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Democratising Automated Compound Screening Strategies in Early Drug Discovery

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Abstract

Novel drugs are continuing to bring improved health benefits to an increasing number of patients. However, the costs of delivering these new treatments continue to grow year by year. Pharmaceutical companies often justify these increasing reimbursement costs based on the persistently high attrition rate of promising new compounds failing through the lengthy drug discovery process. Consequently, early decision making on compound selection needs to become more predictive of the anticipated therapeutic outcomes later on in the clinic. By reducing the high rate of attrition of compounds early on in drug discovery, it is expected that costs of new treatments can be reduced and they can become more widely available to patients even earlier. Small-molecule drug discovery is a complex analytical problem through which multiple compound characteristics are optimised in parallel to discover new drug candidates that are selected for further development. Recent advances in robotics, as well as artificial intelligence systems exploiting machine learning, are now enabling the introduction of greater interactive automation into the drug discovery process. As a result, automation is accelerating time frames for early compound identification and optimisation but can it also improve on the overall current compound attrition rates for compound progression? This timely review aims to assess the effects of democratising compound screening strategies through the networked automation of early drug discovery. Democratising access to modular but connected automated screening technologies and capabilities away from centralised mass screening systems is enabling the evolution of drug discovery. The costs and benefits of the application connected automation in democratising drug discovery are discussed and the potential advances evaluated in this review.

Keywords

Automation, Robotics, Compound screening, Drug discovery

Productivity Problems in Early Drug Discovery

The overall cost of discovering new drugs continues to increase significantly each year. Consequently, the long-term financial sustainability of new drugs is becoming uncertain for new cancer drugs [1], as an example. Health spending continues to rise and as far back as 2012, over 90% of the newly approved cancer drugs were priced above US$100,000 annually [1]. Pharmaceutical companies have partially justified these prices by referencing the need to compensate for the high rate of compound attrition during drug discovery and development [1]. Such arguments underpin the ongoing evolution of research and development strategies in the biotechnology and pharmaceutical industries, particularly with the drive to improve overall productivity [2]. Although investment in drug discovery programmes continues to increase, most drugs tested in clinical trials are still not producing the beneficial medical outcomes that were anticipated. Consequently, the successful products that do make it on to the market are having to compensate for too many compound that are discarded, often too late during the long-term discovery and development processes. An analysis of the probability of success for compounds progressing from early clinical trials through to approval found there was an overall probability of success of 14% based on an analysis of more than 21,000 compounds from different therapeutic areas [3]. Safety, as well as efficacy, issues accounted for many of these failures [4]. Overall, the number of new drugs approved per billion US dollars invested in research and development has halved about every nine years from 1950 to 2010 with no recent signs of significant improvement in that trend [5]. Therefore, the relatively few products that do make

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it into routine clinical practice are having to compensate for too many failures, which are often discarded out too late during development. Further analysis has illustrated how assay validity and reproducibility were correlated across a population of simulated screening and disease models [6]. It has been proposed that an increased role is needed for more relevant or predictive screens being incorporated earlier into the drug discovery process. Enhancing reliance on screening against human target proteins in cell-free assays and with a pathways-based understanding of efficacy and toxicity at multiple biological levels offers a timely way forward. It has been reported that most published research findings are incorrect, which exemplifies the extent to which this reproducibility issue is widespread across many research activities, including drug discovery [7]. It has been proposed that remotely controlled laboratory automation can improve consistency in data quality and that machine learning could enable improved decision making based on the integration of automated data capture in remote laboratories, thus essentially democratising global research networks focused on drug discovery [8].

