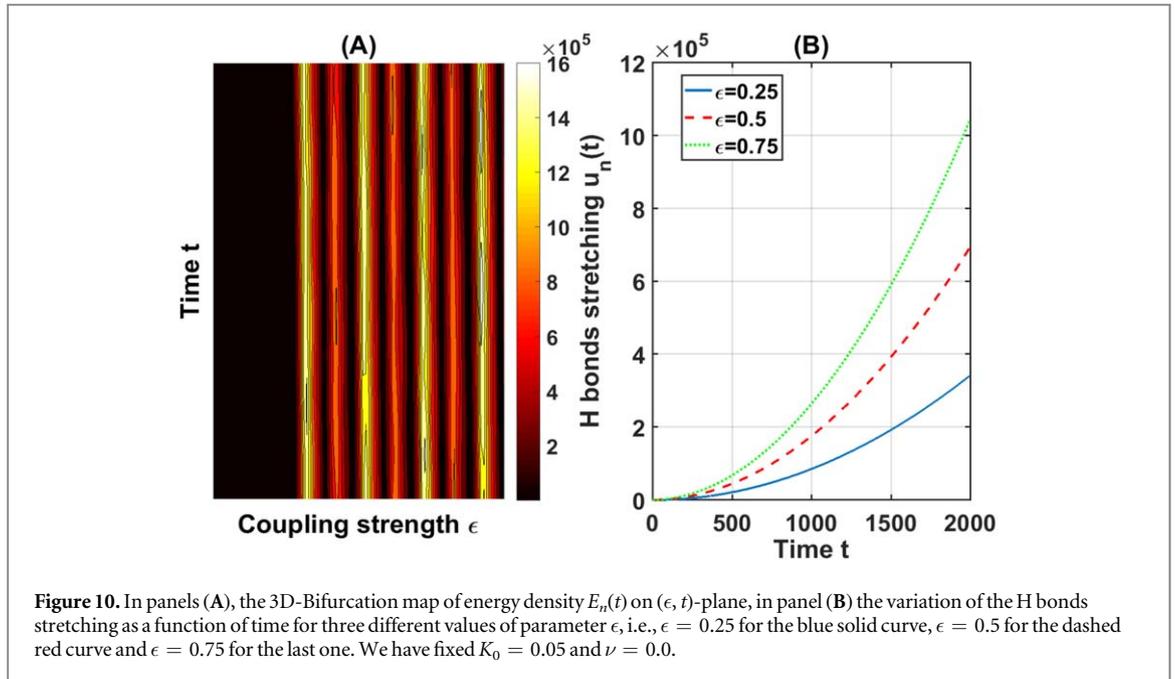
Presumably the circadian phenomenon [50–54] seems to be a better tool for understanding the interaction between DNA dynamics and neural activity. In most mammalian cells, a set of 'clock' genes and proteins forms a regulatory network that produces oscillations with a circadian period close to 24 hours [50]. Indeed, The master clock in the suprachiasmatic nuclei (SCN) is composed of numerous clock cells. The SCN receives sensory (light, temperature) information by a direct retinohypothalamic tract (RHT) to entrain the clock to the 24-h day. The entrained SCN, in turn, coordinates the timing of slave oscillators in other brain areas (for example, cortex) and in peripheral organs (for example, kidney and liver). Kunz *et al* [51] have demonstrated that a model of circadian rhythms based on locally coupled oscillators leads to a richer repertoire of dynamic patterns than a single oscillator model or a model based on global coupling. Along the same line, Bernard *et al* [53] have studied synchronization of circadian oscillators that combine intracellular and intercellular dynamics at the single-cell level and highlighted a dual role for the coupling factors within the SCN, both in maintaining the rhythmicity and in promoting the synchronization between the circadian oscillators. Consistent with the above, there is a better understanding of the physiological mechanisms underlying the interaction between DNA dynamics in the cell nucleus and neural activity. However, to our knowledge no theoretical study has addressed such an issue, despite the increasing experimental evidence for a link between these two important domains of biological information processing. Yet, far from being independent, the two phenomena appear rather complementary by the simple fact that they occur within a same biological entity which is the neuron. Therefore, we propose to study the interaction between neuronal activity and DNA dynamics in an electrically coupled neural network, with emphasis on the microscopic and macroscopic phase transitions that may occur in each subsystem.

To achieve this objective, we present in section 2 the theoretical DNA-neuron model where neuronal activity is coupled with DNA dynamics using radial and Gaussian activation functions. In section 3, the focus is on the numerical analysis of phase transitions observed either in the initiation and the support of action potential by the modulated dynamics of DNA, or in the phenomenon of electrochemical denaturation of DNA due to the phenomenon of nerve irradiation. In addition, we study the neuronal synchronization taking into account successively the continuous and periodic stimulations. In the former case no synchrony state is realized, whereas the latter one give rise to some reliable synchronization criteria in term of both electromechanical coupling strength and stimulation period. Finally, section 4 gives some concluding remarks and perspectives.

2. DNA-neuron interaction and mathematical model

2.1. Physiological DNA-neuron interaction

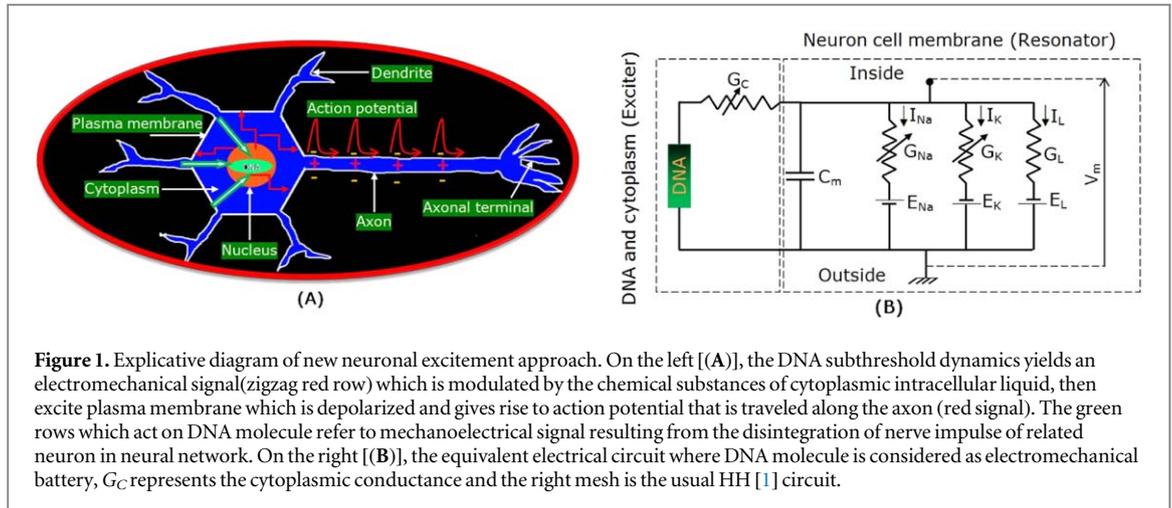
Here we argue that in a vivo process, interaction between DNA molecule and neuron could be result to mutual effects of DNA dynamics and neural activity through the cytoplasmic gap that separates nucleus and plasma



