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SOLVING SYSTEMS OF STIFF ORDINARY DIFFERENTIAL EQUATIONS FROM MODEL OF BIOCHEMICAL REACTION NETWORKS USING IMPLICIT RUNGE--KUTTA METHODS

A. Mustafa [*], M.O. Ibrahim

[*] Department of Mathematics Usmnu Danfodiyo University, Sokoto.
Department of Mathematics University of Illorin,Illorin

ABSTRACT

Dynamic mathematical models in the form of systems of ordinary differential equations (ODEs) play an important role in systems biology. For any sufficiently complex model, the speed and accuracy of solving the ODEs by numerical integration is critical.Here we present an integration scheme that is based on Implicit Runge-Ktta Method and contains other unique features such as stiffly accurate. These features allow the integrator to take larger time steps than other methods. In practical applications, i.e. systems biology models of different sizes and behaviors, the method competes well with established integrators in solving the system equations, and it outperforms them significantly when function evaluation,accuracy and cpu time,is evaluated.

KEYWORDS: Stiff, Chemical Model, Reformulation, Chebyshev polynomials,Implicit Runge-Kutta

INTRODUCTION

A biological system can be viewed as a chemical reaction network [4]. One of the central problems of functional genomics then becomes the identification of biochemical and gene regulatory networks describing how a living system functions[2]. Validating a biological circuit depends upon our ability to simulate a particular reaction network and to predict how the network responds to various experimental perturbations.The study of living structures as reaction networks has utilized several well-studied paradigms like the Repressilator model [10], trp operon [35, 34], HIRES [27],qa gene cluster [15], cell cycle [31], and biological clock [21]. New Numerical Integrator are needed to improve the accuracy obtained in mentioned integrator with these systems.In order to refine and examine the behavior of a biological circuit in a genomic context, an efficient general purpose simulator is needed to compute life. The KINSOLVER [1]is already available to simulate biological circuits represented by coupled nonlinear dierential equations, i.e. compute the time dependant concentrations of each species from a simple interface for specifying and refining the target reaction network. AMonte Carlo ensemble method [3] is proposed to identify the biological circuits statistically, which consists of a probability distribution over the parameter space of possible models. ThisMonteCarlo method is basically doing "guess" the best model thousands of times, and each time a "guess" involves solving the ODE once.Performance of different methods including MATLAB ODE suite are compared too.The efficiency of computation could be improved by a factor of 10 compared to the standard 4th order RK method.But the problem now is that sometimes it just takes too much time to compute due to various reasons, one of which is called stiffness. For a reasonably small biological system such as biological clock for Neuropora crassa[36], it takes almost one month to do the ensemble simulation with 40,000 sweeps through the parameter space, hunting for a good fit.The numerical method for solving ODE systems is a very old topic.

The methods discovered in last century are still the basis of the most effective codes[29]. There is a certain class of problems called stiff problems, which are too expensive to solve due to the inherent difficulty they present to conventional methods, no matter how great an improvement in hardware becomes available. Even if you can bear the expense, conventional methods have to take so many steps that the roundoff errors may invalidate the solution. As a matter of fact, most stiff systems are the systems with physical components with greatly different time constants. And most of the biochemical and gene regulatory systems exhibit this property, There are a number of software packages designed to address stiff problems,such as MATLAB ODE suite (ode15s, ode23s) [28], GEAR and its descendants [16],LSODE and its variants[17],also recently The SUNDIALS [18] ,The KINSOLVER updated by LSODES successfully and efficiently solves many stiff/non-stiff systems , and is comparable in performance to the widely accepted commercial package MATLAB. The performance can be improved by a factor of 10 compared

to the classical 4th order RK method. This improvement is very significant for the MC ensemble method. In other words, the ensemble simulation will take less than one week instead of a month, in view of this a new lobattoIIIA Methods is constructed from reformulation of block hybrid continous multistep method with five offsteps point,in [24],where the method was established to be A-stable and stiffly accurate with a very large region of absolute stabiliy,which is a requirement for an integrator to efficiently solve a stiff differential equations,see [7]. In this seminar paper,the coefficient of the derived method of order twelve(12) are obtained from reformulating One-step Hybrid implicit linear multistep method with five offstep points are constructed and implemented in solving a systems of stiff ordinary differential equations from model of BioChemical Reaction Networks known as Micheaelis-Menten type enzymatic reaction [20] given as $A+B\underset{k_2}{\overset{k_1}{\rightleftarrows}}S\rightarrow A+R$ where A,B,S,R correspond to enzyme,subtrate,enzymes-subtrate complex and product concentrations respectively with mass-action kinetics the reaction network translate to the dynamical systems.Such problems are often well solved by general purpose ODE solvers,but biochemical reation model offer a number of features that require more specialised and efficient solver resulting in faster and/or more precise simulations. For instance, in enzyme kinetics, reversible association and dissociation processes are usually much faster than product formation. The resulting stiffness severely limits the types of numerical methods that can beused for ODE integration. The seminar paper is organized as follows,In section 2,the s-stage LobattoIIIA method with s=7 and will be presented and discuss its stability and accuracy in theory.

