The influence of ion concentrations on the dynamic behavior of the Hodgkin–Huxley model-based cortical network

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Abstract Action potentials (APs) in the form of very short pulses arise when the cell is excited by any internal or external stimulus exceeding the critical threshold of the membrane. During AP generation, the membrane potential completes its natural cycle through typical phases that can be formatted by ion channels, gates and ion concentrations, as well as the synaptic excitation rate. On the basis of the Hodgkin–Huxley cell model, a cortical network consistent with the real anatomic structure is realized with randomly interrelated small population of neurons to simulate a cerebral cortex segment. Using this model, we investigated the effects of Na^+ and K^+ ion concentrations on the outcome of this network in terms of regularity, phase locking, and synchronization. The results suggested that Na^+ concentration does slightly affect the amplitude but not considerably affects the other parameters specified by depolarization and repolarization. K^+ concentration significantly influences the form, regularity, and synchrony of the network-generated APs. No previous study dealing directly with the effects of both Na^+ and K^+ ion concentrations on regularity and synchronization of the simulated cortical network-generated APs, allowing for the comparison of results obtained using our methods, was encountered in the literature. The results, however, were consistent with those obtained through studies concerning resonance and synchronization from another perspective and with the

information revealed through physiological and pharmacological experiments concerning changing ion concentrations or blocking ion channels. Our results demonstrated that the regularity and reliability of brain functions have a strong relationship with cellular ion concentrations, and suggested the management of the dynamic behavior of the cellular network with ion concentrations.

Keywords Cortical network · Hodgkin–Huxley model · Ion concentrations · Dynamic behavior · Regularity · Synchronization

Introduction

A neuron cell membrane generates action potentials (APs) in the form of very short pulses when the cell is excited by any internal or external stimulus that exceeds the critical threshold of the membrane. During AP generation, the membrane potential completes its natural cycle through typical processes such as depolarization, repolarization, and hyperpolarization. In conventional terms, APs are formed by the dynamics of ion channels and gates, intracellular and extracellular Na–K ion balancing mechanisms (Dayan and Abbott 2001), and Na^+ , K^+ , Ca^{2+} , and Cl^- ion concentrations. To simulate these biophysical events, a few theoretical models based on the biological cell model experimentally obtained by Hodgkin and Huxley (1952), have been introduced in neuroscience. The Hodgkin–Huxley (HH) model is known as the best model in representing many features of the biological neuron cell (Koch et al. 2003; Cressman et al. 2009). In many of these mathematical models, ion concentration rates are considered constant, which for some reasons may not be absolutely realistic (Cressman et al. 2009; Barreto and Cressman 2011).

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In spite of the existence of a powerful homeostasis endowed with astrocytes (Volman et al. 2012), disorders that affect brain functions could occur in the mechanism of biological cells (Cressman et al. 2009; Barreto and Cressman 2011). Various neurological diseases such as epilepsy, spreading depression, stroke, hypoxic encephalopathy, migraine, and other brain function-sustaining stabilities are linked to the administration of ion activities (Kager et al. 2000; Fröhlich et al. 2008; Krishnan and Bazhenov 2011). Nevertheless, the behavior of neuronal cells is in some manner modulated by many neuronal processes including disorders that collectively format APs and consequently the electrical activity of the brain. In line with this approach, it may be possible to simulate neurological disorders through computational neuronal (cortical) network models simply by modifying ionic currents and concentrations and synaptic connections (Kager et al. 2000; Krishnan and Bazhenov 2011). Apart from spike formation and axonal and synaptic transmission behavior, cortical network models should possess stability as well as robustness, both of which are required for sensing, evaluating, and storing information in the memory (Fares 2010).

Designing a huge complex network that faithfully simulates the mammalian cortex, reflecting its structure while taking into account thousands of neurons and tens of thousands of synaptic links possessing somehow irregular/random connectivity, is almost impossible. Cortical networks are therefore designed with a set of equations employing some parameters configured on a probabilistic basis. In some studies the unestimated neuronal processes that may occur from minor cellular disorders, synaptic links, ion channels and gates, etc., are considered as channel noise in these equations. Until date, using various noise-added models, the effect of the noise level on the outcome of particular neuronal networks (small-world or scale-free topologies) in terms of synchronization, consistency, and resonance has been analyzed. Through these studies, it has been reported that the noise from under-threshold finite stochastic dynamic components (such as the internal mechanism of voltage-gated ion channels, linkage rates in between neurons and frequency of the pacemaker, frequency of the applied under-threshold excitation, and network topology) in the form of small waves exerts a considerable effect on the dynamics (such as spatial coherence, stochastic resonance, and first spike latency) of neuronal networks (Ozer et al. 2009a, b, c; Sun et al. 2011). The noise coming from synapses or ion channels in HH neural networks, such as the noise with regular behavior in various non-linear dynamic systems, can cause stochastic coherence as well as resonance (Sun et al. 2008, 2011). Wang et al. (2008a, 2010a) showed that in a HH network that possesses Gaussian noise (neither temporally nor spatially correlated noise), the delay in information transmission and network topology have a significant

