CHAPTER V

OPTIMAL DESIGN OF STEP-STRESS MODEL FOR THE
OLIGOMENORRHOEA CASES OF WOMEN BY USING GOMPertz
DISTRIBUTION

5.1. Introduction

For the optimal design stage of the test, a new experiment with test
units different from those tested in the stage of parameter estimation is
conducted. Our aim is to obtain the optimal value of \( \tau \) based on the outputs
of the stage of parameter estimation that are in the same time considered
inputs to the optimal design stage of the test.

It is worth noting that the stress change-time \( \tau \) is a pre-specified time
for the stage of parameter estimation. But for the optimal design stage of the
test, \( \tau \) is considered a switching parameter that to be optimally determined
according to a certain optimality criterion.

This section considers the problem of optimally designing a simple
time-step-stress PALT, which terminates at a pre-specified censoring time.
Optimum test plan for products having a two-parameter Gompertz lifetime

\[ f(t) = \frac{a e^{-a t}}{b + a t} \]

is presented. The optimum criterion is to find the optimum stress level at
which the test is to be stopped. The time of failure is then the time after
which the stress level condition is met.
5.2. Mathematical Model

Notation

\( n \)  
\text{total number of test items in a PALT}

\( \eta \)  
\text{censoring time of a PALT}

\( T \)  
\text{lifetime of an item at normal use condition}

\( Y \)  
\text{total lifetime of an item in a step PALT}

\( f(t) \)  
\text{probability density function at time } t \text{ at normal use condition}

\( \beta \)  
\text{acceleration factor} (\beta > 1)

\( \tau \)  
\text{stress change-time in a step PALT} (\tau < \eta)

\( P_u \)  
\text{Probability that an item fails at normal use condition}

\( P_a \)  
\text{Probability that an item fails at accelerated use condition}

\text{GAV}  
\text{generalized asymptotic variance}

\text{MLE}  
\text{maximum likelihood estimates/estimators}

\( \theta, \alpha \)  
\text{the parameters of Gompertz distribution} (\theta > 0 \text{ and } \alpha > 0)

The probability density function of total lifetime \( Y \) of an item in a step-stress PALT is given by:

\[
f(y) = \begin{cases} 
  f_1(y) & \text{if } 0 < y \leq \tau \\
  f_2(y) & \text{if } y > \tau 
\end{cases}
\]
where

\[ f_1(y) = \theta \exp\{\alpha y - (\theta / \alpha)[\exp(\alpha y) - 1]\}, \quad \text{(5.1)} \]

\[ f_2(y) = \beta \theta \exp\{\alpha[\beta(y - \tau) + \tau] - (\theta / \alpha)[\exp(\alpha[\beta(y - \tau) - 1]\}, \quad \text{(5.2)} \]

\[ \beta > 1, \theta > 0 \text{ and } \alpha > 0. \]

The Newton-Raphson method is applied to obtain the optimal stress-change time \( \tau^* \) which minimizes the GAV. Accordingly, the corresponding optimal numbers of items failed at normal use condition and accelerated use condition can be calculated, respectively, via the following two formulas:

\[ n_{P_u} = n[1 - \exp\{-\hat{\theta}/\hat{\alpha}(e^{\hat{\alpha} \tau^*} - 1)\}], \quad \text{(5.3)} \]

and

\[ n_{P_a} = n[\exp\{-\hat{\theta}/\hat{\alpha}(e^{\hat{\alpha} \tau^*} - 1)\}[1 - \exp\{-\hat{\theta}/\hat{\alpha}(e^{\hat{\alpha} \tau^* - 1})\}]. \quad \text{(5.4)} \]

5.3. Application

5.3.1. Oligomenorrhoea

Oligomenorrhoea is defined by irregular and inconsistent menstrual cycles lasting from 36 to 90 days in length and is a menstrual presentation that is difficult to study due to the nature of its inconsistent characteristics. Figure 1 illustrates actual patterns of urinary metabolites across several menstrual cycles in a previously sedentary eumenorrhoeic subject who underwent an intervention of aerobic exercise and a reduction in dietary
intake and developed an oligomenorrheic cycle. It is important to note the relative degree of hypoestrogenism apparent in this oligomenorrheic cycle.

