Automated quantification study of human cardiomyocyte synchronization using holographic imaging

INKYU MOON,1,* EZAT AHMADZADEH,1,2 KEYVAN JAFERZADEH,1 AND NAMGON KIM1

1Department of Robotics Engineering, DGIST, 333 Techno Jang-gang-daero, Hyeonpung-myeon, Dalseong-gun, Daegu 42988, South Korea
2Department of Computer Engineering, Chosun University, 309 Pilmun-daero, Dong-gu, Gwangju 61452, South Korea
*inkyu.moon@dgist.ac.kr

Abstract: This paper investigates the rhythm strip and parameters of synchronization of human induced pluripotent stem cell (iPS) derived cardiomyocytes. The synchronization is evaluated from quantitative phase images of beating cardiomyocytes which are obtained using the time-lapse digital holographic imaging method. By quantitatively monitoring the dry mass redistribution, digital holography provides the physical contraction-relaxation signal caused by autonomous cardiac action potential. In order to analyze the synchronicity at the cell-to-cell level, we extracted single cardiac muscle cells, which contain the nuclei, from the phase images of cardiomyocytes containing multiple cells resulting from the fusion of k-means clustering and watershed segmentation algorithms. We demonstrate that mature cardiomyocyte cell synchronization can be automatically evaluated by time-lapse microscopic holographic imaging. Our proposed method can be applied for studies on cardiomyocyte disorders and drug safety testing systems.

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1. Introduction

Recent advantages in the human induced pluripotent stem cells (hiPSCs) cardiomyocyte derivation methods [1,2] have provided the opportunity for utilizing these cells as a platform for disease modeling, regenerative approaches toward precision medicine, and toxicity screening. The atria (chambers in which the blood enters) and the ventricles (chambers in which the blood is collected and pumped out) of the heart are composed of cardiac muscle cells or cardiomyocytes (CM). For proper functioning of the heart, cells should be capable of shortening and lengthening their fibers as required, and these fibers must be flexible enough to stretch (for contraction-relaxation). The alternating action of contraction-relaxation is due to electrical stimulation created by ion fluxes in a well-sequenced order, in a process called cardiac excitation-contraction coupling. Each and every cell rapidly changes its 3D shape with the meaningful intermediate events (contraction period, relaxation period, and resting period) which occur at harmonic millisecond intervals. For perfect functioning of the cardiomyocyte system, all single cells should respond to the physical contraction command. This is achieved by the electro-chemical linkage between cells through structures known as gap junctions, which facilitates the action potential to travel to the adjoining cells, resulting in all cells contracting and relaxing simultaneously in a synchronized manner.

Several methods are proposed to study the electrophysiology and biomechanics of the CM. Common methods include patch clamping [3,4], calcium imaging [5,6], and image-based contraction-relaxation studies [7,8]. Mechanical transduction with microposts and traction force microscopy [9,10] are other useful techniques to study the mechanical aspects of CM force microscopy. Also, several techniques have been applied to detect structural changes of CM during the synchronized beating. In order to respond to environmental
changes and coordination of the beating cycle, cells communicate through sending and receiving signals by a specific receptor in the cardiovascular wall. Studies in [11,12] discuss cell communication through chemical signaling and mentioned that the cell responds to a specific signal according to the intensity of the received signal. In [13,14] it is mentioned that cell communication is essential for cell growth and coordination of beating cycle. Monitoring calcium change in [15] indicates that calcium flux is in harmony with cell beating which allows screening of cell beating-related parameters. Electrical stimulation of cardiomyocytes is used to coordinate beating activity in [16]. Studies in [17,18] overview different methods and strategies for cell synchronization evaluation. Quantitative holographic imaging approach is used to study cardiomyocytes and monitoring the 3D cell shape and structure changes while beating [19]. Indeed, the beating signal extracted by the method presented in [19] is a readout of the whole image and no single-cell analysis is discussed. Accordingly, providing an automated means to evaluate synchronization is of great importance for evaluating drug toxicity and cardiovascular health care.

