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Current Opinion in Chemical Engineering

Opportunities and challenges for model utilization in the biopharmaceutical industry: current versus future state

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Processes and manufacturing in the biopharmaceutical industry are mainly based on experimental data and statistical approaches, however, regulatory expectations of increasing understanding and insights into methods behind medicinal products have paved the way for employment of more mechanistic and first principle modeling tools and concepts. Current, advanced modeling tools can basically be divided into four groups: biophysical modeling, mechanistic modeling, computational fluid dynamics, and plant modeling. Although very useful in themselves, the first three modeling concepts may also be used to establish better plant models, where digital twins of manufacturing plants are pursued broadly in the industry. This review presents the current development stage, opportunities, and challenges of the four modeling tools, and activities needed to reach future state of modeling or '*in silico* CMC' (Chemistry, Manufacturing and Controls), a state where modeling, based either on first principles or hybrid approaches combining both empirical and mechanistic approaches, can be routinely employed in lieu of solely empirical or experimental approaches. It builds largely on presentations and discussions at the recent 4th Mini Modeling Workshop from May 25, 2021.

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Current Opinion in Chemical Engineering 2022, **36**:100813

This review comes from a themed issue on **Separations engineering (2021): downstream bioprocessing**

Edited by **Scott Husson** and **Abrham M Lenhoff**

For complete overview of the section, please refer to the article collection, "Separations engineering (2021): downstream bioprocessing"

Available online 15th March 2022

https://doi.org/10.1016/j.coche.2022.100813

Introduction

Modeling tools are increasingly employed in the biopharmaceutical industry to improve and control manufacturing processes with increasing application of chemical engineering approaches [1••,2•]. The models and tools have been developed in academia over the last 100 years [3] and leverage significant advancements in other disciplines including computational chemistry [4] the utility of which is fully recognized (e.g. Nobel Prize for Computational Chemistry in 2013) with the application to complex biomolecular systems and biophysical interactions. Despite the specific investments by academic researchers who laid the first principles foundations for these efforts [5–8], the maturity of these tools have not until recently matched industry expectations/requirements for implementation. However, with the introduction of high-throughput screening (HTS) techniques, increased computational power, and sufficient understanding of the benefits provided by these modeling approaches, implementation has increased in the last decade. Part of the challenge in application of these tools was the perception that the systems were merely too complex. This paper shows, it should be feasible, although challenging, to derive and apply appropriate models for bioprocessing systems. We also list the gaps remaining to apply models to these systems. The adoption of modeling approaches; translated and referred to as digital twins; has increased due to industry 4.0. Emerging from this adoption is not a 'one size fits all' definition of a digital twin but rather a land scape view, product, process, production, and performance (Siemens Digital

Table 1

4th Mini Modeling Workshop	
Biophysics session	
Chairs: Francis Insaidoo, MSD; John Welsh, MSD	
Sean Burgess, Genentech	Using quantitative structure property relationships to predict monoclonal antibody binding properties
David Saleh, BI	Modeling the impact of amino acid substitution in a monoclonal antibody on cation exchange chromatography
Armenio Barbosa, University NUOVA Lisbon	Molecular details of *de Novo* designed affinity-adsorbents
Biophysics breakout session	
Moderators	John Welsh, MSD; Steve Cramer, RPI
Panelist	Lijuan Li, Takeda
Mechanistic modeling — downstream session	
Chairs: Shuchi Yamamoto, Yamaguchi University; Felix Wittkopp, Roche	
Giorgio Carta, University of Virginia	Modeling the chromatographic behavior of conformationally flexible Multidomain proteins
Christian Frech, University of Applied Sciences Mannheim	Modeling and simulation of antibody elution behavior under high load conditions in cation exchange chromatography by using a modified SMA isotherm
Yinying Tao, Eli Lily & Company	Predictive modeling for TFF process development in high concentration self-buffering formulations
Mechanistic modeling — upstream session	
Chairs: Arne Staby, Novo Nordisk; Jan Griesbach, Roche	
Shantanu Banerjee, IIT Delhi	Mechanistic modeling of continuous clarification of Chinese Hamster Ovary (CHO) cells Using Acoustic Wave Separation Technology
Katrin Paul, Novartis	FBA-Based Process Optimization by Decreasing Ammonia Accumulation
Thomas Wucherpfennig, BI	Computational models for bioreactors and cultivation processes in biologicals Development: Stirred, not Shaken!
Mechanistic modeling — breakout session	
Moderators	Felix Wittkopp, Roche; Jan Griesbach, Roche
Panelists	Isabell Hagemann, Bayer AG Gang Wang, Boehringer-Ingelheim Juliane Diedrich, Amgen Research Emmanouil Papadakis, Novo Nordisk
Plant modeling session	
Chairs: Deenesh Kavi Babi, Novo Nordisk; Bob Todd, KBI Biopharma	
Christos T. Maravelias, Princeton University	Batch production scheduling: methods and applications
Lijuan Li, Takeda	Driving strategic decisions making for cost reduction and manufacturability through process economic modeling
Johann Kaiser, Novo Nordisk	A multi-scale approach for monoclonal antibody (mAb) process modeling
Plant modeling breakout session	
Moderators	Suzanne Farid, University College London Deenesh Kavi Babi, Novo Nordisk Arne Staby, Novo Nordisk
Computational fluid dynamics section	
Chair: Steven Hunt, Allogene	
Ross Kenyon, Regeneron Pharmaceuticals	A combined computational and data-driven approach to accelerate drug Product mixing parameter development
Abraham Lenhoff, University of Delaware	Scale-down of precipitation: CFD, population balance models and experiment
Ignacio Montes Serrano, Austrian Centre of Biotechnology	CFD simulations for the hydrodynamic characterization of microtiter plates for the development of a scale-up strategy of downstream processes based on volumetric power input
Computational fluid dynamics breakout session	
Chairs	Abraham Lenhoff, University of Delaware; Bob Todd, KBI Biopharma
Panelists	Eric von Lieres, Research Center Jülich Andrew Zydney, Penn State University
Open challenges session	
Chairs: David Roush, MSD; John Welsh, MSD	
Maximilian Krippl, University of Natural Resources and Life Sciences, Vienna	Increasing efficiencies in bioprocess development and manufacturing through digital process development
Johannes Schmölder, Research Center Jülich	Towards integrated process chain simulation in biotechnology
Sofia Nunes, University College London	A novel approach to quantify floc growth and strength for robust primary recovery operations
Open challenges breakout session	
Moderators	David Roush, MSD; Giorgio Carta, University of Virginia
Panelists	Bernt Nilsson, Lund University Todd Przybycien, Rensselaer Polytechnic Institute

