Fast quantitative image processing methods and biological image analysis

Theses of the PhD Dissertation

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The truth isn't flashy.
Flashy words aren't true.
Educated people aren't always smart.
Smart people don't always have an education.
The virtuous do not bandy arguments.
Those who bandy arguments are not virtuous.
The Masters don't hang on to things.
They're always doing something for other people,
so they always have more to give.
They give away whatever they have,
so what they have is worth more.
If you want to get right with the Way,
help other people, don't hurt them.
The Masters always work with people,
never against them.
(Lao-Ce: Tao Te Ching, 81)

Introduction

The cellular neural-nonlinear network (CNN) and the Cellular Wave Computing paradigm [12, 13, 14, 15, 16, 17] was applied to solve a wide range of challenging problems in the last decade. High speed medical image processing and modeling neural networks are two of these fields that appeared particularly interesting for me. During my studies my curiosity drove me to interact with biologists that made me eager to understand how living organisms work.

The most fruitful but also the most difficult way of getting insight into mechanisms of living organisms is by simple observation of the subject in its original environment and living conditions. There are relatively few methods that provide information about living organisms without severely interfering with their normal behavior. Non-invasive biological imaging methods are of the most widely applied observation strategies. Both in research and in clinical practice, X-ray, magnetic resonance and ultrasound based imaging have a history of several decades.

Details of living organisms below around $1mm$ resolution cannot be imaged with these modalities. Before the advent of medical imaging, microscopes were already used widely to observe and analyze functions at low spatial scale. Microscope based methods are almost always invasive and one must be very cautious in inferring high level behavioral conclusions from microscope based observations. The gap between low-level and high-level analysis appears to be shrinking due to recent advances in both microscope technology and in molecular biology. Combining high-resolution microscopy with image processing and molecular biology techniques can open the way to functional analysis of mechanisms even at molecular scale.

Morphology of living organisms is extremely variable. Therefore long training and extensive experience is required for human observers to be able to interpret recordings from living organisms.

In the recent years imaging modalities started to evolve into the third spatial dimension. After the first enthusiasm, it became clear that the extra amount of data poses two serious problems. First, data storage requires more resources - this issue falls out of the scope of my work. Second, it is much more difficult to visualize, manipulate and interpret 3D recordings efficiently. Handling 3D data is very difficult to our minds that is traditionally trained on visual information seen in books and on flat screens. The ultimate aim of the analysis is always to make some decisions like "does this image show a healthy heart or not?" or "is this recording showing cell type A or B?". Both questions reveal that quantification has to be performed based on our observations. Stepping into the third spatial dimension provides more information for our decisions but humans actually have less processing ability for three dimensional data.

Our lack of processing ability can be complemented by computers. However,

image processing and user interface technologies did not follow innovations in image acquisition technologies. The main reason for this delay is the constant shortage of processing power in computers with respect to the algorithms to be executed. The required processing power can be provided by topographic CNN processor arrays capable of supporting fully parallel algorithms that can process image flows at very high speed and low power consumption. My work focused on developing real-time, quantitative methods for biological image analysis using topographic algorithms.

The first problem I have been working on is the real-time three dimensional reconstruction of human heart cavities from ultrasound recordings. Reliable medical diagnosis requires the accurate estimation of cardiac measures like ejection fraction, cavity volume and wall thickening. Currently, medical experts manually measure these indexes prone to subjective bias and error. In many cases, analysis of the cavity morphologies is required. In the lack of 3D probes and visualization tools, the clinician has to spend considerable amount of time to reconstruct the morphology of the heart in his mind using several 2D views. Reliability of such a reconstruction is questionable due to the high variability of possible morphologies and to the fast moving nature of the heart.

The second problem I addressed was the quantification of the dendritic morphology of retinal ganglion cells (RGC). A fundamental paradigm of neuroscience is that neural structure is related to neural function. At the cellular level it was shown in many studies that neurons with different shapes have different function. At a higher organizational level it was shown that the dendrites and axonal arborization of neurons in several brain regions are organized in thin strata and neural function varies across strata. A striking example is the mammalian retina where the inner plexiform layer (IPL) consists of about ten different, well-defined strata and each strata extracts a different feature from the visual scene forming a stack of image representations in the retina[18].

