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Applicability analysis to evaluate credibility of an *in silico* thrombectomy procedure

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ABSTRACT

Intra-arterial thrombectomy is a minimally invasive procedure in which an obstructing thrombus (clot) is removed using a minimally-invasive device: a stent-retriever. The stent-retriever is first deployed, and then the thrombus is removed during stent-retriever retraction. This procedure can be simulated using a detailed computational model. However, to be useful for an *in silico* trial in a clinical setting, model credibility should be demonstrated. The aim of this work is to apply a credibility process for the validation phases to the thrombectomy procedure in order to deem it credible for use in an *in silico* trial. Validation evidence is proposed for the identified context of use and then used to build credibility to the numerical model. Applicability of the proposed model is justified and assessed using a rigorous step-by-step method based on the ASME V&V40 protocol.

1. Introduction

Computational models might be considered as credible according to their demonstrated ability to replicate the modeled reality within a predefined tolerance (Schruben, 1980). To build credibility, computational experiments should be reproducible; that is, the experiment can be repeated by others to obtain similar results. They should also be reliable; that is, simulated results have satisfactory accuracy and precision (Mulugeta et al., 2018).

Validation, verification and uncertainty quantification (VVUQ) provide methods to ensure model reliability. Verification tests the accuracy of the implementation of the formulated model. In validation, one determines the accuracy of the model formulation. This is often achieved by comparing simulation results with results obtained from a physical experiment. In this way, both validation and verification are responsible for the accuracy of the computational results (Oberkampf et al., 2002). In uncertainty quantification (UQ), one estimates, analyses and, if possible, reduces uncertainty in the results of computational models due to uncertainties in model parameters and initial- and boundary conditions.

The American Society of Mechanical Engineers (ASME) provides a framework for assessing the credibility of computational modeling through verification, validation and uncertainty quantification (VVUQ) approved by the U.S. Food and Drug Administration (FDA). The V&V 40 "Verification and Validation in Computational Modeling of Medical Devices" details the framework for medical devices. This framework provides a guide for the assessment of computational models, and communication of their reliability and validity.

Establishing the credibility of a computational model is paramount when applying the results in safety–critical situations, which is particularly the case for medical applications. Good practice in assessing credibility is to combine VVUQ with a rigorous applicability analysis. A recent paper by Pathmanathan et al. (Pathmanathan et al., 2017) details twelve steps for application analysis. They provide a framework for evaluating and justifying the model validation used for an *in silico* model. An applicability analysis details the relevance of the validation with respect to the context of use (COU) of the model. The applicability of the computational model decreases as the difference between the context of use and the validation conditions increases. The computational model and its validation should mimic as closely as possible the context of use.

In this paper, we provide a step-by-step credibility assessment or applicability analysis based on Pathmanathan et al. (Pathmanathan et al., 2017) following the ASME V&V40 protocol of the *in silico*

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thrombectomy procedure.

Intra-arterial thrombectomy is a minimally invasive procedure for acute ischemic stroke in which the obstructing thrombus (clot) is removed using a minimally invasive device (stent-retriever). The stent-retriever is deployed from the femoral artery access to the thrombus location in the brain. After the deployment of the stent-retriever, the thrombus is removed by the retraction of the stent-retriever (Berkhemer et al., 2015). It is possible to model the critical stage of the thrombectomy process, the part of the procedure that occurs close to the clot, *in silico*. This model incorporates the deployment of the stent in a region local to the thrombus, the interaction between the stent and clot, and the recovery of the clot to the receiving catheter (Luraghi et al., 2021a).

2. Applicability analysis

Twelve steps for the applicability analysis described by Pathmanathan et al. (Pathmanathan et al., 2017) following the ASME V&V40 protocol are here applied to the *in silico* thrombectomy procedure. In the first seven steps, the real environment setting (**R-COU**) and the physical experimental setting (**R-VAL**), and the corresponding computational models (**M−COU** and **M−VAL**) are described (Fig. 1). The following four steps are the central body of the assessment analysis when equalities and differences between all the described ingredients (R-COU, R-VAL, M−COU and M−VAL) are analyzed and commented. The last step presents the conclusion of the credibility assessment.

2.1. Describe the aim of the computational modeling

Assessment of model credibility starts by defining a question of interest. This question describes the intended purpose of the computational model: what question does the computational model hope to answer?.

The main objective of the thrombectomy modeling is to simulate the intra-arterial thrombectomy procedure, performed with stent-retrievers only, in virtual patients. The virtual procedure can be used as a tool to predict procedure outcome: positive if the clot removal is successful, or negative if the clot remains inside the vessel. In this view, the question of interest (**QOI**) is: "Is the thrombectomy procedure with a given stent-retriever capable of successfully removing a clot of a given composition, a given volume, from a given location?".

