Computational NeuroSurgery (CNS) Lab Showcase

Dear Colleagues,
In the current pandemic environment, we have learnt to cope with social distance, any kind of restrictions, and uncertain times. Despite this, we tried to move forward, continuing our surgical and clinical activity, whenever possible and feasible, challenging ourselves to work remotely, and interact with each other in virtual environments (which, most likely will become more and more normal over time, even at the end of the pandemic crisis).

Some research has been stopped, mainly research based on face-to-face or wet-lab experiments while other research hasn't been interrupted, like those involving statistical analyses, meta-analyses and computational analyses.

In such a perspective, I would like to take this occasion to share some of the research done and/or are in progress at the Computational NeuroSurgery Lab that, although limited by the campus access restrictions, has continued to work remotely (using available datasets, computing by means of remote access to our lab workstations, networking with the scholars involved in the research, etc.).

Computational neurosurgery is a new field, so new that it doesn't even have its own allocation in the scientific environment. Although several neurosurgeons over the past years have been involved in the application of computational modelling to neurosurgery and clinical neurosciences, in our field the adjective "computational" has always been associated to "neurosciences", interpreted as the "*the field of study in which mathematical tools and theories are used to investigate brain function. It can also incorporate diverse approaches from electrical engineering, computer science and physics in order to understand how the nervous system processes information*" (definition from the journal *Nature*).

The application of computational modelling, advanced mathematical analysis, fractal geometry, artificial intelligence, etc., to the understanding, diagnosis and treatment of patients affected by diseases of neurosurgical interest is something which has been done (and published) in a sporadic and non-systematic way over the last years.

The ***Computational NeuroSurgery (CNS) Lab***, founded in 2019 thanks to the funding and logistic support from Macquarie University, Faculty of Medicine, Health and Human Sciences, Macquarie Neurosurgery, Royal Australasian College of Surgeons (John Mitchell Crouch Fellowship, which was the first grant allowing the start of the initiative that I had planned several years ago), and recently Australian Research Council (plus interest from private companies in the near future), is the first attempt in Australia, and most likely amongst the first ones in the world, to bring neurosurgeons, neuroradiologists, neuropathologists, cognitive neuroscientists, computational scientists and machine learners, engineers, mathematicians, etc., under the same umbrella with the aim to identify better diagnostic, prognostic and therapeutic markers of diseases of neurosurgical interest, including brain tumours and cerebrovascular diseases, amongst others.

I would like to invite you to explore our MQ webpage:

https://www.mq.edu.au/research/research-centres-groups-and-facilities/groups/computational-neurosurgery-lab

Or come visit us in the post-pandemic area on the first floor of 75 Talavera Road.
But please, do not expect any robots opening the door for you when you are coming… at least for now!

From time to time, I receive questions in regards to what we are doing, or I receive several requests of collaborations. For such reasons, I am glad to share with you some of the projects we have been working on over the last months, and where we are headed to, in order to: 1) Give to you an update on something new happening at Macquarie University (FMHHS); 2) Triggering any new potential collaborations with whoever would like to help and get involved, hoping to expand the social and scientific network towards something that has been in my mind for a long time, the creation of a research centre defined BrAIN (Brain Augmented Intelligence Network), where human expertise can be augmented by machine computing at benefit of patients. Neuroscientific disciplines outside of neurosurgery are also very welcome.

The lab currently relies on a central team formed by myself and Dr Carlo Russo, computer scientist, Laya Jose (2nd year PhD candidate), Robert Newport (1st year PhD candidate), with external collaboration by Dr Sidong Liu (NHMRC Early Career Fellow), Prof John Magnussen, Prof Gillian Heller, Prof Itsu Sen, and several other collaborators within Macquarie University and overseas. Moreover, from July we'll be joined by further RAs and PhD candidates.

The lab activity has also been illustrated in a recent issue of *Surgical News*, the magazine of the RACS, volume 21, issue 01, January-February 2020, "Spotlight on Research & Innovation", page 14, available at:

https://umbraco.surgeons.org/media/4996/janfeb_2020_surgicalnews_final_web.pdf?fbclid=IwAR3RBIOPYJDT_NBwjXgCEuuJHxeIN-CQgY73hEhWVZgR-NjOmebcEeSONAs).

