SINGLE-MOLECULE DNA SEQUENCING: MAKING SEQUENCING TECHNOLOGIES AVAILABLE FOR THE MASSES
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THEORETICAL MODELS OF FOREST DYNAMICS

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Introduction

Why do tropical forests contain so many species? A single hectare can contain over 100 tree species; in 50 hectares, there can be over 1000. Do forests with more species function better, in terms of their capacity to store carbon, purify water or provide other services that benefit humans? And, importantly, what implications does the ongoing destruction of forests worldwide have for forest biodiversity and function? These are the questions we seek to answer in my lab, using the tools of theoretical ecology: a combination of mathematics, computation, statistics and data analysis.

The problem of species diversity has fascinated scientists for centuries. Darwin and Wallace brilliantly explained where species come from, but our understanding of how biodiversity varies in time and space remains largely qualitative. Quantitative theories that can describe and predict biodiversity are in their infancy, and it is these theories that my lab seeks to develop. This basic research programme has strong practical implications as well: A rigorous understanding of how forests function is an essential precursor to effective conservation planning and sustainable forest management. I now describe two of our projects that address specific questions about forest biodiversity and function.

How does Forest Biodiversity change over time?

Traditional theories of biodiversity are centred on the notion of stability and the “niche”. A species’ niche is defined as the particular habitat conditions or resources (e.g., different light conditions or soil nutrients) that it prefers. Niches effectively reduce competition between species and can stabilise the abundances of species over time, thus maintaining the diversity of an ecosystem. More recently, a controversial new theory has been proposed that ignores niches and challenges the view that biodiversity is stable. This theory is called neutral theory, and draws upon neutral theory in population genetics [1]. The essential idea is that a species’ abundance undergoes a slow random walk, typically over millions of years, from the moment it arises through a speciation event to the moment it disappears through stochastic extinction. Despite its radical assumptions (in particular, its disregard of niches) neutral theory accurately describes many static biodiversity patterns [2-5]. But can niche theory or neutral theory describe dynamic biodiversity patterns, such as the change in species’ abundances through time?

Our recent analyses of dynamic biodiversity patterns in 12 forest sites across the world have revealed the limitations of both niche theory and neutral theory. At each site, species abundances were far from stable over decadal timescales: they were fluctuating even more than neutral theory would predict (Figure 1). We attributed these fluctuations to environmental variance: across the world, tree species population sizes appear to be driven strongly by environmental factors such as droughts, typhoons, fires and elephant herbivory. Our statistical analyses suggested that this was true even in forests where we have not yet identified any obvious environmental drivers.
These findings have motivated us to formulate a new paradigm of forest biodiversity in which stability takes a backseat and environmental variation plays a dominant role. We are currently working on theoretical models that will allow us to make quantitative predictions and test our ideas.

**Do more Species make an Ecosystem function better?**

The traditional answer to this question is “yes” [6], based on empirical and theoretical evidence from grasslands [7]. Essentially, this occurs because patches that by chance have more species are more likely to have the most efficient species or to have species that complement or facilitate each other. Less attention has been paid to species richness and ecosystem function in forests, however. In a recent data analysis paper, we looked at 25 forest sites across the world and focussed on the relationship of species richness to one very important aspect of ecosystem function: the capacity to store carbon.

Our analysis [8] showed that a doubling of species richness was associated with a roughly 50% increase in biomass (which is proportional to total carbon stored) and productivity (proportional to the rate at which carbon stored increases over time), consistent with theory (Figure 2A–B). But there was a catch: this was only true when the patches were small (20 m x 20 m = 0.04 ha). When we repeated the analysis with larger patches (50 m x 50 m = 0.25 ha and 100 m x 100 m = 1.0 ha), we found that the results were much more variable: a few sites continued to show positive trends, while others showed flat or statistically significantly negative trends, the latter meaning that forest patches with more species actually stored less carbon (Figure 2C–D).

Why would forest patches with more species store less carbon? We are currently using mathematical and computational models to investigate possible solutions to this question. One possibility is that in the larger patches, we are averaging over many smaller patches and hence over much of the stochastic local variation in species richness, and instead seeing deterministic patterns characteristic of large-scale environmental gradients.

This work has direct implications for forest management and conservation planning: forest managers need to know what combinations of species lead to the maximum yield; conservation planners need to know whether dollars spent conserving biodiversity will also translate to conservation of ecosystem function, or whether separate investments need to be made for biodiversity and function.

