

# An Integrated Quantitative Methodology to Longitudinally Characterize Complex Dynamic Processes Associated with Ovarian Aging and the Menopausal Transition

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## ABSTRACT

An integrative methodology is developed to characterize the complex patterns of change in highly variable dynamic biological processes. The method permits estimation of the population mean profile, multiple change points and length of time-windows defined by any two change points of interest using a semi-/non-parametric stochastic mixed effect model and a Bayesian Modeling Average (BMA) approach to account for model uncertainty. It also allows estimation of the mean rate of change of sub-processes by fitting piecewise linear mixed effect models. The methodology is applied to characterize the stages of female ovarian aging and the menopausal transition defined by hormone measures of estradiol (E2) and follicle stimulating hormone (FSH) from two large-scale epidemiological studies with community-based longitudinal designs and ethnic diversity.

**Keywords:** Complex systematic dynamics, Change detection, Longitudinal data, Epidemiology, Ovarian aging, Hormones

## 1. INTRODUCTION AND MOTIVATION

The ability to describe process dynamics is crucial to portraying patterns of change across time in complex biological and epidemiological systems found in populations.

An example of these dynamics in women includes the ovarian aging process as reflected in the hormone measures of estradiol (E2) and follicle stimulating hormone (FSH)<sup>[1-4,30,31]</sup>, which characterize the female reproductive transition from pre-/perimenopausal status to post-menopausal status. During this transition process, understanding when, how rapidly, and how long the E2 and FSH levels change (increase, decrease, or oscillate) around the final menstrual period (FMP) is important as studies have reported that postmenopausal sex hormone concentrations are risk factors for several major chronic diseases in women, including osteoporosis, breast cancer and endometrial cancer, and, with less certainty, coronary heart disease and osteoarthritis.

Thus, the ability to describe the dynamics of such processes is not only of great theoretical interest but also has important public health and clinical implications for intervention. Description of these complex processes will help define onset of sub-fertility and the initiation of the menopausal transition and lead to identification of relevant factors (e.g, body mass index, smoking, race/ethnicity) that influence these dynamic, including accelerating or decelerating, processes. As shown in Figure 1

using data from two ongoing studies, the  $\log_{10}E2$  and  $\log_{10}FSH$  changing process around the FMP might be a smooth, slow or fast time-varying process with local maxima, and/or an asymmetrical changing process accompanied by multiple change points.

Figure 1a ( $\log_{10}E2$ ) and Figure1b ( $\log_{10}FSH$ ) visualized 100 women's (randomly selected from the study cohort without replacement) individual profiles (marked as solid line segments with star), spline smoothed population mean (marked as solid smoothing lines), and two potential segmented population means (marked as dashed line segments with dot or square). Figure 1 demonstrates that there may exist transition points for  $\log_{10}E2$  and  $\log_{10}FSH$  around FMP reflecting different stages in ovarian aging, e.g., two years before ( $t = -2$ ) and two years after ( $t = +2$ ) FMP. The complexity of identifying these stages stems from:

- a) *The inherent variation in the between-women ovarian aging process over time*, especially during the menopausal transition for middle-aged women. This biological process is time-varying, auto-regressive and may be associated with internal and external factors.
- b) *The unknown functional form of the population trajectory*. Lower order parametric polynomials may be inadequate to capture complex nonlinear trends. In theory, polynomials are capable of approximating continuous functions arbitrarily closely when allowed to be of sufficiently large degree (Weierstrass's approximation theorem). However, applying higher order parametric polynomials may not only have numerical limitations in model fitting but also have limitations in their clinical interpretation. Moreover, polynomials have a significant shortcoming, i.e., they operate in a global fashion. Therefore, splines may be a more appropriate approach by providing a series of piecewise polynomials, joined in a visually smooth fashion, and typically formed as an additive combination of locally defined low order polynomials (or basis functions).
- c) *The unknown number of change points and position of change points occurring within the period of interest*. When these two parameters are known, piece-wise linear regression modeling may be used to segment a process into its sub-processes. An application of this concept would be to consider the subprocess of ovarian aging as a series of stages and identify characteristics of each stage including the cut points demarking the beginning and ending of the stage and the rate of change within each stage. However, in most cases,

these parameters are unknown and have to be identified either by domain knowledge (e.g., biology), by algorithms, or by a combination of both. This gives rise to the uncertainty of model selection which must be addressed during model development.

*d) The efficiency of the algorithm detecting change.* It might be optimal and necessary to detect the change in a timely manner using an on-line algorithm for time-series data with a long run period, e.g., industrial quality monitoring and control. However, in repeated (or longitudinal) health studies, the number of entities (e.g., units or study participants) is usually much greater than the number of repeated measures creating a data environment where off-line detection may be the more appropriate option.

