A novel multi-scale, multi-compartment model of oxygen transport: Towards *in-silico* clinical trials in the entire human brain

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Motivation

- Stroke is one of the leading causes of death and disability worldwide
- Ischaemic stroke accounts for 75% of all stroke
- 2/3 of the patients exhibit no-reperfusion after thrombectomy treatment
- Experimental stroke models
  - Fundamental differences: structural and functional organisations, vascular anatomy and immune system
  - Limited therapies translated into clinical treatments
- Computational stroke models

Aims

- INSIST project (*In-silico* trials for treatment of acute ischaemic stroke)
  - build an *in silico* environment for simulating and evaluating novel treatments (e.g. thrombectomy) for acute ischaemic stroke
- This project
  - develop statistically accurate multi-scale flow and oxygen models of the full human brain
  - incorporate active regulation of the microvasculature into full brain perfusion and oxygen models
  - blood flow aspect of this project is also presented in this conference by Tamas Jozsa in the morning Organ Modelling and Simulation session on the 25^{th} Sep.

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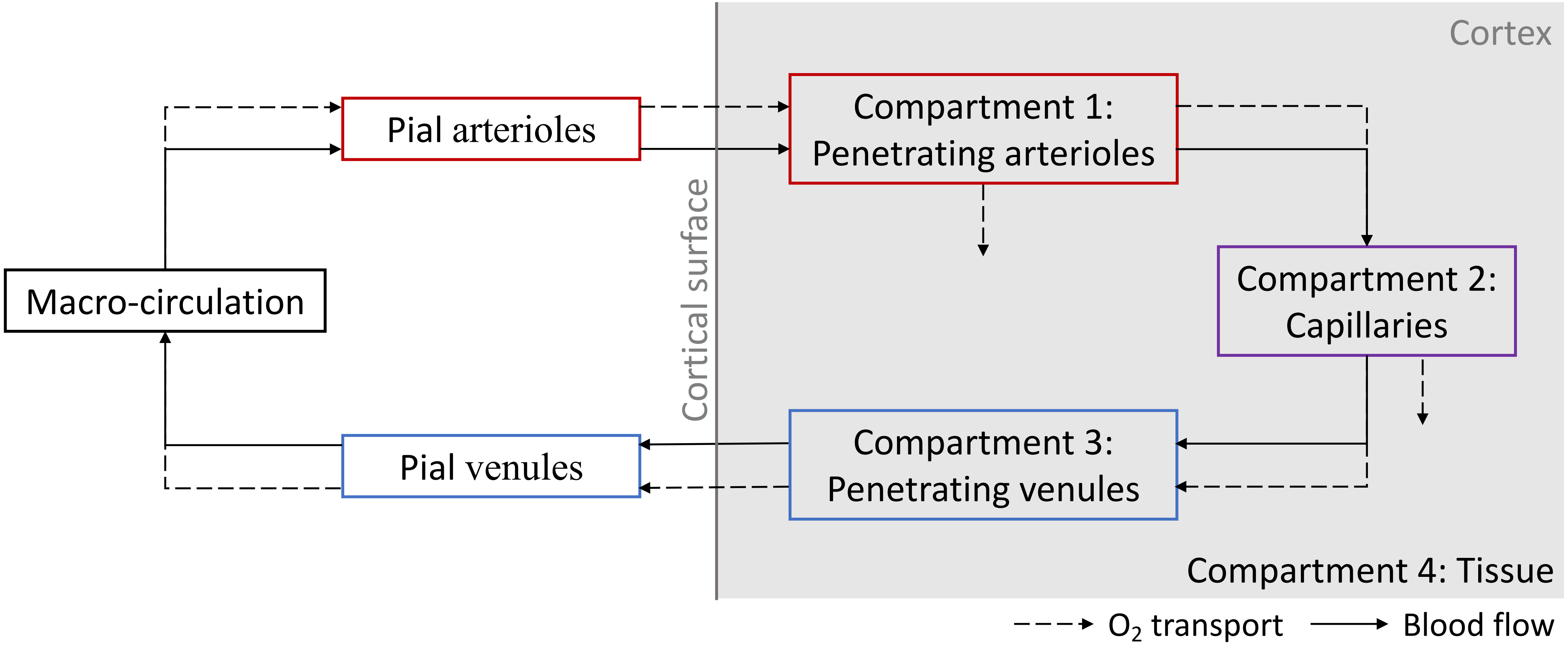
Overview



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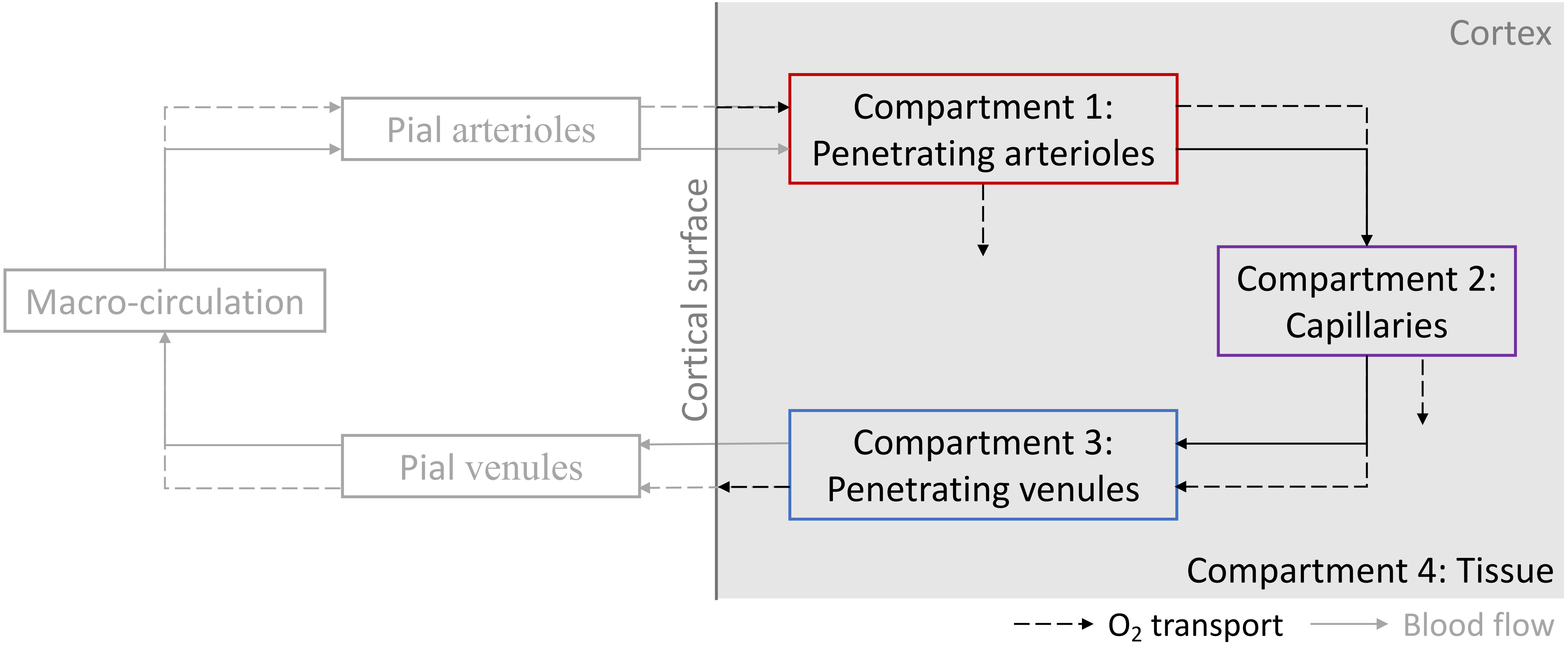
Overview



