Disrupting 3D Printing of Medicines with Machine Learning

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Abstract

3D printing (3DP) is a progressive technology capable of transforming pharmaceutical development. However, despite its promising advantages, its transition into clinical settings remains slow. In order to make the vital leap to mainstream clinical practice and improve patient care, 3DP must harness modern technologies. Machine learning (ML), an influential branch of artificial intelligence, may be a key partner for 3DP. Together, 3DP and ML can utilise intelligence based on human-learning to accelerate drug product development, ensure stringent **quality control**, and inspire innovative dosage form design. With ML's capabilities, streamlined 3DP drug delivery could mark the next era of personalised medicine. This review details how ML can be applied to elevate the 3DP of pharmaceuticals and importantly how it can expedite 3DP's integration into mainstream healthcare.

Keywords: Additive Manufacturing; 3D Printed Drug Products and Formulation; Industry 4.0 and digital health; Personalized Oral Drug Delivery Systems and Medical Devices; Biomedical Engineering and Pharmaceutical Sciences; Translational Pharmaceutics.

Main text

Moving 3D Printing of Pharmaceuticals Beyond the Laboratory and into the Clinic

At its inception 3D printing (3DP) resulted in a burst of innovation, promise, and action; followed by a realisation of the challenges to its widespread adoption [1-4]. Significant interest around pharmaceutical 3DP began towards the turn of the century, at a time when the paradigm was the conventional, large-scale mass-manufacturing of identical dosage forms [5-7]. This inflexible model of medicine offered simplicity and safety, though often left groups of patients with special pharmaceutical needs, such as the elderly and paediatrics, overlooked and unprovided for [8-10]. A key breakthrough for 3DP pharmaceuticals was the United States Food and Drug Agency (FDA) approval of Spritam® in 2015[i]. Spritam® is a disintegrating levetiracetam formulation licensed for the treatment of epilepsy, produced using powder bed inkjet printing. However, rather than highlighting 3DP's capability to produce personalised, on-demand medicines, Spritam® instead aligned itself with the mass-manufacturing market. Though 3DP technology entered the pharmaceutical industry, it had not yet achieved its potential for on-demand, **personalised medicines (see Glossary)**.

In the years following the approval of Spritam®, research supporting the use of 3DP to fabricate bespoke pharmaceutical formulations began an exponential pace [11-20]. Although 3DP was initially employed to produce simple tablets, the academic 3DP community soon developed the expertise to produce complex structures, polypills, drug-loaded medical devices, and 4D designs [21-36]. Special patient populations were actively acknowledged in the movement, exemplified by the case of 3DP tablets incorporating braille designs for the visually impaired [37, 38]. Bioprinting, a branch of 3DP capable of printing living cells, was also conceived, pledging a future of 3DP organs and probiotic therapies [39-42]. Despite

encouraging results when tested *in vitro* and *in vivo* using animal models of disease, very few 3DP pharmaceuticals have entered human studies, and none have followed in the footsteps of Spritam® with market approval. A recent marker of 3DP clinical success was a paediatric trial conducted in a hospital setting for the treatment of a rare metabolic condition, maple syrup urine disease (MSUD) [43]. The MSUD trial used semi-solid extrusion technology to fabricate chewable Printlets™ containing personalised doses of isoleucine, which replaced the need for costly and time-consuming manual extemporaneous compounding. This study highlights the promise of 3DP in a clinical setting: better control of patient's drug plasma levels with lower variability compared with extemporaneous formulations, and 3DP Printlets™ were well accepted by patients in terms of flavour and colour. Unfortunately, such examples of pharmaceutical 3DP translation to clinical settings are isolated – depriving patients of superior, personalised medicines at the point of need.

The purpose of this review is to describe how **machine learning (ML)**, an influential branch of modern artificial intelligence, can be harnessed to accelerate pharmaceutical 3DP's transition from the research laboratory to clinical practice. We first describe the benefits of incorporating ML into the 3DP medicines pipeline. We then present the state of the art applications of ML in 3DP of medicines, followed by insights into challenges that could prevent the two technologies' unification. We conclude with an outlook for clinical adoption of ML-guided 3DP.

