A self-excited threshold autoregressive state-space model for menstrual cycles: forecasting menstruation and identifying within-cycle stages based on basal body temperature

Ai Kawamori

The Institute of Statistical Mathematics,
10-3 Midoricho, Tachikawa, Tokyo 190-8562, Japan

Keiichi Fukaya*

The Institute of Statistical Mathematics,
10-3 Midoricho, Tachikawa, Tokyo 190-8562, Japan
*Corresponding author: `kfukaya@ism.ac.jp`

Masumi Kitazawa

QOL Corporation,
2929, Netsu, Tomi, Nagano 389-0506, Japan

Makio Ishiguro

The Institute of Statistical Mathematics,
10-3 Midoricho, Tachikawa, Tokyo 190-8562, Japan

Summary The menstrual cycle is divided into hypothermic and hyperthermic phases based on the periodic shift in the basal body temperature (BBT), reflecting events occurring in the ovary. In the present study, we proposed a state-space model that explicitly incorporates the biphasic nature of the menstrual cycle, in which the probability density distributions for the advancement of the menstrual phase and that for the BBT switch depending on a latent state variable. Our model derives the predictive distribution of the day of the next menstruation onset that is adaptively adjusted by accommodating new observations of the BBT sequentially. It also enables us to obtain conditional probabilities of the woman being in the early or late stages of the cycle, which can be used to identify the duration of hypothermic and hyperthermic phases, possibly as well as the day of ovulation. By applying the model to real BBT and menstruation data, we show that the proposed model can properly capture the biphasic characteristics of menstrual cycles, providing a good prediction of the menstruation onset in a wide range of age groups. The application of the proposed model to a large data set containing 25,622 cycles provided by 3,533 women further highlighted the between-age differences in the population characteristics of menstrual cycles, suggesting its wide applicability.

1 Introduction

During the reproductive age, women experience recurring physiological changes known as menstrual cycles. The cycle starts on the first day of menstruation, followed by a pre-ovulatory period referred to as the follicular phase. After ovulation, the cycle enters a post-ovulatory period referred to as the luteal phase, lasting until the day before the next menstruation onset. Although menstrual cycles generally last 28 days, the length of the menstrual cycle exhibits significant variation, both within and among individuals.[1] Variation in menstrual cycle length is mainly attributed to the follicular phase, as the follicular phase shows greater variation in length than the luteal phase.[2] Thus, determining the time of ovulation can be difficult.

The basal body temperature (BBT) also reflects this biphasic aspect of the menstrual cycle; BBT tends to be relatively low during the follicular phase (the hypothermic phase), increasing by 0.3 to 0.5 °C after the cycle enters the luteal phase (the hyperthermic phase).[3,4] Since a shift in the BBT may be indicative of ovulation, daily BBT records could be used to estimate the day of ovulation and associated fertile interval. However, given the large variability of the BBT and a potential delay in the shift of the BBT, the estimation of ovulation based on the BBT may be error-prone.[3,5,6]

Considerable effort has been made to develop menstrual cycle-related statistical models. Barrett-Marshall-Schwartz models are a class of statistical models for human fecundability, in which the occurrence of pregnancy is explained by the intercourse pattern and day-specific probability of conception within the fertile interval.[7,8] The fertile interval within the menstrual cycle refers to the time period where the day-specific probability of conception is not negligible; thus, intercourse can result in pregnancy. It is estimated to last about 6 days, starting $\sim$ 5 days prior to ovulation and ending on the day of ovulation.[9,10] The fertile interval can be identified based on various biological markers for ovulation, such as BBT, urinary luteinizing hormone level, and cervical mucus. However, none of these markers identify ovulation perfectly; therefore, error in the identification of the day of ovulation is considered an important issue in studies of human fecundability.[6,11] Time-to-pregnancy models are another class of statistical models for human fecundability, which explain the number of menstrual cycles required to achieve a clinical pregnancy. Additional statistical models for human fecundability have been reviewed in.[12–16]

Another line of research involves the development of statistical models explaining the variability in the menstrual cycle length (MCL). This includes the following types of models:

mixture distribution models explaining the long right tail in the distribution of the MCL[1,17,18]; longitudinal models, accounting for the within subject-correlation in the MCLs[1,18,19]; and a change point model identifying the menopausal shift in the moments of the MCL distribution[20]. Furthermore, Bortot et al.[21] proposed a state-space modeling framework providing a predictive distribution of the MCL that is conditional on the past time series of the MCL. Moreover, recent studies have considered the joint modeling of the MCL and fecundability.[18,22,23]

Although BBT is an easily observed quantity relevant to the menstrual cycle, the development of statistical models explaining periodic BBT fluctuations has received little attention. Scarpa and Dunson[4] applied Bayesian functional data analysis to BBT time series data that characterized BBT fluctuations in normal cycles parametrically and identified abnormal BBT trajectories nonparametrically. Fukaya et al.[24] recently proposed a state-space model involving the menstrual phase as a latent state variable explaining the BBT time series. Applying a sequential Bayesian filtering algorithm enabled the authors to obtain filtering distribution of the menstrual phase, providing a predictive distribution for the onset of the next menstruation sequentially.

In the model proposed by Fukaya et al.,[24] the biphasic nature of the menstrual cycle was not accounted for in an explicit manner. Specifically, the model used a trigonometric series to explain the periodic BBT fluctuations, and the biphasic pattern may thus appear as a result of the model-fitting. In addition, the model assumed a single probability density distribution for the advancement of the menstrual phase, and did not account for differences in the distributions of the length of the hypothermic and hyperthermic phases. However, there is another possible model formulation that is biologically more natural and interpretable, based on previous knowledge of the menstrual cycle. This model involves dividing a cycle into two distinct stages, with each stage characterized by specific statistical distributions for the BBT and the advancement of the menstrual phase.

In the present study, we propose such an "explicit biphasic menstrual cycle model", as an extension of the model proposed by Fukaya et al.,[24] which we refer to as an "implicit biphasic menstrual cycle model". In our explicit model, the probability density distributions of the advancement of the menstrual phase and the BBT switch, depending on a latent state variable. Our model can therefore be seen as a self-excited threshold autoregressive state-space model.[25] Most of the statistical inferences applied to the implicit model described in the previous paper[24] can be similarly applied to the current explicit model. Thus, the conditional distribution of the latent menstrual phase variable can be obtained using a sequential Bayesian filtering algorithm,

which in turn can be used to yield a predictive distribution of the day of menstruation onset. Furthermore, as we describe below, the conditional distribution of the latent menstrual phase variable naturally provides the probability of a subject being in the earlier or later stage of the cycle, which may potentially be used to estimate the timing of ovulation. By applying the proposed model to a large data set of menstrual cycles, we illustrate its wide applicability. We show that the proposed model can properly capture the biphasic characteristics of menstrual cycles, shedding light on between-age differences in the population characteristics of menstrual cycles.

