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MODIFIED SPLITTING AND COMPOSITION METHODS BY PHASE-FITTING FOR SIMULATING BIOLOGICAL OSCILLATORS

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ABSTRACT. A class of modified splitting and composition methods using the phase-fitting properties of the harmonic oscillators are adapted to the numerical simulation of some biological oscillators. The new phase-fitted splitting and composition methods are furnished with a fitting parameter ω. In this paper, we present phase-fitted Lie-Trotter and Strang splitting methods and a phase-fitted triple Jump composition method which are generalization of their prototype methods. The result of the experiments on some biological oscillators show the effectiveness and competence of the modified methods over the prototype methods.

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1. Introduction

Synchronization activities in large population of interacting components are imminent in Science and are studied as physical, biological and chemical systems. In Biology, periodic fluctuations are found at all levels of life either as a result of gene expression, predator-prey interactions or degradation of the circadian clocks in mammals, to mention a few. This interactions are purely dynamic systems which gives rise to sustained rhythms and the biophysical oscillating networks of the interacting species are described by coupled biological oscillator, which are studied with the numerical modelling for qualitative analysis of the dynamical system, for more example see literatures [6], [7], [8], [13], [15], [21].

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In most cases, biological oscillators are described mathematically in form of systems of Ordinary Differential Equations (ODE) (see [5], [6], [7], [8], [3]). To simulate and perform the qualitative analysis of these systems, biologist employ the standard Runge-Kutta (RK) methods available in the MATLAB scientific computation suites. Due to the fact that accuracy is of importance for biological oscillators, standard integration methods require a very high computational efforts and in most cases do not preserve the oscillatory structure of the biological processes, this motivates the construction of special splitting methods with phase-fitting property, see ([4], [17], [19], [24]).

Splitting and composition approach have been identified with the numerical solution of Hamiltonian systems and Partial Differential Equations whose vector fields are separable in a manner of exactly solvable parts (see [1, 2, 12]). Recently, the splitting methods have been used in the effective simulation of Genetic Regulatory Networks (GRN), You et. al. [25] simulated some GRNs and obtained some very good results. The purpose of this paper is to furnish the standard splitting and composition methods with phase-fitting property, such that if a good approximation of the dominant frequency is known in advance, a phase-fitted splitting and composition methods with zero phase-lag are available.

The rest of the article is organized as follows: some standard splitting methods are presented and techniques for modifying the prototype splitting methods are discussed in section 2. In section (4), some classical biological oscillators are tested with the modified methods derived in section 2. Finally, we give some concluding remarks based on the numerical results in section 5.

2. Splitting methods for Biological Oscillators

Consider the initial value problem (IVP) of the autonomous system of ordinary differential equations

$$\dot{y} = f(y), \qquad t > 0, \tag{1}$$

where $y : \quad [0, +\infty) \to \mathbb{R}^d$, "$\dot{y}$" represents the first derivatives of y with respect to time, and $f : \quad \mathbb{R}^d \to \mathbb{R}^d$ is a sufficiently smooth function. Given the experimental observation of many biological oscillators, we make the following assumptions: (i) The system (1) has a stable limit cycle Γ_0; (ii) The function $f(y)$ satisfies $f(y^*) = 0$,

that is, y^* is an equilibrium point of the system (1); and (iii) The equilibrium point y^* lies inside the limit cycle Γ_0 and there is no other equilibrium point inside Γ_0. Therefore, it follows that any solution near the limit cycle is oscillatory.

The basic idea of splitting methods for time integration of the system (1) is that, suppose we can split f in (1), in such a way that the equation has a split structure

$$y' = f^{[1]}(y) + f^{[2]}(y). \tag{2}$$

Assuming that both systems $y' = f^{[1]}(y)$ and $y' = f^{[2]}(y)$ can be integrated exactly (numerically) with solutions $y(x) = \phi_h^{[1]}(x_0)$ and $y(x) = \phi_h^{[2]}(x_0)$, respectively at $x = h$, the time step, we define the following standard splitting or composition method in the following subsection.

2.1. **Some standard splitting and composition methods.**

Definition 2.1. *The Lie-Trotter method (LT) defined by*

$$\begin{aligned} \Psi_h^{[LT]} &= \phi_h^{[2]} \circ \phi_h^{[1]} \\ &= \phi_h^{[1]} \circ \phi_h^{[2]} \end{aligned} \tag{3}$$

is the simplest splitting method for system (1)*, based on* (2) *and it is of order 1.*

Definition 2.2. *The Strang splitting method defined by*

$$\Psi_h^{[ST]} = \phi_{h/2}^{[1]} \circ \phi_h^{[2]} \circ \phi_{h/2}^{[1]} \tag{4}$$

is a symmetric splitting method for system (1)*, based on* (2) *and it is of order 2.*

Definition 2.3. *The general s-stage splitting method for* (1) *based on the splitting of vector field* (2) *is defined by*

$$\Psi_h = \phi_{a_{s+1}h}^{[1]} \circ \phi_{b_s h}^{[2]} \circ \phi_{a_s h}^{[1]} \circ \ldots \circ \phi_{b_2 h}^{[2]} \circ \phi_{a_2 h}^{[1]} \circ \phi_{b_1 h}^{[2]} \circ \phi_{a_1 h}^{[1]}, \tag{5}$$

where $a_1, b_1, \ldots, a_s, b_s, a_{s+1}$ are positive constants satisfying some appropriate conditions.

