Future directions in stroke research: the Lattice-Boltzmann method as a modelling tool

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"When I meet God I will ask him two questions: Why relativity? And why turbulence?"

– Werner Heisenberg

1 Introduction

Over the last 300 years or so, Fluid Dynamics has become one of the largest and most firmly rooted branches of physics. The governing equations and conservation laws are well established and related phenomena are seen throughout everyday life. The theory is used extensively in applications as wide-ranging as aerodynamics, oceanography and oil piping, and there is an ongoing research effort – largely focussed on computational techniques – to tackle the Navier-Stokes equation.

A mathematical description of blood flow – *haemodynamics* – is perhaps the main biological application of fluid dynamical theory, and has attracted much attention over history[1]. Currently, there is a move toward interdisciplinary approaches where mathematical and computational modelling attempt to enhance medical knowledge and treatment of serious blood flow-related diseases.

This essay will focus on *stroke*, which is a major cause of death and paralysis in the developed world. I will outline a haemodynamical model based on the *Lattice-Boltzmann* method and suggest how the issue of vessel elasticity could be addressed within this framework. The modelling is focussed on the study of two causes of stroke: aneurysm and arteriovenous malformation (AVM).

2 Background

2.1 Brain Haemodynamics and Stroke

Arterial flow from the body is fed through the internal carotid and vertebral arteries into the *Circle of Willis*, which has a left-right symmetry and hence creates multiple routes for brain blood flow. Blood reaches different parts of the brain through networks of increasingly small vessels, is then drained into the venous system and returned to the heart deoxygenated. The role of blood in the brain is threefold: to provide the brain with a steady supply of oxygen and nutrients, and to remove cellular waste. Clearly, the brain – and consequently the body – is going to be in a very bad way without it.

Stroke is broadly characterised as the insult suffered when a section of the brain

[1] As an example: Jean Louis Marie Poiseuille (1799-1869) was interested in blood flow – he derived the parabolic velocity profile for laminar flow (that now bears his name) in application to this problem!

is deprived of blood. In the worst cases, stroke can cause death, coma or serious paralysis. This can arise in two general ways: 1. due to blockage of a blood vessel by a clot (*ischemic* stroke) or 2. due to bursting of a vessel (*haemorrhagic* stroke). Haemorrhagic stroke is less frequent, but generally more severe. The clotting processes that lead to ischemic stroke (atherosclerosis, thrombosis) will not be considered here. Two other causes of stroke – namely, aneurysm and AVM – are discussed in simple terms below. While these diseases are quite different, both are associated with vessel branch sites (or *bifurcations*) and require complex fluid-dynamical modelling.

2.1.1 Aneurysm

Since they occur predominantly at arterial bifurcations, blood flows at most sites of aneurysm formation are unsteady and turbulent. A simplistic interpretation for their formation (many details of which are unknown) is as follows. The flow incident on the junction applies a pressure which acts to distend the arterial wall. Over time, this can degenerate the internal elastic lamina, leading to a 'blowing out' of the vessel, and formation of the pathogenic structure (see figure 1). Most aneurysms are thought to develop to their full size over a short time; they then lie dormant and may or may not rupture in the future[2]. It is thought to be uncommon for an aneurysm to develop gradually (Dr. Neil Kitchen, personal communication).

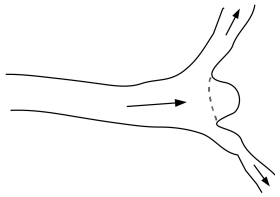


Figure 1: Formation of a typical aneurysm at a bifurcation. The dashed line shows the vessel wall before initiation and growth.

As might be expected intuitively, larger aneurysms are more likely to burst; when they do, the resulting *subarachnoid haemorrhage* (SAH) can have catastrophic results. Normal blood flow to the appropriate part of the brain is disrupted causing stroke, and the surrounding space fills with blood. This can also cause delayed *vasospasm*, which too can lead to necrosis and death. In around 70% of non-fatal SAHs, re-bleeding will occur in the next month or so (Dr Neil Kitchen, personal communication); surgery is a matter of urgency for the survivors.

A number of factors have been linked to aneurysm formation: these include

[2]side aneurysms can also occur on the outside wall of curved vessels, but these are less likely to rupture

smoking, drug use and, perhaps intuitively, arterial hypertension (high blood pressure). A large amount of work has also been concentrated on finding genetic links: for example, it is now well established that aneurysm is more likely in sufferers of Autosomal Dominant Polycystic Kidney Disease (which causes high blood pressure) [7].

