So, hi everyone. Since we’re still waiting for people to join, I will first give a brief introduction to Matthew here. First, it’s my honor to introduce Dr. Matthew Stevens as our seminar speaker today. And Matthew is a professor from human genetics and the statistics at University of Chicago. In the past, his research mainly focused on developing new statistical methods for especially genetic applications. Including, for example, GWAS association studies and fine mapping and populations genetic variants. And today, he will give a talk on some recently developed empirical Bayes methods for the estimation for normal mean models that will introduce the (indistinct) properties such as shrinkage, sparsity or smoothness. And he will also discuss how to apply these methods to a range of practical applications. Okay, so let’s wait for another minute and then I will hand it over to Matthew. So I will hand it over to Matthew from here. Let’s welcome him. Thank you very much. It’s a great pleasure to be here.
and to get the opportunity to present my work to you today. So I guess just a little bit of background. So few years ago...

Well, I guess, I’ve been teaching sparsity and shrinkage for a while, and it struck me that, in practice, people don’t really use many of these ideas directly...

At least not the empirical Bayse versions of these ideas directly in applications. And so, I’m wondering why that is. And partly, it’s the lack of...

User-friendly, convenient methods for applying these ideas. So I’ve been trying to think about how we can make these powerful ideas and methods more generally applicable or easily applicable in applications. These ideas have been around quite some time. But I think we’ve made some progress on actually just making them a bit simpler... maybe

and simpler to apply in practice, so I’m gonna tell you about those today.

Oh, sorry. It’s not advancing, let me see. Okay, so yeah, kind of related to that, the normal means problem is something we teach quite frequently.
It’s not hard to teach but it always struck me whenever I was taught it that it looked like a kind of toy model that statisticians kind of think up to teach students things but never actually use. And then suddenly, I had an epiphany and realized that it’s super useful.

So here’s the normal means model. The idea is that you’ve got a bunch of observations, XJ, that you can think of as noisy observations of theta J and they have some variance. I’m going to allow each variance to be different. But an important point is that we’re going to assume that the variance is unknown, which sounds a bit weird but in applications, we’ll see that there are reasons why we might think that’s an okay assumption in some applications.
Okay, so the basic idea is you've got a bunch of measurements that are noisy measurements of sum theta J and they have known variance, so they have known precision essentially, and you want to estimate the Theta Js. And, of course, the MLE is just to estimate see theta J by its corresponding measurement, XJ.

It was a big surprise, I think. I wasn’t around at the time but I believe it was a big surprise in 1956 when Stein showed that you can do better than the MLE, at least in terms of average squared error expected square there.

And so, there are many different ways to motivate or... To motivate this result.

And I think many of them end up not being that intuitive.

It is quite a surprising result in generality but I think...

So the way I like to think about the intuition for why this might be true, it’s not the only intuition it’s one intuition for why this might be true, is to have an empirical Bayse thinking to the problem.

And so, to illustrate this idea, I use a well-worn device, at this point,
which is baseball batting averages.

Efron certainly has used this example before to motivate empirical Bayes ideas.

This particular example comes from...

The data come from this block here, that I referenced at the bottom, which I quite like as an explanation of basic ideas behind empirical Bayes.

So this histogram here shows a bunch of basic baseball batting averages for a particular season in 1900.

You don’t need to know very much about baseball to know what’s going on here.

Essentially, in baseball, you go and try and hit a ball and your batting average is the proportion of the time you end up hitting the ball. And a good baseball batting average is around 0.3 or so.

And in a professional baseball, no one’s really going to have a batting average of zero 'cause they wouldn’t survive.

But empirically, there were some individuals in this season who had a batting average of zero, that is they completely failed to hit the ball every time they went up to bat.

And there were some people who had a batting average of above 0.4,
which is also completely unheard of in baseball.

Nobody has a batting average that high, so what’s going on here? Well, it’s a simple explanation is that these individuals at the tails are individuals who just had a few at-bats. They only went and attempted to hit the ball a small number of times. And so, maybe these individuals only had two bats and they missed it both times, they got injured or they weren’t selected, or, for whatever reason, they didn’t hit the ball many times...

