



**NUS**  
National University  
of Singapore

Faculty of  
Science

# RESEARCH

Volume 19 Number 1 June 2014



## FEATURES

---

Catalysts for a greener tomorrow p4

Modelling uncertainty in financial  
markets p8

# Table of contents

---

## NEWS ROUNDUP

- 2 New Dean of Science: Professor Shen Zuowei
- 2 Thermo Fisher partners NUS in research
- 3 Lee Kong Chian Natural History Museum

## RESEARCH FEATURES

- 4 Catalysts for a greener tomorrow
- 6 Natural laboratories for evolution in action
- 8 Modelling uncertainty in financial markets
- 10 Electrons in a carbon flatland
- 12 Recent progress in diagnostic medicine
- 14 Characterizing the location of galaxies
- 16 The “miracle molecule” in red wine
- 18 Puzzling genomic regulatory systems

## PEOPLE

- 20 A lifetime of contributions to Science

---

## Faculty of Science Research

The Faculty of Science conducts basic and applied experimental, theoretical and simulation research in a broad spectrum of science, mathematics and technology domains. We cover most of the key fields in biological sciences, chemistry, physics, pharmacy, mathematics and statistics.

Faculty of Science Research is published twice a year. It is written for a broad scientific audience interested to keep up with some of the key areas of science pioneered by researchers at the Faculty of Science.

This publication may be reproduced in its original form for personal use only. Modification or commercial use without prior permission from the copyright holder is prohibited.

For further information on the research in this newsletter, please contact:

Editor: SOH Kok Hoe (scisohkh@nus.edu.sg)  
Deputy Editor: Joanna LIM (scilymj@nus.edu.sg)

Research Section, Dean's Office  
Faculty of Science  
National University of Singapore  
Blk S16, Level 5  
Science Drive 2  
Singapore 117546

For the latest research news, please refer to:  
URL: [science.nus.edu.sg/research/news](http://science.nus.edu.sg/research/news)

**On the cover:** Mathematical modelling of financial markets have become an interdisciplinary field with connections to many branches of science and engineering.

# News Roundup

## New Dean of Science: Professor Shen Zuowei

The National University of Singapore (NUS) has appointed Professor SHEN Zuowei, an internationally acclaimed mathematician, as the new Dean of its Faculty of Science. Prof Shen, who has also been feted by the prestigious Tan Chin Tuan Centennial Professorship is the 22nd Dean in the history of the Faculty of Science from 1 April 2014.

Professor Shen first joined NUS as a lecturer at the Department of Mathematics in 1993. He was appointed Head of Department of Mathematics in July 2012. He held the Tan Chin Tuan Centennial Professorship since January 2013 in recognition

of exceptional academic leadership and international recognition in Mathematics.

Prof Shen commented, “moving forward, I will continue to build upon our strengths in education and research to expand and intensify our research collaborations and attract top students and researchers to our Faculty. I look forward to working with my fellow colleagues at NUS Science to achieve greater peaks of education and research excellence and groom generations of students and scientists who can make significant contributions to society.”



Prof Shen Zuowei, Dean of Science

---

## Thermo Fisher partners NUS in research

Global firm Thermo Fisher Scientific and the National University of Singapore (NUS) have inked a Memorandum of Understanding (MOU) in April 2014 to develop an alliance to advance life sciences research in Singapore. This agreement aims to support future discoveries and development of applications.

Under this agreement, Thermo Fisher Scientific will sponsor multi-year and short-term research projects in life sciences for a period of up to five years. It will also support collaborative efforts with NUS, including a joint symposium to encourage knowledge exchange in the biological and physical sciences.

Focus areas include research in life sciences and healthcare, such as cancer and diagnostics. These programmes will involve the development of analytical technologies, reagents,

# Thermo Fisher SCIENTIFIC

instrumentation, and software for life sciences, healthcare and the environment.

A Joint Scientific Steering Committee, with representatives from the company and NUS has been formed to identify topics for the grant calls and the selection of projects for funding.

Associate Professor Peter Ho, Vice-Dean (Research), Faculty of Science, welcomed the partnership and commented, “we are glad to partner Thermo Fisher Scientific in pushing scientific and technology boundaries. Through this partnership, our academic staff can contribute their domain expertise to help develop new applications to advance healthcare.”

# News Roundup

## Lee Kong Chian Natural History Museum



Artist impression of the Lee Kong Chian Natural History Museum.  
Image: W Architects Pte Ltd

Singapore's first natural history museum, the Lee Kong Chian Natural History Museum is now officially a new academic unit within the National University of Singapore (NUS). The museum is slated to open in the first quarter of 2015 to coincide with the university's 110th anniversary and Singapore's 50th birthday.

When completed, the museum will house one of the largest Southeast Asian collections of biodiversity in the region - more than half a million specimens of flora and fauna - together with three almost-complete dinosaur fossils. The iconic sea-cliff planter wall landscape feature was designed

taking into consideration the need for minimal daylight penetration as the architecture will be used for the storage and exhibition of specimens. The 8,500 square-metre museum space will be used for exhibition, research, education and controlled storage of specimens.

Professor Rudolf Meier, Deputy Head for the new Lee Kong Chian Natural History Museum commented, "We are excited that the museum is now its own academic unit under the Faculty of Science. With the support of many donors, faculty, and university, the museum had steadily grown until it had reached the critical size for becoming

its own unit. For example, thanks to a recent donation we were able to recruit two new biodiversity experts who are studying predatory bugs and Singapore's remaining population of leopard cats. Through additional recruitment, we hope to expand further so that we can do justice to the amazing biodiversity of Southeast Asia which is home to circa 20% of the world's species. We will strive to strengthen the international profile of the new LKCNHM by being an important driving force in species discovery and conservation. At the same time we will intensify our research in Singapore in order to generate critical data for sustaining Singapore's biodiversity."

# Catalysts for a greener tomorrow

Small molecule activation and catalysis with frustrated Lewis pairs (FLPs) can give rise to cheaper, more accessible and greener catalysts

## Green Chemistry

Give a chemist enough energy, and they can make pretty much anything! And thus far, there has been enough energy to transform chemicals, regardless of how inefficient the process. However, recent forecasts predict that fossil fuels may be depleted by next century. In addition, we face the problems of post-peak energy production and climate change. These problems are a driving factor motivating chemists to develop more energy efficient processes. Green chemistry is largely about efficiency. Energy efficiency, atom efficiency and efficient use of solvents (waste reduction). Of course, green chemistry also encompasses other important areas such as toxicity, starting material abundance and reaction viability (e.g. sustainable reaction conditions, or purity of product and the need for further processing) – but no other contemporary issue is as seemingly important as energy usage.

## A Catalyst For A Greener Tomorrow

Catalysis plays two obvious roles in green chemistry; it can reduce the energy needed for a chemical transformation, and it can improve the atom efficiency of a reaction by enabling the reaction of less 'activated' molecules. For example, an area of current research in catalysis is on the use of abundant, inert molecular nitrogen ( $N_2$ ) as a nitrogenation agent, as opposed to the currently used amine, nitrate and azide reagents used today that are much less atom efficient.

Although catalysis is seen as an environmentally friendly improvement on non-catalysed reactions, greener improvements can (and must) be made within the area. For example, many of the most active and efficient

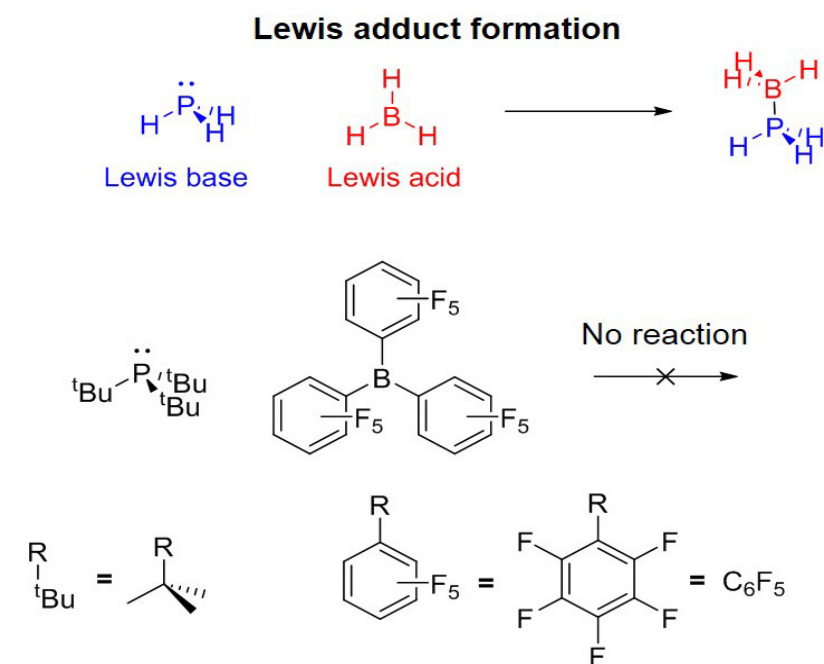


Figure 1: (Top) Lewis adduct formation from Lewis base and Lewis acid. In this example, phosphine and borane react to form phosphine-borane.

(Bottom) Bulky Lewis acids and bases form frustrated Lewis pairs and not Lewis adducts.

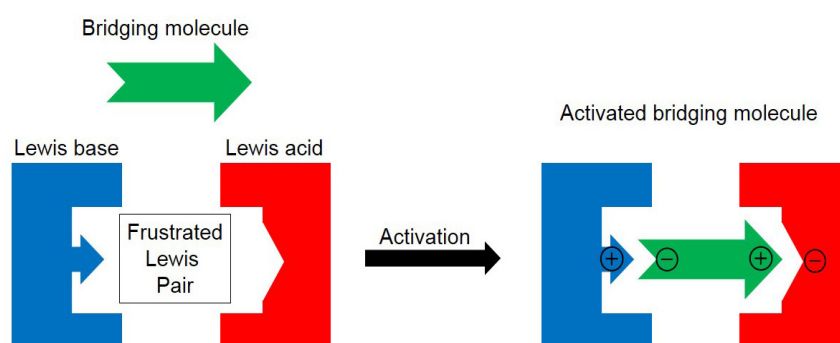


Figure 2: When a molecule bridges a FLP, the bridging molecule becomes polarised as it acts as both a Lewis acid and Lewis base, and it is effectively activated towards further reaction.

catalysts that have been developed rely upon heavy metals to perform the transformations – heavy metals that are largely toxic, non-biological and in short supply. A push is being made to develop either catalysts that contain biological metals, such as iron, zinc or

molybdenum, or catalysts that do not contain any metals at all! In essence, nature has already developed catalysts of this type, through the constraint of 'natural abundance', which we refer to as enzymes. However, extraction

of enzymes for industrial catalysis is not viable because it cannot be performed cost effectively on an industrial scale. Also, natural systems do not always match industrial type chemical reactions. A prime example of this is C-H activation. The presence of molecules containing only carbon-carbon and carbon-hydrogen bonds in biology is rare, however, due to our reliance on fossil fuel resources (i.e. C-H rich starting materials), the ability to transform such molecules is fundamentally important to our society today.

