Life Sciences: SULSA under the microscope
It has been Scottish Funding Council policy for the past five years to invest selectively, in partnership with the Scottish Universities, in key research areas to ensure that Scotland consolidates and strengthens its competitive position as a leading scientific nation. These “Research Pooling Initiative” investments have already had a considerable impact in areas such as physics and chemistry. This edition of Science Scotland reports on the Scottish Universities Life Sciences Alliance (SULSA), the largest of the research pooling investments, which is aimed at ensuring that Scotland remains in the vanguard of life science research.

There is no doubt that that the advances in life sciences will be crucial for providing us with the tools to overcome the great challenges that we face in the 21st Century to secure a healthy, prosperous and sustainable future. Scotland has great strengths in the life sciences but we cannot be complacent, and the aim of the £27 million investment in SULSA, which has been more than matched by parallel investments from the six University Partners (Aberdeen, Dundee, Edinburgh, Glasgow, St Andrews and Strathclyde), is to bring to Scotland some new international research stars to complement and stimulate our existing centres of excellence in the life sciences.

The SULSA investment is focused in three very important areas of molecular and cell biology: cell biology, systems biology and translational biology. These areas reflect the need to advance fundamental research in the life sciences whilst at the same time seeking to translate some of the research into practical applications in medicine and agriculture. Here, we have asked the Director of SULSA, Professor Mike Tyers, to describe his vision for SULSA and his thoughts on the next few years of life science research. We have also invited several of his newly appointed professorial colleagues to share their research plans with us.
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The challenge for SULSA Director Mike Tyers is not just to pursue his own specialist interests (focusing on systems biology and cell division) but also to tie together different institutions, scientists and scientific disciplines as biology embarks on the next phase of its own evolution...

Yeast may not be the most complex organism in the universe, but according to Professor Mike Tyers, the study of yeast could be one of the keys to the human condition – at least biologically speaking. In other words, if we can understand a simple organism like yeast, then we are on the way to understanding far more complex species like ourselves.

Tyers is best known in scientific circles for his work on cell division – or what has been described as his “cell-cycle-centric view of the world.” And at the Tyers Lab in Edinburgh, his team of researchers is pursuing a number of ground-breaking projects including systematic cell size analysis in yeast and mammalian cells, protein recognition in the ubiquitin proteolytic system, and another which involves screening yeast bioactive compounds to identify specific chemical fingerprints for diverse species, including human stem cells.

Yeast has played a major role in Tyers’ academic career, and will also be a focus of attention in the future, he says, as researchers contemplate synthesis of the entire yeast genome – refactoring the genome – to systematically modify the DNA sequence so they can study effects on yeast behaviour under different conditions.

Tyers’ interest in the mechanics of biological systems first developed in graduate school in the early 1980s, when the revolution in molecular biology was just beginning. At that time, he also developed an interest in signal transduction – how cells respond to their environment and communicate – but realised the limits of doing experiments with mammalian signalling systems. “Twenty-five years ago,” Tyers explains, “there were no transgenic mice.” Although Tyers managed to clone an important signalling protein (pleckstrin) as a graduate student, there was no way to analyse its function in a living organism.

Yeast, however, was very amenable to genetic manipulation and therefore the ideal subject for experiments when studying fundamental processes like cell division, which happens much the same in yeast as in human beings. Tyers also studied key regulators of division – proteins known as cyclins – whilst a postdoctoral fellow at the Cold Spring Harbor Laboratory in New York.

Another big advantage of using yeast was that it was the first eukaryotic genome (an organism with a nucleus containing the chromosomes that make up the genome) to be sequenced, enabling biologists to manipulate genes on a genome-scale level, including “knocking out” every one of yeast’s 6,000 genes to study their functions and interactions. Subsequently, Tyers has spent the last few years developing cutting-edge systems biology approaches to fundamental questions such as how cells control the balance between growth and division. This can lead to breakthroughs in various other fields – for example, some of the pathways that control growth in yeast can provide insights into the growth of a tumour – or the genesis and maintenance of tissues and organs.

Over the past few years, Tyers has focused on three large-scale systems biology approaches, all involving yeast, and all of which have led to high-profile discoveries. The first project used genome-scale screening to study how genes control cell size and revealed a complex network of new genes that ensures cells are the right size when they start to divide. Another project probed genetic interactions, systematically combining 6,000 yeast gene deletions with other mutations to see which genes interact with each other.
The result has been a detailed “roadmap” of yeast genes that will help explain how different biological processes cooperate. For example, Tyers explains, dozens of genes are involved in the development of a disease like diabetes, and it is hard to find even one of the genes responsible in human beings. By using yeast to “map the genetic landscape of the cell,” however, scientists can begin to analyse the complex interactions of multiple genes, accelerating their understanding of human diseases, at the same time as taking a lot of the serendipity out of the process.

The third project in Tyers’ lab involved the systematic mapping of protein interactions. In the past, says Tyers, scientists did one-off, *ad hoc* studies of pairs of proteins, but recent approaches use the latest high-throughput mass spectrometry technology to accelerate the process, which Tyers compares to piecing together a mind-bogglingly complex jigsaw. “If you can only see two pieces at a time,” says Tyers, “it would be difficult if not impossible to solve the puzzle. The added complication is that the jigsaw is not two-dimensional, it’s n-dimensional.” And Tyers’ approach allows him to see many of the pieces simultaneously and how they link together.

Most recently, Tyers has extended these approaches to the problem of how small molecules – chemicals such as drugs, industrial compounds or natural products – affect biological systems. According to Tyers, the ultimate aim is “to try to understand how small molecules influence all aspects of a biological system,” and having mapped the complex networks, use chemical biology to control different processes such as the development of different disease states. Most drugs have “promiscuous interactions” with biological systems and the reactions to different drugs vary from person to person, including side-effects. Tyers explains: “The bottom line is that if we can understand the complete response of a biological system to a drug, then we will understand the biological system itself.”

“I strongly believe that chemical biology will re-invigorate drug discovery,” says Tyers. “When we study biological systems now, we don’t just study one gene at a time; the same principle applies to the use of small molecules to interrogate and control networks of interactions between genes.”

For Tyers, SULSA is an excellent environment in which to pursue this research since it draws together so many themes, with an emphasis on interdisciplinary activities. In fact, Tyers believes that biology will be a major driving force of science in general, taking physics and computing in completely new directions, as scientists grapple with phenomena like the individual behaviour of cells as highly complex self-replicating machines. SULSA, says Tyers, is one of the first initiatives of its kind, pooling the resources of several institutions in the same country, and is also a leading example of what can be achieved through close collaboration and the open exchange of ideas.

One of the factors that makes Tyers different is his “systematic mentality” and the fact that he has always been quick to embrace new technologies and apply them to complex biological problems. “Scientists don’t yet fully understand the simplest biological systems,” says Tyers, “and we now know that knowledge of all of the parts encoded by the genome is just the beginning of putting together the puzzle of life.” Yeast has played a critical role in his work until now, and Tyers believes that this will continue as he and others move into the “brave new world” of synthetic biology.
What is synthetic biology?

What’s new about synthetic biology is that instead of using genetic material from existing organisms, it uses computers to design new DNA sequences (genes or entire genomes) which are then chemically synthesised in the laboratory. It also involves using natural genetic components to design novel genetic sequences that encode new biological parts and devices. Scientists aim to create more cost-effective, large-scale solutions for DNA sequencing and DNA synthesis, leading to breakthroughs in new applications for medicine (drugs and diagnostic devices), self-replicating materials, improved food and energy production, as well as expanding our knowledge of biological processes.

Breakthroughs in synthetic biology have already been made. For example, a team of researchers at the University of Edinburgh recently designed and engineered bacteria for use as biological sensors which detect the presence of arsenic in water. Chemists in various countries have also engineered organisms (including yeast) to produce small molecules, chemicals and drugs. They have also modified organisms to produce hydrocarbons – generating ethanol from plant matter. Synthetic biology thus has enormous potential in virtually every aspect of life and economics, including manufacturing as well as health care, biofuels, food production, and environmental remediation.

