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Innovative Applications of O.R.

Approximate dynamic programming algorithms for optimal dosage decisions in controlled ovarian hyperstimulation

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ABSTRACT

In the controlled ovarian hyperstimulation (COH) treatment, clinicians monitor the patients' physiological responses to gonadotropin administration to tradeoff between pregnancy probability and ovarian hyperstimulation syndrome (OHSS). We formulate the dosage control problem in the COH treatment as a stochastic dynamic program and design approximate dynamic programming (ADP) algorithms to overcome the well-known curses of dimensionality in Markov decision processes (MDP). Our numerical experiments indicate that the piecewise linear (PWL) approximation ADP algorithms can obtain policies that are very close to the one obtained by the MDP benchmark with significantly less solution time.

1. Introduction

If a couple has not conceived after trying for 1 year (or 6 months if the female is over 35), they are often considered infertile. According to the Centers for Disease Control and Prevention (CDC, http://www.cdc.gov/ART/) and the National Institute for Health and Clinical Excellence (NICE, http://www.nice.org.uk/), fertility problems affect one in six or seven couples in the United States and UK. In the United States, about 7.4% (2.1 million) of married women aging 15–44 were infertile in 2002. Infertility can be caused by women's problems, men's problems, or a mixture of both, each of which accounts for about one-third of the diagnosed infertility cases.

One necessary condition for pregnancy is that a woman must be able to release a high quality oocyte/egg. However, in a natural menstrual cycle, a woman usually produces only one oocyte/egg (in rare cases two). If the oocyte is of poor quality, the chance of pregnancy becomes very low. Even worse, some women (especially those with infertility problems) may not even be able to produce any oocytes.

Since as early as the 1950s, Robert Edwards had been working systematically to realize his vision that *in vitro fertilization* (IVF) could be useful as a treatment for infertility, which led to the world's first "test tube baby" on July 25, 1978. Since then, *assisted reproductive technology* (ART) procedures, including IVF, have been applied worldwide to help infertile couples give birth to their own children. In the United States, 148055 ART cycles were performed at 436 fertility clinics, resulting in 46326 live births and 61426 infants in 2008, as compared to 142415 ART cycles at 430 clinics, resulting in 43408 live births and 57564 infants in 2007 (Assisted Reproductive Technology Reports at the Centers for Disease Control and Prevention, http://www.cdc.gov/ART/ARTReports.htm). In Europe, 785 clinics from 29 countries reported 367066 cycles in 2004 (ESHRE, 2008). In China, about 20000 ART cycles were performed in 2004.

Among the ART approaches, IVF therapy has been the most commonly used type. 99.9% of ART procedures performed in 2008 among women using fresh nondonor eggs or embryos in the United States were IVF. In 2010, Robert Edwards was awarded the Nobel Prize in Physiology or Medicine, due to his achievement in "the development of human *in vitro fertilization* (IVF) therapy."

A typical IVF procedure (as shown in Fig. 1, He et al., 2010) begins with *controlled ovarian hyperstimulation* (COH). The COH treatment stimulates the growth of *multiple* follicles into oocytes in the woman's ovaries by administrating exogenous gonadotropin (hormone). A COH treatment cycle varies with women and may last 6–20 days (see, for example, Martin et al., 2006). At the end of the COH cycle, clinicians inject the *human chorionic gonadotropin* (hCG) to induce the final maturation of the oocytes. The oocytes are retrieved from the woman thereafter. The high quality oocytes and sperm are then placed together in a culture dish under the controlled lab environment (*in vitro fertilization*, *IVF*). If fertilization happens, the selected (high quality) embryo will be transferred into the woman's body (*embryo transfer*, *ET*). If one or more of the transferred embryos implant within the woman's uterus (positive urine test result), the cycle then may progress to clinical

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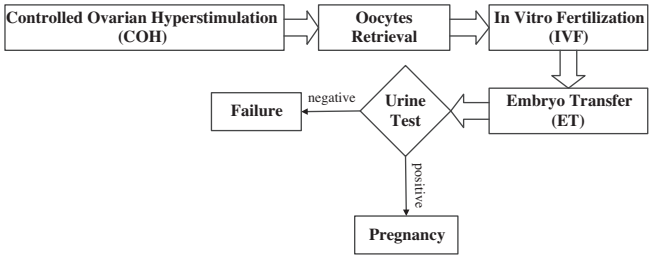

Fig. 1. A typical IVF procedure.

Table 2
The correlation matrices.

Dosage (ampoule)		State		
		$\ln(E_2)$	Ovary	Follicle
2	$\ln(E_2)$	1.00	0.56	0.58
	Ovary		1.00	0.54
	Follicle			1.00
3	$\ln(E_2)$	1.00	0.58	0.59
	Ovary		1.00	0.57
	Follicle			1.00

pregnancy. Finally, the pregnancy may lead to a live birth, the delivery of one or more live-born infants. (The birth of twins, triplets, or more is counted as one live birth.)