To make improvements to catalytic systems, it is necessary to define and understand them. Prof Young and his team focuses on homogeneous catalysis; that is catalysis where the catalyst and reactants are in the same phase (e.g. in liquid solution). Industrial transformations are dominated by the use of heterogeneous catalysts, where the catalyst and reactants are in different phases. This is primarily for ease of separation of the catalyst from the product so that the catalyst can be recycled. Homogenous catalyst offers many advantages in terms of characterization and understanding product formation. In addition to this, many homogeneous catalysts have been successfully deposited onto heterogeneous surfaces, providing the best of both techniques, i.e. a well-defined catalyst that can be easily separated from reaction products.

The current research focuses on the activation of relatively inert molecules towards reaction with abundant chemical resources. An example of this would be the reaction of molecular hydrogen with a hydrocarbon. To achieve this, Prof Young is exploring metal free systems known as Frustrated

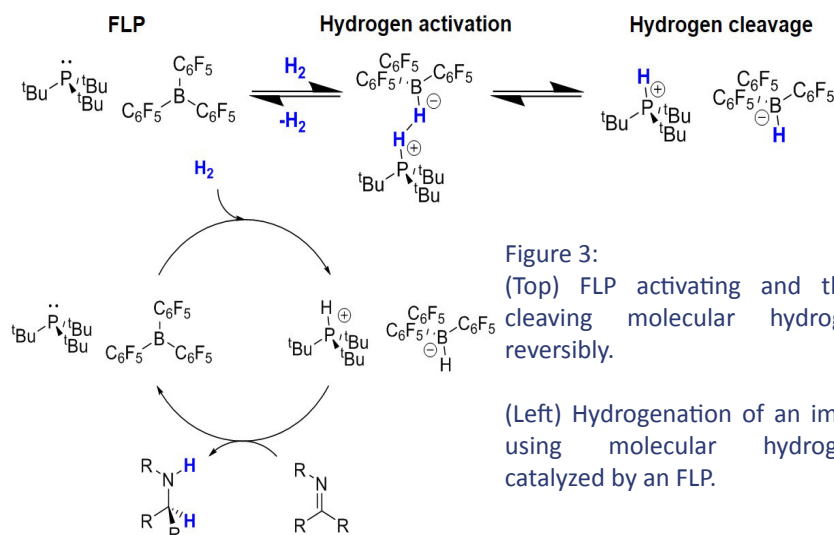


Figure 3:  
(Top) FLP activating and then cleaving molecular hydrogen reversibly.

(Left) Hydrogenation of an imine using molecular hydrogen, catalyzed by an FLP.

Lewis Pairs (FLPs).

### Frustrated Lewis Pairs (FLPs)

Lewis acids and bases are a classification defined by Gilbert N. Lewis in 1923. They are in essence electron pair acceptors (Lewis acids) and electron pair donors (Lewis bases). When a Lewis acid and base combine, they form a Lewis salt, where a bond has formed resulting from the electron donation from one atom to another (Figure 1, top). Frustrated Lewis pairs are substances where bulky groups surrounding a Lewis acid and Lewis base prevent them from forming Lewis salts (Figure 1, bottom). It has been found that the relative acidity/basicity of the FLP can be quenched by small molecules that can bridge between the acid/base pair. Such bridging results in the activation of a mediating molecule which acts both as a Lewis base and a Lewis acid (Figure 2).

Recently, the first report of reversible cleavage of molecular hydrogen (H<sub>2</sub>) by a non-metal was achieved through the use of FLPs (i.e. hydrogen could

be heterolytically split and reformed depending on the reaction conditions) (Figure 3, top) [1]. Subsequently, this break-through has allowed the development of the first non-metallic hydrogenation catalyst (excluding biological systems such as NADH) (Figure 3, left) [2]. Currently, the range of substrates that FLP catalysts can hydrogenate is small, but more of them is being developed which offers added functionality, such as selectivity (i.e. only specific molecule locations are hydrogenated).

### Where To Now?

The activation of a large variety of molecules has already been achieved using FLPs, these include alkenes, alkynes, disulfides, carbon dioxide and nitrous oxide. However, the development of catalytic reactions arising from the activation of these molecules remains an ongoing process. The fact that FLPs are made of earth abundant elements, may mean that these catalysts will one day lead to cheaper, more accessible and greener catalysts.

Rowan YOUNG received his PhD from the Australian National University, where he was awarded the Director's Prize in Chemical Sciences. He then carried out postdoctoral research in the United Kingdom at the University of Oxford, and then at the University of Edinburgh. He joined NUS as an Assistant Professor in the Department of Chemistry in 2014.

#### Reference

1. Welch, G. C., Juan, R. R. S., Masuda, J. D. & Stephan, D. W., "Reversible, Metal-Free Hydrogen Activation", *Science*, Vol 314, pp. 1124–1126 (2006).
2. Chase, P. A., Welch, G. C., Jurca, T. & Stephan, D. W., "Metal-Free Catalytic Hydrogenation", *Angew. Chem. Int. Ed.*, Vol 46, pp. 8050–8053 (2007).



# Natural laboratories for evolution in action

Southeast Asia is a unique natural laboratory that provides unparalleled opportunities for studying evolutionary processes

## Introduction

Nature invents and discards. Species divide, then go extinct or give rise to many more. One-and-a-half centuries after Darwin and Wallace, we have learned much about the mechanisms by which evolution proceeds, but much remains to be investigated. Albeit continual, advances in the field of evolutionary biology have gone through bouts: the Mendelian Laws around the turn of the 19<sup>th</sup>/20<sup>th</sup> centuries, Watson and Crick's seminal insights into the structure and function of DNA and the subsequent Biological Synthesis after the World Wars, and the revolution that brought DNA sequencing in the 1980s. In the last ten years, there has been another such biological revolution, propelled by technological innovations (so called 'next-generation sequencing' or NGS) that allow us to sequence whole genomes as opposed to single genes. The volume of DNA that can be sequenced on any given day now is about 1 million times higher than what it was 10 years ago.

## Genetic Introgression

Our technological capabilities allow us to probe ever deeper into the DNA of the denizens of our planet, searching for patterns that facilitate a reconstruction of their evolutionary past. One of the most surprising results from this inquest is the realization that presumably rigid boundaries between species – thought to be reproductively isolated – are in fact porous. Hybridization events between discrete species, however rarely they may occur, leave traces of 'foreign' DNA in a species' gene pool, a process now widely known as 'genetic introgression'. It takes a large volume of DNA sequence to detect signals of introgression, so our insights into this process are relatively recent

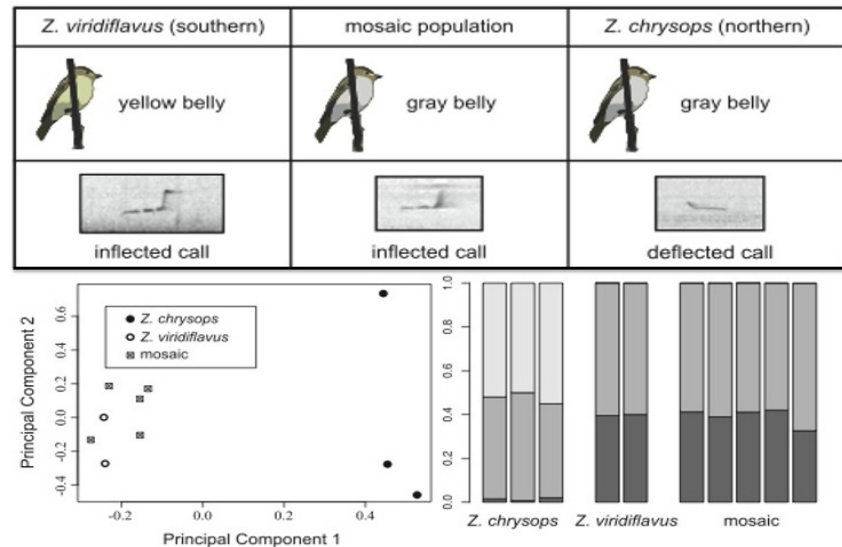


Figure 1:

(Upper panel) Tabular representation of three *Zimmerius* flycatcher populations examined. The table shows that the intermediate 'mosaic population' looks like the northern species but sounds like the southern species.

(Lower left panel) A principal component plot shows the distribution of ten *Zimmerius* flycatcher individuals in space based on genetic variation across 1288 different loci (i.e. places in the genome). The plot clearly demonstrates that mosaic birds are genomically akin to the southern species (i.e. *Z. viridiflavus*).

(Lower right panel) A structure plot shows the genetic affinity of ten *Zimmerius* flycatcher individuals based on 37,361 different loci (=places in the genome). The plot clearly demonstrates that mosaic birds are virtually identical to the southern species (i.e. *Z. viridiflavus*) in their genomic make-up while differing distinctly from the northern species (i.e. *Z. chrysops*).

and incomplete. Amongst animals, birds are relatively well-known and constitute an ideal system to study introgression. In fact, evidence points to introgression being pervasive among closely related bird species [1].

An important question has been whether introgression is largely driven by neutral processes or natural selection. To re-phrase this question in simpler terms: Are the snippets of 'foreign' DNA invading the gene pool just a random selection trickling in via a chance process? Or is the invasion of certain stretches of DNA favored or disfavored by the function or trait they

confer? Inquiry into this burgeoning field is still in its infancy. However, a few important conclusions can be drawn from incipient research. In what was possibly the first introgression study using NGS for non-model animal species, we investigated a pair of South American flycatchers, one grey-bellied from the northern Andes and one yellow-bellied from further south ([2]; Figure 1, upper panel). We were particularly interested in a geographically intermediate population that exhibits the northern species' plumage but the southern species' voice. Genome-wide DNA proved that this mosaic population is

genetically almost purely 'southern' (Figure 1, lower panels). Yet how can a genetically southern individual look identical to the northern species? Although overwhelmingly southern in genomic DNA, the mosaic population did exhibit a significant signal for genetic introgression from northern birds. It became clear that the DNA responsible for the birds' belly plumage must be restricted to few places in the genome (=loci), and that these few loci – but not necessarily many more – are likely affected by introgression. The results of this research were thus strongly supportive of the hypothesis that natural or sexual selection was the driver behind genetic introgression. Hybridization with the birds from the north probably introduced the grey belly type into the mosaic population, and – whatever the reason – birds with 'northern-type' grey bellies seemed to have an advantage over yellow-bellied ones, although most of the remaining genomic DNA of these birds remained 'southern'.

