AUTOMATIC SEGMENTATION OF ANATOMICAL STRUCTURES USING DEFORMABLE MODELS AND BIO-INSPIRED/SOFT COMPUTING

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INTRODUCTION

This PhD dissertation describes the accomplishments of our research, carried out within the Marie Curie project MIBISOC [1] (``Medical Imaging using Bio-Inspired and SOft Computing'', EU FP7 G.A. n. 238819), on the design and development of new intelligent algorithms for the automatic and accurate segmentation of anatomical structures in biomedical images. Hybridizations between Soft Computing (SC) and Computer Vision (CV) techniques have been investigated for application in biomedical imaging-related tasks. Computer Vision studies the computational interpretation of images, while methods related with Soft Computing, also referred to as Computational Intelligence, are mostly search/optimization procedures and other approximate methods that try to emulate humans' abilities, such as dealing with uncertainty, learning from examples, generalizing knowledge, improving their performances based on experience, cooperating to perform difficult tasks, or evolving (where evolution is considered both as a natural/stochastic process driven by "results", and as a conscious process driven by experience or intelligence). Thus, SC is focused on the design of AI systems able to solve problems in the presence of qualitative, uncertain, imprecise or incomplete data.

In collaboration with the Molecular Biotechnology Center of Torino, we have developed specific AI-based tools aimed at extending the current understanding of the complex signaling events occurring in dendritic spines (DS), by integrating state of the art computational and experimental approaches. DS are neuronal protrusions, which receive input typically from one excitatory synapse, containing neurotransmitter receptors, organelles, and signaling systems essential for synaptic function and plasticity. In a first phase we have developed new recognition algorithms for brain anatomical structures, capable of automatically extracting two types of information:

1) the relative abundance of the mRNA of every gene in the main brain areas;

2) the identity of mRNAs that are particularly enriched in dendrites, which are very likely to be involved in DS biogenesis/functions.

The main motivation can be found in the great interest that neurobiologist have for RNA molecules specifically enriched in the neuropil of neuronal cells (and, in particular, in DS), in virtue of their involvement in synaptic structure, plasticity and neuropsychiatric disorders (like fragile-X syndrome, autism spectrum disorders, or schizophrenia). The systematic identification of these molecules is, therefore, a very important task and can be based on visual features, such as image texture, which recur in the regions where they are more densely present. In that regard, the high-resolution images of RNA In Situ Hybridization (ISH) experiments contained in the Allen Brain Atlas (ABA) represent a very rich resource to identify them and, for this task, they have

been exploited, so far, based only on human-expert analysis. ISH is a technique that allows one to precisely localize specific segment of nucleic acid within a histologic section. However, software tools that automatically address the same objective are not easily available or effective. Since the regions of interest, where the molecules under study are more densely present, occupy only a small part of the whole images, a tool for automatically focusing on such regions is essential if a huge number of images is available for processing.

GOALS

The main goals and motivations of this work are four, and can be summarized as follows. Firstly, to study and improve medical image segmentation algorithms. Image segmentation (IS) is the accurate delineation of an object's boundary within an image or, in other words, the partition of an image into meaningful and non-overlapping regions following some kind of criterion. Medical imaging (MI) is the production of visual representations of body parts, tissues, or organs, for clinical diagnosis (medical procedures seeking to reveal, diagnose, or examine diseases) or medical science (including the study of normal anatomy and physiology). Then, MI segmentation is the segmentation of medical images. This is an extremely important task in procedures like detection of lesions, measurement of organ size/volume, quantitative tissue analysis or computer-integrated surgery.

Secondly, the research described in this dissertation started as a collaboration with the Molecular Biotechnology Center of Torino to develop a tool for performing genome-wide experiments (automatically localizing the hippocampus and analyzing its visual features in neuro-genomic images of the mouse brain). To accomplish such a goal, three different segmentation methods that allow for the accurate delineation of a specific anatomical region have been developed.

Third, this PhD work needs to be interpreted within a broader framework: the European Marie Curie Project "MIBISOC". Therefore, one of main objectives of this research was to explore hybridizations between AI and CV to solve MI problems.