Real-world synthetic biology

Until now, Tyers has focused on the systematic dissection of natural biological systems by mass spectrometry, genetics and chemical genomics, but he strongly believes that synthetic biology is the logical next step for him – and for life sciences in general. Synthetic biology is a new discipline where various branches of science, including physics, informatics, chemistry and engineering are now beginning to converge. “Two hundred years from now,” he predicts, “people will look back at the amazing things being done in synthetic biology in the next decade or two and see this as a watershed in science and technology.” Alternatively, Tyers adds, if we don’t invest in synthetic biology now, we may miss an outstanding opportunity to tackle the massive problems we face in energy, food production, disease and climate change.

One of the challenges of synthetic biology, according to Tyers, is to make large-scale synthesis of DNA much cheaper and more efficient. Researchers are currently trying to build bacteria, chromosomes and even simple fungi from scratch, creating biological ‘systems’ by engineering genetic components, and Tyers says that this not only takes us to the frontiers of biology but also drives innovation in other fields. For example, synthetic biology will require new computational platforms and new concepts in computing science.

The creation of organisms capable of capturing and storing excess carbon dioxide, producing biofuels or biopharmaceuticals, or even an artificial pancreas to end diabetic dependence on insulin injections – these are just a few of the potential real world applications of synthetic biology. But if we can take genes and genomes apart and rebuild them from scratch, then the sky is the limit. Tyers argues that the negative image of ‘green goo’ portrayed by some critics is little more than fear mongering – synthetically engineered organisms would not only have ‘fail-safe’ mechanisms, but also would have no chance of survival in the wild because they could not compete with the superior fitness of natural organisms honed by billions of years of evolution.

Even though synthetic biology may seem like a quantum leap for many observers, this impending revolution is simply part of a continuum, according to Tyers. “Synthetic biology is the logical progression of my own research programme,” Tyers declares, “and where everyone else is heading in the long run. It is the melting pot of science.”

Despite the excitement, some biologists adopt a more conservative approach. “Some synthetic biology projects are viewed as mere tinkering,” says Tyers, “and there is sometimes a tension between conventional molecular biologists and synthetic biologists. But as the technology progresses, people will wonder how they did without synthetic biology.”

To stimulate interest in synthetic biology, SULSA is sponsoring up to six teams of students from Scotland to enter the international Genetically Engineered Machines competition (iGEM) at the Massachusetts Institute of Technology (MIT) later this year. The iGEM event may seem more like fiction than science, but some of the spin-offs are serious business, with some of the “biological parts” created by the students being stored in a library called the Registry of Standard Biological Parts, including the building blocks for biosensors and synthetic red blood cells.

Supporting the iGEM event is a long-term investment for SULSA but Tyers is convinced it will be worth it. “As synthetic biology starts to take off,” Tyers says, “the revolution in molecular biology will pale in comparison.”
SULSA on a voyage of discovery

It may have “more ideas than money,” but the Scottish Universities Life Sciences Alliance (SULSA) is also an idea whose time may have come. Based in six institutions, this large-scale research collaboration has recruited a team of leading international scientists, linking up existing labs in Scottish universities to create a network of technologies and people which adds up to more than the sum of its parts...

When the idea of SULSA was born in 2007, the objectives were simple, but even in the time since it was founded, the goalposts have started to move. With £27 million in the bank from the Scottish Founding Council, SULSA set out to “provide a single voice for the sector” and stimulate research by attracting leading scientists to Scotland. It also aimed to train the next generation of researchers and act as a “knowledge exchange catalyst” for life sciences in Scotland. Two years later, SULSA is already well on the way to achieving its primary aims, but the world has changed – making SULSA even more strategically important than originally envisaged.

It was always believed that one of SULSA’s roles would be to “help researchers tackle diseases that are not currently on the agenda of the world’s pharmaceutical and biotechnology sectors,” but the economic downturn has made the commercial sector even more risk-averse and less focused on innovation, according to researchers who have recently returned from industry to academia, and this makes SULSA’s work potentially more critical in the quest for new drug therapies and scientific knowledge.

SULSA’s initial focus is on three broad research themes: systems biology, cell biology and translational biology. Scotland has always been strong in cell biology, and SULSA’s founders also recognised the need to bring together world-class exponents of cell and structural biology, medicinal chemistry, and bioinformatics, already based in the country, to realise the potential in drug discovery (also known as translational biology). At the same time, SULSA has been breaking new ground in the relatively new field of systems biology (using informatics to model biological systems and process the vast amounts of data generated by biologists).

The story so far...

So far, SULSA has recruited eight professors from all around Europe and North America, including two scheduled to take up their posts by the start of next year, plus readers, lecturers and about 50 PhD research students. It has also built up an impressive portfolio of state-of-the-art technologies, providing easy access to a wide range of facilities for researchers in Scotland, including:

> an OMX super-resolution microscope (one of only seven in the world)
> “next-generation” DNA sequencing facilities and bioinformatics support
> high-throughput facilities for protein production and structural analysis
> imaging facilities to support translational research (including PET/CT and biophotonic scanners)
> high-throughput, small-molecule screening services for drug discovery
> unique natural products libraries (mainly marine and plant extracts) for drug screening assays

As well as pooling talents and technologies, SULSA is a catalyst for attracting new research funding to Scotland – for example, the Gene Pool DNA sequencing and bioinformatics facility at the University of Edinburgh, which has recently attracted additional investment of £2.3 million from the UK’s Medical Research Council, on the back of £300,000 funding from SULSA.

Many other projects look set to benefit from SULSA support, as the organisation reaches critical mass and the pooling of resources begins to pay off, but it will also continue to emphasise training – for example, it is supporting teams of Scottish undergraduates to participate in the international genetically engineered machines (iGEM) competition to develop Scotland’s synthetic biology awareness and skills, recognising this will be critical in coming years.

Other countries have also tried pooling resources in similar ways, but Scotland has several advantages, including geography, a disproportionate number of leading researchers and a world-class reputation in fundamental areas such as microbiology and new technologies such as high-resolution imaging and high-throughput, small-molecule screening solutions. In addition, Scotland has already launched similar initiatives in physics and informatics, and SULSA can now learn from their experience, as well as join forces for “cross-education.” Another of SULSA’s key roles is to mediate the partnerships between institutions when it comes to who owns intellectual property rights on collaborative projects, ensuring that knowledge is shared at the same time as giving due credit when breakthroughs are made.

The story so far is encouraging, and speaking at the first SULSA Symposium in Edinburgh in June, Professor Sir Tom Blundell (University of Cambridge and Chair of the SULSA international advisory board) said: “Scientists south of the border are envious at what SULSA is doing.” Professor David Gani of the Scottish Funding Council echoed these words, saying that SULSA was “one of the jewels in the Scottish research crown,” adding that the calibre of staff appointed was “something we could only have dreamed about” two years ago, and that SULSA was a platform which would help Scotland ‘weather the economic storm and bounce back.’

SULSA is already beginning to gather momentum as an engine of change within Scotland, and Director Mike Tyers believes that the challenge is not just to drive innovation in science but also to change the way that Scotland (and the UK) approaches investment in science. “At SULSA, I think we are already very close to achieving our original mandate,” he says. “But now we have to find new ways of funding new initiatives, pooling our resources with informatics and physics, as we call ‘life sciences’ changes dramatically over the next 20 years.”
Origami for proteins

One of SULSA’s latest recruits, Professor Neil Bulleid recently returned to Glasgow where he did his PhD in biochemistry in 1985. In his new job at the Division of Molecular & Cellular Biology (in the Faculty of Biomedical and Life Sciences), he is looking forward to exploring new frontiers in life sciences and breaking down the barriers between the different scientific disciplines in his quest for the truth about how proteins get into shape...

When Neil Bulleid talks about proteins, he uses more metaphors than the average poet. One moment, he is talking about “posting a letter” and the “postcode” which makes sure that molecules get to the right destination. The next moment, he is talking about the “factories” that manufacture proteins, and the “quality control” systems that reject faulty proteins. Then he explains how polypeptides (made from chains of amino acids) form themselves into a particular shape by folding themselves into proteins – like microscopic origami. But how else do you describe the highly complex creation of proteins, without which there would be no life on earth?

