Comparison between in vitro and in silico models of thrombectomy procedures

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1. Introduction

Stroke occurs when poor blood perfusion in a certain region of the brain causes the local death of cells and a consequent impairment of the neurological functions controlled by that area [1]. Depending on the cause, two categories of stroke are distinguished: ischaemic and haemorrhagic. A haemorrhagic stroke occurs when an artery located in the encephalon ruptures, causing an overflow of blood. Ischaemic stroke, on the other hand, occurs when an artery that supplies the brain is obstructed; this obstruction may be caused by the formation of an atherosclerotic plaque and/or by a blood clot forming over the plaque itself or by a blood clot originating from another vascular district [2].

Currently, the two main therapies for the treatment of ischemic stroke are: (i) drug therapy, and (ii) endovascular surgery for mechanical thrombus removal, also known as thrombectomy, which is the subject of interest of this thesis. Mechanical thrombectomy is a minimally invasive endovascular surgical procedure, which involves the insertion of a microcatheter at the occluded cerebral artery, inside which a self-expanding

NiTinol stent retriever is contained. The stent is initially crimped inside the microcatheter, but once the complex is positioned astride the thrombus, part of the catheter is pulled out, allowing the device to expand and the clot to be incorporated. The coagulum-stent-microcatheter complex is then led into a receiving catheter and transported outside the patient [3]. Due to the complex nature of the surgical procedure, conducting in vitro and in silico tests on it (or on the devices used in it) has the potential to deepen our understanding of the procedure itself, to optimise its application and to improve its efficacy.

The first part of this thesis work was aimed at developing in silico models for the reproduction of a set of six in vitro experiments conducted by Cerenovus (Johnson & Johnson Medical Devices Companies, Galway), in which the aforementioned surgical procedure was tested on an experimental bench, making use of three different stents currently commercially available: Trevo XP (Stryker, Michigan, USA), EmboTrap II (Cerenovus, Galway, Ireland) and Solitaire 2 (Medtronic, California, USA). They were applied on thrombi with low or high prevalence of fibrin (45% and 0% of red blood cells – RBC – respectively), inserted into the three-dimensionally

printed internal carotid artery (ICA), filled with saline a saline solution. Specifically, all the thrombi were positioned in the M1 tract of the middle cerebral artery (MCA).

The aim of the second part of the project was to apply the models created - and validated by comparison with the experimental counterpart - to reproduce a second set of six experiments conducted by the company, of which only the images of the initial time instant were provided (showing the stent already positioned astride the thrombus, expanded and ready to be withdrawn), and to analyse how the differences between the starting conditions of the two sets - in terms of the shape and position of the thrombus, the position of the stent tip at the beginning of the withdrawal phase, and the position of the stent tail with respect to one of the three possible distal branches - could influence the outcome of the procedure.

2.   Materials and methods

2.1. Discretization and properties of the components

All the computational models described in this thesis work consist of the following components: i) the **clot**, composed of a solid part, characterised by a mesh of solid (three-dimensional) tetrahedral elements, and a shell, characterised by a mesh of triangular (two-dimensional) shell elements, both types having element dimensions between 0.2 mm and 0.5 mm; ii) the **trajectory** for the positioning and subsequent withdrawal of the stent, discretized in (one-dimensional) beam elements of length 0.5 mm; iii) the **vessel,** discretized with quadrangular shell type elements of minimum size 0.2 mm maximum 0.5 mm, the geometry of which - reproducing the section of the internal carotid artery (ICA) and its subsequent branches into the anterior cerebral artery (ACA) and middle cerebral artery - has been provided by the company; iv) **the positioning catheter**, discretized with quadrangular shell-type elements with an average size of 0.2 mm; v) the **stents**, discretized with beam-type elements 0.2 mm in length; specifically, the geometry of EmboTrap II was provided by the company in CAD format, while, in the case of Solitaire 2 and Trevo XP, the repetitive cells were

reconstructed and then appropriately duplicated to build the entire geometry using MATLAB (MathWorks, Inc, Natick, MA, USA); (vi) **the crimping funnel**, consisting of a mesh of mixed (triangular and quadrangular) shell elements, ranging in size from 0.15 mm to 0.2 mm; (vii) the **receiving catheter**, consisting of a mesh of quadrangular shell elements of size 0.3 mm.