Label-free imaging has the advantage of studying samples using non-invasive approach. Among the label-free imaging techniques available, digital holography in microscopic configuration (DHM) is a promising tool. This technique can help to study red blood cell’s related abnormalities [20], biological microorganism identification [21], studying red blood cells storage lesion and morphological changes in blood bank storage [22], imaging and reconstructing the holograms of micro-organism by in-line holography [23], estimation of the bio-volume of the motile cells [24] and assessment of cancer cells migration in 3D environments [25]. Indeed, this method is used to examine fluctuations of red blood cells [26], studying stem-derived human cardiac muscle cells [27] and studying human cardiac muscle cell activities at the single-cell level [28]. The study presented in [27] applies several

Fig. 1. (a) shows the scheme of off-axis hologram recording, (b) shows a recorded hologram; inset is the magnified section of the area shown by arrow (yellow line is 500µm), and (c) is the quantitative phase image (yellow line is 20µm).
methods in order to quantify the beating at the whole-cell level. Therefore, it does not address the single-cell level quantification study. The study in [28] proposes a method to segment CMs and extract single cells to show the quantification for individual cells.

DHM is capable of imaging cells by recording the phase retardation of a coherent or semi-coherent light wave transmitted through the transparent sample, wherein the transparent specimens shift the phase of light instead of intensity alternations. Consequently, DHM quantitatively visualizes the 3D shape of biological samples and monitors the dry mass redistribution. DHM can directly readout the cell morphological movement which monitors the physical contraction-relaxation when applied to study CMs.

The current study analyzes the quantitative beating profile of cardiomyocytes using phase images obtained by digital holographic imaging at the single cell level for synchronization purposes. In the first section, we introduce a technique to extract the best section of the cell in the phase image using image segmentation methods. The segmented single-cell mostly consists of the nucleus of the cell, since it is the best part of the cardiac cell which can be perfectly segmented by the thresholding. On visual investigation, we observed that all components of the cell get redistributed during dry mass redistribution. Several individual cells from different parts of the phase image are extracted, and multiple parameters related to the contraction and relaxation of each individual cell are investigated to reveal the synchronization through numerical and visual analysis.

2. Time-lapse digital holographic imaging and preparation of cardiomyocytes

2.1 Label-free off-axis digital holographic imaging

The general layout of the off-axis digital holographic microscopic technique based on Mach-Zender interferometer is depicted in Fig. 1. The coherent laser source is split into an object \((O)\) and reference beam \((R)\) (See Fig. 1(a)). The object beam illuminates the specimen and a microscope objective (MO) collects and magnifies the object wavefront. The object and reference wavefronts are joined by a beam collector to create the hologram with a small tilt angle between them to provide the “Off-axis” geometry. At the end point, interferograms (Fig. 1(b)) are recorded by a CCD camera and transmitted to a personal computer for numerical reconstruction [29,30]. The recorded hologram \(I_h\) is the interference between object wave \(O\) and reference wave \(R\), and is equated as follows:

\[
I_h = |R|^2 + |O|^2 + R^*O + O^*R,
\]

where \(R^*\) and \(O^*\) denote the complex conjugates of the reference and object beams, respectively. The small tilt angle between \(O\) and \(R\) enables us to eliminate the parasitic orders and isolate the real image from twin images and zero-order noise. To do so, we implement a spatial filter with properly defined size in order to cover only the bandwidth of the real image. By Fourier transforming the off-axis hologram and then multiplying it in frequency-domain by the filter and applying inverse Fourier transform, only the real image information is preserved by the formula:

\[
I'_h = \text{IFFT}\{\text{FFT}(I_h) \times \text{Filter}\} = R^*O,
\]

where \(FFT\) is the fast Fourier transform and \(IFFT\) is the inverse of the fast Fourier transform. To reconstruct the phase image, the filtered hologram \((I_h)^f\) is multiplied by the digital reference wave, and the phase image is reconstructed by the Fresnel approximation:
\[ \Psi(m,n) = \Phi(m,n) \exp \left[ \frac{i\pi}{\lambda d} \left( m^2 \Delta \xi^2 + n^2 \Delta \eta^2 \right) \right] \times \]
\[ \text{FFT} \left\{ R_{kl}(k,l) I_{kl} \exp \left[ \frac{i\pi}{\lambda d} \left( k^2 \Delta \chi^2 + l^2 \Delta \gamma^2 \right) \right] \right\}_{m,n}, \]

where \( k, l, m, \) and \( n \) are integers \((-N/2 \leq k, l, m, n \leq N/2, N \times N \) is the number of pixels in the CCD camera), and \( \Phi(m,n) \) is the digital phase mask for the phase aberrations correction calculated by:

\[ \Phi(m,n) = \exp \left[ -\frac{i\pi}{\lambda d} \left( m^2 \Delta \xi^2 + n^2 \Delta \eta^2 \right) \right]. \]

