Working at the interfaces of data science and synthetic electrochemistry

Jesus I. Martinez Alvarado[1], **Jonathan M. Meinhardt**[1], **Song Lin**[*]

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY, 14853, United States

Abstract

Electrochemistry is quickly entering the mainstream of synthetic organic chemistry. The diversity of new transformations enabled by electrochemistry is to a large extent a consequence of the unique features and reaction parameters in electrochemical systems including redox mediators, applied potential, electrode material, and cell construction. While offering chemists new means to control reactivity and selectivity, these additional features also increase the dimensionalities of a reaction system and complicate its optimization. This challenge, however, has spawned increasing adoption of data science tools to aid reaction discovery as well as development of high-throughput screening platforms that facilitate the generation of high quality datasets. In this Perspective, we provide an overview of recent advances in data-science driven electrochemistry with an emphasis on the opportunities and challenges facing this growing subdiscipline.

Keywords

Electrochemistry; Electrocatalysis; Data science; Machine learning; Design of experiments; High-throughput experimentation

Innovations in modern organic chemistry are fueled by the desire to invent synthetic transformations that improve upon the efficiency and sustainability of canonical methodologies. Amidst this widespread initiative for green chemistry, electrochemistry has garnered increasing attention from the synthetic community owing to its ability to eliminate the use of traditional oxidants and reductants [1,2]. By directly harnessing electric energy to promote chemical reactions, electrochemistry has not only become a vehicle for improving the sustainability of chemical synthesis, but it has spawned the development of reactivities inaccessible with traditional chemical reagents [3–5]. Furthermore, the ability to precisely tune parameters of potential, current, and electrode composition provides new opportunities for chemists to optimize the efficiency and scope of organic transformations. As electrochemistry enters the mainstream of organic synthesis, the deployment of

[*]Corresponding author. songlin@cornell.edu (S. Lin).
[1]These authors contributed equally.

technologies that enable the rapid development of electrochemical transformations forms the next challenge in this growing field.

Data science has emerged as an increasingly valuable technique within many disciplines of chemistry and is poised to revolutionize synthetic electrochemistry [6–13]. Nevertheless, in comparison to traditional chemical methods, electrochemical reactions present inherently more parameters to investigate. This high dimensionality amplifies the complexity of optimizing electrochemical reactions, as chemists can only sample a small fraction of reaction space within a reasonable timeframe. Similar dilemmas in battery research are being tackled through the use of data science [14,15]. A key challenge in implementing similar strategies in synthetic electrochemistry lies in the limited availability of high quality methods for dataset generation. In recent years, the introduction of standardized electrochemical reactors such as the ElectraSyn and the IKA Screening System have improved the reproducibility of electrochemical methods. These technological advances have provided a critical first step towards producing high quality data for the implementation of data-driven modeling in electrochemistry. In a landscape where modeling and systematic dataset design is becoming increasingly common, the future of electrochemistry would greatly benefit from incorporating data science in discovery and optimization campaigns.

1. Data-drive approaches for electrochemical reaction optimization

Traditionally, electrochemical methods are optimized using the one variable at a time (OVAT) approach where all but one variable is changed while others are held constant. This approach, while convenient to carry out, assumes that variables are independent from one another and can often result in conditions corresponding to local maxima (Fig. 1). This issue is particularly exacerbated when optimizing on a single substrate, making the "optimal" conditions prone to low substrate generalizability. To address these issues, chemists have begun to employ more complex optimization techniques [16]. At the forefront of these approaches is design of experiments (DOE) [17,18]. This systematic approach allows for interaction terms between reaction parameters to be considered, thus allowing for a more thorough sampling of the reaction chemical space towards finding the desired global maxima. However, scaling to higher dimensions can slow down the process, and expert domain knowledge may be required to improve the efficiency of this approach.

