Multifractal analysis of spontaneous hemodynamic fluctuation in the aging brain

Ph.D. theses

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Introduction

Majority of self-organizing natural structures could be described by mathematical models of self-similarity. The advent of analytical tools of fractal geometry enabled the investigation of this phenomenon on empirical (e.g. biological) data which carry fractal properties in a statistical (not exact, like mathematical objects) manner. Eventually, the so-called scale-free behavior of numerous physical, chemical, physiological processes can be quantified with the aid of fractal analytical tools.

Fractal parameters usually varies with time which could be captured by multifractal analysis that is suitable for characterizing local scale-free properties. Traditional monofractal algorithms use the entire record to give an offline (post-acquisition) estimate of a global scale-free parameter. Until now no method has been published that could genuinely perform fractal analysis in real time and give estimates of the time-varying scale-free parameter (such as Hurst exponent) rendering such method potentially effective in monitoring and forecasting applications.

It is possible to describe the local scale-free property with the distribution of local scale-free parameters. This analytical approach is implemented in the *indirect formalism*, which begins

with computing the scaling function: $S(q,s) = \left[\frac{1}{N_s}\sum_{v=1}^{N_s}\mu_v^q(s)\right]^{1/q} \propto s^{H(q)}$ by using statistical moments of the selected measure (e.g. standard deviation). Subsequently, the power-law exponents – generalized Hurst exponent function, $H(q)$ – characterizing the scale-dependence of $S(q, s)$ are estimated by using a linear regression model which is the key step of (multi)fractal analysis. The endpoint of the analysis is the singularity spectrum, which is obtained by the Legendre-transformation of: $q \cdot H(q) - 1$ yielding $D(h) = \inf_q(qh(q) - \tau(q))$. We often observed this sequence of calculation leading to corrupted results.

According to Beer-Lambert law, near-infrared spectroscopy (NIRS) is able to capture hemoglobin (Hb) concentration changes (HbO – oxy-Hb, HbR – deoxy-Hb, HbT=HbO+HbR) in the brain cortex. The long-range correlation (LRC) of HbT fluctuations and bimodal nature (different scaling behavior in the low and high range of temporal scales) have already been recognized, moreover its age-dependence has also been revealed. NIRS signals are influenced by local and systemic effects, having a different impact on HbO–HbR cross-correlation. Among the local effects, neural activity has a major contribution to HbT

fluctuation mediated via neurovascular coupling (NVC) typically accompanied by an anticorrelated HbO–HbR dynamics.

Objectives

Improvement of a real time (RT-) fractal algorithm: My first goal was to achieve the most precise and reliable modification of detrended fluctuation analysis (DFA). The performance was evaluated during a set of numerical tests in a numerical testing framework. The final aim was to demonstrate the applicability of the implemented real-time algorithm.

Focus-based multifractal time series analysis: In order to validate the algorithms developed in our research group, I used multifractal version of DFA to examine the quality of the outcome obtained with the focus-based regression model compared with standard regression. My further goal was to provide numerical and analytical evidences that could explain the results of the test, especially the frequently observed corrupted outcome yielded by the standard indirect formalism.

Clarify the role of of healthy aging in case of cerebral hemodynamic fluctuations: Utilizing validated adaptive bimodal

variant of the implemented focus-based multifractal analytical tool we aimed to elucidate the age-dependency of the multifractal endpoint parameters corresponding to the local scale-free HbT fluctuations. Finally, I aimed to verify if HbO–HbR relationship is responsible for the results, and to what extent.

Methods

Generating statistical fractal processes for testing purposes

In order to test real-time fractal analytical methods (RT-DFA és RT-SSC) in the time domain fGn (fractional Gaussian noise) and fBm signals (fractional Brownian motion) were created with the method of Davies and Harte (DHM) at a given Hurst exponent (defining degree of LRC). Since fractality of empirical data needs to be confirmed prior to analysis, we checked the presence of inverse of power-law relationship ($1/f^{\beta}$) by using a set of reference monofractals generated with the spectral synthesis method. Multifractal time series were obtained with the generalized binomial multifractal cascade model, in which the Hurst exponent and degree of multifractality could be independently controlled.