**Conclusion**

In the year 1760, Daniel Bernoulli, a pioneering theoretical biologist, wrote, “I simply wish that, in a matter which so closely concerns the well being of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide.” He was writing in the context of his research on smallpox, but his sentiments apply equally well to the problems of biological conservation. Ecology is fundamental to the well being of the human race:
ecosystems provide the air we breathe and the food we eat, and they inspire us with awe and wonder. In the Chisholm lab, we adhere to the view that the rigorous use of mathematics and other quantitative tools is an essential component of any conservation strategy in the 21st century.

References


ENSURING FOOD SECURITY, SAFETY AND NUTRIENTS VIA SUSTAINABLE FOOD PROCESSING AND ENGINEERING

Dr Yang Hongshun
Department of Chemistry

Introduction
As the human population keeps growing while available land and natural resources for food production gradually shrink, meeting the demand of sufficient food supply and ensuring its security, safety and nutrients becomes a great challenge. This situation is of greater concern for Singapore considering that the majority of our food is imported.

An effective approach to resolve this problem is to apply sustainable food processing and develop technologies for promoting food supply resilience. For instance in fish processing, approximately 40% to 50% of fish weight will become byproducts when the fish is processed into fish fillets [1]. By using sustainable food technology, these byproducts can be converted into useful food components, which will promote food security and simultaneously reduce the environmental burden related with them.

Research Interests
• Food Security
• Organic Food Processing
• Food Safety Engineering
• Sustainable Food Processing via Byproduct Utilisation
• Food Nanotechnology
• Rapid Detection of Hazards for Food Defense

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Figure 1: Proposed schematic image for the development of gelatin aggregates from catfish skin and corresponding atomic force microscopy images. Note: ‘w’ denotes water; ‘s’ means salt; ‘Ac−’ means the anion of acetic acid; ‘+’ -------- ‘-’ indicates amphiphatic structure of collagen (gelatin) molecule [1].
since modified fishery gelatin shows antimicrobial activity to bacteria [2]. It is promising that these techniques, which could be extended to other mammalian byproducts, could improve food security through the use of fish byproducts.

**Food Safety Engineering especially for Organic Foods**

Organic foods are not absolutely safe as many may think. Sanitisation is a key step ensuring organic foods’ safety during processing. Currently, there are few available choices for organic food processing and only a limited number of synthetic sanitisers can be applied to organic foods or food equipment. Moreover, these chemical synthetic sanitisers have several shortcomings such as limited availability, short shelf life, and limited sanitising effects. Developing organic industry compatible sanitisers to meet the market needs becomes urgent and critical. Neutral electrochemically activated water (NECAW) based on chlorine has great antimicrobial effects and is compatible with the principles for application in organic foods [3]. However, the current sanitising equipment for generating NECAW is too large to be easily transported and used by consumers and producers.

![Figure 2: Sanitizing effects of neutral electrochemically activated water (NECAW) on foodborne pathogens. Note: NECAW with free available chlorine (FAC) 100 mg/L, pH 7.0; Control: deionated water, FAC 0 mg/L, pH 7.0 [3].](image)

Engineering knowledge will be combined with electrochemical science for developing portable and friendly to use equipment for generating sanitisers that are suitable for organic food processors as well as household consumers. This will facilitate the use of organic compatible sanitisers including NECAW in ensuring microbiological food safety, thus improve the shelf-life and safety of organic foods.

**Quality and Nutritional Assessment of Processed Food**

Fruit and vegetables are an important food source for maintaining human health. Adequate consumption of fruit and vegetables can help to prevent many human diseases. However, low consumption of fruit and vegetables has been known to exist widely in many countries and is among the top selected risk factors for global mortality [4].

The serving portion of fruit and vegetables plays a critical role in assessing the amount of nutrients and antioxidants which people consume. For people who find it difficult to consume ‘five-a-day’ fresh produce, consumption of more processed foods becomes a viable option for maintaining a healthy lifestyle. However, different processing treatments may result in a loss of nutrient contents and antioxidant activity to different extents compared to their fresh counterparts. In addition, the amount of processed foods required to provide an equivalent effect as their fresh states is unknown. Thus, it is necessary to define an actual serving portion of fruit and vegetables at fresh and processed states based on scientific evidence [5].

