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In silico trials for treatment of acute ischemic stroke: Design and implementation

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ABSTRACT

An *in silico* trial simulates a disease and its corresponding therapies on a cohort of virtual patients to support the development and evaluation of medical devices, drugs, and treatment. *In silico* trials have the potential to refine, reduce cost, and partially replace current *in vivo* studies, namely clinical trials and animal testing. We present the design and implementation of an *in silico* trial for treatment of acute ischemic stroke. We propose an event-based modelling approach for the simulation of a disease and injury, where changes to the state of the system (the events) are assumed to be instantaneous. Using this approach we are able to combine a diverse set of models, spanning multiple time scales, to model acute ischemic stroke, treatment, and resulting brain tissue injury. The *in silico* trial is designed to be modular to aid development and reproducibility. It provides a comprehensive framework for application to any potential *in silico* trial. A statistical population model is used to generate cohorts of virtual patients. Patient functional outcomes are also predicted with a statistical model, using treatment and injury results and the patient's clinical parameters. We demonstrate the functionality of the event-based modelling approach and trial framework by running proof of concept *in silico* trials. The proof of concept trials simulate the same cohort of patients twice: once with successful treatment (successful recanalisation) and once with unsuccessful treatment (unsuccessful treatment). Ways to overcome some of the challenges and difficulties in setting up such an *in silico* trial are discussed, such as validation and computational limitations.

1. Introduction

Research and development of novel medical devices, drugs, and treatments is expensive—the average cost to bring a new drug to market has been estimated at 1–2.5 billion US dollars [1,2]. Clinical trial failure contributes to the increasing costs and can result in abandoned products, often without a clear understanding of the reason for the failure [3,4]. Several difficulties in traditional clinical trials relate to their dependence on large cohorts of participants to achieve the required statistical power for regulatory approval [5]. Clinical trials for higher prevalence diseases, with high participation, often only capture the average population, thereby missing important effects occurring in only a small percentage of the population. This can lead to unforeseen side-effects when the product is brought to market. In contrast, clinical trials for low prevalence diseases can struggle to recruit the requisite number of patients, making development of treatments for these diseases economically infeasible.

To help counteract difficulties surrounding clinical trials, researchers are exploring computational biomedicine as a way to augment *in vitro* and *in vivo* trials. These *in silico* experiments are facilitated by developments in computational modelling in biomedicine [6–11]. The so-called *in silico* trial (IST) [12] can specifically consider cohorts of virtual patients representing highly specific population subsets. Using results from ISTs, a clinical trial can potentially reduce the number of required patients and be more targeted in patient selection. This reduces development time, and hence costs, for clinical trials, in particular those considering rare diseases.

ISTs are closely related to computational biomedicine and personalised medicine [13]. Personalised medicine aims to predict the outcome of a patient-specific treatment at an individual level, using

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patient-specific characteristics or a virtual representation of the real patient. In contrast, ISTs predict outcome at the population level by modelling disease and treatment over a cohort of virtual patients that provide a statistical representation of the population of interest. In this context, the virtual patient represents a patient using a set of parameters used for the computational models and simulations, and prognostic factors for patient outcome. The goal is to predict the efficacy and efficiency of a treatment, drug, or device; similar to traditional *in vitro* and *in vivo* clinical trials. A summary of the current state of computational modelling in medical product development can be found in the Avicenna Roadmap [12,14]. This roadmap provides a clear vision towards *in silico* methods for development of medical products, together with an in-depth discussion on the benefits and obstacles for ISTs.

There are several technical, modelling, and legal challenges to successfully developing ISTs. One such challenge of patient-specific computational modelling is the requirement for patient-specific parameters. These are often derived from patient data such as clinical measurements and images. Sharing patient data is difficult due to privacy regulations [14–16]. Even without this restriction, outcome predictions would only be valid for the cohort of patients for whom all the required data was measured. Capturing an entire cohort of patients therefore requires a more systematic approach such as a statistical model of the population. A statistical model enables the combination of commonly measured characteristics, e.g. blood pressure and age, with rarely collected characteristics, such as clot histological composition, structure, and length in the case of acute ischemic stroke.

Acute ischemic stroke (AIS) is the disease of interest for this paper. AIS is an occlusion of the arteries supplying blood to the brain and has been estimated to cause 2.7 million deaths globally and account for 51.9 million disability-adjusted life-years [17]. The current standard of care in the EU for treatment of AIS is intravenous thrombolysis, usually within 4.5 h of stroke onset, followed by intra-arterial thrombectomy (for large vessel occlusions), usually within 6 h of stroke onset [18,19]. Though recent trials have shown extending this time window may improve patient outcomes in a selective group of patients with AIS due to large vessel occlusions based on perfusion imaging criteria [20,21]. Development of new thrombectomy devices and thrombolysis drugs require further trials, creating potential use cases for an IST. Other use cases include evaluating new indications for reperfusion therapies (e.g. an *in silico* MR CLEAN Late trial [22]) or different combinations of reperfusion strategies (e.g. an *in silico* MR CLEAN NO-IV [23]).

We are interested in developing an IST for reperfusion therapies in patients with AIS. We only consider patients with ischemic stroke due to a large vessel occlusion who are eligible for reperfusion treatment using thrombectomy, as in the MR CLEAN Trial and Registry [24,25]. Trial results are also limited to the current standard of care: treatment within 6.5 h, as the MR CLEAN Registry and MR CLEAN trial only consider patients treated within 6.5 and 6 h respectively [24,25]. The IST framework presented here has been developed as part of the INSIST project—a collaborative effort of academic and industrial partners to develop ISTs for the treatment of AIS [26–28]. The work within INSIST includes development of a statistical model for generating a virtual population; various computational models of brain injury and stroke treatment predicting infarct (dead tissue) volume; and a statistical clinical outcome model.

We propose an event-based modelling approach for the simulation of brain injury and stroke treatment. In this model we assume that changes to the system, such as the occlusion event and reperfusion after treatment, are instantaneous on the simulated time scale: typically hours between occlusion and treatment, with an additional follow up at 24 h. To capture the physiology of all events we require detailed models which are typically hard to set up, and have high system requirements and long execution times. Due to the event-based approach, the interaction of multiple detailed models is simplified: each model updates the system's state sequentially, generally in a predetermined order. This provides flexibility in the infrastructure used to evaluate the individual models, e.g. compute systems ranging from small workstations to large-scale cloud computing or High Performance Computing (HPC) facilities can be used. Alternatively, computationally expensive models can be replaced easily by more efficient surrogate models by changing the model definitions within the event-driven *in silico* trial.

