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Review

Machine Learning Methods to Improve Crystallization through the Prediction of Solute–Solvent Interactions

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Abstract: Crystallization plays a crucial role in defining the quality and functionality of products across various industries, including pharmaceutical, food and beverage, and chemical manufacturing. The process's efficiency and outcome are significantly influenced by solute–solvent interactions, which determine the crystalline product's purity, size, and morphology. These attributes, in turn, impact the product's efficacy, safety, and consumer acceptance. Traditional methods of optimizing crystallization conditions are often empirical, time-consuming, and less adaptable to complex chemical systems. This research addresses these challenges by leveraging machine learning techniques to predict and optimize solute–solvent interactions, thereby enhancing crystallization outcomes. This review provides a novel approach to understanding and controlling crystallization processes by integrating supervised, unsupervised, and reinforcement learning models. Machine learning not only improves product the quality and manufacturing efficiency but also contributes to more sustainable industrial practices by minimizing waste and energy consumption.

Keywords: crystallization; bioavailability; solute–solvent interactions; algorithm; supervised learning; unsupervised learning; semi-supervised learning; reinforcement learning; ensemble methods

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1. Introduction

Crystallization is a pivotal process in sectors such as pharmaceutical, food and beverage, and chemical production, playing a critical role in defining the quality and characteristics of a wide range of products. This process is fundamental in creating crystalline products that span a diverse array of applications, including bulk chemicals like sodium chloride and sucrose, essential in everyday life, and crucial agricultural fertilizers such as ammonium nitrate [1], potassium chloride [2], ammonium phosphates [3] and urea [4]. In the pharmaceutical industry, crystallization is vital for producing valuable products such as active pharmaceutical ingredients [5] and organic fine chemicals [6], where the purity and morphology of crystals can significantly impact drug efficacy and safety. The burgeoning field of engineered nanoparticles and crystals for the electronics industry also relies heavily on crystallization, integral in advancing technologies in areas like semi-conductors [7,8] and battery production [9]. Additionally, biotechnology products, such as protein and fat crystals, are gaining prominence due to their applications in drug design and medical research [10,11]. The precise control of crystallization conditions—including temperature, concentration, and pressure—allows these industries to enhance product quality, efficiency, and cost-effectiveness. By manipulating the size, purity, and shape of the crystals formed, industries can tailor materials to specific applications, thereby optimizing performance and functionality [12]. This level of control is essential for meeting stringent regulatory standards and consumer demands, particularly in sectors like pharmaceuticals and food production [10]. Continuous innovation in this field is crucial for developing new materials and improving existing products, thereby driving progress across various sectors [12].

In the pharmaceutical industry, the crystallization process can affect the drug's characteristics, like its solubility and bioavailability (the proportion of a drug or other substance that enters the circulation when introduced into the body and so can have an active effect) [13]. Thus, enhancing crystallization conditions can result in the creation of more potent drugs. Similarly, in the food industry, crystallization is vital in the production of items like sugar, chocolate, ice cream, and beverages. Improved crystallization conditions, such as controlling the size of the ice crystals in ice cream, can enhance the texture, quality, and flavor of these products [14]. Between 2021 and 2022, the United States produced approximately 8.37 million metric tons of sugar [15]. Improved crystallization methods could increase this number [16].

Furthermore, from an environmental standpoint, better crystallization can result in less waste and decreased energy consumption [17], contributing to more sustainable industrial practices by reducing unnecessary materials and energy needed to achieve desired crystal properties. Therefore, progress in crystallization technology can have extensive implications for global sustainability [18].

Machine learning to predict solute–solvent interactions:

Machine learning is a specialized branch of artificial intelligence (AI) that focuses on the development of algorithms capable of learning from and making decisions or predictions based on data. Unlike traditional rule-based programming, where explicit instructions are provided for each task, machine learning algorithms "learn" from examples or through interactions with their environment. The ultimate goal is to generalize from the training data to unseen situations in a principled manner.

2. Machine Learning

2.1. Supervised Learning

Supervised learning is the most prevalent form of machine learning. In this paradigm, an algorithm learns from labeled training data, making predictions or decisions based on input data. The process is akin to a teacher-supervised learning environment. The algorithm iteratively makes predictions on the training data and is corrected by the teacher, allowing the model to learn over time [19].

Key concepts

Label: The output variable (y) we aim to predict. In a classification problem like with emails, the label could be categories like "spam" or "not spam" [20]. In a regression problem, it could be a continuous value like house price.

Features: These are the input variables (X) used for making predictions. Features could range from simple univariate data to complex structured data like images, text, and even video [21].

Loss function: This is a function that the algorithm aims to minimize during the training process. The choice of loss function can significantly impact the performance of the model. Common examples include the mean squared error (MSE) for regression tasks and cross-entropy for classification [22].

Algorithms

Linear regression: This is one of the simplest algorithms used for predicting a continuous outcome variable based on one or more predictor variables. The algorithm assumes a linear relationship between the input variables and the single output variable. It can be extended to multiple dimensions and is the basis for many other types of regression analysis, such as logistic regression for classification tasks [23].

Support vector machines (SVMs): These are a more complex algorithm, highly effective in high-dimensional spaces. They are primarily used for classification tasks but can be adapted for regression. The algorithm works by finding the hyperplane that best divides a dataset into classes [24].

Decision trees: These are versatile algorithms used for both classification and regression tasks. They are particularly useful because of their ease of interpretation and visualization. The algorithm makes decisions based on the feature values, breaking down

a complex decision-making process into a series of simpler decisions, thereby forming a tree [25].

