HRV ANALYSIS: UNDEPENDABILITY OF APPROXIMATE ENTROPY AT LOCATING OPTIMUM COMPLEXITY IN MALNOURISHED CHILDREN

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Abstract

Introduction: ApEn is an extensively enforced metric to evaluate chaotic responses and irregularities of RR-intervals sourced from an eletrocardiogram. However, to estimate their responses it has one major problem - the accurate determination of tolerances and embedding dimensions. So, we aimed to overt' this potential hazard by calculating numerous alternatives to detect their optimal in malnourished children.**Materials and methods:** We evaluated 70 subjects split equally: malnourished children and controls. To estimate autonomic modulation the heart rate was measured lacking any physical, sensory, or pharmacologic stimuli. In the time-series attained, ApEn was computed for tolerance, (0.1→0.5 in intervals of 0.1) and embedding dimension, (1→5 in intervals of 1) and, the statistical significances between the groups by their Cohen's d_s, and Hedges's g_s were totalled. **Results:** The uppermost value of statistical significance accomplished for the effect sizes for any of the combinations was -0.2897 (Cohen's d_s) and -0.2865 (Hedges's g_s). This was achieved with embedding dimension =5 and tolerance =0.3. **Conclusion:** ApEn was able to identify a reduction in chaotic response via malnourished children. The best values of embedding dimension and tolerance of the ApEn to identify malnourished children were, respectively, embedding dimension =5 and embedding tolerance =0.3. Nevertheless, ApEn is still an unreliable mathematical marker to regulate this.

Keywords: Child Nutrition Disorders; Nonlinear Dynamics; Autonomic Nervous System; Tolerance; Embedding Dimension

1: Introduction

The RR-intervals derived from an electrocardiographic trace, fluctuate in an irregular and often chaotic manner [1]. Historically, time-series assessments have stimulated academics to examine this niche [2, 3]. The assessment of RR-intervals is called Heart Rate Variability, a method for measuring the autonomic nervous system and hence, its autonomic dysfunction. As a technique, it is simple, dependable and cheap and an important technique for arbitrating physiologically healthy and/or pathological conditions [4-6]. Other techniques such as the sympathetic Skin Response is an alternative but unresponsive [7, 8]. Quantitative Pupillography is complicated and expensive [9]. Throughout medical dynamical systems, high chaotic values may designate healthy physiological status; but losses could be pathological [10, 11].

Heart Rate Variability can be computed by an algorithm described by Pincus (1991); hence, Approximate Entropy (ApEn) [12-15]. The benefits of ApEn include low computer processor demand. It is reliable with small sample lengths (RR<50). Similarly, it can accurately decipher statistics even with considerable signal noise. Nonetheless, this technique has a crucial shortcoming in that its accuracy is very reliant on the following parameter choices -- tolerance, *r* and embedding dimension, *M*. ApEn is as such difficult to interpret.

In this study we systematically applied different combinations of embedding tolerance, *r* and embedding dimension, *M* in normal subjects and compared them to malnourished children. The relationship between malnourishment and complexity metrics is useful in the risk assessment of dynamical diseases associated with the illness and can support the treatment of these children. The crucial purpose is to enforce embedding tolerance, *r* and embedding dimension, *M* groupings to acquire their optimum. Hence, achieving the greatest statistical significances between the groups.

2: Materials and methods

2:1 Population and Sample

The malnourished group entailed children not more than -2 in Z score in relative the height for the age, according with the criteria for age and gender by the World Health Organization (WHO) [16]. The eutrophic group consisted of children with Z scores greater than or equal to -2 and below +3, also consistent with WHO standards. Excluded from this study were obese children (Z-score greater than +3) or who presented with no less than one of the subsequent criteria: children who were taking medications that would influence autonomic activity of the heart, such as propranolol and atropine. Also omitted were children who presented with infections, metabolic diseases or cardiorespiratory system diseases, which affected their cardiac autonomic control.

The subjects and their parents/guardians were duly well-versed as to the procedures and objectives of the study. After agreeing to participate, the parents/guardians signed terms of informed consent. All procedures received approval from the ethics committee of the Institution (Process nº 275.310). Ethical Committee in Research from Sao Paulo State University (UNESP), Marilia, SP, Brazil."

