Probability Model-Based Optimization of IVF Treatment

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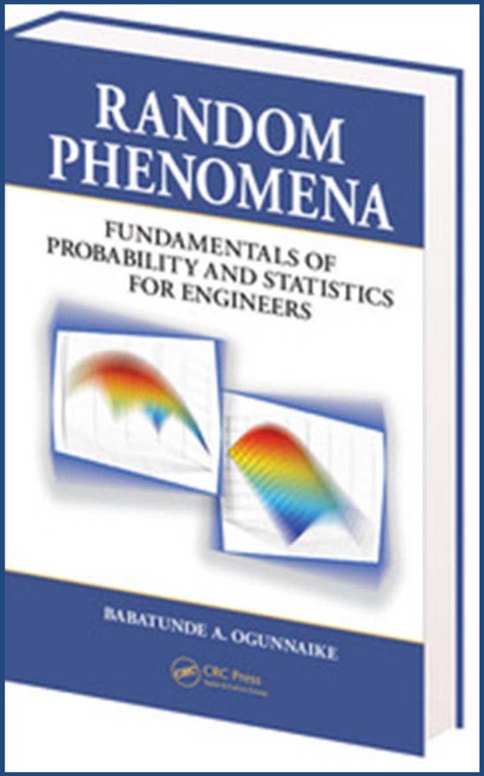
Case Study in Chapter 11



Outline

1. INTRODUCTION & MOTIVATION
2. PROBABILTY MODELING
3. IVF OPTIMIZATION RESULTS AND ANALYSIS
4. SUMMARY AND CONCLUSIONS

1. INTRODUCTION & MOTIVATION

What is In-Vitro Fertilization

http://www.youtube.com/watch?v=GeigYib39Rs

Primary Issues

- Which embryo should be selected for transfer?
- How many embryos should be transferred?
  - Too few: risk of ***failure*** increases
  - Too many: risk of ***multiple births*** increases
  - Objective in IVF: ***balance the two risks***
- Current Practice
  - Transfer as many as possible, opting for improved chances of success
  - Result: too many multiple births ("Octo-Mom!")

Problem Definition

- Determine *n*, number of embryos to transfer,
  - To maximize the chances of obtaining a singleton,
  - And simultaneously minimize the chances of
    - ***failure*** and
    - of ***multiple births***
- Approach
  - Mathematical modeling
  - Optimization using (validated) mathematical model

2. PROBABILITY MODELING

IVF Characteristics

- Each embryo transferred either results in a live birth (*a success*), or not (*a failure*)
- The two outcomes are mutually exclusive
- Which of the two mutually exclusive outcomes is the final result is UNCERTAIN
- The transfer of *n* embryos is akin to *n* simultaneous *but independent* single embryo "attempts"
- *x*, the number of live births resulting from the *n* transferred embryos is also uncertain

SAME CHARACTERISTICS AS BINOMIAL R.V.

Probability Model

- The probability of obtaining *x* live births from *n* embryos transferred:

$$f(x) = \binom{n}{x} p^x (1-p)^{n-x}$$

- Parameter *p*: the single embryo probability of success (also "embryo implantation potential")
- Utility
  - Prediction
  - Analysis & Optimization

Model Prediction

TABLE 11.1: Theoretical distribution of probabilities of possible outcomes of an IVF treatment with 5 embryos transferred and $p = 0.2$

x No. of live births in a delivered pregnancy	$f(x)$ Probability of occurrence	$\eta(x)$ Expected total no. of patients (out of 1000) with pregnancy outcome x
0	0.328	328
1	0.410	410
2	0.205	205
3	0.051	51
4	0.006	6
5	0.000	0