Definition 2.4. *The Triple Jump (TJ) composition method defined by*

$$\Psi_h^{[TJ]} = \Psi_{\gamma_3 h}^{ST} \circ \Psi_{\gamma_2 h}^{ST} \circ \Psi_{\gamma_1 h}^{ST} \tag{6}$$

where $\gamma_1 = \gamma_3 = \frac{1}{2-2^{\frac{1}{3}}}$ *and* $\gamma_3 = -\frac{2^{\frac{1}{3}}}{2-2^{\frac{1}{3}}}$ *is a symmetric composition method for system* (1)*, based on the Strang splitting method* (4) *and it is of order 4.*

For a detailed study of the theory of splitting and composition methods, see literatures [12], [18], [12], [1].

2.2. **Phase-fitted property for separable systems.** In this subsection, we introduce a modified version of (5) given by

$$\Psi_h = \phi^{[1]}_{a_{s+1}(\nu)h} \circ \phi^{[2]}_{b_s(\nu)h} \circ \phi^{[1]}_{a_s(\nu)h} \circ \ldots \circ \phi^{[2]}_{b_2(\nu)h} \circ \phi^{[1]}_{a_2(\nu)h} \circ \phi^{[2]}_{b_1(\nu)h} \circ \phi^{[1]}_{a_1(\nu)h}, \tag{7}$$

where $a_1(\nu), b_1(\nu), \ldots, a_s(\nu), b_s(\nu), a_{s+1}(\nu)$ are functions of $\nu = \omega h$ satisfying some appropriate order conditions.

In what follows, we consider the scalar autonomous initial value problem of the form

$$\dot{y} = i\omega y, \qquad \omega > 0, \tag{8}$$

with the solution $y(t) = Ce^{i\omega t}$. The system (8) can be further reduced to a partitioned system of the form

$$\begin{cases} \dot{q} = \omega p, \\ \\ \dot{p} = -\omega q. \end{cases} \tag{9}$$

with the exact flow φ_t given by

$$\begin{pmatrix} q(t_n + h) \\ \\ p(t_n + h) \end{pmatrix} = R_0(\nu) \begin{pmatrix} q(t_n) \\ \\ p(t_n) \end{pmatrix}, \tag{10}$$

where

$$R_0(\nu) = \begin{pmatrix} \cos\nu & \sin\nu \\ \\ -\sin\nu & \cos\nu \end{pmatrix}, \qquad \nu = h\omega. \tag{11}$$

For the exact flow, the phase-fitting quantities of (10) are

$$P_a(\nu) := \arccos \frac{\mathrm{tr}(R_0(\nu))}{2\sqrt{\det(R_0(\nu))}} = \nu, \qquad D_a(\nu) := \sqrt{\det(M(\nu))} = 1. \tag{12}$$

To derive the phase-fitted splitting or composition methods which share the same phase-fitting properties as the exact flow (10), it necessary to split (8) in the form

$$y' = f^{[1]}(y) + f^{[2]}(y) \tag{13}$$

such that

$$f^{[1]} = \begin{pmatrix} \omega p \\ 0 \end{pmatrix}, \quad f^{[2]} = \begin{pmatrix} 0 \\ -\omega q \end{pmatrix}.$$

Obtaining the exact flows $\varphi_t^{[1]}$ and $\varphi_t^{[2]}$ and applying a specific splitting or composition method yields

$$\begin{pmatrix} q_{n+1} \\ p_{n+1} \end{pmatrix} = R(\nu) \begin{pmatrix} q_n \\ p_n \end{pmatrix}. \tag{14}$$

Definition 2.5 (Wu. et al. [23])**.** *The quantities*

$$P(\nu) := \nu - \arccos \frac{\mathrm{tr}(R(\nu))}{2\sqrt{\det(R(\nu))}} \qquad D(\nu) := 1 - \sqrt{\det(R(\nu))} \tag{15}$$

are called the dispersion (or phase lag) and the dissipation (or amplification factor error) of the splitting or composition method, respectively.

Definition 2.6. *The Phase-lag order is p if*

$$P(\nu) = C_{p+1}(\nu)\nu^{p+1} + \mathcal{O}(\nu^{p+3}),$$

and the dissipation order is q if

$$D(\nu) = C_{d+1}(\nu)\nu^{p+1} + \mathcal{O}(\nu^{p+3}).$$

The method is called zero-dispersive (phase-fitted) or zero-dissipative if $P(\nu) = 0$ and $Q(\nu) = 0$, respectively.