The positioning catheter, the vessel, the receiving catheter and the crimping funnel were modelled as rigid bodies. To the solid component of the thrombus was assigned the mechanical model of a foam, into which stress-strain curves obtained from in vitro tests on thrombus analogues, originating from ovine venous whole blood, were imported [3]. To the stents were assigned the mechanical model of a self-expanding shape memory material with a Young's modulus of 65 GPa and a Poisson's coefficient of 0.3. Between the red thrombi (i.e. 45% RBC) and the wall, a friction coefficient of 0.1 was set, while for the white thrombi (i.e. 0% RBC), two sets of tests were conducted, characterised by a friction coefficient of 0.1 and 0.6, respectively. The latter choice was supported by the presence of studies in the literature demonstrating the greater resistance to drag proposed by thrombi with a greater prevalence of fibrin [4].

2.2. Reproducing the initial conditions of the test benches

The reproduction of the initial conditions of the in vitro test bench was developed through three stages: i) creation of the computational models of the thrombus; ii) realisation of the trajectory to be followed by the catheter and stent; iii) positioning of the stent tip at the beginning of the withdrawal phase.

Creation of computational models of thrombi
From a morphological point of view, the thrombi to be manufactured have been categorised into two categories: bifurcated thrombi (i.e. characterised by a cylindrical body and two protuberances at either end, which give the thrombus a 'T' shape due to the interaction with a vessel bifurcation) and non-bifurcated thrombi.
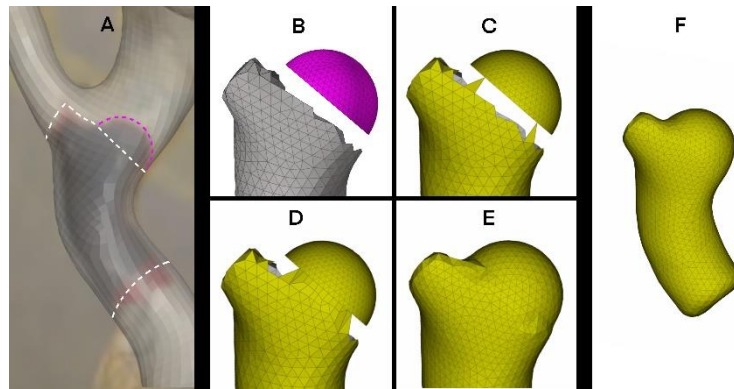
Figure 1 - A) Model of the vase imported into LS-PrePost and superimposed on the experimental photo. The white dashed line highlights the trajectory that was followed to cut the vase; the fuchsia dashed line highlights the hemispherical shape to be recreated; B) Creation of the hemisphere in HyperMesh; C) Manual creation of few missing elements in ANSA; D) Automatic filling of the region between the manually created elements; E) Result of the complete fitting; F) Result at the end of the smoothing process.

The first approach followed for all thrombi was to draw them manually, using the discretised vessel geometry model as a starting point (Figure 1). Of the latter, in each case, the region where the experimental photo showed the presence of the thrombus was isolated and the remaining regions were eliminated. The hollow, jagged ends of the thrombus body were then filled and smoothed within the ANSA software (BETA CAE System, Switzerland).

Of the bifurcated thrombi, it was then decided to make a second version following an alternative approach, based on the idea of not drawing the bifurcation 'a priori' on the thrombus head, but to obtain it as the result of a push of the thrombus - now drawn in a simplified cylindrical shape - on the wall of the bifurcation of the vessel, simulated within LS-DYNA (ANSYS, USA). This approach will henceforth be referred to as the "push method" (Figure 2).
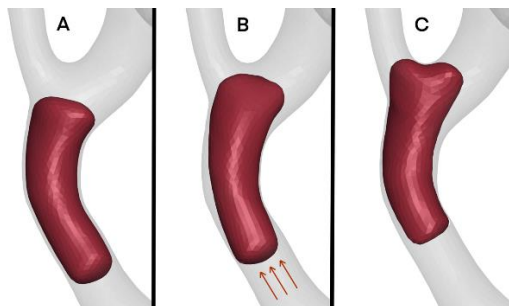

