QUANTITATIVE IMAGE ANALYSIS OF THE PRETERM BRAIN

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ABSTRACT

To estimate the extent of brain injury in life depends on many aspects of biomedicine. Clinical information surfaces in an erratic manner and data must be clustered in a quantitative way before meaningful diagnostic probabilities can emerge and treatment can be targeted to them. This abstract/presentation deals with the currently most widely trusted tool of measuring brain injury, i.e. imaging, more specifically in preterm infants. The view brought forward is mainly from the combined angle of view of neonatologists specialized in acquired preterm brain problems and medical image processing engineers.

Index Terms— Preterm, Brain Imaging, Ultrasound

1. CLINICAL BACKGROUND

Brain injury is due to ischemia, inflammation, metabolic stress (e.g. malnutrition or inborn error of cell metabolism) and a variety of other less common mechanisms. The resulting pathological phenotypes are infarction (arterial, venous or in border zones), selective cell death (neuronal, glial or endothelial), hemorrhage, tumor or tissue dysplasia, see Figure 1.

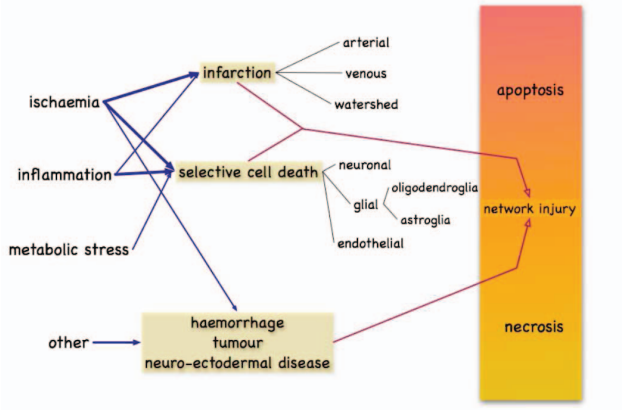


Fig. 1 *Paradigms of injury, lesions and modes of cell death in the brain.*

All primary lesions secondarily influence distant brain regions, connected to the lesioned area, through transaxonal changes (trophic and excitotoxic). This leads to *network injury*. For example, cell death manifests with a continuum of types, any given type situated between typical necrosis and typical apoptosis. Lactate elevation is a marker of infarction, derived from H-MRS (proton-based magnetic resonance spectroscopy).

Biochemical data about the brain can be detected in blood and cerebrospinal fluid (CSF). Markers of cell injury may dissipate from brain cells into tissue and from there on into blood or CSF. For example, glutamate is elevated in CSF following birth asphyxia, lactate is elevated in blood. Brain-specific markers are not routinely used in serum, because their elevation lacks specificity and they are seldom able to estimate the extent of injury. Merely its presence is picked up. However, routine implementation of serum genomics and proteomics at an affordable cost may in the near future drastically change the face of medical biochemistry.

Neurophysiological changes in the nervous system can be registered with raw electro-encephalograms (EEG) and derivates of subsets of channels with several trend possibilities, somato-sensory evoked potentials, (SSEP), brainstem evoked response audiometry, (BERA), and visual evoked potentials (VEP). They are helpful in detecting seizures and extensive brain injury, but also in measuring dysfunction of certain networks like audition and vision.

Finally, *imaging* is still the most widely trusted tool for measuring brain injury. Commonly used modalities are magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and Ultrasound (US). The main problem however is that the diagnostic power is often still related directly to the visual, qualitative inspection of the images. In the case of low-quality imaging, as with US, subjectivity comes into play. To *quantify* injury in these cases is to overcome many problems inherent to subjective judgment.

In this paper, we present a brief overview of the state of the art in quantitative neonatal brain image analysis as well as our most important improvements in the field of US image processing, Section 2. Subsequently, we comment on in which direction we think quantitative image analysis will evolve, Section 3. Finally, some conclusions are presented in Section 4.

2. QUANTITATIVE IMAGE ANALYSIS

We subdivide this section in three major application blocks usually involved in quantitative (brain) image analysis: the classification of structures or tissues, the segmentation of objects of interest and the registration of features or structures (often over different imaging modalities).

