Title: Mobile modeling in the molecular sciences

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The art of modeling in the molecular sciences is highly dependent on both the available computational technology, underlying data, and ability to collaborate. With the ever increasing market share of mobile devices, it is assumed by many that tablets will overtake laptops as the computer of choice in the coming years. As the world shifts to mobile architectures as their primary computing devices, modeling tools need to evolve to provide the required functionality in the slim, portable and interactive tactile environment afforded by these devices. Mobile modeling in the context of molecular sciences is focused on using smartphone or tablet devices (e.g., iPhones, Android phones, BlackBerry phones, Windows phones, iPads, Android tablets, Microsoft Surface, etc.) to perform a variety of modeling tasks, including but not limited to molecular modeling, geometry optimization, chemical structure based calculations, SAR generation, and database lookups.

So why should modeling be mobile? The aforementioned modeling tasks can all be completed using software available via traditional computing formats. Are there really benefits from converting these tools to mobile form factors? The primary benefits of mobile technologies in molecular sciences are corollaries of the general benefits of mobile technologies. The simplistic and intuitive nature of touchscreen interfaces yields a faster learning curve and wider accessibility to non-specialists. Software distribution is via “app stores” which makes installation trivial, updating even easier, and reduces to zero the need for an IT department. The small and portable nature of the devices allows science to be done immediately upon idea formation rather than delaying until in an office setting. This makes it ideal for the new generation of telecommuters, you can maximize research time and minimize downtime by modeling whenever the opportunity arrives.

Unfortunately, the same characteristics that yield benefits are a double edged sword. The simple touchscreen interface limits the complexity of interactions that can be carried out. For example, a molecular visualization interface (e.g., Sybyl, Maestro, MOE, etc.) accessed through a Windows desktop commonly has specific functions based on which mouse button a user presses (atom selection, rotation, menu call up). By switching to an interface where there is only one type of click/drag action, providing equivalent functionality can be difficult. The precision of a finger on a screen is very low compared with a mouse or trackpad, and the screen is partially obscured with each operation. In addition, the smaller size of portable devices naturally means a smaller screen. This smaller screen not only makes viewing complex macromolecules difficult, but also limits the real estate available for adding buttons to increase interface functionality.

The benefits and detriments of mobile devices for complicated scientific applications will likely have little effect on mobile device penetration into the scientific community. As mobile becomes mainstream for less complicated functions commonly completed via a desktop computer, scientific software developers must actively work to provide equivalent functionality for the molecular sciences in these new mobile environments. Efforts by a small community of focused scientists already provide access to key data resources, chemical structure building/viewing applications, and molecular modeling software yielding an ever expanding molecular science toolkits for experts and novices alike. Recent

developments of a sandbox for complex dynamics simulations opens up broader study of the interactions between chemicals and biological systems in a mobile format.

Mobile Database Access

With the ever increasing abundance of data on molecular entities, many investigations of chemicals start with simply finding out what knowledge is already available. To that end, numerous apps provide focused sets of information (e.g. *Green Solvents [http://pubs.acs.org/doi/abs/10.1021/sc3000509], TB Mobile [http://www.ncbi.nlm.nih.gov/pubmed/23497706], Approved Drugs, Reagents, Organic Named Reactions,* etc.). These relatively simplistic apps provide users with ways to explore collated sets of chemical information that are self contained within the app.