Industries Software: Digital Twin. https://www.plm.automation.siemens.com/global/en/our-story/glossary/digital-twin/24465). Generically, a digital twin therefore can be defined as a virtual, cyber-physical system (product, process, production and/or performance) to be used for moving from a current to improved-optimized future state by testing ideas via modeling and simulation.

A thorough assessment of the current state of the broad range of modeling activities to support biologics development and production was obtained during Recovery of Biological Products 4th Mini Modeling Workshop (4MMW) held virtually on 25 May 2021. A total of 127 participants representing 58 diverse academic (21) and industrial (37) institutions contributed to the discussions. The workshop focused on key areas of modeling that have direct relevance to challenges faced in the industry and provided a forum for connecting leading academic researchers with industrial researchers and suppliers. The four main topics included Biophysics, Mechanistic Modeling (Upstream and Downstream), Plant Modeling, and Computational Fluid Dynamics provided in separate sections below, as well as a session for Open Challenges (key areas/technical challenges for future development). The workshop program, contributors and chairs are listed in Table 1. The publication from the 3rd Modeling Workshop [1••] was the substrate to initiate the discussions at 4MMW and to be used as a reference point for assessing progress in the modeling space combined with general trends and developments in the field. A summary of the current progress versus the gaps identified at the 3rd Modeling Workshop is presented in Figure 1. Advances in implementation over the last two years have mainly occurred within the biophysics, mechanistic, and plant modeling areas, and cover elements like, for example, candidate selection support, models for communication with health authorities, and commissioning of plant changes, respectively. Workshop participant survey results are provided in Figure 2. In general, survey respondents viewed later stages of development as requiring more significant research to implement although some are sufficiently mature for commercial use (e.g. Computational Fluid Dynamics, Plant Modeling, Downstream Mechanistic Modeling), whereas modeling in early stages is more ready for deployment. One interesting observation was that the most survey participants identified the red bar (gaps limiting deployment) as the main level of maturity.

The proposed and emerging viewpoint of digital twins for manufacturing development is presented in Figure 3a and b. These show how different scales are connected based on competing complexities and how these are selected based on three main properties, purpose, complexity, and maturity, respectively. One key point from the analyses summarized in Figure 3 is that the computational areas that are sufficiently mature for commercial utilization which begs the question as to what are the impediments to overcome to achieve broad industry adoption? The figure provides an assessment of the current state of investment in the various modeling areas to address the required gaps and support broader implementation.

