



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.

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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);

$$G = k \Delta C_{\text{FSH}}^{\alpha} \quad (1)$$

here, G – follicle growth term, k – rate constant, ΔC_{FSH} – amount of FSH injected and α – rate exponent.

From the literature by Baird (1987) it can be assumed that the number of follicles activated for growth are constant for a

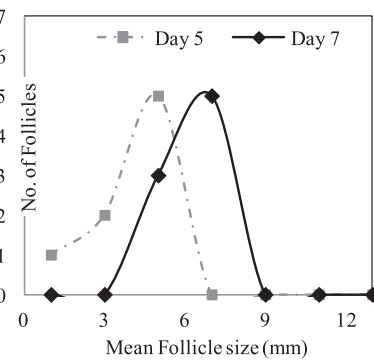


Fig. 1. Follicle size showing Gaussian or Normal distribution on day 5 and 7. (The discrete markers are actual follicle counts and the continuous curves are used to show the smooth distribution.)

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).

$$\mu_0 = \text{constant} \quad (2)$$

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

here, G – follicle growth term and μ_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.

$$\mu_i = \sum n_j(r, t) r_j^i \Delta r_j \quad (4)$$

here, μ_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 Δr – 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).

$$\bar{x} = \frac{\mu_1}{\mu_0} \quad (5)$$

$$CV = \sqrt{\frac{\mu_2\mu_0}{\mu_1^2} - 1} \tag{6}$$

here, \bar{x} – mean follicle size and CV – coefficient of variation. Thus mathematically the objective can be stated as; to minimize the coefficient of variation on the last day of FSH administration ($CV(t_f)$) by controlling the dosage of FSH ($C_{FSH}(t)$).

The optimal control problem can be solved by several methods such as calculus of variations, dynamic programming, maximum principle, and discretized nonlinear programming discussed by Diwekar (2008). The formerly mentioned methods like calculus of variation and dynamic programming involve second order differential equations or partial differential equations respectively. The maximum principle involves only first order ordinary differential equations, making it more attractive as compared to the other two; hence is one of the methods selected for this work. In nonlinear programming whole model equations are discretized into ‘n’ equal time intervals and can be computationally intensive for large problems. However, it enables the inclusion of constraints thus making it the second choice for solution for the control problem.

The model involves nine parameters k, α, μ_0 , and 6 integration constants (c_i 's, where $i = 1, \dots, 6$). Thus the initial two days of FSH administration, observation and data collection are very crucial for determining the overall treatment response. The optimal control starts on the day when the second observation of follicle counts and size along with the FSH dose is reported. In most cases it is the day when the FSH dose is altered after a constant dosing for 4–5 days. Thus by using the evaluated model parameters and moment values as the initial conditions for the Patient A along with the mathematical formulae and assumptions the optimal dosage prediction can be performed. The objective function for the control is represented by Eq. (7) where $C_{FSH}(t)$ is the control variable;

$$\underbrace{\text{Min}}_{C_{FSH}} CV(t_f) \tag{7}$$

Subject to:

- (i) Model equations listed from Yenkie et al. (2013)
- (ii) Additional equations for CV (C_v) (Eq. (8)) and mean (\bar{x}) (Eq. (9)) are added.

$$\frac{dC_v}{dt} = \frac{G\mu_0}{C_v\mu_1} \left\{ 1 - \frac{\mu_0\mu_2}{\mu_1^2} \right\} \tag{8}$$

$$\frac{d\bar{x}}{dt} = G \tag{9}$$

- (iii) The mean size of the follicles must not exceed 22 mm in diameter and the spherical follicle assumption leads to the constraint $\bar{x} \leq 11$.

2.4. Solution by maximum principle

The control problem has a total of nine state variables, and hence nine state equations. For simplicity of notations ‘ y_i ’ is used to denote the i th state variable (see Eq. (11)). The solution method chosen is the Pontryagin’s maximum principle which requires introduction of an adjoint variable (z_i) corresponding to each state variable and hence nine adjoint variables are introduced resulting in nine additional equations (see Eq. (12)). The objective function is then converted to another form called as Hamiltonian (Eq. (13)). The optimality condition for the problem is given by Eq. (14).

$$\text{Max}_{C_{FSH}(t)} \{-y_8(t_f)\} \tag{10}$$

$$\frac{dy_i}{dt} = f(y_i, t, C_{FSH}) \tag{11}$$

Table 1
Data in terms of variation in follicle size (diameter – mm) with time and FSH dose (IU – international units) for Patient A.

