Life begins as a POMDP: improving decision making in the IVF clinic

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***Abstract*—Patient outcomes after in vitro fertilization (IVF) are heavily dependent on subjective treatment decisions made by physicians based on limited information. Because the optimal outcome of IVF is to achieve a singleton pregnancy, physicians often attempt to identify exactly one viable embryo to transfer to patients. However, embryo viability cannot be observed directly and must instead be predicted by a series of morphological assessments. In this study, the period of embryo culture between fertilization and transfer was modeled as a partially observable Markov decision process (POMDP). A near-optimal policy was determined for each of two reward functions which represent desirable outcomes in clinical situations, and the actions resulting from those policies were compared to actions physicians would take in those scenarios. By combining information from POMDP solutions with human decision-making in the IVF clinic, physicians could more reliably choose a treatment plan for each patient which reduces the risk of undesirable outcomes and maximizes overall pregnancy rates.**

Introduction

The process of disease diagnosis and treatment requires physicians to make decisions based on limited observations of a patient's actual condition. In recent years, there has been growing interest in modeling the complex process of medical decision-making as a partially observable Markov decision process (POMDP) in order to more methodically determine optimal courses of treatment[1], [2]. This method has been thus far been applied to a limited range of medical scenarios, including ischemic heart disease[3], Parkinson's disease[4], and breast cancer[5].

In the current clinical practice of IVF, a patient starts a treatment cycle with hormones which stimulate several egg-containing follicles to grow. Once the eggs are determined to be sufficiently mature, they are collected and fertilized via regular IVF or intra-cytoplasmic sperm injection (ICSI), depending on sperm quality. The resulting embryos are then incubated overnight and a fertilization check is performed the following morning to assess whether fertilization actually occured. Typically, the majority of eggs collected are able to fertilize successfully so the clinicians are then tasked with choosing which and how many embryos to transfer back to the patient in hopes of achieving a successful pregnancy. The selection of embryos for transfer is a difficult problem because the desired outcome is not just for the patient to become pregnant, but also to have a *singleton* pregnancy. Multiple gestation pregnancies are associated with significantly higher medical costs, risks of complications, and neonatal mortality, so transferring too many viable embryos will also lead to a suboptimal outcome.

Selecting embryos for transfer requires an assessment of embryo quality to predict viability. The current gold standard to determine quality is to culture embryos for several days after fertilization (typically to the day 3 cleavage stage, or to the day 5-6 blastocyst stage), and simply designate those which do not arrest as viable. Although this method can eliminate many embryos which are not viable from consideration for transfer, is also causes significant stress to all embryos as extended time in culture can negatively affect patterns of gene expression and epigenetic reprogramming[6]. Therefore, it is important to balance the information gathered from extra time in culture with the stress caused by the culture process itself.

In addition to viability determination by attrition, clinicians can also gather information about viability based on morphological features such as cell number, symmetry, and degree of fragmentation. Unfortunately these features are highly subjective and only moderately correlated with viability[7]. Therefore, between the time of fertilization and the time of transfer to the patient, clinicians must make a series of viability assessments, decide how long to culture a group of embryos, and determine which embryos to transfer in order to achieve a singleton pregnancy. In this paper, we model the first 5 days of embryo development as a POMDP and compare the resulting policy to typical treatment decisions made by physicians.

Methods

Approach: The process of embryo development from the time of fertilization check (day 1) to the last possible culture day (day 5) was modeled as a partially observable Markov decision process (POMDP), which includes a set of states S, actions A, and observations Θ as well as a transition matrix $T(s'|s,a)$, an observation function $O(o|s,a)$ and a reward function $R(s,a)$.

$$POMDP = \{S, A, \Theta, T, O, R\}$$

Representation of Embryo Culture: The POMDP is represented by the EmbryoCulture type and parameterized

