doi:10.2533/chimia.2023.31 Chimia 77 (2023) 31–38

Bayesian Optimization for Chemical Reactions

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Abstract: Reaction optimization is challenging and traditionally delegated to domain experts who iteratively propose increasingly optimal experiments. Problematically, the reaction landscape is complex and often requires hundreds of experiments to reach convergence, representing an enormous resource sink. Bayesian optimization (BO) is an optimization algorithm that recommends the next experiment based on previous observations and has recently gained considerable interest in the general chemistry community. The application of BO for chemical reactions has been demonstrated to increase efficiency in optimization campaigns and can recommend favorable reaction conditions amidst many possibilities. Moreover, its ability to jointly optimize desired objectives such as yield and stereoselectivity makes it an attractive alternative or at least complementary to domain expert-guided optimization. With the democratization of BO software, the barrier of entry to applying BO for chemical reactions has drastically lowered. The intersection between the paradigms will see advancements at an ever-rapid pace. In this review, we discuss how chemical reactions can be transformed into machine-readable formats which can be learned by machine learning (ML) models. We present a foundation for BO and how it has already been applied to optimize chemical reaction outcomes. The important message we convey is that realizing the full potential of ML-augmented reaction optimization will require close collaboration between experimentalists and computational scientists.

Keywords: Bayesian optimization · Machine learning · Reaction optimization

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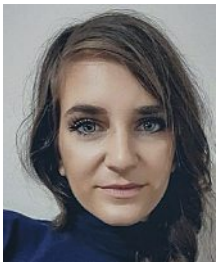

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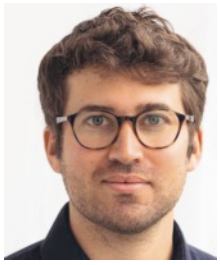

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1. Introduction

Chemical discovery involves iterative decision-making to propose increasingly optimal experiments in response to empirical results. Traditionally, domain experts were tasked with traversing these complex multi-dimensional problems where success typically involved many iterations of design make-test-analyze (DMTA) cycles, often changing only one variable at a time. Recently, machine learning (ML) has been applied in chemistry and has demonstrated success in designing candidate molecules satisfying a set of desired properties[1–5] and computer-aided synthesis planning (CASP)[6–12] to propose actionable synthetic routes. Integrating these ML tools into an experimentalists' workflow can aid decision-making and has started a paradigm shift toward a data-driven scientific process with the potential to accelerate chemical discovery.[13,14] We focus on the fundamental problem of navigating chemical reaction space to optimize a target objective, *e.g.,* reaction yield and selectivity, and highlight the seminal works,[15,16] which have recently gained significant interest in the general chemistry community. The subtleties of

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chemical reactivity are challenging to understand and, to a great degree, are still predominantly explored through a trial-and-error approach. While ML methods can model chemical reactivity within reasonable accuracy, actively deciding the next experiment is still challenging as these models are not guaranteed to generalize to new reaction space, *e.g.,* predicting the effect of a new catalyst on the stereoselectivity.[17,18] Moreover, while a domain expert can, on average, suggest experiments that gradually improve reaction outcomes, the complexities of chemical reactivity present a multi-dimensional problem that is not easily traversed. More recently, Bayesian optimization (BO) has been applied to iteratively suggest new reaction conditions to couple a decision-making mechanism to predictive ML models.[15] These models can suggest reaction conditions that converge on the target objective faster than domain experts. Together with robotic automation, predictive ML models with BO offer an opportunity to greatly accelerate the generation of chemical data and eventually accelerate discovery.[19–21] Here, we first discuss methods to transform chemical reactions into machine-readable representations and the challenges of navigating a large reaction design space. Next, we present the BO framework and discuss the historical works using flow reactors that are foundational to the recent works applying BO for reaction optimization. We end by presenting an outlook on the field and emphasize that the ongoing efforts to digitalize chemical data and collaboration between ML practitioners and experimentalists are crucial to realizing a future with accelerated discovery.

2. Design Space

2.1 *Reaction Representations*

Chemical reactions describe the transformation of reacting substances towards a resulting product. Classic literature uses chemical equations to denote this process, but they are not suitable inputs for modern machine-learning models. A systematic representation of chemical reactions in a computer-readable format is necessary to employ methods like BO. Better chemical reaction representations bring better predictive power to the underlying models, which, in turn, makes optimization faster. We can distinguish two intrinsically different methods that convert chemical reactions into a computer-friendly form (Fig. 1).

