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Advancing personalised care in atrial fibrillation and stroke: the potential impact of AI from prevention to rehabilitation

Supplementary Material

Advancing personalised care in atrial fibrillation and stroke: the potential impact of AI from prevention to rehabilitation

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S1. The need for personalised care across the disease pathway - Illustrating the sex differences

There are sex differences in AF across the scope of the disease pathway and its related adverse outcomes (i.e., stroke), from epidemiology and causative mechanisms to management and outcomes. It has been reported the incidence of AF is greater in men than in women, but this gap closes with advancing age as women usually develop AF ten years later than men. The Atherosclerosis Risk in Communities (ARIC) cohort [1], a group of >15K participants followed for nearly 30 years, showed a lifetime risk of AF of 36% in white men compared to 30% in white women. African American men and women both were found to have a lower lifetime risk of AF, at 21% and 22% respectively.

While women have a lower incidence of AF, its prevalence in men and women age >75 years is greater in women due to their increased longevity, and the absolute number of men and women with AF is similar on a population basis. There are sex differences also in the management of AF. In a recent European AF registry [2], from >7K patients enrolled (2012-2013), women were older and more symptomatic. They were less likely to undergo electrical cardioversion, catheter ablation, or surgical ablation, but were more likely to be prescribed antiarrhythmic medications.

In patients with AF, female sex was previously identified as an independent significant risk factor of stroke, with several older studies supporting the existence of excess risk of stroke in females with AF [3]. However, it is less clear whether this differential association in women is causal. The reason for the increased risk of stroke in women with AF is not fully known and while it may be related to hormonal mechanisms, the evidence is conflicting [4,5].

Preventing stroke is a primary clinical focus for patients with AF, requiring careful risk stratification to balance the benefits of anticoagulation with the potential risk of bleeding [6]. Oral anticoagulation treatments have been shown to effectively reduce the risk of stroke across different patient populations, but data on sex differences in anticoagulation of patients with AF and outcomes are not consistent [7]. Risk scores such as CHA_2DS_2-VASc, included female sex as a risk component. However, more contemporary evidence suggests the non-sex CHA_2DS_2-VASc score (CHA_2DS_2-VA) could be used for initial decision-making [8,9] such that the female sex was a risk modifier rather than a risk factor per se, being additive to stroke risk in the presence of 1 or more non-sex stroke risk factors [10–12]. This has led to recent European guidelines recommending the CHA_2DS_2-VA score [13].

Sex differences are also prevalent in stroke rehabilitation, potentially because they tend to experience stroke at an older age than men [14]. Women tend to experience worse functional recovery than men, with a study in a Danish population showing that females were more dependent on activities of daily living (ADL) than males in the acute phase (first 2 weeks) of stroke rehabilitation [15]. Strokes in older women are commonly more severe than in men and they also experience greater disability following stroke [16,17].

S2. Barriers to the implementation of digital twins in healthcare

The implementation of digital twins in healthcare faces several challenges that limit their adoption and integration into clinical practice, as outlined in a position paper [18] by the EDITH consortium, in seven key barriers (B1-B7). A critical barrier is the lack of advanced, robust predictive models that accurately reflect the complexity and variability of human physiology on an individual level (B1). This deficiency is worsened by challenges in integrating diverse in-silico technologies, from data-driven to knowledge-driven approaches, as well as the scarcity of curated, representative datasets for model development and validation (B2). Strict privacy laws and a limited understanding of required data types further complicate data availability and sharing. Furthermore, regulatory uncertainties, including the absence of harmonised credibility assessments and clear pathways for the evaluation of in-silico methods, create obstacles in adopting these technologies in regulatory frameworks (B3).

