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NEUROMORPHIC
Computing and Engineering

OPEN ACCESS

RECEIVED
31 May 2022

REVISED
3 February 2023

ACCEPTED FOR PUBLICATION
9 March 2023

PUBLISHED
24 March 2023

PERSPECTIVE

Perspective on investigation of neurodegenerative diseases with neurorobotics approaches

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Keywords: automation, embodiment, computational modelling, neurorobotics, neurodegenerative disease, brain

Abstract

Neurorobotics has emerged from the alliance between neuroscience and robotics. It pursues the investigation of reproducing living organism-like behaviors in robots by means of the embodiment of computational models of the central nervous system. This perspective article discusses the current trend of implementing tools for the pressing challenge of early-diagnosis of neurodegenerative diseases and how neurorobotics approaches can help. Recently, advances in this field have allowed the testing of some neuroscientific hypotheses related to brain diseases, but the lack of biological plausibility of developed brain models and musculoskeletal systems has limited the understanding of the underlying brain mechanisms that lead to deficits in motor and cognitive tasks. Key aspects and methods to enhance the reproducibility of natural behaviors observed in healthy and impaired brains are proposed in this perspective. In the long term, the goal is to move beyond finding therapies and look into how researchers can use neurorobotics to reduce testing on humans as well as find root causes for disease.

1. Introduction

Today, diagnosis of neurodegenerative diseases (NDs) (e.g. dementia and Parkinson's disease) is a clinical decision taken when symptoms start to be evident. However, detection while the person is still pre-symptomatic [1] is fundamental to increase quality of life for patients by allowing them to receive therapy that can slow or even change the course of progression of the disease [2]. Furthermore, diagnosis of a specific ND, based only on history and examination leads to misdiagnosis especially when diseases have similar clinical presentations [3–6]. The review by [7] substantiates the difficulty in differential diagnosis (distinguishing between diseases with similar clinical presentations) when it comes to NDs. They note that identification of key clinical features is a significant step in preventing or slowing down these diseases. Researchers have been working towards solving these gaps by utilizing **biomarkers** that are quantifiable indicators of the physiological/pathological processes (see reviews by [8–10]), and applying machine learning (ML) algorithms to analyze subject data (see review by [5]). Nonetheless, these approaches have their limitations and each of these reviews call for further research to increase both the accuracy of diagnosis and the understanding of NDs. A recent review by [11], p 1105, reinforces this perspective, noting that *'In face of the obvious limitations in biological realism, virtual simulations provide extreme flexibility, since pathological states can be simulated at different levels of the system, locally or globally, and different assumptions can be first translated into both circuital and functional model features and then verified in the emerging behavior of the simulated network.'*

Early detection of NDs is required to increase the effectiveness of neuroregeneration, for example through stem cell therapy. In this regard, molecular diagnostics [2] are promising but up until now, the best diagnostic tool, neuropathology, is performed post-mortem. The future of diagnostics requires the integration of biomarkers, imaging, and biochemical techniques [2]. However, this still demands clinical trials to gather the necessary data. This perspective paper contends that the urgent demand for early

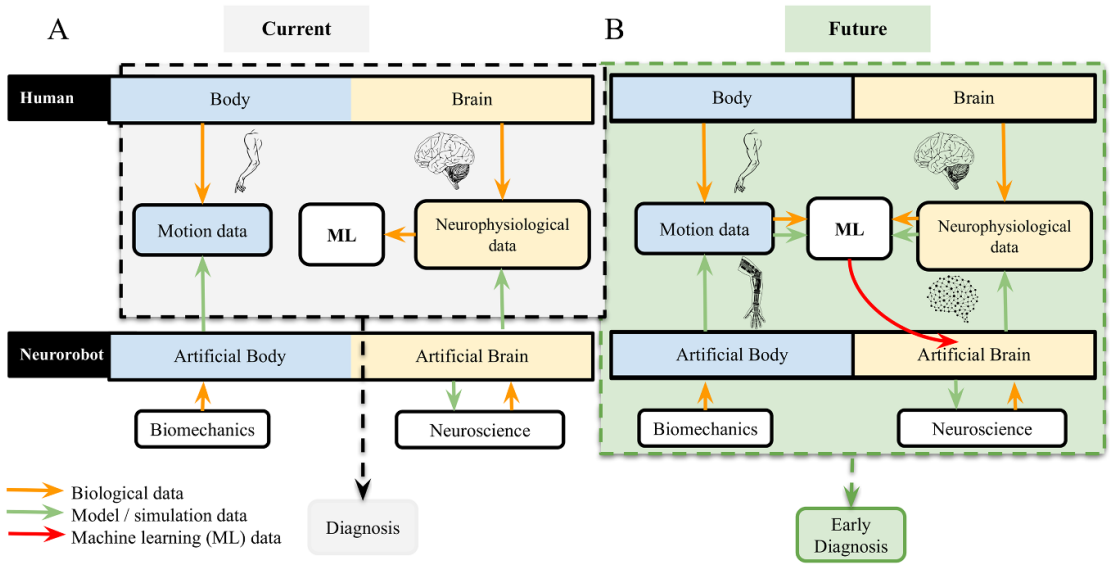

Figure 1. A block diagram outlining the current and future approach for the diagnosis of NDs. Straight arrows signify the flow of data between the blocks, the curved red arrow signifies model adaptation through an iterative process. (A) The current status where only data collected from human beings (motion and neurophysiological) are evaluated for diagnosis of NDs. In the current paradigm, diagnosis from motion data is typically subjective and performed by a clinician. (B) The future perspective where both simulated data obtained throughout neurorobotics experiments and human data are fed into ML algorithms to extract biomarkers of symptoms and fit the artificial brain models embodied in the neurorobot (curved red arrow).