2:2 Experimental Protocol

Before starting experimental procedures, information was noted on age, gender, mass and height. The anthropometric measurements were undertaken following the recommendations of Lohman *et al* [17]. Mass was measured using a digital scale (Filizzola PL 150, Filizzola Ltda., Brazil) with a precision of 0.1 kg, with the children barefoot and wearing only light-weight clothing. Height was measured via a infantometer with a accuracy of 0.1 cm. The data collection was achieved in a laboratory with temperature between 21°C and 23°C and relative humidity between 40% and 60%. Datasets were logged between 14:00 and 17:00 to minimize the circadian rhythm interference. After the initial evaluation, all procedures required for the data collection were explained on an individual basis. Children were told to continue at rest and avoid talking during the data collection.

Next, the heart monitor belt was placed over the thorax; aligned with the distal third of the sternum. The Polar S810i heart rate receiver (Polar Electro, Finland) was located on the wrist [18-21]. The equipment had been previously validated for monitoring beat-by-beat heart rate and the use of these data for Heart Rate Variability analysis in children and adults [20]. The children were positioned in the dorsal decubitus with a cushion and remained at rest with spontaneous breathing for 20 minutes. After the data collection, the child was discharged. The Heart Rate Variability behavior pattern was logged beat-by-beat throughout the monitoring process at a sampling rate of 1 kHz. After the digital and manual filtering for the elimination of premature ectopic beats and artifacts, 1000 uninterrupted RR intervals were required for data analysis. Only series with greater than 95% sinus rhythm were included in this study [22].

3:Mathematical Analysis

3:1 Approximate Entropy

Techniques based on entropy are routinely used in medical signal and data analysis [14, 23]. ApEn [13, 15, 24, 25], is a process that evaluates the level of regularity and the unpredictability of changes over time-series. ApEn is the logarithmic ratio of component-wise matching sequences from the signal length, *N*. Other parameters include *r*, tolerance and *M* the embedding dimension. For instance, with studies assessing Heart Rate Variability in obese children [14], *r* is set to 0.2 and this represents 0.2 or, 20% of the standard deviation of the datasets RR-intervals. A value of zero for ApEn would indicate a totally foreseeable series. ApEn increases with increasing chaotic response and irregularities. Further information regarding ApEn and it computation is found in the Kubios HRV® Manual [26].

3:2 Statistical analysis

At this point, we enforced various effect sizes to study the implications of the data. We did not evaluate normality [27-29] and so did not enforce the one-way analysis of variance (ANOVA1) [30], or Kruskal-Wallis [31] test as in previous studies. These two statistical tests are unable to discriminate adequately between the small changes in significance apparent here. Therefore, we examine the significances' using their effects sizes [32-34].

Cohen's d_s [35] is the foremost subcategory of effect sizes.

$$Cohen's\, d_s = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}}$$

It refers to the standardized mean difference between two groups of independent observations for the suitable sample. It is founded on sample means and provides a biased estimate of the effect size. Throughout the mathematical

algorithm for Cohen's d_s, the numerator is the variation between the means of two groups of observations. The denominator is the pooled standard deviation. These differences are squared. Next, they are summed and divided by the number of observations minus one for bias, in the estimation of the variance. To conclude, the square root is imposed on the denominator.

$$Hedges's\, g_s = Cohen's\, d_s \text{ x } \left[1 - \frac{3}{4(n_1 + n_2) - 9}\right]$$

Hedges's g_s is unbiased [36]. The change between Cohen's d_s and Hedges's g_s is very small in sample sizes >20. With regard, the Cohen's d_s and Hedges's g_s effect sizes designated ranges are 0.01 > very small effect; 0.20 > small effect; 0.50 > medium effect; 0.80 > large effect. These are the benchmarks from Cohen [35] and, Sawilowsky [37].

4: Results

A total of 70 volunteers of both genders between three and five years of age were split equally. Characteristics of the population are given below in Table 1.

