Digital Twins and AI in Biomedical Technology

In-silico meets in-vitro/in-vivo

Christian Baumgartner

Institute of Health Care Engineering with
European Testing Center of Medical Devices

Graz University of Technology, Austria

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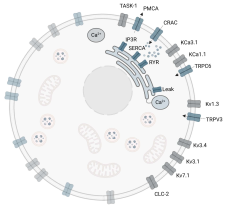
Digital Twins and AI in Biomedical Technology

- **Selected examples** at cell and patient level from our research
- **Regulatory challenges** to approve DW/AI in Biomedical Technology

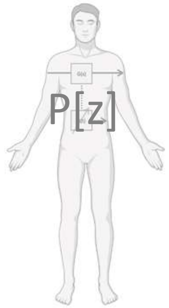
Digital twin of a cancer cell

Functional model of the „electrophysiological system“ of a cancer cell to simulate ion channel modulation during the cell cycle



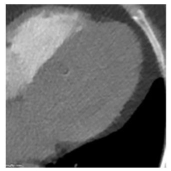
Patient model for the prediction of the cumulative fluid balance (CFB) in intensive care

Phenomenological model to simulate the cumulative fluid balance in a dynamically changing fluid balance system of an individual patient



DL-based image registration in heart perfusion CT imaging

AI-based medical image registration in dynamic computed tomography



AI and ML in Medical Devices and Software as a MD (SaMD)

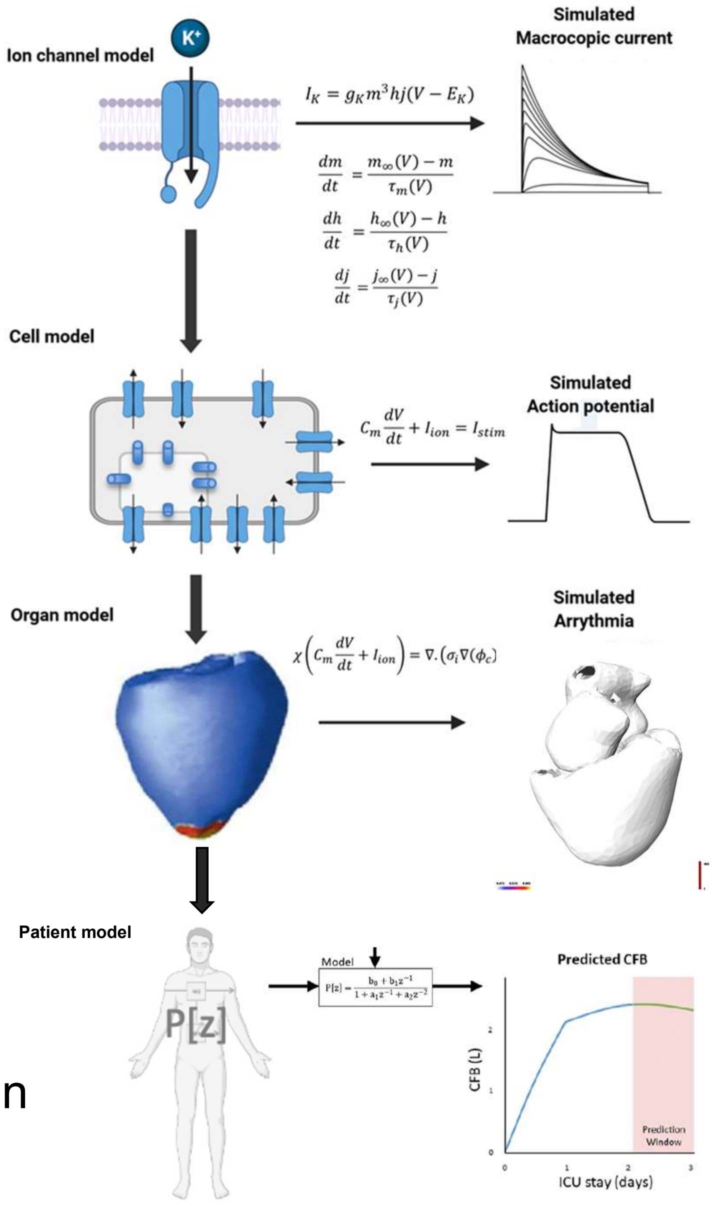
Regulatory challenges to market in the EU and worldwide

What are digital twins?

"Digital twins are in-silico models that represent the virtual counterpart to real physical or biological systems and their interactions with each other at different levels of complexity and abstraction."

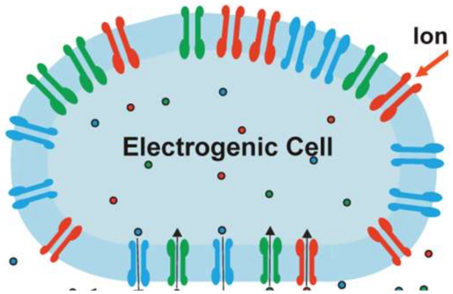
Goal in biomedicine: Model simulations of biological mechanisms, taking into account their unique characteristics (genetic & metabolic associations, signaling pathways, physiological mechanisms, morphology, etc).

Functional vs. phenomenological twins?
Digital model of a biological (sub)system based on physical equations vs. biological phenomenon based on measurements.

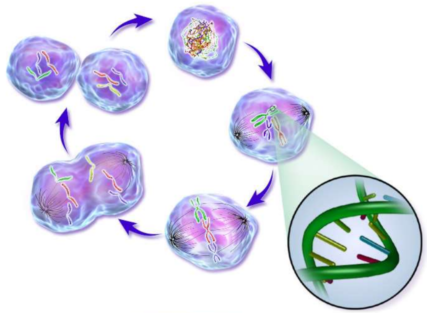


The first digital cell twin in cancer electrophysiology

This digital model represents the bioelectric subsystem of the cell function. No representations of other cellular subsystems (genomic, proteomic associations and signaling pathways, morphology).

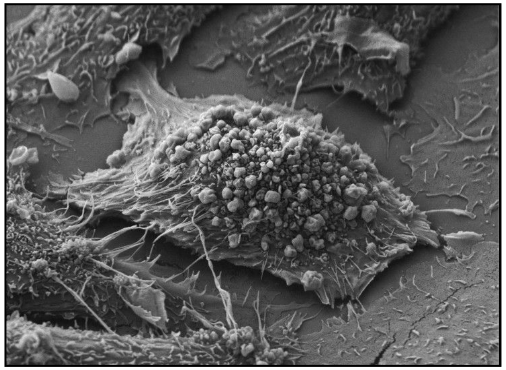


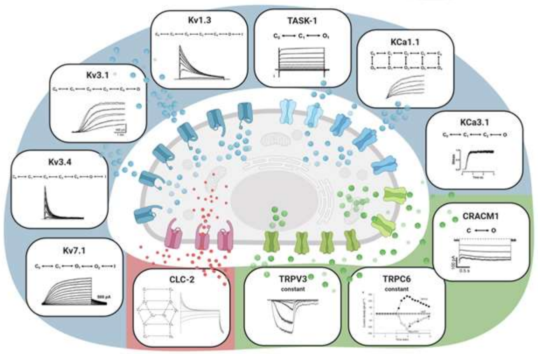
The alteration of the function of ion channels in the plasma membrane and intracellular membranes have an essential influence on cell cycle proliferation.



Selected cell line:

- Adenocarcinomic human alveolar basal epithelial cells (A549 cell line)
- Widley used lung cancer cell model
  - cancer research
  - drug testing

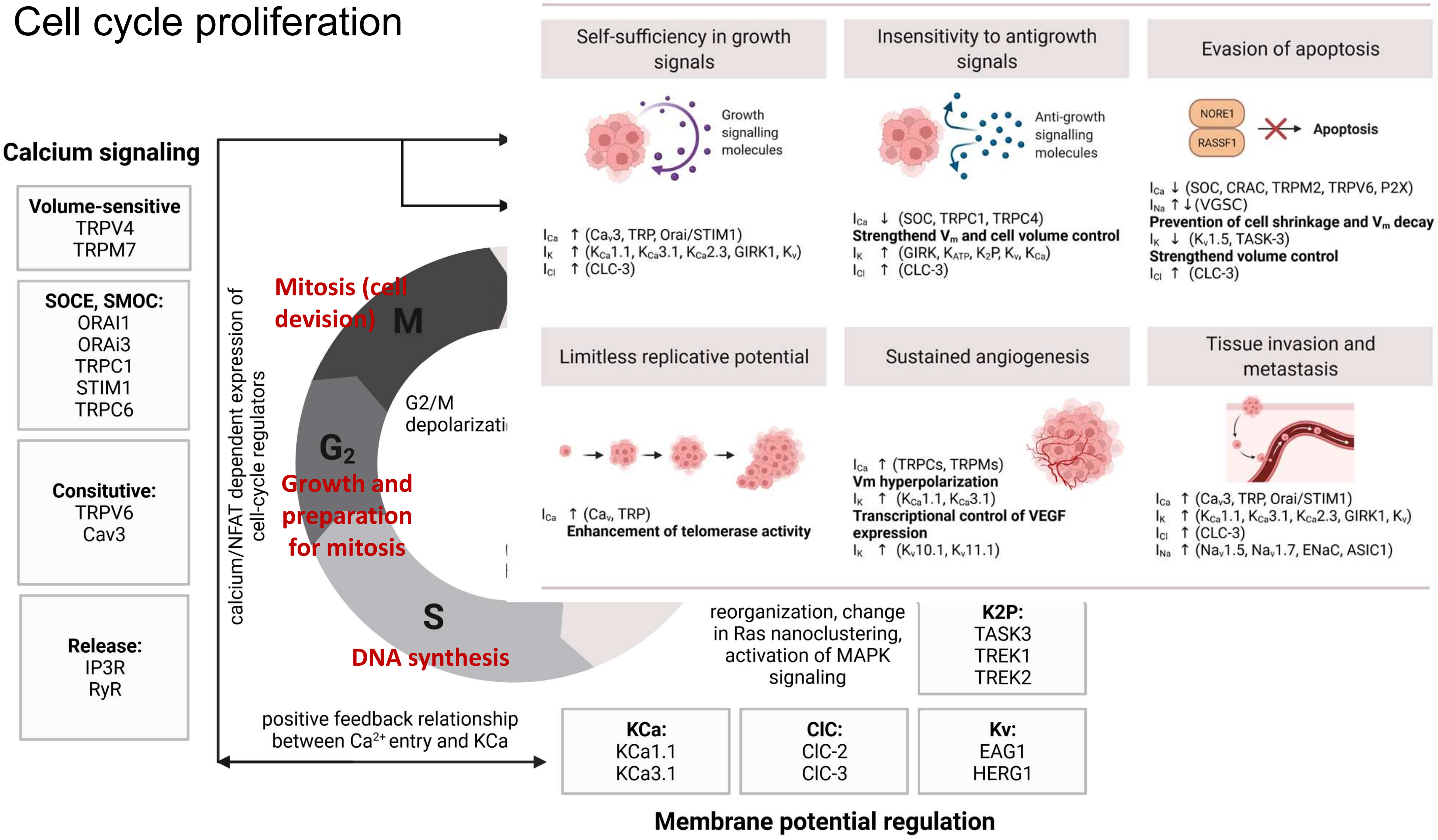




in-vivo/in-vitro ⇋ **in-silico**

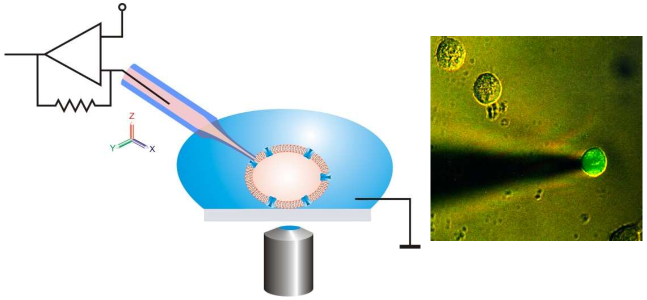
The first digital cell twin in cancer electrophysiology

