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Generating Purkinje networks in the human heart

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ABSTRACT

The Purkinje network is an integral part of the excitation system in the human heart. Yet, to date, there is no in vivo imaging technique to accurately reconstruct its geometry and structure. Computational modeling of the Purkinje network is increasingly recognized as an alternative strategy to visualize, simulate, and understand the role of the Purkinje system. However, most computational models either have to be generated manually, or fail to smoothly cover the irregular surfaces inside the left and right ventricles. Here we present a new algorithm to reliably create robust Purkinje networks within the human heart. We made the source code of this algorithm freely available online. Using Monte Carlo simulations, we demonstrate that the fractal tree algorithm with our new projection method generates denser and more compact Purkinje networks than previous approaches on irregular surfaces. Under similar conditions, our algorithm generates a network with 1219 ± 61 branches, three times more than a conventional algorithm with 419 ± 107 branches. With a coverage of 11 ± 3 mm, the surface density of our new Purkije network is twice as dense as the conventional network with 22 ± 7 mm. To demonstrate the importance of a dense Purkinje network in cardiac electrophysiology, we simulated three cases of excitation: with our new Purkinje network, with left-sided Purkinje network, and without Purkinje network. Simulations with our new Purkinje network predicted more realistic activation sequences and activation times than simulations without. Six-lead electrocardiograms of the three case studies agreed with the clinical electrocardiograms under physiological conditions, under pathological conditions of right bundle branch block, and under pathological conditions of trifascicular block. Taken together, our results underpin the importance of the Purkinje network in realistic human heart simulations. Human heart modeling has the potential to support the design of personalized strategies for single- or bi-ventricular pacing, radiofrequency ablation, and cardiac defibrillation with the common goal to restore a normal heart rhythm.

1. Introduction

In the United States alone, almost half a million people die each year as a result of heart rhythm disorders (American Heart Association, 2015). Abnormal heart rhythms are a consequence of uncoordinated electrical excitation and disturbed electrical conduction, which may critically reduce mechanical function (Mann et al., 2015). One of the key components of the cardiac excitation system is the Purkinje network. Composed of specialized fast-conducting cells, the Purkinje network is located in the sub-endocardium, right beneath the inner wall of the heart. Purkinje cells are larger than cardiomyocytes, with fewer myofibrils and more of mitochondria, to conduct the excitation wave efficiently and more rapidly than any other cell in the heart. A functional Purkinje network is essential to create synchronized contractions of the left and right ventricles and maintain a consistent cardiac rhythm (Dubin, 1996).

The electric activation of our heart originates in the sinoatrial node located in the right atrium. From here, it spreads through the atria and reaches the atrioventricular node, the only electric connection between the atria and the ventricles. The bundle of His connects the atrioventricular node to the Purkinje network, which branches from the basal septum into the left and right ventricles. Purkinje fibers were first observed more than a century ago (Tawara, 2007); yet, to date, there is no in vivo imaging technique to fully reconstruct their geometry (Çetingül et al., 2011). This limitation has given rise to various methods to create model systems of the Purkinje network, both for visualization purposes and computational simulations.

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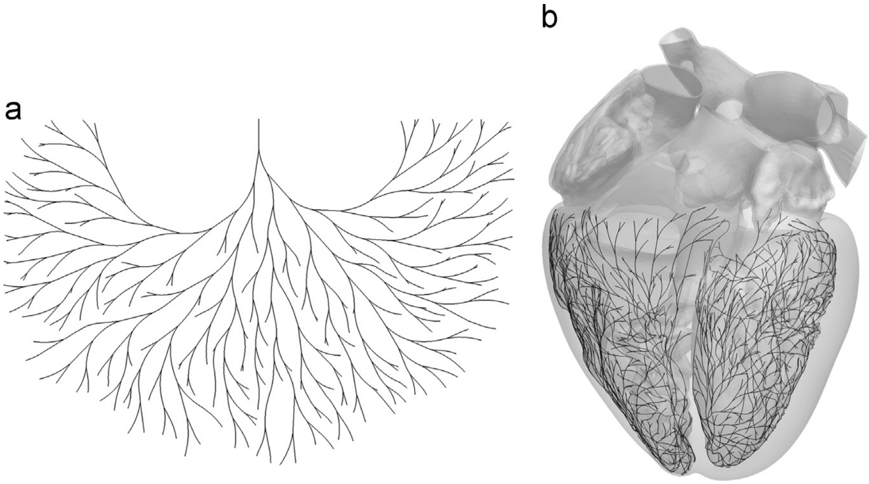

Fig. 1. Generation of the Purkinje network in the human heart. (a) Two-dimensional fractal network. (b) Three-dimensional fractal network projected onto the irregular, non-smooth endocardial surfaces of the left and right ventricles of the human heart.

