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In silico thrombectomy trials for acute ischemic stroke

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ABSTRACT

Background and objective: In silico trials aim to speed up the introduction of new devices in clinical practice by testing device design and performance in different patient scenarios and improving patient stratification for optimizing clinical trials. In this paper, we demonstrate an in silico trial framework for thrombectomy treatment of acute ischemic stroke and apply this framework to compare treatment outcomes in different subpopulations and with different thrombectomy stent-retriever devices. We employ a novel surrogate thrombectomy model to evaluate the thrombectomy success in the in silico trial.

Methods: The surrogate thrombectomy model, built using data from a fine-grained finite-element model, is a device-specific binary classifier (logistic regression), to estimate the probability of successful recanalization, the outcome of interest. We incorporate this surrogate model within our previously developed in silico trial framework and demonstrate its use with three examples of in silico clinical trials. The first trial is a validation trial for the surrogate thrombectomy model. We then present two exploratory trials: one evaluating the performance of a commercially available device based on the fibrin composition in the occluding thrombus and one comparing the performance of two commercially available stent retrievers.

Results: The Validation Trial showed the surrogate thrombectomy model was able to reproduce a similar recanalization rate as the real-life MR CLEAN trial ($p = 0.6$). Results from the first exploratory trial showed that the chance of successful thrombectomy increases with higher blood cell concentrations in the thrombi, which is in line with observations from clinical data. The second exploratory trial showed improved recanalization success with a newer stent retriever device; however, these results require further investigation as the surrogate model for the newer stent retriever device has not yet been validated.

Conclusions: In this novel study, we have shown that in silico trials have the potential to help inform medical device developers on the performance of a new device and may also be used to select populations of interest for a clinical trial. This would reduce the time and costs involved in device development and traditional clinical trials.

1. Introduction

An acute ischemic stroke (AIS) occurs when the blood flow to the brain is disrupted by an occlusion or a thrombus in a major

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intracranial artery. In 2015, the MR CLEAN trial showed the added benefit of endovascular treatment/thrombectomy to mechanically remove the thrombus compared to the use of thrombolytics, that lyse the occluding thrombus, alone [1]. This was subsequently confirmed by several other trials [2]. Since then, thrombectomy has become the standard of care for AIS treatment [3]. Delays to restore blood supply to the affected region, by successfully removing the thrombus, is associated with increased neuronal loss and functional disability [4]. Hence, complete recanalization and reperfusion in a single attempt are accepted measures to evaluate the success of the treatment and performance of devices. The success of treatment depends on several factors including vessel access, and the characteristics of the thrombus play an undeniably important role. Qualitative and quantitative analysis using imaging techniques that are routinely used in AIS care and histological analysis of mechanically retrieved thrombi has shown that thrombi are heterogeneous. They can contain varying number of red blood cells (RBCs), fibrin, white blood cells (WBCs), platelets, calcification and lipids, which can influence the treatment success. For example, fibrin-rich thrombi are stiffer which limits their interaction with the struts of the stent-retriever and hence they are thought to be more difficult to retrieve [5,6].

There is still much to gain in the stroke treatment landscape and several novel devices are currently being developed to better target and personalize stroke treatment. However, up to 90% of the clinical trials testing new treatments are unsuccessful and, by design, clinical trials do not explain why treatments fail, thus increasing the time and costs of introducing new treatments in the clinic. Computational or in silico modelling approaches are becoming increasingly accepted to facilitate the research and development of biomedical products [7–9]. In silico trials (ISTs) can be set up by combining in silico models of disease and treatment with statistical models that generate 'virtual' patients (combination of prognostic clinical factors and parameters required for the in silico models) [10–12]. ISTs can then generate outcome at a population level to predict the efficacy of a treatment.

A common obstacle to running ISTs is the computational requirements of the models. Many models of biological and medical processes can be computationally expensive for a single patient, and hence running these models for potentially hundreds of patients is only possible on advanced high performance computing infrastructure, which may not be readily available to many potential users of IST technology. A method to overcome this limitation is the use of surrogate models (also known as metamodels or emulators). The goal of surrogate modelling is to estimate the outcome of interest, from a complex model, with a computationally inexpensive model. Such an approach is also commonly used in uncertainty quantification, which is another application requiring large numbers of simulations [13–15]. This reduction in complexity often comes with a loss of accuracy and mechanistic understanding of the simulation result. For an IST application, the level of accuracy and understanding of the detailed model for every patient is not required, as the outcomes of interest are at the population scale.

There are several approaches to surrogate modelling. One approach is a reduction in model complexity, for example, a simplification of the physics [16] or a reduction of element order and/or grid resolution in finite element modelling [17]. Alternatively, one can train a statistical model using results from the full model. Common approaches for this are Gaussian Process Models [13,15] and Generalized Linear Models [14] (such as logistic regression models).

Miller et al. [18] and Konduri et al. [19] have previously published a framework for designing and implementing an IST for AIS. In this study, we present and integrate a novel surrogate model, based on logistic regression trained on outcomes from a finite-element model of thrombectomy, into our IST framework [18,19] and validate the model using the MR CLEAN trial [1,20]. We then demonstrate the use of the IST platform, using the surrogate thrombectomy model, for studying the influence of fibrin composition in the thrombus on thrombectomy outcome and comparing the performance of two commercially available thrombectomy devices.

2. Methodology

To execute the proposed ISTs we use the following three steps. First, we implement a surrogate model based on a finite-element (FE) thrombectomy model [21,22]. Secondly, we link the virtual patient characteristics included in the virtual patient generation model used in our IST framework [18] to the thrombectomy model inputs. Finally, we incorporate this surrogate model into our IST framework [18] so we can sample virtual patients from the virtual patient generation model, apply the surrogate model to the generated cohort, and aggregate and report the results on a population-level. In the following sections, we describe the methodology of these three steps in detail. We then describe the three ISTs that were run for this study. Fig. 1 shows a summary of the collection of clinical data and how it is used to develop and validate the models for the IST.

2.1. Surrogate thrombectomy model

Given the computational requirements of FE thrombectomy simulations (19–50 h on 28 CPUs of an Intel Xeon64), it is practically infeasible to use this simulation approach for a large cohort of virtual patients. Consequently, we use a surrogate, logistic regression, model for the trials, trained using FE model simulations across the range of observed patient parameters. The FE model of thrombectomy (Fig. 2) has been previously validated [21] and is described in detail in Luraghi et al. [22]. Implementation details are given in Supplementary Section S3.1. In brief, the FE model simulates a thrombectomy procedure using a stent retriever device (Device A or B) on 100 segmented vascular geometries from patients in the MR CLEAN Registry [3] (described in Section 2.2), as shown in Fig. 1. Only occlusions in the M1 segment of the middle cerebral artery were modelled, as these are most common [1,3].

