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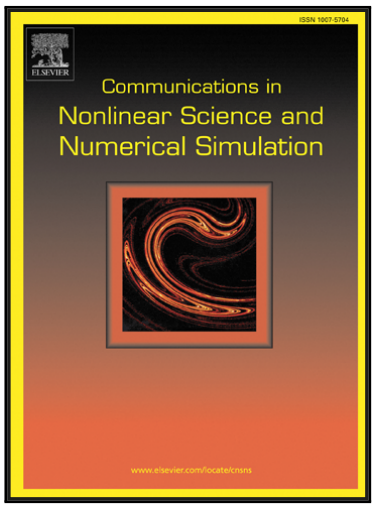

The complexity of intracranial pressure as an indicator of cerebral autoregulation

Nicolás Ciarrocchi, Nicolás Quiróz, Francisco Traversaro, Eduardo San Roman, Marcelo Risk, Fernando Goldemberg, Francisco Redelico

PII: S1007-5704(19)30086-3
DOI: https://doi.org/10.1016/j.cnsns.2019.03.018
Reference: CNSNS 4802

To appear in: *Communications in Nonlinear Science and Numerical Simulation*

Received date: 20 August 2018
Revised date: 12 March 2019
Accepted date: 17 March 2019

Please cite this article as: Nicolás Ciarrocchi, Nicolás Quiróz, Francisco Traversaro, Eduardo San Roman, Marcelo Risk, Fernando Goldemberg, Francisco Redelico, The complexity of intracranial pressure as an indicator of cerebral autoregulation, *Communications in Nonlinear Science and Numerical Simulation* (2019), doi: https://doi.org/10.1016/j.cnsns.2019.03.018

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Highlights

- Loss of complexity is associated with elevated Intracranial Pressure
- The loss of compensatory mechanism in the cerebral autorregulation icreases the Missing Patterns in the Permutation Entropy calculation

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The complexity of intracranial pressure as an indicator of cerebral autoregulation

Nicolás Ciarrocchi[a], Nicolás Quiróz[b], Francisco Traversaro[b,c], Eduardo San Roman[a], Marcelo Risk[b], Fernando Goldemberg[d], Francisco Redelico[b,f]

[a] *Hospital Italiano de Buenos Aires, Servicio de Terapia Intensiva Adultos, Perón 4190 - (C1199ABB) Ciudad Autónoma de Buenos Aires, Argentina.*
[b] *Instituto de Medicina Traslacional e Ingenieria Biomedica, UE de triple dependencia CONICET - Instituto Universitatio del Hospital Italiano (IUHI) - Hospital Italiano (HIBA), Potosí 4239 - (C1199ABB) Ciudad Autónoma de Buenos Aires, Argentina.*
[c] *Facultad de Ciencias Agrarias e Ingenieria, Universidad Católica Argentina (UCA)*
[d] *The University of Chicago Medicine 5841 S. Maryland Avenue, MC 2030 Chicago, IL 60637.*
[e] *CONICET - Hospital Italiano de Buenos Aires, Departamento de Informática en Salud, Perón 4190 - (C1199ABB) Ciudad Autónoma de Buenos Aires, Argentina.*
[f] *Universidad Nacional de Quilmes - Departamento de Ciencia y Tecnología, Roque Sáenz Peña 352 (B1876BXD), Bernal Buenos Aires, Argentina.*

Abstract

Intracranial Pressure (ICP) is one of the main neuromonitories used today to guide the treatment of acute neurological patients in the Intensive Care Unit (ICU).

Within this article the complexity of periods of intracranial hypertension is evaluated and compared with periods of stable intracranial tension. Using the multiparameter intelligent monitoring in intensive care III (MIMIC-III) database from the *Beth Israel Deaconess Medical Center* the complexity of periods of stable intracranial tension and high intracranial hypertension are evaluated using two quantifiers: the Permutation Entropy and their respective number of missing patterns. Both indicate a loss of complexity in hypertension signals. A physiological explanation of this loss of complexity is given using a dynamical model of the Cerebral Autorregulation and Cerebral Hemodynamics.