Model Validation: Data

- From single IVF clinic
  - 42 months; 2173 patients; total of 6601 embryos

TABLE 11.2: Elsner, *et al.* data of outcomes of a 42-month IVF treatment study

x Delivered pregnancy outcome	No. of patients receiving $n = 1, 2, \ldots 6$ embryos with pregnancy outcome x						$\eta_T(x)$ Total no. patients with pregnancy outcome x
	$\eta_1(x)$	$\eta_2(x)$	$\eta_3(x)$	$\eta_4(x)$	$\eta_5(x)$	$\eta_6(x)$	
0	205	288	413	503	28	2	1439
1	22	97	164	207	13	1	504
2	0	17	74	84	5	1	181
3	0	0	10	32	1	0	43
4	0	0	0	6	0	0	6
5	0	0	0	0	0	0	0
Total	227	402	661	832	47	4	2173

Elsner, C.W., M.J. Tucker, C.L. Sweitzer, *et al.*, 1997. Multiple pregnancy rate and embryo number transferred during in vitro fertilization, *Am J. Obstet Gynecol.*, 177 (2), 350–357.

Model Validation: Data vs Model

- Parameters estimated from stratified data
  - Younger (< 36 years)
  - Older (> =37 years)

TABLE 11.5: Stratified binomial model prediction of Elsner, *et al.* data

Delivered pregnancy outcome x	Total number of patients with pregnancy outcome x					
	Younger ($\leq$ 36 yrs)		Older ($\geq$ 37 yrs)		Overall	
	Data	$\eta_T^y(x)$	Data	$\eta_T^o(x)$	Data	$\eta_T(x)$
0	846	816	593	566	1439	1382
1	349	399	155	198	504	597
2	130	118	51	43	181	161
3	31	24	12	6	43	30
4	3	2	3	1	6	3
5	0	0	0	0	0	0
Total	1359	1359	814	814	2173	2173

Model Validation: Data vs Model

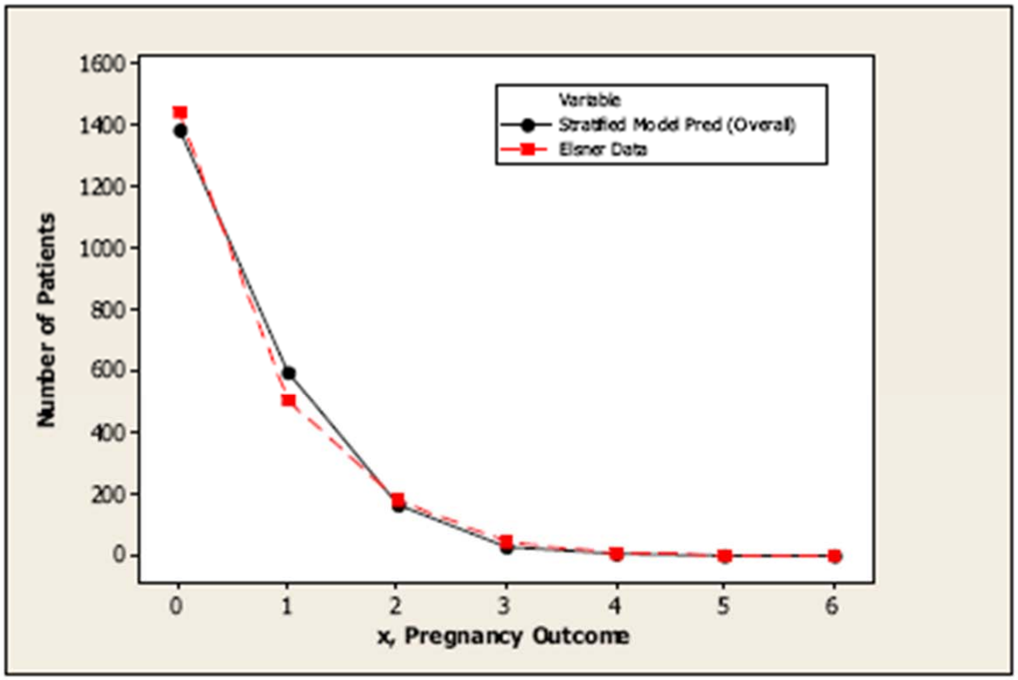


FIGURE 11.6: Complete Elsner data versus stratified binomial model prediction.