The “folding” process used in the manufacturing of proteins has been known about for decades, but biologists are only now beginning to understand how it works – and Bulleid is one of the scientists leading the way, shedding light on how proteins are formed and how they are transported from the inside to the outside of a cell, moving through the secretory pathway to populate the surface.

Human beings have at least 25,000 genes and about a third of them are designed to make the proteins which enter the secretory pathway. The first stage of their journey through the pathway is a cellular organelle called the endoplasmic reticulum. It is within this organelle that proteins entering the pathway are folded and assembled into their correct functional form. Only the correctly folded protein is allowed to exit the endoplasmic reticulum, giving rise to the idea that the organelle acts as a quality control point in the secretory pathway. Proteins that do not attain their correct shape are degraded, thereby preventing their build-up in the cell. And as Bulleid explains it, the way that the protein chain adopts the correct shape involves mind-boggling mathematics. For example, the number of possible shapes that the chains could form could be as many as $10^{47}$ – more than the number of atoms in the whole human body. And the fact that each chain does form a particular shape a few seconds after it comes into being is a “marvel of biology,” according to Bulleid.

In the 1960s, says Bulleid, scientists believed that all the information needed for proteins to fold correctly was contained in the amino acid sequence, like the code in a smart piece of software, but the mathematics suggest that if this were the case, the process may take several years. It was only later they discovered that “chaperone” proteins were needed to facilitate the process, not only helping the proteins to form the right shapes but also looking after quality control. If the proteins don’t meet the quality standard, the chaperones will bind to them and make sure they don’t go anywhere else. The downside to this binding is that if the proteins are not degraded, this can result in a build-up of toxic proteins which may lead to the development of diseases like Parkinson’s or Alzheimer’s. For example, cystic fibrosis is caused by a protein not arriving at the right destination because the quality control system has detected a minor difference in its shape and prevented it from going where it should go. If the “slightly faulty” protein was “passed” by the quality control system, the sufferer may lead a more normal life, but the system has strict rules and sticks to the rulebook. And as we get older, these problems get worse.
Ultimately, scientists like Bulleid want to understand the fundamental processes involved so they can cure or prevent these diseases, and huge advances have been made over the last 15 years, since Bulleid first set up his lab. As an example, one of the more recent breakthroughs is the development of a treatment for Gaucher’s disease, using drugs that bind to mutant proteins so they form the right shape, and drugs for cystic fibrosis which “bend the rules” of the quality control system to allow imperfect proteins out of the cell. The development of these drugs would not have occurred if we did not understand the link between protein folding, quality control and cellular stress.

According to Bulleid, his primary interest is “biochemical reactions in a cellular context,” but he does not like to be pigeon-holed as a cell biologist or biochemist because he sees the future in a broader approach. Even though the questions asked are specialist in nature, says Bulleid, we must adopt a multidisciplinary approach to come up with solutions.

What sets Bulleid apart from many other biologists is the way that he investigates the microscopic universe of proteins, cells and molecules “to look at what really happens” when proteins are formed – something which is technically very difficult to do. “We try to use approaches which will reproduce what happens in the cell,” he explains, “without using an intact cell.” And to do this, he uses a technique which creates naked or “ghost” cells which have no plasma membrane.

To be able to study the initial stages in the life of a protein within the endoplasmic reticulum and watch it in action in an environment in which it is able to fold, Bulleid and his team use a special detergent to “wash away” or “punch holes” in the cholesterol-rich plasma membrane which surrounds the cell. This releases all the cytosolic components but leaves the endoplasmic reticulum intact. These ghost cells can then be used to study the synthesis of individual proteins. One of the proteins he has worked with is procollagen (collagen being the most common protein in our bodies, helping to form bones and skin), which in the past could only be studied by looking at cells grown in culture. Using his “ghost cell” approach in the lab, Bulleid was able to determine which chaperones were needed to fold this protein and has developed a “non-natural” form of collagen, since patented, which could be used in tissue engineering for applications such as skin replacement and ulcerations.

More recently, he has been carrying out research into 17 similar proteins which belong to the same enzyme family. These enzymes are responsible for forming linkages within and between protein chains. No one knows why there are so many enzymes which catalyse the same reaction, but it could be due to each enzyme only working with a distinct set of substrates. Bulleid has used an approach which traps the enzyme with its substrate so that he can identify which proteins are substrates for each enzyme. “We are now beginning to understand which folding enzymes or chaperones are needed to make each protein that enters the secretory pathway,” says Bulleid. “This knowledge is crucial if we are to optimise the production of proteins for therapeutic purposes as many of these proteins enter the secretory pathway.”
In the last few years, says Bulleid, there have been some significant discoveries, including the fact that we now know much more about the by-products involved in the formation of proteins and how they relate to disease – for example, reactive oxygen species (ROS) like hydrogen peroxide which can damage our cells. It is now recognised that the process of protein folding in the endoplasmic reticulum can lead to oxidative stress and cell death. Our increased understanding of the link between protein folding and oxidative stress is crucial if we are to fully understand how many disease pathologies originate.

So why has Bulleid joined the growing number of researchers moving to Scotland under the SULSA scheme? He is keen to plug himself into the network created by SULSA and sees it as a great opportunity to establish a new direction in his research, collaborating with other researchers in Scotland and having easier access to costly equipment and facilities. By joining together and pooling resources, Scottish Universities can provide sophisticated research facilities in the biological sciences and avoid competing against each other for diminishing resources, says Bulleid. He is also looking forward to the “greater degree of freedom” he will get as a SULSA researcher, and to interacting with the wealth of talented researchers at the University of Glasgow.

“My focus is on fundamental research,” Bulleid says. “I’ve always been interested in how things work.” And as part of SULSA, Bulleid will be given every chance to succeed – and find out more about how proteins that enter the secretory pathway keep themselves in shape.
Just like human beings, plants are complex systems which respond to changes in their environment by initiating different processes and types of behaviour. And light is arguably the most important environmental factor for plants, providing energy for photosynthesis and affecting basic features such as architecture, flowering time and seed ripening/germination, plus a range of metabolic pathways. Scientists are now beginning to understand enough about the complex webs of genes responsible for this response to light, and thus may soon be able to change the way plants grow and develop, or transplant these light-sensitive networks into other organisms...

Science often comes up with solutions in search of a problem. For example, if you could make yeast dependent on light for its growth by transplanting a number of genes from a plant and connecting them to the networks which regulate yeast growth, then you could stop it growing simply by switching the light off. So far, no-one has come up with any practical use for such a breakthrough, but such knowledge could have major implications for biology, medical science and agriculture in years to come.

For Professor Ferenc Nagy, who was recently appointed the SULSA Professor of Cell and System Biology in the Biological School of the University of Edinburgh, such scientific breakthroughs have been common throughout his career, ever since he started fusing protoplasts (cell wall free plant cells) in the 1970s in his native Hungary, where he received his PhD in genetics in 1981 at the Biological Research Centre in Szeged. From 1983 to 1988 he worked in New York, at the Laboratory of Plant Molecular Biology headed by Professor Chua Nam-Hai at the Rockefeller University, as part of a team that pioneered the use of transgenic technology for studying regulated expression of genes in plants.

All his early work in Hungary trained Nagy in the fundamentals of tissue culture, including regenerating plants from single cells or fusing two plant cells and then selecting out only those plants that contained a certain combination of desirable features – a process known as ‘somatic cell fusion.’ During his time in New York, he also used his experience in tissue culture techniques to select and regenerate transgenic plants that expressed genes not found naturally in plants. These genes included bacterial and viral genes – as well as the gene coding for the human growth hormone. Professor Chua and his fellow researchers had ‘high hopes’ for this totally new branch of science as a tool to understand and manipulate the molecular circuits that regulate the expression of genes. The experiments also paved the way for later breakthroughs, transferring and expressing novel genes in plants to change their whole metabolism – for example, making them easier to cultivate or more resistant to herbicides, as well as more productive in various ways, such as producing more sugar, starch or oil. At this time, plant biotechnology was only just coming of age, but several years later, as interest in agrotechnology gathered momentum, it stirred up a public debate about the pros and cons of growing genetically modified (GM) crops that continues to grab the headlines today.

