

Emulation of Biological Cells

Jerry Jacob¹, Nitish Patel¹, Sucheta Sehgal¹

¹ Building No 405, Faculty of Engineering, Level 7, Auckland CBD, Auckland, 1010

Abstract

An action potential (AP) is an alteration in the membrane potential of an excitable cell. It occurs due to the size, shape, and type of cell excited. In literature, various differential equation (DE) based mathematical models have been proposed to emulate APs. More recently, a Fourier Series (FS) based technique has been proposed. This paper discusses the methodology to identify the parameters of the FS model for eventual implementation on an FPGA. Four DE models have been investigated. Two implementation techniques - direct digital synthesis (DDS) and double integrator based resonant model (RM) - have been compared in terms of FPGA resource usage. Our observations show that the FS model is an attractive alternative to the DE models. The FS implemented using the RM technique offers good accuracy with ease of FPGA implementation. The FS model has the potential for real-time tissues level emulation on an FPGA.

1. Introduction

Action Potential (AP) is the universal language of the nervous and the cardiac system. The size and the shape of the AP are different for various cells [1]. Also, various ions like sodium, potassium and calcium ions are responsible for this phenomenon. Various mathematical models based on the AP of neurons, ventricular cells and guinea pig ventricular cells will be discussed further.

The pioneer cell model is the Hodgkin-Huxley (HH) model [2] of a giant squid axon. This model has 4 variables, i.e., 1. Membrane voltage 2. Gating variables m, h and j. Variables m and h are related to sodium ions. However, j is related to potassium ions. However, the Fitzhugh Nagumo (FHN) model [3] is a simplified way of using the earlier model. It has two variables, i.e., 1. The excitation variable, v 2. The recovery variable, u. It has a variable, I, which acts as the stimulus current.

Beeler Reuter (BR) model [4] describes the generic model of the ventricular cell. It consists of 8 ordinary non-linear differential equations. Six equations describe the state of the gated channels. The other two equations indicate the intracellular Ca^{2+} concentration and membrane

voltage, V_m . The BR model emphasizes the role of the slow inward current (i_s) due to the plateau region formed in the non-pacemaker cell caused by calcium ions. This model has incorporated 4 currents in its equations, i.e., 1. An initial fast current, i_{Na} 2. A secondary or a slow inward current, i_s caused by the calcium ions 3. A time activated outward current, i_{x1} 4. Time dependant potassium current, i_{k1} .

Luo-Rudy I (LR I) model [5] is the mathematical model of the ventricular cells of a guinea pig. It is almost similar to the BR model. The various currents considered in these equations are 1. Fast sodium current, I_{Na} 2. Slow inward current, I_{si} 3. Outward currents.

Fenton Karma (FK) model [6] is the simplified model of a ventricular cell. It is a generic model. The model comprises three non-linear differential equations. The three variables are 1. Transmembrane potential, u 2. Two gating variables, v and w. The first differential equation is the sum of 1. A fast-inward current, I_{fi} 2. A slow inward current, I_{si} and 3. A slow outward current, I_{so} .

By changing the parameters of the models, the AP can be altered. However, these require solvers in FPGA to take more space. There also exists a physical limit to the number of cells produced in real-time [7]. A Fourier series can be used to represent complex signals with good accuracy and this has been used by Sehgal et al. [8] [9] in developing the Resonant Model (RM). The model is formulated as,

$$V(t, \bar{k}) = a_0(\bar{k}) + \sum_{i=1}^N c_i(\bar{k}) \cos(\omega_i(\bar{k})t + \phi_i(\bar{k})) \quad (1)$$

The coefficients $a_0(\bar{k})$, $\phi_i(\bar{k})$ and $c_i(\bar{k})$ can be constants or could also be functions of an external condition \bar{k} .

The proposed (RM) promises to alleviate both: the need for ODE solvers and tissue size. However, an experimental verification of these benefits is yet to be demonstrated. This paper presents the first steps in validating the claims of ease of implementation together with accuracy of reconstruction.

To establish whether RM has the ability to produce wide variety of morphologies in cells, the existing biophysical models are arranged to produce periodic APs. Cells

that require external stimulus require additional complexity which will be investigated in another experiment.