![Figure 3: Equivalent amount based on phytochemical and antioxidant activity between fresh and processed fruit and vegetables [5].](image)

The research will provide guidance on the amount which food processed by different techniques should be consumed to maintain a healthy lifestyle. It would also provide a simple way for calculating an adequate serving portion of a specific food and help choose appropriate processing technologies in order to maintain the nutritional and functional properties of a specific food product.

**References**


Associate Professor Brian W Dymock
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Introduction

Human disease is better treated today than ever in human history. However, with ageing populations throughout the world, there is still a great deal of unmet medical need [1]. Publicly funded academic organizations play an increasing role now in the discovery and development of new ground-breaking approaches required to solve today’s challenging problems [2,3]. In our lab we focus on the target-based discovery of novel biologically active small molecules, primarily enzyme inhibitors for cancer and other life threatening diseases. Our approach is focused in 3 areas: (i) emerging biological targets; (ii) new strategies for better drugs acting against established targets and (iii) use of novel methodologies for discovery of lead compounds for (i) and (ii). Emerging targets are enzymes, receptors or ion channels which do not have reported inhibitors or very few known modulators. Here there is an opportunity to break significant new ground and discover the first drugs for a new target, for example the growing class of kinesins (motor proteins). Established targets are defined as already having advanced drugs which have shown efficacy in clinical trials such as kinases (e.g. Glivec for CML) and proteases (e.g. Saquinavir, the first HIV protease inhibitor).

Creation of a New Medicine

One of the many challenges in the long process of drug discovery and development (Figure 1) is the discovery of molecular start-points for medicinal chemistry optimization. Depending on the molecular structure of the active site of the drug target, where its substrates or co-factors bind, this lead-finding quest can be either straightforward or very challenging (also known as ‘druggability’). To address more challenging targets in our group we are establishing the first NUS fragment based screening and drug discovery platform, supported by the NUS Drug Development Unit (DDU) [4], focusing on technologies that thrive in an academic environment.

As well as having good affinity for their biological targets, drug-like molecules need to be designed to have properties which make them orally bioavailable, withstand metabolism during oral absorption and in the liver, then reach the site of action in high enough concentration to exert a pharmacological effect. This long and difficult molecular journey defines the profile of the molecule required and drives the medicinal chemistry program. For example, a CNS drug must penetrate the blood brain barrier which requires a narrow range of physical properties. Academic Drug Discovery (ADD) must focus on new problems not being addressed by the pharmaceutical research industry, but at the same time we aim to provide solutions to problems that are potentially applicable to real patients and hence of interest to industry. The NUS Drug Development Unit (DDU) seeks to support such work throughout all of NUS and can offer NUS PIs free consultancy and selected testing of their compounds at no cost in assays not easily obtained elsewhere. Furthermore, protection of such new inventions can be supported by DDU through enhanced interactions with
the NUS Enterprise Industry Liaison Office (ILO). The daunting prospect of filing a patent on your new invention is therefore less of a challenge with DDU support. Refer [4] for more information. We welcome all enquiries. Why not contact us for a friendly chat?

**Fragment Based Drug Design**

In recent decades, there have been many attempts to speed up the drug discovery process through screening more compounds faster (High Throughput Screening, HTS) and synthesizing more compounds faster (combinatorial chemistry). Although useful and relevant tools, the reality is that the best tool is required for the job, there is no ‘one size fits all’ in the quest for drug leads. Even with the largest HTS libraries it is only possible to screen a tiny fraction of drug-like chemical space. The number of theoretical drug-like molecules at MW 450 is estimated to be approximately $10^{18}$ whereas the number of lower molecular weight (MW 190) compounds required to cover their ‘lead-like’ chemical space is vastly smaller at approximately $10^3$ [5]. As a consequence of their size, these smaller molecules, or ‘fragments’, bind less tightly to proteins, however they do bind specifically even at or above 20 millimolar (mM) concentrations. Hence ‘Fragment Screening’ was born: the screening of very small molecules as moderate to weak, but specific, protein binders. Fragment-based drug discovery [6,7] utilizes small-sized fragments typically 150-350 in molecular weight and has been shown to overcome the difficulties and repeated failures of high-throughput screening (HTS) in early drug discovery, particularly for challenging targets which fail to give hits by conventional means [8,9]. These fragment molecules are screened for binding to a biological target using technologies that are capable of detecting the weaker binding that results from the smaller size of the fragments. These weak binding fragment hits are then evolved by bridging or growing them into fully matured tight (binding constants in the nanomolar concentration range) binders to the selected target (Figure 2).

