Machine learning in rare disease

This manuscript (permalink) was automatically generated from jaybee84/ml-in-rd@fd1064d on February 24, 2023.

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Abstract

The advent of high-throughput profiling methods (such as genomics or imaging) has accelerated basic research and made deep molecular characterization of patient samples routine. These approaches provide a rich portrait of genes, molecular pathways, and cell types involved in disease phenotypes. Machine learning (ML) can be a useful tool to extract disease-relevant patterns from high dimensional datasets. However, depending on the complexity of the biological question, machine learning often requires a large number of samples to identify recurrent and biologically meaningful patterns. Rare diseases are inherently limited in clinical cases and thus have few samples to study. In this perspective, we outline the challenges and emerging solutions for using ML in the context of small sample sets, specifically that of rare diseases. Advances in ML methods for rare disease are likely to be informative for applications beyond rare diseases in which sample sizes are small but datasets are high-dimensional (e.g., using genomics data for predictive modeling in precision medicine). We propose that the methods community prioritizes the development of ML techniques for rare disease research.

Introduction

Rare disease researchers increasingly depend on machine learning (ML) to analyze high-dimensional datasets. A systematic review of ML applications in rare diseases (as defined in the European Union, i.e. fewer than 5 patients per 10,000 people) uncovered 211 human studies that used ML to study 74 different rare diseases over the last 10 years.[1] Indeed, ML can be a powerful tool in biomedical research but it does not come without pitfalls, some of which are magnified in a rare disease context. [2] In this perspective, we discuss considerations for using two types of ML – supervised and unsupervised learning – in the study of rare diseases, with a specific focus on high-dimensional molecular data.

ML algorithms are computational methods that identify patterns in data, and use information about these patterns to perform tasks (e.g., pick important data points or predict outcomes). *Supervised learning* algorithms must be trained with data that has specific phenotypes or patient outcome labels. Supervised methods can learn correlations of features (e.g., expression measurements of a large number of genes) with the outcome labels to predict the outcome in unseen or new data, such as predicting which patients will or will not respond to treatment. Therefore, if a study aims to classify patients with a rare disease into well-known molecular subtypes based on high-throughput molecular profiling, a supervised ML algorithm is appropriate to carry out this task. Conversely, unsupervised learning algorithms learn patterns or features from unlabeled training data. In the absence of known molecular subtypes, unsupervised ML approaches can be applied to identify groups of samples that are similar and may have distinct patterns of pathway activation [3]. Unsupervised approaches can also extract combinations of features (e.g., genes) that may describe a certain cell type or pathway. See Box 1 for more examples of how ML can be used in rare disease research.

While ML can be a useful tool, there are challenges in applying ML to rare disease datasets. ML methods are generally most effective when using large datasets; thus analyzing high dimensional biomedical data (i.e. data with typically > 1000 features, e.g. 20,000 genes) from rare diseases datasets that typically contain 20 to 99 samples is challenging[1,4]. Small datasets tend to lack statistical power and magnify the susceptibility of ML to misinterpretation and unstable performance. With insufficient data, an unsupervised model will fail to identify patterns that are useful for biological discovery (i.e. "perform" poorly). Similarly, supervised models require datasets where the phenotype labels have very little uncertainty (or "label-noise") [5] – termed "gold standard" datasets. Datasets with high label-noise decrease prediction accuracy and necessitate larger sample sizes during training [6]. Rare disease datasets often come with significant label-noise (e.g., silver standard datasets) due to limited understanding of the underlying biology or evolving clinical classifications. Additionally, a supervised ML model is of limited utility if it can only accurately predict phenotype labels in the data it was trained on, also known as overfitting. Instead, most researchers aspire to develop models that generalize (maintain performance) when applied to new data that has not yet been "seen" by the model.

While we expect ML in rare disease research to continue to increase in popularity, the field requires methods that can learn patterns from small datasets and can generalize to newly acquired data [7]. In this perspective, we highlight approaches that address or better tolerate the limitations of rare disease data and discuss the future of ML applications in rare disease.

Constructing machine learning-ready rare disease datasets

High-throughput 'omic' assays generate thousands (e.g. transcriptomic sequencing) to billions of measurements (e.g. whole genome sequencing), resulting in high-dimensional dataset. A typical rare disease dataset consists of a small number of samples[1] leading to the "curse of dimensionality" (i.e.,

few samples but many features), which can lead to spurious results or models that do not generalize well [8]. More features often mean increased missing observations (*sparsity*), more dissimilarity between samples (*variance*), and increased redundancy between individual features or combinations (*multicollinearity*) [9], all of which contribute to challenges in ML implementation.

An important factor in machine learning is performance (e.g., the accuracy of a supervised model in identifying patterns relevant for a biological question, or the reliability of an unsupervised model in identifying hypothetical biological patterns supported by post-hoc validation). When small sample sizes compromise an ML model's performance, two approaches can be taken to manage sparsity, variance, and multicollinearity: 1) increase the number of samples, 2) improve the quality of samples. In the first approach, appropriate training, evaluation, and held-out validation sets could be constructed by combining multiple rare disease cohorts (Figure [1]a, Box 2). When combining datasets, special attention should be directed towards data harmonization since data collection methods can differ between cohorts. Without careful selection of aggregation methods, one may introduce variability into the combined dataset and negatively impact the ML model's ability to learn or detect meaningful signals. Steps like reprocessing data using a single pipeline, using batch correction methods [10,11], and normalizing raw values appropriately without affecting the underlying variance in the data [12] may be necessary to mitigate unwanted variability. (Figure [1]a) Data harmonization may also entail standardization of sample labels using biomedical ontologies to normalize how samples are described across multiple datasets.

Improving the quality of a dataset may require improving the accuracy of metadata (e.g., technical variables and phenotypes) for each sample. This may increase the effectiveness of ML models in extracting biologically relevant patterns from small datasets. The recognized need for improved metadata is highlighted by the recent introduction of the Phenopackets standard for sharing clinical phenotype data [15,16]. Collaboration with domain experts to curate and share well-annotated datasets is required to foster effective use of datasets in the future.

How does one know if a composite dataset has undergone proper harmonization and annotation? Ideally, the structure of the composite dataset reflects differences in variables of interest, such as phenotype labels. If the samples from the same cohort tend to group together regardless of phenotype, this suggests that the datasets used to generate the composite dataset need to be corrected to overcome differences in how the data were generated or collected. In the next section, we discuss approaches that help identify and visualize structure in datasets to determine whether composite rare disease datasets are appropriate for ML use.

Learning representations from rare disease data

Dimensionality reduction methods help explore and visualize underlying structure in the data (e.g., [17]), to define sample subgroups (e.g., [18]), or for feature selection and extraction during application of specific machine learning models [19] (Figure [2]c). These unsupervised methods 'compress' information from a large number of features into a smaller number of features [20,21,22] (Figure [2]). A method commonly used for dimensionality reduction is principal components analysis (PCA). PCA identifies new features, termed *principal components* (PCs), that are combinations of original features. The PCs are calculated in a way that maximizes the amount of information (variance) they contain and ensures that each PC is uncorrelated with the other PCs. [21] In practice, researchers often use the first few PCs to reduce the dimensionality without removing what may be important variability in the data. Other methods like multidimensional scaling (MDS), t-distributed stochastic neighbor embedding (t-SNE), and uniform manifold approximation and projection (UMAP) can also help identify useful patterns in the data, though t-SNE and UMAP require adjusting hyperparameters to get results that are not misleading or not reproducible. [22,24] Testing multiple dimensionality reduction methods may be necessary to obtain a more comprehensive portrait of the

data. [25] Nguyen and Holmes discuss additional important considerations for using dimensionality reduction methods such as selection criteria and interpretation of results. [26] Beyond dimensionality reduction, other unsupervised learning approaches such as k-means or hierarchical clustering have also been used to characterize structure in genomic or imaging data. [27,28]

Representation learning approaches (which include dimensionality reduction) learn low-dimensional representations (composite features) from the raw data. For example, representation learning through matrix factorization methods can extract features from transcriptomics datasets made of combinations of gene expression values. [25,29,30] Representation learning can also be utilized to predict rare pathologies from images [31] (Box 1a) or detect cell populations associated with rare diseases [32].

When applied to complex systems, representation learning generally requires many samples and therefore may appear to aggravate the curse of dimensionality. However, it can be a powerful tool to learn low-dimensional patterns from large datasets and then find those patterns in smaller, related datasets. In later sections, we discuss this method of leveraging large datasets to reduce dimensionality in smaller datasets, also known as feature-representation-transfer learning. Once the dimensions of the training dataset have been reduced, model training can proceed using the experimental design as outlined in Box 2.

Reducing misinterpretation of model output with statistical techniques

ML generally works well on data that meet a few critical assumptions. First, the dataset contains an equal number of samples for all categories (no "class imbalance"). Second, the dataset is complete; all samples have measurements for all variables in the dataset (i.e., the dataset is not "sparse", it is not missing data for some of the samples). Third, there is no ambiguity about the labels for the samples in the dataset (i.e., no "label-noise").

Rare disease datasets violate many of these assumptions. There is generally high class imbalance due to small number of samples for specific classes (e.g., only a few patients with a particular rare disease in a health records dataset), the data are often sparse, and there may be abundant label-noise due to incomplete understanding of the disease. All of these contribute to low signal to noise ratio in rare disease datasets. Applying ML to such data without addressing these shortcomings may lead to models that have low reproducibility or are hard to interpret.