relationship with spatial coherence and resonance. Independent of network topology, collective spike regularity and synchronization (firing coherence) reduces with an increase in sodium channel noise intensity (i.e., when the number of blocked sodium channels is increased) and increases with an increase in potassium channel noise intensity (i.e., when the number of blocked potassium channels is increased) (Sun et al. 2011; Ozer et al. 2009b). Wang et al., through a series of experiments using different cell models, showed that in small-world (Wang et al. 2008b, 2010b) and scale-free (Wang et al. 2009, 2011) neuronal networks transmission delay and connectivity power interrelates with the rate of change in spatial synchronization. Following this context, we considered that a study concerning the influence of sodium and potassium concentrations on the regularity and synchronization of the HH network outcome would be interesting.

In this study, a cortical network aiming at simplicity and, as far as possible, consistency with the actual anatomic structure of mammalian cortex organization was realized to simulate in part a small portion of the cerebral cortex. The network was structured with a small population of randomly interconnected HH cells in accordance with the criteria given in the study by Destexhe et al. (2001). This model was chosen because the present study aimed to investigate the effects of changes in Na^+ and K^+ ion concentrations on the dynamics of the network, rather than the effect of stochastic fluctuations in ion channels as the induced channel noise, in terms of consistency and synchronization. In the model, the 4:1 rate of excitatory:inhibitory neurons was achieved (Timofeev et al. 2000; Izhikevich et al. 2004; Destexhe 2009) and the connectivity index was chosen as 2 %, as in previous studies (Traub et al. 1992; Destexhe 2009).

A typical result obtained through the testing of the network is shown in Fig. 1. The cyclic behavior of membrane potential can be observed on the state space dynamic characteristics of membrane potential presented in the figure. The onset and peak voltage values and duration of polarization and hyperpolarization were measured on the evolution of APs, compared to the experimental ones given in previous studies (Destexhe and Paré 1999; Platkiewicz and Brette 2010), and analyzed in terms of regularity, phase coupling, and synchronization. The analysis revealed that while Na^+ concentration affects only amplitude, K^+ concentration significantly influences the form, regularity, and synchrony of APs generated by the network.

Materials and methods

Toward the objective of the present study, to somewhat simulate a small portion of the cerebral cortex, a cortical

Fig. 1 **a** A typical spike train (signal) generated by a neuron, **b** typical temporal phases of a single AP, **c** the behavior of this signal in the state space with the voltage-based parameters specified as follows: **d** minimum voltage levels; **e** threshold levels; and **f** the peak value

network was realized with a small population of randomly interconnected HH cell models. Each HH cell model in the network was a single compartment configured with a fluctuating conductance as given in the study by Destexhe et al. (2001). While 80 % of the total neurons were selected as excitatory neurons, the other 20 % were assigned as inhibitor neurons so that the natural excitatory/inhibitory rate (4/1) of neuron populations was conserved in the design, as given in previous studies (Timofeev et al. 2000; Izhikevich et al. 2004; Destexhe 2009). Concerning the anatomical and morphological limitations with these two neuron groups, the rate of synaptic connectivity of a neuron to another was randomly chosen as 0.02 within and between both neuron groups among all possible synaptic connections, as in previous studies (Traub et al. 1992; Destexhe 2009). Interneuronal excitatory and inhibitory synaptic links

were expressed with g_e and g_i (excitatory and inhibitory synaptic conductivities, respectively) and w_e and w_i (excitatory and inhibitory weights, respectively). While w_e and w_i were assigned with constant values, g_e , g_i , and the onset voltage were considered as randomly alternating in predefined limits. Excitatory and inhibitory synaptic currents were independently defined in terms of exponentially decaying conductivities (Song et al. 2000; Brette et al. 2007).

The cortical network was designed with 1,000 interconnected mammalian neural cell models, as given in previous studies (Destexhe et al. 2001; Destexhe 2009). This number of neurons is considered reasonable in terms of computational cost. Note that, depending on the objective of investigation, a network can be designed with much more cells. However, in this case, the demonstration of the network will last much longer. For the objective of the

present study, it was found that even 100 neurons provides significant results compared with the ones obtained from a large scale network.

In this study, free licensed software (python) with open library sources was used (Goodman and Brette 2008, 2009). In each experiment, the matrices defined for each parameter were updated at every $\Delta t = 0.025$ ms iteration, and the results were calculated after 40,000 iterations. The total computational cost was 1,000 ms.