As well as the magazine of Macquarie University Hospital, Frontier, Summer 2020:

https://muh.org.au/wp-content/uploads/2020/01/frontier_summer_2020.pdf?fbclid=IwAR20rCP90UeheObdHl85jSPYHzI0bcysaA3sGgX86qh2nmWkfEj8eN9LuZw

How machines will help tackle brain disease

MQ Health has established the first Computational NeuroSurgery Laboratory in the world to focus on developing computerised analysis tools in neuroimaging and neuropathology that will improve the diagnostic accuracy of brain disease.

The diagnosis of brain tumours and other diseases is heavily dependent on neuroimaging – in particular MRI. However, the large amount of radiological data generated by MR sequences can be overwhelming to interpret and made more difficult by the possibility of conditions such as 'mimic' tumours, inflammatory disease that can resemble a tumour.

The implementation of multidisciplinary teams (MDTs) has helped significantly to increase accuracy of diagnosis, estimates of prognosis and enhanced decision-making around whether to proceed to surgery.

Now, MQ Health is looking to add the use of artificial intelligence (AI) tools to brain disease diagnosis through its world-first Computational NeuroSurgery (CNS) Laboratory. Led by Associate Professor Antonio Di Ieva, the team is investigating the use of computerised analysis tools to aid surgeon-MDT-based evaluations of radiological images – also the subject of Associate Professor Di Ieva's letter in the November 2019 issue of *The Lancet*.

"Our method is to develop novel diagnostic, prognostic and therapeutic markers of disease, which can then be applied in the development of AI algorithms," said Associate Professor Di Ieva, who received the 2019 John Mitchell Crouch Fellowship from the Royal Australasian College of Surgeons, to complete the first year of research required. "The long-term goal is to enhance treatment and outcomes for patients."

The first stage of work began earlier this year, with researchers characterising the 'fingerprint' of the brain – the highly detailed architecture of the brain in its entire physio-pathological spectrum, from the normal to the diseased.

"The work involves extracting features from pathology slides and MR images of brain disease in order to objectively compare the pattern expressed in different physio-pathological states," explained Associate Professor Di Ieva. "We are doing this using fractal and machine-learning methods, thanks to the expertise of computer scientists, including Dr Carlo Russo, Research Associate at the CNS Laboratory, and other collaborators, including Dr Sidong Liu, research fellow from the Australian Institute of Health Innovation at Macquarie University.

"We are also capturing data on the cognitive processes of surgeons as they review imaging data and identify relevant features of an image to diagnose and develop a treatment plan for a patient."

Data will then be transferred to a computer in order to 'teach' the machine to extract features and characterise patterns of brain disease through complex algorithms, in the same way a surgeon would.

"The aim is to support, not to replace, clinicians (and other experts) in diagnosis and decision-making by parameters confirming or refuting their diagnostic hypothesis," said Associate Professor Di Ieva, who has also recently been awarded an Australian Research Council future fellowship grant to expand his team and extend his research to broader machine vision-related applications.

The CNS Laboratory at MQ Health builds on Associate Professor Di Ieva's pioneering application of computational fractal-based analysis to the quantification of features in gliomas completed as his PhD research in Austria, in 2011, as well as his use of fractal geometry to study brain cancer and other diseases of neurosurgical interest, as summarised in his book *The Fractal Geometry of the Brain*.

This earlier work led to the successful use of computational fractal-based modelling to objectively quantify the patterns of brain and pituitary tumours as well as arteriovenous malformations, and to predict the response to treatment of patients affected by AVMs undergoing Gamma Knife radiosurgery treatment.

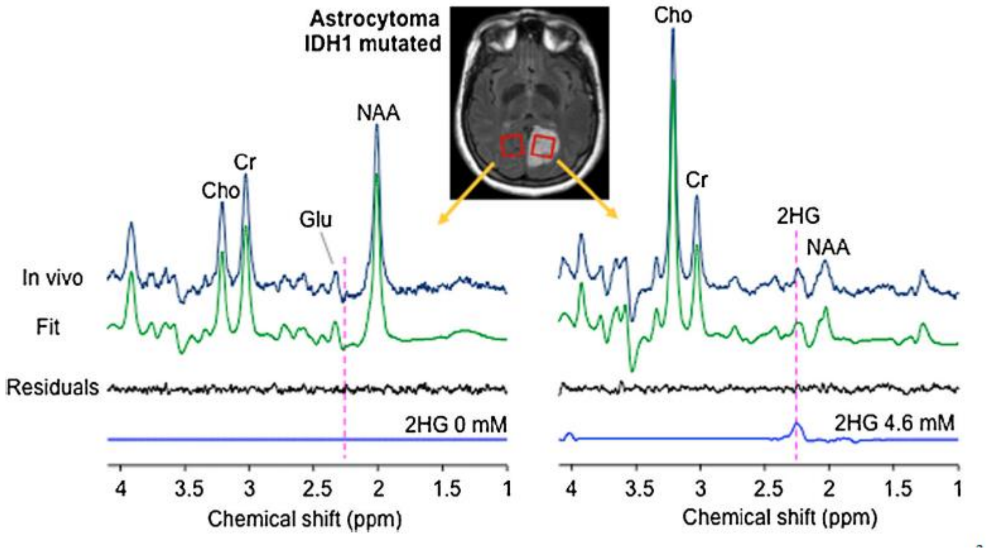
Here the description of some projects/results or future initiative in different domains, currently running at the CNS Lab:

NEURORADIOLOGY

- As you may know, we introduced the concept of "***spectrobiopsy***" in relation to identification of genetic mutations in gliomas by means of Magnetic Resonance Spectroscopy and we were the first ones to introduce in Australia the use of 2HG-MRS for the prediction of the IDH-status in patients affected by gliomas of any grade (papers reported below):

Di Ieva A, **Choi C, Magnussen JS.** *Spectrobiopsy in neurodiagnostics: the new era.* ***Neuroradiology*** 60(2):129-131, 2018. doi: 10.1007/s00234-017-1957-1

Di Ieva A, **Magnussen JS, McIntosh J, Mulcahy MJ, Pardey M, Choi C.** *Magnetic Resonance Spectroscopic Assessment of Isocitrate Dehydrogenase Status in Gliomas: The New Frontiers of Spectrobiopsy in Neurodiagnostics.* ***World Neurosurg*** 133:e421-e427, 2020. doi: 10.1016/j.wneu.2019.09.040.



Now we are advancing the technique by collecting more cases and by analysing multiple metabolites on MRS by means of machine learning techniques (e.g., support vector machine), in order to improve prediction even before surgery (in collaboration with the University of Texas). The improvement of such a technique will eventually overcome the necessity to perform brain tumour biopsies to identify their genetic profile, as emphasised in an article published on the Macquarie University Hospital magazine "Frontiers", available at: https://muh.org.au/news-and-events/our-stories/mapping-genetic-mutation-in-the-brain/.

- **Radiomics analysis** (i.e., quantitative analysis of MRI and nuclear medicine images) of brain tumours. We showed to be able to automatically differentiate glioblastoma from brain metastases on MRI by means of fractal and texture analysis (in collaboration with the University of Belgrade, Serbia):

  Petrujkić K, Milošević N, Rajković N, Stanisavljević D, Gavrilović S, Dželebdžić D, Ilić R, Di Ieva A, Maksimović R. *Computational quantitative MR image features - a potential useful tool in differentiating glioblastoma from solitary brain metastasis.* ***Eur J Radiol*** 119:108634, 2019. doi:10.1016/j.ejrad.2019.08.003.

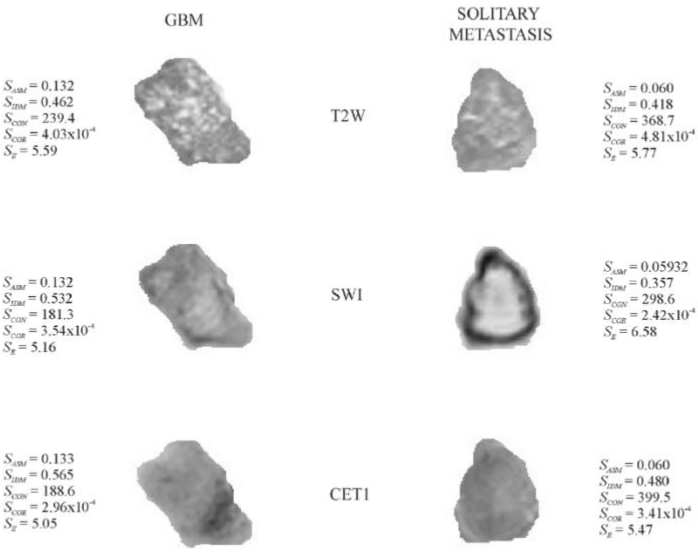


Fig. 3. Example of selected GLCM parameters values in differentiating glioblastoma from solitary brain metastasis.