To capture the effect of thrombus characteristics (length and fibrin composition) on the performance of Device A, we ran two simulations for each vascular geometry, with randomly selected thrombus characteristics (from the empirical distributions). Of these, 184 had a viable outcome, whereas 16 of them encountered numerical instability and would have required *ad hoc* simulation settings. For Device B, 100 thrombectomy simulations were run, with 94 of these resulting in viable outcomes.

In Bridio et al. [23] the importance of vascular anatomy on the outcome of virtual thrombectomy procedures was demonstrated. The 100 patient-specific vasculatures were analyzed with the methodology described in Bridio et al. [23] to extract 28 anatomic parameters for each vascular model.

Each carotid siphon was divided in 4 bends (superior, anterior, posterior and inferior, Fig. 3A) and the following parameters were extracted with a MATLAB (The MathWorks, USA) script, (Fig. 3B–E):

- length of the Internal Carotid Artery (ICA) bends: L^{sup}, L^{ant}, L^{pos}, L^{inf};
- average diameter of the ICA bends: D^{sup}, D^{ant}, D^{pos}, D^{inf};
- radius of curvature of the ICA bends: r^{sup}, r^{ant}, r^{pos}, r^{inf};
- tortuosity of the ICA bends: t^{sup}, t^{ant}, t^{pos}, t^{inf} (calculated as: $t^{bend} = \frac{L^{bend}}{d^{bend}} - 1$, where L^{bend} is the length of the bend along the centerline and d^{bend} is the Euclidean distance between extreme points of the bend);

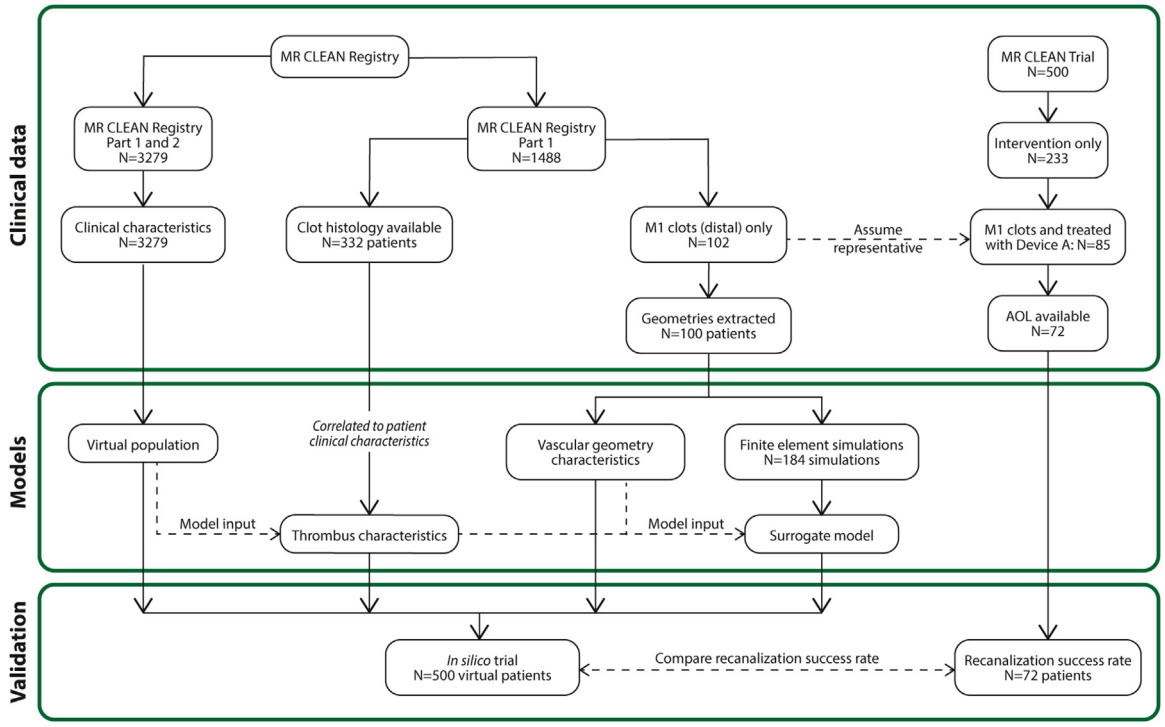

Fig. 1. A summary of the use of clinical data to develop and validate the Device A surrogate model, as well as the interdependence between the different models used within the IST framework.

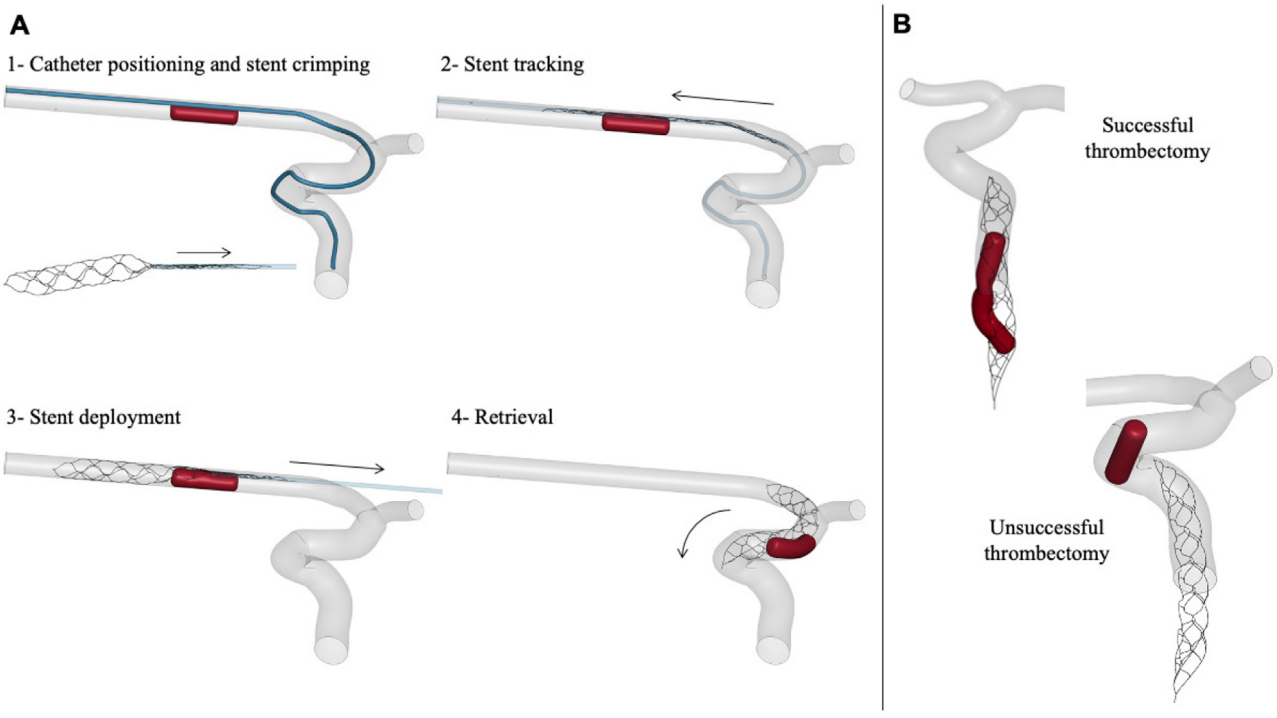

Fig. 2. A) Steps of the thrombectomy simulation. The Middle Cerebral Artery (MCA) of the vascular models is designed as straight, because the images are collected with angiographies with contrast liquid that cannot reach beyond the occlusion site. B) Examples of successful and unsuccessful thrombectomy outcomes.

