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To Err is Human; To Reproduce Takes Time

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HISTORY REPEATS[1]

A looming fossil energy crisis inspires an urgent, world-wide effort to develop alternative energy technologies. The high efficiency and distributed nature of electrochemical energy conversion, particularly water splitting, hold tremendous appeal. Academic electrochemists investigate heavy water electrolysis at room temperature and atmospheric pressure. Wary of being scooped by competitors, they apply for a patent based on their striking results and hold a press conference. The media speculate eagerly that the discovery may represent a virtually unlimited source of clean energy.

The events described above took place over 30 years ago.[2] In the fateful press conference,[3] the researchers reported the emission of an anomalous amount of heat, as well as small amounts of ^{4}He, ^{3}H, and neutrons.[4] The world was captivated by the extraordinary speculation that they might represent products of a sustained nuclear fusion reaction involving ^{2}H atoms dissolved in the palladium cathode. The announcement stunned both the electrochemistry and physics communities, since it violated well-established physical laws.

The phenomenon was quickly dubbed “cold fusion”,[5] and intense scrutiny ensued. Efforts to reproduce the original observations were all over the map, both geographically and scientifically. Independent groups who reported similar observations faced accusations of poor experimental techniques, while negative outcomes were dismissed as incorrectly performed experiments. After several weeks of acrimonious debate about reproducibility, cold fusion claims were resoundingly rejected by the mainstream scientific community.

As the initial public furor over the cold fusion controversy subsided, a new narrative emerged. It focused on the failure of normal processes for vetting and disseminating important and unexpected scientific results. Observers at the time described the intense pressure on the electrochemists to establish priority for their discovery and to secure the anticipated windfall of research funding.[6] This pressure subverted both the dispassion needed to analyze results carefully and the slow process of peer review. The incident was framed using Irving Langmuir’s criteria for “pathological” science.[7]

Although younger scientists may be unaware of the cold fusion debacle (and other infamous examples of “bad science”),[8] most will recognize the intense drives for recognition and research funding, both of which have only become stronger since the 1980s. The demands on researchers to advance quickly in their work, to make broad claims of imminent potential impact, and to popularize their results (including via social media), have affected how science is conducted and communicated. It is hardly surprising, then, that concerns about reproducibility have re-emerged to spur important discussions in many disciplines, including catalysis.

REPRODUCIBILITY IS INSEPARABLE FROM SCIENCE

The modern scientific method, according to the famous 20th century philosopher of science Karl Popper, requires a hypothesis that is both testable and falsifiable.[9] A result that supports or refutes a hypothesis can be confirmed by repeating the experiment. Popper therefore dismissed “non-reproducible single occurrences” as being “of no significance to science”.[10] This criterion suggests grounds for concern about future scientific progress. In a 2016 survey conducted by *Nature*, over 70% of biology researchers reported being unable to reproduce the results of other researchers, while about 60% of researchers confessed they could not reliably reproduce their own results.[11] One provocative paper asserted that most published medical research is wrong because it is not reproducible.[12]

As physical scientists, we have more confidence in our literature than do our colleagues in the medical, behavioral, and life sciences. However, the editors of *Organic Syntheses*, a journal whose entire *raison d’être* is reproducibility in the sophisticated and mature field of organic synthesis, reported that about one in eight procedures submitted for publication in the period 2010−2016 could not be reproduced by members of the journal’s Board of Editors in their own laboratories, despite working in consultation with the authors.[13] The synthesis of complex, heterogeneous catalytic materials is undoubtedly afflicted by irreproducibility at a much higher rate.

A lack of reproducibility in scientific research has important practical consequences: future investigators cannot build on prior results; large quantities of researchers’ time and taxpayers’ money are wasted;[14] and public trust in science is diminished.[15] Technology deployment can be delayed or derailed when findings reported in the scientific literature are found to be difficult or impossible to reproduce, and the resulting distrust can undermine research collaborations between industry and academia.[16] The combined seriousness of all of these outcomes warrants deep reflection by our community on how to enhance reproducibility.

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CLARIFICATIONS AND DEFINITIONS

Although reproducibility is a fundamental principle of science, its precise definition is elusive. There are no generally accepted principles for how or when an experiment or calculation should be repeated, or by whom.[17] Most peer-reviewed journals do not have or enforce specific requirements. Even the statistical significance required for a reported result is an individual (and often unsubstantiated) decision.[18] A common understanding of what constitutes reproducibility will help guide researchers in the conduct of their work and assist editors and reviewers in the peer evaluation of manuscripts and research proposals.

