Volume 3 | Pharmaceutical Discovery, Development, and Manufacturing Forum (PD2M)

The PD2M Pipeline

May 2015

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Message from the Chair: Why PD2M?

Paul Collins

Many of you reading this today may have asked the question "Why PD2M? How is this any different than when we were section 15b at AIChE? What was the point of us becoming a forum and what changes as a result of that?"

Good question. I'm glad you asked.

In some ways, having forum status within AIChE doesn't change anything with regard to Annual Meeting programming. The types of sessions you are used to will continue to occur, plus or minus the typical changes commonly associated with trends over the years. So, if Annual Meeting technical session attendance is your primary interest in PD2M/AIChE, indeed you may not notice much difference. However, if you find that your interest in being part of AIChE/PD2M extends beyond the technical sessions each year, I believe you will be quite interested in what forum status offers us. Being a pharmaceutical forum allows for a greater degree of both internal and external influence. It's my goal as Chair the next two years to help us realize that potential.

One thing that certainly differentiates us from other chemical industries represented at AIChE is our tie to regulatory bodies. These groups play an important role in maintaining patient safety, and the guidance coming out of these groups both inform and frame the problem statements for pharma companies and associated academic research groups. Over the past few years, I've gotten to attend meetings associated with a variety of trade groups, and have noticed that many of them have extremely good FDA attendance and interaction – much more than you would find at AIChE. Most of these other venues, while well connected to regulatory agencies, don't have the process and technical expertise you would find at AIChE. AIChE has by far, in my very biased opinion, the strongest technical sessions you will find in pharma development and manufacturing – spanning the gamut from crystallization to modeling to continuous processing to powder flow and beyond. Our strength in these areas should make us THE leader in working toward the adoption of technologically/scientifically improved pharmaceutical processes. But to do that, we need to nurture a better connection to our regulatory partners. This is one area that I commit to working on over the next two years.

While we will approach that goal in multiple ways, one way I'll share here is our creation of an ongoing FDA-AIChE workshop on technology adoption. The focus here is on the word adoption. It's my premise that most scientific meetings focus on the technology alone and far less on the issues blocking/slowing incorporation into the fabric of pharmaceutical manufacturing. Our meeting will focus on that – what are the barriers and how can we use our technical strength to demonstrate feasible paths forward. We've got good momentum on the meeting so far, as the FDA is willing to co-sponsor it, and our steering team incorporates people across academia, industry, and the FDA. While the inaugural meeting won't actually occur until 2016, PD2M will be working this year to make it a success – and hopefully help establish the impact that we as chemical engineers can make on the pharmaceutical industry. Stay tuned – we are going to do big things!

Modeling and Simulation: Are you only as good as your last DOE?

Joe Hannon

From the DynoChem team at Scale-up Systems. In this edition, we take aim at application of statistical design of experiments to chemical reactions.

We focus below on the types of DOE that are used to optimize reaction conditions (continuous variables) or assess process robustness, once solvent and reagent selection are fixed.

Q: What lab-based activities are essential to understand, design and optimise chemical reaction systems, but are sometimes used as a substitute for thinking?

A: Experiments

Q: Who adopts this latter approach?

A: Those who believe that their system is too complex to understand or predict

Q: Are they correct?

A: Usually, No

Q: Using what terms might such practitioners refer to a difficult chemical reaction?

A: Stubborn

Q: Does the reaction in fact have human traits?

A: No

Q: How many experiments might these practitioners use to design a chemical reaction system?

A: A lot of them

Q: When conducted in groups with impressive sounding names like 'central composite', without any proposed hypothesis or explanation, how may these experiments be described?

A: Designed, as in 'DOE

Q: How does an experimenter appear to colleagues when running a DOE?

A: Busy, productive

Q: What mathematical assumptions does a DOE make about reality?

A: That reality is linear, or at best quadratic

Q: Are the designed experiments suitable for elucidating or dissecting the reaction mechanism?

A: No; the factor variations, heat-ups, multiple phases and inadequate sampling will make this impossible in most cases

Q: What does running a DOE enable users to do?

A: Interpolate between results obtained during the DOE

Q: What does running a DOE not enable users to do?

A: Extrapolate the results outside the range covered by the DOE

Q: Can the results of a typical DOE be used to predict scale-up?

A: No. In fact, the DOE may need to be repeated again at every scale

Q: What may arise if the results are reviewed and the design interrupted before the end of the DOE?

A: An opportunity to redesign the remaining experiments to produce knowledge and understanding

Q: Is there a better method for reaction development and scale-up than DOE?

