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BIO-ECONOMIC MODELING TO SUPPORT POLICY-MAKING FOR SUSTAINABILITY

Dr L. Roman Carrasco
Department of Biological Sciences

Introduction

Problems such as the destruction and degradation of ecosystems, invasive alien species, climate change and disease emergence pose enormous challenges to governments in the 21st century. Despite their apparent diversity, these problems have common characteristics: they present a global scale, are complex and involve interactions between economic and ecological systems.

Perhaps the strongest commonality of all is that they threaten the “sustainability” or “sustainable development” of the planet — where sustainable development is defined as “development that meets the needs of the present without compromising the ability of future generations to meet their own needs” [1]. Several pillars are essential for sustainability, namely economic sustainability, nature conservation, sociopolitical stability and human health.

Although substantial advances have occurred in our understanding of policies that promote sustainability at the local scale, solutions to manage global problems remain elusive [2]. Difficulties arise due to the vast diversity of countries’ political agendas, cultures and income levels. Further difficulties respond to our poor understanding of the relationships between ecosystems and economic growth or between ecosystems, income and disease burden. Even though important advances in individual disciplines such as epidemiology, ecology or economics have occurred, these have evolved in rather parallel ways. As a result, tools to integrate those disciplines to support policy-making are scarce.

Because empirical or field studies of population-level strategies to control or mitigate climate change, tropical deforestation or pandemics are generally either infeasible due to the large scale of the problem or unethical (e.g. withholding vaccination of subpopulations to assess the effect on disease transmission), modeling is one of the only suitable methodologies to enable multiple hypothetical policies to be assessed. Given the complexity and multi-faceted aspects of these problems, flexible models able to capture such complexity and to blend several disciplines are necessary. Bio-economic or ecological-economic models, initially intended for fisheries management, allow for the integration of biology and economics and thus respond to the challenge. This modeling integration facilitates the direct translation of model-generated insights into policy-relevant outcomes and, together with colleagues, I have employed it in the interface between life sciences and economics.

Modeling for food sustainability

There is an urgent need to find solutions that increase agricultural production while minimizing agriculture’s environmental footprint. The situation is exacerbated in the tropics where rapid increases in population density require that larger extensions of land are utilized for agricultural production. In Southeast Asia, this mounting pressure on the land is coupled with the extensive expansion of highly profitable oil-palm production [3].

The loss of the ecosystem services through tropical deforestation can have...
severe consequences for current and future generations inter alia the extinction of endemic species and substantial carbon emissions to the atmosphere.

Ecological-economic policy modeling to support sustainable development offers a unique opportunity to check whether land conversions in the tropics lead to non-decreasing inter-temporal social welfare and, as a result, to identify and correct unsustainable strategies.

Several policies for sustainability have recently been proposed: (i) “green accounting” that allows for the incorporation of the depreciation of the natural capital in national economic accounts; (ii) land sparing policies through agricultural intensification [4]; and (iii) market-based interventions such as payments for avoided CO₂ emissions from deforestation represented by REDD+ (UN program for Reducing Emissions from Deforestation and Forest Degradation) which are part of the broader concept of payment for ecosystem services.

These new strategies to inform and obtain food production sustainability have wide socioeconomic and environmental implications that are however poorly understood. Very little is known about the potential effectiveness of these measures in Southeast Asia and how they should be implemented. Our current work, through a new MOE Tier 2 grant, on the evaluation of the implications of these strategies ex-ante and identifying how the strategies should be implemented offers promising potential to redirect tropical development towards sustainability (Figure 1).

Figure 1: Comparison of the economic externalities generated due to CO₂ emissions in tropical forests deforested between 2000 and 2005 and the economic value of the crops that replaced those forests. These comparisons allow identifying where did land conversion accrued net benefits for the country and the society as a whole.

Modeling for public health

The combination of both models is important given that public health decisions need not be based only on epidemic outcomes but on the economic efficiency of interventions. Epidemic-economic models thus allow to compare the returns of the intervention with the costs of the intervention itself and also to compare between interventions for different diseases. For instance, epidemic-economic models can be used to estimate the optimal stockpile size of antivirals for different countries to prepare against uncertain influenza pandemics [5]. These models are able to identify the countries that might not be able to purchase and maintain their stockpiles and thus require support from the international community. Epidemic-economic models can also be used to evaluate the adoption of a new vaccine. For instance, potential new dengue vaccines were estimated to be cost-effective for Singapore under different price schemes given the economic burden that dengue poses to the country [6].

The application of modeling can also be very useful to identify new methods to scale-up global health aid allocations. For example, mirroring global carbon emissions permit markets, a disability-adjusted life year market was developed. By this system, high-income countries would buy permits that certify their domestic non cost-effective interventions by supporting highly cost-effective projects in low-income countries [7] (Figure 2).

Figure 2: Global map of countries according to their expected global health donations. Net donors are countries that donate beyond their expected contributions. Recipients are countries that need to receive the donations.