2.1. Classification

The usual method of quantification is to measure an image variable related to injury. As such, measuring within selected regions of interest (ROI) has become a standard research tool. For example, grey value characteristics, differing between brain structures, are used to selectively measure the volumes of cortical grey matter, white matter, and ventricular CSF.

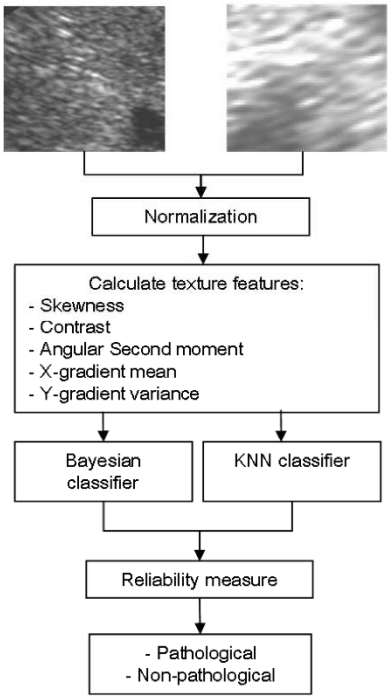


Fig. 2 *Flowchart of the Ultrasound tissue texture classifier*

Measurement of relative grey values in ROI within MRI sequences is easy but has not replaced the swift visual interpretation by the radiologist: this demonstrates the fine complexity of visual interpretation by the trained human brain in high-quality images.
Note that MR scanners now also routinely provide derivates of diffusion-weighted imaging (DWI) in numbers and in maps, like ADC (apparent diffusion coefficient) or FA (fractional anisotropy). These measures have already proven to be very efficient routine tools and should broaden the field of quantitative MRI measurement. Undoubtedly, others will follow.
We, on the contrary have proposed a classification algorithm based on tissue texture information present in, visually more difficult to interpret, 2D ultrasound images [2]. This has resulted in a quantitative measure for pathological white matter, with sensitivity scores that do outperform both existing quantitative measurements and the visual qualitative expert scores, see Figure 2 for a flowchart of the method.
Gain-independent measurement of tissue characteristics using the raw radio-frequency signal of 3D Ultrasound volumes, is an aim for the near future and to be discussed later.

2.2. Segmentation

Next to measuring characteristics within regions of interest, brain (tissue) segmentation has become an important research tool.
Because of its high-quality structural imaging, usually MRI volumes are used to segment white from grey matter and ventricle enlargements. However, obtaining good MRI information from newborn infants is not trivial.
Therefore, we have developed a segmentation algorithm combining texture characteristics and mathematical morphology to measure the extent of white matter injury in (more accessible) US frames [3], obviating in part the misleading subjectivity inherent to the judgment of *flaring* (pathological regions), see Figure 3 for a little flowchart.

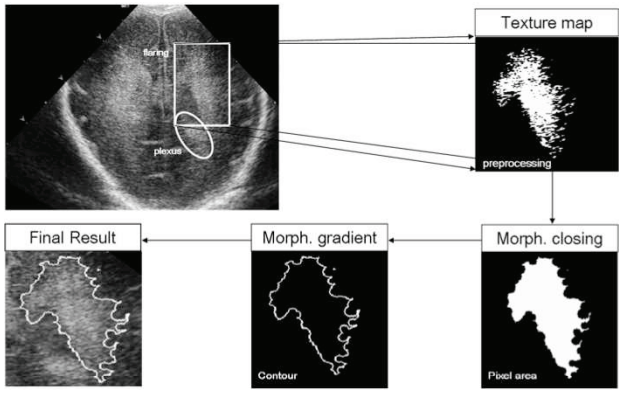


Fig. 3 *Flowchart of the Ultrasound flaring segmentation algorithm*

Next to the absolute delineation of these pathological regions, segmentation superimposed on normalization in space has already provided us with interesting insights into normal and abnormal development of lobar cortical anatomy. These techniques approach (and perhaps replace) the gold standard of postmortem histology.

2.3. Registration

A last method of quantification is to depict the average brain by registering a number of normal brain scans. To this end,

standardization in brain space (normalization) has been successfully initiated in the MRI brain atlas of Talairach and Tournoux [1]. Derivatives (improving the original) have been developed and are available in disk format and on the web (http://www.loni.ucla.edu/ICBM/). A particular patient scan can be compared to the standard brain to visualize or measure differences in many aspects.

