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# High-Throughput Experimentation and Computational Freeway Lanes for Accelerated Battery Electrolyte and Interface Development Research

Anass Benayad, Diddo Diddens, Andreas Heuer,\* Anand Narayanan Krishnamoorthy, Mourmita Maiti, Frédéric Le Cras, Maxime Legallais, Fuzhan Rahamanian, Yuyoung Shin, Helge Stein, Martin Winter, Christian Wölke, Peng Yan, and Isidora Cekic-Laskovic\*

The timely arrival of novel materials plays a key role in bringing advances to society, as the pace at which major technological breakthroughs take place is usually dictated by the discovery rate at which novel materials are identified within chemical space. High-throughput experimentation and computation strategy, now widely considered as a watershed in accelerating the discovery and optimization of novel materials in virtually every field, enables simultaneous screening, synthesis and characterization of large arrays of different material classes toward identification of the lead candidates for given system and targeted application. However, the ability to acquire data, through the continued advancement of automation platforms and workflows especially in the field of battery research and development, often outpaces the ability to optimally leverage obtained data for improved decision-making. Closing this gap inevitably calls for adapted algorithms, development of reliable predictive models and enhanced integration with machine learning, deep learning, and artificial intelligence. This Review aims to highlight state-of-the-art achievements along with an assessment of current and future challenges as well as resulting perspectives toward accelerated development of advanced battery electrolytes and their interfaces.

## 1. Introduction

Applications of energy storage in transportation and grid scale call for next generation batteries, as electrochemical devices, with high energy and power, long cycle life, high energy efficiency, impeccable safety, large sustainability, and low cost.<sup>[1,2]</sup> It is common wisdom that overall performance of batteries is limited by the fundamental behavior of the used materials including electrode active materials, electrolytes, and other supporting, so-called inactive components (binder, current collector, conductive fillers, cell housing, etc.). In all types of past, current and future batteries, electrolyte plays a central role in terms of design and control of the electrode processes, material interactions, overall performance, long-term stability, cost, and last but not least the safety of a battery.<sup>[3]</sup> Although the role of the electrolyte is often considered trivial, its choice is actually

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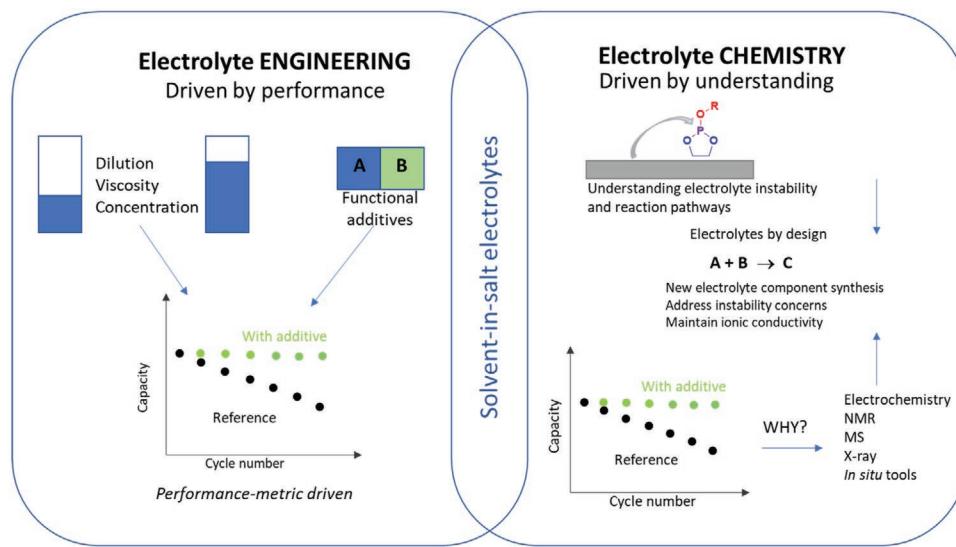
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**Figure 1.** Electrolyte engineering versus electrolyte chemistry approach. Reproduced with permission.<sup>[11]</sup> Copyright 2020, Elsevier.

crucial, and is based on criteria that can differ significantly dependent on application.<sup>[4–7]</sup> Due to the complexity of electrolyte formulation, determined by the physicochemical properties of its components, namely, inorganic fluorinated salts, organic solvents/cosolvents, and functional additives, the overall cell performance is inevitably accompanied by side reactions. The electrolyte is concomitantly unified to 3D interphases that originate from the high reactivity of the electrodes and the intrinsic instability of electrolyte components toward these electrodes. In most cases, electrolyte formulations and their ad hoc interfacial/interphasial chemistries dictate and govern the fate of each battery chemistry and its cell performance. However, interphases forming at electrolyte/electrode interfaces still remain the most important but the least understood components in alkali metal/ion batteries, including lithium metal/ion batteries.<sup>[8–10]</sup> For this reason, a fundamental understanding comprising both i) relevant structural/compositional characteristics, chemical/electrochemical reactions as well as ii) thermodynamic/kinetic behavior thereof, hand in hand with the practical strategies for enhancing interphase properties are of paramount importance for advancement of the overall performance for targeted applications. With all the challenges pointing toward the need for novel electrolyte design, we need to explore the electrolyte frontier and push our current understanding of electrolyte (electro)-chemistry. Due to the complex nature of electrolytes and the complexity involved in their interphase behavior, profound research and development require collaborative efforts involving the disciplines of chemistry, physics, materials science, nanoscience/nanotechnology, as well as computational modeling/simulation that will beneficially impact the current lithium-based technologies and future generations of lithium metal and lithium ion batteries based on polymer, ceramic solid, and hybrid electrolytes (see the paper by Grimaud et al. in this issue). Significant enhancements for battery technologies in the future must therefore definitely focus on an optimization or modification of the electrolyte solution in terms of novel and more beneficial components.<sup>[11]</sup> There are two approaches within the electrolyte design known: i) electrolyte engineering

as the combination (typically physical mixtures) of commonly used conducting salts and solvents/cosolvents resulting in enhancement of physicochemical properties like dielectric constant, viscosity, and ionic conductivity and ii) electrolyte chemistry as the bottom-up design of novel electrolyte components that ultimately allow for finer control of relevant physicochemical properties, such as electrochemical stability and properties beyond ion conductivity (Figure 1). Electrolyte engineering approaches may fail to give insight into molecule structure–property relationships beyond the exact compounds studied as a sole focus is usually set on performance metrics such as “capacity versus cycle number” dependence, excluding understanding of the reaction mechanisms underlying the advancements of electrolyte formulation. Although both approaches are vital for advanced electrolyte development, electrolyte chemistry can lead to discovery of entirely new electrolyte classes with targeted, application oriented properties.

### 1.1. Finding a Needle in a Haystack

By definition, chemical/material space is a concept developed in cheminformatics referring to the property space spanned by all possible molecules and chemical compounds adhering to a given set of boundary conditions and construction principles. Immense in size, it is estimated to be in the order of  $10^{60}$  molecules.<sup>[12]</sup> So far, humans have created  $10^8$  materials. Functional materials possessing one or more physicochemical properties that can be significantly changed in a controlled fashion by external stimuli to result in a desired function are applied in a broad range of technological and energy storage devices. New functional materials with optimized or novel properties of relevance, obtained by a chemical reaction, a modification or by formulation/blending of different substances, may initiate or revolutionize industries and lead to fundamental understanding of their nature through developed structure–property–performance relationships. If something is novel, it is new but also original and unique. Identifying a material with the adequate



**Figure 2.** Search for functional materials: classical experimental approach versus HT experimentation approach.

properties for a targeted application is a highly challenging task usually based on intuition, prior knowledge, and/or predictions.<sup>[13]</sup> The specific individual property can sometimes only be present in unique structures and chemistries. Moreover, not only one, but several properties often need to align adequately to synergistically lead to enhanced performance. Unwanted and inherent correlations between materials properties make this task at hand even more arduous, without even mentioning the important economic constraints. Although tremendous progress has been made in our ability to design materials *de novo* with specific properties, our predictive abilities and our fundamental understanding still remain limited. These limitations, among other battery vital domains, are being addressed within the BATTERY 2030+ Roadmap (see the paper by Edström et al. in this issue).

### 1.2. Accelerating the Search for Functional Materials Is an Ongoing Challenge

Discovery and development of novel functional materials with targeted properties traditionally involves a large number of trial tests following a series of procedures, see, e.g., on flame retardants for liquid electrolytes.<sup>[14–17]</sup> However, these efforts are inevitably far from time-efficient considering the near infinite chemical space. Current materials design approaches are still mostly based on human knowledge and intuition, as well as on low throughput experiments. Efficient investigation of the unexplored chemical space calls for automated techniques with smart navigation (Figure 2).

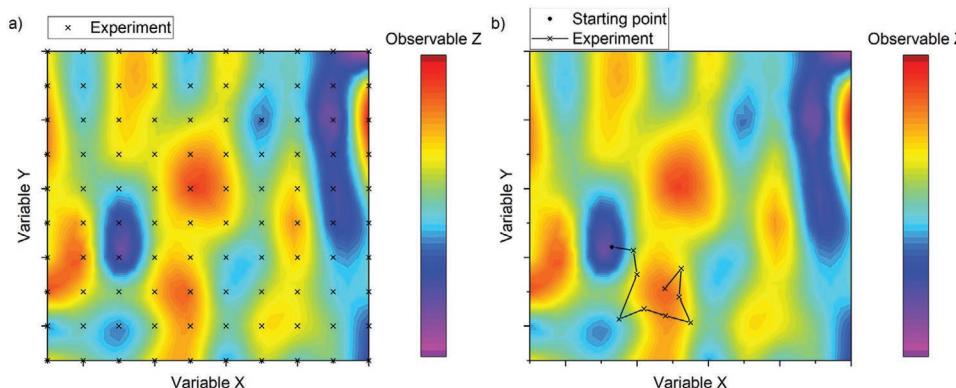
Since the first demonstration of combinatorial synthesis several decades ago,<sup>[18]</sup> there has been tremendous progress in the field of materials discovery through incorporation of combinatorial synthesis<sup>[19,20]</sup> and high-throughput (HT) characterization.<sup>[13]</sup> Utilization of the wealth of metadata accompanying measurement results generated by HT methods became possible through rapid advancement in data management and integration of machine learning (ML), deep learning (DL), and artificial intelligence (AI). Moreover, greater autonomy<sup>[21–23]</sup> in materials discovery is demonstrated by integrating predictive<sup>[24]</sup> or generative models<sup>[25,26]</sup> based on ML and DL techniques. The level of autonomy<sup>[27]</sup> in the framework of materials discovery is determined by the degree of integration of automated tasks, degree of reduction of human intervention (e.g., as shown in

early work by Nikolaev et al.)<sup>[28]</sup> and the degree of materials intelligence. Despite successful examples of material discoveries<sup>[29,30]</sup> and a rapidly growing number of materials databases such as High-Throughput Experimental Materials database, Citrination platform, and the Materials Data Facility, the sheer vastness of the chemical space requires more efficient exploration techniques. Moreover, solid state materials and certain molecules pose challenges due to limited available data, lack of available invertible representation,<sup>[26]</sup> and costly exploration of monolithic, fixed libraries.<sup>[31]</sup> Overcoming those challenges can lead to disruptive advances in materials discovery, not only to autonomously design materials with desired functionalities, but also to predict possible chemical hazard and toxicity of the materials.

## 2. Classical/Traditional Approach

Many of the numerous challenges in battery research have come down to optimization problems. Discover the optimum electrolyte composition (= formulation) for a given set of electrolyte components, discover the optimum electrode composition in a given material family, or discover a charging procedure that results in the highest capacity retention and thus longest lifetime of the battery cell are all fundamentally the same type of problem: discovering the global maximum of an observable with respect to a given set of variables.<sup>[32]</sup>

The methodically simplest approach to finding a solution is the so-called “brute force” approach where every possible combination of variables is verified in order to cover the complete space of possible experiments.<sup>[33]</sup> The advantages of this approach relate to the facile experimental planning, thus excluding *a priori* knowledge on the studied system. Furthermore, as the complete experimental space is covered, the obtained result is automatically a complete picture of the dependencies of the observable on the variables and can reveal unexpected relations.<sup>[34]</sup> In case of variables with continuous dimensions, this is of course not possible as the number of required experiments approaches infinity and each dimension must be quantized. However, even then (assuming equally spaced points in all dimensions) the total number of required experiments is  $X^n$  with  $X$  being the number of points in one dimension and  $n$  being the number of variables (Figure 3a).



**Figure 3.** Graphical representation of a possible variable space with examples of possible experimental coverages. a) Brute force approach with quantized variables. b) Quasi random walk.

This phenomenon is known as “combinatorial explosion” and represents the major drawback of this approach as it can very easily push the number of experiments into regions that are not achievable in a feasible way.<sup>[35]</sup> Especially if the experiments have to be performed sequentially in a classical manual experimentation setup, this can push the required time very easily beyond the available time. If no or limited a priori knowledge is available, another drawback of this approach is that a large number of points may be located in regions of the experimental space that do not make sense since, for example, in a region where certain ratios of electrolyte components may lead to the precipitation of one of the components.

