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Resolving electrocatalytic imprecision in atomically precise metal nanoclusters

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Continuous improvements in the synthesis, characterization, and computational modeling of nanoscale materials have resulted in their tremendous application in electrocatalysis. However, despite remarkable advances, there are important issues that need to be addressed to enable systematic and targeted discovery of electrocatalytically active and selective nanomaterials. Here, we provide an overview of the most recent developments in electrocatalysis of ligand protected metal nanoclusters (LPNCs) and discuss associated 'imprecisions' observed through experiments and computation. We first describe why atomically precise LPNCs are ideal systems to identify catalytic active sites under reaction conditions compared to metal nanoparticles. We then shift to heterometal doping of LPNCs and discuss strategies to tune electrocatalytic behavior as well as challenges associated with their vast materials space. Finally, we highlight some major bottlenecks in the field of LPNC electrocatalysis and provide potential solutions based on applying data-driven approaches which can aid the accelerated catalyst discovery for sustainable fuel and chemicals production.

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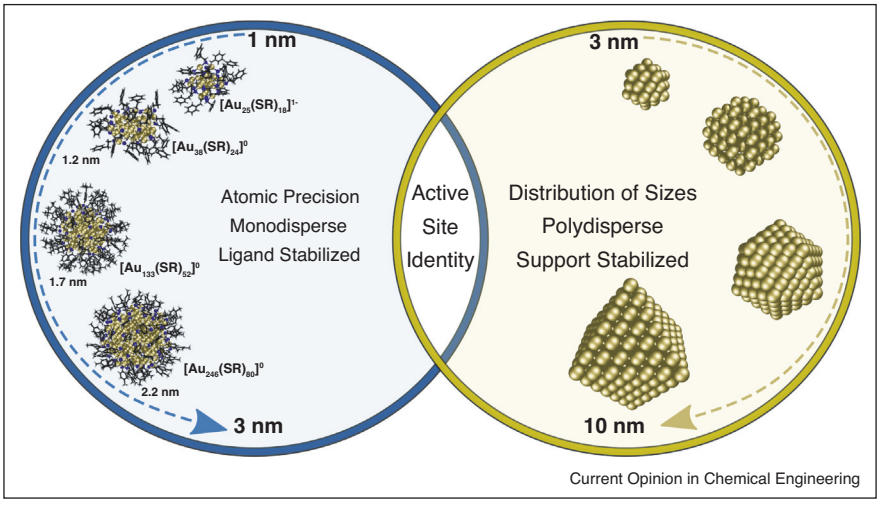
Introduction

In the past few decades, research on metal nanoparticles (NPs) for catalytic applications has expanded dramatically [1–3]. NPs have demonstrated high catalytic activity and selectivity for various industrial-relevant reactions including hydrogenation, oxidation, and C–C coupling [1]. In addition, due to dramatic increase in the surface area of metal catalysts at the nanoscale, catalytic NPs expose a greater amount of active sites to the reagents than larger particles of same mass, exhibiting high activity, while holding the potential to reduce catalyst cost. However, conventional NP synthesis produces a distribution of NP sizes (polydispersity), leading to difficulty in determining atomic-level structure-property relationships (SPRs) and revealing the exact catalytic active sites [4]. Thus, catalytic experiments, catalyst characterization and theory are applied in a synergistic fashion to reveal what metals should comprise a NP and what are the active sites for a particular reaction of interest [5].

Recently, a new class of ultra-small (<3 nm diameter) metal NPs has emerged as promising candidates for various applications in nanotechnology [6]. Ligand protected metal nanoclusters (LPNCs) are atomically precise systems that exhibit unique physicochemical properties, such as molecular-like electronic structure, differentiating them from larger metal NPs (see Figure 1). They are primarily based on Au, protected by thiol ligands and come in 'magic sizes' due to their high stability at specific metal-ligand compositions (represented by $Au_n(SR)_m$) [7]. LPNCs are synthesized in a monodisperse environment and their exact structures are determined through single crystal X-ray diffraction [8]. They consist of a metallic core surrounded by a hybrid metal-organic shell [9]. To date, a vast number of LPNCs have been experimentally synthesized and characterized. Importantly, the atomic-level structural precision of LPNCs enables accurate computational analyses via electronic structure methods, such as Density Functional Theory (DFT). DFT can also aid the discovery of new structures with desirable properties, guiding experimentation.

Because of their unique properties and the growing demand for sustainable chemical and fuel production, the catalytic activity of LPNCs has been investigated for various types of electrochemical reactions [10], including room temperature CO_2 reduction reaction (CO_2RR) [11], oxygen reduction reaction (ORR) [12], oxygen evolution reaction (OER) [13], and hydrogen evolution reaction (HER) [14,15]. From an engineering perspective, recent efforts have also sought to investigate the scalability of LPNC catalysis towards practical and sustainable applications. For example, Kauffman *et al.* demonstrated the large-scale CO_2 reduction capability (400–800 L of CO_2 per gram of catalytic metal per hour with selectivity between 80–95%) of the $Au_{25}(SR)_{18}$ LPNC (abbreviated as Au_{25}), resulting in negative CO_2 emissions using

Figure 1



Venn diagram representing four (out of numerous) LPNCs (blue circle), and bare NPs (yellow circle). The differences between LPNCs and bare NPs are indicated in their respective circles. The common challenge with both types of nanostructured materials is shown in the intersection. Color scheme for atoms: yellow, Au; blue, S; black, C; grey, H. LPNC size is reported in terms of gold core diameter.

inexpensive ($10–$20) solar powered energy sources [11]. At the same time, the LPNC materials space has considerably increased due to successful research efforts in synthesizing heterometal-doped LPNCs [16••,17,18]. The alloying process can result in LPNCs with significantly different electronic properties, thus providing a route towards tuning LPNCs for different electrocatalytic applications [19•,20]. One major advantage of doping atomically precise LPNCs is the ability to elucidate the effect of dopant location, type, and concentration on the catalytic activity and selectivity (as opposed to larger NPs where bimetallic concentration and metal locations are often approximated). Furthermore, the growing library of monometallic and alloy LPNCs provides the opportunity to implement data-driven, computational approaches for accelerated catalyst discovery avoiding expensive trial-and-error experiments.