The Synergistic Power of Machine Learning and Pharmaceutical 3D Printing

Despite the significant potential of 3DP pharmaceuticals, uptake of the technology has still not reached mainstream clinical practice. Firstly, the research and development (R&D) stage of 3DP pharmaceutical formulations is frequently based upon iterative, trial and error approaches.

Here, 3DP's flexibility also plays a role in its downfall; formulation developers are encountered with thousands of options when designing a new product. R&D decisions span from the high-level such as type of 3DP technology, state of drug product, and pharmaceutical excipients, to cumulative precision-level choices, such as fine tuning of printer parameters [44-48]. Options for the type of 3DP alone could include fused deposition modelling (FDM); stereolithography; selective laser sintering; inkjet printing; binder jetting; electron beam melting; and digital light processing. Each will need to be considered from many standpoints, such as formulation requirements, cost, ease of use, maintenance, and regulatory framework. With innumerable decisions often comes inertia, as attempts to sample the entire experimental search space can be overwhelming. Moreover, an iterative approach to formulation development is often resource-costly. The pharmaceutical industry increasingly requires formulation R&D pipelines that are fast, cost-effective, and sustainable. Thus, to be commercially viable, decision-making within 3DP medicines' development should be evidence-based and efficient.

Effective quality control (QC) of 3DP medicines is an area receiving increasing attention. QC is a legal requirement of conventional large-scale pharmaceutical manufacturing. For good reason, patients and manufacturers must be assured that their medicines are produced exactly as intended, resulting in reliable, safe, and efficacious products with the desired effect. Traditionally, mass-manufacturing of pharmaceuticals fulfils QC requirements by sampling subsections of a batch; typically, 20 product units per pharmaceutical batch are selected for QC testing. These representative units must meet certain criteria for the whole batch to pass QC, for example all tablets must contain 95 - 105 % of drug stated on the product's label for the duration of its shelf life, often 2 years [49]. Clearly, for large batches of identically produced pharmaceuticals, conventional QC methods work well. On the other hand, for medicines that are extemporaneously produced in very small unique batches, then destructive QC methods are not viable. With ML's intelligence, 3DP medicines could find the balance between mass-

manufacturing and extemporaneous preparation: producing bespoke formulations in small batches, with validated non-destructive QC. Quality by design (QbD) is another aspect of QC that is promoted by regulatory bodies, including the FDA and EMA, to improve the understanding of pharmaceutical product and the manufacturing process [50, 51]. Certain aspects of the pharmaceutical workflow yield highly multicollinearity in data that traditional predictive models find difficult to simulate [52]. For this reason, ML techniques such as decision trees for hot melt extrusion (HME) and **Artificial Neural Networks (ANN)** for tableting have been utilised to effectively build quality into pharmaceutical products along the pharmaceutical workflow [52, 53].

ML is available to accelerate pharmaceutical 3DP into a future that is strategic, streamlined, and quality assured. First asserting its intelligence in the mastery of chess and other games, ML has now transcended into almost every sector of society, from video streaming platforms to the operating theatre [54-56]. ML achieves intelligence by discerning patterns in often large and multifactorial datasets, enabling complex data insight and accurate prediction-making [57-59]. Whereas humans generally require decades to master their field and reach the stage of reliable prediction-making, ML can be shown a dataset and consequently output expert-level predictions within seconds to minutes [60]. A myriad of ML techniques exists, encompassing multilinear regression to random forest, support vector machines to deep neural networks, each differing in their own learning style. ML is able to detect nuanced changes within data that may have been otherwise overlooked due to natural limitations in human sensing ability.

Primarily adopted by the drug discovery field, ML has been applied to discover novel antibiotics, identify previously unknown oncological protein targets, and plan efficient routes of drug synthesis, to name just a few applications [61-63]. Elsewhere ML has surpassed human ability in the prediction of drug release from polymers, drugs' contribution to tablet properties,

and the lipophilicity of biologics [64-66]. Reker et al. (2021) recently demonstrated how ML can be integrated to accelerate the discovery of therapeutic nanoformulations, resulting in nanoparticles that can achieve high drug loading (94.9%) [67]. Random forest was used to significantly minimise the possible number of formulations to investigate, from 2.1 million down to 100 pairings, consequently accelerating developments. ML can also be employed to directly optimise processes, rather than mapping inputs to outputs for developing a predictive model. One such example is **Bayesian Optimization (BO),** where rather than asking it to make a prediction, such as a true or false classification, the algorithm is asked to determine the optimal value. BO is able to maintain the rapid predictions commonly seen with ML, but also allows researchers to hone in on one specific goal [68].