Registration and preprocessing of hemoglobin fluctuations

In our study (approved by Semmelweis University Regional and Institutional Committee of Science and Research Ethics) 52 healthy volunteers participated, who were assigned to four groups based on age (young: ≤45 years) and gender. Continuous wave NIRS-measurements sampled the resting HbO, HbR and HbT dynamics in one region (channel) in the prefrontal cortex with 2 Hz sampling frequency, collecting $\geq 2^{14}$ data points in the resting state. In order to attenuate non-neural effects on hemodynamics we applied correlation-based signal improvement (CBSI), which builds on the anticorrelated HbO–HbR dynamics elicited locally by NVC. Results of multifractal analyses performed both on raw and CBSI-pretreated signals were evaluated together.

Real-time fractal time series analysis

DFA applies linear detrending (‘) prior to calculation of fluctuation (F), where: $F(v,s) = \sqrt{\frac{1}{s} \cdot \sum_{i=1}^{s} \left(Y_v'(i)\right)^2}$, in the v^{th} time window (of a given size s) for the $Y(i)$ time series obtained via cumulative summation of the raw $X(i)$ signal. Computation of scale-dependent quantity was carried out starting with both $X(i)$ and $Y(i)$ in a sliding window (of size M) by using helper variables

constructed only from preceding points of the time series: $F^2(v,s) = \frac{m^2 \cdot s^2}{3} + \frac{m^2 \cdot s}{2} + \frac{m^2}{6} + m \cdot b \cdot s + m \cdot b + b^2 + \frac{1}{s} \cdot \sum_{i=1}^{s} Y^2(i) - 2m \cdot Y(i) \cdot i - 2b \cdot Y(i)$. The measure of SSC is bridge-detrended standard deviation: $\sigma(v,s) = \sqrt{\frac{1}{s} \cdot \sum_{i=1}^{s} (Y_v'(i) - \langle Y_v' \rangle)^2}$, from a similar formula can be deduced. Subsequent steps were identical with traditional fractal analysis.

Characterization of real-time fractal analytical tools

Precision of algorithm were described in terms of the bias of estimated Hurst exponent ($\hat{H}$), the low value of which indicates stability of floating point calculations. However, variation coefficient was used as a specific measure of numerical instability. In order to eliminate its distorting effect on the analysis, I implemented real-time classification according to the fGn/fBm dichotomy (separated by H=1), the reliability of this procedure were assessed in separate tests. Minimally biased estimation of fractal parameters become possible after identifying signal class not affected by numerical instability. During quantitative tests a population of synthesized fGn and fBm monofractals with different dyadic length ($2^8 \leq L \leq 2^{14}$) and Hurst

exponent ($0<H_{true}<2$, step: 0.01) were evaluated (statistics were obtained for n=100 realization for each L and H_{true}). A specific measure of precision was expressed as a % of signals with bias less than a predefined tolerance (0.05 és 0.2). Finally, the dynamic response of the RT-analysis to time-varying scaling properties in the signal was assessed on synthesized processes (concatenated monofractals with different H) and on cerebral hemodynamics (recorded by NIRS) during cardiac surgery to demonstrate the applicability of the algorithm.

Focus-based multifractal analysis

The indirect formalism of multifractal time series analysis requires a scaling function, in case of multifractal DFA (MF-DFA: $S_F(q,s) = \left\{\frac{1}{N_s}\sum_{v=1}^{N_s}\{F(v,s)\}^{q/2}\right\}^{1/q}$. The scaling exponents (here $\hat{H}(q)$) were obtained both with standard and focus-based regression analysis, where the former refers to a fitting procedure performed independently for each and every q: $\ln(S(q,s)) = C + H(q)\cdot \ln s$. In contrast a focus ($\ln(\hat{S}(L))$) is incorporated in the alternative model, where all estimated parameters ($\hat{H}(q)$ and focus) are obtained once: $\ln(S(q,s)) = \hat{H}(q)\cdot(\ln s - \ln L) + \ln\left(\hat{S}(L)\right)$.