Modeling for biosecurity

The introduction and spread of harmful non-indigenous organisms beyond their natural range can have very negative consequences for food security and biodiversity. Policy-making attempting to prevent, detect and control multiple invasive threats need to strike a balance between the costs of control, potential economic impacts and ecological processes governing the invasion. Bio-economic models coupling population dynamics and dispersal with control activities can for instance help: (i) to identify the cut-off point of eradication campaigns under uncertainty [8]; (ii) to consider life history traits of different invasive species and their ease of detection to allow prioritizing interventions for certain species [9]; and (iii) to consider the complex spatial dynamics of land owners to identify the spread of negative behaviors that can trigger the failure of the policy intervention [10].
Conclusion

The challenges faced by humanity in the 21st century relate to sustainability, present a large scale and are interdisciplinary. The methods necessary to provide policy insights need to match such complex and interdisciplinary characteristics. Bio-economic and ecological-economic models present such potential and will be invaluable to support evidence-based policy making for sustainability.

References


ACADEMIC PROFILE
A/P Beskos joined the Department of Statistics and Applied Probability in December 2012 as an Associate Professor. He obtained a PhD in Statistics from the Department of Mathematics and Statistics, Lancaster University, UK, in 2005. During 2005-08, he worked at the University of Warwick as a Post-Doctoral researcher for 3 years: 2 years at the Mathematics Institute and 1 year at the Department of Statistics. During 2008-12, he was a Lecturer in Statistics at the Department of Statistical Science, University College of London, UK.

RESEARCH INTERESTS
- Markov chain Monte Carlo Methods
- Bayesian Statistics
- Sequential Monte Carlo Methods
- Computational Statistics

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Introduction

Sequential Monte-Carlo (SMC) algorithms apply importance sampling iteratively to obtain samples from sequences of target distributions arising in certain applications. Importance sampling is a general technique for estimating properties of a particular distribution using samples generated from a distribution different from the distribution of intent. It involves: (i) getting samples from an easy-to-handle “proposal” distribution; (ii) assigning them “importance weights” to correct for the discrepancy between target and proposal; the outcome is a discrete-type weighted-particle representation of the target distribution that provides consistent estimates of it’s moments.

SMC is used at important sequential applications (e.g. signal processing) as it combines Bayes rule and importance sampling to provide a natural, statistically justified framework of updating estimates about the state of systems under incoming data streams. However, in high dimensions (e.g. data assimilation in atmospheric sciences) practitioners will typically employ Kalman-Filter-based methods as SMC is still considered to be computationally impractical in such contexts due to weight degeneracy. Kalman Filters are computationally more feasible than standard SMC in high dimensions but are based on linear approximations and, in contrast to SMC, will return biased, inconsistent estimates in the realistic contexts of non-linear model dynamics.

Standard SMC methods could collapse in high dimensions. As the dimension of the state space increases proposal distributions become distanced from targets. This results in a small fraction of particles capturing all probability mass with the rest being discarded, with the extreme scenario of just a single particle remaining to represent the target. Such an observed weight degeneracy for standard SMC methods is found to occur exponentially fast with increasing dimensionality.

Many works on SMC have hinted at a rapid deterioration of efficiency as the dimension of the state space grows, at such a rate that standard SMC methods are considered to be impractical in high dimensions; see the comments in [1]. SMC will in cases break down (particularly in high dimensions) due to weight degeneracy arising, when proposal distributions within importance samplers are bad proxies for targets. For instance, when priors are used as proposals, data information about even a small fraction of a high-dimensional vector can give extremely small likelihood values and, consequently, small weights for all but a few particles. Recent research has analytically quantified this degeneracy. [2] show that for standard proposals, the number of particles must increase exponentially fast with d for the variance of importance sampling estimates to be controllable; [3] report similar exponential rates to avoid the degenerate situation when a single particle will accumulate all probability mass.

Our research takes into account the above-mentioned issues and aims to extend the boundaries in which SMC can be applied in high dimensions. Recent advances in SMC have shown significant impact on scaling down it’s computational costs, particularly in large-scale problems. [4] show empirically that incorporating slowly varying “bridging” distributions between proposal/prior and target/posterior when applying Bayes rule and using MCMC-type Markov transitions for moving particles along such distributions or dispersing them into the state space can sometimes revoke weight degeneracy. In [5], I have
been involved in work that obtains analytical results for such methods showing that computational cost, for SMC methods can be reduced from an exponential function to a quadratic function in d.

**Our Algorithm**

My research aims at greatly improving upon first attempts in the data assimilation literature of using SMC for large-scale problems. We are trying to provide a framework for extending the scope of SMC for problems in meteorology, oceanography and other high-dimensional contexts. From the literature, computational algorithms trying to sample directly from the posterior conditionally on all data are found to be extremely expensive in terms of the computational cost. A sequential incorporation of data will smoothly adjust particles to incoming data via the bridging steps and will facilitate the development of efficient Markov kernels to move particles via exploiting current particle representations to tune such kernels (as in [6] in low dimensions).

SMC provides a more natural and promising direction than direct sampling from the posterior of all the data (via Markov chain Monte-Carlo (MCMC) algorithms) in tackling such high-dimensional problems and is expected to deliver much more efficient algorithms.

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**Application to Navier-Stokes (NS) equation**

We have applied our methodology at a data assimilation problem when the Navier-Stokes (NS) partial differential equation, modeling the evolution of an incompressible fluid in a closed domain in the presence of viscosity and external forcing, is observed at a number of time instances and at a number of locations in the field domain. The statistical question here is to learn the initial condition of the NS dynamics from the information in the observations, by means of learning about its posterior distribution. We applied our computational SMC algorithm on this problem. In Figure 1 we show some algorithmic output, indicating that our methodology can successfully recover the initial condition of the NS equations from observations of the dynamics. In Figure 2 below, we show the posterior distributions for a number of Fourier coefficients of the initial condition, as generated from our algorithm together with their true values, thus again illustrating that our method does well at retrieving the features of the initial condition by assimilating the data.

