

Some problems of mathematical modelling in ecology involving uncertainties

Svetoslav Markov

Bulgarian Academy of Sciences

Abstract

This paper is devoted to identification of models and their parameters applied to ecological and biological problems. More precisely we discuss interpolation and curve fitting in the presence of uncertainties in the input data given in the form of intervals. Our methods involve model functions linear or nonlinear in their parameters. The linear models are formulated in terms of interval arithmetic allowing the computation of verified bounds for the interpolating/approximating functions. Case studies involving enzyme-catalysed reaction and fitting of a logistic model are considered.

Keywords: Estimation Methods, Model Identification, Parameter Identification, Mathematical Modelling, Model Validity, Interpolation, Least Square Approximation, Verification, Enzyme Kinetics, Uncertainties, Interval Arithmetic.

1 Introduction

In the last decades the rapid interaction between mathematics and biology is widely recognized. This interaction takes place in two opposite directions: i) biological and ecological problems require and generate new mathematical results, methods and theories; ii) new mathematical results are implemented in biological and ecological research, in modelling and control of the environment; this new mathematical methods and theories influence biological research. Therefore both mathematics and biology benefit from this interaction.

The beginning of the 20th century was marked by important contributions in the field of mathematical populational biology. Later on substantial applications of mathematical methods in biochemical kinetics, ecology, neurophysiology etc. marked the road of mathematical biology [11]. Recently many international biomathematical conferences are organized. Let us mention the international biomathematical conference in 1995 in Sofia [29], [30]. The Third European Conference on Mathematics applied to Biology and Medicine held in Heidelberg, Germany (6–10 October, 1996) gathered over 350 researchers applying mathematics in: Modelling in Molecular Biology, Molecular Biomechanics, Evolution and Genetic Modelling, Metabolic Modelling, Cell Modelling and Cell Signalling, Morphogenesis and Pattern Formation,

Epidemiology and Immunology, Neuromodelling, Physiology, Pathological Tissue Growth and Cancer, Modelling in Medicine and Applications, Population Dynamics, Ecology. The conference was a forum for the world-wide recognition of the powerful new interdisciplinary field of mathematical biology. Two scientific contributions from Bulgarian scientists have been presented [21], [24]. From 30th June to 3rd July the First Congress on Mathematical models and methods applied to biology and medicine will take place in Alicante, Spain. From 27 to 30 of August an international conference on deterministic and stochastic methods in biology will take place in Sofia. Biomathematics is becoming a more and more active field of research.

In particular, mathematical methods and models penetrate in ecological sciences [6]. Many problems of mathematical modelling in ecology need specialists in subjects like plant metabolism, ecosystems, ecotoxicology, global changes of climate and flora etc. Classical models of photosynthesis, heat transfer in plants and space dynamics of wood and plant ecosystems are used in the prediction of global climatic changes and show that the study of plant species and the related ecosystems is of substantial significance for the preservation of the environment. Thus mathematical modelling of plant and soil metabolism prove to be of big importance for the study of soil pollution and related time bomb effects. The mathematical models of metabolism in living systems and enzyme kinetics enrich both the mathematical theory of chemical kinetics and the methodological concepts of biologists with respect to biochemical processes in organisms and systems. For instance, the mathematical modelling of ecosystems as a living system is an actual and important field of research at present.

Two basic problems of mathematical modelling are: identification of models and identification of parameters of the models. In biology we often need to solve a problem for identification of the model, without having a firm theoretical background related to the form of the model. In such situations the researcher is in the position of G. Galilei when rejecting the linear form of the free fall law and suggesting a better model — the quadratic one, far before the theoretical background has been formulated (in this example — the Newton all-space attraction law). The important problem of discovering basic biological relations needs proper mathematical tools. Thus, besides of the development of particular mathematical theories (like mathematical enzyme kinetics, mathematical genetics, mathematical populational and evolutionary biology etc.), biological research stimulates the development of new mathematical techniques and methodologies, exercising global interaction both on the computational practice and on the techniques for reading off experimental data.

The purpose of this work is to discuss and make available certain new mathematical methods related to model identification and their possible application to biology, and in particular, to ecology and botany. Such new methods have been developed under the pressure of solving highly sensitive problems (such as problems related to enzyme kinetics, see [11], [2]) and of the necessity to operate with data containing heavy uncertainties, combining the lack of statistical hypothesis and the presence of short series of experimental data. Some new methods developed by the author and his collaborators and certain algorithmic and software tools that can be used in relation to these methods are reported. We also give some hints for a new methodology of

collecting experimental data that goes hand by hand with the discussed methods.