Class imbalance in datasets can be addressed using decision tree-based ensemble learning methods (e.g., random forests). [33] (Figure[3]a) Random forests use resampling (with replacement) based techniques to form a consensus about the important predictive features identified by the decision trees (e.g., Box 1c). [34,35] Additional approaches like combining random forests with resampling without replacement can generate confidence intervals for the model predictions (for applications like Box 1d) by mimicking real world cases where most rare disease datasets are incomplete [36]. Resampling approaches are most helpful in constructing confidence intervals for algorithms that generate the same outcome every time they are run (i.e., deterministic models). For decision trees that choose features at random for selecting a path to the outcome (i.e., are non-deterministic), resampling approaches can be helpful in estimating the reproducibility of the model.

In situations where decision tree-based ensemble methods fail when applied to rare disease datasets, cascade learning is a viable alternative. [37] In cascade learning, multiple methods leveraging distinct underlying assumptions are used to identify stable patterns in the dataset [???,38,39]. For example, a cascade learning approach for identifying rare disease patients from electronic health record data (Box 1a) incorporated independent steps for feature extraction (word2vec [40]), preliminary

prediction with ensembled decision trees, and then prediction refinement using data similarity metrics. [37] Combining these three methods resulted in better overall prediction when implemented on a silver standard dataset, as compared to a model that used ensemble-based prediction alone. In addition to cascade learning, approaches that better represent rare classes using class re-balancing techniques like inverse sampling probability weighting [41], inverse class frequency weighting [42], oversampling of rare classes [43], or uniformly random undersampling of majority class [44] may also help mitigate limitations due to class imbalance.

The presence of label-noise and sparsity in the data can lead to overfitting, meaning that the models show high prediction accuracy on the training data but low prediction accuracy on new evaluation data. Overfit models tend to rely on patterns that are unique to the training data (for example, the clinical coding practices at a hospital), and not generalizable to new data (e.g., data collected at different hospitals). [45,46] Regularization approaches can help mitigate these scenarios by adding constraints to a model to avoid making large prediction errors. This not only protects ML models and learned representations from poor generalizability caused by overfitting, but also reduces model complexity by decreasing the feature space available for training [47]. (Figure[3]a) Examples of ML methods with regularization include ridge regression, LASSO regression, and elastic net regression [49], among others. Regularization is often used in exploring functional role of variants in rare disease and immune cell signature discovery studies; much like rare disease, these examples need to accommodate sparsity in data. For example, LASSO regularization reduced the number of features (genes) included as features in an ML model designed to classify brain tissue regions of amyotrophic lateral sclerosis (ALS) patients. [50] In the context of rare immune cell signature discovery, variations of elastic-net regression were found to outperform other regression approaches [51,52]. Other examples of regularization successfully applied to rare disease include Kullback-Leibler (KL) divergence loss or dropout during neural network training. In a study using a variational autoencoder (VAE) (see Box 3) for dimensionality reduction in gene expression data from acute myeloid leukemia (AML) samples, the KL loss between the input data and its low dimensional representation provided the regularizing penalty for the model. [53,54] A study using a convolutional neural network (CNN) to identify tubers in MRI images from tuberous sclerosis patients (an application that can facilitate Box 1a), minimized overfitting using the dropout regularization method which removed randomly chosen network nodes in each iteration of the CNN model generating simpler models in each iteration.[55] Thus, depending on the learning method used, regularization approaches should be considered when working with rare disease datasets.

Building upon prior knowledge and indirectly related data

One strategy to overcome the lack of large normalized datasets in rare disease is to combine a variety of data types and explore rare disease data alongside other knowledge. By using several data modalities (such as curated pathways, genetic data, or other data types), it may be possible to gain a better understanding of rare diseases (e.g., identifying novel genotype-phenotype relationships or opportunities for drug repurposing). Knowledge graphs (KGs) which integrate related-but-different data types, provide a rich multimodal data source (e.g., Monarch Graph Database [56], hetionet [57], PheKnowLator [58], and the Global Network of Biomedical Relationships [59], Orphanet [60]). These graphs connect genetic, functional, chemical, clinical, and ontological data so that relationships of data with disease phenotypes can be explored through manual review [61] or computational methods [62,63]. (Figure[3]a) KGs may include links (i.e. edges) or nodes that are specific to a rare disease of interest (e.g., an FDA approved treatment would be a specific disease-compound edge in the KG) and more generalized information (e.g., gene-gene interactions noted in the literature for a different disease). (Figure [4]a)

Rare disease researchers can repurpose general (i.e., not rare disease-specific) biological or chemical KGs to answer rare disease-based research questions [64] (e.g. Box 1b). One tactic to sift through the large amounts of data encoded in KGs is to calculate the distances between nodes of interest (e.g., diseases and drugs for Box 1b [64]); often done by determining the "embeddings" (linear representations of the position and connections of a particular point in the graph) for nodes in the KG, and calculating the similarity between these embeddings. Effective methods to calculate node embeddings that can generate actionable insights for rare diseases is an active area of research [64].

Another application of KGs is to augment a dataset [65]. Li et. al.[63] used a KG to identify linked terms in a medical corpus from a large number of patients, some with rare disease diagnoses. They augmented their text dataset by map related clinical terms together - e.g., mapping "cancer" and "malignancy" in different patients to the same clinical concept. With this improved dataset, they trained and tested a variety of text classification algorithms to identify rare disease patients within their corpus. (Figure [4]b, Box 1a)

Rare disease researchers have also integrated multiple KGs and applied neural network-based algorithms optimized for graph data, such as a graph convolutional neural network. Rao and colleagues [66] describe the construction of a KG using phenotype information (Human Phenotype Ontology) and rare disease information (Orphanet) and curated gene interaction/pathway data (Lit-BM-13, WikiPathways) [67,68,69]. They then trained a spectral graph convolution neural network on this KG to identify and rank potentially causal genes for the rare diseases from Orphanet, and were able to use this model to accurately predict causal genes for a ground truth dataset of rare diseases with known causal genes. While several groups have used KGs to study rare diseases, we expect that better multi-modal datasets and ML methods to analyze KGs will make them a more popular and important tool in rare disease.

Another approach that builds on prior knowledge and large volumes of related data is transfer learning. Transfer learning leverages shared features, e.g., normal developmental processes that are aberrant in disease or an imaging anomaly present in both rare and common diseases, to advance our understanding of rare diseases. Transfer learning, where a model trained for one task or domain (source domain) is applied to another related task or domain (target domain), can be supervised or unsupervised. Among various types of transfer learning, feature-representation-transfer approaches learn representations from the source domain and apply them to a target domain [70](Figure [5]a-c). That is, representation learning, as discussed earlier, does not need to be applied only to describe the dataset on which the algorithm was trained – it can also be used to elucidate signals in sufficiently similar data (Figure [5]c) and may offer an improvement in descriptive capability over models trained

only on small rare disease datasets (Fig [5]c). For instance, low-dimensional representations can be learned from tumor transcriptomic data and transferred to describe patterns in genetic alterations in cell lines [25](Figure [5]c). In the next section, we summarize specific instances of applying transfer learning, along with other techniques, to the study of rare diseases.

Combining approaches is required for the successful application of machine learning to rare diseases

We have described multiple approaches for maximizing the success of ML applications in rare disease, but it is rarely sufficient to use any of these techniques in isolation. Below, we highlight two examples in the rare disease domain that use concepts of feature-representation-transfer, use of prior data, and regularization.

Our first example includes a large dataset of acute myeloid leukemia (AML) patient samples with no drug response data and a small *in vitro* experiment with drug response data [71]. Training an ML model on the small *in vitro* dataset alone faced the *curse of dimensionality* and the dataset size prohibited representation learning. Dincer et al. trained a variational autoencoder (VAE, Box 3) on a reasonably large dataset of AML patient samples from 96 independent studies to learn meaningful representations in an approach termed DeepProfile [53] (Figure[6]a). The representations or *encodings* learned by the VAE were then *transferred* to the small *in vitro* dataset reducing its number of features from thousands to eight, and improving the performance of the final LASSO linear regression model (Box 1b). In addition to improving performance, the *encodings* learned by the VAE captured more biological pathways than PCA, possibly due to the constraints on the encodings imposed during training (Box 3). Similar results were observed for prediction of histopathology in another rare cancer dataset [53].

While DeepProfile was centered on training on an individual disease and tissue combination, some rare diseases affect multiple tissues that a researcher may want to study (e.g., Box 1d). Studying multiple tissues poses significant challenges and a cross-tissue analysis may require comparing representations from multiple models. Models trained on a low number of samples may learn representations that "lump together" multiple biological signals, reducing the interpretability of the results. To address these challenges, Taroni et al. trained a Pathway-Level Information Extractor (PLIER) (a matrix factorization approach that takes prior knowledge in the form of gene sets or pathways) [72] on a large generic collection of human transcriptomic data [73]. PLIER used constraints (regularization) that learned *latent variables* aligned with a small number of input gene sets, making it suitable for rare disease data. The authors *transferred* the representations or *latent variables* learned by the model to describe transcriptomic data from the unseen rare diseases antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and medulloblastoma in an approach termed MultiPLIER [73]. (Figure[6]b) MultiPLIER used one model to describe multiple datasets instead of reconciling output from multiple models, making it possible to identify commonalities among disease manifestations or affected tissues.

DeepProfile [53] and MultiPLIER [73] exemplify modeling approaches incorporating prior knowledge – thereby constraining the model space according to plausible or expected biology – or sharing information across datasets. These two methods capitalize on similar biological processes observed across different biological contexts and the fact that the methods underlying the approaches can effectively learn about those processes.

Outlook

This perspective highlights challenges in applying ML to rare disease data and approaches that address these challenges. Small sample size, while significant, is not the only roadblock. The high

dimensionality of modern data requires creative approaches, such as learning new representations of the data, to manage the curse of dimensionality. Leveraging prior knowledge and transfer learning methods to appropriately interpret data is also required. Furthermore, we posit that researchers applying machine learning methods on rare disease data should use techniques that increase confidence (i.e., bootstrapping) and penalize complexity of the resultant models (i.e., regularization) to enhance the generalizability of their work. It should be noted that the line between classical statistical methods and ML is fuzzy. Multiple statistical techniques that were considered to be out of scope of this article (e.g. hierarchical models, Bayesian frameworks, association tests) [74,75,76,77], may have substantial potential to enhance the accuracy and generalizability of models, and should be considered in the rare disease study design process.