A broader use case scenario is provided by apps that act as a portal to large online databases. Such apps provide a significant advantage over the corresponding website by solving the problem of allowing users to draw chemical structures for use as queries, as well as leveraging the improved performance and functionality of a native app for browsing the results. Examples include *ChemSpider Mobile*, *SPRESImobile* and *Mobile Reagents*, each of which is tied to a specific service. Apps such as the *Mobile Molecular DataSheet* (MMDS) and *MolPrime*$^{+}$ provide searching as a secondary feature, and facilitate access to PubChem [http://pubchem.ncbi.nlm.nih.gov/], ChEBI [http://www.ebi.ac.uk/chebi/] and ChemSpider [http://www.chemspider.com] in addition to their primary structure-data management capabilities. This provides the user access to millions of chemical structures online with pre-computed properties, associated experimental data and links to additional data across the internet. For example, in the case of the ChemSpider Mobile app over 28 million chemicals can be accessed online with linked information including patents, publications, chemical vendors and a myriad of other related data types. The open availability of the ChemSpider web services allows for the pairing of diverse interfaces, including the mobile app client, making use of the server-based searching and data storage.

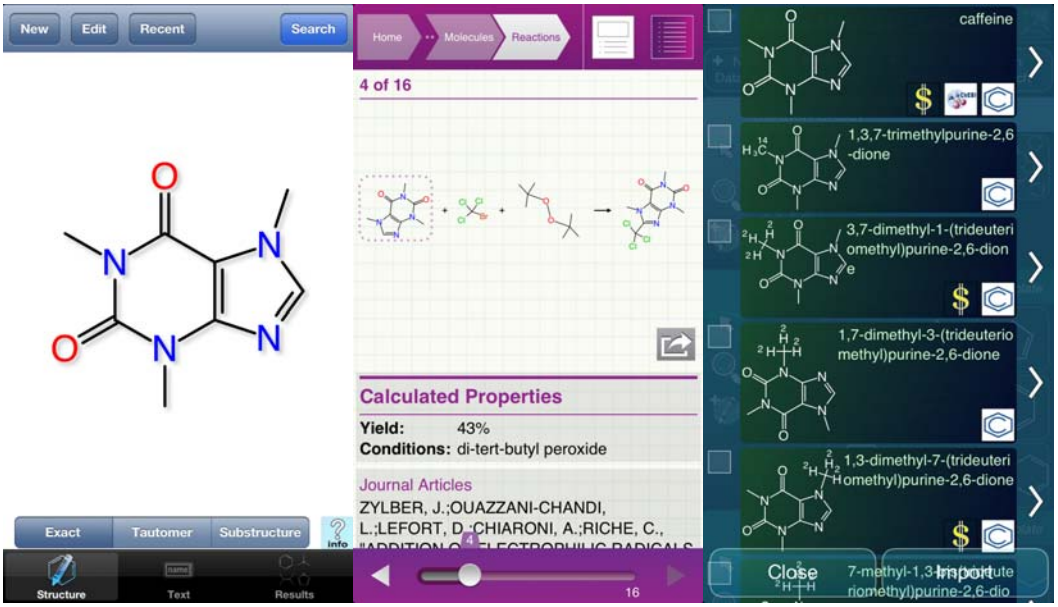

Fig. 1: (a) The *ChemSpider Mobile* app showing the initiation of a structure search. (b) *SPRESImobile* app browsing reaction hit results. (c) *Mobile Molecular DataSheet* (MMDS) app browsing results of a similarity search across multiple databases.

Molecular Visualization

Apps are available for sketching and visualization of 2D structure diagrams, 3D structure models, molecular properties, and collective trends such as structure-activity analysis. Many of the apps currently available are primarily visualisation tools, but increasingly they are able to interface with webservices to utilize user-provided data to generate models which can be studied using the mobile app as the client.