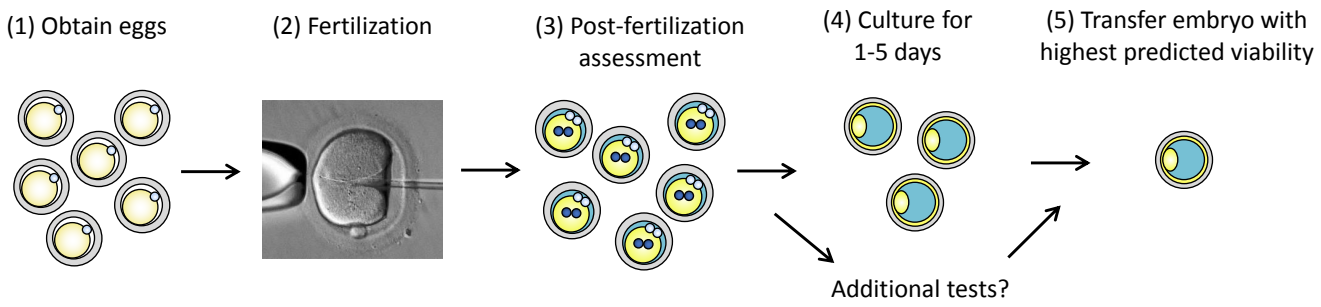

Figure 1. Typical clinical workflow in IVF. After fertilization, clinicians must decide for how long to culture embryos, and then which one(s) to transfer back to the patient to maximize her chances of a singleton pregnancy.

by the number n of embryos which successfully fertilize. The status of the embryos in culture is tracked over 5 days, which is typically the longest possible time physicians can culture embryos before they must decide which to transfer to the patient. Each time step in the model (Δt) represents 1 day in culture, because embryo morphology is generally assessed only once per day by clinical staff.

State Space: The current state of the embryo culture consists of the following variables:

$$EmbryoState = \{n, v, m_v, m_{nv}, d\}$$
$$m_v = [\#m_{v,poor}, \#m_{v,fair}, \#m_{v,good}]$$
$$m_{nv} = [\#m_{nv,poor}, \#m_{nv,fair}, \#m_{nv,good}]$$

In the EmbryoState structure, n is the number of embryos in culture, v is the number of those which are viable, m_v is the 3x1 morphology vector containing the number of viable embryos with poor/fair/good morphology, m_{nv} is the 3x1 morphology vector containing the number of nonviable embryos with poor/fair/good morphology, and d is the day in culture. Because the embryos can be cultured for up to 5 days, d must be an integer from 1 to 6 ($day = 6$ represents a "done" state where the embryos have already been transferred or discarded). The size of the state space is:

$$|S| = 6n \sum_{i=0}^{n} \frac{(i+1)(i+2)(n-i+1)(n-i+2)}{4}$$

There are 6 possible values of d, n possible values of v, and the term inside the sum represents the number of possible arrangements of m_v and m_{nv} for v viable and $(n-v)$ nonviable embryos for $v = i$. An alternate representation of the state space was initially explored containing the viability status and morphology of each individual embryo in culture. However, this resulted in a state space of size 50^n, which was significantly more difficult to deal with computationally and was abandoned in favor of the representation described here.

Action Space: The actions available to the embryologist during embryo culture are represented by the following variables:

$$EmbryoAction = \{a, tr\}$$

$$a \in \{CC, TR, D\} \quad tr \in 1:n$$

In the EmbryoAction structure, a represents the action taken by the embryologist, where CC = "continue culture," TR = "transfer to patient," and D = "discard all." If action TR is chosen, then the tr variable represents the number of embryos to transfer. These are chosen based on morphology, regardless of whether they are viable or nonviable, because the embryologist can only observe morphological information and not viability directly. If there are many embryos with equal morphology, then a random subset of size tr is chosen from among them. The size of the action space for an EmbryoCulture POMDP with n embryos is

$$|A| = 2 + n$$

Observation Space: The variables observed by the embryologist are the following:

$$EmbryoObservation = \{n, m, d\}$$

In the EmbryoObservation structure, n represents the number of embryos in culture, m represents the 3x1 morphology vector of all embryos in culture (because the embryologist does not know which are viable and which are nonviable), and d represents the day in culture. The observation depends on the state as follows:

$$observation.n = state.n$$
$$observation.m = state.m_v + state.m_{nv}$$
$$observation.d = state.d$$

The size of the observation space is

$$|O| = 6\frac{(n+1)(n+2)}{2}$$

There are 6 possible values of d, and the fraction represents the number of possible morphology vectors of n total embryos. In this representation, the observation matches exactly with the morphology of all embryos in culture; in the future, random noise could be added to this observation to reflect the subjectivity of physician assessments of embryo morphology.

