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CEREBRAL ANEURYSMS: FROM CAROTID LIGATIONS TO COMPUTATIONAL FLUID DYNAMICS

Neurosurgery

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KEYWORDS

INTRODUCTION

With the advancements in modern microsurgical and endovascular techniques coupled with improved neuroanaesthetic approaches, the morbidity and mortality figures associated aneurysmal subarachnoid haemorrhage (SAH), have improved significantly. Whereas most of the recent advancements in the neurological therapy of IAs have been achieved in the past 200 years, the journey of success began over 4000 years ago. In order to appreciate these breakthrough achievements, the first half of this manuscript discusses the temporal evolution of different diagnostic and treatment modalities for Ias.

With all this recent technological progress, the protocols to treat the *ruptured* IAs became quite clear over time however, the management of *unruptured* IAs (UIAs) still remains controversial. These uncertainties are mainly due to an incomplete understanding of natural history of IAs and risks associated with active management.[1] The difficulties are further enhanced by the fact that the poor surgical outcome is dictated by the same factors[2] that currently form the basis of surgical decision making.[3]

In order to improve the management of UIAs it is evident that we need some new descriptors to guide the treatment. The hemodynamics is believed to play an important role in the etiopathogenesis of IAs.[4] The evaluation of these variables can provide a useful alternative to predict the behaviour of an unruptured intracranial aneurysm at an early stage. Unfortunately, the detailed *in vivo* measurements of all relevant flow variables in IAs are currently impossible.[5] Motivated by these factors computational fluid dynamics CFD is gaining rapid popularity as scientists have started using this to predict blood flows in IAs.[5]

After discussing the existing controversies in the management of UIAs and the relevance of hemodynamics in this context, the present manuscript describes the emerging role of CFD. The final sections provide an overview of the development process and functionalities of state-of-the-art software @neuFuse and the future research potentials.

The Early Developments

he earliest description of intracranial or subarachnoid haemorrhage (SAH) as a cause of death in human beings dates back to the ancient Biblical times. The first anecdotal evidence of an IA as well as the earliest attempt to treat it comes from Egypt. It is recorded in Ebers Papyrus, one of the oldest preserved medical documents that in 2725 BC Imhotep, who was an Egyptian architect cum physician, tried to treat an aneurysm by using a fire glazed instrument.[6] The term aneurysm, derived from Greek word *aneúrysma* (*ana*; throughout + *eurus*; wide), meaning 'to dilate', was introduced by Claudius Aelius Galen, a philosopher of Greek origin in 200 AD.

In 1664, Thomas Willis,[7] an Oxford-based physician provided the first scientific account of the cerebral vasculature later being honoured by the eponym 'circle of Willis'. Almost a century later in 1761,[9] an Italian anatomist from the city of Padua, published the first anatomical write-up describing the entity of an intracranial

aneurysm. It however, took another four decades to recognize the definitive clinical importance of IAs until Blane in 1800 published the clinical and autopsy findings of a patient with bilateral carotid cavernous aneurysms, described by John Hunter in 1792. The credit of first clinical diagnosis of an intracranial aneurysm goes to Hutchinson[10] in 1861. Based on the neurological signs he successfully diagnosed an intracranial aneurysm in a patient 11 years before his death. However, in spite of the handful of clinical diagnoses, the exact preoperative localization of an IA remained a challenge to clinicians until late.

Thomas Willis
(Source: Medscape)

The Surgical Era

Ujohn Hunter
(Source: Medscape)

Understanding the deadly nature of these lesions, the earliest efforts of modern times to treat them by surgery were started in the form of carotid ligation. The concept presumably stems from an important observation made by Jean-Louis Petit in 1760s that there were no significant adverse effects on the human brain even after the complete occlusion of one carotid artery by thrombosis. The carotid ligation was initially popularised by John Hunter in 1800s, and was known as 'Hunterian ligation' after him.[10] The first ever attempt to treat an aneurysm by 'Hunterian ligation' was endeavoured by Cooper in 1808.[10] Carotid ligation remained popular and appeared a reasonably successful treatment except for the fact that in most of the cases it carried a significant risk of cerebral infarction and hemiplegia. Given the high mortality and morbidity produced by the acute occlusion of the carotids, the concept of gradual occlusion was introduced.[11] Numerous metallic clamps were designed that could be tightened over a period of several days. The clamp could be reopened should the patient become symptomatic. Because of unacceptably high complication rates, the ICA ligation was gradually replaced by common carotid artery ligation

Walter Dandy
(Source: Medscape)

Due to the lack of preoperative localization, most of the initial 'direct surgical encounters' of IAs were unplanned and were limited to their accidental surgical exposures. Sir Victor Horsley[12] was one of the first surgeons to witness an IA during a craniotomy in 1885, when he was operating on a patient with a preoperative diagnosis of a middle fossa tumour, which turned out to be an IA. He treated the patient by ipsilateral carotid ligation.