For Nagy, however, such applications were not his main interest, and in 1988, he returned to Europe to begin his independent research career at the Friedrich Miescher Institute in Basel, Switzerland, “to improve understanding of the biological functions of small-GTP binding proteins.” At this time, he also started to develop an interest in the study of how light affects plant growth and development – what biologists call photomorphogenesis. In 1996, he moved back to Hungary, and since then has published a number of seminal papers describing novel molecular mechanisms and components involved in “mediating light-induced, photoreceptor phytochrome-controlled signalling in plants.”
Nagy explains that plants have about 24,000 genes, with about 3,000 of these involved in photomorphogenesis, responding to different aspects of light (i.e. wavelength, intensity, quality, duration and direction) to mediate changes in growth throughout the life cycle. To achieve this feat, plants have developed special photoreceptors which, after sensing light, send signals to the rest of the plant to determine when to germinate and flower and when to synthesise flavonoids, and how to form leaves and branches and reach different heights (architecture) – as well as how to be successful in the battle for growth and survival. For example, plants living on the forest floor or at the top of the tree canopy should have different ways of responding to light, to optimise photosynthesis or simply help them compete, because features like wavelength (colour) and the intensity of the incipient sunlight are totally different in different locations. If you moved a successful plant from the shade to the sunlight, it may no longer thrive, and vice versa, because its light signalling network had been adapted to particular conditions, thus making it unable to trigger specific responses.

For example, the model plant Arabidopsis thaliana may have more than a dozen different photoreceptors absorbing the blue/UVA and red/far-red part of the spectrum. These different photoreceptors signal using different mechanisms and have specific and partly overlapping physiological functions. A common molecular event in signalling mechanisms launched by these photoreceptors is the regulated degradation or stabilisation of proteins, and Nagy is particularly interested in understanding and identifying the processes that regulate the stability of photoreceptors acting in the red/far-red part of the spectrum. His major challenge, however, is to decode the complex interactions or ‘cross-talk’ between them to identify their own specific functions and characteristics – in other words, find out how they work so we can manipulate particular genes to achieve specific objectives, such as faster growth or the ability to grow in different (perhaps even hostile) conditions.

Plants are sessile organisms (fixed in one position), Nagy explains, and therefore they have to adapt their metabolism to the actual environment. They actively monitor their environment not only for changes in light quality and quantity but also for water and nutrient supply, and have developed special mechanisms to cope with pathogen attacks. For example, some genes send signals which ‘talk’ about light whilst others send signals that talk about water availability or concentration of salt in the soil. If we alter one process in a genetically modified plant, it may promote fast growth or make the plant bigger under certain conditions, but lead to other less desirable features or even have a fatal effect on the plant under different conditions; whereas in naturally-cultivated plants these pathways are flexible and constantly adjust to the ever-changing environment.
According to Nagy, if one gene mutates and changes behaviour, this has a knock-on effect on the others. "For the last four or five years," he says, "we have begun to understand that plants are complex entities, and that there is not a single signal cascade, but lots of cross-talk. We are looking at plants as biological systems, rather than studying their individual components."

One major consequence of this research is that the data generated is becoming increasingly complex to process, and scientists like Nagy are increasingly turning to the high-tech solutions offered by systems biology to speed up the search for more answers, building complex models and performing tests to find out more about the ‘critical parameters,’ to identify the most important genes and receptors involved in certain tasks.

Sunlight has visible and invisible parts, and plants respond like humans to the invisible UVB light. This part of the spectrum is known to be harmful to the majority of living organisms (e.g. skin cancer in humans and burning of leaves in plants), so for these organisms it is essential to develop some sort of defensive mechanism to protect themselves from the mutagenic effects of UV. However, despite decades of intensive research, scientists still debate how organisms sense UV irradiation. "We think there is a special receptor for UV light in plants, which acts somewhat similarly to those that are active in the visible part of the spectrum," says Nagy. During the last few years, as well as hunting the elusive UVB sensor, scientists have also discovered that some of the building blocks of signalling cascades launched by UVB and by visible light irradiation are common. In addition, they have been able to show that the UVB-specific signalling cascades regulate expression of several hundred genes, and Nagy is seeking to identify the most critical ones for defending the plant from the harmful effects of exposure to the mutagenic UVB light.

Nagy, who is also Scientific Advisor and Vice-Director of the Plant Biology Institute in the Biological Research Centre of the Hungarian Academy of Sciences in Szeged, and Honorary Professor at the University of Freiburg in Germany, is also doing major research into chronobiology, to understand how plants – like human bodies – measure time by "isolating new mutants that provide novel information about the molecular composition of the plant’s endogenous timekeeper, the circadian clock."

As Nagy’s work becomes more complex – for example, mathematical modelling of signalling networks controlled by the phytochrome – he has had to learn new scientific ‘tricks’ and use the toolbox of systems biology, and being part of SULSA provides an opportunity to collaborate with other researchers which he hopes will benefit all of them and lead to further breakthroughs in genetic engineering, not only for plants but for humans.
Peter Swain is intrigued by how cells make decisions, but one decision in his life was easy – to come to Scotland as a SULSA professor, based in the Centre for Systems Biology at the University of Edinburgh...

Systems biologists like Peter Swain sometimes live in a world of extremes. One moment, he is trying to think like a bacterium, then the next he is trying to work out the ‘grander design’ which makes life possible and ‘programmes’ evolution.

Like many other systems biologists, Swain also uses a language that traditional biologists would find hard to swallow, talking about stochasticity and “deviant effects” in the same sentence as slime mould. For example, he writes: “We argue that the cellular viewpoint can only be probabilistic and that cellular decision-making strategies occur at three levels, described by ideas from statistical inference, decision theory, and evolutionary game theory.”

But despite this different language, ultimately Swain and his colleagues are concerned with exactly the same biological issues and have the same goals in mind – to improve the quality of life by understanding how organisms grow and develop, and how life evolves, in order to develop drugs to save and sustain human life.

In the process, Swain’s career is heading inexorably in the direction of a new science called synthetic biology, which fits in nicely with the future agenda of SULSA (the Scottish Universities Life Sciences Alliance), which he joined at the end of last year. If you tried to pigeonhole Swain, however, by describing him as a systems biologist or a mathematician (he gained his PhD in mathematics at Imperial College in London), he would sidestep the issue by saying he simply “does science.”

Swain’s journey to Edinburgh was via Northern Ireland, Trinity College in Cambridge, then Imperial College, a Max Planck Institute in Berlin, the department of physics at Tel Aviv University, the Rockefeller University in New York and the department of physiology at McGill University in Canada. Along the way, he gravitated steadily from applied mathematics and the physics of membranes to the new discipline of systems biology, when his early fascination with biology found its expression in the new computational methods that scientists started applying to biology in the late 1990s, at the time of the Human Genome Project. According to Swain, this period also saw a shift in the scientific community and the technology at its disposal, including new tools such as fluorescent protein imaging and developments in microscopy, as well as information technology. As a result, there were mountains of data to process, as biologists struggled to understand complex subjects such as how cells make decisions and communicate, and how genes and proteins interact.

For Swain, a major issue was stochasticity – the random behaviour of cells. Scientists had talked about stochasticity for decades, but Swain set out to prove that the theories were right, starting with the observation that in any biochemical network, stochastic effects become more dramatic when the number of copies of each protein is smaller.

After building mathematical models, the next step was to carry out experiments to quantify the sometimes random behaviour of proteins, then repeat the experiments and process all the data, looking at “noise” in the fluctuating levels of protein produced when genes are switched on and off. According to Swain, characterising such stochasticity, how cells interact and communicate with each other, and the fluctuating environment where the cells live, could lead to an understanding of how cells evolve and adapt to their living conditions by making decisions.
As Swain writes on the home page of the Swain Lab: “We study how cells make decisions. Gathering and processing information is fundamental to life. In all cells, this ability is conferred by biochemical networks, collections of genes and proteins that interact with each other and the extracellular environment. Information is detected by proteins at the cell membrane, processed by biochemical networks in the cytosol and nucleus, and then used to decide an appropriate cellular response. Such cellular decision making is at the core of synthetic biology and its failure causes disease: whether it is a hijacking of the signalling network by a viral invader, the uncontrolled growth of cancer, or mistimings in the contractions of individual heart cells.”

