Robustness of Optimal Designs for the Michaelis-Menten Model under a Variation of Criteria

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Abstract

The Michaelis-Menten model has and continues to be one of the most widely used models in many diverse fields. In the biomedical sciences, the model continues to be ubiquitous in biochemistry, enzyme kinetics studies, nutrition science and in the pharmaceutical sciences. Despite its wide ranging applications across disciplines, design issues for this model are given short shrift. This paper focuses on design issues and provides a variety of optimal designs of this model. In addition, we evaluate robustness properties of the optimal designs under a variation in optimality criteria. To facilitate use of optimal design ideas in practice, we design a web site for generating and comparing different types of tailor-made optimal designs and user-supplied designs for the Michaelis-Menten and related models.

Key Words: c-optimal designs, efficiency, Elfving's method, extrapolation optimal design, uniform design, geometric design.

1. Introduction

The Michaelis-Menten model is very widely used across many disciplines that include agriculture, biochemistry, biology, microbiology, toxicology, environmental science, nutrition science, biopharmaceutical studies, just to name a few. A major reason for the model ubiquity is its simplicity and its ability to provide useful information as a first approximation to describing a complex biological systems, as in the study of saturable phenomena in enzyme kinetics. A sample of exemplary applications of the Michaelis-Menten model in different disciplines include Yu and Gu (2007) in agriculture, Clench (1979) in conservation biology research, Butler and Wolkowicz (1985) in a nutrient uptake study, Rong and Rappaport (1996) in environmental health science and, Heidel and Maloney (2000) in fractal curve analysis. Estimation issues for this model have been extensively discussed in the literature in various fields, see for example, Blunck and Mommsen (1978), Li (1983),

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Jeroen and Raaijmakers, (1987), Ruppert el at. (1989), Mickens and Hence (1998), Hawkes and Wainwright (1999), Juki, Sabo and Scitovski (2007), among many others.

Despite wide spread use of the Michaelis-Menten model, design issues for this model are given short shrift. None of the applied papers mentioned above and almost all work in the applied fields do not discuss design issues. For the couple of papers that do, they do so at a superficial level. Many published work do not justify the designs employed for the Michaelis-Menten model and tend to use many more design points that do not result in greater efficiencies given the goals of the study. Consequently, there is inefficiency and resources are wasted; in some extreme cases, we show here 50% or more resources could be saved using a more efficient design. This critical issue needs to be addressed because of rising cost in experimentation and the need to rein in cost and time.

The main aims of this paper are to provide analytical formulae for a variety of optimal designs for the Michaelis-Menten model and develop a web site to freely generate tailor-made optimal designs for the Michaelis-Menten and related models. In addition the site enables the researcher to compare merits of any user-selected design and study sensitivities of the optimal designs under different optimality criteria.

In Section 2, we describe the Michaelis-Menten model and various commonly used design criteria. In Section 3, we present different types of optimal designs and in Section 4, we compare their efficiencies across different criteria. We also list some popular designs for the Michaelis-Menten model and evaluate their efficiencies under various scenarios. A web-site is introduced to facilitate practitioners to find and compare optimal designs, including user-supplied designs. Section 5 contains a specific application of optimal designs, a justification for the optimal designs is given in Section 6 and Section 7 contains a summary.

2. Model and Design Optimality Criteria

The Michaelis-Menten model continues to be one of the most frequently used model in the biological sciences, particularly in biochemistry and in enzyme reaction studies (Currie, 1982, Xavier, 1992, for example). For this reason, our paper discusses design issues in the context of enzyme kinetic studies but the reader should keep in mind that our results apply directly to other fields.

Typically, the model is used to model enzyme kinetic reactions where a single substrate forms a complex with an enzyme and the mean velocity y of the reaction is expressed as a rational function of the substrate concentration x. The most common and simplest form of the Michaelis-Menten model takes on the following form:

$$E(y) = \frac{ax}{b+x}. \tag{1}$$

Here y is velocity of the reaction and x is the substrate concentration. The constant a is the maximum velocity theoretically attainable and b is the value of the substrate at which the velocity is one-half the maximum velocity. In the literature, b is called the Michaelis-Menten constant. The constants a and b are assumed to be positive and while theoretically x is positive and unbounded, there is usually an upper bound placed on the substrate concentration in practice. In what is to follow we consider the general case when values of x are restricted to the interval $[L, R]$ where L and R are user-selected constants. The observation errors are assumed to be independent and have mean zero and constant variance.