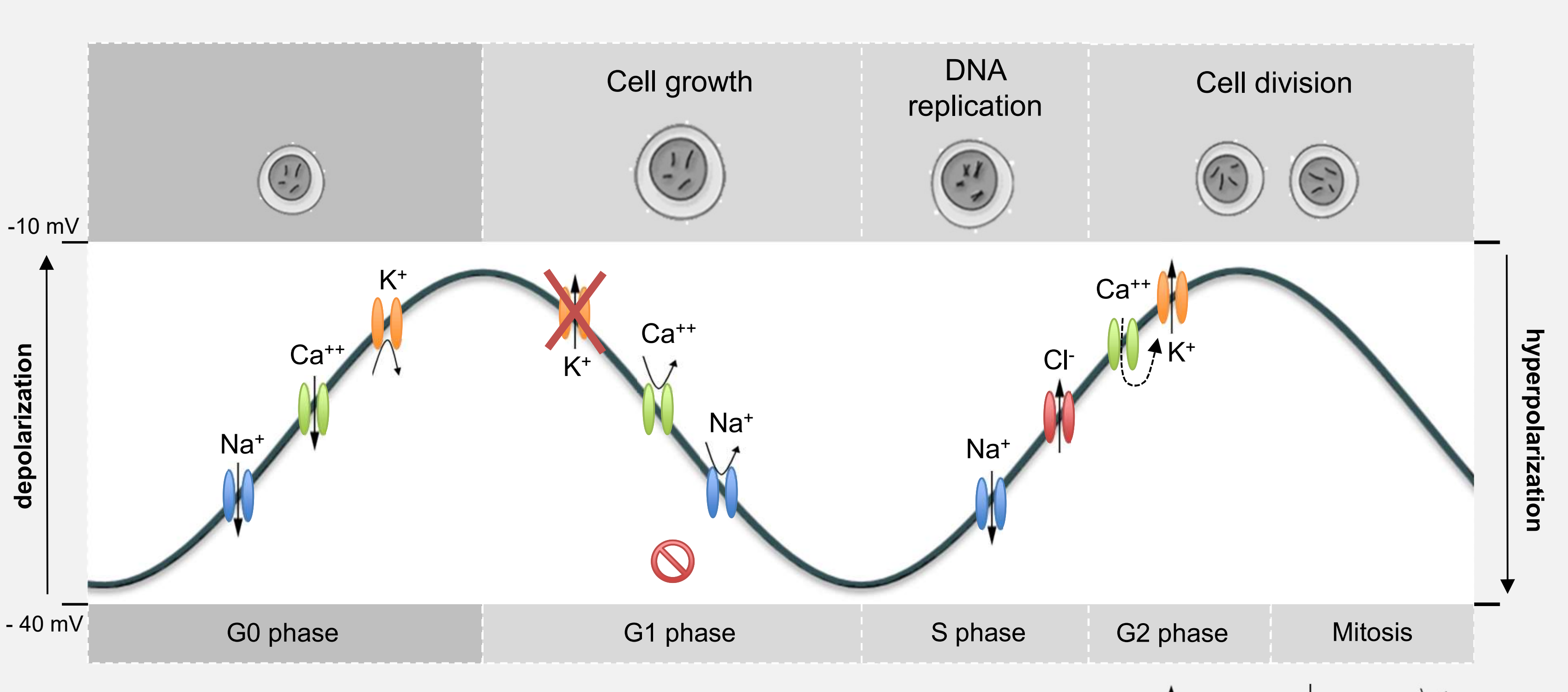
Cell cycle proliferation



The first digital cell twin in cancer electrophysiology

- Rhythmic oscillation of the membrane potential V_m during cell cycle progression
- Changes in membrane potential may interfere cell cycle progression

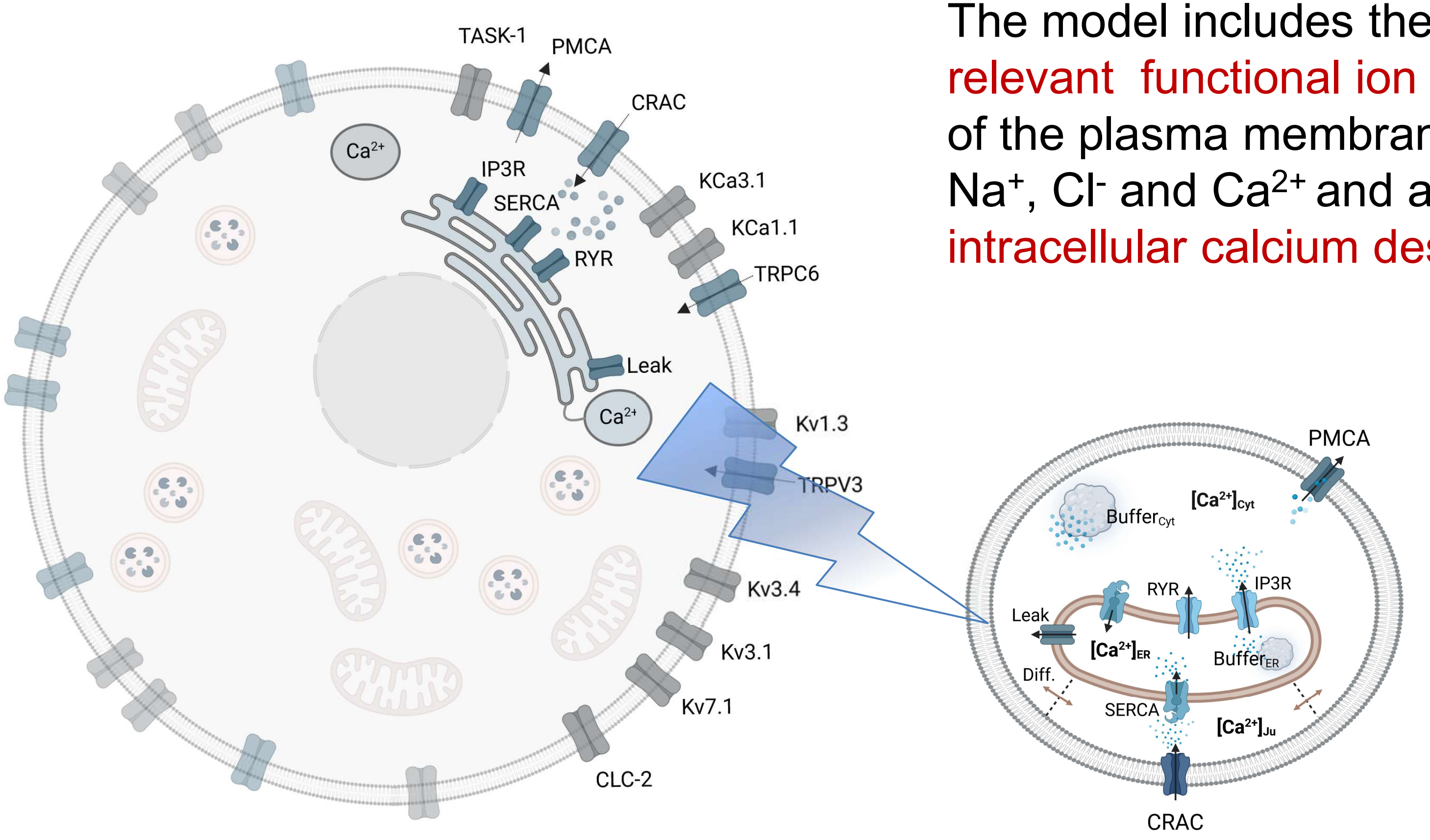




adapted from: V.R. Rao et. al, „Voltage-Gated Ion Channels in Cancer Cell Proliferation“

The first digital cell twin in cancer electrophysiology

The **whole cell ion current model** of the **A549 lung adenocarcinoma cell line**

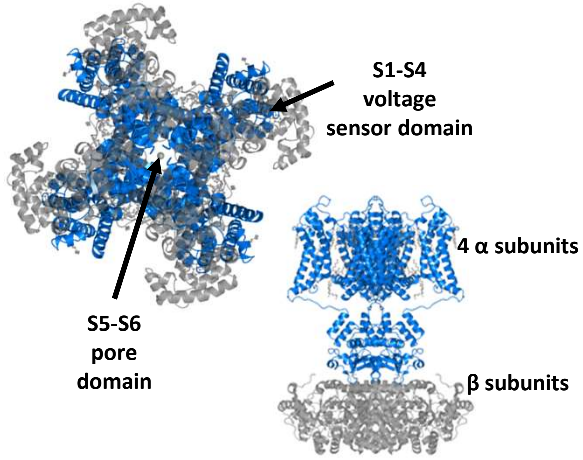


The model includes the most relevant functional ion channels of the plasma membrane (K^+, Na^+, Cl^- and Ca^{2+}) and an intracellular calcium description

The first digital cell twin in cancer electrophysiology

Hidden Markov-based (HMM) models = statistical models that can be used to describe the evolution of observable events that depend on internal factors

Example: Kv1.1 channel



I) Consideration of the protein structure:

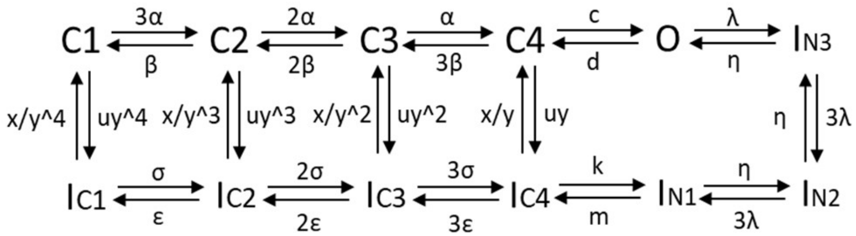
Activation

- voltage-dependent

Inactivation

- fast N-type and slow C-type
- voltage-dependent

II) Definition of the kinetic scheme:



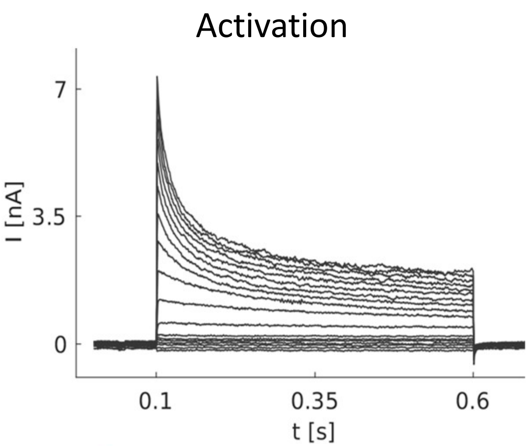
$$\frac{dP_O}{dt} = P_{C_4}(t).c + P_{I_{N3}}(t).\eta - P_O(t).(d + \lambda)$$

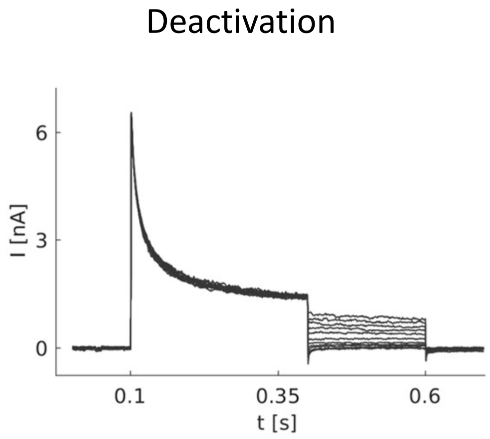
Ideally each state corresponds to one protein conformation - in practice, Markov models are only approximations to the actual channel states

The first digital cell twin in cancer electrophysiology

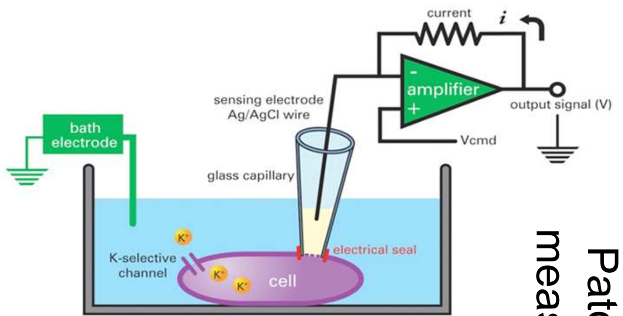
Hidden Markov-based (HMM) models

III) Model parametrization and optimization
Fitting of parameters to experimental data using various measured current curves from different voltage-step protocols simultaneously to model the different kinetics of the channel (nummerical optimization, computational load!).



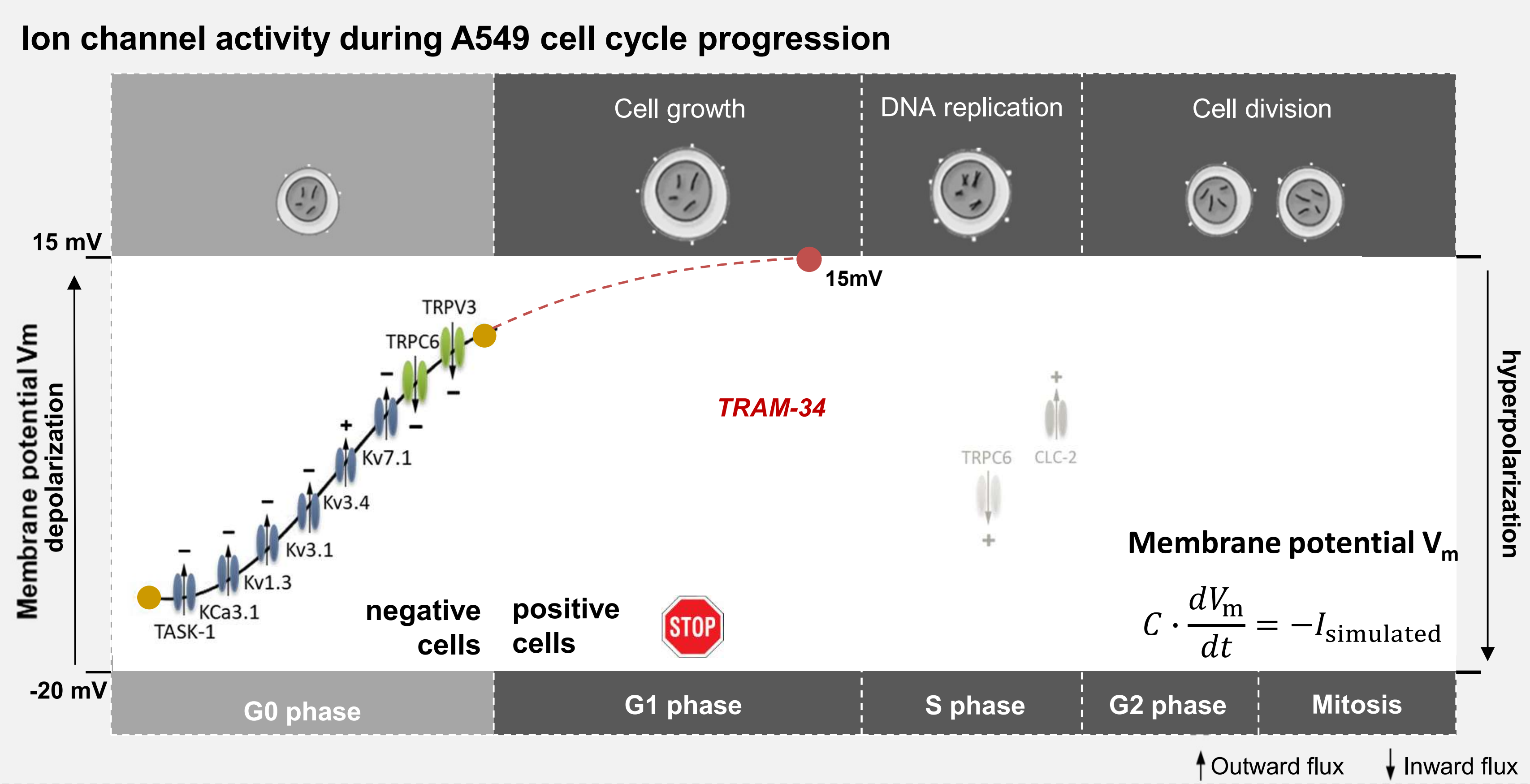


$$\begin{bmatrix} P_{C_1,k+1} \\ P_{C_2,k+1} \\ P_{O_1,k+1} \\ P_{O_2,k+1} \\ P_{I,k+1} \end{bmatrix} = \begin{bmatrix} 1-\alpha\cdot dt & \beta\cdot dt & 0 & 0 & 0 \\ \alpha\cdot dt & 1-(a+\beta)\cdot dt & b\cdot dt & 0 & 0 \\ 0 & a\cdot dt & 1-(b+c)\cdot dt & d\cdot dt & 0 \\ 0 & 0 & c\cdot dt & 1-(d+\eta)\cdot dt & \lambda\cdot dt \\ 0 & 0 & 0 & \eta\cdot dt & 1-\lambda\cdot dt \end{bmatrix} \cdot \begin{bmatrix} P_{C_1,k} \\ P_{C_2,k} \\ P_{O_1,k} \\ P_{O_2,k} \\ P_{I,k} \end{bmatrix}$$

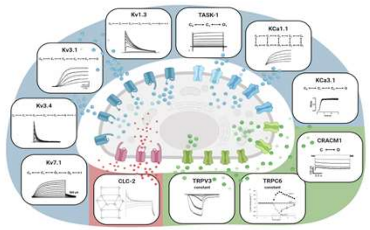


Patch clamp measurements

The first digital cell twin in cancer electrophysiology



Model simulation of human intermediate potassium channel (KCa3.1) channel inhibition in the G1 phase leads to a strong depolarization of V_m (+15mV). This might suppress the transition from G1 to S phase and inhibit further cell cycle progression (cell cycle arrest in G1 phase).



Summary

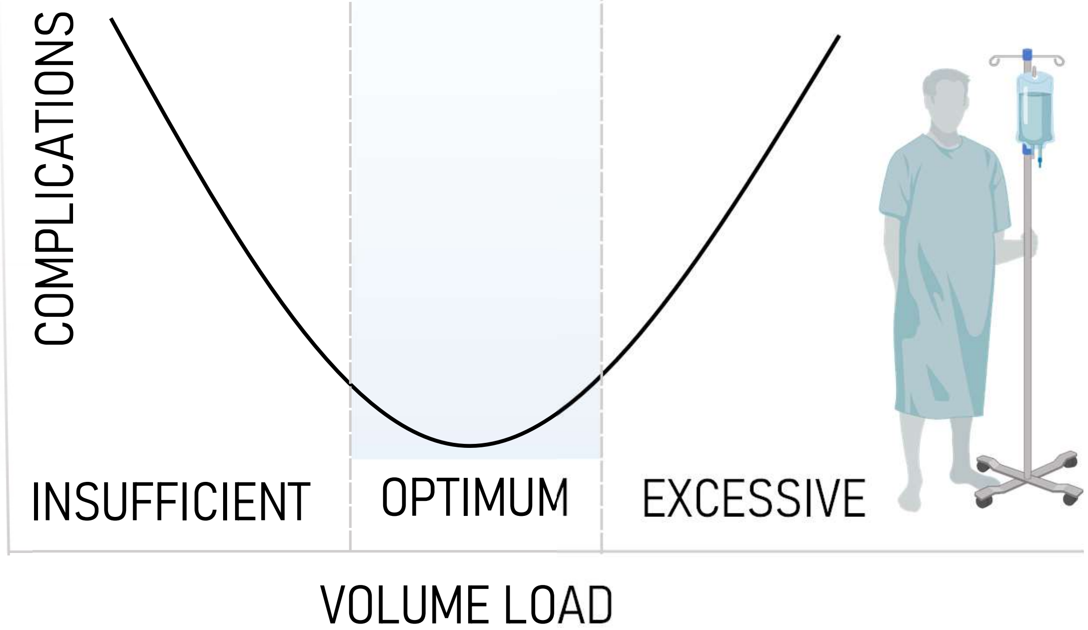
- From **single ion channel** to the **whole cell models**
- **Important starting point** in computational cancer electrophysiology
- **Fundamental basis** for advanced models supporting cancer research

[1] Langthaler S, Zumpf C, Rienmüller R, Fuchs J, Zhou R, Shrestha N, Pelzmann B, Zorn-Pauly K, Fröhlich E, Weinberg S, Baumgartner C. The bioelectric mechanisms of local calcium dynamics in cancer cell proliferation: An extension of the A549 in-silico cell model. ***Front Mol Biosci***. 2024, 11, 1394398
[2] Langthaler S, Rienmüller T, Scheruebel S, Pelzmann B, Shrestha N, Zorn-Pauly K, Schreibmayer W, Koff A, Baumgartner C. A549 In-silico 1.0: A first computational model to simulate cell cycle dependent ion current modulation in the human lung adenocarcinoma. ***PLoS Comput Biol.*** 2021, 17(6), e1009091