2. Results

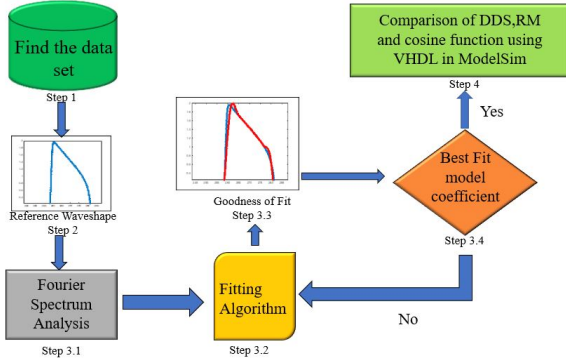


Figure 1. Schematic illustration of simulating a biological cell by determining the coefficients of the Fourier Series and emulating it on ModelSim.

3. Methodology

The first estimate of the model parameters (Fourier coefficients) are obtained using standard Fourier techniques. The model can be optimised by using non-linear regression [10][11] iteratively to reduce the number of parameters.

The methodology used to obtain the RM parameters are illustrated in Figure 1 and explained below:

1. Select candidate cell: Identifying a suitable electrophysiological dataset for the cell to be modeled.
2. Build model: Use the non-linear regression analysis to find the best fit model coefficients using various methodologies in ModelSim.
 - (a) Obtain Fourier Series (FS) coefficient using Fourier Spectrum Analysis.
 - (b) Use heuristics to identify a set of coefficients.
 - (c) Perform a non-linear fit.
 - (d) Determine the goodness of fit.
 - (e) Iterate to (b) if required.
3. Compare implementations: Convert the model parameters into formats required for the two implementation methodologies: Direct Digital Synthesis (DDS), Resonant Model (RM) and trigonometric/math functions in VHDL.

4. FPGA Implementation

The structure of the FS model is suitable for parallel implementations or time-division multiplexing and two techniques have been explored. The DDS technique is widely used and also available in prefabricated integrated circuits.

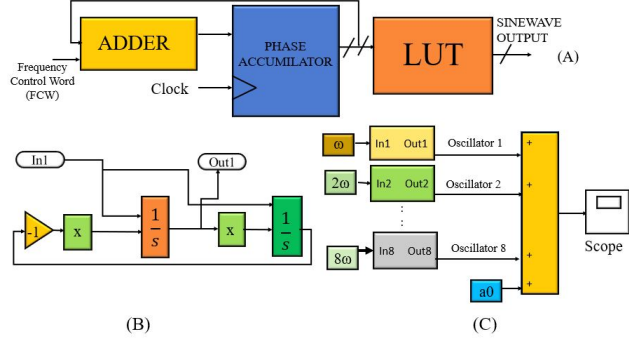


Figure 2. (A) Schematic illustration of the Direct Digital Synthesis (DDS) method. (B) Oscillator implemented with two integrators in series producing sinusoidal waves. (C) A waveshape generator implemented using 8 Fourier terms in SIMULINK.

Our implementation in VHDL is based on the standard designs. The RM methodology is better suited in specific applications as in this case. Both require the model parameters to be converted into integer or fixed point formats and hence the size of the binary word can also be a design factor. Both of these are amenable to FPGA implementation.

4.1. Direct Digital Synthesis (DDS)

Direct Digital Synthesis (DDS) generates periodic or quasi-periodic waveforms using a Look-Up Table (LUT). The DDS model is shown in Fig. 2 (A). This model consists of Frequency Control Word (FCW) of 24 bits, adder, phase accumulator, clock and LUT. The FCW determines the frequency of the sinusoidal waveform to be simulated. The LUT consists of points converted from floating-point to fixed-point values of the sinusoidal waveform. The phase of the waveform can be altered by changing the values in the phase accumulator.

The output of the phase accumulator is added with the FCW using the adder. The new value of 24 bits is the output of the phase accumulator. The first 10 bits of the new value from the phase accumulator act as a LUT pointer. The pointer selects the sinewave output of 16 bits from the LUT. The use of DDS was optimized by using a single LUT for multiple harmonic generators.

4.2. Resonant Model (RM)

Resonant Model (RM) eq 1, simulates AP waveforms of autorhythmic cells and cells that require an external excitation. The RM is based on the Fourier Series decomposition mentioned in Section 2.1. It consists of a waveshape generator and a state controller. The waveshape generator consists of a sum of oscillators depicted in Fig.2(B) and Fig.2(C). The input to the oscillator is related to the cell's

autorythmic frequency, and the oscillator's output is the sinusoidal waveform generated as $c_i \cos(i\omega t + \phi)$.

