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Numerical solution by LMMs of stiff delay differential systems modelling an immune response

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Summary. We consider the application of linear multistep methods (LMMs) for the numerical solution of initial value problem for stiff delay differential equations (DDEs) with several constant delays, which are used in mathematical modelling of immune response. For the approximation of delayed variables the Nordsieck's interpolation technique, providing an interpolation procedure consistent with the underlying linear multistep formula, is used. An analysis of the convergence for a variable-stepsize and structure of the asymptotic expansion of global error for a fixed-stepsize is presented. Some absolute stability characteristics of the method are examined. Implementation details of the code DIFSUB-DDE, being a modification of the Gear's DIFSUB, are given. Finally, an efficiency of the code developed for solution of stiff DDEs over a wide range of tolerances is illustrated on biomedical application model.

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1. Introduction

Formulation in 1975 of the simplest mathematical model of an infectious disease (see Marchuk [21]) marked the beginning of applications of DDEs for studying the immune system and dynamics of infections. This motivated our subsequent research in developing efficient computational algorithms for solving stiff nonlinear DDEs with several constant delays. The basic requirements to the numerical software in problems of immune response modelling include: reliability over a wide range of tolerances, efficiency for stiff systems and/or at high accuracy demands, low cost of interpolation technique being used for the approximation of the DDEs solution at the off-mesh points. The latter is important either for the delayed variables or when the adjoint system is solved. The necessity of high accuracy solution arises in parameter optimization problems, with the finite-difference methods being used to estimate the gradient vector and the Hessian matrix of an objective function [8, 20, 22].

A system of DDEs is considered stiff when it contains processes of widely different time scales. From a computational point of view the stiffness implies that, while solving numerically the corresponding initial value problem by a given method with assigned tolerance, a stepsize is restricted by stability requirements rather than by the accuracy demands. The best candidates for treating the stiff DDEs under the above specified requirements seem to be the LMMs possessing either the $A-$, $A(\alpha)-$ or stiff stability characteristics. We consider the *BDFs* implemented in the Gear's DIFSUB code [13]. In this article we present mathematical analysis of some issues underlying the correct and efficient adaptation to DDEs of the LMMs-based codes and consider the results of treating stiff immunological models.

A key feature of any software for handling DDEs with constant delays is a method of interpolation of delayed variables. Unlike the traditional approach of usage the Lagrange or Hermite interpolation methods, we take the advantage of the natural 'built-in' Nordsieck interpolation technique consistent with the underlying linear multistep formulas.

Concerning various theoretical and practical issues of software development for delay differential equations with general lag functions we refer to the latest reviews made by Neves and Thompson [24], Baker et al. [3], and Zennaro [34] and the many references therein. In spite of the active research in the field, the picture emerges as if standard codes for treating efficiently stiff DDEs over a wide range of tolerances still lack. Even the representative set of test problems has not been specified yet, and comparison of the available experimental codes for DDEs remains to be done.

In Sect. 2 typical examples of DDEs modeling the immune response are introduced. Description of the difference approximation of initial value problem for DDEs based upon the predictor-corrector implementations of the *BDFs* and Adams methods in the Nordsieck form is presented in Sect. 3. Sufficient conditions for the convergence (variable-stepsize), and asymptotic expansion for the global error (fixed-stepsize) of strictly stable LMMs for the DDEs are examined in Sects. 4 and 5, respectively, extending some results on convergence analysis of Nordsieck methods by Gear [14] and Skeel [27, 28], and asymptotic error expansions in the stepsize by Stetter [29], Skeel [27] and Hairer and Lubich [15] (ODEs case). Section 6 presents some absolute stability characteristics of the *BDFs* and Adams methods for a standard test equation. Finally, implementation details of the code for DDEs based on the Gear's DIFSUB and numerical experiments with stiff problem modelling the dynamics of virus infection are discussed.

2. Delay differential models of immune response

The response of an immune system cannot be represented correctly without the hereditary phenomena being taken into account: cell division, differentiation, etc. The kinetic parameters of the models represent high-rate (molecular) and slow-rate (cellular) interactions in the immune system that span a time scale from seconds to days. Therefore, the systems of DDEs appearing in immune response modelling are typically stiff.

An interesting example of the delay differential system modelling an immune response provides the simplest mathematical model of an infectious disease [1, 16, 21]:

$$\begin{aligned}
y_1'(t) &= (\alpha_1 - \alpha_2 y_3(t))y_1(t)\ ,\\
y_2'(t) &= \xi(y_4)\alpha_3 y_1(t-\tau)y_3(t-\tau) - \alpha_4(y_2(t)-\alpha_5)\ ,\\
y_3'(t) &= \alpha_6 y_2(t) - (\alpha_7 + \alpha_8\alpha_2 y_1(t))y_3(t)\ ,\\
y_4'(t) &= \alpha_9 y_1(t) - \alpha_{10} y_4(t),\ \text{ where } \xi(y_4) = \max(0, 1 - y_4(t)/\alpha_{11}), \quad \tau = \text{const.}
\end{aligned}$$

It traces the dynamics of viruses y_1, plasma cells producing antibodies y_2, antibodies neutralizing viruses y_3, and degree of target organ damage by viruses y_4. The method of 'steps' allows us to get an analytical solution or approximation to it in an explicit form, but over limited time intervals and for a special choice of parameters (see [21]). Another approach to solve analytically this model was suggested by Adomian with the decomposition method [1].

Most of delay differential models used in immunology have multiple constant delays. To this particular case of DDEs with several constant delays belong mathematical models developed by Marchuk [22], De Boer and Hogeweg [10], Nelson and Perelson [23], Farooqi and Mohler [12], Behn et al. [5]. It seems worth to notice growing interest to the use of DDEs in chemical kinetics modelling [11].

Assuming that the kinetics of interactions between cells and molecules in immune system is governed by the principles similar to the Mass Action Law, and that durations of division processes of the immunocompetent cells are taken into account explicitly by introducing the time lags into corresponding equations, the typical mathematical model of immune response during infectious disease may be expressed as $\mathcal{N}$-dimensional system of DDEs with m multiple constant delays:

$$\begin{aligned}
\frac{dy}{dt} &= f(t, y(t), y^{[1]}(t-\tau_1), \dots, y^{[m]}(t-\tau_m)), \quad y \in \mathbb{R}^{\mathcal{N}},\\
&\quad y^{[i]} \in \mathbb{R}^{\mathcal{N}_i}, t \in [t_0, t_0 + T],\\
y(t_0) &= \varphi^0, y^{[i]}(t) = \varphi^{[i]}(t), t \in [t_0 - \tau_i, t_0),\\
&\quad \mathcal{N}_i \le \mathcal{N}, i = 1, 2, \dots, m,
\end{aligned} \tag{2.1}$$

with $y \equiv [y^{(1)}, \dots, y^{(\mathcal{N})}]^{\mathrm{T}}, y^{[i]} \equiv [y^{(j_1)}, y^{(j_2)}, \dots, y^{(j_{\mathcal{N}_i})}]^{\mathrm{T}}$ and assigned initial functions φ^0, $\varphi^{[i]}(\cdot)$. Further assume that:

(A1) the function f, $f : [t_0, t_0 + T] \times \mathbb{R}^{\mathcal{N}} \times \mathbb{R}^{\mathcal{N}_1} \times \mathbb{R}^{\mathcal{N}_2} \dots \times \mathbb{R}^{\mathcal{N}_m} \to \mathbb{R}^{\mathcal{N}}$, belongs to the class $C^l([t_0, t_0 + T] \times \mathbb{R}^{\mathcal{N}} \times \mathbb{R}^{\mathcal{N}_1} \times \mathbb{R}^{\mathcal{N}_2} \dots \times \mathbb{R}^{\mathcal{N}_m})$ with $l \ge p$,

p being the approximation order of the linear k-step method to be used, and is Lipschitz-continuous with respect to y and z on the interval $[t_0, t_0 + T]$ with the constants L_1, L_2;

(A2) the initial functions $\varphi^{[i]}(t) : [t_0 - \tau_i, t_0) \to \mathbb{R}^{\mathcal{N}_i}$ are of the class $C^{l^*}([t_0 - \tau, t_0))$, with $l^* \geq l$, and the point t_0 is assumed to be, in general, a zero-order discontinuity point for $y^{(j)}(t)$, i.e., $y^{(j)}(t_0^-) \neq y^{(j)}(t_0)$.