Our designs are approximate designs in the sense they are viewed as probability measures on the user-selected design space $[L, R]$. It follows that the design is fully characterized by specifying the number of concentration levels (k), where these k concentration levels are chosen from $[L, R]$ and the proportion, p_i, of the observations to be taken at concentration level x_i, $i = 1, \ldots, k$. Each p_i is between 0 and 1 and the sum of the p_i's is unity. To implement this design, we first assume the total number of observations N to be taken in the study is pre-determined, usually by cost or time. The number of observations to be taken at each x_i is Np_i and each is rounded to an integer such that they sum to N. Optimal rounding procedures are given in Pukelsheim and Rieder (1992). A main reason for working with approximate designs is that such designs are computationally and analytically easier to determine and study than exact optimal designs. Kiefer pioneered this approach and his work in this area is voluminously documented in Kiefer (1985).

Following convention, we use the Fisher information matrix to measure the usefulness of a design. This 2×2 matrix is the negative of the second derivatives of the log of the likelihood function. For large samples, the variance-covariance matrix of the estimated parameters is inversely proportional to the Fisher matrix and so finding a design on $[L, R]$ that makes the information matrix large in some sense is desirable. The most common way of making the matrix large is to maximize the determinant of the information matrix. Because such design minimizes the generalized variance, the volume of the confidence ellipsoid for the parameters is minimized. This type of design is called D-optimal and is frequently used for parameter estimation. It is important to note that the nonlinear optimization problem involves unknown parameters that we wish to estimate. The simplest approach to handle this problem is to assume nominal values are available for the parameters. These values usually represent the best guess for the true values of the parameters. When this approach is used, the resulting design is called a locally D-optimal design for estimating the two parameters (Chernoff, 1953).

Sometimes the practitioner may be interested in only a subset of the model parameters. The design problem then requires only the determinant of a sub-matrix of the information matrix be made 'large'. The resulting design is a locally D_s-optimal design, with "s" standing for a subset of the model parameters. We call the locally D_s-optimal design for estimating the j^{th} parameter in the Michaelis-Menten model as locally e_j-optimal design with $j = 1, 2$. There are other ways of making the information matrix large. They include making the confidence ellipsoid small by making the sum of the length of the major axes as small as possible (A-optimal designs) or making the largest of the major axes as short as possible (E-optimal design). Sometimes, we are interested in extrapolation design problem, where we wish to make inference on the mean velocity at a substrate concentration outside the design interval $[L, R]$. This happens for example, when it is difficult or unsafe to use substrate at a very high concentration but inference on the mean velocity at that level is still wanted. Optimal design for this purpose is called locally extrapolation optimal design and it minimizes the variance of the estimated response at the extrapolated substrate.

Depending on the objective or objectives of the study and available information at the onset, more complicated design criteria may be required. For instance, if there is adequate information, we may want to use a Bayesian optimality criterion. The practitioner summarizes his or her belief about the model parameters (or some function thereof) in a prior distribution and incorporates the prior beliefs in the design criterion by averaging over the prior density. For example, if we want to construct a Bayesian D-optimal design, we now maximize the expected value of the log of the determinant of the information matrix over all designs on $[L, R]$, and the expectation is with respect to the prior distribution. See Matthews and Allcock (2004) and Murphy, et al. (2005) for the construction of Bayesian designs for the Michaelis-Menten model.

Our experience is that frequently practitioners are unwilling or unable to provide a single best guess for the model parameters. They are however willing to supply for each model parameter a range of plausible values. This seems like a middle ground between the requirements for constructing a locally optimal design and a Bayesian optimal design. Under such a situation, one may adopt a minimax (or equivalently a maximin) design strategy where the optimal design minimizes the maximal loss in some sense. The idea is that each value of each parameter in the given range is plausible and so we want to find a reasonably efficient design that provides us with some global protection against the worst possible scenario. Statistically, this means one wants to maximize the minimum determinant of the information matrices derived from all possible combinations of the values of the parameters. This type of optimal designs, is always much more difficult to find and study analytically. Some minimax or maximin optimal designs for the Micahelis-Mentel model were proposed and discussed in Dette and Wong (1999), Dette, Melas and Pepelyshev (2003) and, Dette and Biedermann (2003). The latter set of authors proposed optimal designs robust to Michaelis-Menten model assumptions using a maximin concept.

For space considerations, we do not discuss more complicated design problems here, including how to design in the presence of several objectives. We refer the reader to recent work in the statistical literature. Wong (1992) discussed general minimax design strategies and, Dette et al. (2003) proposed and discussed a generalized maximin approach for designing a study for the Michaelis-Menten model. For multiple-objective design problems, see Cook and Wong (1994), and Wong (1999) who reviewed and discussed recent advances in design strategies for multiple-objective studies. A specific application to find multiple-objective designs for the Michaelis-Menten model is given in Lopez-Fidalgo and Wong (2002). Additional design issues may arise, such as heteroscedasticity where the variance of the error term depends on the concentration level. Some work in this direction includes Song and Wong (1998) and, Dette and Wong (1999) who considered a class of design problems where the variance of the error was assumed to depend on the mean function.