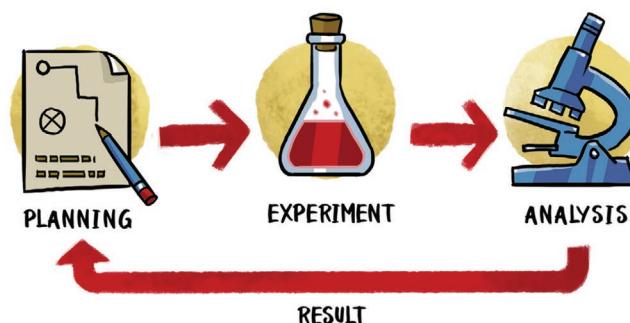
A more common approach in manual experimentation is an iterative process starting from a random point or an “educated guess” if a priori knowledge is available. The obtained result of the experiment is analyzed, the variables more-or-less randomly varied and the next experiment is performed until the maximum is found (Figures 3b and 4). The process is similar to what is known as a random walk with the difference that the next step is not selected randomly, but adjusted based on the previous steps.<sup>[36]</sup> A great advantage of this method is that typically much fewer experiments have to be conducted as compared to the brute force method. However, one has to be wary of the possibility of only finding a local maximum as illustrated in Figure 3b). Once a maximum is found, be it local or global, any alteration of the variables will result in a poorer result. To avoid getting trapped in a local maximum, either great care must be taken in experiment planning for each iteration or several of these sequences have to be performed in different regions of the variable space, ultimately diminishing the advantage over the brute force method. Additionally, one has to bear in mind that, due to the sequential nature of the process, the time saving potential strongly depends on the ratio of the time it takes to conduct an experiment and the time it takes to analyze the experiment. The intrinsic shortcoming of this “classical” approach is that it will never yield the full picture of the variable space, which may or may not be significant, depending on the aim of the research endeavor in question.

However, as time progresses so does technology, and what may have been a painstakingly slow and tedious data processing and analysis 50 years ago, can now be performed by a computer in the blink of an eye. Similarly, significant advancements have

been made in robotics during the last decades, which enable different types of experiments to be performed in large numbers and with little or no human involvement, freeing up the researcher’s precious time for other tasks (Figure 5). Not only does this paradigm shift in research accelerate discoveries, it also builds a solid foundation of a priori knowledge for future research and helps to not just discover good results but to also understand them.

### 3. High-Throughput and Combinatorial Approach

Discovery and development of functional materials is an ongoing game of attrition with the main challenge of finding and selecting 1–2 optimized candidates from the millions of possibilities that will advance the overall performance of a given system and its chemistry for a targeted application. In this process, the possibility of identifying a series of optimized compounds that could take research in new, unexpected directions should be retained as well. In response to aforementioned challenges, combinatorial and HT approaches comprising high capacity information processing and automation of experiments in a feasible large-scale repetition fashion allowing for faster experimentation without sacrificing the quality of the results, have been developed and established.<sup>[37,38]</sup> The combinatorial approach considers change in the nature of



**Figure 4.** Schematic representation of the “classical” iterative experiment loop where the result of the experiment’s analysis feeds back into the planning of the next experiment.



**Figure 5.** Schematic representation of the “brute force” experiment approach where a large number of simultaneous experiments is performed and the results analyzed in bulk.

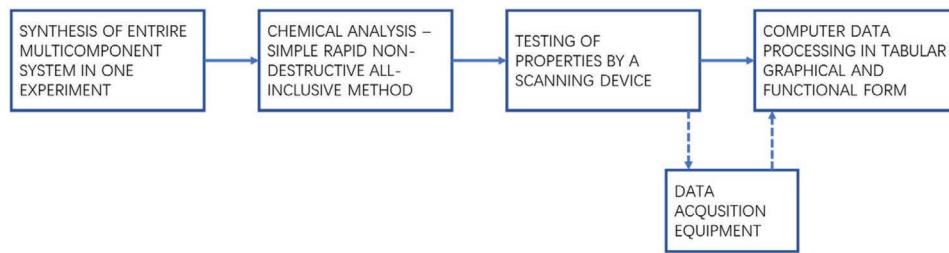
the parameters, such as different components or materials of a recipe, whereas high-throughput refers to the systematic variation of parameters in a wide parameter space of a particular system with a given composition.<sup>[39]</sup> Combinatorial synthesis can be applied to different methods resulting in, e.g., thin films,<sup>[40]</sup> powders,<sup>[41]</sup> and electrolytes.<sup>[42]</sup> Even the combinatorial synthesis of nanoparticles is possible.<sup>[43]</sup> HT measurement techniques mostly consider measurement areas on materials libraries and utilize nondestructive methods.<sup>[13]</sup>

For electrochemistry there has been quite an advancement in terms of HT characterization for catalysts<sup>[44,45]</sup> and batteries.<sup>[46–49]</sup> The synthesis of adequate materials libraries usually goes hand in hand with their analysis. Major tools in HT electrochemistry are the different designs of scanning droplet cells<sup>[50–55]</sup> as well as different kinds of scanning electrochemical microscopies. All of these techniques offer the capability to study three electrode half-cells or two electrode cells<sup>[56]</sup> at unprecedented throughput and reproducibility. Based on materials genomes concept,<sup>[57]</sup> both became valuable tools in materials science, chemistry and engineering to pin down the prediction experimentally, enabling the discovery-to-deployment of advanced functional materials more efficiently, by saving energy, time, and cost. The mutual goal of these methods is to identify functional materials that can provide starting points for further optimization with respect to relevant properties and performance in a given system and simultaneously enable generation of large data libraries.<sup>[58]</sup> This requires careful analysis of many variables, starting with the choice of assay target and ending with the discovery of hit/lead compound(s), broken down in the following subsequent steps: target choice → adequate assay development and validation → high-throughput implementation (screening collection) → data generation, processing, storage, and analysis → hit(s)/lead(s) identification.<sup>[59]</sup> A hit compound is a molecule that shows desired type of activity/effect in a given screening assay. Lead compounds are selected from a collection of hits by refining the screening criteria to enable the selection of the most promising molecules for further development. Being far more than just the simple identification of functional compounds, hit discovery and lead generation stand for a multidisciplinary process in which the most promising candidates get selected from assessed compound series/classes based on well-established criteria for a given system and application direction. During this filtration-based process, relatively unqualified materials get screened out,

followed by extensive preparation and further detailed characterization.<sup>[60]</sup> Every step in this process calls for decisions that can significantly impact the outcome to the point of making it a success or a failure. Although specific guidelines should be established to ensure an acceptable level of quality, sometimes choices require the ability to compromise opposing forces. Three closely interdigitated key success factors are relevant for successful discovery of lead(s): quality of the compound collection to be screened, time (time per sample, samples per day, screens per year, project time) and costs (reagents, consumables, instrumentation, and personnel).<sup>[61]</sup> In addition to that, development of an appropriate assay or collection of assays which can be performed at a throughput, statistical robustness, and reproducibility consistent with the budgetary constraints is of fundamental importance for successful HT screening. By definition, an assay is a precisely defined and efficiently designed experiment measuring the effect of a substance in a process of interest.<sup>[62]</sup> First assays within the pioneering work of Dr. Gyula Takatsky in 1951 were developed in a 96-well format by machined 6 rows of 12 wells in Lucite to result in the first microtiter plate.<sup>[63]</sup> The use of microplates was a revolutionary breakthrough enabling multiple experiments to be carried out simultaneously in a uniform format. The microtiter plate has further grown to include standardized 96, 384, 1536 well formats, with additional 3072 and 3456 well nanoplate formats for specialized reaction assays in domains of biology, medicine, and pharmacy.<sup>[37,61,64–67]</sup>

#### 4. High-Throughput Experimentation

High-throughput experimentation (HTE) can be broadly defined as a workflow of running multiple similar experiments in parallel. These sets of experiments are rationally designed to answer specific questions and achieve targeted goals. HTE comprises several aspects, such as smart design and selection of experiments, search and optimization among a large number of samples with different parameters and conditions to accelerate the whole search process. The preliminary concept of HTE was first mentioned in 1970 by Hanak, who introduced the “multiple-sample concept” to accelerate the development of new binary superconducting compositions.<sup>[68]</sup> This concept in a flow chart includes basic features of HTE: 1) massively parallelized sample synthesis 2) rapid characterization



**Figure 6.** Flow chart of processes needed for the study of entire multicomponent systems in single steps. Adapted with permission.<sup>[68]</sup> Copyright 1970, Springer Nature.

and analysis as well as 3) data collection and processing with the help of computers (**Figure 6**). Due to the limitations of the computer techniques at that time, the method was not immediately implemented worldwide. However, in the following years, combinatorial synthesis and screening of inorganic compounds have been intensively adopted, especially in the pharmaceutical industry for drug discovery.<sup>[69,70]</sup>

In 1995, Xiang et al. developed a HT combinatorial experimentation method and first demonstrated its potential on solid state materials with novel physical/chemical properties.<sup>[71]</sup> Since that, HTE has drawn attention of researchers from various material fields around the world and has been applied in many research fields including photovoltaics,<sup>[72,73]</sup> catalysts,<sup>[74]</sup> thermoelectrics,<sup>[75,76]</sup> polymers,<sup>[77]</sup> and magnetic materials.<sup>[78]</sup>

In the field of electrochemistry, or more specifically in materials development for electrochemical applications, HTE has a great appeal as it offers efficient strategies for overcoming the numerous optimization problems typically encountered during the development of novel materials. Utilization of robotic systems for synthesis and characterization opened the door to material development with exceptional reproducibility and minimal materials investment<sup>[79]</sup> while implementation of advanced software tools to the simultaneously generated, continuously growing knowledge base improves the rational materials design process.<sup>[80]</sup>

#### 4.1. High-Throughput Experiments on a Battery Electrolyte Level

High-throughput and combinatorial experimentation stands for an effective approach in characterizing large amounts of electrolyte materials/components over a broad compositional region in a short time, which enables significant acceleration in the discovery and optimization of lead electrolyte candidates for given battery chemistry and targeted application at low cost.

##### 4.1.1. Liquid Electrolytes

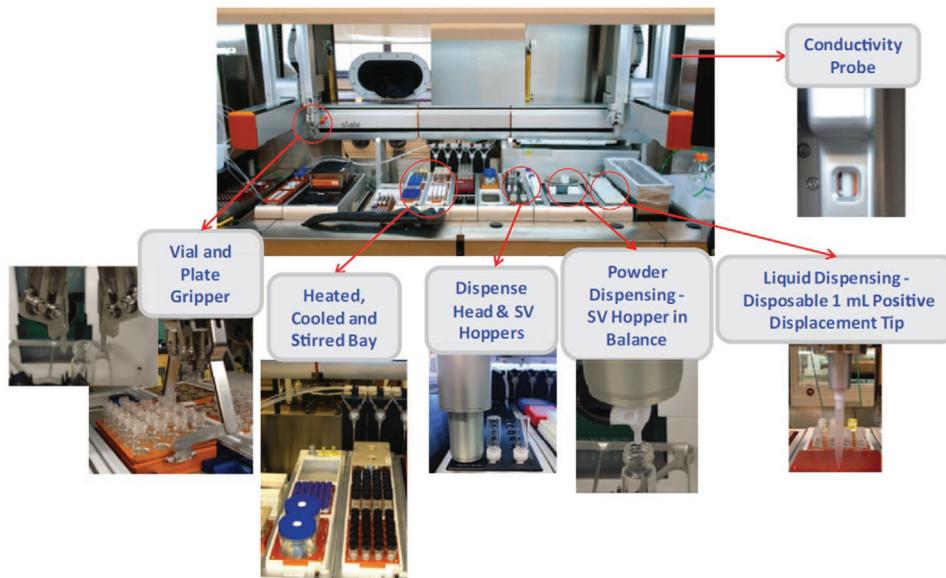
Given the wide variety of liquid electrolyte formulations in terms of conducting salts solvents/cosolvents and functional additives, liquid electrolytes are ideally suited for combinatorial formulation due to the fact that an array of different variants can be achieved via simple mixing. The amount and concentration variation of the electrolyte components, guided in a systematic and meaningful fashion, leads to enhanced relevant

physicochemical, electrochemical, and thermal properties of the resulting electrolyte formulation and impacts the overall performance and safety of a battery. The simplest way is to choose target components, design the experiments to ensure all possible combinations of all the pertinent factors and identify the lead compounds by using filtration effect based on criteria and requirements previously established for each of considered experimental techniques. For example, rational design of the composition of most commonly used organic carbonate-based solvents (ethylene carbonate, propylene carbonate, ethyl methyl carbonate, dimethyl carbonate, diethyl carbonate), leads to enhanced low-temperature power capability of LiNiMnCoO<sub>2</sub>||graphite cells due to the formation of an effective solid electrolyte interphase (SEI) without adding additives as Kafle et al. showed in their study.<sup>[81]</sup>

Su et al. integrated solubility and conductivity measurements in the automated high-throughput screening (HTS) platform to study the 2,5-di-tert-butyl-1,4-bis(2-methoxyethoxy)benzene (DBBB)-based electrolytes in a redox flow battery (RFB), as depicted in **Figure 7**.<sup>[82,83]</sup>

An automated, modular robotic synthesis and characterization system within an inert gas-filled glove box was developed to perform combinatorial studies on electrolyte formulations as a function of composition, concentration and temperature. Combinations of common conducting salts and organic carbonate solvents were systematically explored to enhance the solubility of considered electrolyte components while maintaining or even improving the electrolyte conductivity. A characterization system was used to determine trends in several key parameters (e.g., diffusivity, standard rate constant) known to impact the overall battery cell performance.