Reproducibility includes the similar but distinct concepts of repeatability and replicability. *Repeatability* refers to the same experiment being performed (repeated) within a single study, demonstrating that essentially the same results are obtained. This activity helps researchers to understand the sources and magnitudes of error in their own work. A practice germane to *ACS Catalysis* involves distinguishing between the error in repeat measurements made on the same batch of catalyst, and the error for independently prepared batches (reflecting additional variability in the catalyst synthesis). Reporting catalyst metrics such as surface areas, pore volumes, rates, and selectivities with far more significant figures than their measurement warrants is an unfortunately common practice and reveals a lack of understanding of measurement precision. Furthermore, precision must not be conflated with accuracy. Without proper benchmarking,[19] precise measurements and calculations can be highly inaccurate and correspondingly misleading. It is also important for researchers to explore the repeatability of their data analysis and its interpretation.

In contrast to repeatability, *replicability* describes the use of the original procedure by an independent team of researchers, in order to replicate the original results, their analysis and interpretation. Replicability is therefore a stricter standard for reproducibility than simple repeatability. Finally, *corroboration* refers to gathering new evidence (by performing completely different experiments, or new types of calculations) in additional attempts to try to disprove the original hypothesis (or, in failing, to strengthen the hypothesis).[20] Since reproducing a set of results does not produce new evidence, it cannot provide corroboration.

To ensure that replication is possible, authors should provide their readers with detailed instructions for all of the experimental and computational procedures, and the data generated at each key stage of processing, preferably in both human- and machine-readable form.[21] The use of software that will eventually become obsolete poses a particular problem for reproducibility. Hence, it is important to report raw (i.e., unprocessed) data and computational results in readily accessible forms as much as possible. Since the peer-reviewed literature also serves an important archival function, authors should remember that future readers may not hold the same assumptions about what is common knowledge, or understand today's lab jargon. Both clarity and completeness are necessary in reproducible research.

SPECIFIC CHALLENGES FOR CATALYSIS

Reproducibility issues affect catalysis at many stages of a research project, starting with the synthesis of the catalytic material and its activation, and extending to all types of rate, selectivity, and stability measurements, as well as calculations of the mechanisms and energetics for elementary reaction steps or reaction networks. Irreproducibility not only hinders the progress of individual researchers; it also poses a threat to the use of powerful data science tools to advance our understanding of complex catalytic phenomena.

Homogeneous catalysis may have a reproducibility advantage, because the precise structure and purity of molecular compounds can often be verified by single-crystal X-ray diffraction and elemental analysis, respectively. Crystalline powders such as zeolites and MOFs can be identified by indexing their X-ray diffraction reflections and analyzing their phase purity using Rietveld refinement. However, all of these "uniform" catalytic materials can (and often do) evolve during their activation, and under reaction conditions. Confirming the bulk structure of a well-defined catalyst is therefore no guarantee of reproducible catalytic activity. Minor molecular species, leached components, defects, or rare surface sites can be responsible for much of the observed catalytic activity,[22] memorialized in Jack Halpern's humorous postulate: If you can isolate it, it is probably not the real catalyst.[23] *In situ* activation of molecular precatalysts, the use of amorphous catalysts (i.e., lacking long-range order) or crystalline catalysts with amorphous components, the addition of promoters (often themselves heterogeneous), and the intrinsic non-uniformity of nanocatalytic materials, all present researchers with more complicated reproducibility issues.

Another common problem is the variable and/or unverified purity of catalyst components and reagents. This can be a vexing source of irreproducibility, even in homogeneous catalysis. The Nozaki−Kishi−Hiyama coupling reaction, in which alkenyl halides are added to carbonyl compounds, was initially believed to be promoted by $CrCl_2$,[24] but difficulties in reproducing the reaction led researchers to identify batch-specific contamination by Ni as critical to reactivity. The reaction is now known to require a Ni catalyst in addition to $CrCl_2$. The effectiveness claimed for Au- and Cu-based catalysts in Sonogashira coupling was later attributed to adventitious Pd impurities.[25] Used Teflon-coated stir bars can harbor trace metals and have been shown to supply enough of them to alter the outcomes of some liquid-phase catalytic reactions.[26]

