Modeling the Superovulation Stage in *In Vitro* Fertilization

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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, insemination/fertilization, and embryo transfer. Superovulation is a drug-induced method to enable multiple ovulation per menstrual cycle. The success of IVF majorly depends upon successful superovulation, defined by the number and similar quality of eggs retrieved in a cycle. Modeling the superovulation stage can help in predicting the outcomes of IVF before the cycle is complete. In this paper, we developed a model for superovulation stage. The model is adapted from the theory of batch crystallization. The aim of crystallization is to get maximum crystals of similar size and purity, while superovulation aims at eggs of similar quality and size. The rate of crystallization and superovulation are both dependent on the process conditions and varies with time. The kinetics of follicle growth is modeled as a function of injected hormones and the follicle properties are represented in terms of the moments. The results from the model prediction were verified with the known data from Jijamata Hospital, Nanded, India. The predictions were found to be in agreement with the actual observations.**

***Index Terms*—Batch crystallization, infertility treatment, modeling *in vitro* fertilization (IVF), superovulation.**

I. 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 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 [1], 30–40% cases include infertility problems exclusively in males or females individually and around 10–15% cases are due to problems in both the partners.

The common causes of infertility in females are ovulatory disorders, anatomical abnormalities, and damaged fallopian tubes. Some rare causes include endometriosis, hyperprolactinemia, and thyroid-gland-related issues. In developing nations [2], the causes may include infections of the womb such as gonorrhea, chlamydia, and tuberculosis.

In most of the countries, cost is a major hurdle for access of infertility services [3]. Most centers offering treatment for infertility operate outside of government financed health facilities. The treatment is only accessible to elites who can afford to pay for such high tech therapies. Even in a country like U.S., the cost for an *in vitro* fertilization (IVF) cycle amounts to 20% the total annual income of a median American family. In developing nations, the cost of an IVF cycle is about 50% of the total annual income.

A. IVF [4]

It 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 are implanted back in the uterus for full-term completion of pregnancy.

Four stages in IVF:

1) *Superovulation:* It is the method to retrieve multiple eggs using drug-induced stimulation. In a normal female body, only one egg is ovulated per menstrual cycle, but with the use of fertility drugs and hormones, more number of eggs can be ovulated per cycle.
2) *Egg collection (retrieval):* On the maturation of the multiple eggs produced in the previous stage, the eggs are retrieved through special techniques like ultrasonically guided transvaginal oocyte retrieval.
3) *In vitro fertilization (insemination/fertilization):* This stage is accomplished in the IVF laboratory. Fertilization is done in the incubator using the retrieved oocytes and sperms. The conditions are maintained so as to mimic the *in vivo* environment.
4) *Embryo transfer:* It takes place after several days of oocyte retrieval and after the fertilization stage is successful. The fertilized embryos are implanted into the uterus via a nonsurgical technique using ultrasound guidance.

IVF treatment is an expensive treatment. There are a lot of complications associated with each stage, and hence, the success is highly unpredictable. The major cost of IVF is associated with the superovulation stage where expensive drugs are used and almost daily monitoring is required. Success of this stage in terms of number and quality of eggs affect the outcome of IVF and, hence is a very important stage. Modeling this stage would be helpful in predicting the outcomes of the process before completion and is the focus of the current endeavor.

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B. Superovulation

Superovulation has specific protocols to be followed. This stage affects the patient significantly since it involves the interplay of the fertility drugs and hormones. This causes physical as well as emotional disturbances in the patient.

Functional hormones during the menstrual cycle are the following [5].