Transition Function: Of the n total embryos which we start with in culture, typically only a number v of these will be viable, and this number may decrease over time. Although a particular embryo may start out as viable at day 1, on each subsequent day it may experience a failure in chromosome segregation or some other event which could render it nonviable. Once an embryo becomes nonviable, it will stay that way forever as chromosomal abnormalities hardly ever revert to normal. Therefore, we can represent the viability of a single embryo e over time as:

$$\begin{aligned} &e \in \{viable, nonviable\} \\ &p\left(e(t+1) = viable | e(t) = viable\right) = p_v \\ &p\left(e(t+1) = viable | e(t) = nonviable\right) = 0 \end{aligned}$$

The value of p_v used in this project was 0.9 based on findings in the literature that only around 50-60% of fertilized embryos at day 1 can successfully develop to day 5. If we have a group of v viable embryos, then the number of viable embryos at the next day in culture can be represented by a sum of Bernoulli random variables each with parameter p_v, which is a random variable with the Binomial distribution and parameters v and p_v.

$$p\left(v(t+1)\right) \sim Binomial\left(v(t), p_v\right)$$

All of the n embryos in culture also have a morphological parameter associated with them which is visible to the embryologist. Although morphology is generally a poor predictor of embryo viability, viable embryos have been shown to have slightly better morphological scores than nonviable embryos. The morphology of embryo e in culture at day 1 is therefore initialized as follows (where e_v represents the case of a viable embryo and e_{nv} represents a nonviable embryo):

$$m(e) \in \{poor, fair, good\}$$

$$m\left(e\left(t=1\right)\right) \sim Binomial(2, 0.9)$$

This represents most embryos starting with fairly good morphology, which may change over time depending on the embryo's viability status. At each time step after fertilization, an embryo may retain its morphology, or it may experience a reduction either from $good \rightarrow fair$ or $fair \rightarrow poor$ (but not from $good \rightarrow poor$). Although nonviable embryos may continue to develop normally and retain their morphological status for several days after fertilization, they do have a higher change of experiencing a reduction in morphology compared to viable embryos.

$$p\left(m(e(t+1)) = m(e(t))\right) = \begin{cases} p_{n,v} & e_v \\ p_{n.nv} & e_{nv} \end{cases}$$

In this paper, we used a value of 0.5 for $p_{n,nv}$, and 0.9 for $p_{n,v}$ to represent how at each time step, each embryo will retain its morphology with a certain probability based on whether it is viable or not. Otherwise, its morphology will be lowered by one level. To calculate the transition probability p from EmbryoState $s_t \rightarrow s_{t+1}$, the following procedure was used:

1) If $s_t.v < s_{t+1}.v$, then some $x = (s_t.v - s_{t+1}.v)$ viable embryos must have become nonviable from $t \rightarrow t+1$. Remove the x embryos with the poorest morphology values from $s_t.m_v$
2) Add x embryos with those same morphology values to $s_{t+1}.m_{nv}$
3) Calculate probability that $s_t.m_v$ transitioned into $s_{t+1}.m_v$. Start with embryos with lowest morphology in $s_{t+1}.m_v$ and match those to embryos with lowest morphology in $s_t.m_v$. For each embryo, multiply p by $p_{n,v}$ or $(1 - p_{n,v})$ based on whether that embryo maintained its morphology or went down a level.
4) Repeat step 3 but for $s_t.m_{nv} \rightarrow s_{t+1}.m_{nv}$
5) Multiply p by $p_v^{v-x}\left(1-p_v\right)^x$ since x embryos became nonviable and $v - x$ remained viable.

