In silico ADME/Tox: Why models fail: **Why models work**

Terry Richard Stouch, PhD

Science for Solutions, LLC
Consulting in Drug Discovery and Design
Practice, Technologies, Process
Princeton, NJ

and

Duquesne University

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In silico ADME/Tox: Why models fail

- Real and apparent failures

Stouch, et al, *Journal of Computer-Aided Molecular Design* ***17:*** *83–92, 2003*

Abstract:
By way of example, we discuss the apparent 'failure' of *in silico* ADME/Tox models and attempt to understand the causes. Often, the interpretation of the success of models lies in their use and the expectations of the user. Other times, models are, in fact, of little value. Disappointing results can be linked to the key aspects of the model and modeling procedure, many of these related to the original data and its interpretation. We make recommendations to providers of models regarding the development, description, and use of models as well as the data and information that are important to understanding a model's quality and scope of use

A prediction, good or bad?

- Lots of ways to generate a bad model
- But sometimes a “good” model with genuine value can look bad
- Here, I’ll give the models the benefit of the doubt
  - How to tell the difference between good and bad?
  - How to be fair
  - What to look for in a model
  - What appears to be the current state-of-the-art

My *in silico* ADME/Tox experience & background

- Comp chemist / synthetic chemist
- Long background in property prediction, simulation, QSAR
- Permeation and bioavailability
- 14 years Drug Discovery projects at BMS
- 5 years as head of *in silico* ADME/Tox at Bristol-Myers Squibb
  - CADD, DMPK / Tox, Med Chem, statisticians
  - Deployed models widely
  - Our successes
    - Pampa / Caco-2
    - hERG
    - Cyp 2C9
    - Solubility
    - Tox alerts (G. Pearl, D. Saul)
- 4 years Director, Computational and Structural Biology, Lexicon Pharmaceuticals w DMPK purview
- Consultant in ADME/Tox modeling, software, presentation

Components of *in silico* ADME/Tox

- Intent and Use: Why was the model developed
  - Realistic expectations
  - Different uses for different tasks
- Basis of the model: Experimental Data (training set)
  - Consistency
    - Whose experiment? Yours?
    - Context and interpretation (can it be combined?)
  - Endpoint
  - Accuracy and precision
    - The model can be no better than the data
- Predictive *in silico* approach ("models")
  - Form and interpretation
  - Endpoints:
    - Quantitative or qualitative
  - Error estimates, experiment and *in silico (> experiment)*
- Presentation of results

Understanding the Use/Users & intent of the models

- Useless for one, valuable for another
  - Med Chem, DMPK, Tox, Comp Chem
  - Different needs: precision, accuracy
  - Use: Triage HTS vs next step in optimization

- Examples
  - Solubility: Required precision
    - Sometimes precision even of several orders of magnitude are useful in dealing with "bricks"
    - But, they do not "look" as acceptable as nM precision
  - Metabolite prediction: Over-prediction can seen as be good or bad
    - Metabolism expert can use all possible metabolic permutations of a molecule to *interpret mass spec*
    - Med Chem or Tox will need the most *likely* metabolite
    - Rate may be more important as identity for many uses

Understanding the Use/Users of the models

- More examples:
  - pKa prediction
    - Precision for experiment calibration can be as much as 3 log units
    - Drug design would like < 1 unit precision
  - hERG estimate of error and interpretation
    - BMS hERG model had established 200 nM error of prediction
    - Routinely did better which set "unrealistic" expectations
      - Prediction of 900 nM was seen as a "failure" vs 1.1 uM experiment
    - 1 uM cutoff of acceptable vs unacceptable meant 900 nM prediction was considered "wrong" for a "safe" compound (despite the +-200 nM range)

Understanding the Use/Users of the models

- More examples:
  - Tox prediction or alerts
    - Accurate precise predictions are hard – some say impossible
      - Are quantitative predictions even imaginable?
    - Alerts can be very useful in guiding decision making and design
      - "We're not #$@! librarians", "predictive tox is impossible," (politely anonymous but woefully under-informed computational chemist)
    - Care in their use
      - Retrospective, not prospective
      - Not for running the whole compound deck
      - But rather for detailed analysis
    - Best use to provide information *when a problem is determined*

