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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (C ROBINSON, SECTION EDITOR)

The Role and Applications of Artificial Intelligence in the Treatment of Chronic Pain

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Abstract

Purpose of Review This review aims to explore the interface between artificial intelligence (AI) and chronic pain, seeking to identify areas of focus for enhancing current treatments and yielding novel therapies.

Recent Findings In the United States, the prevalence of chronic pain is estimated to be upwards of 40%. Its impact extends to increased healthcare costs, reduced economic productivity, and strain on healthcare resources. Addressing this condition is particularly challenging due to its complexity and the significant variability in how patients respond to treatment. Current options often struggle to provide long-term relief, with their benefits rarely outweighing the risks, such as dependency or other side effects. Currently, AI has impacted four key areas of chronic pain treatment and research: (1) predicting outcomes based on clinical information; (2) extracting features from text, specifically clinical notes; (3) modeling ‘omic data to identify meaningful patient subgroups with potential for personalized treatments and improved understanding of disease processes; and (4) disentangling complex neuronal signals responsible for pain, which current therapies attempt to modulate.

Summary As AI advances, leveraging state-of-the-art architectures will be essential for improving chronic pain treatment. Current efforts aim to extract meaningful representations from complex data, paving the way for personalized medicine. The identification of unique patient subgroups should reveal targets for tailored chronic pain treatments. Moreover, enhancing current treatment approaches is achievable by gaining a more profound understanding of patient physiology and responses. This can be realized by leveraging AI on the increasing volume of data linked to chronic pain.

Keywords Artificial intelligence · Chronic pain · Machine learning · Neuromodulation · Precision medicine

Introduction

Pain represents an indelible problem for clinical and psychosocial patient outcomes, as well as an economic, social, and individualistic burden on patients and communities. Because of this, it is imperative to understand the social and neurobiological tenets of pain and pain modulation. The International Association of the Study of Pain and the World Health Organization define pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Pain is differentiated based on etiology and duration as acute, subacute, and chronic pain.

Chronic pain is one of the most common comorbidities in the United States with varying estimates of precise prevalence due to subjectivity of symptoms and consensus of diagnosis, but noted to be within the range of 2 to 40% of the general population [2]. Due to the high prevalence and negative downstream health outcomes, appropriate diagnosis and

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treatment of chronic pain has become essential in clinical practice. Untreated chronic pain has been associated with the development of comorbidities including reduced cognitive function, insomnia, sexual dysfunction, increased instances of depression and anxiety, and overall decreased quality of life [3•, 4•]. Moreover, the impact of pain and its management include rising health costs, reduced economic productivity, and excessive strain on healthcare resources [1]. This has led to recognizing the access of pain management as a human right despite a scarcity of tools to manage pain [5]. Therefore, applying the biopsychosocial model and understanding pain at both the physical level of nociceptor sensitivity and psychological level of behavioral patterns, can allow us to understand the current scope of chronic pain and the future of potential management options [6].

Chronic Pain

Chronic Pain and its Comorbidities

Patients diagnosed with chronic pain conditions present to clinicians with numerous secondary health problems including sleep disturbance, mood and anxiety disorders, weight gain, and an increased propensity for substance use disorder [3•, 4•]. Functional imaging studies have shown that many of the neural pathways associated with nociception share mechanisms with those that control behavior and emotion [7]. In fact, growing evidence shows that there is a bidirectional association between chronic pain and mental health disorders [6, 8].

The estimated prevalence of depressive disorder across chronic pain groups ranges from 2 to 61%, dysthymia from 1 to 9%, and bipolar disorder from 1 to 21% [6]. In a population-based study involving 845 adults, study participants with mild or disabling neck or lower back pain were 2.0 to 2.5-times more likely to experience an episode of depression at 6- and 12-month follow-up than those without pain [9•]. Conversely, the patients deemed pain-free with severe levels of depression were found to be 4-times more likely to develop neck or low back pain at equal interval follow-ups. The study also showed that the rate of depression increased when pain severity worsened. Melzack [10] described neural activation and the conceptualization of what he deemed the pain matrix. Instead of these brain processes being unrelated, his work showed a possible hierarchical network between nociceptive processing, cognitive modulation, emotional contextualization, and memory formation. Our inherent interpretation of pain, by the standards of this model, is an individualized experience affected by psychological factors and memory formation at the emotional level. Using this information, clinicians can garner a better understanding of appropriate treatment modalities and possible behavioral modification techniques that can better support their patients.

Sleep disturbance also appears to be a component of chronic pain. It is proposed that sleep disturbance and chronic pain share a bidirectional relationship much like chronic pain and mental health disorders [8]. It has been shown that the estimated prevalence of sleep disturbance in patients with chronic pain ranges between 50 and 80% [11–15]. Moreover, studies show a positive correlation between insomnia severity and increased pain intensity [8]. The overlapping mechanisms involved in pain and sleep functions present a promising target for treatment modalities in the future. [6].

