

Information Theoretical Analysis of Neural Spiking Activity with Temperature Modulation

Young-Seok Choi

Abstract—This work assesses the cortical and the sub-cortical neural activity recorded from rodents using entropy and mutual information based approaches to study how hypothermia affects neural activity. By applying the multi-scale entropy and Shannon entropy, we quantify the degree of the regularity embedded in the cortical and sub-cortical neurons and characterize the dependency of entropy of these regions on temperature. We study also the degree of the mutual information on thalamocortical pathway depending on temperature. The latter is most likely an indicator of coupling between these highly connected structures in response to temperature manipulation leading to arousal after global cerebral ischemia.

Keywords—Spiking activity, entropy, mutual information, temperature modulation.

I. INTRODUCTION

ADVANCEMENTS in Cardio-Pulmonary Resuscitation (CPR) have led to reduced mortality after Cardiac Arrest (CA) but poor neurological outcomes still remain a cause for concern [1]. The use of information theoretical measures like an entropy and an information quantity (IQ) [2] add one more entropy related reference have shown that the electroencephalogram (EEG) during early phase of recovery can be used as an indicator of long-term neurological outcomes. Clinical trials [3], [4] published in the past few years have shown that mild-hypothermia can have a therapeutic effect on brain injury after CA and improve survival and functional outcomes in patients. It has further been shown that hypothermia affects EEG bursting leading to favorable outcomes. However, it has also been shown that hyperthermia leads to worsening of injury [15].

These developments have led to several studies being conducted to study the effect of temperature modulation on neuronal activity. Studies combining CA with therapeutic hypothermia commonly focus on studying surface EEG recordings which represent the spatiotemporal integration of cortical post-synaptic potentials. Our previous work using quantitative EEG as an indicator has shown that immediate shorter-duration hypothermia is known to have a better functional outcome as measured by Histopathological Damage Scoring and the Neuro-Deficit Score [5].

It has been shown that the individual spike amplitude and spontaneous firing frequency decreases in parietal cortex slices from pigs [6]. Despite these developments in understanding the effects of hypothermia the cellular mechanisms describing how

hypothermia works, the optimum time, depth and duration of hypothermia remain undefined. In order to optimize therapeutic use of temperature manipulation on a large scale, it is first important to understand how the information coded in the spiking activities (action potentials) of different neural populations involved in brain arousal systems changes with temperature.

In addition, from a point of view which neurons are essentially ‘communication channels’ in the brain, verifying the strength of transferred information of neural pathway make it easier in characterizing the neural mechanisms of arousal and recovery after CA.

Here, we aim at assessing the effect of temperature manipulation on neural spiking activity from the cortical and sub-cortical neurons using information theoretical measure such as entropy and mutual information.

Neural spiking activities were recorded from a rodent model with temperature modulation of three states (low, normal, and high temperature).

II. METHOD

The Animal Care and Use Committee of the Johns Hopkins Medical Institutions approved the experimental protocol used in this study.

A. Experimental Methods

One adult male Wistar rat was placed in a stereotactic frame and a craniotomy was performed following anesthetization using 1-1.5% halothane. A total of 4 channels were recorded using two 2x1 tungsten microelectrodes (FHC, Bowdoin, ME). The electrodes were placed in the somatosensory cortex and ventral posterior lateral nucleus of thalamus (VPL) respectively. These regions were chosen as targets because our translational focus has led us to the study the sensory pathway during recovery and therapeutic interventions.

Body temperature was varied between three ranges, hypothermia, normothermia, and hyperthermia. Rat was monitored during normothermic baseline for 30 min. After maintaining a target temperature of 32-34°C for 30 min, spike recordings were taken for 10 min. Over the next 30 min, the rats were allowed to return to normothermia (36.5-37.5°C). After this a temperature of 38.5-39.5°C was maintained for 30 minutes, followed by another 15 minute recording. A rectal temperature probe (Mon-a-Therm 6510, Mallinckrodt Medical Inc, St Louis, MO) was used for measuring the body temperature for the duration of the experiment. Hypothermia was achieved using surface cooling with misted cold water and an electric fan. Hyperthermia was obtained using a warming

Y.-S. Choi is with the Department of Electronic Engineering, Gangneung-Wonju National University, 7 Jukheon-gil, Gangneung, 210-702 Republic of Korea (phone: +82-33-640-2429; fax: +82-33-646-0740; e-mail:yschoi@gwnu.ac.kr).

blanket and an infra-red lamp (Thermalet TH-5, model 6333, Phyritemp, NJ, USA).