Neuronal dynamic membrane potential is expressed in terms of ionic, extracellular DC, and integral of synaptic currents using a fluctuating conductance-based HH model (Traub and Miles 1991; Destexhe and Paré 1999; Destexhe et al. 2001; Platkiewicz and Brette 2010).

$$C \frac{dV}{dt} = I_{Na} + I_{Kd} + I_M + I_{leak} + I \quad (1)$$

where I_{Na} is the voltage-dependent sodium (Na^+) current, I_{Kd} is the delayed rectifier potassium (K^+) current responsible for action potential, I_M is the non-inactivating slow voltage-dependent potassium current responsible for spike frequency adaptation, I_{leak} is the leakage current, I represents the collection of excitation (I_{ext}) and total synaptic currents (I_{syn}), V is the dynamic membrane potential, and $C = 1 \mu F/cm^2$ is the per unit area membrane capacitance.

The ionic conductance of sodium, delayed rectifier potassium, slow non-inactivating potassium, and leakage currents are respectively defined as $\bar{g}_{Na}m^3h(E_{Na} - V)$, $\bar{g}_{Kd}n^4(E_K - V)$, $\bar{g}_M p(E_K - V)$, and $\bar{g}_L(E_L - V)$ (Destexhe et al. 2001). The maximum conductance rates for a membrane area of $34,636 \mu m^2$ were adjusted as $\bar{g}_{Na} = 51.6$ mS/cm², $\bar{g}_{Kd} = 10$ mS/cm², $\bar{g}_M = 0.5$ mS/cm², and $\bar{g}_L = 0.0452$ mS/cm², as have been considered in previous studies (Destexhe et al. 2001; Platkiewicz and Brette 2010). Here E_{Na} , E_K , and E_L are reversal potentials (known as Nernst potentials) caused by sodium, potassium, and leakage currents, respectively. m , h , n , and p are time varying activation variables that depend on voltage-dependent rate constants (α_m , β_m , α_h , β_h , α_n , β_n , α_p , and β_p). The rates of change in these variables are defined by a set of differential equations as follows (Traub and Miles 1991; Destexhe and Paré 1999; Destexhe et al. 2001).

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(V)(1 - m) + \beta_m(V)m \\ \frac{dh}{dt} &= \alpha_h(V)(1 - h) + \beta_h(V)h \\ \frac{dn}{dt} &= \alpha_n(V)(1 - n) + \beta_n(V)n \\ \frac{dp}{dt} &= \alpha_p(V)(1 - p) + \beta_p(V)p \end{aligned} \quad (2)$$

The voltage-dependent rate constants were as follows:

$$\begin{aligned} \alpha_m &= 0.32(13 - V + V_T)/[\exp((13 - V + V_T)/4) - 1] \\ \beta_m &= 0.28(V - V_T - 40)/[\exp((V - V_T - 40)/5) - 1] \\ \alpha_h &= 0.128 \exp[(17 - V + V_T)/18] \\ \beta_h &= 4/[1 + \exp((40 - V + V_T)/5)] \\ \alpha_n &= 0.032(15 - V + V_T)/[\exp((15 - V + V_T)/5) - 1] \\ \beta_n &= 0.5 \exp[(10 - V + V_T)/40] \\ \alpha_p &= 0.0001(V + 30)/[1 - \exp((-V - 30)/9)] \\ \beta_p &= 0.0001(-V - 30)/[1 - \exp((V + 30)/9)], \end{aligned}$$

where the variable V_T represents the membrane threshold voltage ($V_T = -63$ mV). In-vivo like synaptic current is modeled with excitatory and inhibitory independent dynamic synaptic currents, as in the previous study (Destexhe et al. 2001):

$$I_{syn} = g_e(t)(V - E_e) + g_i(t)(V - E_i), \quad (3)$$

where $g_e(t)$ and $g_i(t)$ are the time-dependent excitatory and inhibitory synaptic conductivities, respectively, and $E_e = 0$ mV, and $E_i = -75$ mV are the excitatory and inhibitory synaptic reversal potentials, respectively (Destexhe et al. 2001). $g_e(t)$ and $g_i(t)$ are independent stochastic processes similar to those defined in the Ornstein–Uhlenbeck process as follows (Uhlenbeck and Ornstein 1930; Destexhe et al. 2001):

$$\begin{aligned} \frac{dg_e}{dt} &= -\frac{[g_e(t) - g_{e0}]}{\tau_e} + \sqrt{D_e}\chi_1(t) \\ \frac{dg_i}{dt} &= -\frac{[g_i(t) - g_{i0}]}{\tau_i} + \sqrt{D_i}\chi_2(t), \end{aligned} \quad (4)$$

where $g_{e0} = 0.012 \mu S$ and $g_{i0} = 0.057 \mu S$ are mean conductance values, $\tau_e = 2.7$ ms and $\tau_i = 10.5$ ms are time constants, D_e and D_i are noise diffusion constants, and $\chi_1(t)$ and $\chi_2(t)$ are Gaussian white noise with zero mean and unity standard deviation (Destexhe et al. 2001).