The method with seven stage is adopted intoMATLODE Package by [28] which main feature of the programe is its automatic selection of step sizes.In section 3 the derived method is compared with mentioned method in (1) and section 4 the stability analysis of the new method will be analysed include the stability functon of the method and the region of absolute stability will be drawn to arcertain the suitability of the method to solve the mentioned model efficiently and lastly discussion of the results obtained with regard to the efficiency,accuracy and time comsumption by the new method and the existing methods.

MATERIALS AND METHODS

The Reformulated One-step Implicit Adams-Moulton with Three Offstep points

$$\left.\begin{aligned}\phi'(x)&=f(x,\phi)\\ \phi(x_0)&=\phi_0\end{aligned}\right\} \qquad (1)$$

We seek a solution in the range where a and b are finite and we assume that $[a\le x\le b]$ if (1), satisfy the conditions which guarantee that the problem has a unique continuously Differentiable solution, which we indicated by $[\phi(x)]$. Consider the sequence of points $[x_n=a+nh,n=0,1,2...\dfrac{b-a}{h}]$,where the parameter h is the step length and is constant. An essential property of the majority of computational methods for the solution of {1} is that of discritization, that is we seek an approximate solution, not on the continuous interval $[a\le x\le b]$,but on the discrete point set $\{x_n\}$.The k-step Linear Multistep method (LMM) for the solution of (1) is generally written as

$$\sum_{j=0}^{k}\alpha_j\phi_{n+j}=h\sum_{j=0}^{k}\beta_j f_{n+j} \qquad (2)$$

Which has 2k+1 unknown $\alpha's$ and $\beta's$ and and therefore can be of order 2k.But according to [9],the order of equation (2) cannot exceed k+1, if (k is odd) or k+2 if (k is even) for the method to be stable. Several authors such as [13,30,6],proposed the modified forms of (2) which were shown to overcome the Dahlquist barrier theorem .These methods,known as hybrid methods were obtained by incorporating off-step points in the derivation process.

$$\sum_{j=0}^{s}\alpha_j\varphi_{n+j}=k\sum_{j=0}^{s+\mu}\beta_{\tau j}f_{n+\tau j} \qquad (3)$$

Where $\mu\in[0\ 1]$,which were shown to be of order up to 2k+2.Howerever, [14] note that deriving such kind of methods for (3) is more tedious due to the occurrence of the fractional off-step points, which increases the number of predictors needed to implement the method. The hybrid method proposed in this paper, does not share this

disadvantage since it is self-starting .The algorithm was developed by [24,26] ,through continuous interpolants based on the work of [22].We also observe that block methods were first introduced by [23], for only as a means of obtaining starting values for predictor-corrector algorithms and has since then been develop by several researchers such as [8,11,19],Also Chebyshev polynomials appear in many papers as a tool for approximating an ordinary differential equations such as paper [32] ,where a Chebyshev polynomials where employ to obtain the internal stage for Lobatto IIIA implicit Runge-Kutta for the solution of stiff differential equations,to this end,our contionous representation generates a main discrete hybrid method which are combined and implemented as a block method,which simultanously generate approximations $\varphi_{n+j\mu}$ to the exact solution $\varphi(x_{n+j\mu}), j=0,1,2,\ldots,5,$ without loss of generality, the shifted second kind Chebyshev polynomials $U_n(x)$,which is given in terms of three terms recurrence relation in [12]

$$\left.\begin{aligned} U_{n+1}(x) &= 2(2x-1)U_n - U_{n-1} \\ U_0(x) &= 1 \\ U_1 &= 2(2x-1) \end{aligned}\right\} \tag{4}$$

Therefore, for n=2 in (4) we've the fifth degree shifted second kind Chebyshev polynomials given as

$$U_5(x) = 1024x^5 - 2560x^4 + 2304x^3 - 896x^2 + 140x - 6 \tag{5}$$

The companion matrix of (5) is given as

$$A=\begin{pmatrix} \frac{2560}{1024} & -\frac{2304}{1024} & \frac{896}{1024} & -\frac{140}{1024} & \frac{6}{1024} \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix} \tag{6}$$