- angles between adjacent ICA bends: $\alpha^{sup-ant}$, $\alpha^{ant-pos}$, $\alpha^{pos-inf}$;
- distance between the bifurcation point and the starting point of the superior bend: d^{T-sup};
- distances between adjacent ICA bends: $d^{sup-ant}$, $d^{ant-pos}$, $d^{pos-inf}$;
- angles at the T-junction (bifurcation of the ICA into MCA and the anterior cerebral artery (ACA)): $\alpha^{ICA-ACA}$, $\alpha^{ICA-MCA}$, $\alpha^{MCA-ACA}$;
- average MCA diameter (M1 segment): D^{MCA};
- average ACA diameter: D^{ACA}.

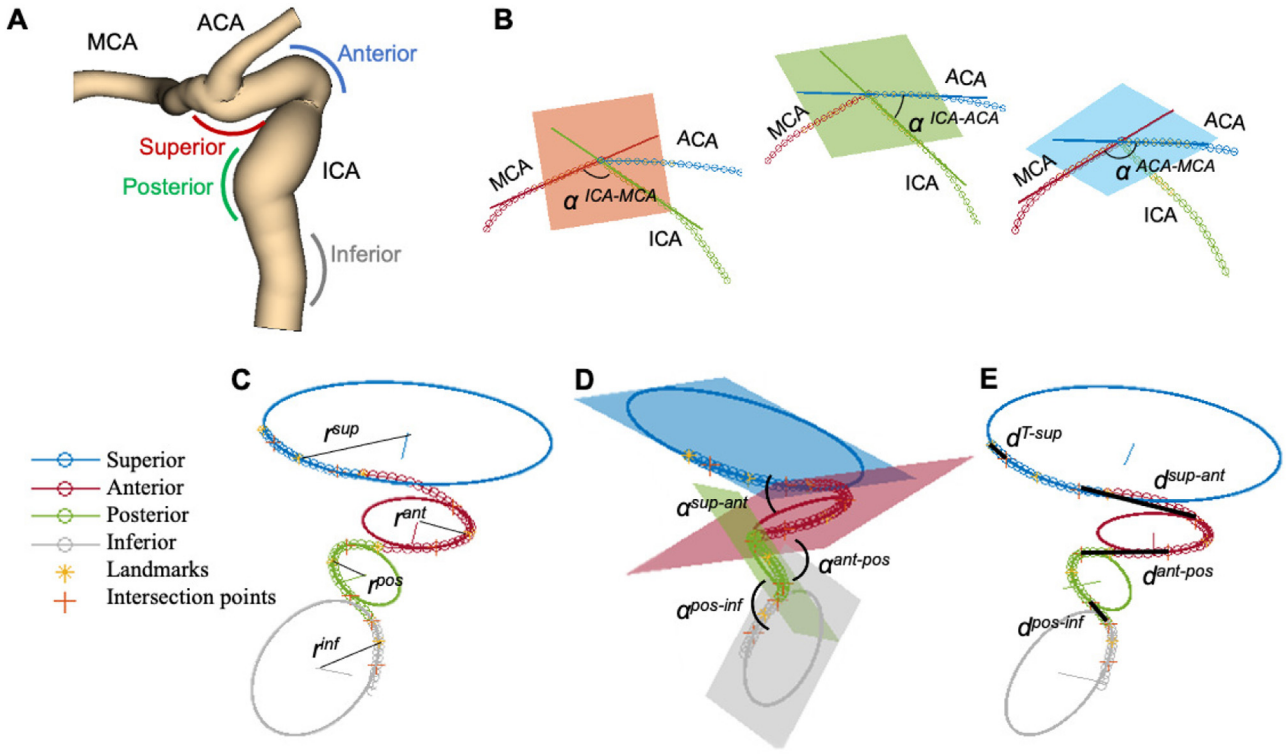

Fig. 3. Geometric characterization of the vascular anatomy: A) four bends of the carotid siphon; B) angles at the T-junction; C) radius of curvature of the ICA bends; D) angles between adjacent ICA bends; E) distances between the bifurcation point and the starting point of the superior bend, and between adjacent ICA bends. Adapted from Bridio et al. [23].

The median and interquartile ranges of the calculated parameters are provided in Supplementary Section S2.1.

The collected anatomy parameters along with the thrombus length (L^{thr}), the fibrin/platelet content (Fib), and the associated simulation outcome are the parameters defining each sample in the training database for the surrogate model to be included in the IST pipeline. A binary classification model was chosen that, given as input the geometry and thrombus parameters, provides as outcome a probability of success of the thrombectomy procedure. In this application, the explanatory variables are the geometric and thrombus parameters of each sample, and the two classes are success or failure of the virtual thrombectomy procedure. The chosen algorithm for performing the classification is logistic regression [24], a widely-used supervised machine-learning algorithm used for binary classification problems. Other algorithms were tested, i.e. Perceptron, Support Vector Machines and Stochastic Gradient Descent: logistic regression showed the best performance in a leave-one-out test (training the classification model excluding one sample at a time, to be used for testing), providing above 90% correct predictions.

To reduce the number of explanatory variables, a univariate logistic regression model was trained for each geometric and thrombus parameter, as input for the classification to determine treatment success. We used a test-train approach with 70% of the samples used for training and 30% for testing. To assess the classification ability of the models, the Receiver Operating Characteristic (ROC) curve [25] was constructed for each of the 30 models. Ten-fold cross-validation was performed to assess the consistency of the results. For the purpose of selecting the most influencing parameters in the determination of thrombectomy outcomes, the parameters associated to classification models that produced a ROC curve with Area Under the Curve AUC ≥ 0.7 were chosen. The explanatory variables were thus reduced from 30 to eight parameters: D^{sup}, r^{sup}, t^{ant}, $\alpha^{ICA-MCA}$, D^{MCA}, D^{ACA}, L^{thr}, Fib.

The final multivariable logistic regression model was trained based on samples described by the eight geometric and thrombus parameters and the simulation outcomes. In the IST pipeline, given the eight parameters for a new virtual patient, the model provides the probability for the patient of belonging to the class of successful or unsuccessful thrombectomy procedure.