Despite advances in the field, several questions remain regarding the use of LPNCs as electrocatalysts. What are the exact active sites on LPNCs for electrocatalysis? How are these active sites influenced by LPNC structure? These questions are encompassed by a larger challenge: How can we identify structures from the vast materials space with optimal electrocatalytic properties for specific applications? In this perspective, we discuss recent efforts towards addressing these questions. Because of the dramatic increase and relevance in research related to sustainable fuel and chemical production [21], we chose to focus on cathodic (i.e. electrochemical reduction) reactions such as CO_2RR, HER and ORR. In the first section we focus on the most relevant studies primarily from the past three years that aimed to unravel the nature of the electrocatalytic active sites on LPNCs. Next, we discuss the importance of heterometal doping LPNCs in the context of electrocatalysis and challenges associated with the vast materials space. Finally, we provide insights into the need for data-driven approaches and potential solutions for accelerated LPNC catalyst discovery.

Identifying active sites for electrocatalysis

LPNCs often exhibit stronger electrocatalytic performance than larger nanostructures [6]. This outcome is contradictory to traditional catalysis concepts since one would expect the presence of ligands on the LPNC surface to limit the accessibility of reactants to the typically active metal sites. Kauffman *et al.* showed that Au_{25} exhibited CO_2RR mass activity ~400 times higher than that of larger Au NPs (1656 ± 163 A g_{Au}^{-1} at −1 V versus RHE for Au_{25} and 14 A g_{Au}^{-1} for 4 nm Au NPs at −0.9 V versus reversible hydrogen electrode (RHE)) [11]. Additionally, the HER activity (current density) of a Au_{25}-MoS_2 composite (59.3 mA cm^{-2}) compared to bare MoS_2 nanosheets (33.2 mA cm^{-2}) was shown to be nearly twice as high at −0.4 V versus RHE [22]. While experiments have captured important metrics for assessing the electrocatalytic performance of LPNCs, identifying the nature of their active sites remains a challenge. DFT can address this challenge by leveraging the atomic precision of LPNCs and investigating detailed electrocatalytic mechanisms. One of the first computational studies towards identifying LPNC active sites during CO_2RR to CO concluded that the fully protected Au_{25} exhibited very high thermodynamic barriers (>1.5 eV) to form the important *COOH intermediate [23,24]. Interestingly, partial -R or -SR ligand removal from the surface

of Au_{25} was shown to be thermodynamically feasible and expose catalytically active S or Au sites, respectively, under reaction conditions (see Figure 2 for schematic of ligand removal). These active sites drastically lowered thermodynamic barriers associated with the CO_2RR pathway [23]. In particular, partial -R ligand removal was exergonic ($\Delta G < 0$) and the exposed S site reduced the thermodynamic barrier for $^{\bullet}COOH$ formation while also promoting CO_2RR instead of the competing HER [23]. Other recent studies have also shown that -SR ligand removal is possible under electrochemical conditions and can expose catalytically active Au sites during CO_2RR [25–27]. Although these results rationalize catalytic activity, the removal of protecting ligands raises concern regarding catalyst stability. A recent experimental study (using X-ray photoabsorption spectroscopy) demonstrated that Au_{25} could lose up to 6 ligands and still maintain structural integrity and electrocatalytic activity under reaction conditions [28]. Furthermore, Nagarajan *et al.* verified (via applying the thermodynamic stability model developed for LPNCs [29] and *ex-situ* experiments) the stability of LPNCs upon multiple ligand removal, revealing that CO_2RR reaction intermediates act as stabilizing ligands during the electrocatalytic cycle [30]. In contrast, the activity of LPNCs towards reactions such as ORR and HER have been attributed to other structural or electronic properties. A comprehensive study by Kumar *et al.* [31] demonstrated that varying the thiolate ligand type (length and aromaticity) within Au_{25} can influence HER activity. For example, Au_{25} stabilized by phenylethyl thiolate (smaller hydrocarbon tail) and dodecane thiolate (larger hydrocarbon tail) groups exhibited a mass activity of -17.8 mA cm^{-2} and -3.6 mA cm^{-2} at -0.7 V versus RHE respectively. The same study also suggested that reducing LPNC size (fewer metal atoms) improved HER and ORR activity by shifting the LPNC d-band position [32] closer to the frontier orbital energy levels of $O_{2(g)}$ and using 'thinner' ligand layers (smaller ligands with reduced aromaticity) provided enhanced charge transfer to the metal core of the LPNC.