The approaches highlighted in this perspective come with challenges that may undermine investigators' confidence in using these techniques for rare disease research. We believe that the challenges in applying ML to rare disease are opportunities to improve data generation and method development going forward. The following two areas are particularly important for the field to explore.

Intentional data generation and sharing mechanisms are key for powering the future of rare disease data analysis

While many techniques exist to collate rare data from different sources, low-quality data may hurt the end goal even if it increases the size of the dataset. In our experience, collaboration with domain experts has proved to be critical in gaining insight into potential sources of variation in the datasets. An anecdotal example: conversations with a clinician revealed that samples in a particular tumor dataset were collected using vastly different surgical techniques (laser ablation and excision vs standard excision). This information, not readily available to non-experts, was obvious to the clinician. Such instances suggest that collaboration with domain experts and sharing of well-annotated data is needed to generate robust datasets in the future.

In addition to sample scarcity, comprehensive phenotypic-genotypic databases are also lacking. Rare disease studies that collect genomic and phenotypic data are becoming more common [78,79,80]. Developing comprehensive genomics-based genotype-phenotype databases that prioritize clinical and genomics data standards is key to fuel interpretation of features extracted using ML methods, possibly by funding or fostering collaboration between biobanking projects and patient registry initiatives. Mindful sharing of data with proper metadata and attribution enabling prompt data reuse is important in building valuable datasets for rare disease research [81]. Finally, federated learning methods, such as those used in mobile health [82] and electronic healthcare records studies [83], may allow researchers to develop ML models on data from larger numbers of people with rare diseases whilst protecting patient privacy.

Methods that reliably support mechanistic interrogation of specific rare diseases are an unmet need

Most ML methods for rare diseases are used for classification tasks. Few methods investigate biological mechanisms; this is likely due to a lack of methods that can handle constraints of rare disease data. Developing methods to address this will be critical for applying ML to rare disease data.

Method development with rare disease applications in mind requires the developers to bear the responsibility of ensuring that the resulting model is trustworthy. The field of natural language processing has a few examples of how this can be achieved [84]. One way to increase trust in a developed model is to help users understand the behavior of the developed model through providing explanations regarding why a certain model made certain predictions [84]. Another approach is to

provide robust *error analysis* for newly developed models to help users understand the strengths and weaknesses of a model [85,86,87]. Adoption of these approaches into biomedical ML is becoming necessary as ML applications become mainstream in research and clinical settings.

Finally, methods that can reliably integrate disparate datasets will likely always remain a need in rare disease research. Methods that rely on finding structural correspondence between datasets ("anchors") may be able to transform the status-quo of using ML in rare disease [88,89,90]. We speculate that this is an important and burgeoning area of research, and we are optimistic about the future of applying ML approaches to rare diseases.

Ethics Declaration

Justin Guinney is currently employed at Tempus Labs, a precision medicine company.

Author Contributions

Authorship was determined using ICMJE recommendations. Conceptualization - J.B., J.N.T, R.J.A, C.G., J.G Data curation - Not applicable Formal Analysis - Not applicable Funding acquisition - R.J.A, Investigation - J.B., J.N.T, R.J.A; Methodology - J.B., J.N.T, R.J.A.; Project administration - J.B. Resources - J.B., J.N.T, R.J.A; Software - Not applicable Supervision - J.B., C.G Validation - Not applicable Visualization - D.V.P Writing - original draft - J.B., J.N.T., R.J.A.; Writing - review & editing- J.B., J.N.T., R.J.A., C.G., J.G.

References

1. The use of machine learning in rare diseases: a scoping review

Julia Schaefer, Moritz Lehne, Josef Schepers, Fabian Prasser, Sylvia Thun Orphanet Journal of Rare Diseases (2020-12) https://doi.org/ghb3wx

DOI: <u>10.1186/s13023-020-01424-6</u> · PMID: <u>32517778</u> · PMCID: <u>PMC7285453</u>

2. Opportunities and Challenges for Machine Learning in Rare Diseases

Sergio Decherchi, Elena Pedrini, Marina Mordenti, Andrea Cavalli, Luca Sangiorgi *Frontiers in Medicine* (2021-10-05) https://doi.org/gpthzr

DOI: <u>10.3389/fmed.2021.747612</u> · PMID: <u>34676229</u> · PMCID: <u>PMC8523988</u>

3. Unsupervised Analysis of Transcriptomic Profiles Reveals Six Glioma Subtypes

Aiguo Li, Jennifer Walling, Susie Ahn, Yuri Kotliarov, Qin Su, Martha Quezado, J. Carl Oberholtzer, John Park, Jean C. Zenklusen, Howard A. Fine

Cancer Research (2009-03-01) https://doi.org/d3kvzt

DOI: <u>10.1158/0008-5472.can-08-2100</u> · PMID: <u>19244127</u> · PMCID: <u>PMC2845963</u>

4. https://www.fda.gov/media/99546/download

5. Learning statistical models of phenotypes using noisy labeled training data

Vibhu Agarwal, Tanya Podchiyska, Juan M Banda, Veena Goel, Tiffany I Leung, Evan P Minty, Timothy E Sweeney, Elsie Gyang, Nigam H Shah

Journal of the American Medical Informatics Association (2016-11-01) https://doi.org/f9bxf9
DOI: 10.1093/jamia/ocw028 · PMID: 27174893 · PMCID: PMCID: PMC5070523

6. Classification in the Presence of Label Noise: A Survey

Benoit Frenay, Michel Verleysen

IEEE Transactions on Neural Networks and Learning Systems (2014-05) https://doi.org/f5zdgg

DOI: 10.1109/tnnls.2013.2292894 · PMID: 24808033

7. Looking beyond the hype: Applied AI and machine learning in translational medicine

Tzen S. Toh, Frank Dondelinger, Dennis Wang

EBioMedicine (2019-09) https://doi.org/gg9dcx

DOI: <u>10.1016/j.ebiom.2019.08.027</u> · PMID: <u>31466916</u> · PMCID: <u>PMC6796516</u>

8. The properties of high-dimensional data spaces: implications for exploring gene and protein expression data

Robert Clarke, Habtom W. Ressom, Antai Wang, Jianhua Xuan, Minetta C. Liu, Edmund A. Gehan, Yue Wang

Nature Reviews Cancer (2008-01) https://doi.org/ffksnf

DOI: <u>10.1038/nrc2294</u> · PMID: <u>18097463</u> · PMCID: <u>PMC2238676</u>

9. The curse(s) of dimensionality

Naomi Altman, Martin Krzywinski

Nature Methods (2018-06) https://doi.org/ghrqhp

DOI: 10.1038/s41592-018-0019-x · PMID: 29855577

10. Adjusting batch effects in microarray expression data using empirical Bayes methods

W. Evan Johnson, Cheng Li, Ariel Rabinovic

Biostatistics (2007-01-01) https://doi.org/dsf386

DOI: <u>10.1093/biostatistics/kxj037</u> · PMID: <u>16632515</u>

11. svaseq: removing batch effects and other unwanted noise from sequencing data

Jeffrey T. Leek

Nucleic Acids Research (2014-12-01) https://doi.org/f8k8kf

DOI: 10.1093/nar/gku864 · PMID: 25294822 · PMCID: PMC4245966

12. A scaling normalization method for differential expression analysis of RNA-seq data

Mark D Robinson, Alicia Oshlack

Genome Biology (2010) https://doi.org/cq6f8b

DOI: <u>10.1186/gb-2010-11-3-r25</u> · PMID: <u>20196867</u> · PMCID: <u>PMC2864565</u>

13. Waste Not, Want Not: Why Rarefying Microbiome Data Is Inadmissible

Paul J. McMurdie, Susan Holmes

PLoS Computational Biology (2014-04-03) https://doi.org/f54g5k

DOI: 10.1371/journal.pcbi.1003531 · PMID: 24699258 · PMCID: PMC3974642

14. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2

Michael I Love, Wolfgang Huber, Simon Anders

Genome Biology (2014-12) https://doi.org/gd3zvn

DOI: 10.1186/s13059-014-0550-8 · PMID: 25516281 · PMCID: PMC4302049

15. Phenopackets: Standardizing and Exchanging Patient Phenotypic Data

https://www.ga4gh.org/news/phenopackets-standardizing-and-exchanging-patient-phenotypic-data/

16. What is a Phenopacket? — phenopacket-schema 2.0 documentation https://phenopacket-

schema.readthedocs.io/en/2.0.0/basics.html

17. The art of using t-SNE for single-cell transcriptomics

Dmitry Kobak, Philipp Berens

Nature Communications (2019-11-28) https://doi.org/ggdrfz

DOI: <u>10.1038/s41467-019-13056-x</u> · PMID: <u>31780648</u> · PMCID: <u>PMC6882829</u>

18. Dimensionality reduction by UMAP to visualize physical and genetic interactions

Michael W. Dorrity, Lauren M. Saunders, Christine Queitsch, Stanley Fields, Cole Trapnell *Nature Communications* (2020-03-24) https://doi.org/gggcqp

DOI: <u>10.1038/s41467-020-15351-4</u> · PMID: <u>32210240</u> · PMCID: <u>PMC7093466</u>

