Osteoarthritis and Cartilage 27 (2019) 977–978

Osteoarthritis and Cartilage

Editorial

Machine-learning for osteoarthritis research

Machine learning (ML) algorithms have the ability to automatically learn and improve from experience without being specifically directed. There has been great optimism that such techniques may improve scientific biomedical research in several fields[1]. Although conventional statistical modeling remains the method of choice for etiology-driven and explanatory analyses, ML consists in an interesting approach to identify new associations and patterns in large datasets. This is particularly important now, as it has become possible to generate large quantities of data from each study participant, from sources such as high-resolution MRI imaging, serum sample analysis, genome sequencing, and electronic medical records. Big data analysis by humans be limited not only by time availability but also often biased by a priori knowledge of the research subject. Not surprisingly, ML algorithms have been often perceived as the holy grail of big data analysis[1,2], although they still may have some important inherent limitations, such as selection biases regarding included studies, overfitting of the regression models and the questionable generalizability of its findings without external prospective validation in the target group[3,4]. This has led some experts to view such type of big data analysis in a more critical way, especially regarding the relevance of the obtained results[5]. Despite having been deemed by some as having promising prospects for osteoarthritis (OA) research[6], some journal reviewers have even come up with a new term, the so-called "NSQIP fatigue" to describe the lack of scientific relevance of "one more additional big data analysis based on the National Surgical Quality Improvement Program".

ML approach in osteoarthritis (OA) research is a relatively new endeavor, but it may possibly open the door to exciting new avenues, especially in terms of enabling better and more clinically relevant subgrouping of affected patients. Decades of OA research have unveiled several imaging findings, serum biomarkers and symptoms that are now considered important for understanding in OA progression. Determining the relative importance of such variables can lead to identification of new phenotypes of OA that represent different pathways. A different approach is to define clinically important outcomes and subsequently employ ML algorithms to identify the relative contributions of each variable for each one of them.

In a study published in this edition of OAC[7], the authors employed this latter strategy to analyze a large and well-recognized database: the FNIH Biomarkers Consortium[8]. Within the pre-specified list of variables in that dataset the authors compared the relative importance of those in each clinically predefined progression groups. Interestingly, the authors then used clustering methods based on a standard score for each variables to define disease progression based on imaging and pain for knee OA at 48 months of follow-up.

In this study the authors employed some innovative statistical techniques which have been found to be particularly useful in the analysis of high dimensional low-sample size datasets. Distance weighted discrimination (DWD), a technique proposed by Marron et al.,[9] relies on the comparison between the distance of vectors (which represent each variable) in high-dimensional data. Direction-Projection-Permutation (DiProPerm) is a framework which uses DWD[10] and was initially employed almost exclusively in genetic studies of single-nucleotide polymorphisms[11] where it was shown to enable simultaneous analysis of several thousands of variables. Recently DiProPerm has been used to phenotype and subgroup analysis in OA studies.[12]

The article by Nelson et al.[7] demonstrates the usefulness of ML techniques for clustering important variables in predefined clinically relevant subgroups with knee OA. Osteoarthritis is a heterogeneous disease, and selected biomarkers might help to identify high-risk individuals and will potentially make interventional trials in well profiled subgroups feasible. The horizon of such type of analyses, tend to keep on broadening. So far most studies have been focusing on phenotyping biologically relevant subgroups and ML has been employed to define biomarker panels from 'omics' and imaging data[13,14]. In the future, it is expected that such type of analysis would enable the identification of specific phenotypes with a higher likelihood of improvement with specific treatment.

Ultimately, more than the direct impact of the specific results which were obtained in this commendable study by Nelson et al. (such as the observed influence of bone marrow lesions, osteophytes, medial meniscal extrusion, and urine CTX-II upon knee OA progression at 48 months), we believe the main value of this article consists in its successful use of machine-learning techniques. It is also reassuring for the OA research community to see ML algorithms confirming the findings of previous studies. The horizon of this type of analysis, in terms of its dedicated hardware and software platforms, will keep on broadening. As demonstrated by the obtained results, such type of approach might be the key in future research employing big data analysis to identify new and clinically meaningful osteoarthritis patterns. Understanding patterns of symptoms and trajectories of pain and functional decline in OA is of paramount importance, especially in diseases in which fluctuations of symptoms are common. With methods that are now able to handle multivariate time series data sets this has potential to identify variables which are important for each patient-group in a specific time scale. This will hopefully support robust study design and have a potential to make a step-change in improving patients outcomes by distinguishing the responders from the non-responders to a given therapy. With hypothesis driven analyses it may be feasible to investigate overlap between different known phenotypes based on suggested

https://doi.org/10.1016/j.joca.2019.04.005

pathophysiological mechanisms, for example the potential overlap between inflammatory and metabolic OA phenotypes. With more unbiased data gathering and novel algorithms, including the recent emergence of quantum ML algorithms[15], we might be able in the near future to successfully define unexpected patient's phenotypes linked with responsiveness to specific treatments. Such type of research is highly relevant as currently available tools for clinical and imaging diagnostics are still somewhat unsatisfactory, ultimately leading to a delay in the development and testing of effective new OA modifying agents.

Author contributions

Both authors equally contributed to the final manuscript. T.M. and S.K. conceived of the presented idea discussed the results and drafted manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Acknowledgements

This work was not supported by any specific funding.

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