In silico clinical trials for new devices can be carried out by answering this QOI. These *in silico* clinical trials for acute ischemic stroke will focus on optimization of use of stent-retrievers to improve procedural and periprocedural aspects of therapy and/or improvement of personalized thrombectomy treatment.

2.2. Describe the reality (R-COU) and model elements (M−COU) of the COU

The reality of the context of use (R-COU) is the intended use of the model in the real-world context. The model elements of the context of use (M−COU) defines the way in which the model will be used for R-COU, i.e. the simulations that will be performed. These terms are described in further detail in Pathmanathan et al. (Pathmanathan et al., 2017).

R-COU: In the real-world environment, the thrombectomy model will be used to address questions related to a thrombectomy clinical trial that may involve hundreds of patients (Konduri et al., 2020). For each patient undergoing intra-arterial thrombectomy, a stent-retriever is selected from a (commercially) available device library. For the thrombectomy procedure, a balloon guide catheter is first positioned at the cervical ICA (internal carotid artery) level, out of which the stent, crimped in a microcatheter, is positioned relative to the clot location (the stent-retriever is placed distally with approximately two-thirds of the stent beyond the clot). The stent is then deployed in the vessel by withdrawing the microcatheter. Once the clot is trapped in the stent struts, the stent and entrapped clot are retrieved back to the (receiving) balloon guide catheter (still at the cervical ICA level), with the balloon inflated during the retrieval phase to stop the flow (Berkhemer et al., 2015).

There are a number of sources of variability associated with the procedure:

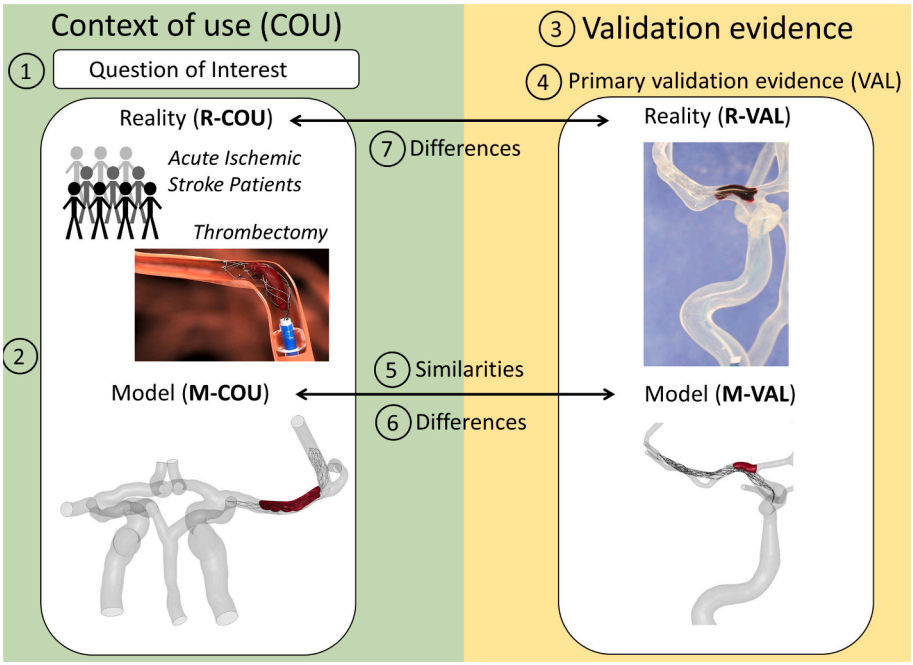

Fig. 1. The reality elements of the contest of use (green box): the real environment setting (R-COU) and the corresponding computational model that is used to assess the question of interest (M−COU). The primary validation elements (yellow box): the physical experimental setting (R-VAL) and the corresponding computational model (M−VAL). The first seven descriptive steps are also shown.

- The geometric details of the patient vessels (Chen et al., 2018; Mokin et al., 2020): (i) diameters and lengths of the segments of interest (internal carotid artery—ICA, anterior artery—A1, middle cerebral arteries—M1 and M2), (ii) curvatures and tortuosity of each segment and (iii) bifurcation angles between the segments.
- The specific clot characteristics (Boodt et al., 2020; Gersh et al., 2009): (i) location of the clot, (ii) length and (iii) clot composition (red blood cell or fibrin dominant).
- The mechanical properties of the vascular tree and the blood flow conditions of the patient (e.g. pressures, flow rate) (Kühn et al., 2020).
- The procedure itself (Ospel et al., 2019): (i) if the patient undergoes thrombolysis with intravenous administration of alteplase before thrombectomy, which alters the clot mechanical properties; (ii) the model and size of the selected stent-retriever; (iii) if the crimped stent is correctly positioned across the thrombus; (iv) the position of the balloon guide catheter that can change according to the tortuosity of the ICA segment.

