# LEAST ABSOLUTE DEVIATIONS PROBLEM FOR THE MICHAELIS–MENTEN FUNCTION

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ABSTRACT. In this paper, we consider the problem of the existence of a least absolute deviations estimator for the Michaelis–Menten model function. We give necessary and sufficient conditions under which the least absolute deviations problem has a solution. In order to illustrate the usefulness of such conditions we give several numerical examples.

1. INTRODUCTION

Michaelis-Menten enzymatic reaction represents one of the most basic and simplest chemical reactions ([18]). It was first introduced by L. Michaelis and M. Menten in [16]. This reaction contains a substrate S, reacting with an enzyme E to form a complex C, which in turn converts to product P and enzyme E and it can be represented schematically as follows:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} E + P. \tag{1.1}$$
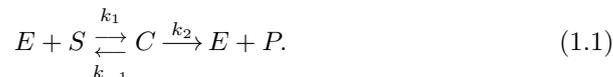
The terms k_1, k_{-1} and k_2 are rate constants for the association of a substrate and an enzyme, the dissociation of an unaltered substrate from the enzyme and the dissociation of the product from the enzyme, respectively. A double arrow indicates that the first reaction is reversible, while a single arrow indicates that the second reaction can go just in one way.

By applying the law of mass action on the chemical reaction (1.1) and using the so–called quasi–steady state approximation (see [16], [18]), the functional relation between the reaction velocity and the concentration of a substrate can

be obtained as:

$$V(S) = \frac{V_{\max}S}{K_M + S}, \tag{1.2}$$

where V is the reaction velocity at substrate concentration S, $K_M = \frac{k_{-1}+k_2}{k_1}$ is the half–saturation constant (also known as the Michaelis constant); that is, the value of S, where $V(S)$ is half-maximal and $V_{max} = k_2 E_{total}$, is the maximum velocity of this reaction wherein E_{total} is the total amount of enzyme.

Function (1.1) is known as the Michaelis–Menten function. Since $V_{\max}, K_M > 0$, the function $S \mapsto V(S)$ defined by (1.2) is positive, increasing and concave on $[0, \infty\rangle$, its graph passes through the origin and has a horizontal asymptote $V = V_{\max}$. Let us mention that Michaelis–Menten function has been widely used to describe physical and biological phenomena with saturation (see e.g. [13], [15]).

Let us suppose that data–points (w_i, S_i, V_i), $i = 1, \ldots, m$ are given, where $S_i > 0$ are the measured values of the substrate concentration, $V_i > 0$ are the measured values of the reaction velocity and $w_i > 0$ are the corresponding data weights, which describe the assumed relative accuracy of the data. The unknown parameters $V_{\max} > 0$ and $K_M > 0$ of the Michaelis-Menten function have to be estimated on the basis of the given data–points.

One of the most popular approaches to the estimation of unknown parameters in practical applications, especially in the case when measurement data are contaminated by normally distributed random errors, is the *least squares principle*. The least squares principle is based on minimizing the function $G \colon \mathcal{P} \to [0, \infty\rangle$ defined by

$$G(V_{\max}, K_M) = \sum_{i=1}^{m} w_i \left(\frac{V_{\max}S_i}{K_M + S_i} - V_i \right)^2, \tag{1.3}$$

where $\mathcal{P} = \{(a, b)\} : a, b > 0\}$ (see e.g., [11, 12, 22]). An ordered pair of optimal parameters $(V_{max}^\star(ls), K_M^\star(ls)) \in \mathcal{P}$ such that

$$G\left(V_{max}^\star(ls), K_M^\star(ls)\right) = \min_{(V_{\max}, K_M) \in \mathcal{P}} G(V_{\max}, K_M) \tag{1.4}$$

is called *a least squares estimator*, if it exists. Numerical methods for solving the nonlinear least squares problem are described in [6, 8]. In [11], it was shown that it is possible that a least squares estimator does not exist. It is also shown that it is possible that problem (1.3)–(1.4) has infinitely many solutions. Finally, sufficient conditions were given on data that guarantee the existence of a least squares estimator. More precisely, in [11], the following statements were proved:

(I) *If the data (w_i, S_i, V_i), $i = 1, \ldots, m$, $0 < S_1 \leq \ldots \leq S_m$, $S_1 < S_m$, $m \geq 3$, are such that*

   (i) *the points (S_i, V_i), $i = 1, \ldots, m$, all lie on some slanted line $y = k\,t$, $k \neq 0$ or*

(ii) $V_1 = V_2 = \ldots = V_m$,
then the least squares problem given in (1.3)–(1.4) has no solution.

(II) *If the data (w_i, S_i, V_i), $i = 1, \ldots, m$, $m \geq 3$, are such that $0 < S_1 \leq S_2 \leq \ldots \leq S_m$, $V_i > 0$, $w_i > 0$ and $S_1 = S_m =: \xi_0$, then any point $(a, b) \in \mathcal{P}$, such that $a = \frac{\overline{V}}{\xi_0}(b + \xi_0)$, $\overline{V} = \frac{\sum_{i=1}^{m} w_i V_i}{\sum_{i=1}^{m} w_i}$, $b > 0$ is a least squares estimator, i.e., there exist infinitely many least squares estimators for the Michaelis–Menten function.*

(III) *If the data (w_i, S_i, V_i), $i = 1, \ldots, m$, $m \geq 3$, are such that $0 < S_1 \leq S_2 \leq \ldots \leq S_m$, $V_i > 0$, $w_i > 0$ and if they fulfill the following conditions*

$$\sum_{i=1}^{m} w_i \left(\sum_{i=1}^{m} w_i S_i V_i \right)^2 \leq \sum_{i=1}^{m} w_i S_i^2 \left(\sum_{i=1}^{m} w_i V_i \right)^2$$
$$\sum_{i=1}^{m} \frac{w_i}{S_i} \sum_{i=1}^{m} w_i V_i > \sum_{i=1}^{m} w_i \sum_{i=1}^{m} w_i \frac{V_i}{S_i} \tag{1.5}$$

or

$$\sum_{i=1}^{m} w_i \left(\sum_{i=1}^{m} w_i S_i V_i \right)^2 \geq \sum_{i=1}^{m} w_i S_i^2 \left(\sum_{i=1}^{m} w_i V_i \right)^2$$
$$\sum_{i=1}^{m} w_i S_i V_i \sum_{i=1}^{m} w_i S_i^3 > \sum_{i=1}^{m} w_i S_i^2 \sum_{i=1}^{m} w_i S_i^2 V_i, \tag{1.6}$$

then a least squares estimator for the Michaelis-Menten function exists.

Cases (I) and (II) suggest on possibility of numerical instability of the corresponding numerical procedure for searching an optimal parameters for Michaelis–Menten function if the set of data–points "almost fulfilled" these requirements.

