AI in Action for Manufacturing Process Improvement

A success case study of AI application to improve the granulation process in drug manufacturing

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XAVIER HEALTH

ACKNOWLEDGMENTS

This study was developed under the leadership of the Xavier Health program at Xavier University in partnership with industry professionals, as a planned output from the Xavier AI Summit. We would like to thank everyone who contributed to the creation and the review of this paper—without their work, this paper would not have been possible[1]. We also want to acknowledge the significant contributions from the following people:

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Our hope is that this paper provides the foundation for new learnings and best practices in this rapidly evolving field to help deliver the promise and potential of AI.

XAVIER AI WORKING TEAMS

Through the Xavier Artificial Intelligence Initiative, chartered working teams have been established during the face-to-face setting of the annual Xavier AI Summit. The teams that are currently formed are as follows, and are accepting new members:

AI in Operations (AIO) Team
The AIO Team is an organized, cross-industry discussion group of FDA officials and industry professionals working to increase the predictive assurance of product quality across all operations through the power of AI. →**Learn more**

Good Machine Learning Practices (GMLP) Team
The GMLP Team is bringing the world of AI activity into one place in order to increase the awareness of good work that has already been done and to collaboratively further solutions that address challenges related to AI implementation across the industry. →**Learn more**

AI at the Point of Care (AI@POC) Team
The AI@POC Team is designed for physicians and healthcare system members seeking to leverage augmented intelligence to improve patient care, clinical workflow and system operations. →**Learn more**

[1] Please note that the opinions and viewpoints expressed by the contributors do not necessarily reflect the opinions and viewpoints of their organizations.

INTRODUCTION

The AI in Operations Team (AIO) is an organized, cross-industry discussion group of FDA officials and industry professionals working to increase the predictive assurance of product quality across all operations (i.e., manufacturing, quality, supply chain, etc.) through the power of artificial intelligence (AI). This team works under the AI Xavier Health initiative and is split into two sub-teams. One of these sub-teams is AI in Development (AID) and is focused on real AI experiences in Pharma. During the course of 2019 - 2020, this team worked to identify ways to improve manufacturing operations by using AI. The team used data generated in real production environments from a top 25 global pharmaceutical company in an effort to determine the root cause of non-optimal batches. Importantly, the team noted how best and when to engage subject matter experts, and what type of communication bridged the gaps between data and process experts. The team wanted to ensure data security, data access control, AI capabilities to manage the data workflow, AI models, and the visualization functionalities all in one application. The Aizon platform was chosen for this purpose.

The global pharmaceutical company provided the AID team with a dataset that contained the records of over 350 batches of the granulation process. The dataset included vessel pressures, mix times, line temperatures, motor rotations, hold times, and other common manufacturing attributes. Critical Process Parameters (CPPs) were also included. These batches were manufactured between 2015 and 2019 using two different processing suites. Two of the recent batches had poor flowing powder for an unknown reason. All critical processing parameters were in range and all Critical Quality Attributes (CQAs) passed. This was a process improvement initiative to try and determine why two batches had poor flowing powder. A dataset was provided to the AIO Team to aid in this exploration. The dataset included over 250 variables measured during the batches. Many of the parameters have a known relevance and are being used in the current numerical analysis. The dataset also contains many variables that are currently not being taken into account due to the limited capability of traditional analytics.

ABOUT XAVIER HEALTH

Xavier Health is more than an organization. It is a community of hundreds of FDA, industry experts, thought leaders and academics. Xavier Health was formed in 2008 as an outreach of Xavier University charged with making a difference in the pharmaceutical, medical device, and combination products industries. Our mission is inspiring collaboration, leading innovation, and making a difference in all that we do.

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APPROACH

First, the AID Team carried out an exploratory analysis of the dataset and applied principal component analysis (PCA). A subset of variables clearly showed a split between the batches produced on Production Line 0 and Production Line 1. For example, there was a clear divide between batch duration: batches on line 1 were consistently longer in duration than those on line 0. The data scientists met with the process experts for further analysis of the batch duration behavior. The process experts explained the binary behavior of batch duration: the two lines used different brands of filters causing Line 1 to take longer to dry. Although the variation between batches and dryers can be explained, the known differences might affect the performance of the lines when combined with the slight variation from several other hundred parameters.