Theorem 2.1. *The Lie-Trotter (LT) splitting method is dispersive of order 3.*

Proof:

$$R^{LT}(\nu) = \begin{pmatrix} 1 & \nu \\ -\nu & 1-\nu^2 \end{pmatrix}. \tag{16}$$

Therefore

$$\begin{aligned} P^{LT}(\nu) &= \nu - \arccos\left(1 - \frac{\nu^2}{2}\right) \\ &= -\frac{\nu^4}{24} + \mathcal{O}(\nu^5). \end{aligned} \tag{17}$$

Theorem 2.2. *The Strang (ST) splitting method is dispersive of order 3.*

Proof:

$$R^{ST}(\nu) = \begin{pmatrix} 1 - \frac{\nu^2}{2} & \nu(1 - \frac{\nu^3}{4}) \\ -\nu & 1 - \frac{\nu^2}{2} \end{pmatrix}. \tag{18}$$

Therefore

$$P^{ST}(\nu) = -\frac{\nu^4}{24} + \mathcal{O}(\nu^5). \tag{19}$$

Theorem 2.3 (Zhang et al. [26])**.** *For the method* (7) *with* $\sum_{i=1}^{s+1} a_i = 1$*, the first to fourth order conditions are given as follows:*

- *Order one requires* $\sum_{i=1}^{s} b_i = 1 + \mathcal{O}(\nu^4)$
- *Order two requires in addition* $\sum_{i=1}^{s}(d_i^2 - (d_i - b_i)^2) = \mathcal{O}(\nu^3)$
- *Order three requires in addition* $\begin{cases} \sum_{i=1}^{s}(d_i^3 - (d_i - b_i)^3) = \mathcal{O}(\nu^2) \\ \sum_{i=1}^{s}(2b_i d_i - b_i^2)c_i = \mathcal{O}(\nu^2) \end{cases}$
- *Order four requires in addition* $\begin{cases} \sum_{i=1}^{s}(d_i^4 - (d_i - b_i)^4) = \mathcal{O}(\nu) \\ \sum_{i=1}^{s}(d_i^3 - (d_i - b_i)^3)c_i = \mathcal{O}(\nu) \\ \sum_{i=1}^{s}(d_i^2 - (d_i - b_i)^2)c_i^2 = \mathcal{O}(\nu) \end{cases}$

where $d_i = \sum_{j=1}^{i}(b_j - a_j)$ *and* $c_i = \sum_{j=1}^{i} a_j$*,* $i = 1, 2, \ldots, s$.

The phase-fitted splitting or composition methods are presented in the following section.

3. Construction of Phase-fitted splitting and composition methods

3.1. **Phase-fitted Lie-Trotter method.** The modified Lie-Trotter splitting method is given by

$$\Phi_h^{LT}(\nu) = \varphi_{b(\nu)h}^{[2]} \circ \varphi_{a(\nu)h}^{[1]}, \tag{20}$$

where $a(\nu)$, $b(\nu)$ are functions of $\nu = \omega h$. Applying the splitting method to (9), we obtain

$$\begin{aligned}\begin{pmatrix} p_{n+1} \\ \\ q_{n+1} \end{pmatrix} &= \Phi_h^{LT}(\nu) \begin{pmatrix} q_n \\ \\ p_n \end{pmatrix} = \left(\varphi^{[2]}_{b(\nu)h} \circ \varphi^{[1]}_{a(\nu)h}\right) \begin{pmatrix} q_n \\ \\ p_n \end{pmatrix} \\ &= \varphi^{[2]}_{b(\nu)h} \begin{pmatrix} q_n + a(\nu)\nu p_n \\ \\ p_n \end{pmatrix} = \begin{pmatrix} q_n + a(\nu)\nu p_n \\ \\ p_n - b(\nu)\nu(q_n + a(\nu)\nu p_n) \end{pmatrix} \\ &= \begin{pmatrix} 1 & a(\nu)\nu \\ \\ -b(\nu)\nu & 1 - a(\nu)b(\nu)\nu^2 \end{pmatrix} \begin{pmatrix} q_n \\ \\ p_n \end{pmatrix},\end{aligned} \tag{21}$$

$$\Phi_h^{LT}(\nu) = \begin{pmatrix} 1 & a(\nu)\nu \\ \\ -b(\nu)\nu & 1 - a(\nu)b(\nu)\nu^2 \end{pmatrix}. \tag{22}$$

$$\det\left(\Phi_h^{LT}(\nu)\right) = 1, \tag{23}$$

For the Lie-Trotter splitting method to be phase-fitted, we impose the following:

$$\operatorname{tr}\left(\Phi_h^{LT}(\nu)\right) = 2\cos(\nu), \tag{24}$$

which implies that

$$a(\nu)b(\nu) = \frac{2 - 2\cos(\nu)}{\nu^2} = \frac{4\sin^2(\nu/2)}{\nu^2}. \tag{25}$$

