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Brief Communication

Fifty Years of Motor Unit Number Estimation

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ABSTRACT: The objective was to use bibliometric analysis to create an infographic of motor unit number estimation methods over the past 50 years. The original method was published in 1971, but secondary and tertiary waves of research using alternative methods occurred in the early 2000s and a decade later. A metric of influence was used to determine if different methods had clear peaks of use over the past 50 years. While the original method continues to register influence, the MUNIX method introduced in 2004 stands out as the most influential method to estimate the innervation status of skeletal muscles.

RÉSUMÉ : Cinquante années passées à estimer le nombre d'unités motrices. L'étude visait à tracer un tableau infographique des méthodes d'estimation du nombre d'unités motrices (MUNE, en anglais) qui ont vu le jour au cours des 50 dernières années, et ce, à l'aide d'une analyse bibliométrique. La toute première méthode d'estimation a fait l'objet de publication en 1971, mais des vagues secondaires et tertiaires de travaux de recherche reposant sur de nouvelles méthodes d'estimation se sont produites au début des années 2000, puis une décennie plus tard. Nous avons employé une mesure de l'influence afin de déterminer si certaines méthodes avaient atteint des pics marqués au cours de cette période de 50 ans. Bien que la méthode initiale occupe encore une place enviable, la méthode MUNIX, établie en 2004, s'est imposée comme la championne des méthodes dans l'évaluation de l'innervation des muscles squelettiques.

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The year 2021 marks 50 years since Alan McComas' publication of the original method to evaluate the motor innervation status of a muscle.[1] Professor McComas identified a problem; there were no practical methods to estimate the number of motor units in a human limb muscle. The proposed solution used the tools of electrophysiology, similar to conventional nerve conduction principles, to produce an outcome measure known as motor unit number estimation or MUNE. Simply put, the number of motor units in a muscle could be estimated by measuring the response when all motor axons were activated simultaneously, the maximum compound muscle action potential (CMAP), then dividing by an estimate of the average response of a single motor unit. McComas' original methodology could be considered a heuristic technique; it used a practical, accessible method that was imperfect but perhaps sufficient to approximate the number of motor units in a particular muscle. The potential applications appear broad, encompassing many physiological or pathological conditions affecting the lower motor neurons: neurodegenerative conditions like motor neuron disease, intensive care unit-acquired weakness, traumatic and nontraumatic spinal cord injuries, lesions of spinal nerve roots, plexus or peripheral nerves, and the natural history of aging in the neuromuscular system. However, for most of its history, MUNE has remained a research tool and not a standard clinical electrodiagnostic technique. Recently, there has been renewed interest in using MUNE as a biomarker and outcome measure in clinical trials.[2] But perhaps the key barrier to wider adoption of MUNE has been the diversity of methods to perform the assessment.

A number of excellent reviews of MUNE have provided detailed descriptions of the pros and cons of the different methods.[3,4] Many have discussed detailed comparisons of important metrics such as test-retest reliability, sensitivity to change, and practical issues of implementation. Still when introducing trainees to the field of MUNE we noted a gap: a concise overview of the historical timeline of investigation in this field was missing. This prompted the question of whether research on MUNE has progressed steadily over the past 50 years and whether the influence of different MUNE methods could be enumerated using bibliometric analysis.

A search of the MEDLINE, EMBASE, Scopus, and Web of Science databases was initially performed in June and repeated in October 2020 resulting in 449 studies after removal of duplicates. An additional 11 studies were added manually from the bibliographies of included papers for a total of 460 studies that were evaluated for inclusion. To be included, a study had to report original research using human participants and present MUNE data as