M−COU: The cerebral arterial branch geometry is pre-processed to obtain a finite-element patient domain. The vessel walls are discretized with rigid quadrilateral elements. The geometries of the three most widespread stent retriever devices (Trevo XP ProVue by Stryker, EmboTrap II by Cerenovus, Solitaire X by Medtronic) are discretized with beam elements with a cross-section integration defined by measuring the real devices with a confocal laser scanning microscope. Uniaxial tensile tests are performed on each device in a temperature-controlled chamber, and then computationally simulated to calibrate the NiTi stent material model parameters (Allegretti et al., 2018). A shape memory alloy material constitutive formulation available in the adopted commercial solver (LS-DYNA, ANSYS) is used to model the mechanical behavior of the device. Clot geometries are placed in the occluded vessel segment with the patient-specific length and with a diameter equal to 95% of the vessel diameter. They are discretized with tetrahedral elements. The clot material model uses a compressible hyperelastic formulation (Kolling et al., 2007) available in the commercial solver. Unconfined compression tests on ex-vivo clots with two different compositions (red: red blood cell dominant and white: fibrin dominant) with and without administration of alteplase are performed (Johnson et al., 2017) and the resulting curves are directly loaded in the solver to fit the material model parameters.

The simulation of the thrombectomy procedure consists of four steps:

I. Catheter tracking/stent crimping: the clot is deformed and pushed against the vessel wall by the microcatheter. At the same time, the stent is crimped in the microcatheter.
II. Stent tracking: the crimped stent is positioned at the location of the thrombus by pushing it along the microcatheter.
III. Deployment: the stent is released by unsheathing the microcatheter and hence it comes into contact with the clot.
IV. Retrieval: the clot, trapped by the stent struts, is then retrieved along the vessel until the receiving catheter is reached at the ICA cervical level.

If the clot reaches the receiving catheter positioned at the ICA cervical level at the end of the simulation the virtual thrombectomy is considered successful. Otherwise, if the clot remains inside the vessel, due to escape from the stent during the retrieval phase, the procedure is considered unsuccessful (Luraghi et al., 2021b). Fragmentation of the clot is not here considered an option because it is not possiblewith the adopted constitutive model of the clot.

2.3. Describe the sources of validation evidence

In this step, we describe available experimental results for model validation. As per Pathmanathan et al. (Pathmanathan et al., 2017), we select one of these as our primary validation evidence. The sources of validation evidence are:

I. Validation of the constitutive model for the clot: Mechanical testing on clots are performed using a parallel plate experimental rig developed for unconfined compression testing of clots in saline solution. Red synthetic clots, and ex vivo red and white clots with and without thrombolysis are subject to confined compression and the testing is numerically reproduced to validate the adopted constitutive material model.
II. Validation of the crimp and release kinematics of the stent: crimping simulations of each device in a microcatheter followed by unconstrained release are carried out to validate the crimping and release kinematic of the modeled device (Fig. 2a).
III. Validation of the thrombectomy procedure in a glass U-bent vessel with one of the three stent-retrievers (the EmboTrap II device) and a red clot (Fig. 2b).
IV. Validation of the thrombectomy procedure in a silicone funnel-shaped vessel with the EmboTrap II device and a red clot (Fig. 2c).
V. Validation of the thrombectomy procedure in a silicone 3D-printed patient-like branch with the EmboTrap II device and a red clot (Fig. 2d).

The final validation evidence (V) is considered the primary validation evidence because the vessel geometry (diameters, lengths, curvatures, tortuosity and bifurcation angles) is the most representative of a patient, despite the mechanical properties of the vessel. Hence it is the most significant model for the purposes of the applicability analysis.

2.4. Describe the reality (R-VAL) and model elements (M−VAL) of the primary validation evidence

In this step, we provide more detail on the primary validation evidence that was selected in Step 3. This detail covers the experimental setup and execution (R-VAL) and the equivalent setup and execution in the model (M−VAL) (Pathmanathan et al., 2017).

R-VAL (Luraghi et al., 2021a): The *in vitro* thrombectomy test is performed in a silicone 3D-printed patient-like vascular branch, designed using physiological dimensions. The averaged diameters of the ICA, M1 and M2 segments measure 3.5, 2.6 and 2.1 mm, respectively. A red clot analog fabricated using ovine blood (Duffy et al., 2017) is placed at the right proximal M1 segment. EmboTrap II size 5x33 mm is used. The experiment is carried out in a stationary flow of saline solution heated to 37 °C. The experiment is repeated three times to ensure repeatability of the results and the thrombectomy runs are all performed by the same person. The experiment is video recorded for comparison purposes: the final displacement of the clot is the measured QOI of the *in vitro* test, which reveals the thrombectomy outcome.

