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Personalized medicine for in vitro fertilization procedure using modeling and optimal control

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ABSTRACT

In vitro fertilization (IVF) is the most common technique in assisted reproductive technology and in most cases the last resort for infertility treatment. It has four basic stages: superovulation, egg retrieval, fertilization, and embryo transfer. Superovulation is a drug-induced method to enable multiple ovulation per menstrual cycle and key component towards a successful IVF cycle. Although there are the general guidelines for dosage, the dose is not optimized for each patient, and complications, such as overstimulation, can occur. To overcome the shortcomings of this general system, a mathematical procedure is developed which can provide a customized model of this stage regarding the size distribution of eggs (follicles/ oocytes) obtained per cycle as a function of the chemical interactions of the drugs used and the conditions imposed on the patient during the cycle, which provide a basis for predicting the possible outcome. Uncertainty and risk are modeled and included in optimal drug dosage decisions. This paper describes the theory, model, and the optimal control procedure for improving outcomes of IVF treatment for one of the four protocols used in real practice. The validation of the procedure is performed using clinical data from the patients previously undergone IVF cycles. Customized patient-specific model parameters are obtained by using initial two-day data for each patient. Subsequently, this model is used to predict the FSD for the remaining days of the cycle. This procedure was conducted for 49 patients. The results of the customized models are found to be closely matching with the observed FSD. These results thus validate the modeling approach and consequently its use for predicting the customized optimal drug dosage for each patient. Using the customized model and the optimized dosage, the FSD at the end of the cycle was determined. A small double-blind clinical trial was also conducted in India. The results from the trial show that the dosage predicted by using the model is 40% less than the suggestion made by the IVF clinicians. The testing and monitoring requirements for patients using optimized drug dosage is reduced by 72%. Work on the other three protocols and for patients in the USA is started and is showing promising results.

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1. Introduction

A survey conducted by the World Health Organization (WHO) in 2010 using data from 190 countries over a period of 20 years found that around 2% women suffer from primary infertility and 10% women suffer from secondary infertility. Primary infertility is the inability to conceive a first live birth and secondary infertility is the inability to conceive after a prior live birth. Certain regions of Eastern Europe, North Africa, Middle East, Oceania and Sub Saharan Africa showed greater prevalence of infertility (Mascarenhas et al., 2012). In the United States itself, data collected by the Center for Disease Control (CDC) over a 4-year span showed 6.7% of married women to be suffering from infertility (NCHS, 2016).

In vitro Fertilization process is one of the most commonly recommended treatments in Assisted Reproductive Technologies (ART). 1.7% of infants were born through ART in the United States in 2015 (Sunderam et al., 2018). *In vitro* fertilization (IVF) is a process by which oocytes or egg cells are fertilized by a sperm outside the body in a laboratory simulating similar conditions in the body, and then the fertilized eggs or embryos are implanted back in the uterus for a full-term pregnancy. It has four basic stages (Fritz and Speroff, 2010): superovulation, egg retrieval, insemination/ fertilization and embryo transfer and are shown in Fig. 1.

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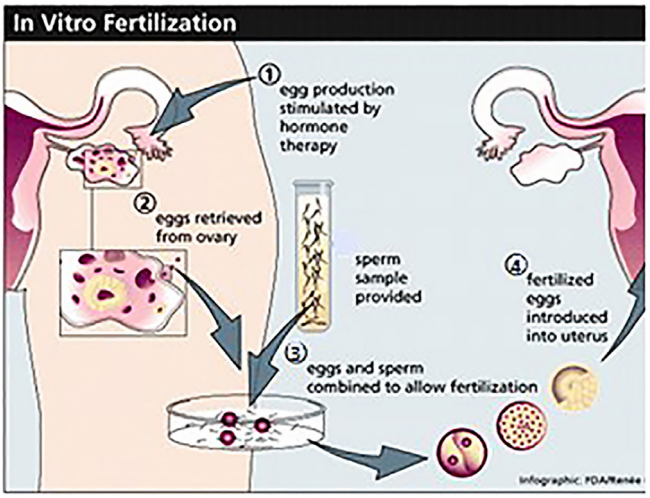

Fig. 1. Schematic Diagram of *In vitro* Fertilization procedure (Gordon, 2011).