In this paper we present our event-based modelling approach and the IST framework, developed based on the strategy described in the INSIST white paper [28]. This is one of the first comprehensive frameworks incorporating all aspects required to run an IST using multiple models, and the first we are aware of that has been applied to acute ischemic stroke. We analyse the use of an event-based modelling approach to combine models of blood flow, tissue perfusion, thrombolysis, thrombectomy, and tissue death and provide an accompanying open source application to support the generation, simulation, and analysis of event-based ISTs. Results are compared for two proof of concept trials, run on the same virtual population cohort. In one trial all patients have successful recanalisation (best case), and in the other all patients have unsuccessful recanalisation (worst case). Further challenges in setting up an IST trial are also discussed.

2. Methods

2.1. INSIST framework

For the IST we implement the 4 module approach proposed in the INSIST white paper [28]. The clinical trial is split into its basic components, which we call modules in the INSIST framework: Module I) generate a population of virtual patients; Module II) model the disease/condition and treatment; Module III) estimate patient outcome; and Module IV) determine the trial outcome. The final outputs of Module II are infarct volume and procedural (treatment) outcomes, which is then passed to Module III along with the patient's clinical data from Module I. Module III estimates clinical outcomes for each patient, which are then collated across the population in Module IV. These modules, and the workflow, are shown in Fig. 1.

2.1.1. Module I: virtual population

The first module—the virtual population generation—generates a cohort of virtual patients for the IST. INSIST uses a statistical model to generate these patients. An alternative would be to build a population using samples of real patient data. Generating a cohort of virtual patients using a statistical population model is a way to overcome (some of) the privacy issues surrounding the use of real patient data. A secondary benefit is the potential to sample an arbitrary number of patients at the extremes of distributions, which have limited representation in traditional clinical trials, to assist in the design of clinical trials. However, significant sampling at the extremes of the distribution is contingent on proving the credibility of the virtual population model at the extremes.

In the context of INSIST, a virtual patient consists of a set of parameters, such as clinical and thrombus parameters, and other relevant variables, including vessel geometries, required for the simulation of AIS, treatment, and outcome estimation. The statistical model to generate the virtual population's clinical data (age, blood pressure, etc.) is a vine copula model [29] developed in R using rvinecopulib [30]. Data from 3180 ischemic stroke patients who underwent thrombectomy (MR CLEAN Registry [25]) was used to fit the model. Parameters were selected based on required inputs for Module II, but also on their prognostic value [31]. Imaging and thrombus characteristics are linked to clinical data using linear regression models for a subset of patients [32–34]. A list of the parameters, and the number of observations used, is given in Table 1. Users can also specify inclusion and exclusion criteria, limited by the included model parameters, to generate sub-populations of virtual patients.

2.1.2. Module II: modelling stroke and treatment

The second module simulates AIS, treatment, and brain tissue injury.

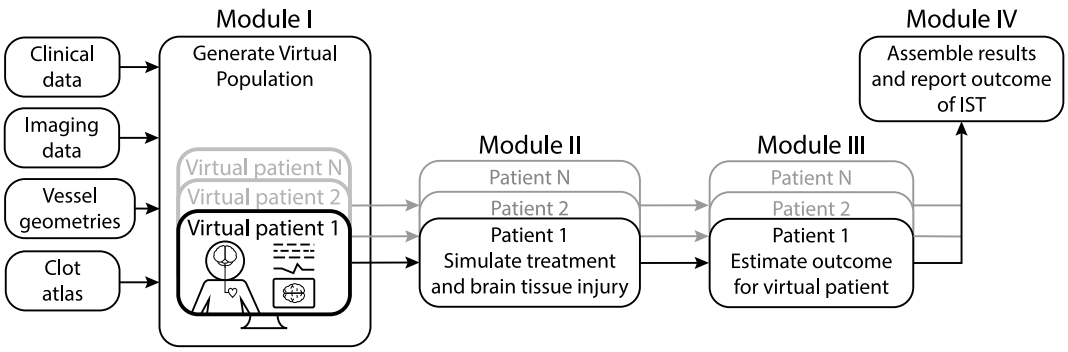

Fig. 1. A schematic view of the set-up of the INSIST framework, showing the flow between the various modules of the IST. Patient data is used to create the statistical population model that generates the virtual cohort. For each patient brain tissue damage after stroke and treatment are simulated. These simulation outcomes are used to predict the virtual patient's clinical outcome. Finally, the results of all virtual patients are combined and analysed, providing a clinical report of the IST's outcome.

Table 1
The parameters from the virtual population, split into those found to be significant in determining patient outcome, and those used in the models in Module II. Imaging and thrombus data observation count varied between variables, and is indicated in the parenthesis after each parameters. M1: M1 segment of middle cerebral artery; ICA: internal carotid artery.

	Clinical data	Imaging and thrombus data
Number of observations	3180	Varies (counts for each parameter given in parentheses)
Prognostic parameters	age, sex, occlusion location, diabetes mellitus, NIHSS at baseline, time from onset to ER, time from ER to thrombectomy	
Module II parameters	occlusion location, time from onset to ER, time from ER to thrombectomy, systolic blood pressure, diastolic blood pressure	Clot percent fibrin (332), clot length (399), ICA radius (122), M1 radius (122), ICA length (122), ICA tortuosity (122)

The outcome of interest from this module is the infarct volume and procedural outcomes. In order to simulate the tissue injury, it is necessary to know the change between the pre-stroke, stroke (occluded), and post-treatment state of the brain. As such, models may be required to be run for several events, as shown in Table 2. Given the characteristic time periods occurring between stroke and treatment, we use an event-based modelling approach in which changes between states are assumed to be instantaneous compared to the timescale of the simulated time span (onset of stroke to final outcome). This is described in detail in section 2.2.

There will be five interacting physics based models in Module II. The five models are:

1. *Arterial blood flow* models the blood flow from the heart to the pial surface. We use a 1D pulsatile model covering vessels with diameters greater than 0.1 mm. The state of blood flow in the vessels of the vasculature is mapped to the pial surface of the brain mesh and provides the boundary condition for the perfusion model (below). The governing equations for the model are given in Appendix A.1, and details on this model, and its one way coupling to the perfusion model, can be found in Ref. [35].
2. *Perfusion* models the blood perfusion within the brain. This is a 3D steady state finite element model describing blood flow in the microcirculation using three porous compartments: arteriole, capillary, and venule. Governing equations for the model are given in Appendix A.2. and a detailed description of the model can be found in Ref. [36]. The output steady state perfusion distribution (in both grey and white matter) provides the input to the tissue health model.
3. *Tissue health* models reversible and irreversible tissue damage as a result of blood flow shortage, and consequently hypoxia [37]. This is done based on the perfusion simulation results. Further details are given in Appendix A.3.
4. *Thrombolysis* models dissolution of the thrombus after drug, typically tPA (tissue plasminogen activator), administration [38,39]. This could be a lattice boltzmann model of tPA transport to a thrombus, composed of heterogeneous fibrin and blood cells, or an empirical model depending on the level of detail required.
5. *Thrombectomy* models the thrombectomy procedure. A detailed model of thrombectomy using finite element analysis was developed [33,40], but the trial will use a surrogate kriging model fitted on a sample of full model simulations for computational reasons.