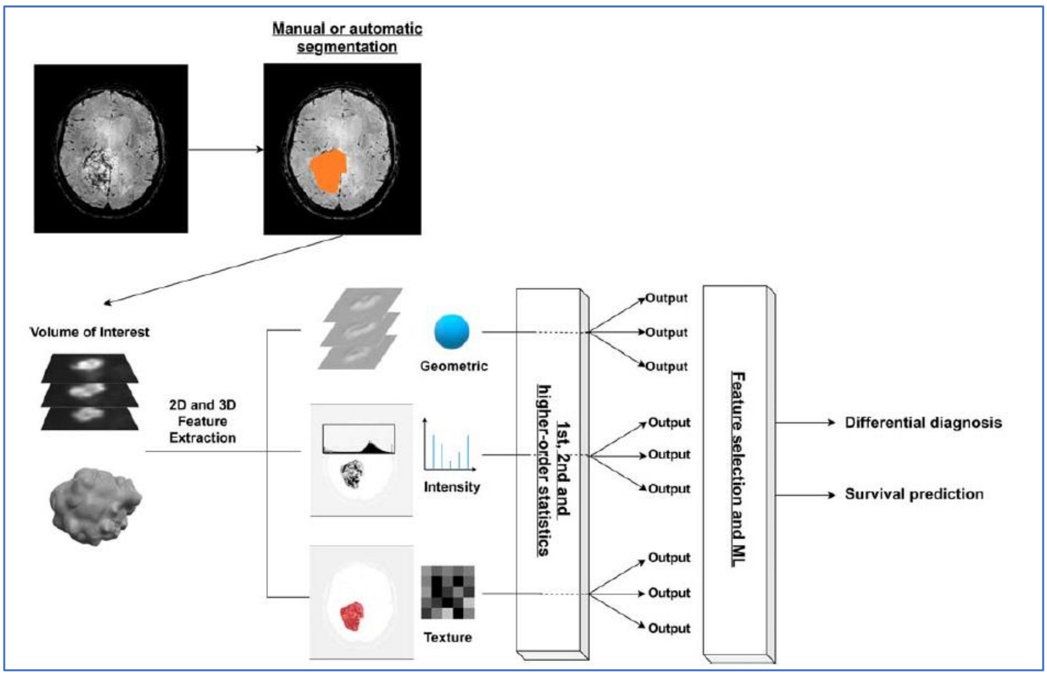
Moreover, we introduced new fractal-based parameters for the characterisation of intratumoural features in SWI (paper deposited on bioRxiv):

Di Ieva A, Russo C, Le Reste PJ, Magnussen JS, Heller G. *Advanced computational and statistical multiparametric analysis of Susceptibility-Weighted Imaging to characterize gliomas and brain metastases.* ***bioRxiv 2020****;* doi.org/10.1101/2020.04.24.060830.

Available at: https://www.biorxiv.org/content/10.1101/2020.04.24.060830v1

If you have interest in radiomics, you can find useful this recently published review (pdf in cc):

Jang K, Russo C, Di Ieva A. Radiomics in gliomas: clinical implications of computational modeling and fractal-based analysis. ***Neuroradiology. 2020*** doi:10.1007/s00234-020-02403-1.