overview on the H bonds breaks of hundred nucleotides which account dsDNA induced by neuronal activity is presented in figure 11 while spatiotemporal dynamics of H bonds stretching is surfed with increasing coupling parameter ϵ as in figure 10(B). Therein, we observe how the plane waves split into multisolitons-like excitations which draw different levels of denaturation bubbles in dsDNA. These modulated structures are known to bring more visibility in any phase transition occurring in a dynamical systems and to be very crucial in many biological processes such as replication and transcription phenomena, transport and energy localization within protein or nerve impulse propagation [9, 10, 12, 31, 33–36, 38, 40]. In summary, a modulated subthreshold neuronal activity causes H bonds breaks. Therefore the electrochemical denaturation of the DNA molecule is triggered thus resulting in expression of early-response genes in neurons during transcription and replication processes [27].

4. Concluding remarks

In conclusion, reciprocal effects of neuronal activity and DNA dynamics in neural network were studied where a DNA-neuron mathematical model has been developed by means of coupling functions method. Then through numerical simulations, biological properties of this model have been explored and can be summarized as



membrane of neuron. Indeed, in the induction process of neuronal activity by DNA signaling the free dynamics of DNA which is confined in the nucleus releases an electromechanical signal which after being modulated by the cytoplasmic proteins stimulates the plasma membrane. When the stimulus intensity reaches a certain threshold, the plasma membrane depolarizes itself by emitting an action potential which propagates along the axon in agreement with the self-depolarization process. In addition, as in the Homeostatic processes [55, 56] the underlying activity of DNA could lead with a certain kinetics of several minutes to the expression of ion channels within the cell membrane which would lead to a change of the conductances in the classical Hodgkin-Huxley (HH) model. In the other direction, we provide that each neuron receives nerve impulses from its nearest neighbors, which are always modulated by the cytoplasmic proteins before irradiating the molecule of DNA. In fact the intracellular Ca^{2+} computes the average neuronal spike activity and then in turn induces signalling cascades which activate DNA supercoils. Physiologically, the process of nerve irradiation of DNA can lead to the activation of Topoisomerase $II\beta$, an enzyme responsible for removing DNA supercoils during transcription and DNA replication processes thus resulting in the expression of early-response genes within neurons [27]. In figure 1, we present the schematic model describing the mutual interaction between DNA and neuron, although the emphasis is on the generation of nerve impulse.

2.2. A DNA-neuron model

Now we consider a network of N neurons electrically coupled with nearest neighbors interactions. Each neuron includes one DNA molecule which obeys to a Watson-Crick pairing [57]. To simplify, we also suppose that the double stranded DNA (dsDNA) possesses N identical bps coupled among them by nearest neighbors interactions. According to the previous physiological analysis, both subsystems interact via the modulated signals which can be considered as the coupling functions. Hence the DNA-neuron model reads:

$$\begin{aligned}\dot{\mathbf{x}}_n &= \mathbf{F}_1(\mathbf{x}_n) + \nu \mathbf{G}_1(u_n), \\ \ddot{u}_n &= F_2(u_n) + \epsilon G_2(x_n),\end{aligned}\quad (1)$$

where \mathbf{x}_n represents a dimensionless dynamical vector variable describing neuronal electrical activity for site n in N -oscillator array, u_n is the transverse displacement also dimensionless, of the bp from its equilibrium state. \mathbf{F}_1 and F_2 are vector and scalar fields describing the isolated dynamics of the membrane potential for the first and the free stretching of the bp for the latter. \mathbf{G}_1 and G_2 are the coupling function used to modulate neuronal activity with DNA dynamics and reciprocally. ν represents the electromechanical coupling strength enabling to activate (or deactivate) the coupling function \mathbf{G}_1 in order to stimulate the emission of action potentials while ϵ designates the mechano-electrical coupling strength used to sustain G_2 in the DNA electrochemical denaturation process. The reader can realize that when these two coefficients i.e. ν and ϵ cancel each other simultaneously, the dynamics of the two oscillators become independent. Likewise, the coupling strengths ν and ϵ give us a quantitative measure of the information flow between dsDNA and cell membrane. Otherwise ν and ϵ characterize the reversibly conversion rates of u_n -variable to x_n -variable and can be also regarded as the scaling parameter of the coupling functions \mathbf{G}_1 and G_2 . To further, an emphasis will be paid on the nature of dynamical and coupling functions that contain all information about the properties of model of equation (1). Although the equivalent electrical circuit (figure 1(B)) involving neuronal activity is represented according to the HH model, it should be noted that several simplified models [2–4] have been derived from this basic model in order to faithfully reproduce the rich activity of biological neurons. Among them we have adopted the HR model [2] known to exhibit a multi-time-scale spike-burst behavior which become chaotic for $2.92 < I_{ext} < 3.40$ [15], I_{ext} being the external stimulus current which will be set to 0 throughout this work. Accordingly, the vector field \mathbf{F}_1

which includes the fast and the slow variables is given by:

$$F_1(\mathbf{x}_n) = (y_n - ax_n^3 + bx_n^2 - z_n + K(x_{n+1} - 2x_n + x_{n-1}) + I_{ext}, c - dx_n^2 - ey_n, r[s(x_n - x_e) - z_n]), \quad (2)$$

so that the vector state $\mathbf{x}_n = (x_n, y_n, z_n)$ where x_n is the membrane potential, y_n is associated with the fast current Na^+ and z_n with the slow current, for example Ca^{2+} . K is the synaptic coupling strength that connects the nearest-neighbors neurons in the network while $a = 1.0$, $b = 3.0$, $c = 1.0$, $d = 5.0$, $e = 1.0$, $s = 4.0$, $r = 0.006$ and $x_e = -1.60$ are the generic constants of HR model. In recall, x_n and y_n are fast variables, z_n is a slow variable, r is the ratio of fast/slow time scales. On the other hand, several models have been developed [31, 33, 34] without being exhaustive, in order to describe different biological, physical and chemical processes in which DNA is involved. Here we have paid our attention on the Joyeux and Buyukdagli (JB) model [34] in which the stacking interaction potential is finite in contrary to the Peyrard-Bishop-Dauxois (PBD) model [33] where such interaction potential is infinite. Very recently Yao *et al* [35] have showed that the JB model supports envelope solitons and discrete breathers that have been demonstrated to be very crucial in the transport and localization energy processes [43, 36–38, 42]. The Hamiltonian of an homogenous JB model reads:

$$H = \sum_n \left[\frac{m\dot{r}_n^2}{2} + D(1 - e^{-\alpha r_n})^2 + W(r_n, r_{n+1}) \right], \quad (3)$$

