1. Introduction and Objectives:

Continuous pharmaceutical manufacturing is rapidly being adopted as a preferred method of manufacturing in Industry, but standard methods for designing, implementing, and controlling pharmaceutical processes are yet to be robustly developed. As a result, the need for systematic methods and tools to efficiently manage the manufacturing process and resulting data are highly desired, and urgently needed. Currently, pharmaceutical companies are adapting their process and data management tools designed for batch operations to continuous processes. However, continuous manufacturing is exceedingly data rich and requires careful consideration in selecting process and data management tools. Our decade-long experience with these systems has shown that management and integration of data in a consistent, organized, reliable manner is a big challenge for continuous processes. Conventional tools have different functionalities, strengths and limitations. As the technology is evolving rapidly, there are substantial uncertainties among regulators and pharmaceutical manufacturers regarding the selection and appropriate use of suitable tools. For continuous manufacturing to achieve its full potential, the effective management, integration and efficient analysis of data is of paramount importance.

A continuous manufacturing plant is operated via control hardware and software platforms (e.g. DeltaV (Emerson), PCS7 (Siemens)) that collect real-time operational data. These software tools have continuous historians and the ability to implement different types of control architecture. However, in-line sensing and Process Analytical Technology (PAT) methods cannot be developed and multivariate data (i.e. most common form of PAT data) cannot be collected and stored within these software tools as currently available. The historian functionalities of these tools are not ideal for long-term data storage and management since the data can be over-written. Therefore, other PAT data management tools (e.g. synTQ (Optimum), SiPAT (Siemens), Process Pulse II (CAMO)) as well as a data hub are needed. These PAT data management tools have the capacity of generating, collecting and managing PAT data, but only for short periods of time. As a result, more flexible data management tools (e.g. OSIsoft Process Information (PI)) are needed as well. These tools, playing the role of permanent historian, are able to receive data from control platforms as well as PAT data management tools. For instance, PI has the capability to build up recipe hierarchical structure using the Event Frame functionality. It also has the capability to push the data into a cloud system for permanent enterprise-wide data storage and efficient sharing. The price of this combination of multiple tools is complexity in implementation and performance optimization and further research needs to be performed prior to the efficient use of such informatics-based tools.

The specific gaps to be addressed are several: As the pharmaceutical industry seeks more efficient methods for the production of higher value therapeutics, there is a tremendous need for more efficient data integration, visualization and analysis that spans laboratory and plant equipment, control hardware and historians and storage platforms. In **Figure 1**, the end-to-end integration of an informatics infrastructure that supports the necessary integration of the above components is depicted. In the current state of drug product manufacturing, the primary integration is focused in Levels 0-2 and there is limited data, information and knowledge that transcends to the upper

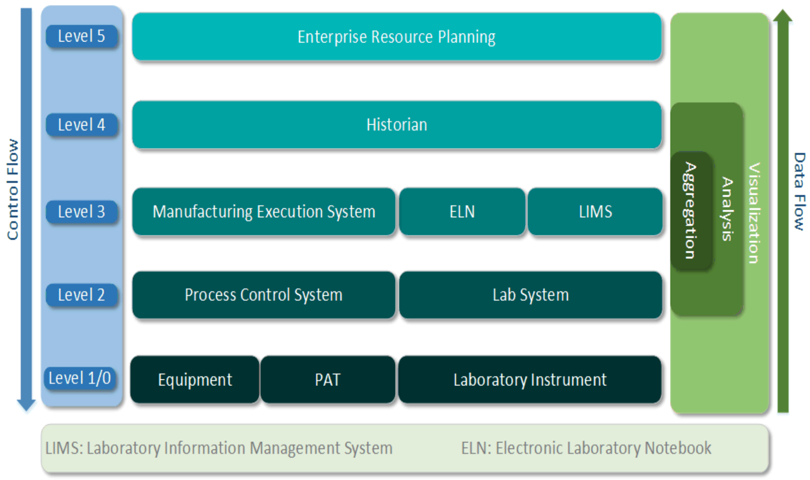

Figure 1: Proposed informatics infrastructure for a CM process [1].

levels. This results in the following specific gaps, elaborated below, in the overall informatics infrastructure that is necessary to achieve overall efficiency and quality in pharmaceutical manufacturing.

