Towards a generation of Digital Twins in Healthcare of Ischaemic and Haemorrhagic Stroke

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Abstract. We introduce our approach towards development of Digital Twins in Healthcare for both ischemic and haemorrhagic stroke, in relation to aetiology and prevention, treatment, and disease progression. These models start their development as generic Digital Twins and in a series of steps are stratified to become fully patient-specific. The example of a Digital Twin in Healthcare for treatment of ischemic stroke is described, and an outlook on the need and applicability of such digital twin in relation to stroke is provided.

Keywords: Digital Twin in Healthcare, Stroke.

1 Introduction

1.1 Context

Within the context of the recently started GEMINI project [1] our aim is to deliver validated multi-organ and multi-scale computational models for improved treatment and fundamental understanding of acute strokes, both ischaemic and haemorrhagic, and demonstrate the added benefit of these computational models for personalised disease management. This contribution describes our vision and approach towards fully personalized credible Digital Twins in Health for ischemic and haemorhaggic strokes.

1.2 Stroke

Neurological diseases are amongst the most challenging and expensive diseases around us, of which strokes are by far the most significant and expensive for society.[2] In the last decades, momentous progress has been realised in the understanding and treatment of stroke, resulting in some of the most effective novel treatment introductions in the whole field of medicine, namely the thrombectomy for intracranial large vessel occlusion stroke and endovascular treatment of intracranial aneurysms. However, we might hit a block regarding treatment advancement, as the large parts of previous improvements are based on (1) treatment on a population level as the results of clinical trials and (2) decades of research with animal models. While valuable approaches, these efforts do not cover the patient-specific and multifaceted aspects of stroke (e.g., comor-

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DOI: 10.1007/978-3-031-63759-9_29

bidities, multi-organ involvement, the initiation of the stroke, and the subacute progression of the diseases) that are required to advance the field of stroke prevention, diagnosis, treatment, and monitoring, and improve patient care. Indeed, medical professionals currently lack patient-specific decision-making tools and well-established models that can accurately assist in the diagnosis and stratification of stroke patients for tailored treatments and device choice. Personalised computational modelling provides a viable, promising, and clinically required approach to improve patient management. On top of that, personalised computational modelling can address other (clinical) needs regarding stroke, such as fragmented knowledge from different medical specialties, evidence obtained in selected populations in protected environments, simplistic mono-organ disease models, and interdependencies between factors that are now considered independent. [3]

1.3 Digital Twin in Healthcare

We follow the definitions as used in the coordination action EDITH, [4] where a Digital Twin in Healthcare (DTH) is defined as a computer simulation that predicts quantities of interest necessary to support decision-making within a specific context of use in healthcare. A DTH can be (1) generic: the predicted value is within the range of the values measured experimentally in a reference population, (2) population-specific: the predicted value is sufficiently close to some central property (e.g., mean, median) of the range of the values measured experimentally in the reference population, or (3) subject-specific: the predicted value is sufficiently close to the value measured experimentally in each individual in the reference population. Typically, model development starts generic, after which models are combined into workflows and turned into a generic DTH, which in rounds of development and stratification are moving to population-specific DTH and finally to fully personalised subject-specific DTH. This requires that the context of use becomes more and more specific, and that sufficient relevant clinical data is available to allow for validation of the DTHs.

2 Clinical needs

2.1 Acute ischaemic stroke

An acute ischaemic stroke occurs when an artery that supplies blood to the brain is blocked by a blood clot. This results in a sudden loss of blood circulation to an area of the brain, resulting in loss of neurologic function, as the blockage-induced deprivation of oxygen and nutrients to the brain causes brain cell death. The effects of acute ischaemic stroke can be very severe: stroke is the second-leading cause of death (12% of total deaths) and the leading cause of serious long-term disability (5.7% of total disability-adjusted life years) globally. [5] On average, every 25 seconds someone has a stroke in Europe resulting in an estimated 1.3 million Europeans having a first stroke each year. [6]

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DOI: 10.1007/978-3-031-63759-9_29

2.2 Intracranial Aneurysm

Intracranial Aneurysm (IA) is a disease of the vessel wall resulting in the deformation and enlargement of the vascular lumen. The aneurysms may rupture if the deformation process remains active, potentially resulting in haemorrhagic stroke and loss of blood circulation to the brain, resulting in a sudden headache in all cases and loss of consciousness or focal neurologic deficits. All vessels can be affected by an aneurysm, but structural and hemodynamic particularities of intracranial vessels justify the study of IAs as a distinct entity. [7] The major risk with IAs is their rupture resulting in a Sub-Arachnoid Haemorrhage (SAH). [9] IAs are mostly quiescent and asymptomatic but when rupturing, IAs potentially induce severe brain damage and death. The prevalence of IAs is high (2 to 5%) and affects young people (median: 50 years). [8] SAH occurs in 6.3 per 100,000 inhabitants per year in Europe. [10]

