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Biomedical image and signal processing by means of transformation methods

Theses of the PhD Dissertation

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Introduction

In this dissertation, I address some specific problems of biomedical signal and image processing. I aimed to develop automatic methods that provide reliable solutions to real practical problems, and that are constructed by a problem-specific, theoretically well founded mathematical model. My main research interest is the transformation methods, and related approximation problems, numerical optimization, segmentation, classification, and cluster analysis. I have studied these topics under the supervision of *Prof. Sándor Fridli*, as PhD student of the ELTE Doctoral School of Informatics, then as assistant lecturer of ELTE IK Department of Numerical Analysis. My work is connected to research activities of the Department of Numerical Analysis, especially ECG signal analysis by means of rational systems, as introduced by *Prof. Ferenc Schipp* and *Prof. Sándor Fridli* (see [FriLocSch12]). As a continuation of this research, I investigated further possible applications in the field of ECG and CT processing, and the corresponding mathematical background.

The electrocardiogram (ECG) records the electric field generated by the human heart using electrodes placed on the skin. Based on the leads recorded, medical information can be extracted about the heart activity and condition. ECG, as a non-invasive technology, is the most widely used diagnostic tool in clinical cardiology. Besides that, it is also more and more common for everyday usage, in form of hand and smart devices. ECG itself raises several signal processing problems, and the computer-assisted analysis may be an efficient tool for cardiologists, as it helps to handle certain clinical situations. I investigated the problems of heartbeat arrhythmia classification, and waveform segmentation. To this order, I developed adaptive rational transformation methods evaluated on real ECG databases annotated by medical experts. In addition, I discussed an approximation problem, the sensitivity of system parameters of the rational transformation utilized for heartbeat representation.

Compouted tomography (CT) is the most widely used three-dimensional imaging technology, primarily for medical purposes, for diagnostic and surgical support. The CT scanner takes X-ray measurements form different angles, from which the 3D image of the inner structure can be reconstructed. Since X-ray is an ionizing radiation, the technology is invasive, it may damage the tissues and it has a carcinogenic effect. Therefore, an important question is the radiation dose of the measurement. Dose reduction may allow wider use of the technology, see the low dose CT scans for lung screening purposes, but it also leads to the degradation of the image quality. I investigated image quality measurement techniques for low dose human lung CT scans, and related modelling problems: CT simulation and lung phantom construction.

Mathematical and computer science background

The main tool of the proposed methods is the mathematical transformation techniques. To this order, consider the signals as a sampling of a proper function $f \in I \to \mathbb{K}$, where $I \subset \mathbb{R}$ is an interval, and $\mathbb{K} = \mathbb{R}$ or $\mathbb{C}$. I discuss the transformation methods in the Hilbert space $L^2_w(I)$ that is the square integrable real or complex functions over the interval $I \subset \mathbb{R}$ with respect to the weight function $w : I \to \mathbb{R}$. The mathematical background of the transformation is the approximation theorems for Hilbert spaces: Fourier expansion is possible using a given system, where the partial sums of the expansion can be utilized for approximation purposes. Let $(H, \langle\cdot,\cdot\rangle)$ be a separable Hilbert space with a given base set and scalar product, and let $e_k \in H$ ($k \in \mathbb{N}$ or $\mathbb{Z}$) be one of its basis. Approximate the function $f \in H$ with the Fourier partial sum of order $m \in \mathbb{N}^+$, i.e. by $f \approx P_m f$. Here, P_m denotes the projection operator of the subspace $S_m \subset H$ spanned by the system $e_k \in H$ ($|k| < m$). Transformation methods are important tools in signal processing, as they allow the proper representation and dimension reduction of the signals, reflecting only to the relevants details of them. Here I mention the classical trigonometric Fourier transform, Hermite and Walsh functions, and wavelets, as examples. Although these methods perform generally well, adaptive techniques may be more effective in certain cases. Consider now the system $e_k^\alpha \in H$ ($|k| < m$), which elements depend on a non-linear system parameter $\alpha \in \Gamma$. If α is fixed, then it leads to a simple transformation method: the signals are approximated by the projection operator of the subspace spanned by the system . However, if we allow the variation of α, then an adaptive system can be constructed that fits to the given signal or signals, resulting better approximation and representation properties. The parameter $\alpha \in \Gamma$ may be selected according to the following minimization condition (see *variable projections*, [GolPer73]):