![Figure 1: Top and Bottom Right panel: the true initial vorticity and true initial velocity field respectively for the Navier-Stokes equations. Top and Bottom Left panel: their corresponding estimates generated by algorithm after assimilating Eulerian observations. The black points in the field show the locations of the observations.](image1)

**References**


ELLIPITC CURVES, MODULAR FORMS AND THE LANDLINGS PROGRAM

Professor Gan Wee Teck
Department of Mathematics

Innocuous Equations

Number theory is traditionally concerned with finding integer solutions to equations. For example, one may like to find integers A, B and C so that

\[ A^2 + B^2 = C^2. \]

We all realize that solving this equation in integers is looking for right-angle triangles with integer sides, thanks to Pythagoras' theorem. One such triple of solutions is (3,4,5), but there are in fact infinitely many such Pythagorean triples and one knows (since antiquity) how to write all of them down.

However, Number Theory has the tendency of throwing up similar innocuous looking problems which turn out to be very difficult to solve. Here are two of them:

(i) (Fermat’s Last Theorem)

Show that there are no nonzero integers satisfying \( A^n + B^n = C^n \).

(ii) (Congruent Number Problem)

Find all positive integers \( N \) which are the area of a right angle triangle with rational sides, i.e. such that the following system of simultaneous equations have solutions with \( A, B, C \) rational numbers:

\[ A^2 + B^2 = C^2 \quad \text{and} \quad 2N = AB. \]

Both these problems are easily understood by school children, but are notoriously hard to solve. Indeed, (i) was proposed by Fermat some 350 years ago, and was only resolved in 1995 by Andrew Wiles [1] (of Princeton University then). On the other hand, (ii) is still an open problem today.

It is natural to ask what significance the two problems above possess. As they stand, they are indeed mere idle curiosities, no more important than any other equations one might care to write down. However, in trying to resolve (i), generations of mathematicians were led to uncover many fundamental questions and subjects areas and to develop many sophisticated machineries, leading to the creation of the field of algebraic number theory. More pertinently, the eventual solution of (i) and the proposed approach to (ii) turns out to be related to an important class of objects known as Elliptic Curves.

Elliptic Curves

An elliptic curve is basically a curve in the plane described by a cubic equation of the form

\[ Y^2 = aX^3 + bX + c, \]

with \( a, b, c \) rational numbers:

\[ A^2 + B^2 = C^2 \quad \text{and} \quad 2N = AB. \]

Why are such cubic equations interesting? Well, it turns out that if one considers quadratic equations (like the Pythagorean equation), one knows that they have infinitely many rational solutions. On the other hand, if one considers equations of degree higher than 4 (such as the Fermat equation with large \( n \)), then an amazing theorem of Faltings [2] (winning him the Fields medal in 1986) says that they will only have finitely many rational solutions. Thus, cubic equations (i.e. elliptic curves) are very interesting because they happen to sit on the boundary between heaven
The “fact” that two classes of objects are the same is useful as it allows one to transfer a problem about one class of objects to the other, where it may be more readily solvable. In his resolution of Fermat’s problem, what Wiles did was to build enough of this bridge between number theory and representation theory, so that he may transfer the question of nonexistence of a particular elliptic curve to the question of nonexistence of certain modular forms, and this latter question turns out to be trivial. For the congruent number problem, one needs to understand the L-function L(s, E), and one expects that such L-functions are more easily understood if one has the bridge to pass to the world of modular forms.

To conclude, much of my own research has been focused on:

(a) Helping to build a part of the bridge or dictionary between number theory and representation theory; an example is my work with S. Takeda [6] on the local Langlands conjecture for GSp(4) and related groups.

(b) Using this dictionary as a tool to resolve interesting problems on either side of the Langlands program; an example is my work with B. H. Gross and D. Prasad [7] on some branching problems in representation theory.

The Langlands program has seen a lot of progress in the past decade, resulting in the proofs of many classic conjectures in number theory. Moreover, the underlying principle of the Langlands program is so universal that it has been applied in geometry and string theory. Some people have claimed that these ideas will lead to a grand unification of vastly different areas of mathematics. Only time will tell.

Reference


Chiral Diene Ligands for the Rhodium-Catalyzed Asymmetric C–C Bond Forming Reactions

