Journal of proteome research

Perspective

Cite This: J. Proteome Res. 2018, 17, 1335−1339

pubs.acs.org/jpr

Conversations with 100 Scientists in the Field Reveal a Bifurcated Perception of the State of Mass Spectrometry Software

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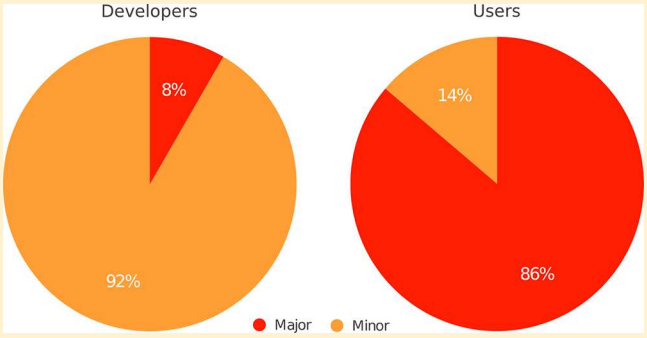
ABSTRACT: Mass spectrometry is an important tool used by many scientists throughout the world. Nonetheless, feedback on the strengths and limitations of current software is often restricted to anecdote rather than formal inquiry. Over the course of 100 interviews over the state of mass spectrometry software, surprising patterns coalesced on several topics: perception of the frontier, perception of software quality, and differences between commercial and nonprofit environments. Most notably, interviews suggested a substantial schism between user satisfaction with current software and developer perceptions of software quality. Scientists' anonymized responses are presented and summarized into their suggestions for improving the state of the art.



KEYWORDS: *computational mass spectrometry, proteomics software, bioinformatics*

INTRODUCTION

Mass spectrometry is an observational tool used by many thousands of scientists around the world every day to characterize molecules in chemical and biological samples.[1] Because of the large amount of data generated (ranging from gigabytes to terabytes per study), data analysis software is a linchpin of the field; therefore, qualities and limitations in current software broadly affect scientists' ability to transform this raw spectral data into usable conclusions relevant to scientists.[2]

We recently interviewed 100 mass spectrometry professionals about their experiences with modern mass spectrometry data processing software. Interviewees included users and developers of mass spectrometry software in both academia and industry from across the United States (Figure 1). Fifty-one percent of interviewees were primary investigators, 38% were senior personnel, and the rest held either executive or junior positions (see Figure 2). Most interviewees work principally with proteomics, but those with interests in closely related life sciences areas of mass spectrometry, such as metabolomics, lipidomics, and extractables, were included.

Interviews were conducted in a free-form manner by initially prompting interviewees with questions such as "what do you use mass spectrometry for?", "what software do you use?", "what are the strengths and weaknesses of the software you use?", and "what, in your view, is the biggest unsolved problem in computational mass spec?" Interviewees guided the conversation, with similar followup questions as necessary in the rare case that more prompting was required.

These responses were anonymized and pooled. Anonymity not only allowed all scientists to speak more freely, it also let us include responses from corporate scientists who may be precluded from discussing such matters publicly. Respondents' answers were then classified according the following topics: perception of software quality, differences between commercial and nonprofit tools, and perception of the frontier. By sharing trends in these responses, we hope to briefly describe the current state of software development in mass spectrometry and to improve communication between developers and users of tools. A careful understanding of the needs of users is crucial for future software development.

SOFTWARE VALUE AND QUALITY

Many scientists have not evaluated most of the existing software. They provided several reasons for this. The most common reason given was that there are so many software packages available that it is difficult to know about them all, let alone try them. Many users complained that there are too many software platforms available, and very few had a good awareness of what is available. In the words of one scientist, "There is too much proliferation of one-off software." Second, many interviewees expressed that many software platforms are so hard to install that the scientist was unable to successfully install them to try them. Multiple users said that they could not give many software platforms a fair evaluation because learning their difficult interfaces took up to one year, and in most cases they were not willing to dedicate that much time. Some scientists actually overcome these barriers and feel that the software they tested provides poor results, lacks critical functionality, or requires too much manual control (e.g., time-intensive adjustment of parameters and settings on each data set).