$$\alpha \in \operatorname*{arg\,min}_{\beta \in A} \|f - P_m^\beta f\|.$$

I investigated adaptive transformation methods by means of rational systems following [FriLocSch12], in order to model ECG signals. Denote the open and closed complex unit disk by $\mathbb{D}$ and $\overline{\mathbb{D}}$, and the Hardy space of square integrable functions that are analytic on the unit disk by $H^2(\mathbb{D})$. Consider the *basic rational functions* of the form

$$r_a(z) := \frac{1}{1 - \overline{a}z}, \qquad r_{a,k}(z) := r_a^k(z) = \frac{1}{(1 - \overline{a}z)^k} \qquad (z \in \overline{\mathbb{D}}),$$

where the free system parameter $a \in \mathbb{D}$ is the so-called *inverse pole*, and $k \in \mathbb{N}^+$ is the order of the function. Every proper rational function that is analytic on the unit disk can be expressed as the linear combination of basic rational functions, and also a modified version may be defined that can be used the expression of every rational function. In a signal processing point of view, it is enough to take the restriction of these functions to th unit circle $\mathbb{T}$. This allows the approximation of functions from $L^2(\mathbb{T}) \equiv L^2[-\pi, \pi]$. To this order, consider the system of basic functions

$$\{r_{a_j,k_j} : j = 1, 2, \ldots, n; k_j = 1, 2, \ldots, m_j\},$$

generated by a set of distinct inverse poles $\mathfrak{a} = (a_j) \in \mathbb{D}^n$, and the associated multiplicities $\mathfrak{m} = (m_j) \in (\mathbb{N}^+)^n$. Now, a function $f \in L^2(\mathbb{T})$ can be approximated by $P_{\mathfrak{m}}^{\mathfrak{a}} f$, that is the projection to the subspace $R_{\mathfrak{m}}^{\mathfrak{a}}$ spanned by the rational system above. The approximation can be expressed in orthogonal (Malmquist–Takenaka) and in biorthogonal basis, as well. The main motivation behind the utilization of rational systems is the connection between the basic rational functions and the ECG waveforms. Another important aspect is the mathematical simplicity and high flexibility of the system. We have an arbitrary number of free parameters that can be selected according to the signals, resulting adaptive transformation methods. Based on the connection between the inverse poles and the shapes of the basic rational functions, we can conclude that the inverse poles and the coefficients carry direct medical information about the ECG signals. The most important practical question is the identification of the proper pole combination that fits to the specific task and to the signals as well. Pole identification is usually addressed as a non-linear optimization problem. The questions are the selection of the number, multiplicities, and actual values of the inverse poles. Several aspects and strategies may be discussed here, as described in my dissertation in details, focusing mainly on the hyperbolic Nelder–Mead simplex method [Fri+12]. I remark that, according to the experiences, not only the different signal types, but also the different applications may need to be handled differently. For example, see the problems of heartbeat classification and ECG compression. For compression, the goal is the best possible approximation, while in case of classification, it is more important to give a morphologically relevant representation of the heartbeats, even at a slight expense of the approximation error.

The mathematical background of the CT imaging is the *Radon transform* that is the following integral transform of integrable function on the plane:

$$\mathcal{R}f(L) := \int_L f \qquad (L \in \mathcal{L}),$$

where $\mathcal{L} \subset \mathbb{R}^2$ denotes the set of lines on the plane. The reconstruction of the raw CT scans is based on the inversion techniques of the Radon transform, the *filtered backprojection* and the *iterative reconstruction methods*. Based on the properties of the Radon transform, and based on the connection with the affine transformations, analytical models, so-called *phantoms* can be constructed. I investigated elliptical phantoms following the idea of the Shepp–Logan head phantom [SheLog74]. These phantoms act as schematic models of the CT images that allow an analytical test framework for simulation purposes.