Under these assumptions, which are not practically restrictive, the solution $y(t)$ is of the class $C^{(l+1)}$ almost everywhere on $[t_0, t_0 + T]$ except for the finite set of the jump points $\left\{\{\theta_{ji} = t_0 + j\tau_i\}_{j=0}^{l+1}\right\}_{i=1}^{m}$ [4]. However, the solution grows smoother as t increases. The constant delays allow us an easy handling of discontinuities by specifying them in advance and truncating the stepsize to include θ_{ji} in the meshpoints.

3. Difference approximation

A numerical solution on the whole interval $[t_0, t_0 + T]$ can be obtained by the method of 'steps', i.e. by consecutive continuation from one interval of smoothness to another. For notational simplicity the single lag scalar DDE is considered

$$\frac{dy}{dt} = f(t, y(t), y(t - \tau)), \quad y \in \mathbb{R}, \quad t \in [t_0, t_0 + T],$$

$$y(s) = \varphi(s), \quad s \in [t_0 - \tau, t_0]\ , \tag{3.1}$$

under the assumptions (A1)–(A2) of Sect. 2. We develop a difference approximation for (3.1) by the linear k-step methods of an order p on intervals $[t_0 + (j-1)\tau, t_0 + j\tau]$, with $j = 1, 2, \ldots, p + 1$, and for $t \geq t_0 + (p + 2)\tau$, on which the necessary smoothness of $y(t)$ is ensured. In the following, the interval $[t_0 + (j-1)\tau, t_0 + j\tau]$ is denoted as $[t_0, t_0 + T]$.

Let $t_0 < t_1 < \ldots < t_N = t_0 + T$ be an integration mesh, and the stepsize $h_n = t_n - t_{n-1}, n = 1(1)N$, be described by a Lipschitz-continuous step-variation function $\theta(t_n, h)$.

Remark 3.1 Examples of the realistic patterns of step variation are considered in [14, 16, 28]:

a. $\frac{h_{n+1}}{h_n} \in (0, a] \cup [b, c]$ with $0 < a \leq b < 1 < c$;
b. $h_n = h\theta(t_n, h)$ with $h > 0$; $0 < \Delta \leq \theta(t, h) \leq 1$, $t \in [t_0, t_0 + T]$, that is equivalent to $0 < \Delta \leq \frac{h_{n+1}}{h_n} \leq \frac{1}{\Delta}$, $h_n \geq \Delta h$;
c. $h_n = h\theta(t_n)$, with $h > 0$, $\theta(t) \in C^1[t_0, t_0 + T]$, $0 < \Delta \leq \theta(t) \leq 1$, that is equivalent to $\frac{h_{n+1}}{h_n} = 1 + O(h)$.

One step of the linear k-step method is equivalent to constructing a p-th order polynomial $\pi_p(\overline{Y}_{n+1-k,n+1}, t)$, where $\overline{Y}_{n+1-k,n+1} \equiv [y_{n+1-k}, f_{n+1-k}, \ldots, y_{n+1}, f_{n+1}]^{\mathrm{T}}$, satisfying the following conditions:

– for the k-step *BDF*-method of order p, with $p = k$,

$$\pi_p(\overline{Y}_{n+1-k,n+1}, t_j) = y_j, \quad j = n-k+1, \ldots, n+1, \quad \pi_p'(\overline{Y}_{n+1-k,n+1}, t_{n+1}) = f_{n+1}\ ,$$

– for the $(k+1)$-step *Adams* method of order p, with $p = k+1$,

$$\pi_p'(\overline{Y}_{n+1-k,n+1}, t_j) = f_j, \quad j = n-k+1, \dots, n+1, \quad \pi_p(\overline{Y}_{n+1-k,n+1}, t_n) = y_n,$$
$$\pi_p(\overline{Y}_{n+1-k,n+1}, t_{n+1}) = y_{n+1} \ ,$$

Difference method for the DDE, combining a forward-step procedure by means of the p-order LMM, (Ψ_p^S), and an interpolation technique for the delayed variables of order q, $\pi_q(\overline{Y}_{\sigma_1,\sigma_\nu}, t-\tau)$, extending continuously a discrete numerical solution $\overline{Y}_{\sigma_1,\sigma_\nu}$ to a function of t, can be expressed in the form of a 'one-step' recursion in a higher dimensional space similarly to the ODE case [16, 28]:

$$\begin{cases} \bar{y}_{n+1} = SC_{n+1}\bar{y}_n + h_{n+1}\overline{\psi}(t_n, C_{n+1}\bar{y}_n, z_{n+1}, h_{n+1}), \\ \qquad\qquad \bar{y}_n \in \mathbb{R}^{p+1}, \quad C_{n+1} \equiv C(h_{n+1}/h_n) \ , \\ \\ z_{n+1} = \begin{cases} \pi_q(\overline{Y}_{\sigma_1,\sigma_\nu}, t_{n+1}-\tau), \qquad t_{n+1}-\tau > t_0, t_{n+1}-\tau \in [t_{\sigma_1}, t_{\sigma_\nu}], \\ \qquad\qquad \sigma_\nu \le n+1 \ , \\ \varphi(t_{n+1}-\tau), \quad t_{n+1}-\tau \le t_0 \ , \end{cases} \end{cases}$$

where the standard notation is used for a propagation matrix S and a diagonal scaling matrix C_{n+1} allowing for the variation of stepsize. The vector-valued increment function, $\overline{\psi}(t, \bar{y}, y(t-\tau), h) \equiv \bar{l} \cdot \psi(t, \bar{y}, y(t-\tau), h)$, for the predictor-corrector implementation of the LMMs, $P(EC)^M$, with variable number of iterations M, can be specified as follows [14]:

$$\psi(t_n, \bar{y}, z_{n+1}, h_{n+1}) \equiv \psi^{(M)}(t_n, \bar{y}, z_{n+1}, h_{n+1}), \quad \psi^{(0)}(t_n, \bar{y}, z_{n+1}, h_{n+1}) = \frac{(A\bar{y})_2}{h_{n+1}} \ ,$$

– for *Adams*-$P(EC)^M$ method with simple iterations

$$\psi^{(s)}(t_n, \bar{y}, z_{n+1}, h_{n+1})$$
$$= f(t_n + h_{n+1}, (S\bar{y})_1 + h_{n+1} l_1 \psi^{(s-1)}(t_n, \bar{y}, z_{n+1}, h_{n+1}), z_{n+1}), \quad s = 1(1)M \ ;$$

– for *BDF*-$P(EC)^M$ method with the Newton iterations and the Jacobian being fixed during the iteration sequence,

$$\psi^{(s)}(t_n, \bar{y}, z_{n+1}, h_{n+1}) = [I - \mathscr{T}^{-1}]\psi^0(t_n, \bar{y}, z_{n+1}, h_{n+1})$$
$$+ \mathscr{T}^{-1} \cdot f(t_n + h_{n+1}, (S\bar{y})_1 + h_{n+1} l_1 \psi^{(s-1)}(t_n, \bar{y}, z_{n+1}, h_{n+1}), z_{n+1}),$$
$$s = 1(1)M \ .$$