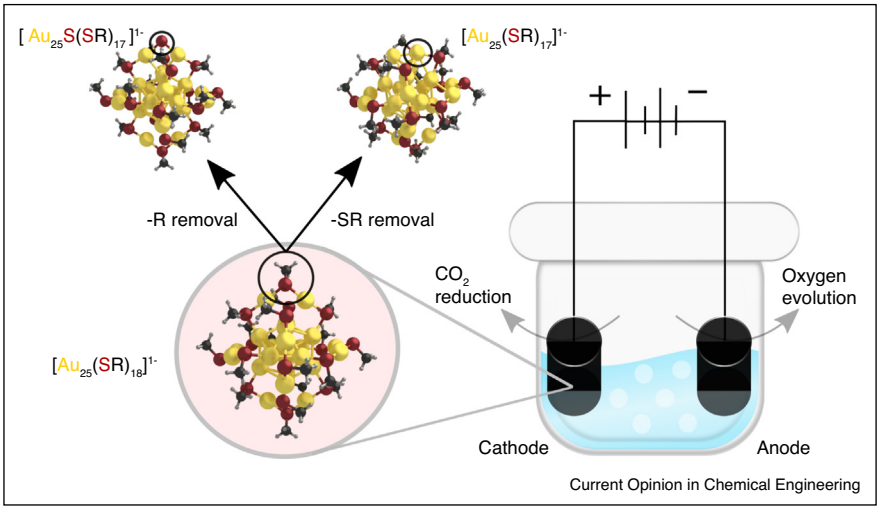
Despite numerous studies demonstrating the high electrocatalytic activity of LPNCs, a lack of consensus regarding the active sites remains. In-depth kinetic and thermodynamic analyses using either DFT or larger-scale molecular dynamics simulations are needed to provide insights into ligand removal mechanisms and their feasibility under electrochemical conditions. It is imperative to mention that ligand removal processes happen under electrochemical environments; therefore, electrocatalysis simulations should account for explicit solvent molecules [33] to accurately model proton-coupled electron transfers and obtain kinetic barriers for active site exposure as well as relevant catalytic reaction steps [34]. From an experimental standpoint, systematic *in-situ* spectroscopic studies that can identify the fingerprints of LPNCs under a range of applied potentials could provide critical information regarding their activation towards various electrochemical reactions. Combining such information with data generated from multiscale modeling can provide a strong foundation for elucidating the true nature of active sites on LPNCs under electrochemical conditions.

Tailoring LPNC catalysts through heterometal doping

Heterometal doping is one of the most adopted methods to tune electronic, structural, and catalytic properties of metal NPs [35], often utilizing inter-metallic synergy [16••]. Recently, heterometal doping of different transition metals (e.g. Pt, Pd, Ag, Cd) has been successfully implemented into various monometallic LPNCs (e.g. Au_{25}, $Au_{23}(SR)_{16}$, $Au_{44}(SR)_{28}$) through extensive experimental efforts [16••]. Interestingly, each LPNC structure can have distinct doping preferences (dopant type, position, and composition) [16••]. For example, Au_{25} can only be doped with a single Cd atom on its core surface [36] while Cd doping into $Au_{23}(SR)_{16}$ (abbreviated as Au_{23}) and $Au_{44}(SR)_{28}$ can only be done on the shell, and forms completely new magic sizes, $Au_{19}Cd_2(SR)_{16}$ (abbreviated as $Au_{19}Cd_2$)and $Au_{47}Cd_2(SR)_{30}$, respectively [37,38]. Of note, the synthesis of stable alloy LPNCs from their stable monometallic precursors or smaller complexes often involves elevated temperatures and various organic solvents to overcome kinetic and thermodynamic barriers. Importantly, heterometal doping uniquely affects electronic properties of LPNCs [16••], and leads to enhanced electrocatalytic activity and selectivity compared to their monometallic precursors [19•,20]. For example, $Au_{47}Cd_2(SR)_{30}$ showed higher faradaic efficiency (FE) (96%) than $Au_{44}(SR)_{28}$ (83%) for CO_2RR at -0.57 V versus RHE [39•]. Similarly, experiments with Pd doped-Au_{25} ($PdAu_{24}$) and $Au_{19}Cd_2$ demonstrated a significantly higher FE as well as mass activity compared to Au_{25} and Au_{23} respectively [19•,20]. DFT results were in agreement with experiment, demonstrating that sites on $PdAu_{24}$ with -R removed (last structure, Figure 3a) exhibited lower thermodynamic barrier for $^{\bullet}COOH$ formation (solid black line, Figure 3b) than equivalent sites on Au_{25}, thus showing higher CO_2RR activity. The higher selectivity of $PdAu_{24}$ was attributed to a positive difference between thermodynamic limiting steps (U_L) for CO_2RR and HER (Figure 3d) [19•]. Similarly, charge redistribution caused by the presence of Cd in the -R removed $Au_{19}Cd_2(SR)_{16}$ led to a lower thermodynamic barrier for $^{\bullet}CO$ formation as well as higher selectivity for CO_2RR compared to HER [20]. It is critical to mention that heterometal doping can uniquely affect the extent of active site exposure [19•] as well as the local chemical environment around the active site [20], thus revealing the importance of dopant atoms in activating LPNCs as well as improving their electrocatalytic performance.

In contrast to Pd, Pt doping in the central positions of Au_{25} and $Au_{38}(SR)_{24}$ favored HER due to smaller

Figure 2



Schematic representing an electrochemical cell with CO_2RR occurring at the cathode and OER occurring at the anode. Activation of Au_{25} occurs through -R or -SR removal [22] as shown on the left of the diagram. Color scheme for atoms: yellow, Au; red, S; black, C; grey, H.

thermodynamic barriers for $^{\bullet}H$ formation with maximum current densities obtained at −0.6 V versus RHE [40,41]. Of note, DFT analyses from Choi *et al.* validated the HER activity of Pt-doped Au_{25} without considering ligand removal, with the active site deemed to be the Au_3 pocket on the core surface [40]. However, Pt-doped Au_{25} after -SR removal demonstrated nearly thermoneutral barriers for HER [42]. Other works utilized the position of d-band center to explain the ORR activity of a range of mono-doped Au_{25} LPNCs [43]. Sun *et al.* showed that among different transition metal dopants in Au_{25}, Hg doping was most beneficial for ORR due to a narrow d-band center closest to the Fermi level [43]. Importantly, they demonstrated that the ORR mechanism on the Au_{25} series can change from $4e^-$ ($H_2O_{(l)}$ product) on the fully protected LPNCs to $2e^-$ ($H_2O_{2(l)}$ product) upon -SR removal.

