

Smartphone Analytics: Mobilizing the Lab into the Cloud for Omic-Scale Analyses

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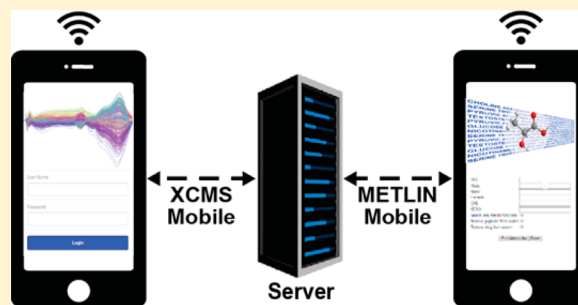
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Supporting Information

ABSTRACT: Active data screening is an integral part of many scientific activities, and mobile technologies have greatly facilitated this process by minimizing the reliance on large hardware instrumentation. In order to meet with the increasingly growing field of metabolomics and heavy workload of data processing, we designed the first remote metabolomic data screening platform for mobile devices. Two mobile applications (apps), XCMS Mobile and METLIN Mobile, facilitate access to XCMS and METLIN, which are the most important components in the computer-based XCMS Online platforms. These mobile apps allow for the visualization and analysis of metabolic data throughout the entire analytical process.

Specifically, XCMS Mobile and METLIN Mobile provide the capabilities for remote monitoring of data processing, real time notifications for the data processing, visualization and interactive analysis of processed data (e.g., cloud plots, principle component analysis, box-plots, extracted ion chromatograms, and hierarchical cluster analysis), and database searching for metabolite identification. These apps, available on Apple iOS and Google Android operating systems, allow for the migration of metabolomic research onto mobile devices for better accessibility beyond direct instrument operation. The utility of XCMS Mobile and METLIN Mobile functionalities was developed and is demonstrated here through the metabolomic LC-MS analyses of stem cells, colon cancer, aging, and bacterial metabolism.



Metabolomics has become a powerful technology for the comprehensive analysis of metabolites, identifying biomarkers and deciphering the mechanistic underpinnings of biological phenomena.¹ Among the different analytical platforms, MS-based metabolomics methodologies coupled to preionization separation techniques such as LC-MS and GC/MS are widely used due to their wide metabolome coverage.² Aside from advances in instrumentation, development in informatic resources for data processing and interpretation has significantly progressed in the past decade, increasing the productivity in many laboratories. Our metabolic data processing platform, XCMS,³ has benefited from numerous updates and developments on the cloud based infrastructure of XCMS Online.^{4,5}

XCMS Online enables the performance of metabolic feature picking, retention-time alignment, and data visualization for thousands of users entirely from one central hardware platform,

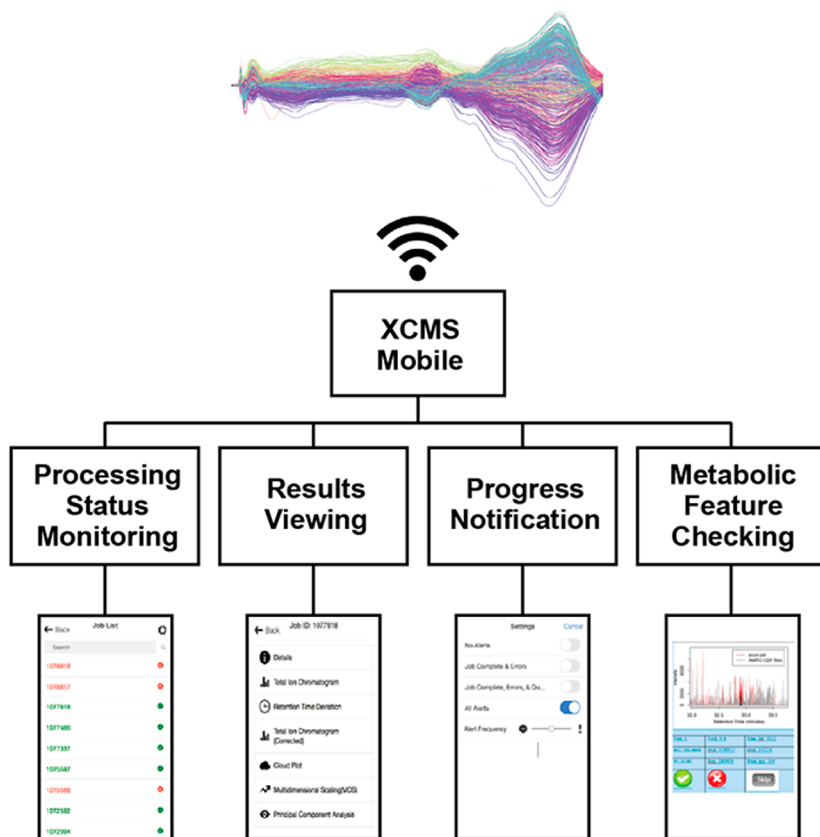
housed at the Scripps Center for Metabolomics (La Jolla, CA). XCMS Online is regularly visited by ~500 IP address daily and performs ~60 jobs a day. One major advantage of XCMS Online is the centralization of resources, removing the need for redundant software and individual powerful computing capabilities. Additionally, taking metabolomic data into the cloud provides the advantage of sharing metabolomic data among XCMS Online users, making it readily available for publication. Another advantage of the Web-based platform is the integration of XCMS with METLIN,⁶ a database of over 240,000 metabolites and 14,000 metabolites with high resolution MS/MS spectra in both positive and negative ion-