3. Optimal Experimental Designs

We now present a variety of optimal designs after the design interval $[L, R]$ is selected by the researcher. The types of optimal designs of interest here are (i) locally D-optimal designs, (ii) locally A-optimal designs, (iii) locally E-optimal designs, (iv) locally optimal designs for estimating the first parameter in the model, (v) locally optimal designs for estimating the second parameter in the model and (vi) locally extrapolation optimal designs.

We use two commonly used tools of approximate optimal design theory to construct our optimal designs. These tools are widely discussed in design monographs, see Atkinson and Donev (1992), Silvey (1980) or Pukelsheim (1993), for example. The first tool is a geometric method introduced by Elfving (1952) and this method is particularly useful for finding optimal design in a regression model with two parameters. Because readers here may not be familiar with applications of Elfving's approach to construct optimal design, we provide exemplary justifications in Section 6. The second tool is an equivalence theorem, which we use to check whether a candidate design is optimal among all designs defined on the design interval $[L, R]$. This result is usually described in terms of an inequality. We show one such inequality in Section 6 for D-optimality. More complicated design criteria such as minimax optimality will require a more involved inequality. Roughly speaking, the inequality states that whenever we can formulate our design criterion as a concave (convex) function over the space of all designs on $[L, R]$, a candidate design is optimal if and only if its first derivative vanishes when it is evaluated at the candidate design. For relatively simple design problems with one objective and one or two covariates in the model, this inequality translates to a graphical plot that can readily be used to confirm whether the candidate design is optimal among all designs on the interval $[L, R]$. Exemplary plots are given in Huang and Wong (1998) and Zhu, Zeng and Wong (2000).

Table 3.1 displays the analytical formulae for different types of optimal designs for the Michaelis-Menten model. They are found using Elfving's theorem and all can be verified to be optimal among all designs on the user-specified design interval [L, R] using an equivalence theorem. In the second row of table, the matrix M is the information matrix for the Michaelis-Menten model. The point x^* in the second column was found by minimizing the criterion among all designs with support points x and L and weights defined in the table.

Criterion	x^*	p
D	$\frac{bR}{2b+R}$	0.5
A	$\min_\xi \mathrm{tr} M^{-1}(\xi, a, b)$	$\frac{(b+z)^2\sqrt{a^2+(b+R)^2}}{z\left(\frac{\sqrt{a^2+(b+z)^2}(b+R)^2}{R}+\frac{(b+z)^2\sqrt{a^2+(b+R)^2}}{z}\right)}$
E	$\frac{(\sqrt{2}-1)bR}{(2-\sqrt{2})R+b}$	$\frac{R((b+z)(b+R)^2(2zR+b(z+R))+a^2(4bzR+b^2(z+R)+zR(z+R)))}{(b+z)^2(b+R)^4\left(\left(\frac{z}{b+z}+\frac{R}{b+R}\right)^2+\frac{a^2(4bzR+b^2(z+R)+zR(z+R))^2}{(b+z)^4(b+R)^4}\right)}$
e_1	$\frac{(\sqrt{2}-1)bR}{(2-\sqrt{2})R+b}$	$\frac{(b+z)^2R}{4bzR+b^2(z+R)+zR(z+R)}$
e_2	$\frac{(\sqrt{2}-1)bR}{(2-\sqrt{2})R+b}$	$\frac{(b+z)R}{2zR+b(z+R)}$
c_e	$\frac{(\sqrt{2}-1)bR}{(2-\sqrt{2})R+b}$	$\frac{R(x_e-R)(b+z)^2}{R(x_e-R)(b+z)^2+z(x_e-z)(b+R)^2}$

Table 3.1. *Locally optimal designs for the Michaelis Menten model with design space $[L, R]$. The optimal design is a two-point design at $z = \max\{L, x^*\}$ and R, with weight p at x^*.*

Rasch (1990) provided locally D-optimal designs and Dette and Wong (1999) provided locally E-optimal designs for the Michaelis-Menten model on the interval $[0, R]$. Our optimal designs are more general in that they are constructed on an arbitrary design interval, that may exclude the zero concentration level in the design interval. This situation can arise in practice; for instance, Mihara el. at (2000) used substrate concentrations that varied from 2 to 80 units. Other fields can benefit directly from this added flexibility as well. In conservation biology research, for example, the Michaelis-Menten model is often referred as the Clench model and is used to model effort-species data sets. The 'x' in the Clench model refers to the accumulated units of collecting effort and the 'y' refers to the accumulated number of observed species (Clench, 1979).

