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Introduction

One of the central problems in science is the management of uncertainties. From engineering applications such as communication and aerospace navigation to more civilian ones such as finance and weather forecast, noise pervades one’s knowledge and must be taken into account to make the best use of the knowledge. Estimation and control theory is the science that addresses this fundamental issue; simply put, it is the science of making good judgments and decisions in the midst of uncertainties. The theory has been tremendously successful in multiple scientific disciplines, but has primarily been applied to big things, such as vehicle control or the stock market. With the advent of nanotechnology, the future of physics and engineering lies in the nanoscopic world, which is governed by the weird laws of quantum mechanics, of which uncertainty is a hallmark. Classical estimation and control theory no longer suffices; one needs a quantum estimation and control theory to deal with quantum noise.

Bayesian Quantum Estimation

A more immediate application of quantum estimation and control theory is quantum sensing, such as gravitational-wave detection, optomechanical force detection (Fig. 1), optical interferometry, and atomic magnetometry, where experiments have demonstrated quantum behavior in the sensors. In recent papers, I have shown how Bayesian estimation and detection techniques can be used to extract useful information from noisy measurements of quantum sensing systems [1, 2]. The classical versions of such techniques have been known in engineering for decades and extensively employed in vehicle control and communication applications, but they must be generalized for quantum applications. Combining quantum measurement theory and stochastic filtering theory, I have proposed a quantum waveform estimation method called quantum smoothing [1] and a quantum hypothesis-testing technique that enables one to compute the likelihood of a hypothesis in a quantum experiment [2]. The quantum smoothing technique was recently demonstrated experimentally by an Australian-Japanese collaboration in an optical phase-locked loop setup [3].

Figure 1: A basic optomechanical force sensor model. An unknown force or gravitational wave $x(t)$ acts on a moving mirror with varying position $q(t)$. The mirror forms part of an optical cavity probed by a continuous laser beam $A_{\text{in}}$. The output beam $A_{\text{out}}$ is measured to infer information about the force. Both the mirror and the optical beam should be modeled as quantum objects in future sensors.
Quantum Noise Control

Bayesian techniques provide the best guess of a signal for a given quantum sensor, but can one actively control and reduce the quantum noise to further improve the sensing performance? The answer is yes, and we have shown how one can apply the same noise cancellation principle widely used in acoustic noise control to cancel excess quantum noise in an optomechanical force sensor [4]. Classical noise cancellation uses the effect of destructive interference to cancel noise. For example, noise-cancellation headphones work by recording the ambient noise using a microphone, then playing it back with opposite amplitude to destructively interfere with the noise reaching the inside of the ear. In the quantum case, we use the same principle of destructive interference. The excess quantum noise of interest is the quantum measurement back-action noise due to radiation-pressure fluctuations in an opto-mechanical sensor. The trick we propose to remove this noise is to introduce another path, which we call the anti-noise path, from the noise source to the sensor output that destructively interferes with the original path. The anti-noise path can be implemented by strategically incorporating more optical components in the sensor. A proposed noise cancellation setup is shown in Fig. 2. We have also recently generalized this noise cancellation technique for arbitrary quantum systems [5].

Figure 2: An optical setup for quantum optomechanical noise cancellation using standard optical components, such as beam splitters (BS) and optical parametric amplifiers (OPA) [4].

Quantum Imaging

Imaging is another important example of sensing. It is now known that a special type of entangled photons can form images with resolution far exceeding the classical Rayleigh-Abbe limit via multi-photon absorption, but it is difficult to produce such photons in sufficient quantities for applications and equally hard to detect them efficiently [6]. As I have discovered, the multi-photon absorption rate for such entangled photons turns out to be substantially worse than the rate for classical photons [7, 8], precisely due to the same quantum entanglement property that enables the photons to form super-resolution images. Fortunately, I have found a much more efficient detection method that involves the use of a photon-counting detector array, such as a CCD camera, followed by post-processing of the images [9]. This technique was recently demonstrated by Robert Boyd’s group at the University of Rochester [10]. In a more recent work, quantum mechanics is also found to play a fundamental role in the measurement techniques of stellar interferometry [11], as shown in Fig. 3.

