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ABSTRACT

We present a computational model of networked neurons developed to study the effect of temperature on neuronal synchronization in the brain in association with seizures. The network consists of a set of chaotic bursting neurons surrounding a core tonic neuron in a square lattice with periodic boundary conditions. Each neuron is reciprocally coupled to its four nearest neighbors via temperature dependent gap junctions. Incorporating temperature in the gap junctions makes the coupling stronger when temperature rises, resulting in higher likelihood for synchrony in the network. Raising the temperature eventually makes the network elicit waves of synchronization in circular ripples that propagate from the center outwardly. We suggest this process as a possible underlying mechanism for seizures induced by elevated brain temperatures.

In the brain, temperature fluctuates a small amount around the normal physiological baseline of 38 °C.[1] Excess of this value by a few degrees can cause cognition impairment, brain damage, aggravated sleep disorders,[2,3] and neuronal pathologies.[4] High temperature affects neurons' excitability by altering the rate at which ions flow in and out of the cell. At elevated temperatures, the flow tends to be faster, making neurons spike at higher frequencies, and possibly requiring stronger coupling to produce neuronal synchrony that could lead to the onset of a seizure.[5–7] Here, we present a temperature dependent network of neurons that illustrates this process. The network contains 225 neurons in a 15 × 15 lattice with periodic boundary conditions, displaying a tonic neuron at the center and all the other neurons bursting. The neuronal equations feature temperature dependence via Arrhenius functions attached to the ion channels' conductances and activation/deactivation variables. Each neuron is connected to its four nearest neighbors by reciprocal gap junctions in the standard diffusive coupling, containing an additional Arrhenius function that extends the influence of temperature to the connections between neurons. The idea is that, similarly to membrane ion channels allowing the flow of ions between the inside and the outside of the cell, gap junctions allow the direct flow of ions between neurons and therefore subject to a temperature influence analogous to the case of ion channels. This implementation of the Arrhenius factor in the network gap junctions is consistent with experimental work in biological cells,[5,8,9] yielding waves of synchrony across the network that mimic the behavior of neurons undergoing a seizure.[10,11]

I. INTRODUCTION

Chaos synchronization though presently well known and understood, still defies common sense. When first introduced in the literature,[12] synchronization of chaotic systems came as a surprise, given the typical exponential divergence of chaotic trajectories started at slightly different initial conditions.[13,14] Nonetheless, chaotic systems may synchronize depending on their nature and strength of the coupling connecting them. Among the several kinds of chaotic synchronization that have been identified,[15] a peculiar

type of synchronization involves oscillating systems that have their phases in step with each other (their phase differences remain less than 2π) while their amplitudes stay uncorrelated, known as phase synchronization.[16] Phase synchronization is present in many systems including the brain.[17–20] Synchrony of brain functions is crucial for the preservation of life, playing important roles in sleep cycles and memory consolidation,[21,22] but can also be troubling in association with certain neurological disorders including epilepsy, Alzheimer's and Parkinson's disease.[23–26]

In this manuscript, we elaborate on the case of a computational network of neurons displaying traveling waves of phase synchrony that start at the center of the grid and move outwardly