The next episodes in our research on introgression will see us target Southeast Asian species, as Southeast Asia is a unique natural laboratory that provides unparalleled opportunities for studying evolutionary processes. An expedition to remote satellite islands off Sulawesi, in eastern Indonesia, in Nov/Dec 2013 resulted in the collection of invaluable DNA specimen samples, including those of more than 5 new bird species to science. For a set of core species, we obtained DNA samples from three islands that differ in their history of land connections. While periodical climate change in the last two million years has created land connections between two of these islands, a third one has remained unconnected to

them throughout the ice ages. This unique dataset will therefore afford us the rare opportunity to study the effects of climate change on patterns of gene flow and introgression between different island species. Laboratory work for this project is well underway.

### Conservation Genetics

Another main focus of this laboratory is conservation genetics, a topic that is becoming ever more pressing in our planet's urbanized landscapes, including those of Singapore. Southeast Asia has the notorious distinction of exhibiting the highest current biodiversity loss of any region on the planet, largely brought about by turbulent economic development. In Singapore, the level of biodiversity loss documented since the World Wars is staggering. However, when put into the context of this city state's extremely high human density, levels of extinction have actually been comparable to or lower than those of many other regions in Southeast Asia. The nation managed to set aside a fair chunk of its territory for the protection of its local rainforest fauna (including parts of the Central Catchment and Bukit Timah), and the challenge now is to preserve what's still here to preclude a total collapse of the remnant rainforest biota.

Although the size of Singapore's nature reserves is now fairly stable, we continue to see species slipping into local extinction even in recent times. It appears, then, as though recent extinction events are not related to any habitat destruction. More and more evidence points to these extinction events having to do with the genetic impoverishment of the gene pool – oftentimes through inbreeding. When Singapore's rainforests yielded to

urban development in the early and mid-20th century, rainforest species hung on to the remaining fragments as well as they could. However, many of them were doomed to a slow process of 'extinction with a time lag', as their gene pool would become more and more impoverished over the decades. With no 'fresh blood' coming in, all individuals within a small rainforest patch would – over time – be each other's cousins or siblings, with catastrophic consequences for their offspring's survival.

This silent slip into extinction is what may be dooming most of Singapore's rare rainforest biota today, and is a harbinger of more region-wide perils in an increasingly globalized world. Our lab has initiated a series of Honour's projects in which NUS Honour's students go out into Singapore's last remaining wildlands, obtain blood samples of their target species and use contemporaneous laboratory and analytical approaches to examine their population-genetic 'health'. Our first year started with conventional sequencing technology, but we are soon stepping this up to use NGS for genome-wide DNA screening. We are hoping that our results will furnish key insights into which species are particularly prone to local extinction, with a hope that the local park authority (NParks) can use these results to mount species-specific protection measures, such as connecting habitat patches with corridors to facilitate gene flow (i.e. the exchange of 'fresh blood') between different populations.

Evolutionary biology is a fascinating field with a wealth of applications and insights. The future looks promising for the thriving of this discipline in Southeast Asia and at NUS.

---

Frank RHEINDT did his PhD at the University of Melbourne where he studied the evolutionary history and cryptic speciation in Neotropical tyrant-flycatchers. He moved on to a postdoctoral stint at Harvard University, where he started using next-generation sequencing technology to investigate patterns of gene flow between tropical bird populations. He joined NUS as an assistant professor in 2013 and is now building up the Avian Evolution Laboratory.

#### Reference

1. Rheindt FE, Edwards SV., "Genetic introgression: an integral but neglected component of speciation in birds", *Auk* 128: 620-632 (2011).
2. Rheindt FE, Fujita MK, Wilton PR, Edwards SV., "Introgression and phenotypic assimilation in *Zimmerius* flycatchers (Tyrannidae): population genetic and phylogenetic inferences from genome-wide SNPs", *Systematic Biology* 63: 134-152 (2014).



# Modelling uncertainty in financial markets

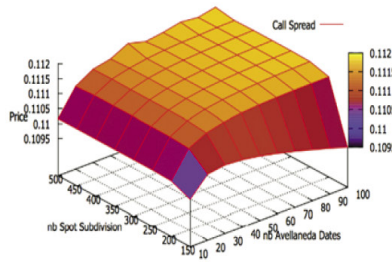
Going beyond traditional approach in quantitative finance provides a broader perspective in terms of “risk management”

## Introduction

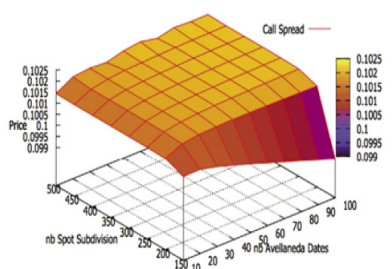
Mathematical modeling of financial markets has a century-long history. Initiated by the French mathematician Louis Bachelier in 1900, the mathematical modeling of financial markets has grown to become an interdisciplinary field with connections to many branches of science and engineering: economics, management, probability and statistics, numerical analysis and simulation. The first generation of mathematical models, beginning with the Bachelier (1900) model and most prominently represented by the Black and Scholes (1973) model, considers the evolution of market prices as exogenous stochastic processes, and proceeds to solve fundamental financial problems such as: valuation and hedging of contracts and derivative securities, optimal investment and risk management. A well-founded economic theory based on non-arbitrage together with the appropriate mathematical tools relying especially on stochastic calculus, led to a spectacular growth of the derivative industry and in parallel to the development of the academic field of Mathematical Finance.

The traditional approach in quantitative finance is to analyze problems where financial risk is presented probabilistically and exogenously: the statistical behavior of risk factors/market variables is assumed to be known and given a priori regardless of investor’s action. However, misspecification of the model may induce important errors in risk analysis. In particular, following the recent financial crisis, people are more aware of model risk and model uncertainty, which need to be considered in suitable mathematical frameworks. Risk and portfolio management robustness with respect

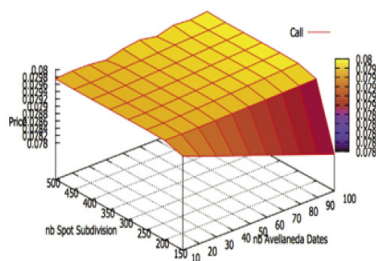
Call Spread (90%-110%) with volatility min = 10% and max = 20%



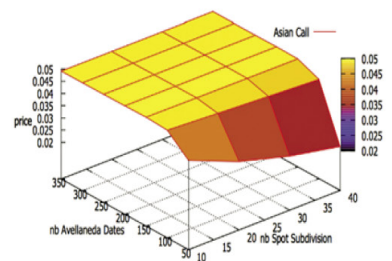
Call Spread (90%-110%) with volatility min = 15% and max = 20%



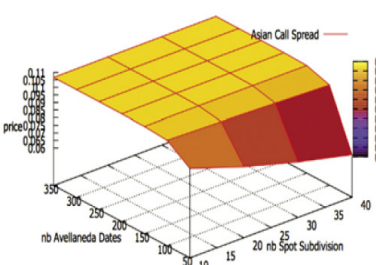
Call option (100%) with volatility min = 10% and max = 20%



Asian call option (100%) with volatility min = 15% and max = 20%



Asian call spread (90% - 110%) with volatility min = 10% and max = 20%



Asian call spread (90% - 110%) with volatility min = 15% and max = 20%

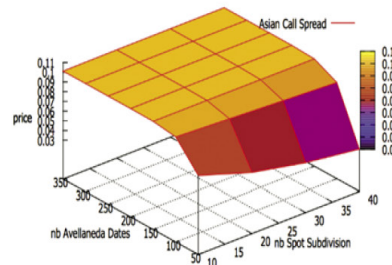


Figure 1: Numerical implementation of Monte Carlo schemes for options pricing with uncertain volatility models.

to model risk and model uncertainty becomes appealing. These new issues show that one has to think about “risk” and “risk management” in a much broader perspective.

## Framework for Model Uncertainty

Recently, a new generation of quantitative models in finance, which go beyond the stochastic modeling of

prices, has attracted much attention of both academics and practitioners. The nonlinear expectation theory and the related stochastic calculus, initiated in Peng [1], provide a suitable mathematical framework for uncertainty modeling. Simultaneously, the second order backward stochastic differential equations (2BSDEs for short) theory and the quasi-sure analysis, introduced in Soner, Touzi

and Zhang [2] offer another viewpoint to consider model uncertainty. These two frameworks are strongly connected and have many applications in various areas such as: probability theory, robust financial risk measures, robust optimization in finance, etc.

My research interest concerns some financial mathematics problems in an incomplete market with model uncertainty, in particular by adopting the viewpoint of 2BSDEs. The key idea was to consider a family of BSDEs defined quasi surely (q.s. for short) under PH a non-dominated class of mutually singular probability measures, which means P-a.s. for every probability measure P in this class. Given a filtered probability space generated by an Rd-valued Brownian motion W, a solution to a BSDE with coefficient f and terminal condition  $\xi$  consists of a pair of progressively measurable processes (Y, Z) such that:

$$Y_t = \xi + \int_t^T f_s(Y_s, Z_s) ds - \int_t^T Z_s dW_s, \quad t \in [0, T], \mathbb{P} - a.s.$$

And we shall consider the following 2BSDE, where B is the canonical process and K a nondecreasing process.

$$Y_t = \xi - \int_t^T \hat{F}_s(Y_s, Z_s) ds - \int_t^T Z_s dB_s + K_T - K_t, \quad 0 \leq t \leq T, \mathcal{P}_H - q.s..$$

(1) We first generalize the 2BSDEs theory initially introduced in the case of Lipschitz continuous generators to quadratic growth generators. This new class of 2BSDEs will then allow us to study the robust utility maximization problem in non-dominated models, which can be regarded as a nonlinear extension of the standard utility maximization problem.

(2) We study the robust utility maximization problem via 2BSDEs theory. This is the first application of 2BSDEs to financial mathematics problems. The problem of utility maximization, in its most general form, can be formulated as follows:

$$V^\xi(x) := \sup_{\pi \in \mathcal{A}} \inf_{Q \in \mathcal{P}} \mathbb{E}^Q[U(X_T^\pi - \xi)],$$

where  $\mathcal{A}$  is a given set of admissible trading strategies,  $\mathcal{P}$  is the set of all possible models,  $U$  is a utility function,  $X_T^\pi$  is the liquidation value of a trading strategy  $\pi$  with positive initial capital  $X_0^\pi = x$  and  $\xi$  is a terminal liability, equal to 0 if  $U$  is only defined on  $\mathbb{R}^+$ .

(3) We introduce 2BSDEs with a lower reflecting obstacle. Reflected backward stochastic differential equations (RBSDEs for short) were introduced by El Karoui et al. [3] to study related obstacle problems for PDE's and American options pricing. In this case, the solution Y of the BSDE is constrained to stay above a

given obstacle process S. In order to achieve this, a nondecreasing process is added to the solution where the last condition, also known as the Skorohod minimum condition means that the process only acts when Y reaches the obstacle S. This condition is crucial to obtain the uniqueness of the solution to classical RBSDEs.