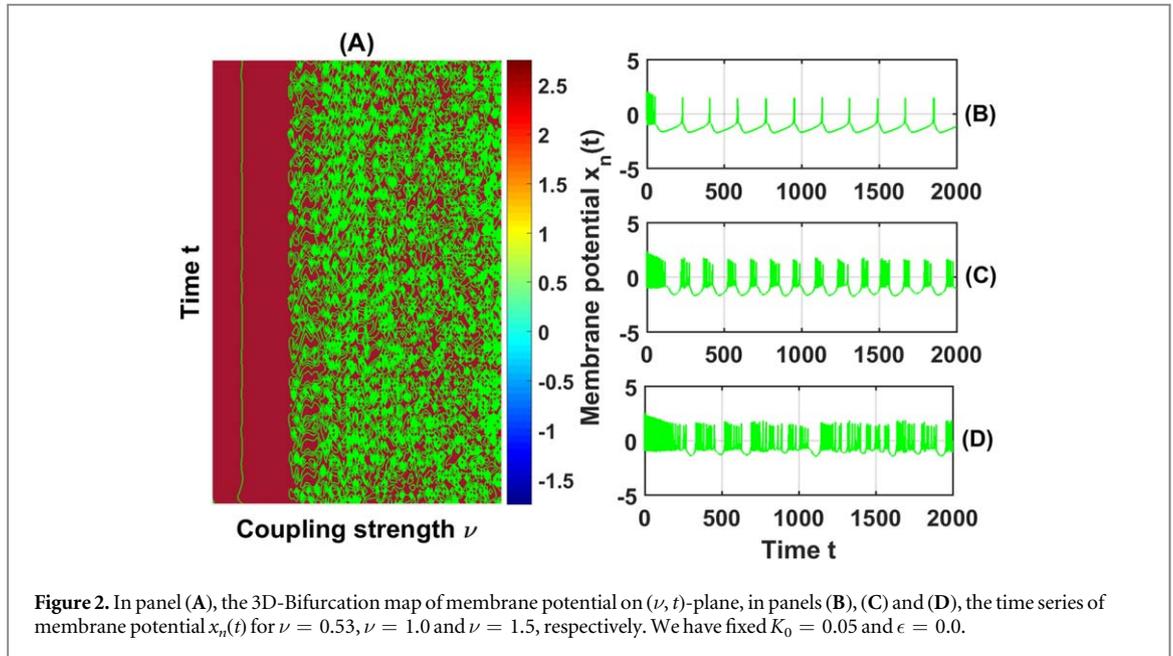
where the first and second terms indicate respectively, the kinetic energy of bp with, m as the reduced mass of the bases and the on-site Morse potential where D denotes the depth and α the width of this potential. The last term given by $W(r_n, r_{n+1}) = K_\beta(r_n - r_{n+1})^2 + \frac{\Delta H}{2}(1 - e^{-\beta(r_n - r_{n+1})^2})$ represents the stacking interaction potential within, $\frac{\Delta H}{2}$ is the finite stacking energy, K_β is the harmonic coupling strength between the nearest-neighbor bases of the same strand, whereas parameter β is homogeneous to the inverse of a length squared. Finally, variable r_n indicates the transverse stretching of H bond connecting the n^{th} bp. Then by means of Hamiltonian canonical equations the dynamical function F_2 is expressed by: $F_2(u_n) = -\partial H'/\partial u_n$, with H' and u_n being the dimensionless forms of H and r_n , respectively. The JB model parameters are given by: $m = 300 \text{ amu}$, $D = 0.04 \text{ eV}$, $\alpha = 4.45 \text{ \AA}^{-1}$, $\Delta H = 0.44 \text{ eV}$, $\beta = 0.1 \text{ \AA}^{-2}$, $K_\beta = 10^{-5} \text{ eV} \cdot \text{\AA}^{-2}$. In addition, since the exchange of information flow between the two subsystems is randomly performed at different time scales, a slower time scale for the transmission of DNA signaling and a fast time scale for the nerve pulse irradiation process, the coupling functions, $\mathbf{G}_1(u_n)$, in the radial form and $G_2(x_n)$, in the Gaussian form, should be defined as $\mathbf{G}_1(u_n) = (\sqrt{2\pi} \exp(u_n^2/2), 0, 0)$ and $G_2(x_n) = \sqrt{2\pi} \exp(-x_n^2/2)$. The different components of \mathbf{G}_1 indicates that DNA signaling only modulates membrane potential patterns without directly affects variables y_n and z_n . It should also be noticed that the coupling functions have been chosen so as to ensure maximum efficiency of the computations carried out either by a neural network or by a DNA oscillator. In general in a given network, the input signals are simply summed [20], thereby giving a helpful internal signal, called cumulative neural stimulation or postsynaptic stimulation. This signal can also be defined as a net value. In reminder, there exist many different coupling functions [20] ranging from linear, sigmoid, threshold, stochastic, Gaussian or radial form which ensure an information exchanges from one biological system to another. While the former are ubiquitous in many areas of bioengineering research, the last two are still almost unexplored and appear in this work to bring information about mutual effects between DNA dynamics and neuronal activity. In agreeing with the above, the DNA-neuron model reads:

$$\begin{aligned} \dot{x}_n &= y_n - ax_n^3 + bx_n^2 - z_n + K(x_{n+1} - 2x_n + x_{n-1}) + \nu\sqrt{2\pi} \exp(u_n^2/2), \\ \dot{y}_n &= c - dx_n^2 - ey_n, \\ \dot{z}_n &= r[s(x_n - x_e) - z_n], \\ \ddot{u}_n &= K_h(u_{n+1} - 2u_n + u_{n-1}) + K_s[(u_{n+1} - u_n)e^{-\sigma(u_{n+1} - u_n)^2} - (u_n - u_{n-1})e^{-\sigma(u_n - u_{n-1})^2}] \\ &\quad + 2e^{-u_n}(e^{-u_n} - 1) + \epsilon\sqrt{2\pi} \exp(-x_n^2/2). \end{aligned} \quad (4)$$