Next, a clustering analysis using the k-means algorithm was used to cluster the batches using multiple variables and known relevant factors. The analysis identified three robust clusters that clearly separated the batches from different lines and dryers. Cluster 1 was almost exclusively batches from Line 0 and Cluster 3 was almost exclusively batches from Line 1. Cluster 2 contained a mix of batches from both lines. The AID team also identified a clear temporal pattern in these clusters. Cluster 2 contained exclusively 2015 and 2016 batches whereas Clusters 1 and 3 contained batches performed between 2017-2019.

Finally, the team focused on quality attributes and batch categorization by quality, with the goal of predicting the batch quality from the known relevant factors. Due to different testing requirements per market and all CQAs being acceptable, the team needed a different way to categorize the quality of the batches. The data scientists again partnered with the process experts who were able to review samples of recent batches and categorize the powder flow. Small samples of the powder were stored in vials and the flow was able to be observed. The batches were classified as good (batches with free-flowing powder, which is the desired outcome), average (some clumping observed but still free-flowing), and suboptimal (large amounts of clumping). All three categories met all quality specifications. The batch categorizations were created solely for the AID Team's analysis. This was done to reduce the number of columns needed for categorization keeping the existing number of rows.

The batch categorization was available for 80 batches from the year 2019 which was a small subset of the original dataset. Among these 80 batches, a majority (53/80 batches) were classified as good, 25 batches as average, and only 2 batches as suboptimal. After verifying that this subset of batches was a representative sample of the entire population, the researchers mapped the classification onto the previous clustering results. These 80 batches belonged to Clusters 1 and 3. However, Cluster 3 contained exclusively batches that were classified as good, whereas Cluster 1 contained a mix of good, average, and suboptimal batches.

The team then performed a new clustering analysis with the 80 classified batches into 3 clusters. Under the hypothesis that these three clusters represent good, average and suboptimal batches. The clustering model achieved 80-90% accuracy in predicting each class. The sensitivity of detecting the average class was worse than others. To complement this classification, the researchers applied isolation forest in a supervised fashion. The classification based on the isolation forest model overall achieved strong concordance with the clustering analysis for all categorizations. In particular, it outperformed the clustering model in detecting suboptimal batches, but performed worse in detecting average batches. Overall, these two independent classification models were able to achieve satisfactory performance and the final model was particularly good at detecting good and suboptimal batches. This approach also illustrates that using multiple complementary approaches simultaneously can be advantageous in situations where each method offers orthogonal information.

Lastly, the AID team aimed to uncover subtle relationships between various variables that would not be obvious to subject matter experts. Although relevant factors that predict the quality of the batch have been identified before by subject matter experts, identifying new relevant factors might aid in the application of advanced analytics and produce better results. Using the Bayesian network model, the team uncovered several potentially interesting relationships between different variables and suboptimal batches. In particular, suboptimal batches tend to be strongly associated with high values of a tank transfer temperature, a minimum mixing temperature, and a minimum tank temperature. Multivariable interactions can be difficult to understand, but AI was able to help guide the subject matter experts to explore the finer details of these parameter values and their relationships to process efficacy.

JOIN THE CONVERSATION

Follow the Xavier AI LinkedIn group, Artificial Intelligence - Advancing the Pharmaceutical and Medical Device Industries, at www.linkedin.com/groups/12078247/

