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# A Computational Model for the Cardiac Action Potential via the Finite Element Approach

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## Abstract

Contemporary cardiac research has shifted from traditional experimental and clinical studies and currently incorporates various computational approaches to understanding heart function and disease. Particularly in the last decade, new insights into the electrophysiology of the heart has led to a detailed biophysical and biochemical understanding of cardiomyocytes. Significant efforts to integrate various aspects of cellular cardiac biology such as signaling cascades and metabolism have shown promising results toward new drug discoveries for heart diseases. To investigate the effectiveness and functionality of therapeutic models in the context of cardiac electrophysiology, this paper aims to understand some mathematical models of the cardiac action potential and their evolution in systems biology. Several examples of mathematical models, from the 1960s Hodgkin-Huxley experiments to present day modifications are attempts to explain a particular biological phenomenon (arrhythmias, resting potential, intracellular ionic regulation, etc.) in a larger context by examining how several biological factors interact in a particular model. In this paper, we consider a model for the action potential propagation through the heart and apply a finite element scheme to analyze its behavior. We use Python and the NumPy library for the computational model to carry out the numerical solution. Additionally, genetic modifications such as optogenetic control mechanisms — in which illumination is used to elicit a bioelectric response in tissue modified to express photosensitive proteins (opsins) to generate spatiotemporally precise responses in targeted cells or tissues — are introduced into the models. The results of these simulations, carried out in Python, can provide physicians and researchers with a theoretical gateway into long-term treatments and cures for rhythm disorders of the heart.

**Keywords: Partial Differential Equations, Mathematical Models, Optogenetics, Neuroscience, Cardiac Electrophysiology**

## 1. Introduction

Contemporary cardiac research has shifted from traditional experimental and clinical studies and now frequently incorporates computational approaches to understanding heart function and disease. Animal models such as mice and zebrafish are being used to study the heart — down to single myocytes — *in vivo* using advanced imaging technology. One consequence of these methods is the ability to study and record intracellular changes in a variety of cardiac cells. Theoretical approaches to understanding these electrical gradients and their consequent ionic currents in the cell are well documented. [1,2,3] From the initial Hodgkin-Huxley experiments with the squid giant axon in 1952, understanding action potentials in the brain and the heart using the properties of intermembrane ionic channels and other co- factors has evolved vastly. [3] Particularly in the last decade, new insights into the electrophysiology of the heart has led to a detailed biophysical and biochemical understanding of cardiac cells. The accumulation of $K^+$ ions in the extracellular medium has been attributed to acidotic conditions in during ischemia or hypoxia. [4] Electrocardiogram (EKG)

interpretations of ischemia are commonly based on generic cardiac geometries but incorporating a patient- specific or even pathology- specific assessment of excitation patterns allows for a much accurate representation of the affected areas of the heart. [5] Such complex understanding of patient- specific geometries can be approached by electrical excitation algorithms to generate a model for the diseased heart. Significant efforts to integrate various aspects of cellular cardiac biology such as signaling cascades and metabolism have shown promising results towards new drug discoveries for heart diseases. [6]

Modeling applications to clinical and physiological settings requires a deeper mechanistic understanding of the cardiac excitatory process. One of the major shortcomings of mathematical models in cardiology is that explanations are isolated and piece-wise for an integrated, cohesive organ system and does not replicate the physiological environment (e.g. ion channels in the cellular membrane in the organ itself). Most models are reductionist models used to elucidate the role of an individual component (i.e. ion channels) in the arrhythmogenicity and the action potential of the cell. Over the past decade, optical mapping studies have been used to provide experimental evidence of these theoretical approaches. Additionally, biochemical models that explain electrophysiological processes as a coupled system have also been developed. [7]

One of the first models describing electrical activity in neurons is the Hodgkin-Huxley model for neuronal action potentials. In 1952, Hodgkin and Huxley demonstrated that the amplitude and rate of rise of an action potential of the squid giant axon is dependent on the extracellular sodium concentration, which leads to a large and specific increase in the permeability of the cellular membrane to sodium ions. Hodgkin and Huxley used the voltage-clamp technique to separate the membrane current into sodium and potassium components to compose a model in which these currents vary with the membrane electrical potential and time. These equations are experimentally determined to reproduce many of the electrical properties of the squid giant axon, including the shape and size of the action potential and the velocity of conduction. [3] The range of biological phenomena that these equations describe have greatly increased since the initial experiments. [4]

