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Detrended Fluctuation Analysis of Intracranial Pressure Predicts Outcome Following Traumatic Brain Injury

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Abstract

Detrended fluctuation analysis (DFA) is a recently developed technique suitable for describing scaling behavior of variability in physiological signals. The purpose of this study is to explore applicability of DFA methods to intracranial pressure (ICP) signals recorded in patients with traumatic brain injury (TBI). In addition to establishing the degree of fit of the power-law scaling model of detrended fluctuations of ICP in TBI patients, we also examined the relationship of DFA coefficients (scaling exponent and intercept) to: 1) measures of initial neurological functioning; 2) measures of functional outcome at six month follow-up; and 3) measures of outcome, controlling for patient characteristics, and initial neurological status. In a sample of 147 moderate-to-severely injured TBI patients, we found that a higher DFA scaling exponent is significantly associated with poorer initial neurological functioning, and that lower DFA intercept and higher DFA scaling exponent jointly predict poorer functional outcome at six month follow-up, even after statistical control for covariates reflecting initial neurological condition. DFA describes properties of ICP signal in TBI patients that are associated with both initial neurological condition and outcome at six months postinjury.

Index Terms

Detrended fluctuation analysis (DFA); intracranial pressure (ICP); monitoring; outcome; traumatic brain injury (TBI)

I. Introduction

Every year, about 1.4 million U.S. citizens suffer a traumatic brain injury (TBI), resulting in varying degrees of long-term disability [1]. Many experience lifelong physical, cognitive, and behavioral changes that negatively impact their ability to function independently and return to former work and leisure activities. An estimated 5.3 million Americans need long-term help in performing daily activities following TBI. TBI is the leading cause of death and permanent disability in young adults in the United States. In older adults, TBI accounts for high rates of hospitalization and death, and poor outcome among survivors. The Centers for Disease Control estimates that \$40 billion (2000 dollars) is spent annually in the United States for treatment of TBI and its sequelae [1].

Prediction of long-term functional outcome after TBI based on information available to clinicians in the acute hospitalization phase remains imprecise. Yet questions about probable degree of recovery are among those most frequently posed to clinical staff by families and patients. It is recognized that the initial injury to the brain is an important early predictor of clinical course and outcome. Several decades ago, however, clinicians became aware that understanding the impact of the initial injury was not enough to predict outcome and guide the best treatment for patients with TBI. It was realized that in addition to primary brain injury, patients with TBI are also at risk for secondary brain injury during the hospitalization phase, and that this potentially preventable secondary injury can have profound effects on long-term outcome.

A common mechanism for secondary injury is an increase in pressure inside the skull, or intracranial pressure (ICP). If this pressure increase is sufficiently large, compression of blood vessels and brain tissue occurs, with potential brain cell death. Thus, reduction of increased ICP to prevent secondary brain injury is a primary focus of TBI management.

With the advent of routine clinical monitoring of ICP came the qualitative realization that the ICP signal in TBI patients was anything but static. Although the primary clinical motivation for monitoring focuses on average ICP level, the signal has variability at all time scales of description, some properties of which may be relevant to the clinical condition and future prospects of the patient. At time scales less than 5 s, the ICP signal is dominated by highly structured components synchronous with the cardiac cycle and respiratory cycle. At time scales longer than 5 s, the signal becomes notably irregular, with variance that seems to significantly grow with increasingly larger time frames of ICP data, suggesting that ICP time series may exhibit fractal scaling, and perhaps may even join the list of physiological signals that are known to exhibit monofractal scale-invariant behavior.

ICP signal properties have been extensively studied at the cardiac cycle scale [2]–[4] and at the respiratory cycle time scale [5]. There has also been important work looking at prognostic univariate and bivariate properties of ICP signals in which components shorter than 5 s and longer than 200 s have been aggressively removed by filtering or averaging [6]. ICP signal variability remaining after filtering out components shorter than 20 s and longer than 180 s has also been recently studied [7].

In this report, we use a technique called detrended fluctuation analysis (DFA) to study the complex variability of the ICP signal over the relatively unexplored range of time scales between 30 s and 2 h. DFA is a mathematical method describing second-order statistical properties of signals that may reflect long memory processes, long-range correlations, fractal scaling, and evolving intrinsic nonstationarities [8]. DFA was first developed by Peng *et al.* to describe complex-appearing variability of information in DNA sequences in terms of random fractals [9], [10], and has since been fruitfully applied to heart rate variability time sequences and many other physiological signals [11]–[18]. The complex variability of the ICP signal has recently been studied using other methods, especially estimates of approximate entropy [19], [20].

