Nonlinear Dynamics, Psychology, and Life Sciences, vol. 22, 439-456.

Lifespan Characterization of Chaotic Dynamics in Menstruation

G. N. Derry
Department of Physics
Loyola University Maryland

P. S. Derry
Paula Derry Holistic Health Perspectives
Baltimore, MD

RUNNING HEAD: Chaos and Menstruation

Correspondence should be addressed to: G.N. Derry, Physics Dept., Loyola University Maryland, 4501 N. Charles St., Baltimore MD. 21210, gderry@loyola.edu, 410-617-2662.

Abstract

In previous work, we found evidence that chaotic dynamics characterize the human menstrual cycle. Here, we examine chaotic dynamics in menstruation year-by-year over the lifespan, with special attention to later life. Using data in the Tremin research program archives, lifelong menstrual cycle histories known for 143 subjects beginning at about age 20 through the final menstrual period (FMP) provided data for time series analysis. Cycle lengths were aggregated and analyzed by year prior to the FMP. Time series data was analyzed with procedures developed by Grassberger-Procaccia and by Judd, and the results summarized by a new measure defined herein, the inter-event correlation parameter (I_{cp}). The menstrual cycle was characterized by chaotic dynamics rather than disorder or randomness throughout life until the FMP. Plots of the I_{cp} *versus* the number of years prior to the final menstrual period showed a small increase approximately 17 years prior to the final menstrual period and a large monotonic decrease during the last 5-8 years before the final menstrual period. The shifts in I_{cp} correspond in time to significant phenomena identified in menstruation research. Assumptions underlying the analysis are discussed in the article. Possible implications of these findings to paradigms of menopause are discussed.

KEYWORDS: Chaos, Time Series, Menstruation, Menopause, Lifespan

INTRODUCTION

A nonlinear dynamical framework offers a rich set of possibilities for study of the menstrual cycle. As conventionally described (e.g., Goodman, 2009), the normal menstrual cycle is the outcome of regularly recurring, cyclic variations in a number of interacting hormones that results in cyclic, predictable outcomes. In this model, the length of the cycle is a standard, canonically 28-day, repetition. Variability, when observed, has often been ignored, or interpreted as uninteresting randomness (around a real 28-day mean), or considered as being due to developmental immaturity in teenagers, a symptom of pathology, or from stresses to the system. When, in the years preceding menopause (the permanent end to menstruation), periods become irregular and otherwise odd, this increased irregularity and unpredictability has often been interpreted as senescence or pathology. However, there are reasons to think that variability may be the result of chaotic dynamics and important to further understand.

Physiologically, the nature of the underlying system is consistent with the possibility that chaotic dynamics exist. Both positive feedback and negative feedback mechanisms are operative in this system, and these endocrine feedbacks are an important component of the dynamics driving the menstrual cycle. Feedback mechanisms exist between the production rates of gonadotropin releasing hormone (GnRH) in the hypothalamus and pituitary hormones (follicle stimulating hormone (FSH) and luteinizing hormone (LH)). Similar feedback mechanisms exist between these hormones and the production of estrogen and progesterone in the ovaries. As is well known, such feedback relationships amongst variables can often result in chaotic trajectories for the variables. The menstruation research literature also suggests the possibility of chaos.

While overlooked, variability and unpredictability are endemic. Empirical data show great variability between and within women in the time intervals between the onset of successive menstrual cycles throughout life and in the lifelong trajectory of menstrual cycle changes (Gorrindo, et al., 2007; Treloar, Boynton, Behn, & Brown, 1967). As would be expected in a chaotic system, individual trajectories differ from the mean (Gorrindo, et al.).

One of our primary motivations in investigating the menstrual system is to better understand changes with time that occur during the human lifespan, particularly changes that occur later in life. The later changes are most often defined as a discrete stage called perimenopause and conceptualized as the physiological changes leading directly to menopause. Perimenopausal physiology is characterized by unpredictability and by deviations from previous feedback relationships (see P.S. Derry & G.N. Derry, 2012, for a discussion of these). For example, estrogen levels do not linearly decline, as was expected, from premenopausal levels to their postmenopausal low; instead, they oscillate unpredictably, with spikes where decreases were expected. These changes might exist during some menstrual cycles with hormone levels and feedback relationships then returning to premenopausal patterns. Instead of following universal laws, hormone and other menstrual cycle changes are found to vary within and between women, apparently unpredictably.

The most typical interpretation of the perimenopausal research literature is the biomedical model (P.S. Derry & G.N. Derry, 2012; Voda, 1997; Voda and Ashton, 2006): Perimenopausal physiology is best understood as senescence and/or pathology in which an unstable and disordered system no longer responds normally to hormonal and

other signals. For example, feedback relationships might be said to change because the ovary has become "resistant" or otherwise less able to respond normally to hormonal signaling; deviations from the norm at younger ages, like increased menstrual cycle variability or increased numbers of anovulatory cycles, are defined as "abnormal." However, this patterning could also reflect the output of a chaotic system. Extreme values, individual trajectories differing from the mean trajectory, and changes in pattern that return to preexisting patterns are all consistent with what would be expected in a chaotic system.

If the mathematical pattern of results is chaotic rather than disordered or random, this suggests that while menopause is the ending or closing of a system, this could be something other than a simple breakdown or failure. That is, in the biomedical model menopause is a biological puzzle and anomaly: Animals should seek to reproduce as long as possible; shifts from maximal fertility signal a declining system rather than a lifespan arc. An alternative to the biomedical model does exist: Menopause is part of the human biological life plan (P. S. Derry, 2006; Hawkes & Coxworth, 2013; Kaplan, Gurven, Winkling, Hooper, & Stieglitz, 2010). Menopause and a long post-menopausal life, as they exist in humans, are all-but-unique in the animal world (Pavelka & Fedigan, 1991), and there is nothing unusual about humans having unusual life stages. Human childhood and adolescence, for example, are unusual compared with other animals (Bogin, 1999). Here, we are suggesting that chaotic dynamics could be consistent with, and perhaps integral to, this perspective.

Testing the hypothesis that chaotic dynamics are responsible for menstrual variability is difficult; data for hormone levels is challenging to acquire due to both

expense and inconvenience to subjects. In our studies, we circumvent this problem by using time intervals between successive menstrual event onsets instead of a time series of hormone levels. Informally, the rationale for this technique is that these menstrual events are an output of the dynamics of the entire system and that hence their time variations are a reflection of these dynamics. Remarkably, the needed data for this technique exists for many women over most of their lives in the Tremin Research Program on Women's Health. (More detail on this technique and the source of the data is provided in the Methods section.) Employing such data in our first study (G.N. Derry & P.S. Derry, 2010), we computed a variety of quantities that indicate the presence of chaos (correlation dimension, positive Lyapunov exponent, KS entropy) using multiple methods and testing the results with surrogate data sets. In addition to this quantitative exploration, offering substantial evidence for chaotic dynamics in the variability of the menstrual cycle, we have also published a paper (P.S.Derry & G.N. Derry, 2012) exploring in more detail the theoretical implications of this result and its potential health implications.