Metal contamination in the reagents or other additives has also been the cause of many irreproducible claims of "metal-free" homogeneous catalytic reactions.[27] Cross-coupling reactions are usually catalyzed by Pd in the presence of a base. Ironically, the extremely high catalytic activity of Pd in C−C coupling chemistry is problematic, since Pd can show high activity even (or especially) at ppb levels.[28] In 2003, Leadbeater and co-workers described a microwave-assisted Suzuki−Miyaura cross-coupling that proceeded "without the need for addition of a transition-metal catalyst".[29] After moving their lab across the Atlantic Ocean, the authors discovered that the reaction worked only with Na_2CO_3 purchased in the U.K. This material was contaminated with about 50 ppb Pd, while US-sourced Na_2CO_3 with lower levels of trace Pd failed to work.[30] It appears that these hard lessons must be relearned by each new generation of researchers.[31] Indeed, a recent *Chemical & Engineering News* cover article[32] described yet another claim of a metal-free Suzuki−Miyaura cross-coupling, in which an amine was the purported catalyst. After publication, the true catalyst was identified to be traces of Pd associated with the amine, which was itself prepared by a Pd-catalyzed process.

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Heterogeneous catalysis has its own versions of these problems. Silver impurities present in high-purity gold powder (>99.99%), or Ag remaining after leaching from AuAg alloys, were shown to be responsible for activating O_2 in catalytic oxidations that were initially attributed to unsupported Au.[33] The presence of leached metals is a recurrent issue for supported Pd catalysts,[34] since vanishingly small amounts of the solubilized metal can be highly active.[35] Concerns about leaching have also been raised for heterogeneous transition metal-based catalysts used in liquid-phase oxidations.[36] The use of Pt counter-electrodes without an ion-exchange membrane can lead to Pt electrodissolution and redeposition that enhance the apparent activity of Au and nonprecious metal electrocatalysts.[37] Degradation of carbon-based materials under electrochemical conditions can also alter reactivity via the dissolution of impurities as well as CO formation, which poisons metal surfaces.[38] Fe impurities present in the KOH electrolyte played a role in enhancing the activity of NiOOH-based electrocatalysts for the oxygen evolution reaction.[39] Trace metal impurities present in graphene were revealed to be the real electrocatalytic sites in some "metal-free" oxygen reduction reactions.[40] All of these experiences remind us to be especially cautious in announcing unprecedented catalytic behaviors for new materials.

The use of proprietary catalysts and/or materials that are not widely available is highly problematic for reproducibility. *ACS Catalysis* requires that catalyst composition and structure be fully disclosed in publications. The high variability inherent in natural materials like raw biomass, and in waste materials like used plastics, makes them unreliable as sources of catalytic materials, despite the appeal of their low cost. Papers with this goal as their motivation are problematic for reproducible catalysis research.

Accurate measurements of reaction rates rely on precise control of all reaction conditions (concentrations, flow rates, temperature, etc.). Small differences in conversion do not necessarily reflect significant differences in catalytic activity, whose repeatability (based on a new experiment performed with an independently prepared catalyst) is rarely better than ±10%. (A simple calculation shows that a reaction with an Arrhenius activation barrier of 90 kJ/mol would show this amount of rate variability at ca. 60 °C due to a temperature change of just 1 °C.) Furthermore, catalyst performance can be strongly impacted by heat and mass transport effects, particularly in microporous materials and in (photo)-electrocatalytic devices, making it difficult to reproduce rate measurements unless the particle size, pore dimensions, and reactor configuration are precisely known. Controversies can arise due to incomplete documentation of procedures and reaction conditions, because even small differences initially perceived as inconsequential (such as the intensity of ambient light at the laboratory bench,[41] or the incubation time of catalyst components prior to reaction)[42] can have dramatic effects on catalyst performance.

Reproducibility in heterogeneous photocatalysis suffers from all the above-mentioned problems with additional concerns regarding temperature uncertainty, especially when power illumination is used, or in the presence of plasmonic materials.[43] In photothermal reactions, accurate measurement of the reaction temperature is not trivial and still highly debated. Issues related to variations in the degree of catalyst dispersion, induction periods, and lamp instability have also been discussed.[44] Furthermore, when figures of merit (e.g., photocatalyst mass) are reported for conditions far from the optimized reaction conditions (and/or in the absence of sufficient supporting data), other researchers are unlikely to be able to reproduce the results and/or make meaningful comparisons with the literature.

