IOSUD - Universitatea Politehnica Timişoara
Şcoala Doctorală de Studii Inginereşti

Computer Aided Diagnosis System for CEUS Focal Liver Lesion Investigation

PhD thesis – Abstract

for obtaining the scientific title of doctor at

Politehnica University of Timișoara

In the doctoral field Electronic Engineering, Telecommunications and Information Technology

Author Eng. Cristina Laura SÎRBU

scientific coordinator Prof. Univ. Dr. Habil. Eng. Cătălin Daniel CĂLEANU

September 2023

The thesis is organized into six chapters and several subchapters (Figure 1), each chapter focusing on a single research topic.

Chapter 1 details the motivation for the research. Based on this, the objectives of the thesis are formulated, which will determine the structure of the work.

Chapter 2 presents the topic of the thesis in the context of medical research in recent years. The structure of a computer-aided diagnostic (CAD) system for the diagnosis of focal liver lesion (FLL) based on contrast substance ultrasound (CEUS) is defined. Basic notions about the anatomy and pathology of the liver are described. Different types of imaging explorations are identified that are used to diagnose focal lesions. Detailed explanations are given about the method of ultrasound investigation with contrast substance. The main focal liver lesions are presented together with spatial characteristics (patterns that are formed in the various phases of exploration) and temporal characteristics (wash-out characteristic).

Chapter 3 deals with architectures and training modalities of artificial neural networks, especially the characteristics of deep-type learning. One section focuses on presenting the fundamental concepts of neural network architectures mentioned in recent literature. This presentation starts from the concept of artificial neuron, classifies the various types of neural networks (RNAs) and extends the discussion to the level of deep neural networks (DNN). In this context, the constituent elements of a typical DNN architecture (convolutional layer, aggregation layer, exclusion layer, etc.) are presented, and then the neural models used in the experimental part are detailed.

Chapter 4 presents the state of current research in the field of computer-assisted diagnosis in the problem of liver pathology. The objectives of the research carried out in this study referred to identifying the characteristics of CEUS datasets and their preprocessing methods, lesion detection and tracking techniques, trait extraction, classification / regression, metrics for evaluation. The investigation follows both classical statistical approaches, but especially those that use deep neural networks.

Chapter 5 has the largest scope and is dedicated to describing a CAD system proposed by the author of the thesis. It includes personal contributions on (1) the pre-processing step by defining an optimal noise removal solution, (2) lesion detection based on optical flow calculation, (3) tracking the region of interest using the KCF algorithm, and (4) various methods for classifying liver lesions with deep learning. The best experimental results were obtained using an "Xception" convolutional neural network architecture.

The last chapter summarizes the main results and personal contributions of the author as well as their dissemination through scientific publications. It concludes with the enumeration of future research directions.

