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Dedicated to the memory of J. Keiper,
whose unselfish guidance we greatly miss

Curve Fitting and Interpolation of Biological Data Under Uncertainties

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Abstract: This paper is devoted to the software implementation of two mathematical methods which are often used in biological applications: interpolation and curve fitting in the presence of uncertainties in the input data given in the form of intervals. The methods involve model functions linear in their parameters and are formulated by means of simple expressions in terms of interval arithmetic allowing the computation of verified bounds for the interpolating/approximating functions. The methods are demonstrated for certain classes of nonlinear modelling functions finding applications in biology. A case study involving enzyme-catalysed reaction is considered. The numerical results are performed in the computer algebra system *Mathematica*, which supports interval-arithmetic computations.

Key Words: Interpolation, least squares approximation, verification, model validation, algebraic manipulations, computer algebra systems, enzyme kinetics, uncertainties, interval arithmetic.
Category: G.1.1, G.1.2, G.4, I.1.1, I.6.4, J.3

1 Introduction

We are witnessing a rapid involvement of mathematics in biological investigations. A characteristic feature of this involvement, which stimulates the development of specific mathematical tools, is the presence of uncertainties in the input data. For biological problems involving both short and uncertain records, it seems that several deterministic mathematical theories and numerical approaches will play major role in the near future: differential inclusions, set-valued analysis, viability analysis, interval analysis and numerical methods with result verification. These tools are now quickly penetrating into biological applications [Belforte et al. 1983], [Fedra et al. 1981], [Gomeni et al. 1986], [Lahanier et al. 1987], [Norton 1986], [Norton 1987], [Walter and Lahanier 1988]. For the successful application of these new mathematical tools and methodologies we need suitable supporting programming tools. Special languages, called SC-languages, have been developed which support the design of numerical methods with verification. Two computer algebra systems are major competitors for the provision of suitable support for qualified mathematical applications:

Maple [Char et al. 1986] and *Mathematica* [Wolfram 1991]. The development of special mathematical tools appropriate for biological applications in fields like mathematical ecology, mathematical immunology, mathematical population genetics and mathematical epidemiology is in progress, (see e. g. [Murray 1989], [Ewens 1979], [Hallam and Levin 1989]).

A typical problem which often arises in biological applications is interpolation involving interval data. One of the simplest problems is interpolation under the assumption that the values for the dependent variable y contain uncertainties, that is, instead of numerical values for y we are given intervals Y [Crane 1975], [Milanese 1989], [Markov 1991]. In a setting involving generalized linear modelling functions often used in biological applications [Brown and Rothery 1994], the problem can be formulated in the following way [Markov and Popova 1996], [Markov et al. 1993]:

Given:

i) a class $\mathcal{L}_m(D,\varphi)$ of generalized polynomials defined for $\xi \in D \subseteq R^k$:

$$\eta\left(\lambda;\xi\right) = \sum_{i=1}^{m} \lambda_i \varphi_i\left(\xi\right) = \varphi\left(\xi\right)^{\top} \lambda, \tag{1}$$

where $\varphi(\cdot) = \left(\varphi_1(\cdot), \ldots, \varphi_m(\cdot)\right)^{\top}$ is a Chebyshev system of m continuous functions on D and $\lambda = \left(\lambda_1, \ldots, \lambda_m\right)^{\top} \in R^m$ is an unknown vector (for example φ_i can be the standard algebraic monomials ξ^{i-1});

ii) an input data $x_j \in D, j \in J = \{1, \ldots, n\}, n \geq m$, such that $x_i \neq x_j,\ i \neq j$, and n interval measurements $Y_j = [y_j^-, y_j^+],\ j \in J$. Let $\mathbf{x} = (x_1, \ldots, x_n)^{\top} \in R^{n\times k}$ and $Y = (Y_1, \ldots, Y_n)^{\top} \in IR^n$, where IR^n is the set of n-dimensional interval vectors.