In an early example, the Hilt group used DOE to optimize an iodination reaction of trimethylsilyl-substituted arenes via anodic oxidation of iodine to generate a reactive iodonium intermediate (Fig. 2A) [18]. Using an OVAT approach, the authors initially identified a set of optimized conditions capable of delivering nearly quantitative yield with their model substrate phenyltrimethylsilane using a MeCN/MeOH solvent mixture. Nevertheless, extension of these conditions to substrates with benzylic C–H bonds resulted in moderate yields due to competitive methoxylation at the benzylic sites. With this side reaction, the authors turned to DOE for optimization, passing methanol concentration, iodide loading, and applied charge to their design. The resulting model suggested that low iodide and methanol concentrations should improve yield. The authors also identified an interaction term between methanol concentration and charge consumption, where higher concentrations of methanol required more charge to improve yield. This finding was proposed to result

from the competitive oxidation of methanol, which reduced the current efficiency of the reaction and is consistent with earlier results obtained through OVAT screening. However, DOE allowed the authors to sample a larger parameter space that revealed more general reaction conditions, which showed good yields for a range of substituted arylsilanes. Several works using DOE-assisted reaction optimization have since been reported in synthetic electrochemistry [19–26].

The application of DOE in flow electrochemistry has also been demonstrated [27–29]. Wirth and coworkers disclosed the decarboxylative alkoxylation of chiral *N*-aryloyl amino acids to generate enantiomerically enriched *N,O*-acetals in flow (Fig. 2B). In this reaction, the stereochemistry of the substrate is retained in the trapping of the incipient acyliminium ion. The authors used a two-level fractional factorial design that included four continuous variables (concentration, flow rate, charge, and temperature) and one categorical variable (electrode material) with yield and enantiomeric excess (e.e.) as outputs. Due to the complexity of this parameter space, a second DOE optimization was explored after identifying parameters with the highest dependencies. The authors ultimately were able to achieve high yield and moderate e.e., demonstrating the amenability of DOE to optimizing an enantioselective electrochemical reaction in flow.

While single and multivariate linear regressions are powerful tools for understanding and correlating experimental data [11], these approaches tend to only represent gradients of chemical reactivity but do not describe the implicit complex reaction surface. Non-parametric algorithms are typically invoked in modeling complex relationships and have seen increasing use in electrochemistry [7,10,30–32]. In 2019, Modestino and coworkers demonstrated that an artificial neural network (ANN) could improve yield and selectivity in the electrochemical synthesis of adiponitrile via the hydrodimerization of acrylonitrile (Fig. 3A) [33]. Controlling mass transport in this process is extremely important in maintaining high selectivity for dimerization and preventing the formation of undesired side products such as acrylonitrile oligomers. To this end, the authors cleverly employed alternating current (AC) electrolysis, which helped mitigate mass transport by restricting the time that the cathode acts on a substrate. The authors then systematically tuned the applied square waveform to improve the rate of adiponitrile formation by 20% and increase the selectivity by 250%. Subsequently, an artificial neural network was built using 16 data points, which allowed for identification of further improved conditions resulting in a 30% increase in adiponitrile production and a 325% increase in product selectivity. It is important to point out that neural networks typically require large quantities of data, and that further validation of this model with additional data points would help qualify its robustness.

Recently, Ding and coworkers described an electro-descriptor-diagram to identify regions of high reactivity using overpotential, Tafel slope, and effective voltage (Fig. 3B) [34]. The last term was defined as the voltage required for a given substrate to produce the same current as the model substrate used for optimization. The authors suggested that this parameter can help discriminate substrates that have similar onset potentials but different kinetics for charge transfer. These data were used to identify areas of high reactivity for several reactions including a phosphonylation of secondary amines, a dehydrogenation of *N*-heterocycles using TEMPO, and an aziridination of alkenes. The authors constructed

a decision tree and a k-nearest neighbors model on their largest datasets. It is worth mentioning that in as early as the 1970's, Perone and coworkers demonstrated the power of clustering analysis on both simulated and experimental voltametric data using a k-nearest neighbors classification algorithm [35–38]. Ding's approach creatively incorporates experimental kinetic and thermodynamic measurements into modeling in the context of synthetic electrochemistry. However, as the authors pointed out, the effectiveness of this approach was hampered by a lack of sufficient data, which could potentially be validated by comparison to baseline models. Indeed, as non-parametric algorithms are incorporated into synthetic electrochemistry, maintaining high validation metrics is essential in ensuring the robustness of predictive models [39–43].