They didn’t go to bat many times and so, their batting average was empirically zero. Think of that as the maximum likelihood estimate. But if you wanted to predict what they would do, say next season, if you gave them more at bats in the long run, zero would be a bad estimate for obvious reasons. And the same applies to these individuals up here with very big batting averages. They also had relatively few at-bats and they just happened to hit it above 0.4 of the time.
166 00:07:38.300 --> 00:07:39.490 out of the at-bats.
167 00:07:39.490 --> 00:07:41.370 And the individuals who had lots of at-bats are
168 00:07:41.370 --> 00:07:43.770 all in the middle here.
169 00:07:43.770 --> 00:07:45.487 So these are binomial observations, basically,
170 00:07:45.487 --> 00:07:47.193 and the ones who have small N are
171 00:07:48.690 --> 00:07:50.000 more likely to be in the tails
172 00:07:50.000 --> 00:07:50.930 and the ones we’re big N are
173 00:07:50.930 --> 00:07:53.470 all going to be around in the middle here.
174 00:07:53.470 --> 00:07:54.303 So what would we do?
175 00:07:54.303 --> 00:07:55.450 What would we want to do
176 00:07:55.450 --> 00:07:57.230 if we wanted to estimate,
177 00:07:57.230 --> 00:07:59.340 for example, for this individual,
178 00:07:59.340 --> 00:08:01.190 their batting average for next season?
179 00:08:01.190 --> 00:08:04.344 If we were gonna predict what they were gonna get.
180 00:08:04.344 --> 00:08:08.100 Well, we would definitely want to estimate
181 00:08:08.100 --> 00:08:11.683 something closer to the average batting average than 04.
182 00:08:12.840 --> 00:08:14.220 That’s the intuition.
183 00:08:14.220 --> 00:08:17.620 And one way to frame that problem is that...
184 00:08:17.620 --> 00:08:18.453 So sorry.
185 00:08:18.453 --> 00:08:20.420 So this is the basic idea of shrinkage.
186 00:08:20.420 --> 00:08:22.680 We would want to shrink these estimates towards,
187 00:08:22.680 --> 00:08:24.230 in this case, towards the mean.
188 00:08:25.300 --> 00:08:26.823 So how are we gonna do that?
189 00:08:26.823 --> 00:08:30.748 Well, one way to think about it is...
190 00:08:30.748 --> 00:08:33.300 Sorry, let me just...
191 00:08:33.300 --> 00:08:34.133 Yes.
192 00:08:35.630 --> 00:08:37.330 Sorry, just getting my slides.
193 00:08:37.330 --> 00:08:40.230 Okay, so here, the red line represents
some underlying distribution of actual batting averages. So conceptually, some distribution of actual batting averages among individuals in this kind of league. So the red line, in a Bayesan point of view, kind of represent a sensible prior for any given individual’s batting average before we saw that data. So think of the red line as representing the variation or the distribution of actual batting averages among players. And in fact, what we’ve done here is estimate that red line from the data. That’s the empirical Bayes part of empirical Bayes. The empirical part of empirical Bayes is that the red line which we’re going to use as a prior for any given player was actually estimated from all the data. And the basic idea is because we know what the variance of a binomial distribution is, we can kind of estimate what the overall distribution of the underlying piece in this binomial look like, taking account of the fact that the histogram is a noisy observations of that underlying P. Every bat...
 Basically, every estimated batting average is a noisy estimate of the true batting average with the noise depending on how many at-bats they have. So once we’ve estimated that red line, that prior, we can compute the posterior for each individual based on that prior. And when we do that, this is a histogram of the posterior means. So these are, if you like, shrunken estimates of the batting average for each individual. And you can see that the individuals who had zero at-bats got shrunk all the way over somewhere here. And that’s because their data really... Although, the point estimate was zero, they had very few at bats. So the information in that data are very slim, very little information. And so, the prior dominates when you’re looking at the posterior distribution for these individuals. Whereas individuals in the middle who have more at-bats, will have the estimate that is less shrunken. So that’s gonna be a theme we’ll come back to later. So how do we form...
252 00:10:57.490 --> 00:10:58.720 That’s a picture.
253 00:10:58.720 --> 00:11:00.380 How do we formulate that?
254 00:11:00.380 --> 00:11:02.570 So those were binomial data,
255 00:11:02.570 --> 00:11:04.790 I’m gonna talk about normal data.
256 00:11:04.790 --> 00:11:07.700 So don’t get confused by that.
257 00:11:07.700 --> 00:11:09.730 I’m just going to assume normality could do
258 00:11:09.730 --> 00:11:11.950 the same thing for a binomial,
259 00:11:11.950 --> 00:11:16.390 but I think the normals a more generally useful
260 00:11:16.390 --> 00:11:18.833 and convenient way to go.
261 00:11:19.960 --> 00:11:22.060 So here’s a normal means model again
262 00:11:23.060 --> 00:11:24.530 and the idea is that that
263 00:11:24.530 --> 00:11:26.370 we’re going to assume that thetas come
264 00:11:26.370 --> 00:11:28.530 from some prior distribution, G,
265 00:11:28.530 --> 00:11:30.760 that was the red line in my example,
266 00:11:30.760 --> 00:11:32.580 and we’re going to estimate G
267 00:11:32.580 --> 00:11:34.240 by maximum likelihood essentially.
268 00:11:34.240 --> 00:11:36.333 So we’re going to use all the X’s,
269 00:11:36.333 --> 00:11:38.110 integrating out theta
270 00:11:38.110 --> 00:11:40.430 to obtain a maximum likelihood estimate for
G.
271 00:11:40.430 --> 00:11:42.180 That’s stage one,
272 00:11:42.180 --> 00:11:43.800 that’s estimating that red line.
273 00:11:43.800 --> 00:11:44.450 And then stage two is
274 00:11:44.450 --> 00:11:46.160 to compute the posterior distribution
275 00:11:46.160 --> 00:11:48.110 for each batting average,
276 00:11:48.110 --> 00:11:50.720 or whatever theta J we’re interested in,
277 00:11:50.720 --> 00:11:52.950 taking into account that estimated prior
278 00:11:52.950 --> 00:11:55.904 and the data on the individual J.
279 00:11:55.904 --> 00:12:00.560 So that’s the formalization of these ideas.
280 00:12:00.560 --> 00:12:02.636 And these posterior distributions are gonna
be shrunk
towards the prior or the primary.
So what kind of...
So I guess I’ve left unspecified here,
what family of priors should we consider for G?
So a commonly used prior distribution is
this so-called point-normal,
or sometimes called spike and slab prior distribution.
And these are...
Sorry, I should say,
I’m going to be thinking a lot about problems
where we want to induce sparsity.
So in baseball, we were shrinking towards the mean
but in many applications,
the natural point towards
natural prime mean, if you like, is zero
in situations where we expect effects
to be sparse, for example.
So I’m gonna be talking mostly about that situation,
although the ideas are more general.
And so, I’m going to be focusing
on the sparsity inducing choices of prior family.
And so, one commonly used one is this point normal
where there’s some mass pi zero,
effectively at zero,
and then the rest of the mass is
normally distributed about zero.
So the commonly used one.
In fact, it turns out, and this is kind of interesting I think, that it can be easier to do the computations for more general families. So for example, just take the non-parametric family that’s the zero-centered scale mixture of normal, so we’ll see that in it, which includes all these distributions of special cases. It’s nonparametric. It includes a point-normal here. It also includes the T-distribution, the Laplace distribution, the horseshoe prior, if you’ve come across that, the zero-centered scale mixture of normals and the surprise is that it turns out to be easier, in some sense, to do the calculations for this family, this more general family than this narrow family, partly because of the convex family. So you can think of this as a kind of a convex relaxation of the problem. So all the computations become... The optimizations you have to do in the simplest case become convex when you use this family. So let me say a bit more about that.
for the non-parametric.