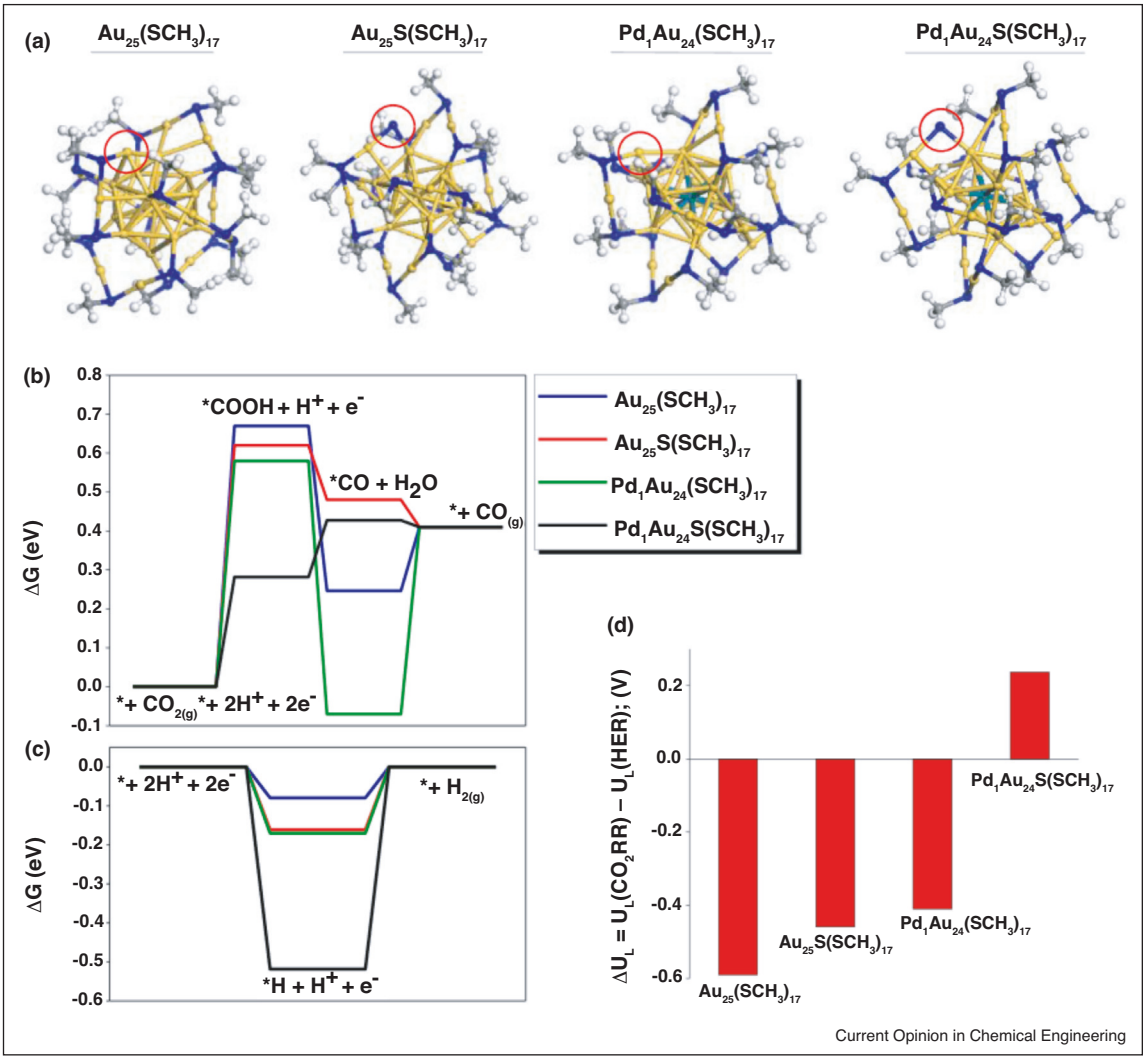
Considering the ambiguity in the origin of electrocatalytic activity and selectivity upon heterometal doping, the exact influence of the location and concentration of dopant atoms remains unaddressed. What drives dopant preferences in LPNCs? Do LPNC activation mechanisms change upon alloying? Importantly, can such mechanisms change with different solvation environments and dopants? Previous electrocatalytic experiments have been conducted with different dopants, ligands, and electrolytes, resulting in complex interfacial chemistry [16••,44]. Thus, it is imperative to investigate the effect of doping on the electrode–electrolyte interface which in turn can have significant impacts on the electrocatalytic performance (stability, activity, and selectivity) of alloy LPNCs. Finally, can we identify structural or electronic descriptors of alloy LPNCs to rationalize the different electrocatalytic results reported in literature? Despite successful efforts showcasing the possibility and catalytic applications of heterometal doping, there is further need for systematic studies to address these questions. Future efforts that help unify our understanding of dopant effects across all LPNCs will be paramount for pairing structures to specific electrocatalytic applications.

The need for data-driven LPNC electrocatalyst design

The large and expanding materials space of LPNCs cannot entirely be explored via experimental design or even accurate electronic structure methods, like DFT, due to increased experimental and computational cost. For example, even the smallest known LPNC, $Au_{15}(SR)_{13}$, has over 32 000 possible bimetallic configurations (i.e. all bimetallic compositions and unique chemical orderings) [45], which yields an even higher number of potential active sites to be examined. Investigating a reasonable fraction of these configurations is computationally intractable with DFT. Thus, there is a need for data-driven approaches to predict desired catalytic properties, which will enable rapid screening towards electrocatalyst discovery.