The remainder of this paper is organized as follows. In Section 2, we detail the proposed method, formulating the model and describing statistical inferences involving latent state variables and parameters. We also explain how the predictive distribution for the next menstruation onset and the probability that a subject is in the first or second stage can be obtained, based on the conditional distribution of the menstrual phase variable. Section 3 presents an application of the proposed model to a real menstrual cycle data set collected from a large number of women. For eight age groups, ranging from the late teens to the early 50s, we report the maximum likelihood estimates of the model parameters, and examine the accuracy of the prediction of menstruation onset. We also provide the joint and marginal distributions of the lengths of the first and second stages, which was judged based on the smoothed distribution of the menstrual phase. A concluding discussion is provided in Section 4.

2 Model description and inferences

2.1 State-space model of the menstrual cycle

Suppose for $i = 1, \ldots, I$ female subjects, a record of BBT measurement, y_{it}, and an indicator of the onset of menstruation, z_{it}, was obtained for days $t = 1, \ldots, T_i$. By $z_{it} = 1$, we denote that menstruation for subject i started on day t, whereas $z_{it} = 0$ indicates that day t was not the first day of menstruation for the subject i. We denote the BBT time series and menstruation data obtained from the subject i up to time t as $Y_{it} = (y_{i1}, \ldots, y_{it})$ and $Z_{it} = (z_{i1}, \ldots, z_{it})$, respectively. We assumed that the time series for each subject was independent from the time series of other subjects.

We considered the phase of the menstrual cycle, $\theta_{it} \in \mathbb{R}$, to be a latent state variable. In the following, we assumed that menstrual cycles are periodic in terms of θ_{it} with a period of 1. We

divided each cycle into two distinct stages, the first stage ($0 \leq \theta_{it} - \lfloor \theta_{it} \rfloor < 0.5$) and the second stage ($0.5 \leq \theta_{it} - \lfloor \theta_{it} \rfloor < 1$), where $\lfloor x \rfloor$ is the floor function returning the largest previous integer for x. We defined a set of real numbers corresponding to the latent menstrual phase being in the first and second stages of the cycle as $\Theta_1 = \{\theta \subset \mathbb{R} \mid 0 \leq \theta - \lfloor \theta \rfloor < 0.5\}$ and $\Theta_2 = \{\theta \subset \mathbb{R} \mid 0.5 \leq \theta - \lfloor \theta \rfloor < 1\}$, respectively.

We let ϵ_{it} reflect the daily advance of the phase for subject i between days $t-1$ and t, and assumed that it was a positive random variable independently following a gamma distribution with varying parameters. Thus, the system model can be described as:

$$\theta_{it} = \theta_{i,t-1} + \epsilon_{it} \tag{1}$$

$$\epsilon_{it} \sim \text{Gamma} \left\{ \alpha \left(\theta_{i,t-1} \right), \beta \left(\theta_{i,t-1} \right) \right\} \tag{2}$$

$$\left\{ \alpha \left(\theta_{i,t-1} \right), \beta \left(\theta_{i,t-1} \right) \right\} = \begin{cases} (\alpha_{i1}, \beta_{i1}) & \text{when} \quad \theta_{i,t-1} \in \Theta_1 \\ (\alpha_{i2}, \beta_{i2}) & \text{when} \quad \theta_{i,t-1} \in \Theta_2. \end{cases} \tag{3}$$

We assumed that the system model parameters switched between two stages, enabling a description of the difference in the variability of the length of these stages. Under this assumption, the conditional distribution of θ_{it}, given $\theta_{i,t-1}$, is a gamma distribution with a probability density function:

$$\begin{aligned} p(\theta_{it} \mid \theta_{i,t-1}) &= \text{Gamma} \left\{ \alpha \left(\theta_{i,t-1} \right), \beta \left(\theta_{i,t-1} \right) \right\} \\ &= \frac{\beta \left(\theta_{i,t-1} \right)^{\alpha(\theta_{i,t-1})}}{\Gamma \left\{ \alpha \left(\theta_{i,t-1} \right) \right\}} (\theta_{it} - \theta_{i,t-1})^{\alpha(\theta_{i,t-1})-1} \exp \left\{ -\beta \left(\theta_{i,t-1} \right) \left(\theta_{it} - \theta_{i,t-1} \right) \right\}. \end{aligned} \tag{4}$$

We assumed that the distribution of the observed BBT, y_{it}, was conditional on the menstrual phase θ_{it}. Assuming a Gaussian observation error, the observation model for the BBT can be expressed as:

$$y_{it} = \mu \left(\theta_{it} \right) + e_{it} \tag{5}$$

$$e_{it} \sim \text{Normal} \left\{ 0, \sigma^2 \left(\theta_{it} \right) \right\} \tag{6}$$

$$\left\{ \mu \left(\theta_{it} \right), \sigma^2 \left(\theta_{it} \right) \right\} = \begin{cases} (\mu_{i1}, \sigma_{i1}^2) & \text{when} \quad \theta_{it} \in \Theta_1 \\ (\mu_{i2}, \sigma_{i2}^2) & \text{when} \quad \theta_{it} \in \Theta_2. \end{cases} \tag{7}$$

Again, observation model parameters $\left\{ \mu \left(\theta_{it} \right), \sigma^2 \left(\theta_{it} \right) \right\}$ switched depending on the underlying stage within the cycle, in order to describe a biphasic pattern in the BBT. Conditional on θ_{it}, y_{it}

then follows a normal distribution with a probability density function:

$$p(y_{it} \mid \theta_{it}) = \text{Normal} \left\{ \mu \left(\theta_{it} \right), \sigma^2 \left(\theta_{it} \right) \right\}$$

$$= \frac{1}{\sqrt{2\pi\sigma^2 \left(\theta_{it} \right)}} \exp \left[-\frac{\left\{ y_{it} - \mu \left(\theta_{it} \right) \right\}^2}{2\sigma^2 \left(\theta_{it} \right)} \right]. \tag{8}$$

For the menstruation onset, we assumed that menstruation starts when θ_{it} crosses the smallest following integer. This can be represented as follows:

$$z_{it} = \begin{cases} 0 & \text{when} \quad \lfloor \theta_{it} \rfloor = \lfloor \theta_{i,t-1} \rfloor \\ 1 & \text{when} \quad \lfloor \theta_{it} \rfloor > \lfloor \theta_{i,t-1} \rfloor. \end{cases} \tag{9}$$

In rewriting this deterministic allocation in a probabilistic manner, z_{it} follows a Bernoulli distribution conditional on $(\theta_{it}, \theta_{i,t-1})$:

$$p(z_{it} \mid \theta_{it}, \theta_{i,t-1}) = (1 - z_{it}) \left\{ I(\lfloor \theta_{it} \rfloor = \lfloor \theta_{i,t-1} \rfloor) \right\} + z_{it} \left\{ I(\lfloor \theta_{it} \rfloor > \lfloor \theta_{i,t-1} \rfloor) \right\}, \tag{10}$$

where $I(x)$ is the indicator function that returns 1 when x is true or 0 otherwise.

