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Fast Drug Action Solving from Cardiac Action Potential by Model Fitting in A Sampled Parameter Space

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Abstract— **Model-based predictive approaches have been receiving increasing attention as a valuable tool to reduce cost in drug development. In this work, a model-fitting-based approach for solving drug actions using cardiac action potential recordings is investigated. Contribution of major ion currents in cardiac membrane excitation has been intensively studied. Cardiac cell models nowadays reproduce APs very precisely. Giving a test AP, the activities of involved ion channels can be determined by fitting the cell model to reproduce the test AP. Using experimental APs recordings both before and after drug dose, drug actions can be estimated by changes in channel activity. Due to the high computational cost in calculating cardiac models, a fast approach using only pre-calculated sample set is proposed. The searching strategy in the sampled space is divided into two steps: in the first step, the sample of best similarity comparing with the test AP is selected; then response surface approximation using the neighboring samples is followed and the estimation value is obtained by the approximated surface. This approach showed quite good estimation accuracy for a large number of simulation tests. Experiments using animal AP recordings from drug dose trials were also exemplified in which case the ICaL inhibition effect of nifedipine [10] was correctly discovered.**

Index Terms— **in silico drug action solving, cardiac cell modeling, optimization in sampled parameter space**

I. Introduction

To make quick decision on new drug development and reduce the increasing cost, it is important to evaluate risk factors of new drugs as early as possible. Model-based predictive approaches have been receiving increasing attention [1], [2]. While the cardiac electrograms are widely used in late phase of drug development for effect verification, Action potentials (AP) are used in relatively early stage to inspect risk factors such as QT prolongation. Different phases of cardiac AP are mainly contributed by different ion currents. Drugs acting on different ion channels cause different changes on the shape of AP. Therefore an experienced inspector is able to make qualitative judgments of the drug's effect/risk based on such shape changes. On the other hand, AP reconstruction has been a basic research target for cardiac cell modeling from the beginning [3]. Recently developed cardiac cell models [4], [5], [6] are capable of reproducing AP waves precisely with respect to dynamics of involving ion channels. Giving a test AP, it is now possible for a simulation-based approach to inversely estimate the activities of involving ion channels using model fitting optimization techniques. Using experimental APs recordings both before and after drug dose, drug actions can be estimated by changes in channel activity. This approach is useful for early stage drug decision making not only because it provides a more quantitative answer for drug action and risk evaluation but also in the great potential hiding in the obtained cell model. Using the estimated models, conditions of cells after drug dose can be completely simulated in silico. It is also possible even to evaluate the heart function by applying the cell model to a whole heart contraction model like in [7].

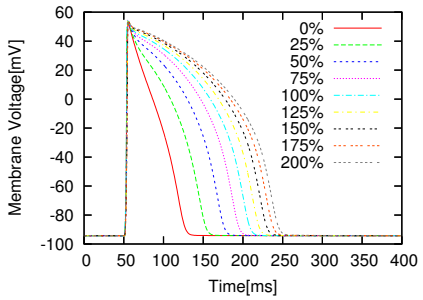
General optimization approaches rely heavily on local gradients to gradually search for the best answer. As a result, a large number of model calculation is always necessary. However the computational cost of a comprehensive cell models is generally too high for a gradient-based approach to perform efficiently. In this work, a fast method which utilize only a pre-calculated sample set of the parameter space is investigated. The searching strategy in the sampled space is divided into two steps: in the first step, the sample of highest similarity with test one among the training set is selected; then a curved surface is fitted in the neighbors of the matched sample and the optimized answer is calculated according to the expression of surface. The efficiency of this sample based approach depends heavily on the selected sample set. An iterative boosting algorithm for adaptive sampling which appends failed test samples to the sample set is presented.

II. Method

In this section, the proposed fast optimization approach utilizes only pre-calculated training samples is addressed. A brief description for cardiac cell model and the properties of cardiac APs is given first. Then the optimization strategy and boosting algorithm are discussed.