Model utilization in the biopharmaceutical industry

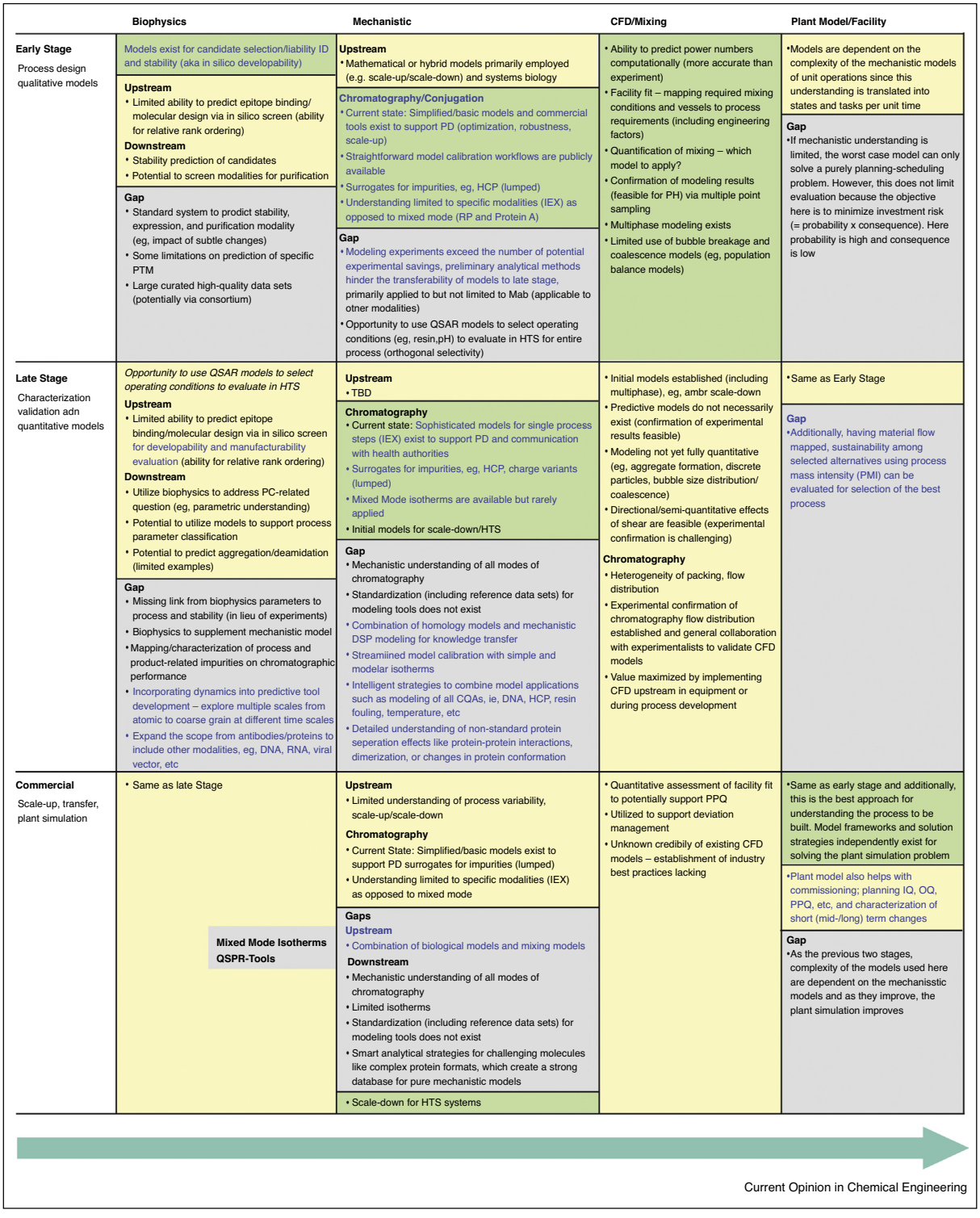
Biophysics

Biophysical modeling has the potential to utilize the biophysical properties of proteins and ligands to direct biologics design, development, and manufacturing. Currently, there are several tools commercially available that can be used to calculate biophysical properties of molecules, (CCG-MOE [9] and Schrödinger [10]). In the instance where no known homologous structure is available to be used as a template to build the structure of a new protein sequence, new tools are in development to build or predict atomic detailed structure of proteins using ML and AI, for example, AlphaFold from Google [11]. Novel molecular properties and descriptors are constantly in development in industry, academia, and other joint collaborations [12•]. Models exist that correlate these biophysical properties to process conditions [5,13]. However, these models tend to be limited in scope and are typically not broadly applicable. Linking molecular properties and descriptors to process related conditions in a way that is not therapeutic molecule specific and modality agnostic is an area that is currently underdeveloped (Figure 1).

An active area of research is the use of QSAR-based models to build predictive properties of monoclonal antibodies. The general assumption in these studies is to identify molecular properties that correlate to experimentally determined values [5,13]. A significant challenge in this approach is the type of structure properties used and how broadly applicable they are to other molecules that are not part of the training set. One practical way to correlate molecular properties to process outcome is to investigate the impact of amino acid substitution on process performance, for example, chromatographic separations. By perturbing the molecular properties of a given molecule and testing under standardized conditions, a better understanding of process development will emerge. However, if these activities are not coupled with a better understanding of ligand properties and effective ligand design, a comprehensive knowledge will not be attained. If a better understanding of ligand properties and linker chemistries is attained, predictive models can extend between chromatographic modalities.