diagnosis can be addressed by integrating alternative approaches and tools, such as neurorobotics experiments, requiring cooperation between scientists from different areas such as neurology, biology, computational neuroscience, and robotics. In particular, this multidisciplinary collaboration aims to further our understanding of the relationship between disease progression and symptom development, improving accuracy of diagnostic tools while reducing reliance on experiments involving humans.

Neurorobotics [12] studies the interaction of brain, body, and environment in closed perception–action loops by using artificial systems such as rigid and soft robots. Robots are controlled by brain-inspired control architectures in which algorithms simulate the central nervous system at varying levels of detail. The intersection between robotics and neuroscience highlights many promising approaches and applications that ultimately lead to intelligent robots [13] that can help with gaining a better understanding of the brain. Figure 1 outlines our vision for the paradigm shift in brain disease investigation by adopting a neurorobotics approach. This perspective highlights the need for an iterative process of developing ML tools to extract biomarkers from the body's motion and the respective neurophysiological activities. Biomarkers can also be extracted from the simulated counterparts. Their benchmark will enable the validation of computational models of the brain and the body.

This paper asserts that not only will this increase biological fidelity of embodied computational models but also inform neuroscience [14] and medicine, leading to early diagnosis of NDs [5]. With the aid of high fidelity brain models and advanced simulation tools, scientists can make up for the limitations of neuroimaging techniques to generate and study activity from different brain regions while repeating behavioral tasks through a neurorobot. Hence, the output from an artificial brain coupled with the ML outcome will make early diagnosis of NDs possible. Altogether, novel neuroscientific theories about the neural mechanisms of the brain can be uncovered using this perspective.

Some previous novel studies in neurorobotics focused on the embodiment of **computational brain models** within robots with the aim of providing synthetic testbeds for replicating symptoms of NDs (see review by [15]). Computational models are an invaluable tool in modelling pathological alterations and consequently investigating causative mechanisms. In particular, they provide the opportunity to reproduce physiological details at the neuronal level and to analyze experimental data collected from different brain areas [16–19]. They can be descriptive or predictive, integrating data from *in vitro* and *in vivo* studies. Highly realistic brain models would enable highly realistic **embodiment** in robots yielding to more realistic observation of the brain skills and mechanisms set in place by **brain-body interplay and interactions with the environment** [20, 21]. However, the lack of computational models based on data collected from humans [18] hinders the reproducibility of much more complex mechanisms that occur during brain-body interactions. Since this observation by [18], 'The Virtual Brain' on the EBRAINs platform [19] has been

launched and offers **simulation** of large-scale networks and extensive data on human brains from patients and healthy subjects. Thanks to simulation technology like The Virtual Brain, personalized computational models can be created which can then be applied within personalized medicine to account for a patient's unique configuration of symptoms and biology (i.e. DNA markers, chromosomal makeup, hormone levels, etc). In their review of computational models shaped by artificial intelligence (AI), [22] expand on this point, where they state that personalized medicine requires improved data translation from clinical research. Importantly, they also highlight that AI can be useful within personalized drug development. However, in order to produce a 'digital twin' of a patient to test different treatments [23], a high level of data synthesis is required. The heterogeneous data collected during clinical trials presents an obstacle in the process of creating such precise models [24]. Here, ML can help to standardize data input, reducing the burden on clinical researchers to structure collected data sets in a specific manner. This is also true for 'organs on chips' which are implantable devices that can used to study disease and biological interactions by collecting data *in vivo*. Synthesizing this kind of multi-modal data can inform the creation of digital twins and other computational models [25]. This is a major advance that allows both the creation and analysis of human-like brain models. The next step will be to incorporate embodiment of such models and continue optimization through ML.

The study of lesions occurring in different brain regions, originally led to theories about the functional role of the impaired regions and mapping of certain functions/behaviors to specific brain regions [14, 26, 27]. However, these mappings that are based on single brain regions, usually neglect the interactions across the brain areas which are crucial for cognition aspects [28]. Consequently, collecting multi-modal data from diverse studies and combining their findings would allow researchers to build more accurate models of the whole brain [29]. While many computational brain models are proposed for reproducing the neural dynamics, such as spiking patterns, in different brain regions [30], verification of these models is not yet formalized. The assessment of the accuracy of the developed computational models relies on either the neurophysiological or behavioral markers. This perspective argues that compared to the limits of the currently available neuroimaging techniques, the robotic embodiment of these models would facilitate studying both types of markers simultaneously while monitoring the activity of all the simulated neurons. Thus, benchmarking can be carried out by comparing data collected from neurorobotics experiments to that recorded from different neuroimaging techniques of the biological counterparts [15]. Upon achieving high biological fidelity, it would be possible to collect data from robotic embodiment experiments as a substitute for human subjects. The combination of the previous key elements would facilitate the analysis of brain diseases while being able to replicate neurophysiological aspects or biological phenomena in neurorobotic embodiments. However, this requires new advancements within computational models in order to more closely resemble brain regions.