The first one concatenates vectors of individual molecular components into a unified digital representation. The second one aims to directly transform the chemical reaction into a vectorized form without separating its components. Typically, initializing an optimization campaign is done in a low-data regime, *i.e.*, a chemist starting a reaction optimization project will likely only have performed a few reactions. The lack of experimental data points coupled with highly complex reaction descriptors can make the optimization goals unattainable. This contrasting setup might be why more straightforward reaction representations like one-hot encodings (OHE) achieve outstanding results in reaction optimization, often matching the outcomes of more costly and elaborate reaction descriptors.[22,23] One-hot encoding defines a reaction through a set of categorized precursors. For example, a reaction composed of different additives, solvents, and catalysts will have a binary representation indicating whether a particular additive, solvent, or catalyst from the design space is present in the reaction or not.[24] Although OHE does not contain structural information, it performs surprisingly well in reaction optimization settings.[22–24] As an alternative, traditional chemoinformatics fingerprints offer more information by encoding the molecular graph of reaction components. Extended-Connectivity Fingerprints (ECFP),[25] for example, construct the molecular vector by encoding connections of each atom within the a radius. Other fingerprints use the simplified molecular-input line-entry system (SMILES)[25] to encode the neighboring connections of atoms[26] and more distanced atom pairs.[27] SMILES[25] are a line notation that encodes the molecular graphs as strings with the addition of limited stereochemistry. SMILES follow the natural graph representation of molecules and convert it to a textual format suitable for natural language processing-based machine learning models. These models exploit the string notation and provide additional techniques to represent molecules. For example, CDDD[28] creates descriptors by translating between equivalent molecular notations using an encoder-decoder network. ChemBERTa[30] utilizes transformer models for molecular property predictions and, as a side-effect, uncovers informative continuous molecular vectors. Unlike the purely data-

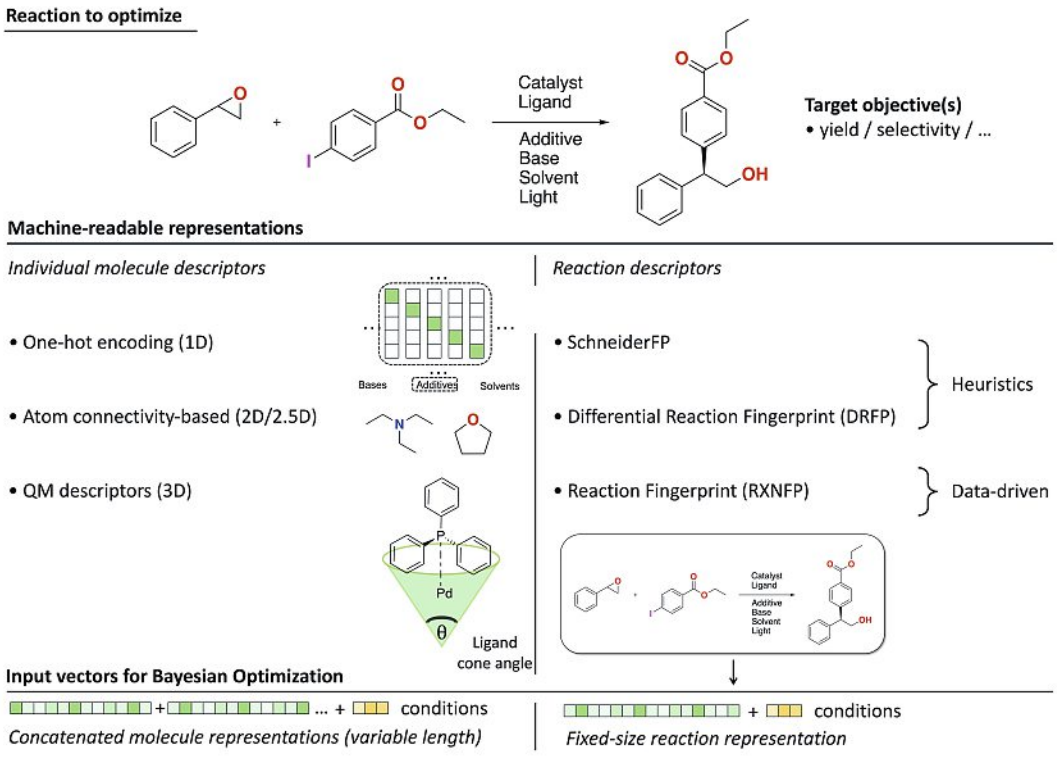

Fig. 1. Reaction representations for Bayesian optimization. Example reaction from Torres *et al*.[16]