From the table, we notice that all our locally optimal designs for the Michaelis-Menten model have the same structure. The locally optimal design has weights p and $1-p$ at the two points

$$\max\{L, x^*\} \quad \text{and} \quad R \tag{2}$$

where the point x^* and the weight are given at the second and third columns in the tables. Note that the right bound R of the design interval is always a support point of the locally optimal design, but this is not necessarily true for the lower bound L. It transpires that for each design problem considered in this paper, there exists a threshold denoted by x^* here such that the locally optimal designs have support points L and R whenever $L > x^*$and supported at x^* and R otherwise.

The table shows that only locally D-optimal designs are equally weighted at two points. This is not surprising because we have two parameters and the optimal design has only two points. We also observe that the support points can vary quite substantially from optimal design to optimal design. As expected, being a maximin type of the design, E-optimal designs consistently have the most complicated analytical formula. A more complicated design criterion called standardized maximin $D - optimal$ was proposed by Dette and Biedermann (2003) for the Michaelis-Menten model defined on [0,R]. An appealing feature of this type of optimal design is that it is able to incorporate the prior information for the Michaelis-Menten b in the form $\beta \in [\beta_0, \beta_1]$ where $b = \beta R$ and both β_0 and β_1 are user-specified. Interestingly, the standardized maximin $D - optimal$ designs are also always equally weighted and are supported at R and

$$x^* = \frac{\beta_1\sqrt{\beta_0(1+\beta_0)} - \beta_0\sqrt{\beta_1(1+\beta_1)}}{\sqrt{\beta_1(1+\beta_1)} - \sqrt{\beta_0(1+\beta_0)}} R.$$

4. Comparison of Optimal Designs under Different Criteria

We now address questions on sensitivity of optimal design to nominal values and design criteria. These are important issues that the practitioner must consider before implementing the design. To facilitate practitioners to study these critical issues, we create an interactive web site for generating a broad range of optimal designs and to evaluate merits of any user-selected design. Our experience is that properties and sensitivities of the optimal design for nonlinear models are typically very dependent on the model and nominal values and so general conclusions on robustness properties of an optimal design are usually elusive. Accordingly, in what is to follow, we focus on a specific application and use it to demonstrate how our web site can be used to construct and study robustness properties of optimal design.

Mihara, Kurihara, Yoshimara and Esaki (2000) studied behavior of CSD plus pyruvate with L-cysteine sulfinate as substrate using a Michaelis-Menten model. The parameters in their setup were given by $a = 16$ and $b = 3.5$ and the design space was the interval $[2, 80]$. Using this set of nominal values, we (i) determine optimal designs described in Section 2, (ii) investigate the efficiency of locally optimal designs with respect to different criteria, (iii) investigate the sensitivity of the locally optimal designs with respect to mis-specifications of the initial parameters, and (iv) investigate the performance of commonly used design. We assume that for extrapolation purposes, we are interested to infer at the substrate concentration level $x_e = 1$.

Our web site is located at http://www.optimal-design.org/optimal/OptimalDesign.aspx and is free to use. (If and when prompted, the password is 'pass'). The web site contains information for constructing many types of optimal designs for a variety of commonly used models in the biological sciences. The visitor first selects a model for his/her study from a list of models provided on the site, and afterwards input model parameters of their choice to generate a tailor-made design. The site also calculates efficiencies of user-supplied design. If the design efficiency is low, the practitioner can adjust the design by changing design points or design weights, or do both and recalculate the design efficiency for the adjusted design. More importantly, the practitioner can add more points to the current design and observe how its efficiency depends on the locations of the additional point or points and the number of points to add. We hope that this web tool enables the practitioner to find a more efficient design after careful consideration of its limitations and strength, including robustness properties of the design to model assumptions and design criteria. We hope that this site enables the practitioner to better appreciate design issues without having to fully understand the theory behind the construction of the designs. References for the construction of the optimal designs are provided at the bottom of each web page.

Table 4.1 displays the efficiencies of the locally optimal designs under various design criteria. As expected, an optimal design can become rather inefficient under another criterion. For instance, the efficiency of the extrapolation optimal design for estimating the first parameter is only 12.17%. This means that the extrapolation optimal design needs to be replicated more than eight times ($100/12.17 = 8.2$) for it to estimate a with the same precision provided by the e_1-optimal design.

