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Cheminformatics workflows using mobile apps

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Abstract

We are perhaps at a turning point for making cheminformatics accessible to scientists who are not computational chemists. The proliferation of mobile devices has seen the development of software or 'apps' that can be used for sophisticated chemistry workflows. These apps can offer capabilities to the practicing chemist that are approaching those of conventional desktop-based software, whereby each app focuses on a relatively small range of tasks. Mobile apps that can pull in and integrate public content from many sources relating to molecules and data are also being developed. Apps for drug discovery are already evolving rapidly and are able to communicate with each other to create composite workflows of increasing complexity, enabling informatics aspects of drug discovery (i.e. accessing data, modeling and visualization) to be done anywhere by potentially anyone. We will describe how these cheminformatics apps can be used productively and some of the future opportunities that we envision.

Key Words: Cheminformatics, Chemistry, Collaboration, ChemSpider, Cloud Computing, Mobile Apps, Structure Activity Relationships, Web Services, Workflows

Area of Interest: Emerging New Technologies

1. Introduction

A new ecosystem is being created with pharmaceutical companies becoming smaller nodes in a complex network in which collaborations (with academics, CROs, public-private partnerships and not-for-profits) are an important component of the business model [1]. Yet, still there is an urgent need to: 1. fundamentally revamp how drugs are developed because so few make it to market and the cost is too high [2][3] and 2. determine methods by which they can be brought to market faster. So what can we do that will address these needs? Technology development is moving faster but pharmaceutical R&D organizations do not appear to be keeping pace as they are still wedded to the

desktop computer and internet of the late 1990-2000s [1]. Recent quotes from pharma suggest even the version of Windows and Microsoft Office are a decade old [4]. We suggest we are now seeing a shift in how chemical data can be shared, stored and interpreted on mobile devices. This current analysis greatly extends upon our recent white paper [5].

Mobile apps (application software(s) for mobile devices) for science and drug discovery continue to expand in number [6], diversity and capabilities. They may be categorized into scientific disciplines and further sub-categorized based on applications within a branch of science. As a service to the community a wiki site called www.scimobileapps.com (Figure 1) has been set up hosting a growing list of scientific apps for all available mobile platforms. This is a valuable resource which will continue to expand in content and may be useful for the creation of future science-focused app stores.

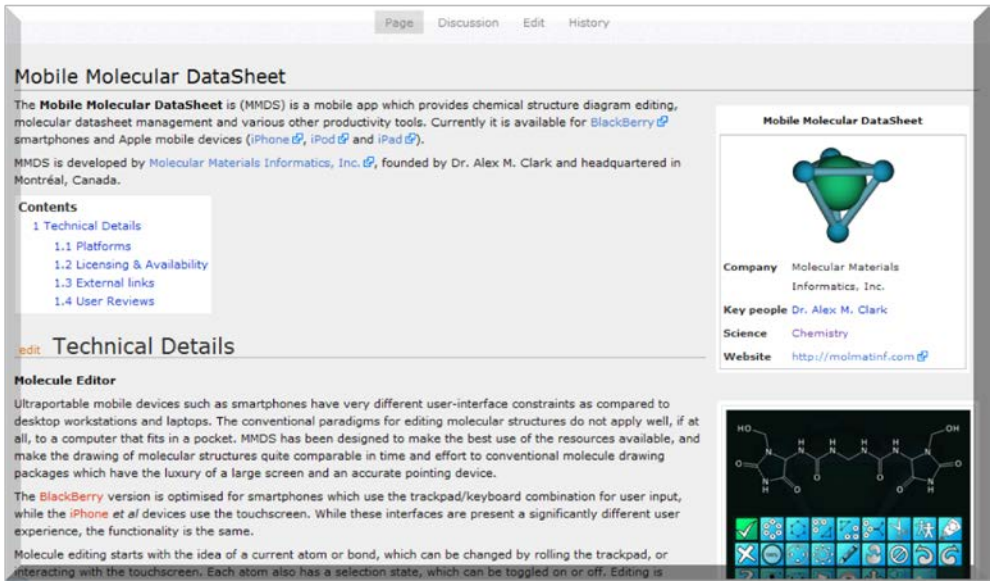


Figure 1. An example of a mobile app description on www.scimobileapps.com.

The user community is demanding a new breed of chemical information software that keeps pace with the rapidly changing dynamics within the industry. Software for drug discovery scientists has to be affordable enough for all to participate (e.g. those in academia and industry), have a sufficiently intuitive user interface that becoming an expert is not mandatory, and be available anywhere, anytime (for example while travelling, and outside of our offices as many work remotely). The pace at which mobile apps have claimed a prominent position within the workflow of many professionals is particularly impressive [7][8] impacting time savings, increased productivity and reduction of costs. Already the capabilities of mobile devices to access, search, manipulate and exchange chemistry-related data relevant to drug discovery almost parallel those capabilities available on desktop computers just a few years ago [6][9][10]. We are confident that this budding ecosystem of chemistry apps (Figure 2) will continue to grow rapidly, and that the ability of these apps to complement each other, as well as workstation-based and server-based software, will secure their place within chemical data workflows.

Figure 2. Examples of mobile apps for cheminformatics and drug discovery (See also www.scimobileapps.com)

Most chemistry apps concentrate on at least one of the following [6]: information delivery, catalog lookup, data visualization, data creation, lab notebooks, collaboration and sharing [11]. Many apps are designed for one way transmission of information such as content consumption (examples include the following apps; Green Solvents [12], Approved Drugs [13], The Elements [14], ACS Mobile [15] and RSC Mobile [16], Reagents [17], Organic Named Reactions [18]). These apps typically have a very simple user interface and are very easy to use. They are mainly used for education and some are relevant to professional uses. Catalog lookup apps are designed to input a search query, submit the query to a server, then display and utilize the results (examples include ChemSpider Mobile [19], SPRESImobile [20], Mobile Reagents [21], iKinase [22] and iProtein [23]). These apps are more complex to produce, with the heavyweight functionality taking place on remote servers which host the data and the search algorithms. Data visualization apps are designed to visualize existing data such as PDB [24] entries and collections of molecules (Examples include Molecules [25], PyMOL [26], SAR Table [27], iMolview [28], iSpartan [29], iMolecule Builder [30]). Data creation apps are some of the most sophisticated as they provide the ability to assemble chemical data within the app such as molecular structures, reactions, scalar data and higher order markup (structure activity relationships). Data can be created with the app user interface or can be imported from other sources (examples include the Mobile Molecular DataSheet (MMDS) [31], MolPrime [32], SAR Table [32], Chirys Draw [33], ChemDoodle Mobile [34] and ChemJuice [35]). Lab notebook apps are designed for entering information about experiments with the ultimate objective being a paperless laboratory. Such mobile laboratory notebooks are mostly generic rather than chemically aware, i.e. not specifically for synthesis (examples include Yield101 [36], LabGuru [37], Irisnote [38]). Collaboration apps have many options for sharing and importing data e.g. email, remote hosting, web sharing and tweeting (examples include MMDS [31], MolSync [39], Reaction101 [40] and Open Drug Discovery Teams (ODDT) [41]).