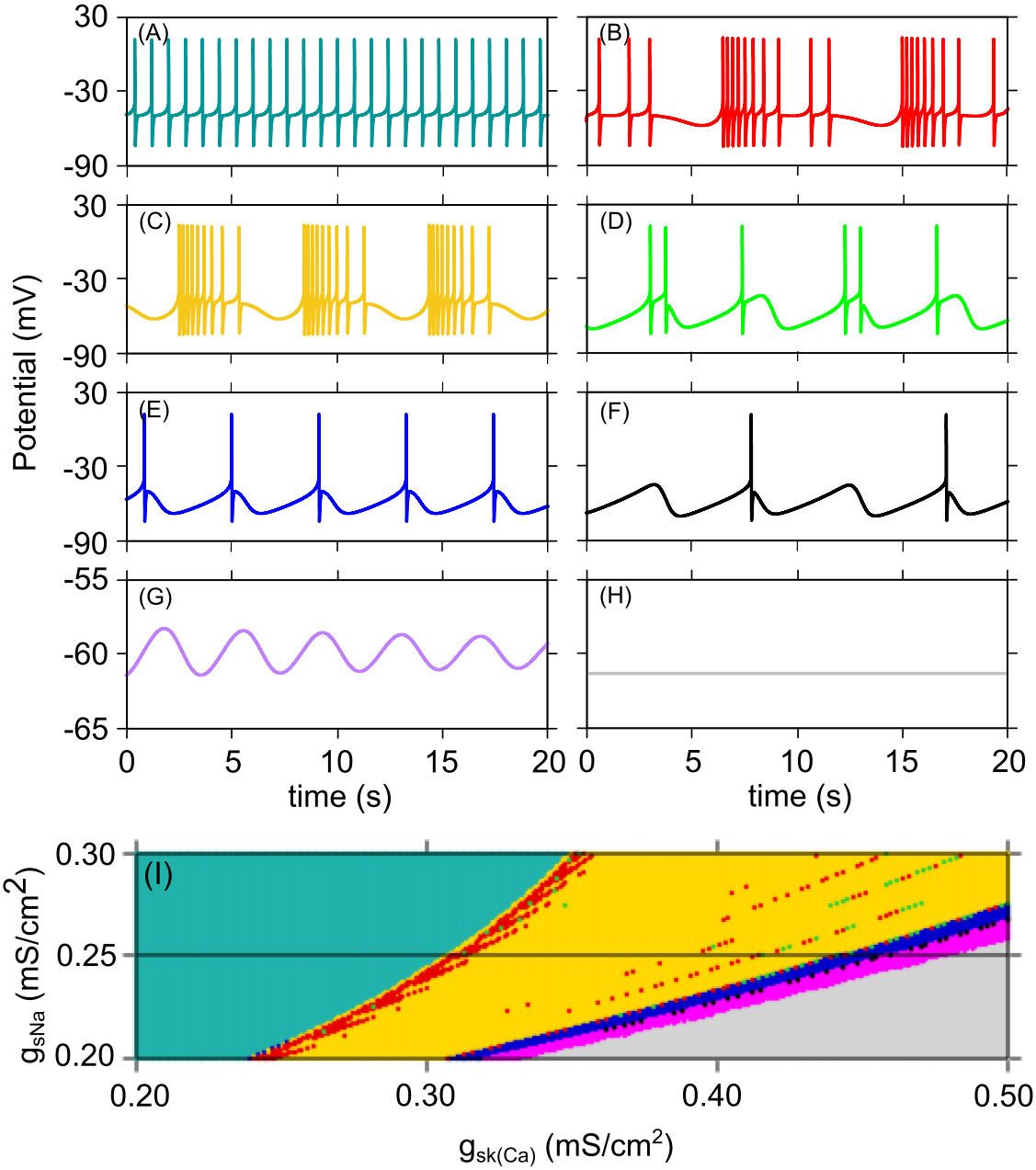

FIG. 1. Membrane voltage traces for (A) $g_{sK(Ca)} = 0.3$, (B) $g_{sK(Ca)} = 0.31$, (C) $g_{sK(Ca)} = 0.45$, (D) $g_{sK(Ca)} = 0.4411$, (E) $g_{sK(Ca)} = 0.45$, (F) $g_{sK(Ca)} = 0.4575$, (G) $g_{sK(Ca)} = 0.458$, (H) $g_{sK(Ca)} = 0.5$. (I) Firing patterns in the parameter space.

as circular ripples of periodic waves. This kind of neuronal output is akin to abnormal synchronization, due to high activity of neurons in the brain, causing seizures possibly associated with epilepsy. Epilepsy is a dysfunction characterized by the occurrence of repeated seizures, placed among the most prevailing brain disorders, and affecting more than 50 million people around the globe.[27] Epilepsy typically elicits recurring seizures with involuntary tremors, sometimes including slips of attention or loss of consciousness. It is an extremely debilitating brain disorder, often precluding patients from leading a normal life and from being less dependent on caregivers. The fact that roughly 75% of epilepsy cases begin in childhood indicates that the developing brain is more susceptible to seizures.[28]

Triggered by fever typically above 38 °C,[29] febrile seizures affect 2% to 5% of children. They are an age-dependent response of the developing brain to fever, occur in children from 6 months to 5 years of age, and in general feature a seizure accompanied by fever, but the fever is not associated with an intracranial infection or a defined cause.[30] Although febrile seizures are thought to be not life threatening, there is up to 9% risk of a child developing epilepsy after having febrile seizures, especially if the child has pre-existing neurological impairment, a family history of epilepsy, or a complicated febrile seizure (prolonged, focal, recurrent).[31] Additionally, there has been evidence that a proportion of children with sudden unexplained death in childhood had a history of febrile seizures, suggesting that febrile seizure may increase the risk for sudden unexplained child death.[32]

Body temperature regulation in many living organisms is crucial for their survival. In humans, small fluctuations around 37°C occur naturally as part of the circadian rhythm. Healthy individuals experience a mean daily temperature variation of 0.5°C, reaching a

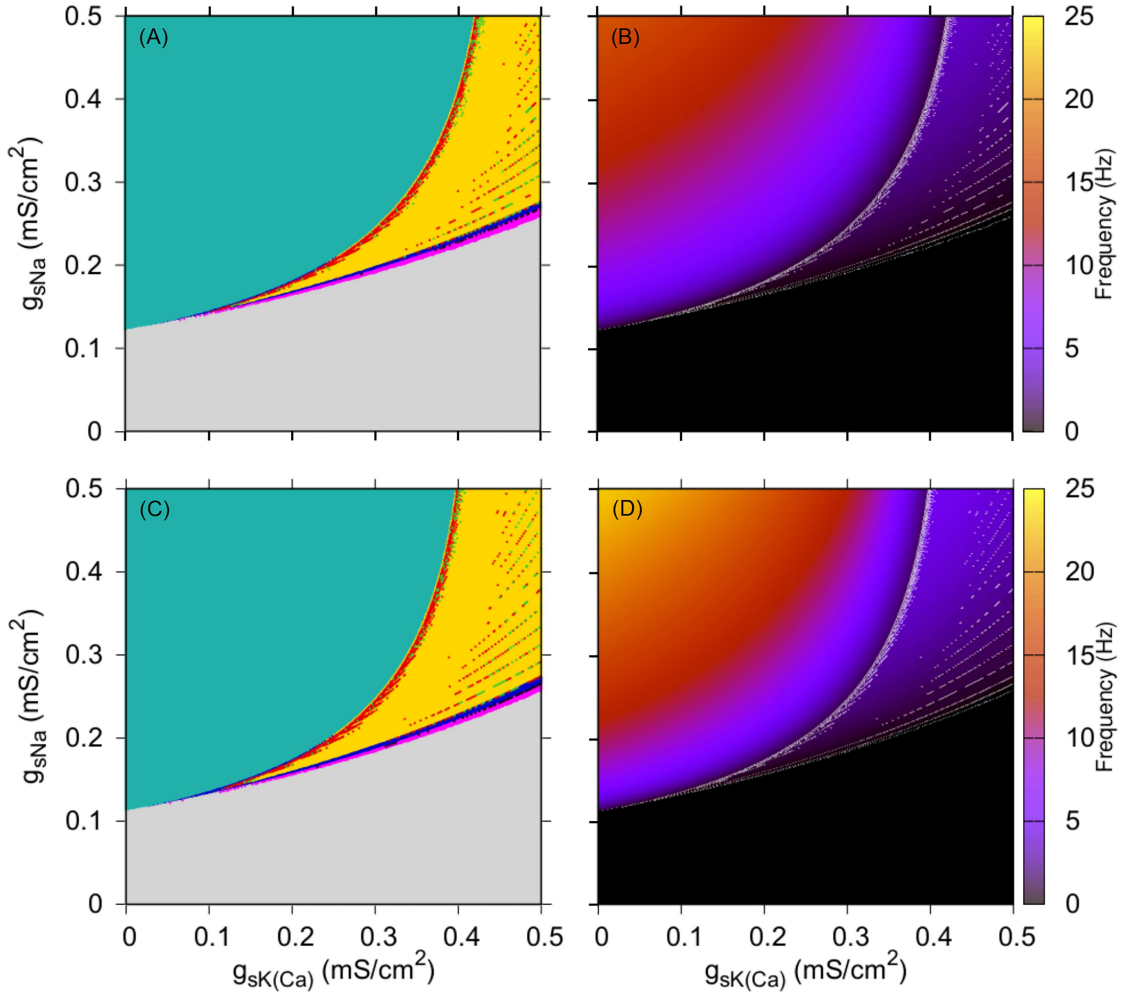

FIG. 2. Firing pattern and frequency color maps for a range of slow potassium and calcium conductances at $T = 38$ °C, plates (A) and (B); and at $T = 41$ °C, plates (C) and (D).

