

1 Modelling the impact of clot fragmentation 2 on the microcirculation after thrombectomy

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12 **1 Abstract**

13 Many ischaemic stroke patients who have a mechanical removal of their clot (thrombectomy) do not
14 get reperfusion of tissue despite the thrombus being removed. One hypothesis for this ‘no-reperfusion’
15 phenomenon is micro-emboli fragmenting off the large clot during thrombectomy and occluding
16 smaller blood vessels downstream of the clot location. This is impossible to observe in-vivo and so we
17 here develop an in-silico model based on in-vitro experiments to model the effect of micro-emboli on
18 brain tissue. Through in-vitro experiments we obtain, under a variety of clot consistencies and
19 thrombectomy techniques, micro-emboli distributions post-thrombectomy. Blood flow through the
20 microcirculation is modelled for statistically accurate voxels of brain microvasculature including
21 penetrating arterioles and capillary beds. A novel micro-emboli algorithm, informed by the
22 experimental data, is used to simulate the impact of micro-emboli successively entering the penetrating
23 arterioles and the capillary bed. Scaled-up blood flow parameters – permeability and coupling

24 coefficients – are calculated under various conditions. We find that capillary beds are more susceptible
25 to occlusions than the penetrating arterioles with a 4x greater drop in permeability per volume of vessel
26 occluded. Individual microvascular geometries determine robustness to micro-emboli. Hard clot
27 fragmentation leads to larger micro-emboli and larger drops in blood flow for a given number of micro-
28 emboli. Thrombectomy technique has a large impact on clot fragmentation and hence occlusions in the
29 microvasculature. As such, in-silico modelling of mechanical thrombectomy predicts that clot specific
30 factors, interventional technique, and microvascular geometry strongly influence reperfusion of the
31 brain. Micro-emboli are likely contributory to the phenomenon of no-reperfusion following successful
32 removal of a major clot.

33 **2 Author summary**

34 After an ischaemic stroke - one where a clot blocks a major artery in the brain - patients can undergo a
35 procedure where the clot is removed mechanically with a stent - a thrombectomy. This reopens the
36 blocked vessel, yet some patients don't achieve blood flow returning to their tissue downstream. One
37 hypothesis for this phenomenon is that the clot fragments into smaller clots (called micro-emboli) which
38 block smaller vessels downstream. However, this can't be measured in patients due to the inability of
39 clinical imaging resolving the micro-scale. We therefore develop a computational model here, based on
40 experimental thrombectomy data, to quantify the impact of micro-emboli on blood flow in the brain
41 after the removal of a clot. With this model, we found that micro-emboli are a likely contributor to the
42 no-reflow phenomenon after a thrombectomy. Individual blood vessel geometries, clot composition,
43 and thrombectomy technique all impacted the effect of micro-emboli on blood flow and should be taken
44 into consideration to minimise the impact of micro-emboli in the brain. Furthermore, the computational
45 model developed here allows us to now build large-scale models of blood flow in the brain, and hence
46 simulate stroke and the impact of micro-emboli on the entire brain.

47 **3 Introduction**

48 Stroke is the second largest cause of mortality and of adult disability globally [1]. Ischaemic stroke –
49 the physical occlusion of a cerebral artery by a blood clot (embolus) restricting blood supply to a part
50 of the brain – is the most common form of stroke, occurring in approximately 85% of strokes [1]. Time
51 is critical in stroke, with every hour of delay without treatment causing a loss of neurons equivalent to
52 3-4 years of ageing [2] and a 6% reduction in positive outcome once the patient is treated [3].

53 Since 2015, the use of intra-arterial thrombectomy – the mechanical removal of a clot via a stent – has
54 become the standard of care for patients with acute ischaemic stroke caused by large vessel occlusion
55 [4,5]. Despite this, many patients do not recover full perfusion in their tissue downstream of the
56 recanalized vessel [6]. This observation, commonly known as the “no-reflow” or “no-reperfusion”
57 phenomenon, has been documented in numerous studies involving both animals and humans [7–12].
58 Hypotheses for this phenomenon include: changes in the ultrastructure of the microvasculature and
59 spontaneous blood clotting [7], capillary stalling and leukocyte adhesion [10,13–15], breakdown of the
60 blood-brain barrier leading to tissue swelling and vessel collapse [12,16,17], vasoconstriction of the
61 capillary vessels due to pericyte death [10,18,19], oxidative stress and inflammatory responses [11],
62 and micro-emboli fragments post-recanalization blocking micro-vessels downstream of the clot [8,20].

63 One of the above hypotheses for the no-reflow phenomenon – a micro-emboli “shower” fragmenting
64 off the clot – is of interest due to the clear clinical treatment pathway via thrombolysis. There is indirect
65 evidence that micro-emboli can fragment off clots and lead to worse patient outcomes. Patients who
66 undergo endarterectomy (surgical removal of a plaque in the vasculature) with stenting in the carotid
67 artery are 3 times as likely to have lesions appear in diffusion weighted MRI scans, and have non-
68 disabling strokes, than those who only had an endarterectomy [21]. There is therefore a potential link
69 between clot fragmentation and the potential for microvascular occlusions and worse patient outcomes.

70 As part of the INSIST (*IN-silico clinical trials for treatment of acute Ischaemic STroke*) consortium
71 (www.insist-h2020.eu) we are developing full brain models of blood flow and oxygen transport in

72 health, after an ischaemic stroke, and post-thrombectomy/thrombolysis [22]. The goal of INSIST is to
73 advance in-silico clinical stroke trials for biomedical products for the treatment of ischaemic stroke. As
74 such, an accurate model of clot fragmentation during thrombectomy is required to simulate the effect
75 of micro-emboli on reperfusion post-recanalization. This will help in deducing whether micro-emboli
76 are a major reason for no-reperfusion.

77 Due to the intrinsically microvascular nature of the no-reflow phenomenon, it is impossible to assess
78 the impact of micro-emboli showers in humans, with most microinfarcts being < 1 mm in size making
79 in-vivo detection of them challenging [23]. However, silicone in-vitro models of human cerebral
80 vasculatures have been used to quantify how a clot fragments during thrombectomy using a range of
81 removal techniques and different clot consistencies [20,24]. Most other experimental works analysing
82 the impact of occlusions on the microvasculature come from mouse models [25–28]. Recently, an in-
83 silico study on a mouse cortex microvascular network found that the severity of micro-strokes in the
84 capillary bed were heavily influenced by the local network topology, with decreases in flow of up to
85 80% in the local vicinity of the capillary [29].

86 On the macro-scale, full organ models of blood flow in the brain have been developed [30,31]. These
87 models treat the microvasculature in the brain as a continuous porous medium, effectively smoothing
88 out the local topology and variations in blood flow. Crucially, these models are parameterized by
89 simulations of blood flow in the microvasculature [32]. As such, in order to achieve the aim of
90 simulating a micro-emboli shower in the microvasculature and to determine its effect on the large-scale
91 blood flow, a multi-scale model of micro-occlusions will be developed here. This model will link the
92 blood flow in the microvasculature to the parameters used to model full brain blood flow and the effect
93 of thrombectomy on the microcirculation, both at the penetrating vessel scale and the capillary scale.
94 To the best of our knowledge no models of micro-emboli occlusions have been developed for post-
95 thrombectomy patients.

96 This paper then seeks to answer, through modelling informed by in-vitro experiments, the following
97 questions: To what extent is clot fragmentation responsible for the post-thrombectomy no-reflow

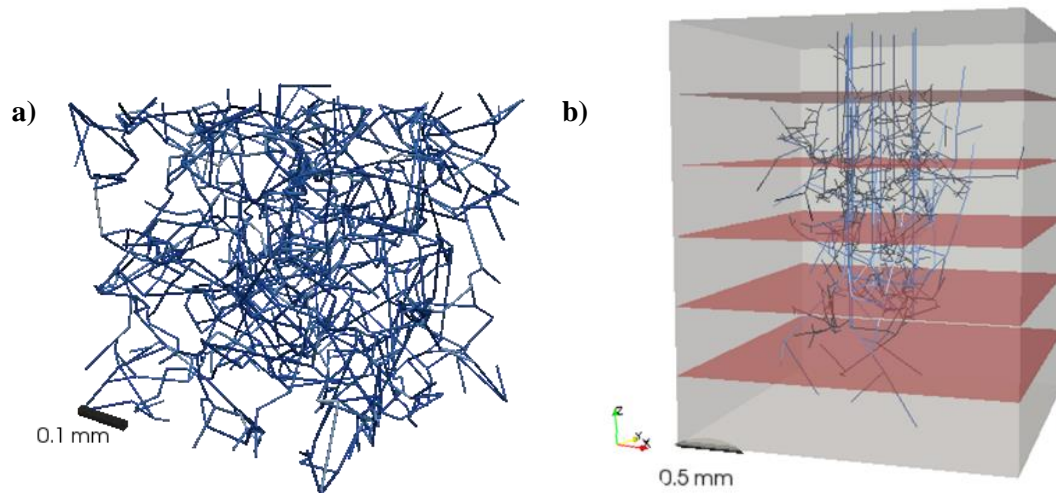
98 phenomenon? Can the changes in the blood flow modelling parameters due to micro-emboli showers
99 be accurately quantified such that they can be used in the full organ models? What impact do
100 thrombectomy technique and clot consistency have on downstream blood flow post-thrombectomy?

101 **4 Materials and methods**

102 **4.1 Modelling framework**

103 In order to investigate the effects of micro-emboli on the cerebral microvasculature, a modelling
104 framework must first be developed. There are two main ways in which the cerebral microvasculature
105 can be modelled – either as a network of individual vessels [35–37], or as an averaged porous medium
106 [30,31,33,38]. We model the microvasculature as a porous medium in order to allow large regions of
107 the brain to be modelled computationally feasibly.

108 The microvasculature will be parameterised following on from previous research developed by our
109 group [32,33,39]. Firstly, statistical models are developed which match morphological properties of the
110 human cerebrovascular network [40–43]. The microvasculature is then split into 2 different spatial
111 scales – the capillary bed, and the penetrating arterioles. In order to scale up the microvasculature to
112 larger regions, the capillary bed blood flow is parameterised with a permeability, as are the penetrating
113 arterioles. The flow from the penetrating arterioles to the capillary bed is parameterised through
114 coupling coefficients – which represent the conductance of the pre-capillary arterioles. The
115 parameterisation method is explained in Section 4.7. Example networks of the different microvascular
116 scales and their coupling can be seen in Fig 1.



