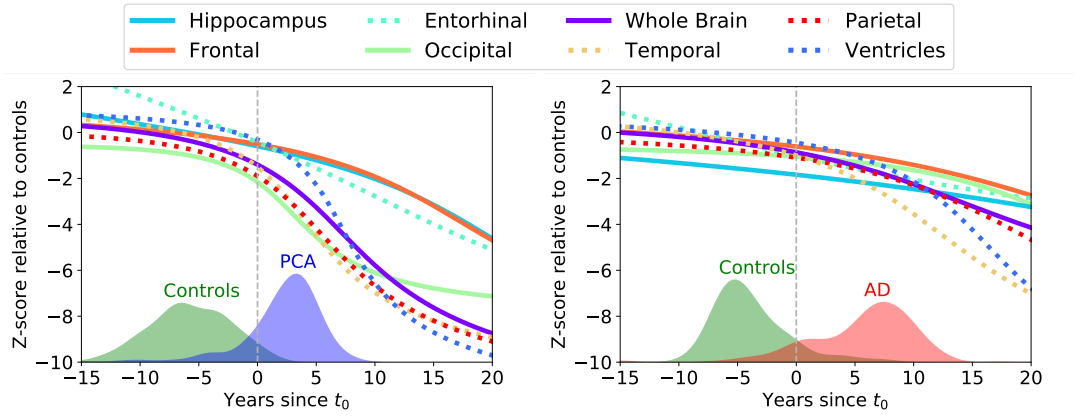
Razvan Marinescu - Research Statement

I work on **Machine Learning for medical applications**, with a strong focus on neuroscience and neurology applications. I dream that one day, robots and algorithms will be able to understand, prevent and solve human diseases, thus enabling the highest quality healthcare for everyone. AI and Machine Learning (ML) algorithms have already been demonstrated for decision-making in radiology, drug design, testing and re-purposing, protein prediction, image-guided interventions such as radiotherapy, health monitoring systems, and disease understanding through population studies powered by image analysis models. However, due to unique challenges that these medical problems pose, combined with the complexity of healthcare systems, such ML systems are not yet ready to be adopted on a wider scale.

My work [1–12] focuses on novel ML models as well as applications of such models for solving important medical problems, eventually leading to their adoption in healthcare systems around the world. On the theory side, I focus on generative models, based on both (i) bayesian time-series frameworks that estimate continuous disease evolutions from structured data, as well as (ii) deep learning approaches operating on raw images. These theoretical models have been motivated by estimation of progression of Alzheimer's disease, a key neurodegenerative disease affecting 50 million people worldwide. In my research, I try to find answers to the following questions:

- How can one correctly model the disease as a *continuous process* using bayesian time-series models? – instead of considering the disease as a binary variable (healthy or disease)
- How can one estimate *long-term disease progression*, over 15-20 years, when each patient in a typical dataset only provides a short-term (1-3 years) "glimpse" of that progression at unknown disease stages?
- How can one estimate the progression of *rare diseases*, where there is a lack of sufficient data?
- How can one *improve the quality of medical images*, in order to extract better quantitative measures and to enable better clinical decisions?

Below, I present steps towards these directions.



(a) Posterior Cortical Atrophy

(b) typical Alzheimer's disease

Figure 1: In [2], I used statistical models to estimate the temporal progression of brain atrophy in (a) Posterior Cortical Atrophy (PCA), and contrast it with the same evolution in (b) typical Alzheimer's disease. Our study was the first to perform a population-wide longitudinal analysis for PCA, and showed that there are marked differences in the progression of the two diseases.

Modelling the progression of a rare, visual variant of Alzheimer's disease: Posterior cortical atrophy (PCA) is a progressive neurodegenerative syndrome causing predominantly visuospatial and visuoperceptual impairments. It is considered a visual variant to Alzheimer's disease, yet as opposed to typical Alzheimer's disease, its mechanisms and progression are very poorly understood. With collaborators from the Dementia Research Center UK [2], I performed the first major longitudinal study of PCA using two different modeling techniques, one based on a bayesian latent-variable discrete model, and the other using a differential equation model model for estimating temporal progression. I used these models to quantitatively map the evolution of neurodegeneration in PCA and