We are using fragments to develop novel inhibitors of new targets but also for a new concept termed the ‘transient drug’ (NMRC-CBRG grant awarded Aug’13). A transient drug is defined as a molecule which binds weakly to two or more targets, the combination of which elicits a powerful pharmacological response. Figure 3 illustrates the concept schematically. Fragments are discovered for each target and then evolved into more potent molecules using medicinal chemistry, synthesis of structural analogues that, with biological feedback, gradually direct us towards the desired molecular profile. Evolved fragments are then combined or merged together to form hybrid molecules which bind both targets. With further optimization of molecular properties such molecules can be assessed in cell lines for target efficacy.

**Figure 3: Illustration of fragment screening for transient drug discovery.**

We have chosen to focus on two technologies for screening fragments: Surface Plasmon Resonance (SPR) [11], and Weak Affinity Chromatography tandem Mass Spectrometry (WAC-MS) [12,13]. This choice is based on (i) high sensitivity, (ii) low protein requirement, (iii) immediate kinetic data (SPR) and (iv) ability to screen mixtures (WAC-MS). Hit compounds will be confirmed by Nuclear Magnetic Resonance (NMR) [14] and high concentration screening (biochemical assay). With the recent introduction of WAC (affinity LC/MS) a powerful high-throughput technology has been introduced which enables the researcher to screen various molecular libraries including biological extracts and stereoisomers at high speed where affinity and kinetics information can be rapidly obtained [15]. As WAC can be performed on a standard LC/MS platform, it is well suited for the academic environment with limited resources. Further, as many protein targets are fragile, WAC promises to increase their stability by immobilizing them in a protective polymer network. There is evidence of proteins being stable and still folded in their active conformations after as long as one year [16]. We have built a proprietary fragment library of over 2,000 compounds which will be screened against various proteins targets by the above methods.
Case Study: HSP90

My past experience includes various drug discovery projects such as HSP90 [17-19] and PDK1 [20]. HSP90 provides an illustrative example of fragment based drug design leading to a clinical candidate, BEP800 [19]. A fragment screen gave a number of very weak binding pyrimidine hits (e.g. compound 1, Figure 4). Their binding modes were studied using available structural information and new bicyclic fragments, the pyrimidothiophenes, were designed and synthesized but they were also of quite weak activity (compound 2). However, 2 provided a better base template and with one change in substituent of amine to 2,4-dichlorophenyl, potent compounds were obtained (3) which led to BEP800 following medicinal chemistry optimization, truly a journey from the small to the powerful.

Figure 4: Evolution of a fragment to a clinical candidate and crystal structure of BEP800 bound to HSP90 (pdb code 2WI7).

In summary, fragment based drug design has been highlighted as a particular focus of our group where we will be applying SPR and WAC-MS technologies in the pursuit of new targets and concepts in medicinal chemistry. Our mission to grow the influence and impact of the NUS DDU is of foremost importance to the potential for NUS to impact globally in the pursuit of innovative medicines. We look forward to supporting many more projects in NUS in the near future.

References

3. Known as ‘academic drug discovery’ (add) many institutions have come together to support each other, such as the add consortium (www.Addconsortium.Org).


NUCLEAR RECEPTORS AS REGULATORS OF DRUG DISPOSITION

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Introduction
Drug disposition encompasses the complex processes of drug absorption, distribution, metabolism/biotransformation, and excretion. Modulation of drug disposition pathways leads to changes in drug levels, efficacy, and/or toxicity. As such, questions on how the disposition pathways are regulated are clinically important. Drug-metabolizing enzymes and drug transporters play major roles in the drug disposition pathways. For several decades, it was not known which nuclear receptors regulate the expression of drug metabolizing enzymes or drug transporters. In 1998, an exciting seminal discovery in the field of drug metabolism was made, where pregnane X receptor was discovered to regulate a major drug-metabolizing enzyme (cytochrome P450 3A4; CYP3A4) [1-3]. Although constitutive androstane receptor was first identified in 1994 (referred to as MB67) [4], it was not until 1999 when it was first known to regulate another human drug-metabolizing enzyme (CYP2B6) [5]. Due to these seminal discoveries, intensive research has been done to understand the pharmacology of these receptors and their mechanism of regulation of drug disposition.