M−VAL (Luraghi et al., 2021a)**:** The CAD geometry of the 3D-printed branch is discretized with rigid quadrilateral elements. The geometries of the EmboTrap stent (size 5 × 33 mm) is discretized with beam elements with a cross-section integration defined by measuring the real devices with the confocal laser scanning microscope. The NiTi stent material is modeled with a shape memory alloy material constitutive formulation, and the material parameters are calibrated by coupling *in vitro/in silico* uniaxial tensile test. The geometry of the red clot is drawn using the real dimensions of the clot used in the experiment. The clot is discretized with tetrahedral elements and is positioned in the right proximal M1 segment. The nominal stress–strain curve from an unconfined compression test, performed on the red clot analog, is used by the solver to model the compressible hyperelastic behavior of the clot.

The simulation of the thrombectomy procedure to replicate the R-VAL (*in silico* thrombectomy in a silicone 3D-printed patient-like vascular branch) consists of four steps, similar to M−COU, executed

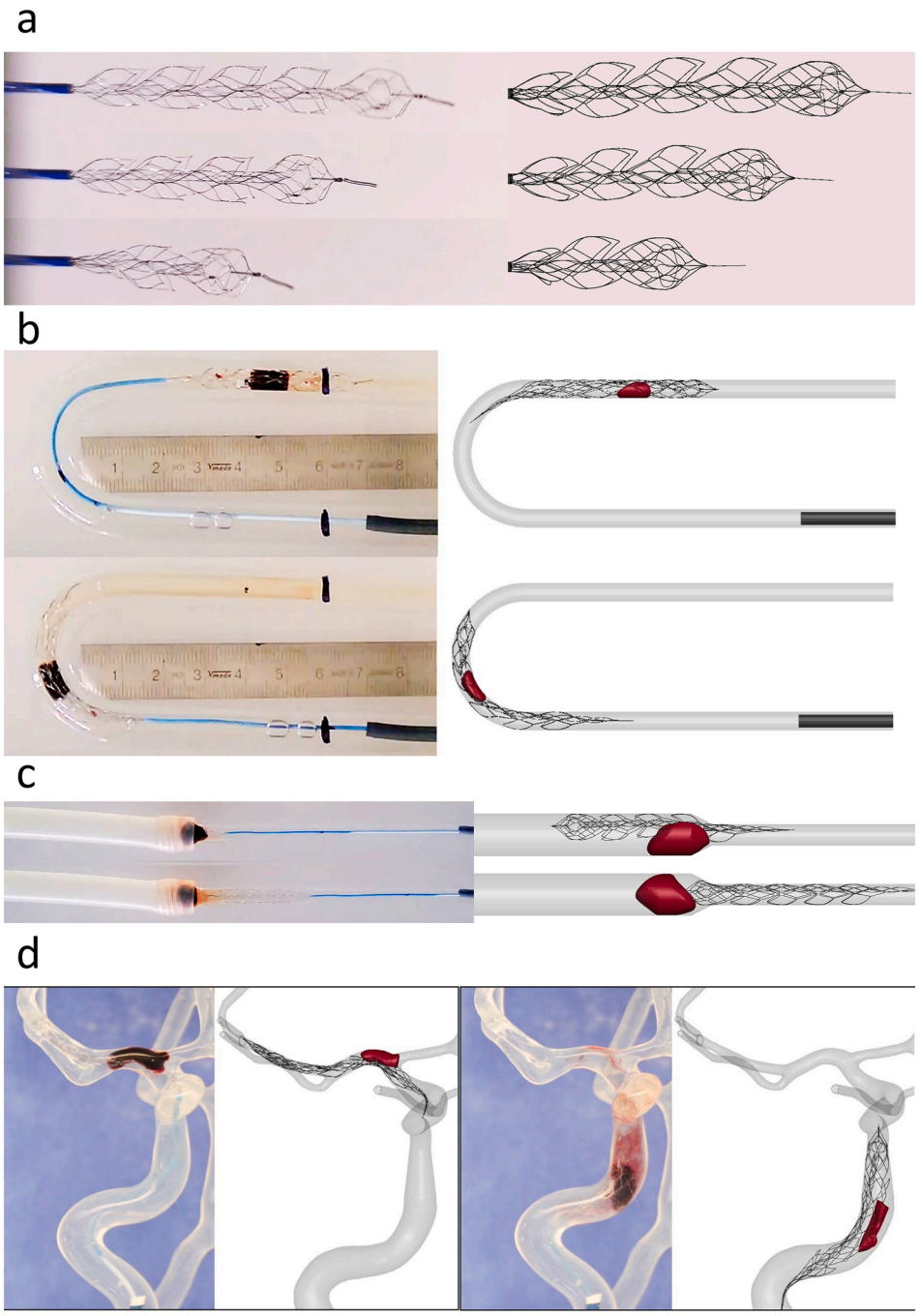

Fig. 2. Validation Models: (a) crimp and release test of the EmboTrapII stent, (b) thrombectomy test in a glass U-bent vessel, (c) thrombectomy test in a silicone funnel-shaped vessel, (d) thrombectomy test in a silicone 3D-printed patient-like branch.