Gap 1: It is of critical importance to integrate lab and plant data to a cloud computing/storage. This is because historians themselves have limited use for storing large amounts of data, algorithms and models which must be actively accessed for visualization, analysis, risk assessment and rectification, and cloud capabilities offer both flexibility across multiple sites and personnel to achieve the above. However, transfer of data from a historian to a computing/storage cloud is non-trivial since cross-platform support is not guaranteed to be available on a cloud service of choice (e.g. Amazon, Microsoft, IBM). There is the option of using the application program interface (API) provided by the cloud service but the heterogeneity in the API's provided by different services makes this approach difficult. **Gap 2:** It is also of critical importance to integrate disparate sources of data (different types, formats and origination) into a common platform so that sorting, storage and treatment of data is efficient. To this end, data historians are very useful but are often not predominant in pharmaceutical manufacturing where often disparate devices (e.g. localized control hardware of simpler data management devices) are utilized. **Gap 3:** It is of critical importance to implement an electronic lab data management system to ensure that only accurate, error-free and validated data is transferred to the upper levels and that standardized laboratory procedures have been followed. **Gap 4:** The foremost role of process informatics systems is to inform and support real time process decisions. However, currently much of the data generated is not used optimally for real-time learning and decision-making.

1.1. Objectives

The overall goal of this proposal is to scientifically and technologically advance the operability of a continuous and integrated pharmaceutical process. This can be accomplished by enabling real-time learning and decision-making for the purpose of continuous process improvement and risk mitigation. The specific aims of the work are as follow:

Specific Aim 1: Scientific and technological advancement of a cyber-infrastructure and informatics enabled integrated data management framework for continuous pharmaceutical manufacturing.

Specific Aim 2: Development of process knowledge extraction strategies and HPC enabled Machine Learning (ML) strategies, which utilize the informatics systems established under Aim 1 for overall process improvement efficiency and real-time decision making.

2. Research plan

2.1. Specific Aim 1: Scientific and technological advancement of a cyber-infrastructure and informatics enabled integrated data management framework for continuous pharmaceutical manufacturing.

Rationale: The ultimate goal of the proposed work is to initiate progress towards the development of a "next-generation" manufacturing process for pharmaceutical production that integrates product and process informatics with knowledge management and real-time decision making (a. k. a. Industry 4.0). Such an infrastructure builds upon the previous work by our group [2-5] (e.g. science based process modeling, real-time sensing and release, closed-loop control) to further aid in continuous process improvement, risk mitigation and regulatory assessment.

Proposed Approach:

Integration of data historian to cloud computing and storage platforms

In order to address these issues, we propose to implement an open source data transfer pipeline between the data historian (level 4) computing/storage clouds (cross-platform devices) using 'davfs', a specific implementation of WebDAV (Web-based Distributed

Authoring and Versioning, an extension of the Hypertext Transfer Protocol (HTTP) that allows a user (client) to remotely create/edit web content.

The design challenge is to determine whether to go with extensions based upon traditional web services (as outlined above), or whether to refactor to exploit advances provided by the trio of ElasticSearch – LogStash – Kibana (ELK) for fully open source stack for logging and events management on Cloud Platforms of choice. The simple extension are easier to implement but adequate scalability and responsiveness need careful engineering; in contrast ELK has an integration overhead but essentially assured performance and scalability "out of the box".

Recipe based integration of plant and laboratory data into data historian.

For the integration of the data historian, we will use a PI system, which is an enterprise infrastructure for management of real-time data and events provided by OSIsoft. PI consists of a suite of software products that are used for data collection, historicizing, finding, analyzing, delivering, etc. **Figure 2** illustrates the structure and data flow of the PI system, in which PI Data Archive and PI Asset Framework (AF) are the keys parts. After the PI Interface receives data from a data source (e.g. control software) via the OPC server, PI Data Archive obtains the data and routes it throughout the PI System providing a common set of real-time data. PI AF is a single repository for objects, equipment, hierarchies, and models. It is designed to integrate, contextualize and references data from multiple sources including PI Data Archive and non-PI sources such as human input and external relational databases. Together, these metadata and time series data provide a detailed description of equipment or assets. Data generated from both process equipment and PAT tools will be sent into control software systems and organized according to the ISA-88/95 recipe model. The PI system is able to receive data from control software and build up recipe hierarchical structure using the PI Event Frame.

