Chapter 4

BAYESIAN F-OPTIMAL DESIGNS

§4.1 Introduction

The general need for Bayesian optimal designs was motivated in Chapter 3. However, Chapter 3 only addressed the D-optimality criterion. Another criterion that is particularly important for the design of impaired reproduction studies is that of F-optimality. Often minimizing the variance of the coefficients is not as important as a criterion that deals with estimating an EC of interest. For example, in the Air Force study a researcher may be interested in accurately estimating the amount of jet fuel that at which 90% of maximum reproduction occurs (only 10% impairment). The design which allows the researcher to estimate this EC as accurately as possible is called an F-optimal design. The F-optimal design ensures precise estimation of an EC by minimizing the width of a confidence interval on the effective concentration (Finney, 1971). This interval is also known as a Fieller interval. In her dissertation, Chiacchierini (1996) showed that the F-optimal design is one which minimizes $\mathrm{var}(b_1)$ in the single regressor case, as a result this design is also called slope optimal design.

§4.2 Two Level Bayesian F-Optimal Designs under the Uniform Prior

The focus now turns to the development of the Bayesian design criterion under the uniform prior for the parameters. Again, the joint prior will be a product of the two marginals since it is assumed that β_0 and β_1 are independent. The priors are developed in the same way as in Section 3.2 of Chapter 3. So, $\beta_0 \sim U(a,b)$ where $a = \ln\lambda_{c,L}$ and $b = \ln\lambda_{c,U}$. Also, $\beta_1 \sim U(c,d)$ where $c = \frac{\ln(q_i)}{EC_L}$ and $d = \frac{\ln(q_i)}{EC_U}$. For the Bayesian F-optimal design, the $\operatorname{var}(b_1)$ is the Bayes risk rather than the negative of the Bayes risk as in the D-case. So, the goal is minimization of the criterion rather than maximization. The Bayesian F-optimal criterion is

$$\min_{\delta\in\mathcal{D}} \int R(\delta,\beta)\pi(\beta)d\beta = \min_{\delta\in\mathcal{D}} \int \operatorname{var}(b_1)\pi(\beta)d\beta \tag{4.2.1}$$

$$= \min_{\delta\in\mathcal{D}} \int \frac{n_1 e^{\beta_0+\beta_1 x_1} + n_2 e^{\beta_0+\beta_1 x_2}}{n_1 n_2 e^{\beta_0+\beta_1 x_1} e^{\beta_0+\beta_1 x_2} (x_1 - x_2)^2} \frac{1}{(b-a)} \frac{1}{(d-c)} d\beta$$

$$= \min\left[\frac{(e^{-a} - e^{-b})}{(b-a)(d-c)(x_1-x_2)^2}\left(\frac{(e^{-cx_2} - e^{-dx_2})}{n_2 x_2} + \frac{(e^{-cx_2} - e^{-dx_2})}{n_1 x_1}\right)\right]$$

Note that the expression for $\operatorname{var}(b_1)$ is taken from the information matrix. Like the D-optimal design, the F-optimal design is independent of the prior on β_0 since minimization of the function does not depend on the constant resulting from integration over its prior. With this quantity removed, the expression to minimize is given by

$$\left[\frac{1}{(d-c)(x_1-x_2)^2}\left(\frac{(e^{-cx_2} - e^{-dx_2})}{n_2 x_2} + \frac{(e^{-cx_2} - e^{-dx_2})}{n_1 x_1}\right)\right]. \tag{4.2.2}$$

An additional similarity to the D-optimal design is that the F-optimal design can also be classified as ratio constant. Recall that ratio constant means that the optimal Bayesian design for $\beta_1 \sim U(c,d)$ is the same as the optimal design for $\beta_1 \sim U(ac,ad)$ where a>0 in terms of effective concentrations and number of experimental units allocated to these ECs. The proof of ratio invariance is very similar to that of the D-case and is detailed in Appendix B.

The minimization of the expression by the Nelder-Mead algorithm yields the designs in Table 4.2.1. The first row is the ratio of the bounds for the uniform prior on β_1, $\frac{c}{d}$. The second row lists the EC of the non-control design point. Keep in mind that this is translated into natural units via the formula $x_i = \frac{\ln q_i}{\left(\frac{c+d}{2}\right)}$. The final row lists the amount of experimental units to be allocated to the non-control design point.

Table 4.2.1 Two Level F-Optimal Designs under the Uniform Prior.

