UvA

Computational Science

Towards Digital Twins in Healthcare

(and some reflections on Computational Science)

Alfons Hoekstra

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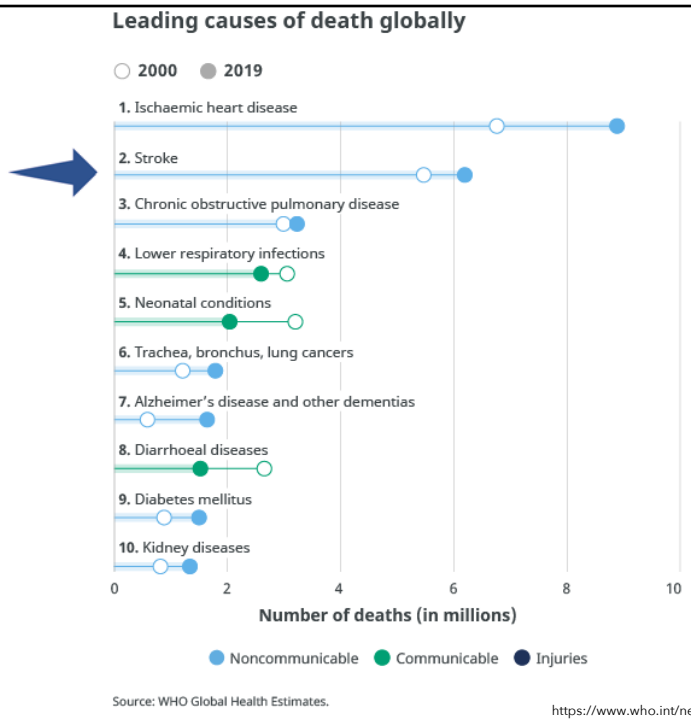
1

Part 1	The Application Pull
Intermezzo 1	*Computational Models*
Part 2	Digital Twins
Part 3	Digital Twins in Healthcare
Intermezzo 2	*Credibility*
Part 4	A Digital Twin in Healthcare for Acute Ischemic Stroke

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PART 1 – APPLICATION PULL

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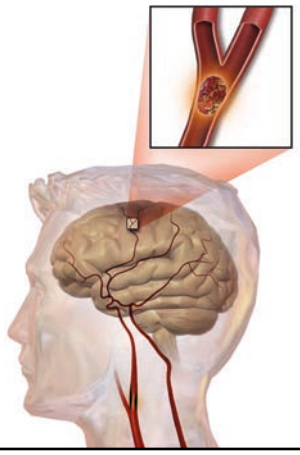


https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

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Acute Ischemic Stroke

- Most common type of stroke: ≃87%
- 3 million deaths globally per year
- "Time is brain"





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Acute Ischemic Stroke

2015: a new treatment, start of a new era

Up to 2015: standard treatment

- IV thrombolysis
- Not effective in large vessel occlusions



2015: new effective treatment of acute ischemic stroke (NEJM 2015;372:11-20)

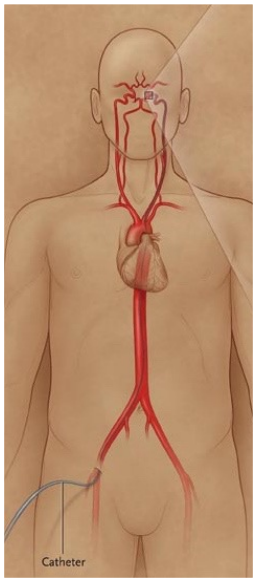
- Endovascular thrombectomy
- Effective and safe 0-6 hours after onset

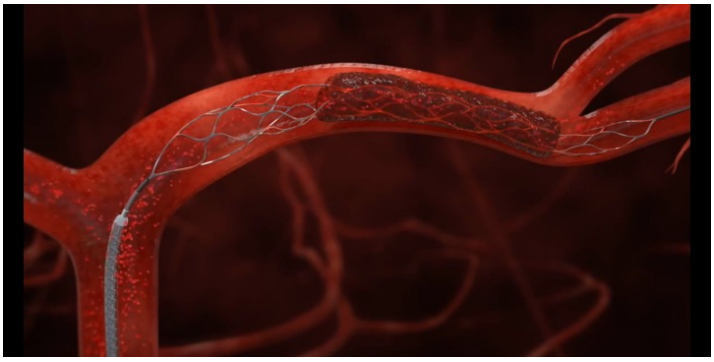
MR CLEAN

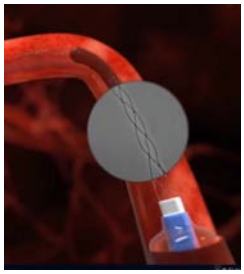
A Multicenter Randomized CLinical trial of Endovascular treatment for Acute Ischemic stroke in the Netherlands

6

Endovascular Thrombectomy



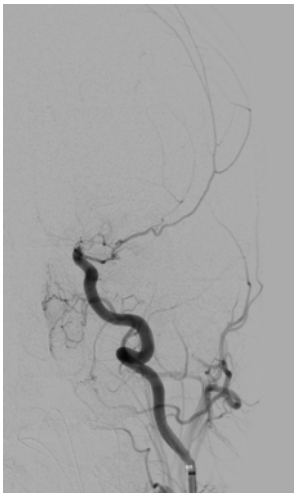


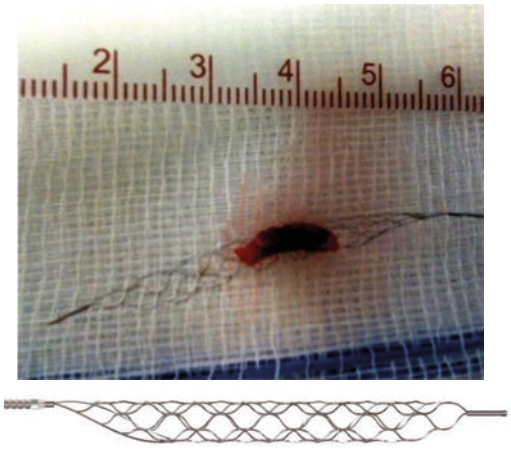


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Endovascular Thrombectomy

Before





After

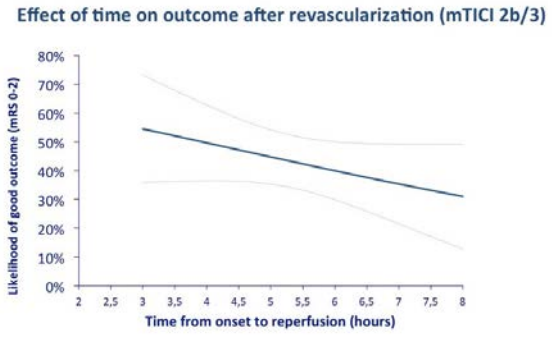


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Endovascular Thrombectomv

Disappointment

- Only 33-50% recovers after EVT



Causes

- No recanalization
- Large infarct core, no penumbra
- Incomplete (micro)vascular reperfusion
- …….

Further improvement of medication and devices needed

9

Which new treatment can improve outcome further?

By performing

- Animal experiments
- New clinical trials

CONTRAST

COllaboration for New TReatments of Acute STroke

How can we treat more patients (successfully)?

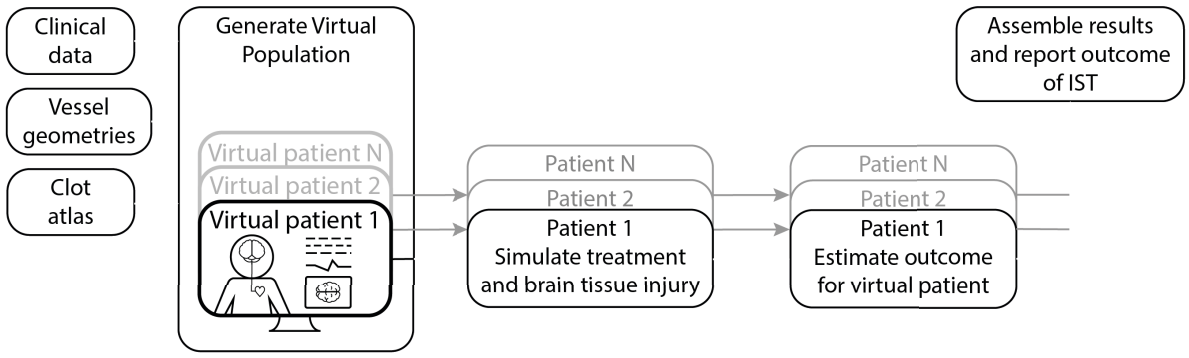
Pre-clinical research & 4 RCTs (2500 patients)

- In Silico Trials
  - Translation from computer simulations to clinical research

INSIST HORIZON 2020

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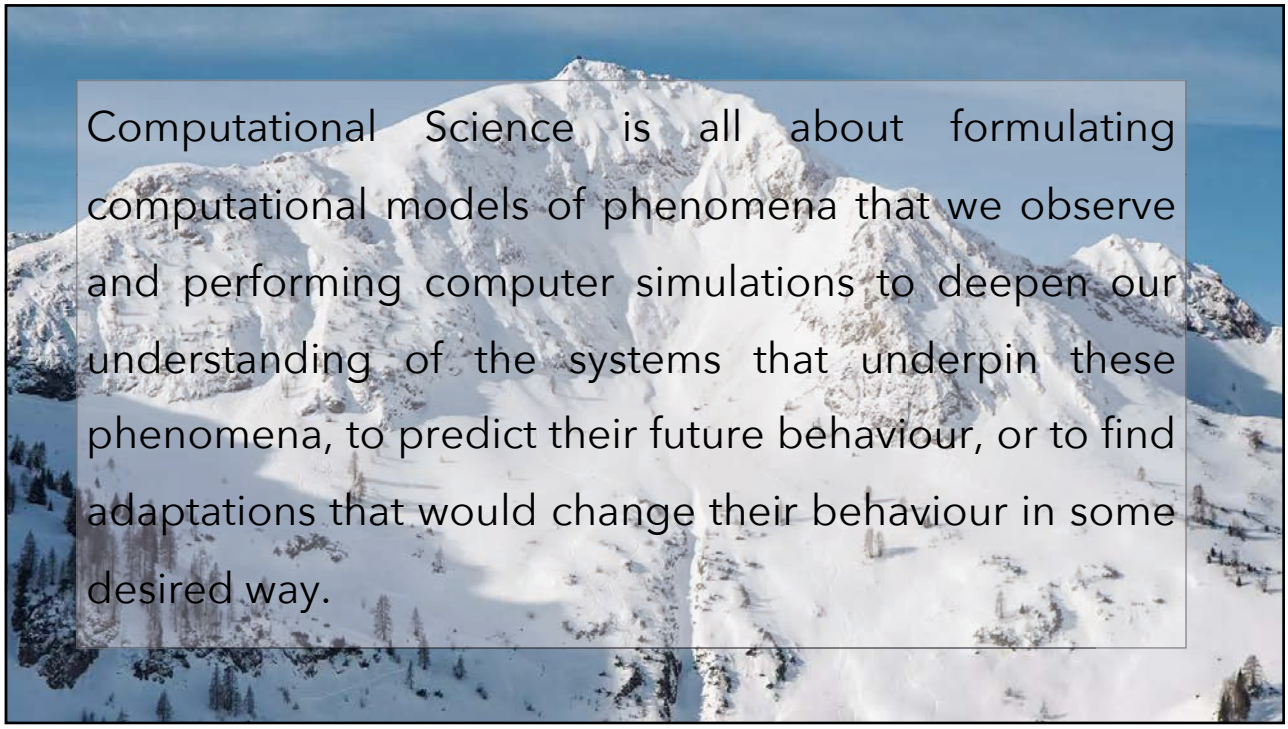
In Silico Trials of Acute Ischemic Stroke



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INTERMEZZO 1 – COMPUTATIONAL MODELS

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Computational Science is all about formulating computational models of phenomena that we observe and performing computer simulations to deepen our understanding of the systems that underpin these phenomena, to predict their future behaviour, or to find adaptations that would change their behaviour in some desired way.