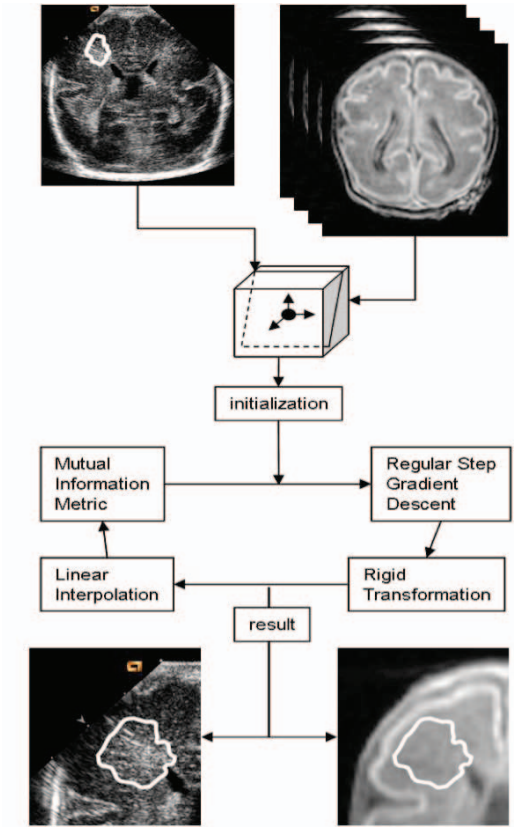


Fig. 3 *Flowchart of the 2D Ultrasound to 3D registration algorithm*

This type of measuring is again not easily applied to the newborn. Viable newborns range in maturation from 24 to 40 weeks of gestation may have altered cortical development and may even vanished cortical ribbons, all of which make registration on a maturation-corrected virtual brain still impossible. In the near future, this will have to be achieved using less patient scans than available in adult medicine.

In Ultrasound however, we already developed a first successful interactive 2D US to 3D MRI neonatal brain registration method [4] to cross-validate our flaring segmentation algorithm, see Figure 3 for a flowchart.

3. FUTURE OF NEONATAL BRAIN IMAGING

Apart from the image analysis we already have at our disposal, the vastly growing field of medical imaging provides us with some nice challenges for the future.

Over the last few years, visualization of restricted proton diffusion by DWI and DTI has become a powerful clinical tool. Derivatives of this technique are the basis of what is called *tractography*. Using a combination of DWI, vascular anatomy and segmentation we come closer to visualizing infarct core, penumbra and network injury, see Figure 4.

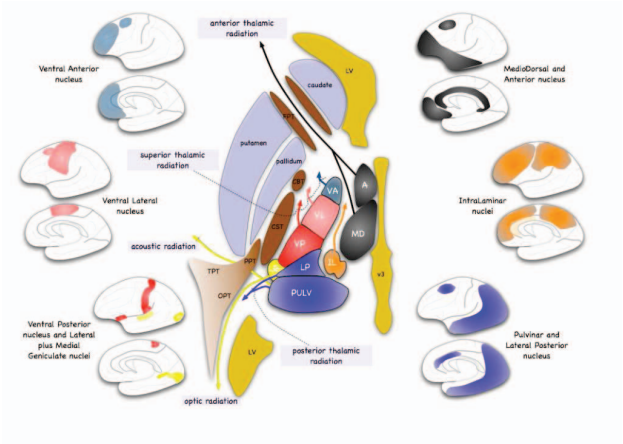


Fig. 4 *Network injury in the thalamocortical system*

Recent work we did in that direction lead to the first "normal" DTI-atlas of a population of 7 benign data sets of 27 week old preterms, presented visually in Figure 5.