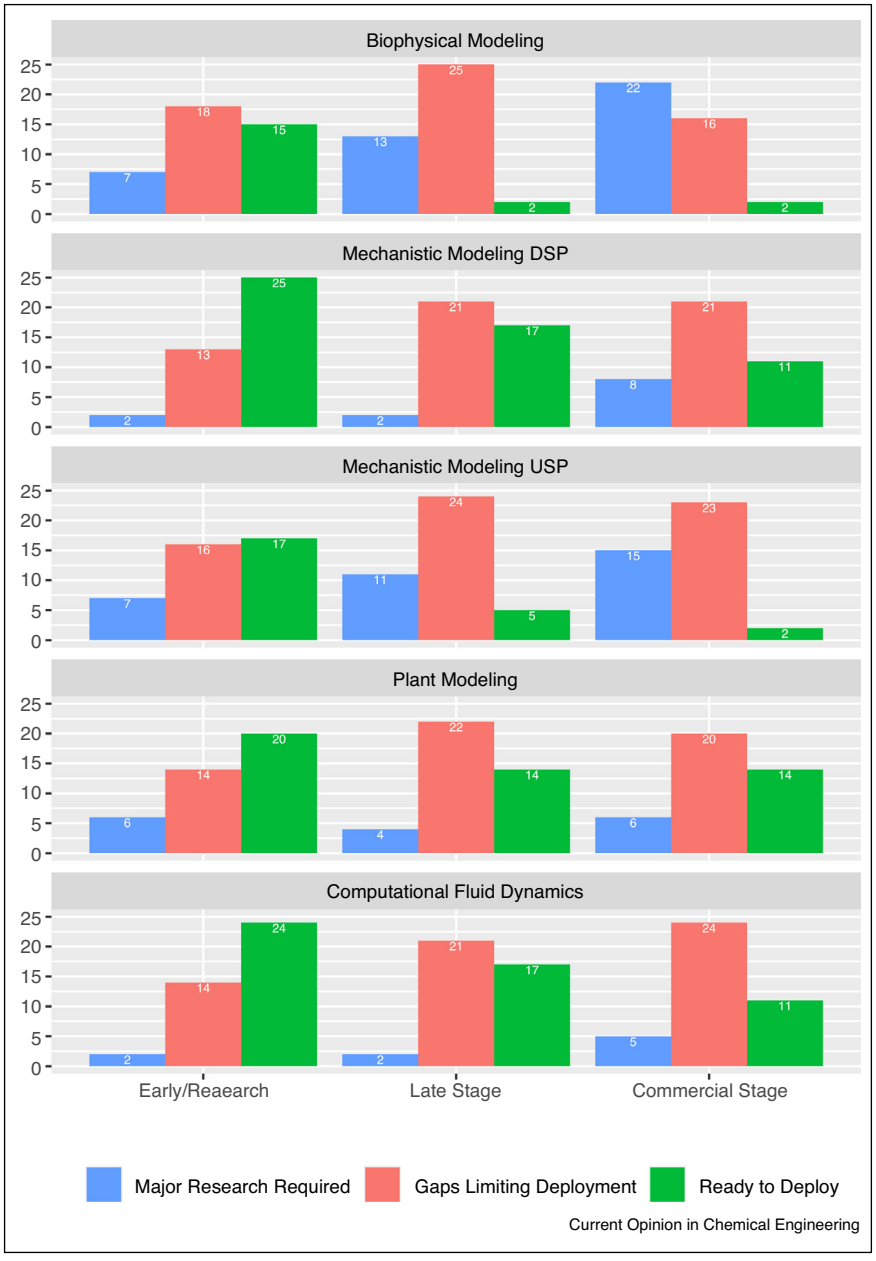
A general limitation of a robust and broadly applicable biophysical model for biologics process development is the limited data set available for model building. A

Figure 1



Current state and gaps to achieve future state of *in silico* application of modeling concepts in industry. Green: models are sufficiently developed to support implementation now. Yellow: gaps identified that require modest investments to address before implementation (2–5 years). Gray: opportunities for exploration or significant gaps required to achieve realization (5–10 years) or may not be scientifically feasible (initial assessment required). Early stage indicates models appropriate for supporting first-in-human studies or developmental studies. Late stage indicates quantitative models potentially applicable for licensing applications. Blue text indicates advances in modeling implementation in the last two years [1••].