Table 1

Childhood malnutrition's effect on the autonomic dysfunction has been established by chaotic global analysis [38]. It was demonstrated to lessen the chaotic responses and irregularities of RR-intervals. Then, ApEn is methodically applied to 25 parameters for tolerance, r and embedding dimension, M, (Figure 1 & Table 2). This determined that under 50% were appropriate when judged physiologically. This is since, chaos and irregularities usually decrease for pathological states [10, 11, 38]. In Table 2, ApEn for controls and malnourished children have tolerances, r (0.1→0.5 in intervals of 0.1) and embedding dimensions, M (1→5 in intervals of 1). A similar survey of parameter space was achieved in the study with subjects exhibiting type I diabetes mellitus [13] and Chronic Obstructive Pulmonary Disease [15].

Figure 1

In this study on malnourished subjects, as the embedding dimension, M increases the level of tolerance, r is less critical. For, M=1.0, two of the values for r are fitting as malnutrition has (and, should have) a lesser chaotic response than the control with negative effect sizes. This is physiologically accurate and was demonstrated by chaotic globals [38]. Here when, M=2.0 three out of five r values were apt and still negative effect sizes. Similarly, for M=3.0 one of the values for r is suitable and for M=4.0 two of the five values for r are suitable. At M=5.0 four out of the five values for r are apposite. All appropriate values have negative effect sizes for both statistical procedures, Cohen's d_s and Hedges's g_s.

Also, whilst the embedding dimension, M approaches 5.0 those values that are physiologically accurate have enlarged negative effect sizes by both measures. When studying the results in Table 2 we notice that the optimal statistical combination of M is 5.0 and r is 0.3 with ES = -0.2897 (Cohen's d_s) and -0.2865 (Hedges's g_s).

On closer inspection, where the M values are fixed this could be surpassed. Perusing in finer detail (Table 3), setting values of M and manipulating r. We set M=3 and r = 0.1833→0.4167 in intervals of 0.0167, hence 15 values of ApEn. Then, M=4 and r = 0.1833→0.4167 in intervals of 0.0167, hence a further 15 values of ApEn, and so forth, until an M value of M=6. For combinations of M and r we determine that M=5 acheives the greatest significance when tolerance, r=0.3 This corresponds to ES = -0.2897 (Cohen's d_s) and -0.2865 (Hedges's g_s), hence both with small effect sizes. This is the highest value of statistical significance reached for any of the combinations presented in either Tables 1-3.

Table 2

Table 3

5: Discussion

We endeavored to evaluate different combinations of r and M in malnourished children. Malnutrition in children has been demonstrated as a condition that greatly reduces chaotic response [10, 39]. Results demonstrated that ApEn is able to identify the reduction in chaotic response and the best combination of M and r for this study were 5.0 and 0.3 respectively.

ApEn measurements have some advantages in that they can be applied to short time-series (RR<50). Likewise, it is reasonably accurately at responding in the presence of substantial levels of signal noise. Nevertheless, its foremost disadvantage is the optimal choice of parameters for tolerance, r and embedding dimension, M.

In this study, initially, we enforced 25 different combinations r (0.1→0.5 in intervals of 0.1) and embedding dimension, M (1→5 in intervals of 1). It was anticipated that since malnutrition is a condition which lessens the chaotic response of Heart Rate Variability [38], those combinations of r and M which increase their responses for malnutrition can be disregarded. They are physiologically inappropriate. These inapt values reached positive effect sizes for both Cohen's d_s and Hedges's g_s.

Thirteen out of twenty-five of the permutations provided a higher value for the control than for malnourished subjects. So, less that half of the computations provided an true assessment. When scrutinizing the results further in Table 2 we can detect that the optimum combination of M is 5.0 and r is 0.3. We now need to examine the values more closely regarding the tolerance, r levels, whilst fixing M, embedding dimension (Table 3).

Consequently for Table 3 we fixed the values of M and inspected the values more closely regarding its tolerance, r. Tolerance, r was initially set at 0.1833 and increased up to 0.4167 in equal units (0.1833→0.4167 at intervals of 0.0167). Therefore, we computed 15 values for each value of embedding dimension, M. In Table 3, the embedding dimension, M varies from 3 to 6. The results for the two effect sizes were similar. The highest level of discrimination for the suitable physiological responses by Cohen's d_s and Hedges's g_s was ES = -0.2897 and -0.2865, respectively (small effect size for M=5.0 and r=0.5). This is synonymous to Table 2.

