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Improved Hierarchical Parameter Optimization Technique - Application for a cardiac myocyte model -

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***Abstract*—We propose a hierarchical parameter optimization technique which further enhances our original technique for an accurate biological cell simulation. Our original technique generates a k-d tree and uses the coefficient of multiple determination (R^2) for tree-branching, however it requires a huge computation time since it processes the response surface at every leaf node of the k-d tree, including those that do not have optimum parameters. In our parameter optimization problem, the objective function is defined as the difference between the measured and calculated waveform of action potentials in a cardiac myocyte. The function value is always non-negative, and is equal to zero if and only if the best optimized parameter is included in the leaf node. To minimize the computational cost problem, our proposed technique takes advantage of the aforementioned conditions and only processes a leaf node if the corresponding Hessian matrix of the objective function is found to be a positive definite matrix. We confirmed the effectiveness of the proposed parameter optimization technique by searching for some pre-determined parameters.**

I. INTRODUCTION

RECENTLY, there have been several developments in biological cell simulation technologies. All living bodies are composed of sets of cells. In other words, it can be said that a life phenomenon is a collection of the several reactions occurring inside a cell. Recent developments in the field of Bioinfomatics have enabled us to analyze cell mechanisms in the finest detail. The Heart Simulation Project at Kyoto University aims at unifying the analytic research on a genome, proteome, etc., and searching for a new principle, making full use of the calculation power of a computer. The project has developed a cardiac myocyte model (KYOTO Model [1]), which is composed of the majority of known sarcolemmal ion channels and transporters, sarcoplasmic reticulum, and contractile elements. This model is based on the Hodgkin-Huxley model, and simulates cell behavior by numerically integrating the differential equation and generates action potentials, intracellular Ca transient, contraction, and intracellular ATP consumption by using initial parameter values of major ion channel currents.

Since most of these parameters used in the cell simulation cannot be directly measured by experiment, these are identified by simulated experimental results. Parameter identifications of the cardiac myocyte model were regarded as an optimization problem that minimizes an objective function defined as a difference between a measured and a calculated waveform of action potentials in a cardiac myocyte. The parameter optimization technique is also expected to shed a light on the extrapolation of the effects of drugs on cardiac action potential through a combination of models and experiments [2].

In the past, we proposed a parameter optimization technique using Response Surface Methodology (RSM) for the accurate biological cell simulation [3]. In RSM, a quadratic polynomial is generally used, and a mathematical technique is used to calculate the extreme points. Because our parameter space cannot be approximated by a single quadratic polynomial surface, we adopted a recursive subdivision technique and used the coefficient of multiple determination (R^2) to represent the response surface in each subspace for the criteria of the subdivision. This process generates a k-d tree in which each leaf node has a response surface. In this technique, it takes huge computational time since we construct and analyze a response surface at every subdivided space, whether or not the optimum parameters are included.

To solve this problem, we propose a hierarchical parameter optimization technique which processes a leaf node only if its Hessian matrix is found to be a positive definite matrix. In our parameter optimization problem, we can easily find that the objective function has always non-negative values, and is equal to zero if and only if the best optimum solution is included in the leaf node. This means that the objective function should be approximated by a response surface whose Hessian is a positive definite matrix at areas close to the optimum solution. These conditions lead to an efficient implementation of our optimization technique.

II. RELATED WORK

Willms et al. estimated the parameters of Hodgkin-Huxley model by fitting each conductance trace from a voltage-clamp experiment [4]. They employed a standard nonlinear least-squares optimization algorithm to minimize the objective function. Saitoh et al. utilized the E-Cell simulation environment as a framework for estimating the parameters for the accurate cell simulation by employing Genetic Algorithm (GA) in addition to standard optimization algorithms, such as the Rosenbrock method and the Modified Powell method [5]. In the standard optimization algorithm,

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the quality of the solution is highly dependent on the assignments of the initial values of the parameters to be estimated. Although GA might solve the potential problem caused by the initial values, it might take a long computational time and might not take into account the local distribution of the objective function.

To cope with these problems, we employed Response Surface Methodology (RSM) [6] as the optimization technique. RSM has generally been used for optimization of the process of a product design etc, and thermal simulation [7,8,9]. In RSM, a quadratic polynomial is generally used, and a mathematical technique is used to calculate the extreme points. After we evaluate our parameter space, which is composed of three parameters, we understand that no quadratic polynomial surface can fit in the parameter space. To solve this problem caused by many local minima, we adopted a recursive subdivision technique [3].

