Multiple sclerosis and computational biology (Review)

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Abstract. Multiple sclerosis (MS) is an autoimmune neurodegenerative disease whose prevalence has increased worldwide. The resultant symptoms may be debilitating and can substantially reduce the of patients. Computational biology, which involves the use of computational tools to answer biomedical questions, may provide the basis for novel healthcare approaches in the context of MS. The rapid accumulation of health data, and the ever-increasing computational power and evolving technology have helped to modernize and refine MS research. From the discovery of novel biomarkers to the optimization of treatment and a number of quality-of-life enhancements for patients, computational biology methods and tools are shaping the field of MS diagnosis, management and treatment. The final goal in such a complex disease would be personalized medicine, i.e., providing healthcare services that are tailored to the individual patient, in accordance to the particular biology of their disease and the environmental factors to which they are subjected. The present review article summarizes the current knowledge on MS, modern computational biology and the impact of modern computational approaches of MS.

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Contents

1. Introduction

Multiple sclerosis (MS) is a complex neurodegenerative disease of the central nervous system (CNS) and is considered to be of autoimmune nature (1). MS is a potentially debilitating disease, and although somewhat uncommon, its prevalence has increased substantially in numerous regions worldwide since 1990, particularly among females, and healthcare systems need to be prepared to adapt under these changing trends (2,3). Therefore, there is a need for a more in-depth investigation of the biological background of MS, as well as for the optimization of diagnostic, prognostic and therapeutic approaches for the disease. Computational biology and artificial intelligence (AI), fields that have been garnering attention in modern biosciences, can support a modern framework for the management and effective treatment of patients with MS.

Computational biology refers to the use of *in silico* tools and methods as an alternative or complement to laboratory procedures, in an effort to better answer biological and biomedical questions at a reduced cost (4). This scientific field heavily overlaps with the field of bioinformatics, which mainly focuses on biological data management and analysis, and both terms are often used interchangeably, a concession the present review will also make (5). Computational biology has numerous applications in the organization and interpretation of multi-faceted clinical and biomedical data, clinical decision making, disease diagnosis and treatment planning, as well as in designing novel therapeutics (6-8). In the age

of big data, -omics and cutting-edge computational systems, the high-throughput analysis of clinical and scientific data is now possible (9,10). Therefore, such tools can provide novel approaches in the face of potentially debilitating diseases, such as MS, with an aim of providing a management and treatment plan tailored to the individual patient.

Personalized medicine, at times used interchangeably with the term precision medicine, is the practice of treating a patient based on their individual genomic, biochemical, environmental and behavioral characteristics (11). The treatment of diseases, such as MS can be immensely improved under the prism of personalized medicine. Personalized medicine can help reduce healthcare costs, drug-development costs and development time, and it may also assist in avoiding the use of drugs that may lead to adverse side-effects to a particular subpopulation (12).

The present review article summarizes the current knowledge on MS, modern computational biology and the impact of modern computational approaches, such as AI, on various aspects of MS prognosis, diagnosis, management and treatment. Moreover, it highlights the need for personalized medicine in the context of complex and heterogeneous diseases, such as MS.