How do we actually do these non-parametric computations? Well, we actually approximate the non-parametric computation using a grid idea.

So here’s the idea. We modeled our prior, as a mixture of... I like to think of this K as being big.

A large number of normal distributions. All of these normal distributions are centered at zero, that’s this zero here, and they have a different variance.

Some of them have very small variances, perhaps even one of them has a zero variance, so that’s the point mass at zero.

And the variance is sigma...

Think of getting gradually bigger until the last Sigma squared K is very big. So we’re just gonna use a lot of them.

Think of K as being, let’s say 100 or 1,000 for the...

In practice, we find 20 is enough but just think of it as being big and spanning a lot of different variances, going from very, very small, to very, very big.

And then, estimating just comes down to estimating these pis,
these mixture proportions.
And that, then of course, is a finite dimensional optimization problem in the normal means model, it’s a convex...
Well actually, for any mixture, it’s a convex problem,
and so there are efficient ways to find the MLE for pi, given the grid of variances.
So let’s just illustrate what’s going on here.
Here’s a grid of just three normals.
The one in the middle has the smallest variance, the one over here has the biggest variance.
And we can get a mixture of those, looks like that.
So you can see this is kind of a spiky distribution.
but also with a long tail,
even with just a mixture of three distributions.
And so, the idea is that you can get quite a flex...
It’s a flexible family by using a larger number of variances than three.
You can imagine you can get distributions that have all sorts of spikiness and long-tailed behavior.
So maybe just to fill in the details here;
with that prior as a mixture of normals, the marginal distribution, P of X, integrating out theta is analytic.
because the sum of normals is normal.

So if you have a normally distributed variable and then you have another variable that's a normal error on top of that, you get a normal.

So the marginal is a mixture of normals that's very simple to work with and estimating pi is a convex optimization problem.

You can do it. You can do an EM algorithm but convex methods, as pointed out by Koenker and Mizera, can be a lot more reliable and faster.

Okay, so let's just illustrate those ideas again.

Here's a potential prior distribution and here's a likelihood.

This is an estimate... Think of this as a likelihood for theta J in a normal means model.

So what does the posterior look like when we combine this prior, the black line, with this likelihood, the red line?

It looks like this green line here.
So what you can see is going on here is that you get shrinkage towards the mean, right?

But because the black line is long-tailed because of the prior in this case has a long tail, and because the red line...
The likelihood lies quite a ways in the tail, the spiky bit at zero doesn’t have very much impact because it’s completely...

Zero is basically inconsistent with the data and so the posterior looks approximately normal.

It’s actually a mixture of normals but it looks approximately normal ‘cause of weight and there, zero is very, very small.

Whereas if a...

Here’s a different example, the black line is covered by the green line this time because it’s...

So I plotted all three lines on the same plot here.

The black line is...

Think of it as pretty much the green line.

It’s still the same spiky prior but now the likelihood is much flatter.

The XJ is the same.

Actually, it’s one and a half but we have an SJ that’s much bigger.

So what happens here is that the prior dominates because the likelihood’s
relatively flat, and so the posterior looks pretty much like the prior and you get very strong shrinkage. So think of this as corresponding to those individuals who had very few at-bats, their data are very imprecise, and so their posterior, the green line, looks very like the prior, the black line. Okay, so we're gonna shrink those observations more. So the key point here, I guess, is that the observations with larger standard error, larger SJ get shrunk more. I should say "larger standard deviation" get shrunk more. Here's another intermediate example where the red line... The likelihood’s kind of not quite enough. It illustrates the idea that the posterior could be bimodal because the prior and the likelihood are indifferent, have weight in different places. So you can get different kinds of shrinkage depending on how spiky the prior is, how long-tailed the prior is, how flat the likelihood is etc. So obviously the shrinkage, the amount of shrinkage you get,
depends on the prior, \( G \), which you're gonna estimate from the data. It also depends on the standard error or the standard deviation, \( S_J \). And one way to summarize this kind of behavior, the shrinkage behavior, is to focus on how the posterior mean changes with \( X \).

So we can define this operator here, as the \( X \) posterior mean of \( \theta_J \) given the prior and its variance or standard deviation and that we observed \( X_J \) is equal to \( X \). I'm gonna call this the shrinkage operator for the prior, \( G \), and variance, \( S \) for standard deviation, \( S \). Okay, so we could just plot some of these shrinkage operators. So the idea here is... Sorry, this slide has \( B \) instead of \( X \). Sometimes I use \( B \) and sometimes I use \( X \). I've got them mixed up here, sorry. So these different lines here correspond to different priors.