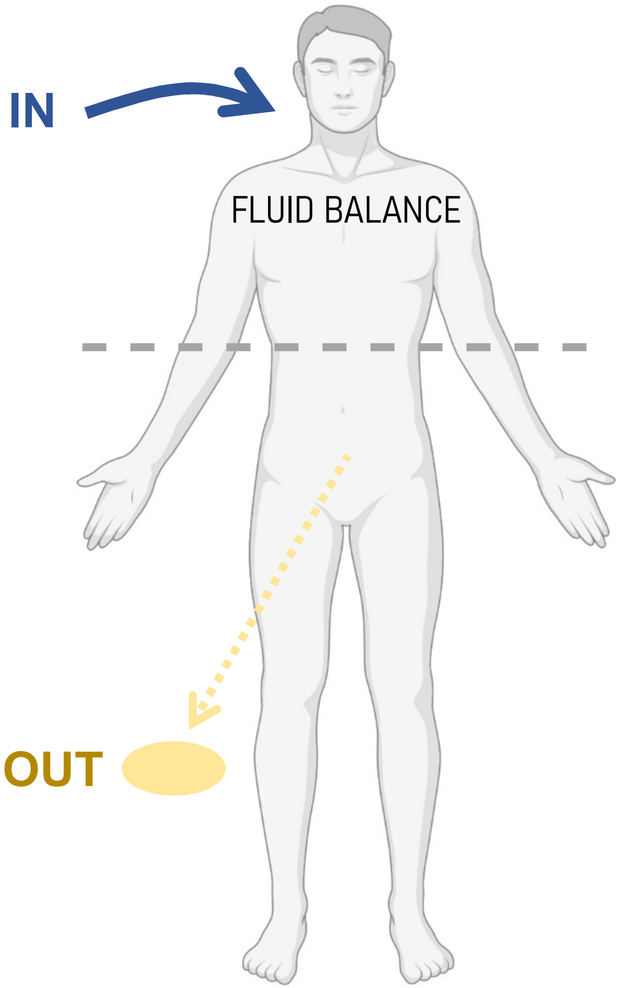
System theory-based patient model for predicting the cumulative fluid balance in intensive care patients

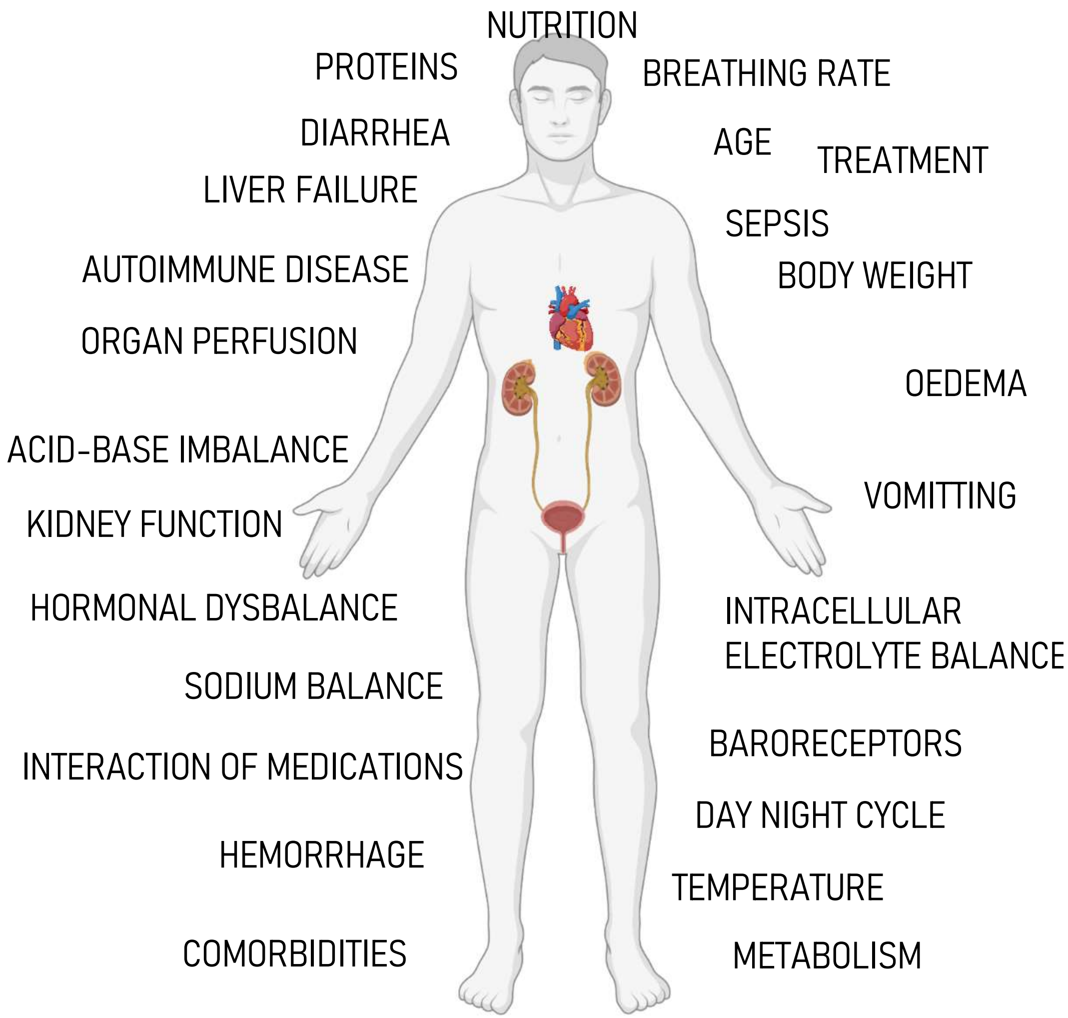
Since fluid balance is influenced by a complex interplay of patient-, operation- and ICU-specific factors, the prediction of fluid balance is difficult and often inaccurate.

A **patient-individual model** may enable the estimation of cumulative fluid balance progression in a dynamically changing patient fluid balance system by simulating the response to current fluid management.

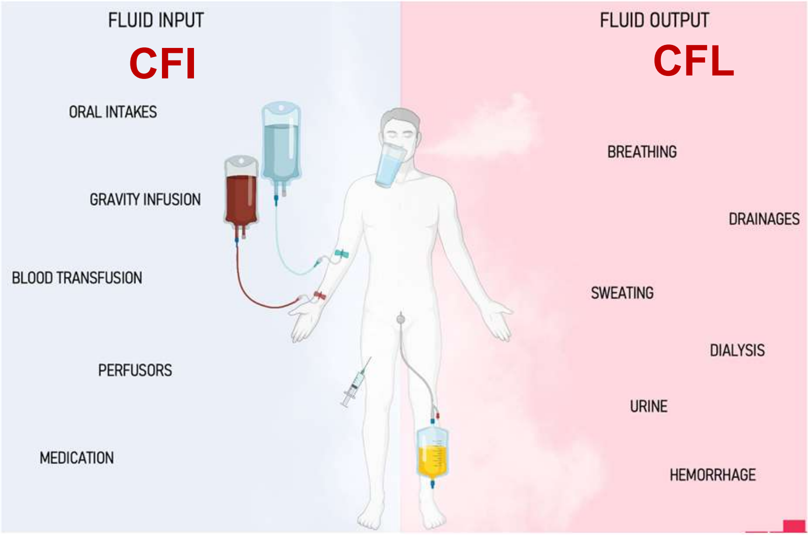


System theory-based patient model for predicting the cumulative fluid balance in intensive care patients





System theory-based patient model for predicting the cumulative fluid balance in intensive care patients

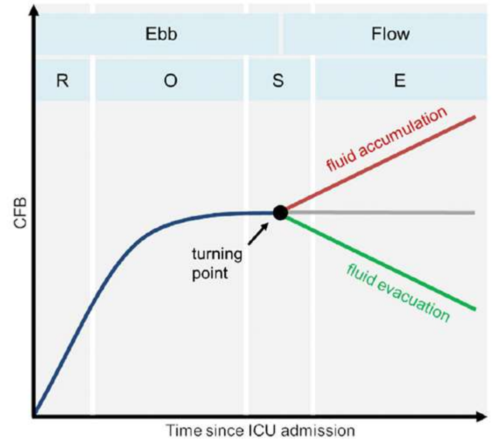


Phenomenological model:
The **cumulative fluid balance (CFB)** is estimated as cumulative fluid intake (CFI) minus cumulative losses (CFL) over ICU stay.

CFB = CFI - CFL

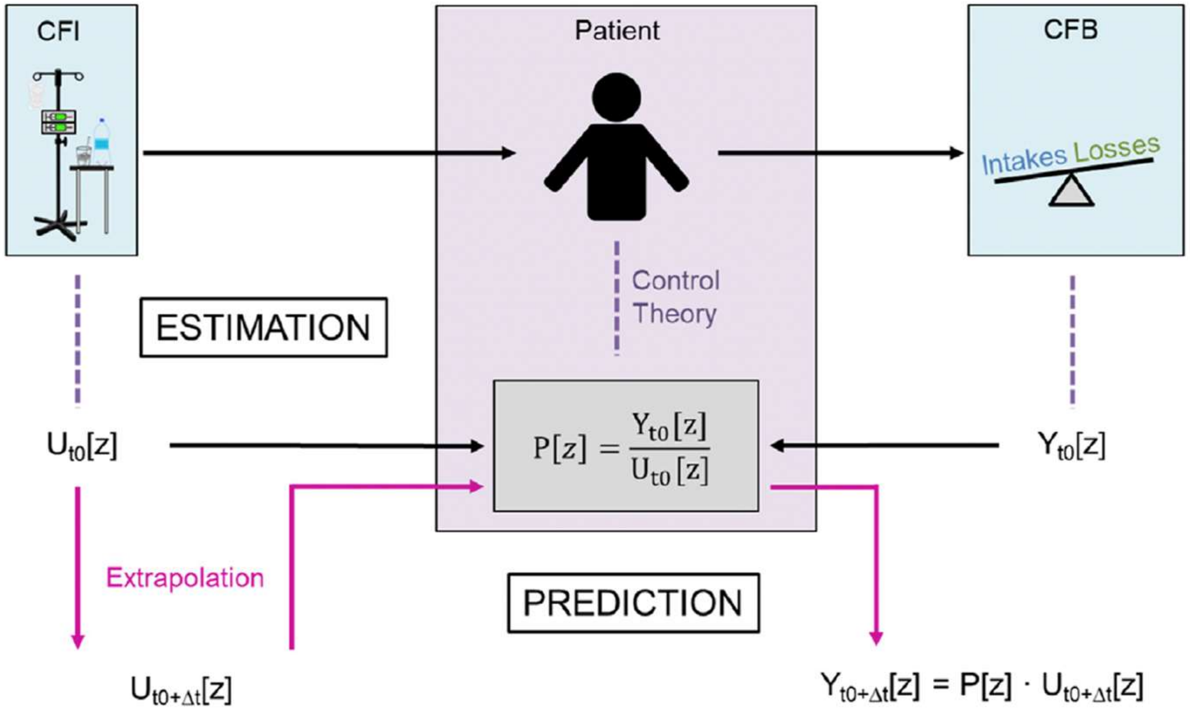
Possible trajectories of cumulative fluid balance (CFB) in postsurgical patients during the four consecutive phases of fluid therapy.