Swain also describes the decision making of cells in terms of “flipping” from one state to another. The cell is not programmed to do only one thing but is capable of several different actions, depending on the circumstances or a whim of nature – e.g. producing more or less enzymes, or consuming more or less sugar.

But Swain is more concerned with higher things – not just the basic functions performed by the biochemical networks in cells [e.g. amplifiers and switches] but how the whole biochemical network is built – not so much the individual soldiers and the way that they fight but the generals, the battles and the whole war itself. In other words, Swain wants to understand how cells grow and evolve, as if they are consciously making strategic decisions, like people.

Evolution tends to make things more efficient by optimising a cell’s response to the environment, but this is often full of contradictions. Cells rarely operate alone but as part of a network or system of other cells, and an individual cell may ‘choose’ to cooperate with other cells so that all of them do well together, or it may decide to ‘cheat’ and pursue its own selfish agenda [e.g. consume a common resource such as sugar quickly but inefficiently rather than slowly and more efficiently], thus ensuring it wins at the expense of its ‘team-mates.’ In order to make its strategic decisions, via gene expression or biochemical processes, a cell appears to act as an intelligent being who processes data and makes statistical inferences, and this is where Swain has to think like a cell, not necessarily making the obvious choice, as he models the decision-making process and analyses probability in the quest to see how cells decide and respond.

“Ten years ago,” says Swain, “some scientists thought we should focus on breaking biochemical networks down into functional modules, which was very influential, but now I want to understand at a higher level and find the strategy implemented by the network to make decisions, and how that strategy is influenced by competition and cooperation with other cells. We’ve already established the presence of stochasticity, and so we expect that making reliable decisions is not easy for cells because they have to process stochastic signals with biochemistry that itself behaves stochastically.”

Cells do not always behave as expected, and this is where stochasticity comes into play. For example, if you treat bacteria with antibiotics, some of them may be resistant – say, one per cent. If you then treat the resistant bacteria (known as ‘persisters’) with the same antibiotics again, you would expect most if not all to survive once again, but only one per cent may be resistant, the same as the original sample. It’s like a football team made up entirely of goalkeepers (or resistant bacteria) – when it comes to match day (treatment with antibiotics), some will act as strikers and others will act as defenders as they find new positions to play in the game, or randomly ‘flip’ from one state to another.
Some biologists simply believe that stochasticity proves “variety is the spice of life.” Others are more intrigued by the overall strategy, and Swain is even starting to apply game theory to the whole process, using the same kind of concepts used during the Cold War, when the hawks and the doves tried to out-guess one another and brought the planet to the brink of destruction. “Game theory makes sense,” says Swain, “because organisms don’t operate alone – and they co-operate and cheat in a way similar to people. And sub-optimal behaviour in one context may be a good thing in another situation.”

When it comes to applications, Swain hopes that his work will contribute in a number of ways – for example, speeding up experiments and testing by building mathematical models which work out how therapeutic molecules target particular proteins, and helping to design drugs (like antibiotics) with a much better chance of success, because they take account of the strategies used by cells in the fight for survival. In Swain’s own words, his aim is to “quantitatively model stochasticity, find out how stochasticity has affected evolution and cellular design and then how we can exploit stochasticity for medicine and biotechnology.” Cancer and stem cell therapies may be among the first fields to benefit from his research, but the sky is the limit and the next step for Swain may be synthetic biology, where ideas such as building new circuits in cells may emerge in the very near future, putting engineering ideas into practice.

SULSA is a major step in this direction, and Swain is looking forward to forming new partnerships with fellow researchers and gaining access to the nationwide facilities available, to carry out experiments and test his latest theories. Already, he is talking to another university in Scotland with interests in synthetic biology, while closer to home, he is working with the Tyers Lab in Edinburgh on projects which focus on yeast. He also hopes to take advantage of the microfluidics devices being built by the Scottish Microelectronics Centre, also in Edinburgh, which would help to test the decisions made by individual cells.

By deciding to become part of SULSA, Swain is living proof of his own mathematical theories, but the beauty of stochasticity is that even he does not know where the project will take him and how his own work will evolve, as he responds to the environment around him.
Mind-expanding science

When you find out that biologists are studying cannabinoids, you may think that science is ‘going to pot,’ but if they can understand what these mysterious molecules do to the brain, their research may lead to many biological and pharmacological breakthroughs...

It all goes back to 1968 and the ‘Summer of Love’ when cannabis was first widely used in the West as a recreational drug, but it is only now that scientists are beginning to understand the effects of the active components in cannabis, and in the process solve the mystery of how brain cells communicate using endocannabinoids – natural compounds in the brain which affect behaviour in the same way as tetrahydrocannabinol (THC) the major psychoactive component in cannabis.

Cannabis is mentioned in the Bible and has been used for many centuries by doctors in China, but it was only about 40 years ago that scientists began to understand its precise mode of action in the brain. Roger Pertwee, now Professor of Neuropharmacology at the Institute of Medical Sciences in Aberdeen, was one of the scientists who helped to discover the active ingredients in Cannabis sativa in the late 1960s. And today a few metres away from his office, the scientific quest continues, as Professor Tibor Harkany, one of SULSA’s recently appointed international researchers, explores a new dimension of cannabis research, seeking major breakthroughs in our scientific understanding of how nerve cells communicate in the brain and “the specific roles the endocannabinoid system plays in shaping the relevant molecular processes.”

One of the most interesting things about cannabis is that the brain has specific receptors for THC. And these receptors are the same ones that sense endocannabinoids, the compounds found in every mammal’s brain. Endocannabinoids do not help us ‘get high’ but instead are critically important in modulating the functions of complex neuronal networks, thus affecting processes such as memory, mood, pain and appetite.

Research in the area of endocannabinoid research has progressed through a number of stages, but it wasn’t till the early 1990s that researchers cloned the first cannabinoid receptor in the brain and identified the endogenous molecules that bind to the receptors. In 2001, researchers then started to work out how endocannabinoids behave in the brain by establishing how they limit different forms of communication between nerve cells.

In the course of this research, researchers rewrote the textbook for synaptic signalling. The scientific axiom, first established in the late 1940s, was that signals only went in one direction within a synapse, the junction where information is transferred from one neuron to another. The presynaptic terminal had one specific role – to effectively release a neurotransmitter which in turn solely engaged its cognate receptor at the recipient (postsynaptic) cell in order to induce a physiological response. In 1991, scientists made the first observations that suggested that the model of unidirectional communication may be wrong. Partly thanks to research into endocannabinoids, says Harkany, scientists learned that if you stimulate the postsynaptic cell appropriately then it can respond to this by releasing compounds that will travel the synapse in a reverse (retrograde) fashion. These compounds, called retrograde messengers, will find their respective receptors on the presynaptic terminal, thus creating a feedback loop between the two synapses – two-way traffic.
To investigate the different effects of retrograde messenger molecules on their respective receptors, Harkany and his colleagues asked a series of questions, with particular reference to the coordination of activity in neuronal networks underpinning cognition, movements and emotions. And for Harkany the big question was whether molecules responsible for establishing two-way communication in the adult brain are only present when the synapses are mature and functional, or instead actively contribute to defining a synapse’s identity during its course of development. According to Harkany, it’s also like asking: “What comes first, the chicken or the egg?” Do these molecules affect the development of a synapse or does a functional synapse recruit its own specific feedback loop?

Harkany is also therefore interested in the different effects of endocannabinoids on the brains of adults and adolescents, and on the developing brain of the foetus. If there are specific effects, are they limited to one phase of development? Consequently, if endocannabinoids are needed for communication between different brain cells, how is that process disrupted by taking extra molecules on board via exposure to cannabis?

Psychologists have already established that there may be psychological problems associated with cannabis, and also that babies exposed to cannabis in the womb may develop various problems, but Harkany’s challenge was to find the biological evidence and understand what was happening “when the staggering complexity of our brains evolves.”