The Nordsieck representation of the correct value function $\bar{y}(t)$ [16], $\bar{y}_n \equiv [y_n, h_n y_n', \dots, \frac{h_n^p \cdot y_n^{(p)}}{p!}]^{\mathrm{T}} \in \mathbb{R}^{p+1}$, provides an interpolation technique for the delayed variables at the off-mesh points, which is consistent with the underlying LMM: $y(t-\tau) = \pi_p(\overline{Y}_{n-k,n}, t-\tau) \equiv \pi_p(\bar{y}_n, t-\tau) = \mathbf{1}C(\alpha)\bar{y}_n + O((\alpha h_n)^{p+1})$, $(t-\tau) \in (t_{n-1}, t_n]$, where $\mathbf{1} = [1, \dots, 1]$, $C(\alpha) = \operatorname{diag}[1, \alpha, \dots, \alpha^p]$, $\alpha = \frac{(t-\tau-t_n)}{t_n - t_{n-1}}$. The usage for approximation of the delayed variables of the Nordsieck vector taken from the nearest to the right meshpoint, with respect to the argument $(t-\tau)$ (instead of that to the left), means that the 'corrector' polynomial is used, providing an interpolation rather than extrapolation. Notice, that the 'predictor' interpolant is to be used when the delay is vanishing compared to the stepsize taken by the accuracy control mechanism, i.e. $\tau < h_n$.

Remark 3.2 For the $\mathscr{N}$-dimensional system of DDEs with m different constant delays (2.1) the one-step recurrence for $\bar{y}_n \in \mathbb{R}^{(p+1)\mathscr{N}}$, representing the LMM based discretization (Ψ_p^S, π_q), takes the form

$$\bar{y}_{n+1} = (S \otimes I)(C_{n+1} \otimes I)\bar{y}_n + h_{n+1}(\bar{l} \otimes I)\psi(t_n, (C_{n+1} \otimes I)\bar{y}_n, z_{n+1}^{[1]}, \ldots, z_{n+1}^{[m]}, h_{n+1}) \ ,$$

where $\otimes$ denotes Kronecker tensor product.

4. Order of convergence

In this section the lower bound is specified on the order q of the interpolation technique, π_q, for delay variables to be used with the p-th order LMM to keep the p-th order convergence of the combined method on each subinterval between two consecutive discontinuity points for a step-variation scheme $\theta(t, h)$. The step-changing functions specified in Remark 3.1 are implied, with $h = \max_{1 \le n \le N} h_n$. Convergence analysis of the DDE method (Ψ_p^S, π_q)

$$\bar{y}_{n+1} = SC_{n+1}\bar{y}_n + h_{n+1}\bar{l}\psi(t_n, C_{n+1}\bar{y}_n, \pi_q(\bar{Y}_{\sigma_1,\sigma_\nu}, t_{n+1} - \tau), h_{n+1}) \ , \tag{4.1}$$

deals with the behaviour of the global error $\bar{\epsilon}_n = \bar{y}_n - \bar{y}(t_n)$ as $h \to 0$. The standard Euclidean norm ($\|\cdot\|$) is considered, unless otherwise specified.

Theorem 4.1 *Let the following assumptions hold for a step-changing function $\theta(t, h)$:*

(A1) The method Ψ_p^S is p-th order consistent for ODEs:

$$\bar{d}_{n+1} = SC_{n+1}\bar{y}(t_n) + h_{n+1}\bar{l}\psi(t_n, C_{n+1}\bar{y}(t_n), y(t_n), h_{n+1}) - \bar{y}(t_{n+1}) = O(h_{n+1}^{p+1}) \ ,$$

and is p-th order convergent, $\|\bar{y}(t_n) - \bar{y}_n\|_{\mathbb{R}^{p+1}} = O(h^p)$, $0 \le n \le N$.

(A2) The increment function $\psi(t, \bar{y}, z, h)$ satisfies the Lipschitz condition with respect to $\bar{y}$ and z : $\|\psi(t, \bar{y}, z, h_n) - \psi(t, \bar{y}^*, z^*, h_n)\| \le L_y\|\bar{y} - \bar{y}^*\|_{\mathbb{R}^{p+1}} + L_z|z - z^*|$,

$$\forall \bar{y}, \bar{y}^* \in \mathbb{R}^{p+1}, \forall z, z^* \in \mathbb{R}, \forall t \in [t_0, t_0 + T], \forall h_n \in (0, h], \quad 0 \le n \le N \ .$$

(A3) The q-th order interpolation polynomial $\pi_q(\bar{Y}_{\sigma_1,\sigma_\nu}, t)$ satisfies the Lipschitz condition on $[t_0, t_0 + T]$:

$$\|\pi_q(\bar{Y}_{\sigma_1,\sigma_\nu}, t) - \pi_q(\bar{X}_{\sigma_1,\sigma_\nu}, t)\| \le L_\pi \max_{0 \le \sigma_1 \le j \le \sigma_\nu \le n} \|\bar{y}_j - \bar{x}_j\|_{\mathbb{R}^{p+1}} \ ,$$

$t \in [t_{\sigma_1}, t_{\sigma_\nu}]$, $0 \le n \le N$.
Then the method (Ψ_p^S, π_q) is convergent and $\|\bar{y}(t_n) - \bar{y}_n\| = O(h^{\min(p,q+1)})$ $\forall t_n \in [t_0, t_0 + T]$.

Proof. The proof is an extension of the techniques of [27, Sect. 3; 28, Sect. 2] and is based on bounding the solution for the global error equation $\bar{\epsilon}_n \in \mathbb{R}^{p+1}$:

$$\bar{\epsilon}_{n+1} = SC_{n+1}\bar{\epsilon}_n + h_{n+1}\bar{\epsilon}_n^* + \bar{d}_{n+1} \;, \tag{4.2}$$

with $\bar{\epsilon}_n^* = \bar{l}\{\psi(t_n, C_{n+1}\bar{y}_n, \pi_q(\bar{Y}_{\sigma_1,\sigma_\nu}, t_{n+1} - \tau), h_{n+1}) - \psi(t_n, C_{n+1}\bar{y}(t_n), y(t_{n+1} - \tau), h_{n+1})\}$. It can be shown that solving equation (4.2) gives

$$\bar{\epsilon}_{n+1} = \sum_{j=1}^{n+1} S_{n+1,j} h_j \cdot \bar{\epsilon}_{j-1}^* + \sum_{j=1}^{n+1} S_{n+1,j} \bar{d}_j \;, \tag{4.3}$$

where $S_{n,j} \equiv SC_n SC_{n-1} \ldots SC_{j+1}$, $S_{n,n} \equiv I$. For a p-th order consistent and convergent method Ψ_p^S the norms $\|S_{n+1,j}\|$, $n = 1, 2, 3, \ldots;\; j = 0, 1, \ldots, n+1$, are bounded.

Under assumptions 1 and 2 the $\bar{\epsilon}_n^*$ can be bounded by

$$\|\bar{\epsilon}_n^*\| \le \|\bar{l}\|\{L_y \|C_{n+1}\| \|\bar{\epsilon}_n\| + L_z L_q \max_{0 \le j \le n} \|\bar{\epsilon}_j\| + L_z e_{\text{int}}\} \;, \tag{4.4}$$

with $\|C_{n+1}\|$ being the subordinate norm to given vector norm $\|\bar{\epsilon}_n\|_{\mathbb{R}^{p+1}}$ and e_{int} denotes the interpolation error.