Two other important discoveries that altogether changed the ways of diagnosis and management of IAs can be considered as contributing to the dawn of modern neurovascular surgery. Quincke introduced the technique of lumber puncture in 1891[13] while Egaz Moniz discovered the cerebral angiography in 1927.[14] The first direct planned surgical intervention to treat an intracranial aneurysm however, was endeavoured by Norman Dott on April 22 1931, when he stopped bleeding from an intraoperatively ruptured carotid aneurysm by wrapping a muscle around it.[15] The preoperative diagnosis of a carotid bifurcation IA was localised clinically and the procedure was tolerated well.

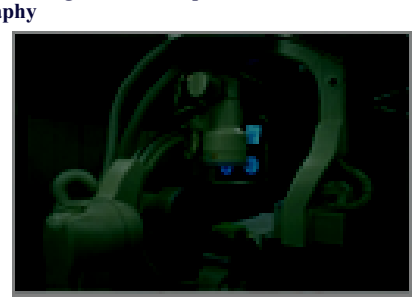
The efforts were further matured by Walter Dandy who gets the credit for the first successful *clipping* of a preoperatively diagnosed IA.[16] In March 1937 he treated a man of 43 by applying an ordinary flat silver clip to a pea sized IA of distal ICA. The operation was performed around six-years after Egas Moniz demonstrated the first IA by cerebral angiography in 1931. The diagnosis however, was localised solely on the basis of clinical signs. Dandy himself admits that such a precise clinical localization of an IA warranting a surgical attack is but a rare phenomenon.[16] Clipping became established as a new procedure to secure the ruptured IA, soon after Dandy published his monograph in 1938.

Justification of Surgery: In absence of clear scientific evidence it was often difficult for earlier neurosurgeons to justify their surgical decisions against medical or conservative management. Strong doubts were raised about the effectiveness of surgery as most of the studies failed to show any advantage of surgery as compared with medical management.

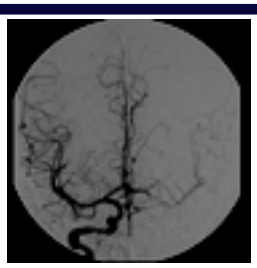
Continuing refinement in surgical techniques and instruments, coupled with the advancements in the neuro critical care, made the surgery progressively safer. Greenwood[17] brought in the bipolar cautery in 1940, while the hypothermia was introduced by Lougheed, White and Sweet[18] in 1953 for cerebral protection during cerebrovascular procedures. Almost a decade later Uihlein et al[19] performed the first intracranial aneurysm clipping using induced hypothermia and total circulatory arrest. The entity of vasospasm was demonstrated by Ecker and Riemenscheidner in 1951.[20] The first operating microscope was introduced by Carl Zeiss Inc. in 1953,[21] a company established by the visionary German optician Carl Zeiss in 1846. Theodore Kurze from Los Angeles was the first neurosurgeon to use an operating microscope in neurosurgery in 1957.[22] The twin benefits of illumination and magnification offered by the operating microscope, laid the pavement for microneurosurgery, led by Yaşargil and others.

One of the earliest publications to attract the attention towards ineffectiveness of medical management of SAH came from Tappura in 1962.[23] He showed that rebleeding rates were as high as 55% without any active intervention with 75% mortality. In the same year Norlén[24] published the results from his series of 134 patients of IAs managed surgically. He reported an astonishing success with a mortality of less than 2.5%. Over a period of time, the growing scientific evidence unequivocally established the superiority of intracranial surgery as compared to both, carotid ligation and bed rest. By the late 1970s direct clipping was accepted unanimously as a 'gold-standard' for the treatment of ruptured IAs.

Neuro radiological Developments & Invent of Cerebral Angiography



A modern angiographic suite



A typical angiogram
(Source: Medscape)

A group of researchers, including Sir Godfrey Hounsfield[25] developed the first computed tomographic (CT) head scanner which became operational by 1971. The CT scan proved to be a crucial aid to the diagnosis of SAH due to its ability to pick subarachnoid and intraventricular blood. The early report about the first NMR image of a live human body was published by Damadian and colleagues[26] in 1977 and MRI came into clinical practice in 1982. It surpassed every available imaging modality in providing exquisite soft tissue differentiation.