Table 2
Models run for each event (pre-stroke, stroke, treatment, and final outcome), and the order of execution. In the final outcome event, the tissue death model uses the change in states and timings of each of the events to integrate the model from the stroke onset to the follow up time.

	Pre-stroke	Stroke	Treatment	Final outcome
Thrombolysis			5	
Thrombectomy			6	
Arterial blood flow	1	3	7	
Perfusion	2	4	8	
Tissue death				9

For the results shown in this paper, we only use the arterial blood flow, perfusion, and tissue death models. The run time per virtual patient, in this paper, is approximately 16 min. This includes generation of the virtual cohort, distribution and running all patient simulations, and analysis of outcome. Of these 16 min, 200 s are spent in the blood flow model, 350 s within the perfusion models (totals for the two events), and 400 s in the tissue health model. Future work will incorporate the thrombolysis and thrombectomy models into the pipeline, as well as ongoing improvements to the models already included here.

2.1.3. Module III: estimating patient outcome

The third module of INSIST determines the neurological deficit and functional outcome outcome for each patient. The two clinical outcome measures of interest are NIHSS (National Institutes of Health Stroke Scale) and mRS (modified Rankin Scale). NIHSS categorises stroke impairment from 0: no symptoms to 42: severe stroke. Similarly, mRS categorises functional outcome between 0: no symptoms and 6: death.

Procedural outcomes and infarct volume from Module II and the patient's clinical parameters from Module I are used as predictors to estimate clinical outcome. Data on follow-up infarct volumes from the MR CLEAN trial were used to estimate the regression coefficient for predicting mRS and NIHSS after treatment [24]. The clinical parameters

from the virtual population model determined significant for patient outcome and used in these models are listed in Table 1 (prognostic parameters).

The model for NIHSS is a linear regression model. The model for mRS is an ordinal logistic regression model, similar to the model used in Ref. [31]. This mRS model provides the probability of being each mRS category for each patient. For the results in this paper, we randomly assign an mRS category using the distribution of each patient.

2.1.4. Module IV: reporting trial outcome

The final module collates the outcomes from all the patients and presents population summaries and statistics in an automatically generated HTML report. The report presents the summary statistics and distribution plots for both the generated clinical parameters from Module I and the determined outcomes of interest: mRS, NIHSS, infarct volume, and procedural outcomes from Modules II and III. The module also returns the notebook (RMarkdown [41]) file used to generate the report. This allows users to easily modify the report if further information or plots are required.

2.2. Event-based modelling

We use an event-based simulation approach to combine the models in Module II and predict tissue injury. The timescale of interest for this model encompasses the period from stroke onset to the end of treatment: on the order of 0–6 h, plus follow up time: on the order of 24 h. Consequently, we assume major changes to the state of the system, which we call events (such as stroke onset or the effect of treatment), can be modelled as instantaneous changes in the system. The justification of this assumption for each of the events is discussed in detail below. Using this approach, Module II becomes a series of events for which the relevant models are run in order to update the system to its new steady state, as shown in Fig. 2. In this framework, the term event encompasses both the trigger event, such as occlusion of an intracranial vessel, and the resulting change in the state of the system: the blood flow and perfusion. The timing of these events is determined per patient in Module I.

As seen in Fig. 2, though we model the system as a series of events it is technically a hybrid system as tissue death occurs throughout the simulated time period, continuously increasing the size of the infarct region. In order to incorporate this within the system, we integrate the time-driven tissue death model in a single event at the end, using information about the time periods between each event and resulting perfusion states.

In the AIS model, four events are required: pre-stroke, stroke onset, treatment, and final outcome (Fig. 2). Table 2 lists the models in the order of execution for each event. Each patient starts with a pre-stroke simulation. Arterial blood flow and tissue perfusion are computed

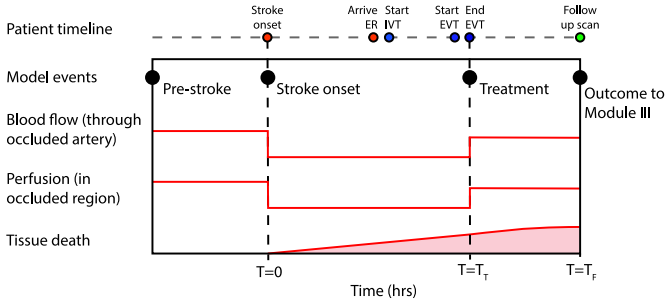

Fig. 2. The DES implementation showing the events. Four events (changes in state of the blood flow and perfusion model) are modelled: pre-stroke, stroke, treatment, outcome. The treatment event accounts for the treatment success of both IVT and EVT at the end of the EVT. The change between states is assumed to be instantaneous compared to the simulated time span. IVT: intravenous thrombolysis. EVT: endovascular thrombectomy. Note: not to scale (e.g. follow up scan usually occurs 1 day after treatment).

before the onset of stroke. This model event has no timing associated with it—its purpose is to predict the original homeostatic state of the system. Stroke onset is simulated by placing a clot within one of the proximal intracranial arteries in the arterial blood flow model. Arterial blood flow and tissue perfusion are then updated accordingly.

The relevant effect of the clot on blood flow and brain injury is the acute occlusion of the vessel. Modelling stroke onset as an instantaneous event is a good approximation as a clot is typically formed elsewhere in the body and travels through the vasculature until it occludes an artery [42–44]. Changes in blood flow through the large vessels of the vasculature are fast—the waveforms of the cardiac cycle, e.g. pressure, volume flow rate, reach a new periodic cycle within a few seconds (based off model convergence). Consequently, given the hour time scale of the simulation, the error introduced by the instantaneous assumption would be negligible.

