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# Comparison of different methods for predicting customized drug dosage in superovulation stage of *in-vitro* fertilization

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ABSTRACT

*In-vitro* fertilization (IVF) is one of the highly pursued assisted reproductive technologies (ARTs) worldwide. Superovulation is the most crucial stage in IVF, since it involves injection of hormones externally to stimulate development and maturation of multiple oocytes. A model for the follicular dynamics as a function of injected hormones and patient characteristics has been developed and validated in our previous studies. Using the same model as a predictive tool along with the application of optimal control principles; the optimal dose and frequency of medication customized for each patient is predicted. The objective of successful superovulation is to obtain maximum number of mature oocytes/follicles within a particular size range, which is translated into mathematical form by using concepts from normal distribution. The problem is solved by different optimal control methods like the maximum principle and discretized non-linear programming. The results from both the approaches are compared and their advantages are discussed.



## 1. Introduction

Infertility is the inability of a couple to achieve conception or to bring a pregnancy to term after a year or more of regular, unprotected intercourse. The World Health Organization (Grad, 2002) has estimated that about 8–10% couples experience some form of infertility problems. The occurrence of infertility in male and female population is almost identical. According to the statistics reported by de Melo Martin (1998) and Häggström (2010), 30–35% cases include infertility problems exclusively in males or females individually and around 10–15% cases are due to problems in both the partners while there are some unexplained causes which cannot be diagnosed by using the current methods. The rate of fertility is constantly declining in the developed nations due to advanced maternal age resulting into primary infertility in which no conception occurs at all. On the contrary, in the developing world the reasons for infertility involve prevalence of sexually transmitted diseases, infections increasing the rate of secondary infertility involving miscarriage.

Medical science has come up with many ARTs like *in-vitro* fertilization and embryo transfer (IVF-ET), intracytoplasmic sperm injection (ICSI), frozen embryo replacement (FER) and oocyte donation (OD) to treat infertility (Choi, 2011). More than 40% of infertile couples resort to IVF-ET since it is the most promising among the listed methods. It involves fertilization of oocytes by sperm outside the body in a laboratory simulating similar conditions in the body and then implanting the fertilized eggs back in the uterus of carrier mother for full term pregnancy. However, cost is a major hurdle in the access of ART services. Even in a country like United States, the cost for an IVF cycle amounts to 20% the total annual income of a median American family. In developing nations, this ratio escalates to almost 50% of the annual income (Nachtigall, 2006). Major risks involved in IVF treatment are failure to conceive, multiple pregnancies, ectopic pregnancy, ovarian hyperstimulation syndrome (Speroff and Fritz, 2005).

The success of IVF is primarily dependent on the quality of eggs retrieved from the superovulation stage. At present the treatment protocols followed by medical practitioners are the same for all patients irrespective of their specific conditions and treatment responsiveness, referred as 'blanket approach' by Fischel and Jackson (1989). They suggest an individualistic approach with more caution to avoid the risks associated with excessive stimulation which is also the focus of the current endeavor.

Previously, control methods have been applied successfully to biological systems for energy efficiency and process time

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minimization however their applications to biomedicine have been limited due to their wider implications on human life and inherent process variability (Doyle et al., 2011). The key applications of control in biomedical systems have been in cardiovascular problems and endocrinology. In recent years, optimal control has been used for predicting cancer chemotherapy (Castiglione & Piccoli, 2007) and tumor degradation. It has also been applied for drug scheduling in HIV infection treatment (Shim, Han, Chung, Nam, & Seo, 2003) and for blood glucose regulation in insulin-dependent diabetes patients (Ulas & Diwekar, 2010).

The biomedical applications of optimal control for drug dosage prediction for cancer chemotherapy and insulin injections in diabetic patients gave us the idea that we can apply optimal control for predicting hormonal dosage in superovulation too. The functional hormones (Janat-Amsbury, Gupta, Kablitz, & Peterson, 2009) which are manipulated during the IVF cycle are gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen, progesterone and human chorionic gonadotropin (hCG). Among these, FSH stimulates the ovarian cells and is required for development of mature oocytes which can be fertilized. The superovulation stage has specific protocols to be followed and affects the patient significantly since it involves the interplay of the fertility drugs and hormones on a daily basis for a time period over a month. This causes physical as well as emotional disturbances in the patient. The superovulation protocol most widely used is the 'long lupron protocol' as reported by Wong, Gillman, Oehninger, Gibbons, and Stadtmauer (2004).