The purpose of this study was to explore the applicability of DFA methods to ICP signals recorded in patients with TBI. In addition to establishing the degree of fit of the power-law scaling model of detrended fluctuations of ICP in TBI patients, we also examined the relationship of DFA coefficients (scaling exponent and intercept) to: 1) measures of initial neurological functioning; 2) measures of functional outcome at six month follow-up; and 3) measures of outcome controlling for patient characteristics and initial neurological status. We also estimated the strength of predictive models of outcome including ICP DFA parameters.

II. Methods and Materials

A. Sample

The physiologic signal analyses presented in this paper address secondary aims of a larger study whose primary purpose was a randomized clinical trial of continuous cerebral perfusion pressure monitor display technology [21]. Eligible subjects in the parent study were consecutive adult patients 16 years of age or older admitted to an intensive care unit (ICU) at a level I trauma center with moderate-to-severe TBI, who underwent invasive ICP and ABP monitoring as part of normal clinical care. Subjects were enrolled within 24 h of the insertion of the ICP monitoring catheter. Approval of study procedures for protection of human subjects was received from the University of Washington Institutional Review Board; written consent for follow-up was obtained from the patients or their surrogates as appropriate. There were 156 subjects in the parent study, but nine of these did not have sufficient ICP data for the present analyses. Therefore, the sample size for analyses presented in this paper is 147.

B. Study Measures

Information about patient characteristics, such as age, gender, mechanism of injury, injury severity, and performance of craniectomy, were extracted from clinical chart records. The Glasgow Coma Scale (GCS) is an extensively used measure to assess level of consciousness in patients with acute brain injury [22] that has been shown to be predictive of outcome [23]. While the full GCS has three components (eye opening, verbal, and motor), use of only the motor component obviates some difficulties associated with obtaining the full GCS score and retains predictive value in relation to outcome [24]. The initial postresuscitation GCS motor component score (GCS-M; rated 1–6, higher score is better) was therefore used in this analysis. Craniectomy is a surgical operation in which a section of the cranium is removed, for a variety of reasons, for an extended period of time. This changes the physical environment in which brain pressure is realized, and it is not unreasonable to hypothesize that craniectomy might alter brain pressure dynamics. A dummy variable coding for the performance of a craniectomy was used as a controlling variable in statistical analyses.

Functional outcome at six month follow-up was assessed with the Extended Glasgow Outcome Scale (GOSE) [25], [26] using a structured interview by trained evaluators on the research project staff. Scores on the GOSE range from 1 (dead) to 8 (upper good recovery), with higher scores reflecting better function.

ICP was measured in the course of normal clinical monitoring using a Camino fiber-optic transducer-tipped catheter (Integra LifeSciences, Plainsboro, NJ), inserted intraparenchymally. Fiber-optic ICP sensors are reliable and consistent in long-term placement (five day typical drift less than ± 1 mmHg/day). The analog ICP signal displayed on institutional clinical monitors (0–12.0 Hz bandwidth) was acquired using a 16-bit A/D at 100 samples/s. To attenuate morphologically structured cardiac (about 1–2 Hz) and respiratory (generally, 0.2 Hz or faster) components, the ICP samples were then processed through an finite impulse response (FIR) low pass (LP) smoothing filter with a span of 2048 samples (20.48 s) designed to have an LP high frequency cutoff of 0.1 Hz. The highly smoothed output of this filter, which attenuates signal components with periods shorter than 10 s, was down-sampled 500:1 by block averaging, that is, by partitioning into sequential 500 point (5 s) blocks, each of which was averaged into a mean pressure value.

This generates a uniform time series data structure composed of a sequence of 5-s mean ICPs. Because the data was passively recorded in real ICU environments from patients with different clinical situations, there was considerable variation in length of the recordings (2–14 days). The analyses presented focus on the first four days (96 h) of monitoring, a time frame when

patients are at high risk for ICP abnormalities. At least four days of ICP data were available for about 89% of the TBI subjects in this sample.

All ICP data sequences were manually scanned and labeled for artifact and outliers (by investigators Robert L. Burr and Catherine J. Kirkness). In general, missing and invalid data were infrequent in this TBI data sample. During the clinically homogeneous first four days, gaps in usable ICP data of varying lengths were noted, including one or several long gaps (0.87–6.4 h) in 43 (29.3%) subjects, and many shorter gaps (5 s to 8.3 min) in all of the subjects.