Pregnane X Receptor and Constitutive Androstane Receptor

The transcriptional activity of PXR and CAR may be modulated by numerous exogenous and endogenous ligands, including drugs [9,10], environmental toxicants [11], phytochemicals [12,13], and herbal medicines [14,15]. Despite the structural differences in PXR and CAR, they share an overlapping set of ligands [16]. PXR is known to be "promiscuous" and its ligands are structurally diverse, due in part to the large and flexible ligand-binding domain [8]. An important point to note is that PXR and CAR exhibit pronounced species differences in ligand binding. It has also been reported that naturally-occurring splice variants of hCAR have distinct ligand-activation profiles [15,17], thereby leading to a postulation that these may result in inter-individual variations in response to drugs, toxicants, or other chemicals. Mechanistically, certain hCAR splice variants (hCAR-SV23 and hCAR-SV24) could be activated by at least two mechanisms: i) direct activation that involves ligand binding to the ligand-binding domain of the receptors; and ii) indirect activation that does not involve

Academic Profile
Dr Lau received a Bachelor of Science (Honours) in Pharmacy and a Doctor of Philosophy from the Department of Pharmacy at the National University of Singapore. She completed pre-registration pharmacist training at National University Hospital and has been a registered pharmacist since 2001. After receiving her Ph.D. in 2007, she pursued postdoctoral research training in the Laboratory of Drug Metabolism and Toxicology, Molecular and Cellular Pharmacology Group in the Faculty of Pharmaceutical Sciences at the University of British Columbia (Vancouver, British Columbia, Canada). She joined the National University of Singapore in June 2013 and currently holds a joint appointment as an Assistant Professor in the Department of Pharmacy, Faculty of Science and Department of Pharmacology, Yong Loo Lin School of Medicine.

Research Interests
- Nuclear Receptor Pharmacology
- Drug Metabolism and Transport
- Drug-Drug Interaction
- Disease-Drug Interaction

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transactivation of the ligand-binding domain or recruitment of steroid receptor coactivators [15,17]. Although the exact mechanism of indirect activation of hCAR is still not known, mouse CAR has been reported to be activated indirectly by signal transduction mechanisms, such as inhibition of epidermal growth factor receptor signaling [18].

**Role of Pregnane X Receptor and Constitutive Androstane Receptor in Drug Disposition**

PXR and CAR were initially identified as “xenobiotic sensors” that play a central role in regulating the expression of genes involved in detoxification, bioactivation, and transport of endogenous and exogenous chemicals [19]. These receptors coordinately regulate a distinct but overlapping set of target genes and biological functions [16]. They are often implicated in drug-induced toxicity and drug-drug interaction [19]. Several drug transporters involved in multidrug resistance (e.g. ABCB1; also known as P-glycoprotein) are also target genes of PXR and CAR. Figure 1 shows several of the target genes of PXR and CAR involved in drug transport and metabolism. Overall, the functional activity of these nuclear receptors may impact the pharmacokinetics, efficacy, and toxicity of drugs. Given that PXR and CAR also modulate the metabolism and transport of endogenous chemicals and regulate the expression of many other genes with physiological or pathophysiological functions [20], there is now increased interest and research on the roles of these nuclear receptors in disease mechanisms.

![Figure 1: Regulation of drug-metabolizing enzymes and transporters by nuclear receptors [20].](image)

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Quantitative Finance After the Recent Financial Crisis

Professor Steven Kou
Department of Mathematics

Introduction
A common misperception, especially before the recent financial crisis, is that quantitative finance focuses on two research areas, option pricing and portfolio optimization. Here I will discuss four of my research projects related to the recent financial crisis: (1) robust risk measures for Basel accords; (2) profit sharing in hedge funds; (3) real estate securities; (4) jump risk during the crisis. Note that none of them involves either option pricing or portfolio optimization.

Mean or Median: Robust Risk Measures for Basel Accords
Elementary statistics teaches us that both mean and median measure the average size of a random quantity, but they have different properties. In particular, if we want to obtain a robust measurement, then median is a better choice than mean. Now what does this have to do with trading book capital requirements? In the consultative document released by the BIS (Bank of International Settlement) on May 3rd, 2012, it is stated that the proposal is to “[move] from value-at-risk (VaR) to expected shortfall (ES), a risk measure that better captures tail risk.” We have serious concerns about this proposal. In particular, in Kou, Peng, and Heyde [1] we provide an axiomatic framework to justify VaR.