In recent years, machine learning (ML) has been essential for developing data-driven solutions that address various issues in catalysis [46]. Although ML in LPNC research is still in its infancy, there are recent works in literature demonstrating its potential. One of the first applications of ML to develop SPRs of LPNCs was from Panapitiya *et al.* [45] Aided by DFT and a random forest classifier with numerous structural based features, the authors were able to predict CO adsorption energies on different sizes

Figure 3



(a) LPNC structures with the proposed active sites circled in red. Atom colors: Au: yellow, Pd: turquoise, S: blue, C: gray, H: white. **(b)** Free-energy diagram for electrochemical CO_2RR and **(c)** HER, at U = 0 V versus RHE. **(d)** Difference in U_L for CO_2RR and HER [$\Delta U_L = U_L(CO_2RR) - U_L(HER)$]. Reprinted (adapted) with permission from ACS Catal. 2020, 10, 12011–12016. Copyright 2020 American Chemical Society.

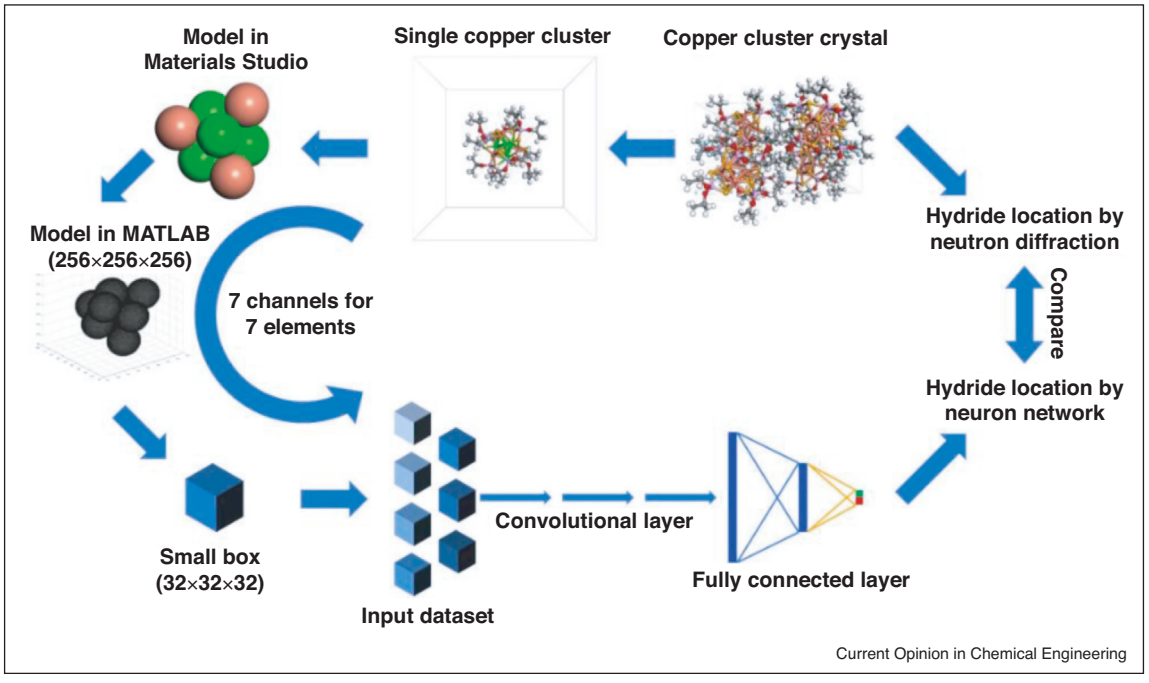
of LPNCs (Au_{25}, $Au_{36}(SR)_{24}$, and $Au_{133}(SR)_{52}$) with reasonable accuracy (root-mean-square error, RMSE, between 0.17 eV and 0.22 eV) [45]. It is worth noting that these results were achieved by training ML models solely on structural information based on data that can be obtained without DFT calculations [45]. This work emphasizes the importance of feature engineering in developing physically relevant ML models for LPNC-based catalysis. Despite its successes, the work highlights a major challenge in ML: generalizability, which often requires more data to overcome. Each LPNC size required a retraining of the ML model. Therefore, directly translating such approaches to investigate properties of a wide range of alloy LPNCs with a single model will require large, high-quality datasets obtained from experiments and/or DFT. Such large datasets are still lacking in the relatively new field of LPNC catalysis (compared to NP catalysis). Thus, the community should work towards generating large, high-quality reproducible LPNC datasets, which will enable training ML models for accelerated LPNC structure-property predictions.

Alternatively, it has been shown that certain deep learning (DL) architectures can expand our understanding of LPNCs even with relatively small amounts of data. In particular, Siamese neural networks (SNN) and graph convolutional neural networks (GCNN) were employed by Wang *et al.* to rationalize LPNC synthesis [47]. This

work involved the use of only 54 examples along with various synthetic parameters to train the two NNs. The result was a quantitative probability pattern that showed good agreement with previously reported LPNC synthesis protocols. More recently, a 3D-CNN coupled with symmetry constraints was utilized to elucidate the location of hydrides in Cu-based LPNCs [48••]. The model was trained using 674 localized 3D 'images' constructed from only 23 Cu clusters (see Figure 4 for workflow overview), revealing the importance of ML problem design and intelligent data augmentation. Even with little training data, the final model achieved strong agreement (based on previously reported predictions and DFT analysis) with two Cu LPNCs whose hydride locations have not been experimentally determined. This result is important in the context of LPNC electrocatalysis, as the presence of hydrides can tune the selectivity of Cu LPNCs for CO_2RR to produce formic acid over CO [49]. These results exemplify the capabilities of DL to not only work on small data problems, but also create generalized models that apply to various systems (e.g. different LPNC sizes). Thus, extending such methodologies to LPNC electrocatalysis offers great opportunities for tackling important challenges like identifying and tuning LPNC active sites.