The model involves, under no restriction, a total of $8 \times I$ parameters; that is, the model has an independent set of parameters $(\alpha_{i1}, \alpha_{i2}, \beta_{i1}, \beta_{i2}, \mu_{i1}, \mu_{i2}, \sigma_{i1}, \sigma_{i2})$ for each subject i. However, in most cases, it is likely that data are not sufficiently abundant to estimate parameters separately for each subject. Restricted versions of the model can be considered by assuming that certain parameters are equal among subjects. For example, we can assume that a set of parameters $(\alpha_{i1}, \alpha_{i2}, \beta_{i1}, \beta_{i2}, \mu_{i1}, \mu_{i2}, \sigma_{i1}, \sigma_{i2})$ is equal for all I subjects, in which case there would be only 8 parameters to be estimated. This approach pools information across subjects and allows the estimation of parameters, even when the time series is not of sufficient length for each subject. Between-subject variation can be accounted for using covariate information, such as the age of the subject, when available. For example, between-subject differences in $\alpha_{i1}(> 0)$ can be modeled as: $\log \alpha_{i1} = \gamma_0 + \sum_j \gamma_j x_{ij}$, where x_{ij} is the jth covariate for subject i. In this case, the γs are the parameters to be estimated.

Let $\boldsymbol{\xi}$ be a vector of the parameters of the model. Given data (Y_{iT_i}, Z_{iT_i}) and a distribution specified for initial states $p(\theta_{i1}, \theta_{i0})$ for each subject i, the parameters in $\boldsymbol{\xi}$ can be estimated using the maximum likelihood method. The log-likelihood for subject i can be expressed as:

$$l_i(\boldsymbol{\xi}; Y_{iT_i}, Z_{iT_i}) = \log p(y_{i1}, z_{i1} \mid \boldsymbol{\xi}) + \sum_{t=2}^{T_i} \log p(y_{it}, z_{it} \mid Y_{i,t-1}, Z_{i,t-1}, \boldsymbol{\xi}), \tag{11}$$

where

$$\log p(y_{i1}, z_{i1} \mid \boldsymbol{\xi}) = \log \int \int p(y_{i1} \mid \theta_{i1}) p(z_{i1} \mid \theta_{i1}, \theta_{i0}) p(\theta_{i1}, \theta_{i0}) d\theta_{i1} d\theta_{i0}. \tag{12}$$

For $t = 2, \ldots, T_i$,

$$\log p(y_{it}, z_{it} \mid Y_{i,t-1}, Z_{i,t-1}, \boldsymbol{\xi}) = \log \int \int p(y_{it} \mid \theta_{it}) p(z_{it} \mid \theta_{it}, \theta_{i,t-1}) p(\theta_{it}, \theta_{i,t-1} \mid Y_{i,t-1}, Z_{i,t-1}) d\theta_{it} d\theta_{i,t-1},$$
$$\tag{13}$$

which can be sequentially obtained using the Bayesian filtering technique described below. Note that, for each subject i, $p(y_{it} \mid \theta_{it})(t \geq 1)$ and $p(\theta_{it}, \theta_{i,t-1} \mid Y_{i,t-1}, Z_{i,t-1})(t \geq 2)$ depend on $\boldsymbol{\xi}$; however, this dependence is not explicitly described here for notational simplicity. Since the subject time series is assumed to be independent, the joint log-likelihood is the sum of the I subject log-likelihoods:

$$l(\boldsymbol{\xi}; Y_{1T_1}, \ldots, Y_{IT_I}, Z_{1T_1}, \ldots, Z_{IT_I}) = \sum_{i=1}^{I} l_i(\boldsymbol{\xi}; Y_{iT_i}, Z_{iT_i}). \tag{14}$$

2.2 State estimation and calculation of log-likelihood by using sequential Bayesian filtering

The joint distribution of the phase of subject i at successive time points t and $t-1$, conditional on the observations obtained up to time u, $p(\theta_{it}, \theta_{i,t-1} \mid Y_{iu}, Z_{iu})$, is referred to as a predictive distribution when $t > u$, as a filtering distribution when $t = u$, and as a smoothed distribution when $t < u$. Given a state-space model, its parameters, and data, these conditional distributions can be obtained by using recursive formulae for the state estimation problem, which are referred to as the Bayesian filtering and smoothing equations. Details regarding the state estimation of state-space models have been previously described (e.g.,[26,27]).

Although these conditional probability distributions are often analytically intractable for non-linear, non-Gaussian state-space models, they can be obtained approximately for the self-excited threshold autoregressive state-space model described above. To this end, we applied Kitagawa's non-Gaussian filtering procedure,[28] which provides a numerical approximation of the joint conditional probability density $p(\theta_{it}, \theta_{i,t-1} \mid Y_{iu}, Z_{iu})$. The numerical procedure applied to the implicit biphasic menstrual cycle model described by Fukaya et al.[24] can be used to our explicit biphasic menstrual cycle model in the same manner. Since the subject time series are assumed to be independent, conditional probability distributions can be obtained separately for

each subject i. Once the numerical approximation of the joint conditional probability density $p(\theta_{it}, \theta_{i,t-1} \mid Y_{iu}, Z_{iu})$ is obtained, the marginal probability densities (e.g., $p(\theta_{it} \mid Y_{iu}, Z_{iu}) = \int p(\theta_{it}, \theta_{i,t-1} \mid Y_{iu}, Z_{iu}) d\theta_{i,t-1}$) can also be obtained straightforwardly; these are used to obtain the predictive distribution for the day of menstruation onset and the conditional probabilities for the stages of the cycle as described below. The log-likelihood for data at a particular time (Equations 12 and 13) can be calculated for each subject as a by-product of obtaining the filtering distribution. Missing observations are allowed in the sequential Bayesian filtering procedure. More details can be found in.[24]

2.3 Sequential Bayesian prediction for the day of menstruation onset

Fukaya et al.[24] reported that the filtering distribution of the menstrual phase in their state-space model could be used to obtain the predictive distribution for the next menstruation onset (i.e., a predictive distribution for the length of the current cycle), which was conditional on the accumulated data available at the time point of the prediction. Since filtering distributions of the menstrual phase can be obtained using the Bayesian filtering procedure, the prediction of the day of onset for the next menstruation can be adaptively adjusted by accommodating new observations sequentially. This sequential predictive framework can be applied to the current explicit model in the same manner; however, the detailed calculations are more complicated due to the biphasic nature of the system model.