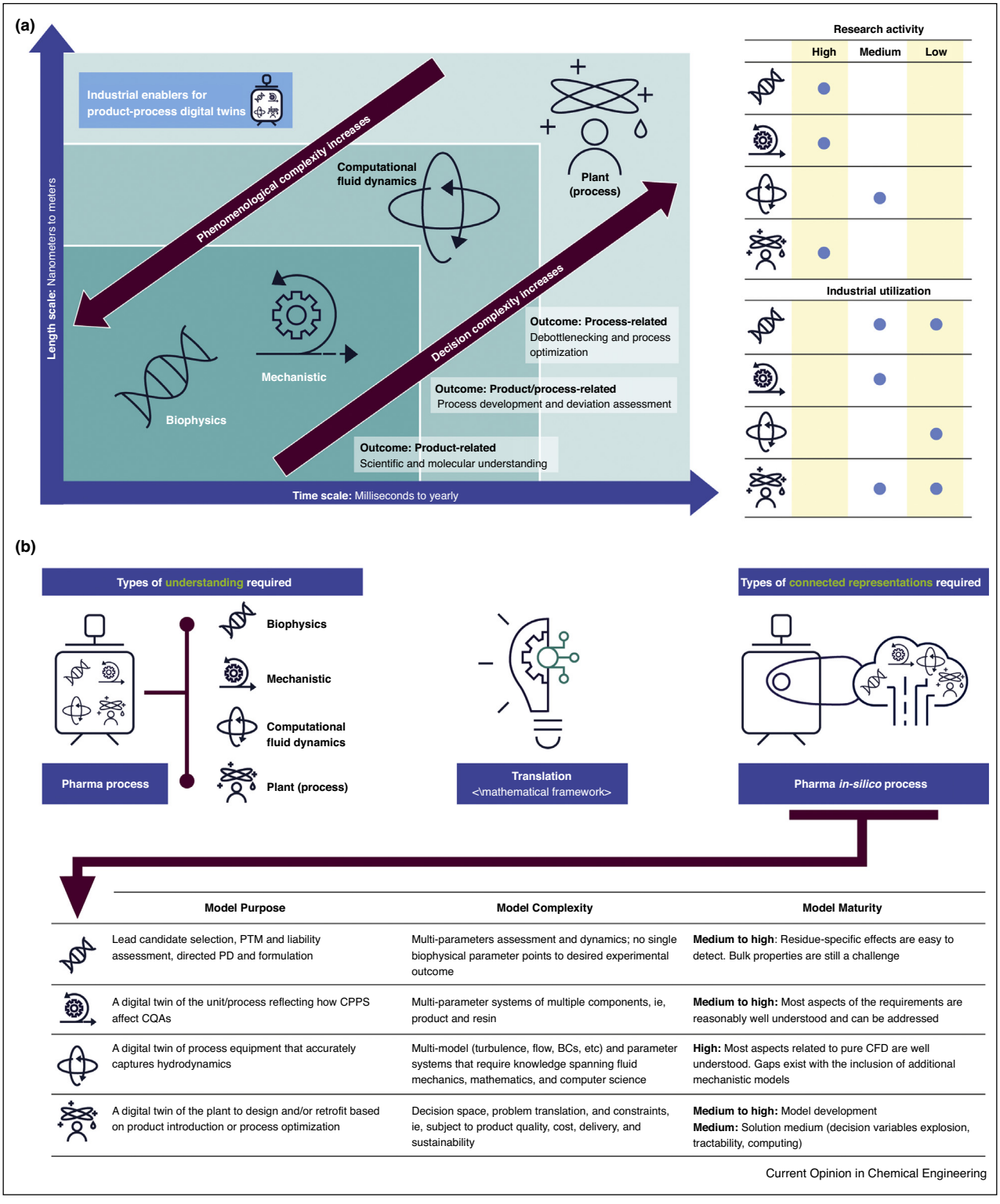
Figure 2



Workshop participant survey indicating the current maturity level of Biophysical Modeling, Mechanistic Modeling (USP and DSP), Plant Modeling, and Computational Fluid Dynamics for Research/Early Stage Development, Late Stage Development, and Commercial Stage. Maturity level is scored by three levels: Major Research Required (5–10 years), Gaps Limiting Deployment (2–5 years), or Ready to Deploy. The y-axis depicts the number of survey respondents that indicated the given stage of deployment in each category.

general rule of thumb is to ensure that the training set should be as diverse as the potential application space. Another layer of complexity is the types of molecular descriptors and how accurately they describe the molecules and processes to be predicted. A more informative set of descriptors emerge as the number of experimental observations increase. Novel concepts like protein and ligand dewetting coupled with molecular dynamics hold the potential to accurately describe most chromatographic systems. These types of molecular dynamics simulations are very computationally expensive to fully sample conformational space. As computational power increases, increased use and applicability of these types of simulations will be very valuable.

Figure 3



(a) Modeling Trajectory across different model modalities (multiscale) for enabling Product-Process Digital Twins categorized by research effort and industrial usage (2019–2021), and **(b)** Modeling Connectivity across the multiscale highlighting key properties: purpose, complexity, maturity, for selecting the appropriate model based on industrial requirements.

Top challenges

1) Design accurate molecular descriptors for predictive modeling — artificial intelligence (AI), machine learning (ML), quantitative structure property relationship (QSAR)
2) Incorporate dynamics into predictive tool development — explore multiple scales from atomic to coarse grain at different timescales
3) Predict optimal process conditions from structure and biophysical properties — developability, formulation and manufacturability
4) Predict chromatographic changes from molecular properties and accurately map out the experimental design space
5) Expand the scope from antibodies/proteins to include other modalities, for example, DNA, RNA, viral vector, and so on

If some of these gaps and challenges can be overcome, there are two-specific areas where biophysical modeling could have broad applicability: 'developability' assessments during candidate selection and formulation development, and prediction of bioseparations (Figure 2). Developability assessments are a common way to predict molecular liabilities such as aggregation, fragmentation, and deamidation propensity before costly development and clinical investments are made [14–16]. While some of these assessments already include sequence and some structural information, better biophysical information and descriptors could lead to significantly better predictions and formulations. A recent study and workshop presentation from Saleh *et al.*, has also begun to look at the impact of sequence modifications on chromatographic performance, see Ref. [17] and Table 1.

For bioseparations, typical processes rely on filtration or chromatography unit operations for impurity removal. Previous studies have demonstrated QSAR to be useful for chromatographic predictions of model proteins [5,13]. More recent work has looked to create *in silico* heat maps as reported by Burgess at the workshop (see Table 1) that are similarly predictive to high throughput screening tools [18–20]. Another impactful application to bioseparations currently under investigation, as suggested by Armenio Barbosa in the workshop (see Table 1), would be to use biophysical structures to design novel ligands, thereby creating customized and highly specific separation mechanisms.

Mechanistic modeling

The term mechanistic modeling describes the mathematical description of data applying physical fundamentals. In contrast to empiric approaches, the degrees of freedom of mechanistic models are restricted by considering key mechanisms like for instance kinetics or mass balances. Mechanistic modeling approaches of chromatography build on the work done by Irving Langmuir on gas–solid phase equilibria [21], Tiselius on different modalities of chromatography [22] and many subsequent authors. The most common isotherm for ion-exchange is the steric mass-action (SMA) isotherm, which has been established in the 1990s [6•] and is still the foundation of a lot of chromatography modeling, but many other approaches do also apply [23,24].