For model identification of biological processes involving both short uncertain records and unstable solutions (as is usually the case whenever enzyme reactions are present), 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. Such tools are quickly penetrating in biological applications [1], [4], [5], [8], [12]–[14]. For the successful application of these mathematical tools and methodologies we need suitable supporting programming tools. Special languages, such as SC- and XSC-languages, have been developed to support the design of numerical methods with verification. Computer algebra systems have been developed to provide suitable support for qualified mathematical applications, such as *Maple* and *Mathematica*.

2 Model and parameter identification under uncertainties

The mathematical methods discussed below are tightly connected to specific approaches of collecting and reading off experimental quantitative data in the form of intervals. The experimental scientist should make some additional effort in the process of collecting data from biological experiment/observation by providing intervals that contain the true values of the measured/observed quantities. A careful consideration of the measured quantities and of the physical construction of the measurement tools is of immense importance for the new methodology. We recommend the assigning of three types of intervals to each measured/observed quantity: i) an interval (called the 100%-guaranteed interval) which contains the true value with absolute guaranty; ii) an interval that contains the true value with “almost full guaranty”, and, iii) an interval that contains the true value with high probability. The intervals from second and the third cases can be called conditionally $X\%$ -guaranteed intervals, where according to the experimental researcher’s “feeling” X may take some specific value, say 99 in case ii), resp. 95 in case iii). After constructing an algorithm for the solution of the problem, the mathematician can easily obtain the solution for these sets of input data (the 100%-guaranteed and the $X\%$ -guaranteed data). The comparison of the different solutions of a model identification problems can be of big value for the final interpretation and the global study of the particular biological process.

Typically problems arising in biological applications involve uncertain data in the form of intervals. 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 [3], [9], [23]. In a setting involving generalized linear modelling functions [2], the problem can be formulated in the following way [32], [28]. Given:

i) a class of modelling functions $\mathcal{L}_m(D, \varphi)$ (called generalized polynomials) defined

for $\xi \in D \subseteq R^k$:

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

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

ii) input data $x_j \in D$, $j \in J = \{1, \dots, n\}$, $n \geq m$, such that $x_i \neq x_j$, $i \neq j$, and n interval measurements $Y_j = [y_j^-, y_j^+]$, $j \in J$. Let $\mathbf{x} = (x_1, \dots, x_n)^\top \in R^{n \times k}$ and $Y = (Y_1, \dots, Y_n)^\top \in IR^n$, 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 a model function of the class (1), then these conditions can be written as $\varphi(x_j)^\top \lambda \in Y_j$, $j \in J$, or in matrix notations: $\Phi(\mathbf{x})\lambda \in Y$, where $\Phi(\mathbf{x})$ is the full rank matrix

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

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

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

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 .

Another typical problem arising in biological applications is related to the situation when the data contain uncertainties both from statistical and nonstatistical origin and when some hypothesis on the statistical error is available. The statistical hypothesis leads to the choice of an estimator, e. g. the least-square estimator. The problem has two variants — fitting and smoothing; below we give a possible formulation of the fitting problem; the smoothing problem is considered in [33].

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 $H : R^{n \times k} \rightarrow R^{m \times n}$, 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" [9] is:

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

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 [9]. For example, the parameter set corresponding to Problem 1 is a convex polytope $\Lambda = \{\lambda \in R^m \mid \Phi(\mathbf{x})\lambda \in Y\}$.

Interval arithmetic: For the presentation of the interval-valued solution functions (2), (3) we shall use two interval arithmetic operations [10]. By IR we denote the set of all intervals Y of the form $Y = [y^-, y^+] = \{y \mid y^- \leq y \leq y^+\}$, where $y^-, y^+ \in R$. We define addition of two intervals $X, Y \in IR$ by $X + Y = [x^-, x^+] + [y^-, y^+] = [x^- + y^-, x^+ + y^+]$. Multiplication of an interval X by a real scalar $\alpha \in R$ is defined as the interval with end-points αx^- and αx^+ , symbolically

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

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

$$\alpha_1 Y_1 + \alpha_2 Y_2 + \dots + \alpha_n Y_n = \alpha Y. \quad (4)$$

The interval-arithmetic expression αY for the set $\{\alpha y \mid y \in Y\}$ is short and convenient; to see this the reader is advised to compute the end-points of the interval $\{\alpha y \mid y \in Y\}$. In what follows we shall make use of expression (4) to present and compute the solution functions (2) and (3). Below we discuss some typical situations of model identification involving linear models.