Qualitative assessment of multifractal analytical tools

Focus-based formalism were tested on a population of synthesized multifractal time series (n=50 realizations for each preset $H(q)$). Signals were created at two different signal lengths (L_1=1024 or L_2=16384) and wide parameter space was explored in terms of degree of LRC and multifractality. The DFA-specific scaling function values were calculated at dyadic scales and at a predefined set of statistical moments: $Q_{MF} \coloneqq \{\forall q \in Z \mid -15 \leq q \leq +15\}$. I compared the behavior of standard- and focus-based methods based on the quality of the obtained $D(h)$, distinguishing a corrupted multifractal spectrum showing an ill-defined functional relationship with an inversion.

Variance profiles of NIRS-signals, HbO–HbR relationship

Time series of the original and CBSI-pretreated hemoglobin fluctuations were analyzed by focus-based multifractal SSC (FMF-SSC), the scaling function of which were obtained at 60 logarithmically spaced scales between s_{min}=16 and s_{max}=8192 and Q_{MF}: $S_\sigma(q,s) = \left\{\frac{1}{N_s}\sum_{v=1}^{N_s}\{\sigma(v,s)^2\}^{q/2}\right\}^{1/q}$. The signal contains L values of Hb concentration and is divided into N_s = int(L/s) non-overlapping time windows (index: v = 1, 2, ..., N_s).

Variance profiles of HbO, HbR and HbT=HbT dynamics are defined as $S_\sigma(2,s)$ for q=2. Their exact relationship is expressed by the so-called Bienaymé-formula: ${}^{T}S_\sigma(2,s)^2 = {}^{O}S_\sigma(2,s)^2 + {}^{R}S_\sigma(2,s)^2 + 2r_\sigma(s) \cdot {}^{O}S_\sigma(2,s) \cdot {}^{R}S_\sigma(2,s)$, where $r_\sigma(s)$ is the scale-wise cross-correlation coefficient. This measure of HbO–HbR relationship can be derived from the above equation.

Scaling-range adaptive bimodal multifractal analysis (FMF-SSC) was performed directly yielding estimates for $H(q)$ and focus, separately for the low and high range of temporal scales, representing a slow and fast dynamics. For each of these component, the obtained $\hat{H}(q)$ and $D(h)$ were characterized by the following endpoint-parameters: $\hat{H}(2)$ and h_{max} (Hölder exponent belonging to $D(h)$ maximum, where D=1); ΔH_{15}=H(-15)–H(15), and full-width at half maximum (*fwhm*) of $D(h)$ in addition to the $\ln(\hat{S}(L))$.

Statistical analyses

One-sided tests were used to compare NIRS-signals with a population of signals with known stochastic/fractal properties to verify true multifractality, while F-test was used for the assessment of bimodality. Only correlation-type bimodal multifractals were made subject of further analyses.

Group-level comparisons were carried out depending on normality of distributions for each independent sample and homogeneity of variances. Means or medians of different groups were compared with two-way ANOVA (second factor: gender, post-hoc test: Tukey) or Mann-Whitney U test, respectively. Null-hypothesis was rejected in case of $p<0.05$.

Statistical evaluation of the Bienaymé-formula was carried out in general linear model (GLM) framework (dependent variable was the variance profile of HbT) for describing the effect of HbO–HbR relationship. Multiple regression analyses were performed with scale-wise correlation coefficient as a regressor; while age- and gender-related effects were taken into account only during analysis of covariance (AnCOVA), while $r_\sigma(s)$ was a covariate.