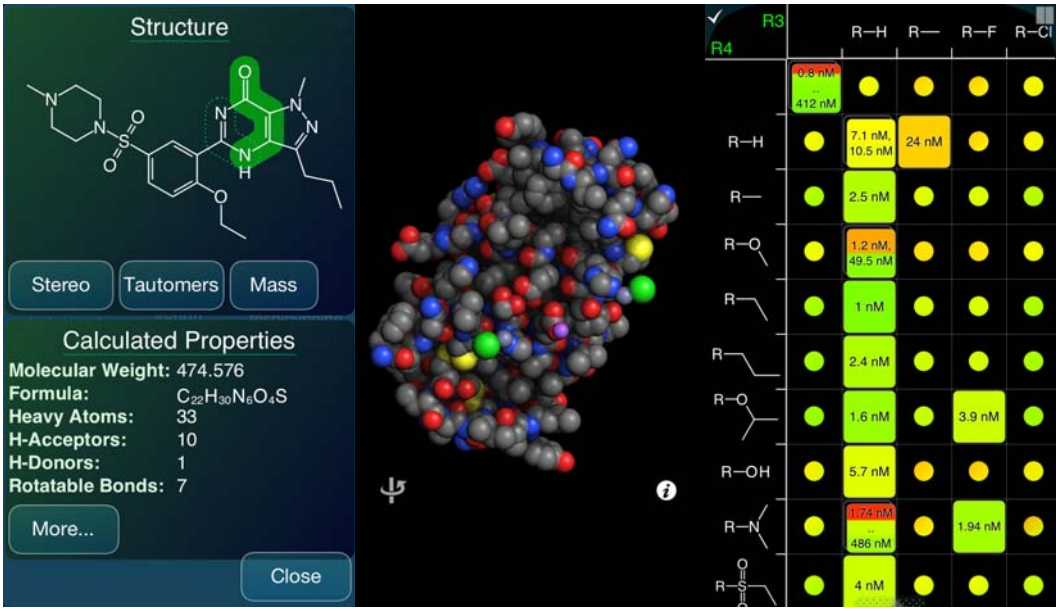

Fig. 2: (a) *MolPrime*$^+$ app showing an interactive tautomer explorer. (b) The *Molecules* app rendering a protein. (c) The *SAR Table* app showing actual and predicted activity for R-group correlation.

Mobile Molecular Collaboration Platform

Mobile apps have access to strong collaboration features, owing to their origins as portable communications devices. Because apps are typically quite modular relative to desktop software, a workflow often operates by passing documents between different apps, and between heterogeneous platforms, e.g. sending and receiving email attachments, downloading data from the internet, and interacting with online storage services such as *Dropbox*.

It is also possible to connect with nanopublication services such as *Twitter*, and emit chemical data as well as images and commentary. Using specific hash tags corresponding to topics of interest is a way to publish data to projects in an app such as *Open Drug Discovery Teams [ref http://www.ncbi.nlm.nih.gov/pubmed/23198003]* , which has an app-based interface for presenting scientific data on rare and neglected diseases as well other research topics of interest, which is chemistry aware, as shown in Figure 3. Many of these apps can be used in an integrated workflow as data is passed from one app to another [https://www.jstage.jst.go.jp/article/cbij/13/0/13_1/_article].

Fig. 3: (a) Topic display for the Open Drug Discovery Teams app. (b) Recent documents for the Malaria topic. (c) In-app preview of a datasheet containing structures of malaria inhibitors.

Mobile Systems Modeling

The interactions between chemicals and their environments have long been the domain of dynamics simulation software (such as matlab). Since pharmacokinetic and pharmacodynamic models are typically crafted in the form of Ordinary Differential Equations (ODEs), any ODE solver can theoretically be used to run such models. Coding an ODE solver is not complicated and several have been made available on both the GooglePlay store and iTunes App Store. As computational power in mobile devices increases, It may well be that developing more complex models that use these software tools is the next frontier for the mobile molecular sciences. We chose one particularly well-developed tool, MathMinion (http://www.redtree.com/mm), to test mobile capabilities for generating and running a mobile PBPK model.

MathMinion provides the user with a graphical interface for formulating their model. The interface allows the definition of all relevant variable in a dynamic simulation and the necessary ODEs to be simulated. The program uses uses a variant of the Adam Moulton method for non-stiff problems and Backwards Difference Formulas (BDF) when the problem is designated as stiff. In addition, MathMinion will automatically analyze the units defined for all parameters, make conversions, and notes inconsistencies. In MathMinion, we easily implemented a functional model of styrene pharmakokinetics that was previously published ((a) Ramsey, J.C. and Andersen, M.E. (1984). A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73, 159. (b) Poulin and Thiel, J Pharm Sci 91(1) 2002 (c) Styrene model: http://www.thehamner.org/docs/Day2.Exercise1.Styrene.pdf). Figure 4 shows the model and the result of a simulation.