Time	No. of follicles			
	Day 1	Day 6	Day 8	Day 10
Size bins (mm)				
0–4	0	0	0	0
4–8	5	2	2	2
8–12	3	5	3	2
12–16	0	1	3	3
16–20	0	0	0	1
20–24	0	0	0	0
FSH dose (IU/ml)	150	300	450	450

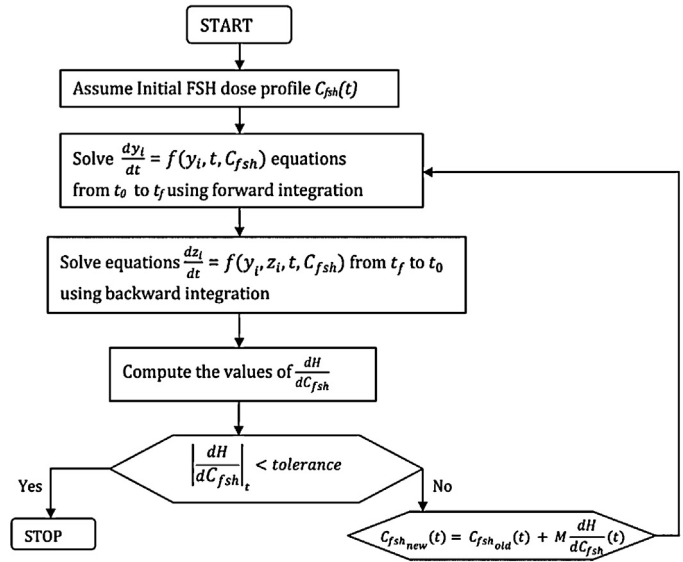


Fig. 2. Flowchart for optimal FSH dosage evaluation using maximum principle.

$$\frac{dz_i}{dt} = \sum_{j=1}^9 z_j \frac{\partial f(y_i, t, C_{FSH})}{\partial y_i} = f(y_i, z_i, t, C_{FSH}) \tag{12}$$

$$H = \sum_{i=1}^9 z_i f(y_i, t, C_{FSH}) \tag{13}$$

$$\left. \frac{dH}{dC_{FSH}} \right|_t = 0 \tag{14}$$

In maximum principle initial values are available for the state variables whereas final values are known for the adjoint variables. This results in a two point boundary value problem. Table 4 shows the input values for Patient A for applying maximum principle. The system of Eqs. (11) and (12) are solved stepwise by using an iterative solution procedure (Fig. 2) called steepest ascent of Hamiltonian (Diwekar, 2008). Maximum principle cannot handle constraints on the state variables. In order to include the complete problem since with patients having higher growth term value can go beyond the desired size range of 9–12 mm, we need to include the constraints.

2.5. Non-linear programming optimization method

In NLP optimization, the discretized dosage amounts of FSH on each day of the cycle are the decision variables. We consider the integrated moment equation model (Eqs. (15)–(20)) and additional equations for mean follicle size (Eq. (5)) and coefficient of variation (Eq. (6)). The optimization problem is the same as stated in Eq. (7).

Subject to the integrated form of the model equations and bounds on the mean size and follicle number in follicle size bins higher than 12.

$$\mu_1 = G\mu_0t + c_1 \tag{15}$$

$$\mu_2 = G^2\mu_0t^2 + 2Gc_1t + c_2 \tag{16}$$

$$\mu_3 = G^3\mu_0t^3 + 3G^2c_1t^2 + 3Gc_2t + c_3 \tag{17}$$

$$\mu_4 = G^4\mu_0t^4 + 4G^3c_1t^3 + 6G^2c_2t^2 + 4Gc_3t + c_4 \tag{18}$$

$$\mu_5 = G^5\mu_0t^5 + 5G^4c_1t^4 + 10G^3c_2t^3 + 10G^2c_3t^2 + 5Gc_4t + c_5 \tag{19}$$

$$\mu_6 = G^6\mu_0t^6 + 6G^5c_1t^5 + 15G^4c_2t^4 + 20G^3c_3t^3 + 15G^2c_4t^2 + 6Gc_5t + c_6 \tag{20}$$

here, μ_i – i th moment, G – follicle growth term and c_i – integration constants. The bounds on the follicle size can be imposed by using formulae of normal distribution. The moment values can be converted to follicle size distribution by the probability density distribution (PDF) function for Gaussian (Eq. (21)). The follicles are assumed to lie within the range of 1–15 mm (radius). Thus, 15 size bins are assumed when evaluating the size distribution.

$$f(r) = \frac{1}{\sigma\sqrt{2\pi}} e^{-((r-\bar{x})^2/2\sigma^2)} \tag{21}$$

here, r – the value of the follicle radius in each of the size bins (1–15); σ – the standard deviation given by $\bar{x}.C_v$.