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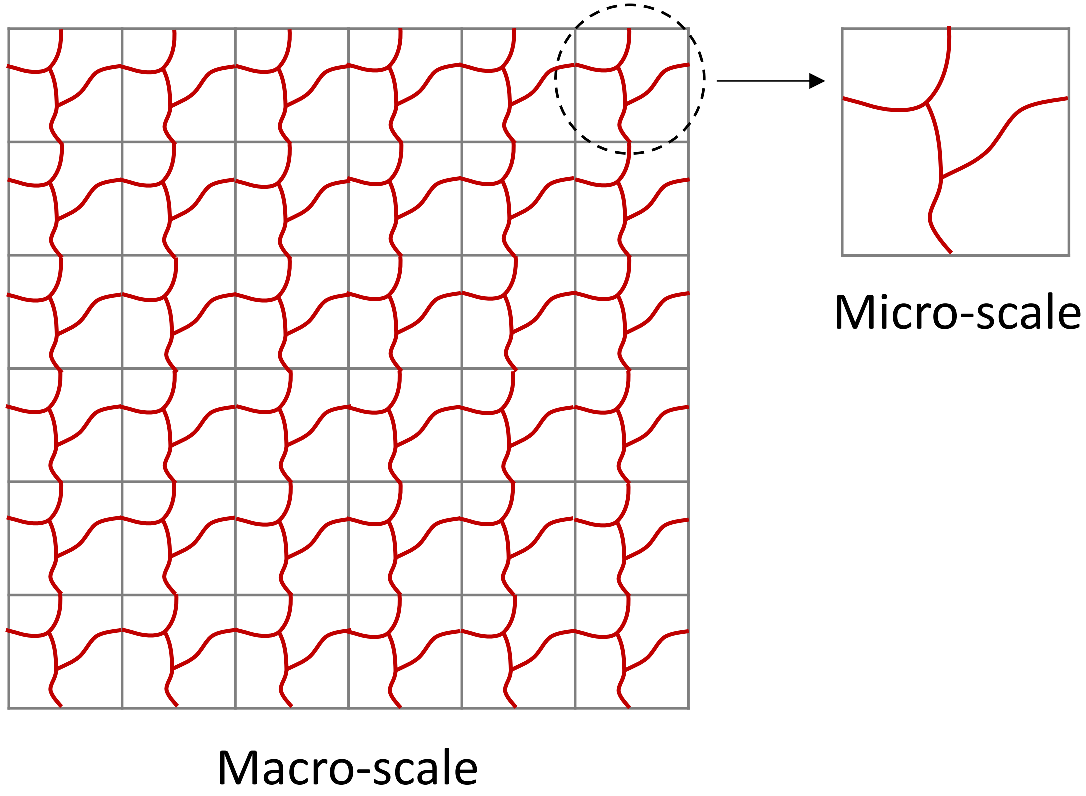
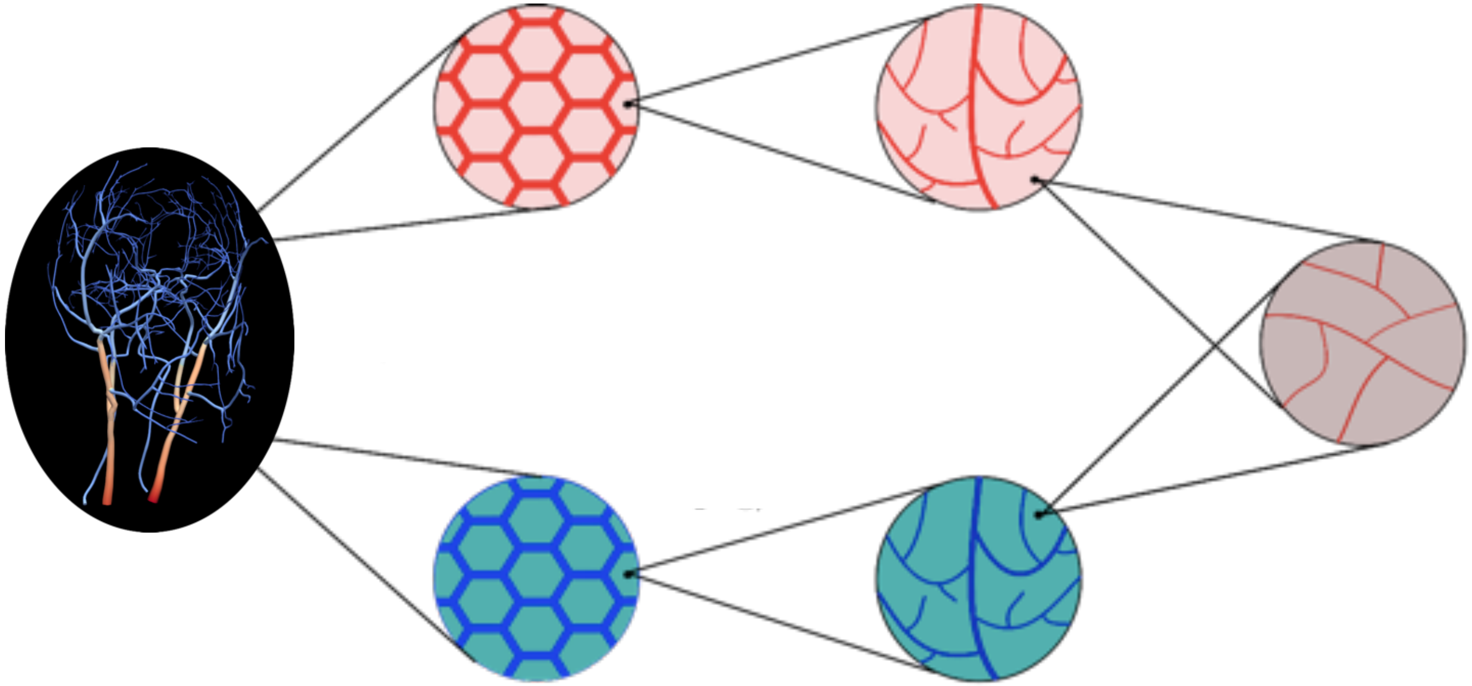
Homogenisation



- Homogenisation concerns finding the macro-scale properties of a material that has heterogeneities on the microscopic scale.
- Here, we extend the work of Shipley and Chapman[1] by reiterating the homogenisation procedure over multiple spatial scales.

