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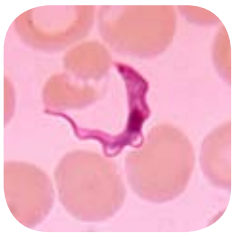

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Cover Image: Di Lu from the Research School of Chemistry

The Editor's Corner

Under the Microscope - Technological Limits and Physical Limits

Dr Tim Wetherell

We're running a story in this edition about a group of researchers using lasers and holography to create an optical neuron stimulator that can also operate as a multi-photon microscope. The project combines expertise from many areas and uses a number of advanced technologies to create something quite extraordinary. It also highlights what I believe is one of less widely understood things about scientific advance, that is the difference between technological limitations and limitations of physics. Looking at the history of microscopy provides a beautiful illustration of this distinction.

The very first microscopes were simple biconvex magnifying lenses placed between the eye and the specimen and have been in use since at least the Middle Ages. But regardless of the shape of the lens and the geometry of the microscope, the highest magnification that can be generated in this way is only about 100x. This is what's known as a technological limitation - there is a better way, you just haven't found it yet.

That better way was discovered in the seventeenth century with the invention of the compound microscope. The compound microscope employed two lenses, one near the specimen called the objective and a second near the eye called the eyepiece. Although early compound microscopes were plagued by optical aberrations, they gave a huge advance in performance over a simple magnifier.

By the nineteenth century opticians had learned how to correct for all the aberrations in objectives and eyepieces and were producing superb microscopes capable of magnifying several thousand times. But here they ran into a problem. No matter how good the lenses and how high the magnification, the very smallest feature that could ever be seen was about 0.5µm across. What they were experiencing is known as a limitation of physics - Regardless of how clever your design is, the laws of nature prevent any improvement in performance using that particular technology.

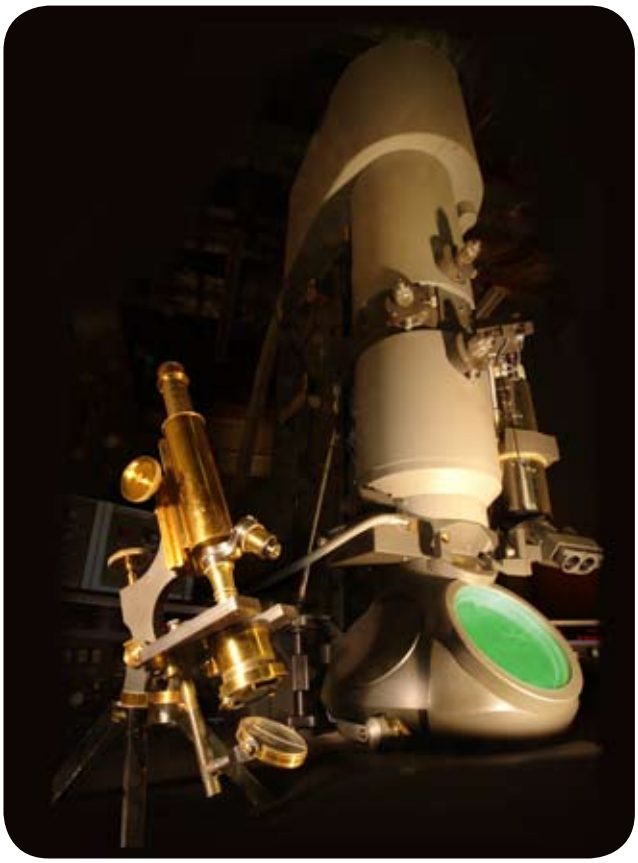
This problem was caused by the wave properties of light. Any wave passing through any aperture experiences diffraction which serves to spread the energy. In a microscope this means that light waves bouncing off a particle are spread into what's known as an Airy disk, the size of which depends on the wavelength of the light. Because visible light has a wavelength of about 0.5µm, no matter how you configure the optics, the smallest thing you can ever see in a visible light microscope is a fraction of a µm across.

It wasn't until the 1920s that physicists were able to get around this using a completely different technology. A piece of early quantum mechanics known as de Broglie wave-particle duality tells us that every particle behaves as a wave and visa-versa. The de Broglie relation gives the equivalent wavelength of any particle by:

$$\lambda = h/p$$

Where λ is wavelength, p is momentum and h is Plank's constant (6.626 × 10-34 J seconds). From this, the wavelength of a moving electron can be exceedingly small if the electron's momentum is high enough.

Because electron trajectories are bent by magnetic fields, it's possible to make electron lenses using electromagnets. This enabled physicists to create electron microscopes with sub-nanometer wavelengths allowing us to see detail down to those scales.



A modern transmission electron microscope and an optical microscope from around 1900. Often technological advancement runs into obstacles created by the laws of nature and the only way forward is to move to a different technology.