The modular nature of the first generation of mobile apps means that it is often necessary to use more than one app to accomplish a particular workflow segment, e.g. using a database searching app to locate data, and another to organize it into a collection. Passing data back and forth between apps is therefore an integral and frequent activity. Currently, mobile apps are being created and used for science as individual components with little integration [9].

Some of the restrictions of mobile apps include the limited choice of development environments: native or web, which represents a stark choice of quality versus portability. Another limitation is the touchscreen being small, inaccurate, and doing double duty by also providing the onscreen keyboard. While mobile processors are fast, respecting battery life requires careful conservation of CPU resources. Limited memory and constricted multi-tasking requires an app to have a tightly defined lifespan and is expected to be lightweight, with minimal state dependency. Persistent storage on the device itself is limited, and typically isolated from other apps. Many apps

make use of storage and calculation resources via the network, which means that when a device is offline, its utility is severely reduced. Ultimately when these limitations can be overcome, the combination of mobile interfaces and cloud-based services can be highly competitive with traditional desktop computing workflows.

2. Appifying data

A myriad of data and multitude of datasets for drug discovery are already available to us online but the challenge is to get them into a format that is useful. For example, structure activity tables in papers and supplemental data are rarely thought of as useful outside of the context of a single publication. What if this content was made available via a mobile app or the data tweeted into an app that could mine the data and structures? The combination of a user interface designed and optimized for the mobile form factor, cloud-based server functionality for data warehousing and extra computational capacity, and collaboration features for integration into an overall workflow, makes this not only technologically feasible, but in many ways preferable to traditional software.

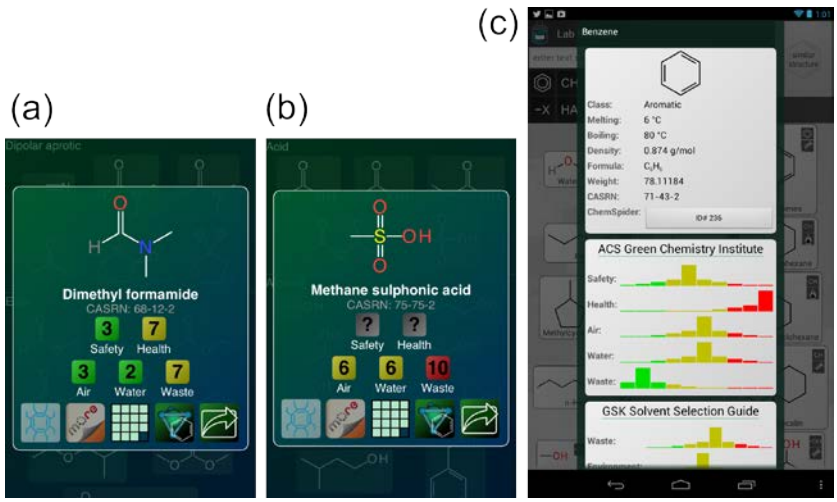


Figure 3. The Green Solvents app for iOS: (a) dimethyl formamide, (b) methane sulphonic acid; and (c) the Lab Solvents app for Android.

As one example of appifying (making software for mobile devices) data, we have used the ACS GCI Pharmaceutical Roundtable solvent selection guide data (a PDF with molecule names and data) as a starting point to develop the first mobile app for green chemistry called Green Solvents (Figure 3 (a) and (b)). The app is freely available for iPhone, iPod and iPad. The ACS GCI Pharmaceutical Roundtable [42] solvent selection guide rates the listed solvents against 5 categories: safety, health, environment (air), environment (water), and environment (waste). Key parameters and criteria were then chosen for each category (e.g. flammability is one of the safety criteria). The summary table assigns a score from 1 to 10 for each solvent under the respective categories, with a score of 10 being of most concern and a score of 1 suggesting few issues. This is further simplified by using color coding with scores in the range 1 to 3 shown as green, 4 to 7 as yellow and 8 to 10 as red. This allows quick comparison between various solvents. The app was built using the Objective-C programming language, the API provided by Apple for native iOS development, and the MMDSLib library for

cheminformatics functionality such as structure rendering [10][43]. The Green Solvents app [12][44][45] uses solvent structures grouped by chemical class as the primary point of entry. These solvents are also color coded with a brown background suggesting less desirable and a green background suggesting more desirable. The user can scroll through all the solvents and click on a molecule of interest. This opens a box which lists the molecule name, CAS registry number, scores for each category with color coding as well as links out to the ChemSpider website [46], the Mobile Reagents app [21] and the Mobile Molecular DataSheet [43]. More recently, we have produced the Lab Solvents app [47] which is available for Android-based devices. The Lab Solvents app also includes data from the GSK Solvent Selection Guide [48].

A second example of appifying data is TB Mobile [49] (Figure 4). There has been a considerable increase in high throughput screening to identify hits as starting points for potential compounds active against *Mycobacterium tuberculosis (*Mtb*)*. Even though 1000's of hits have been identified in the last few years [50][51][52] we are lacking target assignments which would help in assessing utility and for target-based optimization. The recent collation of >700 molecules screened versus Mtb and their targets could help in this task [53]. This data was previously only available in Collaborative Drug Discovery, Inc. (CDD) along with published data on target, essentiality, links to literature (PubMed), genes (tbdb.org), pathways (TBCyc, which provides a pathway-based visualization of the entire cellular biochemical network) and human homolog information [54]. This data was used to create TB Mobile that displays molecule structures and links to the bioinformatics data. By input of a molecule structure and performing a similarity search one can infer potential targets or search by targets to retrieve compounds known to be active. The app also has filters to limit the visible molecules by target name, pathway name, essentiality and human ortholog. Each molecule can be copied to the clipboard then opened with other apps (e.g. MMDS, MolPrime, MolSync, ChemSpider, and from these exported via Twitter or email) or shared via Dropbox. This is an example of an approach to appification which could exploit other drug discovery datasets and potential free them from web-based databases.