with the solver LS-DYNA (ANSYS):

I. Catheter tracking/stent crimping: the clot is deformed and pushed against the vessel wall by the microcatheter. At the same time, the stent is crimped in the microcatheter. The virtual microcatheter has the same diameter of 0.5 mm of the real microcatheter.
II. Stent tracking: the crimped stent is positioned at the location of the thrombus by pushing it along the microcatheter. The position of the crimped stent is defined to be the same position measured in the experiment.
III. Deployment: the stent is released by unsheathing the microcatheter and it comes into contact with the clot.
IV. Retrieval: the clot, trapped by the stent's struts, and the stent are then retrieved along the vessel until a receiving catheter is reached at the ICA cervical level, in the same position as the experiment.

2.5. Describe the aspects of the computational model that are the identical in M−VAL and M−COU

The following modeling settings are identical in M−COU (the model of *in silico* thrombectomy model) and M−VAL (the model of the primary validation):

I. The element formulation used to discretize each part. The vessels' walls are discretized with quadrilateral rigid elements. The stents are discretized with the same formulation of beam elements and the cross-sections are determined by measuring all the stents with the same microscope. The clots are always discretized with the same formulation of tetrahedral elements. The characteristic dimension of the quadrilateral elements (vessels), the beam elements (stents) and tetrahedral elements (clots) are also the same.
II. The material behavior to model the NiTi material of the stents. The material parameters are calibrated by performing uniaxial tensile tests with the same protocol on each device. The compressible hyperelastic behavior used to model the clots is also the same.
III. The four steps of the simulations (catheter tracking/stent crimping, stent tracking, deployment, retrieval) and their timing. In addition, the numerical details of each step of the simulations are the same: damping coefficients (Luraghi et al., 2018), time-step size, contact algorithms, friction coefficients of the contacts (Gunning et al., 2018). The same commercial explicit finite element solver is also used.
IV. The QOIs—both aim to evaluate the outcome of the procedure, being the successful or unsuccessful removal of the clot.

2.6. Describe the aspects of the computational model that are different between M−VAL and M−COU

The following modeling settings are different in M−COU (the model of *in silico* thrombectomy model) and M−VAL (the model of the primary validation):

I. Vessel geometries. In the M−COU the cerebral arterial branch presents the specific dimensions of the virtual patient, while in the M−VAL the vessels' dimensions are derived from the CAD model of the 3D-printed branch.
II. Stent device. The virtual thrombectomy of the M−COU can be performed with any device selected from the available device library (Trevo XP ProVue by Stryker, EmboTrap II by Cerenovus, Solitaire X by Medtronic) with a specific size. The M−VAL only uses the EmboTrap II, size 5×33 mm.
III. Clot geometry, composition, and location. In the M−COU the clot is located in the virtual patient-specific occluded segment, presents with a patient-specific length and could be red or white. In the M−VAL the length and the location of the red clot are defined to be the same as the experiment.
IV. The stress–strain curves used to fit the clot's material model. Though the material model is the same, the curves used in the M−COU are derived from compression tests performed on *ex-vivo* red and white clots, while the curves used in the M−VAL are derived from a red clot analog.
V. The positions of the crimped stent with respect to the location of the clot and the position of the receiving catheter. In the M−VAL these positions reflect the stent position observed in the experiment, while in the M−COU these positions could vary between virtual patients. The position of the receiving catheter could also change as it depends on the ICA tortuosity.

2.7. Describe the relevant differences between R-VAL and R-COU (ΔR)

The following modeling settings are different in R-COU (the thrombectomy procedure on patients) and R-VAL (the *in vitro* thrombectomy model):

I. Vessel geometries, mechanical properties and constraints. In the R-COU the cerebral arterial measurements of the acute ischemic stroke patients are measured from images. These measurements include the diameters, lengths, curvatures and tortuosity of the ICA, A1, M1 and M2 segments, and bifurcation angles between the segments. The silicone 3D-printed branch of the R-VAL is fabricated with physiological "averaged" dimensions. The mechanical behavior of the vessel walls in the R-COU is nonlinear anisotropic, whereas the vessel walls in the R-VAL are silicone which is isotropic. The vessels are in the R-COU surrounded by brain tissues, whereas in the R-VAL are only constrained on the external ends.
II. Stent device. The thrombectomy of the R-COU could be performed with any commercially available device, with a size according to the dimensions of the patient's occluded vessel. The stent of the R-VAL is the EmboTrap II; size 5x33 mm.
III. Clot geometry, composition, location, and mechanical properties. In the R-COU the clot length, composition (red or white) and segment location are patient dependent. In the R-VAL the red clot analog presents an "averaged" length and is placed in the most commonly occluded segment (M1) (Dutra et al., 2019). The clot mechanical behavior can also vary between the real clots and the clot analogs.
IV. The procedure. In the R-COU the positions of the crimped stent with respect to the location of the clot and the position of the receiving catheter. Thrombolysis could also be performed before the thrombectomy. In the R-VAL the stent is correctly positioned across the clot, the receiving catheter is positioned in its usual location (cervical ICA level) and no thrombolysis is considered. The timing of each step (positioning of the catheter and of the crimped stent, release and retrieval phases) could also be different between R-COU and R-VAL, as it is dependent on the interventional neurologist.
V. The R-VAL is performed with stationary flow of saline solution heated to 37 °C, whereas in reality the fluid is blood at 37 °C. The thrombectomy performed in the R-COU uses balloon-inflation during the retrieval phase to stop the blood flow. However, it is possible that some secondary blood flows from anterior arteries may be present.