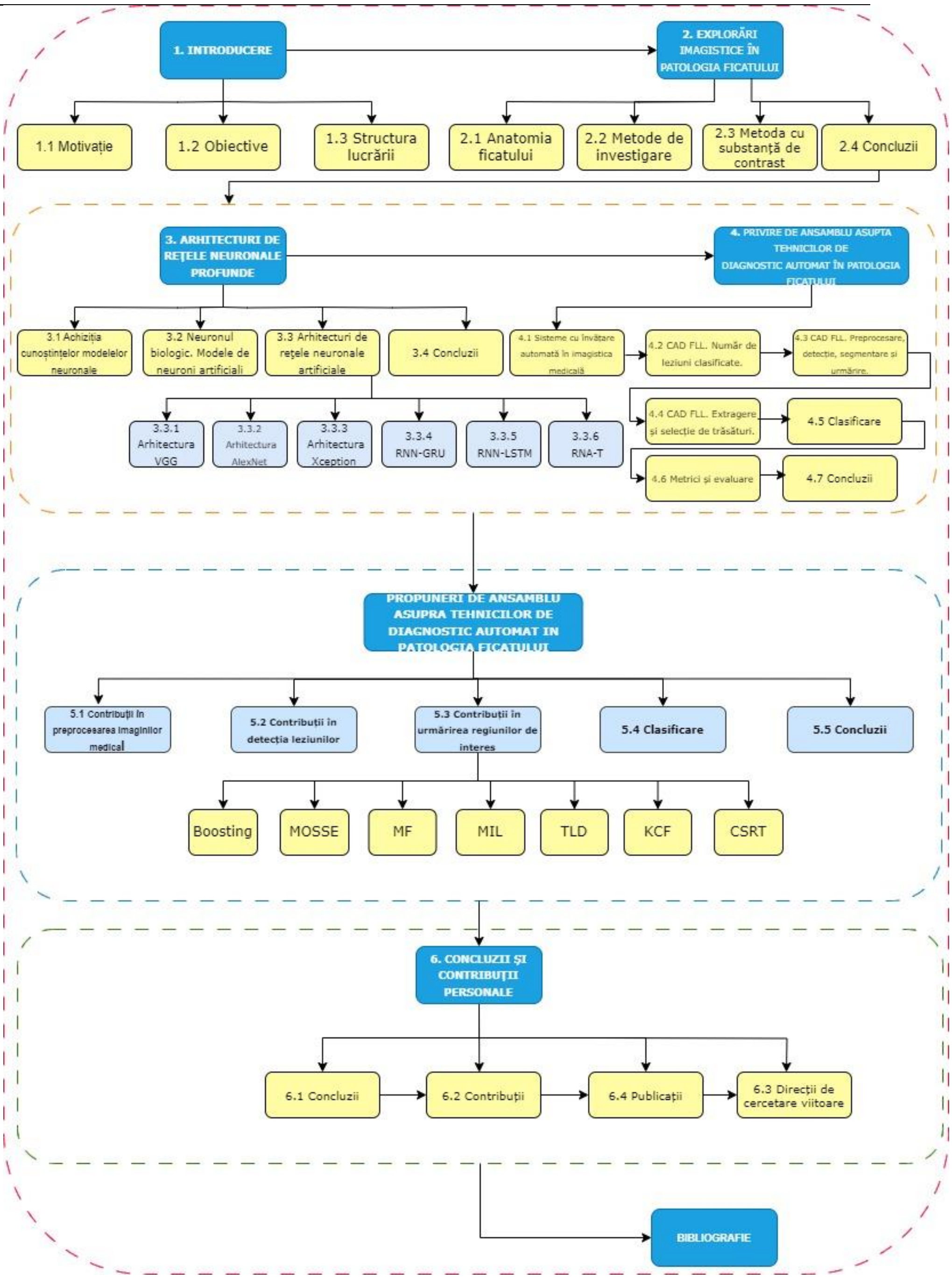

Figure 1: Architecture of the paper by subchapters.

Motivation

The primary motivation underlying the approach to this topic in the doctoral thesis is the incidence of liver pathology. For example, liver cancers are deadly diseases with a very high incidence, being the sixth most common form of cancer worldwide and the third cause of death [1].

Secondary motivation relates to two aspects: (1) progress in current artificial vision systems ("Computer Vision") and (2) the possibility of implementing them through technologies based on deep neural networks ("DNN"). The success of technologies based on deep neural networks and the related learning paradigm called deep learning (DL) has manifested itself mainly in image and video processing, including medical imaging. The field of automated visual recognition has gained momentum with the advent of Convolutional Neural Networks (CNN), specific hardware that enables accelerated computing and the availability of large-scale datasets.

It was found that DNNs were successfully applied to automate the detection and classification of lesions in medical images, creating the premises for the emergence of the concept of Computer Assisted Diagnosis ("Computer Assisted/Aided Diagnosis" (CAD). This tool can be used as a "second opinion" to improve decision-making by doctors.