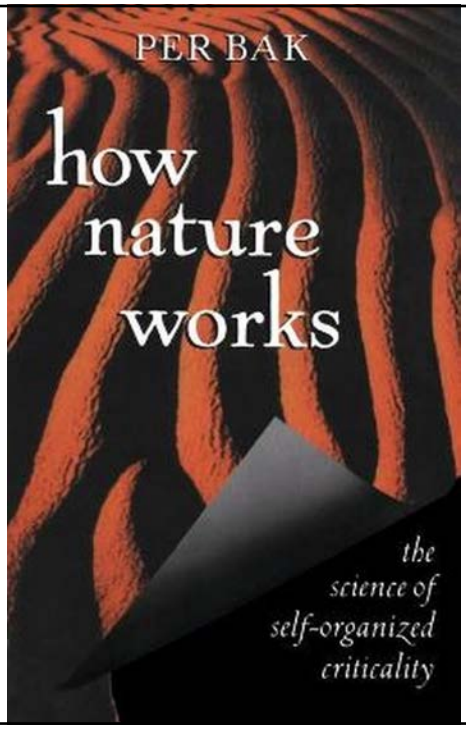
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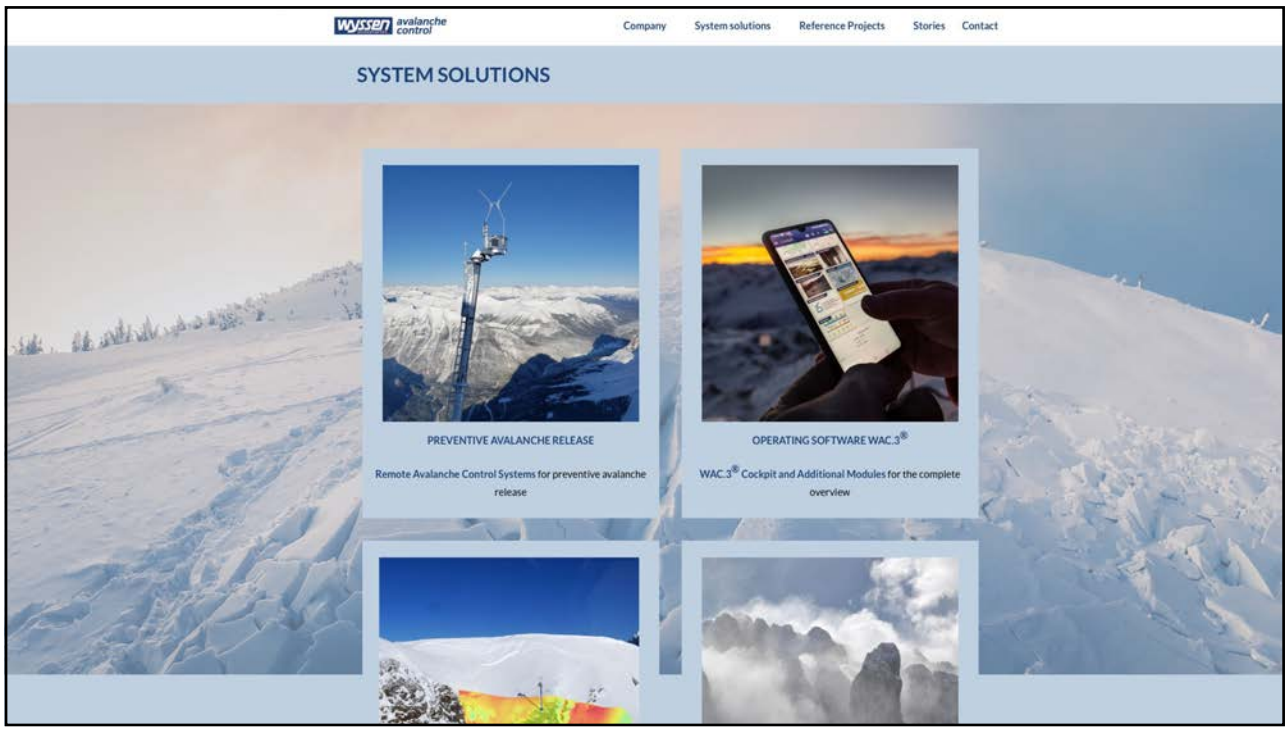
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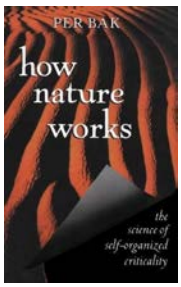
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PER BAK
how nature works
the science of self-organized criticality

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WYSSEN avalanche control
Company
System solutions
Reference Projects
Stories
Contact
SYSTEM SOLUTIONS
PREVENTIVE AVALANCHE RELEASE
Remote Avalanche Control Systems for preventive avalanche release
OPERATING SOFTWARE WAC.3®
WAC.3® Cockpit and Additional Modules for the complete overview

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PER BAK
how nature works
the science of self-organized criticality


SYSTEM SOLUTIONS

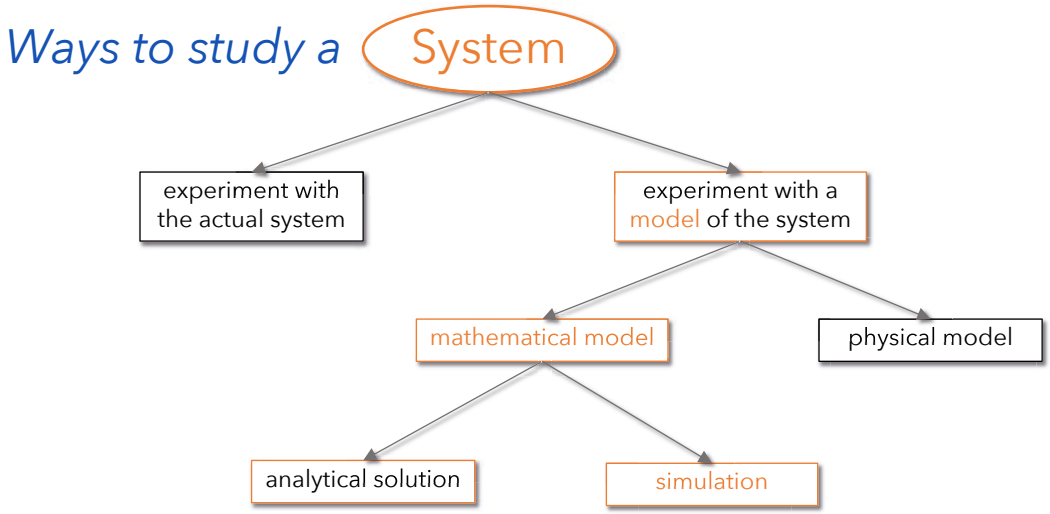
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Generic model ⟵ Systems-range model ⟶ System-specific model

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So, what is a model?

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A system is a potential source of data

Bernard Siegler, *Theory of Modeling and Simulation*, 1976.

An experiment is the process of extracting data from a system by exerting it through its inputs.

François Cellier, *Continuous System Modelling*, 1990.

A model M for a system S is anything to which the same experiment E can be applied to answer questions about S

Marvin Minski, *Models, Minds, Machines*, 1965.

The resulting data of $E(M)$ should be close enough to the resulting data of $E(S)$.

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S and E are related to the Context of Use (CoU)

$f(E(S))$ expresses the Questions of Interest (QoI)

$\|f(E(M)) - f(E(S))\|$ together with the CoU determine validity for the specific QoI

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Computational Models

mathematical models



Taken from https://www.auca.kg/en/las_mathematical_modeling/

data models



Taken from https://intellipaat.com/blog/data-modeling-tutorial-for-beginners/

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Computational Models

knowledge driven models ⟪ hybrid models ⟫ data driven models

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Challenges

- How do we validate hybrid models?

- How do we create fully system-specific models? How do we prove their validity and how to parametrize them given data taken from specific systems?

- Etc.

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PART 3 - DIGITAL TWINS

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Living Models at Nasa – Apollo XIII









15 <u>simulators</u> were used to train astronauts and mission controllers

- Simulator → digital twin?

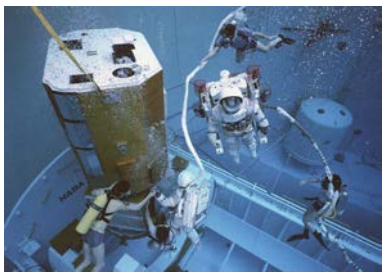
Adapted to match conditions of actual spacecraft

High fidelity model used to explore solutions and predict results

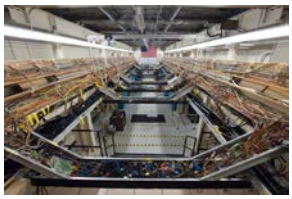
Slide from B. Dannette Allen, Digital Twins and Living Models at NASA, ASME Digitial Twin Summit, November 2021

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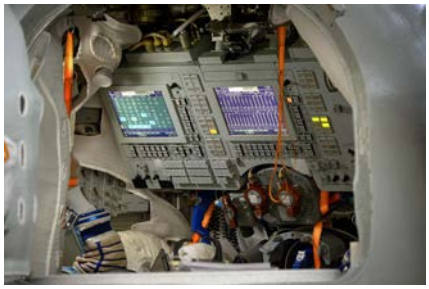
Simulators







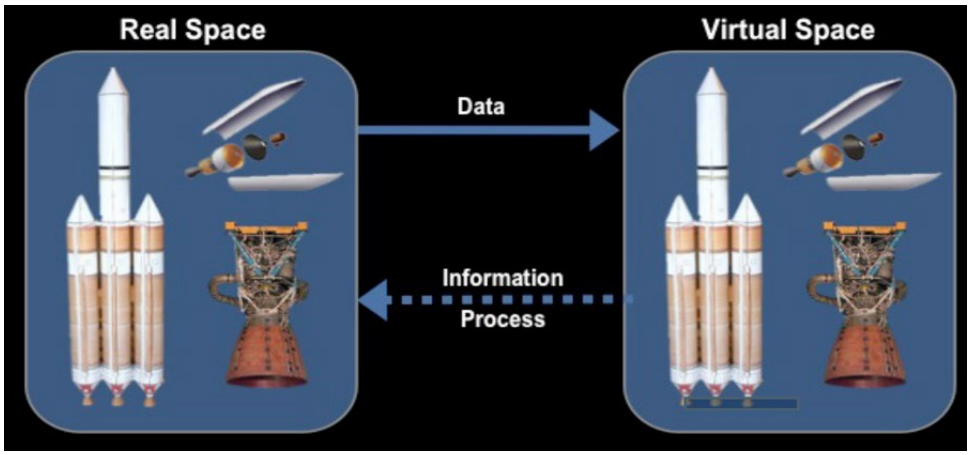




Slide from B. Dannette Allen, Digital Twins and Living Models at NASA, ASME Digitial Twin Summit, November 2021

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Digital Twin



Slide from B. Dannette Allen, Digital Twins and Living Models at NASA, ASME Digitial Twin Summit, November 2021

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PART 3 – DIGITAL TWINS IN HEALTHCARE (DTH)

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EDITH-CSA: Building an Ecosystem for Digital Twins in Healthcare

EDITH

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771.