Additional challenges include a lack of awareness and understanding among key stakeholders (policymakers, clinicians, patients, and industry executives) about the benefits and risks of digital twin technologies (B4). Poor scalability and computational inefficiency limit the deployment of population-scale models in accessible, secure environments (B5). The healthcare sector also faces a shortage of trained professionals equipped with the necessary technical expertise to develop, implement, and regulate these technologies (B6). Finally, immature business models and uncertainties in commercialising digital twin solutions present barriers to market adoption (B7). Addressing these interrelated challenges is crucial for advancing digital twin adoption and transforming clinical care and research.

Earlier studies such as Mohamed et al [19], also identified challenges related to the quality of the data, involving data collection and validation, knowledge extraction, and noise; as well as the modelling, including model validation, level of abstraction and representation, and process automation, which are (to some extent) reflected in the key barriers outlined in [18]. Data-related challenges focusing on collection, security, privacy, and ownership, as well as other technical challenges related to modelling the virtual representations of the physical entities, were also highlighted in a systematic review by Xames and Topcu [20]. In addition, requirements for strong data infrastructures and the need for trustable methodologies and technologies are also some of the challenges highlighted by Zayed et al [21].

Practical challenges also emerge in aligning the infrastructure and methodologies necessary for implementing these tools, as recognised in the aforementioned barriers. For instance, the inconsistent structure and quality of data from disparate sources complicate its usability, often requiring significant preprocessing and curation efforts. Ensuring robust anonymisation and compliance with privacy frameworks while maintaining data usability for high-fidelity modelling is a delicate balance. Moreover, the limited interoperability of current tools and devices with electronic health record (EHR) systems hinders seamless integration, reducing the potential for real-time updates and feedback in clinical workflows. Addressing these gaps requires not only technical advancements but also the establishment of common standards, collaborative frameworks, and a supportive regulatory landscape to foster innovation and ensure these technologies are deployed effectively and securely in practice.

S3. Personalised stroke care today: how far have we come? Survey of the literature

To survey the literature on advances in personalised approaches to stroke care, searches were conducted in PubMed/MEDLINE and SCOPUS (see Figure S1). The searches focused on English-language sources, and they involved searching in the title, the abstract and the keywords for the following terms: “stroke” + “AI OR artificial intelligence OR machine learning OR deep learning” + “personali?ation OR personali?ed OR digital twi*”. A total of 330 articles were extracted (date: 2nd March 2024), of which 92 were excluded as they were either review articles (78) or editorials, letters or notes (14). After further screening of the titles and abstracts, 219 articles were also excluded because a) they were duplicated, b) the proposed approach related to stroke care was not personalised (even if it could lead to tailored and personalised approaches in the future) or c) they were not relevant (e.g. referred to stroke in the context of handwriting). The remaining 19 articles were read and reviewed in full, and a further 5 articles were removed due to lack of detail or quality, e.g. no details about the data source or data cohort used. The final list of 14 articles is summarised in Table S1, and a selection is discussed next. It is also worth mentioning that the majority (95%) of these selected articles were published in the last five years (since 2019).