	D	**A**	**E**	$\mathbf{e_1}$	$\mathbf{e_2}$	$\mathbf{c_e}$
D	100	97.36	93.47	64.80	84.57	62.01
A	98.37	100	99.31	72.18	100	55.48
E	96.40	99.41	100	73.50	77.81	52.90
$\mathbf{e_1}$	68.09	55.50	48.73	100	27.94	17.31
$\mathbf{e_2}$	88.34	76.26	68.50	39.48	100	83.35
$\mathbf{c_e}$	55.41	28.14	22.49	12.17	66.33	100

Table 4.1. *Efficiencies of locally optimal designs for the Michaelis-Menten model with respect to various alternative criteria (in percent). The nominal parameters were* $a = 16$ *and* $b = 3.5$ *and the design space was the interval* $[2, 80]$. *The locally extrapolation optimal designs was calculated for the point* $x_e = 1$.

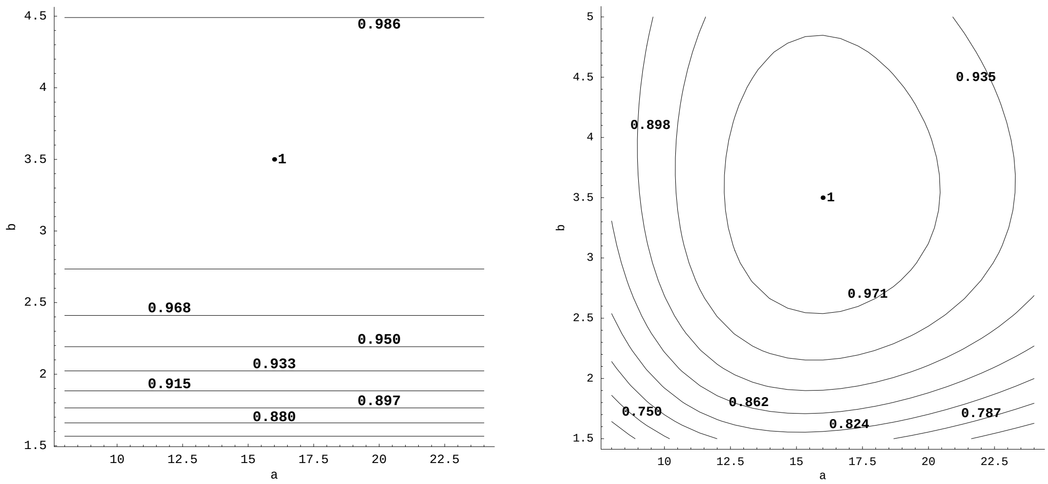

Figure 1: *Efficiencies of the locally optimal designs for the Michaelis Menten model when nominal values of the parameters are mis-specified. Left panel: D-optimality; right panel E-optimality.*

Next we study the robustness of the locally optimal designs with respect to mis-specification in the nominal values of the model parameters. For space consideration, we discuss only D- and E-optimality criteria. Figure 1 displays the efficiency contour lines of the locally optimal designs for the Michaelis Menten model when the parameters a and b have been mis-specified. The left panel shows D-efficiencies and the right panel shows E-efficiencies when the true values for a and b are 16 and 3.5 respectively. Unlike the E-optimal design the locally D-optimal design does not depend on the parameter a. We observe that even when either or both nominal values are under or over-specified by 40% or more, the D-efficiencies are still very high, averaging about 90% and the E-efficiencies averaging around 75%. In summary for this example, locally D- and E-optimal designs are very robust with respect to mis-specification of the initial parameters.

We next evaluate the efficiencies of some popular designs under a change of optimality criteria. The designs and their rationale are described in Lopez-Fidalgo and Wong (2002) and are listed in Table 4.2 for the setup here. Table 4.3 shows the six types of efficiencies for each of these designs. They generally have D-efficiencies averaging about 77%; however for other criteria, their efficiencies are poor, ranging from 22% to 61%. These popular designs have several more points than the two points required in the optimal design without providing additional gain in efficiency. While the additional points can be used to check model assumptions, the practitioner must be cognizant that it comes with a high price in that these popular designs do not have high efficiencies.

Watts' design	2	2.95	5.73	10.67	22.24	80
Geometric design	2	2.56	4.18	8.75	23.39	80
Inverse linear design	2	3.26	5.28	9.02	18.27	80
Logarithmic design	2	4.18	8.75	18.29	38.25	80
Arithmetic design	2	17.6	33.2	48.8	64.4	80

Table 4.2. *Popular designs for the Michaelis Menten model on the design space* $[2, 80]$.