117

118 **Fig 1. a) An example of a statistically accurate capillary network, b) An example of a voxel used**
119 **to simulate flow through the penetrating arterioles. The grey region represents the homogenized**
120 **capillary bed to which the terminal vessels of the trees couple. The red planes denote the dividing**
121 **planes between the 6 layers of the voxel over which the blood flow characteristics will be**
122 **calculated.**

123 **4.2 In-vitro emboli quantification**

124 Previous in-vitro studies generated micro-emboli distributions from thrombectomy procedures. In brief,
125 a silicone cerebrovascular model built from clinical imaging data was used in a flow loop with a
126 peristaltic pump to simulate blood flow through the cerebral vasculature [24,44]. A thrombus was
127 injected into the cerebrovascular replica to form a middle cerebral artery (MCA) occlusion. The thrombus
128 was either defined as a soft or hard clot, and validated for bulk mechanical properties based on clinical
129 specimens [45]. Four different clot removal techniques (thrombectomy) were then deployed to remove
130 the clot from the MCA. Specifics on the 4 thrombectomy techniques – abbreviated as ADAPT,
131 Solumbra, BGC, and GC at cervical ICA – can be found in Chueh et al. [20]. The number and size
132 distribution of the clot fragments that break off the thrombus during thrombectomy are quantified using
133 a Coulter counter (Beckman Multisizer 4, Brea, California). Each removal technique is repeated 8 times
134 for each clot type, resulting in 64 sets of clot fragment data.

135 When sampling from this data for our in-silico models the 8 experimental micro-emboli density
136 distributions (for a given removal technique and clot type) are averaged such that for any given
137 technique and clot type there is only one average set of micro-emboli results relating number density
138 and particle size. The smallest clot measurable, due to the aperture used in the Coulter counter, was
139 8.034 μm in diameter, with smaller clots binned under this size.

140 **4.3 Simulating blood flow in the microvasculature**

141 Prior work has shown how blood flow can be simulated in a coupled model of the penetrating vessels
142 and a porous representation of the capillary bed [33]. This model is adapted here such that it can be
143 used to determine the permeability of the penetrating arterioles in health and with micro-emboli
144 occluding the vessels.

145 An example voxel, where the penetrating arterioles are coupled to the capillary bed, is shown in Fig 1b.
146 Flow through the penetrating vessels is assumed to be steady-state, non-pulsatile (Womersley number
147 $\ll 1$) and fully developed, hence approximated by Poiseuille flow:

$$148 \quad q = \frac{\pi R^4 \Delta P}{8\mu(R)L} \quad (1)$$

149 where q is the blood flow through the vessel, R is the radius of the vessel, ΔP is the pressure drop across
150 that vessel, L is the length of the vessel, and $\mu(R)$ is the apparent viscosity of blood in the vessel
151 correcting for the Fåhræus-Lindqvist effect with a constant discharge haematocrit of 0.45 [46].

152 As flow is conserved at each bifurcation node i , the net flow at each node in the tree is zero except for
153 the one inlet node and the multiple terminal nodes that end in the capillary bed. Therefore, the flow
154 through each internal node for n nodes can be written as:

$$155 \quad \sum_{i=1}^n (P_i - P_j)G_{ij} = 0 \quad (2)$$

156 where G_{ij} is the flow conductance between nodes i and j and is defined as $\frac{\pi R^4}{8\mu L}$ as in equation (1). The
157 conductance is zero unless there is a vessel between nodes i and j . P_i and P_j are the pressures at nodes
158 i and j respectively. The inlet flow and terminal flows are handled by the boundary conditions at the
159 inlet to the arteriole and at the coupling points to the capillary bed. This set of n equations can be written
160 in matrix form and solved as in Su et al. [47].

161 The capillary bed can be modelled as a porous medium using a volume-averaged form of Darcy's law
162 [32,48]:

$$163 \quad \mathbf{u}_c = -K_c \nabla p_c \quad (3)$$

164 where \mathbf{u}_c is the volume averaged capillary velocity, K_c is the permeability (as the permeability is
165 isotropic this can be treated as a scalar), and ∇p_c is the pressure gradient across the capillary bed. The
166 permeability K_c encapsulates the micro-scale geometry of the capillary bed in one averaged parameter,
167 hence allowing for large-scale regions to be modelled computationally efficiently. This equation can be
168 combined with mass conservation to give:

$$169 \quad \nabla \cdot (K_c \nabla p_c) = -S \quad (4)$$

170 where S is the volumetric source/sink term [$\text{m}^3 \text{s}^{-1} \text{m}^{-3}$] that comes from the terminal nodes of the
171 penetrating vessels. The healthy capillary permeability value has previously been found be 4.28×10^{-4}
172 $\text{mm}^3 \text{s}^{-1} \text{kg}^{-1}$ [32]. Equation (4) is the Poisson equation that can be solved for capillary pressure over an
173 appropriate 3D domain.

174 **4.4 Coupling penetrating vessels and capillary bed**

175 The coupling between the penetrating vessel terminal nodes and the porous capillary bed has a
176 mathematical singularity at the point of coupling between 1D flow and 3D tissue. Previous models have
177 approximated the Dirac delta singularity with a function that is spatially variant yet maintains mass
178 conservation [30]; have approximated the pressure drop in the vicinity of the coupling point to deal with
179 the strong pressure gradients that appear there [49]; or have simply taken the discretised element nearest

180 the terminal node as the outlet region [33,50]. Here, we use a spatially variant function to approximate
181 the volumetric source terms [30]. A shape function is introduced that replaces the Dirac delta singularity
182 with an exponential in the vicinity of the source. The shape function, η , is defined as

$$183 \quad \eta := \begin{cases} C \exp\left(\frac{1}{\left|\frac{x}{\epsilon}\right|^2 - 1}\right), & \left|\frac{x}{\epsilon}\right| < 1 \\ 0, & \left|\frac{x}{\epsilon}\right| \geq 1 \end{cases} \quad (5)$$

184 where x is the distance measured from the source/sink node and ϵ is the radius of the sphere over which
185 the flow will be distributed from the arteriole source to the capillary bed (here set as 15 μm). C is a
186 constant that acts to normalise η to ensure mass conservation across the capillary bed elements coupled
187 to the terminal tree node. Therefore, the volumetric source term for each finite element within ϵ radius
188 of the terminal node will be

$$189 \quad S_k = \sum S * \eta(x - x_k) \quad (6)$$

190 where S_k is the volumetric source term for one element within ϵ radius of the terminal node and x_k is
191 the coordinate of the terminal node. A summation is used to account for the potential that multiple
192 terminal nodes may feed an individual element. As the shape function η conserves mass, $\int \eta(x) dx = 1$
193 and hence $\sum_k S_k = S$.

194 **4.5 Solving for blood flow under healthy conditions**

195 The voxel size chosen to simulate the flow is 2 x 2 x 2.5 mm (on the order of an MRI voxel), with 8
196 arterioles /mm² penetrating into the voxel [51]. This voxel was situated in a capillary bed of 2.25 x 2.25
197 x 2.5 mm to avoid terminal nodes being at the face of the voxel (Fig 1b). As the parameterisation of
198 micro-emboli occluding the penetrating arterioles was primarily of interest here, the venules were not
199 included in the simulation. As well as this, the permeability of the capillary bed was chosen such that
200 the maximum possible flow could be obtained through the arterioles (in this case K_c was set to 4.2×10^{-5}
201 $\text{mm}^3 \text{ s kg}^{-1}$). The arterioles have a mean diameter of $20 \mu\text{m} \pm 5 \mu\text{m}$, with a mean length of $1.25 \text{ mm} \pm$

202 0.31 mm. An inlet pressure of 12.3 kPa is imposed at the tree inlets [52]. Dirichlet boundary conditions
203 were imposed at the top and bottom of the voxel with $P_{top} = 12.3 \text{ kPa}$ at $z = 0$ and $P_{bottom} = 8 \text{ kPa}$
204 at $z = 2.5 \text{ mm}$, with periodic boundary conditions on the 4 other faces.

205 The finite element method is used to simulate the capillary bed partial differential equation using
206 FEniCS, an open source finite element solver [53]. Equation (4) is solved with the parameters and
207 boundary conditions using 870,000 linear Lagrangian elements to obtain the pressure in the capillary
208 bed. The equations above were solved iteratively. The pseudo-algorithm below details the solution
209 steps:

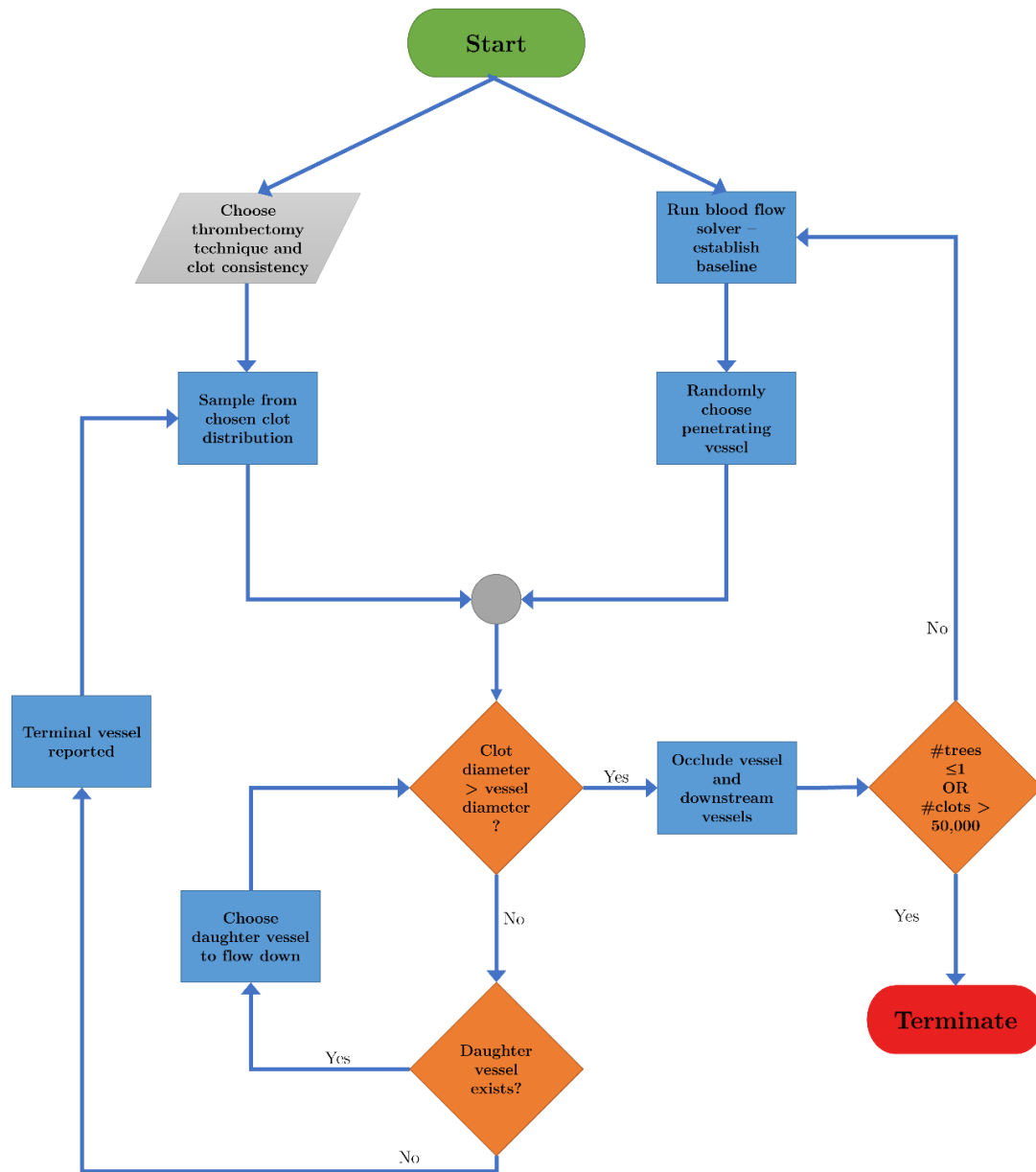
210 Flow Solver Algorithm

- 211 1. Set Dirichlet boundary conditions on the top and bottom of the voxel and periodic boundary
212 conditions on the 4 sides;
- 213 2. For all tree outlets coupled to capillary bed, determine elements in mesh coupled to the outlet
214 node, and determine their η weightings using equation (5);
- 215 3. Set desired inlet pressures for penetrating vessels and set initial terminal outlet pressures = 0
- 216 4. Solve for the pressure in the trees using equations (1) and (2), hence solve for the outlet flows
217 from the trees into the capillary bed weighting the volumetric source terms using equations (5)
218 and (6);
- 219 5. Set the volumetric source terms in equation (4) and solve for the capillary bed pressure using
220 the finite element method;
- 221 6. Update penetrating vessel terminal node pressure values using an η weighted average of the
222 capillary bed pressures related to the given terminal node;
- 223 7. Go to step 4 and repeat, unless a steady state is reached where pressures in terminal nodes and
224 capillary bed have converged to a tolerance of $1 \times 10^{-3} \text{ Pa}$;

225

226 4.6 Simulating micro-emboli post-thrombectomy

227 In order to simulate the effect of micro-emboli on the microvasculature, an algorithm is presented here
228 that samples from the in-vitro experimental thrombectomy data and occludes vessels sequentially. The
229 algorithm flowchart is schematically represented in Fig 2.



230

231 **Fig 2. Flowchart representation of the micro-emboli occlusion algorithm**

232 A clot technique and clot consistency are chosen from one of our 8 clot distributions as described in
233 Section 3.2. The algorithm initially runs the healthy flow solver above to establish baseline healthy

234 blood flow. A clot size is then sampled pseudo-randomly using Python's inbuilt 'random' module from
235 the experimental distributions derived from the in-vitro models [20].

236 A penetrating arteriole is randomly chosen on the pial surface through which the clot is sent through.
237 The clot is assumed to be perfectly spherical. A check is then made to determine whether the clot is
238 larger than the diameter of the vessel it is entering. If the clot is smaller than the vessel, the clot is
239 assumed to travel until the next bifurcation. At the bifurcation, the clot enters one of the two daughter
240 branches based on a probability that is linearly weighted by the blood flow in the daughter branches.
241 For example, if one daughter vessel has 3 times as much flow as the other daughter vessel, the clot has
242 a 75% chance of going down the vessel with more flow.

243 The clot continues to travel through vessels if its diameter is smaller than the diameter of the vessel it
244 is entering. If the clot enters a vessel with a smaller diameter, it is assumed that the clot completely
245 occludes that vessel. When that occurs, it is assumed no blood can enter the occluded vessels or any
246 vessels downstream of the occluded vessel. The algorithm recalculates a baseline blood flow and
247 resamples a clot to loop through the steps again.

248 If the clot reaches a terminal vessel, and it is still smaller than the vessel, it is assumed that the clot
249 generates no occlusions in the penetrating vessels and enters the capillary bed. As we are trying to
250 quantify the damage done by micro-emboli to the penetrating vessels, we do not create capillary bed
251 occlusions in this simulation. The effect of micro-emboli on the capillary bed is thus considered
252 separately in Section 4.9. As such, no vessels in the penetrating tree are occluded, and a new clot is
253 sampled to loop through the algorithm again.

254 The algorithm described, shown in Fig 2, is repeated until only one penetrating vessel remains or until
255 50,000 clots have been sampled, whichever comes first. The large number of maximum clots is chosen
256 such that we can ensure that all the vessels are eventually occluded, allowing us to track the damage
257 done by micro-emboli sequentially.

258 4.7 Parameterising the penetrating arterioles

259 There are 2 specific parameters of interest when attempting to model the penetrating vessels over a
260 large scale – the permeability and the coupling coefficients. The permeability of the penetrating vessels
261 represents the ability of the trees to drive blood flow deeper into the grey cortex due to their 1-
262 dimensional nature [54], and the coupling coefficients represent the pre-capillary arterioles' ability to
263 deliver blood to the capillary bed. These parameters are necessary to simulate large regions of the human
264 brain blood flow efficiently [31]. However, these parameters also effectively average out the micro-
265 scale fluctuations in the vasculature, replacing a complex network with one parameter. This can be
266 problematic with the penetrating vessels when considering, for example, the terminal nodes of the trees.
267 It is highly unlikely they are distributed evenly through the grey matter with depth. It is also highly
268 unlikely that the permeability of the trees is constant with depth through the voxel. We mitigate this
269 problem by splitting the voxel into 6 layers, similar to other approaches [37,55]. Permeabilities and
270 coupling coefficients are then calculated for each of the 6 layers through the voxel, increasing the
271 resolution of the large-scale simulations.

272 **Permeability.** As the permeability of interest is defined as the ability of the penetrating vessels to
273 drive blood flow deeper into the cortex, it is calculated in the vertical direction only. The angle that
274 every vessel makes with the vertical is calculated (situating the vertical at the vessel node where flow
275 enters the vessel). The vertically projected flow of the vessel, $Q_{z,i}$, is then calculated as

$$276 \quad Q_{z,i} = Q_i \cos(\phi) \quad (7)$$

277 where ϕ is the angle between the vessel and the vertical, and Q_i is the absolute flow through the vessel.
278 The arterial blood flow, $Q_{z,i}$, through each of the six layers is then summed separately and the
279 permeability calculated as

$$280 \quad K_{a,l} = \frac{Q_l}{\Gamma_z \nabla P_l} \quad (8)$$

281 where $Q_l = \sum Q_{z,i}$ through layer l , $K_{a,l}$ is the arteriolar permeability in layer l , Γ_z is the cross-sectional
282 area through which the blood flows (in this case the area of the voxel), and ∇P_l is the pressure gradient
283 across the layer. Using this method provides 6 different estimates of arteriolar permeability at 6 different
284 depths in the grey matter.

285 **Coupling coefficients.** The method to calculate the coupling coefficients can be found in Hyde et al.
286 [56]. The coupling coefficients can be thought of as a conductance (or 1/resistance) to flow from the
287 arteriolar compartment to the capillary compartment via the pre-capillary arterioles. This can be written
288 as

$$289 \quad Q_t = \beta_{ac}(\langle p_a \rangle - \langle p_c \rangle) \quad (9)$$

290 where β_{ac} is the coupling coefficient between the arteriolar and capillary compartments, $\langle p_i \rangle$ is the
291 volume averaged pressure of compartment i , and Q_t is the flow of the arterioles which terminate in the
292 capillary compartment. This can be rewritten as

$$293 \quad \beta_{ac}(l) = \frac{Q_t(l)}{|\langle p_a(l) \rangle - \langle p_c(l) \rangle|} \quad (10)$$

294 where the bracket l term refers to the values in layer l . The volume averaged flow in layer l , $Q_t(l)$, can
295 be calculated using equation (1). The volume averaged pressure of the arteriolar compartment $\langle p_a(l) \rangle$
296 is calculated via

$$297 \quad \langle p_a(l) \rangle = \frac{\sum_{n,l} P_n V_n}{\sum_{n,l} V_n} \quad (11)$$

298 where P_n is the average nodal pressure of vessel n in layer l , and V_n is the volume of vessel n in layer
299 l . Six values of average pressure are calculated, one for each layer.

300 Finally, the volume averaged capillary pressure at each layer $\langle p_c(l) \rangle$ is calculated by taking the volume
301 average of the pressures in the finite element mesh of the capillary bed. This allows for the permeability
302 and coupling coefficients of the penetrating vessels to be fully characterised. In order to be able to
303 characterise the variable permeabilities and coupling coefficients calculated above, a polynomial least

304 squares fit is used to derive a function of how these coefficients vary with depth which is then fitted
305 over the 100 simulations conducted on the statistically accurate voxels.

306 **4.8 Investigating thrombectomy technique, clot composition, and individual** 307 **microvasculatures**

308 Based on the pipeline previously presented, we now seek to investigate whether the different micro-
309 emboli distributions from thrombectomy have an impact on the permeability (and hence perfusion) of
310 the penetrating arterioles following the introduction of micro-emboli. The micro-emboli algorithm is
311 therefore used to simulate an emboli shower for 8 different scenarios – 4 techniques used on ‘hard’ or
312 ‘soft’ clots.

313 As well as this, we investigate the impact that differing microvasculatures have on the resulting drops
314 in permeability and coupling coefficients. Each of the 100 statistically accurate voxels can be thought
315 of as an ‘individual’ microvasculature. We randomly choose 3 of these voxels and, for each voxel, we
316 simulate 100 different sampled clot distributions entering the penetrating vessels. These simulations are
317 compared to another simulation where we take our 100 voxels and run the same sampled clot
318 distribution through each voxel – this is done for 3 different sampled clot distributions. The question
319 that we seek to answer is whether it is the microvasculature or the clot distributions that primarily
320 determine microvascular robustness to drops in perfusion. Differences between distributions are
321 quantified using the correlation matrix distance (CMD) on the covariance matrices of each distribution
322 [57].

323 **4.9 Micro-occlusions in the capillary bed**

324 Finally, the effect of micro-emboli on capillary beds is considered. Previously, we demonstrated how
325 statistically accurate models of capillary beds can be homogenized into a porous medium [32]. This
326 method is combined here with a vessel occlusion algorithm to simulate the effect of micro-emboli
327 entering the capillary bed. The decrease in permeability as a function of the vessel fraction lost, surface

328 area fraction lost, and volume fraction lost are all quantified. This allows for the scaling up of partially
329 occluded capillary networks to large regions of tissue.

330 Details of the blood flow simulation and homogenization of the capillary bed can be found in El-Bouri
331 & Payne [32]. In brief, Poiseuille flow is assumed through the capillary vessels, with the capillary
332 network being periodic. A pressure gradient is imposed in one direction and the permeability – the ratio
333 of the volume-averaged flow and the pressure gradient – is calculated. This is repeated for the 3
334 principal directions of the capillary network. The result is a 3x3 tensor, with 3 principal permeabilities
335 (the permeability in the direction of the pressure gradient) and 6 cross-permeabilities.