## 1.1 The FitzHugh-Nagumo Model

Other widely recognized models which use a phenomenological approach to understanding the cardiac action potential, specifically, consist of the FitzHugh-Nagumo-type models (Figure 2). These models are derived from the original FitzHugh-Nagumo two-variable system of equations: [2,8]

$$\begin{aligned} \dot{\phi} = f^{\phi} = c[\phi[\phi - \alpha][1 - \phi] - r], \\ \dot{r} = f^{r} = \phi - br + a, \end{aligned} \tag{1}$$

where $\phi$ and $r$ represent the potential and recovery variables, respectively. The Aliev-Panfilov model is an adaption of FitzHugh-Nagumo-type models for action potentials that has been customized using experimental data from a canine myocardium. These modifications incorporate the following source terms: [2,8]

$$\begin{aligned} \dot{\phi} = f^{\phi} = c\phi[\phi - \alpha][1 - \phi] - r\phi \\ \dot{r} = f^{r} = \left[\gamma + \frac{\mu_1 r}{\mu_2 + \phi}\right]\left[-r - c\phi[\phi - b - 1]\right], \end{aligned} \tag{2}$$

where, again $\phi$ and $r$ represent the potential and recovery variables, respectively, while the rest are constant parameters. [8] All the variables in (1) and (2) are non-dimensional, including the temporal and spatial derivatives. Thus, initially published as a simplified, two-variable approach to the multi-system Hodgkin-Huxley equations, Aliev and Panfilov's model uses a phenomenological approach to explain the basic properties of cardiac tissue. The Aliev-Panfilov equations quantitatively reproduce important characteristics of action potential propagation of cardiac tissue, such as the duration and velocity of each action potential, the recovery period, and the shape of the cardiac action potential.

Aliev and Panfilov's model provides a more realistic shape of the cardiac action potential compared to the original FitzHugh-Nagumo model, since the hyperpolarization overshoot is eliminated and an evident 'plateau' region is obtained (Figure 1). However, these equations do not explain dynamics of the action potential as thoroughly as an

ionic model that incorporates dynamics of ionic channels in the cell membrane. They are mainly used to model specific, multicellular cardiac cell experiments conducted. Changes in the extracellular ion concentrations or drug therapy that affects these concentrations will significantly alter any variables in such models. Gathering experimental data and using ionic models to 'fit' the data and compute desired properties of the action potential has been reported to be a better approach. Ionic models therefore incorporate a larger number of currents and conductivities based on detailed, single-cell experimental data. [9,10]

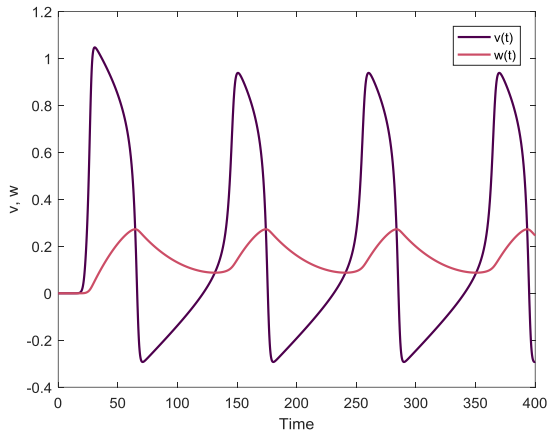


Figure 1. Pulse profile of the FitzHugh-Nagumo model

## 2. Development of the Mathematical Model

For the purposes of the simplified approach taken in this paper, the mathematical model implemented relies on established FitzHugh-Nagumo-type models for modeling the cardiac action potential. In the FitzHugh-Nagumo system, a sufficiently large perturbation from the steady state sends the state variables on a trajectory that initially runs away from equilibrium before returning to the steady state (Figure 2). The system's excitation is characterized through four phases in the phase plane: the regenerative phase with a fast increase of the membrane potential; the active phase with a high and almost constant membrane potential causing a slow increase of the recovery variable $r$; the absolutely refractory phase with a fast decrease of the membrane potential at almost constant recovery $r$; and the relatively refractory phase with a slow decrease of the recovery variable $r$ as the solution gradually returns to the equilibrium point.