3 On the identification of linear models in the presence of uncertainties

Let us briefly present 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)

$$\eta(\mathbf{x}, Y; \xi) = \left(\varphi(\xi)^\top \Phi^{-1}(\mathbf{x}) \right) Y. \quad (5)$$

For $m < n$ the problem becomes mathematically more difficult; however this case is of big interest in mathematical modelling. We propose the following method to compute at a fixed point $\xi \in D$ the interval function $\eta(\mathbf{x}, Y; \cdot)$: intersect the values at ξ of all interval functions of the type (5), symbolically,

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

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. $\mathbf{x}^Q = (x_{q(1)}, \dots, x_{q(m)})^\top$ and $Y^Q = (Y_{q(1)}, \dots, Y_{q(m)})^\top$. If the intersection is empty then Problem 1 has no solution [28]–[32].

Interval Curve Fitting. Using (4) we can present the interval solution (3) explicitly by

$$\begin{aligned}\eta^\phi(\mathbf{x}, Y; \xi) &= \{\varphi(\xi)^\top \lambda, \lambda = Hy \mid y \in Y\} \\ &= \{\varphi(\xi)^\top (Hy) \mid y \in Y\} \\ &= \{(\varphi(\xi)^\top H) y \mid y \in Y\} \\ &= (\varphi(\xi)^\top H) Y = \Gamma^\phi(\xi) Y.\end{aligned}\tag{6}$$

The interval-valued function (6) gives an explicit expression for the exact bounds for the solution set.

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

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

Substituting in (6) we have

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

4 Model identification: two case studies using ecological data

We shall discuss two examples of model (and parameter) identification problems under uncertainties arising in ecology.

Case study 1: identification of logistic type model (Verhulst law). The logistic model (Verhulst law) which is frequently used in ecology has the form

$$y = \frac{k}{1 + e^{-r(t-k)}}.\tag{7}$$

An usual technique to fit this model to a given set of data $(x_i, y_i)_{i=1}^n$ is to fit the logarithm $z = \ln y$ (which is a linear model) to the data $(x_i, z_i)_{i=1}^n$, where $z_i = \ln y_i$. In what follows we shall assume that k is a known parameter. We then compute the parameters of the linear model z ; from these parameters we compute the parameters of the logistic model. The corresponding formulae are:

$$\begin{aligned}z &:= \ln \left(\frac{k}{y} - 1 \right), \quad a := -r, \quad b := rh; \\ z &= at + b, \quad r = -a, \quad h = -\frac{b}{a}.\end{aligned}\tag{8}$$

We are interested in the fitting of the logistic model under interval data. Assume that instead of numerical values for y_i we are given interval values Y_i . In this case we can still follow the above scheme, arriving to a linear fitting of a set of interval data

$$Z_i = \ln \left(\frac{k}{Y_i} - 1 \right), i = 1, \dots, n. \quad (9)$$

Using formula (6) we can find the linear interval function approximating the set of interval data; the parameter set can be determined, too. Applying the inverse transformation, we obtain the boundaries of the parameter set of the logistic curves, resp. the boundaries of the interval logistic function.

It is sometimes possible to obtain observations about monotonicity of the model function. Such observations may be due either to the preassigned type of the modelling function or to the empirical experiments (or both). In the case of the logistic model such monotonicity arguments may play important role [27].

Consider the following experimental data of *Verhulst* growth taken from a realistic ecological problem. The data are measured at every 30 minutes from $t_1 = 0.5h$ to $t_2 = 15h$:

$$y = (0.3, 0.3, 0.4, 0.5, 0.6, 0.7, 0.7, 0.8, 1.0, 1.1, \\ 1.3, 1.6, 1.8, 2.1, 2.5, 2.9, 3.4, 3.9, 4.4, 4.9, \\ 5.4, 5.9, 6.3, 6.8, 7.1, 7.3, 7.4, 7.5, 7.5, 7.5).$$

Suppose that the accuracy of each measurement is 0.2, that is $Y_i = [y_i - 0.2, y_i + 0.2]$, $i = 1, \dots, 30$, see Fig. 2. Using (9) we obtain intervals for z . Then we fit the linear model (8) to the interval data. Fig. 1 presents the boundaries of the family of all linear regression functions. Returning to the original coordinate system, we obtain the set of all logistic functions; the boundaries of this family are given on Fig. 2.