A. Cardiac Cell Model and its APs

Cardiac action potentials are known to be effected by many interactions between involved ion currents during the membrane excitation process. When a cardiac cell is induced by a stimulus current over certain level, the opening of voltage-gated ion channels causes the positively charged ions to move out of the cell, i.e. the cell shifts from the resting



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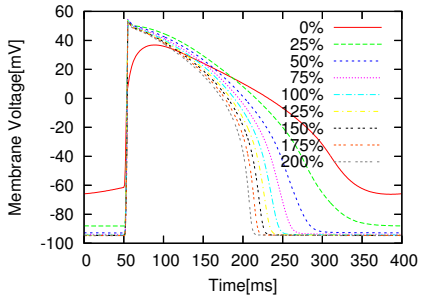

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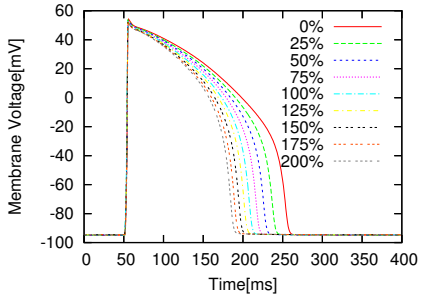

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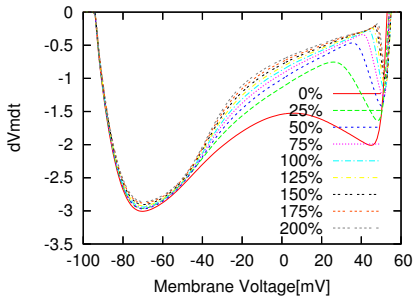
Fig. 1. Effects of the three ion channels on action potential of KM: A. ICaL, B. IK1 , and C. IKr.



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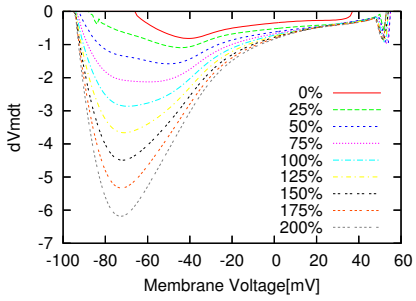

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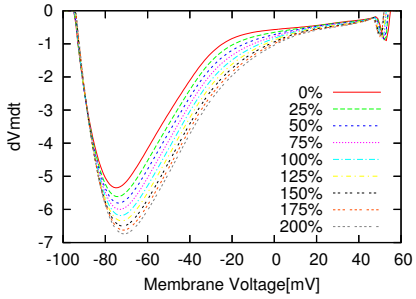

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Fig. 2. Effects of the three ion channels on dVmdt of KM: A. ICaL, B. IK1 , and C. IKr.

state to depolarization stage. The opening of voltage-gated calcium channels in the depolarization stage induces release of Ca^{2+} from the t-tubules. The influx of Ca^{2+} further causes calcium-induces calcium release from the sarcoplasmic reticulum, and such free Ca^{2+} causes muscle to contract. After a certain period of delay, potassium channel reopens and the resulting flow of K^{+} out of the cell (repolarization) finally causes the cell to return to its resting state.

The contribution of major ion currents such as the calcium channel and potassium channel in cardiac membrane excitation has been intensively studied. Cardiac cell models developed recently are capable of integrating all major channels and reproducing APs very precisely. In this work, Kyoto Model (KM) [6], [8] becomes our choice because of its accuracy as well as its ability to simulate mechanical contraction. KM is a comprehensive ventricular cell model for guinea pig and its major currents affecting cellular repolarization stage are the L-type calcium channel (ICaL), the inward rectifier current (IK1), and the rapidly activating potassium channel (IKr). In Fig. 1 and 2 the deformation of AP (Vm) and its differential tranjectory (dVmdt) with respect to different channel activities are illustrated. The ranges of channel activity parameter are from 0 to 200 percent of the initial steady state value of KM. Note that changes in shape of dVmdt are more distinguishable than shape of AP for different channels. For the complete mathematical expressions and other model details of KM, refer to the original paper.

The computational cost of a comprehensive cardiac cell model is general too high for an ordinary gradient-based optimization approach to accomplish efficiently. In case of KM, simulation of the cellular state after drug dose over 5 minutes takes roughly 3 and half minutes on an PentiumIV 3.0GHz intel machine with 2.0G bytes of memory. Optimization approaches that need thousands calculation of model will take weeks. We discuss a quite simple but fast optimization strategy using only a sample set of the parameter space.