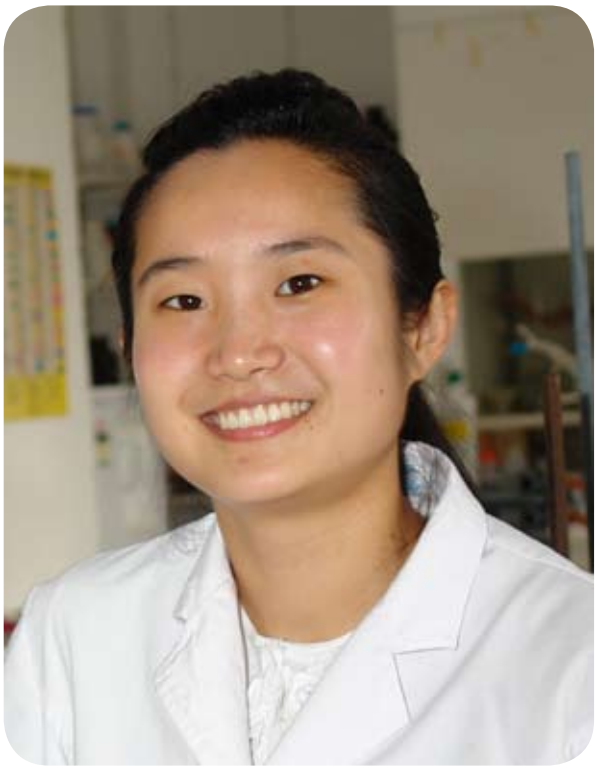
Arsenic in Sponges

The Promise of Naturally Occurring Compounds in Medicine

Arsenicin A, $As_4O_3(CH_2)_3$ is a complex molecule containing four arsenic atoms in a cage-like structure. It's found in tiny quantities in the New Caledonian marine sponge Echinochalina bargibanti and is the first poly-arsenic compound to have been isolated from nature. Its role in the marine sponge remains unknown, partly because of a lack of detailed knowledge about its chemical structure. The difficulty in determining its structure is that the quantity of Arsenicin A that can be extracted from living sponges is miniscule so the only diagnostic techniques chemists have been able to apply are those only requiring very small quantities, such as nuclear magnetic resonance and mass spectrometry.

However, to really get to grips with the detailed structure of the Arsenicin A molecule and its biochemical properties, requires much larger samples that can be studied by techniques like X-ray crystallography and analytical chemistry. Given the low natural concentrations of Arsenicin A, the most effective way to obtain a large quantity is to develop a method of synthesising it in the lab. Di Lu, is a graduate student in the Ligand Design and Synthesis Group at the Research School of Chemistry doing just that. Her honours project was to develop a synthetic process to construct Arsenicin A from other simpler arsenic compounds.

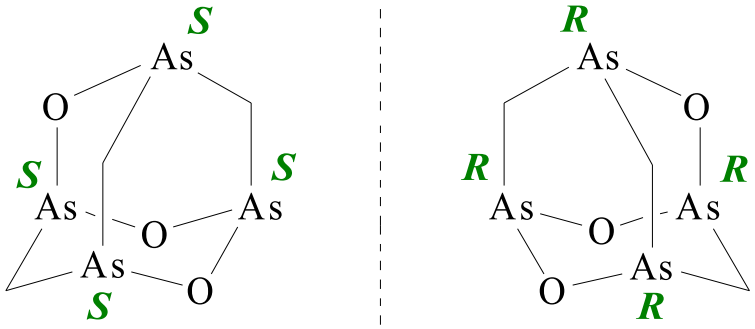
"Designing a synthesis process was particularly difficult when the exact structure of the desired compound wasn't well known." Di explains, "Computational chemists had calculated that there were six possible configurations of Arsenicin A based on the NMR data, but until we had enough to do a complete analysis it was very difficult to know which form the actual molecule took."



Di Lu

After almost a years work, Di succeeded in developing a viable synthetic route to Arsenicin A. Spectral data for the product are consistent with those reported for the tetraarsenic compound isolated form the New Caledonian marine sponge and the structure has been confirmed by X-ray crystallography.

Following on the success of her Honours year, Di is now expanding her Arsenicin A work as part of her PhD studies. "Quite apart from providing substantial quantities of Arsenicin A for analysis, having a known method for its synthesis means that if it has useful properties we already have a way to create lots of it." Di says. And there's every reason to suspect it will



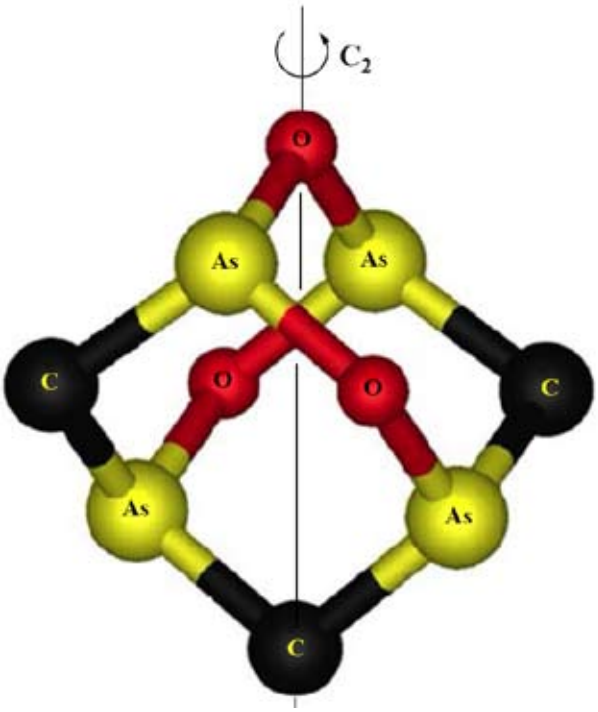
$(R_{As}^{*},R_{As}^{*},R_{As}^{*},R_{As}^{*})$-Arsenicin A

Structure of Arsenicin A showing the two enantiomers (which are mirror image of each other) containing four stereocentres

have useful properties because Arsenicin A is a very similar compound to arsenic trioxide, except that it contains four rather than three arsenic atoms. Arsenic trioxide is well known as a highly effective treatment for a type of leukaemia known as Acute Promyelocytic Leukaemia.

"Arsenic compounds have quite a long history of medicinal use, although because Arsenic is a well known poison, patients are often apprehensive about its use." Di says, "But you eat arsenic compounds every single day in many foods. And providing it's the right compound and you don't eat huge amounts, it's fine because our bodies have quite a high tolerance to it."

In fact in the days before antibiotics, arsenic compounds like Arsphenamine (also known as Salvarsan) were the only effective treatments for diseases like syphilis and sleeping sickness. Even today, arsenic compounds provide an effective treatment pathway for certain types of fungal and bacterial infections that cannot be treated with antibiotics. As work progresses on the understanding of the biological role of Arsenicin A, scientists like Di are hopeful that they may provide new and powerful tools in the treatment of disease.