The ultimate goal of the thesis is to develop a CAD system for automatic diagnosis of focal liver lesions ("Focal Liver Lesion", FLL) in contrast ultrasound investigation ("Constrast Enhanced Ultrasound", CEUS). The development of such a system can help reduce human errors in diagnosis, quickly process large amounts of data and access to medical services for a large number of patients.

Following an exhaustive review of the literature, the performances of current CAD systems were identified, and their improvement was aimed at qualitatively (several types of injuries identified), quantitatively (increasing prediction accuracy) and evaluation/testing of their performance.

Imaging explorations in liver pathology

Medical imaging plays a major role in identifying, characterizing and stabilizing tumor lesions of the musculoskeletal system. The vast majority of these neoplasms are benign, and it is important to recognize and differentiate them from malignant lesions.

Liver cancers are deadly diseases with an important frequency in the world and are due to various liver diseases [1]. Being an organ with a high degree of vascularization, the images obtained are affected by noise. Resection is one of the treatments available, but it can only be applied under certain conditions involving tumor size. Therefore, early diagnosis and accurate assessment of tumors are critical.

The introduction of a CAD system is a modern technique for investigating liver damage (Figure 2). Computer assisted diagnosis is designed to help classify, identify and segment lesions based on medical imaging. CAD systems are essential for disease diagnosis and treatment plan formulation. Moreover, the introduction of machine learning technologies [2] in such systems CAD has the potential to extend the applicability of CEUS investigation [3].

The output of a CAD system (Figure 2) represents a certain diagnosis, but this decision is usually intended to be used as a second opinion. A CAD system involves implementing the following steps: (1) image preprocessing, (2) defining and extracting regions of interest (ROI), (3) feature extraction and selection, and (4) classification.

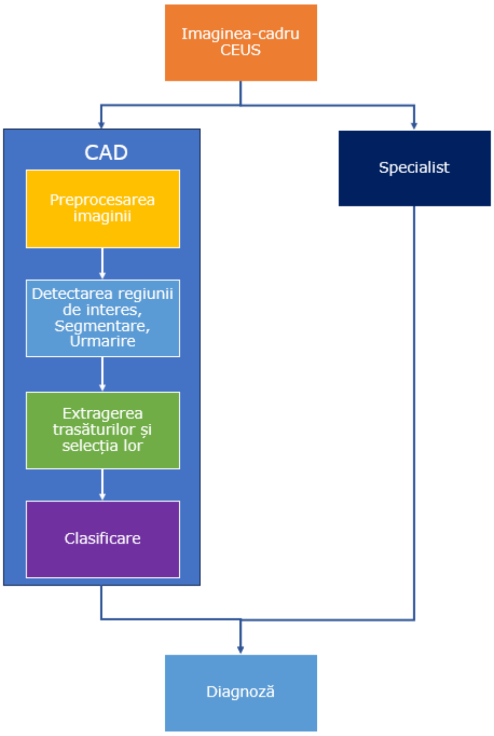

Figure 2: Block diagram of a CAD for CEUS.

The liver is the largest organ of the body (about 2% to 3% of average body weight) and is a basic one for survival [4]. Located in the right upper quadrant of the abdominal cavity below the right hemidiaphragm, the liver is protected by the rib cage. Liver imaging is affected by various movements (patient, probe) and breathing. Although several imaging modalities are currently used in medical investigation, for example, X-rays, magnetic resonance imaging (MRI) or computed tomography (CT), ultrasound (US) is currently a ubiquitous visualization and diagnostic tool. The use of contrast agent leads to CEUS investigation techniques that have further improved the diagnostic utility of US in general and for liver imaging. Also, CEUS brings certain advantages such as high sensitivity, specificity, easy access, high safety, low incidence of side effects.

The three different phases of CEUS exploration are: arterial phase (AP), portal venous phase (PVP) and late (sinusoidal) phase (LP), see Figure 3.