In the present paper, we further investigate the role of chaotic dynamics across adult life, motivated by our interest in understanding the nature of the lifelong trajectory of the menstrual cycle. Since women's age at menopause varies, we use the final menstrual period (FMP) as a reference point. We evaluate each year prior to the FMP as to whether chaotic dynamics are found in order to replicate and expand our previous finding of lifelong chaos, and to look for evidence of changes across the lifespan in the strange attractor. Lastly, we examine how our findings compare with previous research

results and inform implications for a lifespan/developmental perspective on the menstrual cycle and menopause.

METHODS

The data for this study consists of sequences of menstrual cycle lengths obtained from the archives of the Tremin Research Program on Women's Health (Mansfield & Bracken, 2003). Tremin has provided a rich and unique source of data for menstrual cycle research. Begun in 1934, with data collected through 2008, cohorts of subjects were recruited who reported on a daily basis whether or not they were menstruating, with an option of indicating "spotting," using a form that was turned in to the experimenters each month. There were therefore no recall issues as found in retrospective reports, and compliance could be determined by inspecting the data in the monthly record. Subjects were asked to continue recording their menstruation experience throughout life. Our study used subjects from Cohort 1 (2,350 University of Minnesota undergraduates recruited 1936-1939) and Cohort 2 (1,367 University of Minnesota students recruited 1961-1963). Cohort 1 was recruited from all incoming freshmen at a required physical exam; cohort 2, from mailed solicitations. We randomly selected 143 women from these cohorts for whom menstrual cycle data existed from approximately age 20 until the final menstrual period. The age at which the FMP occurs varies considerably among different women, usually within a range from 45 to 55 years. Additional information about the subjects, attrition rates, etc., can be found in Mansfield and Bracken and in Treloar, et al. (1967).

We followed Tremin norms for defining menstrual cycle length: A cycle is the time interval between day 1 of flow of one cycle and the next, provided these are

separated by at least 2 days of nonflow or spotting. While some information exists about health problems and pregnancies, this information is uneven across the years of data collection. Treloar et al. (1967) did report that roughly 1% of the intervals recorded were associated in time with surgeries or illnesses (page 81). As in our previous studies, to avoid artifacts due to pregnancy, health issues that might influence cycle length, or gaps in the record, we eliminated cycle lengths that were extremely short or extremely long. Again, the protocol we use to accomplish this is the criterion employed by Treloar and typical in Tremin research: We eliminated the highest 5% and lowest 5% of the time intervals. Again, more detailed information about Tremin methodology can be found in Mansfield and Bracken and in Treloar et al.

In a standard time series analysis, we would have a time series consisting of some characteristic variable measured at equally spaced time intervals. However, since data of this sort is not available, we instead use the time interval sequence described above to do time series analysis. It has been shown that, under the appropriate conditions, using inter-event time intervals yields the same results as using a time series of some dynamical variable, though the precise specification of the required conditions has not yet been established (Hegger & Kantz, 1997; Sauer, 1995).

The main nonlinear quantity of interest in this study is I_{cp}, the inter-event correlation parameter of the data, which is sensitive to the state of the nonlinear dynamical system that generates the events. The computational algorithm of I_{cp} is essentially the same as the computation of the correlation dimension in a state space reconstruction (Takens, 1985). In other words, an *m*-dimensional vector is constructed from a consecutive sequence of *m* inter-event time intervals, analogously to a state space

reconstruction from a time series, in which *m* would be the embedding dimension. In this state space, the number of pairs of points N that are separated by a distance less than r obey a scaling relationship

$$N(r) \sim r^{\mathrm{Icp}} \qquad (1)$$

similar to the scaling relationship in which the exponent is D_c, the correlation dimension of the dynamical system that generated the data. We then follow the prescription of the well-known analysis devised by Grassberger and Procaccia (1983): the number of points N_i that have distances less than some value r_i are counted for a range of r_i values; a scaling region where $\log(N_i) \sim \log(r_i)$ is identified; these quantities are plotted; and the slope of the resulting straight line yields the desired quantity. The procedure in the present study is basically identical, with the slope of the line being the inter-event correlation parameter I_{cp}.

In our previous publications, we have, for obvious reasons, identified the quantity we computed in this manner as the correlation dimension of the system (G. N. Derry & P. S. Derry, 2010; P. S. Derry & G. N. Derry, 2012). More recent work, however, has indicated that some necessary condition was not satisfied in these computations, and that the actual correlation dimension of the dynamical system underlying the menstrual cycle is considerably smaller than the inter-event correlation parameter I_{cp} that we are measuring. This methodological work includes time series analysis of empirical data from a well-understood system (the Chua circuit) (G. N. Derry, 2016) and time series analysis of computed output from an elaborate nonlinear model of the menstrual cycle (G. N. Derry, 2013), comparing in both cases the results found using dynamical variables with results using inter-event time intervals. A detailed description of these results is

beyond the scope of the present paper and will be reported elsewhere, but one conclusion is that the most likely reason for the difference between the inter-event correlation parameter I_{cp} and the correlation dimension D_c is that the time intervals between the events are very large compared to the time required for the delay coordinates of the state space reconstruction.

For the purposes of the present study, the most important conclusion of this methodological work is that I_{cp} carries nonlinear dynamical information and that its numerical value is sensitive to the state of the system. The key point here is that the sensitivity of I_{cp} to the state of the underlying nonlinear dynamical system allows us to use it as a probe for studying changes in that system over the lifespan of the subjects. In other words, the dynamical state of the physiological system we are indirectly studying influences the fractal morphology of the system's strange attractor, so changes in that dynamical state alter the attractor's morphology. The numerical value of the I_{cp}, in turn, depends on the morphology of the attractor and hence on the dynamical state of the system. Therefore, without necessarily having any detailed knowledge concerning the nature of such dynamical changes, we are able to employ the I_{cp} as an indicator of whether changes (of any sort) are occurring or not.

For this analysis, the range Δr was approximately the same for all cases and the embedding dimension was kept fixed at $m = 10$. In order to avoid any bias in the choice of the scaling region, and at the same time to conform as well as possible to the desired $r \to 0$ limit, the protocol used in the work reported here was to choose for our range the smallest possible value of r_{min}, which effectively meant that the smallest values of N are <10 in almost all cases. The value of r_{max} for the range we chose was then determined by

where the data started to deviate from the proper scaling, which typically turned out to be $\approx 3r_{min}$ resulting in a rather narrow scaling range for r. The accompanying scaling range for N, however, is typically greater than two orders of magnitude over this range of r.