Criterion	**D**	**A**	**E**	$\mathbf{e_1}$	$\mathbf{e_2}$	$\mathbf{c_e}$
Watts	77.8	58.0	49.5	34.1	59.8	55.6
Geometric	79.9	60.9	52.3	34.5	66.9	62.4
Inverse linear	76.4	54.5	46.0	31.0	59.4	57.7
Logarithmic	79.6	63.7	55.6	43.2	54.5	45.6
Arithmetic	68.6	55.2	48.3	66.5	31.7	21.8

Table 4.3. *Efficiency of popular designs for the Michaelis Menten model on the design space* $[2, 80]$. *The parameters are given by* $a = 16$ *and* $b = 3.5$. *The locally extrapolation optimal designs are calculated for the point* $x_e = 1$.

5. An Application to a Biopharmaceutical Study

Condomina et al. (2002) conducted a kinetic study and showed that intestinal transport of zinc in the intact intestine of the rat follows a saturable process, which can be fitted by the Michaelis-Menten model. The design for measuring the transportrate in 3 different sections of the intestine (proximal, mid, distal) has 6 equal weighted points spaced between $7 \cdot 10^{-4}$mM and 11.01mM. As with many such studies, the authors provided no justification for their experimental design. Table 5.1 shows the fitted values of the parameters in the Michaelis-Menten curves and their standard deviations provided by the authors. Table 5.2 displays the efficiencies of the implemented design under different optimality criteria. These efficiencies are calculated relative to the optimal design; for example, in the case of extrapolation efficiency, c_e, the efficiency is simply the variance of the fitted response at the extrapolated point using the optimal design divided by the corresponding variance using the implemented design. The range of efficiencies in each cell in Table 5.2 is found by using the nominal values ± 1 standard deviation given in the corresponding cell in Table 5.1.

It is evident the efficiencies of the implemented design are all unacceptably low ranging from about 19% for extrapolating at just x = 12 to a high of near 40% for estimating both the parameters in the mid-part of the intestine.

Part of intestine	a ($\frac{\text{mmol}}{\text{cm}^2\text{h}} \cdot 10^3$)	b (mM)
Proximal	8.39 ± 2.98	10.78 ± 4.40
Mid	1.62 ± 0.25	1.94 ± 0.39
Distal	3.42 ± 0.41	3.04 ± 0.44

Table 5.1. *Parameters of the fitted Michaelis Menten model.*

Part of intestine	D	E	A	e_1	e_2	c_e
Proximal	26.4 - 32.2	24.1 - 34.6	24.1 - 34.6	24.1 - 34.6	20.7 - 29.2	21.0 - 23.2
Mid	38.3 - 39.8	29.6 - 33.3	29.6 - 33.3	29.6 - 33.3	35.2 - 35.6	18.5 - 18.8
Distal	36.3 - 37.8	34.3 - 36.2	34.3 - 36.2	34.3 - 36.2	34.4 - 35.5	18.9 - 19.4

Table 5.2. *Range of efficiencies of the implemented design for the Michaelis Menten model on the design space* $[0.0007, 11.01]$ *using estimated values of the two parameters from Table 5.1. The locally extrapolation designs are calculated for the point* $x_e = 12$.

6. Justifications for the Optimal Designs

We provide for completeness some proofs of the optimal designs in Table 3.1. For illustrative purposes, we provide justifications for the e_1-optimal design and the D-optimal design. The proofs of the rest can be obtained using similar reasoning either given here or elsewhere. For instance, to justify our E-optimal designs on the interval $[L, R]$, the argument given in Dette and Wong (1999) when the interval is $[0, R]$ can be modified to establish the E-optimal designs given here. For A-optimality, we note that the weights are determined using results given in Pukelsheim and Torsney (1993).

First we find the e_1-optimal design for the Michaelis Menten model when $L = 0$. Such design provides the minimum variance for the estimated parameter a in the model. The e_1-optimal design is a special c-optimal design problem, where $c = (1, 0)^T$ [see Ford, Torsney and Wu (1992)]. The object to focus on is the induced design space defined by

$$G_1 = \left\{ (\frac{x}{b+x}, -\frac{ax}{(b+x)^2})^T \Big| x \in [0, R] \right\} = \left\{ (z, -\frac{az(1-z)}{b})^T \Big| z \in [0, \overline{z}] \right\}$$

where $\overline{z} = R/(b + R)$. The Elfving set ES is the convex hull of the set $G_1 \cup -G_1$ and this is displayed in Figure 2. To determine the e_1-optimal design, find two points $P_1, P_2 \in$ ES such that the intersection of the boundary of ES and the line $\{\lambda \cdot e_1 \mid \lambda \in \mathbb{R}\}$ can be represented as a convex combination of P_1 and P_2.