1) *Gonadotropin releasing hormone (GnRH):* This hormone is secreted by the hypothalamus in a pulsating manner to stimulate the pituitary gland to release the gonadotropin hormones like LH and FSH. The GnRH is rapidly broken down by serum proteases and, hence, has a very short half life of 2–5 min.
2) *Luteinizing hormone (LH):* LH along with FSH regulates the production of estrogen and progesterone.
3) *Follicle stimulating hormone (FSH):* FSH stimulates the ovarian cells and is required for the development of mature oocytes which can be fertilized. In the normal cycle, FSH usually promotes 6–8 follicles from antral to preovulatory phase; however, later when the level decreases, there is only one fully developed oocyte, which contributes in the suppression of FSH supply to the other promoted follicles.
4) *Estrogen:* The growing follicle secretes high levels of estrogen. This estrogen level is an indicator of the maturation of the oocyte and sends signal to the hypothalamus and pituitary, which then release LH to enable further development of the oocyte, its extrusion from the follicle, and the follicle forms the corpus luteum.
5) *Progesterone:* Progesterone is secreted from the secretory cells of the follicle; it promotes changes in the endometrium to sustain pregnancy.
6) *Human chorionic gonadotropin (hCG):* If fertilization occurs, the growing embryo starts secreting hCG which prolongs the life of corpus luteum, thus maintaining the levels of progesterone for sustaining the endometrium and pregnancy.

The protocols include daily injections of multiple agents from a time duration varying in weeks to months. The expense increases due to the high cost of medication and frequent monitoring. Variation in the protocol depending upon patient's condition, earlier medical history, and responsiveness will make the method more effective, and hence, a higher success rate could be anticipated as against using the same protocol for every patient. The decrease in overall treatment cost can be expected since the dosage will be optimum and also the frequency of monitoring the patient can be reduced.

C. Previous Studies

Earlier work on follicular growth was mostly theoretical and involved the study of ovarian dynamics as a function of gonadotropins. Peters *et al.* [10] mentioned the emerging of a single follicle from a pool of small follicles. Apart from the influence of gonadotropins for its growth, the selection of the growing follicle is a function of the total mass of the small follicles and the substances produced by atretic follicles. This selection phenomena were later mentioned by Baird [11] under the specific gonadotropin environment that facilitates the growth of dominant follicle while suppressing the others causing follicular atresia.

Chang *et al.* [12] also mentioned the antral follicle count affecting the early follicle growth. The relationship between age, dominant follicle, estrogen levels, and antral follicle count during final maturation was analyzed. The antral and dominant follicle counts were found to be more in successful assisted reproduction cases. Gougeon *et al.* [13] studied age-related changes to growing and nongrowing follicles. They applied regression analysis to model the decrease in follicle count.

Previous studies by Selgrade *et al.* [14] and Reinecke and Deuflhard [15] report about the hormonal control of the normal menstrual cycle in terms of mathematical equations. It focused on model development for further analysis in drug design. The model [15] was highly complex involving the dynamic studies in the pituitary and ovaries. It involved delayed differential equations depending upon the response time for the desired action. The single follicle dynamics was studied and the hormones LH and FSH were the ones affecting significantly. However, the model did not refer to external stimulation and multiple ovulation (desired from the superovulation stage) which is a novel aspect in our model.

TABLE I
ANALOGY BETWEEN BATCH CRYSTALLIZATION AND IVF SUPEROVULATION STAGE

BATCH CRYSTALLIZATION	SUPEROVULATION (IVF STAGE I)
PRODUCTION OF MULTIPLE CRYSTALS	PRODUCTION OF MULTIPLE OOCYTES OR EGGS
CRYSTAL QUALITY IS DETERMINED IN TERMS OF SIZE DISTRIBUTION AND PURITY	OOCYTE QUALITY IS DETERMINED IN TERMS OF NO ABNORMALITIES, SIMILAR SIZE.
THE RATE OF CRYSTALLIZATION OR CRYSTAL GROWTH VARIES WITH TIME AND PROCESS CONDITIONS	THE RATE OF OVULATION OR OOCYTE GROWTH VARIES WITH TIME AND DRUG INTERACTIONS
PROCESS IS AFFECTED BY EXTERNAL VARIABLES LIKE AGITATION, AND PROCESS OPERATING VARIABLES LIKE TEMPERATURE, PRESSURE, ETC.	PROCESS IS AFFECTED BY EXTERNALLY ADMINISTERED DRUGS AND BODY CONDITIONS OF THE PATIENT UNDERGOING THE PROCESS

D. Analogy Between Superovulation and Batch Crystallization

In this study, we follow the analogy between batch crystallization and superovulation to model the superovulation process. The moment model for follicle number and size is adapted from the concept of batch crystallization [6] based on the analogy between batch crystallization [7], [8] and superovulation [4] presented in Table I.