IVF is an expensive treatment, and the out-of-pocket costs per cycle tend to be around $10,000-$15,000. This cost varies and increases with multiple factors such as unsuccessful IVF cycles, multiple births, low birth weight infants and preterm births occurring from IVF cycles (Sunderam et al., 2018). The cost of IVF depends upon the cost of superovulation. Currently, this step is executed using almost daily monitoring of the follicular development using ultrasound and blood test. The daily dosage of hormones is customized for each patient based on these tests. Conventionally doses are prescribed based on empirical data instead of randomized control trials and start at 150 or 225 IU. Devroey and team employed initial low dose FSH (Follicle Stimulating Hormone) (100 IU) on a relatively young age group and recorded a high number of retrieved oocytes (Devroey et al., 1998). Prescribed minimum dosages start from 150 to 300 IU for younger patients and reach the absolute maximum at 450 IU for poor responders (Jungheim et al., 2015; Rombauts, 2007; Dorn, 2005). Certain factors which come into play when choosing an FSH dose for a patient are usually female age, anamnesis, clinical criteria and ovarian markers such as AFC (Antral Follicle Count) and AMH (Anti-Mullerian Hormone) (La Marca and Sunkara, 2013). FSH starting dose based on AFC was found to be less than 225IU for most patients under the age of 35 years (La Marca et al., 2013). Although there are general guidelines for the dosage limits, the dose is not optimized for each patient. IVF procedure can have side-effects such as the Ovarian Hyper Stimulation Syndrome (OHSS) (Alper et al., 2009), and the remedial actions are still unidentified. Around 1–2% of women undergoing IVF suffer from a serious case of OHSS (Klemetti et al., 2005). Patients suffering from Polycystic Ovarian Syndrome (PCOS) are found to be the ones most susceptible to OHSS. However, many patients who do not suffer from PCOS may also develop OHSS after stimulation. Protocols based on factors like age, AMH, AFC, FSH, BMI (Body Mass Index) levels and smoking history predict optimal protocols with highest follicle yield and reduced occurrence of OHSS (Yovich et al., 2016).

Models predicting the outcome of the IVF cycle have been developed based on parameters such as- patient characteristics, historical *in vitro* fertilization cycle data, embryo morphology or biomarkers during culture to create a cost-effective customized treatment strategy. Post-treatment predictors included number of eggs collected, cryopreservation of embryos and embryonic stage when transferred (Simopoulou et al., 2018). Another branch of personalized treatment for IVF used the âĕnomogramâg as a mathematical tool to predict the ovarian response and starting FSH dose based on predictors such as age, FSH, AMH and AFC (Allegra et al., 2017; Di Paola et al., 2018; La Marca et al., 2013; Moon et al., 2016; Papaleo et al., 2016).Response variability based on FSH, LH/FSH ratio, AMH (Anti-Mullerian Hormone), BMI (Body Mass Index), AFC and age demonstrate the complexity and diversity in biological and clinical features of each patient. Biological diversity in patients adds uncertainty to the estimation of IVF outcomes, thus indicating the need for customized patient-specific and cycle-specific predictive models (Simopoulou et al., 2018). However, all the existing protocols are based on patient history, testing and monitoring, and professional judgment of the physician. The complications such as overstimulation or unsuccessful superovulation do occur. The cost associated with patient monitoring and testing as well as the hormonal drugs make the superovulation stage very expensive. The evidence is building in support of personalized IVF treatment and tools that can suggest optimal patient-specific drug dosage profiles to reduce hyperstimulation, cost of treatment, improve the oocyte quality and quantity to increase the overall success rate of IVF, resulting in successful pregnancies and live-birth.

The work presented here is a continuation of the mathematical modeling and computerized algorithm to generate customized hormonal dosing for enhanced superovulation as proposed by Yenkie et al. (2013), Yenkie and Diwekar (2014). Yenkie et al., 2013 presented model equations. However, they integrated the differential equations analytically using the same dose from time zero to the specified time. This resulted in a discrete model for each integration time they were comparing the error between model and actual data. Therefore, their estimated parameters did not represent the solution of the continuous differential equations and they could not identify the patient dependent and patient independent parameters of the model. In this work, we have used the continuous differential equation model for IVF cycle where the dosage can be different for each time step. The model dependent and independent parameters are identified. This is also consistent with the proposed optimal control strategy. There are four commonly used protocols for IVF. The four protocols (Scoccia, 2017) are (1) Long Lupron agonist Protocol, (2) Microflare agonist protocol, (3) Four stop Lupron agonist Protocol, and (4) Flexible GnRH antagonist (Ganerelix or Cetrorelix) Protocol. The approach is presented for the first of the four protocols at this stage. The validation of the procedure is carried out using clinical data from patients who have previously undergone IVF cycles. Initial two-day data for each patient is used to obtain parameters of the model for that patient. The model is used then to predict follicle size distribution (FSD) for the remaining days of the cycle. This procedure was conducted for 49 patients. The results of the customized models are found to be closely matching with the observed FSD on the successive days of the IVF superovulation cycle. This customized model is then used to optimize the dosage for this patient. Using the model and the optimized dosage, the FSD at the end of the cycle was determined. A small clinical trial was also conducted in India. This was a double-blinded trial. The results show that the dosage predicted by using the model is 40% less than that suggested by the IVF clinicians. It also shows that the number of mature follicles obtained at the end of the cycle using the dosage predicted by the model is significantly higher than that of physician suggested dosage. These results were consistent with all patients in this clinical trial. The testing requirements for these patients with optimized drug dosage is also reduced by 72%.

The next section presents the modeling and optimal control methodology, followed by results and discussions section. Section 4 presents the summary and future work.

2. Methodology

In the earlier work, a model for superovulation was developed based on principles of batch crystallization. The method of

moments was used for representing the follicle growth and number prediction model (Yenkie et al., 2013). This section presents the model briefly below, followed by the optimal control strategy.