2. Multiple sclerosis

The main characteristics of MS are the loss of oligodendrocytes and demyelination (13). Oligodendrocytes are the essential cells for CNS myelination and originate from oligodendrocyte progenitor cells (14). The myelin sheath is a protective covering composed of lipids that insulates nerves and helps transmit electrical signals down the length of an axon (15). The destruction of the myelin sheath is termed demyelination and leads to plaques or lesions that produce clinical symptoms (16). The traditional view of MS pathogenesis, also known as the 'outside-in' hypothesis, is that a dysregulated immune system mainly attacks CNS components. Specifically, dysregulated auto-reactive T-cells in the periphery cross into the blood-brain barrier and, along with macrophages and B-cells, proceed to attack CNS components, such as myelin and oligodendrocytes (13,15). A competing theory known as the 'inside-out' hypothesis though, proposes that the primary degeneration of oligodendrocytes and myelin is the initial event of MS, with oligodendrocyte death and subtle myelinopathy preceding, and therefore driving a secondary autoimmune attack. This secondary autoimmune attack then leads to the characteristic demyelination and symptoms present in MS (13). Some of the potential symptoms of MS are relatively harmful and feature mobility issues, spasticity, bladder and bowel dysfunction, fatigue, pain, visual disturbances, speech distortions and cognitive impairment (17). The disease course of MS is either relapsing-remitting MS (RRMS), which is characterized by discrete episodes of neurological symptoms, or chronic progressive MS (primary progressive MS or secondary progressive MS), which is characterized by a continuous worsening of neurological symptoms (18). A recent study by ten Bosch *et al* (19) provided a new take on MS pathophysiology, in which the erroneous overactivity of the mitogen-activated protein kinase pathway ERK ($MAPK^{ERK}$) was shown to lead to microglial malfunction. These authors highlighted the fact that locoregional demyelination, one of the hallmarks of MS, has been linked to microglia with overactive MAPK, while factors traditionally linked to the risk of developing MS, such as Epstein-Barr Virus (EBV) infection and smoking, potentially add to abnormal $MAPK^{ERK}$ overactivity (19).

As previously demonstrated, the precise etiology behind MS remains a topic of debate, although the characteristic immune dysregulation observed is generally considered to be triggered by a variety of genetic and environmental factors (20). Similar to several other autoimmune diseases, MS cases cluster in families, with monozygotic twins having a higher concordance rate (20-30%) compared to dizygotic twins (2-5%), with the siblings of an affected individual being 10 to 15-fold more likely to develop MS than the general population, and second- and third-degree relatives, but not spouses, also carrying a somewhat increased risk of developing MS (21). On the other hand, the most well-established environmental factors are EBV infection, vitamin D deficiency and smoking (22). The association between EBV infection and MS may be causal, since EBV persists for the lifetime of the host in B-cells, which are considered to play an essential role in MS, and can regulate their function (23). The environmental influence on MS is also visible when observing the latitude-associated differences in disease prevalence. The incidence of MS is rare in tropical and subtropical regions (24). This fact may be due to sun exposure and has led to numerous studies that have suggested that higher levels of vitamin D potentially play a protective role, and that vitamin D deficiency is strongly associated with the risk of developing MS (20). The causal link between smoking and MS remains elusive however, although it may be due to the inhalation of toxic substances in the case of cigarette smoking or lung irritation caused by cigarette smoke, which triggers the pro-inflammatory effect of smoking via Toll-like receptors (25).

The diagnosis of MS is highly dependent on clinical judgement (26). This poses an issue, since MS is a relatively heterogeneous disease, and proper diagnosis is vital. Particularly, the diagnosis of MS is based on a combination of clinical, imaging [e.g., magnetic resonance imaging (MRI)] and laboratory [e.g., cerebrospinal fluid (CSF) biomarkers] findings (27). The currently available clinical and imaging markers however, do not allow for in-depth individual characterization, which highlights the importance of the currently used biomarkers and the identification of novel and easily quantifiable molecular biomarkers (28). Research on molecular biomarkers is intense; however, only a few studies have advanced into the validation stage and have achieved clinical use (29). Thus, the discovery of novel biomarkers is essential for the progress of MS diagnosis.

Prognostic factors are also critical in MS. MS is well known for having an uncertain trajectory, and although the majority of patients with MS initially experience a relapsing-remitting phase, a large portion of them eventually reach a progressive phase, where disability accumulates (30). Disease prediction and the identification of patients with a high risk of disability progression may enable the development of optimal management strategies and therapeutic approaches (31). Therapy-wise, there have been a number of notable advances made over the past years with the emergence of highly effective approaches, particularly as regards the relapsing forms of the disease (32).

