1. **Description of the assignment of the project and the focus of your work**

Digital pathology: introduction to the problem

*In digital pathology a diagnosis is carried out by analysing histopathological samples which are pieces of human tissues extracted via surgical operation. Specimens are typically stained with H&E (haematoxylin and eosin) so that different structures come in different shades between blue (haematoxylin binds to cell nuclei as they are negatively charged) and pink (eosin binds to extracellular matrix and cytoplasm as they are positively charged) for better distinguish between them [2].*

*The traditional approach consists in the visual examination of samples with the aim of detecting abnormalities, counting nuclei and so on, carrying out a certain diagnosis i.e. if a tissue is cancerous or not. Visual examination is time consuming, prone to inter-reader and intra-reader variability and non-reproducible: making available to the pathologists a tool that supports them during the evaluation can help overcoming these issues [3] as nowadays digital slides [4] are obtained by scanning specimens placed on conventional glass slides; such multi-resolution slides are called WSI (Whole Slide Images) and can be elaborated numerically with many related advantages enabling, among all, telepathology that is a key requirement for second opinions on cases and remote consults. [1]*

*The focus of the project and clinical insights*

*The focus of the project is developing a software able to produce an attention-map for cancer detection that drives pathologists’ attention to certain areas of the slice that might be pathological.*

*(image)*

*Uncertainty is a crucial aspect of such application and it is modelled with deep neural networks, more specifically with a Bayesian CNNs trained with WSI images representing AD tissue( short for adenoma, a benign tumour of epithelial tissue with glandular origin or characteristics), AC tissue (short for adenocarcinoma, a malign tumour) and healthy tissue.*

*(images)*

1. **Theory about CNNs focused on the application outline, providing references**

*CNNs*

*Neural networks (NNs) are a machine learning approach that do not consist in one single computational unit but that relies on several units, called neurons, differently interconnected via weights: NNs take inspiration from the way the brain is organised. The knowledge of the network is preserved in the weights that stand for biological synapses and the behaviour is related to its hierarchical architecture: the learning process consists in adjusting the weights, extracting a mathematical model that fits training data giving as output a result or a prediction. Such model is usually too complex to be obtained by a human.*

*Among all the networks we have CNNs (short for Convolutional Neural Networks) that emulate the visual cortex especially as regards the local connectivity between multiple layers and the hierarchical representation of the input: they consist in a input later, a variable number of hidden layers and a output layer. Each hidden layer is dedicated to identifying a multiple feature of the input: low-level features are condensed in the deepest layers while problem-specific features belong to last layers; such characteristics allow the network to be more flexible when extracting different combination of small patterns eventually combining them for the aim of the network.*

*(image)*

*Classification tasks and CNNs*

*There are many challenges in the automatic analysis of digital pathology images such as the variability of the morphology of the sample due to the pathology and to the preparation of slides or variations in staining and the variability between patients that have always made tedious to find handcrafted features that can make the system robust, efficient and reliable : deep learning methods overcome these issues deriving a feature space from the data itself and gaining the capability of generalization when unseen data is presented to the network. [6]*

*The aim of CNNs is give a output that is a class or a prediction of the input and this is accomplished via several different layers that can be differently organized while information is processed similar to how the brain process information: the 3 characteristic layers are convolutional layers, non-linear layers and pooling layers. As hidden units are connected to local receptive fields and share weights, the input can have a high dimension without resulting in a large number of parameters, these parameters are learned during the training via backpropagation.[7]*

*The backpropagation algorithm is the most used method for training neural networks and consists in the update of the weights, initially random initialised, basing on an loss term that is computed with the output given by the network and the desired output.*

* *Input features propagates in through the network in the forward direction computing the output and the loss associated with the parameters*
* *The training loss is derivate with respect to the weights and computed back towards the input later*

*This is an iterative procedure that is repeated until a certain stopping condition is reached: the tuning of the parameters of the backpropagation is proportional to the size of data.*

*(details?)*

*The core of CNNs is the convolutional layers that is composed by a set of filters: each filter activates when a specific feature is detected in the input.*

*(details about the layers…?)*

*Bayesian CNNs*

*Typical drawbacks of conventional CNNs are, firstly, the risk of overfitting when the network is not trained on very large datasets and, secondly, the absence of a measure of uncertainty related to the prediction: Bayesian CNNs were thought to handle these problems by estimating uncertainties placing provability distributions over either the model parameters or the model outputs; the uncertainty in parameter estimation is propagated into predictions.*

*Bayesian CNNs are based on Bayes’ theorem: the Bayesian inference the hypothesis probability is updated when more information is available.*

*(details)*

*Bayesian CNNs come with a high computational cost and the exact Bayesian inference is intractable.*