19. Feature Selection

Rama Chellappa, Pavan Turaga

Computer Vision (2020) https://doi.org/ghgqb9

DOI: <u>10.1007/978-3-030-03243-2 299-1</u> · ISBN: <u>9783030032432</u>

20. Handbook of Data Visualization

Chun-houh Chen, Wolfgang Härdle, Antony Unwin

Springer Berlin Heidelberg (2008) https://doi.org/ckmkfp

DOI: <u>10.1007/978-3-540-33037-0</u> · ISBN: <u>9783540330363</u>

21. Principal component analysis: a review and recent developments

Ian T. Jolliffe, Jorge Cadima

Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences

(2016-04-13) https://doi.org/gcsfk7

DOI: 10.1098/rsta.2015.0202 · PMID: 26953178 · PMCID: PMC4792409

22. UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction

Leland McInnes, John Healy, James Melville

arXiv (2020-09-17) http://arxiv.org/abs/1802.03426

DOI: 10.48550/arxiv.1802.03426

23. Visualizing Data using t-SNE

Laurens van der Maaten, Geoffrey Hinton *Journal of Machine Learning Research* (2008) http://jmlr.org/papers/v9/vandermaaten08a.html

24. How to Use t-SNE Effectively

Martin Wattenberg, Fernanda Viégas, lan Johnson *Distill* (2016-10-13) https://doi.org/gffk7g

DOI: 10.23915/distill.00002

25. Compressing gene expression data using multiple latent space dimensionalities learns complementary biological representations

Gregory P. Way, Michael Zietz, Vincent Rubinetti, Daniel S. Himmelstein, Casey S. Greene *Genome Biology* (2020-12) https://doi.org/gg2mjh

DOI: <u>10.1186/s13059-020-02021-3</u> · PMID: <u>32393369</u> · PMCID: <u>PMC7212571</u>

26. Ten quick tips for effective dimensionality reduction

Lan Huong Nguyen, Susan Holmes

PLOS Computational Biology (2019-06-20) https://doi.org/gf3583

DOI: 10.1371/journal.pcbi.1006907 · PMID: 31220072 · PMCID: PMC6586259

27. Clustering cancer gene expression data: a comparative study

Marcilio Cp De Souto, Ivan G Costa, Daniel Sa De Araujo, Teresa B Ludermir, Alexander Schliep *BMC Bioinformatics* (2008-12) https://doi.org/dggbn6

DOI: <u>10.1186/1471-2105-9-497</u> · PMID: <u>19038021</u> · PMCID: <u>PMC2632677</u>

28. Removing Batch Effects From Histopathological Images for Enhanced Cancer Diagnosis

Sonal Kothari, John H. Phan, Todd H. Stokes, Adeboye O. Osunkoya, Andrew N. Young, May D. Wang

IEEE Journal of Biomedical and Health Informatics (2014-05) https://doi.org/gdm9jd

DOI: 10.1109/jbhi.2013.2276766 · PMID: 24808220 · PMCID: PMC5003052

29. Deriving disease modules from the compressed transcriptional space embedded in a deep autoencoder

Sanjiv K. Dwivedi, Andreas Tjärnberg, Jesper Tegnér, Mika Gustafsson

Nature Communications (2020-02-12) https://doi.org/gg7krm

DOI: <u>10.1038/s41467-020-14666-6</u> · PMID: <u>32051402</u> · PMCID: <u>PMC7016183</u>

30. CoGAPS: an R/C++ package to identify patterns and biological process activity in transcriptomic data

Elana J. Fertig, Jie Ding, Alexander V. Favorov, Giovanni Parmigiani, Michael F. Ochs *Bioinformatics* (2010-11-01) https://doi.org/cwqsv4

DOI: 10.1093/bioinformatics/btq503 · PMID: 20810601 · PMCID: PMC3025742

31. **Automatic detection of rare pathologies in fundus photographs using few-shot learning** Gwenolé Quellec, Mathieu Lamard, Pierre-Henri Conze, Pascale Massin, Béatrice Cochener

Medical Image Analysis (2020-04) https://doi.org/ggsrc7
DOI: 10.1016/j.media.2020.101660 · PMID: 32028213

32. Sensitive detection of rare disease-associated cell subsets via representation learning

Eirini Arvaniti, Manfred Claassen

Nature Communications (2017-04-06) https://doi.org/gf9t7w

DOI: 10.1038/ncomms14825 · PMID: 28382969 · PMCID: PMC5384229

33. Enhancing techniques for learning decision trees from imbalanced data

Ikram Chaabane, Radhouane Guermazi, Mohamed Hammami

Advances in Data Analysis and Classification (2020-09) https://doi.org/ghz4sz

DOI: 10.1007/s11634-019-00354-x

34. Random Forests

Leo Breiman

Machine Learning (2001-10-01) https://doi.org/10.1023/A:1010933404324

DOI: 10.1023/a:1010933404324

35. Evaluating predictive modeling algorithms to assess patient eligibility for clinical trials from routine data

Felix Köpcke, Dorota Lubgan, Rainer Fietkau, Axel Scholler, Carla Nau, Michael Stürzl, Roland Croner, Hans-Ulrich Prokosch, Dennis Toddenroth

BMC Medical Informatics and Decision Making (2013-12) https://doi.org/f5jqvh

DOI: <u>10.1186/1472-6947-13-134</u> · PMID: <u>24321610</u> · PMCID: <u>PMC4029400</u>

36. Integrative Analysis Identifies Candidate Tumor Microenvironment and Intracellular Signaling Pathways that Define Tumor Heterogeneity in NF1

Jineta Banerjee, Robert J Allaway, Jaclyn N Taroni, Aaron Baker, Xiaochun Zhang, Chang In Moon, Christine A Pratilas, Jaishri O Blakeley, Justin Guinney, Angela Hirbe, ... Sara Jc Gosline *Genes* (2020-02-21) https://doi.org/gg4rbj

DOI: <u>10.3390/genes11020226</u> · PMID: <u>32098059</u> · PMCID: <u>PMC7073563</u>

37. Learning to Identify Rare Disease Patients from Electronic Health Records

Rich Colbaugh, Kristin Glass, Christopher Rudolf, Mike Tremblay Volv Global Lausanne Switzerland *AMIA ... Annual Symposium proceedings. AMIA Symposium* (2018-12-05)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6371307/

PMID: <u>30815073</u> · PMCID: <u>PMC6371307</u>

38. Component-based face detection

B. Heiselet, T. Serre, M. Pontil, T. Poggio

Proceedings of the 2001 IEEE Computer Society Conference on Computer Vision and Pattern Recognition. CVPR 2001 (2001-12) https://ieeexplore.ieee.org/document/990537

DOI: 10.1109/cvpr.2001.990537

39. The Architecture of the Face and Eyes Detection System Based on Cascade Classifiers

Andrzej Kasinski, Adam Schmidt

Computer Recognition Systems 2 (2007) https://doi.org/cbzq9n

DOI: <u>10.1007/978-3-540-75175-5 16</u> · ISBN: <u>9783540751748</u>

40. Efficient Estimation of Word Representations in Vector Space

Tomas Mikolov, Kai Chen, Greg Corrado, Jeffrey Dean *arXiv* (2013-09-10) https://arxiv.org/abs/1301.3781

41. Improving random forest predictions in small datasets from two-phase sampling designs

Sunwoo Han, Brian D. Williamson, Youyi Fong

BMC Medical Informatics and Decision Making (2021-12) https://doi.org/gp5pj6

DOI: 10.1186/s12911-021-01688-3 · PMID: 34809631 · PMCID: PMC8607560

42. A System for Classifying Disease Comorbidity Status from Medical Discharge Summaries Using Automated Hotspot and Negated Concept Detection

K. H. Ambert, A. M. Cohen

Journal of the American Medical Informatics Association (2009-07-01) https://doi.org/dhg6jb

DOI: 10.1197/jamia.m3095 · PMID: 19390099 · PMCID: PMC2705265

43. SMOTE: Synthetic Minority Over-sampling Technique

N. V. Chawla, K. W. Bowyer, L. O. Hall, W. P. Kegelmeyer

Journal of Artificial Intelligence Research (2002-06-01)

https://www.jair.org/index.php/jair/article/view/10302

DOI: 10.1613/jair.953

44. Survey of resampling techniques for improving classification performance in unbalanced datasets

Ajinkya More

arXiv(2016) https://doi.org/gp5pj7

DOI: 10.48550/arxiv.1608.06048

45. Deep learning

Ian Goodfellow, Yoshua Bengio, Aaron Courville

The MIT Press (2016) ISBN: 9780262035613

46. Generalization in Clinical Prediction Models: The Blessing and Curse of Measurement Indicator Variables

Joseph Futoma, Morgan Simons, Finale Doshi-Velez, Rishikesan Kamaleswaran

Critical care explorations (2021-06-25) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8238368/

DOI: 10.1097/cce.000000000000453 · PMID: 34235453 · PMCID: PMC8238368

47. Regularized Machine Learning in the Genetic Prediction of Complex Traits

Sebastian Okser, Tapio Pahikkala, Antti Airola, Tapio Salakoski, Samuli Ripatti, Tero Aittokallio *PLoS Genetics* (2014-11-13) https://doi.org/ghrqhq

DOI: 10.1371/journal.pgen.1004754 · PMID: 25393026 · PMCID: PMC4230844

48. Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events

Menelaos Pavlou, Gareth Ambler, Shaun Seaman, Maria De Iorio, Rumana Z Omar

Statistics in Medicine (2016-03-30) https://doi.org/ggn9zg

DOI: <u>10.1002/sim.6782</u> · PMID: <u>26514699</u> · PMCID: <u>PMC4982098</u>

49. Regularization and variable selection via the elastic net

Hui Zou, Trevor Hastie

Journal of the Royal Statistical Society: Series B (Statistical Methodology) (2005-04)

https://doi.org/b8cwwr

DOI: <u>10.1111/j.1467-9868.2005.00503.x</u>

50. Gene targeting in amyotrophic lateral sclerosis using causality-based feature selection and machine learning

Kyriaki Founta, Dimitra Dafou, Eirini Kanata, Theodoros Sklaviadis, Theodoros P. Zanos, Anastasios Gounaris, Konstantinos Xanthopoulos