Solving (32) and $a(\nu) = b(\nu)$, we obtain

$$a(\nu) = b(\nu) = \frac{2\sin(\nu/2)}{\nu}.$$

The first order condition is verified as follows. Suppose $y_0 = y(t_0)$, as $h \to 0$,

$$\varphi_h^{[1]}(y_0) = y_0 + h\frac{\partial \varphi_h^{[1]}(y_0)}{\partial h}\Big|_{h=0} + \mathcal{O}(h^2) = y_0 + hf^{[1]}(y_0) + \mathcal{O}(h^2),$$

$$\begin{aligned}
(\varphi_h^{[2]} \circ \varphi_h^{[1]})(y_0) &= \varphi_h^{[2]}\big(\varphi_h^{[1]}(y_0)\big) \\
&= \varphi_h^{[2]}\big(y_0 + hf^{[1]}(y_0) + \mathcal{O}(h^2)\big) \\
&= \big(y_0 + hf^{[1]}(y_0) + \mathcal{O}(h^2)\big) \\
&\quad + hf^{[2]}\big(y_0 + hf^{[1]}(y_0) + \mathcal{O}(h^2)\big) + \mathcal{O}(h^2) \\
&= y_0 + hf^{[1]}(y_0) \\
&\quad + h\big(f^{[2]}(y_0) + h\frac{\mathrm{d}f^{[2]}}{\mathrm{d}y}(y_0)f^{[1]}(y_0)\mathcal{O}(h^2)\big) \\
&\quad + \mathcal{O}(h^2) \\
&= y_0 + hf^{[1]}(y_0) + hf^{[2]}(y_0) + \mathcal{O}(h^2) \\
&= y_0 + hf(y_0) + \mathcal{O}(h^2) \\
&= \varphi_h(y_0) + \mathcal{O}(h^2).
\end{aligned}$$

Thus from the result, we define the following:

Definition 3.1. *The phase-fitted Lie-Trotter (PLT) method defined by*

$$\begin{aligned}
\Psi_h^{[PLT]} &= \phi_{b(\nu)h}^{[2]} \circ \phi_{a(\nu)h}^{[1]} \\
&= \phi_{a(\nu)h}^{[1]} \circ \phi_{b(\nu)h}^{[2]}
\end{aligned} \tag{26}$$

with

$$a(\nu) = b(\nu) = \frac{2\sin(\nu/2)}{\nu} = 1 - \frac{1}{24}\nu^2 + \frac{1}{1920}\nu^4 + \mathcal{O}(\nu^6) \tag{27}$$

is the simplest phase-fitted splitting method for system (8) *and it is of order 1.*

3.2. **Phase-fitted Strang splitting method.** Similarly, we apply the technique for the strang splitting as follows:

$$\Phi_h^{ST}(\nu) = \varphi_{a(\nu)h/2}^{[2]} \circ \varphi_{b(\nu)h}^{[2]} \circ \varphi_{c(\nu)h/2}^{[1]}, \tag{28}$$

where $a(\nu)$, $b(\nu)$ and $c(\nu)$ are functions of $\nu = \omega h$. The splitting method (28) is applied to (9) to obtain

$$\begin{aligned}
\begin{pmatrix} p_{n+1} \\ q_{n+1} \end{pmatrix} &= \Phi_h^{ST}(\nu) \begin{pmatrix} q_n \\ p_n \end{pmatrix} = \big(\varphi_{a(\nu)h/2}^{[2]} \circ \varphi_{b(\nu)h}^{[2]} \circ \varphi_{c(\nu)h/2}^{[1]}\big) \begin{pmatrix} q_n \\ p_n \end{pmatrix} \\
&= \begin{pmatrix} 1 - b(\nu)c(\nu)\nu^2 & -a(\nu)b(\nu)c(\nu) + (a(\nu) + c(\nu))\nu \\ -b(\nu)\nu & 1 - a(\nu)b(\nu)\nu^2 \end{pmatrix} \begin{pmatrix} q_n \\ p_n \end{pmatrix},
\end{aligned} \tag{29}$$

$$\Phi_h^{ST}(\nu) = \begin{pmatrix} 1 - b(\nu)c(\nu)\nu^2 & -a(\nu)b(\nu)c(\nu) + (a(\nu) + c(\nu))\nu \\ -b(\nu)\nu & 1 - a(\nu)b(\nu)\nu^2 \end{pmatrix}. \tag{30}$$

$$\det\big(\Phi_h^{ST}(\nu)\big) = 1, \tag{31}$$

For Strang splitting method to be phase-fitted, we impose the following:

$$\operatorname{tr}\big(\Phi_h^{ST}(\nu)\big) = 2 - b(\nu)(a(\nu) + c(\nu))\nu^2 = 2\cos(\nu), \tag{32}$$

and from (30), observe that

$$\frac{1}{2}(a(\nu) + c(\nu))\nu - \frac{1}{4}a(\nu)b(\nu)c(\nu)\nu^3 = \sin(\nu)$$

and if we impose the condition that $a(\nu) = c(\nu)$, we solve the equations for $a(\nu)$, $b(\nu)$ and $c(\nu)$ to obtain

$$a(\nu) = c(\nu) = \frac{2\sin\nu}{\nu(\cos\nu + 1)}$$
$$b(\nu) = \frac{\sin\nu}{\nu}$$