Using inequality $\|C_{n+1}\| \le K$, which holds for the step-changing functions under consideration, and applying the difference analogue of Bellman-Gronwall inequality we get:

$$\|\bar{\epsilon}_{n+1}\| \le K \sum_{j=0}^{n+1} \|\bar{d}_j\| + KL_z \|\bar{l}\| T e_{\text{int}}, \quad 0 \le n \le N \;.$$

Omitting the technical details, we arrive at the estimate

$$\|\bar{\epsilon}_n\| \le K \cdot T \cdot O(h^p) + KL_z \|\bar{l}\| \cdot T \cdot O(h^{q+1}) = O(h^{\min(p,q+1)}), \quad 0 \le n \le N \;,$$

which means that the method (Ψ_p^S, π_q) converges with the order $\tilde{p} = \min(p, q+1)$. □

Remark 4.1 The variable-stepsize convergence analysis of the LMMs presented in [14, 28] for the ODEs can be directly extended to the DDE case for the following classes of interpolation techniques: Lagrange, Hermite or Nordsieck interpolants. To this end one needs to check whether the Assumption 3 of the Theorem 4.1 holds for given stepsize variation functions.

5. Asymptotic expansion for global error

It is known that global error of the p-th order LMM, satisfying the strict root condition (SRC) and possessing a smooth increment function, admits an asymptotic expansion of the form [15, 27, 29]: $\bar{y}_n - \bar{y}(t_n) = h^p \bar{e}(t_n) + O(h^{p+1})$, $n = 0(1)N$, where the function $\bar{e}(t)$, the principal error term, satisfies a certain variational system related to the ODE problem and the local discretization error $\overline{d}_n = h^{p+1} \cdot \overline{\mathscr{F}}_{p+1}(t_n) + O(h^{p+2})$:

$$\frac{d\overline{e}(t)}{dt} = \Lambda f_y(t, y(t)) M^{\mathrm{T}} \overline{e}(t) + E \overline{\mathscr{F}}_{p+1}(t), \quad \overline{e}(0) = 0 \ . \tag{5.1}$$

Here, the matrix E is a component of S corresponding to the eigenvalue one, $S = E + T$, and $E = \Lambda M^{\mathrm{T}}$, where $S\Lambda = \Lambda$, $M^{\mathrm{T}} S = M^{\mathrm{T}}$, and $\psi(t, \Lambda y, 0) = \Lambda f(t, y)$. The starting values are supposed to be exact.

Adaptation of the LMM codes for DDEs implies that the local error estimation procedure should be modified to take into account an additional error introduced at every integration step by a particular interpolation technique for the delayed terms [2, 26]. It is practically important to specify sufficient conditions ensuring that the global error expansion exists and its leading term does not depend on the interpolation method. The following theorem examines the asymptotic behavior of the global discretization error in the fixed-stepsize case:

Theorem 5.1 *Let the following assumptions hold:*

(A1) The method Ψ_p^S satisfies the SRC and is p-th order convergent, $p \geq 1$;

(A2) The local discretization error of the method Ψ_p^S admits an asymptotic expansion with the following leading term: $\overline{d}_n = h^{p+1} \cdot \overline{\mathscr{F}}_{p+1}(t_n) + O(h^{p+2})$;

(A3) An interpolation method $\pi_q(\overline{Y}_{\sigma_1, \sigma_\nu}, t)$ satisfies the Lipschitz condition with respect to $\overline{Y}_{\sigma_1, \sigma_\nu}$ on $[t_0, t_0 + T]$;

(A4) The function $f(t, y, z)$ is of C^l class with $l = \max(p+1, q+1)$ and is Lipschitz continuous with respect to y and z;

(A5) The increment function $\psi(t, \overline{y}, z, h)$ meets the same smoothness and Lipschitz continuity requirement with respect to $\overline{y} \in \mathbb{R}^{p+1}$ and $z \in \mathbb{R}$ as $f(t, y, z)$ for y and z in $[t_0, t_0 + T]$ and for $h \in (0, \tilde{h}]$.

If $q \geq p$, then the global error of the method (Ψ_p^S, π_q) for DDEs with exact starting values admits an asymptotic expansion of the form: $\overline{y}_n - \overline{y}(t_n) = h^p \overline{e}(t_n) + O(h^{p+1})$, $n = 0(1)N$, where the function $\overline{e}(t)$ is a solution of the following IVP for the variational DDE system

$$\frac{d\overline{e}(t)}{dt} = \Lambda \left\{ \frac{\partial f}{\partial y} M^{\mathrm{T}} \overline{e}(t) + \frac{\partial f}{\partial y_\tau} M^{\mathrm{T}} \overline{e}(t - \tau) \right\} + E \overline{\mathscr{F}}_{p+1}(t), \ \overline{e}(s) = 0, s \in [t_0 - \tau, t_0] \ . \tag{5.2}$$

Proof. The equation for the global error at grid points t_n is:

$$\overline{\epsilon}_n = S \overline{\epsilon}_{n-1} + \overline{d}_n + h \{ \overline{\psi}(t_{n-1}, \overline{y}_{n-1}, \pi_q(\overline{Y}_{\sigma_1, \sigma_\nu}, t_n - \tau), h) - \overline{\psi}(t_{n-1}, \overline{y}(t_{n-1}), y(t_n - \tau), h) \}, \quad 0 \leq \sigma_1 \leq \sigma_\nu \leq n - 1 \ . \tag{5.3}$$

Let the approximation method for the delayed terms be exact. Then the leading term of the global error would be $h^p \overline{e}(t)$, with $\overline{e}(t)$ satisfying a variational system similar to (5.1). Taking the Frechet derivative of the right-hand side function of

DDE $f(\cdot, y(t), y(t-\tau))$ w.r.t. $y(\cdot)$, one gets the differential system for $\bar{e}(t)$ in form the given by (5.2), with $y_\tau \equiv y(t-\tau)$.

The difference $\overline{w}_n = \bar{\epsilon}_n - \bar{e}(t_n)h^p$ characterizes those component of the global error of the method (Ψ_p^S, π_q), which stems from the interpolation procedure for the delayed terms, π_q. It will be shown that the assumptions of the Theorem ensure that $\|\overline{w}_n\| = O(h^{p+1})$.

Introduce the discretization operators $\Delta_{-\nu}^{\sigma_\nu}$ and $\Delta_{-\nu}^{n,\sigma_\nu}$ determined by

$$\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t) = [\bar{y}(t_{\sigma_1}), \bar{y}(t_{\sigma_2}), \ldots, \bar{y}(t_{\sigma_\nu})]^{\mathrm{T}},$$
$$\Delta_{-\nu}^{n,\sigma_\nu}\bar{y}(t) = [\bar{y}^{\mathrm{T}}(t_{\sigma_1}), \bar{y}^{\mathrm{T}}(t_{\sigma_2}), \ldots, \bar{y}^{\mathrm{T}}(t_{\sigma_\nu}), \bar{y}^{\mathrm{T}}(t_n)]^{\mathrm{T}} .$$

We add and substract into the right hand side of (5.3) the term $\overline{\psi}(t_{n-1}, \bar{y}(t_{n-1}),$ $\pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)$ to obtain:

$$\begin{aligned}\bar{\epsilon}_n &= S\bar{\epsilon}_{n-1} + \bar{d}_n + h\{\overline{R}_{1n}\} + h\{\overline{R}^*_{2n}\}\\ &= S\bar{\epsilon}_{n-1} + \bar{d}_n + h\{\overline{\psi}(t_{n-1}, \bar{y}(t_{n-1}), \pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)\\ &\quad - \overline{\psi}(t_{n-1}, \bar{y}(t_{n-1}), y(t_n-\tau), h)\} + h\{\overline{\psi}(t_{n-1}, \bar{y}_{n-1}, \pi_q(\overline{Y}_{\sigma_1,\sigma_\nu}, t_n-\tau), h)\\ &\quad - \overline{\psi}(t_{n-1}, \bar{y}(t_{n-1}), \pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)\} .\end{aligned}$$