Endovascular Interventions

The history of the evolution of endovascular treatment of the aneurysms is a fascinating story of groundbreaking work done by the early geniuses. Whereas roots for some of these endovascular techniques can be traced to the early nineteenth century it's only through incredible progress in the technology over last couple of decades that made their safe and widespread clinical application possible.

Extra Cranial Endo Vascular Interventions

Medical Measures: Apart from masterly inactivity, workers started trying various medical compounds to induce thrombosis in aneurysmal sacs. The most commonly used pharmacological compound was potassium iodide,[27] administered systemically. Various other medical measures tried were; vinegar, iron perchloride solutions, alcohol, gelatin, ergot salts, and even hypothermia by local ice packing.[27] These procedures however, soon had to be discontinued due to inconsistent and unpredictable results.

Insertion of foreign bodies/ wiring techniques: After abandonment of medical measures various investigators started attempting to treat aneurysms by inserting foreign bodies. The earliest description of such an endovascular procedure to treat an aneurysm is given by Ransohoff,[28] reciting Sir E Herne who by the turn of eighteenth century induced thrombosis in an iliac artery aneurysm by inserting heated needles into it. The same concept was later applied to treat aortic aneurysms by many authors who replaced needles with metallic wires. In spite of initial enthusiasm among its advocates the overall results from these 'wiring' procedures remained poor. These procedures were ultimately abandoned during the first half of the twentieth century.

Emergence of the concept of electrothrombosis: The limited success of these 'wiring' techniques stimulated investigators to search for more efficient alternatives. It was realised that one of the important reasons for failure was the lack of sufficient thrombus formation attributed mostly to inadequate aneurysmal packing. The idea of using galvanic current as an adjunct to enhance the thrombogenicity of these metallic coils presumably has taken its inspiration from the early experimental works done by Scudamore[29] in 1824. It was however Phillips in 1832[30] who gave birth to the concept of electrocoagulation in aneurysms. CH Moore introduced wiring for the treatment of aortic aneurysms in 1864. Another dimension to it was added when Corradi in 1879[31] passed the electric current through the wire. The technique was later called Moore-Corradi method after both the workers. The method remained in use for next 40 years and was adopted by many investigators.

Trans Cranial Approaches

Due to understandable limitations in the precise localization and difficulties in accessing an IA, the early endovascular interventions were limited to the large and extracranial arteries. The initial attempts to treat an IA by iatrogenically induced thrombosis were therefore carried under direct vision during a craniotomy. In 1936 WJ Gardner[32] packed an accidentally opened giant IA with cotton sponges. The credit

of the first successful 'thermiocoagulation' of an IA however, goes to Werner.[33] Working with Blakemore and King, in 1941 he treated a giant paraclinoid IA in a young girl. The aneurysm, resistant to multiple Hunterian ligations, was approached transorbitally. A ten-foot long silver wire was inserted through its fundus and heated for 40 sec, reportedly curing the aneurysm.

Transition from transcranial to intravascular approach: The idea of using blood vessels as natural access to treat the cerebrovascular lesions may probably have taken motivation from the pioneering work done by Brooks.[34] He is credited with the first endovascular intervention to treat a cerebrovascular pathology. After exposing the ICA surgically, he embolised a traumatic carotid cavernous fistula in 1930 by placing a strip of muscle intravascularly. Switching from the transcranial to intravascular approach was nevertheless, not straightforward. Tortuosity, delicacy and narrowness of intracranial vasculature as well as the presence of the carotid siphon were the main obstacles for intracranial catheter navigation. This important shift could only be made possible through the development of sophisticated micro-catheter systems and intravascular delivery devices.

Luessenhop and Spence[35] remained pioneers in cerebral endovascular navigation; they successfully cannulated an ICA to embolize an arteriovenous malformation (AVM) using flow-directed silastic spheres in 1960. They also set another important milestone in endovascular navigation in 1964; what is believed to be the first successful catheterization of intracranial vessels in a human being, finally shifting the focus from a transcranial to intravascular approach. With the help of a glass chamber, surgically connected to the external carotid artery, they delivered a length of silastic tubing into intracranial arteries. The balloon at the tip of this flow-directed catheter was inflated temporarily to occlude the neck of a posterior communicating artery aneurysm.