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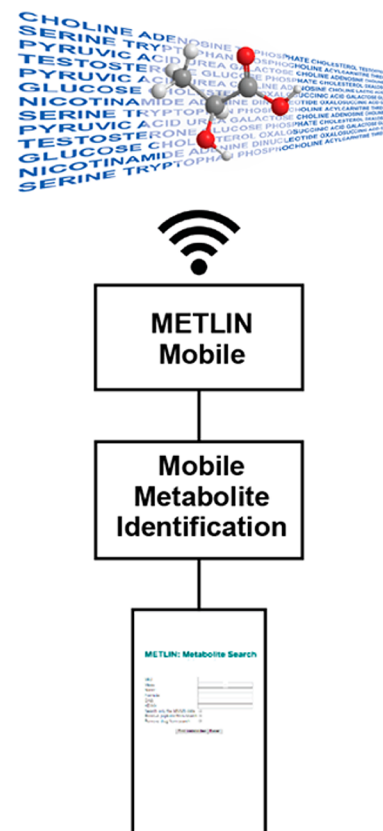


Figure 1. Flowchart and functions of XCMS Mobile (A) and METLIN Mobile (B) applications.

mode at 4 different collision energies, which facilitates the metabolite identification to around 11,000 users.⁷

One major disadvantage of most bioinformatic tools is their typical limitation to personal computers (PCs) usage, and once outside of the laboratory, data and instrument access is typically limited to a Virtual Private Network (VPN) based connection. Furthermore, in the past few decades, research has become more data-intensive and specialized equipment is often shared between different groups. These changes have not only caused an increase in the amount of time necessary for analysis but also instrument access can be limited to only nontraditional working hours.⁸ Mobile devices, particularly smartphones, offer the advantage of accessibility to a wide range of operations and functionalities at relatively economic prices. Moreover, the use of smartphones has widely spread across the United States to 185 million devices.⁹ In addition, frequent personal use of these devices has been reported to around 85 ± 55 times per day.¹⁰ To take advantage of the rapidly evolving mobile hardware and software technologies, we have developed two mobile apps: XCMS Mobile and METLIN Mobile to facilitate data monitoring beyond the laboratory. XCMS Mobile allows for monitoring, controlling data processing, and analysis in the cloud from common cellular devices using iOS and Android operating systems (OS) such as Apple and Android devices, respectively. METLIN Mobile auto select Web design (beta version) allows metabolite identification using the METLIN metabolite database. These apps allow XCMS users to make progress in the metabolomics study workflow independently of the location through hand-held mobile devices. The two mobile apps are now available from app stores linked via <https://>

xcmsonline.scripps.edu/. Depending on the type of the mobile device (Apple or Android), XCMS Mobile can also be directly installed from App Store or Google Play; METLIN Mobile can be accessed via <https://metlin.scripps.edu> using Firefox or Chrome Web browsers.

Herein, we describe the functionalities of XCMS Mobile and METLIN Mobile presented in the context of microbial biofilms metabolic influence on colon tissue and cancer occurrence in a LC-MS based metabolomics study.¹¹ The functions available in these platforms are processing status monitoring, results viewing, progress notification metabolic feature checking, and metabolite identification (Figure 1). Our integration of mobile apps with metabolomics study shows considerable benefits, including high accessibility and mobility without compromising user-friendliness, resulting in improved research productivity.