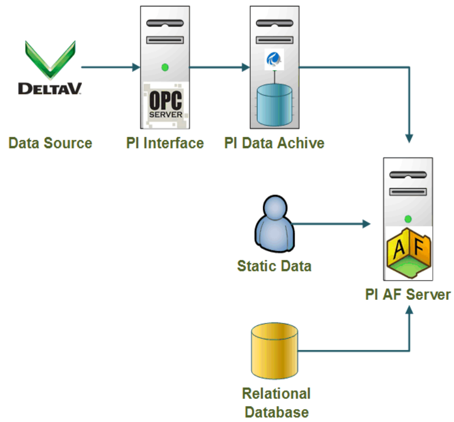

Figure 2: Proposed integration of lower level data to historian.

Recipe based Electronic Laboratory Data Management System.

An electronic lab notebook (ELN) system (Level 3, **Figure 1**) serves to provide the necessary functionalities for the management of raw material and product characterization data. This system must have sufficient capability of documenting experimental procedures and gathering data from various analytical platforms in order to provide material property information that complies with a recipe model framework. The basic workflow of using ELN to support experiment documentation that we will develop is illustrated in **Figure 3**. The first step is to select the master recipe developed for this specific test and create a control recipe. If such master recipe does not exist, then it needs to be created and approved. Once approved, users can change the control recipe, adding/deleting steps or parameters, according to their particular experimental plan. In **Figure 3**, the typical user workflow of such an electronic laboratory data management system is shown, with suitable color coding to facilitate user navigation. Once all of the required steps are completed and confirmed, the data file

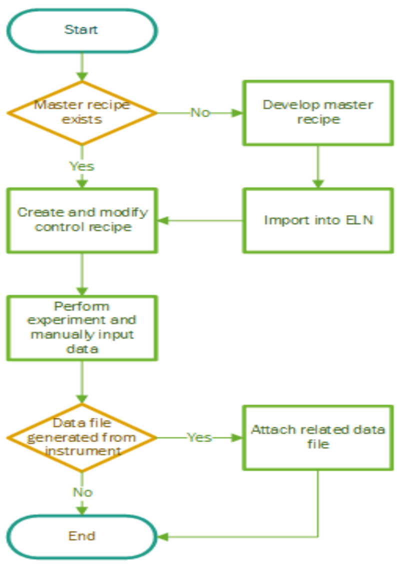

Figure 3: Workflow of an electronic data management system.

generated manually or by an analytical instrument is uploaded and saved.

Rigorous testing of these systems to assess implementation and functional aspects critical to supporting robust manufacturing and to establish best design and operational practices
The recipe-based management system will be integrated with flowsheets model to enable the testing of these ideas *in-silico*. The model will be first utilized as a virtual plant and connected to the data historian to test and further develop the ideas as outlined in the previous tasks of this specific aim. In order to more efficiently extract process knowledge from these information systems, it is required to systematically use a simulation-based approach to evaluate and optimize the process. We are further proposing the use of Global Sensitivity Analysis (GSA) [6] to identify the most critical process inputs that have a critical influence on process behaviors. [7, 8]. For dynamic systems, the critical process parameters may change with respect to time. Such changes can be reflected by using Dynamic GSA approaches, which calculate time-profiles of the sensitivity information. The Dynamic GSA has also been used in pharmaceutical processes [9]. This information can be further utilized to access the design space as we have illustrated in our previous work [2, 10-12]. In order to capture time-dependent changes in the design space, Dynamic Feasibility Analysis has been applied for pharmaceutical processes [2].

For the purpose of optimally designing and operating a pharmaceutical process, mathematical optimization methods can be used on the basis of process models. Traditional optimization methods require the derivative information of the model, which may not always be easily accessible to decision makers. Recently, surrogate-based optimization approaches have been developed to efficiently identify the near-optimal operation conditions within a limited sampling budget. Such methods rely on building a surrogate model to represent the process simulation and using it to direct the search towards the optimal solution. The efficacy of applying surrogate-based optimization to improving pharmaceutical processes has been demonstrated for both deterministic systems [13-15] and stochastic systems [16].

The second objective of this subtask is to enable the use of data utilizing on-line integration to adapt and further improve the model accuracy. Towards this goal, HPC-enabled machine-learning capabilities will be investigated to identify patterns efficiently and assist in refining the models. This will utilize the infrastructure we propose in Aim 2 and for which we provide details in 2.2. It is worth mentioning that the online clustering and pattern detection algorithm as well as anomaly detection algorithms will be implemented using the HPC-enabled ML infrastructure.

