We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

186,000

200M

Download

154
Countries delivered to

Our authors are among the

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us? Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Chapter

Advances in Signal and Image Processing in Biomedical Applications

Mathiyalagan Palaniappan and Manikandan Annamalai

Abstract

Our bodies are continually passing on information about our prosperity. This information can be collected using physiological instruments that measure beat, circulatory strain, oxygen drenching levels, blood glucose, nerve conduction, mind activity, and so on. For the most part, such estimations are taken at unequivocal spotlights in time and noted on a patient's outline. Working with conventional bio-estimation apparatuses, the sign can be figured by programming to give doctors continuous information and more noteworthy bits of knowledge to help in clinical evaluations. By utilizing progressively modern intends to break down what our bodies are stating, we can conceivably decide the condition of a patient's wellbeing through increasingly noninvasive measures.

Keywords: patient, bio signals, Medical image, processing, decision

1. Introduction

The signals are measured and analyzed from the organs of human body using various instruments. These types of signal processing called bio signal processing. The major challenges are to remove the noise from the signals and the resulting information is more useful for the clinicians [1–10].

The MRI, PET, CT, etc., generates more images and these images are processed using Artificial Intelligence and machine learning algorithms. The bio signal processing and machine learning [12] based medical image analysis accurately diagnosis the diseases by doctors.

2. Advancement of biomedical applications

This section aims to collect a diverse and complementary set of emerging techniques that demonstrate new developments and applications of advanced signal and image processing in medical imaging. It will help both physicians and radiologists in the image interpretation, and help technicians to exchange the latest technical progresses.

2.1 Signal processing in networked cyber-physical systems

A noteworthy test for execution of sign handling arrangements in cyber-physical systems (CPS) is the trouble of gaining information from topographically circulated

perception hubs and putting away/preparing the amassed information at the combination focus (FC) [1, 2]. All things considered, there has been an ongoing flood of enthusiasm for improvement of conveyed and shared sign preparing advancements where adjustment, estimation, as well as control are performed locally and correspondence is constrained to nearby neighborhoods.

Cyber-physical systems provides major facilities and it has more potential digital and physical assaults by enemies on sign handling modules could prompt an assortment of extreme outcomes including client data spillage, devastation of foundations, and jeopardizing human lives [3]. Then again, the requirement for participation between neighboring hubs makes it basic to anticipate the revelation of delicate nearby data during conveyed data combination step.

2.2 Cyber-physical systems in signal processing

Cyber-physical systems give strategies and help to tackle prognostic issues in an assortment of medicinal areas [4]. Machine leaning algorithms (ML) are used to examine the significance of clinical parameters, e.g. expectation of ailment movement, therapeutic learning, patient administration, etc.., [5]. ML is being utilized for information examination in medical field [6]. It contend that the fruitful execution of ML strategies can help the combination of PC based frameworks in the medicinal services condition giving chances to encourage and upgrade crafted by medicinal specialists.

2.3 Multimodal multimedia signal processing

Analysts in various fields use multimodal information. One of its most regular usages is in the field of human computer interaction (HCI). Here, a methodology is a characteristic method for collaboration: discourse, vision, confront articulations, penmanship, motions, head, and body developments [7, 8]. Multimodal interfaces encourages human computer interface [9] supplant the conventional console and mouse. Multimodal speaker recognition, distinguishes the dynamic speaker in a sound video grouping, which contains a few speakers, in light of the connection between the sound and the development in the video [10].

2.4 Statistical signal processing

Statistical signal processing is an approach to signal processing which treats signals as stochastic processes, utilizing their statistical properties to perform signal processing tasks. Statistical techniques are widely used in signal processing applications [13, 14].

2.5 Signal processing techniques for data hiding and audio watermarking

In signal processing techniques for data hiding a novel system for embeddings and recuperating "shrouded" information in sound documents. In this procedure, the period of picked segments of the host sound flag is controlled in a way that might be identified by a collector with the best possible "key" [15]. Without the key, the shrouded information is imperceptible; both aurally and through visually impaired computerized flag handling assaults. The technique portrayed is both aurally straightforward and vigorous and can be connected to both simple and computerized sound flags, the last including uncompressed and additionally packed sound record designs. Information stowing away present by relative stage encoding and quantization record adjustment stage encoding technique [16].