driven descriptors, more chemically meaningful chemical reaction representations come as a mixture of molecular and atomic QM properties.[24] They provide significantly more insights into the reaction dynamics but are expensive to calculate. Still, the price we pay for calculating these descriptors is reasonable compared to the time and cost needed for running the entire design space of chemical reactions. Contrary to the expectation, however, their performance is often similar to the one obtained with simple OHE.[15,24] Concatenating different molecular precursors to form a reaction representation offers a lot of freedom and information in defining the final vector. However, it comes with a curse of dimensionality. Concatenated vectors can grow fast in size based on the number of reaction components. An additional concern is a limited generality, as a variable number of reaction components creates a variable-sized vector which is not convenient for machine learning models.

Alternative recent approaches map reactions directly to a fingerprint, making them independent of the number of reaction components. Schneider[31] uses the difference between the molecular fingerprints of the reactants and the product to define a novel chemical fingerprint used for large-scale reaction classification and similarity. DRFP[32] calculates the symmetric difference between two sets of circular molecular n-grams generated from the reactants and reagents on one side and products on the other. Schwaller *et al*.[33] introduces fully data-driven reaction representations as a result of transformer models employed for reaction classification (RXNFP). Recently, van Gerwen *et al*.[34] introduced novel physics-based reaction fingerprints that build bond-based reaction representations.

Additional reaction space diversity comes from the reaction condition parameters that can be tuned, *e.g*., temperature. During a reaction optimization campaign, chemists often vary one variable at a time while keeping others constant to isolate the effect of the variable on the outcome. Problematically, even a modest number of variables can lead to a combinatorial explosion of possible reaction conditions. Strategies to navigate a large reaction space are discussed next. Nonetheless, to make the reaction representation complete, these parameters are concatenated with the structural representation (Fig. 1).

2.2 *Navigating Design Space*

Traditionally, reaction data are generated solely through manual effort and the majority of published literature are comprised of such experiments. More recently, the application of robotic platforms has enabled high-throughput experimentation (HTE), which has either supplemented or replaced manual experimentation in certain scenarios.[15,24,35] The reaction space diversity is an important distinction between HTE and literature data generated during methodology development (Fig. 1). HTE typically aims to manipulate a few variables and almost exhaustively queries the search space.[36] By contrast, methodology data typically encompasses both optimization and substrate scope experiments.[37] The latter greatly increases the reaction space diversity as the standard protocol is to probe the compatibility of different 'scaffolds' and 'R-groups', which can span numerous chemotypes. In any optimization campaign, there is generally an inverse relationship between reaction space diversity and ease of convergence, *i.e*., it is more difficult to find the optimal conditions in large design spaces (needle in a haystack problem). Provided access to HTE, traversing a relatively narrow design space is perfectly feasible by exhaustive screening and removes the need to make decisions on the next condition to try. However, limited access to HTE platforms coupled with large design spaces makes traversing multi-dimensional reaction space challenging. Progress is usually driven by domain experts that make design choices by iteratively extracting mechanistic insights gained from previous experimental outcomes. Consequently, the question is how one can navigate reaction space efficiently, especially in large design spaces where HTE is infeasible. Ideally, we want to minimize the number of experiments performed to reach convergence. The next section introduces BO, which has demonstrated success in ML-guided reaction space navigation. The underlying premise of BO essentially mimics what is done by domain experts, where experimental observations guide sequential decision-making. An important note, however, is that domain experts may be inherently biased to propose reaction conditions known to work for *similar* reactions. While this is sometimes true, reactions are so complex that even if these reaction conditions work, they are likely not the optimal choice. In some sense, BO is less prone to this bias and explores *uncommon* reagents which has proved to be advantageous in reaction optimization campaigns.[15]

