Project title: Digital twin brains for predicting outcomes after therapy

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Aim of the Project

Despite widespread use in material science and much recent interest in the medical domain, fewer than 10% of publications on Digital Twins mention the brain. Yet being able to predict the brain's response to interventions such as chemotherapy for cancer in the body, or epilepsy surgery on the brain itself to stop seizures, would be very valuable. We have recently obtained funding for two very large (106cm) field-of-view Positron Emission Tomography (PET) "Total Body" (TBP) scanners. They will now regularly include the brain in the field-of-view when the remainder of the body is scanned for oncological reasons, and conversely will include most of the body when the brain is scanned e.g. ahead of epilepsy surgery.

In this project, we will first leverage the extra information collected through TBP to model body determinants of brain FDG distribution. These models will then be applied to predict responses to chemotherapy and epilepsy surgery.

Project Description

[18F]FDG (radiolabelled glucose) is the most commonly used radiopharmaceutical in PET. In oncology which represents ~90% of PET activity, FDG is used for detecting tumours and metastases and, in longitudinal studies, to check therapy response and adjust therapy (e.g. Johnson P et al. N Engl J Med 2016). About 25% of FDG is taken up by the central nervous system (cf. Figure below), and FDG is also used for assessing brain function. The three main indications are

- memory disorders (dementias such as Alzheimer's have spatial patterns of reduced uptake, representing synaptic density x synaptic activity, e.g. Minoshima S et al. Semin Nucl Med 2021);
- epilepsy (focally reduced uptake generally corresponds to the epileptogenic focus that may be amenable to epilepsy surgery, e.g. Flaus A et al. PET Clinics 2024);
- brain tumours (FDG correlates with tumour grade, e.g. Horowitz T et al. Rev Neurol 2023).

With traditional PET/CT scanners with a field-of-view of 15-25cm, only single-organ views were possible. A "Standardised Uptake Value" (SUV) has been used (SUV = voxel concentration image [kBq/ml] × (weight [kg]) / (decay-corrected injected activity [kBq])), Kenney JM et al. Radiology 1941). SUVs are very useful in oncology, but one key motivation for creating digital brain twins is that there is a large contribution of unknown factors to variation in brain FDG uptake – FDG global uptake has a coefficient

of variation of ~30%, compared to ~10-12% for fully quantified neuroreceptor data. Standardisation by other non-imaging measures, e.g. lean body mass, only partially alleviates the issue.
With the advent of TBP, it is now possible to follow the injected activity in all of the body. In addition, methods for multi-organ segmentation are emerging (see section Proposed Workplan) and can be used to derive organ-specific uptake. The CT component with its quantitative Hounsfield units can be leveraged to measure muscle mass, abdominal fat, subcutaneous fat, adding to liver uptake, renal excretion etc. In this project, we will develop much better standardisation - and for the first time use "absolute" measures to determine total synaptic activity. This will be highly relevant for mild cognitive impairment and dementia and conditions such as chemotherapy-related cognitive impairment (Chiaravalloti A et al. J Nucl Med 2023). Crucially, this effect is likely global (e.g. Sorokin J et al. Clin Nucl Med 2014) and therefore better accessible to independently standardised values than clinically standard visual pattern recognition.

There is also emerging evidence about molecular connectivity, not only between brain areas (e.g. Horowitz T et al. PET Clinics 2024, Reed MB et al. bioRxiv 2024) but also the brain and the remainder of the body: amygdala activity (a brain region linked to stress) was linked to markers of inflammation such as bone-marrow activity, arterial wall uptake, and, crucially, cardiovascular events over the next ~3.7 years (Tawakol A et al. Lancet 2017). Arterial wall uptake in particular will be much better quantifiable with TBP than traditional PET/CT (e.g. Alberts I et al. Eur J Nucl Med Mol Imaging 2021 and Figure below). In addition, there is a societal dimension of this research as the above pathway is also linked to socioeconomic disparity (Tawakol A et al. J Am Coll Cardiol 2019).

Requirements:

The project will be suitable for students with a keen interest in the subject matter and ready to embrace its highly interdisciplinary character, e.g. physicists, neuroscientists, computer scientists, modellers, and biologists or medically trained students with a strong quantitative interest.