2.2. Specific Aim 2: Development of process knowledge extraction strategies and HPC enabled ML strategies, which utilize the informatics systems established under Aim A. for real-time improvement of process, sensor and control models.

Rationale: The basic objective of process informatics systems is to enable the use of data for real time decision-making. These decisions can extend beyond process operations to business choices such as material and product supply management and manufacturing resource allocation. In this work however we will focus on knowledge extraction and HPC-enabled machine learning strategies to support real time production line decisions and specifically real time quality assessment of products.

Proposed approach:
Dynamic RTD

Tracking material in continuous manufacturing requires the dynamic estimation of the residence time of a given segment of material, in each equipment component within the process operations. To achieve this, a statistical approach is often adopted and the material residence time distribution (RTD) is determined for each unit operation. The characterization of RTDs has been an active research area in pharmaceutical continuous manufacturing. Typically, the response of a step change in API composition or the downstream propagation of a tracer composition is experimentally or numerically characterized to develop flowsheet models [7, 17] dimensionless RTD models [18], or empirical transfer function models [19]—among the most recent contributions. Since these RTDs correspond to nominal steady state operating conditions, in the context of continuous manufacturing with active process control it is imperative to understand and characterize RTDs under dynamic operating conditions. This task will investigate the application of RTDs for material tracking under transient conditions where material nonconformity is identified and process is actively controlled until satisfactory conditions are reestablished.

A dynamic RTD can be envisioned under the hypothesis that any unit operation can be described as a series of confined perfectly mixed tanks, for which the RTD is known, and hence that the exchange flowrates of components can be estimated by experiments or more detailed models [9, 20]. Under this task, we will first further investigate the development of a dynamic RTD model of integrated continuous line [21]. Once the model is verified and best practices for its calibration are identified, the dynamic RTD model will be used to demonstrate in the Rutgers pilot plant its capabilities in predicting both API composition response and its corresponding RTD under active control strategy. While the control system is returning API composition back to normal range under a feeding disturbance, it is worth noting that the nonconforming material lot may not be confidently determined as the lot solely between the start of deviation detection and the end of deviation elimination. Hence, the timely RTD information will assist the operator to gain more insight of the impact of the disturbance on the system, not only in magnitude but also in time. This will help the decision to completely divert out-of-specification material, e.g., depending on the product risk assessment level of the disturbance, widening the diverting-off windows time may reduce risk further. The proof-of-concept of dynamic RTD model will then be extended to the downstream processing equipment, e.g., dry granulation, wet granulation, tableting, by transferring the RTD information sequentially from equipment to equipment. Therefore, the RTD of the whole processing line can be understood and used to track a disturbance or change in property under the risk assessment framework (**Figure 4**).

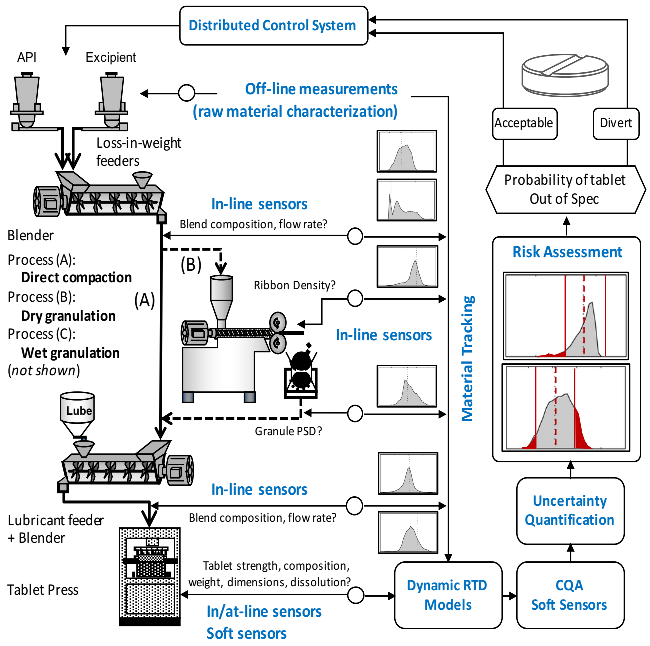

Figure 4: Proposed real time product risk assessment for CM.