2.8. Is it appropriate to use the model aspects listed in Step 5 to make predictions about R-COU? provide Rationale, Evidence, or Discussion. Assume that these model aspects are appropriate for R-VAL (or refer to the validation Results) and then consider each of the differences in ΔR (Listed in Step 7)

Step 5 described the ways in which M−VAL and M−COU are identical. The light-blue cells in Table 1 list the identical aspects between the two models: M−VAL and M−COU. The grey cells list the differences between the two realities: R-VAL and R-COU. This step provides an answer to the question: "for each numerical setting that we assume to be appropriate to model the R-VAL because of the validation results, it is also appropriate to model R-COU in light of the differences between R-VAL and R-COU?"

Element formulations – Are the element formulations adequate to model the parts of the thrombectomy of R-COU? The vessels are deformable in both the R-VAL and the R-COU; however, in both the M−VAL and M−COU are modeled with rigid elements. In the primary validation analysis, the vessel is made with silicone and, observing the recorded video of the experiments the vessels appear not to deform during the procedure. The comparison between the experimental and simulation results provides confidence in this assumption and similarly, the nonlinear vessels' walls of the R-COU are modeled with rigid elements. An additional observation regarding the rigid vessel assumption in M−COU is that, differently to the R-VAL where the silicone vessel is unconstrained from surrounding tissue, actual cerebral vasculature in R-COU is highly constrained by surrounding tissue favoring the rigid vessel assumption for the simulations.

The stent-retrievers are all modeled with the same formulation: beam elements with an integrated cross-section, whose dimensions are

Table 1
Model aspects that are identical between M−VAL and M−COU in light of the differences between R-VAL and R-COU.

Differences between R-VAL and R-COU	Identical aspects between M-VAL and M-COU			
	Element formulations	Material models	Steps of the simulations	QOIs
Vessel (geometry/material)	*Are the element formulations adequate to model the parts of the thrombectomy of R-COU?*		*Are the simulation settings adequate to model the thrombectomy of R-COU?*	
Stent (device and size)				
Clot (geometry, composition and location)		*Are the material models adequate to describe the deformable parts of the thrombectomy of R-COU?*		
Procedure (thrombolysis, stent position, catheter position, timing)				
Fluid (stationary saline solution / blood flow)				*Is it correct not to model the fluid with respect to the QOI?*

defined with direct measures on the real devices. This is a significant simplification in comparison to solid (hexahedral elements) discretization techniques and may cause discrepancies in the integrated stresses and strains. However, the primary validation showed that the adopted beam discretization technique is adequate to properly describe the kinematics of the stent. In fact, the QOIs of both the reality M−COU and the validation M−COU are the thrombectomy outcome prediction, evaluated from the clot and stent interaction and kinematics. In this application, the stress and strain fields within the stent are not explicitly used to answer the QOIs. Moreover, one supporting validation evidence (validation II in Step 3) aims properly at assessing the kinematics of all the stents available in the device library of R-COU with crimping and release simulations.

The clots are modeled with the same tetrahedral element formulation, which has been proven from the validation evidence to adequately describe the large deformation of the clots. The appropriate element formulation mainly depends on the loading modes that the deformable parts are subject to (and these modes remain the same between R-VAL and R-COU). Hence this formulation is independent of the clot geometry, as well as the vessel and stent geometry.

Material models - Are the material models adequate to describe the deformable parts of the thrombectomy of R-COU? The rigid vessel material has already been discussed in the previous section (element formulation). The deformable component in the M−VAL and M−COU is the clot. Unconfined compression tests are performed on red and white clot analogs, on *ex-vivo* red and white clots not exposed to a thrombolytic agent and on *ex-vivo* red and white clots exposed to a thrombolytic agent. The resulting stress–strain curves are directly fitted by the solver to define the parameters of the hyperelastic clot material model. The goodness of the material formulation has been proven by numerically replicating the compression tests and comparing the numerical and experimental stress–strain curves (Validation I in Step 3). The agreement between R-VAL and M−VAL in terms of clot deformation provided confidence in the adopted material model for the clot (red and white, and with and without a thrombolytic agent).