The most crucial function of an automation HTS platform is the high accuracy aspiration/dispensing system for either liquid or solid components.<sup>[84]</sup> This system is embedded in a multiaxis robotic arm to enable the movement of the aspiration/dispensing system between sample reservoirs and sample trays to formulate the electrolyte with different components. One of the problems we might encounter during the formulation is that when handling highly volatile solvents, the solution is prone to volatilization leading to low accuracy due to an unpredictable continuous changing of the mixing ratio of the solvents. Therefore, a combinatorial strategy uses temperature-controlled reservoirs to decrease the vapor pressure of the solvents and select a suitable technique to protect from the mixing of solvent during the aspiration/dispensing steps.<sup>[84]</sup> An additional feature of the automation HT platform is modularity: module(s) of interest can be introduced to realize



**Figure 7.** Modular robotic platform. Reproduced with permission.<sup>[82]</sup> Copyright 2014, IOP.

the required function. For instance, the solubility of the electrolyte can be determined by using a dynamic light scattering analyzer equipped with an optical camera and temperature controller.<sup>[82,83]</sup> Besides, the conductivity measurements can be performed with a conductivity meter with probe.

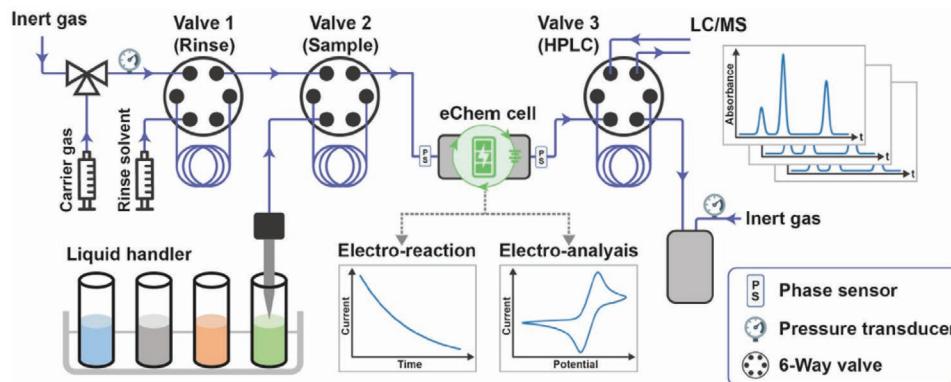
Another approach of automation HT platform is based on the microplate technique, frequently used in biochemical research. Microplate-based electrochemical cells can be considered as the battery inside the sample well.<sup>[85]</sup> The entire system, consisting of a liquid dispenser for the electrolyte formulation and a robotic arm for transporting the microplates, is placed in the glove box under inert gas. The only difference is that the electrolyte is directly dispensed into the microplate-based electrochemical cells instead of aluminum vials. In addition, a 96 channel electrochemical analyzer was integrated into this platform to evaluate battery performance. With the help of this platform, Matsuda et al. screened 2002 samples and identified a specific combination of five additives that can significantly enhance the Coulombic efficiency of lithium metal batteries.<sup>[85]</sup>

The automation HT platform is very flexible due to its modularity. However, the key point is the high accuracy robotic dispensing system, equipped with a rinsing system to avoid cross-contamination. Nevertheless, what if high precise pumps are used instead of the robotic arm system? The formulation of the electrolyte comprises simple mixing of the different electrolyte components by the help of pumps and valves, controlled by custom software that varies the inputs of pump speed, acceleration, direction, and strokes for each component and steps.<sup>[86,87]</sup> There are two outlets of the valve, which are connected with mix vessel and waste, respectively. Between the dispensing of different electrolyte components, the valves will be flushed or cleaned to avoid mixing components. With a series of flow-through devices this platform is capable of mixing complex electrolyte solutions and characterizing physical and electrochemical performance in a semicontinuous fashion. Dave et al.

built a system named “Otto” to enable HT automated formulation and characterization for liquid aqueous battery electrolytes.<sup>[88,89]</sup> Compared to traditional low throughput experiments, this system allows much faster formulation of 140 electrolytes within 40 h. In addition, the machine learning method coupled with automated evaluation of the acquired datasets enables inverse material design. The optimal electrolyte was found to be a novel dual-anion sodium electrolyte that exhibits a wider electrochemical stability window than the baseline sodium electrolyte.

Recently a low-cost with HT method called “microfluidic chip” was applied to accelerate the screening and optimization process due to increased electrode surface area and enhanced cell conductivity.<sup>[90,91]</sup> The automated microfluidic platform developed by Mo et al., resembles the “Otto” system, however instead of pumps, microfluidic chips are utilized to enable rapid and material-efficient electrochemical reaction condition screening and reaction kinetics measurements (**Figure 8**).<sup>[92]</sup>

The liquid handler can withdraw the liquid from the vials to prepare the microfluidic droplet injected into the sample loop, and then the microfluidic droplet will be moved into the eChem flow cell for electrochemical analysis. Subsequently, the microfluidic droplet will be introduced into the HPLC valve to analyze the reaction outcome. Furthermore, the system will be cleaned after each experiment to avoid cross-contamination. This team uses this platform to screen the radical–radical cross-coupling reaction on microfabricated interdigitated electrodes and measure the kinetics for mediated anodic oxidations. This approach has a great potential for the liquid electrolyte study as the droplet has a small enclosed volume. For example, two droplets can be merged based on hydrodynamic coupling.<sup>[92]</sup> In this way, by changing the flow rate of the liquids, the concentration can be varied from one drop to the next, which allows to explore the considered part of chemical space of electrolyte formulations.



**Figure 8.** Schematic of the automated microfluidic platform for electrochemical reactions and analysis. Reproduced with permission.<sup>[92]</sup> Copyright 2020, Wiley-VCH GmbH & Co. KGaA.

Another significant advantage of the microfluid refers to the fact that the fluid inside the microfluidic chip is in a laminar flow, allowing for measurement of the diffusion coefficients at small dimensions and the multiple microchannels enable HT sample preparation.<sup>[93,94]</sup> Chen et al. reported this HT approach for multiplex measurements of diffusion in a zinc battery, ten times faster than the conventional diffusion electrochemical approach.<sup>[95]</sup> The microfluidic chip was combined with Raman microspectroscopy, enabling HT measurement of the diffusion in zinc electrolytes at different concentrations. Determined diffusion coefficients are found to be in a good agreement with the literature values.

#### 4.1.2. Solid State Polymer Electrolytes

With the high demand for safety and high energy density, solid state batteries (SSBs) became a dominant research field. Depending on the specific chemistry, solid state electrolytes offer a wide electrochemical stability window, thus enabling the use of high voltage cathode and increasing the specific energy density.<sup>[96]</sup> Solid state electrolyte chemistry can be roughly divided into polymer and ceramic electrolytes. The usual way to advance the performance of polymer electrolytes is either to find novel conducting salt and inorganic fillers for solid polymer electrolytes or use plasticizer and inorganic fillers for gel polymer electrolytes.<sup>[97,98]</sup> Considering that these effects lead to a systematic influence on ionic conductivity and mechanical strength, HT methods application in the field of polymer electrolytes has an extraordinary potential. Although HT methods have been applied to polymers for the industry for many years, polymer electrolyte characterization is much less advanced. A report by Alcock et al. highlights a new HT characterization method for rapid screening of polymer electrolytes<sup>[99]</sup> by employing a 64-electrode array, used to characterize electrode materials.<sup>[100]</sup> Electrochemical impedance spectroscopy (EIS), X-ray diffraction, and differential scanning calorimetry were conducted in a HT fashion to determine the highest ionic conductivities over the range of ternary polymer electrolyte system. So far, there are no reports on the HT fabrication of polymer electrolytes in lithium ion batteries. Chen et al. used a HT method called projection stereo-micro-lithography to

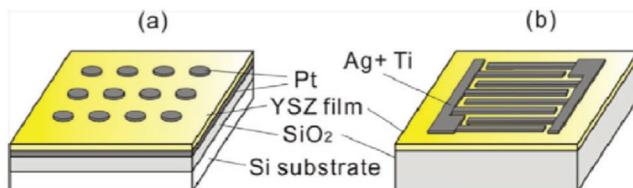
fabricate a 3D lithium ion microbattery, which is a technology for small-scale energy storage.<sup>[101]</sup> The projection stereo-micro-lithography technique enables parallel fabrication of multiple microbatteries on a single substrate with low cost compared to the conventional photolithography technique. Although the production of 3D lithium ion microbattery is yet more expensive than conventional 2D battery, this work showed the feasibility of microbattery fabrication as promising method for future research and development.

#### 4.1.3. Solid State Ceramic Electrolytes

Among the methods developed for synthesizing ceramic solid state electrolytes, the most used one is high-throughput physical vapor deposition system (HT-PVD). This synthetic method was used to synthesize solid state thin film libraries for metal alloys by coevaporation of the multiple pure elements on temperature-controlled substrates.<sup>[102,103]</sup> The basic configuration of the HT-PVD system consists of a PVD chamber under an ultrahigh vacuum environment, which has off-axis sources and electron beam evaporators or Knudsen cell sources.<sup>[104]</sup> This method not only has the advantages of HT and simplicity but also enables the synthesis of solid state electrolytes with a large compositional range without the need of heat treatment. Yada et al. identified a ternary oxide structure as an electrolyte–cathode interlayer for high voltage lithium SSBs based on this technique.<sup>[105]</sup> Beal et al. used this technique to synthesize a thin film sample library for the ion conductor  $\text{Li}_{3x}\text{La}_{2/3-x}\text{TiO}_3$  and applied data analysis techniques to determine the key parameters.<sup>[106]</sup> Gigante et al. developed a HT wet chemistry approach to synthesize the close-hydroborates solid state electrolyte by exploiting inexpensive and safe precursors in a five step solution-based synthesis to obtain a superionic conductor and stable electrolytes  $\text{Na}_4(\text{B}_{12}\text{H}_{12})$  ( $\text{B}_{10}\text{H}_{10}$ ).<sup>[107]</sup> This method is cost-effective and has the potential for a large-scale synthesis for future studies. Another wet chemistry approach is using the curtain coating method in which one of the most significant advantages is that the thickness of electrolyte can be easily tuned by changing the flow rate or web speed. It is a wet coating, roll-to-roll process combined with a drying device used in electrode

fabrication of lithium ion batteries (LIBs). The hydrodynamic assist<sup>[108,109]</sup> during the curtain coating enables the coating speeds faster than 2000 m min<sup>-1</sup> and film thickness less than 1 μm. Baada and Wood used this method to synthesize thin layer solid state electrolyte and demonstrated an 80 m min<sup>-1</sup> production of the uniform thin film.<sup>[110]</sup> Nevertheless, the coating speed of solid electrolytes is still not compatible with the coating speed of 2000 m min<sup>-1</sup> in other industries due to high viscosity and high solid contents slurries. A suitable slurry formulation therefore needs to be considered for the curtain coating. However, compared to the HT-PVD method, the wet chemistry approach requires high sintering temperatures, which inhibit cofiring of SSE and cathode particles.<sup>[111]</sup> Another approach refers to needleless electrospinning, as a fiber production method used for preparing various nanofibers<sup>[112]</sup> and attractive for increasing the throughput.<sup>[113]</sup> Rosenthal et al. presented a HT manufacturing of solid electrolyte nanofibers using needleless electrospinning by using Li<sub>7</sub>La<sub>3</sub>Zr<sub>2</sub>O<sub>12</sub> (LLZO) nanofibers as proof-of-concept and showed a practical HT synthesis of LLZO materials.<sup>[114]</sup>

In the high voltage region, ceramic electrolyte solid state batteries tend to have large charge transfer resistance.<sup>[115,116]</sup> Ionic conductivity is one of the most important electrolyte bulk properties influencing the performance of solid state electrolytes. The most common method to determine ionic conductivity for thin film solid state electrolytes is EIS, particularly useful and simple to determine a single sample. However, to realize high-throughput approach for conductivity determination, the thin film configuration in combination with the deposition technique containing two types of electrode geometry setups: out-of-plane and in-plane, was applied as shown in Figure 9. In the out-of-plane configuration, the thin film is sandwiched between the top and bottom metal electrodes and the measurement may be strongly affected by the close spacing of the electrodes. Furthermore, both electrodes are deposited on the top of thin film for the in-plane configuration and the spacing between electrodes is 5–10 μm, which causes less influence on ion conduction.<sup>[117]</sup> However, the in-plane configuration often suffers from artifacts due to stray capacitance and conductance through the substrate.<sup>[118,119]</sup> Duan et al. reported a feasible HT measurement of ionic conductivity in thin films of multiple oxide systems<sup>[117]</sup> by measuring the oxygen ionic conductivity of thin film yttria-stabilized zirconia using two different configurations, out-of-plane and in-plane as shown in Figure 9. On the other hand, Huang et al. demonstrated a HT measurement of ionic conductivity of solid state electrolytes by using an out-of-plane configuration.



**Figure 9.** Schematic of a) out-of-plane configuration and b) in-plane (integrated) configuration for electrical measurements. The IDE footprint was 1 mm × 1 mm. Reproduced with permission.<sup>[117]</sup> Copyright 2013, American Chemical Society.

The array of microdot metal on the top of electrodes enables measurements of hundreds of compositions in a single library.

A more straightforward and considerably faster way is to use an NMR probe that allows fast screening of solid state electrolytes. In line with this, Schiffmann et al. developed a high-throughput solid state NMR probe to determine the ionic conductivity of the solid state electrolyte.<sup>[120]</sup> This method allows the evaluation with a HT of >100 samples per hour and is easily upscalable. Besides, Tirosh et al. demonstrated a HT mapping method based on the F-doped tin oxide darkening effect for screening the ionic conductivity in solid state electrolytes.<sup>[121]</sup> Each measurement requires only 5 min which is 100× faster compared with the traditional EIS method. However, the distinction between grain and bulk lithium ion conductivity cannot be realized.

Finally, the selection of HT experiments should not be limited to any method. Each of the different liquid and solid electrolytes has different requirements and criteria, and the characterization methods also vary. Accelerated research by running large-scale and automated experiments will be beneficial in advancing future materials research.