The further development of ML tools and algorithms for biomarker extraction from a variety of data [5] is expected to provide a better fitting procedure to replicate neural responses [30], and so enhance the prediction of disease (i.e. as seen in Parkinson's disease (PD)—[31]). Furthermore, realistic body models are necessary to allow a better match between artificial and living system performance to show healthy and impaired human-like skills. Nevertheless, a robotic embodiment allows fast generation of data through repeatable experiments in a controlled environment. The main advantages of this approach are that scientists can formulate hypotheses about the diseases of the human brain, avoid invasive testing on animals, and keep human subjects away from monotonous and repetitive exercises [15].

In the following sections, the current status of interdisciplinary studies aimed at investigating NDs leveraging **computational modeling**, **bioinspired embodiment** and **machine learning approaches** is presented together with the future needs. This perspective addresses the crucial need for devising new strategies for early diagnosis, uncovering root causes of NDs, and automating the testing of novel treatments.

2. Current status

2.1. Computational brain models

In the current paradigm, computational modelling is already accepted as a viable method to answer open questions regarding NDs [32]. There have been advances in understanding the effects of disease characteristics on brain functionality [33–39], modelling disease progression [40, 41], and testing relevant therapies or treatments [42–46] using computational modelling techniques.

Many studies have focused on the role of dopamine in NDs [33, 36, 38, 39, 47]. Results from these studies are able to confirm biological hypotheses about dopamine but focusing on a single neurotransmitter limits the amount of information that can be obtained. The review by [18] acknowledges that computational models have significantly contributed to the understanding of the cause, symptoms, and treatments of PDs. However, even with all that has been learned regarding the connection between dopamine and NDs, they still leave the reader with many open questions. For example, how does dopamine loss effect brain areas outside

the striatum? What is the correlation between neural dynamics and dopamine level? Furthermore, the current studies tend to focus on single brain regions, again limiting the scope of impact. For example, even though it has been shown that the cerebellum and basal ganglia are interconnected [48], computational models ignore their subcortical communication. Computational models need to be implemented at multiple levels in order to understand the many small elements interacting with each other during NDs [33].

Studies such as [34] look into specific symptoms of a neurological disorder and are able to find correlations between symptoms and biomarkers. In the case of [34], they were able to link dopamine depletion to akinesia and tremor. Lindahl and Kotaleski [38] correlated symptoms with neuronal dynamics, such as firing synchrony and increased oscillations in the brain. These confirmations show the promise of studying NDs with computational models, creating new insights into how different network characteristics and parameters can affect behaviors. However, the **underlying causes** behind what initiates system changes remains largely unknown [32]. Geminiani *et al* [14] took a step in this direction by replicating different types of damage to the cerebellar cortex, successfully modelling the associated cerebellar impairment. Their approach provided insight into how different types of damage translate to functional impairment and supports the expectation that modelling impaired networks can lead to an understanding of causal mechanisms.

Just as computational models can provide insight into neurological diseases, they can also help investigate the effectiveness of treatment strategies. For example, [42, 44, 45] study the impact of deep brain stimulation (DBS) on an ND by simulating DBS within a computational model. Others take a slightly different approach, modelling the aberrant patterns in brain regions and then applying different treatment techniques to understand which might be most effective [43]. Both methodologies have proven to be fruitful. Instead of moving directly to human trials, these strategies can be tested with robots to add the benefits of embodiment while allowing for fast data collection and precisely controlled, repeatable experiments [15].

2.2. Bioinspired embodiment

Robots are utilized as vessels to embody the computational models of different brain regions. This embodiment allows researchers to study the neural mechanisms governing the activity in these regions and how cognition arises. The limitations of neuroimaging have driven many scientists to use robotic embodiment, which were called then brain-based devices (BBDs), to study the nervous system and the collective behavior of brain areas [49, 50]. The fact that BBDs are embodied allows researchers to closely monitor neural activity while interacting with the environment and executing specific tasks. Hence, viable comparisons can be made between the embodied models and their biological counterparts. To study a behavior selection mechanism, [51] embedded a model of the basal ganglia in a mobile robot to mimic an animal foraging task of choosing between different objects. When choosing among multiple alternatives with high salience, it showed behavioral disintegration which is similar to that observed in animals. This type of study shows that embodiment of computational models is capable of reproducing biological behaviors.