There does not currently appear to be any universally accepted method of accommodating missing data in DFA analyses, although a number of recent methodology studies have begun to address the issue [27]–[29]. An operational decision was made that if an unusable data section lasted longer than a nominal 10 min (for example, if a patient is disconnected and transported out of the ICU for diagnostic imaging), the surrounding data sequence was partitioned into two shorter separate analysis segments. Because it was desired to study DFA effects at analysis time scales n out to 2 h, each patient was required to have at least one contiguous 24-h data segment, so as to ensure minimum data record lengths at least a decimal order of magnitude longer than the longest studied analysis time scale n . As noted earlier, nine subjects were excluded from reported analyses based on this criterion. More than 63% of the subjects had a full length unsegmented 96 h long data record.

Many short gaps in usable data were also observed in otherwise valid sequences of time series data in all subjects. The median within-subject number of short gaps was 36 per subject recording. Median length of each of these short gaps was 15 s (three 5-s samples), with 94% less than 1 min in length. The single longest short gap segment in the study was 8.3 min.

To keep analysis sequences as long as possible without segmentation, gaps up to a nominal 10 min in length (less than 0.2% of a 96 h record) were interpolated with a smooth function that approximates the trend in the local mean of surrounding data. The advantage of this interpolation strategy is that it accurately preserves long time scale correlation properties of the signal and allows analysis to proceed for longer time scales n . However, a disadvantage of trend interpolation of missing data in DFA is that imputed data segments are unrealistically smooth, with potential to introduce a downward bias in the estimated mean square fluctuation amplitude. Overall, the across-subject median percentage of within-subject data that was interpolated for analysis segments used in this study was 0.23% (equivalently 13 min of imputed data distributed over a 96-h record). The single worst case was a subject who required about 54 min of interpolation of many short gaps of missing/invalid data distributed over a full 96 h data segment (<1% missing data). Although observed rates of missing/invalid data in this clinical monitoring study may seem unlikely to introduce significant bias in DFA parameter estimates, the presented results should be interpreted cautiously.

C. Detrended Fluctuation Analysis

The algorithm for calculation of the detrended fluctuation curve for each subject's ICP data sequence is conceptually simple, but can be computationally intensive for long data sequences [8], [18], [30]. For a data sequence $ICP(i)$, $i = 1, \dots, N$, the steps are as follows:

1. the grand mean ICP for the entire series is subtracted from each element to create a centered, zero-mean signal

$$ICP_{\text{centered}}(i) = ICP(i) - \left(\frac{1}{N}\right) \sum_{j=1}^N ICP(j), \quad i=1, \dots, N;$$

2. the centered series is cumulated

$$\text{ICP}_{\text{cum}}(j) = \sum_{i=1}^j \text{ICP}_{\text{centered}}(i), \quad j=1, \dots, N;$$

3. the cumulated series is then split into *k* nonoverlapping equal-length blocks of size $n = N / k$. Within each block, a local low-order polynomial (often linear) trend model is fit to $\text{ICP}_{\text{cum}}(j)$ using least squares regression. Across the k blocks, each of length n , these models can be assembled into a piecewise local trend approximation of the cumulated series, $\text{ICP}_{\text{pwt}}(n, i)$, $i = 1, \dots, N$;
4. next, the root mean square fluctuation value $F(n)$, for block size n , can be computed based on residuals of the cumulated series with respect to its piecewise local trend approximation:

$$F(n) = \sqrt{\left(\frac{1}{N}\right) \sum_{j=1}^N [\text{ICP}_{\text{cum}}(j) - \text{ICP}_{\text{pwt}}(n, j)]^2}; \text{ and}$$

5. steps 3 and 4 are typically repeated for many possible choices of block size n , and the results assembled into a curve $\{n, F(n)\}$ to study the putative power law growth of $F(n)$ as a function of block size n , $F(n) = \gamma \cdot n^\alpha$, where γ is the reference amplitude when $n = 1$, and α is the power law scaling exponent. Usually both n and $F(n)$ are logarithmically transformed to allow a linear least squares estimate of the DFA scaling exponent ($= \alpha$) and DFA Intercept ($= \log(\gamma)$), where the logarithm is taken to any consistent base.

In the current study, DFA curves for each patient's ICP time series were computed using the PhysioToolkit program "DFA. c," downloaded from the PhysioNet website (<http://www.physionet.org>). Specification of the DFA software can be found at <http://www.physionet.org/physiotools/dfa/> and description of the overall National Center for Research Resources (NCRR) supported PhysioNet project [31] can be found at <http://circ.ahajournals.org/cgi/content/full/101/23/e215>.