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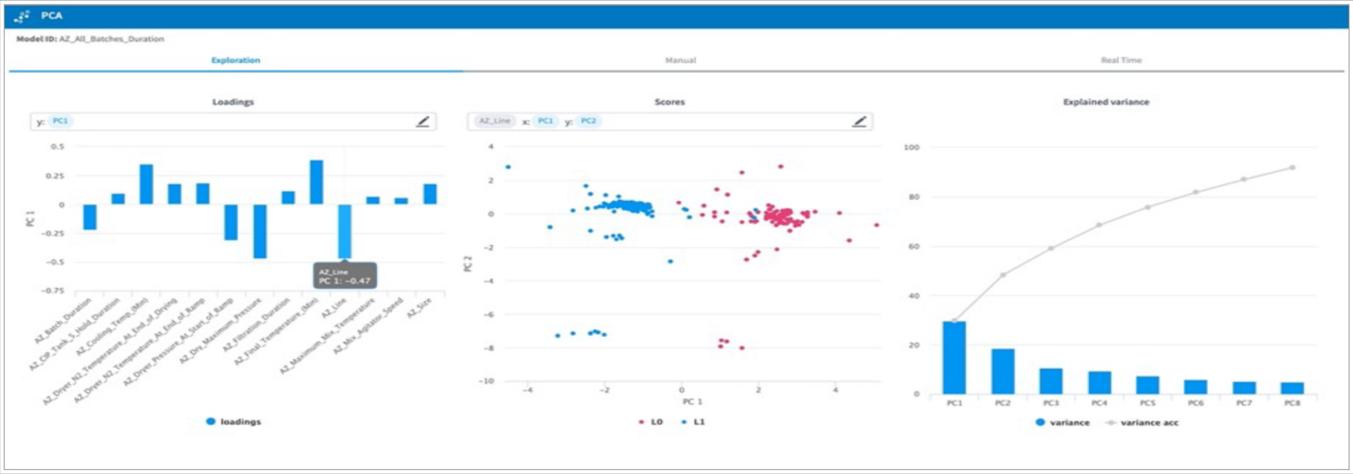
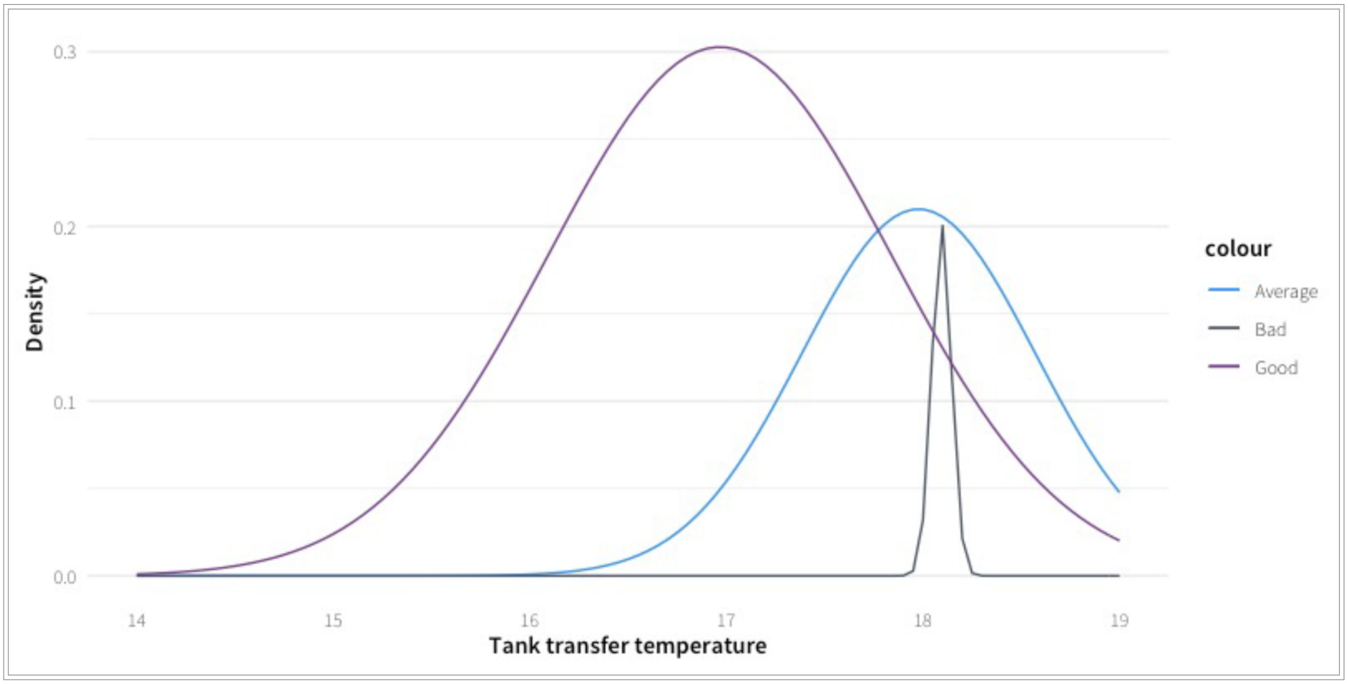