Ratio	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**
Non-Control Design Point	$EC_{7.8}$	$EC_{8.33}$	$EC_{9.27}$	$EC_{10.1}$	$EC_{10.8}$	$EC_{11.4}$	$EC_{12.0}$
Percentage at Non-control	78%	78%	78%	77%	77%	77%	77%

Some comments about the table are in order. In the F-optimal case where the prior is the point prior, the design found by Nelder-Mead is the same as the one found by Chiacchierini (1996). Also, in contrast to the D-optimal case, the non-control ECs tend to move toward the center rather than toward the edge of the design region as the prior becomes more variable. However, there is not a large change in the non-control EC for adjacent priors. In fact, many of the differences are so small that the researcher would not be able to distinguish between them in practice. In addition, the percentage of experimental units allocated to the design points remains fairly constant. Both of these characteristics indicate that these designs are fairly insensitive to the prior.

§4.2.1 Two Level F-Optimal Design Example

Using the same experimental setup as the two level D-optimal design examples, an F-optimal two level design will be specified in natural units. Recall in the Air Force study example that $\lambda_c = 1.3$ million organisms and $\beta_0 = 14.7$. The bounds placed on the EC_{50} were 0.2888 to 1.1552. This was translated into a prior on β_1 such that $\beta_1 \sim U(-2.4,-0.6)$ for a ratio of 4 and a mean of -1.5. The F-optimal design for a ratio of 4 places 77% of the experimental units at the $EC_{12.00}$ and the remaining 23% at the control. Solving the equation for the value of the toxicant in natural units yields $EC_{12.00} = 1.41$ ml. With 180 available experimental units, this means that 139 would be placed at a level of concentration of 1.41 ml jet fuel and the remaining 41 would be placed at the control (no fuel). The F-optimal design and the comparable D-optimal designs for both priors are listed in Table 4.2.2. One can see that the three criteria produce very different designs under similar priors. Thus, the design that is used in practice depends on the importance of estimating a particular EC or minimizing the variance of the coefficients.

Table 4.2.2 Two Level Design Examples.

Design	p_c n_c	p_1 n_1	EC_{100q} x_1
F-Optimal **Uniform**	23% 41	77% 139	$EC_{12.00}$ 1.41
D-Optimal **Uniform**	50% 90	50% 90	$EC_{6.07}$ 1.87
D-Optimal **Normal**	50% 90	50% 90	$EC_{9.37}$ 1.58

§4.3 Type I Three Level F-Optimal Bayesian Designs Under the Uniform Prior

The expression to minimize in order to find the traditional three level F-optimal design is

$$\frac{n_1 e^{\beta_1 x_1} + n_2 e^{\beta_1 x_2} + n_3 e^{\beta_1 x_3}}{n_1 n_2 e^{\beta_1 x_1} e^{\beta_1 x_2} (x_1 - x_2)^2 + n_1 n_3 e^{\beta_1 x_1} e^{\beta_1 x_3} (x_1 - x_3)^2 + n_2 n_3 e^{\beta_1 x_2} e^{\beta_1 x_3} (x_2 - x_3)^2}. \tag{4.3.1}$$

The complicated nature of the Bayesian criterion using (4.3.1) as $R(\delta,\beta)$ makes it well suited to Monte Carlo integration. The same method of Monte Carlo integration used in the D-optimal case was carried out for the F-optimal case to simulate the expected value of the risk given in (4.3.1). When three level designs were left unconstrained, they degenerated to two level designs so Type I restrictions were once again placed on the three level criterion in order to establish usable three level designs. These restrictions place one level at the control, force the non-control levels to be symmetric around the region of operability, and force equal allocation at the two non-control design points. The regions of interest were specified as [EC_5,EC_{80}], [EC_{10},EC_{80}], and [EC_{20},EC_{80}]. Tables C1-C3 in Appendix C contain the actual designs and Figure 4.3.1 shows their efficiencies graphed by ratio. An efficiency for an F-optimal design for the Poisson exponential model is $E = \frac{\text{var}(b_1) \text{ for the optimal design}}{\text{var}(b_1) \text{ for the design of interest}}$. The efficiencies are calculated against the restricted non-Bayesian F-optimal design with known parameters on the same region.