2.2. Unsupervised Learning

Unsupervised learning is a type of machine learning where algorithms learn from data without any labeled responses. The system tries to identify patterns and structures in the data autonomously [26].

Key concepts

Clustering: This is the task of dividing the population or data points into several groups based on the feature set. The algorithm tries to group data that are similar to each other in some way [27].

Dimensionality reduction: This involves reducing the number of random variables under consideration by obtaining a set of principal variables. It can be divided into feature selection and feature extraction [28].

Algorithms

K-means: This is an algorithm used to find groups in the data, with the number of groups represented by the variable K. The algorithm works iteratively to assign each data point to one of the K centers [29].

Principal component analysis (PCA): This is a statistical procedure that uses an orthogonal transformation to convert correlated features into a set of linearly uncorrelated features called principal components [30].

2.3. Semi-Supervised Learning

Semi-supervised learning is an intermediate between supervised learning and unsupervised learning. In semi-supervised learning, the algorithm is trained on a dataset that contains both labeled and unlabeled data. Generally, a small amount of data is labeled, while a large amount of data is unlabeled [31].

Key concepts

Pseudo-labeling: This is a technique where we use a small amount of labeled data and a large amount of unlabeled data to create an artificial dataset. The algorithm is initially trained on the labeled data, and its predictions on the unlabeled data are used to add additional training examples [32].

Algorithms

Label propagation: This algorithm uses the labeled data to label the unlabeled data based on the similarity between the points. It assumes that if two data points are close to each other in the feature space, they are likely to have similar labels [33].

2.4. Reinforcement Learning

Reinforcement learning is a type of machine learning where an agent learns how to behave in an environment by performing actions and observing the rewards of those actions. It is commonly used in areas like robotics, game-playing, and navigation [34].

Key concepts

Agent: This is the learner or decision-maker in the reinforcement learning model.

Environment: This is what the agent interacts with. The environment takes the agent's current state and action as the input and returns the agent's reward and the next state as the output.

Action (A): This is the set of all possible moves the agent can make.

State (S): This is the current situation returned by the environment.

Reward (R): A scalar value that the agent receives as feedback, which it tries to maximize over time [35].

Algorithms

Q-learning: This is a model-free algorithm used for learning a policy, which tells an agent which action to take under which circumstances. It defines a function Q(s, a), representing the quality or the utility of taking action "a" in state "s" [36].

Deep Q network (DQN): This is an extension of Q-learning that uses deep learning to predict Q-values. It was used by DeepMind to train agents that could play a range of Atari games to a superhuman level [37].

2.5. Ensemble Methods

Ensemble methods use multiple learning algorithms to obtain better predictive performance than could be obtained from any of the constituent learning algorithms alone. They are often used to improve the performance of weak learners [38].

Key concepts

Bootstrap aggregating (Bagging): This is used to reduce the variance of a decision tree. Multiple subsets of the original dataset are created using bootstrapping, a model is trained on each, and the models are averaged (for regression), or a majority vote is taken (for classification).

Boosting: This is an iterative technique that adjusts the weight of an observation based on the last classification. If an observation is classified incorrectly, it tries to increase the weight of this observation [39].

Algorithms

Random forest: This is an ensemble of decision trees, generally trained with the "bagging" method. It creates multiple decision trees during training and merges them to obtain a more accurate and stable prediction.

AdaBoost: This is one of the most successful boosting algorithms for binary classification problems. It works by weighing instances in the dataset by how easy or difficult they are to classify, allowing the algorithm to pay more or less attention to them in the construction of subsequent models [39].

3. Solute–Solvent Interactions

3.1. Introduction to Solute–Solvent Interactions

Solute–solvent interactions are the interactions that occur between the solute (the substance being dissolved) and the solvent (the substance dissolving the solute). Solubility is defined as the ability of a compound to be dissolved. These interactions can vary significantly depending on the nature of the solute and solvent involved. For example, polar solvents like water are good at dissolving polar solutes such as salts, while non-polar solvents like oil are better suited for dissolving non-polar solutes like fats.

Solute–solvent interactions are influenced by a multitude of factors. Temperature, for instance, plays a significant role in these interactions. An increase in temperature typically increases the kinetic energy of molecules or particles, leading to increased movement and interaction between the solute and solvent molecules. This often results in the increased solubility of solids in liquids [40]. However, for gas molecules dissolved in liquids, an increase in temperature often decreases the solubility, as the increased kinetic energy allows the gas molecules to escape from the solution [40]. The temperature dependence of the solubility is shown in Figure 1.

The pH of a solution can also affect solute–solvent interactions, especially for acidic or basic solutes. Certain solutes may react with the solvent under acidic or basic conditions, like calcium fluoride being more soluble in acidic conditions.

Another factor is concentration. At higher concentrations, solute ions are more likely to interact with each other rather than the solvent, which can lead to precipitation or reduced solubility. According to Henry's Law, a higher molarity causes lower solubility. Pressure, on the other hand, mainly affects the solubility of gases in liquids. According to Henry's law, the solubility of a gas in a liquid is directly proportional to the pressure of the gas above the liquid, meaning that increasing the pressure increases the solubility of the gas.