In this paper, the patient specific parameter estimation method developed in Yenkie, Diwekar, and Bhalerao (2013) will be revisited which will provide the basis for the development of the patient specific control procedure based on clinical data. This shall lead to a new way in optimized treatment scheduling for medical procedures currently based on trial and error. The drug dosage scheduling problem shall be solved by two different methods. The similarities and differences in the drug dosing policies will be discussed. The crucial factors like objective function formulation, role of constraints and the advantage of each method will be discussed in detail.

## 2. Materials and methods

The material and methods is divided into five sections. Section 2.1 discusses the moment model (Yenkie et al., 2013) for superovulation briefly, Section 2.2 describes the data preparation for model fitting and optimization, Section 2.3 talks about optimal control problem formulation, Section 2.4 focuses on the first solution method of maximum principle and the last Section 2.5 discusses the second solution method of discretized non-linear programming.

### 2.1. Moment model for superovulation

The model for superovulation (Yenkie et al., 2013) is developed by deriving analogies from the particulate process of batch crystallization (Hill, Korovessi, & Linninger, 2006; Yenkie & Diwekar, 2013). The moments correspond to certain characteristics of the particles (Randolph & Larson, 1988); the 0th moment corresponds to the number, 1st to the size, 2nd to the area and so on. Similarly, the moments in superovulation will correspond to the characteristics of the follicles. The follicle growth is dependent on the FSH administered. The growth term is written as shown in Eq. (1);

$$G = k\Delta C_{FSH}^{\alpha} \tag{1}$$

here, $G$ – follicle growth term, $k$ – rate constant, $\Delta C_{FSH}$ – amount of FSH injected and $\alpha$ – rate exponent.

From the literature by Baird (1987) it can be assumed that the number of follicles activated for growth are constant for a particular protocol initiation in a specific patient. Hence the 0th moment has a constant value for that patient during the ongoing cycle. The 0th–6th order moments are used because they enable efficient recovery of the follicle size distributions as against the lower order moments (Flood, 2002). Moment equations are shown in Eqs. (2) and (3).

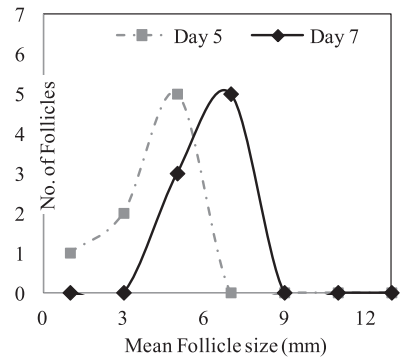


**Fig. 1.** Follicle size showing Gaussian or Normal distribution on day 5 and 7. (The discrete markers are actual follicle counts and the continuous curves are used to show the smooth distribution.)

$$\mu_0 = \text{constant} \tag{2}$$

$$\frac{d\mu_i}{dt} = iG(t)\mu_{i-1}(t); \quad (i = 1, 2, \ldots 6) \tag{3}$$

here, $G$ – follicle growth term and $\mu_i$ – $i$th moment. This model has already been fitted and validated for superovulation cycle data available for 50 patients from our collaborative hospital in India.

### 2.2. Data preparation

The model for follicular growth involves moments whereas the data is available in terms of follicle size and number. Thus it is necessary to convert it into mathematical moments. The follicles are assumed to be spherical in shape and the expression (Hu, Rohani, & Jutan, 2005) shown in Eq. (4) is used to convert the data into moments.

$$\mu_i = \sum n_i(r, t) r_i^i \Delta r_i \tag{4}$$

here, $\mu_i$ – $i$th moment, $r_j$ – mean radius of $j$th bin, $n_j(r,t)$ – number of follicles in bin '$j$' of mean radius '$r$' at time '$t$' and $\Delta r$ – range of radii variation in each bin.

### 2.3. Optimal control in superovulation

According to literature on superovulation protocols (Meniru & Craft, 1997) and the data on successful superovulation cycles, the expected size of mature follicles range from 18 to 22 mm (diameter). Thus the objective of superovulation is '*to obtain high number (maximum possible) of uniformly sized (18–22 mm) follicles on the last day of FSH administration*'. The data on superovulation cycles indicates that after the initial 4–5 days of FSH administration the follicle size and number plots tend to follow a Gaussian distribution (Fig. 1) and as the time progresses this distribution continues to follow a Gaussian form with a change in the mean value and variance.

The moment model for follicle size distribution prediction and the method for deriving normal distribution parameters have been used for deriving expressions for the mean (Eq. (5)) and coefficient of variation (Eq. (6)) for the follicle size distribution (John, Angelov, Oncul, & Thevenin, 2007).

$$\bar{x} = \frac{\mu_1}{\mu_0} \tag{5}$$