EXPERIMENTAL SECTION

Development of XCMS Mobile and METLIN Mobile Applications. XCMS Mobile and METLIN Mobile were developed using the programming languages JavaScript, HTML5, and CSS3 and the mobile framework jQuery Mobile to be compatible across Android and iPhone platforms. The platforms iPhone/iPhone 3G, iPhone 3GS, and newer (Apple Inc., Cupertino, CA) as well as Android 1.0–4.4 (Google Inc., Mountain View, CA) are all supported in the current version. Backend database management and functionality of the mobile application was developed using a REST API provided by the DreamFactory REST framework. The client side of the application was developed to make calls to the REST API, which returns data back in JSON format. This data was

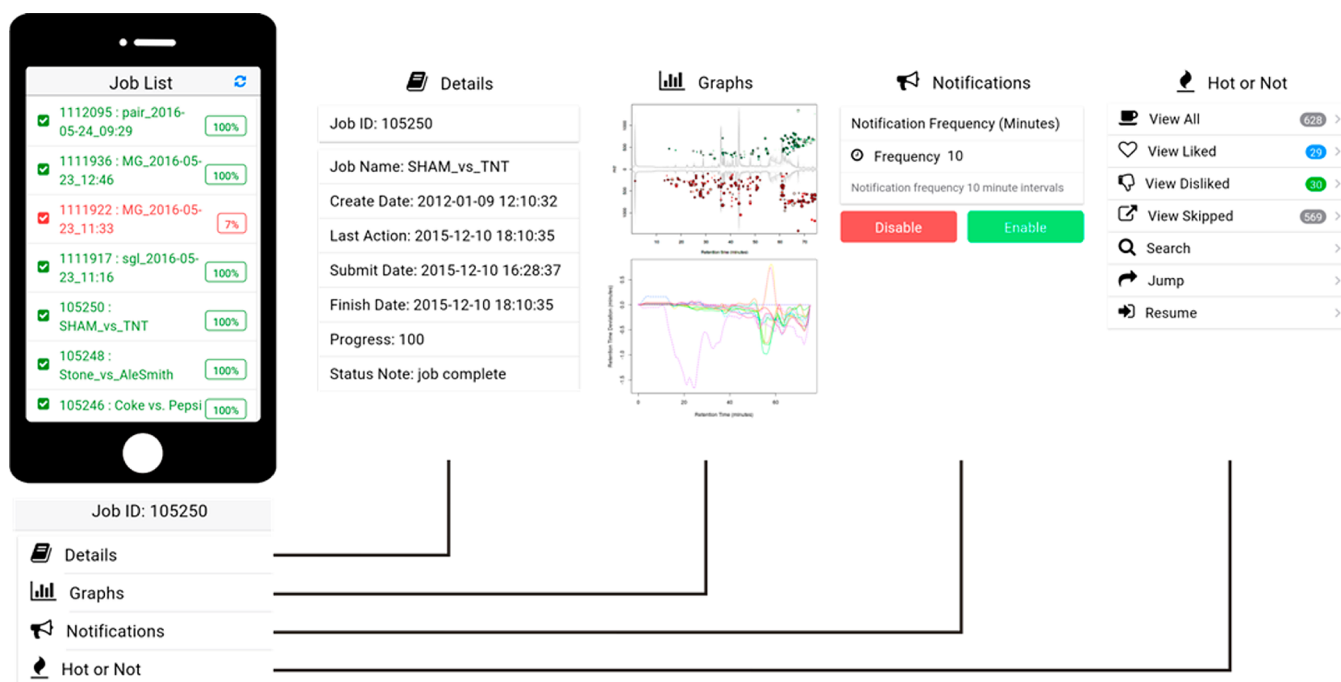


Figure 2. XCMS Mobile menu and visualization functions. “Job List” displays all jobs submitted to XCMS online with their respective progress. In “Details”, further information regarding each job can be accessed. Data analysis visualization graphs such as cloud plots are available under “Graphs”. “Notification” settings can be enabled and set to different frequencies. Lastly, “Hot or Not” displays EIC of the different metabolic features allowing the user to mark features of interest for further analysis.

manipulated using JavaScript, to allow for user-friendly visualization and interaction with the data. jQuery Mobile framework and CSS3 were used in the creation of the front end look and feel of the mobile apps.