Let us mention that inequalities (1.5) and (1.6) from (III) are in connection with the well known Chebyshev sum inequality (see e.g. [17]). Chebyshev sum inequality is usually stated as follows. Let $0 < x_1 \leq x_2 \leq \ldots \leq x_m$ and $0 < y_1 \leq y_2 \leq \ldots \leq y_m$. Then for $p_i > 0$, $i = 1, \ldots, m$:

$$\sum_{i=1}^{m} p_i \sum_{i=1}^{m} p_i x_i y_i \geq \sum_{i=1}^{m} p_i x_i \sum_{i=1}^{m} p_i y_i. \tag{1.7}$$

Equality holds if and only if $x_1 = x_2 = \ldots = x_m$ or $y_1 = y_2 = \ldots = y_m$. The inequality (1.7) can be reversed. If $0 < x_1 \leq x_2 \leq \ldots \leq x_m$ and $y_1 \geq y_2 \geq \ldots \geq y_m > 0$, then for $p_i > 0$, $i = 1, \ldots, m$:

$$\sum_{i=1}^{m} p_i \sum_{i=1}^{m} p_i x_i y_i \leq \sum_{i=1}^{m} p_i x_i \sum_{i=1}^{m} p_i y_i. \tag{1.8}$$

Similarly, equality holds if and only if $x_1 = x_2 = \ldots = x_m$ or $y_1 = y_2 = \ldots = y_m$. Consequently, if we suppose that data–points (w_i, S_i, V_i), $i = 1, \ldots, m$ satisfy

the following conditions

$$S_1 \leq S_2 \leq \ldots \leq S_m,\, S_1 < S_m,$$
$$V_1 \leq V_2 \leq \ldots \leq V_m,\, V_1 < V_m,$$

then for

$$p_i := w_i, \quad x_i := V_i, \quad y_i := \frac{1}{S_i}, \quad i = 1, \ldots, m,$$

the inequality (1.5) follows from Chebyshev sum inequality (1.8). Similarly, if we suppose that data–points (w_i, S_i, V_i), $i = 1, \ldots, m$ satisfy the following conditions

$$S_1 \leq S_2 \leq \ldots \leq S_m,\, S_1 < S_m,$$
$$V_1/S_1 \geq V_2/S_2 \geq \ldots \geq V_m/S_m,\, V_1/S_1 > V_m/S_m,$$

then for

$$p_i := w_i S_i^2, \quad x_i := S_i, \quad y_i := V_i/S_i, \quad i = 1, \ldots, m$$

the inequality (1.6) follows from Chebyshev sum inequality (1.7).

Motivated by the results from [11] and using the ideas from [5], in this paper, we consider some existence aspects of the parameter estimation problem for the Michaelis–Menten model function based on the *least absolute deviations principle*:[1] (see e.g. [2, 7, 9]), i.e., by minimizing the function

$$F(V_{\max}, K_M) = \sum_{i=1}^{m} w_i \left| \frac{V_{\max} S_i}{K_M + S_i} - V_i \right| \tag{1.9}$$

on the set $\mathcal{P} = \{(a, b)\} : a, b > 0\}$. An ordered pair of optimal parameters $(V_{max}^\star(lad), K_M^\star(lad)) \in \mathcal{P}$ such that

$$F\left(V_{max}^\star(lad), K_M^\star(lad)\right) = \min_{(V_{\max}, K_M) \in \mathcal{P}} F(V_{\max}, K_M) \tag{1.10}$$

is called *a least absolute deviations estimator*, if it is exists. Since the function $F \colon \mathcal{P} \to [0, \infty\rangle$ is non-differentiable, in order to solve the least absolute deviations problem (1.4)–(1.10), some special numerical method for non–smooth optimization should be used (see [1, 9, 24]).

The least absolute deviations principle is an important approach in various fields of applied research, especially in the case if among the measurement data a substantial amount of outliers (i.e., wild points) might appear (see e. g. [3, 10, 19, 20, 23]) or when the measurement data are contaminated by random errors coming from the Laplace distribution.

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[1]The principle is attributed to Josip Rudjer Bošković (1711-1787), Croatian scientist (mathematician, physicist, astronomer and philosopher) born in Dubrovnik. Powerful computers have recently caused great interest in and popularity of that principle, which can be seen in numerous papers published in journals as well as presented at international conferences dealing with this issue. A series of such conferences has been dedicated to J. R. Bošković (see [7]).

The main purpose of this paper is to give the existence results for the least absolute deviations estimator for the Michaelis–Menten model function. The paper is organized as follows. In Section 2, we give a brief review of the weighted median of data. In Section 3, we present necessary and sufficient criteria that guarantee the existence of a least absolute deviations estimator. These criteria are only theoretical in nature and not suitable for applications, but they have a very important and practical consequence that presents a useful sufficient existence result. In Section 4, throughout the numerical experiments we illustrate the usability of the mentioned sufficient existence results.

2. Weighted median of data

In this section, we will define the weighted median of data and give the corresponding properties. The weighted median of data and some of its properties will be crucial for the main existence results. Let (w_i, z_i), $i = 1, \ldots, m$, $m \geq 1$, be some given data, where $z_i \in \mathbb{R}$ and $w_i > 0$ are the corresponding data weights. The function $f : \mathbb{R} \to \mathbb{R}$

$$f(\alpha) = \sum_{i=1}^{m} w_i \, |\alpha - z_i|, \tag{2.1}$$

is convex and attains its global minimum. The set $\underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j)$ of all global minimizers (i.e., points of global minima) of the function f is convex. Any element of the set $\underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j)$ is called a *weighted median of the data* and we denote any of these by $\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, z_j)$ i.e.

$$\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, z_j) \in \underset{\alpha \in \mathbb{R}}{\mathrm{argmin}} \, f(\alpha).$$

The following lemma [21, 23] shows that the set $\underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j)$ can be a one–point set, in which case it is one of the z_i's, or a segment between two subsequent data.

Lemma 2.1. *Let (w_i, z_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, be some data, where $z_1 \leq z_2 \leq \ldots \leq z_m$ are real numbers and $w_i > 0$ are the corresponding data weights. Then there exists a $\mu \in I$, such that $y_\mu \in \underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j)$. Therefore, by denoting*

$$J := \Big\{ \nu \in I : \sum^{\nu} w_i \leq \frac{W}{2} \Big\},$$

where $W := \sum_{i=1}^{m} w_i$, the following holds:[1]
- *(a) if $J = \emptyset$, then $\underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j) = \{z_1\}$;*
- *(b) if $J \neq \emptyset$ and $\nu_0 := \max J$, then*
    - *(i) if $\sum_{i=1}^{\nu_0} w_i < \frac{W}{2}$, then $\underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, z_j) = \{z_{\nu_0+1}\}$;*

(ii) if $\sum_{i=1}^{\nu_0} w_i = \frac{W}{2}$, then $\operatorname*{Med}_{j=1,\ldots,m} (w_j, y_j) = [z_{\nu_0}, z_{\nu_0+1}]$.

Note that, if especially $m = 1$ or $z_1 = \ldots = z_m$, then $\operatorname*{Med}_{j=1,\ldots,m} (w_j, z_j) = \{z_1\}$.