Problem 1 (Interval interpolation): Assume that $\eta(\lambda; x_j) \in Y_j,\ j \in J$. If η is of the class (1), then these conditions can be written as $\varphi(x_j)^{\top}\lambda \in Y_j,\quad j \in J$, or in matrix notations: $\varPhi(\mathbf{x})\lambda \in Y$, where $\varPhi(\mathbf{x})$ is the full rank matrix

$$\varPhi(\mathbf{x}) = \begin{pmatrix} \varphi_1(x_1) & \ldots & \varphi_m(x_1) \\ \vdots & \ddots & \vdots \\ \varphi_1(x_n)) & \ldots & \varphi_m(x_n) \end{pmatrix}.$$

For a fixed $\xi \in D$, we let

$$\begin{aligned} \eta(\mathbf{x}, Y; \xi) &= \{\eta(\lambda;\xi) \mid \eta(\lambda; x_j) \in Y_j,\ j \in J\} \\ &= \left\{\varphi\left(\xi\right)^{\top} \lambda \mid \varPhi(\mathbf{x})\lambda \in Y\right\}. \end{aligned} \tag{2}$$

Formula (2) defines an interval-valued function $\eta(\mathbf{x}, Y; \cdot)$ on D, which presents the envelope of the set of functions η of the form (1) interpolating the vertical segments (x_j, Y_j), $j \in J$, whenever this set is not empty. We need to compute numerically the interval function $\eta(\mathbf{x}, Y; \cdot)$ in D.

Problem 2 (Interval curve fitting): In the familiar situation when the measurements y are assumed to be real numbers, the curve fitting problem involves a matrix operator $H : R^{n\times k} \to R^{m\times n}$, which depends on $\mathbf{x}$ but not on Y, i. e. we have $H = H(\mathbf{x})$. Denote by ϕ an operator (called estimator) which maps

$y \in R^n$ via H linearly into the parameter space R^m, i. e. $\lambda = \phi(y) = Hy$. Consider now the situation where intervals Y are given instead of numerical values y. For a fixed $\xi \in D$, the "estimates uncertainty set" [Milanese 1989] is

$$\eta^{\phi}(\mathbf{x}, Y; \xi) = \{\varphi(\xi)^{\top}\lambda\ ,\ \lambda = Hy\ \mid\ y \in Y\}. \tag{3}$$

The problem is to present and compute the interval-valued function (3) in a given domain for the variable ξ. The function $\eta^{\phi}(\mathbf{x}, Y; \cdot)$ is the enveloping function of the set of solutions of the curve fitting problems (generated by the operator ϕ) corresponding to all possible data $(\mathbf{x}, y)$ whenever $y \in R^n$ varies in the interval vector $Y \in IR^n$.

Problems 1 and 2 are related to the problems of finding (or enclosing) the corresponding parameter sets [Milanese 1989]. For example, the parameter set corresponding to Problem 1 is a convex polytope

$$\Lambda = \{\lambda \in R^m \mid \Phi(\mathbf{x})\lambda \in Y\}\,. \tag{4}$$

Interval Arithmetic: For the presentation of the interval-valued solution functions (2), (3) we shall use two interval arithmetic operations [Moore 1966]. By IR we denote the set of all intervals Y of the form $Y = [y^-, y^+] = \{y \mid y^- \leq y \leq y^+\}$, where $y^-, y^+ \in R$. For our purposes we shall need addition of two intervals $X, Y \in IR$ given by $X + Y = [x^- + y^-, x^+ + y^+]$ and multiplication of an interval X by a real $\alpha \in R$ which can be expressed by:

$$\alpha X = [\alpha x^{-sgn(\alpha)}, \alpha x^{sgn(\alpha)}] = \begin{cases} [\alpha x^-, \alpha x^+], & \alpha \geq 0, \\ [\alpha x^+, \alpha x^-], & \alpha < 0, \end{cases}$$

where $x^{--} = x^+,\ \ x^{-+} = x^-$.

