Roaming wild: Tigers are among those species that may become extinct in the wild, even though their survival in captivity is assured. By engaging in education and conservation work, zoos can help to make sure that this situation does not become a more widespread phenomenon. The picture shows a Bengal Tiger in Karnataka, India. (Photo: Karunakar Rayker.)

in Phoenix, Arizona, USA, for instance, supports conservation projects *in situ* with its annual grants launched in 2009 (http://phoenixzoo.org/conservation/global-conservation/). In total, the more than 200 accredited members of the (US) Association of Zoos and Aquariums (AZA) spend over $160 million each year on *in situ* conservation initiatives based in countries around the world (https://www.aza.org/conservation-funding/).

Bristol Zoo (UK) has recently completed a fundraising appeal to save 750 abandoned African penguin chicks, which were then successfully reintroduced into the wild. This species is endangered to the point that saving individual chicks is of crucial importance for its survival. In a press statement, Christoph Schwitzer, Director of Conservation at Bristol Zoological Society, said: "Unless conservation charities such as us intervene, these chicks would starve to death. We wanted to help so we launched an urgent appeal. Recent research shows that penguin chicks hand-reared at the rescue centre in South Africa survive and reproduce just as well as those naturally reared, when reintroduced back into the wild. We would like to say a massive thankyou to all those who supported the appeal — the money raised will literally help to save a species." In situations like these, captive animals can serve as ambassadors to motivate people to help saving their conspecifics in the wild.

Outlook

Given that wildlife attractions tend to attract not only millions of visitors but also a lot of media attention as well as the critical gaze of just about anybody who worries about the relations between humans and animals, they too may have to adapt to the times of climate change and biodiversity loss. In the future, taxpayers and visitors may demand that the zoos and aquariums prove their claims that they are doing good deeds for humans and animals alike, beyond the traditional mission of just offering access to wildlife for entertainment.

Nobody would want the zoos and aquariums to become repositories of numerous species labelled 'extinct in the wild'. So the challenge for all these institutions is to find their role in helping the animals that are still wild and free.

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Q & A

Alcino Silva

Alcino Silva is a Professor in the Departments of Neurobiology, Psychiatry, and Psychology and Director of the Integrative Center for Learning and Memory at the University of California in Los Angeles. He was one of the pioneers of the field of Molecular and Cellular Cognition, and in 2002 founded and became the first President of the Molecular and Cellular Cognition Society. His laboratory has made seminal contributions to learning and memory mechanisms, including the discovery of memory allocation mechanisms in neuronal networks. His laboratory has also developed treatments in mice for learning and memory disorders, including neurofibromatosis type I and tuberous sclerosis. Recently, he was awarded the Order of Prince Henry, a MERIT award from the NIA, the Senior Roche Award for Translational Neuroscience, and became a fellow of the American Association for the Advancement of Science.

Why did you decide to become a neuroscientist? I grew up in Portugal, and the standard high school curriculum there included philosophy courses. Although I have long forgotten most of what I learned, an age-old epistemology question stayed with me all of these years: "how can we be sure of what we know?" This question fascinated me because the answer could potentially affect every single aspect of human existence, including every single discovery in science. For example, how can we be sure of anything we learn, if we do not understand how our brains acquire, process and store information? Perhaps, all human knowledge could be biased by the peculiarities of our brains, which were designed to survive the wilderness of Africa. It is unlikely that evolution optimized our neurobiology for grasping physics, chemistry or biology! When I had an opportunity to come and study in the USA, I took it without hesitation, and the rest of my life seemed to follow its course the moment I landed in Kennedy Airport in the summer of 1978…