## 4.2. High-Throughput Experiments on a Battery Electrode Level

### 4.2.1. High-Throughput Characterization of Thin Film Battery Materials and Related Electrode|Electrolyte Interfaces

LIB technology and lithium metal battery (LMB) technology tackles new challenges at fundamental and industrial level to face the complexity of the new LIB generation, for instance in solid state batteries.<sup>[122]</sup> In this context, material characterization of LIB components, i.e., the anode, the cathode, and the electrolyte was progressively improved at the level of single and correlative multiple characterization technique. Several characterization techniques have been developed to accompany materials synthesis and to study the reactivity of electroactive materials toward liquid or solid electrolytes in *in situ*/*operando* and postmortem ways using adequate protocols. Besides, the limited knowledge on the redox processes accruing during lithiation and delithiation of electrode materials, about the mechanisms of the SEI/cathode electrolyte interphase (CEI)<sup>[123]</sup> formation, growth and dissolution, interface/interphase design and its stability, characterization technique limitations associated with material sensitivity and/or the techniques themselves are still bottlenecks for widening our understanding for optimum LIB/LMB performance. Access to complementary information on the same material is relevant, but usually, it is carried out sequentially and separately. Therefore, acceleration of materials discovery for outperforming LIB/LMB materials design needs a multiscale approach from the material to the characterization level. Developing new correlative characterization workflows (CCWFs) adapted to LIB/LMB with the aim to become generic characterization solutions could yield acceleration in materials design while saving time and cost. The CCWFs include harmonized characterization protocols, and data treatment steps dedicated to data classification. CCWFs will not only assist to gather key characterization techniques but also to establish synergies between techniques

to correlate the various types of information and generate a high added-value consolidated set of data. It is therefore necessary to design a HT approach starting from materials over, components and processes to systems to ensure wide transferability of results to industrial level. Therefore, common characterization methodologies go together with a harmonization of experimental protocols as well as data treatment, in terms of classification, types, format, curation, and establishment of infrastructure facilitating management and sharing information.

Studying a region of interest, for instance, bulk as well as interfaces and interphases in LIB/LMB with a multidimensional characterization approach faces several challenges from sample preparation to data treatment level. Quantitative and qualitative chemical, morphological, structural, and dynamic properties of materials are often recorded separately, and this at different length and time scales. In-depth understanding of interfaces/interphases can be achieved through single techniques, however correlative analyses provide advanced levels of understanding.<sup>[124–126]</sup>

Structural and chemical mapping using combined transmission electron microscopy/electron energy loss spectroscopy/energy dispersive X-ray spectroscopy on electrode materials at different state of charge enhance our knowledge of phase distribution and particle cracking of active material at nanometer scale.<sup>[127–130]</sup> Correlative study combining chemical analyses using XPS, Fourier-transform infrared spectroscopy (FT-IR), and EIS paved the way to deep understanding of SEI and CEI composition at the micrometer scale.<sup>[9,131,132]</sup> Considering large volume, X-ray tomography performed in operando condition provides a low resolution overall picture of structural and some dynamic processes, for example, Li dendrite growth or particle expansion.<sup>[133–135]</sup> Through these three examples, certain techniques showed the possibility of successful correlative analyses, however a general multiscale correlative CCGF remained unestablished. Considering the overall view of different degradation and ageing processes taking place in LIB/LMB cells,<sup>[136,137]</sup> correlative analyses can be designed according to separate strategies of acquisition and corresponding workflows as, for instance,

- from nondestructive to destructive characterization methods,
- from global characterization, covering a large volume of the region of interest, to local view characterization. This step can be repeated at different length scale, combining two or several characterization techniques.
- from dynamic (*in situ/operando*) to postmortem, through combined electrochemical and physicochemical characterization, and
- adequate sample preparation to fit with characterization technique constraints (environment, beam size, sample holder, length and time scale acquisition, etc.).

In similar ways, collection of multidimensional data must follow a correlative workflow considering

- classification of samples with enhanced quality of reproducibility and traceability, through combinatorial material design or material design by road map,<sup>[20,138]</sup>

- single dataset, often specific for each characterization technique, manipulation, analysis (quantitatively and qualitatively), and reconstruction within multidimensional datasets. Some software allowed the manipulation of data sets from single to general element, to create multi-output datasets,<sup>[139]</sup> with the assumption of perfect matching of the analyzed area probed by both techniques.
- raw and/or treated data storage through harmonized formats. The large volume of data that can be produced through different subsequent workflows needs specifically structured big-data treatment strategies for optimum multiscale data exchange and manipulation within reasonable time scales.
- Data manipulation should keep retroactive loops of data processing possible.

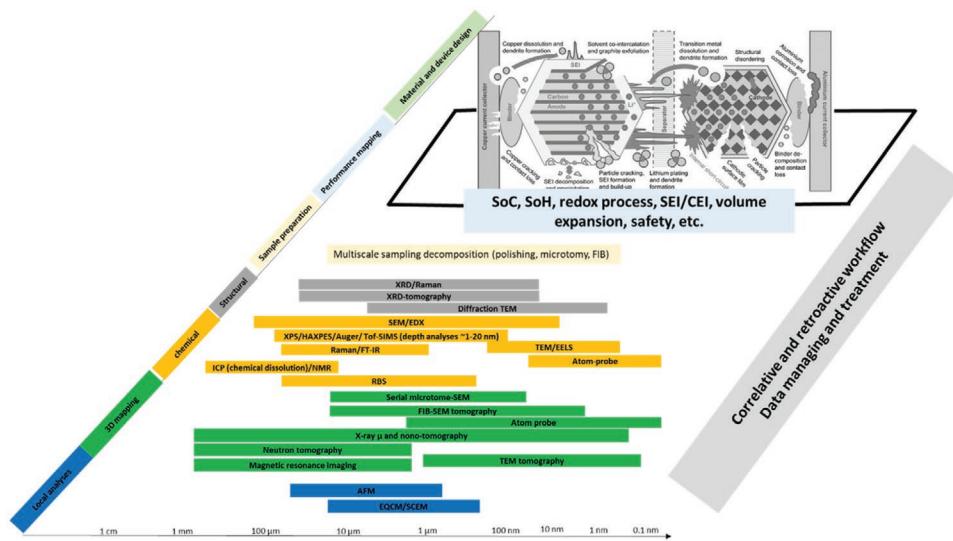
Developing correlative workflow analyses for battery accelerating design across multiscales of different chemical and physical properties requires dedicated computational approaches such as science-based, machine learning-based or HT based.<sup>[140–143]</sup>

Using the example illustrated in **Figure 10**, the correlative approach needs new characterization paradigms where every aspect must be designed taking in account the modalities and the time/length scale inside the established workflow.

#### *4.2.2. Thin Film Materials as a Medium for High-Throughput Experimentation of Surface and Interface Properties*

The assessment of the role and the influence of materials interfaces on the operation the LIB cells, and the rational improvement of appropriate material connections inside the electrochemical chain via an HTE approach can appear particularly challenging. The 3D arrangement of the different components of the battery cell, the multiplicity of its constituting materials and the even larger number of interfaces and interphases they form, contribute simultaneously to the operation of the cell and influence its ageing, but makes difficult the characterization of a particular interface/interphase and the assessment of its specific influence in the system. Additionally, the achievement of controlled compositional, geometrical, structural gradients regarding the interface/interphase of interest is generally not straightforward, since each of the latter might result from the influence of various (and possibly unknown) parameters.

In this respect, controlled preparation and characterization of 2D model surface/interfaces/interphases can be a valuable tool for the HTE for material optimization regarding interfacial phenomena. 2D model components are being commonly used in some conventional fundamental studies related to battery materials, with the aim to get a simpler electrochemical system, to precisely tune one of its parameter at a time, and finally to get a clear insight into the influence of the latter on the electrochemical response.<sup>[145]</sup> Most of these model components consist in thin film materials (single or multilayers) deposited on polished wafers, single crystals, or on metallic foils by vacuum deposition techniques. The latter include chemical vapor deposition (plasma-enhanced chemical vapor



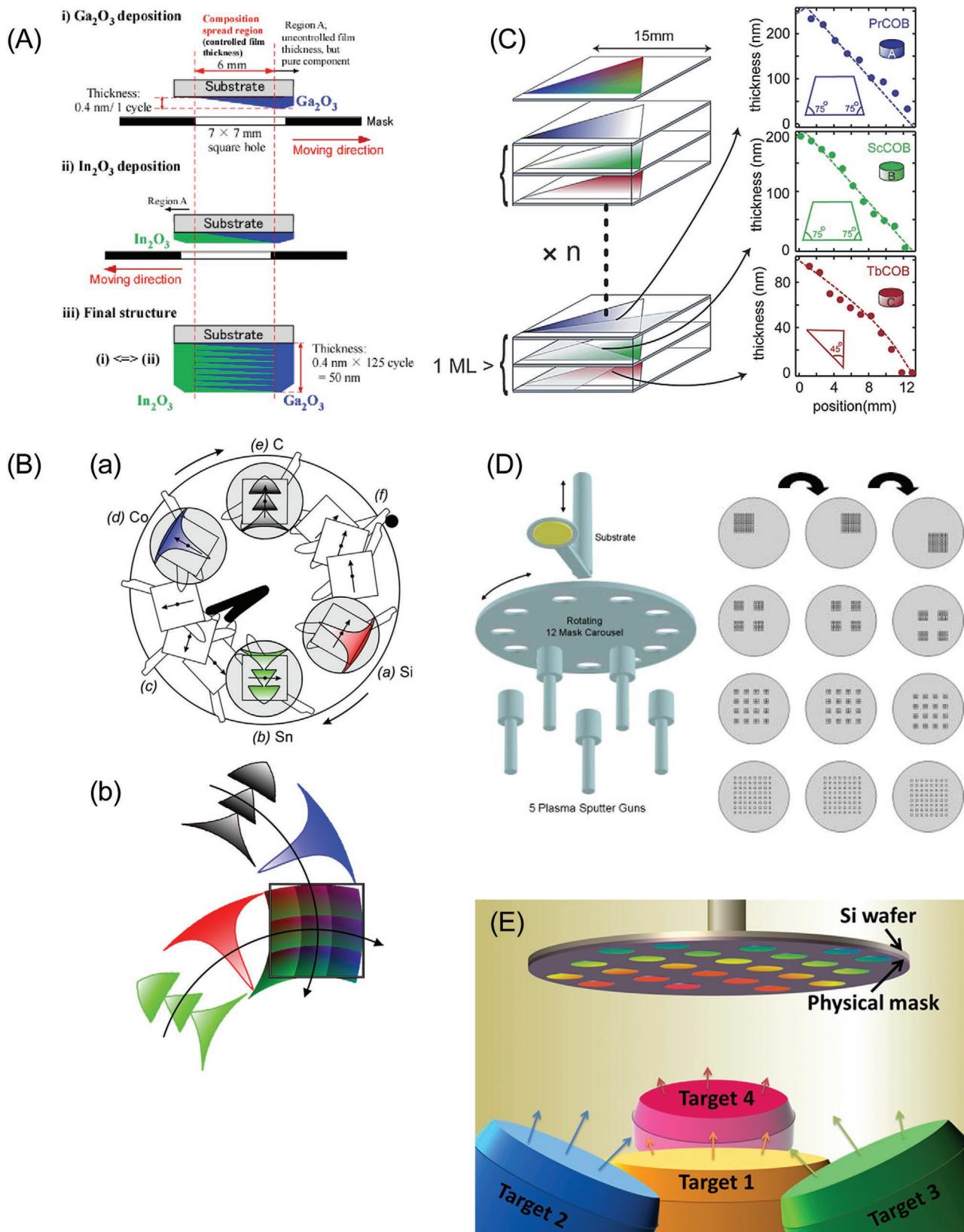
**Figure 10.** Overall view of correlative workflow for material by design battery, performance mapping, and multiscale characterization with regards to degradation processes in LIB cells. Some part of the figure use some figure and elements reported elsewhere.<sup>[136,144]</sup> Adapted with permission.<sup>[144]</sup> Copyright 2019, Springer Nature.

deposition, low pressure chemical vapor deposition, and atomic layer deposition)<sup>[146–149]</sup> and physical vapor deposition (magnetron sputtering, thermal or e-beam evaporation, pulsed layer deposition, and molecular beam epitaxy).<sup>[102,149–151]</sup> The benefit of using thin film materials lies in the fact that i) the electrode or the solid electrolyte can be studied as a pure compound, ii) its thickness can be easily monitored, so that the contribution of surface phenomena relative to bulk ones can be amplified, and iii) its planar geometry, and possibly its low roughness, generate clear surface and interface that ease the use of surface characterization techniques and the interpretation of the results. For example, this configuration has been successfully used to get a comprehensive insight into the behavior of the LiCoO<sub>2</sub>/electrolyte interface due to complementary techniques: determination of the Li<sup>+</sup> ion transfer through particular planes of the layered structure,<sup>[152]</sup> observation of the diffusion profiles of Li<sup>+</sup> ions (time-of-flight secondary ion mass spectrometry/glow discharge optical emission spectroscopy),<sup>[153]</sup> dynamics of the formation of an CEI (X-ray reflectivity under in operando conditions, polarization modulated-FTIR, and XPS),<sup>[154,155]</sup> evolution of the surface morphology, contact stiffness, and surface potential (atomic force microscopy)<sup>[156]</sup> or the effect of a particular coating (LiPON) on high voltage stability.<sup>[157]</sup>

The introduction of this approach into the HTE process is at first conditioned by the capability to generate thin film materials libraries in a massive and reproducible way. Actually, among vacuum deposition techniques, magnetron sputtering has been identified since the 1970s<sup>[68]</sup> as a convenient means to combine multiple components in order to generate on single substrate thin film materials with compositional gradients (combinatorial synthesis) in a single experiment, and therefore as a tool for conducting accelerated assessment of materials in different scientific and technical areas.<sup>[158,159]</sup> However, since the approach aimed at generating spatially distributed materials libraries is against the flow of the conventional use of this deposition technique, it requires some specific adapta-

tions of the process or/and the experimental set-up in order to reach this goal. Different designs that involve either sequential or simultaneous deposition are shown in Figure 11. This approach was introduced and developed in the field of battery materials research by Dahn et al.<sup>[46,160,161]</sup> 20 years ago for the assessment of Si and Sn-based negative electrode compositions, and led to the identification of a ternary compound later introduced in Sony's NEXELION lithium ion cells.<sup>[162]</sup> From then, it has been also applied to the development of various inorganic compounds including lithium-nickel-manganese-oxide and lithium-nickel-manganese-cobalt-oxide cathode materials.<sup>[163]</sup> The combinatorial synthesis of specific compounds of interest for battery applications is indeed not limited to the combination of simple elements and the synthesis of amorphous materials. Nevertheless, the investigation of specific compositions and structures of materials using vacuum deposition techniques, and particularly mass spectrometry (MS), can be particularly challenging, as conditioned by the availability of specific targets and/or substrates, the relative values of the sputtering yield, the deposition rate, a need for reactive deposition, for operando/ex situ annealing, etc.