Given a real valued vector $\alpha = (\alpha_1, \ldots, \alpha_n)$ and an interval valued vector $Y = (Y_1, \ldots, Y_n)^{\top}$, we can present the set $\{\alpha y\ \mid y \in Y\}$ by

$$\alpha_1 Y_1 + \alpha_2 Y_2 + \ldots + \alpha_n Y_n = \alpha Y\ . \tag{5}$$

The interval-arithmetic expression αY for the set $\{\alpha y\ \mid y \in Y\}$ is short and convenient; to see this the reader may compare it to conventional expressions for the end-points of the interval $\{\alpha y \mid y \in Y\}$. In what follows we shall make use of the interval-arithmetic expression (5) to present and compute the interval-valued solution functions (2) and (3).

2 Methods for Interpolation and Fitting Under Interval Data

In this section we briefly present some simple interval-arithmetic expressions for the solutions of Problems 1 and 2.

Interval Interpolation. For $m = n$ the matrix $\Phi^{-1}(\mathbf{x})$ is well defined and we have for (2)

$$\eta(\mathbf{x}, Y; \xi) = \left(\varphi(\xi)^{\top}\Phi^{-1}(\mathbf{x})\right) Y. \tag{6}$$

For $m < n$ the interval function $\eta(\mathbf{x}, Y; \cdot)$ can be computed at a fixed point $\xi \in D$, e. g. by one of the following two methods:

A. Intersecting the values at ξ of all interval functions of the type (6), i. e.

$$\eta(\mathbf{x}, Y; \xi) = \bigcap_{Q \subseteq J} \eta(\mathbf{x}^Q, Y^Q; \xi) = \bigcap_{Q \subseteq J} \left(\varphi(\xi)^\top \Phi^{-1}(\mathbf{x}^Q)\right) Y^Q,$$

where $Q = \{q(i)\}_{i=1}^m$ is a subset of J of m elements and $(\mathbf{x}^Q, Y^Q)$ are data $(\mathbf{x}, Y)$ reduced to Q, e. g. $\mathbf{x}^Q = \left(x_{q(1)}, \ldots, x_{q(m)}\right)^\top$ and $Y^Q = \left(Y_{q(1)}, \ldots, Y_{q(m)}\right)^\top$. If the intersection is empty then Problem 1 has no solution.

B. Solving two constrained linear optimization problems and presenting the solution $\eta(\mathbf{x}, Y; \xi)$ at $\xi \in D$ in the form

$$\left[\min_{\Phi(\mathbf{X})\lambda \in Y} \left\{\varphi(\xi)^\top \lambda\right\}, \max_{\Phi(\mathbf{X})\lambda \in Y} \left\{\varphi(\xi)^\top \lambda\right\}\right].$$

The case $k = 1$. For $k = 1$ the input data $\mathbf{x}$ is a vector of real components $x = (x_1, \ldots, x_n) \in R^n$. Assume that the components of x belong to an interval $X = [x^-, x^+]$, and $x_0 = x^- \leq x_1 < x_2 < \ldots < x_n \leq x^+ = x_{n+1}$; in particular, we may have $x_0 = x^- = -\infty$, $x_{n+1} = x^+ = \infty$. The following theorem characterizes $\eta(x, Y; \cdot)$ in X.

Proposition 1. *[Markov et al. 1993], [Markov and Popova 1996]. Let the set of functions $\eta(\lambda; \cdot) \in \mathcal{L}_m(X, \varphi)$ interpolating (x, Y) be not empty and let $\eta(x, Y; \cdot)$ be the envelope (2) of this set. Then in every (x_i, x_{i+1}), $i = 0, 1, \ldots, n$, the upper and lower boundary functions of $\eta(x, Y; \cdot)$ are functions from $\mathcal{L}_m(X, \varphi)$.*

