From the Apollo programme to the EM algorithm and beyond

Nan Laird is the Harvey V. Fineberg professor of biostatistics (emerita) at the Harvard T. H. Chan School of Public Health, and the winner of the 2021 International Prize in Statistics. In this interview with **Ed Hirschland**, she discusses her career and contributions

Ed Hirschland (EH): In 2016, you won the Statistician of the Year award from the Chicago Chapter of the American Statistical Association. The list of winners is like a who's who in statistics: John Tukey, Frederick Mosteller, George E. P. Box, Bradley Efron, W. Edwards Deming, Janet Norwood and David Cox, among others. It's interesting to note that every winner of the International Prize in Statistics so far, including you, had previously won the Chicago Chapter's award. You came to Chicago and gave a splendid acceptance talk recalling some highlights of your career.

Nan Laird (NL): It was a terrific honour for me. I'm not sure I knew at the time that I was selected by the previous winners, so as you say, it's like a who's who in statistics. It was a great privilege and I very much enjoyed going out to Chicago for a visit. I met a lot of new people, but I was especially pleased to catch up with three young women who had graduated previously from our department at Harvard while I was chair. They were Jolene Birmingham, Denise Scholtens and Mary Morrissey Kwasny. It was such a pleasure to see them. I was so impressed with how well they were doing in their jobs and their professionalism and their success. It was very satisfying and something that every department really should strive for. But I'd also like to talk about a previous visit to Chicago, if I may.

When I was finishing my PhD and applying for jobs – this was in 1975 – I was asked to visit the University of Chicago because they thought they were going to have a faculty position. So I flew out there and I really had a lovely visit. I met many faculty: Steve Stigler, David Wallace and Shelby Haberman stand out. I remember I was so impressed by the tradition they have of meeting up for lunch at the faculty club; I had lunch with them there. I thought it was just a lovely, friendly department, but when I got up to give my speech, I looked around the audience. It was quite well attended, but there were no women. I wasn't really used to that, because most stat departments had at least a good number of female graduate students. I made a joke. At least I thought it was a joke. I said, "Well, I guess the women in this department aren't Bayesians." The title of my talk had Bayes in it, so I thought, "It's a good joke." Well, nobody laughed.

EH: I'm laughing.

NL: I think they didn't get the joke. But anyway, it was early on when you had to write everything on the blackboard. There were no transparencies or overheads or anything like that. So I was writing a few things on the blackboard with my back to the audience and I turned around, and there suddenly appeared several women in the room who were sitting quite prominently in the front row. I think the word got out, and I gave the department high marks for effort. But anyway, over lunch, we all heard the news that the dean didn't approve the position, so I didn't go to Chicago, but I enjoyed my visit very much.

EH: You once mentioned that you weren't funded by Harvard when you started there. What happened? How could you afford the programme? Were you discriminated against in any way?

NL: Harvard wasn't so expensive back then. My parents were very generous. My mother gave me all of her Social Security money in order to go back to school. I didn't get a fellowship, but I did have a research assistantship. I worked with Fred Mosteller on various projects of his. I heard several years later that Harvard's department of statistics had one fellowship to give out the year that I applied, but there was a fellow who applied the same year I did, and they were torn because apparently they thought we were equally strong, but somebody remarked, "Oh, well, she'll just go off and be a housewife, so we wouldn't want to waste the fellowship on her," so they gave it to the guy. Whether or not it's true I don't know, but I knew I wasn't going to go off and be a housewife, so I wasn't insulted. I enjoyed the freedom of paying my own way. I felt it gave me a little bit more leeway than other students to do what I wanted to do. I remember in my third year while I was working on my dissertation, I took off six weeks and went to South America to visit my sister. It would have been a little harder to do if I'd been on a fellowship.

EH: How, if at all, has being a woman in the field affected you? Are there any disadvantages, any pluses?