Top challenges

1) Combination of homology models and mechanistic downstream processing (DSP) modeling to enable transfer of existing models and process knowledge to upcoming projects
2) Streamlined model calibration with simple and modular isotherms
3) Intelligent strategies to overcome existing gaps in current industrial model applications such as modeling of all critical quality attributes (CQA) parameters such as DNA, host cell proteins (HCPs), resin fouling, temperature and so on and enable full mechanistic filings
4) Detailed understanding of non-standard protein separation effects like protein-protein interactions, dimerization, or changes in protein conformation. Collaborations with academia might be a good way forward.
5) High throughput, high resolution, and orthogonal analytical strategies for challenging molecules like complex protein formats, which create a strong database for pure mechanistic models

Yet, it has taken the pharmaceutical industry quite some time to adopt this technology due to lack of coding ability and rigorous experimental requirements. Software Tools for mechanistic modeling (ChromX®/DSPX®, CADET, ChromWorks®, a.o.) are, however, now available and reduce the entry barrier to chromatography modeling and in some cases even other unit operations. Workflows for model calibration have been standardized and work in many cases [25,26]. Even less common processes using membrane adsorbers have been successfully modeled by companies and used in their process development/characterization efforts. More and more companies are taking the final step and are discussing modeling approaches in downstream processing with the regulatory agencies and in particular the US FDA. Even frameworks that govern the quality assurance paradigms and lifecycle of a certain model are now being presented to the agencies and, as discussed at the workshop, are generally well received by authorities (Good modeling practice for industrial chromatography [27•,28•,29•]). In addition, companies make use of modeling data, albeit only to some extent, in their regulatory filings. Although the submission of modeling data to the regulatory agencies is seen as the pinnacle of modeling, most workshop

participants see the value of using modeling to a large extent for better process understanding during process development.

Tools for all unit operations to model the platform monoclonal antibody (mAb) process have been established, starting with Protein A chromatography [30], molecular modeling of affinity Chromatography [31], cation exchange (CEX) and anion exchange (AEX) chromatography, mixing and tangential flow filtration (TFF) models [32••,33]. Hence, a standard mAb process can have its digital twin demonstrating the maturity of the field.

However, the field has suffered several setbacks. For chromatography, the standard SMA isotherm does not accurately reflect the experimental behavior [34], that is, when the ligand density varies between lots [35], at high load densities or over wide pH ranges. Extensions are thus needed which derails the standard calibration workflow, some CQAs are inherently difficult to model (i.e. HCPs), and a lack of high throughput, high resolution and orthogonal analytical data is still limiting the field. Furthermore, there is a gap in data availability that could be used for training and validating the model, similarly as mentioned for Biophysics above. Within a single company where the transferability from lab data to process scale data is not possible, as they have been recorded with different systems or purposes, publicly available datasets are not available that would allow easy testing of new model isotherms and other approaches. Validating a new model often requires generating all the data needed from scratch for model development.

As is evident in the presentations by Prof. Carta on the influence of different conformations and binding configurations of a bispecific mAb on adsorption and Prof. Frech on the elution behavior at high load densities at the workshop, see Table 1, some of these issues are being efficiently addressed by the academic community, either alone or in industry-academic partnerships (NIIMBL). These academic-industry partnerships [36•] hold the promise to address some of the remaining theoretical gaps in downstream processing, which are robust isotherms for mixed-mode chromatography and/or HIC chromatography, functionalized depth filters which are in general not very well understood and frameworks on how to deal with diverse impurities such as HCPs. Lastly, the intersection of making use of biophysical parameters for a certain molecule to supplement the mechanistic model and reduce the initial investment in experimentation is an area that is being addressed by industry-academic collaborations [13,17].

It would be beneficial if the tools that are currently available for mechanistic modeling better support the user in selection of the appropriate isotherm and guide the user through an efficient calibration workflow. A comprehensive review of downstream mechanistic modeling is provided in Ref. [37••], and multiple examples of industrial application are presented in Ref. [2•].

The workshop also comprised a session on mechanistic modeling of upstream processes, however, this publication is focused on the downstream aspects of mechanistic modeling. The mechanistic modeling of upstream processes is somewhat more challenging than for downstream processes. The upstream process consists of at least three very different elements, the equipment and input materials, the biological system of the cell and the target output molecule, that is, the antibody and its various embodiments. The equipment is reasonably well understood as described in the computational fluid dynamics (CFD) section of this manuscript. The biological system of the Chinese hamster ovary (CHO) cell is sufficiently well understood and there are metabolic-flux-analysis models and other models that can well describe the growth behavior of the cells. In addition, the products such as antibodies are very well characterized. The challenge seems to lie in correlating changes in equipment or process parameters not to cell growth or behavior but on the output of the product. Further insights into to the status of upstream modeling may be found in Refs. [38•,39].

Plant modeling

Plant modeling (can also be referred to as flowsheet modeling), is the combination of complex causal relationships from the lower scales, see Figure 3 into interconnected unit operation models to study, analyze and evaluate the full decision space of a given end-to-end process. The benefit of developing and employing such a model (whether at steady state or dynamic) is having the opportunity for process design and idea testing (so called 'what if analysis') considering, where necessary, uncertainty (e.g. robustness analysis). Plant modeling activities range from research over research-industrial to industrial activities. There is a clear gap from participants on plant modeling, see Figure 2, on three main things, what is the objective, why such a problem is complex and how to navigate it, and what commercial tools exist that are ready to deploy.