(4) From the literature, we know that in the case of a filtered probability space generated by both a Brownian motion and a Poisson random measure with a compensator, one can consider a natural generalization of BSDE to the case with jumps. We define a notion of 2BSDEs with jumps, for which we prove the existence and uniqueness of solutions in appropriate spaces. We can interpret these equations as standard BSDEs with jumps, under both volatility and jump measure uncertainty. These equations are the natural candidates for the probabilistic interpretation of fully nonlinear partial integro-differential equations.

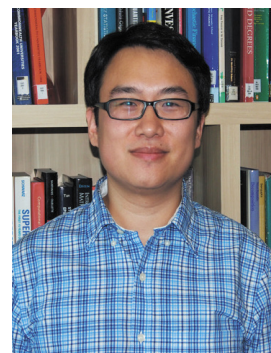
(5) At last, we implement some existing numerical schemes and make improvement in practice.

We implement some existing schemes for pricing options with uncertain volatility model, with both backward computations and backward-forward computations. We also suggest some techniques to improve the scheme in practice. From the numerical test results, we generally observe that the Monte Carlo method performs well for non-path-dependent options and can provide prices with good precision for path-dependent ones. Moreover, the pricing precision depends essentially on the quality of the approximation of conditional expectations by regression. In order to get more precise results with this method, we should improve the approximation of conditional expectations by using better regression procedure, suitable control variates and/or non-parametric regressions in higher dimension. In particular, special knowledge of financial products could be used to have better result.

ZHOU Chao obtained his PhD in Applied Mathematics in Finance from Ecole Polytechnique in 2012. He joined the Department of Mathematics, NUS in May 2013 as an assistant professor, and is concurrently affiliated member of the Centre for Quantitative Finance.

#### Reference

1. Peng S., "G-expectation, G-Brownian motion and related stochastic calculus of Ito type", *Proceedings of 2005, Abel symposium*. Springer (2006).
2. Soner, H.M., Touzi, N. & Zhang J., "Wellposedness of second order BSDE's", *Prob. Th. and Related Fields*, 153(1-2) (2012).
3. El Karoui, N., Kapoudjian, C., Pardoux, E., Peng, S. & Quenez, M. C., "Reflected solutions of backward SDE's, and related obstacle problems for PDE's", *Annals of Applied Probability*, 25(2): 702-737 (1997).



# Electrons in a carbon flatland

Understanding the physics of electron interactions could lead to more energy efficient computers

## Introduction

The effects of electron interaction and disorder in topological materials in two dimensions is an area of research interest for Prof Adam. This article will explain what exactly such systems entail, why they are interesting theoretically, and how, by understanding them better, it might revolutionize the electronics industry.

Electrons in two-dimensions actually just refers to the behaviour of the electronic wavefunction. Using electric fields, the electrons' wavefunction can be effectively squashed into zero, one or two spatial dimensions. Two dimensional electrons are actually quite common: there are more than one billion transistors in a laptop computer, and each one is a small puddle of two dimensional electrons.

More recently, scientists have been able to cleave bulk materials, peeling off layers that are just one atom thick. To contemplate how thick is a single atomic monolayer, imagine that the diameter of a single strand of human hair has more than 25,000 atomic layers. The first material to be cleaved in this way was graphene – a single atomic sheet of graphitic carbon – but this technique has now been extended to several materials. One exciting area of contemporary research is cleaving down monolayers of different materials and then reassembling them again like lego blocks into new materials that do not exist naturally. These new materials are called van der Waals heterostructures, and in most cases, the resulting electrons have their wavefunction behave in a two-dimensional manner.

The theoretical challenge is to predict which assemblies of these layers would produce interesting properties which the experimentalist can then assemble

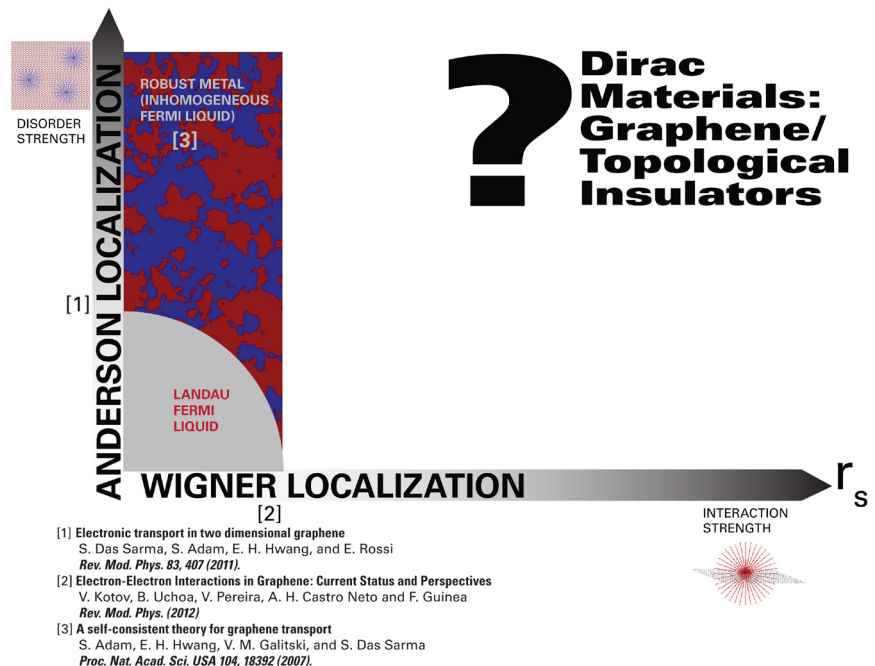


Figure 1: Effects of disorder and interaction on two dimensional Dirac electrons. Weak disorder and weak interactions are captured by Landau's Fermi liquid paradigm, and are somewhat understood theoretically. The regime of strong disorder and strong interactions in Dirac materials is the subject of Prof Adam's research.

and verify the unique properties. This article will concentrate on graphene, where the electrons live in a two dimensional carbon flatland.

## When Electrons Go Flat

The carbon atoms that make up graphene form a honeycomb (a plane of hexagons with each carbon atom bonded to three other carbon atoms). Of the four valence electrons in carbon, three form strong sp<sup>2</sup> bonds with other carbon atoms, and contributing the remaining itinerant electron to the two-dimensional electron gas. But this is no ordinary electron gas. The topology of the carbon honeycomb makes the energy of the resultant electron gas scale linearly with momentum (similar to photons in light) and these electrons are known as Dirac electrons. The two

dimensional electrons in your laptop are called Schrödinger electrons and their energy scales as the square of the momentum (similar to the classical billiard balls in high-school physics textbook). Prof Adam and his team had examined the similarities and differences between Dirac electrons and their more familiar Schrödinger counterparts [1]. Some of the most striking differences occur both in how Dirac electrons interact with each other (dubbed "interaction effects") and how the electrons interact with accidental defects or external dopants (generically called "disorder").

## To Conduct Or Not To Conduct, For Electrons, That Is The Question

In 1958, Philip Anderson noticed that electrons in two-dimensions had a rather peculiar property. Even with

vanishingly small disorder, when treating the electrons as quantum objects, they got stuck and could not conduct. When awarded the Nobel Prize in physics about 20 years later for this work, Anderson noted:

“Localization was a different matter: very few believed it at the time, and even fewer saw its importance ... It has yet to receive adequate mathematical treatment, and one has to resort to the indignity of numerical simulations to settle even the simplest questions about it.”

When graphene and other Dirac electrons (like topological insulators) became topics of scientific research, a question arose as to whether these new kind of electrons will get stuck just like Schrödinger electrons, or if they would continue to conduct even in the presence of disorder. Surprisingly, it was found that disorder actually made graphene more conductive rather than less. Dirac electrons in graphene were a special case where you could not stop the electrons from conducting unless you destroyed the hexagonal topology of the original carbon lattice.

### Electrons Far Away From Each Other Interact More Strongly

In an advanced undergraduate course in solid-state physics, it is common to pose the following paradox to students: “For electrons in two dimensions, why are the effects of electron-electron interactions stronger when the electrons are further apart?” The resolution of this conundrum lies in understanding that it is not the absolute value of the Coulomb interactions between electrons that determine its importance, but rather the ratio of the electron interactions

relative to their kinetic energy. Both effects depend on the average electron spacing, but for Schrödinger electrons in two dimensions, the kinetic energy grows faster with inverse spacing than do the Coulomb interactions, and so it dominates at small electron separations (and by similar reasoning, the Coulomb interaction dominates when the electrons are far apart).

This highlights the important complication that for Schrödinger electrons, the density of electrons is inexorably linked to how strongly they interact. Dirac electrons do not have this complication and carrier density and interaction strength can both be tuned independently. This means that when Graphene electrons are made strongly interacting, without any disorder, they should get stuck into a Coulomb lattice. This behaviour is analogous to what was proposed for Schrödinger electrons by Eugene Wigner (another Nobel Laureate).

### Disorder And Interactions – The Holy Grail

Experiments done in situations where both disorder and interactions are weak revealed that the interactions could mostly be ignored. Lev Landau outlined the theoretical underpinnings for this puzzle. He demonstrated that when electrons interact weakly with each other, the system could be described by new particles (called quasi-particles) that don’t interact with each other. But these quasi-particles interact with disorder in a manner similar to how non-interacting particles interact with disorder. This Landau paradigm is the now the starting point for understanding electrons in condensed matter physics.

In one of Prof Adam’s research areas, he used the Landau paradigm to address how Dirac electrons behave in the presence of weak disorder and weak interactions providing an explanation for why experiments on graphene found a finite minimum conductivity, even when the average carrier density vanished.

This had led to the understanding that this conductivity without carriers puzzle is explained by the very unusual situation where disorder in graphene creates puddles of electrons. These electrons, by interacting with each other, effectively weakened the effect of the impurity potential by rearranging to compensate for the disturbance caused by the disorder. By solving for the electron arrangement self-consistently [2], the correct electron state in the presence of both weak disorder and weak interactions can be obtained.

One of the biggest issues facing microchip manufacturers is the heating up of the transistors used in computers. As each quasi-particle jumps through the electron puddle it transfers its energy to the environment. Having strongly interacting electrons all behave collectively, one could reduce the energy dissipated by several orders of magnitude. The only problem is that this transition is poorly understood theoretically when both interactions and disorder are present.

Since in graphene the three knobs of carrier density, interaction strength and disorder can each be tuned independently, it is an ideal system to study and understand how this aspect of physics works, and perhaps might lead to making more energy efficient computers.

---

Shaffique ADAM received his Ph.D. in theoretical physics from Cornell University. He was a postdoctoral researcher at the University of Maryland, and subsequently worked at the Center for Nanoscale Science and Technology at the United States National Institute of Standards and Technology. In 2013, he was awarded the NRF Fellowship and appointed as an Assistant Professor of Physics both at Yale-NUS College and the Department of Physics, NUS.