A: Yes

Q: By what name is this method known?

A: The Scientific

Q: What are the essential components when applied to chemical reactions?

A: Experiments alongside development of a mechanistic / kinetic model, each influencing and helping to design the other

Q: Tell us more

A: See the next edition of PD2M

This edition of PD2M is intended to be thought-provoking. With that in mind, we adopted the question and answer style of Myles Copaleen (aka Flann O Brien), the celebrated Irish author who took aim at the over-use of clichés in the vernacular of his day.

Discovery: Identifying Therapeutic Targets using Mathematical Models of Metabolic and Signal Transduction Networks

Jeffrey Varner

Despite early promise and many example models in the literature, computational systems biology has yet to fundamentally impact the development of new therapies for cancer, cardiovascular diseases, or the treatment of acute events like thrombosis during surgery (1). Biological model uncertainty, reticence on the part of biologists to embrace mathematical modeling, and perhaps most significantly lack of understanding of the biological processes at play in complex disease such as cancer have all been cited as issues restraining progress
(2-3). However, as the field of systems biology and biological network modeling matures, new developments in how we model biology, as well as our ability to experimentally interrogate disease systems, could allow us to make good on the earlier promises of systems biology.

Simulating complex diseases such as cancer requires much more than isolated models of gene expression or signal transduction processes. Rather, it requires holistic multiscale approaches which integrate molecular signaling with changing environmental cues (4). Unfortunately, such holistic approaches quickly become infeasible. Thus, one of the most promising recent developments has been the reemergence of effective or logical models of biological networks. Small yet predictive network models could be integrated with multiscale tools to give more predictive multiscale simulations. Gene expression models based upon boolean logic have been prevalent in the developmental biology community for nearly twenty years (5). Boolean logic has also effectively captured metabolic regulation in constraints based metabolic models (6). Other promising approaches to limit model complexity such as data-driven systems approaches (7,8) or logical model formulations such as contained fuzzy logic (9,10) are also emerging paradigms that constrain model complexity by data availability. Another promising approach is the use of model ensembles. Sethna and coworkers showed that complex model behavior is often controlled by only a few parameter combinations, a characteristic seemingly universal to multi-parameter models referred to as sloppiness (11). Thus, reasonable model predictions are often possible with only limited parameter information using potentially uncertain models. Model ensembles have been interrogated using tools such as sensitivity or robustness analysis (12,13) to estimate fragile or robust network components that also reflect cell-to-cell (14,15) or even patient-to-patient heterogeneity (16).

The rapid advancement of experimental techniques have also closed the gap between the promise and reality of computational systems biology. Next generation sequencing technologies have enabled an unprecedented view of the genetic basis of many cancers including pancreatic, and breast cancers (17,18). RNA-sequencing (RNA-seq) methods are also greatly expanding our knowledge of the dynamic nature of the transcriptome, including the regulatory role of small RNAs (19). High-throughput upgrades to traditional biochemical methods, such as microwestern arrays, have enabled the quantitative assessment of protein abundance and modifications for tens or perhaps even hundreds of proteins in the future (20). At the metabolite level, new *in-situ* Forster Resonance Energy Transfer (FRET)-based sensor technologies are changing the way we interrogate cellular metabolism, and especially our knowledge of critical metabolites such as Lactate (21). Taken together, advancements in experimental measurement technologies will be critical to our understanding of the origins of complex diseases such as cancer, as well as to our ability to construct and validate better mathematical models.

See Appendix for References

Regulatory and Manufacturing

John Lepore, Kevin Seibert, Tim Watson

In July, the FDA published a snapshot of their thinking on quality by design (QbD), along with a host of other regulatory items[1]. This article also discussed the Question Based Review (QBR), and how the FDA plans to improve on the consistency of regulatory review by implementing this approach for all applications and standardizing the review process. On a related note, the FDA has implemented its long predicted reorganization into the Office of Pharmaceutical Quality, and we all are anxious to see how the new single standard review process is realized.

At the International Conference of Harmonization (ICH) in November, it seems that ICH Q7 Q&A, providing clarification of uncertainties due to the interpretation of certain sections, is progressing towards completion, with an additional Q&A document in the planning stages for ICH Q11. It is also intended to progress a new guidance (Q12) on lifecycle management.

Lastly, the European Medicines Agency has recently published a guideline on expectations for formal risk assessments to be employed for the selection of excipients for medicinal products. While much of this guidance is related to good manufacturing practice considerations, there is a subset that sets expectations for considering the intersection of excipient properties with form and function of the active ingredients.

