MONITORING CARDIOMYOCYTE MOTION IN REAL TIME THROUGH IMAGE REGISTRATION AND TIME SERIES ANALYSIS

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ABSTRACT

Preclinical test for drug response on cardiomyocyte populations is a key component in drug development. The apparent motion of the cardiomyocytes can be captured using video microsopy, and analyzed using image analysis techniques. In this paper, we describe a system for real-time and automatic monitoring of cardiomyocyte motion . The system first computes in real-time the motion fields through GPU acceleration. A 1-D signal that represents the motion patterns is then extracted using principal component analysis, and is studied using autoregressive spectral analysis. It is shown that the autoregressive model adequately characterizes this signal, thereby providing a basis for automatic detection of anomalies resulting from drug injection. The approach was applied to two types of cardiomyocyte populations and demonstrated promising results.

Index Terms— Cardiomyocyte, Demons, CUDA, autoregression,

1. INTRODUCTION

Cardiac toxicity induced by drugs has been a major concern for drug safety and drug development. In the past, certain drugs have been withdrawn from the market due to their high risk to the heart that was not discovered during the drug development. The adverse side effects on cardiovascular system have been the number one cause of drug withdrawal and early termination of drug development [1]. Therefore screening for cardiac toxity is a key step for drug development. Recently, stem-cell derived cardiomyocytes have been adopted for assessing preclinical drug responses for cardiotoxicity because they closely resemble the functional cardiomyocytes of human heart. The cardiomyocytes can be analyzed using methods like microelectrode array (MEA), which studies drug response by measuring and analyzing the electrophysiological potentials of cardiomyocytes [2]. However MEA could cause undesirable tissue response to implantation, and is not suitable for high-throughput analysis.

Recently, Sebastian et al. [3] proposed to use video microscopy to capture the apparent motion of cardiomyocytes, and analyze it using image analysis method. The rational is that the apparent motion of cardiomyocytes is an outcome of the underlying biological functions. The biological changes caused by drugs will directly affect the motion periodicities, which can be detected and characterized through image and signal processing techniques. Instead of analyzing single cells, the authors in [3] computed motion fields of the entire cell population over time and extracted the most prominent patterns. The resulting one dimensional (1-D) signal was shown to resemble the periodic motion of the cardiomyocytes well, and could also be correlated to the tissue electrical potentials. Their approach demonstrated the feasibility of non-invasive and contact-free monitoring of cardiomyocyte motion using the optical modality. However, several technical difficulties remained before the cardiomyocyte screening process could be truly automated. In paticular, online monitoring of cardiomyocyte motion requires a real-time solution for motion analysis as well as methods for automated characterization of the output signal.

In this work, we extend the work in [3], and develop a system for *automatic* and *real time* analysis of cardiomyocyte motion through fast image registration and comprehensive time series analysis. Our contribution is two-fold. First, we provide a real-time solution of the algorithm presented in [3] with the graphics processing unit (GPU) implementation. Secondly, we analyze the extracted 1-D cardiomyocyte motion signal by statistical modeling and studying its spectral properties. We show that an autoregressive (AR) model [4] provides a good characterization of the motion signal. The AR modeling helps to track the cardiomyocyte beating patterns as a function of time, thus providing the basis for real-time monitoring of changes in motion periodicities.

2. METHODS

Our approach for real-time analysis of cardiomyocyte motion is illustrated in Fig. 1. The approach includes two steps: motion analysis and time series analysis. The motion analysis step is similar to [3]. First, the motions are computed in real-time using GPU-accelerated Demons registration [5] and represented as a sequence of vector fields over time. Second, the vector fields at steady state are processed to extract the most representative motion components using principal component analysis (PCA). Then the motions in subsequent time are decomposed based on PCA results and represented by a 1D time