Current state of the art

- Recent literature comparisons of programs and methods
  - logP
  - pKa
  - Solubility

Current state of the art: logP

- Evaluation of a 30 available programs (encompassing many methods)
- A public dataset and 2 "in house" datasets
  - Nycomed (882) and Pfizer (95809).
- Many (but not all) produced reasonable results for public data
  - RMSE from 0.4 to 2.0
- Low prediction accuracy of "in house" for most of existing methods
- Only seven methods were successful on the both in house datasets.
  - Among the best methods, ALOGPS, SþlogP, XLOGP3, OsirisP, ALOGP, and ALOGP98
  - **All RMSE>1.00 for the "in house"Pfizer dataset**
  - **Consensus logP, calculated an RMSE <1.00 for the Pfizer dataset**

Calculation of Molecular Lipophilicity: State-of-the-Art and Comparison of Log P Methods on More Than 96,000 Compounds, R Mannhold, GI. Poda, C Ostermann, IV Tetko, *Journal of Pharmaceutical Sciences,* **98** (3) 2009

Current state of the art: pKa

- pKa's of 211 Discovery (druglike) compounds
- Fresh, consistent in-house (AstraZeneca)experimental results
- Predicted by five different commercially available packages
  - ACDLabs/pK$_a$, Marvin (ChemAxon), MoKa (Molecular Discovery), Epik (Schrodinger), and Pipeline Pilot (Accelrys)
    - Simulations-Plus (unpublished, R Fraczkiewicz**)**
- Best results: RMS error of about 1 p*Ka unit*
- Appeared to be randomly distributed across chemical series.

Evaluation of p*Ka Estimation Methods on 211 Druglike Compounds,* John Manchester, Grant Walkup, Olga Rivin, and Zhiping You (AstraZeneca), *J. Chem. Inf. Model.,* 2010, **50**, 565–571

Current state of the art: Solubility

- Solubility challenge:
  - 11 commercial models evaluated
  - 132 diverse drug-like compounds
  - Newly assayed data
- Results
  - R2: 0.2 – 0.57
  - SE 0.8 – 1.2 log units 30X
  - RMSE: 0.8 – 1.6 log units 40X
- Simple approach proved superior to some more complex models.

In Silico Prediction of Aqueous Solubility: The Solubility Challenge. M. Hewitt, M. T. D. Cronin, S. J. Enoch, J. C. Madden, D. W. Roberts, and J. C. Dearden, *J. Chem. Inf. Model. 2009, 49, 2572–2587*

Solvation energy challenge: SAMPL2

J Comp-Aided Mol Design, 24(4), 2010.


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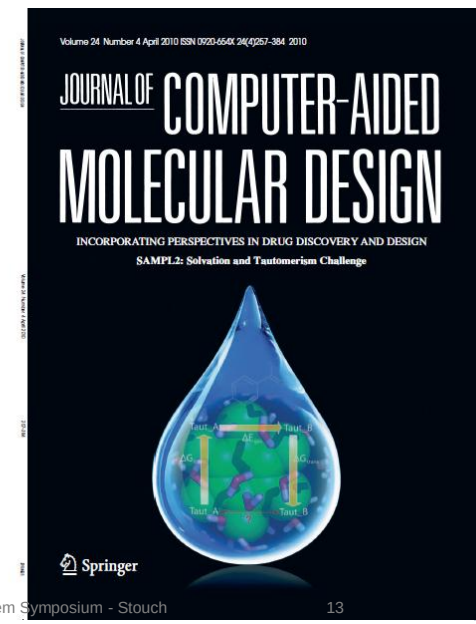


Tautomers: latest in experiment and prediction

J Comp-Aided Mol Design, 24(6-7), 2010.