Received: January 8, 2018
Published: March 16, 2018

DOI: 10.1021/acs.jproteome.8b00015
J. Proteome Res. 2018, 17, 1335−1339

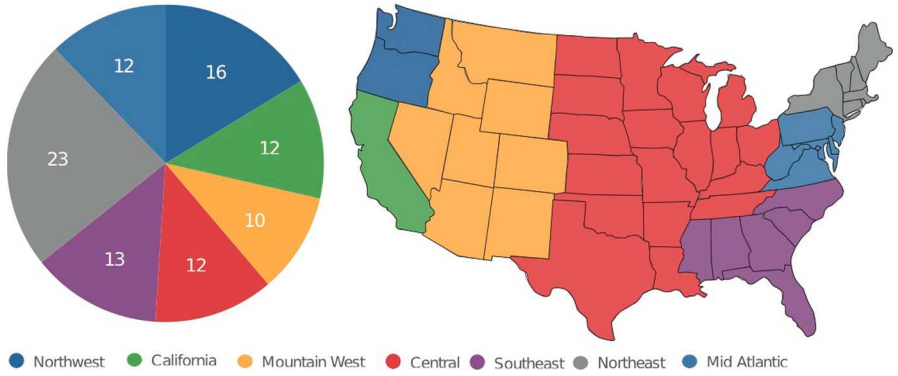


Figure 1. Of the 100 mass spectrometry scientists interviewed, 98 were in the United States, 1 in Canada, and 1 in Europe. 66 scientists were employed in industry, and the rest were employed in nonprofit laboratories.

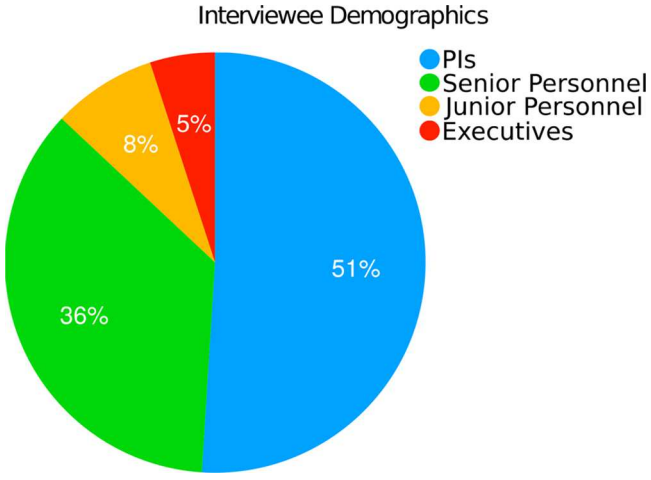


Figure 2. Most interviewees were primary investigators (PIs), with many senior personnel.

Some users mentioned that popular tools are not necessarily popular because they are better than alternatives. Published tools are rarely evaluated qualitatively, let alone quantitatively,[3] and are presented as end-to-end solutions without evaluations of subcomponents. Some users felt that instead of being driven by proven capability, all too often, software adoption occurs because of name recognition. In the words of one PI, widespread computational approaches achieve adoption because "a big name researcher helped develop it, a big name vendor supports it, and a spin-up company handles it."

Interviewees commonly complained about the lack of user-friendly software. Parameter setting and manual interaction is a significant time consumption for mass spectrometry scientists. Twenty-seven interviewees specifically mentioned how manual intervention required a significant amount of their time, with percentages ranging 10−50%. Users also spend a significant amount of time in learning how to use software. User complaints about software included hard to learn interfaces, inefficient interfaces, and broken features.

Lack of support was a common complaint. In general, even participants who felt they had a special relationship with a software provider still had significant complaints about support. One PI of a large pharmaceutical mass spectrometry team explained that they felt that customer responsiveness just is not part of the current culture of mass spectrometry software developers.

Developers also registered concerns. A principal concern was the lack of proper market incentive to invest developer resources into fixing complaints raised by end users. For-profit developers lamented competing against so-called "free" vendor software. One scientist said, "There are people who can't decouple free in terms of dollars and free in terms of time. Free software is not zero cost, even if you don't write a check." The "cost" of free software is vastly underestimated. No-cost software can have extensive time costs if the interfaces are hard to use or the capabilities are limited. The most popular software tools are free, yet users of these software offerings are almost uniform in their perception that these tools regularly miss identifications, produce incorrect matches or quantities, and are nontransparent (that is, nonmodular—one cannot go into an end-to-end analysis and inspect en route findings). Free software frequently has significant manual tuning and parameter setting requirements and could require the user to have significant coding skills.

