Abstract

The size and location of ischaemic lesions provides vital clues to the origins of a stroke. This study performs three-dimensional (3D) stroke simulations for comparison with brain images to predict the size and location of emboli. Simulated emboli were released into a 3D in silico vasculature, supplying grey and white matter brain volumes, to generate individual 3D lesion estimates and probabilistic lesion overlap maps. Computer generated lesions were compared with real world radiological images obtained from the Anatomical Tracings of Lesions After Stroke (ATLAS) dataset by a panel of three clinically qualified experts. Simulations of large single emboli entering the vasculature reproduced similar middle cerebral artery (MCA), posterior cerebral artery (PCA) and anterior cerebral artery (ACA) lesions to those observed clinically. Estimated infarct volume as a percentage of total brain volume was found to be related to embolus diameter according to the following expression:

\[ \text{diameter} = \left[ \frac{\% \text{ infarct volume}}{a} \right]^{1/b} \]

where \( a = 2.54 +/- 0.062 \, \text{mm}^b \), \( b = 3.380 +/- 0.030 \) (with diameter in mm). Maximum embolus sizes observed were consistent with those observed clinically. Probabilistic lesion overlap maps were created, confirming the MCA territory as the most probable resting place of emboli in the computational vasculature, followed by the PCA then ACA. We conclude that 3D stroke simulations are capable of reproducing radiologically observed lesion distributions following embolic stroke. Personalised stroke simulations aimed at rapid diagnosis of the location and source of a stroke, have potential to distinguish cardioembolic sources from other types of stroke, facilitating rapid access to targeted treatment. Future work will focus on matching patient-specific simulation results to real-world brain imaging to inform future predictive diagnostics.
1. Introduction

The consequences of solid emboli entering the cerebral vasculature can be devastating. In particular, cardioembolic stroke results in more severe stroke presentations than other sub-types, and the incidence is projected to triple by 2050 [1]. In this paper we introduce a computational approach for simulating strokes that can be used to determine the size and provide useful information on the origin of emboli based on features that are readily available from routinely acquired brain images (e.g. lesion size and location, and brain volume). At present, clinicians deduce the likely source of a stroke by recognising typical patterns of lesions; for example, unilateral multiple emboli are frequently associated with carotid rupture, whereas bilateral or larger emboli would be more characteristic of cardiac sources. In addition to radiological findings, the treating clinician will also consider the patient’s physiology, symptoms, demographic characteristics and risk factors, often requesting additional tests to inform their diagnosis. Rapid identification of the source of emboli, and ability to distinguish between cardioembolic and other causes of stroke, has the potential to guide clinical treatment and improve patient outcomes. In this paper we demonstrate how 3D stroke simulations can be used to relate lesion volumes and locations to embolus properties.

Given the differing aetiologies, investigation, and management of acute ischemic stroke sub-types, early differentiation facilitates clinical decision-making, accelerating focussed investigation and management of patients. Analysis of the radiological features of stroke can support this process, as the location, size, and pattern of infarcts often indicate likely aetiology. However, at present there are no quantitative criteria or tools by which this is assessed, relying on the skills of an experienced Radiologist, or treating Clinician. Understanding the properties of emboli by matching in silico predictions to real-world imaging could transform and extend image interpretation methods, and save neuroradiologists’ time, through automated feature extraction and analysis of images to predict the size, location and probable source of emboli.

In this paper we describe a 3D stroke simulation, which leads to the proposition of a simple formula for determining the diameter of the embolus causing a lesion of specific volume, and the construction of probabilistic lesion overlap maps. This computational model is a major extension of our previous stroke simulation techniques [2,3,4,5]. We introduce a 3D brain model containing an automatically generated brain vasculature and simulation of embolus pathways. This 3D in silico stroke model tracks emboli as they move through the vasculature to determine the locations at which they generate lesions. The Monte Carlo nature of the simulation makes it possible to construct probabilistic lesion overlap maps mimicking large cohort or population studies. This could be a useful basis for future ‘in silico’ clinical trials aimed at investigating the impact of clinical interventions on the incidence, volume and location of new lesions or quantifying epidemiological population-based trends in stroke imaging and outcomes over time. The ability to model and understand the formation of stroke lesions, based on computed tomography (CT) or magnetic resonance imaging (MRI), could have important clinical applications. For example, the early identification of treatable cardio-embolic sources, such as atrial fibrillation, could reduce investigation burden and delays to initiating anticoagulation for these patients.
2. Methods