336 As the smallest measurable clot was 8.034 μm , and the average diameter of a capillary is $6.23 \pm 1.3 \mu\text{m}$
337 [40], the micro-emboli algorithm above could not be used on the networks as they would always occlude
338 the inlet vessel. As such, a random vessel was chosen in the network and this vessel was fully occluded,
339 with the permeability being recalculated after every occlusion. Three cube sizes were used to simulate
340 the micro-occlusions with lengths of 375, 500, and 625 μm . Normalised permeability changes are
341 calculated, and the effect of the micro-emboli on the capillary bed is quantified such that it can be used
342 in full-brain simulations. Constrained least squares optimization is used to fit a line of best fit with the
343 equation

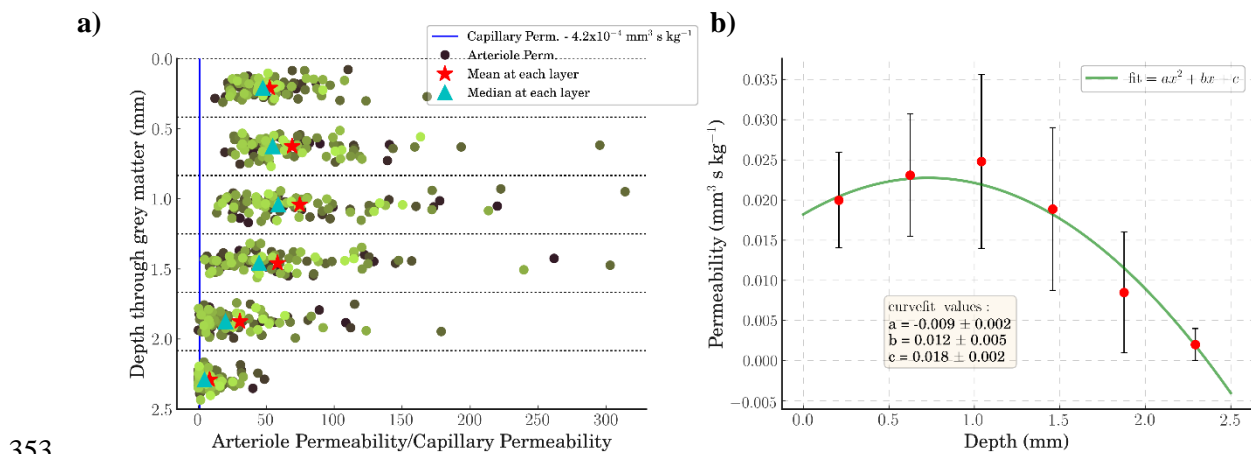
$$344 \quad P_f = 1 + Bx_i \quad (12)$$

345 where P_f is the permeability fraction, x_i is the change in either vessel fraction, volume fraction, or
346 surface area fraction of the networks, and B is the gradient. All parameters calculated for the capillary
347 bed are based on 500 statistically accurate capillary networks at each cube size (1500 total).

348 5 Results

349 5.1 Healthy blood flow in the penetrating arterioles

350 Blood flow was simulated in 100 statistically accurate voxels of the cerebral microvasculature. The
351 permeability and coupling coefficients were quantified for the penetrating arterioles in the ‘no-
352 occlusion’ scenario. The permeability results are shown in Fig 3.



353

354 **Fig 3. a) A scatter plot of the permeability of the 100 voxels at each of the 6 depth layers. The cyan**
355 **triangle indicates the median permeability of the capillary bed. The mean arteriolar permeability**
356 **is indicated with a red star at each layer. b) A quadratic line of best fit over the median**
357 **permeabilities at each layer – error bars are interquartile ranges**

358 The permeability increases with depth until the middle layers before dropping off towards the bottom
359 layers, as not all penetrating vessels penetrate the full depth of the grey matter (Fig 3a). The mean value
360 of the permeability across the layers is approximately 50 times the capillary permeability. At each layer
361 the average permeability ranges from around 30x at the top layer, to 75x in layer 3, to 9x at the bottom
362 layer. A quadratic curve fit is used to derive a function that models arteriolar permeability with depth,
363 such that it can be used in future porous model implementations (Fig 3b). The permeability distribution
364 at each layer can also be characterised as log-normal (Shapiro-Wilks test, $\alpha = 0.05$) up to and including
365 layer 4 (S1 Table).

366 The coupling coefficients demonstrate a similar drop from the top layers to the bottom layers, driven
367 by the fact that there are fewer terminal nodes at the bottom layers [33]. The variability in the coupling
368 coefficients from voxel-to-voxel is larger than the permeability variability (S1 Fig). The median values
369 of the coupling coefficients are 2.8×10^{-5} , 4.4×10^{-5} , 4.3×10^{-5} , 2.7×10^{-5} , 1.1×10^{-5} , and $4.3 \times 10^{-6} \text{ Pa}^{-1} \text{ s}^{-1}$
370 (from layers 1 – 6). A quadratic curve-fit is used to derive a function that models the coupling
371 coefficients with depth for future porous model implementations (S1 Fig). The coupling coefficient
372 distribution can be characterised as log-normal (Shapiro-Wilks test, $\alpha = 0.05$) up to and including layer
373 4 (S2 Table).

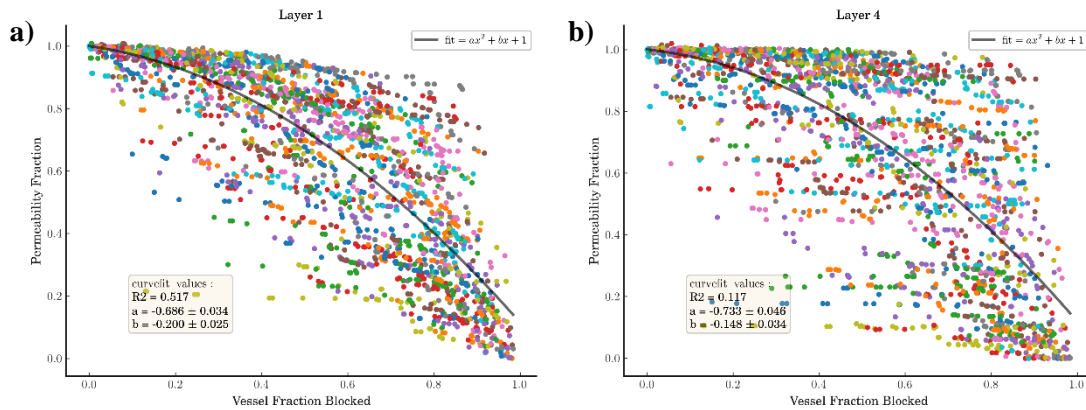
374 The above results parameterise the healthy penetrating vessels so they can be scaled up to large regions
375 of the brain. More importantly, however, these healthy results provide a baseline from which the effect
376 of micro-occlusions can be quantified.

377 **5.2 The arterioles are robust to micro-emboli at the population level**

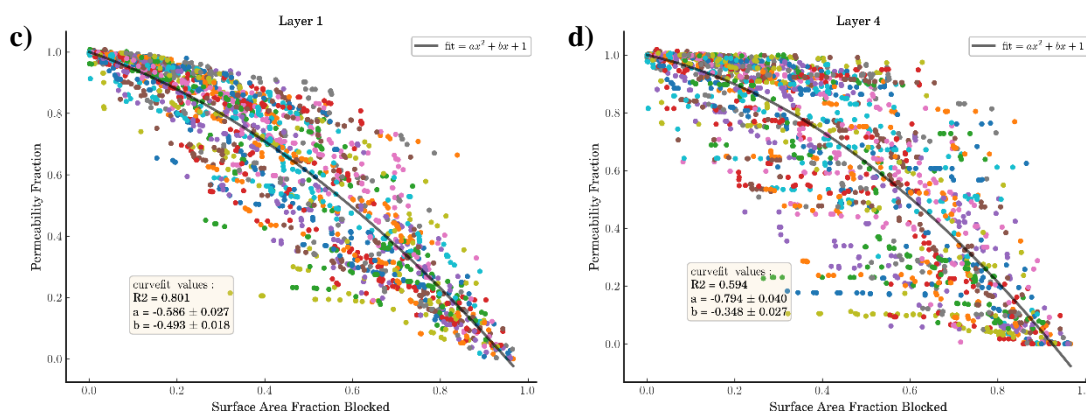
378 As there are 4 thrombectomy techniques used with 2 clot consistencies to give 8 different micro-emboli
379 distributions to choose from, a baseline must be chosen to conduct the following simulations. Here we
380 choose the ADAPT technique with a hard clot to present the following results. A comparison with other
381 techniques and clot consistencies can be found in Sections 5.4, 5.5.

382 The variable of interest here is the fractional drop in permeability. This is defined as the permeability
383 divided by the initial healthy permeability. We compare this independent variable against 3 dependent
384 variables – the fraction of vessels occluded, the fraction of vessel surface area occluded, and the fraction
385 of vessel volume occluded. The surface area and volume drops have been calculated as these geometric
386 parameters control oxygen transport in the microvasculature and can in future be used for validation.
387 Fig 4 shows these results for 2 different layers – the top-most grey matter layer, and the middle layer
388 (from 1.25 – 1.67 mm depth). An example of the permeability decrease against volume fraction decrease
389 in all 6 layers can be found in S2 Fig.