Reward Function: The reward function was designed to encourage the transfer of a single viable embryo to the patient. A high positive reward was provided for transferring exactly one viable embryo (and any number of nonviable embryos) to the patient. A smaller reward (or no reward) was provided for transferring two viable embryos, and no reward (or a negative reward) was provided for transferring 3 or more viable embryos. These rewards reflect the strong preference that most patients have towards becoming pregnant vs not, but also the preference to just have one baby rather than twins or more. A strong negative reward was provided for transferring only nonviable embryos, as this would represent the patient not becoming pregnant, or potentially experiencing a miscarriage.

If it is likely that there are no viable embryos, the embryologist also has an option to discard all the embryos and avoid wasting the patient's time with a transfer that fails to result in a pregnancy. There is a small negative reward for discarding all embryos if none are viable, and a large negative reward for discarding all embryos if one or more is viable. This setup incentivizes discarding all embryos if none are viable, but transferring at least one embryo if one or more are viable.

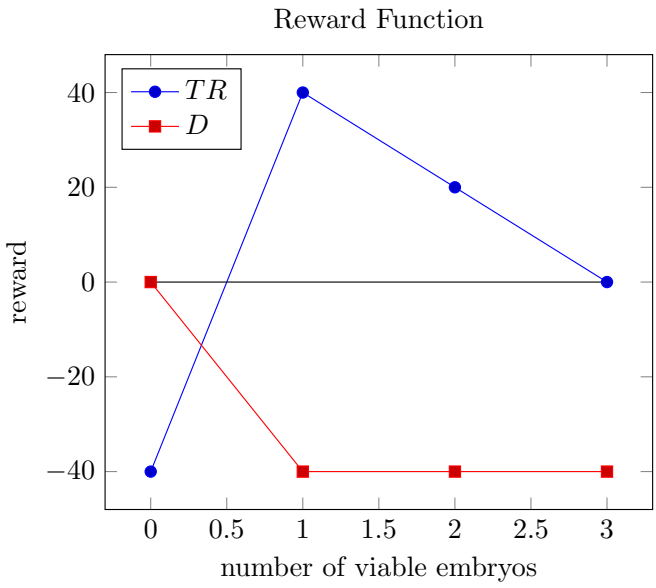

Figure 2. Example reward function shape depending on which action (TR = transfer some, D = discard all) is taken.

Finally, there is a small negative reward for choosing to do nothing (continue culture), but by the 5th time step, the embryos must be either transferred or discarded because culture cannot continue any further. Once a transfer or discard action has been performed, the embryo culture is put in a terminal state (regardless of which day the transfer or discard was performed) and no further rewards can be obtained.

Solution Methods

The embryo culture scenario was represented in Julia using the POMDPs package. Solutions were obtained using the SARSOP[8] package for scenarios with up to 3 embryos, and a discount factor of 1 was used to apply equal importance to rewards at all time steps. The following reward functions were tried to reflect different clinically desirable outcomes:

R1 : Prioritize transfer of single viable embryo, strongly discourage transfer of no viable embryos. For number of viable embryos transferred $v = [0, 1, 2, 3+]$, the reward given is $R = [-80, 80, 0, 0]$. This represents an ideal reward scenario that many IVF clinics would like to follow (avoid twins or higher gestation pregnancies due to medical risks).

R2 : Prioritize pregnancy with more tolerance to failed cycle (transfer of no viable embryos). For number of viable embryos transferred $v = [0, 1, 2, 3+]$, the reward given is $R = [-40, 40, 20, 0]$. This represents the reward scenario typically used in IVF clinics (where many patients just want to get pregnant rather than not due to the time and money they are investing).

	average reward	95% CI (lower bound,upper bound)
R1	-13.31	(-15.6, -11.0)
R2	-13.24	(-16.1,-10.3)

Table I
AVERAGE REWARDS FROM POLICIES FOR R1 AND R2

RESULTS

Using the policies obtained from running the SARSOP algorithm on the reward profiles mentioned above, 160 simulations were performed. Outcome information was recorded regarding the reward obtained, the day the transfer (or discard) was performed, and the number of embryos transferred . The simulations sampled a wide range of starting states by varying the number of viable embryos in culture from 0 to 3, and by randomly generating the starting morphology distributions of the viable and nonviable embryos. In some scenarios, nonviable embryos had the same starting morphology as the viable embryos, and in other scenarios they had on average poorer starting morphology. Average rewards over 500 simulations and 5 time steps are displayed in Table 1 and were found to be approximately the same for both policies. The fact that average rewards are negative means that even with the "optimal" policy calculated with the SARSOP algorithm, less than 50% of patients have a positive outcome after IVF, which mirrors what we see in the real world (~20-30% of IVF cycles result in a pregnancy).