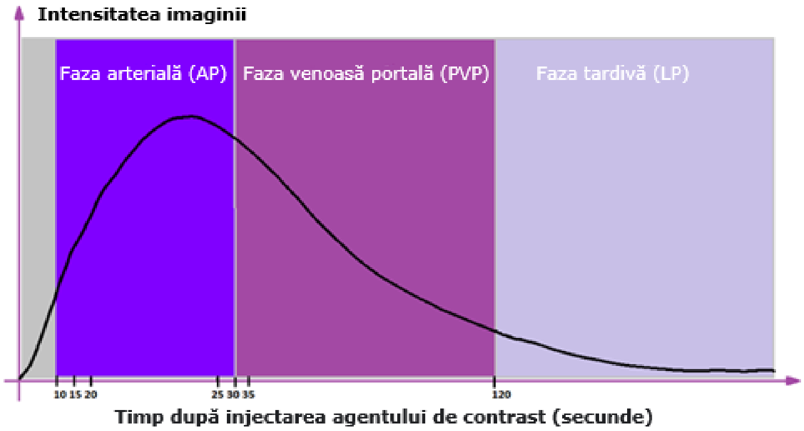

Figure 3: Phases of exploration with contrast material.

Deep neural network architectures

In the field of medical services – in general – and that of medical imaging – in particular – DNN and DL are today extremely present, with major contributions in clinical research, analysis of patient data, development of surgical robots, etc. [5].

This chapter presents fundamental concepts of neural network architectures mentioned in recent literature (Figure 4). This presentation starts from the concept of artificial neuron, classifies the various types of RNA and extends the discussion to DNN. In this context, the constituent elements of a typical DNN architecture (convolutional layer, aggregation layer, exclusion layer, etc.) are presented, and then the neural models used in the experimental part are detailed (convolutional neural networks, VGG, Inception, Xception, RNN-GRU, RNN-LSTM, Transformer).

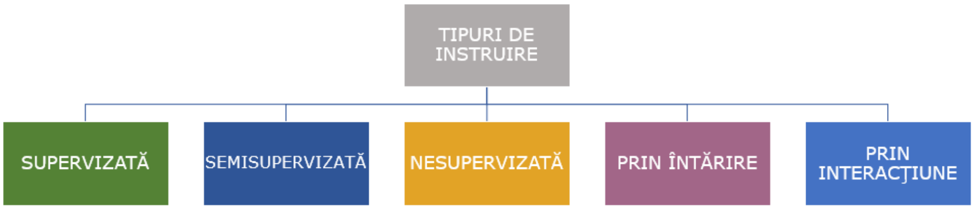

Figure 4: Types of training.

Overview of automatic diagnostic techniques in liver pathology

The classification of focal liver lesions in contrast ultrasound recording is becoming a topic of interest as it could effectively assist healthcare practitioners in the diagnostic process. Like all DNN-based solutions, the performance of the model largely depends on the quality of the training set. To produce quality training datasets, specialists must manually label thousands of frames, which is labor-intensive and error-prone process.

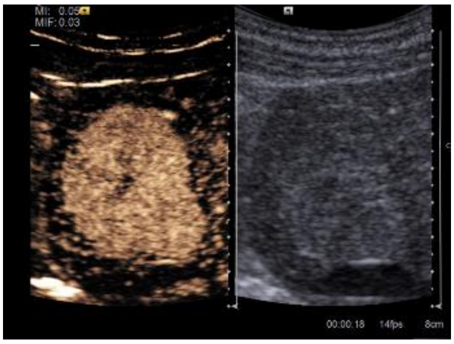

Figure 5: Sample from database. CEUS vs US image.

In this chapter were investigated the possibilities of preprocessing, detection, segmentation, tracking, trait extraction, classification, metrics, evaluation. Despite the fact that there are several review articles on how to apply the principles of machine learning in the analysis of medical images, they have a broad character, with application in clinical medicine in general [6] or, very specifically, limited, for example, to DL technology for US [7] or FLL [8]. The present research differs from that undertaken by the authors listed above by investigating several key aspects of this issue: the number of FLLs identified by the CAD system, image preprocessing operations (filtering, binarization, etc.) including detection, segmentation and tracking of lesions, extracted and selected characteristics used for diagnosis and classification scheme together with datasets, metrics, evaluation procedures and experimental results.

