Simulation as Evidence: In Silico Methods in the Regulation of Medical Technologies

OR ....

Why We Model: Regulatory Evidence when Complexity Outruns Data

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School of Health Sciences, Faculty of Biology, Medicine and Health
The University of Manchester, UK

Disclosure: Founder, Board Member and Shareholder

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CIMIM Center for Computational Imaging & Modeling in Medicine

Royal Academy of Engineering

UK Research and Innovation

MANCHESTER 1824
The University of Manchester

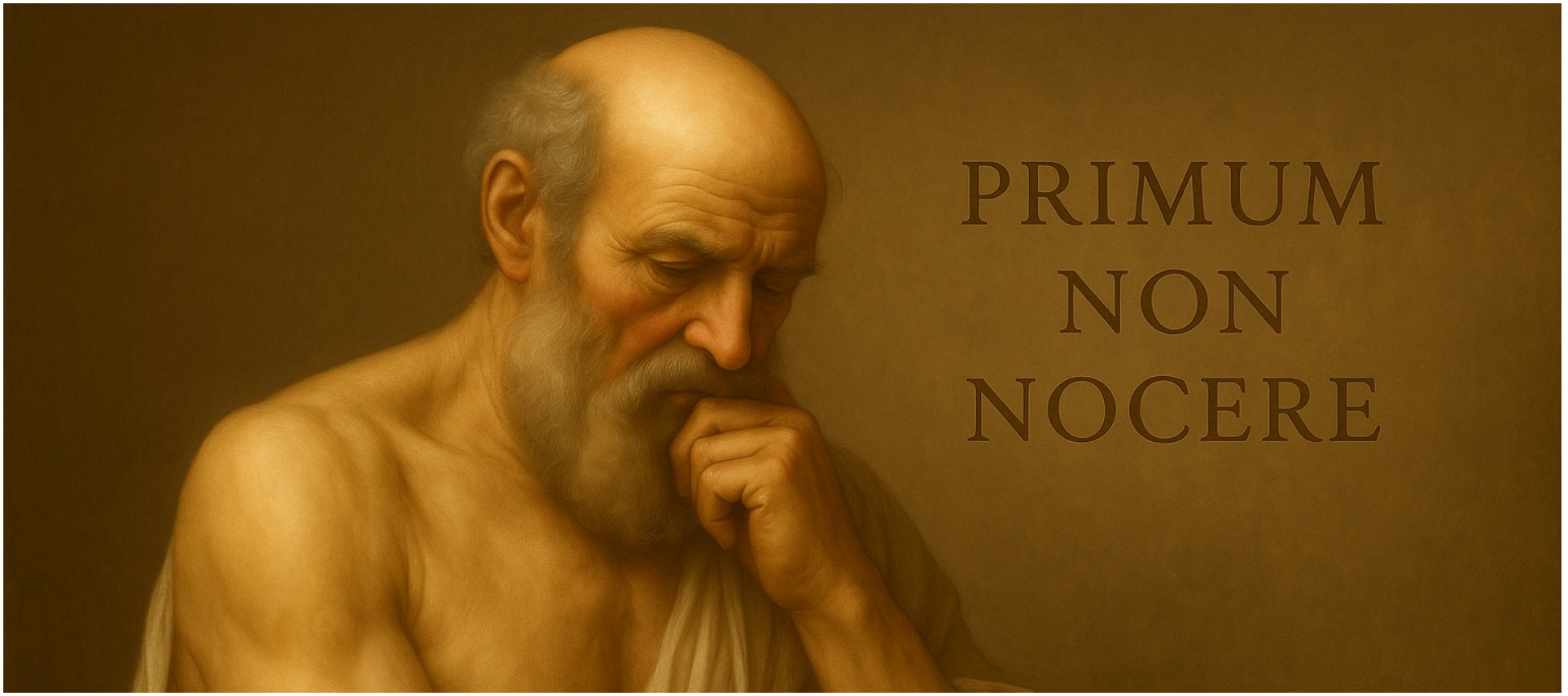
Outline

- Safety and efficacy in healthcare: and their systems impact
- The vision in action — digital evidence for the digital era
- AI in service of *in silico* medicine
- Building trust within complex systems
- Conclusions and outlook — one open question

Safety and efficacy in healthcare: and their systems impact

DIGITAL EVIDENCE FOR THE DIGITAL ERA

The Hippocratic Oath

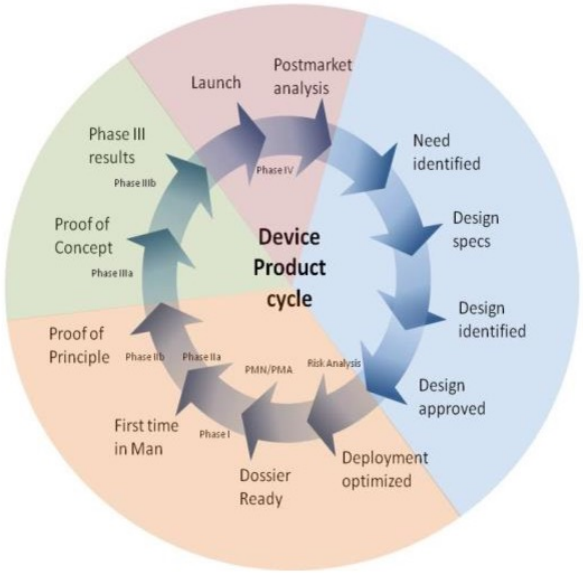


Innovation in Medical Products and Regulatory Evidence

The Imperative of Solid Scientific Evidence on Safety and Efficacy



Source: https://www.avicenna-alliance.com/avicenna-roadmap.html

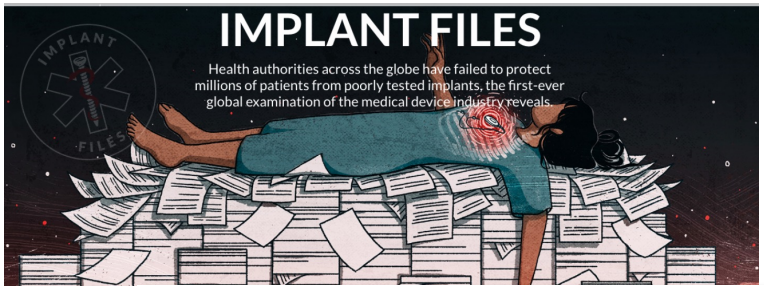


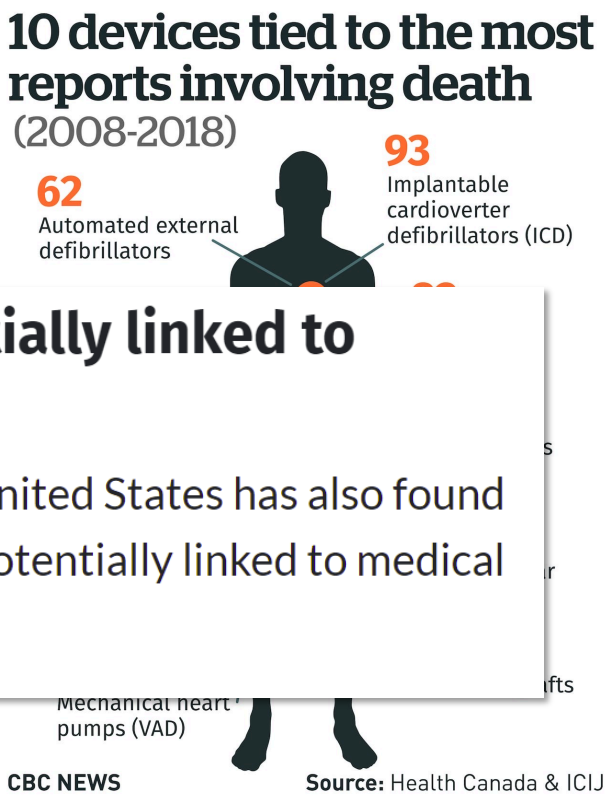
But actually… are they?

- **Experimental paradigm**: randomised experiments are the "gold standard" of evidence, and all other methods are evaluated in terms of how closely they resemble the gold standard.
- **Pragmatist paradigm:** scientific claims are inferred, using practical criteria, from diverse bodies of evidence that may but need not include experiments.

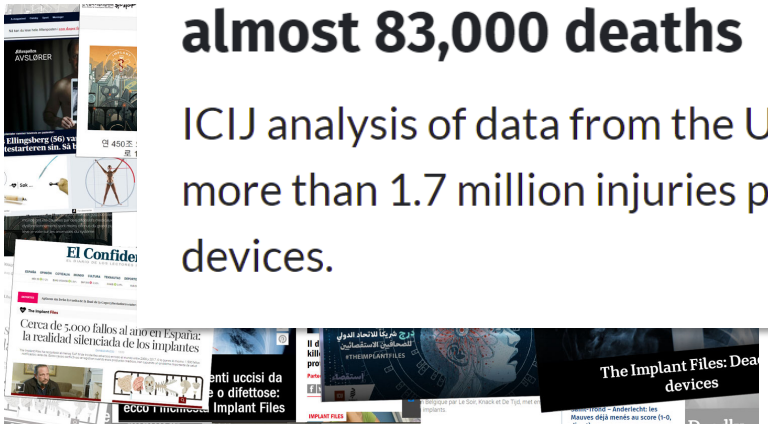
Reiss, J. (2015). A Pragmatist Theory of Evidence. Philosophy of Science, 82(3), 341–362.

The scale of the problem – revisiting patient safety









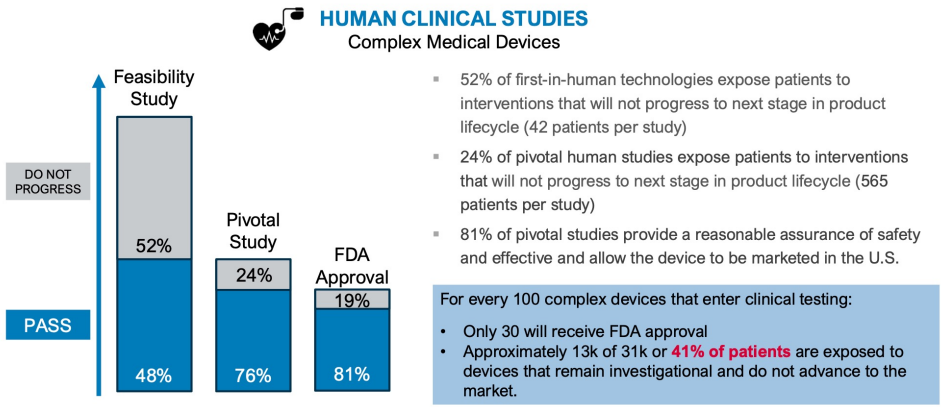


www.icij.org/investigations/implant-files/

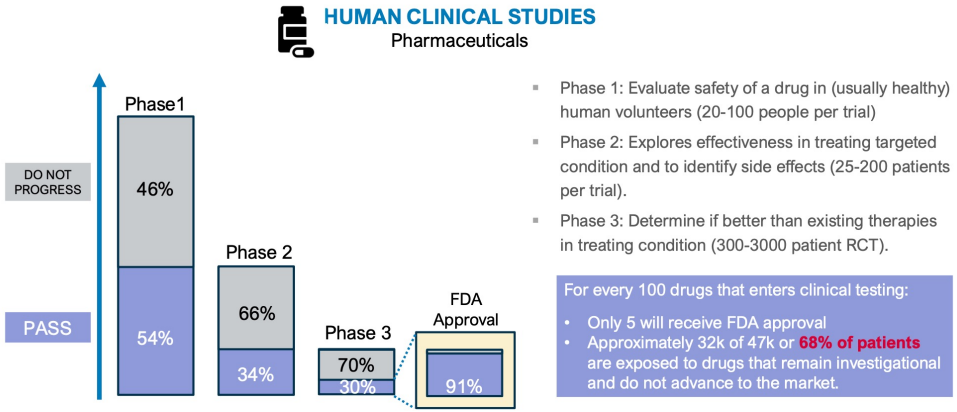
www.immdsreview.org.uk

The Ethical & Safety Imperative

Minimise Patient Exposure to Unproven Therapies



(Adapted from Serkaya, et al., *JAMA Network Open*, 2022)



(https://www.trialsearch.com/clinical-trials/phases)

Courtesy of Dr Tina Morrison (FDA) and Dr Mark Palmer (ANSYS)

The Economic & Financial Imperative

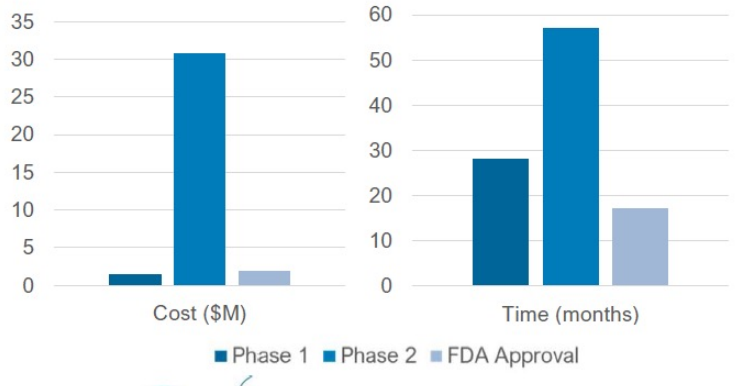
Sustainable care and affordable innovation

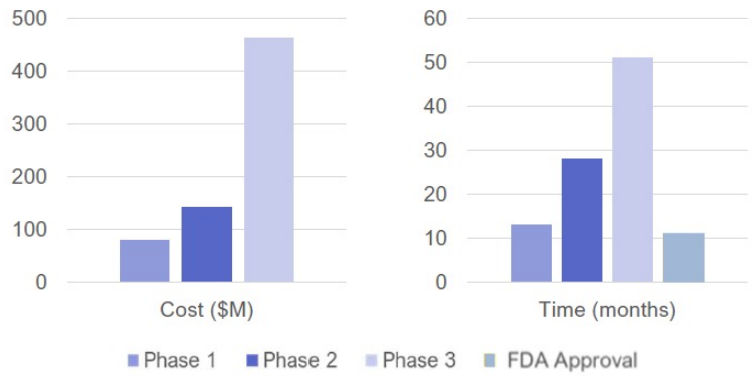
Complex Medical Devices:

- Average cost from discovery to launch continues to increase
- Average cost to successfully deliver an asset to market is $0.52B
- Range in cost varies from $0.205B to $3.4B
- Average total time is 13 years

Pharmaceuticals:

- Average cost from discovery to launch continues to increase
- Average cost to successfully deliver an asset to market is $2.3B
- Range in cost varies from $0.74B to $6.7B
- Total time is 14-16 years

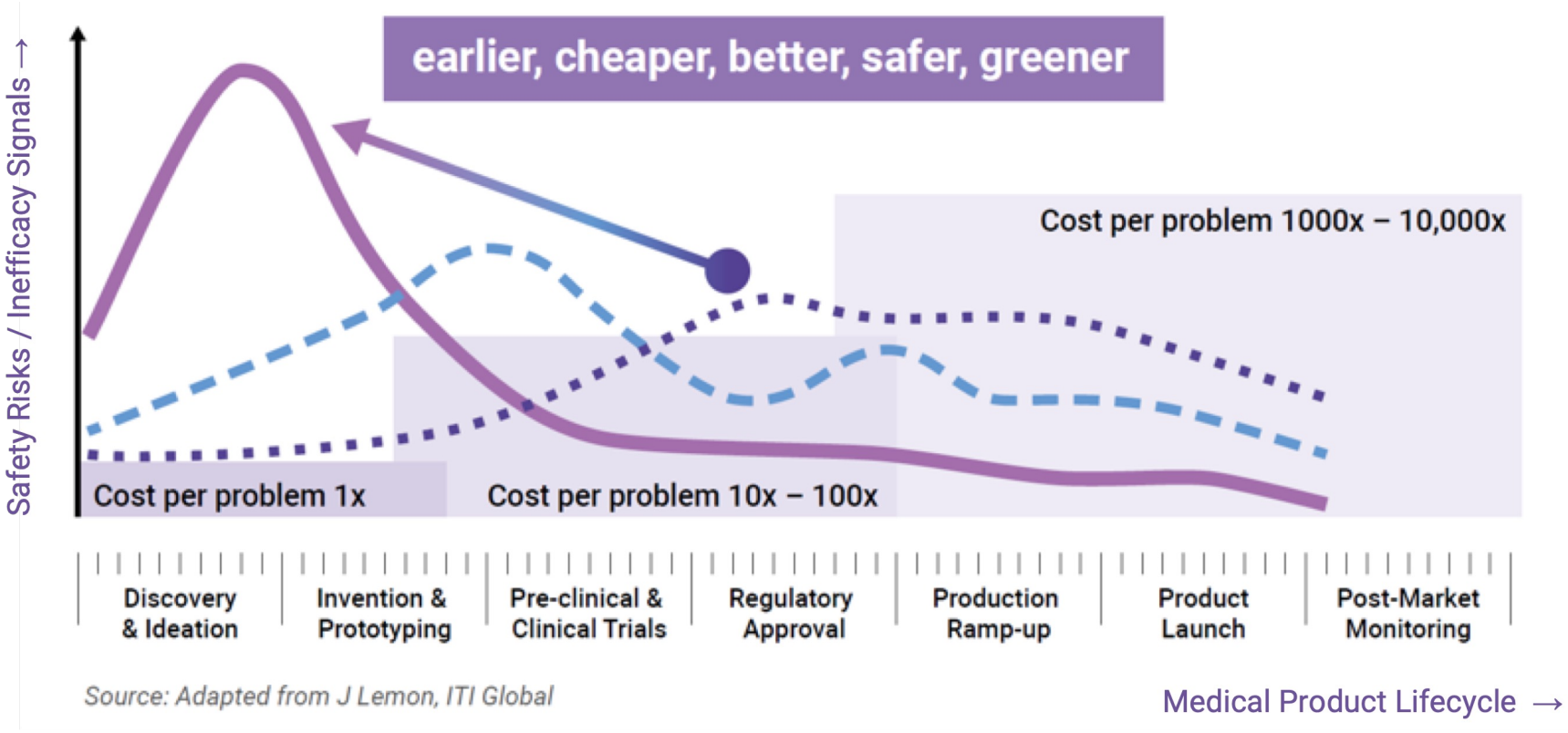




Courtesy of Dr Tina Morrison (FDA) and Dr Mark Palmer (ANSYS)

The Innovation Imperative

Better Products, Less Failure, Reduced Time to Revenue



Lessons from the $1.7tn Automotive Sector Transformation

- Rapid advances in car reliability, efficiency, and intelligence over the past 20 years.
- Modelling, simulation, sensing, and big data drove innovation and quality.



1990 Citroen XM



2000 Toyota Yaris

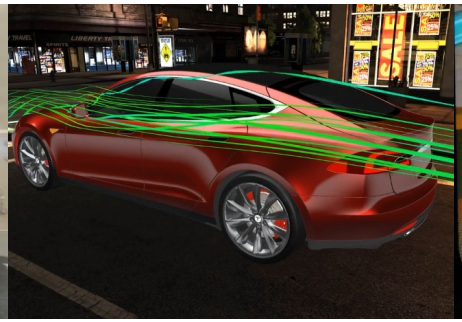


2010 Ford Fusion

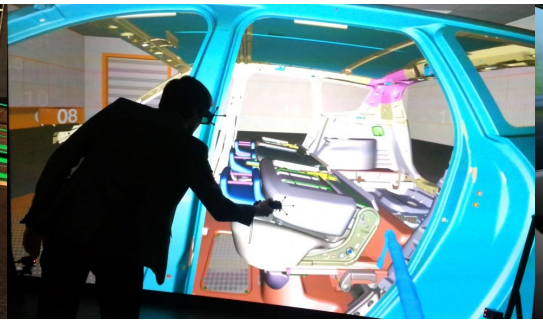


2024 Tesla





virtual wind tunnel



virtual prototyping

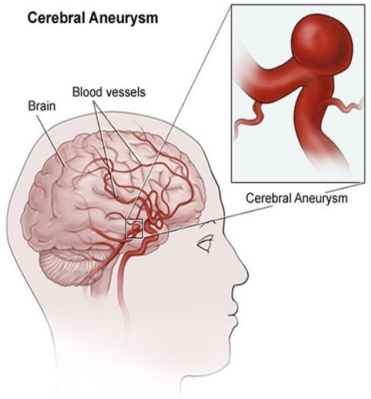


self-driving cars

Healthcare innovation in MD, per comparison, remains largely incremental.

> yet the impact of failure can be devastating for the patient, industry and society

EVERY 8 MINUTES AN ANEURYSM RUPTURES
50% of those individuals die within minutes

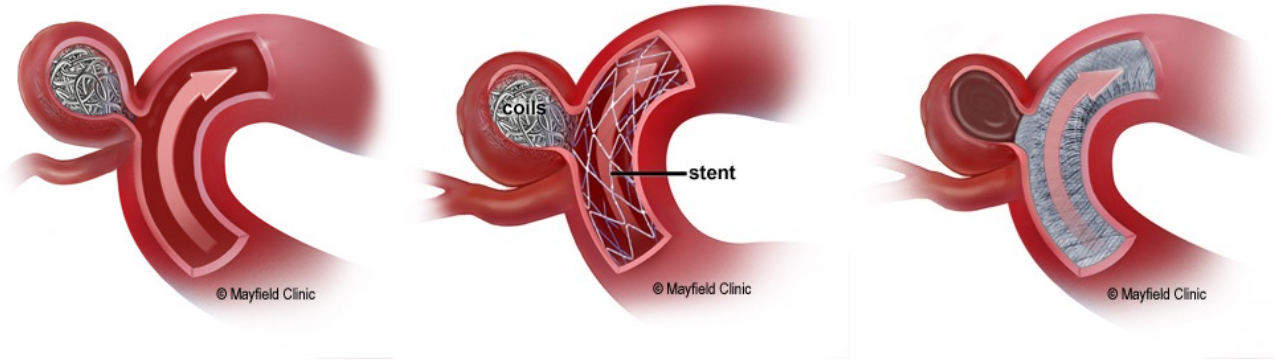


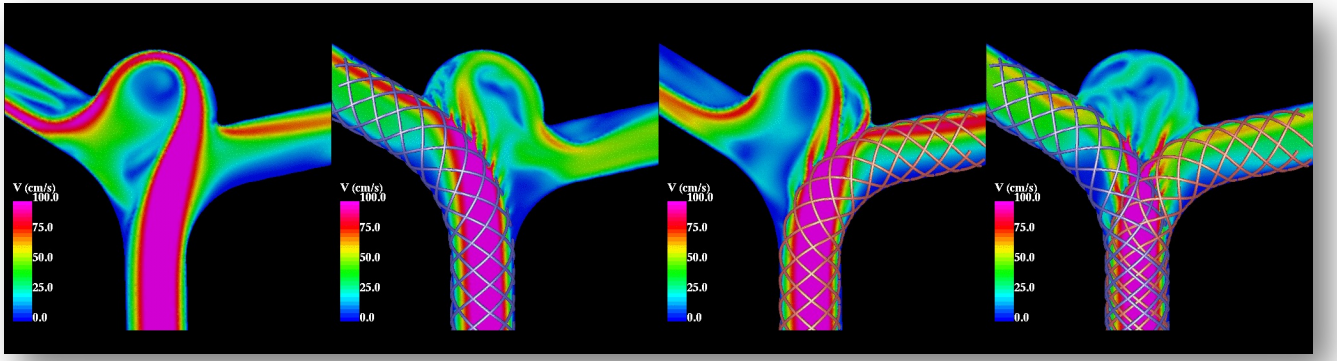
- Approx. 6 million people in the US have a brain aneurysm
- 1 in 15 people will develop a brain aneurysm
- Most common in ages 35-60, but can occur in children as well
- Women, more than men, suffer from brain aneurysms, at a ratio of 3:2

After 30 years R&D
17% complication
2.8% mortality

Zhou G, Su M, Yin YL, Li MH. Neurosurg Focus. 2017 Jun;42(6):E1

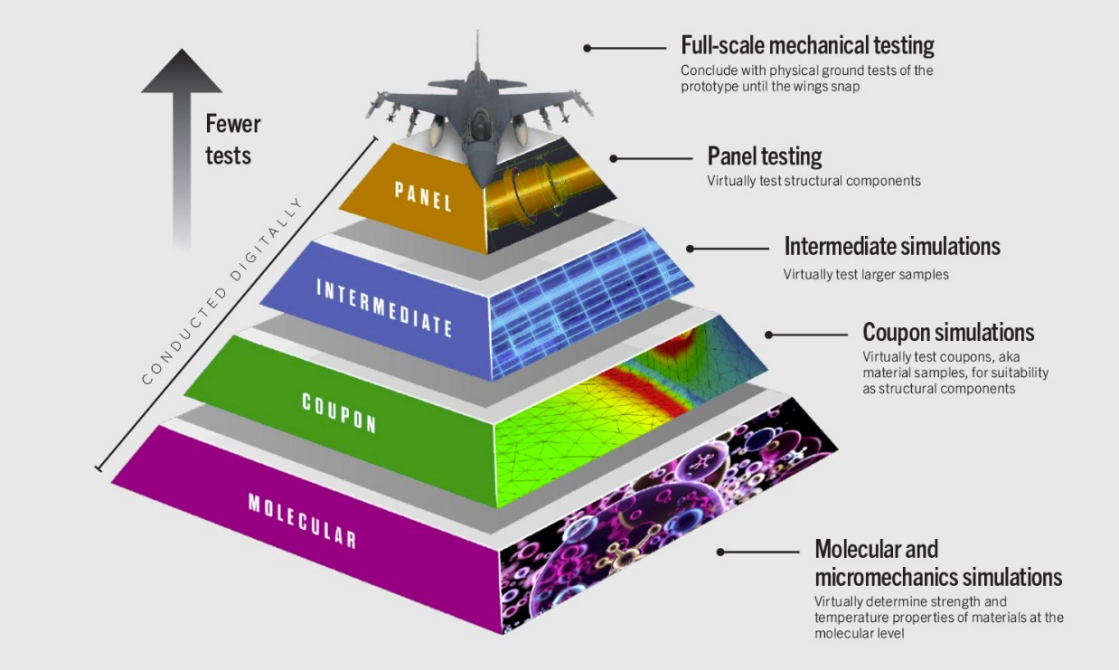
1990 2000 2020



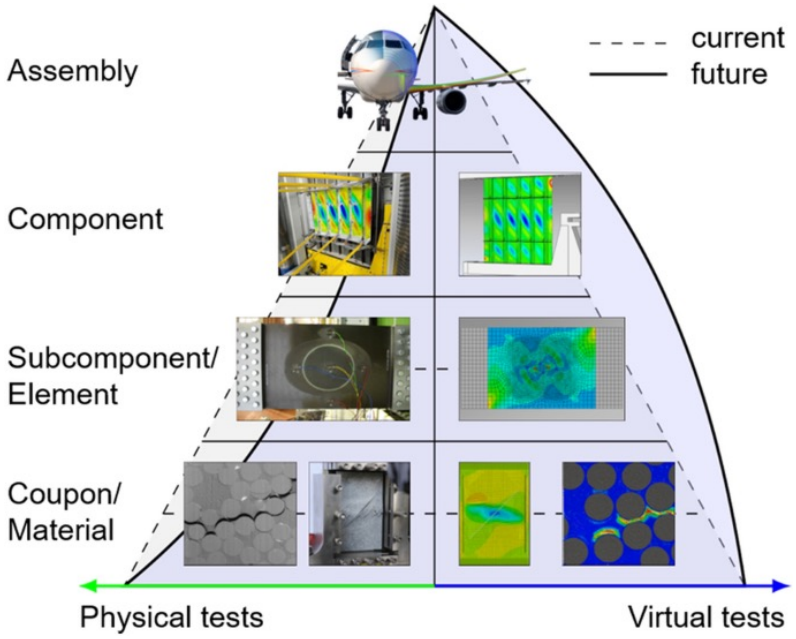


Upfront simulation – The paradigm shift

This trend away from the physical is already happening
in other industry sectors like the automotive or aerospace industry



https://aerospaceamerica.aiaa.org/departments/the-case-for-more-virtual-testing/



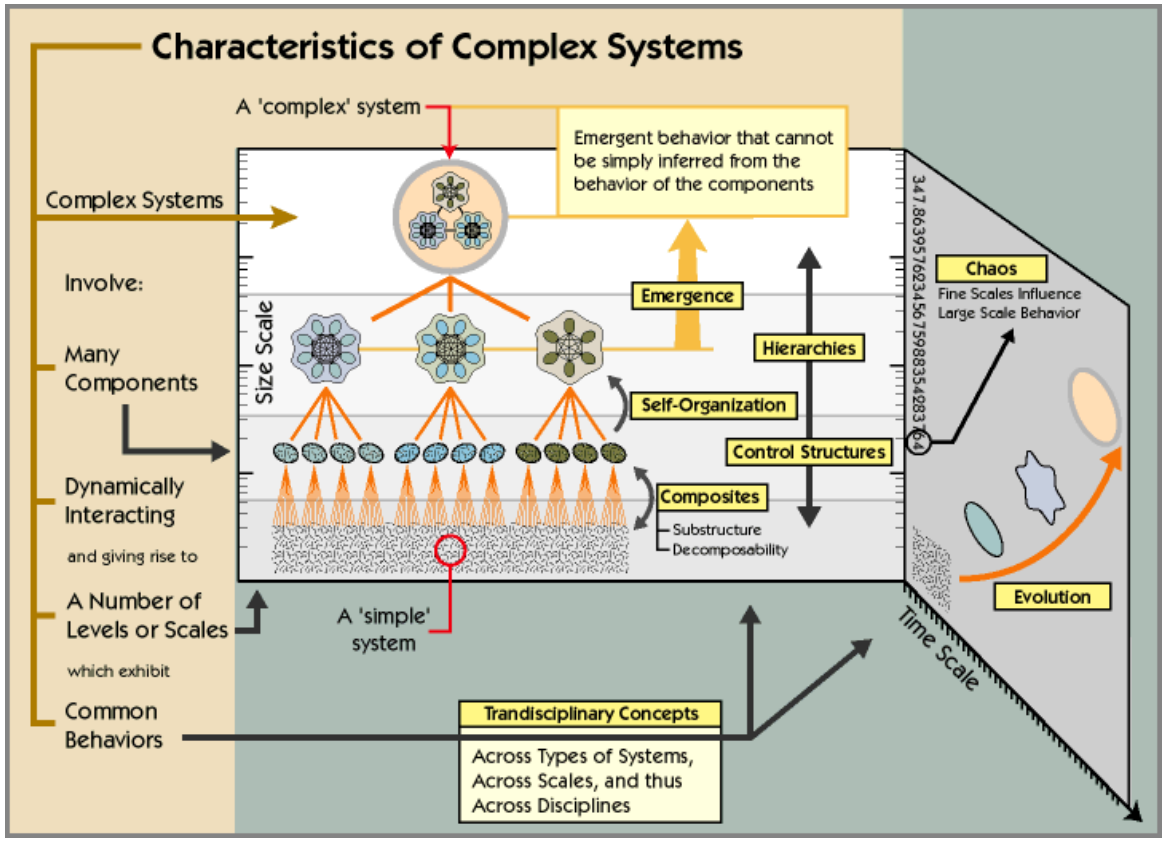
Hollmann, R.W., Schäfer, A., Bertram, O. et al. Virtual testing of multifunctional moveable actuation systems. CEAS Aeronaut J 13, 979–988 (2022).

What is a complex system?

"There is no precise technical definition of a "complex system", but that "most researchers in the field would probably agree that it is a system composed of many interacting parts, such that the collective behaviour of those parts together is more than the sum of their individual behaviours"

Some Properties of Complex Systems

- Interacting components: Systems are made of many individual elements, or agents, that interact with each other.
- Emergence: The system as a whole displays behaviours that cannot be predicted by simply examining the individual components in isolation.
- Nonlinearity: Small changes in the input or initial conditions can lead to disproportionately large changes in the system's output.
- Feedback loops: The output of the system can loop back to influence its input, often in a nonlinear and adaptive way.
- Self-organization: Components can spontaneously organize into patterns and structures without a central organiser or controller.
- Lack of central control: There is no single point of command or control; the system's behaviour arises



https://necsi.edu/visualizing-complex-systems-science

Newman, M. E. J. (2011). Resource letter CS-1: Complex systems. American Journal of Physics, 79(8), 800–810. https://doi.org/10.1119/1.3590372

Estrada, E. What is a Complex System, After All?. *Found Sci* 29, 1143–1170 (2024). https://doi.org/10.1007/s10699-023-09917-w

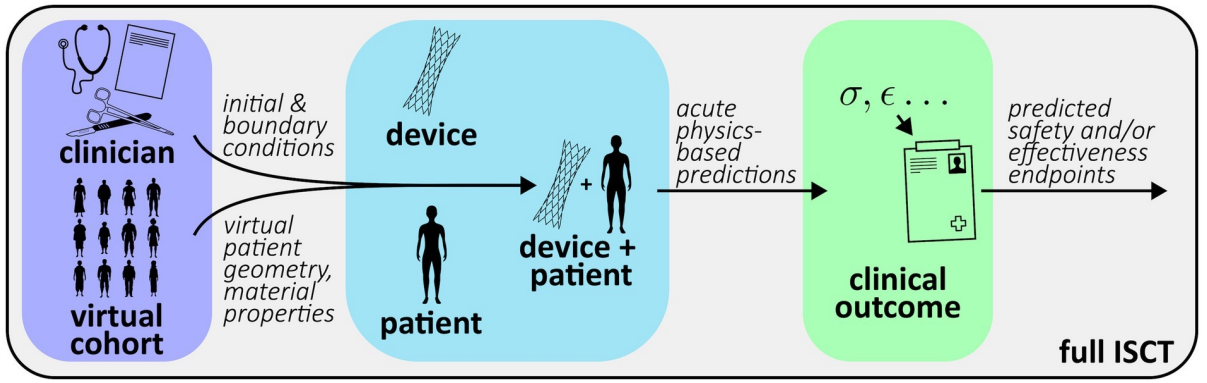
Disrupt a Stagnant R&D Innovation & Regulatory System

ISTs are models of two complex systems– the medical product interacting with the body

In silico testing/trials:

computer-based tests/trials using detailed prediction models on highly controlled virtual conditions or virtual cohorts

representing realistic operational conditions or target populations for the intended use



IN SILICO = evidence derived from real-world data plus computational modelling and simulation, including AI

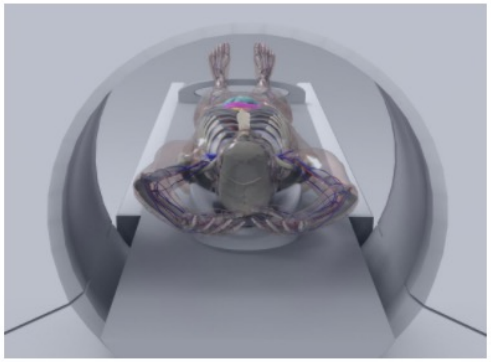
Value Proposition: *Reduce RDR from "Years to Months" & Safety Risks "Failing fast & earlier "*

Aycock KI, Battisti T, Peterson A, Yao J, Kreuzer S, Capelli C, Pant S, Pathmanathan P, Hoganson DM, Levine SM, Craven BA. Toward trustworthy medical device *in silico* clinical trials: a hierarchical framework for establishing credibility and strategies for overcoming key challenges. Front Med (Lausanne). 2024 Aug 12;11:1433372.