So these different lines here correspond to different priors.
00:20:50.350 --> 00:20:53.590 So this prior here shrinks very strongly to zero.
00:20:53.590 --> 00:20:57.000 This green line shrinks very strongly to zero
00:20:57.000 --> 00:21:00.900 until B exceeds some value around five,
00:21:00.900 --> 00:21:02.900 at which point it hardly shrinks at all.
00:21:04.010 --> 00:21:06.580 So this is kind of a prior that has
00:21:06.580 --> 00:21:08.783 kind of a big spike near zero.
00:21:09.790 --> 00:21:11.333 But also a long tail,
00:21:11.333 --> 00:21:14.880 such that when you get far enough in the tail,
00:21:14.880 --> 00:21:16.780 you start to be convinced
00:21:16.780 --> 00:21:18.100 that there’s a real signal here.
00:21:18.100 --> 00:21:18.990 So you can think of that
00:21:18.990 --> 00:21:20.010 as this kind of...
00:21:20.010 --> 00:21:22.105 This is sometimes called...
00:21:22.105 --> 00:21:24.210 This is local shrinkage
00:21:24.210 --> 00:21:25.509 and this is global.
00:21:25.509 --> 00:21:28.690 So you get very strong local shrinkage towards zero
00:21:28.690 --> 00:21:30.860 but very little shrinkage
00:21:30.860 --> 00:21:32.600 if the signal is strong enough.
00:21:32.600 --> 00:21:34.090 That kind of thing.
00:21:34.090 --> 00:21:35.180 But the real point here is that
00:21:35.180 --> 00:21:36.980 by using different priors,
00:21:36.980 --> 00:21:39.440 these different scale mixture of normal priors,
00:21:39.440 --> 00:21:43.460 you can get very different looking shrinkage behaviors.
00:21:43.460 --> 00:21:45.390 Ones that shrink very strongly to zero
00:21:45.390 --> 00:21:46.420 and then stop shrinking
00:21:46.420 --> 00:21:50.313 or ones that shrink a little bit all the way, etc.
00:21:50.313 --> 00:21:54.610 And so, if you’re familiar with other ways
00:21:54.610 --> 00:21:56.270 of doing shrinkage analysis,
00:21:56.270 --> 00:21:57.800 and this is one of them,
or shrinkage, is to use a penalized likelihood. Then you can try and draw a parallel and that’s what I’m trying to do here. Draw a parallel between the Bayesian method and the penalized likelihood-based approaches to inducing shrinkage or sparsity. Another way to induce shrinkage is to essentially... This is the kind of normal log likelihood here and this is a penalty here. You add for this. This could be an L1 penalty or an L2 penalty or an L0 penalty, or some other kind of penalty. So there’s a penalty function here. And you define the estimate as the value that minimizes this penalized log likelihood. Sorry, yeah, this is a negative log likelihood. Penalized least squares, I guess this would be. Okay, so now eight is a penalty function here and Lambda is a tuning parameter that says how strong, in some sense, the penalty is. And these are also widely used to induce shrinkage, especially in regression contexts. And so, here are some commonly used shrinkage operators, corresponding to different penalty functions. So this green line is what’s called
the hard thresholding, which corresponds to an L0 penalty. If you don’t know what that means, don’t worry. But if you do, you make that connection. At the red line here is L1 penalty or soft thresholding. And these two other ones here are particular instances of some non-convex penalties that are used in regression context, particularly in practice. And I guess that the point here is that, essentially, different prior distributions in the normal means model can lead to shrinkage operators, shrinkage behavior that looks kind of similar to each of these different types of penalty. So you can’t actually mimic the behavior exactly. I’ve just... Or actually, my student, (indistinct) Kim, chose the priors to visually closely match these but you can’t get... Some of these have kinks and stuff that you can’t actually, formally, exactly mimic but you can get qualitatively similar shrinkage behavior from different priors as different penalty functions. So you should think about the different priors
as being analogous to different penalty functions.

And so, the key...

How does EB, empirical Bayes shrinkage, differ from, say, these kinds of penalty-based approaches,

which I should say are maybe more widely used in practice?

Well, so shrinkage is determined by the prior, $G$,

which we estimate in an empirical Bayes context

by maximum likelihood.

Whereas in typical shrinkage...

Sorry, typical penalty-based analyses,

people use cross validation to estimate parameters.

And the result is that cross-validation is fine

cross-validation is fine for estimating one parameter

but it becomes quite cumbersome

to estimate two parameters,

and really tricky to estimate three or four parameters

’cause you have to go and do a grid of different values

and do a lot of cross-validations

and start estimating all these different parameters.

So the point here is really

because we estimate $G$ by maximum likelihood,

we can actually have a much more flexible family in practice

that we can optimize over more easily.
It’s very flexible, you can mimic a range of penalty functions so you don’t have to choose whether to use L1 or L2 or L0. You can essentially estimate over these non-parametric prior families. Think of that as kind of deciding automatically whether to use L0, L1, L2 or some kind of non-convex penalty, or something in between. And the posterior distribution, of course then, another nice thing is that it gives not only the point estimates but, if you like, it also gives shrunken interval estimates which are not yielded by a penalty-based approach. So I guess I’m trying to say that there are potential advantages of the empirical Bayse approach over the penalty-based approach. And yeah, although I think, people have tried, particularly Efron has highlighted the potential for empirical Bayse to be used in practical applications, largely in the practical application. So I’ve seen empirical Bayse shrinkage hasn’t really been used very, very much. So that’s the goal, is to change that.
So before I talk about examples, I guess I will pause for a moment to see if there are any questions. And I can’t see the chat for some reason so if anyone...