For each patient, the ICP DFA parameters scaling exponent and intercept were estimated from their DFA curve using least squares linear regression. For the primary results presented in this paper, regression coefficients were fit to a broad DFA time scale ranging from 30 s to 2 h. To enhance interpretability, the regression intercept was set to correspond to a DFA local model time scale n equivalent to 60 s.

D. Statistical Analysis Plan

First empirical ICP DFA curves for total sample of TBI patients will be described. Then, estimated DFA scaling exponents will be tested against the three theoretically interesting values (0.5, 1.0, and 1.5) using one-sample t-tests. Systematic differences within the TBI sample will then be explored, by describing the relationship of patient characteristics at the time of hospitalization (particularly, the GCS-M assessment of initial neurological status) with the ICP DFA scaling exponent and intercept parameters, using spearman rank order correlation. Similarly, simple unadjusted relationships of ICP DFA parameters with six month functional outcome (as measured by the GOSE) will be examined, using spearman rank order correlation.

Next, adjusted and unadjusted relationships of ICP DFA parameters to dichotomous outcomes derived from the GOSE will be compared, using multivariate logistic regression analysis models, with the particular goal of determining whether significant unadjusted relationships hold up after statistical control for baseline covariates reflecting patient characteristics and initial neurological assessment known to be predictive of outcome.

Finally, to quantify the proportion/percentage of variance (PV) prediction effect sizes for DFA scaling exponent and intercept, adjusted and unadjusted relationships of the ICP DFA parameters with the GOSE scale will be compared using nested multivariate linear regression models.

III. Results

A. Descriptive Characteristics of the Traumatic Brain Injury Patient Sample

Table I briefly summarizes demographic and clinical characteristics of the study participants. More than three quarters were male, and about half the sample was less than 33 years of age. At least half the TBI subjects were hospitalized for more than 19 days. Mortality by the six month followup time point was 17% (25/147). The mean (SD) GOSE score at six months was 4.3(2.1), falling at the boundary between “upper severe disability” and “lower moderate disability” on the interpretive range of the 8-point GOSE rating scale. Less than 12% of the subjects were rated as having a “good” recovery (GOSE = 7 or 8), although 58% were rated as having a relatively favorable outcome (“lower moderate disability” or better, GOSE > 4).

B. DFA Results for the TBI Sample

Over the range of DFA time scales n depicted (30 s through 24 h) in Fig. 1, the average ICP DFA profile for the 147 TBI patients is a monotonic nondecreasing, mildly nonlinear curve. Because of concerns about stability and validity of DFA fluctuation amplitudes estimated at time scales longer than one-tenth of the raw data record length [32], extraction of the DFA parameters intercept and scaling exponent was based on the portion of each subject's DFA profile corresponding to time scales between 30 s and 2 h. This corresponds to fitting regression models for each subject over approximately the left-most two-thirds of the logarithmic range of scales shown in Fig. 1. Over this restricted range, the within-subject DFA profiles are well approximated by least-squares linear fits, with a median within-subject $R^2 = 0.988$. The smallest observed within-patient fit was an $R^2 = 0.953$.

The DFA curves based on a linear local detrending model do not display any rollover knees or breaks in the slope that might be visual evidence of time scale-specific extrinsic nonstationarities [27], [32], [33]. Given the length of the data sequences used in this study, sensitivity analyses using cubic (order 3) and quintic (order 5) polynomial local detrending models were undertaken to assess and mitigate effects of complex evolving nonstationarities. The resulting DFA profiles for local model polynomials of order 1, 3, and 5 were notably parallel on a log-log graph. Only DFA parameters based on first-order (linear local trend) analyses will be reported in the remainder of this paper.

Using a one-sample t-test to compare the estimated DFA scaling exponent parameters against the three theoretically interesting canonical values {0.5, 1.0, and 1.5} corresponding to random noise, simple monofractal, and integrated random walk processes, respectively, all comparisons are strongly significantly different ($p < 0.001$). No individual patient's estimated DFA scaling exponent was smaller than 0.5 or larger than 1.5, so rejection of those hypotheses was overwhelming. While the average DFA scaling exponent (Mean [SD] = 1.1123 [0.0879]) appears in Fig. 1 to be closest to the monofractal scaling exponent = 1.0 case, it is statistically

significantly larger ($p < 0.001$) than unity. Fewer than 13% of the patients in this TBI sample had an estimated DFA scaling exponent less than or equal to one.

Across subjects, the mean ICP level had a significant positive correlation with the ICP DFA intercept ($r = 0.399$, $p < 0.001$), but not with DFA scaling exponent ($r = 0.053$, $p = 0.527$). The two DFA parameters scaling exponent and intercept had a substantial inverse correlation with each other ($r = -0.429$, $p < 0.001$).