2.1.2 AVMs

Arteriovenous malformation (AVM) is a congenital condition where the branching network between arterial and venous systems is locally tangled. The normal capillary network is replaced by a spaghetti-like jumble of channels which bypass their function of brain perfusion [11]. AVMs are characterised by higher-than-binary branching and offer lower cardiovascular resistance than normal capillary networks. As a consequence, there is abnormally large "shunt" flow through these regions which can cause the already fragile vessels to fatigue and haemorrhage. The AVM also "steals" blood from neighbouring brain areas, causing chronic ischemia. Associated blood flows are firstly complex due to the geometry and flow rate, and are also unsteady – normal capillary networks give steady venous return but AVM shunt does not.

2.2 The modelling goal

The aforementioned cerebrovascular diseases have attracted much attention from a haemodynamic modelling perspective. A plethora of different techniques have been employed in an attempt to better understand the causes of stroke and the effects of their surgical treatment. Although an "ultimate goal" where computer simulations offer patient-specific surgical advice should perhaps make one feel a little uneasy, there is no doubt that associated collaborative research will enhance medical knowledge of these cerebrovascular diseases. As way of a quick overview, some of the recent approaches to aneurysm and AVM modelling are discussed below.

2.2.1 Review: aneurysms

Owing to their size ($\simeq 1cm$ in width), accurate aneurysm imaging can be achieved with angiography (X-ray, Magnetic Resonance). Commonly, blood flows are simulated with the *Finite Element Method*[3] on vessel geometries that are generated from these images. In [2], pulsatile flows were simulated in developed branch and side aneurysms. The computed pressure was found to be greater in branch aneurysms (as might be expected) and fairly constant over the flow cycle. In a similar study [8] the computed *wall shear stress* was found to be significantly lower on aneurysm walls than on the nearby vessels.

The use of image data to generate simulation geometry is clearly integral to

[3] A geometrically flexible, *unstructured* grid method for solving the governing equations through difference methods

a patient-specific "stroke prediction" framework. However, **aneurysms are asymptomatic** so this would only be useful in the lucky cases where check-up scans (currently not available on the NHS) reveal an aneurysm, or for patients that have a known genetic susceptibility. A better use of the computational effort, then, is to gain valuable insights into the pathogenesis mechanism, i.e. aneurysm initiation, development and possible rupture.

Despite its limitations (the Finite Element Method requires rigid boundaries [2, 8]) the aforementioned work may have contributed toward a key finding. Physiological levels of (laminar) shear stress are known to suppress endothelial cell apoptosis [5]. The low wall shear stress reported in aneurysm simulation [8] suggests that this 'controlled' cell death could contribute to their development and possible rupture. This will be consider later.

2.2.2 Review: AVMs

Unlike aneurysms, AVMs **do** produce symptoms (usually severe headache). Although AVMs are appreciably large ($\simeq 3cm$ across), their tangled and tortuous geometry prevents an "angio-image $\rightarrow$ simulation-boundary" technique being used reliably. Indeed, any attempt at simulating an AVM in its vascular neighbourhood will be highly complex, especially if intricate geometry is used. The current research direction is instead to look at AVMs as idealised *networks* of vessels.

In an analytic study on multi-branching tube flow (unknown *streamfunctions* for each daughter are determined using appropriate boundary conditions and an incoming quadratic flow profile from the mother [9]), it was found that *mass flux increases linearly with the number of daughters*. It is reassuring that a fluid-dynamical approach can recover this phenomenon – this bodes well for further AVM modelling.

Incorporation of the multi-branch into a network model was suggested in later work [3]. A full model of this form would analyse fluid flow through a binary-tree network (the normal vessels) where one of the branches – at some depth in the tree – has *more than two daughters* (the AVM, see figure 2 overleaf). Branches would then fed back into a single output (venous return), and the flow rate through each route calculated. The hope is that the model would recover large AVM-flow and could then be used to investigate the effect of blocking these routes (simulating a common surgical procedure known as *embolization*). Extending network models to include vessel elasticity is, again, non-trivial.