B. Optimization Strategy in A Sampled Parameter Space

The problem of model fitting for AP can be defined as: giving an unknown test AP u_i and a cardiac model M, find the best ion channel parameters of $(ICaL, IK1, IKr)$ for

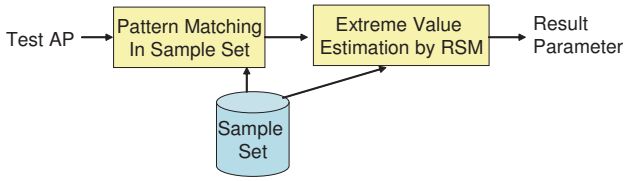


Fig. 3. Optimization strategy in a sampled parameter space.

M that bestly reproduces u_i. The optimization strategy using a set of samples $s_i (i = 1, \ldots, N)$ and a similarity evaluation function $Sim(p_1, p_2)$ is as below:

1) Find sample s_i in the sample set that of highest similarity with the test AP u_i.
2) For samples in the neighbor of s_i, take three channel parameters as input and the similarity $Sim(s_i, u_i)$ as output and approximate this relation using a surface of second order. The optimized answer can be calculated using the appoximated surface.

Step 2 is actually the response surface method (RSM) [9] for finding local extreme. which can be used here totally without new model calculation if only neighbouring samples are used.

The similarity evaluation function is a weighted sum of the normalized correlation of AP and dVmdt waves

$$Sim(p_1, p_2) = w_{vm} Corr(p_1, p_2) + w_{dvm} Corr(d_1, d_2),$$

where d_i is the corresponding dVmdt wave of p_i, $Corr(p_1, p_2)$ is the normalized correlation of p_1, p_2, and the value of weight coefficients are $w_{vm} = 0.25, w_{dvm} = 0.75$.

C. Adaptive Sampling by Boosting

Since the proposed optimization approach using only pre-calculated sample set, its efficiency depends heavily on the sample set used. Generally the local property of the considering parameter space has to be thoroughly studied to perform an adaptive sampling, which is of formidable computational load. A noval idea from statistical learning theory is to use an iterative boosting technique for adaptive sampling. The iterative boosting process is as follows:

1) Collect the initial training sample set using equally spaced samples for each parameter.
2) Using the training sample set to solve a random test AP. If the error of estimated parameters is over a threshold then the test random sample is appended to the training sample set.
3) Test resultant sample set using an independent random test set. Terminate the boosting process if the result accuracy is good enough or if a number of iterative steps are reached. Otherwise go back to step 2 and continue.

III. Results

A. Sample Set and Similarity Distribution

Ranges for activity value of channel ICaL,IK1 and IKr are from 0 to 200 percent of its initial steady state value

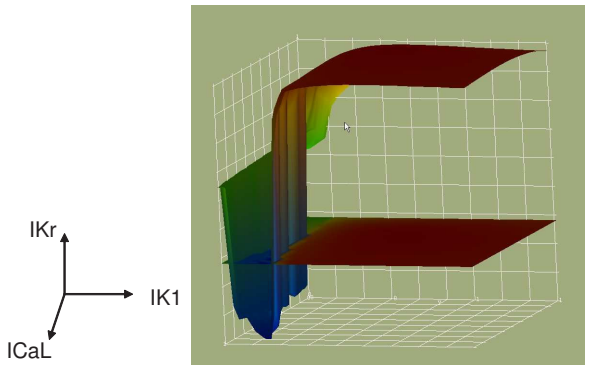


Fig. 4. Cross-section view of distribution of similarity of each sample in train set with the steady state AP of KM: The lower flat plane indicates the position of the cross section, and the height/color of the upper surface stand for similarity values. (Graph axes: ICaL is from back to front, IK1 from left to right, and IKr from bottom to top)

of KM. The initial sample set equally divides the ranger of each parameter into 32 regions. As a result a sample set of number $33 \times 33 \times 33 = 35937$ is created. AP cycle is 400ms for gunie pig and the range of dVmdt signal is from -100mV to 60mV. Dimension of AP and dVmdt signals are 400 and 160 respectively. It takes nearly 60 hours to create the sample set on a IBM P690 machine with 30 CPUs. In the boosting process, 100000 number of random samples are used, and tests result in total estimation error of three channel parameters over 0.05 are appended. This boosting process ends up with nearly 5000 samples being added to the initial sample set.