Sample Preparation and LC-MS Analysis. Samples were analyzed by reverse-phase liquid chromatography-quadrupole time-of-flight mass spectrometry (RPLC-QTOF) as previously described.^{11,12} Full data sets are available as a public shares on XCMS Online.

Data Streaming with XCMS Mobile and METLIN Mobile. Data streaming strategy¹³ was applied to upload LC-MS data onto XCMS Online upon acquisition completion. Data processing was actively monitored using an iPhone 6 (Apple Inc., Cupertino, CA) with XCMS Mobile and METLIN Mobile installed. Notification frequency was set to a default of 10 min.

WORKFLOW

XCMS Mobile. XCMS Mobile allows for remote monitoring and interpretation of the metabolomic data processed on XCMS Online. The current version of XCMS Mobile has four modules (Figure 1A): data processing status monitoring, progress notification, results viewing, and metabolic feature checking. Examples of these 4 modules with their respective tabs are shown in Figure 2.

Data Processing Status Monitoring. The data processing status monitoring function allows for the tracking of the processing status of the submitted jobs to XCMS Online on mobile devices. An overview of all the job status submitted or an in-depth view of individual job status is available in this function. The overview of all the job status is presented on the home page upon user log in to XCMS Mobile using the user corresponding XCMS Online login information. On the overview page, each job listed has a unique job ID, job name,

and progress indicator. The data processing progress is displayed by a percentage value overlaid on a blue progress box indicating that the data processing steps are in progress. While a green progress box indicates completion of the data processing steps. On the other hand, a red progress bar indicates an error during data processing steps. Further detailed job status information, such as submission date, completion date, status note, log (errors), and warnings can be accessed under the “Details” tab.

Results Viewing. The results viewing function can be accessed under the “Graphs” tab, and it allows for a quick graphical glance of the processed metabolomic data. These data visualization graphs have the capabilities of providing relevant information about the performance of the analysis and the quality of the data before advancing onto more detailed data interpretation. Currently, the data visualization graphs include the original TIC of all the samples, retention time deviation plots, nonmetric multidimensional scaling, PCA score plots, box-plots, and cloud plots.

Progress Notification. Progress notification, an important function in XCMS Mobile, is accessed through the “Notifications” tab and allows the remote monitoring of ongoing data processing by notifications in mobile devices. These notifications can be activated and deactivated by the user, and the display rate of the current data processing progress can be set at a user defined frequency (e.g., 10 min).

Metabolic Feature Checking. Metabolic feature checking in XCMS Mobile allows the user to manually confirm the metabolic features that will be used for further identification and interpretation through a binary selection system found under the “Hot or Not” tab. Usually, such metabolic feature checking is a time-consuming process, taking researchers hours to days in front of the computer examining metabolic features. On the contrary, the mobile metabolic feature checking

function allows users to inspect and filter metabolic features on hand-held devices independently of the location. After examining each extracted ion chromatogram (EIC) of individual metabolic features presented on the screen of the mobile device, the different features can be selected or discarded by “swiping” right or left, respectively (Figure 3).

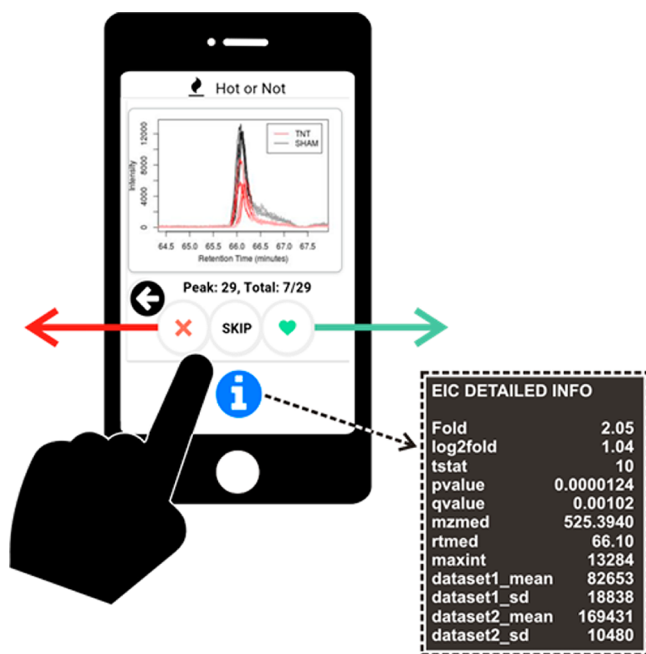


Figure 3. Metabolic feature checking (Hot or Not). Individual features EIC can be analyzed and marked for future analysis by swiping to the right (green arrow) or by pressing the green button. Conversely, uninteresting features can be swiped to the left (red arrow) or by pressing the red button. The blue “i” button displays information about each feature such as fold change, m/z , retention time, etc.