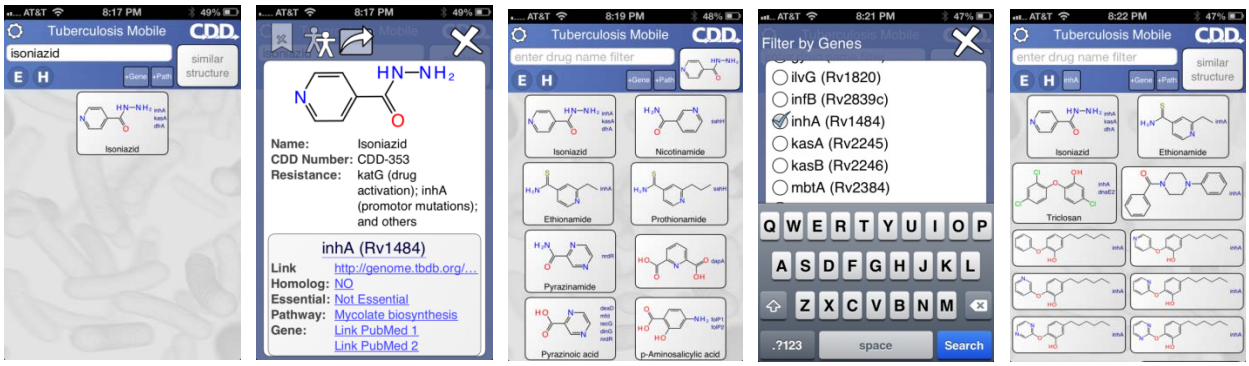


Figure 4. TB Mobile can be used to search for molecules e.g. the frontline drug isoniazid. Molecule information and links out can be viewed, shared or copied to the clipboard. Similarity searching within the app enables ranking of other molecules active against TB and inference of potential targets. Data can also be filtered by target name, pathway name, essentiality and human ortholog.

3. A cheminformatics workflow

The following example demonstrates a potential realistic workflow that uses several iOS cheminformatics apps and makes use of cloud-hosted web services. The sequential tasks are based on a relatively straightforward medicinal chemistry exploration which investigates new tuberculosis molecules. Each step uses technology that is currently available, while some of the apps are relatively recent they represent the evolving state of the art in cheminformatics mobile apps. It should also be pointed out that some of the apps are free while others can be purchased for a fee.

In this example, the ChemSpider Mobile app is used to look up a core scaffold (1,3-benzothiazin-4-one) for a series of known Mycobacterium tuberculosis (*Mtb*) inhibitors [55] (Figure 5).

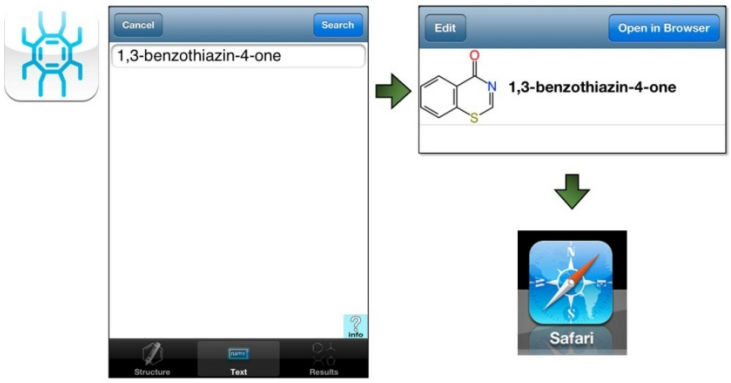


Figure 5. Looking up a chemical substructure in the ChemSpider mobile app.

The record can be viewed in the mobile browser and the structure can be downloaded as an MDL molfile [56] which in turn can be opened directly in mobile apps. If MMDS is on the device, this can be selected to open the molecule (Figure 6).

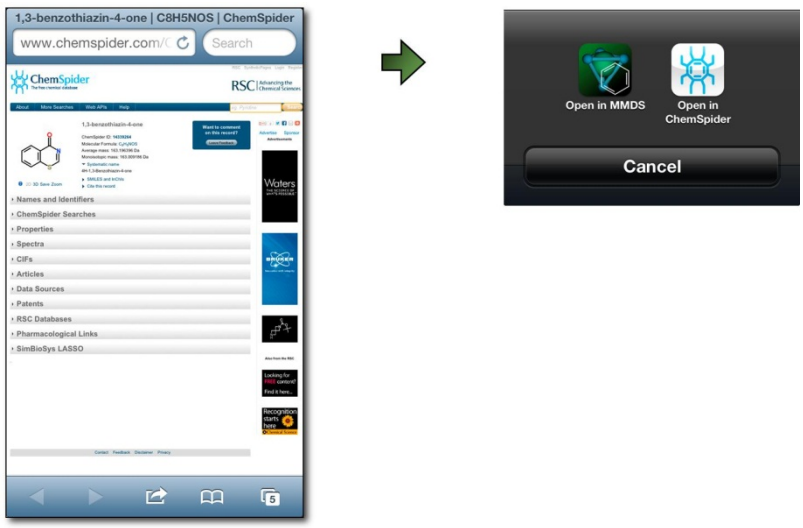


Figure 6. Saving the structure in the ChemSpider Mobile App as a molfile and opening in the MMDS app.

The imported molecular structure can be viewed in a scratch sheet in the app and then the Run Web Service feature can be opened (Figure 7).

Figure 7. Viewing the structure in the MMDS app

A substructure search using the core scaffold using ChEBI can be used to produce a new datasheet (Figure 8).

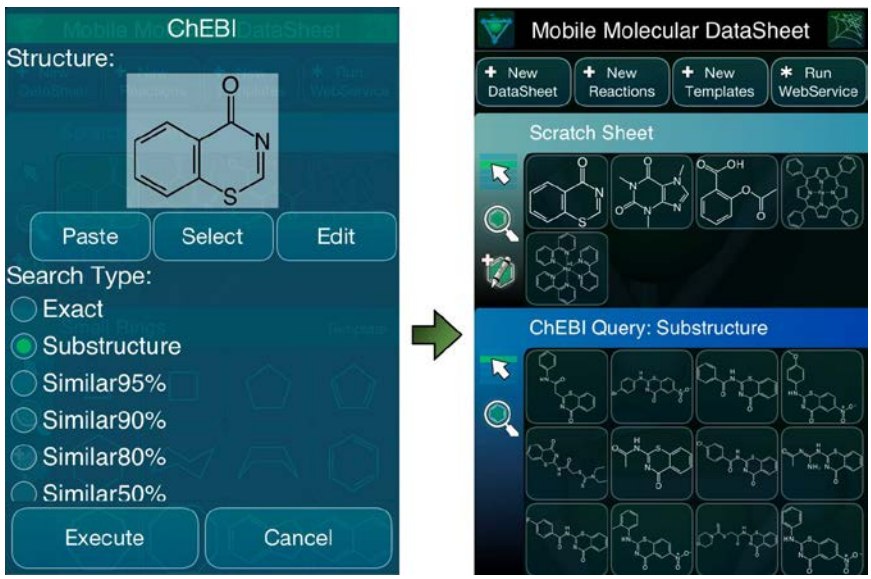


Figure 8. Substructure searching ChEBI using the MMDS app

The results of the search can be opened in the SAR Table app (Figure 9) and represents a table of compounds as scaffolds and substituents (Figure 10).