Case study 2: an enzyme-catalysed reaction. This example is devoted to an enzyme catalysed reaction discussed in [2] (see pp. 347, 425). The measured data for this example are taken from [7]; 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 nonlinear of the form $v = as/(b + s)$; some computed values for the parameters using standard techniques are $a = 23.6$, $b = 0.0175$. However this values give no information of how much they are influenced by perturbations in the input data. In what follows 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. Assume that the data for the velocity v of the enzyme-catalysed reaction are bounded by a magnitude of 0.5; e. g.

$V_1 = (21.0, 22.0)$, $V_2 = (20.5, 21.5)$, ..., $V_8 = (6.5, 7.5)$; in reality such interval values V_i should be obtained experimentally using the arguments described in the beginning of section 2. The corresponding interval segments (s, V) are visualized in Fig. 4. 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. 3. Fig. 4 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 [2].

Other examples of modern mathematical applications to ecology and botany developed by the author and his collaborators can be found in [19]–[46].

5 Conclusion

The results and algorithmic 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 used for model identification in biological and ecological 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 classes of nonlinear problems and to formulate corresponding numerical tools for them. Computer algebra systems like *Mathematica* and *Maple* can deal with interval-arithmetic expressions and are suitable environments for the development of such packages. Extensive graphics capabilities allow the user to generate two- and three-dimensional graphics, which can be useful in the process of mathematical modelling.

A package written in *Mathematica* [17] for interpolation/approximation under uncertainties has been developed [32]. The package is suitable for mathematical modelling in biology whenever generalized linear modelling functions are used. Models like the logistic-Normal model, the rectangular hyperbola-Normal model etc. play an important role in biomathematical applications [2]. The package offers the possibility to compute and visualize the interval solution functions (2), (3) as well as the corresponding parameter sets. One can also easily observe individual solution functions, or to compare different solution functions. 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.

Acknowledgements

This work has been supported in part by the Bulgarian Academy of Sciences in the frames of the project: Mathematical Modeling in Biology and by the National Fund for Scientific Research under project No. MM-521/1995.

Received: November 1996

Address:

Svetoslav Markov,
Institute for Mathematics and Informatics, section Biomathematics,
Bulgarian Academy of Sciences,
email: smarkov@iph.bio.acad.bg

References

- [1] **A. Model/parameter identification under uncertainties with application to biology and ecology**

Belforte, G., Bona, B. & Milanese, M. 1983. Advanced Modelling and Identification Techniques for Metabolic Processes. — CRC Journal Biomed. Eng., **10**, 4: 275–316.
- [2] Brown, D. & Rothery, P. 1994. Models in Biology: Mathematics, Statistics and Computings. — Wiley.
- [3] Crane, M. A. 1975. A Bounding Technique for Polynomial Functions. — SIAM J. Appl. Math., **29**, 4: 751–754.
- [4] Fedra, K., Van Straten, G. & Beck, M. B. 1981. Uncertainty and Arbitrariness in Ecosystems Modelling: A Lake Modelling Example. — Ecological Modelling, **13**: 87–110.
- [5] Gomeni, R., Lahanier, H. & Walter, E. 1986. Study of the Pharmacokinetics of Betaxolol Using Set Membership Set Estimation. — Proc. 3rd IMECO Congress on Measurements in Clinical Medicine, Edinbourg.
- [6] Hallam, T. & Levin, S. 1989. Mathematical Ecology. — Springer.
- [7] Kuhn, R., “Über Spezifität der Enzyme. II Saccharase- und Raffinasewirkung des Invertins”; Hoppe-Seyler’s Zeitschr. f. Physiol. Chemie, 125, (1923), 28–92.
- [8] Lahanier, H., Walter, E., Gomeni, R.: “OMNE: A New Robust Membership Set Estimator for the Parameters of Nonlinear Models”; J. Pharmacokin. Biopharm., 15 (1987), 203–219.
- [9] Milanese, M: “Estimation and Prediction in the Presence of Unknown but Bounded Uncertainty: A Survey”; Robustness in Identification and Control (M. Milanese, R. Tempo and A. Vicino, Eds.), Plenum, New York (1989), 3–24.

