

Jurassic World: just how impossible is it?

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In the movie business, bigger is usually better, bigger spaceships, bigger disasters, bigger dinosaurs and the latter was especially true in the latest installment of the *Jurassic Park* franchise, *Jurassic World*. Although the *Indominus rex* knocked the *Tyrannosaurus rex* into a cocked hat when it came to size, strength, speed and special abilities, the 'scientific' details of its creation are perhaps not so far-fetched if you accept the original premise of *Jurassic Park*. However, that is a big IF! Twenty years ago many of us enjoyed the scientific ideas suggested by *Jurassic Park*, either in the Michael Crichton book or in the Spielberg film. For those younger readers who haven't seen the original film; the idea was that scientists had managed to extract dino-DNA from a mosquito that had been trapped in prehistoric amber. This DNA was attached to a nucleic acid scaffold from a frog and 'voila!' there were more Stegosauri, Brontosauri and *T. rex*'s than you could shake a pipette at! Inevitably as we left the cinema, we asked if this would ever be 'possible'? Indeed there are current efforts to recreate long-extinct creatures, although on a slightly less ambitious scale. Whatever the source of your dinosaur DNA; be it from fossilized bones or from an amber-trapped mosquito, the chances of it being intact are essentially nil making the idea of the creation of new dinosaurs from preserved DNA more fiction than fact.

Elephant in the room

Since the publication of the mammoth genome sequence in 2008¹, there has been interest in the possibility of recreating this relative of modern Asian elephants². Basically, this involves using our current knowledge of genetics and gene function in order to predict which genes allowed the mammoth to develop its telltale traits of hairiness, smaller ears and extra fatty layers. The genes that control these processes are still present in modern elephants, but they might have slight mutations to change their function or perhaps more importantly, they will have different spatial or temporal patterns of activity. Apparently, good progress is being made with attempts to introduce changes to modern elephant DNA in order to grow 'mammoth-like' tissues in the lab³. This may be a more intellectual than practical challenge but how relevant are these experiments to any attempt to recreate dinosaurs?

Frankly, not very relevant. The first and primary issue is timescale, something that humans in general aren't very good at grasping. Mammoths lived between 5 million years ago and 5000 years ago, so DNA samples are coming from samples aged in the 1000's of years. Dinosaurs lived 100 million years ago, at least 20 times longer than even the most moderately useful mammoth DNA.

A few years ago, a group of Kiwi researchers (and clearly Jurassic Park killjoys) showed that the half-life of a DNA molecule is ~521 years⁴. This means the DNA in any sample would be all gone in 6.8 million years, let alone there being anything useful to use. However this study, which attached scientific rigour to something that we all suspected anyway, hasn't stopped attempts to isolate dino-DNA.

Quest for dino-DNA

Arguably the most famous have been the attempts of Jack Horner and team who managed to isolate dino-haem and dino-blood vessels, but alas no DNA⁵. These costly exercises are good for public engagement, but offered limited chance of isolating dino-nucleic acid. Therefore, the classification of dinosaurs does not have molecular input, but rather remains based on detailed anatomical studies, which have placed the dinosaurs as predecessors of modern-day birds. Interestingly, a number of researchers are currently attempting to recreate the dino-like characteristics of tails or teeth in modern-bird embryos. This atavistic work has had some recent success as by altering gene expression in the bird face researchers have managed to create

an ancestral-like beak structure, which resembles a 'dinosaur bill'⁶. These minute changes will be rather unsatisfying for those people hoping to see dinosaurs hatching in their lifetimes and again reminds us, if it were needed, that the changes that evolve over literally millions of years cannot be easily reproduced in a decade of lab work!

However, let's put all that negativity aside and imagine that indeed it was possible to isolate dino-DNA. Initially we'd want to know what would be the best genome 'scaffold' in which to add the dinosaur DNA. Recent evidence suggests this wouldn't be a frog as Michael Crichton suggested, but rather some species of bird would be the best candidate. If we then gained more complete dino-DNA we'd be able to identify genes that are either slightly different from modern-day birds or those that have no similarly at all or that might have novel functions.

However, in all honesty even this information would have limited use. Humans are separated from apes by many millions of years of evolution yet many

of our cellular functions are the same, so it is likely that actual genes will be almost identical between birds and dinosaurs. The differences in where and when these genes have activity will determine the different patterns of development. This is impossible to calculate from just looking at the DNA sequence and can only be experimentally determined.

Therefore, understanding how a dinosaur differs from a bird is greatly complicated by the fact that it is not just the gene sequence that determines these changes but rather where and when the genes are expressed. This is controlled by all the other parts of the genome that surround the actual genes. Recently the ENCODE project⁷ confirmed that only 1.5% of the human genome contains sequences that code for proteins and that large areas, previously thought to be 'junk' or 'silent', are in fact very important in deciding how the genes are expressed and ultimately function. Understanding the full role of this extra-genic DNA is one of molecular biology's current great challenges.



So, when trying to create our dinosaur we don't 'just' need to know about the genes but also about ALL the other DNA that controls how the genes work.

Organismal complexity

This leads on to a question about what is the minimum number of genes (and associated sequences) that is needed to produce an organism? Well that is the aim of the ambitious Yeast 2.0 synthetic biology project, which is hoping to understand how a single yeast cell works⁸. They are using increasingly cheap DNA synthesis technology to reconstruct 'synthetic' versions of each of the 16 chromosomes of yeast (which means they have been synthesized in a lab and not extracted from the yeast). They are attempting to work out which pieces of DNA they are able to remove and still get a functional yeast cell. This set of experiments aims to discover what are the minimum elements needed to 'be' a eukaryotic cell.

