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Simulating Action Potential as a Linear Combination of Gating Dynamics.

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***Abstract*—**In this research we show that the dynamics of an action potential in a cell can be modeled with a linear combination of the dynamics of the gating state variables. It is shown that the modeling error is negligible. Our findings can be used for simplifying cell models and reduction of computational burden i.e. it is useful for simulating action potential propagation in large scale computations like tissue modeling. We have verified our finding with the use of several cell models.

***Keywords*—**Linear model, Action potential, gating dynamics**.**

I. Introduction

THE history of channels hypothesis dates back to over 50 years ago when Hodgkin and Huxley published their paper [1]. From that time to the present many scientists have worked on the mechanism of the action potential (AP) and have created different models to reproduce it. Channels have gates and ion flow is controlled through the opening and closing of these gates. The gating property in excitable cells has been verified by experimental measurements and observations [2].

According to our present knowledge, different channels are located on the cellular membrane and each channel regulates the passage of a specific ion. The position of a gate in a channel depends on the membrane's voltage. When the cell is at rest, the gates are in a stable state; fully open or close depending on their type. When a stimulus is applied to the cell, first the sodium gates begin to open, the inward sodium current increases and this in turn leads to depolarization or an increasingly positive membrane voltage. Because the state of the gates in different channels depends on the membrane's voltage, this increment in the membrane potential leads to further changes in the states of the gates, which in turn results in additional changes in the membrane potential. Under normal circumstances this feedback mechanism continues until a complete action potential is generated and the cell comes back to rest again. The above process is shown in the block diagram of Fig. 1.

Although in existing models of the cell complex equations relate the AP to its creating factors [2], it is worth noting that the main source of the action potential dynamics is the gating behavior. This is the main fact which has been led to our hypothesis.

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In this paper we show that the dynamics of an AP can be modeled as a linear combination of gating dynamics with a negligible least squares error(LSE).

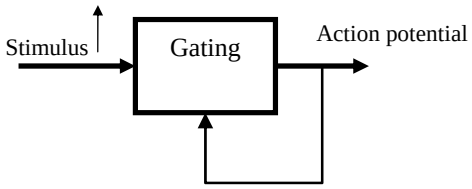

Fig. 1 Gating mechanism creates AP. AP has feed backs on gating

II. Materials and Methods

An "*n*" time point observation can be assumed to be an "*n*" dimensional vector. The hyper volume enclosed by "*n*" dimensional vectors is a measure of their dependence (independence) [3].(see Appendix).

It is well known from combinatorial analysis that, given a set of "*q*" elements, the number of possible combinations of "*p*" elements; *m* will be:

$$m = \frac{q!}{p!(q-p)!} \quad (1)$$

Using our computer program written in matlab, we can obtain all possible combinations of "*p*" vectors from a set of "*q*" vectors and compute the enclosed hyper volume among the vectors of a combination. The combinations which have the least enclosed hyper volume have the most similarity.

Suppose that we stimulate a cell at time=0 and record the AP for 1 sec with sampling time of 0.5 *msec*, so we have an 2000 points observation which can be assumed to be a vector in 2000 dimensional space. This observation is normalized and depicted in Fig. 2. Fig. 2 also depicts another observation; iNaCa at the same time. Considering Fig. 2, it is clear that these observations have some dynamical similarities. But in fact the angle between them is 45.5 degrees [3] and the enclosed surface is large i.e. 0.71; it means that we can not explain the dynamics of AP as a coefficient of iNaCa.

In Fig. 3 the gating coefficient h and the AP are depicted. It is clear that there are more dynamical (morphological) similarities between these two observations. In other words more information in the AP can be recovered from h. In fact the angle between the AP and h is 9.74 degrees and the enclosed surface is 0.16 which is less than the iNaCa case.

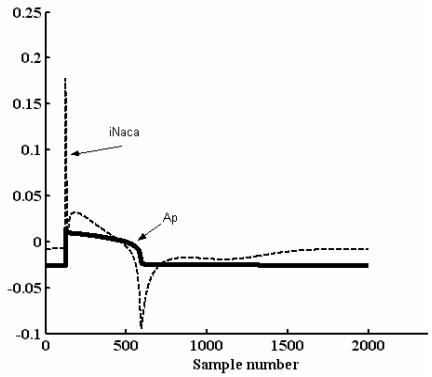

Fig. 2 Although Ap and iNaCa have some similarities but they are independent vectors. The enclosed area between is 0.71

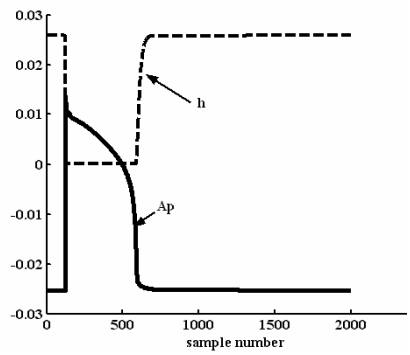

Fig. 3 AP and h have more similarities. The enclosed area between the two vectors is 0.16

III. Methods

In this work we used COR. COR is a cellular open resource i.e. a public environment for modeling biological function [4].