#### Reference

1. Das Sarma S., Adam S., Hwang E.H., and Rossi E. “Electron transport in two dimensional graphene”, *Reviews of Modern Physics*, 83, 407 (2011).
2. Adam S., Hwang E.H., Galitski V.M., and Das Sarma S, “A self-consistent theory for graphene transport”, *Proceedings of the National Academy of Sciences USA* 104, 18392 (2007).



# Recent progress in diagnostic medicine

Receiver operating characteristic based approaches provides an objective tool for comparing different classifiers

## Introduction

ROC (Receiver Operating Characteristic) based approaches were first developed for classification studies with categorical outcomes. They have been extensively used in biomedical studies because of their flexibility and robustness. Consider, for example a study with the binary disease status (e.g. healthy and diseased) as outcome and diagnostic marker(s). As a classifier evaluation tool, the ROC curve displays the specificity and sensitivity for the whole range of cutoff of marker values. The AUC (Area under the ROC Curve) provides a much more comprehensive description of the classification performance of a classifier (which can be a marker or combination of markers) than the simple classification error. It also provides an objective tool for comparing different classifiers. As a classifier construction tool, the ROC does not make strong assumptions on the link function and can be more robust than for example the logistic regression.

## Time-dependent ROC

In a series of recent studies, the ROC approaches have been extended to accommodate survival data. At each time point, survival data is equivalent to binary data with status being alive or dead. Thus, the ROC approaches can be applied at each time point. An overall accuracy measurement can be obtained by integrating the AUC over time. Of note, the time-dependent ROC is usually much more complicated than an integrated ROC because of censoring and the time-dependent nature of the study cohort. Censoring causes the status of censored subjects to be not well defined at certain time points. Thus, at a fixed time point, not all observations are equally informative. In addition, unlike with cross-sectional studies and categorical

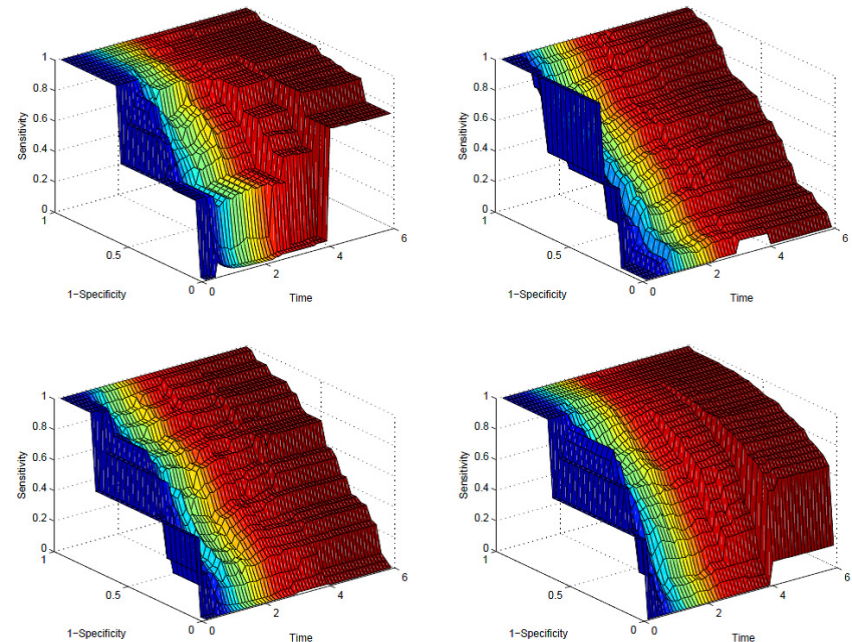


Figure 1: Analysis of HDS: Estimated time-dependent ROC curves for TR360 (upper left), BMI (upper right), AGE (lower left), and their linear combination (lower right).

outcomes, the study cohort changes as time passes. Thus, the reliability of AUC also changes over time. Instead of a simple integration, a weighted integration with time- and data-dependent weights is desirable.

In practice, censoring patterns are much more complicated than right censoring and are routinely encountered. Consider for example, a special type of interval censored data where the event time is never accurately observed and only known to lie in a finite interval. Compared with uncensored and right censored data, intuitively, such interval censored data is much less informative. Quantities, which have simple formulations for uncensored and right censored data (e.g., the Kaplan-Meier estimates), do not have closed analytic forms. For ROC, we examine the formulations in Li and Ma (2013) [1] and others and find that they cannot be directly extended to data under interval censoring and

other complex censoring patterns.

## Hypobaric Decompression Sickness Data (HDS) Study

The Hypobaric Decompression Sickness Data (HDS) study was conducted by NASA to investigate the risk of decompression sickness in hypobaric environments. The outcome of interest is the time to onset of grade IV venous gas emboli, which was mixed-case interval censored because of measurement limitations. The HDS contains 549 records, among which 124 were interval censored and the rest were right censored. One record has missing measurements and is removed from downstream analysis. Besides censoring times and event indicators, values of the following markers were recorded: (a) AGE, which ranges from 20 to 54 with median 30; (b) BMI, body mass index; and (c) TR360, which measures the decompression stress and is defined

as the ratio of the partial pressure of nitrogen to ambient pressure at the final altitude. This is an experimental variable and related to the particular pre-breathe protocol being tested.

For the three markers, we use the approach described in Li and Ma (2013) and compute their time-integrated AUCs as: Age : 0:583 [0:581; 0:586]; BMI : 0:530 [0:527; 0:532]; TR360 : 0:518 [0:516; 0:520]; where the numbers in [ ] are the 95% bootstrap confidence intervals. Although their AUCs are statistically significantly higher than 0.5, all three markers have very weak discriminatory ability for the development of grade IV venous gas emboli.

The integrated AUC reflects the overall prognostic performance. To gain further insights, we explore the ROC curve as a function of time. In Figure 1, for the three markers and their linear combination obtained above, we plot their time-dependent ROC curves. We note that, at different time points, the effective sample sizes may differ, with a larger sample size leading to more reliable estimates. Not all the estimated ROC curves in the spanned surface deserve the same attention due to the varying degree of efficiency. To reflect the variation of sample size, we use different colours in Figure 1, with cold colour (for example blue) corresponding to small sample sizes and warm colour (for example red) corresponding to large sample sizes. The change of colour from blue to red corresponds to the increase of sample size. Figure 1 suggests that, for all markers considered, the prognostic performance improves as time passes.

### Calcification Study

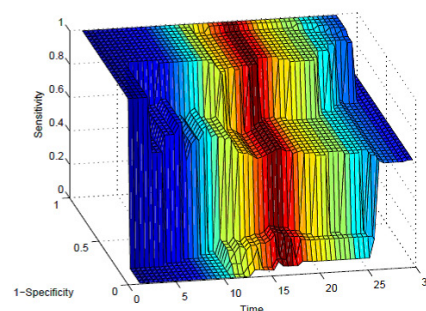
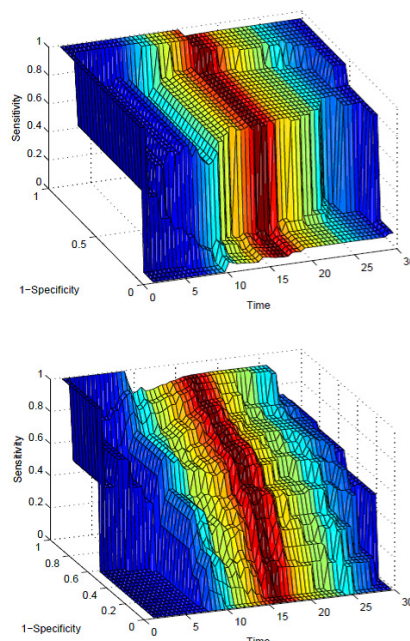


Figure 2: Analysis of Calcification study: Estimated time-dependent ROC curves for incision length (upper left), incision width (upper right), and AGE (lower).

The Calcification study investigated hydrogel intraocular lenses, which is an infrequently reported complication of cataract treatment. In this study, patients were examined by an ophthalmologist to determine the status of calcification at a random time ranging from 0 to 36 months after implantation of the intraocular lenses. Thus, all observations were case 1 interval censored. At the examination, the severity of calcification was graded on a discrete scale ranging from 0 to 4. Among the 378 subjects with complete measurements, 48 experienced calcification during the follow-up. The markers of interest include AGE, incision width, and incision length. For the three markers, we compute their time-integrated AUCs as Age : 0:503 [0:494; 0:511]; incision width : 0:658 [0:647; 0:667]; incision length : 0:805 [0:795; 0:814]. Among the three markers, AGE has no prognostic power. The marker incision length has the largest AUC and can make around 80% correct discrimination between

the calcified and normal subjects. We plot the ROC curves as a function of time in Figure 2. With this dataset, the effective sample size is small at the two ends of the time line and is relatively large in the middle. Simply eyeballing Figure 2 suggests that the ROC curves for the incision length dominate those of incision width and age at almost all time points.

### Multi-category ROC: HUM Calculator

As real applications often deal with more than two classes, multicategory ROC analysis and the corresponding Hypervolume Under the Manifold (HUM) measure have become a topic of growing interest. To support researchers in carrying out multicategory ROC analysis, Prof Li has developed two tools in different programming environments which feature user-friendly, object-oriented and flexible interfaces and enable the user to compute HUM values and plot multicategory ROC curves.

LI Jialiang obtained his PhD in Statistics from the University of Wisconsin, Madison in 2006. He joined the Department of Statistics and Applied Probability and has adjunct positions at the Duke-NUS Graduate Medical School (Duke-NUS) and Singapore Eye Research Institute (SERI). He conducts methodology development research in various fields in biostatistics, including diagnostic medicine, survival analysis and longitudinal data analysis and is on the editorial board of Biometrics.

#### Reference

1. Li J., & Ma S., "Survival Analysis in Medicine and Genetics", Chapman & Hall/CRC Press (2013).



# Characterizing the location of galaxies

The galaxy counts-in-cells distribution is a simple but powerful statistic to characterize galaxies

## Introduction

The galaxy counts-in-cells distribution is a simple but powerful statistic which characterizes the locations of galaxies in space. It includes statistical information on voids and other underdense regions, on clusters of all shapes and sizes, on filaments, on the probability of finding an arbitrary number of neighbors around randomly located positions, on counts of galaxies in cells of arbitrary shapes and sizes randomly located, and on galaxy correlation functions of all orders. These are just some of its representations [1,2] which describe different aspects of the cosmic web.

The counts-in-cells distribution is also a natural way to approach galaxy clustering where the following question is asked: "Given a large number of galaxies in space, such as the 2MASS, SDSS or COSMOS catalogs, what is the simplest and most effective way to make sense of this information?". The counts-in-cells approach adopts a natural response to this question where the number of galaxies in a given region of space (a cell) is counted.

The counts-in-cells distribution is thus a distribution which describes the probability that a given cell of volume  $V$  contains  $N$  galaxies, which is denoted by  $f(V,N)$ . It is discrete in  $N$  and continuous in  $V$  and there are two approaches to study this distribution. The first approach is to let  $V$  be constant resulting in  $f_v(N)$  which gives the distribution of the number of galaxies  $N$  for cells of a given volume  $V$ .