Computational Modelling and Simulation
Regulatory Science & Innovation



Virtual Participants & Populations



Virtual Examinations & Interventions



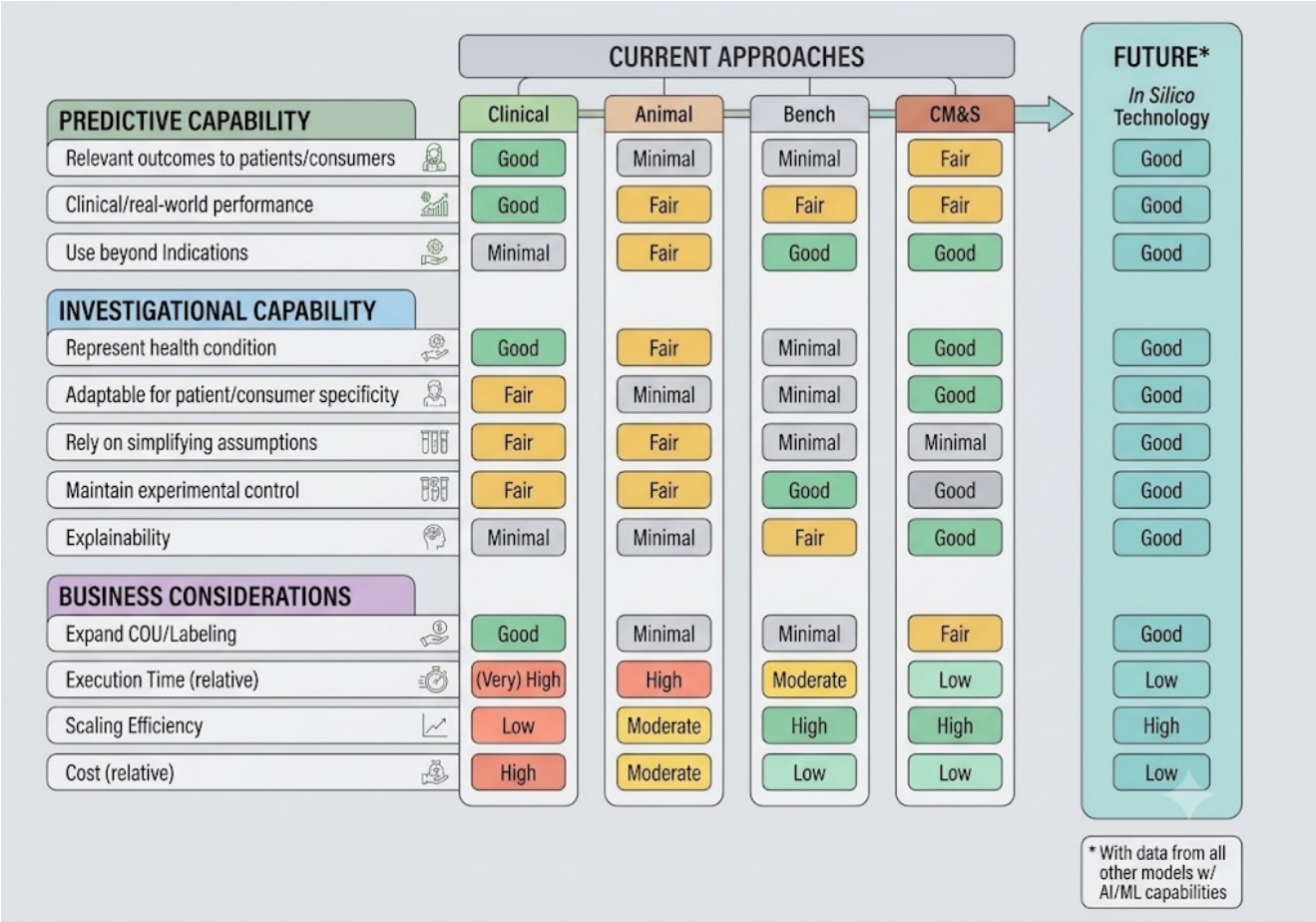
Virtual Readers & Outcomes

Source: adapted from cvit.duke.edu/research

The Future?

Proportionate and risk-informed evidence framework

No single source of evidence provides the highest evidence rigour for all categories



https://reaganudall.org/publications/silico-technologies-strategic-imperative-accelerating-breakthroughs-and-market

In silico Trial Space

> A Large-Scale Complex System…

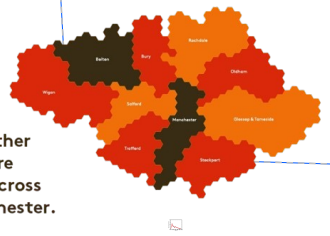
Population Data & Real-World Evidence

biobank uk
Improving the health of future generations

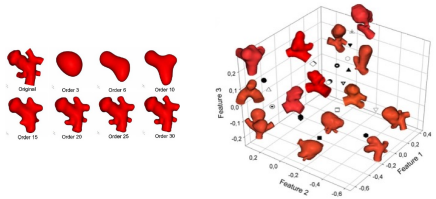
GREATER MANCHESTER IMAGING NETWORK

GREATER MANCHESTER PATHOLOGY NETWORK

GM Care Record

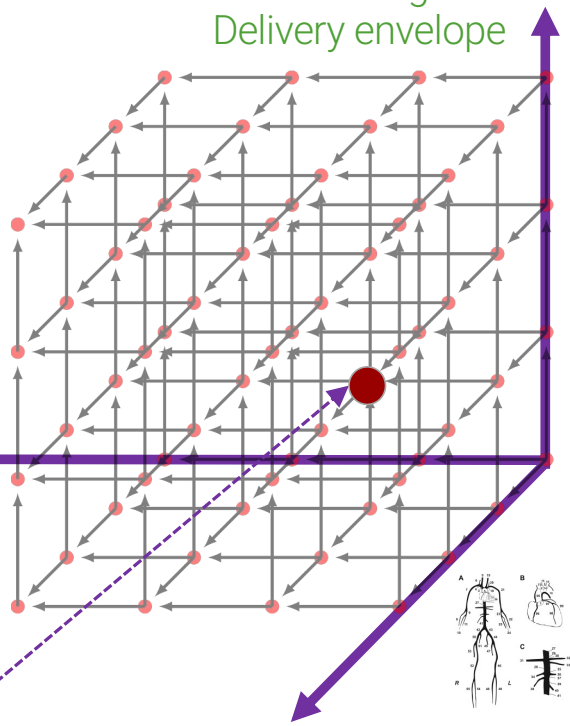


Bringing together health and care information across Greater Manchester.



Anatomical, Mechanical & Rheological envelope

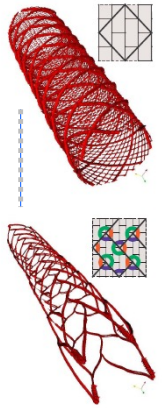
Device Design & Delivery envelope

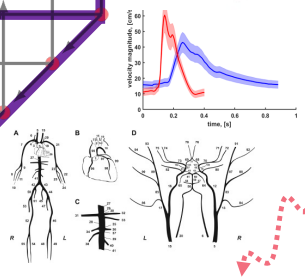


virtual experiment

Health Innovation Manchester

Lifestyle, Physiological & Operational envelope







Experiments & Device Manufacturers

Population Data & Real-World Evidence

Credible models, credible evidence: where simulations already provide insights
At scale, not just at demo: virtual populations, stress testing, and faster iteration

THE VISION IN ACTION

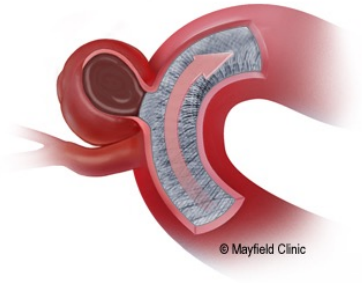
In silico Trial – Driving Exemplars

Endovascular Devices

Flow diverters (FD) to treat Intracranial Aneurysms

- **FDs are stent-like devices used to treat Intracranial Aneurysms by reducing blood flow & inducing clotting – e.g. Pipeline embolization device (PED)**
- **Can our IST reproduce trends/findings of real clinical trials and answer questions that actual trials cannot answer:**

  - Better understanding and clinical guidelines for management IA with FD
  - Long-term complications (rupture, stroke, etc.) despite excellent angiographic outcome
  - Influence of aging, smoking, hypertension, etc. on FDs' performance.
  - Influence of deployment factors, particularly, stent oversizing, on FDs' performance.
  - Expand prescription of FD to posterior circulation and Sylvian bifurcation aneurysms

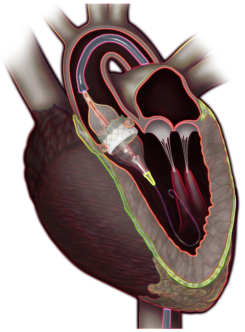


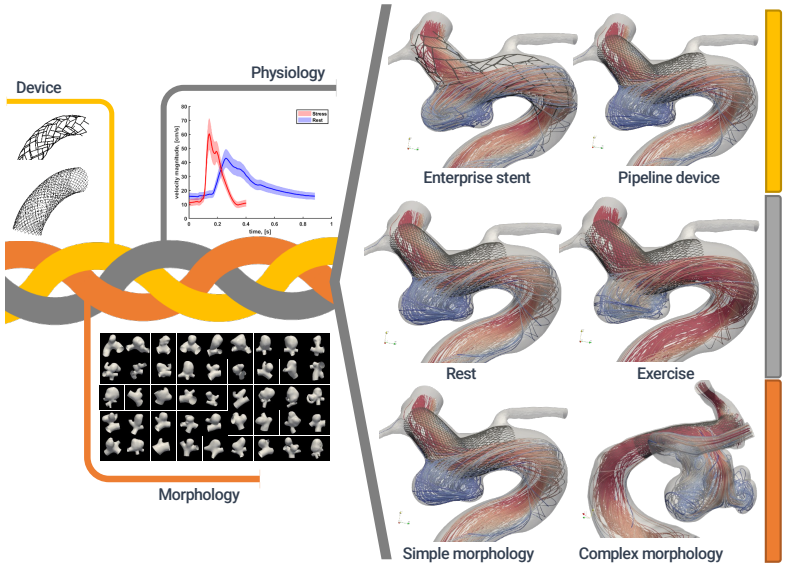
Cardiovascular Devices

Transcatheter aortic valve implantation (TAVI) to treat aortic valve stenosis

- **TAVI has revolutionised treatment of severe AV stenosis, but key challenges remain**
- **Can our IST reproduce the REPRISE III clinical trial (by Boston Scientific) and assess:**

  - Long-term durability of transcatheter valves
  - Efficacy and safety of TAVI in key sub-groups (bicuspid anatomy, valve-in-valve, TAVI-in-TAVI)
  - Early valve failure (due to thrombosis, mispositioning, coronary occlusion, or conduction abnormalities)
  - TAVI safety in patients with calcified aortic stenosis



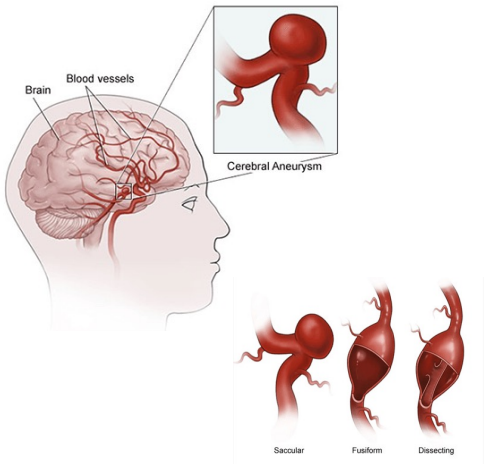


Exemplar I

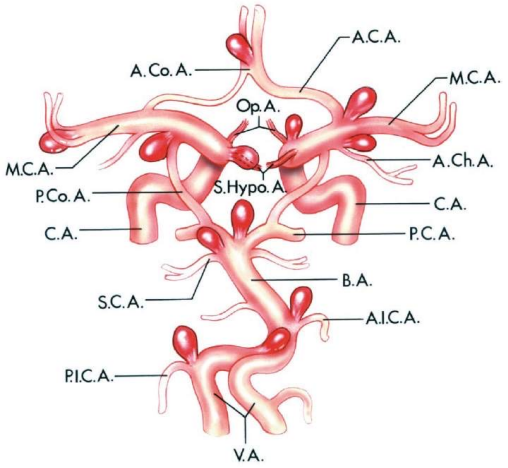
ENTIRE *IN SILICO* TRIAL EXPERIENCE

IN SILICO REENACTMENT /
PHYSICS+BIOLOGY+PHYSIOLOGY /
EMERGING BEHAVIOURS

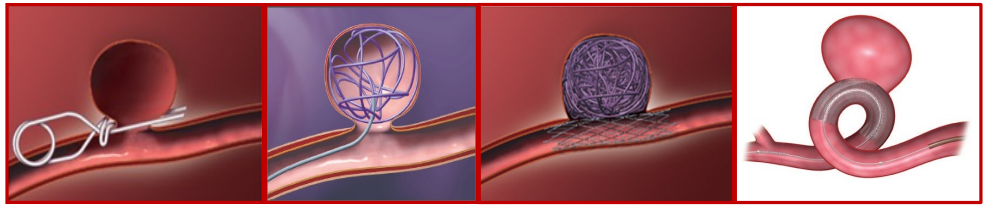
Haemorrhagic stroke: intracranial aneurysms

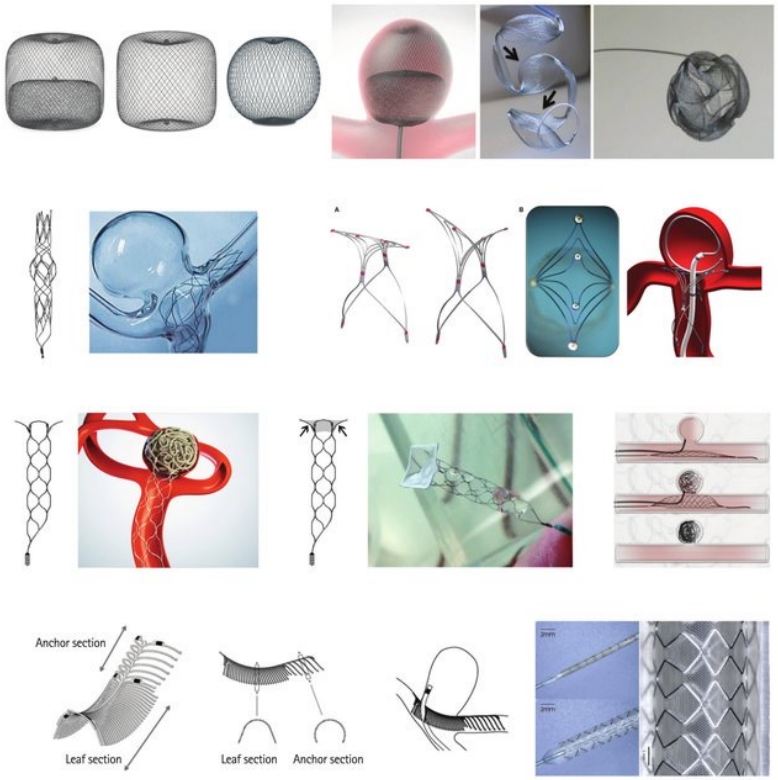


www.rwjbh.org/rwj-university-hospital-new-brunswick/treatment-care/neurosciences/neurosurgery/for-patients/new-jersey-brain-aneurysm-avm-program/what-is-a-brain-aneurysm-/



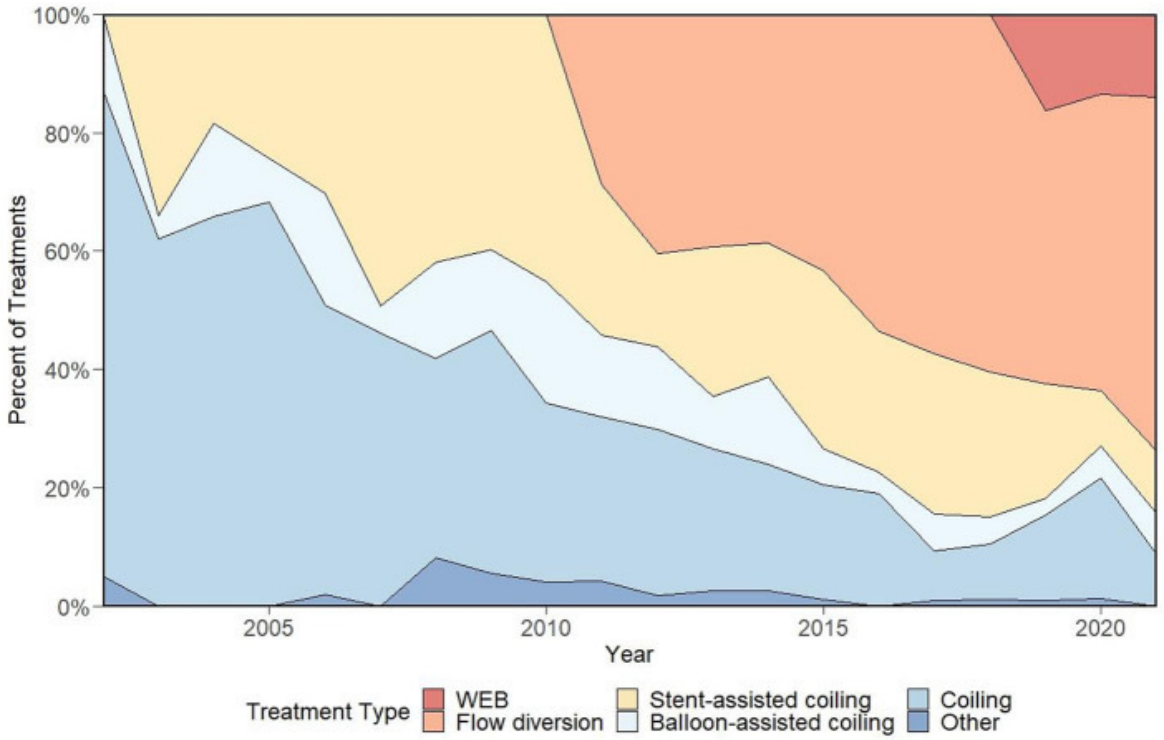
www.neurosurgicalatlas.com/neuroanatomy/most-common-sites-of-saccular-aneurysms





Jia ZY, Shi HB, Miyachi S, Hwang SM, Sheen JJ, Song YS, Kim JG, Lee DH, Suh DC. Development of New Endovascular Devices for Aneurysm Treatment. J Stroke. 2018 Jan;20(1):46-56. doi: 10.5853/jos.2017.02229.
Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, Macho J, Derakhshani S, Foa Torres G, Pereira VM, Arat A, Wakhloo AK, Ortega-Gutierrez S. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg. 2021 Jan;13(1):54-62.

Device selection for elective aneurysm treatments at a US center over 20-year

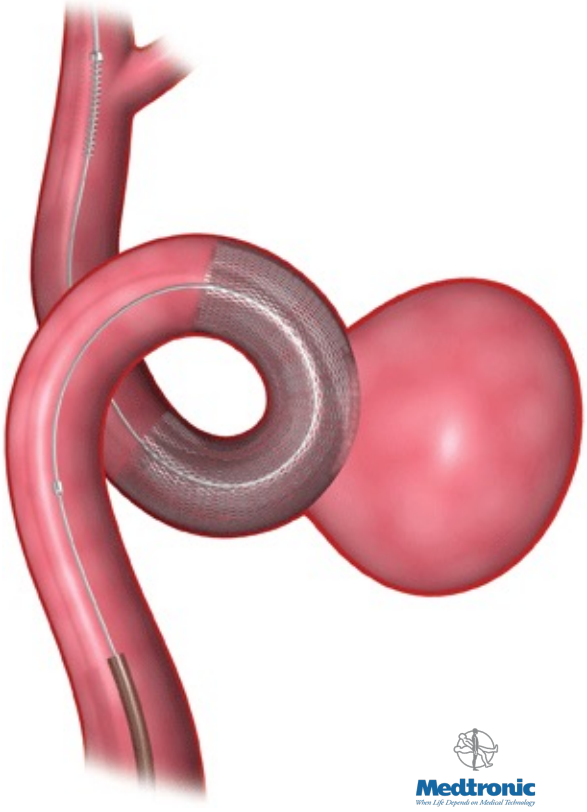


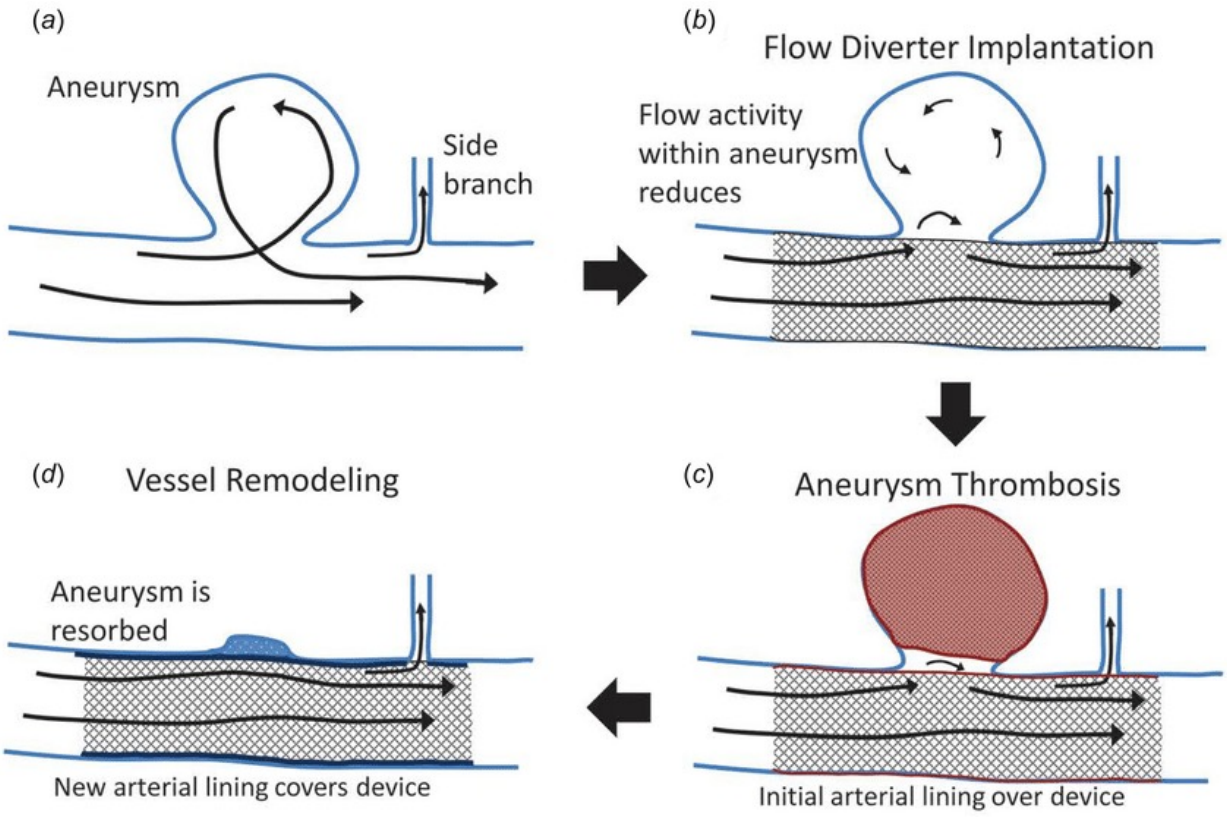
Device	Manufacturer and year of FDA approval	Material	Detachment
Coils			
Target (Guglielmi) detachable coil	Target, 1995	Bare platinum	Electrolytic
Micrus microcoil	Micrus, 2001	Bare platinum	Mechanical (using resistive heating)
HydroCoil embolic system	Microvention, 2002	Hydrogel-coated bare platinum coils	V-grip detachment controller with self-contained integral power supply
Orbit detachable coil	Codman, 2003	Bare Platinum	Mechanical/Hydraulic
Matrix bioactive coil	Boston Scientific/Target, 2003	Polyglycolic acid–coated bare platinum coils	Electrolytic
Cerecyte coil	Micrus, 2004	Platinum coils with polyglycolic acid running through lumen of primary platinum wind	Mechanical (using resistive heating)
Orbit Galaxy coil	Cerenovus, 2010	Bare platinum	Mechanical (using resistive heating)
PC400 coil	Penumbra, 2012	Bare platinum	Mechanical
Codman Trufill coil	Johnson and Johnson, 2013	Bare platinum	Mechanical (hydraulic)
Axium	Medtronic, 2014	Bare platinum	Mechanical
Barricade coil	Balt, 2015	Bare platinum	Electrolytic
Axium prime	Medtronic, 2017	Bare platinum	Mechanical
Optima coil	Balt, 2020	Bare platinum	Thermal
Stents			
Device	Manufacturer and Year of FDA Approval	Material	Delivery System (size)
Neuroform stent	Boston Scientific/Target, 2002	Nitinol, open-cell design	0.027-inch microcatheter
Enterprise stent	Cordis Neurovascular, 2007	Nitinol, closed-cell design coated with insulating polymer (Parylene C)	0.021-inch microcatheter
LVIS, LVIS Jr	Microvention, 2018	Nitinol, closed-cell braided design	0.021-inch, 0.0165-inch microcatheter, respectively
LVIS EVO	Microvention	Nitinol, closed-cell braided design	0.0165-inch microcatheter
Neuroform Atlas	Stryker Neurovascular, 2019	Nitinol, laser-cut open-cell design	0.0165-inch microcatheter
Flow diverters			
Device	Manufacturer and year of FDA approval	Material	Delivery catheter size
Pipeline Embolization Device	Medtronic Neurovascular, 2011	36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio	0.027-inch microcatheter
Pipeline Flex Embolization Device	Medtronic Neurovascular, 2018	36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio	0.027-inch microcatheter
Pipeline Flex with Shield	Medtronic Neurovascular, 2021	36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio, phosphorylcholine polymer surface coating	0.027-inch microcatheter
Pipeline Vantage	Medtronic Neurovascular	36 or 48 cobalt-chromium strands, 12 or 16 platinum-tungsten strands woven in 3:1 ratio, phosphorylcholine polymer surface coating	0.021-inch or 0.027-inch microcatheter
FRED	Microvention, 2019	Self-expanding braided 66 nitinol wires	0.027-inch microcatheter
FRED Jr	Microvention, 2019	Self-expanding braided 54 nitinol wires	0.021-inch microcatheter
FRED X	Microvention	Self-expanding braided 54 or 66 nitinol wires, protective nano-polymer hydration layer	0.021-inch or 0.027-inch microcatheter
Surpass Streamline	Stryker Neurovascular, 2018	72 or 96 cobalt-chromium wires	0.053-inch intermediate catheter, passed over 0.014-inch microwire
Surpass Evolve	Stryker Neurovascular, 2020	64 cobalt-chromium wires	0.027-inch microcatheter
Silk	Balt Extrusion	48 braided nitinol wires	0.021-inch or 0.025-inch microcatheter
Silk Vista	Balt Extrusion	48 braided nitinol wires	0.021-inch or 0.025-inch microcatheter
Silk Vista Baby	Balt Extrusion	48 braided nitinol wires	0.017-inch microcatheter
Other			
Device	Manufacturer and year of FDA approval	Material	Delivery catheter size
Onyx HD-500	ev3, 2007	20% Ethylene vinyl alcohol copolymer dissolved in DMSO with suspended micronized tantalum powder	0.014-inch microcatheter
PulseRider Device	Cerenovus, 2018	Nitinol, Y or T-shape	0.021-inch microcatheter
pCONUS	Phenox	Nitinol, radially-flaring distal petals	0.021-inch microcatheter
pCONUS 2	Phenox	Nitinol, radially-flaring distal petals	0.021-inch microcatheter
pCONUS 2-HPC	Phenox	Nitinol, radially-flaring distal petals with hydrophilic coating	0.021-inch microcatheter
WEB	Microvention, 2018	Nitinol wires with platinum coil, now single layer of mesh	0.017, 0.021, 0.027, or 0.033-inch microcatheter
Contour	Cerus	Dual-layered structure of 2 × 72 nitinol wires	0.021-inch or 0.027-inch microcatheter
Balloons			
Device	Manufacturer and Year of FDA Approval	Lumen type	DMSO compatible?
Commodore	Cordis Neurovascular, 1999	Single lumen	No
Equinox	Micro Therapeutics, 2000	Single lumen	No
Ascent	Micrus, 2008	Single lumen	No
HyperGlide	Medtronic Neurovascular, 2010	Single lumen	Yes
HyperForm	Medtronic Neurovascular, 2010	Single lumen	Yes
Scepter	Microvention, 2012	Dual lumen	Yes
Transform	Stryker Neurovascular, 2015	Single lumen	No
Eclipse	Balt, 2019	Dual lumen	Yes

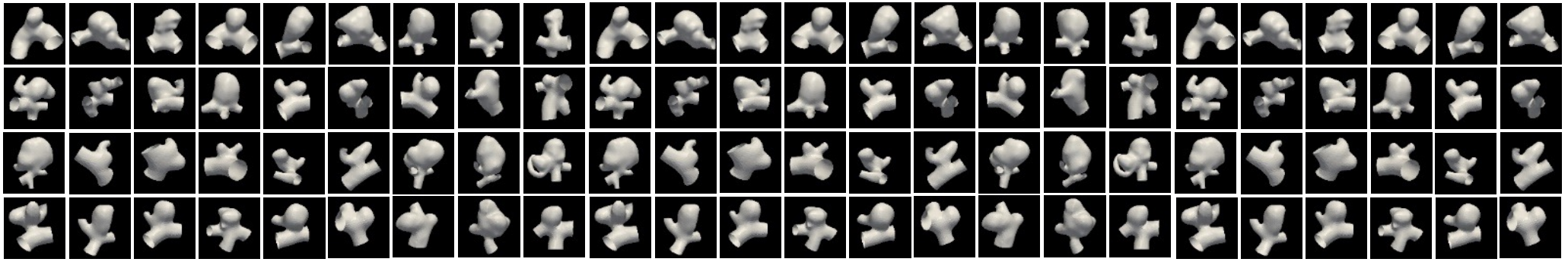
Year of FDA approval provided for devices available in the United States.
Similar to device evolution, there have been dramatic changes in device manufacturers with many mergers and buyouts. For example, Microtherapeutics was acquired by ev3; Cordilan was acquired by Medtronic; Target was acquired by Boston Scientific, which was later acquired by Stryker; and Micrus was acquired by Codman serving as a subsidiary of Johnson and Johnson.

Lauzier DC, Huguenard AL, Srienc AI, Cler SJ, Osbun JW, Chatterjee AR, Vellimana AK, Kansagra AP, Derdeyn CP, Cross DT, Moran CJ. A review of technological innovations leading to modern endovascular brain aneurysm treatment. Front Neurol. 2023 Apr 11;14:1156887. doi: 10.3389/fneur.2023.1156887.

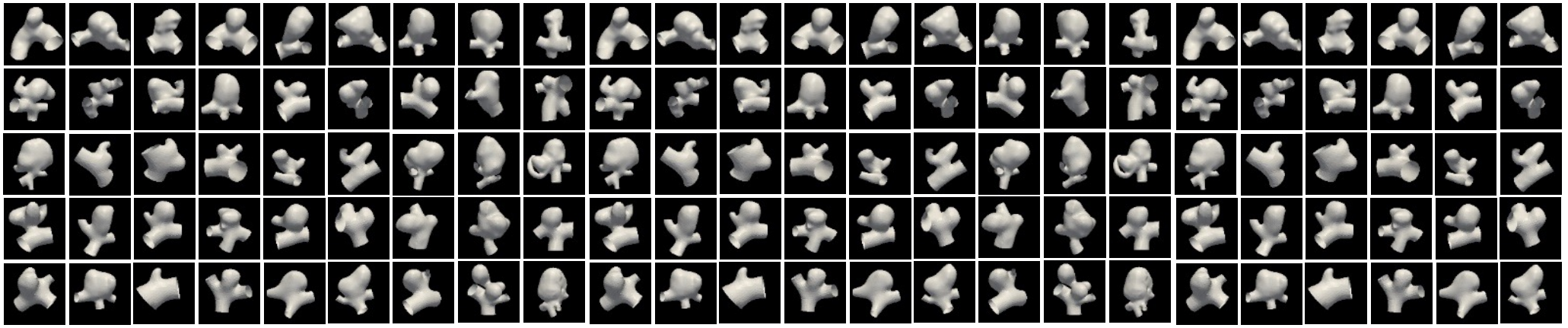
Flow-Diverter Mechanism of Action







Can *in silico* trials replicate and expand conventional clinical trials?