2.2. Linking virtual patient characteristics to the surrogate thrombectomy model parameters

The virtual population model is based on the data of patients enrolled in the MR CLEAN Registry: a prospective, observational, multi-center study from 16 intervention hospitals in the Netherlands. It includes all AIS patients above the age of 18 who underwent endovascular treatment since the completion of the MR CLEAN Trial in 2014 [3]. The methods used to implement the virtual population model have been previously described [18]. In summary, the virtual population model is developed using the probability density functions of the most prognostic and/or relevant patient characteristics. Statistical (vine copula and linear regression) methods are then employed to create correlations between these density functions that allows the creation of cohorts of AIS patients based on patient characteristics of interest. Our virtual population generation model to create virtual AIS patient cohorts is publicly available (https://mdmtest.shinyapps.io/INSIST-VP/).

2.2.1. Generating local geometric characteristics

The eight local geometrical [23] and thrombus parameters that were significant to the thrombectomy outcome were extracted for a subset of the MR CLEAN Registry patients ($N = 100$) with distal M1 occlusions and sufficient image quality [21]. The flowchart describing the patient selection is in Fig. 1.

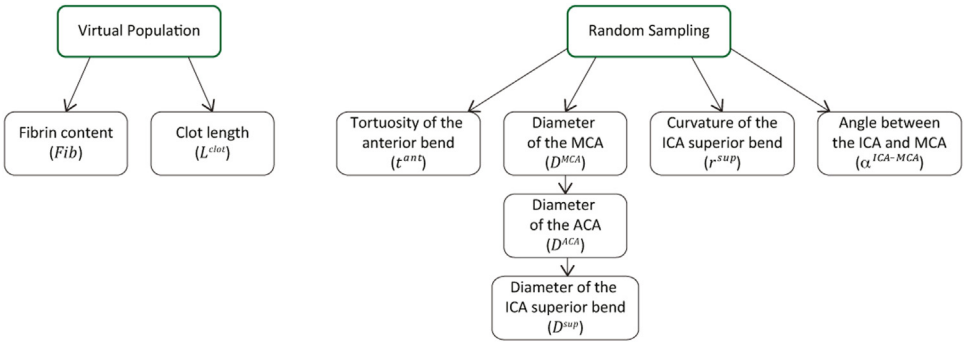

Fig. 4. Selection of parameters for each patient. Thrombus characteristics were correlated to clinical characteristics. Geometric characteristics were randomly sampled from patient distributions, with MCA diameter, ACA diameter, and ICA diameter correlated.

An analysis of the complete MR CLEAN Registry patient cohort and selected patients showed that they were representative of the full population in terms of clinical characteristics. The results of this analysis are given in Supplementary Section S2.2.

Since these local geometrical parameters were not significantly correlated to clinical characteristics used for describing the virtual patients, these parameters could not be directly linked to the virtual patients. Hence, four parameters (t^{ant}, D^{MCA}, r^{sup} and $\alpha^{MCA-ACA}$) were randomly sampled from distributions calculated from the 100 patients. Since three artery diameter parameters (D^{MCA}, D^{ACA}, D^{sup}) were correlated to each other, D^{ACA} and D^{sup} were determined based on these correlations. Details on the correlations between the geometrical parameters is provided in the Supplementary Section S1.1. A schematic representation of the linkage between the virtual patient and local geometrical parameters is provided in Fig. 4.

2.2.2. Generating patient-specific thrombus characteristics

In addition to the local geometric parameters, the surrogate thrombectomy model requires thrombus characteristics. The composition of the thrombus is also the population characteristic of interest for one of the exploratory trials presented in this paper. As shown in Fig. 1, to link the thrombus characteristics (composition and length) with the clinical characteristics in the virtual population, we assessed the association of various clinical variables with the thrombus characteristics using multivariate linear regression. The clinical variables that were included in the models were selected based on previous studies and clinical knowledge and included age, sex, history of previous stroke, history of diabetes mellitus, history of atrial fibrillation, occlusion location, presence of hyperdense artery sign (HAS), collateral score, ASPECT score, systolic blood pressure, NIHSS at baseline, and time from symptom onset to groin puncture. Variables with a P-value of < 0.157 (Akaike's Information Criterion) in the multivariate model were selected for the final model, which predicts the thrombus characteristic of interest. The significant variables were sex, occlusion location and the hyperdense artery score (binary imaging marker for thrombus density as a proxy for fibrin content).

Because the described approach only showed three categorical or binary clinical characteristics to be significantly associated, the resulting distributions for thrombus composition and length did not reproduce the variation observed in the data. To account for the unexplained variation due to the use of categorical data and other unknown characteristics, we added noise to the thrombus characteristics. To represent the noise, we used a Gumbel distribution which was fit to the relative error in the predictions for the training population.

2.3. Integration into the in silico trial framework

The surrogate thrombectomy model was integrated into our IST framework, 'des-ist' [18,26]. The des-ist framework provides easy integration of multiple data-driven and mechanistic models for running (event-based) ISTs. Models are included into the framework in independent Docker [27] or Singularity [28] containers, and inputs and outputs are linked using a common API [26]. For the ISTs used in this paper, the simulation steps were:

Step 1. Generate a virtual population of patients using a statistical model;
Step 2. For each patient, determine their local geometric and thrombus characteristics based on their clinical characteristics;
Step 3. For each patient, predict recanalization status based on patient characteristics;
Step 4. Collate the patient recanalization outcomes and determine the recanalization success rate.

Steps 1, 2 and 3 were described in detail above. Step 4 is a part of the trial outcome module that has previously been described in Miller et al. [18]. This module uses RMarkdown [29] to autogenerate a report with statistics on all patient input characteristics and output data.

2.4. In silico trials

In this paper, we present three ISTs using the described models and framework: a validation trial, and two examples of exploratory ISTs. The outcome of interest in the trials is defined as the proportion of the population that experience complete recanalization of the occluded artery due to thrombectomy.

We sample 500 virtual patients for each arm of the trials. The surrogate thrombectomy model is stochastic. Hence, for a single trial realisation, we randomly sample for success or failure for each patient based on their recanalization probability predicted by the model. We run 1000 realisations of this success/failure sampling (on the same patient cohort) to determine a distribution of the recanalization success rate of the population. The mean of this distribution is then used in a two-proportion Z-test to determine if there is a significant difference between the two trial arms (or between the IST and the clinical data in the case of the Validation Trial).

2.4.1. Validation trial

We first run a validation trial to validate the surrogate thrombectomy model. This trial's results are compared with recanalization success rates observed in the intervention arm of the MR CLEAN Trial [1]. The inclusion criterion to generate the virtual

population for this are similar to the MR CLEAN Trial, with the addition of M1 occlusion and treatment only with Device A. The main inclusion criterion for the MR CLEAN Trial are: age of at least 18 years, AIS due to an intracranial large vessel occlusion (assessed on a CT Angiography scan), NIHSS at baseline of 2 or more, duration between onset and treatment less than 6 h, and systolic blood pressure less than 185 mmHg [20].