2.1 Monte Carlo simulations

A Monte Carlo method was used to simulate strokes. Our method was previously used with a generic vasculature that lacked spatial information [2,3,4,5]. We have extended our Monte Carlo method with the in silico simulated annealing model of the brain (SAMbrain) vasculature, which we shall refer to as the in silico vasculature throughout the rest of this paper [6, 7]. The in silico vasculature is grown using the simulated annealing vascular optimisation (SALVO) technique [6,8,9] and consists of 8192 segments representing vessels connected by bifurcations, grown according to the distribution of grey and white matter from images of a healthy individual, and with input vessel situated at the approximate location of the circle of Willis [6]. We have symmetrized the vasculature about the sagittal plane to create a 16384 segment tree. The generated vasculature contains three major arteries, approximating the middle, posterior and anterior cerebral artery perfusion territories (MCA, PCA and ACA, respectively). Figure 1 shows the computationally generated vasculature alongside its resulting perfusion territories [6]. We note some differences between the perfusion territories in the in silico vasculature and the human brain. In the in silico model, PCA and cerebellar territories are fused and the MCA territory is larger than typical. We note a large branch from the in-silico PCA that supplies a region of the cerebellum and may act as a proxy for the inferior cerebellar arteries. The advantage of the computationally generated vasculature over imaging is that there is no lower bound on vessel size and we are able to include vessels in our model down to the capillary scale. This means that we can estimate lesion volume as well as incorporate the differing metabolic demands of grey and white tissue.

To each leaf (terminal) vessel of this symmetrized vasculature we add a symmetric vascular tree with 32 elements, such that the vessel diameters in each hemisphere run from 3 mm to 11.2 microns, which is comparable with MCA diameters in humans. The root vessels of the two hemispheres are joined at a single input for convenience. Into this tree we place simulated emboli. These move until they either exit the vasculature or block a vessel. At each bifurcation, an embolus passes down one of the two branches with a probability decided by the relative flow in each direction, unless (a) one of the branches has a smaller diameter than the embolus, in which case it travels down the larger branch (which we consider more likely due to forces on the embolus from the flow) or (b) both branches have a smaller diameter than the embolus, in which case the parent vessel is obstructed. The ability for emboli to travel different paths reflects the complexity of fluid dynamics, which is highly sensitive to initial conditions. Leaf nodes of the whole tree are monitored for lack of flow (ischaemia), and a lesion is deemed to have formed if no flow has been received for a simulated period of 4 hours. The embolus dissolution rate is taken to be a reduction of 0.4mm diameter per 24 hours (5 days for a 2mm diameter embolus). While these are approximate values, the key factor here is that the dissolution rate for a large embolus is much greater than the timescale for ischaemia. We ran the model with various embolus sizes and Monte Carlo sequences, to explore a range of stroke scenarios and outcomes (replicating various lesion sizes and distributions).
2.2 Consensus meetings

Consensus meetings were undertaken by specialists in neuroradiology (DS), stroke and geriatric medicine (TGR, LB). Firstly, the Anatomical Tracings of Lesions After Stroke (ATLAS) database was reviewed by one researcher (LB), and typical examples of anterior, middle, posterior, and multiple territory embolic stroke were selected from the database. The ATLAS dataset is a large open access database of 304 manually segmented T1-weighted MRI stroke images [10]. Manual segmentation is currently the gold standard method for segmenting brain lesions on T1-weighted imaging. Images were selected for this study by consensus discussion between the three Clinicians to ensure they were representative of embolic lesions and to confirm the perfusion territory affected. Images were selected from the ATLAS data-set that were representative of the following radiological characteristics associated with embolic stroke: multiple vascular territories and or hemispheres affected, cortical, cerebellar, or brainstem location, >1.5 cm diameter lesions, and multiple infarcts [11,12]¹. These images were reviewed at a consensus meeting held between LB, TGR and DS and the best examples for each territory were selected for replication by the stroke simulation based on the same criteria. Following image selection, initial simulated images were compared at a further consensus meeting against the original images from the ATLAS dataset. Qualitative feedback was obtained with regard to the size of the simulated perfusion territories and limitations of the model and the number of sample simulations was increased to 1000 before matching to the clinical images, resulting in a final set of simulations for review by the consensus group. Clinical feedback from the original simulated images was used to identify matching images from a larger number of simulations. Qualitative feedback from the clinical consensus meeting was that:

- Smaller MCA strokes were well replicated in the simulation images but larger MCA strokes were too extensive, involving other perfusion territories (ACA and PCA).
- ACA stroke in some of the simulated images included an area affecting the MCA region which was not typically seen clinically and may be due to the mis-match between in silico and human perfusion territories.
- PCA stroke was well replicated in the simulated images.
- Borderzone infarcts were less well replicated in terms of location and shape of the infarct.

Finally, 50 simulation images were reviewed by LB and classified according to whether they would be likely to be observed in a clinical setting (follow up clinic) and assigned a characterisation of ‘yes’, ‘no’ or ‘rare’.

3. Results

We start by examining specific instances of stroke, as presented in Figure 2. The left hand panels of Figure 2 show examples of stroke from the ATLAS database, and the right hand panels show examples of similar strokes generated by our computational model. In each computational case, a single embolus was introduced into the vascular tree and allowed to

¹ Multiple infarcts will be discussed in a future publication.
propagate through the arterial tree. The results have been compared with scans from the ATLAS database that were confirmed to be representative of embolic stroke by the specialist clinicians (TGR, DS, LB). Strokes occurred in the MCA, PCA and ACA territories of the \textit{in silico} vasculature, although we note that ACA strokes were particularly rare.

Large strokes, filling the majority of each territory of the \textit{in silico} vasculature, are presented in Fig. 3. These allow the perfusion territories to be delineated, showing that the MCA territory of the simulation is further to the rear of the brain than usual, and that the cerebellar and PCA territories are fused. This is reflected in the patterns of ischaemia in the computational model seen in Fig. 3. The large PCA territory strokes predicted by the model caused ischaemia across part, but not all, of the cerebellum.

Simulations featuring emboli of varying size entering the \textit{in silico} vasculature show that infarct volume grows rapidly with embolus diameter, following a power-law distribution as shown in Fig. 4. The infarct volume as a percentage of total brain volume fits well to a power law given by:

\begin{equation}
\%\text{ infarct volume} = ad^b
\end{equation}

where \(a=2.54 +/- 0.062\) mm\(^b\), \(b=3.38 +/- 0.030\), and the diameter, \(d\), is in mm. The reason for providing this result as a percentage of total brain volume is that the expression is independent of variations in individual brain volume. Equation 1 can be inverted to determine the diameter of an embolus causing an infarct as:

\begin{equation}
d = \left(\frac{\%\text{ infarct volume}}{a}\right)^{1/b}
\end{equation}

where \(d\) is expressed in mm. Variations in the infarct volume occur because emboli of similar sizes may travel different paths due to the Monte Carlo nature of the simulations, and were typically less than a factor of two.

Figure 5 shows assessment of simulated strokes by a clinician as to whether they resembled lesions seen in a follow up clinic. The simulated lesions identified as similar to those typically seen in clinics ranged to a maximum of 2.1 mm in diameter. Some \textit{in silico} lesions caused by emboli of between 1.9 and 2.3 mm diameter were classified as rarely seen in clinic. Most \textit{in silico} lesions generated by emboli of 2.3 mm or greater were not consistent with those typically seen in clinic. This is in alignment with clinically observed lesions, which are typically caused by emboli with diameters of 2 mm or less. Cross referencing with Figure 4 associates these large emboli with infarcts affecting up to \(~30\%) of brain volume.