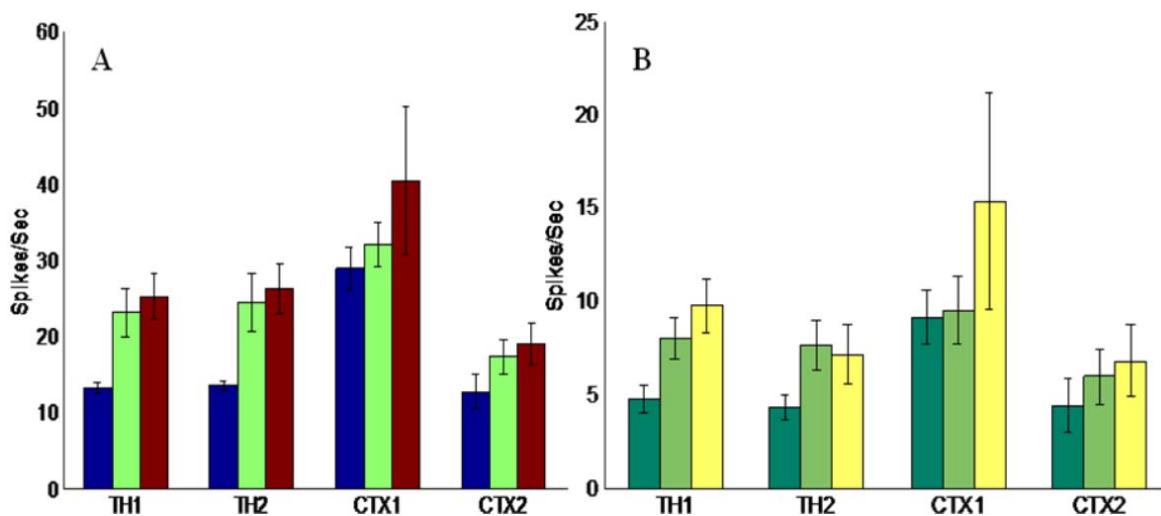


Fig. 1 Population count firing rate with mean and standard deviation (A) and the firing rate of the primary neuron cluster from each channel (B). The three bars in each sub-group from left to right represent conditions of hypothermia, normothermia and hyperthermia respectively. It can be seen that the single unit firing activities are proportional to population firing activities under different temperature.

B. Data Acquisition and Preprocessing

The MUA was digitized at a sampling frequency of 6103.5 Hz by the TDT system (Tucker-Davis Technologies, Alachua, FL), followed by fourth order butterworth band-pass filtering between 300 and 3000 Hz and notch filtering at 60 Hz to remove AC noise from the power lines. The spikes were detected using a biorthogonal family of wavelets as described in [7].

C. Data Acquisition and Preprocessing

After the detection and sorting of spikes, multi-unit spike trains were constructed, and population count firing rate was computed by counting spikes in 20 sec long non-overlapping rectangular windows. A wavelet based spike sorting software [8] was used to extract the primary cluster for each of the 4 channels and individual spike trains were constructed. The primary cluster, in this paper, is defined as the neuron that contributes to the majority of the spikes recorded at an electrode site. Other clusters were relatively small in comparison and were ignored. After computing firing rate of individual units the following analyses were performed on the single-unit spike trains:

1. Shannon Entropy (SE)

The inter-spike interval (ISI) series was binned into N=30 bins and the size of each bin was chosen such that the maximum ISI was three times the standard deviation of the interval series of spontaneous activity. The typical SE [9] was applied as:

$$SE = \sum_{i=1}^N p_i \log_2 p_i$$

where p_i is the i-th bin count normalized to series length.

2. Multi-Scale Entropy (MSE)

The ISI series of the primary clusters were subjected to MSE analysis [10] to study complexity on several time scales. Coarse-grained series were constructed from the interval series up to a maximum scale factor $\tau=20$ using:

$$ISI_{\tau}(k) = \frac{1}{\tau} \sum_{i=(k-1)\tau+1}^{k\tau} ISI_o(i)$$

where ISI_o is the original interval series.

Sample entropy (SampEn) of each coarse-grained series was computed using the approach described in [11]. SampEn is a measure of the log likelihood that a set of patterns of length m are similar to the next set of patterns of length m+1. The similarity criterion r was selected to be 15% of the normalized standard deviation of the original ISI series. A maximum template length m=2 was used for the analysis. Finally, the SampEn for each series was plotted against the scale factors to obtain the MSE curves. A purely independent sequence has a monotonically decreasing MSE profile whereas the profile for a long-range correlated sequence is steady across time scales [10]. Saturation values for each curve were computed as the average of the SampEn values for $\tau > 10$ to account for fluctuations around the stable steady state.