Keywords: Intracranial Pressure, Clinical manifestation of Complexity, Permutation Entropy

Preprint submitted to Communications in Nonlinear Science and Numerical Simulation March 19, 2019

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Introduction

Intracranial Pressure (ICP) is one of the main neuromonitories used today to guide the treatment of acute neurological patients in the Intensive Care Unit (ICU) [1]. It is determined by the relation of the cranial cavity and its content (brain tissue, cerebrospinal fluid and blood volume) and regulated by a complex mechanism that allows to maintain its value in different situations [2]. One component of this mechanism is Cerebral Autoregulation (CA) that enables changes in blood flow and volume in the face of changes in blood pressure. CA and ICP have a complex interrelation where the maintenance of ICP depends on the preservation of CA and this depends in turn on ICP since the presence of intracranial hypertension (ICH) exhausts CA mechanism. Many mathematical models were proposed to understand the CA dynamics [3, 4, 5]. From a system's dynamics point of view and following the model proposed by Ursino *et al.* [5] for the interaction between ICP and cerebral hemodynamics (Fig. 1), there are three different negative feedback control loops that preserve cerebral autoregulation, and a positive feedback loop that causes instabilities due to active changes in the arterial-arteriolar blood volume. The instability in CA caused by the feedback IV (See Fig. 1) is the type of instability studied in this article using a complexity framework: if the patient has a modest Cerebrospinal Fluid (CSF) outflow resistance and an a low intracranial compliance, this triggers a cycle of positive feedback where, as intracranial compliance worsens, the positive feedback cycle becomes more influential in intracranial dynamics, moving the system away from optimal equilibrium, analogue to Rosner's vasodilatadory cascade. When the pressure in cerebral perfusion decreases, it also generates a decrease in the Cerebral Blood Flow (CBF) with the consequent vasodilatation effect to maintain a constant flow, leading to an increase in Cerebral Blood Volume (CBV), thus increasing the ICP, which causes a greater decrease in Cerebral Perfusion Pressure (CPP) generating a vicious circle, i.e. positive feedback. The other three feedbacks are escape ways that try to hold the ICP in normal values.

The study of the complexity in physiological systems begins with the work by Kaplan *et al.* [6]. In that article the difference between the complexity of the heart rate frequency between a group of young patients (21-35 years) and adult patients (62-90 years) was quantified, finding a reduction in the complexity of the former with respect to the latter. The hypothesis of reduction in the complexity of physiological systems with respect to

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age and disease was postulated by Lipzsitz and Goldenberg [7]. Since then, there have been many published articles supporting this hypothesis, in such different subjects as *Epilepsy* [8, 9], *Congestive Heart Failure* [10], *Dilated Cardiomyopathy* [11], *Subarachnoind Hemorrhage* [12], among others. While there are many working definitions about complexity [13], within this article we adopt a definition of structural complexity, following the taxonomy proposed by Tang *et al.* [14], using a global quantifier: the Permutation Entropy (PE) proposed by Bandt and Pompe in [15]. The PE is an informational quantifier [16] that takes into account the time correlation structure of the signal. Its computation is fast, requires not too long time series [17], it is robust against noise [18] and distributional assumptions of the time series [19]. PE was previously used as an useful complexity tool in neuroscience in several papers: *Epilepsy* ([19, 20]), *Anesthesia* ([21, 22, 23, 24, 25, 26]), and *Cognitive Neuroscience* ([27, 28, 29]), however we have not found its use in the analysis of signals in intensive care patients.
PE measures the degree of expectation in the correlation structure of a time series, *so high values of PE indicate high unpredictability and therefore high structural-global complexity.* Although in Section 1 we present a synthesis of the calculation of PE we refer to [8, 15, 17] for a more detailed study on this quantifier and its relationship with complexity. For all of this, within this article complexity and PE are equivalent. Due the interaction of the four loops in Fig. 1, the attractor of the ICP dynamics is a fixed point hence the direction of the change of the complexity in the presence of a pathology is expected to be negative, and in fact it happens.

