Interview, Building trust in medical AI algorithms with veridical data science

Interview with Prof. Bin Yu, Department of Statistics, University of California, Berkeley

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Professor Bin Yu is Chancellor's Distinguished Professor and Class of 1936 Second Chair in the Departments of Statistics and Electrical Engineering and Computer Sciences, as well as the Center for Computational Biology at the University of California (UC) at Berkeley. She received her Bachelor's degree in Mathematics from Peking University and her Master's degree and PhD in Statistics from UC Berkeley. She has held faculty positions at several prestigious institutions, including UW-Madison and Yale University. Additionally, she worked in industry at Bell Labs in the late 90's (on leave from Berkeley) and currently works at Microsoft Research (while on a 50% leave from Berkeley). Prof. Yu is a highly distinguished researcher and educator in the fields of statistics and computer science, with particular expertise in statistical machine learning and artificial intelligence for biomedical data problems. Her research addresses some of the most pressing challenges in this area, such as understanding the complex relationships between genetic factors and disease risk, predicting patient outcomes, and analyzing fMRI data in neuroscience. One notable achievement of her research is the development of predictive models of fMRI brain activity in vision neuroscience with the Jack Gallant Lab and her students, which made "mind-reading" possible (i.e., reconstruction of movies using only fMRI signals). Throughout her career, Prof. Yu has received numerous accolades for her contributions to the field, including being a member of the U.S. National Academy of Sciences and the American Academy of Arts and Sciences. She has also served as the President of the Institute of Mathematical Statistics (IMS) and has been awarded the Guggenheim Fellowship, the Tukey Memorial Lecturer of the Bernoulli Society, the Rietz Lecturer of IMS, and the COPSS E. L. Scott Prize. At the Joint Statistical Meetings (JSM) in August, 2023 at Toronto, she is to deliver the Wald Lectures, which are the highest honor bestowed by IMS. As a former postdoc in Prof. Yu's group from 2018 to 2020, I had the pleasure of working with her and experiencing her research, expertise, and insights in the field of statistics, machine learning, and AI in medical applications.

Behr: You have been a professor in statistics and computer science for around 30 years now, with many groundbreaking contributions in machine learning (ML) and data science, including various inter-

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disciplinary collaborations in the bio-medical field. Why did you decide to become a researcher in statistics and computer science, in general, and what do you find fascinating about working together with researchers from the bio-medical field?

Yu: To be more precise, I have been a statistics professor for around 30 years, and became an EECS (Electrical Engineering and Computer Sciences) professor 15 years ago.

I became a graduate student in 1984 entering Peking university's probability/statistics graduate program after being an undergraduate there in pure math because the professor in functional analysis that I wanted to work with turned me down despite the fact that I ranked first in math subject exams to enter the graduate program. It was actually my most successful failure, for it allowed me to switch to statistics that is a perfect fit for me. I had always wanted to be useful growing up hearing stories of many people in my family taking on social responsibilities.

Then with some luck, I was able to come to Berkeley to do a PhD in statistics. I fell in love with information theory during my PhD study under Lucien Le Cam and Terry Speed. I did half of my thesis under Terry on minimum description length (MDL) principle of Rissanen at the interface of statistics and information theory and often also in collaboration with Jorma Rissanen who was at IBM Research then. Under MDL, I first read about Turing Machines. The other half of my thesis under Lucien on empirical process theory or VC theory for dependent data. After my PhD, I did more information theory, and went to signal processing from there. Then I spent two years in Lucent Bell Labs after getting tenure at Berkeley despite a non-smooth tenure review process. I got into machine learning while I was at Bell Labs: I visited Peter BÃ$\frac{1}{4}$hlmann at ETH and joined Peter on a project analyzing bagging. After I went back to Berkeley in 2000 from Bell Labs, my colleague Leo Breiman further encouraged me to get into Machine Learning and I have not left machine learning since. I believe Peter was also influenced by Leo when Peter spent two years at Berkeley in the mid-90's. So it was one thing that led to another, not a particular decision at any point. I went to information theory because I thought that was more interesting to me than theoretical statistics at the time because information theory was both elegant and useful. Machine learning caught my attention because it felt just right to formally take computation into account, which I had already believed in before getting into ML.

I have been a curious person from an early age and biomedical science is very important for society as well. So both, satisfying curiosity about the inner workings of the amazing human body, which were absent in my education, and being useful, have been two driving forces behind my working in biomedical data problems.

Behr: What was your first collaboration with medical researchers?