Electrode material intimately influences the kinetics and selectivity of electrochemical reactions. However, parametrizing electrode material is challenging due to heterogeneity of surface properties and activities between different electrodes and between different regions of the same electrode [44]. In addition, limited access to supercomputers may impede costly featurization of electrode materials using density functional theory (DFT). Nevertheless, Sargent and coworkers recently applied active machine learning to extend DFT simulations using a random forest regressor to identify electrodes capable of reducing CO_2 (Fig. 4) [45]. The authors first mined electrode materials from The Materials Project database [46] and generated automated scripts to calculate their CO adsorption energies. In their workflow, the authors conducted DFT simulations on a subset of materials, which were used to train the regressor. The regressor then predicted adsorption energies for the whole dataset from which new materials with optimal predicted values were selected for additional DFT calculations. With these new computational outputs, the model was re-trained, and the process was continued until an optimal catalyst was identified. After many iterations, this approach allowed the authors to identify and experimentally test a Cu–Al alloy with exceptionally high Faradaic efficiency for CO_2 reduction to ethylene. An analogous strategy could also be applied to synthetic electrochemistry to facilitate the optimization of electrode materials.

2. High-throughput experimentation vs directed optimizations

Data science relies on large data sets for training and adequate validation. In this regard, high-throughput experimentation (HTE) will be vital for dataset generation in synthetic electrochemistry (Fig. 5) [47]. HTE allows researchers to efficiently explore chemical space by systematically running and analyzing experiments in parallel rather than through a traditional, OVAT approach. However, the establishment of HTE technologies specific to a synthetic subdiscipline is a key bottleneck in the realization of these benefits. Indeed, the introduction of standardized high-throughput platforms for photochemistry [48,49] and biocatalysis [50,51] have substantially accelerated the pace of research in these areas in recent years. The development of widely available platforms for high-throughput electrochemistry is advantageous in two respects: to enable the efficient development of new reactions as well as to provide electrochemists with high-quality datasets for modeling efforts.

Currently, large datasets in electrochemistry that vary multiple parameters like electrode type, electrolyte, and additives are non-existent [52]. Notwithstanding this limitation,

pioneering efforts in the late 1990's and early 2000's made headway towards a simple HTE setup for electrochemistry [53]. More recently, the Waldvogel, Baran, and Lin groups have independently contributed to the development of electrochemical screening platforms that attempt to address this limitation [54,55]. In particular, HTE electrochemistry platforms including e-Hive and HT*e*Chem have recently been commercialized. The potential scalability of these reactors offers electrochemists a more reliable method for obtaining high-quality datasets. Parallel efforts in flow chemistry have also laid the foundation for promoting HTE electrochemistry, opening another direction for data-driven reaction optimization [56–58]. In the future, the ability to perform such screening in a continuous flow system with tandem NMR or MS analysis would provide a powerful tool for rapid data collection [59,60]. We anticipate that the union of these emerging technologies with data science techniques has the potential to greatly accelerate the pace at which new electrochemical reactions are discovered. Trade-offs between implementation of HTE versus an optimization algorithm in electrochemistry will have to be considered to balance the benefits each approach offers.

3. Future directions: training and collaboration

The merger of data-driven modeling with synthetic electrochemistry—two prominent emerging technologies in modern organic synthesis—presents new challenges and opportunities. With the deployment of standardized parallel electrochemical reactors and their integration with well-established screening infrastructures, data shortages facing electrochemistry will be addressed. Meanwhile, in comparison to rapid technological innovation at the forefront of electrochemistry and data science, training and education efforts in these areas have lagged behind in most traditional chemistry graduate programs. Improvement in this regard will play critical roles in the future advancement of these areas as well as their integration. Furthermore, initiatives that promote interdisciplinary collaborations such as the NSF Center for Synthetic Organic Electrochemistry, NSF Molecule Maker Lab Institute, and the Electrolyte Genome Project [61] will be crucial in facilitating knowledge transfer between chemists and data scientists. Collaborative projects between these areas of expertise will launch synthetic electrochemistry into a new data-rich era.

Acknowledgements

Abbreviations

OVAT	one-variable-at-a-time
DOE	design of experiments
e.e.	enantiomeric excess
ANN	artificial neural network

AC	alternating current
DFT	density functional theory
HTE	high-throughput experimentation
ML	machine learning

