Simulation of cardiac excitation patterns in a three-dimensional anatomical heart atlas


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Abstract

Computerized anatomical atlas systems enable interactive investigation of digital body models. Here we present a three-dimensional atlas of the human heart, based on image data provided in the Visible Human Project. This heart atlas consists of multiple kinds of cardiac tissues and offers unlimited possibilities for its visual exploration. A temporal dimension is added to the underlying heart model by simulation of cardiac excitation spreading. For this purpose a second generation cellular automata algorithm is adapted to the excitation kinetics of cardiac tissue. The presented system is shown as a successful method for the visualization-based investigation of cardiac excitation.

Keywords: Interactive visualization; Knowledge-based systems; Cellular automata; Excitable media; Information fusion

1. Introduction

Computer-based anatomical atlas systems are on their way to substituting traditional paper-based atlases. Both computer- and paper-based atlases aim at giving a detailed spatial description of the body by a combination of visual and symbolic knowledge. Traditional paper-based atlases, such as the Netter atlas [1], combine static images with a textual interpretation. Many of today’s computer-based atlas systems use the new abilities of digital
media by simply increasing the amount of images and text displayed. More advanced model-based atlas systems, such as VOXEL-MAN [2], use the computer for construction of a three-dimensional (3D) voxel model of the human body and its interactive manipulation. These advanced computer-based anatomical atlas systems can provide a relatively accurate spatial reconstruction of the body.

In the presented work, a 3D model-based atlas of cardiac anatomy is reconstructed from the photographic slices of the Visible Human data set [3]. This anatomical heart atlas has been segmented into multiple kinds of different tissues. It offers unlimited possibilities for its interactive visual exploration in the computer. However, in reconstructing the heart, dynamic phenomena such as excitation spreading are playing a major role. Therefore we combine the spatial heart model with a simulation of cardiac excitation spreading. Each discrete volume element (voxel) of the anatomical model is seen as a voxel automata cell of a 3D cellular automata. A drawback of all cellular automata, which have been previously used for heart tissue simulation, is their lack of essential features of excitation spreading. To overcome this limitation, we adapt a second generation cellular automata model. This cellular automata model was originally designed by Gerhardt et al. [4] for simulation of an oscillating chemical reaction.

The resulting atlas system enables interactive visual exploration of excitation spreading in the whole heart. No attention is paid in this stage of work to the contraction of cardiac muscle cells and the resulting deformation of the cardiac muscle.

2. Construction of a 3D heart model

As a prerequisite, a detailed geometrical 3D model of the heart and its different kinds of tissues is needed. To construct a 3D geometrical voxel model of the heart, we used a stack of two-dimensional image slices (Figs. 1 and 2). These high resolution image slices are provided as space filling for the entire human body by the National Library of Medicine in the Visible Human Project [3]. A colour-threshold segmentation method [5] was used to reconstruct a 3D geometry of the heart muscle from these 2D image slices. Since the VOXEL-MAN atlas system is a software for anatomical knowledge representation, a geometry of vessels and valves was modelled, although not needed for the simulation of cardiac physiology in this stage of work (Figs. 3 and 4a, b).

The atrial shape of the geometrical model approximates structures such as the crista terminalis, but disregards the inner atrial trabecular structure such as the pectinate muscles (Fig. 4c). The atria were completely separated from the ventricles by manual slicewise editing of the orthogonal image slices, constructing the fibrotic tissue separating the atria from the ventricles (Fig. 4d). Since postmortem rigor had already occurred, the resulting hypercontraction of the left ventricle was corrected by a digital outscraping of the computer model's left ventricle, using morphological image processing operators (Fig. 4e).

Geometry of myocardial cells, specialized in the generation and conduction of cardiac excitation, cannot be recognized on macroscopic images. So the spatial position of the voxels representing the sinus node, the atrio-ventricular node, the His bundle and the Tawara branches were defined manually in the anatomical model (Fig. 4f), according to a description
in a classical anatomical atlas [1]. The Tawara branches are constructed as lines of voxels. An approximation of the Purkinje fibres, building the connection to myocardial tissue, is defined as the two surrounding voxel layers.