With such modeling function freely available, models for usage in pre-clinical and clinical environments are sure to follow. Such models could direct scientists in pharmaceutical development on the proper dosing for animal studies, inform doctors on how to optimize radio-contrasting agents in radiology or

anesthetics prior to surgery, even protect field risk assessors (superfund sites or DHS/NHSRC or environmental risk assessment and waste management) by allowing them to quickly determine if an environmental exposure is likely to cause high internal doses. A framework such as math minion can enable the development of dynamic system models that detail the influence of a chemical on its environment over time and as such feed into a plethora of other realms of molecular sciences.

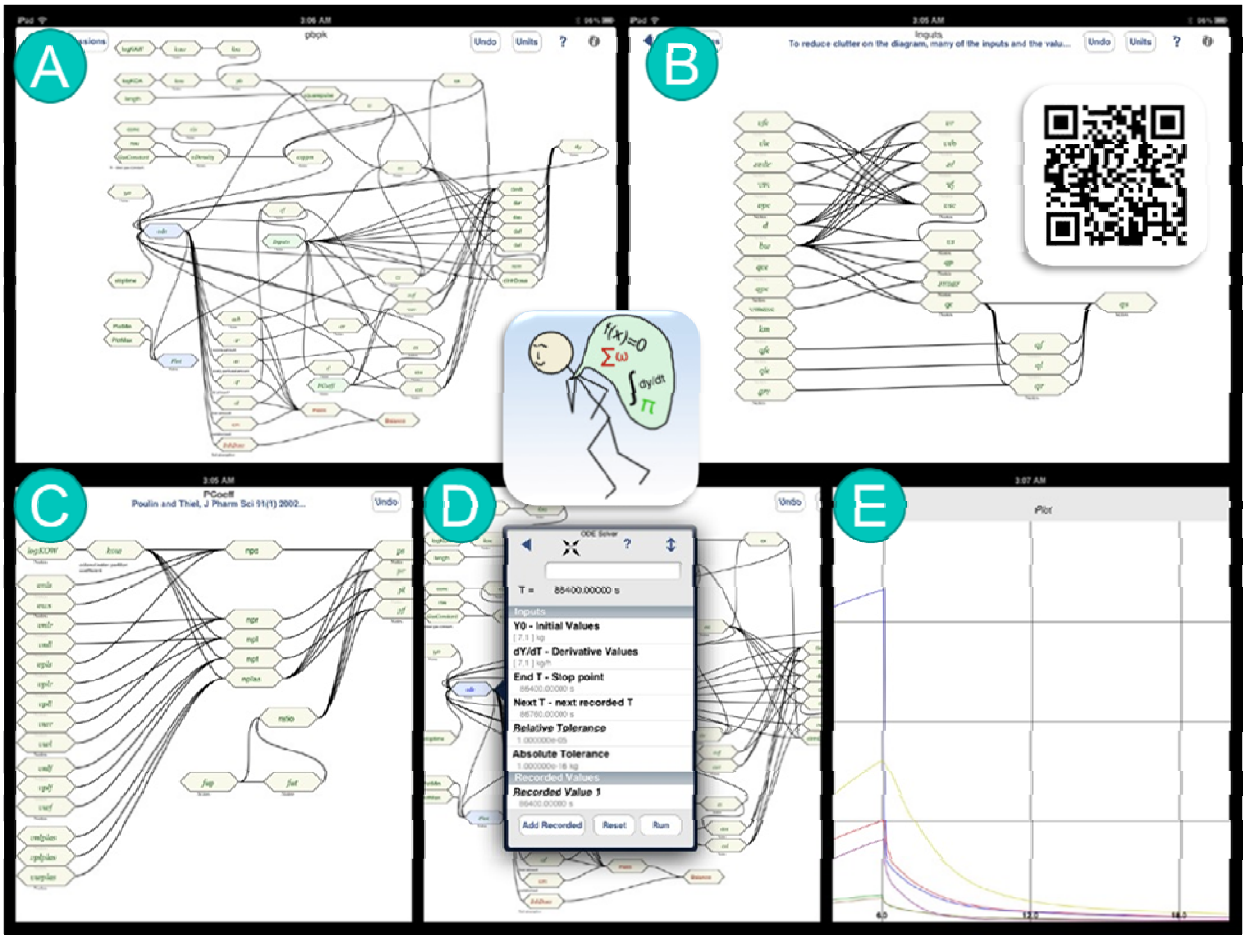

Fig. 4: A 5-compartment Physiologically-Based Pharmacokinetic (PBPK) model of styrene inhalation in a rat (adapted from.....). (a) The complete visual representation of expression, variables, solvers, and plots through a "mind-map" interface (b) an expanded section containing various physiological input parameters (c) chemical specific tissue partitioning parameters derived by the Poulin & Thiel approach (the LogP can be calculated using other apps such as the ChemSpider mobile app) (d) the ODE solver performing relevant integrations for chemical disposition across each compartment and (e) the final tissue concentration plots. The entire model can run on an iPod touch, an iPhone, an iPad or iPad mini and on the Mac OSX environments. The model runs about an order of magnitude faster on the Mac, but still only takes a few seconds to run on the iOS devices and can be downloaded http://goo.gl/VMfPs.

Server-Side and Cloud Applications

In addition to the numerous client-side mobile applications that can be used in molecular sciences, it must always be remembered that many server-side web-enabled applications can be used to round out any missing functionalities. While such tools toe the line between mobile and traditional formats (often allowing access via both mediums), they are accessible via mobile devices using focused app interfaces