What is emerging from Harkany’s research is that during foetal development and during puberty, when the brain is busy making neural connections to help the adaptation of brain cells to the increasing amount of stimuli each individual receives, cannabis disrupts the natural functions or spatial and temporal integrity of the signals which pass at synapses. “Quite simply, the cells get confused,” says Harkany. When psychoactive phytocannabinoids flood the brain, he explains, they interfere with the normal ‘on/off’ functions of endocannabinoids which can lead to cells increasingly shutting down, and this has a knock-on effect on the rest of the brain as well as on long-term refinement of neuronal communication.

One immediate outcome of Harkany’s recent research was to attract worldwide media attention when his team announced that taking cannabis while pregnant may affect the brain development of the unborn child. Adolescents may also experience significant problems when they use cannabis during the most critical postnatal phase of brain development, according to Harkany. When asked about the ethical aspects of these conclusions, Harkany says that we do not know everything yet about the effects of cannabis, but the evidence strongly suggests that the brain may be damaged, so his advice to pregnant women as well as teenagers is simply: “Stay away from cannabis.”
Harkany’s experimental data confirms the harmful effects of overloading the brain with phytocannabinoids, but he says that many people “have trouble accepting the biological importance of endocannabinoid signalling” because they confuse it with the social and ethical issues rather than focus on the scientific concepts involved. Harkany explains: “The fact that cannabis is a recreational drug and has become part of our culture provides a clear rationale for this type of research. However, knowing that it may affect our offspring makes these scientific findings socially sensitive.”

According to Harkany, several studies that followed people from birth till their twenties have established the detrimental effects of cannabis on brain development, and his work – processing experimental data from various sources – confirms many of these conclusions, “and now we are beginning to understand the process at the molecular level,” he adds.

THC is the most likely candidate for these disruptive effects, but some work still has to be done to eliminate others, says Harkany. Cannabis is a notoriously ‘dirty’ drug in the sense that it contains several dozen compounds which may have different effects in the human body and can interact with each other. People who use cannabis inevitably do other things – ingesting a chemical ‘cocktail’ – and this ‘polydrug’ use may also make it difficult to study how cannabis affects human beings, since it’s hard to isolate every ingredient.

As well as the effects on early brain development, Harkany’s work on endocannabinoids also has implications for ageing – the ‘mirror of what happens in the womb.’ “If we can work out how the synapse is built, then perhaps we could prevent its breakdown by being able to pinpoint the most sensitive processes that can lead to cognitive impairment in later life,” Harkany says. Harkany has also done groundbreaking research into the parallels between Alzheimer’s and epilepsy, studying “the common molecular process underlying perturbed communication between different cells.”

Ultimately, says Harkany, if we can understand the ‘rules’ of the endocannabinoid system, and the full impact of THC and other compounds, we will advance our understanding of the brain as a whole, leading to better diagnosis and more ‘personalised’ treatment of various diseases.

If anyone in the 1960s ever suspected that studying cannabis would open the door to a wide range of medical therapies for learning disorders and ageing, and “a fundamental understanding of synaptic plasticity,” you would have thought they had been smoking too much marijuana. But Harkany is proving that cannabinoids may hold the key to a number of biological mysteries far beyond the wildest dreams of any pot-smoking hippy.
Even ten years ago, systems biology was regarded by many researchers as more science fiction than science, but now it has become an indispensable part of the biologist’s toolkit, and Scotland’s ‘digital laboratories’ are leading the way – with a little help from international colleagues...

Rainer Breitling started thinking about systems biology in the early 1980s, long before the science was officially invented, when he imagined using computers to ‘simulate’ living organisms. If you can generate spectacular patterns like fractals, he thought, then why not model complex biological functions? At that time, he was still at school in Germany, but thanks to IBM (his father’s employers), Breitling was one of the first of a new generation to grow up with PCs at home, and already saw computers as the ‘digital laboratories’ of the future. At that time, most biologists would have laughed at the idea. But soon they’ll wonder how they ever managed without it – and Breitling has found his vocation.

In January 2010, Dr Breitling will take up a new position as SULSA Professor of Systems Biology (now a well-established science), based in the Faculty of Biomedical & Life Sciences at the University of Glasgow. He will not only benefit from newly-acquired computer resources in Glasgow – including a Sun 200 processor system in the Systems Biology Centre, plus GRID access via the eScience centre – but also a collaborative cluster of fellow researchers in Scotland. Breitling will also maintain his close links with his colleagues in the Netherlands, where he is currently Assistant Professor at the Bioinformatics Centre of the University of Gröningen, sharing his computer resources with astronomers and astrophysicists, whose radio telescopes generate similarly huge streams of data.

“I find this parallel between the study of the macrocosm (the universe) and the microcosm inside the cell/body highly intriguing,” says Breitling. “Both are very complex systems with an amazing number of components and we are only beginning to understand how they work – there are still surprising amounts of ‘dark matter’ in both of them.”

Like a number of SULSA researchers, Breitling brings an international flavour to the project. “That’s part of the fun of science,” says Breitling, whose own career has taken him from Germany to Scotland, California and the Netherlands, and from biochemistry via bioinformatics to systems biology.

“Systems biology brings together scientists from every direction; for example, engineers, statisticians and computer scientists, as well as biologists. Our challenge is to get all these people to speak the same language, and bridge the gap between experimentalists and informatics.” Breitling says that he is still “emotionally attached” to biochemistry, but also looks forward to his new job in Glasgow, where part of his task will be training the next generation of systems biologists, as well as pure research. Even though systems biology is still at the early stages of development, Breitling thinks the science has begun to reach critical mass, and the facilities at his disposal in Glasgow are evidence of growing academic commitment – and a reflection of the fast-growing confidence in this new field.

According to Breitling, systems biology was an “underground stream” in the 1970s and 1980s but started to gather momentum when the Human Genome Project got underway in the 1990s. By the time the Project was completed in 2003, systems biology had already emerged as a new branch of science because computational approaches had proved they could speed up advances in biology. Combined with the massive amount of information provided by the genome sequences, the special algorithms used in systems biology could now be used to “begin elucidating the molecular circuitry of living cells.”

The Human Genome Project identified about 30,000 genes, and about 100 of these genes may be involved in the development of cancer or diabetes, for instance. None of these genes works in isolation, but they rather function via complicated and very dynamic networks of interactions, which can only be analysed using computers. And the situation gets even more complex as many other factors and ‘knock-on’ effects are involved in the progress of any disease, says Breitling. With diabetes, for example, lifestyle and diet may be critical. The genetic component that people inherit may only trigger the disease in a certain percentage of people, and the big question is to identify what other factors may cause or prevent it, including other genes as well as certain types of molecules, enzymes and proteins.
Or, in Breitling’s words: “What makes a gene a critical gene? People realised the need to take the concept of systems biology to a new level. They also realised they needed an holistic approach that would provide opportunities for large-scale quantitative analysis.” And since those early days, systems biology has passed the ‘proof of principle’ test and is now producing practical results.

Breitling’s research interests include the development of innovative computational approaches for post-genomic systems biology, statistical methods for high-throughput biological experimentation, and the dynamic modelling of cellular systems. One of his specialist interests is ‘high-accuracy’ metabolomics – studying networks of metabolites or “measuring very small molecules and how they respond to perturbation.” In basic terms, metabolites are involved in biological processes like growth and development, or perform ecological functions such as defending organisms from disease. They are also biomarkers that can indicate the early signs of health problems. Breitling is also searching for new molecules which may influence biological processes, and even entire new families of signalling molecules.

As well as studying variations in genes, Breitling analyses the molecular networks associated with certain conditions – like the switches that turn on or turn off diseases or other malfunctions. Sometimes, this means identifying influential ‘hot spots’ or genetic variations which explain why diseases develop in some individuals but not in others with similar genes. Much of this work is carried out in model organisms in the laboratory. According to Breitling and other biologists, many human diseases have the same genetic origin as diseases in other species, and that is why studying plants, worms or fruit flies, for example, can lead to significant breakthroughs in understanding human diseases by discovering ‘fragilities’ at critical nodes in the regulatory circuitry of a cell.