Examples of mean ICP pressure series (each eight hours in length) for two subjects and corresponding DFA linear fits are contrasted in Fig. 2. Subject A [see Fig. 2(a)] is a 46-year-old male who suffered a moderate head injury in a motor vehicle accident. His initial GCS-M score was 6 (best score possible). The mean ICP waveform visually demonstrated complex variability at several time scales. His ICP DFA intercept was 0.4950, and the ICP DFA scaling exponent was 0.9535. Subject A was discharged to his home, and his six month GOSE functional outcome score was 8 (upper good recovery). Subject B [see Fig. 2(b)] was a 33-year-old male who suffered a severe head injury, also in a motor vehicle accident. His initial GCS-M score was 1 (worst possible score). The mean ICP waveform visually appears to have progressively reduced variability at shorter time scales. The DFA intercept was -0.2320 , and the DFA scaling exponent was 1.2368. Subject B was discharged from the hospital to a skilled care nursing facility for long-term care, and was no longer alive by the six month outcome evaluation. DFA lines for subjects A and B, fit to the individual DFA profiles at time scales n between 30 s and 2 h, are presented in Fig. 2(c), along with the unity slope DFA scaling exponent case for comparison.

C. Relationship of DFA Parameters With Patient Characteristics and Initial Neurological Status

Several characteristics of the TBI patients, including the important GCS-M initial assessment of neurological status, are related to the ICP DFA parameters scaling exponent and intercept. As can be seen in Fig. 3, lower (worse) GCS-M scores are weakly associated with lower DFA intercept [see Fig. 3(a), spearman $\rho = 0.095$, nonsignificant trend; $p = 0.250$], but are strongly linked with higher DFA scaling exponent [see Fig. 3(b), spearman $\rho = -0.413$, $p < 0.001$]. Note particularly that the lower 95% confidence intervals for the mean scaling exponent for all three TBI groups in Fig. 3(b) exclude the ICP DFA scaling exponent = 1.0 value.

The ICP DFA parameters for this sample do not differ by gender. Similarly, neither of the DFA parameters is related to age ($p > 0.4$). The patients who underwent a craniectomy have significantly lower DFA intercepts ($p < 0.001$), but are not different in DFA scaling exponents ($p = 0.458$).

D. Relationship of ICP DFA Parameters With Six-Month Functional Outcome

1) Unadjusted Relationships to Outcome—For the 147 TBI patients in this sample, there is a statistically significant relationship between ratings on the full 8-point GOSE functional outcome assessment at six months and both the ICP DFA intercept (spearman $\rho = 0.309$, $p < 0.001$) and the ICP DFA scaling exponent (spearman $\rho = -0.226$, $p = 0.006$). These associations are depicted in Fig. 4(a)–(b), where the original 8-point scale has been collapsed into three clinical categories: dead (GOSE = 1), unfavorable outcome ($1 < \text{GOSE} < 5$), and favorable outcome (GOSE > 4).

Descriptive summary statistics of the ICP DFA parameters for these three clinical subgroupings of six month functional outcome are presented in Table II. Also presented are descriptive summaries of demographic and initial neurological status, to illustrate the relationships of age, gender, and initial condition with six month outcome. The subjects who did not survive to the

six month followup time point were, on average, 18 years older, and had average GCS-M scores that were 1.5 points lower, than those in the “favorable” outcome classification. Female TBI patients in this sample were over represented in the middle GOSE subgrouping (surviving, but demonstrating an unfavorable functional outcome at the six month follow-up).

2) Adjusted and Unadjusted Relationships to Dichotomous Outcome Variables: Logistic Regression Models—Binary logistic regression was used to further explore the degree to which the ICP DFA parameters predict six month survival and favorable outcome, comparing models that either include or do not include a base set of covariates reflecting initial neurological status and patient characteristics, such as age, gender, mean ICP level, GCS-M, and craniectomy. Fig. 5(a) and (b) graphically depict the adjusted standardized odds ratios (ORs) for survival and favorable outcome, based on ICP DFA scaling exponent and intercept.