The expected outcome of this task will be to elevate process understanding from the conventional a priori steady-state RTD knowledge to real-time dynamic RTD predictions, which will facilitate real-time process decision-making and the elucidation of material tracking best practices. Real time determination of the probability that a suitable increment of processed material meets all of the critical product specifications will need to be made from a combination of real time measurements, such as the active pharmaceutical ingredient (API) content, and suitable soft sensor predictions, such as tensile strength/hardness, weight and dissolution, which should be supported by periodic at-line measurements.

Soft Sensor Development

Process analytical technology (PAT) aids in helping practitioners to better understand and control processes via the in-line measurement of critical process parameters or material attributes that are known to affect product quality. A key limitation of PAT especially for continuous manufacturing is that some key measurements (e.g. tablet dissolution rates) require physical sensors that currently take significant amount of time (in the order of hours) to provide a signal/measurement. Therefore, these sensors cannot be used for real-time sensing, learning and/or decision-making.

In this aim, we propose to develop and utilize a soft-sensor approach via the implemented informatics framework in Aim 1, to be able to sense and predict tablet dissolution rates in real-time. Such a development would be of scientific, technological and commercial importance, as it would greatly reduce the time taken to obtain such an important measurement that directly correlates with continuous process improvement and risk mitigation. Furthermore, this is part of the Real Time Release Testing (RTRT) paradigm mandated by the U.S FDA for pharmaceutical manufacturing under the overall advanced manufacturing initiative to enhance the ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls (ICH Q8 guidance)

In this study, a soft-sensor model dependent approach will be pursued to replace existing the HPLC method (physical sensor-based approach) to measure tablet dissolution rates. The current HPLC method while accurate is unsuitable for in-line sensing due to the 1-2 hours it takes to provide the measurement. We will develop a statistical model via the Projection to Latent Structures (PLS) approach that utilizes HPLC and Near-infrared (NIR) spectroscopy data as a benchmark for training and can predict the dissolution profile of tablets using NIR data in the order of seconds.

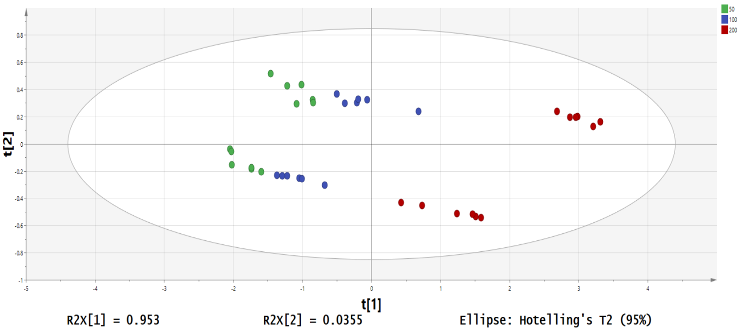

Figure 5: Variation in Compaction Force

NIR spectra will be acquired by using a Brucker Optics Multi-purpose analyzer (MPA) FT-NIR spectrometer (Billerica, Massachusetts). For computational efficiency, each spectrum and background is the average of 64 scans with a resolution of 8 cm^{-1}. OPUS 7.5 software is used to control the instrument in diffuse reflectance mode. The reflectance acquisition was performed with the integrating sphere unit in the spectral range of 12,000–4,000 cm^{-1}. Principal component analysis (PCA) will be used to classify variability in process parameters and/or material properties that NIR spectra and in turn affect tablet dissolution (see **Figure 5**).

Figure 5 shows that there is clear clustering of data points when there is a variation in tablet compaction force (e.g. of a CPP) that is known to result in different dissolution profiles. Initial results show that particularly for the 200KN force (in red), the NIR shows a distinct shift in spectra but the shift in spectra is less distinct from the 50 to 100 KN change (green to blue). This implies that the model will be able to predict dissolution rates via the soft-sensor model accurately for the 200KN (**Figure 6**) condition but less so for the 50 or 100KN (**Figure 7**) cases.