- [10] Moore, R. E.: “Interval Analysis”; Prentice Hall, Englewood Cliffs, N. J. (1966).
- [11] Murray, J. D.: “Mathematical Biology”; Springer (1989).
- [12] Norton, J. P.: “Problems in Identifying the Dynamics of Biological Systems from Very Short Records”; Proc. 25th Conf. on Decision and Control, Athens (1986).
- [13] Norton, J. P.: “Parameter Bounding for Biomedical Models Based on Small Sets of Observations”; Biomed. Meas. Infor. Contr., 2 (1987), 101–107.
- [14] Walter, E., Lahanier, H.: “OMNE Versus Least Squares for Estimating the Parameters of a Biological Model from Short Records”; Proc. 12th IMACS World Congress on Sci. Comput., Paris (1988), 85–87.
- [15] L. Jaulin and E. Walter, *Guaranteed Nonlinear Parameter Estimation via Interval Computations*, Interval Computations, 3, 1993, 61–75.
- [16] S. H. Mo, J. P. Norton, *Recursive Parameter-Bounding Algorithms which Compute Polytope Bounds*, Proc. 12th IMACS World Congress, Paris, 1988.
- [17] S. Wolfram, *Mathematica: A System for Doing Mathematics by Computer*, Second Edition, Addison-Wesley, 1991.
- [18] Qiu, Z. P., Chen, S. H., Elishakov, I.: Natural Frequencies of Structures with Uncertain but Nonrandom Parameters, J. of Optimization Theory and Applications, 86, 3, 669–683, 1995.

B. Mathematical methods with application to ecology and botany developed by the author and his collaborators:

- [19] Dimitrova, N., Zlateva, P.: Investigation of the Methane Fermentation Process Using Interval Analysis. Automatica & Informatics, 5–6, 1994, 120–123 (in Bulgarian).
- [20] Dimitrova, N., Zlateva, P.: Study of the Steady-State of Methane Fermentation under Uncertain Data. Lecture Notes in Biomathematics and Bioinformatics’95, M. Candev (ed.), DATECS Publ., Sofia, 1995, 90–99.
- [21] Dimitrova, N., I. Simeonov: Steady-states Analysis of some Biotechnological Processes under Uncertainties. Lecture delivered at the 3rd European Conf. on Mathematics Applied to Biology and Medicine, Heidelberg, Oct. 1996.
- [22] Markov, S., Y. Akyildiz, *Fitting of Biological Data under Uncertainties*, Journal of Universal Computer Science, Special Issue (to appear).
- [23] Markov, S., Mathematical Modelling of Dynamical Processes under Interval Experimental Data, IIASA WP-91-004, April 1991, 1–29.

- [24] Markov, S., M. Candev: A Global Mathematical Model of Enzyme-catalytic Processes in an Organism under Uncertainties. Lecture delivered at the 3rd European Conf. on Mathematics Applied to Biology and Medicine, Heidelberg, Oct. 1996.
- [25] Markov, S.; Popova, E.: New Aspects of Mathematical Modelling: Curve Fitting, in: Mathematical Modelling and Scientific Computations (A. Andreev et al. Eds.), Publ. House of the Bulg. Acad.of Sci., Sofia, pp. 49-63, 1991.
- [26] HIFICOMP: Subroutine library for Highly efficient and accurate COMPUTations, Methodological guide. Center for Informatics and Computer Technology, Bulgarian Academy of Sciences, 1987, CINTI Reg.No.1.A.066.02112-01 37
- [27] Akyildiz, Y.; Candev, M., Markov, S.; Simeonov, I.: Curve Fitting and Smoothing under Uncertainties: the Logistic Model, In: Proc. Symp. on Modeling, Analysis and Simulation, IMACS/IEEE Multiconference on Computational Engineering in Systems Applications, Lille, France, July 9-12, 1996, 1151–1155.
- [28] Akyildiz, Y.; Markov, S.; Popova, E.; Schulze, J.: Computer-Aided Interval Interpolation. In: Dimov, I.; Sendov, Bl.; Vassilevski, P. (Eds.): Advances in Numerical Methods and Applications, World Scientific, Singapore, 1994, pp. 3-10.
- [29] BIOMATH-95, International Symposium and Young Scientists School on Mathematical Modelling and Information Systems in Biology, Ecology and Medicine, Datecs Publ., Sofia, 99 p., Eds: E. Popova, S. Markov, C. Ullrich.
- [30] BIOMATH-95, Computers and Mathematics with Applications, 32, 11 (Special Issue, December 1996, Guest Eds. C. Ullrich, S. Markov), 123 p.
- [31] Markov, S. *Least-Square Approximation Under Interval Input Data*, Contributions to Computer Arithmetic and Self-Validating Numerical Methods, C. Ullrich (Ed.), J. C. Baltzer Sci. Publishing, IMACS, 1990, 133–147.
- [32] Markov, S. and Popova, E. : “Linear Interpolation and Estimation Using Interval Analysis”, Bounding Approaches to System Identification (M. Milanese et al., Eds.), Plenum, New York (1996), 139–157.
- [33] Markov, S. *Some Interpolation Problems Involving Interval Data*, Interval Computations, 3, 1993, 164–182.
- [34] Markov S., Popova, E.: Curve Fitting under Interval Data for the Measurements: Software Tools and Numerical Examples, In: Mathematics and Mathematical Education, BAS, Sofia, pp. 322-332, 1992.
- [35] Markov, S.; Popova, E.: Estimation and Identification using Interval Arithmetic. Proceedings of 9th IFAC/IFORS Symposium on Identification and System Parameter Estimation, Pergamon Press, pp. 769-772 (1991).
- [36] Markov, S., E. Popova, U. Schneider, J. Schulze: On Linear Interpolation under Interval Data. Mathematics and Computers in Simulation, 42, 1, 35–45 (1996).