Yu: It was with urologist Dr. Anobel Odisho at UCSF (University of California San Francisco, which is a medical school). Several years ago, Anobel reached out to the Berkeley Institute of Data Science (BIDS) to look for a collaborator in NLP (Natural Language Processing) and his email was forwarded to a student of mine who was a BIDS Fellow then and she forwarded Anobel's email to me. With Anobel and his colleagues at UCSF, we (statistics PhD students Nick Altieri, Briton Park, CS colleague John De Nero and me from Berkeley) worked on extracting structured information from unstructured cancer pathology reports. We are continuing this collaboration with Anobel to see how large language models work relative to our previous simpler models for this pathology report problem.

Behr: And what is the most exciting research project you are currently working on?

Yu: That is a hard question. Many exciting projects - one is most exciting on some days and another is on other days. In the area of biomedicine, one exciting project is a long term project trying to figure out more about genetic drivers of a heart condition related to cardiac hypertrophy after some successful first collaboration under a CZ (Chan Zuckerberg) Biohub Intercampus Award. For the Biohub project, we have obtained experimental validation based on our recommendations using UK Biobank data with the Ashley Lab at Stanford Medical school and other researchers. You did the heavy lifting with Dr. James Priest from Stanford Medical School, and Karl Kumbier from our team in the first phase of the project, Merle, when we were working on a positive control of red-hair phenotype as a proof of concept before tackling the harder heart diseases.

Behr: With your many years of experience and a strong network to both theoretical and applied researchers in the field, how do you see the development of ML and artificial intelligence (AI) in the medical field over time? And what do you think are the biggest challenges for AI in medicine?

Yu: AI or ML algorithms for medicine are being developed by many research groups, but these algorithms are most of the time not deployed in the doctors' offices since doctors do not trust them very much yet. Publishing papers on some benchmark medical data is not enough and a lot more vetting and regulations need to be put in place. The biggest challenge is to build trust in AI algorithms in medicine by the doctors and patients alike. Without easy access to large amounts of medical data by researchers and without a rigorous data science process from data to clinical decision support, algorithms can be fragile - this trust is hard to build.

Behr: Many areas of our everyday life are currently revolutionized by AI (e.g., Google maps, self-driving cars, ChatGPT, etc.). In medicine, this sometimes seems less the case. Going to the doctor today still seems similar to how it used to be 20 years ago. Do you think the development of ML and AI in the medical field is substantially different than in other application areas?

Yu: Well, medical people definitely are looking into chatGPT so I hope some trustworthy advances will happen in medicine using chatGPT. Medical AI is at high stakes and more regulations are necessary too so it is different from self-driving cars, which by the way are not really happening either for most people. Google maps are so much easier than medical AI because the former deals with mostly static entities not like living or dynamic entities as in medicine.

Behr: In recent years medicine has seen a lot of new massive data sources, like imaging data, omics data, or also patients' electronic health records data. You have been working with all these data sources. Which one has the highest potential for AI?

Yu: All of them in an integral fashion, because they are all part of a patient's health history and conditions. Depending on the data quality and quantity relative to a particular medical problem, one type of data might contain more relevant info than others. A non-trivial challenge is data integration and data integrity.

Behr: In medicine often p-values are required (e.g., by health authorities). AI and ML methods do not often allow for classical statistical uncertainty quantification. Does that hinder the use of AI in medicine?

Yu: As we know, p-values are often not working very well on the ground for medicine and they need re-thinking. So that AI and ML don't use classical p-values is not necessarily a bad thing. But they do have to address uncertainty in some way and many AI algorithms in medicine are predictive algorithms for which prediction intervals can be constructed in AI or ML so I don't see obviously more of a hindrance for AI in medicine than statistics.

As one way to re-think p-values, you and I and our collaborators have done some work together on PCS p-values for epistasis detections with the phenotype red-hair and UK Biobank data.

Behr: You have been working for and collaborating with industry, e.g., at Bell's lab very early in your career and currently for Microsoft Research at 50% *and remote. What do you think are the most important synergies arising from these contacts?*

Yu: These industry stays satisfy my curiosity and are about finding a different way of doing research, at a faster pace, and with a different type of organization structure. I also like to challenge myself in a new situation so I feel fully alive. :-) The Bell Labs days set me on a path to do applied statistics and interdisciplinary research that I had wanted to do before Bell Labs, and having many like-minded, kind and brilliant colleagues to learn from at Bell Labs (Mark Hansen, Gerald Schuller, Diane Lambert, and Bill Cleveland, just to name a few), was a true blessing. My Bell Labs work with Gerald and others on audio compression based on combining predictors was handy when we did our covid death prediction work in the spring of 2020 to help a non profit to ship PPEs (Personal Protective Equipment) to the most needy hospitals. Right now at MSR (Microsoft Research) it is most exciting to have a front-row seat to see how large language models like chatGPT are changing how we get information, esp. given the alliance of OpenAI and Microsoft. Being close to the heart of AI at MSR also gives me opportunities to share my views including PCS and hopefully to help make AI more trustworthy.