Advanced forms of ML, including ANNs have also been extensively trialled by traditional pharmaceutical technologies presenting numerous successful examples that could be mapped to pharmaceutical 3DP. A pre-formulation tool has ANNs to determine key physicochemical properties of amorphous polymers, which included hydration characteristics, glass transition temperature, and rheological properties, with a low error (0-8% of prediction) [69]. An ANN approach has also modelled the effects of excipient concentrations and process parameters on prednisolone release from pellets, monitoring the root mean square error until a satisfactory value was obtained [70]. Additionally, HME process parameters have been evaluated using ANNs for vaginal film performance with predicted values within a 1% error of the experimental data [71]. A further example constructed ANNs for the quality-by-design based development of a biopharmaceutical classification system (BCS) Class IV compound to establish acceptable material attributes and limits for process parameters. Later, these manufacturing processes were scaled-up and the formulations were tested by two clinical bioequivalence studies [52]. Elsewhere, ANNs have been utilised for QC purposes: quantifying

a ranitidine hydrochloride polymorphic form in multi-component tablets using non-destructive X-ray powder diffractometric assays [72].

When applied to large datasets concerning pharmaceutical 3DP, ML holds several advantages over other computer-aided optimisation techniques frequently used in the pharmaceutical industry, such as design of experiment (DoE) [73-76]. Each traditional modelling technique possesses distinct disadvantages that has so far limited its application within 3DP. For example, DoE can only handle low-dimensional datasets, which will restrict the number of parameters explorable during one analysis. DoE methods can also become complex when applied to variables with non-linear relationships, something easily interpreted by ML [77]. ML is a cheap, versatile technique capable of interpreting numerous types of information including numbers, images, and text. This analysis of heterogenous data can be specifically applied in 3DP to predict optimal formulation design: saving time, money, and resources. Such processes may include designing 3DP product morphology to achieve a desired drug release profile or predicting the printability of formulations to avoid physically testing unviable options. Another promising opportunity for ML in 3DP could be intelligent automation of the printing process; removing operator error and optimising standardised production of 3DP pharmaceuticals. Post-printing ML can also facilitate non-destructive 3DP QC, thus accelerating the time from printer to patient. However, ML also carries its own challenges. These include data availability, output interpretability, and current requirement for ML specialists [78, 79]. Such barriers to the unification of 3DP and ML will be discussed further herein. An overview highlighting the applications of ML in pharmaceutical 3DP, and demonstrating how ML can be at the center of pharmaceutical discoveries is provided in **Figure 1**

Applications of Machine Learning in Pharmaceutical 3D Printing

Product Design

The ability to seamlessly fabricate complex pharmaceutical products with high precision is a significant advantage of 3DP of patient-centred medicinal products [80]. In practice, however, design of products with novel morphologies, functionalities, or drug release mechanisms is lengthy, subjective, and requires theoretical thinking [81]. A popular trend in recent years within pharmaceutical sciences is to design products based on mechanisms seen in nature; appropriately named bioinspiration. Whilst bioinspiration can aid strategic novel design, exemplified well by insect stinger-inspired 3DP microneedles for dermal drug delivery, it is not always translatable or guaranteed to succeed outside of nature [23, 82]. ML can be utilised to expedite 3DP's design process, by drawing on vast knowledge from the literature (including bioinspiration) and applying mathematical models to pair design features with end-product characteristics. Within pharmaceutics, ML has already been used to design new dosage form, primarily using **deep learning** [83]. As 3DP design is already digitalised, ML is well-suited for incorporation in this process. **Generative adversarial networks (GANs)** are a type of ML technique clearly exploitable for 3DP product design (**Figure 2**) [84]. GANs are documented for their ability to solve creative problems. Elsewhere, GANs have created new drug-like chemical structures [85]. GANs have also been applied for data augmentation in areas lacking data, to help increase the size of the dataset and improve the performance of ML models. One recent example involved using GANs to augment the number of film-forming formulations to allow DNN to achieve a remarkable predictive accuracy, as demonstrated by the *f2* score of 99.99 for all formulations [86].

