論 文 の 内 容 の 要 旨

論文題目　Optimization of ablation strategy by *in silico* learning for radical treatment of tachyarrhythmia
（頻脈性不整脈の根治に向けた*in silico*学習による焼灼戦略最適化）

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The spiral excitation that occurs in the heart is known to be the cause of tachyarrhythmias such as atrial fibrillation (AF) and ventricular fibrillation (VF). AF is one of the most common tachyarrhythmias, affecting about 1% of the population in the world. In addition, AF is known to increase the risk of fatal diseases such as heart failure and stroke, and a reliable treatment for AF is needed. Catheter ablation surgery is known as a promising treatment for tachyarrhythmia. Although various strategies have been proposed for effective catheter ablation surgery, these strategies have not shown sufficient therapeutic efficacy in clinical studies, or therapeutic efficacy has not been sufficiently confirmed. In addition, they were basically devised subjectively based on the prior knowledge and clinical experience of the proposer, and there is still much discussion about the optimal ablation strategy. On the other hand, in recent years, machine learning has been applied to optimization problems in various fields, and *in silico* learning, which is a combination of numerical simulation and deep reinforcement learning, has been attracting attention. The application of *in silico* learning to the problem of catheter ablation is hampered by computational cost. In this study, the objective and quantitative optimization of the ablation sites by *in silico* learning using a simple cardiac electrophysiological simulator was attempted.

In Chapter 2, a simple two-dimensional cardiac tissue simulator was constructed for the environment of *in silico* learning, and the possibility of optimizing the ablation sites by *in silico* reinforcement learning was investigated. In the cardiac simulator, the cardiac cell model of human atrial myocytes was used, and for the cardiac tissue model, a monodomain model, which simulates only the intracellular domain was used to reduce computational cost. For reinforcement learning, a policy-based algorithm that is supposed to be suitable for optimization problems with large action spaces was used, and a deep neural network-based ablation model (DAM) was trained to estimate the proper ablation sites from the movie of the membrane potential distribution. The DAM was based on the 3D convolutional neural network and designed to input a 3D membrane potential data of 64 pixels × 64 pixels × 128 frames, which represents 38.4 mm × 38.4 mm × 512 ms cardiac excitation and output an array which means ablation preferability of 8 pixels × 8 pixels. Since it is desirable that the ablated area is as small as possible for maintaining cardiac function, the two loss functions were used in the reinforcement learning: mean absolute error to improve the probability of spiral termination and L1 norm to keep the ablated area small. The random ablation (RND) and the rotor ablation (ROT), which is a common conventional method, were prepared for the comparison of the trained DAM. The comparison was made on the ratio of spiral termination for 340 test data that were not used for training. The results showed that the percentages of ablation areas of RND, ROT, and best trained DAM were 7.0±2.8%, 12.5±5.7%, and 6.5±2.4%, respectively, and the termination rates of spiral excitation were 12.6%, 8.5%, and 74.1%, respectively. After evaluating the ablation strategy obtained by learning, the DAM learned to effectively terminate spiral excitations by ablating the area from near the spiral center towards the tissue boundary without any prior knowledge. Although the obtained ablation strategy as the *in silico* learning was similar to the linear ablation already proposed, it is of high interest that the reinforcement learning method, which is not bound by prior knowledge, selected a similar ablation strategy from a huge number of ablation pattern candidates. Furthermore, although conventional linear ablations were based on anatomical information, this study showed that linear ablation that takes into account the excitability of the heart, including the location of the spiral excitation may be effective. Although some limitations remain, such as the complexity of the cardiac simulator and the degree of freedom of the ablation, this chapter showed the possibility that *in silico* learning can be used to optimize the ablation pattern for effective termination of the tachyarrhythmia.

In Chapters 3 and 4, an experimental system using *in vitro* tissue samples was constructed, and verification experiments were conducted to confirm whether the ablation strategy obtained in Chapter 2 is applicable to actual biological tissues.

The present study suggests that *in silico* learning may be able to achieve objective optimization independent of prior knowledge in the control of cardiac excitability, which is one of the reaction-diffusion systems. Although this study was limited to a simple two-dimensional cardiac tissue model due to the computational cost, combining technologies such as personalized cardiac simulators and deep neural network simulator acceleration, which have been the focus of attention in recent years, may enable objective and quantitative optimization of the ablation sites in a patient's heart model in the future.