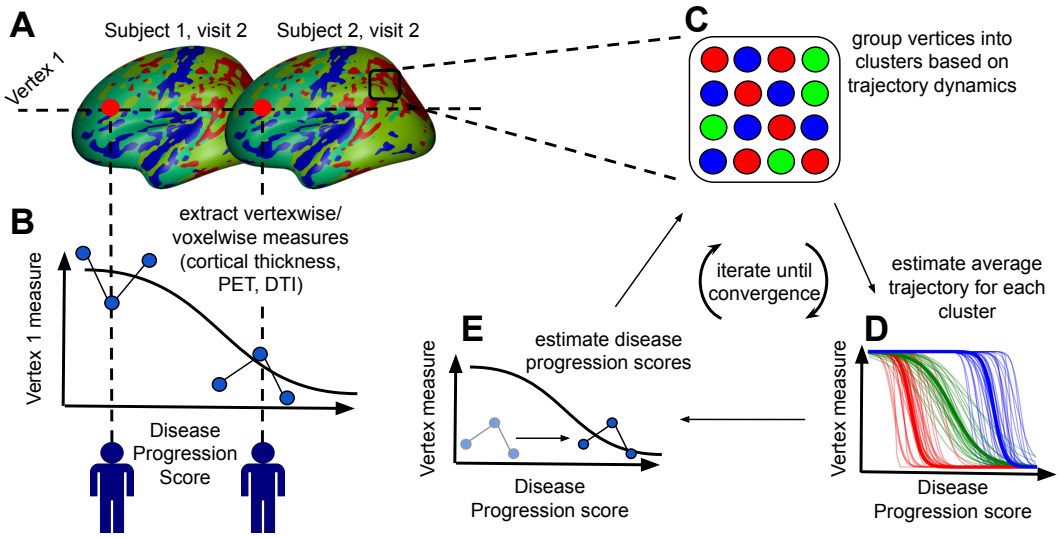


Figure 2: Diagram of the DIVE model [1]. DIVE is an unsupervised learning method that clusters voxelwise brain biomarker data, such as cortical thickness or levels of toxic proteins such as amyloid or tau, according to the full temporal evolution of that biomarker over the course of a neurodegenerative disease. (A-B) For each location in the brain, the model estimates the temporal progression of a biomarker at that location using parametric trajectories. The inference uses the EM algorithm in three stages: (C) in the E-step, vertices are assigned into clusters using the time-series model; (D-E) in the M-step, the latent disease stages of subjects and mean biomarker trajectories for each cluster are estimated. As opposed to previous methods, DIVE estimates changes in the brain over both space and time, and also estimates unknown disease stages and progression speeds of the Alzheimer's subjects.

contrasted it to typical Alzheimer's disease (see Fig. 1). My findings indicated that posterior cortical atrophy and typical Alzheimers disease have distinct sites of neurodegeneration onset and different profiles of spatial and temporal progression. This further motivated the investigation of biological factors underpinning disease heterogeneity, and informed the selection of measures for clinical trials in posterior cortical atrophy.

Unsupervised clustering of imaging features based on disease trajectories: Estimating spatiotemporal brain trajectories from short-term longitudinal data is very difficult due to the fact that each subject provides few observations of a complex disease process at various, unknown stages of that process. Classical methods were all assuming known disease stages (i.e. X-axis values against which to perform regression), which is not realistic in clinical situations, since we only observe proxy measures such as cognitive tests or biomarkers measuring accumulation of toxic proteins (e.g., amyloid, tau) or neurodegeneration.

In [1,7], I developed a bayesian model that estimates latent disease stages for each subject independently, against which voxelwise biomarkers are regressed using parametric curves, resulting in spatiotemporal disease trajectories that describe the subjects' evolution (Fig 2). I cluster voxels in the brain according to the similarity of their temporal disease trajectory, while a Markov Random Field ensures spatial smoothness. This work was one of the first to estimate spatiotemporal brain trajectories, while also estimating latent disease stages and progression speed for each subject. It also lead to an entirely new segmentation of the brain based on biomarker dynamics.