In brain regions where different functions are encoded in different strata, a powerful morphological approach would be to quantitatively define the strata which are formed by dendritic and axonal arborization of neurons. Then from simply knowing the depth of stratification of a stained neuron one could deduce its function. I developed an automated algorithm that can scan a large number of cells from a retina and quantify the ramification depth of their dendrites.

I acquired experience in solving demanding 3D image processing via solving the two above mentioned problems. During my work, I realized that experienced human observers can extract relevant information about 3D structures quickly. The same task is very challenging for computers. I attended neurobiology courses during my doctoral studies and realized that the massively parallel CNN visual microprocessor I worked on was similar to living neural structures. Discussions with biologists about retinal architecture raised my interest in understanding how

neural circuits process information.

One candidate mechanism that can play a role in efficient information processing is synchronization. Synchronization phenomena are apparent in many fields of physics and biology but we do not know what synchronization does and how it might play a role in information processing. The main problem in analyzing synchronization phenomena in oscillatory networks is that models are non-linear, high dimensional systems. The state of the art mathematical toolset can analyse very simplified models only that are quite far from oscillator networks observed in nature. Even for simple models it is very difficult to get closed form expressions on conditions for synchronization.

The desire to explore cooperating behavior in oscillatory networks motivated me to overcome the barrier that our mathematical toolset is very limited to study synchronization phenomena in realistic networks. I developed an algorithm that can teach dynamical behavior to a network of oscillators. Using this algorithm, I uncovered two exciting new phenomena. The first phenomenon may be considered counter intuitive and gave counter examples to existing theory. In [19] Liu et al. claim that when coupling is added to a network of chaotic oscillators with double- or multi-scroll attractor, Lyapunov exponents being zero in the uncoupled system become positive as coupling is increased. They suggest that this rule is general, however, this may not always be true since I could show examples where the largest Lyapunov exponent in the coupled cells is zero, i.e. the qualitative behavior of cells became simpler due to the coupling.

The second phenomenon is related to [20] where it was shown that symmetries of the network topology with nearest neighbor connections and uniform interaction weights lead to synchronization in multiple, coexisting cell groups. I demonstrated for the first time, that highly asymmetric interaction weights can also synchronize multiple, coexisting cell groups. In addition, despite the asymmetry in the interaction pattern, the spatial layout of the synchronized cell groups followed the topological symmetries of the network.

Cellular Nonlinear Networks composed of oscillatory cells are high dimensional and non-linear dynamical systems. Developing constructive approaches that can unfold new phenomena is therefore very difficult. My results represent a step toward bridging the gap in our understanding between systems that are simple thus mathematically tractable and systems that are physically more realistic but require large efforts to be analyzed.

Methods

The development of topographic cellular algorithms were done in a simulation environment based on Matlab using the MatCNN [21] toolbox. In the case of my

work in 3D echocardiography, the following methods were used.

The first step in algorithm development was the collection of raw 3D ultrasound recordings. A collaborating expert, Zsolt Czeilinger (György Gottsegen Institute of Cardiology), prepared and scanned six in-vitro phantom objects, and collected over 100 recordings from children using a Philips Sonos 5500 scanner with transesophageal transducer.

The right atrium of the heart has no established geometrical model thus algorithmic approaches in the literature based on model fitting were not applicable. Human experts traced endocardial boundaries of the 3D recordings manually that were used as references during the development and validation of the automated boundary tracking algorithm. Raw 3D ultrasound data, manually traced references, clinical diagnosis and algorithm results were collected into a database that was made accessible through the internet.

Development of the 3D visualization were done in Autodesk 3D Studio Max by András Vobornik (Analogic-Computers Ltd) an expert in computer graphics. Time consuming operations were directly coded in C. After expected results were obtained in simulation, the method was ported to the ACE-BOX, later to the Bi-i system to both the DSP and the ACE16k CNN visual microprocessor. The Bi-i system represents and ideal combination of sequential and parallel processing and served as a common platform to evaluate the performance of different algorithm implementations. To ensure robust operation on the actual CNN chip, templates were tuned to the actual ACE16k processor using a global optimization method [22].