Where the eigenvalue of A are the zeroes of (5) given as

$$\mu_1 = \frac{1}{2} - \frac{1}{4}\sqrt{3}, \mu_2 = \frac{1}{4}, \mu_3 = \frac{1}{2}, \mu_4 = \frac{3}{4}, \mu_5 = \frac{1}{2} + \frac{1}{4}\sqrt{3}$$

Which are incorporate as the off steps point into 1-step hybrid Adams-Moulton to obtain the block methods,In this paper our aim is to generate a one-step implicit continuous hybrid block methods with five off-step points from zeroes of (5) and to demonstrate the efficiency in its implementations on stiff problems.

DERIVATION OF THE METHOD

In this section, our objective is to derive the main hybrid block method of the form

$$\alpha_j \varphi_{n+j} = h\sum_{j=0}^{5} \beta_{\mu[j]} f_{n+\mu[j]} \tag{7}$$

Where α_j and $\beta_{\mu[j]}$ are unknown constant, also $\mu[j]$ are the zeros of (5) in the interval of $\mu \in [0,1]$. In order to obtain the unknown coefficients in (8) we now consider collocation polynomial [25] of the form

$$\varphi(\mathrm{x}) = \sum_{j=1}^{t+s-1} a_j x^j \tag{8}$$

Which can now be express inform of

$$\varphi(x)=\left\{\sum_{j=1}^{t-1} a_{j,t+s-1}\varphi_{n+j}+h\sum_{j=0}^{s-1}\beta_{j,t+s-1}f_{n+j}\right\}\left(1,x,x^2\ldots x^{t+s-1}\right)^T \quad (9)$$

Thus, we can express equation (9) explicitly as follows

$$\varphi(x)=\left(\varphi_n\ldots\varphi_{n+t-1},f_n,\ldots,f_{n+s-1}\right)C^T\left(1,x,x^2\ldots,x^{t+s-1}\right)^T \quad (10)$$

Where

$$C=\begin{pmatrix} & & \\ c_{1,1} & c_{1,t}\ldots.. & c_{1,t+s} \\ c_{2,1} & c_{2,t}\ldots. & c_{2,t+s} \\ . & . & . \\ c_{t+s,1} & c_{t+s,t} & c_{t+s,t+s} \end{pmatrix} \quad (11)$$

$$DC=I \quad (12)$$

Therefore

$$C=D^{-1}$$

$$D=\begin{pmatrix} & & \\ 1 & x_n\ldots.. & x_n^{t+s-1} \\ 1 & x_{n+1}\ldots. & x_n^{t+s-1} \\ 0 & . & . \\ 0 & x_{n+s} & x_{t+s-1}^{t+s-2} \end{pmatrix} \quad (13)$$

The matrices (11) and (12) are of dimensions $(t+s)*(t+s)$.We call the D the multistep collocation and interpolation matrix which has a very simple structure. It is similar to Vander monde matrix, consisting of distinct elements nonsingular, and of dimension $(s+t) x(s+t)$ .This matrix affect the efficiency of (14).The choice of $C=D^{-1}$ leads to the determination of (14) is convergent with order p=t+s-1 of the constant coefficients $\alpha_{j,i+1}$ and $\beta_{j,i+1}$ ..It was shown in [33],that the method (12) is convergent with order $p=t+s-1$.We thus construct a k-step multistep method by imposing the following conditions.

$$\left.\begin{aligned}\varphi(x_{n+\mu j})&=\varphi_{n+j},\quad j=0,1,2,s-1\\ \varphi'(x_{n+\mu j})&=f_{n+j},\quad j=0,1,2,s-1\end{aligned}\right\} \quad (14)$$

Where $\mu\in[0,1],\varphi(x_{n+\mu[j]}),\ f_{n+\mu[j]}=f(x_{n+\mu[j]})$

n is the grid index. It should be noted that equation (11) and (12) leads to a system of t+s equations which must be solved to obtained the coefficientsa_j algebraic computation, our method yields the expressing in the form

$$\varphi(x)\ =\sum_{j=0}^{t-1}\alpha_j\varphi_{n+j}+h\sum_{j=0}^{s-1}\beta_{\mu[j]}f_{n+\mu[j]} \quad (15)$$

Which is used to generate the main discrete hybrid block method in the form of (15)