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Vision for the Virtual Human Twin

The Virtual human twin (VHT) is

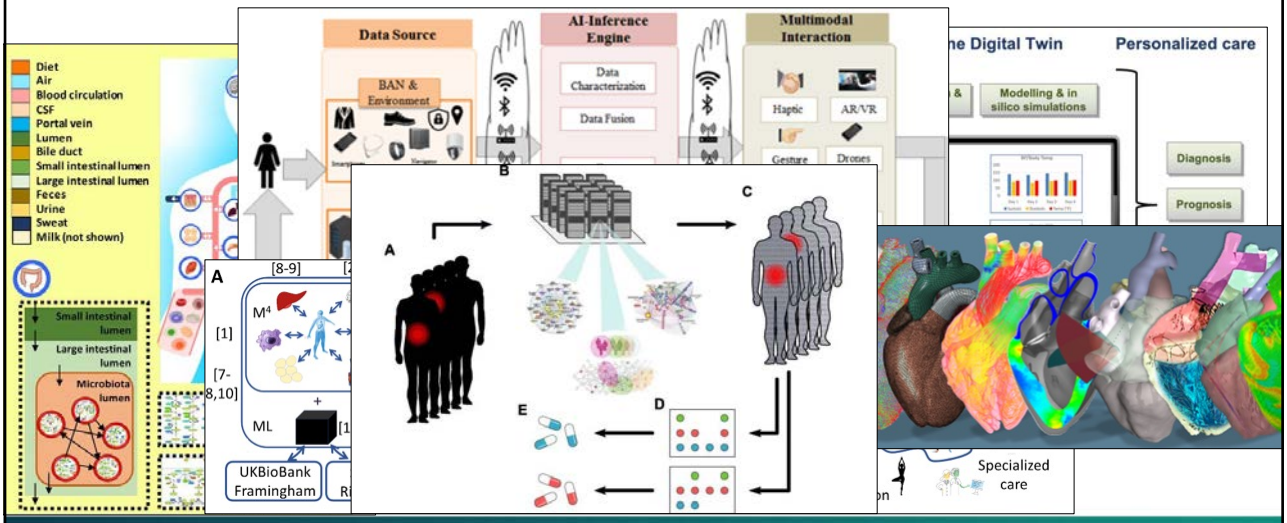
an **integrated multi-scale, -time and -discipline digital representation of the whole body**

enabling the comprehensive characterization of the physiological and the pathological state in its heterogeneity and

allowing **patient-specific predictions** for the prevention, prediction, screening, diagnosis and treatment of a disease, as well as the evaluation, optimization, selection, personalization and de-risking of intervention options.

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Vision for the virtual human twin



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Some tentative definitions

- Reference Populations are singles or groups of human beings whose health status can be affected by these decisions.
- Quantities of Interest (QoIs) are the quantification of constructs that represent the health status in the decision-making process.
- The Context of Use (CoU) defines how the QoI informs a specific decision-making process relevant to human health and under which specific conditions such process occurs.

- A Digital Twin in Healthcare (DTH) is a computer simulation that predicts (as opposed to measuring experimentally) QoIs necessary to support decision-making within a specific context of use in healthcare.

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Some tentative definitions

- The most crucial feature of a DTH is their accuracy. We have:
  - Generic DTH, for which the expected accuracy is that the predicted value is within the range of the values measured experimentally in the reference population;
  - Population-specific DTH, for which the expected accuracy is that the predicted value is sufficiently close to some central property (typically mean or median) of the range of the values measured experimentally in the reference population;
  - Subject-specific DTH, for which the expected accuracy is that the predicted value is sufficiently close to the value measured experimentally in each individual in the reference population.
- By "sufficiently close", we mean that the predictive accuracy of the DTH is sufficient for its purpose as defined in the CoU.

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Some tentative definitions

- Because of gaps in available knowledge and data, currently, we can develop DTHs designed to predict just one or a small number of QoIs with the necessary accuracy only in a narrowly defined reference population.
- The Virtual Human Twin is a framework to develop a new generation of DTHs, capable of predicting any QoI necessary for any CoU and reference population. This is achieved by:
  - Supporting the sharing of data and knowledge resources
  - Making easier the reuse of these resources
  - The collegial monitoring of resources' quality
  - Supporting the progression of technology readiness for DTHs

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EDITH

Building the European Virtual Human Twin

Call: Accelerating best use of technologies (DIGITAL-2021-DEPLOY-01)
Work program year: DIGITAL-2021-2022
Topic: ID DIGITAL-2021-DEPLOY-01-TWINS-HEALTH
Grant Agreement No: 101083771

Deliverable 3.2
First draft of the VHT roadmap

Due date of delivery: 31 July 2023
Actual submission date: 31 July 2023

Start of the project: 01 October 2022
End date: 30 September 2024

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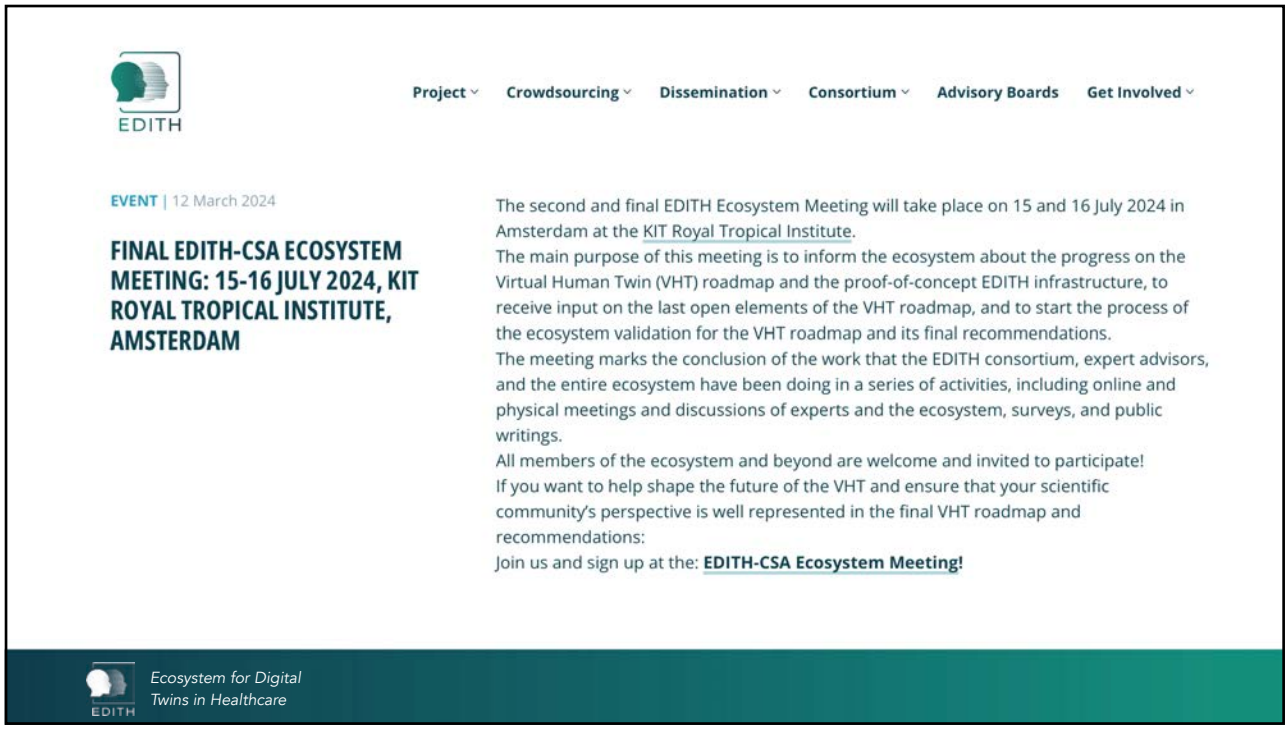
https://www.edith-csa.eu/wp-content/uploads/2023/04/EDITH_D3.1_vision_roadmap_outline_final.pdf

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https://www.virtualhumantwins.eu

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http://www.edith-csa.eu

Deliverables available under tab 'dissemination/material'

Indication of interest via de contact form

EDITH

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771.

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INTERMEZZO 2 - CREDIBILITY

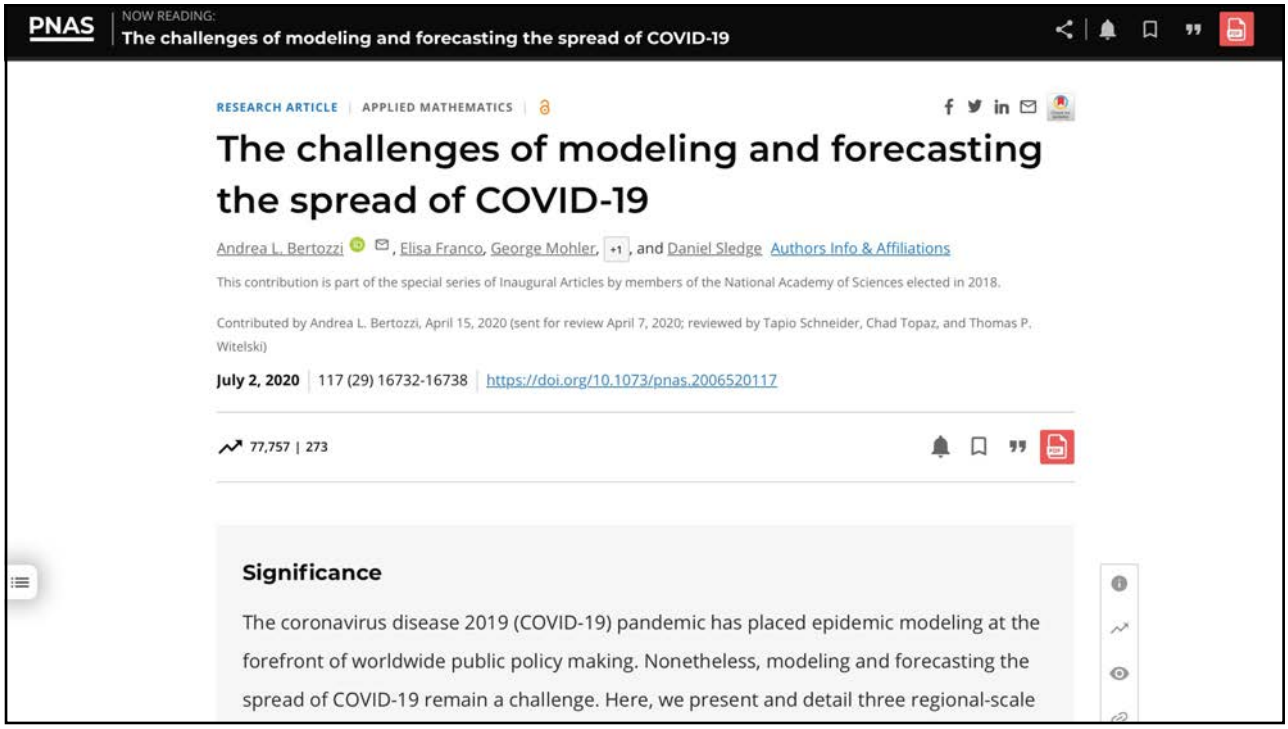
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Why would a third party believe our models?

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What would a third party need in order to believe the predictions of our simulations and act upon it?