2.6 Optical signal processing

Optical signal processing unites different fields of optics and signal processing to be specific, nonlinear gadgets and procedures, simple and computerized signal, and propelled information tweak arrangements to accomplish fast signal processing capacities that can conceivably work at the line rate of fiber optic interchanges [17, 18]. Data can be encoded in abundancy, stage, wavelength, polarization and spatial highlights of an optical wave to accomplish high-limit transmission. Different optical nonlinearities and chromatic scattering have been appeared to empower key sub-framework applications, for example, wavelength transformation, multicasting, multiplexing, demultiplexing, and tunable optical postponements. Optical flag preparing utilizing cognizant optical recurrence looks over could have different potential applications for optical correspondences. At first a way to deal with accomplish a tunable optical high-arrange QAM [19] age in light of multichannel total and an all-optical pilot-tone based self-homodyne-recognition is utilized by two situations: (i) numerous WDM channels with adequate intensity of pilot tones, and (ii) a solitary channel with a low-control pilot tone. At long last, a divided data transmission assignment empowered by reconfigurable channel cutting and sewing.

2.7 Virtual physiological human initiative

The virtual physiological human is synonymous with a program in computational biomedicine that plans to build up a system of strategies and advancements to examine the human body in general [20, 21]. It is predicated on the transformational character of data innovation, offered as a powerful influence for that most essential of human concerns, our own wellbeing and prosperity. The VPH is a composed gathering of computational structures and ICT-based instruments for the multilevel displaying and recreation of the human life structures and physiology. Once adequately built up, the VPH [22] will give a fundamental innovative foundation to the Physiome Project, to pathology-particular activities in translational research, and to vertical answers for the biomedical business.

2.8 Brain-computer interfaces

Research in electroencephalogram (EEG) based brain-computer interfaces (BCIs) has been extensively extending during the most recent couple of years. To Such extent owes an enormous degree to the multidisciplinary and testing nature of BCI inquire about. Sign preparing and example acknowledgment without a doubt comprise fundamental segments of a BCI framework. Sign handling calculations are connected to the EEG sign to interpret mental states which are pertinent for BCI activity. In this instructional exercise, the fundamental BCI ideas, for example, mind movement checking, BCI task, and the important mental states for BCI, are presented. The fundamental kinds of significant mental states for BCI, to be specific engine symbolism (ERD/ERS), enduring state visual evoked possibilities (SSVEP) [23], and occasion related possibilities are introduced alongside commonsense application precedents.

The EEG preparing for mental state disentangling is depicted inside and out. The multivariate idea of the EEG joined with the neuroscience learning on hemispheric cerebrum specialization is beneficially considered to infer ideal mixes of the individual sign creating the EEG [24]. BCIs are named by the kind of mind action utilized for control. Among a few classifications of EEG-based BCIs, including P300, unfaltering state visual evoked potential (SSVEP), occasion related desynchronization (ERD), and moderate cortical potential based sign preparing.

3. Neural networks and computing

In humans, interactions between neuron circuits, systems and signals among micro-, meso- and macro-scales of brain dynamics underpin the functional organization of the brain that supports our daily life activity. Mathematical, computational and experimental neuroscientists apply a variety of methods, techniques and algorithms, both in animals and humans, ranging from single cell recordings to whole brain imaging, in order to identify the core mechanisms that govern the interactions among these scales. Although our knowledge of neural mechanisms, circuits and networks underlying brain dynamics and functions constantly grows, the integration of this knowledge to provide a conceptual framework of emergent behavior [25] and pattern formation occurring on different levels of spatial organization remains challenging.

4. Big data in bioinformatics

In biomedical calculation, the nonstop difficulties are: the board, investigation, and capacity of the biomedical information. The Spark engineering enables us to create suitable and productive strategies to use an enormous number of pictures for characterization, which can be redone as for one another [27]. In prescription, the information experienced are for the most part acquired from patients. This information comprise of physiological sign, pictures, and recordings. They can be put away or transmitted utilizing proper equipment and systems. One of the administrations utilized in prescription for the capacity and transmission of picture information is the picture archiving and communication system (PACS).

The enormous information innovations are ordered into four classes [28, 29]: (1) information stockpiling and recovery, (2) mistake ID, (3) information examination, and (4) stage mix arrangement. These classifications are related and may cover; for example, most information input applications may bolster basic information examination, or the other way around.