The actual number of follicles in each of the size bins can be obtained from Eq. (22).

$$fol.num(jth\ bin, \ time) = f(r, t) \times \left(\frac{\mu_0}{2}\right) \tag{22}$$

Thus, the constraints included in the problem are

$$\bar{x}(t) \leq 11 \tag{23}$$

$$fol.num\{r \in (12, 13, 14, 15), t\} \leq 0 \tag{24}$$

The NLP optimization problem is solved in *Matlab* using the constrained optimization algorithm ‘*fmincon*’. These results are then compared with the maximum principle outcomes.

3. Calculations

The patient data is available in the form of follicle size and number as shown in Table 1 for Patient A. This is converted into the moment form using Eq. (4) and is shown in Table 2. The moment

Table 2
Experimental moments evaluated for Patient A.

Time	Moment values			
	Day 1	Day 6	Day 8	Day 10
Moments				
μ_0	16	16	16	16
μ_1	60	76	84	92
μ_2	240	384	480	592
μ_3	1020	2044	2916	4124
μ_4	4560	11,376	18,480	30,352
μ_5	21,180	65,836	120,564	232,412
μ_6	101,040	394,464	802,560	1,834,192
FSH dose	150	300	450	450

Table 3
The inversion matrix A (6 × 6) to recover size distribution from moment values.

A=	2	6	10	14	18	22
	2	18	50	98	162	242
	2	54	250	686	1458	2662
	2	162	1250	4802	13,122	29,282
	2	486	6250	33,614	118,098	322,102
	2	1458	31,250	235,298	1,062,882	3,543,122

data in Table 2 is used for model fitting, validation and dosage prediction by both the optimal control methods. The model has nine parameters to be estimated and hence initial two day observations are sufficient in evaluating the patient specific parameter values. The model projection results on successive days of FSH administration is in the form of moments which are required to be converted into follicle size distribution. The conversion method is adapted from literature by Flood (2002) and is discussed in detail as the follicle number prediction algorithm in Yenkie et al. (2013). The method suggested is represented in Eq. (25)

$$\mu = A \times n \tag{25}$$

here, n – number of follicles in n bins at i th day, μ – moments for i th day and A – inversion matrix derived from Eq. (4). The inversion matrix A (6 × 6) to recover size distribution from moment values is shown in Table 3. The elements in matrix A are evaluated using the formula shown in Eq. (26).

$$a_{i,j} = \bar{r}_j^i \Delta r_j \tag{26}$$

here, i – order of the moment (increment in rows), j – representative bin (increment in columns), \bar{r} – mean radius of the bin and Δr – range of the bin.

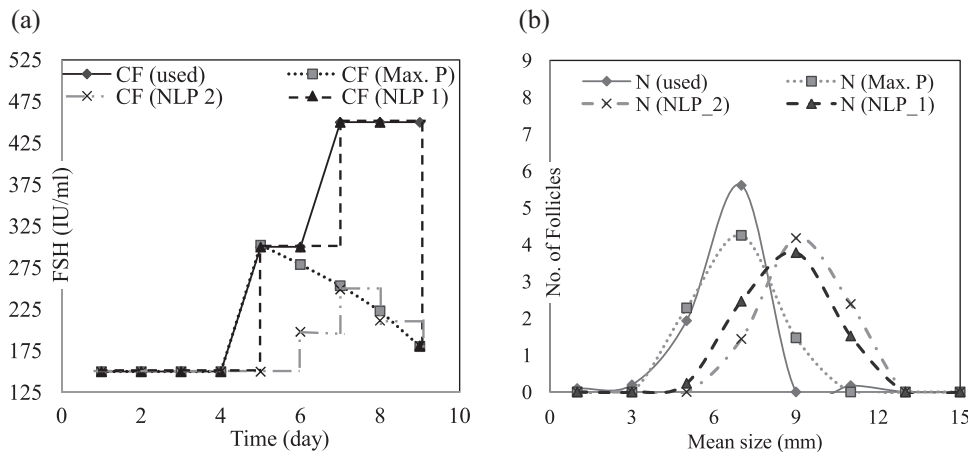


Fig. 3. (a) Comparison of optimal FSH dose profiles for Patient-A. (Max. P – denotes the optimal profile for maximum principle, NLP 1 and 2 denote the optimal profiles for different initial guesses used while solving the problem). (b) Comparison of follicle size distributions on final FSH administration day for Patient-A. (N(used) – denotes the FSD from superovulation data, N(Max. P) – denotes the FSD from maximum principle, N(NLP 1) and N(NLP 2) denote FSDs from different optimal NLP profiles).