Molecular Medicine (2023-01-24) https://doi.org/grsmn6

DOI: <u>10.1186/s10020-023-00603-y</u> · PMID: <u>36694130</u> · PMCID: <u>PMC9872307</u>

51. Regularized logistic regression with adjusted adaptive elastic net for gene selection in high dimensional cancer classification

Zakariya Yahya Algamal, Muhammad Hisyam Lee

Computers in Biology and Medicine (2015-12) https://doi.org/f73xvj

DOI: 10.1016/j.compbiomed.2015.10.008 · PMID: 26520484

52. An elastic-net logistic regression approach to generate classifiers and gene signatures for types of immune cells and T helper cell subsets

Arezo Torang, Paraag Gupta, David J. Klinke

BMC Bioinformatics (2019-12) https://doi.org/gg5hmj

DOI: 10.1186/s12859-019-2994-z · PMID: 31438843 · PMCID: PMC6704630

53. DeepProfile: Deep learning of cancer molecular profiles for precision medicine

Ayse Berceste Dincer, Safiye Celik, Naozumi Hiranuma, Su-In Lee *Bioinformatics* (2018-03-08) https://doi.org/gdj2j4

DOI: <u>10.1101/278739</u>

54. Auto-Encoding Variational Bayes

Diederik P Kingma, Max Welling arXiv (2013) https://doi.org/gpp5xv

DOI: 10.48550/arxiv.1312.6114

55. Deep learning in rare disease. Detection of tubers in tuberous sclerosis complex

Iván Sánchez Fernández, Edward Yang, Paola Calvachi, Marta Amengual-Gual, Joyce Y. Wu, Darcy Krueger, Hope Northrup, Martina E. Bebin, Mustafa Sahin, Kun-Hsing Yu, ... on behalf of the TACERN Study Group

PLOS ONE (2020-04-29) https://doi.org/gpp5xt

DOI: 10.1371/journal.pone.0232376 · PMID: 32348367 · PMCID: PMC7190137

56. The Monarch Initiative: an integrative data and analytic platform connecting phenotypes to genotypes across species

Christopher J. Mungall, Julie A. McMurry, Sebastian Köhler, James P. Balhoff, Charles Borromeo, Matthew Brush, Seth Carbon, Tom Conlin, Nathan Dunn, Mark Engelstad, ... Melissa A. Haendel *Nucleic Acids Research* (2017-01-04) https://doi.org/f9v7bz

DOI: 10.1093/nar/gkw1128 · PMID: 27899636 · PMCID: PMC5210586

57. Systematic integration of biomedical knowledge prioritizes drugs for repurposing

Daniel Scott Himmelstein, Antoine Lizee, Christine Hessler, Leo Brueggeman, Sabrina L Chen, Dexter Hadley, Ari Green, Pouya Khankhanian, Sergio E Baranzini *eLife* (2017-09-22) https://doi.org/cdfk

DOI: <u>10.7554/elife.26726</u> · PMID: <u>28936969</u> · PMCID: <u>PMC5640425</u>

58. A Framework for Automated Construction of Heterogeneous Large-Scale Biomedical Knowledge Graphs

Tiffany J. Callahan, Ignacio J. Tripodi, Lawrence E. Hunter, William A. Baumgartner *Bioinformatics* (2020-05-02) https://doi.org/gg338z

DOI: 10.1101/2020.04.30.071407

59. A global network of biomedical relationships derived from text

Bethany Percha, Russ B Altman

Bioinformatics (2018-08-01) https://doi.org/gc3ndk

DOI: 10.1093/bioinformatics/bty114 · PMID: 29490008 · PMCID: PMC6061699

60. **Orphanet** https://www.orpha.net/consor/cgi-bin/index.php

61. Structured reviews for data and knowledge-driven research

Núria Queralt-Rosinach, Gregory S Stupp, Tong Shu Li, Michael Mayers, Maureen E Hoatlin, Matthew Might, Benjamin M Good, Andrew I Su

Database (2020-01-01) https://doi.org/ggsdkj

DOI: <u>10.1093/database/baaa015</u> · PMID: <u>32283553</u> · PMCID: <u>PMC7153956</u>

62. Learning Drug-Disease-Target Embedding (DDTE) from knowledge graphs to inform drug repurposing hypotheses

Changsung Moon, Chunming Jin, Xialan Dong, Saad Abrar, Weifan Zheng, Rada Y. Chirkova, Alexander Tropsha

Journal of Biomedical Informatics (2021-07) https://doi.org/gmpgs6

DOI: 10.1016/j.jbi.2021.103838 · PMID: 34119691

63. Improving rare disease classification using imperfect knowledge graph

Xuedong Li, Yue Wang, Dongwu Wang, Walter Yuan, Dezhong Peng, Qiaozhu Mei *BMC Medical Informatics and Decision Making* (2019-12) https://doi.org/gg5j65 DOI: 10.1186/s12911-019-0938-1 · PMID: 21801534 · PMCID: PMC6894101

64. A Literature-Based Knowledge Graph Embedding Method for Identifying Drug Repurposing Opportunities in Rare Diseases

Daniel N. Sosa, Alexander Derry, Margaret Guo, Eric Wei, Connor Brinton, Russ B. Altman *Biocomputing 2020* (2019-12) https://doi.org/gmpgs7

DOI: <u>10.1142/9789811215636_0041</u> · ISBN: <u>9789811215629</u>

65. Rare disease knowledge enrichment through a data-driven approach

Feichen Shen, Yiqing Zhao, Liwei Wang, Majid Rastegar Mojarad, Yanshan Wang, Sijia Liu, Hongfang Liu

BMC Medical Informatics and Decision Making (2019-12) https://doi.org/gm48cq

DOI: <u>10.1186/s12911-019-0752-9</u> · PMID: <u>30764825</u> · PMCID: <u>PMC6376651</u>

66. Phenotype-driven gene prioritization for rare diseases using graph convolution on heterogeneous networks

Aditya Rao, Saipradeep Vg, Thomas Joseph, Sujatha Kotte, Naveen Sivadasan, Rajgopal Srinivasan *BMC Medical Genomics* (2018-12) https://doi.org/gnb3q7

DOI: <u>10.1186/s12920-018-0372-8</u> · PMID: <u>29980210</u> · PMCID: <u>PMC6035401</u>

67. The Human Phenotype Ontology in 2021

Sebastian Köhler, Michael Gargano, Nicolas Matentzoglu, Leigh C Carmody, David Lewis-Smith, Nicole A Vasilevsky, Daniel Danis, Ganna Balagura, Gareth Baynam, Amy M Brower, ... Peter N Robinson

Nucleic acids research (2021-01-08) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7778952/
DOI: 10.1093/nar/gkaa1043 · PMID: 33264411 · PMCID: PMCID: 10.1093/nar/gkaa1043 · PMID: 10.1093/nar/gkaa1043 · PMID: 10.1093/nar/gkaa1043 · PMID: 10.1093/nar/gkaa1043 · PMID: 10.1093/nar/gkaa1043 · PMID: 10.1093/narticles/PMC7778952 · PMID: 10.1093/narticle

68. A Proteome-Scale Map of the Human Interactome Network

Thomas Rolland, Murat Taşan, Benoit Charloteaux, Samuel J. Pevzner, Quan Zhong, Nidhi Sahni, Song Yi, Irma Lemmens, Celia Fontanillo, Roberto Mosca, ... Marc Vidal

Cell (2014-11) https://doi.org/f3mn6x

DOI: <u>10.1016/j.cell.2014.10.050</u> · PMID: <u>25416956</u> · PMCID: <u>PMC4266588</u>

69. WikiPathways: connecting communities

Marvin Martens, Ammar Ammar, Anders Riutta, Andra Waagmeester, Denise N Slenter, Kristina Hanspers, Ryan A. Miller, Daniela Digles, Elisson N Lopes, Friederike Ehrhart, ... Martina Kutmon *Nucleic Acids Research* (2021-01-08) https://doi.org/gh6dq2

DOI: <u>10.1093/nar/gkaa1024</u> · PMID: <u>33211851</u> · PMCID: <u>PMC7779061</u>

70. A Survey on Transfer Learning

Sinno Jialin Pan, Qiang Yang

IEEE Transactions on Knowledge and Data Engineering (2010-10) https://doi.org/bc4vws

DOI: 10.1109/tkde.2009.191

71. A machine learning approach to integrate big data for precision medicine in acute myeloid leukemia

Su-In Lee, Safiye Celik, Benjamin A. Logsdon, Scott M. Lundberg, Timothy J. Martins, Vivian G.