Thus, ApEn has been demonstrated to be a moderately reliable marker if the embedding dimension, M and tolerance, r are carefully chosen such that the differences are maximized by Cohen's d_s and Hedges's g_s. There is at present no procedure or algorithm by which these values can be selected. So, ApEn can be viewed as an unpredictable marker which can only be used effectively when the M and r are selected by trial and error. Routinely, when assessing Heart Rate Variability studies we set M=2.0 and r=0.2 where this represents 20% of the standard deviation of the time series [14]. Now, in this study that would give a positive effect size and as such, physiologically inapt. The chaotic global analysis would seem more reliable and dependable [38]. This is vital if we were enforcing ApEn when results were required online or under conditions that need to be calculated quickly as, for example, in an intensive care unit. It would be too slow and laborious to calculate all the possible values of ApEn. It would necessitate performing multiple calculations for every statistical outcome to reach the exact values to assess if an individual is pathological or healthy.

ApEn has been recognized to be an undependable mathematical marker. Yet, it has advantages such as performing well on short time-series, even in the presence of substantial signal noise. Based on the results obtained, we encourage the use of the chaotic global methods as a substitute for judging severity of pathological conditions. Chaotic global analysis is easier to enforce, performs well on relatively short time-series (RR>256) [40], even with levels of noise, discriminates between the groups better and needs less computational time [10, 11, 41, 42].

Some points need to be addressed in our study. The present results should not be interpreted to smaller sample sizes, as we evaluated just 70 individuals. Different autonomic approaches were not used, including barorelex sensitivity, skin conductance and neuroelectromyograph. It would provide additional physiological data for our analysis. And finally, our study reinforces the importance to emphasize the relationship between experimental HRV with clinical practice.

6: Conclusion

Childhood malnutrition has been established as a dynamic condition which lessens chaotic response. In this study, ApEn was able to identify the reduction in chaotic response during malnutrition. Until now, ApEn has been confirmed to be a relatively unreliable mathematical marker.

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9: Conflicts of Interests & Data Statement

The authors declare that there is no conflict of interests regarding the publication of this article. Data and Matlab code used in the study remain confidential for commercial reasons.

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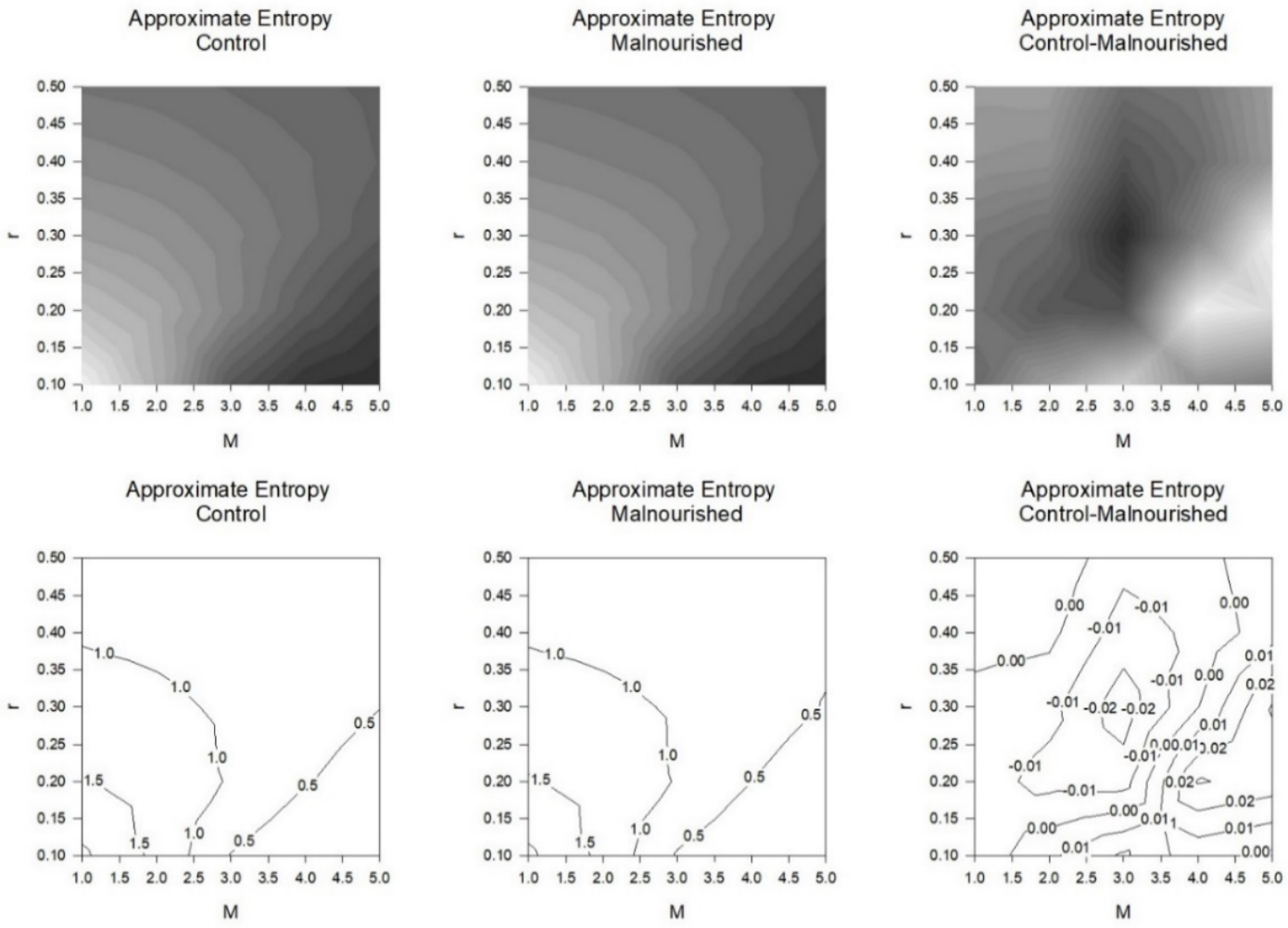