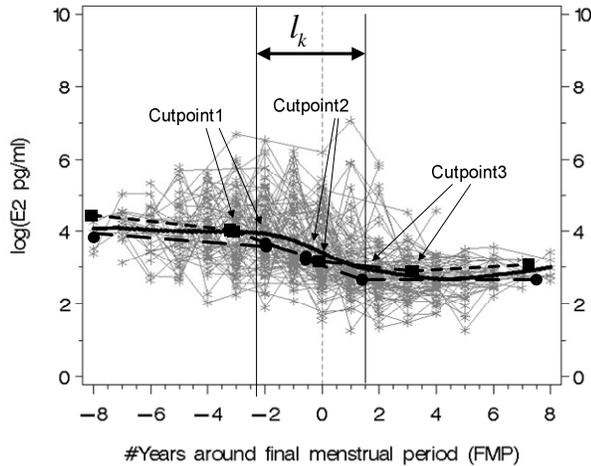


Figure 1a: Individual and mean profiles of  $\log E_2$  with illustration of segmentation: SWAN

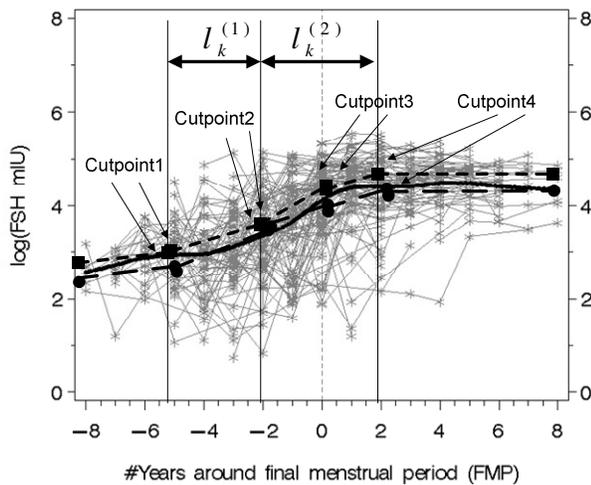


Figure 1b: Individual and mean profiles of  $\log FSH$  with illustration of segmentation: SWAN

Thus, it is highly desirable to have a flexible method for modeling this kind of complex process and identifying biologically-relevant change points. This paper describes the development of a systematic and novel methodology for addressing longitudinal epidemiological dynamic data. It incorporates factors at multiple levels by integrating non-parametric estimations of instantaneous changes in a dynamic

trajectory, parametric curve segmentation based on piecewise linear mixed models while using a Bayesian Model Averaging (BMA) approach. The method is applied to two large-scale longitudinal epidemiological hormone studies [Michigan Bone Health and Metabolism Study (MBHMS) and the Study of Women's Health Across the Nation (SWAN)] to identify when, where, how rapidly, and how long the patterns change around the FMP.

This paper is organized as follows. Section 2 provides an overview of the change detection. The systematic structure of the algorithm and mathematical models are described in detail in section 3. Section 4 demonstrates the algorithms applied to data from the MBHMS and SWAN studies. Finally, section 5 concludes with results and identifies the need for future work.

## 2. OVERVIEW OF CHANGE DETECTION

Change detection problems are of theoretical importance in research with potential applications in diverse areas in which there are dynamic processes and spatial or temporal data. Questions associated with change detection may include: (a) are there any changes occurring? (b) how many change points are there? and (c) when and where are the change points? In general, change point detection is the process to identify point(s) at which properties of sequential data change<sup>[5]</sup>. Statistically, change detection is related to the detection of the changes in probability distribution of a stochastic process or time series.

Methodologically and quantitatively, the parametric and non-parametric methods for change detection and piecewise linear models have been described, e.g., kernel and nearest-neighbor nonparametric regression<sup>[6]</sup>, data iteration in regression for searching threshold (DIRST)<sup>[7]</sup>, Spren't's assumption of enforced continuity<sup>[8]</sup>, the smallest residuals sum of squares (RSS) and "optimization" as a criteria for satisfying the estimation on thresholds<sup>[9]</sup>, smoothing the connection of two adjacent models<sup>[10]</sup>, and piecewise regression models<sup>[11-12]</sup>. Sigmoid (or double-sigmoid) functions are an appealing tool to model curves of S-shapes and has been used in numerous applications including, e.g. hormone profiles<sup>[3]</sup>, fatigue profiles in mice<sup>[13]</sup>, pattern recognition<sup>[14]</sup>, and growth patterns<sup>[15]</sup>. Algorithms to describe change detection include on-line, off-line, Bayes, and minimax, as identified in references 16 through 23.

Frequently, studies are limited in that 1) response data are assumed to be independent and ignore potential sources of the correlation within the longitudinal data; 2) model uncertainties are not considered; 3) the study sample size is limited; 4) functional forms are assumed to be parametric with a known prior shape; and 5) sources of variability, including between-subject heterogeneity, within-subject biological variation, and measurement error are not fully modeled. Each of these features is relevant in public health, clinical and epidemiological studies and they have to be considered during the model development.

## 3. THE SYSTEMATIC STRUCTURE AND MODELS

Motivated by the need to model the functional form of the female ovarian aging process with an unknown prior shape, we developed an integrated methodology that incorporates four major steps (see Figure 2 for the systematic structure that progresses from the longitudinal data inputs, through the modeling, to the specified change outputs of interest).

The function of each module and input-output relationship are described in Figure 2 and sections 3.1-3.4.