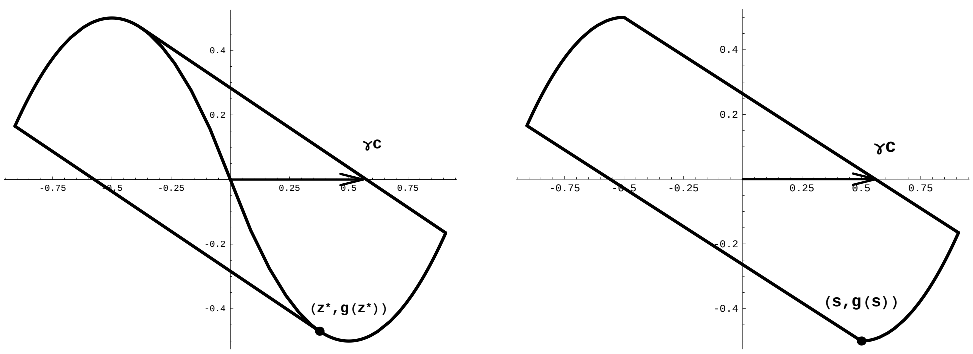

Figure 2: Elfving set ES with $a = 2$, $b = 1$ and $R = 10$ for determining the e_1-optimal design. Left panel: $L < x^*$; right panel $L \geq x^*$.

First we find the line that touches the curve $g(z) = -az(1-z)/b$ at some point $P^* = (z^*, g(z^*))$ with $z^* \in [-\overline{z}, 0]$. Since the line has to join the points $(\overline{z}, -a\overline{z}(1-\overline{z})/b)^T$ and $(-z^*, az^*(1-z^*)/b)^T$ and has to be a tangent to the curve in z^* the equation of the line is $y = (-a/b)\cdot((1-2\cdot z^*)x - z^{*2})$. Inserting $x = \overline{z}$ and $y = -a\overline{z}(1-\overline{z})/b$ into this equation gives $z^* = (\sqrt{2}-1)\overline{z}$. Now we have to solve the following equations (for $j = 1$):

$$(1-p)\cdot(\overline{z}, -a\overline{z}(1-\overline{z})/b)^T + (-1)\cdot p\cdot(z^*, -az^*(1-z^*))^T = (\gamma, 0)^T,$$

where γ is a scaling factor, such that $c \cdot \gamma \in \partial\text{ES}$. Since p is the only variable, it is enough to solve the second equation. Transforming the solution back to the x-space, the e_1-optimal design sought on $[0, R]$ is supported at R and

$$x^* = \frac{(\sqrt{2}-1)bR}{(2-\sqrt{2})R+b}$$

with weights $1-p$ and

$$p = \frac{b}{\sqrt{2}b+(3\sqrt{2}-4)R}$$

respectively. Now we have to observe what happens, when $L \neq 0$. If $L \leq x^*$, the Elfving set is the same, that means that the design above is also locally e_j-optimal in this case. On the other hand, if $L > x^*$, the first support point is L, because of the convexity of the Elfving set. This case is displayed in Figure 2 for some choice of parameters.

We omit the justification for the e_2-optimal design because the argument is similar.

For D-optimality, we first show that the locally D-optimal design has two points. If $M(\xi, a, b)$ is the information matrix of the design ξ, the equivalence Theorem of Kiefer and Wolfowitz (1960) says ξ is locally D-optimal if and only if the inequality

$$\left(\frac{x}{b+x}, -\frac{ax}{(b+x)^2}\right)M^{-1}(\xi, a, b)\left(\frac{x}{b+x}, -\frac{ax}{(b+x)^2}\right)' - 2 \leq 0$$

holds for all $x \in [L, R]$ with equality at the support points of ξ. Multiplying both sides by $(b+x)^4$ we obtain on the left hand side a quartic polynomial bounded above by 0 on the interval $[L, R]$. To argue that the D-optimal design has 2 points, we note that it requires at least two points, otherwise the information matrix is singular. On the other hand, the above polynomial could have at most two roots ; if it has three or more roots and is bounded above by 0, then the polynomial has to have at least degree 5. So the D-optimal design has 2 points and a direct application of the geometric-arithmetic inequality shows these 2 points must be equally weighted. It follows that if x_1 and x_2 are the support points, the locally D-optimal design is determined by maximizing the function

$$\mid M(\xi, a, b) \mid = \frac{1}{2^2}\left|\begin{pmatrix} \frac{x_1}{b+x_1} & -\frac{ax_1}{(b+x_1)^2} \\ \frac{x_2}{b+x_2} & -\frac{ax_2}{(b+x_2)^2} \end{pmatrix}\right|^2 = \frac{1}{4}\frac{a^2x_1^2(x_1-x_2)^2x_2^2}{(b+x_1)^4(b+x_2)^4}. \tag{3}$$