5. Results

The reconstruction of FitzHugh Nagumo, Beeler Reuter, Luo Rudy and Fenton Karma models are compared using three FS model structures i.e. with 4, 6 and 8 coefficient (C) Fourier Series. Two performance metrics have been used : ratio of RMS and R^2 are used in this study. These are tabulated in Table 1. RMS_{mat} and RMS_v are the ratios of the RMS values of any two AP's with zero DC. R^2_{mat} and R^2_v is the standard R^2 metric. The formulation of these parameters are shown below:

1. RMS ratio of the MATLAB reconstruction and the solution of the models denoted as RMS_{mat} . It is depicted as in Equation.(2).

$$RMS_{mat} = \frac{rms(m)}{rms(s)} = \frac{\sqrt{\frac{1}{n}(m_1^2 + m_2^2 + \dots + m_n^2)}}{\sqrt{\frac{1}{n}(s_1^2 + s_2^2 + \dots + s_n^2)}} \quad (2)$$

where n is the number of points, $m=y_{mat}-\bar{y}_{mat}$ where y_{mat} represents the points of the MATLAB reconstruction and \bar{y}_v is the mean of the overall reconstruction, $s=y_{sol}-\bar{y}_{sol}$ where y_{sol} represents the points of the solved models and \bar{y}_{mat} is the mean of the solution.

2. RMS error between VHDL simulation and the solution of the models denoted as RMS_v . It is depicted as in Equation.(3).

$$RMS_v = \frac{rms(v)}{rms(s)} = \frac{\sqrt{\frac{1}{n}(v_1^2 + v_2^2 + \dots + v_n^2)}}{\sqrt{\frac{1}{n}(s_1^2 + s_2^2 + \dots + s_n^2)}} \quad (3)$$

where n is the number of points, $v=y_v-\bar{y}_v$ where y_v represents the points of the VHDL simulation and \bar{y}_v is the mean of the simulation, $s = y_{sol}-\bar{y}_{sol}$ where y_{sol} represents the points of the solved models and \bar{y}_v is the mean of the VHDL simulation.

3. Coefficient of determination between the MATLAB reconstruction and it's corresponding solutions. It is denoted as R^2_{mat} . It's formulation is shown in Equation.(4).

$$R^2_{mat} = 1 - \left(\frac{SSE_{mat}}{SST} \right) \quad (4)$$

where

$SSE_{mat} = (y_{sol} - y_{mat})^2$ where SSE_{mat} is the sum of square error between the solved model, y_{sol} and the MATLAB reconstruction, y_{mat} .

$SST = (y_{sol} - \bar{y}_{sol})^2$ where SST is the sum of square in total which is the difference between the solved model, y_{sol} and its mean \bar{y}_{sol} .

4. Coefficient of determination between VHDL simulation

and it's corresponding solutions. It is denoted as R^2_v . It's formulation is shown in Equation.(5).

$$R^2_v = 1 - \left(\frac{SSE_v}{SST} \right) \quad (5)$$

where

$SSE_v = (y_{sol} - y_v)^2$ where SSE_v is the sum of square error between the solved model, y_{sol} and the MATLAB reconstruction, y_v .

$SST = (y_{sol} - \bar{y}_{sol})^2$ where SST is the sum of square in total which is the difference between the solved model, y_{sol} and its mean \bar{y}_{sol} .

Table.1 depicts the various values computed for each cell model using the DDS, the RM and it's corresponding floating point implementation in ModelSim. The R^2 and the RMS values of MATLAB and VHDL simulations are compared with respect to the solutions of each cell models. For C=4, for both technique, the AP replication is the worst for the LR I model when compared to other models. With C=6, the FK wavsshape results in the poorest reconstruction. However, when C=8 both techniques show a better reconstruction of the AP wavsshapes across all the tested models. Hence with C=8, both RM and DDS offer good performance metrics and hence we focus on the resource usage. Since the floating point implementation is unsynthesizable on an FPGA, this method is only used for benchmarking purposes.

Table.2 shows the variation in silicon usage in both

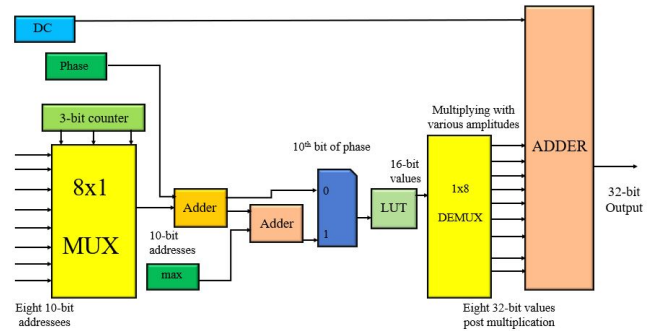


Figure 3. DDS model with different components in terms of NAND gates.