We denote, for $k = 1, 2, \ldots$, the probability that the next menstruation of subject i occurs on the $t + k$th day, conditional on the data available for her at the tth day as $h(k \mid Y_{it}, Z_{it})$. Given the marginal filtering distribution for the phase state $p(\theta_{it} \mid Y_{it}, Z_{it})$, the conditional probability is as follows:

$$h(k \mid Y_{it}, Z_{it}) = \int f(k \mid \theta_{it}) p(\theta_{it} \mid Y_{it}, Z_{it}) d\theta_{it}, \tag{15}$$

where $f(k \mid \theta_{it})$ is the conditional probability function for the day of menstruation onset.[24] We provide details for calculation of $f(k \mid \theta_{it})$ under the proposed explicit biphasic menstrual cycle model in the supplementary material for this article. Briefly, although $f(k \mid \theta_{it})$ can be obtained for $\theta_{it} \in \Theta_2$ straightforwardly, it is more involved for $\theta_{it} \in \Theta_1$. This is because the probability that the first stage of the cycle lasts until the $t + j - 1$th day and the next menstruation occurs on the $t + k$th day, denoted as $\phi(j, k \mid \theta_{it})$ $(j = 1, \ldots, k)$, is needed to obtain $f(k \mid \theta_{it})$ such that $f(k \mid \theta_{it}) = \sum_{j=1}^{k} \phi(j, k \mid \theta_{it})$. Furthermore, the calculation of $\phi(j, k \mid \theta_{it})$ requires convolutions of

probability distributions, rendering it being approximated numerically.

We can choose the k giving the highest probability, $\max h(k \mid Y_{it}, Z_{it})$, as a point prediction for the day of menstruation onset of subject i.

2.4 Identification of stages of the cycle

For some t and u, the probability that the menstrual phase of subject i at time t is in the first stage of the cycle, conditional on data obtained by time u, can be given as:

$$\Pr(\theta_{it} \in \Theta_1 \mid Y_{iu}, Z_{iu}) = \int_{\Theta_1} p(\theta_{it} \mid Y_{iu}, Z_{iu})d\theta_{it}. \tag{16}$$

By contrast, the conditional probability that the menstrual phase is in the second stage of the cycle can be given as:

$$\Pr(\theta_{it} \in \Theta_2 \mid Y_{iu}, Z_{iu}) = \int_{\Theta_2} p(\theta_{it} \mid Y_{iu}, Z_{iu})d\theta_{it}$$

$$= 1 - \Pr(\theta_{it} \in \Theta_1 \mid Y_{iu}, Z_{iu}). \tag{17}$$

Note that these probabilities are prospective when the conditional distribution of θ_{it} is a predictive distribution $(t > u)$, whereas they are retrospective when a smoothed distribution is used $(t < u)$.

A subject i can be judged as being in the first or second stage of the cycle based on the above probabilities. We can decide $\theta_{it} \in \Theta_1$ when $\Pr(\theta_{it} \in \Theta_1 \mid Y_{iu}, Z_{iu}) \geq 0.5$, and $\theta_{it} \in \Theta_2$ otherwise. We applied this decision rule in the analysis shown in section 3, although other rules could be applied.

An R script illustrating how to implement the numerical procedures for sequential Bayesian filtering, menstruation onset prediction, and judgement of stages is provided as a supplementary web material.

3 Application

3.1 Data

We organized data comprising daily recorded BBT and the day of menstrual onset, which were collected from a total of 3,784 women between 2007 and 2014 via a web service called *Ran's story* (QOL Corporation, Tomi, Japan). Details of *Ran's story* service, of which users were supposed to be ethnically Japanese, were described in.[24] We focused on menstrual cycle data that were

provided by users aged between 15 and 54 years during this period, and classified each menstrual cycle into eight age groups (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, and 50–54 years) based on the age of the user at the beginning of the cycle.

Cycles containing one or more BBT observations during the first seven days were defined as applicable to our analyses, as we used BBT data in that time period to standardize the level of BBT as explained below. In addition, for each age group, the longest and shortest 5% of cycles were discarded to omit cycles with extreme length. This data selection procedure resulted in a data set containing 25,622 cycles provided by 3,533 unique users (Table 1, top rows).

In order to elucidate age-specific characteristics, we further generated a subset of the above data set, which was randomly sampled while eliminating the within-woman dependency as much as possible, and was used to estimate model parameters and the accuracy of the prediction of menstruation (Table 1, middle and bottom rows). For each of the 20s and 30s age group, in which a large number of users were registered, 450 users were selected randomly, so that 450 cycles can be sampled from unique users. Cycles were then assigned to 300 cycles for parameter estimation and 150 cycles for the assessment of predictive accuracy. Similarly, for each of the 40s age group, 450 cycles were sampled randomly, and then divided into 300 cycles for parameter estimation and 150 cycles for the assessment of predictive accuracy. However, due to the limited number of users, not all cycles were attributed to unique users in these age groups. Finally, for the late teens and early 50s age groups, all available cycles were assigned randomly for parameter estimation and the assessment of predictive accuracy, because the number of cycles in these age groups was the most limited. For the 15–19 years age group, 300 cycles were used for parameter estimation and the remaining 111 cycles were used for the assessment of predictive accuracy. For the 50–54 years age group, 120 cycles were assigned for parameter estimation and the remaining 52 cycles were used for the assessment of predictive accuracy.

As the level of BBT time series varies between cycles, we used standardized BBT data in the following analyses. For each cycle, BBT time series was standardized by subtracting the median of BBT recorded in the first seven days of the cycle from the raw BBT data.

3.2   Parameter estimation

For each age group, an explicit biphasic menstrual cycle model was fitted to the data for parameter estimation (Table 1, middle rows). We treated cycles within each age group as independent and assumed that a set of age-specific parameters was applicable. Model parameters

were estimated by maximizing the joint log-likelihood function (Equation 14) numerically, with the specification of a uniform prior distribution for the initial states $p(\theta_{i1}, \theta_{i0})$ of each cycle, i. In order to fit the model and evaluate the log-likelihood, we used a non-Gaussian filter discretizing the state space into 512 intervals.

Parameter values were distinctly different between two stages (Table 2). System model parameters were characterized by larger values of α and β in the first stage, except for the oldest age group (50–54 years). These estimates generally implied that the first stage is on average longer and is more variable than the second stage (Figure 1). Between-age differences in the stage length distribution were also discernible: the stage length tended to become variable in late teens and early 50s (Figure 1).

As expected, in all age groups, mean BBT was estimated to be higher in the second stage: the increase in BBT ($\mu_2 - \mu_1$) ranged from 0.342 to 0.413 (Table 2). No clear difference was found in the standard deviation of observation errors of BBT (Table 2).