3. Bayesian Optimization

BO is a sequential optimization strategy widely used in many applications, including molecular discovery[4] and chemical reaction optimization.[15] BO consists of two components: a probabilistic surrogate model (also known as a response surface) that learns the relationship between the input and the output of the function, and an acquisition function (AF) that is used to propose new inputs to be evaluated on the real function. In the case of chemical reactions, the inputs are the chemical reaction conditions and the real function may be the experimentally measured yield or selectivity. The AF considers both the prediction and the uncertainty of the surrogate model and guides the optimization process to sample inputs that are most likely to be optima. The AF proposes the next experiments based on the previous observations. Correspondingly, the BO loop consists of training/retraining the surrogate model and subsequently proposing new reaction conditions to try *via* the AF, repeating the process until convergence or the experimental budget is exceeded (Fig. 2). For a detailed discussion of the mathematical aspects of BO, we refer the reader to the Supplementary Information and the review by Shahriari *et al*.[38]

3.1 *Surrogate Model*

Different probabilistic models, which map the inputs, *i.e.,* chemical reaction components, to the outputs, *e.g.,* yield or selectivity and an associated uncertainty or confidence on the prediction, can be used as surrogate models. We will discuss the Gaussian process (GP), decision-tree-based models, and neural network (NN) models.

The ***Gaussian Process (GP)*** is one of the most popular surrogate models for Bayesian optimization due to its flexibility and interpretability.[38,39] GPs assume that the function values of different inputs are jointly Gaussian. The covariance of these Gaussian variables is specified by a kernel function. The kernel function takes the distance between the inputs as the input and outputs the similarity between them. Therefore, the kernel function can be used to incorporate our prior knowledge about the structure of the function.

Random Forests (RFs) are an ensemble of decision trees that by themselves often suffer from overfitting, *i.e.,* memorizing the training data to the point where the model cannot generalize to new data.[40] RFs mitigate overfitting by adding stochasticity generally at two levels. Firstly, each decision tree in the ensemble is trained with a different dataset generated by bootstrapping, *i.e.,* sampling the original dataset with replacement. Secondly, a random subset of features is used to train each decision tree instead of the full set of features in regular decision trees. The output of regression RFs is the arithmetic mean of the individual trees' predictions and uncertainty can be extracted *via* the standard deviation of these predictions.

Neural Networks (NN) are not often used in BO applications for reaction discovery due to small reaction dataset sizes, as these models typically require more training data. Nonetheless, examples exist in which feed-forward neural networks (FFNN)

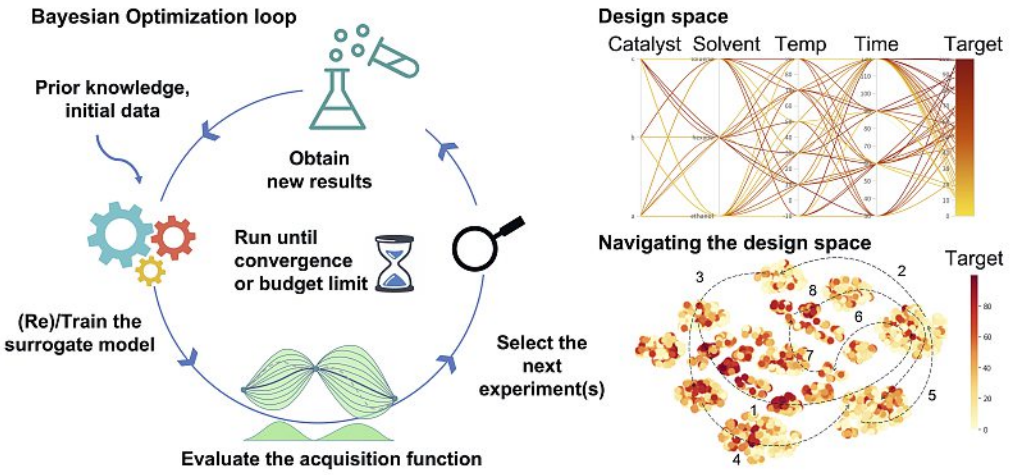

Fig. 2. Bayesian optimization for chemical reactions - process overview.