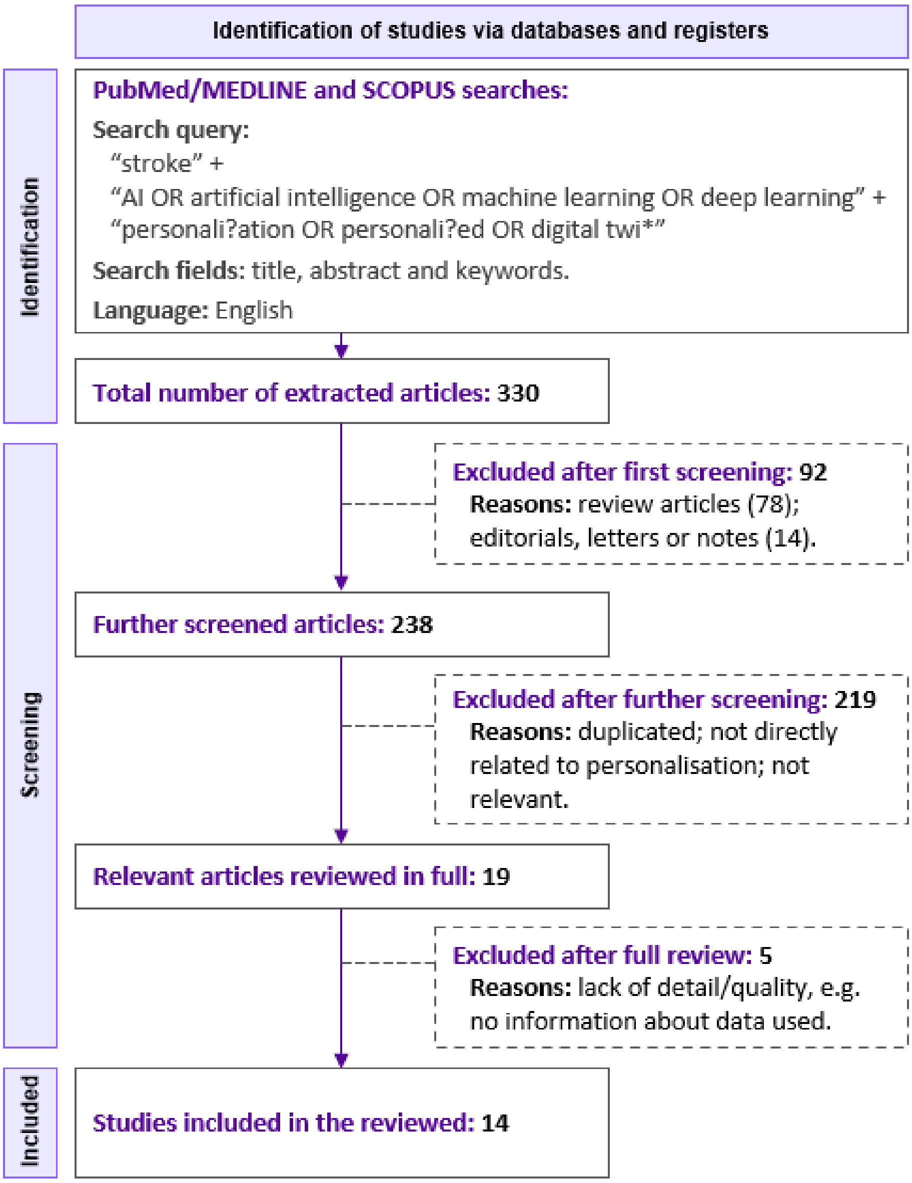

Figure S1. Flowchart with the selection of articles relevant to this review.

Table S1. Summary of the 19 articles fully reviewed.