3.3   Accuracy of the prediction of menstruation onset

The accuracy of the prediction for the day of menstruation onset of the explicit biphasic menstrual cycle model was compared to that of several variants of state-space models for menstrual cycles and the conventional calendar calculation method. Models used for this comparison are summarized in Table 3. Like the fully explicit model, parameters of other state-space models were estimated by fitting the model to data for parameter estimation (Table 1, middle rows). The predictive error was measured by the root mean square error (RMSE). As the explicit model and implicit model can adaptively adjust the prediction based on the daily BBT records, for these models, RMSE was estimated for several points in time within the cycle; namely, at the day of onset of the previous menstruation, as well as 21, 14, 7, 6, 5, 4, 3, 2, and 1 day(s) before the day of the next menstruation onset. Cycles that were shorter than 21 days were omitted from the RMSE calculation for 21 days before the day of onset of next menstruation. The calendar calculation method predicts the next menstruation day as the day after a fixed number of days from the onset of preceding menstruation, which thus does not update the prediction within the cycle. For each age class, we used a fixed number of days for calendar-based prediction that gave the lowest RMSE.

Results are shown in Figure 2. Overall, the predictive error (RMSE) was found to be larger in young age groups (late teens and early 20s) and the oldest age group. In the fully explicit model,

RMSE was in general gradually decreased as the onset day of next menstruation approached. In all age groups, the model prediction was superior to the conventional calendar calculation method in the last few days of the cycle. On the other hand, RMSE tended to increase in the late stage of the cycle in the restricted explicit model, except for the oldest age group. The model prediction may be considerably worse than the calendar calculation method, especially in the middle age classes. Implicit models tended to give relatively poor prediction in the early stages of the cycle. However, in the last few days of the cycle, they attained small RMSE that was comparable to the fully explicit model. In the 50–54 years age group, results from the implicit models were identical. This was because in this age group, the system model parameters (i.e., α and β) were estimated to be very small, which almost always predict the onset of next menstruation occurring in the following day (a phenomena that was previously known to occur in the implicit models[24]). In this setting, RMSE decreases constantly, and finally reaches to zero 1 day before menstruation onset. However, such a manner of prediction is of course meaningless. The results together indicate that introducing the biphasic structure into the system model was critical to improve predictions in a wide range of age class.

3.4 Distribution of the length of two stages

Based on the stage identification method described in section 2.4, we determined lengths of the first and second stages of each menstrual cycle in the entire data set (Table 1, top rows). We used the smoothed probability distribution of the menstrual phase to determine the conditional probability of each stage. The joint and marginal distributions of the length of those stages are shown in Figure 3. In all age groups, there was a negative correlation between the length of the first and second stages. We also found that in the second stage of some age groups, there was a peak located at 0 or 1, indicating the existence of monophasic cycles.

The summary of two stage lengths is shown in Table 4. We found that in all age groups, the first stage is longer, on average, and is more variable than the second stage. The standard deviation of both stages tended to increase in either end of the age group. Furthermore, the percentage of monophasic cycles, which were arbitrarily defined as cycles that the length of the second stage was estimated to be less than three days, was also higher in these age groups.

4   Discussion

In the present study, we developed a self-excited autoregressive state-space model that explicitly accommodates the biphasic nature of the menstrual cycle, as an extension of the state-space model for the menstrual cycle proposed by Fukaya et al..[24] The present model was fitted to menstrual cycle data obtained from a large number of women in different age groups. We found that the estimated parameters were clearly different between the first and second stages of the cycle (Table 2). Mean BBT was estimated to be lower in the first stage of the cycle and to increase by approximately 0.4 °C in the second stage of the cycle. This result is consistent with that of Scarpa and Dunson,[4] in which BBT data obtained from a European fertility study were analyzed and the BBT was shown to shift an average of 0.4 °C in normal menstrual cycles exhibiting a biphasic pattern. Furthermore, estimates of the system model parameters suggested that the model predicts the length of the first stage as longer and more variable than that of the second stage (Figure 1). This result coincides with the fact that variability in the MCL can be mainly attributed to variability in the length of the follicular phase.[2] Thus, the results indicate that the proposed model adequately captures the characteristics of the two phases in the menstrual cycle, based on time series data of the BBT and menstruation.

The merit of the proposed biphasic model is that it can provide a model-based judgement of the stage of the cycle. This led to the observation of a mild negative correlation between the lengths of the first and second stages in a wide range of age groups (Figure 3), which agrees with a previous study reporting a similar tendency in the lengths of the follicular and luteal phases.[2] Furthermore, we found that the length of the second stage was extremely short in a portion of the menstrual cycles, indicating the existence of menstrual cycles exhibiting a monophasic BBT pattern, which has been recognized to occur in approximately 20% of cycles even when data were collected from normally cycling women.[3] These results affirm that the explicit biphasic menstrual cycle model can provide a reasonable judgement of the subject being in the hypothermic or hyperthermic phase. We note that our analysis highlighted between-age group differences in the phase length distribution, where the durations of hypothermic and hyperthermic phases were more variable in the late teens and early 50s (Table 4). It was also evident that monophasic cycles appear most often in these age groups (Table 4).

The conditional probabilities for a subject being in the first or second stages of the menstrual cycle could be used for a model-based judgement of the day of ovulation.[9,10] Several methods

have been proposed to objectively identify the day of ovulation based on the BBT, which include a widely-used rule of thumb called the three-over-six rule,[21,29,30] a method based on the cumulative sum test,[31] and a stopping rule based on a change-point model.[32] A limitation shared among these methods is that they may be difficult to apply, or less effective,[32] when observations in the BBT time series are missing. However, missing values can be formally handled in the state-space modeling framework; thus, the proposed method does not suffer from missing observations. Furthermore, judgements regarding ovulation can be made in a prospective, real-time, or retrospective manner, depending on the type of conditional distribution (i.e., predictive, filtering, or smoothed distribution, respectively). The proposed model may therefore be considered as a new approach to identify the day of ovulation based on the BBT, for which previous methods are considered to be error-prone.[3–5] However, the magnitude of the identification error is currently unknown, and further validation is required in the future. A possible delay in the shift of BBT relative to ovulation[5] may deserve a careful consideration: we realize that our estimates of the length of the second stage (Table 4) were consistently shorter than those previously reported (ca. 12.5 – 14.0 days; see Fehring et al.[2] and references therein).

Another merit of the proposed model is that it can derive a predictive distribution of the length of the current menstrual cycle sequentially. Our analysis showed that with the accumulation of the within-cycle trajectory of the BBT, the proposed model can provide a prediction that was superior to that for the conventional calendar calculation (Figure 2). Furthermore, an explicit consideration of the biphasic characteristics enabled the proposed model to give a better prediction in a wide range of age groups compared to that with implicit models (Figure 2). Although it is beyond the scope of this study, a further optimization of the predictive accuracy could be considered by exploring better system or observation components, or both. To this end, a previous study suggested a hybrid approach, in which the conventional prediction method is used in the earlier stages of the cycle.[24] We note that Bortot et al.[21] proposed another state-space modeling framework that can be used to predict the length of the current menstrual cycle, based on the subject's past time series of the MCL. We did not compare the predictive accuracy of the proposed model to that of the model of Bortot et al.,[21] because the data in the present study did not include a sufficiently long time series for each subject. A comparison between the models of Bortot et al.[21] and Fukaya et al.[24] is reported elsewhere.[24]

As described in Section 2.1, the model can accommodate variations in the parameters by including covariates, which can be useful in explaining differences in the characteristics of the

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menstrual cycles associated with subject-specific characteristics and/or conditions that vary between cycles within a subject.[33,34] Another possibility for modeling variability in the parameters involves the inclusion of random effects. However, this complicates the calculation of the log-likelihood considerably, rendering parameter estimation more challenging. Specifically, the inclusion of random effects requires an alternative estimation approach, such as Bayesian estimation using the Markov chain Monte Carlo method, which may result in a considerable increase in computational time. Finally, we note that the proposed method assumes that the BBT of the subject fluctuates under natural conditions. Therefore, the proposed method may not be useful for women utilizing hormonal contraception, which can interfere with physiological phenomena related to the menstrual cycle.