At this time, the ideal and optimal approach to chronic pain management is multidisciplinary treatment that incorporates both pharmacological intervention and physical rehabilitation, but many times, due to discordant care or cost, does not occur at the patient level [16]. Because of these shortcomings, the complexity of pain etiology, and the high prevalence of chronic pain in the population, it is important to find alternative means to better tailor care to the individual patient. In the current practice, many clinicians increase health expenditure costs by ordering expensive diagnostic tests and invasive treatment strategies that may provide little to no benefit to the patient. Employing low barrier technologies that can be applied to existing data is the next fundamental step in creating efficient and cost-effective care. As the trend towards digitizing medicine increases, the use of artificial intelligence (AI) and machine learning (ML) has become integral to clinical application [17•]. Through use of these technologies, we are better able to utilize aggregated data sets of patients as well as larger amounts of pain-related data which include genomic information, medical imaging, and clinical phenotype data [17•].

The Consequences of Chronic Pain

In 2022, $4.1 trillion was spent on healthcare in the United States [18•], with much of the cost concentrated on those suffering chronic neck and lower back pain [19]. Moreover, chronic pain in the United States leads to an estimated $79.9 billion in lost wages, with its impacts exacerbated by its correlation with mental health conditions stemming directly from pain-related outcomes and decreased functionality [3•].

The social landscape is significantly influenced as well. With the emergence of the pain movement in the 1990s, opioid analgesics became widely regarded as a cornerstone for pain management. Many prescribers during this time had little to no pain management training but were still expected to fulfill patient expectations and ascribe pain as a "fifth vital sign." The tandem of opioid marketing, prescriber behaviors, and changes to pain management lead to the opioid crisis as we know it today [20]. From 1991 to 2021, nearly

645,000 people died from overdose involving opioids [21], and though it is difficult to parse out all-cause mortality, a percentage of these cases were chronic pain patients [22].

The prevalence of chronic pain poses a unique dilemma to medicine and future public policy. In order to improve and mitigate opioid usage, it is imperative to look at root cause problems. Thus, the future of chronic pain management and improved patient outcomes must emphasize finding multimodal approaches for treatment and improving our understanding of the complex array of psychosocial factors that contribute to chronic pain and opioid use.

The Future of Chronic Pain Diagnosis and Management

Chronic pain has a profound impact on both patients and healthcare. Its treatment presents challenges due to the complexity of the condition and the considerable variability in how patients experience and respond to different treatments. Current therapeutic options often fail to provide long-term relief, and the benefits of these treatments rarely outweigh their risks, such as dependency or other side effects.

Much work has focused on (1) developing novel treatments, (2) improving current treatment modalities, and (3) identifying subpopulations of patients with unique phenotypes to facilitate development of patient-specific interventions. State-of-the-art AI and ML approaches have recently emerged as a necessary means to disentangle the relationship between patient phenotype and disease manifestations, particularly when using complex, often noisy, medical data that includes genomic, transcriptomic, metagenomic, and proteomic sequencing data; structured and unstructured electronic medical record data; clinical trial and pharmacological data; and neuronal signal processing data. For example, it has been estimated that the amount of genomic sequencing data alone will soon surpass the total amount of other forms of biological and medical data [23]. Hence, with the rapid pace of data generation, there is a clear need for automated algorithms that can learn from these data and shed light on underlying patterns and signals [24].

In this review, we first introduce the field of ML and define the necessary terminology and architectures. We then discuss the approaches relevant to subgroup identification and, potentially, precision medicine. Finally, we present the current literature on neuromodulation and how ML can be leveraged. Throughout this review, we will speculate on the potential of AI and ML in each respective field.

A Primer on Machine Learning

Chronic pain management stands at the forefront of medical challenges, demanding innovative solutions to alleviate suffering and improve patient outcomes. In recent years, the integration of AI and ML has emerged as a promising avenue for transforming the landscape of chronic pain care. AI refers to the simulation of human intelligence processes by machines, encompassing a broad range of techniques aimed at enabling computers to perform tasks that typically require human intelligence (see Table 1). ML, a branch of AI, focuses on the development of algorithms that allow computers to learn from and make predictions or decisions based on data, without being explicitly programmed.