Behr: PCS stands for 'Predictability - Computability - Stability', a very successful data science framework which you introduced in recent years. Another related research focus of yourself and the data science community, in general, is the question of causality, which seems to be particularly important in medicine. How does AI and causality go together in medicine from your perspective? And what is the connection to the PCS framework?

Yu: Causal inference has a long history in economics, statistics, medicine, and other social science fields such as political science, and is being picked up by ML and AI people, first through A/B testing and now also in discussions of fairness of algorithms, including in medical AI. Supervised learning has found a healthy inroads into heterogeneous treatment effect estimation as in our X-learner [6] (with a former PhD student Sören Künzel and colleagues Jas Sekhon and Peter Bickel) and other methods that are underlying precision medicine, using data from both randomized clinical trials and observational studies. As in political science, economics, and epidemiology, assumptions need to be made for causal conclusions even with randomlized clinical trial data in medical AI. Assumptions made for observational studies are often impossible to check so randomized clinical trials are the gold standard, but not without some assumptions such as the SUTVA (Stable Unit Treatment Values) assumption in the Neyman-Rubin model. Reinforcement learning in AI has a close connection with sequential design or dynamic regime design in statistics.

I have taken an approach to causal inference based on our PCS framework for veridical data science [12], which integrates and expands on best ideas and practices in ML and statistics to insist on reality check often through prediction evaluation on test data and take into account neglected sources of uncertainty in the data science life cycle, such as those from human judgment calls in data cleaning and algorithm choice. A recent article in PNAS [2] by 73 teams of social scientists provides very strong support for PCS. This article documents results from these teams using the same data about the same prominent social science hypothesis regarding the impact of immigration on public opinions towards public policies. The conclusions about the hypothesis from these 73 teams vary from the very positive to the very negative and anything in between. This is largely due to the algorithm choices made by the teams or due to the team effect. In an applied stats graduate class project at Berkeley (stat215A in fall 2021), we asked three teams of graduate students to work on the same data set about traumatic brain injuries of kids in ER (Emergency Room) and design a clinical design rule regarding whether to send them to CT (Computerized Tomography) scans. Each team also had a UCSF ER doctor to work with. The three teams were given the same data cleaning guidelines and were asked not to discuss with each other. They ended up with three different cleaned data sets. One team cleaned away 23% of the raw data and got the best performance on the cleaned data, which was very unlikely to be reproduced in a real clinical setting. Further analysis showed that the variability in performance assessment (sensitivity say) from different versions of the cleaned data is similar in magnitude to that from bootstrapping one cleaned data set. Hence this layer of uncertainty needs to be formally considered together with the team effect or algorithm choice uncertainty as the simple to sample variability as in traditional statistics. PCS requires a PCS documentation to go with the data analysis work that records the whole process including problem formulation, data choice, data clearing, EDA (Exploratory Data Analysis), modeling or algorithm choice, results summarization and communication choice, and conclusion and we have a PCS document template to share at https://yu-group.github.io/vdocs/TCGA-BRCA-Example.html.

Back to causality, we have used PCS by insisting on stability analysis after reality check through prediction with observational data to suggest scientific hypotheses for follow-up external studies in the wet lab or through clinical trials for proof of causality. The stability addition to predictive analysis can help remove many confounding factors so the follow-up external study becomes more efficient or enjoys higher yields than without the stability analysis. We have had a success story with the cardiology project mentioned above and we are writing up the results with two bright young researchers as co-first authors: Tiffany Tang (a senior graduate student of mine at Berkeley) and Qianru Wang (a postdoc of Euan Ashley at Stanford).

Behr: In what sense is the stability principle (the 'S' in 'PCS') different from the concept of robustness?

Yu: 'S' is a detailed articulation on the concept of robustness in the context of data science and AI, and it is a significant expansion on the concept of robustness in robust statistics beyond the modeling stage to every stage of a data science life cycle, starting from problem formulation, data cleaning, EDA, model/algorithm development, results summarization and conclusions. Even in the modeling stage, stability covers both data perturbation and model/algorithm perturbation, not just model perturbation as in robust statistics. 'S' also connects with the concept of stability in numerical analysis and control theory - putting them in the same unifying umbrella. It allows data augmentation as a form of data perturbation as well, as long as there is a good argument in the PCS documentation to back it up as serving some legitimate purpose.