*The aim of Bayes theorem is finding the probability of model parameters (posterior) H given some data X.*

[*https://medium.com/neuralspace/bayesian-neural-network-series-post-2-background-knowledge-fdec6ac62d43*](https://medium.com/neuralspace/bayesian-neural-network-series-post-2-background-knowledge-fdec6ac62d43)

*P(H) is estimated before seeing the data, P(X|H) is the likelihood and stands for data distribution. P(X) is the evidence (…?) that can be computed integrating over all possible model values H.*

*The only way to solve this solution is approximation. The posterior is the desired function that we want to estimate starting with a density function (gaussian) that is changed until is close to the desired function.*

[*https://medium.com/neuralspace/bayesian-neural-network-series-post-2-background-knowledge-fdec6ac62d43*](https://medium.com/neuralspace/bayesian-neural-network-series-post-2-background-knowledge-fdec6ac62d43) *FINIRE*

*(Variational inference?)*

1. **Detailed description of the method you used (describe most salient aspects of your code too)**

* Pipeline schematica
* Motivazione scelta dell’architettura della rete
* Processing delle immagini
* Validazione

Dropout method ([Srivastava et al., 2014](https://www-sciencedirect-com.ezproxy.biblio.polito.it/science/article/pii/S0895611117300502" \l "bib0255)) assists in reducing overfitting, especially when the available training data is limited such as the WSI data. During each iteration, individual nodes along with incoming and outgoing edges are removed from the network and are later returned along with their initial weights. In our approach, after each of the first two fully-connected layers, the dropout ratio i.e. the probability of dropping any input for both stages is set to 0.25. [7]

1. Detailed description of the results (provide graphs, tables, etc.);
2. Results discussion;
3. Future development

Possibilità di rendere disponibile il tool a diversi patologi per concordare sulla diagnosi in base alla mappa proposta, permettendo di annotare direttamente l'immagine prima di inviarla per un consulto 🡪 tele-istopatologia

**References**:

* **[1]** Image analysis and machine learning in digital pathology: Challenges and opportunities <https://www.sciencedirect.com/science/article/abs/pii/S1361841516301141>
* **[2]** Chan JK (2014). [*"The wonderful colors of the hematoxylin-eosin stain in diagnostic surgical pathology"*](https://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&tool=sumsearch.org/cite&retmode=ref&cmd=prlinks&id=24406626). Int J Surg Pathol. **22** (1): 12–32. [*doi*](https://en.wikipedia.org/wiki/Digital_object_identifier):[*10.1177/1066896913517939*](https://doi.org/10.1177%2F1066896913517939). [*PMID*](https://en.wikipedia.org/wiki/PubMed_Identifier) [*24406626*](https://www.ncbi.nlm.nih.gov/pubmed/24406626)

# [3] Deep Convolutional Neural Networks Enable Discrimination of Heterogeneous Digital Pathology Images <https://www.sciencedirect.com/science/article/pii/S2352396417305078>

# [4] <https://www.sciencedirect.com/topics/medicine-and-dentistry/digital-pathology>

# [5] Deep convolutional neural networks for automatic classification of gastric carcinoma using whole slide images in digital histopathology [Harshita Sharmaa](https://www.sciencedirect.com/science/article/abs/pii/S0895611117300502#!) <https://www.sciencedirect.com/science/article/abs/pii/S0895611117300502>

# [6] Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases [Andrew Janowczyk](https://www.ncbi.nlm.nih.gov/pubmed/?term=Janowczyk%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27563488)1 and [Anant Madabhushi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Madabhushi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27563488)

# [7] Deep convolutional neural networks for automatic classification of gastric carcinoma using whole slide images in digital histopathology <https://www.sciencedirect.com/science/article/abs/pii/S0895611117300502>

# Receptive fields, binocular interaction and functional architecture in the cat's visual cortex [D. H. Hubel](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hubel%20DH%5BAuthor%5D&cauthor=true&cauthor_uid=14449617) and [T. N. Wiesel](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wiesel%20TN%5BAuthor%5D&cauthor=true&cauthor_uid=14449617)

# Bayesian Neural Network Series Post 1: Need for Bayesian Neural Networks <https://medium.com/neuralspace/bayesian-neural-network-series-post-1-need-for-bayesian-networks-e209e66b70b2>

# CNN Architectures: LeNet, AlexNet, VGG, GoogLeNet, ResNet and more… <https://medium.com/analytics-vidhya/cnns-architectures-lenet-alexnet-vgg-googlenet-resnet-and-more-666091488df5>

* Deep Bayesian Active Learning with Image Data <https://arxiv.org/pdf/1703.02910.pdf>

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