First of all, if we want to capture the tail risk, e.g., the size of the loss beyond the 99% level, we can either use ES at 99% level, which is tail conditional mean at 99%, or, alternatively, median shortfall (MS) at 99% level, which is defined as the median of the conditional distribution of the loss given that the loss exceeds the 99% VaR. The MS at 99% level is simply equal to VaR at 99.5% level if the underlying loss distribution is continuous, and the two tend to be very close even if the distribution is not continuous. Hence, just like ES, MS (equivalently, VaR at a higher level) also measures the riskiness of a position by taking into account both the size and likelihood of losses.

Secondly, robustness is indispensable for regulatory risk measures. In the internal models-based approach for determining trading book capital requirements, regulators impose the risk measure and allow institutions to use their own internal risk models and private data in the calculation. From a regulator’s viewpoint, a regulatory risk measure must be unambiguous, stable, and capable of being implemented consistently across all the relevant institutions, no matter what internal beliefs or internal models each may rely on. The external risk measure should be robust; otherwise, different institutions can be required to hold very different regulatory capital for the same risk exposure, which makes the risk measure unacceptable to both the institutions and the regulators. The requirement of robustness for regulatory risk measures is not anything new; in general, robustness is essential for law enforcement, as is implied by legal realism, one of the basic concepts of law.

Profit Sharing in Hedge Funds
Many people believe that a cause of the recent financial crisis is the limited liability of fund managers, which means profits are shared but not losses. This has serious consequence in terms of risk taking. For example, suppose one has a trading strategy that leads to 20 percent gains 99 percent of the time. Then it is not clear at all whether a rational individual should use the strategy, as those 1 percent cases may lead to huge losses. However, it is
optimal for fund managers and corporations to pursue such a strategy due to the limited liability protection. Since the limited liability protection is a fundamental principle of firm structure, there is no way to eliminate it.

But one can have still some checks and balances. For example, the fund managers can set up a deposit, such as 10 percent of fund capital, by using the manager’s own money, and if there is a loss, the deposit money will be used first to offset the losses; in return the fund manager can ask for higher profit sharing such as 40%, versus the current hedge fund standard of 20%. The above compensation scheme is called the first-loss scheme. It has been quite popular in China for privately held funds (which are similar to hedge funds in the U.S.), and is emerging in the U.S. according to a CBS Marketwatch report on May 23, 2011.

In He and Kou [2] we analyze both the first loss scheme and the traditional scheme, in which the fund managers invest 10% regular capital and get 20% profit sharing. By using the s-shaped utility function from behavioral finance, we find that if the 10-30 first-loss scheme (i.e. 10% as the first loss capital in return for profit sharing at 30%) is used, then both fund managers and investors will be better off than under the traditional scheme, as measured by their utility functions. Furthermore, the risk of the hedge fund strategy is lower in the 10-30 first-loss scheme.

**Real Estate Securities**

To a large extent, the financial collapse in 2007–2009 was the result of a national real estate market that proved to be much more tightly interconnected --- much more systemically risky --- than had previously been recognized. This market is also closely linked to the public sector: the U.S. Federal Reserve, which traditionally held only Treasury securities, currently holds over $1 trillion in mortgage-backed securities; and the Treasury’s actions in the crisis made explicit the government guarantee of debt securities issued by Fannie Mae and Freddie Mac. The creation and continued existence of these government sponsored enterprises reflects the public interest in supporting home ownership; but the near collapse of these giants also reflect large-scale failures of risk management.

Spatial interaction has been well studied in the spatial econometrics literature. Instead of studying prices of houses and apartments that are illiquid and difficult to be sold short, we study the risk and return of real estate securities that are liquid and can be easily shorted, such as futures contracts on the S&P/Case-Shiller Home Price Indices (CSI Indices). More precisely, in Kou, Peng, and Zhong [3] we attempt to connect spatial econometrics, which emphasizes the statistical modeling of spatial interaction, with classical asset pricing models including the capital asset pricing model (CAPM) and the arbitrage pricing theory (APT), which characterize risk-return relationship of financial assets that can be freely traded, especially be sold short. Furthermore, we give rigorous econometric analysis of the models by deriving identifiability conditions for the parameters and asymptotic properties of estimators and studying test statistics needed for implementing the models. Finally, an empirical study of the futures contracts on S&P/Case-Shiller Home Price Indices shows that the spatial APT is not rejected and the spatial interaction parameter is statistically significant.

**Jump Risk during the Crisis**

It is well known that jump risk affects equity returns significantly. In Kou, Yu, and Zhong [4] we attempt to answer two questions about jumps in equity indices: (i) How did jumps in equity index returns change during the financial crisis 2007–2011; in particular, were there significant changes in jump rates or in jump sizes, or both? (ii) Were there finite number of large jumps or infinite number of small jumps in equity returns before and during the crisis?

