A clash of cultures in discussions of the *P* value

To the Editor: In their exchange of letters, van Helden[1] and Halsey *et al.*[2] debate the utility of the *P* value and of the confidence interval (CI) for interpreting experiments. In addition to the specific points raised, their exchange illustrates a clash of cultures that may be illuminating for readers to note. Namely, there are two broad mindsets:

The craftsman—a single *P* value is reported as an end result of the analysis of a predefined single question, as is the case for, say, a clinical trial or a small-scale biological experiment.

The industrialist—*P* values are used to summarize a screen of many hypotheses, as in gene expression analysis, genome-wide association studies and other types of high-throughput biology. Typically, such analyses involve iterative data exploration, and the 'result' is only an intermediate step, to be followed by more analysis. Importantly, the distribution of all the other *P* values gives a lot of contextual information for each particular *P* value.

A clash can arise between the craftsmen (exemplified by the arguments of Halsey and colleagues) and the industrialists (exemplified by van Helden). For instance, the claim made by Halsey *et al.*[2] that "the problem with running the test many times is that this virtually never happens in practice" is true for the craftsman but blatantly wrong for large-scale testing. The figure presented by van Helden[1] (including volcano plots and *P* value histograms) shows that he is thinking large.

How does this affect the alleged fickleness of the *P* value? A single *P* value can be fickle. In particular, if the null hypothesis is true (i.e., there is no effect) or if the analysis is underpowered, the *P* value can lie anywhere between 0 and 1 with equal probability, and therefore it will be irreproducible. However, the distribution of many *P* values, industrially produced, is very reproducible, by virtue of the law of large numbers. In fact, in large-scale testing, *P* values are easier to deal with than CIs. Multiple testing is naturally and intuitively reasoned about in terms of *P* values, whereas this is roundabout with CIs. The contextual information of all *P* values can be modeled using Bayesian concepts, such as local false discovery rates and empirical nulls[3]. Moderated tests[4] can avoid some of the fickleness, and these approaches have been hugely successful.

Common to both sides' arguments is the observation that the *P* value alone is an insufficient summary of an inferential process. To usefully report the results of a statistical analysis, scientists should provide not only *P* values but also the underlying data and the complete analysis workflow, using a reporting tool such as Jupyter or Rmarkdown.

COMPETING FINANCIAL INTERESTS
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The democratization of cryo-EM

To the Editor: The cryo-electron microscopy (cryo-EM) community is in the throes of a 'resolution revolution'[1]. Years of technical development have led to hardware and software that can provide refined atomic structures with resolutions adequate for obtaining novel biological insights and for structure-based drug design[2,3]. However, these advances come at the cost of a multi-million-dollar investment that is required to establish a cutting-edge microscope, a detector and computational support. We believe that there is now the opportunity, and need, to provide democratic access to maximize the impact of cryo-EM on basic and applied science.

Possible models for such access are already emerging, following lessons learned from the experience accumulated over the past two decades, especially at synchrotron facilities across the world[4]. Crystallography beamlines are excellent examples of how the organization of large facilities, pioneered in physics, can shape the landscape in biological and biomedical research. Cryo-EM can learn from this experience. Several good initial exemplars, including the eBIC center in the United Kingdom (http://www.diamond.ac.uk/Science/Integrated-facilities/eBIC.html), the NeCEN center in the Netherlands (http://www.necen.nl), the Janelia Farm campus of the Howard Hughes Medical Institute (https://www.janelia.org/support-team/cryo-electron-microscopy) and the newly created national cryo-EM facility at the US National Cancer Institute (http://www.cancer.gov/research/resources/cryoem), are enabling users to access high-end cryo-EM infrastructure.

Such centralized facilities allow a broad spectrum of users to focus on fundamental biological questions with the knowledge that excellent infrastructure will be available. Interactions between the technical staff at the facilities and users with academic and commercial backgrounds can help optimize pipelines and establish a 'team culture', as at synchrotrons where industry groups bring a keen eye for efficiency. Other models for access are those driven by commercial consortia, such as the Cryo-EM Consortium in Cambridge, UK (http://www2.mrc-lmb.cam.ac.uk/cambridge-pharmaceutical-cryo-em-consortium/). Another model enabling the collectivization of research and partnering with industry is found in cooperative research centers[5], which have helped foster scientific excellence and shaped regional competitiveness in, for example, the Basque region (https://issuu.com/innobasque/docs/oecd_assessment___recommendations).

Cryo-EM is rapidly maturing from a technique limited to a relatively small circle of expert users to one of very broad interest. Waiting times to gain access to equipment are long in most places, and the establishment of additional cryo-EM hubs would drive scientific synergy, training and technological development with academic and industrial sectors, stimulating both science and the economy.

Open access to synchrotron facilities enabled a step change that led X-ray crystallography to permeate the global life science community and become an indispensable part of the drug discovery process. Establishing a free market between synchrotrons drove technical developments and increased efficiency, leading to improvement by orders of magnitude in data-acquisition speed, data quality, automation and remote access. Such changes also bring challenges, such as the emergence of a generation of scientists who are less experienced users, but we suggest that this is natural in the evolution of any new technology. The evolution of the crystallography field taught