2.1. Mathematical modeling of in vitro fertilization

Superovulation is the first stage in IVF where external hormonal injections cause multiple follicles to enter the growth phase and increase in size. The number of follicles activated for growth remains constant for a particular patient (Baird, 1987). The superovulation stage of IVF is markedly similar to the particulate process of batch crystallization (Hill, 2005; Yenkie and Diwekar, 2012). The moment model discussed here was developed on the basis that properties of a particulate system can be represented by moments of its particle size distribution, concepts of batch crystallization and resemblance of superovulation to growth of seeded batch crystals (Hill, 2005; Hu et al., 2005; Yenkie et al., 2013; Randolph, 2012). The moments are calculated using the baseline data for each patient and using the general expression in (1).

$$\mu_i = \sum n_j(r,t) r_j^i \Delta r_j \tag{1}$$

Where μ_i is the ith moment, $n_j(r, t)$ is the number of follicles in bin 'j' of mean radius 'r' at time 't',r_j^i is the mean radius of jth bin and Δr_j is the range of follicle radii in each bin. The model for predicting follicle size and distribution utilizes follicle growth rate and moment equations. It is assumed that the follicle growth rate (G)) is directly dependent on the dose of FSH administered (ΔC_{fsh}) as shown in (2). Here, k and α are the rate constant and the rate exponent respectively.

$$G(t) = k\Delta C_{fsh(t)}^{\alpha} \tag{2}$$

The moment equations for calculating moments from the zeroth moment up to the 6th order were derived from the general expressions in (3) and (4). It can be seen from (4) that the $(n+1)$th moment is dependent on the nth moment.

$$\mu_0 = constant \tag{3}$$

$$\frac{d\mu_i}{dt} = iG(t)\mu_{i-1}(t);\ (i = 1, 2, \ldots 6) \tag{4}$$

In *in vitro* fertilization process, the measurements for follicle size and growth are conducted on different cycle days to observe sufficient growth. While there is only 1 measurement, the follicles are grouped by size in 6 bins ranging from 0 to 24 mm in diameter. Thus, six moment values can be obtained per day and 2-day data can be used to obtain the values of the 3 parameters. The values for parameters μ_0, k and α for the model are calculated by fitting the results from Eqs. (1) to (4) to the moment data at different times in the cycle. The moment values predicted by Eqs. (2) to (4) are converted to follicle size distribution (FSD) to validate the output. The follicle distribution was approached by using an inversion matrix (A) combined with non-linear optimization techniques as shown in Eqs. (5) and (6) (Flood, 2002; Yenkie et al., 2013).

$$\mu = An \tag{5}$$

$$n = A^{-1}\mu \tag{6}$$

Where, n - vector of number of follicles in all size bins for the ith cycle day, μ - moment vector for ith cycle day and **A** - inversion matrix of size 6x6. The inversion matrix is shown in Table 1 below.

In the clinical (experimental) settings, initial dosage for the patient is determined by the physician based on various patient factors. For the first 4 days of the cycle, same dose is continued. After the 4th day, blood testing and ultrasound tests are used to determine dose for each day. The validity of the model was evaluated by comparing the follicle size distribution as predicted by the model from 5th day on with that of the experimental data.

Table 1
Inversion matrix **A**.

A					
2	6	10	14	18	22
2	18	50	98	162	242
2	54	250	686	1458	2662
2	162	1250	4802	13122	29282
2	486	6250	33614	118098	322102
2	1458	31250	235298	1062882	3543122

2.2. Optimal control

Optimal control method evaluates the time-varying values of control variables which aid in achieving the desired outcome. The variable to be optimized in an optimal control problem is a time varying vector which makes optimal control method apt for predicting customized dosages over time. Some applications of optimal control in biomedical field include- predicting cancer chemotherapy and tumor degradation (Castiglione and Piccoli, 2007; Czakó et al., 2017), drug scheduling in HIV infection treatment (Khalili and Armaou, 2008) and blood glucose regulation in insulin-dependent diabetes patients (Acikgoz and Diwekar, 2010). Of the various methods for solving optimal control problems such as calculus of variations, dynamic programming, maximum principle, and nonlinear programming; the maximum principle method is applied here (Diwekar, 2008). The maximum principle method solution is obtained through solving first order ordinary differential equations thus making the process easier as compared to other methods. The control variable is the value of hormonal doses per day of the IVF cycle. The objective of superovulation is to obtain a high number (maximum possible) of uniformly sized (18–22 mm diameter) follicles on the last day of FSH administration.

2.2.1. Mathematical formulation

After initial 4–5 days of treatment with FSH, the follicle size and number plots follow Gaussian/ Normal distribution and this trend continues with a shift in mean and variance. Also, The available patient data reflected a normal distribution and thus it was assumed as an apriori distribution for follicles. Thus normal distribution is used to define objective function in terms of moments. The moment model for FSD prediction as discussed above and the method for deriving normal distribution parameters are used as the basis for deriving expressions for the mean and coefficient of variation.The coefficient of variation and mean of the normal distribution expressed in terms of moments are derived using the method presented by John et al. (2007). The mean ($\bar{x}$) and coefficient of variation (CV) for the normal distribution of follicle size expressed in terms of moments are shown in Eqs. (7) and (8).