However, the main challenge of HTE of thin film materials is probably the necessary development of appropriate (non-destructive) characterization tools able to provide spatially resolved information about the chemical composition, the local and/or global structure, and other features (dimensional, (electro)chemical, mechanical) of the thin film material library. To map (electro)chemical properties of the films, two main set up designs already exist to carry out measurements on a single planar substrate. These set ups are based either on a fixed array of cells generated on the top (the resolution is then limited by the intercell distance, measurements can be made simultaneously on several if not all cells),<sup>[165,166]</sup> or on an X-Y moving probe that can be positioned above each point of the substrate (the resolution is limited by the diameter of the tip from tens of μm (scanning electrochemical microscopy) to mm, the



**Figure 11.** Schematic diagrams of sequential depositions in combination with masking techniques or simultaneous deposition by cosputtering. A) Combinatorial synthesis of  $(\text{Ga}_x\text{In}_{1-x})_2\text{O}_3$  using a mobile mask with a squared-shape hole. Reproduced with permission.<sup>[262]</sup> Copyright 2020, American Chemical Society. B) Combinatorial synthesis of Co-C-Sn-Si quaternary thin film using rotatable substrate and fixed mask over the targets.

probe possibly contain a reference electrode, measurements have to be conducted sequentially).<sup>[167]</sup> The rest of the physical/chemical characterizations of the materials libraries is probably less straightforward given the thin film form of the materials, their possible amorphous character, and the presence of light elements (including Li). Due to inappropriateness to the HTE approach of some techniques such as Rutherford backscattering spectrometry and nuclear reaction analysis for example, additional approaches mentioned above consisting in the combination/global processing of more or less complete, low/high accuracy sets of measurements will probably appear as a necessity and a new frontier.

#### 4.3. High-Throughput Experiments on a Battery Cell Level

Evaluating long-term performance as well as (time and/or cycle dependent) degradation mechanisms is the last but foremost challenge in pushing lithium ion and post-LIB advancements. Due to manual lab scale manufacturing, there are only a few studies that evaluate larger numbers of cells on a laboratory scale.<sup>[168,169]</sup> Full cell manufacturing requires significant capital investments,<sup>[170,171]</sup> hence the few studies published utilized commercially available cells. Contrary to thin film-based studies,<sup>[172]</sup> full cell configurations require large amounts of material, and tests may last for months or even years. A general theme is therefore a batched experimentation. However, moving cell cycling capability (especially for commercial cells) from low throughput to HT can be as trivial as increasing the capacity for experiments, i.e., buying more cyclers and is probably the worst possible solution. High quality hardware is usually quite expensive and research budget as well as available space is quite limited for many groups. Herein lies the elegance of the work of Severson et al. who used statistical methods on cycling data to develop a purely data-driven model that is capable of accurately predicting the lifetime of a battery cell based on the first 100 charge/discharge cycles.<sup>[169]</sup> This allows to finish cycling experiments within days rather than months and thus significantly increase the throughput of an experimental setup without changes to the hardware. In a following study, the group demonstrated this by combining their prediction model with a closed loop optimization algorithm, which suggests a batch of experiments to perform next based on the previous batch.<sup>[168]</sup> Using both methods in combination, they were able to find the optimum from 224 different fast charging protocols using only 185 commercial cells and 16 days of actual cycling time. This work demonstrates the great potential of modern data analysis and ML techniques when applied to optimization problems often encountered in materials research.

An alternative way of predicting long term effects refers to galvanostatic cycling of a battery cell via ultrahigh precision

chargers<sup>[173]</sup> that allow for early failure prediction through careful analysis of Coulombic efficiencies.<sup>[174]</sup> However, as this requires specialized equipment and comparatively long experiment durations, broad application in HTE is not feasible yet.

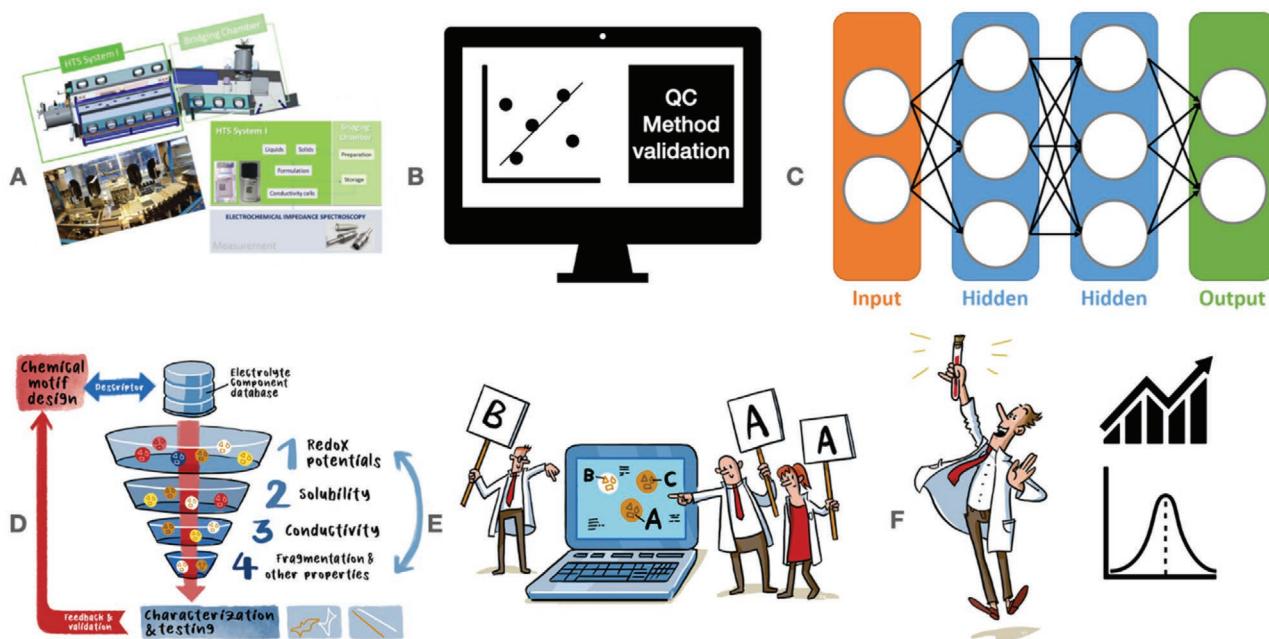
Some studies do however require very long experimental times and exhibit very smooth trends such as calendric ageing studies changing the perspective of the efficacy of acceleration of experiments through automatization versus acceleration of research through automatic analysis.<sup>[175]</sup>

### 5. High-Throughput Virtual Screening

The idea of material discovery has been evolving for generations. Most of the groundbreaking material discoveries happened by categorical approaches from experimentalist, rational design, or by accidents. This is due to the fact that screening through the chemical space for all combinations of molecules to achieve desired properties was extremely difficult. With the recent advances in automation technologies, the experimental screening of these compounds has been accelerated by manifolds. Nevertheless, the broadness of the chemical space makes the experimental screening a challenging task. With regard to desired material application and with considerable chemical intuition one can narrow down the chemical screening space to a large extent, however the cost of screening the remaining ( $>1000\,000$ ) sets of molecules still remains very high. With recent advances in computer architecture and parallelization, molecules can be screened through a theoretical approach to further reduce the chemical screening space. This process of using a combination of high performing computer architecture and theoretical models to screen through large chemical space represents the philosophy of high-throughput virtual screening (HTVS). Several HTVS studies have been reported in the field of materials science,<sup>[176]</sup> as for instance for semiconductors<sup>[177]</sup> and perovskites.<sup>[178]</sup> In the field of battery science, many studies have been carried out for solid electrolytes, e.g., with regard to their phase stability,<sup>[179–182]</sup> transport properties,<sup>[180]</sup> geometric and bond valence site energy<sup>[182–186]</sup> or mechanical properties,<sup>[187]</sup> the latter being important for the suppression of dendrites. Similarly, a high-throughput computational screening process is reported for identifying lithium containing fluorides for battery cathode coatings.<sup>[188]</sup> Further studies on ML-driven automated screening for lithium-based batteries are also reported.<sup>[189,190]</sup> A recent review discusses the importance of computational techniques to predict novel candidates for superionic conductors and to reveal the underlying mechanisms of fast ion diffusion.<sup>[179]</sup>

The concept of HTVS based on a recent publication by Aspuru-Guzik and co-workers combines experimentally

Schematic diagram of (a) the rotating table showing “snapshots” of one of five substrate tables at various instants in time in a sputtering reactor and (b) four-element thin film resulting from the sputtering run. Gaussian-shape mask is illustrated. Reproduced with permission.<sup>[263]</sup> Copyright 2006, IOP Publishing, Ltd. C) Combinatorial laser molecular-beam epitaxy synthesis of calcium oxyborates of Tb, Sc, and Pr using trapezoid and triangular-shaped rotatable masks. Reproduced with permission.<sup>[264]</sup> Copyright 2004, American Chemical Society. D) Set of 12 shadow masks used for the preparation of ternary compounds as catalysts for OER/ORR in Li-air batteries. Reproduced with permission.<sup>[265]</sup> Copyright 2005, AIP Publishing. E) Principle of cosputtering. Reproduced with permission.<sup>[164]</sup> Copyright 2016, Springer Nature.



**Figure 12.** High-throughput virtual screening process. A) High-throughput experimental measurements to determine ionic conductivity, viscosity, density, electrochemical stability, etc. of liquid electrolyte formulations. B) Initial screening to validate suitable theoretical approaches (QC/MD) to calculate desired properties of interest. C) Accelerating the computational speed of QC/MD methods using machine learning and data driven algorithms. D) Computational funnel screening approach. E) Approval of target candidates. F) Postprocessing and data analysis of high-throughput screening experiments with data driven methods.

validated density functional theory (DFT) calculations with ML algorithms.<sup>[191]</sup> Notably, the latter further supports the acceleration of calculations, which in turn accelerates the material discovery process. Figure 12 displays a schematic of this HTVS approach that has been implemented in a stepwise fashion.<sup>[29]</sup>

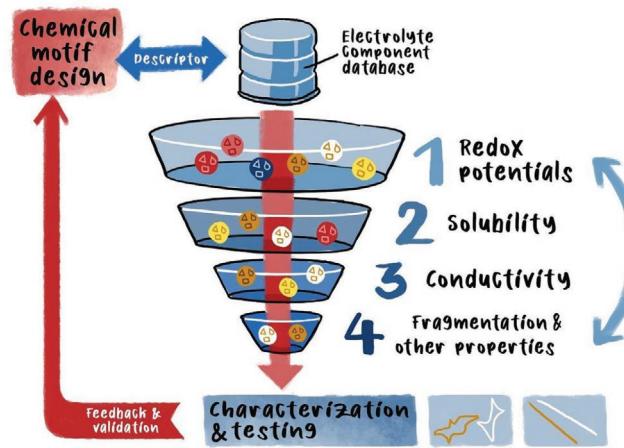
- A) Experimental measurements – The fundamental goal of HTVS is to identify quantitative structure–property relationships that provide directions to predict novel materials for, e.g., battery applications in order to complement experimental HTS approaches. Material prediction follows two directions denoted by forward and inverse mapping principles. Forward directions predict materials properties using structure of the material or composition as input, whereas inverse mapping design follows predictions of material structure or compositions with target material property as input. The challenges involved in the inverse material design process for inorganic solid material are discussed by Noh et al.<sup>[192]</sup> as well as by Elton et al.<sup>[25,193]</sup> Even though high-throughput experiments are automated and fast in nature, the initial cost might be very high for screening a large complex material space, required in the field of battery applications. Thus, computational approaches and theoretical models are necessary to assist experimental techniques.
- B) Computational models and validation – Although theoretical methods<sup>[194,195]</sup> such as DFT or molecular dynamics (MD) may accelerate experimental HTS approaches, it is of prime importance to validate the predictions of the calculations for experimental accuracies. DFT is an ab initio technique, which by definition only relies on natural constants and thus does not require an extensive parametrization once the employed

functional itself is validated. State-of-the-art DFT calculations typically rely on so-called hybrid or even generalized gradient approximation functionals, which show a significantly reduced computational demand as compared to wave function methods that explicitly take electron correlation into account. In this way, one is confronted with a trade-off between the amount of screened substances and the accuracy of the computed results.<sup>[29,196]</sup> However, for a reliable assessment of material properties, it is important that the problem under consideration is well defined and directly related to the underlying atomic or molecular properties via so-called descriptors.<sup>[197]</sup> For instance, the energy levels of the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO) are frequently used to predict both the adsorption characteristics of organic photovoltaics or the electrochemical stabilities of electrolyte components, that is, one aims to establish a link between molecular and material properties. Moreover, these descriptors also play a central role for the development of ML models as feature variables, although in this particular context also experimental descriptors such as the composition of an electrolyte may be defined. Finally, the correspondence between molecular and material properties established by the descriptors results in a robust way to create material databases which are a fundamental component of the HTVS process. This process also includes automated data job management processes<sup>[198]</sup> ranging from input file generation to final data storage. These software protocols formulate genomic projects. The electrolyte genome project and polymer genome are examples of the pioneering works done for battery applications.<sup>[199,200]</sup> Unlike DFT, MD simulations relying on classical force fields have

mainly been used in the field of drug discovery.<sup>[201,202]</sup> However, in a recent perspective article,<sup>[203]</sup> Makeev and Rajput advocate the use of MD to, e.g., compute viscosities or solubilities of multicomponent systems, ideally combined with an automated force field generation.