Top challenges

1) Problem translation — formulation of challenges into explicit problem definitions that satisfy full scale manufacturing constraints
2) Technology/topologies — how to efficiently generate, screen and select appreciated technologies/topologies before large investments in dedicated, multi-product, multipurpose, mixed, and modular designs
3) Batch & Continuous evaluation — how to generate topological process alternatives either for batch or

continuous or in combination and selection of the best based on quality and manufacturing requirements
4) Solution methods — how to incorporate and handle decision variables (integer and continuous) in both deterministic and stochastic instances
5) Computer-aided tools — selection of the right tool for the right problem incorporating research and development methods for obtaining efficient solutions

The three gaps mentioned above will be addressed based on the three presentations and the Break-out session given at the workshop (see Table 1) and the current state in transitioning from academia to industry. In an industrial context, many different types of challenges exist, for example, what are the key design decisions for new processes, how to identify retrofit for increased capacity, how to introduce a new product into an existing process, and so on? To be able to navigate these and other challenges, there is a need to both categorize and define these challenges into clear problem definitions. Here, three problem definitions are defined as seen emerging from the industry thereby giving rise to different digital twins (Siemens Digital Industries Software: Digital Twin. https://www.plm.automation.siemens.com/global/en/our-story/glossary/digital-twin/24465). Problem 1, referred to as the design problem where for a new product with specified requirements (throughput, purity, yield etc.), designs a (core) process to achieve these requirements [40]. Problem 2, referred to as the retrofit problem where for an existing product and known achievable requirements, modifies an existing design of a (core) process to improve processing [41]. Problem 3 and often overlooked referred to as the incorporation problem where for a new product with specified requirements, retrofits an existing design of a (core) process to incorporate this new product. The three defined problems give rise to different, terminal process designs as follows: dedicated processes, multi-product processes, multi-purpose and modular processes [7]. Dedicated processes are defined by: as topology is fixed, product is fixed, and the mode of operation can either be batch or continuous. Multi-product processes are defined by: as topology is fixed, product is varying, and the mode of operation can either be batch or continuous. Multi-purpose processes are defined by: as topology is varying, product is varying, and the mode of operation can either be batch and/or continuous. Modular processes are defined by: how units, process sections and thereby, process are defined in terms of unit-unit connectivity and combination, if these are to generate modules that can be utilized in a plug and play fashion. This introduces both flexibility (e.g. increasing capacity) and agility (e.g. the rate at which capacity can be increased) [42,43].

Plant modeling is generally approached and solved as a multiscale problem where different scales of information must be analyzed, curated, and combined for representation of system complexities both at the process and plant levels. The plant model is defined as the combination of the different processes (core, auxiliary or supporting) working in synchronicity to achieve product requirements. For plant modeling the multiscale, combinatorial abstraction of the problem can be explained by interlinked phenomena, that is, a unit operation coupled to the unit operation model, coupled to the process model (multiple unit operations connected), and coupled to the auxiliary model (e.g. raw material supply) and supporting systems (e.g. solvent systems), respectively. Therefore, the decision space is huge and gives rise to a mixed-integer non-linear (MINLP) problem [44,45].

At the plant scale, the product is produced at the required quantities based on the market demand. At this scale, for example, phase III clinical trials are also manufactured due to the amounts required. Based on both the regulatory environment for maintaining patient safety via product quality and documentation, changes to the process for phase III manufacturing are challenging and undesired. Therefore, a dilemma arises on how to a priori generate, screen, select and test ideas that can be implemented in new as well as existing plants in order to achieve product requirements both economically and sustainably.

Early stage techno-economical evaluation utilizing a modular analytical approach where bill of materials (BoM), overall (projected) process performance and realized efficiencies from known products can be combined and used to evaluate scenarios [46]. This allows the identification of where to focus, for example, should raw materials be replaced to improved sustainability or should the process be improved to enhance product economy and so on. Highlighted computer-aided tools that are available off-the-shelf for this type of early stage evaluation include BioSolve Process and the industrial-university consortium Techno-Economic Engine [47]. Next is screen and select, where detailed process models representing the existing plant virtually at both the unit operation and process level can be developed as a digital twin and used to perform 'what if analysis' to select the best, sustainable ideas for final implementation [42]. Computer-aided tools for this type of detailed material flow analyses include GAMS, PYOMO INOSIM, gPROMS, SuperPro Designer, and though less specific, Anylogic and ExtendSim. Finally, continuous improvement for process optimization [48••] can be performed for minimizing cost, maximizing sustainability, maximizing throughput and so on, and computer-aided tools are a combination of those aforementioned, subject to limitations of uncertainties and potential, known/expected sensitivities.

Computational Fluid Dynamics (CFD)

Computational Fluid Dynamics is a specific type of mechanistic modeling that refers to the numerical method of simulating steady and unsteady fluid motion

using numerical methods and has become a commonly applied engineering tool for simulating complex fluid flows involving solid interactions. The ever-growing availability of high-performance computing (thanks to Moore's law [49]) and development of numerous commercial codes has fueled the uptake in applying CFD modeling over the past two decades. In fact, most major biopharmaceutical companies have now established some internal CFD capability. It is now common to see CFD applied to systems involving agitated vessels (e.g. mixing tanks [50,51], bioreactors [8,52–54], and UFDF tanks), and increasingly common in its application to other biopharmaceutical unit operations, for example, chromatography [55–60] and for general validation [61–63]. The apparent maturity of CFD is presented in Figure 2.