Several interviewees raised the concern of the hidden but significant annual update costs for many "free" software platforms, which are all but required to publish research. According to one academic PI, "In the academic space, you have to report versions in your papers, and the reviewer will reject your paper if you don't have the updated version."

Whereas, as discussed, the overwhelming sentiment of software quality was negative, there was a marked difference in software quality between free/vendor and third-party software products (see Figure 3). One notable exception to this general perception of free software was Skyline.[4] When asked how Skyline achieved a good match to what people

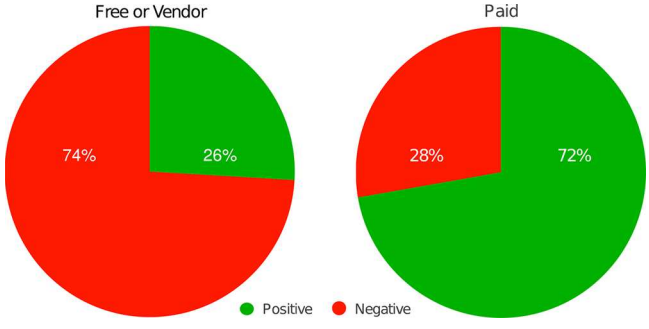


Figure 3. Perceived quality of free and vendor-supplied software versus the perceived quality of Paid third-party software. A more positive experience is reported with paid third party software.

DOI: 10.1021/acs.jproteome.8b00015
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wanted, Dr. Michael MacCoss said that the software development team treats Skyline like a "product" instead of a "research project". The goal from the start has been to create a tool for the community and not create software that fulfilled a student requirement or to generate a specific publication. This meant that the people recruited to work on the project were those with experience in developing and supporting a software product. A greater emphasis was placed on robustness and usability than what the average academic lab might do for a research project. The software development team, managed by Brendan MacLean, also has an explicit user focus. They actively seek out feature requests and feedback. They have and continue to invest in industrial-strength development practices, including automated testing, releasing frequent updates, and rapid response to support requests. They have also focused an enormous amount of effort on training, with numerous tutorials, webinars, and even week-long courses offered throughout the year.

COMMERCIAL AND NONPROFIT USER DIFFERENCES

Sixty-six of our interviewees were employees of for-profit companies in biotech, pharmaceuticals, and agriculture.

Corporate mass spectrometry interviewees shared the concerns of their academic peers but also had additional frequently mentioned concerns. Reappearing themes included that commercial users seem to have less time or willingness to evaluate software alternatives and, more frequently mentioned, that existing software did not fit their experimental goals and/or situational use-cases.

Two trends in particular appeared to be industry-wide. First, external access to these scientists is incredibly limited. The development of software that satisfies user requirements requires that developers can interact with the intended users of the software. Across the industry, it seems to take a year to get to the point where a software company can obtain IT, legal, and accounting permission to begin speaking with the mass spectrometry scientists who work there, even when the scientists are very interested. Corporate users indicated 3−12 month approval periods for obtaining NDAs. According to one PI, "It takes us 9 months to get a CDA, and we need a CDA before we can load a demo program." One commercial PI who had previously worked in academia said, "It takes at least 3 months to get a CDA and a year to get a software purchase approved." The red tape applies equally to internal data sets that can be used to better evaluate and drive the public state of the art. One commercial PI said, "It takes one year for us to release a data set we produce." In the words of one commercial developer, "It is a disaster." Another software writer described how requirements are mostly gathered from academics because industry scientists are so hard to access. While academics can serve as a proxy for requirements gathering, academic workflows can vary significantly from industry workflows in throughput, bug tolerance, ease-of-use required, and use cases.

As a result of access challenges, many commercial operations attempt to solve the prevailing problems in mass spectrometry in-house. While a specific company can definitely come up with a solution to a very specific, small-scale problem, it is irrational to think that a company with a few internal personnel can solve what an entire industry of dedicated experts has not been able to solve.

While protection of intellectual property is an obvious concern, there is a trade-off between IP concerns and the technical benefits that come from external collaborations. With greater access, the mass spectrometry software development companies could do a much better job at building better software.

Perceived value is another challenge for industrial mass spectrometry scientists. Most commercial scientists mentioned a lack of software or personnel resources to do what they were hired to do.