[1] Shipley and Chapman (2010) Bull Math Biol

Homogenisation



Macro-scale Pial vessel scale Penetrating vessel scale Capillary scale

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El-Bouri and Payne (2015) J Theor Biol
El-Bouri and Payne (2018) NeuroImage

Coupled flow-oxygen model

- Arteriole $$\frac{\partial c_a^{(0)}}{\partial t} + \left(\langle \boldsymbol{u}_{\boldsymbol{a}}^{(0)} \rangle_{\boldsymbol{a}} \cdot \nabla_x c_a^{(0)}\right) = -\gamma_a \frac{S_a}{V_a}\left(c_a^{(0)} - c_t^{(0)}\right) - \beta_{ac}\left(p_a^{(0)} - p_c^{(0)}\right) c_a^{(0)}$$
- Capillary $$\frac{\partial c_c^{(0)}}{\partial t} + \left(\langle \boldsymbol{u}_c^{(\boldsymbol{0})} \rangle_c \cdot \nabla_x c_c^{(0)}\right) = \nabla_x \cdot \left[\underline{\boldsymbol{D}_{\boldsymbol{c}}^{\boldsymbol{dif}}} \nabla_x c_c^{(0)}\right] - \gamma_c \frac{S_c}{V_c}\left(c_c^{(0)} - c_t^{(0)}\right) + \beta_{ac}\left(p_a^{(0)} - p_c^{(0)}\right) c_a^{(0)} + \beta_{cv}\left(p_v^{(0)} - p_c^{(0)}\right) c_c^{(0)}$$
- Venule $$\frac{\partial c_v^{(0)}}{\partial t} + \left(\langle \boldsymbol{u}_{\boldsymbol{v}}^{(0)} \rangle_{\boldsymbol{v}} \cdot \nabla_x c_v^{(0)}\right) = \beta_{cv}\left(p_c^{(0)} - p_v^{(0)}\right) c_c^{(0)}$$
- Tissue $$\frac{\partial c_t^{(0)}}{\partial t} = \nabla_x \cdot \left[\underline{\boldsymbol{D}_{\boldsymbol{t}}^{\boldsymbol{dif}}} \nabla_x c_t^{(0)}\right] + \gamma_c \frac{S_c}{V_t}\left(c_c^{(0)} - c_t^{(0)}\right) + \gamma_a \frac{S_a}{V_t}\left(c_a^{(0)} - c_t^{(0)}\right) - \frac{M c_t}{c_{50} + c_t}$$

Coupled flow-oxygen model

- Arteriole
$$\frac{\partial c_a^{(0)}}{\partial t} + \left(\langle \boldsymbol{u}_a^{(0)} \rangle_a \cdot \nabla_x c_a^{(0)}\right) = -\gamma_a \frac{S_a}{V_a}\left(c_a^{(0)} - c_t^{(0)}\right) - \beta_{ac}\left(p_a^{(0)} - p_c^{(0)}\right) c_a^{(0)}$$

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- Venule
$$\frac{\partial c_v^{(0)}}{\partial t} + \left(\langle \boldsymbol{u}_v^{(0)} \rangle_v \cdot \nabla_x c_v^{(0)}\right) = \beta_{cv}\left(p_c^{(0)} - p_v^{(0)}\right) c_c^{(0)}$$

- Tissue
$$\frac{\partial c_t^{(0)}}{\partial t} = \nabla_x \cdot \left[\underline{\boldsymbol{D}_t^{dif}} \nabla_x c_t^{(0)}\right] + \gamma_c \frac{S_c}{V_t}\left(c_c^{(0)} - c_t^{(0)}\right) + \gamma_a \frac{S_a}{V_t}\left(c_a^{(0)} - c_t^{(0)}\right) - \frac{M c_t}{c_{50} + c_t}$$

Coupled flow-oxygen model

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Coupled flow-oxygen model

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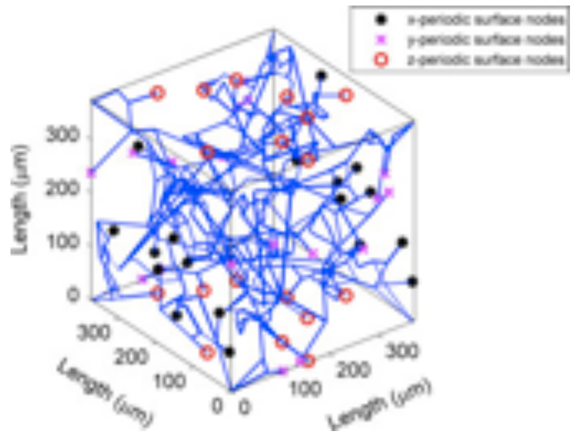
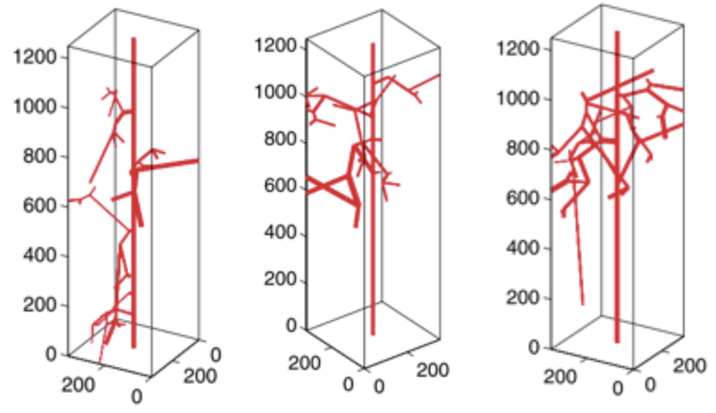
Parameter extraction

- We used statistically accurate microvascular models[1,2] to find the necessary parameters required by the equations.
- A range of different vasculature was selected randomly.
- Distribution of each parameter was obtained accounting for the variability of the physiological values.