Proposition 1 states that for every i there exist two parameters $\lambda_i^-, \lambda_i^+ \in R^m$ generating the envelope in the whole interval (x_i, x_{i+1}); that is, for $\xi \in (x_i, x_{i+1})$

$$\eta^-(x, Y; \xi) = \eta(\lambda_i^-; \xi) = \varphi(\xi)^\top \lambda_i^-,$$

$$\eta^+(x, Y; \xi) = \eta(\lambda_i^+; \xi) = \varphi(\xi)^\top \lambda_i^+.$$

Numerical algorithm (for $k = 1$). Compute $\eta(x, Y; \cdot)$ at some point ξ_i from the open interval (x_i, x_{i+1}), e. g. $\xi_i = (x_{i+1} + x_i)/2$, by computing at ξ_i the values of the boundary functions η_i^- and η_i^+ using either method **A** or **B**. Proposition 1 states that there are two unique generalized polynomials $\eta_i^- = \eta(\lambda_i^-; \xi)$ and $\eta_i^+ = \eta(\lambda_i^+; \xi)$ which are the boundary functions of $\eta(x, Y; \cdot)$ in the interval $[x_i, x_{i+1}]$. Using method **A** we obtain two m-dimensional subsets Q_i^- and Q_i^+ of J and two m-dimensional sets of binary variables $\mathcal{A}^- = (\alpha_{q(1)}^-, ..., \alpha_{q(m)}^-)$ and $\mathcal{A}^+ = (\alpha_{q(1)}^+, ..., \alpha_{q(m)}^+)$, $\alpha_{q(i)}^-$, $\alpha_{q(i)}^+ \in \{+, -\}$, $i = 1, ..., n$, such that for $\xi \in [x_i, x_{i+1}]$:

$$\eta^-(x, Y; \xi) = \left(\varphi(\xi)^\top \Phi^{-1}(\mathbf{x}^{Q_i^-})\right) (Y^{Q_i^-})^{\alpha_{q(i)}^-},$$

$$\eta^+(x, Y; \xi) = \left(\varphi(\xi)^\top \Phi^{-1}(\mathbf{x}^{Q_i^+})\right) (Y^{Q_i^+})^{\alpha_{q(i)}^+}.$$

(Note that the pairs $(Q_i^-, \mathcal{A}_i^-)$, $(Q_i^+, \mathcal{A}_i^+)$ may not be unique, and any such pair can be used). Fig. 1–3 show solutions of problem 1 for different values of m and n ($k = 1$ for all examples). Fig. 1 shows the graphs of two interval-valued functions interpolating $n = 9$ vertical segments placed symmetrically with respect to the origin using the basic functions $\varphi_i = \xi^{i-1}$: the outer interval function is the solution involving $m = 9$ parameters and the inner function involves $m = 7$ parameters. Individual boundary functions are shown in Fig. 4 for $n = 7, m = 2$.

The above algorithm has been programmed in *Mathematica* Version 2.2, which supports interval arithmetic [Keiper 1993]. The following program produces the outer solution presented in Fig. 1:

```
n = 9; m = 9;
Do[x[i] = -1 + (2 * (i - 1))/(n - 1), {i, n}];
Do[y[i] = Interval[{-2^(-1), 1/2}], {i, n}];
Do[fi[i, t_] = t^(i - 1), {i, m}];
sausage[ksi_, set_] := (fi[#1, ksi]&)/@Range[m].
                       Inverse[Table[fi[i, x[set[[j]]]], {j, m}, {i, m}]].
                       (z[#1]&)Range[m]/.Table[z[i]- > y[set[[i]]], {i, m}];
sampleDraw := Module[{segment}, segment[x_, y_] :=
                                   Line[{{x, Min[y]}, {x, Max[y]}}];
                       Graphics[{(segment[x[#1], y[#1]]&)/@Range[n]}]];
iplot[y_, r_, opt__] :=
                       Plot[{Min[y], Max[y]}, r, AspectRatio- > 1, opt];
Show[sampleDraw, iplot[sausage[ksi, Range[n]], {ksi, -1.03, 1.03},
                       DisplayFunction- > Identity],
                       DispalyFunction :> DispalayFunction,
                       Frame- > True, Axes- > True,
                       PlotRange- > {-6, 6},
                       FrameLabel- > {"n = 9; m = 9"}];
```

Alternatively, by using method **B** the parameters λ_i^- and λ_i^+, $i \in J$, can be found (see Proposition 1). Using these parameters we can find both the interval-valued function (2) and the corresponding parameter set (see Fig. 4).