Moreover, \( \Delta \xi, \Delta \eta \) are the sampling intervals in the observation plane expressed by:

\[ \Delta \xi = \Delta \eta = \frac{\lambda d}{N \Delta x}, \]

where \( d \) denotes the distance between the camera plane (hologram plane) and observation plane. A fine adjustment of \( k_x, k_y, \) and \( D \) can be performed in the absence of fringes by removal of residual gradients or curvature of the reconstructed phase distribution in some areas of the image where a constant phase is presumed \([30]\). The digital phase mask resolves the phase aberrations caused by inserting microscopic objectives in the object wave arm, as shown in Fig. 1(a). Eventually, phase image (Fig. 1(c)) is obtained by the argument of:

\[ \phi(x, y) = \text{tan}^{-1} \left\{ \frac{\text{Im}[\Psi(m,n)]}{\text{Re}[\Psi(m,n)]} \right\}. \]

2.2 Phase unwrapping

Since the numerically reconstructed phase value is limited between \(-\pi \) and \(+\pi \) and the result is given modulo \( 2\pi \), discontinuities arise with values approximating \( 2\pi \). The phase unwrapping procedure converts the undesired phase values to the desired ones by adding or subtracting \( 2\pi \) from the pixel value, thereby resolving the issue. Different approaches can be used for performing phase unwrapping; in this study, we followed the method explained in reference \([31]\). This is a two-step technique, which first finds a reliable value for each pixel. For a pixel in an image, the values of its orthogonal and diagonal neighbors in a \( 3 \times 3 \) window are required. These values are fed into a function, and reliability of the pixel is calculated according to gradients or differences between a pixel and its neighbors. The values are then used by another function to determine the unwrapping path. In conventional unwrapping algorithms, since the unwrapping path is simply calculated column-wise or row-wise, they are unable to resolve errors that occur due to variables such as discontinuity in the phase wraps, under-sampling in local areas, etc. Nevertheless, finding an unwrapping path with the use of reliable values can address these errors. The unwrapping path resolves the edges with a higher reliability prior to those with the less reliable edges. Since the unwrapping path is discrete, the unwrapping operation is therefore considered to be localized \([31]\). The definition of phase retardation recoding is difficult to be addressed in biological applications. The more understandable concept is the optical path difference (OPD) which is related to the physical properties of a sample \([32]\). The optical path difference (OPD) and phase values can be exchangeable, and are obtained by the following equation:

\[ \text{OPD}(x,y) = \frac{\lambda \times \phi(x,y)}{2\pi}, \]
where \( \phi(x, y) \) denotes the phase value at the pixel \((x, y)\) obtained by Eq. (6).

### 2.3 Cardiac cell preparation and imaging details

Cardiomyocytes from human induced pluripotent stem cells (iPS) were procured from Cellular Dynamics Int. (Madison, WI), and were cultured and grown for 14 days according to the manufacturer’s instructions, before recording the holograms. Measurements were acquired in a Chamlide WP incubator system with a 96-well plate (LCI, South Korea), with culture conditions set at 37°C/5% CO\(_2\) and high humidity. To record images, a commercially available DH T-1001 from LynceeTec SA (Lausanne, Switzerland) is used. In this setup, the microscope magnification factor and field of view were set at 20 × /0.4NA and 280\(\mu\)m, respectively. CCD sensor size is 11.3mm × 7.1mm and pixel size \((H \times V)\) is 5.86\(\mu\)m × 5.86\(\mu\)m. CCD resolution is 1920 × 1200 pixel (the hologram size is cropped to be 1024 × 1024 pixels for efficient FFT computations). The transverse resolution is around 200nm in a good agreement with classical Abbe criterion \((0.61\lambda \times NA)\). The phase stability of the system is around \(\Delta\phi = 0.5^\circ\) which in studying of the biological sample with the limited refractive index is equivalent to several nanometer thickness. A 666nm red laser source delivered intensity of \(\sim200\mu\)W/cm\(^2\) to the specimen plane, which is nearly six orders of magnitude less than intensities typically associated with confocal fluorescence microscopy. With this amount of light, the required exposure time was only 0.4ms. The reconstruction process of QPIs was conducted online using a standard PC, at a rate of several images per seconds. Overall, 540 holograms recorded at 10Hz were reconstructed for each sample. Image analyses were carried out using the MATLAB 2018a software.