Under Assumptions 3 and 5 we have an estimate $\|\overline{R}_{1n}\|_{\mathbb{B}^{p+1}} \le L_z \cdot e_{\mathrm{int}} = 0(h^{q+1})$. The term R^*_{2n} can be expressed, using the Frechet derivative w.r.t. the relevant argument of the operator $\overline{\psi}(\cdot, \bar{y}(\cdot), \pi_q(\Delta_{-\nu}^{\sigma_\nu}y(\cdot), \cdot), \cdot)$ as follows: $\overline{R}^*_{2n}$ = $\overline{\psi}'_{\bar{y}}(t_{n-1}, y(t_{n-1}), \pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)(\overline{Y}_{\sigma_1,\sigma_\nu,n-1} - \Delta_{-\nu}^{n-1,\sigma_\nu}\bar{y}(t)) + \overline{R}_{2n}$. Here $\overline{\psi}'_{\bar{y}}(t_{n-1}, \bar{y}(t_{n-1}), \pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)$ is a $(p+1)(\nu+1)(p+1)$ matrix and $\overline{Y}_{\sigma_1,\sigma_\nu,n}$ is the vector $[\bar{y}^{\mathrm{T}}_{\sigma_1}, \bar{y}^{\mathrm{T}}_{\sigma_2}, \ldots, \bar{y}^{\mathrm{T}}_{\sigma_\nu}, \bar{y}^{\mathrm{T}}_n]^{\mathrm{T}}$. The remainder can be estimated as $\|\overline{R}_{2n}\| = O(\|\overline{Y}_{\sigma_1,\sigma_\nu,n-1} - \Delta_{-\nu}^{n-1,\sigma_\nu}\bar{y}(t)\|^2) = O(h^{2p})$ since the method (Ψ_p^S, π_q) is p-th order convergent. Thus, we arrive at

(5.4)
$$\begin{aligned}\bar{\epsilon}_n =& S\bar{\epsilon}_{n-1} + \bar{d}_n + h\{\overline{R}_{1n} + \overline{R}_{2n} + \overline{\psi}'_{\bar{y}}(t_{n-1}, \bar{y}(t_{n-1}), \pi_q(\Delta_{-\nu}^{\sigma_\nu}\bar{y}(t), t_n-\tau), h)\\ &\times(\overline{Y}_{\sigma_1,\sigma_\nu,n-1} - \Delta_{-\nu}^{n-1,\sigma_\nu}\bar{y}(t))\}\end{aligned}$$

Making use of the differential equation (5.2) discretized by the Euler scheme one gets

$$\bar{e}(t_n) = \bar{e}(t_{n-1}) + h\{\Lambda F'_{n-1}(y, y_\tau)M^{\mathrm{T}}\bar{e}(t_{n-1})\} + hE.\overline{\mathscr{F}}_{p+1}(t_{n-1}) + O(h^2) , \tag{5.5}$$

where

$$\begin{aligned}&F'_{n-1}(y, y_\tau)\\ &\equiv \left\{\frac{\partial f(t_{n-1}, y(t_{n-1}), y(t_{n-1}-\tau))}{\partial y} + \frac{\partial f(t_{n-1}, y(t_{n-1}), y(t_{n-1}-\tau))}{\partial y_\tau}D_\tau\right\}\end{aligned}$$

and D_τ stands for the backward shift operator $D_\tau y(t) \equiv y_\tau \equiv y(t-\tau)$. By subtracting (5.5) multiplied by h^p from (5.4) and using the SRC we obtain the equation for $\overline{w}_n$

$$\overline{w}_n = S\overline{w}_{n-1} + h^{p+1}\{\overline{\mathscr{F}}_{p+1}(t_n) - E\overline{\mathscr{F}}_{p+1}(t_{n-1})\} + h\{\overline{R}_{1n} + \overline{R}_{2n}\}$$
$$+ h\{\overline{\psi}_{\overline{y}}(t_{n-1}, \overline{y}(t_{n-1}), \pi_q(\Delta^{\sigma_\nu}_{-\nu}\overline{y}(t), t_n - \tau), h)(\overline{Y}_{\sigma_1,\sigma_\nu,n-1} - \Delta^{n-1,\sigma_\nu}_{-\nu}\overline{y}(t))$$
$$- \Lambda F'_{n-1}(y, y_\tau) M^{\mathrm{T}} \overline{e}(t_{n-1}) h^p\} \ . \tag{5.6}$$

Introduce the vector $\overline{W}_n = \overline{\mathscr{L}}_n - h^p\overline{\mathscr{E}}_n$, with $\overline{\mathscr{L}}_n = \overline{Y}_{\sigma_1,\sigma_\nu,n} - \Delta^{n,\sigma_\nu}_{-\nu}\overline{y}(t) \equiv [\overline{\epsilon}^{\mathrm{T}}_{\sigma_1}, \overline{\epsilon}^{\mathrm{T}}_{\sigma_2}, \ldots, \overline{\epsilon}^{\mathrm{T}}_{\sigma_\nu}, \overline{\epsilon}^{\mathrm{T}}_n]^{\mathrm{T}}$, $\overline{\mathscr{E}}_n = [\overline{e}(t_{\sigma_1}), \overline{e}(t_{\sigma_2}), \ldots, \overline{e}(t_{\sigma_\nu}), \overline{e}(t_n)]^{\mathrm{T}}$, $\overline{W}_n, \overline{\mathscr{L}}_n, \overline{\mathscr{E}}_n \in \mathbb{R}^{(\nu+1)(p+1)}$. Using assumptions on the consistency and twice continuous differentiability of the increment function $\overline{\psi}(t, \overline{y}, z, h)$ in $\overline{y}$ and z, the equation (5.6) can be further transformed to the form

$$\overline{w}_n = S\overline{w}_{n-1} + h\overline{\psi}'_{\overline{y}}(t_{n-1}, \overline{y}(t_{n-1}), \pi_q(\Delta^{\sigma_\nu}_{-\nu}\overline{y}(t), t_n - \tau), h)\overline{W}_{n-1}$$
$$+ h\{\overline{R}_{1n} + \overline{R}_{2n} + O(h^{\min(p+1,q+1)})\} + h^{p+1}\{\overline{\mathscr{F}}_{p+1}(t_n) - E\overline{\mathscr{F}}_{p+1}(t_{n-1})\}$$
$$= S\overline{w}_{n-1} + \overline{R}_n + h\overline{\psi}'_{\overline{y}}(t_{n-1}, \overline{y}(t_{n-1}), \pi_q(\Delta^{\sigma_\nu}_{-\nu}\overline{y}(t), t_n - \tau), h)\overline{W}_{n-1} \ , \tag{5.7}$$

where $\overline{R}_n \equiv h\{\overline{R}_{1n} + \overline{R}_{2n} + O(h^{\min(p+1,q+1)})\} + h^{p+1}\{\overline{\mathscr{F}}_{p+1}(t_n) - E\overline{\mathscr{F}}_{p+1}(t_{n-1})\}$. Denoting the product in the last term in (5.7) by $h \cdot \overline{W}^*_{n-1}$, we arrive at

$$\overline{w}_n = S\overline{w}_{n-1} + h\overline{W}^*_{n-1} + \overline{R}_n \ ,$$

which is similar to the fundamental stability equation. Its solution is bounded by

$$\|\overline{w}_n\| \le \sum_{j=1}^{n} \|S^{n-j}\| h \max_{t_0 \le t_{n-1} \le t_0+T} \|\overline{\psi}'_{\overline{y}}(t_{n-1}, \overline{y}(t_{n-1}), \pi_q(\Delta^{\sigma_\nu}_{-\nu}\overline{y}(t), t_n - \tau), h)\|$$
$$\times \max_{l \le j} \|\overline{w}_l\| + \max_{0 \le n \le N} \|\sum_{j=0}^{n} S^{n-j}\overline{R}_j\| \ .$$