Yvonne C. Martin
Perspectives Editor JCAMD

Informal Pharma survey of *in silico* ADME/Tox

- 12 Questions regarding:
  - Use
  - Preferences
  - Data
  - Properties
- 12 Pharma companies, 13 respondents
- Computational chemists, some Med Chemists

Informal Pharma questionnaire – Q1

- Do you or your company currently use in silico ADME / Tox?
- Responses:
  - Yes/No:
    - We do use in silico ADME/Tox but its application & impact is uneven.
    - There are some that do not do ADME modeling at all (as always) and some that do quite a bit
  - Yes
  - Yes
  - Yes
  - Yes
  - Yes
  - Yes/No
    - My company does but I and my group do not. We are oddballs in this respect. This lack of experience will color my later answers but I'll do my best.
  - Yes
  - No
    - Insufficient in-house data
    - Med chem was not interested

Informal Pharma questionnaire – Q2

- Who are the principal users (e.g. Comp Chem Group, Medicinal Chemists, DMPK specialists/experimentalists)?
  - **Chemistry** and **comp chem** with scattered use within other groups.
  - **All** these, depending on the project needs.
  - More or less in the **following order dmpk specialists, comp chem, med chem**
    - but there are wild fluctuations as we are a big company. Also depends on the model. e.g. egan egg and alerts used more widely by med chemists, but modelers use more in vitro models. Its a matter of peoples comfort level and experience.
  - Derek is used by the **genetic toxicology** group, Simulations Plus by **DMPK**, more general models by **Comp Chem** and **Medicinal Chemists**
  - **DMPK** specialists, primarily
  - **Comp Chemists**
  - **All** of the above, but in different ways
    - » Comp chemists tend to build local models to address project specific issues
    - » Medicinal chemists tend to use global models for library prioritization
    - » DMPK folks tend to use software for identifying sites of metabolism and metabolites to interpret metabolite id studies
    - » These are trends, specific use can vary

Informal Pharma questionnaire – Q3 -1

- Were/Are the models generated in house?
  - If so, where did you get the data?
  - Would you use data drawn from the 'literature'?
  - If not, why not?
- Responses:
  - The large majority of models are generated **in-house** using **internally generated data**.
    - Our use of literature data depends on the endpoint & modeling methodology being considered. Generally, when QSAR is the primary avenue for modeling we avoid literature data; when the modeling method is "more physical" (whatever that means), we consider it.
  - Sometimes **published data**, but the more usual thing [is **in house** data]
  - Most models i**n-house**
    - Data **in house and literature** (when in-house is insufficient)

Informal Pharma questionnaire – Q3 -2

- Responses (cont):
  - Mostly **in house** (sometimes from lit if the data is well understood or appropriate for the problem -- sometimes training sets are published). For some models, there is only lit data (usually from one lab)
  - Data: **in house, some literature**
  - **Not in house. Would not use literature data**.
    - Data not uniform/reliable.
  - **Only with locally [in house] generated data**.
  - **In house** models. Generally in-house assays
    - Although some external data may be used sometimes. [literature data].
    - Generally it is not robust in either curation or diversity or both
  - **In house:** Absolutely! **In house assays**. **Literature: no**:
    - "- Too much variability between labs, molecules are nothing like our molecules, dynamic range of the data doesn't match what we're looking for "

Informal Pharma questionnaire – Q 4 and 5

- Were/Are any of the models "commercial" "canned" models (i.e. from a software vender like Accelrys, Simulations-Plus, or others).
- Would you use "commercial" or "canned" models?
  - If not, why not?

- Responses
  - **Very few .. commercial** … we have not found many to be worthwhile.
    - They are usually too black-box for our users to be comfortable and do not correspond to our internal data very *well within a series of related compounds*
  - …some success in using a **published** (as opposed to commercial or canned) model
    - for a particular problem a program was having; in this case, they didn't have enough internal data yet, and so this was a first step to just probe whether it was worth taking the time to measure more compounds and build an internal local model.
  - **No [commercial]** (though we do use Metasite & Derek).
    - Insufficient control over building; quality of data sets, curation etc. Price!