Proposals for implementing an assisted diagnostic system for focal liver lesions

In this chapter we presented our own contributions to the development of a CAD for automatic/assisted diagnosis of focal liver lesions. Manually tagging entire video files is a labor-intensive, elaborate, highly skilled task. Therefore, solutions have been provided in automating the process of tagging and extracting ROIs from video files.

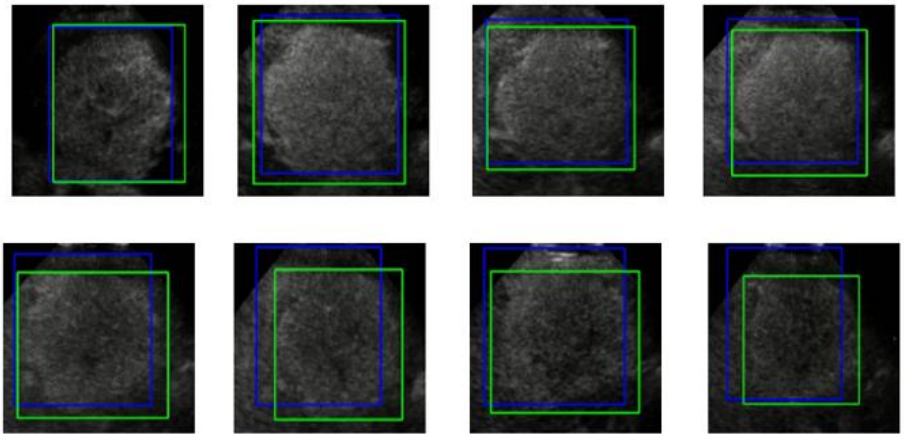

Figure 5: Examples of tracking a lesion, truth (green) and tracking module used (blue). The IoU value is between 75% and 90%.

Specifically, these contributions have manifested themselves in several aspects. The first of these concerns the proposal of a lesion detection method based on optical flow calculation. Optical flux is an approximation of the movement of individual pixels between consecutive image frames, and important information can be extracted based on pixel movement.

Once the lesion was detected, we proceeded to evaluate several possibilities of tracking it throughout the video sequence. Research has shown that the KCF correlation filter tracking algorithm performs best in terms of quality (76% IoU). It also offers the lowest execution time (37.7 frames / second) among solutions of similar quality.