Mathematical Problem Formulation

- Three probabilities of interest
  - $P_0=P(X=0)$: probability of unsuccessful treatment
  - $P_1=P(X=1)$: probability of singleton
  - $P_{MB}=P(X>1)$: probability of multiple births

$$P_0 = (1-p)^n \quad \text{Minimize}$$

$$P_1 = np(1-p)^{n-1} \quad \text{Maximize}$$

$$P_{MB} = 1-(1-p)^n - np(1-p)^{n-1} \quad \text{Minimize}$$

- Constraint: $P_0 + P_1 + P_{MB} = 1$

Maximizing P_1 simultaneously minimizes $(P_0 + P_{MB})$

Mathematical Problem Formulation

- Determine *n* to maximize

$$f_n(1) = np(1-p)^{n-1}$$

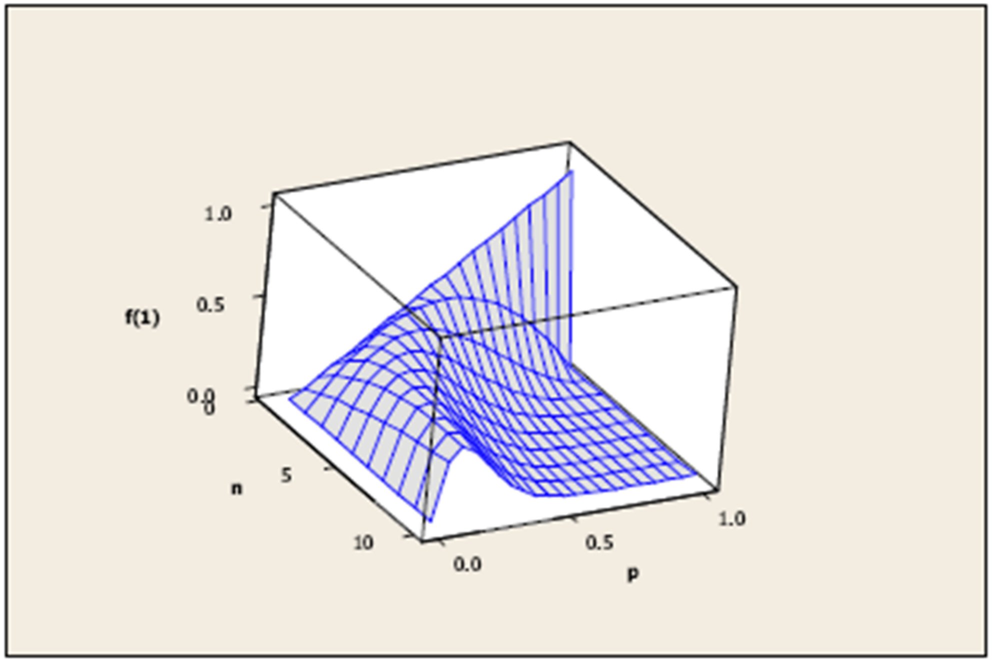


FIGURE 11.8: Surface plot of the probability of a singleton as a function of p and the number of embryos transferred, n.

Problem Solution

- Use calculus:
  - df/dn = 0 [or d(ln f)/dn = 0]
  - Solve for n*

$$\frac{1}{n^*} = \ln\left(\frac{1}{1-p}\right)$$

Given p, the probability that a particular single embryo will lead to a successful pregnancy, the optimum number of embryos to transfer during IVF is given by the expression in Eq (11.16) rounded to the nearest integer.