In the case of a large number of data, calculation of the weighted median of the data may require a long computing time. Several fast algorithms can be seen in [10].

The connection between the weighted median of data and the least absolute deviations line which passes through the origin is given by the following lemma.

Lemma 2.2. *Let* (w_i, x_i, y_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, *be some data, where* $x_i, y_i > 0$ *and* $w_i > 0$ *are the corresponding data weights. Then*

$$\operatorname*{med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j) \in \operatorname*{argmin}_{k>0} \sum_{i=1}^m w_i |k x_i - y_i|,$$

for every $\operatorname*{med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j) \in \operatorname*{Med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j)$.

Proof. For any $k > 0$, immediately from the definition of the weighted median it follows

$$\sum_{i=1}^m w_i |k x_i - y_i| = \sum_{i=1}^m w_i x_i \left| k - \frac{y_i}{x_i} \right| \geq \sum_{i=1}^m w_i x_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j) - \frac{y_i}{x_i} \right|$$

$$= \sum_{i=1}^m w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j) x_i - y_i \right|,$$

where equality holds if and only if

$$k = \operatorname*{med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j) \in \operatorname*{Med}_{j=1,\ldots,m} (w_j x_j, y_j/x_j).$$

$\square$

Without proof (see [21, 23]), we give one corollary that shows that there exists a best least absolute deviations line which passes through at least two different points of the data. Let us mention that the corresponding proof is based on Lemmas 2.1 and 2.2.

Corollary 2.0.1. *Let* (w_i, x_i, y_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, *be some data, where* $x_i, y_i > 0$ *and* $w_i > 0$ *are the corresponding data weights. Then there exist* $\eta, \kappa \in I$, $\eta \neq \kappa$ *and* $x_\eta \neq x_\kappa$ *such that*

$$\left(\frac{y_\eta - y_\kappa}{x_\eta - x_\kappa}, y_\eta - \frac{y_\eta - y_\kappa}{x_\eta - x_\kappa} x_\eta \right) \in \operatorname*{argmin}_{(\alpha,\beta)\in\mathbb{R}^2} \sum_{i=1}^m w_i |\alpha x_i + \beta - y_i|.$$

Finally, let us mention that in the case of a large number of data, calculation of the weighted median of the data may require a long computing time. Several fast algorithms can be seen in [10].

3. Existence results

In this section, we give necessary and sufficient conditions that guarantee the existence of a least absolute deviations estimator (Theorem 3.1). The main disadvantage of this result is that sometimes it is not easy to verify the conditions for the given data. However, it is theoretically significant since its consequence is very practical and it has a useful sufficient existence result (Proposition 3.2). At the end of this section, we also give some important corollaries of Theorem 3.1.

Theorem 3.1. *Let (w_i, S_i, V_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, be some data, where $S_i, V_i > 0$ and $w_i > 0$ are the corresponding data weights. The least absolute deviations problem for the Michaelis–Menten function (1.9)–(1.10) has a solution if and only if there exists a point $(a_0, b_0) \in \mathcal{P}$, $\mathcal{P} = \{(a, b) : a, b > 0\}$, such that*

$$F(a_0, b_0) \leq \min \left\{ \sum_{i=1}^{m} w_i \left| \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, V_j) - V_i \right| , \right.$$

$$\left. \sum_{i=1}^{m} w_i \left| \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j S_j, V_j/S_j) S_i - V_i \right| \right\}, \qquad (3.1)$$

for some $\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, V_j) \in \underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j, V_j)$ *and* $\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j S_j, V_j/S_j) \in \underset{j=1,\ldots,m}{\mathrm{Med}} \, (w_j S_j, V_j/S_j).$

Proof. Let us suppose that the problem (1.9)–(1.10) has a solution $(V_{\max}^{\star}(lad), K_M^{\star}(lad)) \in \mathcal{P}$. Then

$$F(V_{\max}^{\star}(lad), K_M^{\star}(lad)) \leq F(a, b), \quad \forall (a, b) \in \mathcal{P}.$$

Particularly, for all $b > 0$ there hold $F\left(V_{\max}^{\star}(lad), K_M^{\star}(lad)\right) \leq F\left(\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, V_j), b\right)$ and $F\left(V_{\max}^{\star}(lad), K_M^{\star}(lad)\right) \leq F\left(b \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j S_j, V_j/S_j), b\right)$, from where by taking the following limits we obtain

$$F\left(V_{\max}^{\star}(lad), K_M^{\star}(lad)\right) \leq \lim_{b \to 0^+} F\left(\underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, V_j), b\right)$$

$$= \sum_{i=1}^{m} w_i \left| \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j, V_j) - V_i \right|,$$

and

$$F\left(V_{\max}^{\star}(lad), K_M^{\star}(lad)\right) \leq \lim_{b \to \infty} F\left(b \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j S_j, V_j/S_j), b\right)$$

$$= \sum_{i=1}^{m} w_i \left| \underset{j=1,\ldots,m}{\mathrm{med}} \, (w_j S_j, V_j/S_j) S_i - V_i \right|.$$

Finally,

$$F\left(V_{\max}^{\star}(lad), K_M^{\star}(lad)\right) \leq \min\left\{\sum_{i=1}^{m} w_i \left|\operatorname*{med}_{j=1,\ldots,m}(w_j, V_j) - V_i\right|,\right.$$

$$\left.\sum_{i=1}^{m} w_i \left|\operatorname*{med}_{j=1,\ldots,m}(w_j S_j, V_j/S_j)S_i - V_i\right|\right\}.$$

Let us show the converse. Since $F \geq 0$, there exists $F^{\star} = \inf_{(a,b)\in\mathcal{P}} F(a,b)$. Let $(a_n, b_n) \in \mathcal{P}$ be a sequence such that

$$\lim_{n\to\infty} F(a_n, b_n) = F^{\star}, \tag{3.2}$$

and let us show that then a sequence (a_n, b_n) is bounded on $\mathcal{P}$. In order to do this, let us assume the contrary, i.e., that a sequence (a_n, b_n) is unbounded.

If $b_n \to \infty$, then one of the following three cases may occur:

$$(i)\,\frac{a_n}{b_n} \to 0, \qquad (ii)\,\frac{a_n}{b_n} \to k > 0, \qquad (iii)\,\frac{a_n}{b_n} \to \infty.$$

For any of the previous cases, let us show that the infimum $F^{\star}$ of the function F cannot be attained.