Pipeline for Uncoilable or Failed Aneurysms (PUFS) Trial

ORIGINAL RESEARCH ■ NEURORADIOLOGY

Pipeline for Uncoilable or Failed Aneurysms: Results from a Multicenter Clinical Trial[1]

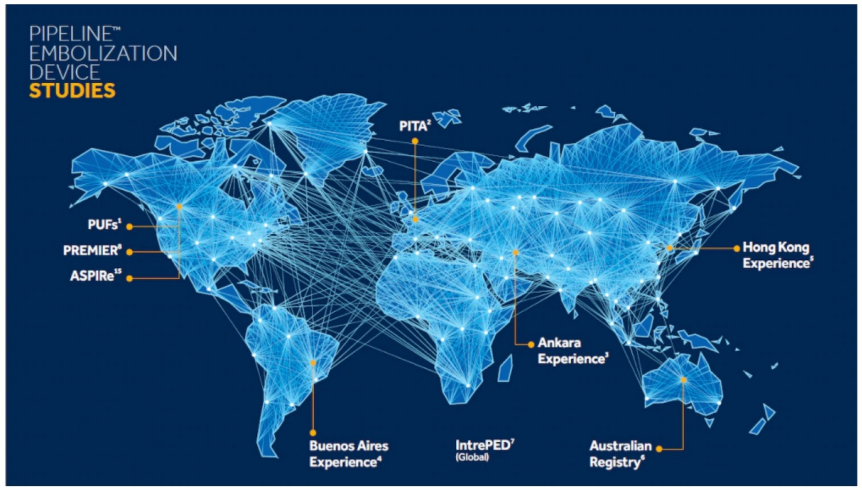
Tibor Becske, MD
David F. Kallmes, MD
Isil Saatci, MD
Cameron G. McDougall, MD
István Szikora, MD, PhD
Giuseppe Lanzino, MD
Christopher J. Moran, MD
Henry H. Woo, MD
Demetrius K. Lopes, MD
Aaron L. Berez, MD
Daniel J. Cher, MD
Adnan H. Siddiqui, MD, PhD
Elad I. Levy, MD
Felipe C. Albuquerque, MD
David J. Fiorella, MD, PhD
Zsolt Berentei, MD

Purpose: To evaluate the safety and effectiveness of the Pipeline Embolization Device (PED; ev3/Covidien, Irvine, Calif) in the treatment of complex intracranial aneurysms.

Materials and Methods: The Pipeline for Uncoilable or Failed Aneurysms is a multicenter, prospective, interventional, single-arm trial of PED for the treatment of uncoilable or failed aneurysms of the internal carotid artery. Institutional review board approval of the HIPAA-compliant study protocol was obtained from each center. After providing informed consent, 108 patients with recently unruptured large and giant wide-necked aneurysms were enrolled in the study. The primary effectiveness endpoint was angiographic evaluation that demonstrated complete aneurysm occlusion and absence of major stenosis at 180 days. The primary safety endpoint was occurrence of major ipsilateral stroke or neurologic death at 180 days.

Radiology

Design to Publication 8 years
Recruitment 6 years
108 patients ca. £30-40m
https://clinicaltrials.gov/ct2/show/NCT00777088



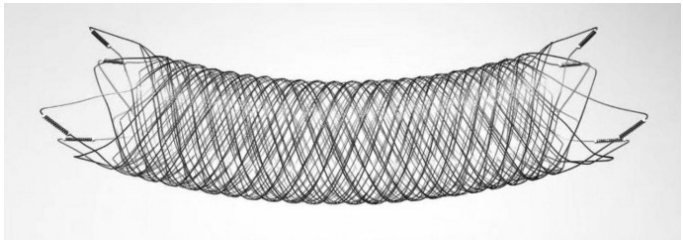
PREMIER[7] n=141	PUFs[1,2] n=106	Buenos Aires Experience n=53	Hong Kong Experience[15] n=178
ASPIRe[11] n=191	PITA[13] n=31	Ankara Experience[14] n=251	Australian Registry[16] n=5

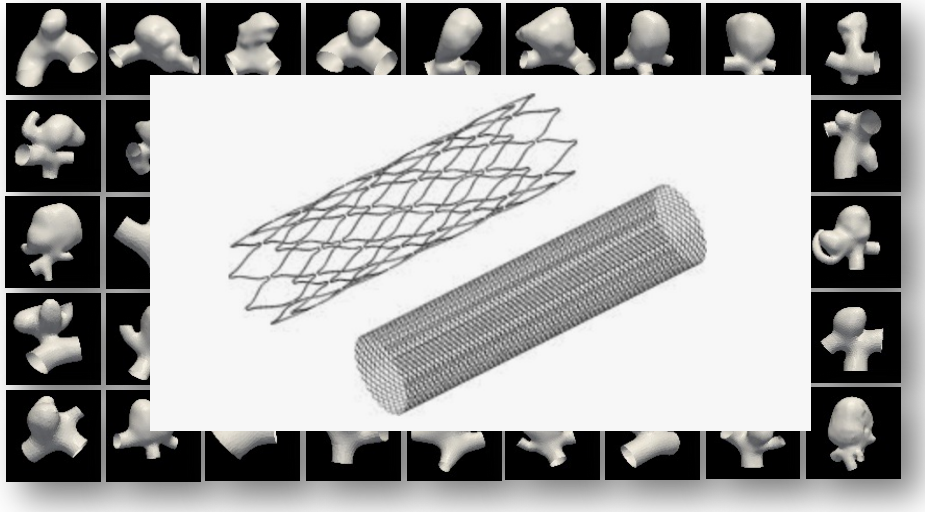


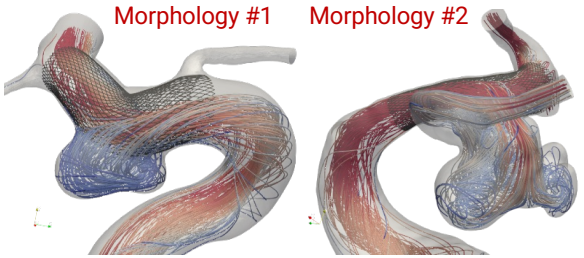
In silico trials – Concrete example: cerebrovascular flow diversion devices

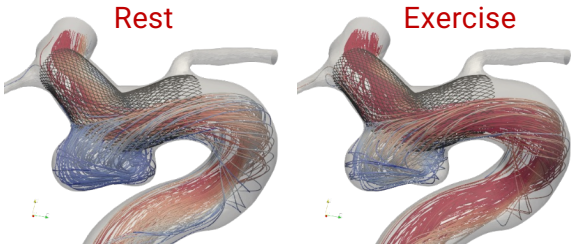
Systematically explore design space & test it against available knowledge

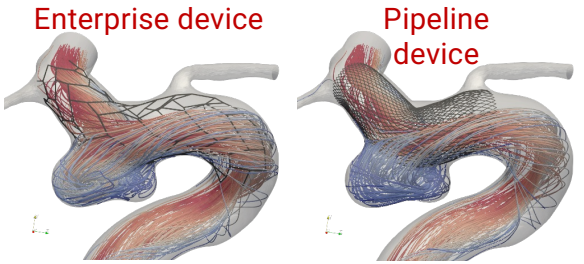












Surrogate end point:
Reduction in max time-averaged velocity at the neck

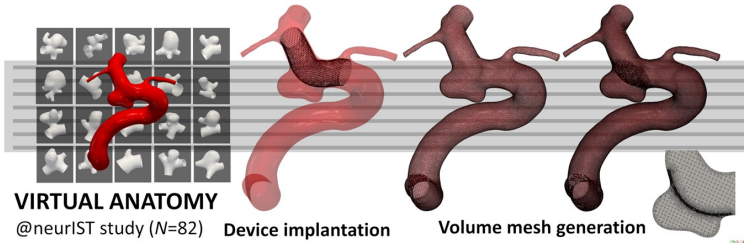
Anatomy #1: 64%
Anatomy #2: 27%

Rest 64%
Exercise 56%

Enterprise: 10%
Pipeline: 64%

Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

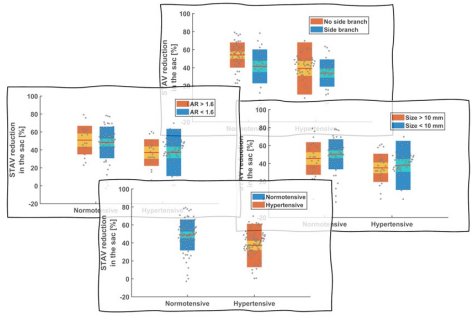
Flow diversion devices
> intracranial aneurysms



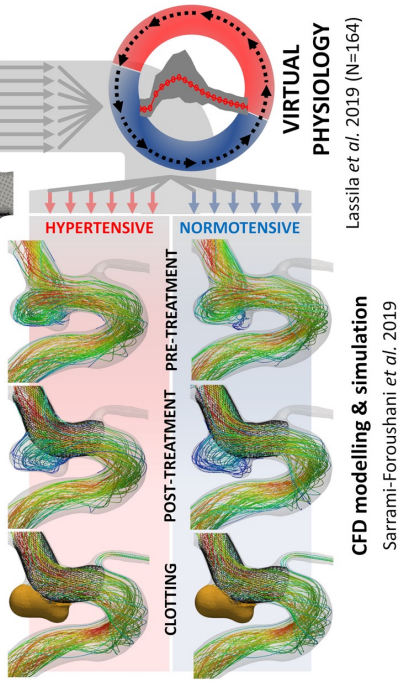
VIRTUAL ANATOMY
@neurIST study (*N*=82)
Villa-Uriol *et al.* 2011

Device implantation
Larrabide et al. 2012

Volume mesh generation
ICEM CFD (Ansys, Canonsburg PA)



Statistical analysis of device performance
Flow reduction -related endpoint (AMVR) acts as surrogate for complete occlusion (clinical endpoint)



VIRTUAL PHYSIOLOGY
Lassila *et al.* 2019 (N=164)

CFD modelling & simulation
Sarrami-Foroushani *et al.* 2019

nature COMMUNICATIONS

Medtronic

ARTICLE

https://doi.org/10.1038/s41467-021-23998-w OPEN

In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials

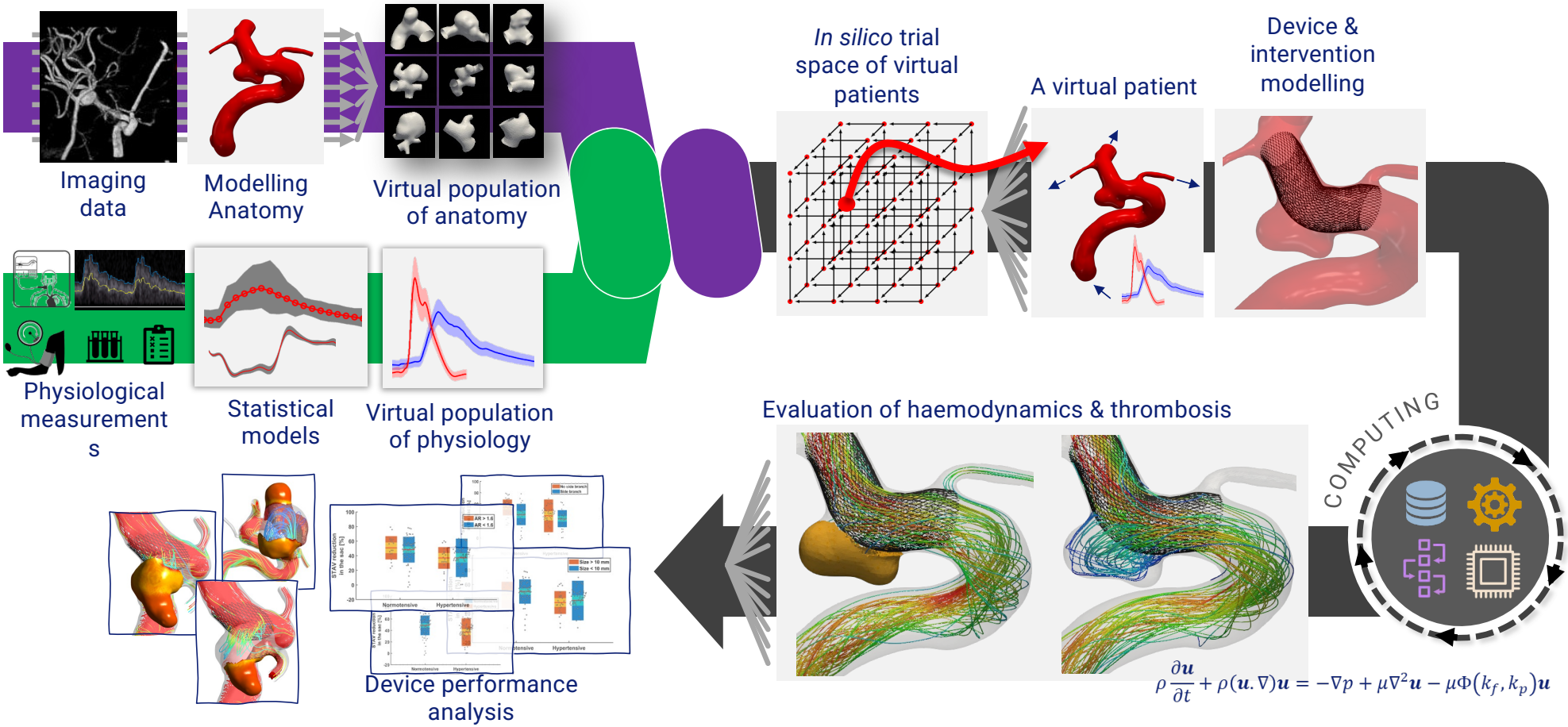
Ali Sarrami-Foroushani[1,2], Toni Lassila[1], Michael MacRaild[1], Joshua Asquith[1], Kit C. B. Roes[3], James V. Byrne[4] & Alejandro F. Frangi[1,2,5,6]

The cost of clinical trials is ever-increasing. In-silico trials rely on virtual populations and interventions simulated using patient-specific models and may offer a solution to lower these costs. We present the flow diverter performance assessment (FD-PASS) in-silico trial, which models the treatment of intracranial aneurysms in 164 virtual patients with 82 distinct anatomies with a flow-diverting stent, using computational fluid dynamics to quantify post-treatment flow reduction. The predicted FD-PASS flow-diversion success rates replicate the values previously reported in three clinical trials. The in-silico approach allows broader investigation of factors associated with insufficient flow reduction than feasible in a conventional trial. Our findings demonstrate that in-silico trials of endovascular medical devices can: (i) replicate findings of conventional clinical trials, and (ii) perform virtual experiments and sub-group analyses that are difficult or impossible in conventional trials to discover new insights on treatment failure, e.g. in the presence of side-branches or hypertension.



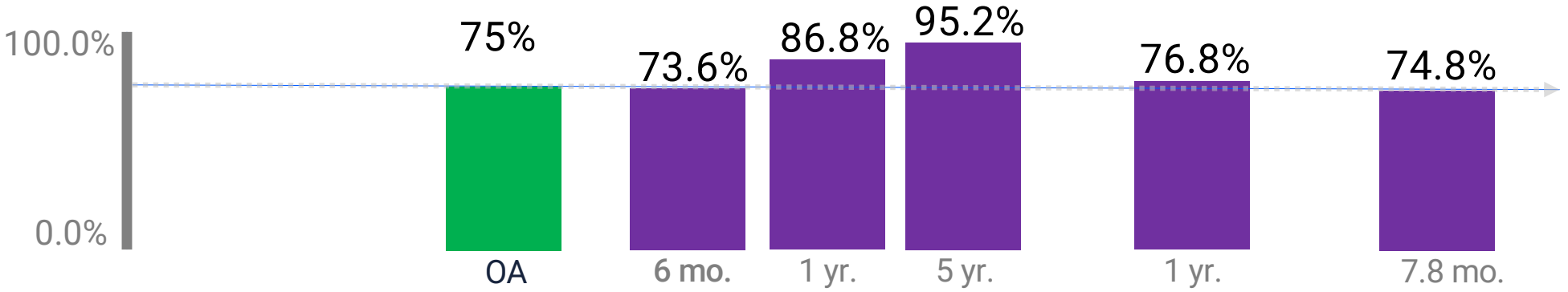
Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. *In silico* trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861. doi: 10.1038/s41467-021-23998-w.

FD-PASS workflow — step 1 of 9



Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. *In silico* trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

FD-PASS replicated complete occlusion rates in three clinical trials



FDPASS	PUFS	PREMIER	ASPIRe
2021 *In silico* trial Small, large, and giant aneurysms	2008-2014 Clinical trial Large & giant aneurysms (size > 10mm)	2014-2015 Clinical trial Small & medium aneurysms (size < 12mm)	2016 Observational registry Small, large, and giant aneurysms

PUFS—Outcome improvement over time—Three possible explanations:
1/ The aneurysm occlusion process can be prolonged in some cases. As time passes, more aneurysms heal.
2/ Some cases received re-treatments: 6 aneurysms re-treated
3/ Dropouts or failure in follow-ups Y1: 86.8% (79/91), Y3: 93.4% (71/76), and Y5: 95.2% (60/63).

Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

FD-PASS: Safety Risks

Identify cases at risk of post-treatment complications

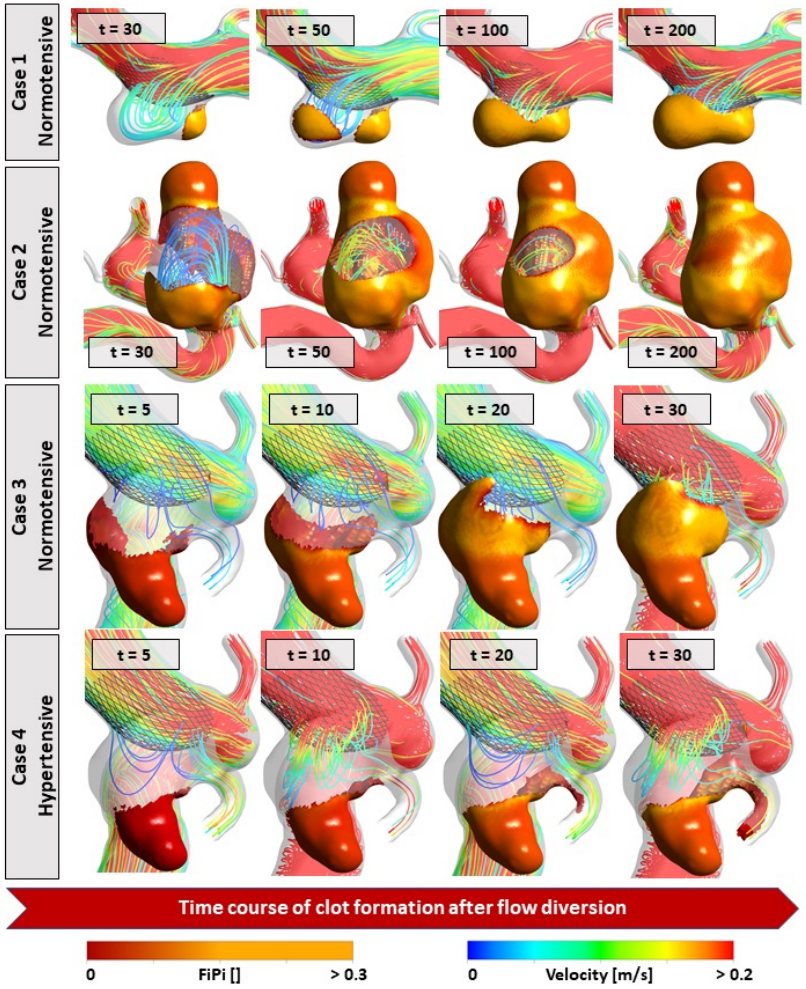
The IntrePED registry

Brinjikji et al., Am J Neuroradiol, 2016

- Higher risk of haemorrhagic stroke in those with **large/giant** aneurysms
- Higher risk of ischaemic stroke in **hypertensive** patients

Likely to lead to delayed rupture (haemorrhagic stroke)

Likely to lead to PCoA occlusion (ischemic stroke)



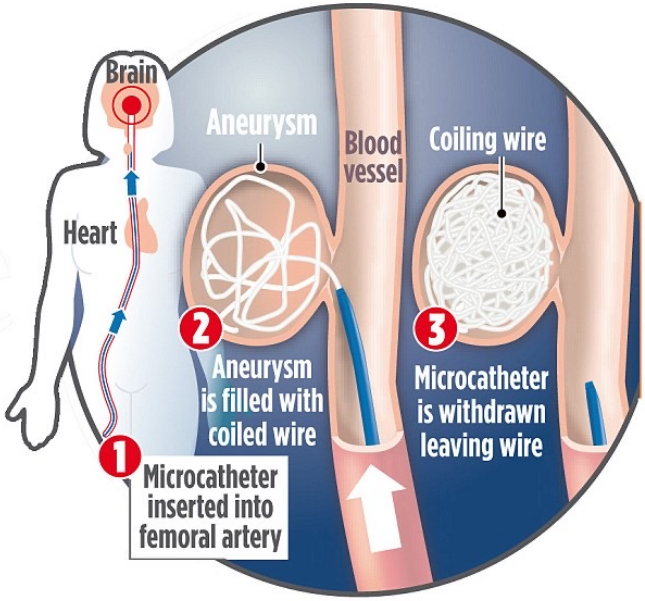
Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

Exemplar II

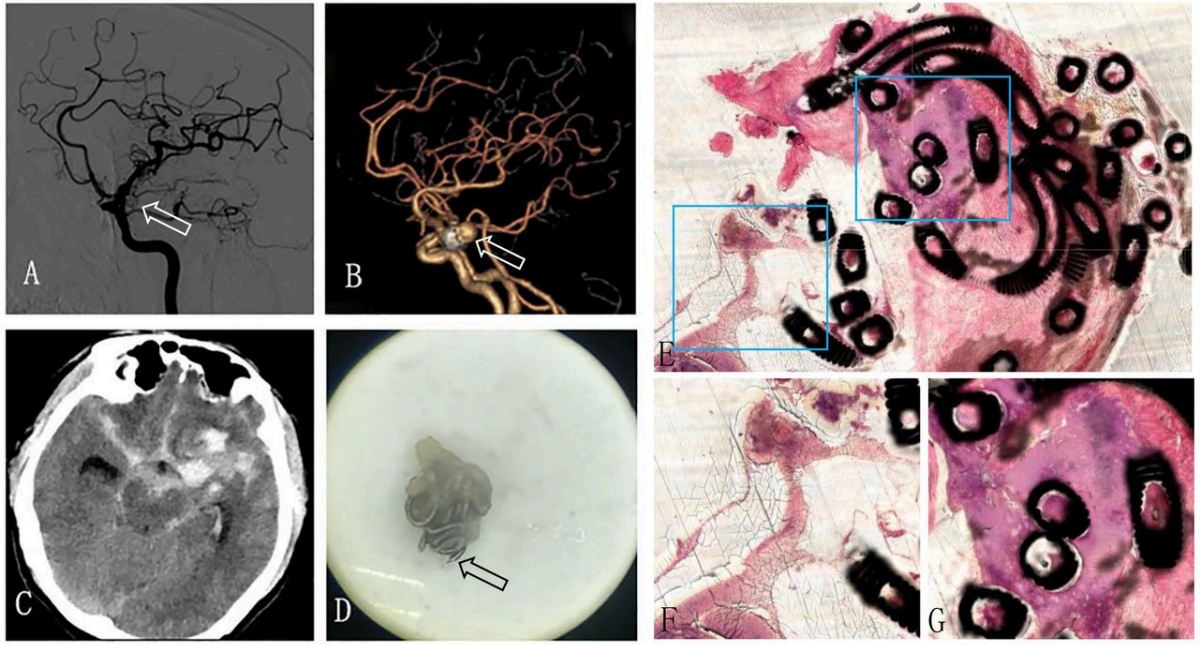
IN SILICO TREATMENT STRATIFICATION

OPERATOR INFLUENCE / COST EFFECTIVENESS
EMERGING BEHAVIOUR

Intracranial aneurysms' coiling
A second device



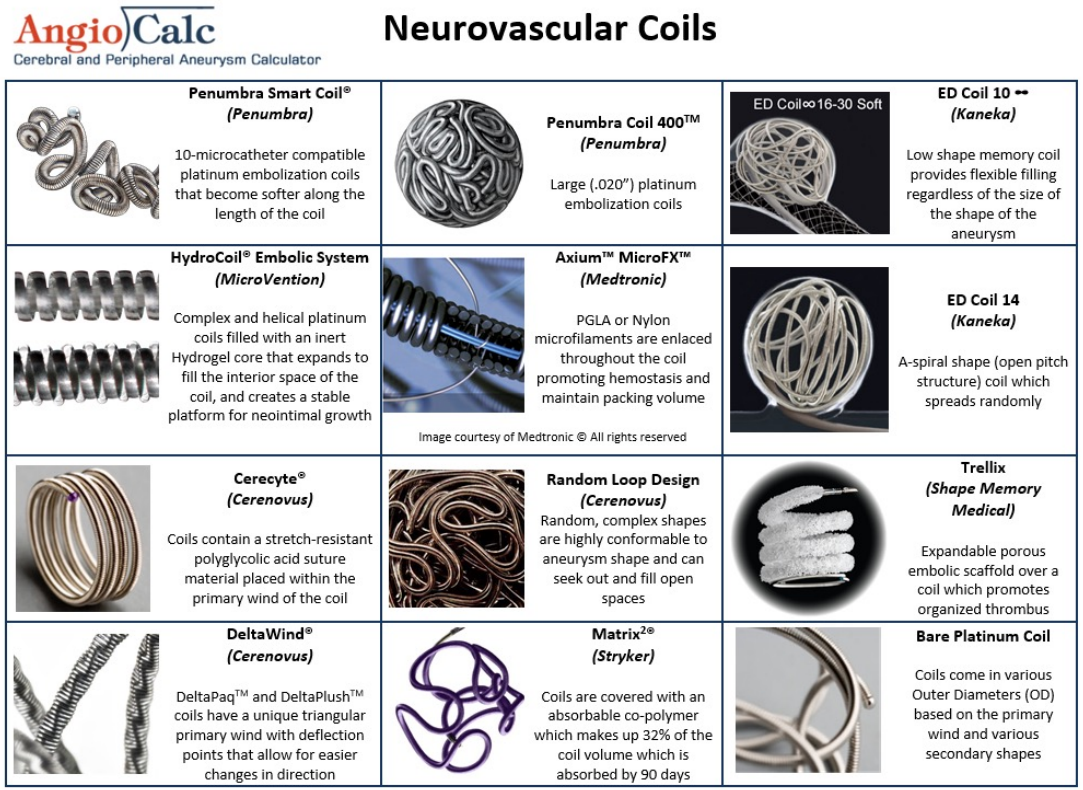
https://www.dailymail.co.uk/health/article-2054726/The-tiny-coil-wire-inserted-body-saves-thousands-stroke.html



Wang C, Li M, Chen H, Yang X, Zhang Y, Zhang D. Histopathological analysis of in vivo specimens of recurrent aneurysms after coil embolization. J Neurointerv Surg. 2021 Oct 21:neurintsurg-2021-017872. doi: 10.1136/neurintsurg-2021-017872.

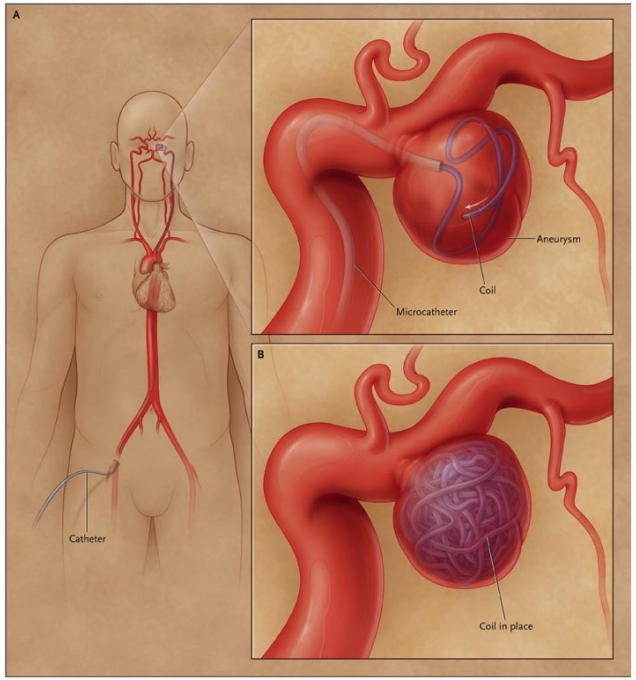
Intracranial coils

- Biocompatible metal wires (NiTi, Pt, Ni)
- Coils fill aneurysm to prevent its rupture
- Features:
  - Diameter
  - Length
  - Design (structural configuration)
  - Softness
- Operators' skills and coil type ⇒ different outcomes [1,2,3]



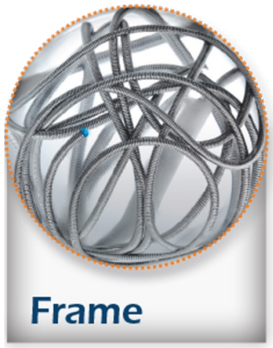
[1] White, J. B., C. G. ken, et al. (2008) "Coils in a nutshell: a review of coil physical properties" AJNR Am. J. Neuroradiol., 29(7):1242-6.
[2] Sluzewski, M., W. J: van Rooij, et al. (2004). "Relation between aneurysm volume, packing and compaction in 145 cerebral aneurysm treated with coils." Radiology 231(3): 653-8.
[3] Piotin, M., L.Spelle, et al. (2007). "Intracranial aneurysms: treatment with bare platinum coils--aneurysm packing, complex coils, and angiographic recurrence." Radiology 243(2): 500-8.

Coiling: the basics



[Penumbra Smart Coil Insertion]
[Generic Call Insertion (short)]

Packing density is defined as **the ratio between the inserted coils and aneurysm volume**.



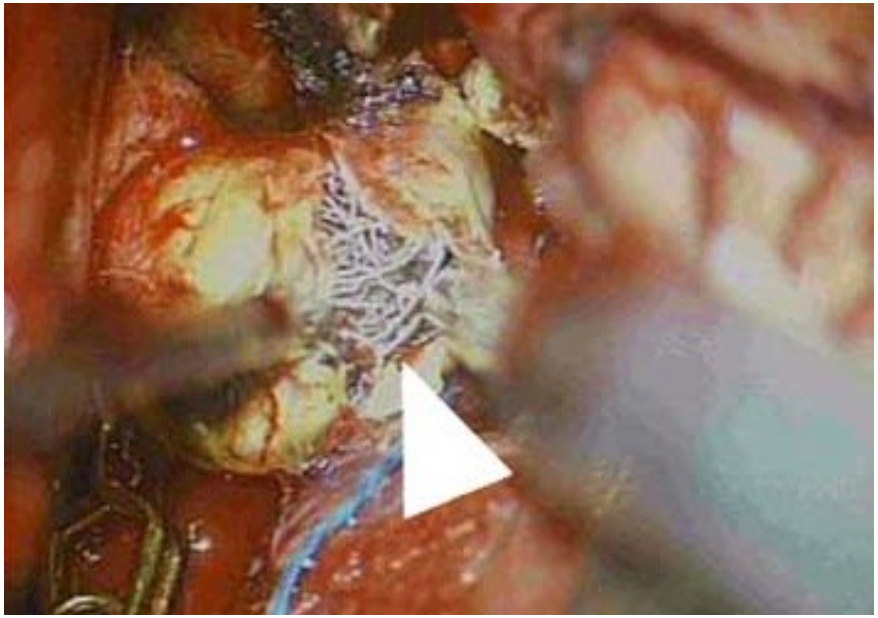




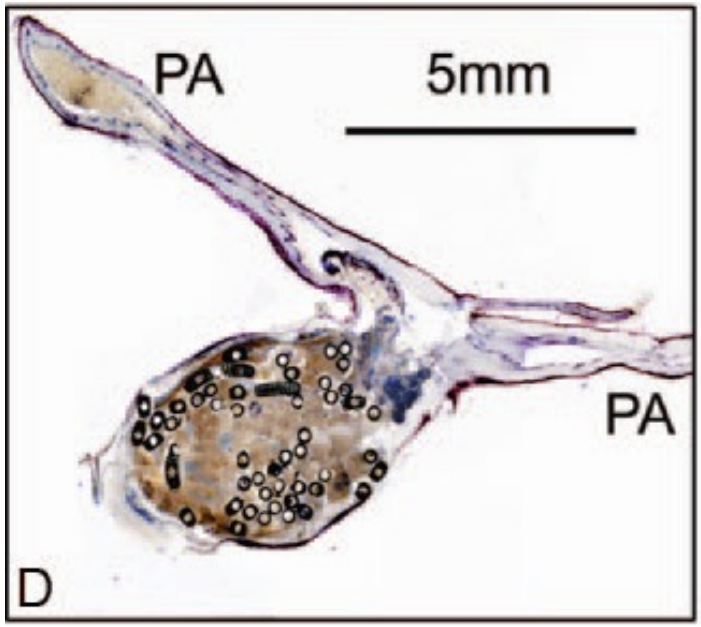
Morales HG, Kim M, Vivas EE, et al. How do coil configuration and packing density influence intra-aneurysmal hemodynamics?. AJNR Am J Neuroradiol. 2011;32(10):1935-1941. doi:10.3174/ajnr.A2635

Coil distribution in intracranial aneurysms

Dehdashti *et al.*



Sherif *et al.*



Dehdashti AR, Thines L, Willinsky RA, Tymianski M. Symptomatic enlargement of an occluded giant carotido-ophthalmic aneurysm after endovascular treatment: the vasa vasorum theory. Acta Neurochir (Wien). 2009 Sep;151(9):1153-8

Sherif C, Bavinzski G, Dorfer C, Kanz F, Schuster E, Plenk H Jr. Computerized assessment of angiographic occlusion rate and coil density in embolized human cerebral aneurysms. AJNR Am J Neuroradiol. 2009 May;30(5):1046-53.

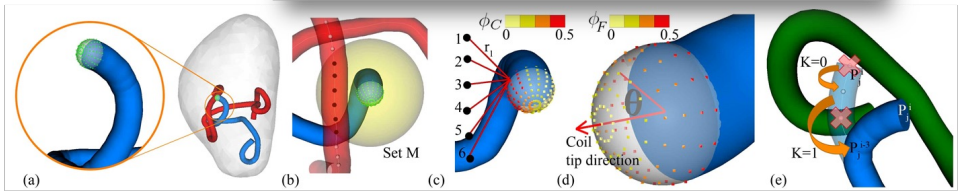
Virtual Coiling validation & verification

Virtual Coiling: the intuition

- Inspired on minimum-cost path planning algorithms
- Cost functions replicate physics of coil behaviour

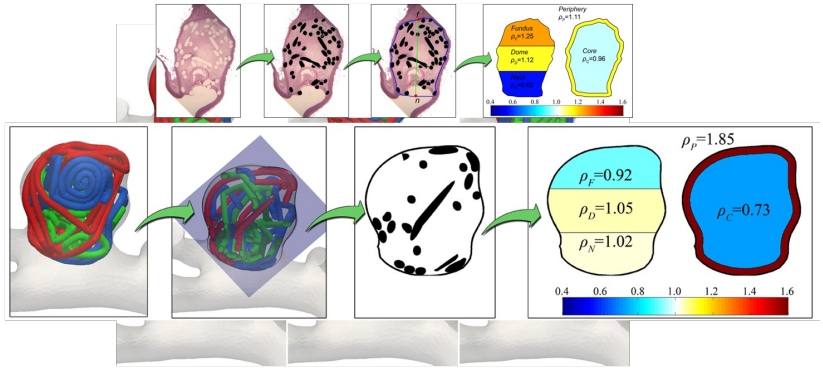
$$\phi(\mathbf{h}_j^{i,q}) = \phi_D(\mathbf{h}_j^{i,q}) + \phi_F(\mathbf{h}_j^{i,q}) + \phi_{PB}(\mathbf{h}_j^{i,q}).$$

$$\phi_D(\mathbf{h}_j^{i,q}) = \phi_A(\mathbf{h}_j^{i,q}) + \phi_C(\mathbf{h}_j^{i,q}).$$



Morales HG, Larrabide I, Geers AJ, San Roman L, Blasco J, Macho JM, Frangi AF. A virtual coiling technique for image-based aneurysm models by dynamic path planning. IEEE Trans Med Imaging. 2013 Jan;32(1):119-29.