Validation of the algorithm were done in Matlab using several metrics (Hamming, Hausdorff, nonlinear wave, right atrium volume comparison).

Classification of retinal ganglion cells were done in cooperation with Botond Roska (Harvard Medical School, Friedrich Miescher Institute), who prepared the retinas. Confocal recordings of the cells were acquired using a Zeis 510 laser scanning microscope. Algorithm development were done in Matlab. Results were evaluated on a large database consisting of 170 cells.

Exploration of synchronization phenomena on oscillator arrays were done in Matlab with time consuming code parts implemented in C. Coupled simulated annealing (CSA) method was used in the learning process. Other global optimization methods were also tested but CSA requires considerable less function evaluations than other methods to reach a given cost value.

Summary of scientific contributions

Thesis 1 *On-line reconstruction of the right atrium with the quantification of cavity volumes and the size of the atrial septum defect from 3D ultra-*

sound recordings via topographic cellular active contour algorithms [1] [4] [5] [6] [7] [8]

I developed a computational method providing on-line, automated 3D reconstruction of the right atrium together with the visualization of the atrial septal defect (ASD). I evaluated the accuracy of the method via comparing algorithm results with phantom and clinical echocardiographic data sets manually traced by independent cardiologist experts. Error of the algorithm proved to be comparable to the inter-observer variability between independent experts. Interactive planning of surgical interventions in pediatric cardiology was presented as an illustrative example demonstrating the clinical potential of the method.

1.1 I introduced new algorithmic solutions to ensure robust detection of the endocardial boundary of the right atrium performed via constrained wave computing

The Constrained Wave Computing (CWC) method segments the object to be detected as the steady contour of a dynamic wave initiated from patches called sources. The evolution of the dynamic wave can be stopped using a grayscale spatial constraint calculated from the input image(s). Where wall segments are missing on the ultrasound image, proper spatial constraint cannot be generated to stop the wave propagation. However, a properly chosen time-constraint can always be applied and thus a solution will be obtained in a non-equilibrium state of the network. I developed four algorithmic steps that select proper time constraint automatically.

1. An initial guess on cavity size can be made by fitting an ellipse using robust statistics on a few contour points localized by 1D edge detectors along lines stemming from the center of the cardiac cavity. The ratio of the major and minor axes of the ellipse reflect the elongated shape of the cavity. Using this ratio, the expansion speed of the contour can be spatially distorted to ensure that the expanding contour arrives approximately at the same time to the image features constraining the propagation.

2. Pixels of the contour that change during the evolution of the propagating wave front are called active pixels. Measuring the number of active pixels can be used to estimate the value of the time constraint. The contour is initialized as the eroded version of the contour detected for the previous frame. At this initial stage, there is no or very few spatial constraint close to the contour thus all pixels of the contour will expand. As the contour gets constrained by image features, the number of active pixels decreases. When wall segments are missing and the contour flows outside the target object, the number of active pixels starts to increase again. The correct propagation

time limit is reached when the number of active pixels begins to increase. This step fine tunes the rough time limit estimation from step 1.

3. Contour expansion of subsequent frames can be initialized by the eroded version of the detected cavity shape from the previous frame. Erosion is performed by the same operator but with reversed direction. Time constant for erosion is determined by checking the proportion of the number of active pixels and the length of the shrinking contour. Once the two are equal, i.e. no spatial constraint is close to the contour, shrinking can be stopped and the required time can be used as time constant. This way the ellipse fitting is only necessary for the first frame or when the process is reinitialized in case the difference between the result of contour detection from consecutive frames is too high.

4. From the previous detection, the contour can expand in two steps. First expand the eroded version of the detected cavity shape from the previous frame with the time constraint chosen with the algorithmic steps 1-3. Then the expanded contour is further propagating with the same time constraint again. The second expansion results in heavy outflows where wall segments are missing. The difference between the results from the first expansion and from the second is a contour with outward protrusions where wall segments are missing. Applying the skeletonization and the pruning operators on this object corrects outflows and smoothes the result.