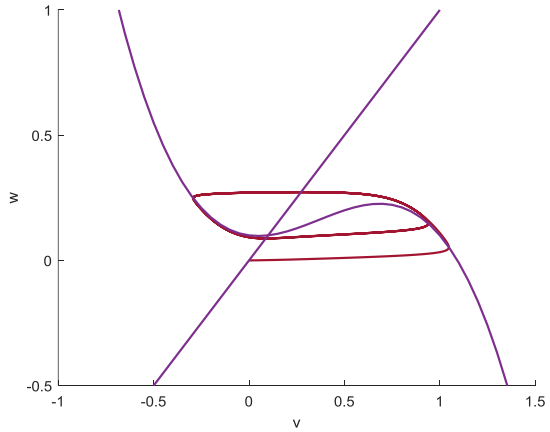


Figure 2. Nullclines of the FitzHugh-Nagumo model

In order to build a model for the entire heart, the mechanistic properties need to be taken into consideration. For this, one needs to add a phenomenological diffusion term $div\ \boldsymbol{q}\ (\phi)$ to the original local version of the FitzHugh-Nagumo equations, where $q(\phi)$ is the potential flux, which is modeled as $q(\phi) = \nabla\phi$. [8]

$$\begin{aligned} \dot{\phi} &= div\ \boldsymbol{q}\ (\phi) + f^{\phi}(\phi, r) \\ \dot{r} &= f^{r}(\phi, r) \end{aligned} \tag{3}$$

The right-hand sides are summarized in two source terms $f^{\phi}(\phi, r)$ and $f^{r}(\phi, r)$. In order to analyze the behavior of the solution via a finite element approach, the equations are cast in the residual form and passed to the weak formulation over element domains:

$$\begin{aligned} R^{\phi} &= \dot{\phi} - div(\boldsymbol{q}) - f^{\phi} \doteq 0\ in\ \mathcal{B}, \\ G^{\phi} &= \int_{\mathcal{B}^e} \delta\phi\ \dot{\phi}\ dV + \int_{\mathcal{B}^e} \nabla\delta \cdot \boldsymbol{q}\ dV - \int_{\partial\mathcal{B}^e} \delta\phi\ \bar{q}\ dA - \int_{\mathcal{B}^e} \delta\phi\ f^{\phi}\ dV = 0. \end{aligned} \tag{4}$$

The membrane potential $\phi$ is introduced as global degree of freedom on each finite element node in a four-node quadrilateral element, whereas the recovery variable $r$ is treated as an internal variable and is stored locally at the integration point level, i.e. the local element level. Decomposing the potential in terms of the piecewise-linear shape functions $N^i$, and using backward finite difference for the temporal derivative, we obtain the following discrete residual $R_I^{\phi}$:

$$R_I^{\phi} = \boldsymbol{A}_{e=1}^{n_{el}} \int_{\mathcal{B}^e} N^i \frac{\phi - \phi_n}{\Delta t} + \nabla N^i \cdot \boldsymbol{q}\ dV - \int_{\partial\mathcal{B}^e} N^i\ \bar{q}\ dA - \int_{\mathcal{B}^e} N^i\ f^{\phi}\ dV \doteq 0 \tag{5}$$

The operator $\boldsymbol{A}$ symbolizes the assembly of all element contributions at the element nodes $i = 1, \dots, n_{en}$ to the residual at the global node points $I = 1, \dots, n_{nd}$. $\mathcal{B}$ denotes the element domain, and $\partial\mathcal{B}^e$ is its boundary. The above system is solved at each time instance using a Newton-Raphson iteration, for which one also needs the derivative matrix:

$$\partial_{\phi_j} R_I^{\phi} = \boldsymbol{A}_{e=1}^{n_{el}} \int_{\mathcal{B}^e} (N^i \frac{1}{\Delta t}\ N^j + \nabla N^i \cdot d_{\nabla\phi}\ \boldsymbol{q} \cdot \nabla N^j - N^i\ d_{\phi} f^{\phi} N^j)\ dV \tag{6}$$