Further related topics are the *classification* and *cluster analysis* methods, that I discuss in a *machine learning* point of view. Here the task is to categorize objects described by their *feature vectors*, according to given conditions. I dealt with two special cases: the classification based on reference data as supervised, and the cluster analysis based on the similarity between the objects as unsupervised machine learning. Support vector machines (SVM, see [CorVap95]), and artificial neural networks (ANN, see e.g. [Sch15]) are utilized for classification, K- and C-means (see [Llo82; Bez81]) and their improvements (see e.g. [ZhaChe04]) for cluster analysis.

Theses of the Dissertation

In the following I summarize my results in form of theses, as discussed in my dissertation.

Thesis 1: ECG heartbeat classification

> *I developed a novel classification method based on a patient-specific modelling of the heartbeats, that outperforms the previous ones.*

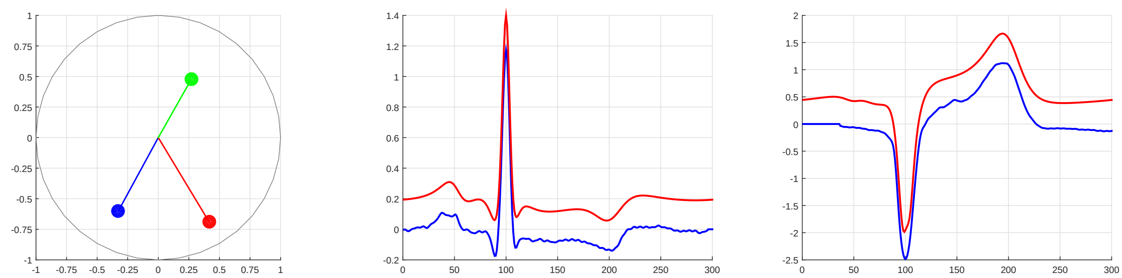
The computer-assisted analysis of arrhythmia is a useful diagnostic tool for ECG signals. Cardiac arrhythmia is a wide set of conditions that characterizes the abnormal behaviour or activities of the heart. Here I investigated the classification into 5 or 16 classes recommended by the standard [AA12]. These conditions are not directly life threatening, but still needs medical treatment in order to avoid complications. The problem is important and relevant for several aspects: a reliable automatic classification method may help the work of cardiologist in certain clinical situations (e.g. intensive care, 24 hours Holter), and my be useful in hand and smart devices as well.

The field has extensive literature (see e.g. [ChaODwRei04; YeVKCoi12; Luz+16]). The general methodology consists of the preprocessing of the ECG signal, heartbeat extraction, modelling of the heartbeats by a proper transformation method, feature extraction from the transformation (e.g. utilizing the coefficients), and the perform a supervised machine learning. The methods are evaluated on the *MIT-BIH Arrhythmia Database* [MooMar01] available on the PhysioNet [Gol+00], that is a real ECG database annotated by medical experts.

The base idea of my research is to develop an adaptive transformation method by means of rational function, replacing the usual transformation of general nature. The proposed pole identification strategy leads to morphologically relevant representations of the heartbeats, where not only the coefficients of the projection, but also the system parameters carry medical informations about the signal. In my work I improved the general methodology and I suggested new concepts. I achieved the following new results:

1. I developed an adaptive technique for the heartbeat extraction, that preserves the advantages of the previous methods, but provides a more reliable segmentation result.
2. I introduced a patient-specific pole optimization strategy to model the heartbeats. The resulted adaptive rational transformation provides good approximation and morphologically accurate representation of the heartbeats. (See Fig. 1)
3. I suggested an adaptive initial guess for the optimization, that improved its efficiency.
4. I extended the feature vector utilized for classification with the pole angles as global morphological descriptors.
5. I discussed the fusion of multiple strategies in order to improve the accuracy.