Hence, we define the following:

Definition 3.2. *The phase-fitted Strang (PStrang) splitting method defined by*

$$\Psi_h^{[PST]} = \phi^{[1]}_{a(\nu)h/2} \circ \phi^{[2]}_{b(\nu)h} \circ \phi^{[1]}_{c(\nu)h/2} \tag{33}$$

with

$$\begin{aligned} a(\nu) = c(\nu) = \frac{2\sin\nu}{\nu(\cos\nu + 1)} &= 1 + \frac{1}{12}\nu^2 + \frac{1}{120}\nu^4 + \mathcal{O}(\nu^6) \\ b(\nu) = \frac{\sin\nu}{\nu} &= 1 - \frac{1}{6}\nu^2 + \frac{1}{120}\nu^4 + \mathcal{O}(\nu^6) \end{aligned} \tag{34}$$

is a symmetric phase-fitted splitting method for system (8) *and it is of order 2.*

3.3. **Phase-fitted Triple-Jump composition method.** The idea for the derivation for the Trip-Jump composition follows similarly from the derivation of the Lie-Trotter and Strang Splitting methods. However, to obtain the result we use the strang splitting method derived in subsection 3.2 as the base method.

Definition 3.3. *The phase-fitted Triple Jump (PTJ) composition method defined by*

$$\Psi_h^{[PTJ]} = \Psi^{ST}_{\gamma_3(\nu)h} \circ \Psi^{ST}_{\gamma_2(\nu)h} \circ \Psi^{ST}_{\gamma_1(\nu)h} \tag{35}$$

where

$$\begin{aligned}\gamma_1(\nu) = \gamma_3(\nu) = \; & \frac{1}{2-2^{1/3}} - \left(\tfrac{1}{108} + \tfrac{1}{108}2^{2/3} + \tfrac{1}{54}2^{1/3}\right)\nu^2 \\ & + \left(\tfrac{5}{216} + \tfrac{1537}{90720}2^{2/3} + \tfrac{1067}{45360}2^{1/3}\right)\nu^4 + \mathcal{O}(\nu^6) \\ \gamma_2(\nu) = \; & -\frac{2^{1/3}}{2-2^{1/3}} + \left(\tfrac{1}{54} + \tfrac{1}{54}2^{2/3} + \tfrac{1}{27}2^{1/3}\right)\nu^2 \\ & - \left(\tfrac{31}{1080} + \tfrac{253}{11340}2^{2/3} + \tfrac{94}{2835}2^{1/3}\right)\nu^4 + \mathcal{O}(\nu^6)\end{aligned}$$

is a symmetric composition method for system (8)*, based on splitting method* (4) *and it is of order 4.*

Remark 3.1. *The splitting and composition methods presented in subsection 3 reduce to the corresponding standard splitting and composition methods presented in subsection 2.1 as* $\nu \to 0$*. For a theory of the higher order conditions of splitting and composition methods, see Hairer* [12]*, Blanes* [1]*.*

4. Numerical modelling and efficiency of some biological oscillators

In this section, we apply the methods to some biological oscillators that have appeared in the literature. It is instructive to also note that for models which do not have equilibrium at the origin, a suitable transformation is employed to address that problem (see [25]).

4.1. **Lotka Volterra Model. Lotka** [14]**.** Consider the mutual interactions of between two species, the prey X_1 and the predator X_2. Let $X_1(t)$ and $n_2(t)$ denote the population of X_1 and X_2, respectively. The number n_A of the food items A is assumed to be unchanged by consumption during the time scale of interest, (see [12]). The Lotka Volterra problem which models this process is given by

$$\dot{X}_1 = (k_2X_2 - k_1n_A)X_1, \quad \dot{X}_2 = (k_3 - k_2X_1)X_2. \tag{36}$$

The vector field of the equation (36) is split into

$$f^{[1]}(y) = \begin{pmatrix} (k_2 X_2 - k_1 n_A) X_1 \\ \\ 0 \end{pmatrix}, \qquad f^{[2]}(y) = \begin{pmatrix} 0 \\ \\ (k_3 - k_2 X_1) X_2 \end{pmatrix} \tag{37}$$

The values for the parameters used to solve the problem are taken as follows:

$$k_1 = k_2 = k_3 = 1, \quad n_A = 2.$$

The exact solution of $y' = f^{[1]}(y)$ on $[0, h]$ is

$$X_1(h) = \exp^{h(X_2(0)-2)} X_1(0), \qquad X_2(h) = X_2(0). \tag{38}$$

The exact solution of $y' = f^{[2]}(y)$ on $[0, h]$ is

$$X_1(0) = X_1(0), \qquad X_2(0) = \exp^{h(1-X_1(0))} X_2(0). \tag{39}$$

Combining these two flows (38) and (39) using (5) gives the desired method. The system is integrated for initial values $\{X_1(0) = 2, \quad X_2(0) = 2\}$ on the interval $[0, 100]$ with stepsizes $h = 1/2^j, j = 2, 3, 4, 5$ and the fitting frequency was taken as $\omega = \frac{2\pi}{4.62}$. The efficiency curves are presented in Fig. 1.