Figure 1: Contours Greyscale (Above) & Contour Lines (Below) Approximate Entropy (ApEn) for controls and subjects with Malnutrition (both n=35). There were precisely 1000 RR-intervals. Other parameters consist of tolerance, *r* and, embedding dimension, *M*. There were 25 groups of values for tolerance, *r* (0.1→0.5 in intervals of 0.1) and embedding dimension, *M* (1→5 in intervals of 1) hence a grid of 5-by-5. The ApEn for the controls (left), those with Malnutrition (middle), the difference in ApEn between the controls and those with Malnutrition (right).

Table 1: Description of the characteristics of the population by group, gender, age (years), weight (kg), height (cm) and Z-Score (mean ± SD).

Group	Gender	Age (years)	Weight (kg)	Height (cm)	Z-score
Malnutrition	23 Girls	3.71 ± 0.75	13.02 ± 1.71	91.53 ± 5.47	-2.80 ± 0.59
Eutrophic	20 Girls	4.09 ± 0.85	17.89 ± 3.04	106.83 ± 8.15	0.191 ± 1.28

Table 2: Approximate Entropy (ApEn) for controls and malnourished (MAL) subjects (both n=35). There were exactly 1000 RR-intervals for each subject. Other parameters consisted of tolerance, *r* and, embedding dimension, *M*. There were 25 groups of values for tolerance, *r* (0.1→0.5 in intervals of 0.1) and embedding dimension, *M* (1→5 in intervals of 1). Illustrated are the ApEn for the mean controls with standard deviation, mean malnourished and standard deviation, then their effect sizes for control versus malnourished by Cohen's d_s and Hedges's g_s.