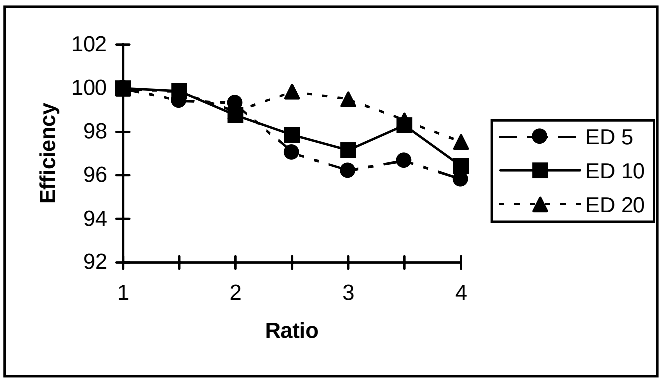

Figure 4.3.1 Efficiencies vs. Ratio For Type I F-Optimal Designs under the Uniform Prior

As in the D-optimal case, the efficiencies for these designs are quite good. The efficiencies have a slight downward trend as the prior gets wider. Again, these designs are fairly insensitive to the prior both in allocation of design points and levels. As in the D-case, the same formation of groups for the designs on the [EC_5,EC_{80}] are seen. This separation occurs after the ratio of two. The first three designs have similar design points and allocation percentages as do the last four designs.

§4.4 Robustness Issues and Type II Three Level F-Optimal Bayesian Designs

Now that the Type I three level designs have been discussed, an exploration of their performance under parameter misspecification is appropriate. When this performance was examined in a preliminary robustness study, results were extremely unfavorable. In some cases efficiencies against the two level designs under parameter misspecification were as low as 55%. Again, this poor performance results mainly from the sample size restriction placed on the two non-control levels in the Type I design. The Type II three level F-optimal designs offer vast improvements over the Type I design in terms of robustness. Note that Type II F-optimal designs have been altered slightly from those for the D-optimal design. This is due to the difference in the D and F criteria and their respective optimal two level designs. Recall that the Type II design still forces one of the design levels to be the control and requires that the two non-control levels be symmetric around the center of the region of operability. However, the sample size restriction is altered so that more observations are allowed to accumulate at the lower end EC in the F-case. In order for this to happen, the control and the upper end EC are forced to have equal sample sizes. The Type II designs and their efficiencies against the Chiacchierini's three level designs are listed in Appendix C in Tables C4-C6. The efficiencies for the Type II designs surpass Chiacchierini's for all regions and all priors. Not only are these designs efficient, but they also perform well in the robustness study.

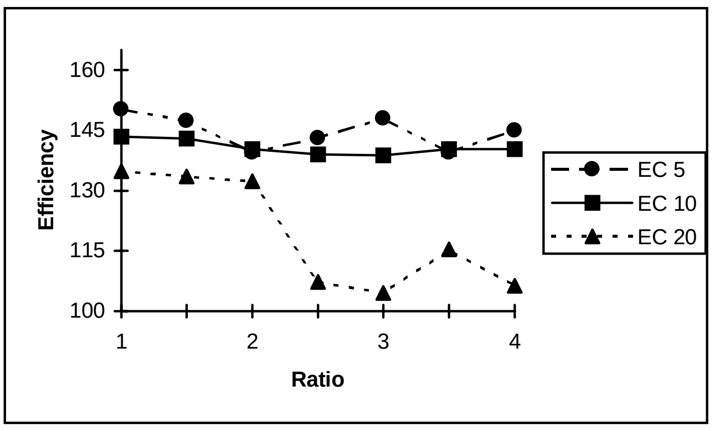

Figure 4.4.1 Efficiencies vs. Ratio for Type II F-Optimal Designs under the Uniform Prior

The study follows the same format as the D-optimal case. Three designs on the [EC_5,EC_{80}] with ratios of 1, 2.5, and 4 were examined. It is assumed that the prior on the EC_{50} is actually a prior on one of the following: EC_{30}, EC_{40}, EC_{45}, EC_{55}, EC_{60}, or EC_{70}. This severely affects the values of the true ECs of the design points with respect to the assumed prior. (For details on determining the true value of β_1 and the true ECs, see Section 3.10 of Chapter 3 for an example.) The results of the robustness study appear in Tables C7-C9 in Appendix C. The efficiencies of the

Type II designs under misspecification are graphed in Figure 4.4.2. These efficiencies were calculated against the optimal *two level design*.