However, the existence of an *iatrogenic complication* named *ovarian hyperstimulation syndrome* (OHSS) casts a constant concern in the ART practices. OHSS can be mild, moderate or severe, among which severe OHSS may jeopardize the woman's life. Typical syndromes of severe OHSS include weight gain, tense ascites, hemodynamic instability (orthostatic hypotension, tachycardia), respiratory difficulty (tachypnea), progressive oliguria, and laboratory abnormalities. The severe OHSS rates reported in the medical literature are inconsistent: for example, Klemetti et al. (2005) reports that the incidence of severe OHSS varies between 0.7% and 1.7%, while Delvigne and Rozenberg (2002) report a range from 0.5% to 5%. While the pathology of OHSS has not yet been fully understood, it is widely accepted by clinicians that overdosing of exogenous gonadotropin is the main trigger of OHSS.

Moreover, one of the common causes of infertility, *polycystic ovary syndrome* (PCOS), especially exposes women undergoing the COH treatment with higher OHSS risk, because PCOS patients are *more sensitive* to gonadotropin stimulation compared with normal patients (Balasch et al., 2001; Aboulghar and Mansour, 2003; Tarlatzis, 2002). A study by Delvigne and Rozenberg (2002) reports that 63% of severe OHSS patients show ultrasonically diagnosed PCOS, while another study of 128 Belgian OHSS patients shows that 37% of them suffer from PCOS compared with 15% PCOS incidence among 256 non-OHSS patients. PCOS patients are the target group of this study.

With the increase of gonadotropin dosages, the probability of more follicles growing into high quality oocytes, and thus the pregnancy probability, increases. Yet the OHSS risk becomes greater with heavier dosing (over-stimulation), particularly for PCOS patients. In Heijnen et al. (2004), the authors propose "the most informative end-point of success in IVF to be the term singleton birth rate per started IVF treatment in the *overall context of patient discomfort, complications and costs*." Besides the overall live-birth rate, CDC's Assisted Reproductive Technology Reports present "a second measure of success based on the delivery of a live singleton. Singleton live births are a key measure of ART success because they carry a much *lower risk* than multiple-infant births for *adverse health outcomes, including prematurity, low birthweight, disability, and death*." On the other hand, the pregnancy probability becomes low with insufficient gonadotropin dosage administration (understimulation). A failed COH treatment results in a heavy burden for patients physiologically, psychologically, and economically. Therefore, in each COH treatment cycle, clinicians have to closely monitor the physiological responses of each *individual* patient, to *dynamically* decide the proper gonadotropin dosages (level of stimulation), to trade off the pregnancy probability and OHSS risk.

In He et al. (2010), we formulate the optimal dosing problem in the COH treatment cycle as a discretized Markov decision process (MDP), and solve it exactly using a slightly modified backward dynamic programming method. We then analyze the impact when clinicians misclassify a patient's physiological sensitivity to gonadotropin dosages.

However, the MDP implementation takes about 41.2 h to obtain the optimal dosing policy, as a result of the well-known *curses of dimensionality*, i.e., the explosion of the state, outcome, and decision spaces. In this paper, we design three approximate dynamic programming (ADP) algorithms to tackle the problem of dimensionality, one of which spends less than eight seconds to obtain the dosing policy with similar performance as the MDP benchmark. The successful ADP design lies in our understanding and utilization of problem structures.

Our study contributes mainly in three aspects. Firstly, we introduce the ADP modeling and algorithmic tool to assist clinical decision making (optimal dosing) in the COH treatment. Secondly, the flexibility in ADP modeling and the significant reduction of solution time offers the potential to analyze the dosage problem in more realistic and complicated settings as well as integrating successful clinical practices. Furthermore, we also experiment on some ADP algorithmic issues, which enriches the ADP literature on algorithm design and experimentation.

Next, we describe the mathematical model of the optimal dosing problem in Section 2 and briefly review the discretized MDP implementation in Section 3. In Section 4, we describe our design of ADP algorithms and key algorithmic issues. In Section 5, we report our experiment results on the ADP algorithm performances. We conclude the paper in Section 6.

Table 1
The truncated normal distributions.

	Dosage (ampoule)	$\ln(E_2)$ (ln(pg/ml)/day)	Ovary (mm/day)	Follicle (mm/day)
μ	2	0.46	1.90	1.25
	3	0.57	2.53	1.36
σ	2	0.13	0.35	0.63
	3	0.10	0.24	0.52
LB		0.20	1.00	0.50
UB		0.60	4.00	2.00

2. The mathematical model

We study the *controlled ovarian hyperstimulation* (COH) treatment of high-responsive PCOS patients, who tend to be sensitive to exogenous gonadotropin administration (He et al., 2010). Each individual patient may respond differently and her physiological responses are unknown until the gonadotropin is administered. We assume the responsiveness of the PCOS patients can be described statistically, and we can obtain the probability distribution of their responsiveness based on clinical literature, statistical fitting of clinical records, and expert opinions.

In this section, we formulate a stochastic dynamic optimization model to study the dosing problem in the COH treatment cycle, where clinicians adjust the gonadotropin dosages according to