Treatment usually starts within 6 h of stroke onset. In the event of a stroke, timing is critical: due to impaired blood flow, neurons are damaged and die fast due to their high energy demand [45]. Therefore, the reperfusion treatment needs to be started as soon as possible. In the trial thrombolysis followed by thrombectomy is simulated. After this arterial blood flow and tissue perfusion are updated.

As can be seen in Fig. 2, the treatment for AIS can take place over a period of hours, which does not intuitively align with the instantaneous event assumption. However, we assume that the event of interest for reperfusion of the occluded territory is recanalisation of the vessel, either due to intravenous thrombolysis or endovascular thrombectomy. After recanalisation, the restoration of blood flow after removal of the clot is on the order of a few seconds, which, as in the case of stroke onset, is negligible compared to the time scale of the tissue injury simulation.

In the case of thrombectomy, recanalisation occurs at the end of the procedure. The rest of the procedure, from groin puncture to the deployment of the balloon and stent, likely has little effect on the flow of blood through the obstructed vessel. In the case of thrombolysis, either the thrombolysis is successful and recanalisation occurs when the clot completely dissolves, or the new clot length is passed to the thrombectomy model. Given thrombolysis is a time-dependent process, similar to the tissue death model, the model at the treatment event determines the change in clot length that would have occurred over the whole thrombolysis adminstration period.

The assertion that recanalisation is the only event of interest for thrombolysis requires us to assume that blood flow through the clot does not change significantly during the thrombolysis period. Consequently, it is necessary to assume that thrombolysis does not affect clot properties enough to significantly change clot permeability, and the only significant change is to clot length. This assumption is supported to a degree in a study by Rossi et al. [46] which found that thrombolysis (rtPA) reduces clot size but does not affect recanalisation outcome or number of passes in thrombectomy. If, however, this assumption is incorrect and thrombolysis does result in a significant change in blood flow through the clot (for a significant period of time), this will result in a, likely small, over-prediction of the infarct volume by the current model. If this error is found to be significant, multiple stepwise changes can easily be added to the proposed framework.

Other situations that we don't consider in the current setup are fragmentation and distal migration of the clot during treatment—clot migration has been found to occur in around 22% of cases from a sample of MR CLEAN Registry patients [47]—which would require additional models. Models of clot fragmentation are currently under development [48] and clot migration could be implemented in the future if it is determined to have a significant effect.

2.3. Container implementation

The event-based simulation approach in INSIST is enabled by `desist` [49]. This supporting application exploits containerised environments for the generation, simulation, and analysis of ISTs that can be

implemented as discrete event simulations. This application captures the order of events, i.e. the evaluation order of the previously discussed models, as a directed, acyclic graph. Each node in this graph corresponds to a specific containerised environment, either using a Docker [50] or Singularity [51] container. Using containerised environments provides numerous advantages for ISTs such as collaboration independent of operating systems or hardware, straightforward reproducible simulation environments, and scaling towards large-scale cloud and HPC environments [52].

Once a cohort of virtual patients are generated, `des-ist` orchestrates the evaluation of all necessary simulation steps and ensures the simulations are evaluated in the desired order for all patients present in the IST. For large cohorts, `des-ist` can evaluate the numerical simulations in parallel on large-scale cloud or HPC compute environments. Various approaches are possible for parallelisation, such as running complete patient simulations per CPU or evaluating the all simulations of a single module in parallel. This flexibility allows to find the most efficient approaches considering the computational costs of individual events with respect to the available computational resources. Once all simulations are completed, regardless of their scheduling, the results are collected and analysed to provide an overview of the IST outcome.

3. Results

We run proof of concept trials with the INSIST trial framework. For this context, Module II consists of the arterial blood flow and tissue perfusion for three events: pre-stroke, stroke, and treatment, plus the tissue death model to determine patient infarct volume. Without detailed treatment models, solely binary treatment outcomes are considered representing complete reperfusion and no reperfusion. Consequently, the treatment model is hard coded to true and false respectively for two runs of the trial (on the same cohort). The two outcomes are equivalent to the best and worst case scenarios corresponding to successful and failed treatments.

3.1. Trial cohort

The generation of the trial cohort is the first module of the INSIST framework. We base our cohort off the inclusion/exclusion criteria of the MR CLEAN trial. The MR CLEAN trial evaluated the efficacy of thrombectomy on patients with an intracranial large vessel occlusion by randomising patients between standard medical care and standard medical care plus endovascular thrombectomy [24,53]. The criteria used to define the population, from Ref. [53], are given in Table 4. Using this set of criteria we generate a cohort of 500 patients. Some characteristics of the population are shown in Fig. 3 and summarised in Table 5.

Table 3
Assumptions related to each model relevant to the event-based modelling approach.

Model	Assumptions
Module II	Events (changes to state) are instantaneous (seconds) in comparison to the time scale of the treatment (hours)
Arterial blood flow	New steady state (pre-stroke to clot, and clot to treatment) achieved on a time scale of heart beats (seconds)
Perfusion	New steady state (pre-stroke to clot, and clot to treatment) reached on a time scale of heart beats (seconds)
Thrombolysis	No significant change to clot properties during thrombolysis—only significant change is the final clot length and whether the clot dissolved or not.
Thrombectomy	No significant change to system except at end of procedure, when recanalisation occurs or not.
Tissue death	Only significant changes are when the clot occurs, and if and when recanalisation occurs

Table 4
Inclusion criteria for the trial. ER: emergency room. *Note, the onset to ER criteria replaces the MR CLEAN trial criteria of 6 h between onset to start of thrombectomy treatment.

Characteristic	Criteria
Age	>18 years
NIHSS at ER	≥2
Onset to ER*	<6 h
Systolic blood pressure	<185 mmHg

3.2. Patient 'case study'

We follow a single virtual patient in detail through second and third modules of the framework for both the best and worst case trials. Note that the `des-ist` framework handles all virtual patients automatically, storing simulation data for each virtual patient in a separate directory. In Module II, the pre-stroke, stroke, and treatment events are run for the arterial blood flow and perfusion models. The blood flow and perfusion results for both the pre-stroke and stroke states are shown in Fig. 4. The treatment state will be either the same as the stroke state or revert to the pre-stroke case for the worst (unsuccessful recanalisation) and best (successful recanalisation) case trials respectively. From the change in perfusion between the three events, we can estimate the infarct volume at 24 h after treatment in both cases: successful recanalisation (best case) and unsuccessful recanalisation (worst case), with the tissue death model. The best and worst case infarct volumes (at 24 h) for this patient are 225 mL and 332 mL respectively. Fig. 5 shows the final (post-treatment) perfusion state and calculated infarct for the worst case scenario. Patient characteristics and outcomes are summarised in Table 6.