minimum around 4 A.M. and a maximum around 6 P.M. Larger variations of a few degrees below or above 37°C for an extended period of time can be harmful.[33]

In the brain, an organ with only 2% of the whole body mass and still using 25% of the total body glucose consumption and 20% of the total oxygen utilization, the average temperature is higher, at 38.5°C. While the brain temperature can fluctuate 2–4°C within the normal physiological range,[1] increased core temperature is known to affect brain function. High temperatures have been associated with sudden infant death syndrome (SIDS),[34] can cause cognition impairment, aggravate sleep disorders, and trigger seizures.[2,3] In view of the current reality of increased numbers of extreme weather events including heat waves, there are serious concerns that neurological disorders in general, and epilepsy in particular, will become more pervasive.[4,35,36] Even though the large amount of research work done on the seizures triggering mechanisms, there still is much to be learned, particularly in the case of seizures linked to temperature.

II. NEURONAL MODEL EQUATIONS

The model neuron used in the network is based on the landmark equations developed by Alan Hodgkin and Andrew Huxley,[37,38] comprising differential equations for the voltage across the cell membrane, and the functions for potassium channel activation and sodium channel activation and inactivation, as time-dependent variables. As an extension of the Hodgkin–Huxley equations, the Huber–Braun model implemented here also comprises four differential equations but including two slow currents, depolarization for sodium and repolarization for potassium. These peculiar features grant the Huber–Braun model the capability for generating a wide range of patterns of action potentials, including *tonic* (regular fast spiking), *bursting* (trains of regular fast spiking interspaced with longer subthreshold oscillations), and *chaos* (irregular spiking),[39,40] as illustrated in the voltage vs time graphs (*A*) through (*H*) in Fig. 1. Dynamical transitions between states of tonic and bursting firings mediated by chaos are of particular relevance in this model[41,42] and play important roles on how temperature[43,44] affects neuronal output.

The time evolution of the potential V across the cell membrane is given by

$$C\dot{V} = -I_{\text{leak}} - I_{\text{Na}} - I_{\text{K}} - I_{\text{sNa}} - I_{\text{sK(Ca)}} - I_{\text{inj}}, \tag{1}$$

where C is the membrane capacitance and I_{inj} is a constant injected current used as control parameter. The leak current, here approximated to be ohmic, is written as $I_{\text{leak}} = g_{\text{leak}}(V - V_{\text{leak}})$, where g_{leak} is the leak conductance and V_{leak} is the corresponding equilibrium potential. The fast and slow currents for sodium and potassium mentioned above and labeled Na, K, sNa and sK(Ca), respectively, are written as $I_{\text{n}} = \rho g_{\text{n}} a_{\text{n}}(V - V_{\text{n}})$ where n denotes Na, K, sNa, or sK(Ca). V_{n} represents the equilibrium potential for the n$^{\text{th}}$ corresponding current, g_{n} the n$^{\text{th}}$ maximum conductance, and $\rho(T)$ is the Arrhenius temperature function for the ionic currents.

Characteristic time constants τ_{n} control the opening and closing of the various ion channels, with the sodium channels, in particular, considered to activate rather quickly, with an activation function given by $a_{\text{Na}} = \frac{1}{1+e^{-s_{\text{Na}}(V-V_{0_{\text{Na}}})}}$, where s_{Na} sets the slope of the sigmoidal curve and $V_{0_{\text{Na}}}$ corresponds to the half-activation potential. The equations for the other three activation variables are

$$\dot{a}_{\text{K}} = \frac{\phi}{\tau_{\text{K}}}(a_{\text{K}\infty} - a_{\text{K}}), \tag{2}$$

$$\dot{a}_{\text{sNa}} = \frac{\phi}{\tau_{\text{sNa}}}(a_{\text{sNa}\infty} - a_{\text{sNa}}), \tag{3}$$

$$\dot{a}_{\text{sK(Ca)}} = -\frac{\phi}{\tau_{\text{sK(Ca)}}}(\nu_{\text{acc}} I_{\text{sNa}} + \nu_{\text{dep}} a_{\text{sK(Ca)}}). \tag{4}$$

The activation functions $a_{\text{j}\infty}$ are modeled by sigmoidal steady state curves given by $a_{\text{n}\infty} = \frac{1}{1+e^{-s_{\text{n}}(V-V_{0\ \text{n}})}}$, n = K, sNa, sK(Ca).

In this model, $a_{\text{Na}} \equiv a_{\text{Na}\infty}$ as a result of the very fast Na^{+} channel activation. Ca^{++} accumulation and depletion are included, respectively, in ν_{acc} and ν_{dep}, and $\phi(T)$ is the Arrhenius temperature function for the activation/deactivation variables. The Arrhenius functions $\rho(T)$ and $\phi(T)$ are here written as $\rho(T) = \rho_0^{(T-T_{\text{ref}})/10^{\circ}\text{C}}$ and $\phi(T) = \phi_0^{(T-T_{\text{ref}})/10^{\circ}\text{C}}$, where $\rho_0 = 1.3$, $\phi_0 = 3.0$. These are temperature scaling parameters borrowed from the Arrhenius law relating chemical reaction rates to a temperature change of 10 °C,[45,46] where T is the neuron's temperature and T_{ref} is a reference temperature that can be conveniently adjusted to allow the model be applied to a variety of settings.[44,47] For the purpose of this work,