Year	Reference	Methodology	Data origin	Data size (N)	Results
Risk prediction					
2022	Zheng et al. [22] (Original article)	• Six models developed: logistic regression (LR), k-nearest neighbours (KNN), Naïve Bayes, XGBoost, random forest (RF), and neural networks (NN). • LIME and SHAP used for explaining the ML models and to draw case-level details for individual patients.	Private data. • Modelling dataset: Second Affiliated Hospital of Shandong First Medical University. • External dataset: Dongping People's Hospital.	• Models trained on: N=10,476 (4,999 stroke patients) using 80/20% split for train/test. • External validation: N=3,935 (1,076 stroke)	• Best model: XGBoost. • Modelling data AUCs (95% CI): 0.91 (0.90–0.92) • External validation AUCs (95% CI): 0.92 (0.91–0.93)
2022	Doborjeh et al. [23] (Original article)	• Proposed a method to identify associations between clinical and environmental data. • The methodology uses KNN and spiking neural networks (SNN) to develop what the authors call a 'personalised' model. • There is possible data leakage.	Private data. • Patient data: from Auckland, NZ (data origin not detailed). • Environmental data: Auckland city, (same period as patient data).	• N=804 stroke patients. • Environmental data: 10 meteorological monitors in Auckland city, NZ. • No external validation data used.	• Significant differences found in the interactions for all the environmental variables for all models in high vs low risk.
2021	Allen et al. [24] (Original article)	• Developed a model of disease progression using variational autoencoder (VAE) and used it to generate synthetic samples resembling the input data, which authors called digital twins.	Publicly available data. • MIMIC-IV database.	• N=1,216 stroke patients. Training: 1,094 and test: 122. • No external validation data used.	• Real and simulated data exhibited indistinguishable covariate distributions.
2021	Jia et al. [25] (Conference paper)	• Trained a convolutional neural network (CNN) enhanced with expert knowledge and patient-derived data to detect AF on a cardiac monitoring device. • Manually verified ECGs of AF episodes are required to ensure reliability.	Publicly available data. • Four ECG databases: Chapman dataset; China Physiological Signal Challenge 2018 (CPSC) dataset; The Long Term AF Database (LTAFDB); and the MIT-BIH-AF.	• Chapman and CPSC (for modelling). Train: N=16,781 subjects. Test: N=4,195 subjects. • LTAFDB and MIT-BIH-AF used for personalisation of the model.	• Best model: CNN-ResNet-Prior • F1=0.898, accuracy=0.976. • No AUC reported.
Management					
2021	Buoso et al. [26] (Original article)	• Proposed a method to simulate left-ventricular biomechanics coupling NNs with a simplified circulation model, more efficient than the reference Finite Element model used.	Private data. • Multi-Modal Whole Heart (MMWH) dataset.	• Left-ventricular anatomies from N=75 cases of the dataset.	• New model was 30x faster than the reference. • Used performance metrics of clinical interest, e.g. ejection fraction.
2020	Litman E. [27] (Conference paper)	• Developed an SNN model on temporal electroencephalographic (EEG) data to detect cerebral ischaemia.	Publicly available data. • Temple University Hospital EEG Corpus (TUEG).	• N=92 subjects (46 stroke patients, 46 healthy), using 70/30% split for train/test. • No external validation data used.	• Cross-validation. • F1=0.94 • Accuracy=0.945 • Precision=0.923 • Recall=0.962. • No AUC reported.
2019	King et al. [28] (Original article)	• Proposed a mechanistic method for simulating left ventricular pressure-volume control. • The approach uses a logic-based conditional finite state machine based on the four pressure-volume phases of the left ventricle.	Publicly available data. • MathWorks' Simulink, Simscape, and Simscape Fluids.	• Parameters derived from the literature.	• The difference between desired and simulated pressure and volume set points produced an error of <1 mmHg and <1 mL.
Rehabilitation					
2023	Winner et al. [29]	• Developed a data-driven approach based on recurrent NNs to predict gait dynamics of individuals, representing them in a low-	Publicly available data. • Emory Rehab Hospital Motion Analyses Lab.	• N=7 able-bodied healthy participants and N=7 stroke survivors (>6 months post-stroke).	• Used a leave-one-out subject approach for model evaluation,