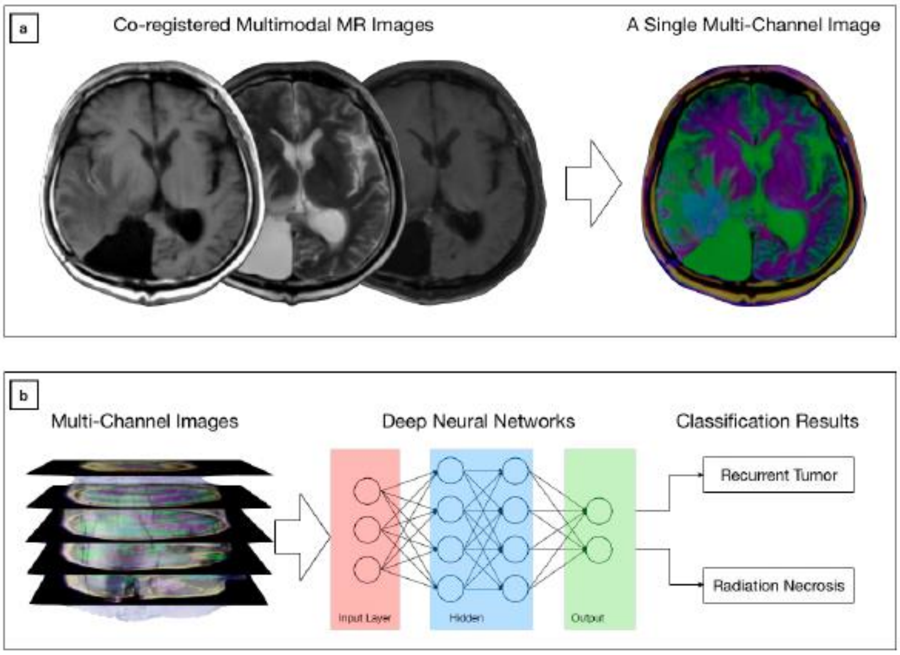


Next steps: Radiomics of intratumoural features of more types and sub-types of brain tumours on further imaging modalities (e.g., different MRI sequences + different modalities, including CT and PET), also aimed to differentiate tumours from mimics (i.e., lesions resembling brain tumours but being other entities, such as infections, infarct, inflammatory lesions, tumefactive multiple sclerosis, etc.). Some analyses will be also performed on the peri-tumoural regions as well as in images of other neurological diseases (including neurodegenerative diseases). Moreover, more studies will be performed to identify radiomics prognostic image markers, e.g., radiological features which can already predict patient's prognosis.
Furthermore, a 6th year Medical Student (Anna Jian, University of Melbourne) and a Master of Research student (Dr. Kevin Jang, University of Sydney) are working within the CNS Lab activity on some radiomics-based projects and on a systematic review on radiogenomics.

- Use of deep learning for automatically differentiation of post-RT radiation necrosis from glioma recurrence on multimodal MRI:

Gao Y, Xiao X, Han B, Li G, Ning X, Wang D, Cai W, Kikinis R, Berkovsky S, Di Ieva A, Zhang L, Ji N, Siu L. *Differentiating glioma recurrence from radiation necrosis using multimodal MRI and deep learning methods.* (submitted to the Journal of Medical Internet Research Medical Informatics). Pre-print available at:

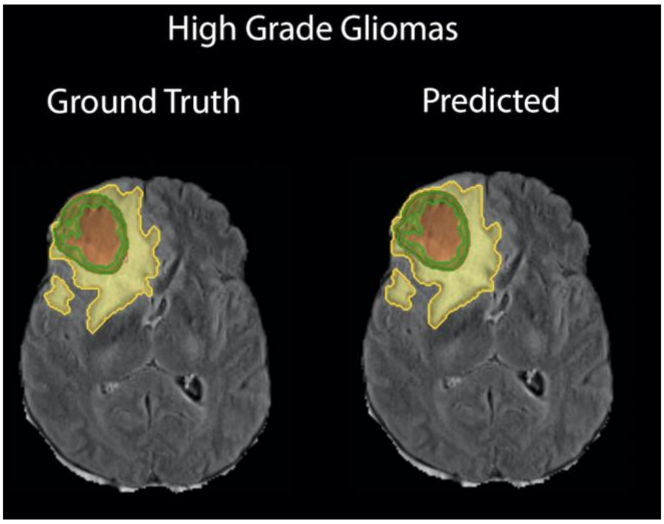
https://preprints.jmir.org/preprint/19805



Next steps: Increasing Artificial Intelligence accuracy to differentiate glioma recurrence from pseudoprogression on MRI multimodal imaging and/or PET.

- AI for automatic segmentation of brain tumours on MRI (papers in progress). In this work, we replicated the results of the Multimodal Brain Tumour Segmentation (BraTS) Challenge, organised yearly by the MICCAI (the Medical Image Computing and Computer Assisted Intervention Society), improving the technique on single MRI sequences, and translating it to other-than-gliomas tumours, including vestibular schwannoma, metastases, etc.