The superovulation follicle growth model in general resembles greatly to the growth of seeded batch crystals. The aim of seeded batch crystallization is to allow the seeds added to the solution to grow to desired shape and size and truncate the process of nucleation by maintaining certain process conditions. The

TABLE II
VARIATION OF FOLLICLE SIZE (DIAMETER) WITH TIME AND FSH DOSE

Days → / Bins ↓	Day 2	Day 5	Day 7	Day 9
0-4	8	4	0	0
4-8	6	4	2	0
8-12	4	10	14	4
12-16	0	0	2	11
16-20	0	0	0	3
20-24	0	0	0	0
FSH dose (IU/ml)	300	300	300	225

numbers of seed added to the solution are constant, and hence, the zeroth moment of seeded batch crystals which corresponds to its number is constant. Similarly, when we look at superovulation, the number of follicles activated during an IVF cycle is constant. Thus, the moment model for both the processes remain the same; the growth term, which is a function of process variables such as temperature and supersaturation in batch seeded crystallization, will become a function of medicinal dosage in case of superovulation process.

II. MODEL DEVELOPMENT

Due to ovarian stimulation using externally injected hormones, the number of follicles activated to enter into the ovulation stage is more in number as compared to a single follicle in a normal menstrual cycle. The superovulation cycle data, obtained from Jijamata Hospital, Nanded, India, had measurements of follicle size and number representing growth on some days of the FSH administration. The data from a successful superovulation cycle for Patient A are shown in Table II. The information about multiple ovulation along with the amounts of FSH administered reveals that during the FSH dosage regime, as time progresses, the size of eggs/follicles keep increasing.

A. Moment Evaluation

Previously, in Section I-D, the process analogy between batch crystallization and superovulation has been discussed. In batch crystallization modeling, most researchers try to reduce the model order using methods involving crystallization moments. Such reduction provides an advantage, since the complex population balance equations used to describe the particle size distribution in crystallization can be converted to ordinary differential equations. In this paper, we apply the similar concept of moments to the follicle size. The follicle size data shown in Table II can be converted to moments using the general expression shown in (1) [6]. This data shall be used for model parameter estimation

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

Here, 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 is the mean radius of jth bin, and Δr is the range of radii variation in each bin.

TABLE III
EXPERIMENTAL MOMENTS EVALUATED FOR PATIENT A

Day	2	5	7	9
μ_0	36	36	36	36
μ_1	92	132	180	248
μ_2	324	580	932	1764
μ_3	1340	2724	4980	12920
μ_4	5988	13156	27428	97188
μ_5	27932	64452	155700	749048
μ_6	133764	318340	911012	5901924
FSH dose	300	300	300	225

The selection of order of moments for the process model is an important aspect in size distribution modeling and prediction. In the current process, there are 6 number of bins into which the follicle sizes are divided. For efficient process modeling, it is essential to consider at least the first six order of moments along with the zeroth moment [9]. Table III shows the moment values evaluated using (1) along with the FSH dose on the days of follicle size measurement.

B. Model Equations

The moment-based model for predicting follicle size and number will involve the follicle growth rate expression along with the equations for moments of different orders. We assume in this study that follicle growth is dependent on FSH administered. Thus, we write the growth term in the simplest form as

$$G = kC_{\mathrm{fsh}}^{\alpha}. \tag{2}$$

Here, G is the follicle growth rate, k is the rate constant, C_{fsh} is the amount of FSH injected, and α is the rate exponent.