3. Mutual Information (MI)

Segments of the cortical and thalamic single unit trains were used to compute MI using:

$$MI(TH; CTX) = \sum_{i=1}^N \sum_{j=1}^N p_{ij} \log_2 \frac{p_{ij}}{p_i p_j}$$

where p_{ij} represents joint probability of the ISI distributions

from a single cortical (CTX) and thalamic (TH) channel and p_i , p_j are the marginal probability distributions of the ISI's from TH and CTX channels respectively [12]. If SE is used as the measure to characterize the entropy, referred to as I , in the spike trains then we can express MI as:

$$MI(TH; CTX) = I(TH, CTX) - I(CTX|TH) - I(TH|CTX)$$

where $I(TH,CTX)$ is the joint entropy of the two channels, $I(CTX|TH)$ quantifies what we do not know about the CTX

given TH activity and $I(TH|CTX)$ measures the amount of uncertainty in TH given that CTX is known. Therefore MI gives us an indication of the degree of dependence between the spike trains from these two regions. Even though this measure tells us nothing about directional connectivity, the higher the value of MI, the higher is the degree of dependence between the two spike trains. It is worthy to note that the mutual information between two independent distributions is 0.

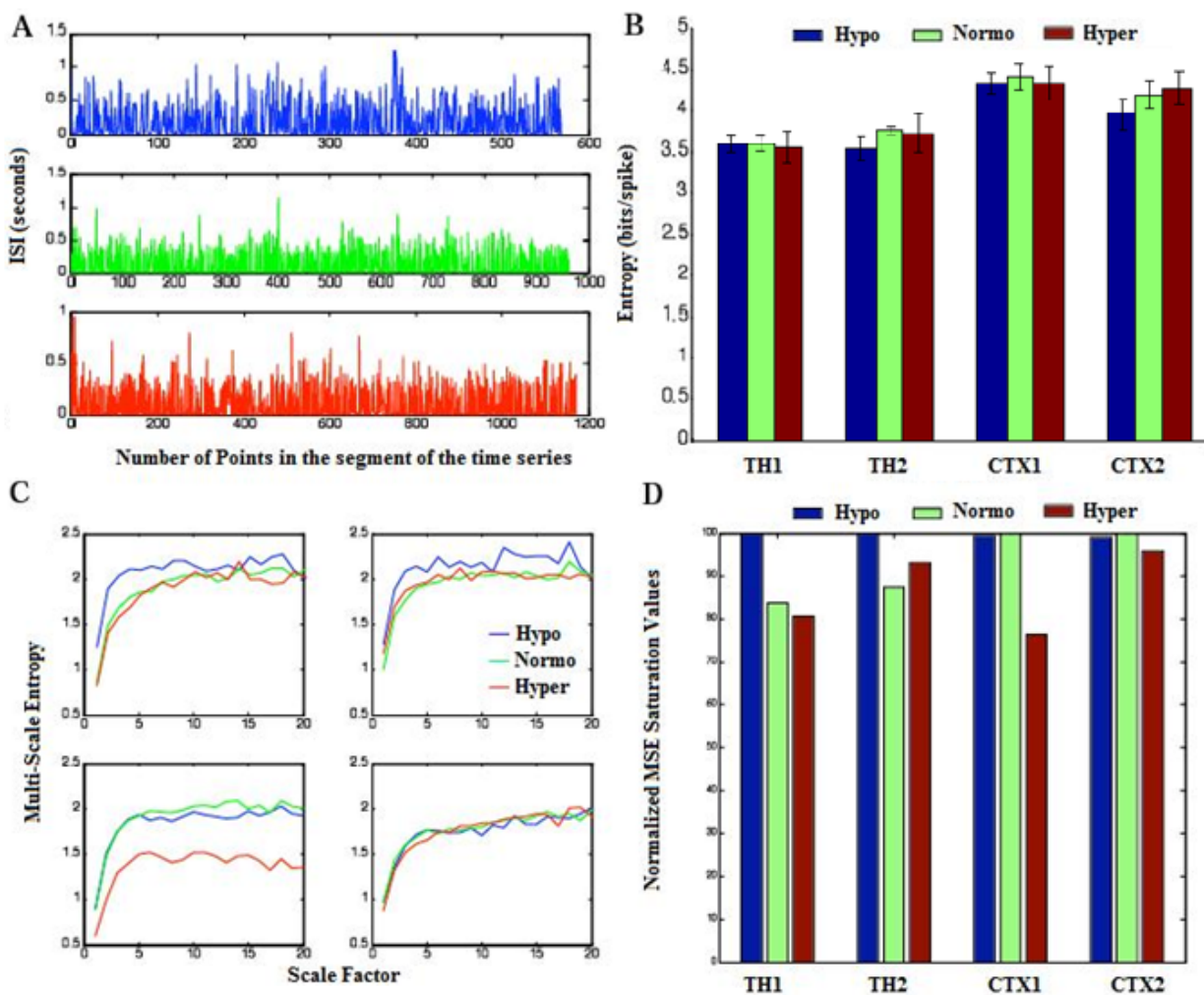


Fig. 2 Entropy analysis on SUA (A) ISI series for the thalamic channel TH1. The three sub-panels from top to down are representative sequences from the low, normal and high temperature phases of the experiment respectively. Only 10% of the points in each of the ISI series are plotted. (B) SE for each of the channels. The bars from left to right represent hypothermia, normothermia and hyperthermia respectively. It can be seen that hypothermia has lower entropy (except CTX1) while the other two phases are quite close to each other. (C) MSE curves for the thalamic (top 2) and cortical (bottom 2) SUA. In the case of hypothermia and normothermia there is a lot of fluctuation after a scale factor of about 12 which requires further analysis. The trends do not show a clear correlation between the temperature and the MSE values but one consistent trend is the low saturation point in hyperthermia. Furthermore, it can be seen that normothermia in the thalamus has lower value than hypothermia which could indicate that is directly affected by temperature change after induction of hypothermia. (D) Normalized MSE saturation values for the channels.

III. RESULTS AND DISCUSSIONS

The firing rates of the cortical - thalamic neural populations and single units are shown in Fig. 1. As expected, the firing rate

at both levels of activity is directly proportional to the temperature with the exception of the single-unit activity in TH2 which can be attributed to injury due to hyperthermia.