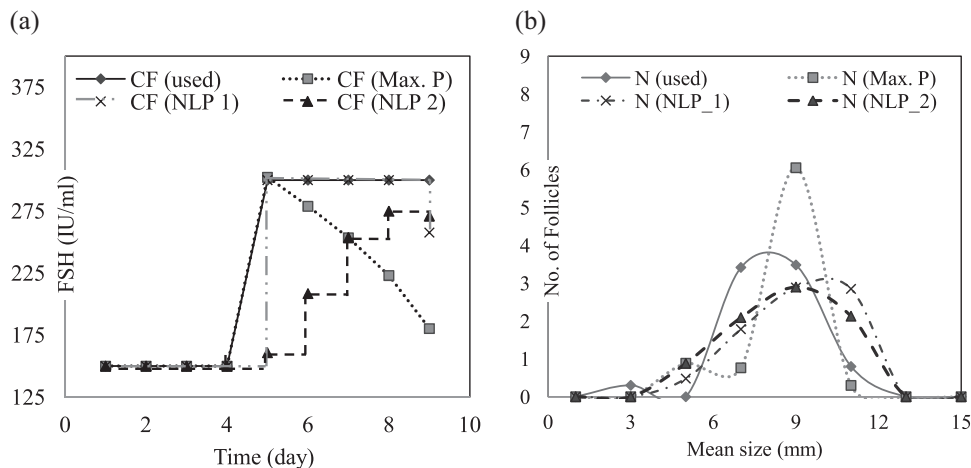


Fig. 4. (a) Comparison of optimal FSH dose profiles for Patient-B. (b) Comparison of follicle size distributions on final FSH administration day for Patient-B.

Table 4
Input data for Patient A.

Case I: Patient A			
Parameter	Value		
k	1.535	t_0	6
α	-0.216	t_f	10
State variable	Initial value (t_0)	Adjoint variable	Final value (t_f)
$\mu_0 (y_1)$	16	z_1	0
$\mu_1 (y_2)$	76	z_2	0
$\mu_2 (y_3)$	384	z_3	0
$\mu_3 (y_4)$	2044	z_4	0
$\mu_4 (y_5)$	11,376	z_5	0
$\mu_5 (y_6)$	65,836	z_6	0
$\mu_6 (y_7)$	394,464	z_7	0
$CV (y_8)$	0.252	z_8	-1
Mean (y_9)	4.75	z_9	0

Both the optimal control procedures yields the optimal dosage regime of FSH for successful superovulation procedure for the specific patient under consideration. The predicted results are in the form of the amounts of FSH to be given to the patient on each day of the cycle. However in order to verify whether the predicted dose gives a better outcome in terms of the final day follicle count or oocytes and their size it is essential to get the results in terms of a follicle size distribution. The FSH dose along with the model parameters for the specific patient are known, so if they are plugged in the integrated form of the model equations for the superovulation

stage the moment values can be evaluated. Once again the follicle number prediction algorithm is used to find the number and size of the follicles from the moments. The follicle size distribution for the final FSH day predicted using the optimal FSH is compared against the final day follicle size distribution observed under the FSH dose actually given to the patient under study for comparison.

4. Results and discussions

The optimal control performed by using the non-linear programming (NLP) method is compared against the maximum principle (Max. P) results. The solutions obtained for Patient A are shown in Fig. 3a and b. While performing the NLP-1 optimization the initial guess is the 'actual FSH' used for the patient. In NLP-2 optimization the initial guess is a constant value of '150 IU/ml' for all the successive days. From the two profiles it is obvious that the system has multiple solutions. Table 5 summarizes the results for Patient A in terms of percentage savings in the FSH requirement and follicle count within the desired size range.