- C) Machine learning model development – HT calculations on electrolytes have mainly been considered for single molecule properties like redox potentials, densities, and electrochemical stabilities. Even though DFT/MD algorithms predict material properties with considerable accuracy, it takes up sufficient computational time to screen through large chemical spaces. Nonetheless these tools are too expensive to determine diffusion behavior, ionic conductivities, and other bulk thermodynamic properties. MD and coarse grained models can estimate these properties, though the accuracies of these models are not up to DFT/MD, but with the advent of novel descriptors and ML-based interatomic potentials, these properties can be determined with ab initio accuracies.<sup>[180,204]</sup> These models are computationally too demanding to screen millions of molecule compositions. To accelerate the screening process surrogate models can be used, which provide property estimates with low computational expense and with equivalent accuracy to the trained model. Suitable regression models or neural network models are used to achieve the desired chemical accuracies.<sup>[191]</sup> These surrogate models are then used in the construction of necessary material databases for the material discovery process.
- D) Computational funnel approach – Next step in the HTVS process is screening of materials with respect to the properties of interest for battery applications. In many cases, not only redox stabilities, but also other parameters are of interest for a certain problem, such as calculating salt solubility. In this case, one typically applies a sequential scheme that is referred to as “computational funnel approach.”<sup>[29,180,197,205]</sup> Each quantity of interest corresponds to an individual step in the screening, and unsuitable compounds from the candidate pool are discarded at each step according to a certain criterion, leaving behind a substantially reduced set of candidates, which can be validated experimentally or via more sophisticated theoretical calculations (Figure 13).

The order of the assessed quantities may vary depending on the system, e.g., for multivalent ions, electrolyte solubility is extremely important and thus screened in a first step,<sup>[197,205]</sup> whereas for LIBs or RFBs, the electrochemical stability window (ESW) is of prime importance.<sup>[197]</sup> Solubilities are typically computed from an implicit or explicit solvation model, in which the vacuum state serves as reference<sup>[205,206]</sup> due to the fact that the crystal structure of novel compounds (whose identification is the main purpose of high-throughput computing (HTC) screenings) is not necessarily known. For instance, Klamt performed solubility calculations of several electrolyte solvents for calcium-based batteries via COSMO-RS,<sup>[207]</sup> followed by calculations of the ESW for the remaining molecules. Further molecules were discarded in a third step on the basis of viscosity, flash point, and boiling point estimates. Finally, for the lead candidate, the stability of the solvation shell was computed in DFT calculations with explicit solvent molecules and four different anions to rationalize the ion-pairing behavior.



**Figure 13.** Schematic illustration of the computational funnel approach.<sup>[197]</sup> A possible example would be finding a suitable electrolyte formulation. In this example, the circles would represent different formulations comprising of, e.g., conductive salt, solvent, and additive(s). At each step, candidates from the initial pool are discarded based on specified criteria. The remaining candidates can subsequently be investigated more thoroughly in experiments or refined calculations. Note that the quantities of interest as well as their order may vary depending on the considered problem.

- E) Refinement based on human intuition – Once the pool of desired candidates is established from a large database, it is further screened by chemical intuition and voting from scientists, which is used only to exclude compounds that are not appropriate. The final dataset is again put into experimental validation for suitable material property predictions. Further screening is based on ranking of the down-selected candidates on the basis of their structure and ease of synthesis. Based on this approach, recently, a study based on integrated organic functional material design that incorporates theoretical insight, quantum chemistry, cheminformatics, ML, industrial expertise, organic synthesis, molecular characterization, device fabrication, and optoelectronic testing has been reported.<sup>[191]</sup> This HTVS process enables a fast screening of more than 1.6 million molecules, resulting in external quantum efficiencies of materials that are comparable to state of the art material OLED devices.
- F) Analysis of final candidates – Experimentally and computationally, it is very expensive to validate several thousands of candidates that may exist in chemical space. Thus, one needs a screening protocol that leverages HT calculations, ML and data driven algorithms, and experimental validation for identifying the right candidate material. This combinatorial process enables a fast screening of millions of molecules for the identification of suitable battery electrolytes and interfaces.<sup>[208]</sup>

Having outlined the interplay between experiments, theoretical modeling as well as ML techniques in HTVS, the focus on the computational part is set on the basis of two examples: liquid carbonate-based electrolyte additives and redox-flow anolytes/catholytes. Furthermore, descriptors with different complexity will be discussed, followed by an outlook on the

incorporation of ML-based molecular modeling techniques into HTVS approaches.

### 5.1. Simple Descriptors

In case of screening approaches for liquid electrolyte compounds, a common example is the prediction of oxidation and reduction potentials of LIB electrolytes.<sup>[209,210]</sup> This is due to the fact that the performance of an LIB cell is critically linked to the formation and the properties of protective interphase layers at the anode (SEI) and cathode (CEI), which prevent the electrolyte from continuous electrochemical decomposition. DFT calculations can guide the search for novel electrolyte components that meet requirements by screening large sets of potential candidates and discarding molecules that are deemed too unstable according to a certain criterion. This approach is closely related to the computational funnel approach described in part D, and narrows down the initial set to a substantially reduced number of candidate molecules, which can then be investigated via more sophisticated calculations or experiments. For organic carbonate-based electrolytes, Hall and Tasaki performed a large-scale screening of EC derivatives already a decade ago.<sup>[209]</sup> They estimated the redox stabilities of these compounds via HOMOs and LUMOs, as well as their ionization potentials (IPs) and electron affinities (EAs). The latter quantities are intimately related to the former, but additionally involve another QC calculation of the oxidized/reduced molecule, rendering the screening procedure more accurate, however, computationally more demanding. Later, Korth and co-workers performed similar calculations on a broader range of organic molecules that may serve as solvents for LIB electrolytes, additionally assessing the performance and accuracy of different semiempirical schemes, DFT functionals, and wave function methods.<sup>[210,211]</sup> Notably, such schemes can also be implemented as volunteer computing projects due to the large number of independent calculations.<sup>[212]</sup> Naturally, HTVS screening approaches are not limited to a particular system such as LIBs, but were also reported for various types of electrolyte additives,<sup>[213]</sup> electrolytes for supercapacitors<sup>[214]</sup> or calcium batteries.<sup>[205]</sup> Once data sets are generated, they can be analyzed via regression techniques or ML concepts to relate the chemical structure to the molecular properties. For instance, Okamoto and Kubo employed molecular features such as the number of atoms of a certain element or the presence of ring structures in two different regression algorithms to estimate the redox potentials.<sup>[213]</sup>

Importantly, HTVS approaches were also employed in the search for optimal candidates for the active compound in anolyte and catholyte solutions in RFBs.<sup>[206,215]</sup> Besides conventional anolytes/catholytes, relying on heavy metal ions as redox-active species, organic materials such as quinones or alloxazines in nonaqueous solution are highly promising due to the fact that they are cheap and can be tailor-made to meet specific demands as a consequence of the vast chemical space spanned by organic molecules.<sup>[29]</sup> Certainly, the latter point highlights the role HTVS approaches can play in order to optimize these materials. Another reason why HTVS approaches

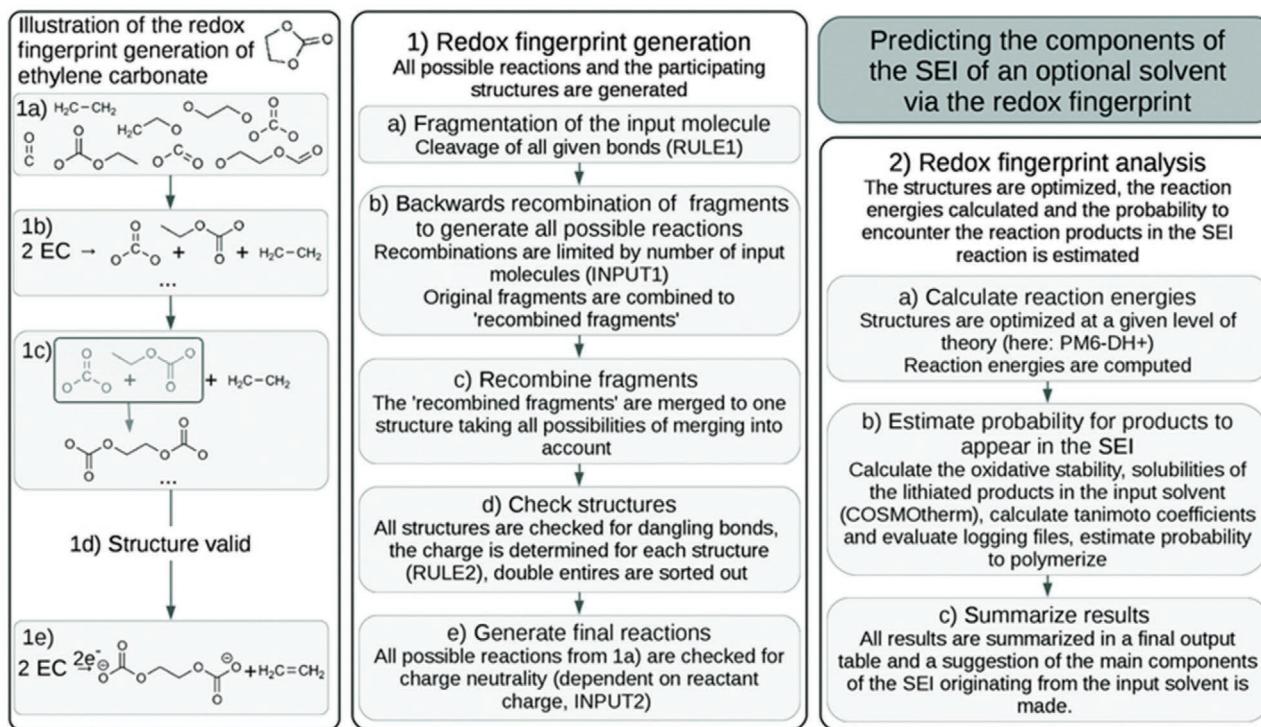
were particularly performed for RFB compounds is grounded in their theoretically high reversibility upon galvanostatic cycling. That is, side-reactions ideally play a marginal role due to the fact that the excess charge upon oxidation/reduction is well stabilized by the large organic molecules utilized in RFBs.

### 5.2. Incorporating Reaction Pathways

The situation for HTVS screening of RFBs stands in stark contrast to that of LIB electrolytes, which necessarily form protective layers at either electrode (SEI and CEI) via a plethora of side reactions and cascades. Clearly, these reactions pose a serious challenge for HTVS approaches, as a straightforward calculation of HOMOs/LUMOs or of IPs/EAs only yields the limiting redox stabilities,<sup>[216,217]</sup> that is, the stabilities of isolated molecules. Borodin et al. demonstrated that by explicitly taking various initial decomposition reactions such as hydrogen transfer into account in QC calculations, the true electrochemical stability can be lowered by as much as 2 V as compared to the IPs/EAs of single molecules.<sup>[218–220]</sup> To account for such effects in HTC approaches, it has been suggested to compute changes in the molecular geometry upon oxidation/reduction.<sup>[197]</sup> Whenever the geometry of a molecule changes by more than a preset value, it can be subjected to closer inspection. In this context, large-scale computational screening approach of possible fragmentation reactions of organic carbonates in LIBs is noteworthy.<sup>[212]</sup> Here, fragments of various carbonates were automatically generated and recombined according to a few predefined chemical rules, and the resulting reaction energies were computed (Figure 14). Subsequently, a ranking was created based on energy values as well as similarity metrics such as the Tanimoto coefficient between reactants and products to estimate the likeliness of a given reaction when considering the necessary rearrangement of atoms. However, although important reactions can be automatically identified in this way, kinetic information is not included as the reaction barriers are not explicitly calculated. Besides electrochemical reactions, it has been demonstrated that the inclusion of lithium ions (in case of reduction) or anions (for oxidation) affects computed redox potentials significantly.<sup>[218–220]</sup> Interestingly, for the case of EC reduction, the potential is rather sensitive to the position at which the lithium ions are inserted in the calculation (with a difference of  $\approx$ 0.1–0.2 V), which should be considered in an HTC screening.<sup>[218]</sup> As a technical side note, range separated hybrid DFT functionals have shown improved accuracy as compared to conventional functionals for redox reactions<sup>[221]</sup> due to the fact that the electronic self-interaction error in DFT is mitigated.<sup>[222]</sup>