Embodiment does not always require the robot to be mobile, in a study by [52], a model was built for the premotor cortex, primary motor cortex, and cerebellum using a spiking neural network (SNN) based on the Neural Engineering Framework to control a robotic arm. The cerebellar and cortical models played the role of dynamics and kinematics adaptation, respectively. This work presented metrics to compare activity in the simulated models to their biological counterparts. Moreover, it challenged the classical view concerning the neural activity representation, where the findings refer to the neurons directly encoding torques, and hence dynamics, not only the kinematics. In [21, 53], a spiking forward cerebellar model provided sensory predictions to give corrections to a motor cortex-like spiking network to guide robot motion in sensor-guided control while maintaining realistic firing rates. These studies were completed with a robot arm and they did not account for the motion in a musculoskeletal arm. On the contrary, in [54], a bio-mimetic cortical spiking model was coupled with a musculoskeletal arm model to achieve realistic dynamics from the physiological perspective. One aim of this work was to provide a faithful musculoskeletal model that considers the biomechanical and anatomical properties of human arms. Such biologically-realistic models impose truthful constraints for the motion dynamics, hence they promote more realistic firing dynamics in the modeled brain areas. Embodiment is not always about developing a computational model of the central nervous system, [55] use a humanoid robot arm to investigate the plausibility of growing tissue for grafting onto humans. This is a preliminary investigation showing promising results, reinforcing the idea that embodiment is necessary for developing life-based technologies compatible with human physiology.

Neurorobotics can help improve **reproducibility, explainability, and trustworthiness** of neural model by providing a physical instantiation of the model, which can be used to validate the model's predictions and behavior in a real-world setting. This allows researchers to test their models in a more realistic and ecologically valid environment, which can help to increase the external validity and generalizability of the research.

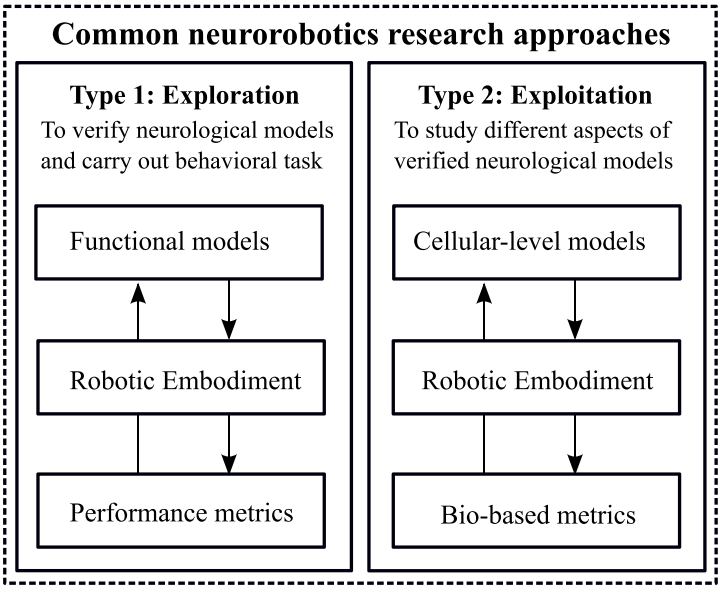

Figure 2. The common approaches in neurorobotics research. The left block introduces the neurorobotics research paradigm called exploration that focuses on replicating behavioral functions. The right block introduces the exploitation paradigm that focuses on the biological plausibility of the embodiment process.

Reproducibility: Using standardized hardware platforms, such as the iCub robot [56], aids in reproducibility, as the same physical systems can be used for different experiments, allowing for direct comparison between results. This can help to ensure that differences in the results are due to the specific neural model being tested, and not due to variations in the physical platform. Furthermore, by using neurorobotics, it is possible to use real-world sensor data as input to the model, which can help to increase the realism of the model and better replicate real-world scenarios.

Explainability: By providing a way to observe and analyze the behavior of the model in a real-world setting, a deeper understanding of how the model is making decisions and behaving can be gained [57]. The interpretability is thus improved through the use of visualizations and simulations that allow to see how the model is processing information and making decisions. This can include visualizing the internal state of the model, such as the activation of individual neurons, as well as visualizing the model's output in the form of simulated or real-world actions.

Trustworthiness: By providing a way to validate and test models in a real-world setting. This can include testing the model's predictions and behavior in a variety of different scenarios and conditions, and comparing the model's performance to that of human experts or other benchmark models.

To achieve these goals, two main approaches are followed in neurorobotics studies as presented in figure 2. Exploration versus exploitation is a trade-off occurring in the human brain [58] so this naturally translates to neurorobotics when attempting to model these biological systems. The first approach focuses on mimicking behavior and performance with a robot that is guided by a bio-inspired functional model (Type 1, exploration, seen in figure 2) as in [51, 59]. Such models attempt to test new theories about the neural mechanisms responsible for a specific behavior in humans/animals. While the second approach focuses on the embodiment of biologically-plausible cellular-level neural models (Type 2, exploitation, seen in figure 2) as in [21, 60]. Such models emulate validated models to reproduce neural activity of different brain regions while engaged in a behavioral task. Hence, the former approach is considered more adequate for exploration of novel models and the latter is more adequate for the exploitation process. Although these approaches are not contradictory, some limitations (e.g. limited computational power necessary for real-time operation, the lack of computationally-efficient biologically-realistic neuron models) reduce the possibility of employing cellular-level models in an exploration theme.