Drug Product Development

Pharmaceutical formulation is a specialism unto itself, owing to the vast number of options available to drug development scientists when designing a formulation. Seemingly small adaptations in formulation components can result in dramatic end-product effects. For example, a photoreactive monomer used in stereolithography was recently found to have an unexpected reaction with one of the formulation's drugs, despite the drug only forming a minor portion of the overall formulation [87].

The requirement for formulations to be effectively printed, known as printability, poses an additional complexity within 3DP. A formulation may meet pharmaceutical requirements, but if it is not printable then it is ultimately not suitable for 3DP. A software known as M3DISEEN has recently been released utilising ML for the prediction of the printability of drug-loaded filaments by FDM [88]. The online software enables 3DP formulation scientists to predict whether their filament will be printable by FDM, based on just the pharmaceutical excipient trade names. M3DISEEN was trained on a dataset comprised of 614 drug-loaded formulations including 145 unique excipients. **Supervised** ML techniques utilised include multivariate linear regression, *k*-nearest neighbours, support vector machines, random forest, traditional neural networks and deep learning. Such software demonstrates how ML can be used to streamline the pharmaceutical 3DP process. Rather than exerting time and resources through manual testing of the printability of 3D drug products, ML can provide predictions before laboratory work is begun; vastly reducing the number of formulations requiring testing (**Figure 3**).

Intelligent Automation of 3D Printing Processes

An attractive goal within 3DP of medicines is to achieve a fully automated fabrication process. With the automation of 3DP, optimal printing parameters would be automatically selected based on the product specifications; vastly simplifying methods and removing operator error and subjectivity. Whilst traditional DoE techniques have attempted to model formulation characteristics with optimal printing parameters, they are inflexible to new information and adaptations in operating procedures [74]. Current 3D printers do not have the capacity to predict optimal printing parameters alone, currently requiring the expertise of the 3DP scientists to select parameters based on their experience. Here, ML could replace the need for on-hand 3DP experts by directing what parameters to select based on the requirements of the drug-loaded product to be printed. **Reinforcement learning (RL)**, an advanced form of ML based on neuroscience concepts, has the potential to lead the automation of pharmaceutical 3DP [89-91]. RL solves problems by attempting operations and grading their utility based on how much closer they move the system towards its end goal. This process is continuous, therefore operators can leave RL to independently solve complex tasks and redirect their time elsewhere. RL is an advanced form of ML that is still emerging, and may be a few years before it is readily applied to 3DP of medicines. In the meantime, other forms of ML can be applied to predict optimal printer settings. Six ML techniques have recently been applied to predict optimal printing and extrusion temperatures for drug loaded FDM filaments [88]. Elsewhere GANs have been applied to detect 3DP faults, ideal for application in automatic printer maintenance [92]. Such ML intelligence can be easily applied to improve and standardise pharmaceutical 3DP processes, accelerating the development of optimised formulations.

Prediction of Drug Product Properties

Often, formulation scientists wish to predict how subtle formulation changes will affect the pharmaceutical characteristics of their product. This is especially useful in 3DP, when

designing medicines with bespoke drug release profiles or sensing abilities. ML has already been shown to accurately predict 3DP medicines' characteristics before they have been printed. Artificial neural networks have correctly projected the dissolution profiles of ibuprofen loaded Printlets™ produced by digital light processing [93]. In another study, the dissolution behaviour of FDM formulations was predicted using rheological data [94]. The performance indicator *f2* similarity is a unitless value used to determine the effectiveness of a prediction. In this case, these predictions were found to have an *f2* similarity score of 90.9. A non-modern ML predictive method, partial least square, achieved an *f2* of just 57.5.. The FDA has suggested that a similarity score of over 50 indicates that predicted values are adequately similar to true values recorded experimentally, in the context of immediate release solid dosage form dissolution[ii]. These studies highlight the timesaving benefit that ML can bring to 3DP technology. Manual drug dissolution studies are currently a mandatory part of pharmaceutical formulation development, and are often timely, costly, and resource intensive. ML prediction of 3DP medicines' dissolution behaviour offers an attractive way for researchers to screen formulations prior to printing, for rapid identification of those that will fulfil dissolution requirements.