Disclaimer: *the purpose of this essay is not to critically review current approaches, nor is it to create a complete method that exceeds the capabilities of existing ones. In the next section I will first discuss why the fluid dynamics is so difficult in this haemodynamic context and then suggest what I believe is a* ***possible*** *way of obtaining detailed flow simulation in non-simple geometry, while allowing for changing vessel shape (i.e. elasticity).*

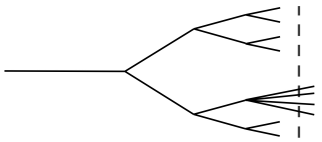


Figure 2: A schematic representation of an AVM network model. The AVM is represented by a multi-branched structure which breaks the symmetry between arterial and venous sides (the dashed line).

3 Future directions?

3.1 Fluid dynamics in a nutshell

The Navier-Stokes equation is essentially Newton's 2nd law for fluid motion. Per unit volume, we have $\rho \mathbf{a} \equiv \rho \frac{D\mathbf{v}}{Dt}$ where ρ is the fluid density (and use D since the velocity *field* can change in space and time). The full derivative chucks out two terms:

$$\frac{D\mathbf{v}}{Dt} = \frac{\partial}{\partial t}\mathbf{v} + \frac{\partial \triangle \mathbf{r}}{\partial t}\frac{\partial \mathbf{v}}{\partial \mathbf{r}} \equiv \dot{\mathbf{v}} + (\mathbf{v} \cdot \nabla)\mathbf{v}$$

which is known as the convective derivative. Now we need the "sum of forces". The internal forces that arise from the non-uniformity of the fluid stress tensor is given by

$$\mathbf{f} = \nabla \cdot \boldsymbol{\sigma} = \eta \nabla^2 \mathbf{v} - \nabla P$$

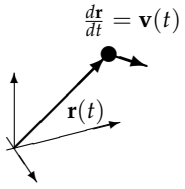
where η is the shear viscosity of the fluid and ∇P the pressure gradient in it. Adding in the possibility of external forces (e.g. gravity) we have the infamous *Navier-Stokes equation* below, which contains practically all of fluid dynamics:

$$\rho \dot{\mathbf{v}} + \rho(\mathbf{v} \cdot \nabla)\mathbf{v} = \eta \nabla^2 \mathbf{v} - \nabla P + \mathbf{f}_{ext}. \tag{1}$$

When approached with such a formidable-looking equation, we look – in true reductionist style – to throw away terms. Let us consider each of them in turn. Many flows are *steady* ($\dot{\mathbf{v}} = 0$). Unfortunately, in (arterial) blood-flow problems, the flow is clearly pulsatile owing to pumping from the heart. The second and third (inertial-convective and viscous) terms contain the most essential physics. The ratio of their characteristic magnitudes is known as the **Reynolds Number** and is given by

$$Re = \frac{\rho v^2/L}{\eta v/L^2} = \frac{\rho v L}{\eta} \tag{2}$$

where L is the characteristic length-scale of the flow event ($\nabla \sim 1/L$). When $Re \ll 1$, we can neglect the convective term and we have a *linear* differential



Tracking the 'particle'

equation. When $Re \gg 1$ we instead neglect the viscous force and have a non-linear equation with no dissipation. In the haemodynamic regimes considered here (aneurysm and AVM), we find ourselves in this boat ($Re \sim 10^2$); branching flows are *turbulent* and *accurate modelling will have to rely on computational techniques*. Lastly, the external force terms do not usually cause much trouble (as is the case here).

To complete this ramshackle description of fluid dynamics we need to mention **boundary conditions** and **conservation laws**. The *no-slip* boundary condition imposes that fluid near the boundary must be at rest. In a flow accelerated from rest, *no-slip* generates a "skin-depth" of non-zero vorticity (little whorls of fluid) which diffuses inwards over time until a steady state is reached – the viscous stress takes over and prevents further acceleration (Poiseuille flow). In long arteries, the model solution is a pulsatile version of parabolic profile known as Womersley flow[4].

Other than the universal conservation laws, fluids obey – to a very good approximation – *volume* conservation; $\nabla \cdot \mathbf{v} = 0$ (this was in fact used implicitly in the pseudo-derivation of (1) above). Incompressibility means that for steady flows, the *flow rate* through a vessel is constant. It should be noted here that blood is usually modelled as a Newtonian fluid (viscosity independent of shear rate), which is a good approximation to the non-Newtonian truth.