(SAs, SAs, SAs,SAs)-Arsenicin A showing the C2 axis. Hydrogen atoms have been omitted for clarity

New Caledonian marine sponge Echinochalina bargibanti

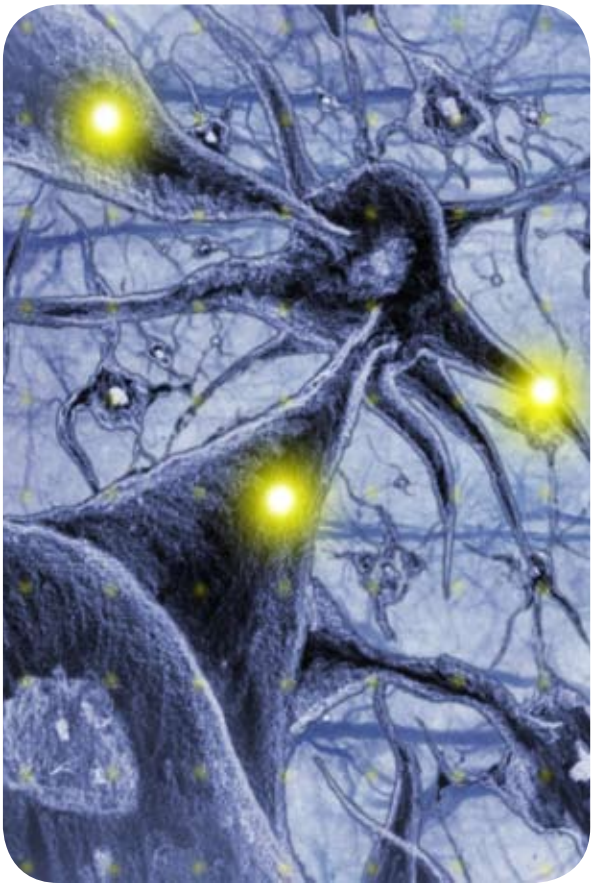
The Holographic Neurone

Tim Wetherell

When physics and biology combine

For some time neuroscientists have been using microscopic electrodes to excite nerve cells in order to study their response to various stimulation patterns and to unravel the secrets of how nerves process information. However, inserting an electrode into a dendrite only a few µm thick is a very difficult task. Doubly so if you require multiple points to be stimulated at the same time. This approach is also slow and painstaking so you can't really select and excite a sequence of contact points anywhere near as fast as it happens in living neural networks.

This reliance on electrodes has posed some limitations on the types of experiments neurobiologists have been able to conduct. However, two neurobiologists, Dr. Christian Stricker and Prof. Steve Redman of the John Curtin School of Medical Research, have recently achieved a breakthrough in this area in a collaborative project with physicists at the ANU Department of Quantum Science.



The Holographic Neurone Stimulator uses localised light pulses to stimulate points on living neurones in real time.

"We were looking for a system that could generate real time images of living neurones in three spatial dimensions and then stimulate those neurones at several specific points." Dr Stricker explains. "So we approached physicists Professor Hans Bachor and Dr. Vincent Daria to explore what we might be able to achieve collaboratively." As often happens with collaborations, experts from diverse fields were able to pool their expertise and create a system that none of them could have built individually. The result was a new tool in neuroscience which the team have christened the Holographic Neuron Stimulator.

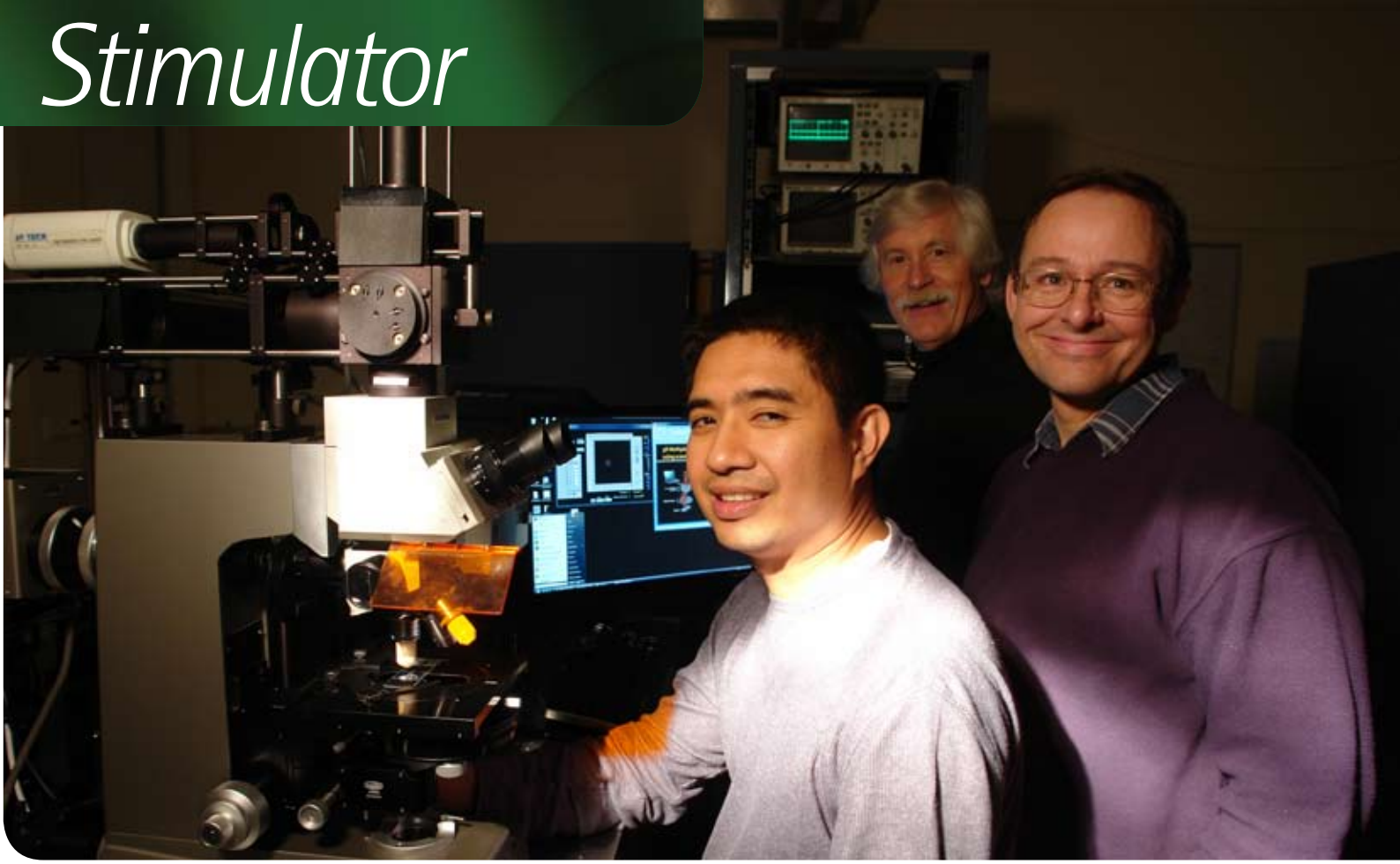
The Holographic Neuron Stimulator works by immersing a sample of living neurones in a solution containing neurotransmitters - a class of molecules that stimulate neuronal firing. Of course if the cells were simply bathed in active neurotransmitters they would fire constantly. So scientists have adapted a "caged" neurotransmitter molecule such that it only becomes active (or "uncaged") in the presence of a strong light field.