In order to examine the effects of varying the protocol choices, a different set of analyses were undertaken in which the effects of varying *m* were explored and the robustness of the methodology was tested by employing the method proposed by Judd (1992, 1994) in addition to the more commonly used Grassberger-Procaccia algorithm described above. Judd's work suggests that the relationship between N and r should be given by

$$N(r) \approx r^{\mathrm{Icp}}(a + br + cr^2) \qquad (2)$$

where I_{cp} is the inter-event correlation parameter and the coefficients a, b, and c are constants (in Judd's work, of course, the exponent is D_c, the correlation dimension). Note that the Grassberger-Procaccia result is equal to the limit of the Judd result for small r, and we can think of this equation as a generalization of the more typical formalism that's not restricted to the low-r limit. The major advantage of using this generalization is that, in addition to not being restricted to small values of r, we do not in fact need to choose any scaling region at all. Instead, the data are binned into counts N_k for the number of pairs with distances within the intervals Δr_k, forming a distribution with a monotonically decreasing tail below some value of $r \equiv r_{max}$. All the data for $r < r_{max}$ are then used, eliminating the need to choose a scaling region. Since the choice of the scaling region is sometimes ambiguous and can affect the numerical results, this method has the advantage of using more of the data and avoiding subjective judgments. The disadvantage of the method is that it introduces more fitting parameters, and these

parameters can be extremely sensitive to small variations in the data and to the choice of the Δr_k (multiple trials using slightly different Δr_k choices were conducted and combined in the fitting process to correct for this problem). In the present context, however, the major advantage of using this method alongside the more familiar Grassberger-Procaccia method is that it serves as another crosscheck on the validity of the reported results.

In all of the work reported here, using both of these methods, randomly chosen subsets of pairs were chosen to compute the N_i rather than using every possible pair available. This protocol was carefully checked to insure that it yields the same results as using all pairs. There are two advantages to using random subsets of pairs. First, the time to perform the computation decreases by approximately an order of magnitude. Second, the computation can be repeated several times using the same data set (but with different random subsets of pairs) in order to formulate a rough idea of the uncertainty. In almost all cases, <5% of the available pairs are needed to get good results.

Interpreting the meaning of observed changes in the I_{cp} in some simple straightforward manner is problematic. In addition to the difference between I_{cp} and D_c, which is still under study, measures of dimensionality such as D_c are themselves difficult to relate simply to the observational behaviors and other properties of a system. Such measures of dimensionality offer information about the geometry of a strange attractor in the phase space of a system, and this information alone does not tell us anything specific about the dynamics that generated the attractor. More particularly, the numerical value of such a measure does not necessarily imply any knowledge concerning the degree of complexity (however defined) in those dynamics (Bradley & Kantz, 2015). What a change in the

I_{cp} *does* tell us unambiguously is that some *change* in the dynamics of the system has occurred (for example, a control parameter might have altered its value, or feedback relationships between variables may have changed, or a new variable might have begun to affect the system, and so on). In order to ascertain the nature of such changes, we must have some theoretical understanding of the dynamics, e.g. a mathematical model of the system; such work is underway, but is presently in an early stage.

In order to study age dependence in the menstrual cycle's nonlinear dynamics, we prepared a data set in the following manner: For each of the 143 individual subjects, the beginning of each menstrual cycle was tagged with the age of the subject (in days) when that event occurred. The age when the final menstrual period (FMP) occurred for each subject is recorded and serves as the temporal reference point; in other words, we now measure how long prior to the FMP each menstruation onset occurred. Since the developmental changes in individual women occur at different ages, the use of the FMP provides a much more valid time scale than the chronological age of the subjects. For each of the years prior to the FMP, all of the menstrual cycle lengths (i.e. the inter-event time intervals) occurring during that year are collected together for each subject, and then all of this data is aggregated into a single data record for analysis (i.e. we are analyzing all of the menstrual cycles of all of the women occurring during each of the years prior to menopause). This procedure is repeated until we have done this for 31 years of data. (As another crosscheck, we also did this for 1.5 year intervals in one analysis, to insure that no artifacts were caused by the arbitrary choice of one year aggregations.) These individual one-year data records each contain $\sim 10^3$ data points for analysis, which proved

to be sufficient. It is important to emphasize both the need to have one-year aggregations and the need to use the FMP as a temporal reference point rather than using birth (i.e. chronological age); in a previous preliminary study of this question, much longer aggregation times and chronological age were employed resulting in more ambiguous results.

RESULTS

An example of the inter-event time interval data used in this study is shown in Figure 1, where the menstrual cycle lengths of all 143 subjects during the 28^{th} year prior to the FMP are plotted. All of the year-long data sets, aggregating data for all of the subjects in that year, are qualitatively similar to the one illustrated here, except for the visibly increasing variability during the last 5 years (approximately) prior to the FMP. The data in each of these year-long sets is analyzed independently in order to calculate the inter-event correlation parameter for that data.

In Figures 2 and 3, we present results obtained using a single consistent set of methodological choices. The embedding dimension for all of these results has been kept fixed at m=10, the value of r_{min} was chosen to keep N_{min}~5, and the delay has been fixed at unity (i.e. each vector consists of 10 consecutive time intervals). Keeping these methodological values fixed, the inter-event correlational parameter was calculated separately for age-aggregated sets of menstrual cycle data across the entire age range of the subjects.

Figure 2 is a plot of $\log(N)$ *vs* $\log(r)$ for data in the 14^{th} year prior to the FMP, demonstrating the typical scaling behavior observed in our results. As noted above, the scaling range of r is comparatively narrow, but the resulting range of N is approximately

two orders of magnitude. The slope of this plot yields the inter-event correlation parameter, with $I_{cp} \approx 6.88$ for the data shown in the figure. Each measurement was redone at least four times using different sets of 40000 randomly chosen pairs to obtain an estimate of the scatter (for example, the standard deviation of I_{cp} was ≈ 0.3 for multiple re-samplings of the data used in Figure 2). The average values resulting from this procedure are reported here.

Repeating this procedure for all of the sets of data aggregated at different ages of the subjects, we obtain the results shown in Figure 3, which is a plot of the I_{cp} values *versus* the number of years prior to the FMP. Our main concern here is whether there is any effect of age or development on the nonlinear dynamical behavior of the menstrual cycle variability, and if so how to characterize that effect. The results in Figure 3 clearly demonstrate the existence of such effects, with an observable increase in the value of I_{cp} at about 15-17 years prior to the FMP and a marked decrease in the I_{cp} during each of the final 5 years until menopause. The increase occurring at 15-17 years prior to the FMP is small, but it is a measurably real effect. Using the mean values of I_{cp} and their standard deviations over ranges of 18-31 years and 8-15 years prior to the FMP, we find an increase of 6.41 ± 0.33 to 7.23 ± 0.19 in the I_{cp}. Concerning the dramatic decrease in I_{cp} during the last 5 years prior to the FMP, it is noteworthy that the decrease is consistently monotonic over this time rather than being a single stepwise decline.