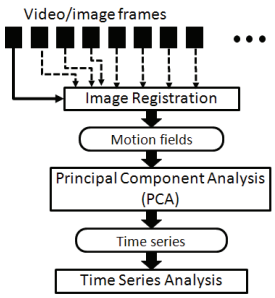


Fig. 1. The flow chart of cardiomyocyte motion analysis

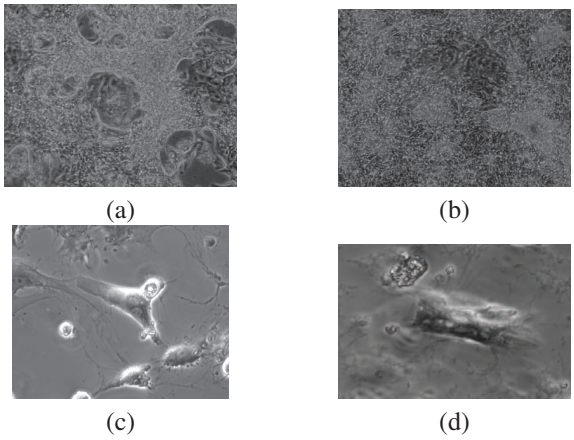


Fig. 2. Example cardiomyocyte images. (a-b) are cardiomyocyte populations, and (c-d) are single cell examples.

series. In the time series analysis step, the 1D signal is analyzed using AR models to detect the frequency and pattern changes over time.

2.1. Real Time Motion Estimation

Fig. 2 shows example images captured using video microscopy. Given a sequence of images $\{I(\mathbf{x}, t_n)\}_0^N$ with $\mathbf{x}$ being the spatial locations and t_n being the time frames, we first compute the motion fields $\mathbf{M}(\mathbf{x}, t_n)$ from the reference time t_0 to all subsequent times. The image sequences captured with the microscopy have a fixed field of view and constant illuminance and contrast, and thus it becomes a natural choice to compute the motion fields using image registration. In particular, Demons method [5] is chosen because it is fast, simple, accurate, and ideal for monomodal registration. Moreoever, it is very suitable for GPU implementation because it can be easily parallelized.

In this work, we implemented Demons method using NVIDIA's CUDA programming toolkits [6]. The extreme parallelism of GPU computing has been utilized by many highly-parallel applications in medical image processing and shown tremendous speedup. CUDA provides a relatively simple programming interface, which hides GPU-specific details

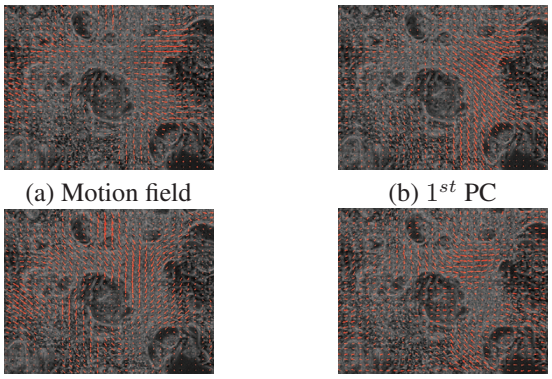


Fig. 3. Motion analysis examples. (a) Motion field on a selected time frame computed using GPU-accelerated Demons. (b-d) The first three components computed using PCA.

and makes GPU programming easier. Our CUDA implementation of Demons is similar to [7]. It is run on a NVIDIA GeForce GTX 580 GPU with 512 cores and 1.5 GB GDDR5 shared memory. Experiments showed that our CUDA implementation takes less than 30 msec to register two 500 by 500 images, which is more than 200x faster than the CPU implementation using the Insight Toolkit (http://www.itk.org). This means the motion can be computed in real-time, making online monitoring possible. Fig. 3(a) shows an example of the computed motion field.

2.2. Signal Extraction

The computed motion fields are in a very high dimensional space, which makes it difficult to directly correlate motions at different time frames. We reduce the dimensionality by extracting the principal motion components (PCs) using PCA, similar to [3]. The motion fields are then projected onto the first several PCs that represent the most representative motion patterns. This is similar as in [3]. Figs. 3(b-d) show example results of the PCA analysis.