M	*r*	Approximate Entropy (n=35)				Effect Sizes (ES)	
		Mean Control	±SD Control	Mean MAL	±SD MAL	Cohen's d_s	Hedges's g_s
1.0	0.1	2.0835	0.1995	2.0906	0.2154	0.0343	0.0340
1.0	0.2	1.5309	0.2084	1.5361	0.2214	0.0242	0.0240
1.0	0.3	1.1877	0.1928	1.1911	0.2099	0.0170	0.0168
1.0	0.4	0.9567	0.1806	0.9528	0.1916	-0.0208	-0.0205
1.0	0.5	0.7859	0.1607	0.7791	0.1764	-0.0402	-0.0397
2.0	0.1	1.3842	0.0531	1.3760	0.0778	-0.1217	-0.1204
2.0	0.2	1.3296	0.1700	1.3430	0.1759	0.0775	0.0767
2.0	0.3	1.0904	0.1821	1.0974	0.1897	0.0377	0.0373
2.0	0.4	0.8996	0.1735	0.8969	0.1790	-0.0149	-0.0148
2.0	0.5	0.7508	0.1546	0.7435	0.1680	-0.0458	-0.0453
3.0	0.1	0.4799	0.1499	0.4581	0.1389	-0.1508	-0.1491
3.0	0.2	0.9566	0.0630	0.9709	0.0886	0.1859	0.1838
3.0	0.3	0.9349	0.1180	0.9608	0.1491	0.1925	0.1904
3.0	0.4	0.8117	0.1383	0.8263	0.1637	0.0962	0.0951
3.0	0.5	0.6899	0.1295	0.6966	0.1604	0.0464	0.0459
4.0	0.1	0.1028	0.0660	0.0996	0.0876	-0.0404	-0.0400
4.0	0.2	0.5306	0.1294	0.4997	0.1301	-0.2383	-0.2356
4.0	0.3	0.7356	0.0668	0.7360	0.0901	0.0040	0.0040
4.0	0.4	0.7125	0.1016	0.7202	0.1252	0.0678	0.0671
4.0	0.5	0.6306	0.1138	0.6344	0.1389	0.0299	0.0296
5.0	0.1	0.0199	0.0181	0.0224	0.0350	0.0888	0.0879
5.0	0.2	0.2365	0.1294	0.2109	0.1265	-0.1995	-0.1973
5.0	**0.3**	**0.5068**	**0.1030**	**0.4760**	**0.1097**	**-0.2897**	**-0.2865**
5.0	0.4	0.5952	0.0616	0.5892	0.0826	-0.0829	-0.0820
5.0	0.5	0.5735	0.0868	0.5664	0.1096	-0.0722	-0.0714

Table 3: Effect Sizes (ES) by Cohen's d_s and Hedges's g_s for the ApEn for controls versus malnourished subjects (both n=35). Exactly 1000 RR-intervals were required in the calculations for each subject. Other parameters consisted of tolerance, *r* and embedding dimensions, *M* which are fixed at 3,4,5, & 6. There were 15 groups of values for tolerance, *r* (0.1833→0.4167 in intervals of 0.0167).

r	**Effect Sizes (ES) by Cohen's d_s**				**Effect Sizes (ES) by Hedges's g_s**			
	M=3	**M=4**	**M=5**	**M=6**	**M=3**	**M=4**	**M=5**	**M=6**
0.1833	0.0782	-0.2110	-0.1033	-0.0140	0.0773	-0.2087	-0.1021	-0.0138
0.2000	0.1859	-0.2383	-0.1995	-0.1044	0.1838	-0.2356	-0.1973	-0.1033
0.2167	0.1893	-0.1565	-0.1878	-0.1123	0.1872	-0.1548	-0.1857	-0.1110
0.2333	0.2561	-0.1466	-0.2336	-0.2010	0.2532	-0.1450	-0.2310	-0.1988
0.2500	0.1593	-0.1078	-0.1675	-0.0742	0.1576	-0.1066	-0.1657	-0.0733
0.2667	0.1575	-0.0566	-0.1652	-0.1336	0.1557	-0.0559	-0.1634	-0.1321
0.2833	0.1844	0.0555	-0.1942	-0.1943	0.1824	0.0549	-0.1921	-0.1922
0.3000	0.1925	0.0040	**-0.2897**	-0.2515	0.1904	0.0040	**-0.2865**	-0.2487
0.3167	0.1501	0.0103	-0.2324	-0.2004	0.1484	0.0102	-0.2298	-0.1982
0.3333	0.1210	0.0292	-0.2467	-0.2080	0.1197	0.0289	-0.2440	-0.2057
0.3500	0.1369	0.0728	-0.1922	-0.2246	0.1354	0.0720	-0.1901	-0.2221
0.3667	0.1185	0.0791	-0.1401	-0.1916	0.1172	0.0783	-0.1385	-0.1895
0.3833	0.1103	0.0689	-0.1545	-0.2382	0.1091	0.0681	-0.1528	-0.2355
0.4000	0.0962	0.0678	-0.0829	-0.2056	0.0951	0.0671	-0.0820	-0.2033
0.4167	0.1006	0.0680	-0.0975	-0.2783	0.0995	0.0672	-0.0965	-0.2752