Thus, in Fig. 5(a), it can be seen that having a DFA intercept that is one standard deviation higher is associated with an increased OR for six-month survival of 2.957, $p = 0.001$. When the base set of covariates is added to the model, the odds ratio for survival remains nearly unchanged (OR = 2.980), but the confidence interval has expanded and the p-value is slightly less significant ($p = 0.004$). The pattern is similar for the OR for the prediction of favorable outcome (GOSE > 4) from the ICP DFA intercept, in that the unadjusted OR = 1.711 is strongly significant ($p = 0.005$). After inclusion of the controlling base model, the adjusted odds ratio is larger, but the confidence intervals have again expanded, and the adjusted effect is somewhat less significant (OR = 1.806, $p = 0.032$).

When ICP DFA scaling exponent [see Fig. 5(b)] is used to predict six-month survival (GOSE > 1), the standardized odds ratio is significant (OR = 0.493, $p = 0.005$). (Note that the estimated OR is less than unity, because a higher ICP DFA scaling exponent value corresponds to the prediction of a poorer outcome.) When the base set of covariates is added to the model, the adjusted OR for the ICP DFA scaling exponent parameter remains significant (OR = 0.486, $p = .027$). Similarly, the unadjusted standardized odds ratio associated with the prediction of favorable outcome (GOSE > 4) for the ICP DFA scaling exponent parameter is strongly significant (OR = 0.591, $p = 0.003$), but after controlling statistically for the base set of covariates, the adjusted OR for DFA scaling exponent weakens to a nonsignificant trend (OR = 0.788, $p = 0.161$).

3) Adjusted and Unadjusted Relationships to Full 8-Point GOSE Scale: Linear Regression Models and Strength of Prediction—Table III summarizes quantitative information about the predictive relationship between the ICP DFA parameters and the full 8-point GOSE scale at six month follow-up, using multivariate linear regression. As individual terms in the models, DFA intercept explains about 11% (M1, $p < 0.001$), and DFA scaling exponent more than 5% (M2, $p = 0.004$), of the outcome variance. Adding DFA scaling exponent to a simple model that already includes DFA intercept does not significantly improve the overall model fit (M3, $p = 0.188$).

A base covariate model (M4) including age, gender, GCS-M, ICP mean level, and craniectomy explains about 34% of the outcome variance. Adding DFA intercept to the base covariate model increases explained variance more than 6% (M5, $p = 0.001$), but adding DFA scaling exponent to the base model by itself is not significant (M6, $p = 0.325$). However, adding DFA scaling exponent to a model already containing the base covariates and DFA intercept increases the explained variance an additional 5% (M7a, $p = 0.001$). Alternatively, adding DFA scaling exponent and DFA intercept together as a set to the base covariate model increases the explained variance about 11.7% (M7b, $p < 0.001$) compared with the base covariate model, resulting in a combined model explaining about 45.5% of the overall variance of the six month follow-up GOSE rating.

IV. Discussion

The linear least squares regression fits of a power-law model to within-subject ICP DFA profiles for DFA time scales n in the range between 30 s and 2 h are strong. This is consistent with, but not proof of, monofractal behavior or the presence of intrinsic long range correlation properties in ICP signals. The mean ICP DFA scaling exponent for the TBI patient sample was slightly, but significantly, larger than unity.

The ICP DFA scaling exponent has a statistically strong relationship with the initial assessment of neurological status using the GCS-M. Individuals with poor initial status, especially those with $\text{GCS-M} < 4$, have much higher DFA scaling exponents and somewhat lower DFA intercepts, consistent with an ICP signal that is slower and smoother in texture, in the sense of having relatively less short-term variability as compared to longer-term variability.

Functional outcome at six-month follow-up, as assessed by the GOSE, is significantly related to both ICP DFA scaling exponent and DFA intercept, but not average ICP level. After statistical control for the base set of covariates, the link between DFA intercept and six month outcome remains strong. While the relationship between DFA scaling exponent and six month GOSE is somewhat reduced in the presence of covariates, it remains significant in the prediction of six month survival, and adds 5% to the explained variance in a model predicting the full 8-point GOSE scale (M7a to M5 comparison in Table III). The slightly weakened relationship between outcome and DFA scaling exponent after adjustment for covariates may be partially due to the net reduction in effective data degrees of freedom in the augmented model, but is probably also related to the strength of the association between DFA scaling exponent and GCS-M.

Difficult analysis decisions were occasioned by the 25% of the patients on whom surgical craniectomy had been performed shortly before ICP data collection. In the present TBI patient sample, craniectomy patients are not significantly different with respect to either GCS-M during the hospitalization phase or to GOSE at six-month follow-up. Craniectomy is significantly associated with lower DFA intercept, but is notably nonsignificant in its relationship to DFA scaling exponent. That probably means that craniectomy reduces variability at all scales, but preserves the uniformity of the growth of variability with scale. Because of theoretical concerns about the role of craniectomy on outcome and on ICP, it was decided to incorporate a dichotomous dummy variable for craniectomy in the set of base covariates used in all the adjusted analyses, even though that variable never played a significant empirical role in any of the predictive models of outcome.