Professor Tamio Hayashi
Department of Chemistry

Introduction for Rhodium-Catalyzed Asymmetric C–C Bond Forming Reactions

The development and exploration of highly selective asymmetric carbon-carbon bond forming processes are of high fundamental importance, and transition metal catalysis plays a key role in realizing unprecedented type of asymmetric reactions. Although various kinds of carbon-carbon bond forming reactions and their asymmetric variants have been reported so far, we have focused on development of a new type of asymmetric transformations where carbon-metal intermediates create stereogenic carbon centers at asymmetric addition to carbon-carbon or carbon-heteroatom multiple bonds. In 1998, we reported the first example of rhodium-catalyzed asymmetric 1,4-addition [1], which is later called “Hayashi-Miyaura Reaction” (Scheme 1). In the first report, it was concerned with the addition of organoboronic acids to α,β-unsaturated ketones in the presence of Rh(acac)(binap) as a catalyst. Immediately after the first publication, the rhodium/binap-catalyzed reaction was extended by ourselves and others to many other electron deficient olefins, α,β-unsaturated esters, amides, alkynylphosphonates, nitroalkenes, and so on [2]. In 2002, the catalytic cycle of the rhodium-catalyzed 1,4-addition of phenylboronic acid was fully understood by characterization of all the three intermediates, phenylrhodium, oxamallylrhodium, and hydroxorhodium, involved in the catalytic cycle [3] (Scheme 2). During the mechanistic studies, we found [Rh(OH)(binap)], which is more catalytically active than Rh(acac)(binap), and more importantly, we found that the conjugate addition is accelerated by diene ligands on the rhodium catalysts. Typically, the addition of phenylboronic acid to methyl vinyl ketone is more than 20 times faster with cod (1,5-cyclooctadiene) ligand than with binap ligand. On the basis of this experimental result which demonstrates the high catalytic activity of diene/rhodium complexes, we have designed and prepared chiral diene ligands and used them successfully for the asymmetric version of the rhodium-catalyzed addition reactions.

Scheme 1: The first example of rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids [1].

Scheme 2: Catalytic cycle of rhodium-catalyzed conjugate addition of phenylboronic acid.

Chiral Diene Ligands for the Rhodium-Catalyzed Asymmetric C–C Bond Forming Reactions

In 2003, as conceptually new chiral ligands, we reported the synthesis of enantiomerically pure chiral dienes, whose basic diene skeleton is bicyclo[2.2.1]hepta-2,5-diene (nbd*), bicyclo[2.2.2]octa-2,5-diene (bod*), or bicyclo[3.3.1]nona-2,6-diene (bnd*) [4,5] (Figure 1). They have two alkyl or...
aryl substituents on the double bonds, one on each of the two double bonds. The chiral diene ligands were found to be better than the conventional chiral ligands represented by chiral bisphosphines in terms of both catalytic activity and enantioselectivity in some of the catalytic asymmetric reactions. Their high performance was observed in rhodium-catalyzed asymmetric addition of organoboron reagents to α,β-unsaturated ketones, N-sulfonylimines, and many other related reactions (Scheme 3).

Recent Advances in the Asymmetric Reactions with Chiral Diene Ligands

The rhodium catalysts coordinated with chiral diene ligands have been recognized to be much better than those of other types of chiral ligands represented by chiral phosphine ligands in terms of both catalytic activity and enantioselectivity in more than 50 publications [6]. Some of the recent results obtained with chiral diene ligands are shown hereafter.

Rhodium-catalyzed addition of sodium tetraarylborates to N-tosyl ketimines was achieved by use of chiral diene ligand, constructing chiral amine derivatives possessing α-tetrasubstituted carbon stereocenters with high enantioselectivity [7] (Scheme 4). This reaction does not take place with other types of ligands.

Catalytic asymmetric synthesis of (triaryl)methylamines with high enantioselectivity was realized by rhodium-catalyzed asymmetric arylation of cyclic ketimines substituted with two aryl groups at the imine carbon. Thus, the addition of aryloboroxines to cyclic N-sulfonylimines and N-acyl ketimine precursors in the presence of a rhodium catalyst coordinated with a chiral diene ligand [(R)-diene* or (S,S)-Fc-tfb] gave high yields of the corresponding arylation products with up to 99% ee. The chiral benzosultams obtained were transformed into the chiral (triaryl)methylamines by breaking the cyclic structure [8,9] (Scheme 5).

Scheme 4: Rhodium-Catalyzed Asymmetric Arylation of N-Tosyl Ketimines.

Scheme 5: Catalytic Asymmetric Synthesis of (Triaryl)methylamines.

A rhodium/diene complex was found to be active as catalysts for 1,4-addition of aryloborane reagents, tetrathyronboranes and aryloboroxines to β,β-disubstituted α,β-unsaturated ketones to give ketones bearing quaternary carbon stereocenters at β-position [10,11]. One example for the addition of phenylboron reagent to 3-methylcyclohexenone is shown in Scheme 6. This carbon–carbon bond formation takes place only with diene ligand on the rhodium catalyst.

Scheme 6: Rhodium-Catalyzed Asymmetric 1,4-Addition to β,β-disubstituted enone.

A 2-phenyl-alkenylrhodium intermediate, generated by addition of a phenylrhodium intermediate to alkyne, was found to undergo 1,4-shift of rhodium from alkenyl carbon to ortho-position of phenyl group to form 2-alkenyl-phenylrhodium species. Taking advantage of this rearrangement at a key step in the catalytic cycle, new type of asymmetric transformation reactions were realized [12,13]. As a typical example, the reaction of 3-(3-butynyl)-2-cyclohexenone with tetraphenylborate in the presence of a chiral diene/rhodium catalyst gave a spirocarbocycle with high enantioselectivity (Scheme 7).

Scheme 7: Rhodium-Catalyzed Asymmetric Synthesis of Spirocarbocycle.
Scheme 7: Asymmetric Synthesis of Spirocarbocycles by Way of 1,4-Rhodium Shift.