(i) From $\frac{a_n}{b_n} \to 0$, it follows

$$\lim_{n\to\infty} F(a_n, b_n) = \sum_{i=1}^{m} w_i \left|\frac{\frac{a_n}{b_n}S_i}{1 + \frac{S_i}{b_n}} - V_i\right| = \sum_{i=1}^{m} w_i V_i =: F_1.$$

Let us show that there exists a point from the set $\mathcal{P}$ in which the function F attains the value less than F_1. In order to do this, let us choose an index $r \in \{1, \ldots, m\}$ such that $V_r = \min\{V_1, \ldots, V_r\}$ and let us consider the following class of Michaelis–Menten curves

$$S \mapsto \frac{V_r S}{b + S}, \, b > 0.$$

Since $V_i \geq V_r \geq \frac{V_r S_i}{b+S_i}$, for all $i \in I$ it follows

$$V_i = V_i - \frac{V_r S_i}{b + S_i} + \frac{V_r S_i}{b + S_i} \geq \left|\frac{V_r S_i}{b + S_i} - V_i\right|, \, i \in I,$$

and finally

$$F(V_r, b) \leq \sum_{i=1}^{m} w_i V_i, \quad \text{for all } b > 0. \tag{3.3}$$

(ii) For $\frac{a_n}{b_n} \to k > 0$, immediately from Corollary 2.2 it follows

$$\lim_{n \to \infty} F(a_n, b_n) = \lim_{n \to \infty} \sum_{i=1}^{m} w_i \left| \frac{\frac{a_n}{b_n} S_i}{1 + \frac{S_i}{b_n}} - V_i \right| = \sum_{i=1}^{m} w_i |kS_i - V_i|$$

$$\geq \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right|$$

$$\geq \min \left\{ \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|, \right.$$

$$\left. \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \right\}.$$

In accordance with assumption (3.1), there exists a point $(a_0, b_0) \in \mathcal{P}$ such that

$$F(a_0, b_0) \leq \min \left\{ \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|, \right.$$

$$\left. \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \right\},$$

i.e., the infimum of the function F cannot be attained in this case.

(iii) From $\frac{a_n}{b_n} \to \infty$, it follows

$$\lim_{n \to \infty} F(a_n, b_n) = \sum_{i=1}^{m} w_i \left| \frac{\frac{a_n}{b_n} S_i}{1 + \frac{S_i}{b_n}} - V_i \right| = \infty,$$

and in this way the functional F cannot attain its infimum.

Note that it has been proved that a sequence (b_n) is bounded. Let $b_n \to K_M^\star \geq 0$.

If $a_n \to \infty$, then $\lim_{n \to \infty} F(a_n, b_n) = \infty$, contradicts (3.2), and it follows that a sequence (a_n) is bounded, i.e., $a_n \to V_{\max}^\star \geq 0$.

It remains to prove $K_M^\star \neq 0$ and $V_{\max}^\star \neq 0$. If we suppose that $V_{\max}^\star = 0$, then for all $b > 0$ we have $F(V_{\max}^\star, b) = \sum_{i=1}^{m} w_i V_i = F_1$. In accordance with (3.3), there exists a point at which the function F attains a smaller value and it means that the function F cannot attains its infimum in this case.

If $K_M^\star = 0$, then for all $a > 0$ it follows

$$F(a, K_M^\star) = \sum_{i=1}^{m} w_i |a - V_i| \geq \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|.$$

In accordance with assumption (3.1), it follows that there exists a point $(a_0, b_0) \in \mathcal{P}$ such that

$$F(a_0, b_0) \leq \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|,$$

and that means that the function F cannot attains its infimum in this way.

Finally, it has been proved that $(V_{\max}^{\star}, K_M^{\star}) \in \mathcal{P}$. Since the function F is continuous, we have

$$\inf_{(a,b) \in \mathcal{P}} F(a, b) = \lim_{n \to \infty} F(a_n, b_n) = F\left(V_{\max}^{\star}, K_M^{\star}\right).$$

$\square$

The following corollary shows that it is possible that the least absolute deviations estimator does not exist.

Corollary 3.1.1. *Let (w_i, S_i, V_i), $0 < S_1 \leq S_2, \leq \ldots \leq S_m$, $S_1 < S_m$ $V_i > 0$, $i \in I = \{1, \ldots, m\}$, $m \geq 3$, be some data. If*

    a) *all points (S_i, V_i) lie on some line $y = k\,t$, $k > 0$,*
    b) *all points (S_i, V_i) lie on line $y = l$, $l > 0$,*

then the least absolute deviations estimator does not exist.

Proof. Note that in both of these cases

$$\min \left\{ \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|, \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \right\} = 0.$$

Since the line $y = k\,t$, $k > 0$ (i.e., $y = l$, $l > 0$) and the Michaelis-Menten function have at most two (i.e., one) intersection points and $m \geq 3$, there holds $F(a, b) > 0$, for all $(a, b) \in \mathcal{P}$ and in accordance with Theorem 3.1, the least absolute deviations estimator does not exist. $\square$

The next corollary shows that there exist data–points such that the least absolute deviations problem has infinitely many solutions.

Corollary 3.1.2. *Let (w_i, S_i, V_i), $0 < S_1 = S_2 = \cdots = S_m =: \bar{S}$, $V_i > 0$, $i \in I$ be a data; then the least absolute deviations problem has infinitely many solutions.*

Proof. Note that every point $\left(\frac{b+\bar{S}}{\bar{S}} \operatorname*{med}_{j=1,\ldots,m} V_j, b \right) \in \mathcal{P}$, $b > 0$ is a least absolute deviations estimator for the Michaelis–Menten function. Indeed, by using

Lemma 2.2 we obtain

$$
\begin{aligned}
F(a,b) &= \sum_{i=1}^{m} w_i \left| \frac{a\bar{S}}{b+\bar{S}} - V_i \right| = \sum_{i=1}^{m} w_i \frac{\bar{S}}{b+\bar{S}} \left| a - \frac{b+\bar{S}}{\bar{S}} V_i \right| \\
&\geq \sum_{i=1}^{m} w_i \frac{\bar{S}}{b+\bar{S}} \left| \frac{b+\bar{S}}{\bar{S}} \operatorname*{med}_{j=1,\dots,m} V_j - \frac{b+\bar{S}}{\bar{S}} V_i \right| \\
&= \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\dots,m} V_j - V_i \right|,
\end{aligned}
$$

where the equality holds for $a = \frac{b+\bar{S}}{\bar{S}} \operatorname*{med}_{j=1,\dots,m} V_j$ for any positive real number b. $\qquad\square$

Unfortunately, necessary and sufficient criteria given in Theorem 3.1 are only theoretical in nature and not suitable for applications. The following proposition gives a practical sufficient existence result.