Interval Curve Fitting. Using (5) we can present the interval solution (3) explicitly by

$$\begin{aligned}\eta^{\phi}(\mathbf{x}, Y; \xi) &= \{\varphi(\xi)^{\top}\lambda\ ,\ \lambda = Hy \ \mid\ y \in Y\} \\ &= \{\varphi(\xi)^{\top}(Hy) \mid y \in Y\} \\ &= \{\left(\varphi(\xi)^{\top}H\right) y \mid y \in Y\} \\ &= (\varphi(\xi)^{\top}H)Y \ = \ \Gamma^{\phi}(\xi)Y\ . \end{aligned} \tag{7}$$

The interval–valued function (7) gives an explicit expression for the exact bounds for the solution set.

Special case: Multiple linear regression. Let $\xi = (1, \xi_1, \ldots, \xi_{m-1})$ and assume $\varphi_i(\xi) = \xi_i$, $i = 0, \ldots, m-1$, so that $\eta(\lambda; \xi) = \varphi(\xi)^{\top}\lambda = \lambda_0 + \lambda_1\xi_1 + \ldots + \lambda_{m-1}\xi_{m-1} = \xi\lambda$. Multiple linear regression involves a matrix $H = (X^{\top}X)^{-1}X^{\top}$ with X of the form

$$X = \begin{pmatrix} 1\ x_{11}\ \ldots\ x_{1m-1} \\ \ldots \\ 1\ x_{n1}\ \ldots\ x_{nm-1} \end{pmatrix}.$$

Substituting in (7) we have

$$\eta^{\phi}(x, Y; \xi) = \Gamma^{\phi}(\xi)Y = (\xi H)Y = \left(\xi (X^{\top} X)^{-1} X^{\top}\right) Y.$$

3 A Case Study Involving Biological Data

A *Mathematica* package for interpolation and curve fitting involving interval data for the dependent variables has been developed. The package is suitable for mathematical modelling in biology whenever generalized linear modelling functions are used. Such models like the logistic-Normal model, the rectangular hyperbola-Normal model etc. play an important role in biomathematical applications [Brown and Rothery 1994]. The package offers the possibility to compute and visualize the interval solution functions (2), (3) as well as the corresponding parameter sets (see Fig. 1–4). One can also easily observe individual solution functions (Fig. 2), or to compare different solution functions (see Fig 1.). If a solution set does not exist for a particular interpolation problem, then a variety of classes of modeling functions (e. g. involving different number of parameters or various basic functions) can be used.

The numerical examples presented in Fig. 1–4 are related to interval interpolation (Problem 1) and are self-explanatory. Figures 1–3 visualize interval solution functions (2) for the presented interval data. Fig. 4 visualizes the parameter set (4) corresponding to the solution from Fig. 3.

In case that a satisfactory interpolation solution cannot be found at all, if interested, the user can always find an interval curve fitting solution. This is illustrated in Fig. 9, where the interval segments are situated in a way that suggests the use of quadratic polynomial functions. The envelopes (8) of the sets of quadratic least-square fitting polynomials are computed.

Case study: an enzyme-catalysed reaction. Fig. 5–8 are devoted to an enzyme catalysed reaction discussed in [Brown and Rothery 1994] (see pp. 347, 425). The measured data for this example are taken from [Kuhn 1923]; s are values of the substrate concentrations and v are values for the velocity of the reaction at s:

s	0.1970	0.1385	0.0678	0.0417	0.0272	0.0145	0.0098	0.0082
v	21.5	21.0	19.0	16.5	14.5	11.0	8.5	7.0