### 3. Segmentation and contraction-relaxation signal extraction

#### 3.1 Phase image segmentation

Once we obtained the phase images of CM by digital reconstruction, we utilized several image processing techniques for extracting single cells from the phase image. To reduce the noise of the images, a spatial median filter with size of 3 × 3 pixels was applied to each single image in the time stack. A two-step image segmentation method based on \(k\)-means clustering method and marker-controlled watershed algorithm extracted the best part of each cell for cell-to-cell synchronization analysis. In this procedure, which was applied only once on a single still image, internal markers obtained from \(k\)-means clustering algorithm act as an input for the marker-controlled watershed segmentation algorithm. Our proposed two-step segmentation method (Fig. 2) allows us to efficiently retain most of the nuclei section of the CM [28]. After segmentation, several important dynamic characteristics related to cardiomyocyte beating activities were calculated at the single cell level.

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Fig. 2. (a) Original phase image of cardiac muscle cells obtained by off-axis digital holographic imaging, (b) Cardiomyocyte image showing cell regions, internal and external markers which are obtained by using the marker-controlled watershed algorithm and \(k\)-means clustering method, (c) Final segmented cardiomyocyte image (some cells are labeled for the further discussion). Color bar is the same for (a) and (c).
The extracted single cell consisted mostly the nucleus of the cardiac muscle cell. Since OPD value of the nucleus is higher than the surrounding cytoplasm and membrane section, it is imperative for having perfectly segmented nucleus. The segmented region includes a small portion of the cytoplasm within which the nucleus is enclosed.

3.2 Contraction-relaxation profile extraction

During the excitation-contraction activity of the cardiac system, cells shorten and lengthen their fibers, thus altering the entire 3D shape of the cell. Imaging the CM with a digital holographic microscope enables in obtaining a direct readout of the dry mass redistribution during the physical movement of cells. This provides the beating profile of the sample and the useful periods during the beating activity. In order to numerically quantify the beating profile of cells, we used variance of each OPD image frame subtracted from its successive frame. OPD image variance is obtained by the equation:

\[ \delta^2_{\text{opd}} = \text{std}[\text{opd}_{i+1} - \text{opd}_i], \]

where \( \text{opd}_i \) and \( \text{opd}_{i+1} \) denote the \( i_{th} \) and \( i+1_{th} \) OPD images in stack, and \( \text{std} \) represents the standard deviation function.

![Graph showing OPD variance over time for contraction and relaxation periods.](image)

Fig. 3. (a) Detailed information about contraction and relaxation point of an isolated cardiac cell, (b) detected positive peaks for contraction and relaxation points of beating profile of the cardiac cell.

<table>
<thead>
<tr>
<th>Measured parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraction</strong></td>
<td></td>
</tr>
<tr>
<td>Contraction beating rate</td>
<td>The total number of positive contraction peaks during one minute.</td>
</tr>
<tr>
<td>Contraction beating period AVG</td>
<td>The average time between two adjacent contraction peaks during one minute.</td>
</tr>
<tr>
<td>Contraction beating period STD</td>
<td>Standard deviation of contraction beating period.</td>
</tr>
<tr>
<td>Contraction beating period CV</td>
<td>Standard deviation/average value for contraction signal.</td>
</tr>
<tr>
<td><strong>Relaxation</strong></td>
<td></td>
</tr>
<tr>
<td>Relaxation beating rate</td>
<td>The total number of positive relaxation peaks during one minute.</td>
</tr>
<tr>
<td>Relaxation beating period AVG</td>
<td>The average time between two adjacent relaxation peaks during one minute.</td>
</tr>
<tr>
<td>Relaxation beating period STD</td>
<td>Standard deviation of relaxation beating period.</td>
</tr>
<tr>
<td>Relaxation beating period CV</td>
<td>Standard deviation/average value for relaxation signal.</td>
</tr>
</tbody>
</table>
As shown in Fig. 3, the cardiomyocyte beating cycle includes two phases: the first is contraction, in which cell regions become denser and rise, and the entire cell changes its 3D shape; the second is the relaxation, in which the cell initiates resting. Figure 3(a) demonstrates the contraction and relaxation points of the beating curve of the cardiac cell; accordingly, the detected positive peaks for contraction and relaxation points are represented in Fig. 3(b). In order to numerically explore synchronization between single cardiac cells, we measured several parameters related to contraction and relaxation points. Table 1 summarizes the measured parameters and their corresponding description. In order to measure the above-described parameters, positive peaks are detected by applying the first derivative technique to the original data curve.