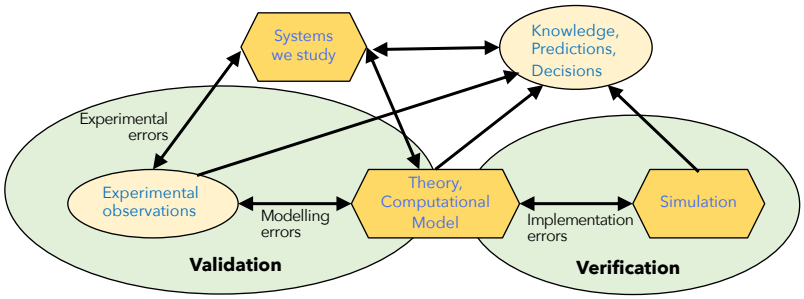
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verification & validation → risk informed credibility → actionable computational science

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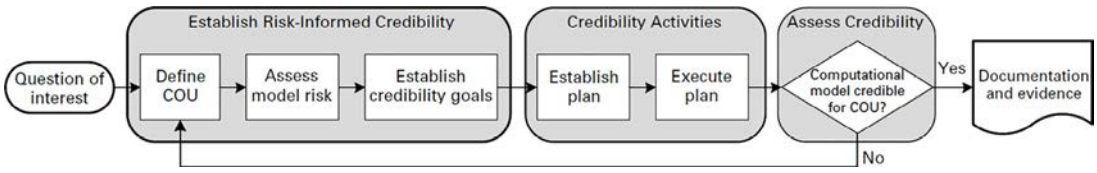


Fig. 1. The risk-informed credibility assessment framework of ASME V&V40-2018 (reprinted from ASME V&V 40-2018 by permission of the American Society of Mechanical Engineers. All rights reserved).

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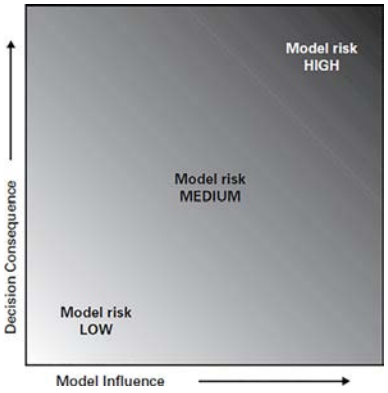


Fig. 2. The risk assessment matrix of ASME V&V40-2018 (reprinted from ASME V&V 40-2018 by permission of the American Society of Mechanical Engineers. All rights reserved).

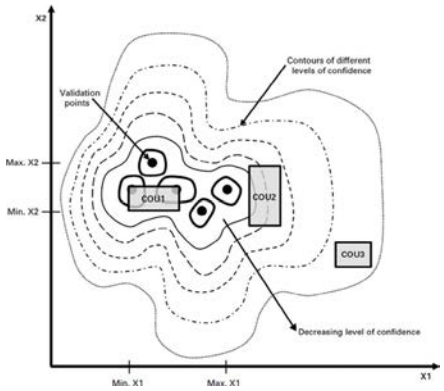


Fig. 3. Schematic representation of applicability (reprinted from ASME V&V 40-2018 by permission of the American Society of Mechanical Engineers. All rights reserved).

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Trends

Generic model ⟵ Systems-range model ⟶ System-specific model

knowledge driven models ⟵ hybrid models ⟶ data driven models

verification & validation → risk informed credibility → actionable computational science

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Challenges

- How do we validate hybrid models?

- How do we create fully system-specific models? How do we prove their validity and how to parametrize them given data taken from specific systems?

- How do we go from risk informed credibility to actionable computing performed by third parties, based on hybrid models?
- Etc …

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PART 4 – A DTH FOR ACUTE ISCHEMIC STROKE

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In Silico clinical trials for treatment of acute Ischemic Stroke

Amsterdam UMC University Medical Centers

KU LEUVEN

NUI Galway OÉ Gaillimh

POLITECNICO MILANO 1863

UNIVERSITY OF AMSTERDAM

Erasmus MC University Medical Center Rotterdam

Lomonosov Moscow State University

UNIVERSITÉ DE GENÈVE FACULTÉ DES SCIENCES

SERVIER

UNIVERSITY OF OXFORD

CERENOVUS PART OF THE Johnson & Johnson FAMILY OF COMPANIES

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777072. This presentation reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains

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Special thanks to …



Dr. **Raymond Padmos**, University of Amsterdam, now with Technical University Delft, the Netherlands



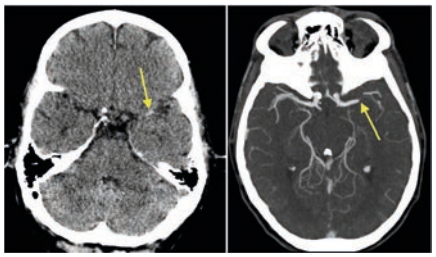
Dr. **Tamás Józsa**, Oxford University, now at Cranfield University, UK



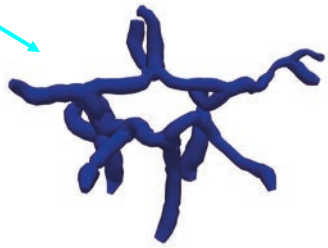
Dr. **Claire Miller**, University of Amsterdam, now in Auckland, New Zealand

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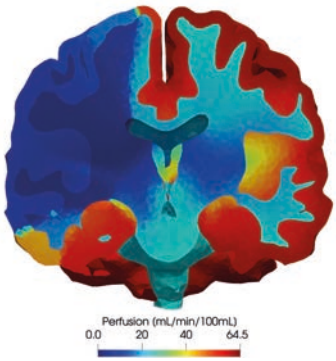
Predicting Infarct volume after acute ischemic stroke



Patient enters the hospital



?



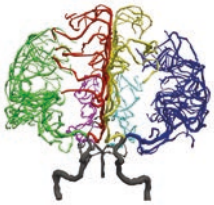
See http://www.svuhradiology.ie/case-study/occluded-middle-cerebral-artery-ct-angiography/

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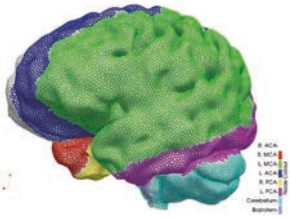
Model Scales



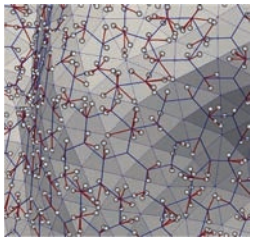
Large Arteries



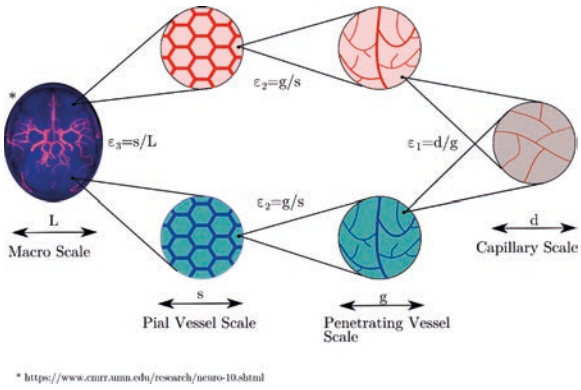
Cerebral Arteries



Pial surface



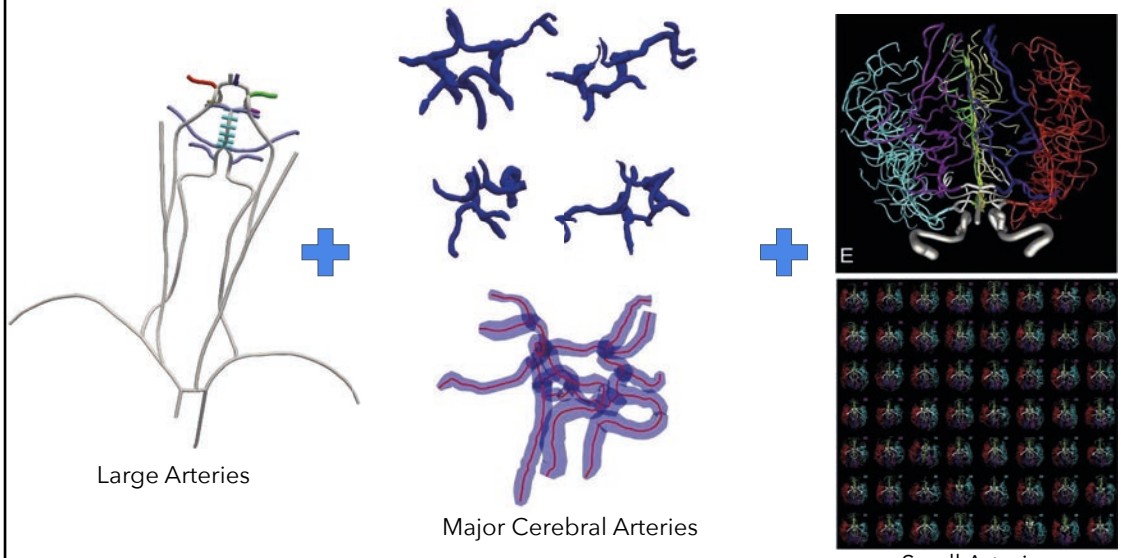
Penetrating arteries



Capillary vessels

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Extending the Vasculature 1



Large Arteries

Major Cerebral Arteries

Small Arteries

See Wright2013

R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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1D time dependent blood flow model

- 1D Navier Stokes Equations

$$\frac{\partial A}{\partial t}+\frac{\partial A v_x}{\partial x}=0$$

$$\frac{\partial v_x}{\partial t}+(2\alpha-1)v_x\frac{\partial v_x}{\partial x}+(\alpha-1)\frac{v_x^2}{A}\frac{\partial A}{\partial x}+\frac{1}{\rho}\frac{\partial p}{\partial x}=\frac{-2\alpha\mu\pi v_x}{(\alpha-1)\rho A}$$

- plus a pressure–area relationship to model the elasticity of the vessel and an experimental relationship between vessel radius and thikness

$$p=p_{ref}+\frac{Eh}{(1-\nu^2)}(r-r_0)\ ;\ h=r_o(ae^{br}+ce^{dr})$$

- Solve the resulting equations with the MacCormack method, a second-order finite difference method.
- The initial conditions are zero velocity and diastolic pressure everywhere.
- Vessels are linked together at the bifurcations by the method of characteristics for continuous propagation of characteristics, conservation of mass and total continuity of pressure.
- The resulting equations are solved with the Newton–Raphson method.
- The simulation is run for a small number of heart beats and iterated until the tolerance between iterations is below a threshold.
- Special procedure to handle the outlets (see paper)

R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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1D static blood flow model

- Blood vessels are modelled as thin elastic tubes and blood as an in-compressible viscous fluid.
- Every vessel segment is modelled as a pressure-dependent resistance.
- The vessels are discretised to a minimum of three nodes, i.e. two terminal and one internal node, and to a maximum resolution of 2.5mm along the length of the vessel.