$$\bar{x} = \frac{\mu_1}{\mu_0} \tag{7}$$

$$CV = \sqrt{\frac{\mu_2\mu_0}{\mu_1^2} - 1} \tag{8}$$

Superovulation involves obtaining similar sized follicles on the last day of the cycle. Thus, the objective of superovulation in mathematical form can be; to minimize the coefficient of variation on last day of FSH administration ($CV(t_f)$) where the control variable is the dosage of FSH with time ($C_{fsh}(t)$). To customize the model for each patient, the parameters are evaluated using the initial two-day observations of the follicle size and counts along with the FSH administered. The optimal dosage prediction for the desired superovulation outcome is represented as Eq. (9). The objective

function is subject to the follicle growth term and moment model constraint, equation for the coefficient of variation in terms of moments and mean as presented in Eqs. (10) and (11) and the constraint on mean follicle size ($\bar{x}$) to not exceed beyond 22 mm diameter.

$$\min_{C_{fsh}} CV(t_f) \tag{9}$$

s.t.

$$\frac{dCV}{dt} = \frac{G\mu_0}{CV\mu_1}\left[1 - \frac{\mu_2\mu_0}{\mu_1^2}\right] \tag{10}$$

$$\frac{d\bar{x}}{dt} = G \tag{11}$$

2.2.2. Maximum principle method

The optimal control problem presented here has 9 state variables with 9 state equations. In the maximum principle method of optimal control, one adjoint variable corresponding to one state variable is introduced resulting in 9 adjoint variables with 9 adjoint equations. The *i*th state variable is denoted as $'y_i'$ and the 9 state variables are shown in Eq. (12). The *i*th adjoint variable is denoted as $'z_i'$. Then the objective is converted to the Hamiltonian form(H), which on expansion involves both state and adjoint variables. These expressions are shown in Eqs. (13) to (16). The optimality condition for this problem and tolerance level for the derivative of Hamiltonian with respect to control variable is expressed in Eq. (17).

$$y_i = [\mu_0, \mu_1, \mu_2, \mu_3, \mu_4, \mu_5, \mu_6, CV, \bar{x}] \tag{12}$$

$$Max_{C_{fsh(t)}}[-y_8(t_f)] \tag{13}$$

$$\frac{dy_i}{dt} = f(y_i, t, C_{fsh}) \tag{14}$$

$$\frac{dz_i}{dt} = \sum_{j=1}^{9} z_i \frac{\delta f(y_i, t, C_{fsh})}{\delta y_i} = f(y_i, t, C_{fsh}) \tag{15}$$

$$H = \sum_{j=1}^{9} z_i f(y_i, t, C_{fsh}) \tag{16}$$

$$\left|\frac{dH}{dC_{fsh}}\right| = 0 \tag{17}$$

Table 2
Tabular representation of Number of Follicles observed and the prescribed dosages on different cycle days for a patient.

Number of Follicles						
Day bins/day	1	5	7	9	10	11
0-4	1	0	0	0	0	0
4-8	3	1	0	0	0	0
8-12	4	6	2	0	0	0
12-16	0	1	6	7	5	2
16-20	0	0	0	1	3	4
20-24	0	0	0	0	0	2
Cfsh (IU)	150	150	150	150	150	150

These set of equations are solved stepwise. The state equations are integrated in forward direction from starting time t_0 till the end of the cycle t_f and the adjoint equations are integrated backwards. It is also checked that the optimality condition is satisfied at each time.

The model presented in here is applied for the data available for 49 patients from Jijamata Hospital, Nanded, India. The data included details like prescribed dose profile, follicle measurements on different cycle days, patient age, previous infertility or pregnancy for Indian women. However, the initial prescribed dose, follicle measurements and cycle time were the only inputs to the model. An example of utilized input data for a Patient is presented in Table 2.

3. Results & discussion

The results for fit of the mathematical model against available data, results from parameter estimation, optimal control and the results from clinical trial are presented and discussed in this section.

3.0.1. Model validation

The mathematical model described in Section 2.1 uses the data collected on the first and fifth day to calibrate the model. However, the model fit using all day data is going to be much better. Fig. 2 shows the FSD for various days observed in real practice (denoted as experimental values (E)) compared to the model predictions (denoted as (M)) considering data from considering all day data (Fig. 2.a) and considering only the two-day data (Fig. 2.b) for patient 1. Similarly, the results are presented for patient 2 in Fig. 3.a and 3.b respectively. This shows that the model performs very well for these two patients irrespective of two-day or all-day

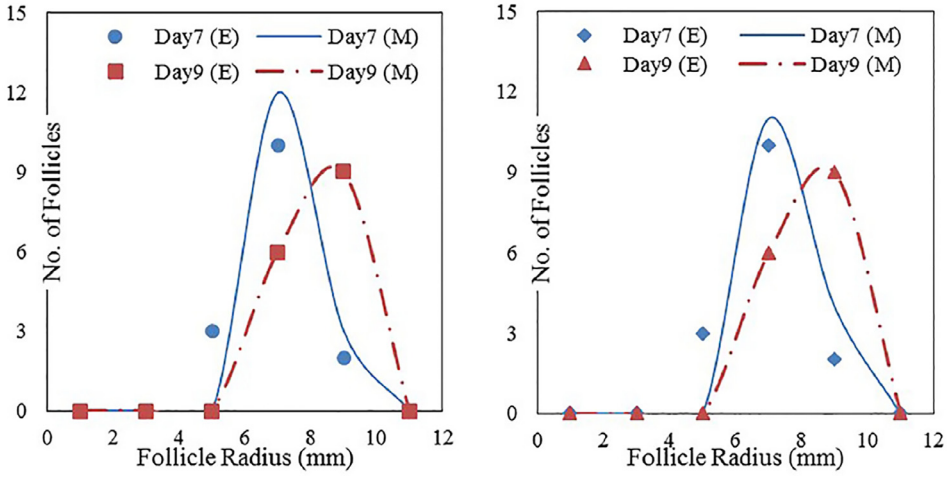

Fig. 2. Comparison of Observed (E) Follicular Distribution with the Follicle Size Distribution Predicted by Customized Model (M) for Various Days for Patient 1: (a) Patient Parameters Estimated from All Day Data, (b) Patient Parameters Estimated using Two-day Data.