The rhodium-catalyzed asymmetric addition was applied successfully for the 1,6-addition of arylboronic acids to β-alkynyl acrylamides substituted with a silyl group on the alkyne terminus. The reaction took place with a ferrocene-substituted chiral diene ligand, Fc-tfb, to give a high yield of axially chiral allenylsilanes with high enantioselectivity. With other chiral diene ligands, the selectivity in giving the allenylsilane is very low [14] (Scheme 8).

Scheme 8: Rhodium-Catalyzed Asymmetric Synthesis of Axially chiral Allenylsilane.

We have previously reported that perfect 1,6-addition manner is observed in the iridium-catalyzed reaction of arylboronic acids with α,β,γ,δ-unsaturated carbonyl compounds, while the use of rhodium complexes gives both 1,4- and 1,6-addition products non-selectively. The asymmetric version of the 1,6-addition was realized by use of an iridium catalyst coordinated with chiral diene ligand. Although the substrate scope is not very broad, the chiral Me-tfb/iridium catalyst gave the corresponding 1,6-addition product with high (98–99% ee) enantioselectivity [15] (Scheme 9).

Scheme 9: Iridium-Catalyzed Asymmetric 1,6-Addition to α,β,γ,δ-unsaturated Ketones.

In addition to the catalytic asymmetric carbon–carbon bond forming reactions described above, the chiral diene ligands have shown their high performance in several other types of reactions. The chiral diene ligands are promising because they have powerful chiral surroundings and high modularity in tuning steric and electronic characters. Although the chiral diene ligands have been used mainly for rhodium- and iridium-catalyzed reactions to date, they will be successfully applied, for example, to palladium-catalyzed reactions by appropriate electronic tuning of the diene moiety.

References


ENGAGING THE FUTURE OF PATIENT CARE IN THE DIGITAL WORLD

Dr Kevin Yap
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Introduction

Informatics and internet technologies are becoming extremely popular in today’s healthcare system, giving rise to the domain known as ‘digital healthcare’ (or digital health). The advancement of information and communication technologies in recent years has led to the development of various software, hardware, tools, internet and mobile applications and services; which can be used as aids by healthcare professionals and patients to address various health problems and challenges, as well as improve health-related outcomes. Digital healthcare systems have many potential benefits in terms of patient care management [1]. However, several issues have surfaced from the use of such technologies, which can affect the quality of care provided to patients.

The practice of pharmaceutical care forms the cornerstone of pharmacy and it involves identifying, solving and preventing drug-related problems with regards to patients’ drug therapies. Simply put, it helps patients make the best use of their medications. In recent years, two upcoming fields have emerged in the pharmacy domain to address new drug-related problems that have surfaced in the cyber-age, so that care and safety of patients can be enhanced [2]. The first field, known as pharmaco-informatics, involves the development of various tools and applications that target drug/medication-related problems through the use of informatics, communication and internet technologies [2]. These tools/applications can be used as aids by healthcare professionals for delivering optimum pharmaceutical care and health-related outcomes. Pharmaco-cybernetics (also known as cybernetic/cyber-pharmacy), the second field, goes a step further by adopting approaches to support medicines and drugs use through the merging of technologies with human-computer-environment interactions, and evaluation of these technologies so as to reduce or prevent drug-related problems [3]. We are all intertwined with the technologies that we use and the environment in which we live. Our interactions and social experiences of sharing information and exchanging ideas are critical for the success of pharmaco-informatics tools and cybernetic systems, which in turn are affected by the environment at different levels [3]. An application example is shown in Figure 1.

The science of cybernetics has further led to the term ‘cyberspace’, which is now ubiquitously used to describe anything that is associated with computers, information technology, and the internet. The popularity of the World Wide Web and more recently, social media, has affected the way in which health-related and drug-related information is distributed and accessed over cyberspace. The internet is rapidly gaining importance for both healthcare professionals and patients. It is therefore essential that pharmaco-informatics tools and cybernetic systems can be evaluated for their usefulness, practicality, quality and safety. Cybernetic/cyber-pharmacists in these interdisciplinary fields, combined with their knowledge in pharmaceutical care, can help enhance the quality and safety of integrated care provided to patients.
Figure 1. Application example of how a breast cancer patient is intertwined with the different levels of her environment when she searches for information about her condition.

Patients in the Digital Age and Emerging Model of Healthcare

When a patient visits the doctor, his medical and health information are stored in many different forms (Figure 2). This information can resemble multiple separate ‘trees’ of patient data that are potentially useful for patient profiling. Over the years, as the patient visits multiple doctors at various institutions, these ‘trees’ become a diverse ‘forest’ [4].

With a trend towards a growing elderly population (i.e. the ‘silver tsunami’), this forest is expected to grow denser with time. Singapore has one of the fastest aging populations in the world. Approximately 15% of the population (600,000 people) will be aged 65 years or older by the year 2020 [5]. As such, medication use is expected to grow due to the increasing number of elderly patients with multiple chronic diseases and co-morbidities. These patients may be overwhelmed by concerns regarding their disease and/or treatment options.