have demonstrated success in predicting reaction outcomes.[41] FFNNs can handle uncertainty quantification (UQ) *via* ensemble approaches, *i.e.,* training multiple FFNNs and taking the variance in their predictions as the uncertainty. An alternative method is Monte Carlo (MC) dropout[42] where the FFNN is trained with dropout, *i.e.,* deactivating neurons with some probability during training. During inference, keep dropout such that repeated queries to the model yield different outputs since the model weights would differ depending on which neuron is deactivated. These UQ methods have been shown to be amenable to uncertainty-based AFs for reaction optimization.[41]

3.2 *Acquisition Functions*

The second crucial component in BO is the AF. AFs are heuristics used to select the next best experiments to execute.[38] Generally, AFs balance between *exploration* and *exploitation* in an attempt to identify the global optimum. Exploration and exploitation refer to selecting query points where the surrogate model has high uncertainty, *i.e.,* the space is underexplored and the model does not have enough information to be confident, or predicts a high target value, respectively. Intuitively, exploration selects query points where the model is most uncertain, *i.e.,* the target output *may or may not* be good, but one hopes it leads to a new optimal. By contrast, exploitation selects query points similar to optimal points that the model has already observed, *i.e.,* selecting an input similar to other inputs that are known to be favorable, *should* also yield a favorable target output. In practice, a balance between exploration and exploitation is required to explore enough design space to identify the global optimum rather than a local optimum. For a more detailed discussion on AFs, see the Supplementary Information.

4. Reaction Optimization

Reaction optimization is a fundamental problem in methodology development and process scale-up for pharmaceutical ingredients and materials. The previous sections attempt to lay a foundation for the discussion of applied BO for reaction discovery which has recently garnered significant interest in the general chemistry community.[15,43] There is, however, a rich history of reaction optimization from chemical reactor engineering that needs to be acknowledged. In this section, we first discuss the historical foundations for reaction optimization and then show the natural progression of the field to the present day, where wider adoption of BO methods has been enabled by open-sourced code.

4.1 *Closed-loop Self-optimization Using Flow Reactors*

Over the last two decades, significant work in closed-loop reaction optimization has been enabled by flow reactors equipped with heuristic optimization algorithms, in which Simplex,[44–46] Stable Noisy optimization by Branch and FIT (SNOBFIT),[47] Steepest Descent and Conjugate Gradient,[48–50] and evolutionary algorithms.[51] are popular. Integration of analytical instruments enables closed-loop workflows, where real-time monitoring of reaction progression and outcome is crucial for self-optimization.[52–55] Exemplary works from McMullen *et al*.,[56,57] Parrott *et al*.,[58] Bourne *et al*.,[59] O'Brien *et al*.,[60] Moore *et al*.,[61] Sans, Porwol, Dragone, Cronin *et al*.,[62] Amara *et al*.,[63] Houben *et al*.,[64] Holmes *et al*.,[65] Cortés-Borda *et al*.,[66] Fitzpatrick *et al*.,[67] and Echtermeyer .[68] demonstrate this paradigm and navigate continuous reaction variables space, *e.g*., temperature, to optimize yield, reactor efficiency, and waste minimization. These flow reactors can also optimize simultaneously over continuous and discrete reaction variables, *e.g*., catalyst choice, as shown by Reizman *et al*.,[69,70] Baumgartner *et al*.,[71] and Hsieh *et al*.[72] While these significant advancements in closed-loop optimization demonstrate the utility of robotic automation to increase productivity and ensure reproducibility across replicate experiments, their domain of applicability is often limited due to inflexible reactor setups that have mostly been applied to process optimization.

4.2 *Towards More General Flow Reactors*

More recent development has focused on enhancing generalizability such that the same reactor is compatible with a wide range of reactions where individual reaction steps can require different reaction mediums, *e.g.,* a pressurized reaction vessel. Li *et al*.[73] report an automated platform using a chromatographic set-up that can strategically release desired intermediates based on reaction need. Bédard *et al*.[74] report a reconfigurable flow reactor where compartments can be changed based on reaction requirements. Coley *et al*.[75] integrated an open-sourced synthesis planning tool, ASKCOS, for route recommendation, which can be subsequently executed on a robotic platform. Steiner *et al*.[76] Mehr *et al.*,[77] Angelone *et al*.,[78] and Vaucher *et al*.[79,80] report efforts to turn synthetic procedures into computer code that is executable and portable across different reactors.