1. Materials and Methods

This a retrospective analysis using the multiparameter intelligent monitoring in intensive care III (MIMIC-III) which is a large publicly available database comprising de-identified health-related data associated with over 40000 patients in critical care units at the *Beth Israel Deaconess Medical Center* (BIDMC) between 2001 and 2012 [30, 31]. The MIMIC-III Waveform Database Matched Subset (*http://physionet.org/physiobank/ database/mimic3wdb/matched/*) contains all MIMIC-III waveform records that have been associated to MIMIC-III Clinical Database records containing 22317 waveform records and 22247 numeric records matched with 10282 clinical data [32, 30] Despite the large number of patients registered at the MIMIC-III Waveform Database Matched

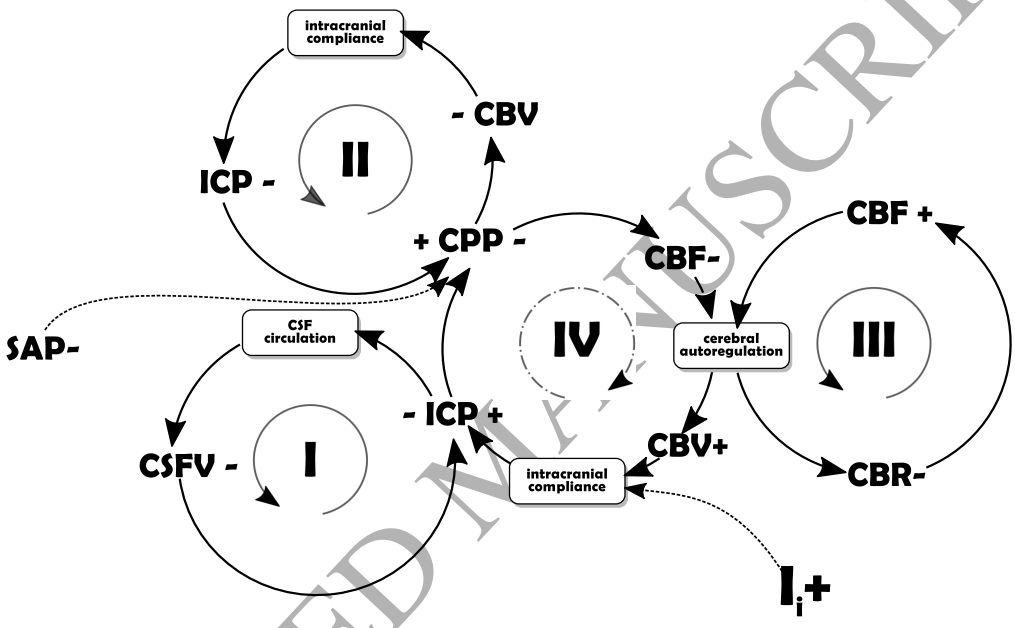

Figure 1: The interaction between Intracranial Pressure and cerebral hemodynamics. There are three different negative feedback control loops that preserve cerebral self-regulation; *feedback I*: *the cerebrospinal fluid (CSF) loop*, *feedback II*: when a diminution of the Systemic Arterial Pressure is present, the Cerebral Perfusion Pressure (CPP) also decreases, generating the decreases of the Cerebral Blood Volume (CBV) that induces, via the intracranial compliance, a reduction of the intracranial pressure (ICP), and the effect of self-regulation in Cerebral Blood Flow (CBF) (*feedback III*), thus increasing the ICP, which leads to greater decrease in CPP generating a positive feedback (*feedback IV*).

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Subset, only a small fraction corresponds to patients with acute neurological disease (see Table I) whose records contain ICP signal measurements. They account for a total of 37 days of ICP signals measured at a 125 Hz sample rate (15 GB of signal data). Both physiological and clinical data were downloaded following the recommendations in [33, 30, 32, 34, 35]. In order to have access to the MIMIC-III Clinical Database, the completion of a CITI Data or Specimens Only Research course was required as well as the creation of an account at PhysioNet.(*https://www.citiprogram.org/verify/?k8e6410f7-6dbc-41d8-ae12-9b29f7b6372f-24580999*).