Figure 2 - Initialization of bifurcated thrombi using the push method

Creating the trajectory for the withdrawal phase

For the realisation of the trajectory to be followed by the catheter, a geometric line corresponding to the axis of the vessel - supplied by the company - was extracted from the starting model of the vessel in all its ramifications - henceforth referred to as the 'centreline' - and used as a starting point. The following modifications were then applied to it using Hypermesh software (Altair Engineering, Michigan, USA): **(i)** reduction of the curvature at the vessel loops, to simulate the stretching effect that occurs on the catheter as a result of the application of the withdrawal force; **(ii)** removal of two of the three possible end branches in the M2 region of the MCA, depending on the position of the stent tail occupied in the various test benches; **(iii)** customisation of the trajectory in the vicinity of the thrombus, based on comparison with the experimental photos of each case.

Positioning the stent tip

In order to determine at what height the stent should stop at the end of the positioning phase, a visual comparison was made between the reference image and the respective in silico model, the latter observed from the same perspective as captured by the experimental snapshot. The node of the computational trajectory matching the point where the device head stops in reality was then identified. The node in question was finally set as the final co-ordinate of the translation imposed on the device during the positioning phase.

Table 1 - Results of the first set of simulations, linked to the first set of six experiments

Thrombus	Stent	In vitro outcome	Point of loss of in vitro thrombus	In silico outcome	Point of loss of in silico thrombus
Red (T-shape)	Trevo XP	Positive	/	Negative	ICA horizontal section
	EmboTrap II	Positive	/	Negative	Bifurcation between ICA and ACA
	Solitaire 2	Negative	Siphon[1]	Negative	Siphon
White (low friction)	Trevo XP	Negative	Siphon	Positive	/
	EmboTrap II	Negative	Base of the ICA	Positive	/
	Solitaire 2	Negative	Siphon	Negative	Base of the ICA

2.3. Modelling the clinical procedure

The computational modelling of the surgical procedure was carried out according to the process developed by Luraghi et al. [3] which involves the subdivision of the former into several stages: i) **crimping**, in which the stent is inserted inside a funnel with a minimum diameter of 0.5mm, appropriately activating contacts that allow the device to deform towards a radially compressed configuration; ii) **stent positioning**, in which the device is slid into the catheter – the latter previously positioned so that it adheres to the desired trajectory - until the tip reaches the position requested by the operator (iii) **deployment**, in which the contacts between the stent and the positioning catheter are deactivated, allowing the expansion of the stent and the interaction with the thrombus; (iv) **retrieval**, in which the stent and the thrombus trapped in it are dragged along the pre-determined trajectory until a receiving catheter is reached. The simulations were carried out using a computer equipped with 28 Intel-MPI 2018 Xeon 64 processors, with 250 GB RAM.

3. Results

3.1. Model validation

For the first six experiments conducted by the company, a first series of simulations was conducted, in which all thrombi were faithfully drawn from the snapshots of the in vitro tests and a friction coefficient of 0.1 was set between each thrombus and the vessel. Once the results were obtained, Cerenovus provided integral videos of the correlated in vitro thrombectomy procedures. The results of all these tests are reported in the Table 1. It can be seen that there was a considerable discrepancy in outcomes between in vitro and in silico tests (consistency in two out of six outcomes). Regarding the red thrombi, it was hypothesized that the cause of this discrepancy could concern their initial T-shape which they were designed with; in fact, they maintain the protuberances of the bifurcation during the withdrawal phase, contrary to what occurs in vitro, resulting in a high number of interactions with the wall - especially in correspondence of the curvatures and section narrowings - which facilitate the loss of adhesion on the stent (Figure 3). For white thrombi, on the other hand, it was hypothesized that the cause might relate to the friction coefficient between thrombus and vessel, as white clots in vitro showed greater resistance to dragging than red clots; a hypothesis confirmed by the literature [4]. A second series of computational simulations was therefore initiated by applying certain modifications: bifurcated red thrombi were obtained by the push method and white thrombi were assigned a friction coefficient of 0.6.