Table 1 Key terms

Term	Definition
Artificial intelligence (AI)	The simulation of human intelligence in machines, programmed to mimic human actions
Machine learning (ML)	A branch of AI that uses models to learn from data, identify patterns, and make decisions or predictions based on that learning
Natural language processing (NLP)	A branch of AI that uses models to understand, interpret, and generate human language
Deep learning (DL)	A branch of ML that uses artificial neural networks (NNs) with many layers ("deep") to model complex problems
Large language model (LLM)	A type of model used in NLP that typically leverages DL (such as transformers) to generate human language
Labels	The outcomes or categories that a ML model is trying to predict
Features	The individual measurables of the data that are used as inputs in ML models
Unsupervised learning	A type of ML where the model is trained on unlabeled data to learn the structure of the data without any guidance on what the output should look like
Supervised learning	A type of ML where the model is trained on labeled data to learn a relationship (a “mapping”) between the input (features) and output (e.g., labels) variables
Classification	A type of supervised learning where the goal is to predict the label of new observations based on past observations with known labels
Dimensionality reduction	The process of reducing the number of features in a dataset to simplify the dataset by capturing the most important information while discarding redundant or irrelevant features

Supervised Learning

Supervised learning is a foundational concept in ML where the algorithm learns from labeled data. In this paradigm, each training example consists of an input feature vector (such as patient weights, morbidity scores, lab values, etc.) paired with a corresponding output label (such as mortality, length of stay, complications, etc.). The goal is to learn a mapping or relationship between the input features and the output labels, allowing the algorithm to generalize and make predictions on new, unseen data. Common tasks in supervised learning include regression, where the goal is to predict a continuous value, and classification, where the goal is to predict a categorical label. For example, in chronic pain management, supervised learning algorithms can be trained on patient data with labeled pain intensity scores to predict the effectiveness of different treatments or interventions. A range of supervised ML algorithms have been explored for patient selection and diagnostic aid in pain progression. Pateria and Kumar [25•] found that decision tree regressor models using clinical measures and functional magnetic resonance imaging (fMRI) data, as well as classifiers built using electroencephalogram (EEG) and positron emission tomography (PET) data, can predict neuropathic pain following spinal cord injury. Nijeweme-d'Hollosy et al. [26] employed ML algorithms on patient-reported data to model treatment selection for low back pain. They evaluated the ability of the model to learn from the data, which, in turn, demonstrated the feasibility of using ML for decision-making processes regarding treatments. They evaluated 25 ML models, with BayesNet and Naive Bayes performing best. Additionally, Zmudzki and Smeets [27•] developed a multidimensional ML framework for chronic musculoskeletal pain treatment.

Unsupervised Learning

Unsupervised learning, on the other hand, involves learning patterns or structures from unlabeled data. In this paradigm, the algorithm seeks to identify underlying patterns or groupings within the data without explicit guidance from labeled examples. Unsupervised learning tasks include clustering, where the goal is to partition data into distinct groups based on similarity, and dimensionality reduction. The objective is to reduce the number of input features while preserving important information, which can aid interpretation for downstream ML tasks.

In the context of chronic pain management, unsupervised learning techniques can help uncover hidden subtypes of pain conditions or identify clusters of patients with similar symptom profiles, potentially revealing personalized treatment approaches. A range of unsupervised learning techniques have been applied to identify biomarkers of pain and treatment. Kharghanian et al. [28] proposed a hierarchical unsupervised approach for pain detection from facial images, achieving near 95% accuracy. Loetsch et al. [29] applied unsupervised ML to identify patient subgroups with different pain intensities in rheumatoid arthritis and then used supervised ML to identify meaningful features for persistent pain, achieving accuracy of 70%. These studies demonstrate the potential of unsupervised learning techniques in identifying biomarkers of pain and potential avenues for treatments.

Reinforcement Learning

Reinforcement learning is a paradigm of ML where an agent learns to make decisions by interacting with an environment. Unlike supervised learning, reinforcement learning does not rely on labeled input–output pairs but instead learns through trial and error based on feedback from the environment. The agent performs actions in the environment and receives rewards or penalties based on its actions, guiding its learning process.

In chronic pain management, reinforcement learning can be applied to optimize treatment strategies by adapting to changes in patient responses over time. Multiple studies have explored the potential of reinforcement learning in critical care settings [30, 31•, 32•]. Lopez-Martinez et al. [30] applied this approach to pain management with morphine, demonstrating its ability to provide personalized dosing recommendations. However, Roggeveen et al. [31•] described the feasibility and efficacy of employing an online reinforcement learning agent to tailor personalized physical exercise recommendations, with a specific focus on alleviating endometriosis-related pain. The research not only introduces an innovative trial design but also sheds light on the transformative potential of such interventions at enhancing patient outcomes.