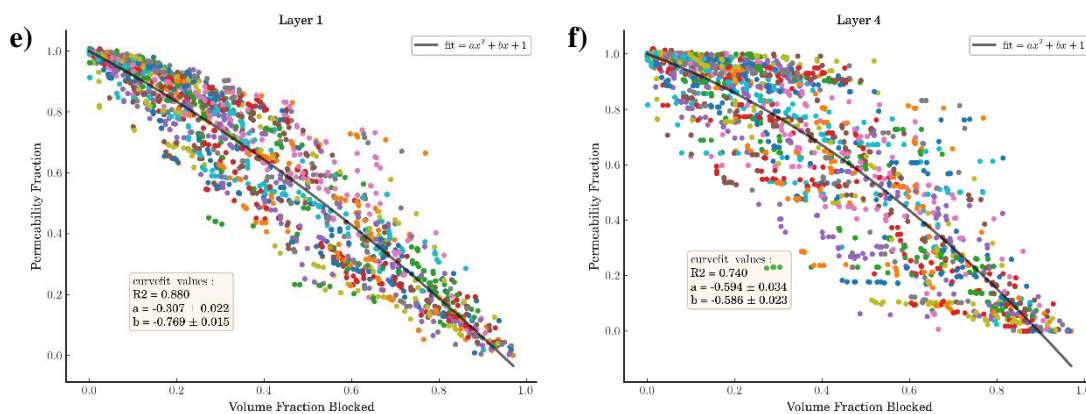
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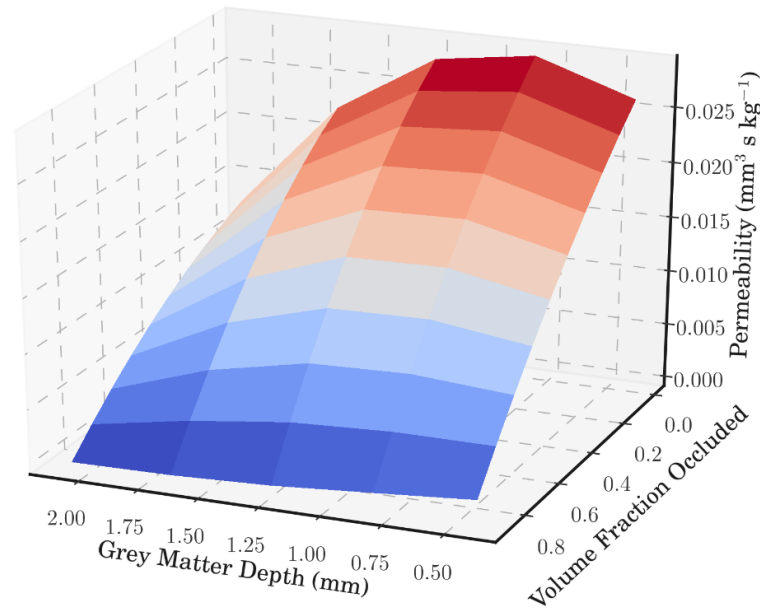
393 **Fig 4. a,b) The fractional drop in permeability against the fraction of vessels blocked where a) is**
 394 **in the top layer of the voxel and b) is the middle layer. c,d) The fractional drop in permeability**
 395 **against the fraction of vessel surface area blocked where c) is in the top layer of the voxel and d)**
 396 **is the middle layer. e,f) The fractional drop in permeability against the fraction of vessel volume**

397 **blocked where e) is in the top layer of the voxel and f) is the middle layer. The middle layer is at**
398 **a depth of 1.25 – 1.67mm. A line of best fit is plotted in black, with the fit equation in the top right**
399 **corner of each graph, with the bottom left of the graph giving the coefficients of the line of best**
400 **fit and the R^2 goodness-of-fit metric.**

401 The permeability is generally robust with vessel fraction blocked, up to around 50 % of the vessels
402 before the permeability starts to drop more rapidly. This can be explained by the fact that many small
403 vessels are occluded first – due to 98% of all emboli having a diameter of $< 20 \mu\text{m}$ for this configuration
404 of clot consistency and thrombectomy technique – which has a relatively small impact on the
405 permeability. On the other hand, the permeability drops almost linearly with volume fraction blocked
406 with a 1:1 ratio in the top layer.

407 Interestingly, in the middle layer for all 3 dependent variables, the permeability's robustness to
408 occlusions appears to improve over the first 40-50% of vessel/volume occlusions. As the vessels
409 continue to be occluded, however, the drop off in permeability is quicker than in the topmost layers.
410 The variability increases with depth until by the time the bottom two layers are reached, there is almost
411 a dichotomous choice between a permeability of 1 and 0 (S2 Fig). This is due to the sparse number of
412 vessels in the lower layers, leading to them being vulnerable to very few micro-emboli.

413 The permeability, and its drops with successive micro-emboli, can thus be characterised as a 2-
414 dimensional surface. The equation for the healthy permeability distribution with depth can be
415 multiplied, at each depth layer, by the respective permeability drop equation for that depth layer. An
416 example of a 2-dimensional surface generated with volume fraction as the dependent variable, ADAPT
417 as the thrombectomy technique, and a hard clot can be found in Fig 5 (calculated using the healthy
418 permeability equation from Fig 3b). These 2-dimensional functions can be calculated for all the
419 different possible combinations of thrombectomy, clot, and dependent variable. This provides a simple
420 look-up table to determine the change in permeability for a given technique, clot, depth, and fraction
421 occluded.



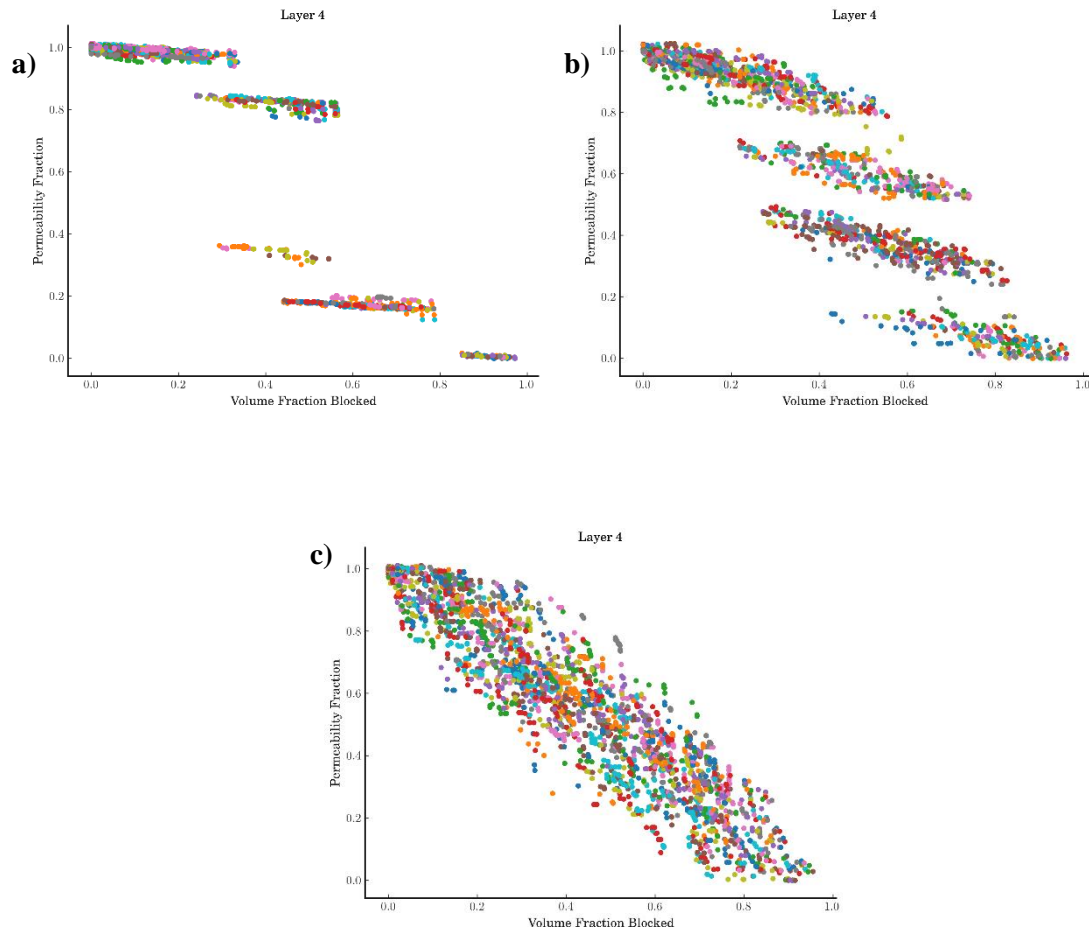
422

423 **Fig 5. A 2-dimensional surface plot for the ADAPT thrombectomy technique removing a hard**
424 **clot. The permeability is plotted against voxel depth and volume fraction of the vessels occluded.**

425 The coupling coefficients also display non-linear behaviour with micro-emboli occlusions, but this
426 behaviour is far more variable than the permeability results. This is due to blood being rerouted as
427 occlusions occur, leading to coupling coefficients increasing as well as decreasing from the baseline.
428 As well as this, the coupling coefficients are also dependent on the pressure in the capillary beds and
429 terminal arterioles (Eq (10)). An example of the change in coupling coefficients with depth and volume
430 occlusions can be found in S3 Fig.

431 **5.3 The microvascular geometry dictates robustness to micro-emboli smaller than the** 432 **penetrating vessel inlet diameter**

433 To investigate the role of the microvasculature on robustness to micro-emboli, 3 voxels were chosen
434 from our 100 voxels. Each voxel had 100 micro-emboli simulations with each simulation having a
435 different clot distribution sampled. Fig 6 shows the changes of permeability for these 3 voxels for the
436 middle-layer. As can be seen, it appears that the microvascular topology dictates the response to micro-
437 emboli, with clear banded regions with non-linear jumps for some voxels, whilst other voxels have an
438 almost linear drop with increasing occlusions.



439

440

441 **Fig 6. A comparison of the permeability drop against volume fraction occluded for 3 different**
442 **voxel geometries simulated with 100 different clot distributions (for the ADAPT technique, hard**
443 **clot) a) Voxel 1, b) Voxel 4, c) Voxel 31**

444 In comparison, we simulated 100 different voxels but with the same sampled clot distribution entering
445 each voxel (we fix the random seed sampling the clot distribution to be the same for each voxel). The
446 aim of this was to investigate the effect of the sampled clot distribution variability on perfusion
447 characteristics (similar to how we investigated the effect of microvascular variability in Fig 6). There
448 was little visual difference found for the 3 sampled clot distributions (S4 Fig). Similar behaviour is
449 also seen for the coupling coefficients, with linear drops in coupling coefficients seen for some voxels
450 (S5 Fig).

451 Quantifying the statistical differences between these distributions was complicated by the bivariate
452 nature of the distributions. As such, to provide a simple comparison, we use the correlation matrix
453 difference (CMD) to compare the covariances of each distribution against the baseline distribution
454 (Fig 4f). The CMD has a value of 0 when the covariance matrices are identical and a value of 1 when
455 they are orthogonal. When comparing the 3 constant microvascular simulations the range of the CMD
456 was 1×10^{-4} to 2.85×10^{-3} . For the constant clot simulations, the range was 7×10^{-6} to 3×10^{-4} indicating
457 that variability and robustness to micro-emboli is dominated by the microvascular geometry.

458 **5.4 Hard clot micro-emboli lead to larger drops in permeability**

459 The above analysis has all been conducted using ‘hard’ clot fragmentation data. We now simulate ‘soft’
460 clot fragmentation and the effect of these micro-emboli on flow characteristics. We are interested to
461 observe whether clot consistency impacts downstream flow post-thrombectomy.

462 Visually, there is no discernible difference for the relationship between permeability and the dependent
463 variable on the population level, but certain voxels display changes in their permeability relationship
464 (S6 Fig). Comparing individual microvascular geometries in both hard and soft clot simulations, the
465 CMD score ranges between 3×10^{-4} and 7×10^{-3} , indicating a similar variability to that found between
466 voxel comparisons. The results are similar for the coupling coefficients.

467 Regardless of whether there was a visual difference or not, all voxels with soft clot simulations required
468 on average twice as many occluding clots to develop the same drops in perfusion as for the hard clots.
469 As well as this, around 4.5% of the clots sampled from the hard clot distributions went into occluding
470 penetrating vessels (the rest passed through the arterioles into the capillary bed). For the soft clots, this
471 was only 2.5% (Table 1). Clearly, for a given number of micro-emboli the smaller clot fragments of the
472 soft clot lead to smaller drops in permeability.