Probabilistic lesion overlap maps showing spatial distributions of lesions resulting from different size distributions of emboli are shown in Figure 6. These maps provide an estimate of the risk that an embolus causes a lesion at a specific brain location. The spatial distribution of lesions was found to be highly dependent on embolus size. Figure 6 shows the probability of lesions for (a) emboli of 0.6 mm diameter, (b) emboli of 1.2 mm diameter, and (c) emboli of 1.8 mm diameter. 0.6mm diameter emboli lead to a more even distribution of lesions across the brain affecting multiple perfusion territories. 1.8mm diameter emboli preferentially block the MCA territory. 1.2mm diameter emboli preferentially reach the MCA and PCA territory, with some ACA territory strokes. Thus, the size of emboli influences their
trajectories through the vasculature and indicates a preference for larger emboli travelling into the MCA territory, leading to larger lesions occurring in the MCA territory.

When a flat distribution featuring equal numbers of emboli of differing sizes, up to a maximum of 2 mm diameter is introduced to the in silico vasculature, obstruction of the posterior MCA territory was most common, with further blockages occurring in the PCA territory, and the remainder of the MCA territory, but fewer in the ACA territory, Figure 6(d). A flat distribution is used because the true distribution of embolus sizes relating to strokes seen in clinics is not known. In the ATLAS data-set, MCA infarcts are most probable. This is also true in our in silico vasculature, although the most probable location in the simulations was found to be towards the superior-posterior region of the MCA territory. Our simulations have large numbers of lesions in the PCA territory. ACA infarcts were rare in both the ATLAS dataset and our simulations.

4. Discussion

In this study, we demonstrated that 3D embolic stroke simulations can be used to make predictions about the distributions and locations of lesions due to specific patterns of embolisation. There are several advantages to stroke modeling in this way. Firstly, spatial information is available enabling direct comparison with radiological images. Secondly, in silico clinical trials could be conducted. Thirdly, the simulations require no prior knowledge of the patient’s anatomy or status other than that already contained within standard brain imaging data.

This study is strengthened by comparison with a large real-world image database which used manual lesion segmentation. Furthermore, the ability of the model to replicate real-world images was reviewed by clinical consensus, providing a clinical context for image interpretation. A strength of our simulation method is inclusion of vessels on all length scales, and tracking of embolus paths through the tree. We note an alternative model of stroke where vessels are effectively pinched off in silico [13], which does not include a Monte Carlo element and only contains vessels from imaging data, leading to pruning of the vasculature at a vessel diameter of approximately 0.3 mm.

This study was limited by the use of chronic rather than acute stroke images, which are not currently available in the ATLAS dataset. Images provided through ATLAS were not always segmented by experts in neuroradiology; all scans from the dataset were reviewed by a consultant neuroradiologist before inclusion in this study. A limitation of our simulations was that in silico perfusion territories reproduced by the model were not fully consistent with those seen in the human brain: for example, the large numbers of lesions in the PCA territory may occur because the PCA territory of the computationally generated vasculature is too large (or due to the difference between the as yet unknown clinical distribution of embolus sizes and those used as input to the stroke model). Another limitation of our simulations is that the current vascular tree is consistent with a complete circle of Willis, which applies to approximately 50% of the population. Finally, simulations only feature the major vessels of the brain, while other arteries, such as ophthalmic arteries, may be relevant to the passage of emboli.
Determining the cause of an acute ischaemic stroke (AIS) is a complex problem, which is currently based on analysis of a range of factors including patient characteristics and risk factors, as well as neurological symptoms and imaging data. Up to 25% of strokes are currently classified as embolic of undetermined source (ESUS). In particular, correctly identifying and treating atrial fibrillation (AF) is thought to occur in only 50% of eligible patients, representing a significant barrier to timely anticoagulation. This is despite a 70% reduction in stroke recurrence with early anticoagulation for AF, making it a preventable condition. Furthermore, in a large, prospective, multicentre study, AF was associated with greater mortality, poorer neurological outcomes, and more complications than non-AF stroke. Prolonged cardiac monitoring up to one year can increase the capture of AF, but leaves the patient vulnerable to recurrent stroke in the intervening period. Thus, strategies that can improve prediction of the source of embolism and extraction of embolus properties from acute stroke images have the potential to reduce time to diagnosis and support earlier initiation of anticoagulation in high risk patients with cardioembolism.