	(Original article)	dimensional space after applying principal component analysis (PCA).		• No external validation data used.	comparing differences in loss.
2023	Korivand et al. [30] (Original article)	• Proposed a pipeline for rehabilitation, focusing on upper limb movement. • It involved classification (Naïve Bayes, KNN, NNs, etc.), source localisation, and visualisation of EEG.	Private data. • University of Maryland, Baltimore.	• N=1 healthy 35-year-old male participant, who performed several arm-reaching movements. • No test on multiple subjects. • No external data used.	• Best model: the Decision Trees. • Accuracy=0.956 • AUC=0.890
2023	Faria et al. [31] (Original article)	• Proposed a cognitive profiling and training methodology. • It used AI (embedded into an existing platform) to optimise neurorehabilitation prescription.	Private data. • University of Madeira.	• Methodology tested on N=10 stroke survivors. • No external validation data used.	• No AI-related results reported. • Results suggest improved short-term cognitive and functional abilities.
2020	Lee et al. [32] (Conference paper)	• Assessed the quality of upper limb rehabilitation exercises. • It used Markov Decision Process to find an optimal feature set, and then applied several ML algorithms (incl. LR, RF, and NN). • Integrated Expert knowledge using ensemble techniques.	Private data. • Own collected dataset.	• N=11 healthy (165 unaffected motions) and N=15 post-stroke subjects (150 affected motions). • No external validation data used.	• Leave one out used for evaluation. • Best model was hybrid. • Average performance: F1-score=0.912±0.023.
2020	Rose et al. [33] (Conference paper)	• Developed a model-free control technique that learns gait patterns for control of a lower limb exoskeleton. • The technique is based on deep reinforcement learning.	Publicly available data. • OpenSim's Gait2392 model (anatomically representing a human with height=1.8m and mass=76.16kg).	• Musculoskeletal model derived from OpenSim's Gait2392 model. • No external data used.	• The learned torque control allowed the exoskeleton to follow the trained gait pattern.
2019	Jung et al. [34] (Conference paper)	• Used RF for regression to predict the post-treatment cognitive impairment level using baseline information (mental status and game performance).	Private data. • University of Massachusetts, USA. Heeyeon Rehab. Hospital, South Korea.	• N=14 post-stroke patients. • No external validation data used.	• R^2=0.87. • Root mean square error (RMSE)=0.58. • Normalized RMSE (NRMSE)=9.8%
2016	Munoz-Organero et al. [35] (Original article)	• Proposed a system to automatically detect different walking strategies used by stroke survivors. • For this, it analysed insole pressure sensors data using decision trees.	Private data. • Collected by the CATCH HomeLab, at the University of Sheffield.	• N=14 stroke survivors and N=10 healthy controls. • No external data used.	• Results showed that insoles can help characterise walking strategies found in stroke survivors.

References

[1] The ARIC Investigators. The Atherosclerosis Risk In Communities (ARIC) Study: Design and Objectives. Am J Epidemiol 1989;129.

[2] Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: Primary results of the PREvention oF thromboemolic events-European Registry in Atrial Fibrillation (PREFER in AF). Europace 2014;16. https://doi.org/10.1093/europace/eut263.

[3] Corica B, Lobban T, True Hills M, Proietti M, Romiti GF. Sex as a Risk Factor for Atrial Fibrillation-Related Stroke. Thromb Haemost 2024;124:281–5. https://doi.org/10.1055/s-0043-1776394.

[4] Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Hormone replacement therapy and adverse outcomes in women with atrial fibrillation: An analysis from the atrial fibrillation follow-up investigation of rhythm management trial. Stroke 2014;45. https://doi.org/10.1161/STROKEAHA.114.006668.

[5] Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: Analysis of 2012 participants in the SPAF I-III clinical trials. Stroke 1999;30. https://doi.org/10.1161/01.STR.30.6.1223.

[6] Chao TF, Potpara TS, Lip GYH. Atrial fibrillation: stroke prevention. The Lancet Regional Health - Europe 2024;37:100797. https://doi.org/10.1016/j.lanepe.2023.100797.

[7] Nielsen PB, Overvad TF. Female Sex as a Risk Modifier for Stroke Risk in Atrial Fibrillation: Using CHA 2 DS 2 -VASc versus CHA 2 DS 2 -VA for Stroke Risk Stratification in Atrial Fibrillation: A Note of Caution. Thromb Haemost 2020;120. https://doi.org/10.1055/s-0040-1710014.

[8] Lip GYH, Teppo K, Nielsen PB. CHA2DS2-VASc or a non-sex score (CHA2DS2-VA) for stroke risk prediction in atrial fibrillation: contemporary insights and clinical implications. Eur Heart J 2024. https://doi.org/10.1093/eurheartj/ehae540.