Steps of the simulations: Are the simulation settings adequate to model the thrombectomy of R-COU? The four steps of the simulations (Catheter tracking/stent crimping, Stent tracking, Deployment and Retrieval) reflect the real procedure steps of R-COU and the thrombectomy performed in R-VAL. The R-VAL replicates the real clinical procedure as faithfully as possible. Each step of the simulation was compared with the recorded experiment, in terms of stent and clot kinematics, in the primary and supporting validation evidence. In fact, in the supporting validation tests (Validations III and IV in Step 3) the geometry of the vessel, the material of the vessel, the clot dimension and location, the position of the stent with respect to the clot, and the receiving catheter are different to the primary validation test, and the simulation setting proved adequate to reproduce the *in vitro* thrombectomy conditions (Validations III, IV and V in Step 3). Consequently, this proves the robustness and versatility of the developed numerical analysis (and simulation settings). The R-COU can similarly change the device geometry, the clot location, dimension and composition, and the procedure settings (crimped stent and receiving catheter location), and the model's formulation can accommodate these changes.

QOIs: The aim of both the M−COU and the M−VAL is to determine if there's a positive outcome from the procedure, i.e. the effective removal of the clot. Hence, the main focus of these models is the clot/stent interaction and the final displacement of the clot. For this reason neither of models include the fluid domain. In the R-COU the vessels are filled with blood and during the procedure a balloon is inflated in the cervical ICA to arrest the flow, although a small flux from anterior arteries could be present. The R-VAL is performed under a stationary flow of saline solution at 37 °C. The steadiness of the fluid allows simplification of the fluid–structure interaction problem into a structural one. The fluid forces acting on the structures can be reasonably neglected on both the R-VAL and R-COU.

2.9. Do the modifications to the computational model (Listed in Step 6) result in trustworthy predictions for the COU? provide Rationale, Evidence, or discussion

Step 6 described the ways in which M−VAL and M−COU differ. Each difference is here described and discussed.

Vessel geometry – The vessel geometry of the M−COU differs from the one of M−VAL because the former derives from the specific patient of R-COU and the latter from the CAD model of the 3D-printed branch. Change in vessel geometry means a change in the diameters and length of the ICA, A1, M1 and M2 segments, the curvature and tortuosity of each segment and the bifurcation angles between adjacent segments. From a practical point of view, different vessel morphologies result in different displacements during the Catheter tracking and the Retrieval steps of the simulation. However, this does not affect the trustworthy prediction of the M−COU as demonstrated with the supporting validation evidence using different vessel geometries (Validations III, IV and V in Step 3).

Stent device – The virtual thrombectomy of the M−COU can be

performed with a device selected from the available device library (Trevo XP ProVue by Stryker, EmboTrap II by Cerenovus, Solitaire X by Medtronic) with a specific size. All the modeled stent retrievers are discretized with the same elements (formulation and element size), measured with the same microscope, modeled with the same material law and characterized by the same tensile test protocol. The supporting validation evidence (Validation II in Step 3) validates the kinematics of the device during the crimping and releasing phases for all the modeled stents. From a practical point of view, different devices change only the applied displacement when the stent is crimped because of the different lengths. The different crimped lengths of each device are also considered in the Stent tracking phase to position the stent with respect to the clot.

Clot geometry – The clot in the M−COU comprises patient-specific length and location, while the clot of M−VAL size and location is the same as the R-VAL. The change in length and location of the clot can be accounted for in the simulation settings by changing the position of the catheter and the crimped stent. The flexibility of the numerical model has already been proven by a comparison of the different validation evidence with different clot dimensions and locations (Validations III, IV and V in Step 3).

The stress–strain curves used to fit the clot's material model – Although the material constitutive law used to model the clots in M−COU and M−VAL is the same, the curves used in the M−COU are derived from compression tests performed on *ex-vivo* red and white clots and *ex-vivo* red and white clots exposed to a thrombolytic agent, while the curves used in the M−VAL are obtained from a red clot analog. However, the validation of the constitutive law of the clots is performed with different stress/strain curves from all the tested clots (Validation I in Step 3).

The positions of the crimped stent with respect to the location of the clot and the position of the receiving catheter – The geometry of the vessel and the clot location and dimension affect the tracking of the catheter and the tracking of the crimped stent (in these steps the displacement applied to the catheter and the stent depends on the centerline of the vessel). The tortuosity of the ICA segment also affects the location of the receiving catheter. Finally, the position of the crimped stent changes according to the length of the stent. All these procedural aspects vary from one patient to another and the M−COU settings need to be changed in accordance. Once again, the ability of the model to accommodate all these changes is proven by the conducted validation evidence that uses different vessel geometries and clot geometries and locations (validation III, IV and V in Step 3).