Results

Performance of real-time fractal analytical methods

Numerical instability was observed for fGn signal with lowest H_{true} value and for persistent fBm ($H_{\text{true}}>1.5$) processes. The implementation of real-time signal classification ($\hat{H}<1$: fGn; $\hat{H}>1$: fBm) proved to be effective for eliminating this source of

bias. Less precise estimates were obtained for signals with H_{true} ≈1 (close to 1/*f* boundary separating fGn and fBm class) due to misclassification and for shorter signals. RT-DFA and RT-SSC did not differ from each other in terms of neither signal classification nor precision. Interestingly, $\hat{H}$s obtained by RT-DFA were less biased compared to „offline" DFA without signal classification. Dynamic responses of the algorithm to processes with time-varying *H* were faster in case of smaller sliding window size. In addition, the analysis followed a step decrease in *H* with shorter delay compared with signals featuring a step increase in *H* (with same magnitude). Real-time algorithms turned out to be applicable on *in vivo* – acquired during cardiac surgery – NIRS-signals, specifically the result of RT-DFA was influenced both by hemodynamic artefacts and stage of operation.

Focus-based multifractal time series analysis

Inversion of singularity spectrum obtained with FMF-DFA was not observed at all neither for *in vivo* NIRS-records nor for synthesized signals. I evaluated the analytical behavior of both standard (MF) and focus-based (FMF) regression model. Using binomial logistic regression (dependent variable: presence / absence of $D(h)$ inversion, independent variable: sum of square

error describing goodness of model fit, SSE) allowed statistical comparison of the models and revealed a significant positive correlation between the ratio of FMF-SSE to MF-SSE and the inversion of $D(h)$.

True bimodal multifractality of hemoglobin-fluctuations

In case of eight subjects, their recorded spectrum significantly deviated from the $f^{-\beta}$-model which features fractal processes. In addition, bimodality was not confirmed for hemodynamic signals of two other subjects, therefore results from 42 subjects were promoted to group-level statistical comparison.

Impact of age on multifractal endpoint parameters

Signal component of raw HbT associated with low range of temporal scales (slow: ^{s}) and another component CBSI-pretreated HbT spanning across a range of high temporal scales (fast: ^{f}) showed age-dependence. Specifically: slow component of the HbT was found more correlated (increased $\hat{H}(2)$ and h_{max}) in the elderly group, while there were no age-group differences in foci. Parallelly, a decrease in $\hat{H}(2)$, h_{max} and $\ln(\hat{S}(L))$ was found for the fast component CBSI-HbT. Degree of multifractality did not differ between young and aged group. Notably, significant

influence of gender has not been identified regarding any of the calculated endpoint parameters.

Age-dependence and significance of HbO–HbR relationship

The scale-wise cross-correlation coefficients were elevated in case of elderly participants, with a significant difference at high temporal scales (>2000 seconds) correlating with higher $\hat{H}(2)$, too. Statistical analysis of the Bienaymé-formula confirmed the significant effect of altered $r_{\sigma}(s)$ on the variance profile of HbT on almost every time scale independently from age and gender.

Conclusions

Real-time fractal analysis

With the aid of RT-DFA method, calculation of scaling function for monofractal analysis is fast and the approximation of monofractal paramaters at least as precise as obtained with offline DFA. Moreover, the methods described in the dissertation are capable of estimating fractal measures in real-time.

- I obtained less biased estimate of Hurst exponent by implementing real-time signal classification, which prevented

a major source of error in the calculations due to numerical instability. Accordingly, I demonstrated the dynamic behavior of the real-time signal classification methods using synthesized signals with time-varying H and assessing the $H(t)$ function from hemodynamic signals recorded from the brain cortex during cardiac surgery.