[9] Teppo K, Lip GYH, Airaksinen KEJ, Halminen O, Haukka J, Putaala J, et al. Comparing CHA2DS2-VA and CHA2DS2-VASc scores for stroke risk stratification in patients with atrial fibrillation: a temporal trends analysis from the retrospective Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) cohort. The Lancet Regional Health - Europe 2024;43:100967. https://doi.org/10.1016/j.lanepe.2024.100967.

[10] Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation. Circulation 2018;137. https://doi.org/10.1161/circulationaha.117.029081.

[11] Teppo K, Airaksinen KEJ, Jaakkola J, Halminen O, Salmela B, Kouki E, et al. Ischaemic stroke in women with atrial fibrillation: temporal trends and clinical implications. Eur Heart J 2024;45:1819–27. https://doi.org/10.1093/eurheartj/ehae198.

[12] Nielsen PB, Brøndum RF, Nøhr AK, Overvad TF, Lip GYH. Risk of stroke in male and female patients with atrial fibrillation in a nationwide cohort. Nat Commun 2024;15:6728. https://doi.org/10.1038/s41467-024-51193-0.

[13] Van Gelder IC, Rienstra M, Bunting K V, Casado-Arroyo R, Caso V, Crijns HJGM, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024. https://doi.org/10.1093/eurheartj/ehae176.

[14] Persky RW, Turtzo LC, McCullough LD. Stroke in women: Disparities and outcomes. Curr Cardiol Rep 2010;12. https://doi.org/10.1007/s11886-009-0080-2.

[15] Liljehult MM, von Euler-Chelpin MC, Christensen T, Buus L, Stokholm J, Rosthøj S. Sex differences in independence in activities of daily living early in stroke rehabilitation. Brain Behav 2021;11. https://doi.org/10.1002/brb3.2223.

[16] Wiley E, Noguchi KS, Moncion K, Stratford PW, Tang A. Sex Differences in Functional Capacity in Older Adults With Stroke: An Analysis of Data From the National Health and Aging Trends Study. Phys Ther 2022;102. https://doi.org/10.1093/ptj/pzac077.

[17] Lang C, Seyfang L, Ferrari J, Gattringer T, Greisenegger S, Willeit K, et al. Do Women with Atrial Fibrillation Experience More Severe Strokes?: Results from the Austrian Stroke Unit Registry. Stroke 2017;48. https://doi.org/10.1161/STROKEAHA.116.015900.

[18] Viceconti M, De Vos M, Mellone S, Geris L. Position Paper from the Digital Twins in Healthcare to the Virtual Human Twin: A Moon-Shot Project for Digital Health Research. IEEE J Biomed Health Inform 2024;28. https://doi.org/10.1109/JBHI.2023.3323688.

[19] Mohamed N, Al-Jaroodi J, Jawhar I, Kesserwan N. Leveraging Digital Twins for Healthcare Systems Engineering. IEEE Access 2023;11. https://doi.org/10.1109/ACCESS.2023.3292119.

[20] Xames MD, Topcu TG. A Systematic Literature Review of Digital Twin Research for Healthcare Systems: Research Trends, Gaps, and Realization Challenges. IEEE Access 2024;12. https://doi.org/10.1109/ACCESS.2023.3349379.

[21] Zayed SM, Attiya GM, El-Sayed A, Hemdan EED. A review study on digital twins with artificial intelligence and internet of things: concepts, opportunities, challenges, tools and future scope. Multimed Tools Appl 2023;82. https://doi.org/10.1007/s11042-023-15611-7.

[22] Zheng Y, Guo Z, Zhang Y, Shang J, Yu L, Fu P, et al. Rapid triage for ischemic stroke: a machine learning-driven approach in the context of predictive, preventive and personalised medicine. EPMA Journal 2022;13. https://doi.org/10.1007/s13167-022-00283-4.