NL: I guess I always just accepted it as a fact of life. I think there are certainly advantages and disadvantages. Some of the disadvantages are that you may be passed over for fellowships or scholarships or other opportunities just because people have a prejudice about what women are and what they do. To give you an example of that, when I got promoted after many, many years – I got promoted from assistant to associate professor – I was advised by various people I knew that at that point that it was a good idea to go to your department chair, who at that time was Marvin Zelen, and ask, "What do you think my chances are of getting tenure here?" He dodged that bullet very nicely. He said, "You should go and see the dean. That's in his hands." So I went to see, not the full dean, but the academic dean who was in charge of promotions. I asked him what he thought, and to be honest, I was totally shocked at his response. He said, "Well, you have a kid, don't you, Nan?" I said, "Yes." He said, "When I was your age at your point in the profession, I used to work 80 hours a week. I didn't get home until 8:00 at night. I worked weekends and evenings. I was in the lab all that time and I went to meetings. I was asked to give talks at conferences, and I wrote papers." What was shocking to me is he didn't know anything about me except that I had a child. He obviously hadn't read my CV because I'd been to conferences and was asked to give all kinds of talks and had lots of important publications. He just made an assumption about me based on the fact that I was a mother; he assumed it meant I couldn't work as hard as someone who didn't have childcare responsibilities. Anyway, I survived him. He left the faculty before I was promoted to tenure.

But I think that this was sort of a common way that people often reacted to women: "Well, of course women aren't going to be doing all the things that you expect them to do because they have a family, they have children." I have to say that I was actually the first woman who was promoted to full professor at the Harvard School of Public Health who had a family, had children and had a husband. There were a number of other tenured women at the school, but none of them had a family.