The results of this second series are shown in the Table 2 from which greater agreement with the in vitro counterpart can be seen, both in terms of the outcome of the procedure (five out of six) and of the final position assumed by the thrombus. In the red thrombi made with the push method, the initial cylindrical shape is recovered once the bifurcation between ICA and ACA is passed; the latter reproduces the thrombus dynamics in the subsequent vessel sections more accurately, with a lower number of interactions between clot and vessel. Regarding simulations with white thrombi, a higher friction coefficient allows a concordance of outcomes to be obtained in the case of the Trevo XP (Figure 4) and a better reproduction of the final position assumed by the thrombus in the case of the Solitaire 2, while no substantial differences are noted in the case of the EmboTrap II.

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[1] Characteristic curvature of the ICA, preceding the ACA-MCA bifurcation.

Table 2 - Results of the second set of simulations, linked to the first set of six experiments.

| Thrombus	Stent	In vitro outcome	Point of loss of in vitro thrombus	In Silico outcome	Point of loss of in silico thrombus
Red (Push method)	Trevo XP	Positive	/	Positive	/
	EmboTrap II	Positive	/	Positive	/
	Solitaire 2	Negative	Siphon	Negative	Siphon
White (high friction)	Trevo XP	Negative	Siphon	Negative	Siphon
	EmboTrap II	Negative	Base of the ICA	Positive	/
	Solitaire 2	Negative	Siphon	Negative	Siphon
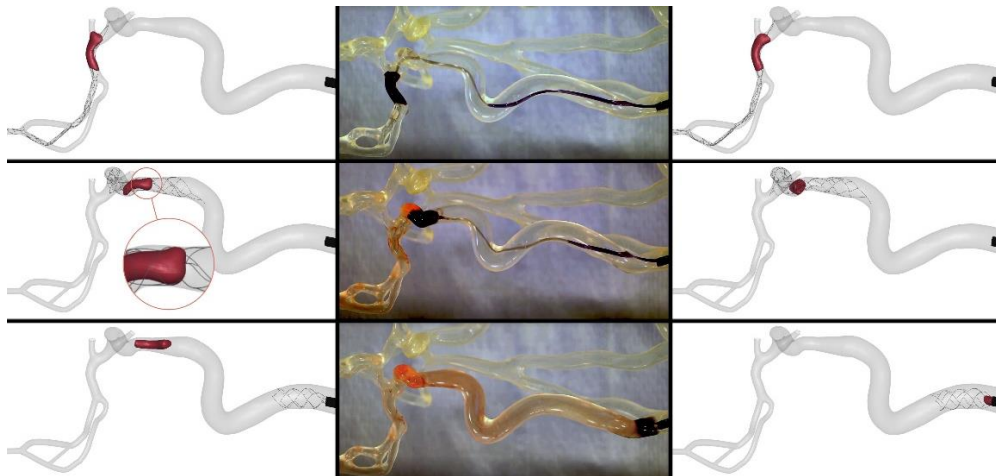
Figure 3 - Trevo XP paired with a red thrombus. From left to right, respectively, three frames extracted from: simulation of the first series (i.e. T-thrombus), in vitro experiment and simulation of the second series (i.e. push method).
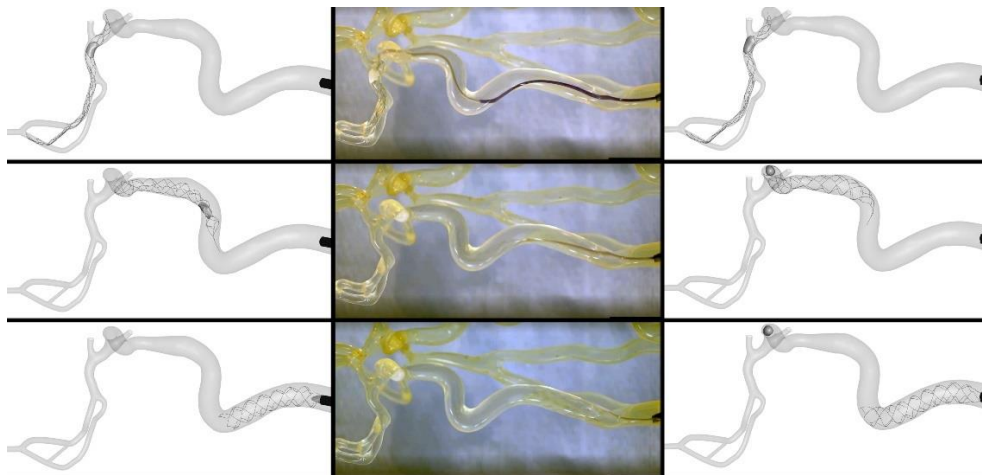

Figure 4 - Trevo XP coupled to a white thrombus. From left to right, respectively, three frames extracted from: simulation of the first series (low friction), in vitro experiment, simulation of the second series (high friction).