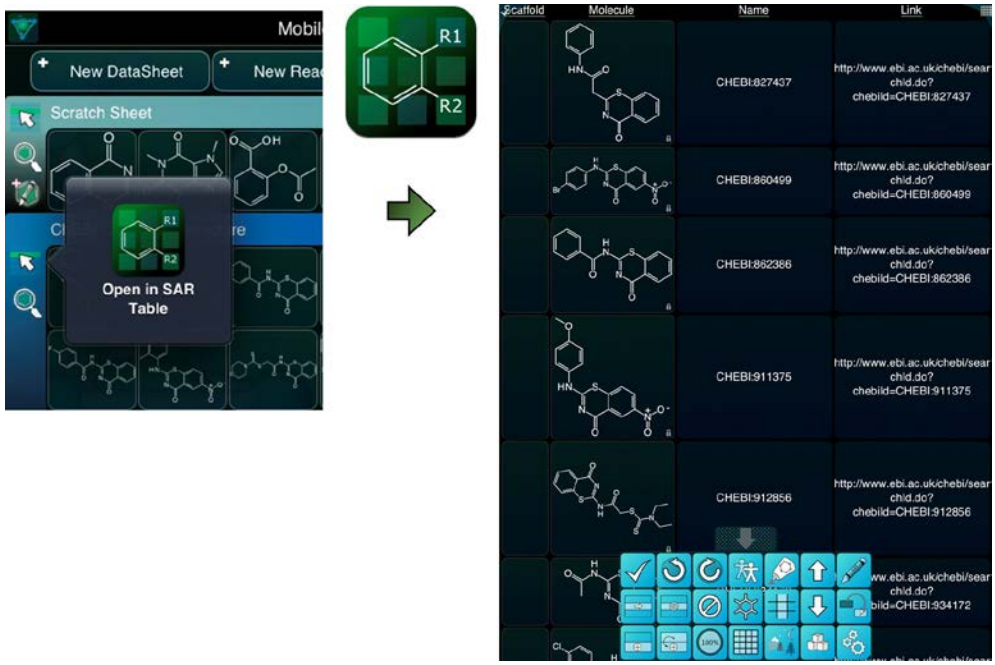


Figure 9. Opening a molecule from the MMDS app and assigning scaffolds in the SAR Table app

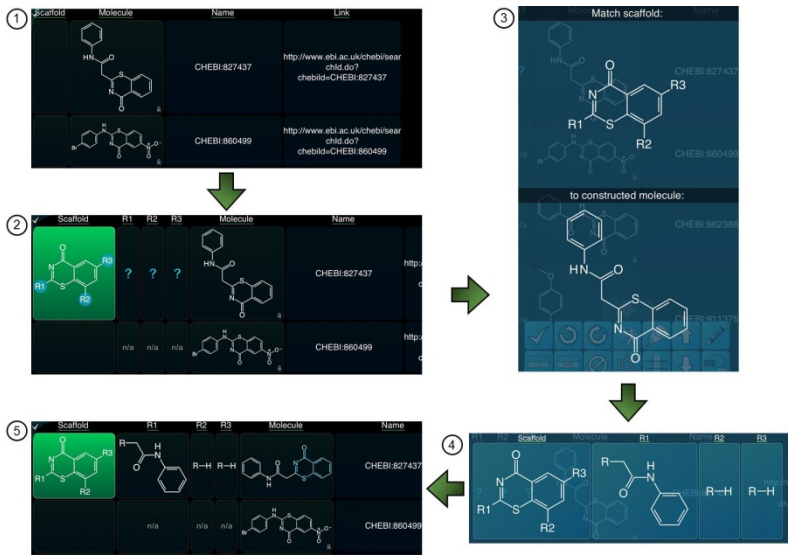


Figure 10. Generating the table of substituents in the SAR Table app

The development of a structure activity relationship is aided by classifying scaffold and substituents. The assignment process is partly manual and partly automated as structure fragments can be drawn within the app and copied to other cells or computed by a web service (Figure 10).

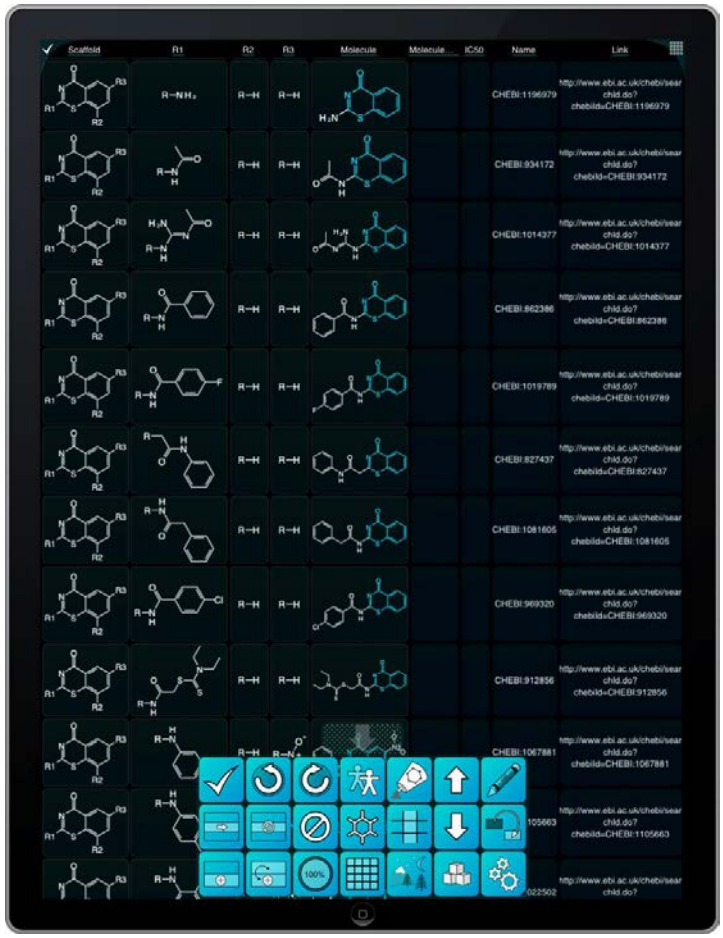
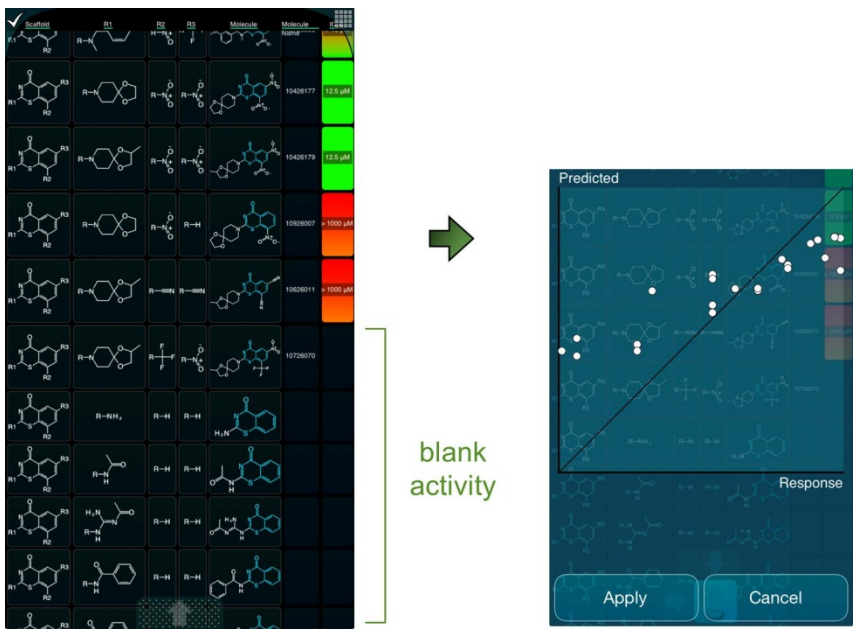