For the first question, the increases of jump rates when market is in distress, especially for the 1987 crash and the tech-bubble burst around 2001--2002, are well documented. However, whether there are significant changes in jump-sizes during financial crises has not been addressed in the existing literature. Also the previous empirical studies in general do not distinguish positive and negative jump rates.

Based on the latest data on S&P 500 daily returns up to December 2011, we find both positive and negative jump rates increased significantly during the financial crisis, while, somewhat surprisingly, there is little evidence that average jump sizes changed before and after the crisis.

The results in the existing literature regarding the second question are mixed; furthermore, most of the empirical studies on the subject assume normally distributed jumps in equity returns. We found that a simple affine jump-diffusion model with both stochastic volatility and double exponential jump sizes [5] in returns fits S&P 500 daily return data well before and during the crisis. Therefore, our answer to the second question is that there seems to be finite number of large jumps in equity returns. In short, affine jump-diffusion model with a proper jump size distribution can fit equity return data well both before and after the crisis. Intuition behind this lies in the differences between the two jump-size distributions.

In terms of small jumps, the normal distribution does not have monotone structure. For example, it can be seen from the figure below (normal density on the top and double exponential density on the bottom) that, if jump sizes are normally distributed with mean -2%, jumps down -2% is more likely to occur (i.e. has a higher density) than jumps down just -1%. The monotone structure of double-exponential jumps provides better model fit of small jumps in equity returns.
In terms of large jumps, the double-exponential distribution is also suitable because it has heavy tails. Heyde and Kou [6] show that it is difficult to distinguish exponential-type tails from power-type tails from empirical data. For example, far at the right-tail, say, at the probability of 0.01%, the population quantile of the exponential distribution is 6.02, which is larger than 5.97, the population quantile of normalized Student-distribution with degree of freedom 7, even we know that the Student-t distribution should have an asymptotically heavier tail than the exponential-type distribution. The heavy-tail feature of the double exponential distribution helps to fit the large jumps during the crisis.

References


NANO-BIO-PHYSICS: TOWARDS SINGLE-MOLECULE DNA SEQUENCING

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Introduction
The last decade in science has seen huge advances in two distinctive research fields: nanoscience and single-molecule biology. Both influenced our perception of the world and defined the modern technology. Nanoscience deals with solid-state “hard” objects whose dimensions are so small (in the order of nanometers) that their physical properties no longer depend on their chemical composition alone, but on their sizes and shapes. Those nanosystems are often produced top-down, with variety of exquisite nanofabrication tools, and act as small laboratories where quantum-physical concepts could be simplified and investigated. On the other hand, biophysics of individual molecules gave us insight into the fascinating inner working of molecular machines driving life, and fostered biomedical technology. This “soft-matter” is assembled bottom-up with single-atom precision, and its behaviour is mostly defined by the thermodynamics and stochastic processes.

My research program lies at the overlap of nanoscience and single-molecule biophysics. I am interested in understanding interactions of solid-state nanoelectronic devices and nanostructured surfaces with individual biomolecules, ions and water. My long-term goal is to interface semiconducting devices with biological matter, whereas the immediate goal is to electrically control and analyse individual biomolecules (DNA and proteins) with sub-nanometer precision. Our flagship project is the development of a new method for physical DNA sequencing based on nanoelectronic devices, one that would be order of magnitude cheaper and faster than the current technologies (Figure 1).

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Figure 1: (left) Cost of the full mammalian genome sequencing dropped by 4 orders of magnitude in last decade, and another 10-fold decrease is required for sequencing technologies to enter the mainstream healthcare applications (adapted from [1]). The most prominent contender for the next-next generation of DNA sequencing in nanopore sequencing (right), which rely on pulling individual DNA molecule through a nanometer-sized pore, while detecting the passing nucleotides.
Physical DNA Sequencing