Figure 3: (a) A stellar interferometer that combines the light collected at two telescopes coherently using a beam splitter before measurement. (b) A different setup that performs separate measurements at the telescopes first before combining the results. It turns out that method (a), which maintains quantum coherence in the measurement, is fundamentally superior to method (b) according to quantum mechanics. This is a signature of quantum nonlocality [11].

Fundamental Quantum Limits

The study of quantum sensors has motivated the question of whether quantum mechanics imposes fundamental limits to the accuracy of sensors. To bridge the gap between the toy models widely adopted in quantum information science and the more realistic quantum sensors, we have generalized a quantum version of the celebrated Cramér-Rao bound to the case of waveform estimation [12], such that it is applicable to optomechanical force and gravitational-wave sensing and magnetometry. For the purpose of waveform detection, we have also recently discovered fundamental quantum limits to the detection errors [13]. These studies resolve a long-standing problem in quantum measurement theory regarding the existence of fundamental quantum limits to waveform sensing and are envisioned to influence the design of all future quantum sensors. One shortcoming of the quantum Cramér-Rao bound is that, like its classical counterpart, it can grossly underestimate the achievable estimation error. I have recently discovered an alternative called the quantum Ziv-Zakai bound [14], which can improve upon the Cramér-Rao bound by orders of magnitude and offer a much better prediction of the realizable performance of a quantum sensor.

Outlook

The central goal of my research at NUS is to establish quantum estimation and control as a relevant engineering discipline. Many believe that we are at the dawn of a
second quantum revolution, which will be responsible for key technological advances in sensing, communication, and computing. For that to happen, practical applications and implementations should not be afterthoughts but at the forefront of our concerns. By applying engineering methodologies to quantum research, not only will we bring quantum technology closer to reality, we might just be able to discover new insights in fundamental physics and solve some age-old physics problems as well.

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References


The search for new Mathematical axioms

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Introduction

Mathematicians prove theorems. But what does it mean to prove a theorem? The way it is commonly understood in Mathematics, it means to deduce a proposition expressed in a certain language from a set of axioms using a fixed collection of inference rules. This has been the ideal of Mathematics at least since the time of Euclid, though it was not always expressed in these terms. This formulation immediately raises the issue of how a proposition is recognized as an axiom. Traditionally axioms have been thought of as propositions that "neither need nor admit of proof". However, perceptions about which propositions need proof have changed through history. To take a famous example, Euclid considered his fifth postulate to be an axiom. In two dimensional geometry the fifth postulate says that given a line L and point p not on L, there exists exactly one line through p that does not intersect L. But mathematicians after Euclid thought that this needed proof, and many attempts were made to prove this from Euclid’s other axioms. With the recognition of non-Euclidean geometries in the nineteenth century, it became clear that the fifth postulate was indeed independent of Euclid’s other axioms; that is, it cannot be proved from his other axioms.

Figure 1: The Poincaré disk consists of the Points in the interior of the circle \( C \). The "line through P and Q" and the "line through A and B" are shown. Note that the Points on the circle \( C \) represent infinity, so neither "line" has any endpoints.

At this point, you may object that when Euclid set down his axioms he had in mind a certain meaning for the words "point" and "line", and this is not what he meant. To be sure, Euclid did not have the Poincaré Disk in mind. However, the words "point" and "line" occur as primitive undefined terms in Euclid’s axioms, and if all you have told me about points and lines are Euclid’s first four axioms, then I am free to interpret these terms any way I want, as long as the four things you have told me about them come out true under my interpretation.
Or to put it another way, if all you know about points and lines are the first four axioms, then you do not know enough to be able to distinguish between the usual "flat" two dimensional space and the Poincaré Disk, and the existence of these two interpretations shows that the fifth postulate is independent of the other four because it holds in the usual interpretation while failing in the alternative one.

