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Big Techs and startups in pharmaceutical R&D – A 2020 perspective on artificial intelligence

Alexander Schuhmacher [a,d,*], Alexander Gatto [b], Michael Kuss [c], Oliver Gassmann [d], Markus Hinder [e]

[a] Reutlingen University, Alteburgstrasse 150, DE-72762 Reutlingen, Germany
[b] Sony Europe B.V. – Stuttgart Technology Center, Hedelfinger Strasse 61, DE-70327 Stuttgart, Germany
[c] PricewaterhouseCoopers AG, Birchstrasse 160, CH-8050 Zurich, Switzerland
[d] Institute of Technology Management, University of St Gallen, Dufourstrasse 40a, CH-9000 St Gallen, Switzerland
[e] Novartis Institute of BioMedical Research, Postfach, Forum 1, CH-4002 Basel, Switzerland

We investigated what kind of artificial intelligence (AI) technologies are utilized in pharmaceutical research and development (R&D) and which sources of AI-related competencies can be leveraged by pharmaceutical companies. First, we found that machine learning (ML) is the dominating AI technology currently used in pharmaceutical R&D. Second, both Big Techs and AI startups are competent knowledge bases for AI applications. Big Techs have long-lasting experience in the digital field and offer more general IT solutions to support pharmaceutical companies in cloud computing, health monitoring, diagnostics or clinical trial management, whereas startups can provide more specific AI services to address special issues in the drug-discovery space.

Keywords: Artificial intelligence; AI; research and development (R&D); Pharma; Big tech; Startup; Machine learning; Deep learning

Artificial intelligence (AI) involves an emerging and rapidly growing set of technologies that have the potential to change the way how pharmaceutical research and development (R&D) will be done in the future, potentially offering opportunities to increase R&D efficiency [1]. When comparing leading pharmaceutical companies with respect to their internal and external AI-related R&D activities, we were able to show that the pharmaceutical industry is in an 'early mature' phase of AI use in R&D [2]. Some companies, such as AstraZeneca and Novartis, have utilized AI more intensively, whereas other leading companies, such as Gilead Sciences or Takeda, have been 'Selective AI Explorers' rather than 'Digital Pharma Players'. In this study, we aimed to investigate what kind of AI technologies are currently being utilized in pharmaceutical R&D, and which sources of AI-related competencies ('Big Techs' and AI startups) can be leveraged by pharmaceutical companies.

Approach

First, we investigated the degree of AI utilization in pharmaceutical R&D, broken down into machine learning (ML) and deep learning (DL) approaches, by reviewing scientific publications from the top 20 pharma companies from the period 2014 to 2019 (2019 without Q4). Second, and

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with respect to pharmaceutical R&D, we examined the AI activities of the leading technology companies (Big Tech) Alphabet (that is, Google, Verily Life Sciences, DeepMind and Calico), Amazon, Apple, IBM, and Microsoft as of January 2021 by analyzing scientific publications and collaborations with pharmaceutical companies. Our third dataset refers to the AI competencies of 398 startups. In order to be classified as competent, startups needed to meet the following three criteria:

(1) determination, as illustrated by corporate communications making an explicit claim that AI is used in their business models;
(2) knowledge, proven by scientific publications and/or patent applications involving the use of AI approaches in diagnostics, drug discovery, drug development or healthcare;
(3) ability to execute AI strategies, documented by collaborations with pharmaceutical companies or Big Techs.

We applied the definitions of ML and DL used in computer science. ML uses algorithms to parse data, learn from that data, and make informed decisions on the basis of what it has been learned. DL is the evolution of ML and structures algorithms into layers to create an 'artificial neural network' (ANN) that can learn and make intelligent decisions on its own [3–5].

To categorize the results of the second and third datasets, we assigned the search results to one of the following fields of pharmaceutical R&D: diagnostics, drug discovery, drug development, or healthcare. In context of this publication, drug discovery refers to the application of AI in the discovery or research phase, including preclinical development, as exemplified by the use of ML in image profiling in drug discovery [5]. Drug development refers to the use of AI in clinical development phases 1–3 or in biomarker development, safety pharmacology and pharmacovigilance [6]. Diagnostics refers to the application of AI technologies in diagnosing a human disease or in analyzing disease-related parameters [3]. Healthcare refers to the use of AI in any other human disease-related manner, as exemplified by the Sepsis Watch [7] system.

For more information with respect to the approach see 'Supplementary Information'.

