Nature Podcast

Introduction

This is a transcript of the 5th July 2018 edition of the weekly Nature Podcast. Audio files for the current show and archive episodes can be accessed from the Nature Podcast index page (http://www.nature.com/nature/podcast), which also contains details on how to subscribe to the Nature Podcast for FREE, and has troubleshooting top-tips. Send us your feedback to podcast@nature.com.

[Jingle]

Host: Benjamin Thomspon
Welcome back to the *Nature Podcast.* This week, we're finding out some of the issues affecting LGBTQ+ people in research, and looking into the genome of one of Australia's most iconic animals.

Host: Adam Levy
Plus, we'll hear about the computer coded in DNA. I'm Adam Levy.

Host: Benjamin Thompson
And I'm Benjamin Thompson.

[Jingle]

Host: Adam Levy
First up this week, we have some koala-ty content for you.

Host: Benjamin Thompson
Why did you say it like that?

Host: Adam Levy
Like what?

Host: Benjamin Thompson
Well, you said quality a bit weird.

Host: Adam Levy
Did I?

Host: Benjamin Thompson
This better not be a koala pun. We are a serious science podcast Adam.

Host: Adam Levy
Ben, you know I take this e-koala-ly as seriously as you.

Host: Benjamin Thompson

Right, well just get on with it then. Tell us all about the koalas.

Interviewer: Adam Levy
What makes you think this is about koalas? So, koalas are not usually something you'd associate with cutting-edge genetics. But while they're not as popular amongst geneticists as good old *E. coli*, scientists have finally been able to sequence the koala genome. So, koalas join the esteemed list of species that have had their genome sequenced. But even among marsupials, koalas are unusual and their genes give some insights into their unique lifestyles, as well as providing information for conservation projects. I met Rebecca Johnson, leader of the Koala Genome Project, and started off by asking her for some facts that we should all know about koalas.

Interviewee: Rebecca Johnson
Everyone probably already knows that the koala is cute. But things that are interesting to know and that people should know, is that they're the only living species from their entire family. And over evolutionary time, there were probably up to 20 different koala species, but we only have the one now, and their closest living relative is the wombat.

Interviewer: Adam Levy
What do they mean to you personally then?

Interviewee: Rebecca Johnson
To me they're really an icon of conservation. So, they're an icon of the attention we should give to the natural world and also to stop and think what our actions as humans might have on the natural world.

Interviewer: Adam Levy
How are koalas doing as a species? Are they under any kind of threat at the moment?

Interviewee: Rebecca Johnson
Yes, they are. So, once upon a time they would have been found across the entire country, but as the climate became more arid, they're only now found on the east coast. And particularly because of the impacts of European settlements which is only very relatively recent in Australia, there's a lot of development and there's a lot of removal of habitat and also they suffer from diseases, and this is unfortunately impacting populations.

Interviewer: Adam Levy
So why actually sequence the koala genome?

Interviewee: Rebecca Johnson
Well, the koala in general has such a specific lifestyle. They've got such specific adaptations to living in the trees and eating a very narrow diet of largely eucalyptus, to the point where it would be toxic or fatal to most other mammals.

Interviewer: Adam Levy
Well let's not beat around the bush – what did sequencing the genome tell you about how they manage to maintain this quite ridiculous diet?

Interviewee: Rebecca Johnson
Yeah, so we found that they're basically super detoxers. So, there's a group of metabolic enzymes called the Cytochrome P450s, and these are enzymes that are so important for metabolism of things in the environment. Every organism has them, from very basic multicellular organisms right up to humans have many of them as well. Koalas seem to have many, many more than any other species.

Interviewer: Adam Levy
And this isn't the only thing you've found out about the koala's diet. You were also looking at how the koalas managed to be quite picky eaters.

Interviewee: Rebecca Johnson
Yes, so they eat a really restricted diet. They are trying to avoid eating as much poison as possible, and we've found that they seem to have a lot of bitter taste receptors. And this is probably to help them avoid toxins and probably also helping them to optimise the nutrient content that they're choosing.

Interviewer: Adam Levy
But it wasn't just diet that you were looking at here, it was also how the immune system of the koala can cope with various problems that koalas are currently facing.