Problem Solution

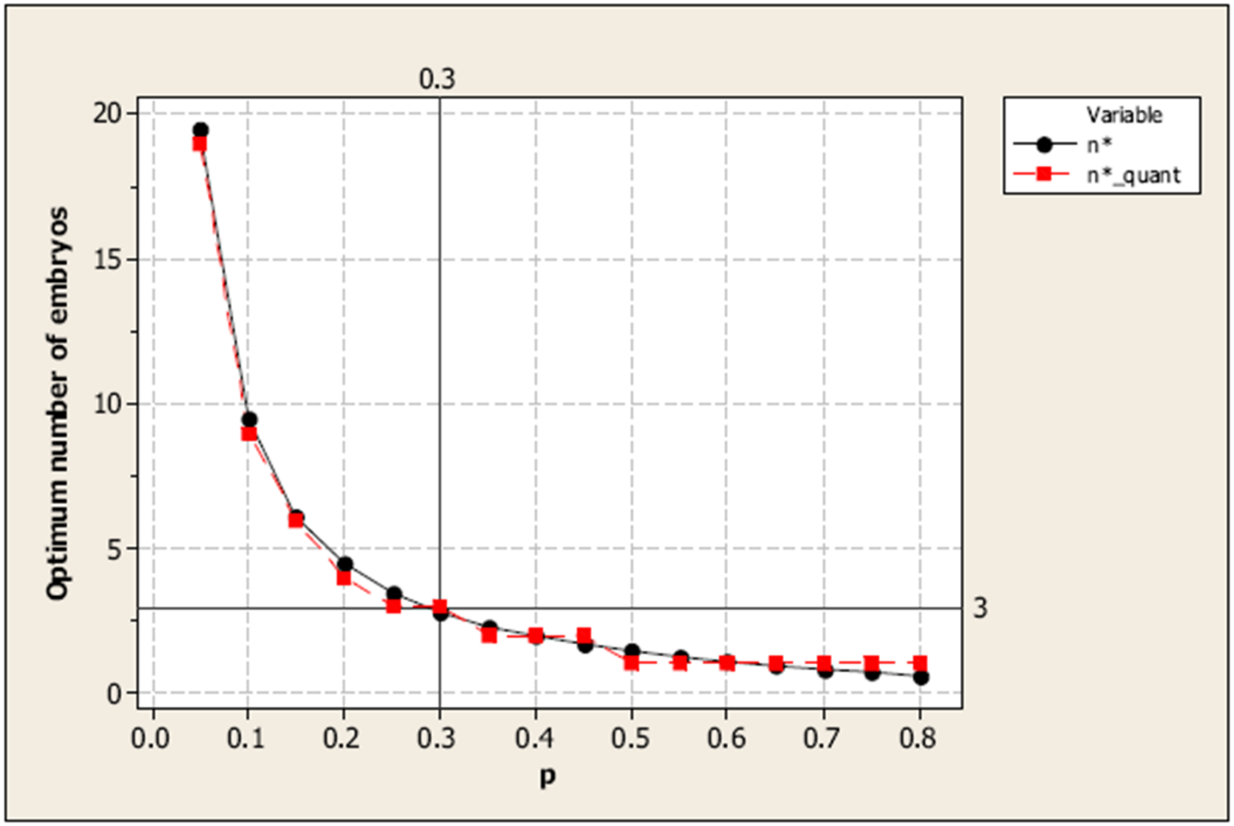


FIGURE 11.7: Optimum number of embryos as a function of p.