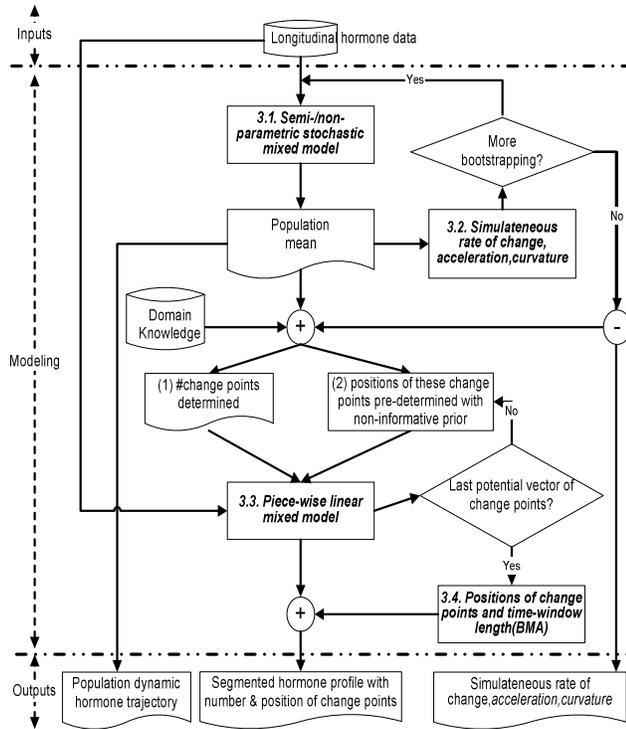


Figure 2 Systematic structure of the proposed integrative approach

### 3.1 Semi-/non-parametric stochastic mixed model

The parametric assumptions for modeling longitudinal data might not be appropriate for some circumstances, e.g., relationships between hormone change and time may not be appropriately modeled by quadratic or cubic terms or other simple functional forms (e.g., sigmoid, exponential, etc) due to nonlinearity, unknown shape and multiple change points. Therefore, a semi-/non-parametric stochastic mixed effects modeling approach is appropriate to characterize complicated curves when there is inadequate prior knowledge available about its shape<sup>[24]</sup>. In general, the semi-parametric stochastic mixed model can be formulated by:

$$Y_{ij} = \mathbf{X}_{ij}^T \boldsymbol{\beta} + f(t_{ij}) + \mathbf{Z}_{ij}^T \mathbf{b}_i + U_i(t_{ij}) + \varepsilon_{ij} \quad (1)$$

where:  $Y_{ij}$  is the response for the  $i$ 'th ( $i = 1, 2, \dots, m$ ) subject at time point  $t_{ij}$  ( $j=1, 2, \dots, n_i$ );  $\boldsymbol{\beta}$  is a  $p \times 1$  vector of regression coefficients associated with covariates  $X_{ij}$  of interest.  $f(t)$  is a twice-differentiable smooth function of time;  $b_i$  are independent  $q \times 1$  vectors of random effects associated with covariates  $Z_{ij}$ ;  $U_i(t_{ij})$  are independent random processes used to model serial correlation;  $\varepsilon_{ij}$  are independent measurement errors.

The fundamental assumptions for this model are:  $b_i$ ,  $U_i(t_{ij})$ , and  $\varepsilon_{ij} \sim \text{iid } N(0, \sigma^2)$ .  $b_i \sim \text{normal}(0, D(\varphi))$ ,  $D$  is a positive definite matrix depending on a parameter vector  $\varphi$ ;  $U_i(t_{ij})$  is a mean zero Gaussian process with covariance function or a

non-homogeneous Ornstein-Uhlenbeck (NOU) process,  $\text{cov}(U_i(t), U_i(s)) = \gamma(\zeta, \alpha; t, s)$  depending on a parameter vector  $\zeta$  and a scalar  $\alpha$ , which is used to characterize the variance and correlation of the process  $U_i(t)$ .

As a special case, in order to capture the characteristics of the  $\log_e$  Hormone mean and variance (in these examples, E2 and FSH) as they vary over time, the model can be formulated as a non-parametric form:

$$Y_{ij} = f(t_{ij}) + b_{0i} + b_{1i}t_{ij} + U_i(t_{ij}) + \varepsilon_{ij} \quad (2)$$

where  $U_i(t)$  is a NOU process satisfying:

$$\text{var}(U_i(t)) = \xi(t) \quad (3)$$

where:

$$\log(\xi(t)) = A_0 + A_1t + A_2t^2 \quad (4)$$

$$\text{corr}(U_i(t), U_i(s)) = \rho^{|t-s|}$$

Each subject's serial correlation is assumed to be the same. The smoothing function  $f(t)$  represents the response mean profile for the population of subjects over time.

### 3.2 Change characteristics of population mean profile

Assume the population mean response profile/trajectory changes over time and follows a non-linear pattern. The instantaneous changes of these trajectories can be characterized by rate of change, acceleration / deceleration, and curvature which are first- and second-order derivatives of the mean profile, as well as the hinge/bend of the mean profile integrating the rate of change and acceleration, respectively. The cubic spline approach is used to estimate the rate of change as well as acceleration or deceleration.