The above discussion raises an important point about the language in which mathematical propositions are expressed. This language has varied from time to time. For Euclid this language was Greek. No matter what this language is, it always contains some primitive undefined terms. The mathematician who uses these terms may have a certain picture of what they represent in his or her mind, but while proving a theorem only the information that is declared in the axioms may be used. The language of modern mathematics is an extremely precise and wholly artificial language in which only a small number of primitive terms occur. In fact, apart from some logical terms connected with reasoning in general, only one primitive term occurs: the notion of a set. The rules for forming a meaningful sentence in this language are so precise, the axioms governing the usage of the primitive terms are so easy to list, and the rules of inference sufficiently well-defined, that it is possible for a computer program to recognize when a certain string of symbols is a meaningful sentence in this language, and when a sequence of such sentences constitutes a proof. Needless to say, mathematicians do not think in terms of this artificial language, but all theorems and proofs can, at least in principle, be translated into it.

**Notion of a Set**

Why did modern mathematics evolve such an artificial language and what is the notion of a set? This is a complex story, but a very brief outline is as follows. In the nineteenth century several mathematicians felt a need for greater rigour in dealing with the concepts of calculus such as the concept of a limit, which till then were based on geometric intuition. This led them to redefine these notions in terms of just real numbers and operations performed on them. Then real numbers were reduced to the rational numbers, which in turn were reduced to the familiar natural numbers of arithmetic. This trend went hand in hand with two other trends. The first was an expansion in the sense of the term "function". Functions, which had initially denoted certain mathematical expressions, came to denote arbitrary correspondences. This led Frege to think of predicates and relations as functions that map objects to truth values. For example, he thought of the relation "is the father of" as a function whose arguments are a pair of objects $x$ and $y$ and it returns the value "true" if $x$ is the father of $y$ and the value "false" otherwise. Other functions could then be defined that took such functions as their arguments, and this process could be iterated. He built an artificial language using such functions and showed that this language was very useful for formalizing mathematical proofs. The second closely related trend was the study of arbitrary collections or sets of objects (usually mathematical objects such as real numbers), without any fundamental distinction being made between finite and infinite collections. This was initiated by Cantor, who showed that there were different kinds of infinite collections – some infinities were much bigger than others.

This trend towards studying arbitrary functions and sets eventually led to some paradoxes that resulted when certain sets with self-referential definitions were considered. To give a simple illustration of these paradoxes, suppose that there is a town in which there is a barber, who is male, and he shaves all and only those men in the town who do not shave themselves. Does the barber shave himself? By our hypothesis he shaves himself if and only if he does not. So such a barber simply cannot exist. Similarly it was realized that sets with such self-referential definitions cannot exist either, and axioms specifying exactly what kinds of sets exist were drawn up. Thus was born the axiom system known as ZFC, which is expressed in the artificial language referred to above. The axioms of ZFC provide all the information about sets that is relevant to mathematics, including information about what sets exist. All theorems proved by mathematicians today can be translated into the language of ZFC and proved from its axioms.

**ZFC Axiom System**

But is it the case that the axioms of ZFC can, at least in principle, be used to settle all mathematical questions? The answer is no, and in fact this answer is not unique to ZFC. In the 1930 Gödel proved that there there are propositions in the language of ZFC that are independent of the axioms of ZFC. That is, there are sentences in the language of ZFC that stand in the same relation to its axioms as Euclid’s fifth postulate stands in relation to his other four – these sentences can neither be proved nor disproved using the axioms of ZFC. So for any one of these independent sentences, there exist two different interpretations of the term "set", one in which the sentence is true and another one in which the sentence is false, even though all the axioms of ZFC hold under both interpretations. All of the techniques of modern mathematics can be implemented with ZFC; therefore these independent sentences express mathematical questions that cannot be resolved using any mathematical technique, unless of course, one is willing to accept new axioms. It is worth noting that this predicament is not unique to ZFC or to the concept of "set". Gödel showed that for any axiom system that is powerful enough for the development of modern mathematics and whose axioms are simple to list, there will be sentences in the language of that axiom system that are independent of it, and this is regardless of the primitive concepts used.