Informal Pharma questionnaire – Q 4 and 5 - 2

- Responses
  - **[no commercial models]** that I'm aware of, but wouldn't surprise me if someone somewhere @ … is using something
    - Actually, there is use of the gastro plus software (and some from MSI). We have another group that deals with .. [PK modeling]. …// Sometimes we used commecial/canned models if the model is more the boundary rather than the data (e.g. egan egg or golden triangle)
  - Simulation-Plus seems pretty good; Derek is a nice entry into the literature
  - **Commercial,** logD, Simulations Plus. [Others ..?] **No**, need more control over data, etc.
  - **Generally not [commercial]** / no competitive advantage
  - **No** / We've tried xxx, yyy, and zzz for CYP and Solubility and found that the performance to be inferior to our internally developed models.

Informal Pharma questionnaire – Q 7

- What ADMET properties have been most successfully modeled?
- Responses
  - **hERG**, **solubility**, **pxr**
  - In general, distribution properties such as **protein binding**, **brain penetration** ... **P450 inhibition**, **hERG** are generally reasonably modelled
    - (though the models do not always work for every specific project!)
  - **Yes/no [qualitative] with most endpoints of interest**
  - Probably **Herg** or **permeability**
  - **CYP inhibition(rev** & irrev), CYP metabolism (all isozymes), **HERG**, CYP induction, **PGP**
  - **logP**
  - **Solubility**, **CYP** activity, **sites of metabolism**

Informal Pharma questionnaire – Q 8

- What ADMET properties are difficult or impossible to model?
- Responses
  - **protein binding**, **metabolic rates**
  - we know very little about where to even start with **toxicity**,
    - and there's an extreme paucity of suitable and sufficient data sets even behind the walls of pharma, much less in the real world.
  - Many in vivo PK parameters and **toxicity/safety** properties (other than listed above).
  - **tox** is the most difficult. but we use alerts (knowldege based)
  - **Quantitative models seem more evasive**
  - **Bioavailability**
  - Where we dont consistently do well is in **Caco permeability**, **BBB** penetration, **solubility**.
  - got my suspicions but won't guess
  - **hERG** (although we've had some success with matched molecular pairs here), anything PK related (CL, t1/2, %F), Tox

Summary of feasibility

Property	Feasible	Difficult
hERG	4	1
Solubility	1	1
Protein binding	1	1
Bioavailability		1
Permeability	1	
Caco		1
BBB	1	1
Cyp	3	
PGP	1	
PXR	1	
logP	1	
Toxicity		4
Metabolic rates	1	1
PK		1

Informal Pharma questionnaire - Q 11

- Has in silico ADME/Tox been transformative in any projects? Have it made clear impact in the progression of drug candidates?
  - No, I don't think it has been transformative. Even so, it **has made a clear impact in the progression of drug candidates** in several projects that I can think of, touching roughly a 1/3 of all projects in the last 4 years or so with 3 notable impacts in the last year. One was a local QSAR model involving tissue distribution, another was a global/local hybrid model of metabolic stability, and the other was a structure-based model of a common liability.
  - As to his final question this depends how you view the word transformative but **certainly in silico ADMET has made clear impact on the progression of candidates** and in particular to focus attention on the important regions of property space thereby eliminating a lot of potentially wasted effort.
  - I know of no such examples.
  - i'm not sure if I can say it's been transformative, the models are one of a number of factors considered during the lead optimization process. **I can think of one case where a local model for protein binding was critical in moving a series forward.**

Informal Pharma questionnaire: Summary

With qualifications and caveats

- (Most) Everyone uses *in silico* ADME / Tox
- Primarily
  - Internal models
  - Internal data
- Some suspicions and discontent with commercial models
- Cautious of literature data
- Global and local models
- Range of users and purposes: different models have different value
- Impact has been demonstrated