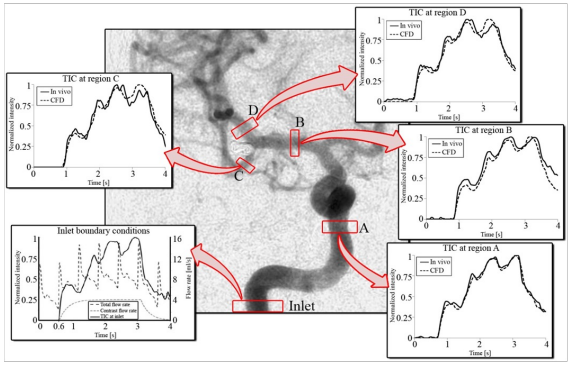
Virtual coiling evaluation vs. histology



Morales HG, Larrabide I, Geers AJ, Dai D, Kallmes DF, Frangi AF. Analysis and quantification of endovascular coil distribution inside saccular aneurysms using histological images. J Neurointerv Surg. 2012 Aug 21. [Epub ahead of print]

Virtual Coiling vs. hemodynamic impact

- Comparison of time-intensity curves of real/virtual angiographies.



Morales *et al.* Towards the Validation of a Virtual Coiling Technique Using a Real Versus a Simulated Bolus Injection. Proc. CMBE, 2011.

Coiling: *in silico* trials /device understanding

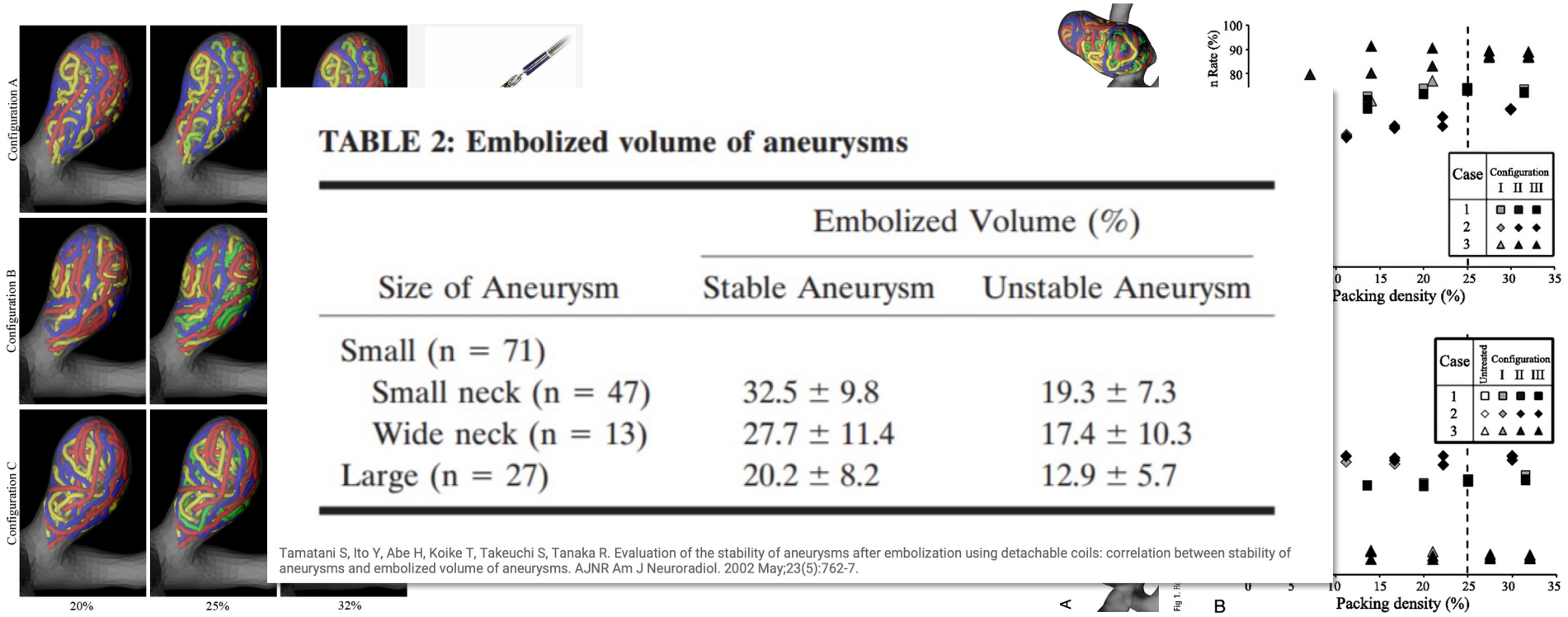


TABLE 2: Embolized volume of aneurysms

Size of Aneurysm	Embolized Volume (%)	
	Stable Aneurysm	Unstable Aneurysm
Small (n = 71)		
Small neck (n = 47)	32.5 ± 9.8	19.3 ± 7.3
Wide neck (n = 13)	27.7 ± 11.4	17.4 ± 10.3
Large (n = 27)	20.2 ± 8.2	12.9 ± 5.7

Tamatani S, Ito Y, Abe H, Koike T, Takeuchi S, Tanaka R. Evaluation of the stability of aneurysms after embolization using detachable coils: correlation between stability of aneurysms and embolized volume of aneurysms. AJNR Am J Neuroradiol. 2002 May;23(5):762-7.

Morales HG, Larrabide I, Geers AJ, San Roman L, Blasco J, Macho JM, Frangi AF. A virtual coiling technique for image-based aneurysm models by dynamic path planning. IEEE Trans Med Imaging. 2013 Jan;32(1):119-29.
Morales HG, Kim M, Vivas EE, Villa-Uriol MC, Larrabide I, Sola T, Guimaraens L, Frangi AF. How do coil configuration and packing density influence intra-aneurysmal hemodynamics? AJNR Am J Neuroradiol. 2011 Nov-Dec;32(10):1935-41.

Exemplar III

IN SILICO EVIDENCE FOR NEW TREATMENTS

WORK IN PROGRESS

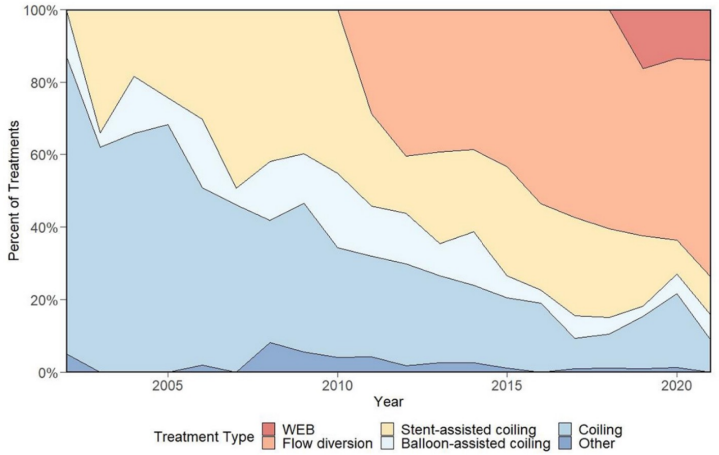
Intrasaccular Devices – expanding evidentiary basis

- Flow diverter and Stent-coiling are successful procedures but come with a price:

Factor	Flow diverter	Stent + Coiling	Intrasaccular Devices
Alteration in parent lumen flow[1]	High	Moderate	Minimal
Antiplatelet therapy[1]	DAPT	DAPT	No need
Wall – Device contact[1]	High	Yes	Minimal
Intraparenchymal Haemorrhage risk[2,3]	2-5 %	1-2%	< 1%

- Intrasaccular aneurysm treatment can alleviate these problems

Not for every aneurysm:
- Best suited to wide-neck aneurysm
- Large, fusiform, sidewall aneurysms still need flow diverter and stent-coiling



Intrasaccular devices (WEB) usage* getting prominence[4]

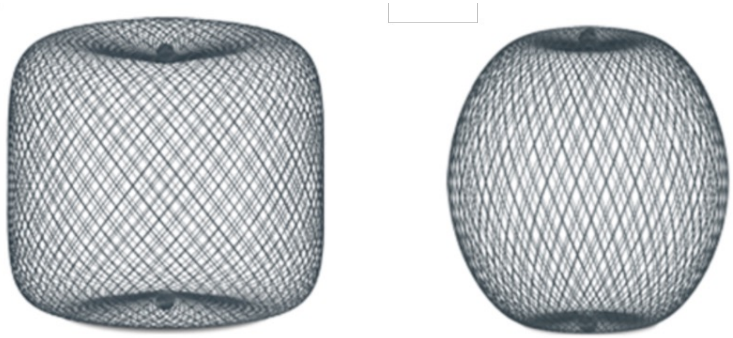
* At Washington University in St. Louis School of Medicine, USA

Intrasaccular devices:
1) Woven EndoBridge (WEB) – MicroVention (Terumo); FDA PMA 2019
2) Contour Neurovascular System – Cerus Endovascular (now Stryker); CE marked
3) Nautilus Intrasaccular System – EndoStream; CE marked
4) Artisse – Medtronic; CE marked

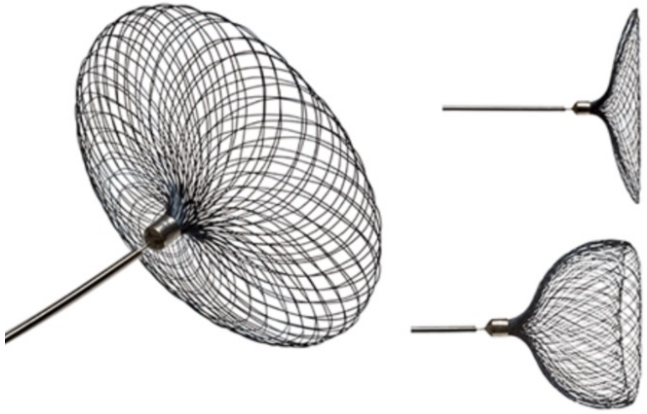
[1] Gaub et al., 2024, [2] Brinjikji et al. 2015, [3] Kayan et al. 2016, [4] Lauzier et al. 2023 · device names are trademarks of their respective manufacturers

Intrasaccular devices: Fill Sac or Seal Neck?

- **WEB (Woven EndoBridge; MicroVention/Terumo): fills the sac — intrasaccular flow disruption**
- **Contour (Contour Neurovascular System; Cerus/Stryker): seals the neck — neck-bridging flow disruption**
- WEB is the only FDA-approved intrasaccular device (PMA 2019; WEB-IT n=150, 84.6% adequate occlusion at 1 yr)
- Early non-randomised series suggest Contour may offer:
  - shorter, simpler deployment than WEB[1,2]
  - earlier angiographic occlusion than WEB[1,2]
  - lower retreatment rate (2.5% vs 6%) than WEB[1,2]
- **Why model Contour?**
  - Limited computational and *in silico* evidence compared with WEB
  - Limited sizing guidance and no positioning guidance
  - Device sizing and positioning determine the deployed shape, which influences bifurcation flow patterns and ultimately treatment efficacy
  - Opportunity to identify optimal anatomy, sizing, and deployment strategies and support ongoing clinical evaluation



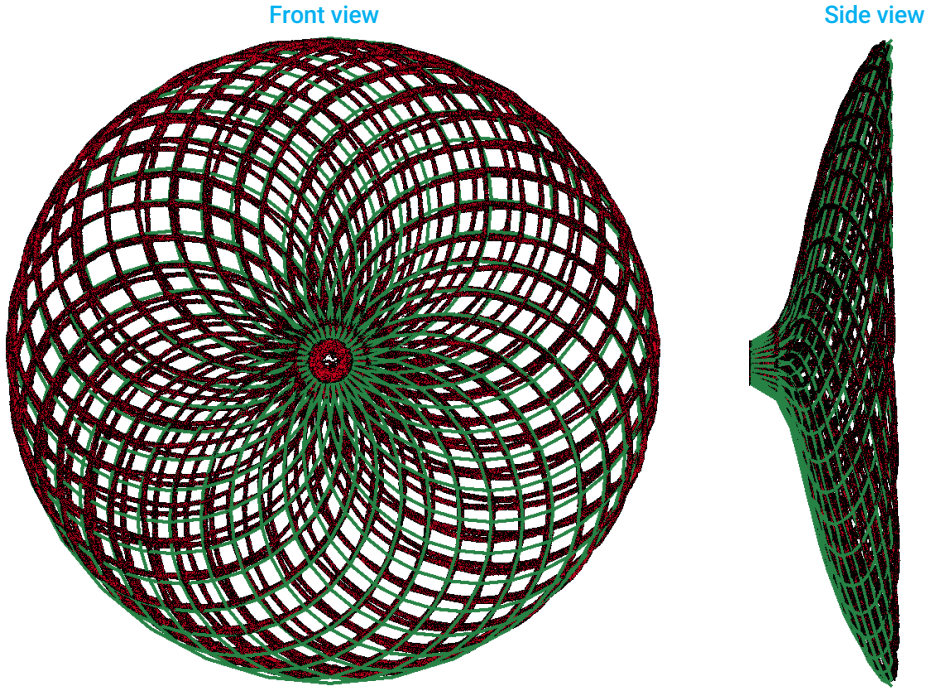
Woven EndoBridge (WEB)[1]



Contour Neurovascular System[1]

[1] Hecker et al., 2023, [2] Gärtner et al. 2025 · no randomised head-to-head data · device names are trademarks of their respective manufacturers

Modelling Contour: from micro-CT to a deployable model

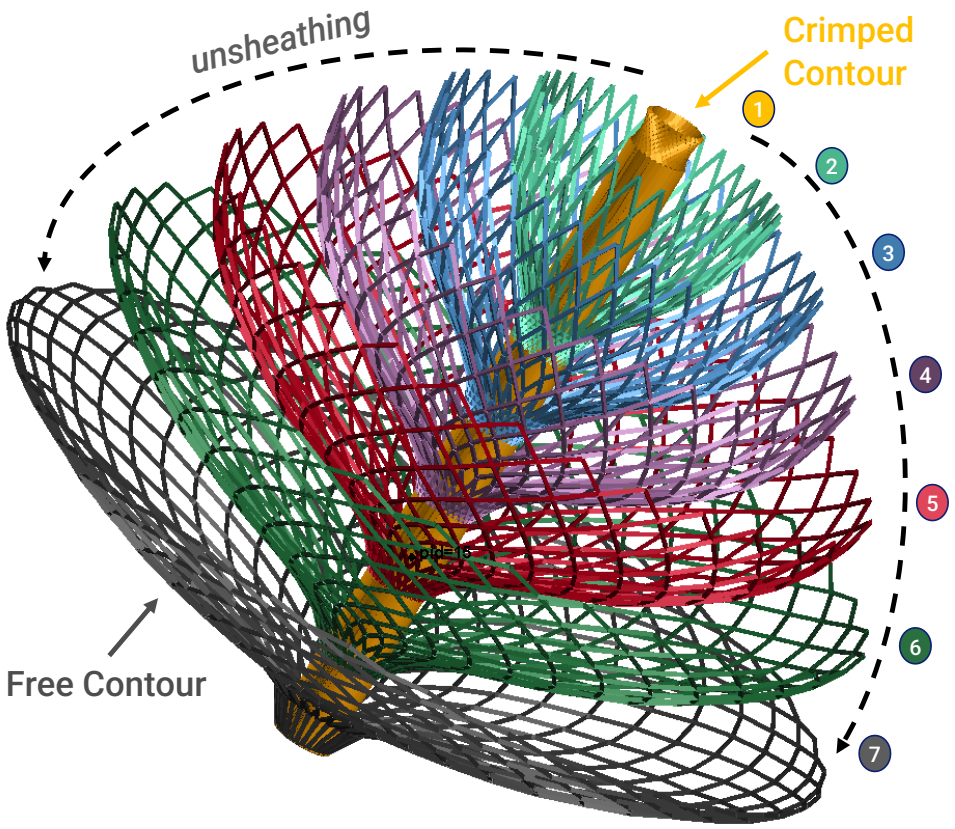


----- Braids reconstructed from µCT imaging

----- Braids generated from parametric model

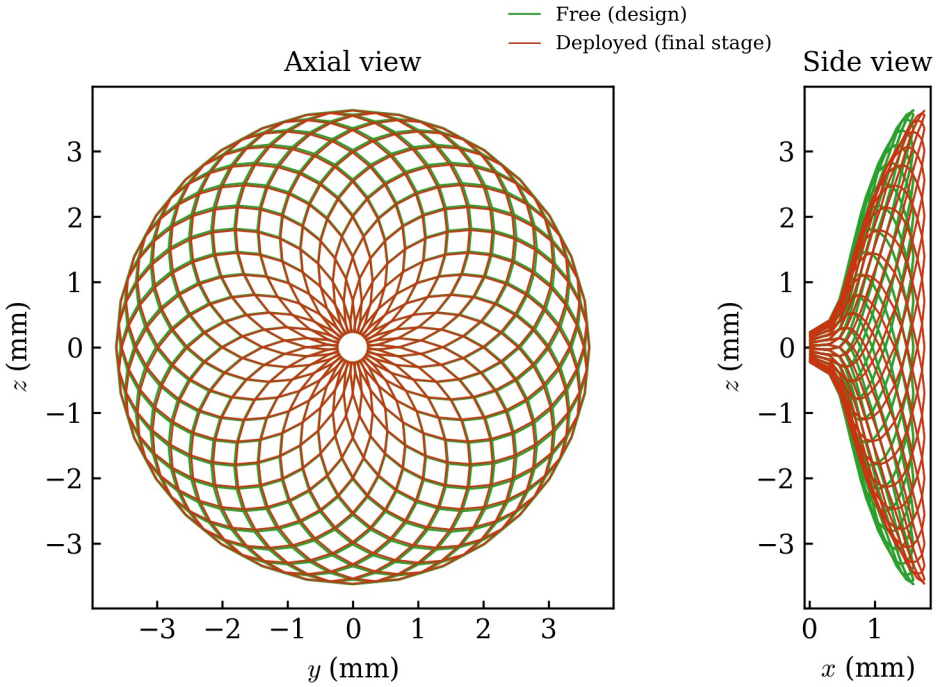
- CIMIM has previously conducted *in silico* trials for flow diverters
- The deployment and meshing components of the pipeline must be adapted for Contour
- Accurate device geometry and deployed shape is essential to predict intra-aneurysmal flow reduction and occlusion
- Parametric model is developed to reproduce the single-layer braided geometry reconstructed from micro-CT imaging
- A spring-mass-based Fast Virtual Deployment (FVD) framework for deployment
- Deployment simulation time: seconds to hours (depending on case complexity), compared with days to weeks for FEM-based approaches.

Fast virtual deployment



7 stages of unsheathing of Contour in free environment

Shape recovery validation from crimped configuration

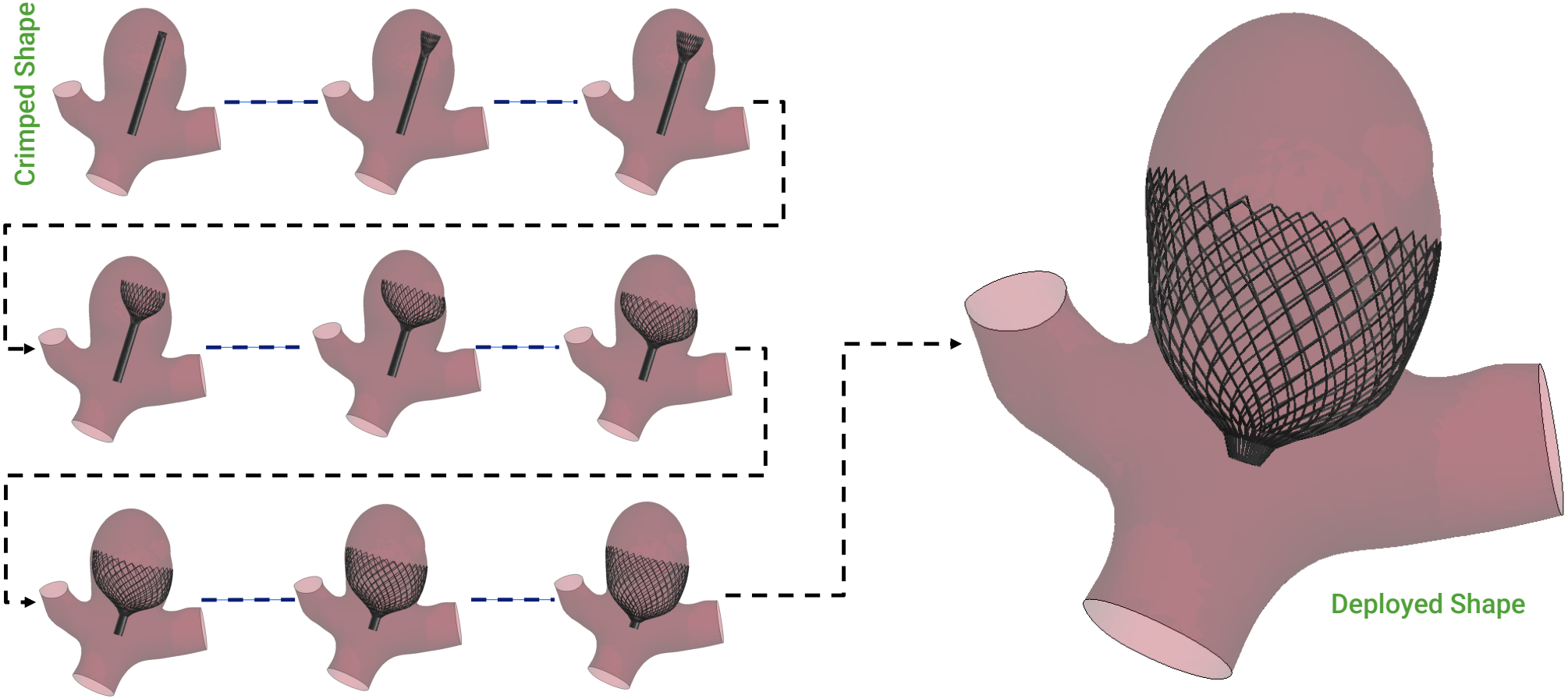


Deviation = 3.3%

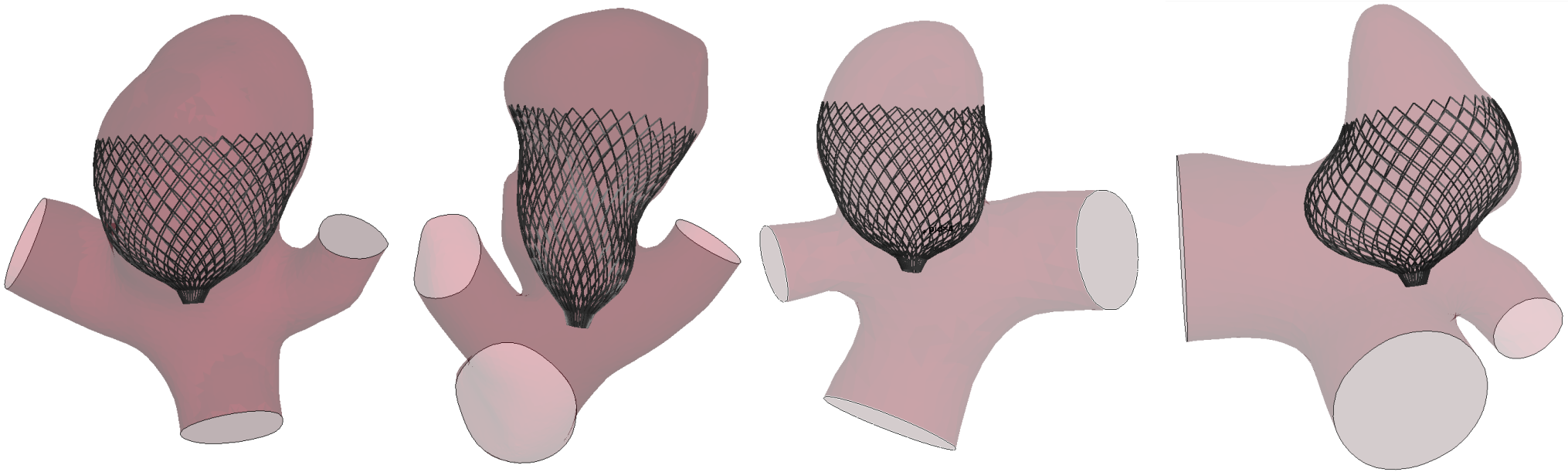
Computational time = 14 seconds

Deployment of Contour in the aneurysm sac

Fast virtual deployment



Sample results of Contour deployment across patient-specific aneurysm sacs



ASD_0015 UPF_P0024_ID1 UPF_P0076_ID1 ASD_006

case-id from @neurIST dataset


Better population coverage
Complex or Rare Diseases
Underserved communities
Pediatric applications
Combination therapies – co-simulation
Off-label or Foreseeable Misuse
Dose–Device Coupling
Virtual First-in-Body
Communicating RCT risk to patients
...
Fragile Physiology Zone
Pregnancy Protected Window
Comorbidity Jigsaw
Evidence for the Global South
Pre-test inclusion/exclusion
Incremental Equivalence Proof
Supply Chain Substitute Swap
Reprocessing & Reuse Validator
Operator Variability Reactor
...
Magnetic Environment Immunity
Extreme Physiology Checker
Recall Scope Optimiser
Recurrence Predictor Sandbox
Adaptive Arm Optimiser
Non-Inferiority Cushion Finder
Bespoke Manufactured Devices
Bioresorbable Horizon Scan
Clinician Learning Curve
...
The tip of the iceberg

Data methods are not the full solution, but part of it

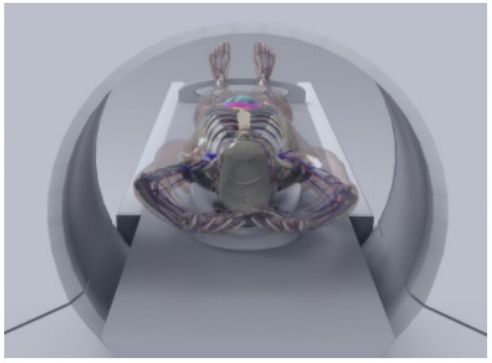
AI IN SERVICE OF IN SILICO MEDICINE

In silico trial – a Model with Multiple Sub-models



Virtual Participants & Populations

- Generalisation of synthetic data
- Anatomical organ(s) variation(s)
- Organ function & structure variation
- Physiological & biological variability
- Pathology presence/heterogeneity
- Effect of ageing, lifestyle, co-morbidities
- Inclusion of complex covariates on demographics, environment, socioeconomics, etc.



Virtual Examinations & Interventions

- Physics of diagnostic imaging process
- Device mechanisms of action and associated mechanobiology,
- Organ/tissue response & remodelling: e.g. radiobiology, radiotracers, tissue absorption, drug uptake, etc.
- Operator Influence – e.g. uncertainty on optimal device placement, sizing & settings, or therapy planning, etc.



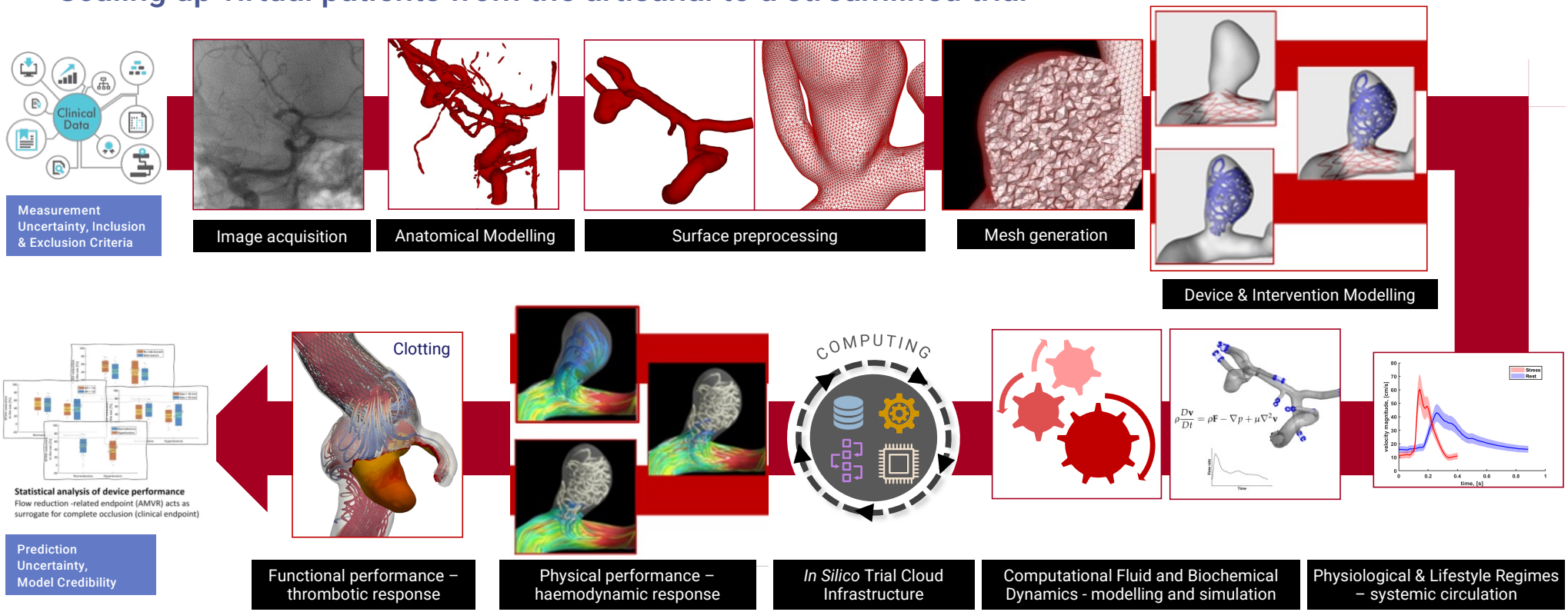
Virtual Readers & Outcomes

- Biomarkers read outs (e.g. AI-derived imaging biomarkers)
- Clinical surrogate end-points
- Computational Physiology
- Computational Anatomy

Source: adapted from cvit.duke.edu/research

In silico trial execution workflow

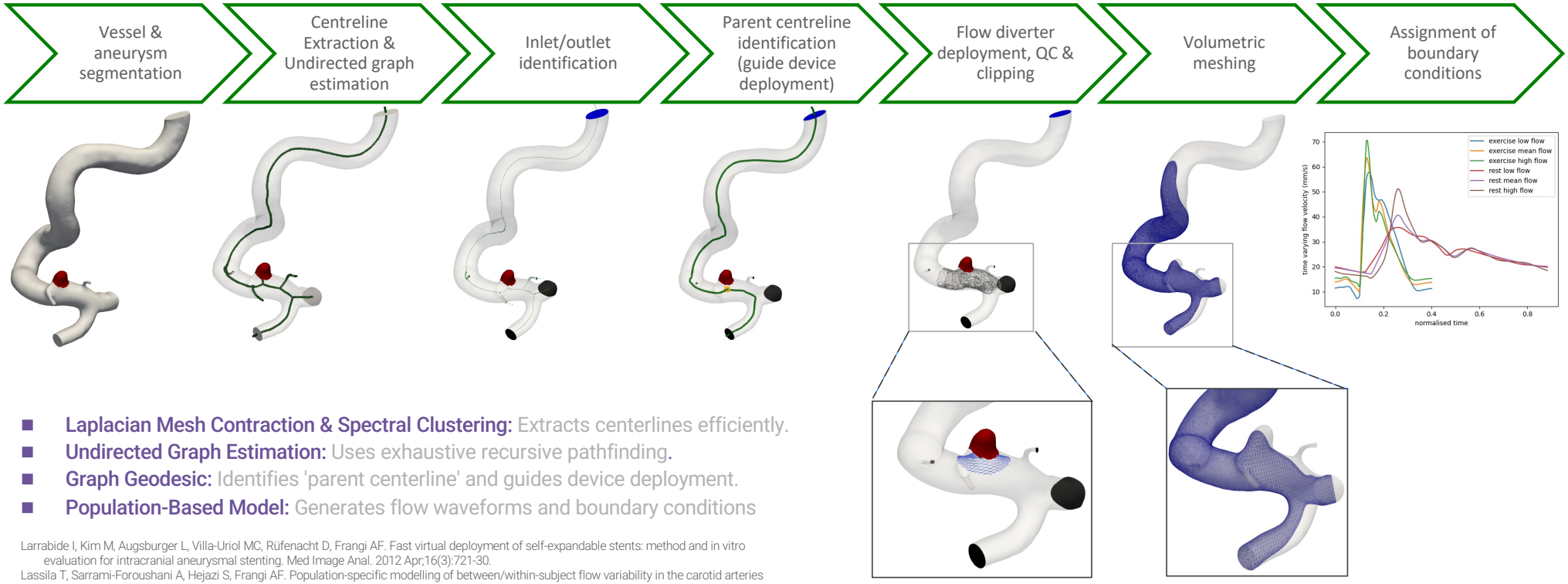
> Scaling up virtual patients from the artisanal to a streamlined trial



1. Larrabide I, Kim M, Augsburger L, Villa-Uriol MC, Rüfenacht D, Frangi AF. Fast virtual deployment of self-expandable stents: method and in vitro evaluation for intracranial aneurysmal stenting. Med Image Anal. 2012 Apr;16(3):721-30
2. Morales HG, Larrabide I, Geers AJ, San Román L, Blasco J, Macho JM, Frangi AF. A virtual coiling technique for image-based aneurysm models by dynamic path planning. IEEE Trans Med Imaging. 2013 Jan;32(1):119-29
3. Cebral JR, Castro MA, Appanaboyina S, Putman CM, Millan D, Frangi AF (2005).Efficient Pipeline for Image-Based Patient-Specific Analysis of Cerebral Aneurysm Hemodynamics: Technique and Sensitivity, IEEE Trans on Medical Imaging. 24(4):457-67.
4. Villa-Uriol M.C., I. Larrabide, J.M. Pozo, M. Kim, O. Camara, M. De Craene, C. Zhang, A.J. Geers, H. Morales, H. Bogunovic, R. Cardenes, A. F. Frangi (2010) Toward integrated management of Intracranial Aneurysms, Phil. Trans. R. Soc. A., 2010;368:2961-2982.
5. Lassila T, Sarrami-Foroushani A, Hejazi S, Frangi AF. Population-specific modelling of between/within-subject flow variability in the carotid arteries of the elderly. Int J Numer Method Biomed Eng. 2020 Jan;36(1):e3271
6. Sarrami-Foroushani A, Lassila T, Hejazi SM, Nagaraja S, Bacon A, Frangi AF. A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms. J Biomech. 2019 Jun 25;91:7-13
7. Sarrami-Foroushani A, Lassila T, Frangi AF. Virtual endovascular treatment of intracranial aneurysms: models and uncertainty. Wiley Interdiscip Rev Syst Biol Med. 2017 Jul;9(4).