Deep Learning

Deep learning (DL) has gained significant traction in various domains, including healthcare, due to its ability to learn intricate patterns from data. At the core of deep learning lies artificial neural networks (NNs), which are inspired by the structure and function of the human brain. NNs consist of interconnected nodes organized into layers, including an input layer, one or more ("deep") intermediate ("hidden") layers, and an output layer. Each node performs a simple computation, and the connections between nodes are assigned weights that are adjusted during training to minimize prediction errors. Deep NNs are widely used for tasks involving structured data, such as electronic health records or physiological signals.

Among the different types of DL models, convolutional neural networks (CNNs) excel in processing grid-like data, such as images, by leveraging spatial hierarchies of features. This makes CNNs particularly useful in medical imaging tasks, where they can aid in detecting abnormalities or anomalies in scans related to chronic pain conditions. Shin et al. [33] highlighted the effectiveness of CNNs in computer-aided detection, with a focus on different CNN architectures, dataset characteristics, and transfer learning. Patel [25•] further emphasized the utility of CNNs in medical image segmentation, particularly in tasks such as x-ray, MRI, computed tomography (CT), ultrasound, and PET. Recurrent neural networks (RNNs), on the other hand, are well-suited for sequential data processing, making them valuable for time-series analysis, including longitudinal patient data or physiological signals [34]. In the context of chronic pain, RNNs can capture temporal dependencies and dynamics in pain trajectories, enabling better prediction and management strategies. Wang et al. [35] introduced a hybrid RNN (a bidirectional Long Short-Term Memory (LSTM)) model for pain recognition, which combines auto-extracted and handcrafted features.

Moreover, DL techniques have shown remarkable success in natural language processing (NLP) tasks, including sentiment analysis, language translation, and clinical text mining. Techniques like LSTMs are particularly effective in modeling text where words have contextual relationships between other words that are distantly separated, making them indispensable in analyzing clinical narratives, patient reports, or social media data related to chronic pain experiences. By integrating deep learning techniques into chronic pain research and clinical practice, one can harness the power of data-driven insights to improve diagnosis, treatment, and management strategies for individuals living with chronic pain.

Self-Supervised Learning

Self-supervised learning offers a compelling approach for extracting meaningful representations from unlabeled data, a common scenario in chronic pain research where labeled datasets are often limited in terms of amount and quality. One prominent technique within self-supervised learning is the use of autoencoders (AEs). AEs are NNs designed to learn representations of input data that ideally generalize to unobserved data. AEs have been successfully applied to diverse medical data modalities, including medical image analysis [36•], medical image synthesis [37], and mammogram compression [38]. Zhou et al. [39•] demonstrated the effectiveness of a masked AE self-pre-training for tasks such as lung disease classification, CT abdomen multi-organ segmentation, and MRI brain tumor segmentation. By encoding the salient features of these data types into a low-dimensional latent space, AEs facilitate the discovery of underlying patterns and associations relevant to pain pathology and treatment response. AEs, particularly variational AEs and denoising AEs, have shown promise in extracting biologically-relevant features from non-image-based data, genomic, and gene expression data. Way and Greene [40] introduced Tybalt, a variational AE method that effectively captures aberrant pathway activation and identifies treatment vulnerabilities in cancer gene expression data. Similarly, Tan [41] introduced denoising AEs as a method for unsupervised feature construction and knowledge extraction from breast cancer gene expression data. These AEs were found to successfully construct features containing both clinical and molecular information, including tumor presence, estrogen receptor status, and molecular subtypes.

Another self-supervised learning approach gaining traction is contrastive learning. Contrastive learning focuses on learning representations by contrasting similar and dissimilar pairs of data points within an embedding space. This technique has shown promising results in various domains, including computer vision and NLP, by encouraging the model to distinguish between similar and dissimilar pairs. Contrastive learning can be leveraged to identify latent similarities or subgroups within heterogeneous patient populations [42•, 43] (Table 2).

Table 2 Relevant work applying ML approaches to chronic pain. RF, random forest. PCA, principal component analysis. LSTM, long short-term memory

Study	Aim	Approach
[25•]	Predict neuropathic pain after spinal cord injury with fMRI, EEG, and PET data	Decision trees
[26]	Benchmark ML models for decision support of low back pain treatments	Multiple models including BayesNet
[27•]	Decision support of chronic musculoskeletal pain	Multiple models including decision trees
[28]	Pain detection from facial images	Convolutional deep belief network
[29]	Identify subgroups and features based on pain intensities in rheumatoid arthritis	Multiple models including RF, PCA
[30]	Dosing of morphine for pain management	Reinforcement learning
[31•]	Alleviating endometriosis-related pain	Reinforcement learning
[32•]	Exercise recommendations	Reinforcement learning
[35]	Pain recognition based on bio-signal data	Bidirectional LSTM