Proposition 3.2. *Let (w_i, S_i, V_i), $i \in I = \{1, \dots, m\}$, $m \geq 2$, be some data, where $S_i, V_i > 0$ and $w_i > 0$ are the corresponding data weights. Lets $\mu, \nu \in \{1, \dots, m\}$ such that $\operatorname*{med}_{j=1,\dots,m}(w_j, V_j) = V_\mu$ and $\operatorname*{med}_{j=1,\dots,m}(w_j S_j, V_j/S_j) = \frac{V_\nu}{S_\nu}$, for some $\operatorname*{med}_{j=1,\dots,m}(w_j, V_j) \in \operatorname*{Med}_{j=1,\dots,m}(w_j, V_j)$ and $\operatorname*{med}_{j=1,\dots,m}(w_j S_j, V_j/S_j) \in \operatorname*{Med}_{j=1,\dots,m}(w_j S_j, V_j/S_j)$. Then the least absolute deviations problem for the Michaelis-Menten function has a solution if one of the following two conditions holds*

$$
\sum_{i=1}^{m} w_i \left(|V_\mu - V_i| - \left| \frac{V_\nu}{S_\nu} S_i - V_i \right| \right) \geq 0 \tag{3.4}
$$

$$
\sum_{i=1}^{m} w_i \operatorname{sign}\left(V_\nu S_i - V_i S_\nu \right) S_i \left(S_i - S_\nu \right) > 0, \tag{3.5}
$$

or

$$
\sum_{i=1}^{m} w_i \left(|V_\mu - V_i| - \left| \frac{V_\nu}{S_\nu} S_i - V_i \right| \right) \leq 0 \tag{3.6}
$$

$$
\sum_{i=1}^{m} w_i \operatorname{sign}\left(V_\mu - V_i \right) \frac{S_\mu - S_i}{S_i} > 0. \tag{3.7}
$$

Proof. Let us suppose that data points satisfy conditions (3.4)–(3.5). In accordance with Theorem 3.1, it is enough to show that in this case there exists a

point $(a_0, b_0) \in \mathcal{P}$ such that

$$
\begin{aligned}
F(a_0, b_0) \leq \min \Bigg\{ & \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\dots,m} (w_j, V_j) - V_i \right|, \\
& \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\dots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \Bigg\} \\
= & \sum_{i=1}^{m} w_i \left| \frac{V_\nu}{S_\nu} S_i - V_i \right|.
\end{aligned}
$$

In order to do this, let us consider the following class of Michaelis-Menten curves

$$
S \mapsto \frac{y_\nu (b + S_\nu) S}{S_\nu (b + S)}, \quad b > 0.
$$

There holds

$$
\lim_{b \to \infty} F\left(\frac{V_\nu}{S_\nu} (b + S_\nu), b \right) = \sum_{i=1}^{m} w_i \left| \frac{V_\nu}{S_\nu} S_i - V_i \right|.
$$

Note that there exists sufficiently large $B > 0$ such that the function

$$
b \mapsto F\left(\frac{V_\nu}{S_\nu} (b + S_\nu), b \right) =: \Phi(b)
$$

is continuously differentiable on $\langle B, \infty \rangle$ and consequently there exists

$$
\begin{aligned}
\lim_{b \to \infty} b^2 \frac{\partial \Phi(b)}{\partial b} &= \frac{V_\nu}{S_\nu} \lim_{b \to \infty} \sum_{i=1}^{m} w_i \operatorname{sign}\left(\frac{V_\nu (b + S_\nu) S_i}{S_\nu (b + S_i)} - y_i \right) \frac{b^2 S_i (S_i - S_\nu)}{(b + S_i)^2} \\
&= \frac{V_\nu}{S_\nu} \sum_{i=1}^{m} w_i \operatorname{sign}\left(V_\nu S_i - V_i S_\nu \right) S_i (S_i - S_\nu) > 0.
\end{aligned}
$$

Therefore, there exist sufficiently large $\overline{B} \geq B$ such that the function $b \mapsto \Phi(b)$ is strictly increasing on $\langle \overline{B}, \infty \rangle$, i.e., for every $b \in \langle \overline{B}, \infty \rangle$ there holds

$$
F\left(\frac{V_\nu}{S_\nu} (b + S_\nu), b \right) = \Phi(b) \leq \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\dots,m} (w_j S_j, V_j/S_j) S_i - V_i \right|.
$$

Let us now suppose that data points satisfy (3.6)–(3.7). Similarly to the previous cases, in accordance with Theorem 3.1, it is enough to show that in

this case there exists a point $(a_0, b_0) \in \mathcal{P}$ such that

$$F(a_0, b_0) \leq \min \left\{ \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|, \right.$$

$$\sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \right\}$$

$$= \sum_{i=1}^{m} w_i \left| V_\mu - S_i \right|.$$

In order to do this, let us consider the following class of Michaelis-Menten curves

$$S \mapsto \frac{V_\mu (b + S_\mu) S}{S_\mu (b + S)}, \quad b > 0.$$

There holds

$$\lim_{b \to 0^+} F \left(\frac{V_\mu}{S_\mu} (b + S_\mu), b \right) = \sum_{i=1}^{m} w_i \left| V_\mu - V_i \right|.$$

Note that there exists sufficiently small $\beta > 0$ such that the function

$$b \mapsto F \left(\operatorname*{med}_{j=1,\ldots,m} (w_j, V_j), b \right) =: \Psi(b)$$

is continuously differentiable on $\langle 0, \beta \rangle$ and consequently there exists

$$\lim_{b \to 0^+} \frac{\partial \Psi(b)}{\partial b} = \frac{V_\mu}{S_\mu} \lim_{b \to \infty} \sum_{i=1}^{m} w_i \operatorname{sign} \left(\frac{V_\mu (b + S_\mu) S_i}{S_\mu (b + S_i)} - V_i \right) \frac{S_i (S_i - S_\mu)}{(b + S_i)^2}$$

$$= -\frac{V_\mu}{S_\mu} \sum_{i=1}^{m} w_i \operatorname{sign} (V_\mu - V_i) \frac{S_\mu - S_i}{S_i} < 0.$$

Therefore, there exist sufficiently small $\underline{\beta} \leq \beta$ such that the function $b \mapsto \Psi(b)$ decreases on $\langle \underline{\beta}, \infty \rangle$, i.e., for any $b \in \langle 0, \underline{\beta} \rangle$ there holds

$$F \left(\frac{V_\mu}{S_\mu} (b + S_\mu), b \right) = \Psi(b) \leq \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|.$$

$\square$

Corollary 3.2.1. *Let (w_i, S_i, V_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, be some data, where $0 < S_1 \leq S_2 \leq \ldots \leq S_m$, $S_1 < S_m$, $V_i > 0$ and $w_i > 0$ are the corresponding data weights. If the data satisfy the following two conditions*

$$V_1 \leq \ldots \leq V_m, \quad V_1 < V_m \tag{3.8}$$

$$V_1/S_1 \geq \ldots \geq V_m/S_m, \quad V_1/S_1 > V_m/S_m, \tag{3.9}$$

then the least absolute deviations problem has a solution.