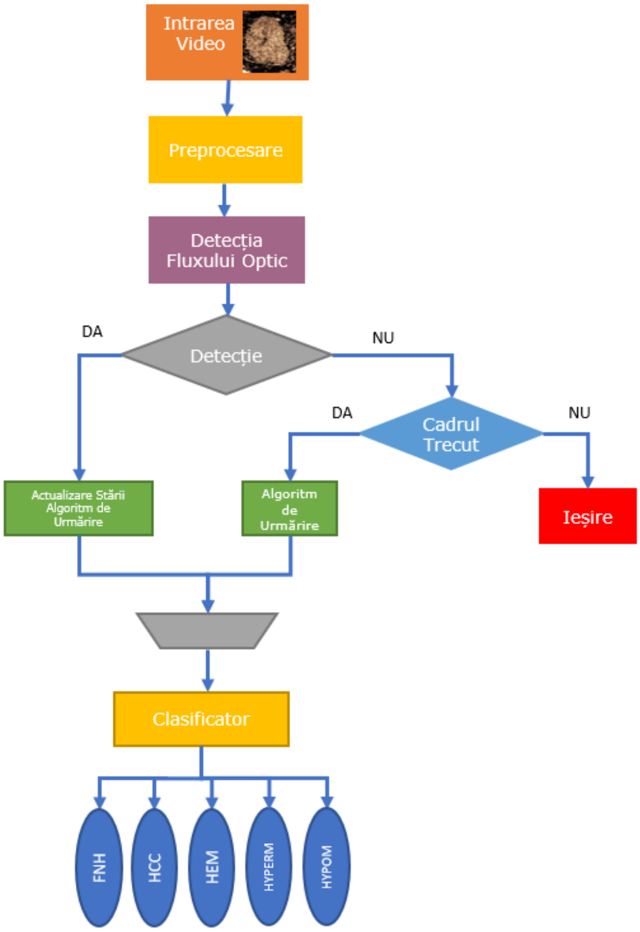

Figure 6: Block diagram of the proposed method for detecting liver lesions.

We compared custom CNN DNN models with state-of-the-art predefined architectures (pre-trained or trained from scratch) (Table 1) using a new assessment procedure that involves excluding one patient at a time. LOPO (*leave-one-patient-out)* allowed me to define and implement different types of voting schemes for patient-oriented diagnosis of lesions. For example, a hard-voting scheme uses class labels predicted for majority voting, while soft-voting estimates the class label based on the *argmax* result of the sum of probabilities.

Table 1: Influence of the neural architecture and the optimizer.

Model	Batch	Training Epochs	Input Size	Adam Optimizer	SGD Optimizer	RMSprop
Seq. M	**32**	**50**	**180x180**	**95,71**	**93,19**	**94.59**
Seq. M	16	100	80x80	94,76	94,88	88.90
Seq. L	32	50	80x80	91,25	88,24	88.11
Seq. L	32	100	80x80	93,31	92,94	81.68

The system we proposed for detection-tracking-classification with hard-voting scheme and "Xception" neural classifier (Table 2) offers 92.31% accuracy in the automatic diagnosis of five types of focal lesions.

Table 2: Mean accuracy [%] per lesion

Model/Patients-FLL	**16 FNH**	**30 HCC**	**23 HMG**	**11 HYPERM**	**11 HYPOM**	**91 Patients Accuracy**
MobileNetV2	100	100	93	36	72	**80**
NASNetMobile	100	88	82	68	83	**84**
EfficientNetB0	81	100	90	74	63	**82**
DenseNet121	92	100	94	78	70	**87**
ResNet50	100	100	100	72	67	**88**
Xception	100	100	93	82	73	**92**

Conclusions

The incidence of liver cancers is the third leading cause of death in the world, and thus one of the major health problems. Technological progress in current artificial vision systems and the possibility of implementing technologies based on deep neural networks have allowed their use in solving the above-mentioned problem. The doctoral thesis presents the results of using different DNN solutions, for classifying focal liver lesions in ultrasound and contrast image images. An important concern is to implement a complete system that is easily available to practitioners.

The main contribution of this thesis is the study, description and implementation of all necessary steps for an automated, computer-assisted diagnostic solution, based on deep neural networks, which can be used for ultrasound explorations with contrast substance in liver pathology: acquisition and preprocessing of several specific databases, ways to remove noise from their images, lesion detection and tracking, trait extraction and classification.

Within the doctoral program I studied over 180 bibliographic titles and I also published an article in the ISI journal (Quartile Q1 – MDPI Sensors), 8 articles at conferences indexed by ISI Proceedings and an article accepted for publication at the time of writing this material. I would like to note that for my published articles I have over 40 citations, of which one article within the thesis has 22 "Google Scholar" citations / 10 WOS citations in prestigious journals, with high impact factor such as "Artificial Intelligence in Medicine" (ISI journal indexed Q1), "Ultraschall in der Medizin" (ISI journal indexed Q1), "World Journal of Gastroenterology" (ISI journal indexed Q1), "Engineering Applications of Artificial Intelligence" (ISI journal indexed Q3). Below, I will list my own contributions.