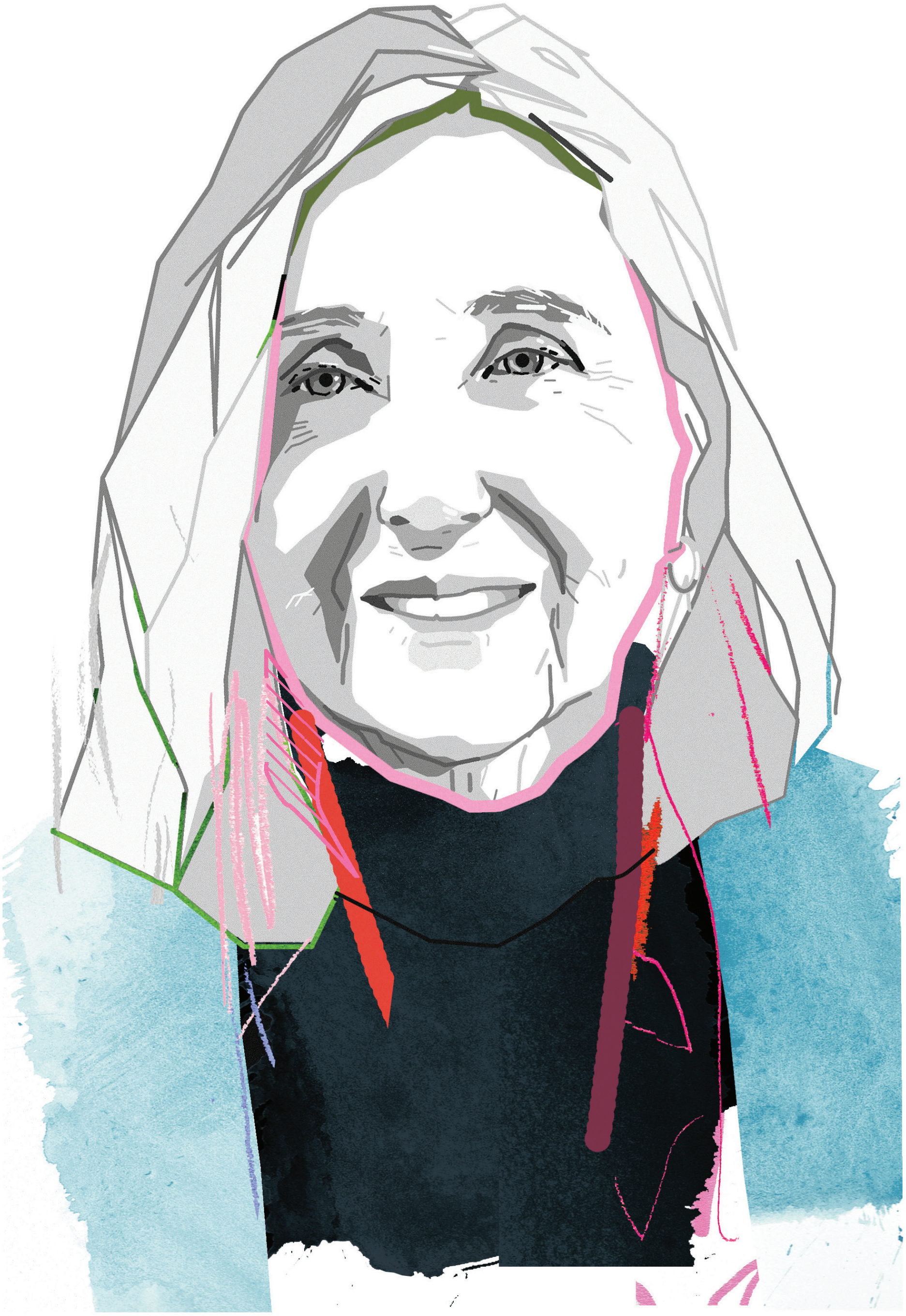

Illustration by Paddy Mills

EH: That's a good opening to talk about your family. Was it hard for you to have kids and work? Was it hard on your husband and the children? Was it hard on you?

NL: Yes, it was hard. I don't think it was hard on my husband because he had a more relaxed attitude towards work than I did. My husband's work allowed him a more flexible schedule so that he was available to take care of the kids when I could not. We had two children, a son who's now in his fifties, and a daughter, now in her forties. I'm very proud of my children. I think it wasn't so easy for them, but I think they've done well in their lives. I think it's important to have a sympathetic partner. That goes for both males and females, to have a partner who can share in the home life and childcare responsibility. Childcare is something that's a problem that I think has not been solved in modern life, and I don't know how it's going to be. It's a problem that needs a lot of work.

EH: I want to ask you how you got started in statistics. I think, if I'm not mistaken, you were in French, maybe?

NL: Here's what happened. As an undergraduate, I went to Rice University. I had really enjoyed maths in high school, and I had done well in maths. When I got to Rice, I thought I would major in maths, but at the time that I went there, it was a disaster for me. It was a huge class. Everybody, whether you were in liberal arts, engineering or hard sciences, everybody took the same maths course.

It was predominantly a male student body, so I would find myself in sections being the only girl. I just felt intimidated about being in the class. I had a hard time. I moved over to French, but I dropped out of my undergraduate studies at Rice, and later I went to the University of Georgia in Athens. By then, I decided I wanted to go do something totally practical, so I thought, "I'll be a computer programmer," because, when I first went to Rice, people had heard about computers, but they weren't mainstream.

But by the time I got to the University of Georgia, people were really beginning to use computers a lot in the classroom and for research. At that time, computing and statistics were in the same department. I went to the chairman, who was a statistician. I said, "I want to study computing." He said, "OK, but I think you should take my course first."

So I took his course, which had nothing to do with computing and little to do with statistics, but it was taught from Herman Chernoff's book on elementary decision theory. I just loved that book. It was an eye-opener to me, the whole idea that you could make rational decisions on how to lead your everyday life based on mathematical formulas. He had one example on whether to take your umbrella to work. It would be based on mathematical formulas and probabilities. I was just so impressed with this book. To this day, I remember how much delight that was to me, reading that book. I immediately changed my major to statistics.

EH: What prompted you to change your focus from statistics to biostatistics?

NL: I don't think of biostatistics as being radically different. It is true we deal with different applications, but the basic idea is pretty much the same. Why did I join a biostatistics department? Well, it was expedient. At the time that I was applying for jobs, I wasn't at all keen about relocating [from Cambridge, Massachusetts]. I was offered a job at the [Harvard] School of Public Health, and I took it. It was expedient, but I haven't regretted it. It has been a tremendous place to be. It's perhaps more applied in its orientation than many statistics departments, and I've really enjoyed that aspect of it.

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EH: You're known in academic circles as one of the finest mentors a student can have. How do you balance mentoring students with your other professional responsibilities?

NL: I found that not hard to balance because I loved mentoring students, and especially the work that I did, the research I was engaged in – we always needed help. I was always trying to recruit students to work with me. I always tried to be engaged with the students at various levels – not only with the research, but with how things were going more generally in their lives. I think I got that from Fred Mosteller, who was one of my professors when I was a graduate student. He was such a wonderful mentor. He saw you as a whole person and he really wanted to help you develop in the profession, not just by writing papers on specific subjects, but learning about everything: how to give speeches, how to make connections with people, how to write papers.