Since these types of small-data-high-accuracy methods rely on the ability to capture rich structural information from their inputs (molecular graphs, images, etc.), one cannot rely on such models to achieve high accuracy property prediction for a wide range of structures. However, these models can still act as an effective screening tool to investigate the materials domain for structures of interest. One could then use DFT to study (in-depth) these structures, thus achieving a hybrid ML-DFT approach for identifying new LPNC electrocatalysts. Moving forward, ML (and DL) applications hold immense potential in LPNC research [50,51]. We envision future experimental and theoretical studies on LPNC-based electrocatalysis to emphasize consistency while expanding current datasets. Currently, experimental reports of reactions such as CO_2RR, HER, and ORR involve different ligands on LPNCs, electrodes (supports), pH conditions, mass loading and electrolytes [21] and each of these factors can affect electrocatalytic performance. Likewise, theoretical studies on LPNC electrocatalysis employ different methodologies (e.g. different DFT functionals, solvation models, codes etc.). Such differences can result in very different reaction energetics and catalyst performance, preventing us from consistently comparing results across literature. Systematic studies involving standardized experiments as well as computation can unify efforts on both fronts. The result of such efforts would be high-quality datasets with consistent parameters that will fuel future ML and DL approaches. The resulting models can then be a principal

Figure 4



The process of generating an input dataset and the sample architecture of 3D-CNN. The loop begins with the copper cluster crystal. Reproduced with permission from Angew. Chem. Int. Ed. 2021, 60, 12289 –12292. © 2021 John Wiley and Sons, Inc.

component of computational frameworks that enable the discovery of highly tunable atomically precise nanostructures for tailored electrocatalytic applications.

Conclusion

In this perspective, we reviewed the most recent developments in the field of LPNC electrocatalysis, highlighting groundbreaking studies that have provided fundamental insight into various electrochemical reactions. We demonstrate that depending on the reaction of interest, the origin of electrocatalytic behavior of LPNCs can be attributed to different factors including electronic and structural characteristics, as well as to the generation of active sites during electrocatalysis. We highlight the growing materials space of alloy LPNCs and the role of heterometals in tuning catalytic performance. This vast materials space of LPNC with atomically precise structures gives the opportunity to apply data-driven approaches, like ML, to address some of the challenges encountered in the rapidly expanding field of electrocatalysis. Further systematic studies are required to gain mechanistic insight into the catalytic behavior and formation of active sites under electrochemical reaction conditions. Combining ongoing experimental and theoretical efforts with accelerated methods like ML will help resolve persisting electrocatalytic 'imprecisions' and notably increase the application of LPNCs in the field of sustainable fuel and chemical synthesis.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Astruc D: **Introduction: nanoparticles in catalysis**. *Chem Rev* 2020, **120**:461-463.

2. Zhang X, Yuan X, Jiang L, Zhang J, Yu H, Wang H, Zeng G: **Powerful combination of 2D g-C_3N_4 and 2D nanomaterials for photocatalysis: recent advances**. *Chem Eng J* 2020, **390**:124475.

3. Shi Y, Lyu Z, Zhao M, Chen R, Nguyen QN, Xia Y: **Noble-metal nanocrystals with controlled shapes for catalytic and electrocatalytic applications**. *Chem Rev* 2021, **121**:649-735.

4. Chakraborty I, Pradeep T: **Atomically precise clusters of noble metals: emerging link between atoms and nanoparticles**. *Chem Rev* 2017, **117**:8208-8271.

5. Seh Zhi W, Kibsgaard J, Dickens Colin F, Chorkendorff I, Nørskov Jens K, Jaramillo Thomas F: **Combining theory and experiment in electrocatalysis: insights into materials design**. *Science* 2017, **355**:eaad4998.

6. Higaki T, Li Y, Zhao S, Li Q, Li S, Du X-S, Yang S, Chai J, Jin R: **Atomically tailored gold nanoclusters for catalytic application**. *Angew Chem Int Ed* 2019, **58**:8291-8302.

7. Cowan MJ, Mpourmpakis G: **Towards elucidating structure of ligand-protected nanoclusters**. *Dalton Trans* 2020, **49**:9191-9202.

8. Jin R, Zeng C, Zhou M, Chen Y: **Atomically precise colloidal metal nanoclusters and nanoparticles: fundamentals and opportunities**. *Chem Rev* 2016, **116**:10346-10413.

9. Walter M, Akola J, Lopez-Acevedo O, Jadzinsky PD, Calero G, Ackerson CJ, Whetten RL, Grönbeck H, Häkkinen H: **A unified view of ligand-protected gold clusters as superatom complexes**. *Proc Natl Acad Sci U S A* 2008, **105**:9157.

10. Kwak K, Lee D: **Electrochemistry of atomically precise metal nanoclusters**. *Acc Chem Res* 2019, **52**:12-22.

11. Kauffman DR, Thakkar J, Siva R, Matranga C, Ohodnicki PR, Zeng C, Jin R: **Efficient electrochemical CO_2 conversion powered by renewable energy**. *ACS Appl Mater Interfaces* 2015, **7**:15626-15632.

12. Zou X, He S, Kang X, Chen S, Yu H, Jin S, Astruc D, Zhu M: **New atomically precise M_1Ag_{21} (M = Au/Ag) nanoclusters as excellent oxygen reduction reaction catalysts**. *Chem Sci* 2021, **12**:3660-3667.