As many of you have seen, a request for abstracts for the AIChE 2015 Annual Meeting has been sent out, and we are hopeful that many readers will have ideas to contribute. Other forums presenting good opportunities for regulator-industry interaction include the DIA Annual Meeting in June and Pacifichem in December, representing a joint meeting of chemical societies based in Pacific Rim countries. Presentation opportunities for the latter are still available; see www.pacifichem.org for further information.

As before, we'd like to reach out to the PD2M community with an open invitation to provide analysis or opinion on various regulatory topics. If there is a topic that you would like to contribute to, or hear something about, please contact the PD2M newsletter staff. Diversity of input will maximize the value for everyone. Until next time!

See Appendix for References

Consortia Update: Precompetitive Collaboration

Steve Baric

"Precompetitive collaboration is not a new concept. It's happening, and it delivers results. So the real question is how can we make that happen on a larger scale?"

- Stephen Eck, *Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Product Development*, 2011

Precompetitive collaboration was certainly not a new concept in 2011 when Stephen Eck, then of Eli Lilly, wrote those words. But what was once an interesting concept primarily driven by academic institutions looking for additional research funding and vendors looking for a partner to help them develop the next breakthrough instrument has gained new interest for the pharmaceutical industry. This is reflected in the growing number of groups and consortiums established to support these pharmaceutical industry collaborations. The imperatives driving pharmaceutical companies into these collaborations include (a) internal R&D pressures to deliver new drugs more efficiently, (b) looming patent cliffs on many top-selling drugs, (c) the rising cost of safety and efficacy requirements brought on by regulatory hurdles and (d) the fact that pharmaceutical R&D continues to be a long, expensive process with a tremendous amount of associated risk.

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AIChE and PD2M members recognize the potential in precompetitive collaboration opportunities and the value to the pharmaceutical community. A key session at last November's annual AIChE meeting in Atlanta, GA was on *Pre-Competitive Collaborations in the Pharmaceutical Industry: Perspective and Opportunities*.

The strong attendance and participation at this session, Chaired by Jean Tom (BMS) and Joe Hannon (Scale-Up Systems), reflected the level of interest in the pre-competitive collaboration space and the diversity of approaches. Speakers included:

- Brian Glennon and Jon O'Halloran from SSPC
- Srinivas Tummala, Kevin Seibert and Margaret Faul from IQ Consortium
- Andreas Bommarius from the Center for Pharmaceutical Development (CPD)
- Joel Hawkins, Daniel Hallow and Leen Schellekens showcasing and industrial/vendor collaboration

A core challenge of precompetitive collaboration is balancing each party's interests and assets with the advantages possible from collaboration. This is where independent organizations can play a key role in fostering, facilitating and nurturing collaboration, helping to ensure the benefits to all involved while also helping to protect the interests (and IP) of all involved.

The IQ Consortium, a pharmaceutical and biotechnology association which aims to advance innovation and quality in the biopharmaceutical industry, is familiar to many of the PD2M members. One of IQ's working groups is focused around understanding the precompetitive collaboration opportunities available to its member companies.

The IQ Consortium defines precompetitive collaboration as one (a) between two or more pharmaceutical companies, potentially including academics, government agencies or vendors which (b) is designed to produce an efficiency-enhancing advancement or refinement that will be made broadly available to the public, either thru publication, commercialization of a new product, or other means and (c) in which the pharmaceutical companies will retain no proprietary interest.

IQ has made a lot of progress towards establishing an acceptable framework for it's member companies, including (1) establishing what falls into the pre-competitive category, (2) identifying 5 areas of initial focus including Automation, PAT, Modeling, Crystallization and Flow Chemistry, (3) defining an acceptable operating model (i.e. "honest broker") to facilitate efficient collaborations and (4) proposing a number of working groups to address areas of collaboration to gain the small wins and deliver initial results quickly.

While the IQ Consortium is defining a set of best practices to assist in the pre-competitive collaboration, universities and other organizations are also taking advantage of the opportunities to change traditional practices.

Many of the organizations below pre-date the important work that the IQ Consortium is doing and represent early pre-competitive models that have driven innovation in a broad range of related fields. While some of the areas of focus may be outside the core interest of our PD2M members they are nonetheless related and may be worth further investigation.

Allotrope Foundation (www.allotrope.org)

Allotrope Foundation is an international association of pharmaceutical and biotech companies dedicated to the building of a "Laboratory Framework" to improve efficiency in data acquisition, archiving, and management.