The inherent complexity of the Purkinje network makes its manual generation complicated and time consuming (Krishnamoorthi et al., 2014). Recently, algorithms based on fractal trees (Lindenmayer, 1968) have emerged has a tool for automatic network generation. Fig. 1 illustrates a two-dimensional fractal network and its projection onto the irregular endocardial surfaces of the left and right ventricles. The first attempt to create Purkinje network models using fractal trees was motivated by studying high-frequency electrocardiograms (Abboud et al., 1991). The underlying network consisted of straight segments, which were placed in a simplified representation of the ventricles. Recent models introduced non-straight branches with controllable curvature (Ijiri et al., 2008), and generated hierarchical networks with sub-sequentially smaller fibers (Sebastian et al., 2011, 2013). Alternatively, other classes of models focused on creating patient specific Purkinje networks (Vergara et al., 2014) by optimizing the resulting activation times (Palamara et al., 2014). However, all these approaches represent the ventricles as regular, smooth surfaces, and ignore non-smooth but important substructures such as the papillary muscles.

The papillary muscles are often completely covered by the Purkinje network (Veenstra et al., 1984), and a dysfunctional Purkinje-fiber–papillary-muscle interaction can become the origin of severe arrhythmias and ventricular fibrillation (Li et al., 1992; Pak et al., 2006). In addition to their electrical importance, the papillary muscles also play a crucial mechanical role in activating the mitral and tricuspid valves at precisely the right point within the cardiac cycle. Including the papillary muscles is therefore especially relevant when modeling the behavior of the whole heart (Baillargeon et al., 2014). To work around the difficulty of covering the irregular papillary muscle surface of a rabbit heart with a Purkinje network, a recent study suggests to subdivide each network branch into several small segments (Bordas et al., 2011). Motivated by this idea, we propose a novel fractal tree algorithm for the automatic generation of Purkinje networks in the human heart. This method provides controllable curvature of the branches and is suitable for both regular and irregular surfaces independent of segment length. More importantly, it is able simulate the essential features of cardiac excitation under physiological and pathological conditions.

2. Methods

In this section, we briefly describe the generic algorithms to create a two-dimensional fractal network in Section 2.1 and to project a three-dimensional fractal network onto a non-smooth surface in Section 2.2. We then illustrate how to use these algorithms to generate a Purkinje network on the endocardial surfaces of the left and right ventricles in Section 2.3 and summarize the Monte Carlo method for sensitivity analyses with respect to the fractal network parameters in Section 2.4. Finally, we summarize the finite element method used to simulate realistic excitation sequences in Section 2.5, introduce the Living Heart model as the basis for our human heart model in Section 2.6, and show how to extract electrocardiograms for model calibration and model validation in Section 2.7. The source code of our algorithm for generating three-dimensional fractal trees on given triangulated surfaces is freely available online at https://simtk.org/home/fractal-tree and https://github.com/fsahli/fractal-tree.

2.1. Two-dimensional fractal network

To create a two-dimensional fractal network, we selected the initial node of the network and defined the direction in which the initial branch will grow (Ijiri et al., 2008). From the end terminal of the initial branch, we created two new branches and iteratively continued this process (Lindenmayer, 1968) as described in Algorithm 1.

Algorithm 1. Fractal Network Generation.

```
for Generations = 1 to Number-of-Generations do
  shuffle Branches-to-Grow
  for Mother-Branch in Branches-to-Grow do
    for Child = 1 to Number-of-Children do
      Create Branch
      if Branch did not collide and is in the surface then
        add branch to Branches-to-Grow
      end if
    end for
  end for
end for
```

Fig. 2 illustrates the iterative generation of the two-dimensional fractal network. Branches are represented as polylines of n segments and $n+1$ nodes that repel each other to generate curved lines. This is accomplished by determining the direction of each

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