Proof. Let $\mu, \nu \in \{1, \ldots, m\}$ such that

$$V_\mu = \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) \in \operatorname*{Med}_{j=1,\ldots,m} (w_j, V_j)$$

and

$$\frac{V_\nu}{S_\nu} = \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) \in \operatorname*{Med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j).$$

Since the data satisfy conditions (3.8)–(3.9), there holds

$$V_1 \leq V_2 \leq \ldots \leq V_{\mu-1} \leq V_\mu \leq V_{\mu+1} \leq \ldots \leq V_m, \, V_1 < V_m$$

$$V_1/S_1 \geq \ldots \geq V_{\nu-1}/S_{\nu-1} \geq V_\nu/S_\nu \geq V_{\nu+1}/S_{\nu+1} \geq \ldots \geq V_m/S_m, \quad V_1/S_1 > V_m/S_m$$

and

$$S_1 \leq S_2 \leq \ldots \leq S_{\mu-1} \leq S_\mu \leq S_{\mu+1} \leq \ldots \leq S_m, \, S_1 < S_m,$$

and consequently

$$\sum_{i=1}^{m} w_i \operatorname{sign}(V_\nu S_i - V_i S_\nu) S_i (S_i - S_\nu) > 0 \text{ and } \sum_{i=1}^{m} w_i \operatorname{sign}(V_\mu - V_i) \frac{S_\mu - S_i}{S_i} > 0.$$

Immediately from Proposition 3.2 it follows that a least absolute deviations estimator for the Michaelis-Menten function exists. $\square$

At the and of this section, let us note that in various applications different linearizations of the Michaelis–Menten function are also considered, such as (see e.g., [14]):

(i) Lineweaver–Burk transformation: $\frac{1}{V} = \frac{1}{V_{\max}} + \frac{K_M}{V_{\max}} \frac{1}{S}$,

(ii) Hannes–plot transformation: $\frac{S}{V} = \frac{K_M}{V_{\max}} + \frac{S}{V_{\max}}$,

(iii) Eadie–Hofstee transformation: $V = V_{\max} - K_M \frac{V}{S}$.

In this way, the nonlinear fitting problem could be approximated with the following linear least absolute deviations problems:

$$\left. \begin{aligned} \sum_{i=1}^{m} w_i \left| \frac{1}{V_{\max}} + \frac{K_M}{V_{\max}} \frac{1}{S} - \frac{1}{V_i} \right| = \sum_{i=1}^{m} w_i \left| \alpha \frac{1}{S} + \beta - \frac{1}{V_i} \right| \to \min_{(\alpha,\beta) \in \mathcal{P}} \\ \alpha := \frac{K_M}{V_{\max}}, \quad \beta := \frac{1}{V_{\max}}. \end{aligned} \right\}, \quad (3.10)$$

$$\left. \begin{aligned} \sum_{i=1}^{m} w_i \left| \frac{K_M}{V_{\max}} + \frac{S}{V_{\max}} - \frac{S_i}{V_i} \right| = \sum_{i=1}^{m} w_i \left| \alpha S_i + \beta - \frac{S_i}{V_i} \right| \to \min_{(\alpha,\beta) \in \mathcal{P}} \\ \alpha := \frac{1}{V_{\max}}, \quad \beta := \frac{K_M}{V_{\max}} \end{aligned} \right\}, \quad (3.11)$$

$$\left. \begin{aligned} \sum_{i=1}^{m} w_i \left| V_{\max} - K_M \frac{V_i}{S_i} - V_i \right| = \sum_{i=1}^{m} w_i \left| \alpha \frac{V_i}{S_i} + \beta - V_i \right| \to \min_{(\alpha,\beta) \in \mathcal{P}} \\ \alpha := -K_M, \quad \beta := V_{\max} \end{aligned} \right\}. \quad (3.12)$$

The linear least absolute deviations problems (3.10)–(3.12) can be solved by using the method for searching for a best least absolute deviations line proposed in [21] and [23]. From Corollary 2.0.1, it follows that problems (3.10)–(3.12) have an optimal solutions but the corresponding optimal parameters may not be positive. Finally, the following proposition shows that under the conditions

$$V_1 < \ldots < V_m, \tag{3.13}$$

$$V_1/S_1 > \ldots > V_m/S_m, \tag{3.14}$$

problems (3.10)–(3.12) have positive optimal solutions.

Proposition 3.3. *Let (w_i, S_i, V_i), $i \in I = \{1, \ldots, m\}$, $m \geq 2$, be some data, where $0 < S_1 \leq S_2 \leq \ldots \leq S_m$, $S_1 < S_m, V_i > 0$ and $w_i > 0$ are the corresponding data weights. If the data satisfy conditions (3.13)–(3.14), then problems (3.10)–(3.12) have positive optimal solutions.*

Proof. Let us suppose that the data satisfy conditions (3.8)–(3.9). Let us consider problem (3.10). In accordance with Corollary 2.0.1, there exists $\eta, \kappa \in I$, $\eta \neq \kappa$, and $S_\eta \neq S_\kappa$ such that

$$\frac{K_M}{V_M} = \frac{\frac{1}{V_\eta} - \frac{1}{V_\kappa}}{\frac{1}{S_\eta} - \frac{1}{S_\kappa}} = \frac{S_\eta S_\kappa}{V_\eta V_\kappa} \left(\frac{V_\kappa - V_\eta}{S_\kappa - S_\eta} \right) > 0,$$

$$\frac{1}{V_M} = \frac{1}{V_\eta} - \frac{\frac{1}{V_\eta} - \frac{1}{V_\kappa}}{\frac{1}{S_\eta} - \frac{1}{S_\kappa}} \frac{1}{S_\eta} = -\frac{S_\eta S_\kappa}{V_\eta V_\kappa} \left(\frac{\frac{V_\eta}{S_\eta} - \frac{V_\eta}{S_\eta}}{S_\eta - S_\kappa} \right) > 0$$

.

Similarly, for problems (3.11) and (3.12) we obtain

$$\frac{1}{V_{\max}} = \frac{\frac{S_\eta}{V_\eta} - \frac{S_\kappa}{V_\kappa}}{S_\eta - S_\kappa} > 0, \quad \frac{K_M}{V_{\max}} = \frac{S_\eta}{V_\eta} - \frac{\frac{S_\eta}{V_\eta} - \frac{S_\kappa}{V_\kappa}}{S_\eta - S_\kappa} S_\eta = \frac{S_\eta S_\kappa}{V_\eta V_\eta} \left(\frac{V_\eta - V_\kappa}{S_\eta - S_\kappa} \right) > 0,$$

and

$$K_M = -\frac{V_\eta - V_\kappa}{\frac{V_\eta}{S_\eta} - \frac{V_\kappa}{S_\kappa}} > 0, \quad V_{\max} = V_\eta - \frac{V_\eta - V_\kappa}{\frac{V_\eta}{S_\eta} - \frac{V_\kappa}{S_\kappa}} \frac{V_\eta}{S_\eta} = \frac{V_\eta V_\kappa}{S_\eta S_\kappa} \left(\frac{S_\eta - S_\kappa}{\frac{V_\kappa}{S_\kappa} - \frac{V_\eta}{S_\eta}} \right) > 0,$$

respectively. □

4. NUMERICAL EXAMPLES

In this section, we give three numerical examples. The first example shows that it is possible that a least absolute estimator for the Michaelis–Menten function exists and at the same time that linearized problems (3.10)–(3.12) have negative solutions.
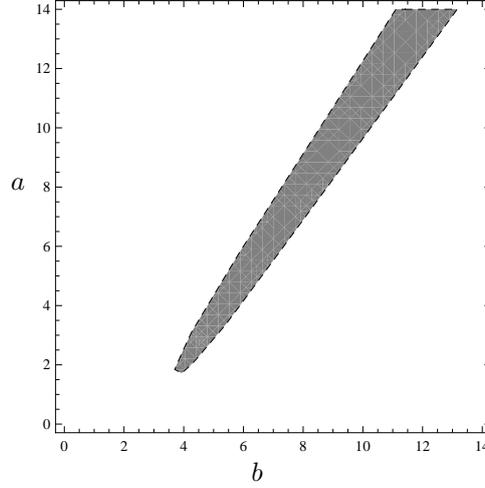
FIGURE 1. The region $\mathcal{D} = \{(a,b) \in \mathcal{P} : F(a,b) \leq F_E\}$ generated by Mathematica instruction `RegionPlot`

