

# Computational simulations can help understand and treat cardiac rhythm disorders

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Computational models of the human heart can be very useful in studying not just the basic mechanisms of heart function, but also to analyze the heart in a diseased state, and come up with methods for diagnosis and therapy.

Dr. Natalia Trayanova's Computational Cardiology Lab at the Johns Hopkins University is doing just that—her group uses mathematical models to look at [cardiac function](#) and dysfunction, examining the mechanisms behind disorders such as cardiac arrhythmias and pump dysfunction.

In a plenary lecture at the SIAM Conference on [Computational Science](#) and Engineering in February, Dr. Trayanova described how her lab uses imaging data from clinics, such as MRIs and CT scans, to create heart models. Using detailed information from such images, the team geometrically constructs 3-D computer models by incorporating information about chemical and protein interactions as well as cardiac fiber orientation.

A normal heart beats at a steady, even rhythm— usually between 60 and 100 times a minute. "Cardiac arrhythmia" is a condition caused by a disruption of the normal rhythm of the heart.

## Analyzing drug interactions:

Sodium channels are [membrane proteins](#) located in cardiac cells, which play a central role in the proper conduction of [electrical impulses](#) within the heart, and are hence important for normal cardiac electrical activity. Altered [sodium channel](#) function is associated with various arrhythmias, including potentially lethal arrhythmias that result from sodium channel disease.

Given their importance, clinically, drugs for arrhythmia usually target sodium channels. Many drugs used to treat arrhythmia tend to exhibit pro-arrhythmic effects – while they may cure one component, they can induce another. Hence, clinical trials for arrhythmia drugs have often resulted in more people dying from them than from placebos, says Trayanova. Previously, there has never been a platform to evaluate drug interactions for arrhythmia in order to predict a drug's pro- or anti-arrhythmic effects. But with heart models, that's possible.

Drug companies often test drugs at the cell level, which does not give as complete a picture as the whole-heart level, says Trayanova. Hence, Trayanova's team constructed a computational framework under which drug interactions with the whole heart can be studied. Their model focuses on the sodium channel, particularly sodium channel blockers, which are often used as drugs in arrhythmia treatments. The modeling of drug-channel interactions in order to determine the effects of drugs on electrical activity in the heart can help develop a drug-screening system for treatment applications.

## **Treatment of arrhythmias:**

Trayanova's team also studies other methods to terminate arrhythmias using computational models.

## **Defibrillation**

Atrial fibrillation— or [cardiac arrhythmia](#) that occurs in the heart's upper chambers—is a common form of arrhythmia. It is one of the most predominant diseases affecting our aging population. While it is not lethal, it is a major risk factor for stroke, and can be extremely unpleasant, says Trayanova.

A procedure that is often used by physicians to treat atrial fibrillation, called defibrillation, delivers an electric shock to the patient's heart, resetting it to a normal rhythm.

However, this process can be inconsistent. In some cases, the frequency or magnitude may be insufficient to block the arrhythmia, and the process fails. In addition, defibrillation that is currently used clinically is an extraordinarily painful process, says Trayanova. Hence, her lab has used models to come up with a new way to simultaneously defibrillate the heart while blocking nerve conduction in the nerves that carry pain, targeting them for pain suppression.

## **Cardiac Ablation**

Another commonly-used procedure for terminating arrhythmias is cardiac ablation, which works by scarring or destroying tissue in the heart that triggers the abnormal heart rhythm, also called the organizing center of the arrhythmia. However, determining optimal targets for ablation with current mapping techniques remains a challenge clinically.

Since it is hard to tell which cells are causing the abnormal rhythm, physicians currently use an electrical probe to test several areas over the whole surface of the heart for the crucial organizing center. The process is very crude, usually performed non-invasively through a catheter, and can last up to eight hours or more.

Trayanova is developing a new individualized methodology for this procedure, wherein heart models of patients are constructed from clinical images. Through a model of the patient's heart constructed from a noninvasive MRI scan, doctors can better navigate the probe to the location of the organizing center as determined by the model. Such guided delivery of the ablation could make it more precise, leading to an improvement of therapy.

Trayanova and her group were able to validate their models by replicating and retrospectively predicting clinical results in both successful and failed cases of ablations. Furthermore, they were able to successfully predict the optimal ablation site, which not only terminated the arrhythmia, but whose lesion size was also smaller than those used in clinical procedures.

## **Analyzing the causes of heart rhythm disorders:**

Trayanova and her group are trying to determine what processes trigger abnormal heart rhythm, particularly when people age. It is known that fibrosis, which is the growth of excess connective tissue among [cardiac cells](#), may contribute to arrhythmias by altering or inhibiting conduction. But the exact process is not well understood.

Using human heart images from clinical samples, Trayanova's computational cardiology lab has constructed a model of the human atrium, which represents these fibrotic regions. Through these models, the group has shown that the coupling of fibroblasts with myocytes (two different cell types in the heart) can lead to changes in ion channel activity leading to arrhythmias.

## **Other applications:**

Another clinical application for these computational models could be to remedy misidentification of arrhythmia. In many cases, patients are needlessly implanted with defibrillators, as seen from the observation that only five percent of these patients experience a subsequent arrhythmia triggering activation of the device. Trayanova's team is using models to make predictions on which patients are at high risk for arrhythmia, and thus need defibrillators.

An exciting new technique that is being considered for cardiac therapies is optogenetics, a procedure that can stimulate heart muscle cells with low-energy light. This is achieved by coupling donor cells optimized for light responsiveness with heart cells. Using an electromechanical heart model, Trayanova's group has shown that if such light sensitivity is expressed in the Purkinje system, the network of fibers that cause synchronized contraction in the heart's lower chambers, the threshold for stimulating the heart with light is much lower. Leveraging computational simulations to design and conceptualize new techniques such as this is exciting, because it raises the potential of using light instead of electrical shock for defibrillation.

Trayanova's group is working on bringing these simulations and models to the clinic. Several projects are already underway where models are being integrated into clinical practice. "We want to translate these models for clinical care," she said. "To use them routinely in a personalized way to help patients and to administer the best therapy."

In a very engaging plenary lecture, Dr. Trayanova described how computationally-simulated hearts can be used to not only detect and treat heart disorders such as arrhythmias more efficiently, but also how they can help us better understand the fundamental mechanisms and physiology of the heart, and hence, determine the causes of such disorders.

View a brief video overview of her talk and an interview with Dr. Trayanova here:

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