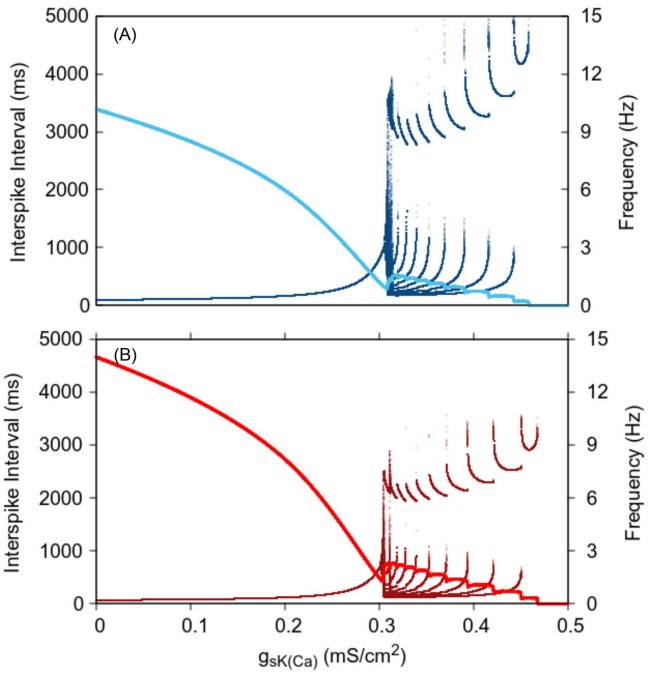

FIG. 3. Bifurcation diagram and firing rate for the neuron model as a function of $g_{\text{sK(Ca)}}$ for (A) $T = 38$ °C (dark-blue, left y axis for the interspike interval) showing a route to chaos through period doubling cascade. Neuronal firing rate shown in the same plot (light-blue, right y axis). (B) $T = 41$ °C left y axis for the interspike interval (burgundy) and neuronal firing rate right y axis shown in the same plot (red).

we set the baseline normal temperature of the brain at $T = 38\,^{\circ}\mathrm{C}$ and the reference temperature at $T_{\mathrm{ref}} = 60\,^{\circ}\mathrm{C}$. The computer simulations were carried out by applying the standard Runge–Kutta fourth-order numerical integration method with 0.1 ms step of integration, and unless otherwise explicitly mentioned in the text, the parameter values used throughout this work are as shown in the Appendix.

Among the various physiologically relevant parameters in the Huber–Braun model, the potassium calcium-dependent slow repolarization conductance $g_{\mathrm{sK(Ca)}}$ provides a useful control for creating a wide range of neuronal output patterns, as shown in the color map of Fig. 1(I), with $g_{\mathrm{sK(Ca)}}$ on the x axis and g_{sNa} on the y axis, and colors coded with the voltage traces (A) through (H). The voltage traces and color map shown in Fig. 1 are for the case where the neuron is at its baseline temperature of 38 °C.

III. TEMPERATURE AS SEIZURE FACILITATOR

A. Temperature effects on the single neuron dynamics

Temperature changes can affect the neuronal behavior as illustrated in Fig. 2 showing the different types of voltage patterns [color coded with the voltage traces in Fig. 1 graphs (A) through (H)], and frequency (color coded with the vertical color bar in Hertz on the right-hand side of the figure), in g_{sNa} vs $g_{\mathrm{sK(Ca)}}$ parameter space for $T = 38\,^{\circ}\mathrm{C}$ [top panels (A) and (B)], and $T = 41\,^{\circ}\mathrm{C}$ [bottom panels (C) and (D)]. In particular, this variation in temperature modifies the curved borderline [red stripe going from the top right-hand side of the color maps (A) and (C) downward bending to the left-hand side], separating the tonic area (cyan) from the chaos/bursting areas (red and other colors). The gray (resting potential) area at $T = 41\,^{\circ}\mathrm{C}$