The iterative updates for the Newton-Raphson scheme are then calculated:

$$\phi_I^{k+1} = \phi_I^k - \sum_J \left[\partial\phi_J R_I\right]^{-1} R_J(\phi^k)\,, \tag{7}$$

or in the vector form:

$$\begin{bmatrix} \phi_1^{k+1} \\ \phi_2 \\ \vdots \\ \phi_{nd} \end{bmatrix} = \begin{bmatrix} \phi_1^k \\ \phi_2 \\ \vdots \\ \phi_{nd} \end{bmatrix} - \begin{bmatrix} \partial\phi_1 R_1 & \partial\phi_2 R_1 & \dots & \partial\phi_{nd} R_1 \\ \partial\phi_1 R_2 & \partial\phi_2 R_2 & \cdots & \partial\phi_{nd} R_2 \\ \vdots & \vdots & \ddots & \vdots \\ \partial\phi_1 R_{nd} & \partial\phi_2 R_{nd} & \dots & \partial\phi_{nd} R_{nd} \end{bmatrix}^{-1} \begin{bmatrix} R_1^k \\ R_2 \\ \vdots \\ R_{nd} \end{bmatrix}. \tag{8}$$

The constitutive equations for the source terms $f^{\phi}$ and $f^{r}$ are defined for distinct cell types, since the profile of the action potential and individual excitation characteristics can be quite different for different cell types. The pacemaker cells are taken to be of FitzHugh-Nagumo type, and their action potentials are modeled via the corresponding source terms. On the other hand, the heart muscle cells are modeled by the Aliev-Panfilov equations with the appropriate $f^{\phi}$ and $f^{r}$ (Equations 1 and 2). The recovery variable $r$, is treated as a local variable, and a simple local Newton-Raphson method is applied to the finite difference discretized equation for each of the element node at each time. [8]

## 3. The Numerical Scheme

For the computational model, the spatial distribution consists of a square-shaped flat cardiac tissue divided into 21x21 elements. The central element corresponds to oscillatory pacemaker cells, modeled by the FitzHugh-Nagumo equations, while the rest of the elements represent heart muscle cells and are modeled by Aliev-Panfilov equations. The overall solutions algorithm is as follows.

```
Initialize ϕ[0], r[0]
for n=0 to N do
       ϕ[i] ← ϕ[n,i]
       r ← r[n]
       while |R^ϕ|>Tol do
              while |R^r|>Tol do
                     r ← r-[∂_r R^r]^-1 R^r
              compute ∂_ϕ R^r, d_ϕ r, f^ϕ, d_ϕ f^ϕ, ∂_ϕ R^ϕ
              ϕ ← ϕ-[∂_ϕ R^ϕ]^-1 R^ϕ
       r[n+1] ← r
       ϕ[n+1,i] ← ϕ[i]
```

The algorithm presented by the pseudocode above is implemented in Python using NumPy. The residual and its derivatives for the central element are computed using FitzHugh-Nagumo source terms, while for the rest of the elements, Aliev-Panfilov source terms are used. The boundary values on the external boundary of the square are of vanishing Neumann type. Functions such as `residual_phi` and `residual_r` and their partial derivative matrix calculations are called via the main algorithmic loop and evaluate $R^{\phi}$ and $R^{r}$ at each element-level node. The double integrals and various gradients of the shape functions as well as the test values for $\phi$ have been evaluated numerically using MATLAB and are provided as a matrix input in the computation to minimize computational time and optimize the Newton scheme (Figure 3).

```
for n in time:
    R_phi_global = np.ones((global_matrix_size,1))
    Tol = np.ones((global_matrix_size,1))*tol
    phi_global=phi_global_time[:,(n-1)] ##using the 'passed' phi_global frm previous time
    while sum(abs(R_phi_global)) > sum(Tol):
        print('The residuals have not passed tolerance. Recalculating...')
        phi_step[n]+=1
        phi[n,:] = f.global_to_element_21x21(np.zeros(1764),phi_global)
        for z_d in np.arange(0,1761,4):
            nodes = [z_d,(z_d+1),(z_d+2),(z_d+3)] ##assign node values & print variable
            (r,R_phi,p_phi_R_phi)=element_calcs(nodes,R_phi,p_phi_R_phi,phi,r,n)

            ##FHN element
            if z_d==880:
                nodes=[z_d,(z_d+1),(z_d+2),(z_d+3)]
                k=min(nodes)
                for j in [0,1,2,3]:
                    r[n,(j+k)] = f.r_FHN(r[(n-1),(j+k)],phi[n,(j+k)])
                    R_phi[j+k] = f.residual_phi_FHN(j,phi,r,nodes,n)
                    for m in [0,1,2,3]:  ##partial derivative matrix
                        p_phi_R_phi[(m+k),(j+k)] = f.partial_derivative_phi_R_phi_FHN(j,m,phi,r,nodes,n)

        ##assembling 1764 element nodes to 484 global nodes
        (R_phi_global,p_phi_R_phi_global)=f.element_to_global_21x21(R_phi, p_phi_R_phi)

        ##Newton's iteration for phi
        phi_global=phi_global-np.matmul(np.linalg.inv(p_phi_R_phi_global),R_phi_global)
        print('This is the maximum value of the residual for the current iteration: '
              + str(max(abs(R_phi_global)))+'.')
        phi_global.shape=(global_matrix_size,) ##makes shape compatible for matrix update
        phi_global_time[:,n]=phi_global ##updates global phi matrix for time loop
```