Acknowledgements

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Table 1: Summary of the menstrual cycle data. Note that users who provided records over several years can be counted in multiple age groups.

				Age (years)				
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54
Entire data set								
No. of subjects	118	542	1,020	1,090	781	364	134	19
No. of cycles	411	2,636	5,087	6,496	5,903	3,479	1,438	172
Range of cycle length	(15, 53)	(21, 50)	(24, 48)	(24, 44)	(23, 40)	(21, 41)	(20, 56)	(16, 87)
Mean of cycle length	30.4	31.8	31.5	30.4	29.2	27.9	28.8	32.3
Median of cycle length	30	31	31	30	29	27	27	28
SD of cycle length	6.7	5.6	4.7	4.1	3.4	3.6	5.8	12.7
No. of observations	12,660	84,538	161,531	198,871	173,563	97,610	41,647	5,582
Percentage of missing observations	13.7	15.8	14.0	10.8	10.5	9.0	8.8	4.0
Data for parameter estimation								
No. of subjects	97	300	300	300	300	148	84	17
No. of cycles	300	300	300	300	300	300	300	120
Range of cycle length	(15, 53)	(21, 49)	(24, 47)	(24, 43)	(24, 40)	(22, 40)	(20, 51)	(16, 87)
Mean of cycle length	30.4	31.7	32.0	30.8	29.8	28.1	28.1	31.4
Median of cycle length	30	31	31	30	29	27	27	28
SD of cycle length	6.7	5.4	4.8	4.4	3.8	3.6	4.8	11.8
No. of observations	9,281	9,822	9,887	9,537	9,247	8,701	8,674	3,819
Percentage of missing observations	13.5	16.9	16.0	14.1	12.8	9.0	9.1	3.7
Data for predictive accuracy estimation								
No. of subjects	64	150	150	150	150	101	70	15
No. of cycles	111	150	150	150	150	150	150	52
Range of cycle length	(16, 49)	(21, 49)	(24, 45)	(24, 42)	(24, 40)	(22, 40)	(21, 56)	(17, 77)
Mean of cycle length	30.5	33.4	32.1	31.0	29.7	27.9	29.6	34.3
Median of cycle length	30	32	31	31	29	27	27	29.5
SD of cycle length	6.7	6.4	4.6	3.9	3.8	3.9	6.7	14.6
No. of observations	3,481	5,162	4,962	4,803	4,610	4,333	4,577	1,827
Percentage of missing observations	13.9	17.4	16.3	14.5	12.7	10.1	8.6	4.4

Table 2: Maximum likelihood estimates of the parameters and their 95% confidence intervals (in brackets). † Confidence intervals were not calculated because the Hessian of log-likelihood was singular.

	Age (years)							
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54
System model								
First stage								
α_1	0.632	0.942	0.871	1.316	0.952	1.000	0.644	0.054
	(0.475, 0.842)	(0.691, 1.283)	(0.672, 1.128)	(0.665, 2.602)	(0.755, 1.201)	†	(0.511, 0.811)	(0.036, 0.080)
β_1	34.923	52.320	43.145	64.430	40.455	42.920	26.902	1.853
	(25.792, 47.287)	(37.764, 72.488)	(32.794, 56.762)	(33.701, 123.177)	(31.706, 51.618)	†	(21.017, 34.434)	(0.970, 3.542)
Second stage								
α_2	0.216	0.271	0.350	0.364	0.533	0.398	0.334	0.177
	(0.181, 0.258)	(0.228, 0.321)	(0.293, 0.418)	(0.304, 0.435)	(0.413, 0.688)	(0.337, 0.469)	(0.279, 0.399)	(0.126, 0.249)
β_2	1.837	2.865	5.141	5.218	8.669	5.783	4.472	2.170
	(1.330, 2.536)	(2.183, 3.759)	(4.013, 6.586)	(4.020, 6.772)	(6.245, 12.033)	(4.688, 7.134)	(3.455, 5.789)	(1.186, 3.969)
Observation model								
First stage								
μ_1	−0.040	−0.040	−0.029	−0.012	−0.023	−0.024	−0.018	−0.054
	(−0.047, −0.034)	(−0.047, −0.033)	(−0.035, −0.022)	(−0.018, −0.005)	(−0.031, −0.015)	(−0.029, −0.019)	(−0.024, −0.012)	(−0.063, −0.044)
σ_1	0.231	0.239	0.228	0.217	0.252	0.207	0.203	0.226
	(0.226, 0.235)	(0.235, 0.244)	(0.223, 0.233)	(0.213, 0.221)	(0.247, 0.257)	(0.204, 0.211)	(0.199, 0.207)	(0.220, 0.233)
Second stage								
μ_2	0.371	0.374	0.369	0.377	0.363	0.333	0.325	0.345
	(0.359, 0.382)	(0.363, 0.384)	(0.360, 0.378)	(0.368, 0.387)	(0.354, 0.372)	(0.325, 0.341)	(0.317, 0.333)	(0.330, 0.359)
σ_2	0.247	0.224	0.220	0.223	0.205	0.199	0.196	0.216
	(0.239, 0.255)	(0.217, 0.231)	(0.213, 0.227)	(0.217, 0.230)	(0.198, 0.211)	(0.193, 0.204)	(0.191, 0.202)	(0.207, 0.225)
Shift in BBT								
$\mu_2 - \mu_1$	0.411	0.413	0.398	0.389	0.386	0.357	0.342	0.398
	(0.399, 0.423)	(0.402, 0.425)	(0.387, 0.408)	(0.378, 0.400)	(0.375, 0.397)	(0.348, 0.367)	(0.333, 0.352)	(0.382, 0.414)

Table 3: A list of models for which accuracy of the prediction of menstruation onset was examined. Note that in our application, the index i denotes cycles rather than subjects.