Finally, after carefully studying the scientific literature (see Chapter 4 of the PhD dissertation), we discovered several methodological issues that needed to be addressed. First, to develop completely automatic methods (not initialized/supervised by a human user) because manual segmentation is tedious, time-consuming, and error-prone. Second, to avoid extremely ad-hoc and poorly tested algorithms. In many publications, the algorithms developed are tested just over one single MI modality or over very few sample images. So, we developed general segmentation approaches, and we tested them using a large test set, statistical tests and standard segmentation metrics. Third, to initially focus on important, but traditionally ignored, biomedical image modalities (like ISH), since the vast majority of works deals with Magnetic Resonance Imaging (MRI), Computerized Tomography (CT) or Ultrasound (US) imaging.

METHODS

The first method that has been developed [2, 3, 4, 5] preliminarily processes a training set of images, from which the deformation range and the main modes of variation of a parametric deformable model (DM) are empirically assessed. Based on these data one can define very simple templates, managed by a fast method which allows genome-wide experiments on thousands of images. This approach is divided into four different stages: initialization, localization using DMs and metaheuristics

(MHs), segmentation, and expansion of the segmentation using ensemble classifiers; it can be seen as a smart way of selecting promising regions to be subsequently processed by a fast and well-established image segmentation/analysis technique (see Figure 1). The main advantages of this approach are its execution time and accuracy, while its main disadvantages are its ad-hoc nature (it needs a training set of shapes/textures, and suitable parametric models of the object to locate), and the impossibility of managing topological changes. This localization/segmentation algorithm was successfully applied to the real-world problem previously described [6]: the automatic method permitted the exploration of ISH data and the discovery of neuropil-enriched RNAs in the mouse hippocampus. We called it Hippo-ATESC (Automatic Texture Extraction from the Hippocampal region using Soft Computing), and bioinformatics validation showed that it is actually very effective in recognizing RNAs which are manually identified by expert curators as neuropil-enriched in the same image series. The code is freely available on the web at http://ibislab.ce.unipr.it/software/hippo/. Also, as part of the research, the method was implemented using general purpose GPU programming in CUDA [7, 8, 9, 10], which led to the development of a library which includes the first GPU-based implementation of Scatter Search [11]. The contribution of AI techniques to this method is two-fold: first, MHs are used to tackle a complex optimization problem that classical (gradient-based and local) methods clearly failed to solve, and second, ensemble classifiers are used to refine the segmentation results obtained (many approaches were compared to this purpose: Multi-Layer Perceptron, AdaBoost, Random Forest, Bagging, and Support Vector Machines, among others) [4].
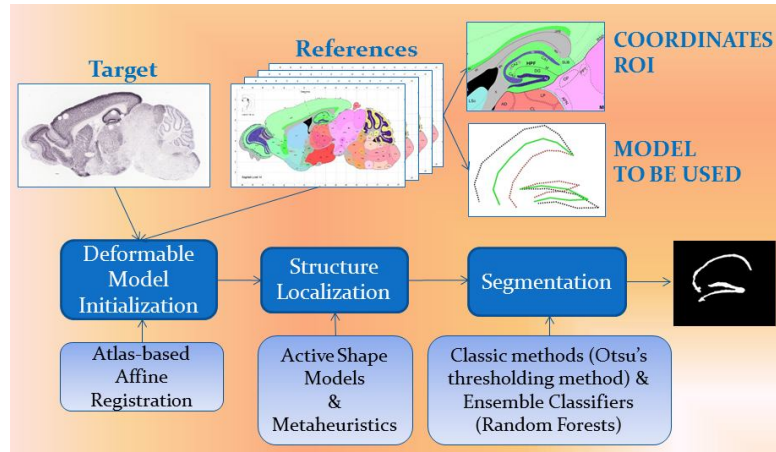

Figure 1: Main pipeline of Method 1

The second method [12] developed during our research uses the Level Set (LS) method to allow topological changes. The templates are created automatically using principal components analysis to derive texture, mean shape and shape variability from the training set (see Figure 2). After that, a MH is used to evolve the segmenting contour by optimizing the weights of a linear combination of the different eigenshapes and the mean shape, based on an intensity- and texture-based fitness function. Thus, again MHs were used to tackle a multimodal and high-dimensional optimization problem that classic method are unable to solve. This method has obtained reasonably good results, even if it is less precise than the previous approach and requires a longer