Capillary network



Penetrating trees

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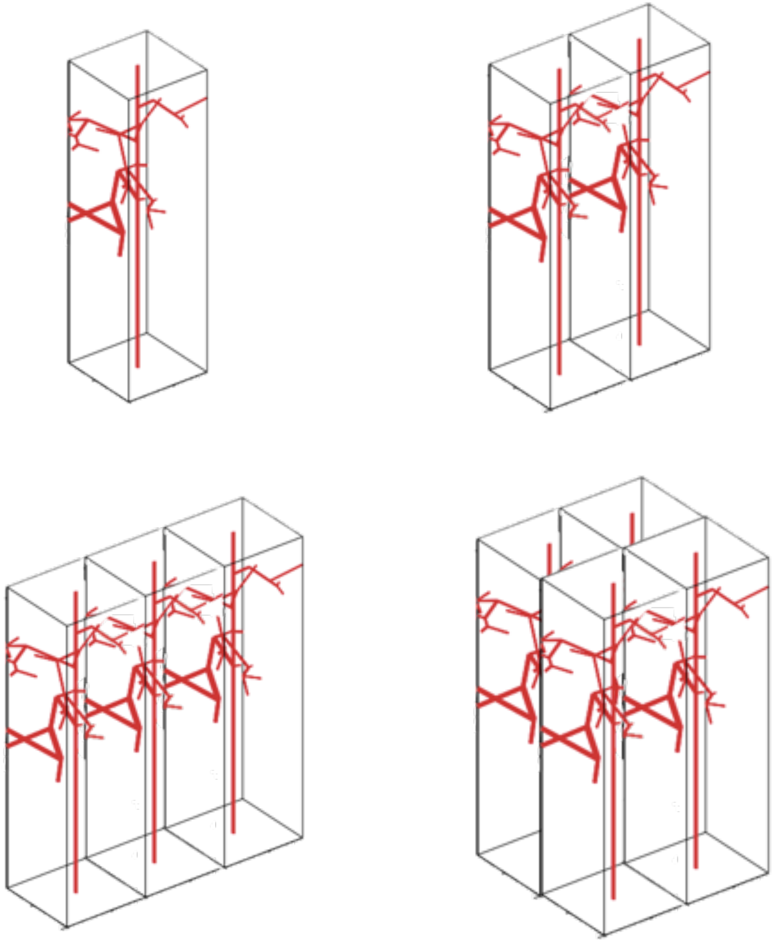
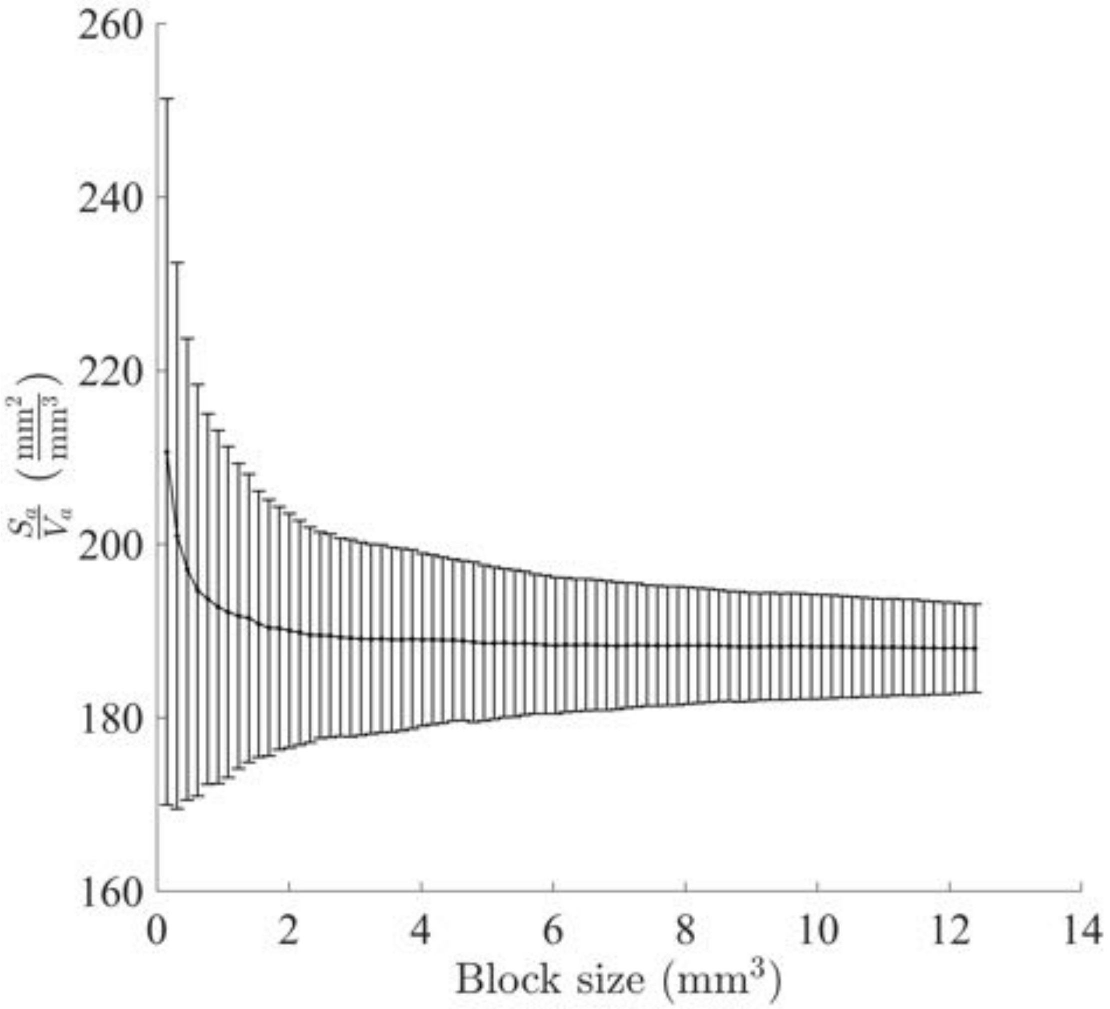
[1] El-Bouri and Payne (2015) J Theor Biol
[2] El-Bouri and Payne (2016) Microcirculation

Parameter extraction





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Parameter extraction

	$\frac{V_{vessel}}{V_{block}}\ (\%)$	$\frac{V_{vessel}}{S_{vessel}}\ (\mu m)$	$\frac{S_{vessel}}{V_{block}}\left(\frac{mm^2}{mm^3}\right)$	$\frac{S_{vessel}}{V_{vessel}}\left(\frac{mm^2}{mm^3}\right)$	$\frac{S_{vessel}}{V_{Tblock}}\left(\frac{mm^2}{mm^3}\right)$
Arteriole	1.814 ± 0.131	5.320 ± 0.168	3.406 ± 0.155	188.232 ± 6.179	3.526 ± 0.279
Capillary*	1.415	1.624	8.702	615.579	9.001

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* Capillary parameter logarithm values exhibit normal distribution; here we only report the natural mean values for easy comparison.