Focus-based multifractal analysis

Algorithms following standard indirect multifractal formalism apply the Legendre-transformation that potentially, often leads to corruption of singularity spectrum (inversion of $D(h)$). Indeed, this phenomenon has often been observed in case of ideal stochastic multifractal that we generated for testing purposes, more frequently for shorter than for longer signals.

- During the examination of model fit, I revealed that the source of error was the finite size effect attributable to the finite length and discrete representation of the analyzed process. Consequently, the values of generalized Hurst exponent function become biased often leading to a non-monotonously decreasing $\hat{H}(q)$ implicated by the geometry of the scaling function. In fact, the non-concave property of $\tau(q)$ is directly

responsible for the inversion of $D(h)$, since it violates the prerequisite of Legendre-transformation.

- Relying on the analytical evaluation of $\tau(q)$ concavity ($d^2\tau(q)/dq^2<0$) I give a proof for the tight relationship between this feature and monotonicity of $\hat{H}(q)$. The negativity of $\frac{2dH(q)}{dq} + q \cdot \frac{d^2H(q)}{dq^2}$ (the second derivative of $\tau(q) = q \cdot H(q) - 1$) is dominated by the monotonous decay of $\hat{H}(q)$. Furthermore, it can be shown that focus-based regression model – building on the monotonously decreasing $\hat{H}(q)$ – ultimately guarantees inversion-free $D(h)$. The successful handling of finite size effect is due to enforcing the convergence of scaling function profiles. The ratio behind such model fitting procedure is that *i*) in case of $s=L$ the obtained $S(q,s)$ values become independent from moment order and *ii*) monotonicity suggested by the algebraic inequality between power means: $q_2 > q_1 \Rightarrow S(q_2, \mathrm{s}) > S(q_1, \mathrm{s})$.

Impact of aging on local scale-free properties on hemoglobin fluctuations in the brain cortex

In case of the majority of participants, the measured rsNIRS signal proved to be true bimodal correlation-type multifractal. The corresponding endpoint parameters and measures of HbO–HbR relationship were subsequently analyzed for a statistically significant effect of age and gender (group level statistical significance was not affected by the excluded subjects whose hemoglobin fluctuations could not be fitted with a genuine fractal model).

Based on the bimodality of local scale-free behavior of both raw and CBSI-pretreated signals it become possible to interpret changes in calculated variables as age-dependent neurogenic and vasogenic influences. Accordingly, we found that the significant age-related increase of $\hat{H}(2)$ and $h_{\max}$ obtained for the slow component of raw NIRS signals disappeared after applying CBSI, suggesting the vasogenic origin of group-level difference. Vice versa, the age-related differences of the calculated $\hat{H}(2)$, $h_{\max}$ and focus revealed for the fast component of only the CBSI-pretreated signal should reflect altered neurogenic fluctuations. The most likely explanation is that such age-related difference existing also between raw HbT signals was obscured by vasogenic fluctuations and became detectable of after the majority of this signal component – as it mainly renders the dynamics of HbO–HbR

relationship more correlated – was removed by CBSI. Spectral analyses of the raw and CBSI-HbT signals also support this view, and several studies have evidenced, that the age-dependent changes of the slow component of raw HbT fluctuations occur dominantly due to vascular (e.g. endothelial), while such changes regarding the fast component of CBSI-HbT are dominated by neural factors. Regarding the latter component, the observed decrease in the calculated endpoint parameters can be interpreted as the decreased incoming signaling to the region of interest of the elderly persons participating in our study. Difference between parameters reflecting degree of multifractality of the examined cerebral hemodynamics was not age-dependent.

- I found the elevation of scale-wise cross-correlation coefficient especially at high temporal scales. This pattern contributes to the causal explanation of age-dependent changes of the multifractal parameters concerning the vasogenic influences based on the Bienaymé-formula. Furthermore, the statistical analysis of this formula reveals the significant effect of $r_{\sigma}(s)$. These observations suggest an age-related attenuation of NVC, which is also indicated by an increased cross-correlation of HbO–HbR dynamics.

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