Streamlined/automated modelling & simulation pipeline

Example: digital twins of intracranial aneurysms treated with endovascular devices



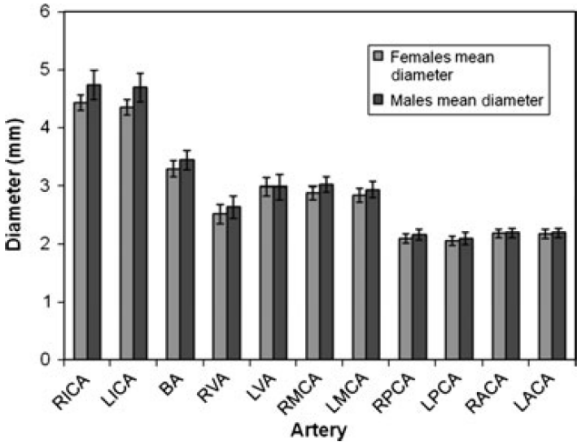
- **Laplacian Mesh Contraction & Spectral Clustering:** Extracts centerlines efficiently.
- **Undirected Graph Estimation:** Uses exhaustive recursive pathfinding.
- **Graph Geodesic:** Identifies 'parent centerline' and guides device deployment.
- **Population-Based Model:** Generates flow waveforms and boundary conditions

Larrabide I, Kim M, Augsburger L, Villa-Uriol MC, Rüfenacht D, Frangi AF. Fast virtual deployment of self-expandable stents: method and in vitro evaluation for intracranial aneurysmal stenting. Med Image Anal. 2012 Apr;16(3):721-30.

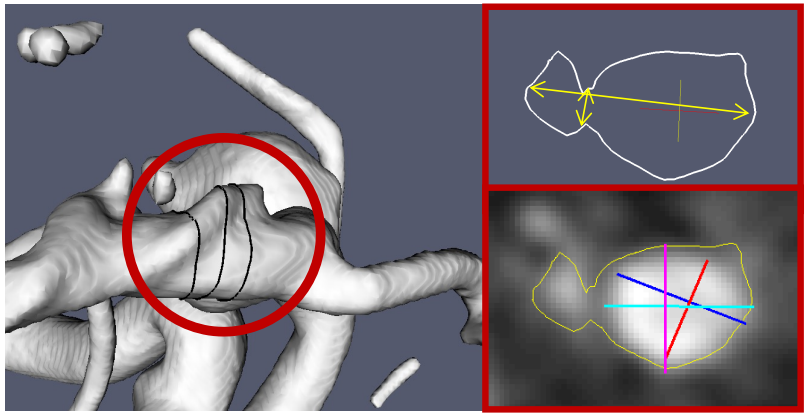
Lassila T, Sarrami-Foroushani A, Hejazi S, Frangi AF. Population-specific modelling of between/within-subject flow variability in the carotid arteries of the elderly. Int J Numer Method Biomed Eng. 2020 Jan;36(1):e3271.

3D vascular models from multimodal imagery: challenges

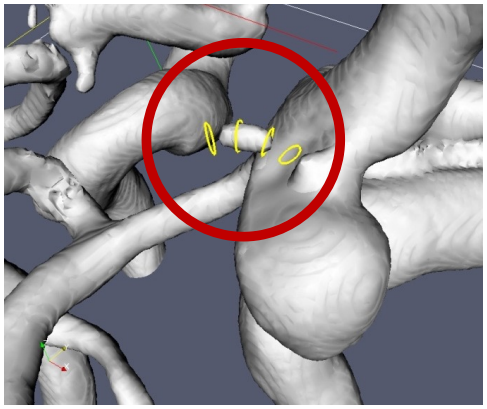
- High-throughput segmentation & modelling are challenging
  - limited resolution, anisotropy, noise and artefacts
  - complex vascular territory; the need for watertight models
  - relevant vessels radii close to image resolution (1-4 mm)
- Need to deal with kissing/missing vessels



El-Barhoun EN, Gledhill SR, Pitman AG. Circle of Willis artery diameters on MR angiography: an Australian reference database. J Med Imaging Radiat Oncol. 2009 Jun;53(3):248-60.



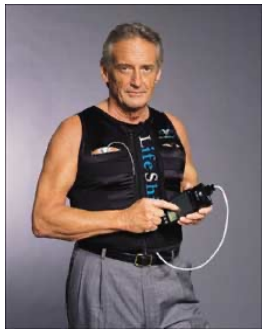
Kissing vessels



Missing vessels

Understanding physiology and lifestyle influence

- One-dimensional systemic models is the way to go to incorporate dynamic boundary conditions
- Pervasive sensing and body sensor networks might provide real-time physiological BCs
- Use of reduced order methods to solve Navier-Stokes on real-time around a baseline solution?
- ***Which will be the typical conditions under which this patient will be at risk?***





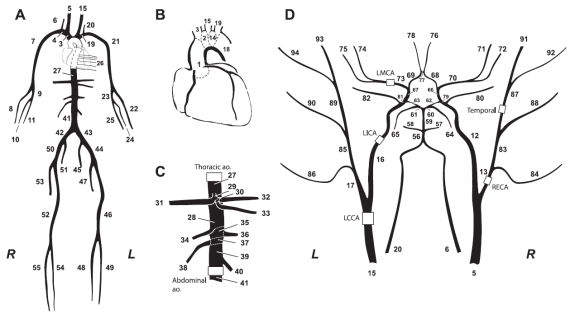


Fig. 1. Schematic representation of the arterial tree adapted from Reymond et al. (23). *A*: main systemic arterial tree. *B*: detail of the aortic (ao.) arch (coronary arteries are not taken into account). *C*: detail of the principal abdominal aorta branches. *D*: schematic of the detailed cerebral arterial tree, which is connected via the carotids (segments 5 and 15) and the vertebrals (segments 6 and 20) to the main arterial tree shown in *A* (anterior choroidal arteries are left out). Locations where in vivo measurements were performed are presented. L, left; R, right; LMCA, left middle cerebral artery; LICA, left internal carotid artery; LCCA, left common carotid artery; RECA, right external carotid artery.

Reymond P, Bohraus Y, Perren F, Lazeyras F, Stergiopulos N. Validation of a patient-specific one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol. 2011 Sep;301(3):H1173-82.

Reymond P, Merenda F, Perren F, Rüfenacht D, Stergiopulos N. Validation of a one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol. 2009 Jul;297(1):H208-22.

Shaltis PA, Reisner AT, Asada HH. Cuffless blood pressure monitoring using hydrostatic pressure changes. IEEE Trans Biomed Eng. 2008 Jun;55(6):1775-7.

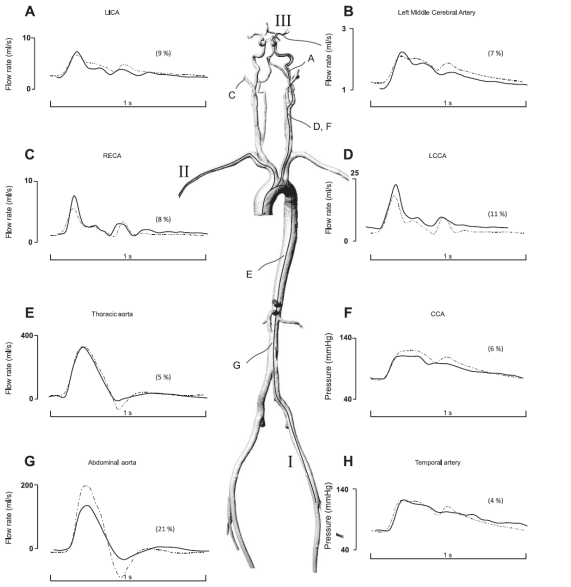
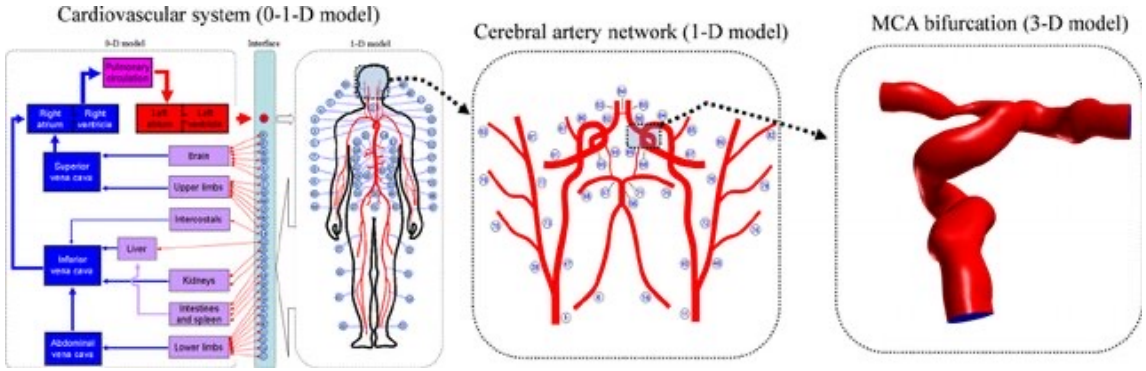
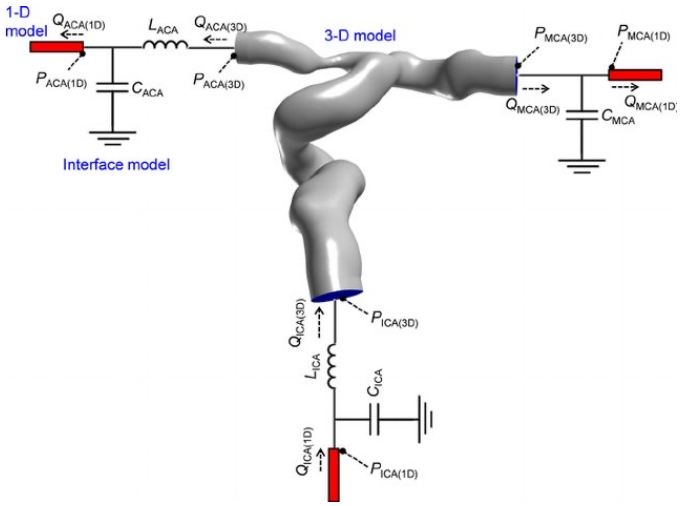


Fig. 2. Model predictions (dash dot) compared with in vivo measurements of flow and pressure waves (continuous line) for different systemic and cerebral arteries. Flow is measured with B-mode color-coded duplex flow imaging technique in the LICA (*A*), LMCA (*B*), and RECA (*C*), with phase-contrast (PC)-MRI in the LCCA (*D*) in the thoracic aorta (*E*) and in the abdominal aorta (*G*). Pressure was measured with applanation tonometry in the common carotid artery (CCA; *F*) and superficial temporal artery (*H*). The central picture is the representation of the 3-dimensional geometry of the patient-specific arterial tree from MRI angiography. In parenthesis are root mean square of the error (RMSE) computed between simulations and measurements and expressed in percentage relative to the in vivo systolic values. Centerlines originate from the ascending aorta, toward the lower limb arteries (I), the right radial artery (II), and the LMCA (III).

Multi-scale coupling in fluid dynamics



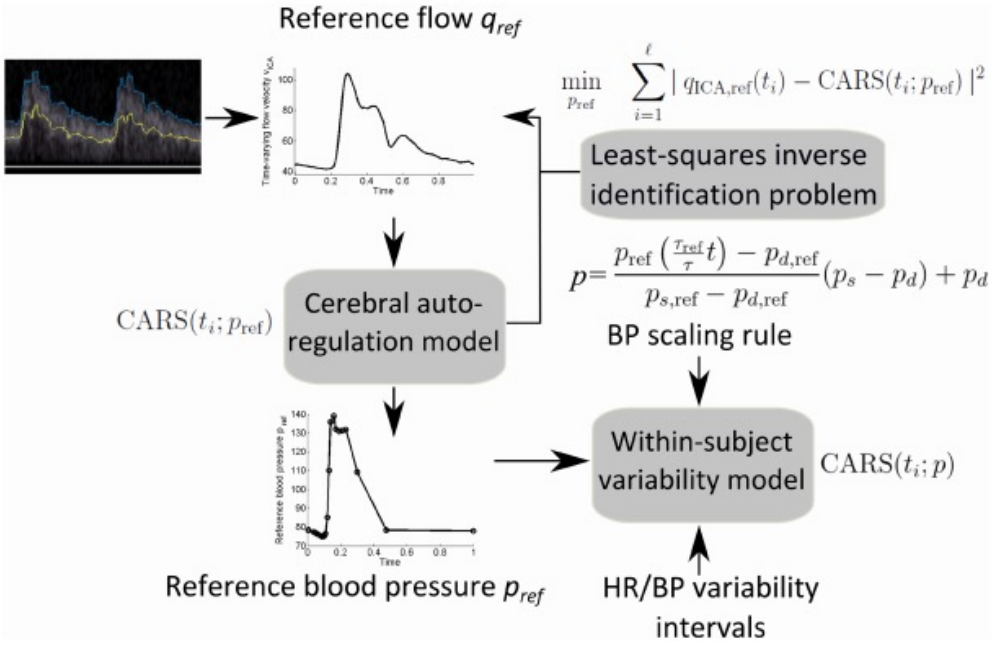


Liang F, Oshima M, Huang H, Liu H, Takagi S. Numerical Study of Cerebroarterial Hemodynamic Changes Following Carotid Artery Operation: A Comparison Between Multiscale Modeling and Stand-Alone Three-Dimensional Modeling. J Biomech Eng. 2015 Oct;137(10):101011. doi: 10.1115/1.4031457. PMID: 26343584.

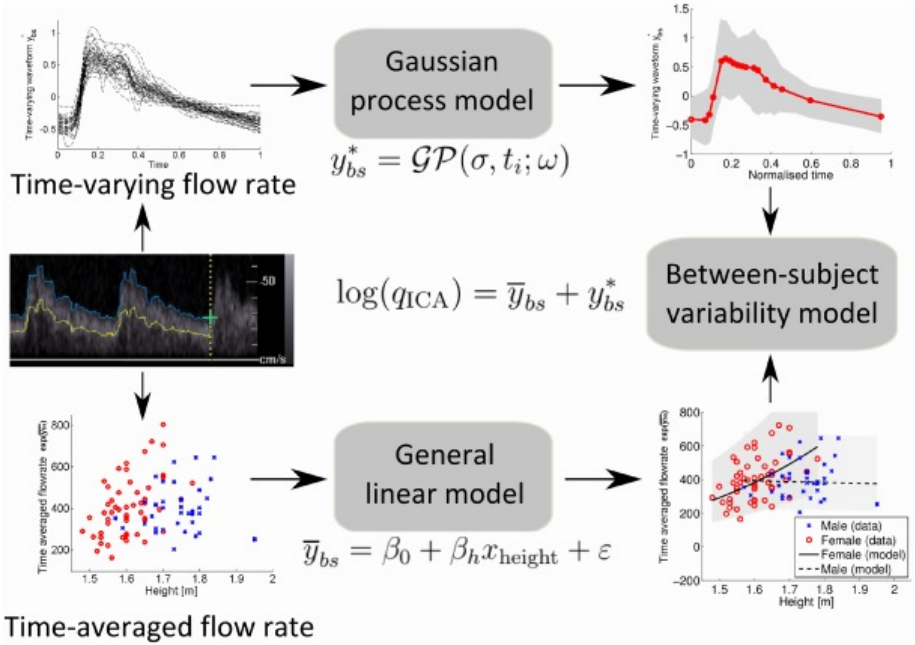
Physiological uncertainty and lifestyle variability– modelling

- Significant variability in intra- and inter-subject flow.
- Quantifying uncertainty in intra-aneurysmal blood flow amid systemic blood flow variability.
- Impact of ICA waveform variability on aneurysmal WSS vector field.

Intra-subject variability



Inter-subject variability

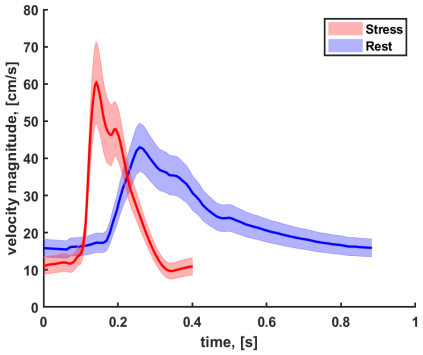


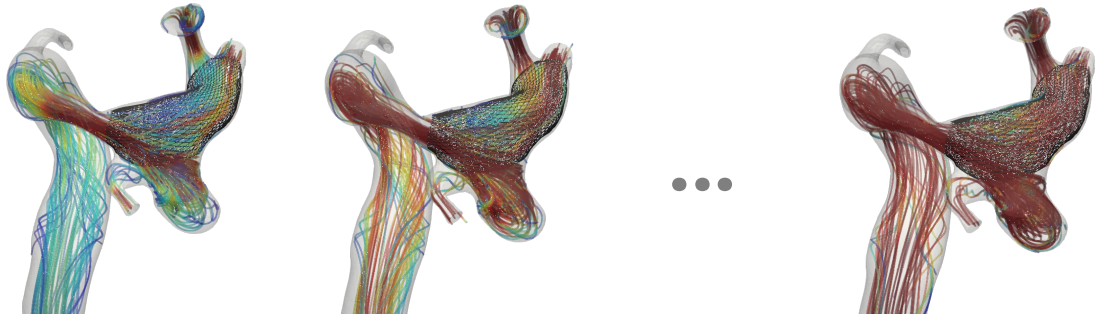
Lassila T, Sarrami-Foroushani A, Hejazi S, Frangi AF. Population-specific modelling of between/within-subject flow variability in the carotid arteries of the elderly. Int J Numer Method Biomed Eng. 2020 Jan;36(1):e3271
Sarrami-Foroushani A, Lassila T, Gooya A, Geers AJ, Frangi AF. Uncertainty quantification of wall shear stress in intracranial aneurysms using a data-driven statistical model of systemic blood flow variability. J Biomech. 2016 Dec 8;49(16):3815-3823.

Physiological uncertainty and lifestyle variability– modelling

Intra-subject variability

Why? Patient-specific flow/pressure measurements are not representative of physiological variability of the subject.

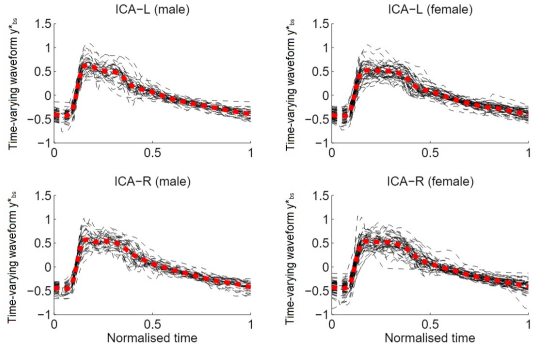


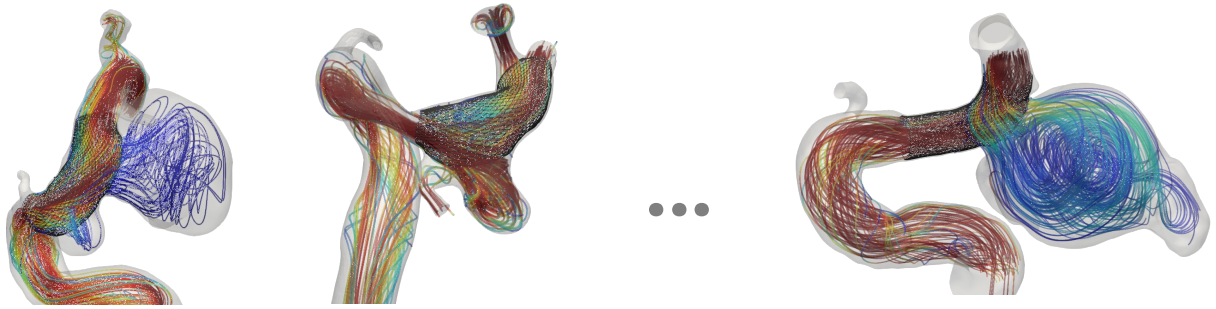


Stress level #1 Stress level #2 Stress level #M

Inter-subject variability

Why? Patient-specific flow/pressure measurements, if not impossible, are rarely available in the clinical routi



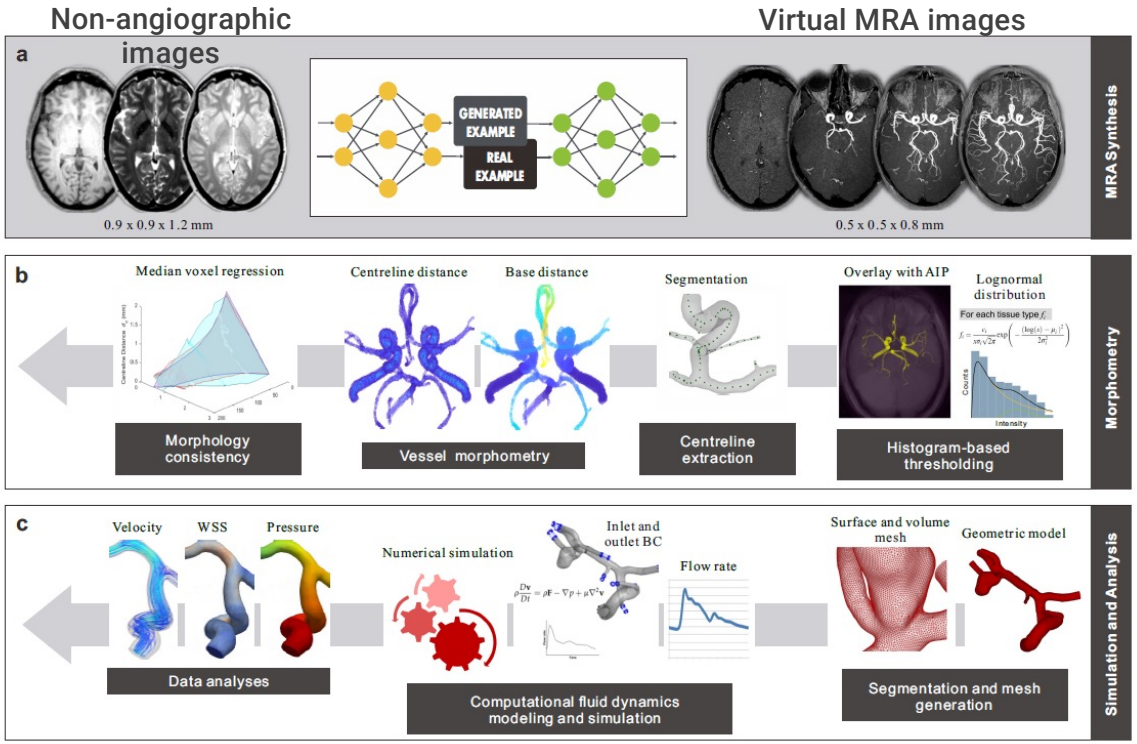


Patient #1 Patient #2 Patient #N

Lassila T, Sarrami-Foroushani A, Hejazi S, Frangi AF. Population-specific modelling of between/within-subject flow variability in the carotid arteries of the elderly. Int J Numer Method Biomed Eng. 2020 Jan;36(1):e3271
Sarrami-Foroushani A, Lassila T, Gooya A, Geers AJ, Frangi AF. Uncertainty quantification of wall shear stress in intracranial aneurysms using a data-driven statistical model of systemic blood flow variability. J Biomech. 2016 Dec 8;49(16):3815-3823.

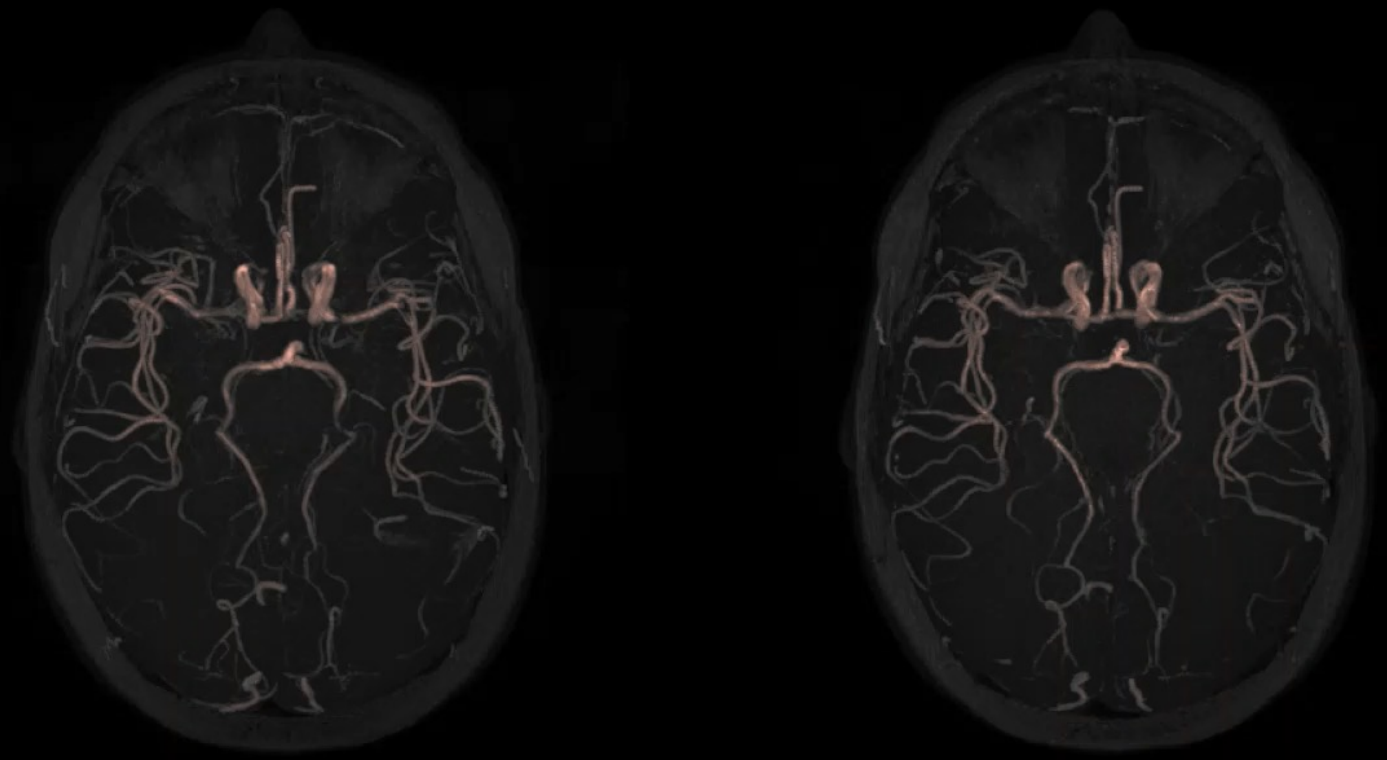
Virtual Populations from Virtual Imaging: Virtual Populations as a Synthesis Problem

- Generate virtual patients and digital twins of vascular anatomy at scale for use in *in silico* trials
- Very few large databases with imaging modalities (such as MRA) that enable quantitative characterisation of whole-brain vasculature and for haemodynamic analysis
- For instance, UK Biobank contains 40K brain MRI images but no angiograms available for building vascular models
- Create digital twin cohorts for UKB, whereby *in silico* trials be evaluated at scale



Xia Y, Ravikumar N, Lassila T, Frangi AF. Virtual high-resolution MR angiography from non-angiographic multi-contrast MRIs: synthetic vascular model populations for *in silico* trials. Med Image Anal. 2023 Jul;87:102814.

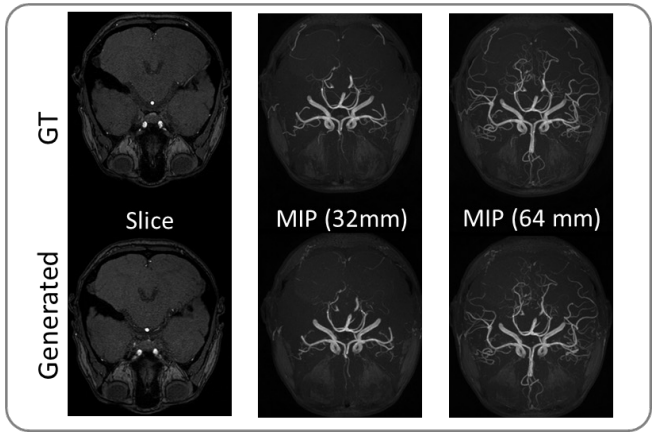
Turing Test – Which image is synthesised?

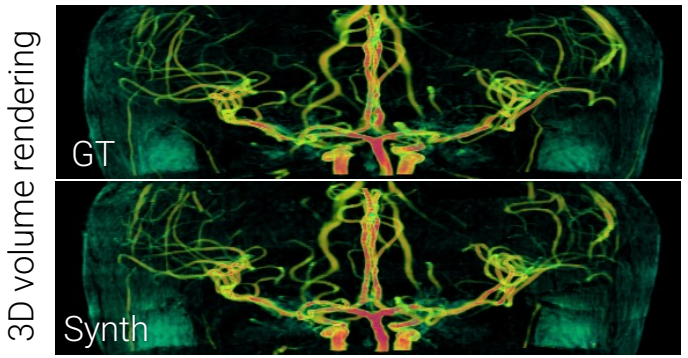


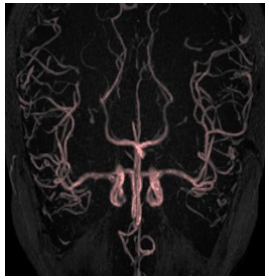
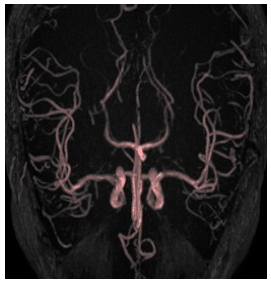
Synthetic

MRA Synthesis: Results

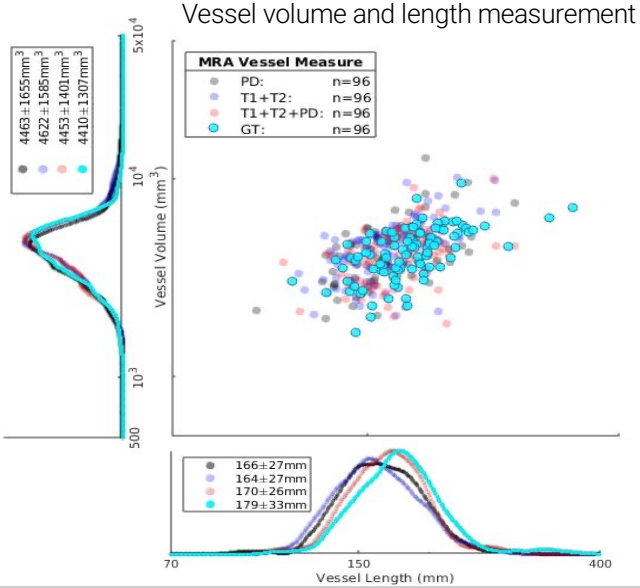
- IXI database: Training (N=300), Test (N=96)
- T1+T2+PD – best results
- T1+T2 (available in UKBB) – marginal decrease in MRA quality
- PD helps capture fine vessels





GT	From T1+T2+PD	From T1+T2	From PD
			
SSIM (96 samples)	0.868 ± 0.020	0.843 ± 0.021	0.822 ± 0.062

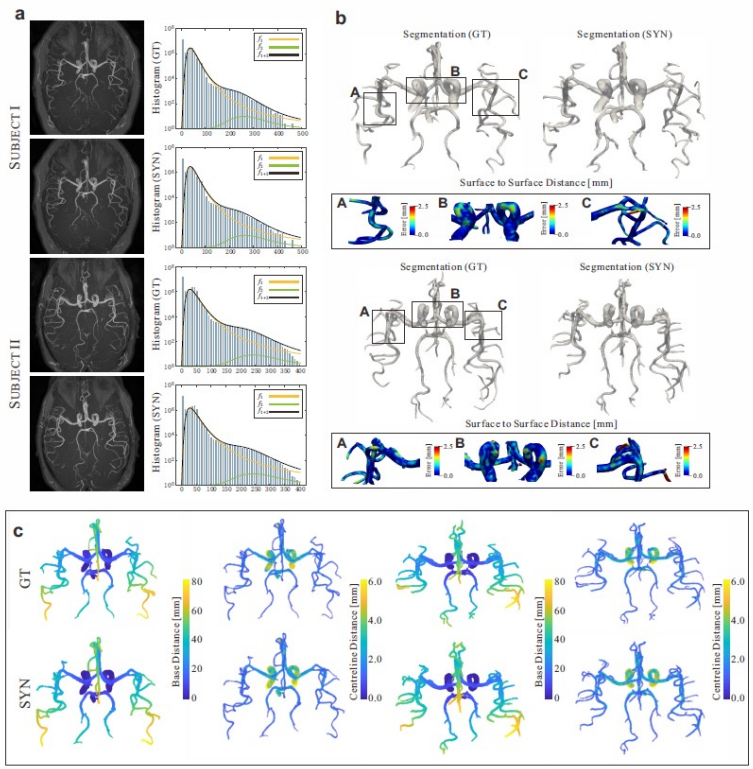
Vessel volume and length measurement



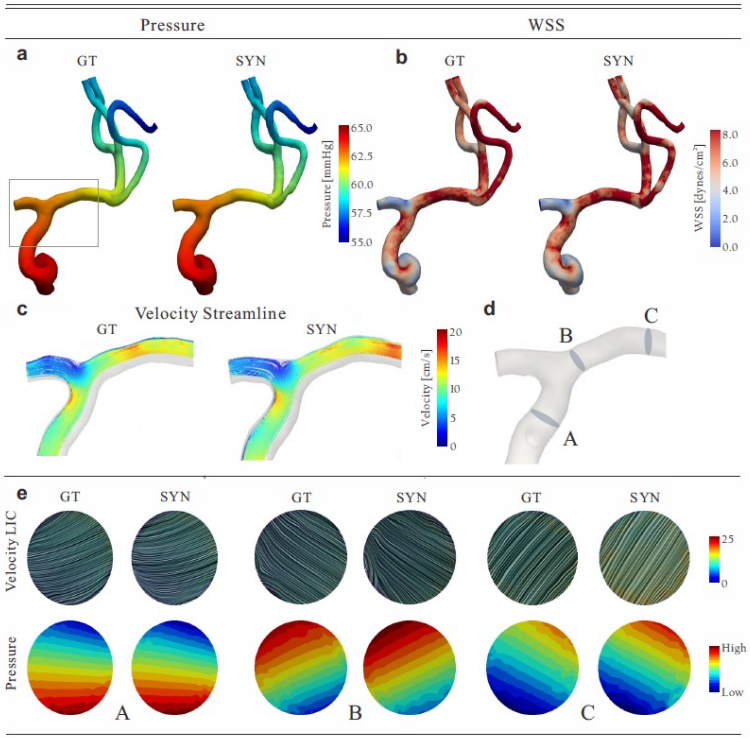
Xia Y, Ravikumar N, Lassila T, Frangi AF. Virtual high-resolution MR angiography from non-angiographic multi-contrast MRIs: synthetic vascular model populations for *in silico* trials. Med Image Anal. 2023 Jul;87:102814.