Similar control methods were applied to four more patients B, C, D and E. The results for Patient B are presented in Fig. 4a and b, Patient C in Fig. 5a and b, Patient D in Fig. 6a and b and Patient E in Fig. 7a and b. Table 6 summarizes the results for the other four patients B, C, D and E. The results obtained indicate an increase in the follicle count in the desired size range with both the optimal control methods. In most of the cases we see a reduction in

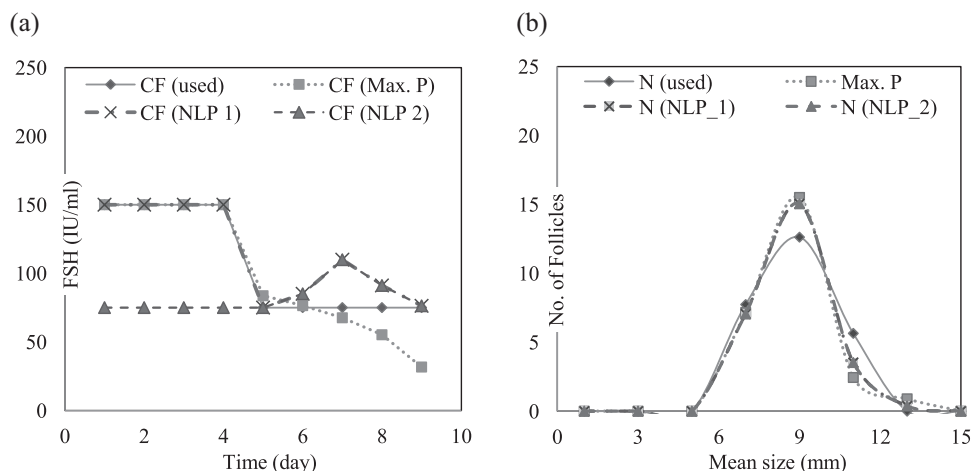


Fig. 5. (a) Comparison of optimal FSH dose profiles for Patient-C. (b) Comparison of follicle size distributions on final FSH administration day for Patient-C.

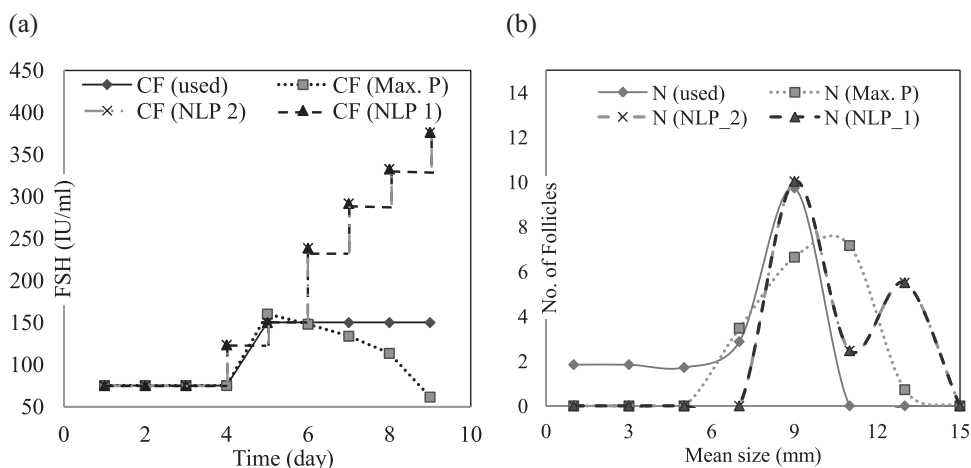


Fig. 6. (a) Comparison of optimal FSH dose profiles for Patient-D. (b) Comparison of follicle size distributions on final FSH administration day for Patient-D.