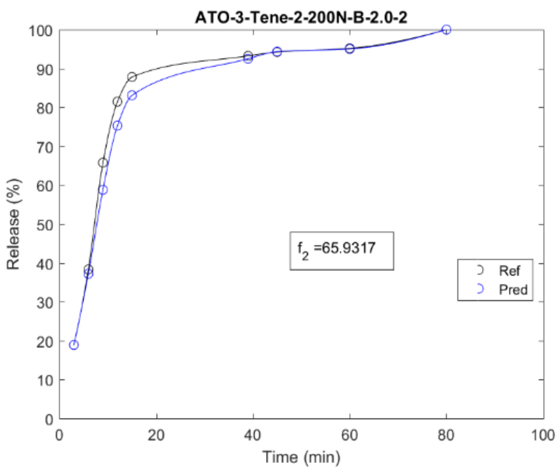

Figure 6: Predicted and reference dissolution rate at the 200KN force

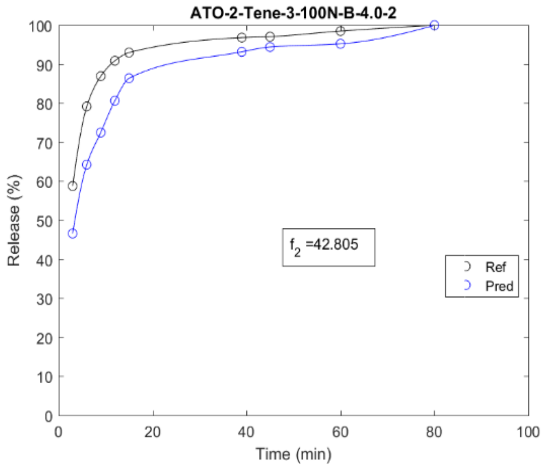

Figure 7: Predicted and reference dissolution rate at the 100 KN force

For the cases where there is discrepancy between the predicted (PLS/PCA/NIR soft sensor model) and the reference (physical HPLC method), we will use a HPC-enabled machine learning approach that is able to utilize more NIR spectra and higher resolution scans to generate a more accurate model. The developed soft-sensor models (i.e. both the statistical and machine learning models) will be fully integrated into the informatics framework so that they can be dynamically updated and reconciled with real-time NIR measurements.

HPC-enabled machine learning for real-time process improvement

To advance the ability to make Real-Time Learning and Decision-Making in Engineered Systems requires research in data-science and cyberinfrastructure research along the following tracks:

- Track A: Investigate the trade-off between real-time solution versus accuracy: (i) Explore different ML algorithms, and (ii) suitable learning frameworks.
- Track B: Research and prototype Distributed Machine Learning (ML) Infrastructure: (I) Real-time versus Batch mode computing, (ii) streaming and coordination services.

Recent developments in data-science, ML algorithms and software, and computational platforms allow the use of advanced real time learning approaches of sufficient sophistication to solve interesting and meaningful problems. A plethora of tools like TensorFlow and pyTorch have been developed, each supporting different algorithms with different capabilities. Typically, these are geared towards cloud systems where computational is abundant (even if costly) and "elastically" available, i.e., the acquisition overhead for N units of resource is equivalent to 1 unit. However the engineering problems of relevance require answers in well-bounded time intervals but do not always scale to utilize elastic resources. This imposes the difficult requirement of trading off accuracy (of solution) with rigid bounds on time-to-solution. This requires careful and in-depth performance characteristics of training and prediction phases of different algorithms and an analysis of their accuracy as function of time (resource) [22].

Further complexity is introduced when real-time learning and decision making can happen in a distributed cyberinfrastructure comprised of heterogeneous resources such as "edge devices" (as epitomized in the internet-of-things), clouds and high-performance computing systems [23]. In particular, many sensors act as "edge devices" which support non-trivial computing and thus many of the inference can be offloaded onto these edge devices. In addition, the resources provided by the ecosystem range from architectures with multiple cores and multiple nodes, to many-core system, and GPU based systems. Determining the optimal distribution of training and inference over HPC/Clouds versus edge devices, as well as determining efficiency and time-to-solution of ML is dependent on the problem, frameworks and platforms employed.

Despite early analysis of determining the performance of algorithms, platforms etc., there is a need for a conceptual framework that will help determine suitable configuration of platforms, and algorithms for a given (desired) accuracy for the specific problems under considerations. We propose to build such a framework and our performance characterization will use a number of different edge devices, clouds and HPC resources, which span from x86 based to using KNL cores and GPU based. Our dataset will be compromised of test, fabricated and data streams from actual sensors in different parts of the manufacturing process.