Assume the time  $t$  is equally spaced with step  $h = t_{k+1} - t_k$  ( $k = 1, 2, \dots, n-1$ ), where  $n$  is the total number of distinguishable time points. Let  $f(t)$  be the response mean profile (trajectory) and  $S_3(t)$  be its cubic spline approximation with the following property:

$$|f^\alpha(t) - S_3^\alpha(t)| = O(h^{4-\alpha}), \alpha = 0, 1, 2, 3 \quad (5)$$

The rate of change can be approximated by solving " $m$ " equations:

$$m_{k-1} + 4m_k + m_{k+1} = 3(f(t_{k+1}) - f(t_{k-1})) / h \quad (6)$$

where  $m_k = f'(t_k)$ ,  $k = 2, 3, \dots, n-1$ . The  $m_1$  and  $m_n$  can be approximated by the 5-points method using first and last 5-points, respectively,

$$m_1 = \frac{1}{12}h \cdot \begin{bmatrix} -25f(t_1) + 48f(t_2) - 36f(t_3) \\ +16f(t_4) - 3f(t_5) \end{bmatrix} \quad (7)$$

$$m_n = \frac{1}{12}h \cdot \begin{bmatrix} 3f(t_{n-4}) - 16f(t_{n-3}) + 36f(t_{n-2}) \\ -48f(t_{n-1}) + 25f(t_n) \end{bmatrix} \quad (8)$$

The acceleration / deceleration can be approximated by solving " $M$ " equations:

$$\begin{aligned} & M_{k-1} + 4M_k + M_{k+1} \\ & = 6 \frac{1}{h^2} \cdot (f(t_{k+1}) - 2f(t_k) + f(t_{k-1})) \end{aligned} \quad (9)$$

where  $M_k = f''(t_k)$ ,  $k = 2, 3, \dots, n-1$ . The  $M_1$  and  $M_n$  values satisfy the boundary conditions:

$$2M_1 + M_2 = \frac{6}{h} \cdot \left( \frac{1}{h} (f(t_2) - f(t_1)) - m_1 \right)$$

$$M_{n-1} + 2M_n = \frac{1}{h} \cdot \left( m_n - \frac{1}{h} (f(t_n) - f(t_{n-1})) \right) \quad (10)$$

The instantaneous curvature of mean profile, representing the degree of bend of the curve, is approximated by

$$\left| f''(t_k) \right| / \left| 1 + (f'(t_k))^2 \right|^{3/2} \quad (11)$$

The 95% confidence bands of these characteristics can be obtained by using a bootstrapping approach<sup>[25]</sup>.

### 3.3 Piecewise linear mixed model to segment the process

Given the number and position of change points, the piecewise linear mixed model is developed to capture segment characteristics (i.e., rate of change within each segment). Statistical comparisons of the slopes from two consecutive segments around a change point are tested to ascertain if one slope is different than the adjacent slope. The piecewise linear mixed model is formulated as follows:

Assume the independent variable of interest  $t \in T \subset R^1$  (e.g., the time to the FMP as an event of interest in ovarian aging). Let

$$\Omega = \left\{ t_{(k)}^*, 1 \leq k \leq K \mid t_{(1)}^* < t_{(2)}^* < \dots < t_{(K)}^* \right\} \quad (12)$$

be one known division of  $T$ , where  $K$  is the total number of turning points used to split  $T$  into  $(K+1)$  non-overlapping intervals. Denote:

$$\left( t_{ij} - t_{(k)}^* \right)_+ = \begin{cases} t_{ij} - t_{(k)}^* & , t_{ij} > t_{(k)}^* \\ 0 & , t_{ij} \leq t_{(k)}^* \end{cases} \quad (13)$$

Then, the mean structure of piecewise linear mixed effect model is given by:

$$E[y_{ij}] = \beta_0 + \beta_1 t_{ij} + \sum_{k=1}^K \beta_k^{(1)} \left( t_{ij} - t_{(k)}^* \right)_+$$

$$+ \sum_{l=1}^L \beta_l^{(2)} x_{ijl} + \sum_{l=1}^L \sum_{k=1}^K \beta_{l,k} \left( t_{ij} - t_{(k)}^* \right)_+ x_{ijl} \quad (14)$$

where  $x_{ijl}$  ( $l=1, 2, \dots, L$ ) are the covariates for  $i$ th subject at time  $t_{ij}$  and  $L$  is the total number of covariates of interest. The random effects include random intercept and random slopes. The variance-covariance structure and model assumptions follow a linear mixed model<sup>[26]</sup>.

### 3.4 Bayesian model averaging (BMA) to estimate the change points and durations of sub-processes

The change points in the population mean response profile are estimated based on values obtained from the above processes and are used to segment the trajectory of interest (in this case, hormone trajectories) into stages. Around each identified change point, time is increased by a specified step and a sequence of piece-wise linear mixed models is fitted. The sequence of models is integrated using a BMA method to account for the uncertainty associated with the model selection process. The posterior mean and variances of the quantity of

interest  $\Delta$  (e.g., regression parameter, rate of change, length of time-window, etc) are<sup>[27]</sup>:

$$E[\Delta | D] = E_{M|D} [E(\Delta | D, \mathbf{M})] = \sum_{k=1}^K \hat{\Delta}_k pr(M_k | D) \quad (15)$$

$$Var(\Delta | D) = E_{M|D} [Var(\Delta | D, \mathbf{M})] + Var_{M|D} [E(\Delta | D, \mathbf{M})]$$

$$= \sum_{k=1}^K \left( Var[\Delta | D, M_k] + \hat{\Delta}_k^2 \right) pr(M_k | D) - E[\Delta | D]^2 \quad (16)$$