MRA Synthesis: Performance

- Preservation of key vascular morphological characteristics



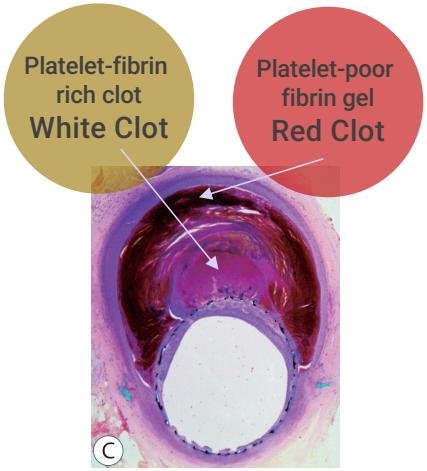
- Haemodynamic analysis: no significant differences between the real vascular geometries and synthesised ones
- This is the first study to show virtual patients can be used for CFD



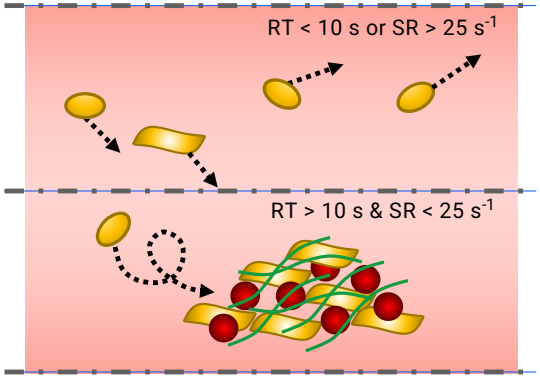
Xia Y, Ravikumar N, Lassila T, Frangi AF. Virtual high-resolution MR angiography from non-angiographic multi-contrast MRIs: synthetic vascular model populations for *in silico* trials. Med Image Anal. 2023 Jul;87:102814.

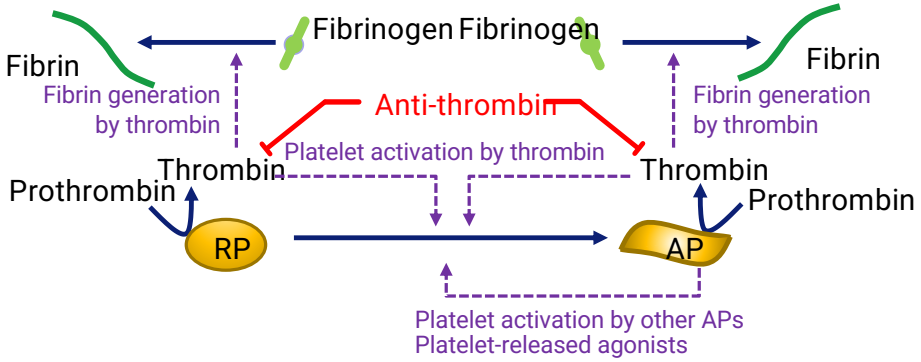
Thrombus formation in intracranial aneurysms – modelling

We developed a computational model to predict thrombus composition & stability (red/white) after flow diversion.



Model structure (thrombin generation, and inhibition, fibrin generation, platelet activation and aggregation)





Blood Flow – Navier-Stokes equations

$$\rho\frac{\partial u}{\partial t}+\rho(u.\nabla)u=-\nabla p+\mu\nabla^2 u-\mu\Phi(k_f,k_p)u$$

$$\Phi(k_f,k_p)=\frac{1}{k_{fi}}\phi_p^{fi}+\frac{1}{k_p}\phi_p^{bp}$$

Transport of coagulation factors and platelets – convection-diffusion-reaction equations:

$$\frac{\partial C_i}{\partial t}+u.\nabla C_i=D_i\nabla^2 C_i+S_i$$

FiPi evaluates the impact of post-flow diversion on platelet delivery to the clotting site for complete stagnation.

$$\mathbf{FiPi}=\frac{C^{BP}_{\text{Open system}}}{C^{BP}_{\text{Closed system}}}-1$$

$$\mathbf{FiPi}=\frac{C^{BP}}{C_0^{AP}+C_0^{RP}}-1$$

Sarrami-Foroushani A, Lassila T, Hejazi SM, Nagaraja S, Bacon A, Frangi AF. A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms. J Biomech. 2019 Jun 25;91:7-13.

Model complexity

The **thrombosis model** includes

17 primary parameters (Table 1), along with approximately
8 additional fixed constants, defined in the text for fluid properties and threshold functions.

Which are critical?

Sarrami-Foroushani A, Lassila T, Hejazi SM, Nagaraja S, Bacon A, Frangi AF. A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms. J Biomech. 2019 Jun 25;91:7-13. doi: 10.1016/j.jbiomech.2019.04.045.

Journal of Biomechanics 91 (2019) 7–13

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www.JBiomech.com



A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms

Ali Sarrami-Foroushani [a], Toni Lassila [a], Seyed Mostafa Hejazi [b], Sanjoy Nagaraja [c], Andrew Bacon [d], Alejandro F. Frangi [a,e,*]

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[b] Department of Electronic and Electrical Engineering, The University of Sheffield, Sheffield, UK
[c] Sheffield Teaching Hospitals, Sheffield, UK
[d] Department of Neurosurgery, Royal Hallamshire Hospital, Sheffield, UK
[e] Biomedical Imaging Department, Leeds Institute for Cardiovascular and Metabolic Medicine (LICAMM), School of Medicine, University of Leeds, Leeds, UK

ARTICLE INFO

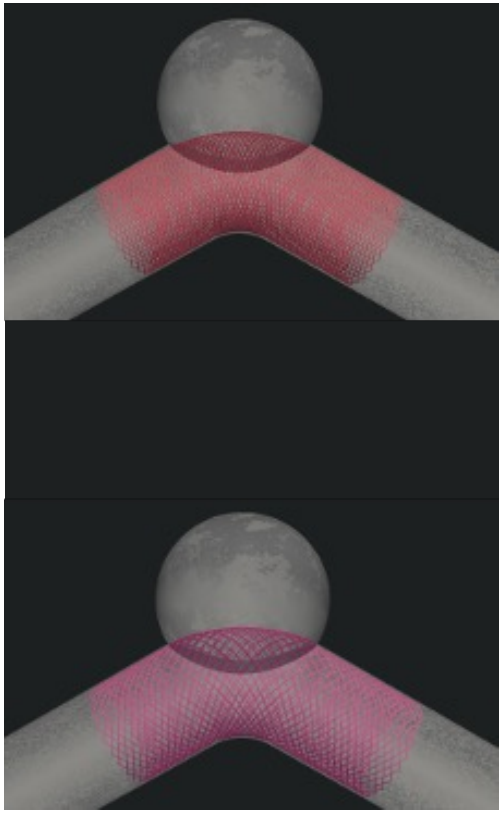
Article history:
Accepted 30 April 2019

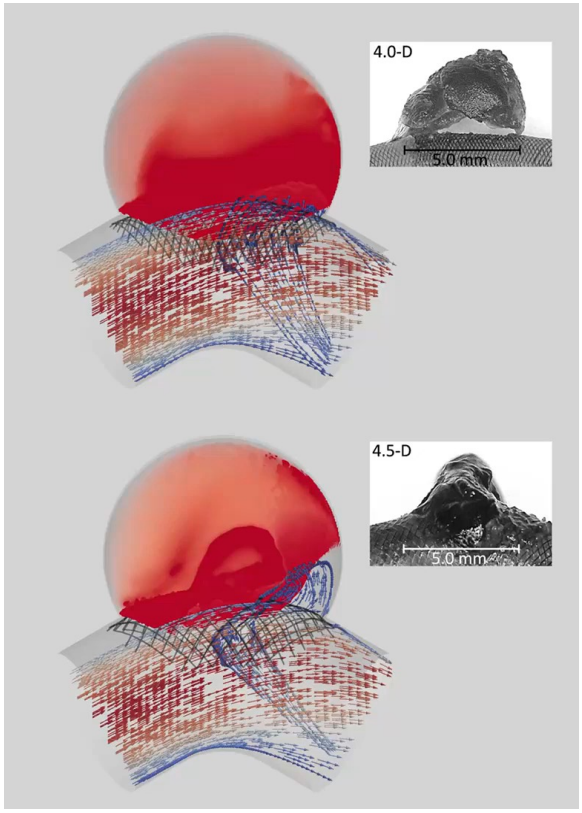
Keywords:
Flow diverter
Intracranial aneurysms
Thrombosis
Computational fluid dynamics

ABSTRACT

Treatment of intracranial aneurysms with flow-diverting stents is a safe and minimally invasive technique. The goal is stable embolisation that facilitates stent endothelialisation, and elimination of the aneurysm. However, it is not fully understood why some aneurysms fail to develop a stable clot even with sufficient levels of flow reduction. Computational prediction of thrombus formation dynamics can help predict the post-operative response in such challenging cases. In this work, we propose a new model of thrombus formation and platelet dynamics inside intracranial aneurysms. Our novel contribution combines platelet activation and transport with fibrin generation, which is key to characterising stable and unstable thrombus. The model is based on two types of thrombus inside aneurysms: red thrombus (fibrin- and erythrocyte-rich) can be found in unstable clots, while white thrombus (fibrin- and platelet-rich) can be found in stable clots. The thrombus generation model is coupled to a CFD model and the flow-induced platelet index (FiPi) is defined as a quantitative measure of clot stability. Our model is validated against an in vitro phantom study of two flow-diverting stents with different sizing. We demonstrate that our model accurately predicts the lower thrombus stability in the oversized stent scenario. This opens possibilities for using computational simulations to improve endovascular treatment planning and reduce adverse events, such as delayed haemorrhage of flow-diverted aneurysms.
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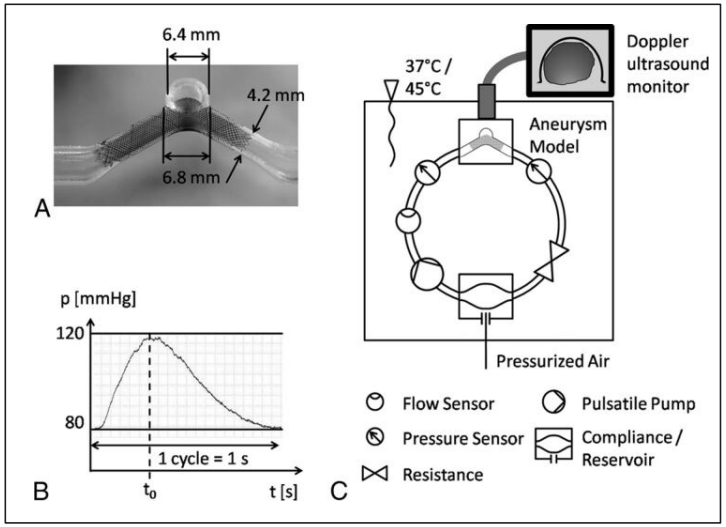
Thrombus formation: *in silico* prediction





White Clot

Red Clot



Gester K, Lüchtefeld I, Büsen M, Sonntag SJ, Linde T, Steinseifer U, Cattaneo G. In Vitro Evaluation of Intra-Aneurysmal, Flow-Diverter-Induced Thrombus Formation: A Feasibility Study. AJNR Am J Neuroradiol. 2016 Mar;37(3):490-6.

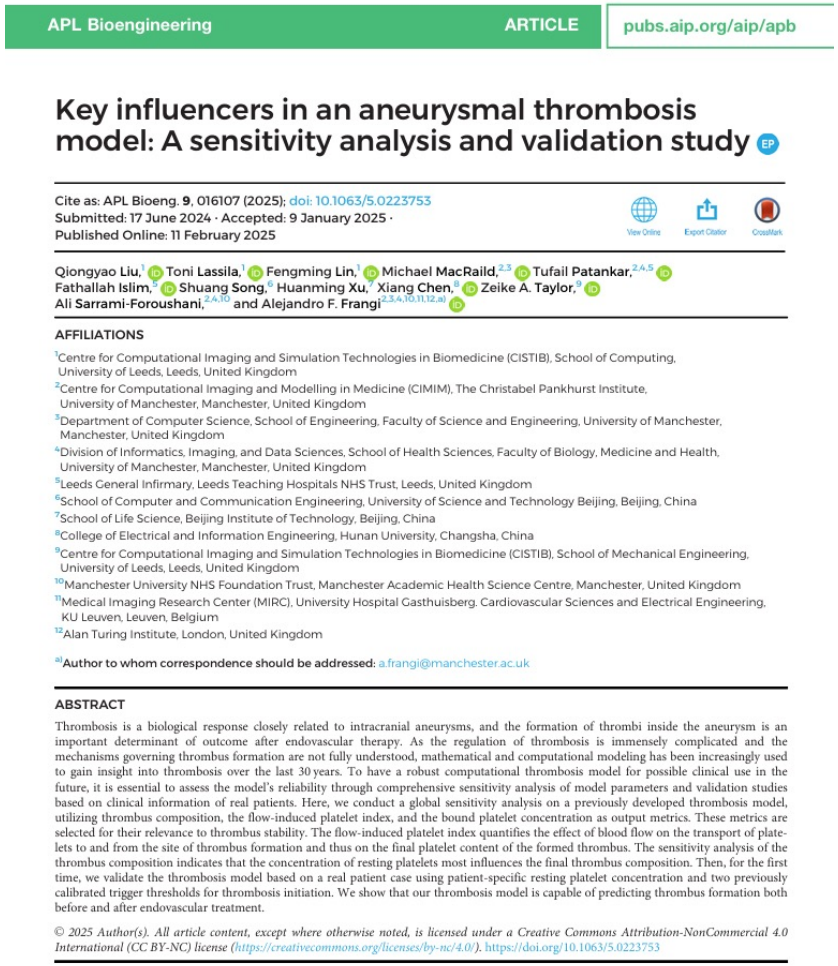
Sarrami-Foroushani A, Lassila T, Hejazi SM, Nagaraja S, Bacon A, Frangi AF. A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms. J Biomech. 2019 Jun 25;91:7-13.

Patient-Specific Aneurysmal Thrombosis Modelling for Clinical Application

- Our comprehensive sensitivity analysis of 31 parameters identified **resting platelet concentration as the most influential factor in aneurysmal thrombosis** modelling, highlighting its critical role in determining thrombus composition and stability.

- We **validated our thrombosis model using a patient-specific case**, successfully predicting thrombus formation both before treatment (spontaneous thrombosis) and after endovascular intervention (flow diverter and coiling), demonstrating the model's clinical relevance.

Liu Q, Lassila T, Lin F, MacRaild M, Patankar T, Islim F, Song S, Xu H, Chen X, Taylor ZA, Sarrami-Foroushani A, Frangi AF. Key influencers in an aneurysmal thrombosis model: A sensitivity analysis and validation study. APL Bioeng. 2025 Feb 11;9(1):016107.



APL Bioengineering ARTICLE pubs.aip.org/aip/apb

Key influencers in an aneurysmal thrombosis model: A sensitivity analysis and validation study

Cite as: APL Bioeng. 9, 016107 (2025); doi: 10.1063/5.0223753
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Published Online: 11 February 2025

Qiongyao Liu,[1] Toni Lassila,[1] Fengming Lin,[1] Michael MacRaild,[2,3] Tufail Patankar,[2,4,5] Fathallah Islim,[5] Shuang Song,[6] Huanming Xu,[7] Xiang Chen,[8] Zeike A. Taylor,[9] Ali Sarrami-Foroushani,[2,4,10] and Alejandro F. Frangi[2,3,4,10,11,12,a)]

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[12]Alan Turing Institute, London, United Kingdom

[a)]Author to whom correspondence should be addressed: a.frangi@manchester.ac.uk

ABSTRACT

Thrombosis is a biological response closely related to intracranial aneurysms, and the formation of thrombi inside the aneurysm is an important determinant of outcome after endovascular therapy. As the regulation of thrombosis is immensely complicated and the mechanisms governing thrombus formation are not fully understood, mathematical and computational modeling has been increasingly used to gain insight into thrombosis over the last 30 years. To have a robust computational thrombosis model for possible clinical use in the future, it is essential to assess the model's reliability through comprehensive sensitivity analysis of model parameters and validation studies based on clinical information of real patients. Here, we conduct a global sensitivity analysis on a previously developed thrombosis model, utilizing thrombus composition, the flow-induced platelet index, and the bound platelet concentration as output metrics. These metrics are selected for their relevance to thrombus stability. The flow-induced platelet index quantifies the effect of blood flow on the transport of platelets to and from the site of thrombus formation and thus on the final platelet content of the formed thrombus. The sensitivity analysis of the thrombus composition indicates that the concentration of resting platelets most influences the final thrombus composition. Then, for the first time, we validate the thrombosis model based on a real patient case using patient-specific resting platelet concentration and two previously calibrated trigger thresholds for thrombosis initiation. We show that our thrombosis model is capable of predicting thrombus formation both before and after endovascular treatment.

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Parameter Space Compression – model parsimony

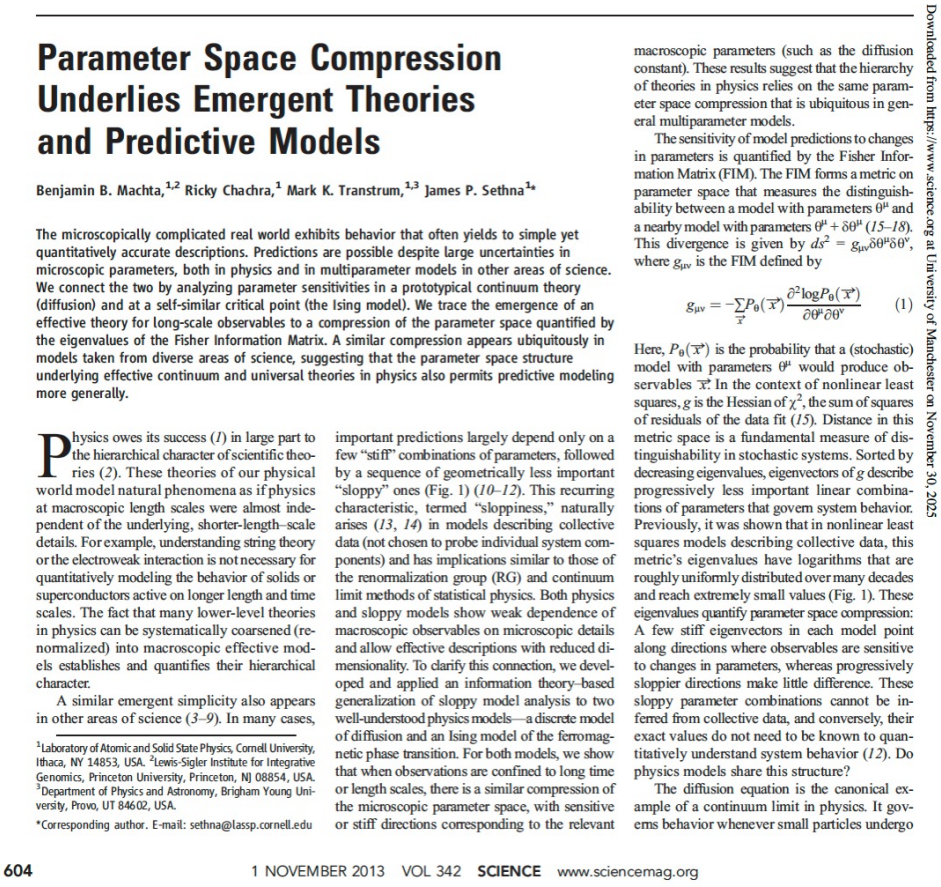
Core Principle: Stiff vs Sloppy Parameters

In many complex multiparameter models (both in physics and other sciences like biology), system behaviour often depends strongly on only a few "*stiff*" combinations of parameters, while being largely insensitive to many other "*sloppy*" directions.

- **Stiff Parameters:** A small number of parameter combinations that dictate the macroscopic behaviour (e.g., diffusion constant, net drift).
- **Sloppy Parameters:** A vast number of parameter combinations that have little to no effect on the observable outcomes (e.g., microscopic details of particle collisions)

Geometric Interpretation via Fisher Information

The **Fisher Information Matrix (FIM)** acts as a Riemannian metric on the parameter space, measuring how distinguishable a model is from a nearby model when parameters change. The eigenvalue spectrum of the FIM quantifies the "importance" of different parameter directions.



Parameter Space Compression Underlies Emergent Theories and Predictive Models

Benjamin B. Machta,[1,2] Ricky Chachra,[1] Mark K. Transtrum,[1,3] James P. Sethna[1]*

The microscopically complicated real world exhibits behavior that often yields to simple yet quantitatively accurate descriptions. Predictions are possible despite large uncertainties in microscopic parameters, both in physics and in multiparameter models in other areas of science. We connect the two by analyzing parameter sensitivities in a prototypical continuum theory (diffusion) and at a self-similar critical point (the Ising model). We trace the emergence of an effective theory for long-scale observables to a compression of the parameter space quantified by the eigenvalues of the Fisher Information Matrix. A similar compression appears ubiquitously in models taken from diverse areas of science, suggesting that the parameter space structure underlying effective continuum and universal theories in physics also permits predictive modeling more generally.

Physics owes its success (*1*) in large part to the hierarchical character of scientific theories (*2*). These theories of our physical world model natural phenomena as if physics at macroscopic length scales were almost independent of the underlying, shorter-length–scale details. For example, understanding string theory or the electroweak interaction is not necessary for quantitatively modeling the behavior of solids or superconductors active on longer length and time scales. The fact that many lower-level theories in physics can be systematically coarsened (renormalized) into macroscopic effective models establishes and quantifies their hierarchical character.

A similar emergent simplicity also appears in other areas of science (*3*–*9*). In many cases, important predictions largely depend only on a few "stiff" combinations of parameters, followed by a sequence of geometrically less important "sloppy" ones (Fig. 1) (*10*–*12*). This recurring characteristic, termed "sloppiness," naturally arises (*13*, *14*) in models describing collective data (not chosen to probe individual system components) and has implications similar to those of the renormalization group (RG) and continuum limit methods of statistical physics. Both physics and sloppy models show weak dependence of macroscopic observables on microscopic details and allow effective descriptions with reduced dimensionality. To clarify this connection, we developed and applied an information theory–based generalization of sloppy model analysis to two well-understood physics models—a discrete model of diffusion and an Ising model of the ferromagnetic phase transition. For both models, we show that when observations are confined to long time or length scales, there is a similar compression of the microscopic parameter space, with sensitive or stiff directions corresponding to the relevant macroscopic parameters (such as the diffusion constant). These results suggest that the hierarchy of theories in physics relies on the same parameter space compression that is ubiquitous in general multiparameter models.

The sensitivity of model predictions to changes in parameters is quantified by the Fisher Information Matrix (FIM). The FIM forms a metric on parameter space that measures the distinguishability between a model with parameters θ^μ and a nearby model with parameters $\theta^\mu + \delta\theta^\mu$ (*15*–*18*). This divergence is given by $ds^2 = g_{\mu\nu}\delta\theta^\mu\delta\theta^\nu$, where $g_{\mu\nu}$ is the FIM defined by

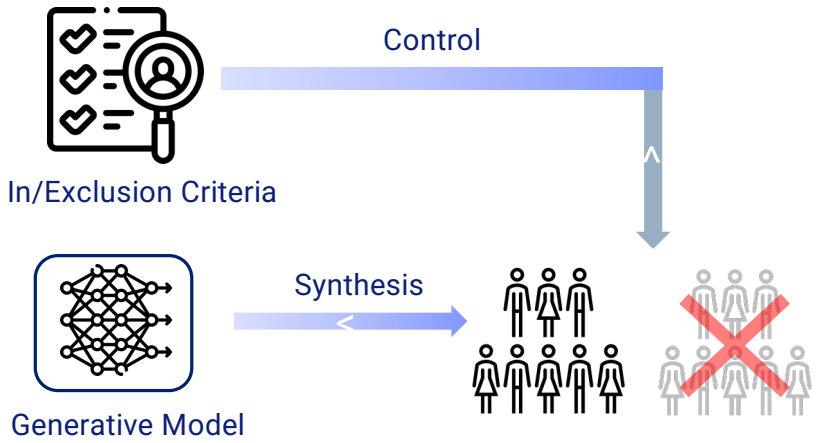
$$g_{\mu\nu} = -\sum_{\vec{x}} P_\theta(\vec{x}) \frac{\partial^2 \log P_\theta(\vec{x})}{\partial\theta^\mu \partial\theta^\nu} \quad (1)$$

Here, $P_\theta(\vec{x})$ is the probability that a (stochastic) model with parameters θ^μ would produce observables $\vec{x}$. In the context of nonlinear least squares, g is the Hessian of χ^2, the sum of squares of residuals of the data fit (*15*). Distance in this metric space is a fundamental measure of distinguishability in stochastic systems. Sorted by decreasing eigenvalues, eigenvectors of g describe progressively less important linear combinations of parameters that govern system behavior. Previously, it was shown that in nonlinear least squares models describing collective data, this metric's eigenvalues have logarithms that are roughly uniformly distributed over many decades and reach extremely small values (Fig. 1). These eigenvalues quantify parameter space compression: A few stiff eigenvectors in each model point along directions where observables are sensitive to changes in parameters, whereas progressively sloppier directions make little difference. These sloppy parameter combinations cannot be inferred from collective data, and conversely, their exact values do not need to be known to quantitatively understand system behavior (*12*). Do physics models share this structure?

The diffusion equation is the canonical example of a continuum limit in physics. It governs behavior whenever small particles undergo

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*Corresponding author. E-mail: sethna@lassp.cornell.edu

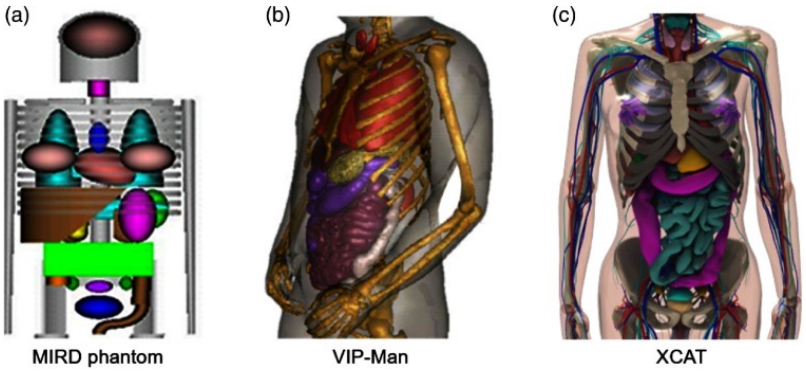
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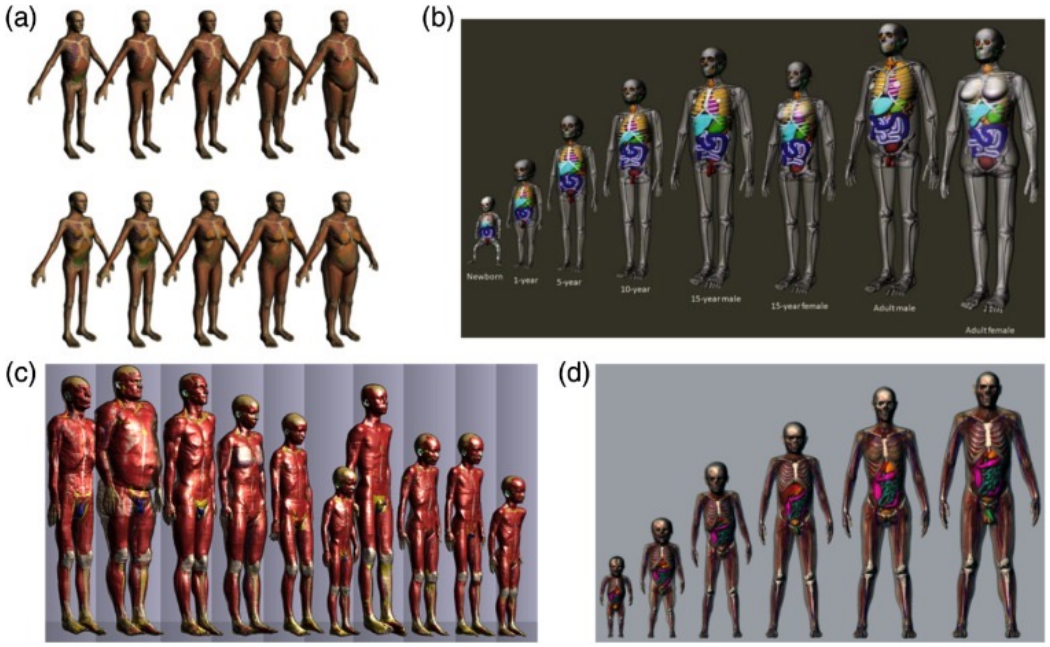
Where alternative AI meets *in silico* evidence/trials

BUILDING SYNTHETIC PATIENTS AND VIRTUAL POPULATIONS

Digital Twins, Virtual Patients, Virtual Populations Trials



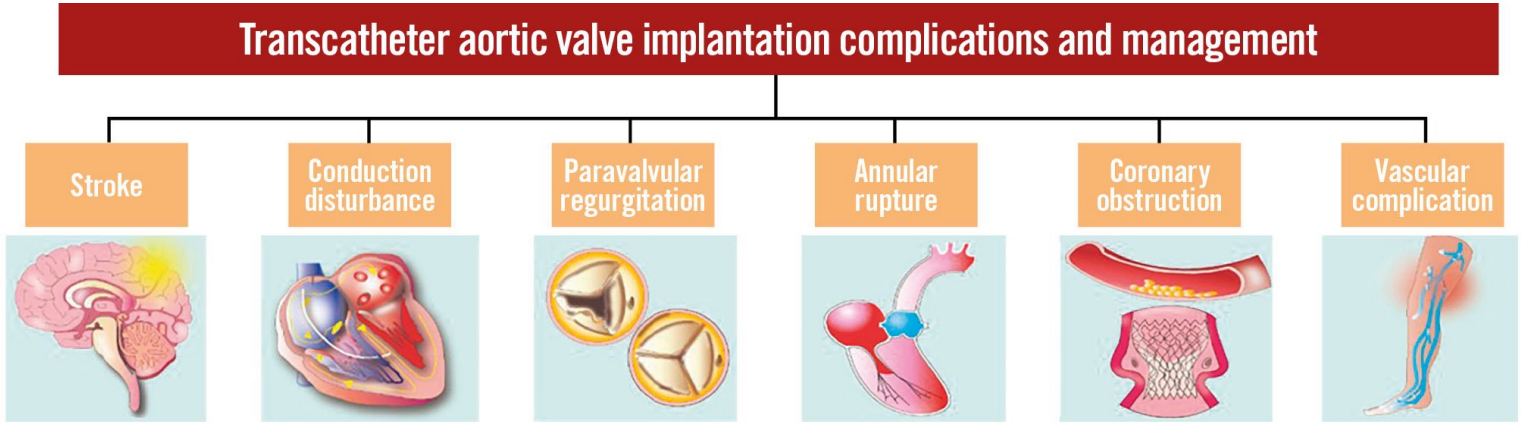
Three main categories of computational phantoms: (a) mathematical based on equations or geometric primitives, (b) voxelized based on segmented imaging data, and (c) BREP based on segmented data but fitting high-level surfaces to the structures. The MIRD[5] VIP-Man[6] and XCAT[7] phantoms are shown as examples.