Oehler, Elihu H. Estey, Chris P. Miller, Sylvia Chien, Jin Dai, ... Pamela S. Becker

Nature Communications (2018-01-03) https://doi.org/gcpx72

DOI: <u>10.1038/s41467-017-02465-5</u> · PMID: <u>29298978</u> · PMCID: <u>PMC5752671</u>

72. Pathway-level information extractor (PLIER) for gene expression data

Weiguang Mao, Elena Zaslavsky, Boris M. Hartmann, Stuart C. Sealfon, Maria Chikina *Nature Methods* (2019-07) https://doi.org/gf75g6

DOI: <u>10.1038/s41592-019-0456-1</u> · PMID: <u>31249421</u> · PMCID: <u>PMC7262669</u>

73. MultiPLIER: A Transfer Learning Framework for Transcriptomics Reveals Systemic Features of Rare Disease

Jaclyn N. Taroni, Peter C. Grayson, Qiwen Hu, Sean Eddy, Matthias Kretzler, Peter A. Merkel, Casey S. Greene

Cell Systems (2019-05) https://doi.org/gf75g5

DOI: 10.1016/j.cels.2019.04.003 · PMID: 31121115 · PMCID: PMC6538307

$74. \ Phenotype \ Similarity \ Regression \ for \ Identifying \ the \ Genetic \ Determinants \ of \ Rare \ Diseases$

Daniel Greene, Sylvia Richardson, Ernest Turro

The American Journal of Human Genetics (2016-03) https://doi.org/f8fqks
DOI: 10.1016/j.ajhg.2016.01.008 · PMID: 26924528 · PMCID: PMCID: PMC4827100

75. Rare-Variant Association Testing for Sequencing Data with the Sequence Kernel Association Test

Michael C. Wu, Seunggeun Lee, Tianxi Cai, Yun Li, Michael Boehnke, Xihong Lin *The American Journal of Human Genetics* (2011-07) https://doi.org/bc6nrt

DOI: <u>10.1016/j.ajhg.2011.05.029</u> · PMID: <u>21737059</u> · PMCID: <u>PMC3135811</u>

76. Identification of Rare Causal Variants in Sequence-Based Studies: Methods and Applications to VPS13B, a Gene Involved in Cohen Syndrome and Autism

Iuliana Ionita-Laza, Marinela Capanu, Silvia De Rubeis, Kenneth McCallum, Joseph D. Buxbaum *PLoS Genetics* (2014-12-11) https://doi.org/f6vdbt

DOI: <u>10.1371/journal.pgen.1004729</u> · PMID: <u>25502226</u> · PMCID: <u>PMC4263785</u>

77. A Fast Association Test for Identifying Pathogenic Variants Involved in Rare Diseases

Daniel Greene, Sylvia Richardson, Ernest Turro

The American Journal of Human Genetics (2017-07) https://doi.org/gbnhnj DOI: 10.1016/j.ajhg.2017.05.015 · PMID: 28669401 · PMCID: PMC5501869

78. Rare-disease genetics in the era of next-generation sequencing: discovery to translation

Kym M. Boycott, Megan R. Vanstone, Dennis E. Bulman, Alex E. MacKenzie *Nature Reviews Genetics* (2013-10) https://doi.org/ghvhsd

DOI: 10.1038/nrg3555 · PMID: 23999272

79. Paediatric genomics: diagnosing rare disease in children

Caroline F. Wright, David R. FitzPatrick, Helen V. Firth *Nature Reviews Genetics* (2018-05) https://doi.org/gcxbr8

DOI: <u>10.1038/nrg.2017.116</u> · PMID: <u>29398702</u>

80. Next-Generation Sequencing to Diagnose Suspected Genetic Disorders

David R. Adams, Christine M. Eng

New England Journal of Medicine (2018-10-04) https://doi.org/gf49m7

DOI: 10.1056/nejmra1711801 · PMID: 30281996

81. Responsible, practical genomic data sharing that accelerates research

James Brian Byrd, Anna C. Greene, Deepashree Venkatesh Prasad, Xiaoqian Jiang, Casey S. Greene *Nature Reviews Genetics* (2020-10) https://www.nature.com/articles/s41576-020-0257-5

DOI: 10.1038/s41576-020-0257-5

82. The future of digital health with federated learning

Nicola Rieke, Jonny Hancox, Wenqi Li, Fausto Milletarì, Holger R. Roth, Shadi Albarqouni, Spyridon Bakas, Mathieu N. Galtier, Bennett A. Landman, Klaus Maier-Hein, ... M. Jorge Cardoso *npj Digital Medicine* (2020-09-14) https://doi.org/ghmnwd

DOI: 10.1038/s41746-020-00323-1 · PMID: 33015372 · PMCID: PMC7490367

83. A Continuously Benchmarked and Crowdsourced Challenge for Rapid Development and Evaluation of Models to Predict COVID-19 Diagnosis and Hospitalization

Yao Yan, Thomas Schaffter, Timothy Bergquist, Thomas Yu, Justin Prosser, Zafer Aydin, Amhar Jabeer, Ivan Brugere, Jifan Gao, Guanhua Chen, ... Jimmy Phuong JAMA Network Open (2021-10-11) https://doi.org/gpz2bw

DOI: 10.1001/jamanetworkopen.2021.24946 · PMID: 34633425 · PMCID: PMC8506231

84. "Why Should I Trust You?": Explaining the Predictions of Any Classifier

Marco Ribeiro, Sameer Singh, Carlos Guestrin

Proceedings of the 2016 Conference of the North American Chapter of the Association for Computational Linguistics: Demonstrations (2016) https://doi.org/gg8.ggb

Computational Linguistics: Demonstrations (2016) https://doi.org/gg8ggh

DOI: 10.18653/v1/n16-3020

85. Errudite: Scalable, Reproducible, and Testable Error Analysis

Tongshuang Wu, Marco Tulio Ribeiro, Jeffrey Heer, Daniel Weld *Proceedings of the 57th Annual Meeting of the Association for Computational Linguistics* (2019) https://doi.org/ggb9kk

DOI: 10.18653/v1/p19-1073

86. https://direct.mit.edu/coli/article/37/4/657/2124/Towards-Automatic-Error-Analysis-of-Machine

87. Recognizing names in biomedical texts: a machine learning approach

GuoDong Zhou, Jie Zhang, Jian Su, Dan Shen, ChewLim Tan

Bioinformatics (2004-05-01) https://doi.org/bxts7r

DOI: 10.1093/bioinformatics/bth060 · PMID: 14871877

88. Domain Adaptation with Structural Correspondence Learning

John Blitzer, Ryan McDonald, Fernando Pereira

Proceedings of the 2006 Conference on Empirical Methods in Natural Language Processing (2006-07) https://aclanthology.org/W06-1615

89. Heterogeneous domain adaptation using manifold alignment

Chang Wang, Sridhar Mahadevan

Proceedings of the Twenty-Second international joint conference on Artificial Intelligence - Volume Volume Two (2011-07-16) https://dl.acm.org/doi/10.5555/2283516.2283652

ISBN: 9781577355144

90. Comprehensive Integration of Single-Cell Data

Tim Stuart, Andrew Butler, Paul Hoffman, Christoph Hafemeister, Efthymia Papalexi, William M. Mauck, Yuhan Hao, Marlon Stoeckius, Peter Smibert, Rahul Satija

Cell (2019-06) https://doi.org/gf3sxv

DOI: <u>10.1016/j.cell.2019.05.031</u> · PMID: <u>31178118</u> · PMCID: <u>PMC6687398</u>

91. Reproducible RNA-seq analysis using recount2

Leonardo Collado-Torres, Abhinav Nellore, Kai Kammers, Shannon E Ellis, Margaret A Taub, Kasper D Hansen, Andrew E Jaffe, Ben Langmead, Jeffrey T Leek

Nature Biotechnology (2017-04) https://doi.org/gf75hp

DOI: <u>10.1038/nbt.3838</u> · PMID: <u>28398307</u> · PMCID: <u>PMC6742427</u>

92. Applied Predictive Modeling

Max Kuhn, Kjell Johnson

Springer New York (2013) https://doi.org/c432

DOI: <u>10.1007/978-1-4614-6849-3</u> · ISBN: <u>9781461</u>468486

93. The Elements of Statistical Learning https://link.springer.com/book/10.1007/978-0-387-21606-5

94. A guide to machine learning for biologists

Joe G. Greener, Shaun M. Kandathil, Lewis Moffat, David T. Jones

Nature Reviews Molecular Cell Biology (2022-01) https://doi.org/gmsvvn

DOI: <u>10.1038/s41580-021-00407-0</u> · PMID: <u>34518686</u>

95. Deep Convolutional Neural Networks for Computer-Aided Detection: CNN Architectures, Dataset Characteristics and Transfer Learning

Hoo-Chang Shin, Holger R. Roth, Mingchen Gao, Le Lu, Ziyue Xu, Isabella Nogues, Jianhua Yao, Daniel Mollura, Ronald M. Summers

IEEE Transactions on Medical Imaging (2016-05) https://doi.org/gcgmbg

DOI: <u>10.1109/tmi.2016.2528162</u> · PMID: <u>26886976</u> · PMCID: <u>PMC4890616</u>

96. [No title found]

Leo Breiman

Machine Learning (2001) https://doi.org/d8zjwg

DOI: <u>10.1023/a:1010933404324</u>

Figure Legends

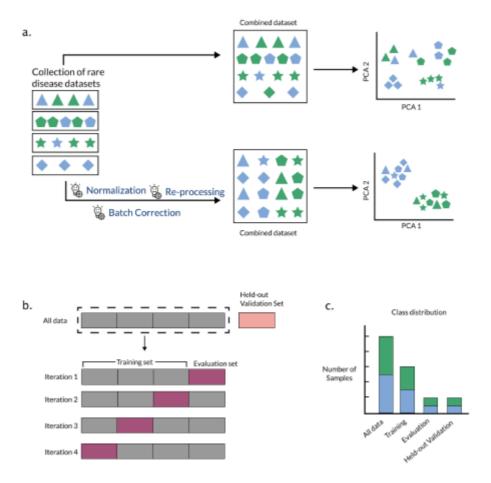


Figure 1: Combining datasets to increase data for training machine learning models. a) Appropriate methods are required to combine smaller datasets into a larger composite dataset: The left panel shows multiple small, rare disease datasets that need to be combined to form a dataset of higher sample size. The color of the samples suggests classes or groups present in the datasets. The shape represents the dataset of origin. The middle panel shows methods that may be used to combine the datasets while accounting for dataset-specific technical differences. The right panel shows Principal Component Analysis of the combined datasets to verify proper integration of samples in the larger dataset. b) Composite datasets can be used to make training, evaluation, and validation datasets for machine learning: Left panel shows the division of the composite dataset into training dataset and a held-out validation dataset (top). The held-out validation set is a separate study that has not been seen by the model. The training set is further divided into training and evaluation datasets for k-fold cross-validation (in this example k=4), where each fold contains all samples from an individual study. This approach is termed study-wise cross validation and supports the goal of training models that generalize to unseen cohorts. c) Barplot showing the class distribution of the training, evaluation, and held-out validation datasets from panel (b).