Figure 3. Finite Element Method algorithm implementation in Python

Suppose one would want to solve this system for 10-time steps. The algorithm first assumes a $\phi$ value for each $i$ node in the element-level system for each time step. Suppose this value is zero for each node for $t = 0$ in an element characterized by Aliev-Panfilov-type cells, and a given non-zero value for each node in an element characterized by FitzHugh-Nagumo-type cells. For the 'FitzHugh-Nagumo-element' the residual and derivatives for this element are computed separately from Aliev-Panfilov-type cells using appropriate source term equations for the same time step. Similarly, for the rest of the nodes, the algorithm computes values for the residual and the associated values of $\phi$ and $r$ required for their Newton iteration, such as: $\partial_\phi R^r, d_\phi r, f^\phi, d_\phi f^\phi, \partial_\phi R^\phi$. This implies that the numerical scheme evaluates each value at the element level in a system of 1764 element nodes (4 per element) and 484 global nodes for a 21x21 mesh. Finally, to run the Newton iteration for $\phi$, the element nodes are assembled into global nodes using simple loops in an element-to-global `assembly` function. Then, the scheme proceeds with the Newton iteration for $\phi$ in the global system which is then recorded as the value of $\phi$ at each of the node at the $n + 1$ time instance.

## 4. Results

The working algorithm in Python and associated functions and matrices used in MATLAB are available online at `https://github.com/zahramansoor/pyrhythm/`. There are some limitations with the current algorithm and its output values for the membrane potential $\phi$ and associated recovery variable $r$. Considering the algorithm does not work through a 'black box' PDE or finite element solver, the challenges in building such algorithms lie in understanding and executing the mathematical model via a computationally accurate and robust method.

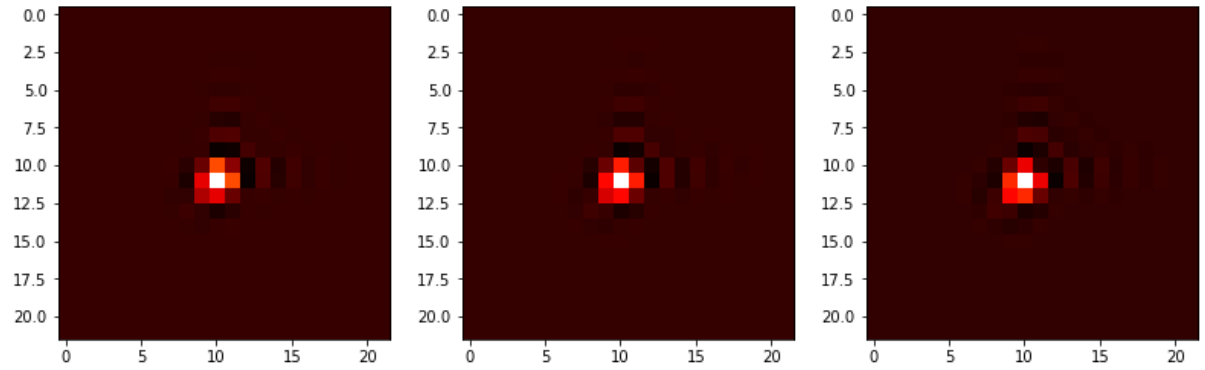


Figure 4. Single central pacemaker element of FitzHugh-Nagumo-type exciting the remainder of a square ventricular tissue block of Aliev-Panfilov-type through isotropic conduction for (from left to right) $t = 0.005, t = 0.006$, and $t = 0.007$. Heatmap shows dimensionless $\phi$ values. Asymmetric distribution of potential and accumulation compared to expected results are observed.