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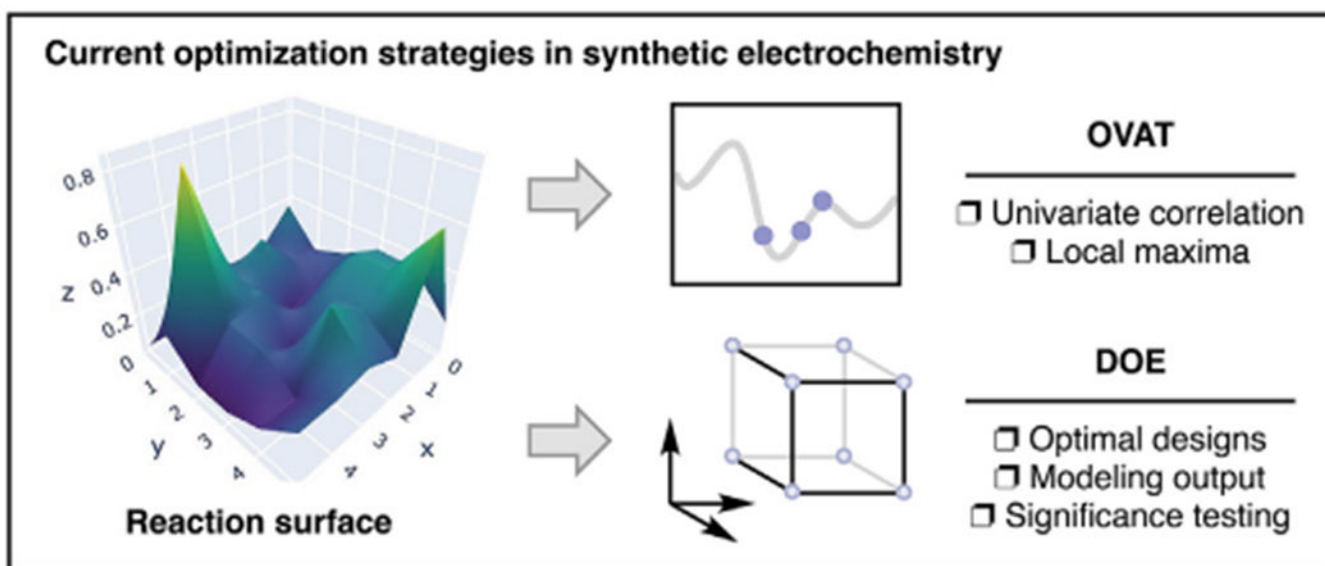
Fig. 1.
Graphical overview of current optimization strategies in synthetic electrochemistry: a one variable at a time approach and design of experiments. Each strategy attempts to locate a maximum in yield.
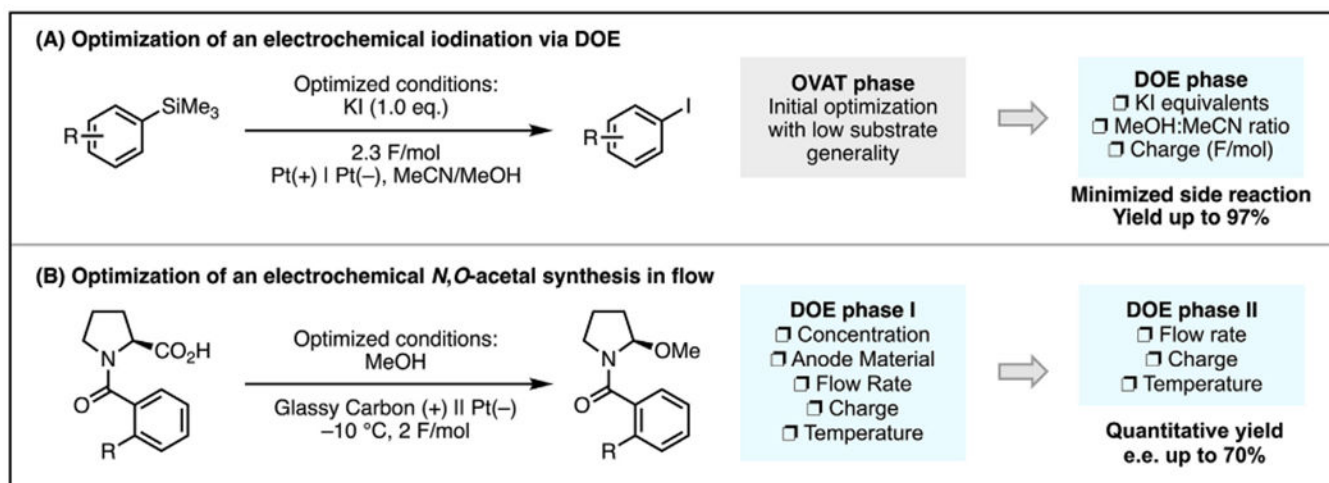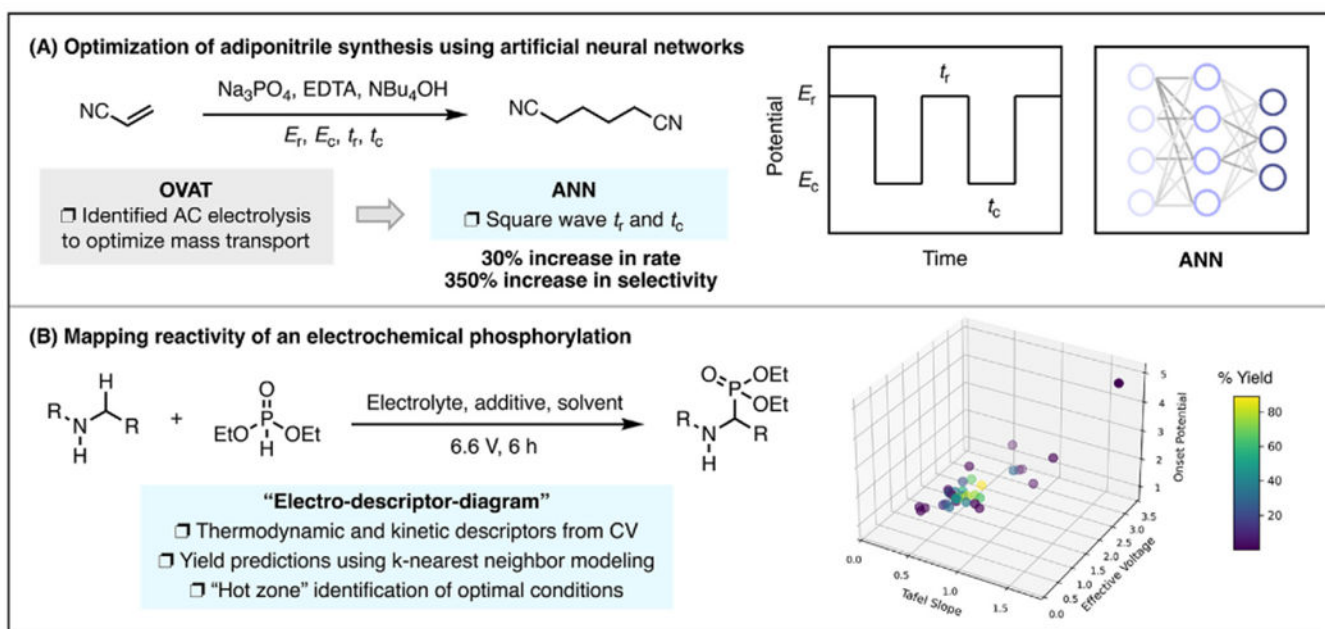
Fig. 2.
Examples of electrochemical reactions optimized using DOE. (A) Development of an electrochemical iodination of silyl arenes using a combination of OVAT and DOE optimization. (B) Development of an enantioselective decarboxylative alkoxylation in flow using two phase DOE optimization.