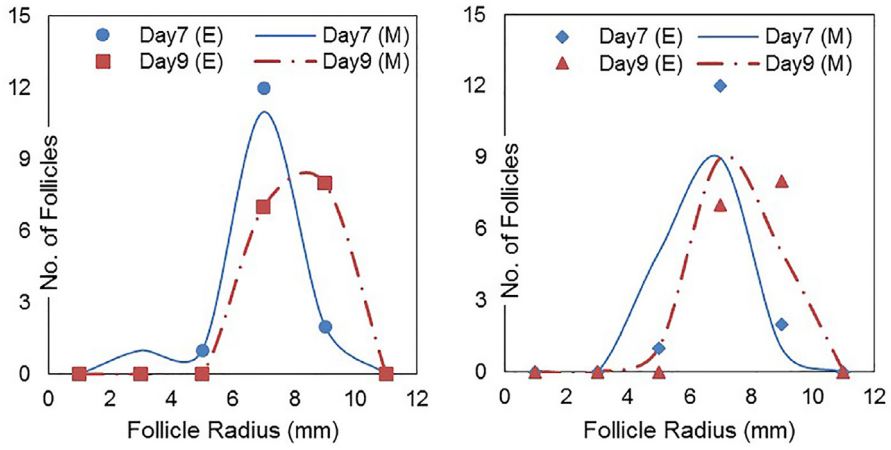

Fig. 3. Comparison of Observed (E) Follicular Distribution with the Follicular Distribution Predicted by Customized Model (M) for Various Days for Patient 2: (a) Patient Parameters Estimated from All Day Data, (b) Patient Parameters Estimated using Two-day Data.

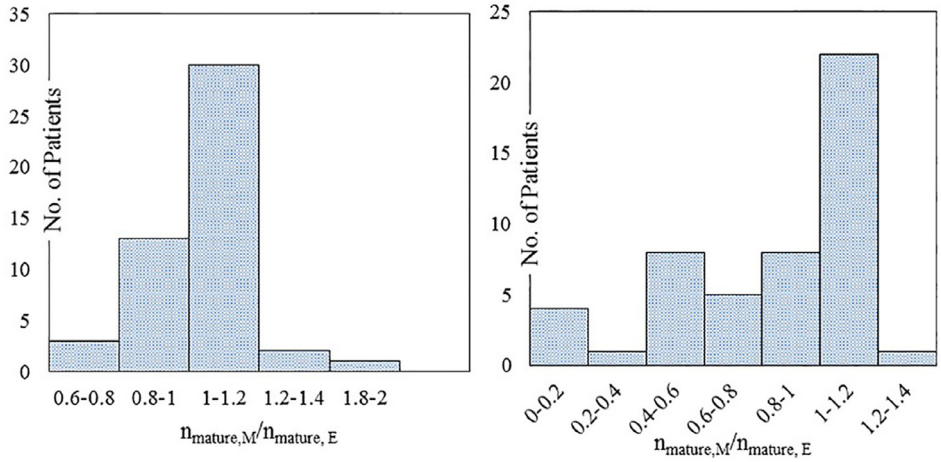

Fig. 4. Histogram of $(n_{mature,M})/(n_{mature,E})$ for 49 patients: (a) Model Fitted using All Day Data, (b) Model Fitted using Two-day Data.

data. The results of these two patients are selected as they represent two ends of the different age spectrum. As stated earlier, data has been gathered for 49 patients from Jijamata Hospital, India. This data is used to study the predictive capability of the model for the final day of stimulation. A histogram of the ratio of final day mature follicles predicted by the model $(n_{mature,M})$ to final day mature follicles observed experimentally $(n_{mature,E})$ in real practice is presented in Fig. 4. Fig. 4.a presents the prediction from all day data and Fig. 4.b presents predictions from two-day data. For most of the patients (more than 90%) of the patients, the model gives a good fit for all-day data versus 70% for two-day data predictions. Although, the model predictions are not that good for 30% of the patients for the two-day data, it is important to find out whether the optimal control profile can be still used for these patients.