So please unmute yourself if you have a question.

- I don’t think people are (indistinct) every question in the chat.

Okay, thank you.

It’s all clear.

I’m happy to go on but I just wanna...

Okay, so we’ve been trying to...

My group has been trying to think about how to use these ideas, make these ideas useful in practice for a range of practical applications.

We’ve done work on multiple testing, on high dimensional linear aggression, and also some on matrix factorization. From previous experience,

I’ll probably get time to talk about the first two and maybe not the last one, but there’s a pre-print on the archive. You can see if you’re interested in matrix factorization.

Maybe I’ll get to talk about that briefly. But let me talk about multiple testing first.
So the typical multiple testing setup, where you might typically, say, apply a Benjamini-Hochberg type procedure is you’ve got a large number of tests, So J equals one to N, and test J yields a P value, PJ, and then you reject all tests with some PJ less than a threshold gamma, where that threshold is chosen to control the FDR in a frequented sense.

So that’s the typical setup. So how are we going to apply the normal means model to this problem? Okay, well, in many applications, not all but in many, we’re looking at different genes here. So Beta J hat might be the estimate of the difference in expression, let’s say, of a gene, J, between, say, males and females.
And Beta J would be the true difference at that gene. You’re interested in identifying which genes are truly different... Have a different mean expression between males and females here. And the reason that SJ is approximately known is because you’ve got multiple males and multiple females that you’re using to estimate this difference. And so, you get an estimated standard error of that Beta hat as well. And so, once you’ve set the problem up like this, of course, it looks suddenly like a normal means problem and we can kind of apply the empirical Bayes normal means idea. We’re gonna put a prior on the Beta Js that is sparsity inducing. That is, it’s kind of centered at zero, maybe it’s got a point mass at zero. But we’re gonna estimate that prior from the data. Okay. And so, not only can you get posterior means for Beta, as I said, you can get posterior interval estimates. So you can kind of do things like compute the posterior in 90% credible interval,
given that prior and the likelihood
for each Beta J and we could reject, for example,
if the interval does not contain zero.
And I’m not going to talk about this in detail
because the details are in
a biostatistics paper from 2017.
I should say that the idea of using empirical Bayes for FDR
actually dates back to before Benjamini and Hoffberg.
Duncan Thomas has a really nice paper
that was pointed out to me by John Witty
that actually contains these basic ideas
but not nice software implementation,
which maybe explains why it hasn’t caught on
in practice yet.
Efron’s also been a pioneer in this area.
So...
Okay, so I don’t want to dwell on that
because, actually, I think I’ll just summarize
what I think is true compared with Benjamini-Hochberg.
You get a bit of an increase in power
by using an empirical Bayes approach.
The Benjamini-Hochberg approach is
more robust to correlated tests though,
so the empirical Bayes normal means model
does assume
that the tests are independent
and, in practice, we have seen
that correlations can cause problems. If you’re interested in that, I have a pre-print with Lei Sun on my website. But the empirical Bayes normal means also provides these interval estimates, which is kind of nice. Benjamini-Hochberg does not. So there are some advantages of the empirical Bayes approach and maybe some disadvantages compared with Benjamini-Hochberg. But I think that the real benefit actually comes when we look at multi-variate extensions of this idea. So I just wanted to briefly highlight those and spend some time on those. So here’s the multi-variate version of the empirical Bayes normal means models. And now, my Beta Js are a vector of observations. So I think of this as measuring, say, gene J in multiple different tissues. Think of different tissues. You look at at heart you look at lung, you look brain, you look at the spleen. In fact, we’ve got 50 different tissues in the example. I’m gonna show in a minute.
So we’ve measured some kind of effect in each gene, in each of these 50 different tissues and we want to know where the effects are...

Which genes show effects in which tissues. So Beta J is now a vector of length R, the number of tissues. R is 50 in our example.

And so you’ve got... We’re gonna assume that the estimates are normally distributed with mean, the true values and some variance, covariance matrix now, which we’re going to assume, for now, is known.

That’s actually a little trickier but I’m gonna gloss over that for... If you want to see details, take a look at the paper.

I just wanna get the essence of the idea across. We’re still going to assume that Beta J comes from some prior, G, and we’re still gonna use a mixture of normals, but now we’re using a mixture of multi-variate normals. And unlike the univariate case, we can’t use a grid of...

We can’t use a grid of values that span all possible covariance matrices here. It’s just too much.

So we have to do something to estimate
these covariance matrices, as well as estimate the pis. And again, if you want to see the details, take a look at a Urbut et al. But let me just illustrate the idea of what’s going on here, or what happens when you apply this method to some data. So this is... I said 50, we have 44 tissues in this particular example. So each row here is a tissue. These yellow ones here are brain tissues, different brain tissues, and I think we’ll see one later that’s blood. I think this one might be blood. Anyway, each one is a tissue; lung, blood, etc. You don’t need to know which ones are which, for now. And so, what we’ve done here is plot the Beta hat and plus or minus two standard deviations for each tissue at a particular... In this case, a particular snip, actually (indistinct). So this is an eQTL analysis, for those of you who know what that means. If you don’t, don’t worry about it. Just think of it as having an estimated effect plus or minus two standard deviations in 44 different tissues,
and we want to know which ones are quote, "significantly different from zero." And so what happens...