execution time. Thus, it can be looked upon as an intermediate stage that led us to develop the third segmentation method.
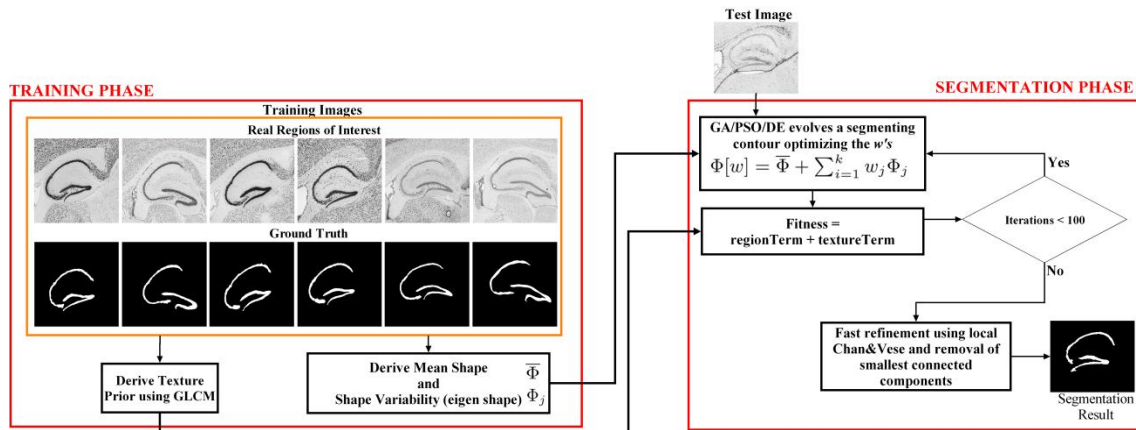

Figure 2: Main pipeline of Method 2

The third method, called HybridLS [13, 14] , tries to solve all the problems that hamper the applicability of the other two approaches. In this method, firstly, the LS method is used again to manage possible topological changes. Secondly, three different sources of information are taken into account (intensity, boundaries, and shape). Third, the automatic MH-based tuning procedure allows one to apply the same method to different image modalities and anatomical structures, and makes this a general approach (tested on CT, MRI and microscopy histological images). Finally, only a single previously segmented reference image is necessary to perform the segmentation instead of a complete training set (see Figure 3). This is possible thanks to a deformable registration process in which the target image is aligned with the corresponding image of an Atlas. In terms of generalization and accuracy, this method obtained the best results in comparison to seven state-of-the-art segmentation approaches.
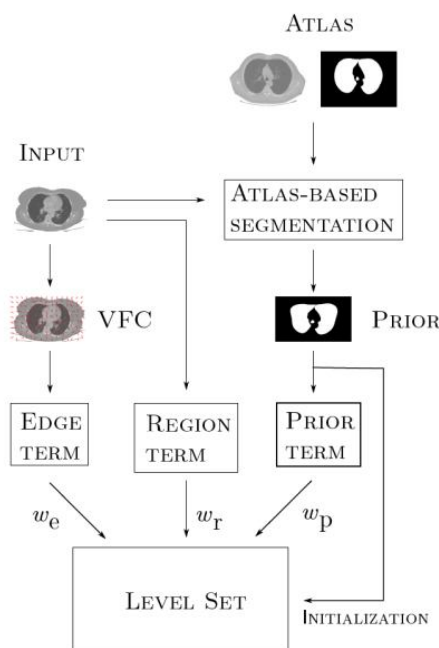

Figure 3: Main pipeline of Method 3 (HybridLS)

RESULTS

Two main **practical results** were obtained during this PhD:

- Bioinformatic validation showed that the Hippo-ATESC, using MHs and classifiers, is <u>very effective in recognizing RNAs which are manually identified by expert curators as neuropil-enriched on the same image series</u>. Moreover, we showed that <u>our method can also highlight genes revealed by microdissection-based methods but missed by human visual inspection</u>. We experimentally validated our approach by identifying a non-coding transcript enriched in mouse synaptosomes.

- We developed HybridLS: an <u>accurate, as well as general, segmentation method</u> which obtains very good results with all the medical image modalities tested, overcoming well-consolidated techniques, and whose overall performance standard deviation is the lowest among the different methods being compared. Therefore, we can affirm that our approach is consistent and stable in terms of performance. Also, it does not need a training set of textures or shapes to segment the object of interest (it needs only one reference image to obtain the shape prior). <u>Thanks to AI techniques (MHs), it performs self-adaptation of its own parameters (an optimization task that could not be done using classic methods) depending on the medical image modality to segment, and it generates the shape prior.</u> Thanks to the automatic learning of the model parameters, our hybrid proposal is able to perform an effective segmentation with very different medical image modalities, adapting the importance of every term to each image modality and anatomical structure.