It is my believe that, looking back from the future, our age will be remembered chiefly by rapid advances in DNA sequencing technologies and the scientific revolutions it fostered in diverse disciplines. DNA molecule is a long polymer consisting of a phosphate backbone, and a string of chemical groups, nucleobases. Nucleobases carry the genetic code that is “software and data” required for running the cellular machinery of every living organism. Since the first attempts to sequence human genome, the torrent of technological developments lowered the price of full mammalian genome sequencing by six orders of magnitude [1], grossly over-performing Moore’s law in electronics. The continuous increase in affordability made the DNA sequencing tools available to the general scientific community, revolutionizing biomedical and agricultural sciences, anthropology, history and many other scientific endeavors. As more genetic code is sequenced, more we realize we need new and faster sequencing technologies – the height of curiosity is in genomic population difference, cancer genome, even cell-to-cell genome variations, all demanding disruptive approach to sequencing. For full-genome sequencing technologies to enter the healthcare, where the real benefit lies with personalized and preventive medicine, the price tag for sequencing has to drop another order of magnitude. This is not achievable by incrementally improving current technologies, and completely new approach to sequencing is required.

Current DNA sequencing technologies rely on amplification (multiplication) of the genetic material, and its fragmentation into segments of 100-1000 bases in length. A specific chemical reaction is performed on nucleotides within the segments – the effects of that chemistry is detected, often optically, and assigned to nucleotides. The template DNA molecule is spent in the process. All the separate segments are then reassembled in a huge puzzle-game, requiring large computation power. In all those aspects, the new nanopore-sequencing scheme is the exact opposite.

Nanopore

A nanopore detector consists of an individual few-nanometer-sized pore perforating a very thin membrane that separates two reservoirs filled with aqueous ionic solution. The nanopore comprises the only path the ions and molecules can use to move between the two reservoirs. The voltage bias applied across the membrane induces flow of ions (recorded as baseline ionic current) and biomolecules through the nanopore. The voltage stretches negatively charged DNA molecule as it is pulled through the nanopore in single file fashion. The passing DNA molecule physically blocks the pore, reducing the flow of ions through the pore. The instantaneous current drop is a sensitive measure of the size and chemical properties of part of the DNA molecule dwelling within the pore at that given instant. Therefore, the different nucleotides along the DNA molecule should block the ionic current differently, and nanopore should be able to read out the individual nucleotides in their natural sequence. That is, only if the nanopore detector has: (a) sufficient sensitivity to distinguish between different nucleotides; (b) has sufficient resolution to distinguish small enough features along the DNA molecule; (c) is capable to slow down and control the passage of the DNA molecule. All those requirements are not trivial, and they are subject of intense research efforts.

Recently, we have discovered a new class of nanopores based on graphene [2], which have potentially much better detection properties than protein and solid-state pores previously used[3]. Graphene is mono-atomically thin membrane of hexagonally bonded carbon atoms with remarkable physical and chemical properties, and high mechanical durability [4]. We have demonstrated that the effective thickness of freestanding graphene membrane in water is only 0.6nm and concluded that graphene nanopore has a potential to
achieve single-nucleotide resolution along the DNA molecule [2]. In subsequent work [5], we demonstrated extremely high sensitivity of tightly-fitting graphene nanopores. Thus, the graphene nanopore could likely achieve the nucleobase contrast required for the DNA sequencing, provided pores’ sizes and shapes can be controlled with the atomic precision.

In all those experiments, DNA molecules was passing too fast for the direct detection of individual nucleotides, and currently our significant research efforts are focused on controlling speed and position of DNA molecules with sub-nm precision.

Electrical Detection

A nanopore can localize sequential nucleobases within its perimeter, but the nucleotide recognition could be achieved by using methods other than the ionic current, like using nanopore-integrated electrical sensors, or optical detection. One distinctive advantage of graphene is that it is electrically conducive, and electrically sensitive to its local chemical environment. In our lab, we aim to articulate solid-state nanopores with graphene device, to be use as a tunneling [3, 6] or field-effect DNA detector [3, 7]. In the first case, the tunneling current between two opposing electrodes is disturbed by passing DNA molecule, whereas in the later, the conductivity of a strip of graphene perforated by a nanopore is modulated by the translocating DNA.

Outlook: Probing Molecules and Dynamic Processes

As we hone our analytical tools with DNA molecules, we are looking into investigation of other biomolecules. The next frontier is in using nanopore “microscope” to dissect proteins: understand their sequence, physical shape and surface charge distribution in native, physiological environment. The fast characteristic times scales of the nanopore detector allow us to look into dynamic processes: protein shape evolution and protein-DNA interactions. Although nanopore detection is a single-molecule detection technique, its high throughput allows us to bridge the gap between single-molecule and ensemble-average detection techniques, and peek into fundamental riddles of polymer and statistical physics. The future is exciting.

References


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