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# Nested Implicit Runge-Kutta Method for Simulating Cardiac Cell Models

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***Abstract.*** The simulation of the electrical activity in cardiac cells is known to require a large number of stiff ordinary differential equations (ODEs). This system of ODEs has been continually developed to provide an increasingly detailed description of cellular physiology. An efficient simulation is needed to contribute significantly in the numerical solution of two and three dimensional electrical activity of the myocardium. In this paper, we will be exploring the usage and efficiency of Gauss-type nested implicit Runge-Kutta technique to solve cardiac cell models. The method is of order 4 and has only explicit internal stage that leads to practical implementations. Comparison with other numerical methods employed in the context of electrocardiology will be presented.

*Keywords:* Nested Implicit Runge-Kutta, cardiac cell models, transmembrane potential, numerical methods for stiff ordinary differential equations.

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## 1. Introduction

Due to the enormous and often prohibitive cost of developing new drugs for treatment of heart conditions, the usage of mathematical models in the early development stages is increasing. This can be attributable to the fact that accurate models can decrease the amount of physical trials needed and therefore greatly decrease the cost. Current electrophysiological models vary greatly in both complexity and accuracy. These models often involve a set of partial differential equation coupled with a large number of stiff ODEs (see [Sundnes et al., 2005] and [Vigmond et al., 2002]). These ODEs attempt to simulate the flow of ionic currents present in the cellular level of the heart which can be used to predict the resulting electrical activity. However, the stiffness has the effect of decreasing the speed of the solving process since the stability is often the limiting factor for the solution and therefore explicit and semi-implicit schemes are not suitable for simulating cardiac cell models. The reader is referred to [Hairer and Wanner, 1992], [Shampine, 1994] and [Hundsdorfer and Verwer, 2003], for more details about stability restriction of explicit and semi-implicit methods.

One way to overcome the stiffness difficulties is the use of stable numerical techniques and therefore implicit schemes are nearly always necessary for obtaining efficient results. A wide range of implicit methods have been developed for stiff ODE systems. These are normally difficult to implement in a robust manner, however, a special class of implicit methods called Singly diagonally implicit Runge-Kutta methods (SDIRK) is often used to solve stiff ODEs (see [Hairer and Wanner, 1992]). In the context of electrocardiology, a third order method of this class with an explicit first stage (ESDIRK3) has been used for Winslow model in [Sundnes et al., 2001]. Other numerical methods have been also explored for cardiac cell models. In [Spiteri and Dean, 2008], an implicit-explicit Runge-Kutta method (IMEX-RK) was used in order to decrease the added effort required by the implicit methods by using a splitting technique. In this contribution, the performance of several numerical methods, including the Rush-Larsen method [Rush and Larsen, 1978], for approximating solutions to ODEs found in 4 popular mathematical models of cardiac electrical activity was instigated and compared to IMEX-RK method. Furthermore, in [Ying et al., 2008] the backwards Euler method as well as a second-order one-step two-stage composite backward differentiation formula (C-BDF2) was implemented using fixed time step size and deemed simple to implement as well as giving increased efficiency. Additionally, the non standard finite difference methods (NSFD), which are drastically more efficient than the forward Euler method, were investigated in [Maclachlan et al., 2007].

In this paper, we will be exploring the usage and efficiency of a Gauss-type nested implicit Runge-Kutta (NIRK) technique in the application of cardiac cell models. This method has been introduced in

[Kulikov and Shindin, 2009]. The method is A-stable, stiffly accurate and has a cheap practical implementation by virtue of its explicit internal stages. The stability and low computational effort make NIRK ideal for implementation of electrophysiological models which require both. Numerical simulations have been performed using two cell models, the Luo-Rudy model [Luo and Rudy, 1991] of guinea-pig ventricular tissue that consists of 8 non-linear ODEs and takes into consideration 6 ionic currents, and the Hund and Rudy model [Hund and Rudy, 2004] that is used to simulate canine ventricular action potentials and consists of a system of 29 ordinary differential equations. For both models, a comparison between the proposed numerical method, ESDIRK3, and SDIRK4 will be presented.