Now For k=1, taking the zeroes of equation (5) and t=1, S=7, $x^i,i=0,1,2,3,4,5,6$ and thus interpolating (15) at

$$x_{n+\mu j}=\{x_n,x_{n+\mu 1},x_{n+\mu 2},x_{n+\mu 3},x_{n+\mu 4},x_{n+\mu 5},x_{n+1}\} \quad (16)$$

We generate the following continuous hybrid block method which can also be represented in a Block form as follows:

$$A=\begin{pmatrix}\varphi_n\\ \varphi_{n+\mu[1]}\\ \varphi_{n+\mu[2]}\\ \varphi_{n+\mu[3]}\\ \varphi_{n+\mu[4]}\\ \varphi_{n+\mu[5]}\\ \varphi_{n+\mu[1]}\end{pmatrix}=\begin{pmatrix}0 & 0 & 0 & 0 & 0 & 0 & 0\\ \frac{\sqrt{3}}{280}+\frac{53}{2520} & \frac{47\sqrt{3}}{4032}-\frac{4}{63} & \frac{19\sqrt{3}}{280}-\frac{2269}{20160} & \frac{31\sqrt{3}}{420}-\frac{41}{315} & \frac{19\sqrt{3}}{280}-\frac{2339}{20160} & \frac{145\sqrt{3}}{4032}-\frac{4}{63} & \frac{\sqrt{3}}{280}-\frac{17}{2520}\\ \frac{1}{280} & \frac{3\sqrt{3}}{64}+\frac{37}{504} & \frac{233}{2240} & -\frac{23}{1260} & \frac{23}{2240} & -\frac{3\sqrt{3}}{64}+\frac{37}{504} & \frac{1}{280}\\ \frac{53}{2520} & \frac{\sqrt{3}}{36}+\frac{4}{63} & \frac{319}{1260} & \frac{41}{315} & -\frac{31}{1260} & -\frac{\sqrt{3}}{36}+\frac{4}{63} & -\frac{17}{2520}\\ \frac{3}{280} & \frac{3\sqrt{3}}{64}+\frac{3}{56} & \frac{489}{2240} & \frac{39}{140} & \frac{279}{2240} & -\frac{3\sqrt{3}}{64}+\frac{3}{56} & \frac{3}{280}\\ -\frac{\sqrt{3}}{280}+\frac{53}{2520} & \frac{145\sqrt{3}}{4032}+\frac{4}{63} & \frac{19}{280}+\frac{2269}{20160} & \frac{31}{420}+\frac{41}{315} & \frac{19\sqrt{3}}{280}+\frac{2339}{20160} & \frac{47\sqrt{3}}{4032}+\frac{4}{63} & -\frac{\sqrt{3}}{280}-\frac{17}{2520}\\ \frac{1}{70} & \frac{8}{63} & \frac{8}{35} & \frac{82}{315} & \frac{8}{35} & \frac{8}{63} & \frac{1}{70}\end{pmatrix}\begin{pmatrix}f_n\\ f_{n+\mu[1]}\\ f_{n+\mu[2]}\\ f_{n+\mu[3]}\\ f_{n+\mu[4]}\\ f_{n+\mu[5]}\\ f_{n+1}\end{pmatrix} \quad (17)$$

STABILITY ANALYSIS

It has been shown in \cite{CHOL18} that a block linear multistep method is said to be zero stable if the roots of

$$\rho(R)=\det\left\{\sum_{i=0}^{k}A^{+(i)}R^{k-i}\right\}=0, R_j,\ j=1(1)k \quad (18)$$

the first characterises polynomials satisfies $|R_j|\le 1$ and the multiplicity must not exceed two, we then apply [20] to check for the zero stability of the derive block method in (17),after some simplification the roots of the block method is (0,0,0,0,0,1),which confirm the zero stability of the block method.

4.1 Order and error constant

We adopt [8] to obtain the order and error constant of the block method.

Which state that the block linear multistep method is said to be of order p if $\overline{c_0}=\overline{c_1}=\overline{c_2}=\ldots\overline{c_p}=0,\ \overline{c_{p+1}}\neq 0$

And the local truncation is expressed as

$$T_n=c_{p+1}h^{p+1}y^{p+1}(x_n) \quad (19)$$

Now to determine the order and error constant of the derived method we apply [19] for the order and (18) for truncation error, which we obtained as follow:

The integrators (18) is a one block one step hybrid methods of order (7,7,7,7,7,7) with error constants

$$c_{p+1}=c_7=\{6.3073*10^{-10},-3.5000*10^{-9},0,-3.5000*10^{-9},-6.3070*10^{-10},-1.1000*10^{-11}\}$$