In every step of a data science life cycle, human judgment calls are rampant and they bring a layer of uncertainty to the data conclusion - all these uncertainties need to be recorded and accounted for if possible.

Stability is a common sense principle if we quote Plato from the Meno: 'For true opinions, as long as they remain, are a fine thing and all they do is good, but they are not willing to remain long, and they escape from a man's mind, so that they are not worth much until one ties them down... That is why knowledge is prized higher than correct opinion, and knowledge differs from correct opinion in being tied down.'

I started to advocate and use the stability principle in my 2012 Tukey Lecture of the Bernoulli Society and in my 2013 paper 'Stability' [9] that is based on the Tukey Lecture. The more I pursue the stability principle, the more sense it makes to me as a unifying basic principle in data-driven work including data-driven AI.

It is worth mentioning that I and my team have used PCS in many projects by now with excellent results in areas ranging from methodology development as in iterative random forests [1] for predictive and stable Boolean interaction discovery, and selection of number of components in NMF (Non-negative Matrix Factorization) (staNMF, [8]), drug discovery (staDRIP, [7]), and subgroup discovery in randomized experiments (staDISC, [3]). The best reception of PCS happened at a US National Academy of Sciences (NAS) study workshop on testing and evaluation of AI systems for the Air Force in 2022. The Air Force people care deeply about the safety of their pilots in AI-enabled jets and hence the quality of the data-driven algorithm development process. A study committee member kindly sent a note later describing my talk on PCS as 'superb. ... absolutely perfect' and the endless questions during my talk showed great interest from the participants of whom many were from the Air Force. Medical AI is also high-stakes as AI systems for the Air Force.

The most recent two papers of mine and team's on PCS application are in fact for medicine: one is to use PCS to stress-test a clinical decision rule or serve as an internal validation that can save much costs on external studies; the second is to apply PCS to show contribution of the microbiome to a metabolomic signature predictive of risk for pancreatic cancer. The first was a collaboration of my team (CS (Computer Science) PhD student Chandan Singh) with Dr. Aaron Kornblith and other ER doctors at UCSF and other places, and the second a collaboration between my team (stats PhD student Tiffany Tang and postdoc Ana Keney) with doctors and biostatistics researchers Ehsan Irajizad, Johannes Fahrman, Sam Hanash and others at MD Anderson Cancer Center.

Behr: Why is PCS particularly relevant for AI in medicine?

Yu: Because medicine has high stakes - people's lives are on the line. The uncertainty in the data analysis process to design a data-driven AI algorithm in medicine is most of the time underestimated significantly and reality check of the model or algorithm is often not adequately done. As a result, positive treatment effects for treatments are exaggerated from even randomized clinical trials (for which data cleaning and algorithm choice cause unaccounted for uncertainty in the traditional statistical framework) to pass FDA (Food and Drug Administration, US federal agency) approval when they should not have. Obviously, this could do much harm to the patients. With more and more AI algorithms being used or considered for use in medicine, it is high time to more fully account for uncertainty and insist on more rigorous reality-check for models and algorithms as the PCS framework requires, with serious PCS documentation to encourage AI algorithm developers to be vigilant in their process and invite oversight from the user side including regulators, doctors, and patients.

Behr: You have also recently written a book, together with your co-author and former student Rebecca Barter. What is the book about?

Yu: Our book is called Veridical Data Science: The Practice of Responsible Data Analysis and Decision Making. It is guided by the three basic unifying principles of data science, predictability, computability, and stability (PCS) as mentioned earlier. We concentrate on narratives to cultivate critical thinking in the whole data science life cycle, connect data with reality through understanding into the data collection process and domain knowledge, and ground algorithms in the context of many practical real world problems. It takes a holistic approach and aims at training students to solve domain problems that have relevant data.

There are many important issues arising in doing data science in practice that are not addressed in traditional textbooks, but we do: for example, we have a chapter on data cleaning, and we address how to integrate results from multiple algorithms after screening or reality-check candidate algorithms through test set prediction (or cross-validation if data is limited). The book emphasises good coding practices and documentation of all the human judgment calls in a data analysis. It reminds the reader constantly about the future scenario where the current data science work will be used and asks the reader to set aside the test set as the best proxy to mimic this future situation. It introduces PCS prediction intervals to take into account both data cleaning and algorithm choice uncertainties. There is much more - we are about to submit the book to the MIT Press and they will do a review that we will address the comments back. Printing will also take some time and I think the hard copy will be out in 2024 and we can have free on-line copy then for every one. Please watch out for an announcement at my website: https://binyu.stat.berkeley.edu/

Behr: For whom is the book intended? Could it also be used as a textbook for an undergraduate or graduate class?