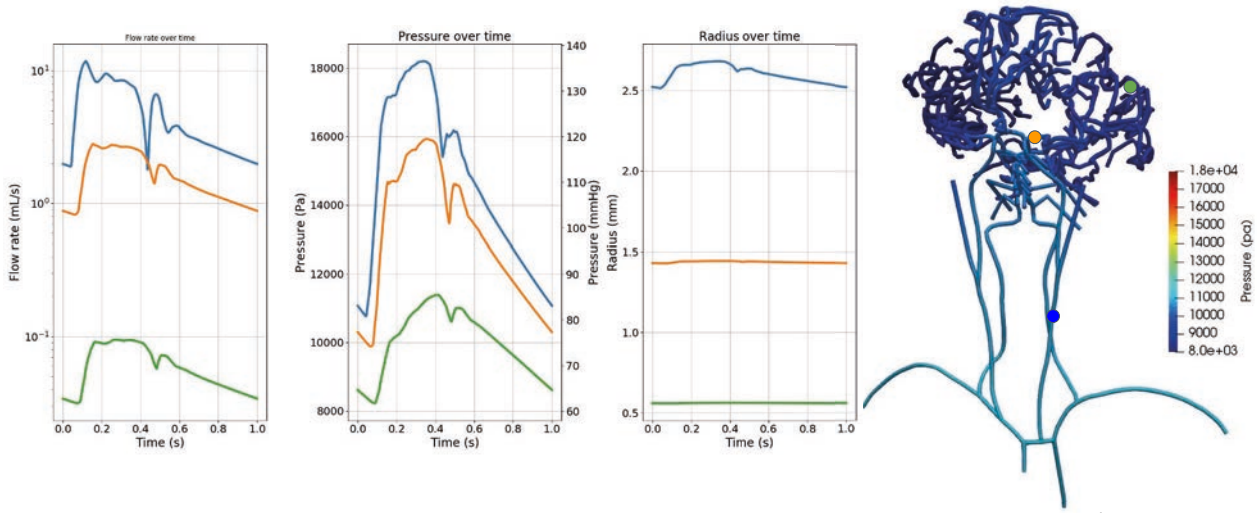
  $\sum_j G_{ij}(P_i - P_j) = S_i$; with P_i pressure at node i and G_{ij} the conductance between nodes i and j.

  $G = \frac{\pi R^4}{2(\zeta+2)\mu L}$; $p = p_{ref} + \frac{Eh}{(1-\nu^2)}(r - r_0)$; $h = r_o(ae^{br_0} + ce^{dr_0})$.
- Equations are solved iteratively until convergence in the pressures is achieved.

R.M. Padmos, N.A. Terreros, T.I. Józsa, G. Závodszky, H.A. Marquering, C.B.L.M. Majoie, A.G. Hoekstra, Med. Eng. Phys. 91 (2021) 1–11. doi:10.1016/j.medengphy.2021.03.003.

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Time dependent blood blow simulations

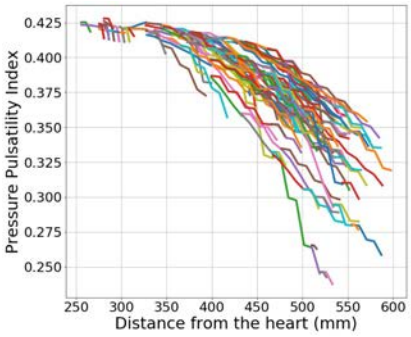


R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

⅕ Speed

60

Pulsatility indices



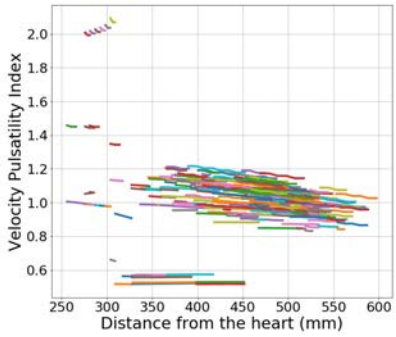


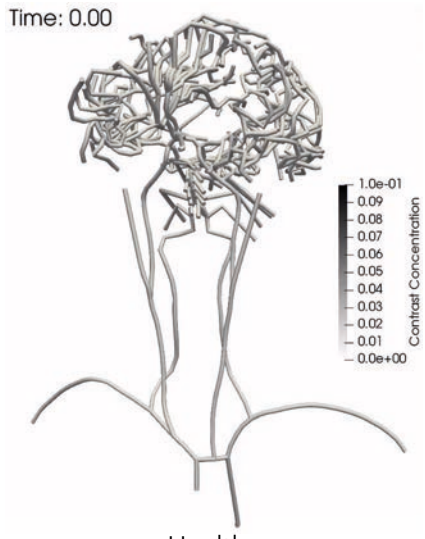
Table 2.3: Velocity pulsatility index of the MCA

Origin	Mean (SD)
Model (default anatomy)	1.02
Model with patient data	1.08
[61]	0.754 (0.110) (Women) 0.823 (0.154) (Male)
[62]	0.74 (0.04)
[59]	0.86 (0.18)
[63]	0.92 (0.21) (Women) 0.94 (0.19) (Men)

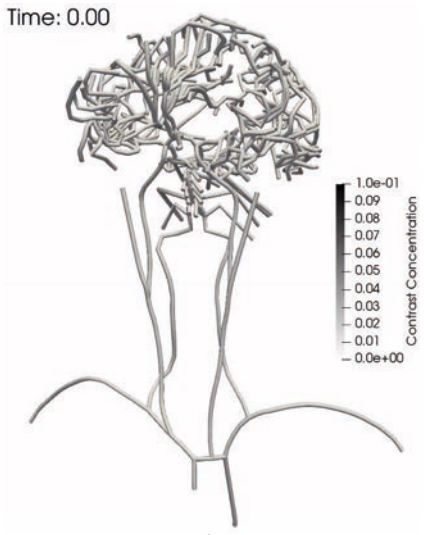
R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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Healthy vs Clot



Healthy



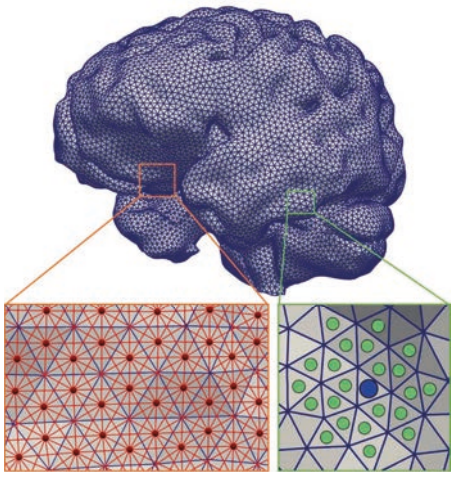
Clot

R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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Coupling 1D model to pial surface

- The pial surface as a uniform triangulated mesh.
- Nodes are the centres of the triangles (red circles), and connected by red lines if they share a vertex. The distance between connected nodes is the Euclidean distance.
- The outlet of a vessel is projected to the surface, blue circle. The nearest surface elements, i.e. triangles, are assigned to the nearest outlet, green circles.

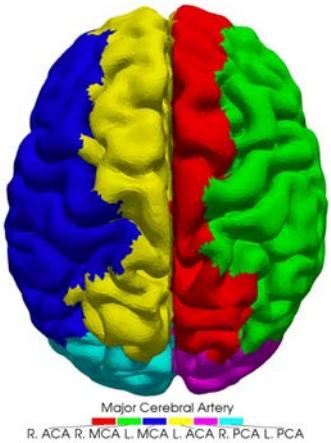


R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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Perfusion territories

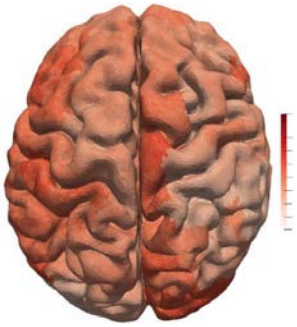
- The pial surface mapped by the coupling algorithm.
- The major region ID for each triangle of the pial surface mesh is shown. Note that this result is enforced by the algorithm.



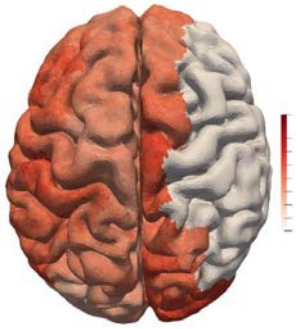
R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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Mean blood flow velocity at the pial surface



Healthy patient. The mean volume flow rate divided by the cluster area for each vessel outlet to the pial surface is shown. All values are within one order of magnitude of each other.



A patient with a stroke. There is a clot in the right MCA. Pressure after the clot is equal to that of the venous system and flow is zero.

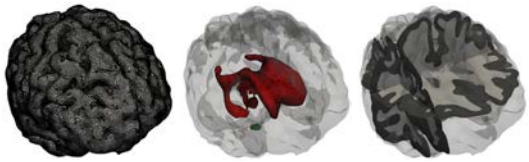
R.M. Padmos, T.I. Józsa, W.K. El-Bouri, P.R. Konduri, S.J. Payne, A.G. Hoekstra, Interface Focus. 11 (2021) 20190125. doi:10.1098/rsfs.2019.0125.

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Brain perfusion modelling

Multi-compartment porous continuum models for the microcirculation (three compartments, arteriole, capillary, venule)

$$\nabla \cdot (\boldsymbol{K}_a \nabla p_a) - \beta_{ac}(p_a - p_c) = 0;$$
$$\nabla \cdot (\boldsymbol{K}_c \nabla p_c) + \beta_{ac}(p_a - p_c) - \beta_{cv}(p_c - p_v) = 0;$$
$$\nabla \cdot (\boldsymbol{K}_v \nabla p_v) + \beta_{cv}(p_c - p_v) = 0;$$



Computational domain and mesh: (a) the pial surface; (b) ventricles (red) and the cut-plane of the brainstem (green); (c) subdomains including grey and white matters visualized along a coronal, a sagittal and a transverse plane.

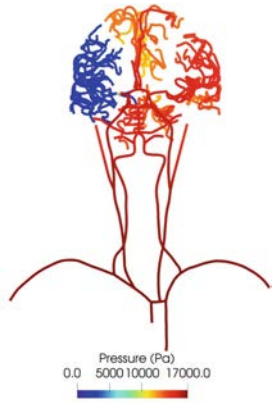


Perfusion distribution corresponding to simulation with anisotropic permeabilities along the transverse (a), sagittal (b) and coronal (c) planes. The solid lines show the location of the slices.

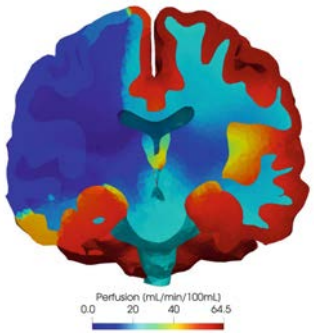
T.I. Józsa, R.M. Padmos, N. Samuels, W.K. El-Bouri, A.G. Hoekstra, S.J. Payne, Interface Focus. 11 (2021) 20190127. doi:10.1098/rsfs.2019.0127.

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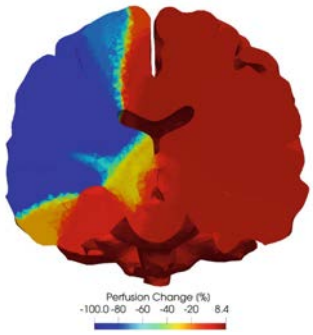
Modelling a stroke, occlusion in left MCA



Pressure



Tissue perfusion



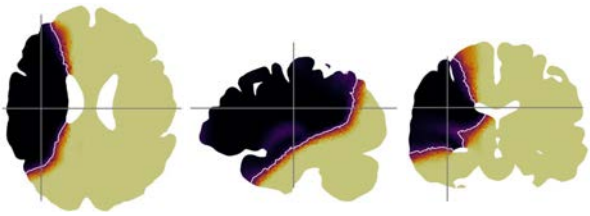
Tissue perfusion change compared to healthy

R.M. Padmos, T.I. Józsa, W.K. El-Bouri, G. Závodszky, S.J. Payne, A.G. Hoekstra,, Lect. Notes Comput. Sci., 12744 LNCS (2021) 670–683. doi:10.1007/978-3-030-77967-2_56.