The average number of embryos transferred over all simulations is shown in the left panel of Figure 3, split by the starting number of viable embryos in the simulation. In the first reward scenario (R1 = [-80,80,0,0]), the number of embryos transferred increases as the number of viable embryos in culture increases. However, the trend appears to level off when there are 3 viable embryos present in culture, as this scenario penalizes the transfer of too many viable embryos. For the second reward scenario (R2 = [-40,40,20,0]), the correlation between the number of viable embryos in culture and the number of embryos transferred is much stronger. This policy makes sense because there are still rewards to be had even when 2 viable embryos are transferred, so the policy has no reason to avoid transferring too many viable embryos.

The outcomes of the two policies in the left panel of Figure 3 are shown in the right panel of the same figure. As expected, the policy derived from the second reward function R2 results in a much higher percentage of cases where 2 or more viable embryos are transferred to the patient (and thus over double the rate of multiple gestation pregnancies compared to the policy derived from R1). However, the R2 policy also results in many fewer cases of failed transfers (transfers with no viable embryos) compared to the R1 policy. Although the singleton pregnancy rate resulting from R1 is higher, the overall pregnancy rate from R2 is higher. It is clearly difficult to optimize

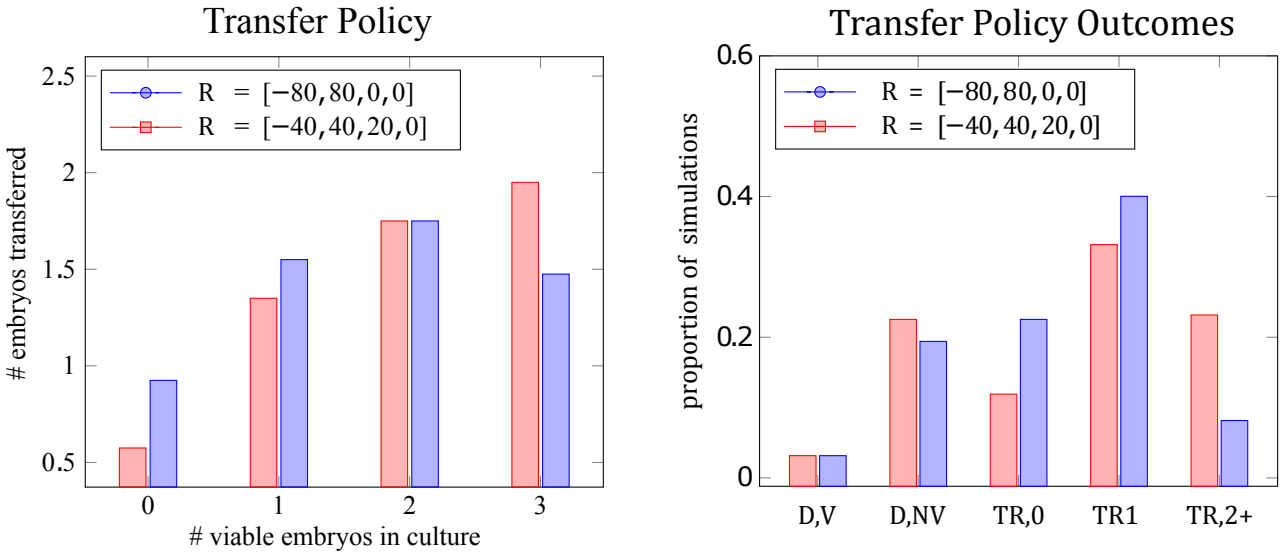

Figure 3. Average transfer policies and outcomes derived from two different reward profiles: R1 = [-80,80,0,0] and R2 = [-40,40,20,0] for transferring $v = [0, 1, 2, 3+]$ viable embryos. Key: D,V = at least one viable embryo was discarded (patient could have become pregnant if better choice was made). D,NV = all embryos were discarded but none were viable (best possible outcome if no viable embryos present in culture). TR,0 = Embryos were transferred to patient but none were viable (no pregnancy resulted). TR,1 = Exactly one viable embryo (and possibly other nonviable embryos) was transferred to patient (singleton pregnancy). TR,2+ = At least 2 viable embryos were transferred to patient (multiple gestation pregnancy).