Model	Code	System model	Observation model	Sequential Bayesian prediction
Fully explicit	FE	$\theta_{it} = \theta_{i,t-1} + \epsilon_{it}; \epsilon_{it} \sim \text{Gamma}\{\alpha(\theta_{i,t-1}), \beta(\theta_{i,t-1})\}$ $\{\alpha(\theta_{i,t-1}), \beta(\theta_{i,t-1})\} = \begin{cases}(\alpha_1, \beta_1) & \text{when} & \theta_{i,t-1} \in \Theta_1 \\ (\alpha_2, \beta_2) & \text{when} & \theta_{i,t-1} \in \Theta_2\end{cases}$	$y_{it} = \mu(\theta_{it}) + e_{it}; e_{it} \sim \text{Normal}\{0, \sigma^2(\theta_{it})\}$ $\{\mu(\theta_{it}), \sigma^2(\theta_{it})\} = \begin{cases}(\mu_1, \sigma_1^2) & \text{when} & \theta_{it} \in \Theta_1 \\ (\mu_2, \sigma_2^2) & \text{when} & \theta_{it} \in \Theta_2\end{cases}$	yes
Restricted explicit	RE	$\theta_{it} = \theta_{i,t-1} + \epsilon_{it}; \epsilon_{it} \sim \text{Gamma}(\alpha, \beta)$	$y_{it} = \mu(\theta_{it}) + e_{it}; e_{it} \sim \text{Normal}\{0, \sigma^2(\theta_{it})\}$ $\{\mu(\theta_{it}), \sigma^2(\theta_{it})\} = \begin{cases}(\mu_1, \sigma_1^2) & \text{when} & \theta_{it} \in \Theta_1 \\ (\mu_2, \sigma_2^2) & \text{when} & \theta_{it} \in \Theta_2\end{cases}$	yes
Implicit 1	I1	$\theta_{it} = \theta_{i,t-1} + \epsilon_{it}; \epsilon_{it} \sim \text{Gamma}(\alpha, \beta)$	$y_{it} = \mu(\theta_{it}) + e_{it}; e_{it} \sim \text{Normal}(0, \sigma^2)$ $\mu(\theta_{it}) = a + b_1 \cos 2\pi\theta_{it} + c_1 \sin 2\pi\theta_{it}$	yes
Implicit 2	I2	$\theta_{it} = \theta_{i,t-1} + \epsilon_{it}; \epsilon_{it} \sim \text{Gamma}(\alpha, \beta)$	$y_{it} = \mu(\theta_{it}) + e_{it}; e_{it} \sim \text{Normal}(0, \sigma^2)$ $\mu(\theta_{it}) = a + \sum_{m=1}^{2} b_m \cos 2m\pi\theta_{it} + c_m \sin 2m\pi\theta_{it}$	yes
Implicit 3	I3	$\theta_{it} = \theta_{i,t-1} + \epsilon_{it}; \epsilon_{it} \sim \text{Gamma}(\alpha, \beta)$	$y_{it} = \mu(\theta_{it}) + e_{it}; e_{it} \sim \text{Normal}(0, \sigma^2)$ $\mu(\theta_{it}) = a + \sum_{m=1}^{3} b_m \cos 2m\pi\theta_{it} + c_m \sin 2m\pi\theta_{it}$	yes
Calendar calculation	C	NA	NA	no

Table 4: Summary of lengths of two stages. Monophasic cycles were defined as cycles in which the length of the second stage was estimated to be less than three days, based on the phase identification method described in section 2.4. The smoothed probability distribution of the menstrual cycle phase was used to determine the stage of the menstrual cycle.