Technological breakdown of AI applications in pharmaceutical R&D

To understand which AI technologies are already used in pharmaceutical R&D, we analyzed 271 AI-related publications from top 20 pharmaceutical companies, 117 dedicated to drug discovery (2014–2018) and 154 referring to drug development (2014–September 2019). Altogether, ML and DL approaches were utilized 200 times in drug discovery and 222 times in drug development. These totals differ from the number of identified publications as several approaches were explored or benchmarked in parallel in some papers. ML was used much more often than DL: 144 versus 44 times in drug discovery and 175 versus 33 times in drug development, respectively. A clear breakdown was not possible for 13 publications that did not precisely specify the underlying AI technology.

As illustrated in Fig. 1, we also used a more detailed technological classification for the ML and DL approaches used most often in pharmaceutical R&D. As many fewer publications used DL rather than ML, the categorization for DL is limited to convolutional neural networks (CNN), the AI technology most commonly used to analyze visual imagery, and other types of network architecture ('Other ANN'). With respect to ML, random forest (RF), a decision tree approach, dominated (43 hits in drug discovery and 32 hits in drug development) followed by support vector machines and a set of various regression approaches ('Others regression').

AI competencies sourced from Big Tech

A total of 456 scientific publications in which AI was used in diagnostics, drug discovery, drug development, and healthcare were identified for the five Big Techs and a group of 76 AI startups as per January 2021 (Fig. 2). IBM was the leading Big Tech company in our investigation with a total of 169 scientific publications: 53 publications in diagnostics, 12 in drug discovery, 32 in drug development, and 72 in healthcare illustrate a broad spectrum of AI knowledge. Next to IBM, Alphabet (56 hits) and Microsoft (46 hits) also demonstrated AI knowledge, with both companies focusing on diagnostics and healthcare. Amazon (9 publications) and Apple (1) were found considerably less frequently in all analyzed AI application fields.

Table 1 provides a detailed view of the AI knowledge profiles that IBM, Alphabet and Microsoft have developed in recent years. Regardless of the AI-related scientific publications that could not categorized specifically as ML or DL, the majority of publications for all three Big Techs refer to the use of ML and DL in diagnostics (103 publications), followed by healthcare (64 publications), and to a lesser extent drug development (18 publications) and drug discovery (11 publications). Alphabet seems to have a focused position in the use of DL in healthcare, whereas Microsoft and in particular IBM are more broadly positioned.

In practice, Big Tech companies already collaborate with pharmaceutical companies in the fields of data analytics, diagnostics, patient management, and real-world evidence (RWE), through either electronic health records (EHR) or health monitoring (examples include Apple Watch and Verily Study Watch). For example, Verily is collaborating with Novartis, Otsuka, Pfizer, and Sanofi in the 'Baseline' project, using its technologies to increase patient and clinician engagement, to reduce the duration of studies and to generate more insightful data in order to improve clinical research [8]. Verily has also formed several independent entities in partnership with pharmaceutical companies to develop new therapeutic options: Galvani Bioelectronics Inc. (together with GlaxoSmithKline) to foster R&D of bioelectronic medicines [9]; Onduo (joint venture with Sanofi) to build integrated and intelligent diabetes management solutions [10]; and a joint venture with Santen to design ophthalmic devices [11]. Calico Inc. collaborates with AbbVie to discover new therapies for age-related diseases [12]. Google has partnered with Sanofi, forming a healthcare innovation lab that is based on Google's cloud computing services and AI capabilities [13]. Working with Watson Health, IBM leverages its broad AI capabilities to provide services in the fields of diagnosis, personalized treatment, and clinical trials [14,15]. For example, it assists in protocol development and it streamlines clinical trial processes [15,16]. Finally, Microsoft has built an ecosystem

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FIGURE 1

Overview of machine learning (ML) and deep learning (DL) technologies utilized in (a) drug discovery (2014–2018) and (b) drug development (2014–September 2019) by leading pharmaceutical companies (as reviewed in [2]). Numbers in brackets represent how often the respective technologies were identified within publications. The manifold artificial neural networks (ANNs) and many types of decision tree applied in the investigated publications were summarized as 'Others ANN' and 'Others decision trees'. Only convolutional neural networks (CNNs), i.e. the most-utilized ANN type, and the most-utilized decision tree approaches (elastic net, logistic regression, gradient boosted decision trees (GBDT) and random forest (RF)) were indicated separately. Further, a set of non-frequently used classifications and clustering approaches in ML are summarized as 'Others classification' and 'Others clustering'. Abbreviations: kNN, k-nearest neighbors; SVM, support-vector machine.