5. Image reconstruction and analysis

The examination model has been recently abused as an option in contrast to the traditional scanty amalgamation model for planning picture recreation techniques. Applying an appropriate examination administrator on the picture of intrigue yields a cosparse result [30] which empowers us to remake the picture from under sampled information. Moreover earlier in the investigation setting and hypothetically ponder the uniqueness issues as far as examination administrators when all is said in done position and the particular 2D limited distinction administrator. In light of the possibility of iterative co-bolster discovery (ICD) a novel picture remaking model and a successful calculation, accomplishing essentially better recreation execution.

5.1 Biomedical imaging

Utilization of computer-aided technologies in tissue engineering research and development has evolved a development of a new field of computer-aided tissue engineering (CATE). Three dimensional (3D) printing is an added substance producing process. This innovation furnishes us with the chance to make 3D structures by including material a layer-by-layer premise, utilizing various types of materials, for example, earthenware production, metals, plastics, and polymers. These days,



Figure 1.
Tumor MR image taken after 15 days.

tissue building examinations are occurring on an across the board premise in the fields of recovery, reclamation, or substitution of blemished or harmed useful living organs and tissues. 3D bio-printing [31] is a flexible developing innovation that is discovering its way through all parts of human life. The capability of 3D printers can be abused in territories of biomedical designing, for example, key research, tranquilize conveyance, testing, and additionally in clinical practice. About all present therapeutic nonorganic inserts, for example, ear prostheses, are made in foreordained sizes and designs that are generally utilized for patients. This method permits more precise customized assembling of gadgets made to the patient's own particulars. Bio-printing is being utilized to make more exact nonbiologic and organic research. Describe a method for hiding data in audio files that employs the manipulation of the phase of selected spectral components of the host audio file we describe a method for hiding data in audio files that employs the manipulation of the phase of selected spectral components of the host audio file.

For an example, in **Figure 1** automated quantification of tumors remains to quantify signal intensity changes in MR images, and this is a difficult problem because of the artifacts affecting images such as partial volume effects and intensity in homogeneities. Low level segmentation methods such as intensity thresholding, edge detection, region growing, region merging and morphological operation are not well suited for automated quantification of the signal abnormalities as these techniques rely on image operators that analyze intensity, texture or shape locally in each voxel, and therefore too easily mislead by ambiguities in the image or require user interaction.

5.2 Intelligent imaging

Data driven systems have gotten expanding consideration as of late to solve different issues in biomedical imaging. Information driven models and methodologies so forth., give promising execution in picture remaking issues in attractive reverberation imaging, processed tomography, and different modalities in respect

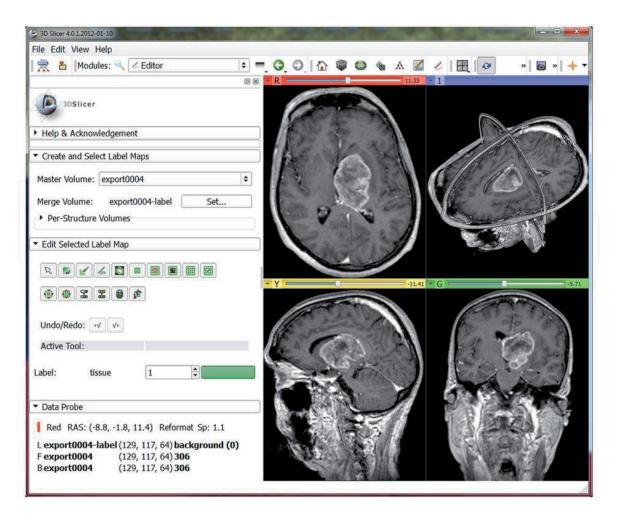


Figure 2. 3D MRI image visualization using 3D slicer. Image courtesy of the 3D slicer.

to conventional methodologies utilizing hand-created models, for example, the discrete cosine change, wavelets. In this term envelops the most recent methodologies for making all parts of imaging framework information driven, including information procurement and examining, picture recreation, and handling/examination. Intelligent imaging frameworks would ceaselessly gain from huge datasets and on-the-fly and adjust for speed, productivity, and picture execution or quality.