The dimensionless model of equation (4) constitutes a new self-sustained biological oscillator where neural activity and DNA dynamics are mutually induced. The term $\nu\sqrt{2\pi} \exp(u_n^2/2)$ plays the role of exciting current and reports for global effect of DNA dynamics on neural activity, whereas the term $\epsilon\sqrt{2\pi} \exp(-x_n^2/2)$ can be viewed as applied force due to global effect of neural activity on DNA dynamics. When $\nu = 0$ and $\epsilon = 0$ cancel each other simultaneously we find uncoupled generic HR and JB models. In the following, the so-called DNA-neuron model will be explored in the different phase transitions, including firing activity and cooperative behavior of neural network and DNA electrochemical denaturation.

3. Numerical results and discussion

Here we show that the model described by equation (4) is more suitable to explain: (1) the stimulation of neuronal activity by the modulated dynamics of DNA, (2) incoherent and coherent behavior of neural activity and (3) the phenomenon of electrochemical denaturation of DNA molecule when it is continuously irradiated



by the nerve impulses of afferent neurons. For this purpose, the system of equations (4) was integrated using the fourth-order Runge-Kutta method with periodic boundary conditions since we consider a cyclic network where neurons communicate with each other via the nearest-neighbor interaction. Initial conditions obey to the form of [46] with time step $\Delta t = 10^{-2}$ and $N = 100$ as a total oscillators number that are interact in each subsystem.

3.1. Neurons firing induced by DNA dynamics

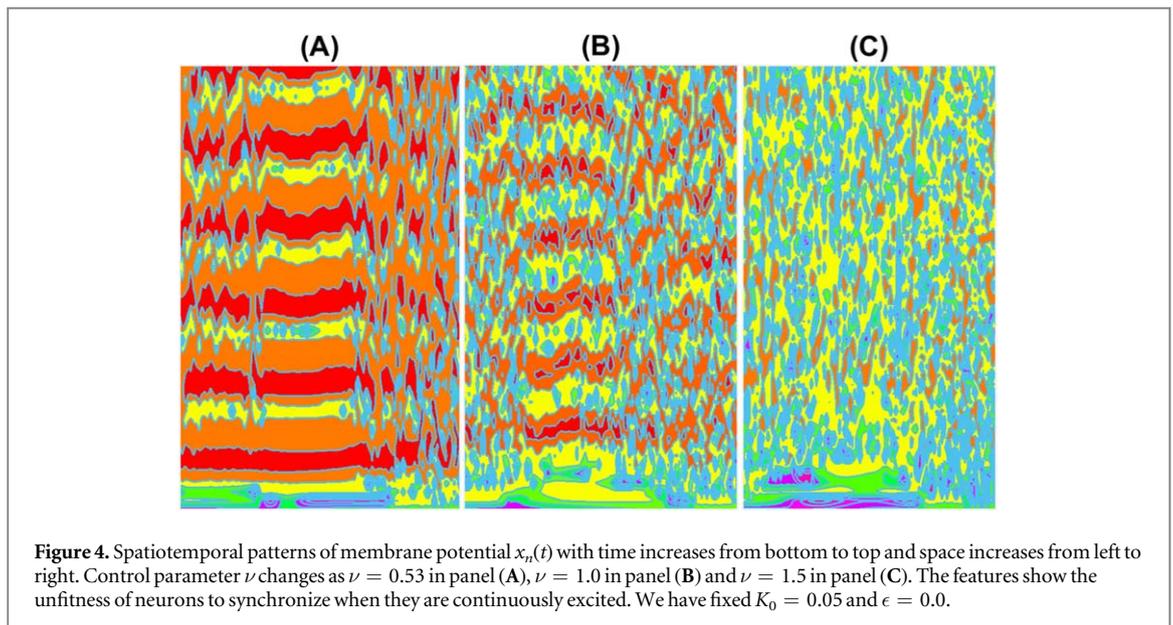
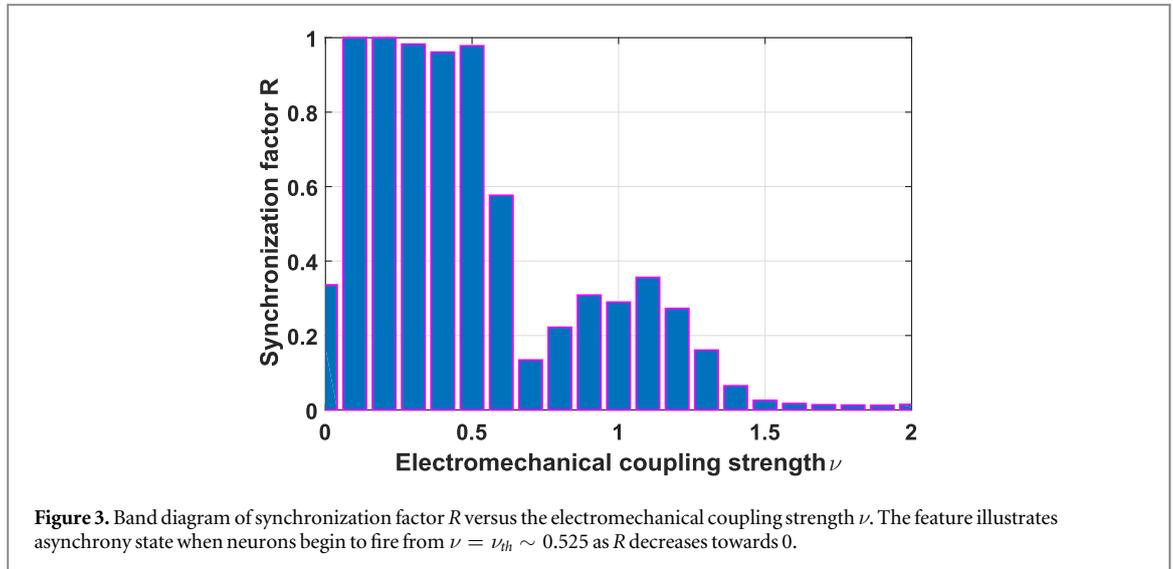
For this, we activate the coupling function G_1 by varying the coupling strength ν in the range $[0; 2]$ while setting $\epsilon = 0$. The results are shown in figure 2 where the bifurcation diagram of the membrane potential $x_{50}(t)$ is displayed on panel (A) with time increases from bottom to top and coupling strength increases from left to right. In panels (B) $\nu = 0.53$, (C) $\nu = 1.0$ and (D) $\nu = 1.5$, time series of membrane potential of the selected node are presented. It is found that regardless of time, the membrane potential bifurcates from the critical value $\nu_c = 0.525$, that is to say when $\nu \geq \nu_c$ neurons begin to fire with formation of green nonlinear patterns while no firing is expected elsewhere (red area). Physiologically, this phenomenon correlates perfectly with the all-or-nothing law that governs the generation and conduction of action potential. In another view, we can argue that as long as the intensity of the signal delivered by base pairs vibrations and modulated by the cytoplasmic substances remains below a certain threshold, no neuronal activity is possible. Along the same line, the observed time series highlight the effect of the intensity of the stimulus on the shape of the membrane potential which is characterized by spiking regime for $\nu = 0.53$, bursting regime for $\nu = 1.0$ and chaotic regime when $\nu = 1.5$. These results are in perfect agreement with those obtained in the [9–12] where neurons are commonly excited by the external current I_{ext} . In this case, it has been established that [18] spiking, bursting and chaotic modes are obtained when, $1.32 < I_{ext} < 1.57$, $1.57 < I_{ext} < 2.92$ and $2.92 < I_{ext} < 3.4$, respectively. In short neural network exhibits a routine multi-time-scale activity under DNA dynamics in the absence of external stimuli. This consolidates the reliability of the mathematical model developed in this paper as well as the realistic choice of the coupling function G_1 that modulates neuronal activity with DNA dynamics.