Interviewee: Rebecca Johnson
Yeah, that's right. So, koalas suffer unfortunately from chlamydia, but they get it in their eyes and they also get it in their reproductive tract. And this, if untreated, can result in blindness or them becoming infertile, and ultimately death and it is presumably incredibly painful. So being able to characterise the immune genes was amazing because we can then start looking at how these are expressed in animals that either have chlamydia or have recovered from chlamydia, or even animals that are used in a chlamydia vaccine trial. So, an incredibly powerful set of genes that we can now see how individual animals respond.

Interviewer: Adam Levy
So far, lots of very interesting information about koalas, but how would this actually feed into efforts for conservation?

Interviewee: Rebecca Johnson
Yeah, so we've shown that the animals that are very genetically diverse are the ones in Queensland and New South Wales, which are also the ones that are showing declining populations, very significantly in some cases. The Queensland population is estimated to decline by 50% in the next 3 generations, which is only 20 years. The New South Wales population similarly is thought to decline by estimated to be about 30% in the next three generations. So, something really needs to be done now, and the genome got enough attention from the New South Wales government that they decided to use genetic markers as a form of management going forward.

Interviewer: Adam Levy
So, this information about diversity is already feeding into conservation decisions. Are there other insights from this work that could help maintain koala populations' diversity?

Interviewee: Rebecca Johnson
We've been able to reconstruct what koala populations looked like through history, and this is really important for management because it's very tempting to manage a species just the way you see it now. So, to bring in the way a species has been historically for 10, 20, 30,000 years is the best practice for managing it because you're allowing them to exchange the genes that remain in the population. So, it's incredible to be able to document that diversity and ensure that we are making decisions using those data.

Interviewer: Adam Levy
Do you think there's more that can be done now based on this work that could help conservation?

Interviewee: Rebecca Johnson
I think that's the amazing thing about a genome, any genome project. It's an incredible achievement and we know so much, but we also know how much we don't know. And so, it provides an incredible springboard for future studies – everything from looking at how the variation in their bitter taste receptors might vary across the population. Some animals are known to love certain trees, and how does that, what is the interplay between the trees that they choose and the variation that they show in their own genome. So, having a genome is really just the beginning.

Host: Adam Levy
That was Rebecca Johnson, Director of the Australian Museum Research Institute. You can find her paper in *Nature Genetics*: nature.com/ng. There's also a short video about the research on our YouTube Channel: youtube.com/NatureVideoChannel. Don't worry, there are no puns in the video.

Interviewer: Benjamin Thompson
Thursday 5th July 2018 is LGBTSTEM Day. It's a day to recognise marginalised sexualities and gender identities in science, technology, engineering and maths. It aims to help raise awareness and support and strive for increased inclusivity and diversity. In this week's *Nature*, Jon Freeman from New York University has written a Comment piece looking at the reasons that LGBTQ+ people are dropping out of science. I gave him a call and started by asking him about his own experiences of academia.

Interviewee: Jon Freeman
I've had a number of experiences in my career as an undergraduate – a professor warned me that I wouldn't get into any PhD programmes if I kept 'looking the way the way I did'. And also, cases where for example, as a starting out faculty member when I was interviewing postdoctoral candidates for my lab, and you know a colleague pulled aside a postdoc candidate from my lab to let him know that I'm gay, just in case it might be 'a problem'. So, this is not at all something that is from decades ago for example, this perspective really is more on how this affects us today.

Interviewer: Benjamin Thompson
I mean, what is the state of play then at the moment for people who are LGBTQ+ in STEM? You know, you say that they're dropping out – what's going on?

Interviewee: Jon Freeman
So, research on LGBTQ people in STEM fields is extremely scarce. From the few studies that exist which have really come out recently, the results are quite sobering. So, estimates suggest that LGBTQ people are roughly 20% less represented in STEM fields than expected. Now, studies that can really get at the mechanism a little bit more and say what's going on, are those studies that you know, look at dropouts in particular. So, there was one study published this year, what they found was that men from sexual minorities who started university specialising in STEM fields were far more likely to drop out of those STEM-focused degrees after 4 years. However, they were more likely to pursue practical research experience and more likely to get involved in labs. And besides that, with this underrepresentation and with this attrition or this dropout, when they do continue on in STEM, it's very clear in recent surveys showing that LGBTQ people report more negative work-based experiences – 69% felt uncomfortable in their department. So, with all this information what it's suggesting is that you know STEM fields are not really being a welcoming environment for LGBTQ people.