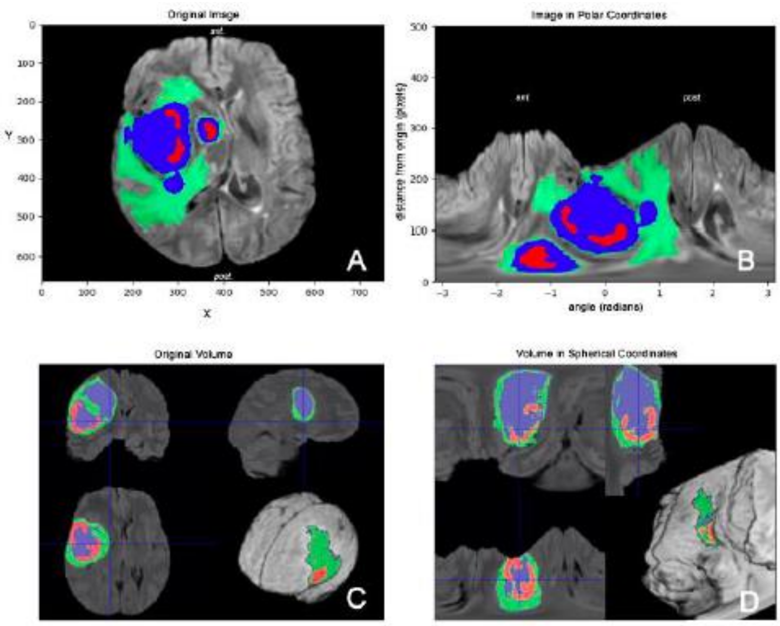
Di Ieva A, Russo C, Liu S, et al. *Deep learning for automatic segmentation of brain tumors on MRI.* (Paper in progress)



Next steps: improving the computerised detection and segmentation of brain tumours for automatic volumetric and radiomics analyses. Further computational models are under investigation (e.g., *Dynamic Quantum Clustering*, in collaboration with the University of Madrid). Automatic segmentation will be used for several tasks, including intra-operative navigation, pre-operative surgical and/or radiotherapy/radiosurgery planning, etc.

- In regards to automatic tumours' segmentation, we also introduced a new technique based on objects' topological transformation:

Russo C, Liu S, Di Ieva A. *Spherical coordinates transformation pre-processing in deep convolutional neural networks for brain tumor segmentation in MRI*. (submitted).



- Quantitative analysis of a novel radiological MRI sequence called "MAGiC", which indeed is a "magic technique" to synthetise different MR images starting from a single MR source sequence (in collaboration with universities and centres in Beijing):

Liu S, Russo C, Di Ieva A, Berkovsky S, Dou W, Meng TB, Qian L. *Volumetric and Fractal Analysis of Brain Synthetic MRI: A Comparative Quantitative Study on the impact of Spatial Resolution.* (Submitted).

NEUROPATHOLOGY

You may know that over the last years, computational modelling, fractal analysis and AI have been successfully used to extract features from histological specimens with the aim to identify types and subtypes of brain tumours.
In the field of gliomas' angiogenesis, years ago we showed that the microvascular patterns, quantified by fractals, can be used to categorise the WHO grade:

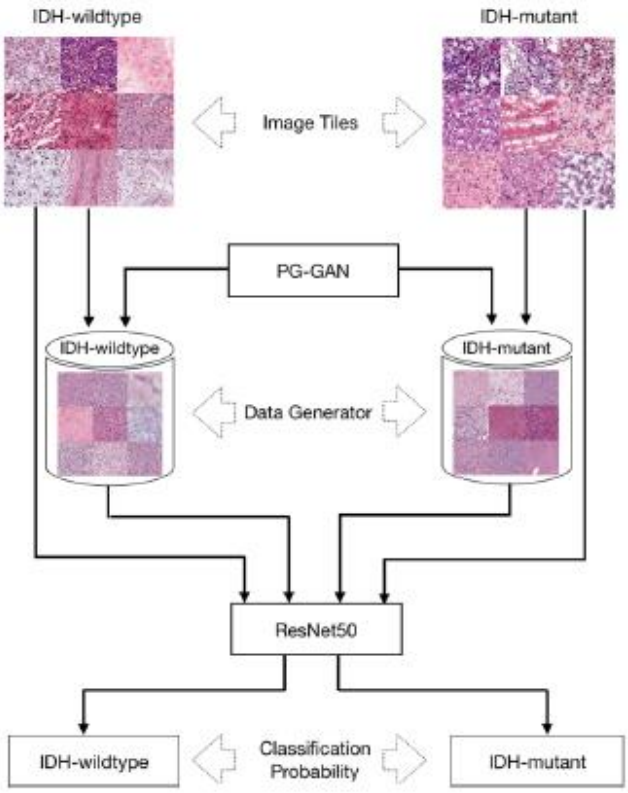
Di Ieva A, Bruner E, Widhalm G, Minchev G, Tschabitscher M, Grizzi F. *Computer-assisted and fractal-based morphometric assessment of microvascularity in histological specimens of gliomas.* ***Sci Rep 2012***, available at:

https://www.nature.com/articles/srep00429

Now, at the CNS able we have shown that deep learning methodologies can be used to predict IDH status on haematoxylin and eosin specimens of gliomas even before performing immunohistochemistry and/or genetic sequencing (research in collaboration with the Yeditepe University, Istanbul, and University of Doha). Moreover, in this work we showed that the technique is even applicable with small dataset, thanks to the creation of synthetic images of gliomas used to train the machine, by means of a deep learning technique called Generative Adversarial Network (GAN):