The model fitted by least-squares is $v = as/(b + s)$; some computed values for the parameters are $a = 23.6$, $b = 0.0175$. We shall assume that the concentrations s are exact and the velocities v are uncertain but bounded in certain intervals V. We shall then ask how precise are the computed parameters a, b and how does the uncertainty reflect on the computed model. It has been assumed that the data for the velocity v of the enzyme-catalysed reaction has been bounded by a magnitude of 0.5; e. g. $V_1 = (21.0, 22.0)$, $V_2 = (20.5, 21.5)$, ... , $V_8 = (6.5, 7.5)$ — these values are taken for illustration; in reality the interval values V_i may be found experimentally. The corresponding interval segments (s, V) are visualized in Fig. 8. We consider the problem of finding the envelope of the set of rectangular hyperbolas of the form $v = as/(b + s)$ (with a, b unknown), interpolating the segments (s_i, V_i). This problem has been solved by first linearizing the interval data by expressing s/v as a linear function of s (Hanes-Woolf plot) and finding the set of linear functions interpolating the transformed segments $(s_i, s_i/V_i)$ whose envelope is shown in Fig. 5. The vertices of the corresponding parameter set are shown on Fig. 6 — these vertices are the four points: $(0.000739532, 0.0431465)$, $(0.000751904, 0.0416378)$, $(0.000759625, 0.0428501)$, $(0.000779215, 0.0414991)$. These points are then converted back to the parameters (a, b) to find the bounding interpolating hyperbolas of the original problem of the form $v = as/(b + s)$. We obtain the following four points (a, b): (23.1768, 0.01714), (24.0167, 0.0180582), (23.3371, 0.0177275), (24.0969, 0.0187767), (see Fig. 7), which are the vertices of the parameter set for (a, b). It can be shown that this set is a quadrilateral and therefore uniquely determined by the four vertices. Fig. 8 shows the enveloping interval function for the interpolating hyperbolic functions. This example shows that for the interval interpolation problem, the intermediate linearization approach causes no additional problems, as is the case when curve fitting is performed. Recall that the curve-fitted solution of the original problem does not retain the type of fitting estimator (e. g. least square estimator), of the corresponding intermediate linearized problem, which implies the use of more sophisticated methods, like weighted least-squares.

4 Conclusions

The results and programing tools described above can be used by experimental scientists, for checking hypotheses with respect to the type of the modeling functions. Our method for interpolation of interval data is simple and can be very useful for applications. The case study discussed above shows that the method can be applied not only for linear models but also for certain classes of nonlinear models. It is an open problem to specify such nonlinear problems and to formulate corresponding numerical tools for them. *Mathematica* can deal with interval-arithmetic expressions and is a suitable environment for the development of such packages. Its extensive graphics capabilities allow the user to generate two- and three-dimensional graphics, which can be useful in the process of mathematical modelling.

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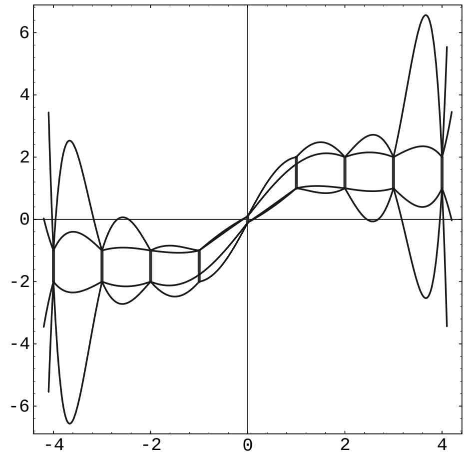