Oh, and I remember once when I had written my very first paper all by myself and I sent it off to *Biometrika*, and I got back a letter which said, "Dear so-and-so, I'm very sorry to inform you that your paper in its present form cannot be accepted by this journal." I was just so horrified by that first line that I just put the whole review in the drawer and didn't look at it. Fred asked me, "Well, what about the review?" I said, "It was a terrible review." He said, "Let me see it."

I gave it to him, and he read the whole thing. That first opening line, that's the way all journals write to you if they intend to publish your paper, but they just want you to make changes. And the more you read, the more you understood, well, actually we can publish it if you do the following three things. So Fred said to me, "This isn't a bad review." He'd read a little more and he said, "In fact, this is a very *good* review." But I did need somebody to explain that to me, because I didn't know. I had to have someone explain to me what a good review and a bad review looked like. That was Fred. He was always willing to help you out.

EH: To the specifically informed public, I'm guessing that your work on prohibiting smoking in aeroplanes is your best-known achievement. Can you tell us how that came to be?

NL: I often get a lot of comments about that. Early on in commercial airline history, aeroplanes were designed so that during flight, they took in fresh air. The fresh air was very cold because they were high up, so it had to be heated, and then it would have to be cooled again to a comfortable temperature. That became extremely expensive to do, especially as the price of fuel went up, so the airlines had redesigned the cabins so that there was no fresh air on the flight, and all the air was recirculated. The air was taken into a filtering system, and then it came out and was recirculated in the cabin.

But of course, the filter didn't take out everything, so there were still plenty of contaminants left in the air after that, and in order to deal with this problem, the airlines decided that they would create a smoking section so that hopefully the environmental tobacco smoke would be concentrated in a particular area of the plane. They typically put that right next to the galley.

The flight attendants really complained about that, because the smoke could become very dense in their primary work area. The flight attendants' union took it up, and the flight attendants of course were in a very good position to get the ear of people in Congress because they knew the Congressmen, who flew frequently. They would talk to them about this issue, and they lobbied very hard to get Congress to take this issue up. Congress did authorise the National Academy of Sciences to undertake a study on the air quality in aeroplanes and the potential health effects.

I was very young at the time; probably Fred Mosteller had recommended me for the job. I was the only statistician on this committee.

Also, it was MDs and engineers and environmental people. There was, however, an epidemiologist, Genevieve Matanoski. Of course, the obvious question from the two of us was: what were the health effects of being exposed to environmental tobacco smoke?

Our committee made some measurements; we calculated the doses for flight attendants; and then Genevieve and I looked through the literature to determine what the health effects were of exposure to passive smoking. This was an era when there were beginning to be quite a few studies on this subject, and the studies were showing that there was a small effect. Most of these studies were done on couples, where one member of the pair was a smoker, and one was not, and then couples where neither spouse smoked. The studies looked at the cancer death rates of the non-smoker in the smoker/non-smoker couples and compared it with the rate among the non-smoker/non-smoker couples. They did find small but clear evidence of an elevation of lung cancer death rates in the spouses of smokers.

At the end of this study – and of course we looked at lots of different components of the problem – the committee agreed that the only way you could reasonably bring the environmental tobacco smoke down to an acceptable level was to eliminate smoking on aeroplanes completely. That was our primary and first recommendation. Sure enough, Congress voted in a ban just a few months later, and I think many people were worried about feedback from the tobacco industry, but it never materialised. They couldn't get off the ground. Everybody was happy about it. Congress was happy, the non-smokers were very happy, and the airlines were happy, because it was a very inexpensive solution to an expensive problem for them.

EH: Your paper before the Royal Statistical Society in late 1976, "Maximum Likelihood from Incomplete Data via the EM Algorithm", is one of the most cited in all of science. One blog rates it in the top 10 statistics papers in the last 50 years. Please tell us about EM in lay terms. What led up to your paper? What are some applications that might be of interest to the layperson?