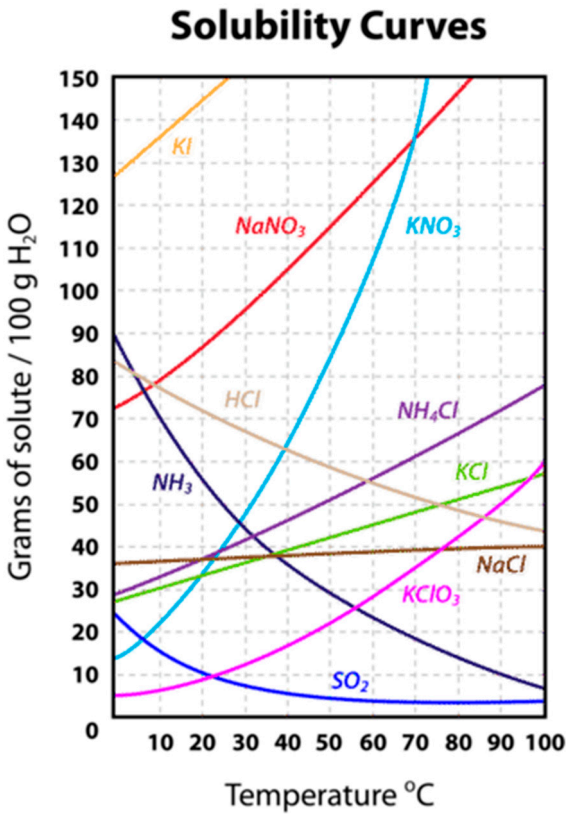


Figure 1. Graph showing solubility as a function of temperature by Christopher Auyeung; reprinted with permission from CK-12 Foundation under CC BY-NC 3.0 licence.

Inherent solubility, the solubility of a compound in its uncharged state, is another key factor. The inherent solubility of a solute in a particular solvent will greatly affect their interaction. Solubility is defined as the maximum amount of solute that can dissolve in a solvent at a given temperature [40].

The nature of solute–solvent interactions is governed by various factors. These include the polarity of the solute and solvent, their molecular size and shape, and the presence of functional groups.

Machine learning can be used to predict these solute–solvent interactions. The first step in this process is to gather a large dataset of known solute–solvent interactions. This data can include information about the solute and solvent's molecular structure, polarity, size, and other relevant properties. It can also include data about the resulting interaction, such as the solubility of the solute in the solvent [41]. This data can be found in scientific databases, academic institutions, industry partnerships, government and regulatory bodies, simulations and computations, data providers, and open data repositories. It can be inputted as numerical data, categorical data, time-series data, or text.

Once the aforementioned data is gathered, it can be used to train a machine learning model. Using machine learning, this model will learn to recognize patterns in the data and make predictions based on these patterns. After the model is trained, using the 25:75 machine learning ratio, it can be used to predict solute–solvent interactions for new pairs of solutes and solvents. For example, given a new solute and solvent, the model could predict whether the solute would be soluble in the solvent and to what extent. These predictions could be used to guide experiments and save time and resources in the laboratory [42].

Machine learning offers a powerful tool for predicting solute–solvent interactions. By learning from datasets of known interactions, machine learning models can make accurate predictions for new solute–solvent pairs.

3.2. Solute–Solvent Interactions' Effect on Crystallization Conditions

Crystallization is a fundamental process in various scientific fields, including chemistry, physics, and materials science. It is the process by which a solid forms, where the atoms or molecules are highly organized into a structure known as a crystal. Solute–solvent interactions play a significant role in determining the crystallization conditions. For instance, the solute–solvent interactions can influence the solubility of the solute, the rate of crystallization, purity, size, and shape of the crystals that form within a thermodynamic context where factors such as enthalpy and entropy govern the process.

The solute–solvent interactions can affect the solubility of the solute. If the interactions between the solute and solvent are strong, the more solute can be dissolved, and it may be more difficult for the solute to separate from the solvent and form crystals.

The rate of crystallization is another factor that can be influenced by solute–solvent interactions. If the interactions between the solute and solvent are strong, it may take longer for the solute to separate from the solvent and form crystals. On the other hand, if the interactions are weak, the solute may separate from the solvent more quickly, leading to faster crystallization [43].

The size and shape of the crystals that form can also be affected by solute–solvent interactions. For example, for salicylic acid, if the interactions between the solute and solvent are strong, the crystals that form may be smaller and more irregular in shape. Conversely, if the interactions are weak, the crystals may be larger and more regular in shape [44].

The temperature and pressure conditions under which crystallization occurs can also be influenced by solute–solvent interactions. For example, if the interactions between the solute and solvent are strong, crystallization may occur at higher temperatures and pressures. Conversely, if the interactions are weak, crystallization may occur at lower temperatures and pressures.

3.3. Enthalpy

Enthalpy (H) is a thermodynamic quantity that encapsulates the total heat content of a system. It is often conceptualized as the internal energy of the system. In chemical reactions, the change in enthalpy (ΔH) serves as a measure of the heat absorbed or released. An exothermic reaction, characterized by $\Delta H < 0$, releases heat into the surroundings, whereas an endothermic reaction, with $\Delta H > 0$, absorbs heat [45].

3.4. Entropy

Entropy (S), on the other hand, is a measure of the disorder or randomness of a system. In a sense, it quantifies the number of microscopic configurations corresponding to a macroscopic state. An increase in entropy ($\Delta S > 0$) typically signifies a transition towards a more disordered state, while a decrease ($\Delta S < 0$) indicates a move towards orderliness [46].

3.5. Gibbs Free Energy

The concept of Gibbs free energy (G) serves as a vital thermodynamic metric that amalgamates the contributions of both enthalpy (H) and entropy (S) to contribute to an understanding of solute–solvent interactions. Defined by the equation $G = H - T \times S$, where T is the absolute temperature, Gibbs free energy provides a criterion for the spontaneity of a process, including precipitation and dissolution. A negative change in Gibbs free energy (ΔG) is indicative of a spontaneous process, while a positive ΔG suggests non-spontaneity [47].