We have also assumed the follicle number activated for growth to be a constant; hence, the zeroth moment will have a constant value. We use the first- to sixth-order moment since they help in better prediction of moment values as well as help in efficient recovery of the size distributions as against the lower order of moments. The moment equations for the follicle dynamics can be written as

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

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

Here, G is the follicle growth rate and μ_i is the $i\mathrm{th}$ moment.

C. Solution Method

We integrate (3) and (4) for predicting the kinetic constants in the follicle growth expression for each patient separately using the nonlinear optimization algorithm. The experimentally evaluated moments are used as the data for model fitting. The moment values obtained from the model equations and the experimentally evaluated moments are compared and it is observed that while all the moments show a fairly good fit, the lower moments show some deviations, and the fit is much better for higher moments. In real practice, the model will be calibrated with the

TABLE IV
PARAMETER VALUES OBTAINED FROM OPTIMIZATION PROGRAM FOR PATIENT A

Parameter	Values
k	85.89
α	-0.9248
c_1	60.984
c_2	180.502
c_3	352.3183
c_4	1992.789
c_5	9997.686
c_6	100000.2

first two days of data and then used for prediction of follicle dynamics over the complete cycle.

The integrated equations for the moments are presented in the following equations:

$$\mu_1 = G\mu_0 t + c_1 \tag{5}$$

$$\mu_2 = G^2\mu_0 t^2 + 2Gc_1 t + c_2 \tag{6}$$

$$\mu_3 = G^3\mu_0 t^3 + 3G^2 c_1 t^2 + 3Gc_2 t + c_3 \tag{7}$$

$$\mu_4 = G^4\mu_0 t^4 + 4G^3 c_1 t^3 + 6G^2 c_2 t^2 + 4Gc_3 t + c_4 \tag{8}$$

$$\mu_5 = G^5\mu_0 t^5 + 5G^4 c_1 t^4 + 10G^3 c_2 t^3 + 10G^2 c_3 t^2 + 5Gc_4 t + c_5 \tag{9}$$

$$\mu_6 = G^6\mu_0 t^6 + 6G^5 c_1 t^5 + 15G^4 c_2 t^4 + 20G^3 c_3 t^3 + 15G^2 c_4 t^2 + 6Gc_5 t + c_6. \tag{10}$$

Here, μ_i is the ith moment, G is the follicle growth rate, and c_i are the integration constants.

As stated earlier, we estimate the model parameters (kinetic constants and the integration constants) using nonlinear optimization algorithm in MATLAB for every patient. The parameter values for Patient A are given in Table IV.

III. MODEL VALIDATION METHOD

The model presented in Section II-B predicts the moment values for the patient. In order to predict the success or failure of the IVF superovulation cycle, we need the results in terms of number of follicles and their sizes. The maximum number of follicles within the required size range is the desired feature for a successful superovulation cycle. In order to convert the moment data obtained from model simulations to follicle number, we follow a model validation method adapted from the literature by Flood [9]. The method is modified to predict the size distribution of follicles for each day.

The method suggested in [9] is represented as

$$\mu = An. \tag{11}$$

Here, n is the number of follicles in n bins at ith day, μ is the moment for i*th* day, and A is the inversion matrix derived from (1).

For the current bin size of 2 mm (radii) and number of bins as 6, the inversion matrix A in (11) is shown in Table V.

TABLE V
INVERSION MATRIX A (6×6) TO RECOVER SIZE DISTRIBUTION FROM MOMENT VALUES DERIVED FROM (1)

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

A. Follicle Number Prediction Algorithm

To predict the number of follicles in a particular size bin on a cycle day of FSH dosage regime, we use a constrained optimization algorithm. The optimization variables in the current algorithm are the number of follicles per day in the cycle.

Step 1: Assign some initial values to n (number of follicles/day) within the different size bins used in the model.

Step 2: Obtain the moment values by multiplying matrix A with the initially assumed n values.