Module III uses the infarct volume and patient clinical parameters to determine the functional outcomes of NIHSS and mRS. This patient had a predicted mRS of 1 and 2, and an NIHSS of 8 and 13, in the best and worst case scenarios respectively.

3.3. Trial results

Using the infarct and outcome results for each patient, Module IV aggregates the data and provides population level details. Results are again shown here for two trials: a best case trial (successful recanalisation after treatment), and a worst case trial (failed treatment with unsuccessful recanalisation after treatment).

The infarct results for the worst case proof of concept trial are shown in Fig. 6, split by clot location. As can be seen here, there is minimal variation between patients with the same infarct location and side. The use of the same brain mesh for all patients, and an impermeable clot, would explain why patients with the same side and location occlusion have very similar infarct volumes. This will be addressed in future versions of the framework. The difference between infarct on opposite sides of the brain is more significant. Asymmetries in the system, such as in the brain mesh and vascular network, would explain the difference between the results for the different sides.

Fig. 7 shows the distributions for pre-stroke ability comparing functional outcomes for the worst and best case trials, using the modified Rankin Scale Score (mRS). These appear qualitatively reasonable, however these trials are a proof of concept and results should not yet be considered credible. It is not yet feasible to perform a validation of these results as the treatment models, as well as the cell death and perfusion models, are not fully implemented, and variation in estimated outcomes are not taken into account. Such a validation study is future work for the project, using the MR CLEAN trial data [25,53] and the data of the HERMES collaboration [54,55]. Additionally, uncertainties around patient outcomes will be included in future versions of the framework.

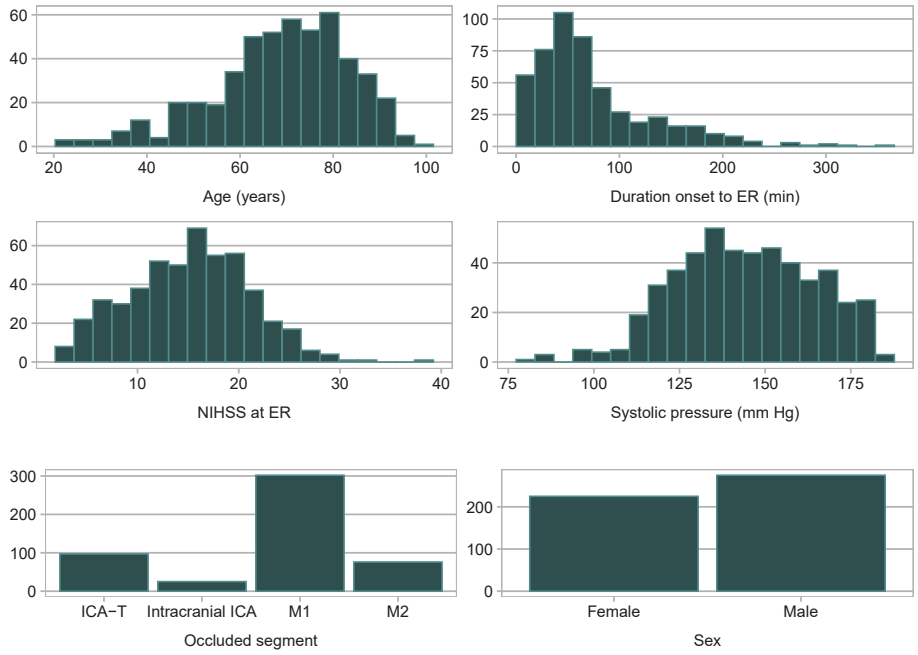

Fig. 3. A selection of baseline parameters for the generated virtual population using Module I. Results are for 500 patients. Duration onset to ER determines the timing of the events in the event-based model; systolic pressure and occluded segment are used for the models in Module II; and all these variables factor into the patient outcome in Module III. Occluded segments: middle cerebral artery sections M1 and M2, intracranial internal carotid artery (ICA), internal carotid artery terminus (ICA-T). NIHSS: National Institutes of Health Stroke Scale.

Table 5
Baseline (at ER) characteristics of the population.

Characteristic	Median (IQR)
Age (years)	68.9 (60.9, 79.3)
NIHSS at ER	15.4 (11.0, 19.1)
Duration onset to ER (mins)	57.2 (34.7, 96.4)
ASPECTS at ER	9 (7, 10)
Sex (% Male)	55%

4. Discussion

There are many publications about the advantages and limitations of ISTs [11,12,56–61], and their potential applications and challenges continue to emerge. Some expected use cases for ISTs include: 1) aiding trial design by providing additional information; 2) drug rescue and detailed explorations of drug failures in phase III trials; 3) reducing time for trial in rare diseases as lower numbers of patients required in the real clinical setting; 4) ability to explore tails of distribution; 5) predicting best and worst outcomes for patients to evaluate potential benefits of treatment development; 6) refinement, reduction, and replacement of animal trials. Additional to these use cases, there are several other advantages to using ISTs concurrently with traditional trials: 1) multiple treatments options can be tested on the same virtual patient; 2) reducing the number of participants and duration, and hence cost, of traditional clinical trials; 3) ability to take measurements not possible in a clinical setting; 4) higher accuracy than animal trials [62].

The IST presented here is an event-based simulation where models are called sequentially. The models are stand-alone packages due to the containerisation provided by either Docker or Singularity. The framework is designed to be expandable and modular. An event-handler executes the models and can easily be extended to include more events and models.

In section 2.2 we detailed the applicability of the event-based approach for the application. We determined it to be appropriate for the all models, though both the tissue death and thrombolysis require time-driven models. In order to account for this, we integrate thrombolysis model over the relevant treatment time in the treatment event, and similarly the tissue death model is integrated across the entire simulation period, using the different perfusion states and timings, in the follow up event. The main limitation to this approach is the error introduced if thrombolysis is found to affect clot structure enough that blood flow conditions through the occluded vessel change significantly in the hours prior to the treatment event. If this is the case, it would be possible to add intermediate update events to reduce this error.

Though event-based modelling is appropriate for the processes modelled here, the approximation of events as instantaneous is not always possible. In addition, models may need to be coupled in a more complex way than has been used here. For instance, two-way coupling between the arterial blood flow and tissue perfusion models is currently being developed to capture effects such as retro-grade flow and collateral flow. It is well-established that the presence of collateral vessels (as indicated by the collateral score) has a significant impact on patients' outcome [63]. A collateral circulation model has been proposed recently [64] which can be straightforwardly added to the 1D blood flow model. The individual models will otherwise be identical to the models used in this work. However, the boundary conditions of the models will be updated based on a coupling algorithm that captures the vasculature between the models. This will allow the capture of the collateral circulation including variability between patients.