Parameter extraction

		$\frac{V_{vessel}}{V_{block}}$ (%)	$\frac{V_{vessel}}{S_{vessel}}$ (μm)	$\frac{S_{vessel}}{V_{block}}$ $\left(\frac{mm^2}{mm^3}\right)$
Literature	Cassot *et al.* (2006)	1.4[T]/2.44(1-4)	4.55	5.37
	Lauwers *et al.* (2008)	1.4-2[T]/2.69(2-4)	2.3	11.74
	Risser *et al.* (2009)	2.74	3.51	7.87
Sim	Capillary	1.415	1.624	8.702
	Capillary & arteriole	3.229	3.250*	6.372*

[T] values concerning only the capillaries (vessel diameter ≤ 10μm)

* calculated with arteriole accounting 44% of the volume and capillary accounting 56% of the volume (Risser *et al.,* Int J Devl Neuroscience, 2009)

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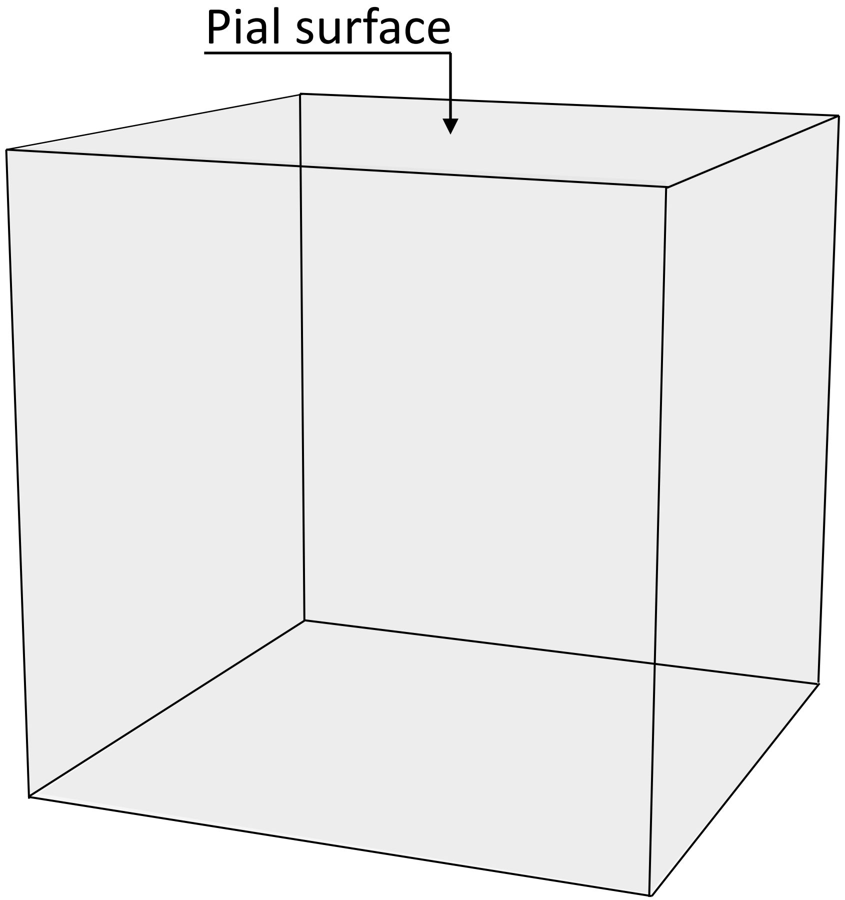
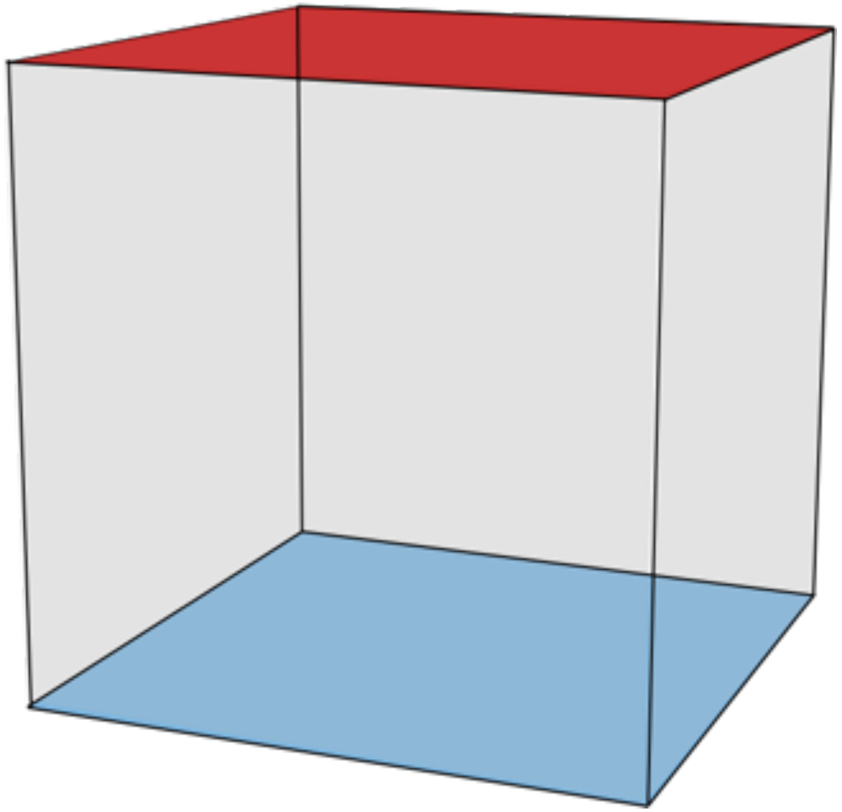
Simulation setup



- Model implemented for the grey matter on a unit cube through FEM using FEniCS[1]
- A polynomial based manufactured solution was used to test the implementation and find the optimum numerical setup
- Physiological values were then used to perform the simulation