4. Cardiac cell synchronization analysis

For the optimal functionality of the cardiac muscle system, cells have to respond to the commands of mechanical contraction. The signal will propagate amongst whole cells, resulting in the myocardium pumping the blood out of the ventricle chamber. This requires synchronization between cells; i.e., the contraction and relaxation times need to be well tuned with no time-lag between the signals of two cells of the same sample. In the following sections, we present the same visually and by analyzing the cross-correlation between two signals.

4.1 Cell-to-cell synchronization analysis: visualization and cross-correlation analysis

After segmentation and extracting several cells, we compared the contraction and relaxation points of cells labelled in Fig. 2(c), and evaluated the data collected to reveal synchronization.

![Fig. 4. (a-b) Contraction and relaxation points for cell numbers 7 and 8, and (c) comparison of rhythm strips to detect and visualize synchronization.](image-url)
Figures 4(a) and (b) show the detected positive peaks for contraction and relaxation points of two single cardiac cells. Figure 4(c) represents the rhythm strip comparison of isolated extracted cells for visual demonstration of synchronization during the time. As shown in Fig. 4(c), individual cells are fully synchronized for more than one cycle, considering both the rising and falling time of contraction and relaxation points. We investigated the synchronization in terms of comparing the measured parameters for isolated cells to reveal cardiomyocyte synchronization (Table 2). We observed common characteristics between measured parameters, including beating rate and beating period, and also relaxation and contraction period. In addition, two other individual cells were analyzed to check for the beat-rate synchronization.

<table>
<thead>
<tr>
<th>Measured parameters</th>
<th>Value (7th cell)</th>
<th>Value (8th cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraction beating rate</td>
<td>24.37</td>
<td>24.3</td>
</tr>
<tr>
<td>Contraction beating period AVG</td>
<td>1.39 (second)</td>
<td>2.0 (second)</td>
</tr>
<tr>
<td>Contraction beating period STD</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>Contraction beating period CV</td>
<td>0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Relaxation beating rate</td>
<td>24.25</td>
<td>24.4</td>
</tr>
<tr>
<td>Relaxation beating period AVG</td>
<td>1.42 (second)</td>
<td>1.43 (second)</td>
</tr>
<tr>
<td>Relaxation beating period STD</td>
<td>0.45</td>
<td>0.02</td>
</tr>
<tr>
<td>Relaxation beating period CV</td>
<td>0.32</td>
<td>0.13</td>
</tr>
</tbody>
</table>

The beating activity profile of two extracted individual cardiac cells is shown in Fig. 5 (cell numbers 3 and 4). Positive peaks for contraction and relaxation are marked by the automated detection method. To obtain the peaks, the larger value among two adjacent values
is considered as local maxima or so-called a positive peak. After finding a set of peaks made up of contraction, relaxation and other unwanted peaks, a general threshold can only keep the largest peaks (contraction peaks). The threshold value is chosen by trial-error approach to get the best results. Eventually, only one peak between two contraction peaks is preserved as relaxation peak. In this way, we can keep only the contraction and relaxation peaks and the other peaks are filtered out.

Monitoring synchronization by comparing beating activity profile of single extracted cells is presented in Fig. 5(c). As clearly seen in Fig. 5(c), the beating activity of individual cells were synchronized in terms of rising and falling time of contraction and relaxation. In order to better quantify, we measured critical parameters related to the beating profile of each individual cell, as described in Table 3. The probe to reveal synchronization with focus on beating critical characteristics revealed that this pair of cells are synchronized in terms of parameter measurements.