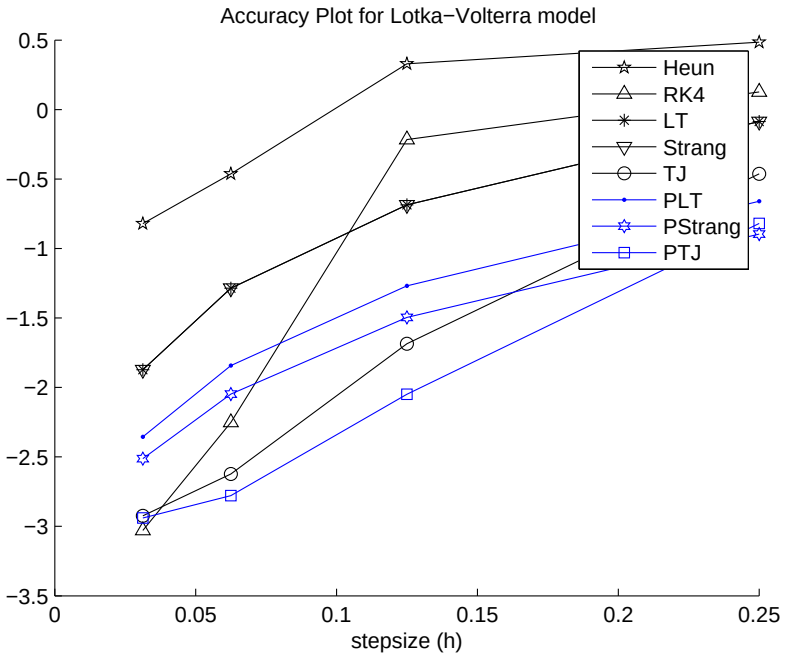

FIGURE 1. Accuracy plot for Lotka-Volterra model

4.2. **Genetic regulatory systems.** Proteins are essential functional units in a cell system. Most of the cell decisions in response to environmental conditions, developmental stage of the cell, stress are determined by protein expression levels. With principles of dogma of molecular biology, systems biologists have developed many models which describes patterns from the dynamical interactions between the elements in a network (see [3]). In what follows, we briefly introduce some standard models for gene regulation mechanisms.

mRNA-protein networks
An N-gene regulated network can be described by the following system of ordinary differential equations (see [16]):

$$\begin{aligned} \dot{r}(t) &= -\Gamma r(t) + F(p(t)) \\ \dot{p}(t) &= -Mp(t) + Kr(t) \end{aligned} \tag{40}$$

where $r(t) = (r_1(t), \ldots, r_N(t))$ and $p(t) = (p_1(t), p_2(t), \ldots, p_N(t))$ are N-dimensional vectors representing the concentrations of mRNAs and proteins at time t, respectively, $F(p(t)) = (F_1(p_1(t)), \ldots, F_N(p(t)))$, $\Gamma = \text{diag}(\gamma_1, \ldots, \gamma_N)$, $M = \text{diag}(\mu_1, \ldots, \mu_N)$ and $K = (\kappa_1, \ldots, \kappa_N)$ are diagonal matrices. The variables r and p are the concentrations of mRNA and the corresponding protein respectively; Γ and M, positive constants, are the degradation rates of mRNA and protein, respectively, K is a positive constant; and $F(p(t))$, the regulatory function determining the cooperativity of two genes.

A natural decomposition of (40) is of the form:

$$f^{[1]}(z) = \begin{pmatrix} -\Gamma & 0 \\ K & -M \end{pmatrix} z, \qquad f^{[2]}(z) = \begin{pmatrix} F(p(t)) \\ 0 \end{pmatrix}. \tag{41}$$

The genetic regulatory system is simulated with the approach of You et al. [25]. We use the transformation $x(t) = r(t) - r^*$, $y(t) = p(t) - p^*$ to translate the steady state of the system to the origin and (40) becomes

$$\begin{aligned} \dot{x}(t) &= -\Gamma x(t) + F'(p^*)y(t) + G(y(t)) \\ \dot{y}(t) &= Kx(t) - My(t) \end{aligned} \tag{42}$$

where $F'(p^*)$ is the jacobian matrix of $F(p)$ at the point p^* and $G(y(t)) = F(p^* + y(t) - F'(p^*)y(t) - F(p*)$. Therefore, we have the

vector field split as

$$f^{[1]}(z) = \begin{pmatrix} -\Gamma & F'(p*) \\ K & -M \end{pmatrix} z, \qquad f^{[2]}(z) = \begin{pmatrix} G(y(t)) \\ 0 \end{pmatrix}. \quad (43)$$

4.2.1. *One-gene auto-repression model. Xiao and Cao* [22]. We consider the one-gene regulatory network for $N = 1$ in (40). The model was simulated with the parameters given in You et al. [25],

$$\gamma = 1, \quad \alpha = 3, \quad \mu = 1.5, \quad \kappa = 5, \quad \theta = 1,$$

using stepsizes $h = 1/2^j, j = 0, 1, 2, 3$ and the fitting frequency was taken as $\omega = \frac{\sqrt{935}}{20}$. The efficiency curves are presented in Fig. 2.