1.2 I implemented the Constrained Wave Computing topographic cellular active contour (TCAC) method extracting endocardial boundaries in real-time from the raw ultrasound data on the massively parallel ACE16k visual microprocessor. I compared this implementation to two other TCAC methods implemented on various architectures. I used a novel common hardware-software environment to compare the performance of TCAC methods exploiting different complexity levels of CNN computing.

Implementation of algorithms on cellular analogic processor arrays is in itself a challenging task. I developed a Matlab toolbox that makes porting MatCNN algorithms to the ACE16k [23] chip very straightforward. I implemented the CWC algorithm on the ACE16k chip. With the help of the template tuning toolbox, I demonstrated a robust solution to the boundary tracking problem running above 500 frames per second that represents more than 1.5 order of magnitude speed gain compared to the fastest approach in the literature.

Note that it is extremely difficult to quantitatively compare the performance of two different active contour algorithms. The novelty of my experiments was to go

as far as possible in comparing three TCAC methods (CWC continuous time, CWC discrete time, PLS [24]) in a common hardware-software framework. I compared the CWC continuous time method implemented on the ACE16k with the PLS method implemented on the ACE4k and with the CWC discrete time method implemented on the Texas 6202 DSP and on the ACE16k and on a Pentium 4 3GHz processor. The difference between contours extracted by the different TCAC implementations were not significant.

The comparison showed the outstanding speed of the ACE16k processor capable of executing propagating templates in a single instruction.

1.3 I conceived and implemented a method for the validation of the volume quantification of the RA and the size estimation of the ASD.

There is no crystallized validation protocol to assess the performance of medical image analysis algorithms. Chalana and Kim in [25] introduced a protocol for validation procedures relying on multiple observers, but debated issues persist in defining proper methods for validation [26]. Other studies compared only either the area enclosed by algorithm and by expert traced contours (Hamming distance) (e.g. [27]) or the averaged Euclidean distance between closest contour points for validation (Hausdorff distance based). Another approach is to compute the distances between corresponding landmark and reference points. Establishing corresponding contour points is very problematic in lack of a cavity model for the right atrium. It was shown earlier that neither Hamming nor Hausdorff distances are robust metrics. I applied the non-linear area weighted Hausdorff (wave) metric [28] to compare endocardial boundaries.

Besides comparing the contours, I also evaluated the accuracy of volume estimation of the right atrium on six phantom and six clinical data and the accuracy of size estimation for of the ASD on six clinical recordings.

Thesis 2 *Morphology based method for the classification of ganglion cells in the mammalian retina. I developed a novel method for automated, quantitative estimation of the depth of dendritic ramification of RGCs from confocal image stacks. I proposed and used an improved, high-throughput scanning protocol. [2] [9]*

Neural morphology is an important predictor of function in living neural networks. Many parts of the nervous system are organized in multiple laminae, each incorporating a unique set of cell types with unique functionality. The inner plexiform layer of the mammalian retina is comprised of about ten different strata [18], formed by the dendritic arborization of a dozen different functional classes of ganglion cells. So far, tedious manual analysis was needed to estimate the depth of ramification of a retinal ganglion cell (RGC). Automated quantification of bi-

ological features is very difficult due to the high variance in the morphology of biological features and artefacts caused by the acquisition procedure.

The proposed algorithm quantifies the depth of dendritic ramification for each labeled ganglion cell from the DAPI and Alexa 488 stained cells recorded by a confocal microscope. In a scan containing the target ganglion, robust quantification is achieved by extracting four types of landmark features: the ganglion cell layer (GCL) border, inner plexiform layer (INL) border, the ganglion cell soma and the local dendrite feature. I developed an algoritmized model quantifying the relative depth positions of the four landmark types. The depths of dendrites in the stack are determined relative to the GCL border and the INL border. The GCL border (0% depth) is defined as the depth of the peak DAPI fluorescence intensity in the GCL (Fig. 1) and the INL border (100% depth) is defined as the depth where the DAPI florescence was 66% (66% is a level high enough to differentiate the INL from the GCL peak and it is not distorted by fluorescence intensity variations) of the maximum measured in the INL. Dendritic depths are calculated locally near each dendritic segment to eliminate artifacts caused by the fact that the retina is not entirely flat.