Fig. 3.
(A) Use of an artificial network for optimizing an electrochemical synthesis of adiponitrile under alternating current conditions. (B) Integration of intrinsic properties of a substrate to map the reactivity of an electrochemical phosphorylation. Regression models incorporating experimental kinetic and thermodynamic data were used to identify conditions for yield prediction.
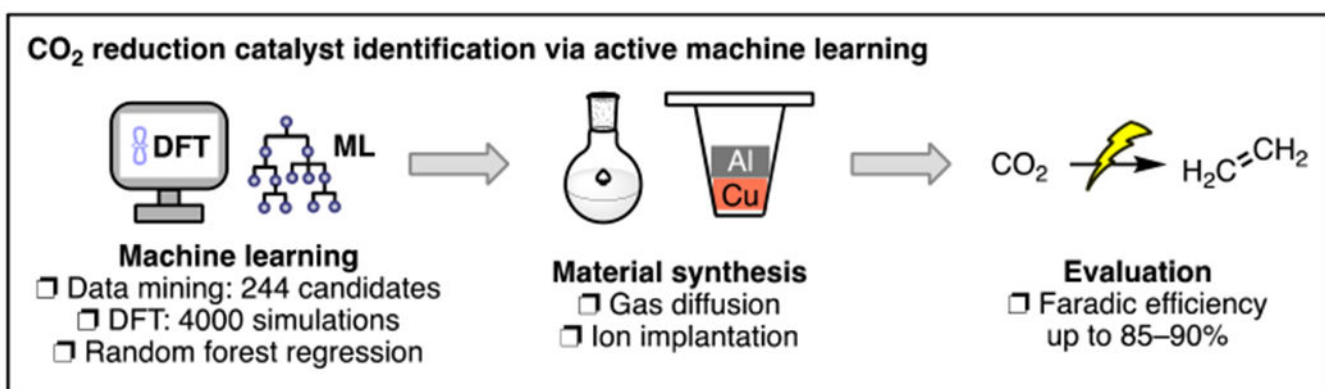
Fig. 4.