![Menstrual Cycle Profile during a 3-Month Energy-Delitch Imposing Diet and Exercise Intervention](image)

**Figure 5.3.1.1**

*An actual example of an oligomenorrheic cycle from a subject in a prospective study examining the effects of an exercise and diet intervention on the menstrual cycle. The subject began the study with normal length, ovulatory cycles, then exercised five times per week for three menstrual cycles and consumed a hypocaloric diet (~30% fewer calories). During the last cycle of the intervention, this subject exhibits an oligomenorrheic cycle, denoted by the extended length compared to her earlier cycles. Ovulation could not be confirmed. PGD = pregnanediol 3-glucuronide; EIG = estrone glucuronide.*
5.3.2. Anovulation

Anovulation is defined as the absence of an ovulatory event when LH and FSH secretion are low in association with reduced E$_2$ levels and the absence of luteinization [65]. Cycle length can vary in anovulatory cycles and therefore anovulation can be associated with oligomenorrhoea. Although anovulation is characterized by low E$_2$ and progesterone levels throughout the cycle, debate in the clinical forum continues regarding the specific criterion for confirming anovulation [39, 112] have reported a 16% prevalence of anovulatory cycles, i.e., where menses occurs at regular (26-32 days) intervals but without an ovulatory event, in women who exercise at recreational levels, i.e., running ~ 12-15 miles a week. McConnell [118] have reported that ovulation could not be detected in 32% of Division I athletes from a wide variety of sports who reported regular menstrual bleeding (self report of cycles 26-32 days). In all cases, a higher level of E$_2$ is present in anovulatory cycles compared to amenorrhoeic cycles such that characterization of the cycle with daily ovarian steroid assessment is likely to show more E$_2$ production in a 30 day period than an equivalent period in an amenorrhoeic athlete (AA).
5.4. Mathematical Results

E1G (ng/ml)

LH (mlU/ml)
Comparison of probability that an item fails at normal use condition 
and accelerated use condition

Pu - Probability that an item fails at normal use condition
Pa - Probability that an item fails at accelerated use condition
[i.e., oligomenorrhoea cases]
5.5. Conclusion

For the optimal design stage of the test, a new experiment with test unit to obtain the optimal value of $\tau$ based on the outputs of the stage of parameter estimation is obtained. By using this model the probability is compared for the normal and oligomenorrhoea cases [95]. The probability that an item fails in oligomenorrhoea cases is higher than the normal cases.

5.6 Detection of Exercise – Associated Menstrual Disturbances

5.6.1 Methods of Detection

Much of the data that has been collected in attempts to define menstrual status, length and regularity in athletic populations has been the product of survey, questionnaire and self – report data. The use of other techniques to assess menstrual status includes hormonal measures made in blood, urine and saliva and is discussed below. The inherent difficulties and inaccuracies ascribed to recall and self – report are well documented. Significant errors in memory distortion can occur when assessing cycle regularity or irregularity that relies on recall of menstrual cycle length. A review of the literature of large studies conducted on the distribution of menstrual cycle lengths across large groups of women of varying ages reveals a large range in what is considered ‘typical’ or ‘regular’. There is no accepted objective criterion for what constitutes regularity or irregularity.
The commonly observed interval between menstrual cycles is 26 – 30, 24 – 32 and 24 – 35 days respectively [159]. In studies of menstrual function in exercising women, the range of 26 -32 days has frequently been used to denote ‘normal menstrual cycle length’ [39]. Adoption of this range as ‘normal’ is well within the findings of many larger epidemiological studies of healthy women in non-exercise related studies, and remains consistent with many studies of female athletes in the literature. Self-reported cycle length may be useful if the shortcomings of such data are recognized, and cycles deemed to be ‘irregular’ are clearly outside commonly accepted ranges.