At any time, as a presynaptic potential stimulates an excitatory and/or inhibitory synapse, a constant increase occurs in g_e and/or in g_i (Goodman and Brette 2008), after which they decay out exponentially with the format of time constants (Song et al. 2000; Brette et al. 2007). The weights $w_e = g_e^{\max}/N_e = 6$ nS and $w_i = g_i^{\max}/N_i = 67$ nS are appointed for scaling excitatory and inhibitory synaptic connectivity, respectively. Here N_e and N_i are the number of excitatory and inhibitory synaptic links, respectively. In terms of extracellular and intracellular ion concentrations, the electrochemical or reversal Nernst potential is given as follows (Hille 2001; Izhikevich 2007):

$$E_i = \frac{RT}{zF} \ln \frac{[Con_i]_{out}}{[Con_i]_{in}} = \frac{RT}{zF} \ln [CR_i], \quad (5)$$

where $[Con_i]_{out}$ and $[Con_i]_{in}$ are respectively extracellular and intracellular ion concentrations, CR_i is the ratio of

extracellular concentration to the intracellular concentration, here i symbolizes an ionic element such as Na^+ or K^+ , $R = 8.31 \text{ J/(K mol)}$ is the universal gas constant, $F = 96,489 \text{ Coulombs/mol}$ is Faraday's constant, T is the absolute temperature ($K = 273.16 + ^\circ\text{C}$), and z is the ion valence (here the value of z was 1 for Na^+ and K^+ , -1 for Cl^- , and 2 for Ca^{2+}).

The leakage reversal potential caused by the leakage current as the integral of chlorine and other ionic currents was $E_L = -80 \text{ mV}$ (Destexhe et al. 2001). The typical ion concentrations for a mammalian neuron were $[Na^+]_{out} = 145 \text{ mM}$, $[Na^+]_{in} = 5\text{--}15 \text{ mM}$, $[K^+]_{out} = 5 \text{ mM}$, and $[K^+]_{in} = 140 \text{ mM}$ (Izhikevich 2007).

In the demonstrations provided, the value of one of these concentrations was altered by $\pm 1/13.3$ of the original value and others were considered as constant. The ionic E_{Na} and E_K reversal potentials were calculated at $T = 36^\circ\text{C}$ (body temperature) using Eq. (5). For each case, the effects of sodium and potassium ion concentrations on the dynamic outcome of this cortical network for newly calculated reversal potential values were investigated. Thus, some voltage- and time-based parameters relating to the evolution or spike streams of APs from the network were measured and evaluated.

The irregularity of the network outcome was investigated in terms of the coefficient of variation (CV) of the spikes given as follows (Gabbiani and Koch 1998; Nawrot 2010):

$$CV = SD(ISI)/mean(ISI), \quad (6)$$

where ISI represents interspike interval and SD for standard deviation. The phase couplings occurring over the outcome spike train were quantified using vector strength (VS) obtained by the total number of phase vectors sharing the same phase angle in the phase space. VS is used to quantitatively measure the phase locking condition and the synchronization emerging between two coupled signal components (Nawrot 2010), which in turn can, to some extent, determine the synchronization between individual neuronal cells.

The phase locking condition has been reported as a process in which temporal information is somewhat coded (Carr and Friedman 1999; Ashida and Carr 2010). The VS index quantifies the degree (amount) of phase locking occurring in the interval ($0 < \theta_j < 2\pi$) with a reference some frequency of stimulus, (f_{signal} , average frequency of the spike stream). Here the phase angle $\theta_j = 2\pi f_{signal} t_j \pmod{2\pi}$ is the j th coupling emerging at time t_j . VS can be calculated as follows (Goldberg and Brown 1969; Ashida and Carr 2010):

$$X = \frac{1}{N} \sum_{j=1}^N \cos(2\pi f_{signal} t_j)$$

$$Y = \frac{1}{N} \sum_{j=1}^N \sin(2\pi f_{signal} t_j), \quad (7)$$

where N is the total number of spikes and $VS = \sqrt{X^2 + Y^2}$.

VS takes values over 0–1 open interval for a limited time period T , where 1 represents perfect synchronization, while 0 represents the worse case or no synchronization (Zahar et al. 2009; Ashida and Carr 2010).