The constructed voxel model of the heart now defines the topology of our 3D cellular automata. The parameters governing the dynamical behaviour of a certain type of simulated heart tissue are given as static attributes of the anatomical object, to which the voxel belongs. State variables of the voxel automata cells can be attached to the anatomical voxel model as dynamically changing attributes.

Fig. 1. Phase plane diagram showing the local rules of the cellular automation. The excitation variable $u$ may take the values 0 or 1. The recovery variable $v$ increases when $u = 0$. Excitation can be triggered if the cell is sufficiently recovered, i.e. $v < V_{exci}$.
3. Simulation of cardiac excitation

3.1. The basic GST-Algorithm for simulation of excitable media

Gerhardt et al. use their second generation cellular automata, the so-called GST-Algorithm, for simulation of the Belousov–Zhabotinsky reaction, an oscillating chemical reaction [4,6–8]. An excitable medium is modelled by a rectilinear grid of cells. The state of each cell (Fig. 1) is characterized by two integer state variables. An excitation variable $u$ indicates the unexcited or excited state and a recovery variable $v$ indicates the recovery state of a cell, with:

$$u \in \{0, 1\} \quad \text{and} \quad v \in \{0 \ldots V_{\text{max}}\}.$$  

The rule for temporal evolution of the state variables is that the recovery variable, $v$, increases by a value, $g_{\text{up}}$, each timestep until $v = V_{\text{max}}$, if a cell is in the excited state ($u = 1$). When $v = V_{\text{max}}$ the excitation variable, $u$, switches to the unexcited state ($u = 0$) and $v$ decreases each timestep by a value, $g_{\text{down}}$, until the cell reaches the stable rest state ($u = 0$ and $v = 0$).

This can be expressed as:

\begin{align}
   v_{t+1} &= \min\{v_t + g_{\text{up}}, V_{\text{max}}\} \quad \text{if} \quad u = 1 \\
   v_{t+1} &= \max\{v_t - g_{\text{down}}, 0\} \quad \text{if} \quad u = 0
\end{align}  

The rule for the spatial spread of excitation is as follows: an unexcited cell ($u = 0$) will become

Fig. 2. Orthogonal slice from the thorax region of the visible human female dataset.
Fig. 3. To find the kinetic parameters of the GST-Algorithm phases of cardiac action potential were matched to the automata cell cycle phases.
Fig. 4. Anatomical heart model generated from the VHF data shown from different viewpoints. Various tissues are assigned different colours.
excited \((u = 1)\) in the next time step, if it is sufficiently recovered \((v < V_{\text{exc}})\) and if the number of neighbours being already in the excited state exceeds a threshold \(k_{\text{exc}}(v)\):

\[
\text{excited neighbours} > k_{\text{exc}}(v)
\]

Neighbours of a cell are taken to be all cells within a cube of the ‘radius’, \(r\), centred on a given cell. Isotropic excitation spreading is modelled with cellular square neighbourhoods, while anisotropic excitation spreading can be modelled with rectangular neighbourhoods.

The excitability threshold for a relative refractory cell \(k_{\text{exc}}(v)\) is assumed to be the linear function between the minimum and maximum excitability threshold:

\[
k_{\text{exc}}(v) = k_{\text{exc}}(0) + \frac{[r(2r + 1) - k_{\text{exc}}(0)]v}{V_{\text{exc}}}
\]

The minimum excitability threshold of an automata cell is given by the threshold of the resting medium \(k_{\text{exc}}(v = 0)\), the maximum threshold by the transition point from the absolute to the relative refractory state \(k_{\text{exc}}(v = V_{\text{exc}})\). De-excitation of an excited cell occurs in the GST-Algorithm if the recovery variable \(v\), reaches the value \(V_{\text{max}}\) or preliminary, if a sufficient number of neighbours are in the unexcited state.