[1] A. Logg and G. N. Wells (2010) ACM TOMS

Simulation setup



- Boundary conditions:
  - Arteriole compartment

Dirichlet BC

Homogenous Neumann BC

Periodic BC

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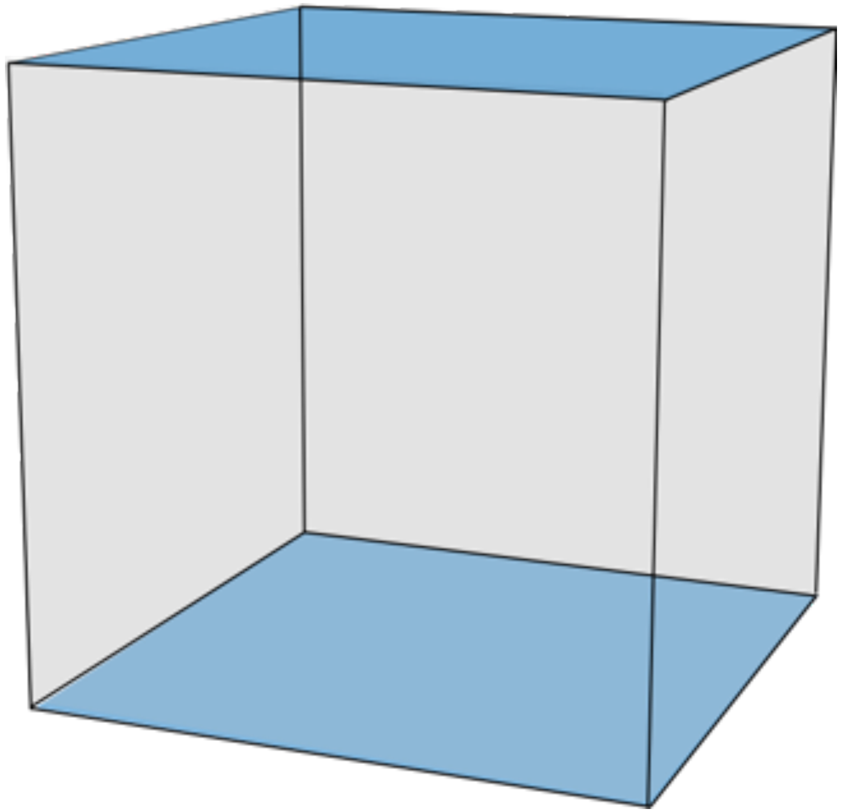
Simulation setup



- Boundary conditions:
  - Capillary, venule and tissue compartments

Homogenous Neumann BC

Periodic BC

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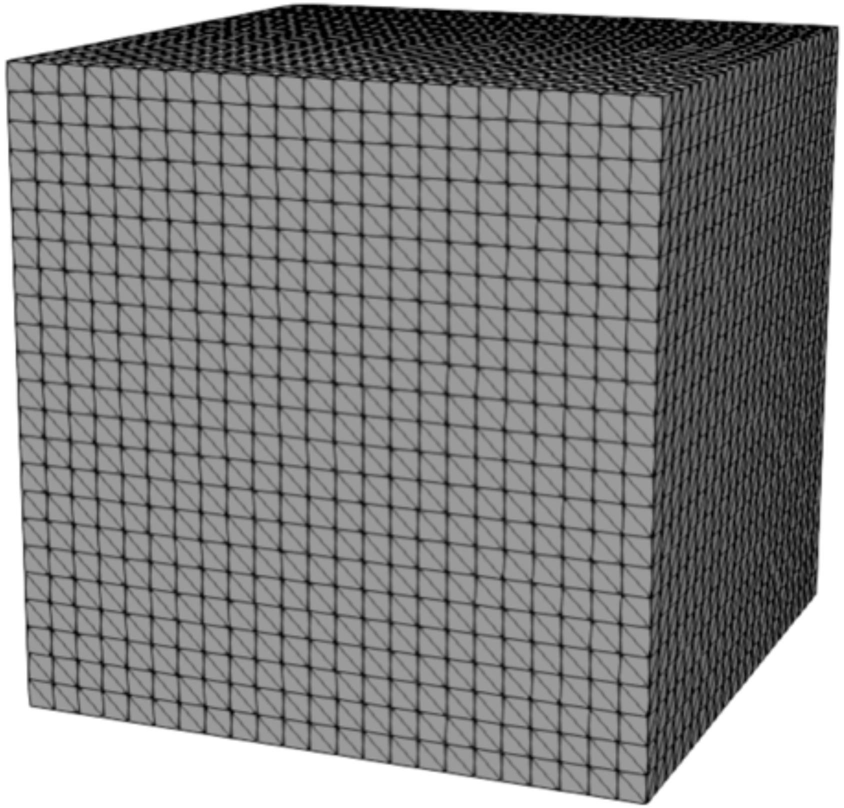
Manufactured solution



- Number of element: 73,002
- Element degree: 2
- Time discretisation: backward Euler
- Time step size: 0.2s
- Choice of solution:

$$\sin(t) + 16x^2 - 32x^3 + 16x^4 \\ + 16y^2 - 32y^3 + 16y^4 \\ + 16z^2 - 32z^3 + 16z^4$$