Liu S, Shah X, Sav A, Russo C, Berkovsky S, Qian Y, Coiera E, Di Ieva A. *Isocitrate dehydrogenase (IDH) status prediction in histopathology images of gliomas using deep learning.* ***Sci Rep*** (in press). Available at:

https://www.nature.com/articles/s41598-020-64588-y



The problem of small dataset and pre-processing analyses for improving machine training for automatic features extraction and patterns recognition in gliomas is matter of research by our PhD student Laya Jose. Amongst other papers in cc, a review summarises the state of the art of the problem:

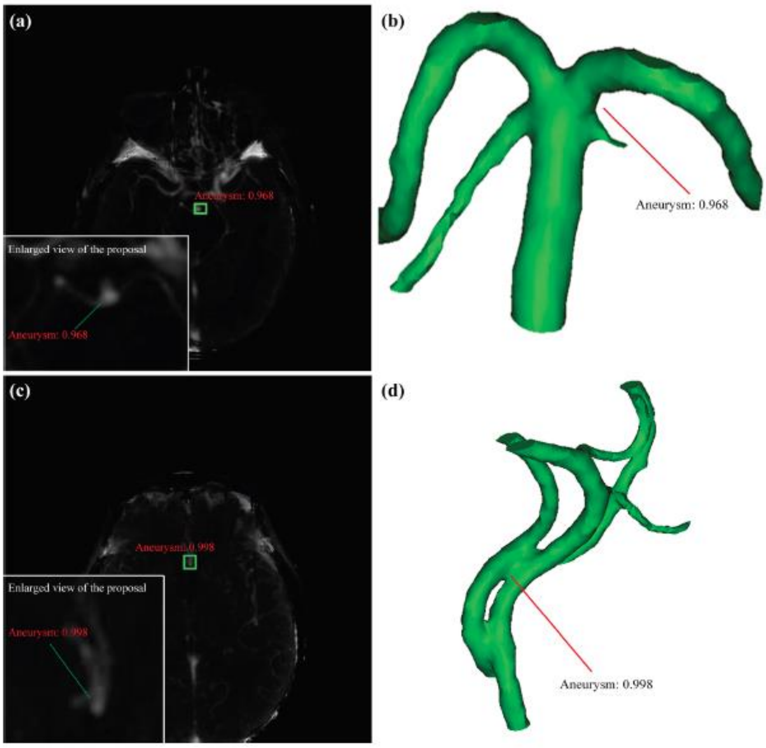
Jose L, Liu S, Russo C, Nadort A, Di Ieva A. *Generative Adversarial Networks in Digital Pathology: A review on histopathology image processing.* (In progress).

Next steps: increasing the digital pathology dataset in order to improve accuracy in extracting features, predicting patients' outcome and enhancing decision-making.

VASCULAR NEUROSURGERY

- Use of deep learning for automated detection of brain aneurysms on CT images:

Dai X, Huang L, Qian Y, Xia S, Chong W, Liu J, Di Ieva A, Hou X, Ou C. Deep learning for automated cerebral aneurysm detection on computed tomography images. ***Int J Comput Assist Radiol Surg.*** 2020 Apr;15(4):715-723. doi: 10.1007/s11548-020-02121-2.



Next steps: Increasing collaborations with Prof. Qian's lab and others for AI-based detection of aneurysms, computational fluidodynamics, etc.

- Computational modelling and arteriovenous malformations.

Although we haven't started yet at the CNS Lab, it may be known that some years ago we showed that fractal analysis is a powerful tool to characterise the geometrical complexity of the nidus, not only for diagnostic purposes, but also for therapeutical aims, as it was confirmed that the nidus' angioarchitecture relates to the post-Gamma Knife radiosurgery outcome:

> **Di Ieva A, Niamah M, Menezes RJ, Tsao M, Krings T, Cho YB, Schwartz ML, Cusimano MD.** *Computational fractal-based analysis of brain arteriovenous malformation angioarchitecture.* ***Neurosurgery 75:72-79, 2014.***

This paper was awarded the *Neurosurgery* Editor's choice and an international research award from the Italian Neurosurgical Society in 2015.