where  $K$  is the total number candidate models,  $\hat{\Delta}_k = E(\Delta | D, M_k)$ ;  $\mathbf{M} = \{M_1, M_2, \dots, M_K\}$  denotes the set of all models being considered and  $\Delta$  is the quantity of interest, e.g., a parameter of the regression model; and  $pr(M_k | D)$  is the posterior probability of model  $M_k$ . More specifically, we employed the posterior probability as<sup>[28-29]</sup>

$$pr(M_k | D) = \frac{pr(M_k) \exp \left( -0.5 (BIC(M_k) - \overline{BIC}(M_k)) \right)}{\sum_{i=1}^K pr(M_i) \exp \left( -0.5 (BIC(M_i) - \overline{BIC}(M_i)) \right)} \quad (17)$$

where  $BIC(M_k)$  is the Schwarz's Bayesian Information Criterion ( $BIC$ ) of model  $k$  and  $\overline{BIC}(M_k)$  is the mean of  $BIC$ s over all models being considered. The prior model probability  $pr(M_k)$  is assumed to be from the uniform distribution  $pr(M_k) = 1/K$ . The  $BIC$  is used to form a weighted average over all models, in which these weights depend on the degree to which the data support each model, i.e., the better the fitted model, the greater the weight.

## 4. APPLICATION: LONGITUDINAL HORMONE DATA

This proposed method has potential important applications in biological and epidemiological studies as it allows description of a variable in terms of critical change points while identifying discrete segments or stages that may have clinical and epidemiological relevance, e.g., defining stages of ovarian aging and the menopausal transition characterized by reproductive hormone data for serum levels of estradiol (E2) and follicle-stimulating hormone (FSH).

### 4.1 Biological, clinical and epidemiological relevance

It is known that, during women's reproductive lives and into the early menopausal transition, population levels of the circulating hormone estradiol (E2) change minimally when measured in the early follicular phase and assessed either cross-sectionally or longitudinally. However, more information about the dynamics of change in E2 as women transition through menopause as well as of follicle-stimulating hormone (FSH) patterns across the reproductive period and through the menopausal transition is needed to help refine definitions of increasingly diminished ovarian reserve (representing the quantity and quality of the ovarian follicle pool) and to properly stage the transition from prime reproductive capacity to menopause and post-reproductive life.

Here, we are interested in understanding when, how rapidly, and how long the E2 and FSH levels change around the time of the final menstrual period (FMP).

#### 4.2 Description of the data

The proposed methodology is applied to characterize the dynamics of the female ovarian aging process using serum E2 and FSH data from two large-scale longitudinal epidemiological studies: *Michigan Bone Health and Metabolism Study (MBHMS)* [1-2] and *Study of Women's Health Across the Nation (SWAN)* [30].

**MBHMS** is a population-based longitudinal study of the natural history of reproductive endocrinology as it relates to the development of musculoskeletal and metabolic diseases and functional limitations in Caucasian women during young and mid-adulthood. MBHMS includes 664 age-eligible (24-44 years in 1992/3) women covering a 15-year period from 1992/3 through 2006/7, excluding 18- and 14-month funding lapses in 1997 and 2003, respectively. 629 women contributed one or more sex steroid data points to the longitudinal data analyses. On average, participants contributed more than 9 annual sex steroid data points out of a total possible 11 annual opportunities, as of 2007.

**SWAN** is a multi-site, longitudinal cohort study being conducted in community-based groups of women. In SWAN, participants were enrolled at seven clinical sites in the following geographic areas: Boston MA, Chicago IL, the Detroit area MI (and excluding the MBHMS population), Los Angeles CA, Hudson County NJ, Oakland CA, and Pittsburgh PA. All sites used a single common assessment protocol. At baseline, 3302 women who belonged to one of five ethnic/racial groups were recruited including Caucasian (n=1550), African American (n=935), Japanese (n=281), Chinese (N=250), and Hispanic (n=286). Eligibility criteria for entry into the SWAN longitudinal cohort were: age 42 to 52 years; intact uterus and at least one ovary; no current use of estrogens or other medications known to affect ovarian function; at least one menstrual period in the three months before screening; and, self-identification as a member of one of the five eligible ethnic groups. The 3302 women contributed one or more sex steroid data points to the longitudinal data analyses with the mean value 7 out of a total possible 10 annual opportunities from baseline to follow-up 9.

More specifically, these analyses include data from 1215 women from **SWAN** with a definitive FMP and at least one hormone value from baseline through follow-up 09, providing 9404 observations from FMP +/- 8 years (Table 1); and 181 women with 1672 data points from **MBHMS** (Table 2) with a definitive natural FMP date (i.e., no ambiguity generated by exogenous hormone use or reproductive surgery). These MBHMS data provide us with information for hormone levels at the time of FMP +/- 10 years.

Measured reproductive hormones are the primary independent variables, and included E2 and FSH. In MBHMS, a fasting venipuncture serum sample was acquired in days 2-7 of the follicular phase of the menstrual cycle. If women were no longer cycling regularly, venipuncture was secured on the anniversary ( $\pm 15$  days) of their initial annual visit. In SWAN, women were scheduled for venipuncture prior to 10 am on days 2-5 of a spontaneous menstrual cycle occurring within 60 days of recruitment at the baseline visit, and annually thereafter. Two attempts were made to obtain the day 2-5 sample. If a timed sample could not be obtained, a random fasting sample was

taken within a 90-day window of the anniversary of the baseline visit.

