Journal of Theoretical Biology 367 (2015) 76–85

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Uncertainty in clinical data and stochastic model for in vitro fertilization

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HIGHLIGHTS

- First study to analyze the uncertainty in the ongoing superovulation cycle.
- Ito process models are capable of capturing time-dependent uncertainties in superovulation.
- Stochastic differential equation model predictions are better matched with the clinical data.
- A promising approach for efficient and robust modeling of biomedical processes

ARTICLE INFO

Article history:
Received 3 May 2014
Received in revised form
23 September 2014
Accepted 3 November 2014
Available online 4 December 2014

Keywords:
Infertility
Assisted reproduction
Multiple ovulation
Uncertainty
Stochastic model

ABSTRACT

In vitro fertilization (IVF) is the most widely used technique in assisted reproductive technologies (ART). It has been divided into four stages; (i) superovulation, (ii) egg retrieval, (iii) insemination/fertilization and (iv) embryo transfer. The first stage of superovulation is a drug induced method to enable multiple ovulation, i.e., multiple follicle growth to oocytes or matured follicles in a single menstrual cycle. IVF being a medical procedure that aims at manipulating the biological functions in the human body is subjected to inherent sources of uncertainty and variability. Also, the interplay of hormones with the natural functioning of the ovaries to stimulate multiple ovulation as against single ovulation in a normal menstrual cycle makes the procedure dependent on several factors like the patient's condition in terms of cause of infertility, actual ovarian function, responsiveness to the medication, etc. The treatment requires continuous monitoring and testing and this can give rise to errors in observations and reports. These uncertainties are present in the form of measurement noise in the clinical data. Thus, it becomes essential to look at the process noise and account for it to build better representative models for follicle growth. The purpose of this work is to come up with a robust model which can project the superovulation cycle outcome based on the hormonal doses and patient response in a better way in presence of uncertainty. The stochastic model results in better projection of the cycle outcomes for the patients where the deterministic model has some deviations from the clinical observations and the growth term value is not within the range of '0.3–0.6'. It was found that the prediction accuracy was enhanced by more than 70% for two patients by using the stochastic model proejctions. Also, in patients where the prediction accuracy did not increase significantly, a better match with the trend of the clinical data was observed in case of the stochastic model projections as compared to their deterministic counterparts.

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 word infertility literally translates to 'non-fertile' and therfore can be interpreted as sterile. However, this is not true, infertility is a medical condition with diminished ability or inability to produce offspring in either the male or female partner and they are better categorized as 'subfertile' (Habbema et al., 2004). According to worldwide statistics, around 80 million couples experience some kind of infertility problems (Ombelet and Campo, 2007). Hence, these patients have an option to seek medical aid and there are several assisted reproduction technologies (ARTs) like IVF which can help them in conceiving. Nearly 200,000 IVF cycles are performed world-wide annually and more than 1,000,000 children have been born

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http://dx.doi.org/10.1016/j.jtbi.2014.11.004
0022-5193/

since the first successful birth of the 'test-tube' baby, Louise Joy Brown in 1978, as per the data reported by Bayer et al. (2007). In the year 2010, Robert G. Edwards was awarded the Nobel prize in the category of 'Physiology or Medicine' for the development of human IVF therapy (Nobel Media, 2010). This reveals the prevalence of infertility, the number of people sorting to IVF as a therapy and the overall significance of its development to benefit mankind.

IVF involves fertilization of oocytes by a sperm outside the body in a laboratory simulating similar conditions as in the human body and then implanting the fertilized eggs back in the uterus of the carrier mother for full term pregnancy. It is a four stage medical procedure (Speroff and Fritz (2005)) and the success of superovulation, its first stage, is critical to proceed with the next stages in the IVF cycle. Also it requires maximum medical attention and investment of time and money as compared to the other stages. The major hormonal drug involved in superovulation is the follicle stimulating hormone (FSH), which is responsible for follicle growth and development (Janát-Amsbury et al., 2009). In our previous work (Yenkie et al., 2013a), a deterministic model for the prediction of multiple follicle growth, dependent on the amount of FSH dosage was built by drawing similarities with the particulate process of batch crystallization (Hill et al., 2006; Yenkie and Diwekar, 2013). This model was validated with clinical data from 50 IVF cycles, available from our collaborating hospital in India. The model fitted very well to most of the data and almost 85% predictions were within 0 to 30% range of the mean error (Yenkie et al., 2014). However, the fact that IVF is actually a medical procedure that involves manipulations in the biological functions of the human body and specifically to the functioning of the ovaries, is subjected to inherent sources of uncertainty and variability.