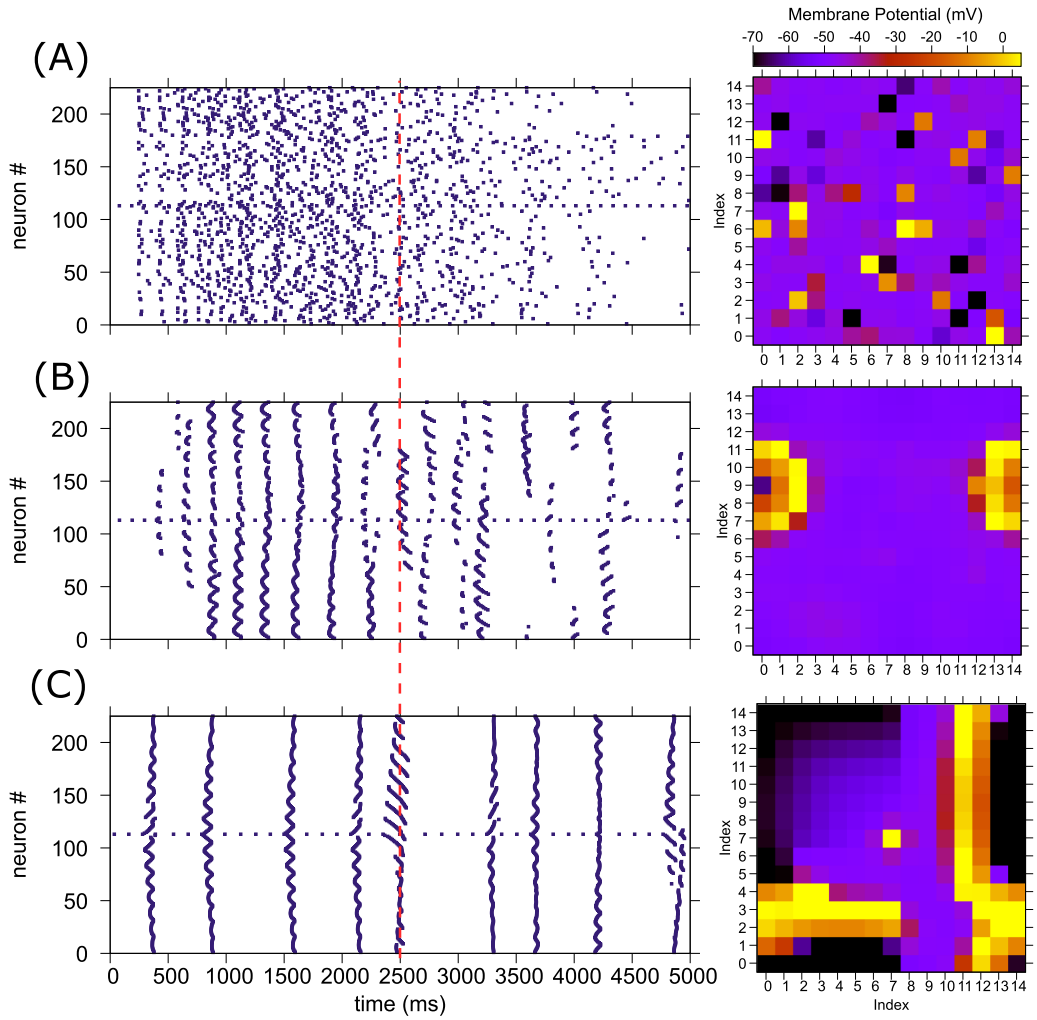

FIG. 4. Raster plots of spiking times for (A) $\eta = 0.0$, (B) $\eta = 0.5$, (C) $\eta = 1.0$ (left-hand side panels), along with the corresponding frames, each at time $t = 2500$ ms (right-hand side panels). Synchronization index are $R_{(A)} = 0.1$, $R_{(B)} = 0.13$ and $R_{(C)} = 0.27$. Normal brain temperature at $T = 38\,^{\circ}\mathrm{C}$.

is slightly smaller in panel (C) than in panel (A) at $T = 38\,^{\circ}\mathrm{C}$, indicating more active neurons at higher temperatures. Overall, the neurons in panel (D) at $T = 41\,^{\circ}\mathrm{C}$ fire at higher rates compared to the corresponding ones in panel (b) at $T = 38\,^{\circ}\mathrm{C}$, noticeable by the area in panel (D) with yellow/orange/red coded frequencies being larger than the corresponding area in panel (B). This increase in the neuron's firing rate with increase in temperature may play a role in the mechanism underlying neuronal synchronization under higher temperatures.

A cross section of the maps in Fig. 2 at $g_{\mathrm{sNa}} = 0.25$ showing the dynamics of the single neuron for $0 \le g_{\mathrm{sK(Ca)}} \le 0.5$ is displayed in Fig. 3, with panel (A) showing the bifurcation diagram and firing rate for $T = 38\,^{\circ}\mathrm{C}$, and panel (B) showing the same graphs for $T = 41\,^{\circ}\mathrm{C}$. For both temperature cases, the bifurcation diagrams exhibit the typical tonic-bursting chaotic transition,[42] with temperature enacting seemingly minor but relevant changes, especially the overall increase in the neuron's firing rate at higher temperatures.

For example, for $g_{\mathrm{sK(Ca)}} \approx 0.05$ (tonic) at $38\,^{\circ}\mathrm{C}$, the neuron's firing rate is 10.2 Hz going up to 14 Hz at $41\,^{\circ}\mathrm{C}$. However, for the same two temperatures, the corresponding increase in the firing rate for a neuron with $g_{\mathrm{sK(Ca)}} \approx 0.31$ (bursting) is from 2 to 3 Hz. This means that if the two neurons were to be coupled to become synchronized, it would be more likely that they would synchronize in a tonic regime at $T = 41\,^{\circ}\mathrm{C}$, given the more predominant firing rate of the tonic neuron compared to that of the bursting neuron at a higher temperature.[44,48] However, it might be the case that temperature increase by itself would not be sufficient for the neurons synchronize, requiring additional action from another process to achieve synchronization.

The tonic-bursting transition[49] mediated by chaos discussed here is known to be associated with a number of neuronal features and processes including ion channel conductances,[42] coupling strength in networks,[48] neuromodulation,[50] and temperature.[44] Here, we are interested in understanding how temperature increase can affect neuronal synchronization and potentially lead to the onset of seizures.

B. Networked neurons

Our neuronal network consists of a regular square lattice with periodic boundary conditions containing 15×15 neurons reciprocally connected via gap junctions, or electrical synapses, to their four next-door neighbors. The core central neuron (112) is selected to be in the tonic regime ($g_{\mathrm{sK(Ca)}} = 0.05$), and the remaining 224 neurons are chosen to be in the bursting regime with $g_{\mathrm{sK(Ca)}}$ values in a random uniform distribution in the interval [0.31, 0.33]. Gap junctions are associated with fast flow of ions between neurons and considered to be part of important synchronizing mechanisms in the brain, particularly in the case of seizures.[51–54] The synapses in our model are implemented by including a diffusive coupling current $I_{\mathrm{coupl,i}}$ into Eq. (), which now reads

$$C\dot{V}_i = -I_{\mathrm{leak}} - I_{\mathrm{Na}} - I_{\mathrm{K}} - I_{\mathrm{sNa}} - I_{\mathrm{sK(Ca)}} - I_{\mathrm{inj}} - I_{\mathrm{coupl,i}}, \quad (5)$$

with

$$I_{\mathrm{coupl,i}} = \eta \sum_{j=1}^{N} A_{ij}\gamma(T)(V_j - V_i), \quad (6)$$

in which η is the coupling strength, N is the total number of neurons, A_{ij} is the adjacency matrix, $\gamma(T)$ is the Arrhenius function, and V_i and V_j are the instantaneous voltages across the membranes of neurons i and j, respectively. The Arrhenius function $\gamma(T) = \gamma_0^{(T-T_{\mathrm{ref}})/10^{\circ}\mathrm{C}}$ is here introduced following the standard modeling of temperature dependency for individual neuronal [see the equations for $\rho(T)$ and $\phi(T)$ in the text below Eq. (4)]. Given that gap junctions can be viewed as channels for the direct flow of ions between neurons, we implemented in our network model gap junctions with the equivalent temperature dependency. The idea is that gap junctions should have their own dependency on temperature, akin to the ionic currents' dependency. This implementation follows a heuristic approach and is consistent with experimental outputs obtained from measurements in cardiac cells[8] and in induced pairs of transfected human HeLa cells.[9]

In order to characterize the collective dynamics of the network, we use the synchronization index R given by

$$R = \frac{\langle X^2\rangle - \langle X\rangle^2}{\frac{1}{N}\sum_{i=1}^{N}[\langle \mathrm{V_i}^2\rangle - \langle \mathrm{V_i}\rangle^2]}, \quad (7)$$

where $X = \frac{1}{N}\sum_{i=1}^{N} \mathrm{V_i}$, N is the number of neurons, $\mathrm{V_i}$ is the voltage over time, and $\langle\bullet\rangle$ represents the mean variable over time. Neurons in the network simulations are initiated with random initial conditions, the first 70 000 transient points are eliminated, and the synchronization index is computed over 50 000 data points after the transient. The synchronization index R gives values between 0 and 1, where 0 means no synchronization, 1 means complete synchronization, and any value between 0 and 1 means partial synchronization. The synchronization measure used in this work is applied to the