3.2. From asynchronous to synchronous neural network

There are several approaches to study the synchronization phenomenon [11, 15, 16, 25, 58, 59]. In this framework the spatial synchronization factor R [25] is adopted and calculated as follow:

$$R = \frac{\langle F^2 \rangle - \langle F \rangle^2}{\frac{1}{N} \sum_{n=1}^N [\langle x_n(t)^2 \rangle - \langle x_n(t) \rangle^2]}, \quad F = \frac{1}{N} \sum_{n=1}^N x_n(t), \quad (5)$$

where $\langle \cdot \rangle$ denotes the time averaging. The value of R is between 0 and 1, and it increases with decreasing average membrane potential errors. That is to say, perfect synchronization is realized when the synchronization factor is close to 1 and non-perfect synchronization is reached when the factor of synchronization is close to 0. Recently, a large number of neural stimulation shapes, including deep brain stimulation [60–62], coordinated reset stimulation paradigm [63], charge-balanced biphasic pulses [64] have been proposed either for the treatment of Parkinson's disease [60–63] or for the treatment of epileptiform activity [64]. In this study a new pathway based



on both continuous and periodic stimulations of neural activity is proposed to control such brain seizures, especially using DNA dynamics as a potential neurostimulator. In the first case, electromechanical coupling strength ν will take a continuous value $\nu_0 > \nu_c$ throughout time, whereas in the second case it will periodically take two values 0 and ν_0 .

Hence in the first case, we have obtained the results of figures 3–4. Figure 3 pictures synchronization factor R versus parameter ν . Although for some values ($0.1 \leq \nu \leq 0.5$) of this parameter, R tends to 1, it is impossible to speak about of synchronization because for these values, neurons have not yet started to fire according to the firing criterion $\nu > \nu_c = 0.525$. Remarkably when neurons begin to fire, R decreases from 0.5766 to a value close to 0 and network remain in an asynchronous state. All these assumptions are confirmed in figure 4 where spatiotemporal patterns of membrane potential are surfed in the (n, t) -plane under the variation of ν as in (A) $\nu = 0.53$, in (B) $\nu = 1.0$ and in (C) $\nu = 1.5$. Therein, we observe how intensification of spikes frequency with increase of coupling strength ν increasingly produces robust and incoherent patterns, which indubitably leads to an asynchronous state.

Consider now the case where each neuron is regularly excited after and during a time interval T_0 . Explicitly, we set a value ν_0 of ν taken in the neuronal firing domain, then we subdivide the total duration of the simulations t into m regular and equal intervals with amplitude T_0 , that is to say $t = mT_0$. Thus, in first period $\nu = \nu_0$, in the second $\nu = 0$, and so on. The panels of figure 5 give more understanding about the stimulation process where the coupling strength ν adopts the shape of a square signal on the left panels and the corresponding time series of membrane potential are plotted in the right panels. From top to bottom, T_0 is equal to 25, 50 and 100,