473 **Table 1. Summary of the differences between thrombectomy technique and clot consistency when**
474 **considering total micro-emboli sampled and those micro-emboli that occlude vessels. The values**

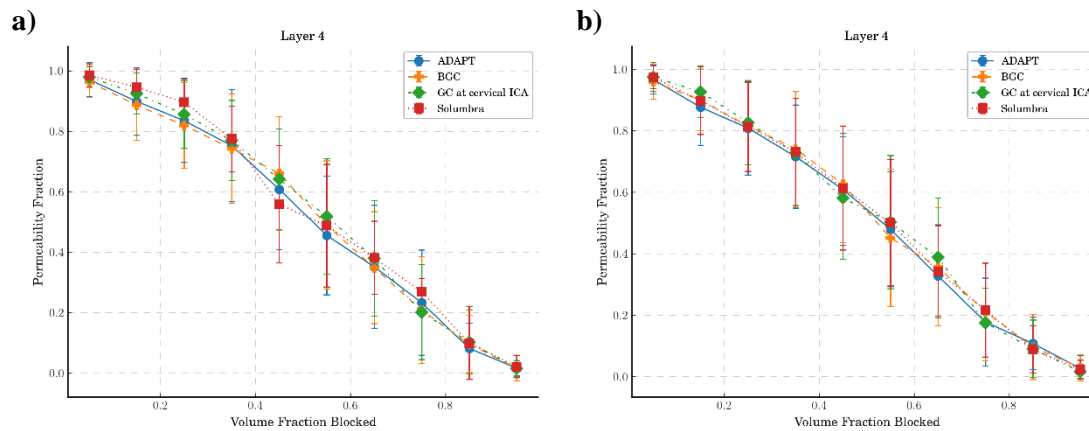
475 are averaged over the 100 voxel simulations. The percentage of sampled clots occluding vessels is
 476 the average of the 100 individual percentages.

<i>Thrombectomy Technique</i>	<i>Clot Consistency</i>	Average number micro-emboli sampled	Average number micro-emboli occluding vessels	Percentage of sampled clots occluding vessels (%)
<i>ADAPT</i>	<i>Hard</i>	616.1	24.3	4.5
<i>ADAPT</i>	<i>Soft</i>	2704	48.1	2.5
<i>BGC</i>	<i>Hard</i>	208.5	25.8	14.0
<i>BGC</i>	<i>Soft</i>	994	26.4	3.0
<i>GC at cervical ICA</i>	<i>Hard</i>	1152.7	29.0	2.9
<i>GC at cervical ICA</i>	<i>Soft</i>	1146.6	22.9	2.3
<i>Solumbra</i>	<i>Hard</i>	76.4	18.6	26.3
<i>Solumbra</i>	<i>Soft</i>	1720.2	36.3	2.6

477 **5.5 Thrombectomy technique has a large impact on clot fragmentation and downstream**
 478 **flow characteristics**

479 The last variable of interest here is the thrombectomy technique. In the in-vitro experiments, 4
 480 techniques were used; these are abbreviated as ADAPT, BGC, GC at cervical ICA, and Solumbra [20].
 481 The emboli distributions from these 4 techniques used on hard and soft clots were used to simulate

482 occlusions in the penetrating vessels. The results are shown in Fig 7 where the scatter plots have been
483 binned into deciles with mean and standard deviation for ease of viewing.



484

485 **Fig 7. Comparison of the permeability drops against volume fraction blocked in the middle layer**
486 **for 4 different thrombectomy techniques: a) removing hard clots and b) removing soft clots**

487 Despite there being little visual difference between the 4 techniques, when analysing the numbers of
488 clots required to reach similar drops in permeability, large differences emerge (summarised in Table 1).

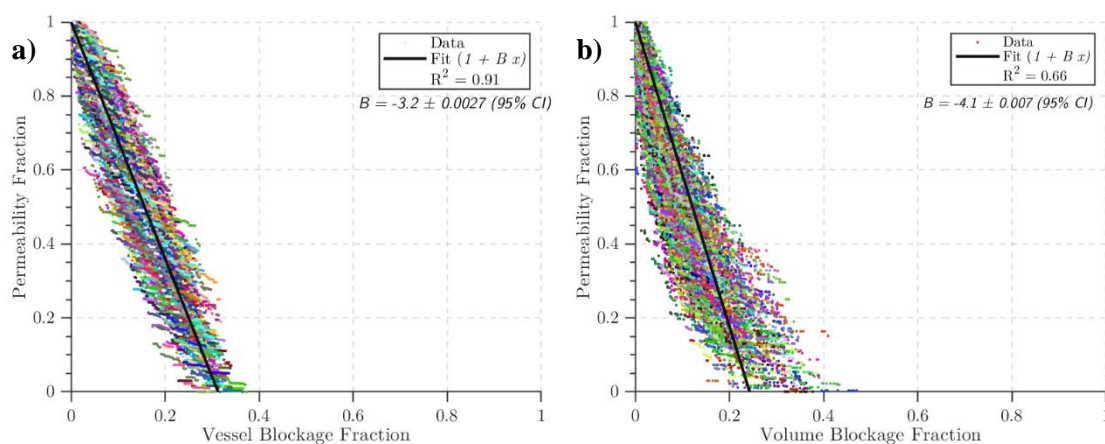
489 We measured: the average number of micro-emboli sampled in total to fully occlude the voxel (column
490 3 of Table 1); the average number of these micro-emboli that occlude a penetrating vessel (column 4 of
491 Table 1); and hence the percentage of sampled clots that occluded the penetrating vessels (column 5 of
492 Table 1). Simulating the Solumbra technique on a hard clot resulted in the fewest clots required to fully
493 occlude the voxel; on average over the 100 voxels 18.6 clots (and hence 26% of sampled clots) sent
494 through the penetrating vessels were required to fully occlude the voxel. The BGC technique had the
495 next fewest clots required with 26 clots and 14% of the sampled clots. The GC at cervical ICA
496 technique, on the other hand required 29 clots and 2.9% of the sampled clots.

497 In contrast, when using the soft clots, the numbers of clots required to achieve similar permeability
498 drops drastically increased – except for GC at cervical ICA which had similar results compared to when
499 using the hard clots. Both the Solumbra and ADAFT techniques saw a doubling of the clots required.

500 Clearly, there is a trade-off between the number of emboli that fragment off a clot, the size of these
501 emboli, and the impact they have on downstream flow. The BGC and Solumbra techniques were
502 previously reported to minimise the fragmentation of hard clots [20], but this also means that these clots
503 are larger and hence more prone to occlude larger vessels (as indicated by our large percentage of clots
504 that occlude vessels in the above results). On the other hand, the ADAPT and Solumbra techniques used
505 on soft clots lead to twice as many clots being required to occlude the penetrating vessels to achieve
506 similar drops in permeability.

507 **5.6 Occlusions in the capillary bed lead to large drops in permeability**

508 Finally, we simulated micro-emboli occluding capillary bed networks. These were simulated for 500
509 statistically accurate networks at 3 different cube length sizes (375 μm , 500 μm , and 625 μm). As the
510 results were not statistically different over the 3 sizes, only the 375 μm results are presented in Fig 8.
511 The permeability maintained its isotropy in the presence of micro-emboli hence it is presented here as
512 a scalar.



513

514 **Fig 8. The drops in permeability over 500 statistically accurate capillary networks with a cube**
515 **length of 375 μm . Lines of best fit are in black, with the gradient B in the top right corner of**
516 **each graph. a) The fractional drop in permeability with fraction of vessels occluded ($B = -3.2$),**
517 **b) the fractional drop in permeability with vessel volume occluded ($B = -4.1$).**

518 The permeability drop in the capillary bed was large in comparison to the drop in the penetrating vessels:
519 -8 % / % surface area lost, -3.2 % / % vessel blocked, and -4.1 % / % volume blocked (see Fig 8). This
520 is in line with a previous study where a -2.5 % drop in CBF/ % vessels blocked was found in simulations
521 of occlusions in mouse and human vascular networks, as well as mouse synthetic networks [13]. It
522 should be noted that the synthetic networks used in [13] had uniform diameter and length, unlike the
523 networks in this paper which have length and diameter distributions that match physiological
524 distributions.

525 Assuming a micro-emboli shower is spread evenly over the MCA territory (approx. 100 mL of tissue),
526 1.5% of this volume is capillary vessels, and a vessel density of 8000 vessels/mm³, around 120,000
527 micro-emboli would have to enter the capillary bed to cause a 4% drop in permeability (note that this
528 is an overestimate as micro-emboli are not likely to spread evenly over the brain tissue). Depending on
529 thrombectomy technique, the number of micro-emboli fragmenting off the clot can vary from a few
530 thousand to over 500,000 [20]. It therefore appears that if micro-emboli enter the capillary bed there is
531 significant potential for damage and large drops in perfusion.

532 **6 Discussion**

533 We return to the questions posed at the end of the introduction. First, can the changes in the blood flow
534 modelling parameters due to micro-emboli showers be accurately quantified such that they can be used
535 in the full organ models? Using a combination of in-vitro experiments of clot fragmentation and in-
536 silico blood flow modelling, we have developed simulations of micro-emboli occluding vessels in the
537 penetrating arterioles and capillary bed. Using these models we characterised ‘averaged’ flow
538 parameters, such as permeability and coupling coefficients, in healthy conditions and under micro-
539 emboli showers, for a range of thrombectomy techniques and clot consistencies. This now enables us
540 to simulate the impact of these micro-emboli showers – after a thrombectomy – on the downstream
541 tissue and its potential contribution to the ‘no-reperfusion’ phenomenon.

542 Second, what impact do thrombectomy technique and clot consistency have on downstream blood flow
543 post-thrombectomy? Clot consistency and thrombectomy techniques have been shown here to have a
544 large impact on the blood flow parameters. Whilst the relationship between permeability and volume
545 of vessel occluded was similar, the numbers of micro-emboli required were substantially different, with
546 soft clots on average requiring twice as many micro-emboli to reach similar drops in permeability. The
547 Solumbra and BGC techniques used on hard clots resulted in larger micro-emboli entering the
548 microvasculature, and hence fewer vessels needing to be occluded to reach large drops in permeability.
549 Therefore, whereas the Solumbra and BGC techniques result in fewer emboli fragmenting off the clot
550 [20], these emboli can cause more damage to the microvasculature due to their larger sizes.

551 In addition to this we investigated the impact of microvascular morphometry on blood flow parameters.
552 Microvascular morphometry determined the robustness of penetrating vessels to occlusions, not the
553 sampled micro-clot distribution. Therefore, if we can measure the microvasculature, even if only
554 indirectly, we can determine whether the microvasculature will be robust to a micro-emboli shower.
555 Characterising the microvasculature and its robustness, e.g. through the residue function [34], will be
556 the subject of future work.