Studies in the neurorobotics field are evolving and have advanced enough to begin studying neurological diseases by computationally replicating lesions in relevant brain areas. Most of the studies that investigate NDs focus on PD, as it is accompanied by various motor symptoms, making robotic embodiment a good candidate to reproduce such symptoms. In [61], a model of the basal ganglia, built using leaky-integrator neurons, was embedded in a LEGO mobile robot with the goal of demonstrating the ability to choose among behavioral actions. In this study, PD and Huntington's disease were modeled by changing the network parameters to mimic the effect of the depletion of dopamine. However, the main focus for this study was to

develop a bio-inspired behavioral selection mechanism for robotics. On the other hand, [59] were interested in modelling the effects of PD. For this, they modelled the basal ganglia within a reinforcement learning paradigm such that the indirect pathway was responsible for the exploration activity, while the direct pathway was responsible for the exploitation, and the dopamine release was linked to the error in a reaching task. Based on the amount of error, the dopamine controlled switching between exploration and exploitation. The modeling of PD in this case involved reducing the dopamine release to reduce the complexity of the exploration activity. Further work looking into PD was completed by [60] where they embedded a computational model of the basal ganglia-thalamus-cortex in a humanoid-like robot. The model was built based on data derived from experiments with rats to reproduce the tremor symptoms that characterize PD by modulating the synaptic conductance as observed in cases of dopamine depletion. This approach is promising as it embeds a faithful representation of the basal ganglia network from [62] in a robot. However, more complex interactions with the environment are necessary to differentiate results obtained from experiments conducted in simulation to that involving the rich dynamical interactions of a physical setup.

2.3. ML approaches

ML is a form of AI that enables discovery of patterns and relationships in high-dimensional, sparse, and noisy datasets [63]. ML approaches can aid in early and precise diagnosis [64], in disease progress prediction [65], and can reveal important insights into disease mechanisms. For example, promising findings have shown that the time to perform clinical assessment can be decreased thanks to the application of ML methods on motor function and language [5]. However, for rating scale assessment of the disease, they have not yet been fully evaluated and validated [66]. With the aim to investigate brain activity, neuroimaging techniques such as magnetic resonance imaging and computed tomography, electroencephalography (EEG), and other methods can be applied together with ML-driven data analyses to distinguish patients affected by an ND from healthy subjects [67], as well as to detect functional changes in neurons [68] such as fluctuations of the neural oscillations that are mostly characterized by their frequency, amplitude, and morphology. In order to apply the ML algorithms, data from healthy and unhealthy individual brains have to be gathered, for instance collection of electrical frequency activity over time in different brain areas [5]. However, there exist many ML algorithms and choosing the correct one is crucial to obtain reliable results.

The most commonly applied ML methods are *supervised* algorithms for classification and regression (i.e. neural networks, random forest, support vector machines) that require large volumes of accurately labelled data [64]. For example, they have been applied to predict PD among healthy and not healthy people (see survey by [69]), and to classify neurodegenerative disorders according to symptoms [5]. In [70], scalable and automated procedures enabled the generation of high-quality data that allowed to identify PD-specific signatures in fibroblasts. On the contrary, *unsupervised* ML algorithms (i.e. neural networks, network diffusion algorithm) do not require labelled data and they have been used for gene regulator analysis, disease progression classification, image and video analysis, natural language processing, and pattern recognition (see [5] for a review on these applications). Lastly, *reinforcement learning* approaches that are based on trial and error learning have been widely used for automation and robotics, but not in medicine, though use is increasing [71], for example for determining medication regimens or for modelling the progression of an ND [72].

So far, studies using ML methods were limited to the analysis of motor symptoms, kinematics, and wearable sensor data. On the contrary, non-motor symptoms are used as valid supportive diagnostic criteria [73] but they lack specificity and are complicated to assess and/or yield variability from patient to patient. Studies have revealed that features extracted from multiple data modalities could lead to high-patient level diagnostic performance, while facilitating accessible and non-invasive data [31]. Therefore, by combining different data modalities, we may identify relevant features that are not traditionally used in the clinical diagnosis of PD. Actually, only a small number of studies validated these technical approaches in clinical settings using human participants. Thus, there is a gap between model development and their clinical applications. Supplying clinicians with ML approaches based on multi data modalities may support clinical decision making in patients with ambiguous symptom presentations, and/or improve diagnosis at an earlier stage [31].

An additional issue that may lead to challenges in the integration of newly acquired data and previously published data, is the irregular reporting standards of methods and results in some of the published studies using ML, as well as inaccurate descriptions of data acquisition and pre-processing protocols [64]. There is a huge need for higher transparency of data collection, pre-processing protocols, model implementation, and study outcome. In [70], authors applied reproducible, automated data generation protocols together with unbiased deep learning techniques. These findings pave the way to uncover novel patient-specific cellular phenotypes with valuable implications for personalized medicine such as new drug discovery strategies.

Relevant studies have been proposed for the detection of biomarkers for ND [8, 74], but the majority of them are too expensive and rely on relatively invasive methods (such as positron emission tomography and cerebrospinal fluid) that are also not widely available [75], thus limiting the applicability. Very recent research findings showed that deep learning using convolutional neural networks (CNN) with novel cost-effective biomarkers (e.g. blood-based biomarkers) [8], and brain image-based biomarkers [76] are promising for ND diagnosis [64]. Moreover, their combination can help build a more comprehensive picture of neuronal changes happening during the ND, which in turn is likely to improve disease prediction and consequently enable therapy at the earliest possible stage [77].

