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Editorial

Specific contributions of artificial intelligence to interdisciplinary life science research – exploring and communicating new opportunities

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# Artificial intelligence between hype and reality

Artificial intelligence (AI) is lauded as an auspicious problem solver in many areas. However, the understanding of AI methods is often lim- ited. Hence, an aura of mystery –and also concern– might be generated around AI. For example, the expectation that machines would “think” independently and reach autonomous decisions beyond human reason- ing is not factual. In science, the popularity and promise of AI mostly originate from notable advances in a few fields, but are also influenced by business-driven hype and unrealistic expectations.

As *Artificial Intelligence in the Life Sciences (AILSCI)* is completing its second year, this contribution aims to put developments in AI that are particularly relevant for the journal into scientific perspective. It is based upon –and further extends– two recent open access publications address- ing a wide life science audience [[1](#_bookmark0),[2](#_bookmark1)].

In computer science, various disciplines are covered under the term AI [[3]](#_bookmark2). Among these, deep learning (DL) using deep neural networks (DNNs), a sub-discipline of machine learning (ML), has been responsible for recent progress in areas such as computer vision (image analysis) or natural language processing. These advances have greatly contributed to the popularity of AI in science. Robotics, another AI discipline, is a main- stay in industry and also plays an important role in laboratory automa- tion. Furthermore, expert and recommender systems, which also belong to the AI spectrum, are explored in different scientific fields. Similar to AI-driven developments in physics, theoretical biology, or quantum chemistry, AI is beginning to impact the life sciences including early- phase drug discovery on a larger scale. Here, the term AI is for the most part synonymously used with DL when applied at interfaces between computation and experiment [[2](#_bookmark1),[4–6](#_bookmark3)]. In medicine, DL is employed in

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different therapeutic areas [[7]](#_bookmark4) such as radiology or oncology [[8](#_bookmark5),[9](#_bookmark6)]. In clinical practice, medical image analysis represents a prime growth area for DL [[8](#_bookmark5),[10](#_bookmark7)].

For these developments in the greater life science arena, *AILSCI* rep- resents a well-positioned publication venue. One of *AILSCI’s* core values is ensuring high scientific standards of publications, including method development and AI applications.

# Characteristics of deep machine learning

Generally, ML uses algorithms for the extraction of feature patterns from training data to classify test objects or address regression tasks. Hence, ML methods are statistical in nature and derive predictive mod- els capturing linear or non-linear instance-feature relationships based on inference from data. DNNs are well suited for feature extraction from large volumes of unstructured data (such as pixels in images) and for learning new object representations. DL relies on systematic correlation of feature patterns and known class labels and derives models with de- cision functions that are not pre-programmed. Hence, there is nothing mysterious about this type of supervised “machine intelligence”.

Shallow NNs were popular during the early stages of ML in biology, chemistry, and drug discovery, but were largely replaced by other ap- proaches such as decision tree methods (random forest, gradient boost- ing), Bayesian modeling, or support vector machines. This was largely due to a general tendency of shallow NNs to overfit models to train- ing data and their high sensitivity to varying parameter settings. The increasingly popular second-generation DNNs represent highly versa- tile computational architectures. In computer science, a great variety of DNNs and associated learning strategies have been introduced, some-

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times described with terms like a network “jungle” or “zoo” [[11]](#_bookmark8). This architectural variety has pros and cons. For many applications, alterna- tive DNNs can be considered, but finding preferred solutions is not nec- essarily straightforward. Moreover, complex DNN models are often de- rived without demonstrating that their complexity is indeed required for the predictions tasks at hand. Compared to other ML approaches, DNNs are particularly rich in hyper-parameters and derivation of DNN models requires substantial knowledge, skills, and experience. Accordingly, al- though public domain software is available for constructing DNNs, DL is not an approach that is readily accessible to non-experts. There is a strong discrepancy between the mechanics of model building, which might be handled by less experienced users, and the evaluation of re- sults and recognition of potential caveats or model errors, which re- quires much more expertise. Importantly, similar to other –but not all– ML methods, DNNs have notorious “black box” character [[12]](#_bookmark9), meaning that it is not transparent how these models reach their decisions. The black box of DNNs is a major issue in life science and drug discovery applications, as further discussed below.

# Data heterogeneity

Life science and drug discovery data are highly heterogeneous in terms of volumes, composition, and complexity. Early-phase drug dis- covery concentrating on target validation, bioassays, compounds, and activity assessment is not a data-rich discipline compared to other ar- eas where DL has made a strong impact. In early-phase drug discovery, data sets from medicinal chemistry are typically confined to test results for compound series and therefore limited in size. This also applies to data sets from, for example, probe investigations in chemical biology, time series experiments in biology, or confirmatory assays in biological screening. A consequence of data heterogeneity and sparseness is that suﬃciently large data sets for “hungry” DNNs are often not available. Moreover, informatics approaches in the life sciences have traditionally employed pre-defined object (for example, target or compound) repre- sentations (descriptors) and not relied on representation learning. To further complicate matters, effective ML/DL models can also be gener- ated on the basis of very small data sets [[13]](#_bookmark10). Hence, there are many incentives to undertake expeditions into the DNN jungle, further ana- lyze learning characteristics of different methods, and compare ML/DL models of different complexity.