13. Zhao S, Jin R, Abroshan H, Zeng C, Zhang H, House SD, Gottlieb E, Kim HJ, Yang JC, Jin R: **Gold nanoclusters promote electrocatalytic water oxidation at the nanocluster/$CoSe_2$ interface**. *J Am Chem Soc* 2017, **139**:1077-1080.

14. Hu G, Wu Z, Jiang D-E: **Stronger-than-Pt hydrogen adsorption in a Au_{22} nanocluster for the hydrogen evolution reaction**. *J Mater Chem A* 2018, **6**:7532-7537.

15. Li Y, Li S, Nagarajan AV, Liu Z, Nevins S, Song Y, Mpourmpakis G, Jin R: **Hydrogen evolution electrocatalyst design: turning inert gold into active catalyst by atomically precise nanochemistry**. *J Am Chem Soc* 2021, **143**:11102-11108.

16. •• Kang X, Li Y, Zhu M, Jin R: **Atomically precise alloy nanoclusters: syntheses, structures, and properties**. *Chem Soc Rev* 2020, **49**:6443-6514

This comprehensive review constitutes work that has been done by many groups in understanding the synthetic accessibility as well as applications of alloy LPNCs.

17. Taylor MG, Mpourmpakis G: **Rethinking heterometal doping in ligand-protected metal nanoclusters**. *J Phys Chem Lett* 2018, **9**:6773-6778.

18. Fei W, Antonello S, Dainese T, Dolmella A, Lahtinen M, Rissanen K, Venzo A, Maran F: **Metal doping of $Au_{25}(SR)_{18}$– clusters: insights and hindsights**. *J Am Chem Soc* 2019, **141**:16033-16045.

19. • Li S, Alfonso D, Nagarajan AV, House SD, Yang JC, Kauffman DR, Mpourmpakis G, Jin R: **Monopalladium substitution in gold nanoclusters enhances CO_2 electroreduction activity and selectivity**. *ACS Catal* 2020, **10**:12011-12016

This work utilized experiment and theory to investigate the feasibility of ligand removal from the surface of doped LPNCs under reaction conditions to expose sulfur and metal active sites responsible for the activity and selectivity towards CO_2 RR.

20. Li S, Nagarajan AV, Alfonso DR, Sun M, Kauffman DR, Mpourmpakis G, Jin R: **Boosting CO_2 electrochemical reduction with atomically precise surface modification on gold nanoclusters**. *Angew Chem Int Ed* 2021, **60**:6351-6356.

21. Wang G, Chen J, Ding Y, Cai P, Yi L, Li Y, Tu C, Hou Y, Wen Z, Dai L: **Electrocatalysis for CO_2 conversion: from fundamentals to value-added products**. *Chem Soc Rev* 2021, **50**:4993-5061.

22. Zhao S, Jin R, Song Y, Zhang H, House SD, Yang JC, Jin R: **Atomically precise gold nanoclusters accelerate hydrogen evolution over MoS_2 nanosheets: the dual interfacial effect**. *Small* 2017, **13**:1701519.

23. Austin N, Zhao S, McKone JR, Jin R, Mpourmpakis G: **Elucidating the active sites for CO_2 electroreduction on ligand-protected Au_{25} nanoclusters**. *Catal Sci Technol* 2018, **8**:3795-3805.

24. Zhao S, Austin N, Li M, Song Y, House SD, Bernhard S, Yang JC, Mpourmpakis G, Jin R: **Influence of atomic-level morphology on catalysis: the case of sphere and rod-like gold nanoclusters for CO_2 electroreduction**. *ACS Catal* 2018, **8**:4996-5001.

25. Alfonso DR, Kauffman D, Matranga C: **Active sites of ligand-protected Au_{25} nanoparticle catalysts for CO_2 electroreduction to CO**. *J Chem Phys* 2016, **144**:184705.

26. Chen S, Li M, Yu S, Louisia S, Chuang W, Gao M, Chen C, Jin J, Salmeron MB, Yang P: **Ligand removal of Au_{25} nanoclusters by thermal and electrochemical treatments for selective CO_2 electroreduction to CO**. *J Chem Phys* 2021, **155**:051101.

27. Kauffman DR, Alfonso D, Matranga C, Ohodnicki P, Deng X, Siva RC, Zeng C, Jin R: **Probing active site chemistry with differently charged $Au_{25}q$ nanoclusters (q = −1, 0, +1)**. *Chem Sci* 2014, **5**:3151-3157.

28. Seong H, Efremov V, Park G, Kim H, Yoo JS, Lee D: **Atomically precise gold nanoclusters as model catalysts for identifying active sites for electroreduction of CO_2**. *Angew Chem Int Ed* 2021, **60**:14563-14570.

29. Taylor MG, Mpourmpakis G: **Thermodynamic stability of ligand-protected metal nanoclusters**. *Nat Commun* 2017, **8**:15988.

30. Nagarajan AV, Juarez-Mosqueda R, Cowan MJ, Jin R, Kauffman DR, Mpourmpakis G: **Elucidating the stability of ligand-protected Au nanoclusters under electrochemical reduction of CO_2**. *SN Appl Sci* 2020, **2**:680.

31. Kumar B, Kawawaki T, Shimizu N, Imai Y, Suzuki D, Hossain S, Nair LV, Negishi Y: **Gold nanoclusters as electrocatalysts: size, ligands, heteroatom doping, and charge dependences**. *Nanoscale* 2020, **12**:9969-9979.

32. Nigam S, Majumder C: **Atomically precise noble metal clusters (Ag10, Au10, Pd10 and Pt10) on alumina support: a comprehensive DFT study for oxidative catalysis**. *Appl Surf Sci* 2021, **547**:149160.