Has your work actually addressed the question that motivated you to become a neuroscientist? I like to believe that every experiment that I have ever done as a scientist has ultimately targeted that one question one way or the other. I decided to do my PhD work with Raymond White because I believed that the then new field of human genetics would provide a strong anchor into brain mechanisms of learning and memory. While I was a graduate student, I learned about Mario Capecchi's revolutionary molecular genetics work with mice, and immediately decided to use knock-out mice to study molecular and cellular mechanisms of learning. This technology completely changed neuroscience from a discipline of many silos — molecular neurobiology, neurophysiology, systems neuroscience, behavioral neuroscience, and so on — to a more integrated discipline, where explanations of behavioral phenomena included multidisciplinary studies with molecular, neurophysiological, and behavioral components. For example, in Susumu Tonegawa's lab, I targeted a synaptic kinase, the alpha calmodulin kinase II, and with Charles Stevens lab at the Salk and Jeanne Wehner's lab at the University of Colorado, we were able to show that this synaptic kinase is critical for long-term changes in synaptic strength and for learning in mice! In my own laboratory, I continued to study not only learning, but also different phases of memory. For example, we showed that the transcription factor CREB is critical for both the stability of synaptic plasticity and memory in mice. Later on, we worked on the mechanisms responsible for remote memory, and showed that synaptic plasticity in neocortical networks is essential for this late phase of memory. So, this and related work from our lab and many other labs around the world has demonstrated that synaptic plasticity has a critical role in learning and memory, and by implication, that this form of cell biology must play a critical role in our ability to learn about and radically transform the world around us.

What about your studies of neurodevelopmental disorders such as neurofibromatosis type I and tuberous sclerosis — how does this work tie in to your epistemological quest? I realized that it was critical to connect the molecular, cellular and circuit mechanisms we were discovering in mice with cognitive processes in humans. My PhD years in Ray White's lab taught me about the power of human genetics, and I realized that the study of mechanisms responsible for learning disorders could provide a bridge between our studies in mice and learning mechanism in humans. If we were successful in using mechanism-based treatments developed in mice to help patients, we would have a compelling bridge between studies of learning in mice and humans. And then, I met the families affected with these disorders and the work took on an entire new degree of urgency and importance for me. The idea that our work may one day help the millions of people around the world with NF1 and TSC is simply wonderful. I will never forget the first time we realized we had in our hands conclusive evidence that the learning deficits associated with NF1, a neurodevelopmental disorder that affects millions of people world-wide, could be reversed in *adult* mice! That result changed the way we looked at this class of disorders, as many people were convinced that the only real hope was to intervene during development. Within a few years there were many other examples that reinforced the hope that adult treatments may actually be successful in neurodevelopmental disorders.

Do you have any scientific heroes? Absolutely! I always feel chills up my spine when I see the prescient drawings that Ramon Cajal made of cellular networks in the cortex! Many people do not realize that the act of seeing in science is deeply creative. Cajal literally created many of our modern notions of cells and their possible functions in the brain. In my own field, the very models that guide our work to this day go back to ideas and hypotheses that Cajal proposed now more than 100 years ago! On the other end of this spectrum, I deeply admire many of the young people

that worked with me over the years. It is hard when they leave the lab, but many times I felt like getting up in a meeting and bragging that so-and-so that just gave an amazing talk was once in my lab!

You mentioned your students — what is the best advice you have ever been given? That would be what Jim Watson told me when I was setting up my own lab in Cold Spring Harbor laboratory. He told me that I should always surround myself with people that made me slightly uncomfortable because they were smarter than me. I loved that advice for several reasons. For one, it implied that laboratories should be intellectually open and rankless places, where ideas and ability, not hierarchy, should be first and foremost.

What do you think is the single most important thing that could be done to accelerate our search for the biological mechanisms of cognitive function? To my mind, the answer is unequivocal. There is an enormous problem, a problem so large and serious that I think it is emerging as the single biggest impediment to real progress in the biological sciences, including neuroscience: we no longer can navigate the immensity of the published record and optimize research decisions! The size, complexity and interconnectedness of information in biology are growing at an unprecedented pace that urgently demand new tools and new