Applications of Automation and Robotics to Drug Discovery

The iterative drug discovery cycle of identifying a chemical starting point, making new analogues and testing them drives the optimisation of novel compounds in drug discovery, which can be automated and driven by machine-learning algorithms [9]. The selected development candidate needs to possess an adequate balance of efficacy, pharmacokinetics and safety pharmacology to be progressed. Traditionally, this process needs around 10,000 new compounds to be synthesised and screened to discover a new drug but automation can reduce the number of cycles required to optimise a development candidate, especially when also increasing the predictivity of the assays driving the optimisation process [9]. Improved compound selection driven by assays with high predictive validity in comparison with the more traditional linear sequence of drug discovery, requires pivotal decision-making to be introduced much earlier in the drug discovery process [10]. These pivotal decisions then set in motion the long-term development processes that are not as easy to automate though the use of robotics.

Initiating the automated medicinal chemistry optimisation process described above requires new chemical starting points are required, which are typically found in drug discovery networks by screening targeted compound libraries, such as those for kinase inhibitors [11], which have yielded many drugs [12]. Diverse libraries of compounds of well over 100,000 can also be screened, when suitable targeted libraries are unavailable but they are less easy to democratise across many smaller laboratories. The screening of such compound libraries is mostly used for cell-free assays [13]. However, high-content screening systems have now evolved to become capable of imaging cell-based screens and analysing the captured data [14]. Consequently, there is now an opportunity to introduce more complex biological assays earlier into the drug discovery process, as they can be produced consistently at scale to support both active hit-finding strategies, as well as long-term medicinal chemistry programmes. When grown on an industrial scale using automated bioprocessing technology [7] or grown from cells in screening plates *in situ* [15], complex assays can now be used routinely for robust high-throughput compound screening. A recent publication demonstrates the benefits of using patient-derived organoids in semi-automated screening systems with novel kinase inhibitors, which highlighted the value of phenotypic readouts as a quantitative method to assess drug-induced effects in a relevant preclinical model [16].

Potential Benefits of Democratising Drug Discovery

For several decades or more, there have been various endeavours to use strategic outsourcing and technology collaborations to accelerate drug discovery research across the pharmaceutical sector [17]. In principle, there were two parallel outsourcing approaches being adopted: firstly, to reduce the cost of labour by moving outsourced research and development to locations where the full-time equivalent rate of a research scientist was significantly lower; secondly, to invest in new technologies to improve the success rates in drug discovery significantly. Overall, neither of these strategies has yet been successfully proven to have delivered more cost-effective drugs. While the costs of employing scientists have been reduced on a global basis, paying researchers less has not produced significant productivity gains that can be translated into reduced costs of new drugs [1]. While the past decades have seen huge advances in many of the scientific and technological factors that should, at least in theory, tend to raise the efficiency of commercial drug research and development, this had not yet been the case [5]. The introduction of automated high-throughput screening, combinatorial chemistry and biotechnology solutions has not yet produced the significant productivity gains that were originally envisaged. However, the implementation of remotely controlled laboratory but networked automation has already changed conventional working practices, by altering how many researchers work and interact. Location independence has evolved to reinforce greater organisational plasticity. Analytical methods based on decision theory and implement by machine learning have demonstrated that small changes in the “predictive validity” of an assay have a remarkably significant impact on success rates [8]. The mathematical basis of decision theory is now poised to be implemented through novel algorithms networked together, which is beginning to democratise the drug discovery process away from large, isolated laboratories. It is also hoped that these new strategies can potentially reduce the carbon emissions of the he pharmaceutical industry [8], which is thought to be more emission-intensive than the automotive industry [18].

Conclusions

The costs of introducing new drugs into a clinical setting often impede their widespread use in patients. The high prices

of these new patented medicines are typically justified by the need to compensate for the high attrition rates of potentially promising compounds throughout the drug discovery process and into clinical development. Early decisions on compounds can be poorly predictive of their envisaged therapeutic effects that are subsequently observed in patients. As a result, many apparently attractive new drugs fail to deliver meaningful endpoints in clinical trials. This review has analysed the challenges and novel solutions required to allow the widespread application of democratised screening strategies into drug discovery. If these challenges can continue to be overcome but the implementation of these novel screening strategies, then it is envisaged that the cost of new drugs can be reduced and, therefore, made more widely available to patients. The potential future economic and medical benefits of this democratised approach are clear but now need to be proven in practice.

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