The other approach to studying  $f(V,N)$  is to let  $N$  be constant resulting in  $f_N(V)$  which gives the distribution of the volume  $V$  occupied by  $N$  galaxies of which the void probability function (VPF), where  $N = 0$ , is a special case.

To avoid these complications, most attempts to study  $f_N(V)$  have focused on the simpler case where  $N = 0$  but the void probability function is very insensitive to clustering at large scales because large regions of space with no galaxies are very difficult to find.

The counts-in-cells distribution thus allows us to represent the galaxies of the cosmic web, such as the map in Figure 1, in the form of a single distribution. The moments of this distribution contain information on the correlation functions of all orders,



Figure 1: A map of galaxies from the Sloan Digital Sky Survey. Each dot represents a galaxy.

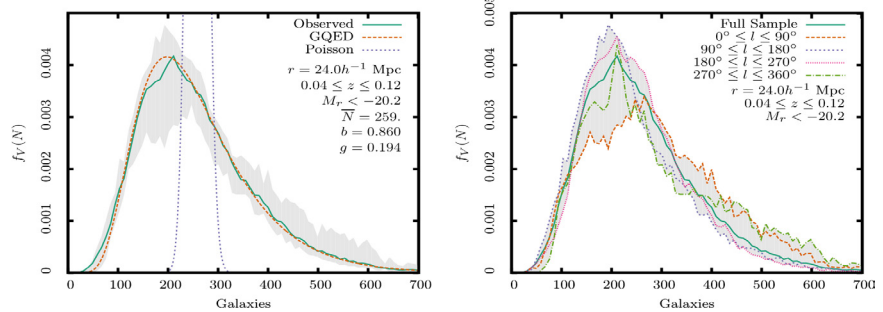


Figure 2: The observed counts-in-cells distribution for fainter galaxies in the low redshift range. The GQED and Poisson distributions are plotted over the observations in the left plot, while observations from individual quadrants are plotted on the same graph in the right plot.

while the form of the counts-in-cells distribution contains information on the physics behind galaxy clustering. Thus, by measuring the counts-in-cells distribution for a given sample of galaxies, we relate their clustering to other commonly-used measures of clustering such as the correlation function. By matching the observed counts-in-cells distribution to a theoretical model, there can be better understanding of the physics behind galaxy clustering and the gravitational many-body problem.

## Counts-in-cells and Physics

A physical form of the counts-in-cells distribution comes from statistical mechanics where each galaxy is

treated as a particle within a box. Galaxies attract each other by their mutual gravity, and thus have potential energy. They also move around so they have kinetic energy. Since there are no walls around a cell, the "box" is open and the grand canonical ensemble have been used to allow energy and galaxies to cross cell boundaries.

However, self-gravitating systems are not in equilibrium, so at first glance the usual rules of thermodynamics and statistical mechanics do not apply. To get around this problem, we look at the timescales involved and find that the large scale structure of the universe evolves on much longer timescales than the time it takes an average galaxy to move across a cell. Thus on the

timescales that pertain to individual cells, the universe is approximately in equilibrium. This physically motivated form of the distribution function is referred to as the gravitational quasi-equilibrium distribution (GQED).

The GQED is a discrete distribution which turns out to be a Poisson distribution compounded with a truncated Borel distribution.

### Procedure

To sample the counts-in-cells distribution, actual observations of the sky or simulated universes can be used.

In this work, the focus is on archived catalogs generated by sky surveys, being the more realistic representation of the universe. Thus, given a list of galaxies and their positions, brightnesses and colours, the counts-in-cells distribution can be constructed.

To do so, the observed parts of the sky is tiled with cells of a predefined size and shape, and the number of galaxies within each cell counted to get samples for  $f_v(N)$ . For convenience, spherical or circular cells can be taken so that it can be easily determine whether a galaxy belongs to a cell by looking at its distance to the cell centre. This captures the essence of the galaxy distribution, including clusters and underdense regions and by varying the cell size, structures of different sizes can be examined.

Using brightness as a proxy for galaxy mass, where more massive galaxies tend to be brighter, a cutoff brightness is defined where the galaxy sample is truncated. This means that only galaxies more massive than a given threshold mass is considered, as less

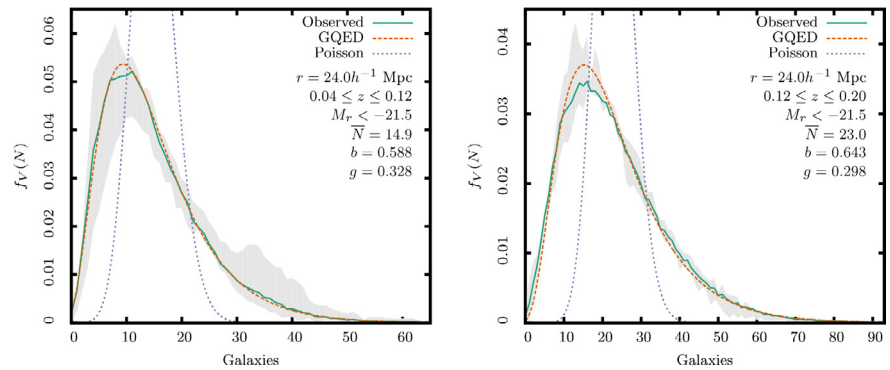


Figure 3: The observed counts-in-cells distribution for brighter galaxies in the low and high redshift ranges. The GQED and Poisson distributions are plotted over the observations. The left plot shows the histogram for the low redshift range; the right plot shows the histogram for the high redshift range. The shaded region represents the extent of the quadrant to quadrant variations.

massive galaxies are less likely to contribute to the overall gravitational interaction than more massive galaxies.

From the samples, the counts-in-cells histogram is built using data release 7 of the SDSS and its mean and variance calculated as a function of cell size. Then, using the variance, the clustering parameter  $b$  is also calculated. This is performed for a low and high redshift range, representing closer and more distant galaxies respectively. To get a sense of the variability in the data, the counts-in-cells histogram for four different subsamples, each taken from different quadrants of the sky selected by galactic longitude is plotted. These histograms, and the corresponding GQED fits are plotted in Figure 2 and 3.

### Conclusion

The observed counts-in-cells distribution of galaxies  $f_v(N)$  varies greatly between different sections of the survey with a lot of noise in the form of bumps and wiggles in the histogram curve. However, within these variations, the GQED agrees

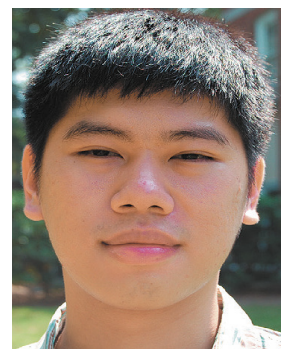
with the data, indicating that the basic principles of the GQED apply to the universe. The clustering parameter of  $b = 0.86$  for fainter galaxies in the low redshift range shows that these fainter galaxies are rather strongly clustered, as would be expected since less massive galaxies tend to orbit more massive galaxies. Brighter galaxies however are less strongly clustered than fainter galaxies, which is intuitively expected since these bright galaxies tend to be more massive and hence move slower than less massive galaxies.

In contrast, large superclusters such as the SDSS great wall and the Coma wall do not contribute significantly to the counts-in-cells distribution despite being very noticeable. Instead, we find that these superclusters are composed of many smaller clusters interspersed with underdense regions. These galaxy “walls” are thus likely to be rather porous. Furthermore, while the SDSS great wall is a string of galaxy clusters that spans over 400 Mpc, its physical extent is only a small fraction of the survey volume and is thus unlikely to dominate over the rest of the survey.

Abel YANG joined the Department of Physics in 2012 as a lecturer. He obtained a PhD in Astronomy from the University of Virginia in 2012. His research interest includes galaxy clustering, large scale structure of the universe and observational cosmology. He has been involved in astronomy education and outreach, and currently teaches Sky and Telescopes.

### Reference

1. Saslaw W. C., “The distribution of the galaxies: gravitational clustering in cosmology”, (Cambridge, UK: Cambridge University Press, 2000).
2. Saslaw W. C., Yang A., in Lecture Notes of the Les Houches Summer School: Long-Range Interacting Systems, ed. T. Dauxois, S. Ruffo, & L. F. Cugliandolo, Vol. XC (Oxford, UK: Oxford University Press), 377–398 (2010).



# The “miracle molecule” in red wine

Pharmacokinetic investigation enables the selection of appropriate candidates for medicinal applications

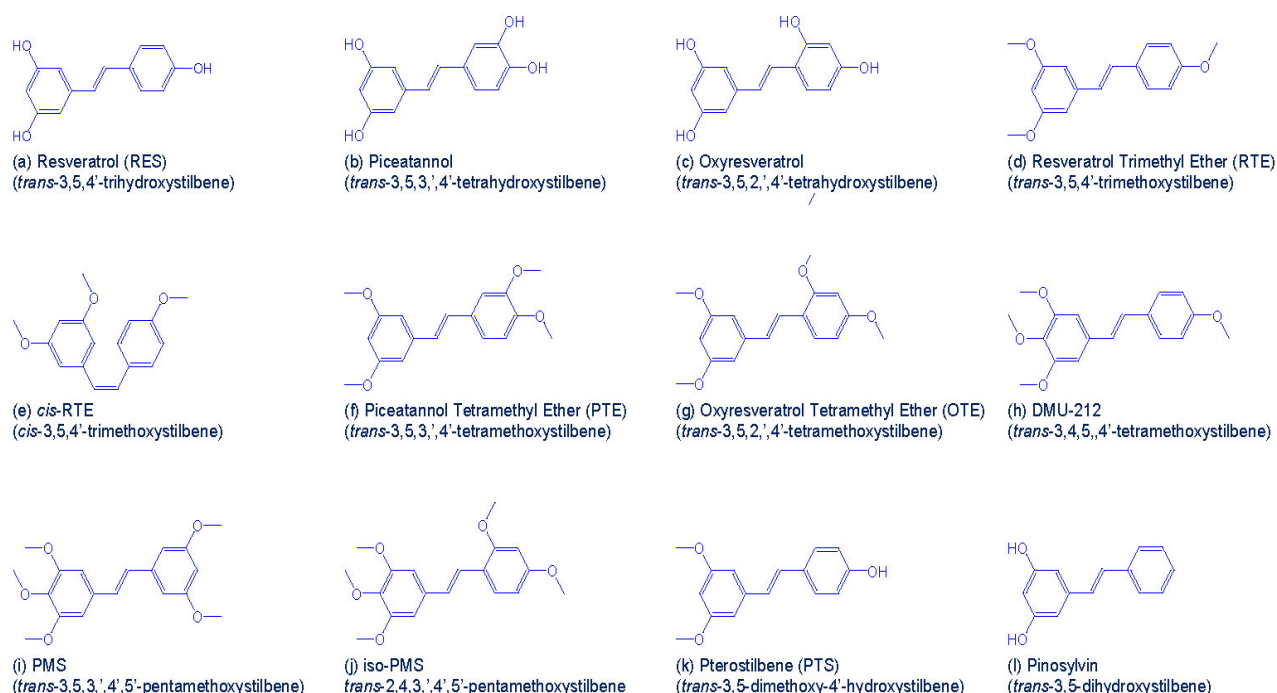


Figure 1: Structures of resveratrol and some of its derivatives.