An important parameter within pharmaceutical 3DP is drug loading [95]. 3DP formulations with high-drug loading are often sought after, as they will result in dosage forms that are concentrated enough to be administered as small units. Size of oral formulations is especially important within specialities such as paediatrics and care of the elderly, where swallowing large solid dosage forms can be a challenge [96]. However, high drug loading in 3DP typically results in unprintable formulations, whether due to high viscosity or embrittlement of a filament. Thus, it is desirable for researchers to identify a uniform method of predicting maximal 3DP drug loading capacity, without affecting printability. In a recent study investigating drug loading into commercial FDM filaments, ML techniques were able to

predict the drug loading efficiency for several filaments by establishing a correlation between drug loading and filament roughness, stiffness, and solubility [97]. Hence, ML can provide a simpler and more efficient way of predetermining the loading capacity of a printing filament.

Achieving Non-Destructive Quality Control

The achievement of validated QC within pharmaceutical 3DP could greatly expedite the technology's translation to clinical practice [49, 98-100]. In recent years, several appropriate methods for the QC of 3DP medicines have been reported [101-103]. Most of these techniques utilise spectroscopic technologies, such as Raman and near-infrared (NIR) spectroscopy, capable of performing in-line, non-destructive measurements for dose verification. Spectroscopic techniques may be the solution to QC of 3DP medicines; however, they do produce complex spectra that require interpretation by trained individuals. Wherever possible, to facilitate 3DP's uptake into clinical settings, it is favourable to diminish the need for onsite specialist 3DP scientists, to make printing accessible and cost effective. ML's image-processing could allow it to be trained to read spectra of 3DP drug products, fulfilling gold-standard QC without human supervision. This could lead to ML algorithms working in partnership with spectroscopy techniques to support the dose validation of 3DP medicines in healthcare settings. Already, a branch of ML known as **principal component analysis (PCA)** has shown it possible to measure drug concentrations in 3DP tablets [104]. Here, PCA, an **unsupervised** decomposition method, was used to visualise haloperidol distribution in tablets using Raman chemical imaging. PCA has also aided visualisation of NIR hyperspectral trends, allowing quantification of theophylline in personalised inkjet-printed dosage forms [105]. Khorasani and colleagues have also used NIR imaging with multivariate curve resolution-alternating least squares (MCR-ALS) combined with PCA analysis, to predict the spatial

distribution of indomethacin and polycaprolactone within films, showcasing ML's potential as a QC tool [106].

ML may also aid the QC process of 3DP medicines by supporting anti-counterfeit measures. Drug counterfeiting and 'fake medicines' is a critical global issue[iii]. During its translation into clinical practice, pharmaceutical 3DP must be protected from the damaging and illegal trade of substandard, spurious, falsely labelled, falsified and counterfeit medicines [107]. ML's intelligence is well-placed to fulfil the authentication requirements of anti-counterfeit systems within 3DP. Liu et al. have demonstrated how 3DP and ML can be combined for such measures (**Figure 4**) [108]. The group produced non-destructive, inkjet-printable, and unclonable security labels formed of quantum dots. These quantum labels were subsequently decodable by deep ML networks to verify their true source using a tamper-proof design. This technology can be adapted for verification of 3DP medicines, whereby dosage forms would contain security labels on their surface, decodable by ML at the location of administration.