Overall summation of the recent literature

- Lots of gratuitous publications that proclaim success
- More complex properties are more difficult
- Something more physically detailed than "statistical" models may be necessary for some properties
  - E.g. Solubility
- "Models"
  - Development of models is easy, even models that have good statistics
  - Predictive accuracy for *your* compounds is more difficult and less precise
- Consensus models leverage advantages of multiple models
- Need more – and more consistent - data

Some interesting recent publications

Consensus models:

Greater Than the Sum of Its Parts: Combining Models for Useful ADMET Prediction, Sean E. O'Brien and Marcel J. de Groot, *J. Med. Chem. 2005, 48, 1287-1291*

Incorporation of priority, uncertainty, sensitivity in multi-dimensional decision making:

Beyond Profiling: Using ADMET models to guide decisions. , M. D. Segall, E. Champness, O. Obrezanova, C. Leeding., *Chemistry and Biodiversity*, 2009, 6, 2144-2151

Successful site of metabolism prediction:

Metabolic Soft Spot Identification and Compound Optimization in Early Discovery Phases, Using MetaSite and LC-MS/MS Validation, Markus Trunzer, Bernard Faller, and Alfred Zimmerlin , *J. Med. Chem. 2009, 52, 329–335*

CYP2C9 Structure-Metabolism Relationships: Substrates, Inhibitors, and Metabolites, Marie M. Ahlstro m,*,†,‡ Marianne Ridderstro m,† and Ismael Zamora, *J. Med. Chem. 2007, 50, 5382-5391*

Nice overview:

Cytochrome P450 in Silico: An Integrative Modeling Approach, Chris de Graaf,Nico P. E. Vermeulen, and K. Anton Feenstra, *Journal of Medicinal Chemistry, 2005, Vol. 48, No. 8*

What to ask/look for in an ADME/Tox prediction

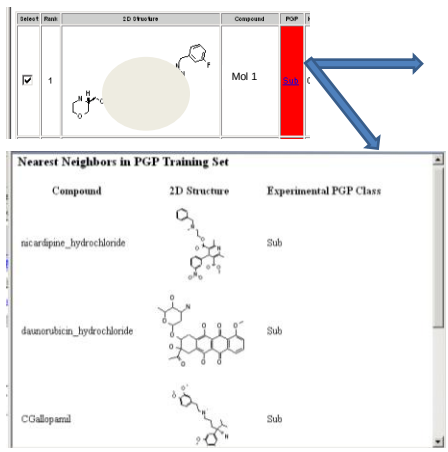
- Source of training set data
  - Is it reliable?
- Evaluation/triage of training set
  - Does the developer understand the data
- Training set compounds
- Experimental endpoint
  - Experimental error
- Prediction endpoint
  - Prediction error
- Comparison of your compound to the training set (Applicability domain)
- Prediction reported with error estimate
- Additional information to guide the interpretation
- Interpretability of the model
- Who are the primary users
- Ask for success stories

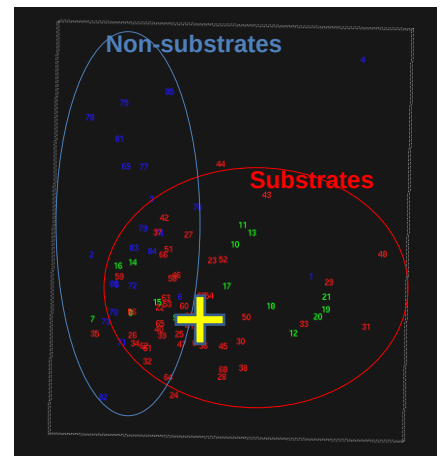
Interpretability

- A model that makes sense is reassuring
  - Physical and chemical properties that can be understood
  - Relative importance of features
- Aids in the next step
  - Properties and features that can be modified
- A cavaet: It might not be possible in complex cases
  - If it works it works!