In the context of solute–solvent interactions, both enthalpic and entropic factors coalesce to dictate the overall ΔG. For instance, a dissolution process with a favorable enthalpy change ($\Delta H < 0$) and an increase in entropy ($\Delta S > 0$) would most likely result in a negative ΔG, thereby facilitating spontaneity. Conversely, an endothermic enthalpy change ($\Delta H > 0$) coupled with a decrease in entropy ($\Delta S < 0$) would elevate ΔG, making the process non-spontaneous under standard conditions [47].

It is crucial to note that temperature plays a pivotal role in modulating the contributions of enthalpy and entropy to ΔG. At elevated temperatures, the entropic term T × ΔS may dominate, rendering a process spontaneous even if it is endothermic. Conversely, at lower temperatures, the enthalpic term ΔH may prevail, making an entropically unfavorable process spontaneous. Understanding the nuanced interplay between enthalpy and entropy through the lens of Gibbs free energy is key to understanding solute–solvent interactions [47].

Gibbs free energy for solvation has been predicted using machine learning with relatively high accuracy. Recent improvements in this field come from the use of neural networks, which are uses of machine learning that resemble human intelligence [41,48]. The advantage of using machine learning to find Gibbs free energy for solvation comes from the wide array of possibilities that come out of this topic. There are a vast number of solutes, solvents, and, therefore, combinations of the two. So, by way of machine learning, this complex problem can be simplified using algorithms that have the aforementioned relatively high accuracy. This predicted Gibbs free energy can be used as an input for machine learning and lead to a more accurate prediction of optimal crystallization conditions.

In addition to these factors, solute–solvent interactions can also affect the purity of the crystals that form. Take, for example, salicylic acid. If the interactions between the solute and solvent are strong, the solvent may be more likely to become incorporated into the crystal structure, leading to impure crystals. On the other hand, if the interactions are weak, the solvent may be less likely to become incorporated into the crystal structure, leading to purer crystals [49].

Solute–solvent interactions play a crucial role in determining the conditions under which crystallization occurs. Understanding these interactions can help scientists optimize the crystallization process, leading to the formation of high-quality crystals. This can be important in many fields [49].

Impact

Understanding and optimizing solute–solvent interactions and their effect on crystallization conditions can have a profound impact on various industries. For instance, in the pharmaceutical industry, the ability to control crystallization conditions can lead to the production of drugs with improved properties. By controlling the size and shape of the crystals, pharmaceutical companies can influence the drug's dissolution rate, which in turn can affect the drug's bioavailability. This means that the drug can be more effectively absorbed by the body, improving therapeutic effects.

In the chemical manufacturing industry, the ability to control crystallization conditions can lead to improved product purity and yield. By optimizing the solute–solvent interactions, manufacturers can control the rate of crystallization, which can influence the size and purity of the crystals. This can lead to a more efficient manufacturing process, reducing waste and lowering production costs [49].

In the food and beverage industry, controlling crystallization conditions can improve the texture and taste of products. For example, in the production of ice cream, controlling the size of ice crystals can influence the smoothness and creaminess of the final product. Similarly, in the production of confectionery items like chocolate and hard candies, controlling crystallization can influence the product's hardness, glossiness, and melting properties [50].

In the field of materials science, understanding solute–solvent interactions and their effect on crystallization can lead to the development of new materials with unique properties. For example, in the production of semi-conductors, controlling the size and shape of crystals can influence the material's electrical and optical properties. This can lead to the development of more efficient electronic devices [51].

In conclusion, understanding and optimizing solute–solvent interactions and their effect on crystallization conditions can have a profound impact on various industries. By controlling these interactions, industries can improve product quality, enhance efficiency,

reduce costs, and even develop new materials with unique properties. Therefore, research in this area is of great importance and can lead to significant advancements in various fields.

4. Analysis

The effectiveness of using machine learning methods in the field of crystallization is evident. As shown in Table 1, a multitude of machine learning techniques are viable for predicting solute–solvent interactions and improving crystallization. These include supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, and ensemble methods. They can be applied in many ways as well, with a broad range of uses. Methods can be used to predict properties [52] and tailor to specific properties such as chirality [53], ultimately saving time [54] and costs [55]. Figure 2 shows how machine learning can be used to improve crystallization for an example compound, compound x.

Table 1. Types of machine learning and insights into their applications to crystallization.

Type of Machine Learning	Overview	Past Uses	Applications
Supervised learning	In supervised learning, the algorithm is trained on a labeled dataset, which means each training example is paired with an output label. For predicting solute–solvent interactions, a dataset could be created where the features include various properties of the solute and solvent (e.g., polarity, molecular weight, etc.), and the label could be the type or strength of the interaction (e.g., hydrogen bonding, van der Waals forces, etc.). Algorithms like linear regression or support vector machines (SVMs) could be employed to predict these interactions.	Pharmaceuticals: supervised learning has been extensively used in drug discovery and development. Algorithms like SVMs have helped in predicting the bioactivity of compounds based on their chemical properties, which is analogous to predicting solute–solvent interactions [56]. Material science: linear regression and other supervised techniques have been used to predict material properties, such as tensile strength or thermal conductivity, based on their molecular composition [57].	Once the model is trained to predict solute–solvent interactions, it can be applied to optimize crystallization processes in various industries. For example, in pharmaceuticals, knowing how a particular solute interacts with potential solvents can help in creating crystals with desired properties like solubility and bioavailability.
Unsupervised learning	Unsupervised learning algorithms work with datasets without labeled responses. Clustering techniques like K-means could be used to group different types of solute–solvent interactions based on their properties.	Chemical engineering: unsupervised learning, especially clustering, has been employed to understand complex chemical processes. For example, clustering has been used to categorize different catalysts based on their performance characteristics [58]. Environmental science: clustering techniques have been used to analyze and group pollutants in water sources, providing insights similar to those for solute–solvent interactions [59].	The clusters can reveal hidden patterns in how different solutes and solvents interact, which can be invaluable for improving crystallization methods. For instance, solutes prone to forming undesired crystal structures might be clustered together, allowing for targeted optimization.