Subgroup Identification

Natural Language Processing of Clinical Text

NLP is a branch of AI that focuses on developing models that understand, interpret, and generate human language that is both meaningful and useful. Examples of NLP in healthcare include (1) named entity recognition (NER) where sequences of text are associated with a concept [44, 45]; (2) information retrieval where spans of text are identified that meet specific criteria [46]; and (3) relation extraction where semantic relationships between components in a document are obtained [47, 48]. For example, Branco et al. [49•] used supervised approaches and latent semantic analysis to identify placebo responders based on text from patient interviews. Fodeh et al. [50] developed a classifier to identify pain assessment information. Schirle et al. [51] selected relevant terms from clinical notes using Term Frequency-Inverse Document Frequency (TF-IDF) to identify chronic pain patients with opioid use disorder. Lastly, Goudman et al. [52•] extracted relevant topics that summarize a popular chronic pain subreddit.

NLP can benefit from various ML architectures; however, NNs have entrenched themselves as a vital means to extract meaningful information from text. A simple NN for text involves "embedding" words into a numerical space that can aid in recognition of meaningful patterns as well as being more conducive for downstream ML approaches. This approach can be applied to either raw clinical text [53, 54] or genomic sequence information [55]. For example, CNNs have been leveraged to classify International Classification of Diseases (ICD) codes indicative of low back pain from clinical notes [56].

Research has demonstrated the use of DL for analyzing clinical notes [57], ICD coding [58], genomic sequencing data [59], and adverse drug events [60]. Squarcina et al. [61] highlighted the promising results of deep learning in predicting treatment response in depression, a common comorbidity of chronic pain. Leveraging deep learning in NLP can provide insights into patient-reported outcomes, treatment responses, or socio-psychological factors influencing chronic pain management [62••].

Furthermore, large language models (LLMs), such as BERT (bidirectional encoder representations from transformers), have revolutionized NLP by training on text to capture contextual representations of words or phrases. "Fine-tuning" LLM-based models on domain-specific data, such as clinician notes, enables more accurate and context-aware predictions, facilitating personalized interventions or decision support systems. Specifically, BERT models have been used to summarize patient views on chronic pain treatments, their side-effects, and self-medicating approaches from Twitter posts [63•]; identify persistent opioid use after spine surgery [64•]; and associate chronic low back pain with social determinants of health disparities [65•]. Belyaeva et al. [66•], on the other hand, developed a multimodal LLM framework which achieved high performance in estimating disease risk using diverse data modalities.

'Omics, the Potential Role of the Microbiome, and the Goal of Precision Medicine

The use of precision medicine is an emerging field for the treatment of chronic and acute pain, offering medical practitioners the opportunity to improve outcomes by tailoring treatments to patients, particularly by leveraging specific genetic variants and the metabolic pathways that can lead to different pain states and pain-related phenotypes [67, 68]. One field that offers much potential in precision medicine involves the large-scale analysis of functional and structural aspects of multiple biological components, consisting of technologies such as genomics and transcriptomics, often collectively referred to as "omics." Omic methods are used to analyze aspects of a single biological system, as opposed to meta-omic methods which focus on analyzing an environment consisting of multiple organisms [69]. A general pipeline for processing omic data is shown in Fig. 1.

Previous work has applied NNs to gene expression data to identify disease subtypes and phenotypic clusters. For example, transcriptomic approaches have identified breast and ovarian cancer subtypes [41, 70] as well as predicted potential candidate genes targets [71, 72]. Omic techniques have been used to derive a number of biomarkers associated with pain conditions [73, 74•, 75].

Additionally, recent evidence suggests that the microbiome plays a role in the pathogenesis of several chronic pain disorders [76, 77, 78•, 79•]; hence, analysis of host-microbiome omic data may reveal pathways for targeted treatments. Investigations into the gut microbiome have uncovered taxonomic diversity biomarkers relating to chronic widespread pain [76], fibromyalgia [80•], and irritable bowel syndrome [81•, 82•], as well as chronic pain syndrome [83•, 84•, 85•, 86•, 87•]. Through state-of-the-art shotgun-sequencing, information characterizing species and function can be obtained. ML architectures are used for high-throughput classification of metagenomic subsequences [88, 89•, 90, 91] and genome reconstruction [92–95], allowing for abundance estimation of microbial communities and description of specific genes and phenotypes.