Having an non-linear N-S equation to deal with is in itself a frightful task. We would also like to model aneurysm formation (requiring vessel elasticity and unsteady arterial flow) and better understand the intricacies of AVM flow (also unsteady). The question is, what method can do all of this?

3.2 From Cellular Automata to Lattice-Boltzmann Methods

The text that follows is covered in more depth by Wolf-Gladrow [12].

The last 50 years or so has seen the development of a powerful computational paradigm known as *Cellular Automata* (CA). Computation space is divided up into discrete cells, which can either be occupied or unoccupied (`1 or 0`). The binary states evolve in discrete time-steps according to a set of specified rules (which can be either deterministic or probabilistic) that involve 'interaction' with their nearest neighbours. For each time-step there are two separate processes, known as *streaming* (where the particles hop synchronously along the lattice vectors that link nodes) and *collision* (where the rule is implemented and occupancies updated). Together, these give the state-evolution equation

$$n_i(\vec{r} + \vec{c}_i, t+1) - n_i(\vec{r}, t) = \triangle_i \qquad i = 1, ..., b \tag{3}$$

[4]which has an extra time-oscillating term written in Bessel functions (for circular cross-sections)

where n is the state description (`1 or 0`), $\vec{c}_i$ the ith *lattice velocity* and b the number of nearest neighbours. The Boolean collision map is labelled $\triangle_i$.

While CA – and variants thereof – have widespread use in simple scientific modelling (e.g. the spread of fire through a randomly-distributed forest) and more abstract issues (e.g. John Conway's game of *Life*), they are plagued by various *diseases* that make them unsuitable for fluid-dynamical modelling. Their two-state nature creates statistical *noise*. Since all multi-particle collisions are counted, the collision operator has a complexity of 2^b (this is huge for CA in 3D). Also, unless care is taken with the lattice symmetry, the automata produces *spurious invariants* that have no physical counterpart.

An extension to Cellular Automata was advanced in the 1980s. This combined the ideas of CA with the *Boltzmann equation*[5] to cast the computational particles in terms of probability distributions rather than hard bits. Using the popular BGK approximation, which expresses the condition that hydrodynamical equilibrium is reached in each cell for each step[6], the **Lattice-Boltzmann equation** (LBE) reads

$$F_i(\vec{r} + \vec{c}_i \Delta t, t + \Delta t) - F_i(\vec{r}, t) = -\frac{1}{\tau}(F_i - F_i^{eqm}) \tag{4}$$

where F is the mean occupation number derived from the distribution function $f(\mathbf{x}, \mathbf{v}, t)$, and the superscript ^{eqm} refers to that derived from the *equilibrium* distribution function (Maxwellian). The time-scale for this relaxation is set by τ, which must be smaller than the time-step Δt.

This formalism solves the problem of statistical noise, and reduces the complexity of the 'collision map' ($\sim b^2$ since it essentially deals with 2-particle collisions only). The Lattice-Boltzmann method (LBM) has, with reason, been welcomed by the fluid dynamics community. Like CA, it is completely *local*, i.e. the evolution of each node depends only on its nearest neighbours – crucially, this makes the algorithms suitable for *parallel* frameworks and will be discussed later. The extension of both CA and LBMs to three dimensions (i.e. the "real world") is fairly straightforward. Also, *the Navier-Stokes equation can – perhaps amazingly – be recovered from the LBM*[7]. We can therefore have full confidence that if use a sufficiently small lattice spacing (at an increase in computational cost) and can code the geometry and Reynolds number appropriately, then the LBM can simulate complex flows.

[5] Ludwig Boltzmann (1844-1906) was a great physicist who made huge contributions to statistical physics

[6] the lattice-spacing must be greater than the mean-free path of physical molecular collisions, i.e. $l_{mfp}/\Delta x \ll 1$

[7] in 5 pages of tensor algebra! [12]

3.3 Putting it together for haemodynamics

Trawling the literature reveals that LBMs are already being used in haemodynamical modelling. The LBM agrees with Finite-Volume grid methods in simulations of steady flow incident on symmetric vessel bifurcations [1]. Although this study was highly reduced (steady flow and rigid geometry), the results are promising. Even with the fairly coarse grid chosen, flows became more complex at high *Re*, and regions of low shear stress were found at the bifurcation points – supporting the suggested link between endothelial apoptosis and aneurysm development [5, 8].