3.1. Results from parameter estimation

It has been observed that the model parameter k (follicle growth rate constant) is unchanging across patients and is approximately valued at 22. Therefore, it can be concluded that k is patient independent. However, α (follicle growth rate exponent) changes for each patient. The probability distribution for $\alpha_{all-day}$ and the distribution of error in α_{2-day} compared to $\alpha_{all-day}$ is shown in Fig. 5.a and 5.b respectively. Analysis of the outliers from the histograms is presented in Fig. 5.a. It is observed that there are two patients who are outliers. Further analysis of these two patients revealed that α_{2-day} value for both is above -0.92. Thus, it

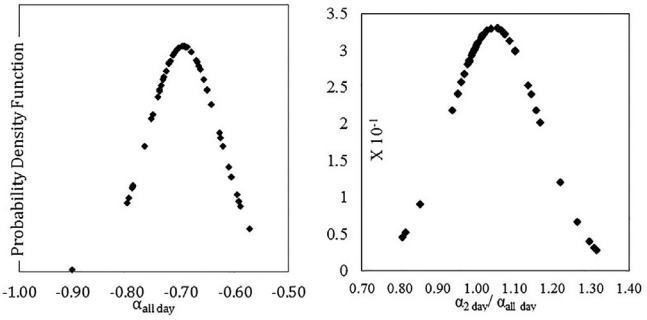

Fig. 5. Probability density function for the patient parameter α: (a) Distribution of $\alpha_{all-day}$ (b) Distribution of error $\alpha_{2-day}/\alpha_{all-day}$.

can be concluded that the model is the best fit for values of alpha ranging from -0.5 to -0.9. It should be noted that the model presented here is identifiable for values of alpha between (-1.4, 0).

3.2. Optimal control

As stated earlier, same dose is used from day 1 to day 4, and no testing is done till 5th day. Optimal control method is applied to find dosage from 5th day onwards using the maximum principle. The patient parameters estimated using the two-day data are used and the maximum principle method is applied to determine

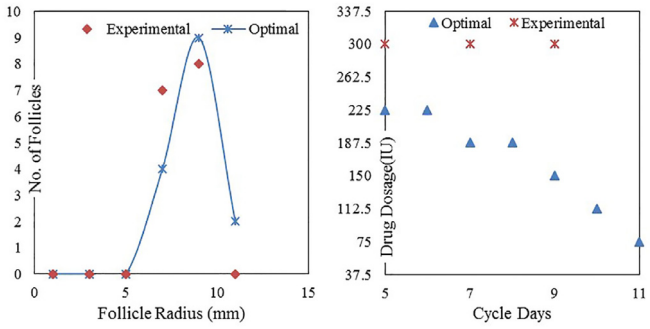

Fig. 6. (a) Follicular distribution for Patient 2 predicted by optimal control with two-day parameters for the next day of the cycle vs observed follicle distribution from experiments for the last day of the cycle (b) Optimal dosage for Patient 2 predicted by optimal control with two-day parameters vs experimental dosage prescribed by clinician.

dosage from 5th day. The optimal drug dosages for each patient are calculated based on the starting dose, cycle days and the initial follicle size distribution observed in each patient. The final day mature follicle count using optimal control is then compared with observed mature follicles using the dosage specified by the attending physician for these 49 patients. It is to be noted that, the model is personalized for each patient by considering 2-day data consisting of follicle measurements and prescribed doses from that patient. After that, optimal control was applied to calculate the optimal dosage profile for that patient. Since the parameters from all-day data is more accurate than two-day data, those parameters are used with optimal control profile predicted by the two-day data for comparison. The optimal control results for a patient are shown in Fig. 6. Fig. 6.a shows the mature follicle distribution optimal versus experimental and the optimal dosage versus experimental dosage is shown in Fig. 6.b. The cumulative dose for this patient is found to be 2662.5 IU compared to clinician prescribed dose of 3600 IU. These results serve as an example of the significant reduction in dosage which consequently reduces the costs to the patient. The initial data for 50 patients along with the results from optimal control for all the 49 patients is presented in Table 3 attached in the appendix. 1 patient was excluded from the analysis due to insufficient initial data. The table shows the age of each patient, values for parameters- K and α_{2-day}, Experimentally observed follicles, Model predicted optimal follicles on the last cycle day, Cumulative dosage prescribed by clinician and Dosage predicted by the model with 2-day data for each patient.

The optimal control profile was calculated and customized for each patient for the clinical data available on 49 patient cycles. The histograms of the results are presented in Fig. 7. Fig. 7.a shows the histogram of the ratio of optimal mature follicles to mature follicles observed using physician suggested dosage. Fig. 7.b shows the percent(%) reduction in dosage for each patient. It has been found that 98% of the patients show higher mature follicles for the optimal control profile than the physician specified dosage. Most of these patients also show a significant reduction in dose requirements for successful superovulation. This also shows that the two-day data is sufficient to predict the optimal dosage for each patient. Typically, older patients (age > 35 years) are prescribed dosages on the higher side ranging from 300-450IU. Even for older patients like Patient 3 (40 years), the results show that the actual dose needed to get similar outcomes is much less than as prescribed. Also, the starting doses are lower at 300 IU and 225IU, thus corroborating the idea that lower starting doses can also achieve similar responses in patients. This study found no correlation between the age of patients and higher doses of 300-450IU. Ovarian Hyperstimulation Syndrome (OHSS) is a risk that is compounded by administration of higher doses of FSH. While the phenomenon of OHSS is not considered in the objective function here, the optimal dosages predicted by the model are less than the prescribed doses. Since the occurrence of OHSS is highly correlated to higher dosages, the reduction of dose through optimal doses subsequently minimizes the onset of OHSS. Further our model predicts all day distribution of follicles which shows that OHSS does not occur for all the patients. Thus, the lower optimal doses minimize the onset of OHSS as well.