Interviewer: Benjamin Thompson
You say in your Comment that invisibility is a problem for LGBTQ scientists – what did you mean by that?

Interviewee: Jon Freeman
Being from a sexual or gender minority, being a LGBTQ person, is not visually conspicuous often in the sense that people often can't tell if someone is LGBTQ. But in science, it's so critical to have for underrepresented groups, role models and peers and other people that look like you and are like you. And this is something that has been explored a lot with women in STEM fields and those from minority ethnic groups. And so, there's a number of reasons how LGBTQ people when they're in STEM, are not deciding to be visible and that can be a problem. Because you know there's other LGBTQ scientists, and especially trainees and students won't really benefit from a sense of belonging and inclusion that they might feel if they saw visible role models and saw visible peers and other people, where it's an implicit signal that this is a community where they can participate in and belong.

Interviewer: Benjamin Thompson
Well Jon, what needs to be done to create an inclusive environment for LGBTQ researchers?

Interviewee: Jon Freeman
So, I think a number of steps should be taken. I think that the diversity initiatives of federal funding agencies and of universities widely should really consider including LGBTQ people in an official manner, and that would do a number of things, I think. For one, certainly, directly they would foster LGBTQ representation in STEM fields. It would also send, I think, an official signal to the scientific community that this is a valued form of diversity – LGBTQ people – and that this is a kind of diversity that science cares about and wants to see adequate representation of.

Interviewer: Benjamin Thompson
I mean, we can't have this conversation really without mentioning that of course it's LGBTSTEM Day this week. My question to you Jon is because obviously, that's a big deal

right, it's the first international day, who's doing good work in this sphere at the moment, in terms or raising awareness of the issues and what have you.

Interviewee: Jon Freeman
There's a lot of good work being done by a number of organisations. So, Out in STEM and the National Organisation of Gay and Lesbian Scientists and Technical Professionals, and Pride in STEM and a number of other groups. Recently there's been a visibility campaign called 500 Queer Scientists online that's taken place this month, where you know LGBTQ scientists can post their bios and their stories and a photo and kind of be part of this sort of database where you can see other people. And when I was looking through it, it made me realise how powerful it is and how much of an issue of invisibility it is. To see you know 500+ LGBTQ scientists on this website that you can you know just Google and get to, not only is it great for visibility, but also, I think in terms of next steps that you know departments could be taking when inviting speakers, you can now go into the database and find these people. And I think that will be really valuable moving forward in trying to be more inclusive and to do all the kind of small and subtle steps to make it a more visible and welcoming environment that we know will lead to positive effects for LGBTQ representation and reduce this dropout rate that we're seeing.

Interviewer: Benjamin Thompson
That was Jon Freeman from New York University. You can read his Comment over at nature.com/nature.

Host: Adam Levy
Later in the show, it's the News Chat, where we'll find out whether there's an upper limit on how old humans can get. Before that though, Ellie Mackay is here with this week's Research Highlights.

[Jingle]

Interviewer: Ellie Mackay
If you've ever awkwardly tried to guess if a friend is pregnant, then you know how marine biologists feel. They've got their work cut out for them with the somewhat heavyset humpback whale, where there's simply no way to tell if these oceanic giants are expecting just by looking at them. But now, scientists have developed a humpback pregnancy test. By firing a dart into a female whale's blubber to obtain a tissue sample, her fat stores can be tested for progesterone, a tell-tale sign of pregnancy. This gives an indication of the whale's reproductive state without needing to judge from the size of her belly. The scientists hope to use this test to study reproduction patterns in whales and other rotund marine mammals. If you think that story was swell, find it in *Conservation Physiology*.