3. Future needs and perspective

The current status section introduces some of the gaps in the current research landscape. This perspective maintains that these limitations can be addressed through computational modelling, embodiment, and ML.

3.1. Computational brain models

3.1.1. Increase biological fidelity

Even though computational models have been used to successfully further understanding of ND effects and treatments, these models can still be improved [18]. For example, the connection between circuit function and disease progression is not currently known. It is not clear if it is strictly one way meaning that circuits breakdown due to disease progression or if there is a circular influence so that circuit breakdown also further contributes to progression [32]. In order to further the current research landscape, biologically-plausible computational models must continue to be developed including different levels of abstraction from single-purpose neural circuits to single brain areas and expanding to communication between brain regions. These models can be elaborated by including different types of neurons [21], adding gap junctions [78], including neuromodulators such as dopamine [79], and including non-neuronal glial cells [80] in order to increase the fidelity of simulated network architectures and neuronal activity. The challenge faced when developing increasingly complex models is that it is computationally expensive leading to increased energy needs and long simulation times. There is always a compromise to be made to balance computational cost versus model accuracy. Methods that reduce spiking activity while maintaining accuracy can help both conserve energy and computational cost [81]. CNNs using artificial neurons can also be used in conjunction with spiking models to increase efficiency such as the electrocardiogram (ECG) classification method proposed by [82]. Han and Roy [83] also confirm an increase in energy efficiency by utilizing both artificial and spiking neurons in an image recognition task. Energy can also be conserved using event-based hardware platforms inspired by the brain known as neuromorphic chips. Implementations on these chips significantly reduce computational load, for example, [84] show up to 90× fewer operations than a standard deep neural network in an optical flow estimation task when using Intel's Loihi2 chip. Based on these studies, we contend that while increasing biological fidelity will increase complexity, there are mitigating steps that can be taken to keep energy and computational costs at a reasonable level.

3.1.2. Identify underlying causes

As the models move closer to biology, the represented activity and behaviors can be analyzed to find the root causes of ND because progression can be monitored on a neurophysiological level. The initiation of neural degradation in different ways can be tested and compared to biological datasets at various stages of disease progression. The ability to control and change single parameters at disease onset is unique to simulation since there are so many interdependencies in living systems [85]. Complex computational models can take into account the inter-dependency between biomarkers including both clinical and biomedical biomarkers.

3.1.3. Leverage simulation for testing of therapies

Understanding the onset and progression of disease naturally leads to a better understanding of how to treat the symptoms, and halt or slow progression, as evidenced by studies in molecular diagnostics [2]. An advantage of simulation is that the speed can be increased so that trials of new therapies do not need to occur in 'real time' [15]. This reduces the time of the iterative process necessary for developing new therapies or treatments.

3.2. Bioinspired embodiment

3.2.1. Optimize models through embodiment

By embedding these complex computational models in robots it becomes possible to take the motion dynamics into consideration. Studying the body-environment interaction allows for the reproduction of realistic firing patterns while executing behavioral tasks. However, real time operation is crucial in this case.