Superselective catheterization and magnetic navigation: Frei and colleagues[36] from Rehvoth, Israel, added another dimension to endovascular navigation by introducing their novel microcatheter system in 1966. This high-tech system, also called POD (para-operational device) by its inventors, made superselective catheterization of intracranial vessels possible. The tip of the catheter was made of specialised soft silicone rubber to minimise vessel trauma. A micromagnet of 1 millimetre diameter, strategically placed inside the tip of the microcatheter was used to manipulate it with the help of external magnetic fields. In 1974 Hilal et al[37] published their experience with safe intracranial catheterization in 120 patients. Using a slightly modified version of magnetically directed POD catheter they catheterized many difficult to reach intracranial vessels and more importantly performed electrocoagulation of one basilar tip aneurysm, giving birth to the concept of neuroendovascular electrothrombosis.

Following their initial success the magnetically directed catheters remained in use until the late 70s, however the lack of precise operator control and distortion of the fluoroscopic images by strong magnetic fields drove researchers to look for alternative methods of intracranial catheter navigation.

Balloons: Convinced with the idea first given by Luessenhop and Rothenberg as early as in 1960s,[36] most of the investigators started realising with time that the best force to propel the endovascular catheter was the antegrade flow of blood itself. TJ Fogarty[38] and co-workers introduced a novel balloon-tipped catheter system in 1963 to extract the arterial emboli. Fogarty catheter system proved as a milestone in the advancement of catheter technology and opened doors for the development of a range of endovascular catheters including the modern balloon-tipped catheters. The most important discovery in microcatheter technology however, was the invention of Tracker® microcatheter system in mid 1980s by Engelson.[39] By virtue of its unique externally steerable tip it revolutionised the way intracranial arteries were negotiated.

Montgomery et al from Massachusetts Institute of Technology (MIT), USA, designed the first detachable balloon catheter in 1970 using a modified POD catheter by mounting a balloon on its tip (Fig). However, it was Fedor A. Serbinenko[40] from Burdenko Neurosurgery Institute, Moscow, who not only established endovascular interventions as a treatment modality for IAs but also gets the credit for founding Endovascular Neurosurgery as a new medical discipline. Inspired by a simple observation of helium-filled balloons at May Day celebrations in Moscow's Red Square in 1959, he spent relentless hours in the laboratory to create prototype silicone and latex balloon catheters. Using these flow-directed balloon-tipped catheters he mastered the art of balloon embolization of IAs and AVMs and performed 304 balloon endovascular procedures between 1969 and 1972 with just two mortalities[40] laying the foundation stone for modern endovascular neurosurgery. The seminal works done by him changed the management of IAs forever and he is therefore rightfully called father of endovascular neurosurgery.

From balloons to endovascular coiling: Due to wide spread application and growing experience, a number of shortcomings of the balloon embolization started to become apparent. Owing to the fixed and rigid shape (round or oval) of the balloons, it was difficult to achieve 100% occlusion of the IAs, frequently leaving an insecure aneurysm at the end of the procedure. Furthermore, this potential space and the balloon-aneurysm complex together, when subjected to the continuous pulsations arising from the pulsating arterial blood column, were thought to produce a 'water-hammer' effect. This 'water-hammer' effect was reported to facilitate the IA recanalization, enlargement or delayed rupture.[41] Additionally, the balloons have also been reported to undergo slow-deflation, slowly loosening the packing further. All these drawbacks together formed the basis for the shift from balloons to coils for the endovascular treatment of the IAs.

Transcatheter electrocoagulation: Therapeutic transcatheter vessel-occlusion (TCVC), which was introduced in 1930s for the treatment of carotid-cavernous fistulae,[42] slowly became a well established technique by the 70s. Thompson and colleagues provided a thorough and methodical description of the technique and uncovered its various merits and shortcomings. They also demonstrated that the clot size and the extent of thrombosis were directly related to the product of amount and duration of the current applied. Due to difficulties in precise placement of the anode in IA, TCEC was mostly used to occlude the vessels only.