However, an ongoing challenge is navigating reaction space efficiently for multi-objective optimization (MOO), especially when the design space is relatively large. Importantly, access to robotic reactors remains limited, yet the potential of accelerated convergence from optimization algorithms should be accessible to any potential chemist. The concurrent development of open-sourced BO software packages has drastically lowered the barrier to entry in applying these algorithms for reaction discovery. Correspondingly, proof-of-concept works describing the application of BO to general reaction discovery have started a paradigm

shift from traditional wet-lab labor-intensive chemistry to one that is augmented by ML.[81]

4.3 *Bayesian Optimization for Chemical Reactions*

Recently, numerous BO software packages have been open-sourced, including general frameworks such as GPyTorch,[82] BoTorch,[83] Dragonfly,[84] Scikit-learn,[85,86] and chemistry specialized frameworks including GAUCHE,[87] Phoenics,[88] Chimera,[89] and Gryffin,[90] and benchmarks.[91,92] Correspondingly, Shields *et al*.[15] and Torres, Lau, Anchuri *et al*.[16] build upon these frameworks and develop the Experimental Design *via* Bayesian Optimization (EDBO) web application aimed at equipping any chemist with a BO tool. The potential of BO to accelerate reaction optimization was demonstrated retrospectively using HTE data for Buchwald-Hartwig and Suzuki-Miyaura cross-coupling reactions from Ahneman *et al*.[24] and Perera *et al*.[35] Prospective experiments were then designed to show the applicability of EDBO to optimization problems encountered in daily chemistry research tasks. Specifically, the optimal conditions for a Mitsunobu reaction and a deoxyfluorination of alcohols with design spaces of 180,000 and 312,500, respectively, were found within 30–50 experiments using DFT descriptors and outperforming human experts.[15] Choi *et al*. used the same HTE data for Buchwald-Hartwig[24] and Suzuki-Miyaura[15] reactions in addition to data from an arylation reaction[93,94] and their own generated Ullmann and Chan-Lam HTE data to show an improved Hybrid-type Dynamic Reaction optimization algorithm using graph-neural networks (GNNs) which can outperform human experts.[95] Ranković *et al*.[96] applied DRFP and RXNFP to optimize the yield of a nickel-catalyzed reaction retrospectively. The dataset measures the effect of changing only the additive and is thus not amenable to OHE, *i.e*., every single data point would feature a different OHE vector. The use of DRFP and RXNFP shows significantly improved performance to a random search, demonstrating the importance of having complementary methods for reaction representation.

Moreover, drawing from extensive historical developments in flow reactors, there has recently been a surge in works describing the integration of BO algorithms into ML-augmented robotic synthesis platforms. Schweidtmann *et al*.,[97] Amar *et al*.,[98] and Clayton *et al*.[99] apply the Thompson Sampling Efficient Multi-objective optimization (TS-EMO)[100] BO algorithm to optimize SnAr, N-benzylation, Sonogashira, Claisen-Schmidt condensation, and asymmetric hydrogenation reactions using flow reactors. Burger *et al*.[19] report a mobile robotic chemist that operated autonomously to perform 688 experiments guided by BO and successfully identified photocatalysts for hydrogen production from water with increased activity. Sugisawa *et al*.[101] use BO to optimize the yield of an unsymmetrical sulfamides reaction using a flow reactor. Christensen *et al*.[20] use Phoenics[89] and Gryffin[91] with DFT descriptors to optimize the stereoselectivity of a Suzuki-Miyaura reaction and explore human and ML-guided selection of monodentate phosphine ligands, thus handling both continuous and categorical features. Gérardy *et al*. use Dragonfly[85] to optimize a photochemical reaction using flow reactors, showcasing the use of another open-sourced BO software package. Nambiar *et al*.[102] attempt to achieve increased autonomy by coupling ASKCOS[76] for synthetic route recommendations with Dragonfly[85] and flow reactors for MOO of yield, reactor productivity, and reagent cost for Sonidegib synthesis (an anti-cancer medication). However, bottlenecks exist that impair full autonomy, including the need for human experts to investigate the solubility of proposed reagents and specifying intricate details in experimental protocols that are crucial for success, *e.g.,* which reagents to mix first to mitigate side-product formation. Recently, Angello *et al*.[21] leverage BO with robotic automation to identify general conditions for a Suzuki Miyaura cross-coupling reaction which is akin to a chemist exploring the substrate scope of a newly discovered reaction. Furthermore, the generalizability and democratization of BO algorithms have led to applications in other reaction classes. Exemplary examples include work by Xie *et al*.[103] and Naito *et al*.[104] to improve the crystallinity of metal-organic frameworks (MOFs) and optimize the yield and current efficiency of a reductive carboxylation of imines *via* an electrochemical transformation, respectively. It is worth noting that Xie *et al*.[103] use an RF prior in contrast to GPs, which are by far the most common surrogate model.