or through the web browser functionality. Key abilities that may not be otherwise accessible on mobile platforms due to computational or storage limitations can still be done using mobile devices as long the necessary infrastructure is available elsewhere. Many tools (including some of those mentioned above such as ChemSpider Mobile) rely on the connected nature of mobile devices to provide users with the functionality they need on the devices they desire.

While many of these tools have interfaces specially formatted for mobile devices providing a seamless integrated feel (e.g. apps that link out to data sources or mobile formatted websites), there are many tools that were originally designed for traditional computing environments that can perform operations beyond the scope of current "more mobile" tools. For example, to examine the interactions between a set of compounds and a protein of interest several servers (e.g., Dock Blaster [http://blaster.docking.org], SwissDock [http://www.swissdock.ch/], DOCKING Server at [http://www.dockingserver.com/web/], etc.) provide mobile modelers with access to protein-ligand docking capabilities. Web-based toolkits for application or generation of statistical QSAR models are available (e.g., Chembench [http://chembench.mml.unc.edu/] and OCHEM [http://ochem.eu)]. It is important to note that because many of these web-tools are designed for desktop environments and require formatted file inputs, file manipulation applications and/or non-native web-browsers with file system access functions are required.

Conclusions

While many tools exist for scientific mobile apps (www.scimobileapps.com), those tailored exclusively to the mobile modeler is still sparse in comparison to the offerings in a desktop environment leaving a lot of room for further development. While it has been documented that rather complex molecular science investigations can be completed by combining several apps together, integrated research environments still remain elusive in the mobile environment. However, as the inclusion of Windows 8 into new mobile devices blurs the line between traditional computing and mobile computing, the expansion of molecular science software available to scientists working exclusively on mobile devices will surely accelerate.

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Additional off-line reading (4-5 max)

http://www.sciencebase.com/science-blog/science-goes-mobile-scimobileapps.html

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