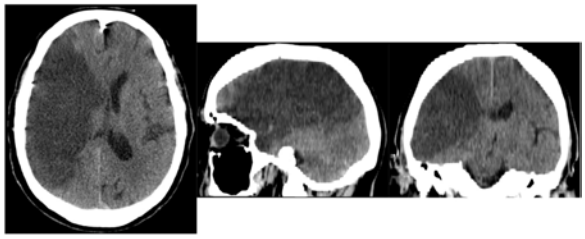
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Modelling infarction

- Using a cut off in drop in perfusion….
  - which ignores the actual growth of the infarct
- Or actually modelling metabolism coupled to the perfusion simulations



Relative change of perfusion as a result of a total blockage of the right middle cerebral artery (R-MCA)

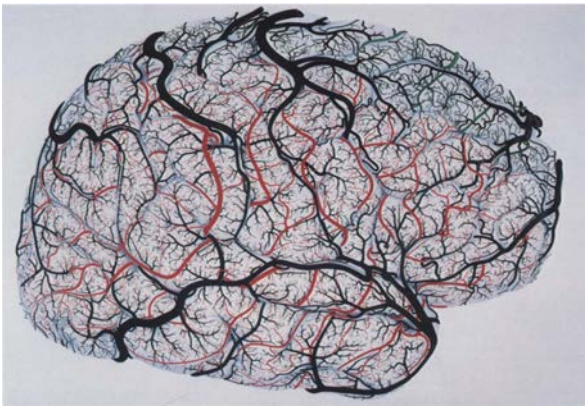


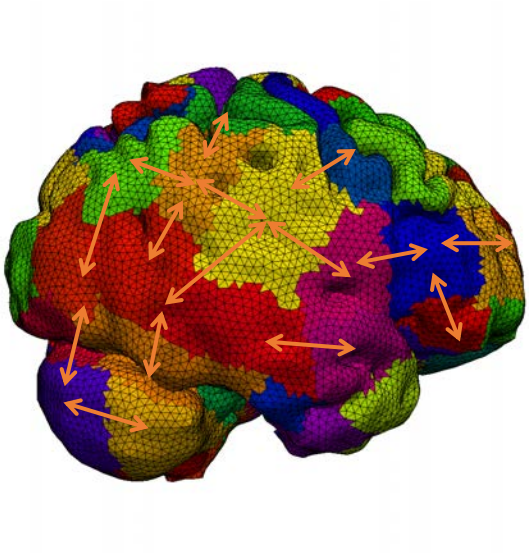
Non-contrast CT images of a patient showing an infarct caused by R-MCA occlusion.

T.I. Józsa, R.M. Padmos, N. Samuels, W.K. El-Bouri, A.G. Hoekstra, S.J. Payne, Interface Focus. 11 (2021) 20190127. doi:10.1098/rsfs.2019.0127.

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Adding collaterals on the Pial surface

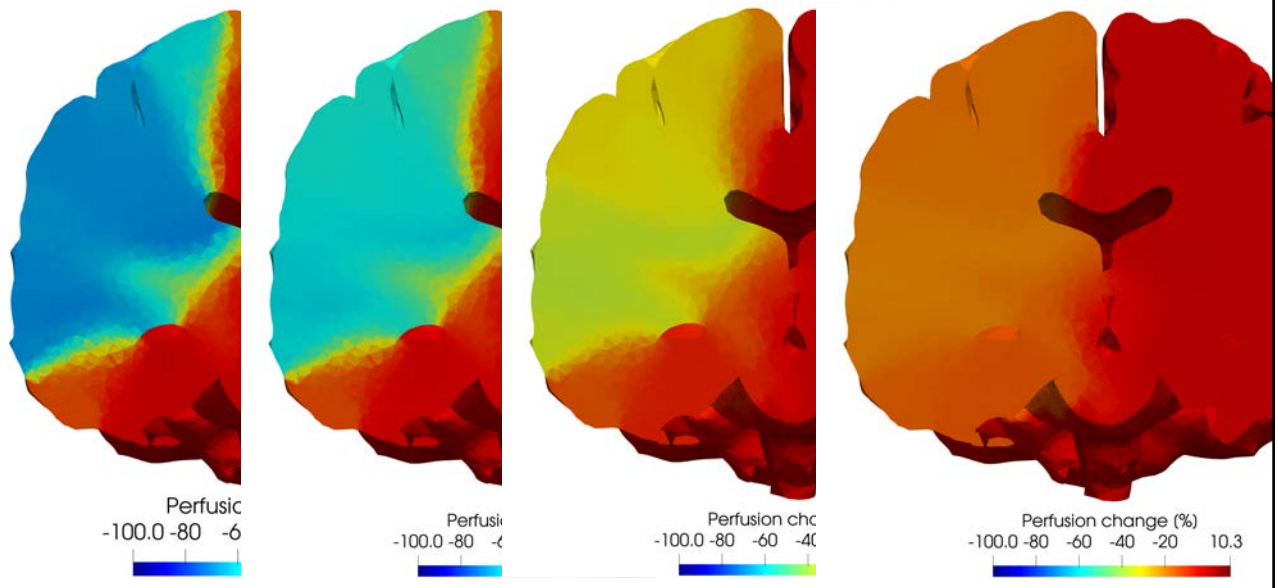




H. M. Duvernoy, S. Delon, and J. L. Vannson, "Cortical blood vessels of the human brain," *Brain Res. Bull.*, vol. 7, no. 5, pp. 519–579, Nov. 1981, doi: 10.1016/0361-9230(81)90007-1.

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Collateral score and perfusion in a simulated stroke



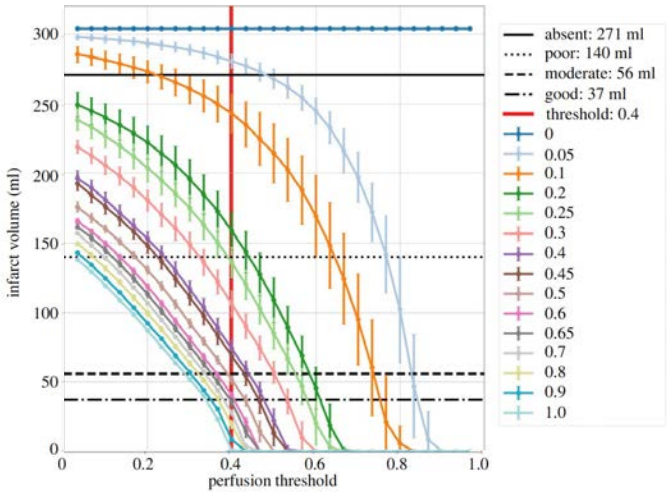
70

Infarct volume and collateral score

- The estimated infarct volume for a range of collateral scores, from zero to one as a function of the perfusion threshold. The thrombus is located in the right MCA and completely impermeable.
- The four black lines show the median final infarct volumes as measured for AIS patients for different collateral scores. The red vertical line shows the threshold at 0.4, i.e. 60% relative flow rate compared with the healthy simulation.

Table 2. Patient measurements (taken from [6]) and model estimates with the perfusion threshold at 0.4.

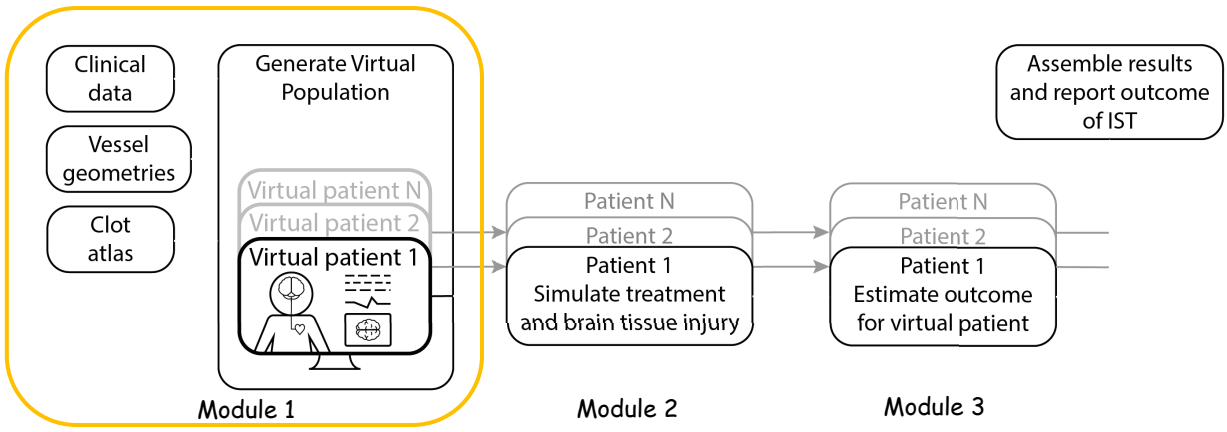
collateral score	number of patients	final infarct volume median ml (IQR)	model mean infarct volume (ml)
absent	20	271.0 (105.8–411.8)	280.5
poor	126	139.8 (63.9–228.1)	136.0
moderate	180	55.9 (27.4–107.8)	51.7
good	123	36.9 (15.4–87.6)	35.8



R.M. Padmos, N.A. Terreros, T.I. Józsa, G. Závodszky, H.A. Marquering, C.B.L.M. Majoie, Stephen J. Payne, and Alfons G. Hoekstra, J. R. Soc. Interface. 19 (2022). doi:10.1098/RSIF.2022.0649.

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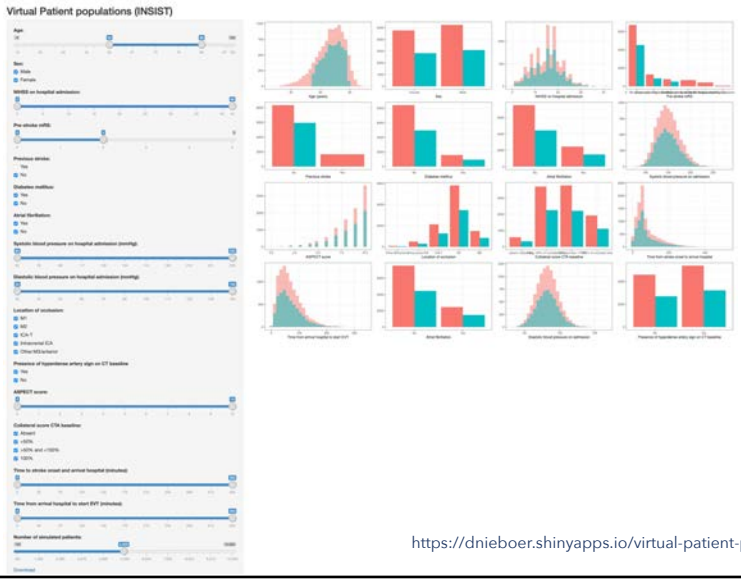
In Silico Trials of Acute Ischemic Stroke



C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, Stephan J. Payne, Alfons G. Hoekstra, Comput. Biol. Med. 137 (2021) 104802. doi:10.1016/J.COMPBIOMED.2021.104802.