A best example of intelligent imaging is the identification of affected and healthy images based on the discrimination capabilities in fundus image textures. For this purpose, as a texture descriptor for retinal eye images has been done and the area and time consumption has been reduced by the means of extended binary patterns (EBP). The main aim is to reduce the size and time consumption and also differentiate between age-related macular degeneration (AMD) and diabetic retinopathy (DR), and normal fundus images with the retina background texture by leaving lesions previous segmentation stage with the proposed procedure and obtaining promising results. The best results of each experiment on the model set are highlighted in tables. This work makes use of the EBP operator. In particular, the performance of EBP was compared with LPB as shown in **Figure 2**.

5.3 PDE based image analysis

The real issue with the exact mode disintegration (EMD) calculation is its absence of a hypothetical system. In this way, it is hard to portray and assess 2-D case, the utilization of an elective usage to the algorithmic meaning of the alleged "filtering process" utilized as a part of the first EMD strategy. This approach,

particularly in light of fractional differential conditions (PDEs) and depends on a nonlinear dissemination based sifting procedure to tackle the mean envelope estimation issue. In the 1-D case, the productivity of the PDE-based technique, contrasted with the first EMD algorithmic rendition, was additionally delineated in an ongoing paper. As of late, a few 2-D expansions of the EMD strategy have been proposed. Regardless of some exertion, 2-D adaptations for EMD show up inadequately performing and are extremely tedious. So an expansion to the 2-D space of the PDE-based approach is widely depicted. This approach has been connected in instances of both flag and picture decay. The acquired outcomes affirm the value of the new PDE-based filtering process for the disintegration of different sorts of information. The adequacy of the approach empowers its utilization in various signal and image applications such as denoising, detrending or texture analysis.

5.4 Visualization of 3D MRI brain tumor image

Figure 2 demonstrates the visualization of 3D MRI image using 3D slicer used to perform various analysis on brain tumor in early stages.

5.5 Hyperspectral imaging

In recent years, hyperspectral imaging (HSI) [32] has risen as a promising optical innovation for biomedical applications, principally forever sciences look into, yet in addition went for nonintrusive conclusion and picture guided medical procedure. Hyperspectral imaging (HSI) innovations have been utilized broadly in medicinal research, focusing on different organic wonders and various tissue writes. Their high ghostly determination over an extensive variety of wavelengths empowers procurement of spatial data comparing to various light interacting natural mixes. It is fit for giving constant quantitative data to a few organic procedures in both solid and ailing tissues. Hyperspectral inspecting and determination are for the most part considered the key factors that recognize HSI and MSI, while MSI centers around discrete and generally separated wavelength groups, HSI basically uses extremely tight and neighboring otherworldly groups over a nonstop phantom range, as to recreate the range of every pixel in the image.

5.6 Artificial neural networks in image processing

Medicinal imaging procedures have generally been being used in the finding and identification of disease. Microcalcifications and masses are the soonest indications of tumor which must be identified utilizing current procedures. The trouble in characterization of generous and harmful microcalcifications [33] likewise causes a critical issue in restorative picture handling. Computerized classifiers might be valuable for radiologists in recognizing benevolent and dangerous examples. Consequently, an artificial neural system (ANN) [11, 26] which can be filled in as a computerized classifier is examined. In medicinal picture preparing, ANNs have been connected to an assortment of information order and example acknowledgment errands and turn into a promising characterization instrument in bosom malignancy. In this way, extraordinary determinations of picture highlights will bring about various arrangement choices. These requests can be parceled into three sorts: in any case, the method in light of estimations, for instance, support vector machine; second, the methodology in perspective on oversee, for instance, decision tree and unforgiving sets; and third, fake neural framework. Diverse ANNs made rely upon extending the veritable positive (TP) revelation rate and decreasing the bogus positive (FP) and false negative (FN) acknowledgment

rate for the perfect result. Use of wavelet in ANNs, for instance, particle swarm optimized wavelet neural network (PSOWNN), biorthogonal spline wavelet ANN, second-orchestrate dim dimension ANN, and Gabor wavelets ANN can improve the affectability and explicitness which are acquired in masses and microcalcification acknowledgment.