Graphic 1: PCA performed in order to identify the variables that better explained the variability of the problem. Additionally, two clear behaviours were identified automatically by the calculation. The two colours correspond to the two Granulation lines.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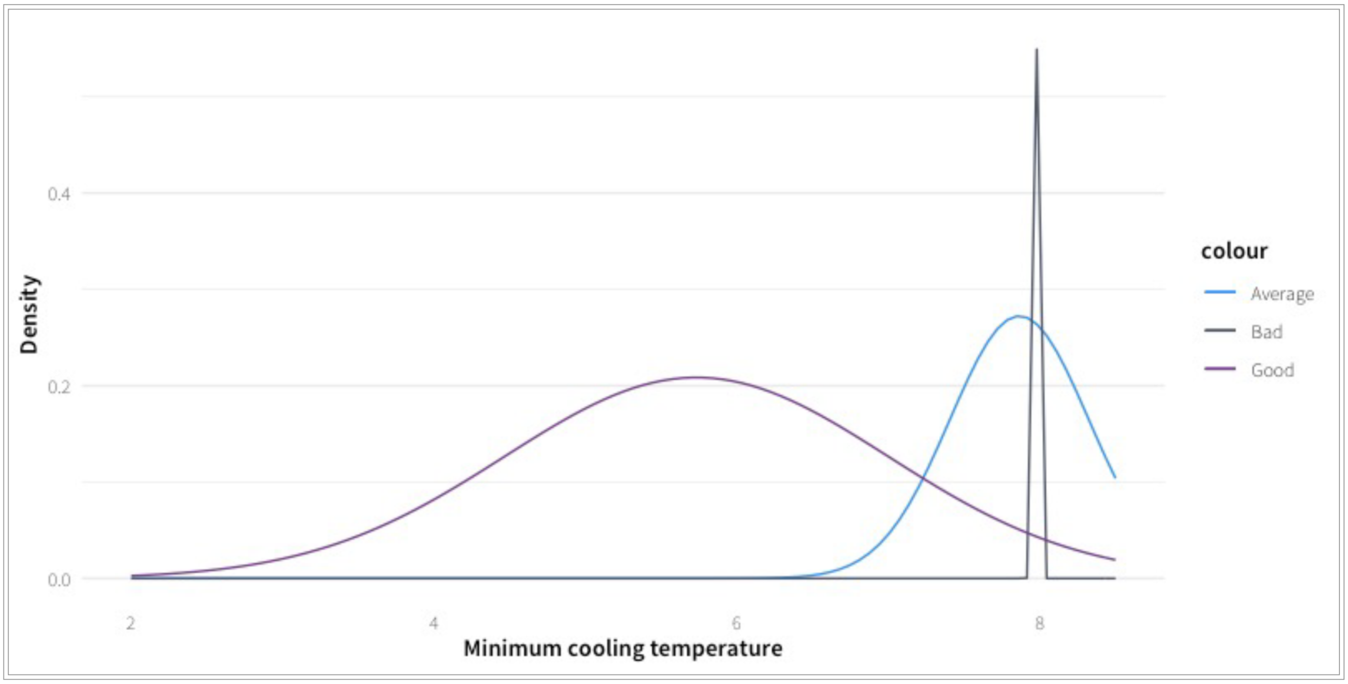
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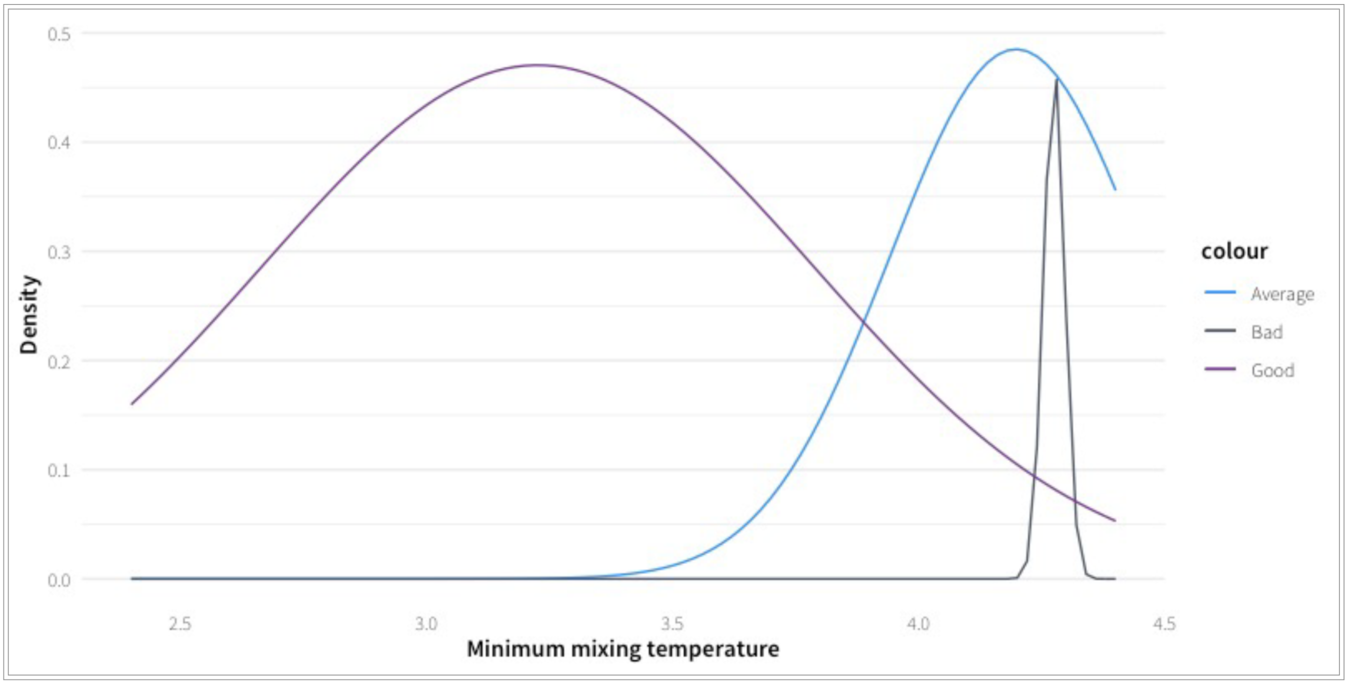