2.3 Screening for primary stroke or IA rupture has limited value

It is important to note that for *ischaemic disease*, prevention of the primary event is nearly impossible. Although many behavioral characteristics have been associated with the prevalence of stroke (like obesity and smoking), the effects of addressing these are very small or adherence is complicated (e.g., to a healthy lifestyle). We focus on optimal treatment instead, since the right and swift treatment can have huge benefits for the patient's health. Here, time is crucial. Each hour without successful treatment, the brain loses as many neurons as it does in 3-4 years of ageing. [6] Moreover, effectiveness of stroke treatment is strongly reduced with delay. [7, 9]

For IAs, theoretically, a complete screening of the population would allow detecting all IAs and possibly to prevent aneurysm rupture. This strategy, being very expensive, is currently only recommended for subjects with a positive family history for IA or SAH. [11] For the general population, screening of healthy subjects generates substantial stress, and preventive treatment does not offer a sufficient benefit in terms of quality of life, [11] which does not justify the screening of the full population. Nevertheless, the increase in the number of imaging facilities and the improving imaging quality results in an increase in incidental IA diagnosis. Too low a threshold for treatment exposes patients to unnecessary treatment-induced morbidity and mortality. Too frequent monitoring exposes patients to unnecessary stress and society to unnecessary costs. Careful selection of cases to be monitored and customisation of the monitoring protocol as well as adequate selection of an optimal treatment modality are major tools to prevent IA rupture and associated morbidity and mortality as well as care-induced stress, morbidity, mortality, and direct and indirect costs.

2.4 Need for patient-specific models in Stroke

When patients are diagnosed with stroke, many initial questions arise. For *acute ischaemic stroke*, which treatment or treatment combinations are optimal for specific patients? What is the origin of the stroke (e.g., thrombus in the heart, thrombus coming from carotid plaques, or an origin in the brain)? Should thrombolytics be given? Which device or combination of devices should be used to achieve fast complete recanalization

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and reperfusion? Is there a risk for haemorrhagic transformation or early stroke recurrence? For *intracranial haemorrhage*, most of the improvement leverage is on prevention. What is the population at risk of having an intracranial aneurysm? Will a diagnosed aneurysm rupture, causing a haemorrhagic stroke? What are the different intracranial aneurysm treatment options to prevent IA rupture? What are the risks associated with treatments? How will the haemorrhage evolve into delayed cerebral infarction? Will there be a rebleed? What treatments are possible to limit the risks of delayed cerebral infarction? In the long run, should the patient's lifestyle be altered?

The answers to all these questions strongly depend on patient-specific factors and treatments available. In current clinical practice, treatment decisions are taken based on evidence generated in a relatively small number of clinical trials, so based on the effects on general or stratified populations and pragmatically assuming known relevant factors involved are independent. Validated and proven computational tools that enable a personalised patient-specific treatment and management of stroke patients integrating interdependencies on a knowledge base would be a significant step beyond current state of the art.

3 Towards DTH for Stroke

There is a clear clinical need for improved diagnosis of stroke patients, identification of patients at risk of a (secondary) event, and additional treatment and monitoring options. We have identified and prioritised these clear-cut clinical needs, resulting in a series of multi-scale multi-organ models to address them (see Fig. 1).

	Ischaemic stroke		Haemorrhagic stroke	
	Clinical need	GEMINI will model	Clinical need	GEMINI will model
Aetiology & Prevention	Prediction tool for stroke recurrence (long term) in patients +/- atrial fibrillation	Atrial fibrillation Plaque formation Thrombus characteristics	Identification tool patients at risk for IA rupture incl. gender differences	Aneurysm dome wall irregularity, Stability/growth at the aneurysm level and more focally
Treatment	Treatment allocation decision-making tool (thrombectomy +/- thrombolysis + timing)	Thrombolysis Endovascular thrombectomy	Treatment allocation decision-making tool (treatment modality + timing, gender differences)	Coil and stent placement and resulting effect on luminal flow and thrombosis
Disease progression	Prognosis and decision-making tool for management of patients +/- atrial fibrillation with subacute disease progression	Oedema formation Haemorrhagic transformation	Prognosis and decision-making tool management for SAH	Post diagnosis mortality & morbidity and probability of progression after UIA or SAH diagnosis and treatment

Fig. 1. Clinical need addressed by GEMINI per acute stroke subtype and per disease stage. Areas that will be modelled per disease and disease stage are indicated. We address two distinctly different diseases with similar characteristics in the effect on patients: acute ischaemic stroke and subarachnoid haemorrhage. For both diseases, we model its aetiology & prevention, treatment, and subacute disease progression.

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DOI: 10.1007/978-3-031-63759-9_29

We will (further) develop and deliver a focused set of models at different stages of development to move into clinical practice addressing prevention, diagnosis, treatment, and monitoring of stroke. These models will be validated and combined into specific DTHs for ischaemic and haemorrhagic strokes. We start with further developing and integrating multi-scale (patho) physiological models that are then composed into population specific DTHs for ischaemic and for haemorrhagic strokes. Three selected DTHs, for treatment options for ischaemic and haemorrhagic strokes, and for risk of rupture of IAs, will then be fully personalized, and finally, the DTH for treatment of ischaemic stroke will be tested on clinical effect in a clinical trial. Fig. 2, visualizing the work package structure of the GEMINI project, summarizes this approach.