Additionally, other metabolic information, such as fold change, m/z , and retention time to name a few, can be displayed by pressing the blue “i” button. Lastly, upon metabolic feature checking the results are sent to the cloud-based XCMS Online server, providing subsequent PC accessibility.

METLIN Mobile. METLIN Mobile (beta version) is an auto select Web design, which provides rapid and accessible metabolite identification and information using mobile devices (Figure 1B). In its current version, METLIN Mobile allows users to perform simple and advanced metabolite searches (Figures S1 and S2, respectively) based on single or multiple metabolic searching criteria such as METLIN ID (MID), molecular mass, m/z , metabolite name, chemical formula, and CAS or KEGG number. Furthermore, fragmentation data (MS/MS) can be accessed, both directly and indirectly through metabolite name and links in the search results, respectively (Figures S3 and S4). It is worth mentioning that the search graphical user interface is optimized so that all information can be easily displayed on the mobile device, minimizing the necessary screen manipulation and is currently being beta tested in an ongoing aging study (Figure 4).

Applications. To demonstrate the performance of XCMS Mobile and METLIN Mobile through the data analysis workflow, a LC-MS metabolomic study comparing the metabolomic differences between paired colon cancer tissues and normal tissues in association with microbial biofilms from

30 individuals was selected. During the data processing, progress notifications every 10 min were received over the entire data processing time of 24 h. Subsequently, results were examined on the mobile device, with TIC, PCA, and other plots highlighting their differences. 150 metabolic features were statistically significant ($p < 0.01$) with fold changes in the range of >1.5 or <0.67 . Metabolic feature checking was performed on XCMS Mobile, where 135 metabolic features were correctly extracted by XCMS. Finally, METLIN Mobile was used to putatively identify these 135 metabolites by mass matching against METLIN with a mass tolerance of 5 ppm. Among them, 80 metabolic features got positive putative identifications, available for further validation and interpretation.

In this work, we described the functionalities of two developed mobile apps, XCMS Mobile and METLIN Mobile, to actively and remotely screen and interpret metabolomic data as well as perform metabolite identification. The current version of XCMS Mobile provides four important modules (Figure 1): processing status monitoring, progress notification, results viewing, and metabolic feature checking. Additionally, METLIN Mobile provides one module, remote metabolite identification by accessing METLIN database information. Compared to conventional metabolomic bioinformatic tools,^{14,15} which are typically restricted to be used on PCs, XCMS Mobile and METLIN Mobile are designed to access and display metabolomic data from mobile devices in the cloud, improving researchers' productivity. Regardless of conventional metabolomic tools designed to implement more comprehensive functions, the functions provided by the mobile apps are more suitable for quick and convenient data screening and data visualization, particularly outside laboratory settings. Most importantly, these two mobile apps are designed for the robust and widely used metabolomic platform: XCMS Online server and METLIN spectra library platform, which will benefit over 10,000 metabolomics researchers worldwide.

The different functions available for these mobile apps for metabolomics studies were exemplified using a colon cancer study. Overall, three major advantages are clearly determined in terms of improving research productivity by using XCMS Mobile and METLIN Mobile. First, data processing can be monitored remotely and independently from the location. Considering the automatic data processing of 60 individual samples on XCMS Online took 24 h, the processing status monitoring and progress notification function allows for the supervision of data processing status remotely with fast response capability while performing other tasks. For example, upon a progress error notification during data processing, we immediately were able to correct the error and continue to process, minimizing delays in the study. Second, following data processing completion notification, processed data can be visualized in graphs, such as TIC, retention time correction, PCA, cloud plot to name a few, and provide an assessment of instrumental performance as well as differences in metabolic signatures between the different sample groups. These preliminary results allowed for the planning of follow-up experiments for validation and quantitation in advance. Third, data interpretation and metabolite identification can be performed under more flexible time conditions away from the laboratory or office PC. In this particular work, the manual feature confirmation of 150 metabolic features and metabolite identification was performed remotely during nontraditional working hours. It is worth mentioning that for this metabolic study only about 20 min of regular office hours were used over