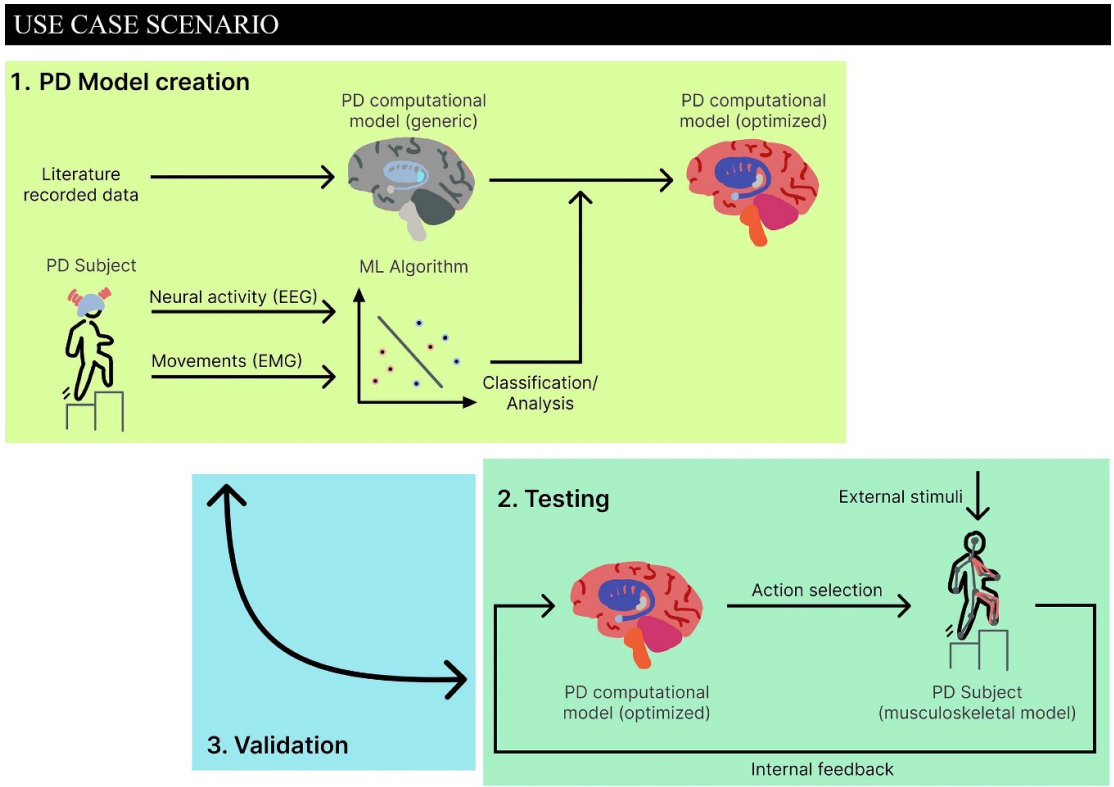

Figure 3. Holistic approach. Figure 3 shows an envisioned use case scenario for the investigation on PD that consists of three main stages: **(1) PD Model creation.** A computational brain model is built to simulate its neural mechanisms underlying the action selection task thanks to dopaminergic modulation in the basal ganglia. Response patterns and firing rates obtained from the literature are mimicked to obtain a simulated PD model. An ML algorithm empowers the classification and analysis of data related to the neural activity (EEG signals) and movements (EMG signals) of a PD subject (e.g. a rat, a human) such that biomarkers of PD symptoms are obtained. The disease model is then optimized and personalized based on the biomarker analysis. **(2) Testing**. The model is nested into a closed-control loop to replicate the action selection behavior with a musculoskeletal model of the PD subject through the interplay of the external stimuli and internal feedback. In this way, brain pathology is directly linked to motor behavior. **(3) Validation**. Finally the model is validated against the biological data collected from the PD subject. The proposed approach based on neuromusculoskeletal modelling and simulation offers a unique and intuitive visual analytics tool for the clinicians to support a qualitative assessment and their medical decision tasks.

Therefore, it underlines the need to develop hardware (e.g. neuromorphic chips [86], FPGAs, GPUs) or software (e.g. NEURON, NEST, Brian, GeNN) capable of running large scale networks in real time.

3.2.2. Increase accessibility of models

The development of graphical tools for rapid deployment of novel neural architectures by making the creation of complex computational models accessible to clinical researchers is also necessary to accelerate the research in the neurorobotics field. The NeuroRobotics Platform under the EBRAINS initiative [19] allows embedding SNNs in different simulated robots [87], thus aiming for customizable and generalizable implementations. However, the currently available interface needs specific programming skills which may slow down progress for clinical researchers.

3.2.3. Create realistic brain-body-environment interactions

While neurorobots can provide new insights through the combination of motion and neurophysiological data, a transition to musculoskeletal models is also crucial to further increase biological fidelity. There are intrinsic properties of robots that are fundamentally different from biological bodies [88] and this has implications for how the body interacts with the environment. The ability to then model the body '*in vivo*' through musculoskeletal models allows the opportunity for a deeper understanding of NDs and can inform new treatments [89].

3.3. ML

3.3.1. Find new biomarkers

Applying ML techniques allows handling/processing an enormous amount of multidimensional data recorded from different brain regions. Given unified protocols for data collection from healthy subjects and multiple disease groups, ML can help build better predictive models that consider the activity and signals