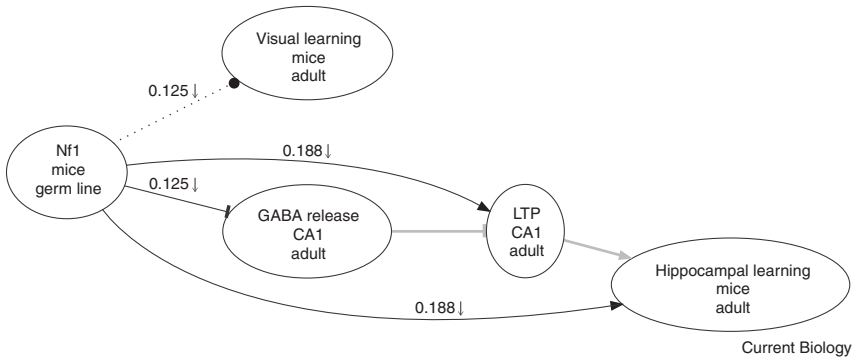

Figure 1. A research map representing results from a research paper.
Each node in the graph has three items that describe the name of the node (top), as well as spatial (middle) and temporal (bottom) information that defines it. Nodes are connected by edges that characterize the nature of the causal relations represented, including excitatory (sharp edges), inhibitory (dull edge) and no relation (dotted line). Hypothetical edges (in gray with no edge weights or symbols) reflect hypotheses that help to structure the data pictured in the graph. Each edge representing experiment(s) also has a score that reflects the amount of evidence supporting that connection, and symbols that reflect the types of experiments carried out, including an upward arrow for Positive Manipulations, a downward arrow for Negative Manipulations, and a triangle for Mediation Experiments (see text for definitions). This graph was generated by a free and open source web app (researchmaps.org).

approaches. It is simply no longer possible for individual biologists to be aware of even a fraction of the published findings potentially pertinent to their work. The library of medicine, for example, now includes the results of more than an estimated 100 million experiments. This number will probably double in the next ten years! Things do not get any better even at an individual level. In the last couple of years, for example, I read very carefully a couple of hundred research papers because they are directly and critically relevant to work in my lab. Those papers reported approximately two to three thousand experiments. I know that I have forgotten the majority of these experiments, and remember incorrectly or incompletely a scarily large number of them. I actually know this because of our researchmaps.org project, because I kept track of many of these experiments in a database. Even for this very limited research set, it is simply impossible for me, or anyone else for that matter, to reason systematically through all of those results, remember them with clarity and compute their implications! When the implications of what has already been published remain buried in the ever-growing size, complexity and interconnectedness of information in biology, how can scientists, like myself, reasonably optimize future research plans? The key is that biology has not always been this way: I remember that, as a student, biology was made up of disciplines that were like little self-sufficient islands of information, where individual scientists could master and remember most of the relevant information.

There is a great deal of work that tackles the big data problems you just described: what is your lab specifically doing in this area? We have developed graphical and interactive web tools — researchmaps, alluded to in the previous answer — that track, map and weight causal evidence. Although causal assertions are the very fabric of biology, there are currently no tools to help biologists keep track of the increasingly more complex network of causal connections derived from published findings. Simply put, the tools we engineered help biologists keep track of causal information. Importantly, the framework and principles used to build research maps, including convergency and consistency, reflect common practices in biology. It is important to stress that we did not invent these principles. We simply derived algorithms that capture their intent, and automated the process of systematically using them to map and manipulate causal information. Because all of this is kept in interactive and graphical databases that preserve the provenance of each mapped experiment, it is a matter of a few key-strokes to get to either a graphical summary of any paper in the database, or to generate tailor made graphical summaries that combine specific experiments from any paper in the database. We have essentially build an app that biologists can use to keep track of important information, and that allows them to manipulate that information in ways that would be essentially impossible without it. The web app, researchmaps.org, that we engineered is an open source, completely free academic resource. The maps are easy to generate, combine, manipulate, query, and so on.

What do research maps actually include? Research maps are simply networks where biological phenomena, their identity and properties (the nodes in the map) are linked by weighted causal connections, the edges in this network (Figure 1). These edges represent one of three possible types of causal connections between any two phenomena of interest: excitatory, where one phenomenon promotes the other; inhibitory, where one inhibits the other; or simply a lack of measurable effect of one on the other. Users can also include hypothetical edges in their maps. Amongst other things, hypothetical edges can help to organize information in the maps. A score from zero to one assigned to each edge gives users a sense of the strength and consistency of evidence represented by each connection among the phenomena represented. Additionally, symbols inform users of the types of experiments represented in each edge.

Although there are tens of millions of experiments testing causal relations in biology — for example, between two phenomena A and B — they fall into four classes: Positive Manipulations, where A's levels or activity are increased and the result measured on B; Negative Manipulations, when A's levels or activity are decreased; Non-Interventions, the goal of which is to track how A co-varies with B; and Mediation experiments, designed

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to determine whether C is part of the mechanism by which A contributes to B. Biologists use convergency and consistency amongst these experiments to judge the strength of any causal assertion. Therefore, in research maps convergency and consistency amongst results increases the score assigned to each edge, while contradictory results have the opposite effect. By selecting any one edge in a particular research map, users can be directed to the exact experiments and associated research papers represented by that edge. Of course, there is much more to researchmaps, but this gives you a sense of what these maps are all about.