While the Python code provides a robust computational paradigm, the 21x21 test case leads to deviations from the expected results (Figure 4). [8] A larger lattice will be needed to get more realistic values, though the generalization is straightforward. This work centered around building the computational paradigm, which can be generalized to larger lattices and more general geometries in straightforward ways

## 5. Future Work

This paper pursued the goal of building a computational model for the cardiac action potential, implemented in an open-source environment. The model is computationally inexpensive and robust. Although the finite element-based algorithm described in this paper operates in isotropic conditions of media and does not account for many electromechanical phenomena of myocardial fiber orientation and mechanics, using appropriate generalizations can lead to a significant expansion of this phenomenological model to anisotropic conditions, which can also be used to examine spiral wave re-entry. A similar finite element scheme can also be applied to biologically-relevant ionic models for studying the action potential and can be further modified to incorporate optogenetic interventions. [9]

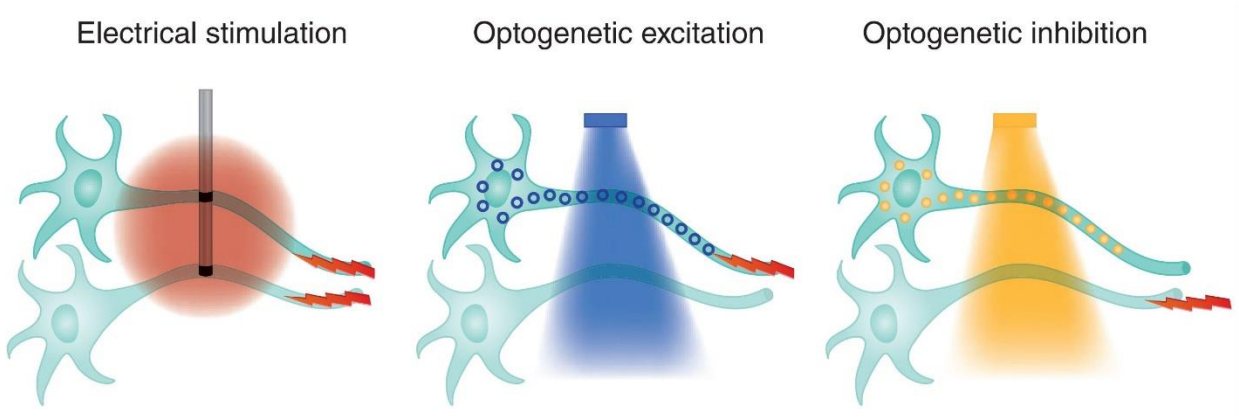


Figure 5. Principle of optogenetics in neuroscience. Targeted excitation (as with a blue light–activated channelrhodopsin) or inhibition (as with a yellow light–activated halorhodopsin), conferring cellular specificity and even projection specificity not feasible with electrodes while maintaining high temporal (action-potential scale) precision. Adapted from Deisseroth, 2011. [10]

Optogenetics — the precise interrogation, stimulation, and control by light of excitable tissue, genetically altered to become light- sensitive rooted in spatial-temporal studies in neuroscience — is being slowly and successfully integrated into the study of cardiac morphologies (Figure 5). Optogenetic markers inserted into embryonic stem cells is gaining recognition as a research outlet with a prolific future in cardiac medicine. [11] Light- sensitive cardiac cells have been proposed to be used as gene or cell therapy and as an alternative to implantable pacemakers and cardioverters/defibrillators. Such therapies have significantly expanded the scope of addressing cardiac pathologies as well. [12] With the use of computer simulations, coupling optogenetic control of cardiac cells by growing light-sensitive cardiomyocytes and modeling cellular and ionic behavior is theoretically possible. [13] The initial Hodgkin-Huxley model — a coupled system of four ordinary differential equations — and further improvements, such as the Luo-Rudy model, can be successfully adapted for such a task. [14,15]

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