Table 1. *Cont.*

Type of Machine Learning	Overview	Past Uses	Applications
Semi-supervised learning	In semi-supervised learning, the algorithm is trained on a dataset that contains both labeled and unlabeled data. This approach is particularly useful when acquiring a fully labeled dataset is expensive or time-consuming.	Biotechnology: semi-supervised learning has been used in genomic sequencing, where only a part of the genetic data is labeled. This parallels predicting solute–solvent interactions in cases where only partial information is available [60]. Sensor data analysis: in manufacturing, semi-supervised learning has been applied to sensor data where only some data points are labeled, aiding in predictive maintenance [61].	A semi-supervised model could be trained on a partially labeled dataset to predict solute–solvent interactions. The model could then be used to predict the interactions in a crystallization process, allowing for adjustments in real time to achieve the desired crystal properties.
Reinforcement learning	Reinforcement learning involves agents who take actions in an environment to achieve a goal. In the context of solute–solvent interactions, the agent could be programmed to find the optimal conditions for a desired type of interaction, receiving rewards based on the quality of the crystals formed.	Robotics: reinforcement learning has been pivotal in robotics for tasks like object manipulation and navigation, which require adaptive learning similar to optimizing crystallization conditions [62]. Energy management: In smart grids, reinforcement learning has been used to optimize energy distribution and consumption, a concept that can be applied to managing crystallization processes [63].	Reinforcement learning could be used to dynamically adjust conditions like temperature, pressure, and concentration during the crystallization process to achieve optimal crystal properties, thereby saving costs and improving efficiency.
Ensemble methods	Ensemble methods combine multiple algorithms to improve performance. For example, a random forest algorithm could be used to predict solute–solvent interactions by leveraging the strengths of multiple decision trees.	Financial forecasting: ensemble methods, particularly random forests, have been used in stock market prediction, dealing with complex patterns much like those in predicting solute–solvent interactions [64] Weather prediction: the use of ensemble methods in weather forecasting models demonstrates their effectiveness in handling complex systems with many variables, akin to crystallization processes [65].	Ensemble methods can provide more robust and accurate predictions, which is crucial for processes like crystallization, where small changes can have significant impacts. By accurately predicting solute–solvent interactions, the crystallization process can be optimized for better yield and quality.

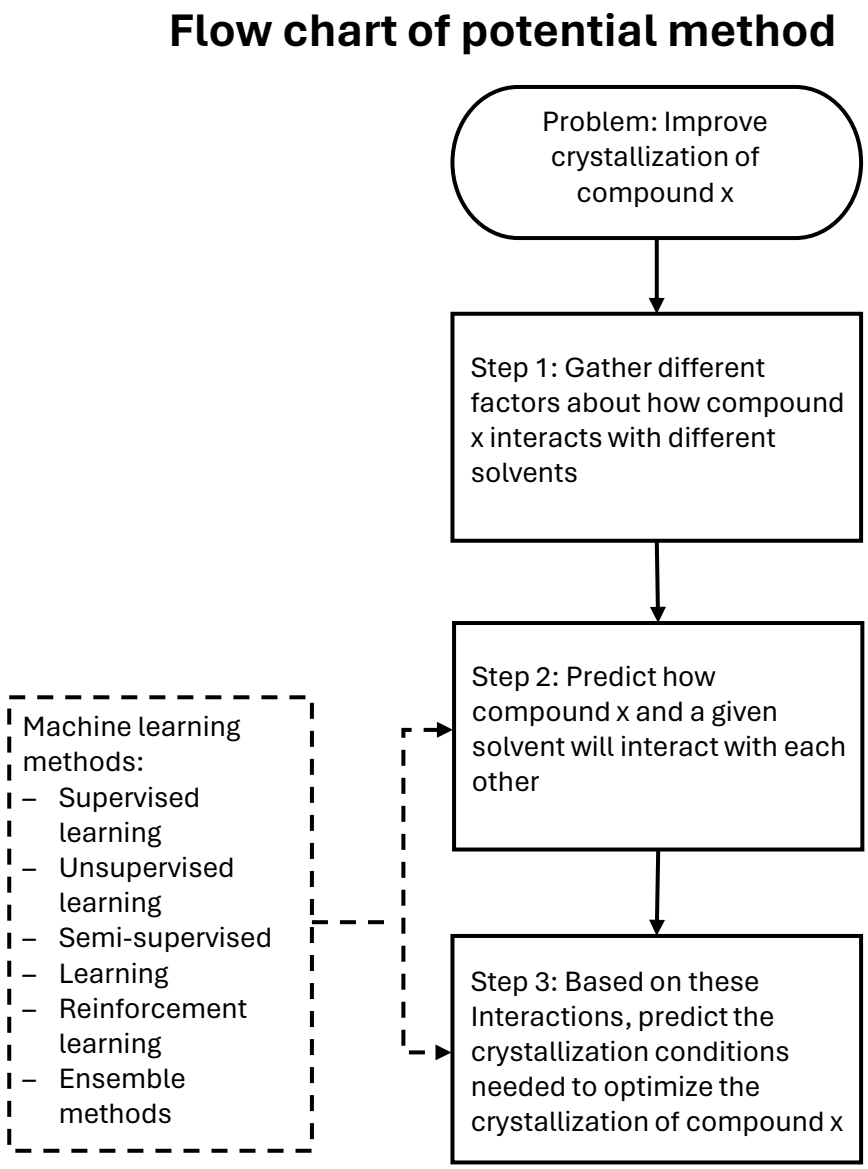


Figure 2. Flowchart showing an example process of how crystallization can be improved using machine learning.