4.2 Stability Function of the block method

The stability function of the block Method are determine through the application to test equation

$$y'=\lambda y \quad \lambda<0$$

Applying of(22) to (10) gives the stability function of the method as

$$R_5(z)=\frac{(2580480+1290240z+291840z^2+38400z^3+3108z^4+146z^5+3z^6)}{(2580480-1290240z+291840z^2-38400z^3+3108z^4-146z^5+3z^6)} \quad (20)$$

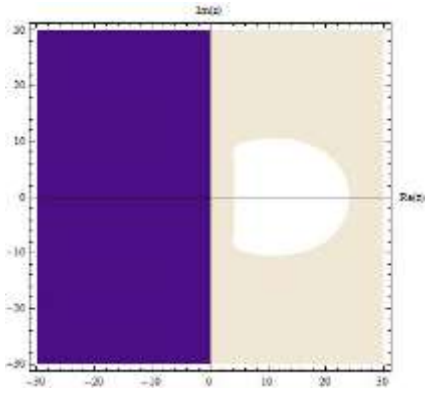
It can be seen from (20) that the one step block method is A-stable in the spirit of [5],which requires that all and , must have a dominant eigenvalue such that,from the analysis of (20), we obtained the eigenvalues as \$(0,0,0,0,0,0,1)\$ and the dominant eigenvalue is the function in (20) of z.

4.4 Absolute stability region of the block method

To plot the region of absolute stability regions of (10),they are reformulated as General Linear Methods of [6] where they used a partition $(s+t)*(s+t)$ matrix containing A,B,U,V ,express as in [8],where the absolute stability region of the method is defined as

$A=x\in C:\rho(\eta,z)=1\Rightarrow|\eta|\le 1$.In our on case, Maple is used to obtained the stability polynomials of the method.The stability polynomial is used in mathematica environment and produces the region of absolute stability of the block method as shown in figure 1.

Figure:



Region of absolute stability of the block method

The stability region for the method lie outside the bounded region. Since all the region in the half plane is in the stability region with large region of absolute stability, therefore the method is A-stable suitable for stiff problems.

NUMERICAL EXPERIMENT

The Repressilator Model

The system is composed of three genes, each coding for an mRNA transcript and the corresponding translated protein. This gives us six species to model and we denote the three mRNA species , m_1, m_2, m_3 ,and the three protein species p_1, p_2, p_3 where 1,2 and 3 refer to the TetR, λ cI and LacI genes respectively. We have a systems differential equation for the time evolution of each species and the model takes the form,the model was found to be oscillatory with stiffness ratio of 20:680.The model was adpted from [34].

$$\left.\begin{aligned}
\frac{dm_1}{dt} &= -m_1 + \frac{\alpha}{1+p_3^n} + \alpha_0 \\
\frac{dp_1}{dt} &= -\beta(p_1 - m_1) \\
\frac{dm_2}{dt} &= -m_2 + \frac{\alpha}{1+p_1^n} + \alpha_0 \\
\frac{dp_2}{dt} &= -\beta(p_2 - m_2) \\
\frac{dm_3}{dt} &= -m_3 + \frac{\alpha}{1+p_2^n} + \alpha_0 \\
\frac{dp_3}{dt} &= -\beta(p_3 - m_3)
\end{aligned}\right\} \qquad (21)$$

Problem 1

where $[\alpha_0 = 1, \alpha = 1000, \beta = 0, n = 1.75]$ is the basal rate of expression of each gene, α is the repression strength, β is the protein and mRNA degradation rate constant (assumed equal) and *n* is the Hill coefficient due to the cooperativity of the repression.

Now we are going to examine the solution to the system when the intial conditions are given by $[m_1, p_1, m_2, p_2, m_3, p_3 = 5, 0, 15, 0, 0, 0]$ respectively .Here we stimulate the model with different stiff ode integrator including the MATLAB build-in method and the proposed method,the MATLAB integrator use here include ode45,ode15s,ode23t and ode23s,and also compared with propsed method interms of function evalution.