Step 3: Introduce the constraint for total number of follicles. We have assumed a constant number of follicles entering the growth stage in the IVF cycle for a particular patient to be μ_0. Hence, for each day, the number of follicles must sum up to the assumed constant value.

Step 4: Restrict the values of n to be either positive or zero since the number of follicles can never be negative.

Step 5: Write the objective function to minimize the sum of square of errors between the model predicted moments described earlier in Section II-B and the moment values obtained from (11).

Step 6: Use a constrained nonlinear optimization method to obtain the values of n.

Step 7: Compare the optimum values of n obtained from this constrained optimization method to the actual data observed for the patient.

Using this follicle number prediction algorithm; the moment model for follicle growth can be validated for a given patient.

IV. RESULTS

The results from the validation studies and the actual observations are plotted on the same figure for comparison. The plots in Fig. 1 show that the back prediction of the number of follicles using the moment values obtained from the model is very much in agreement to the original follicle number and size data. Thus, the model can be a good indicator for predicting the success of the superovulation stage.

The observed (O) size distribution is shown by discrete symbols, while the continuous curve shows the model predicted values (S) after using the inversion method.

We carry out the similar model predictions for successful superovulation data available for other patients. The methods mentioned earlier in Section II for simulated moment values and Section III for back prediction of n (number of follicles per day), are applied for patients B–E separately to test the

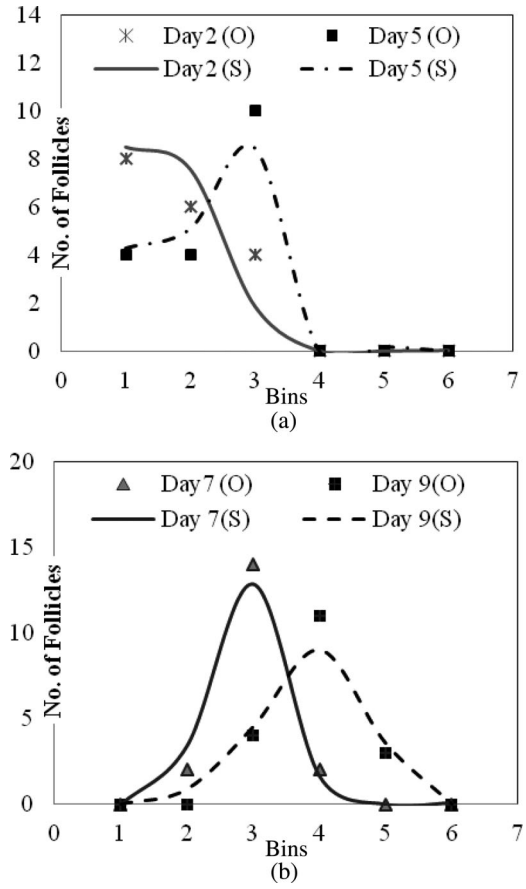

Fig. 1. (a) Comparison of the number of follicles from actual measurements and model prediction for days 2 and 5 for Patient A. (b) Comparison of the number of follicles from actual measurements and model prediction for days 7 and 9 for Patient A.

predictability of the model for different datasets. The model gives good predictions for the last days in the superovulation cycle for all of the patients considered in this study. This is highly beneficial since based on the knowledge about the size of the follicles and number predicted for the final days, one can predict the success or failure of the superovulation cycle. Fig. 2 shows results for other four patients B–E. We have selected two cycle days randomly for each patient for the purpose of result representation. These plots provide a general idea about the model accuracy and utility.

The experimental size distribution is shown by symbols, while the continuous curve shows the model predicted values after using the follicle prediction algorithm mentioned in Section III-B. It can be seen that the predicted values are close to experimental size distribution.

V. Discussion

The aim of this study is to develop a follicle growth model, which involves the externally injected hormones as the growth factors. This is the first attempt to model follicular growth in the form of differential equations that are able to predict the follicle size and number changing with time.