Moreover, we published several papers on automatic extraction of edges and features of AVMs. Of course, the next steps at the CNS lab will be the application of AI for automatic segmentation of the nidus and identification of diagnostic, prognostic and therapeutic image markers of AVMs.
Any collaboration, dataset sharing, support, etc., will be more than welcome!

DECISION-MAKING IN NEUROSURGERY

- On the perspective to improve differential diagnosis and decision-making in multidisciplinary teams by means of AI:

Di Ieva A. *AI-Augmented Multidisciplinary Team: Hype or Hope?* ***Lancet 394:1801, 2019.***

As well as an overview on the current limitations of MDT, proposing, again, AI as a potential future solution. Project performed by a medical student from the James Cook University, QLD (Jenny Kim):

Kim J, Preda V, Di Ieva A. *Barriers, Challenges and Limitations of Contemporary Multidisciplinary teams care – A critical review.* (In progress).

Further projects in relation to neurosurgical decision-making and also in the fields of neuro-laws and neuro-ethics are commencing in collaboration with the University of Sydney and the Macquarie University Research Centre for Agency, Values, and Ethics (CAVE).

MACHINE VISION and COGNITIVE NEUROSCIENCE

Within the frame of my ARC Future Fellowship, we are expanding our computational analyses in the much wider field of machine vision in general, in several domains, not restricted to the clinical neurosciences, but also radiology and pathology in general, figurative arts, astronomy, geology, qualitative and quantitative analysis in teaching & learning, etc. The project is based on computational modelling and visual tracking. A first-year PhD candidate, Robert Newport, is working on the computational aspects of such analysis, whilst a further PhD student will commence in July-August, focused more on the eye-tracking analysis. More updates will come over the next months/years.

OTHER

Chiari Malformation. In collaboration with Prof Stoodley, we are starting a new project on the use of AI in MRI diagnosis and assessment of patients with Chiari Malformation. A Macquarie Neurosurgery registrar, Kaishin Tanaka, and some future honours students are going to work on the project, too.

MORE THAN MEDICINE: As computational modelling is very translational, it is not difficult to merge different scientific fields and applications. Indeed, some of our previous fractal-based analyses used to characterise brain tumours were implemented to quantify forest fragmentation, in the field of dynamic ecology (in collaboration with the University of Bucharest):

Andronache I, Marin M, Fischer R, Ahammer H, Radulovic M, Ciobotaru AM, Jelinek HF, Di Ieva A, Pintilii RD, Drăghici CC, Herman GV, Nicula AS, Simion AG, Loghin IV, Diaconu DC, Peptenatu D. Dynamics of Forest Fragmentation and Connectivity Using Particle and Fractal Analysis. ***Sci Rep.*** 22;9(1):12228, 2019.

Available at: https://www.nature.com/articles/s41598-019-48277-z

In a recursive fashion, by means of that research we were able to propose new fractal indices, that are under investigation in new research focused on quantifying the extent of deforestation and reforestation, as well as the neoplastic “front of invasion” in gliomas and metastases (papers in progress).

And much more…

We are trying to work on further projects for the creation of a platform to put together all the above-mentioned projects. Moreover, we are keen to start more analyses soon in relation to spine surgery, pituitary pathology, concussion neuroimaging (including MEG, in collaboration with Prof. Paul Sowman) and risk stratification, pain score by means of machine learning (in collaboration with A/Prof Tillman Boesel), radioneuroanatomy, eventually neuro-ICU and neuro-critical care, etc.

If you have been able to reach the end of the page, I reckon that you are interested or at least curious of the novel field of research and eventually keen to participate to this journey which is trying to shift the paradigms of the current care, decision-making and treatment of neurosurgical/neurological patients.

At this point, it should be clear that our efforts are towards implementing clinical practice with the power of machine, in order to obtain more objective, reproducible and valid description of neurosurgical diseases, and less subjectivity in data interpretation and patients-related decision-making.

In such a perspective, to re-iterate what I wrote at the beginning, every kind of collaboration and support will be very welcome. Feel free to contact me or any of the collaborators at the CNS Lab for brainstorming, questions, ideas, data to share, etc.

Best regards,

Antonio Di Ieva

10 May 2020