The problem of vessel elasticity has also attracted attention. It was recently suggested that boundaries could be treated as Cellular Automata while Lattice-Boltzmann methods perform the fluid simulation simultaneously[8] [6]. While this hybrid approach was not investigated in detail, its potential is obvious: we can supply rules that (should) have some physiological grounding to update "fluid nodes" to "wall nodes" and *vice-versa*. It is this approach that I believe could be useful for aneurysm and AVM modelling.

3.3.1 A simple model

Regrettably, any implementation of the general LBM-CA framework is far beyond the scope of this essay (and my time constraint). Instead, I will present a highly hypothetical and simple model which I believe could be developed into something of worth. Some computational issues will then be discussed in the next section.

Assuming that the relevant initial and boundary conditions can be coded (i.e. flow profiles into the haemodynamical site of interest, the *bounce-back* rule for no-slip [12]) and the geometry constructed with relative ease, the LBM should be able to perform flow simulation on rigid boundaries without difficulty. However, *this is obviously easier for aneurysms than for AVMs*. The common bifurcation sites for brain aneurysm are on large arteries (Womersley in-flow is a good assumption and the geometry involves only one mother and two daughters) but AVMs occur deeper in the arteriovenous network, geometry is complex and vessels are many. Based on these observations, the main goal I have in mind for the following *pseudo*-model is simulation of aneurysm initiation and growth.

To address the issue of vessel elasticity and degradation, we consider the following things:

A Vessel elastance and compliance: a sufficient pressure will distend the arterial wall, which will move back on removal of the pressure (up to an elastic limit)

[8] LBM-only methods have also been suggested [4], but these are less intuitive

B The supposed link between low wall shear-stress and endothelial cell apoptosis, which would leave the elastic lamina exposed to blood flow

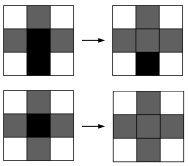
C The inter-relation between **A** and **B**

NOTE : *by "pressure" I mean that imparted mechanically by the computational fluid, and NOT its internal pressure (which is proportional to the hydrodynamic density and is conserved)!*

A (seemingly) simple way to simulate elasticity and compliance (**A**) is to implement a cellular automata *at the boundary*, in which the following node-flips are made:

$$\texttt{if } p_n \begin{cases} < p_{comp} & \text{fluid node switches to wall node (vessel relaxes)} \\ > p_{el} & \text{wall node switches to fluid node (vessel distended).} \end{cases}$$

After these updates have been made, *another* set of rules need to be imposed to "smooth" the boundary, i.e. to remove artefacts and fill holes (see margin - these are symmetric for node type). This is to prevent the automata from generating boundaries that could set up very small length-scales for unphysical flows. Further refinement could be done either by using smaller grids at the boundaries (computationally costly) or implementation of "diagonal" boundary rules in which the node presenting a corner is shared by fluid and wall [6].



Smoothing rules [6]

The biggest computational problem with this CA method is the calculation of pressure applied at each boundary node each update, which is governed by the Lattice-Boltzmann microdynamics and *not* by an analytical expression! Hence, a quick and preferably *local* way of determining this from the LBM formalism is needed. This might be achieved by averaging the *normal component of the velocity* near the boundary over T timesteps – for a physically justified T – and may require extra attention in coding to prevent a bottleneck in the algorithm.

We now turn to **B**. To a first approximation, we can model the apoptotic effect of low shear stress on endothelial cells (ECs) by saying : `if` $\sigma_{EC} < \sigma_{crit}$, then the EC dies and the elastic lamina is no longer shielded from the blood flow at this site. This is assumed to have some effect on the elasticity of the membrane. Turning to the simulation, we at once realise there is no explicit barrier between our fluid and 'elastic' wall. The only way we can manifest this change (with the existing simulation) is to alter the parameters p_{comp} and p_{el} at the affected site. Intuitively, we might expect the wear-and-tear on the exposed lamina to make it more 'plastic', i.e. unable to do its job perfectly. This could be achieved by decreasing p_{comp} and increasing p_{el} for these nodes. Wall shear stress can be immediately calculated *locally* from the distribution functions – calculation of velocity profile derivatives is not required [1].

