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

Objective

The procedure of *in vitro* fertilization (IVF) relies heavily on subjective treatment decisions which are made based on limited information. For this project, I propose to model early embryo development as a partially observable Markov decision process (POMDP) and determine an optimal sequence of actions for a given set of embryos.

Problem Description

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.

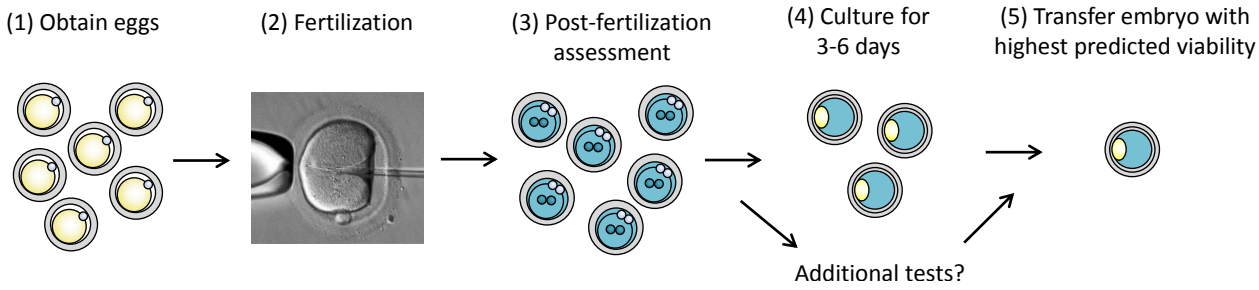

Figure 1: Typical clinical workflow in IVF. After fertilization, clinicians must decide for how long to culture embryos, and then which one(s) to transfer back to the patient to maximize her chances of a singleton pregnancy.

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. 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. These features are highly subjective and only moderately correlated with viability, but are noninvasive and easy to perform. Recent advances in research have also resulted in new, more accurate assessments of viability such as preimplantation genetic diagnosis and time lapse imaging. These tests can improve prediction over a morphological assessment alone, but have varying degrees of invasiveness and cost significantly more.

Therefore, between the time of fertilization and the time of transfer to the patient, clinicians must make a series of decisions regarding which assessments of viability to conduct, how long to culture, and which embryos to transfer in order to achieve a singleton pregnancy. It is possible that by modeling this process as a POMDP, we can come up with an optimal decision-making policy to maximize success rates.

Approach

The process of embryo development from the time of fertilization check to the time of transfer will be modeled as a POMDP, where:

1. If a patient starts with n fertilized embryos, there will be ground truth viability information for all embryos represented as an $nx1$ vector.
2. The **state space** describes each embryo's internal state with two parameters per embryo. The first of these two refers to the developmental status of the embryo, which is either arrested or still developing. The second parameter refers to the embryo's probability of arresting each day, which is related to its ultimate viability but also to its time in culture and also other random factors.
3. The **action space** consists of decisions the clinician may make each day. These consist of transferring one or more embryos, ordering additional viability tests, or simply doing nothing and waiting another day in culture.
4. The **observation space** consists of embryo morphological data, and it may also contain the results of optional viability tests ordered by the clinician. The **observation model** will account for the fact that clinician assessments of morphology and arrest are highly subjective and user-dependent.
5. The **reward model** will give positive rewards for transferring viable embryos, with a significant bonus for transferring only one viable embryo. It will give negative rewards for every additional day spent in culture, each additional viability test ordered, with a large negative penalty for transferring no viable embryos.
6. The **transition model** will advance the state of each embryo one time step based on its developmental status and its probability of arrest.

To test out this approach, I have a data set from research which contains data on morphology, developmental stage, time lapse parameters, and chromosomal status for 50-60 embryos. Since solving a POMDP may require a large amount of data, I am also considering simulating a much larger data set based on published statistics on human embryo viability and morphology.

Outcome Measures

The success of this approach will be measured by (a) the percentage of cycles which result in the transfer of at least one viable embryo, and (b) the percentage of cycles which result in the transfer of exactly one viable embryo. In IVF today, over 35% of pregnancies represent twins or higher order multiples, mainly due to the practice of transferring several embryos at once. For this reason, a huge percentage of IVF babies are born prematurely, have low birth weight, and are at increased risks of developmental delays. If this model is able to increase the rate of singleton pregnancies beyond 65%, it could eventually enable clinicians to improve their pregnancy rates, reduce complications, and even reduce the overall cost of IVF for their patients.