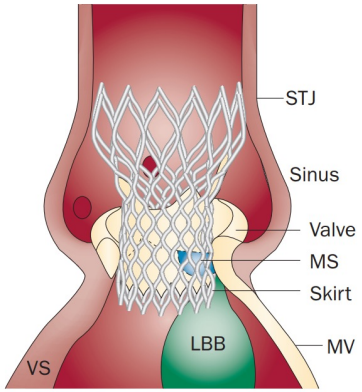


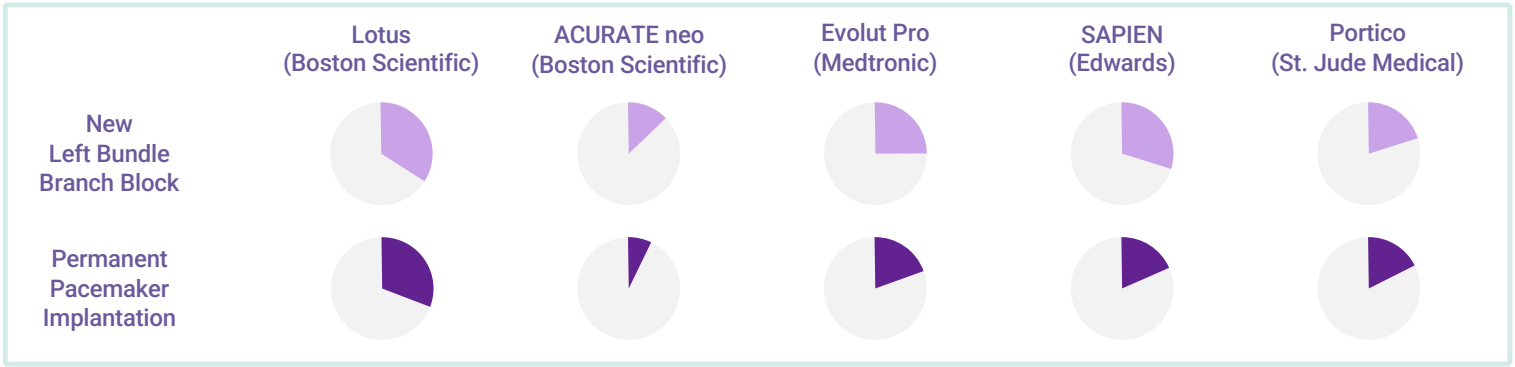
Example whole-body phantoms developed by (a) RPI, (b) UF/NCI, (c) IT'IS, and (d) the XCAT series developed by Duke and JHU.

Abadi E, Segars WP, Tsui BMW, Kinahan PE, Bottenus N, Frangi AF, Maidment A, Lo J, Samei E. Virtual clinical trials in medical imaging: a review. J Med Imaging (Bellingham). 2020 Jul;7(4):042805. doi: 10.1117/1.JMI.7.4.042805.

Complications caused by TAVI devices

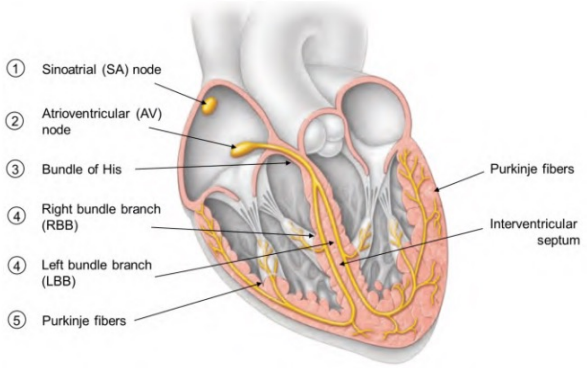




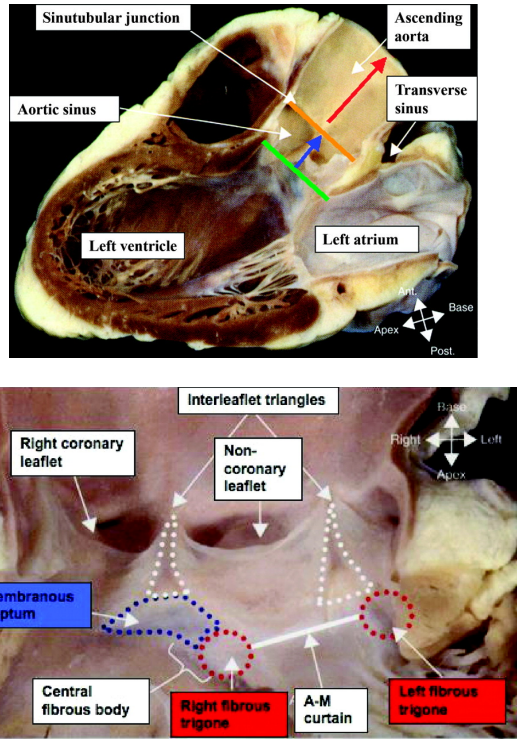


Bansal, A. et al., 2025. *EuroIntervention*, **21**(8), pp.e390-e410. Van der Boon R. M. et al., 2012. *Nature Review Cardiology*, **9**, pp.454-463.

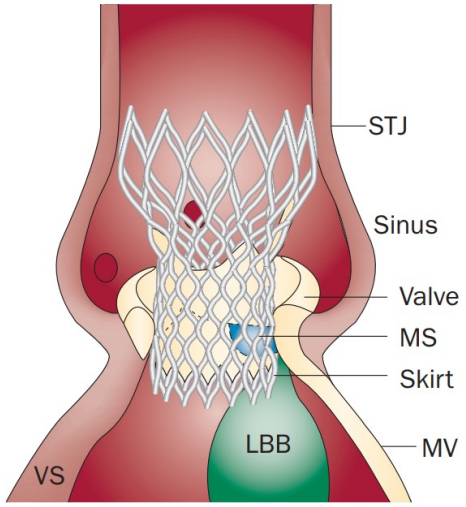
The contact injury to the conduction tissue as a potential cause of conduction abnormalities (CAs) after TAVI



Cardiac conduction system (Marieb and Hoehn, 2007)



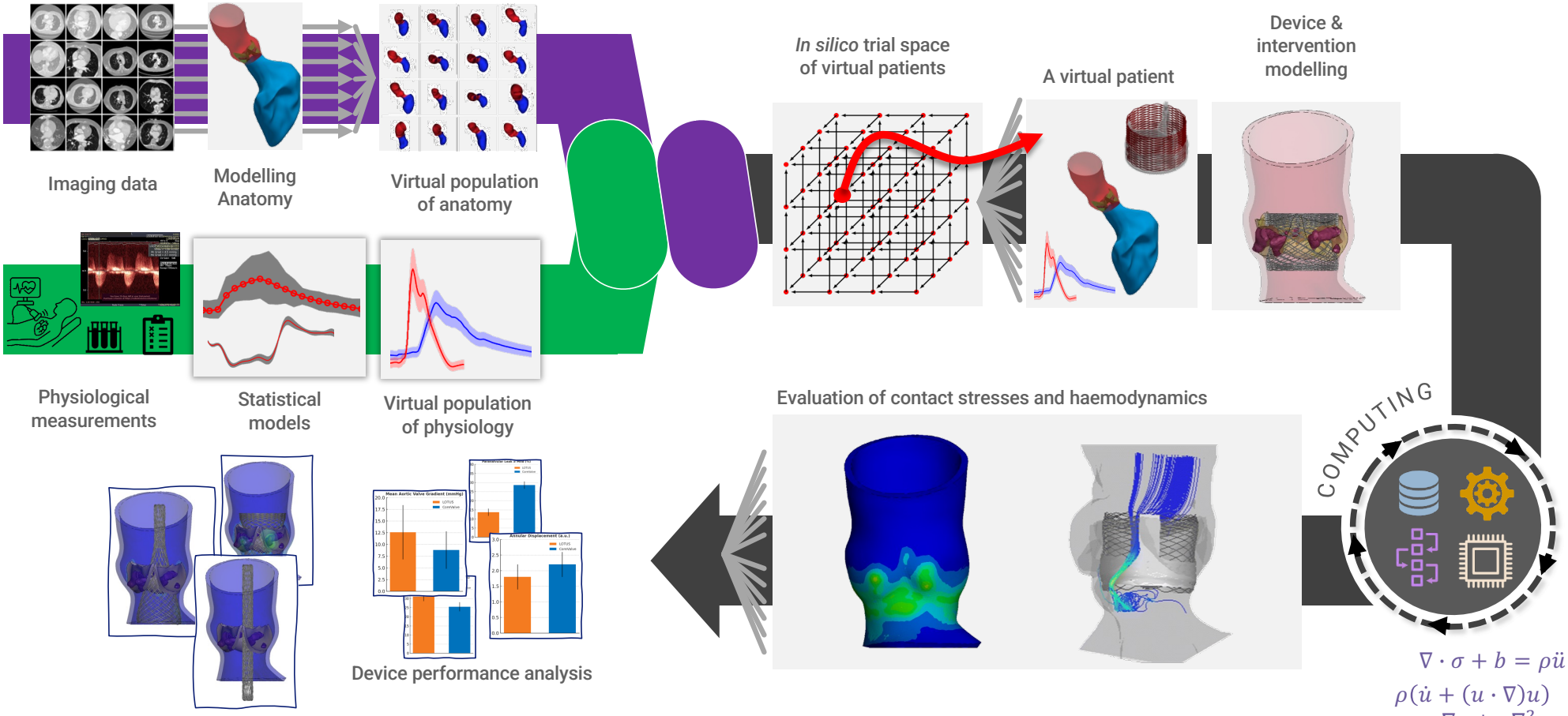
Views of the aortic root anatomy, where the conduction system is close to the blue region (Piazza et al., 2008).



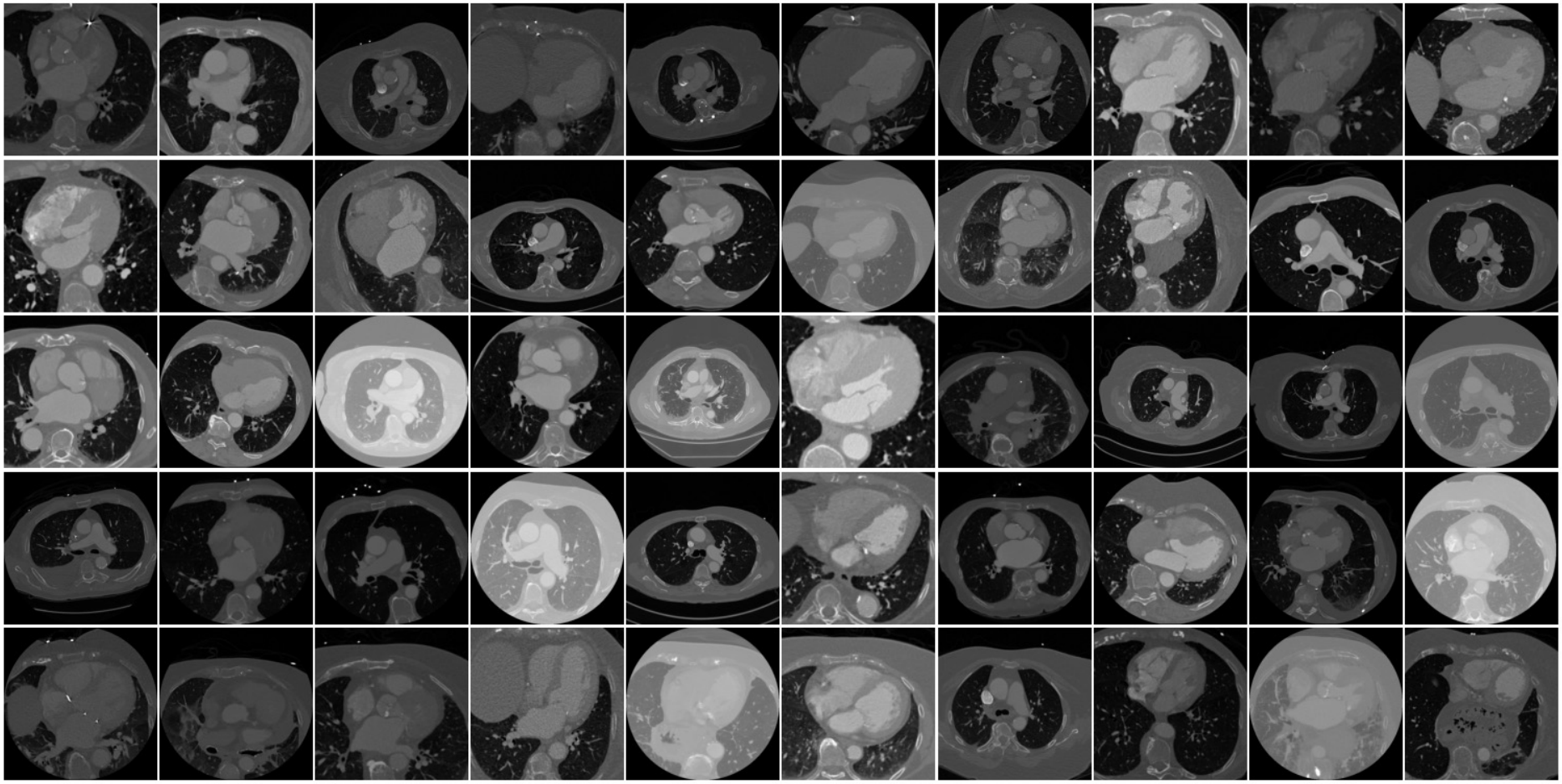
(Van der Boon et al., 2012)

Marieb, E. N. and Hoehn, K., 2007. *Human anatomy & physiology*. Pearson education. Piazza, N. et al., 2008. *Circulation: Cardiovascular Interventions*, 1, pp.74-81. Van der Boon R. M. et al., 2012. *Nature Review Cardiology*, 9, pp.454-463.

TAVI simulation pipeline



3D CTA images from RCT (50 cases)

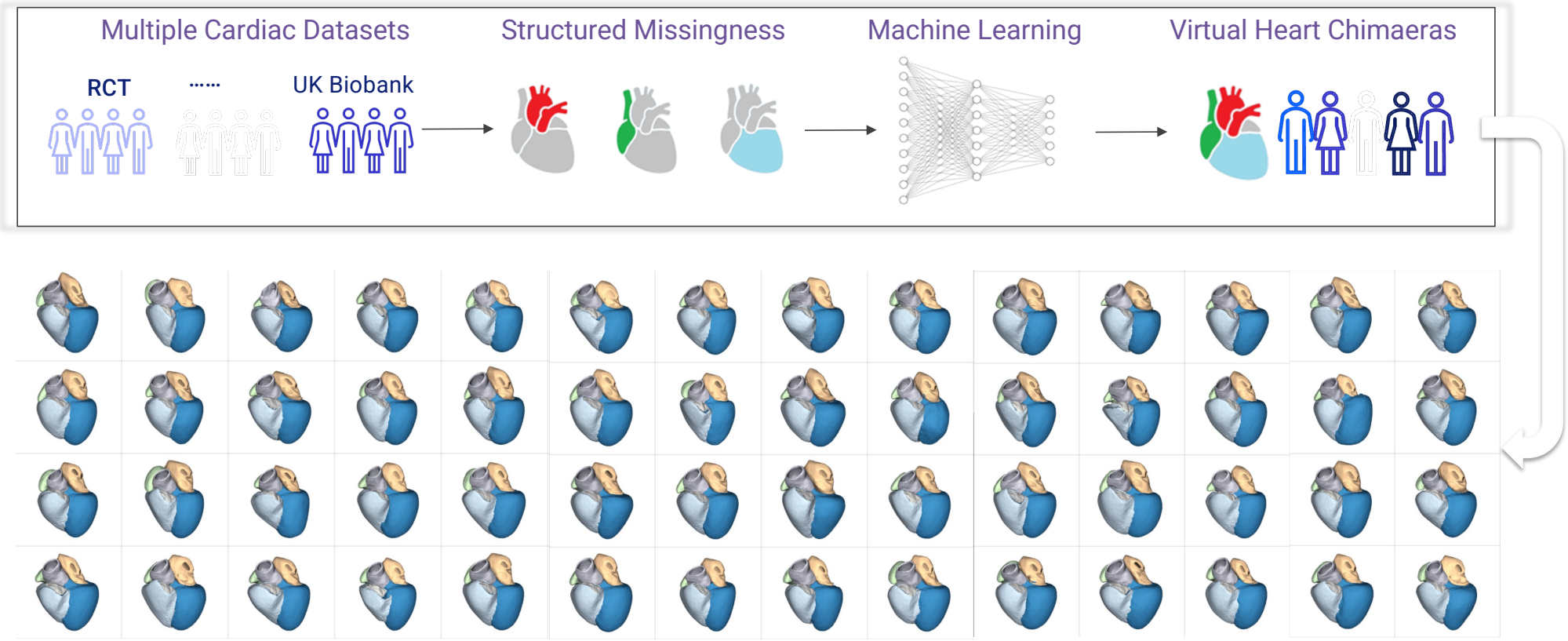


Feldman, T.E. et al., 2018. *JAMA*, **319**(1), pp.27-37.

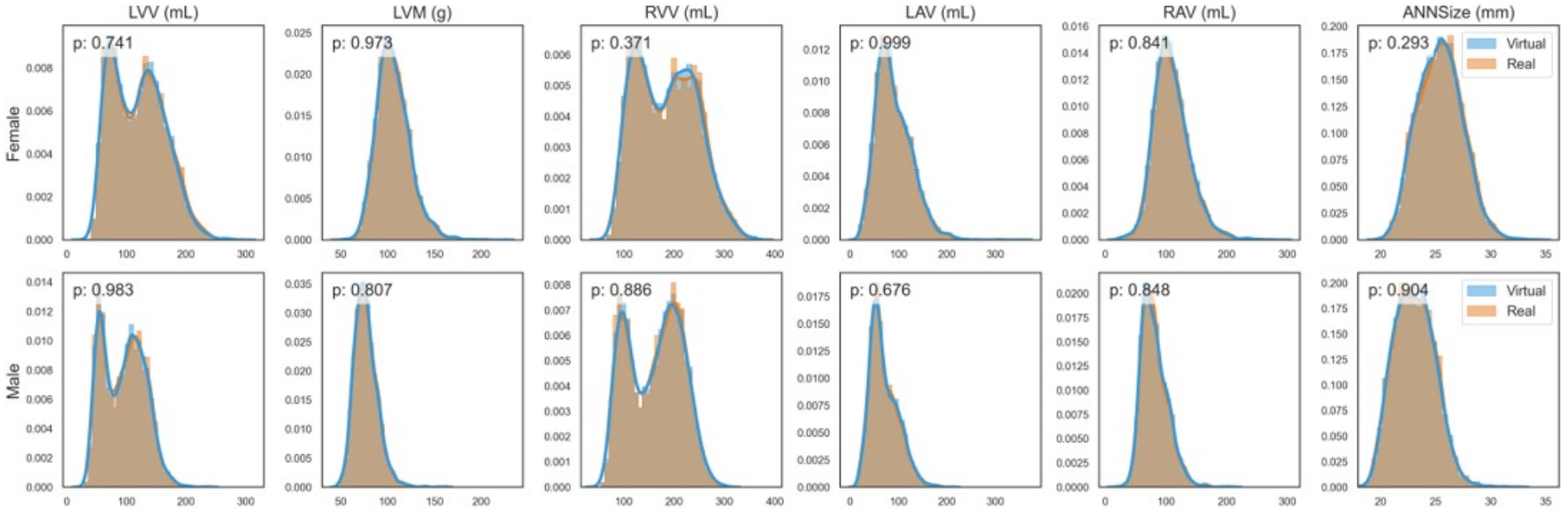
Digital twins for RCT (same 50 cases)



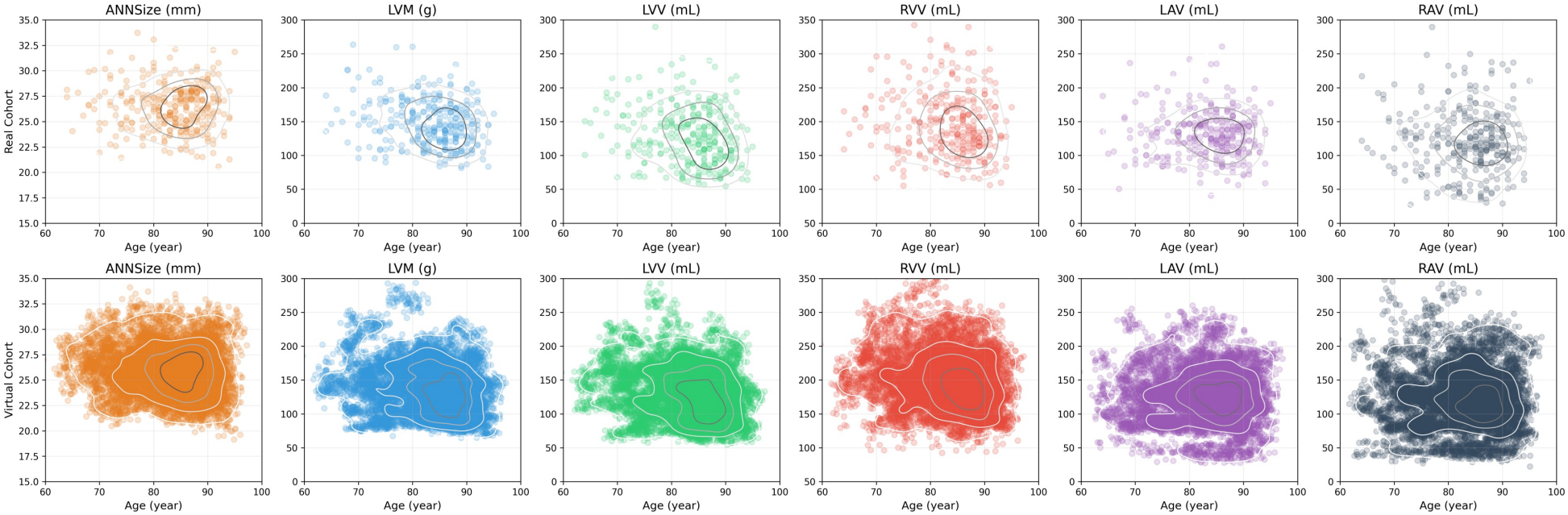
Populations of Virtual Chimeras - The Concept



Probability Distribution: synthesis vs real – UKBB



Probability Distribution: synthesis vs real – RCT

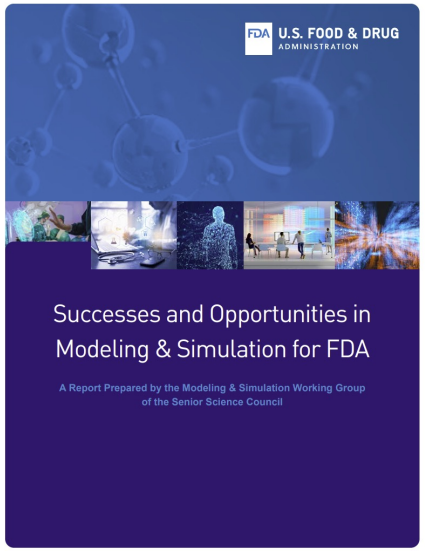


From Science to Policy: Cross-sector Collaboration and Cocreation

BUILDING TRUST WITHIN COMPLEX SYSTEMS

International regulators – Ready for prime time?





"**Model-informed [product] development** is the way of the future [at FDA]! […]
Modelling will become the leading science."

— *Food & Drug Administration, Dr Patrizia Cavazzoni*



Wadman M. FDA no longer has to require animal testing for new drugs. *Science*. 2023 Jan 13;379(6628):127-128.



NEWS | IN DEPTH

ANIMAL RESEARCH

FDA no longer has to require animal testing for new drugs

Agency can rely on animal-free alternatives before human trials

By **Meredith Wadman**

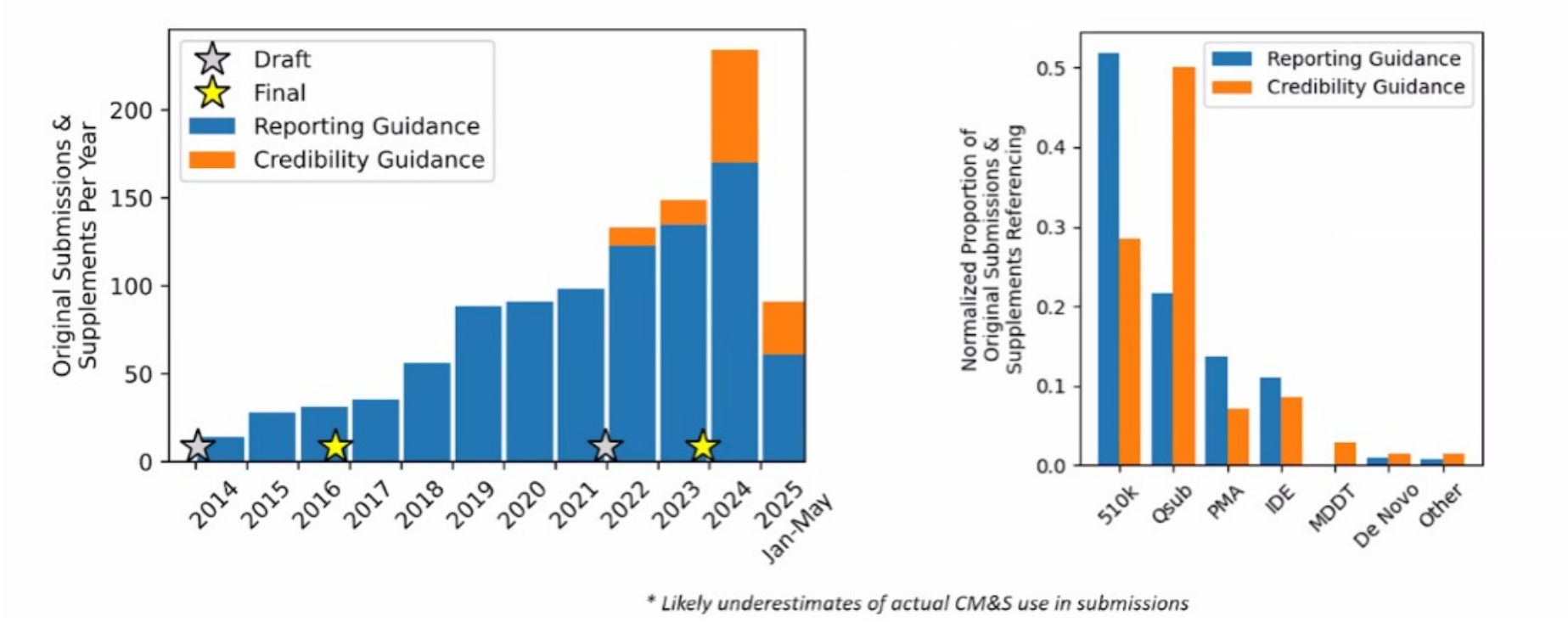
New medicines need not be tested in animals to receive U.S. Food and Drug Administration (FDA) approval, according to legislation signed by President Joe Biden in late December 2022. The change—long sought by animal welfare organizations—could signal a major shift away from animal use after more than 80 years of drug safety regulation.

"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

In place of the 1938 stipulation that potential drugs be tested for safety and

CM&S in FDA Regulatory Submissions

FDA Guidances' Citations and Uptake



Source: Presentation at the 2025 Virtual Human Global Summit, Pras Pathmanathan, FDA

UK CEiRSI Community of Interest

Medical Devices & Pharmaceutical Companies

Medtronic · Boston Scientific · stryker · PHILIPS · element · AstraZeneca · GSK · ZIMMER BIOMET Moving You Forward. · Edwards · ucb Pharma · SIEMENS Healthineers · varian · apc · GRAU INNOVATIVE METALLE · AMBER THERAPEUTICS · IMPULSE DYNAMICS · MatOrtho · ResMed · DePuy Synthes · Elekta

CEiRSI

Centre of Excellence on in-silico Regulatory Science & Innovation

Supply Chain

Ansys · aws · IBM · DASSAULT SYSTEMES · adsilico · ddn · ALTAIR · NVIDIA · Exponent · CERTARA · Simcyp · esqLABS WE EMPOWER HEALTH CARE · SYNOPSYS

Catalysts

INDUSTRIAL BIOTECHNOLOGY INNOVATION CATALYST · TURING INNOVATION CATALYST MANCHESTER · HIRANI

Capital

LocalGlobe · praetura VENTURES · Albion Capital · NORTHERN GRITSTONE THE VALUE OF IDEAS

Consultant

KPMG · MILLS & REEVE Achieve more. Together. · NEXER · RLS

Funders, Charities & Academies

UKRI Innovate UK · UKRI Engineering and Physical Sciences Research Council · UKRI Medical Research Council · NIHR National Institute for Health Research · NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research · British Heart Foundation · CANCER RESEARCH UK · Royal Academy of Engineering · The Royal Society of Medicine

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NHS England · HDRUK Health Data Research UK · ukbiobank Enabling scientific discoveries that improve human health · GM Care Record · We are better together · North West SECURE DATA ENVIRONMENT · NHS Great Ormond Street Hospital for Children NHS Foundation Trust · bsci · WOMEN'S & REPRODUCTIVE HEALTH · Manchester Rare Conditions Centre · NICOR · NHS Greater Manchester · NHS Manchester University NHS Foundation Trust · National Joint Registry · NHS Nottingham University Hospitals NHS Trust · NHS Oxford University Hospital NHS Foundation Trust · NHS Barts Health NHS Trust · MIDLANDS HEALTH ALLIANCE · Health Innovation Manchester · nhsa A Health Partnership for Northern England

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MANCHESTER 1824 The University of Manchester · HENRY ROYCE INSTITUTE · CANCER RESEARCH UK Manchester Centre · University of York · UCL · THE UNIVERSITY of EDINBURGH · University of OXFORD · University of Nottingham UK | CHINA | MALAYSIA · Queen Mary University of London · Swansea University Prifysgol Abertawe · UNIVERSITY of LIVERPOOL · University of Sheffield · AMRC ADVANCED MANUFACTURING RESEARCH CENTRE · UNIVERSITY OF SURREY · UNIVERSITY OF LEEDS · University of Strathclyde Glasgow · UNIVERSITY OF BIRMINGHAM · cpi · NIHR Leicester Biomedical Research Centre · NIHR HealthTech Research Centre Accelerated surgical care · NIHR Greater Manchester Patient Safety Research Collaboration · NIHR Barts Biomedical Research Centre · NIHR Manchester Biomedical Research Centre · Ollscoil na Gaillimhe University of Galway · Duke · UNIVERSITY OF MARYLAND · AUCKLAND BIOENGINEERING INSTITUTE · Fraunhofer IMTE · CERSI · CERSI University of Maryland · DTNet · UNDERSTANDING THE Physics of Life · BIOREME

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ABHI HealthTech for Life · NAFEMS · abpi Bringing medicines to life · techUK FOR WHAT COMES NEXT · I·M3 Institute of Materials, Minerals & Mining · bionow · CRITICAL PATH INSTITUTE · MDIC Medical Device Innovation Consortium · Avicenna Alliance Association for Data Driven Medicine · VPH Institute Building the Virtual Physiological Human · TOPRA

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MHRA · NHS Health Research Authority · NICE · Department for Science, Innovation, & Technology · Department of Health & Social Care · Office for Life Sciences · Office for Product Safety & Standards · Food Standards Agency · HSE · UK Health Security Agency · GMCA GREATER MANCHESTER COMBINED AUTHORITY · NPL · TEAM AB · TÜV SÜD · bsi. · intertek Total Quality. Assured. · FDA U.S. FOOD & DRUG ADMINISTRATION · ASME SETTING THE STANDARD · ISO · IEC

Mapping Sector's Barriers

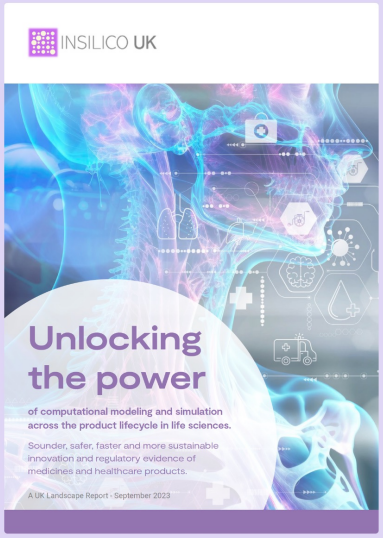
InSilicoUK Pro-Innovation Regulations Network

Unlocking the power of computational modelling and simulation across the product lifecycle in life sciences

A UK Landscape Report

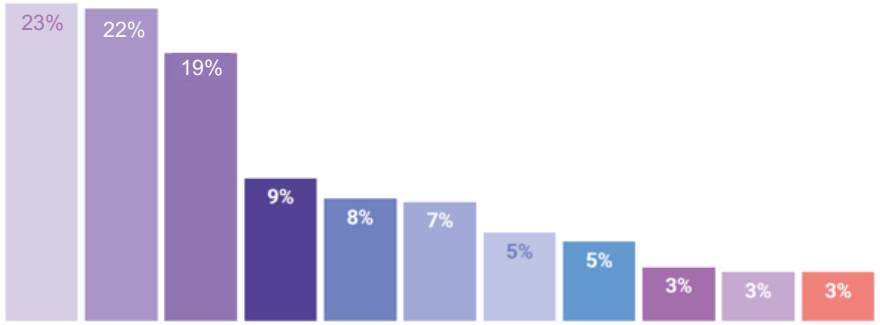
This report

- Outlines the public health and economic benefits of using in silico technologies (ISTs) to refine, reduce, and even replace the need for conventional human clinical trials and animal and physical testing in the development of new medical products,
- Describes current barriers to the expanded use of ISTs,
- Identifies opportunities for the UK to spearhead the global effort to develop ISTs, making the UK a leader in the field and, therefore, friendly to inward investors,
- Details the significant commercial and economic benefits in the development of the UK life sciences sector and broader societal benefits to the NHS, UK, and the world in general,
- Makes recommendations on how the UK government can support this initiative.



Frangi, A., Denison, T., Myles, P., Ordish, J., Brown, P., Turpin, R., Kipping, M., Palmer, M., Flynn, D., Afshari, P., Lane, C., de Cunha, M., Horner, M., Levine, S., Marchal, T., Bryan, R., Tunbridge, G., Pink, J., Macpherson, S., … Thompson, M. (2023). Unlocking the power of computational modelling and simulation across the product lifecycle in life sciences: A UK Landscape Report. InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.8325274

What do you perceive to be the top 5 barriers for *in silico* trial adoption as a source of regulatory evidence?



- CMS/IST Regulatory Acceptance Uncertainty
- CMS Scientific Maturity & Model Credibility
- Insufficient CMS Skills & Expertise/ Awareness in Regulators
- Insufficient CMS Skills & Expertise in Industry
- No relevant CMS & IST UK Standards or Guidelines
- Insufficient Data Availability (e.g. to build Virtual Populations in UK populations)
- Lack of UK Use Case Studies or ISTs Success Stories
- Lack of UK leadership on ISTs for Regulatory Science & Innovation
- ISTs Implementation Costs compared to Conventional Trials
- Return on Investment in Running a CMS Capability
- Insufficient funding for Industry - Academia-NHS collaboration

Adapted from a presentation by Prof AF Frangi at the InSilicoUK Innovation Network Launch Event,[88] InSilicoUK Community Survey #1: Enablers and Barriers.

“The gap isn’t legality but confidence; we need an authoritative, positive framework to turn tacit allowance into trusted adoption”.