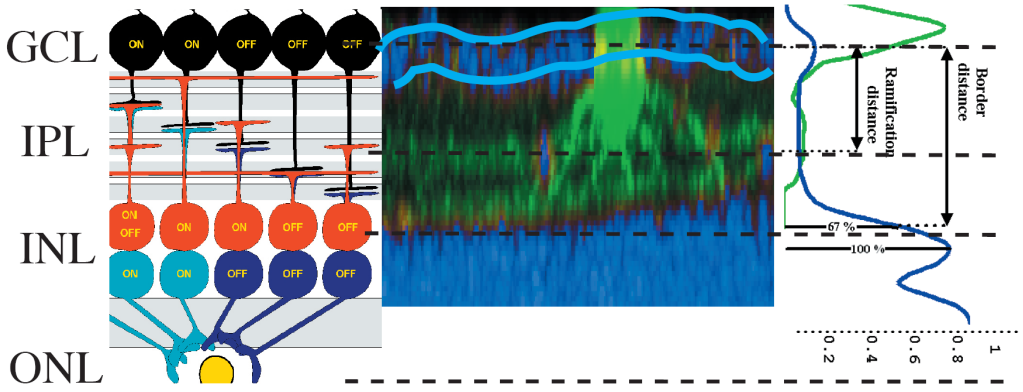

Figure 1: Left: A drawing of the retina. GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, ONL: outer nuclear layer. Middle: Side projection of a GFP labeled ganglion cell in mouse retinal optical slice counterstained with DAPI. Right: Fluorescent profile of the GFP and DAPI stain along the z direction. Note that due to the many artifacts (cell body, retina is not flat, etc...), one cannot see the dendritic stratification on the GFP plot. This is the reason I developed the proposed algorithm.

I used the 405, 488 and 633nm laser lines of a Zeiss LSM 510 Meta confocal microscope to excite cells stained with fluorescent DAPI, Alexa 488 and Alexa 633 respectively. To determine the dendritic depths of genetically labeled ganglion

cells I acquired confocal stacks of 170 ganglion cells. The improvement on previous scanning protocols was twofold: First, I applied an automatic stage control algorithm that can automatically scan a set of stacks at manually marked positions. In each imaging session I marked 20-30 ganglion cells per retina in about 30 minutes and then all confocal stacks were acquired at each location unattended. This improvement created a workflow with much higher throughput than manually configuring each scan. Second, based on my observations during the development of the quantification method, the scanning parameters of the protocol were modified so that the retina is scanned above the GCL and well into the photoreceptor layer. Before, many scanned cells could not be quantified automatically because the extraction of the GCL and/or INL landmark features was not feasible in a robust way.

Thesis 3 *New forms of cooperative behavior in cellular oscillator arrays [3] [10] [11]*

I demonstrated that using a numerical optimization framework it is possible to explore and analyze the information processing capabilities of cellular nonlinear oscillator networks. I presented the way in which a properly formulated cost function can be used to achieve synchronization and at the same time impose qualitative behavior on an array of chaotic oscillators. My approach aims to add an application motivated aspect to existing results that so far focused on conditions for synchronization. To demonstrate the potential of the optimization framework I showed on a simple case study that network configurations corresponding to partial synchronization regimes can be learned. The same can also be done with imposing various types of qualitative behavior on individual oscillators.