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an outcome measure. Excluded studies included animal studies, mathematical modeling, no reported MUNE data, or those categorized as an editorial or review. Following screening and full-text review, 263 studies were included. Those studies were assigned to six categories determined *a priori* based on recent reviews: Incremental Stimulation (Dr McComas' original technique), Multiple Point Stimulation (MPS, including F-wave methods), Spike-Triggered Averaging (STA, including methods using intramuscular and high-density grid surface EMG), Statistical (including Bayesian analysis), Motor Unit Number Index (MUNIX), and Compound Muscle Action Potential Scans (S-CMAP). The brevity of the present manuscript precludes a lengthy description of the six categories which are available elsewhere.[3,4] The six papers that we assigned as the originating descriptions of the different methods are given with other supplemental material on Figshare at https://doi.org/10.6084/m9.figshare.13411829. Studies reporting data using multiple methods were included in multiple categories. An influence metric was calculated in 5-year increments. Linear regression analysis was used to estimate a publication inflation factor to normalize for the increase in number of publications of electrodiagnostic papers over the years 1971–2019. This analysis used numbers of publications from two indicator journals: Muscle & Nerve, and Clinical Neurophysiology to estimate the inflation factor. Influence of a particular MUNE method is the number of papers multiplied by the number of different research groups contributing to the papers divided by the inflation factor. The influence metric does not account for the valence of a publication; that is, if a publication is critical of a particular method there is no penalty applied. The influence metric is also not a quality assessment of the different methods, simply a way to visualize the number of papers and centers using the method.

We found that the use of the term "MUNE" showed two clear peaks in English books indexed by Google (Figure 1 top trace, https://bit.ly/2MyoFxz). The first peak was associated with an increase in citation frequency for McComas et al.,[1] which was cited 522 times over the time frame of analysis leveling to a citation rate of about 20/year for the last five years (Figure 1, histogram). The introduction of new methods was staggered over time (Figure 1, left side whiskers indicate the originating papers) followed by a delay to publication of the bulk of original research using each method (Figure 1, boxes represent the interquartile range, IQR). The two frequency peaks in the top trace are temporally associated with the IQR of publications for the secondary (MPS, STA, Statistical) and tertiary methods (MUNIX, S-CMAP). The original incremental stimulation method continues to demonstrate influence to the present, though its influence was negligible from 1980 to 1995. Only the statistical method seems to have lost all influence in the last 5-year increment (2016–2020). Currently, the most influential method is MUNIX which is also clear from the number of studies found (Figure 1, N = 95). In fact, MUNIX has the most influence of any method in the history of MUNE.

These results illustrate that progress was not steady over the past 50 years, rather Dr McComas' insight initiated a maturity lifecycle for MUNE that shares similarities to other models of innovation, e.g. the Gartner hype cycle.[5] Typically after the initiating trigger, there is a 'peak of inflated expectations' followed by what is referred to as the 'trough of disillusionment' and perhaps a rise to a 'plateau of productivity'. This general model of a Gartner hype cycle (e.g. https://en.wikipedia.org/wiki/Hype_cycle) seems to fit the historical pattern of citations for McComas et al.[1] After the initial peak in the mid-70s, there was a long period when the influence was negligible. The rise from this