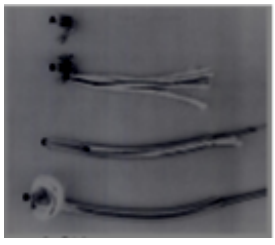


Fig-1: Gianturco 'pushable' coils

From 'pushable' coils to 'detachable' coils (GDC®): In the quest of selective and safe embolization of IAs Gianturco and colleagues invented a novel mechanical device in 1975, called 'wool coils'[43] (Fig-1). It was one of the earliest 'pushable' coils where the 'wool' could be 'pushed' into target using a guidewire. In 1989 Hilal et al reported another use of short 'pushable' coils for the treatment of IAs. Although being relatively stiff, it was almost impossible to achieve a dense packing of IAs with these coils. Moreover, these coils were inherently non-retrievable and hence difficult to control. These 'pushable' coils later formed the basis of more advanced 'detachable' coils.

The credit of inventing the modern detachable coils (commonly known as GDC®) can safely be attributed to Guido Guglielmi.[44] Guido Guglielmi was born in Rome, Italy and initially studied engineering for a while before opting for medicine as a career. Due to his great interest in engineering he studied the concept of electrothrombosis of IAs in detail and conducted a series of animal experiments in the 1980s. Guglielmi later moved to Los Angles where he came in contact with Ivan Sepetka, a research and development engineer at Target® Therapeutics. The genesis of this state of the art coiling system that changed the way Neurovascular surgery is practiced is a unique example of a creative interdisciplinary collaboration between these two masterminds.

Working together they mounted soft platinum coils of different sizes to a stainless steel guidewire (Fig-2). The thrombosis was achieved by passing an electric current to the coil once it is placed inside the IA. The coil would 'detach' from the delivery wire during the process of electrothrombosis due to the low melting point of the metal used to attach it to the guidewire. Another very important feature of these coils was their retrievability and softness, which at gave the operator added

control over the procedure. The first GDC® was used in a human by Dr Viñuela on 6th March 1989 by treating a cavernous sinus fistula. The first IA was treated by GDC® in January 1991 at UCLA, Los Angeles. The techniques of endovascular interventions for the treatment of IAs have exploded in the past few decades. From a second line treatment in the early 1990s it has rapidly become a primary therapeutic option in most of the centres worldwide.

Guido Guglielmi

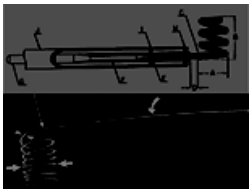


Fig-2: A GDC® coil and guidewire

A large, multicentric, prospective, randomised, controlled, clinical trial, the International Subarachnoid Aneurysm Trial (ISAT), was conducted under the leadership of Neurovascular Research Unit, Oxford, UK. It has indicated that the outcome in terms of survival free of disability at 1 year is significantly better with endovascular coiling as compared to surgical clipping. It however, showed that the risk of rebleed is slightly higher with coiling.

The Enlarging Realm of Unruptured Intracranial Aneurysms

The easy availability and widespread use of non-invasive neurodiagnostic modalities, has brought to clinical attention a large and ever increasing group of patients harbouring unruptured and asymptomatic IAs. These UIAs are also diagnosed coincidentally at the time of catheter angiography done for a ruptured IA in a patient with multiple lesions. The increasing awareness of the relatively bleak prognosis related to aneurysmal rupture amongst the general public and clinicians, forces neurosurgeons to come up with a definitive answer for these asymptomatic lesions. As we have noted above, the management protocols for UIAs are unfortunately not clear.

Finding the new descriptors: the role of hemodynamic, morphological and structural factors

The flow of blood inside the intracranial vasculature, the shape of the IA and its structural properties, has long been thought to play a role in their etiopathogenesis. There is a rapidly growing body of literature affirming the importance of these factors in this context (Table-1). These factors can be used as new descriptors to predict the risk of rupture for these lesions. The important hemodynamic factors are described in detail:

Wall Shear Stress (WSS): WSS is a tangential force exerted by flowing blood on the arterial endothelium, and is proportional to the blood viscosity and velocity. Mean arterial WSS has been suggested by Malek et al to lie within the range of 1.5-2.0Pa (Table-1). There is good evidence that high WSS plays a role in the initiation of IAs (Table-1). This is further supported by the observation that IAs most frequently occur at bifurcations and arterial bends. These are regions which are exposed to constantly high WSS. A number of different mechanisms have been proposed to explain how WSS influences the natural history of an IA. It has been established that the normal behaviour of arterial endothelial cells (ECs) is regulated by haemodynamic shear stress. Sho et al[45] observed that increased WSS stimulates ECs to produce matrix metalloproteinase (MMP-13) which, in turn, leads to degeneration of the internal elastic lamina. It has been demonstrated that WSS increases the production of NO by the ECs by inducing an enzyme responsible for its synthesis (iNOS; inducible nitric oxide synthase). iNOS is believed to be a prerequisite for *de novo* development of IAs in cerebral vessels.