557 Finally, we compared drops in permeability for the penetrating vessels and capillary bed. Whilst the
558 penetrating vessels had an approximately 1:1 relationship between volume lost and permeability drop,
559 the capillary bed lost 4% of permeability per 1% volume drop. This lack of robustness to occlusions in
560 the capillary bed is surprising but has previously been reported elsewhere with capillary stalling in
561 mouse capillary beds. In blood flow simulations, Cruz-Hernandez et al. found that for every 1% of
562 vessels stalled, the flow drops by 2.5% [13]. Our results indicate a 3.2% drop in permeability (a
563 surrogate for flow) for every 1% of vessels blocked, which show good agreement for early studies.
564 Permeability is a more robust metric than CBF here due to CBF being dependent on the volume of
565 tissue simulated. As well as this, Schmid et al. found that the severity of a micro-occlusion in the
566 capillary bed depends on the connectivity and original flow rate of the occluded vessel, with large
567 reductions in flow for specific types of connectivities [29]. As we found for the penetrating vessels,
568 morphometry of the microvasculature plays a large role in robustness to micro-occlusions.

569 The smallest micro-emboli sizes available from our experimental data were 8 μm . While this was
570 sufficient for micro-emboli occlusions in the penetrating vessels, we did not have information on
571 smaller micro-emboli that would occlude the capillary vessels. This meant we could not track emboli
572 through the capillary bed. In future, data on micro-emboli $< 8 \mu\text{m}$ in diameter would help in more
573 clearly understanding how micro-emboli affect the capillary bed. The diameters measured were the
574 Feret diameters of the micro-emboli, however we used these diameters to assume spherical micro-
575 emboli. It is therefore possible that our drops in permeability are over-estimated, as the clot could orient
576 along a smaller dimension and pass through the vessel.

577 It should be noted that a limitation of the analysis presented here is the separate treatment of the
578 penetrating arterioles and capillary bed. This was done for two reasons. Firstly, to provide a comparison
579 to previous studies, as discussed above. Primarily, however, this was done to fit into our full brain
580 modelling framework where the capillary bed and penetrating arterioles are treated as separate
581 compartments coupled together via coupling coefficients. The effects of extravasation of the micro-
582 emboli in the capillary bed have also been neglected, and these will likely result in restoration of flow
583 over several days [28]. This model is also purely passive, with no hyperaemia or regulation of vascular
584 tone, which likely impact passage of micro-emboli through the microvasculature.

585 The final question posed was: To what extent is clot fragmentation responsible for the post-
586 thrombectomy no-reflow phenomenon? We only analysed the impact of micro-emboli in voxels, or
587 cortical columns of microvasculature. In order to fully understand the impact of micro-emboli on the
588 vasculature, a full brain simulation is required. In future, we will use the work developed here to
589 simulate micro-emboli showers in a full-brain in-silico simulation of thrombectomy. Blood flow
590 parameters in the full-brain model will be updated using the parameters derived here, and the impact of
591 micro-emboli in a region of the brain can be compared and validated against CT perfusion and MR
592 scans of patients pre- and post-thrombectomy. Furthermore, we will investigate further the impact of
593 microvascular morphometry on blood flow drops and how this can potentially be used to infer patient
594 robustness to micro-emboli.

595 **7 References**

- 596 1. Owens Johnson C, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national
597 burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. 2019;
598 doi:10.1016/S1474-4422(19)30034-1
- 599 2. Saver JL. Time is brain - Quantified [Internet]. Stroke. Lippincott Williams & Wilkins; 2006. pp. 263–
600 266. doi:10.1161/01.STR.0000196957.55928.ab
- 601 3. Fransen PSS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, et al. Time to
602 Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA
603 Neurol. United States; 2016;73: 190–196. doi:10.1001/jamaneurol.2015.3886
- 604 4. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A Randomized
605 Trial of Intraarterial Treatment for Acute Ischemic Stroke. N Engl J Med. Massachusetts Medical Society;
606 2014;372: 11–20. doi:10.1056/NEJMoa1411587
- 607 5. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8
608 Hours after Symptom Onset in Ischemic Stroke. N Engl J Med. Massachusetts Medical Society;
609 2015;372: 2296–2306. doi:10.1056/NEJMoa1503780
- 610 6. Behme D, Tsogkas I, Colla R, Gera RG, Schregel K, Hesse AC, et al. Validation of the extended
611 thrombolysis in cerebral infarction score in a real world cohort. PLoS One. Public Library of Science;
612 2019;14. doi:10.1371/journal.pone.0210334
- 613 7. Ames A 3rd, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia. II. The no-reflow
614 phenomenon. Am J Pathol. 1968;52: 437–453.
- 615 8. Molina CA. Reperfusion Therapies for Acute Ischemic Stroke: Current Pharmacological and Mechanical
616 Approaches. Stroke. 2011;42: S16–S19. doi:10.1161/STROKEAHA.110.598763
- 617 9. Kurre W, Vorlaender K, Aguilar-Perez M, Schmid E, Bätze H, Henkes H. Frequency and relevance of
618 anterior cerebral artery embolism caused by mechanical thrombectomy of middle cerebral artery
619 occlusion. Am J Neuroradiol. American Journal of Neuroradiology; 2013;34: 1606–1611.

620 doi:10.3174/ajnr.A3462

621 10. Kloner RA, King KS, Harrington MG. No-reflow phenomenon in the heart and brain. *Am J Physiol Hear*
622 *Circ Physiol.* 2018;315: 550–562. doi:10.1152/ajpheart.00183.2018.-The

623 11. Bai J, Lyden PD. Revisiting cerebral postischemic reperfusion injury: New insights in understanding
624 reperfusion failure, hemorrhage, and edema. *International Journal of Stroke.* Blackwell Publishing Ltd;
625 2015. pp. 143–152. doi:10.1111/ijvs.12434

626 12. Mohamed Mokhtarudin MJ, Payne SJ. Mathematical model of the effect of ischemia-reperfusion on brain
627 capillary collapse and tissue swelling. *Math Biosci.* Elsevier Inc.; 2015;263: 111–120.
628 doi:10.1016/j.mbs.2015.02.011

629 13. Cruz Hernández JC, Bracko O, Kersbergen CJ, Muse V, Haft-Javaherian M, Berg M, et al. Neutrophil
630 adhesion in brain capillaries reduces cortical blood flow and impairs memory function in Alzheimer’s
631 disease mouse models. *Nat Neurosci.* Nature Publishing Group; 2019;22: 413–420. doi:10.1038/s41593-
632 018-0329-4

633 14. Erdener ŞE, Tang J, Kılıç K, Postnov D, Giblin JT, Kura S, et al. Dynamic capillary stalls in reperfused
634 ischemic penumbra contribute to injury: A hyperacute role for neutrophils in persistent traffic jams. *J*
635 *Cereb Blood Flow Metab.* SAGE Publications Ltd STM; 2020; 0271678X20914179.
636 doi:10.1177/0271678X20914179

637 15. Ritter LS, Orozco JA, Coull BM, McDonagh PF. Leukocyte accumulation and hemodynamic changes in
638 the cerebral microcirculation during early reperfusion after stroke. *Stroke.* Lippincott Williams and
639 Wilkins; 2000;31: 1153–1161. doi:10.1161/01.STR.31.5.1153

640 16. Kloner RA. No-reflow phenomenon: maintaining vascular integrity. *J Cardiovasc Pharmacol Ther.* United
641 States; 2011;16: 244–250. doi:10.1177/1074248411405990

642 17. Granger DN, Kvietys PR. Reperfusion therapy—What’s with the obstructed, leaky and broken
643 capillaries? *Pathophysiology.* Elsevier B.V.; 2017. pp. 213–228. doi:10.1016/j.pathophys.2017.09.003

644 18. O’Farrell FM, Atwell D. A role for pericytes in coronary no-reflow. *Nature Reviews Cardiology.* Nature
645 Publishing Group; 2014. pp. 427–432. doi:10.1038/nrcardio.2014.58

- 646 19. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced
647 by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral
648 artery. *Nat Med.* Nature Publishing Group; 2009;15: 1031–1037. doi:10.1038/nm.2022
- 649 20. Chueh J-Y, Puri AS, Wakhloo AK, Gounis MJ. Risk of distal embolization with stent retriever
650 thrombectomy and ADAPT. *J Neurointerv Surg.* England; 2016;8: 197–202. doi:10.1136/neurintsurg-
651 2014-011491
- 652 21. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. New ischaemic brain lesions
653 on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International
654 Carotid Stenting Study (ICSS). *Lancet Neurol.* England; 2010;9: 353–362. doi:10.1016/S1474-
655 4422(10)70057-0
- 656 22. Konduri PR, Marquering HA, van Bavel EE, Hoekstra A, Majoie CBLM. In-Silico Trials for Treatment
657 of Acute Ischemic Stroke. *Front Neurol.* Frontiers Media S.A.; 2020;11: 558125.
658 doi:10.3389/fneur.2020.558125
- 659 23. van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, et al. Detection, risk factors,
660 and functional consequences of cerebral microinfarcts. *Lancet Neurol.* 2017;16: 730–740.
661 doi:10.1016/S1474-4422(17)30196-5
- 662 24. Chueh J-Y, Kühn AL, Puri AS, Wilson SD, Wakhloo AK, Gounis MJ. Reduction in Distal Emboli With
663 Proximal Flow Control During Mechanical Thrombectomy. *Stroke.* 2013;44: 1396–1401.
664 doi:10.1161/STROKEAHA.111.670463
- 665 25. Nishimura N, Schaffer CB, Friedman B, Lyden PD, Kleinfeld D. Penetrating arterioles are a bottleneck
666 in the perfusion of neocortex. *Proc Natl Acad Sci U S A.* National Academy of Sciences; 2007;104: 365–
667 370. doi:10.1073/pnas.0609551104
- 668 26. Schaffer CB, Friedman B, Nishimura N, Schroeder LF, Tsai PS, Ebner FF, et al. Two-Photon Imaging of
669 Cortical Surface Microvessels Reveals a Robust Redistribution in Blood Flow after Vascular Occlusion.
670 *PLOS Biol.* Public Library of Science; 2006;4: e22. Available:
671 <https://doi.org/10.1371/journal.pbio.0040022>