A large part of modern set theory is devoted to constructing various different interpretations of the term "set". Just as the

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1. For more on non-Euclidean geometries see [1]. You may also wish to google "Escher’s Circle Limit ".
2. Technically, it is the relation of set membership.
3. Consult [2] for the original sources relating to the development of the artificial language in which ZFC is expressed, for the development of the set concept, and for the evolution of the axioms of ZFC.
4. Gödel's original papers are in [2].
interpretations of the terms "point" and "line" were carefully constructed in the Poincaré Disk example to ensure that Euclid’s first four postulates were true, these interpretations of "set" are carefully constructed to ensure that the axioms of ZFC are all true. Such an interpretation is known as a model of ZFC. Now, given a mathematical sentence, if there is a model of ZFC in which that sentence is true and also a model where it is false, then the question of whether that sentence is true cannot be answered by usual mathematical techniques. One of the aims of investigating models of ZFC is this kind of delimitation of possibilities. It is worth noting here that these models are constructed using tools available in ZFC (this is similar to the Poincaré Disk being defined using Euclidean circles). So this is an exploration of the limits of mathematics from within itself. Another aim of this study is to discover new possible axioms. The traditional view of axioms was that they have to be self-evident. However, we may also discover sentences independent of ZFC, which when added as new axioms give such a coherent and appealing picture of some class of mathematical structures that we are tempted to enlarge ZFC in that direction. In fact, two distinct types of such sentences have been recognized over the last several decades of research. The first class may be called "minimality hypotheses". Very roughly, they say that the universe of sets is as thin as possible. The picture they present of certain infinite combinatorial structures is one of "non—structure", meaning that they imply that such combinatorial structures are disparate and impossible to classify. The other class of sentences are collectively known as "forcing axioms". Very roughly, they say that the universe of sets is as wide as possible. They tend to imply that a structure theory exists for several classes of combinatorial structures, meaning that the objects in these classes are not so diverse and must belong to one of a small number of types. Another aim of studying models of ZFC is to discover new theorems of ZFC. Sometimes showing that a statement is independent of ZFC can suggest candidates for new theorems and can provide hints as to what techniques to use for proving them. In [4] Shelah calls this the "Rubble Removal Thesis": after the independent statements are cleared away, we may be left with unexpected theorems.

In my own work, I have made small contributions to this ongoing study of models of ZFC. To illustrate, in [5] a limit on possibilities is set by showing that the existence of a certain set of real numbers is independent of ZFC. In [6], I have studied the consequences of some forcing axioms. In [7], I prove a theorem of ZFC, which could have been discovered classically, but was found only after several independence results in its vicinity were proved, and its proof uses techniques that are reminiscent of independence proofs.

5. There is a technical issue that is being swept under the rug here. Strictly speaking, it is not possible to construct a model of ZFC within ZFC, but only models of arbitrarily large finite fragments of it. This turns out to be good enough.

6. For more on forcing axioms and structure theorems for classes of combinatorial structures, see [3].
Electrocatalysis for Sustainable Energy Conversion Reactions

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Introduction

More than 85% of the world’s energy needs are met by burning fossil fuels such as oil or natural gas. The supply of these fuels is intrinsically limited and will eventually run out. Combustion of fossil fuels also generates carbon dioxide (CO\(_2\)), a suspected accelerant of global warming. Nitric and sulfur oxides are similarly emitted and these react with water molecules in the atmosphere to give acid rain. A one-step solution for solving these problems is to recycle the emitted CO\(_2\) into hydrocarbon fuels such as methane (CH\(_4\)) and methanol (CH\(_3\)OH). This is one of the most important scientific challenges for the 21st century, and is also a long-standing dream of the energy industries [1]. The key advantage of this approach is that hydrocarbon fuels are already the backbone of our energy infrastructure. Hence, our existing gasoline-powered machines do not need to be extensively modified. Moreover, these fuels can be stored and transported conveniently.