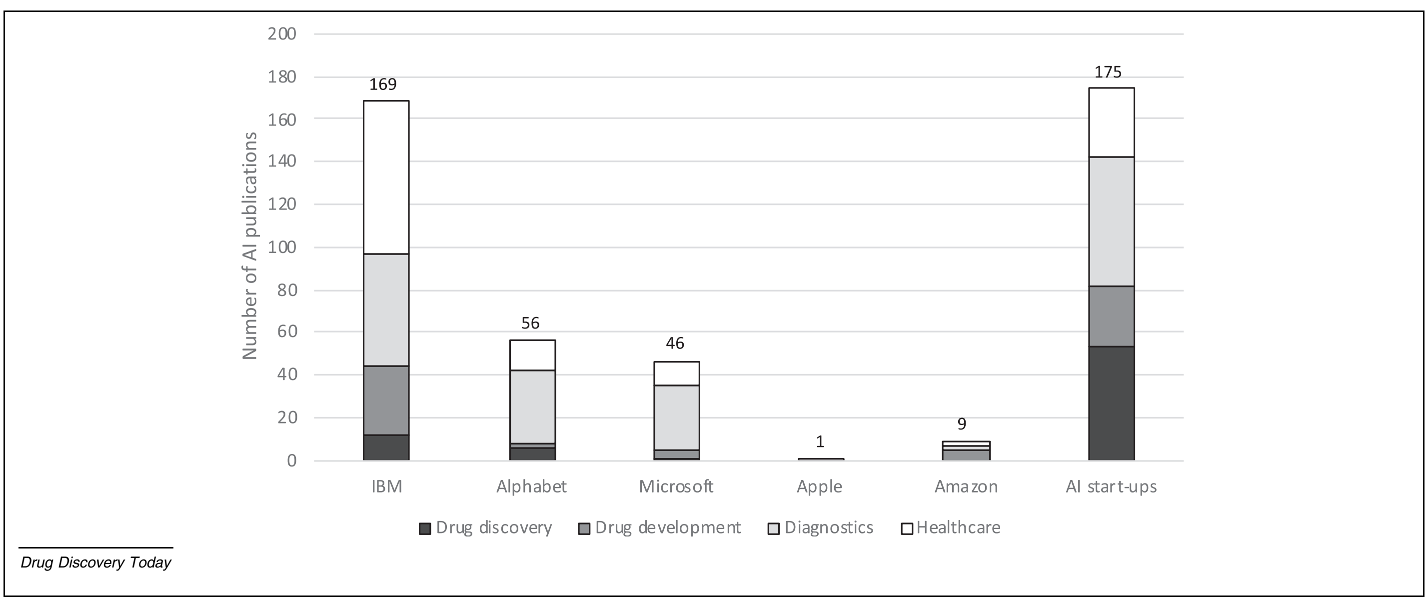

FIGURE 2

Number of artificial intelligence (AI)-related publications from Big Techs and AI startups (by January 2021) in pharmaceutical R&D-related application fields: diagnostics, drug discovery, drug development and healthcare.

with several smaller health IT companies to design pharma-specific solutions that are based on Microsoft's cloud infrastructure and AI, exemplified by its partnership with Novartis to improve operational excellence in R&D [17,18].

AI competencies sourced from startups

In contrast to the Big Tech companies that have proven skills in digital, the startup

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TABLE 1

Number of artificial intelligence (AI)-related publications from Big Techs and AI startups broken down by technologies and pharmaceutical R&D-related application fields. Publications up to January 2021 were counted. Pharmaceutical R&D-related application fields were drug discovery, drug development, diagnostics, and healthcare. AI, Artificial Intelligence (unspecific); DL, Deep Learning; ML, Machine Learning.