Additional information: more than a prediction

- Aids in understanding the prediction, its reliability, the problem at hand





Summary

- Progress is being made
  - A factor of 10 accuracy?
  - Still some way to go
  - Varies greatly depending on the property
  - Tox is tough
- Be aware of the use and intent
  - Just because it did (not) work once, does not mean it will (not) work a second time
    - Evaluate more than the prediction
- Applicability to *your* compounds
  - Be aware of level of accuracy
    - Take care with similar "local" compounds with similar values
  - Optimization
    - Local, in-house, data and local models
- Use the check list to evaluate the "model"

Do you have an opinion or success story?

Please send to me for inclusion of an extended compilation:
tstouch@gmail.com

Acknowledgments

- A whole group of anonymous survey takers
- Robert Fraczkiewicz, Simulations-Plus
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- Michael Sinz
- Kenneth Santone

Science for Solutions, LLC

End of presentation

Terry Richard Stouch, PhD

President, Science for Solutions, LLC

Consulting in Drug Design, Pharmaceutical Research, Technologies, Process; Molecular Simulation; Computational Sciences; Structural Biology

–Duquesne University, Adjunct Professor of Chemistry and Biochemistry, Bayer School of Natural and Environmental Sciences,

–The University of Kentucky, Adjunct Professor, Department of Pharmaceutical Sciences, School of Pharmacy

–Senior Editor-in-Chief, Journal of Computer-Aided Molecular Design, Springer Publishing

–Protein Data Bank, Research Collaboratory on Structural Bioinformatics

–AAAS Fellow, IUPAC Fellow

tstouch@gmail.com

1-609-275-7234

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Extra Slides Follow

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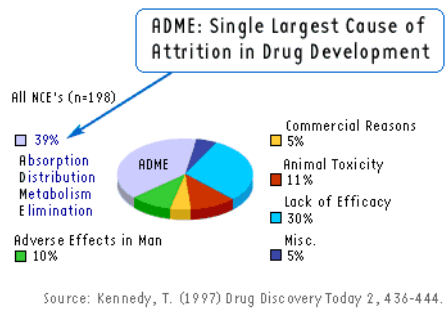
Importance of ADME / Tox

It goes without saying….



Some terms

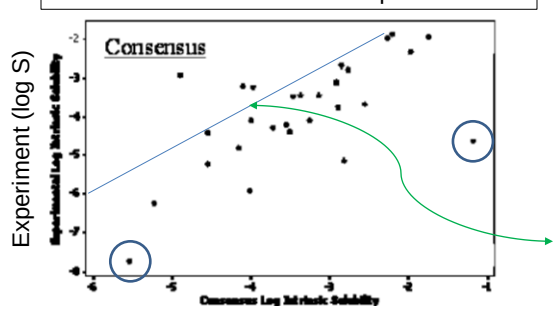
- General vs Local
  - The “universe” of chemistry
    - Or at least “drug” space
  - An analogous series of compounds
    - *Relatively* limited variation
- Public vs “in-house”
  - Open literature or databases
  - *Your* data
    - Although it might not be *consistent* throughout the company
      - Modifications for special cases

What has been *your* experience with *in silico*?

- Has *in silico* ADME / Tox helped your work?
- Has it been transformative?
- Do you think its nonsense?

Solubility results

Best final consensus model predictions



Identity line suggests solubility is over predicted

Current state of the art: logP

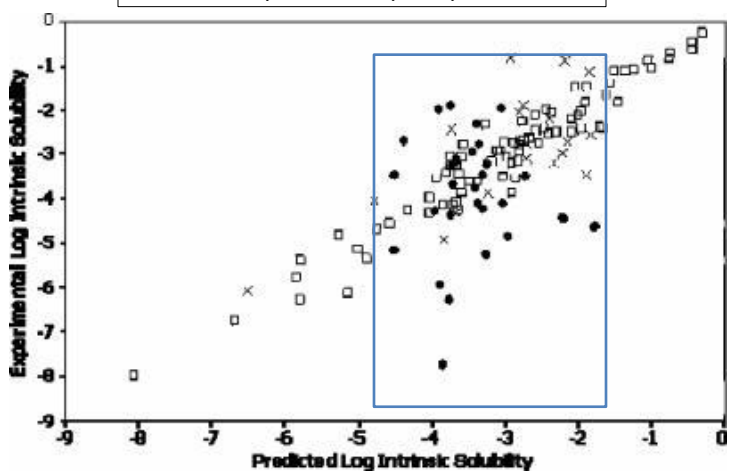
- Accuracy of models declined with the number of nonhydrogen atoms.
- A simple equation based on the number of carbon atoms and the number of hetero atoms, outperformed a large number of [the other] programs
- All models failed to calculate predictive models for molecules with number of non-hydrogen atoms >30–35.