In the MR CLEAN Trial, the recanalization status of the occluded artery was defined using a 4-point modified Arterial Occlusion Lesion (mAOL) score ranging from 0 (complete occlusion of the primary occlusive lesion) to 3 (complete recanalization of the occluded artery with any distal flow). Although eTICI score (a measure of reperfusion as assessed on procedural Digital Subtraction Angiography scans) is the clinical standard for assessing treatment success, since the thrombectomy models estimate recanalization, for this Validation Trial, we define a thrombectomy to be successful if AOL is 3.

2.4.2. Thrombus composition trial

One potential application of ISTs is comparing outcomes for different subpopulations. We use our IST platform to compare the recanalization rates of a commercially available device (Device A) in patients with different composition of the occluding thrombus. The thrombus composition is defined based on the proportion of fibrin to red blood cells and is divided into two categories: high fibrin ($\geq$75% fibrin) and low fibrin content ($\leq$ 75% fibrin). The threshold was chosen based on the median fibrin content in the Validation Trial. To corroborate our results in the Thrombus Composition Trial, we use data from patients in the MR CLEAN Registry. We use the model presented in Section 2.2.2 to estimate the fibrin composition of the patients in the MR CLEAN Registry with a distal M1 occlusion who were treated with Device A. For this dataset, the eTICI score was used as a substitute for mAOL score as the measure of recanalization, as the mAOL scores are not available in the MR CLEAN Registry. We define recanalization success as an eTICI score of 2B–3, as is common practice in clinical assessments.

2.4.3. Device comparison trial

We demonstrate the use of our IST platform to compare the performance of two commercially available stent retrievers. We label these devices 'Device A' and 'Device B'. The inclusion criteria used was the same as for the Validation Trial described above. For this trial, we used a sample of 500 patients in both arms of the trial.

3. Results

3.1. Validation trial

We generated 500 virtual patients with an M1 occlusion, who would be treated with Device A based on the inclusion criterion of the MR CLEAN Trial. A comparison of the inclusion criteria and other key characteristics of the generated virtual patients with the patients from the intervention arm of the MR CLEAN Trial is provided in Table 1. The cohort of 72 MR CLEAN Trial patients used had a M1 occlusion, were treated with Device A and had an available mAOL score.

The mean recanalization rate aggregated over 1000 realizations in the Validation Trial is 85.2. This rate is within the 95% confidence interval of MR CLEAN Trial cohort (81.9, IQR:73–91), and a two-proportion Z-test on the proportions gives a p-value of $p = 0.6$ (Table 2). The distribution of the recanalization rate over the realisations can be found in Supplementary Figure S2a. Consequently, though we do not have sufficient data to fully interrogate the credibility of the model, the results show no evidence to support the hypothesis that the model is not credible.

Table 1
Population characteristics of the MR CLEAN Trial (M1 thrombi only) and the generated in silico population. Results are given as: median (interquartile range) unless specified otherwise.

Characteristic	MR CLEAN (M1 thrombi, $N = 72$)	In silico trial ($N = 500$)
Clinical		
Age (yr)	68 (56–76)	71 (61–80)
Male sex—no./%	36/50%	276/55%
NIHSS	16 (14–20)	15 (11–19)
Systolic blood pressure (mmHg)	145 (130–161)	145 (131–159)
Workflow		
Onset to randomization (mins)	221 (155–292)	NA
Onset to ER (mins)	NA	56 (36–92)
ER to EVT (mins)	NA	102 (66–143)
Thrombus		
Proportion fibrin (%)	NA	76 (61–85)
Length (mm)	NA	12 (9–18)

Table 2
Recanalization success rate of MR CLEAN Trial [1] compared to the thrombectomy model, for M1 occlusions using Device A. CI: 95% confidence interval for population success rate based on sample success rate. SD: standard deviation on the success rate (over 1000 realisations of the trial on the same cohort of 500 patients). The confidence interval on the MR CLEAN Trial refers to the expected rate in the (stroke) population given the 72 patient sample size.

Trial	Patient count	Recanalization success (%)
MR CLEAN	72	81.9 CI: 73–91
In silico Trial	500	85.2 SD: 1.4

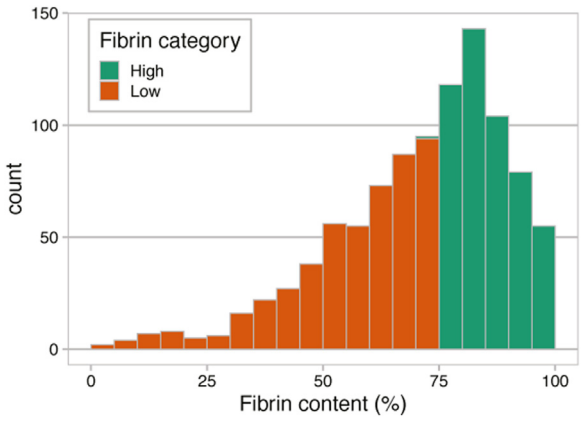

Fig. 5. Thrombus composition in the two arms of the trial.

Table 3
In silico trial results for the two arms of the Thrombus Composition Trial. Recanalization success is the percentage of patients who successfully recanalized due to thrombectomy in the trial. Mean and standard deviation are given for 1000 realisations of the thrombectomy model on the same set of patients.

	Recanalization success (%)	
Fibrin category	Mean	Std dev.
High ($\geq$75%)	81.8	1.5
Low ($\leq$75%)	89.1	1.3

3.2. Thrombus composition trial

The distribution of thrombus composition for the two arms is shown in Fig. 5 and the recanalization success rates are shown in Table 3. The full distribution of success rates for the 1000 realisations of each trial arm can be found in Supplementary Figure S2b. A two proportion Z-test on the mean success rates gives a p-value of $p = 0.001$. This trend can also be observed in the data from the

Table 4
In silicotrial results for the two arms of the Device Comparison Trial. Recanalization success is the percentage of patients who successfully recanalized due to thrombectomy in the trial. Mean and standard deviation are given for 1000 realisations of the thrombectomy model on the same set of patients.

	Recanalization success (%)	
Device	Mean	Std dev.
A	85.2	1.4
B	90.8	1.3

MR CLEAN Registry (M1 thrombi): eTICI 3 was 32% for high fibrin thrombi and 46% for low fibrin.

3.3. Device comparison trial

The results for 1000 samples of the trial, using the same cohort of 500 patients and for both devices, indicate that Device B may have improved recanalization outcomes for patients. This improvement is found to be statistically significant—a two proportion Z-test p-value is $p = 0.007$. The recanalization rates are given in Table 4. The distributions of the success rates for the trial can also be found in Supplementary Figure S2c.