Figure:Solution of the model using the MATLAB Iintegrator and the proposed method

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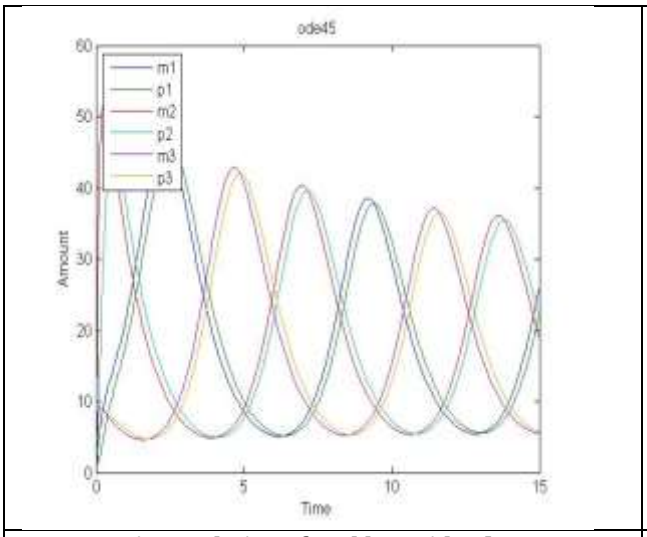

Fig1: Solution of problem with ode45

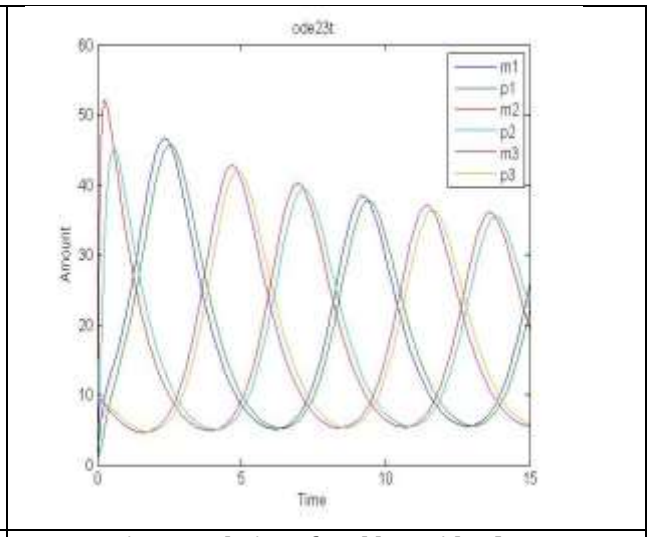

Fig2: Solution of problem with ode23t

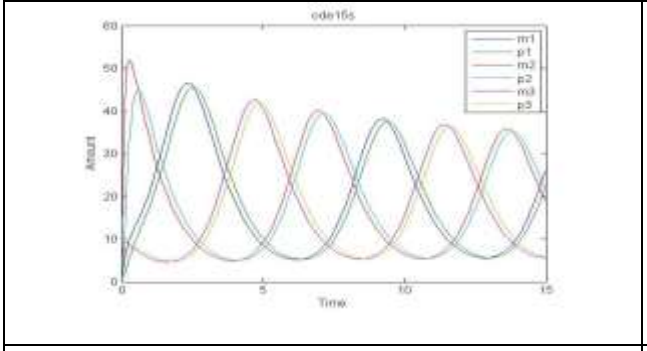

Fig3: Solution of problem with ode15s

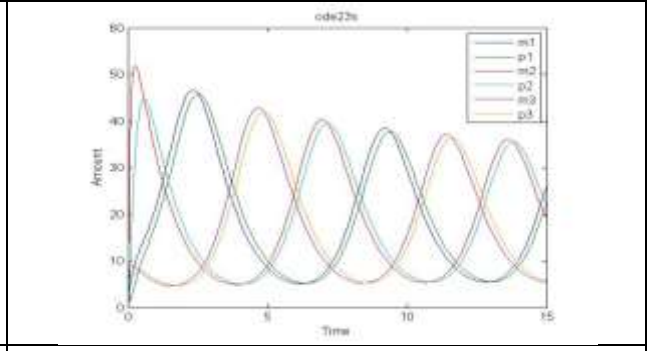

Fig4: Solution of problem with ode23s

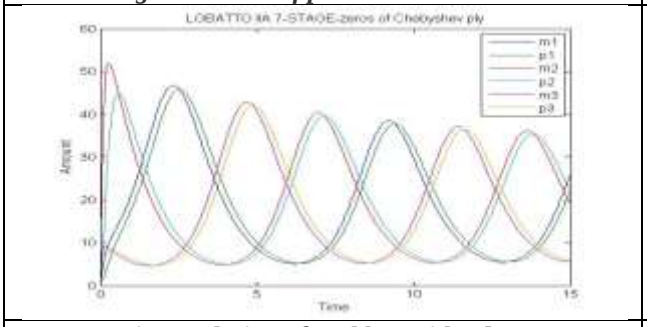

Fig5: Solution of problem with ode45

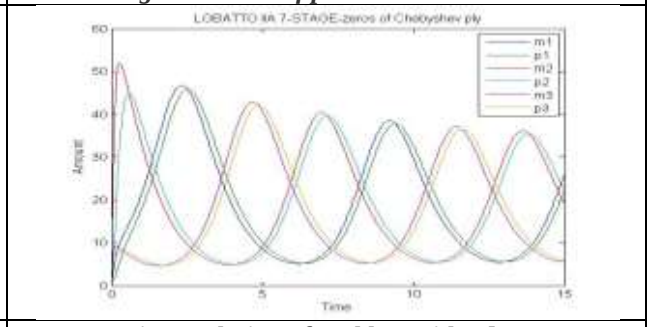

Fig6: Solution of problem with ode45

Figures:Comparative analysis of the methods interms of their no. of steps,function evaluation and time cost