Results

The designed cortical network was run for Na^+ and K^+ concentrations given in a previous study (Izhikevich 2007), and the acquired results were considered as normal or standard values and therefore taken as reference values. The network was then demonstrated for Na^+ and K^+ altered by $\pm 30\%$ of their normal values one by one, while keeping the others at the reference values. That is, the CR_i given in Eq. (5) was altered, and the algorithm was executed for 1,000 ms. The parameters characterizing the evolution of APs, such as the resting state, threshold, peak, and hyperpolarization voltage levels, as well as the temporal phases between these voltage levels, such as the time elapsed between onset and peak (depolarization or rise time; RT), the time between peak and end of repolarization (repolarization or fall time; FT), and the time between onset and the next minimum (ONM) were measured. Because of the lack of space, the responses of all neurons in the network are not yet presented. In order to give an idea, the outcome of a typical neuron in response to alterations in ion concentrations is presented in Fig. 2. The deviations in spike traces and the evolution of their phases on the state space can be observed from the figure. The measurements were performed for the overall network, and the histograms for voltage-based parameters were also presented in the figure. The mean values of the measured voltage and time-based parameters were tabulated as given in Table 1. The spike rate (SR), CV , and VS were calculated from the information revealed by these measurements. Mean values of SR and CV for the overall network and percentage of $CV < 1$ and $CV > 1$, together with spike behavior information, are presented in Table 2. For each trial, the calculated SR , ISI , and overall CV and VS distributions are presented in Figs. 3 and 4. The CV and VS information for the overall network does show the quantitative and qualitative ranks of the network in terms of regularity, phase locking, and synchronization.

As the characteristic parameters of spike trains presented in Fig. 2 were analyzed, in the normal case, the membrane potential showed a stable regular spiking stream with a normal distribution. For the overall network, as given in Table 1, in the normal case, the resting membrane potential (V_m), threshold voltage levels (TH), peak voltages (PV), and the deep hyperpolarization potential (HP) levels

Fig. 2 Typical spike trains, their phase space representations, and distributions of voltage-based parameters CR_{Na^+} and CR_{K^+} ; **a** normal CR_{Na^+} and CR_{K^+} ; **b** decreased CR_{Na^+} and normal CR_{K^+} ; **c** increased

CR_{Na^+} and normal CR_{K^+} ; **d** normal CR_{Na^+} increased CR_{K^+} ; and **e** normal CR_{Na^+} and decreased CR_{K^+}

Table 1 Role of ion concentrations on characteristic AP voltages, and the temporal phases going between these parameters

Trial	V_m at rest (mV) mean $\pm$ SD	TH (mV) mean $\pm$ SD	PV (mV) mean $\pm$ SD	HP (mV) mean $\pm$ SD	RT (μ s) mean $\pm$ SD	FT (μ s) mean $\pm$ SD	ONM (μ s) mean $\pm$ SD
Norm [CR_{Na^+}] & Norm [CR_{K^+}]	-64.55 ± 6.58	-50.12 ± 0.88	41.39 ± 2.44	-67.98 ± 4.31	705 ± 56	$1,386 \pm 73$	$2,119 \pm 569$
Dec [CR_{Na^+}] & Norm [CR_{K^+}]	$-63.93 \pm 6.71^*$	$-49.17 \pm 0.94^*$	15.12 ± 1.85	$-65.75 \pm 3.66^*$	736 ± 56	$1,382 \pm 73$	$2,204 \pm 656$
Inc [CR_{Na^+}] & Norm [CR_{K^+}]	$-64.97 \pm 6.50^*$	$-50.76 \pm 0.86^*$	67.26 ± 2.88	$-68.98 \pm 5.60^*$	685 ± 55	$1,417 \pm 71$	$2,118 \pm 530$
Norm [CR_{Na^+}] & Inc [CR_{K^+}]	-59.41 ± 8.08	-47.76 ± 1.98	28.50 ± 12.23	-53.31 ± 6.78	735 ± 48	$1,508 \pm 677$	$3,206 \pm 1,478$
Norm [CR_{Na^+}] & Dec [CR_{K^+}]	$-66.75 \pm 7.21^*$	$-50.28 \pm 0.89^*$	$41.46 \pm 1.12^*$	-79.94 ± 3.19	696 ± 54	$1,231 \pm 62$	$1,737 \pm 215$

* Almost not changed

were approximated as -64.55 ± 6.45 , -50.12 ± 0.88 , 41.39 ± 2.44 , and -67.98 ± 4.31 mV, respectively. For other conditions, these characteristic values showed variations that may be linked to particular disorders caused by ion concentrations. The global distributions derived from the entire network for each of these values also showed variations particularly in their averages and standard deviations (SD), as shown in Fig. 2.