The ICP DFA parameters together predict about 12% of the variance in GOSE six-month functional outcome assessment beyond that explainable by a base set of covariates. This could be important in understanding the basic science, or even in predicting outcome for individual patients, but it needs to be remembered that about 88% of the variance in outcome is not predicted by these variables. In some methodological evaluations, a PV effect size of 10% is considered the minimum necessary for an index or marker to have potential to be clinically meaningful, as contrasted with merely being statistically significant. The combination of the two DFA parameters minimally meets this threshold. In comparison, the base set of covariates used in our model comparisons predicts a substantial 34% of outcome variance, with age and GCS-M playing the most important roles in the regressions. It is interesting that adding both ICP DFA parameters to the base model increases overall predictiveness of the combined regression model to about 45.5% of the outcome variance of the GOSE scale. That is quite a respectable prognostic model for functional outcome, given the many intervening factors that potentially affect recovery of TBI patients over the first six months after the hospitalization phase.

Limitations of the current study include collection of physiological data in a real clinical context at one specific institution, with a specific culture of medical management for patients with TBI. In present study, it was not possible to study or to control for the impact of medications, although some agents (e.g., mannitol) are overtly intended to affect ICP level, and might possibly affect the qualities of variability that are measured by ICP DFA intercept and scaling exponent.

Another methodological limitation concerned our technique for accommodating the inevitable sections of missing or invalid data. We partitioned analysis segments around long gaps, but chose to impute values through shorter gaps using smooth local interpolation. After segmentation, missing data rates in the ICP analysis segment time series were considerably less than 1%, with over half of the interpolated intervals spanning gaps of 15 s or less. Nevertheless, the variability of the series in the imputed segments was not typical of the series as a whole. This has potential to bias estimates of fluctuation amplitude for individual subject DFA profiles to lower values. Thus, the presented results should be interpreted cautiously.

In this study, we looked at DFA of ICP in only one of many possible ways. The ICP signal was preaggregated into a sequence of 5 s average pressures, deliberately precluding the analysis of potentially interesting patterns of variability associated with the cardiac and respiratory cycles at time scales shorter than 5 s. Our analyses focused on describing the scaling structure over lengthy data segments (24–96 h), using a wide range of DFA time scales n (30 s to 2 h), and did not look closely at shorter segments of data. For example, it would be clinically interesting to study the prognostic potential of DFA parameters based on brief segments of ICP data collected shortly after admission. Analyses presented in this paper were based on multiday records, but did not explore how ICP DFA parameters might change within days (e.g., circadian) and across days (e.g., clinical progression) in the ICU. All of these issues are potential directions for future research into the application of DFA to ICP signals.

V. Conclusion

The scaling exponent and intercept parameters extracted from DFA curves estimated from multiday physiological recordings describe interesting features about the variability and complexity of ICP signals in TBI patients. ICP DFA scaling exponent is associated with clinical ratings assessing initial neurological function and functional outcome at six-month follow-up. ICP DFA intercept is strongly predictive of dichotomous and full scale ratings evaluating functional outcome at six-month follow-up, even after statistical control for a base set of covariates that include patient age and initial neurological function.

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Biographies

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Fig. 1.

Average empirical ICP DFA profile for the total sample of TBI patients is depicted by the solid curve. The abscissa represents local model piecewise time scales n , ranging (on a $\log_{10}$ scale) from about 30 s to 24 h. The ordinate represents the $\log_{10}$ rms amplitude $F(n)$ of fluctuations or residuals from the corresponding family of local detrended models of the cumulated zero mean signals. Also shown on the figure are the theoretical DFA profiles corresponding to pure random noise (DFA scaling exponent = 0.5), simple monofractal (scaling exponent = 1.0), and an integrated random walk (scaling exponent = 1.5).

Fig. 2.

Examples of mean ICP pressure series (each 8 h in length) for two subjects and corresponding DFA fits. Subject A [see Fig. 2(a)] experienced good functional outcome at six month follow-up, while subject B [see Fig. 2(b)] died before the six month assessment point. DFA lines for subjects A and B, fit to the individual profiles at time scales n between 30 s and 2 h, are presented in Fig. 2(c). The unity slope DFA scaling exponent = 1 line is overplotted on the figure for comparison.

(a)

(b)

Fig. 3.