Current state of the art: Solubility

- Conclusions
  - "The results obtained in this study clearly indicate that no one model was able to predict solubility accurately"
  - Predicting aqueous solubility is still a formidable challenge!
  - Probably not a result of inadequate modeling methodologies,
  - Insufficient appreciation for the complexity of the solubility phenomenon

Solubility results

ANN “best practices” model training set with predictions (black)



Today’s points

Abstract:

despite extensive effort in their development, reports on the success of these models has been mixed and range from accounts of great success to some of total failure. Possible reasons for this are

the actual adequacy of the models
the interpretation of their results
the predilection of the user, among others.
In fact, even a "good" model can actually "fail",
a successful model could be perceived to fail depending on interpretation of the results, and a "good" result for one user might be "bad" for another. In this talk, I will expand on and update observations provided in "In silico ADME/Tox: why models fail," T. R. Stouch, et al. J Comput. Aided Mol Des 2003, 17 (2-4), 83. Current best principals practice in model development, model deployment, and model use will be discussed with examples. "Model-independent" paths forward to addressing ADME/Tox will be discussed.

Informal Pharma survey - 1

1. Do you or your company currently use in silico ADME / Tox?
2. Who are the principal users (e.g. Comp Chem Group, Medicinal Chemists, DMPK specialists/experimentalists)?
3. Were/Are the models generated in house?
    1. If so, where did you get the data?
    2. Would you use data drawn from the 'literature'?
    3. If not, why not?
4. Were/Are any of the models "commercial" "canned" models (i.e. from a software vender like Accelrys, Simulations-Plus, or others).
5. Would you use "commercial" or "canned" models?
    1. If not, why not?
6. How are your models deployed? (E.g. Web, individual install, other)?
7. What ADMET properties have been most successfully modeled?
8. What ADMET properties are difficult or impossible to model?
9. Do you use "general" models, "local" models, or both?
10. Do you use your own in-house or commercial software to do your modeling?

Informal Pharma questionnaire - 2

11. Has in silico ADME/Tox been transformative in any projects? Have it made clear impact in the progression of drug candidates?
    1. If so, can you share this information?
12. Do you know of publications or references or case studies where this is the case?

Informal Pharma questionnaire – Q 9

- Do you use "general" models, "local" models, or both?
- Responses:
  - Both
  - Both
    - deploy a bunch of global models, but we have a **semi-strong preference for local** (preferably interpretable) models.
  - Sometimes **both**
    - use statistical methods to try to estimate global 'worthiness' otherwise its a local model
  - both
  - both
  - **Global models don't work** - does not matter where the data comes from If these models do have a Validity Domain estimate attached, then one can at least initially start with a "test" of the model to your local project specific chemical space **Local models** - the predictivity is much better & the applicability is as well.
  - both
  - Both
    - depending on the task, general models tend to work well for library prioritization, while local models can often be useful within a series (when you have sufficient data).

Informal Pharma questionnaire – Q 10

- Do you use your own in-house or commercial software to do your modeling?
- Responses
  - Both
  - Mostly commercial but not just one package. Tend to use expert stats packages rather than general-purpose modelling programs.
  - - depends on the modeler. sometimes R (free), or Matlab (not free), or stuff from volsurf
  - **Mainly Pipeline Pilot**
  - mix of both
  - Mostly in-house, some commercial
  - A mixture, most of our ADME models are home-grown, but we use OpenEye and Schrodinger software for everyday modeling. We've also built a lot software for specific tasks.