In order for the system to work effectively, the triggering light has to be highly localised at selected points in space. The team decided that the best way to achieve this was to use a holographic projection technique.

A normal photographic hologram is a combination of dense and transparent regions in a photographic emulsion that don't outwardly look like anything recognisable. But when illuminated by a broad plane coherent wave, such as that produced by an expanded laser beam, the dense and transparent regions in the hologram project an interference pattern that mimics an object in 3 dimensional space. In conventional holography, the hologram is recorded on a photographic plate using the reverse process – laser illumination of a real object and interference with a second beam. Although many holograms are recorded in this photographic way, it's quite possible to calculate the holographic pattern of an object using optical theory alone. Such pre-calculated holographic patterns are commonly called Computer Generated Holograms (CGH). A programmable electronic light modulator can be encoded with such a CGH, and project a complex three dimensional light pattern from a single laser.

The projected light pattern from the hologram can be in the form of tiny spots of light, which could in principle be used to create bright spots within sections of neural tissue. If that tissue were surrounded by an inactive "caged" neurotransmitter solution, the holographically projected bright spots would release (or uncage) the transmitters at various points in the sample. If those points were made to correspond with the location of a nerve cell membrane, the result would be to stimulate the cell and potentially initiate a nerve impulse.

Stimulator



Dr. Vincent Daria, Dr. Christian Stricker and Professor Hans Bachor with the prototype Holographic Neurone Stimulator

This is precisely what the Holographic Neuron Stimulator does. Using a programmable hologram to alter the shape of the laser beam and a powerful computer, the machine creates a series of patterns of spots in precisely determined locations for stimulating various sections in a neuron. This is more versatile than using a simple mask or lens. Another advantage is that it can be changed in real time allowing the light spots to be switched and moved every few milliseconds. In this way scientists can stimulate several points on the same neurone either simultaneously or in a set temporal sequence.

A significant challenge with any optical neurone stimulating system is correlating your light spots with features on the actual neurones in the sample. The Holographic Neuron Stimulator achieves this by using the same holographic technique to create a special kind of microscope known as multi-photon fluorescence microscope or MFM.

An MFM works by using a femtosecond-pulse laser to excite natural molecules in the sample into fluorescence. The simplest kind of fluorescence is when a molecule absorbs a highly energetic photon and re-emits a less energetic one. This is commonly seen when things glow under ultraviolet light. This isn't very useful in microscopy as it would cause the entire sample to absorb light and glow at once. So the fluorescence event employed by a MFM is the absorption of two or more low-energy infrared photons to excite one molecule, which then emits in the visible spectrum. Because of quantum rules, in order to raise the energy in two jumps, both photons must be absorbed by the molecule at exactly the same time. Hence, to increase the probability of simultaneous multi-photon absorption, the density of photons at an instant of time needs to be very high, which can only be achieved in a strongly focussed pulsed-laser with pulse-width in the order of several femtoseconds (10^{-15} s.)

Prior to using the Holographic Neuron stimulator to excite impulses, a 3D image of the neuron sample is created by switching the system to MFM mode. By raster scanning the femtosecond-pulse laser beam across the sample very quickly, a beautiful crisp three dimensional image of the neuron is generated. Once the 3D image of the neuron is acquired, the hologram for projecting the appropriate light spot pattern is calculated and encoded on the programmable hologram.

To a neuroscientist trying to understand how billions of individual neurones integrate together to create complex structures like the human brain, this new technique offers a very exciting opportunity to do new science. "The great thing about this set up is that you can generate an image of a living neurone in situ, identify points that you wish to stimulate, then switch to stimulate mode and directly hit those points in any sequence you like. " Dr Stricker says. "In neuroscience we are always looking to push the boundaries and this should really help us do so." He is looking forward to the first trial runs of the stimulator.

Growing Trees in Future Tents

David Salt

Probing the Response of Plants to Climate Change

How will our plants grow in a greenhouse future? It's projected that our atmosphere will contain elevated levels of carbon dioxide (CO_2). Carbon dioxide is essential for plant growth, so does having more of it around mean plants will grow faster? And if they do, will they absorb greater amounts of carbon from the atmosphere? The answers to these deceptively simple questions have massive implications for agriculture and our understanding of climate change. Plant scientists in the School of Biology (SoB) (in collaboration with partners at the University of Western Sydney) are attempting to throw more light on these issues by studying how trees respire when raised in an atmosphere of the future. This is achieved by growing a whole tree in a massive transparent tent – a Whole Tree Chamber – in which CO_2 is present in concentrations expected to be experienced in 50 to 60 years time.