In the theory of excitable media, the diffusion coefficient relates normal velocities of curved wavefronts to plane wave conduction speed. For calculation of the plane wave conduction speed \(c\) and diffusion coefficient \(D\) of the excitation variable \(u\), the following formulas were derived by the authors of the GST-Algorithm:

\[
c(r) = r - \left(\text{int}\frac{k_{\text{exc}}(0) \text{ cellwidth}}{2r + 1 \text{ timestep}}\right)
\]

\[
D(r) = 0.032(2r + 1)^2 \text{ cellwidth}^2 \text{ timestep}^{-2}
\]

The GST-Algorithm gives an efficient method to compute the general features of excitable media. Formula (3) can be used to scale the cellular automata algorithm in space and time.

Here we can give a very comprehensive description of the GST-Algorithm. A more detailed presentation of the GST-Algorithm is described by [4,6–8].

Since the authors use the algorithm for the simulation of a chemical reaction, the ‘right address in parameter space’ for the simulation of heart excitation had to be found, and this is discussed in the following section.

### 3.2. The GST-Algorithm for modelling cardiac excitation

#### 3.2.1. Modeling spatiotemporal properties of myocardial tissue

A plane wave conduction speed \(c = 0.5 \text{ m/s}\) and a diffusion coefficient \(D = 0.76 \text{ cm}^2/\text{s}\) are reported [9] for myocardial tissue. If the cellular neighbourhood radius, \(r\), is set to three voxel cells, these values result from the Formula (3a,b) for a cellwidth of 1/3 mm and a timestep of 2 ms. The Visible Human Female data set has an original spatial resolution of 1/3 mm isotropic voxel cellwidth. To speed up computation, the size of the data was reduced by the factor 2 in
each dimension. As mentioned the cellwidth of the applied cellular automata model is fixed to 1/3 mm due to the speed–curvature relation. This leads to a decreased size of the anatomical model compared to the original heart. So the heart model size corresponds rather to the size of a child’s heart than to the size of an adult heart.

Conduction in the atroioventricular node is slowed down in real hearts to a speed of about $c = 0.05–0.1 \text{ m/s}$. This means that only a distance of half of a voxel automata cellwidth has to be passed by the wave front per timestep. Therefore the size of the neighbourhood radius is minimized to one cell and these cells can only become excited every odd timestep.

Conduction speed in the Tawara branches is increased, compared to normal myocardial tissue. In the Tawara branches of the model, increased voxel automata cell neighbourhood radii generate increased conduction speed, according to Formula (3a).

### 3.2.2. Excitation and recovery of voxel automata cells

A voxel automata cell can be seen as an encapsulation of the average behaviour of the much smaller myocardial cells contained within the voxel. So the phases of the voxel automata cell excitation period can be related to the phases of the cardiac action potential (Fig. 3). By this consideration, we have a method to find the ratios of the parameters $V_{\text{max}} / g_{\text{up}}, V_{\text{max}} / g_{\text{down}}$ and $V_{\text{exc}} / V_{\text{max}}$. These ratios determine excitation and recovery of the voxel automata cells. Since we know from scaling the automata in space and time how many milliseconds correspond to one voxel automata time step, the above parameter ratios can now be calculated from the values known for excitation and recovery of myocardial cells.

The rapid upstroke in myocardial excitation, determining wave conduction speed in real hearts, is simply modelled by setting an automata cell from the unexcited to the excited state.

In cardiac physiology for modelling APD dependency on the length of the previous diastolic interval ($d_i$), the formula

$$\text{APD}(\text{diastolic interval}) = \text{APD}_{\text{max}} \left(1 - \exp\left(-\frac{\text{diastolic interval}}{\tau}\right)\right)$$

with a time constant $\tau$ of about 200 ms is known [10].