The methodology was kept as consistent as possible in calculating the results shown in Figure 3, in order to minimize the effects of methodological changes on the results and to thus isolate the age of the subjects (relative to the FMP) as the dominant variable affecting the numerical value of the I_{cp}. In order to explore how the

methodological choices themselves might have affected the results, and how robust these results are, we have also done a number of experiments using different protocols. Instead of the Grassberger-Procaccia method shown in Figure 3, we employed the method devised by Judd, described above. Additionally, the embedding dimension was varied in order to observe how this affects the results, and the aggregation time span was varied in one trial to 1.5 years. Because no scaling region needs to be identified, the range of r in these trials is also greater than it is for the results shown in Figure 3.

An example of the method is illustrated in Figure 4, using data from the 12th year prior to the FMP and an embedding dimension of 10. The vertical spread in the data is due to differences in the Δr_k binning choices, with $r_{max} \approx 8.9$, while the solid line is a plot of Equation 2 with the constants determined by a best fit to all of the data. The inter-event correlation parameter was determined by the fitting process to be $I_{cp} \approx 8.15$ in this example. For these tests, only one trial of randomly sampled pairs was conducted in each case, but the I_{cp} values for the highest and the second-highest r_{max} cut-offs were averaged.

The results of this procedure over the entire age range, for three different embedding dimensions and two aggregation time intervals, are shown in Figure 5. These results verify the trends observed in Figure 3, namely a clearly observed increase in the value of I_{cp} at about 17-18 years prior to the FMP and a considerable decrease in the I_{cp} during the final 5-8 years until menopause. In this case, the quantitative change in the mean values (at 17-18 years prior to the FMP) was from 5.84±0.54 (20-30 years) to 8.02±0.81 (10-18 years). While the quantitative agreement is not exact, the qualitative trends are unmistakably the same. There do not appear to be any systematic differences due to the differing protocol choices (e.g. embedding dimension), though such

differences may be masked by the considerable degree of scatter in the results. This large scatter reflects the considerable uncertainty in the I_{cp} measurements, which is consistent with our previous studies. Despite this uncertainty, however, the observed trends are robust and reproducible.

Thus, there is good evidence for the effects of age and development on the nonlinear dynamical behavior of the menstrual cycle. More specifically, there is a step-wise increase in the inter-event correlation parameter at about 17 years prior to the final menstrual period, and about 10 years after that there is the onset of a monotonic decrease in the inter-event correlation parameter that continues until the final menstrual period occurs.

DISCUSSION

This work provides further evidence that the menstrual cycle is the output of a nonlinear dynamical system. Results presented here dovetail with and support our previous research providing evidence for chaotic dynamics (G.N. Derry & P.S. Derry, 2010). An inter-event correlation parameter indicating the presence of a chaotic system was found each year throughout adult life from approximately age twenty to the FMP. The state of that system varied over the course of a woman's life: The I_{cp} varied naturally over the life span, with a measurable increase in I_{cp} at about 17 years before the FMP and a considerable monotonic decrease during the 5-8 years preceding menopause.

The present results are also qualitatively consistent with other research on the menstrual cycle. An average increase in menstrual cycle irregularity 4-8 years before menopause is so frequent a finding that an increase in irregularity is a common operational definition of perimenopause (Harlow, Gass, Hall, Lobo, Maki, & Rebar,

2012); Lisabeth, Harlow, & Qaqish, 2004; Treloar, 1981). Parallel to these findings, we measure changes in the I_{cp} approximately 5-8 years before the FMP.

The change in the value of the Icp found in the present study, approximately 17 years before the FMP, is consistent with the age-range for a number of other changes reported in the literature (though we note that these studies used chronological age rather than time before the FMP). For example, researchers have found a variety of subtle shifts in the menstrual cycle that begin prior to irregular cycles, during a woman's mid-thirties or early forties. Mitchell, Woods, & Mariella (2000) found that changes in menstrual cycle qualities like the amount or length of flow were common, and Prior (Prior and Hitchcock, 2011) reported a constellation of subjective symptoms like hot flashes increasing around this age. Lisbeth et al. (2004) found that the correlation between the length of one cycle and the next begins to decline in the mid-thirties and accelerates around age 40. How to interpret these earlier changes has been controversial, in part because their meaning so many years prior to menopause is unclear; also, some of these changes are subtle and they vary from woman to woman. Some (e.g., Mitchell, et al.; Prior) but not all (e.g., Harlow, et al.) researchers argued that these earlier changes are markers for a stage of the transition to menopause that precedes cycle irregularity.

The change in the I_{cp} approximately 17 years before the FMP is also consistent with research on the follicle depletion rate in the female reproductive system. The number of follicles in a woman's ovaries declines throughout life, beginning prenatally and continuing throughout childhood and adulthood; at menopause, follicles are close to being depleted. A genetic timetable underlies this process, which is largely due to the self-destruction of follicles ("atresia") rather than ovulation. Faddy, Gosden, Gougeon,

Richardson, and Nelson (1992) found that the number of follicles declines with age bi-exponentially; the rate of destruction accelerates at approximately age 37 in their data. Fertility rates also begin to decline in a woman's thirties.

Hence, our results offer support for the existence of a shift, suggested by the work of a number of investigators, approximately 17 years before the FMP. That is, taken together, the appearance of a subtle constellation of subjective experiences, subtle changes in the nature of menstrual flow, a lower correlation between the length of successive menstrual cycles, the change in rate of atresia, a shift in fertility to a declining slope, all suggest some kind of shift in the underlying system coincident with a shift in the Icp. Research based on chronological age rather than time before the FMP, not surprisingly, shows an age range for these changes relative to the shift in the Icp.

The consistent age-dependent behavior of the I_{cp} supports the interpretation that menstrual variability is generated by some underlying nonlinear dynamical process that is governed by developmental physiology and that changes in a coherent manner (though environmental influences also plays a role). While there is variability in outward signs, we found consistency in the trajectory of the strange attractor underlying them. The variability in cycle length that exists throughout life between and within women, individual trajectories over the lifespan that differ from the mean trajectory, and lack of universal stages (Gorrindo, et al., 2007; Mansfield, Carey, Anderson, Barsom, & Koch, 2004) are all consistent with what would be expected in a chaotic system. The presence of a chaotic system suggests that this variability is normal, expected, and important. Understanding when variability does indicate dysfunction and pathology becomes a question to be explored and researched.