Measuring respiration rates in leaves on trees being grown in atmospheres of the future

Understanding the interaction of CO_2 and plants is central to our understanding of the global carbon cycle. Humans currently release around 6-7 gigatonnes of carbon into the atmosphere every year but plants take up around 20 times that amount through photosynthesis. A significant proportion of this carbon is then released in plant respiration, the process of growth that uses the stored energy captured by photosynthesis.

"To effectively model the future carbon economy we need a thorough understanding of how plants photosynthesise and respire at elevated levels of CO_2," says Associate Professor Owen Atkin from the Functional Ecology Group at the SoB. "While there are many ways of estimating this, one of the best is to grow a whole plant in an atmosphere with elevated CO_2 levels. Other methods include sealing up leaves and branches in bags containing a modified atmosphere but the gold standard is looking at the whole plant."

And this is exactly what's being attempted in the Hawkesbury Forestry Experiment, a unique national facility that has been established at the University of Western Sydney (UWS). It involves growing blue gum trees, a fast growing plantation species, in large chambers in which the CO_2 and moisture can be controlled.

"The trees were planted in 2007 and they were placed in chambers which enabled the environment around individual trees to be manipulated," explains Atkin. "They have 12 chambers, six of which have ambient atmospheric CO_2 concentrations and the other six have elevated CO_2 concentrations. The elevated levels simulate CO_2 concentrations that we'll have later this century, around 640 parts per million.

"But the experimental facility is looking at more than just CO_2 levels because one of the expected impacts of climate change is an increased frequency of drought. So the experiment will also look at this. In the ambient and elevated chambers half the trees have been subjected to drought conditions, and the other half to a well watered regime."

While the experimental facility is being managed by UWS and associated partners, it is a national resource established to study a global phenomenon. Researchers from around the country have been invited to participate and apply their special research strengths on the encased trees. Associate Professor Atkin's interest is in plant respiration under varying environmental conditions, and the opportunity to work with the trees has allowed him to fill in an important information gap in modelling carbon exchange and respiration.

"The process of respiration releases a huge amount of CO_2," says Atkin. "Anywhere between 20-80% of the carbon that

Owen Atkin is attempting to understand plant respiration under elevated levels of carbon dioxide.

comes in through photosynthesis is respired everyday by whole plant respiration. Half of it takes place in leaves and the other half largely happens in the roots. So it's a big player in terms of the carbon economy of an individual plant, and it's also a big player from the point of view atmospheric CO_2 concentrations.

"Most of the global circulation models that predict future climate have a photosynthesis component and a respiration component. But the respiration component has several weaknesses in its underlying assumptions. For example, one assumption is that respiration increases exponentially with rising temperature but we know that it doesn't. Respiration doesn't just keep going up with temperature; it acclimates, it seasonally shifts its temperature response curve as you get a warming.

"And large scale models are unable to predict accurately respiratory rates that are occurring in forest trees. Without that we can't properly model how quickly those trees will grow and the contribution those trees will make to atmospheric CO_2 either in a negative or positive way.

"So, it's extremely important that we understand how environments impact on this process of respiration in plants. This experiment was very useful because it enabled us to access whole plants that were going to experience future elevated levels of CO_2. Plus we could study the impact of drought.

"I was excited to take part in the Hawkesbury Forestry Experiment because it's the only facility of its type in Australia. It enables us to quantify the rate of carbon uptake by entire canopies through time. And the Whole Tree Chambers also

have a partition between the above and below ground part of the tree that allows them to separate the shoot processes from the soil and the roots so we can quantify CO_2 release from the below ground part as well."

Working with ANU-based postdoctoral fellows Kristine Crous and Joana Zaragoza-Castells, and colleagues at UWS (Professors David Ellsworth and David Tissue) Atkin has been travelling up to visit the enclosed trees every 4-6 weeks in the latter half of 2008. Each visit lasted several days during which they measure respiration rates from 5am in the morning through till 11.30pm at night.

They found that the trees growing with elevated CO_2 levels were exhibiting elevated rates of photosynthesis and were respiring at higher rates. This was expected but they also found that the leaves were thicker and there was a change in leaf chemistry with lower levels of nitrogen being present.

"We've found that elevated CO_2 affects the plant's respiration rates," explains Atkin. "It enhances it on an area basis, though not so much on a mass basis.

"Drought has a big impact on respiration on elevated and ambient CO_2 trees. Significantly, the decrease under drought was quite pronounced under elevated CO_2. Under drought conditions, respiration rates come right down to the same basal rates of the ambient level plants. So, they both have dropped their rates, but one set of trees (the plants growing in elevated CO_2) start a bit higher.

"It makes sense when you consider that the plants have to respire; if the leaves don't respire they're dead. So there's a certain basal rate they must maintain in order for their tissues to remain viable. Remaining viable during drought means that when water becomes available they can start taking advantage of it.

In a modelling context, drought has a much bigger impact on the respiratory fluxes of a CO_2 elevated plant; they start from a higher point but they come down to a similar point. These kinds of empirical data are critical if our models are to be valid."

The first crop of trees grown in the enclosures has now been harvested and the hope is that the Hawkesbury Forestry Experiment might grow several more crops over the coming years to better explore trees and carbon exchange.

"Carbon sequestration is a big strategy for managing global carbon but there's so much we don't know on how climate change impacts on the rate of carbon movement in and out of trees," says Atkin. "Working with experimental facilities such as this will be critical if our efforts to effectively manage carbon with trees works over time."