[Jingle]

Interviewer: Ellie Mackay
If you're anything like me, you spent your youth standing awkwardly in the corner at parties. But to date, nobody has known where giant manta ray youths spend their time, as the rays are usually only sighted once they are adults. Now, scientists may have finally solved the mystery of the missing mantas, with the discovery of a marine nursery off the

coast of Texas. The researchers found that 95% of the mantas in this sanctuary were juveniles. They believe the plankton-rich waters are an attractive haven for baby and teenage rays before they brave the wider ocean. For more on that story, glide on over to *Marine Biology*.

[Jingle]

Host: Adam Levy
Next up, reporter Lizzie Gibney has been finding out how to calculate using DNA.

Interviewer: Lizzie Gibney
Even if your handwriting is pretty terrible, if you wrote down the number 7, I could tell that it wasn't a 6. That's because each 7 will share common features – a line across the top, and one going down. But the exact shape can vary a lot, so computers find recognising patterns like this hard. One way computers can handle this kind of image recognition is to use an artificial neural network, a kind of algorithm modelled on the way the brain works. In neural networks, connections between artificial neurons have different strengths, known as weights. That depends on how likely a particular feature is to exist in the pattern you are trying to recognise. This allows the algorithm to automatically recognise scrawled numbers as the correct digits. Now, scientists from Caltech have come up with a way to create a neural network, but not using a silicon-based computer. Instead, they're using DNA. Here's bioengineer Kevin Cherry.

Interviewee: Kevin Cherry
So, in our DNA-based computer, we use the identity of molecules and we encode them to perform a set of chemical reactions that we've designed to compute some function.

Interviewer: Lizzie Gibney
This is not the first DNA computer. But up until now, they've all been pretty simple.

Interviewee: Kevin Cherry
A lot of work in the field has been focused on building logic like AND/OR gates. But the neural network architecture allows us to do a lot more powerful computation within sort of the same size of molecules. And so, we implemented a type of neural network which allows us to compute and recognise much more sophisticated patterns, all with about the same number of molecules.

Interviewer: Lizzie Gibney
These new DNA computers literally live inside test tubes. But the neural network Kevin built needs to recognise images. So, the first hurdle is to work out how to represent an image using DNA molecules in a test tube.

Interviewee: Kevin Cherry
When we take a handwritten digit, and we put it on to a 10-by-10 grid of pixels, and each of those pixels is represented by a short DNA sequence of about nucleotides. And when we choose a specific handwritten digit, we can take the pixels that are in that pattern and then pipet those DNA molecules into the liquid solution in order to do the computation.

Interviewer: Lizzie Gibney
So, the input image is represented as a series of strings of DNA, but what is the computer? Well, that's made of DNA too.

Interviewee: Kevin Cherry
And then we have a weight matrix which we've trained using a computer and then added to the test tube. So in that case, it looks like DNA molecules which store the patterns that we want to recognise.

Interviewer: Lizzie Gibney
A different set of molecules – the weight matrix – encodes the computer's memory for each number. One matrix is designed to detect the number 6, and one detects the number 7, and so on. Each matrix is made up of many strands of DNA. Like the input image, each strand of the matrix corresponds to a particular pixel in the 10-by-10 grid. To make the DNA computer, Kevin adds a different concentration of each of these DNA strands. These concentrations represent the likelihood that a coloured-in pixel would appear in a number. In neural network jargon, these likelihoods are called weights, and they're calculated using a regular computer.

Interviewee: Kevin Cherry
And so currently we programme it on the computer, so we logically come up with some pattern that we want to recognise, and find an appropriate set of weights. And then I go into the lab and pipet the DNA molecules into the mixture in order to build that specific network.

Interviewer: Lizzie Gibney
Now that the weight matrix is in the test tube with the DNA representing the image, the calculations can begin. The weight molecules and the molecules representing the image interact, producing output molecules. So how does all this make a calculation? Well, remember that if a particular pixel crops up often in a number, there will be a lot of memory molecules in the weight matrix for that particular pixel. So, if that same pixel is also in the input pattern, you get lots of reactions and lots of output molecules from that memory. If the pixel has a low weight in the matrix, you don't get so many. This means that when all the output molecules are tallied, the total reflects how similar the input pattern is to the number that that matrix represents. That means if you put two weight matrixes in the same solution, the one that the input is most similar to will produce the most reactions, and so more of its own output molecules. The resulting outputs can then be processed and made to fluoresce a different colour, depending on which has won out. In this way, just by chucking a bunch of molecules in a test tube, the DNA computer is able to calculate which number it thinks the pattern is most like. And it was pretty accurate.