From the measured parameters shown in Tables 1 and 2, it is understood that both extracellular and intracellular sodium concentrations exert a negligible effect on spike characteristics, except the peak voltage and the rate of change in AP. From Table 1, CR_{Na^+} is obviously effective on PV but not on the other voltage levels so that the increase in CR_{Na^+} increases PV, while the decrease in CR_{Na^+} decreases PV. Furthermore, CR_{Na^+} had a parallel relation to repolarization time but an inverse relation to depolarization and ONM times. On the other hand, the potassium concentration rate CR_{K^+} had an opposite effect on PV and HP but a negligible effect on TH. The increase in CR_{K^+} decreased the value of V_m , the decrease in CR_{K^+} slightly affected depolarization time but barely affected repolarization time, and consequently ONM time. That is, when CR_{K^+} was reduced, the re-polarization and ONM times decayed downward. In contrast, when CR_{K^+} was increased, the depolarization time slightly elevated; however, interestingly, ONM time was significantly increased. Furthermore, SD of both FT and ONM were markedly affected by CR_{K^+} (in a parallel manner). The increase in SD suggests the rate of irregularity of the spike train. The decrease in the mean ONM was also positively related to spike regularity. These results, apart from the dynamics of the sodium and potassium channels of the membrane, may be linked to the effectiveness of mobility of potassium ions through the membrane compared with that of sodium ions (Cressman et al. 2009).

As the network outcome was analyzed in terms of irregularity (Table 2) the change in sodium concentration clearly had almost no effect on spike irregularity or the reliability of neurons in terms of spike generation. On the other hand, when intracellular K^+ was decreased (i.e., $CR_{K^+}CR_{Na^+}$ increased), the network outcome showed an irregular bursting spike stream with a bimodal occurrence or frequency distribution (FD), whereas when it was increased (i.e., CR_{K^+} decreased), the spike streams presented a better synchronization and much better reliability, which could be easily perceived from the phase space representations shown in Fig. 2 and the CV values presented in Table 2. Mimics conveyed to these parameters as well as to the evolution of AP stream may also be correlated to particular neurological conditions that need to be assessed.

From Fig. 3 and Table 2, it is seen that the change in CR_{Na^+} does not significantly affect the spike rate and CV.

Table 2 Effect of ion concentrations on spike rates (SR), regularity, format of spectral distribution, and spike formats in the whole network

Trials	SR (spike/s)	CV	Neur % (CV < 1) Mean CV	Neur % (CV > 1) Mean CV	FD	Spike behavior
Norm [CR_{Na^+}] & Norm [CR_{K^+}]	35.55	1.02	56.9 % 0.88	43.1 % 1.14	Normal	Irregular (Poisson dist.)
Dec [CR_{Na^+}] & Norm [CR_{K^+}]	34.86	1.07	45.1 % 0.90	54.9 % 1.15	Normal	Minor increase in irregularity
Inc [CR_{Na^+}] & Norm [CR_{K^+}]	35.81	1.01	58.6 % 0.88	41.4 % 1.12	Normal	Minor decay in irregularity
Norm [CR_{Na^+}] & Inc [CR_{K^+}]	79.60	1.48	0 % NaN	100 % 1.45	Bi-modal	Irregular
Norm [CR_{Na^+}] & Dec [CR_{K^+}]	27.37	0.93	75.7 % 0.83	24.3 % 1.10	Normal	Regular

As CR_{Na^+} was decreased, the percentage of neurons with $CV < 1$ decreased and those with $CV > 1$ was increased. This observation suggests that the irregularity of network for overall neurons decayed out. In other words, it may be considered that, as the ratio of K^+/Na^+ diverges from the normal ratio, the irregularly spiking behavior of the membrane increases. This rate may work as part of a balancing mechanism for controlling the spike generation format.

On the other hand, an obvious change in the spike rate and CV was detected with alteration in potassium concentration. With the increase in CR_{K^+} , the spike rate increased almost threefold over normal values, but with the decrease in CR_{K^+} , a significant decay in this parameter was detected (Fig. 3). With the increase of CR_{K^+} , CV for all spike trains became >1 , and hence, none of the neurons generated regular spike trains. Conversely, with the decrease in CR_{K^+} , most of the spike trains (75.7 %) had $CV < 1$, which statistically reveals the generation of many regular spikes by neurons in the network. From this experiment, it was understood that both intracellular and extracellular potassium ion concentrations are particularly influential in determining the regularity of neuronal activity.

To assess the network outcome from phase locking and synchronization points of view, VS values for the overall network were calculated and presented in Fig. 4. As shown in the figure, CR_{Na^+} and CR_{K^+} evidently affected the synchronization or phase locking quotient of the signal. This measure remained <0.5 , which showed a very low synchronization, an expected value due to the complexity of the neuronal structure. With the increase in CR_{K^+} , the VS value became lower than that in the other cases, showing an increase in the irregularity of spike streams generated by cells.