If the variability in the menstrual cycle is the natural outcome of chaotic dynamics in the system rather than being due to random processes, this raises the question of whether such variability serves some important purpose. The physiological value of variability is a question with an extensive history in studies of chaos (see, e.g., Schuldberg, 2015; Bassingthwaighte, Liebovitch, & West, 1994; Glass, 2015). One important argument is that introducing natural variability into a system makes it more flexible and adaptable to environmental changes. This argument may well be applicable in the present case, since the menstrual cycle is an open system that must respond to influences such as stress and nutrition. Another facet of the discussion of variability is whether there is some optimum amount of it (and if so, how much?). The literature is ambiguous on this point, since both lower variability and higher variability have been identified with ill health (see, e.g. Hartman, et al., 1994; Kaplan, et al., 1991). The question is again an interesting and relevant one for the present case, because observable variability increases during perimenopause. The major contribution of the present study to such questions is that we now have an indicator of the underlying dynamics to compare with the overt observed variability. Although there appears to be a substantial alteration in the dynamics of the system about 17 years before the FMP, the observable changes in cycle variability at this time are extraordinarily subtle. Meanwhile, during what appears to be a major increase in variability during perimenopause we find a substantial monotonic decrease in the I_{cp} that plausibly suggests a contraction in the dimensionality of the underlying dynamics. Further interpretation of these findings is not presently possible without a better theoretical understanding of the system's

dynamics. Some light might be shed on the issue by measurements that are more directly related to order (e.g. AppEn), which have not yet been performed.

The results presented here (and a chaotic dynamics perspective more generally) offer an alternative explanation for increasing menstrual cycle variability found in the years before the FMP. Though we find changes that culminate in the end to menstruation, these are changes in an underlying system, weakening support for the idea that menopause involves the failure of a cause-and-effect system seeking stability to respond normally to hormonal and other signals. Cycle changes in the years preceding the FMP remain characterized mathematically by chaotic dynamics rather than randomness or disorder. Our results are thus consistent with extreme values, individual trajectories differing from the mean trajectory, and changes in pattern that return to preexisting patterns, characteristics that might be expected in a chaotic system.

Our results also have implications for metatheories about menopause. Menopause signals the end of reproduction. However, is change, especially in midlife and beyond, always best thought of as senescence or pathology? Another possibility is that a process is completed and ends naturally. We argue that our results are more consistent with the metatheory that menopause is part of the human biological life plan than the biomedical model: Menopause is part of a biologically-based lifespan trajectory that includes a life stage of healthy functioning after reproduction ends (P. S. Derry, 2006; Hawkes & Coxworth, 2013; Kaplan, et al., 2010). Menopause is an oddity in nature: An end to reproduction that is universal, involves follicle depletion, and occurs before old age is all-but-unique to human females (Pavelka & Fedigan, 1991). Menopause occurs decades before the senescence of all other bodily systems (i.e. “old age”). Researchers with an

evolutionary perspective have suggested that, whatever its cause, menopause and a consequent life stage of healthy, post-reproductive adulthood may be adaptive in an evolutionary sense or serve an important cultural purpose, perhaps because grandmothers help their grandchildren to survive or perhaps because of unique technological and social aspects of human groups (Hawkes & Coxworth; Kaplan, et al.).

The earlier shift in the Icp has an intriguing relationship to this possibility. One pathway to evolutionary change is when a shift in the rate of a physiological process results in structural or functional change (Bogin, 1999). We speculate that the bi-exponential shift in rate of follicle death could be such a mechanism; if the rate of follicle atresia did not accelerate, women would reach menopause in their seventies (Faddy et al., 1992).

The present study has a number of limitations. Our Tremin database provided rich data for a large number of women with which to study baseline patterns. However, like all databases, it had limitations. Our data set consisted of healthy, Caucasian, college-educated women, largely from the mid-Western United States. We do not in all cases have complete information about their health status or information about self-selection factors. Although we are interested in the life-developmental course of the menstrual cycle, the subjects in this study are all at least 20 years of age and so we have no information about menarche and the earliest years of menstruation. Though we hope to extend the study in this way in the future, much less data exists for that age cohort.

We would like to develop methodologies to study problematic issues and pathologies, like polycystic ovary syndrome or women with distressing perimenopausal experiences, by determining if differences in underlying chaotic dynamics might exist

compared to the baseline found here. Conversely, if the menstrual system naturally exhibits variability, then are there physiological or health effects of suppressing natural variability, as happens with oral contraceptives? These questions bear on issues of defining optimum variability, as well as a consideration of what multiple factors constitute or interact with and influence a chaotic system in a living organism.

There are also important issues concerning the interpretation of the inter-event correlation parameter. A detailed understanding of the meaning of the I_{cp} is presently difficult to formulate and is the subject of continuing work. The most important conclusion, though, is the following: I_{cp} is sensitive to changes in the dynamical state of the system. For this reason, I_{cp} can be used as an indicator of changes in the state of the system, regardless of whether we can deduce the exact nature of those changes. It is reasonable to assume that I_{cp} is related to the correlation dimension of the system, given that it is calculated using methodologies based on the same kind of scaling relationships. However, the quantitative nature of the relationship between I_{cp} and D_c is not yet fully understood, though work done so far demonstrates that changes in I_{cp} do accompany changes in D_c (at least for computational model systems). That work also strongly suggests that the order of magnitude of the inter-event time measurements (i.e. the length of the menstrual cycles) is much larger than the characteristic time scale for changes in the system. In any event, variations in the I_{cp} over time offer us an important window into the changes over time of the physiological system's dynamical states.

Clearly, there are still many unanswered questions about the role of chaotic dynamics in a lifespan perspective and the underlying physiological process that these dynamics reflect. However, the results presented here suggest that the state of these

dynamics undergoes a change about 17 years prior to the FMP, and that this change appears to correspond to a variety of observations found in the research literature. In addition, the results presented here also suggest that the state of this system evolves continuously in a regular fashion during the final years prior to the FMP, which we interpret as evidence in favor of a life-developmental paradigm for the existence of menopause in contrast to a biomedical model paradigm of senescence.

ACKNOWLEDGMENTS

We would like to thank the Tremin Research Program on Women's Health for permission to download and utilize their database of women's menstrual histories.

REFERENCES

Bassingthwaighte, J. B., Liebovitch, L. S., & West, B. J. (1994). *Fractal Physiology*. New York, NY: Oxford University Press.

Bogin, B. (1999). *Patterns of human growth*. Cambridge: Cambridge University Press.

Bradley, E. & Kantz, H. (2015). Nonlinear time-series analysis revisited. *Chaos, 25*, 097610-1-10.

Derry, G. N. & Derry, P. S. (2010). Characterization of chaotic dynamics in the human menstrual cycle. *Nonlinear Biomedical Physics, 4*:5.

Derry, G. N. (2013, July). *Chaotic Trajectories in Nonlinear Modeling of the Human Menstrual Cycle.* Paper presented to the 23th annual international conference of the Society for Chaos Theory in Psychology and the Life Sciences, Portland, OR.

Derry, G. N. (2016, July). *Using Chua's Circuit to Test Novel Nonlinear Analysis Methodologies*. Paper presented to the 26th annual international conference of the Society for Chaos Theory in Psychology and the Life Sciences, Salt Lake City, UT.