Plots of means and error bars representing the 95% confidence intervals about the means for ICP DFA intercept [see Fig. 3(a)] and ICP DFA scaling exponent [see Fig. 3(b)] as a function of GCS-M, a clinical rating of neurological function at the time of admission to the ICU after TBI (scale ranges from 1–6, higher values coding better function).

Fig. 4. Plots of means and error bars representing the 95% confidence intervals about the means for ICP DFA intercept [see Fig. 4(a)] and DFA scaling exponent [see Fig. 4(b)] as a function of GOS, a clinical rating of functional outcome at six month follow-up (scale ranges from 1 = dead to 8 = upper good recovery).

Fig. 5.

Error bar plots representing the 95% confidence intervals for the standardized odds ratios for survival until six months, and for favorable outcome at six months (GOSE > 4), based on DFA intercept [see Fig. 5(a)] and DFA scaling exponent [see Fig. 5(b)]. The odds ratios were determined by binary logistic regression, first without covariates, and then, for comparison, with covariate control of age, gender, GCS-M, mean ICP level, and craniectomy.

Table I
Traumatic Brain Injury Study Participant Characteristics ($n = 147$)

Sex: % female	22%
% male	78%
Age: [years; Mean (SD)]	37.4 (18.5)
Injury Mechanism:	
% Automobile Accident	46%
% Motorcycle Accident	12%
% Falls	19%
% Other*	23%
(*includes physical assaults, gun shot wounds, struck by flying objects, bicycle accidents, other).	
Initial Glasgow Coma Scale Motor Score (GCS-M):	
[1-6; Mean (SD)]	4.2 (1.6)
Initial Injury Characteristics:	
% Contusion	68%
% Subdural Hematoma	44%
% Epidural Hematoma	26%
% Diffuse Axonal Injury	32%
Craniectomy Procedure:	
% undergoing surgery	25.2%
Mean ICP level (first four days):	
[mmHg; Mean (SD)]	16.4 (5.85)
% > 20 mmHg	22.1%
% > 25 mmHg	4.8%
DFA Intercept (referenced to 60 second scale):	
[Mean (SD)]	0.1288 (0.2481)
[Median (MAD)]	0.1376 (0.1992)
DFA Scaling Exponent:	
[Mean (SD)]	1.1123 (0.0879)
[Median (MAD)]	1.1109 (0.0750)
Extended Glasgow Outcome Scale (GOSE) at six month follow-up:	
[1-8; Mean (SD)]	4.30 (2.06)
% Mortality (by six months)	17.0%
% GOSE > 4 ("favorable")	57.9%
% GOSE > 6 ("good")	11.6%

Table II
Patient Characteristics by Six Month Functional Outcome Category

	GOSE = 1 N = 25	GOSE 2-4 N = 37	GOSE 5-8 N = 85
Sex/Gender [% female]	24%	43%	12%
Age [Mean (SD)]	49.8 (23.3)	41.9 (20.5)	31.8 (13.1)
GCS-M [Mean (SD)]	3.20 (1.76)	3.46 (1.91)	4.78 (1.18)
Craniectomy [% having surgery]	36%	19%	25%
Mean ICP level [Mean (SD)]	17.7 (7.68)	15.1 (4.98)	16.6 (5.54)
ICP DFA Intercept [Mean (SD)]	-.0167 (.218)	.1045 (.262)	.1822 (.234)
ICP DFA Exponent [Mean (SD)]	1.1599 (.076)	1.1220 (.085)	1.0940 (.087)

Table III

Summary of Multivariate Linear Regression Models Predicting the Full 8-point Scale for GOSE at Six Month Follow-up, Based on Different Subsets of Independent Variables, Including Baseline Covariates, ICP DFA Intercept, and ICP DFA Scaling Exponent

Model #	Terms	R^2	p-value	Models compared
1	INT	.109	.001	M1 – M0
2	EXP	.055	.004	M2 – M0
3	(INT)+EXP	.120	.188	M3 – M1
4	BASE [B]	.338	.001	M4 – M0
5	(B)+INT	.402	.001	M5 – M4
6	(B)+EXP	.343	.325	M6 – M4
7a	(B+INT)+EXP	.455	.001	M7a – M5
7b	B+(INT+EXP)	.455	.001	M7b – M4

INT: ICP DFA Intercept; EXP: ICP DFA scaling exponent; BASE [B]: base covariate model composed of age, gender, GCS-PR-M, ICP mean level, and craniectomy; R^2 : total R^2 for multivariate linear regression using listed terms; p -values: based on difference in nested model log likelihood estimates for the models listed in the last column.