NL: EM is short for "expectation maximisation". This is a computational algorithm which is used in a setting where the data that you have in hand are incomplete. This notion of incomplete can be extremely general, and the missing data can even be fabricated, as a way of making the computations simple. I'll give some examples of that. When you're in the setting where data are incomplete, the computations can be sometimes very difficult, and what the EM algorithm does is to try and simplify the computations for this setting, and it does so in two distinct steps. One is the E-step, and one is the M-step.

What makes it so attractive as a computational algorithm is that the two steps are usually very familiar statistical computations, and they're often easy to do. At the E-step, what you're essentially doing is calculating the expectation of the data that are missing, and then, at the M-step, you assume that you *have* the data that are missing, and you do the full maximum likelihood as if you have complete data. Exactly how this works depends upon what type of incompleteness you have.

Regarding the origin of the EM, the ideas behind EM and many examples of EM were kicking around in the literature for at least 25 years before we wrote the paper. One of the earliest references we found from the 1950s was on estimating gene frequencies in randomly mating populations. EM had been used in many different papers, but it hadn't ever been recognised that all of these separate uses are actually part of the same general problem. And of course, we gave it a name.

Now, let me say something about examples that people might be interested in. The most obvious one that will be familiar to most people is that if you do a survey to get people to tell you who they're going to vote for, a lot of people don't respond. If you base your predictions just on the people who respond, you're likely to be very far off from the vote. I wrote a paper with a former student, Stuart Baker. We used data from the very famous presidential election in 1948, where the newspapers were so confident that Dewey was going to win, they had already printed up the papers before the results were out. The most famous headline says, "Dewey Defeats Truman." The day after the election, they had Truman holding up a photograph of the paper with that headline, with a big grin on his face.

What we did was to look at the data from the actual polls that were used, and there are additional data about people that turned out to be important: their economic class. There were four different levels of economic class. Another thing that was important was the time the poll was done. There were data from four successive polls that were done. Stuart Baker and I used these actual data, and we did a big model on response and how it might be related to your economic class, and also to the non-response itself, as well as the time of the survey.

We used the EM algorithm in this example. Essentially the way we did it was to build this big model that's estimating the probability that you would vote for one or the other, Dewey or Truman, given information on whether or not you responded and what your economic class was and what survey you were in. Given that model, you could predict, for the non-respondents, who they would vote for. Then you would treat those predictions as if they were actual data and refit your model. It iterated around with the EM and we found that using various different models, you could obtain estimated percentages that were actually much closer to the actual vote. Of course, this was in 1948, and what people did at the time and even for a long time afterwards – they just used information on respondents. But now, I think many of the polling companies are much more sophisticated in handling the non-responses.

I always tried to be engaged with the students – not only with the research, but with how things were going more generally in their lives

EH: Can you tell us some of your favourite experiences as a biostatistician?

NL: Besides teaching and working on research with colleagues, I enjoyed consulting. I remember one problem that I enjoyed a great deal was working with a law firm that had been engaged by Johnson & Johnson to look at an advertising campaign mounted by Bristol Myers Squibb. The two products involved were Tylenol and Excedrin. Tylenol and Excedrin are basically the same compound, except that Excedrin has caffeine added to it.

Bristol Myers Squibb had done some experiments designed by statisticians for the purpose of evaluating which compound was more effective in alleviating chronic headaches. Because this was done for the FDA [Food and Drug Administration], it was also a requirement that you needed to include a placebo in the study, so there were three compounds being compared.

They had a group of subjects who suffered from chronic migraines, so they wanted to use these subjects on more than one occasion. They thought that the comparisons of two different agents on the same subject would be much more efficient than using two different subjects. They were reluctant to use the same subject three times because they felt many subjects might not want to participate if they knew one of the compounds was a placebo.

What they did was have subjects take two compounds only, but since there were three under study, not all subjects got all three compounds; this is what's known as a balanced incomplete block design. The block here is a person. It's a very classical design, and it's done when you think that you really have limitations as to how many drugs a person can take. It was conventional at the time to do this, because it's easy to analyse if you use only one type of information. If you think about it, there are two types of information. If you want to compare Tylenol and Excedrin, the simplest thing to do is to take people who took both Tylenol and Excedrin and just make that simple comparison between the two observations made in that group. Everybody got the same two compounds, and so it's simple to make the comparison. That's called the within-subject comparison.