Finally, to assess the reliability of the results obtained here, the network was tested using the same strategy for a

minimum of 10 times. The parameters obtained in each trial were than statistically evaluated for their consistency. The p values for all of the parameters individually were obtained assuming the null hypothesis that the parameters would not be consistent among trials. For all of the parameters, it was found that $p < 0.05$, which clearly shows the reliability of the information revealed in this particular study.

Discussion

Numerous pharmacological experiments have been conducted on nerve cells to investigate the potential relations between AP configuration and ion concentrations or ionic currents using different isotonic solutions for changing ion concentrations or blocking ionic channels. Some of the pioneering experimental studies conducted using frog leg muscles (Overton 1902), a huge squid axon (Hodgkin and Katz 1949), ommatidial cells of a horseshoe crab (Kikuchi et al. 1962), and male bee retinula cells (Fulpius and Baumann 1969) have mainly reported that with the reduction of extracellular potassium concentration, the generated APs enter into an imperceptible form, their amplitude diminishes, and finally no further excitation occurs. Similarly Huxley and Stämpfli (1951), Brady and Woodbury (1960), Niedergerke and Orkand (1966), Seyama and Irisawa (1967), and Diamond et al. (1958), as well as many other co-workers not cited here, have shown the existence of a direct relation between sodium concentration and the AP peak value. Similar to the results published by the studies mentioned above, our simulation-based results revealed that other than the AP peak value, $[Na^+]_{out}$ affected AP characteristics such as threshold and hyperpolarization stages only marginally.

Using the HH neuron model, Gong et al. (2010) showed that the blocking of channels of neuronal cells affected

Fig. 3 The spike rates (A₁–E₁), ISI distribution (A₂–E₂), and the calculated CV values (A₃–E₃), for the whole network with the strategy concerned in this study. **a** Is for Norm [CR_{Na^+}] & Norm [CR_{Na^+}]; **b** is for Dec [CR_{Na^+}] & Norm [CR_{K^+}]; **c** is for Inc [CR_{Na^+}] & Norm [CR_{K^+}]; **d** is for Norm [CR_{Na^+}] & Inc [CR_{K^+}]; and **e** is for Norm

[CR_{Na^+}] & Dec [CR_{K^+}]. The rates ($x\% - y$) shown on the top of histograms in (A₃–E₃) reveal that $x\%$ of neurons generated spikes with $CV < 1$ (regular; overall average $CV = y$), while $x\%$ of neurons with $CV > 1$ (irregular; overall average $CV = y$)

spike irregularity and synchronization. Ozer et al. (2009a) also showed the existence of a strong interrelation between the embedded channel noise arising from the internal mechanism of the voltage-gated ion channels in the HH networks, which have Newman–Watts small-world topology, and the stochastic resonance, linkage rates in between neurons, and frequency of the pacemaker. Similarly, the

authors showed that the first spike latency following a stimulus, which has great importance in terms of functional neural physiology, has a strong relationship with the channel noise and frequency of the applied under-threshold excitation in this type of network (Ozer et al. 2009c). These studies demonstrated that the rate of the active ion channel, because it identifies channel noise intensity, has an impact

Fig. 4 VS distributions for overall network

on the neuronal dynamics (Ozer et al. 2009b), (in practice, toxins such as tetraethylammonium, tetrodotoxin, and saxitoxin are widely used for blocking ion channels for controlling neuronal activity). Through numerical simulations, a strong relationship between spike stream regularity, firing coherence, and the rate of the active ion channels (i.e., channel noise intensity), and network topology has been demonstrated (Sun et al. 2011; Ozer et al. 2009b). Furthermore, in studies unrelated to network topology, it has been found that collective spike regularity reduces with an increase in the number of blocked sodium channels and increases with an increase in the number of blocked potassium channels (Sun et al. 2011; Ozer et al. 2009b). With the use of scale-free networks, a strong relationship between transmission delay, connectivity power, and the rate of change in spatial synchronization has also been reported in literature (Wang et al. 2009, 2011).

Through the present study, similar to the above studies but from an ion concentration point of view, it has been observed that as CR_{Na^+} decreases, the number of neurons generating spikes somewhat similar to irregular spikes increases, and conversely, as it increases, the number of neurons generating regular spikes decreases. Somjen (2002) and Krishnan and Bazhenov (2011) reported that the extracellular sodium concentration had decreased during the epileptogenic phase. In addition, Ebert et al. (1997) experimentally showed that antiepileptic drugs (Phenytoin) affect sodium channels, and consequently affect the seizure threshold, or coherence and the synchronization level.