Figure 11. An example of a full SAR Table shown on an iPad

An existing data table created from the literature [55] can be used to color code bioactivity and also be used as a dataset for modeling and prediction for new molecules (Figure 12).



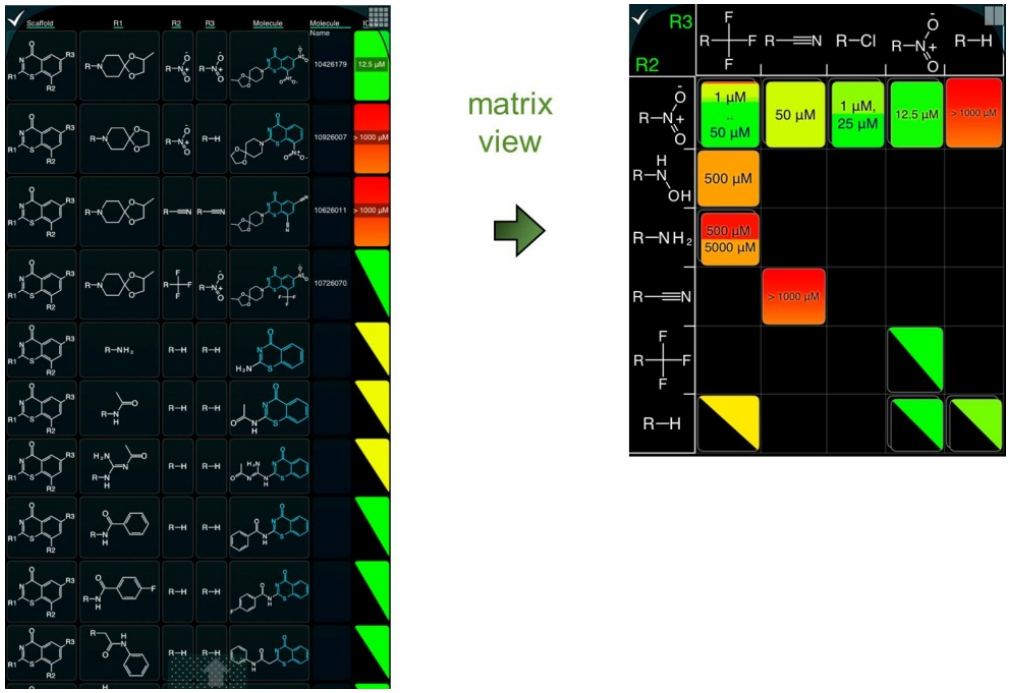


Figure 12. Predicting missing activities (top) Color coding the activity data and predictions for missing values (bottom) in the SAR Table app

The results of such predictions can suggest potential molecules to make (Figure 13) or obtain from elsewhere.

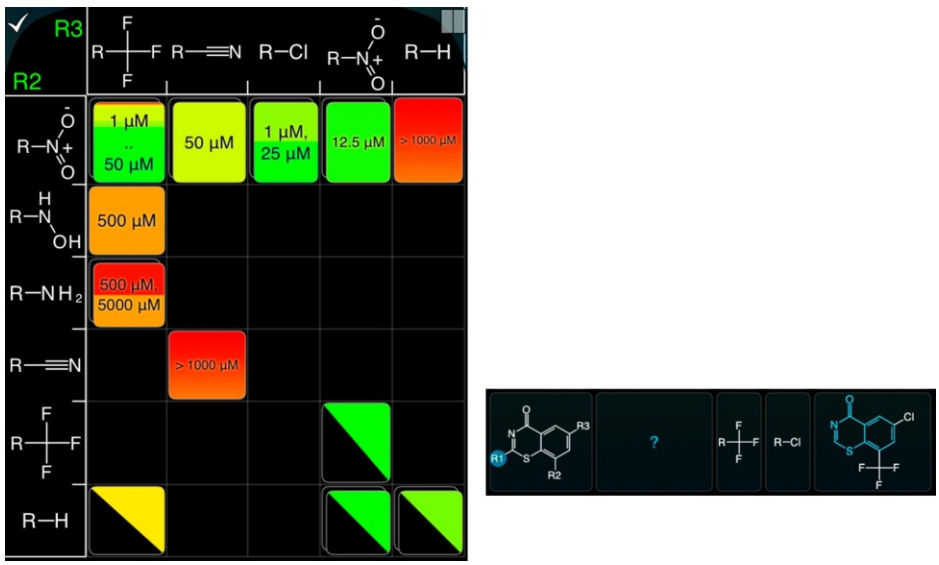


Figure 13. Suggesting molecules to make based on SAR Table app predictions

Synthetic information for a potential analog can be obtained using the SPRESImobile app by opening the core structure and searching for similar structures as a product to find a potential synthesis that may be adapted (Figure 14). Once found it will link to the literature that can be opened in Safari Mobile.