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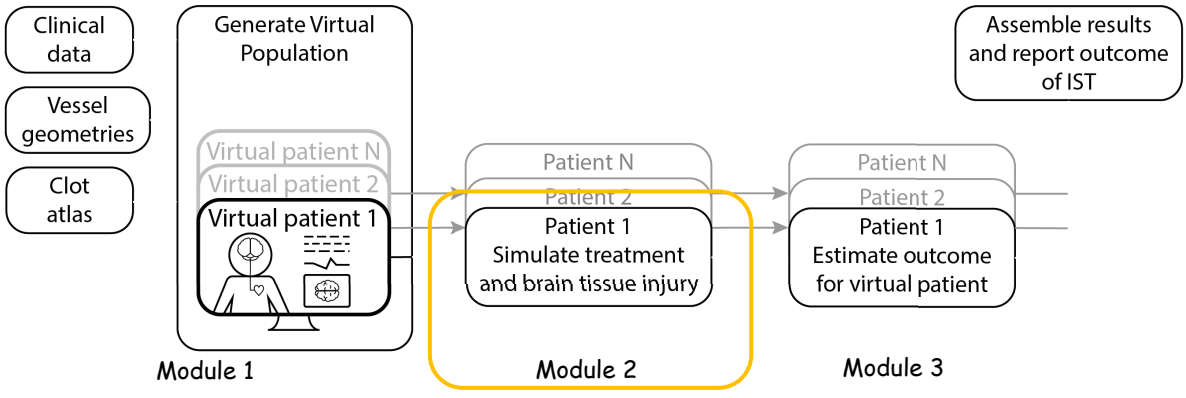
Virtual population



https://dnieboer.shinyapps.io/virtual-patient-population/

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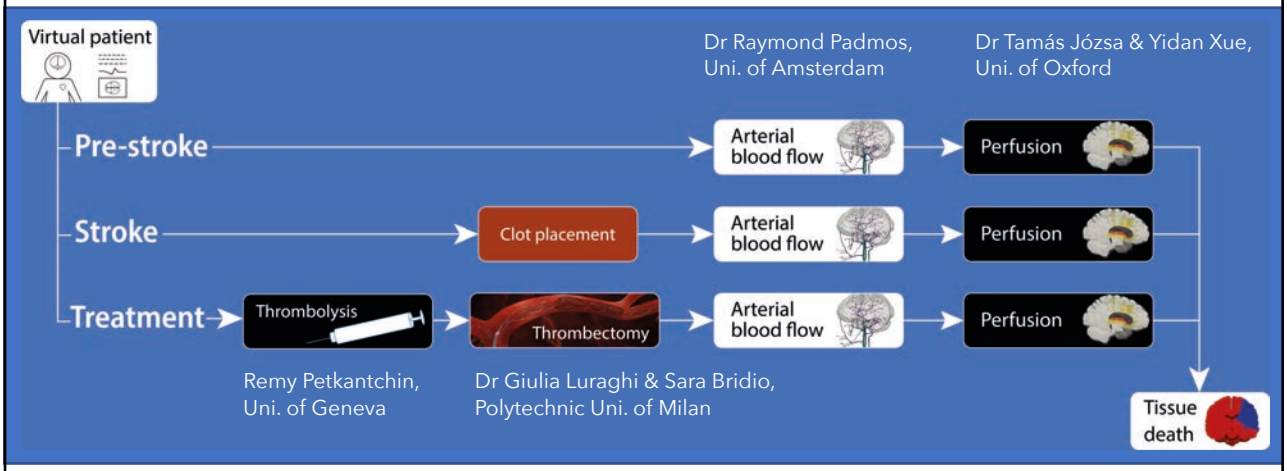
In Silico Trials of Acute Ischemic Stroke



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Simulating AIS and treatment



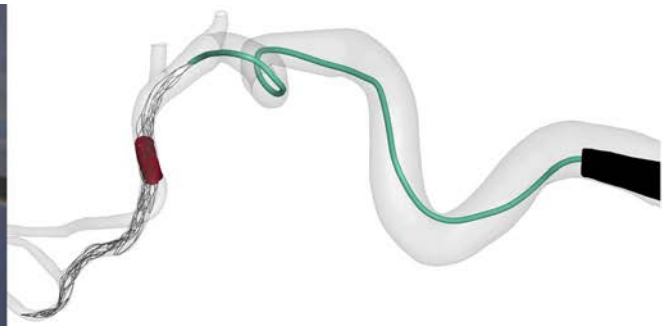
C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, Stephan J. Payne, Alfons G. Hoekstra, Comput. Biol. Med. 137 (2021) 104802. doi:10.1016/J.COMPBIOMED.2021.104802.

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Thrombectomy simulations plus validations

LaBS



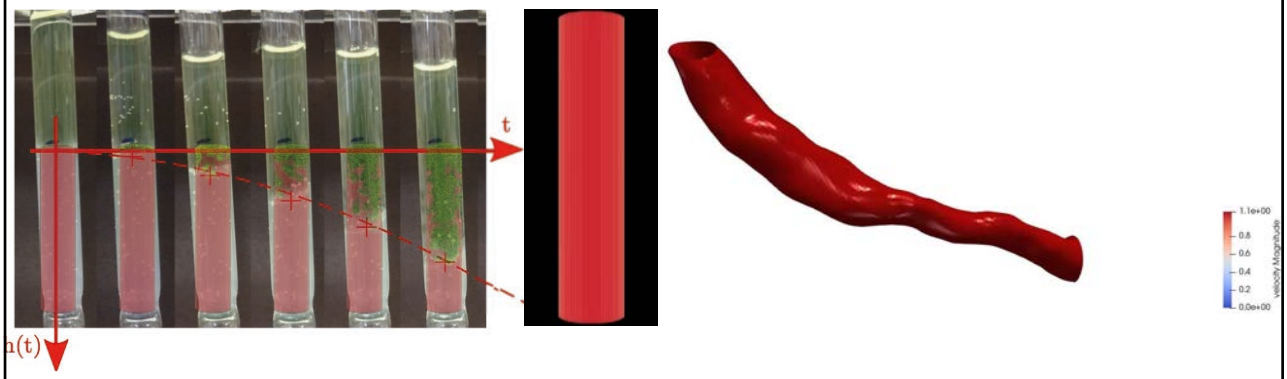


Experiment performed by Cerenovus

simulation performed by Luraghi G., Politecnico di Milano

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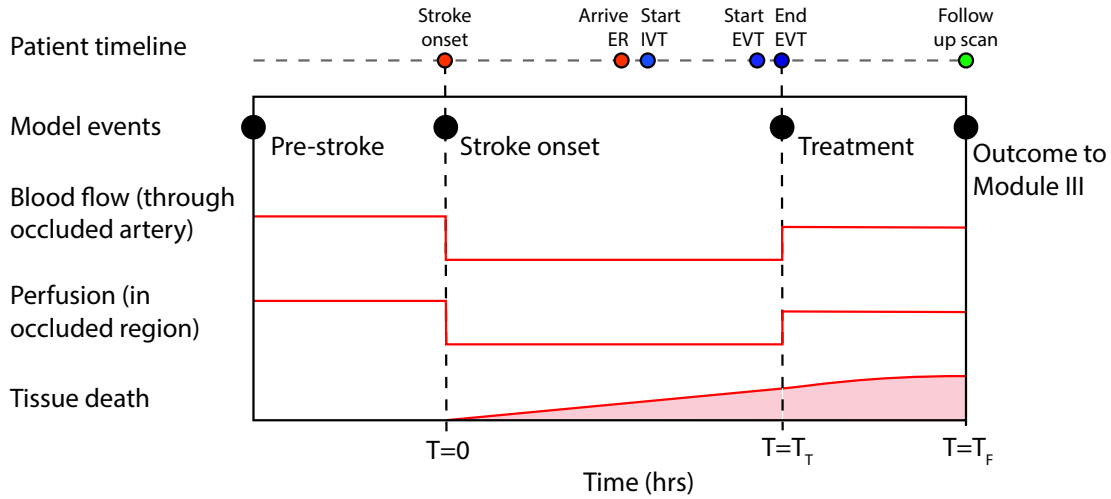
Thrombolysis



University of Geneva, Prof Bastien Chopard et al

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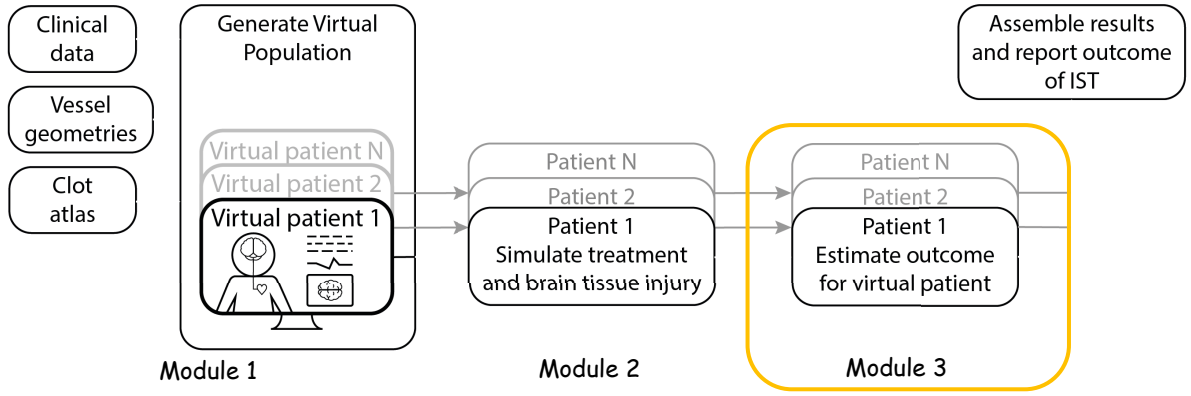
Discrete Event Simulation



C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, Stephan J. Payne, Alfons G. Hoekstra, Comput. Biol. Med. 137 (2021) 104802. doi:10.1016/J.COMPBIOMED.2021.104802.

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In Silico Trials of Acute Ischemic Stroke

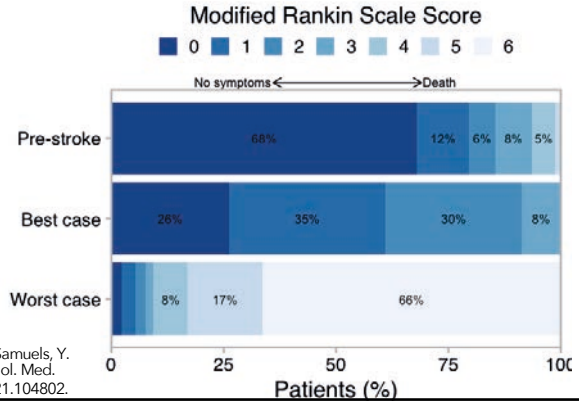


C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, Stephan J. Payne, Alfons G. Hoekstra, Comput. Biol. Med. 137 (2021) 104802. doi:10.1016/J.COMPBIOMED.2021.104802.

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Module 3

- Statistical model linking the simulated infarction to outcome for the virtual patients
- Learned based on the existing set of clinical trial data, few thousand patients.



C. Miller, R.M. Padmos, M. van der Kolk, T.I. Józsa, N. Samuels, Y. Xue, Stephan J. Payne, Alfons G. Hoekstra, Comput. Biol. Med. 137 (2021) 104802. doi:10.1016/J.COMPBIOMED.2021.104802.