Derry, P.S. (2006). A lifespan biological model of menopause. *Sex Roles, 54*, 393-399.

Derry, P.S. & Derry, G.N. (2012). Menstruation, perimenopause, and chaos theory. *Perspectives in Biology and Medicine, 55*, 26-42.

Derry, P.S. & Derry, G.N. (2014). Analysis of the STRAW operational definition of the early menopausal transition. *Women's Reproductive Health, 1*, 21-30.

Faddy, M., Gosden, R., Gougeon, A., Richardson, S., & Nelson, J. (1992). Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Human Reproduction, 7,* 1342-1346.

Glass, L. (2015). Dynamical disease: Challenges for nonlinear dynamics and medicine. *Chaos, 25*, 097603-1-097603-11.

Goodman, H. M. (2009). *Basic medical endocrinology (4th edition).* Amsterdam: Elsevier Academic Press.

Gorrindo, T., Lu, Y., Pincus, S., Riley, A., Simon, J., Singer, B., et al. (2007). Lifelong menstrual histories are typically erratic and trending. *Menopause, 14*, 74-88.

Grassberger, P. & Procaccia, I. (1983). Characterization of strange attractors. *Physical Review Letters, 50*, 346-349.

Harlow, S., Crawford, S., Dennerstein, L., Burger, H., Mitchell, E., & Sowers, M. (2007). Recommendations from a multi-study evaluation of proposed criteria for staging reproductive aging. *Climacteric*, *10*, 112–119.

Harlow, S., Gass, M., Hall, J., Lobo, R., Maki, P., Rebar, R., et al. (2012). Executive summary of the stages of reproductive aging workshop+10: Addressing the unfinished agenda of staging reproductive aging. *Journal of Clinical Endocrinology and Metabolism*, *97*, 1159–1168.

Hartman, M. L., Pincus, S. M., Johnson, M. L., Matthews, J. D., Faunt, L. M., Vance, M. L., Thorner, M. O., & Veldhuis, J. D. (1994). Enhanced basal and disorderly growth hormone secretion distinguish acromegalic from normal pulsatile growth hormone release. *Journal of Clinical Investigation, 94*, 1277-1288.

Hawkes,K. & Coxworth, J. (2013). Grandmothers and the evolution of human longevity: a review of findings and future directions. *Evolutionary Anthropology, 22*, 294-302.

Hegger, R. & Kantz, H. (1997). Embedding sequences of time intervals. *Europhysics Letters, 38*, 267-272.

Judd, K. (1992). An improved estimator of dimension and some comments on providing confidence intervals. *Physica D, 56*, 216-228.

Judd, K. (1994). Estimating dimension from small samples. *Physica D, 71*, 421-429.

Kaplan, D. T., Furman, M. I., Pincus, S. M., Ryan, S. M., Lipsitz, L. A., & Goldberger, A. L. (1991). Aging and the complexity of cardiovascular dynamics. *Biophysical Journal, 59*, 945-949.

Kaplan, H., Gurven, M., Winking, J., Hooper, P., & Stieglitz, J. (2010). Learning, menopause, and the human adaptive complex. *Annals of the New York Academy of Sciences, 1204*, 30-42.

Lisabeth, L., Harlow, S., & Qaqish, B. (2004). A new statistical approach demonstrated menstrual patterns during the menopausal transition did not vary by age at menopause. *Clinical Epidemiology, 57*, 484-496.

Mansfield, P. & Bracken, S. (2003). *Tremin: A history of the world's oldest ongoing study of menstruation and women's health.* Lemont, PA: East Rim Publishers.

Mansfield, P., Carey, M., Anderson, A., Barsom, S. H., & Koch, P. B. (2004). Staging the menopausal transition: Data from the Tremin research program on women's health. *Women's Health Issues*, *14*, 220–226.

Mitchell, E., Woods, N.F., & Mariella, A. (2000). Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: toward a more precise definition. *Menopause, 7*, 334-349.

Pavelka, M., & Fedigan, L. (1991). Menopause: A comparative life history perspective.

Yearbook of Physical Anthropology, *34,* 13–38.

Prior, J. & Hitchcock, C. (2011). The endocrinology of perimenopause: need for a paradigm shift. *Frontiers in Bioscience, S3*, 474-486.

Sauer, T. (1995). Interspike interval embedding of chaotic signals. *Chaos, 5*, 127-132.

Schuldberg, D. (2015). What is optimum variability?. *Nonlinear Dynamics, Psychology, and Life Sciences, 19*, 553-568.

Takens, F. (1985). On the numerical determination of the dimension of an attractor. In Braaksma, B., Braer, H., & Takens, F. (Eds.), *Dynamical systems and bifurcations* (pp. 99-106). Berlin: Springer-Verlag.

Treloar, A. (1981). Menstrual cyclicity and the pre-menopause. *Maturitas, 3*, 249–264.

Treloar, A., Boynton, R., Behn, B., & Brown, B., (1967). Variation of the human menstrual cycle through reproductive life. *International Journal of Fertility, 12*, 77-126.

Voda, A. (1997). *Menopause, me and you.* Haworth Press: Binghamton, NY.

Voda, A., & Ashton, C. (2006). Fallout from the Women's Health Initiative Study: A short-lived vindication for feminists and the resurrection of hormone therapies. S*ex Roles, 54*, 401-411.

Figure Captions

Figure 1—Menstrual cycle lengths aggregated for all 143 subjects during a span of 1 year, with the age of all subjects such that they are the same number of years prior to their final menstrual period.

Figure 2—Plot of log(N) *vs* log(r), where N is the number of points in the embedding space separated by a distance less than r, demonstrating the scaling relationship in the data; the slope of the plot is the inter-event correlation parameter, I_{cp}.

Figure 3—Plot of I_{cp} *vs* the number of years prior to the final menstrual period, using the method illustrated in Figure 2 and keeping all methodological choices as consistent as possible.

Figure 4—Plot of N *vs* r/r_{max}, where N is the number of points in the embedding space separated by a distance within range Δr centered on r; the solid line is a plot of Equation 2, with I_{cp} and the other parameters determined by a fit to the data.

Figure 5—Plot of I_{cp} *vs* the number of years prior to the final menstrual period, using the method illustrated in Figure 4 and varying the methodological choices in order to examine their influence on the results.