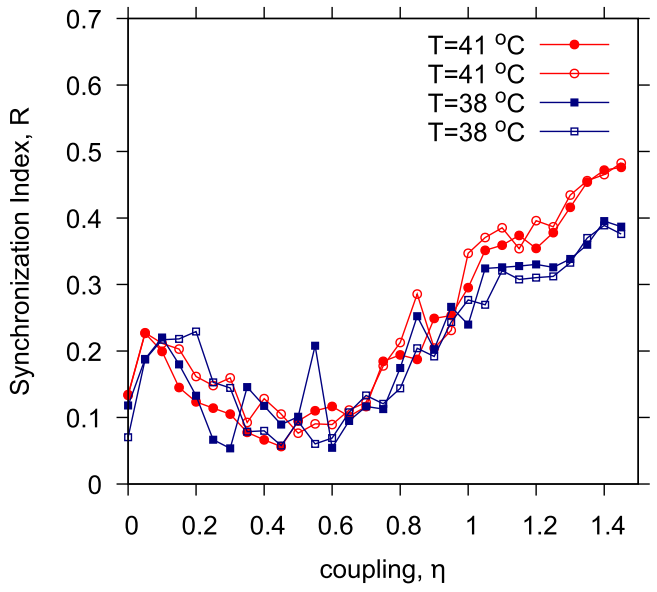

FIG. 5. Synchronization index R for increasing values of the coupling strength for $T = 38\,^{\circ}\mathrm{C}$ and $T = 41\,^{\circ}\mathrm{C}$. Empty square line ($T = 38\,^{\circ}\mathrm{C}$) and empty circle line ($T = 41\,^{\circ}\mathrm{C}$) are for another set of random initial conditions..

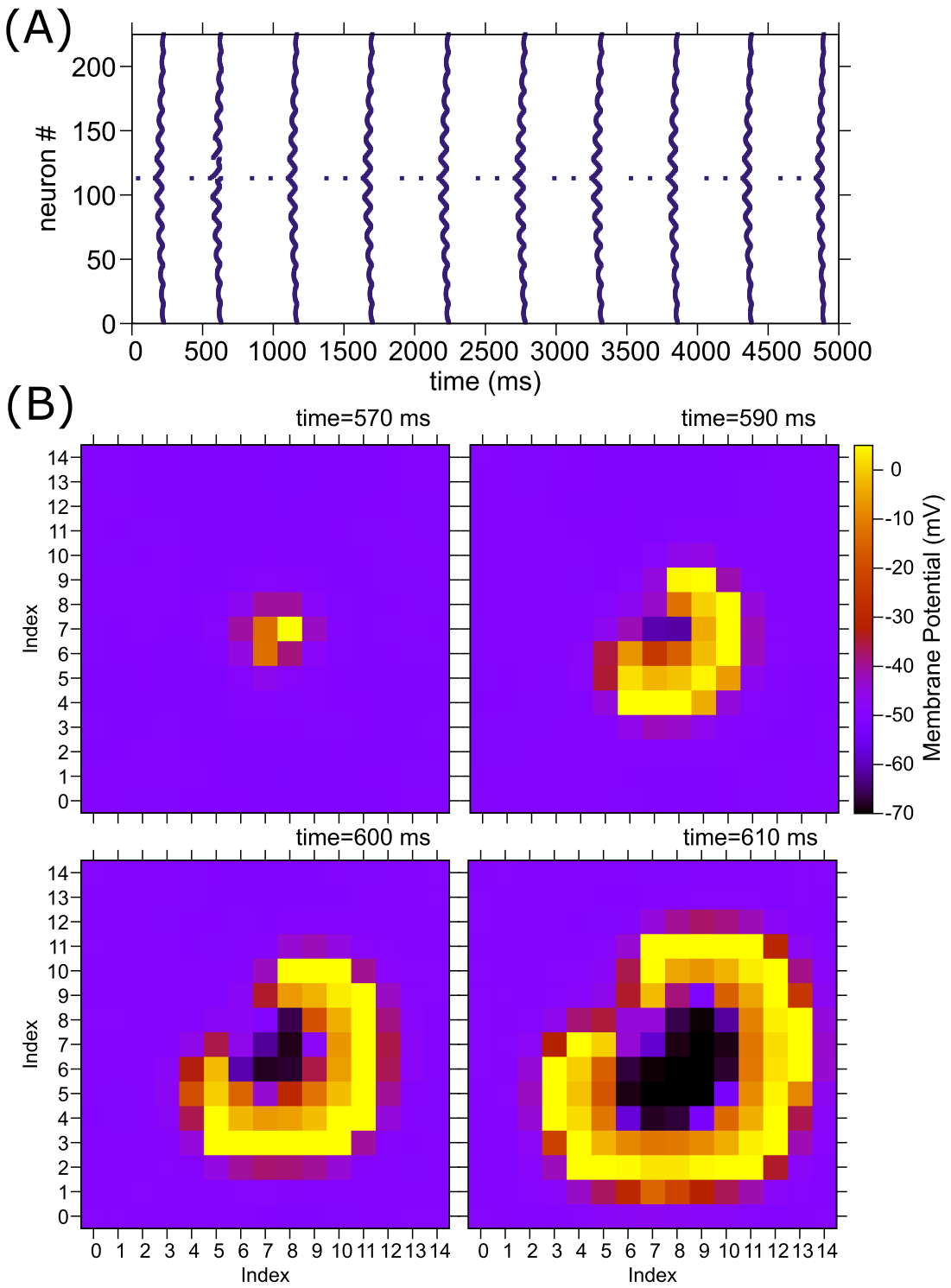

FIG. 6. (A) Raster plot of spiking times for $T = 38\,^{\circ}\mathrm{C}$, $\eta = 1.23$, (B) snapshots of neuron's voltage at times $t = 570$ ms, $t = 590$ ms, $t = 600$ ms, and $t = 610$ ms.