The preceding description only attempts motivation of a very primitive model. Clearly, a far greater biomechanical knowledge is required for better treatment

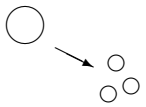
of **A**, **B** and especially **C**. Hence, it may be extremely valuable for future work to be done in collaboration with experts in this area. Other limitations that stand out are as follows. There is nothing 'outside' the geometry specified – more advanced modelling would include the nearby subarachnoid space and some concept of intracranial pressure. Glaringly, any possibility of haemorrhage has not been included – the current model would need to be tested and extended (to include "tension" in stretched walls) before this could be investigated.

Despite its limitations, the extended model could still be useful. Its major advantage over other methods is that the simulated flow (which is likely to be turbulent in the regions of interest) doesn't care that the geometry has been updated; it ploughs on regardless and explores any new fluid space given to it. If vessel rupture could be simulated reliably, a parametric investigation into its occurrence could be undertaken. *Does rupture depend on initial geometry? Incoming flow rate? Blood pressure? An elastic or apoptotic parameter?*

3.4 Computational Issues

The ideas described in this section are covered in more detail by Succi [10].

The importance of high-speed computing to the booming field of computational fluid dynamics cannot be overstated. The top speed that semiconductor chips can achieve is now being limited by heating, quantum effects and the speed of light. *Parallel Computing* is the method by which processors are linked together to attack the same algorithm simultaneously, and is suited to particle methods such as CA and LBM because of their *local* nature. This section is a quick overview of some key issues, and is included because it is important to consider the implementation and limits thereof before constructing the model itself – we can only get out what the computer can give us.


Divide and Conquer

How parallel? Let us consider two extreme cases; a completely serial implementation of the LBM/CA method and a completely parallel one (in which each node has its own processor). The serial method would involve a whopping `for` loop that has to run to completion each time-step. However, the over-parallel case would incur huge communication overheads since each processor has to share information with and "talk to" its nearest neighbours. Clearly, there is an optimum somewhere between these two extremes that minimises the completion time. This depends on *communication overheads* and the CPU time spent in the parallel portion of the code and is hence algorithm-specific.

Problem-to-processor mapping The best way to divide up the computation space between the P processors is usually the simplest topologically. If the simulation is on an isotropic cube (N^3 nodes), each processor takes a cuboidal slice of $1/P$th the volume to minimise the inter-processor exchange needed.

Load balance This is equivalent to the team-maxim *you're only as fast as your slowest man*. If one region of the computation space is particularly demanding, more processors (or, the fastest processors) should be assigned to it.

3.4.1 For the model....

The Reynolds number quantifies the relative importance of inertial and viscous forces in the flow. However, it also describes the scale to which energy – or equivalently *flow structure* – is transferred from the governing length-scale L. The coarsest lattice spacing we should use, therefore, is given by L/Re. For a 3D simulation, the number of nodes used then scales as $\sim Re^3$. On the commonly used $D3Q19$ lattice we have a **memory demand** of

$$2 \cdot 19 \cdot Re^3 \cdot \texttt{sizeof(float)}$$

where the factor 2 is for collision and streaming arrays, and `sizeof(float)` is the number of bytes used to store a floating point number (usually 4). With $Re = 200$, the demand is just under 5GB! Clearly, this cannot be done on any old computer (my laptop has 2GB). For this reason, 2D abstractions of the real-world model are a good place to start, but one should have in mind that parallel computing will be needed for full simulations.

Lattice-Boltzmann methods are known to have favourable computation to communication ratios [10]. For load balance, it should be noted that the fluid and boundary algorithms are very different. For this reason, it may be prudent to have a dedicated set of processors that deal with the boundary nodes (which will change with time – the allocation needs to be *dynamic*).

The output of the simulation should be easy-to-visualise, show the flow field, vessel geometry and time-scale. It is unlikely that these computationally-intensive methods can compete with biological time, but hopefully the simulations will contribute toward a better understanding of aneurysm development, AVM shunt & steal and the haemorrhage of both. As mentioned before, geometry and location make aneurysm a more realistic target.

4 Summary

Though fluid dynamics is finding increasing application in haemodynamics, many questions in cerebrovascular disease remain unanswered and many problems unaddressed. *I have motivated the Lattice-Boltzmann method – with Cellular Automata boundaries – as a modelling tool that can simulate complex flows on elastic geometry. I believe it may be a good direction for future work to take, and that it could eventually enhance understanding of aneurysm and arteriovenous malformation*.

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