Sorry.

Didn't expect that to happen.

Sorry, okay.

Yeah, these are just...

These are just two examples.

So this is one example,

here's another example

where we've done the same thing.

Estimated effects, plus or minus two standard deviations.

So what you can see in this first one is that it looks like, at least,

that the brain tissues have some kind of effect.

That's what you're supposed to see here.

And maybe there are some effects in other tissues.

There's a tendency for effects to be positive,

which might suggest that maybe everything has a small effect to everywhere,

but particularly strong in the brain.

And whereas in this example,

this one appears to have an effect

in just one tissue.

This is the blood actually.

So this is an effect in blood

but mostly, it doesn't look like

there's an effect in other tissues.

But these, just to emphasize,
these are the raw data, in the sense that they’re the Beta hats and the standard errors. There’s no shrinkage occurred yet. But the idea is that the empirical Bayse approach takes all these examples, examples like this and examples like this, to learn about what kinds of patterns are present in the data. That is, ”What does G look like?” So it learns from these examples that there are some effects that look like they’re shared among the brain tissues, and there are some effects that are... These are actually somewhat rare but rarely, there’s an effect that’s specific to one tissue like, in this case, blood. And it also learns, in this case actually, that there’s a lot of null things, because there are a lot of null things as well. So it puts lots of mass on the null as well and that causes the shrinkage. And then, having estimated those patterns from the data, it computes posteriors. And so, here’s the data and then the posterior intervals for the same... For that first example. And what you can see is that because of
the combining information across tissues, you get standard errors that are getting smaller, the brain estimates all get shrunk towards one another, and all these...

There’s some borrowing strength of information, borrowing information across these tissues, to make these look like some of them are kind of borderline significant. Now, it looks like there’s probably an effect in every tissue but a much stronger effect in brain. Whereas this example here, it recognizes that this looks like an effect that’s specific to blood. And so, it shrinks everything else strongly towards zero because it knows that most things are null, it’s learned that from the data, but the blood estimate gets hardly shrunk at all. We saw that kind of behavior where things that are near zero can get shrunk towards zero, whereas other things that are far away don’t get shrunk as much. And it’s really hard to do that kind of thing without doing some kind of model-based analysis, doing Benjamini-Hochberg type art non-model based
without making any assumptions or making minimal assumptions, very hard to capture this kind of thing, I think. So I think the empirical Bayse approach has big advantages in this setting. I'll pause before I talk about regression. Any questions there? So Matthew, I have some basic questions. So in your means multivariate multiple testing case, I guess for each of the plot, you are looking at maybe a particular genes influence on some... Good, yeah. Sorry, I did skip over it a bit. So these are eQTLs. So actually, what I'm plotting here is each... This is a single snip associated with a single gene. And this is it’s, "How associated is this snip with this genes expression level" in the different brain tissues, "in the blood tissue in lung and spleen, etc?" The idea is that... What the scientific goal is to understand which genetic variants are impacting gene expression in different tissues, which might tell us something about the biology of the tissues.
and the regulation going on in the different tissues.

- Got it.

So in this case, I don’t think I fully understand why it’s multivariate multiple tests, not univariate because you are looking at each gene versus each snip.

Think of J indexing eQTL. So we’ve got 2 million potential eQTLs, so that’s the multiple part of it. For 2 million potential eQTLs, that’s...

And then each eQTL has data on 44 tissues, so that’s the multi-variate part of it. (speaking over each other)

If you thought about it in terms of say P values or maybe Z scores, you have a matrix of Z scores. There are two million rows and there are 44 columns and you have a Z score or a P value for each element in that matrix, and what we’re assuming is that the rows are independent, which is not quite true but still, we’re assuming that the rows are independent and the columns,