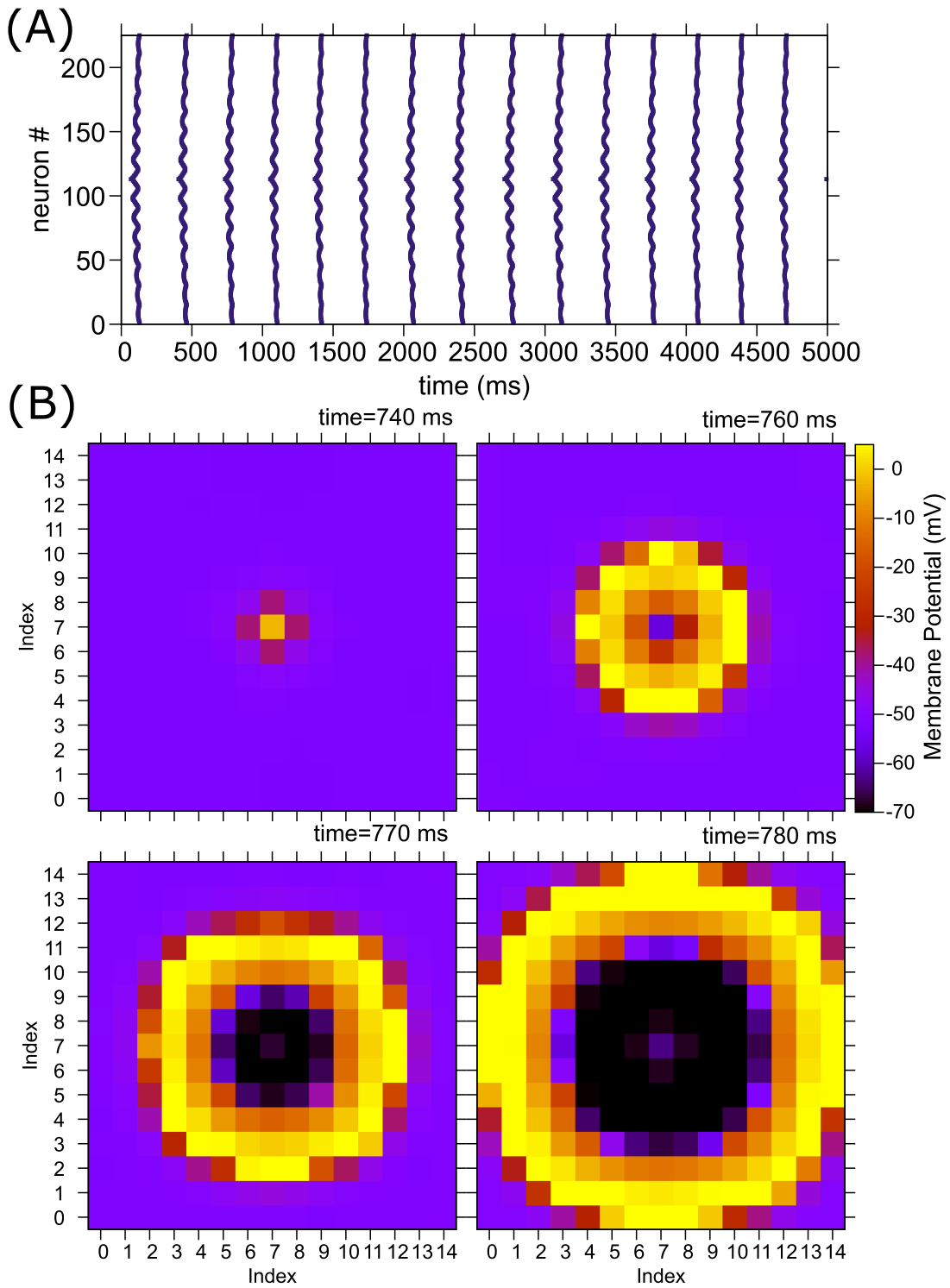

FIG. 7. (A) Raster plot of spike times for $T = 41\,^{\circ}\mathrm{C}$, $\eta = 1.23$; (B) snapshots of neuron's voltage at times $t = 740$ ms, $t = 760$ ms, $t = 770$ ms, and $t = 780$ ms.

noiseless network synchronized in the periodic tonic regime, where complete and phase synchronization may overlap. This is not the case in phase synchronization with stochastic resonance where the phases and the amplitudes of the wave may not overlap and need to be distinguished from each other.[43,55]

Initially, we investigate the case of maintaining the neurons at the brain's normal temperature, $T = 38$ °C, with increasing values of the coupling strength η. Our simulations indicate that starting with no coupling ($\eta = 0$), where the neurons fire independently of each other [Fig. 4(a)], the network output evolves to sparse spots of synchronous behavior for $\eta = 0.5$ [Fig. 4(b)], and to a more structured but still incomplete synchronous state for $\eta = 1$ [Fig. 4(c)]. The corresponding raster plots[24] and snapshots of the network activity shown in Fig. 4 illustrate the trend, confirmed by the respective values for the synchronization index as $R_{(A)} = 0.10$, $R_{(B)} = 0.13$, and $R_{(C)} = 0.27$.

Figure 5 shows how the synchronization index R responds to increasing values of the coupling constant η for the temperatures of 38 and 41 °C, using two different initial conditions for each temperature. The blue lines with empty and filled squares correspond to $T = 38$ °C and the red lines with empty and filled circles correspond to $T = 41$ °C. For increasing values of the coupling strength starting at $\eta \approx 0.5$ the synchronization index also increases, but for $\eta > 1$, higher values of R are consistently obtained at $T = 41$ °C compared to those at $T = 38$ °C. This indicates that higher temperature is facilitating more synchronization among the neurons as a direct result of the implementation of the Arrhenius function in the synapses.