Figure 1: $n = 9$; $m = 7$ and $m = 9$

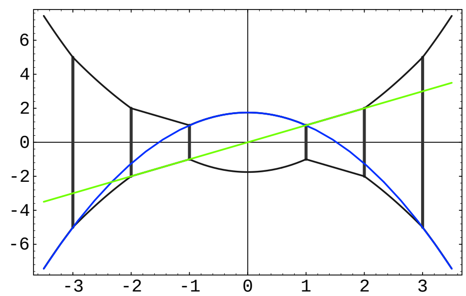

Figure 2: $n = 7$, $m = 2$

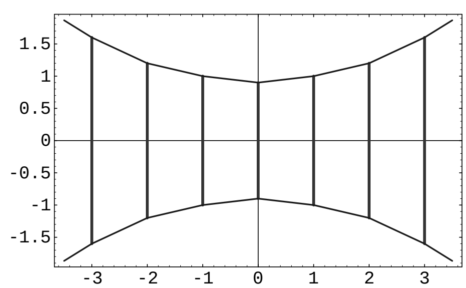

Figure 3: $n = 7$, $m = 1$

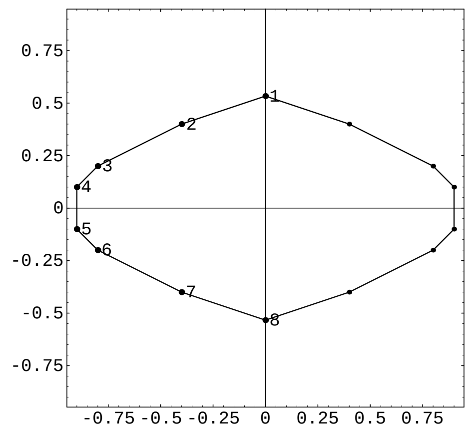

Figure 4: The parameter set for the problem of Fig. 3

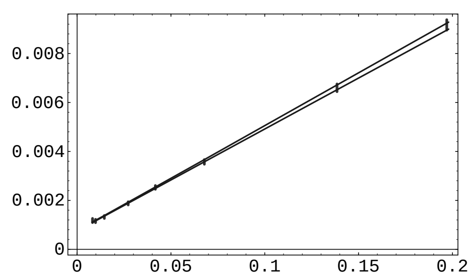

Figure 5: Linearized interval data, resp. interval solution ($m = 2$, $n = 8$)

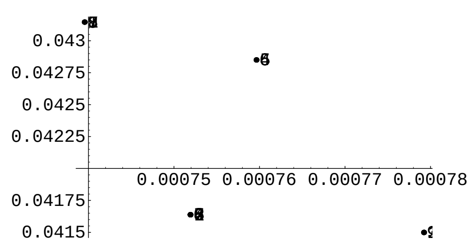

Figure 6: The parameter set of the linearised problem

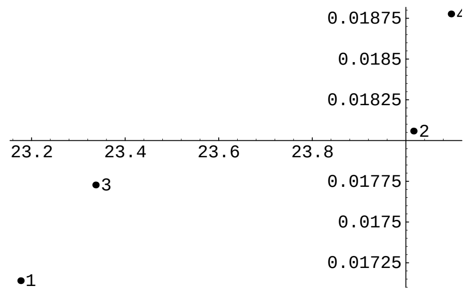

Figure 7: The parameter set for the original problem

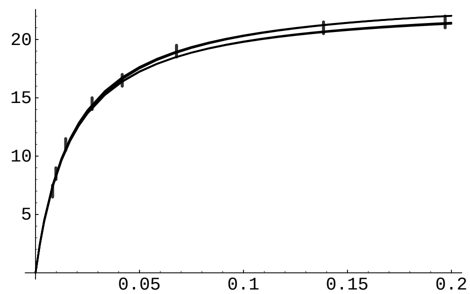

Figure 8: Interval data (s_i, V_i) for an enzyme-catalysed reaction and the final interval solution function

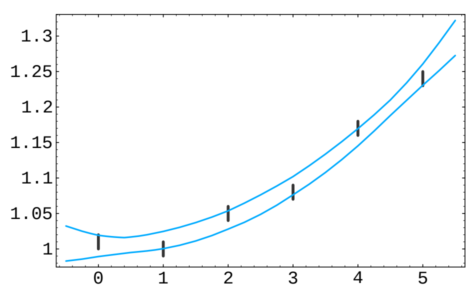

Figure 9: Least square interval regression using quadratic functions

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