[23] Doborjeh M, Doborjeh Z, Merkin A, Krishnamurthi R, Enayatollahi R, Feigin V, et al. Personalized Spiking Neural Network Models of Clinical and Environmental Factors to Predict Stroke. Cognit Comput 2022;14. https://doi.org/10.1007/s12559-021-09975-x.

[24] Allen A, Siefkas A, Pellegrini E, Burdick H, Barnes G, Calvert J, et al. A digital twins machine learning model for forecasting disease progression in stroke patients. Applied Sciences (Switzerland) 2021;11. https://doi.org/10.3390/app11125576.

[25] Jia Z, Shi Y, Saba S, Hu J. On-device Prior Knowledge Incorporated Learning for Personalized Atrial Fibrillation Detection. ACM Transactions on Embedded Computing Systems, vol. 20, 2021. https://doi.org/10.1145/3476987.

[26] Buoso S, Joyce T, Kozerke S. Personalising left-ventricular biophysical models of the heart using parametric physics-informed neural networks. Med Image Anal 2021;71. https://doi.org/10.1016/j.media.2021.102066.

[27] Litman E. Computer-aided Ischemic Stroke Classification from EEG Data Using a Single-tiered Spiking Neural Network Framework. 2020 11th IEEE Annual Ubiquitous Computing, Electronics and Mobile Communication Conference, UEMCON 2020, 2020. https://doi.org/10.1109/UEMCON51285.2020.9298099.

[28] King JM, Bergeron CA, Taylor CE. Finite state machine implementation for left ventricle modeling and control. Biomed Eng Online 2019;18. https://doi.org/10.1186/s12938-019-0628-3.

[29] Winner TS, Rosenberg MC, Jain K, Kesar TM, Ting LH, Berman GJ. Discovering individual-specific gait signatures from data-driven models of neuromechanical dynamics. PLoS Comput Biol 2023;19:e1011556. https://doi.org/10.1371/JOURNAL.PCBI.1011556.

[30] Korivand S, Zhu X, Jalili N, Koh K, Zhang LQ, Gong J. Toward personalized rehabilitation employing classification, localization, and visualization of brain–arm movement relationships. Smart Health 2023;28. https://doi.org/10.1016/j.smhl.2023.100397.

[31] Faria AL, Almeida Y, Branco D, Câmara J, Cameirão M, Ferreira L, et al. NeuroAIreh@b: an artificial intelligence-based methodology for personalized and adaptive neurorehabilitation. Front Neurol 2023;14:1258323. https://doi.org/10.3389/FNEUR.2023.1258323/BIBTEX.

[32] Lee MH, Siewiorek DP, Smailagic A, Bernardino A, Bermúdez I Badia S. Interactive hybrid approach to combine machine and human intelligence for personalized rehabilitation assessment. ACM CHIL 2020 - Proceedings of the 2020 ACM Conference on Health, Inference, and Learning, 2020. https://doi.org/10.1145/3368555.3384452.

[33] Rose L, Bazzocchi MCF, Nejat G. End-to-End Deep Reinforcement Learning for Exoskeleton Control. Conf Proc IEEE Int Conf Syst Man Cybern, vol. 2020- October, 2020. https://doi.org/10.1109/SMC42975.2020.9283306.

[34] Jung HT, Lee H, Kim K, Kim B, Park S, Ryu T, et al. Predicting cognitive impairment level after a serious game-based therapy in chronic stroke survivors. 2019 IEEE EMBS International Conference on Biomedical and Health Informatics, BHI 2019 - Proceedings, 2019. https://doi.org/10.1109/BHI.2019.8834484.

[35] Munoz-Organero M, Parker J, Powell L, Mawson S. Assessing walking strategies using insole pressure sensors for stroke survivors. Sensors (Switzerland) 2016;16. https://doi.org/10.3390/s16101631.