While reproducibility may appear to be more straightforward in computational catalysis, challenges arise in the use of proprietary software or nonpublicly available custom code.[45] Coordinates and energies for all computed structures should be published to enable replication, and some publishers are also starting to require that source codes, as well as input codes and output files, be made available. However, such requirements are undercut by the rapid obsolescence of computing platforms and can raise intellectual property concerns.

■ TEMPTATIONS AND DISTORTED INCENTIVES

Irreproducibility can be a result of intentional dishonesty in research, including data falsification, fabrication, and plagiarism (FFP). Their incidence has been associated with social and institutional pressures on researchers.[46] Poor training can also be at the root of unethical research practices, such as the selective reporting of data (known as "cherry-picking"); discarding outlying data; and erasing or obscuring inconvenient peaks in spectra. Other improper types of data manipulation include p-hacking (collecting or selecting data until a desired effect appears to be statistically significant),[47] HARKing (hypothesizing after results are known or basing a hypothesis on the data then using it as evidence to support the hypothesis),[48] and data dredging or fishing (looking for statistically significant correlations in a data set, after the original hypothesis has been discarded).[49] While formulating new hypotheses midproject is not always problematic,[50] articulating (and documenting) hypotheses about fundamental relationships prior to collecting and analyzing data may be particularly important in the emerging "science" of data mining, which is at high risk of finding spurious correlations.[51] A famous (and hilarious) example of improper statistical analysis of false positives concerns the magnetic resonance imaging demonstration of brain activity in a dead fish,[52] which earned its authors a well-deserved Ig Nobel Prize.[53]

Widespread concern about the reproducibility of published research suggests that various kinds of unethical practices may be more common than is currently acknowledged.[54] The growing use of preprint servers to disseminate nonpeer-reviewed results is further adding to this concern and raising alarms about its potential to distort research priorities.[55] More discussion about accountability in the use of such servers is needed.[56] Nevertheless, reproducibility problems are not always the result of ill intent. A major driver can be the need to wrap up studies quickly and publish them to demonstrate accountability to employers and funders. This pressure sets up a direct conflict between research productivity and time-consuming reproducible research. Scientists are not incentivized to allocate time to repeating and replicating prior results when the outcome is lower publication rates and less favorable comparisons in research assessments, student recruiting, and research funding competitions.[57] One social science model predicted that the "publish or perish" ethos combined with the constrained availability of research funding could lead to a decline in the trustworthiness of research results over time.[58]

Even in careful research, a lack of awareness about various types of cognitive bias can lead to systematic errors that impact reproducibility, caused by researcher selection of the types of data that are deemed to be worth reporting. Anchoring bias leads researchers to place too much faith in their initial hypothesis.[59] Confirmation bias, driven by overconfidence, causes them to emphasize (or even, to seek) results that support their hypothesis and to de-emphasize results that do not.[60] Indeed, seeking confirmation (as opposed to falsification) of a hypothesis, and presenting that confirmation as scientific evidence, is a hallmark of pseudoscience.[61] These ideas have a long history: Francis Bacon described similar problems afflicting scientific progress over 400 years ago.[62]

One issue that Bacon could not have anticipated is publication bias. It arises because journals (or, more precisely, their editors and reviewers) tend to be more impressed by unusual or strongly positive results, leading researchers to avoid mentioning weak or negative results or to consign them to a less visible role in the Supporting Information (formerly, in the file-drawer, hence an alternative name: file-drawer bias). As other researchers attempt to reproduce an exciting new result, the evidence for it often becomes weaker.[63] This is the "decline effect". It is now well-documented in many areas of physical science research, especially where statistical analysis is required to distinguish real data signals from the noise.[64] Yet studies that report declining effects are usually relegated to less visible journals compared to those that published the initial claims, providing little incentive for researchers to do them in the first place. Unfortunately, then, the reproducibility of many strong claims may not be verified.

■ REPRODUCIBILITY REQUIRES DILIGENCE

Reproducible research implies scientific results whose complete and accessible documentation makes the acquisition, processing, and analysis of the data fully transparent. Achieving this high standard of disclosure is time-consuming and will require significant changes to our usual practices. In publications, written synthesis procedures should include as much detail as possible, which could be facilitated by the automated logging of conditions and protocols, supplemented by video documentation. Manuscript reviewers should check that experimental and computational procedures are described in enough detail either in the main text or the Supporting Information to allow independent researchers to replicate them. A forum for reproducible catalyst synthesis procedures (analogous to *Organic Syntheses* and *Inorganic Syntheses*) could be helpful. The archival format of unprocessed catalytic data (for example, kinetic profiles or spectra) must allow others to replicate the data analysis as well. Many of these goals will require stable, long-term data repositories, which journals can play a role in providing.