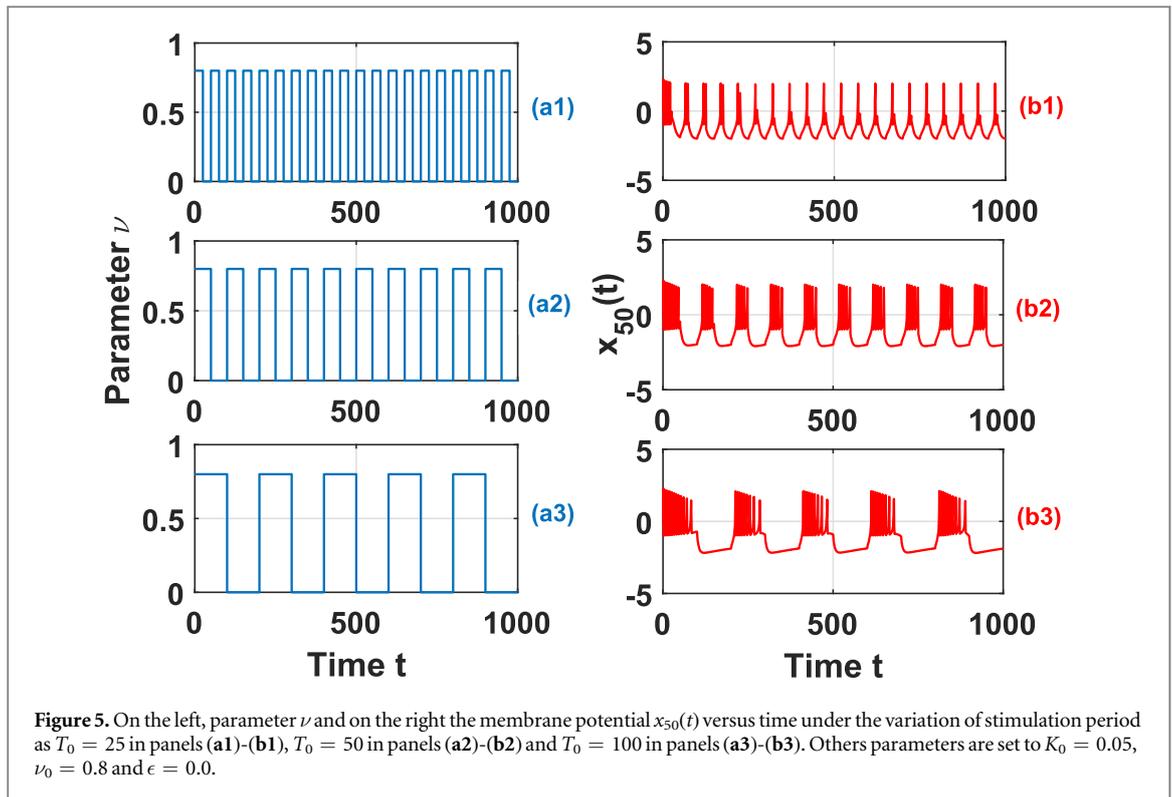


Figure 5. On the left, parameter ν and on the right the membrane potential $x_{50}(t)$ versus time under the variation of stimulation period as $T_0 = 25$ in panels (a1)-(b1), $T_0 = 50$ in panels (a2)-(b2) and $T_0 = 100$ in panels (a3)-(b3). Others parameters are set to $K_0 = 0.05$, $\nu_0 = 0.8$ and $\epsilon = 0.0$.

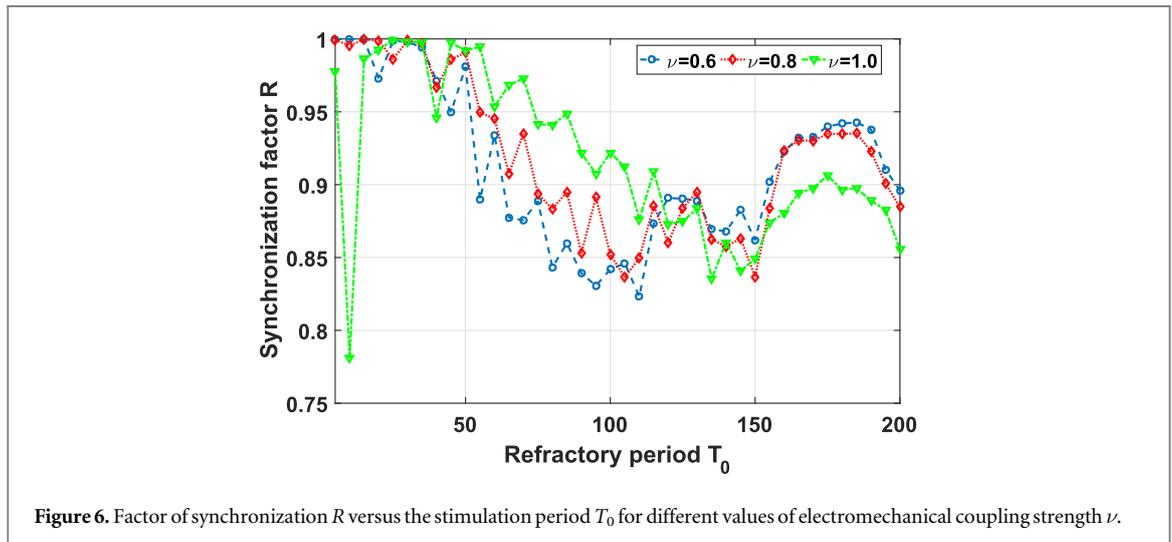
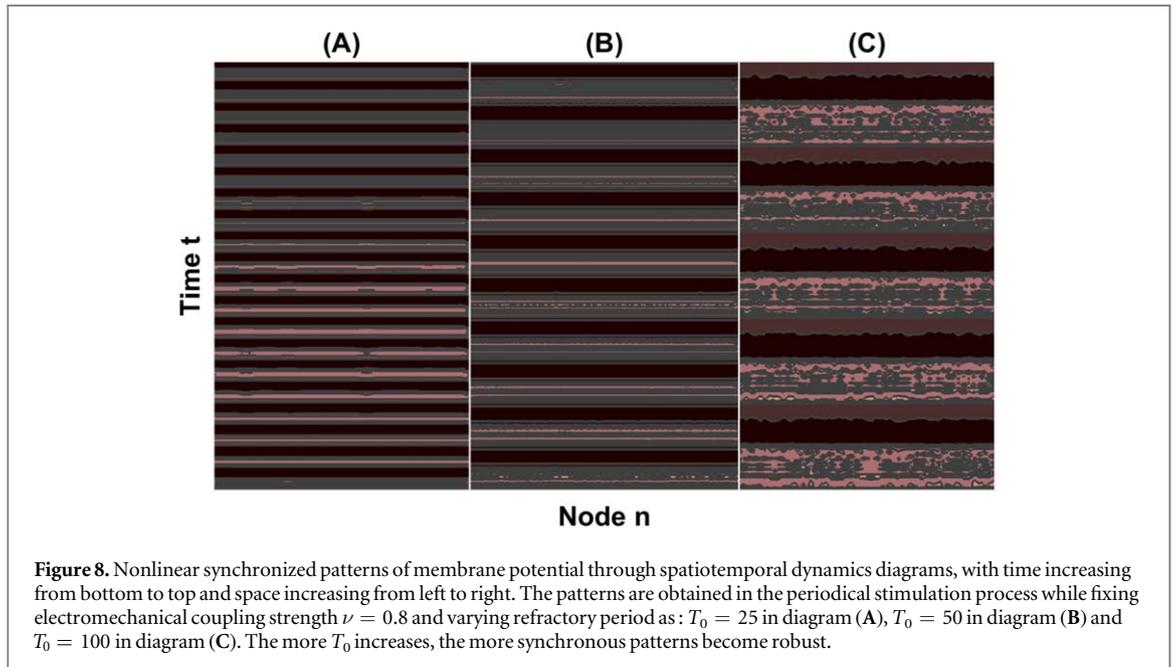
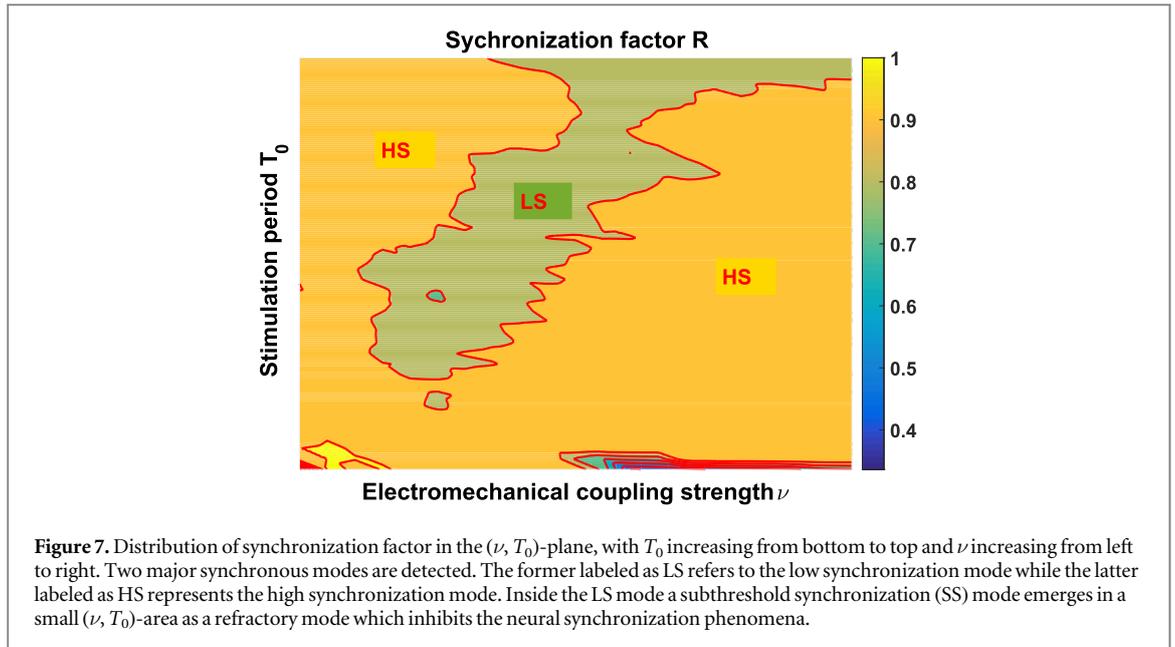