Cross-sector Co-creation In Practice

IN SILICO REGULATORY AIRLOCK

In silico Regulatory Airlock Initiative

We focus on applying and evaluating the strengths and limitations of existing **international model credibility frameworks**.

Why do we need a Regulatory Airlock Initiative?

- Double-derisking: managing change in regulators and industry
- Problem-based learning boosts awareness, confidence & competence
- Precompetitive co-creation builds trust among stakeholders
- Collaborative learning enhances engagement
- Focused primarily on early regulatory impacts
- Consider broader socio-technical questions

Pilot Convenors	#	Theme
Resmed	1	CPAP Mask Evaluation: CO2 Venting and Rebreathing Performance Using In-Silico Techniques for Regulatory Compliance
stryker	2	Flow-Diverter Device: Pre/Post Implantation Intracranial Aneurysm Blood Flow & Clotting Models for In-Silico Trials
Boston Scientific	3	Transcatheter Aortic Valve Implantation: Conditional Generative Virtual Populations of Heart Anatomy for Targeted In-Silico Trials
Edwards	4	Transcatheter Aortic Valve Implantation: Frame Release and Pre/Post Implantation Blood Flow Models Predicting Aortic Stresses and Valve Leakage for In-Silico Trials
AMBER THERAPEUTICS	5	Deep Brain Stimulation: Closed-Loop Physiological Bidirectional Control System Model for Early Safety/Performance Assessment
DePuy Synthes	6	Spinal Pedicle Screw System: In-Silico Bench Testing for Confirming System Integrity after Introduction of a Cannulation
MatOrtho	7	Total Hip-Joint Replacement: Computational Simulator for Patient-Centered Wear Testing of Orthopaedic Device
ZIMMER BIOMET Moving You Forward	8	Total Knee Replacement Device: Augmentation of National Joint Registry with Data Derived from In-Silico Trial Insights
GSK	9	Vaccines: Quantitative systems pharmacology (QSP) computational models for finding optimal dosing regimens
SIEMENS Healthineers / varian	10	Radiotherapy treatment system: in-device integration of treatment data and models of radiobiology for optimised radiotherapy performance

Frangi, A. F. (2024). The *In silico* Regulatory Airlock Initiative for Advancing Model-Informed Evidence Adoption (v 6). InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.12745437

In Silico Regulatory Airlock

Learnings that Persist and Set Standards

YouTube

CEiRSI Centre of Excellence on in-silico Regulatory Science & Innovation

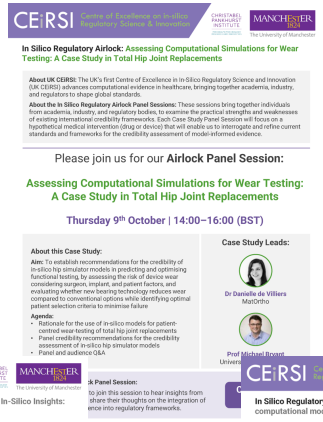
Learning and Dissemination Hub

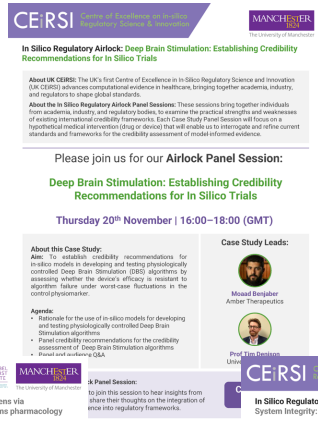
SKILLS AND CONVERSATIONS ACCELERATING ADOPTION

Funded by UK Research and Innovation

Sponsored by Medicines & Healthcare products Regulatory Agency









Joint ISO/IEC WG from TC62/ahC11

Others:
ISO 18969
ISO 14155

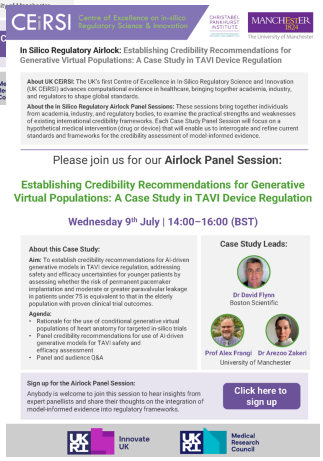
bsi. IEC ISO

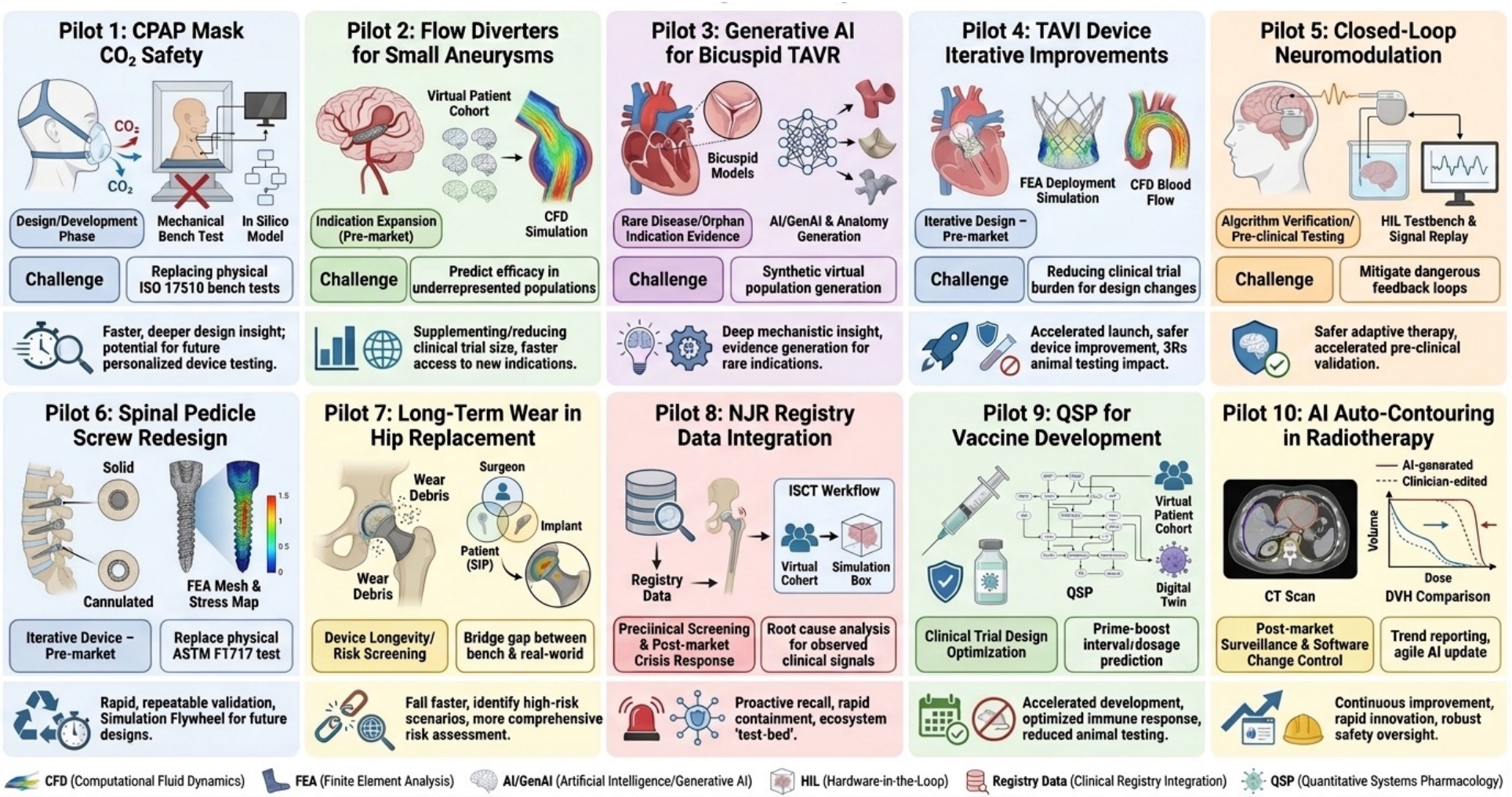
International Standards



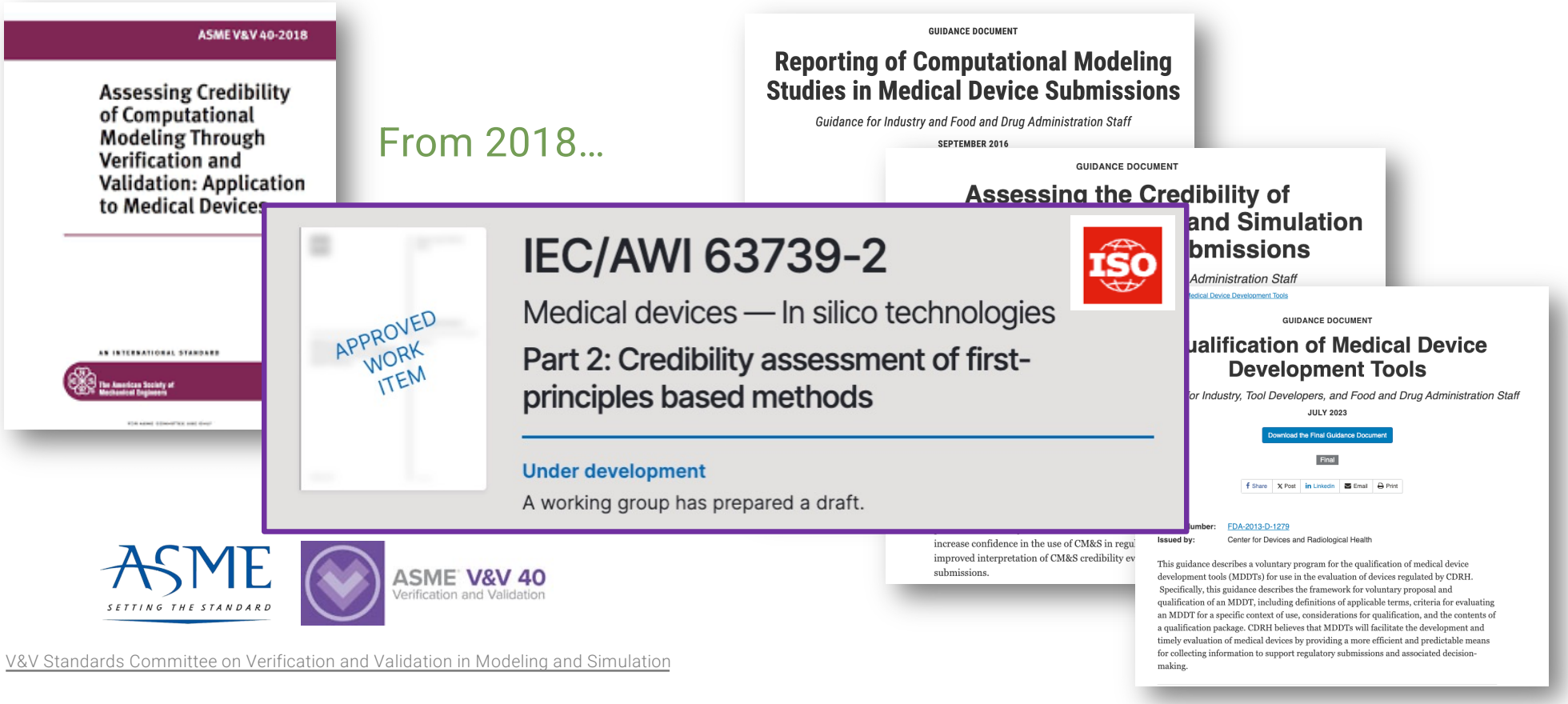







Pilot 1: CPAP Mask CO_2 Safety
CO_2
CO_2
Design/Development Phase
Mechanical Bench Test
In Silico Model
Challenge
Replacing physical ISO 17510 bench tests
Faster, deeper design insight; potential for future personalized device testing.
Pilot 2: Flow Diverters for Small Aneurysms
Virtual Patient Cohort
Indication Expansion (Pre-market)
CFD Simulation
Challenge
Predict efficacy in underrepresented populations
Supplementing/reducing clinical trial size, faster access to new indications.
Pilot 3: Generative AI for Bicuspid TAVR
Bicuspid Models
Rare Disease/Orphan Indication Evidence
AI/GenAI & Anatomy Generation
Challenge
Synthetic virtual population generation
Deep mechanistic insight, evidence generation for rare indications.
Pilot 4: TAVI Device Iterative Improvements
FEA Deployment Simulation
CFD Blood Flow
Iterative Design – Pre-market
Challenge
Reducing clinical trial burden for design changes
Accelerated launch, safer device improvement, 3Rs animal testing impact.
Pilot 5: Closed-Loop Neuromodulation
Algcrithm Verification/ Pre-clinical Testing
HIL Testbench & Signal Replay
Challenge
Mitigate dangerous feedback loops
Safer adaptive therapy, accelerated pre-clinical validation.
Pilot 6: Spinal Pedicle Screw Redesign
Solid
Cannulated
FEA Mesh & Stress Map
1.5
1
0.5
0
Iterative Device – Pre-market
Replace physical ASTM F1717 test
Rapid, repeatable validation, Simulation Flywheel for future designs.
Pilot 7: Long-Term Wear in Hip Replacement
Wear Debris
Wear Debris
Surgeon
Implant
Patient (SIP)
Device Longevity/ Risk Screening
Bridge gap between bench & real-world
Fall faster, identify high-risk scenarios, more comprehensive risk assessment.
Pilot 8: NJR Registry Data Integration
Registry Data
ISCT Werkflow
Virtual Cohert
Simulation Box
Preciinical Screening & Post-market Crisis Response
Root cause analysis for observed clinical signals
Proactive recall, rapid containment, ecosystem 'test-bed'.
Pilot 9: QSP for Vaccine Development
Virtual Patient Cohort
QSP
Digital Twin
Clinical Trial Design Optimlzation
Prime-boost interval/dosage prediction
Accelerated development, optimized immune response, reduced animal testing.
Pilot 10: AI Auto-Contouring in Radiotherapy
AI-ganarated
Clinician-edited
Volume
Dose
CT Scan
DVH Comparison
Post-market Surveillance & Software Change Control
Trend reporting, agile AI update
Continuous improvement, rapid innovation, robust safety oversight.
CFD (Computational Fluid Dynamics)
FEA (Finite Element Analysis)
AI/GenAI (Artificial Intelligence/Generative AI)
HIL (Hardware-in-the-Loop)
Registry Data (Clinical Registry Integration)
QSP (Quantitative Systems Pharmacology)

Standards and Guidance to industry and regulatory staff



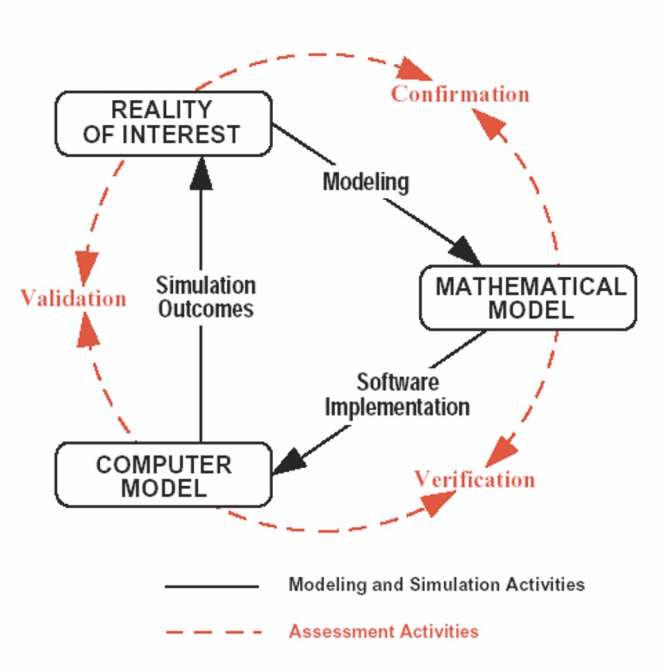
V&V Standards Committee on Verification and Validation in Modeling and Simulation

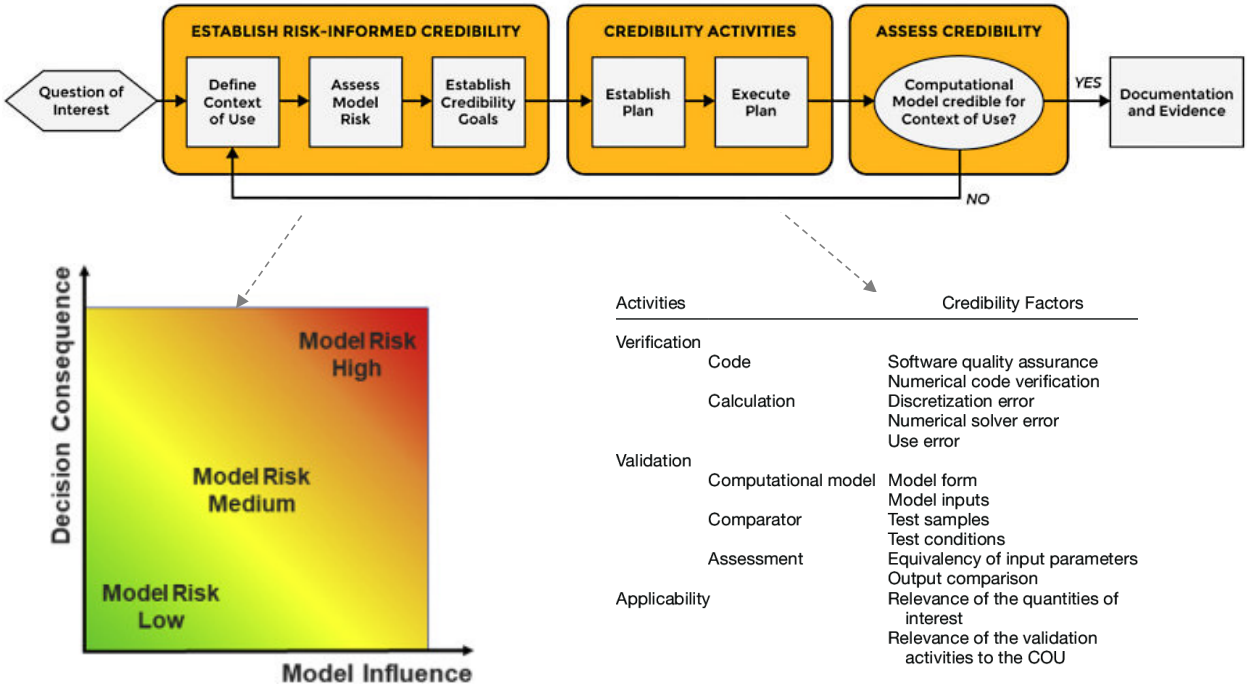
Global Standards – Filling the Gap

Validation, Verification and Uncertainty Quantification Framework

ASME SETTING THE STANDARD

ASME V&V 40 Verification and Validation





Activities		Credibility Factors
Verification		
	Code	Software quality assurance
		Numerical code verification
	Calculation	Discretization error
		Numerical solver error
		Use error
Validation		
	Computational model	Model form
		Model inputs
	Comparator	Test samples
		Test conditions
	Assessment	Equivalency of input parameters
		Output comparison
Applicability		Relevance of the quantities of interest
		Relevance of the validation activities to the COU

Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba F. *In silico* trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods. 2021 Jan;185:120-127.

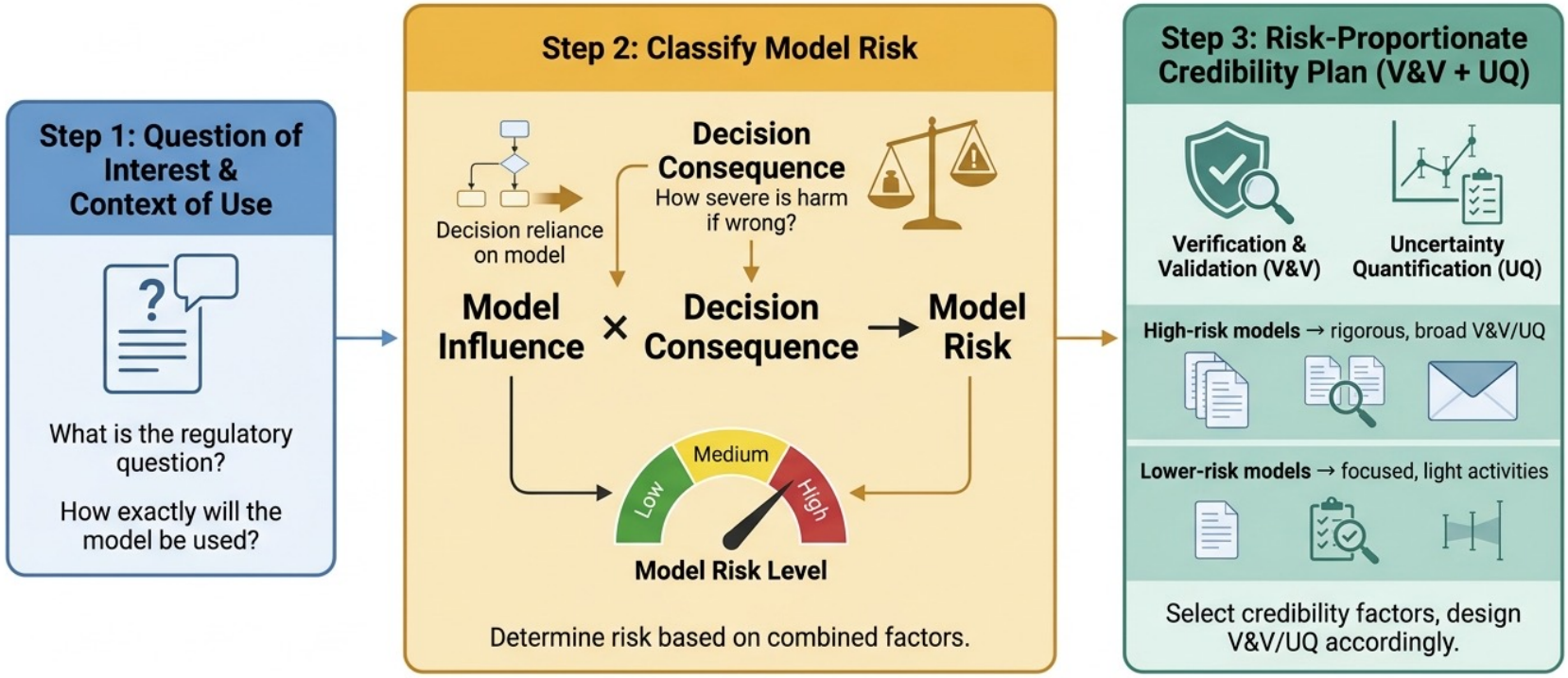
Viceconti M, Emili L, Afshari P, Courcelles E, Curreli C, Famaey N, Geris L, Horner M, Jori MC, Kulesza A, Loewe A, Neidlin M, Reiterer M, Rousseau CF, Russo G, Sonntag SJ, Voisin EM, Pappalardo F. Possible Contexts of Use for *In Silico* Trials Methodologies: A Consensus-Based Review. IEEE J Biomed Health Inform. 2021 Oct;25(10):3977-3982.

Model Risk vs Decision Consequence

- **Decision consequence**
  "How bad it is for patients if this decision is wrong (severity × likelihood of harm)."
  - "Under-predicting valve fracture risk in a high-risk implant has higher decision consequence than slightly mis-estimating trial sample size."

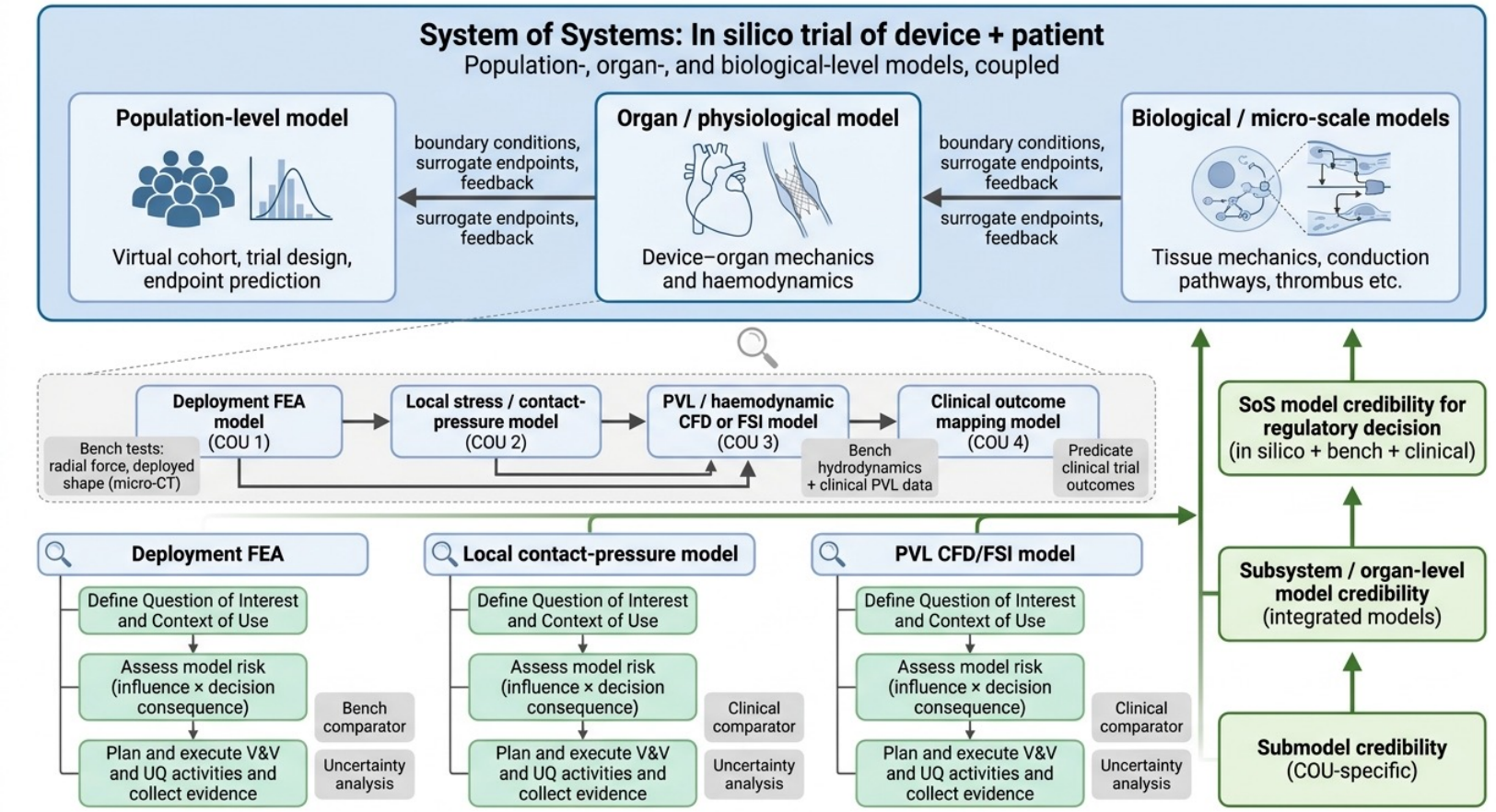
- **Model influence**
  "How much the decision relies on this model compared with other evidence (bench tests, clinical data, expert judgement)."
  - "Under-predicting valve fracture risk in a high-risk implant has higher decision consequence than slightly mis-estimating trial sample size."

Risk based Model Credibility



Risk classification drives how much and what kind of evidence is needed; credibility is not one-size-fits-all.

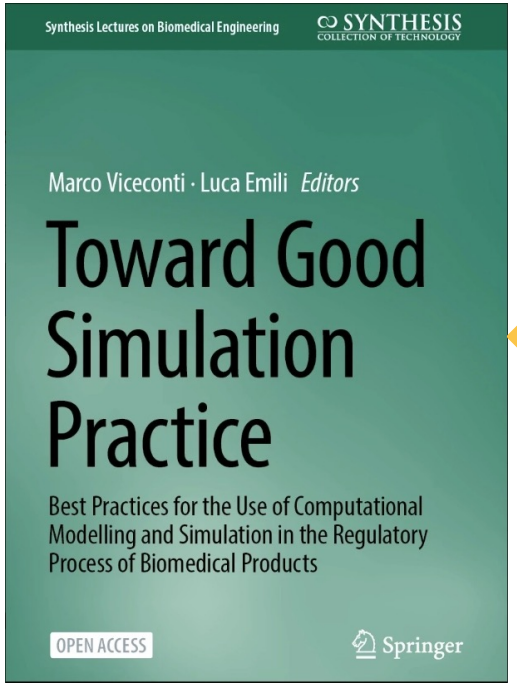
Model Credibility Assessment in Complex Systems



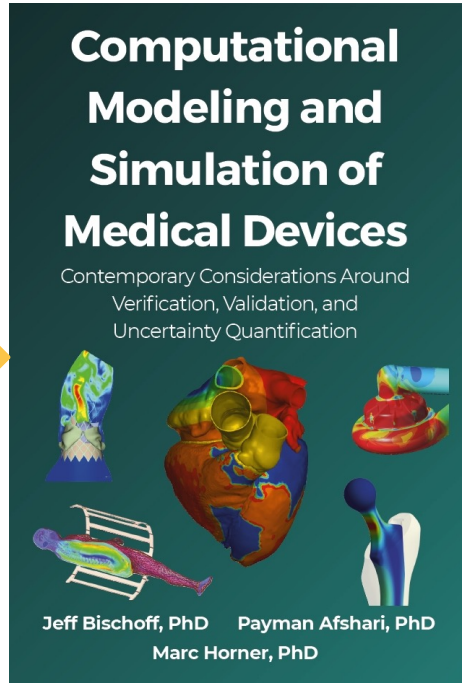
Best Practices – from practitioners

Led by:

INSILICO WORLD







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Conclusions and Outlook

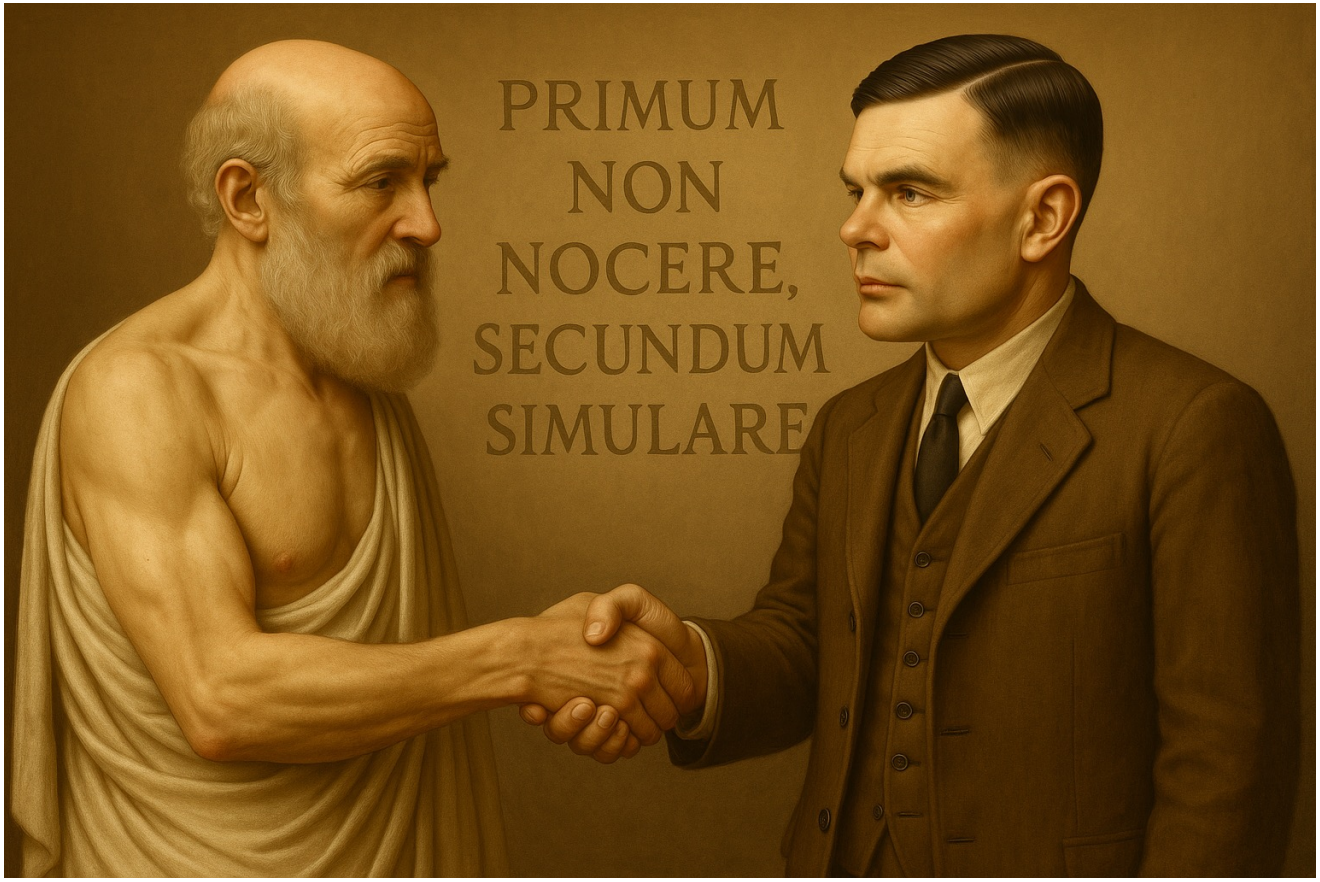
1. **From Artisanal to Industrial Scale.** Digital twins have matured from bespoke, single-patient models to high-throughput **virtual populations**, enabling statistically powered *in silico* trials that match or exceed the scale of traditional clinical studies.

2. **Predictive Power Beyond Replication.** Validated digital twins (e.g., FD-PASS) do not merely replicate historical trial data; they expose **emergent behaviours** and stratify risks in underserved patient groups, off-label scenarios, and complex anatomical variants where physical trials are infeasible.

3. **The "Regulatory Airlock" for Trust.** The primary barrier to adoption is no longer technical but regulatory confidence; a collaborative **"Regulatory Airlock"** framework is essential to co-create the validation standards that transform *in silico* predictions into admissible regulatory evidence.

4. **The "Fail Fast" Safety Paradigm.** Digital twins shift the risk curve by enabling exhaustive **virtual stress-testing** against edge cases, allowing manufacturers to "fail fast" *in silico*—protecting patients and dramatically compressing the time-to-market for medical innovations.

A New Medical Oath for the Digital Age: from Hippocrates to Turing



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