5. Conclusions

In summary, machine learning offers a plethora of techniques to predict solute–solvent interactions, each with its unique strengths and applications. These predictions can be invaluable for optimizing crystallization processes in various industries, from pharmaceuticals to food production.

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References

1. Doxsee, K.M.; Francis, P.E. Crystallization of Ammonium Nitrate from Nonaqueous Solvents. *Ind. Eng. Chem. Res.* **2000**, *39*, 3493–3498. [CrossRef]
2. Behrens, M.A.H.; Lacmann, R.; Schröder, W. Crystallization of potassium chloride: The additives ZnCl2, Na6 [(PO3)6] and K4 [Fe(CN)6]. *Chem. Eng. Technol.* **1995**, *18*, 295–301. [CrossRef]
3. Wang, Y.; Qiu, L.P.; Hu, M.F. Magnesium ammonium phosphate crystallization: A possible way for recovery of phosphorus from wastewater. *IOP Conf. Ser. Mater. Sci. Eng.* **2018**, *392*, 032032. [CrossRef]
4. Singh, M.K. Simulating Growth Morphology of Urea Crystals from Vapour and Aqueous Solution. *CrystEngComm* **2015**, *17*, 7731–7744. [CrossRef]
5. Kim, S.; Wei, C.; Kiang, S. Crystallization Process Development of an Active Pharmaceutical Ingredient and Particle Engineering via the Use of Ultrasonics and Temperature Cycling. *Org. Process. Res. Dev.* **2003**, *7*, 997–1001. [CrossRef]
6. Tung, H.H.; Paul, E.L.; Midler, M.; McCauley, J.A. *Crystallization of Organic Compounds: An Industrial Perspective*; Wiley: Hoboken, NJ, USA, 2024.
7. Nebol'sin, V.A.; Swaikat, N. About Some Fundamental Aspects of the Growth Mechanism Vapor-Liquid-Solid Nanowires. *J. Nanotechnol.* **2023**, *2023*, e7906045. [CrossRef]
8. Zhang, L.; Yang, M.; Zhang, S.; Niu, H. Unveiling the Crystallization Mechanism of Cadmium Selenide via Molecular Dynamics Simulation with Machine-Learning-Based Deep Potential. *J. Mater. Sci. Technol.* **2024**, *185*, 23–31. [CrossRef]
9. Ma, Y.; Svärd, M.; Xiao, X.; Gardner, J.M.; Olsson, R.T.; Forsberg, K. Precipitation and Crystallization Used in the Production of Metal Salts for Li-Ion Battery Materials: A Review. *Metals* **2020**, *10*, 1609. [CrossRef]
10. Lewis, A.; Seckler, M.; Kramer, H.; Van Rosmalen, G. *Industrial Crystallization: Fundamentals and Applications*; Cambridge University Press: Cambridge, UK, 2015.
11. Qi, A.; Zhang, L. Review of Computer-Aided Methods in Fat Crystallization Studies. *J. Am. Oil Chem. Soc.* **2024**. [CrossRef]
12. Karpiński, P.; Bałdyga, J. Batch Crystallization. In *Handbook of Industrial Crystallization*; Cambridge University Press: Cambridge, UK, 2019; pp. 346–379. [CrossRef]
13. Varshosaz, J.; Ghassami, E.; Ahmadipour, S. Crystal Engineering for Enhanced Solubility and Bioavailability of Poorly Soluble Drugs. *Curr. Pharm. Des.* **2018**, *24*, 2473–2496. [CrossRef]
14. Adapa, S.; Schmidt, K.A.; Jeon, I.J.; Herald, T.J.; Flores, R.A. Mechanisms of Ice Crystallization and Recrystallization in Ice Cream: A Review. *Food Rev. Int.* **2000**, *16*, 259–271. [CrossRef]
15. Statista. United States: Sugar Production 2023/24. Available online: https://www.statista.com/statistics/249661/us-sugar-production/ (accessed on 11 February 2024).
16. Wu, G.; Yion, W.T.G.; Dang, K.L.N.Q.; Wu, Z. Physics-informed machine learning for MPC: Application to a batch crystallization process. *Chem. Eng. Res. Des.* **2023**, *192*, 556–569. [CrossRef]
17. Heist, J.A.; Hunt, K.M. Material Recycling and Waste Minimization by Freeze Crystallization. Final Technical Report, August 1993–April 1994 (Technical Report). OSTI.GOV. Available online: https://www.osti.gov/biblio/189745 (accessed on 1 May 1995).
18. Das, P.; Dutta, S.; Singh, K.; Maity, S. Energy saving integrated membrane crystallization: A sustainable technology solution. *Sep. Purif. Technol.* **2019**, *228*, 115722. [CrossRef]
19. Liu, Q.; Wu, Y. Supervised Learning. In *Encyclopedia of the Sciences of Learning*; Springer: Boston, MA, USA, 2012. [CrossRef]
20. Renuka, D.K.; Hamsapriya, T.; Chakkaravarthi, M.R.; Surya, P.L. Spam Classification Based on Supervised Learning Using Machine Learning Techniques. In Proceedings of the 2011 International Conference on Process Automation, Control and Computing (PACC), Coimbatore, India, 20–22 July 2011; pp. 1–7.
21. Domala, V.; Kim, T.-W. A Univariate and Multivariate Machine Learning Approach for Prediction of Significant Wave Height. In Proceedings of the OCEANS 2022, Hampton Roads, VA, USA, 17–20 October 2022; Available online: https://ieeexplore.ieee.org/document/9977028 (accessed on 11 February 2024).
22. Hodson, T.O.; Over, T.M.; Foks, S.S. Mean Squared Error, Deconstructed. *J. Adv. Model. Earth Syst.* **2021**, *13*, e2021MS002681. Available online: https://agupubs.onlinelibrary.wiley.com/doi/full/10.1029/2021MS002681 (accessed on 11 February 2024). [CrossRef]
23. Schneider, A.; Hommel, G.; Blettner, M. Linear Regression Analysis. *Dtsch. Arztebl. Int.* **2010**, *107*, 776–782. [CrossRef] [PubMed]
24. Evgeniou, T.; Pontil, M. Support Vector Machines: Theory and Applications. In *Advanced Course on Artificial Intelligence*; Springer: Berlin/Heidelberg, Germany, 2001; pp. 249–257. [CrossRef]
25. Song, Y.-Y.; Lu, Y. Decision tree methods: Applications for classification and prediction. *Shanghai Arch. Psychiatry* **2015**, *27*, 130–135. [CrossRef] [PubMed]
26. Naeem, S.; Ali, A.; Anam, S.; Ahmed, M.M. An Unsupervised Machine Learning Algorithms: Comprehensive Review. *Int. J. Comput. Digit. Syst.* **2023**, *13*, 911–921. [CrossRef] [PubMed]
27. Caron, M.; Bojanowski, P.; Joulin, A.; Douze, M. Deep Clustering for Unsupervised Learning of Visual Features. In Proceedings of the European Conference on Computer Vision (ECCV), Munich, Germany, 8–14 September 2018.
28. Roman, V. Unsupervised Learning: Dimensionality Reduction. Available online: https://towardsdatascience.com/unsupervised-learning-dimensionality-reduction-ddb4d55e0757 (accessed on 17 April 2021).
29. Sinaga, K.P.; Yang, M.-S. Unsupervised K-Means Clustering Algorithm. *IEEE Access* **2020**, *8*, 80716–80727. [CrossRef]