Based on our characterization, and by using functional and timing performance metrics, we will provide automated decision-making heuristics (or models). It will be able, based on the learning algorithm, data, and resource characteristics to provide real-time insight.

3. Broader Impact of the Proposed Research

The ultimate goal of this work is the development a "next-generation" autonomous manufacturing process for pharmaceutical production that integrates product and process informatics with knowledge management (i.e. industry 4.0). The integration of process data, process models, and information management tools will provide more flexibility to industry for their manufacturing operations as they will be able to adaptively adjust the operating conditions to adjust for variability based on their raw materials and changing needs. A key component of informatics-based pharmaceutical "smart manufacturing (SM)" is the requirement of a new kind of workforce. This requires the attraction of a workforce that is very comfortable with using web tools, rapidly evolving data and information management. SM can be the key to reinvigorating the manufacturing workforce and attracting and nurturing the younger talent pool that historically may not have considered a career choice in the manufacturing industry. Therefore, we expect as part of this proposal to train students and industrial practitioners that is consistent with the advanced manufacturing initiatives proposed by the federal government to enhance the competitiveness of the U.S. economy. The scientific and technological improvements made in the proposed work will increase the overall efficiency of the pharmaceutical supply chain that historically are complex and inefficient. Therefore, we expect energy and cost improvements made to the manufacturing line via SM to propagate and extend to the overall supply chain.

4. Results from Prior NSF Support

The investigative team consisting of Ierapetritou, Ramachandran and Jha have successfully completed an NSF Project whose details are enclosed below. Therefore, the current proposed project is synergistic to the previous work since it utilizes the findings and results to advance the science and technology that is highly relevant to both the scientific and industrial community.

NSF Award Number: 1547171
Amount: $284,184
Project/Grant Period: 09/01/2015 - 08/30/2017
Project Title: Cybermanufacturing: Advanced modeling and information management for pharmaceutical manufacturing
Number of Publications (From NSF Award): 2 published [1, 24], 1 submitted [25]
Goals of the Project: To develop a data-enabled computational framework for the efficient solution of process models for pharmaceutical unit operations.
Significant Results: We have demonstrated significant computational speed-up of high-dimensional population balance models for granulation systems. This enables the community to use practical and realistic models of granulation in control and optimization
Intellectual Merit: To provide flexible solutions for pharmaceutical manufacturing dealing with complex process models and large data sets.
Broader Impacts: To train the next generation of students and impart skills at the cusp of chemical and computer engineering that is needed in today's process industries such as pharmaceuticals. The project also incorporates the involvement of a faculty member from Electrical and Computer Engineering thus promoting cross-disciplinary exposure.
Evidence of Research Products and Availability: The data generated from this work has already been utilized to publish 2 journal papers [1, 24].