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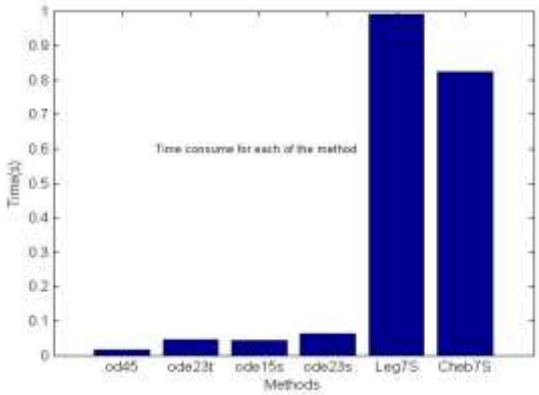

Fig7: time consume by each of the Method

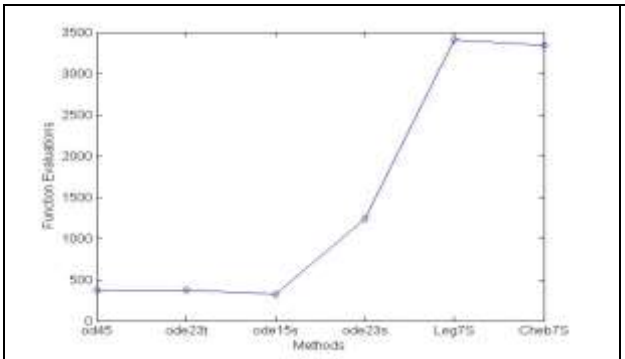

Fig 9 : Function Evaluation for each of the method

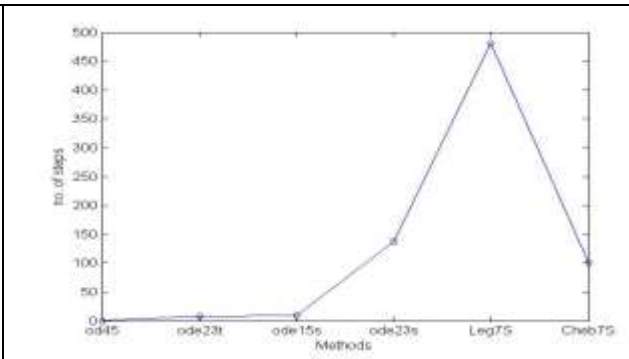

Fig10: Number of steps for each of the method

RESULTS AND DISCUSSION

The performance of each of the methods based on function evaluations and the number of steps used to integrate the stiff problem were also surveyed.The summary of performance given in *fig*(8) which shows time consume by each of the method to integrate the problem was shown,which shows that upon all the method considered here ode45 consume less time due to the fact that the method is explicit require no calculation of jacobian also given in *fig*(9) is the function evalution and fig10 shows the number of steps taken by each of the method,but here our proposed method has less number of steps,which means it uses a large interval of intergration which most of MATLAB Build-in intergrator uses either variable steps strategy or variable order strategy which are very complicated to design.In our on case we use fixed step size in intergrating the model.Therefore the only advantage of our propsed method over the Build-in intergrator is that the implement as well as the designs are easy to understand.

CONCLUSION

In this paper, the construction of an implicit Lobattto-IIIA method appropriate for solving systems of initial value problems that arises as results of chemical reaction model, was described.The resulting methods is A-stable and exhibit the favourable characteristics of being sysmmetric and stiffly accurate.We have also obtained explicit formula for coefficients of the methods for this method from reformulation of one step Adams–Moulton Method by adding five offsteps point at collocations points ,where the offsteps points are obtained from zeros of fifth degree Chebyshev polynomials which compute favourable with that existing MATLAB build-in integrator.