More specifically, one of the mainly used therapeutic approaches includes the use of immunomodulatory or immunosuppressive drugs that reduce the frequency of episodes of the relapsing forms of the disease. These drugs however, display a lackluster efficacy in preventing the transition to the progressive phase of MS and are of no benefit after such a process has commenced (33). This poor efficacy is due to the fact that these therapies provide partial protection against the neurodegenerative component of MS (32). Other examples of immunomodulators include inhibitors that reduce the proliferation of T-lymphocytes, second-generation fumarates and inhibitors of Bruton's tyrosine kinase (BTK) (34-36). BTK, in particular, participates in the downstream signaling of receptors on lymphocytes and innate immune system cells, leading to a potential effect on peripheral and brain-centric immune reactions (37). Several BTK inhibitors are in various phases of study, with evobrutinib set to enter phase III clinical trials in patients with RRMS, tolebrutinib soon to enter phase III trials (NCT02975349), and fenebrutinib in late-stage clinical development (36,38). Branching away from standard disease-modulatory therapies, certain remyelination-enhancing agents have been investigated as a potential therapy for MS, although their relevance in a clinical setting remains to be confirmed (39). Moreover, various targets are being explored, such as histone deacetylase (HDAC), which regulates gene transcription and mediates epigenetic modulations involved in MS pathogenesis (40). CKD-506, a selective HDAC6 inhibitor, has been shown to exert therapeutic effects in a rodent model of MS, indicating the potential of alternative MS therapy routes (41). Overall, immunomodulation and immunosuppression have so far been the pillars of experimental therapeutic strategies against MS, as guided by the autoimmune pathogenesis of the disease. Nevertheless, a deeper understanding of the underlying mechanisms of MS is warranted in order to explore novel therapeutic approaches, which will guarantee maximum efficiency and the minimization of adverse effects.

3. Computational biology in the era of biomedical big data

The technological advances of the 21st century have allowed the generation of biological datasets of immense proportions (42). These data may come in various forms, such as genomic sequences, molecular pathways, electronic health records and molecular and medical imaging data (43). This huge and heterogeneous pool of digital information, currently termed big data, may be invaluable for biomedical research; however, it also requires novel approaches for its efficient management and analysis (42). Modern computational tools allow the exploitation of such datasets, with the resulting information being used for standard processes, such as genome annotation, gene function prediction, gene expression analyses, as well as for more demanding goals, such as the creation of trainable predictive models, the screening of vast data libraries for novel drugs and drug targets, as well as for the development of novel diagnostic and prognostic tools (44,45).

Systems biology is an excellent example of a scientific discipline that largely evolved due to the modern advancements in computational tools (46). This discipline includes the study and modeling of biological systems in a holistic manner, including the interaction network between the factors and components comprising the biological system (47). Systems biology makes use of mathematical models and partial representations of biological systems to provide predictions on the state of a disease or the effects of individual therapy, elucidate potential molecular mechanisms, underlying biological processes and diseases, and simulate various biological processes (48). Mathematical models have already been used to predict disease spread in outbreaks and to help determine control measures, while modern computational frameworks, such as aneurIST can use patient-specific medical data to assess the risk of aneurysm rupture and subsequently adjust patient treatment (49). In the complex field of neurodegenerative diseases, the use of multivariate computational tools has enabled the identification of causative mechanisms based on the analysis of multi-dimensional omics datasets (50). These accomplishments of systems biology are fairly promising, and suggest that this scientific discipline can help elucidate complex diseases whose pathogenicity and pathophysiology remain elusive.

In order to bridge the gap between the expanding volume and complexity of biomedical big data, and the need for the discovery of meaningful patterns, associations and analysis, high performance computing solutions and AI are a rapidly gaining field. High performance computing solutions, such as GPU computing and cluster computing, can provide the platforms needed to operate software for big data analysis (51). The vast quantities of biological data stemming from broadly used, high-throughput experiments can be handled through cloud computing, which moves away from in-house computing infrastructures to computing delivered through the internet (52). AI refers to the use of computers and technology to simulate intelligent behavior and critical thinking similar to that of a human being (53). Big data analysis and tasks, such as data mining are prime areas of AI implementation, using techniques such as simulation models, decision algorithms and artificial neural network modeling (54). The application of continuously evolving AI computing models in biomedical research has greatly helped to navigate unclear and heterogeneous data (55). In the clinical context, robust AI can enhance and facilitate the work of a clinician by executing variety of tasks, such as workflow management, image analysis, the automation of various procedures, clinical decision making, the development of medical devices and patient monitoring (56). Moreover, AI can directly help patients by coaching them to perform standard care acts themselves and by promoting better medical knowledge about their condition through applications, such as educational games (57). These characteristics of AI showcase that its prospect as an essential tool in managing and treating chronic diseases (58).