4. Discussion

In this study, we present the application of an IST framework to execute a validation and two exploratory AIS trials. In the validation trial, we showed that the treatment success rates assessed by the surrogate thrombectomy model that was integrated into our IST framework are comparable to those observed in the real-life MR CLEAN Trial. The first exploratory trial, assessing the performance of a commercially available device in relation to the fibrin composition of the occluding thrombus, showed that the chance of retrieving fibrin-rich thrombi is lower than thrombi with low fibrin / high red blood cell concentrations. The second exploratory trial showed that our IST framework can be used to compare the performance of two (commercially available) devices to successfully retrieve the thrombus.

ISTs have the potential to provide significant economical advantages (time and money) for the medical industry [7]. As such, an increasing number of models and frameworks are being developed for virtual patient generation and ISTs. Many of these frameworks have focused on vaccines or drug treatments. Such models are often less computationally complex to simulate compared to medical devices. For example, the Universal Immune System Simulator (UISS) [30] has been used to run ISTs for both tuberculosis [30] and COVID-19 [31] vaccines in virtual populations. Other examples include interrogating treatment regimes for HIV [12], pre-clinical trials of novel drug therapies [32], or the UVA/PADOVA Type 1 Diabetes simulator of insulin response in Type 1 Diabetes [33]. Of these, only the UVA/PADOVA has been accepted by the FDA for use in pre-clinical trials [34]. Such ISTs could be particularly influential for rare diseases, such as the IST for congenital pseudothrosis of the tibia [35], a rare condition for which clinical trials take large amounts of time and money due to low patient recruitment and data.

One example of the application of an IST for a surgical device is the study by Sarrami-Foroushani et al. [36]. This study used an ANSYS computational fluid dynamics model to simulate the flow diversion before and after device implantation for treatment of intracranial aneurysms. Simulations were performed on geometries extracted from 82 patients. Such an approach is useful to run highly credible and detailed ISTs on the 82 patients, such as the response in hypertensive compared to normotensive scenarios that was explored in the study. However, the addition of new patient geometries using this approach is time consuming, and scale-up to hundreds of patients is computationally infeasible. By combining the statistical virtual population model and surrogate thrombectomy model, we can easily predict outcome in patients with geometric parameter combinations not present in the original patient set. Consequently, we are able to run much larger trials and explore different subsets of the population very easily and quickly. This has the potential to be exceedingly useful in refining clinical trial inclusion criteria during the development of new thrombectomy devices. Though the surrogate model comes with a loss of patient-level accuracy and detail, the loss is considered acceptable because we are interested in the population-, rather than patient-, scale outcomes, and we can evaluate credibility at a population scale.

Like most of the ISTs discussed, our IST uses statistically generated cohorts of virtual populations and we have validated the models against available clinical data. The extensive data that is available to us also allows us to corroborate some of our observations using small sample sets which would otherwise not be considered sufficient for proof of efficacy. This provides another example of the potential value of ISTs such as these. Notably, the subset of patient data that was available in our validation trial was small ($n = 72$) and would have been insufficient to provide proof of efficacy of the device. Yet, by executing an IST with 500 patients, we showed that the 95% confidence interval of the recanalization status predicted by the IST and that observed in the clinical data were comparable.

Our finding from the first exploratory IST that fibrin-rich thrombi are more difficult to retrieve is in line with several other *in-vivo* and clinical studies assessing the influence of thrombus composition on treatment success. Fibrin-rich thrombi are stiffer and have a higher coefficient of friction compared to RBC-rich thrombi. This is associated with decreased interaction with the struts of the stent, and consequently these fibrin-rich thrombi require more treatment attempts and longer procedure times to successfully retrieve [5,6]. A similar (but not significant) trend was also observed in the clinical data from the MR CLEAN Registry. However, the treatment success rates observed in the MR CLEAN Registry were much lower than those in IST. This observation could be due to several reasons. Firstly, the current in silico thrombectomy model does not simulate thrombus fragmentation, which was frequently observed in the MR CLEAN Registry patients. Approximately, 74% of the patients with low-fibrin thrombi and 71% of the patients with fibrin-rich thrombi had reperfusion of up to 50% of the downstream territory suggesting the restoration of the antegrade flow with the formation of distal thrombi. These treatment success rates, though not significantly different between fibrin-rich and low fibrin subgroups, are more comparable to those estimated by the IST.

Secondly, although our assumption that the occluding thrombi are always homogeneous was necessary to simplify the simulations, it is not always true in real-life scenarios. Several histopathological studies have shown that thrombi are heterogeneous and contain varying proportions of fibrin, platelets, RBCs, WBC, lipids and calcification. The heterogeneity of the thrombus influences its interaction with the stent and can impact the treatment outcome [6].

Thirdly, our treatment model assumes that the stent-retriever is always placed in accordance to the BADDASS approach (BAlloon guiDe with large bore Distal Access catheter with dual aspirate with Stent-retrever as Standard approach) which recommends the stent-retriever to be placed two-thirds behind the thrombus [37]. The influence of not following this recommendation on treatment success has not yet been established on clinical data, but it could be a plausible cause of treatment success overestimation by the IST.

Lastly, and most importantly, our IST framework does not account for the influence of thrombolysis. Treatment with intravenous alteplase prior to thrombectomy is part of standard stroke care. Alteplase is a fibrin specific activator that converts plasminogen to plasmin and helps to soften thrombi, especially those that are RBC-rich. Treatment with alteplase can impact the length and structure of the thrombus prior to thrombolysis, but it is known that the ability of alteplase to completely recanalize the occluding thrombus is limited, especially in patients with a large vessel occlusion [38].

In the second exploratory trial we showed Device B performed better than Device A. An advantage of an IST is the ability to compare different treatments on the same cohort of patients. However, it is important to note that since Device B is a newer device, fewer training simulations were run to build the surrogate thrombectomy model as there was insufficient data for model validation. When data becomes available we intend to further investigate the validation of this model. Nevertheless, the execution of this second exploratory trial suggests that the performance of two devices may be compared using in silico approaches. The execution of this trial also highlights a key advantage of in silico approach over clinical trials: testing the performance of two devices on the same patients. The thrombectomy model presented in this study was only developed for M1 occlusions. Although, M1 occlusions are most frequently observed in AIS patients with a large vessel occlusion in the anterior circulation, extending our treatment model to include all occlusions, especially those occluding the distal arteries is crucial to strengthen the findings obtained in our study.

Despite the above mentioned limitations, to the best of our knowledge, this is the first project that has successfully implemented and executed ISTs for AIS. With this experiment, we have shown that in silico modelling approaches, when validated, could allow us to make plausible hypothesis towards treatment selection at a population level. Due to the proof of concept nature of our study, making such hypotheses remains outside the scope of this study. Nevertheless, ISTs can help to elucidate the reasons for treatment failure. This knowledge would allow us to quantify the potential benefit of implementing in silico modelling approaches.