Oscillatory shear index (OSI): OSI is a measure of the oscillatory nature of shear forces. This index, which has a range of between 0 and 0.5, represents the fraction of the cardiac cycle over which the instantaneous shear force vector forms an angle greater than 90 degrees to the time-average direction of the same force. Consistently high values of OSI have been associated with EC dysfunction and changes in cell structure secondary to cyclic mechanical stress have been demonstrated reporting disruption of the actin cytoskeleton of ECs. Damage to ECs produced by high OSI is supposed to contribute to IA formation (Table-1).

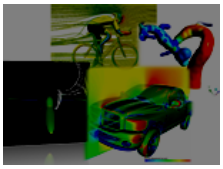
Table-1: The literature-based evidence on the importance of WSS and OSI in the etiopathogenesis of IAs

Hemodynamic factors	Intracranial Aneurysm			Proposed mechanism(s)	References
	Initiation	Growth	Rupture		
Wall Shear Stress (WSS)	High	Low	Low	Increased WSS increases the production of MMP-13 which in turn leads to vessel wall damage Decreased WSS increases iNOS synthesis- NO induced damage to vessel wall Low WSS increases endothelial proliferation and apoptosis	Boussel et al, Fukuda et al , Gao et al, Jou et al, Malek et al, Meng et al, Ujie et al
Oscillatory Shear Index (OSI)	High	High	High	Degenerative changes in endothelium	Glor et al, Goubergrits et al, Mantha et al

NB: MMP-13; matrixmetalloproteneases-13, NO; nitric oxide, iNOS; inducible-NO synthase

Computational Fluid Dynamics (CFD): the Concept and the Need

CFD constitutes a relatively new approach in the study of fluid dynamics, emerging around the 1960s with the advent of high-speed computers and the development of accurate numerical algorithms. CFD is the science of predicting fluid flow, heat and mass transfer, chemical reactions, and related phenomena by solving numerically the set of mathematical equations (conservation of mass, momentum, energy, species etc.) that govern a particular physical system. In the past decades it has been successfully used in the automotive sector; in improving the aerodynamics of vehicles, civil engineering; to design more efficient cooling systems, and nautical architecture; to design more efficient keels, etc.



The behaviour of a particular physical problem is often represented by a set of partial differential equations (governing equations, i.e. conservation of continuity, momentum, energy, etc.) whose solution is sometimes tedious, if not impossible. In the case of fluid flows these equations are the Navier-Stokes equations. In complex physical problems the solution is often not available. In these contexts CFD offers the possibility to solve the g overning equations by approximation. CFD solvers are based on the discretization of the fluid-flow domain (i.e. the region traversed by flow). The domain is subdivided into a set of sub-volumes or cells called mesh or grid (Figure). Figure-3 shows the discretization of a pipe flow fluid region. By using this discretization the governing differential equations of Navier-Stokes can be approximated and solved, but only at certain points (i.e. cell corners) of the domain, thus providing the solution in terms of pressure or velocity of the fluid at these points.

Figure-3:

CFD is providing a useful alternative to predict blood flows where detailed *in vivo* measurement of hemodynamic flow variables is not possible. The process of CFD analysis for an IA typically consists of following steps: a) Construction of 3D computer models from a medical image (such as 3D rotational angiogram, CT angiogram or MR angiogram); this step is done with the help of state-of-art software @neuFuse described here in detail, b) computation of the relevant flow variables with the help of a fluid solver software (Ansys® CFX™ for example) and, c) Postprocessing and visualization of the results.

@neu Fuse: The Vision and Overview

By definition, @neuFuse is a CAM (computer aided medicine)-application software that integrates the visualization, modelling and simulation of multimodal biomedical data with specific respect to IAs. In the broad context of an integrated IT system for IA management, the *role* of such a suite is to gather clinical structured information from electronic medical records, and the unstructured functional imaging, to provide a state-of-the-art environment for medical imaging processing and modeling aimed at producing a structure of three distinguished complex derived indicators viz. morphological, hemodynamic, and structural. The derived data is then used by epidemiologists to find the definitive correlations to assess the risk of rupture. Innovative key elements are the capability of combining medical imaging data, simulation results and morphological indicators into a coherent set of patient-specific data, properly fused and interactively accessible from within an easy-to-use application and the development of a *fat client* that exploits the client hardware capabilities in advanced visualization while being fully integrated with the backend Grid infrastructure.[46]