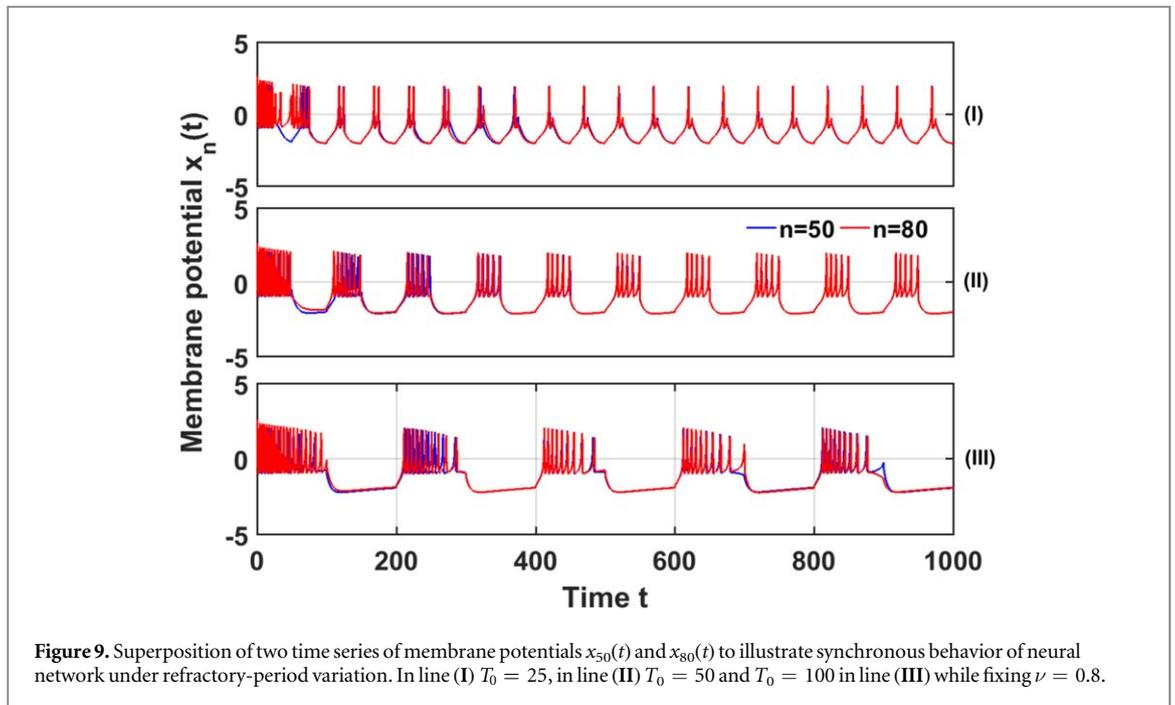
Figure 6. Factor of synchronization R versus the stimulation period T_0 for different values of electromechanical coupling strength ν .

respectively. Physiologically this approach based on the periodical stimulation of nerve cells is logical since such cells are characterized by a refractory period during which no stimulus can produce an action potential. To further, it is important to track the behavior of the synchronization factor when the stimulation period T_0 increases in order to have a real insight on the neural network cooperativity degree. Interestingly, the curves of figure 6 show how the synchronization factor almost always remains above a suitable value ($R = 0.8232$) when the stimulation period T_0 increases for synchronization phenomenon to be achieved regardless the value of coupling parameter ν . Therefore better than the coupling strength, the stimulation period appears here as a trustworthy parameter for controlling the neuronal synchronization induced by the dynamics of the DNA in neural network. To be convinced, the synchronization factor has been surfed in figure 7 versus the coupling strength ν and the stimulation period T_0 . Therein, two main synchronization modes have been detected, the low synchronization (LS) mode for $0.8 < R < 0.9$ and the high synchronization (HS) one for $0.9 \leq R \leq 1$. In the LS mode, the neurons synchronize weakly while for the HS mode, they synchronize strongly. Inside the LS mode we found a subthreshold synchronization (SS) mode delimited by a small region of (ν, T_0) -values. In the (SS) mode, synchronization phenomenon decreases and suggests that it is an inhibitory mode. In figure 8, spatiotemporal dynamics of membrane potential is presented under periodical stimulation process while fixing