## Introduction

Resveratrol (*trans*-3,5,4'-trihydroxystilbene, RES, Figure 1 a) is a polyphenol that can be found in our daily diets such as bilberry, blueberry, cranberry, grapevine and peanut. Widely known as the “miracle molecule” present in red wine, it attracted substantial interests in biomedical research during the past 15 years. Its health-promoting activities, including anti-ageing, anti-cancer, anti-diabetic, anti-inflammatory, anti-obesity, anti-oxidation, cardio-protection and neuro-protection have been extensively reported. However, due to its unfavorable pharmacokinetics, which can be characterized by short half-life, extensive phase II metabolism and low bioavailability, RES does not appear to be an appropriate drug candidate for further pharmaceutical development. It is therefore of great interests to identify RES derivatives with superior potency and improved pharmacokinetics.

## The Impact of Aqueous Solubility and Dose on the Oral Bioavailability of RES

The aqueous solubility of RES is limited and this could be a hinderance to its oral absorption. Moreover, as RES suffers from extensive phase II metabolism, dose manipulation may be a practical strategy to improve its oral bioavailability by saturating its metabolism at higher dose. Therefore, a pharmacokinetic study was carried out in Sprague-Dawley rats to investigate the impact of aqueous solubility and dose on the oral bioavailability of RES. Similar to the previous reports, RES was found to possess extremely rapid clearance upon intravenous administration. Interestingly, aqueous solubility only affected the speed but not the extent of RES absorption while dose manipulation (up to 50 mg/kg) did not have a significant impact on the oral bioavailability of RES. Based on the literature and this study, it was concluded that the poor oral bioavailability of RES was mainly due to its metabolic instability.

## Methoxylated RES Derivatives Possess Improved Metabolic Stability

Resveratrol trimethyl ether (*trans*-3,5,4'-trimethoxystilbene, RTE, Figure 1 d) is a naturally occurring and pharmacologically active RES derivative. As it is completely methoxylated, phase II metabolism is avoided and this could lead to improved metabolic stability. To test such hypothesis, the pharmacokinetic profiles of RTE were examined. Upon intravenous administration, RTE displayed moderate clearance, a fairly long terminal elimination half-life and abundant plasma exposure. Of note, the clearance (Cl) of RTE was about 8-9 folds slower than that of RES. Clearly, the improved intravenous pharmacokinetic profile could be attributed to the improved metabolic stability. Similar results were also observed with several completely methoxylated RES analogs including *cis*-resveratrol trimethyl ether, piceatannol tetramethyl ether, oxyresveratrol tetramethyl ether,

trans-3,4,5,4'-tetramethoxystilbene (DMU-212), trans-3,5,3',4',5'-pentamethoxystilbene, and trans-2,4,3',4',5'-pentamethoxystilbene.

As the methoxylated RES derivatives are more lipophilic than RES, their aqueous solubility may be a problem and pose an issue in oral bioavailability. When given orally in suspension, RTE was poorly absorbed with negligible bioavailability (< 1.5%) and fasting further decreased its bioavailability (< 1%). However, when administered in a solution formulated with randomly methylated- $\beta$ -cyclodextrin, RTE was rapidly absorbed with good bioavailability. Obviously, aqueous solubility appeared to be a barrier to the oral bioavailability of the methoxylated stilbenes. Therefore, solubility enhancing technology may be required to deliver these complete methoxylated RES derivatives.

### Superior Pharmacokinetic Profiles of Pterostilbene

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene, PTS, Figure 1 k) is a RES derivative present in our daily diets such as grapes, deerberries, blueberries, peanuts and wine [1,2]. Similar to RES, PTS exhibited various beneficial biological activities [2]. Moreover, PTS displayed excellent safety in both pre-clinical and clinical studies. As a hybrid compound of RES and RTE, PTS may possess appropriate metabolic stability and aqueous solubility. To test our hypothesis, the pharmacokinetic profiles of PTS were examined [1,2]. Upon intravenous administration (2.5 mg/kg), PTS had rapid clearance ( $Cl=68.2\pm9.8$  mL/min/kg) and moderate terminal elimination half-life ( $t_{1/2\lambda z}=93.9\pm22.3$  min). Dose-escalation to 25 mg/

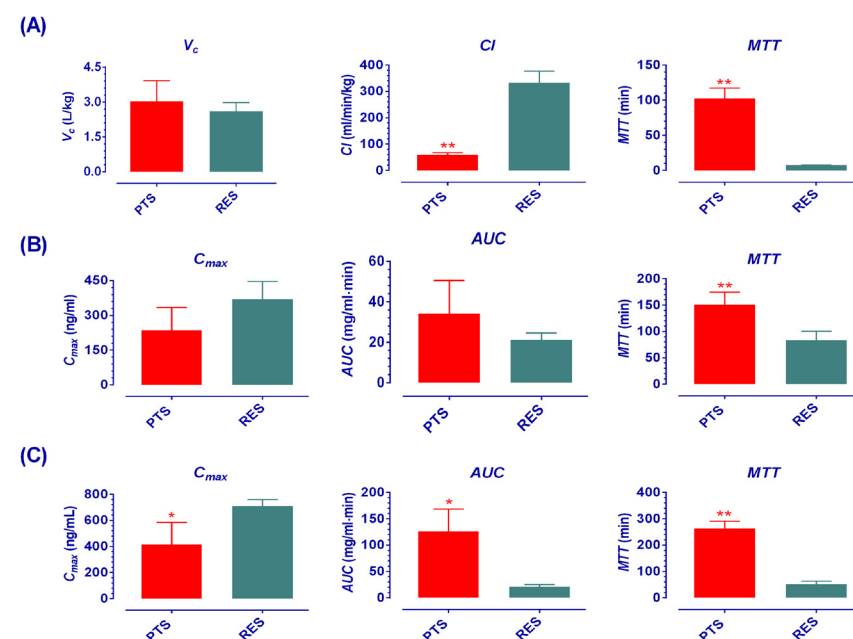


Figure 2: Pharmacokinetic comparison between PTS and RES (A) after single intravenous injection (dose: 10 mg/kg); (B) after oral administration of suspension (dose: 15 mg/kg); (C) after oral administration of solution (dose: 15 mg/kg). RES, n = 4; PTS, n = 6. Columns represent mean values and error bars represent SD. \* P < 0.05, \*\* P < 0.01, Mann-Whitney test. This figure is extracted from [2].

kg led to about 2-fold decline in clearance ( $Cl=36.4\pm7.8$  mL/min/kg). When given as an oral suspension (15 mg/kg), PTS had relatively low bioavailability ( $F=15.9\pm7.8$  %) while fasting substantially attenuated its bioavailability ( $F<5.5\%$ ). However, when dosed in a solution formulated with 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) (15 mg/kg), PTS possessed good bioavailability ( $F=59.2\pm19.6$  %). Dose-escalation resulted in about 2-fold increase in bioavailability at the dose of 60 mg/kg. Statistical comparison clearly indicated that the pharmacokinetics of PTS was more favorable than resveratrol (Figure 2). Moreover, the oral delivery of PTS was less dependent on solubility enhancing technology such as cyclodextrin.

Therefore, PTS appears to be a more appropriate candidate for medicinal application than RTE and RES.

### Future Studies

As PTS displayed potent biological activities and superior pharmacokinetic profiles, it is well-substantiated that further studies of its therapeutic potential in various diseases are conducted. The team plans to assess the in vitro and in vivo disease modifying effects in some inflammatory diseases. Furthermore, as aqueous solubility is still a barrier to its oral absorption, they will continue to explore innovative drug delivery strategies to optimize its application.

Lin Haishu graduated with a Doctor of Philosophy from the Department of Pharmacy at the National University of Singapore (NUS) in 2002. In 2004, he was awarded a fellowship from the Economic Development Board, Singapore for training in drug discovery and development in Paris at ProSkelia, a biopharmaceutical company spun-off from Aventis. He re-joined the Department of Pharmacy, NUS, at the end of 2005 and was appointed an Assistant Professor in 2012.

### Reference

- Lin H.S., Yue B.D. & Ho P.C. "Determination of pterostilbene in rat plasma by a simple HPLC-UV method and its application in pre-clinical pharmacokinetic study", *Biomed. Chromatogr.*, Vol 23, pp. 1308-1315 (2009).
- Yeo S.C., Ho P.C. & Lin H.S. "Pharmacokinetics of pterostilbene in Sprague-Dawley rats: the impacts of aqueous solubility, fasting, dose escalation, and dosing route on bioavailability", *Mol. Nutr. Food Res.*, Vol 57, pp. 1015-1025 (2013).



# Puzzling genomic regulatory systems

Computational and experimental methods to precisely model multiple levels of genomic regulatory control

## Introduction

Genomic regulatory systems, which control cell fate in both normal development and disease, are at the heart of a fascinating puzzle: how is it that the single genome of an organism gives rise to vastly differing cell morphology and behaviour? This fundamental problem of biology occupies the careers of many developmental biologists, but the same puzzle also raises centrally important questions for understanding human disease.

Over the last decade, new technologies to interrogate and control genomes have made it possible to ask entirely new questions of genomic regulation. Instead of considering individual genes or individual control elements, scientists are looking at regulatory modules, in which multiple control elements and multiple regulatory factors act in concert. The ENCODE project — an international project to map regulatory elements used across the human genome — is revealing how epigenetic patterns differ among different types of cells. Systems biologists are able to measure and model the dynamics of both intercellular and intracellular signalling. Biology is a quantitative science.

Prof Tucker-Kellogg's research interest is in genomic regulatory systems, primarily at the level of the cell, and the importance of these systems for disease and treatment in individual patients. His work in industry for over a decade was focused on genomic applications in oncology: new molecular targets, genomic validation of poorly understood targets, and using genomic biomarkers to predict outcome in individual patients [1]. To understand the basic mechanisms that give rise to these differences, his lab

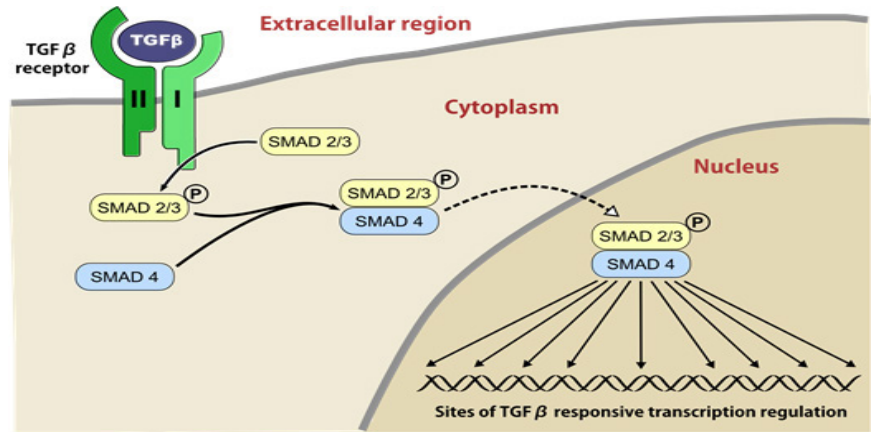


Figure 1: Trunk of TGFβ signaling pathway.

at NUS is working on computational and experimental methods to more precisely model multiple levels of regulatory control. Two projects illustrate their approach.