If $x_1 < x_2$, this function is increasing in x_2 on $[L, R]$ and so we should take 50% of the observations at $x_2 = R$. With this choice, the function in (3) becomes

$$T(x) = \frac{a^2x^2(x-R)^2R^2}{4(b+x)^4(b+R)^4}$$

where $x = x_1$. We now have to find the maximum of $T(x)$. A direct calculation shows

$$\frac{\partial T}{\partial x}(x) = \frac{a^2 x(x-R)R^2(2bx - bR + xR)}{2(b+x)^5(b+R)^4}$$

and the zeros of this derivative are given by

$$\begin{aligned} x_1 =& 0 \\ x_2 =& x^* = \frac{bR}{2b+R} \\ x_3 =& R. \end{aligned}$$

It follows that $T(x)$ has three (local) extrema. Since $T(x_1) = 0$, $T(x_3) = 0$ and $T(x) \geq 0$ for all $x \geq 0$ the extrema in x_1 and x_3 correspond to local minima. If $0 < x^* = \frac{xR}{2b+R} < R$, $T(x)$ has a local maximum at x^*. So $T(x)$ is strictly increasing on the interval $[0, x^*]$ and strictly decreasing on $[x^*, R]$ (Figure 3). Hence $T(x)$ has its maximum on the interval $[L, R]$ at x^* whenever $L < x^*$ and attain its maximum at L if $L > x^*$. The resulting D-optimal design is given in Table 3.1.

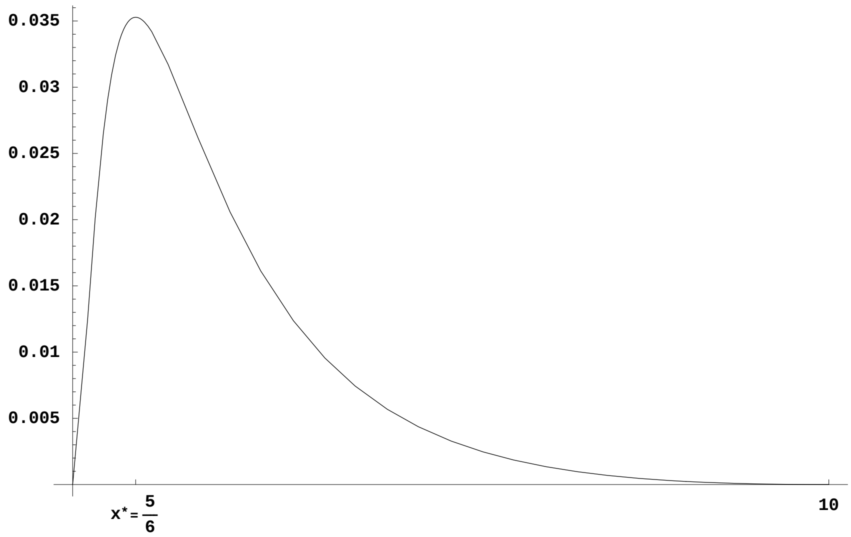

Figure 3: Graph of the function $T(x)$ with $a = 2$, $b = 1$ and $R = 10$.

7. Summary

We have constructed various optimal designs for the Michalis-Menten model and investigated efficiencies of optimal designs under a change of criteria. It is interesting to observe that D-efficiencies of the different designs in Table 4.2 are consistently higher than other efficiencies considered here. The popular designs have more points but they do have high efficiencies.

We have assumed a fixed set of design parameters for the two model parameters in our entire numerical study. It is important to remember that if this set of values is changed, our conclusions may be different. But such is the problem we often encounter in studying nonlinear models where useful and broad-ranging conclusions remain stubbornly elusive. This motivates the web site we have and continue to build. We hope that site will enable practitioner to generate efficient designs and study properties of designs more fully. The site can be used to generate many types of optimal designs for the Michaelis-Menten model and other models frequently used in the biological sciences. For example, we also provide different types of optimal designs for the 3-parameter EMAX model, which is an extension of the Michaelis-Menten model. In addition, our web site evaluates the efficiency of user-supplied design, thereby enabling the practitioner to decide if a particular design is appropriate for his or her problem. If the practitioner wants to use a non-optimal design, the practitioner can use the site to generate and compare alternative designs and study their merits. The site also lists useful references for the theory behind the construction of the optimal designs and also discussion of design problems with multiple-objectives.

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