For a real-time monitoring system, the PCs are only computed from a subset of motion fields when the cardiomyocyte motion is in steady state. Afterwards, the subsequent motions are projected onto the PCs to extract the 1D (or low dimensional) time series, which is then characterized and analyzed in real time using autoregressive models.

2.3. Autoregressive Modeling

The use of autoregressive (AR) models for characterizing time series data is well-known as AR models encode information about the frequency content and sources of variation in a time series. In contrast to the nonparametric methods based on fast fourier transform (FFT) techniques, AR model based approachs produce power spectrums that are smoother

and more easily interpretable, and have been successfully applied to high-resolution spectral analysis of biomedical signals such as heart rate variability and electroencephalogram tracings (e.g., [8, 9]).

An AR model of order p, AR(p), for a zero mean stochastic process Y is given as

$$y_t = \sum_{k=1}^{p} b_k y_{t-k} + \epsilon_t, \tag{1}$$

where $\mathbf{b} = (b_1, b_2, \ldots, b_p)$ is a vector of model parameters or coefficients, and ϵ is the residual which is assumed to be a stationary white process, and y_t is the observed time series. Training of an AR model involves finding the coefficients, $\mathbf{b}$, that can best describe the temporal dependence in Y. The coefficients are generally obtained using the ordinary least squares (OLS) method,

$$\hat{\mathbf{b}} = \underset{\mathbf{b}\in\mathbb{R}^p}{\operatorname{argmin}} ||Y - \Phi\mathbf{b}||, \tag{2}$$

where Φ denotes the design matrix consisting of delayed values of Y. Further, the model order p (see Eq. (1)) is typically unknown *a priori*, and determined by minimizing a loss function such as the prediction error variance, $\sigma_\epsilon^2 = \frac{1}{N-p}\sum_{t=p+1}^{N}(y_t - \hat{y}_t)^2$. The approach is called Best-Fit. Other well-known approaches, especially useful in absence of a validation dataset, include optimization of Akaike information criterion (AIC) [10] or Rissanen minimum description length (MDL) [11]. These methods mitigate model overfitting by penalizing σ_ϵ^2 with a term proportional to the number of fitted parameters, so as to find the simplest model to characterize the data.

Once the AR model is constructed, it can be inverted and viewed as a linear filter with the residual sequence as its input. Then spectral analysis can be performed on an AR model and give information about the frequency characteristics and variations in a time series with high frequency resolution (see [4] for details). In this work, we track the cardiomyocyte beating patterns over time using a sliding window based spectral analysis of AR models, and show the approach is effective in detecting changes or anomalies in the motion periodicities.

3. EXPERIMENTS AND RESULTS

3.1. Data and Image Analysis

Seven datasets were captured using a video microsopy on two types of cardiomyocyte populations, i.e., dense populations (3 datasets), and single cells (4 datasets). The datasets had frame rates varying from 15 to 30 frames per second, image sizes from 264x322 to 480x720 pixels, and video lengths from 28 seconds to several minutes. All the data were acquired without injecting drugs, but certain changes in the motion patterns were observed in the single cell datasets. Example images were shown in Fig. 2.

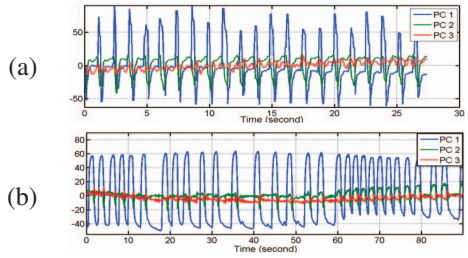


Fig. 4. The motion signals computed from PCA on two datasets hown in (a) Fig. 3 and (b) Fig. 2(d).

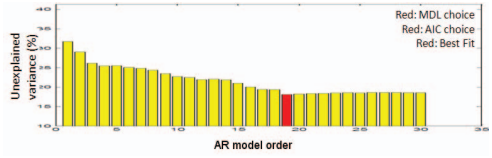


Fig. 5. Model order selection using three approaches.