30. Jolliffe, I.T.; Cadima, J. Principal component analysis: A review and recent developments. *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.* **2016**, *374*, 20150202. [CrossRef]
31. Reddy, Y.C.A.P.; Viswanath, P.; Reddy, B.E. Semi-supervised learning: A brief review. *Int. J. Eng. Technol.* **2018**, *7*, 81–85. [CrossRef]
32. Lee, D.-H. Pseudo-Label: The Simple and Efficient Semi-Supervised Learning Method for Deep Neural Networks. In *Workshop: Challenges in Representation Learning (WREPL)*; ICML: Honolulu, HI, USA, 2013.
33. Iscen, A.; Tolias, G.; Avrithis, Y.; Chum, O. Label Propagation for Deep Semi-Supervised Learning. In Proceedings of the 2019 IEEE/CVF Conference on Computer Vision and Pattern Recognition (CVPR), Long Beach, CA, USA, 15–20 June 2019; pp. 5065–5074.
34. Sivamayil, K.; Rajasekar, E.; Aljafari, B.; Nikolovski, S.; Vairavasundaram, S.; Vairavasundaram, I. A Systematic Study on Reinforcement Learning Based Applications. *Energies* **2023**, *16*, 1512. Available online: https://www.mdpi.com/1996-1073/16/3/1512 (accessed on 11 February 2024). [CrossRef]
35. Nancy, J. Basics—Reinforcement Learning. Analytics Vidhya (Blog). Available online: https://medium.com/analytics-vidhya/basics-reinforcement-learning-66aae5da4c85 (accessed on 5 May 2020).
36. Watkins, C.J.C.H.; Dayan, P. Q-learning. *Mach. Learn.* **1992**, *8*, 279–292. [CrossRef]
37. Varga, B.; Kulcsár, B.; Chehreghani, M.H. Deep Q-learning: A robust control approach. *Int. J. Robust Nonlinear Control.* **2022**, *33*, 526–544. [CrossRef]
38. Dietterich, T.G. Ensemble Methods in Machine Learning. In *Multiple Classifier Systems, Proceedings of the First International Workshop on Multiple Classifier Systems, Cagliari, Italy, 9–11 June 2000*; Springer: Berlin/Heidelberg, Germany, 2000; pp. 1–15. [CrossRef]
39. Freund, Y.; Robert, E.S. A Short Introduction to Boosting. *J. Jpn. Soc. Artif. Intell.* **1999**, *14*, 1612.
40. Behera, A.L.; Su, S.; Sachinkumar, P. Enhancement of Solubility: A Pharmaceutical Overview. *Pharm. Lett.* **2010**, *2*, 310–318.
41. Ferraz-Caetano, J.; Teixeira, F.; Cordeiro, M.N.D.S. Explainable Supervised Machine Learning Model To Predict Solvation Gibbs Energy. *J. Chem. Inf. Model.* **2023**, *64*, 2250–2262. [CrossRef] [PubMed]
42. Alibakhshi, A.; Hartke, B. Improved prediction of solvation free energies by machine-learning polarizable continuum solvation model. *Nat. Commun.* **2021**, *12*, 3584. [CrossRef] [PubMed]
43. Karunanithi, A.; Luke, A. Chapter 4 Solvent Design for Crystallization of Pharmaceutical Products. *Comput. Aided Chem. Eng.* **2007**, *23*, 115–147. [CrossRef]
44. Khamar, D. Investigating the Role of Solvent–Solute Interaction in Crystal Nucleation of Salicylic Acid from Organic Solvents. *J. Am. Chem. Soc.* **2014**, *136*, 11664–11673. [CrossRef]
45. Keifer, D. Enthalpy and the Second Law of Thermodynamics. *J. Chem. Educ.* **2019**, *96*, 1407–1411. [CrossRef]
46. Brissaud, J.-B. The meanings of entropy. *Entropy* **2005**, *7*, 68–96. [CrossRef]
47. Chen, L.-Q. Chemical potential and Gibbs free energy. *MRS Bull.* **2019**, *44*, 520–523. [CrossRef]
48. Chung, Y.; Vermeire, F.H.; Wu, H.; Walker, P.J.; Abraham, M.H.; Green, W.H. Group Contribution and Machine Learning Approaches to Predict Abraham Solute Parameters, Solvation Free Energy, and Solvation Enthalpy. *J. Chem. Inf. Model.* **2022**, *62*, 433–446. [CrossRef] [PubMed]
49. Li, X.; Wang, N.; Huang, Y.; Xing, J.; Huang, X.; Ferguson, S.; Wang, T.; Zhou, L.; Hao, H. The role of solute conformation, solvent–solute and solute–solute interactions in crystal nucleation. *AIChE J.* **2023**, *69*, e18144. [CrossRef]
50. Bund, R.K.; Hartel, R.W. Blends of delactosed permeate and pro-cream in ice cream: Effects on physical, textural and sensory attributes. *Int. Dairy J.* **2013**, *31*, 132–138. [CrossRef]
51. Patel, D.G.D.; Benedict, J.B. Crystals in Materials Science. In *Recent Advances in Crystallography*; IntechOpen: London, UK, 2012. [CrossRef]
52. Xiouras, C.; Cameli, F.; Quilló, G.L.; Kavousanakis, M.E.; Vlachos, D.G.; Stefanidis, G.D. Applications of Artificial Intelligence and Machine Learning Algorithms to Crystallization. *Chem. Rev.* **2022**, *122*, 13006–13042. [CrossRef] [PubMed]
53. Kovács, E.A.; Szilágyi, B. A synthetic machine learning framework for complex crystallization processes: The case study of the second-order asymmetric transformation of enantiomers. *Chem. Eng. J.* **2023**, *465*, 142800. [CrossRef]
54. Kirman, J.; Johnston, A.; Kuntz, D.A.; Askerka, M.; Gao, Y.; Todorović, P.; Ma, D.; Privé, G.G.; Sargent, E.H. Machine-Learning-Accelerated Perovskite Crystallization. *Matter* **2020**, *2*, 938–947. [CrossRef]
55. Meyer, C.; Arora, A.; Scholl, S. A method for the rapid creation of AI driven crystallization process controllers. *Comput. Chem. Eng.* **2024**, *186*, 108680. [CrossRef]
56. Kolluri, S. Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: A Review-PMC. *AAPS J.* **2022**, *24*, 19. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8726514/ (accessed on 11 February 2024). [CrossRef]
57. Zhong, X. Explainable Machine Learning in Materials Science. *npj Comput. Mater.* **2022**, *8*, 204. Available online: https://www.nature.com/articles/s41524-022-00884-7 (accessed on 11 February 2024). [CrossRef]
58. Dobbelaere, M. Machine Learning in Chemical Engineering: Strengths, Weaknesses, Opportunities, and Threats. *Engineering* **2021**, *7*, 1201–1211. Available online: https://www.sciencedirect.com/science/article/pii/S2095809921002010 (accessed on 29 July 2021). [CrossRef]
59. Zhu, J.-J.; Yang, M.; Ren, Z.J. Machine Learning in Environmental Research: Common Pitfalls and Best Practices. *Environ. Sci. Technol.* **2023**, *57*, 17671–17689. [CrossRef] [PubMed]