Challenges facing utilisation of Machine Learning in 3D Printing

The unification of ML and 3DP is not without challenges. Developers of ML-guided 3DP software should identify and mitigate these potential barriers early on, for optimal transition to clinical practice. Many such challenges are universal to the ML in general, with a few specific to pharmaceutical 3DP. Possibly the greatest universal challenge is the availability of big data for ML training. Though ML algorithms capable of interpreting small data are emerging, generally ML predictions are more accurate when they are supplied with large volumes of training data [109-112]. Ideally, large, unified, and accessible databases would be available, containing 3DP-relevant data analysable by ML [113]. However, a common reality is that data is not always made publicly available due to protection of intellectual property (IP). If IP issues

can be overcome, leading to publishing of accessible databases, then researchers' time in individually generating large quantities of 3DP data can be spared. This highlights the benefit of making study results Open Access, dissolving barriers to collaborative scientific advancement. Furthermore, the data must be unified and cleaned appropriately, removing experimental noise and missing values, hence facilitating ML algorithms to perform to their full potential.

Another ongoing challenge is the 'black-box' effect of ML, especially in the pharmaceutical industry, whereby the learning process is not shown to ML operators and hence cannot be interpreted. Consequently, there has been a shift towards producing 'explainable' ML algorithms, where the user is informed of the ML decision-making process [114-116]. Currently, researchers can output graphical representations to explain how some ML techniques learn, such as decision trees or biplots [116]. These can be interpreted by users to ensure that the algorithm is learning the correct information (also referred to as sanity checks). However, many sanity check methods are only practical in low-dimensional datasets and become difficult to interpret with very large data. This mystification around results can lead to policy makers becoming wary of adopting ML-guided decisions, especially if they themselves do not understand ML theory [117]. This issue can be addressed by the uptake of ML algorithms that output clear cause and effect relationships between variables, allowing operators to interpret how exactly features affect outcomes.

A challenge specific to the use of ML in 3DP of pharmaceuticals is professional liability. Before ML-guided 3DP is introduced in healthcare settings, decisions must be made regarding accountability in the event of software failure or operator malpractice. Such decisions may be further complicated where 3DP and ML tools are owned by separate commercial entities. For example, in the event where a ML QC check produces a false positive, allowing an unsafe formulation to be administered to a patient, which party is liable? The ML software,

3D printer supplier, or the administering healthcare professional? Although this concept is new to the 3DP sector, it is not new to medical devices. It is likely that policy in 3DP pharmaceuticals will be similar to that often applied to licensed medical machines; if the product is maintained and used within manufacturer's specifications, then healthcare professionals will not be at fault in the event of device failure[iv].

A Clinical Future for 3D Printing and Machine Learning

The advent of 3DP within the clinic would greatly advance personalised medicine, in which patients are prescribed and administered bespoke formulations according to their personal requirements. In an ideal situation, a prescriber or pharmacist could input a drug, dose, and formulation design to be supplied to a patient, and then a 3DP would provide the medicine onsite. With incorporation of ML, the clinician could also be supplied with guidance on what drug, dose, and formulation design to select based on their patients' individual characteristics. As a standalone technology, 3DP would require the constant presence of skilled operators to run and maintain machines for viable translation to healthcare settings. When paired with ML, printing processes and maintenance could be automated, removing the need for constant human supervision. In this way, the incorporation of ML into 3DP is not only beneficial for patients, but also for their healthcare professionals. Most global healthcare institutions now function 24/7, with critical medicines supply a key task performed outside of normal working hours. Reliable, automatic 3DP of medicines could dramatically reduce clinicians' workload during nights and weekends. Such functionalities could also be of great benefit to the clinical trials sector, who often need to adjust formulation doses at short notice [118].

Healthcare providers are generally positive regarding the uptake of ML [119]. For instance, the American Society of Hospital Pharmacists has stated that forms of artificial intelligence can be employed provided 'they perform as well or better than pharmacists' [120].

Moreover, Britain's National Health Service (NHS) has pledged to modernise its systems by integrating emerging technology to support its service needs, driven by its partner, NHS Digital[v]. This high-level support is a positive indicator for the uptake of ML-guided 3DP in clinical settings. Large healthcare providers such as the NHS are well-suited for the adoption of ML, due to their access to large quantities of digitalised patient data. Electronic health records provide reliable and unified datasets that can be interpreted by ML for the 3DP of pharmaceuticals. In short, ML provides 3DP with the tools to leverage the clinical resources around it for the ultimate benefit of patient care.