Representation Learning

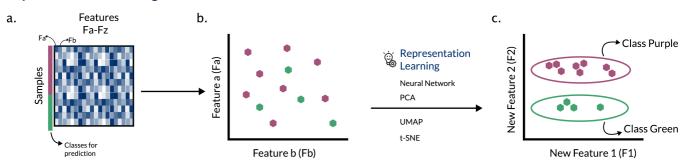


Figure 2: Representation learning can extract useful features from high dimensional data. a) The data (e.g., transcriptomic data) are highly dimensional, having thousands of features (displayed as Fa-Fz). Samples come from two separate classes (purple and green row annotation). b) In the original feature space, Fa and Fb do not separate the two classes (purple and green) well. c) A representation learning approach learns new features (e.g., New Feature 1, a

combination of Fa, Fb Fz, and New Feature 2, a different combination of Fa, Fb Fz). New Feature 2 distinguishes class, whereas New Feature 1 may capture some other variable such as batch (not represented). New features from the model can be used to interrogate the biology of the input samples, develop classification models, or use other analytical techniques that would have been more difficult with the original dataset dimensions.

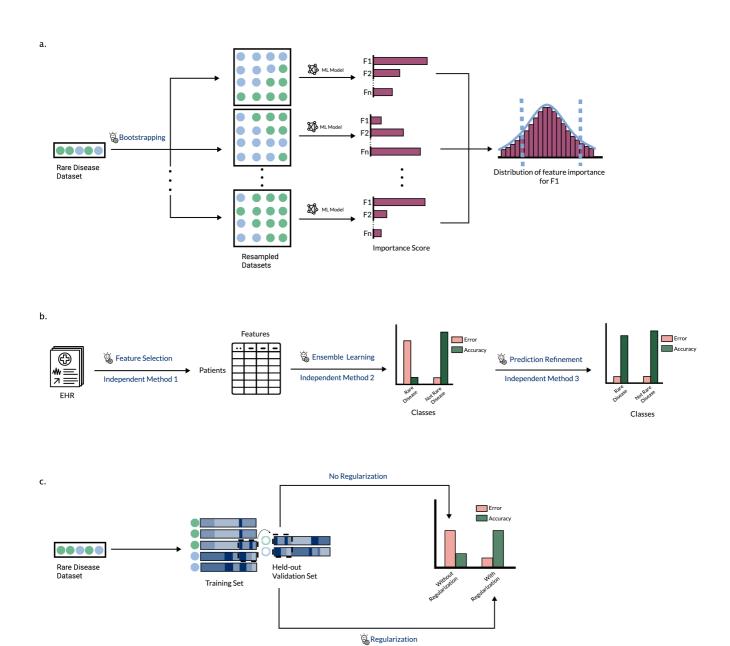


Figure 3: Strategies to reduce misinterpretation of machine learning model output in rare disease. a) Bootstrapping: Left panel shows a small rare disease dataset, which can be resampled with replacement using bootstrap to form a large resampled dataset (middle panel). Running the same ML model on multiple resampled datasets generates a distribution of values for the importance scores for each feature utilized by the ML model (right panel), b) Cascade Learning: A schematic showing the different steps in a cascade learning approach for identifying rare disease patients from electronic health record data. The bar plot in the middle panel schematically represents patient classification accuracy after ensemble learning. The accuracy is high for non-rare diseases, but low for rare diseases. The bar plot on the right panel depicts classification accuracy after implementation of cascade learning. The accuracy is high for both non-rare and rare diseases. c) Regularization: A schematic showing the concept of regularization to selectively learn relevant features. The samples (green and blue circles) in the rare disease dataset on left panel can be represented as a combination of features. Each horizontal bar in the middle panel (training set) represents a feature-by-sample heatmap for one sample each. In the held-out validation dataset, for a sample of unknown class (open circle), some features recapitulate the pattern present in the training set, while others do not. The right panel depicts accuracy of predicting the class of the open circles with or without using regularization during implementation of the ML models on rare disease data. Without regularization the classification accuracy is low due to presence of only a subset of learned features (denoted by dashed rectangle in middle panel), but with regularization this subset of features is sufficient to gain high classification accuracy.

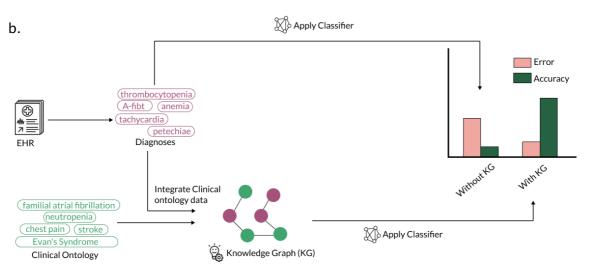
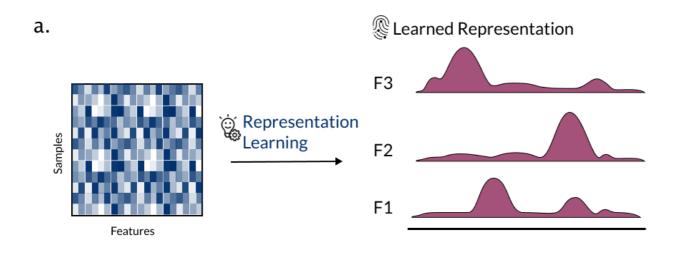
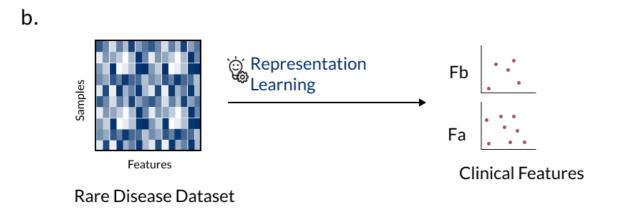


Figure 4: Application of knowledge graphs can improve machine learning in rare disease. a) Knowledge graphs integrate different data types (e.g., genetic, functional, clinical, chemical, and ontological data) and may allow models to learn from connections that are rare disease-specific or happen in many biomedical contexts. There are a variety of possible applications of this approach, including identifying new disease-drug relationships [64], augmenting data to improve accuracy of models trained on the data [65], or mining prior knowledge to discover important gene sets and pathways in rare diseases [66]. b) Knowledge graphs can also be used to augment data. Li et. al. [63] applied a classifier to an EHR corpus to identify rare disease patients. They trained a classifier on the EHR data alone (e.g., thrombocytopenia, anemia) and trained another classifier on data augmented with medically-related concepts from a knowledge graph (e.g., neutropenia, stroke). The classifier trained on knowledge-graph augmented data has lower error and higher accuracy (right panel).





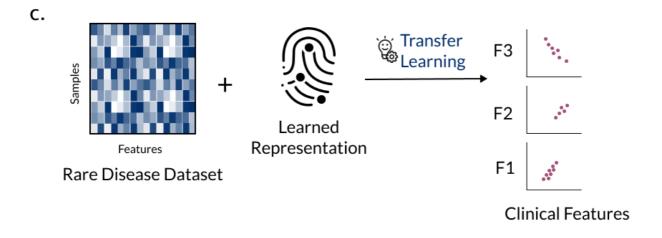


Figure 5: Feature-representation-transfer approaches learn representations from a source domain and apply them to a target domain. a) Combination of features representing samples of a large dataset (transcriptomic data from tumors) are learned by an ML model through representation learning. b) When applied to a small cell line dataset, the representations extracted by an ML model tend to be incomplete and correlate poorly with clinical or drug sensitivity features. c) When a representation learning model trained on the large dataset (a) is applied to the small cell line dataset to extract consistent combinations of features based on the combinations found in the larger training dataset, the extracted representations correlate strongly with the clinical or drug sensitivity features

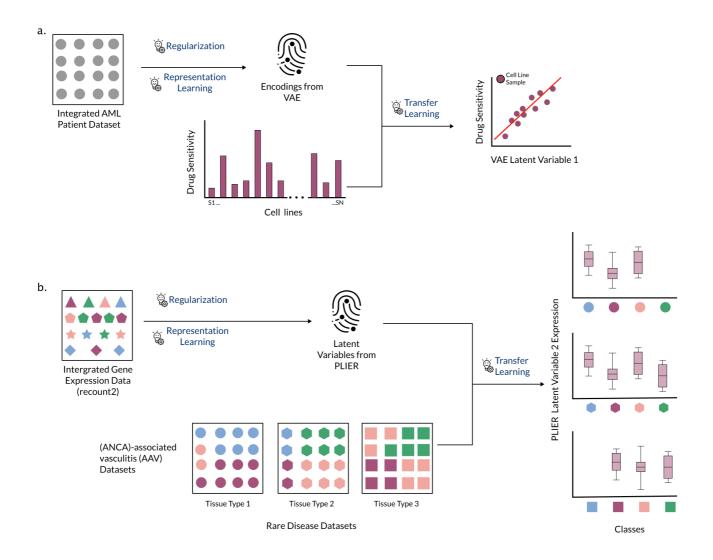


Figure 6: Combining multiple strategies strengthens the performance of ML models in rare disease. a) The authors of DeepProfile trained a variational autoencoder (VAE) to learn a representation from acute myeloid leukemia data without phenotype labels, transferred those representations to a small dataset with phenotype labels, and found that it improved prediction performance in a drug sensitivity prediction task [53]. b) The authors of MultiPLIER trained a Pathway-Level Information ExtractoR (PLIER) model on a large, heterogeneous collection of expression data (recount2 [91]) and transferred the representations (termed latent variables) to multiple datasets from rare diseases that were not in the training set [72]. Expression of PLIER latent variables can be used to check for concordance between datasets, among other applications.