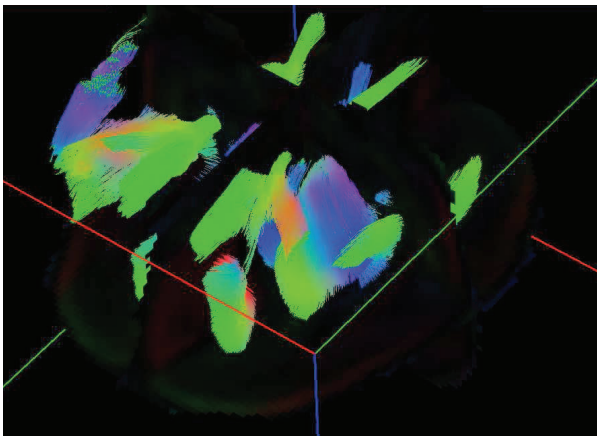


Fig. 5 *Visualisation of the first 27 week old preterm's DTI brain atlas*

To visualize altered perfusion with US, MRI or CT is sufficient for diagnosing lesions like vascular anomalies. However, simple visualization comes short of the promise to study maturation of vessel development or to relate perfusion to haemodynamic parameters. To that end, quantified perfusion will have to be compared with diffusion imaging, e.g. to study stroke treatment. Exactly this

quantification of perfusion change is the basis of *functional MRI*, drawing on the BOLD (blood-oxygen-level dependent) principle.

Another elegant, non-invasive method to study perfusion depends on the absorption of *near-infrared light* (NIRS) in a defined brain path. Although quantification is still problematic (as are motion artifacts), some very exciting clinical findings have been reported with newborn brain NIRS.

Molecular imaging (mainly in combination with MRI) will probably drastically influence the near future of brain imaging. Contrast agents destined to enhance paramagnetic effects can pick up tumors with higher sensitivity than gadolinium-perfusion imaging (the use of which depends in part on changes at the blood-brain barrier): manganese and iron oxide are examples that approach clinical use. *AnnexinV* imaging is one way of depicting apoptosis and undoubtedly others will appear to show brain areas with different types of cell death in the continuum from apoptosis to necrosis. CEST (chemical exchange saturation transfer) agents sensitive to pH or glucose may also become useful in this respect.

Another last point we want to stress is the entrance of augmented reality in medical diagnosis. Although ever more-performing visualization software packages appear, the possibility for a medical expert to virtually interact with fused image volumes should lead to new possibilities and diagnostic finesse. A promising example of this is the *I-SPACE*™ [5], i.e. a virtual environment where experts can register multi-modal image data.

Finally, in this paper we have worked on B-mode images as far as US imaging is concerned. As mentioned in a previous section on classification. new and even more quantitative approaches involve RF-signal analysis. Preliminary results were presented as far as this work is concerned in [6] and a schematic approach can be found in Figure 6.

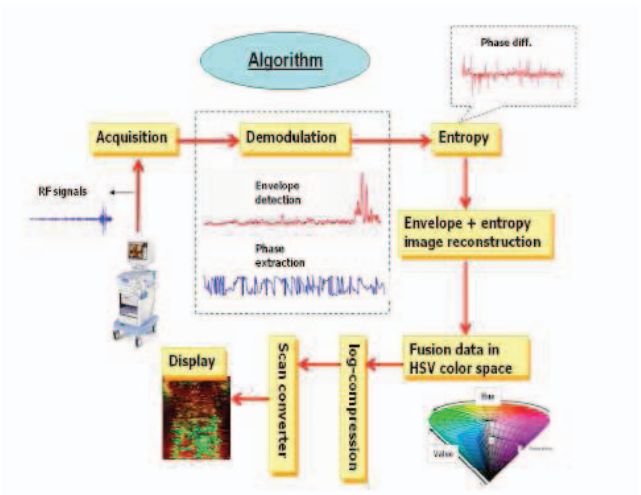


Fig. 6 *Algorithm for RF-based entropy measurements of the preterm brain*

4. CONCLUSION

The advent of ever more-performing imaging modalities results in a growing gamut of potentially complementary diagnostic data. Consequently, in the near future the collaboration between engineers and mathematicians on one side and medical doctors on the other will become of increasing importance. Nowadays, in major institutions image processing groups are already embedded in the clinical environments, resulting in quantitative (semi)-automated computer-aided diagnostic tools that allow the experts to navigate through the data in daily practice, both in an accurate and time-efficient manner.

Concerning neonatal brain imaging specifically, the future will be multi-modal imaging combining the best of US, MRI and EEG/NIRS imaging. The fine complexity of the brain enables experienced medical doctors to make educated guesses about diagnoses of injury to itself but reproducible measurements offered by engineers are of great value to confirm or refute these diagnoses with increasing accuracy.

5. REFERENCES

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