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MR Clean Trial (intervention arm)

- Do not account for effect of thrombolysis
- M1 clots only
- 500 patients

C. Miller, P. Konduri, S. Bridio, G. Luraghi, N. Arrarte Terreros, N. Boodt, Noor Samuels, Jose F. Rodriguez Matas, Francesco Migliavacca, Hester Lingsma, Aad van der Lugt, Yvo Roos, Diederik Dippel, Henk Marquering, Charles Majoie, Alfons Hoekstra, Comput. Methods Programs Biomed. 228 (2023) 107244. doi:10.1016/J.CMPB.2022.107244.

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MR Clean virtual population and thrombectomy

	MR CLEAN Trial	MR CLEAN Registry	In silico MR CLEAN (M1)
Patient count	233 intervention arm (154 M1)	1488	256
Median duration onset to groin in min (IQR)	260 (210–313)	208 (160-265)	178 (130–237)
Collaterals	0: 3.9% 1: 30.7% 2: 38.1% 3: 27.3%	0: 7.0% 1: 33.3% 2: 38.7% 3: 20.9%	0: 5.5% 1: 38.7% 2: 38.7% 3: 17.2%

Thrombectomy recanalisation success:

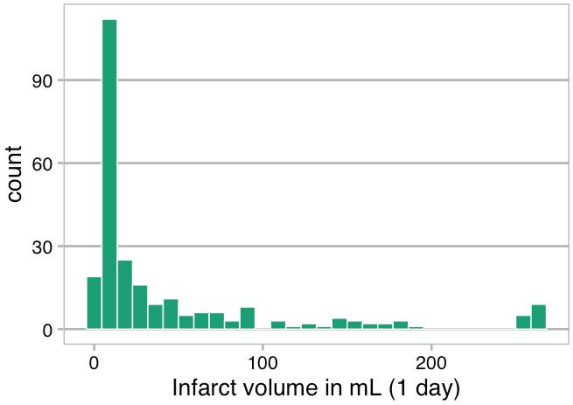
MR CLEAN recanalisation rate (Trevo device, M1 clots, AOL 3)	In silico MR CLEAN
81.9% (CI: 73-91)	85% (CI : 82-88)

C. Miller, P. Konduri, S. Bridio, G. Luraghi, N. Arrarte Terreros, N. Boodt, Noor Samuels, Jose F. Rodriguez Matas, Francesco Migliavacca, Hester Lingsma, Aad van der Lugt, Yvo Roos, Diederik Dippel, Henk Marquering, Charles Majoie, Alfons Hoekstra, Comput. Methods Programs Biomed. 228 (2023) 107244. doi:10.1016/J.CMPB.2022.107244.

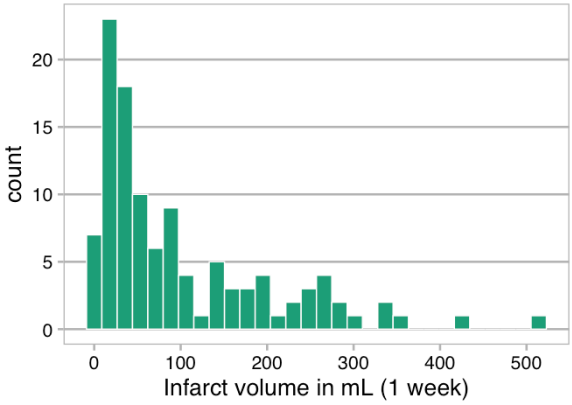
82

MR Clean trial infarct volume

In silico MR CLEAN Trial



MR CLEAN Trial, intervention arm, M1 clots

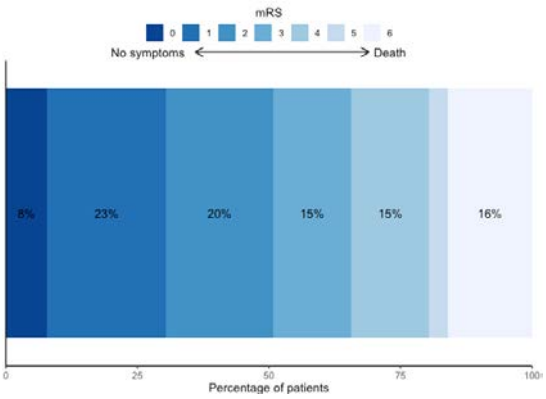


C. Miller, P. Konduri, S. Bridio, G. Luraghi, N. Arrarte Terreros, N. Boodt, Noor Samuels, Jose F. Rodriguez Matas, Francesco Migliavacca, Hester Lingsma, Aad van der Lugt, Yvo Roos, Diederik Dippel, Henk Marquering, Charles Majoie, Alfons Hoekstra, Comput. Methods Programs Biomed. 228 (2023) 107244. doi:10.1016/J.CMPB.2022.107244.

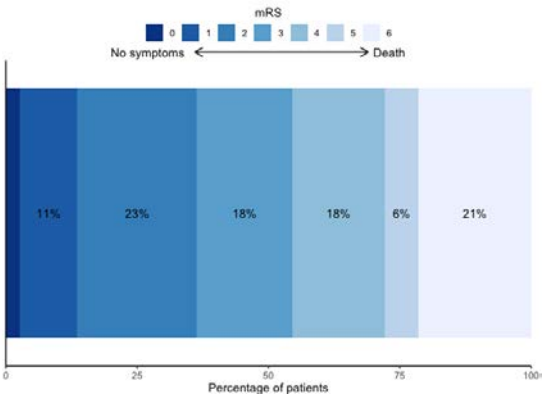
83

MR Clean trial mRS distribution

In silico MR CLEAN Trial



MR CLEAN Trial, intervention arm, M1 clots

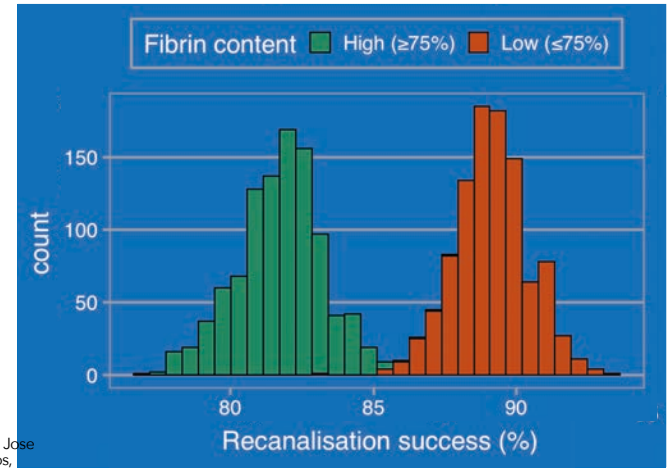


C. Miller, P. Konduri, S. Bridio, G. Luraghi, N. Arrarte Terreros, N. Boodt, Noor Samuels, Jose F. Rodriguez Matas, Francesco Migliavacca, Hester Lingsma, Aad van der Lugt, Yvo Roos, Diederik Dippel, Henk Marquering, Charles Majoie, Alfons Hoekstra, Comput. Methods Programs Biomed. 228 (2023) 107244. doi:10.1016/J.CMPB.2022.107244.

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3. Proof of concept In-Silico Stroke Trials
Impact of Clot Composition

	Recanalisation success rate	
Fibrin content	Mean	IQR
High (≥75%)	81.9%	[80.8, 82.9]
Low (≤75%)	88.0%	[88.4, 90.0]

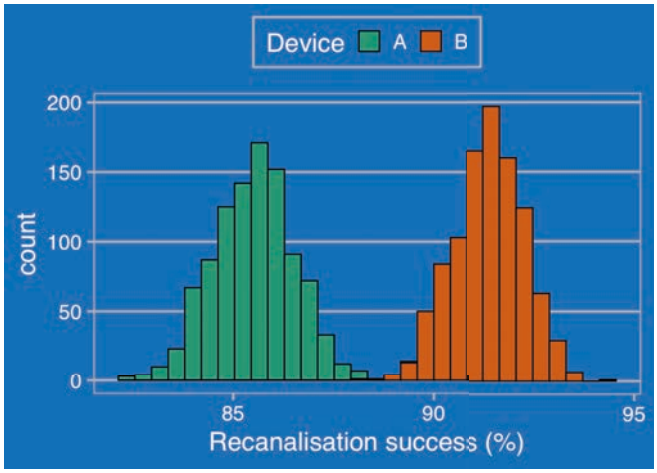


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3. Proof of concept In-Silico Stroke Trials
Comparing efficacy of two devices

Device	Recanalisation success rate (1,000 realisations)
A	85.5% (IQR: 84.9–86.2)
B	91.4% (IQR: 90.8–92.0)



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Perspectives of human digital twin technology for treatment of AIS

- Large potential to help improving treatment options in Acute Ischemic Stroke.
- Large potential for patient specific applications, e.g. in decision support scenarios.
- Thrombectomy simulations already led to first new insights to be further tested.
- Big challenges remain validation of the in-silico trial and its components.
- Strong support both by industry, clinicians, and regulatory bodies.

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Next Steps



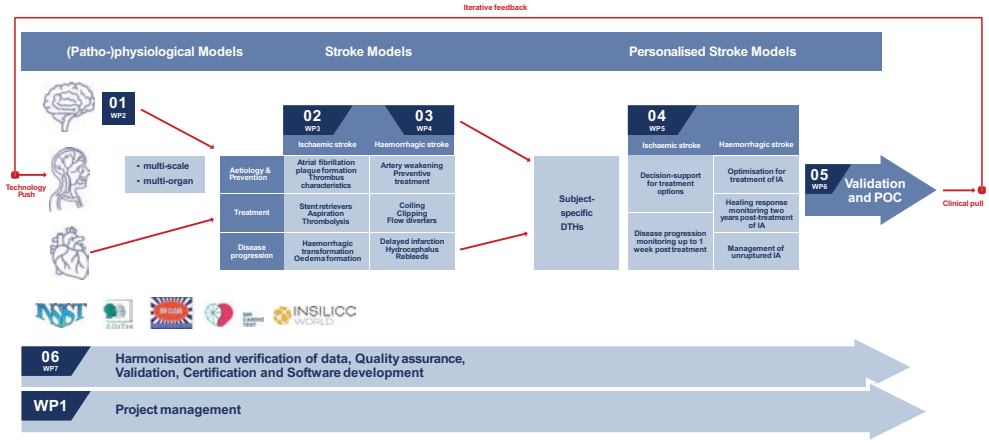
The GEMINI project

Towards GEMINI: A GEneration of Multi-scale digital twINs of Ischaemic and haemorrhagic stroke patients

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GEMINI

GEMINI will deliver multi-organ and -scale Digital Twins in Healthcare (DTH) to improve understanding of and support treatment selection for stroke, addressing both acute ischaemic and haemorrhagic stroke.



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New developments in relation to the cerebrovascular system

- Basic Multi-scale models of cerebral, vascular and cardiac (patho-) physiology
  - blood flow circulation covering the whole heart-brain axis
  - cerebral circulation, brain perfusion, metabolism, vasospasm, and oedema
  - thrombus and plaque formation in the heart, the carotid arteries and the brain
  - vessel wall remodelling, rupture, and healing
- Ischaemic - and Haemorrhagic stroke models
  - From generic to fully personalised DTHs
- Proof of clinical value
  - Generate POC of the technical effectiveness, patient benefit, and general quality of healthcare value of the personalised treatment decision-making tool for ischaemic stroke in a multicentre clinical trial.

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To Conclude

- A population-specific DTH for acute ischemic stroke was presented
  - To be applied for in-silico trials for new treatment options in acute ischemic stroke
- New project underway to go to patient-specific DTH for strokes
  - To be applied as decision support in the acute treatment phases of stroke.

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Thank you

Computational Science

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