The results are published in articles [BogFri18; BogFri19a; DozBogKov19]. Comparing to the previous results, I can conclude that the proposed method provides a better representation of the heartbeats, and results a more reliable classification.



(a) Pole combination (b) Normal heartbeat (c) PVC heartbeat

Figure 1: Pole optimization and rational approximation of heartbeat classification
Data source: MIT-BIH Arrhythmia Database

Thesis 2: ECG segmentation

> *I suggested a novel modelling, segmentation, and reconstruction of the ECG waveforms. The proposed fiducial point detector method outperforms the previous ones with respect to the localization of the P wave.*

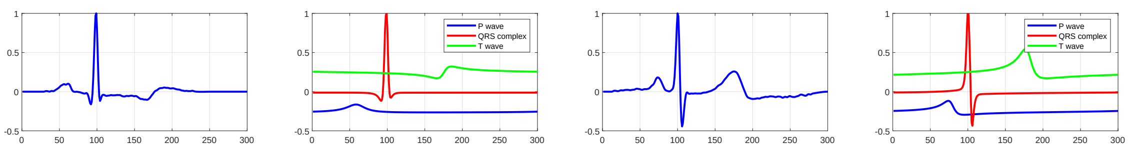
Similarly to the arrhythmia classification, another useful computer-assisted tool for ECG signals is the analysis of the ECG waveforms, the P, QRS, and T waves. The shapes, the location, and the time intervals between the waveforms carry medical information. The common way to analyse the waveforms is the detection of their fiducial points (onset, peak, and offset points). Based on the fiducial points further medical descriptors may be derived that can be used to describe to current medical status, the change of status in time, and to detect certain abnormalities.

From the literature precedents, I mention the methods [LagJanCam94; Mar+04; Kov+17] that are based on the proper modelling of the heartbeats, and the analysis of the model curves. Here the evaluation is based on the *QT Database* [Lag+97] of PhysioNet [Gol+00], that is an annotated database for waveform evaluation purposes.

The base idea of my research is to model the waveforms by rational functions, motivated by the previous experiences. The proposed models provide a morphologically accurate representation of the heartbeats, and fiducial point detection techniques can be derived. The results achieved are as follows:

1. Geometric interpretation of the QRS complex is given based on rational model curves, in order to extract fiducial points and medical descriptors.
2. I discussed reconstruction techniques to solve the inverse problem, i.e. to restore signals based on the medical descriptors. I showed the practical relevance of these methods. This concept serves as a heartbeat synthesizer and alternative pole identification method, as well.
3. I developed a deterministic method to segment the ECG waveforms and to detect fiducial points. To this order I suggested adaptive filtering methods, and introduced a suitable patient-specific pole optimization method. (See Fig. 2)

The results are published in articles [BogSch18; BogFri19b]. Comparing the segmentation to the previous results, I can conclude that the proposed method provides an efficient and accurate representation of the waveforms by means of rational functions. The reconstruction methods may have further applications as a pole selection method, for heartbeat synthesis, and to evaluate other methods.



(a) Heartbeat 1. (b) Waveforms 1. (c) Heartbeat 2. (d) Waveforms 2.

Figure 2: Heartbeats and delineated waveforms

Data source: QT Database

Thesis 3: Sensitivity of the inverse poles

> *Related to approximation problems with respect to rational systems, I gave a sufficient upper limit for the perturbation of the magnitude of the inverse poles, depending on the acceptable approximation error.*

The adaptive rational transformations developed for heartbeat classification and waveform segmentation raise several questions about the sensitivity of the inverse poles. The error of rational approximation of heartbeats has direct or indirect impact on the representation. It describes the accuracy of the model (see ECG compression), and it influences the reliability of the parameters extracted (see coefficients and fiducial points). However, the pole optimization provides only an approximation of the optimal combination. This raises the question of the sensitivity, i.e. how the perturbation of the inverse poles affects the approximation error. Practical experiences and theoretical considerations show, that the system is sensitive to the change of the pole arguments, and on the other hand, the identification of the pole arguments seems to be stable, regarding to per-heartbeat or per-patient optimization as well. Based on these reasons, I focused on the perturbation of the pole magnitudes. As result, I provided conditions on the possible perturbation of the pole argument based on the acceptable error rate. The results may have a direct or indirect usage, e.g. the quantization of the inverse poles and the pole optimization methods can be controlled during the adaptive rational transformations. Important partial results are the formulae for the scalar products of the rational functions, and the Cholesky decomposition of the rational Gram matrices.