Since this dependency is an important feature of heart excitation, it has to be included in the algorithm. Therefore the originally fixed parameter, $g_{\text{up}}$, in Formula (1a) and the diastolic interval, $d_i$, of a voxel automata cell were introduced as further state variables. The value of $g_{\text{up}}$ is now calculated in each voxel automata cell excitation cycle, depending on the length of the previous diastolic interval according to the above formula by

$$g_{\text{up}} = \frac{V_{\text{max}}}{A_{\text{max}} \left(1 - \exp\left(-\frac{\text{diastolic interval}}{\tau}\right)\right)}$$

(4)

So the maximum duration of a voxel automata cell’s excited state, defined by the parameter $A_{\text{max}} = \text{APD}_{\text{max}} / \text{timestep}$, is shortened depending on the cells previous $d_i$. The parameter $\text{APD}_{\text{max}}$ was varied between 100 ms in the sinus node and 280 ms in the Tawara branches.

In modelling the Belousov–Zhabotinsky reaction, Gerhardt et al. [4,6–8] allow preliminary recovery of automata cells, due to an unexcited neighbourhood. This preliminary recovery is
disabled in modelling heart excitation, because of lacking physiological evidence for this behaviour in real myocardial cells.

Duration of the recovery period, corresponding to phase III of cardiac action potential, is determined by the parameter ratio $V_{\text{max}} / g_{\text{down}}$ in Formula (1). Since biological systems do not behave in a strictly deterministic manner, this parameter is transferred into a cellular state variable and calculated as the sum of a non-random part $g_{\text{down\_fixed}}$ and a random part $g_{\text{down\_random}}$

$$g_{\text{down}} = g_{\text{down\_fixed}} + g_{\text{down\_random}}$$

For sake of simplicity, the random element is taken from an uniform probability distribution, varying recovery time randomly between 130 and 160 ms in all types of voxel automata cells. By setting the parameter ratio $V_{\text{exci}} / V_{\text{max}} = 1/2$, the recovery period is divided in equal parts in an absolute and a relative refractory part, according to data given in Antoni [11].

Since no spontaneous excitation occurs in the original GST-Algorithm, the voxel automata cell excitation cycle is supplemented with a new phase. A new internal state variable $w$ is introduced. If a voxel automata cell reaches the rest state ($u = 0$ and $v = 0$), $w$ is increased by a parameter value $g_{\text{up\_slow}}$ each timestep by the following rule:

$$w_{t+1} = \min\{w_t + g_{\text{up\_slow}}, W_{\text{max}}\} \quad \text{if} \quad u = 0 \quad \text{and} \quad v = 0$$

When $w$ reaches the threshold $W_{\text{max}}$, the cell is set to the active state and $w$ is reset to 0. So the newly introduced parameter $g_{\text{up\_slow}}$ can be used, to trigger excitation with various frequencies from primary or secondary pacemaker areas of the voxel automata model.

As mentioned above, we know how many milliseconds correspond to one automata timestep from scaling in time and space, using the speed–curvature relationship. Therefore, all excitation and recovery parameters of voxel automata cells can be chosen according to actual values of real myocardial cells.

4. Results

In the normally activated heart, excitation is generated in the sinus node and stops after sequential activation of the atria and ventricles, because it is surrounded by refractory tissue. The presented model-based heart atlas shows the whole heart excitation cycle close to pictures known from cardiac physiology [1,10,12]. In the presented images (Fig. 5) the heartbeat is generated in the sinus-node with a frequency of 90 heartbeats/min. It spreads consecutively over the atria (Fig. 5a). The av-node is reached after 40 ms and the atria are completely excited after 60 ms (Fig. 5b). Conduction is delayed in the av-node and depolarisation of the ventricular septum starts after 150 ms in the interventricular septum (Fig. 5c). The ventricles are completely activated after 200 ms. After about further 140 ms of complete ventricular activation (Fig. 5e), repolarisation of the ventricles begins in the middle part of the septum (Fig. 5f). The global excitation pattern is derived from modelling the properties of its voxel automata cells, encapsulating the behaviour of the contained myocardial tissue. The simulated excitation cycle of the whole heart results from the excitation cycles of the single volume
Fig. 5. Excited areas are shown in yellow. The upper half of the ventricles has been removed for visualization to give insight into the ventricular cavities.
elements. Diffusion of excitation in the volume can be simulated and visualized from arbitrary points of view [13]. For the investigation of cardiac excitation, our model-based heart atlas can be run on common single processor workstations.