The Hawkesbury Forestry Experiment is growing whole trees in chambers in which future atmosphere's can be simulated

The Importance of Trees

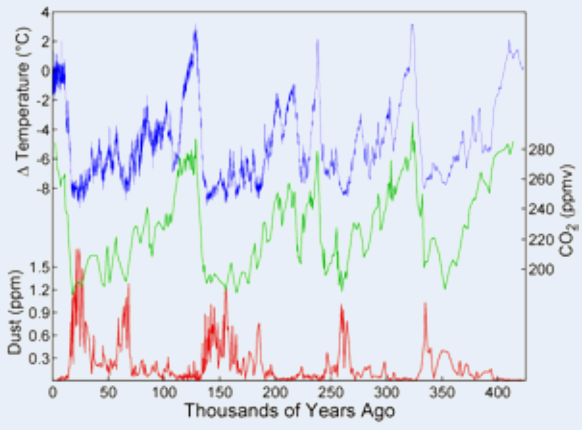
The Earth's climate is generated by a hugely complex series of interactions between solar radiance and the atmosphere, oceans and landmass. There are many natural factors that influence this such as long term variations in the Earth's orbit known as Milankovitch cycles, volcanism and continental drift. However in recent years the greatest concern has become the effect of increased atmospheric CO_2 caused by burning fossil fuels.

Because climate systems exhibit chaotic behaviour it's very difficult for scientists to create models that predict future scenarios with perfect accuracy. There are however clearly identifiable trends that emerge and that are backed up by data from the Earth's past. Once such data set is a series of cores taken through the Vostok glacier in Antarctica. By analysing the ice and air bubbles trapped inside it, scientists have been able to build up a picture of the levels of CO_2 and temperatures going back over 400,000 years. The correlation of CO_2 levels with temperature rise is very clear to see.

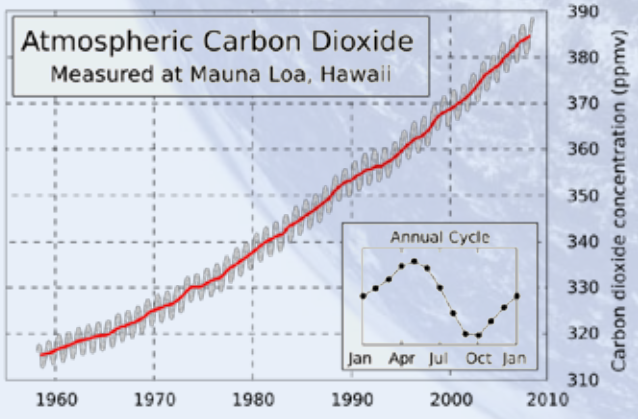
Given the existing elevated levels of atmospheric CO_2 and the seeming inevitability of them climbing even further in future years, it seems that the Earth will become warmer in the future. Just how much warmer depends not only on how much CO_2 we release, but also on how natural carbon sinks like vegetation respond to this.

Plants both on land and in the oceans consume massive amounts of CO_2 in photosynthesis and play an essential role in regulating the Earth's atmosphere. The influence of trees alone can be seen by an annual rise and fall in atmospheric CO_2 levels as the deciduous trees that dominate the northern hemisphere loose their leaves and regrow them each year, a phenomena known as the Keeling Curve.

Given the great influence of trees on climate it's vitally important that scientists better understand how they will be affected by increasing levels of CO_2 so that we can make best use of them in offsetting the effects of human activity. It's also essential to have hard data about how trees behave in increased CO_2 atmospheres in refining climate models.



Graph of CO_2 (Green graph), temperature (Blue graph), and dust concentration (Red graph) measured from the Vostok, Antarctica ice core as reported by Petit et al., 1999. Higher dust levels are believed to be caused by cold, dry periods.



The Keeling Curve showing annual fluctuation in carbon dioxide is caused by seasonal variations in carbon dioxide uptake by land plants. Since many more forests are concentrated in the Northern Hemisphere, more carbon dioxide is removed from the atmosphere during Northern Hemisphere summer than Southern Hemisphere summer.

Fire, science and biodiversity

Anyone who has visited Booderee National Park at Jervis Bay on the NSW south coast will have marvelled at its stunning white beaches, rugged hills, forests, woodlands, heaths, swamps and marshes. Its varied landscapes support a range of precious ecosystems and an impressive number of native animals and plants, many of which are threatened. It's a birdwatcher's paradise. What's not so apparent on first view, however, is the important role that fire has played in sculpting and sustaining these ecosystems. In recent years, ecologists from ANU have been playing a pivotal role in understanding this rich tapestry of fire and nature, and their work is playing a crucial role in managing the unique values of this area.

"Fire is a major natural ecological process that influences and shapes Australian ecosystems and the native wildlife that inhabit them," says Professor David Lindenmayer, the scientist in charge of the Jervis Bay Fire experiment. "Managing fire is also a hotly contested debate. Fires in eastern Australia in recent years have resulted in many commentators calling for more frequent and widespread use of fires to reduce fuel loads. It's argued that such practices will reduce the occurrence and intensity of wildfire, and assist in fire control. But the impacts of fire on biota is complex and not well understood. What is known is that inappropriate fire regimes have contributed to the extinction of two species and three subspecies of birds, and are a major threat to more than 50 other bird species, and nearly 20 plant species.

"To inject a little hard science into this debate we've established a project in Booderee National Park which studies the long term effects of fire on the mammals, birds and reptiles inhabiting a range of vegetation types found in the park. The key aim is to quantify changes in vertebrate biota within vegetation types subject to alternate burning strategies."

Within the park there are a total of 134 monitoring sites representing different types of vegetation, different fire histories and different prescriptive burning regimes. At each site, a permanent transect has been established, with 6 pitfall traps connected by drift fences. The program represents one of

A diamond python slithers through a fire-blackened bushscape in Booderee National Park at Jervis Bay. Photo: Mason Crane

at Jervis Bay

the largest pitfall and drift fence studies established anywhere in the world. Elliot trapping coincides with pitfall trapping, and spotlight and bird surveys are also conducted at each of the sites.