Moreover, transcriptomics, proteomics, and meta-bonomics may be used to profile the transcripts, proteins, and metabolites, respectively [96]. For example, Miettinen et al. [97•] performed a supervised ML approach to identify key metabolite features that could be implicated in chronic pain, specifically metabolic pathways involved in sleep and obesity. Furthermore, integrated

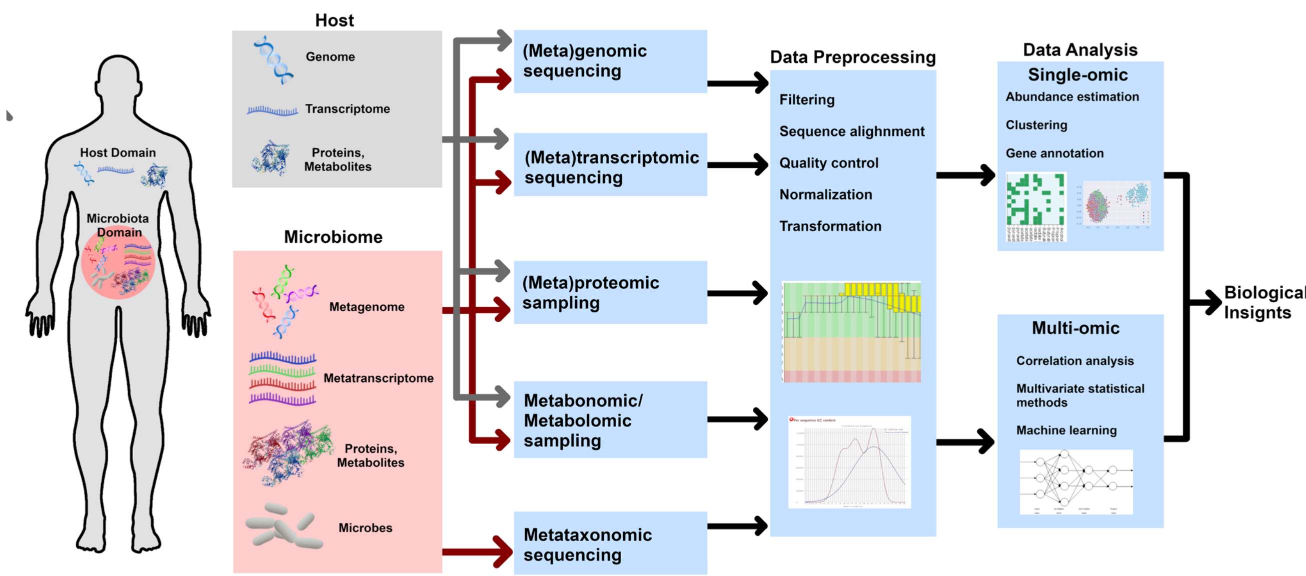

Fig. 1 Input data can be categorized into two groups: Host and Microbiome. Data is first gathered using the respective technique (mass spectrometry, sequencing, etc.), then preprocessed to remove any suboptimal data or to transform/normalize data for easier downstream analysis. The resulting data can then be analyzed for insight into the respective biological system

multi-omic approaches have been successful at predicting treatment responses and disease states in Crohn's disease [98–100], which may prove useful when applied to chronic pain. Tools such as RNA-seq [101] can also be used to significantly improve gene prediction when used in combination with other omic approaches. Gene expression can be estimated for both the host [102] and multiple species [103]. Another approach involves measuring the structure and function of proteins through mass spectrometry [104–108], which can provide a unique look into the metabolic pathways associated with a gene, as well as the taxonomy and metabolism of the microbiome. Together, this can help uncover drug-host-microbiome interactions that may impact treatment [109, 110, 111•].

The complexity of multi-omic data lends itself naturally towards ML-based approaches. Promising work is also being done to differentiate between healthy and disease states and aid in the discovery of novel biomarkers [112–114]. Various ML methods are used, both in supervised and unsupervised capacities, for analysis of integrated multi-omics datasets, which have enabled better understanding of biological systems [115] (Table 3).

Neuromodulation: Current Methods and Potential Areas for Improvement via Machine Learning

Spinal Cord Stimulators

Recent advances in brain computer interfaces (BCIs), neuroprosthetics, and neuromodulation are offering new opportunities to restore function in patients with catastrophic spinal cord nerve injuries, chronic pain, and hearing loss, paving the way for restoration of motor and hearing deficits, decreased pain, and the means for further rehabilitation [116–118, 119•]. Such breakthroughs offer promise for improving quality of life in these select individuals [120•]. The development of BCIs and neuroprosthetics is closely linked to AI and ML, which play a crucial role in interpreting the intricate patterns of neuronal activity responsible for movement [121•, 122]. These patterns can be detected through various monitoring techniques, including noninvasive methods such as EEG, MRI, and fMRI, as well as invasive methods such as electrocorticography (ECoG).