The evolution of the internet in the Web 2.0 era has changed the way health-related information is disseminated by allowing users to interact with online content. Many patients, including the elderly, are becoming more comfortable with surfing the internet. This growing group of so-called ‘silver surfers’ actively go online to search for health information. A study identifying local cancer patients who were ‘silver surfers’ found that ~40% (186/460 patients) used the internet for health-related purposes (e.g. understanding their diagnoses and treatments) [6]. Another group of digitally savvy patients worth mentioning are the Generation Y of 18 to 34 year olds. Also described as the ‘Generation Cs’, these young adults not only use the internet naturally and extensively, but they ‘connect’ through digital media, socialize and share experiences through devices more than any other age group [7]. With patients becoming more technology savvy, a new model of healthcare is emerging, whereby patients can act as a partner in their care (Table 1). The digital technologies employed for this new model can also combine the diverse ‘forest’ of health-related data into one ‘canopy’, so as to aid healthcare professionals access relevant information as and when they need in their practices.

Table 1. Differences between the old and new models of healthcare.

<table>
<thead>
<tr>
<th>Old model of healthcare</th>
<th>New model of healthcare</th>
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<tr>
<td>Focus on acute conditions, reactive management</td>
<td>Focus on long-term conditions, prevention and continuing care</td>
</tr>
<tr>
<td>Hospital-centered, disjointed episodes</td>
<td>Integrated with people’s lives in homes and communities (i.e. ‘hospital in a home’)</td>
</tr>
<tr>
<td>Doctor dependent</td>
<td>Team-based, shared-records</td>
</tr>
<tr>
<td>Patient as passive recipient, self care infrequent</td>
<td>Patient as partner, self-care encouraged and supported</td>
</tr>
<tr>
<td>Use of digital technologies rare</td>
<td>Dependent on digital technologies and devices</td>
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**Singapore's Vision and Trends in Digital Healthcare**

In May 2005, a steering committee from the Infocomm Development Authority of Singapore (IDA) spearheaded a ten-year masterplan (Intelligent Nation iN2015) to leverage on info-communication technologies in various sectors [8]. Its vision was to develop technologies that allow access to information anytime and anywhere, and react according to one’s environment and experiences. Various digital healthcare trends can be applied in line with the iN2015 vision, some of which I am currently exploring.

**(i) Patient Health Records**

The potential of electronic health records to improve patient safety has been shown in pharmacovigilance studies through improving access to patients’ health information, real-time detection of adverse drug events, and automated warning alerts, among others [9]. The integration of mobile technologies and social networking sites has also led to the development of personal and personally controlled health records. In Singapore, the National Electronic Health Records system was launched in 2010, so that patients could have one consolidated ‘canopy’ record shared among different healthcare institutions. It is essential that research continues in this area in order to target the seamless integration of health records systems between hospitals and the community. My cyber-pharmacy research aims to make sense of this diverse ‘forest’ of data generated from patient health records, so that clinical practices can be improved and patient safety can be enhanced.

**(ii) Telemedicine and M-health**

Telemedicine has been explored in many chronic diseases ranging from heart and respiratory diseases, to diabetes and even chemotherapy side-effects [10-13]. The rapid growth of the mobile app industry has also shifted the healthcare paradigm towards ‘mobile health’ or ‘m-health’. Many different mobile software and apps that can model or enable patient reporting of health statuses are currently available. In Singapore, the mobile penetration rate is at 146%, suggesting an average of more than one mobile phone per person [8]. M-health systems are expected to grow more complex with time as we cater towards increased quality and functionality, integration, interoperability and a wider outreach to patients. As we move towards personalized medicine, and preventive care and monitoring, m-health research is a necessary step forwards. My cyber-pharmacy research involves developing, translating and evaluating m-health tools and apps for use in healthcare education and clinical practices by healthcare professionals, healthcare students and patients.

**(iii) Digital and Social Media**

The social media revolution, spearheaded by various forms of technology, opened up new channels for communication and learning. Media-sharing sites allowed any form of media (e.g. vidcasts and podcasts) to be posted almost instantaneously on the internet, thereby reaching a wide target audience. Social networking sites also gained rapid popularity worldwide. In fact, Singapore was the top country whereby people spent most of their time on Facebook, overtaking the UK (top 4th) and US (top 5th) [14]. The uniqueness of these channels was their openness and ability for two-way exchange of user-generated content, communication and collaboration. Therefore, these channels have been leveraged upon by various organizations for health promotion, patient and practitioner education, and community outreach. Furthermore, many medical wikis have sprung up following the popularity of Wikipedia (e.g. Ganfyd.org, RxWiki.com, AskDrWiki.com, Medpedia.com). Wikis targeting molecular biology have been developed in the quest for personalized medicine [15, 16]. The quality of these channels in terms of content accuracy, reliability and biasness can pose potential risks and compromise the safety of patients should they follow the medical advice or drug therapy proposed. My cyber-pharmacy research focuses on quality evaluations of health-related and drug-related content in these channels, so as to minimize medical errors and enhance their robustness. This is a necessary step towards improving patient care and safety.

**(iv) Virtual games and social worlds**

Serious games, the use of gaming for health-related purposes, allow players to react and interact with the games so that they can manage their own health. Studies have shown that gaming is popular among adults, and they target people from all walks of life [17]. Gaming systems, such as the Nintendo Wii, PlayStation and Xbox Kinect, can provide social and interactive experiences for patients and healthcare students. The use of avatars also enables virtual interactions and collaborations with others. The Singapore government is encouraging game development and research for the benefit of patients and healthcare students. The provision of interactive, stimulating and immersive environments will not only enhance patient-practitioner communication, but also benefit healthcare students by training them to think critically and analyze situations before entering clinical practice. My cyber-pharmacy work explores the use of these systems for healthcare education, monitoring of patients with chronic diseases and improving their quality of life.