In the present study, we also showed that when CR_{Na^+} decreases, the number of neurons that generate irregular spikes increases. This result, to some extent, shows the existence of an interrelation between sodium concentration and spike irregularity, which, hence, verifies the reports of experimental studies that revealed that extracellular Na^+ concentration decreased during epileptic seizures. Furthermore, medicines blocking Na^+ channels have proven

that Na^+ is an important factor in increasing not only the threshold required for epileptic seizures but also the seizure's phase as well as affecting the termination of paroxysmal oscillations during interseizure periods. This result shows that Na^+ concentration is effectively involved with neurological diseases.

Kikuchi et al. (1962) and Baker et al. (1962) reported that as the extracellular potassium increases, or conversely, as the intracellular potassium decreases, the amplitude or peak value of spike reduces, but spike frequency increases. Almost during the same time in their experimental study, Brady and Woodbury (1960) and Fulpius and Baumann (1969) determined a reverse correlation between the AP peak value and extracellular potassium concentration. These two results are quite parallel to those obtained from the demonstration of the artificial cortical network used in this study.

The simulation results also showed that intracellular K^+ concentration has an extreme effect on the threshold, peak voltage, hyperpolarization, and spike stages of AP, except depolarization. Using a mathematical model, Bazhenov et al. (2008), Fröhlich et al. (2008), and Ostby et al. (2009) showed that an inconvenient extracellular potassium concentration correlates with epileptic seizure formation. That is, it increases the probability of seizure occurrence. Fröhlich et al. (2006, 2010), Fröhlich and Bazhenov (2006), and Somjen et al. (2008) showed that tonic spiking and bursting bistability correlates to the potassium concentration.

In this study, as CR_{K^+} was increased, the network outcome showed an irregular bursting characteristic, whereas as CR_{K^+} was decreased, regular spikes with tonic characteristics—more regular than those under normal conditions—were observed. As the experimental and simulation studies, some of which have been mentioned above, were considered, because of bistability, the momentary transitions between tonic and bursting conditions resembled the behavior of real neurons during epileptic seizures. This shows that an artificial system administered through the control of K^+ concentration may be constructed to simulate, to some extent, the real epilepsy mechanism.

Studies conducted so far have revealed that apart from the epileptogenic behavior (Bazhenov et al. 2008; Boucetta et al. 2008; Fröhlich et al. 2006, 2008, 2010; Kager et al. 2000; Krishnan and Bazhenov 2011; Ostby et al. 2009; Somjen et al. 2008; Volman et al. 2012) and spreading depression (Grafstein 1956; Kager et al. 2000, 2002; Somjen et al. 2008), various neurological diseases are related to K^+ concentration.

The present study results concerning K^+ concentration are also in line with those available in the literature. Diseases such as epilepsy, spreading depression, stroke, hypoxic encephalopathy, and migraine, and many other

neurological diseases may be treated with ion concentration management (Barreto and Cressman 2011; Bazhenov et al. 2008; Boucetta et al. 2008; Fröhlich et al. 2006, 2008, 2010; Kager et al. 2000, 2002; Krishnan and Bazhenov 2011; Grafstein 1956; Ostby et al. 2009; Somjen et al. 2008; Volman et al. 2012). The results obtained also suggest that administration of the balance of cellular Na^+ and K^+ concentrations, as has been reported by other researchers (Barreto and Cressman 2011; Bazhenov et al. 2008; Cressman et al. 2009; Fröhlich and Bazhenov 2006; Fröhlich et al. 2006, 2008, 2010; Kager et al. 2000, 2002; Krishnan and Bazhenov 2011; Ostby et al. 2009; Somjen et al. 2008; Volman et al. 2012), primarily needs to be considered in the development of new strategies for the treatment of neurological diseases.

In addition to the effect of blockage of sodium and potassium channels on synchronization, through the present study, it was understood that CR_{K^+} also had an effect on the synchronization of the network outcome such that when both concentrations were decreased the synchronization decayed out, whereas when the concentrations were increased the synchronization increased. The role of synchronization in the cortex has been linked to perception and information processing (Wang 2010). These results show that ion concentrations are involved in cellular information processing; however, it is not clear how, and this suggests the existence of a mechanism controlling the rate of change in ion concentrations during perception and/or information processing.

Conclusion

In the present study, the effects of ion concentrations on the behavior of a cortical network based on the HH cell model were investigated in terms of regularity and synchronization of the generated spikes. The ion concentrations were found to be effective. Particularly, potassium concentration significantly affected APs and the regularity and synchronization of the network outcome.

The obtained results were parallel to those obtained through physiological and pharmacological experiments. The results presented here showed that the regularity and reliability of brain functions had a strong relationship with the cellular ion concentrations, and showed the possibility of changing the behavior of neurons and consequently the firing rate of spikes in such a cortical network by changing only the ion concentration balance.

It is not yet known how to address this issue in a radical manner on pharmacological basis, and further studies that take into account the management of synaptic connections in a probabilistic manner are needed.

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