Each physiological signal data is composed of a list of waveform segments. These segments were independently processed. In order to get complete and free of artifact signals an imputation method was applied to estimate for both missing values (NA) and out of range data in each signal. The imputed value is the mean of the 10 nearest neighbors of the patient's signal missing value. Next, in order to avoid the pulsation effect of respiration and heartbeat, a moving average filter was applied with a sliding window of 10 seconds span and a maximum overlap [36]. The segments may or may not contain episodes of Intracranial Hypertension (ICH), defined as ICP $\geq$ 20 mmHg during a period of 5 min. Following this criteria, an autonomous episode detector was developed to identify ICH criteria in all segments. The resultant episode subsets were visually examined and either confirmed or rejected (i.e. artifacts in recordings). Finally, each accepted episodes can be divided into three adjacent non-overlapping segments with the following characteristics: A maximum 300 s stable zone (ST), a 10 - 240 s transition zone (TZ), and at maximum 20 s critical zone (CR). We used three criteria to identify acute episodes of ICH: the difference between the minimum value in the critical region and the maximum value in the stable region must be at least 5 mmHg, the minimum value in the CR must be greater than 20 mmHg; and the maximum value in the ST must be less than 20 mmHg [37]. The original ICP signal for patient 87969 and the corresponding filtered signal as well as an schematic representation of both the ICH and all regions are showed in Fig. 2, based in [38, 39]. These criteria were applied to get two non-overlapped signals, i.e. the ST and CR zones, to quantify the loss of complexity between them.

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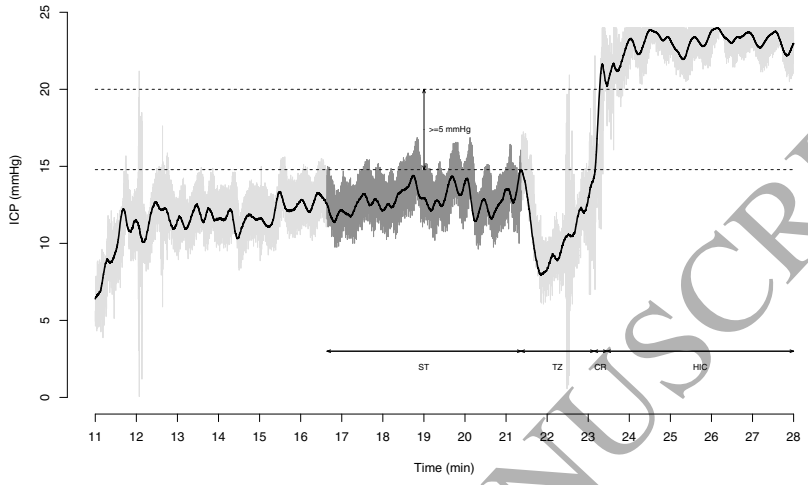

Figure 2: ICP signal for the third ICH episode detected in segment 368853 corresponding to patient 87969. The light gray is the actual 18 min long ICP signal sampled at 125 Hz, the dark line is the 10 s moving average for the same signal.

1.1. Permutation Entropy

One measure for complexity is named Entropy, which is defined as a quantifier of the uncertainty present in a system. One of the most well accepted formula is named Shannon Entropy since Claude Shannon [40], and it is defined as:

$$\mathcal{H} = \left\{ -\sum_{i=1}^{m!} P(\pi_i)\ \ln(P(\pi_i)) \right\} / S_{max}, \tag{1}$$

where $P(\pi_i)$ represents the probability that the system belongs the state π_i and S_{max} is the Shannon Entropy for the equilibrium state. In our case the system under study is the cerebral autoregulation through the intracranial pressure signal obtained from a given patient and the $P(\pi_i)$ are calculated by the evolution of that signal embedded in a m-dimensional vector. When the probabilities $P(\pi_i)$ are calculated by the probability of occurrence of certain patterns derived from Bandt and Pompe methodology of symbolization [15] it is called Permutation Entropy (PE) . One important concept derived from PE is the number of missing patterns (NMP) defined as the number of

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patterns that the m-dimensional vector never arise. The reader interested in mathematical details will fund a brief discussion in Fig. 3, Appendix I and in [15, 8]