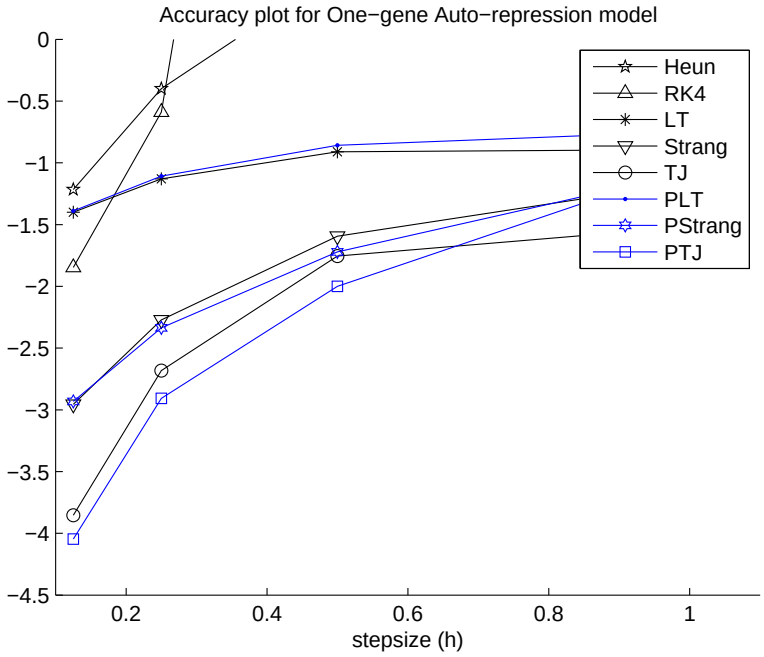

FIGURE 2. Accuracy plot for one-gene auto-repression model

4.2.2. *The repressilator. Elowitz and Leibler* [5]. Here, we simulate the repressilator model given in Elowitz and Leibler [5] for parameters

$$\alpha = 216.404, \quad \alpha_0 = 0.2164, \quad \beta = 0.2, \quad n = 2.$$

We solve the system on the interval $0 \leq t \leq 100$ using stepsizes $h = \{\frac{1}{5}, \frac{1}{10}, \frac{1}{20}, \frac{1}{50}\}$ and the fitting frequency was taken as $\omega = 0.51$. The efficiency curves is presented in Fig. 3.

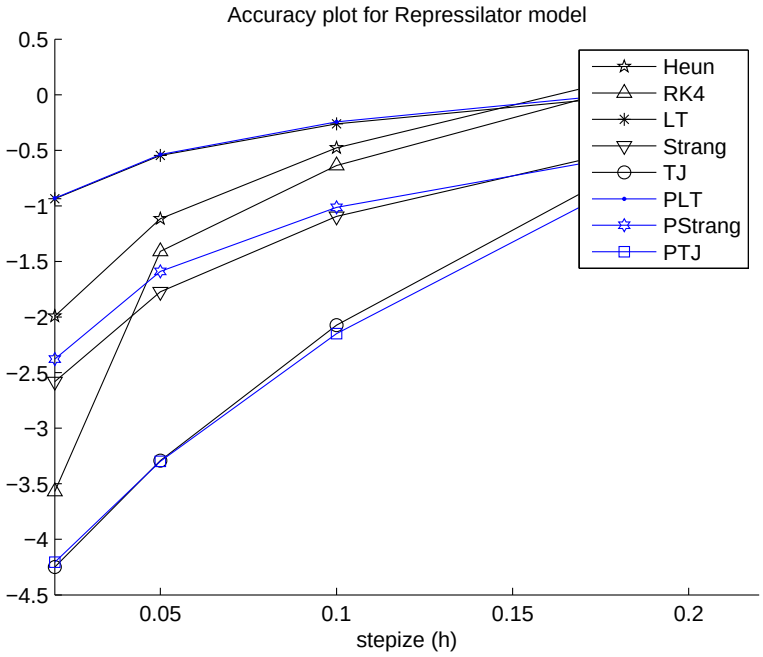

FIGURE 3. Efficiency curve for repressilator model.