- Physical runtime: 2s
- Iterative solver

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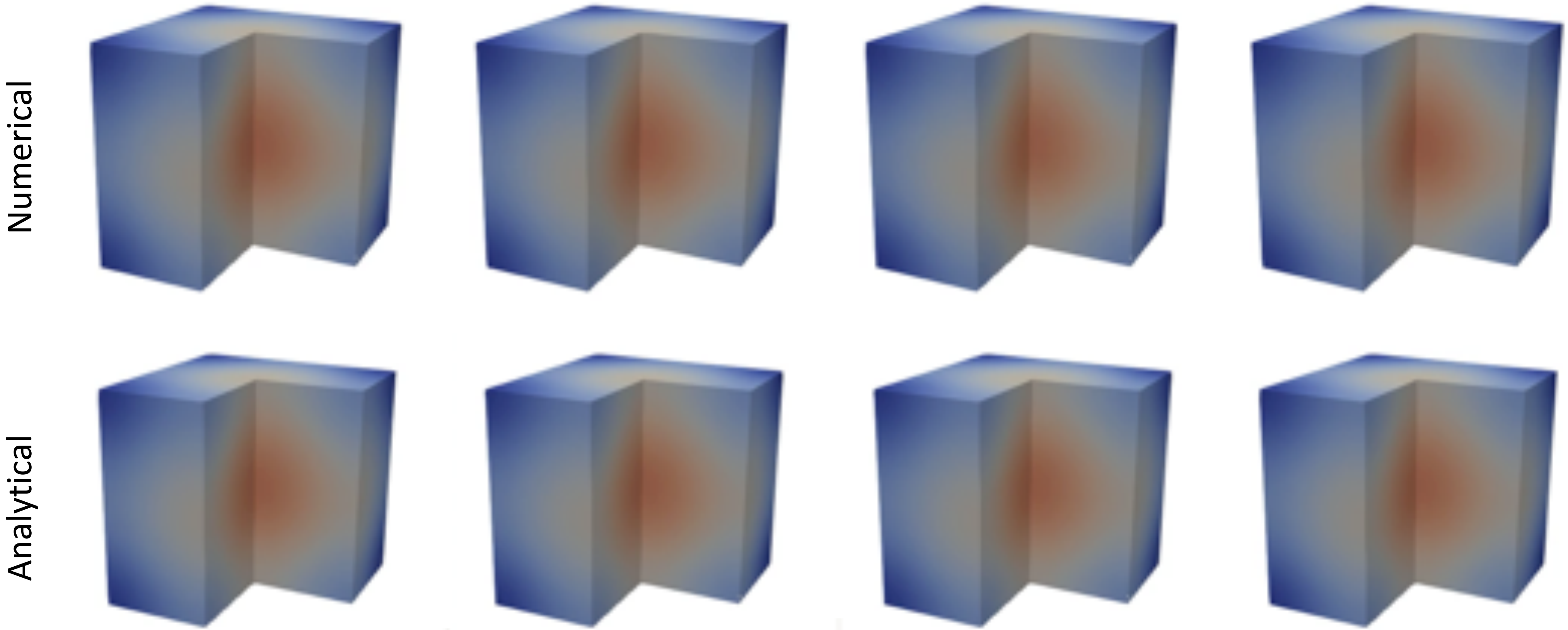
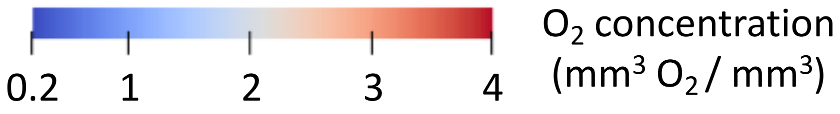
Manufactured solution

	Arteriole	Capillary	Venule	Tissue
	l^2=0.0198	l^2=0.0582	l^2=0.1617	l^2=0.0327





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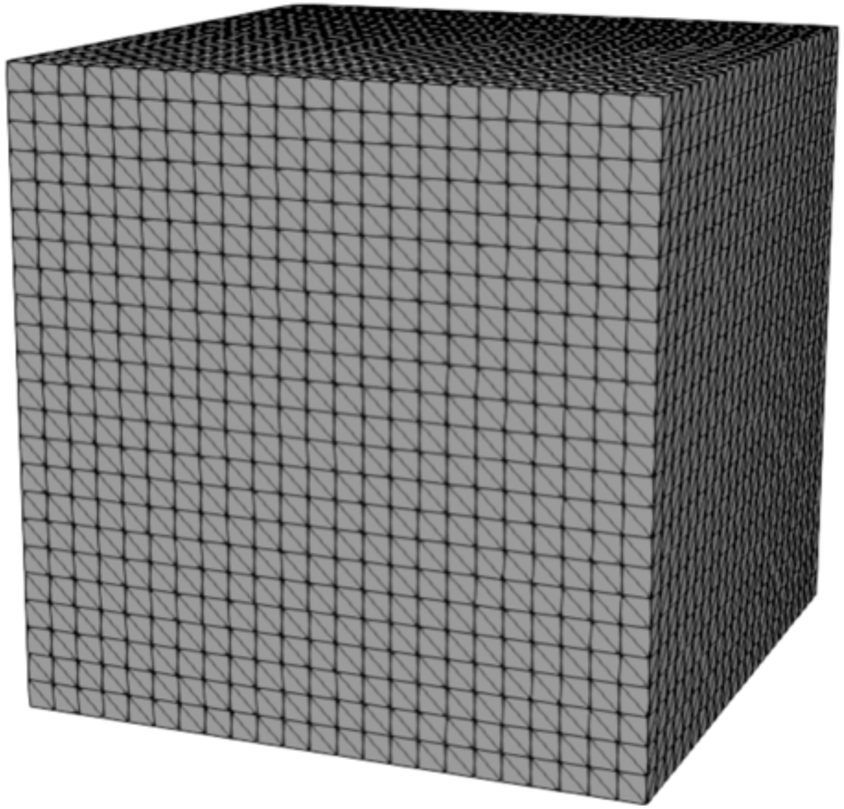
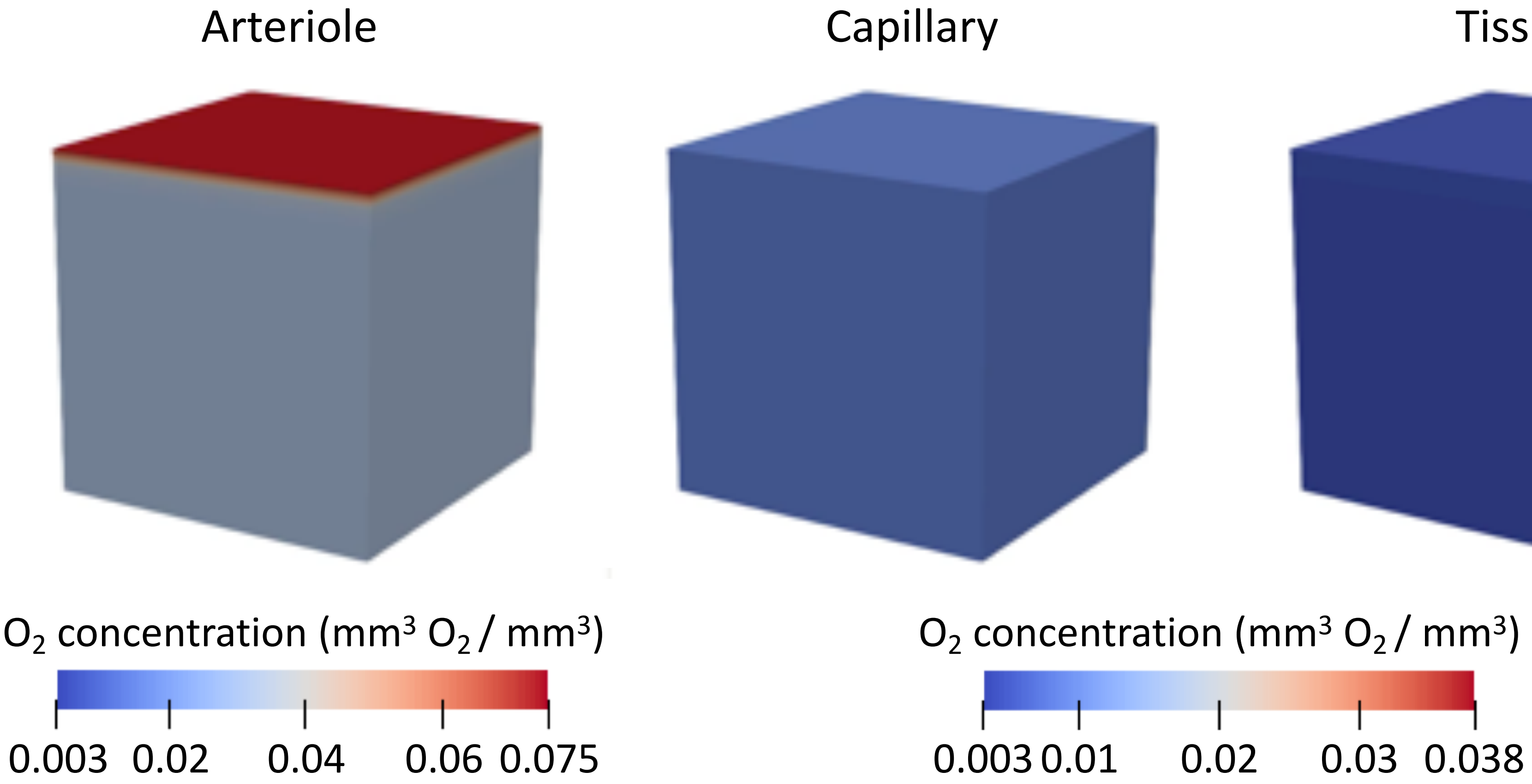
Preliminary result