NOTE: Collaboration in the knowledge management space appears to be an area of unaddressed opportunity and one that PD2M would like feedback from it's members on whether this is a candidate for a precompetitive collaboration.

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The software environment currently found in the analytical community consists of a patchwork of incompatible software, proprietary and non-standardized file formats, which is further complicated by incomplete, inconsistent and potentially inaccurate metadata that results from an overreliance on manual text entry. This pathology leads to a wide array of downstream symptoms that affect the analytical community, worldwide.

The Mission of Allotrope Foundation is to address the root cause of this "disease" instead of just treating the symptoms through an array of helper applications, data conversion projects, local standardization efforts of varying effectiveness, such as is done today. We believe the "cure" to the "disease" is the development of a comprehensive and innovative Framework consisting of metadata dictionaries, data standards, and class libraries for managing analytical data throughout its lifecycle. To accomplish this mission, Allotrope Foundation is working to create an open "ecosystem" through collaboration and consultation with vendors and the analytical community.

Allotrope Foundation is a member driven organization, funded by Pharmaceutical companies and driven by subject matter experts from the funding companies. Allotrope Foundation has partnered with an independent software contractor to develop the Framework.

CMAC – Continuous Manufacturing and Crystallization

(http://www.strath.ac.uk/tic/cmaccontinuousmanufacturingandcrystallisation)

As part of the Technology and Innovation Centre at the University of Strathclyde, the CMAC vision is to accelerate the adoption of continuous manufacturing and crystallization processes, systems and plants for the production of high-value chemical products; improving their quality at lower costs, more quickly and sustainably. The aim is to create an effective partnership with industry, academia and public bodies.

The physical hub is at Strathclyde University with Glasgow, Heriot-Watt, Edinburgh, Cambridge, Loughborough and Bath Universities contributing to an exceptional multi-disciplinary academic team.

From initial funding from Scottish Funding Council more than £28m has been raised from various sources. The key research platform is the EPRSC National Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization, with a vision to accelerate the adoption of continuous manufacturing processes, systems and plants for the production of high-value chemical products to higher quality, at lower cost and more sustainably.

CPAC – Center for Process Analysis & Control (http://cpac.apl.washington.edu)

CPAC, established at the University of Washington in 1984, is a consortium of Industrial, National Laboratory and Government Agency Sponsors addressing multidisciplinary challenges in Process Analytical Technology (PAT) and Process Control through fundamental and directed academic research.

CPAC's core areas of research are focused on: Chemometrics & Process Control Algorithms, Sensors, Spectroscopy/Imaging, Chromatography, Continuous Flow Chemistry and Analysis, and Process Control.

CPAC is a multidisciplinary team of faculty, research staff, visiting scientists, and graduate students from a selection of universities. Presently, CPAC is supporting research projects across a number of academic disciplines including: chemistry, electrical engi-

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neering, chemical engineering, forest resources, health sciences/genetics, food science, and mechanical engineering at selected universities including: University of Delaware, University of Maine, University of Minnesota, University of California at Davis, and the University of Washington. CPAC is also conducting collaborative research with several research institutes, including: the Norwegian Food Research Institute (MATFORSK), Instituto di Chimica, Pisa, Italy. Universities are selected according to technologies of interest to sponsors and how they enhance the CPAC technology programs.

SSPC – The Synthesis and Solid State Pharmaceutical Centre (http://www.sspc.ie)

The Synthesis and Solid State Pharmaceutical Centre (SSPC), a Global Hub of Pharmaceutical Process Innovation and Advanced Manufacturing, funded by Science Foundation Ireland and industry, is a unique collaboration between 22 industry partners, 9 research performing organizations and 12 international academic collaborators.

The SSPC research program aims to deliver relevant solutions that address the manufacturing needs of the pharmaceutical industry and in-turn lead next generation drug manufacture.

The SSPC builds upon the success and foundations of the Solid State Pharmaceutical Cluster (2007-2013), which was funded by Science Foundation Ireland's Strategic Research Cluster program. The Solid State Pharmaceutical Cluster research program focused exclusively upon the crystallization stage of the manufacturing process. Within the pharmaceutical industry, this stage is the most challenging aspect of manufacturing, as there is a significant lack of fundamental understanding of the science and engineering challenges at this stage of the process.

The SSPC research program now spans the entire pharmaceutical production chain from synthesis of the molecule, to the isolation of the material, and the formulation of the medicine.