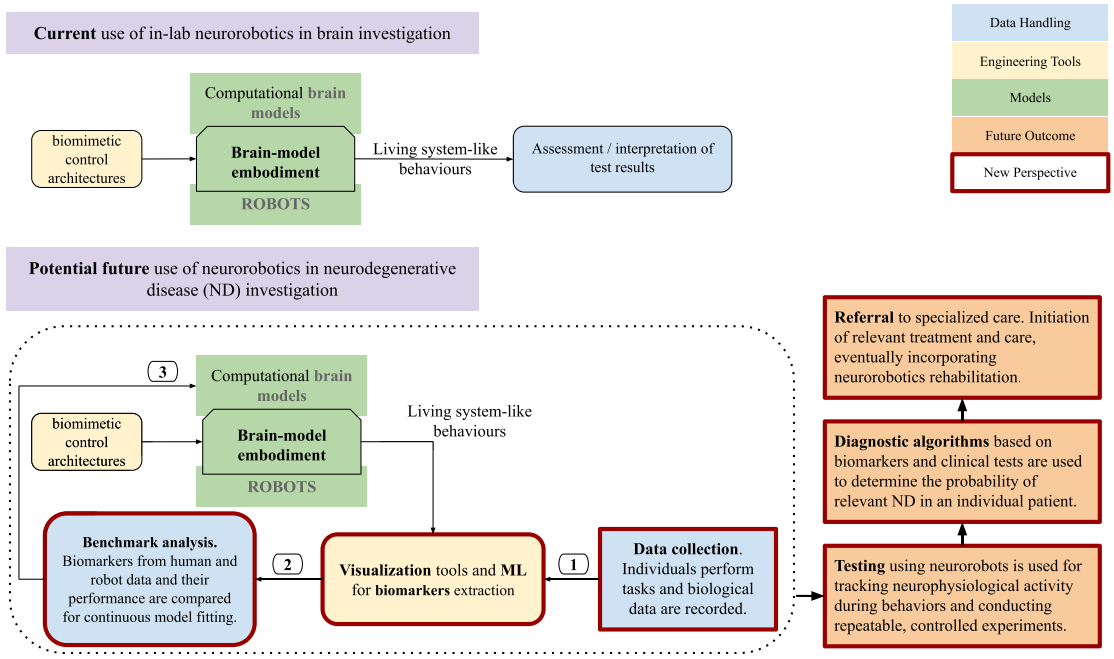

Figure 4. Future of neurorobotics in neurodegenerative research, introducing a flow of iterative development. From biological data collection (1), machine learning tools can analyze and compare biological signals to output from neurorobots (2), this benchmark analysis can then be applied to the computational models to increase biological fidelity (3). The outcome of this iterative development process are synthetic testbeds for NDs, creation of diagnostic algorithms for early diagnosis and prediction, and the possibility to increase the personalization of patient care.

across brain regions. Novel biomarkers can then be introduced based on the developed models [29]. These biomarkers can be extracted from neuroimaging, behavioral, and neurophysiological data collected in both clinical and simulation trials. The availability of this multimodal data means their results can be cross-referenced to create new biomarkers for diagnosing NDs early [5].

3.3.2. Establish a standardized methodology

ML algorithms are being applied to biological data with promising results [31, 64]. The next step is to standardize a methodology for when to apply specific ML algorithms. The results of these algorithms must be analyzed systematically to then determine when a biomarker exists versus a coincidental signal artifact. Finally, the way that data from embodied computational models is compared to biological signals must also be agreed upon to ensure benchmarking is consistent across models.

3.4. The future of ND research as a holistic approach

The introduced neurorobotics approach (figure 1(B)) aims to reveal the root causes or the mechanisms of an ND. By achieving this, early diagnosis will be possible. Furthermore, by means of robotic embodiment, new therapies can be introduced that avoid or limit the use of drugs and costly or invasive tests on human beings. In the end, neurorobots will serve as a testbed to reproduce the brain activity under specific conditions, to test novel neuroscientific theories, and to assess the effects of the novel rehabilitation therapies on the disease mechanisms. Figure 4 visualizes this future perspective by highlighting how it expands on the current paradigm. The embodiment of computational models is already a wide-spread approach (see *current use* in figure 4). While these models need to increase in biological-plausibility by ways of using spiking neural networks and musculoskeletal models, this perspective adds the novel neurorobotics approach of combining bioinspired embodiment and ML algorithms to create a holistic methodology.

The embodied computational models provide data for analysis through ML, producing an output which can be compared to biological data. The results are used to improve the computational models in an iterative process of development. Once the models are optimized, the embodied models can be used for testing of therapies and to monitor the neurophysiological and behavioral effects on a neurorobot before prescribing experimental practices to patients. This understanding leads to the development of predictive algorithms based on what is learned about the underlying mechanisms and causes of NDs and the impact of various therapy regimens. Finally, this can customize healthcare for those living with an ND, allowing referral to relevant specialists and tailored therapies. In this way, the brain model embodiment, together with imaging analysis, and accurate AI for biomarker extraction will enable personalized neurorehabilitation strategies.

Autonomous and intelligent robotic devices together with the incorporation of motivational elements, e.g. games, have transformed rehabilitation to become more efficient and give patients a better access to it [90], for example in recovering after a major operation, loss of sensory functions, stroke effects, etc. Neurorobots have the potential to open-up cost-effective development of rehabilitation for treatment of ND. However, if and how to achieve a proper rehabilitation for ND is still an open question. Therefore neural control strategies that aim to regain neuroplasticity, and, thus, the control of movement, must be investigated. With this aim, BBDs will be increasingly used to allow virtual testing in different scenarios and optimize the rehabilitation routines. Moreover, the possibility to interact with a BBD through bio signals, will make it possible to create a new generation of rehabilitation devices to overcome the current challenges faced in the rehabilitation of subjects with brain and motor disabilities. Gaining a better understanding of neural mechanisms is critical for endowing robots with superior interaction capabilities with their environment, or for facilitating seamless robot-robot or human-robot interactions. Neurorehabilitation robotics imposes some concerns related to robot ethics and the role of therapists necessitated by human-robot interaction. The laws proposed by [91] will allow engineers and clinicians to work closely together on a new generation of neurorobots.

4. Conclusion

The advances in computational modeling, embodiment, and ML have led us to the point where we can now 'close the loop' for iterative development of a biologically-plausible system. Researchers can use the various strengths of each discipline to formulate new hypotheses, test current hypotheses, and move experimentation with biomimetic models closer to biological processes. This requires a shift in the approach to researching neurodegeneative diseases, requiring a novel interdisciplinary paradigm. It is the assertion of this perspective that this approach will have a clear impact within studies of NDs—uncovering the underlying causes, leading to early diagnosis, and automating the testing of cutting-edge rehabilitation strategies.

Data availability statement

There is no data since it is a perspective paper. The data that support the findings of this study are available upon reasonable request from the authors.

Acknowledgment

This work was partially funded by Lundbeck Foundation through the Grant No. R370-2021-948

Conflict of interest

The authors declare no competing, financial, or commercial interests in this research.

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