4.4 *Multi-objective Optimization*

Recent works have demonstrated the viable application of BO for chemical transformations beyond process chemistry, especially through the development of BO web applications which remove the need for technical expertise in ML.[15,16] However, encouraging wide adoption of BO into a chemist's daily workflow will likely require further work to demonstrate enhanced efficiency for MOO and Pareto front optimization, *i.e.,* when improving upon one objective further comes at a necessary trade-off on another objective.[97] Thus far, most works showcasing the integration of optimization algorithms with robotic platforms define target objectives either more relevant to process chemistry or are not representative of the challenges encountered by synthetic chemists. For example, a quintessential MOO task for a synthetic chemist is the simultaneous optimization of yield and stereoselectivity, which presents a considerably more challenging problem, yet is representative of everyday research.[16] Works describing the successful application of optimization algorithms to these tasks would be most convincing to a chemist interested in adopting ML-augmented workflows and do exist, albeit comparatively fewer. Amar *et al*.[98] use TS-EMO[100] to optimize the yield and diastereoselectivity of an asymmetric hydrogenation reaction and convincingly show enhanced performance compared to a human benchmark. Interestingly, the authors provide a discussion around the covariance matrix in their GP model which can be queried for some notion of feature importance, *i.e.,* which reagent in the reaction seems to be important to achieving the desired outcome. We note that the ability to extract feature importance is not exclusive to GP models and tree-based models such as RFs are well suited for this. Furthermore, Torres, Lau, Anchuri *et al*.[16,105] use their web application for BO, EDBO, with a GP and q-Expected HyperVolume Improvement (q-EHVI)[106] acquisition to optimize yield and enantioselectivity for Suzuki-Miyaura and Nickel photoredox-catalyzed reactions. Different substrates were also investigated, thus mimicking an entire workflow of a chemist, *i.e.,* optimizing yield and enantioselectivity and then probing the substrate scope.

A key question that must be addressed when considering adopting a BO workflow for reaction optimization is: to what extent can BO accelerate convergence relative to manual experiment and HTE? The benefits compared to manual experiments can be more easily reasoned as several works have shown that BO algorithms can consistently identify optimal conditions compared to human experts.[15,16,98] By contrast, HTE can exhaustively screen reaction conditions and query exact outcomes. In such scenarios, it is clearly better to know with certainty than rely on a statistical model.[15,24,36,96] However, in relatively large design spaces, *i.e.,* reactions involving many reagents, HTE can become infeasible or prohibitively expensive. In a situation like this, Christensen *et al*.[20] argue that the ability for BO to navigate both continuous and discrete variables space can make it more efficient than HTE or Design of Experiment (DoE) strategies, although only a theoretical comparison is drawn. In our opinion, a compelling argument can be drawn by contrasting the ease of access to BO frameworks with literature support demonstrating the possible benefit over HTE and DoE with the limited accessibility to robotic automation

by the average chemist. Thus, while there is no guarantee that BO will always outperform human experts, the ease of access to these algorithms should at least warrant a try in reaction optimization campaigns.