Even though MUA does not preserve the timing information of the spiking activity at the single neuron level it gives a good indication of the tone of activity in the neuronal pool around the recording electrode. As discussed in [13] single unit recordings fail when used to study dynamic interactions in central brain circuits where several networks are working at multiple spatiotemporal scales. SUA would also be difficult to capture and hold throughout the injury experiments and loss of neurons due to injury or death would also be a real possibility.

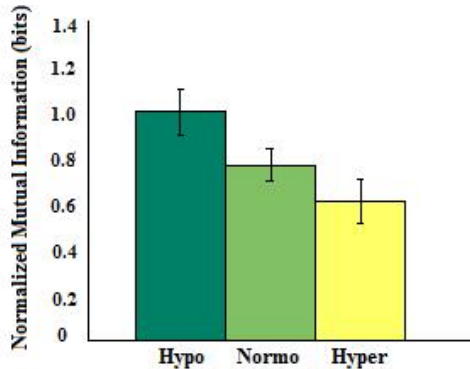


Fig. 3 MI was estimated using single-unit ISI distribution. The plot shows that the dependency between CTX1 and TH1 is the higher during hypothermia

As can be seen in Fig. 2 traditional SE gives different results from MSE. The SE of the hypothermia phase is the lowest of all 4 channels whereas the MSE saturation values during hypothermia are the highest. It can also be observed that MSE during hyperthermia saturates at a lower value than that of hypothermia. Using the fundamental understanding of MSE as a measure of structural complexity of a physiologic signal we can hypothesize why hypothermia leads to better neurological outcomes after an ischemic insult.

After the near zero-activity CA phase the brain needs to be 'woken up' in order to come out of the comatose state. Even though reduction in temperature reduces metabolic needs of the brain and lessens the excitotoxic effects of neurotransmitters like glutamate, the temperature change in itself acts as a stimulus for thalamic activation. Thalamic neuron bursting may serve as a 'wake-up call' to the cortex [14], which in turn may lead to the arousal of the cortex. According to this hypothesis, both increases and decreases in temperature should lead to arousal. The reason as to why hypothermia has a higher complexity and a therapeutic effect than hyperthermia is that the latter leads to neuronal injury [15].

It can also be seen that the MSE values during normothermia are lower in the thalamus than in the cortex. This may indicate that thalamic firing is more directly affected by a temperature change and that the change in cortical activity is a downstream change. The direct effect on the thalamus may be the result of its location in deeper brain regions where temperature gradients, blood flow or effects of neuro-protective strategies may be different than at the cortex. As a preliminary indicator of dependence between the thalamus and cortex, MI was

computed and Fig. 3 shows that this dependence increases during hypothermia.