we’re assuming that they can be correlated. And in particular,
we’re assuming that the...
Well, we’re assuming that both
the measurements can be correlated,
so it’s V,
but also that the effects can be correlated.
So that’s to capture the idea
that there might be some effects
that are shared between say brain tissues--
I see.
So this multi-variate is different
from our usual notion where the multivariate
and multivariate snip.
So there’s multivariate tissue.
I guess, are the samples from the same cohort?
Yeah, so in this particular case,
the samples are from the same individuals.
So these different brain tissues...
There’s overlap anyway, let’s say.
And so, that’s what causes this...
That causes headaches, actually, for this--
Okay, got it, thanks. - Yeah.
Just to emphasize,
it doesn’t have to be different tissues.
The whole method works
on any matrix of Z scores, basically.
As long as you think that the rows correspond
to different tests
and the columns correspond
to different, say, conditions for the same test.
So examples might be
you’re looking at the same snip across lots of different phenotypes, so looking at schizophrenia, looking at bipolar, looking at different diseases or different traits, and you can have a Beta hat for that snip and a standard error for that snip in every trait. And you could try to learn, "Oh look, there are some traits that tend to share effects and other traits that don’t," or, often in experiments, people treat their samples with different treatments. They challenge them with different viruses. They look to see which things are being changed when you challenge a cell with different viruses or different heat shock treatments or any kind of different treatment. So yeah, basically, the idea is very generic. The idea is if you’ve got a matrix of Z scores where the effect, say, look likely to be shared among column sometimes and the rows are gonna be approximately independent, or at least you’re willing to assume that, then you can apply the method. Okay, got it, thanks.
So, actually, that’s an important kind of... 
Also, something that I’ve been thinking about a lot is 
the benefits of modular or generic methods. 
So if you think about what methods are applied 
in statistics a lot, 
you think T-test, linear regression. 
These are all kind of very generic ideas. 
They don’t... 
And Benjamini-Hochberg. 
The nice thing about Benjamini-Hochberg is 
you just need a set of P values 
you can apply Benjamini-Hochberg. 
You don’t have to worry too much 
about where those P values came from. 
So I think, for applications, 
it’s really useful to try to think about 
what’s the simplest type of data 
you could imagine inputting into the procedure 
in order to output something useful? 
And sometimes, that involves making compromises 
because to make a procedure generic enough, 
you have to compromise on what... 
On maybe what the details of what are going in. 
So here, what we’ve compromised on is 
that we take a matrix of Z scores, 
or potentially Beta hats and their standard errors, 
we can do either,
and that’s the input. So that makes it relatively generic. You don’t have to worry too much about whether those Beta hats and the standard errors, or the Z scores, are coming from logistic regression or linear regression, or whether that controlling for some covariance from a mixed model, etc. As long as they have the basic property that the Beta hat is normally distributed about the true Beta with some variance that you are willing to estimate, then you can go. So in practice, how you choose... How many mix... How many distribution you want to mixture like the (indistinct)? - (indistinct)? Yeah, so great question. And my answer, generally, is just use as many as you want. So as many as you can stomach. The more you use, the slower it is. And so, you might worry about over-fitting, but it turns out that these procedures are very robust to over-fitting.
because of this fact that the mean is fixed at zero.

So all the components have a mean zero and have some covariance and because of that, they have limited flexibility to overfit. They’re just not that flexible. And in the univariate case, that’s even more obvious, I think.

That in the univariate case, every one of those distributions, any mixture of normals that are all centered at zero is unimodal at zero and has limited...

Can’t have wiggly distributions that are very spiky and overfitting. So these methods are relatively immune to overfitting in practice.

If you’re worried about that, you can do a test-train type thing where you use half your tests to train, and then you look at the log likelihood out of sample on others, and then tweak the number to avoid overfitting.

And we did do that early on in the methods but we don’t do it very often now, or we only do it now when we’re worried ’cause generally it seems like overfitting doesn’t seem to be a problem, but if we see results are a little bit weird
or a bit concerning, we try it to make sure we’re not overfitting.

Okay, thank you.

I should say that, in the paper, we kind of outlined some procedures we use for estimating these variance, co-variance matrices. I'm kind of thinking of, potentially here. And the errors normal. And so, the empirical Bayes idea would be to assume that the Bs come from some prior distribution, G, which comes from some family, curly G. And what we’d like to do is estimate G and then shrink the estimates of B,
using empirical Bayes type ideas and posterior count computations. But it’s not a simple normal means model here, so how do we end up applying the empirical Bayes methods to this problem? Well, let’s just...

I’m gonna explain our algorithm by analogy with penalized regression algorithms because the algorithm ends up looking very similar, and then I’ll tell you what the algorithm is actually kind of doing.

So a penalized regression would solve this problem. So if you’ve seen the Lasso before... I hope many of you might have. If you’ve seen the Lasso before, this would be solving this problem with \( H \) being the L1 penalty, absolute value of \( B \), right? So this...

There are many, many algorithms to solve this problem but a very simple one is coordinate ascent. So essentially, for each coordinate, it just iterates the following. For each coordinate,

you have some kind of current estimate for \( B \).

(indistinct)
So what you do here is you form the residuals by taking away the effects of all the Bs except the one you’re trying to update, the one you’re trying to estimate. So X minus J here is all the covariates except covariate J.

B minus J is all the corresponding coefficients. So this is the residual, RJ is the residual, after removing all the current estimated effects apart from the Jth one. And then you basically compute a estimate of the Jth effect by regressing those residuals on XJ.

And then you shrink that using a shrinkage operator that we saw earlier. Just to remind you that a shrinkage operator is the one that minimizes this penalized least squares problem. And it turns out, it’s not hard to show that this is coordinate ascent for minimizing this, penalized objective function.

And so every iteration of this increases that objective function or decreases it. Okay, so it turns...
So our algorithm looks very similar. You still compute the residuals, you compute a Beta hat by regressing the residuals on XJ. You also, at the same time, compute a standard error, which is familiar form. And then you, instead of shrinking using that penalized regression operator, you use a... Sorry, I should say, this is assuming G is known. So you can shrink... Instead of using the penalty-based method, you use the posterior mean shrinkage operator here that I introduced earlier. So it’s basically exactly the same algorithm, except replacing this penalty-based shrinkage operator with an empirical Bayesian or a Bayesian shrinkage operator. And so, you could ask what that’s doing and it turns out that what it’s doing is minimizing the Kullback-Leibler Divergence between some approximate posterior, Q, and the true posterior, P, here under the constraint that this Q is factorized. So this is what’s called
a variational approximation or a mean-field, or fully factorized variational approximation.

If you’ve seen that before, you’ll know what’s going on here. If you haven’t seen it before, it’s trying to find an approximation to that posterior that minimizes the Kullback-Leibler Divergence between the approximation and the true value under in a simplifying assumption that the posterior factorizes, which, of course, it doesn’t, so that’s why it’s an approximation.

So that algorithm I just said is a coordinate ascent algorithm for maximizing $F$ or minimizing the KL divergence.