Personal contributions present under Chapter 2:

- We defined the role of liver analysis in pre/intra/post operative imaging;
- We identified the optimal structure of a CAD system together with the implementation of related subsystems, with the results published in the article [9];
- We synthesized medical notions about the functional and physiological anatomy of the liver;
- We compared the methods of imaging the liver, identifying their advantages and disadvantages in publications [10] and [11];
- We highlighted the advantages of CEUS as a non-invasive, safe, robust, easy-to-perform, versatile method that offers good performance in terms of discrimination between benign and malignant lesions, as well as differentiation within them. Issues related to this issue were published in [12];
- We have described the most common types of focal lesions and the characteristics highlighted by the contrast method, published in [9];

Personal contributions present under Chapter 3:

- We conducted a bibliographic study at the beginning of the chapter, where we compared the biological neuron with the mathematical model and presented different architectures of artificial neural networks used in the present research, with publication in the paper [13];

Personal contributions present under Chapter 4:

- We analyzed and evaluated state-of-the-art solutions existing in the field for determining liver pathology;
- We presented the results of CAD systems studied and published in the literature;
- It is intended to publish an overview study based on the material presented in this chapter;

Personal contributions present in Chapter 5:

- We processed and prepared all the data sets used in this research, following the selection of the batch received from the partners from Victor Babes Hospital Timisoara; published in [12] [9].
- We proposed an optical flow detection method for tracking the lesion and classifying it, results published in [14];
- We made an experimental characterization on the detection and tracking modules, by performing several tests on the dataset, and analyzed the impact and relevance of parameter changes on images; Results published in [15];
- I participated in tagging a public dataset of three liver lesions with a medical professional; Published in [15];
- I created and generated a new medical database; Posted on [15];
- We have proposed and implemented a new method of evaluating the performance of a CAD that provides a more accurate characterization and closer to the clinical reality of the performance of a diagnostic system, with publication in [9].
- We tested the performance of the proposed methods using several datasets of variable size, published in [12] [9] [15];

Personal contributions present under Chapter 6:

1. We presented the future directions of the research by proposing a new

Visual Transformer (ViT) architecture for classifying focal lesions, presenting preliminary experimental results.

Selected references

[1] G. 2002, "International Agency for Research on Cancer," CANCERMondial Website, http://www-dep.iarc.fr, 2002.

[2] Q. Huang, F. Zhang and X. Li, "Machine Learning in Ultrasound Computer-Aided Diagnostic Systems: A Survey," vol. 2018, pp. 1-10, 2018.

[3] S. Turco, T. Tiyarattanachai, K. Ebrahimkheil, J. Eisenbrey, A. Kamaya, M. Mischi, A. Lyshchik and A. El Kaffas, "Interpretable machine learning for characterization of focal liver lesions by contrast-enhanced ultrasound," *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*, vol. 69, p. 1670–1681, 2022.

[4] J. S. Dooley, A. S. Lok, G. Garcia-Tsao and M. Pinzani, Sherlock's diseases of the liver and biliary system, John Wiley & Sons, 2018.

[5] B. Lakshmipriya, B. Pottakkat and G. Ramkumar, "Deep learning techniques in liver tumour diagnosis using CT and MR imaging - A systematic review," *Artificial Intelligence in Medicine,* vol. 141, p. 102557, 2023.

[6] C. J. Haug and J. M. Drazen, "Artificial Intelligence and Machine Learning in Clinical Medicine, 2023," *New England Journal of Medicine,* vol. 388, pp. 1201-1208, 2023.

[7] S. Liu, Y. Wang, X. Yang, B. Lei, L. Liu, S. X. Li, D. Ni and T. Wang, "Deep learning in medical ultrasound analysis: a review," *Engineering,* vol. 5, p. 261–275, 2019.

[8] S. Survarachakan, P. J. R. Prasad, R. Naseem, J. P. de Frutos, R. P. Kumar, T. Langø, F. A. Cheikh, O. J. Elle and F. Lindseth, "Deep learning for image-based liver analysis—A comprehensive review focusing on malignant lesions," *Artificial Intelligence in Medicine,* p. 102331, 2022.