Schematic workflow depicting design of CO_2 reduction catalysts aided by DFT computations and machine learning. Optimized Cu–Al catalyst was identified and experimentally tested in the electrochemical conversion of CO_2 to ethylene.
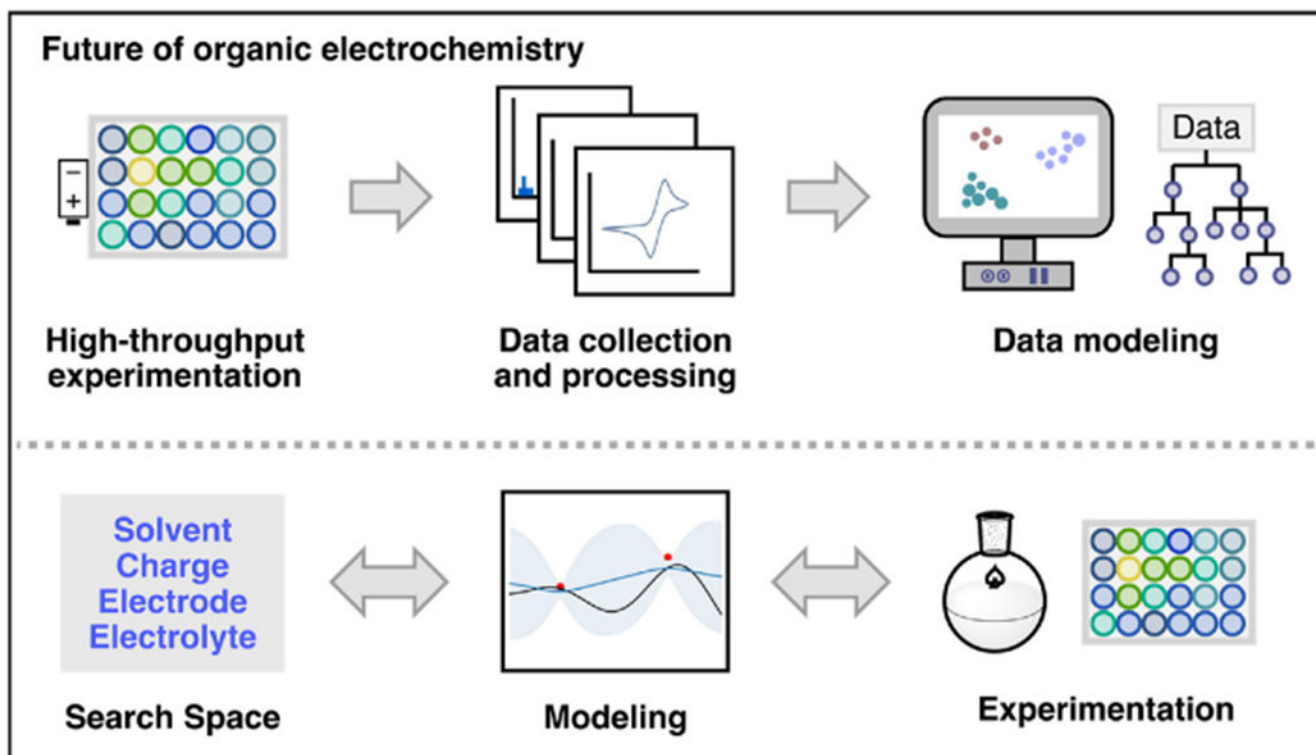
Fig. 5.
Future directions for reaction optimization aided by data science. Approaches using high-throughput experimentation or delineated optimization algorithms provide viable strategies for the identification of desired maxima.