Optimized Probability of Singleton

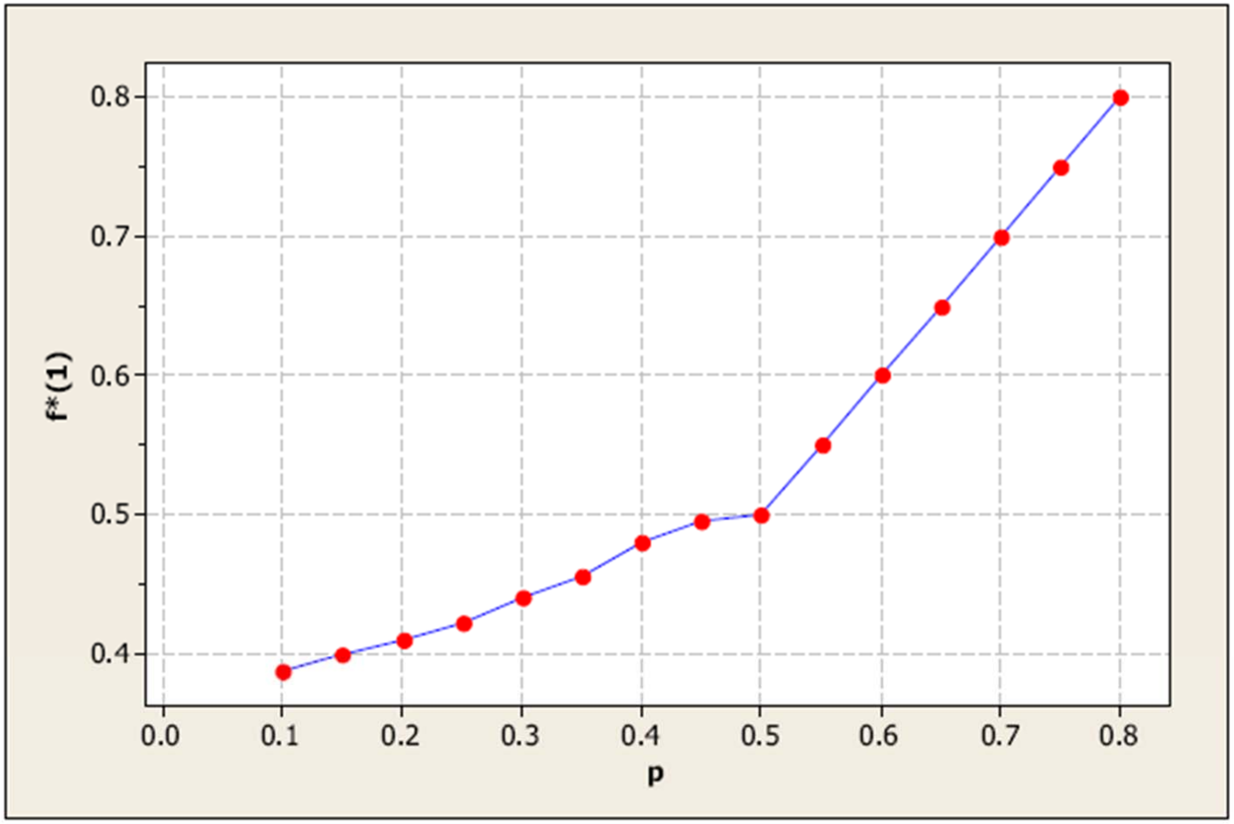


FIGURE 11.9: The (maximized) probability of a singleton as a function of p when the optimum integer number of embryos are transferred.

Problem Solution Implications

- Results and Recommendations
  - For “Good Prognosis” patients ($p>=0.5$), $n^*=1$
  - For “Medium Prognosis” patients ($0.25 < p < 0.5$)
    - ❖ $n^*=2$ (for $p > 0.35$)
    - ❖ $n^*=3$ (for $p < 0.35$)
  - For “Poor Prognosis” patients ($p < 0.25$), use formula
- Results agree with and generalize heuristics and government guidelines!

SUMMARY & CONCLUSIONS

- IVF Treatment outcome
  - *x* live births resulting from n embryos
  - is uncertain
- Rational IVF treatment Objective:
  - balance risk of failure against risk of multiple births
- Mathematics (probability/calculus) used to formulate and solve problem
  - Binomial Probability Model provides valid mathematical representation of reality
  - Used to determine optimum *n* given *p*
- Results agree with and generalize heuristics and government guidelines!