IV. CONCLUSION

This study has shown that firing rate, measured by SUA and MUA, is directly proportional to core body temperature within the range 32-38°C, just like in in-vitro neuronal cultures [6]. SUA further revealed that to understand the underlying complexity of neurons, MSE presents a better picture than SE. Lastly; it was shown that there is a higher interaction between the cortex and thalamus during hypothermia. Future works will be carried out to develop optimum conditions of hypothermia including onset time, duration and temperature. Directional measures for studying spatiotemporal correlation will also be presented.

REFERENCES

- [1] W. Rosamond, K. Flegal, G. Friday, K. Furie, A. Go, K. Greenlund, N. Haase, M. Ho, V. Howard, B. Kissela, S. Kittner, D. Lloyd-Jones, M. McDermott, J. Meigs, C. Moy, G. Nichol, C. J. O'Donnell, V. Roger, J. Rumsfeld, P. Sorlie, J. Steinberger, T. Thom, S. Wasserthiel-Smoller, and Y. Hong, "Heart disease and stroke statistics--2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation*, vol. 115, pp. e69-171, Feb 6 2007.
- [2] H. C. Shin, S. Tong, S. Yamashita, X. Jia, R. G. Geocadin, and N. V. Thakor, "Quantitative EEG and effect of hypothermia on brain recovery after cardiac arrest," *IEEE Trans Biomed Eng*, vol. 53, pp. 1016-23, Jun 2006.
- [3] "Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest," *N Engl J Med*, vol. 346, pp. 549-56, Feb 21 2002.
- [4] S. A. Bernard, T. W. Gray, M. D. Buist, B. M. Jones, W. Silvester, G. Gutteridge, and K. Smith, "Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia," *N Engl J Med*, vol. 346, pp. 557-63, Feb 21 2002.
- [5] X. Jia, M. A. Koenig, H. C. Shin, G. Zhen, C. A. Pardo, D. F. Hanley, N. V. Thakor, and R. G. Geocadin, "Improving neurological outcomes post-cardiac arrest in a rat model: immediate hypothermia and quantitative EEG monitoring," *Resuscitation*, vol. 76, pp. 431-42, Mar 2008.
- [6] Y. S. Mednikova, N. V. Pasikova, and F. V. Kopytova, "Effects of temperature on the spike activity of cortical neurons in guinea pigs," *Neurosci Behav Physiol*, vol. 34, pp. 459-65, Jun 2004.
- [7] Z. Nenadic and J. W. Burdick, "Spike detection using the continuous wavelet transform," *IEEE Trans Biomed Eng*, vol. 52, pp. 74-87, Jan 2005.
- [8] R. Q. Quiroga, Z. Nadasdy, and Y. Ben-Shaul, "Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering," *Neural Comput*, vol. 16, pp. 1661-87, Aug 2004.
- [9] C. Shannon, "A mathematical theory of communication," *Bell Syst. Tech. J.*, vol. 27, pp. 379-423/623-656, 1948.
- [10] M. Costa, A. L. Goldberger, and C. K. Peng, "Multiscale entropy analysis of complex physiologic time series," *Phys Rev Lett*, vol. 89, p. 068102, Aug 5 2002.
- [11] A. L. Goldberger, L. A. Amaral, L. Glass, J. M. Hausdorff, P. C. Ivanov, R. G. Mark, J. E. Mietus, G. B. Moody, C. K. Peng, and H. E. Stanley, "PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals," *Circulation*, vol. 101, pp. E215-20, Jun 13 2000.
- [12] A. Kraskov, H. Stogbauer, and P. Grassberger, "Estimating mutual information," *Phys Rev E Stat Nonlin Soft Matter Phys*, vol. 69, p. 066138, Jun 2004.
- [13] G. Buzsaki, "Large-scale recording of neuronal ensembles," *Nat Neurosci*, vol. 7, pp. 446-51, May 2004.
- [14] S. M. Sherman, "A wake-up call from the thalamus," *Nat Neurosci*, vol. 4, pp. 344-6, Apr 2001.
- [15] R. W. Hickey, P. M. Kochanek, H. Ferimer, H. L. Alexander, R. H. Garman, and S. H. Graham, "Induced hyperthermia exacerbates neurologic neuronal histologic damage after asphyxial cardiac arrest in rats," *Crit Care Med*, vol. 31, pp. 531-5, Feb 2003.