The organization of this paper is as follows. In Section II, the Gauss-type nested implicit Runge-Kutta is introduced and the singly diagonally implicit Runge-Kutta method is briefly recalled. Section III is devoted to numerical results showing the performance of the proposed method using the first Luo-Rudy model and Hund and Rudy canine ventricular model. Finally, section IV provides a summary of the proposed technique.

## 2. Numerical Techniques

As mentioned, modeling the action potential of a single cell involves a stiff system of ODEs of the form:

$$\frac{dV_m}{dt} = -\frac{1}{C_m}(I_{ion} + I_s). \tag{1}$$

where $V_m$ is transmembrane potential, $C_m$ is the membrane capacitance, $I_{st}$ is the stimulus and $I_{ion}$ is the total transmembrane ionic current. In the Luo-Rudy model, we have 7 additional ODEs and in the Hund and Rudy model we have 28 additional ODEs which are non-linear. Full details and complete expressions of the ODE equations for Luo-Rudy model and Hund and Rudy model can be found in [Luo and Rudy, 1991], and [Hund and Rudy, 2004] respectively. Thus, this paper will focus on numerical techniques to solve the following system

$$\frac{dy}{dt} = f(t, y(t)), \quad t \in [t_0, t_f], \quad y(t_0) = y^0. \tag{2}$$

Where $t_0$ and $t_f$ are initial and final time respectively and $y^0$ is the initial solution.

### 2.1. Singly Diagonally Implicit Runge-Kutta

SDIRK methods are often considered efficient when solving stiff system of the form (2) (see [Hairer and Wanner, 1992]). An SDIRK4 method is employed in this paper, it has 5-stages, L-stability and is of order 4. The Butcher tableau defining this technique is presented in table 1.

***Table 1.*** *Tables Butcher tableau of SDIRK 4*

$$\begin{array}{c|ccccc}
c_1 & \gamma & & & & \\
c_2 & a_{21} & \gamma & & & \\
c_3 & a_{31} & a_{32} & \gamma & & \\
c_4 & a_{41} & a_{42} & a_{43} & \gamma & \\
c_5 & a_{51} & a_{52} & a_{53} & a_{54} & \gamma \\
\hline
 & b_1 & b_2 & b_3 & b_4 & b_5
\end{array}$$

The coefficients $a_{ij}$, $b_i$ and $\gamma$ are provided in [Hairer and Wanner, 1992] on page 100.

A third order method of this class with explicit first stage (ESDIRK3) is also employed in this paper. This method has been used in the context of electrocardiology in [Sundnes et al., 2001] and the reader is referred to this paper for more details about ESDIRK3.

### 2.2. Nested Implicit Runge-Kutta

All one-step methods for solving ODEs system of the form (2) consider

$$y_{k+1} = y_k + h\phi(t_k, y_k, t_{k+1}, y_{k+1}, h)$$

where $h$ is the time step size. The Nested Implicit Runge-Kutta (NIRK) of order 4 formula considers, at each subinterval $[t_k, t_{k+1}]$, a two-point quadrature formula of the form

$$y_{k+1} = y_k + h(b_1 f(t_k + c_1 h, x_1) + b_2 f(t_k + c_2 h, x_2)), \tag{3}$$

where

$$x_1 = a_{11} y_k + a_{12} y_{k+1} + h(d_{11} f(t_k, y_k) + d_{12} f(t_{k+1}, y_{k+1})),$$

and

$$x_2 = a_{21} y_k + a_{22} y_{k+1} + h(d_{21} f(t_k, y_k) + d_{22} f(t_{k+1}, y_{k+1})).$$

The coefficients $a_{ij}$, $b_i$, $c_i$, and $d_{ij}$ for $i, j = 1,2$ are fixed and given by

$$a_{11} = \theta, \quad a_{12} = 1-\theta, \quad a_{21} = 1-\theta, \text{and } a_{22} = \theta.$$

$$b_1 = \frac{1}{2}, \quad b_2 = \frac{1}{2}, \quad c_1 = \frac{3-\sqrt{3}}{6}, \text{and } c_2 = \frac{3+\sqrt{3}}{6}.$$

and

$$d_{11} = \frac{6\theta - 2 - \sqrt{3}}{12}, \quad d_{12} = \frac{6\theta - 4 - \sqrt{3}}{12},$$