## Context Dependent Genomic Switching of TGFβ Signalling

The growth factor TGFβ and its family members are involved in cell growth, differentiation, and homeostasis from the earliest stages of development to terminally differentiated cells. Despite the deceptively simple nature of the TGFβ signalling pathway, the consequences of pathway activation vary widely. The core components of the signalling pathway are shown in Figure 1. This is a highly simplified representation, but illustrates that after a key initiation triggered by receptor binding, the rSMAD proteins SMAD2 and SMAD3 are phosphorylated. The phosphorylated SMADs associate with SMAD4 and are then translocated into the nucleus, where they regulate gene transcription. Which genes are regulated, and how the effects of TGFβ are ultimately manifest in the cell, depends on the epigenetic exposure of SMAD binding elements as well as the involvement of cofactors. In addition, the distinct targets mediated by SMAD2 and SMAD3 are not well

understood, although there is evidence in the literature that these two highly similar proteins can mediate distinct phenotypic effects.

The TGFβ pathway not only has different consequences in development, but different consequences in disease. The limited understanding of how this pathway is rewired in disease has implications for drug development and treatment choices of cancer patients, because TGFβ suppresses cell growth in normal epithelial cells, but sometimes — not always — promotes cell growth at later stages of tumourigenesis. This switching is often associated with the epithelial mesenchymal transition, an important stage in the development of tumour metastases, but the consequences of this switch are different in different tumours and in different contexts of the same tumour type.

Their approach is to use systems biology, synthetic biology, and computational biology to control and interrogate precise nodes of the pathway to understand how the switch from tumour suppressor to tumour promoter happens in different contexts. They are focused on two related questions. The first is to distinguish how SMAD2 and

SMAD3 differ in their regulation of genes, and how that regulation is connected to phenotypic changes in the cells. The second is how other transcription factors act as guides to recruit SMAD2/3/4 complexes to specific binding sites in the genome. Recent studies have shown that in early development, the “master transcription factors” of embryonic stem cells help to position SMAD complexes on the genome to respond by stimulation of nodal (a TGFb family member). If this holds true for TGFb in cancer cells, SMAD binding positions on the genome can be used to “fish” for cofactors used in different cancer types.

### Chromatin Computation: Rethinking Computational Models Of Chromatin Dynamics

Genomic regulation happens not only within a cell, through conventional signalling, but through heritable changes in gene regulation. Heritable changes are termed “epigenetic” when they are not due to changes in DNA sequence. How should such heritable epigenetic changes be modelled on top of short-term dynamic regulatory changes, and how should changes in regulatory circuitry be connected to intercellular and intracellular signalling?

Analogies between algorithmic processes and living processes are almost as old as the fields of molecular biology and computer science. Sometimes the parallels have inspired new computer science approaches, such as genetic algorithms and neural networks, based upon biological processes. But the success of this cross-fertilisation has extended far beyond the ability to model biological

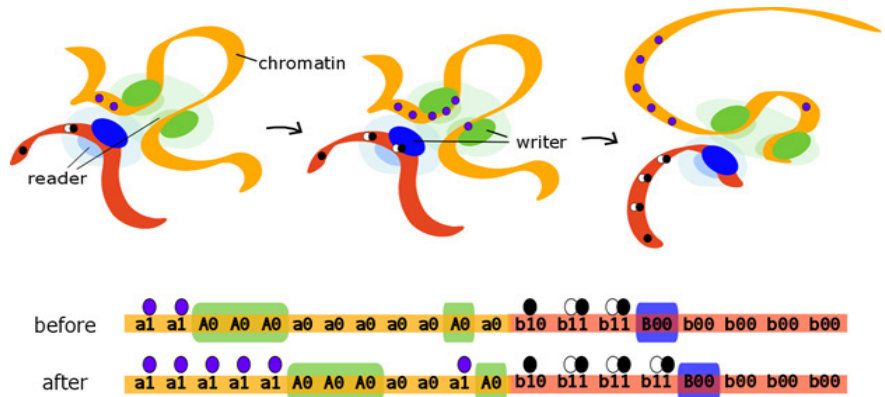


Figure 2: (Top) cartoon representation of a piece of chromatin being modified by a set of enzymes; (Bottom) the same process represented as modifications of memory at distinct positions.

processes: important fields of computer science, including both artificial intelligence and evolutionary computation, have grown from those insights. Influence has also run in the other direction. In 1994, the computer scientist Leonard Adelman performed the first DNA computing study, solving the Hamiltonian Path problem by ligating DNA in an in vitro experiment. More recently, biological systems have been shown to solve well studied signal optimisation problems in novel and efficient ways.

In 2012, Barbara Bryant proved that modifications of chromatin could be seen as a form of stochastic general computation [2], and solved using simulated chromatin the Hamiltonian Path problem that had been solved by Adelman using DNA. Unlike DNA computing, the biological processes used in chromatin computing actually occur in ordinary living systems. The team have been developing and extending this model, called Chromatin Computation, to represent chromatin dynamics and to understand whether higher-order processes, such as the ones we think of as computing

algorithms, might actually occur in biological systems (Figure 2).

Their simulator, called codachrom, readily simulates dynamic processes experimentally measured in chromatin, such as formation and spread of heterochromatin.

They are also testing the utility of chromatin computing to solve both simple and complex mathematical problems. On the complex end, we have extended Bryant’s results to solve a general form of the Hamiltonian Path problem, exploiting features such as looping in chromatin, and shown that simply changing the simulations of enzyme kinetic properties can provide a rudimentary computational learning engine. On the simple side, they have designed simple logic gates and arithmetic machines using chromatin simulations. These seem like toys, but there are some combinations of enzymes that appear to match the required behaviours. With the growing interest in synthetic biology, it may be possible to envision constructing biocomputing devices using the components of chromatin.

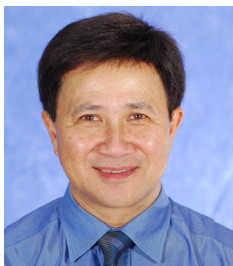
Greg TUCKER-KELLOGG received his PhD in Molecular Biophysics and Biochemistry from Yale University. After his postdoc, he went into the biotechnology industry, first at Genetics Institute where he pioneered early studies of RNA profiling with gene chips, and then at Millennium Pharmaceuticals, where he led bioinformatics research for personalized medicine. He joined Eli Lilly and was promoted to Chief Technology Officer, Lilly Singapore Centre for Drug Discovery, in 2007. In 2012, he joined NUS.

#### Reference

1. G. Tucker-Kellogg, A. Aggarwal, K. L. Blanchard, and R. Gaynor, “Systems Biology in drug discovery: using predictive biomedicine to guide development choices for novel agents in cancer,” in *Systems Biomedicine: Concepts and Perspectives*, E. Liu and D. Lauffenburger, Eds. Academic Press (2009).
2. B. Bryant, “Chromatin computation.,” *PLoS One*, vol. 7, no. 5, p. e35703 (2012).



# A lifetime of contributions to Science



Professor Hardy CHAN from Department of Chemistry had been with NUS since 1981, as a Lecturer in Department of Chemistry. Well-liked by students, he was awarded Best Lecturer in Materials Science in 1995. Hardy had been awarded the Standard Council Distinguished Award in 2002, National Day Long Service Award in 2010 and Public Admin Medal (Bronze) in 2011. In 2014, he was conferred the national science academy fellowships as a co-Director of Singapore-Massachusetts Institute of Technology (MIT) Alliance. He was a council member of the Pacific Polymer Federation (1996) and coordinated the Polymer and Molecular Electronics in Devices TSRP for A\*STAR (2003).

Correction.

In the print version, it was wrongly reported that Professor Hardy CHAN had been with NUS since 2000. Sorry.



Professor KOH Khee Meng from Department of Mathematics had been with NUS since 1972. He started off as a Lecturer in Department of Mathematics and had risen through the ranks to become a Professor Fellow. During his time in NUS, he had been the recipient of several prestigious awards and accolades. Khee Meng's passion in teaching has been well recognised by his peers. He was appointed chair of the Department Teaching Excellence Committee for more than 10 years. He also served on the Faculty Teaching Excellence Committee for 6 more years, contributing significantly to the evaluation, development and quality of teaching. Over a span of 18 years, he had consistently achieved high ratings and garnered numerous compliments from students and more than 20 teaching awards.



Professor LEONG Yu Kiang's long relationship with NUS began when he was a student in Department of Mathematics. With a strong interest in Mathematics and passion for teaching, Yu Kiang began his teaching career in NUS since 1972. He has imparted knowledge on a wide variety of topics such as Algebra, Mathematics Impressions, Elementary Number Theory, Inquiring with Mathematics, Analogy & Intuition in Mathematics and Turning Points in the History of Mathematics. Yu Kiang has an outstanding list of publications under his belt, which includes the book titled "Creative Minds, Charmed Lives" featuring interviews of 38 eminent mathematicians and mathematical scientists.



Professor QUEK Tong Seng from Department of Mathematics began his teaching career in 1971 when he first graduated from NUS. His passion for Mathematics led him to pursue his Ph.D. in NUS and subsequently joined NUS as a lecturer in 1981. Prof Quek was also a member of the Singapore Mathematical Society and the Southeast Asian Mathematical Society. He has taught and made contributions to a variety of topics such as Calculus, Mathematical Methods in Engineering, Mathematical Analysis, Complex/Functional Analysis, Measure & Integration, Multivariable Calculus, Lebesgue Integration, Real Analysis and Linear Algebra.



Professor BAI Zhidong from Department of Statistics and Applied Probability was amongst the first batch of 18 PhDs conferred by the State Council of the People's Republic of China in 1983. Zhidong has served as researcher and professor at the University of Pittsburg, Temple University, National Sun Yat-sen University and Northeast Normal University (China) before joining NUS in 1997 as a Senior Fellow and became a full Professor in 1999. He has been an elected fellow of the Third World Academy of Sciences since 1989 and elected fellow of the Institute of Mathematical Statistics since 1990. In his long career as a prominent statistician, Zhidong had published three monographs and over one hundred papers.



Faculty of  
Science