4.5 *Batch Experiments: Enabling Practical Chemistry*

Chemists typically perform experiments in parallel, and AFs should be easily adaptable for batch acquisition, *i.e*., proposing parallel experiments. A straightforward method is to acquire the top *N* reactions based on the ranking by the AF. However, BO algorithms work ideally by iteratively suggesting new query conditions based on previous observations. If *N* reactions were acquired as a batch, the proposed reaction conditions would all be based on the same previous posterior. In an extreme case, this could potentially lead to sub-optimal performance. For example, if an exploitation-heavy AF were used and *N* conditions (which are similar) were acquired as a batch, poor performance for one condition would likely translate to the other conditions as well. By contrast, in the sequential acquisition workflow, the surrogate model would be updated after observing a poor performance of that one reaction condition, potentially removing the resource sink for the *remaining N-1* conditions in the case of a batch acquisition. An alternative strategy for batch acquisition draws inspiration from Ginsbourger *et al*. and is known as Kriging Believer (KB).[107] In KB, new query points are acquired sequentially, and the corresponding prediction by the surrogate model is taken by faith and used to update the model. This process is repeated until the desired *N* is acquired and is known as Batch Expected Improvement (qEI) if Expected Improvement (EI) is used.[108,109] Shields *et al*.[15] observe and show by statistical testing that KB performs equally well as normal sequential acquisition involving posterior update for reaction optimization. Another batch acquisition strategy uses Thompson Sampling (TS) and is known as Parallel and Distributed Thompson Sampling (PDTS).[110,111] A distinct difference between qEI and PDTS other than the acquisition heuristic is that PDTS acquires the batch of query points in parallel and, thus, can be partitioned on numerous computing nodes and is more scalable on large datasets. We note, however, that reaction datasets are typically so small that the difference in required computing resources for qEI and PDTS strategies is negligible. Another heuristic similar to KB is Constant Liar (CL), where new query points are also acquired sequentially but are assigned a predefined constant value.[107] If the value were favorable, then it encourages exploitation behavior and exploration otherwise, *i.e.*, if the acquired point is assigned a poor evaluation and the posterior is updated, it is likely that the next acquisition will be different. While CL has not been applied to reaction optimization, it could be used to encourage exploration in cases with large design spaces. Overall, strategies exist to enable batch acquisition such that it is practical for a chemist to integrate BO workflows into their research.

5. Outlook

The recent release of open-sourced BO software packages has enabled their 'out-of-the-box' application for reaction optimization. Furthermore, efforts in the chemistry community to create user-friendly tools such as EDBO[15,16] have drastically lowered the barrier of entry to adopting these workflows for everyday research. While access to robotic automation, whether HTE or flow reactors, remains limited, these algorithms can still propose useful experiments that can at least be used to supplement domain experts' decision-making. One of the biggest obstacles to address is that chemistry is still mostly a web-lab science, and efforts to adopt data-driven workflows are only gradually becoming more prevalent. A prime example is the historical method of recording experimental procedures and observations in physical notebooks, which are often difficult to parse and risks data being lost. The community effort to address this problem comes in the form of encouraging the adoption of Electronic Lab Notebooks (ELNs) and initiatives such as the Open Source Reaction Database[112] which aims to curate an open-sourced database of chemical reaction data. The increased availability of *correct and complete* data will only help ML-based algorithms for reaction optimization. Another obstacle is the ability to predict MOO objectives, especially stereochemistry, which is a challenging problem commonly faced by research chemists. Recent works have proposed informative featurization strategies such that simple ML models can capture stereochemical relationships, and further developments will enhance the capability of BO to predict stereoselectivity.[17,18,113] Moreover, related frameworks like HTE are complementary to BO and will see continued development as it is ubiquitous in industrial laboratories[36] and best practices to apply ML to HTE data will further benefit BO applications.[114] Finally, the collective developments in ML models for chemical datasets, data availability, robotics, and optimization algorithms will drive progress toward achieving autonomous discovery.[115–117] We end by expressing that the field is progressing rapidly and will likely accelerate as more tools become open-sourced, with practically every recent work demonstrating the capability of BO algorithms to accelerate convergence. It will only be through effective collaboration between ML practitioners and experimentalists that a future with accelerated and autonomous chemical discovery can be realized.

Acknowledgments

This publication was created as part of NCCR Catalysis (grant number 180544), a National Centre of Competence in Research funded by the Swiss National Science Foundation.

Supplementary Information

Supplementary Information for this publication is available on https://chimia.ch/chimia/article/view/2023.31.

Received: December 1, 2022

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