for only singleton pregnancy outcomes in IVF, likely due to the poor predictive value of choosing embryos based on morphology alone.

The relationship between observed morphology and type of discard/transfer action taken was also explored. Although the optimal action depends on the belief state and not directly on the observation (some observations could lead to more than one action depending on belief state), there was a clear correlation between morphology distribution and number of embryos transferred.

The "D" action (discard all) was generally chosen when there were no observed embryos with good morphology. Because nonviable embryos have a much higher chance of experiencing a reduction in morphology from one day to the next, a lack of good morphology embryos likely indicates a lack of viable embryos. The "TR2" and "TR3" actions (transfer top 2 or 3 embryos according to morphology, respectively) were chosen when there were embryos with both good and poor morphology present. It is likely that this action was chosen because the good morphology embryos were most likely to be viable, and transferring additional embryos of lower quality could compensate in the event that the good morphology embryos were actually not viable. The "TR1" action was generally chosen when there were only fair and good quality embryos observed. Because in this scenario it is likely that all observed embryos are viable, only one embryo is chosen for transfer.

The policy reflected in Figure 4 matches up fairly well with physician actions in the IVF clinic; although generally physicians strive for single embryo transfer, many patients have only poor or fair morphology embryos available and it is difficult to choose a single viable embryo based on morphology alone. In these cases, physicians may choose 2 or more embryos for transfer to the patient, which is reflected in the policy derived here.

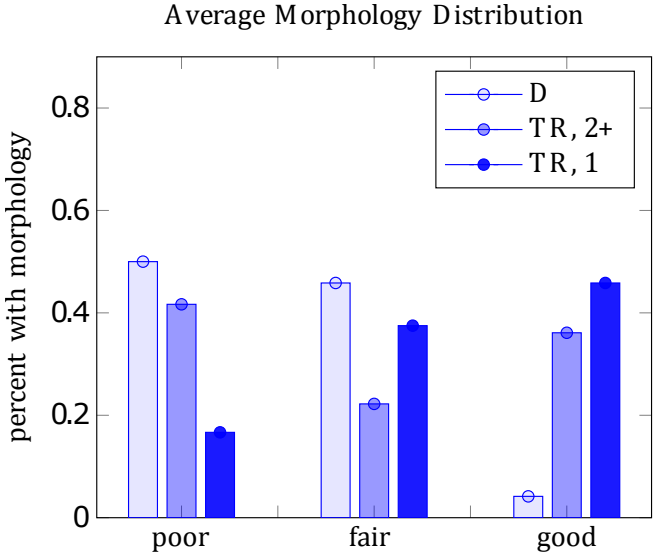

Figure 4. The action chosen by the policy depends heavily on the observed morphology distribution at that time step. In general, only one embryo is transferred when there are mostly good morphology embryos observed, and more are transferred when there are poor and fair morphology embryos present as well. If there are no good morphology embryos present, then usually they are all discarded.

Discussion

The modeling of embryo culture after IVF as a POMDP in this paper represents a first attempt at reproducing

and optimizing the decision-making process physicians must repeat every day in order to maximize benefits to patients. The policy derived from application of the SARSOP algorithm to a POMDP with 3 embryos appeared to match reasonably well with the policy currently practiced in the IVF clinic. When a patient has embryos with mostly good morphology, physicians feel comfortable conducting single embryo transfer because it is likely they are transferring a viable embryo. When a patient has embryos with mixed or poor morphology, physicians often transfer more in the hopes that at least one will be viable (and take the risk that the patient will end up with twins or triplets). Rarely, physicians discard all embryos in culture if they have mostly poor morphology to avoid wasting the patient's time in a failed transfer.