- Number of element: 73,002
- Element degree: 1
- Time discretisation: backward Euler
- Time step size: 0.2s
- Physical runtime: 60s
- Direct solver

Preliminary result



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Continuation

- Parameter optimisation in both grey matter and white matter
- A patient specific brain model (geometry from Garcia-Gonzalez *et al.*[1])
- Model verification using data from MR CLEAN trial

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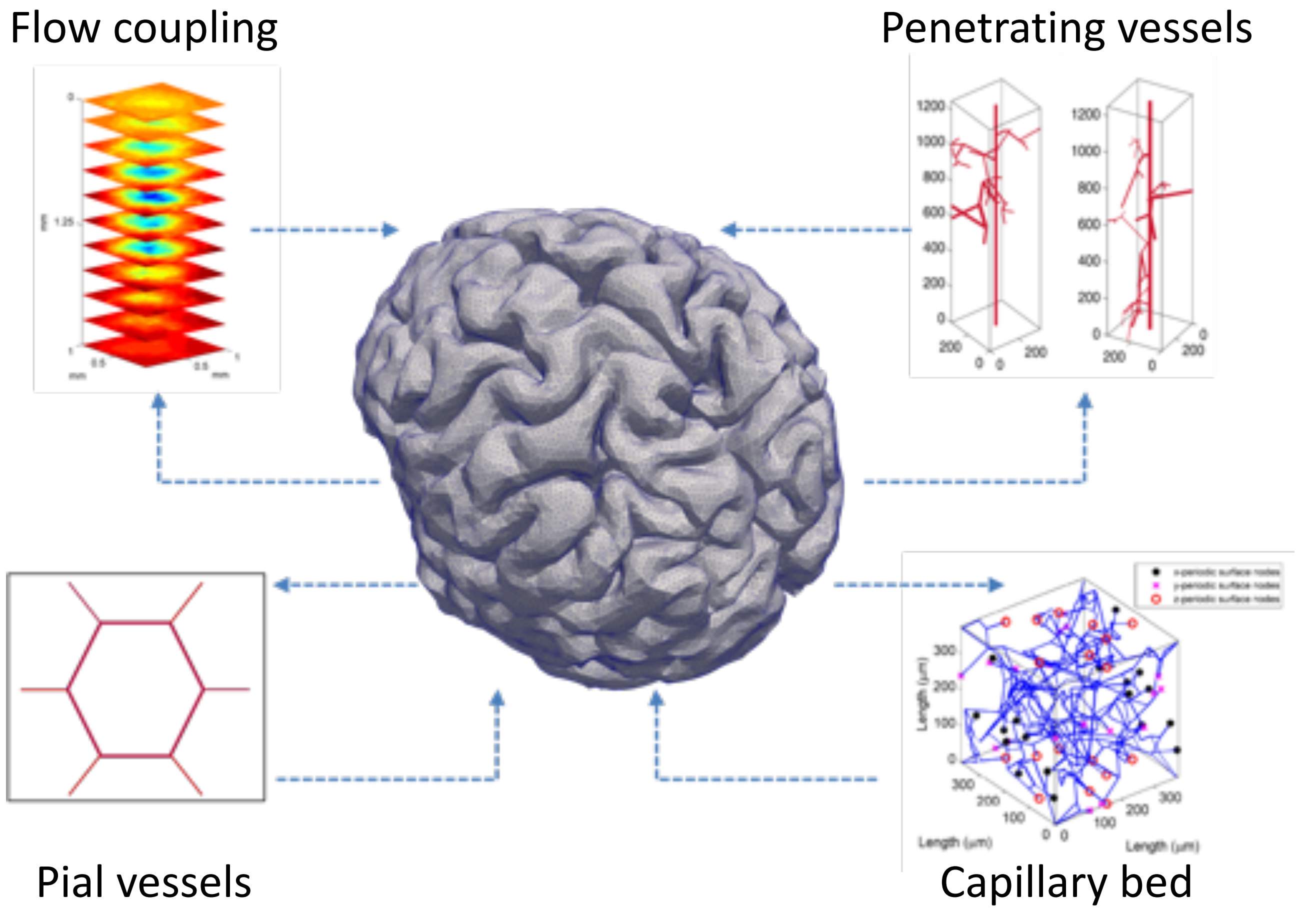
[1] Garcia-Gonzalez *et al.* (2017) J Mech Behav Biomed Mater

Conclusion

- Multi-scale, multi-compartment coupled flow-oxygen model
- Large scale parameters found through microscale models
- Manufactured solution and preliminary result on a cube
- Patient specific brain
- Active regulation within the brain



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