Example 1. We are given the set of data–points $\{(w_i, S_i, V_i) : i \in I\}$, $I = \{1, \ldots, 5\}$, where

w_i	1	1	1	1	1
S_i	1	2	3	4	5
V_i	0.07	6.84	2.15	0.19	2.03

Figure 1 shows the region $\mathcal{D} = \{(a,b) \in \mathcal{P} : F(a,b) \leq F_E\}$, $\mathcal{P} = \{(a,b) : a, b > 0\}$ (see Theorem 1), where

$$F_E = \min \left\{ \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j, V_j) - V_i \right|, \sum_{i=1}^{m} w_i \left| \operatorname*{med}_{j=1,\ldots,m} (w_j S_j, V_j/S_j) S_i - V_i \right| \right\}$$
$$= 8.73.$$

Since $\mathcal{D} \neq \emptyset$, in accordance with Theorem 1, it follows that a least absolute deviations estimator exists. It can also be easily verified that the data satisfy the conditions from Proposition 3.2. On the other hand, optimal parameters (see Table 1) obtained by solving the minimization problem for the linearized Michaelis Menten model function (3.10)–(3.12) are not positive.

The next example illustrates the usefulness of sufficient conditions proposed in Proposition 3.2 and its comparison with the existence of optimal parameters obtained from linearized problems (3.10)–(3.12).

Parameters	Lineweaver–Burk	Hannes–plot	Eadie–Hofstee
$V_{\max}$	-0.33833	1.87318	0.09634
K_M	-5.83333	-0.38627	-1.97183

TABLE 1. Optimal parameters for the linearized Michaelis–Menten model–function

Example 2. A set of data–points $\{(1, S_i, V_i) : i \in I\}$, $I = \{1, \ldots, m\}$ is given such that

$$S_i = i,\ V_i = \frac{2S_i}{1 + S_i} + \epsilon_i,$$

where $\epsilon_i \sim \mathcal{L}(0, 0.4)$ is a Laplace-distributed additive error with scale parameter $\sigma = 0.4$. For any $m \in \{10, 30, 50, 70, 90, 110, 130\}$ 1,000 data sets are generated. Figure 2 shows the dependence of the number of data–points m and the number of generated sets satisfying the sufficient existence condition from Proposition 3.2, i.e., for which optimal parameters are obtained by solving the linearized least absolute deviations problems (3.10)–(3.12).
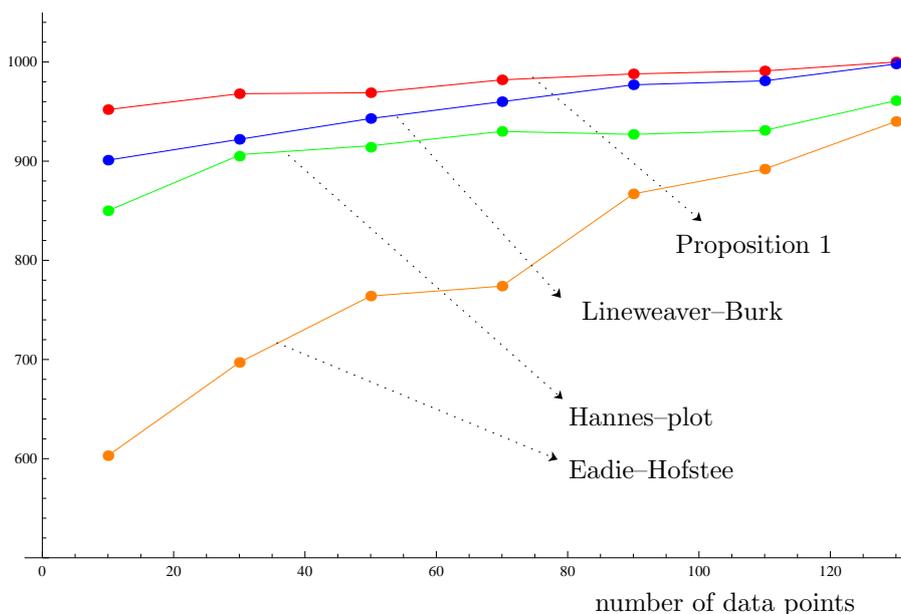

FIGURE 2. The number of generated sets of data–points satisfying the existence conditions on the dependence of the number of data–points

Figure 2 illustrates that the number of sets of data–points satisfying the sufficient condition from Proposition 3.2 is always larger than the number of data sets for which linearized problems (3.10)–(3.12) have a solution. Note also that an increase in the number of data m results in an increase in the number of data–sets for which least absolute deviations problems (1.9)–(1.10), i.e., (3.10)–(3.12) have solutions.

In Corrollary 3.1.1 it is shown in which cases it is possible that the least absolute deviations estimator does not exist. Similarly, in Corrollary 3.1.2 it is shown that there exist data–sets such that corresponding least absolute deviations problem has infinitely many solutions. For both of cases there is a very little probability that a data–set satisfies these conditions. The following example illustrates some difficulties with stability of numerical procedure for searching an optimal parameters for Michaelis–Menten function for the case when data–points "almost fulfilled" requirements from Corollaries 3.1.1 and 3.1.2.

Example 3. Let $I = \{1, \ldots, 50\}$. Sets of data–points

$$\mathcal{S}^{(1)}(\sigma) = \left\{ (w_i, S_i, V_i) := \left(1, \frac{10i}{m}, \frac{10i}{m} + \epsilon_i \right) : i \in I \right\},$$

$$\mathcal{S}^{(2)}(\sigma) = \left\{ (w_i, S_i, V_i) := \left(1, \frac{10i}{m}, 5 + \epsilon_i \right) : i \in I \right\},$$

$$\mathcal{S}^{(3)}(\sigma) = \left\{ (w_i, S_i, V_i) := \left(1, 10 + \epsilon_i, \frac{10i}{m} \right) : i \in I \right\},$$