In the IST presented here, coupled models would be added as a single black box. Models that are completely time-driven, and not suited to the instantaneous event assumption, could also theoretically be run within the framework using a single event, similarly to the approach used for tissue death and thrombolysis, or using multiple events allowing stepwise change.

One significant obstacle relevant to modelling stroke injury and treatment for large numbers of patients is the computational challenge related to modelling processes occurring on seconds over time periods of hours. Using the approach present here each patient, with three events, ran in 16 min on average. Statistical and surrogate modelling can be used to speed up the IST by replacing complex and computationally expensive models. For example, this will be implemented for the thrombectomy model, as a full FEA analysis for every patient is not currently computationally feasible. The requirement for a high detail model is also expected to be unnecessary given we are interested in population level outcomes for the trial. Hence speed is prioritised over per-patient detail provided the surrogate model is sufficiently validated to the level required for the trial's credibility requirements. In certain scenarios, computational models are not available and statistical

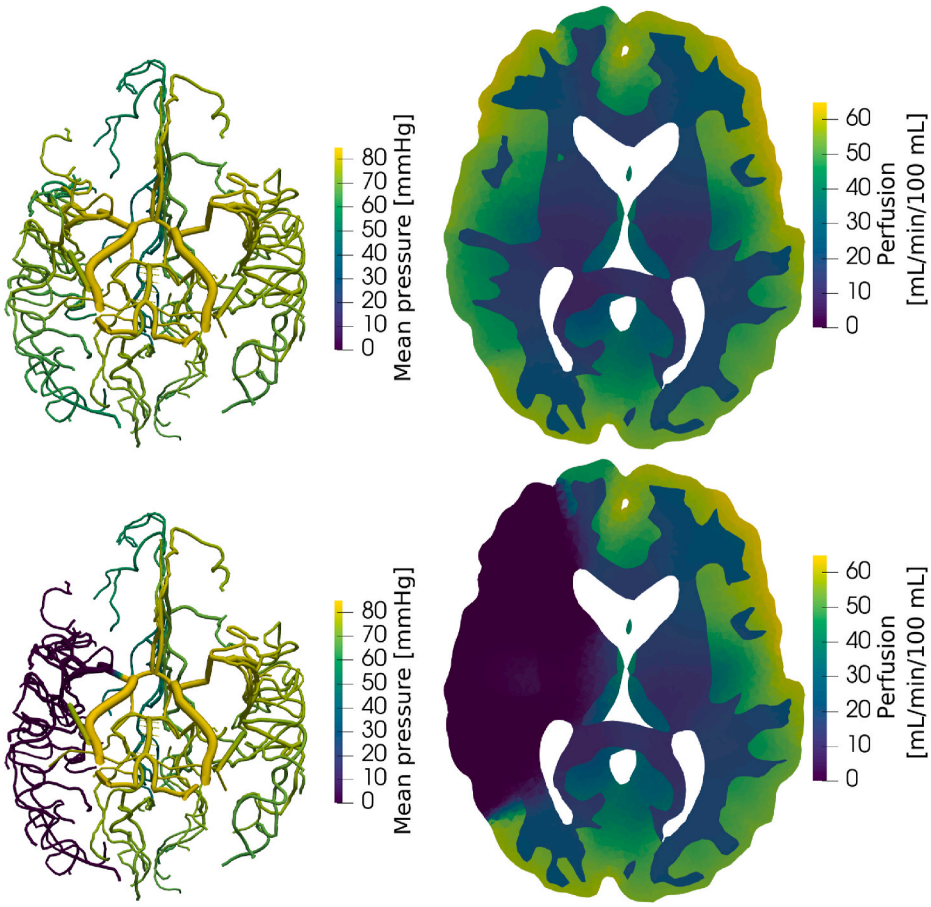

Fig. 4. Transverse view of pressure distributions estimated by the 1D blood flow model (left) and perfusion model predictions (right) in the healthy baseline case (top) and in stroke state (bottom) for a virtual patient.

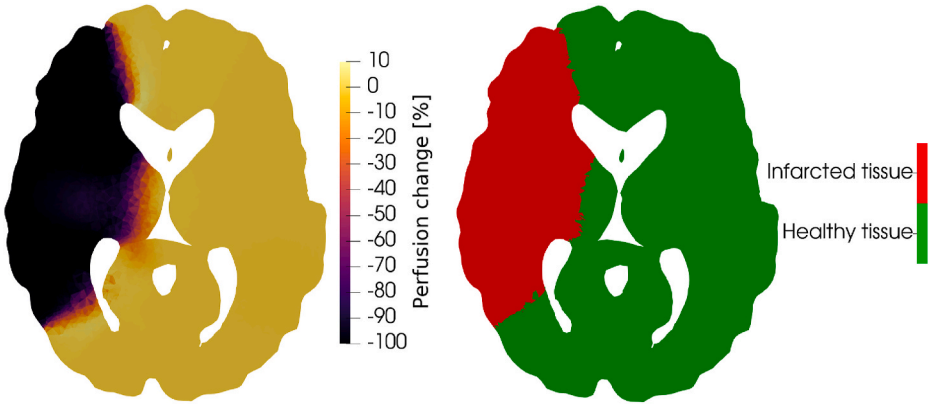

Fig. 5. Transverse view of perfusion change (left) and the corresponding infarct (right) for a virtual patient in the worst case scenario. The estimated worst case infarct volume is 332 mL.

modelling is the only choice.

Another major challenge for ISTs is the development of policy and procedures around proving credibility of the trial via validation, verification, and uncertainty quantification (VVUQ) practices [14]. Currently, the individual models within the trial are undergoing independent validation activities, including the virtual population model, patient outcome model, and the physics-based models in Module II, using both clinical and *in vitro* testing [65,66]. However, the individual credibility of each individual models does not necessarily translate directly to the credibility of the trial.

For the trial level verification, validation, and uncertainty quantification (UQ) processes we will take guidance from the V&V40 standard from the ASME [67]. We do not yet include the treatment models required to perform a robust validation of the framework, and additionally the tissue death model is still under development. Consequently, the proof of concept trials shown in this paper are purely a demonstration of the framework and the methodologies and results should not be interpreted as validated nor representative of expected outcomes. Once the remainder of the models are included, it will be possible to validate the trial software against previous trial data from MR CLEAN Trial and

Table 6
Patient characteristics and outcomes. Best case corresponds to successful recanalisation, and worst case is unsuccesful recanalisation (with no change to clot). Baseline is on presentation at the ER. MCA: Middle cerebral artery.