We began examining our hypothesis with the use of Noble 1998 model [2] which is one of the cell models installed in COR. Then we used some other models for further verification of our hypothesis.

We generated a set of 34 different kinds of observations listed in Table I so *q*=34. The duration of each observation was 1 sec with sampling time of 0.5 msec so each observation was a vector in 2000 dimensional space we normalized the observations. As we see in Table I, we have used different kind of observations like currents, concentrations, gating and so on.

TABLE I
THE 34 OBSERVATIONS WHICH WE HAVE USED IN OUR RESEARCH [2, 4]

f2ds f2 d i_Ca_L x_ACh Ap i_KNa xs i_ks xr2 xr1 i_kr Na_i K_i Ca_up Ca_rel Ca_i Ca_ds Ca_Trop Ca_Calmod m h i_Na light_chain cross_bridge ProdFrac f ActFrac i_b_Ca i_NaCa 'i_k1' i_to r s

First we tried to explain AP dynamics as a coefficient of another observation i.e. finding a vector which has the least angle with the AP, so we set "*p*=2, q=34" in (1) which gave "*m*=561" i.e. we had 561 pairs of observation. With the use of our program in matlab we computed the enclosed surface (angle) between two observations in all pairs and sorted the angles increasingly. The results for nine pairs of observation are shown in Table II.

TABLE II
NINE PAIRS OF MOST DEPENDENT OBSERVATIONS

1st observation	xr1	m	f'	h	m	m	ikr	Xr2	ito
2nd observation	xr2	d	[Na]i	Ap	Xr2	Xr1	Xr2	iks	ica
Angle between (degrees)	6.6	7.7	9.5	9.7	16.4	17.9	18.0	18.8	18.9

It is clear from Table II that one of the most dependent pair of observations are "*AP*" and "*h*"; the angle between them is 9.74 degrees and the enclosed surface is 0.16. It is interesting to recall that *"h"* reflects the dynamics of sodium inactivation gates. With the use of our program we explain "*AP*" as a coefficient of "*h*"; the coefficient is computed so that the length of error vector is minimized (least squares error; LSE) and we name the approximate *AP*; "*AP1*" which is described as *AP1*= - 0.98 *h*. AP1 and AP are shown in Fig. 4. Here the length of the error vector is 0.16 which is 16% of the AP vector's length. The shape of AP1 in Fig. 4 means that there is some information in *AP* which can not be simulated by the dynamics of "*h*".

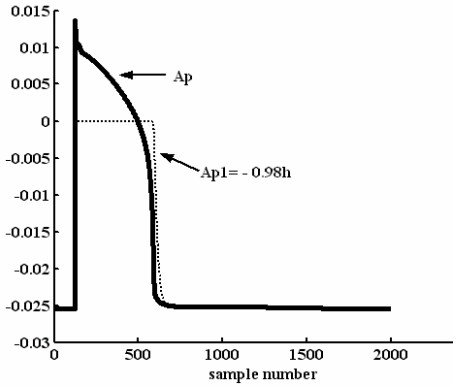

Fig. 4 Explaining *Ap* as a coefficient of *h*. The dynamics of *Ap* can't be recovered with dynamics of *h* perfectly

IV. Results

We repeated the above algorithm for "*p*=3, 4, 5, 6, 7" the out comes were AP2, AP3, AP4, AP5, AP6, which are depicted in Fig. 5 through Fig. 9 respectively. It is clear from Fig. 9 that the beast result is for explaining *"AP"* as a linear combination of gating coefficients: *d, m, h, f, f2, r, s*. i.e. this set of gating coefficients can recover *"AP"* dynamics better than the other observations in Table I. We verified our hypothesis with some other cell models i.e. tried to simulate AP as a linear combination of other observations. The best (LSE) results for examined models are summarized in Table III. It is clear that the best results are for explaining AP as a linear combination of gatings. It is note worthy that the reduction of sampling time and changing the integral method in the COR had no influence on the results. For all examined models in our research we could not reduce the error to less than 2.5%. Some times when we ran our program we saw a non smooth re polarization like in Fig. 6 and Fig. 10 which seems to be because of numerical and computational problems.