Transfer learning through sharing of disease mechanisms: By necessity, models of disease progression require large datasets – in addition they should be both multimodal and longitudinal. Such data is not always available in rare neurodegenerative diseases. Most datasets for rare diseases come from local clinical centres, are unimodal (e.g. MRI only) and limited both cross-sectionally and longitudinally – this makes the application of disease progression models such as [1, 2, 7] extremely difficult. Moreover, such a model estimated from common diseases such as typical AD may not generalise to specific variants. For example, in Posterior Cortical Atrophy (PCA) – a neurodegenerative syndrome causing visual disruption – posterior regions such as the occipital lobe are affected early, instead of the hippocampus and temporal regions in typical AD.

In [10], I propose Disease Knowledge Transfer (DKT), a model that estimates continuous multimodal biomarker progressions for multiple diseases simultaneously – including rare neurodegenerative diseases – and which inherently performs transfer learning between the modelled diseases. This is achieved by exploiting biomarker relationships that are shared across diseases, whilst accounting for differences in the spatial distribution of brain pathology. We applied DKT on Alzheimer's variants and demonstrated its ability to predict non-MRI trajectories (e.g. markers

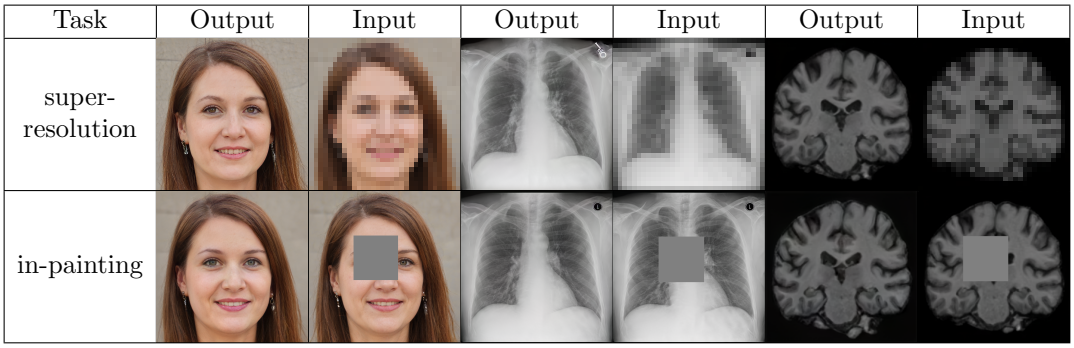


Figure 4: Image reconstructions using Bayesian inversion, where the left-side images are reconstructions of the right-side input images. A pre-trained generator model (GAN) models the prior over clean images, and a separate forward corruption model estimates the corruption that created the input image [13]. Strong reconstruction results can be obtained by just using a powerful, pre-trained generator. No re-training or fine-tuning is required for each corruption task.

of hypometabolism, amyloid and tau) for patients with Posterior Cortical Atrophy, in lack of such data.

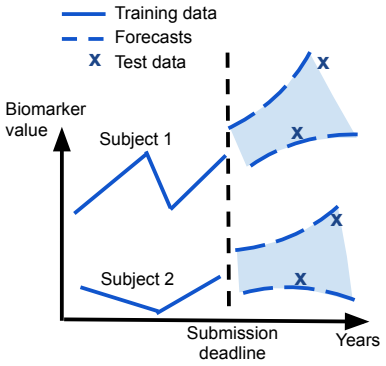
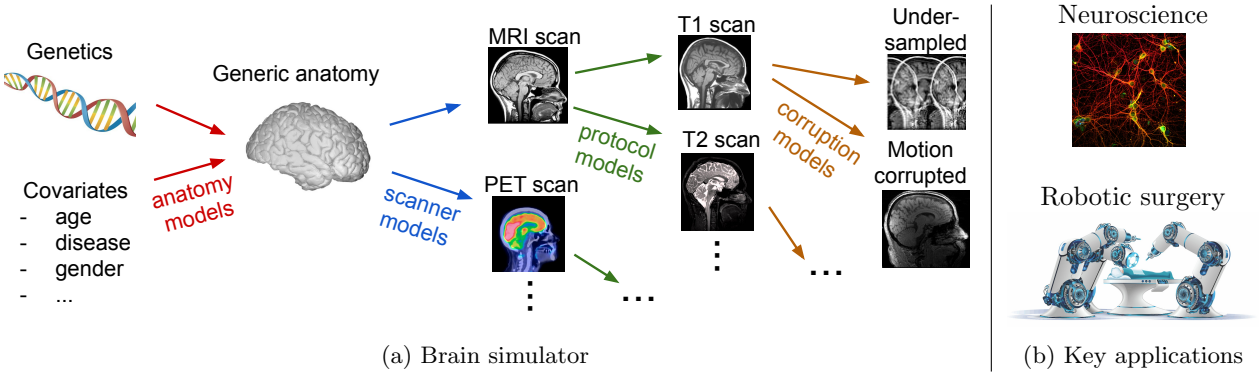