In both studies, blood was refrigerated 1-2 hours after phlebotomy and then, following centrifugation, the serum was aliquotted, frozen, and batched for shipment to the central laboratory for assay. The same laboratory and assays were used for both studies.

FSH assays were conducted in singlicate and E2 assays in duplicate using an ACS-180 automated analyzer (Bayer Diagnostics Corporation, 115 Norwood Park South, Norwood, MA). E2 concentrations were measured with a modified, off-line ACS-180 (E2-6) immunoassay. Inter- and intra-assay coefficients of variation averaged 10.6% and 6.4%, respectively, over the assay range and the lower limit of detection was 1 pg/mL. Serum FSH concentrations were measured with a two-site chemiluminometric immunoassay. Inter- and intra-assay coefficients of variation were 12.0% and 6.0%, respectively, and the lower limit of detection was 1.1 IU/L. The absolute concentrations of FSH are somewhat higher in this assay as compared to values from many clinical laboratories, based on differences in the standards selected.

In the model development, both hormones are natural logarithm-transformed to satisfy the model assumptions.

**Table 1:** Descriptive characteristics (median (IQR<sup>a</sup>) or n(%)) of SWAN women with an observed naturally-occurring FMP (n=1215)

Variables	Groups	Baseline n=1212	Follow-up 09 n=833
Age (years)		47.16(4.02)	56.01(3.96)
BMI(kg/m <sup>2</sup> )		26.37(9.62)	27.32(9.66)
FSH(IU/L)		19.25(20.94)	99.30(53.80)
E2 (pg/mL)		55.08(59.30)	18.40(10.35)
Race <sup>b</sup>	AA	386 ( 31.85% )	283 ( 33.97% )
	CA	511 ( 42.16% )	352 ( 42.26% )
	CH	121 ( 9.98% )	98 ( 11.76% )
	HI	71 ( 5.86% )	N/A
	JP	123 ( 10.15% )	100 ( 12% )
Overall health status	Worse	181 ( 14.93% )	135 ( 16.21% )
	Same	762 ( 62.87% )	287 ( 34.45% )
	Better	260 ( 21.45% )	398 ( 47.78% )
	Missing	9 ( 0.74% )	13 ( 1.56% )
Smoking at baseline	Never	691 ( 57.01% )	497 ( 59.66% )
	Past	285 ( 23.51% )	195 ( 23.41% )
	Present	209 ( 17.24% )	125 ( 15.01% )
	Missing	27 ( 2.23% )	16 ( 1.92% )

<sup>a</sup>IQR: interquartile range

<sup>b</sup>Race: AA = "African American", CA = "Caucasian", CH = "Chinese", HI = "Hispanic", JP = "Japanese"

**Table 2:** Descriptive characteristics (mean (SD) or %) of MBHMS women with a naturally-occurring and observed FMP (n=181)

Variables	Groups	Initial exam <sup>a</sup>	Most recent <sup>b</sup>
Age(years)		39.9 ± 3.4	55 ± 3.5
BMI(kg/m <sup>2</sup> )		27.3 ± 5.6	29.4 ± 6.4
FSH(IU/L)		6.2 ± 4.7	63.8 ± 34.1
Obesity(%)	BMI<30	74%	53%
	BMI>30	26%	47%
Smoking	Never	54%	50%
	Former	23%	37%
	Current	23 %	13%
Menopausal status	Premenopause	81%	--
	Perimenopause	5%	--
	Postmenopause	2%	100%
	Surgical menopause	--	--
	Exogenous hormone use <sup>c</sup>	12%	--

<sup>a</sup>Initial examination for more than 95% of cohort (n = 600/629) is 1992/93 (excluding potential information from women who were pregnant or lactating)

<sup>b</sup>Current examination is 2007/08 for the 80.4% of the cohort enrollees (n = 506/629) who are still alive, living within 2.5 hours of the clinical site, and participating in the study.

<sup>c</sup>Oral contraceptive or hormone therapy use

### 4.3 Results

Figure 1 shows randomly selected 100 individual hormone profiles from 1215 women around the FMP using SWAN data and provides an illustration of the segmented sub-processes to characterize the population ovarian aging with “pre-determined” cut-points. The black line and red line are two piece-wise linear mixed models.  $l_k$  is the length of time-span of  $\log_{10}$  Hormone window of interest around the FMP. The change points and duration of  $l_k$  are estimated under the developed method.

For SWAN data, the four  $\log_{10}$ FSH change points (95% CI) in years around FMP are -6.53 (-6.63, -6.43), -2.05 (-2.07, -2.03), -0.40 (-0.39, -0.41), and 2.00 (1.99, 2.01), respectively. The length of the time-window defined by change point pairs ( $P_1, P_2$ ) and ( $P_2, P_4$ ) are 4.48 (4.38, 4.58) and 4.05 (4.03, 4.07), respectively. The three  $\log_{10}$ E2 change points (95% CI) in years around FMP are -2.03 (-2.07, -1.99), -0.01 (-0.03, 0.01), and 2.17 (2.15, 2.19), respectively. The length of the time-window defined by change point pair ( $P_1, P_3$ ) is 4.19 (4.15, 4.23).