2.10. Provide rationale for trustworthiness if the COU QOIs differ from validation QOIs

The COU and VAL QOIs are identical as they both aim to evaluate the outcome of the thrombectomy procedure. If the clot reaches the receiving catheter positioned at the cervical ICA the thrombectomy succeeds, otherwise the clot remains inside the arterial vessel and the thrombectomy fails.

2.11. Consider the overall computational model M−COU, in the context of differences between R-VAL and R-COU (ΔR)

In light of the already discussed points in Step 8 and 9, one additional question is "Does the M−COU model consider all the aspects of the thrombectomy procedure?". Considering also that improvements to the intra-arterial thrombectomy are still ongoing, another question is "Does the M−COU model different thrombectomy techniques?" (Table 2). As declared in Step 2, the R-COU is the intra-arterial thrombectomy performed as described: a balloon guide catheter is positioned at the cervical ICA level from which the stent, crimped in a microcatheter, is positioned relative to the clot location and is then deployed in the vessel by withdrawing the microcatheter. Once the clot is trapped in the stent struts, the clot and the stent are retrieved together up to the (receiving) balloon guide catheter positioned at the cervical ICA level while the balloon is inflated to stop the blood flow during the retrieval phase. In addition, the virtual treatment could also include thrombolysis with intravenous administration of alteplase before thrombectomy.

This proposed applicability analysis is applicable only to the described thrombectomy procedure. The source of variability is from the generation of virtual patients—the generation of virtual thrombectomy procedures has been already discussed. The authors believe that any modification to the procedural thrombectomy needs to be reconsidered in a different applicability analysis. For example, the assumption of the presence of balloon-inflation in the retrieval phase of the procedure led to the conclusion that the fluid domain modeling is not necessary for the M−COU. Of course, if the thrombectomy is conducted with blood flow, the fluid domain inclusion would need to be reconsidered. Another innovative aspect of the procedure is the inclusion of a single or double aspiration (McTaggart et al., 2017; Ospel et al., 2019), which would involve the inclusion of this aspect in the M−COU with consequent applicability discussion and/or different primary validation evidence choice.

2.12. Assess the overall applicability of the computational model for the COU using sound scientific (albeit subjective) judgment

Our credibility assessment showed that the developed numerical model is credible for conducting *in silico* thrombectomy procedures on virtual patients. In particular, once the generation of a virtual ischemic stroke patient is performed, the numerical workflow generates a discretized patient-specific arterial branch with an occluded vessel. Patient-specific characteristics of the clot are considered. The generation of the virtual procedure includes the choice of the device, the administration, or not, of thrombolysis before the intervention, the position of the receiving catheter and the correct position of the crimped stent with respect to the clot location. All these aspects are considered when

Table 2
Several additional issues regarding M−COU given the differences between R-VAL.

Differences between R-VAL and R-COU	Additional questions regarding M-COU
Vessel (geometry/material)	No additional questions
Stent (device and size)	No additional questions
Clot (geometry, composition and location)	No additional questions
Procedure (thrombolysis, stent position, catheter position, timing)	Does the M-COU model consider all the aspects of the thrombectomy procedure?
Fluid (stationary saline solution / blood flow)	Does the M-COU model use a different thrombectomy technique?

determining the steps of the simulations. The numerical results include the stress and strain fields of the stent-retriever and the clot, but, with respect to the QOI, the only relevant result is the final position of the clot, which determines the overall outcome of the procedure.

3. Conclusions

Model credibility refers to the level of trust that we place in the computational model with regards to the identified context of use. This trust is evaluated through a number of credibility factors. These factors refer to the activities that need to be undertaken in order to establish how well the model can be trusted. These actions include code verification, validation of the computational model including sensitivity analysis and uncertainty quantification, and evaluation of the applicability of the computational model with regards to the context of use.

Recently, the regulatory process for biomedical devices started receiving and accepting *in silico* evidence from modeling and numerical simulations (Viceconti et al., 2020). VVUQ could be considered as good practice, contributing to simulation credibility (Mulugeta et al., 2018), and provides specific evidence for a given regulatory procedure (Viceconti et al., 2020). The V&V 40 standard aims at "assessing the degree to which the computational model is an accurate representation of the reality on interest" but how the credibility of the model has to be established is subjective (The American Society of Mechanical Engineers, 2018). In this regard, our framework is based on the guidlines proposed by a group working at FDA (Pathmanathan et al., 2017).

In this study, an applicability assessment of an *in silico* thrombectomy model was performed, and the differences between the context of use and the validation conditions were argued and discussed. After demonstrating the credibility of *in silico* models for a specific context of use, e.g. in an *in silico* stroke trial, a formal qualification is needed, after which the results of the *in silico* model can be used in producing evidence in the regulatory process related to a new medical device. To help the credibility assessment of a clinical procedure, in general, we suggest designing the validation evidence and the corresponding models only once the context of use and the main questions of interest are clearly stated and defined.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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