**Strategy to Engage the Future of Patient Care**

The innovation process for digital healthcare technologies exists as an iterative cycle comprising of 5 main processes (Figure 3). My work has also defined the Four Pharmaco-cybernetic Maxims (in terms of quality, quantity, relationship and manner of drug-related content) that designers and developers of pharmaco-informatics tools are encouraged to follow [3]. As a ‘cybernetic pharmacist’ or ‘cyber-pharmacist’, my interdisciplinary nature enables me to participate and fit into any stage of the digital healthcare innovation cycle. Therefore, my research aims to translate the development of pharmaco-informatics tools and applications to healthcare practices, so that the flow of drug-related information and knowledge between the user (i.e. healthcare professional and/
or patient) and the systems, tools or environment is enhanced to ultimately improve the pharmaceutical care in patients.

Figure 3. The digital healthcare innovation cycle.

References


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Introduction

Condensed matter physics is a branch of physics that deals with the physical properties of phases of matter, such as solids and liquids. A physical property of central importance is the electrical conductivity. We distinguish solid materials according to their ability to conduct electricity and classify them as metals, semi-conductors or insulators. The basic concepts of understanding why some materials are metals, and others are insulators, have been developed nearly 100 years ago [1], but scientific progress offers some surprises: there are electrically conducting ceramic compounds [2], typically classical insulators [3]. There is a new class of materials which conduct only at the surface, but the bulk material constitutes an insulator. And there are low dimensional systems which display electrical conductance in a quantized manner. Low dimensional electronic systems include the recently discovered free-standing membranes, such as graphene and transition metal dichalcogenides [4].

All the above mentioned materials cannot be understood within the simple textbook theory. Many of the strange effects have their origin in electronic interactions or a reduction in spatial dimension, or both.

Electronic interactions

What do we mean by electronic interactions? And what do we mean with low dimensional systems? Let’s start with the interactions. We all know that electrons carry electrical charge. Actually, this refers to the ancient Greek word for amber, ‘electron’ (known to produce electrostatic effects). Surprisingly, the basic properties exhibited by many metals can be explained by electrons “without” charge. What does this mean? Well, it means that an electron does not feel electrostatic repulsion from the other electrons in the metal. How can that be? Firstly, we have to acknowledge the fact that in a metal there are negatively charged electrons, but also positively charged nuclei. And these charges balance out (screen) the electro-static effects between electrons very efficiently.

Secondly, electrons move so quickly and with sufficiently high kinetic energy that we can often neglect the remaining electrostatic interactions. Besides the direct electrostatic interactions, there are additional and more complex contributions to electronic interactions, in particular the so-called exchange interaction which is a truly quantum mechanical phenomenon [1].

Tuning interactions

An interesting aspect is whether it is possible to tune the strength of the interactions in a given material. Following the above argument we may suspect that increasing the density of electrons should result in a larger contribution of electronic interactions. With a higher electron density, the electrons are pushed closer together and interactions between electrons should become more important. Surprisingly, it turns out that this is not quite true! Interactions do become stronger, but the kinetic energy increases even more. As a result the relative strength of interaction is smaller at high electron densities and conversely, interactions are actually more important at low electronic densities.
Low dimensions

Another way to increase interactions is to limit the (phase-) space of electrons and confine them to lower dimensions. In a 3-dimensional world the electrons can easily avoid each other. Let us imagine that we could confine electrons into a 1-dimensional line where the electrons can only move either to the left, or to the right. In such a 1-dimensional system left- and right-moving electrons necessarily collide: there is simply no space to avoid collision. It is possible to confine electrons in real materials into 1- or 2-dimensions in a quantum-mechanical sense and electronic interactions are indeed more prominent in such low dimensional electronic systems.

As indicated above, it is not the absolute strength of the interaction, but rather the relative strength between interaction and kinetic energy which is important. Therefore, another way to boost interactions is to reduce the kinetic energy of the electrons, in other words, to slow down the electrons. Since we are talking about electrons in a crystal this is not a trivial task, but we can employ a trick. Instead of slowing down the electrons, we just force electrons to move on a circular orbit. In a 2-dimensional system, electrons become effectively localized. This effect can be realized by the application of an external magnetic field [1].

Electron localization and the quantum Hall effects

The investigation of 2-dimensional electron systems in the presence of a strong magnetic field yielded a Nobel prize for the discovery of the integer quantum Hall effect (without interactions) and the fractional quantum Hall effect (with interactions). For a detailed understanding of the quantum Hall effects a fundamental understanding of the physics of electron localization is vital and a direct imaging technique of the localized states is desired.

It is possible to image localized states and this was first demonstrated with an experimental technique which I will introduce now also to NUS: the measurement of the local electronic compressibility using a scanning Single Electron Transistor (scanning SET). We were able to show that electrostatic Coulomb interactions play a vital role in the formation of localized states in the quantum Hall regime [5]. Furthermore, we were the first to observe the localization of composite Fermions with fractional charge in the fractional quantum Hall regime (see Figure 1) [6].