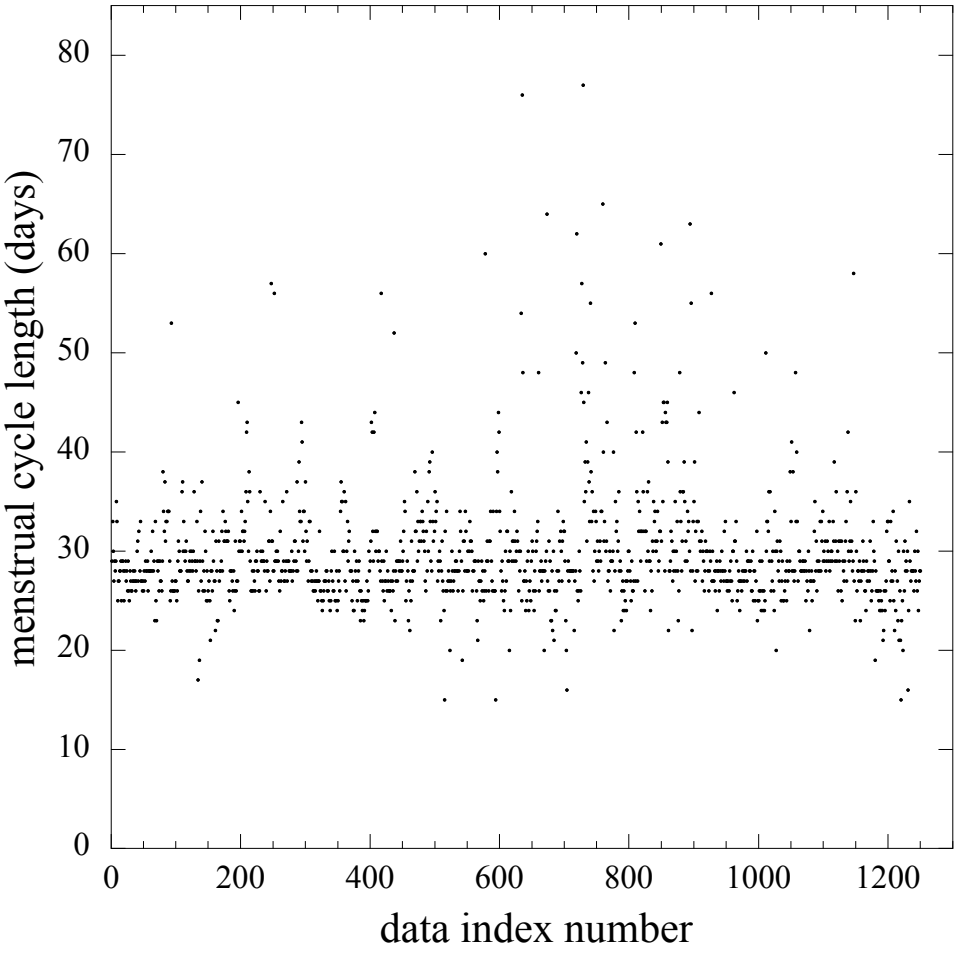
menstrual cycle length (days)
0
10
20
30
40
50
60
70
80
0
200
400
600
800
1000
1200
data index number