RESULTS

The results were reviewed with the subject matter experts who validated that the parameters individually were significant. All the parameters were within normal operating ranges so looking at the parameters individually would not have raised any alarms. AI was able to identify three parameters of interest that the subject matter expert team can now monitor more closely as the team continually learns about the process.

TAKEAWAYS

Effective tools begin with a clear problem statement. AI tools are no exception. The team was given a clear business problem with a clear technical problem statement, which defined the scope of the project and determined project success. A clear problem statement keeps the team focused, manages expectations, and prevents scope creep. The team was very open minded to the approach and viewed AI as a tool that will help the engineers perform a better investigation. Realizing that AI is a tool like any other statistical approach allowed the process team to collaborate with the AID Team and accept the AI models. Difficult problems require the collaboration of experts transcending administrative boundaries.

In gathering data, does one go with a larger sample size or more relevant data? In this example, two separate processing lines were combined to increase the sample size even though both suboptimal batches came from one line. Would eliminating the second line provide different significant parameters? This is a case by case consideration. Having data security, data access control, AI capabilities to manage the data workflow, AI models, and the visualization functionalities all in one platform allowed the analysis to easily progress as new questions were asked. Moving from clustering to random forest to Bayesian networks while creating visualizations was an easy transition when the data is secured all within the same analytics platform. Sharing data through e-mail and Excel would not allow for this type of integrated exploration.

The multiple results and outputs provided by the AI Models are not easy to interpret. The data scientists described the AI conclusions to the process experts. From data to actions, from information to knowledge, a specific communication task is required to transform dimension reduction, predictions and clusters into recommendations and actions. Transforming algorithms into graphics is an operation that should be considered when complex results must be shared with a multidisciplinary team. These actions allowed the process experts to understand the analysis process and next steps. The process experts appreciated the explanations and made them feel included as part of the process. In the end, this helped with acceptance and trust of the model.

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