Time between fires is one of the key variables determining the responses from native animals and plants. One of the big advantages of working in Booderee is its fire history has been well mapped so it has been possible to set up monitoring and different fire management treatments in four classes of time since last fire (0-10 years, 11-20 years, 21-30 years and > 30 years).

"This project is one of the few large-scale and long-term experiments on fire in Australia," comments Professor Lindenmayer. "It's unique in the way it addresses key issues across a broad and diverse range of vegetation types and groups of biota."

Soon after the experiment was set up, a massive wildfire ripped through the park in late 2003 burning a large proportion of Booderee and a number of the newly constructed sites. What at first appeared to be a major set back, turned out to be a great opportunity as it enabled Professor Lindenmayer, and his team of researchers from the Fenner School of Environment and Society, to directly measure the faunal response to wildfire. Many animals survived the fire event, and live in the recovering vegetation.

"We've been monitoring native wildlife in Booderee over several years now," explains Professor Lindenmayer. "One surprising result is that if you manage other threats to wildlife, like foxes, you enable many native species to bounce back quickly after wildfire.

"For example, half the park was burned by the wildfire in 2003, and it was expected that it might take many years before some of the fire sensitive species returned, if they returned at all. To our surprise, many of these species, like the eastern bristlebird, reappeared very shortly after the fire and returned to pre-fire population levels very quickly. We believe this happened not because of the absence or presence of prescriptive burning but because fox control is a high priority for park managers and low fox numbers allowed animals to recover quickly."

David Lindenmayer (on the left) discusses the Jervis Bay Fire Experiment to a group of fire and wildlife researchers from around Australia who visited Booderee National Park earlier in the year to discuss the role of science in fire management.

A number of single species studies are also being undertaken in and around the fire study. Chris MacGregor is studying the home range, habitat use and nesting habits of the long-nosed bandicoot under different fire regimes. Damian Michael is investigating the spatial ecology of the little understood diamond python. Martin Westgate is looking at frog behaviour and habitat use while Felicia Pereoglou is working on the conservation biology of the threatened eastern chestnut mouse.

"Booderee is a wonderful natural laboratory for studying fire and nature," says Professor Lindenmayer. "We work closely with the park managers and I believe our research is helping them in their day-to-day management roles as well as creating an important and lasting scientific legacy on how to best work with fire in Australia's varied landscapes."

Sleep No More

Mandy Thoo

A Discovery that Could Open up Doors to Prevent Sleeping Sickness

Sleeping sickness continues to be a worrying disease in many regions of the world. Having a probable history of thousands of years, it still affects 50,000 to 70,000 people in sub-Saharan Africa, with an estimated 30,000 new victims each year. Scientists have worked to come up with cures, though few have been successful. The low success rate could be due to the lack of a full understanding of its causative parasite Trypanosoma brucei. However, hope has resurfaced from the results of research in recent years, including a ground breaking discovery resulting from a collaborative study between the University of Edinburgh and the Australian National University.

Having made contact with each other in a conference, Professor Keith Matthews of the University of Edinburgh and Professor Kiaran Kirk of the Australian National University, together with their research students Sam Dean and Rosa Marchetti (respectively) dedicated themselves to study the proteins and signals that enable the parasite to undergo its various transmission stages. The research has resulted in the discovery of PAD (proteins associated with differentiation), and that PAD is crucial for the transmission of Tryponosoma brucei from its "stumpy-form" to its procyclic form. The encouraging part lies in the fact that without PAD Tryponosoma brucei will not be able to transmit into the procyclic stage to proliferate in the tsetse fly and therefore cannot be transmitted to humans.

"It is an important first step that we have made, and we hope that with this piece of puzzle, we can now engage in the process of gaining a better picture of the parasite", Rosa Marchetti said.

Trypanosoma brucei, the "sleeping sickness" parasite, is a polymorphic single celled organism that can shift its shape from a long, slender form with a flagellum – "a tail" – to a short stumpy structure with no flagellum. The parasite depends on tsetse flies as a means of transmission, and exists in the "stumpy-form" when sucked up by the flies. When the infected Tsetse flies proceed to bite other hosts, they release T. brucei into the victim. T. brucei then shifts to its slender flagellated forms and proliferates in the blood and lymph. As the trypanosome invades the central nervous system, it sets off the chronic infection stage when the victim suffers from increasing apathy, mental dullness, paralysis or convulsions and ultimately, death.

The fight against sleeping sickness has spanned many decades. Some drugs have proved effective, though they come with damaging side effects, and the parasite has started to build up its resistance to them. As a full understanding of the parasite has not yet been achieved, there are no vaccines, and it is difficult to treat the sickness as the symptoms often occur in many other conditions.

It is hoped that this latest discovery could begin a new era for research on trypanosomes. Until now it was known that the parasite could not proliferate in its "stumpy-form" until it shifted to the procyclic form, but its intermediate mechanism was unclear. However, now that this study equips us with the knowledge of proteins (PAD) responsible for the transmission to its procyclic form, there is potential for therapeutic agents to be produced. Should the therapy work in keeping the parasite in its "stumpy-form", it would prevent the transmission of the parasite to humans.

This collaboration has proved to be a rewarding experience for our ANU researchers – apart from the discovery, it was a thoroughly refreshing journey for Professor Kirk and Rosa, who both specialise on Plasmodium – the Malaria parasite.

Rosa appreciated the opportunity, "It was a change to be able to study another parasite. I think that Trypanosomes don't get the same attention as Plasmodium because the sleeping sickness isn't as common as Malaria. Thus this collaboration allowed us to contribute to helping with understanding this fascinating parasite."

Both teams maintained communication via emails and web

conferences, and the collaboration experience was further enhanced by a visit from Sam to Professor Kirk's laboratory, having obtained a grant by the Journal of Cell Science. It was then that Rosa was able to practice her scientific communication skills.