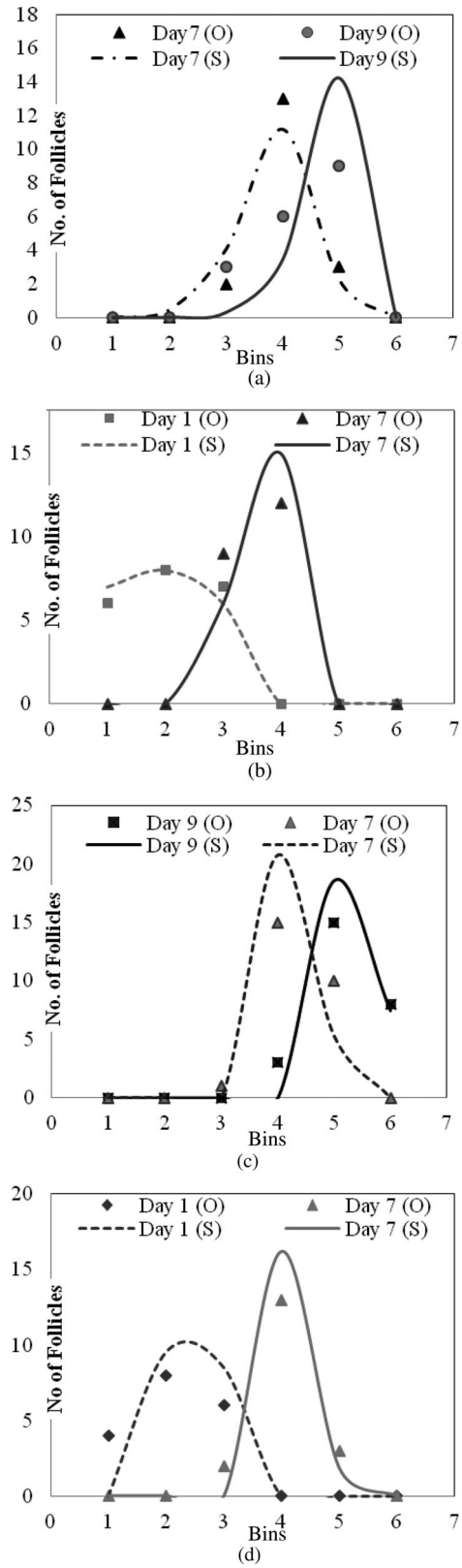

Fig. 2. (a) Comparison of number of follicles from actual measurements and model predictions for days 7 and 9 for Patient B. (b) Comparison of number of follicles from actual measurements and model predictions for days 1 and 7 for Patient C. (c) Comparison of number of follicles from actual measurements and model predictions for days 7 and 9 for Patient D. (d) Comparison of number of follicles from actual measurements and model predictions for days 1 and 7 for Patient E.

The current model can be used to formulate a mathematical function relating to the follicle size and growth. The aim of superovulation is to maximize the number of follicles retrieved in the desired size range for the next stages of IVF. The mathematical model would prove beneficial in predicting the optimal dosage regime for desired outcome by application of optimal control theory to the system. The current model does not consider variability depending upon the patient's medical history, age, and treatment response. This model can be extended to involve such variations and solve the problem for optimal dose. Thus, the current model has several advantages in terms of predictive value and will aid the medical community and society in an area that was previously based on trial and error and required continuous medical supervision. This could bring down the cost of the medicines as well as patient monitoring. Most importantly, it will reduce the IVF failure rates and help in initial decision making regarding continuing the superovulation or starting the IVF from donor eggs.

VI. Conclusion

The moment model developed for IVF superovulation predicts the follicle size distribution that is in good agreement with the actual size distribution seen in the IVF cycle data for the five patients shown in this study. The model can be used to predict the cycle outcome if the initial data is available for a patient. This study will aid in reducing the almost daily requirement of monitoring and testing. The model can also provide a basis for predicting the optimum dosage for the desired outcome from the superovulation stage. Later, we aim to include the process complexities and model the system uncertainties, using more data for analysis, modeling, and validation.

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