Devices to accomplish CO\(_2\) reduction in a sustainable way have been proposed, one of which is depicted in Figure 1. A light absorber such as a semiconductor first produces electrons (electrical charges) using solar energy. The electrons are transported to the electrocatalysts (red balls) where they serve to reduce CO\(_2\) and H\(^+\) to CH\(_4\) and/or CH\(_3\)OH. Alternatively, H\(_2\)O itself could be reduced to H\(_2\) gas fuel. The oxidation of H\(_2\)O to O\(_2\), or oxygen evolution reaction (OER, 2H\(_2\)O → O\(_2\) + 4H\(^+\) + 4e\(^-\)) at the anode (green balls) generates electrons for the reduction reactions. As long as there is sunshine, water and CO\(_2\), the device will produce the required hydrocarbon fuels. The workings of such a system mimics that of a leaf, which is the reason for it being termed artificial photosynthesis.

The electrocatalysts on the anode and cathode form the heart of such a device. Catalysts are materials that can lower the activation barrier of chemical reactions, without being chemically or physically altered in the process. In this article, we shall review our work on developing efficient catalysts for the oxygen evolution reaction.

Figure 1: The scheme of a device for producing solar fuels using CO\(_2\), H\(_2\)O and solar energy.
Understanding the Mechanism of the Oxygen Evolution Reaction

The oxygen evolution reaction is an inefficient process. To obtain a reasonable Faradaic current of ~10 mA/per cm² of catalyst surface, an overpotential of a few hundred millivolts (mV) is required. For this reason, much effort has been devoted to understanding and improving OER catalysts.

The chemical intermediates formed during the oxidation of H₂O to O₂ have never been clearly identified in experiments. As such, it is difficult to determine the elementary processes contributing to OER overpotential and their relationship to the anode composition and morphology. We embarked on an in-situ Raman spectroscopy experiment to identify intermediates formed during water oxidation on gold [2]. Gold, rather than a more active catalyst such as iridium, was chosen for investigation because it is an excellent surface-enhanced Raman spectroscopy (SERS) substrate.

We have ascertained that hydroperoxy (O-OH) intermediates were formed during OER, as indicated by its O-O stretching vibration at 820 cm⁻¹ in the Raman spectrum (Figure 2). This band only appears at the onset of oxygen evolution ≥1.4 V (vs. Ag/AgCl reference). Moreover, its frequency shifts in the correct range (+2 cm⁻¹) when the H in O-OH is replaced with D. This is the first report identifying intermediates of OER, and will contribute significantly towards the understanding of the elementary processes involved in the process.

Developing Efficient Electrocatalysts for the Oxygen Evolution Reaction

The oxides of ruthenium and iridium are the best materials for catalyzing OER. However, these metals are also the rarest elements on earth and, hence, are not practical to use for large-scale applications. Cheaper alternatives are needed. Cobalt is an earth-abundant metal, but it is a less optimal catalyst. Previous studies have suggested that the efficiency of cobalt oxide as an OER catalyst could be enhanced by increasing the population of Co⁴⁺ centers present at the oxide surface [3]. We hypothesize that a way to achieve this goal would be to deposit a thin layer of cobalt oxide on the surface of a highly electronegative support such as gold (which has the highest Pauling electronegativity of all the metals. Example: 2.54 for Au, 1.88 for Co).

To test out this hypothesis, we measured the efficiency of oxygen evolution catalyzed by Co oxide deposited onto the surface of Au (Figure 3) [4]. In itself, pure Au is a weak OER catalyst. However, the net OER activity of ~0.4 monolayer of Co oxide deposited on Au is forty times higher than that of the bulk oxide! As the thickness of Co oxide on Au increases, the OER activity decreases until it approaches that of bulk Co oxide. This phenomenon shows that Au is playing an active role in enhancing the activity of Co oxide at its interface (Figure 3). To verify the effect of the support, Co oxide was also deposited onto Cu, Co, Pd and Pt substrates. The OER activity of a sub-monolayer of Co oxide decreases in the order of Au > Pt > Pd > Cu > Co, which scales approximately with decreasing electronegativity of the substrate. For comparison, OER experiments were also carried out with a bulk Ir electrode. Under equivalent electrochemical conditions, the CoOx/Au system is roughly three times more active than that of Ir!