Box 1: Common uses for machine learning in rare disease:

(a) Identifying patients with rare diseases

ML can be used to identify features in high dimensional data that correlate strongly with a patient or sample phenotype and subsequently predict the presence or absence of a rare disease. For example, supervised ML models can be trained on electronic health records, genetic data, or medical images to identify potential new patients with a rare disease.

(b) Drug discovery or repurposing

ML can help identify potential drug candidates for rare diseases. For example, unsupervised and supervised algorithms trained on genetic and molecular data from high throughput screens can identify novel therapeutic targets for a rare disease. Additionally, algorithms utilizing knowledge graphs, genomic data, and databases of existing approved drugs can identify potential therapeutic candidates for rare diseases.

(c) Clinical trial design improvement

Optimized study design and identification of appropriate trial participants can greatly reduce costs while increasing the likelihood of successful outcomes for clinical trials. ML approaches can benefit clinical trial study design. For example, unsupervised ML approaches can be used to identify subgroups of patients who are more likely to respond well to a particular treatment. Supervised ML approaches can also be used to predict drug response in rare disease patients.

(d) Molecular subtyping of disease

Rare diseases often show overlapping and heterogenous phenotypes. ML approaches can be used to identify molecular subtypes of the disease for better understanding. For example, unsupervised ML approaches can help identify new subtypes of a rare disease using molecular and genetic data. The same approaches can help identify the important molecular features that define the subtypes.

(e) Patient prognosis prediction

Rare diseases can suffer from lack of in-depth understanding of disease mechanism. Biomarkers or clinical features that correlate strongly with adverse outcomes can be beneficial in predicting prognosis of a patient. Supervised ML algorithms can be useful in identifying factors contributing to risk of adverse outcomes or progression to advanced disease in rare disease patients. Patient stratification can help identify patient subpopulations who can benefit by early and aggressive interventions.

Box 2: Understanding experimental design of ML to inform requirements for data:

Components of ML experiments

ML algorithms identify patterns that explain or fit a given dataset. Every ML algorithm goes through training, where it identifies underlying patterns in a given dataset to create a "trained" algorithm (a model), and testing, where the model applies the identified patterns to unseen data points. Typically, a ML algorithm is provided with: 1. a training dataset, 2. an evaluation dataset, 3. a held-out validation dataset. These input data can be images, text, numbers, or other types of data which are typically encoded as a numerical representation of the input data. A training dataset is used by the model to learn underlying patterns from the features present in the data of interest. An evaluation dataset is a small and previously unused dataset which is used during the training phase to help the model iteratively update its parameters (i.e., hyperparameter tuning or model tuning). In many cases, a large training set may be subdivided to form a smaller training dataset and the evaluation dataset, both of which are used to train the model. In the testing phase, a completely new or unseen test dataset or held-out validation set is used to test whether the patterns learned by the model hold true in new data (i.e., they are generalizable). While the evaluation dataset helps us refine a model's fit to patterns in the training data, the held-out validation set helps us test the generalizability of the model.

If a model is generalizable, it is able to make accurate predictions on new data. High generalizability of a model on previously unseen data suggests that the model has identified important patterns in the data that are not unique to the data used for training and tuning. Generalizability can be affected if data leakage occurs during training of the model, i.e., if a model is exposed to the same or related data points in both the training set and the held-out validation set. Ensuring absence of any overlap or relatedness among data points or samples used in the training set and evaluation set is important to avoid data leakage during model training. Specifically, in cases of rare genetic diseases where, for example, many samples can contain familial relationships or data from the same patient could be collected by multiple specialists at different clinical facilities, special care should be taken while crafting the training and testing sets to ensure that no data leakage occur and the trained model has high generalizability.

Training and testing

The implementation of a ML experiment begins with splitting a single dataset of interest such that a large proportion of the data (e.g., 70-90%) is used for training (generally subdivided into the training dataset and the evaluation dataset), and the remaining data is used for testing or validation (as the held-out validation dataset). Ideally, a *held-out validation dataset* is an entirely new study or cohort, as researchers typically aim to build models that generalize to unseen, newly generated data. In rare diseases where multiple datasets may be combined to make a large enough training dataset, special care should be taken to standardize the features and the patterns therein. Although ML algorithms generally expect that datasets have uniform features, normalizing training and testing data together may introduce similarities between samples (causing inadvertent data leakage) that hamper the goal of training models that are highly generalizable.

The iterative training phase helps the model learn important patterns in the training dataset and then use the evaluation dataset to test for errors in prediction and update its learning parameters (hyperparameter tuning). The method by which the trained model is applied to the evaluation dataset to measure performance and update the hyperparameters is called cross-validation. There are multiple approaches that can be deployed to maximally utilize the available data when generating training and evaluation datasets e.g., leave-p-out cross-validation, leave-one-out cross-validation, k-fold cross-validation, Monte-Carlo random subsampling cross-validation.[92] In the case of k-fold cross-validation, a given dataset is shuffled randomly and split into *k* parts. One of the k parts is reserved as the *evaluation dataset* and the rest are combined and used as the *training dataset*. In the next iteration, a different part is used as the evaluation dataset, while the rest are used for training. To avoid data leakage, and to promote generalization of models to new studies, researchers can use *study-wise cross-validation*, such that all samples from a study are in the same fold and no individual study is represented in both the training and evaluation datasets. Once the model has iterated through all k parts of the training and evaluation datasets, it is ready to be tested on the held-out validation dataset.(Figure [1]b)

The held-out validation dataset is exposed to the model only once to estimate the accuracy of the model. High accuracy of a model during cross-validation but low accuracy on the held-out validation dataset is a sign that the model has become overfit to the training set and has low generalizability. If this is encountered, researchers should revisit the construction of the dataset to make sure they meet the best practices outlined above.

Box 3: Definitions:

Knowledge Graph

A knowledge graph is a network representation of human knowledge about a domain, abstracted into nodes and edges. Any entity of interest (for example a gene, a disease, a protein, or a cell-line) can be represented as a node in a knowledge graph. All nodes can be linked through edges that represent known relationships between the nodes. Edges can be directed, indicating that the order of the nodes is important for encoding the relationship, or undirected. For example, a gene (node) can be linked to a protein (node) using a directed edge that represents the relationship that the protein is generated through the transcription and translation of the gene. Knowledge graphs serve to integrate data that exist in distributed sources, encode human readable knowledge in machine readable format, and evolve in a flexible manner to integrate new knowledge as it becomes available.

Machine Learning

Machine learning is a scientific discipline at the intersection of computer science and statistics, which combines computational and statistical methods to identify patterns in sample data.[93] In this discipline, one intends to use data as input and apply or fit predictive models to recognize patterns in the data or identify informative groups among the data using objective computational methods.

Rare Disease

According to the Orphan Drug Act[4] of United States of America, diseases or conditions that impact less than 200,000 people in the U.S are considered to be rare diseases. The European Union defines a disease as rare when it affects less than 1 in 2,000 people.

Regularization

Regularization is an approach to reduce overfitting of models to training data, where a penalty or constraint is added to a model trained on a training dataset to avoid making large prediction errors on the evaluation dataset.

Transfer Learning

Transfer learning is an approach where a model trained for one task or domain (source domain) is applied to another, typically related task or domain (target domain), for example a model pre-trained natural images from the ImageNet dataset can potentially be used to classify medical images.[95] Transfer learning can be supervised (one or both of the source and target domains have labels), or unsupervised (both domains are unlabeled).

Variational Autoencoder

Variational Autoencoders or VAEs are unsupervised neural networks that use hidden layers to learn or encode representations from available data while mapping the input data to the output data. VAEs are distinct from other autoencoders since the distribution of the encodings are regularized such that they are close to a normal distribution, which may contribute to learning more biologically relevant signals [25].

Classification in the Presence of Label Noise: a Survey

[6]

Frénay and Verleysen (2014) define and describe sources of label noise, consequences of label noise on ML model development, and techniques that can help mitigate the resulting issues. It also suggests few quality metrics that may be used to test newly developed models to understand their performance in presence of noisy data.

Random Forests

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Breiman (2007) describes the theory underlying random forest algorithm which is a popular ML method with applications in almost every high-dimensional data field, including medicine and life sciences. The paper also highlights the behavior of random forests in the presence of data where each individual feature is not strong enough to distinguish between classes (weak inputs). This scenario is frequently encountered in biomedical data and especially rare disease data.

Deriving disease modules from the compressed transcriptional space embedded in a deep autoencoder

[29]

Dwivedi, et. al. (2020) apply representation learning to meaningfully group genes into modules in a data-driven manner. The authors turned the deep neural network into a "glass-box" by layering knowledge-based interpretation on the gene modules identified using a variational autoencoder to provide insights into what each layer of their model represent.

Pathway-level information extractor (PLIER) for gene expression data

[72]

Mao and colleagues (2019) use the principles of representation learning combined with prior-knowledge to develop a model that capitalizes on correlated gene expression to identify meaningful biological pathways and reduce noise in data introduced due to technical variation. This method has been the foundation of mutiple recent works applying ML on rare disease gene expression data.

Automatic detection of rare pathologies in fundus photographs using few-shot learning

[31]

Quellec, et. al. (2020) train a convolutional neural network (CNN) to identify rare pathologies in retinal images. They used an approach called few-shot learning, in which the CNN is trained on a large cohort of retinal images and then trained on a very small number of examples of retinal images with rare pathologies.

A Literature-Based Knowledge Graph Embedding Method for Identifying Drug Repurposing: Opportunities in Rare Diseases

<u>64</u>]

Sosa and colleages (2020) develop a knowledge graph of drug, disease, and gene relationships from pubished medical literature. They then use a graph embedding method to explore the knowledge graph and predict drug repurposing opportunities.