Parameter	Baseline	Best case	Worst case
Duration onset to ER	23.2 min		
Duration onset to treatment	61.5 min		
ASPECTS at baseline	8		
NIHSS at baseline	9		
Clot location	Right MCA		
Systolic blood pressure	157.4 mm.Hg		
Infarct volume at 24 h		225 mL	332 mL
mRS		1	2
NIHSS at 24 h		8	13

more detailed data from clinical practice included in the MR CLEAN Registry [24,25,53].

Preliminary trial level UQ analyses have been performed on the one way coupled arterial blood flow and perfusion models in Ref. [68]. In the future, a more extensive UQ analysis will be performed to understand the effect of the variability of parameters not measured in a clinical setting, and hence not included in the virtual population model. Additionally, trial outcomes will incorporate uncertainty around the patient's functional outcome, which can be directly determined from the ordinal logistic model, allowing for a better understanding of the variation that can occur in patient outcomes given the limitations of the clinical information available, as in Ref. [31]. UQ activities will also consider the potential errors introduced when using lower computational versions of the models, such as the exclusion of collateral modelling.

A key requirement for the validation activities is available, and shareable, high quality patient data and anatomies. Additionally, such data is needed to create virtual patients and their relevant parameters for the models. In order to minimise legal patient data issues for the trial itself, we use a virtual patient generation model to generate synthetic patients. However, these issues still remain for the validation activities.

5. Conclusion

We have presented a comprehensive framework, using an event-based modelling approach, for an *in silico* trial (IST), and applied it to acute ischemic stroke (AIS). The framework includes four modules for generating patients, modelling disease and treatment, determining functional outcome, and collating population level results.

By using a statistical model for the patient generation, we are able to work around privacy limitations involved with data sharing. Predicting complex phenomena, such as infarct volume, requires linking together multiple models. In the second module, several physics-based models need to be combined in order to determine the brain injury for each patient. We use an event-based modelling approach where changes to the state of the brain are considered instantaneous, such as stroke and treatment. This approach aids in overcoming technical difficulties in combining models that use different mathematical approaches and time scales bridging three orders of magnitude. Additionally, surrogate models will be used for models with large computational requirements, such as the thrombectomy procedure, in order to make the model computationally feasible for large numbers of patients.

The use of containerised environments aids in reproducibility of IST results. Additionally, using Docker or Singularity containers combined with a modular framework, we have built `des-ist` so that it is straightforward to add further models to the system. The two models for AIS treatment are still under development, and hence this paper presents two proof of concept trial comparing outcomes for successful and unsuccessful recanalisation on the same virtual population cohort. The treatment models will be integrated into the trial in the future and will allow us to test the applicability of the instantaneous change assumption for the treatment event (Table 3). We will also then be able to investigate the impact of different aspects of treatment, such as number of thrombectomy passes and thrombolysis administration time, with respect to

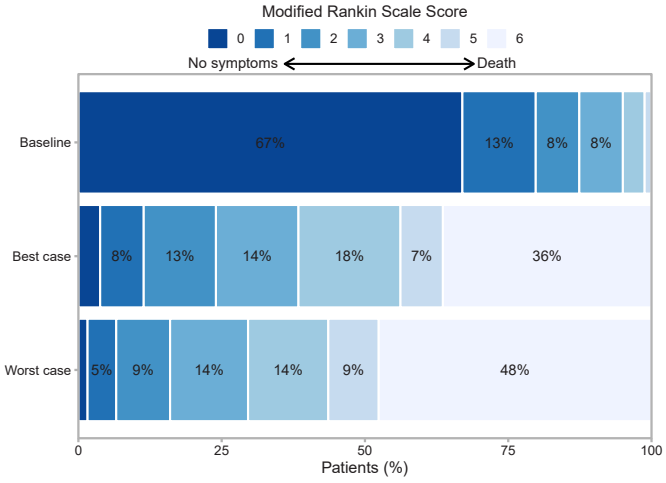

Fig. 7. The modified Rankin Scale Score, determined from infarct volume and patient characteristics, for the baseline (at ER); and best (successful recanalisation) and worst (unsuccessful recanalisation) case scenario for each patient.

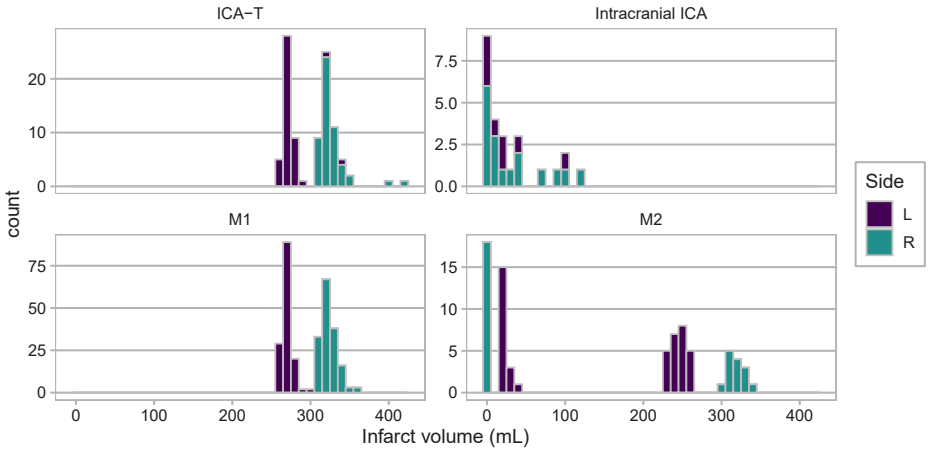

Fig. 6. Infarct volumes from the worst case (unsuccessful recanalisation) trial. L: left side, R: Right side. Infarct locations: middle cerebral artery sections M1 and M2, intracranial internal carotid artery (IICA), internal carotid artery terminus (ICA-T).

model sensitivities and also trial outcome.

Many challenges still remain for ISTs. One significant being proving the credibility of the framework. We plan to undertake validation, verification, and uncertainty quantification on the trial [68], using MR CLEAN trial data and drawing on recommendations from the V&V40-2018 standard [67]. Being able to prove the credibility of the trial is critical for future approval of the software as a part of the R&D process for new drugs and treatments.