5. Conclusion

In this study, we have presented an approach to implement and execute in silico trials (ISTs) of thrombectomy treatment for acute ischemic stroke (AIS). We believe that the insights provided from validated in silico modelling approaches would allow us to obtain a better understanding of the patho-physiology of AIS and reasons for treatment failure at patient and population levels. They will also allow device manufacturers to optimize device design before entering into expensive pre-clinical and clinical testing. ISTs will not replace randomized clinical trials. However, we concur with the recommendations of the FDA and other regulatory bodies that ISTs will contribute towards the level of evidence required to establish the efficacy of a treatment device. This will, in the future, provide valuable input to improve the design of clinical trials, better patient stratification techniques, and aid in faster and more efficient implementation of new treatments in clinical practice.

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Declaration of Competing Interest

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iCAFE (© 2016–2018 University of Washington. Used with permission. iCafe was developed by the Yuan Lab at the University of Washington.), a semi-automated software, was used to extract centerlines, local radii, and label arteries [39].

Supplementary material

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References

[1] O.A. Berkhemer, P.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J. Wermer, M.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L. de Kort, W.J.J. van Rooij, J.S. van den Berg, B.A. van Hasselt, L.A. Aerden, R.J. Dallinga, M.C. Visser, J.C. Bot, P.C. Vroomen, O. Eshghi, T.H. Schreuder, R.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E. Sprengers, S.F. Jenniskens, L.F. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B. Majoie, D.W. Dippel, A randomized trial of intraarterial treatment for acute ischemic stroke, New Engl. J. Med. 372 (2015) 11–20, doi:10.1056/NEJMoa1411587.

[2] M. Goyal, B.K. Menon, W.H. van Zwam, D.W.J. Dippel, P.J. Mitchell, A.M. Demchuk, A. Dávalos, C.B.L.M. Majoie, A. van der Lugt, M.A. de Miquel, G.A. Donnan, Y.B.W.E.M. Roos, A. Bonafe, R. Jahan, H.-C. Diener, L.A. van den Berg, E.I. Levy, O.A. Berkhemer, V.M. Pereira, J. Rempel, M. Millán, S.M. Davis, D. Roy, J. Thornton, L.S. Román, M. Ribó, D. Beumer, B. Stouch, S. Brown, B.C.V. Campbell, R.J. van Oostenbrugge, J.L. Saver, M.D. Hill, T.G. Jovin, Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials, Lancet 387 (2016) 1723–1731, doi:10.1016/S0140-6736(16)00163-X.

[3] I.G.H. Jansen, M.J.H.L. Mulder, R.J.B. Goldhoorn, Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN registry), BMJ 360 (2018), doi:10.1136/bmj.k949.

[4] J.L. Saver, Time is brain quantified, Stroke 37 (2006) 263–266, doi:10.1161/01.STR.0000196957.55928.ab.

[5] S. Staessens, O. François, W. Brinjikji, K.M. Doyle, P. Vanacker, T. Andersson, S.F. De Meyer, Studying stroke thrombus composition after thrombectomy: what can we learn? Stroke 52 (2021) 3718–3727, doi:10.1161/STROKEAHA.121.034289.

[6] R. Cahalane, N. Boodt, A.C. Akyildiz, J.-a. Giezen, M. Mondeel, A. van der Lugt, H. Marquering, F. Gijsen, A review on the association of thrombus composition with mechanical and radiological imaging characteristics in acute ischemic stroke, J. Biomech. 129 (2021) 110816, doi:10.1016/j.jbiomech.2021.110816.

[7] M. Viceconti, A. Henney, E. Morley-Fletcher, In silico clinical trials: how computer simulation will transform the biomedical industry, Int. J. Clin. Trials 3 (2016) 37, doi:10.18203/2349-3259.ijct20161408.