But you're wasting information, because a lot of people out there got Tylenol and a placebo, and then a lot of other people got Excedrin and a placebo, so you could compare the people who got Tylenol and a placebo with the people who got Excedrin and a placebo. That's called the between-block information. It's been conventional to discard the between-block information, because it's not very efficient unless the correlation between your two responses is high.

When the paper was presented to the FDA, they did the conventional thing and just used the within-subject comparisons. That suggested that Excedrin gave better relief than Tylenol. When I was asked to look at the paper, I was puzzled about, "Well, why not look at the whole picture and use both the within-subject and the between-subjects data?" The first thing we did was to look at the correlation, and the correlation was 0.4, which is a reasonable correlation for these types of data.

It had been shown in a previous paper that there was a lot of information in the between-block analysis if the correlation was higher than 0.4, so immediately we did the full analysis that combined the information from the within block and the complete block, and sure enough, it turned out that the advantage for Excedrin disappeared. This was a fun case, and it was written up in the *Wall Street Journal* that the judge was very impressed by a sophisticated statistical analysis – without going into any further details than that. Of course, Bristol Myers Squibb didn't like it so well, but Johnson & Johnson was pleased.

A lot of things I've done have given me satisfaction. Banning smoking on aeroplanes, developing the EM algorithm. Plus, the work with Jim Ware

EH: During the last part of your career before you retired, you worked in statistical genetics. How did that come about and what were your contributions there?

NL: I had always actually been interested in statistical genetics because some of the earliest papers using the EM algorithm were examples from statistical genetics. Before the Human Genome Project, it was not simple to measure genetic variants. Consider the haemoglobin gene and the A, B, O blood-type classification. You could easily determine a person's blood group (A, B, AB or O) from a blood test; but it didn't show you what your genetic make-up was at the haemoglobin gene. At the haemoglobin gene, you could have one of three different genetic variants: A, B or O.

The EM algorithm was used early on in that kind of setting to estimate your genetic variants based on your observed blood test. I was very interested in that, and then I did notice – I guess this was around 2000 when the Human Genome Project was undertaken – that people were beginning to use genetic data in health and medicine studies and incorporate it into statistical analyses. I was very curious about that, because people really weren't doing much of that at the School of Public Health, and I thought it would be important to find out what that was all about.

I took a sabbatical year and visited a psychiatric genetics lab at MIT, and also the Broad Institute. I got onto a project there which involved a new method for analysing genetic data, which was very popular at the time. It was called the transmission disequilibrium test. The idea was simple, really, and intuitive. You take a group of people with a certain disorder or disease, and you look at the genetic make-up of the person and their two parents. This was a simple test designed to determine if there was a relationship between the information at this genetic locus and the disease. You just looked to see what genes were transmitted from the parents to the diseased offspring.

You know from Mendel's law what the probability of an offspring's genotype is. If there are far more of a particular variant being transmitted than you could calculate just assuming Mendel's law, that would suggest an association. It was a very popular, simple test, but there were many other situations where people were trying to apply it, and I thought that it was a good place for statisticians to make contributions. For example, if you didn't have the genetic data on the parents but you had genetic data on siblings, could you reconstruct the test? What if the outcome was not just diseased offspring, but suppose you had a measured variable like lung function or height, how to generalise that? I recruited a postdoc, Christoph Lange, and we worked on several different generalisations of this simple test.

EH: What part of your history has given you the most satisfaction? In other words, of all your enormous accomplishments under your belt, which do you think are the most important to you?

NL: A lot of things that I've done have given me a lot of satisfaction. Banning smoking on aeroplanes, developing the EM algorithm, and just the pleasure of working with students and seeing them grow and thrive and take off

Edward C. Hirschland is president of The Landhart Corporation, a consultancy headquartered in Chicago, Illinois. He has been a board member of the Chicago Chapter of the American Statistical Association since 1980, and has twice served as chapter president.

and develop their own interests and their own careers. Plus, the work with Jim Ware, which we have yet to talk about.

Jim Ware came to the school a few years after I did. I was there maybe three or four years before he came. He was recruited to work on an ongoing study in environmental health. This was the Harvard Six Cities study. This study had enrolled some 10,000 children and adults of various ages in 1974, and they followed them for up to six years. They took measurements of a lot of different health outcomes, but the one that Jim was most interested in at the time was the pulmonary function.