The results are published in article [BogFri19c].

Thesis 4: CT image quality measurement

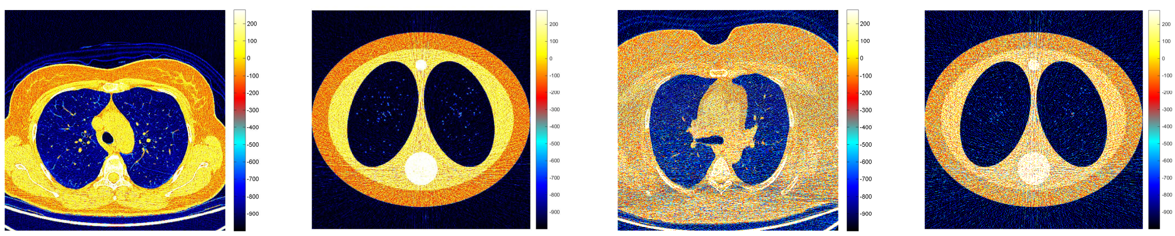
> *I introduced a novel image quality measurement method to characterize the objective quality of low dose human lung CT scans, and I developed a CT simulation framework based on an adapted noise model and a newly constructed lung phantom.*

The main problem of low dose CT screening is the image quality degradation caused by the dose reduction, that may directly affect the diagnostic evaluation of recordings. I aimed to provide an objective measurement technique to describe the image quality. Such a metric may be utilized during the CT scan to evaluate the current quality and adaptively fine tune the dose. Another possible application is to incorporate the metric as the cost function of iterative reconstruction methods.

Image quality measurement is a well-investigated topic (see [LinKuo11]), but the main focus is on the analysis of natural images, and images with reference data. The former one is important to analyse photos, and the latter one is to evaluate image processing algorithms. Obviously, CT images are not natural images, a good quality reference image is usually not available, and the methodology is not well developed yet (see CNR and SNR that are based on the comparison between the background and foreground). These motivated me to developed a fully automatic, objective image quality metric, that also allows the comparison of different CT images. The development and evaluation is based on the low dose lung CT scans provided by the Pozitron Diagnostic Health Centre, and the public databases ELCAP [Ree+09] and LIDC-IDRI [Arm+11]. Although these sources consist of several recordings, they usually have only one measurement for each patient, that limits the evaluation. In order to avoid that I created a simulation framework that allows to synthesize images with adjustable quality, similar to those real CT images. This framework provides an objective base for algorithm testing purpose. I achieved the following new results:

1. I adapted a noise model and I synthesized artificial CT images driven by noise parameters.
2. I constructed a lung phantom based on analytic mathematical model. The lung phantom together with CT simulation provides a easy to handle, flexible, and controllable modelling technique to synthesize artificial CT images of various quality, similar to the real images. (See Fig. 3)
3. I developed a no-reference image quality metric for lung CT scans. The method is fully automated and allows the direct evaluation of CT images. The result is a numeric metric value, that is comparable between the records. The metric is proved to be relevant for low and normal dose lung CT scans as well.

The results are published in article [Bog15; Bog16]. The experiences show that the synthesized images simulated with the lung phantom have similar characteristics as the real lung CT images, but allowing an adjustable noise level. The proposed image quality metric follows the perceptible quality according to objective evaluation using the simulation, and according to subjective evaluation based on expert scores, as well.



(a) Lung CT 1. (b) Lung phantom 1. (c) Lung CT 2. (d) Lung phantom 2.

Figure 3: Comparison of low dose lung CT scans and lung phantom simulations
Data source: Pozitron Diagnostic Health Centre

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