Rescue (R), Optimization (O), Stabilization (S), Evacuation (E)



System theory-based patient model for predicting the cumulative fluid balance in intensive care patients

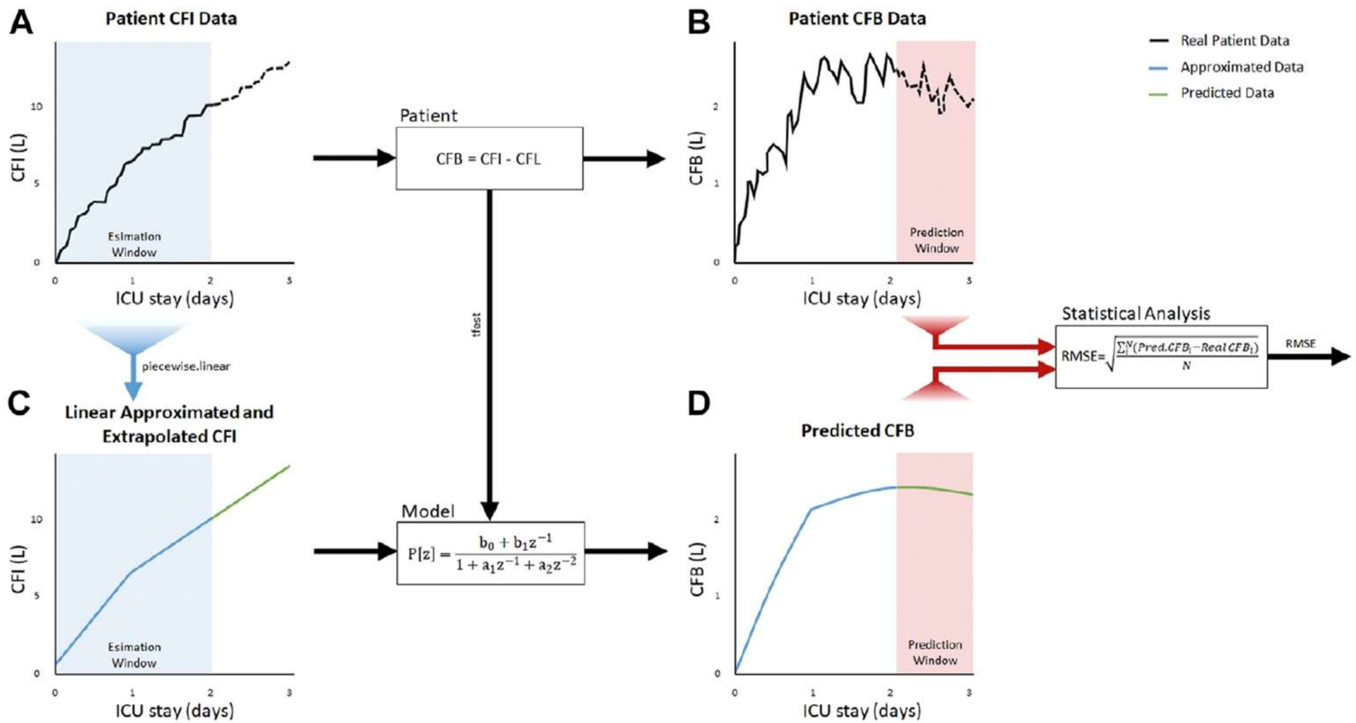
Control theory-based digital (transfer function P[z]) model



Overall approach to predicting the course of **cumulative fluid balance (CFB)** using the **cumulative fluid intake (CFI)** as the only input parameter of the model.

System theory-based patient model for predicting the cumulative fluid balance in intensive care patients

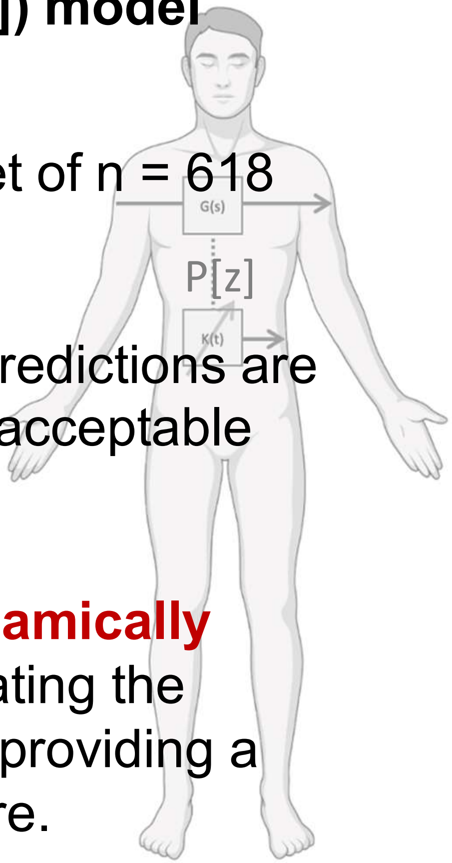
Control theory-based digital (transfer function P[z]) model



Individual patient model with an estimation window 0-48 h after ICU admission (blue), which was used to determine the **transfer function P[z]** with the **measured CFI** and **calculated CFB** patient data.

System theory-based patient model for predicting the cumulative fluid balance in intensive care patients

Control theory-based digital (transfer function P[z]) model



- **Patient-individual models** (evaluated on a dataset of n = 618 cardiac intensive care patients).
- With an **8-h prediction time**, nearly 50% of CFB predictions are within ±0.5 L, and 77% are still within the clinically acceptable range of ±1.0 L (clinically relevant).
- Model allows **estimation of CFB course** on a **dynamically changing patient fluid balance system** by simulating the response to the current fluid management regime, providing a useful digital tool for clinicians in daily intensive care.

Polz M, Bergmoser K, Horn M, Schörghuber M, Lozanovic Sajic J, Rienmüller T, Baumgartner C. A System Theory Based Digital Model for Predicting the Cumulative Fluid Balance Course in Intensive Care Patients. ***Front Physiol.*** 2023, 14, 1101966.

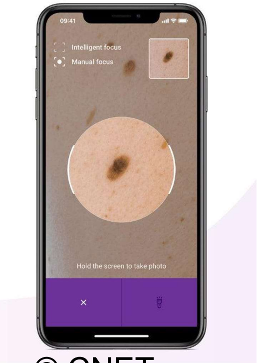
Artificial Intelligence and Machine Learning in Biomedical Technology

Artificial Intelligence *is a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. Artificial intelligence systems use machine- and human-based inputs to perceive real and virtual environments; abstract such perceptions into models through analysis in an automated manner; and use model inference to formulate options for information or action.*

Machine Learning *is a set of techniques that can be used to train AI algorithms to improve performance at a task based on data.*

Some real-world examples of artificial intelligence and machine learning technologies include:

- An imaging system that uses algorithms to give diagnostic information for skin cancer in patients.
- A smart sensor device that estimates the probability of a heart attack.



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https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

Artificial Intelligence and Machine Learning in Biomedical Technology

How Are Artificial Intelligence and Machine Learning (AI/ML) Transforming Medical Devices?

*"AI/ML technologies have the potential to **transform health care** by deriving new and important insights from the vast amount of data **generated during the delivery of health care every day**.*

*Medical device manufacturers are using these technologies to innovate their products to **better assist health care providers** and **improve patient care**. One of the greatest benefits of **AI/ML in software** resides in its ability to learn from real-world use and experience, and its capability to improve its performance".*

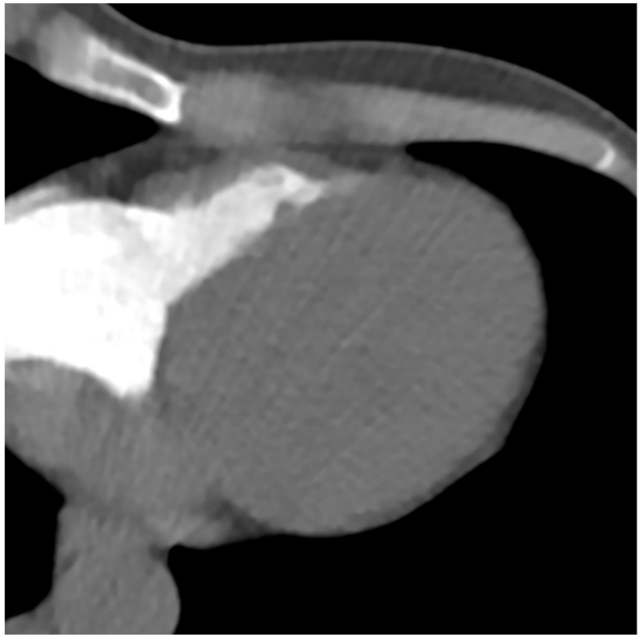
https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

Deep learning based image registration in dynamic heart perfusion CT imaging

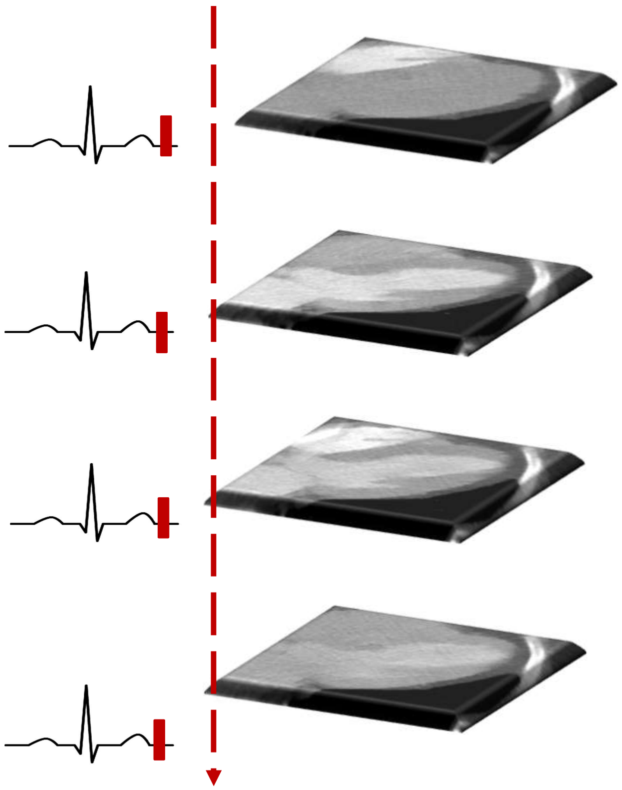
Medical image registration seeks to find an optimal spatial transformation that best aligns the underlying anatomical structures