Interviewee: Kevin Cherry
We took the whole set of 6 and 7 digits from a well-known database of handwritten numbers, and so there was approximately 12,000 in this case. And we simulated the reaction for all of those digits, and more than 98% of them are able to compute correctly. And then we targeted a set of about 50 of them to experimentally demonstrate in the laboratory.

Interviewer: Lizzie Gibney
They key thing about a neural network is that because it's based on weights and probabilities, it's flexible. An image doesn't have to be an exact match to the memory. Instead, the network can detect which number an image is most like. Right now, the network has to be programmed by manually pipetting in different concentrations of DNA to represent the different weights. One day, he wants to create a DNA computer which learns on its own.

Interviewee: Kevin Cherry
Yes, that is something that I'm currently working on. The benefit of this type of neural network architecture is that we can set it up with sort of blank memories and then trigger the memories via the molecular environment. And so, then it would be capable of learning without the input of the experimenter at all.

Host: Adam Levy
That was Kevin Cherry from the California Institute of Technology in the United States. You can read his paper over nature.com/nature.

Interviewer: Benjamin Thompson
Well, listeners it's that time again. It's the News Chat and this week I'm joined by Richard Van Noorden, Features Editor here at *Nature*. Hi Richard.

Interviewee: Richard Van Noorden
Hi Ben.

Interviewee: Benjamin Thompson
Well for our first story today Richard, we're going to talk about old age and we've got a story suggesting there's actually maybe no natural limit for how old a human can live. What's going on here?

Interviewee: Richard Van Noorden
Well, as we get older the risk that we'll die in the next year generally increases, but a new study is suggesting that if you make it past about 105, your change of passing away the next year levels off around 50/50. And if death risk does flatten out like this rather than continuing to increase as we get older, this study suggests that there may be no natural upper limit to human lifespan.

Interviewee: Benjamin Thompson
Alright, so let me get this straight then, so as I approach my nineties, the risk of me dying increases but once I get over that little hump, I'm more likely to stay alive?

Interviewee: Richard Van Noorden
Yeah, that's what this study suggests and it's a very controversial topic. And the background to this is that in 2016, a geneticist estimated that there was a ceiling, it was about 115 years old, maybe 125 tops, and essentially, we as a species had reached our natural limit of lifespan. And that work was heavily criticised and this new study in *Science* is saying that in fact, there could be what they're calling a 'mortality plateau' – when we get very old, our

risk of dying might go down a bit. And now, they don't know if you get to 115, 120, might the risk of dying go up again year by year? So, they're not saying that lifespans are infinite, they're saying that as far as we know, something weird is going on when you get to those very old ages.

Interviewee: Benjamin Thompson
And you mentioned at the start then 50/50 year to year, so almost on the toss of a coin then.

Interviewee: Richard Van Noorden
Yeah, so these researchers Elisabetta Barbi and Francesco Lagona who are Italian, they looked at records from every Italian who's more than 105 years old from 2009 to 2015 – that's almost 4,000 people. In that data, they find this mortality plateau. Now, that's a very impressive data collection because they looked at birth certificates, death certificates – they're very sure that these people are the age that they say they are, and that really bugged the earlier 2016 study. Those guys looked at an international database across lots of countries, and one of the criticisms was can you really be sure that people aren't exaggerating their ages and that you know people are the ages that they say they are. Here we have very, very good data. So, that's a strike in favour of this latest conclusion. Unfortunately, of course not everyone is buying this finding. One demographer Jean-Marie Robine told us that there's unpublished data from France, Japan and Canada that suggests that the evidence for this mortality plateau is not as clear-cut. And in general, we're still talking about tricky statistics and small amounts of data. In this Italian study, fewer than 100 people lived beyond age 110, so even small inaccuracies in the data or a few changes to the data point could lead to a spurious conclusion or change the trend line. So, I think we're just starting to explore this question of whether there is a natural upper limit on our lives.