| | Age (years) | | | | | | | |
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54
All cycles								
First stage								
Mean	21.4	22.0	20.6	19.5	18.5	17.4	18.3	23.2
Median	21	21	20	19	18	17	17	18
SD	7.6	6.6	5.7	5.0	4.4	4.9	7.2	15.2
Second stage								
Mean	9.1	9.8	10.9	10.9	10.7	10.5	10.4	9.1
Median	10	10	11	11	11	11	11	10
SD	5.3	4.4	3.9	3.6	3.4	3.8	4.5	6.5
Without monophasic cycles								
First stage								
Mean	20.4	21.3	20.2	19.2	18.2	16.9	17.4	18.3
Median	20	21	20	19	18	16	16	16
SD	7.1	6.2	5.4	4.7	4.1	4.4	6.3	10.0
Second stage								
Mean	10.5	10.6	11.3	11.1	11.0	11.0	11.2	11.9
Median	10	11	11	11	11	11	11	11.5
SD	4.4	3.7	3.4	3.3	3.0	3.2	3.8	4.9
Percentage of monophasic cycles	15.6	8.5	3.8	2.8	2.9	4.9	8.1	24.4
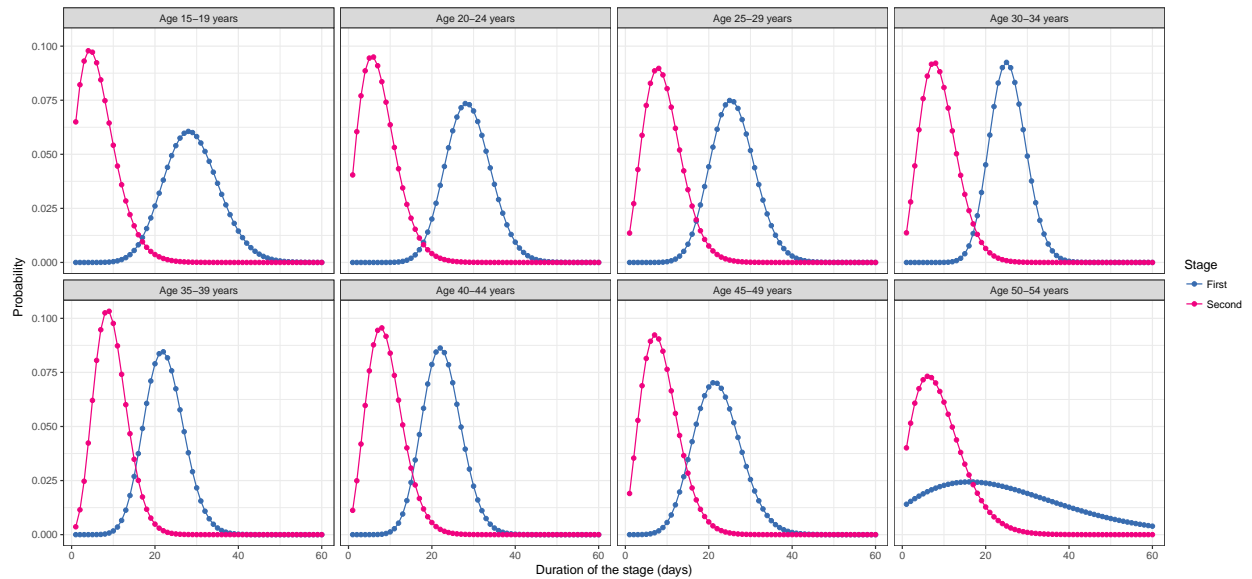
Figure 1: Distribution of the stage length derived from estimated parameters. The probability distribution of the length of m-th stage $f_m(k)(m = 1, 2)$ was obtained as: $f_m(1) = 1 - G(0.5; \alpha_m, \beta_m)$ and for $k > 1$, $f_m(k) = G\{0.5; (k-1)\alpha_m, \beta_m\} - G(0.5; k\alpha_m, \beta_m)$, where $G(\cdot; s, r)$ is the distribution function of the gamma distribution with shape parameter s and rate parameter r. Each panel depicts the results for an age group.
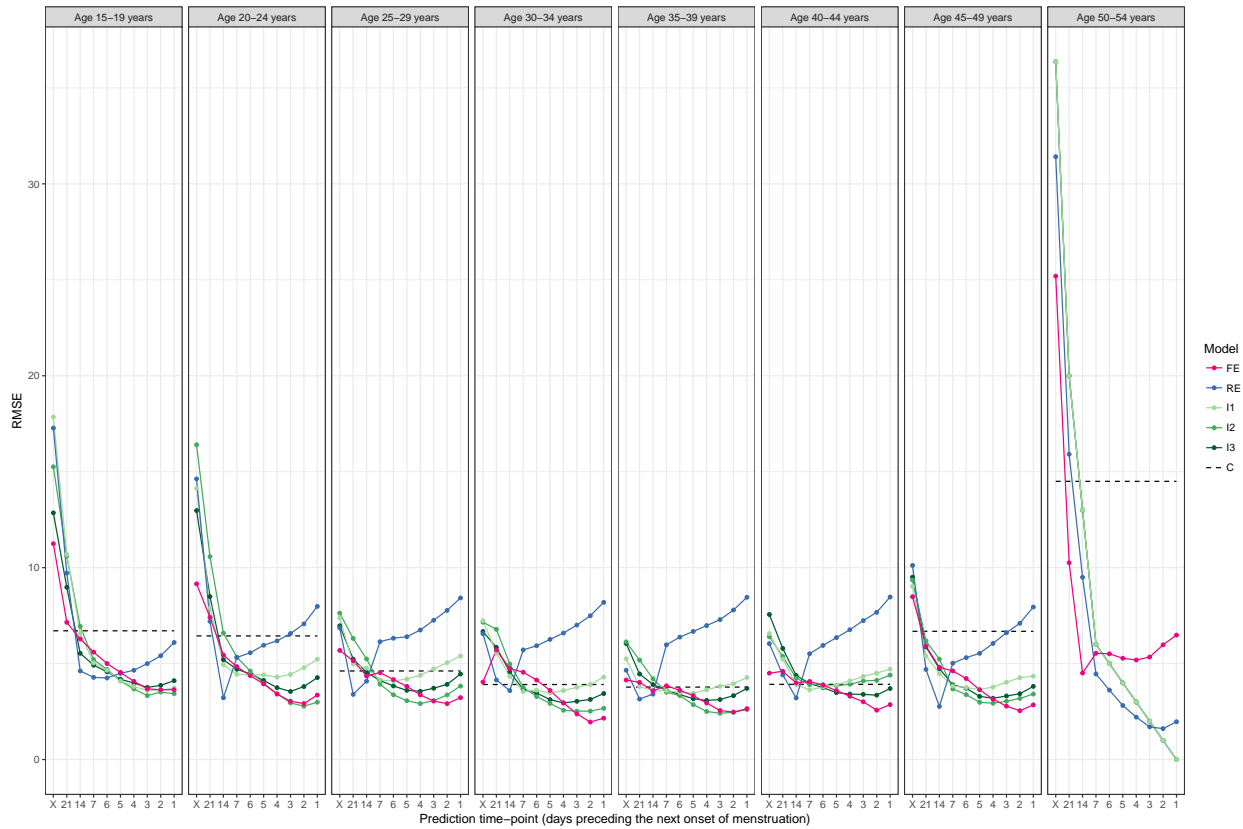
Figure 2: Root mean square error (RMSE) of prediction of the day of onset of menstruation across the day at which prediction was made. "X", on the horizontal axis, indicates the day of onset of previous menstruation. FE: Fully explicit model; RE: Restricted explicit model; I1: Implicit model 1; I2: Implicit model 2; I3: Implicit model 3; C: Calendar calculation method; refer to Table 3 for details.
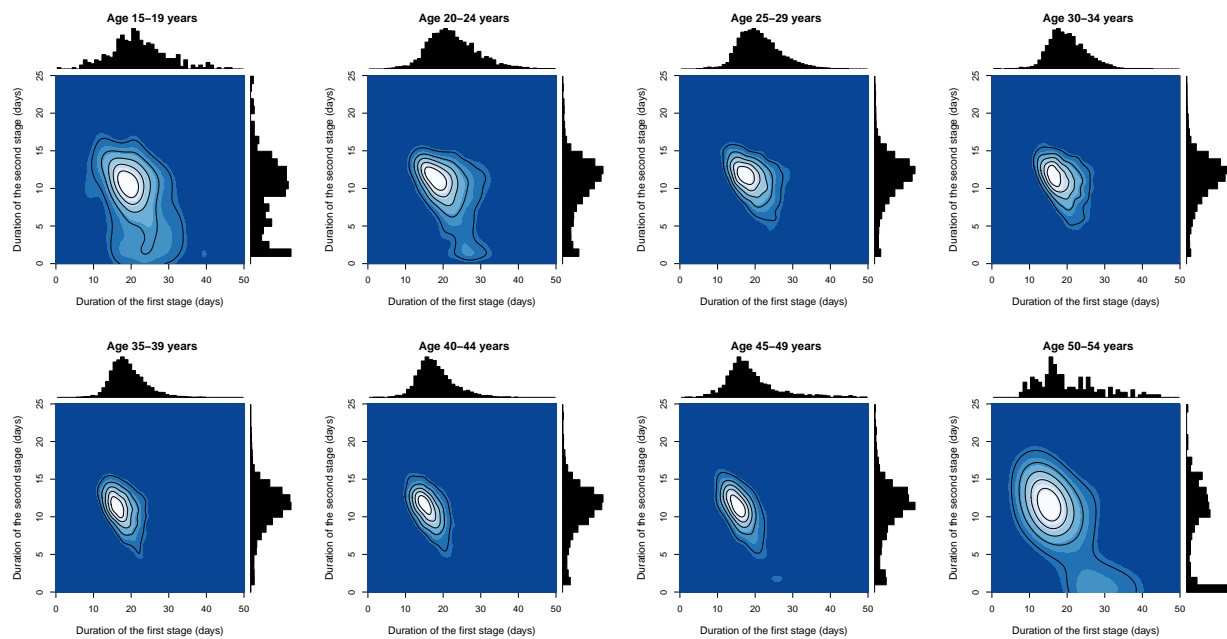
Figure 3: The contour plots show the kernel density estimates of the durations of the first and second stages. Dense regions are drawn in brighter colors. The marginal distributions of the stage lengths are shown on the upper and right side of the plots.