- [37] Ognjanova-Rumenova, N.; Popova, E.: CCA used for Neogene Paleoecological Reconstruction of Sofia Basin, South Bulgaria. Proceedings of Fifth Workshop on Diatoms, Irkutsk, March, pp. 16–20, 1993.
- [38] Ognjanova-Rumenova, N.; E. Popova: Diatom biostratigraphy and comparative core correlation within the Sofia Basin, Bulgaria. In: Kovar-Eder, J. (ed.) Paleovegetational Development in Europe, Museum of Natural History, Vienna, pp. 197–203, 1992.
- [39] Peneva, P.; Popova, E., Kuzmanov, B.: Morphological Variation of *Matricaria recutita* L. I. Cluster Analysis, *Fitologija*, vol. 36, pp. 15–25, 1989 (in Bulgarian).
- [40] Popova, E.; Peneva, P.: Morphological Variation of *Matricaria recutita* L. II. Discriminant Analysis. *Genetics and Breeding*, vol. 20, 4, pp. 319–326, 1987 (in Bulgarian).
- [41] Popova, E.; Peneva, P.: Grundfaktoren der Morphologischen Variabilitaet bei der Echten Kamille-*Matricaria recutita* L. *Compt. Rend. Acad. Bulg. Sci.*, vol. 40, 4, pp. 89–92, 1987 (see also vol. 40, 5, pp. 89–92, 1987).
- [42] Shkodrov, G., Markov, S.: A Dynamical Model of Synaptic Transmission by Acetylcholine, In: *Lecture Notes on Biomathematics and Bioinformatics'95* (Ed. M. Candev), Datecs Publ., Sofia, 1995, 108–113.
- [43] Stoeva, M.; Popova, E.; Uzunova, K.: Population Variability of *Carex sempervirence* Vill. complex and *Carex kitaibeliana* Degen in Bulgaria. In: Kozhukharov K., Kuzmanov B. (eds.): *Evolution of the Flowers and Florogenesis*. BAN Publ. House, Sofia, pp. 140–159, 1991 (in Bulgarian).
- [44] Stoeva, M.; Popova, E.: Variation Patterns within the Genus *Carex* L. sect. *Digitatae* (Fries) Christ. in Bulgaria, *Folia Geobotanica et Phytotaxonomica*, Praga, vol. 26, 4, pp. 379–395, 1991.
- [45] Stoeva, M., E. Popova: Taxonomical evaluation of the Bulgarian populations of genus *Carex* L. sect. *Glaucæ* (Ascherson) Christ. *Compt. Rend. Acad. Bulg. Sci.*, vol. 45, 9, pp. 99–101, 1992.
- [46] Stoeva, M., E. Popova: Cytotaxonomic study of *Carex* sect. *Acrocystis* (Cyperaceae) in Bulgaria. *Fragmenta Floristica et Geobotanica*, vol. 38, 1, pp. 29–43, 1993.