Figure 3: The design of TADPOLE challenge [5, 12], which aimed to predict Alzheimer's disease, was unique due to it's prospective nature. The test data *did not exist* at submission deadline, and was acquired afterwards, ensuring an entirely unbiased evaluation of prediction algorithms.

Evaluation of ML models for Alzheimer's disease prediction: Accurate prediction of progression in subjects at risk of Alzheimer's disease is crucial for enrolling the right subjects in clinical trials. However, a prospective comparison of state-of-the-art algorithms for predicting disease onset and progression was lacking. I designed, organised, and presented the findings of *The Alzheimer's Disease Prediction Of Longitudinal Evolution* (TADPOLE) Challenge [12], a competition which compared the performance of 92 algorithms from 33 international teams at predicting the future trajectory of 219 individuals at risk of Alzheimer's disease. Challenge participants were required to make a prediction, for each month of a 5-year future time period, of three key outcomes: clinical diagnosis, cognitive tests, and total volume of the brain ventricles. The results of the challenge revealed that, while many algorithms made good predictions, Alzheimer's disease is not a solved problem. No single submission was best at predicting all three outcomes. For clinical diagnosis and ventricle volume prediction, the best algorithms strongly outperformed simple baselines in predictive ability. However, for cognitive tests, no single submission was significantly better than random guessing. On a limited, cross-sectional subset of the data emulating clinical trials, performance of best algorithms at predicting clinical diagnosis decreased only slightly (3% error increase) compared to the full longitudinal dataset. Through our work, we created, for the first time, a benchmark for predicting Alzheimer's disease progression that brought an entire community together to focus on this specific goal.

Generative models as priors for image reconstruction: Generative models such as Generative Adversarial Networks can be used to build powerful image priors, that can be used for many downstream tasks, in particular image reconstruction tasks [13]. Using Bayes' theorem, one can estimate a posterior over the distribution of potential image reconstructions, given an instance of a noisy or corrupted image (Fig. 4). As compared to previous supervised learning approaches, which model in the anti-causal direction by taking as input the corrupted image and outputting the restored image, my approach is causal, by trying to identify which clean image, when passed through the forward corruption process, yields the queried corrupted image. By design, our approach follows the data generation process, can easily account for distribution shits in either the image dataset or the corruption process, and is more generalisable due to its compositionality.



(a) Brain simulator (b) Key applications

Figure 5: (a) In future work, I plan to build a powerful brain simulator through deep causal generative models that follow the data generation process. Given genetic and covariate data of various subjects, generative models will be used to simulate their final scans, which will be compared against actual scans taken by those subjects. Compared to classical discriminatory ML approaches, such an approach doesn't need to re-learn known anatomy for every new task, is robust to domain shift and interventions, can be locally modified through the various sub-models, and can be built through distributed cooperation of research groups. (b) Key downstream applications for the simulator range from the ability to answer neuroscience questions and identifying novel drug targets and up to computer-aided diagnosis and robotic surgery.

Future work

My long-term vision is to leverage the latest state-of-the-art advances in Machine Learning and Computer Vision models for medical problems. In addition to that, I also plan to do theoretical work on causal ML, for creating robust and flexible methods necessary in healthcare, devising efficient parameter inference schemes, as well as provide guarantees for correctness.

Biological simulators: My long-term vision is to build on generative models to create powerful simulators. One such example is the construction of a powerful brain simulator (Fig. 5), that can generate images given a structured latent space that accounts for genetics, cell types, metabolism and up to morphology and high-level anatomy. These generated images would be personalized based on an individuals' data and validated using the latest MRI, PET or CT scanning technology. Such a simulator would be fundamental for research in neuroscience and neurology, for understanding brain diseases and pathologies, and development of corresponding drugs and therapies. Another key application would be its use as a template in brain surgery. Simulators for other organs or whole-body anatomy could be created in a similar fashion.