3.3. Overall approach for customized medicine

The model and optimal control methods are implemented in integrated software for clinical trials. This software is called OPTIVF (Diwekar, 2018). The software uses the initial two-day data from the patient, i.e., their follicle size distribution and hormone dosage, as an input to the model. Optimization based parameter estimation (iterative) of the moment model described in Section 2 is carried out to customize the model for each patient. The parameters then are used along with the iterative optimal control capability to find optimal drug dosing profile for the remaining days of the cycle. Fig. 8 shows a schematic of this procedure. Thus, daily tests are avoided, and a reduced amount of drugs can be used to obtain significantly better outcomes.

3.3.1. Clinical trial

Recently, the first clinical trial was conducted in Jijamata Hospital, Nanded, India. The trial involved 10 patients and 3 decision

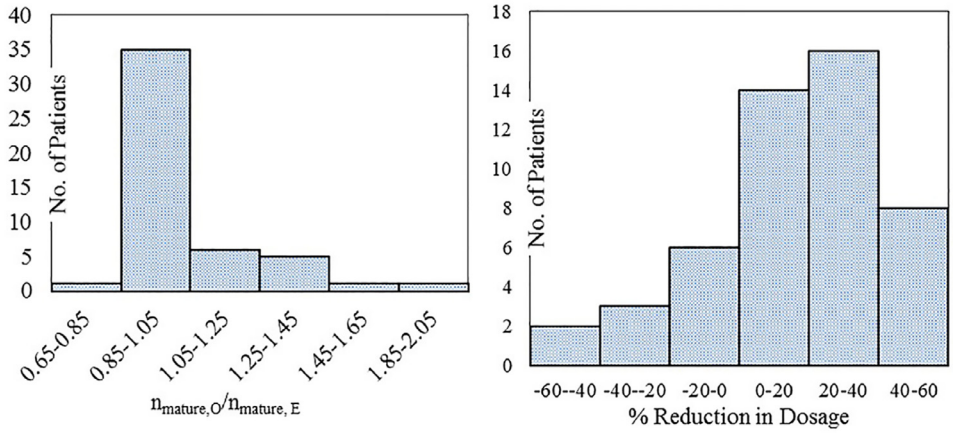

Fig. 7. Histogram of all patients: (a) Ratio of optimal mature follicles to experimental mature follicles, (b) % Reduction in dosage.

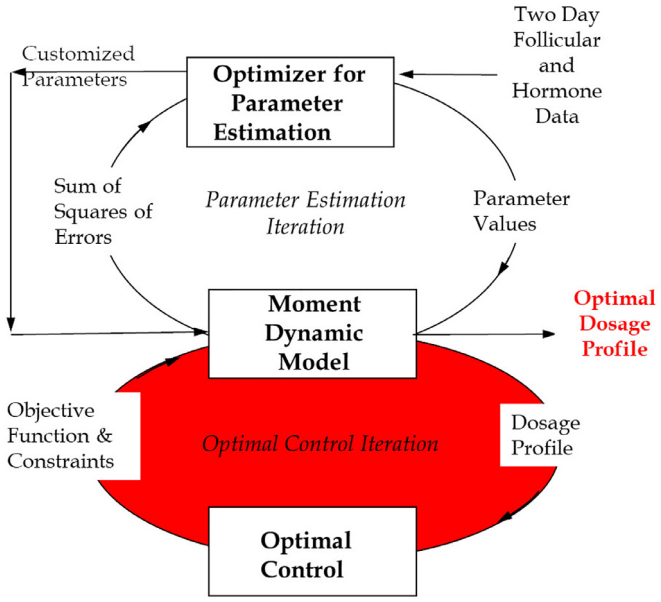

Fig. 8. Schematic of the overall approach and the steps in the OPTIVF software package.

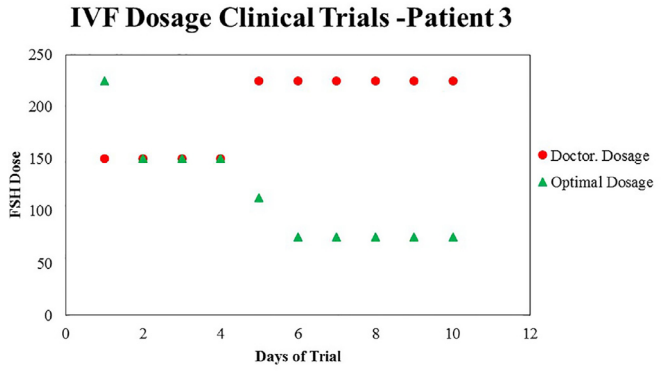

Fig. 9. Clinical trial patient 3, customized dosage comparison.

makers - 2 clinicians and 1 modeler. It was a double-blinded trial. Half of the patients were given dosage by the attending physician, and the other half were given the dosage predicted using this new approach. For each patient, dosage is determined by 1 doctor and the modeler. The second doctor chose which dosage profile to use for each patient. At the end of the clinical trial, the outcomes were examined in terms of quantity and quality of follicles on the last cycle day. Fig. 9 shows the outcome for one of the patients in the clinical trial. Using the model and the optimized dosage, the follicular distribution at the end of the cycle in a clinical trial for this patient, it has been observed that the dosage predicted by using the model is 1162.5IU which is 40% less than that the 195IU as suggested by the IVF clinicians. It is also observed that the number of mature follicles obtained at the end of the cycle using the model predicted dosage is significantly higher at 11 mature follicles (almost 100%) than the 5 follicles from the physician suggested dosage. Percentage of good quality eggs were similar from both the procedures. These results were consistent with all patients in this clinical trial. The testing requirement for patients using the optimized drug dosage policy predicted is reduced by 72%, and the number of follicles obtained were more than twice the number obtained by physician predicted dosage.