Sometimes, “unlikely candidates” emerge from research. One metabolite may initially be associated with a particular disease or biological process – in the same way as cholesterol may indicate a cardiovascular problem – but then be discovered to influence a totally different disease, often as the result of unexpected ‘cross-talk’ in the molecular networks.

Breitling is also concerned with a concept called ‘robustness’ – the ability of living things to resist diseases despite sometimes dramatic variations in genes and environmental conditions. This involves studying the ‘feedback loops’ in the networks of genes and metabolites, which sometimes can form ‘vicious circles’ from which the organism cannot recover – for example, once someone develops advanced diabetes, the condition tends to be chronic.
Will this research lead to a cure for diseases like cancer? In Breitling’s view, the first aim is to understand the basic process, since if we know how and why problems occur, we can intervene in order to prevent them from developing. Early screening and diagnosis based on improved biomarkers and a better understanding of how they interact may indicate problems before a person ever gets ill; in this way, it may be possible to design personalised prevention strategies that would be more efficient than trying to ‘cure’ a chronic disease later on.

Breitling and his systems biology colleagues don’t ‘get their hands dirty’ in laboratory work but develop methods to interpret the large datasets generated in the experiments carried out by their research collaborators. In Breitling’s view, it makes a big difference, however, if the systems biologist has some experience in experimental science, since this makes them more sensitive not only to their colleagues but also to the data.

For Breitling, systems biology is now an integral part of the biologist’s toolkit, and can be used in a wide range of projects. For example, his work at the moment covers everything from synthetic biology (using soil bacteria to develop new antibiotics) to research into diabetes (the ‘geneticist’s nightmare’), sleeping sickness (working with parasitologists to develop new, less toxic drugs) and Parkinson’s disease (using nematode worms to mimic the human brain). He is also ‘open for business’ with respect to other topics for research. “If it’s an interesting or innovative concept, and it excites me, I’ll think about taking it on,” he explains.

Sometimes, Breitling sounds like a computer scientist, talking about biological processes in terms of data and “how information passes through the network,” but he also recognises that the key to the success of SULSA and his own future research will not only be computational power but ‘human chemistry’ – how people work together in Scotland and beyond. In his own words: “Systems biology is a social enterprise which offers fascinating opportunities for collaboration across traditional disciplines.”
Within five years, the pharmaceutical industry will see about 40 per cent of its patents lose most of their value overnight. Meanwhile, drug discovery appears to be losing momentum and costs are rocketing, so any methodology which improves efficiency and lowers costs would not only save lives but money – in developing countries as well as in more affluent societies. Andrew Hopkins is not just building new computational and biophysical tools for designing new drugs but also questioning the underlying assumptions of the whole drug discovery process...

If you read his curriculum vitae, Professor Andrew Hopkins seems well qualified to work in a variety of scientific disciplines, including biophysics, chemistry and informatics, but even though he would love to be part of the team that comes up with the next new blockbuster drug, he is just as keen to talk about philosophy and poetry, and how they help us understand the mysteries of science. One moment, he is trying to explain "the global mapping of pharmacological space" and how to design "promiscuous drugs," and the next he is discussing T. S. Eliot and Popper.

Whilst many scientists and pharmaceutical companies are desperate for original ideas, Hopkins is also concerned about where ideas come from. To illustrate the complexity of scientific creativity, he quotes from Eliot’s poem The Rock, and the "endless cycle of ideas and action" involved in invention, discussing the dramatic difference between "the eureka moment" and innovation – putting new ideas to practical use. "Science asks if it is true," he explains, "while technology asks if it works."

Hopkins is also concerned about "social technologies" or how to build the "virtuoso teams" which think up new concepts and develop new products, recognising that conventional structures and organisations do not always come up with the goods. Hopkins also thinks it is time to rethink the relationship between the pharmaceutical industry and academia, as we enter an era of greater openness in scientific research, when collaboration matters more than competition and researchers provide open access to data rather than treating it as an industrial secret.

Hopkins, who is SULSA Research Professor of Translational Biology and the Chair of Medicinal Informatics at the College of Life Sciences in the University of Dundee, also talks about the "paradox" of current pharmaceutical research, with more and more money (at least $80 billion a year) going into new projects, yet outcomes declining. The challenge, he says, is to translate the knowledge we already have into concrete results, including understanding how existing drugs work, and developing new technologies to improve productivity. "Drug discovery is still a cottage industry in many ways," Hopkins explains. "There has not been the Darwinian pressure to evolve. Due to declining productivity, for the first time in four decades, the pharmaceutical industry is now facing a decline in revenues. And I believe this crisis of confidence is the ideal moment for innovation – there has never been a better time for academia to grasp the opportunities for new research."

We also need a radical change in the way that new research is funded, says Hopkins, especially when it comes to neglected diseases, with non-governmental organisations and charities joining forces with academia and industry to drive major projects and scale up drug discovery for tropical diseases, for example.

"Tropical diseases offer academia and industry an invaluable opportunity to experiment with new ways of conducting drug discovery – organisationally, technologically and scientifically," Hopkins continues. "We should be bold in proposing a grand 'moon-shot' type of mission in this area to develop ten new drugs for the ten major neglected diseases by 2020."
Hopkins’ latest work in network pharmacology also suggests that the successful design of new drugs will need a major rethink of the way we think of targets, seeing them as part of complex networks rather than as individual targets which exist in isolation. “The dominant paradigm in drug discovery is the concept of designing maximally selective ligands to act on individual drug targets,” Hopkins wrote in *Nature Chemical Biology* last year. “However, many effective drugs act via modulation of multiple proteins rather than single targets.”

There may be few targets to aim for, he says, but the targets may have multiple receptors and the interactions between different targets and networks of targets make the process even more complex, and this is where network pharmacology may come to the rescue. “By targeting networks of proteins,” adds Hopkins, “we also circumvent toxicity.”

Part of Hopkins’ work in Dundee is to build the computational tools which will help to turn the concept of multiple targets into reality – mapping the networks of targets as well as the complex interactions between them. Hopkins also sees medicinal informatics “casting its nets” in research, not only modelling and analysing data from experiments but also exploring the existing published data to identify patterns which may lead to unforeseen discoveries. This is part of a process called chemogenomics – developing new methods to prioritise potential drug targets from a pathogen genome by analysing the collective pharmacology knowledge already available, including genome sequences, protein structures and literature abstracts.

Open access to data is another pet subject for Hopkins, who explains that we are “very dependent on data to develop medicinal informatics.” One of the first things he did when he came to Dundee was to work with others to persuade the Wellcome Trust to invest almost £5 million to create an open access database for medicinal chemistry data, to put more data into the public domain and “spur innovation.”

Computational tools, says Hopkins, could not only help to automate the drug discovery process, reducing costs and increasing efficiency, but also play a key role in clinical trials. Drug discovery accounts for about half of total research costs, but Hopkins sees the whole drug development process as a continuous cycle, with informatics feeding back data from clinical trials to sharpen available knowledge, thus making future trials more likely to succeed by understanding previous failures. In addition, says Hopkins, about 40 per cent of the drug sales on the market are the result of “alternative indications” – scientific accidents like Viagra, a drug which started off as a cardiovascular treatment rather than a cure for erectile dysfunction.
“I’m also interested in what we can learn from the successful discovery strategies of the master drug hunters like Paul Janssen and Sir James Black,” says Hopkins. “We are currently developing an informatics version of Black’s maxim that the most fruitful basis for the discovery of a new drug is to start with an old drug by developing an automated evolutionary approach to drug design.”

The pharmaceutical industry also needs to adopt a more interdisciplinary approach to research, says Hopkins, and Scotland offers several advantages, making it easy to partner with different institutions and scientific disciplines, and relate research to available clinical records. In his own career, Hopkins himself has worked in a number of fields, including chemistry, crystallography, bioinformatics and data mining, and in his current work he seeks to integrate these different skills, and “break down the underlying assumptions” which lie behind various branches of science.