Current neuromodulation strategies can also be broadly categorized into invasive and noninvasive approaches. Invasive methods, such as deep brain, spinal cord, sacral nerve, and vagus nerve stimulation, offer greater precision and efficacy, but come with surgical risks during implantation, battery replacements, repairs, and removal. Noninvasive approaches, such as transcutaneous (TENS), vagus, ultrasonic, magnetic, alternating current, direct current, and near-infrared laser stimulation, lack surgical risks but may be limited in their effectiveness due to lower penetrating power, increased inter-user variability in terms of treatment response, and bulkiness [123•].

The emergence of "smart" technologies enables AI training to (1) detect neural signals associated with pain, (2) provide optimized feedback to reduce pain signals or perception (e.g., Medtronic's spinal cord stimulation (SCS) device AdaptiveStim [124]), and (3) continuously refine the

Table 3 Relevant work applying natural language processing (NLP) and 'omic approaches to chronic pain. SVM, support vector machine. CNN, convolutional neural network, BERT, bidirectional encoder representations from transformers. TF-IDF, Term Frequency-Inverse Document Frequency. NN, neural network, LASSO, least absolute shrinkage and selection operator. LDA, Latent Dirichlet allocation. GWAS, genome-wide association study

Study	Aim	Approach
[49•]	Predicting placebo responders in chronic pain management	Latent semantic analysis, logistic regression, SVM
[50]	Identify deficits in pain care quality including pain assessment, treatment, and reassessment	Multiple models including decision trees, RF, SVM
[51]	Development of a text-based risk assessment tool for opioid use disorder in a chronic pain population	TF-IDF
[52•]	Identification of keywords and location of chronic pain in online support groups	LDA
[56]	Classification of acute versus chronic pain in patients suffering from lower back pain	CNN
[63•]	Identification of self-reported chronic pain in social media	RoBERTa
[64•]	Classification of persistent opioid use following surgical procedures	BERT
[65•]	Extraction of social determinants of health from medical notes of chronic lower back pain patients	RoBERTa
[74•]	Identification of biomarkers from GWAS data for low back pain	LASSO
[75]	Classification of chronic pain in primates using gene expression data	NN
[97•]	Identified metabolites and metabolic pathways associated with chronic pain	RF, PCA, clustering

feedback for a patient-specific intervention. These smart technologies can leverage ML to develop feedback circuits and identify potential biomarkers necessary for finely tuned feedback. Specific biomarkers may include (1) body position in space measured by accelerometry; (2) shifts in spinal cord position, which could reflect cardiovascular and respiratory changes; (3) electrically evoked compound action potentials from Aβ fibers for pain suppression; (4) overcoming neuronal adaptation elicited by repetitive neurostimulation overtime, and, potentially, (5) local field potentials of regions that contribute to pain signal generation including the anterior cingulate cortex, orbitofrontal cortex, and primary somatosensory cortex, which are thought to be in desynchrony in chronic pain [125].

Several studies have demonstrated advancements in utilizing prospective targets. For example, asynchronous stochastic bursts have shown efficacy in overcoming neuronal adaptation [126, 127], while differential target multiplexed stimulation (of neurons and neighboring glial cells) has been effective in improving pain relief compared to standard techniques, with recent randomized control trials (RCTs) showing improved pain relief when compared to standard stimulation techniques [128•, 129]. Moreover, the type, target, and frequency of neurostimulation waveforms can significantly impact its efficacy, with some studies showing superior pain relief with specific targets (e.g., dorsal root ganglion) and lower frequency stimulation [130–134].

It has been postulated that dyssynchrony between affective, cognitive, and somatosensory components of pain are responsible for chronic pain; hence, this dyssynchrony could be modulated, restoring normal state-space signaling [135]. Most neuromodulation techniques are currently programmed as open-loop systems, which do not adapt to patient-specific physiological states [123•]. However, closed-loop systems, such as closed loop evoked compound action potential SCS, where the stimulation current is adjusted to maintain consistent spinal cord activation within a patient's therapeutic window, have shown superiority over fixed open-loop stimulation in treating chronic leg and back pain [136]. Walton et al. [137] showed with magnetoencephalography that type 1 complex regional pain syndrome (CPRS) is associated with low frequency somatosensory activity in the theta and delta band range and that increased low frequency is likely associated with peripheral chronic pain that lacks underlying nerve damage. Accordingly, studies have shown that interfering with low-frequency bursts via deep brain stimulation could potentially alleviate neuronal dysrhythmias associated with chronic pain syndromes such as CPRS [138]. Also, differential target multiplexed SCS that deliver electrical pulses that vary in terms of frequency, charge, amplitude, and duration have shown to be efficacious in treating chronic back pain [129, 139].