4.3. **Goodwin model. Goodwin** [10]**, Gonze and Abou-Jaoudé** [9]**.** Lastly, consider the Goodwin model, a simple and widely used model for molecular oscillations (and especially circadian) for delayed negative feedback loops. The model is given by

$$\begin{aligned} \dot{X} &= k_1 F(Z) - k_2 X \\ \dot{Y} &= k_3 X - k_4 Y \\ \dot{Z} &= k_5 Y - k_6 Z. \end{aligned} \tag{44}$$

The variables X, Y and Z can be interpreted as the concentration of a given gene mRNA, the corresponding protein, and a transcriptional inhibitor, respectively. The feedback loop is achieved by the repression exerted by the inhibitor to the mRNA synthesis and is described by a Hill function:

$$F(Z) = \frac{K^n}{K^n + Z^n}.$$

In fact. Griffith [11] demonstrated that limit-cycle oscillations can be obtained only if the Hill coefficients n is larger than 8. For $n \leq 8$, the model displays damped oscillations.

For parameters

$$k_1 = k_3 = k_5 = 1, \quad k_2 = k_4 = k_4 = 0.1, \quad k = 1, \quad n = 10.,$$

we solve the system on the interval $0 \leq t \leq 100$ using stepsizes $h = 1/2^j, j = 0, 1, 2, 3$ and the fitting frequency was taken as $\omega = \frac{2\pi}{40}$. The efficiency curves is presented in Fig. 4.

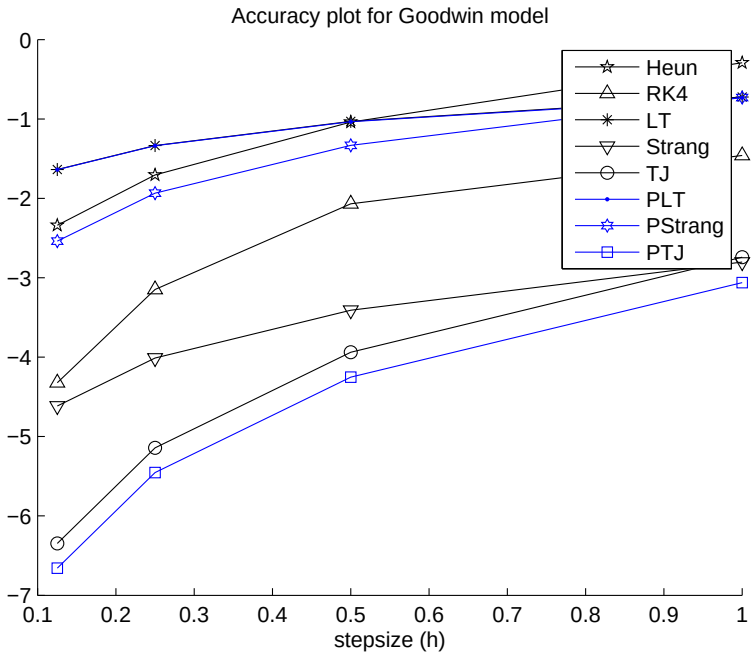

FIGURE 4. Efficiency curve for Goodwin model.

In Fig. 1 of the accuracy plot on the Lotka-Volterra model (36), Heun's method yields the least accurate results, while the numerical results of the strang and the Lie-Trotter splitting methods coincide. The phase-fitted Lie-Trotter and the Strang splitting methods, though of order 2 yield more accurate results than the Runge-Kutta methods for larger step sizes. But the Phase-fitted triple jump method yields the most accurate result for the model (36). In the one-gene auto-repression model, Fig. 2 shows that all the splitting and composition methods performs better than the

Heun and Runge-Kutta method. In fact, for larger stepsizes, the results obtained blow out completely. But the result shows that, the Phase-fitted splitting and composition methods yields more accurate results than the standard splitting and composition methods. Unfortunately, for the repressilator model, Fig. 3 shows that the effect of the phase-fitting properties is not pronounced as the standard splitting and composition methods coincide exactly as their phase-fitting counterparts. But, the Strang splitting methods outperforms the Runge-Kutta methods for larger stepsizes. In this problem, the Triple-Jump methods yield the most accurate results. Lastly, in Fig. 4 for the Goodwin model (44), the phase fitted triple jump yields the most accurate results.

5. Conclusion

In this paper we have discussed the derivation of phase-fitted splitting and composition methods for the numerical simulation of biological oscillators. The derivation of such methods has been done using the phase-fitting properties of the harmonic oscillators. Three practical methods namely, phase-fitted Lie-Trotter, phase-fitted Strang and phase-fitted triple jump splitting and composition methods were derived. Numerical experiments were reported for the simulation of the Lotka-Volterra model, genetic regulatory systems and the goodwin model. We observed that the new phase-fitted methods gives a more satisfactory result than the classical methods in the MATLAB ODE solvers. We note that the coefficients of the methods depends on the fitting frequency ω which can be estimated, although the fitting frequency is usually unknown, we refer the reader to Vigo-Aguiar and Ramos [20]. As a future research, we may extend the concept of phase-fitting by combining a case where a numerical methods solved a vector field, while the exact solution of the other vector field can be evaluated.

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