Yu: It is intended for upper division undergraduate students and beginning graduate students and anyone else who wants to get into data science, for example, students from other disciplines. It goes very well with traditional statistics or ML books since we try not to use many math notations at all. When I teach Berkeley's applied statistics graduate class (215A), I use the book draft to go with David Freedman's book on Statistical Models [4], and as a recommended book also Friedman, Hastie and Tibshirani's Elements of Statistical Learning [5].

Behr: How do you see the interplay between theoretical and empirical understanding of ML and AI methods?

Yu: For me and now, the goal is to solve data problems in the real world. The theoretical and empirical understanding of ML and AI methods is for the same goal: how could this understanding help me solve real problems? Theoretical understanding is always under some conditions that are often uncheckabe in practice. So having a theoretical understanding under idealized conditions of a method does not guarantee it works in real world problems. I prefer to see ample evidence of empirical success of an ML or AI method before I want to do theoretical analysis under idealized assumptions. I think this is a better way to use my energy towards the goal of solving real problems. Because of many empirical successes (and perils) of deep learning models, it is high time for some insightful theoretical understanding and we have seen in recent years some of such understanding into deep learning under the infinite width limit, for example.

Behr: And how do you see the role of statistics in AI research?

Yu: I actually wrote a short article [11] with my PhD student at the time, Karl Kumbier, called Artificial Intelligence and Statistics a few years ago. The frontier of AI is data-driven and hence statistical high level thinking/framing is very important, but it needs to be expanded to cover the whole data science life cycle if we want to get trustworthy AI algorithms - this motivated the development of PCS.

To quote most of the abstract in this paper:

'Artificial intelligence (AI) is intrinsically data-driven. It calls for the application of statistical concepts through human-machine collaboration during the generation of data, the development of algorithms, and the evaluation of results. This paper discusses how such human-machine collaboration can be approached through the statistical concepts of population, question of interest, representativeness of training data, and scrutiny of results (PQRS). The PQRS workflow provides a conceptual framework for integrating statistical ideas with human input into AI products and researches. These ideas include experimental design principles of randomization and local control as well as the principle of stability to gain reproducibility and interpretability of algorithms and data results.'

Behr: If I were a high-school student and I wanted to work in AI in medicine, which degree should I pursue?

Yu: It depends on which level of education you want to get. If you want to find a job after an undergraduate degree, CS (computer science) or stats or DS (data science, Ed.) degrees will serve you well if you also take some basic biology courses. Similarly at the graduate level. The key is to follow the growth model. That is, learn how to learn in college, and keep learning for the rest of your life.

Behr: You are also one of only a few very successful women in the field of statistical ML and AI. Do you have any advice specifically for young female AI-researchers?

Yu: I am not sure 'success' is the right description for a goal even though it is quite common for people to think so. I believe fulfilment is more important and definitely brings more happiness for me. So I would encourage young female and other disadvantaged AI-researchers to find their own callings and their own values and find mentors and peers who share similar values. Different people have different experiences in life and it is useful and productive for research in AI and beyond to bring these experiences and associated values into their research to set meaningful priorities. I hope women believe in themselves with a healthy dose of doubt, and actively find and encourage allies to work together to improve the situation for women and other disadvantaged groups in AI. It takes a village! Women and other disadvantaged groups are very energy-limited as non-dominant groups to change only by themselves long-held habits and explicit and implicit biases, which could take real energy, time, and skills to have a chance to be overcome. I also hope that women do not care too much about the rewards by the system. When one cares too much about the system's rewards, one can get disappointed quickly because the system is pretty noisy right now or often good and substantive work does not get rewarded for a long time. Moreover, it is still much tougher for women in AI, especially with so few in it. In general, we are still in a time in which the system does not reward women as much as it rewards men for the same work. I had decided a long time ago that I would set my own values and try to work according to my values - this way I also control my happiness more, instead of 'outsourcing' it to the 'system'. It has worked for me. If you are interested in learning about my childhood experience during the Cultural Revolution and how it shaped me as a person and researcher, I have written about it in a chapter of an edited book on leadership in statistics and data science [10]. Last but not least, I feel very fortunate to have had the privilege to work with amazing students and postdocs like you at Berkeley and outstanding collaborators in statistics and in sciences including medicine at Berkeley and many other places. The people I have worked with, and the exciting science we created together, made all the difference to me.

Behr: Thank you very much for the interview!

Yu: Thank you for having me! It was fun.

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