Development of @neuFuse: Contributions and Process

@neuFuse is developed by the project @neurIST (www.aneurist.org, IST-2004-027703), a multidisciplinary European initiative funded by the European Commission with a budget € 17 million bringing together Neurosurgeons, neuroradiologists, epidemiologists, engineers, biologists and computer scientists from 32 European institutions. The project aims at improving the current management of IAs. @neuFuse is a result of joint collaboration received from several project partners that contributed at different layers by providing specific algorithmic *plug-ins*, or by providing application's modules for a specific task, or by providing software libraries to connect to a specific service. In brief**, Universitat Pompeu Fabra** (UPF), Barcelona (Spain) provided the advanced medical imaging functionalities such as the segmentation and the skeletonization plug-ins. **NEC Europe Ltd** (Germany) contributed to the data model design and provided routines for preprocessing the geometric models of vessel in an appropriate format for CFD solvers. **Erasmus Medical Center** (The Netherlands) contributed in enhanced imaging filtering *plug-in*. **The University of Sheffield** (UPF) (UK) and **Ecole Polytechnique Federale de Lausanne** (Switzerland) provided and integrated the 1D circulatory model. **GridSystems S.A.** (Spain), **NEC Europe Ltd** (Germany) and **University of Vienna, Institute of Scientific Computing** (Austria) provided the Grid-connectors libraries. **University of Bedfordshire (former University of Luton)** (UK) contributed to develop advanced graphics interface to visualize and manipulate vessel geometries. **Super Computing Solution s.r.l.** (B3C) was responsible for most of the development of the software, the integration and the maintenance. Major versions of @neuFuse applications have been released routinely every six months and it is being used by six clinical pilot centers (UPF, UNIGE, USFD, EMC, OXF, PEC).

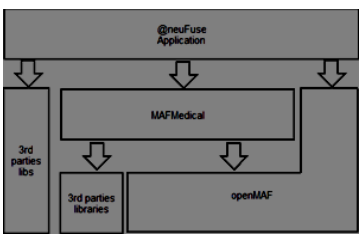


Fig-4: @neuFuse software architecture

All these software components were integrated on an existing back bone, provided by the Multi mod Application Framework (MAF, http://www.openmaf.org). MAF is an open source freely available framework (www.openmaf.org) for the rapid development of applications based on the Visualisation Toolkit (www.vtk.org) and other specialized libraries. It provides high level components that can be easily combined to develop a vertical application in different areas of scientific visualization (Figure-4). *OpenMAF* is further extended by an additional software layer, called *Maf Medical* that contains all MAF components specific to the biomedical application domain. A generic *MAFMedical* application, such as @neuFuse, is defined by choosing from the framework the necessary components, and eventually specialising them. It is also possible to develop *ad hoc* components that are necessary only to the application itself, and plug additional third party libraries.

There are four types of components that form any MAF application viz. Virtual Medical Entities (VME); that are the data objects, *Views*; that provide interactive visualisation of the VMEs, *Operations*; that create new VMEs or modify existing ones, and interface elements; generic graphic user interface (GUI) components that define the user interface of the application.

@neuFuse: Work Flow at a Glance

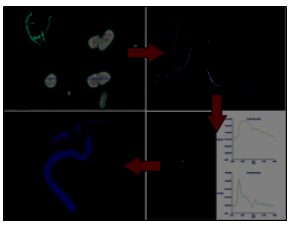


Fig-5: @neuFuse CFD processing toolchain. From top right clockwise: DICOM images are loaded and vessel geometry segmented. Then, the a topologically correct geometric model is processed to extract vessel centreline. This information is then used to map 3D vessels with a 1D circulatory model. This mapping allow to derive flow boundary conditions for the hemodynamic model.

Hemodynamic modeling of cerebral aneurysms involves several steps (Fig-5) starting with the retrieval of medical images in DICOM or V3D format; the creation of a geometric model of the vasculature; the topological reconstruction of the vasculature, the assignment of boundary conditions to the domain from the 1D flow model and, the solution of the flow equations that are actually demanded for a specific off-the-shelf software. The main steps involved in the process are given below.