	IBM				Alphabet				Microsoft				AI startups				
	AI	ML	DL	Sub-total	AI	ML	DL	Sub-total	AI	ML	DL	Sub-total	AI	ML	DL	Sub-total	Total
Drug Discovery	7	4	1	**12**	1	4	1	**6**	0	0	1	**1**	13	13	27	**53**	72
*Target	1	1	0	2	0	0	0	0	0	0	0	0	0	1	0	1	3
*Drug design and optmization	5	3	1	9	1	4	1	6	0	0	1	1	8	7	25	40	56
*other discovery	1	0	0	1	0	0	0	0	0	0	0	0	5	5	2	12	13
Drug Development	16	12	4	**32**	0	2	0	**2**	2	1	1	**4**	11	13	5	**29**	67
*Clinical trial management	6	5	0	11	0	2	0	2	0	0	1	1	5	1	0	6	20
*Biomarker	1	0	0	1	0	0	0	0	0	0	0	0	3	0	2	5	6
*Precision medicine	5	1	0	6	0	0	0	0	1	1	0	2	0	0	0	0	8
*Safety pharmacology	1	3	0	4	0	0	0	0	0	0	0	0	0	2	1	3	7
*Pharmacovigilance	1	2	4	7	0	0	0	0	1	0	0	1	2	1	0	3	11
*Drug repurposing	2	0	0	2	0	0	0	0	0	0	0	0	0	4	1	5	7
*Other development	0	1	0	1	0	0	0	0	0	0	0	0	1	5	1	7	8
Diagnostics	6	24	23	**53**	5	5	24	**34**	3	17	10	**30**	9	27	24	**60**	177
Healthcare	28	38	6	**72**	3	7	4	**14**	5	4	2	**11**	4	23	6	**33**	130
Total	57	78	34	**169**	9	18	29	**56**	10	22	14	**46**	37	76	62	**175**	

companies that had AI competencies had to be identified before we could examine their competencies with respect to AI and pharmaceutical R&D. In our analysis, 398 startups were identified that provided clear value propositions relating to their AI-related technological skills in their corporate communications (determination). Of these startups, 123 companies (30.9%) were identified as having AI knowledge, as proven through AI-related publications and/or patent applications: 76 had at least one scientific publication, 47 had filed at least one patent application, and 15 had both published an AI-related paper and filed a patent application.

Fig. 2 illustrates the total number of scientific papers published by the 76 AI startups that have released at least one AI-related scientific paper in diagnostics, drug discovery, drug development or healthcare as of January 2021. With 176 scientific papers, they have produced as much scientific output as IBM, the leading Big Tech in our investigation, and more than Alphabet or Microsoft. Technologically, the majority of publications refers to the use of ML (27 publications) and DL (24 publications) in diagnostics, DL in drug design and optimization (25 publications), and ML in healthcare (23 publications) (Table 1).

Insilico Medicine (26 publications), BenevolentAI (10 publications) and Owkin (7 publications) are the companies with the highest number of scientific publications covering the use of AI in pharmaceutical R&D. Insilico Medicine is the startup company with the highest total number of scientific publications (more than 100), underpinning its role as an AI technology leader.

The number of AI-related patent applications is relatively small across all peer companies. Kheiron (6 applications), Deep Genomics (5 applications) and Insilico Medicine (4 applications) are leading in this category. Eight startups have filed more than 10 patent applications for AI- and non-AI-related inventions, led by the Butterfly Network (61 applications), Biodesix (23 applications) and BenevolentAI (17 applications).

Finally, we used the number of collaborations with pharmaceutical companies or Big Techs as indicator of the ability of startups to execute AI. In summary, 17 startups have documented partnerships with pharmaceutical companies, led by Atomwise (7 partnerships), Exscientia (7), GNS Healthcare (5), TwoXAR (5) and Linguamatics (5). Likewise, 17 startups have alliances with Big Techs, including Biovotion (5 alliances), Zebra Medical Vision (4), ProteinQure (4), and Arterys (4), and 15 startups have collaborated with both Big Techs and pharma.

In contrast to the Big Techs, most startups primarily provide AI technologies to address specific issues in the drug-discovery space. For example, Insilco Medicine is using DL to identify novel drug targets and to design small molecules with desired properties. They were able to show that the design, synthesis and experimental validation of a kinase inhibitor can be achieved in less than two months [19]. Atomwise uses its deep CNN 'AtomNet' for structure-based drug discovery, such as for the identification of drug candidates for the treatment of rare diseases [20]. BenchSci offers ML applications for scientific literature review and experimental supervision. They help scientists to select the right reagents and to design the right experimental set-ups and protocols to increase research output, reduce discovery time and improve preclinical decision-making [21]. In addition, a publication from BenevolentAI described the use of text mining to extract scientific information from preclinical drug discovery programs, for example from *in vivo* bioassays, thus providing decision-relevant information in the context of translational medicine [22]. The effectiveness of AI in drug discovery has also been exemplified by Moderna, one of the pioneers of mRNA therapeutics. Moderna uses a set of digital technologies, such as AI, cloud computing and automation/robotics, to improve R&D efficiency. It was the second company worldwide to register a COVID-19 vaccine

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with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [23–25].

Perspective and outlook

On the basis of our analyses of the AI maturity levels of leading pharmaceutical companies [1,2], we wondered what kind of AI approaches are currently used in pharmaceutical R&D, and we were interested to find out where the competencies for further digitalization of pharmaceutical R&D may come from.