Concluding Remarks

Pharmaceutical 3DP technology has come a long way since the turn of the century, from the manufacture of simple tablets to the innovative and complex designs seen today. This review examined how an emerging technology, ML, can harness the modern capabilities of pharmaceutical 3DP to accelerate its transition to clinical practice. Examples were provided to how ML can be used at each step of the pharmaceutical 3DP pathway, including innovative formulation design; prediction of drug release profiles; fully automated printing; and non-destructive final product QC. Moreover, examples of how ML-driven 3DP can be translated into clinical settings, and thereby elucidating the advantages it will bring to healthcare systems and patients. Whilst the incorporation of ML into pharmaceutical 3DP presents with challenges (see 'Outstanding Questions'), the unified technologies will be well placed to support the emerging era of personalised medicine. ML has the potential to both streamline the pharmaceutical 3DP process and rapidly inspire new formulation designs, thus accelerating its widespread clinical adoption, ultimately increasing patients' access to safe, personalised, on-demand medicines.

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Resources

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Figure Legends

Figure 1. Stages of potential opportunity for 3DP and ML in the drug development pipeline.

Figure 2. Generating new designs. Currently, 3DP designs are typically theoretically-inspired [121] or bio-inspired [23, 122], however, the thought-process can be left to ML [84]. By feeding ML with examples of desired designs, the algorithm can generate novel similar structures, as demonstrated by previous work [82, 84].

Figure 3. An insight into M3DISEEN software, which utilises several types of ML to predict the printability of drug loaded FDM filaments with an accuracy of 76% [88].

Figure 4. Combining ML with inkjet printing for counterfeit proof designs [108].

Glossary

Artificial neural networks (ANNs)

A machine learning technique that uses an input layer, hidden layer, and output layer, to learn patterns in data and solve problems. ANNs were inspired by models of sensory processing by neurones in the human brain.

Bayesian Optimisation (BO)

A machine learning technique that employs Bayes Theorem to find the optimal value, which is different to common machine learning techniques that make a prediction. For example, ANN can be employed to determine the printing temperature of a given formulation, but if the user requires the formulation that would yield the lowest printing temperature, then BO is better suited.

Deep learning

A subfield of machine learning that utilises artificial neural networks (ANNs) to solve supervised, unsupervised, or **semi-supervised** tasks.

Generative adversarial networks (GANs)

A generative machine learning technique that uses deep learning to generate new data outputs based on patterns learned from a training dataset. It comprises of two networks called the Generator and the Discriminator that are working against each other, hence the 'adversarial'.

Machine learning

A branch of artificial intelligence that uses computer algorithms to analyse and learn patterns within data, allowing specific problems to be solved and predictions to be made.

Personalised medicine

An approach to medical care that bases treatment decisions on individual patient characteristics. For example, 3D printing allows the production of personalised medicines through customisation of dosage form shape, drug-loading, colour, and taste, guided by individual patient needs.

Principal Component Analysis

A commonly used unsupervised learner that transforms the data to new coordinates based by looking to maximise the variance in the raw data.

Quality control

A system of ensuring product quality by measuring aspects of manufactured products against predefined specifications. In the pharmaceutical industry, specifications cover a range of product attributes, including dosage form drug concentration, purity, and appearance.

Reinforcement Learning

A subset of machine learning that seeks to self-learn by taking actions within its environment. Since the algorithm is self-learning it has the capacity to achieve continuous learning.

Semi-supervised learning

A subset of machine learning that sits between supervised and unsupervised learning. Typically, semi-supervised techniques are trained on datasets consisting of mostly unlabelled data. Using the small amount of labelled training data, semi-supervised learning can apply labels to unlabelled datapoints within the training set. In this manner, training datasets are increased in size, and can be subsequently used for supervised machine learning tasks.

Supervised learning

A subset of machine learning that learns patterns in data based on labelled training datasets. Once these patterns are learned, predictions can be made for unlabelled datasets. Examples include regression analysis, support vector machines (SVM), random forest (RF) and artificial neural networks (ANNs).

Unsupervised learning

A subset of machine learning that learns patters in unlabelled datasets based on recognition of shared features amongst datapoints. Once patterns are learned, predictions can be made for new data. Examples include artificial neural networks (ANNs) and k-means clustering.