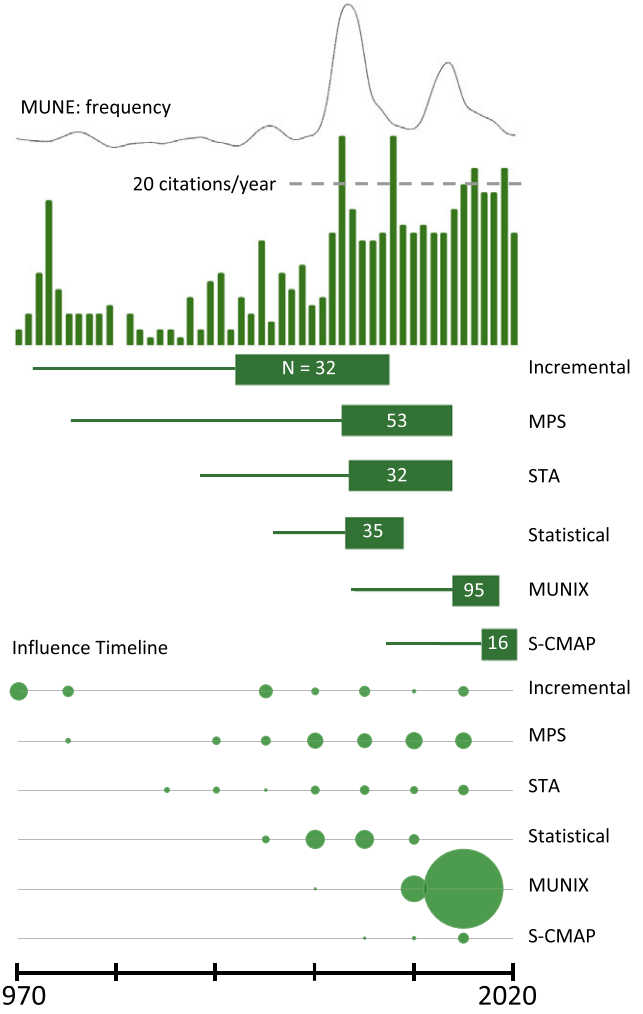

Figure 1: Historical changes in electrophysiological estimation of the number of motor units in human muscles. (Top) Frequency of occurrence of the term "MUNE or MUNIX" in Google Books Ngram search. There are two peaks of increased usage in 2002 and 2012. (Row 2) The distribution of citations per year for McComas et al. (1971). (Row 3) Interquartile range (box) and originating paper (left whisker) for six categories of MUNE techniques. The number in boxes is the number of papers using each technique. (Bottom) Estimates of influence of each technique category adjusted for inflation in publication rates. Size of the circle indicates the influence of that technique over a five-year window.

trough of disillusionment was accompanied by second-generation methods and two international symposiums on MUNE.[6,7] The first three methods introduced (Incremental, MPS, STA) used a straightforward physiological approach of directly measuring a sample of individual motor units to calculate their average size. MPS currently ranks second in influence across all six categories of MUNE.

The introduction of the Statistical method in 1995 marked a technological shift to making inferences about individual motor unit size based on parametric mathematical models. This indirect model-based approach is shared by the two third-generation methods. The promise of the indirect methods (Statistical, MUNIX, S-CMAP) was and is expediency of carrying out an assessment and automated analysis. The first commercially available MUNE method, on Nicolet Viking electromyography (EMG) machines, was Statistical. However, this method was abandoned by 2010 after concerns about confounding variables,[4,7] possibly leading

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to another phase of disillusionment for clinicians that were early adopters.

The emergence of third-generation methods available as commercial solutions has perhaps advanced MUNE to the 'plateau of productivity' of a hype cycle. Software for calculating MUNIX is commercially available from Natus Neuro for their EMG machines, but calculations can be performed manually using data from any clinical system together with an Excel spreadsheet for model fitting and calculations. (An Excel sheet with sample calculation is available with supplementary material on Figshare.) A MUNIX assessment requires voluntary muscle activation by the participant (similar to the STA method), which creates some barriers for use in cases where voluntary compliance may be compromised. MUNIX is an outcome measure of the European Network to Cure ALS, has been implemented in large multicenter trials,[2,8] and used for a wide range of muscles. The most recent implementation of the S-CMAP method for MUNE, MScanFit,[9] can be done with any clinical system together with a freeware version of the software (available on Figshare, a commercial solution is available from Digitimer as part of the QtracW software suite). MScanFit uses direct nerve stimulation (similar to Incremental, MPS, and Statistical methods) which practicably limits the assessment to distal muscles with negligible far-field potentials. It is worth noting that a study assessing the convergent and discriminant validity of MUNIX and MScanFit, used MPS as the benchmark measure for comparison.[10]

Not all innovative ideas progress to a state of maturity and productivity in the Gartner hype cycle. When they do, it is a testament to the fact that the original idea had enduring value. The past 50 years of research illustrate that Alan McComas' idea to estimate the number of motor units in a human limb muscle is worthy of persistence and innovation.

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