Measurements of catalytic performance (activity, selectivity, productivity, etc.) must be repeated and analyzed using appropriate statistical methods to assess their significance. A useful practice our community might adapt from biological research is "triplication," or performing an experiment at least three times before reporting a result or drawing a conclusion.[65] Researchers must clearly distinguish between preparing a catalyst three times to perform an experiment and testing a single catalyst sample in triplicate (establishing only the precision of the measurement).[66] Reviewers should expect authors to discuss potential sources of uncertainty in their experiments or calculations and describe how they were controlled. In the future, papers could include a special section dedicated to this statement, similar to the Contributor Roles Taxonomy (CRediT) section now required by many publishers. Journals could consider making replication data sets a requirement for publication.

Widespread availability of standard catalytic materials would facilitate benchmarking. There are several precedents for this idea. The desire to calibrate activities and facilitate comparisons across wide variations in reactor styles and reaction conditions, as well as over time, motivated the production of several heterogeneous catalysts as reference materials.[67] In Europe, standard metal nanoparticle catalysts (Ni, Pt, Pt−Re) supported on silica and γ-Al_2O_3, as well as V_2O_5/TiO_2, Co-MoS_x/γ-Al_2O_3, and the Ti-substituted zeolite TS-1, were produced in significant quantities and made available to researchers upon request; the World Gold Council undertook a similar project involving Au nanoparticles supported on TiO_2, Fe_2O_3, and C.[68] An unanticipated outcome of these efforts was the difficulty in obtaining consistent results across different laboratories for the reference catalysts themselves, ultimately generating more confusion than clarity in some cases. Most of the catalyst standards were available for only a few years. Consequently, there is little evidence that they played a lasting role in improving reproducibility.

Future efforts in this direction will require more robust ways to making and distributing reference materials. For new catalysts, researchers could become accustomed to synthesizing enough material to provide samples upon request to other researchers for replication and benchmarking studies. While this is not a current practice in catalysis, similar practices are encouraged (indeed, *de facto* expected) in some fields (e.g., cell lines and DNA samples in molecular biology).[69] Intriguingly, "metascience" studies involving the analysis of data across many studies may help to identify reproducibility issues, by revealing where unintentional replication has succeeded[70] and by identifying papers whose results are clearly outliers.[71]

■ INCENTIVIZING REPRODUCIBLE RESEARCH

Catalysis research has been enormously impactful in advancing societal goals for quality of life, and we have much work ahead of us to continue these contributions as we confront new sustainability challenges. To ensure that we can meet these expectationss, we must work harder as a community to set standards that will ensure the reproducibility of our work. Researchers are human,[72] and they will inevitably commit errors while conducting science.[73] Science is often said to be self-correcting, but this process is slow relative to the rapid pace of discovery and the volume of results being generated today.[74] It is essential to put the right incentives in place to correct errors quickly. Research institutions and funding agencies should insist that their principal investigators lead by example in performing reproducible research themselves and in providing training and mentoring to early career researchers based on reproducibility best practices, like triplication.

Investments in reproducibility will be valued when we make it intrinsic to our judgements about research quality. According to sociologist Robert Merton, scientific research should be conducted to expand knowledge or to benefit humanity, rather than for personal gain. Thus, one of the Mertonian norms of good science is disinterestedness.[75] This ethos can come into direct conflict with current metrics for evaluating the performance of researchers, which invariably affect how scientists conduct and present their work.[76] Removing incentives for seeking publication in high-impact journals may reduce the tendency to select for false positives.[58] Publication metrics could be modified to distinguish citations for reproducible work from those with improperly supported and/or discredited claims. Journals could do more to reduce barriers and stigmas associated with paper corrections and retractions.[77] They could also facilitate collaborations and joint publications between teams of researchers to resolve replicability issues.[78] The same journal that published the original study could then take responsibility for publishing follow-up studies.[79]

Finally, while the cold fusion fiasco taught us that taking short-cuts with respect to reproducibility issues leads to bad science, it also exposed the severe penalties that accrue to “maverick” researchers who take risks and break with science norms.[80] We cannot afford to impede the major advances that can emerge from research that defies conventional expectations. The challenge ahead of us is to achieve the right balance between promoting reproducibility and making room for the unexpected.

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Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

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