$$d_{21} = \frac{-6\theta + 4 + \sqrt{3}}{12}, \text{and } d_{22} = \frac{-6\theta + 2 + \sqrt{3}}{12}.$$

where $\theta = \frac{1}{2} + \frac{2\sqrt{3}}{9}$ is employed for all numerical results. This method is of order 4 and $A$-stable. For theoretical details the reader is referred to [Kulikov and Shindin, 2009]. It is clear that NIRK methods (3) possess explicit internal stages that are easily reduced to a single nonlinear equation with respect to $y_{k+1}$ at time step $t_{k+1}$. This nonlinear equation is of the same dimension as the cell model, which make this technique very attractive for solving the stiff system of ODEs involved in electrocardiology. Since NIRK is a Runge-Kutta scheme, its Butcher tableau can be given by

***Table 2.*** *Tables Butcher tableau of SDIRK 4*

| | | | | |
|---|---|---|---|---|
| $0$ | $0$ | $0$ | $0$ | $0$ |
| $c_1$ | $\frac{6(c_1+\theta)-5}{12}$ | $\frac{1-\theta}{2}$ | $\frac{1-\theta}{2}$ | $\frac{6(c_1+\theta)-7}{12}$ |
| $1-c_1$ | $\frac{7-6(c_1+\theta)}{12}$ | $\frac{\theta}{2}$ | $\frac{\theta}{2}$ | $\frac{5-6(c_1+\theta)}{12}$ |
| $1$ | $0$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $0$ |
| | $0$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $0$ |

A Newton method is used to solve the non-linear systems. However, the full Jacobian of method (3) can be replaced with a simplified one, see [Kulikov and Shindin, 2006], that involves, after starting with an initial value, iterations of the form

$$(I - \frac{h}{4} J)^2 \Delta y_{k+1}^l = y_k + h(b_1 f(t_k + c_1 h, x_1^l) + b_2 f(t_k + c_2 h, x_2^l)),$$

where $\Delta y_{k+1}^l = y_{k+1}^l - y_{k+1}^l$ and $J$ is the jacobian of the function $f$ in the system (2). Recomputing the Jacobian at each time step can be expensive and therefore, if the time step is sufficiently small, it is instead approximated by

$$J = \frac{\partial f}{\partial y}(t_k, y_{k+1}^0).$$

A similar technique is used to solve the nonlinear systems in the SDIRK4 and ESDIRK3 methods. This feature leads to a cheap practical implementation for both numerical methods employed in this paper.

## 3. Numerical Results

In this section, the performance of NIRK method described in the previous section will be presented. Since there is no exact solution for cardiac cell models, all numerical results will be compared to a reference solution. This solution is obtained by using the Matlab solver ode45 that is based on the explicit Dormand-Prince method of order 5 (see [Dormand and Prince, 1980] and [Hairer et al., 1993]). Very small absolute and relative tolerances are used for ode45 to generate a reference solution with more than 200000 time steps.

To assess the reliability and accuracy of the suggested technique, all the quantitative results will be presented using $L^{\infty}-$norm, noted $e_{\text{global}}$, and $L^2-$norm, noted $e_2$, of the error between the numerical and reference solution. The form of these norms is

$$e_{\text{global}} = \max |V_m - V_{\text{ref}}|,$$

and

$$e_2 = \sqrt{\int_{t_0}^{t_f} |V_m - V_{\text{ref}}|^2},$$

where the difference $|V_m - V_{\text{ref}}|$ is evaluated at $N$ equally spaced points within the interval $[t_0, t_f]$. A choice of $N = 200$ is used for all numerical results.

For both the Luo–Rudy I and the Hund and Rudy models, the initial values used for the transmembrane potential $V_m$ are around the threshold value to produce the explicit stimulus current. Two different time intervals are used, [0,450]ms for Luo–Rudy model, and [0,200]ms for Hund and Rudy model which correspond to one cycle.

In table 3, different values of the two norms $e_{\text{global}}$, and $e_2$ for the Luo-Rudy model are presented. These norms are calculated for different fixed time steps $h$ to show the evolution of the error according to the time step. For the Hund and Rudy model, similar numerical results are produced and the performance of NIRK4 is reported in table 4.