Table 3 - Results of the series of blind simulations linked to the second set of six experiments.

Thrombus	Stent	In silico outcome	Point of loss of in silico thrombus
Red (push method)	Trevo XP	Negative	Siphon
	EmboTrap II	Positive	/
	Solitaire 2	Negative	ICA vertical section
White (high friction)	Trevo XP	Negative	Siphon
	EmboTrap II	Negative	ICA horizontal section
	Solitaire 2	Negative	Siphon

3.2. Influence of the initial conditions of the experimental tests on the outcome of the procedure

Given the results obtained from the validation phase of the model, it was decided to conduct the blind simulations reproducing the last six experiments (i.e. the second set) with the application of the push method for the initialization of the bifurcated thrombi and the setting of a higher friction coefficient (0.6) between the vascular wall and the white thrombi, the results of which are schematically reported in the Table 3. An in-depth comparison was conducted between the simulations of the first set and their respective counterparts of the second set, which differed in specific features - shape and position of the thrombus, position of the stent tip at the beginning of the withdrawal phase, position of the stent tail with respect to one of the three possible distal branches - in order to understand whether there was a dependence of the simulation result on one or more of these initial features.

The following conclusions were drawn: **(i)** positioning the device too proximal to the thrombotic mass does not guarantee an optimal grip of the device on the clot, favoring instead a push towards undesirable branches (e.g. the ACA); **(ii)** small clots pass more easily through the large cells of the retrieval devices but, at the same time, interact less with the vessel wall during the withdrawal phase, especially at the curvatures; **(iii)** no relevant dependence on the ramifications of the M2 tract in which the stent is inserted was observed **iv)** the closed-tail design of the EmboTrap II proved more effective in maintaining thrombus than the Solitare II and Trevo XP, which are characterised by an open tail.

4. Discussion and Conclusions

Despite the absence of a thrombus fragmentation model and the flow conditions of the saline solution present in vitro, and the simplification of the mechanical properties assigned to the vessel and to the catheter, it emerged that the in silico simulations reproduced the behaviour of the experimentally tested mechanical thrombectomy procedure with high fidelity, thus offering the possibility of using the models as a reliable tool for evaluating the effectiveness of the operation and the devices used in it and for analyzing the factors

involved, as it was done in the second part of this project.

Possible future developments of this thesis work may concern: i) the introduction of a thrombus fragmentation model; ii) the conduction of fluid-structure analyses, which recreate realistic blood flow conditions; iii) the introduction of specific models to describe the mechanical properties of the vascular wall and the positioning catheter; iv) a study on the influence of the initial placement of the catheter with respect to the thrombus.

In conclusion, this study has shown the reliability of the computational model of the thrombectomy procedure, proving the possibility to use the model for further understanding of the success or failure causes of the clinical procedure. The validation of computational models is of fundamental importance for their use in device optimization and in the emerging field of in silico clinical trials, with the aim of reducing time and costs, supporting the design of new devices and/or new procedures, and minimizing animal testing.

Bibliography

[1] [Online].https://www.salute.gov.it/portale/salute/p1_5.jsp?id=28&area=Malattie_cardiovascolari.

[2] [Online].https://www.nhlbi.nih.gov/health-topics/stroke.

[3] G. Luraghi, J. F. Rodriguez Matas, G. Dubini, F. Berti, S. Bridio, S. Duffy, A. Dwivedi, R. McCarthy, B. Fereidoonnezhad, P. McGarry, C. B. L. M. Majoie e F. Migliavacca, «Applicability assessment of a stent-retriever thrombectomy finite-element model,» *Interface Focus,* vol. 11, n. 1, 2021.

[4] S. Patil, J. Darcourt, P. Messina, F. Bozsak, C. Cognard e K. Doyle, «Characterising acute ischaemic stroke thrombi: insights from histology, imaging and emerging impedance-based technologies,» *Stroke & Vascular Neurology,* 2022.