Among the main **conceptual conclusions** of this PhD dissertation we could enumerate the following ones:

- <u>The use of more recent MHs</u> like Differential Evolution, Particle Swarm Optimization or Scatter Search <u>is strongly recommended</u>, since Simulated Annealing and similar approaches, often used in medical image analysis, are obsolete and unable to efficiently solve real-world problems. Obviously, as well, the usually multimodal, non-convex and high-dimensional nature of medical image segmentation problems makes it useless to apply classical local optimization approaches (like Gauss-Newton or Levenberg-Marquardt).

- The use of the level set method and prior shape knowledge using MHs can be one of the most interesting future trends, due to its potentiality and the current lack of publications on the topic. In fact, a very good starting point when segmenting anatomical structures is to <u>use a hybrid approach by including as much prior information as possible</u> (shape, texture, intensity, boundaries), since this can speed the execution time and increase the accuracy of the results obtained.

- The <u>generalization ability of a method can be increased by automatically tuning its parameters</u>, to effectively deal with a particular type of structure to segment and/or a particular MI modality.

FINAL SUMMARY

In summary, we took advantage of the hybridization of DMs and MHs to segment anatomical structures, using prior knowledge from different sources, and embedding the segmentation into an optimization framework. AI techniques (MHs and classifiers) can be used to perform the optimization of the target function defined by the shape model, to automatically tune the system parameters, to perform feature selection, and to refine the results obtained by the segmentation process. Three new different methods, with their corresponding advantages and disadvantages, have been designed, implemented and tested. All methods have been extensively compared and statistically tested using standard segmentation metrics. A broad theoretical discussion, together with an extensive introduction to the state of the art, has also been included to provide an overview necessary for understanding the methods we have developed.

The <u>main contributions</u> of this PhD dissertation can be summarized as follows:

- systematic and rigorous approach to the hybridization between computer vision and AI (metaheuristics and classifiers). This study uses statistical tests and standard quality segmentation metrics extensively, unlike the majority of the work in the field (usually ad-hoc and poorly tested);

- automatic and general segmentation approach, tested over three very different biomedical image modalities: histological brain images (ISH data), computerized tomography and magnetic resonance images;

- it is one of the extremely few cases in which microscopy histological brain images segmentation has been approached using DMs (both parametric and geometric) and MHs, overcoming in many aspects state-of-the-art methods;

- an extensive survey of related work on hybridizations of DMs and MHs, in the absence of any other 'review' like this in the scientific community;

- a large number of publications due to an intensive collaborative activity favored by the participation in the MIBISOC project (see Appendix III in the PhD dissertation): 5 journal and 12 conference papers published during the PhD period, of which the most relevant ones are:

PUBLICATION	TITLE	AUTHORSHIP	QUARTILE
Computerized Medical Imaging and Graphics	"Biomedical Image Segmentation using Geometric Deformable Models and Metaheuristics"	First author	IF2011: 1.467, 43rd of 72 journals indexed in subject category BIOMEDICAL ENGINEERING and 72nd of 116 journals indexed in subject category RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING, 3rd quartile

Pattern Recognition Letters	"Automatic Hippocampus Localization in Histological Images using Differential Evolution-Based Deformable Models"	First author	IF2011: 1.034, 63rd of 111 journals indexed in subject category COMPUTER SCIENCE, ARTIFICIAL INTELLIGENCE, 3rd quartile
Applied Soft Computing	"Particle Swarm Optimization and Differential Evolution for Model-based Object Detection"	Third author	IF2011: 2.612, 13th of 111 journals indexed in subject category COMPUTER SCIENCE, ARTIFICIAL INTELLIGENCE, 1st quartile
PLoS ONE	"Artificial Astrocytes improve neural network performance"	Third author	IF2011: 4.092, 12th of 85 journals indexed in subject category BIOLOGY, 1st quartile
PLoS ONE	"Visual search of neuropil-enriched RNAs from brain in situ hybridization data through the image analysis pipeline Hippo-ATESC"	Second author	IF2011: 4.092, 12th of 85 journals indexed in subject category BIOLOGY, 1st quartile

The full PhD dissertation can be downloaded at http://ibislab.ce.unipr.it/publications/thesis_mesejo.pdf. This PhD research work obtained the maximum possible grade at the University of Parma, including European PhD honors. Also, during this PhD, international collaborations were set up with: Université Libre de Bruxelles (Belgium), European Center for Soft Computing (Spain), Universidade da Coruña (Spain), Henesis srl (Italy), Universidad de Granada (Spain), and Università degli Studi di Torino (Italy).

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