Figure 1

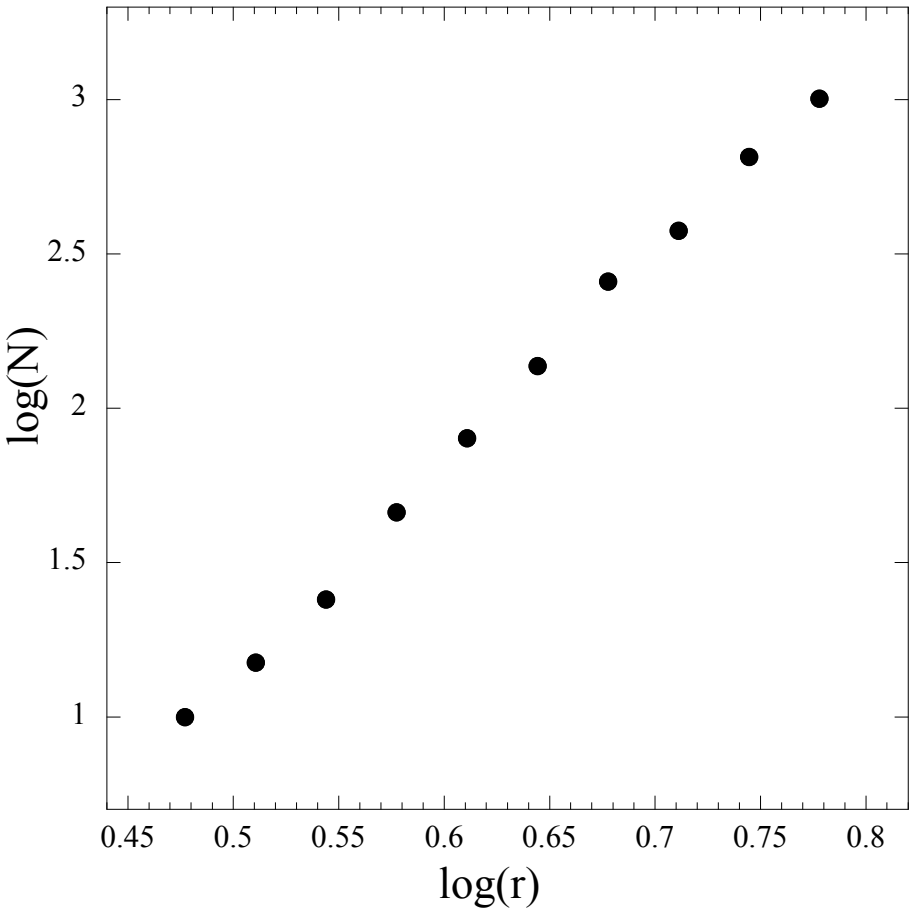

Figure 2

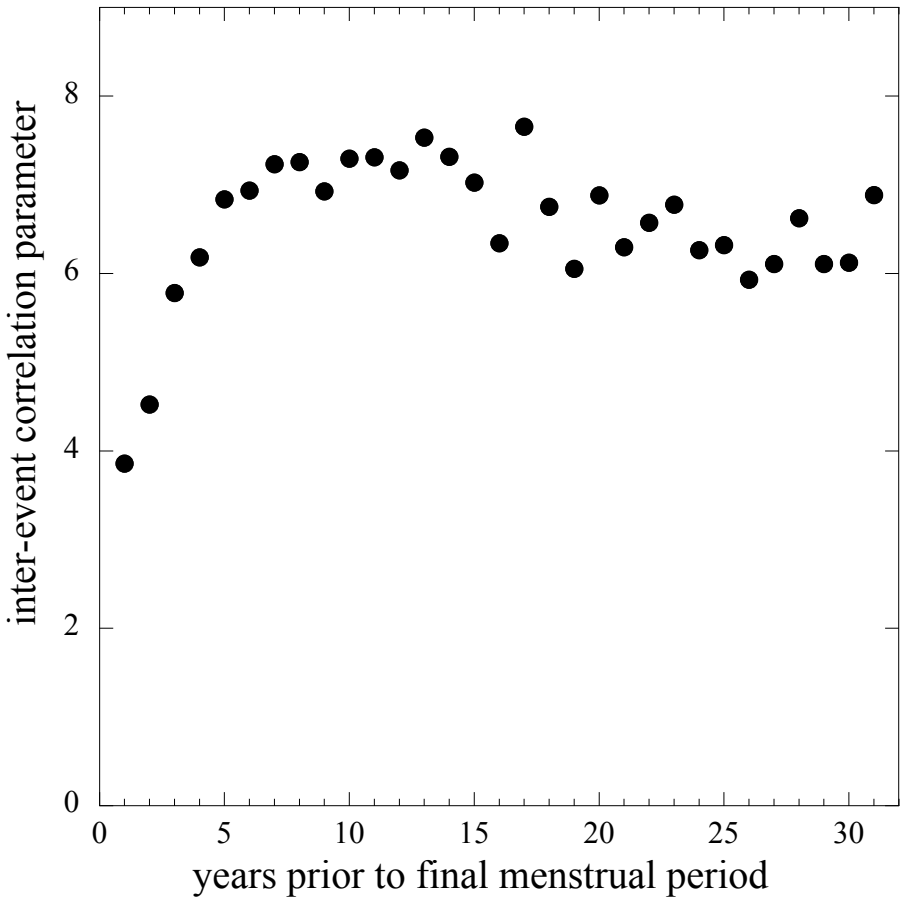
inter-event correlation parameter
0
2
4
6
8
0
5
10
15
20
25
30
years prior to final menstrual period

Figure 3

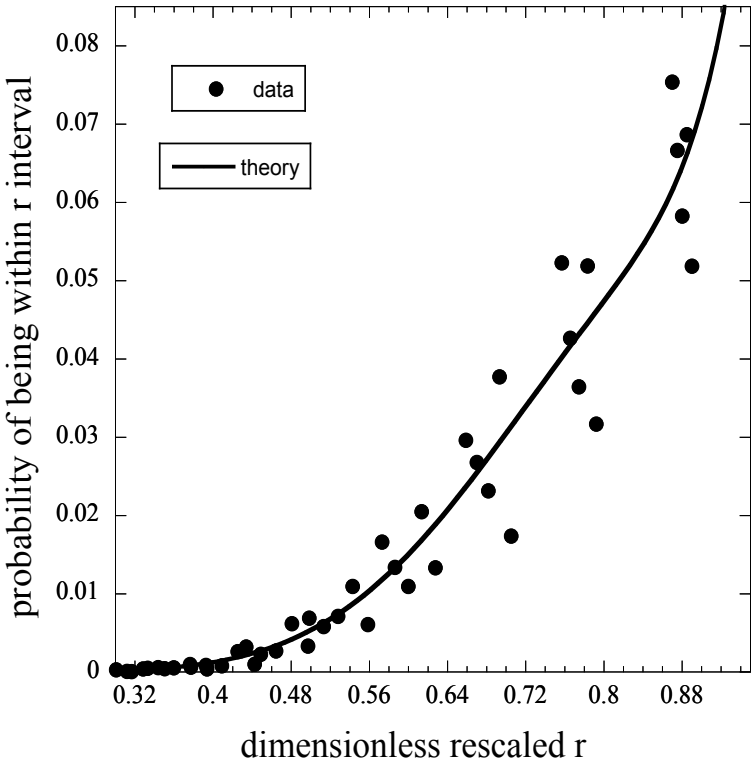
data
theory
probability of being within r interval
dimensionless rescaled r
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.32
0.4
0.48
0.56
0.64
0.72
0.8
0.88

Figure 4

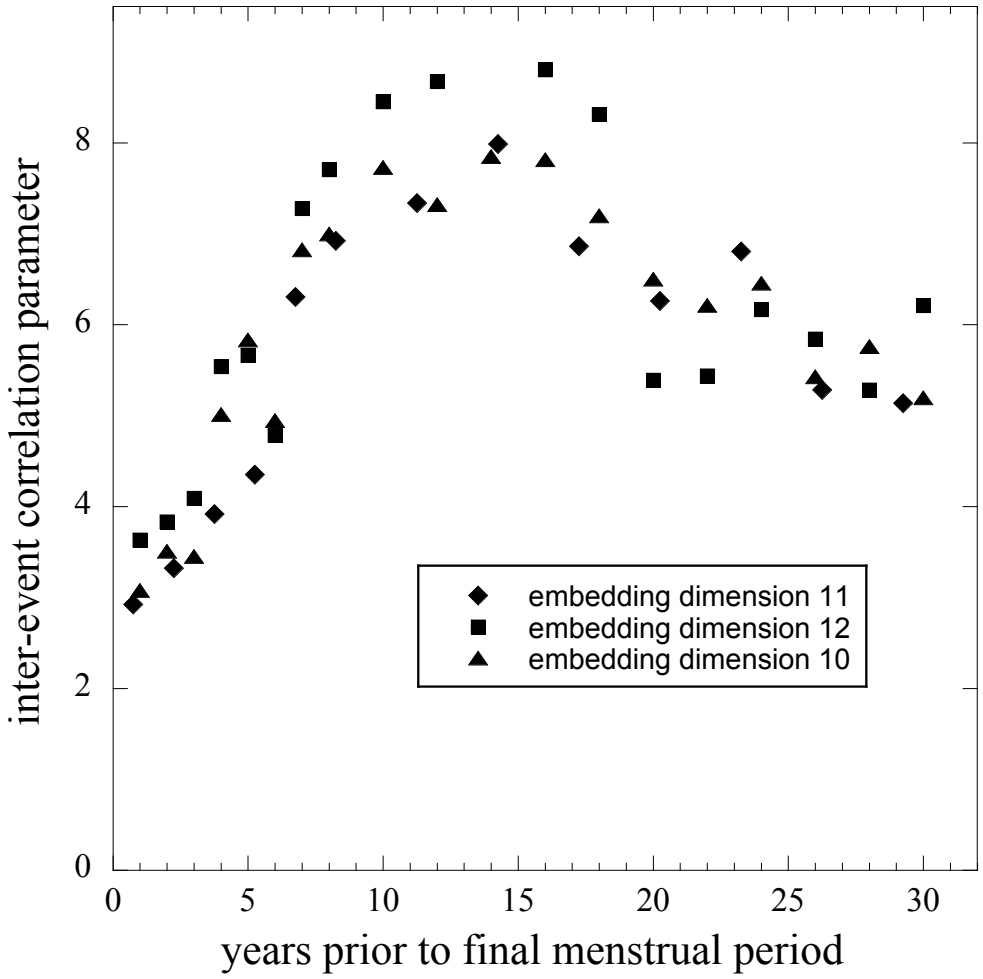
inter-event correlation parameter
0
2
4
6
8
0
5
10
15
20
25
30
years prior to final menstrual period
embedding dimension 11
embedding dimension 12
embedding dimension 10

Figure 5