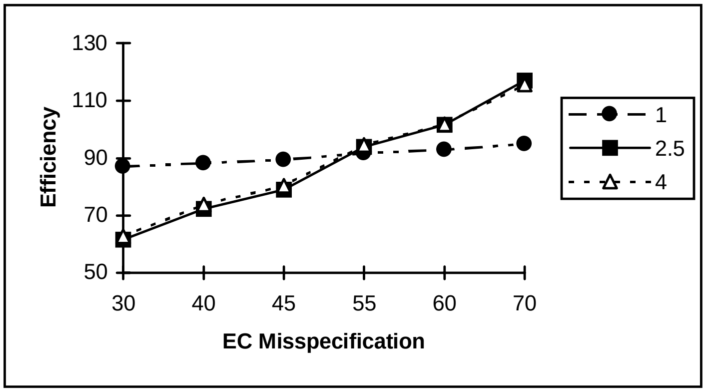

Figure 4.4.2 Two Level Efficiencies of Type II F-Optimal Uniform Designs under Misspecification.

While the Type II efficiencies against the two level design may seem unimpressive in light of the same ones for the D-study, Figure 4.4.3 demonstrates the improvement over the Type I designs. It is a graph of the efficiency of Type II designs vs. Type I designs under misspecification. With all but two efficiencies over 100%, there is no question as to which design to use in those cases.

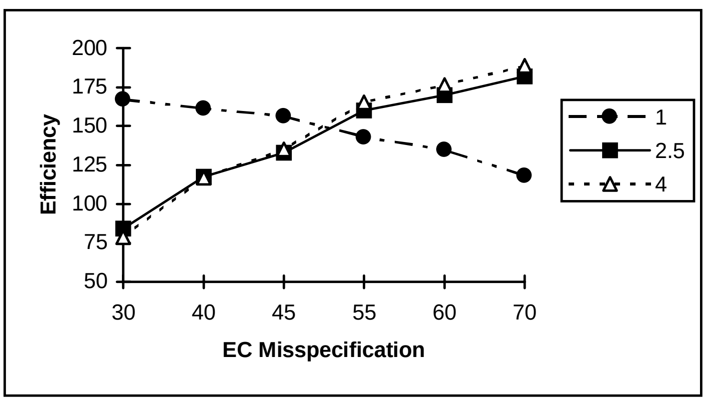

Figure 4.4.3 Three Level Efficiencies of Type II F-Optimal Uniform Designs under Misspecification.

§4.5 Two Level F-Optimal Designs based on the Normal Prior

While F-optimal designs based on the uniform prior are very important, some researchers may prefer designs based on a prior with more weight of the distribution around the center. The latter half of this chapter is devoted to Bayesian F-optimal designs based on the normal prior. Refer to Section 3.11 of Chapter 3 for the development of the normal prior.

The two level Bayesian F-optimal design is the first one to be addressed. As with all of the other Bayesian designs seen in Chapters 3 and 4, the intercept term does not affect the values of x_1 and x_2 which minimize the criterion. With the intercept term eliminated, the Bayesian criterion is

$$\int_{\beta_1} R(\delta,\beta_1)\pi(\beta_1) = \int_{-\infty}^{\infty} \frac{n_1 e^{\beta_1 x_1} + n_1 e^{\beta_1 x_2}}{n_1 n_2 e^{\beta_1 x_1} e^{\beta_1 x_2} (x_1 - x_2)^2} \frac{1}{\sqrt{2\pi}\sigma_{\beta_1}} e^{\frac{-(\beta_1 - \mu_{\beta_1})^2}{2\sigma_{\beta_1}^2}} d\beta_1. \quad (4.5.1)$$

The integral of this function cannot be found in closed form so both the two level and the three level designs were found via Monte Carlo integration. The first quantity in the integrand of (4.5.1) was evaluated at 1000 random deviates from a $N(\mu_{\beta_1}, \sigma_{\beta_1}^2)$ distribution for each combination of (p_1, p_2, x_1, x_2) where $n_i = p_i N$. The F-optimal designs are cataloged by the value of σ_{β_1}. Like the D-optimal design based on the normal prior these designs appear to be sigma constant based on informal simulation studies. The two level designs are listed in Table 4.5.1. The first row contains the value of σ_{β_1}. The second row lists the EC of the non-control design point and the final row lists the percentage of experimental units to be allocated at the non-control points.

Table 4.5.1 Two Level F-Optimal Designs under the Normal Prior.