3.1 I developed a new method that can learn network parameters corresponding to a specified behavior.

The main problem in analysing oscillatory networks is that models are nonlinear, high dimensional systems. State of the art mathematical toolset is limited to analyse very simplified models. Even for simple models it is very difficult to get closed form expressions on conditions for synchronization [29], [20]. Related studies mainly use regular topology, nearest neighbor diffusive coupling with uniform coupling pattern. My approach uses global optimization to search for network parameters that exhibit the expected behavior formulated in the cost function. An important advantage of my approach compared to other studies is that the only requirement on the vector field defining individual oscillators is that they permit the solution to exist and be unique. On the other hand, in some cases this liberty may result in an optimization problem that is very hard to solve if it is possible at all.

3.2 I discovered that coupling patterns can be learnt that modify

the qualitative behavior of oscillatory cells in a network.

Using the global optimization framework, I found examples where the qualitative behavior of cells in a 2×2 network composed of Chua oscillators were different depending on whether cells were coupled or not. One phenomenon is that switching on coupling increased the complexity of the behavior, i.e. cells converging to equilibrium point or being in limit cycle mode became chaotic. The other phenomenon is the opposite: cells exhibiting chaotic behavior change to limit cycle mode when coupling is switched on.

The latter case seems to contradict to previous results. In [19] Liu et al. claim that when coupling is added to a network of chaotic oscillators with double- or multi-scroll attractor, Lyapunov exponents being zero in the uncoupled system become positive as coupling is increased. They suggest that this rule is general, however, the case when the coupling makes the qualitative behavior of cells simpler indicates that this may not always be true.

3.3 I discovered that assymetrical interaction pattern can give rise to partial synchronization regimes

I discovered a new form of synchronization in cellular arrays of chaotic oscillators. Previously it was shown in the literature that symmetries of the coupling topology with uniform interaction weights lead to several coexisting clusters of synchronized cells. I presented a new phenomenon where highly asymmetric interaction weights can give rise to cluster synchronization regimes with partial synchronization. In addition, cluster or partial synchronization regimes corresponding to asymmetric interaction patterns can constrain the effect of the underlying symmetries of the network topology and boundary conditions at the expense of some residual synchronization error.

Application of the results

The results of Thesis 1 and 2 are in their current stage already very application oriented. Although the problems and the methods are different, at a higher abstraction level, these problems can be unified. A common lesson I learned is that the development of a good medical image processing method relies heavily on how much data is available of the target biological organ or feature and how strictly the data acquisition protocol is defined.

Results formulated in Thesis 3 are much more theoretical. Subthesis 2 represents a direct application possibility. As illustrated by subthesis 2, my approach can be a useful tool to test hypotheses made on coupled networks of chaotic oscillators. Rules (either theoretical or empirical) believed as generic can be transformed into a cost function. Then a global optimization process can maximize the cost

function, i.e. it looks for solutions that violate the rule formulated as a cost function. Finding no such solution can be a strong evidence supporting the validity of the original rule.

Confirming generic (theoretical) rules via global optimization might seem improper. However, deriving sound theoretical results is extremely difficult when dealing with coupled networks of chaotic oscillators. Therefore the method showed in Thesis 3 can provide valuable feedback.

Thesis 3 showed that by using a global optimization framework it is possible to get insight into the complex interactions of coupled chaotic oscillators. The method can be useful in guiding investigations and confirming results from theoretical analysis.

My motivation for investigating synchronization phenomena stemmed from the insight I gained into high speed image processing problems. I realized that despite the very good operation per joule figure of CNN processors, performance of machine vision algorithms is still very low compared to the ease of living creatures tackling complicated scenarios. Actually, we still lack the understanding of what mechanisms should be exploited to construct high speed, highly robust, low power vision algorithms. On the other hand, in neurobiology, the same problem arises when trying to understand how neurons actually perform computation.

In the engineering community, study of synchronization of chaotic oscillators became a very active area since a couple of years. Studies are focusing on deriving conditions for synchronization but we only have very limited knowledge why chaotic dynamics is beneficial in neural networks. So far only speculations and conjectures have come to surface suggesting that specific topological configurations and chaotic dynamics are advantageous without pointing out exactly why and in what situations chaotic dynamics is essential. Although synchronization and chaotic dynamics are fascinating topics from a purely scientific approach, it would be highly beneficial to justify the extra efforts needed to deal with such systems. My method could represent a step in this direction.

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