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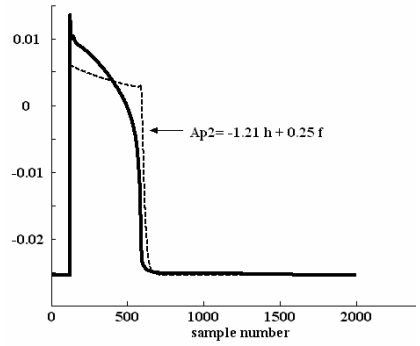

Fig. 5 Modeling *Ap* as a coefficient of *h* and f. here the dynamics of *Ap* can be recovered better than Fig. 4

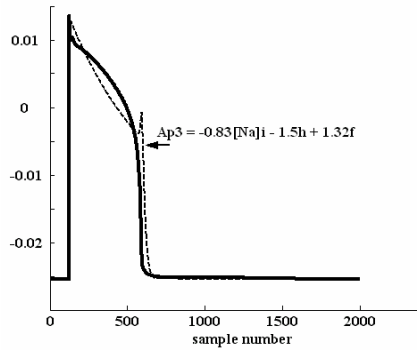

Fig. 6 Explaining *Ap* as a coefficient of *h, f. [Na]i*, here the dynamics of *Ap* can be recovered better than Fig. 5

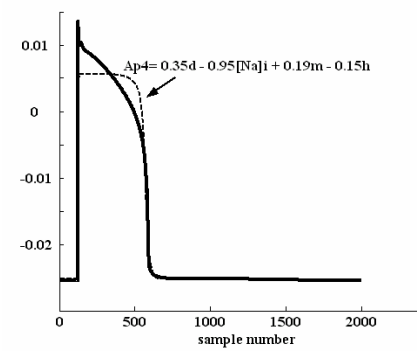

Fig. 7 Explaining *AP* as a coefficient of *h, m. d, [Na]i*, here the dynamics of *Ap* can be recovered better than Fig. 6

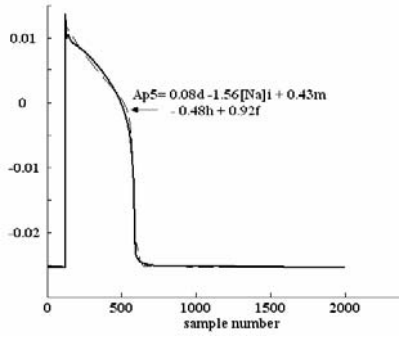

Fig. 8 Explaining *Ap* as a coefficient of *h, m. d, f, [Na]i*, here the dynamics of *Ap* can be recovered better than Fig. 7

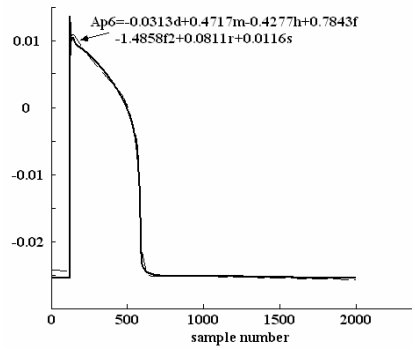

Fig. 9 Explaining *AP* as a coefficient of *h, m. d, f,f2,r*,s. here the dynamics of *AP* can be recovered just a little better than Fig. 8

As we mentioned beforehand, our finding in this research can be used for simplifying cell models and reduction of computational expense in large scales simulations. Cell model simplifying is an open front in biological system modeling and simulations [6, 7]. We verified our claim as follows:

Table IV shows part of COR program which computes the gating coefficient *"h"* in the Noble 1998 model. In Table V, we modified that part of program with the use of our findings in this research i.e. instead of computing "*alpha _h* "," *beta_h* " and solving differential equation for h (*ode(h,time)*) , we computed "h"(*AP)* as a linear combination of AP("h") and some other gatings. Since AP("h") and other gatings have been computed in some part of program beforehand, we pay no computing expense for *"h"*. Although we pay no expense for computing *"h"* but we consider its electrophysiological effects in the cell model (we use *"h"* on the other parts of cell model). We ran the modified model in COR and made AP as an observation the result is depicted in Fig. 10. It is clear from Fig. 10 that the modified model retains the action potential shape satisfactorily.