are given, where $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$ is a normally-distributed additive error with variance σ^2. For any $\sigma \in \{0.1, 0.3, 0.5, 0.7\}$ data sets $\mathcal{S}^{(1)}(\sigma)$ (Figure 3 (1)), $\mathcal{S}^{(2)}(\sigma)$ (Figure 3 (2)) and $\mathcal{S}^{(3)}(\sigma)$ (Figure 3 (3)) are generated such that the existence condition from Proposition 3.2 is satisfied. According to Corollary 3.1.1, if data–points lie on the line $y = k\,t$, $k > 0$ or $y = l$, $l > 0$, the least absolute deviations problem has no solution. Similarly, according to Corollary 3.1.2, if data–points lie on the line $t = t_0$, $t_0 > 0$, then the least absolute deviations problem for Michaelis–Menten function has infinitely many solutions. Note that data–points from sets $S^{(1)}(\sigma)$, $S^{(2)}(\sigma)$ and $S^{(3)}(\sigma)$ respectively lie near lines $y = t$, $y = 2$ and $t = 5$. In order to illustrate possible difficulties with numerical method for searching an optimal parameters for Michaelis–Menten function we will analyze the graph of the function $(a, b) \mapsto F(a, b) = \sum_{i=1}^{m} w_i \left| \frac{aS_i}{b+S_i} - V_i \right|$, $(a, b) \in \mathcal{P}$ for

data–points sets $\mathcal{S}^{(1)}(\sigma)$, $\mathcal{S}^{(2)}(\sigma)$ and $\mathcal{S}^{(3)}(\sigma)$. Since from Lemma 2.2 follows

$$F(a,b) = \sum_{i=1}^{m} w_i \left| \frac{aS_i}{b+S_i} - V_i \right| \geq \sum_{i=1}^{m} \frac{w_i S_i}{b+S_i} \left| a - \frac{V_i(b+S_i)}{S_i} \right|$$

$$\geq \sum_{i=1}^{m} \frac{w_i S_i}{b+S_i} \left| \operatorname*{med}_{j=1,\dots,m} \left(\frac{w_j S_j}{b+S_j}, \frac{V_j(b+S_j)}{S_j} \right) - \frac{V_i(b+S_i)}{S_i} \right| =: \overline{F}(b),\ b > 0,$$

and

$$F(a^\star(lad), b^\star(lad)) = \min_{(a,b)\in\mathcal{P}} F(a,b) \Leftrightarrow \overline{F}(b^\star(lad)) = \min_{b>0} \overline{F}(b),$$

instead of the graph of the function $(a,b) \mapsto F(a,b)$ it is enough to consider the graph of the function $b \mapsto \overline{F}(b)$. Figure 3 shows graph of the function $b \mapsto \overline{F}(b)$ for sets $S^{(1)}(\sigma)$, $S^{(2)}(\sigma)$ and $S^{(3)}(\sigma)$. Since data–points from $S^{(1)}(\sigma)$, $S^{(2)}(\sigma)$ and $S^{(3)}(\sigma)$ satisfy the existence condition from Proposition 1, the corresponding least absolute deviations estimators exist. Note that in the neighborhood of global minimum of the function $b \mapsto \overline{G}(b)$ for sets $S^{(1)}(\sigma)$ and $S^{(3)}(\sigma)$ is "almost constant". On the other hand, optimal parameter $b^\star(lad)$ of the function $b \mapsto \overline{G}(b)$ is located closely to 0. Consequently, it can be expected that the corresponding numerical method for searching an optimal parameters for Michaelis–Menten function will be extremely unstable i.e. calculated optimal parameters will be probably incorrect.

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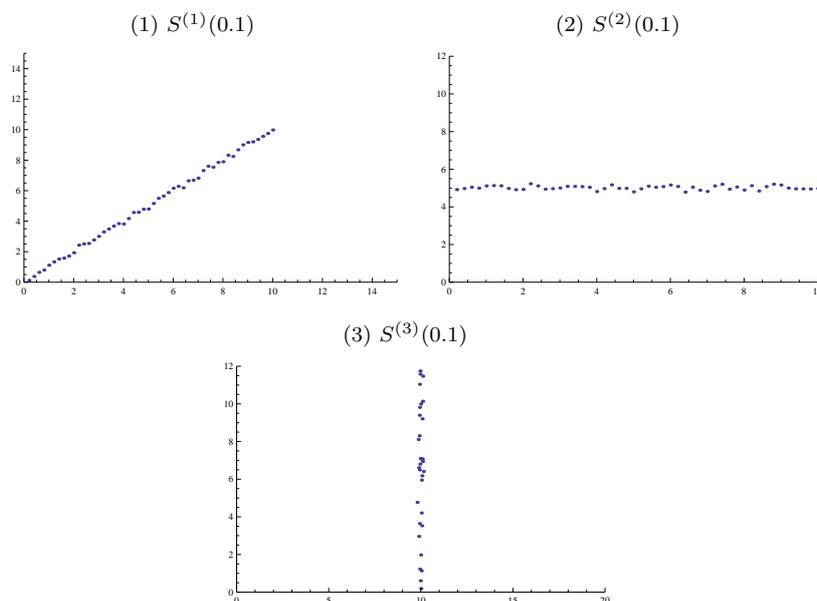(1) $S^{(1)}(0.1)$ (2) $S^{(2)}(0.1)$

(3) $S^{(3)}(0.1)$

FIGURE 3. Data-sets $S^{(1)}(0.1)$, $S^{(2)}(0.1)$ and $S^{(3)}(0.1)$.

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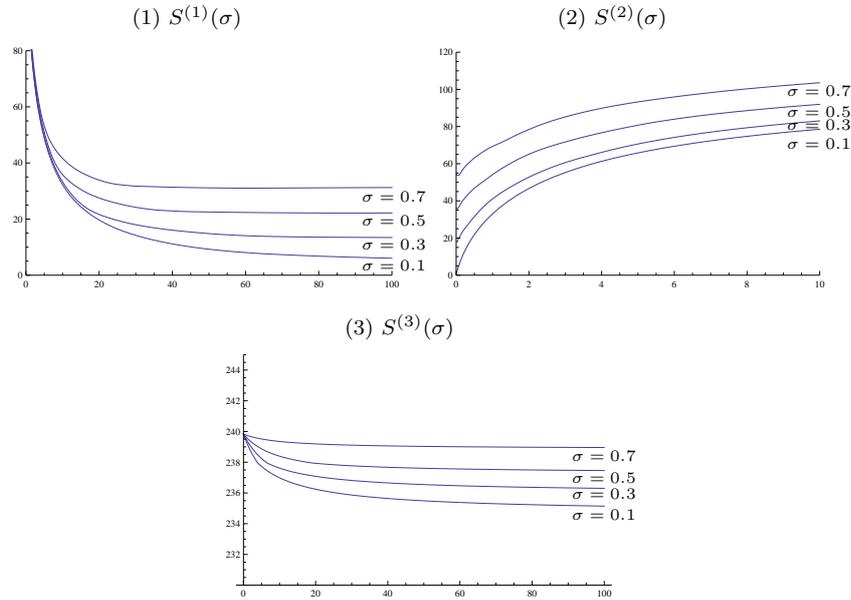
(1) $S^{(1)}(\sigma)$

(2) $S^{(2)}(\sigma)$

(3) $S^{(3)}(\sigma)$

FIGURE 4. Graph of the function $b \mapsto \overline{F}(b)$ for data–sets $S^{(1)}(\sigma)$, $S^{(2)}(\sigma)$ and $S^{(3)}(\sigma)$.

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