The primary goal of this study was to see whether air pollution affected the growth of children's lung function. They used a longitudinal design because they were interested in how children changed over time and whether the air pollution present in their environment affected the change. The children lived in six different cities which had different levels of air pollution in the beginning. Of course, over time, those levels tended to regress to the mean so that by the end of the studies, the differences in air pollution were not quite so pronounced.

It was a complicated study to analyse for many reasons. First of all, children were measured at all different ages so that age at intake was not necessarily the same. Secondly, different children had different measurements because some children entered the study later than others. Thirdly, it wasn't clear what the correct model was for growth of lung function. There had been a lot of different studies and thoughts about how you might make adjustments for covariates, but there wasn't a standard model.

Jim wanted to talk with me about it because he was aware at the time of something called a simple two-step approach. In the two-step approach, you would first take the data on each child with up to six measurements and you would fit a growth curve to that child, and then you would analyse the parameters of that growth curve. In a simple case, you'd fit a straight line and you would analyse the intercepts and slopes. But there were a lot of issues with that, and it was not terribly efficient, so Jim felt that the work that I had done on the EM algorithm and variance components was a natural here.

We developed a model that could be used in this setting, and it is sometimes called the linear mixed model. It applies very broadly, not just to longitudinal data as we typically think of it, but many other methods, and we showed how the EM algorithm could be used to estimate the parameters. It was quite a successful and popular paper. I think part of the reason was that we went out of our way to use very straightforward notation. We used the notation of a simple linear regression, which many statisticians are familiar with. I think what we did was make our approach much more available to statisticians than some of the more complicated approaches that had been available otherwise.

Then, after the success of this paper, Jim and I worked with a lot of different students on refinements of this and how to deal with special extensions and alternative formulations. Some of the people to mention here are Nancy Cook, Dan Stram, Fong Wang Clow, Garrett Fitzmaurice, Joe Hogan, Christl Donnelly, Stuart Lipsitz and Nick Horton. It was a big project that spanned several years and led to the teaching of a course and then the development of a book from the notes from the course.

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EH: Do you have any advice for a budding statistician?

NL: One thing I would suggest is do what you like to do and choose a profession that's going to allow you to succeed in doing what you want to do. This advice arose for me out of counselling a lot of junior faculty members who felt they should be writing papers, but they really hated doing research and writing papers. I would say to them, "Look, you're not going to succeed trying to do something you don't like." It's important to do something that you enjoy doing because you're so much better at doing things that you enjoy. That's my advice to young statisticians. Enjoy doing what you like to do and concentrate on that, and you'll be successful if you enjoy what you're doing.

EH: Great advice. Can I ask you about one more thing? Your role in the Apollo moon project?

NL: When I finished my undergraduate work at the University of Georgia, I had a degree in statistics, and I moved to Cambridge. My first husband was a student at Harvard at the time, and I needed to get a well-paid job. I applied at the Draper Lab, which is part of MIT. The Draper Lab was developing inertial guidance systems for the Apollo project which sent the first person to the moon.

The idea was you could make certain navigation measurements in flight, but you needed to update your location during the flight so you wouldn't miss the moon. People were using Kalman filtering at the time for the updating. Basically, I was hired as a programmer. I ran many, many programs, assuming different inputs and different times of measurements and making various modelling assumptions. Basically, it was like simulations. There was a truck driving this guidance system around all over California, and it would occasionally make location measurements. Then we would update those measurements and we would make predictions about where the truck went next, and they would then tell us about what corrections need to be made.

I didn't really understand all the details of the Kalman filtering model, but I knew that the work that we were doing was for the Apollo moon shot. But I was just a programmer. I would have to say that I don't feel I made unique contributions to the project, but I did learn something about Kalman filtering, which is a Bayesian method for updating systems that most statisticians don't know about.

EH: And your project made it to the moon.

NL: And my project made it to the moon. Yep. I decided after that – I worked there for two years – that I would like to go back into statistics and leave being a computer programmer.

EH: I think you also proved that women could be Bayesians.

NL: That's right, we did. ■

Disclosure statement
The author declares no competing interests.