III. PROPOSED TECHNIQUE

A. *Parameter optimization process using recursive subdivision*

Firstly, users should specify the parameters and their valid ranges. As the first step, the design points are determined via DOE [10]. After that, the computation of numerical simulation is executed using the specified parameter set (Step 2). When this computation is completed, the association measure (X) described below (Eq. 1) is calculated using the obtained results (Step 3).

$$X = \sum_{t=1}^{400} \sqrt{\left(V_0(t) - V(t)\right)^2} \qquad (1)$$

where $V_0(t)$ and $V(t)$ represent the target potential at t (msec), and the calculated potential at t (msec), respectively in the cell simulation. In short, when the value of X is equal to zero, the calculated value perfectly matches with the target waveform. In Step 4, a response surface is generated by using RSM. In Step 5, the eigen decomposition of Hessian matrix at the area delimited by the design points is performed. If all eigen values of the Hessian matrix are positive, i.e. the Hessian matrix is a positive definite, then this indicates the existence of a minimum value at the verified area and the process goes to Step 6. If one of the eigen values is not positive, then the searching process is terminated in the subspace. In Step 6, the coefficient of multiple determination (R^2) is calculated.

$$R^2 = 1 - \frac{RSS/(k-p-1)}{TSS/(k-1)} \qquad (2),$$

where k and p denote the number of parameters and responses. RSS and TSS represent the regression sum of squares, and total sum of squares, respectively. If the obtained R^2 value exceeds a pre-determined criterion, the process goes to Step 7. If this R^2 value is smaller than the pre-determined criterion, then the parameter space subdivision process is performed and the process returns to Step2. This process is recursively executed until a satisfactory R^2 value is found. We divided each of the parameters being analyzed into two [1]. In Step 7, the extreme points are searched for solving the function generated by RSM. When all parameter space is explored, the most extreme point is determined by comparing the local extreme points with each other (Step 8). After that, we finally obtain the set of optimum solutions for the parameters.

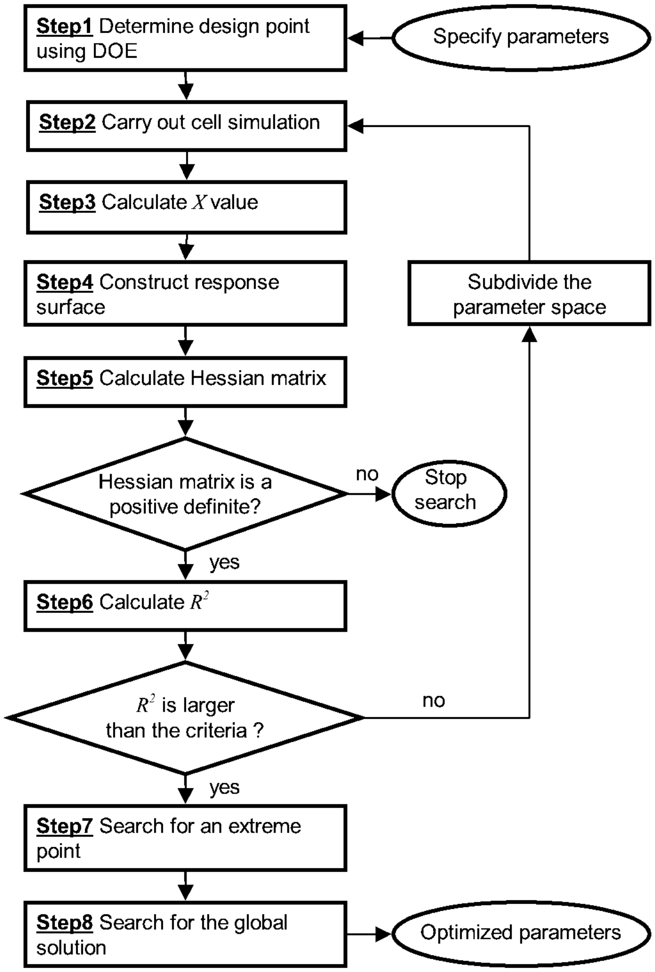
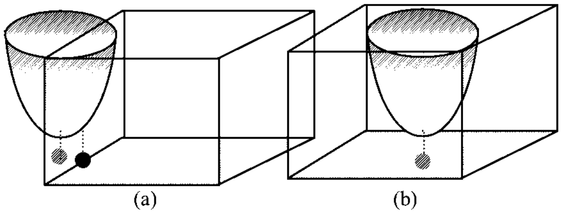


Fig.1 Recursive subdivision optimization process.