Our stroke simulations indicate that further tailoring of simulations to include patient-specific imaging data, coupled with implementation of automated artificial intelligence (AI)-based image segmentation is likely to be feasible for automatically predicting the size (and potentially the source) of embolisation to aid clinical diagnosis. As a first step in this direction, we propose that Equation (2) can be used as a tool to provide estimates of embolus size from imaging data, especially in cases where it is difficult to determine the lumen diameter for an occluded vessel. Additional work in this direction would include improving the representation of the vasculature by seeding the vascular growth algorithm based on patient-specific time-of-flight MR angiography data, with additional arterial inputs for ophthalmic arteries, cerebellar arteries and other major vessels, and representative variants of the circle of Willis (including any related modifications to perfusion territories due to CoW topology). As the simulations and their associated probabilistic lesion overlap maps (and other measures such as the correlation between the hemispheres where multiple lesions occur, or whether the lesions are subcortical) are improved, we suggest that the probability that the embolus has a particular size and type, and ultimately origin information could be extracted by e.g. comparing imaged lesions to the probabilistic lesion overlap maps associated with different embolic sources. Additional steps in this direction should include comparison of simulation results with patient diagnosis and outcome to inform predictive diagnostics. Ultimately, machine learning methods could be used to train the model and improve its predictive capacity, and would allow the patient’s symptoms, physiology, cellular biology, and genetic or demographic data, to be incorporated with advanced image interpretation.

Another future application relates to multiple embolisation events and intraoperative monitoring. We have not considered multiple embolisation events in this paper, instead focusing on the impact of a single large embolus. Monte Carlo methods are ideal for simulating showers of solid and gaseous emboli during cardiovascular interventions, such as cardiac or carotid surgery, cardiac ablation and stent deployment. In these settings, embolic events can be detected intraoperatively and could be directly incorporated into a 3D stroke simulation to predict the impact of emboli on brain tissue perfusion.

An additional future application of our model could also be for quantifying epidemiological changes in embolic stroke at a population level, signaling a shift in the prevalence of different
stroke subtypes due to lifestyle factors, and introduction of statins, or improved management of AF. Finally, we note that existing experimental models of embolic stroke are often animal based [17, 18, 19]. As the sophistication of in silico models improves, there is an opportunity to complement or replace animal models and to extend our model based on cellular biology to perform in silico clinical trials.

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Figure 1: Vessels and perfusion territories in the in silico model. Green and turquoise - ACA territories. Blue and yellow - MCA territories. Purple and red - PCA territory and cerebellum.
Figure 2: Stroke examples extracted from the ATLAS database, compared to an example stroke simulation for the same perfusion territory. (a) Smaller MCA strokes were well replicated in the simulation images, (b) A mismatch was observed in the position of simulated lesions in the ACA perfusion territory, which extends more superiorly from anterior to posterior in the human than in our simulations. (c) PCA territory lesions were well reproduced by the simulation.

(a) MCA stroke

(b) ACA stroke:

(c) PCA stroke:
Fig. 3: Large single territory simulated lesions provide a reference for the location of the MCA, PCA and ACA territories. The watershed territories have broad similarities to those in a real brain, with the caveat of a larger MCA, and PCA territory extending into the cerebellum.

(a) MCA

(b) ACA

(c) PCA + cerebellum
Figure 4: Volume of *in silico* infarcts as a proportion of brain size increases with embolus diameter according to a power law. Both the infarct volume and embolus diameter are plotted on logarithmic scales to clearly demonstrate this power law relationship.

![Graph showing power law relationship between simulated embolus event and infarct volume]

% infarct volume = 2.54d^{3.38}

Figure 5: Clinical classification of simulated strokes. A clinician (LB) was given images of the *in-silico* lesions and asked to assess them as to whether they resemble cases relating to follow-up clinic “likely to be seen in clinic”, “rare in clinic” or “not seen in clinic”. This may suggest the maximum embolus diameter commonly seen in follow-up clinic is 2.1mm.

![Bar chart showing clinical classification results]

% responses

simulated embolus diameter [mm]
FIG 6: Maps showing the probability that emboli of particular sizes will arrive at a location in the brain. Small emboli are evenly distributed, whereas large emboli preferentially come to rest in the MCA territory of the \textit{in silico} model. When receiving a distribution containing emboli of various sizes, emboli arrive preferentially in the posterior + superior MCA territory of the \textit{in silico} model, but lesions are also common in the posterior and superior parts of the brain.