Fig. 3 shows examples of computed motion field and the PCA results on one dataset, and Fig. 4 shows the computed motion signals using PCA on two datasets. For Fig. 4(a), the first PC took 54% of the total variance, and the first 2 PCs took 92% of the total variance. For Fig. 4(b), the first PC took 82% of the total variance, and the first 2 PCs took 97% of the total variance. The first PCs of the rest 5 datasets took 49%, 63%, 64%, 69%, 80% of the total variance, and the first 2 PCs took 82%, 94%, 88%, 84%, 94% respectively. This justified that the first PC can represent the motion pattern very well, and thus we only considered the first PC for time series analysis.

3.2. AR Model Fitting

All the 7 datasets were fit and analyzed using AR models. For each data set, the signal was partitioned into training and testing sets, for model fitting and validation respectively. Fig. 5 plots the unexplained variance (UV) with respect to the model order p on one of the datasets, where UV represents the portion of signal not explained by the model [4]. All three model selection methods (AIC, MDL, and Best-fit) suggested an AR(19) model for this example. In fact these three methods gave very similar results to all 7 datasets. Fig. 6 shows one-step prediction with AR(19) model. It is evident from Fig. 6 that the model provided a good fit to the data. The autocorrelation of model fitting residuals is shown in Fig. 7, which showed that the residuals were uncorrelated and suggested the model successfully captured the characteristics of given data. Similar results were observed on all data.

3.3. Time-Frequency Analysis

In order to track cardiomyocyte motion periodicities over time, we performed AR spectral analysis using a sliding

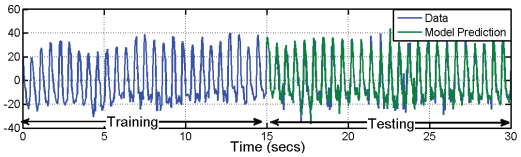
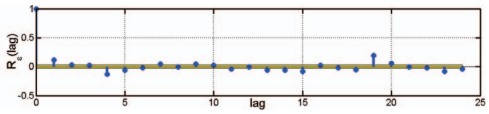


Fig. 6. AR(19) one-step prediction.



(b)

Fig. 7. The residual autocorrelation with respect to the lag.

window approach on all the datasets. At each time point, a window with fixed size is selected and centered at the time point. The data points inside the window were then fitted with an AR model and spectral analysis was performed. The dominating frequency of the constructed model was calculated as the first peak in the power spectrum, and it represents the cardiomyocyte motion frequency at the given time.

Fig. 8 shows the time-frequency functions of the two datasets shown in Fig. 4. In both examples, the sliding window sizes were 10 seconds. It is evident that the motion periodicity changes were successfully tracked. In particular, Fig. 8(b) showed abrupt frequency changes at times 15-20s, 35-40s, and around 60s. It also showed the frequencies before 10s and after 60s were higher than frequencies at 40-55s. These observations were consistent with the original signal (Fig. 4(b)). On the other hand, the signal shown in Fig. 4(a) had little variations which was also evident from Fig. 8(a). The two examples thus demonstrated that the time-frequency analysis from AR models revealed cardiomyocyte motion pattern changes and can be used for abnomality detection and steady state characterization.

4. CONCLUSIONS AND FUTURE WORK

In this paper we describe a system for automated analysis of cardiomyocyte motion on image sequences captured using video microscopy, and demonstrate its effectiveness through experiments. The system includes two parts: extraction of motion signal from image sequence in real time using image registration and PCA, and characterization of signal using time series analysis. Though experiments showed that the first PC could very well represent the motion pattern, using more than one PC will better represent the motion. Subsequently multi-dimensional time series analysis may be required to analyze the multi-dimensional signal. This is part of our future work. Our next step also includes further validating the system using cardiomyocytes with paced motion as well as with drug injection.

(a)

(b)

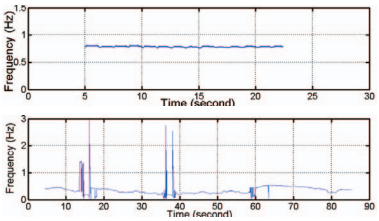


Fig. 8. Time-frequency functions based on AR model fitting.

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