B. *Determination of minimum and most extreme minimum point*

The aforementioned process search for minimum points in a given parameter space. Figure 2 shows two possible placements for minimum values regarding the parameter space. Figure 2(a) shows the case when the minimum value which is obtained from response surface, has the extreme



(a) (b)

Fig. 2 Minimum point placed inside or outside of a given region: (a) Outside the region; (b) Inside the region.

minimum point (red point) outside the given region. Figure 2(b) shows the case when a minimum value, which is also the extreme minimum value, exists inside the given region.

Our proposed system is able to predict this kind of extreme minimum value located outside of a given region by solving the response surface equation. In this paper, we limited the scope on the minimum values since we are striving to minimize the difference between the measured and simulated values.

IV. EXPERIMENT

We applied a parameter optimization process to a numerical simulation of cardiac myocyte model in order to verify the effectiveness of our proposed method. To assist the analysis and to evaluate the obtained results, we developed a visualization system based on KVS (Kyoto Visualization System) which is a set of C++ class libraries for 3D visualization being developed in our visualization laboratory (http://www.viz.media.kyoto-u.ac.jp) at Kyoto University. Detailed description of the Cardiac Myocyte Model as well as the KVS together with the developed visualization system will be presented in the following sections.

A. Cardiac Myocyte Model

The Heart Simulation Project at Kyoto University has been developing a cardiac myocyte model, which is composed of the majority of known sarcolemmal ion channels and transporters, sarcoplasmic reticulum, and contractile elements. This model is based on the Hodgkin-Huxley model, and simulates cell behavior by numerically integrating the differential equation and generates action potentials, intracellular Ca transient, contraction, and intracellular ATP consumption by using parameter values of major ion permeability and amplitude of Ko dependency.

B. Kyoto Visualization System

The Kyoto visualization system (KVS) is a set of C++ class libraries being developed to facilitate the data visualization process. Since KVS is based on the object oriented programming paradigm, this greatly facilitates the development of a visualization system. Apart from the visualization oriented classes, KVS also includes numerical computation oriented classes such as basic matrix calculation classes and maximum likelihood estimation classes such as the RSM. This therefore simplifies the development of integrated systems combining numerical simulation and data visualization.

C. Numerical simulation oriented visualization system

We have developed a KVS-based visualization system in order to visualize the obtained results from our proposed parameter optimization method. In this method, the results are represented by tree structure (Figure 3) because of the use of this data structure in the recursive searching for the extreme points. In our experiment, we evaluated the proposed method by using two parameters. In this case, the calculation result can be represented as quad-tree data structure. In order to construct this tree structure, we used the tree container class which is included in the KVS. Our visualization system can display the sub-regions created by recursive subdivision during the searching for extreme points. In addition, the extreme value in a sub-region or the minimum value at the boundary regions can be displayed by using a sphere in the parameterization space. By simultaneously displaying the shape of utilized objective function, it can greatly facilitate the visual comparison between measured and simulated values.

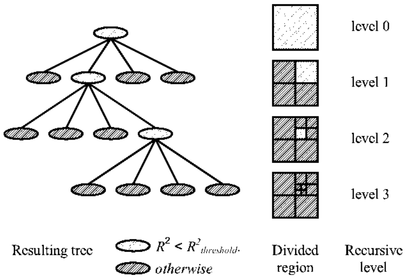


Fig.3. Tree structure. When using 2 parameters, the resulting tree can be represented as quad-tree.

D. Experimental setup

We selected three different conditions for the two selected parameters in order to verify the effectiveness of our proposed parameter optimization technique. Table1 shows three comparative experiments. We have focused our evaluation on the effectiveness of the searching process for a minimum value placed at boundary regions, and also the effectiveness of the process for verifying the Hessian matrix for locating the minimum points.

TABLE I

EXPERIMENTAL SETUP

	Parameter range	**Positive definitive**
Exp1	**Na**[100.0-200.0] **K**[0.1-10.0]	**Considered**
Exp2	**Na**[100.0-200.0] **K**[0.1-10.0]	**Not considered**
Exp3	**Na**[140.0-240.0] **K**[6.0-16.0]	**Considered**

Other setup: Target parameters [Na:140.0,K: 5.4],R^2threshold[0.99].Deepest recursive level[4].