- 672 27. Shih AY, Blinder P, Tsai PS, Friedman B, Stanley G, Lyden PD, et al. The smallest stroke: Occlusion of
673 one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci*. *Nat Neurosci*; 2013;16:
674 55–63. doi:10.1038/nn.3278
- 675 28. Van Der Wijk AE, Lachkar N, De Vos J, Grootemaat AE, Van Der Wel NN, Hordijk PL, et al.
676 Extravasation of Microspheres in a Rat Model of Silent Brain Infarcts. *Stroke*. Lippincott Williams and
677 Wilkins; 2019;50: 1590–1594. doi:10.1161/STROKEAHA.119.024975
- 678 29. Schmid F, Conti G, Jenny P, Weber B. The severity of microstrokes depends on local vascular topology
679 and baseline perfusion. *bioRxiv*. 2020; 2020.07.05.188565. doi:10.1101/2020.07.05.188565
- 680 30. Hodneland E, Hanson E, Sævareid O, Nævdal G, Lundervold A, Šoltészová V, et al. A new framework
681 for assessing subject-specific whole brain circulation and perfusion using mri-based measurements and a
682 multiscale continuous flow model. *PLoS Comput Biol*. Public Library of Science; 2019;15: e1007073.
683 doi:10.1371/journal.pcbi.1007073
- 684 31. Jozsa TI, Padmos RM, Samuels N, El-Bouri WK, Hoekstra AG, Payne SJ. A porous circulation model of
685 the human brain for in silico clinical trials in ischaemic stroke. *Interface Focus*. 2020;In Press.
- 686 32. El-Bouri WK, Payne SJ. Multi-scale homogenization of blood flow in 3-dimensional human cerebral
687 microvascular networks. *J Theor Biol*. 2015;380: 40–47. doi:http://dx.doi.org/10.1016/j.jtbi.2015.05.011
- 688 33. El-Bouri WK, Payne SJ. Investigating the effects of a penetrating vessel occlusion with a multi-scale
689 microvasculature model of the human cerebral cortex. *Neuroimage*. Academic Press; 2018;172: 94–106.
690 doi:10.1016/J.NEUROIMAGE.2018.01.049
- 691 34. Park CS, Payne SJ. A generalized mathematical framework for estimating the residue function for
692 arbitrary vascular networks. *Interface Focus*. Royal Society; 2013;3: 20120078.
693 doi:10.1098/rsfs.2012.0078
- 694 35. Linninger AA, Gould IG, Marinnan T, Hsu CY, Chojecki M, Alaraj A. Cerebral Microcirculation and
695 Oxygen Tension in the Human Secondary Cortex. *Ann Biomed Eng*. Springer US; 2013;41: 2264–2284.
696 doi:10.1007/s10439-013-0828-0
- 697 36. Lorthois S, Cassot F, Lauwers F. Simulation study of brain blood flow regulation by intra-cortical

- 698 arterioles in an anatomically accurate large human vascular network. Part II: flow variations induced by
699 global or localized modifications of arteriolar diameters. *Neuroimage*. United States; 2011;54: 2840–
700 2853. doi:10.1016/j.neuroimage.2010.10.040
- 701 37. Schmid F, Tsai PS, Kleinfeld D, Jenny P, Weber B. Depth-dependent flow and pressure characteristics in
702 cortical microvascular networks. *PLOS Comput Biol*. Public Library of Science; 2017;13: e1005392.
703 doi:10.1371/journal.pcbi.1005392
- 704 38. Gkontra P, El-Bouri WK, Norton K, Santos A, Popel AS, Payne SJ, et al. Dynamic Changes in
705 Microvascular Flow Conductivity and Perfusion After Myocardial Infarction Shown by Image-Based
706 Modeling. *J Am Heart Assoc*. 2019;8. doi:10.1161/JAHA.118.011058
- 707 39. El-Bouri WK, Payne SJ. A statistical model of the penetrating arterioles and venules in the human cerebral
708 cortex. *Microcirculation*. 2016;23: 580–590. doi:10.1111/micc.12318
- 709 40. Cassot F, Lauwers F, Fouard C, Prohaska S, Lauwers-Cances V. A novel three-dimensional computer-
710 assisted method for a quantitative study of microvascular networks of the human cerebral cortex.
711 *Microcirculation*. 2006/01/06. 2006;13: 1–18. doi:10.1080/10739680500383407
- 712 41. Cassot F, Lauwers F, Lorthois S, Puwanarajah P, Cances-Lauwers V, Duvernoy H. Branching patterns
713 for arterioles and venules of the human cerebral cortex. *Brain Res*. 2009/12/17. 2010;1313: 62–78.
714 doi:10.1016/j.brainres.2009.12.007
- 715 42. Lauwers F, Cassot F, Lauwers-Cances V, Puwanarajah P, Duvernoy H. Morphometry of the human
716 cerebral cortex microcirculation: general characteristics and space-related profiles. *Neuroimage*.
717 2007/11/13. 2008;39: 936–948. doi:10.1016/j.neuroimage.2007.09.024
- 718 43. Cassot F, Lauwers F, Lorthois S, Puwanarajah P, Duvernoy H. Scaling laws for branching vessels of
719 human cerebral cortex. *Microcirculation*. 2009/03/21. 2009;16: 331–44, 2 p following 344.
720 doi:10.1080/10739680802662607
- 721 44. Chueh JY, Wakhloo AK, Gounis MJ. Neurovascular modeling: small-batch manufacturing of silicone
722 vascular replicas. *AJNR Am J Neuroradiol*. 2009;30: 1159–1164. doi:10.3174/ajnr.A1543
- 723 45. Chueh JY, Wakhloo AK, Hendricks GH, Silva CF, Weaver JP, Gounis MJ. Mechanical Characterization

- 724 of Thromboemboli in Acute Ischemic Stroke and Laboratory Embolus Analogs. *Am J Neuroradiol.*
725 2011;32: 1237 LP – 1244. doi:10.3174/ajnr.A2485
- 726 46. Pries AR, Secomb TW. Microvascular blood viscosity in vivo and the endothelial surface layer. *Am J*
727 *Physiol Circ Physiol.* 2005;289: H2657–H2664. doi:10.1152/ajpheart.00297.2005
- 728 47. Su SW, Catherall M, Payne S. The influence of network structure on the transport of blood in the human
729 cerebral microvasculature. *Microcirculation.* 2011/11/25. 2012;19: 175–187. doi:10.1111/j.1549-
730 8719.2011.00148.x
- 731 48. Shipley RJ, Chapman SJ. Multiscale Modelling of Fluid and Drug Transport in Vascular Tumours. *Bull*
732 *Math Biol.* Springer-Verlag; 2010;72: 1464–1491. doi:10.1007/s11538-010-9504-9
- 733 49. Peyrounette M, Davit Y, Quintard M, Lorthois S. Multiscale modelling of blood flow in cerebral
734 microcirculation: Details at capillary scale control accuracy at the level of the cortex. *PLoS One. Public*
735 *Library of Science;* 2018;13: e0189474. Available: <https://doi.org/10.1371/journal.pone.0189474>
- 736 50. Rohan E, Lukeš V, Jonášová A. Modeling of the contrast-enhanced perfusion test in liver based on the
737 multi-compartment flow in porous media. *J Math Biol.* 2018;77: 421–454. doi:10.1007/s00285-018-1209-
738 y
- 739 51. Risser L, Plouraboue F, Cloetens P, Fonta C. A 3D-investigation shows that angiogenesis in primate
740 cerebral cortex mainly occurs at capillary level. *Int J Dev Neurosci.* 2008/11/29. 2009;27: 185–196.
741 doi:10.1016/j.ijdevneu.2008.10.006
- 742 52. Tamaki K, Heistad DD. Response of cerebral arteries to sympathetic stimulation during acute
743 hypertension. *Hypertension.* 1986/10/01. 1986;8: 911–917.
- 744 53. Logg A, Mardal KA, Wells GN. Automated solution of differential equations by the finite element
745 method. *Lect Notes Comput Sci Eng.* 2012;84 LNCSE: 1–736. doi:10.1007/978-3-642-23099-8_1
- 746 54. Schmid F, Barrett MJP, Jenny P, Weber B. Vascular density and distribution in neocortex. *Neuroimage.*
747 2017; doi:<http://dx.doi.org/10.1016/j.neuroimage.2017.06.046>
- 748 55. Duvernoy HM, Delon S, Vannson JL. Cortical blood vessels of the human brain. *Brain Res Bull.* Elsevier;

749 1981;7: 519–579. doi:10.1016/0361-9230(81)90007-1

750 56. Hyde ER, Michler C, Lee J, Cookson AN, Chabiniok R, Nordsletten D a, et al. Parameterisation of multi-
751 scale continuum perfusion models from discrete vascular networks. *Med Biol Eng Comput.* 2013;51: 557–
752 70. doi:10.1007/s11517-012-1025-2

753 57. Herdin M, Czink N, Özcelik H, Bonek E. Correlation matrix distance, a meaningful measure for
754 evaluation of non-stationary MIMO channels. *IEEE Vehicular Technology Conference.* 2005. pp. 136–
755 140. doi:10.1109/vetecs.2005.1543265

756

757 **8 Supporting Information**

758 **S1 Table. The main statistics for the distribution of permeabilities in each layer of the healthy**
759 **voxels (for 100 voxels).** The first 4 layers can be approximated as log-normal. The p-value is the Mann-
760 Whitney U-test between adjacent layers to determine if adjacent layers have similar distributions of
761 permeability. For comparison, the capillary bed permeability is $4.28 \times 10^{-4} \text{ mm}^3 \text{ s kg}^{-1}$

762 **S2 Table. The main statistics for the distribution of coupling coefficients in each layer of the**
763 **healthy voxels (for 100 voxels).** The first 4 layers can be approximated as log-normal. The p-value is
764 the Mann-Whitney U-test between adjacent layers to determine if adjacent layers have similar
765 distributions of coupling coefficients.

766 **S1 Fig. a) A scatter plot of the coupling coefficients of the 100 voxels at each of the 6 depth layers.**
767 **The mean arteriolar coupling coefficient is indicated with a red star at each layer. b) A quadratic**
768 **line of best fit over the median coupling coefficients at each layer – error bars are interquartile**
769 **ranges**

770 **S2 Fig. a-f) The drop in permeability with respect to volume fraction blocked over the 6 layers,**
771 **starting with the top layer a) and ending at the bottom layer f).**

772 **S3 Fig. a-f) The change in coupling coefficients with respect to volume fraction blocked over the**
773 **6 layers, starting with the top layer a) and ending at the bottom layer f)**

774 **S4 Fig. Permeability drops for 3 different sampled clot distributions over 100 voxel geometries.**
775 **Results are shown for the middle layer in the voxels.**

776 **S5 Fig. A comparison of the coupling coefficient drop against volume fraction occluded for 3**
777 **different voxel geometries simulated with 100 different clot distributions (for the ADAPT**
778 **technique, hard clot) a) Voxel 1, b) Voxel 4, c) Voxel 31**

779 **S6 Fig. A comparison of the effect of hard and soft clots on permeability drops with respect to**
780 **volume fraction occluded a) Hard clot for all 100 voxels b) Soft clot for all 100 voxels, c) Hard**
781 **clot for Voxel 1 simulated with 100 clot distributions, d) Soft clot for Voxel 1 simulated with 100**
782 **clot distributions, e) Hard clot for Voxel 4 simulated with 100 clot distributions, f) Soft clot for**
783 **voxel 4 simulated with 100 clot distributions**