σ_{β_1}	**0.00005**	**0.1500**	**0.2500**	**0.3214**	**0.3750**	**0.4167**	**0.4500**
Non-Control Design Point	$EC_{7.8}$	$EC_{8.49}$	$EC_{8.73}$	$EC_{8.99}$	$EC_{9.40}$	$EC_{10.07}$	$EC_{10.73}$
Percentage at Non-control	78%	78%	74%	77%	76%	77%	79%

The design based on $\sigma_{\beta_1} = 0.00005$, which is essentially a point prior, is the same as the optimal design found by Minkin in the known parameter case. Note that the non-control EC's from this design move in towards the center as in the F-optimal design based on the uniform prior. However, this movement is not as pronounced as it is in their uniform counterparts. Like the uniform case, these designs are fairly insensitive to the prior placed on β_1. In fact, the change in the value of the EC from prior to prior is negligible which means that the biologist would not be able to distinguish between them in practice.

§4.5.1 Two Level F-Optimal Design Example: Normal Prior

A final addition is made to the design example that has been used throughout Chapters 3 and 4. This addition is the F-optimal design based on the normal prior with $\sigma_\beta = 0.4500$. This design places 79% of the experimental units at the $EC_{10.73}$ and the remaining 21% at the control. The methods detailed in Section 3.10 of Chapter 3 were used to translate this design into the natural units shown in the Table 4.5.2. From the table, one can see that the F-optimal designs are very similar regardless of the type of prior.

Table 4.5.2 More Two Level Design Examples.

Design	**p_c n_c**	**p_1 n_1**	**EC_{100q} x_1**
F-Optimal normal	21% 38	79% 142	$EC_{10.73}$ 1.49
F-Optimal uniform	23% 41	77% 139	$EC_{12.00}$ 1.41
D-Optimal uniform	50% 90	50% 90	$EC_{6.07}$ 1.87
D-Optimal normal	50% 90	50% 90	$EC_{9.37}$ 1.58

§4.6 Type I Three Level F-Optimal Bayesian Designs based on the Normal Prior

The three level design criterion was developed in much the same way as the two level criterion. It is independent of the intercept as well. Like the two level case, it cannot be found in closed form so it will not be listed here. The expected value of the var(b_1) in (4.3.1) was simulated via Monte Carlo integration over the normal prior as described in section 3.6 of Chapter 3. The optimal Type I designs are tabled in Appendix C and the efficiencies are graphed in Figure 4.6.1 by the value of

σ_{β_1} for each region of operability. Again, these efficiencies are calculated against that of Chiacchierini's three level designs (1996).

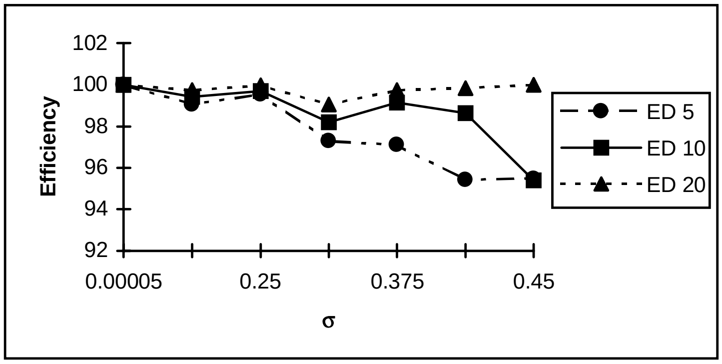

Figure 4.6.1 Efficiencies vs. Sigma for Type I F-Optimal Designs under the Normal Prior

The graph of efficiencies shows these designs in a favorable light. The efficiencies for all of the designs are greater than 95% which indicates that they would make a suitable substitution for the three level design based on known parameters. Note that the efficiencies for the design on the $[EC_{5,}EC_{80}]$ decrease as the prior becomes more variable. This is because levels are being brought in closer to the center as compared to the F-optimal design under known parameters. In the other two regions the design levels are closer to those of Chiacchierini (1996).

§4.6.1 Robustness Issues and Type II Three Level Bayesian F-Optimal Designs

Consistent with the cases thus far, the Type I three level designs did not fare well in the robustness study. Of course, Type II designs were the obvious alternative. Type II designs require one level to be the control and the two non-control levels to be symmetric around the center of the region of operability. The sample size restrictions differ from the Type I designs in that the control and the upper end EC are required to have the same sample size. Type II designs are tabled in Appendix C. Graphs of the efficiencies against Chiacchierini's three level designs are shown in Figure 4.6.2. As one can see, Type II designs provide quite an advantage over Chiacchierini's designs with efficiencies exceeding 130% in every case.