# Artificial intelligence in medicinal chemistry

As an exemplary field with many opportunities for practical applica- tions, one may have a closer look at the state-of-the art of AI in medicinal chemistry, a core discipline of early-phase drug discovery.

ML already has a long history in medicinal chemistry, a traditionally conservative discipline. For more than two decades, ML methods have been used for compound property predictions and other applications. In medicinal chemistry, properties of interest for computational stud- ies include, first and foremost, biological activities of small molecules, but also physiochemical (e.g. solubility) or *in vivo* properties (such as metabolic stability or toxicity). Predictions of such properties aim to support the key task in the practice of medicinal chemistry, that is, de- ciding which compound(s) to synthesize next. Over time, shallow NNs that were popular early on for property predictions were for the most part replaced by other ML methods, as discussed above. Importantly, in medicinal chemistry, chemical intuition, experience, and subjective de- cisions continue to play a major role. Accordingly, black box predictions that cannot be explained in chemical terms work against the acceptance of ML for practical applications. However, the popularity of DNNs and high expectations associated with DL are also changing computational medicinal chemistry.

*Balancing high hopes*

In a publication comparing black box models, explainable, and inter- pretable ML from a computer science perspective [[14]](#_bookmark12), Cynthia Rudin states the following:

“*When considering problems that have structured data with meaningful features, there is often no significant diﬀerence in performance between more complex classifiers (deep neural networks, boosted decision trees, random forests) and much simpler classifiers (logistic regression, decision lists) after preprocessing*.”

This situation exactly applies to medicinal chemistry. Here, one typ- ically does not work with very large sets of low-resolution data (such a pixels comprising images) for representation learning, a notable strength of DNNs. Instead, in medicinal chemistry projects, available data sets are mostly small and well-defined molecular representations are used (e.g. molecular graph-based descriptors). Such conditions explain ob- servations that are frequently made: At least for property prediction in medicinal chemistry, there typically is little, if any detectable advantage of DNNs over other (simpler) ML methods.

In her article, Cynthia Rudin makes another key point that is equally applicable to medicinal chemistry and drug design:

*“There is a widespread belief that more complex models are more accu- rate, meaning that a complicated black box is necessary for top predictive performance. However, this is often not true …”* [[14]](#_bookmark12).

One may rephrase this point and emphasize that methodological complexity does not necessarily scale with predictive performance. Clearly, no complex ML approach is “validated” until it is not conclu- sively demonstrated that simpler methods do not yield comparable re- sults; a critical issue that is often not suﬃciently considered in the liter- ature.

*New opportunities*

While molecular property predictions in medicinal chemistry cur- rently only benefit little from DL, DNNs open the door to novel types of applications, for example, in generative molecular design [[15](#_bookmark14),[16](#_bookmark16)] or chemical reaction analysis and modeling [[17–19]](#_bookmark17), which would be dif- ficult to tackle using other ML methods. Generative compound design aims to construct chemically novel compounds with desired properties. In these and other areas, recent DL applications illustrate the scientific heterogeneity of the field. For example, despite reports of individual success stories in molecular design [[20]](#_bookmark21), caveats remain along the way

[[21]](#_bookmark23) and consistently successful applications of a given approach on different compound classes are rare. While various compound design strategies can be implemented using DNNs the jury is still out whether or not DL is capable of generating new chemical entities that are of higher quality than others. There are recurrent claims by AI-driven drug dis- covery enterprises of breakthroughs in generating novel compounds in record times. However, these claims can typically not be assessed scien- tifically because the data are kept proprietary. In general, scientifically sound reports of practical AI applications with a clear positive impact on medicinal chemistry are still rare [[22]](#_bookmark25).

*Big data trends*

Benefits of DNNs are often associated with learning from “big data”. While early-phase drug discovery is not a data-rich discipline, as noted above, big data trends on a relative scale are also observed in medic- inal chemistry [[23]](#_bookmark6). Major public repositories of compound data have grown to contain millions of bioactive compounds with activity anno- tations for thousands of biological targets. In addition, more than 200 million commercial compounds are offered for medicinal chemistry. Of course, for investigators working in particle physics, genomics, or social media, such data volumes might be a far cry from what they perceive

as big data. However, for medicinal chemistry, which is traditionally not data-driven, these data volumes are challenging. On the other hand, data-driven approaches provide new opportunities for the further devel- opment of medicinal chemistry as a scientific discipline [[24]](#_bookmark7).