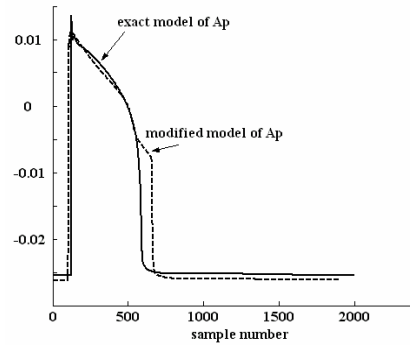

Fig. 10 Using our findings in this paper to modify the Noble 1998 model

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TABLE III
VERIFYING OUR HYPOTHESIS ON SOME CELLULAR MODELS

Model's name[4]	Simulating AP as linear combination of gating coefficients.	Error vector's norm
HH_1952 modified	$Ap \approx -0.7403n + 0.2462m - 0.3761h$	5.46%
Luo_Rudy I 1991	$Ap \approx 0.2736h - 0.0562j + 0.0675m + 0.0144d + 0.4796f + 0.0163x - 1.6850xi$	3.40%
Noble 1998 extended	$Ap \approx -0.0313d + 0.4717m - 0.4277h + 0.7843f - 1.4858f2 + 0.0811r + 0.0116s$	2.5%
Ten_tusscher 2004 endo	$Ap \approx 0.1725d - 0.1559xs + 0.1058r + 0.0266s - 0.8108f - 0.0557g - 0.3382h + 0.2967j + 0.3663m - 0.1982xr1 - 0.1215xr2$	2.3%
Ten_tusscher 2006 epi	$Ap \approx 0.2331d - 0.3911f - 0.2327h + 0.0392j + 0.1767m + 0.1823xr1 - 0.7453xr2 - 0.3958xs - 0.0476r + 0.3812s$	3.6%

TABLE IV
PART OF NOBLE_1998_EXTENDED MODEL IN COR WHICH COMPUTES *H* GATE [4, 5]

```
def comp fast_sodium_current_h_gate as
    var h: dimensionless {init: 0.9944036, pub: out};
    var alpha_h: per_second;
    var beta_h: per_second;
    var V: millivolt {pub: in};
    var time: second {pub: in};

   alpha_h = 20{per_second}*exp(-0.125{dimensionless}*(V+75{millivolt}));
    beta_h = 2000{per_second}/(1{dimensionless}+320{dimensionless}*exp(-0.1{dimensionless}*(V+75{millivolt})));
    ode(h, time) = alpha_h*(1{dimensionless}-h)-beta_h*h;

  enddef;
```

TABLE V
MODIFYING *H* GATE COMPUTATION WITH THE USE OF OUR FINDING IN THIS PAPER

```
def comp fast_sodium_current_h_gate as
    var h: dimensionless {pub: out};
    var m: dimensionless {priv: in};
    var d: dimensionless {priv: in};
    var f: dimensionless {priv: in} ;
    var f2: dimensionless {priv: in} ;
    var r: dimensionless {priv: in} ;
    var s: dimensionless {priv: in} ;
    var V: millivolt {pub: in} ;
    var time: second {pub: in} ;
 h = -1{dimensionless}/40.5353{dimensionless}*V+-5.6546{dimensionless}/40.5353{dimensionless}*d+
       82.3222{dimensionless}/40.5353{dimensionless}*m+68.5469{dimensionless}/40.5353{dimensionless}*f
      -126.4878{dimensionless}/40.5353{dimensionless}*f2+15.7082{dimensionless}/40.5353{dimensionless}*r+
      1.2427{dimensionless}/40.5353{dimensionless}*s
  enddef;
```

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APPENDIX

Two vectors A and B are shown in Fig. A1. In Fig. A1 (a) the vectors have the same orientation or they point to the same direction in the space; i.e. the angle between is zero or no surface is enclosed between them. In this case we can explain each vector as a coefficient of the other one, which means that the two vectors contain the same information. We call these vectors "dependent" or "non independent" vectors.

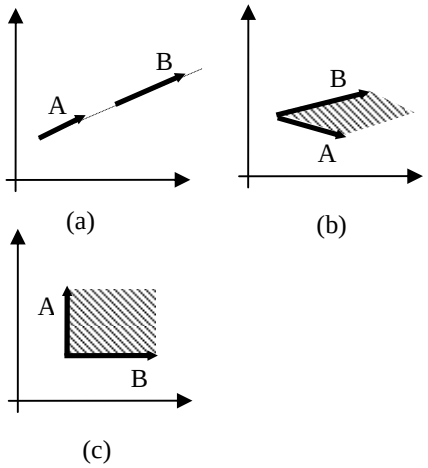
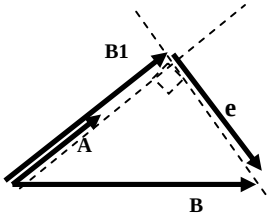


Fig. A1 Two vectors in space
(a) dependent
(b) independent
(c) Fully independent or orthogonal

The enclosed surface between the two vectors is a measure of their independence. The maximum surface is created when the two vectors are orthogonal, in this case they are fully independent i.e. have no common component.

If we normalize the length (energy) of vectors to one, the maximum enclosed surface would be one unit. In Fig. A1(c) two vectors are orthogonal.



$B_1=k.A$
$B=B_1+e$, e=min (error)
$B_1 \approx B$

Fig. A2 Explaining **B** as a coefficient of **A**

Fig. A2 shows two independent vectors *A* and *B*. If we want to approximate *B* as a coefficient of *A*, the best estimate will be *B1*, because in this case the estimate's error i.e. "e" is minimized. We term this kind of estimate as "least squares error" estimate.

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