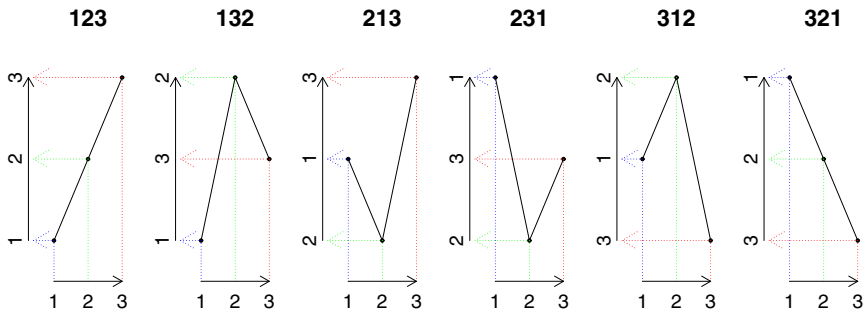

Figure 3: Symbols of the Bandt and Pompe symbolization for $m = 3$. This methodology simply maps each value x_i in the 3-dimensional vector $X_m(t)$ ordering its index $t \in \{1, 2, \ldots, m\}$ according to the increasing amplitude (rank) of each x_i in $X_m(t)$. It can be seen that the indexes of the time axis are fixed in chronological order, and they are mapped onto the vertical (amplitude) axis. For each pattern $X_3(t) = (x_t, x_{t+1}, x_{t+2})$, the resultant symbol π_i can be obtained reading the labels in the vertical axis from the bottom to the top (in the direction of the increasing amplitude).

2. Results

Twelve patients were analyzed looking for ICH and stable regions. As it is shown in Table 1 there were 9 females and 3 males with an age with a range from 32 to 82 years old and a mean of 56.9 ± 14.8 years old, the length of the stay in the ICU was from 9 to 82 days; six patients present subarachniod hemorrahge and six patient, intracranial hemorrage. Only 4 patients present ICH periods as defined in material and methods, three patients present only one ICH each one and one patient present four, leading to 7 signals of ICH, see Table 2.

Permutation Entropy was estimated for all patients for their respective Stable and Intracranial Hypertension, segment 3629298 does not has a Stable region. Across all segments, Permutation Entropy is higher within the stable region than within ICH region and this difference is significant as Table 3 shows no overlapping in the confidence intervals. Fig. 4 shows the histogram of the sampling distribution for the PE estimated over the ICH region and

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Patient	Age	Gender	Diagnosis	Length of stay(d)	Survival
42210	42	F	subarachniod hemorrhage	15 (h)	Y
44789	67	F	subarachniod hemorrhage	24	Y
51909	47	M	subarachniod hemorrhage	16	Y
53639	47	F	subarachniod hemorrhage	17	Y
59991	63	M	subarachniod hemorrhage	34	Y
74438	33	M	intracranial hemorrhage	55	Y
79228	63	M	intracranial hemorrhage	27	N
85892	57	F	intracranial hemorrhage	19	Y
87913	60	F	intracranial hemorrhage	22	Y
87969	78	F	intracranial hemorrhage	82	Y
89002	41	F	subarachniod hemorrhage	21	Y
95951	82	F	intracranial hemorrhage	9	N
$mean \pm sd$	56.9 ± 14.8				

Table 1: There were 9 females and 3 males with an age with a range from 32 to 82 years old and a mean of 56.9 ± 14.8 years old, the length of the stay in the ICU was from 9 to 82 days; six patients suffer for subarachniod hemorrhage and six patients, intracranial hemorrhage and there were 2 nonsurvival patients.

Segments	# ICH episodes	ICH summary	
		Mean(ICP)	Std (ICP)
3365681	1	22.79	0.93
3487247	1	23.41	0.68
3629298	1	28.19	0.2615
		22.97	2.80
368853	4	30.83	0.30
		23.59	0.71
		31.18	1.46

Table 2: Mean and standard deviation of the ICP within the patients segments for the ICH episodes.