### 5.3. Improvements via Machine Learning

As mentioned above, HTVS screening via MD has received substantially less attention in the field of battery research, mainly due to the fact that classical MD require force fields that need to be carefully parametrized—sometimes even for different concentrations for otherwise identical compounds—while



**Figure 14.** Schematic overview of the fragment generation. Electrolyte molecules (e.g., EC) are fragmented according to heuristic chemical criteria. Accordingly, the fragments are recombined in a second step. Various quantities such as reaction energies can be computed from these automatically generated compounds via chosen QC methods. Reproduced with permission.<sup>[223]</sup> Copyright 2015, the Royal Society of Chemistry.

large-scale ab initio MD is computationally extremely demanding. Here, a new methodological avenue was opened by ML-trained force fields, which provide ab initio accuracies at a significantly reduced computational cost.<sup>[224]</sup> In this way, MD simulations can be used to predict structural and dynamical properties of materials at larger time and size scales. Recently, scale-bridging protocols based on active learning approaches coupled with Bayesian optimization algorithm (Section 6.3.2) are used to increase the accuracy of these models, further experimental driven workflows are developed with ML approaches to automate this process.<sup>[225,226]</sup> Such automated workflows could indeed be employed in future HTVS approaches after they have reached sufficient maturity. In this way, MD simulations will likely become more important for screening approaches when ML-based force fields for battery electrolytes have become largely available, or when well-defined and automated workflows to generate these force fields exist.<sup>[203]</sup>

## 6. Data Driven Methods for the Analysis of High-Throughput Experiments

The screening of compounds is usually performed in various layers to narrow down suitable candidates in accordance to the desired property of interest. Of late there has been an unparalleled growth in computational power which resulted in development of novel machine learning algorithms. These algorithms are predominantly employed in classification, regression, sample augmentation, clustering, and dimensionality reduction

task for large heterogenous datasets.<sup>[227–229]</sup> Here we restrict ourselves to supervised learning algorithms whereas for unsupervised approaches we refer the reader to study the work by Hinton and Sejnowski.<sup>[230–234]</sup> Various HTE data analysis tools have been used to assist this process. A detailed explanation of standard statistical practices used for HTE data analysis has been described by Malo et al.<sup>[235]</sup> Due to high-dimension of the feature space, e.g., reflecting the number of components in an electrolyte in battery research, direct interpretation of the experimental or simulation data is somewhat hampered. Therefore, automated data analysis is of paramount importance. In general, surrogate modeling is employed when evaluation becomes extremely expensive both experimentally and by computer simulation.<sup>[236,237]</sup> They may act as an approximate description of the relation between input and output data on a feasible computational level. For construction purposes, ML techniques<sup>[227,238]</sup> may provide a versatile way. Nevertheless, any knowledge about physical or chemical properties of the system (such as, e.g., symmetries) should be incorporated.

Different goals have to be fulfilled in the analysis of HTE data.

- 1) One should be able to describe the dependence of the observed properties on the composition also in systems with many components. This purpose can be achieved by finding a surrogate model with parameters, possessing a direct interpretation. For example, one may directly learn about the explicit impact of the salt content on the conductivity. In this technique, data speaks for itself and provides meaningful

- information about the system, so we do not need to design or program anything specific to extract this information.
- 2) The surrogate model should be able to predict well by balancing between model complexity and generalization error.<sup>[239,240]</sup> Discussion of this aspect involves the analysis of overfitting and underfitting which becomes relevant if too many or too few adjustable parameters are involved as compared to the size of the available data set. Naturally, any expertise and domain knowledge<sup>[234]</sup> as well as known physical or chemical constraints, relevant for the problem at hand, should be taken into account when setting up the model or interpreting the ML-based results.
  - 3) More generally, one may ask how complex a surrogate model can be formulated for a given number of experimental data. Reversely, one may estimate the number of data which is, e.g., required for a sufficient exploration of the high-dimensional feature space. In the case of regression, the complexity is reflected, e.g., by the number of adjustable parameters.
  - 4) In the context of active learning the analysis may suggest for which new experimental data points important new knowledge might be generated. This step would establish a forward-backward relation between experiment (or, alternatively, simulation) and data analysis and is generally described by the interplay of exploitation and exploration.

The selection of methods to be discussed below is guided by the experiences with the analysis of HTE data of electrolyte mixtures. Furthermore, in this way it is possible to address the general goals (1)–(4) in a coherent way and to the pave the way for interesting applications.

## 6.1. Conceptual Framework of Machine Learning-Based Prediction

In general, the complete dataset is divided into three parts: 1) training, 2) cross validation, and 3) test. The model is trained on training datasets using optimization methods. For example, fitting a polynomial on training datasets using steepest descent optimization method, where optimization is carried out to obtain values of prefactors of the polynomial. During the optimization procedure one needs to fix a set of hyperparameters, e.g., the parameters characterizing a steepest descent process. For this set of hyperparameters, the prediction quality is obtained from comparison of the predictions with the information of the cross validation dataset that is not observed by model during training. Subsequently, by minimizing the error, hyperparameters will be updated and optimized. The relevant final error is then determined from predicting the so-far unused test dataset. If the optimization of hyperparameters is not relevant one may just work with a training and a test set. In this case we will separate the  $N$  measured data in  $M$  training data and  $N - M$  test data. The desired but unknown relation between a feature  $x$  and the experimental or numerical outcome  $y$  is denoted  $f(x)$ . In general, the outcome is additionally hampered by noise commonly taken from a normal distribution, thereby incorporating uncertainty so that the outcome is given by

$$y_i = f(x_i) + \eta_i \quad (1)$$

In principle, the feature  $x$  can have some uncertainty as well which will be neglected. The  $N$  measurements are expressed by the index  $i$ . In the limit of infinite  $N$  and homogeneous coverage of all feature values, perfect learning of the function  $f(x)$  would be possible.

The process of estimation involves a function  $h(x, \theta)$  with a parameter  $\theta$ , reflecting, e.g., the regression coefficients. In general, the surrogate model, as expressed by this function, cannot fully recover the full complexity of the system, i.e., the function  $f(x)$ . The determination of  $\theta$  is via minimization of an appropriately chosen cost function which is often taken as the squared error

$$c(\theta) = \sum_{i=1}^N [y_i - h(x_i, \theta)]^2 \quad (2)$$

The optimum is denoted  $\theta_{\text{opt}}$ . Naturally, its value depends on the specific training set  $T_M$ , selected from the available number of data, as well as on the noise realization  $\{\eta_i\}$ . The notation  $\theta_{\text{opt}}(T_M, \eta)$  expresses this dependence. Now one can conceptually think about the limit of the availability of an infinite dataset, which furthermore covers the whole relevant range of feature values  $x$ . For a ternary electrolyte composition  $\alpha A - \beta B - (1 - \alpha - \beta)C$  this would mean that the predetermined interval  $[\alpha_{\min}, \alpha_{\max}]$  is densely covered by values of the mole fraction  $\alpha$  and the same holds analogously for  $\beta$ . In this limit, the resulting optimum  $\theta_{\text{opt}}$  no longer depends on the specific choice of the training set and on the noise.

Generally speaking, two different errors can be defined. First, the in-sample error  $E_{\text{in}}$  denotes the value of the cost function for the calculated optimum  $\theta_{\text{opt}}(T_M, \eta)$ , which is subsequently averaged over different choices of the training set  $T_M$ . For any analytical estimations of the in-sample error one also averages over the random contributions, i.e., the noise realization for a fixed training set  $T_M$ . Basically,  $E_{\text{in}}$  represents the error from a standard fitting procedure. Second, the out-of-sample or generalization error, denoted  $E_{\text{out}}$ , evaluates the cost function in a two-step process. First, similarly to the estimation of the in-sample error an optimum parameter  $\theta_{\text{opt}}(T_M, \eta)$  is estimated from the training set. In a second step, the cost function is evaluated for the test set. Naturally,  $E_{\text{out}}$  characterizes the prediction error since the model is compared with so far unseen data. In general, one expects  $E_{\text{in}} < E_{\text{out}}$  and can write

$$E_{\text{out}} = \langle [y - h(x, \theta_{\text{opt}}(T_M, \eta))]^2 \rangle \quad (3)$$

where the brackets denote the average over the test set. The generalization error is the relevant error when discussing the degree to which the available and often restricted experimental data contain sufficient information to characterize the underlying system. To enable a systematic discussion of the different error contributions, the generalization error can be decomposed into three contributions

$$\begin{aligned} y - h(x, \theta_{\text{opt}}(T_M, \eta)) = & [y - f(x)] + [f(x) - h(x, \theta_{\text{opt}})] \\ & + [h(x, \theta_{\text{opt}}) - h(x, \theta_{\text{opt}}(T_M, \eta))] \end{aligned} \quad (4)$$

The first term denotes the experimental noise as seen from comparison with Equation (1). The second term

compares the true function  $f(x)$  with the optimized estimate  $h$ , obtained in the hypothetical limit of an infinite number of data. This term basically expresses how good the chosen surrogate model can capture the true underlying properties. The third term reflects the differences based on the presence of a finite training set. Most importantly, all three terms are uncorrelated. Thus, following the notation<sup>[241,242]</sup> and by inserting Equation (4) into Equation (3) the generalization error  $E_{\text{out}}$  can be written as

$$E_{\text{out}} = \text{noise}^2 + \text{bias}^2 + \text{variance} \quad (5)$$

The first term can be estimated by performing repeated experiments with the same parameters. The bias-term (term 2) gets smaller if the model becomes more complex, involving a larger number of adjustable parameters. However, the more complex the model is, the higher is the variance-term (term 3) since the fitting is less robust and will more strongly depend on the chosen training set. This term reflects overfitting. This general bias-variance trade-off is a key motif in the field of machine learning.<sup>[243]</sup>

## 6.2. Machine Learning-Based Approaches

For a large amount of data which may be easily available, e.g., for computer simulations, a mapping of the features on the objective functions via neural networks may constitute a very rewarding approach. A recent review discusses the advances of different ML algorithms for the application of solid state material science.<sup>[244,227]</sup> The focus is set on surrogate models beyond linear regression (LR) and Gaussian process regression (GPR) like random forest and neural networks for HT approaches. The discussion LR also helps to specify the general approach, introduced so far.

### 6.2.1. Linear Regression

LR is based on a specification of Equation (1) via

$$\hat{y} = Xb + \eta \quad (6)$$

where  $X$  is the matrix where each of the  $M$  rows contains the  $p$  features (e.g., concentrations) per experiment. The vector  $b$  contains all the  $p$  regression coefficients, which one wants to estimate via the regression procedure. Its use does not necessarily imply that one is restricted to linear relations. For example, in case of the sampling of the chemical space, the independent variables may also represent products of concentrations of different components or higher orders of the concentrations. Minimization of the cost function yields the standard solution

$$\hat{b} = (X^T X)^{-1} X^T y \quad (7)$$

As discussed by Hastie et al.<sup>[242]</sup> from Equation (7) one can estimate the generalization error after averaging over a large training set (here for the limiting case of no bias)

$$E_{\text{out}} = \sigma^2 \left( 1 + \frac{p}{M} \right) \quad (8)$$

where  $\sigma^2$  denotes the experimental/computational noise variance. Higher order terms in the inverse size of the training set are neglected. Note that the in-sample error  $E_{\text{in}}$  involves the expression  $\sigma^2(1 - \frac{p}{M})$  which explicitly shows that here  $E_{\text{in}} < E_{\text{out}}$ . Thus, the complexity of the model, in the case of LR expressed by the value of  $p$ , increases the first term whereas in general it decreases the bias-term. In practice, for a given size of the training set there exists an optimum value of  $p$  and thus an optimum degree of complexity. For a larger training set the complexity of the model can be extended as well to reach a possibly small generalization error. This is schematically shown in Figure 15.

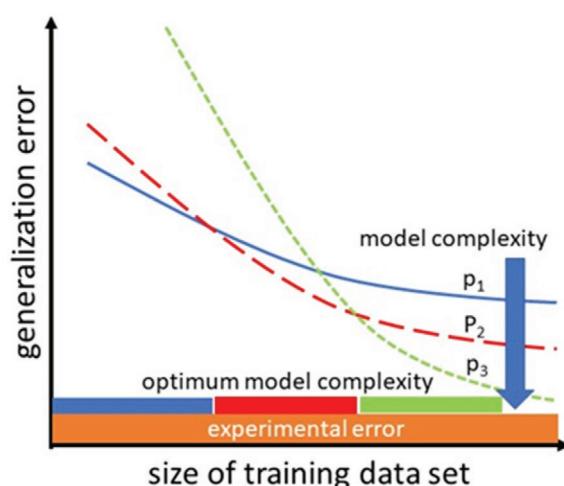
The effects of overfitting can be partially mitigated by adding a regularizer to the loss function. One specific example is the ridge method where the term  $\lambda(b^T b)$  is added, but many regularization terms are possible as well. The value  $\lambda$  is denoted a hyperparameter. As a consequence, Equation (7) is modified and reads ( $E_p$ : unit matrix of dimension  $p$ )

$$\hat{b} = (X^T X + \lambda E_p)^{-1} X^T y \quad (9)$$

A finite value of  $\lambda$  will reduce the size of the regression parameters and, when choosing it appropriately, may reduce the generalization error. Qualitatively, solution of the regularized problem can be interpreted as solving the problem without regularization but with a smaller model complexity, thus reducing overfitting. However, at the same time the regression parameters can no longer be interpreted in a straightforward way.