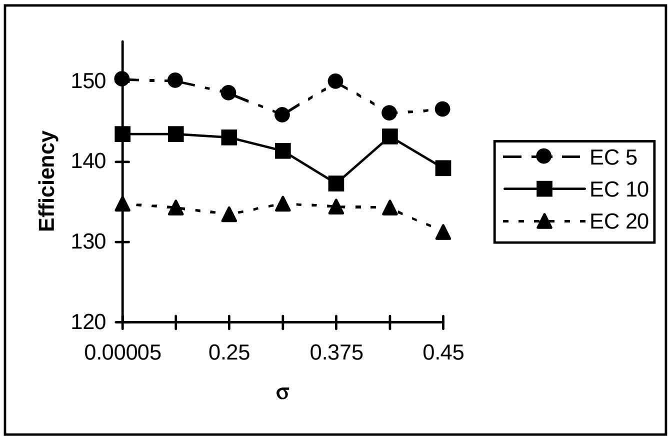

Figure 4.6.2 Efficiencies vs. Sigma for Type II F-Optimal Designs under the Normal Prior

The robustness properties of these designs are also favorable. These properties were explored via the robustness study described previously in Section 3.10 of Chapter 3. The efficiencies of these designs against the two level design under misspecification are graphed in Figure 4.6.3.

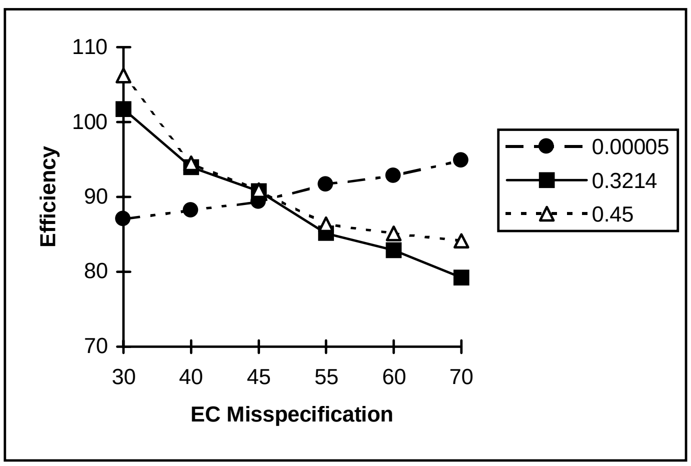

Figure 4.6.3 Two Level Efficiencies of Type II F-Optimal Normal Designs under Misspecification.

While these efficiencies are very good in most cases, the strongest support for using the Type II designs comes from Figure 4.6.4. It shows the efficiencies of the Type II Bayesian designs vs. the Type I Bayesian designs under misspecification. The Type II designs outperform the Type I designs without question.

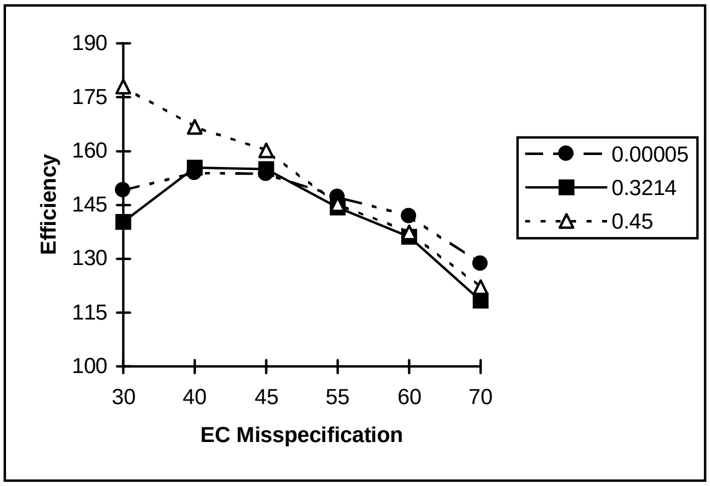

Figure 4.6.4 Three Level Efficiencies of Type II F-Optimal Normal Designs under Misspecification.

An interesting contrast in the F-optimal designs based on the uniform and normal priors can be gathered from Figures 4.4.3 and 4.6.4. Note that the designs based on the uniform prior tend to perform better when misspecification occurs in the upper ECs where as the normal designs tend to perform better when misspecification occurs at the lower EC's.