PERCEPTION OF THE FRONTIER

Although some users had lavish praise for recent progress in mass spectrometry software, it was surprising to learn that the perception of current mass spectrometry software among end users was almost universally negative. One scientist summarized the feelings of most of her peers by stating, "All mass spectrometry software is horrible. All of it." A lead mass spectrometry scientist at a large pharmaceutical company said, "We evaluate every single software that comes out. They are all bad."

The sentiments of the state of the art were quite different between users and developers (defined as those who spend a significant time developing code for others to use). Of the 41 interviewees who addressed the subject, a majority of users made comments that indicated they believed there were major unaddressed problems in mass spectrometry data processing, while a supermajority of developers felt that the unaddressed problems were minor or nonexistent (see Figure 4). For example, one veteran data processing software developer replied to the question of what was the biggest problem in mass spectrometry data processing by saying, "I don't know that there are any big problems remaining." This split is both surprising and troubling, as it suggests a significant disconnect between the perceptions of developers and users regarding user requirements and whether they have been fulfilled.

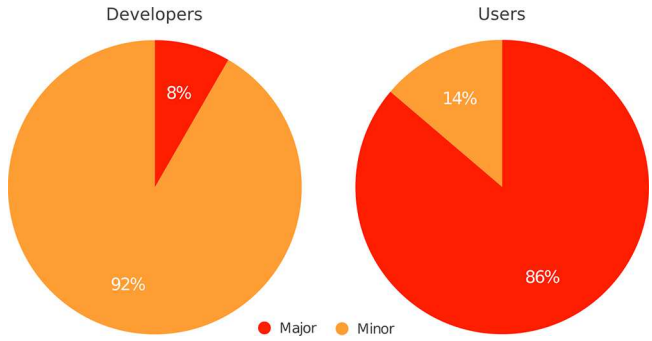

Figure 4. Discrepancy between perception of severity of unsolved problems in mass spectrometry data processing. "Major" indicates that large unsolved problems exist, while "minor" indicates that all of the remaining unsolved problems are "minor". There is a strong discrepancy in responses between those who spend a significant portion of their time writing code (left) versus those who do not (right).

Some users described that certain experiments are precluded by the lack of software suited to them. Although it was clear that some users were unaware of existing tools that provided the functionality they sought, it was also clear that, at least in some cases, this might be due to intentional market decisions by vendors. As one vendor executive explained, high development costs for new features drive vendors' intentional focus on only the most popular use cases. Mass spectrometry users

DOI: 10.1021/acs.jproteome.8b00015
J. Proteome Res. 2018, 17, 1335−1339

represent a widely diverse set of data processing use cases. As a result, many users described that there is no software they were aware of designed for what they do. So, they either analyze their data manually, or they spend significant time attempting to use general-purpose software as best they can.

SUMMARY OF RESPONDENT SUGGESTIONS

Strengthen Distinction between Software and Algorithms

Although many have tried to provide an all-purpose mass spectrometry platform, none have achieved market dominance or a majority base of happy users. One reason why there are so many available alternative methods is that there is a tendency to blur the line between software platforms and algorithms. Although at least some developers are very clear on the distinction, interviewed users often seamlessly intertwined their descriptions of each. An algorithm is a repeatable process for solving a problem. Software, on the contrary, refers to interfaces that implement and provide algorithms for use. The open-source mass spectrometry community would advance the field by creating focused contributions to one or the other category. Software contributions should advance the integration of existing algorithmic alternatives, instruments, data types, and experimental domains. A great piece of software provides an excellent, extensible platform with intuitive interfaces into which multiple algorithms can be developed. Algorithmic contributions should show a distinct advantage over other methods through quantitative evaluations and be reproducibly described. Evaluation of existing methods is crucial to stem the proliferation of existing methods, increase the rigor of the adoption process, and ultimately make it easier for practitioners to remain aware of the state of the art.

When designed well, each type of contribution rate-limits successive alternatives by providing a substantial barrier to publication: No new software or algorithm that is not demonstrably better than what already exists ought to be publishable. Currently, the field of mass spectrometry data processing is swamped by an overabundance of software/algorithm combinations.