Novel 2-dimensional materials: graphene and others

Besides traditional quantum Hall systems, the scanning SET technique was also applied to investigate the novel 2-dimensional material graphene and bilayer-graphene. The electrical conductance near the charge neutrality point is strongly influenced by the presence of charge modulations which have their origin in sample imperfections. We were the first to image the charge modulations (electron-hole puddles) at the charge neutrality point of monolayer graphene and quantitatively investigated the influence of the underlying substrate (see Figure 2) [7]. Soon, it was realized that one way to produce higher quality graphene devices is to avoid having a substrate and produce suspended graphene membranes. We investigate suspended bilayer graphene and discovered an unexpected gap in the electronic band-structure which is most likely a result of electronic interactions [8].

Figure 1: Imaging localized states (LS) in the integer (left) and fractional (right) quantum Hall regime. In the integer regime each dark line corresponds to a single localized electron. In the fractional regime we identify three times more LS: the localization of composite fermions which carry only 1/3 of an electron charge.

Figure 2: Imaging of density modulations near the Dirac point of graphene. The formation of electron and hole puddles has important consequences on the electrical transport properties of graphene.

Outlook

I will continue to work with graphene-related materials, and plan to investigate other layered materials such as the transition metal di-chalcogeneides. These novel 2-dimensional materials allow new questions to be addressed such as what are the effects of mechanical deformation, chemical modification and electronic interactions on the electronic band-structure. A different class of materials are 2-dimensional electronic systems which exist at the interfaces of oxides. These compounds have a very rich electronic phase diagram and the scanning SET promises to produce new insights into the microscopic understanding of these unusual...
2-dimensional interacting systems. I am looking forward to start new collaborations, ranging from the development of new materials and devices, to the theoretical understanding of the experimental results.

References


**Academic Profile**
Dr Esther Woon received her Ph.D. in Medicinal Chemistry from the University of Bath, Department of Pharmacy in 2004. She then received an AICR postdoctoral fellowship to study the mechanism and inhibition of protein-protein interaction at the School of Pharmacy, University College London. In 2008, she was awarded a European Union postdoctoral fellowship to work on epigenetic probe discovery at the University of Oxford, Department of Chemistry. She joined the Department of Pharmacy at the National University of Singapore in 2011.

**Research Interests**
- Epigenetics Probe Discovery
- Dynamic Combinatorial Chemistry
- Obesity and Metabolic Diseases

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**Epigenetics**

The human body contains millions of cells; remarkably, all of them, with the exception of the reproductive cells and red blood cells, have exactly the same DNA content and the same DNA sequence in spite of their different functionalities. This is puzzling because it is immediately apparent that a neuron looks and functions very differently from that of say, a liver cell. So, what is going on? It is increasingly clear that, beyond the inheritance of ‘AGCT’ DNA sequence, there is another level of genetic control. Both the DNA itself, and the histone proteins, can be chemically modified. This controls whether a particular gene gets switched on or off, which in turn affects the behavior of the cell. The study of how these chemical modifications occurs, as a result of an interaction with the diet, environment and lifestyle, to bring about gene regulation is known as epigenetics [1]. My research focused on developing small molecule probe for a key family of chromatin modifying enzymes - the JmjC histone demethylases (see Figure 1). Although many advances have been made in understanding these enzymes, they remain elusive, with no defined physiological substrates and functions. Recently, several of these enzymes have been suggested as potential therapeutic targets for cancers, obesity, inflammatory disorders, and neurodegenerative disorders.

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![Figure 1: The JmjC histone demethylases. Reactions catalyzed by JmjC enzymes and members of the 5 assigned subfamilies of human JmjC enzymes.](image-url)
The research question that we focus on is whether it is possible to selectively inhibit a specific member of this large family of about 20 enzymes. This is challenging as most of the enzymes share remarkably similar structures, especially within the catalytic domain. Answering this question will have significant implications on whether they can be potential therapeutic targets. The discovery of small molecule probes will also provide us with the chemical tool to help us understand the epigenetic basis of diseases.

**Dynamic Combinatorial Mass Spectrometry (DCMS) and Probe Discovery**

In this work, we applied a novel lead discovery strategy, known as “Dynamic Combinatorial Mass Spectrometry (DCMS)”, which combines the permutation power of dynamic combinatorial chemistry and the sensitivity of mass spectrometric detection [2-4]. Conventional approach relies on high throughput screen of millions of compounds. The identified hits will then be optimised through medicinal chemistry efforts. This is highly intensive on resources and is not feasible for most academic labs. In the disulphide-based DCMS technique, a ‘support-ligand’ that binds to the active site and which contains a thiol side chain is allowed to react reversibly (either at the active site or in solution) with a set of thiols to form a mixture of disulfides. We then use non-denaturing electrospray ionisation mass spectrometry (ESI-MS) to analyse the protein-disulfide complexes and to identify those disulfides which bind preferentially to the enzyme. This strategy enables the rapid identification of lead compounds, and has the advantage of being applicable to proteins with unknown substrate (see Figure 2).

This technique has led to the first report of several highly potent and isoform-selective inhibitors of JmjC histone demethylases [2, 5-10], nucleic acid demethylases [3] and other Fe(II)- and 2-oxoglutarate-dependent oxygenases [4, 11,12]. Importantly, through this work, detailed structural information is now available (see Figure 3). A challenge will be to use this strategy to develop selective probes against all other members of the JmjC subfamilies.
References


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