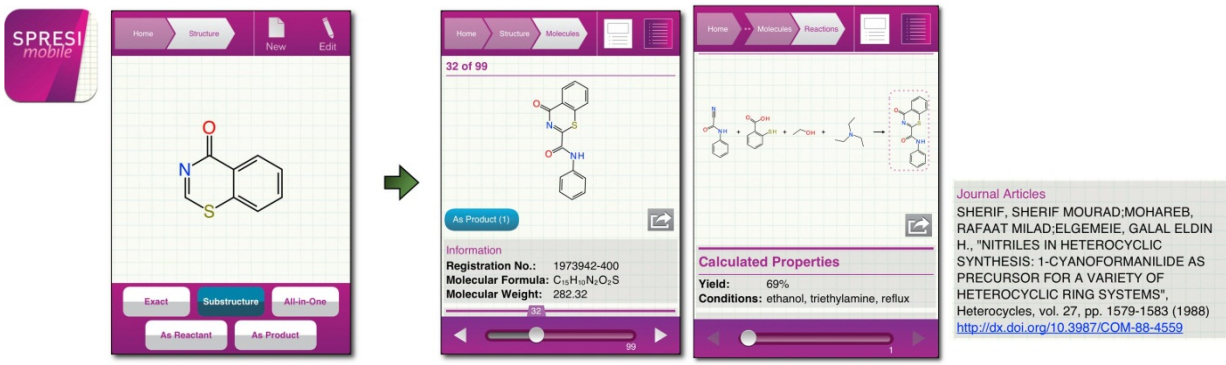


Figure 14. Finding a reaction in the SPRESImobile app

The scientist can then plan the synthesis by opening the reaction from the SPRESImobile app in Yield101. The user can customize the reaction components, add quantities and calculate an expected yield (Figure 15). In addition, the green chemistry property known as the process mass intensity can also be calculated. The data can be used to create a PDF document, printed or emailed, or the mobile device can be used in the lab recording results directly.

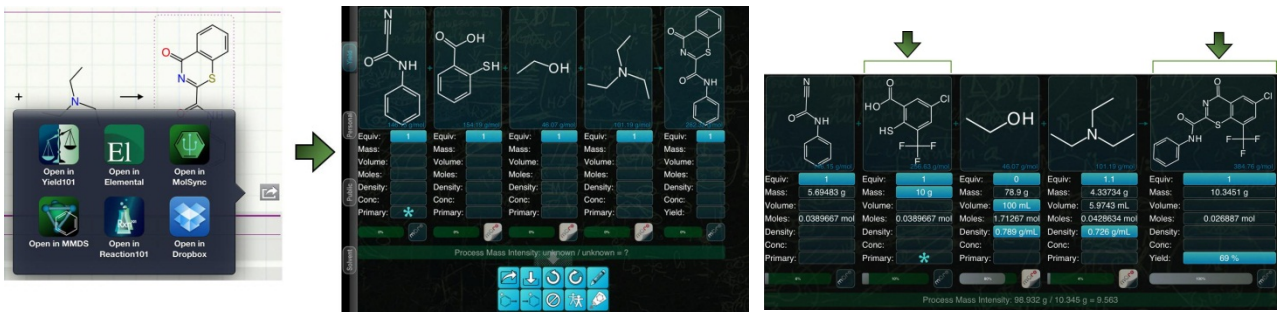


Figure 15. Using the Yield101 app to calculate expected yield after adapting reactant and products (arrows)

The reaction can also be shared in MMDS and from there it can be sent by email, exported in presentation quality graphics, shared on the web, tweeted or uploaded to repositories (e.g. Dropbox). Emails can include several attachments including machine readable data, graphics (MS Word, Excel documents with embedded vector graphics) etc. Datasheets can be linked to Dropbox using the MolSync app and storing data here opens up many secure or open sharing options (Figure 16).

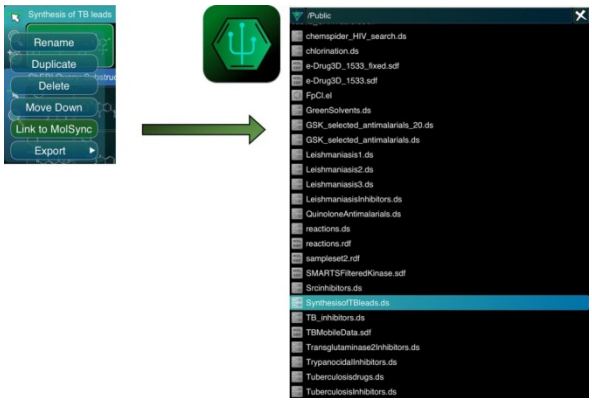


Figure 16. Sharing data with Dropbox using the MolSync app

Mobile apps like Open Drug Discovery Teams can be used to collect relevant tweets that are made available for browsing with the free app. Chemical data is parsed and can be accessed with other apps Figure 17.