As expected however, machine learning and AI approaches are not without limitations and challenges. In the supervised machine learning setting, there exists a point where the addition of data essentially will not increase the performance of a model (59). Furthermore, a number of biomedical datasets, which may serve as input for widely-used classification models, suffer from severe class imbalances and instances of unlabeled data (60). Efforts are being made towards approximating the convergence point of such models, as well as towards the utilization of unlabeled data during training (61).

Setting standards is a crucial step to ensure the proper application of computational biology on biomedical data. The quality of 'omics' data, which serve as input for big data science, depends on robust and reproducible collection and analysis strategies (62). From the selection of the biological material under study, to the execution of essential experimental steps (collection of samples, extraction of genetic material, cell cultures), the standardization of samples continues to pose a challenge (63). The adoption of a unified system of protocols would allow the aggregation of data from different healthcare systems, ensuring comparable measurements.

4. Multiple sclerosis and computational biology

Genome-wide association studies (GWAS), an approach in genetics that allows the testing of a massive number of genetic variants across the genomes of numerous individuals to identify genotype-phenotype associations, have revolutionized the field of disease genetics (64). Specifically, GWAS compare allele frequency at each variant position of the genome between healthy controls and diseased individuals, with significant differences indicating a disease association (65). GWAS on MS have demonstrated that a major portion of the heritability of the disease can be assigned to the major histocompatibility complex (MHC) genetic region (66). Specifically, GWAS have identified one chromosome X variant, 200 autosomal susceptibility variants outside the MHC, and 32 variants within the extended MHC that independently contribute to the pathogenesis of MS (67). Although these studies have advanced the research of MS, an in-depth data analysis is still lacking, and various characteristics of the GWAS dataset, such as sample size and source may affect the results and lead to subpar results. A systems biology approach allows the integration and simultaneous analysis of different types of data (e.g., GWAS and proteomics), which can help uncover hidden patterns in the datasets producing network interaction models, and clearer insights of the mechanisms involved in diseases such as MS (68). Additionally, a systems biology approach that incorporates biological network structures into the analysis of GWAS datasets can provide increased coverage, confidence, precision and accuracy (69).

Another technology that has been extensively used in MS are microarrays (70). Microarrays are a technology mainly used to measure gene expression levels and allow the identification of gene expression differences in healthy and non-healthy individuals (71). It is not surprising then that several microarray datasets of MS case/control cohorts can be collected through publicly available databases (72). The application of various algorithms on such datasets can provide a wealth of information to researchers. Specifically, through a systems biology approach, researchers can generate gene and protein networks and identify genetic variants and novel molecules that heavily contribute to the pathogenesis of MS (73,74). A previous study by Shang *et al* (75), as an example, made use of such techniques and identified differentially expressed genes in MS, while pinpointing a number of genes heavily associated with the disease, including transcription factors (FOS, TP53, JUN and ATF3) and genes whose function was associated with the immune system (OAS2) and inflammation (IL8).

Computational biology studies may also provide novel biomarkers for MS. Studies making use of mass genotyping, DNA arrays, antibody arrays, proteomics and metabolomics analyses from different tissues have identified several molecules associated with MS, which may be potential biomarkers (76). These biomarkers can have several applications, such as the diagnosis of diseases in very early stages, monitoring disease activity, assessing treatment response, and being potential drug targets for novel treatment strategies (77). As regards diagnosis specifically, molecular biomarkers may also help clinicians differentiate MS from other CNS-associated disorders, thus avoiding misdiagnoses (78). Some researchers have already established biomarkers for MS, including CSF biomarkers such as neurofilaments, chitinases, soluble cell surface receptors from microglia and macrophages, and oligoclonal immunoglobulin M antibodies (79).