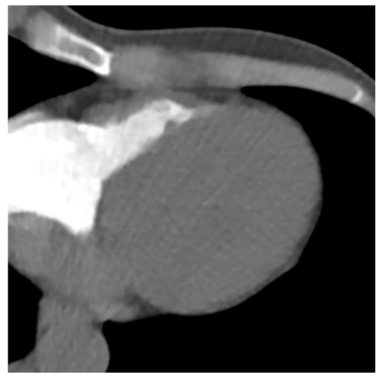
Relevant for (patho)physiological interpretation of the heart function such as the heart perfusion

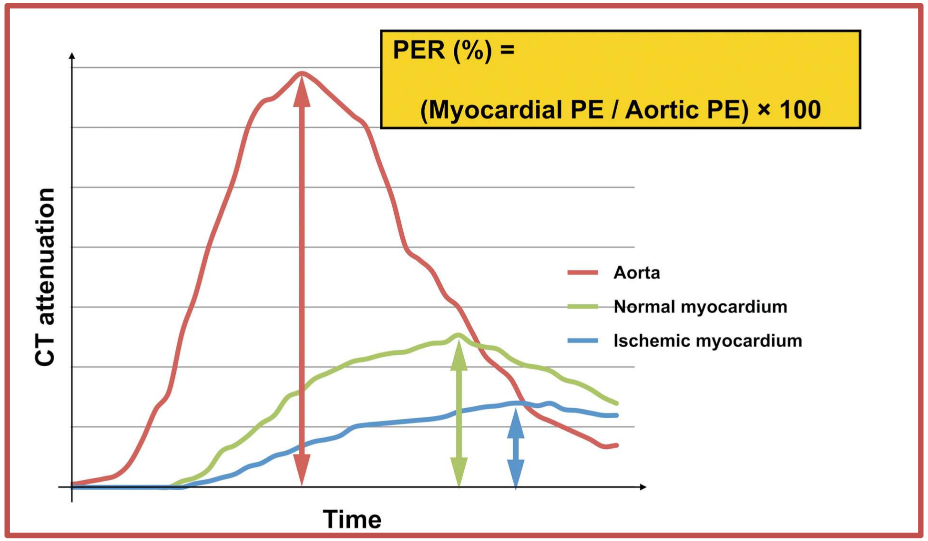
CT scanner, Siemens



Deep learning based image registration in dynamic heart perfusion CT imaging







ECG-gated cardiac CT sequences and corresponding time-attenuation curves

Deep learning based image registration in dynamic heart perfusion CT imaging

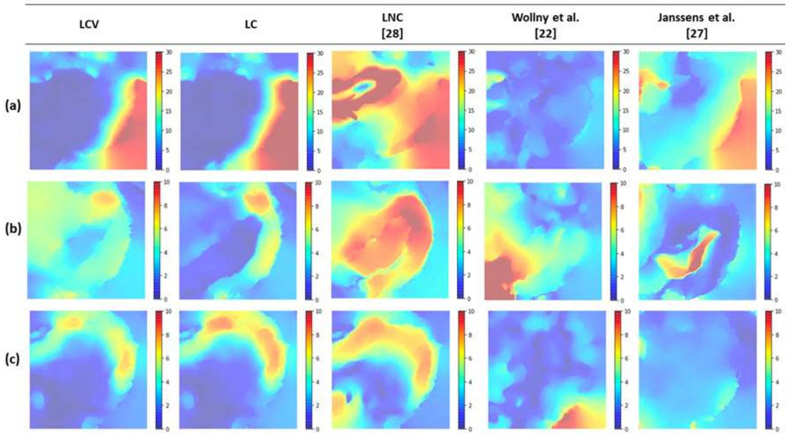
Challenges

- Correct misalignment caused by cardiac stressing, respiration and patient motion
- Lower contrast resolution and less accurate anatomical landmarks
- CT values must remain unaffected
- Shorter processing time
- Tested in a clinical example

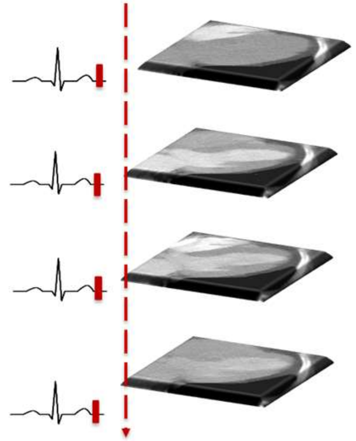
Example myocardial perfusion CT

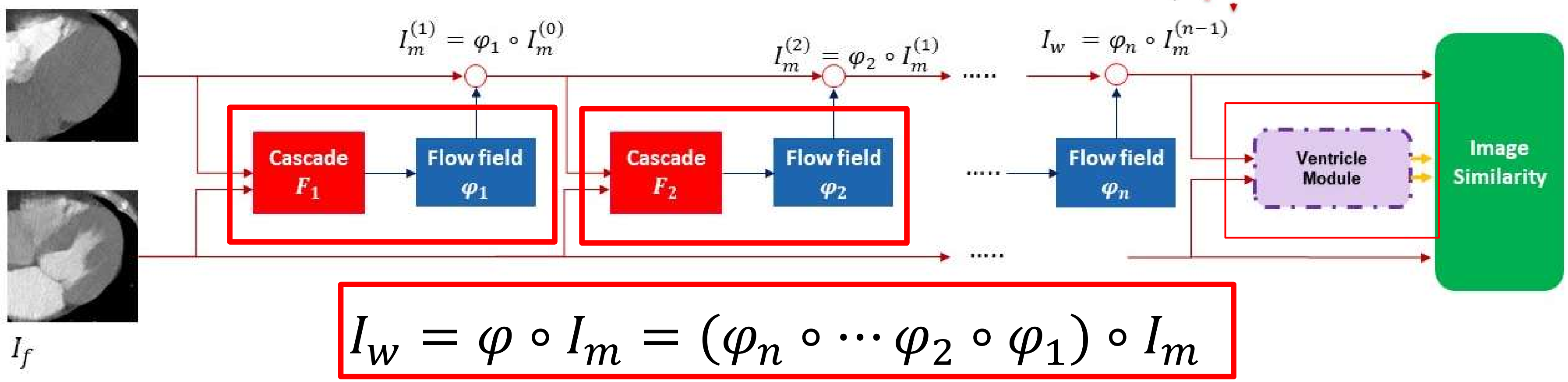
Registration Network

$$I_w = \varphi$$



$$\circ \; I_m$$





$$\boxed{I_w = \varphi \circ I_m = (\varphi_n \circ \cdots \varphi_2 \circ \varphi_1) \circ I_m}$$

Recursive cascade registration network

The warped image I_w is the composition of the flow field k and the moving image I_m (k−1).
The final warped image I_w is obtained by successively warping the moving image I_m along all cascades.

S. Zhao, Y. Dong, E. I.-C. Chang, and Y. Xu, "Recursive Cascaded Networks for Unsupervised Medical Image Registration," *2019 IEEE/CVF International Conference on Computer Vision (ICCV)*, pp. 10599–10609, Oct. 2019, doi: 10.1109/ICCV.2019.01070.

Loss Functions

Quantify the extent of error between predicted and actual images

$$L_{nc}\left(I_f, I_m, \varphi, M_c\right) = L_{sim}\left(I_f, \varphi \circ I_m\right) + L_{reg}(\varphi) \tag{1}$$

$$\boldsymbol{L_{cv}\left(I_f, I_m, \varphi, M_c, M_{RV}, M_{LV}\right) =} \tag{2}$$

$$L_{sim}\left(I_f, \varphi \circ I_m\right) + L_{cont}\left(I_f, \varphi \circ I_m, M_c\right) + L_{vent}(M_{RV}, M_{LV}) + L_{reg}(\varphi)$$

L_{sim} … ***Similarity Loss*** *to penalize the difference in appearance between the fixed and warped image*

L_{cont} …***Contrast Concentration Loss*** *to guide the deformation of the warped image by penalizing the alteration of contrast between the moving and the warped image*

L_{vent} …***Ventricle Loss*** *to measure and optimize the alignment of the right and left ventricle between the fixed and the warped image*

L_{reg} … ***Regularization Loss*** *to encourage the continuity of the flow field*

Dataset and Experiments

Dataset:

From dynamic CT myocardial perfusion study (NTC 02361996)

- 118 subjects with known or suspected coronary artery disease
- Total of 944 2D sequences (30 – 40 frames)
- Data split on subject-level: 80% training and 20% validation

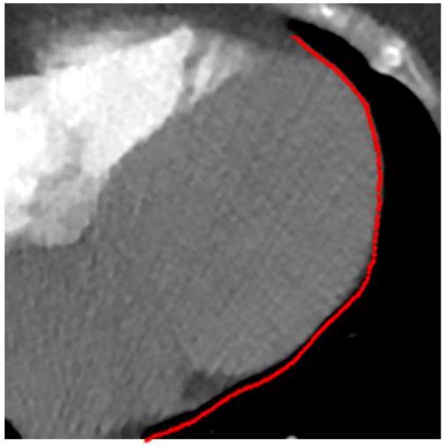
Experiments:

- Implemented models using 3, 5, 7, 10 cascades
- Loss functions: ***LCV, LC, LNC***

- Compared to two iterative registration methods Wollny et al. [2] and Janssens et al. [3]
- Qualitative and quantitative evaluation

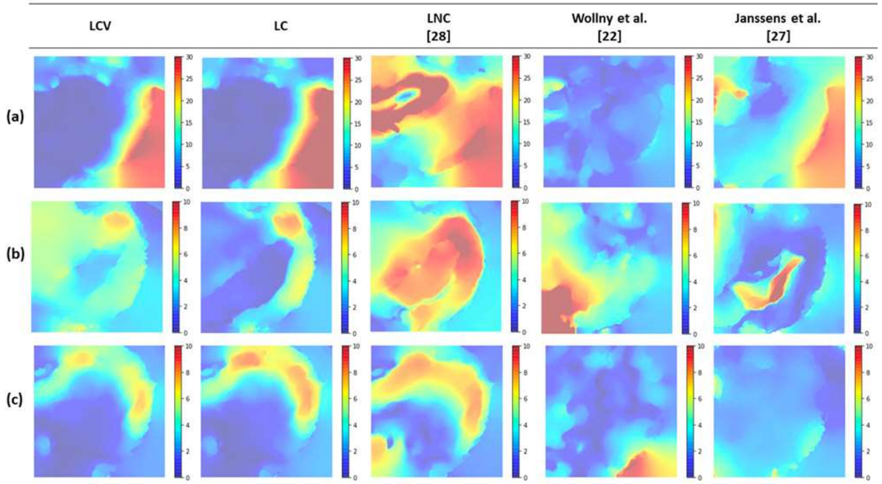
[1] . Zhao, Y. Dong, E. I.-C. Chang, and Y. Xu, “Recursive Cascaded Networks for Unsupervised Medical Image Registration,” *2019 IEEE/CVF International Conference on Computer Vision (ICCV)*, pp. 10599–10609, Oct. 2019, doi: 10.1109/ICCV.2019.01070.
[2]G. Wollny, M. J. Ledesma-Carbayo, P. Kellman, and A. Santos, “Exploiting Quasiperiodicity in Motion Correction of Free-Breathing Myocardial Perfusion MRI,” *IEEE Trans. Med. Imaging*, vol. 29, no. 8, pp. 1516–1527, Aug. 2010, doi: 10.1109/TMI.2010.2049270.
[3] G. Janssens, L. Jacques, J. Orban de Xivry, X. Geets, and B. Macq, “Diffeomorphic Registration of Images with Variable Contrast Enhancement,” *International Journal of Biomedical Imaging*, vol. 2011, pp. 1–16, 2011, doi: 10.1155/2011/891585.