ML can further enhance recent advances in neuromodulation. For instance, SCS fails in upwards of 25% of patients; hence, ML could facilitate selection of ideal candidates for SCS. Hadanny et al. [140•] successfully classified treatment response to SCS based on a 50 to 70% drop in pain scores using demographic, pain outcome, and psychological data. Other work had similar success identifying treatment responders using fMRI [141] as well as identifying responses in a treatment naive group [142]. Accordingly, not only could ML assist in classifying SCS responses, but it too

Table 4 Relevant work applying ML approaches to neuromodulation and facial analysis. SCS, spinal cord stimulation. PSPI, Prkachin and Solomon Pain Intensity Scale

Study	Aim	Approach
[148]	Classified treatment response to SCS from demographic and outcome data	K-means, logistic regression, RF, boosting
[130]	Classified treatment response to SCS from fMRI data	Multiple models including decision trees, SVM
[126]	Classified treatment response to SCS from electronic health record data	Multiple models including regression trees, boosting
[130]	Classified PSPI	SVM
[126, 127]	Pain classification trained on video sequences	CNN, bidirectional LSTM
[152]	Pain classification trained on video sequences	LSTM

could augment or ideally replace SCS trial implantation and lead testing [143]. Lastly, applicable to both the initial trial phase and the subsequent treatment phase, parameterization could be optimized based on patient-specific and population data [144], as well as omic, lymphocytic, and imaging-based data [145•].

Facial Scoring

Previous research has focused on quantifying pain by assessing facial responses elicited by painful stimuli. Scoring methods, such as the Facial Action Coding System (FACS), involve visually describing facial expressions using 46 individual action units (AUs), which can then be used to quantify responses to painful stimuli, particularly with the Prkachin and Solomon Pain Intensity Scale (PSPI). However, these coding systems have limitations as they rely on human coders and are thus susceptible to implicit biases. Additionally, differences in facial expressions across populations, such as cultural variation, can introduce further bias in quantification [146, 147].

With the advancement of ML approaches, efforts have been made to enhance understanding and prediction of facial expressions. ML models, including ImageNet [148] and VGGface [149], have been trained on image repositories, leading to the development of NN architectures such as LeNet [150], AlexNet [151], and GoogleNet [152]. These advancements have laid the foundation for architectures that offer a deeper understanding of facial behavior. Initial work involved the detection of AUs using support vector machines (SVMs), hidden Markov models, and GentleBoost [153]. Subsequent research by Kim et al. [154] improved upon this by employing a hidden conditional ordinal random field to address the variation among subjects, followed by further enhancements using k-nearest neighbors [155] and AEs [156].

Baltrusaitis et al. [157, 158] developed OpenFace, a framework that uses the convolutional experts constrained local model, to capture facial landmarks, eye gaze, facial expressions, and head pose. Further work aimed at associating facial expressions with pain intensity to develop automated systems for decision support in the diagnosis and assessment of pain could prove valuable in the post operative recovery and intensive care settings, where pain scoring is done by medical providers, but is limited by patient participation, illness type, disease status, intubation, and language barriers [159•]. These automated systems could thereby help improve patient care as well as reduce PACU and ICU stays.

Despite these advancements, developing an algorithm for these tasks remains challenging due to variation in subject physical features, behavior, and head position, as well as lighting conditions. Nevertheless, researchers such as Neshov and Manolova [160] have used SVMs to classify PSPI, demonstrating the potential for medical applications. Additionally, Bargshady et al. [161, 162] achieved improved pain classification using a CNN bidirectional LSTM architecture on video sequences, surpassing previous work by Rodriguez et al. [163]. Their approach achieved 91.2% and 90.0% accuracy for the training and test data sets, respectively, showcasing the advancements in pain intensity classification through ML techniques (Table 4).

Conclusion

The intersection of ML, precision medicine, and chronic pain represents a compelling frontier in healthcare innovation. Advances in ML offer unprecedented opportunities for personalized treatment modalities that can optimize patient care, improve patient outcomes, reduce healthcare cost, and advance the understanding of pain mechanisms. Current advancements in the omic domains, along with the ongoing utilization of NLP for analyzing electronic healthcare records, offer a pathway to delineate patient subgroups based on distinct chronic pain-related profiles. This approach can facilitate targeted interventions and lay the groundwork for future research.

Utilization of AI will continue to enhance our understanding of the relationships between mental health, sleep disturbance, substance use disorder, and chronic pain. These algorithms identify meaningful subgroups and patterns that enable more accurate conclusions about patient behavior, neurobiological involvement, and diagnostic phenotypes. Ultimately, this may lead to personalized treatment plans, which in turn may reduce financial costs, optimize patient experiences, and improve health outcomes.

Moreover, optimizing current treatment modalities is possible through a deeper understanding of patient physiology and responses, which can be achieved by applying ML to the ever-growing data associated with chronic pain. As ML continues to advance, so too will medicine as long as the synergy between these fields is maintained.

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- • Of importance
- •• Of major importance

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