60. Kwon, H.; Ali, Z.A.; Wong, B.M. Harnessing Semi-Supervised Machine Learning to Automatically Predict Bioactivities of Per- and Polyfluoroalkyl Substances (PFASs). *Environ. Sci. Technol. Lett.* **2022**, *10*, 1017–1022. [CrossRef] [PubMed]
61. Cai, H.; Zhang, X.; Liu, X. Semi-Supervised End-To-End Contrastive Learning For Time Series Classification. *arXiv* **2023**. [CrossRef]
62. Ibarz, J.; Tan, J.; Finn, C.; Kalakrishnan, M.; Pastor, P.; Levine, S. How to train your robot with deep reinforcement learning: Lessons we have learned. *Int. J. Robot. Res.* **2021**, *40*, 698–721. [CrossRef]
63. Nakabi, T.A.; Toivanen, P. Deep reinforcement learning for energy management in a microgrid with flexible demand. *Sustain. Energy Grids Netw.* **2020**, *25*, 100413. [CrossRef]
64. Wu, H.; Levinson, D. The ensemble approach to forecasting: A review and synthesis. *Transp. Res. Part C Emerg. Technol.* **2021**, *132*, 103357. [CrossRef]
65. Gneiting, T.; Raftery, A.E. Weather Forecasting with Ensemble Methods. *Science* **2005**, *310*, 248–249. [CrossRef]

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