Is this the theme of your recent book **Engineering the Next Revolution in Neuroscience?** I smile every time I read that title… It was intentionally provocative. Nevertheless, the problem we discuss in the book, the problem we tackle in our researchmaps project, is a big problem, and solving it will undoubtedly 'revolutionize' not only neuroscience, but perhaps any other field of science where causal information is key to progress. I know that this is a big claim, but it never pays to be shy about big problems. Beyond big data problems that individual neuroscientists face, the book also discusses the need for formal studies of how to optimize research planning. I dream of a time when scientific choice will be as rigorous and principle-based as algebra and geometry. This by no means excludes human creativity from the scientific process! No, it simply hones our creativity, focuses it onto those areas where it will be most useful and productive. The book really is about these and related themes. By the way: if we are ever to know how we learn and transform the world around us, we need formal tools like researchmaps to get there, and we may even need them to recognize that we have arrived.

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Quick guide

Chromothripsis

Emily M. Hatch and Martin W. Hetzer*

What is chromothripsis? The word 'chromothripsis' literally means 'chromosome shattering'. Chromosomes that undergo chromothripsis first fragment into many pieces and then get stitched back together in a random order by DNA repair processes, most likely non-homologous end joining. This generates a highly rearranged chromosome from a single catastrophic event (Figure 1). Previous complex chromosome rearrangements could be explained by multiple independent breakage and repair events accumulating on a chromosome over time. However, specific features of chromothripsis sequences — including highly clustered breakpoints, no segment amplification, and alternating retention and loss of heterozygosity along the chromosome — make it likely that the chromosome is breaking all at once. Currently, chromothripsis has been identified in cancer cells and in the male germline.

Why haven't I heard about this before? Chromothripsis was discovered fairly recently by paired-end sequencing in chronic lymphocytic leukemia. A mixture of whole genome sequencing, array-based comparative genomic hybridization (aCGH), and single nucleotide polymorphism (SNP) array analyses have now identified these massive chromosome rearrangements in many types of cancer. These data uncovered an unanticipated amount of small chromosome rearrangements and renewed interest in how chromosome structural variation contributes to cancer development.

Several types of 'all-at-once' chromosome rearrangement processes, including chromothripsis, have now been described. Chromoanasynthesis looks very similar to chromothripsis in that it often affects a single chromosome or chromosome arm, but is characterized by the amplification of numerous segments and has signatures of replication-mediated repair. Chromoplexy occurs when multiple DNA breaks are present throughout the genome at one time and each end of each break finds a different partner to pair with during DNA repair. This results in the joining of many distant loci and chromosomes together. The term 'chromoanagenesis' (chromosome rebirth) has been proposed to describe these new types of complex chromosome rearrangements.

How bad is chromothripsis? In tumor cells chromothripsis has been shown to result in the loss of tumor suppressors and dysregulation of genes with known cancer links. In addition, shattering can cause oncogene amplification. Chromosome segments that fail to get reincorporated into the main chromosome can circularize to become double minutes. These small DNA circles are frequently amplified and, if oncogenes such as *MYC* are present within the double minutes, they become massively upregulated. Because chromothripsis affects a large number of genes at once, it can bypass the time delay inherent in the gradual accumulation of mutations and quickly stimulate cancer development or evolution. Consistent with this, chromothripsis is associated with poor prognosis in several cancer types (e.g. neuroblastoma), although it is unclear whether this is a causal link.

The flip side of affecting a large number of genes at once is that most chromothripsis events are going to be lethal. Significant misregulation of gene expression, loss of heterozygosity, and increased aneuploidy as a result of segments being lost are likely to be detrimental to the cell, regardless of which particular sequences are hit. This point is clear from examples of germline chromothripsis. Patients with congenital disease due to chromothripsis typically have few rearrangements and have retained almost all of the chromosome pieces. In cancer, chromothripsis has been correlated with loss of pathways that stabilize genome stability, such as inactivation of p53. In addition, cancer cells often undergo changes, such as an increase in ploidy, that can buffer the deleterious effects of aneuploidy and thus could generate an environment in which the benefits of highly rearranged chromosomes can outweigh the negative consequences.