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stable region respectively. The sampling distribution approximation was obtained using the bootstrap proposed in [8].
Along with PE, the *Number of Missing Patterns* was calculated in the same way. Table 4 shows the NMP calculated over the stable region and the ICH for each patient along with its standard deviation, for all patient the difference is statistically significant, in Fig. 5 the histogram of the sampling distribution for the NMP estimated over the ICH region and stable region is shown. Again, the sampling distribution of the NMP was approximated using the bootstrap proposed in [8].

Segment		Stable	ICH
3365681		0.1736±0.0201	0.1597±0.0021
3487247		0.2249±0.0130	0.1783±0.0042
3629298		-	0.2615±0.003
	1	0.2293± 0.031	0.1743±0.0105
	2	0.2144 ± 0.01001	0.1757 ± 0.0091
3688532	3	0.2106 ± 0.0210	0.2062 ± 0.0035
	4	0.1957 ± 0.0205	0.1754 ± 0.0026

Table 3: *Permutation Entropy* of the Stable and Intracranial Hypertension (ICH) for all patients analyzed within this paper. Patient 85892 does not has a stable region. Across all segments, Permutation Entropy is higher within the stable region than within ICH region. Patient 74438 has suffered 4 ICH episodes.

3. Discussion

The concept of homeostasis in physiology implies that the system operates in a stable state, or fixed point attractor, where the process fluctuates around a stable value. Then we can define a complex biological system as one that is very sensitive to small changes in initial conditions and reacts adaptively to minimal changes in its environment. Therefore, the complexity of such a system can directly correlate with its ability to react to change and, when this capacity is lost, we can postulate that the complexity of the system is also adversely affected. Therefore for these systems, it has been hypothesized that complexity decreases in the presence of a stressor [41]. This is what we see in the Table 3 and in Fig. 4: periods of hypertension

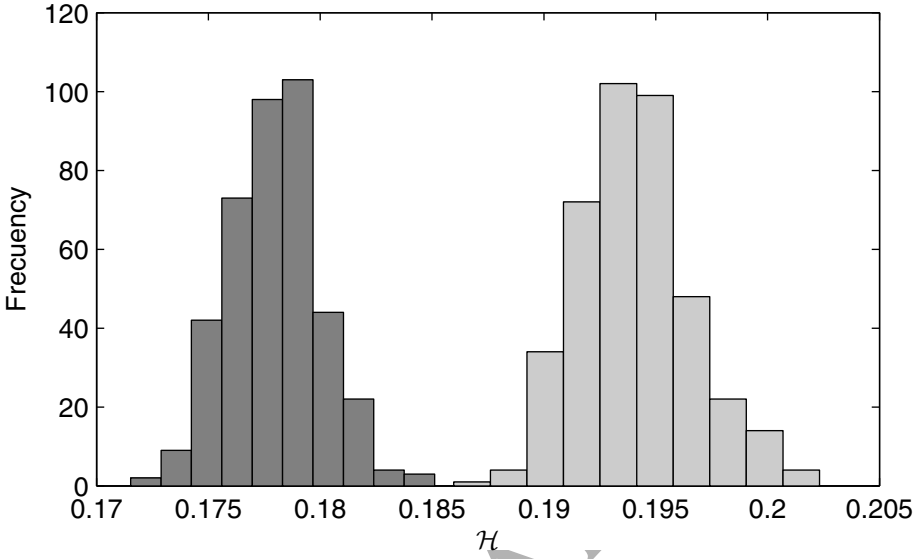

Figure 4: Histogram approximating the sampling distribution of the PE for the stable region (light gray) and the ICH region (dark gray) for the patient 87969. Note the statistically significant reduction in the PE calculated over the ICH region. The sampling distribution of PE was draw using a bootstrap approach presented in [8].

Segment		Stable	ICH
3365681		582 ± 12	672 ± 20
3487247		519 ± 15	580 ± 13
3629298		-	505 ± 11
	1	541 ± 14	632 ± 15
	2	671 ± 11	626 ± 17
3688532	3	605 ± 14	646 ± 15
	4	489 ± 13	625 ± 12

Table 4: *Number of Missing Patterns* (NMP) of the stable region and Intracranial hypertension (ICH) for all patients analyzed within this paper. Patient 85892 does not has a stable region. Across all patients, the NMP is lower within the stable region than within ICH region. Patient 74438 has suffered 4 ICH episodes.