Table 3. Measured parameters of a pair of isolated cardiac cells to detect isolated cell-cell synchronization (cells 3 and 4)

<table>
<thead>
<tr>
<th>Measured parameters</th>
<th>Value (3rd cell)</th>
<th>Value (4th cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraction beating rate</td>
<td>24.37 (second)</td>
<td>24.37 (second)</td>
</tr>
<tr>
<td>Contraction beating AVG</td>
<td>1.39 (second)</td>
<td>2.0 (second)</td>
</tr>
<tr>
<td>Contraction beating STD</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Contraction beating CV</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Relaxation beating rate</td>
<td>24.25 (second)</td>
<td>24.4</td>
</tr>
<tr>
<td>Relaxation beating AVG</td>
<td>1.42 (second)</td>
<td>1.43 (second)</td>
</tr>
<tr>
<td>Relaxation beating STD</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Relaxation beating CV</td>
<td>0.13</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Fig. 6. Rhythm strip comparison: 3D representation of rhythm strips synchronization detection.

Table 3 shows the measured parameters related to beating profile of individual extracted cells. The true test of an individual pair of cells demonstrated reveals common characteristics between measured parameters, including beating rate and frequency and also resting point and contraction beating period. Analysis of cardiomyocyte dynamics were investigated for several isolated cells (see Fig. 6). The combined measurement shows the ability of the proposed method to be useful in any cardiac safety assessment and drug toxicity screen.

From the 3D representation, it is revealed that isolated cells are rising and falling at the exact same time, and positive peak-peak increases are exactly overlapped, indicating a highly synchronous population.
4.2 Cross-correlation analysis between cells

Another analysis evaluated the cross-correlation to check the similarity and synchronization between two signals (two cells). This approach can be extended to other cells, thereby obtaining general synchronization results. To obtain cross-correlation between two signals, we used the following equation:

\[
(f * g)[n] \stackrel{\text{def}}{=} \sum_{m=-\infty}^{\infty} f^*[m]g[m+n],
\]

where \(f^*\) denotes conjugate of \(f\) (first signal), \(g\) is the second signal, and \(n\) is the time lag between the two signals in the time domain \(m\). Cross-correlation has different applications in signal processing fields. In terms of investigating signal synchronization, it is a useful tool for determining the time delay between two heartbeat signals. Maximum cross-correlation of functions indicates the time where the signals are best aligned.

\[T_{\text{delay}} = \arg \max_n ((f * g)(m)). \]  

Figure 7 shows the cross-correlation between the beating signal of two cells. According to this figure, we can see that two signals have the maximal value when the time lag is zero, indicating that the two signals are perfectly synched in time (similar figures were found for other cells, but are not shown here).

With the help of induced pluripotent stem cell derived cardiomyocytes model the chance of performing cardiac drug-treatment tests, the cardiac-toxicity during the drug discovery process and synchronization studies are made possible. To the best of our knowledge, this is
the first research wherein a numerical analysis has been performed in a label-free manner for detecting cardiomyocyte beat-rate synchronization. Our results demonstrate the effectiveness of the proposed method for detecting cell-to-cell synchronization in the cardiovascular system. We propose that this method can be utilized for all kinds of cell synchronization detections in a given cell population. We believe that these numerical tools can also be useful for analyzing various fast dynamic behaviors in other cellular investigations.

5. Conclusions

Our results show that OPD variance analyzed at the single cell level along with different parameters can be used to evaluate cell-to-cell synchronization. The idea can further be generalized for cluster-to-cluster synchronization analysis. The presented work shows potential techniques for automatic synchronization investigation of mature human cardiac cells by visual and numerical parameters. Our study demonstrates that the proposed system can quantitatively detect synchronization for beating dynamics in the individual cardiac cells at the single cell level. The proposed method offers automatic ways of detecting the synchronization of isolated cardiac cells by quantification of critical parameters related to the beating profile, and demonstrates improvements in synchronization detection both by numerical and visual means. The proposed method can also be helpful to detect other abnormalities in the cardiovascular system, and in drug toxicity probes.

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Disclosures

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