Hopkins is also concerned with “ingenuity and utility” – not just how scientists come up with new ideas but also how they turn that inspiration into something that will benefit people. This down-to-earth approach partly derives from his industrial experience, as Head of Chemical Genomics at Pfizer Global Research and Development and Founder of the company’s Indications Discovery strategy. Ultimately, Hopkins wants to make “a real-world difference,” building new computational tools and developing new experimental methodologies. His laboratory in Dundee consists of an informatics group, using chemoinformatics, structural bioinformatics and knowledge discovery techniques, and an experimental biophysics group, headed by Dr Iva Navratilova, specialising in biosensor technologies. Hopkins works closely with the University of Dundee’s Drug Discovery Unit, the ChEMBL group at the European Bioinformatics Institute, the London School of Hygiene and Tropical Medicine, the WHO-TDR Target Network and several pharmaceutical and biotechnology companies.

The ability to focus on the problems of the developing world is not just a political trend but a consequence of recent technological advances which enable researchers to cut costs and use smarter methods to hunt for new leads. And Hopkins believes that improved efficiency and lower costs will encourage the established pharmaceutical firms to get involved in drug discovery in areas which used to be less profitable, as well as the diseases of the rich.

The so-called “drug pipeline” is also going through a period of radical change, according to Hopkins. Instead of a linear process from idea to discovery to clinical trial and eventually market, Hopkins sees the process as a network of relationships and feedback loops, with open access to data accelerating progress.

In his current position, Hopkins is enjoying a new kind of freedom, questioning scientific orthodoxy at the same time as getting down to serious business in the quest for new drugs. “Science is not only driven by curiosity,” Hopkins concludes, “but by needs.”
The first SULSA Symposium in June 2009 in Edinburgh provided a platform for some of Europe’s leading researchers in cell, systems and translational biology, including a Nobel Prize winner who talked about how scientific success can sometimes be an unexpected side-effect of failure...

Two distinguished speakers, **Professor Sir Tom Blundell**, Chair of the SULSA International Advisory Board and **Professor Sir Tim Hunt**, 2001 Nobel Laureate, joined seven new SULSA Professors and Readers, to address an audience of 300 participants from all around Scotland. The event underscored the depth and the breadth of the research in life sciences being carried out today in Scotland and beyond.

Drug discovery does not always translate into products – or profits. Only eight out of every 8,000 lead compounds (chemical compounds with the potential to become pharmaceutical products) ever go on to clinical trials, said Professor Sir Tom Blundell, in the Opening Lecture of the SULSA Symposium, describing the "hit rate" of translational biology. And only one out of the eight compounds tested in clinical trials gets to market – with 'blockbuster' drugs typically costing over one billion dollars before they start to generate any returns.

Professor Blundell, the head of the Department of Biochemistry at the University of Cambridge and co-founder of Astex Therapeutics, which has cancer drugs in early stage clinical trials in the US and the UK, provided the perspective from the start when he talked about the high attrition rate in modern drug discovery and the huge costs involved in bringing new products to market – a model he described as “unsustainable.” The challenge, he said, was how to contribute to making the process more efficient, via automation, including new solutions such as high-throughput crystallography and structural bioinformatics. "We need proper computational systems,” Professor Blundell continued.

When there are 1,000 candidates for new therapeutic solutions, researchers need powerful models for testing, he said. "Drug discovery is not all about screening large libraries,” he added, "but changing those compounds into drugs." And one of the priorities for Professor Blundell is to develop new treatments for neglected diseases, including malaria and tuberculosis.

As well as utilising informatics, we need a multidisciplinary approach to drug discovery, according to Professor Blundell, and also need to “move away from the old divisions between chemistry, physics and biology,” at the same time as building stronger partnerships between academia and industry.

**Professor Manfred Auer** (SULSA Chair in Chemical and Translational Biology, University of Edinburgh) elaborated on this theme in his lecture about strategies for identifying new drugs that interfere with protein-to-protein interactions – which represent potentially powerful but notoriously difficult targets for drug discovery. Auer’s group has developed a new approach to lead and drug discovery that integrates chemical, biological and physical techniques and is particularly suited to cracking the protein-protein interaction problem. **Professor Andrew Hopkins** (SULSA Chair in Translational Biology and Medical Informatics, University of Dundee) illustrated the complexity of “interactions in chemical space” whilst discussing a wide range of issues including automation of the drug design cycle and the need to make more libraries of lead compounds and informatics tools developed by industry available to academic researchers. **Dr John Mitchell** (SULSA Reader in Translational Biology, University of St Andrews) lectured on the chemistry of the reactions catalysed by different enzymes, the implementation of informatics databases to systematically capture this information and the need to “combine bioinformatics and chemoinformatics to identify and measure similarities in enzyme catalysis.”

Moving from drug discovery to more basic research on cell biology, development and disease, **Professor Tibor Harkany** (University of Aberdeen) outlined his work in “endocannabinoids, cannabis and the developing brain.” Harkany explained how cannabis affects the connectivity of the brain and its signalling networks, discussing implications ranging from pre-natal drug addiction and synaptic plasticity to cancer, obesity and memory loss. He highlighted the particular dangers of cannabis use for pregnant women and adolescents, due to the drug’s effects on brain development.

SULSA’s systems biology theme was represented by two leading international researchers recently recruited to Scotland by SULSA. **Professor Peter Swain** (SULSA Chair in Systems Biology, University of Edinburgh) posed the question of how cells make decisions, such as whether or not to eat a given sugar, particularly in a “noisy” environment where variable signals require complex cellular algorithms that have evolved to deal with the problem of uncertainty.
Professor Rainer Breitling (SULSA Chair in Systems Biology, University of Glasgow) described his interest in metabolomics – the systematic study of the thousands of natural chemicals (metabolites) within a cell. This metabolic fingerprint approach depends on sensitive mass spectrometry and advanced computational methods, including special algorithms developed by Breitling to eliminate the background noise and to make the fingerprinting of anonymous compounds at least “five times more accurate.” Breitling is using metabolomics to provide new insights into diseases such as sleeping sickness (African trypanosomiasis). Professor Ferenc Nagy (SULSA Chair in Systems Biology, University of Edinburgh) discussed the molecular aspects of light-regulated plant growth and development, pointing out that light is the single biggest factor in plant life, going on to explain phenomena such as signal transduction and the nucleo/cytoplasmic partitioning of the light-sensing phytochromes.

In closing the Symposium, Keynote Speaker Professor Sir Tim Hunt (Cancer Research UK, London Research Institute) talked about “getting in and out of mitosis” and the ups and downs of his recent research, which seeks to unravel the secrets of the biology of the cell cycle and how it all works, including the phosphatases that regulate mitosis – the process by which cells divide into identical pairs.

“Finding a good problem is critical,” Professor Hunt began, “but it isn’t easy to do so and it’s got to be one you can solve.” And according to Professor Hunt, his current research is still work in progress which has seen disappointments and failures en route – and still has a long way to go. “You only ever learn if you make stupid mistakes,” he said, describing the importance of experiments and the errors that he and his colleagues had made in their search to understand the secrets of mitosis – “the process at the very heart of life.”

Professor Hunt, who won the Nobel Prize for Physiology or Medicine in 2001 for his work on the regulation of the cell cycle, described his current research in considerable detail, including the search for enzymes that catalyse cell division, and how the famous enzyme activator called cyclin, discovered by Hunt and colleagues, is essential to get in and out of mitosis. He also described his more recent studies on other cell cycle regulators and how he had noticed “something funny going on with phosphatases.” His lecture was not just an insight into the more esoteric details of mitosis but a lesson in science in general, focusing on some of his failures as well as the joy of success – and the importance of experiments in an age when computers are beginning to dominate research.

Professor Hunt also confessed that his theory regarding the critical role of a particular phosphatase, called PP2A, had turned out to be somewhat off the mark: “All these experiments can be reproduced,” he explained, “but our interpretation was flawed – the PP2A phosphatase was not the key.” Even Nobel Prize winners don’t always prove to be right in the first instance and, borrowing a phrase from modern politics, Professor Hunt concluded that we need more “experiments, experiments, experiments.”

If the Symposium was one of those experiments, however, it was clearly a major success, not only providing a showcase for the exciting work already being carried out by the SULSA researchers but also highlighting the challenges lying ahead for everyone involved in life sciences – and its many applications in drug discovery and biotechnology.
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