Sequence Registration Results

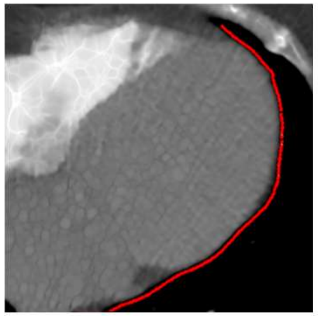
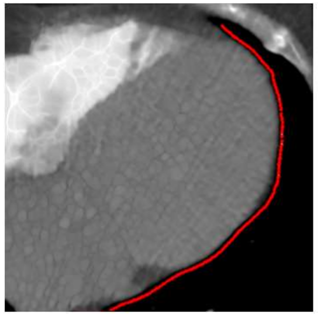
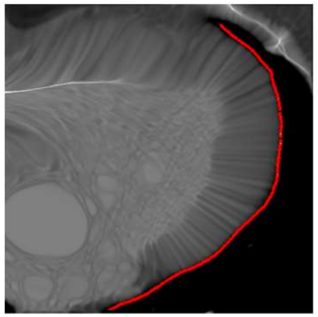
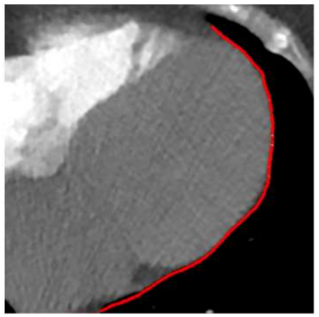
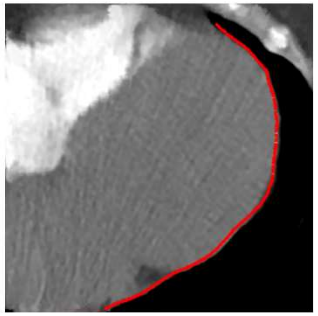


*Reference contour of fixed image

Flow fields



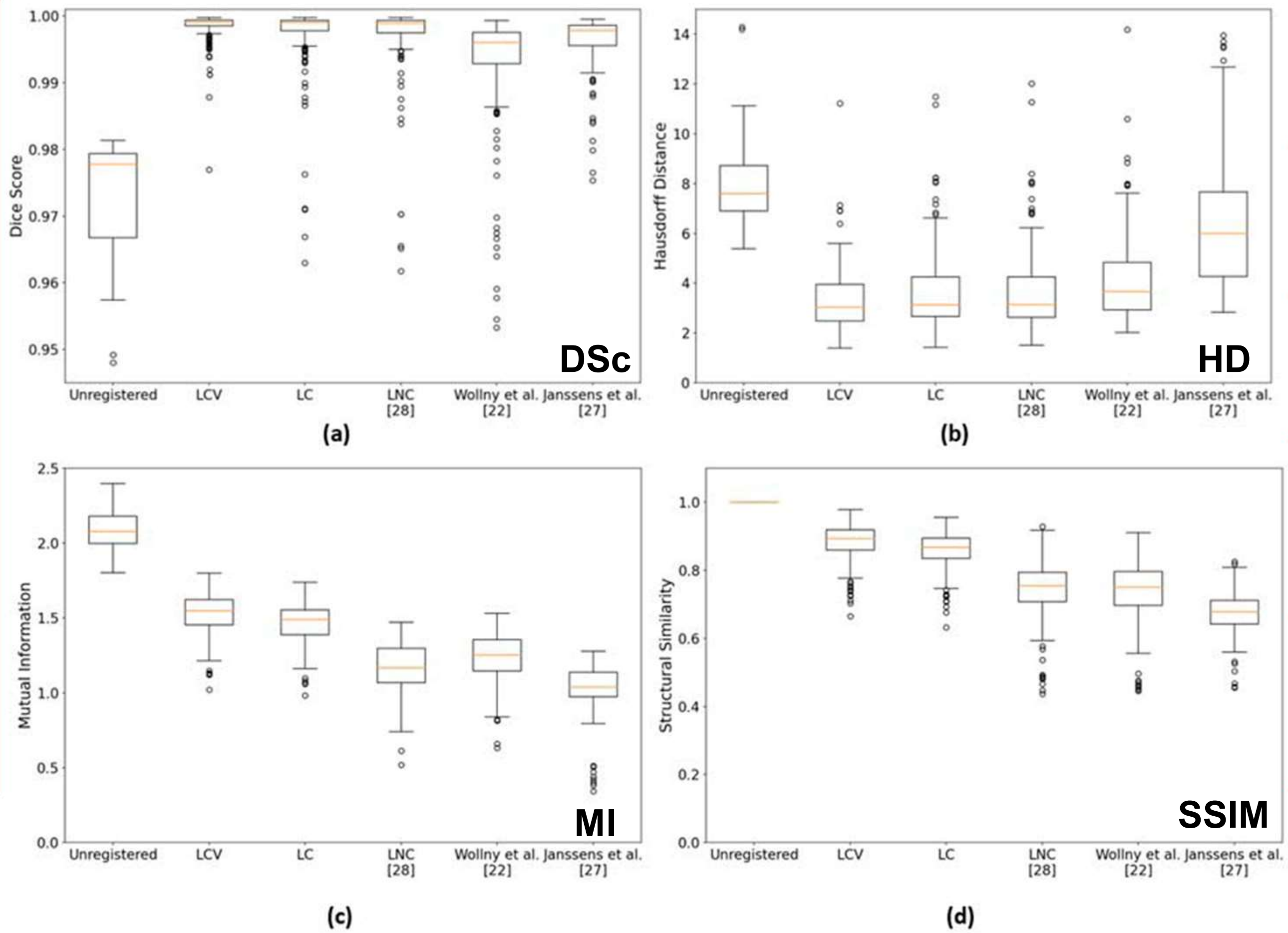
Color red and blue: large and small displacements

LCV	LC	LNC [28]	Wollny et al. [22]	Janssens et al. [27]
				

Results sequence registration

Sequence Registration Results

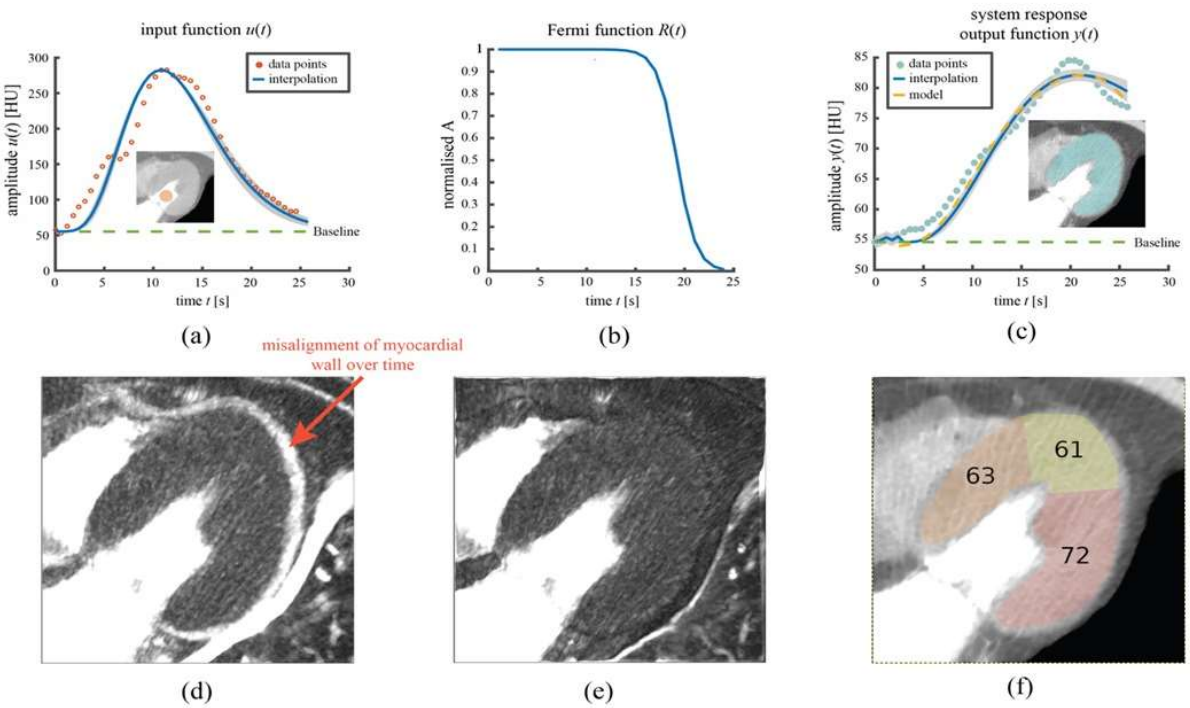
Methods	DSc	HD	MI	SSIM	Running Time (s)	
	Spatial alignment		Image quality		CPU	GPU
					10.8 (2.1)	0.92 (0.18)
					10.8 (2.1)	0.91 (0.18)
					10.8 (2.1)	0.92 (0.17)
					543 (5.9)	-
					13800 (1405)	-



Run time is measured and averaged over 245 2D cardiac sequences

Clinical Example & Summary

Patient with minor coronary artery disease



- First deformable deep learning-based image registration method for cardiac CT perfusion imaging.
- Introduced a novel loss function that accounts for local contrast changes over time and maintains HU (quantitative gray) values.
- Higher registration performance and shorter computational time (**sec**) compared to established methods (**hours**).
- Excellent clinical usability.

(a) CT values time curves obtained from a ROI in the LV cavity (input function u(t))
(b) Fermi-function for deconvolution (c) measured and estimated CT values-time curves in the segmented LV myocardial wall (output function y(t)).
(d) difference in HU values over time for the unregistered images (misalignment of the myocardium over the sequence).
(e) difference in HU values over time for the registered images (aligned LV myocardium after LCV registration).
(f) calculated regional myocardial perfusion in ml/100g/min for the apical (yellow), septal (orange) and lateral wall region (red).

Clinical Usability of AI/ML-based Methods?

Table 8
Assessment of clinical usability in identified papers. The works of [29,43,47,60,71] were evaluated according to the two applications described in the papers (indicated by the symbol "*"). The acronyms in Clinical Usability stand for: Robust Candidate (RC) and Proof of Concept (PoC). The symbol "/" stands for not applicable.