$\nu = 0.8$ and increasing parameter T_0 as $T_0 = 25$ in panel (A), $T_0 = 50$ in panel (B) and $T_0 = 100$ in panel (C). We can notice that the couples $(\nu = 0.8, T_0 = 25)$ and $(\nu = 0.8, T_0 = 50)$ belong to the HS mode whereas the couple $(\nu = 0.8, T_0 = 100)$ belongs to the LS mode. Accordingly we obtain an almost perfect and global synchronization for the first two couples and a partial and less reliable synchronization for the last one. Moreover, the greater the period of stimulation becomes important, the more the synchronization patterns become robust, reflecting the ability of neurons to change their way of communicating according to the constraints to which they are subjected. More explicitly, a long period of neuronal excitation can lead to a global and perfect synchronization with a large flow of information to be transmitted. Similar results are presented in figure 9 where the time series of membrane potentials $x_{50}(t)$ and $x_{80}(t)$ are held on under the effect of the increase of the stimulation period while still fixing $\nu = 0.8$. From top to bottom, we observe the synchronization of spikes, regular and irregular bursts as T_0 increases.

The well-known implications of the neuronal synchronization phenomenon is the emergence of neurodegenerative diseases within cerebral tissues in an abnormal process [15, 16, 26]. However, many studies aimed at controlling these neurological pathologies have received increasingly favorable feedback. For instance, Rubin *et al* have successfully proposed an elimination mechanism of pathological thalamic rhythmicity in a



Computational Model by high frequency stimulation of the subthalamic nucleus [65]. Indeed, it was shown that deep brain stimulation works by replacing pathologically rhythmic basal ganglia output with tonic, high frequency firing. Additionally, Fan *et al* studied the possibility of disinhibition-induced transitions between absence and tonic-clonic epileptic seizures [66]. They found that disinhibition-induced transitions can lead to stable tonic-clonic oscillations as well as periodic spike with slow-wave discharges, which are the hallmark of absence seizures. Interestingly, Chen *et al* [67] have demonstrated that the typical absence seizure activities can be controlled and modulated by the direct GABAergic projections from the substantia nigra pars reticulata to either the thalamic reticular nucleus or the specific relay nuclei of thalamus, through different biophysical mechanisms. They conclude that both decreasing and increasing the activation of substantia nigra pars reticulata neurons from the normal level may considerably suppress the generation of spike-and-slow wave discharges in the coexistence region. By showing that the continuous and periodical DNA dynamics within each neuron produces asynchronous patterns on the one hand and an essentially coherent neuronal activity on the other hand, we thus make a significant contribution in the effective control of certain cerebral pathologies such as epileptic seizures or Alzheimer's and Parkinson's diseases.

3.3. Neural activity induces DNA fast denaturation

To quantify the impact of nervous radiation on DNA, it is sufficient to activate the coupling function G_2 via the increase of coupling strength ϵ . In that respect, we choose energy density $E_n(t)$ as the bifurcation function. Thus, phase transitions arise in DNA molecule when the denaturation criterion $E_n(t) > 1$ is verified. Accordingly, it is found that the denaturation condition is fulfilled for a set of values of ϵ such that $\epsilon > \epsilon_c$, with $\epsilon_c = 0.245$. As it is shown in figure 10(A), energy density is surfed as a function of time t and coupling parameter ϵ . Therein, emergence of localized structures appears from a certain threshold value $\epsilon \sim 0.245$ of parameter ϵ . This threshold value characterizes the onset and ongoing dsDNA denaturation process where the threshold value of energy density is largely exceeded. Remarkably $E_n(t) \rightarrow 16 \times 10^5$ when $\epsilon \rightarrow 1$. A similar results have been obtained by Sadjo and its coworkers [46] in the context of the energy localization in zigzag molecular chains investigation and explain the fact that, in DNA molecule, energy density is distributed in a discontinuous way. The most interesting result is presented in figure 10(B) where H bonds stretching is plotted versus the time under the variation of neuronal activity trough parameter ϵ . Therein, we observe the denaturation curves similar to those obtained by Peyrard and Bishop [31] while studying statistical mechanics of a DNA denaturation with the temperature dependence of the inter-strand separation. In their investigation, they found the minimal temperature from which DNA denaturation appeared. While comparing their results with those presented here, we can conclude that DNA denaturation corroborates with a threshold phenomena while both temperature in (PB) and coupling strength in a so-called DNA-neuron models play the same role although in a different ways. Further, the curves obtained in [31] grow slowly than those which are investigated here in which the H bonds stretch grows roughly with a higher magnitude (10^6 , approximatively). These remarkable differences suggest that electrochemical denaturation with neuronal activity is faster than the thermal denaturation. In addition, an

follows: (1) neuronal activity is induced and sustained by DNA modulated dynamics from a certain threshold value $\nu_c = 0.525$ of electromechanical coupling strength, (2) in a neurons ensemble with nearest neighbors interaction, neuronal activity produces DNA electrochemical denaturation from a certain threshold value $\epsilon_c = 0.245$ of mechano-electrical coupling strength thus supporting some biological processes such as replication and transcription where DNA molecule is involved, (3) in the continuous stimulation process, DNA dynamics produces a strongly incoherent structures in neural network thus blocking a synchronous activity of the network, while (4) in the periodical stimulation process, perfect and global neural synchronization are achieved with emergence of two synchronization modes namely the HS and the LS modes. Our results argue that at constant frequency regime, DNA chemical activity inside each neuron could be used to prevent some cerebral pathologies such as epileptic seizures, Alzheimer's and Parkinson's diseases just to cite a few. However, with a variable frequency regime, the chemical activity of DNA induces a synchronous neuronal activity that supports both working memory and long-term memory and acts by facilitating neural communication and by promoting neural plasticity [22] in normal situation, while such neuronal rhythmic adjustments are known to accentuate the injuries brain risk in abnormal process. These findings seem to be in perfect agreement with those found in [53] where authors have investigated rhythmicity induced by the synchronization of circadian oscillators in the SCN. Likely, a new DNA-neuron model that does not include the effects of long-range on neuronal communication or time delay impacts in synaptic signal transmission, appears very prominent for imminent studies.

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