[8] F. Pappalardo, G. Russo, F.M. Tshinanu, M. Viceconti, In silico clinical trials: concepts and early adoptions, Brief. Bioinform. 20 (2019) 1699–1708, doi:10.1093/bib/bby043.
[9] M. Viceconti, C. Cobelli, T. Haddad, A. Himes, B. Kovatchev, M. Palmer, In silico assessment of biomedical products: the conundrum of rare but not so rare events in two case studies, Proc. Inst. Mech. Eng., Part H 231 (2017) 455–466, doi:10.1177/0954411917702931.
[10] C.D. Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, C. Cobelli, The UVA/PADOVA type 1 diabetes simulator, J. Diabetes Sci. Technol. 8 (2014) 26–34, doi:10.1177/1932296813514502.
[11] M. Pennisi, M.A. Juárez, G. Russo, M. Viceconti, F. Pappalardo, Generation of digital patients for the simulation of tuberculosis with UISS-TB, in: 2019 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), 2019, pp. 2163–2167, doi:10.1109/BIBM47256.2019.8983100.
[12] E. Mancini, R. Quax, A. De Luca, S. Fidler, W. Stohr, P.M.A. Sloot, A study on the dynamics of temporary HIV treatment to assess the controversial outcomes of clinical trials: an in-silico approach, PLoS One 13 (2018) e0200892, doi:10.1371/journal.pone.0200892.
[13] N.E. Owen, P. Challenor, P.P. Menon, S. Bennani, Comparison of surrogate-based uncertainty quantification methods for computationally expensive simulators, SIAM/ASA J. Uncertain. Quantif. 5 (2017) 403–435, doi:10.1137/15M1046812.
[14] V.G. Eck, W.P. Donders, J. Sturdy, J. Feinberg, T. Delhaas, L.R. Hellevik, W. Huberts, A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications, Int. J. Numer. Method Biomed. Eng. 32 (2016) e02755, doi:10.1002/cnm.2755.
[15] F.S. Costabal, K. Matsuno, J. Yao, P. Perdikaris, E. Kuhl, Machine learning in drug development: characterizing the effect of 30 drugs on the QT interval using Gaussian process regression, sensitivity analysis, and uncertainty quantification, Comput. Methods Appl. Mech. Eng. 348 (2019) 313–333, doi:10.1016/j.cma.2019.01.033.
[16] A. Nikishova, L. Veen, P. Zun, A.G. Hoekstra, Semi-intrusive multiscale metamodelling uncertainty quantification with application to a model of in-stent restenosis, Philos. Trans. R. Soc. A 377 (2019) 20180154, doi:10.1098/rsta.2018.0154.
[17] T.I. Józsa, R.M. Padmos, W.K. El-Bouri, A.G. Hoekstra, S.J. Payne, On the sensitivity analysis of porous finite element models for cerebral perfusion estimation, Ann. Biomed. Eng. 49 (2021) 3647–3665, doi:10.1007/s10439-021-02808-w.
[18] C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, S.J. Payne, A.G. Hoekstra, In silico trials for treatment of acute ischemic stroke: design and implementation, Comput. Biol. Med. 137 (2021) 104802, doi:10.1016/j.compbiomed.2021.104802.
[19] P.R. Konduri, H.A. Marquering, E.E. van Bavel, A. Hoekstra, C.B.L.M. Majoie, T.I. Investigators, In-silico trials for treatment of acute ischemic stroke, Front. Neurol. 11 (2020), doi:10.3389/fneur.2020.558125.
[20] P.S. Fransen, D. Beumer, O.A. Berkhemer, L.A. van den Berg, H. Lingsma, A. van der Lugt, W.H. van Zwam, R.J. van Oostenbrugge, Y.B. Roos, C.B. Majoie, D.W. Dippel, MR CLEAN a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial, Trials 15 (2014), doi:10.1186/1745-6215-15-343.
[21] G. Luraghi, J.F.R. Matas, G. Dubini, F. Berti, S. Bridio, S. Duffy, A. Dwivedi, R. McCarthy, B. Fereidoonnezhad, P. McGarry, C.B.L.M. Majoie, F. Migliavacca, Applicability assessment of a stent-retriever thrombectomy finite-element model, Interface Focus 11 (2021) 20190123, doi:10.1098/rsfs.2019.0123.
[22] G. Luraghi, S. Bridio, J.F.R. Matas, G. Dubini, N. Boodt, F.J.H. Gijsen, A. van der Lugt, B. Fereidoonnezhad, K.M. Moerman, P. McGarry, P.R. Konduri, N.A. Terreros, H.A. Marquering, C.B.L.M. Majoie, F. Migliavacca, The first virtual patient-specific thrombectomy procedure, J. Biomech. 126 (2021) 110622, doi:10.1016/j.jbiomech.2021.110622.
[23] S. Bridio, G. Luraghi, J.F.R. Matas, G. Dubini, G.G. Giassi, G. Maggio, J.N. Kawamoto, K.M. Moerman, P. McGarry, P.R. Konduri, et al., Impact of the internal carotid artery morphology on in silico stent-retriever thrombectomy outcome, Front. Med. Technol. 3 (2021) 719909, doi:10.3389/fmedt.2021.719909.
[24] D.G. Kleinbaum, K. Dietz, M. Gail, M. Klein, M. Klein, Logistic Regression, Springer, 2002.
[25] Z.H. Hoo, J. Candlish, D. Teare, What is an ROCcurve?, 2017.
[26] M. van der Kolk, C. Miller, R. Padmos, V. Azizi, A. Hoekstra, DES-IST: a simulation framework to streamline event-based in silico trials, in: M. Paszynski, D. Kranzlmüller, V.V. Krzhizhanovskaya, J.J. Dongarra, P.M. Sloot (Eds.), Computational Science – ICCS 2021, Springer International Publishing, Cham, 2021, pp. 648–654, doi:10.1007/978-3-030-77967-2_53.
[27] D. Merkel, Docker: lightweight Linux containers for consistent development and deployment, Linux J. 2014 (239) (2014) 76–90.
[28] G.M. Kurtzer, V. Sochat, M.W. Bauer, Singularity: scientific containers for mobility of compute, PLoS One 12 (2017) 1–20, doi:10.1371/journal.pone.0177459.
[29] Y. Xie, C. Dervieux, E. Riederer, R Markdown Cookbook, Chapman and Hall/CRC, Boca Raton, Florida, 2020. ISBN 9780367563837
[30] G. Russo, G. Sgroi, G.A.P. Palumbo, M. Pennisi, M.A. Juarez, P.-J. Cardona, S. Motta, K.B. Walker, E. Fichera, M. Viceconti, F. Pappalardo, Moving forward through the in silico modeling of tuberculosis: a further step with UISS-TB, BMC Bioinform. 21 (2020), doi:10.1186/s12859-020-03762-5.
[31] G. Russo, M. Pennisi, E. Fichera, S. Motta, G. Raciti, M. Viceconti, F. Pappalardo, In silico trial to test COVID-19 candidate vaccines: a case study with UISS platform, BMC Bioinform. 21 (2020) 527, doi:10.1186/s12859-020-03872-0.
[32] M. Kleiman, Y. Sagi, N. Bloch, Z. Agur, Use of virtual patient populations for rescuing discontinued drug candidates and for reducing the number of patients in clinical trials, Altern. Lab. Anim. 37 (Suppl 1) (2009) 39–45, doi:10.1177/026119290903701S07.
[33] R. Visentin, M. Schiavon, C. Giegerich, T. Klabunde, C.D. Man, C. Cobelli, Long-acting insulin in diabetes therapy: in silico clinical trials with the UVA/PADOVAa Type 1 diabetes simulator *, in: 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), vol. 1, IEEE, 2018, pp. 4905–4908, doi:10.1109/EMBC.2018.8513234.
[34] R. Visentin, C.D. Man, B. Kovatchev, C. Cobelli, The University of Virginia/Padova Type 1 diabetes simulator matches the glucose traces of a clinical trial, Diabetes Technol. Ther. 16 (2014) 428–434, doi:10.1089/dia.2013.0377.
[35] A. Carlier, A. Vasilevich, M. Marechal, J. de Boer, L. Geris, In silico clinical trials for pediatric orphan diseases, Sci. Rep. 8 (2018) 2465, doi:10.1038/s41598-018-20737-y.
[36] A. Sarrami-Foroushani, T. Lassila, M. MacRaild, J. Asquith, K.C.B. Roes, J.V. Byrne, A.F. Frangi, In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials, Nat. Commun. 12 (2021) 3861, doi:10.1038/s41467-021-23998-w.
[37] J. Ospel, O. Volny, M. Jayaraman, R. McTaggart, M. Goyal, Optimizing fast first pass complete reperfusion in acute ischemic stroke–the BADDASS approach (balloon guide with large bore distal access catheter with dual aspiration with stent-retriever as standard approach), Expert Rev. Med. Devices 16 (2019) 955–963, doi:10.1080/17434440.2019.1684263.
[38] B.K. Menon, F.S. Al-Ajlan, M. Najm, J. Puig, M. Castellanos, D. Dowlatshahi, A. Calleja, S.-I. Sohn, S.H. Ahn, A. Poppe, et al., Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke, JAMA 320 (2018) 1017–1026, doi:10.1001/jama.2018.12498.
[39] L. Chen, M. Mossa-Basha, N. Balu, G. Canton, J. Sun, K. Pimentel, T.S. Hatsukami, J.-N. Hwang, C. Yuan, Development of a quantitative intracranial vascular features extraction tool on 3DMRA using semiautomated open-curve active contour vessel tracing, Magn. Reson. Med. 79 (2018) 3229–3238, doi:10.1002/mrm.26961.