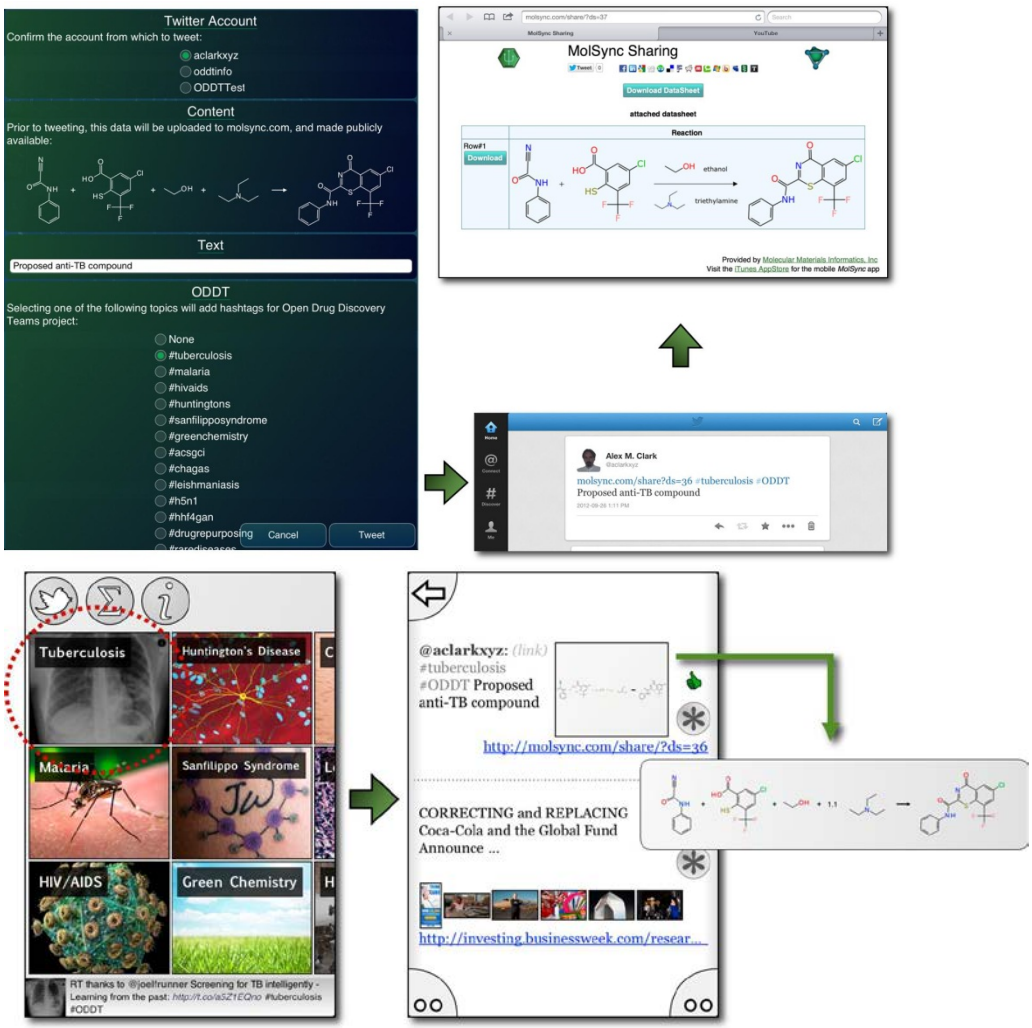


Figure 17. Tweeting a reaction using MolSync (top) and then reading the data in the ODDT mobile app (bottom) under the Tuberculosis topic.

4. Cheminformatics collaboration via mobile apps

One of the useful features of mobile apps is that they are low profile, easy-to-adopt tools that theoretically could remove traditional barriers between information sources. In fact, they have the potential to create a whole new ecosystem of information and users. Nowhere is this more evident, or more important, than in the area of rare and neglected disease research, where disparate (and often desperate) information seekers need better ways to access and share information. Today we are seeing parents becoming bona fide world experts in rare diseases out of necessity, as they form foundations [57][58] and companies [59][60][61] to fund research to help their sick children. Organizations like these do not have the scale of the government research organizations (e.g. NIH), or other large disease foundations. But they are virtual pharmaceutical companies—and they are highly motivated to find cures. What they lack is a way to rapidly access, gather, and share information on disease research that may be occurring anywhere globally. What if we could help these parents and the researchers working on rare diseases work more collaboratively, as recently suggested [62]? At the opposite end of the spectrum there are diseases with millions of patients (rather than one in a million for rare diseases), such as tuberculosis and malaria. Despite their prevalence and the considerable amount of funding they can receive, these diseases are often classed as neglected because progress is slow, not well coordinated, and rarely utilizes informatics, computational tools, and other technologies to capitalize on knowledge accumulated globally. In both of these cases, information exists. While we are surrounded by an increasingly broad array of technologies and forums for sharing our data as scientists, so much research is occurring, but it is impossible to track it all and in many ways can be thought of as occurring in a vacuum. The challenge is how to connect the right people (scientists, funders, clinicians, parents etc.) to the right information at the right time so that they can share, partner, and collaborate. How can we boost the signal to connect those doing the shouting with those who most want to listen, wherever they are in the world? There is potential here to help many diseases and particularly those that receive little attention from the pharmaceutical and biotechnology industries.

In response to this need, Open Drug Discovery Teams (ODDT) was developed. The app was rapidly prototyped and developed [41]. The ODDT project tracks Twitter hashtags and Google Alerts (that correspond to certain diseases), and aggregates the document links under topic headings. Users provide crowdsourced curation by using the app to tweet out endorsements, which allows articles to be "voted in", which in turn incrementally improves both the quantity and quality of the data. The app is chemistry aware so scientists can share the molecules they are making, want to share with others, or need to find. We have even made it possible for structure activity data to be shared in the app. This potentially helps citizen scientists, (which includes parents and patients), who are highly motivated to learn, but would otherwise not be exposed to scientific software (e.g. on a desktop computer), which is typically expensive and difficult to use.

We have found that parent lead disease organizations use social media like FaceBook and Twitter or actively blog to promote the study of their children’s diseases. They are now also using ODDT as another way to highlight their causes and at the same time to endorse content they know is relevant to the community. In the process of developing and communicating ODDT we have actively raised the profile of these diseases [41][45]. While many people are beginning to publish in open access publications, still the majority or research appears in journals which charge for access to the content. ODDT can be used to supplement the academic publication system which locks most important discoveries behind paywalls. By having access to raw data in a readily usable form (as increasingly happens when it is increasingly deposited in public databases), anyone can easily incorporate the data into their own projects, and avoid unnecessary duplication of effort. While ease

of incorporation of data is one thing, mining such data may not be trivial and is likely limited to experts. Making such data accessible also opens it up to the crowd [63] who could help analyze it. This also helps the scientists as a parent may see their work on ODDT and want to offer to fund them or commercialize their discoveries.

We believe that there is a shift towards low-cost consumer-friendly apps. The ODDT project is an effort to bring together professional scientists, charitable foundations, and concerned citizens in an open context, without institutional or geographic barriers. The app also represents a starting point to develop a commercial product provisionally product called Drug Discovery Teams (DDT) which adapts ODDT for licensing to pharmaceutical research institutions for internal use, with appropriate security features to enable retention of IP. Private documents can then be mixed with external data to create a valuable internal resource. These capabilities will complement existing chemical database software as mobile and cloud computing becomes the accepted paradigm for drug discovery.