Our network, as a lattice with a tonic neuron at the center surrounded by bursting neurons, is intended to mimic the behavior of a focal seizure, displaying waves of synchronization starting at the center and spreading radially in approximate circular

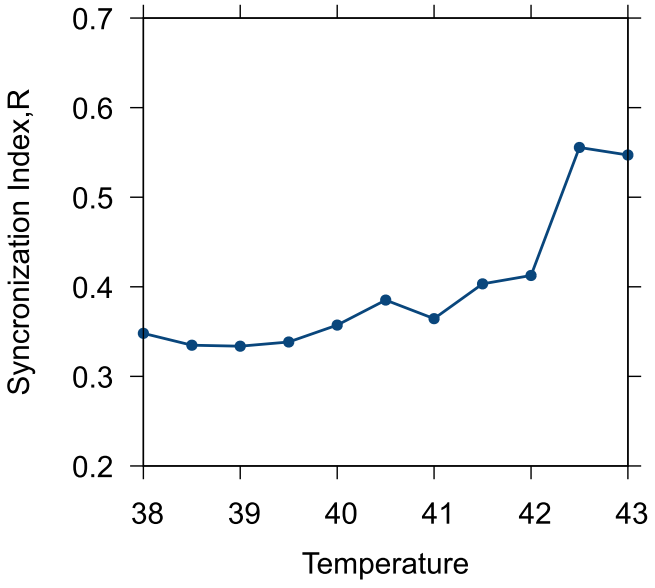

FIG. 8. Synchronization index for coupling constant $\eta = 1.23$ with increasing temperature values.

formation.[10,56,57] Figure 6 raster plot (a) and wave propagation (b) show the initial formation of incomplete waves for $\eta = 1.23$ and $T = 38$ °C, possibly depicting the pre-ictal (aura) stage of the seizure. The raster plot, 6(a), shows the center tonic neuron (112) spiking but not in synchrony with its surrounding neighbors, resulting in an incomplete outgoing wave with a frequency of about 2 Hz, visualized in the four panels of 6(b) with snapshots of the neurons instantaneous voltages taken at times $t = 570$ ms, $t = 590$ ms, $t = 600$ ms and $t = 610$ ms. As the temperature increases to $T = 41$ °C characterizing a febrile state, the central neuron synchronizes with its neighbors as shown in the raster plot, Fig. 7(a), and the snapshots of neuronal activity in the panels of Fig. 7(b), displaying typical waves in ripples as observed in ictal states in the human brain.[11] A more quantitative view of how temperature affects synchrony in the network is depicted in Fig. 8, showing the overall increase of the synchronization index R with higher temperatures for $\eta = 1.23$.

We emphasize that the only difference between the cases depicted in Figs. 6 and 7 is the temperature of the system, at 38 and 41 °C, respectively. In this implementation, the system evolves from a pre-ictal state, with initiation of incomplete waves of synchronous waves at 38 °C, to the total domination of complete synchronous waves typical of seizures at the ictal state at 41 °C.

IV. DISCUSSION

Temperature is among a number of potential causes leading to the onset of seizures, especially if the person already has a pre-existing condition conducive to the event. Higher temperatures increase the excitability of neurons which could facilitate synchronization in connection with their increased coupling. This is a main feature of the neuronal network presented in this work. We implemented an Arrhenius function in the gap junctions connecting the neurons, resulting in coupling strengthening with temperature increase.

The model we propose here is primarily aimed at mimicking the onset of partial (focal) seizures,[58–60] i.e., seizures localized in a brain region with excessive synchronous activity directly linked to high fever or conditions leading to a heat stroke. Partial epileptic seizures can be treated effectively with focal cooling, indicating that while higher temperatures may induce seizures, lower temperatures may not only stop them but also prevent them from happening.[61] The introduction of noise to the system in the context of stochastic resonance[43,55] might enhance synchronization, which if combined with temperature, would be a compounding agent producing cumulative effects facilitating the onset of seizures.

Our network model can be adjusted for studying generalized seizures,[62] characterized by abnormal electrical activity that starts simultaneously in both hemispheres of the brain. This type of synchronization at a distance may be identified as remote synchronization,[63–65] in which case our insights and methods could be applied for studying synchronization of far apart systems, particularly systems that are directly related to climate change.[66]

Moreover, the network model proposed here can be adjusted to study neuropathologies related to sleep, memory, and Parkinson's disease, for example. The topic is of relevance not only to neurological disorders but also to study the adaptability of living organisms

to a quickly changing climate, especially in the context of warming environments.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Rosangela Follmann: Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Software (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Twinkle Jaswal:** Software (equal); Visualization (equal); Writing – review & editing (equal). **George Jacob:** Software (equal); Writing – review & editing (equal). **Jonas Ferreira de Oliveira:** Methodology (equal); Validation (equal); Writing – review & editing (supporting). **Carter B. Herbert:** Methodology (supporting); Visualization (supporting); Writing – review & editing (supporting). **Elbert E. N. Macau:** Funding acquisition (equal); Writing – review & editing (equal). **Epaminondas Rosa Jr.:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

APPENDIX: MODEL PARAMETERS

$g_{leak} = 0.1\,\mathrm{mS/cm^2}$, $V_{leak} = -60\,\mathrm{mV}$, $I_{inj} = 1.0$,
$g_{Na} = 1.5\,\mathrm{mS/cm^2}$, $V_{Na} = 50\,\mathrm{mV}$, $V_{0Na} = -25\,\mathrm{mV}$,
$g_{K} = 2.0\,\mathrm{mS/cm^2}$, $V_{K} = -90\,\mathrm{mV}$, $V_{0K} = -25\,\mathrm{mV}$,
$g_{sNa} = 0.25\,\mathrm{mS/cm^2}$, $V_{sNa} = 50\,\mathrm{mV}$, $V_{0sNa} = -40\,\mathrm{mV}$,
$g_{sK(Ca)} = 0.25\,\mathrm{mS/cm^2}$, $V_{sK(Ca)} = -90\,\mathrm{mV}$, $C = 1\,\mu\mathrm{F/cm^2}$,
$\tau_K = 2.0\,\mathrm{ms}$, $\tau_{sNa} = 10.0\,\mathrm{ms}$, $\tau_{sK(Ca)} = 20.0\,\mathrm{ms}$,
$s_K = 0.25\,\mathrm{mV\text{-}1}$, $s_{sNa} = 0.09\,\mathrm{mV\text{-}1}$, $s_{sNa} = 0.25\,\mathrm{mV\text{-}1}$,
$\nu_{acc} = 0.17$, $\nu_{dep} = 0.012$, $\rho_0 = 1.3$, $\phi_0 = 3.0$, $\gamma_0 = 4.0$,
$T_{ref} = 60\,^{\circ}\mathrm{C}$, $T_{normal} = 38\,^{\circ}\mathrm{C}$.

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