Since the method Ψ^S_p satisfies the SRC, there exists a constant $K_1 > 0$ independent of the n such that $\|S^n\| \le K_1$. Then, by Assumption 5 the following estimate holds

$$\max_{t_0 \le t_{n-1} \le t_0+T} \|\overline{\psi}'_{\overline{y}}(t_{n-1}, \overline{y}(t_{n-1}), \pi_q(\Delta^{\sigma_\nu}_{-\nu}\overline{y}(t), t_n - \tau), h)\| = K_2 \ ,$$

with the constant K_2 not depending on n. Now, using the techniques of [27, 28 Theorem 2.4] based on the minimal stability functional $\|\overline{R}\|_{[S]}$, we can bound $\overline{w}_n$ as follows

$$\|\overline{w}_n\| \le x_n \le \frac{e^{K_1K_2T}}{C_1}\|\overline{R}\|_{[E]} \equiv K \cdot \|\overline{R}\|_{[E]} \ ,$$

with $\|\overline{R}\|_{[E]} \equiv \|\sum_{j=0}^{n} E^{n-j}\overline{R}_j\| = \|\sum_{j=1}^{n-1} E^{n-j}\overline{R}_j\| + \|\overline{R}_n\|$. Substituting the estimates of $\overline{R}_j$ with $\overline{R}_0 = 0$ and making use of the properties of matrix E, we get the bound

$$\left\|\sum_{j=1}^{n-1} E^{n-1}\overline{R}_j\right\| \le O(h^{\min(p+1,q+1)}) + \max_{t_0 \le t_n \le t_0+T} \|\overline{\mathscr{F}}_{p+1}(t_n) - \overline{\mathscr{F}}_{p+1}(t_{n-1})\| h^p \ ,$$

where $\max_{t_0 \le t_n \le t_0+T} \|\overline{\mathscr{F}}_{p+1}(t_n) - \overline{\mathscr{F}}_{p+1}(t_{n-1})\| = K_3 h$ since $\overline{\mathscr{F}}_{p+1}(t_n)$ is a smooth function on $[t_0, t_0 + T]$. This, in turn, leads to the desired estimate

$$\|\overline{w}_n\| \le O(h^{\min(p+1,q+1)}) + 2K \cdot h^{p+1} \cdot \max_{t_0 \le t_n \le t_0+T} \|\overline{\mathscr{F}}_{p+1}(t_n)\| = O(h^{\min(p+1,q+1)}) \ ,$$

which completes the proof of the theorem. □

Remark 5.1 The result of this section shows that a higher degree interpolation method for delayed terms, than that required to keep the p-th order convergence, is necessary to make the leading term of the global error expansion asymptotically insensitive of the interpolation error.

6. Absolute stability characteristics

Every $A-$, $A(\alpha)-$, or stiffly stable LMMs can be adapted for DDEs in a way preserving the stability properties [6, 31]. It seems interesting to specify and compare particular stability domains for the *BDFs* and *ABM*-methods. Characteristic equations of the LMMs in the $P(EC)^M$-mode applied to the scalar test equation $y'(t) = ay(t) + by(t - \tau)$ can be derived using the framework given by Lambert [19], Van der Houwen and Sommeijer [30]. Denote by the pairs $\{\rho^*, \sigma^*\}$ and $\{\rho, \sigma\}$ the predictor and corrector characteristic polynomials, and consider the general case of Lagrange-Hermite interpolation for delayed variables, i.e. $y(t_n - \tau) = \pi_q(\overline{Y}_{n-m-l,n-m}, t - \tau) = \sum_{i=0}^{l}(\Phi_i^0(\mu)y_{n-m-i} + h\Phi_i^1(\mu)f_{n-m-i})$, where $t_n - \tau = t_{n-m-i^*} + \mu h$, $m \ge 0$, $0 \le i^* < l$, $0 \le \mu < 1$.

BDF-methods. For the Gear's realization of the *BDFs* with the Newton method utilized in the correction process it can be easily shown that the characteristic equation is related only to the corrector difference formula. Considering for simplicity the case $\tau = mh$, with m being positive integer, we have the following equation: $\rho(\xi) - (ha + hb\xi^{-m})\sigma(\xi) = 0$. The boundaries of stability domains were located by tracing numerically over a certain grid in the (ha, hb)-plane whether the root condition is satisfied. A set of stability regions obtained for different choices of the *BDF* order and the values of the delay in terms of multiple of the stepsize, $\tau = mh$, are presented in Fig. 1 for real a and b. The test equation stability boundary is marked by a dashed line. One sees the unbounded nature of the stability regions of the *BDFs* with the stability regions for the first and the second order *BDF* incorporating the domain D.

Adams methods. The characteristic polynomial for the Adams-Bashforth-Moulton (*ABM*) methods in the $P(EC)^M$-mode with functional iterations can be specified as follows:

$$\begin{aligned}\chi(\xi) =& \xi^{k+m+l}\beta_0\{\rho(\xi) - \sigma(\xi)ha\} + \xi^{m+l}P_M(ha\beta_0)\{\rho^*(\xi)\sigma(\xi) \\ &- \sigma^*(\xi)\rho(\xi)\} - \xi^k\beta_0\sigma(\xi)hb\Phi(\xi,\mu) \ ,\end{aligned}$$

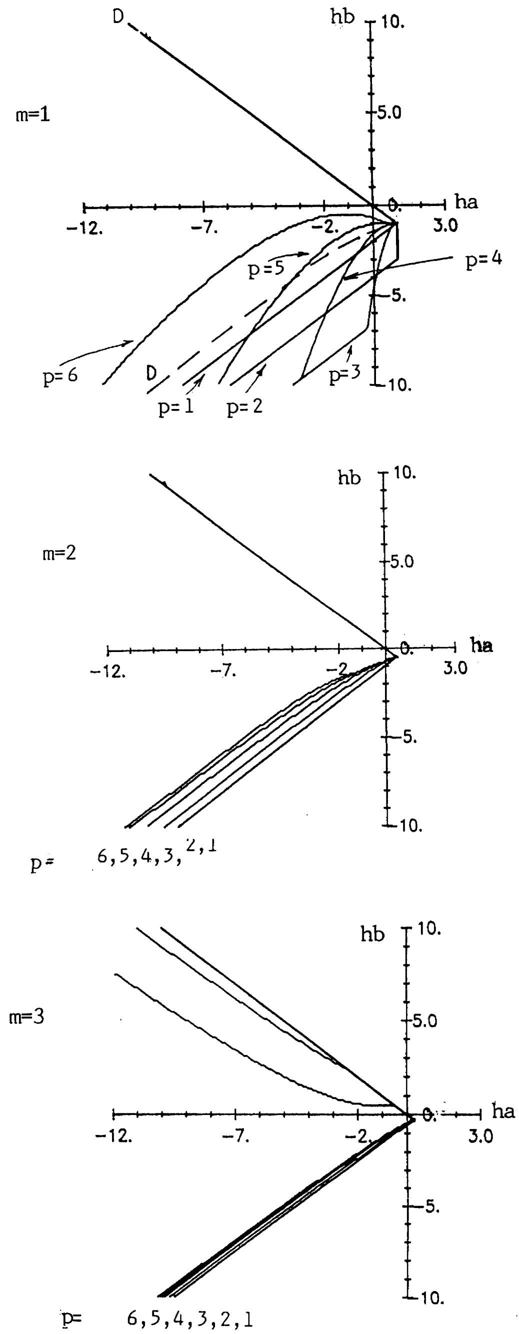

Fig. 1. A set of stability regions for *BDF*/P(EC)-method applied to the test equation $y'(t) = ay(t) + by(t - \tau)$ with real a and b for some of the possible choices of the method order p and the value of the delay in terms of multiple m of the stepsize, $m = 1(1)3$

where $P_M(ha\beta_0) = (ha\beta_0)^M(1 - ha\beta_0)^{1-M}$. Consider the polynomials $\chi_1(\xi) = \xi^l\{\xi^k\beta_0[\rho(\xi) - ha\sigma(\xi)] + P_M(ha\beta_0)[\rho^*(\xi)\sigma(\xi) - \sigma^*(\xi)\rho(\xi)]\}$ and $\chi_2(\xi) = -\xi^k\beta_0\sigma(\xi)hb\Phi(\xi,\mu)$ to represent it as $\chi(\xi) \equiv \chi_m(\xi) = \xi^m\chi_1(\xi) - \chi_2(\xi)$. Now, the results by In't Hout and Spijker [17] can be exploited to specify a necessary and sufficient condition for the method (Ψ_p^S, π_q) to be stable whenever the Ψ_p^S-method is stable. Consider the following statements:

(A) χ_1 is a Schur polynomial and $|\chi_2(\xi)| < |\chi_1(\xi)|$ for $|\xi| = 1$.
(B) χ_m is a Schur polynomial for all $m \geq \mathscr{M}$.
(C) χ_1 is a Schur polynomial and $|\chi_2(\xi)| \leq |\chi_1(\xi)|$ for $|\xi| = 1$.

Theorem 6.1 *Let the integer $\mathscr{M}$ be given by* $\mathscr{M} = \max(0, \text{degree}(\chi_2) - (l + \text{degree}(\chi_1))$. *Then the following implications hold* $(A) \Rightarrow (B) \Rightarrow (C)$.

Proof. It follows immediately by applying the results of [17, Theorem 2]. □

Particular patterns of stability domains for the ABM methods of various orders, $p = 1, 2, \ldots, 7$, were determined numerically with various choices of the corrector iteration number M and the ratio of delay to the stepsize $m = \tau/h$. Corresponding plots are presented in Fig. 2 for real a and b, which show essentially bounded nature of the stability regions of the *ABM*-methods compared to that of the *BDFs*.

7. Numerical example

At present, there exist a number of general purpose codes for non-stiff FDEs or DDEs (see references in Neves and Thompson [24], Oberle and Pesch [25], Oppelstrup [26] for the RK-based adaptations; Bock and Schloder [9], Wille and Baker [33] for the Adams-based methods) and experimental solvers for stiff FDEs or DDEs based either on the LMMs by Kahaner and Sutherland (see discussion of the SDRIV2 in [24]), Watanabe and Roth (see [31]), or on the implicit RK methods by In't Hout [18], Weiner and Strehmel [32]. For numerical integration of stiff or non-stiff initial value problems for moderate size DDEs with several constant delays [7, 22] we developed the DIFSUB-DDE code. Like the original Gear's DIFSUB [13], it makes use of the *BDFs* (of order 1 to 6) and the Adams-Bashforth-Moulton methods (of order 1 to 7) implemented in the $P(EC)^M$-mode and variable-stepsize, variable-order manner. The Nordsieck history arrays are utilized as natural approximation technique for the delayed variables consistent with the underlying LMM. The code includes a facility which allows multiple time delays for the same solution component. Derivative discontinuity points up to the order $(p + 1)$ are calculated in advance and are included among the integration meshpoints by modifying (truncating) the stepsize in the vicinity of the jump points. The first integration step from every jump point is carried out by a LMM with the order being adjusted to the continuity class of the analytical solution. The order q of interpolation formula being utilized for the approximation of delayed variables at $(t_n - \tau)$ is taken equal to the order p of the linear multistep formula which was used to advance the solution over the

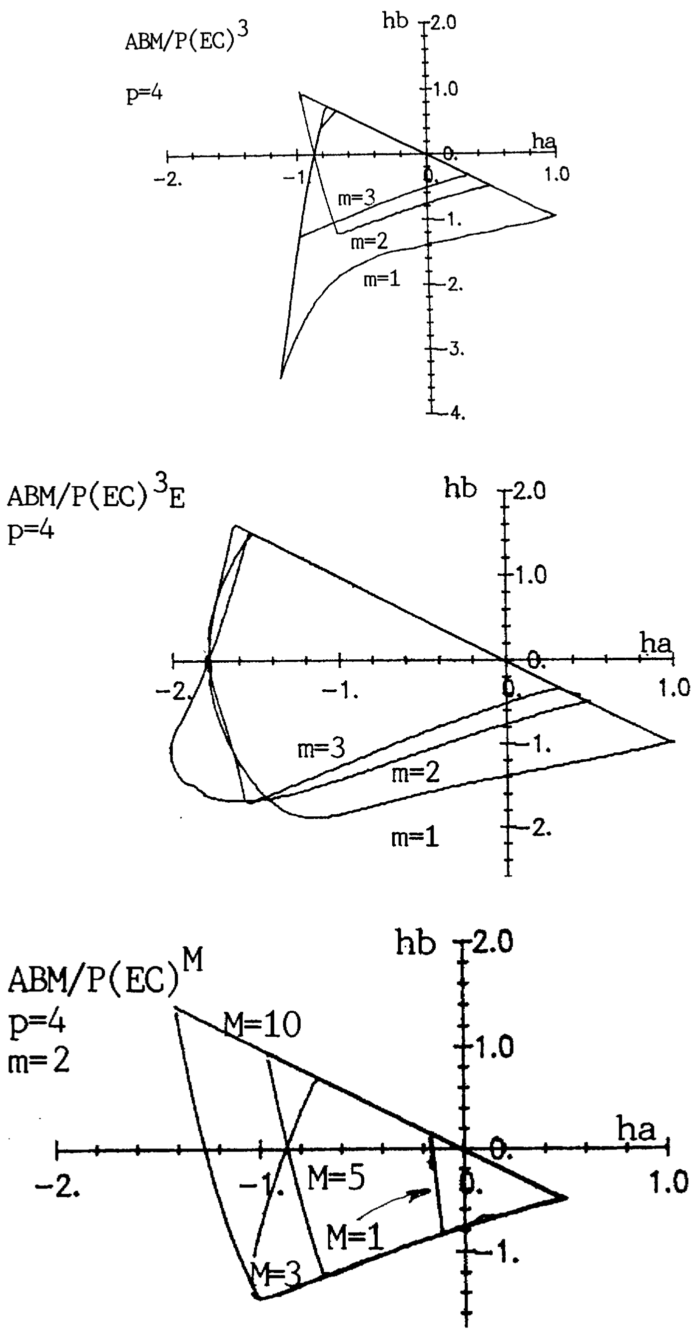

Fig. 2. A set of stability regions for 4-th order ABM-method applied to the test equation $y'(t) = ay(t) + by(t - \tau)$ with real a and b for some of the possible choices of predictor-corrector schemes, with M being the number of corrector iterations, and the value of the delay in terms of multiple m of the stepsize: $\tau = hm$, $m = 1(1)3$

interval containing $(t_n - \tau)$. This type of continuous extension of the numerical solution allowed us to keep the stepsize/order selection strategy employed in the progenitor code, except for the additional control of stepsize to fit exactly the jump points of the first $(p+2)$ solution derivatives. Within the time intervals of sufficient smoothness of analytical solution the integration stepsize is not limited explicitly by particular delay values. A wrap-around addressing technique is used to store the solution computed previously and required for the approximation of delayed variables.