The smoothed and segmented population mean profiles of SWAN data are shown in Figure 3a. For SWAN, the identified change points are about -7, -2, +2 for  $\log_{10}$ FSH, and -2, +2 for  $\log_{10}$ E2 with time FMP = 0 enforced because it has conceptual importance in defining the menopause transition. Table 3 shows the annualized rate of changes in SWAN  $\log_{10}$ FSH and  $\log_{10}$ E2 with

change points rounded up to integer values -7, -2, 0, +2 years around FMP (which is 0).

For progressive segment comparisons of slopes as shown in Figure 3a,  $\log_{10}$ FSH segments “-2 to 0” vs “-7 to -2” and “+2 to +8” vs “0 to +2” have significant changes in the adjacent slopes (p value<0.0001). For  $\log_{10}$ E2 segments “-2 to 0” vs “-8 to -2” and “+2 to +8” vs “0 to +2” have significant changes in the adjacent slopes (p value<0.0001). For both hormones, the slopes of segment “0 to +2” and segment “-2 to 0” are not significantly different (p value ≈ 0.8). However their instantaneous slope curves are different as shown in Figure 3b-3c.

**Table 3** Annualized hormone rate of change: SWAN

Number of years around FMP	Annualized rate of change (SE <sup>a</sup> )	
	$\log_{10}$ (FSH IU/L)	$\log_{10}$ (E2 pg/mL)
-8	-8 ~ -7:	-8 ~ -2
-7	-0.0553(se=0.0696) p=0.4266	-0.0069(se=0.0087) p=0.4251
-2	-7 ~ -2: 0.1189(se=0.0073) p<0.0001	
0	-2 ~ 0: 0.4654 (se=0.0121) p<0.0001	-2 ~ 0 -0.2924(se=0.0159) p<0.0001
+2	0 ~ +2 0.1583(se=0.0119) p<0.0001	0 ~ +2 -0.3024(se=0.0159) p<0.0001
+8	+2 ~ +8 -0.0031(se=0.0068) p=0.6484	+2 ~ +8 0.0143(se=0.0087) p=0.0986

<sup>a</sup> SE: standard error

MBHMS data provides a more extended time –span around the FMP ( $\pm 10$  years). As seen in Figure 4a~4d, a major decline in  $\log_{10}$ E2 rate of change lasts about 4 years (i.e.,  $\pm 2$  years around FMP) (Figure 4b). A minor decline in  $\log_{10}$ E2 rate of change occurs around +7 years post FMP, which is not observed in SWAN  $\log_{10}$ E2. A parametric functional form might not detect this 2<sup>nd</sup> decline. Figure 4c shows that the acceleration / deceleration of  $\log_{10}$ E2 decline may start earlier than the time at which significant changes are observed in rate of change. The instantaneous curvature curve (Figure 4d) of the mean profile, integration of rate of change and acceleration, has two local maxima around -2 and +2 years around FMP.

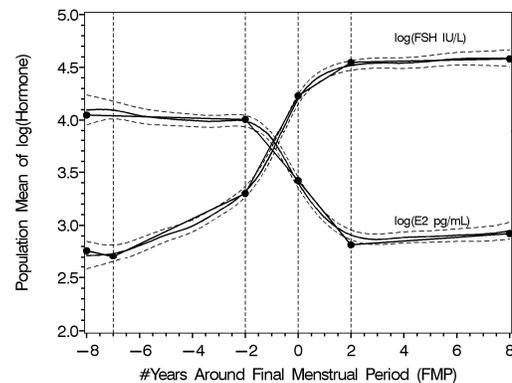


Figure 3a: Smoothed and segmented mean profiles for  $\log_{10}$ FSH and  $\log_{10}$ E2:SWAN