Increase Understanding of True Costs of "Free" Software

The field has failed to produce convincing evidence that free or vendor software can meet or exceed the quality of third-party software. This makes rational sense, as it seems that no public effort has yet to accrue to the financial/personnel resources or purpose focus of for-profit efforts. One commercial developer explained the benefits of commercial software by comparing it to drug patents. He explained that pharma companies invest hundreds of millions of dollars into developing a good drug, and this investment would never happen if they could not have an expectation of recouping the cost. Without that kind of capital investment, the innovations would not exist. Likewise, free software seems to have proliferated many solutions to mass spectrometry data processing that do not satisfactorily address a user need, while avoiding the necessary capitalization of a significant solution. Still, it seems the majority of software used is either open source or instrument-vendor-supplied, not third party.

Good software costs significant amounts of money to develop. This money must be paid by either public grants or private purchase. While a few projects like Skyline[4] have managed to produce high-quality software on the publicly funded model, the publicly funded model is inherently limited in terms of a mismatch between the mechanism for funding and the demands of the user.

Public funds are awarded according to the availability of appropriate calls for proposals and the perception of the funding authorities, not according to the actual needs of users or their perceived value. As a result, it is highly unlikely that there will be a correspondence between the needs of the users, availability of funds, and software features implemented. As a result of this resource−need mismatch, many mass spectrometry software platforms are not the result of an expansive survey of potential users but rather the result of one or a few developers implementing their own perception of what is needed. Interviewees discussed how many vendor products, for example, are commercialized versions of an in-house program designed by a specific lab for a specific lab. While developing in-house programs to solve current needs works well under the public model, publicly funded efforts rarely include the financial, personnel, and software engineering resources required to create the kind of extensive requirements specification and implementation that results in user-friendly, nonbuggy, fully featured platforms.

Academic and commercial laboratories each present challenges to the paid software paradigm. One solution to these challenges is to begin to see mass spectrometry software costs in the same light as instrument or chemical supply costs: a cost that will occur for every experiment and will be more for high-volume or unusually novel experiments. While this perspective may be a difficult transition to make—particularly for nonprofit laboratories who have to deal with funding cycles—it is already something they have to deal with in the cost of most other expenses in their laboratories.

Streamline Corporate IP Processes

Mass spectrometry is used for many purposes in corporate settings. In pharmaceutical settings, for example, mass spectrometry is useful across multiple phases, including drug discovery, toxicology studies, ADME (absorption, distribution, metabolism, and excretion), pharmacokinetics, characterization of drug purity, drug stability, and leachables.

Given the scope of impact of improved mass spectrometry capabilities, corporations would benefit from streamlined NDA and data set release processes. Science suffers from restrictive employer agreements that view mass spectrometry data processing more like custom molecules than basic lab equipment. Test tubes are not regarded as trade secrets, yet the lack of sufficient mass spectrometry software hurts these companies and nonprofits alike as much as not having test tubes would. Commercial operations should realize the value and nature of mass spectrometry data processing. Lack of access to use cases and software needs significantly hampers the quality of and, in many cases, even access to software. Meanwhile, industry presents uniquely challenging data processing problems that may not be similar to the much more accessible problems in the academic space. Commercial data sets should be much more accessible to data processing developers.[5] Allowing more freedom to scientists to work with developers of data processing software would significantly improve their bottom line through reducing the time currently wasted by their scientists in jumping through countless hoops to get legal, technical, and accounting approval before even providing requirements to software providers.

DOI: 10.1021/acs.jproteome.8b00015
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CONCLUSIONS

Mass spectrometry software has significantly advanced in recent years. Nevertheless, in interviews of 100 mass spectrometry professionals, a clear theme of user dissatisfaction emerged. As more scientists in both academic and commercial settings incorporate mass spectrometry into their experiments, it is vital to maintain or improve the pace of advancement in mass spectrometry data processing. While developers are often unaware of unaddressed user needs, users generally believe that there is still much to be done to achieve what is possible in data processing. By reconciling these different visions of the future, as seen by developers and as seen by end-users, the field can better leverage developer expertise to problems seen as most important by end-users. This will certainly be helped by increased transparency, whether by sharing data freely between academic laboratories or by improving the ability for corporate scientists to discuss their findings and needs.

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Notes

The author declares the following competing financial interest(s): R.S. is the CEO of Prime Laboratories, Inc., a mass spectrometry software company whose strategies, like any other for-profit or nonprofit mass spectrometry software-developing organization, ought to incorporate the results reported in this manuscript.

ACKNOWLEDGMENTS

This work was conducted under NSF grant 1741270 to R.S.

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