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REFERENCES

1. B. Aleman-Meza. *Advances in Numerical Simulation of Kinetics Reaction Equations.* Department of Computer Science, The University of Georgia., 2001

2. H.B.and Logan D.A Arnold, J.and Schuttler. Metabolomics in ch. 22 of handbook of industrial mycology. *Marcel-Dekker, NY.*, 27, 2004.
3. D. Battogtokh, D. K. Asch, M. E. Case, J. Arnold, and H. B. SchAuttler. An ensemble method for identifying regulatory circuits with special reference to the qa gene cluster of neurospora crassa. *Proc. of the National Academy of Sciences USA*, 99:16904–16909., 2004.
4. G.W. Beadle and E. I. Tatum. Genetic control of biochemical reactions in neurospora. *Proc. Natl. Acad. Sci. USA*, 27:499–506, 1941.
5. L.A. Brugnano. *Solving Differential problems byMultistep initial and Boundary ValueMethod*. Gordon and Breach Science publishers, first edition, 1998.
6. K. Burage. Non-linear stability for a general class of differential equations methods. *BIT*, 20:185–203, 1980.
7. J. C. Butcher. *NumericalMethods for Ordinary differential equations*. JohnWiley and Sons Ltd, Chikago, 1sth edition, 2003.
8. Peter J. Chollom. *A study of block hybrid with link to two step Runge-Kutta methods for(ODEs)*. PhD thesis, University of Jos, 2006.
9. G. Dahlquist. A special stabilty property for linear multistep methods. *BIT*, 3:27–63, 1963.
10. U.S. Elakhe, A.O.and Aashikpelokhai. Efficient order seven and eight rational integrators. *Nigerian Association ofMathematical Physics*, pages 273–280, 2011.
11. S. Fatunla. Block methods for second order initial value problems. *International Journal of ComputerMathematics*, 41, 1994.
12. W. Gautschi. *Orthogonal Polynomials Computational and Approximation*. New York: Oxford University Press, 2004.
13. ConW. Gear. Hybrid methods for initial value problems in ordinary. *SIAM Journal of Numerical Analysis*, 41:69–86, 1965.
14. ConW. Gear. Implementing second-derivative multistep methods using nordsieck polynomial representation. *Math. Comp. J.*, pages 13–18, 1978.
15. N. H. Giles, M. E., R.and Huiet L. Baum, J.and Geever, V. Patel, and B. Tyler. Gene organization and regulation in the qa (quinic acid) gene cluster of neurospora crassa. *Microbiological Reviews*, 49:338–358, 1985.
16. A. C. Hindmarsh. Gear: Ordinary differential equation system solver. *Lawrence Livermore Labatory report UCID-30001, Rev.*, pages 108–115, 1974.
17. A. C. Hindmarsh. Lsode and lssodi, two new initial value ordinary differential equation solvers. *ACM SIGNUM Newsletter*, 15, 1980.
18. A. C.Hindmarsh and S. Radu. Cvode for initial value ordinary differential equation solvers. *ACMSIGNUMNewsletter*, 15:108–115, 2012.
19. S. Jator. On the hybrid method with three-off step points for stiff ode. *International Journal Of Mathematics Education*, 41:110–118, 2010.
20. M. Johnston. A model fungal regulatory mechanism: the gal genes of saccharomyces cerevisiae. *Microbiolog. Rev.*, 51:458–476, 1987.
21. J.J. Lee, K.and Loros and J.C. Dunlap. Interconnected feedback loops in the neurospora circadian system. *Science*, 289:107–110, 2000.
22. I. Lie and S.P. Nørsett. Superconvergence for multistep collocation. *International Journal Of Mathematics and Computer*, 41:65–79, 2004.
23. W.Milne. *Numerical solution of differential equations*. JohnWiley and Sons, 1953.
24. A.Mustafa and M. O. Ibrahim. Implicit one step continuous hybrid block methods with three off-steps point from third degree chebyshev polynomials,for stiff problems. *ABACUS*, 38:34–38, 2012.
25. P. Onumanyi, D. O. Awoyemi, S. N. Jator, and U. W. Sirisena. New linear multi-step methods with continuous coefficients for the first order ordinary initial value problems. *Journal of NigerianMathematical Society*, pages 37–51, 1994.
26. P.Onumanyi andW. Sirisena. Continuous finite difference approximations for solving differential equations. *Journal ofNig.Math. Soc.*, pages 15–27, 1999.
27. A. Prothero and A. Robinson. On the stability and accuracy of one-step for solving stiff systems of ordinary differential equations. *Math.Comput*, pages 143–162, 1974.
28. L. F.; Shampine and M. Reichelt. The matlab ode suite siam. *J.Sci. Comput.*, 18:1–21, 1997.