6. Discussion

Biomedical sign and picture handling comprises particular interests in the informative and research field in biomedical structure. With the redesigned physiological data, a wide course of action of innovative works in clinical techniques makes usage of this thought in the restorative applications. With headway in biomedical imaging, the proportion of data created by multimodality picture strategies, e.g., stretching out from computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, single photon emission computed tomography (SPECT), and positron emission tomography (PET), magnetic particle imaging, EE/MEG, optical microscopy and tomography, photoacoustic tomography, electron tomography, and atomic force microscopy, has grown exponentially and the possibility of such data has logically ended up being more amazing. This represents an awesome test on the best way to grow new propelled imaging strategies and computational models for productive information handling, investigation and displaying in clinical applications and in understanding the basic natural process. Signal and image processing is pervasive in present day biomedical imaging, as it gives fundamental procedures to picture development, upgrade, coding, stockpiling, transmission, examination, comprehension, and representation from any of an expanding number of various multidimensional detecting modalities. To address this difficulty, usually natural image preprocessing methodology, for example, highlight extraction, picture combination, grouping and division need acclimatized clever strategies that can handle with the mass and decent variety of the data and frequently have the capacity to incorporate and process information from nonimaging sources.

7. Conclusion

This chapter mainly focused on signals and latest techniques in medical image processing which will create more interest in biomedical research fields. With the latest trends in data acquisition, a wide course of action of innovative works in clinical techniques applied in restorative applications. In biomedical imaging the data acquisition systems like computed tomography (CT), magnetic resonance imaging (MRI), ultrasound single photon emission computed tomography (SPECT), positron emission tomography (PET), optical microscopy etc., captures images of the patients. These systems grow exponentially and generate huge data which had more useful information. The high performance computing (HPC) methods analyze the images and visualize images in 3D view as well as pixel wise analysis with very less processing time. The major challenges in the brain tumor detection are to explore the exact location, shape and different tumor tissues and nontumor tissues. The artificial intelligence (AI) and machine learning (ML) address these challenges which supports radiologist and also for patients.

IntechOpen

Author details

Mathiyalagan Palaniappan^{1*} and Manikandan Annamalai²

- 1 Sri Ramakrishna Engineering College, Coimbatore, Tamilnadu, India
- 2 Vivekananda College of Technology for Women, Namakkal, Tamilnadu, India
- *Address all correspondence to: mathiyalagan.p@srec.ac.in

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CCC BY

References

- [1] Jin J, Allison BZ, Wang X, Neuper C. A combined brain-computer interface based on P300 potentials and motion-onset visual evoked potentials. Journal of Neuroscience Methods. 2012;205:265-276. DOI: 10.1016/j. jneumeth.2012.01.004
- [2] Katzenbeisser S, Petitcolas FAP. Information Hiding: Techniques for Steganography and Digital Watermarking. Norwood, MA: Artech House; 2000
- [3] Kohl P, Noble D. Systems biology and the virtual physiological human. Molecular Systems Biology 2009;**292**: 1-6. DOI: 10.1038/msb.2009.51
- [4] Amini S, Veilleux D, Villemure I. Tissue and cellular morphological changes in growth plate explants under compression. Journal of Biomechanics. 2010;43(13):2582-2588
- [5] Saini S, Vijay R. Back propagation artificial neural network. In:
 Proceedings of the 5th International
 Conference on Communication Systems and Network Technologies; Gwalior,
 India. April 2015. pp. 1177-1180
- [6] Behr J, Choi SM, Grosskop S, Hong H, Nam SA, Peng Y, et al. Modeling, visualization, and interaction techniques for diagnosis and treatment planning in cardiology. Computers & Graphics. 2000;24(5):741-753
- [7] McInerney T, Terzopoulos D. Deformable models in medical image analysis: A survey. Medical Image Analysis. 1996;1(2):91-108
- [8] Lustig M, Donoho DL, Santos JM, Pauly JM. Compressed sensing MRI. IEEE Signal Processing Magazine. Mar. 2008;25(2):72-82
- [9] Wang LV. Multiscale photoacoustic microscopy and computed