"Apart from the research context, the lesson that I gained was on how to work with someone who is from an entirely different laboratory and would have different ways of doing things. I had to guide Sam on our procedures, and it proved to be a great teaching experience. The key for me was to have a firm idea of why we do what we do, so we can pass on a clear message to the others."

Both groups are excited with the findings, and further collaborations have been discussed. More work needs to be done, but in the meantime we can be positive about one thing: There is a hope.

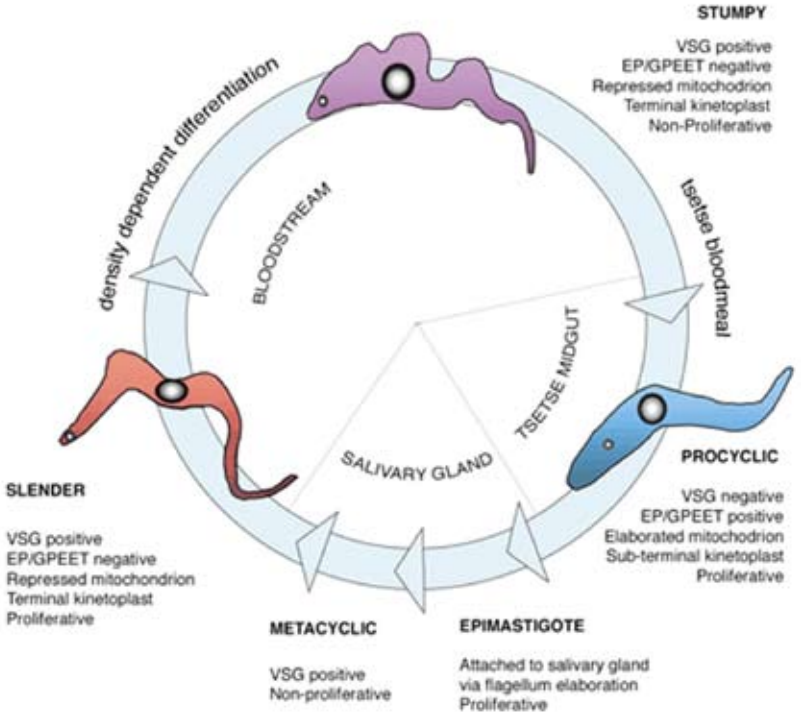
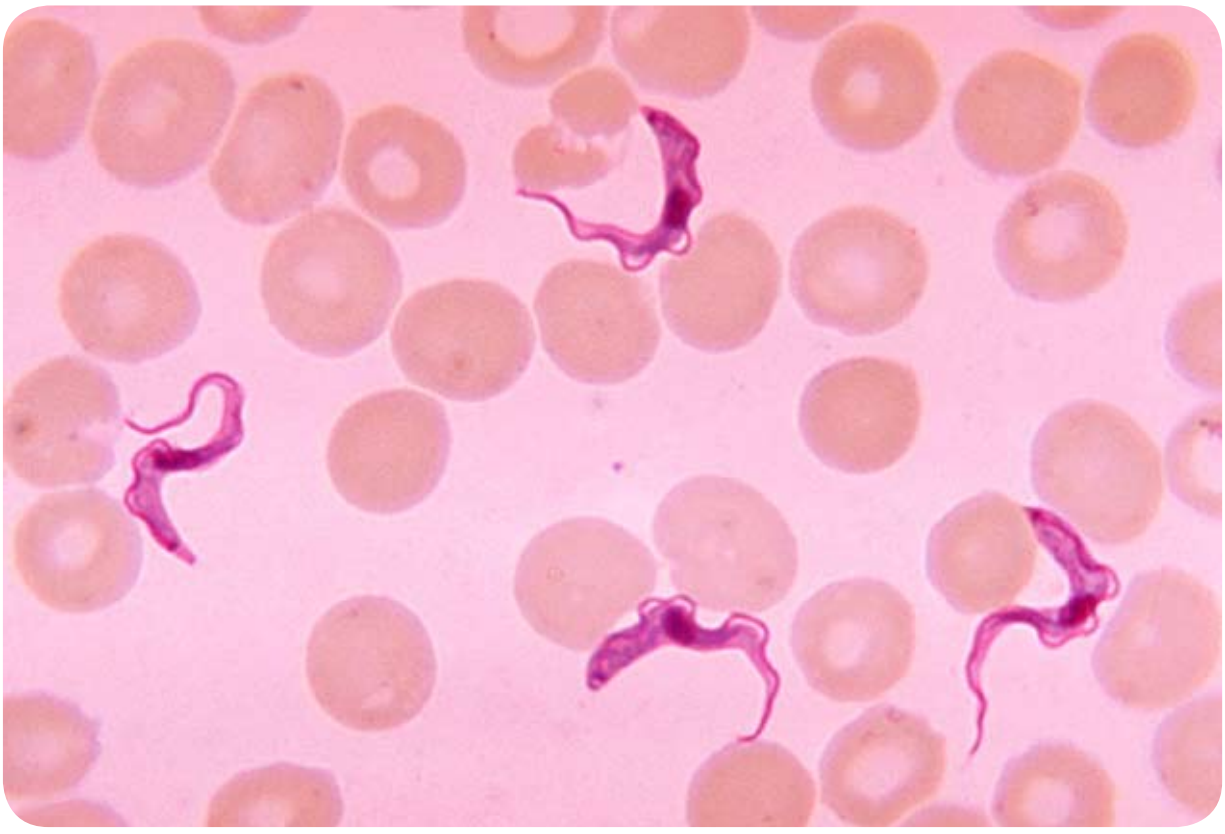


Image: Dean, S., Marchetti, R., Kirk, K. and Keith R. Matthews (2009) "A surface transporter family conveys the trypanosome differentiation signal" Nature 459(213-217).



Trypanosoma forms in blood smear from patient with African trypanosomiasis. Image courtesy CDC/Dr. Myron G. Schultz

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