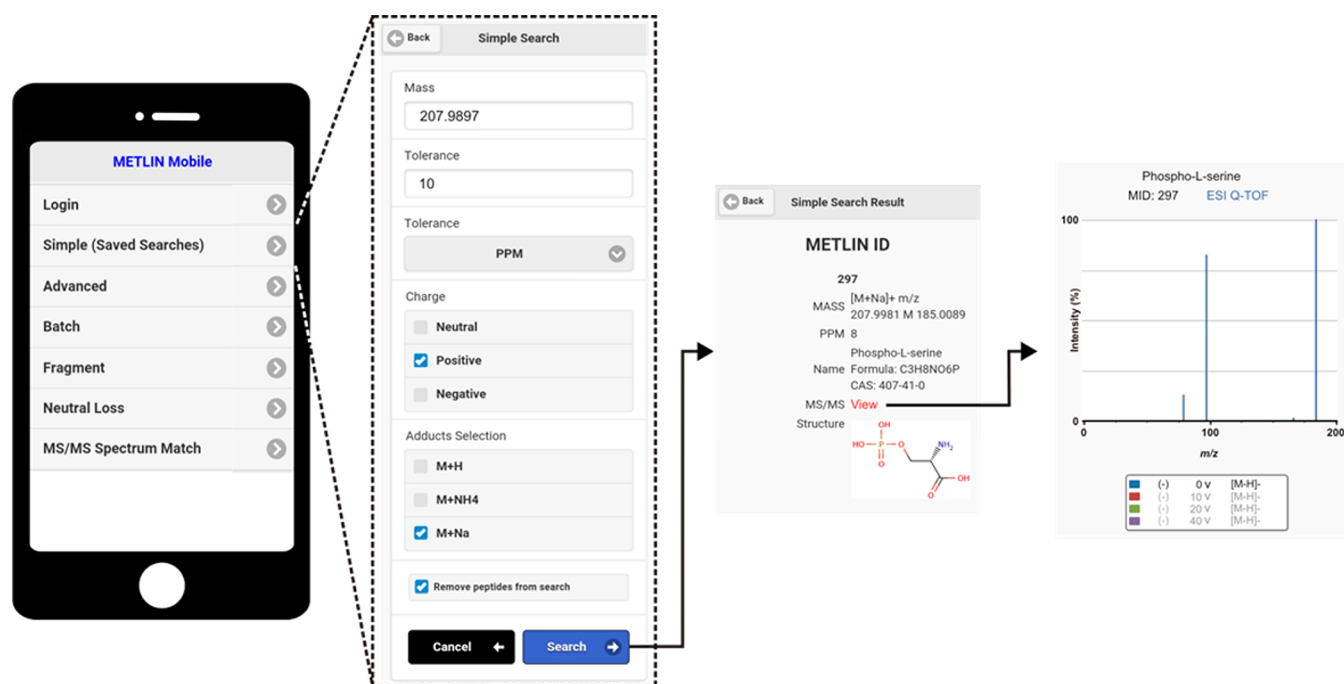


Figure 4. METLIN Mobile provides access to the METLIN database and allows for different search types. In “Simple Search”, a particular m/z value, in this case 207.9897 found to be dysregulated in an ongoing aging study, can be searched for matches with several filter options such as mass tolerance, charge, adducts, and type of molecules. The matching metabolites are displayed in ‘Results’, where information such as molecular formula and structure are shown for the pertaining compound.

a 3 day period without accounting for data acquisition. This demonstrates the potential of taking the lab into the cloud and pursuing several metabolomic studies simultaneously.

CONCLUSION

In summary, we have developed two mobile apps, XCMS Mobile and METLIN Mobile, with the goal of reducing the reliance on personal computers for metabolomic data monitoring and interpretation. Each application was designed to improve research productivity and minimize resources for remote data processing. We demonstrated the advantage and capabilities of using mobile apps in metabolomics on typical metabolomic studies including colon cancer, aging, and bacterial metabolism. To the best of our knowledge, XCMS Mobile and METLIN Mobile are the first mobile apps in the field of metabolomics, and we expect the use of mobile apps in metabolomics could be implemented to other bioinformatic tools, streamlining data analysis by providing greater flexibility to metabolomics researchers. We believe that these mobile applications will greatly increase the accessibility of metabolomics data analysis, enabling students around the world to gain first-hand experience analyzing metabolomic data.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.analchem.6b02676.

Supplemental Figures 1–4 (PDF)

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Notes

The authors declare no competing financial interest.

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