[9] C. D. Căleanu, C. L. Sîrbu and G. Simion, "Deep neural architectures for contrast enhanced ultrasound (CEUS) focal liver lesions automated diagnosis," *Sensors,* vol. 21, p. 4126, 2021.

[10] M. Stănescu, C. L. Sîrbu and C. Orhei, "Mapping the environment at range: implications for camera calibration," in *2022 IEEE 28th International Symposium for Design and Technology in Electronic Packaging (SIITME),* 2022.

[11] C. L. Sîrbu, P. Papazian and M. Băbăiţa, "FPGA Implementation of a IEEE 1451 Compliant Transducer Interface Module," in *2023 33rd International Conference Radioelektronika (RADIOELEKTRONIKA),* 2023.

[12] C. L. Sîrbu, G. Simion and C. D. Căleanu, "Deep CNN for Contrast-Enhanced Ultrasound Focal Liver Lesions Diagnosis," in *2020 International Symposium on Electronics and Telecommunications (ISETC),* 2020.

[13] A. G. Bălănescu, C. L. Sîrbu and C. Orhei, "Intersection detection based on mono-camera sensor," in *2022 45th International Conference on Telecommunications and Signal Processing (TSP),* 2022.

[14] C. L. Sîrbu, G. Simion and C. D. Căleanu, "Improving the Diagnostic of Contrast Enhanced Ultrasound Imaging using Optical Flow for Focal Liver Lesion Detection," in *2022 24th International Symposium on Symbolic and Numeric Algorithms for Scientific Computing (SYNASC),* 2022.

[15] C. L. Sirbu, C. Seiculescu, G. Adrian Burdan, T. Moga and C. Daniel Caleanu, "Evaluation of Tracking Algorithms for Contrast Enhanced Ultrasound Imaging Exploration," in *Australasian Computer Science Week 2022,* 2022, p. 161–167.

[16] T. Albrecht, M. Blomley, L. Bolondi, M. Claudon, J.-M. Correas, D. Cosgrove, L. Greiner, K. Jäger, N. De Jong, E. Leen and others, "Guidelines for the use of contrast agents in ultrasound-january 2004," *Ultraschall in der Medizin-European Journal of Ultrasound,* vol. 25, p. 249–256, 2004.

[17] M. Claudon, D. Cosgrove, T. Albrecht, L. Bolondi, M. Bosio, F. Calliada, J.-M. Correas, K. Darge, C. Dietrich, M. D’onofrio and others, "Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)-update 2008," *Ultraschall in der Medizin-European Journal of Ultrasound,* vol. 29, p. 28–44, 2008.

[18] G. S. a. C. D. C. C. L. Sirbu, "Improving the Diagnostic of Contrast Enhanced Ultrasound Imaging using Optical Flow for Lesion," in *24rd International Symposium on Symbolic and Numeric Algorithms for Scientific Computing (SYNASC),* 2022.

[19] C. L. Sirbu, C. Tomoiu, S. Fancsali-Boldizsar and C. Orhei, "Real-time line matching based speed bump detection algorithm," in *2021 IEEE 27th International Symposium for Design and Technology in Electronic Packaging (SIITME),* 2021.

[20] X. Liang, L. Lin, Q. Cao, R. Huang and Y. Wang, "Recognizing focal liver lesions in CEUS with dynamically trained latent structured models," *IEEE Transactions on Medical Imaging,* vol. 35, p. 713–727, 2015.

[21] I. Sporea, R. Badea, A. Popescu, Z. Sparchez, R. L. Şirli, M. Dănilă, L. Săndulescu, S. Bota, D. P. Calescu, D. Nedelcu and others, "Contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions–a prospective multicenter study of its usefulness in clinical practice," *Ultraschall in der Medizin-European Journal of Ultrasound,* vol. 35, p. 259–266, 2014.