By modeling the process of embryo culture as a POMDP, it could become possible to vary the reward function according to desired clincal outcomes (or a specific patient's wishes), or modify the transition function according to statistics observed in the literature, and re-calculate a near-optimal policy. Physicians could then compare their intended actions to those recommended by the POMDP policy, and possibly receive help in making decisions if they are unsure how to proceed. Still, the policy calculated by the solution algorithm is highly dependent on the specific reward function chosen, which is based on subjective human assessments about the value of various clinical outcomes. For POMDPs to become practical for clinical use, the "rewards" given for clinical outcomes will have to be very carefully tuned, and physicians will have to figure out how to balance the actions recommended by the calculated to policy with their own intuition.

There are also a few limitations specific to the POMDP developed in this paper, the first of which is that only a simplified version of the embryo culture was represented. In reality, there are more types of morphological grades than the good/fair/poor used here, which would add significantly to the state space and further complicate the transition model. There are also several information-gathering actions which the physician can take, all of which have different levels of reliability. These include (but are not limited to) : gathering time lapse parameters which can give a moderately accurate prediction of viability, and performing a biopsy (preimplantation genetic screening, or PGS) which can yield highly accurate information about each embryo's chromosomal status.

The specific transition model used in this paper was also a simplified version of actual transition probabilities during embryo development, which can vary significantly between patients. An additional estimation step could be added in the future based on real patient data to more accurately simulate embryo development between the time of fertilization and transfer.

Finally, the computation time can also easily become an issue when modeling typical clinical scenarios. In the embryo culture POMDP, it took around 5 minutes to write out a pomdpx file and run the SARSOP agorithm for 3 embryos in culture. Although the state space was ultimately reduced to polynomial in size by carefully choosing the problem representation, it still took over 1 hour to find a solution for 4 embryos in culture, and over 12 hours for 5 embryos in culture. Because many patients have 10 or more embryos, some more effort will have to be directed toward fast, practical methods for representing and solving the POMDP of embryos in culture.

References

[1] A. J. Schaefer, M. D. Bailey, S. M. Shechter, and M. S. Roberts, "Modeling medical treatment using Markov decision processes," *Operations Research and Health Care*, pp. 597–616, 2005.

[2] C. C. Bennett and K. Hauser, "Artificial intelligence framework for simulating clinical decision-making: A Markov decision process approach," *Artificial Intelligence in Medicine*, vol. 57, no. 1, pp. 9–19, 2013.

[3] M. Hauskrecht and H. Fraser, "Planning treatment of ischemic heart disease with partially observable Markov decision processes.," *Artificial intelligence in medicine*, vol. 18, pp. 221–244, 2000.

[4] J. E. Goulionis and A. Vozikis, "Medical decision making for patients with Parkinson disease under Average Cost Criterion," *Australia and New Zealand Health Policy*, vol. 6, no. 1, p. 15, 2009.

[5] J. Chhatwal, O. Alagoz, and E. S. Burnside, "Optimal Breast Biopsy Decision-Making Based on Mammographic Features and Demographic Factors," *Operations Research*, vol. 58, no. March 2015, pp. 1577–1591, 2010.

[6] P. Guérin, S. El Mouatassim, and Y. Ménézo, "Oxidative stress and protection against reactive oxygen species in the pre-implantation embryo and its surroundings," *Human Reproduction Update*, vol. 7, no. 2, pp. 175–189, 2001.

[7] C. Racowsky, C. Racowsky, C. M. H. Combelles, A. Nureddin, Y. Pan, A. Finn, L. Miles, S. Gale, T. O. Leary, and K. V. Jackson, "Article Day 3 and day 5 morphological predictors of embryo viability," *Reproductive BioMedicine Online*, vol. 6, no. 3, pp. 323–331, 2003.

[8] H. Kurniawati, D. Hsu, and W. S. Lee, "SARSOP : Efficient Point-Based POMDP Planning by Approximating Optimally Reachable Belief Spaces," *Proceedings of Robotics: Science and Systems IV*, p. w/o page numbers, 2008.