The efficiency of a sub-sampling approach depends largely on basic properties of the parameter space. Using the steady state parameter of KM (the middle point in the figure) as a reference, the distribution of similarity between the reference and sample set is illustrated in Fig. 4. The lower flat plane indicates the position of the cross section. The height/color of the upper surface stands for similarity of the cross section. Though only one cross-section view with fixed IKr is shown, the trend of the distribution is similar across the whole range. The cardiac APs are observed to deform slowly in the most region(region of red) which is desirable for a sub-sampling optimization approach. Problem exists in small region with IK1$<$15% (region of blue) where the shape of AP changes rapidly. Actually these are the region of KM where abnormal automaticity occurs. Since such parameters are obvious not acceptable in practical drug development, they are simply discard.

B. Results for Random Simulation Tests

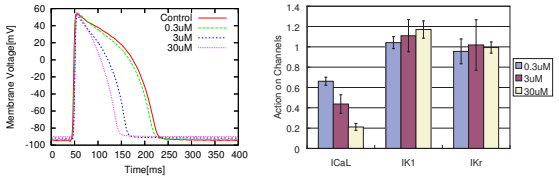
The efficiency of the proposed optimization approach is tested firstly using simulated APs. 36000 APs with random channel values are prepared and tested. Besides the time spend in preparing the sample set, the processing time for one test is about 1 seconds, and it takes almost 10 hours to finished the total test.

Shown in Tab. I is the result estimation error, which is the difference between real channel activity parameters

TABLE I

RESULT FOR RANDOM SIMULATION TESTS

	Mean Error	Worst Error	Error$\geq$ 0.05
ICaL	0.013	0.07	0.55%
IK1	0.009	0.03	0%
IKr	0.017	0.08	0.61%



A B

Fig. 5. Estimated drug action of nifedipine: (A) action potentials, (B) ICaL inhibition effect was correctly discovered.

and estimated ones, and the fraction of error distribution. The error values in the table are normalized with respect to the whole 0-200% range being 1. The result is general good (below 0.02) in terms of mean error. As for the three channels, the IK1 channel is much better behaved and the best accuracy was obtained. For ICaL and IKr, though the fraction is very low, i.e. nearly 0.5% for error greater than 0.05, some difficult tests remain with estimation error up to 0.08. It is also observed that such sample of failure distributes mainly in the areas with both very high ICal and IKr activity near 200%, where the AP is much less sensitive to the change of activity of channels. Comparing the result without boosting process, the mean errors almost remain unchanged but the worst error for ICaL and IKr increased up to 0.11.

C. Results for Drug Dose Experimental AP Recordings

In this experiment, AP recordings of guinea pig before and after dose of a known ICaL inhibitor, nifedipine [10], are tested. The AP assays are originally used for inspection of drug-induced QT interval prolongation [11]. Generally the papillary muscles are firstly prepared in a tyrode solution, then during the perfusion of a test drug compond the stimulation frequency is kept at the base level of 1.0Hz for 30 minutes, finally the stimulation frequency is inceased to 2.5Hz and APs are recorded after the stabilizing period. Dependening on the recording devices used, the original AP recordings can be quite noisy and of different sampling rates with simulation APs. Preprocesses like denoising and resampling are neccesary for such signals. As shown in Fig. 5, the ICaL inhibition effect was discovered as 66%,43%,21% for three levels of dose $(0.3\mu M, 3\mu M, 30\mu M)$ respectively, while parameter of unaffected channels remain almost unchanged at 1.0. These values are near the experemental data from guinea pig ventricular myocytes in [10] where the concentration for 50% inhibition (IC_{50}) is $0.3\mu M$.

IV. CONCLUSION

In this work, a model-based fast optimization approach using only a pre-calculated sample set is proposed to estimate drug actions from cardiac AP recordings. Using only pre-calculated sample set, this approach was very fast and achieved quite good estimation accuracy generally. The limitation was at the area with very high channel activity near 200% of ICaL and IKr where estimation error increased. This is relatively not a critical issue because drugs increase both ICaL and IKr activity by times are very unusual. Estimation result using experiment APs of Nifedipine dose showed a 10%-15% difference with that from reference literature. Variance in detailed experimental protocol and measurement devices may contribute in the result of the estimation. For purpose of early stage drug action estimation, such result should still be quite useful in practice. Also some attempts have been done on using the models to evaluate proarrhythmic effect of drugs [12]. Potential future efforts include a thorough verification using a large number of drug tests and then some new ideas for pharmacological applications will be investigated.

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