- tomography. Nature Photonics. Sep. 2009;**3**(9):503-509
- [10] Beard P. Biomedical photo acoustic imaging. Interface Focus. 2011;**1**(4):602-631
- [11] Ghesu FC et al. Marginal space deep learning: Efficient architecture for volumetric image parsing. IEEE Transactions on Medical Imaging. May 2016;35(5):1217-1228
- [12] Wang G. A perspective on deep imaging. IEEE Access. 2016;4:8914-8924
- [13] Esteva A et al. Dermatologistlevel classification of skin cancer with deep neural networks. Nature. 2017;**542**(7639):115-118
- [14] Okada M. A digital filter for the QRS complex detection. IEEE Transactions on Bio-Medical Engineering BME. 1979;26:700-703
- [15] Ergun E, Batakçı L. Audio watermarking scheme based on embedding strategy in low frequency components with a binary image. Digital Signal Processing. March 2009;19(2):277-286
- [16] Kadambe S, Murray R, Boudreaux-Bartels GF. Wavelet transform-based QRS complex detector. IEEE Transactions on Biomedical Engineering. 1999;**46**:838-848
- [17] Awad ES. Data interchange across cores of multi-core optical fibers. Optical Fiber Technology Volume 26, Part B. December 2015;**26**:157-162
- [18] Hamilton PS, Tompkins WJ. Quantitative investigation of QRS detection rules using the MIT/BIH arrhythmia database. IEEE Transactions on Biomedical Engineering BME. 1986;33:1157-1165

- [19] Kahn JM, Ho K-P. Spectral efficiency limits and modulation/detection techniques for DWDM Systems IEEE. Journal of Selected Topics in Quantum Electronics. 2004;**10**(2):259-272
- [20] Chen SW, Chen HC, Chan HL. A real-time QRS detection method based on moving averaging incorporating with wavelet denoising. Computer Methods and Programs in Biomedicine. 2006;82:187-195
- [21] He B, Li G, Lian J. A spline Laplacian ECG estimator in realistic geometry volume conductor. IEEE Transactions on Biomedical Engineering. 2002;49(2):110-117
- [22] Perrin F, Pernier J, Bertrand O, Giard MH, Echallier JF. Mapping of scalp potentials by surface spline interpolation. Electroencephalography and Clinical Neurophysiology. 1987;66:75-81
- [23] Kawakatsu H. Methods for evaluating pictures and extracting music by 2D DFA and 2D FFT.

 19th international conference on knowledge based and intelligent information and engineering systems. Procedia Computer Science.

 2015;60:834-840
- [24] Kawakatsu H. Fluctuation analysis for photographs of tourist spots and music extraction from photographs. In: Lecture Notes in Engineering and Computer Science: Proceedings of the World Congress on Engineering 2014; WCE 2014: 2-4 July, 2014, London, UK. Vol. 1. 2014. pp. 558-561
- [25] Manandhar P, Ward A, Allen P, Cotter DJ, Mcwhirter JG, Shepherd TJ. An automated algorithm for measurement of surgical tip excursion in ultrasonic vibration using the spatial 2-dimensional Fourier transform in an optical image. 44th annual symposium of the ultrasonic

- industry association. Physics Procedia. 2016;87:139-146
- [26] Bhateja V, Patel H, Krishn A, Sahu A, Lay-Ekualille A. Multimodal medical image sensor fusion framework using cascade of wavelet and contourlet transform domains. IEEE Sensors Journal. 2015;15(12):6783-6790
- [27] Mjahad A, Rosado-Muñoz A, Bataller Mompeán M, Francés-Víllora JV, Ventricular Fibrillation G-MJF. Tachycardia detection from surface ECG using time-frequency representation images as input dataset for cyber-physical systems. Computer Methods and Programs in Biomedicine. 2017;141:119-127
- [28] Arenja N, Riffel JH, Djioko CJ, Andre F, Fritz T, Halder M, et al. Right ventricular long axis strain-validation of a novel parameter in non-ischemic dilated cardiomyopathy using standard cardiac magnetic resonance imaging. European Journal of Radiology. 2016;85:1322-1328
- [29] Mavratzakis A, Herbert C, Walla P. Emotional facial expressions evoke faster orienting responses, but weaker emotional responses at neural and behavioural levels compared to scenes: A simultaneous EEG and facial EMG study. NeuroImage. 2016;124:931-946
- [30] Vuilleumier P, Pourtois G. Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. Neuropsychologia. 2007;45(1):174-194
- [31] Wieser MJ, Brosch T. Faces in context: A review and systematization of contextual influences on affective face processing. Frontiers in Psychology. 2012;3:471
- [32] Olofsson JK, Nordin S, Sequeira H, Polich J. Affective picture processing:

An integrative review of ERP findings. Biological Psychology. 2008;77(3):247-265

[33] Rajeswari J, Jagannath M. Advances in biomedical signal and image processing—A systematic review. Informatics in Medicine Unlocked. DOI: 10.1016/j.imu.2017.04.002