Uncertainties regarding the normal range of values for interpreting the fertility tests is a major concern and this can result in improper diagnosis and treatment specially in cases where the cause of infertility is unexplained (Bachus and Walmer, 1993). Johnson et al. (1987) discuss about the uncertainties experienced by the patients at each stage of the IVF procedure. Sometimes the patients end up overestimating the IVF success rate based on the current popularity of the procedure, while, underestimating the chances of failure in one of the less publicized stage in the overall procedure. The anxiety and stress of the overall procedure can have a huge impact on the patient's responsiveness to the medications. The report on incorporating natural variations into IVF clinic tables by Lemmers et al. (2007) suggest that the result of any IVF cycle will lie within the best-case and worst-case scenario observed at that particular clinic.

The previous studies on uncertainty analysis in IVF are mostly based on anticipation and stress related to the psychology of the patient, emotional state and fears concerning the medical procedure and their ability to accept the fact that medical intervention can help in reproduction (Ardenti et al., 1999; Thiering et al., 1993). In most of their conclusions the results are reported in terms of relative percentage of success of the cycle in depressed and non-depressed patients. The work by Ardenti et al. (1999) suggests that the uncertainty of outcome generates maximum anxiety levels during the oocyte retrieval and embryo transfer. Both these procedures are highly dependent on the success of superovulation. If high number of follicles grow to mature oocytes, the excess oocytes can be saved for the next cycle if the first attempt fails and hence the anxiety levels of the patient can be reduced by providing them with a better outcome in superovulation. Prediction of better superovulation outcomes and enhancement in the success rate by application of optimal control for pre-determined hormonal drug dosage has already been addressed in our previous work (Yenkie and Diwekar, 2014a, 2014b).

However, the uncertainty in the clinical observations has not gained enough attention in the previous work. Since the existing protocols (Meniru and Craft, 1997; Loutradis et al., 2007) for superovulation are largely dependent upon the clinical observations for deciding the hormonal dosage on the next day of the cycle, it is essential to look into the possible errors in the follicle growth measurements and reporting. The uncertainty in the IVF outcomes specific to the particular clinic has been addressed by Lemmers et al. (2007), but we intend to characterize the uncertainty specific to the patient and the ongoing cycle, which makes the procedure more acceptable. In the current work, we are proposing a method to characterize the uncertainty in the ongoing cycle. The clinical data on IVF cycles when used for fitting the deterministic model and validating the projected results had some deviations from the expected behavior (Yenkie et al., 2014). Thus, it can be used for evaluating the effects of uncertainty in the process.

Previously, the work done in our group on uncertainty characterization and modeling has revealed that the Ito processes are quite efficient in capturing the time-dependent uncertainties in batch processes (Ulas et al., 2005; Benavides and Diwekar, 2012; Yenkie and Diwekar, 2013). Also, they were equally efficient in capturing the time-dependent variations in the blood glucose levels of insulin-dependent diabetes patients (Ulas and Diwekar, 2010). IVF being a medical procedure and the superovulation model developed from the principles of batch crystallization, motivated us to look into Ito processes for modeling the associated uncertainties.

2. Methodology

The determinisitic model for the superovulation stage in the form of ordinary differential equations (ODEs) is discussed briefly in Section 2.1. Then the occurence of uncertainty in the clinical data, its characterization as suitable stochastic processes and the development of a more robust model for superovulation in terms of stochastic differential equations (SDEs) is discussed in Section 2.2.

2.1. The determinstic model

The similarities between the process of crystallization and superovulation was used for the modeling of multiple follicle growth under the influence of injected hormones. The concept of the moment based model for crystal growth in batch crystallization (Hu et al., 2005) was used as the basis for modeling superovulation in IVF (Yenkie et al., 2013b) because it had the advantage of evaluation of moments of different orders. From the literature by Randolph and Larson (1988) it is known that moments correspond to specific features of the particles like the zeroth moment (μ_0) corresponds to the particle number, first moment (μ_1) to their size and second (μ_2) to their shape, etc. The growth term in cooling batch crystallization is temperature dependent and hence temperature is considered to be the most promising decision variable for eventually achieving a desired particle size distribution (PSD). On similar lines in IVF, the follicle growth is dependent upon the doses of hormones injected to the patient. Thus, the follicle growth term (G) is dependent on the amount of follicle stimulating hormone (FSH) injected (ΔC_{fsh}) to the patient at the particular time (t) in the cycle and is represented as shown in Eq. (1).

$$G(t) = k\Delta C_{fsh}(t)^{\alpha} \tag{1}$$

Here, k and α are kinetic constants of the growth term.

In the literature by Baird (1987), it was suggested that the number of follicles activated for growth during a particular superovulation cycle is relatively constant for a particular patient, hence the zeroth moment (μ_0) is assumed to have a constant value at all times during the FSH dosage regime. The 0th to 6th order moments are used in the model, since they help in better prediction of