With respect to the future digitalization of R&D, Big Techs and AI startups provide a valuable source of AI technologies that can be used in pharmaceutical R&D. Big Techs (led by IBM) have broad AI knowledge and long-lasting experience in the digital field. They can offer more general IT solutions to increase R&D efficiency, with activities comprising: cloud computing, wearables and health monitoring, AI in diagnostics, AI in big data analytics, and AI in clinical trial management. In addition, more differentiated and specific AI solutions are needed for drug discovery and development. Here, the less diversified startups can provide specific AI services to solve special biomedical problems. Their market positionings allow them to look into subjects that are neither in the strategic focus nor a good fit to the business models of the more broadly positioned Big Techs.

With respect to the kind of AI approaches currently used in pharmaceutical R&D, we found that ML is currently the dominant AI technology used in pharmaceutical R&D. This result is in contrast to the authors' experience and knowledge. We had expected that DL approaches would be the leading AI technology, as already illustrated for diagnostics [3,26] or as demonstrated in small-molecule-based drug research [5,19]. In addition, DL has been illustrated to be superior in biomedical image clustering, and in prediction of biological activity and toxicity [27]. Further fields in which DL have been applied are *de novo* drug design, prediction of ligand–protein interactions, analysis of chemoinformatic, quantitative structure–activity relationships, or cohort selection in clinical trials [6,28,29].

We speculate that the key reasons why DL is applied less often than ML include: the so-called black box character of DL and related ANN architectures, which makes predictions of behavior for untrained (unknown) scenarios very difficult; the lack of powerful graphical processing units (GPUs), which made widespread DL applications impossible for a long time [30]; the lack of large (biomedical) data sets that are required to train DL algorithms (data sets containing information from hundreds or thousands of patients are not considered to be large) [31,32]; the limitation of DL applications due to privacy concerns [32]; the high level of variability in patient data [32]; the cost of DL applications, associated data storage and computer infrastructure [32]; and the cost of generating and acquiring biomedical data (if available) [33].

DL is the most advanced ML approach available today, and we expect that DL will increasingly be applied in pharmaceutical R&D in the future. According to our analysis and the definitions described in the approach section, IBM, Alphabet, and the AI startups seem to be a particularly competent knowledge base for DL applications.

Various factors will be involved in the foreseeable acceleration of DL in pharma and healthcare [35], including: increased digitization of health-related records, improved sharing of digital data, increased capacity of DL to enable digital drug research, more DL applications that make clinical (trial) processes more efficient, and increased sharing of open-source DL applications. In addition, DL operates with unstructured data, reducing the effort required to identify and tag data in a preprocessing step. Moreover, we expect that DL will be applied first in many chronical diseases, such as Alzheimer's disease, cardiovascular diseases, and diabetes, where large longitudinal datasets are available. DL offers the advantage of better performance with (real) big data. It provides the potential to solve more complex tasks, as already proven in other industries, such autonomous driving, preventive maintenance or image processing.

Altogether, pharmaceutical companies can leverage technologies from both Big Techs and AI startups to build successful AI-enabled R&D strategies. Nevertheless, it remains to be proven whether their competencies and services, such as their knowledge about a comprehensive AI algorithm, can be translated into real-world applications that help to increase R&D efficiency and effectiveness [4,34]. For example, potential new and interesting options with DL lie in the prevention of clinically relevant adverse events [4], in finding the next level of biomarkers [31], or even one step further, in the integration of quantum computing and DL [36]. Nevertheless, a necessary requirement for such future opportunities is still the provision of large data sets that are based on the integration of chemical, biomedical, omics, translational, medical and clinical data [27].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2021.04.028.

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Alexander Schuhmacher [a,d,*], Alexander Gatto [b], Michael Kuss [c], Oliver Gassmann [d], Markus Hinder [e]

[a] Reutlingen University, Alteburgstrasse 150, DE-72762 Reutlingen, Germany
[b] Sony Europe B.V. – Stuttgart Technology Center, Hedelfinger Strasse 61, DE-70327 Stuttgart, Germany
[c] PricewaterhouseCoopers AG, Birchstrasse 160, CH-8050 Zurich, Switzerland
[d] Institute of Technology Management, University of St Gallen, Dufourstrasse 40a, CH-9000 St Gallen, Switzerland
[e] Novartis Institute of BioMedical Research, Postfach, Forum 1, CH-4002 Basel, Switzerland

* *Corresponding author.*
alexander.schuhmacher@reutlingen-university.de
(A. Schuhmacher).

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