4. Summary and future work

In vitro fertilization (IVF) is the most common technique in assisted reproductive technology. Superovulation is a drug-induced method to enable multiple ovulation per menstrual cycle. The success of IVF depends on successful superovulation, defined by the number and the uniformly high quality of eggs retrieved in a cycle. Currently, this step is executed using almost daily monitoring of the follicular development using ultrasound and blood test. The daily dosage of hormones is customized for each patient based on these tests. Although there are general guidelines for the dosage, the dose is not optimized for each patient. The cost of testing and drugs make this stage very expensive. To overcome the shortcoming of this system, a computer-assisted approach was presented for customized medicine for IVF. The approach uses customized models for each patient based on initial two-day data from each patient to determine the outcomes. Optimal control methods are then used on these customized models to obtain drug dosage profiles for each patient. It has been found that this procedure provides better outcomes in terms of a higher number of mature follicles, reduced dosage, and reduced testing for most of the patients. This can reduce the side effects of the drugs significantly. A small clinical trial supports these theoretical findings. Further work is being carried out with the clinicians in United States to extend this approach to other protocols and for patients in the United States and the results are looking promising.

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Appendix A. Table of available data and results for 50 patients

Table 3
Table presenting initial available data and results from optimal control model. Initial Data: ID - Patient ID, Age - Patient Age. Results from Parameter Estimation: α_{2-day}- values for parameter α with 2-day data for each patient. Results from Optimal Control: Exp Fol - Experimentally Observed Follicles. Opt Fol (2-day)- Optimal Follicles predicted by model with 2-day data. Presc. Dose (IU) - Dosage prescribed by clinician. Opt Dose (2-day)(IU)- Optimal Dosage predicted by model with 2-day data.

ID	Age	α_{2-day}	Exp Fol	Opt Fol(2-Day)	Presc. Dose(IU)	Opt Dose(2-Day)(IU)
1	34	-0.83	8	8	4050	2062.5
2	36	-0.84	3	4	4650	2212.5
3	26	-0.70	21	19	1650	1800
4	30	-0.90	21	21	2550	1425
5	28	-0.70	22	21	1350	1650
6	23	-0.82	25	19	975	1125
7	30	-0.77	12	14	1725	1350
8	36	-0.66	6	6	6300	2550
9	30	-0.74	2	4	4650	2362.5
10	34	-	18	-	not specified	-
11	30	-0.87	7	8	2400	1425
12	30	-0.64	8	8	2550	1800
13	28	-0.96	5	4	2550	1725
14	32	-0.88	8	8	2400	1650
15	38	-0.74	10	9	2550	1650
16	34	-0.69	5	4	1950	2137.5
17	26	-0.74	6	6	1275	1200
18	30	-0.79	9	9	2250	1500
19	26	-0.95	20	13	1275	862.5
20	28	-0.77	5	7	2550	1462.5
21	34	-0.82	5	5	4500	2850

(*continued on next page*)

Table 3 (*continued*)

ID	Age	α_{2-day}	Exp Fol	Opt Fol(2-Day)	Presc. Dose(IU)	Opt Dose(2-Day)(IU)
22	23	-0.67	4	4	1950	1500
23	28	-0.67	21	20	1800	1875
24	36	-0.60	4	5	3600	2887.5
25	40	-0.63	12	13	3600	2662.5
26	28	-0.66	11	11	2100	1950
27	32	-0.69	10	10	2100	1800
28	-	-0.75	6	4	2250	1800
29	33	-0.80	6	5	2250	1650
30	29	-0.73	8	6	2250	1800
31	27	-0.84	9	5	2625	1612.5
32	35	-1.39	5	6	3525	1837.5
33	32	-0.63	6	6	1800	2287.5
34	40	-0.67	5	5	2700	2325
35	34	-0.74	5	5	2625	1612.5
36	32	-0.69	4	3	1650	2062.5
37	34	-0.67	8	6	1800	1950
38	42	-0.60	6	5	3900	3337.5
39	30	-0.47	12	12	3900	3300
40	32	-0.59	9	9	3900	3225
41	35	-0.61	5	5	3000	3150
42	29	-0.60	4	4	3900	3600
43	38	-0.47	5	5	3900	3412.5
44	30	-0.61	7	7	3900	3037.5
45	29	-0.66	5	3	1950	3000
46	39	-0.69	6	4	2100	1912.5
47	30	-0.80	8	7	2100	1725
48	28	-0.79	4	2	2100	3000
49	26	-0.74	5	3	2100	1875
50	24	-0.65	19	13	1950	2512.5

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtbi.2019.110105.

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