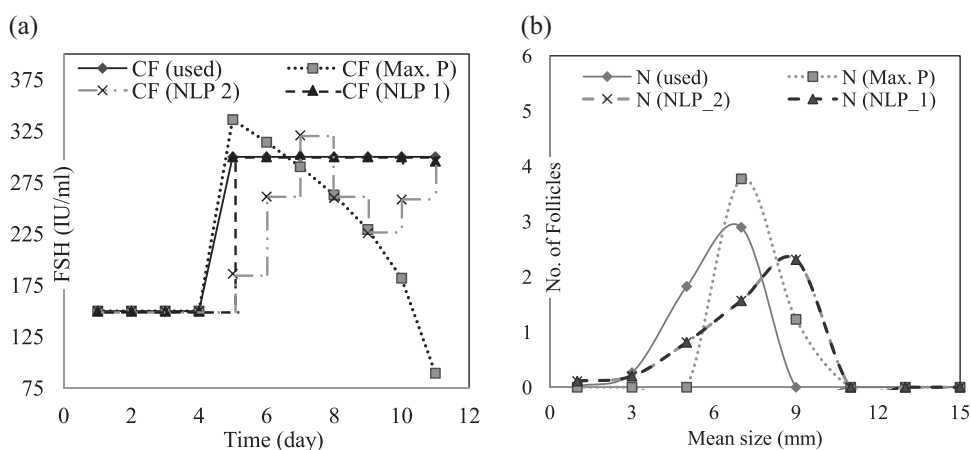


Fig. 7. (a) Comparison of optimal FSH dose profiles for Patient-E. (b) Comparison of follicle size distributions on final FSH administration day for Patient-E.

Table 5
Result summary for Patient A (No. of growing follicles – 8).

Dosage	Cumulative FSH (IU/ml)	Follicles ($9 \leq \text{mean} \leq 11$)	Number ($9 \leq \text{mean} \leq 11$)	% Reduction in FSH
FSH (used)	2550	N (used)	0	N.A.
FSH (Max. P)	1837.91	N (Max. P)	2	38.74
FSH (NLP-1)	1589.44	N (NLP-1)	6	60.43
FSH (NLP-2)	2281.09	N (NLP-2)	6	11.79

Table 6
Result summary for Patients B, C, D and E.

Patient (no. of growing follicles)	Dosage of 'FSH'	Cumulative FSH (IU/ml)	Follicles ($9 \leq \text{mean} \leq 11$) 'N'	Number ($9 \leq \text{mean} \leq 11$)	% Reduction in FSH
B (8)	Used	2100	Used	4	N.A.
	Max. P	1837.91	Max. P	6	14.26
	NLP-1	2057.74	NLP-1	6	2.05
	NLP-2	1768.89	NLP-2	5	18.71
C (26)	Used	975	Used	17	N.A.
	Max. P	914.52	Max. P	18	6.61
	NLP-1	737.45	NLP-1	18	32.21
	NLP-2	1037.45	NLP-2	18	-6.01
D (18)	Used	1050	Used	10	N.A.
	Max. P	916.81	Max. P	13	14.53
	NLP-1	1737.69	NLP-1	17	-39.57
	NLP-2	1737.69	NLP-2	17	-39.57
E (5)	Used	2700	Used	0	N.A.
	Max. P	2304.69	Max. P	1	17.15
	NLP-1	2408.74	NLP-1	2	12.09
	NLP-2	2698.15	NLP-2	2	0.0684

FSH requirement however, in case of Patient C and D we do see an increase in the FSH requirement in the discretized NLP method. In both of the increased FSH cases we observe a higher follicle count in the desired size range (in Patient D the follicle number increase from 10 to 17), which indicates that in some patients the increase in FSH dose could also lead to better outcomes.

Optimal profiles are dependent on initial guess in case of NLP. However, it should be noted that NLP allowed imposition of explicit bounds on the maximum follicle size, whereas, maximum principle did not. Thus in specific patients with a large growth term there is a probability of exceeding the desired follicle size range and hence the NLP method with constraints will be a better choice for deciding the dosage policy.

In biological systems, variability and uncertainty are inherent characteristics of the process. To get a better dosing policy which shall take into account the possible variability, it is essential to develop a stochastic model. The stochastic model will require control methods which can handle uncertainty. The existing work on stochastic maximum principle by Rico-Ramirez and Diwekar (2004) can provide robust solutions under uncertainty. Hence, the maximum principle strategy will prove advantageous in face of uncertainty.

5. Conclusions

The optimal control theory application to superovulation stage provides a new approach for model predictive drug delivery in IVF. The mathematical formulation of the objective function in terms of the coefficient of variation by utilizing the concepts of normal distribution provides a reasonably good measure of the final outcome. The method of maximum principle uses a well-defined strategy and the optimal dosage regime predicted for the patients increase the follicle count in the desired size range. The use of discretized non-linear programming optimization method provides the various possible drug dosage combinations which can lead to increased follicle counts in the desired size range. Predetermined dosage will save the cost of excess medicines and also the requirements of daily monitoring and testing. It will enhance the success rate of superovulation cycles by acting as a guideline to medical practitioners for patient specific protocol variations. Another important aspect of the current work is that; it has been done in collaboration with clinicians by using real patient data, making the study more emphatic when compared to theoretical work.

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