DDS and RM. The synthesis results are based on 32-bit designs. The RM uses merely the shift and add techniques to reconstruct the AP. Hence, only a set of adders/subtractors are involved in it's synthesis compared to the DDS. It has been seen that the silicon utilized by RM implementation is almost 8.5 times smaller than the DDS approach. This comparison is also justified by the estimation of logic utilization using Cyclone V SoC in Quartus Prime 20.1 Lite.

The detailed illustration of the DDS is depicted in Figure.3. It comprises of 8x1 MUX with 24-bit addresses

Table 1. The tabulation the RMS values of VHDL and MATLAB reconstructions on using the 'cos' function, DDS and RM method for 4, 6 and 8 Fourier terms

Models	FHN model				BR model				LR I model				FK model				
Method	C	R^2_{mat}	R^2_v	RMS_{mat}	RMS_v	R^2_{mat}	R^2_v	RMS_{mat}	RMS_v	R^2_{mat}	R^2_v	RMS_{mat}	RMS_v	R^2_{mat}	R^2_v	RMS_{mat}	RMS_v
Floating point implementation	4	94.81	94.81	90.28	90.28	88.40	89.69	90.30	90.34	65.77	68.43	80.67	80.68	83.31	83.04	82.32	82.34
	6	97.15	97.11	96.08	96.08	91.63	91.52	92.40	92.45	84.77	86.81	92.16	92.19	86.78	86.07	87.44	87.45
DDS	8	98.78	98.77	97.85	97.85	93.10	93.29	96.90	96.94	90.61	91.78	94.63	94.67	94.75	95.06	94.63	94.67
	4	94.71	94.80	90.28	90.28	88.39	88.49	90.30	90.31	65.75	63.90	80.68	80.67	83.32	83.30	82.32	82.32
RM	6	97.03	97.09	96.08	96.08	91.65	91.65	94.43	94.42	84.76	83.28	92.17	92.15	86.79	86.70	87.44	87.44
	8	98.74	98.72	97.85	97.85	93.11	93.17	96.91	96.90	90.60	89.42	94.63	94.60	94.76	94.75	95.44	95.44
RM	4	94.76	94.20	90.27	90.25	88.40	89.17	90.30	90.33	65.74	67.21	80.67	80.68	83.30	83.33	82.32	82.34
	6	97.07	96.65	96.08	96.06	91.63	91.66	92.41	92.44	84.74	84.97	92.16	92.34	86.70	86.79	87.44	87.45
	8	98.76	98.41	97.85	97.83	93.10	93.20	96.90	97.16	90.59	90.86	94.63	94.62	94.75	94.46	95.44	95.45

*C-coefficients, RMS_{mat} , RMS_v , R^2_{mat} and R^2_v are in %

Table 2. Synthesis results for the implementation of the RM using different techniques.

Resource	DDS model	RM model
Look-Up Table	65536	0
Adder/Subtractor	5712	9792
Multipliers	11872	0
8x1 Multiplexer with counter	225	0
1x8 Demultiplexer	336	0
Total NAND gates	83681	9792
Logic Utilization on Cyclone V	3409	401

and a 3-bit counter. The first 10-bits of the 24-bit address of each harmonic is added and sent to a phase shifter. The new 10-bit value acts as the address to the Look-Up-Table(LUT). The 16-bit value of the LUT is multiplied by the corresponding amplitudes for each harmonic and added together along with the dc values to acquire a 32-bit output.

6. Conclusion

To conclude, the Fourier Series can be implemented in an FPGA using the DDS and the RM. Moreover, these can emulate a wide range of AP morphologies. The RM model offers a much lower hardware footprint compared to the DDS technique. Thus, the RM model has the potential to implement more cells, i.e., bigger tissues. The proposed hardware implementation implies real-time performance and hence the FS model with the RM technique exhibits a potential for emulating biological tissues or organs.

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- Jerry Jacob:Building No 405, Faculty of Engineering, Level 7, Room no 405.727.J2, Auckland CBD, Auckland, 1010, jjac705@aucklanduni.ac.nz.
 Nitish Patel:Building No 405, Faculty of Engineering, Level 7,Room no 405.767,Auckland CBD, Auckland, 1010, nd.patel@auckland.ac.nz.
 Sucheta Sehgal:Building No 405, Faculty of Engineering, Level 7,Auckland CBD, Auckland, 1010, ssin263@aucklanduni.ac.nz.