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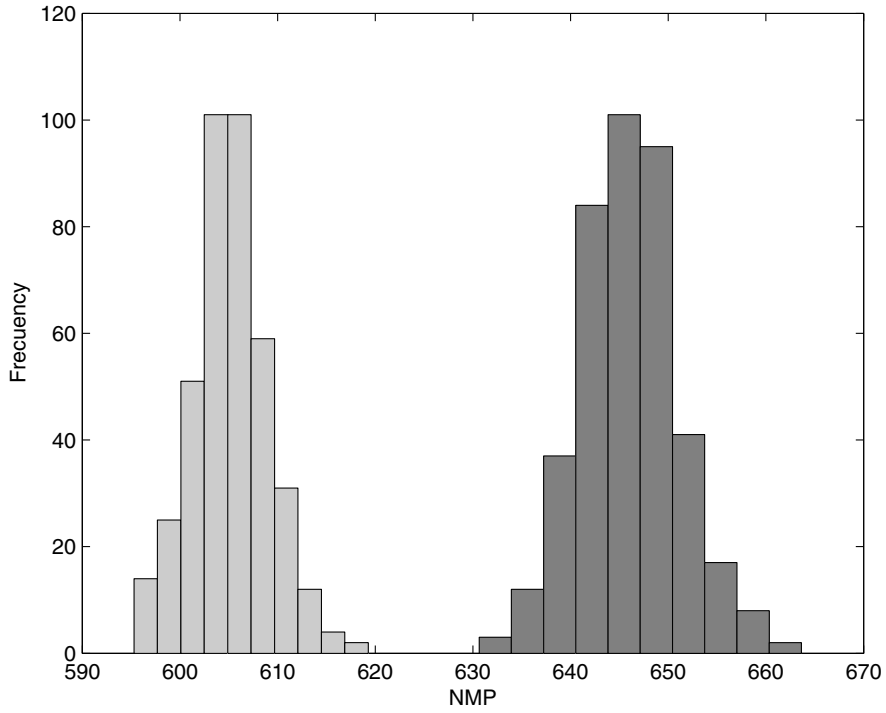

Figure 5: Histogram approximating the sampling distribution of the NMP for the stable region (light gray) and the ICH region (dark gray) for the patient 87969. Note the statistically significant reduction in the NMP calculated over the ICH region. The sampling distribution of NMP was draw using a bootstrap approach presented in [8].

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have a lower entropy than the stable period for each patient. The action of the positive feedback (Rosners vasodilatory cascade), see Fig. 1, causes an instability that when the three negative loops (escapes ways) are not able to counteract this instability, a transition zone is presented and finally a new metastable equilibrium is achieved qith a lower complexity than the initial state.

The state above indicates that a loss of complexity occurs within an hypertension episode and the feedback loop model may lead to an explanation of this loss. According to [41], the loss of complexity may reflect the loss or impairment of functional components of the system, in this case when the mechanism of cerebral auto-regulation exhausts, i.e. the negative loops, the complexity of the ICP decreases and this fact is interesting because complexity measured using the PE reflects a physiological fact and not just an epiphenomena.

In Table 4, and in Figure 5 for patient 87969, there is an increase in the number of missing patterns in the periods of hypertension regarding to the stability stages. This seems to indicate a presence of lower degrees of freedom in the system of the dynamics of the ICP signal that is observed during the periods of ICH demonstrating a lower adaptability of the cerebrovascular system. That is to say, the cerebrovascular system loses the capacity to respond adequately due to the fact that its regulation mechanisms are diminished, and therefore this system loses complexity, so it has a smaller spectrum of possible responses and therefore less adaptability to stress. When losing the ability to respond, secondary lesions may occur due to lack of adaptation to changes in the environment such as blood pressure, temperature, etc. Our results are concordant with those found by Hornero *et al.* [42] in a population of *pediatric patients with traumatic brain injury* and, as *our population are adult patients with strokes of different origins*, *this suggests that the decrease in the complexity of the cerebrovascular system is independent of the type of primary injury and age.*