V. RESULTS AND DISCUSSION

We utilized two evaluation metrics in order to verify the accuracy of the set of parameters obtained by the proposed optimization technique. The first metric is the difference between the calculated and the pre-determined (exact)

TABLE II

RESULTS OF COMPARATIVE EXPERIMENTS

	association measure	**K**	**Na**	**explored depth**	**computation time [minutes]**
Exp1	0.0006	5.393	140.437	4	160.93
Exp2	0.0006	5.393	140.437	4	283.20
Exp3	0.0551	6.000	140.0	1	10.806
EXACT SOLUTION		5.4	140.0		

solution. The other metric is the value of X evaluated by using the calculated solution. Since the exact solutions, are generally not known in advance, the second metric was used in this research.

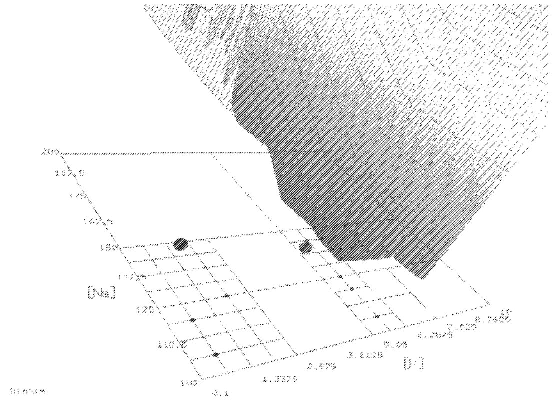


Fig. 4 Na[100.0-200.0], K[0.1-10.0], Existence of minimum points inside the parameter region.

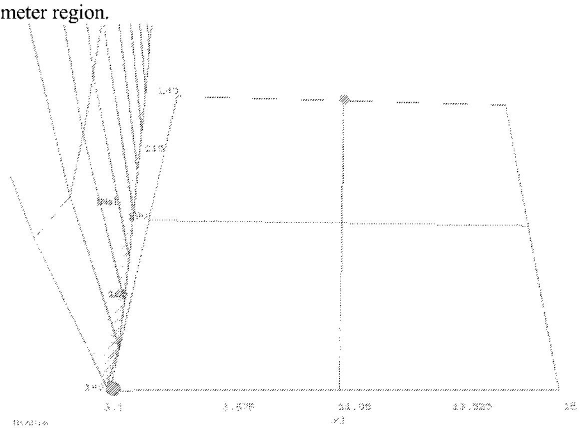


Fig.5 Na[150.0-250.0], K[6.0-16.0], Absence of minimum points inside the parameter region (Only a local minimum point at the boundary region).

Table II shows the experimental results. From this table, we can verify a great reduction in time since our proposed method can execute a smart searching for minimum points based on eigen value determination which excludes the regions which do not possess any minimum points. In addition, even for an area which does not possess the optimum solution, our proposed method can search on the boundary regions to determine whether or not an optimum solution exists in the neighboring regions.

Figure 4 shows the X value (minimum point) distribution in three-dimension. In this figure, the red point represents the most extreme point, and the big blue point shows the calculated extreme minimum point in the local region (Fig.2 (a)). The small blue points on the border area show the existence of a minimum point in the vicinity (Fig.2 (b)). The black mesh shows the subspaces created during the searching process using recursive subdivision. From the visual analysis using the KVS-based visualization system, we can verify the occurrence of recursive subdivision which has generated a complex subdivision field. Figure 5 shows an example of the absence of any optimum solution in a given space. Therefore, a response surface which possesses an extreme minimum point was not generated. However, since a minimum point (the point at the lower left in Fig.5) exists at the position (6.0, 150.0), it is possible to start a searching process by setting this position as the starting point.

VI. CONCLUSION

In this paper, we proposed a hierarchical parameter optimization technique which further enhances our original technique for an accurate biological cell simulation. The idea is to use the R^2 value which shows the degree of conformity of a response surface in order to determine whether to proceed with further subdivision or not. The second idea is to use the eigen decomposition of Hessian Matrix, which can verify whether or not there is an extreme point. We applied this technique to optimize two parameters with the aim of improving the accuracy of biological cell simulation and to verify the effectiveness, which were clearly confirmed.

As future works, we are planning to enhance capability to execute higher dimensional parameter optimization. In addition, we are planning to investigate an uneven region subdivision method which executes more localized and refined subdivision in the neighboring areas with the potential of having minimum points.

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