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If you have any questions or would like to contribute to the newsletter—email viswanathsh@lilly.com

Find us at: http://www.aiche.org/community/sites/divisions-forums/pharmaceutical-discovery-development-and-manufacturing-forum-pd2m/newsletters

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American Institute of Chemical Engineers

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Discovery: Identifying Therapeutic Targets using Mathematical Models of Metabolic and Signal Transduction Networks

Jeffrey Varner

1. Kitano H (2002) Computational systems biology. Nature 420:206 - 210
2. Sainani, K. (2012), Biomedical Computation Review. Published by Simbios, the NIH National Center for Physics-Based Simulation of Biological Structures, Summer 2012 (available at: http://biomedicalcomputationreview.org/content/meet-skeptics-why-some-doubt-biomedical-models-and-what-it-takes-win-them-over-0)
3. Janes KA, Lauffenburger DA (2013) Models of signalling networks – what cell biologists can gain from them and give to them. J. of Cell Sci 126:1913–1921
4. Chakrabarti A, Verbridge S, Stroock AD, Fischbach C and J. Varner (2012) Multiscale models of breast cancer progression. Ann Biomed Eng., 40:2488 - 2500
5. Yuh CH, Bolouri H, Davidson EH (1998) Genomic cis-regulatory logic: experimental and computational analysis of a sea urchin gene. Science 279:1896-902
6. Covert MW, Xiao N, Chen T, Karr J (2008) Integrating metabolic, transcriptional regulatory and signal transduction models in Escherichia coli. Bioinformatics 24:2044-50
7. Janes KA et al. (2005) A Systems Model of Signaling Identifies a Molecular Basis Set for Cytokine-Induced Apoptosis. Science 310:1646 - 1653
8. Cirit M, Haugh JM (2012) Data-driven modeling of receptor tyrosine kinase signaling networks quantifies receptor-specific potencies of PI3K- and RAS-dependent ERK activation. Biochem J 441: 77-85
9. Saez-Rodriguez J et al. (2009) Discrete logic modelling as a means to link protein signalling networks with functional analysis of mammalian signal transduction. Mol. Sys. Biol. 5:331
10. Morris MK, Saez-Rodriguez J, Clarke DC, Sorger PK, Lauffenburger DA (2011) Training signaling pathway maps to biochemical data with constrained fuzzy logic: quantitative analysis of liver cell responses to inflammatory stimuli. PLoS Comput Biol 7: e1001099

11. Machta BB, Chachra R, Transtrum MK, Sethna JP (2013) Parameter space compression underlies emergent theories and predictive models. Science 342: 604-7

12. Stelling J, Gilles ED, Doyle FJ (2004) Robustness properties of circadian clock architectures. Proc. Natl. Acad. Sci. 101:13210–13215

13. Tasseff R, Nayak S, Song SO, Yen A, Varner JD (2011) Modeling and analysis of retinoic acid induced differentiation of uncommitted precursor cells. Integr Biol (Camb) 3: 578–591

14. Lequieu J, Chakrabarti A, Nayak S, Varner JD (2011) Computational modeling and analysis of insulin induced eukaryotic translation initiation. PLoS Comput Biol 7: e1002263

15. Creixell P, Schoof EM, Erler JT, Linding R (2012) Navigating cancer network attractors for tumor-specific therapy. Nat Biotechnol 30: 842-8

16. Luan D, Szlam F, Tanaka KA, Barie PS, Varner JD (2010) Ensembles of uncertain mathematical models can identify network response to therapeutic interventions. Mol Biosyst 6: 2272-86

17. Jones S et al. (2008) Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses. Science 321:1801 - 1806

18. The Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumours. Nature 490:61-70

19. Wang Z, Gerstein M, Snyder M (2009). RNA-Seq: a revolutionary tool for transcriptomics. Nat Rev. Genetics, 10:57–63

20. Ciaccio MF et al. (2010) Systems analysis of eGF receptor signaling dynamics with microwestern arrays Nat. Meth 7:148 - 155

21. San Martın A, Ceballo S, Ruminot I, Lerchundi R, Frommer WB, et al. (2013) A Genetically Encoded FRET Lactate Sensor and Its Use To Detect the Warburg Effect in Single Cancer Cells. PLoS ONE 8(2): e57712. doi:10.1371/journal.pone.0057712

Regulatory and Manufacturing

John Lepore, Kevin Seibert, Tim Watson

[1] The AAPS Journal, Vol 16, No. 4, pp.771-783 (July 2014)