Segmentation: The very first step to build CFD models of IA is extraction of geometrical representation of the cerebral arteries from a medical image. Segmentation is a process where every pixel (or voxel in case of a medical images stack) of the image is labeled in order to form a small set of pixel clusters known as segments, to obtain a representation that is easier to analyze. The first product obtained here as a result of segmentation is the set of voxels that have been labeled as interior surface of the vasculature corresponding. In the literature many different approaches are documented, but many of these methods give acceptable results with a particular imaging modality; other methods are too operator-dependent. To combat the issue an automatic, multi-modal algorithm[47] has been developed and integrated in @neuFuse. Automatic segmentation could compute an accurate model of the arteries in few minutes.

Geometric Healing: Lack of resolution or other contrast medium artifacts could generate errors in the automatic segmentation process that should be resolved by the operator. A typical example is the "kissing vessels" problem due to a lack of the image resolution. Two close vessels are glued together by the reconstruction algorithm, but in reality they are separate. If this problem is not solved before modeling, it may result in a gross error. To address this kind of problem, the @neuFuse operator should check that the resulting geometry is a topologically correct representation of the cerebral arteries and eventually fixes with a set of general-purpose tools, in a way which is similar to photo editing software.

Vasculature Topology: Skeletonization: Once the geometric model is

topologically correct, the next step is to extract the vasculature network. This process is called skeletonization because the result is a kind of graph that represents the vessels.[48] This representation is fundamental for many purposes; with this information it is possible to navigate the vessels, to check vessel diameters along a specific artery and, to plan an endovascular treatment choosing the position for deploying a stent.

Boundary Conditions assignment: In this step the operator defines the domain of the flow simulation by localizing the inlets and outlets in relation to the vessel skeleton. Followed by this each vessel in the patient specific geometry is literally matched with the corresponding vessel in the 1D circulatory system model. The 1D model provides flow and pressure values for each of the arteries. These values will be used later as boundary conditions for the 3D flow model.

Solving the equations: Once the model is completely defined, flow equations are solved. @neuFuse could launch the simulation software locally, or it can connect to the Grid infrastructure and request a remote simulation. To do so, data should be stored in a neutral format, as the simulation software could have several implementations. Then, data are processed and stored in the particular file format depending upon the solver used. The solver used in @neuFuse is ANSYS® ICEM-CFX™ which is then launched and finally results are loaded in @neuFuse.

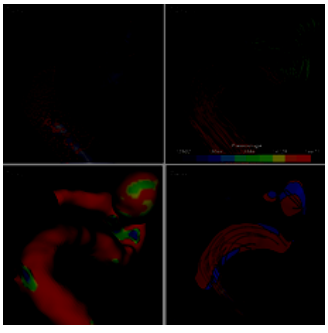


Fig-6: Visualization of hemodynamic simulation in @neuFuse. On the top right, flow particles tracing: erythrocytes are animated according the velocity field. On top left picture, streamlines representation with pressure-coded colouring. On bottom left picture, wall shear stresses on the vessel walls. On bottom right, complex visualization showing streamlines crossing an arbitrary plane coloured according a Doppler-like schema: the red regions represent inward flow, whilst blue regions represent outward flow.

Presenting results: The solution of CFD simulation is a very complex collection of data and it is a challenge to present them in an environment which is coherent with the medical images and the clinical context (Figure-6). Results are composed by multi-scalar and multi-vector time-variant fields sampled on a tridimensional unstructured mesh, where each element represents an infinitesimal solid cell (typically tetrahedral). Typical representations for flow (velocity) fields are streamlines that represent the tangent of the velocity fields. Streamlines then are usually colored according the pressure gradients. To give an idea of the flow pattern, we introduced a particle tracer. It enables the visualization of flow particles' position and to follow their trajectories in the boundaries for each time-stamp of the simulation, by integrating the velocity field. The operator can also visualize 3D representation of the scalar fields. Vessel walls can be colored according to WSS values. Furthermore, it is also possible to superimpose scalar values on 2D original medical images. More complex, representations can also be obtained by combining those already presented.

CONCLUSIONS

With the advent of technology, the diagnosis and management of intracranial aneurysms (IAs) have undergone tremendous evolution. The hemodynamic, morphological and structural variables play an important role in the etiopathogenesis of IAs. The evaluation of these variables can provide a useful alternative to predict the behaviour of an unruptured IA at an early stage. CFD and the state-of-the-art software @neuFuse can offer invaluable help to predict blood flows in this context. In spite of modern technological achievements there is still a long way to go before the management of IAs can be taken to the point where it is no longer regarded as a threat to the community.

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