The parameters determining excitation properties of a certain area, can be varied according to physiological and pathological changes in real myocardial tissue. For example, increasing inhomogeneity of the atrial grid leads to different atrial re-entry patterns. These different re-entry patterns might be interpreted as models for atrial flutter and fibrillation. In this simulation, transition from the flutter-like macro-re-entry pattern to the fibrillation-like pattern, consists of a multiple macro-re-entry path pattern. Experimental studies by Cox et al. [14] have shown a similar transition from an irregular structured macro-re-entry wave to an atrial fibrillation pattern.

A volume sum vector of excitation spreading could be calculated as the difference between the excitation state of each voxel and the excitation state at the previous timestep of the voxel, neighbouring in the direction of the derivation vector. This can help to evaluate whole heart excitation and enable investigation of pathophysiological mechanisms.

5. Earlier and related work

5.1. VOXEL-MAN atlas systems of the human body

VOXEL-MAN atlas systems use computer graphics methods [2,15] for the creation of photorealistic interactive 3D models of human anatomy. Therefore macroscopical image volume data are segmented into their constituents. The membership of voxels to a certain anatomical object is characterized by voxel labels which are stored in voxel attribute volumes congruent with the image volume. The anatomical objects can bear object attributes as well. These object attributes were divided into attributes concerning the visual appearance of objects and attributes concerning the meaning of objects. The resulting description of the spatial distribution of anatomical objects is then combined with a semantic network model for the description of object relationships. VOXEL-MAN atlas systems allow the user to freely navigate both in a spatial and a symbolic description of the human body. Applications of the system range from teaching, over radiological image interpretation, to the simulation of surgical procedures. However, not many attempts have been made to integrate dynamical physiological behaviour into the underlying body models.

5.2. Simulation of excitable media

For the simulation of heart excitation, cardiac tissue can be seen as an excitable medium. Differential equations models of excitable media emphasize realistic modelling of cellular properties such as excitability, refractoriness and recovery [16,17]. All these equation systems have in common is to involve variables changing on very different time scales. So integration of these detailed cellular models into tissue models, requires extremely strong computing resources. That makes them currently unsuitable for our purposes, i.e. interactive investigation
of cardiac excitation in a 3D model-based atlas system, including multiple types of cardiac tissues.

A computationally cheaper approach for the simulation of excitable media are the cellular automata models, which evolve discretely both in time and space. The cellular automata approach for computer simulation of cardiac tissue goes back to Wiener and Rosenblueth [18], and Moe and Abbildskov [19]. These first generation cellular automata models were intuitively attractive and could be used for the general investigation of re-entry mechanisms in a virtual piece of myocard. However, due to their high grade of abstraction, they could not be related to the experimental values characterising wave propagation. Here we use more recent second and third generation cellular automata models, which have overcome these limitations [4,20,21].

5.3. 3D heart models

Previous 3D cellular automata models of the whole heart mainly aim at the simulation of the ECG [22,23]. The basic cellular automata algorithm of Wei et al. [22] is transferred to a more detailed heart model by Werner et al. [24]. These cellular automata models show the importance of different types of myocardial tissues for the correct computation of the cardiac excitation cycle. Wave propagation features, such as curvature and dispersion, play a minor role in this approach. Thus, these cellular automata are less suitable for the visualization-based investigation of wave propagation in myocardial tissue.