***Table 3.*** *Illustration of the error with different value of* $h$

| LuoRudy I: Step-Size $h = 0.1$ | | | |
|---|---|---|---|
| Methods | global error | $e_2$ error | CPU |
| ESDIRK3 | 2.81e-1 | 6.28e-1 | 2.33e0 |
| Sdirk4 | 5.36e-2 | 1.29e-1 | 2.78e0 |
| NIRK4 | 3.14e-2 | 7.34e-2 | 2.72e0 |
| LuoRudy I: Step-Size $h = 0.05$ | | | |
| Methods | global error | $e_2$ error | CPU |
| Esdirk3 | 5.04e-3 | 1.24e-2 | 4.34e0 |
| Sdirk4 | 2.63e-3 | 6.96e-3 | 5.39e0 |
| NIRK4 | 8.10e-4 | 1.12e-3 | 5.01e0 |
| LuoRudy I: Step-Size $h = 0.025$ | | | |
| Methods | global error | $e_2$ error | CPU |
| Esdirk 3 | 4.83e-4 | 1.85e-3 | 0.86e1 |
| Sdirk4 | 1.71e-4 | 4.16e-4 | 1.06e1 |
| NIRK4 | 2.14e-5 | 4.66e-5 | 0.92e1 |

***Table 4.*** *Illustration of the error with different value of* $h$

| Hund and Rudy: Step-Size $h = 0.1$ | | | |
|---|---|---|---|
| Methods | global error | $e_2$ error | CPU |
| Esdirk3 | 1.25e-1 | 1.06e-1 | 7.44e1 |
| Sdirk4 | 1.73e-2 | 8.95e-2 | 8.22e1 |
| NIRK4 | 1.04e-2 | 4.68e-2 | 7.76e1 |
| Hund and Rudy: Step-Size $h = 0.05$ | | | |
| Methods | global error | $e_2$ error | CPU |
| Esdirk3 | 1.69e-1 | 6.37e-2 | 1.47e2 |
| Sdirk4 | 1.15e-3 | 5.94e-3 | 1.61e2 |
| NIRK4 | 1.03e-3 | 1.06e-3 | 1.52e2 |
| Hund and Rudy: Step-Size $h = 0.025$ | | | |
| Methods | global error | $e_2$ error | CPU |
| Esdirk3 | 2.16e-3 | 1.11e-2 | 2.93e2 |
| Sdirk4 | 8.55e-5 | 4.43e-4 | 3.19e2 |
| NIRK4 | 7.01e-5 | 7.76e-5 | 2.99e2 |

As can be clearly seen from the above tables the performance of NIRK4 is superior to that of the commonly used, ESDIRK3 and SDIRK4 methods. In these numerical tests, we can see that at every step-size and with both models we gain an advantage in accuracy by obtaining less global and $e_2$ errors. However, unlike most numerical solvers, this increase in accuracy does not come at the expense of computational time; in all the numerical tests done in this study, NIRK4 took less time to solve the models than ESDIRK3 and SDIRK4 when comparing solutions with the same level of error. Therefore, with the increase in both accuracy and decrease in computational time, we have seen that NIRK4 is an adequate method when solving a stiff system of ODEs involved in electrophysiological cardiac cell models.

When the ODEs are solved as part of an operator splitting algorithm for solving the bidomain or monodomain models, the global accuracy will be limited by the splitting error and it is therefore not recommended to apply ODE solvers with high order of accuracy. However, NIRK4 can present an advantage in the computational time as can be seen when compared to ESDIRK 3 that was employed in [Sundnes et al., 2001] for simulating the bidomain model.

## 4. Conclusions

In this paper, a nested implicit Runge-Kutta method of order 4 was presented in the context of electrocardiology. The efficiency of the NIRK method was presented using two cell models, the Luo–Rudy I and the Hund and Rudy models. A comparison with ESDIRK3, and SDIRK4 methods, that are commonly employed for solving ODEs involved in modeling cardiac cell activity, was also presented showing clearly the advantage of the proposed technique. Overall, the stability and the explicit internal stage of the NIRK method lead to cheap implementation and accurate numerical solutions in electrocardiology.

Only fixed time steps were used in this paper. NIRK is an embedded Runge-Kutta method and therefore variable time step sizes can be implemented. A comparison with other implicit embedded Runge-Kutta methods used for cardiac cell models is necessary to fully establish the potential and performance of the proposed method.

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