As a reflection of menstrual status and reproductive function, cycle length is not nearly as informative as actual endocrine measures of reproductive hormones. Even though anovulation, and inadequate luteal function have both been associated with both short ( < 21 days), and long (> 35 days) cycle lengths [159], these abnormalities can occur when cycle length remains in the ‘normal range’.

5.6.2 Amenorrhea and Oligomenorrhea:

The clinical diagnosis of primary amenorrhea or secondary amenorrhea in an athlete requires a full evaluation by a physician (Speroff
et al., 1994). Once pregnancy has been ruled out, other endocrinopathies associated with menstrual irregularity should be pursued, such as prolactin-secreting pituitary tumours, thyroid problems, polycystic ovarian syndrome, and premature ovarian failure [19, 20]. A full examination, including a pelvic and examination, and appropriate laboratory analyses are required. In a research setting, it is important to establish a thorough reproductive hormone profile for assessing $E_2$ exposure. This will require daily urine samples and measurements $E_2$ and progesterone metabolites, and LH. In an oligomenorrheic athlete, an identical approach should be pursued.

5.6.3 Luteal Phase Defects and Anovulation

Duration of luteal phase length is made by determining the interval between ovulation and menses where ovulation is assessed by the direct determination of the day of the LH surge, which is the technique of choice many laboratories. The use of basal body temperature alone to determine the day of ovulation is inferior to the documentation of an LH surge. Used alone or in combination with luteal phase length, the determination of daily progesterone levels for at least one cycle, but preferably multiple cycles, has been recommended as the ‘gold’ standard for the identification of LPD for research purposes. Other investigation have also noted considerably
variability in menstrual cycles and have recommended that at least three consecutive cycles be monitored for an accurate assessment of menstrual status. The most accurate method to detect ovulation is ultrasound observation of follicular growth and rupture, and when not possible, measurements of mid-cycle LH concentrations combined with luteal phase reproductive steroid levels [118].

5.6.4 Aetiology of Exercise – Associated Menstrual Disturbances (EAMD) in Athletes

It is believed that during times of chronic energy deficiency, a shift in metabolic fuels occurs that repartitions energy away from the costly processes of reproduction and towards the essential processes of cellular, locomotive and other life – sustaining metabolic functions. With respect to exercising women, eloquent short – term experiments by Loucks manipulating both dietary intake and energy expenditure have revealed a close correlation between energy availability and the modulation of the GnRH pulse generator [41]. Studies in AA, combined with observational studies exposing metabolic signs of energy deficiency associated with subtle menstrual disturbances such as LPD and anovulation [38], provide strong evidence that a hypometabolic state exists commensurate with EMAD. This concept is illustrated in Figure 5.6.4.1
The metabolic and reproductive hormone perturbations that have been identified to date and associated with exercise training and menstrual status, including eumenorrhoeic ovulatory cycles, luteal phase deficiency (LPD) cycles and amenorrhoea. All values are depicted by arrows signifying the magnitude of the alteration reported. The proposed relationship to menstrual status is also shown. The repeated transitions from ovulatory cycles and LPD cycles are shown. (Adapted from De Souza et al., 2003.)
This hypometabolic state includes reductions in resting metabolic rate, total T₃, leptin, insulin, glucose, and insulin -- like growth factor binding protein (IGFBP) – 3 and elevations in IGFBP – 1, ghrelin, growth hormone and cortisol. The metabolic and reproductive hormone perturbations that have been identified to date and associated with exercise training and menstrual status, including eumenorrhoeic ovulatory cycles, luteal phase deficiency (LPD) cycles and amenorrhoea. All values are depicted by arrows signifying the magnitude of the alteration reported. The proposed relationships to menstrual status is also shown. The repeated transitions from ovulatory cycles and LPD cycles are shown.