On the other hand, differential equations are used for the visualization-based investigation of excitation in a model of 3D ventricular geometry by Panfilov [25]. This model includes only one type of tissue, disregarding the interaction of different types of myocardial tissues. Berenfeld and Jalife [26] use a similar differential equations approach for modelling Purkinje-muscle interaction in a 3D anatomical model of the ventricles. Discrete Purkinje-muscle junctions, as modelled by Berenfeld and Jalife [26], were important improvements of our anatomical model to be made.

As mentioned above, the computing resources needed for solving these differential equations by standard methods, currently do not allow their use for our purpose. We therefore had to find a different approach which would hold the balance between the computational efficiency of cellular automata and the physiological realism of differential equations.

6. Conclusion

We presented a four-dimensional computer-based atlas of the human heart. For this purpose the cellular automata algorithm developed by Gerhardt et al. [4,6–8] for simulation of the Belousov–Zhabotinsky reaction, was adapted to the excitation kinetics of the heart muscle. In contrast to cellular automata models previously used for the simulation of cardiac excitation, our cellular automata algorithm can be scaled in space and time to myocardial tissue, making use of the speed–curvature relation.

Excitation is modelled on a scale which is above the molecular level. However, Weimar et al. [20] see the GST-Algorithm as a non-standard solution method of a related differential
equation model. So our adaption of the GST-Algorithm can be seen as a step forward from previous cellular automata tissue models towards more realistic ionic models.

In summary, we integrated a simulation of cardiac excitation spreading into an anatomical 3D heart atlas. As outlined by Burgrim et al. [27], integration of knowledge representation systems and dynamical simulations on the scale of cell, tissue and organism, in future will be necessary for the fusion of information from various sources. In this sense, our approach might become useful by enabling systematic virtual experiments, to investigate the effects of localized anatomical or metabolical variations.

7. Summary

Advanced computer-based atlas systems of the human body, such as VOXEL-MAN, use the computer for construction of a 3D digital body model. This model gives the ability for its interactive manipulation in a model-based atlas system. While these model-based anatomical atlas systems provide a relatively accurate spatial reconstruction of the body, the dynamical physiological changes of the body have only played a minor role until now. In the presented work, a 3D model-based atlas of cardiac anatomy is reconstructed from the photographic slices of the Visible Human data set. This anatomical heart atlas includes multiple kinds of different tissues and offers unlimited possibilities for interactive visual exploration in the computer. However, in reconstructing the heart, phenomena in the temporal dimension, such as excitation spreading, are playing a major role.

So we combine the spatial heart model with a simulation of cardiac excitation spreading. Each discrete volume element (voxel) of the anatomical model can be seen as a cell of a 3D cellular automata. However, all cellular automata previously used for simulation of cardiac excitation, disregard essential features of excitation spreading. So we adapt a second generation cellular automata, designed for the simulation of an oscillating chemical reaction, to the heart muscle. This method enables interactive visual exploration of spatio-temporal whole heart behaviour. No attention is paid in this stage of work to the contraction of cardiac muscle cells and the resulting deformation of the cardiac muscle.

The parameters of the cellular automata have to fit the simulated myocardial tissues to experimental data. Therefore, the assumption is made that an automata cell encapsulates the average behaviour of the much smaller myocardial cells contained in the automata cell. Thus, the different phases of the automata cells can be related to the phases of the cardiac action potential.

The presented model-based heart atlas shows the whole heart excitation cycle close to results known from cardiac physiology. On the contrary to previous cellular automata models of cardiac excitation, our cellular automata algorithm can be scaled in space and time to real myocardial tissue, making use of the speed–curvature relation. We were therefore able to build an entire heart model from a realistic algorithmic description, which connects myocardial tissue models and cellular models. This model can be used for an interactive visualization-based investigation of cardiac excitation in a model-based heart atlas.
References


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