Table 1. Parameters corresponding to acute hepatitis B virus infection

α_1	83	α_2	5	α_3	$6.6 \cdot 10^{14}$	α_4	$3 \cdot 10^{11}$	α_5	0.4
α_6	$2.5 \cdot 10^7$	α_7	$.5 \cdot 10^{-12}$	α_8	$2.3 \cdot 10^9$	α_9	0.052	α_{10}	0.15
α_{11}	$9.4 \cdot 10^9$	α_{12}	10^{-15}	α_{13}	1.2	α_{14}	$2.7 \cdot 10^{16}$	α_{15}	2
α_{16}	$5.3 \cdot 10^{27}$	α_{17}	1.0	α_{18}	10^{-18}	α_{19}	$2.7 \cdot 10^{16}$	α_{20}	2
α_{21}	$8 \cdot 10^{28}$	α_{22}	1.0	α_{23}	10^{-19}	α_{24}	$5.3 \cdot 10^{33}$	α_{25}	16
α_{26}	$1.6 \cdot 10^{14}$	α_{27}	0.4	α_{28}	10^{-18}	α_{29}	$8 \cdot 10^{32}$	α_{30}	16
α_{31}	0.1	α_{32}	10^{-18}	α_{33}	$1.7 \cdot 10^{30}$	α_{34}	3	α_{35}	0.4
α_{36}	$4.3 \cdot 10^{-22}$	α_{37}	$.85 \cdot 10^7$	α_{38}	$8.6 \cdot 10^{11}$	α_{39}	0.043		
τ_1	0.6	τ_2	0.6	τ_3	2.0	τ_4	2.0	τ_5	3.0

To illustrate the performance of the code we consider a real-life modelling problem which is stiff (see also [7, 22]). The test results are given for the *BDF*-methods of the code. For the local error control the weighted root-square norm was used: $\|\bar{\epsilon}\| = \sqrt{\sum_{i=1}^{N}(\bar{\epsilon}_i/w_i)^2}$, with the weights specified as $w_i = \max(GROUND(i), |y_i|)$ and the ground parameter $GROUND(i)$ taken as 10^{-28}. Calculations were performed with the IBM PC 386/387. The starting value of the stepsize was $H = HMIN = 10^{-16}$. The following notations are used: *NH* – number of successful steps, *NF* – number of function evaluations, *NJ* – number of Jacobian evaluations, *TOL* – the tolerance parameter, *ERR* – the actual relative error estimated at specified times.

Example 7.1 We present here an example of the mathematical model of antiviral immune response quantitatively describing (with the parameters of Table 1) the dynamics of hepatitis B virus infection over 130 days interval [22]. The disease dynamics is governed by the system of ten nonlinear stiff DDEs with several constant delays:

$$
\begin{aligned}
y_1' =& \alpha_1 y_2 + \alpha_2 \alpha_3 y_2 y_7 - \alpha_4 y_1 y_{10} - \alpha_5 y_1 - \alpha_6 y_1(\alpha_7 - y_2 - y_3)\\
y_2' =& \alpha_8 y_1(\alpha_7 - y_2 - y_3) - \alpha_3 y_2 y_7 - \alpha_9 y_2\\
y_3' =& \alpha_3 y_2 y_7 + \alpha_9 y_2 - \alpha_{10} y_3, \quad \xi(y_3) = 1 - y_3/\alpha_7\\
y_4' =& \alpha_{11} a_{12} y_1 - \alpha_{13} y_4\\
y_5' =& \alpha_{14}[\xi(y_3)\alpha_{15} y_4(t-\tau_1) y_5(t-\tau_1) - y_4 y_5] - \alpha_{16} y_4 y_5 y_7 + \alpha_{17}(\alpha_{18} - y_5)
\end{aligned}
$$

$$
\begin{aligned}
y_6' =& \alpha_{19}[\xi(y_3)\alpha_{20}y_4(t-\tau_2)y_6(t-\tau_2) - y_4y_6] - \alpha_{21}y_4y_6y_8 + \alpha_{22}(\alpha_{23} - y_6) \\
y_7' =& \alpha_{24}[\xi(y_3)\alpha_{25}y_4(t-\tau_3)y_5(t-\tau_3)y_7(t-\tau_3) - y_4y_5y_7] \\
& - \alpha_{26}y_2y_7 + \alpha_{27}(\alpha_{28} - y_7) \\
y_8' =& \alpha_{29}[\xi(y_3)\alpha_{30}y_4(t-\tau_4)y_6(t-\tau_4)y_8(t-\tau_4) - y_4y_6y_8] + \alpha_{31}(\alpha_{32} - y_8) \\
y_9' =& \alpha_{33}\xi(y_3)\alpha_{34}y_4(t-\tau_5)y_6(t-\tau_5)y_8(t-\tau_5) + \alpha_{35}(\alpha_{36} - y_9) \\
y_{10}' =& \alpha_{37}y_9 - \alpha_{38}y_{10}y_1 - \alpha_{39}y_{10}
\end{aligned}
$$

To describe an onset and development of the infectious disease after virus inoculation the initial conditions are specified as follows:

$$
\begin{aligned}
& y_1(0) = 2.9_{-16}, y_2(0) = 0, y_3(0) = 0, y_4(0) = 0, y_5(0) = \alpha_{18}, y_6(0) = \alpha_{23}, \\
& \qquad y_7(0) = \alpha_{28}, \\
& y_8(0) = \alpha_{32}, y_9(0) = \alpha_{36}, y_{10}(0) = \frac{\alpha_{37}\cdot\alpha_{36}}{\alpha_{39}}, \\
& y_4(t)y_5(t) = 0, \text{ for } -\tau_1 \le t \le 0, \quad y_4(t)y_6(t) = 0, \text{ for } -\tau_2 \le t \le 0, \\
& y_4(t)y_5(t)y_7(t) = 0, \text{ for } -\tau_3 \le t \le 0, \\
& \qquad y_4(t)y_6(t)y_8(t) = 0, \text{ for } -\max(\tau_4,\tau_5) \le t \le 0 .
\end{aligned}
$$

A specific feature of the solution to the initial value problem is a considerable variation in magnitude over the 130 days time interval. The stiffness of the problem increases sharply with the time passing from 110 to 120 days. The number of steps required to integrate the problem form 0 to 130 days with $TOL = 10^{-6}$ is $NH = 1274$ and $NF = 7286$. To make possible the comparison with other stiff or nonstiff DDE solvers the reference solution for this IVP is specified at $t^* = 110$ days: $y_1(t^*) = .6134388494_{-11}$ and $y_3(t^*) = .1650911903_{-12}$. Performance characteristics of the DIFSUB-DDE code are presented in Table 2 for two components, the $y_1(t)$ and $y_3(t)$. Notice that by rescaling the state vector $y(t)$ the performance of the integrator in terms of NH can be doubled (see [22]).

Table 2. Numerical results for Example 7.1

TOL	ERR_1	ERR_3	*NF*	*NH*	*NJ*	Method
10^{-2}	$6 \cdot 10^{-1}$	$3 \cdot 10^{-2}$	2356	342	163	*BDF*
10^{-4}	$1 \cdot 10^{-2}$	$4 \cdot 10^{-4}$	2872	432	185	*BDF*
10^{-6}	$2 \cdot 10^{-4}$	$6 \cdot 10^{-6}$	3853	633	221	*BDF*
10^{-8}	$3 \cdot 10^{-6}$	$1 \cdot 10^{-7}$	5006	1062	236	*BDF*
10^{-10}	$7 \cdot 10^{-8}$	$2 \cdot 10^{-9}$	6625	1702	228	*BDF*

Although the full comparison between different codes for stiff initial value problems for DDEs remains to be done, our experience in using the *BDFs*-part of the DIFSUB-DDE code for treating the simulation/identification problems formulated by systems of DDEs (see for further applications of the code [7]) made us to conclude that it can be considered as a robust computational tool for solving over a wide range of tolerances a broad class of stiff initial value problems for moderate size systems of DDEs with several constant delays.

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