Informal Pharma questionnaire – Q6

- How are your models deployed? (E.g. Web, individual install, other)?
- Responses
  - Web, local installations to CADD computers. It depends on the endpoint, speed, and level of automation of the model.
  - largely web
  - all of the above, but mostly accessed by software we wrote internally
  - Both--we prefer web, but this is not always possible.
  - individual install
  - web
  - Models are directly integrated into our electronic lab notebook and into … a modeling platform … for medicinal chemists.

Advice to software developers

- Always leave a data field for error
  - Query user for error on input of data
  - Ask for expected precision
- Supply appropriate significant figures
  - Query user when inappropriate
- Don't "Excel" the data
  - Solubility data of 12.455782 µM !
- Help the user understand their data
  - Value of 24.752 189.293 µM is not helping!

Importance of meta and extenuating data

- Cyp 2C9 inhibition data: triaged by expert
- 25,000 data points in the corporate database
  - 10 years, over 100 drug discovery projects
  - Minus fluorescent complications
  - Minus poor solubility
  - Minus time span where instruments were finicky
  - Minus "difficult" programs
- 5000 reliable data points
  - 4 significant figures in range of 0 – 100%
  - 'Expected' error of 5 – 10%

Expert knowledge

- *In silico* model: 75 – 78% correct prediction of +/- @ 5 uM
  - As good as experiment ! (?)

Importance of meta and extenuating data

- Caco-2 data
  - In house corporate database data not sufficient 'quality' to support *in silico* models – (experimentalist who generated the data)
    - Agreed standards
      - Variable cell lines
      - Too 'high throughput'
  - $2000+ per assay for higher quality from "Lighthouse"
- Solubility
  - High-throughput DMSO precipitation assay, very crude results
    - Essentially shows probability of *insoluble*
  - Reported as molar solubility to 4 significant figures
  - Profiling Governance recommended "red flag"
    - Users protest in favor of 4 significant figures based on "need"
    - Interpreting data based on need
  - Assay discontinued and replaced
    - Now very labor intensive, but much more accurate

The data: do we understand our endpoints?

- What is the known experimental error
  - What sort of error? Experimental, repeated measurements? Multiple trials? Multiple lots
- Precision
- Accuracy
- What was the intent of the data?
- How is the data derived?
- How is the data provided by its originators?
- Do we know where the data came from?
- How do we represent and present our data to end users?
- How do users interpret and use the data?
  - What are their needs?
- Data points could be in error by 10's or 100's of nM
  - Yet people will try to interpret them

- Summary
- Expert Opinion on Drug Metabolism & Toxicology
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- **Structure – ADME relationship: still a long way to go?**
- Tingjun Hou[†1] & Junmei Wang[2] [1]University of California at San Diego, Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, 9500 Gilman Drive, La Jolla, CA 92093-0359, USA +1 858 822 4596; +1 858 822 4236; tingjunhou@hotmail.com
- [2]The University of Texas Southwestern Medical Center, Department of Pharmacology, 5323 Harry Hines Blvd Dallas, TX 75390, USA
- [†]Author for correspondence

Background: Theoretical models for predicting absorption, distribution, metabolism and excretion (ADME) properties play increasingly important roles in support of the drug development process. *Objective*: We briefly review the *in silico* prediction models for three important ADME properties, namely, aqueous solubility, human intestinal absorption, and oral bioavailability. *Methods*: Rather than giving detailed descriptions of the ADME prediction models, we focus on the discussions of the prediction accuracies of the *in silico* models. *Results/conclusion*: We find that the robustness and predictive capability of the ADME models are directly associated with the complexity of the ADME property. For the ADME properties involving complex phenomena, such as bioavailability, the *in silico* models usually cannot give satisfactory predictions. Moreover, the lack of large and high-quality data sets also greatly hinder the reliability of ADME predictions. While considerable progress has been achieved in ADME predictions, many challenges remain to be overcome.