References

[1] H. Cao, S. Mushnoori, B. Higgins, C. Kollipara, A. Fermier, D. Hausner, S. Jha, R. Singh, M. Ierapetritou, R. Ramachandran, A Systematic Framework for Data Management and Integration in a Continuous Pharmaceutical Manufacturing Processing Line. , Processes, 6 (2018) 53.
[2] A. Rogers, M. Ierapetritou, Feasibility and flexibility analysis of black-box processes Part 1: Surrogate-based feasibility analysis, Chemical Engineering Science, 137 (2015) 986-1004.
[3] S. Oka, A. Sahay, W. Meng, F. Muzzio, Diminished segregation in continuous powder mixing, Powder Technology, 309 (2017) 79-88.
[4] R. Singh, A. Sahay, K.M. Karry, F. Muzzio, M. Ierapetritou, R. Ramachandran, Implementation of an advanced hybrid MPC–PID control system using PAT tools into a direct compaction continuous pharmaceutical tablet manufacturing pilot plant, International Journal of Pharmaceutics, 473 (2014) 38-54.
[5] A. Bhaskar, F.N. Barros, R. Singh, Development and implementation of an advanced model predictive control system into continuous pharmaceutical tablet compaction process, International Journal of Pharmaceutics, 534 (2017) 159-178.
[6] A. Saltelli, K. Chan, E.M. Scott, Sensitivity analysis, Wiley New York2000.
[7] A.J. Rogers, C. Inamdar, M.G. Ierapetritou, An integrated approach to simulation of pharmaceutical processes for solid drug manufacture, Industrial & Engineering Chemistry Research, 53 (2013) 5128-5147.
[8] Z. Wang, M.S. Escotet-Espinoza, M. Ierapetritou, Process analysis and optimization of continuous pharmaceutical manufacturing using flowsheet models, Computers & Chemical Engineering, 107 (2017) 77-91.
[9] F. Boukouvala, V. Niotis, R. Ramachandran, F.J. Muzzio, M.G. Ierapetritou, An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process, Computers & Chemical Engineering, 42 (2012) 30-47.
[10] A. Rogers, M. Ierapetritou, Feasibility and flexibility analysis of black-box processes Part 2: surrogate-based flexibility analysis, Chemical Engineering Science, 137 (2015) 1005-1013.
[11] Z. Wang, M. Ierapetritou, A novel feasibility analysis method for black-box processes using a radial basis function adaptive sampling approach, AIChE Journal, 63 (2017) 532-550.
[12] Z. Wang, M. Ierapetritou, Surrogate-based feasibility analysis for black-box stochastic simulations with heteroscedastic noise, Journal of Global Optimization, (2018).
[13] F. Boukouvala, M.G. Ierapetritou, Derivative-free optimization for expensive constrained problems using a novel expected improvement objective function, AIChE Journal, 60 (2014) 2462-2474.
[14] F. Boukouvala, M.G. Ierapetritou, Surrogate-based optimization of expensive flowsheet modeling for continuous pharmaceutical manufacturing, Journal of Pharmaceutical Innovation, 8 (2013) 131-145.
[15] Z. Wang, M.S. Escotet-Espinoza, R. Singh, M. Ierapetritou, Surrogate-based Optimization for Pharmaceutical Manufacturing Processes, Computer Aided Chemical Engineering, Elsevier2017, pp. 2797-2802.
[16] Z. Wang, M. Ierapetritou, A Novel Surrogate-Based Optimization Method for Black-Box Simulation with Heteroscedastic Noise, Industrial & Engineering Chemistry Research, 56 (2017) 10720-10732.
[17] S. García-Muñoz, A. Butterbaugh, I. Leavesley, F. Manley Leo, D. Slade, S. Bermingham, A flowsheet model for the development of a continuous process for pharmaceutical tablets: An industrial perspective, AIChE Journal, 64 (2017) 511-525.
[18] G. Tian, S.L. Lee, X. Yang, M.S. Hong, Z. Gu, S. Li, R. Fisher, T.F. O'Connor, A dimensionless analysis of residence time distributions for continuous powder mixing, Powder Technology, 315 (2017) 332-338.

[19] J. Rehrl, A.-P. Karttunen, N. Nicolaï, T. Hörmann, M. Horn, O. Korhonen, I. Nopens, T. De Beer, J.G. Khinast, Control of three different continuous pharmaceutical manufacturing processes: Use of soft sensors, International Journal of Pharmaceutics, 543 (2018) 60-72.
[20] M. Sen, A. Chaudhury, R. Singh, J. John, R. Ramachandran, Multi-scale flowsheet simulation of an integrated continuous purification–downstream pharmaceutical manufacturing process, International Journal of Pharmaceutics, 445 (2013) 29-38.
[21] J. Liu, Q. Su, M. Moreno, C. Laird, Z. Nagy, G. Reklaitis, Robust state estimation of feeding–blending systems in continuous pharmaceutical manufacturing, Chemical Engineering Research and Design, 134 (2018) 140-153.
[22] A. Canziani, A. Paszke, E. Culurciello, An Analysis of Deep Neural Network Models for Practical Applications, Computer Vision and Pattern Recognition, (2017) https://arxiv.org/abs/1605.07678.
[23] C. Hardy, E. Le Merrer, B. Sericola, Distributed deep learning on edge-devices: feasibility via adaptive compression, Learning https://arxiv.org/abs/1702.04683.
[24] F.E. Bettencourt, A. Chaturbedi, R. Ramachandran, Parallelization methods for efficient simulation of high dimensional population balance models of granulation, Computers & Chemical Engineering, 107 (2017) 158-170.
[25] C. Sampat, F.E. Bettencourt, Y. Baranwal, I. Paraskevakos, A. Chaturbedi, S. Karakala, S. Jha, R. Ramachandran, M. Ierapetritou, A parallel unidirectional coupled DEM-PBM model for the efficient solution and simulation of computationally intensive systems., Computers & Chemical Engineering, Manuscript submitted (2018).