The use of AI may assist in the diagnosis and prognosis of MS (80). Intelligent computer systems provide several advantages when it comes to the diagnosis of MS, including increased diagnostic accuracy and reliability, and decreased time loss and expenses (81). Computational models can be used to discriminate between relapsing-remitting and progressive forms of MS (82). Additionally, several AI algorithms can use patient characteristics, such as age and sex along with clinical data, such as imaging results (MRI data) can be used to predict the disability status of an individual patient in the future (83). Machine learning, a subset of AI, has been increasingly implemented in the risk assessment, diagnosis and prognosis of MS. Machine learning models can accept MRI and functional MRI images, clinical and demographic data as input in order to detect MS lesions. These models, such as support vector machines, Random Forest and convolutional neural networks, are programmed to classify images that may present MS-characteristic lesions (84-86). Clinical data may additionally be used in machine learning implementations, mainly for the diagnosis and prediction of the progression of the disease (82). Linear classifiers, such as the one proposed by Branco *et al*, predict the type of MS progression by using information from a clinical questionnaire (87). Another type of linear classifier, a multi-layer perceptron, made use of MRI metrics generated through graph theory analysis in order to perform classifications of MS types (88). In a recent study, unsupervised machine learning models were trained on cerebral MRI scans from 6,322 patients to define a novel set of MRI-based MS subtypes (89). Lastly, as aforementioned, novel information regarding disability progression of MS is of utmost importance for the management of patients. In a 2021 study by Tommasin *et al* (90), machine learning classifiers were used on a pool of clinical and radiological data for the extraction of features which are important in predicting disability progression.

Personalized medicine applications in MS are highly desirable due to the heterogeneity observed in this specific disease (91). A precision medicine approach medicine can help optimize the diagnosis, treatment and management of patients with MS, by promoting early disease recognition and prevention, providing quality-of-life enhancements, and improving current healthcare services and treatments (92). AI is emerging as a key component in the advancement of personalized medicine (93). Natural language processing, an AI computational

tool that can analyze and interpret text, can be used to mine electronic health records for signs and symptoms of MS, and identify the disease before a healthcare provider (94). AI, as it has already been mentioned, may also be used to predict the disease progression of an individual patient, and can thus tailor treatment options and improve the allocation of healthcare resources. For instance, the incorporation of short-term clinical and brain MRI data in a Support Vector Machine, a powerful classification tool for computational analysis, can provide a prediction of how MS will progress and recommend a subgroup of patients that are suitable for aggressive treatment regimens (95). Lastly, modern computer software allows for a coordinated exchange of health-related information, and patients can interact with healthcare providers at a distance, thus enabling a more consistent disease monitoring and empowering patients to take control of their own health. The resulting data can then be mined through various computational tools and analyzed for novel information regarding the individual's disease progress (96). The existence of an online-accessible framework is of particular importance when standard medical practices and procedures are affected by greater situations. A recent example is the current COVID-19 pandemic, which led to an unprecedented weight on national healthcare systems, and destabilized the management and treatment routines of patients with life-altering diseases, such as cancer or MS.

5. Conclusions and future perspectives

MS affects numerous aspects of the life of an individual and is accompanied by a variety of symptoms, which can severely affect the quality of life of patients. Fortunately, the technological advances of the 21st century have led to breakthroughs in terms of experimental treatment plans and management. The accumulation of disease-related biomedical data and the rapid advancements in computational technology have led to a surge in the use of informatics in biological sciences. Through the use of statistical informatics tools, AI, machine learning and an arsenal of available biomedical software, healthcare providers can enhance every single step of healthcare, from diagnosis and prognosis, to management and treatment. Precision medicine emerges as the future standard for the medical practice, particularly in the case of multi-faceted diseases such as MS, and a robust computational framework can provide the means for its realization. In the case of MS and its observed heterogeneity, disease mechanisms may be elucidated on an individual level, informing a tailored plan of treatment and management, which will complement the disease profile and needs of individual patients.

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Competing interests

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