The situation is different for predictive modeling. In medicinal chem- istry, ML is mostly applied at the level of individual target-directed projects using relatively small data. Each of these projects provides a specific context for modeling. In data science, the context dependence of data structuring and analysis is known to work against generaliza- tion of knowledge extraction, which requires abstraction from project- based data sets and project-specific analysis criteria [[25]](#_bookmark8). By contrast, in medicinal chemistry, project focus takes center stage and confines the applicability of ML. Furthermore, the predominant small data frame- work in medicinal chemistry also suggests alternative strategies for ML. Rather than heavily investigating methodologies whose strengths de- pend upon large data volumes, approaches such as transfer learning

[[26]](#_bookmark9) or active learning [[27](#_bookmark11),[28](#_bookmark13)] can be applied that are capable of pre- dicting molecular properties or new compounds on the basis of sparse data. Transfer learning makes it possible to use data from related pre- diction tasks (targets) for modeling; active learning derives predictive models from minimal sets of informative training instances. In medici- nal chemistry, these approaches are particularly relevant for addressing novel targets with interesting disease biology for which only limited compound information is available. All in all, there is much room for further computational developments with practical utility for medicinal chemistry.

# Model impact and acceptance

Returning to the greater life science arena, there are other areas where DNNs have achieved unprecedented advances such as in de novo protein structure prediction [[29]](#_bookmark15). Regardless, DL will ultimately only become an integral part of interdisciplinary life science research if it measurably impacts experimental programs. Importantly, further estab- lishing DL in interdisciplinary settings is only possible if life science in- vestigators and drug discovery practitioners agree to rely on predictions for experimental design. This requires increasing model acceptance in interdisciplinary research. As is the case with any new technology, time will be required until DL can realize its potential in this area. However, there are specific requirements that must be met to further increase the confidence of experimentalists in predictive models.

# Rationalizing predictions

Experimentalists are naturally reluctant to rely on predictions that are diﬃcult or impossible to understand. Given the black box nature of DNNs, this presents a major obstacle for the acceptance of such models for experimental design. Therefore, increasing attention is being paid to approaches for “explainable AI” (XAI) that make it possible to rational- ize the results of ML/DL models and interpret predictions in chemical or biological terms [[30](#_bookmark18),[31](#_bookmark19)]. Among others, these include methods for the identification of features making largest contributions to individual pre- dictions or the determination of feature sets that are minimally required to produce an accurate prediction. Closely related to XAI approaches are methods to quantify the uncertainty of predictions [[32–34]](#_bookmark20). Obtain- ing uncertainty estimates also helps to build confidence in predictive modeling. Although there are ML approaches that yield prediction un- certainties, for example, probabilistic (Bayesian) modeling [[34]](#_bookmark22), most methods including DNNs produce endpoints without uncertainty esti- mates, which are subject to further analysis.

# Prospective applications

The ultimate assessment of the potential of ML/DL for the life sci- ences depends on prospective applications, that is, predictions leading

to experimental evaluation in real-life projects. In interdisciplinary re- search settings, prospective applications require confidence in predic- tive modeling. However, it must also be considered that predictions re- lying on project data are inevitably influenced by data generation pro- cesses and data integrity [[35]](#_bookmark24) and that predictions might succeed or fail for different reasons. Accordingly, an incorrect prediction might not nec- essarily be attributable to methodological failure. Hence, in prospective applications, predictions should be analyzed, explained, and carefully evaluated within a given project context and care should be taken not to prematurely generalize successes or failures.

# Conclusion

The rise of AI in many scientific fields comes along with promises and new challenges. AI and DL are often synonymously used, although DL is only a part of the AI spectrum. In the life sciences and drug discovery, many DNN variants are being considered for method development and different applications. However, in interdisciplinary research, DL will ultimately only meet expectations if it positively impacts experimental programs. This will require time, making immediate breakthroughs un- likely, especially in drug discovery. For example, medicinal chemists currently witness methodological advances in synthesis design through DL. However, these new approaches are not easily accessible in the prac- tice of medicinal chemistry. Thus, transforming expert-dependent com- putational models into robust and readily usable computational tools is one of the grand challenges in the field. More prospective applications will also be essential to further advance DL in interdisciplinary research and demonstrate true impact on high-profile projects. In turn, this will require narrowing the gap between DL and experiments and further in- creasing the confidence of practitioners in predictions.

For *AILSCI,* method development efforts, practical applications, and perspectives concerning the development of AI approaches at interfaces with the life sciences are equally relevant. High scientific quality is an essential criterion for publication in *AILSCI*, which also strongly encour- ages data sharing and open science initiatives. Furthermore, diversity of authors and research topics is highly desired and submissions of “off- the-beaten-path” contributions are strongly encouraged, for example, as conceptual analysis, methods, or viewpoint contributions. Notably, in line with its specific aims, *AILSCI* has launched several Themed Ar- ticle Collections (TACs), which essentially correspond to special issues and focus on, for example, young investigators or women in AI. Going forward, these and other TACs are expected to play a major role for *AILSCI’s* further development.

# Declaration of Competing Interest

The author declares that he has no known competing financial inter- ests or personal relationships that could have appeared to influence the work reported in this paper.

# Data Availability

No data was used for the research described in the article.

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