So every iteration of that algorithm gets a better estimate estimate of the posterior, essentially.

Just to outline and just to give you the intuition for how you could maybe estimate $G$, this isn’t actually quite what we do so the details get a bit more complicated, but just to give you an intuition.
for how you might think that you can estimate G;

Every iteration of this algorithm computes a B hat

and a corresponding standard error,

so you could imagine...

These two steps here, you could imagine storing these

through the iterations

and, at the end,

you could apply the empirical Bayes normal means procedure

to estimate G from these B hats

and standard errors,

and something close to that kind of works.

The details are a bit more complicated than that.

So let me give you some kind of intuition

for what we’re trying to achieve here based

on simulation results.

So these are some simulations we’ve done.

The covariates are all independent here.

The true prior is a point normal,

that means that most of the effects are zero.

Well, actually maybe here,

one of the effects is nonzero,

five of the effects is nonzero,

50 of the effects are nonzero

and 500 of the effects of nonzero.

And actually, there are 500 effects,

500 variables in this example.

So the X-axis here just shows the number
of non-zero coordinates and the results I’ve shown here are the prediction error, so we’re focusing on prediction error, the out of sample prediction error, using three different penalty-based approaches. The Lasso, which is this line, the L0Learn, which is this line, which is L0 zero penalty, and Ridge, which is this penalty, the L2 penalty. So the important thing to know is that the L0 penalty is really designed, if you like, to do well under very sparse models. So that’s why it’s got the lowest prediction error when the model is very sparse, but when the model is completely dense it does very poorly. Whereas Ridge is designed much more to... It’s actually based on a prior that the effects are normally distributed. So it’s much better at dense models than sparse models. And you can see that at least relative to L0Learn, Ridge is much better for the dense case but also much worse for the sparse case. And then Lasso has some kind of ability to deal with both scenarios, but it’s not quite as good as the L0 penalty.
when things are very sparse,
and it’s not quite as good as the Ridge penalty
when things are very dense.
So our goal is that by learning the prior G from the data,
we can adapt to each of these scenarios and get performance close to L0Learn
and get performance close to Ridge regression
and get performance close to Ridge regression
when the truth is sparse
and get performance close to Ridge regression
when the truth is dense.
And so, the red line here actually shows
the performance of our method.
And you can see, indeed,
we do even slightly better than L0Learn
in this part here
and slightly better than cross-validated Ridge regression
in this here.
The difference between these two is just that
the Ridge regression is doing cross-validation
to estimate the tuning parameter
and we’re using empirical Bayse maximum likelihood
to estimate it.
So that’s just that difference there.
And the Oracle here is using the true...
You can do the Oracle computation
for the Ridge regression
with the true tuning parameter here.
I should say that may be that this...
Maybe I should just show you the results.
So here is a bunch of other penalties, including elastic net, for example, you might wonder, which is kind of a compromise between L1 and L2. And you can see, it does do the compromising but it doesn’t do as well as the empirical Bayse approach.

And here are some other non-convex methods that are more, again... They’re kind of more tuned to the sparse case than to the dense case.

As promised, I’m gonna skip over the matrix factorization and just summarize to give time for questions.

So the summary is that the empirical Bayse normal means model provides a flexible and convenient way to induce shrinkage and sparsity in a range of applications. And we’ve been spending a lot of time trying to apply these methods and provide software to do some of these different things. And there’s a bunch of things on my publications page.

And if you’re interested in... If you can’t find what you’re looking for, just let me know, I’d be happy to point you to it.
Thanks very much.

- Thanks Matthew, that’s a great talk.

I wonder whether the audience have any questions for Matthew.

So I do have some questions for you.

So I think I really like the idea of applying empirical Bayes to a lot of applications.

It’s really seems empirical Bayes has great success.

But I do have a question or some doubt about the inference part, especially in that linear regression model.

So currently, for the current work you have been doing,

you essentially shrink each of the co-efficient that based on, essentially, their estimated value,

but in some applications, such as a GWAS study or fine mapping, different snips can have very different LD score structure.

So in this case,

how much we can trust the inference,

the P value, from this (indistinct)?

- So, great question.

So let me just first...

First emphasize that the shrink...

The estimate here is being done removing the effects,

or the estimated effects.

of all the other variables.
So each iteration of this, when you’re estimating the effect of snip J, you’re taking the estimated effects of the other variables into account. So the LD structure, as you mentioned, that’s the correlation structure between the Xs is formerly taken into account. However, there is a problem with this approach for very highly correlated variables. So let’s just suppose there are two variables that are completely correlated. what does this algorithm end up doing? It ends up basically choosing one of them and ignoring the other. The Lasso does the same in fact. So it ends up choosing one of them and ignoring the other. And if you look to the posterior distribution on its effect, it would be far too confident. because it would assume that the other one had zero effect. And so it would have a small credible and for, let’s say, around the effect size when, really, it should be saying you don’t know which one to include. And so, we’ve worked recently.
on a method for doing that.

A different method, different work than what I've just described here for doing fine mapping using variational approximations that don't have this problem, and it's on my webpage. It's Wang et al in JRSS-B, just recently, this year. 2021, I guess. - That's awesome.

Thanks, so any more question for Matthew from the audience? Okay, I think we're of running out of time also.

So if you have any question about the stuff to (indistinct) you want to use, I think you can contact either the authors of the paper or Matthew off the line. And thank you again for agreeing to present your work here.

It's looks really useful and interesting. Thank you for having me.