Top challenges

1 Established industry best practices
   a No best model for a given unit operation – need to balance complexity with requirements
   b Most CFD models are a combination of CFD and other mechanistic models (turbulence, binding isotherm, porous media, population balance, etc.)
   c There is still a need for collaboration and sharing of best practices / common tools
2 Collaboration between experimentalists is needed to develop and adequately validate CFD models
3 Value is maximized by doing CFD further upstream in equipment or process development

The broad expansion in application of CFD can be attributed to the development of additional mechanistic models (population balance, multiphase models, kinetic expressions, Darcy's law [64] etc.) that can be combined with CFD to extend its predicative capability. In fact, most CFD simulations are now a combination of CFD, and other models that enable capture of additional mechanistic phenomena like bubble breakage/coalescence, chemical reactions, filtration, and precipitation. With these developments arise a need to balance complexity with model requirements and ensure that a model is sufficiently fit for purpose. Depending on the questions being asked of a CFD model, there is often not a single best model for a given unit operation.

As previously discussed [1••], CFD is still generally used to provide directional guidance in early stage activities or as supporting evidence despite its ability to provide high resolution results. The primary regulatory science gaps and challenges that have impeded the biopharmaceutical industry from reaching a future state of having digital twins for equipment are:

- Unknown credibility of existing CFD models: Most of the CFD models developed within the industry receive little to no rigorous evaluation and therefore have unknown credibility. The fact that CFD models can often be predictive without estimating parameters has enabled the directional use of CFD without rigorous comparison to experimental data.
- Lack of experimental methods and data for comparing to CFD results: Accurately characterizing a flow field is complicated and an area where the industry has little experience beyond the use of aggregate measures like mixing time and outlet concentration profiles. Generating appropriate experimental datasets to evaluate up against the CFD and any other models is a critical part of establishing credibility of a model. Good collaboration between experimentalists and model developers is critical to generating the appropriate datasets.
- Lack of established best practices for CFD: These include pre-processing and CFD best practices, and full end to end case studies for common unit operations that include the entire credibility assessment process across a wide range of operating conditions. Limited knowledge exists in the public domain even for the simple case of establishing mixing times in an agitated vessel.

While there has been much, a lack of published industry-accepted approaches for model development and validation still prevents CFD from being used in later stage actives as primary data. This is not a problem specific to CFD but impedes development of improved work processes that use computational models to offset experimental work. Publication of case studies in a peer reviewed journal or establishment of industry wide standards for unit operations commonly modeled with CFD is a necessary first step toward the future state of using CFD models as a digital twin for common unit operations. CFD models should thus encompass computational grid requirements, domain decomposition, model setup, experimental requirements for generating datasets for validation, statistical approaches for validating CFD models, and defining boundaries for where CFD models are predictive.

Conclusion

In addition to the focused modeling areas covered in the 4MMW, a broader discussion of challenges associated with implementation of modeling in lieu of experimentation was discussed in the Open Challenges Session. A detailed summary of the trajectory and opportunities for the modeling field is presented in Figure 3. One of the key challenges is the ability to incorporate modeling into regulatory submissions, especially for biophysics and CFD, when a full mechanistic understanding is not available. Statistical methods like DoE are widely used and accepted in regulatory submissions, thus one potential approach is the utilization of hybrid models which combine mechanistic and empirical components with the general experiments, that needs to be performed anyway.

Experiments at different scales as a mandatory part of process development will complement the hybrid model to handle CQAs that may otherwise only be handled empirically, and the model will thus improve the experimental protocol leading to a better process and/or less experiments.

A key consideration to significantly advance the state of modeling is the various ways that models can be employed to: guide experimentation, control processes, evaluate value proposition for new products (manufacturability). A near term objective is the development of approaches to predict impending failure (e.g. loss of chromatographic column separation performance). Modeling can also be employed to describe and help understand secondary kinetics effects on surfaces such as unfolding and on-column aggregate formation. Although the quantitative requirements for a model may vary based on the application (e.g. directional to guide experimentation versus fully quantitative efficient models for feedback control in continuous processing) all modeling approaches need to be scientifically rigorous not merely abstract mathematical constructs — effectively, a transition from black-box to grey box to white box models [65,66].

One current challenge is the lack of standardization of the modeling tools and the ability to benchmark performance (efficiency and accuracy) versus a standard case. Availability of open-source modeling software that is standardized and useful as a benchmark with a standard experimental system (e.g. NIST mAb [67]) would alleviate this challenge. The linkage to an experimental dataset (or diverse datasets) for model verification coupled with a fundamental understanding of the underlying mechanisms for a specific system are important to avoid 'misuse', leading to incorrect or unphysical results. Perhaps the development and maintenance of this diverse dataset could be pursued by a consortium [1••] or via a standardization organization (NIST). This proposed approach would ensure that modeling tools are mathematically convergent and physically realistic and will serve to continue to build confidence in the approach.

Publication of case studies and a benchmark comparison of hybrid versus mechanistic modeling would also be quite beneficial to further advance the state of modeling into machine learning models that do not stray into unphysical boundaries. Current gaps include Biophysical tools to measure and describe binding to custom affinity ligands.

This review presents the authors' view of the current status of modeling tools in the biopharmaceutical industry, and the challenges to progress the field. The modeling workshop series was established by industry representatives to share knowledge and experiences to advance implementation of advanced modeling tools in the biopharmaceutical processes. The tools will ensure better understanding and development of the processes and thus produce better products for patients, and the workshop series will continue to help advance the developments in the field. The next workshop is planned to occur in 2023.

Conflict of interest statement

Nothing declared.

Acknowledgements

Thank you to all who contributed to the workshop sessions, especially presenters and session chairs mentioned in Table 1, to continue to build a diverse community of modelers and to refine the vision of advancement of the field.

Declaration of Competing Interest

The authors report no declarations of interest.

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