So back to the dinosaur...once we understand which dino-DNA genes are important and then how they are controlled, we can then build them onto our bird-genome scaffold...easy!

However, in *Jurassic World* this task isn't enough for the scientists (who didn't come across as very likable in the film and probably put the debate surrounding GMOs back years). They wanted to go even further and modify the dinosaurs they had already created, to make something 'better' and certainly more ferocious.

Thus *Indominus rex* was born. (NOTE: To be fair to the scientists, they claim that it was the public and investors that had driven them to create new dinosaurs because the *T. rex* wasn't interesting enough. The public wanted "bigger, scarier, cooler".)

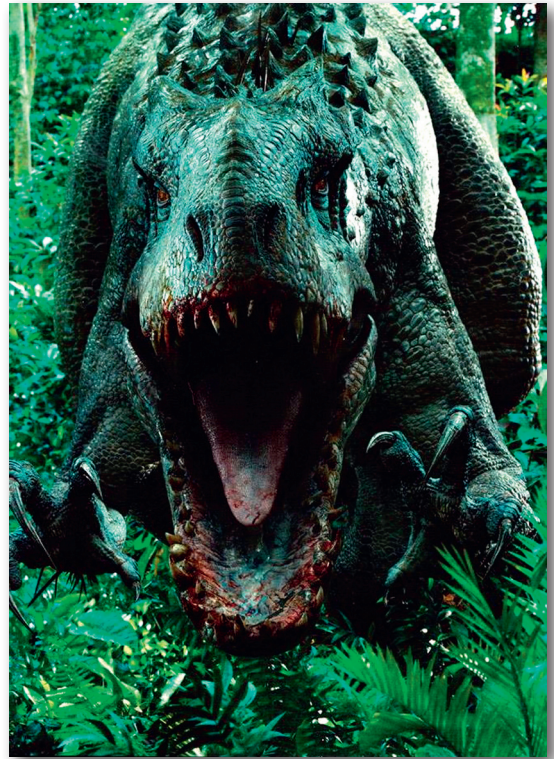
So what do we know about the *I. rex*'s 'genetic makeup'?

The *I. rex* was able to camouflage itself:

"cuttlefish genes were added to help her withstand an accelerated growth rate. Cuttlefish have chromatophores that allow the skin to change colour..."

The *I. rex* hid from thermal technology:

"tree frogs can modulate their infrared output. We used strands from their DNA to adapt her to a tropical climate. But I never imagined..."



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Modern transgenics

So would it be possible to create a hybrid animal that had these types of 'cool' modifications? Transgenic technology has been around for many years so now it's relatively straightforward to add foreign genes to organisms, whether that is adding the capability to produce spider silk in goat's milk⁹, produce flu-vaccine in tobacco leaves¹⁰ or to add glowing jellyfish proteins to many different organisms. However, these examples are built upon many experiments that went before. The ability to genetically modify an organism differs between organisms so what's 'good for the goose, might not be good for the duck', so to speak. It is not well understood why different organisms respond to genetic modification in such varying ways but the organism-specific foibles of the process need to be experimentally determined, which is often time-consuming.

A good example of this surrounds the recent excitement with gene-editing technology. The ability to modify a genome without making that organism 'genetically modified' will be a game changer for the way this type of technology is considered by the

general public. Basically, the addition of the single gene is able to specifically target any genetic change that the researcher wishes to make. The original gene can then be removed but the genetic change remains, potentially altering the organism forever.

Sounds good? Well you'd be right, as this technology has huge potential. However it doesn't work in the same way in all organisms, probably due to the way the added single gene is expressed within the target cell. As ever the 'devil is in the details' so to get this to work correctly will take time. Gene-editing technology might be a panacea, but it's still a slow-moving one.

Back again to the Jurassic World dinosaur lab, although the addition of these genes could in theory be possible, I'm not sure these scientists had enough time to work out the details to get the genetic modification process to work well and I'm definitely sure they didn't do the correct controls!

First green dinosaur?

So as mentioned in the film, would it be possible to add cuttlefish genes to a dinosaur to allow it to camouflage itself? Some insight into answering this question is provided by the recent publishing of the octopus genome¹¹. They found that octopuses have a surprisingly large genome and that they have a higher proportion of genes that are involved in neural development, which might explain their higher-than-your-average-clam intelligence. In addition, the genome contains many new 'zinc-finger proteins' (ZHP) that are involved in controlling the expression of other genes. Importantly, these ZHPs are located in cells that are involved in unique octopoid features, such as the development of suckers or in pigment-containing skin cells. The authors suggest that these new genes might help in the ability of the octopus to rapidly change colour. No doubt the researchers are now trying to figure out which of these new genes specifically help in these colour changes.

So finally, back to the camouflaged *I. rex*. If the scientists had identified the correct colour-change gene(s), if they had engineered the skin cells to respond correctly to the gene(s), if they had worked out the control parts of the genome that allowed expression in these cells and if they had developed the technology to introduce DNA into *I. rex*, then indeed, it would be possible to have a colour-changing dinosaur. In fact this would be a lot easier than the original aim of (re)creating a dinosaur in the first place, which, by the way, is impossible! ■



Geraint Parry is the National Coordinator for GARNet, a BBSRC-funded network based at Cardiff University that supports plant scientists in the UK and beyond. In the current funding period we are supporting technological innovations in synthetic biology, use of big data and the effective translation of basic research. Information about our activities can be found at www.garnetcommunity.org.uk Dr Parry is an honorary lecturer at the University of Liverpool and previously spent a decade of research in the USA. If the premise of this article was proven to be totally incorrect, he'd love to have a baby *Triceratops*.

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