### 6.2.2. Gaussian Process Regression

GPR is an alternative method to model data sets. In contrast to regression it does not rely on a specific function but rather



**Figure 15.** Sketch of the generalization error as a function of the size of the training data set for different model complexities. The optimum model complexity depends on the size. Naturally, the experimental error forms the ultimate minimum for the generalization error, reached for large size and high model complexity.

implicitly uses all possible functions that fit the data. In GPR one starts with a Gaussian process with the mean function  $m(x)$  as well as the covariance function  $k(x, x')$ .<sup>[245]</sup> If no additional knowledge is available one often chooses  $m(x) = 0$ . The kernel determines the covariance of the function at locations  $x$  and  $x'$ , i.e., (using  $m(x) = 0$ )

$$k(x, x') = \langle f(x) \cdot f(x') \rangle \quad (10)$$

Often, one chooses a Gaussian

$$k(x, x') = \sigma_f^2 \exp\left(-\frac{1}{2L^2}|x - x'|^2\right) \quad (11)$$

Two hyperparameters are involved, reflecting the signal variance  $\sigma_f^2$  and the length scale  $L$  along which the functions are correlated. It is also possible to consider the knowledge of the experimental errors at the training points, used to specify the prior  $f(x)$ . A recent review article discusses the scalability of GPs for bigdata, which could be further used for HTS approaches.<sup>[246]</sup> As outlined by Balachandran et al.<sup>[245]</sup> there exist a few related methods (support vector regression with different facets), which act in a related way.

### 6.3. Some Concepts along the Way

#### 6.3.1. Ensemble Methods

The goal of ensemble methods is to combine the predictions of several base estimators built with a given learning algorithm in order to improve generalizability/robustness over a single estimator. Two families of ensemble methods are usually distinguished. In averaging methods, the driving principle is to build several estimators independently and then to average their predictions. On average, the combined estimator is usually better than any of the single base estimators because its variance is reduced. Examples comprise bagging methods<sup>[247]</sup> and random forests.<sup>[248]</sup> By contrast, in boosting methods, base estimators are built sequentially and one tries to reduce the bias of the combined estimator. The motivation is to combine several weak models to produce a powerful ensemble. These methods have gained traction in recent times, where stacked ensemble learning methods used in combination with DFT surrogates tend to improve the accuracy of predicting experimental bandgaps.<sup>[249]</sup> More detailed discussion of these methods with regard to applications in solid state material science is provided by Schmidt et al.<sup>[227]</sup>

Another ensemble method is bootstrapping as a way to increase the information content about uncertainties.<sup>[250]</sup> Starting from the experimental data set with  $n$  measurements one may draw several data sets with replacement, i.e., a data set may contain a data point more than once. For each data set a model can be fitted. As a key result, one obtains information about the possible variations of the model parameters and thus about the variance of the model. Although numerically cumbersome due to the large number of different sets which need to be analyzed, bootstrapping is a very versatile method to characterize statistical properties of the resulting observables in detail. In case of regression this approach, e.g., allows one to estimate the uncertainty error for data from the test.

#### 6.3.2. Bayesian Approach

The Bayesian approach can be used for a generalization of the formulation of surrogate models but also play a major role in more advanced prediction processes.<sup>[251,252]</sup> The measurement process can be generally formulated via the conditional probability  $p(y|x, b)$ . It expresses how the probability distribution of the measurement values  $y$  displays a Gaussian distribution with variance  $\sigma^2$  which is centered around the deterministic values  $y_0 = Xb$  (using linear regression as a show case). The important question, tackled in linear regression, is the estimation of  $b$  for given values of  $x$  and  $y$ , as reflected by the conditional probability  $p(b|x, y)$ . To calculate this probability function, one can start by analyzing the combined probability  $p(b, y|x)$  of experimental results and regression parameters for given feature values. This probability can be formally written in two different ways

$$p(b, y|x) = p(b|x, y) \cdot p(y|x) = p(y|b, x) \cdot p(b|x) \quad (12)$$

which can be rewritten as

$$p(b|x, y) = \frac{p(y|b, x) \cdot p(b|x)}{p(y|x)} \quad (13)$$

The denominator on the r.h.s. only serves for normalization processes. On the r.h.s. knowledge about the so-called prior  $p(b|x)$  is required (typically it does not depend on  $x$ ). Without specific knowledge one may choose  $p(b|x) = \text{const}$ . In general, Equation (11) allows one to estimate the so-called posterior distribution  $p(b|y, x)$ , which is at the core of the estimation process. Furthermore, it is very powerful and informative. 1) Choosing a constant prior, maximization of the posterior yields the standard expressions for regression. Thus, it can be regarded as generalization of the regression procedure. 2) The posterior not only predicts the most likely regression parameter  $b$  but also allows one to estimate its uncertainty. 3) When using a Gaussian distribution of the prior, the regularization via the ridge method can be recovered. This shows that desired effect that regularization implies a downscaling the probability of large regression parameters due to its lower a priori weights. 4) The predictive distribution for the experimental value,  $\tilde{y}$  at a given point  $\tilde{x}$  from the test set, and not just the expectation value, can be estimated via

$$p(\tilde{y}|\tilde{x}, x) = \int db p(\tilde{y}|\tilde{x}, b) p(b|y, x) \quad (14)$$

In summary, the Bayes approach captures the key aspects of the prediction process. Accordingly, the Bayesian framework is an essential ingredient in many HT studies.<sup>[253–256]</sup> Further advances in Bayesian factor modeling for scalable GPs are discussed by Moran.<sup>[257]</sup>

### 6.4. Further Directions to Analyze High-Throughput Experimental Data

#### 6.4.1. Efficient Global Optimization

A key idea for the identification of newly tested systems is to balance the aim of identification of the optimum material,

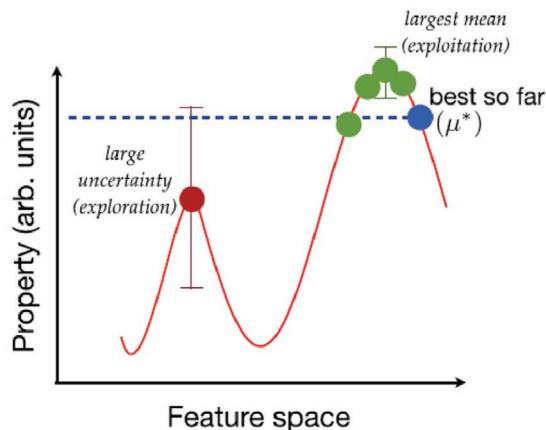


Figure 16. Sketch of the exploitation–exploration balance. Reproduced with permission.<sup>[245]</sup> Copyright 2016, Springer Nature.

denoted exploitation, and the aim of improving the surrogate model via exploration of different regions of the feature space (Figure 16).

In general, it is difficult to formulate a strict mathematical optimization approach. However, there exist heuristic approaches which help to find the balance between exploitation and exploration. One powerful approach is the efficient global optimization.<sup>[245,258]</sup> It starts from the expected improvement at feature space position  $x$ , given that that best  $y$ -value so far is  $\mu^*$  and that, based on the used surrogate model, one can estimate the possible range of  $y$ -values for a given  $x$ , i.e.,  $p(y|x)$ , which is assumed to be Gaussian with variance  $\sigma^2$

$$E(I) = \int_{\mu^*}^{\infty} dy (y - \mu^*) p(y|x) = \int_{\mu^*}^{\infty} dy (y - \mu^*) \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(y-\mu^*)^2}{2\sigma^2}} = \dots = \sigma [\phi(z) + z\Phi(z)] \quad (15)$$

where the variable  $z = (\mu - \mu^*)/\sigma$  has been introduced and straightforward manipulations have been performed. Furthermore, the normal density  $\phi(z)$  and the cumulative distribution function  $\Phi(z)$  have been introduced. This approach implies that for small uncertainties one measures the systems with the highest expected  $y$ -value whereas for large uncertainties the value with the highest uncertainty, thus improves knowledge about so-far unseen regions of the feature space. In practice, one can also add the experimental uncertainty to the measured data points which renders this approach even more realistic. Applications to the optimization of elastic moduli from simulations of solid materials are outlined by Balachandran et al.<sup>[245]</sup> However, as explored,<sup>[259]</sup> it is not always the case to achieve a significant improvement with respect to the base case where new data points are just found via random search.

#### 6.4.2. Multiobjective Optimization

The situation becomes more complex when different objective functions  $f_1(x) \cdots f_k(x)$  are of relevance, e.g., the conductivity as well as the chemical stability.<sup>[38,260]</sup> In general, the optimum for an individual objective function will be found for different values of  $x$ . However, for such situations one can devise Pareto

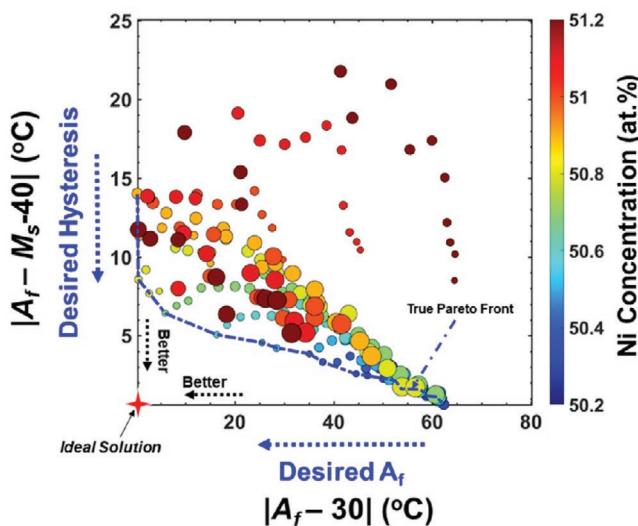


Figure 17. Simultaneous optimization of two objective functions. Reproduced with permission.<sup>[260]</sup> Copyright 2018, Elsevier.

optimality. A feature vector  $X$  is denoted Pareto optimal if any modification of  $X$  does not increase at least one objective function without decreasing the value of any other objective function. In general, there exist many vectors which are Pareto optimal. They are denoted Pareto front (Figure 17). Applications can be found elsewhere.<sup>[260]</sup> Compared to conventional strategies, optimization methods can speed up and down streaming HTS processes and genetic algorithms can be applied to optimize parameters in multidimensional optimization tasks.<sup>[261]</sup>

## 7. Concluding Remarks and Perspective

HTE as a process of scientific exploration comprises effective experimental design, laboratory automation and rapid parallel, and/or serial experiments toward accelerated discovery and development of LIB and LMB battery electrolytes their interfaces/interphases with the electrodes and the resulting battery chemistries for targeted application(s). Multiple advantages for implementing HTE include greater reproducibility and efficiency compared with the traditional one-by-one approach. HTE is ideal to “accomplish more with less” in a much faster fashion. To realize the full benefits of this approach, careful investments in strategy, hardware and software are inevitably required. Targeted HTS of promising electrolyte compositions/formulations based on corresponding design of experiments hand in hand with critical scientific and mathematical thinking yields success. As depicted by the given examples, HTE enables faster synthesis of new battery materials and systematic characterization of electrolytes performance in given battery chemistries toward identification of lead candidates based on the set of previously established requirements. Well-designed HTE workflows result in a wealth of experimental datasets representing a solid foundation for enhanced technical decision making. To fully capture acquired datasets in a findable, accessible, interoperable, reusable (FAIR) fashion, an appropriate informatics infrastructure is required with a

well-designed data repository and query system in order to retrieve and reuse the data. However, in many cases software platforms within the HTE systems are still neglected or even underfunded, thus resulting in lost value and opportunity toward reaching the overall goal.

The ability to test multiple hypotheses in parallel through the continued evolution and improvement of automation platforms produces an exponential increase in data generation. Due to their size, acquired datasets are “mission impossible” for scientists alone to process and make decisions. This inevitably calls for adapted algorithms and high-performance computing to decipher the large data volume.

Here is already a word of caution: if the given data is highly biased it will provide wrong results since the analysis is purely data driven. If we are looking for the highest conductivity of an electrolyte for given solvent components and if the model is trained with a large chunk of data outside that conductivity regime, only little information can be gained about the region of high-conductivity mixtures.

HTVS approaches have been used predominantly to predict the performance of materials for a variety of applications. These approaches provide a perspective pathway to demonstrate the predictive performance of various ML algorithms for battery material application. HTC works as an important tool to minimize the developmental cost of new materials for battery electrolytes and interfaces. Further these tools not only support futuristic material discovery and corresponding experimental setups, but also the underlying statistical approaches may lead to interpretation of relations between feature and prediction parameters that could be used as an input to theoretical models. The elementary building blocks of such analyses, that is screening, calibration with experimental data statistical analysis-based (ML or regression) and feedback loops can be adapted to the problem of interest, lending these approaches large flexibility. Clearly, several challenges remain to be addressed for future applications to further improve the capabilities of HTVS approaches. For instance, the studies discussed above mainly focused on bulk quantities such as redox stabilities or solvation properties. However, for battery chemistries such as LIBs and LMBs, interfaces and interphases are extremely important to the overall cell performance. Therefore, incorporating interfacial properties—although challenging—will likely be extremely rewarding for future approaches. In this context, it is also important to stress that the vast majority of HTVS approaches in the field of battery science relied on ab initio techniques. To assess, e.g., interfacial properties on larger scales, approaches based on classical MD or even ML-derived force fields seem to provide another thriving avenue of research.

In the end, research approaches, which successfully couple HT acquired datasets with ML, DL, and AI by resolving the compatibility and seamless integration challenges will easily differentiate themselves in the large R&D landscape and accelerate development of advanced electrolytes and their interfaces/interphases in considered battery chemistries.

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## Conflict of Interest

The authors declare no conflict of interest.

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batteries, chemical space, electrolytes, high-throughput experimentation, high-throughput virtual screening

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