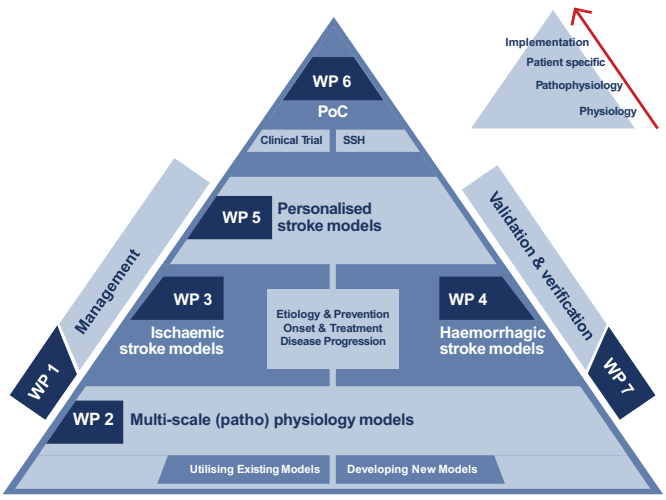

Fig. 2. The pyramid structure schematically depicts how higher work package number build upon the lower ones. WP3 and WP4 make use of the general (patho) physiology models of WP2, WP5 uses the population-based DTHs to build patient-specific DTHs, whereas WP6 takes one of the patient-specific DTHs to evaluate its value in clinical practice. All work packages interact with WP7 (validation and verification).

4 An example, a DTH for treatment of acute ischemic stroke

Treatment options to remove the clot in an acute ischemic stroke patient are thrombolysis, thrombectomy, and aspiration. The INSIST project [12] delivered fully validated models for thrombectomy [13] for M1 occlusions and for two different devices. Since simulating one case requires many hours of execution time on a high-end computer, which was not compatible with the intended use case (in silico stroke trials or personalized decision support in the acute phase), a computationally much more efficient surrogate model has been developed. This surrogate was trained with data from running thousands of instances of the fully mechanistic thrombectomy model [14]. The surrogate model takes as input details of the anatomy of the vasculature, the location of the clot, its size and some other parameters and returns a probability of a successful first-

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pass thrombectomy. More recently, a failure model calibrated with experimental tests on clot analogues was used to simulate thrombus fragmentation during a combined stent-retriever and aspiration thrombectomy procedure. [14] It is important to note that for the initial development and validation of the thrombectomy models in the INSIST project, dedicated benchtop experiments have been performed.

To fully personalize these models, we need to extract patient-specific data for model validation. Relevant input data for the treatment surrogates will be automatically extracted from a minimum of 250 patients (for each thrombectomy treatment). The surrogate ischaemic stroke treatment models will be evaluated on such personalised data. Metrics based on treatment success and patient outcome based on disease progression up to one-week post-treatment will be used. In case of suboptimal accuracy, additional synthetic data will be generated, based on the evaluated patient data, to update the surrogate model.

Finally, the goal is to generate proof of clinical value of the personalised *Ischemic Stroke Treatment Selection DTH* (ISTS-DTH) in clinical practice for health professionals, patients, and the healthcare system. This requires implementing the ISTS-DTH in clinical practice, to determine the added value of the ISTS-DTH in terms of established clinical outcomes, to determine the adaptation, perception, and change in behaviour of patients and clinical professionals exposed to the ISTS-DTH and to identify and mitigate potential biases in ISTS-DTH resulting from differences in training populations and the population addressed in the trial.

The trial will run in the Netherlands, will be run for 12 months, and will include 300 patients. The added value compared to standard-of-care will be evaluated according to three types of outcomes: (1) technical effectiveness of treatment, expressed as first pass eTICI 2C-3, and speed of treatment expressed as the time between entrance of a patient until the finalisation of the stroke treatment, (2) Patient benefit, addressed as functional outcome and measured as NIHSS approximately 1 day after stroke and the mRS 3 months after stroke, and (3) General quality of healthcare estimated as QALY (measure of how many years of life are lived in good health), DALYs (measure of lost healthy life years) and healthcare costs.

5 To Conclude

The GEMINI project aims to develop a series of DTHs relevant to strokes, for aetiology assessment and prevention, for treatments, and for disease progression. Our approach is to start with generic multiscale models of the basic physiology, e.g. brain perfusion and metabolism, and multiscale models of the pathologies, e.g. thrombosis or aneurysm development and rupture. These are then used to create a series of well-defined DTHs for stroke, some of which will then be fully personalized (for treatment of ischemic stroke, for treatment of IA, and for IA rupture risk estimation). Finally, one of these subject-specific DTHs, the DTH for treatment of acute ischemic stroke, will subsequently be tested in a randomized clinical trial as a decision support tool for the neurointerventionist. The effect of using this DTH on the clinical endpoint, the status of the patient six months after treatment, will be assessed in this trial.

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DOI: 10.1007/978-3-031-63759-9_29

Acknowledgments. We acknowledge funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101136438 (GEMINI project)

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DOI: 10.1007/978-3-031-63759-9_29