33. Zhao Q, Martirez JMP, Carter EA: **Revisiting understanding of electrochemical CO_2 reduction on Cu(111): competing proton-coupled electron transfer reaction mechanisms revealed by embedded correlated wavefunction theory**. *J Am Chem Soc* 2021, **143**:6152-6164.

34. Sundararaman R, Goddard WA, Arias TA: **Grand canonical electronic density-functional theory: algorithms and applications to electrochemistry**. *J Chem Phys* 2017, **146**:114104.

35. Xie L, Liang J, Priest C, Wang T, Ding D, Wu G, Li Q: **Engineering the atomic arrangement of bimetallic catalysts for electrochemical CO_2 reduction**. *Chem Commun* 2021, **57**:1839-1854.

36. Yao C, Lin Y-J, Yuan J, Liao L, Zhu M, Weng L-H, Yang J, Wu Z: **Mono-cadmium vs mono-mercury doping of Au_{25} nanoclusters**. *J Am Chem Soc* 2015, **137**:15350-15353.

37. Li Q, Lambright KJ, Taylor MG, Kirschbaum K, Luo T-Y, Zhao J, Mpourmpakis G, Mokashi-Punekar S, Rosi NL, Jin R: **Reconstructing the surface of gold nanoclusters by cadmium doping**. *J Am Chem Soc* 2017, **139**:17779-17782.

38. Liu X, Yao G, Cheng X, Xu J, Cai X, Hu W, Xu WW, Zhang C, Zhu Y: **Cd-driven surface reconstruction and photodynamics in gold nanoclusters**. *Chem Sci* 2021, **12**:3290-3294.

39. • Zhuang S, Chen D, Liao L, Zhao Y, Xia N, Zhang W, Wang C, Yang J, Wu Z: **Hard-sphere random close-packed $Au_{47}Cd_2(TBBT)_{31}$ nanoclusters with a faradaic efficiency of up to 96% for electrocatalytic CO_2 reduction to CO**. *Angew Chem Int Ed* 2020, **59**:3073-3077

This was one of the earliest works demonstrating the effect of heterometal (Cd) doping on the CO_2RR activity and selectivity of LPNCs via a combination of experiments and theory. The alloyed LPNC showed a remarkably high faradaic efficiency of 96% at −0.57V versus RHE.

40. Choi W, Hu G, Kwak K, Kim M, Jiang D-E, Choi J-P, Lee D: **Effects of metal-doping on hydrogen evolution reaction catalyzed by MAu_{24} and M_2Au_{36} nanoclusters (M = Pt, Pd)**. *ACS Appl Mater Interfaces* 2018, **10**:44645-44653.

41. Kwak K, Choi W, Tang Q, Kim M, Lee Y, Jiang D-E, Lee D: **A molecule-like $PtAu_{24}(SC_6H_{13})_{18}$ nanocluster as an electrocatalyst for hydrogen production**. *Nat Commun* 2017, **8**:14723.

42. Choi W, Seong H, Efremov V, Lee Y, Im S, Lim D-H, Yoo JS, Lee D: **Controlled syngas production by electrocatalytic CO_2 reduction on formulated $Au_{25}(SR)_{18}$ and $PtAu_{24}(SR)_{18}$ nanoclusters**. *J Chem Phys* 2021, **155**:014305.

43. Sun F, Deng C, Tian S, Tang Q: **Oxygen electrocatalysis by $[Au_{25}(SR)_{18}]$: charge, doping, and ligand removal effect**. *ACS Catal* 2021, **11**:7957-7969.

44. Jin R, Li G, Sharma S, Li Y, Du X: **Toward active-site tailoring in heterogeneous catalysis by atomically precise metal nanoclusters with crystallographic structures**. *Chem Rev* 2021, **121**:567-648.

45. Panapitiya G, Avendaño-Franco G, Ren P, Wen X, Li Y, Lewis JP: **Machine-learning prediction of CO adsorption in thiolated, Ag-alloyed Au nanoclusters**. *J Am Chem Soc* 2018, **140**:17508-17514.

46. Kitchin JR: **Machine learning in catalysis**. *Nat Catal* 2018, **1**:230-232.

47. Li J, Chen T, Lim K, Chen L, Khan SA, Xie J, Wang X: **Deep learning accelerated gold nanocluster synthesis**. *Adv Intell Syst* 2019, **1**:1900029.

48. •• Wang S, Wu Z, Dai S, Jiang D-E: **Deep learning accelerated determination of hydride locations in metal nanoclusters**. *Angew Chem Int Ed* 2021, **60**:12289-12292

This work utilized a 3D-CNN with limited data to accurately predict the location of hydrides in Cu-hydride LPNCs, thus providing a way to develop important structure property relationships for inorganic material synthesis and their applications.

49. Tang Q, Lee Y, Li D-Y, Choi W, Liu CW, Lee D, Jiang D-E: **Lattice-hydride mechanism in electrocatalytic CO_2 reduction by structurally precise copper-hydride nanoclusters**. *J Am Chem Soc* 2017, **139**:9728-9736.

50. Loeffler TD, Manna S, Patra TK, Chan H, Narayanan B, Sankaranarayanan SKRS: **Active learning a neural network model for gold clusters & bulk from sparse first principles training data**. *ChemCatChem* 2020, **12**:4796-4806.

51. Pihlajamäki A, Hämäläinen J, Linja J, Nieminen P, Malola S, Kärkkäinen T, Häkkinen H: **Monte Carlo simulations of $Au_{38}(SCH_3)_{24}$ nanocluster using distance-based machine learning methods**. *J Phys Chem A* 2020, **124**:4827-4836.