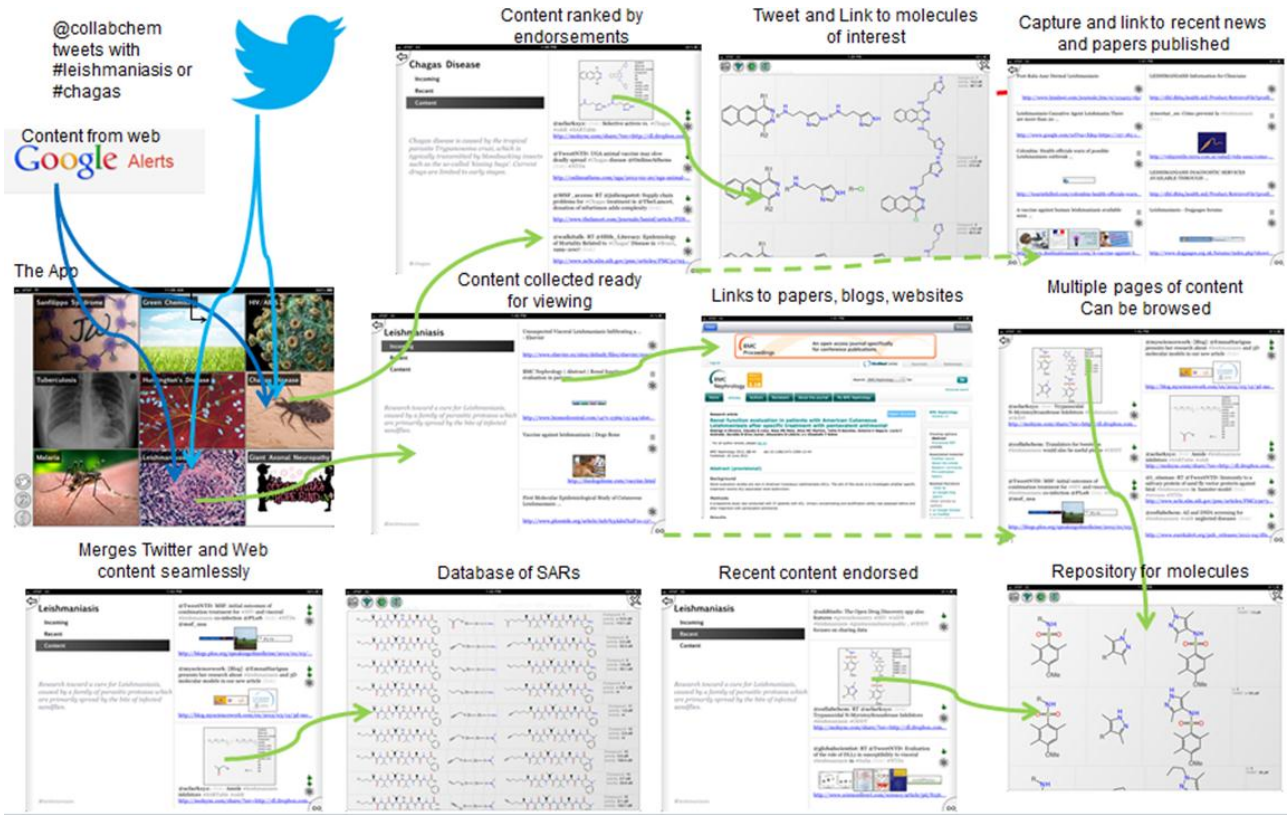


Figure 18. An overview of functions possible using The Open Drug Discovery Teams app applied to neglected tropical diseases.

5. The future of cheminformatics apps

Second generation cheminformatics apps will very likely have the facility to perform many more sophisticated functions. In order to make ever more powerful functionality practical, these apps will need to incorporate data sharing and collaboration features as an integral part of their design, e.g. QSAR data preparation and prediction, pharmacophore analysis, docking clients, 2D

depiction tools for 3D data, to name but a few. Numerous additional data sharing scenarios are possible, e.g. deeper integration with online chemical databases, direct integration with electronic lab notebooks and interfacing with laboratory instrumentation via wireless communication methods. The combination of a user interface designed and optimized for the mobile form factor, cloud-based server functionality for data warehousing and extra computational capacity, and collaboration features for integration into an overall workflow, makes these projects not only technologically feasible, but in many ways preferable to traditional software.

For example, a spreadsheet of molecules and data could be taken to build a pharmacophore which can then be used to search a molecule library, select compounds that can then be ordered by a vendor and tested by a laboratory which then send the results to an app for viewing on the device. Alternatively, a spreadsheet of molecules could be docked in a protein, interactions scored, and this becomes the basis for their selection and testing prior to visualization of actual and predicted data alongside each other. Smaller workflows could be developed, such as taking a dataset and building a predictive QSAR or machine learning model then saving the model on the cloud and later using it to generate predictions for a library of molecules and selecting those for testing.

In the past we have seen many computational models published but few of these models are shared or are available to other non-computational chemists to use. For example in the area of transporter proteins involved in drug disposition, there have been many computational models for different transporters developed [64]. It would be very useful if apps could be developed that make such computational models accessible to any scientist. Such apps then would have the potential to help the scientist decide which experiments to perform and may also assist regulatory authorities in predicting potential for drug-transporter interactions. Such an effort could also be applicable to enzyme, receptor and ion channel models which would make some of the widely described models for P450's, nuclear receptors and channels like hERG available to the chemist or drug designer.

Mobile apps are currently much less well suited to managing big data collections than analogous desktop software, due in large part to their limited computational and storage resources, but this will change in future. Currently apps function as components: frequent data sharing is therefore a necessary part of any workflow, which is effective for small collections, i.e. hundreds of rows of data, rather than thousands or millions. Simple workflows involving big data collections, e.g. submitting a structure search to a server and fetching the best few results, are already well established. Active participation in visualization and maintenance of large data collections will require new methods for task subdivision and integration of apps within pipeline-based workflows [9].

The increased availability of data and algorithms in the cloud, accessible via standard programming interfaces, enables the first generation of scientific apps to access capabilities that require more powerful processing power. In summary, perhaps the most crucial feature for making mobile devices a viable component of a drug discovery workflow is the ability to collaboratively share molecules and data. A second generation of mobile apps is already emerging, which takes advantage of the many different technologies provided by mobile platforms that allow data to be passed back and forth between heterogeneous environments. This is potentially transformational.

Conclusion

We have shown that some moderately sophisticated and quite flexible workflows are already possible using existing mobile cheminformatics apps. These workflows involve content creation, content consumption, network sharing and computation. In order for particular specialization of these tools to occur to adapt to specific case studies some degree of user feedback is needed in

future. Native apps are currently quite good for visualization and data entry but are confined to relatively small datasets and avoid intensive calculations. Such apps generally need network access to offload larger datasets. Bigger data workflows will need specialized servers and protocols, while database querying is a simple example, more complex schemes are in development through the proposed Pistoia Alliance AppStore infrastructure [65] which will provide an alternative storefront for mobile apps and a standardized service infrastructure for big data and calculations. The appification of drug discovery data and the potential for using social media for collaboration lowers the barriers to participation and potentially enables anyone to become involved in drug discovery, anywhere.

In the future we expect there to be more apps designed to solve specific workflows. The consolidation of platforms and APIs will be important. Supporting all current platforms requires over 5 incompatible code bases, there is thus a need to focus on preferably one or two. As there is likely to be more interaction with cloud services, there will also be a need to have support on the back-end. We see a healthy future for mobile cheminformatics apps and associated cloud-based services. The combination of these developments will result in the gradual replacement of mainstream chemical information software.

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