Interviewee: Benjamin Thompson
Well listeners, we actually covered the earlier paper, so if you'd like to learn more about what it found, take a listen to our podcast from the 6th October 2016. In the meantime though Richard, let's move on to our second story, and we're going to go from one end of the age curve to the very, very other I think, and we're going to head over to China, where results have been coming out from a birth-cohort study that's only a few years old. In the first instance, maybe you could tell our listeners what a birth-cohort study is.

Interviewee: Richard Van Noorden
Yeah, so a birth-cohort study is something that tracks babies and their mothers from birth, and hopefully follows the babies all the way to age 18, essentially to discover as much as possible about the links between diseases in childhood and environmental conditions, DNA, eating habits, mental health, any lifestyle factors. And by following so many people, you can start to pick out really statistically significant patterns, and we write about a Chinese study in Guangzhou, that's already recruited 33,000 babies and mothers since 2012, and the first results are coming out. These researchers hope to reach 50,000 sets of mothers and babies by 2020.

Interviewee: Benjamin Thompson
Well Richard, how does this differ from other birth-cohort studies around the world?

Interviewee: Richard Van Noorden
Yeah, there are very large studies in Norway and Denmark, but the Chinese study really stands out because it's looking particularly into links between disease and the microbiome, which other studies haven't done. So far, they've got 1.6 million biological samples and they're recording mothers' mental health and lifestyle factors like the amount of mould in their house, and eating habits, and as I say, the results are coming out right now. One study for example has already found that exposure to the fumes from burning incense, common in southern China, increases the risk of hypertension in expectant mothers. Another study has suggested that progesterone, which is a drug used around the world to try and reduce the risk of preterm births, is sometimes prescribed too early in pregnancy. In more than 40% of the women in the study in fact, when it's given before 14 weeks of gestation, you get a higher risk of postpartum depression and a higher risk of the baby needing to be born by caesarean section, but no necessarily benefits in terms of reducing the risk of a preterm birth. So, these are immediate kind of studies, but perhaps very interestingly, a team from the UK and China is trying to figure out how the microbiomes of babies born via the vagina are different from those of the babies born by caesarean section. So, this study with so many babies could give us the statistical power to separate out the variables that influence the baby's microbiome, and this could include things like antibiotics like medications, could include environmental pollutants. So, there's lots going on and this study might be the key to answering that tricky question.

Interviewee: Benjamin Thompson
So, you mention there that a load of data has already been collected and that researchers are having to follow these children until their 18 years old. What are scientists saying about this cohort study?

Interviewee: Richard Van Noorden
The researchers behind this study say they want scientists from everywhere around the world to work with them, and it's a particularly interesting point in China, not only because in China right now they ended their one-child policy in 2016. So, there's a new opportunity to study women who are having a second child, and an epidemiologist who's directing the project Xiu Qiu says she's using the data to test a sort of tentative finding that older mothers having their second child have a lower risk of depression during pregnancy than women pregnant with their first child. You might expect the opposite because if you have a baby and then you're pregnant again, you might be under more stress, you might have a higher financial burden, be more depressed but that may not be the case, she thinks. So, it's a kind of interesting, unique situation that's going on here, along of course with China's vast resources that they're pouring into this project and very few other countries can achieve this kind of scale.

Interviewee: Benjamin Thompson
Well thank you, Richard. Listeners, for more of the latest science news, head over to nature.com/news, and actually you can also hear Richard in last month's Backchat where we talked a bit more about data and data journalism. So, check that out at wherever you get your podcasts.

Host: Adam Levy
Well that's it for this week's show, but before we go there's just time to tell you about a new video. It highlights the first two weeks of human development, and it contains some amazing images. You can find that, as well as our koala video over on our YouTube channel, that's at youtube.com/NatureVideoChannel. I'm Adam Levy.

Host: Benjamin Thompson
And I'm Benjamin Thompson, thanks for listening.

[Jingle]