From the point of view of the *clinical implication*, in *Lu et al.* [36] showed that *the loss of the complexity of the intracranial pressure signal correlates with worse outcomes. So we should ask if beyond the isolated value of intracerebral pressure, we should not act on changes in the complexity of the signal as it provides important information about the status of cerebral autoregulation and can be already determined in real time. Besides, this could help us to generate therapies to decrease intracranial pressure and thus provide a greater spectrum of responses to avoid secondary damage to the lack*

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of regulation of the cerebrovascular system as discussed above.
We are aware about some limitations of our study, the signals analyzed in this study came from 7 patient, and more patients should be sampled in order to empirically validate the mathematical model; we use an external database and we have no control about the clinical trial and the outcome recorded, and finally no direct or indirect measurements were performed in cerebral autoregulation. In summary, this article presents more evidence of the need of incorporating more information for the evaluation of the complete intracranial pressure signal than the usual waveform obtained by neuromonitoring since these analysis provide us with fundamental information about the pathophysiological aspects of neurocritical patients and help us determine future interventions.

Apendix I

When computing the Shannon Entropy defined in Eq. 1 there are several ways to determine the π_i states. For example, if the histogram is used, once n bins are set, the possible states of the system $S = \pi_1, \ldots, \pi_n$ are fixed and the times where the system is in the p_{ith} state are counted and its relative frequency (probability of appearance, i.e. $P(\pi_i)$), is computed and used in Eq. 1 to quantify the Entropy. Although this method, i.e. using the histogram to determine the possible states and compute their relative frequency, can grasp the difference in the variance, symmetry and kurtosis of the probability distribution function (PDF) of the π_i states, it does not take account for the time dynamic of the system, and this fact can be an issue when a dynamical system, as Cerebral Autoregulation, in under study. One way to cope with this issue is by using the symbolization proposed by Bandt and Pompe (BP-symbolization) in [15] to determine the π_i states and therefore compute $P(\pi_i)$ and Eq. 1. The BP-symbolization consists, from a practical point of view, in mapping the system evolution, given in form of time series, onto a set of symbols $\mathcal{S}_m$. To do that, two parameter must be fixed, the symbol length m, which is related with the information content of each symbol belonging the set $\mathcal{S}_m$ (the higher the m value, the higher the informational content) and the time delay τ, related to temporal scales (within this article $\tau = 1$ to avoid temporal scale difficulties). Due to computational limitations, m goes usually $3 \leq m \leq 6$ and it is set as $m = 6$ within this article. Fig. 3 shows the BP-methodology to compute $P(\pi)$ for $m = 3$. The methodology simply maps each value x_i in the embedding vector $X_m(t) = \{x_t, ...x_{t+m-1}\}$ ordering

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its index $t \in \{1, 2, \ldots, m\}$ according to the increasing amplitude (rank) of each x_i in $X_m(t)$. It can be seen that the indexes of the time axis are fixed in chronological order, and they are mapped onto the vertical (amplitude) axis. For each pattern $X_3(t) = (x_t, x_{t+1}, x_{t+2})$, the resultant symbol $\pi_i \in S_3$ can be obtained reading the labels in the vertical axis from the bottom to the top (in the direction of the increasing amplitude). The higher the value of the Entropy computed using the BP-Methodology, the higher the uncertainty in the correlation structure of the time series and thus, higher the complexity. A related concept along with the BP-symbolization is the Number of Missing Patterns (NMP). Once a time series is mapped onto a group $\mathcal{S}_m$ some symbols π_i could have no occurrence and the corresponding $P(\pi_i) = 0$. If the time series is large enough and the time series has a stochastic nature, NMP has to be 0, otherwise, if the time series were deterministic, NMP may be greater than zero, i.e. NMP could be interpreted as a driver to detect determinism in a time series, provided a large enough time span. An interesting interpretation of the NMP is that their presence could be understood as the degree of freedom of the system, the higher the NMP the lower degree of freedom of the time series; e.g. a random time series has NMP=0 and in contrast a chaotic time series can have NMP ≥ 0, no matter the time series span.

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