Reference	Dataset	Data Annotation	Data Preprocessing	Learning Strategy	Test Performance	Validation	Clinical Usability
Cardiac Segmentation							
Li et al. [40]	1	2	2	3	1	2	PoC
Jafari et al. [41]	2	1	1	3	2	2	PoC
Li et al. [42]	3	3	1	3	2	2	RC
Li et al. [43]*	3	3	1	3	2	2	RC
Savioli et al. [44]	2	1	1	3	3	2	PoC
Yan et al. [45]	3	3	2	3	2	2	RC
Punithakumar et al. [46]	1	2	2	3	1	2	PoC
Qin et al. [47]*	2	1	2	2	2	2	PoC
Myronenko et al. [48]	1	2	1	3	2	2	PoC
LV Quantification and Cardiac Phase Detection							
Dezaki et al. [49]	2	2	1	3	1	2	PoC
Kong et al. [51]	2	1	1	3	2	2	PoC
Li et al. [43]*	2	3	2	3	2	2	RC
Xue et al. [26]	3	3	1	3	2	2	RC
Debus & Ferrante [28]	2	3	1	3	2	2	RC
Cardiovascular Disease Assessment							
Tanno et al. [52]	2	2	1	3	2	2	RC
Isensee et al. [53]	2	1	1	3	2	2	PoC
Zheng et al. [54]	2	1	2	3	2	2	PoC
Chen et al. [30]	2	2	2	3	2	2	RC
Xu et al. [31]	2	2	2	3	2	2	RC
Xu et al. [32]	2	3	2	3	3	2	RC
Zhang et al. [58]	2	2	2	3	3	2	RC
Bello et al. [59]	2	3	2	3	1	1	PoC
Cardiac Motion Tracking and Cardiac Strain Analysis							
Lu et al. [29] (synthetic)*	1	3	1	2	2	2	PoC
Lu et al. [29] (canine)*	1	3	2	2	1	2	PoC
Parajuli et al. [60] (synthetic)*	1	3	2	1	2	2	PoC
Parajuli et al. [60] (canine)*	1	3	2	1	2	2	PoC
Omar et al. [61]	1	3	2	3	2	2	PoC
Wu et al. [62]	1	3	2	3	2	2	PoC
Xue et al. [27]	2	2	1	3	1	2	PoC
Qin et al. [47]*	2	1	2	2	1	2	PoC
Other Applications							
Abdi et al. [65]	2	3	2	3	2	2	RC
Gao et al. [66]	2	3	1	3	2	2	RC
Gao and Noble [67]	2	1	2	3	2	2	PoC
Huang et al. [68]	1	2	2	3	2	1	PoC
Patra and Noble [69]	1	1	2	3	1	2	PoC
Oksuz et al. [70]	2	2	2	3	2	2	RC
Guo et al. [71] (CMR)*	2	/	1	1	2	2	PoC
Guo et al. [71] (CT)*	1	/	1	1	2	2	PoC

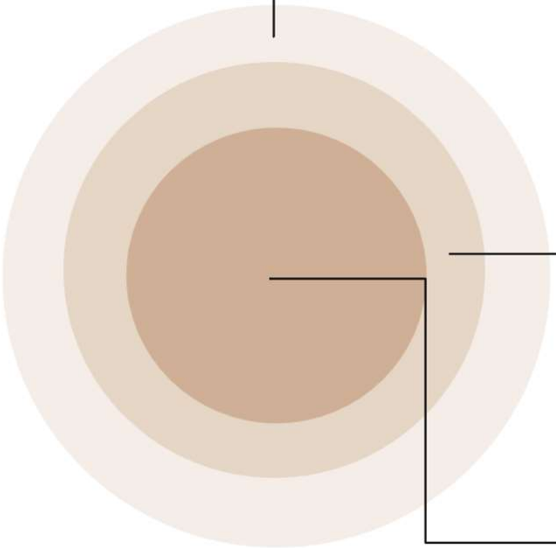
Not a single one of the reviewed papers was classified as a "clinical level" study.

Almost 39% of the articles achieved a "robust candidate" and as many as 61% a "proof of concept" status.

Lara Hernandez KA, Rienmüller TM, Baumgartner D, Baumgartner C. Deep learning in spatiotemporal cardiac imaging: A review of methodologies and clinical usability. ***Comp Biol Med.*** 2021, 130, 104200. https://doi.org/10.1016/j.compbiomed.2020.104200

Lara-Hernandez A, Rienmüller T, Juárez I, Pérez M, Reyna F, Baumgartner D, Makarenko VN, Bockeria OL, Maksudov M, Rienmüller R, Baumgartner C. Deep Learning-Based Image Registration in Dynamic Myocardial Perfusion CT Imaging. ***IEEE Trans Med Imag***. 2023, 42(3), 684-696. https://doi.org/10.1109/TMI.2022.3214380

Artificial Intelligence and Machine Learning in Medical Devices & Software as a Medical Device



Medical device: Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material, or other similar or related article intended to be used, alone or in combination, in human beings for one or more medical purposes.[2]

Software as a medical device (SaMD): Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

Artificial intelligence (AI) as a medical device (AIaMD): A medical device that uses machine learning (ML), in part or in whole, to achieve its intended medical purpose.

Medical devices including software require regulatory approval to market in the EU and before they can be used on patients.

EU: Medical Device Regulation (MDR)

US: FDA Medical Device Approval (510k, PMA, de-novo)

Brazil: ANVISA Medical Device Regulations

Artificial Intelligence and Machine Learning in Medical Devices & Software as a Medical Device

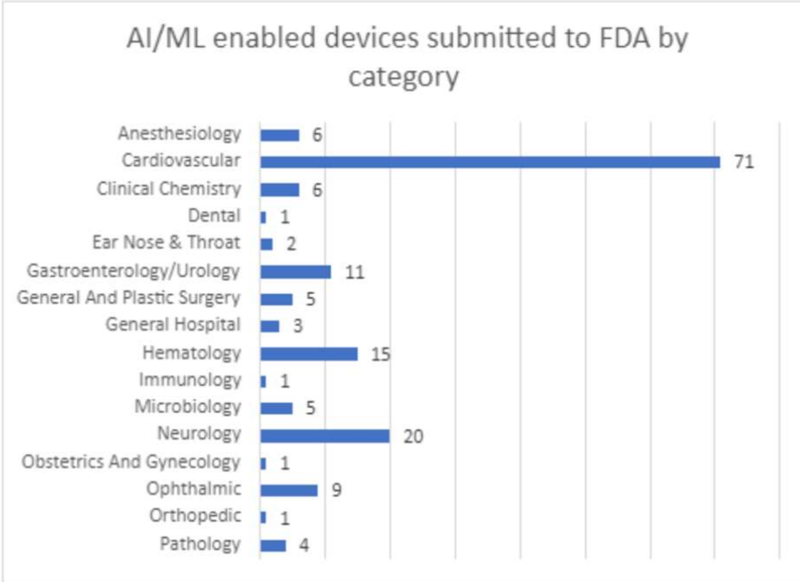
Current state of regulating AI as a Medical Device (MD)

To date, there is no harmonized global standard or body that specifically regulates the use of AI and ML in medical devices.

These devices must comply with existing medical device regulatory requirements (safety and performance requirements , risk and quality management, clinical evaluation, usability, etc.).

Additional requirements and approaches are added to existing requirements to address the unique characteristics of software/AIaMD.

USFDA-approved AI/ML-enabled devices[1] as of 2023



As of July 2023, 692 devices have been approved by the US Food and Drug Administration (USFDA; 531 of them for radiology that are not included in chart). None of the approved devices use generative AI, artificial general intelligence, or are powered by large language models (LLMs).

Artificial Intelligence and Machine Learning in Medical Devices & Software as a Medical Device

Certifiability of continuous-learning AI systems in Europe/USA?

Static AI ('locked' software algorithms with fixed functions): AI that has learnt and works in a learnt state is certifiable.

Dynamic AI („non-locked" adaptive, continuous learning algorithms'): AI that continues to learn in the field is currently <u>not</u> certifiable, as the system must be verified and validated (among other requirements, the functionality must be validated against the intended use)".

Generative AI including LLMs: AI that generates new data, images, text, etc. is currently <u>not</u> certifiable.

In connection with continuously learning AI systems, there are calls for the Predetermined Change Control Plan (PCCP) proposed by the FDA to also be adopted in Europe as part of an anticipatory conformity assessment.

Digital Twins and AI in Biomedical Technology Conclusion

Advantages

Personalized medicine: DW enable the development of personalized treatment plans and therapies, forecasts potential health outcomes, allows for proactive intervention and enhances disease management.

Predictive Analytics: DW can simulate different treatment scenarios, predicting outcomes and helping to choose the most effective intervention.

Big Data Handling: AI/ML can analyze vast amounts of biomedical data much faster than humans, identifying patterns and correlations that might be missed otherwise.

Enhanced Diagnostic Accuracy: AI/ML algorithms can assist in diagnosing diseases with higher accuracy by recognizing complex patterns in medical images, genetic data, and other diagnostic tools.

Digital Twins and AI in Biomedical Technology Conclusion

Challenges

Data Integration and Management:
Complexity of Data: Integrating data from diverse sources such as electronic health records, medical imaging, wearable devices, genomic data can be complex and require advanced data management systems.
Data Quality: Ensuring the accuracy, consistency, and completeness of the data used to create and update digital twins is crucial and difficult to achieve.

Computational Demands:
High-Performance Computing: Simulating a digital twin in real-time requires significant computational power, which can be costly and resource-intensive.
Scalability: Scaling the technology to handle large populations or more complex models can be a significant technical challenge.

Combination of DT and AI:
Increased complexitiy of model construction, verification and validation.

Digital Twins and AI in Biomedical Technology Conclusion

Challenges

Data Quality and Bias:
Training Data: AI systems require high-quality, representative training data. Inadequate or biased data can lead to inaccurate or unfair outcomes.
Generalization: Across diverse populations and settings is crucial & challenging.

Regulatory and Ethical Issues:
Approval Processes: Approvals from bodies like the FDA or NB (EU) for AI in healthcare is complex and time-consuming.
Ethical Concerns: Informed consent, transparency, accountability, and the potential for AI to exacerbate health disparities is essential.

Explainability and Trust:
Black Box Models: Many AI models (e.g. DL) operate as "black boxes," making it difficult to understand and explain their decisions.
Trust: Building trust among healthcare providers and patients in AI-driven decisions and requires transparent and explainable AI systems.

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HCE HEALTH CARE ENGINEERS

TU Graz

Institute of Health Care Engineering with European Testing Center of Medical Devices

Stremayrgasse 16/II

8010 Graz

Phone: +43 (316) 873 - 7377

Fax: +43 (316) 873 - 107377

Office hours: nach Vereinbarung

christian.baumgartner@tugraz.at

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HEALTH CARE ENGINEERS

Digital Twins and AI in Biomedical Technology

In-silico meets in-vitro/in-vivo

Christian Baumgartner

Institute of Health Care Engineering with
European Testing Center of Medical Devices

Graz University of Technology, Austria

42th Conference of Rectors and Presidents of European Universities of Technology,
Sept. 20-21, 2024, Bucharest