Credit author statement

Claire Miller: Investigation, Writing - Original Draft, Visualization. Raymond Padmos: Methodology, Writing - Original Draft, Visualization. Max van der Kolk: Software, Investigation, Writing - Review and Editing. Tamás István Józsa: Methodology, Writing - Review and Editing. Noor Samuels: Methodology, Writing - Review and Editing. Yidan Xue: Methodology, Writing - Review and Editing. Stephen Payne: Supervision. Alfons Hoekstra: Conceptualisation, Writing - Review and Editing, Supervision, Funding acquisition.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A Details of Module II models

A.1 Arterial blood flow model

A one-dimensional blood flow model is used to simulate blood flow and pressure during healthy and stroke scenarios. Blood flow is considered to be at steady state, i.e. variables are considered to be the average over the duration of a heart beat. Blood is modelled as an in-compressible fluid. The pressure in the network is calculated by solving mass-balance equations leading to a linear equation set given by

$$\sum_j G_{ij}\left(P_i - P_j\right) = S_i, \tag{B.1}$$

with G_{ij}, the conductance in $\mathrm{m}^3\ \mathrm{Pa}^{-1}\ \mathrm{s}^{-1}$ between nodes i and j, and S_i a source term for node i. The conductance of a segment is given by $G = \pi R^4/[2(\zeta+2)\mu L]$, where R is the radius, L is the segment length, μ is the dynamic viscosity set to 3.5 mPa s, and ζ is a dimensionless constant related to the velocity profile, with two representing a parabolic profile, i.e. laminar flow, and nine representing a flatter profile used in this model [69]. The larger constant is the result of a blunt velocity profile in the vessels [70]. The volume flow rate in a segment is calculated as $Q_{ij} = G_{ij}\left(P_i - P_j\right)$. Blood vessels are modelled as thin elastic tubes. A pressure-area relationship is used to model the elasticity of the vessel, given by

$$P = P_0 + \frac{\sqrt{\pi}Eh}{A_0(1-\nu^2)}\left(\sqrt{A} - \sqrt{A_0}\right), \tag{B.2}$$

where A is the cross-sectional area, A_0 is the initial area, P is the pressure, P_0 is a reference pressure set to the diastolic pressure, E is the Young's modulus, h is the wall thickness and $\nu = 0.5$ is the Poisson ratio of the vessel wall.

The steady state approach is chosen for its simplicity. In addition, the time scale of interest, i.e. tissue infarction, is much longer than the cardiac cycle. Approximating arterial blood flow as steady state is therefore appropriate in this context. The steady state equations are derived from those commonly used in 1D blood flow modelling with the assumption that the velocity derivatives in time and space are zero. Validation of the entire model is still ongoing. The blood flow model itself is essentially the Poiseuille equation for fluid flow in a pipe, which has been used and validated extensively [71,72].

A.2 Perfusion model

The perfusion model relies on a multi-compartment porous continuum representation of the microcirculation. This approach is becoming a popular choice both in heart [73–75] and brain perfusion modelling [36,66,76–82]. The corresponding governing equations are

$$\nabla\cdot(\boldsymbol{K_a}\nabla p_a) - \beta_{ac}(p_a - p_c) = 0; \tag{B.3a}$$

$$\nabla\cdot(\boldsymbol{K_c}\nabla p_c) + \beta_{ac}(p_a - p_c) - \beta_{cv}(p_c - p_v) = 0; \tag{B.3b}$$

$$\nabla\cdot(\boldsymbol{K_v}\nabla p_v) + \beta_{cv}(p_c - p_v) = 0, \tag{B.3c}$$

where p_i and $\boldsymbol{K_i}$ are the Darcy pressure and the permeability tensor functions in the ith compartment. The subscripts $i = a$, c, and v symbolise the arteriole, capillary and venule compartments. Connection between the ith and jth compartments are established by the terms including the β_{ij} coupling coefficients.

In the healthy baseline scenario, constant pressure is described as boundary condition on the cortical surface of the brain geometry [83,84] both in the arteriole and venule compartments. The arteriole boundary pressure is computed by the arterial blood flow model whereas the venule pressure is selected as the reference value and hence it drops out. In the stroke scenario, zero blood flux is enforced through the cortical surface corresponding to the occluded vessel. Boundary conditions on the remaining surfaces (including the ventricular boundaries in the arteriole and venule compartments, and every boundary of the capillary compartment) ensure zero blood flux (zero pressure gradient) in every case.

It has been demonstrated that the permeability tensors can be replaced with single scalars representing the isotropic capillaries [85], and vessel bundles of penetrating arterioles and venules [36]. The governing equation set (B.2) is discretised using a tetrahedral brain mesh and solved

numerically using FEniCS [86,87], an open-source finite element library. Perfusion is defined as $F = \beta_{ac}(p_a - p_c)$ according to Ref. [81]. Baseline model parameters are determined to match grey and white matter perfusion values corresponding to an average elderly patient so that virtual patients can be generated based on parameter perturbations [36]. Validation results so far indicate that the model predicts realistically blood flow rate through major cortical territories in healthy cases as well as infarcted regions in stroke cases [36,66]. Further validation and uncertainty quantification of the model is in progress based on comprehensive quantitative clinical imaging data.

A.3 Tissue health model

The tissue health model is a set of hypoxia-driven ordinary differential equations based on perfusion in each tetrahedral element of the brain mesh used for the perfusion computation. Due to the limited knowledge of white matter, the perfusion in white matter element is scaled to grey matter level based on the healthy perfusion ratio between the two.

By implementing the Green's function methods [88], oxygen transport and tissue oxygenation can be simulated under a certain perfusion in the physiologically representative human microvascular cubes [85]. With the criteria of hypoxia as $PO_2 < 10$ mmHg [89], the tissue hypoxic fraction (fraction of hypoxic tissue in each cube) can be expressed as a function of perfusion. Here we assume that the relationship between hypoxia and perfusion is homogeneous because oxygen transport has been found to be independent of the variability of microvascular geometry and of length scales up to hundreds of microns [37]. The details of oxygen transport simulations can be found in our previous study [37].

The hypoxic fraction drives a modified 3-state cell death model [37,90]. In the modified 3-state model inspired by Ref. [91], hypoxia activates toxin release which furthers the transition of local cell compartments from alive to dead. There is also a toxin cleaning mechanism, which will dominate over toxin releasing and slow down further tissue damage, when the hypoxia is eased after perfusion restoration. With two thresholds of dead cell fraction for penumbra and core, the model has been tuned and validated against monkey data [92]. By coupling the cell death model with the perfusion model, core and penumbra volumes in a virtual patient brain at a certain time can be predicted easily. Further details of the cell death model development, validation, and application will be presented in a future study.

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