Improved medical image reconstruction: I plan to extend the image reconstruction setup from Fig. 4 for MRI motion correction, k-space compressed sensing, slice-imputation and other types of important reconstruction tasks. This will require extending the state-of-the-art deep generator models to 3D, as they currently only operate on 2D data. Another key direction I plan to explore is to reconstruct 3D anatomy from the 2D X-ray images, by considering the corruption process as a projection operator from 3D space to 2D, perhaps combined with deformations. This will enable doctors, for the first time, to visualise 3D anatomy inferred from cheap and fast 2D X-rays, opening up new diagnostic possibilities.

Joint modelling of imaging, text and other structural data: I plan to develop novel models that generate both medical images and corresponding text describing the image, similar to a medical report written by a radiologist. Apart from images and text, other types of structural data could also be generated alongside, such as laboratory results from blood samples, prescriptions given to patients, etc ... I believe learning relationships between such data types is key to making machines understand human diseases as well as general anatomy.

Generating natural language explanations: In order to enable complex ML models assist doctors in decision making, they need to provide not just a prediction, perhaps quantified by uncertainty metrics, but also with a reason for why that particular prediction was made. For imaging systems based on deep learning, so far only saliency maps have been used, which highlight which image regions were "responsible" for the prediction. However, this is a shallow explanation, and is not suitable for complex decisions that require a series of logical steps to reach that conclusion. I plan to extend current ML models to also provide an explanation, in natural language, of why a particular decision was made. This would increase the trust in the system, and also help with debugging when errors or biases they occur. Since evaluation of explanations is generally difficult, we will also

research novel metrics for automatic evaluation of explanations, and compare these with human studies. I will also compare these explanation methods with approaches that approximate complex deep learning methods into interpretable ML models such as decision trees.

Reinforcement Learning and Active Learning: Instead of learning from a fixed dataset, it would be ideal to have ML models deployed in hospitals, to continuously interact with patients, acquire new data and make decisions. For example, I'm interested in using reinforcement learning (RL) to learn the best points that can be acquired in the MRI k-space to perform efficient compressed sensing. For instance, for detecting a tumour one might not need a full brain scan – instead, a few measurements might suffice. Other types of applications of RL in medicine that I plan to tackle include text-based and vocal assistants to help with mental health problems, as well as generating the best virtual augmentations for robotic surgery. I also plan to use active learning frameworks to speed up segmentations of difficult anatomies, or inquire the opinion of doctors when there is high uncertainty of a certain disease or pathology.

Incorporating domain knowledge by large-scale analysis of scientific articles. Recently, state of the art text-based models such as GPT-3 have showed impressive performance at predicting text from a given snippet. I plan to use such technology to analyse massive databases of scientific articles to extract medical knowledge, and then fuse that knowledge into ML models, for improving performance at disease prediction and segmentation.

Disease progression modelling: I plan to expand my current work on disease progression modelling to methods that use deep learning. To that end, I plan to adapt current generator models, e.g. GANs, to generate a time-series of brain scans of an individual patient, showing the evolution of a disease over time. Such models would be extremely useful for clinicians to make better decisions, including with respect to drug treatments. Moreover, I also plan to extend them to estimate not just subject-specific trajectories, but also population-wide trajectories, which would be particularly important in medical research for comparing across different groups.

Meta-learning and transfer-learning: Many diseases and syndromes in medicine are rare, and due to very limited data available it is often not possible to train complex ML models for such tasks. This is further exacerbated by the fact that data from different clinical centers, using different scanners and protocols is often pooled together. I plan to build on current meta-learning and transfer-learning frameworks, which learning commonalities between different diseases and pathologies, to learn to generalise to a rare disease. Examples include rare neurodegenerative diseases such as Posterior Cortical Atrophy or Dementia with Lewy bodies, as well as segmentation of different types of stroke lesions.

Collaborations: Given that my ML work requires additional medical expertise, I plan to build extensive collaborations with medical research centers and hospitals, to ensure we understand the clinical requirements and solve the most pressing medical problems. During my PhD and postdoc, I have already successfully collaborated and co-authored several articles with clinicians from the Institute of Neurology in London and Harvard Medical School in Boston. Finally, I also plan to develop strong collaborations with industry, to translate all these ML solutions to clinics and hospitals around the world.

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