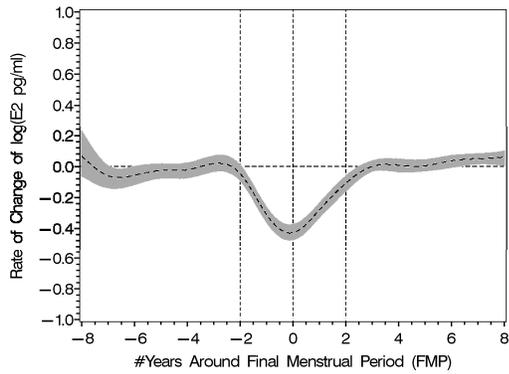


Figure 3b: Rate of change (95%CI) for  $\log E2$ :SWAN

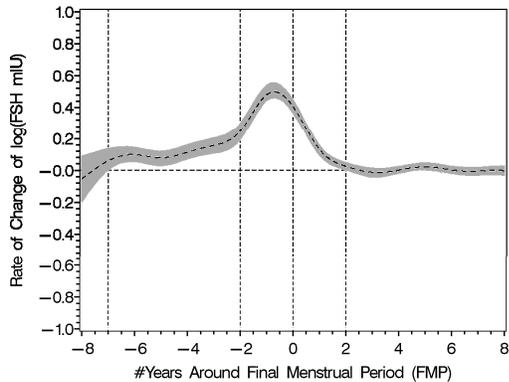


Figure 3c: Rate of change (95%CI) for  $\log FSH$ :SWAN

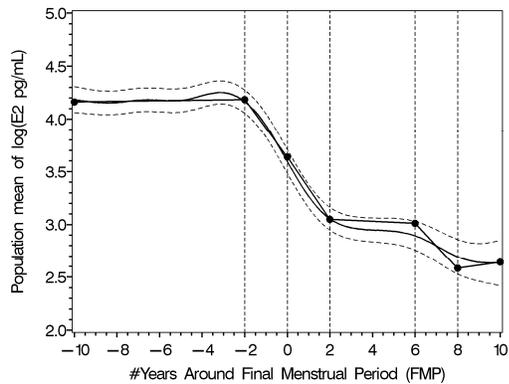


Figure 4a: Smoothed and segmented mean profiles for  $\log E2$ :MBHMS

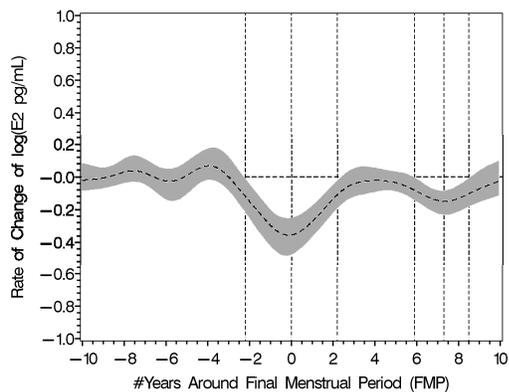


Figure 4b: Rate of change (95%CI) for  $\log E2$ :MBHMS

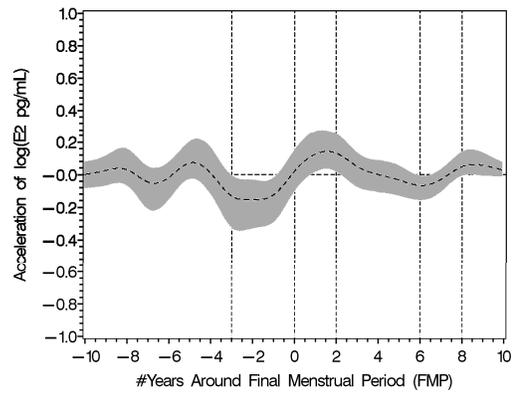


Figure 4c: Acceleration (95%CI) for  $\log E2$ :MBHMS

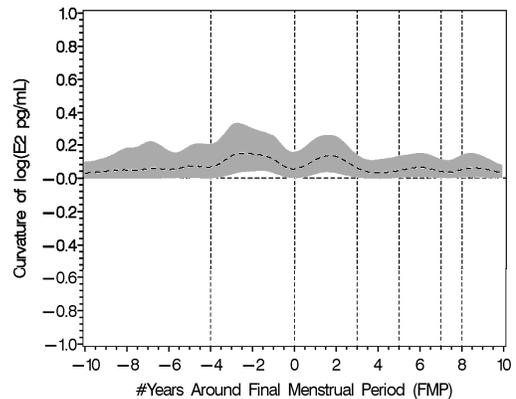


Figure 4d: Curvature (95%CI) for  $\log E2$ :MBHMS

For a more epidemiological discussion of the implications of these findings please refer to [1~2] using *MBHMS* data and one forthcoming paper on E2 and FSH changes using *SWAN* data[31].

## 5. CONCLUSIONS AND FUTURE WORK

Motivated by the study of the ovarian aging process around the final menstrual period in mid-life women defined by the longitudinal hormone measures E2 and FSH from longitudinal cohorts, we formulated the problem of staging the menopausal transition as a change detection problem by comparing slopes from two adjacent time-windows within a study frame. An integrative and novel approach developed to characterize the complex longitudinal patterns of change in biological dynamic processes in populations includes four steps: modeling the population mean profile using semi- / non- parametric stochastic mixed models, approximating instantaneous change characteristics including rate of change, acceleration / deceleration and curvature, segmenting the overall process into sub-processes using piecewise linear mixed models, and estimating the quantities of interest using a Bayesian Modeling Averaging Approach, accounting for model selection uncertainty.

This approach has the capability to estimate the instantaneous population mean profile and population change characteristics, change point(s), the length of time-windows defined by any two change points of interest, and the mean rate of change of derived sub-processes. The major advantage of the methodology is that it does not assume parametric functional forms and thus can be applied to model those complex change patterns in

biological/epidemiological dynamic processes with little prior knowledge of the shape.

During the model development, bootstrapped confidence intervals of rate of change and model average-based change points are evoked. So one element requiring future work includes conducting some comparative studies with parametric settings as well as improving computational efficiency by optimizing the algorithm. In nature, this work represents off-line change detection using all available data within Bayes perspective. However, in MBHMS and SWAN, more data are being collected at subsequent follow-up visits. So future work includes determining the feasibility of adaptively updating the change points or detecting new change points when additional and informative data enters into the data pool. In epidemiological studies, there are correlated ordinal outcomes which might be addressed having similar constraints, i.e., log-odds as a function of some variable (e.g, time) might be complex and unknown, e.g, nonlinear, nonparametric. Thus, it would be valuable to extend this approach to longitudinal ordinal outcomes.

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