Figure 2: (a) Sequence of SER spectra recorded from a Au electrode in 1 M HClO₄ during a linear sweep voltammetry scan from 1.0 to 1.65 V. (b) Blowup of the spectra taken at 1.0 and 1.4 V. Representation of the surface-bound OOH is shown in the accompanying cartoon. (c) Current –potential curve measured during the linear sweep voltammetry. Reprinted with permission from [2].

Figure 3: (a) Linear sweep voltammetry curves of the ~0.4 ML cobalt oxide /Au system, pure Au and pure Co electrodes in 0.1 M KOH. (b) A plot of turnover frequencies (TOF) of the different Co oxide/Au electrodes (evaluated at 700 mV) vs. the number of monolayers of Co oxide present. The TOFs for pure Co and Au are also included in this plot.

We attribute the enhancement in OER activity of Co oxide deposited on Au to an increase in surface Co⁴⁺ population. This is likely mediated by the highly electronegative Au support. Our conclusion is supported by the in-situ Raman spectra of Co oxide supported on Au, which show vibrational frequencies...
resembling that of $\text{Co}^{\text{IV}}$-O species. Our work provides the first systematic study of how metals can be used to enhance the activity of metal oxide for the electrochemical evolution of oxygen.

Quantum chemical simulations and in-situ X-ray absorption spectroscopy would further aid our understanding of the interaction between Au and Co oxide. A whole suite of imaging techniques such as tip-enhanced Raman spectroscopy has also been developed over the years to map out the chemical content of surfaces with nanometer spatial resolution [5]. These methods, when used in tandem, will give us a more holistic picture of the exciting chemistry taking place, and guide our efforts to develop better OER electrocatalysts.

**References**


Dissecting the Morphological Pathways of Endocytosis

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Endocytosis process

What distinguishes living organisms from the test tube reactions is that reactions occurring in living organisms are highly compartmentalized. This is achieved by the encapsulation of cellular contents via the formation of lipid-bound structures. In eukaryotic cells, such structures include the plasma membrane, various organelles and intermediate membrane carriers. Membrane compartmentalization, together with lateral membrane segregation, gives rise to the spatial localizations of numerous cellular signalling events and greatly enhances the complexity of the overall signal transduction scheme. At the same time, membrane compartments are dynamically shaped and maintained by the collective protein-lipid interactions.

We are very interested in the molecular mechanisms regulating the plasma membrane identity and homeostasis, in particular, the process of endocytosis, the inward traffic from the plasma membrane.

During endocytosis, a small invagination can be formed (i.e. budding) and eventually pinched off (i.e. fission), leading to the uptake of the ligands that are bound to the surface receptors on the plasma membranes, a portion of the membrane itself together with some extracellular fluids [1]. Biochemical and genetic studies have implicated the involvement of a large set of molecular players in this seemingly simple process [2, 3]. In the past two decades, a lot of efforts have been invested in characterizing various components that make up the endocytic machinery. Optimal execution of the endocytic reaction likely relies on synergistic interaction of many factors because an emerging theme seems to be that perturbation of an individual component often leads to defects in endocytosis, but rarely abolishes it completely. This apparent lack of linearity in the endocytic pathway may reflect the redundancies among accessory factors, but it might also be an indication of endocytosis as a versatile and plastic process whose organizational principles have yet to be established.

We are interested in using a reconstitution approach to advance our mechanistic understandings of this process because the best way to understand how something works is to break it apart and then to put it back together. Cell-free system was chosen because it can potentially bridge a gap between over-simplified in vitro systems and living systems (Fig. 1). To visualize the cell-free reaction in time and at single vesicle level, we developed a planar membrane-based assay that can reconstitute the complete flow of events [4]. Although a single endocytic event likely involves hundreds of proteins, it all happens on the scale of tens to hundreds of nanometers, well below what can be seen by conventional light microscopy. Therefore, we have employed many

Figure 1: Cell-free reconstitution fills the gap between in vitro systems and in vivo systems.
Endocytosis is indispensable for many housekeeping functions that are general and fundamental in all eukaryotic cells, such as nutrient uptake, receptor and membrane turnover. By adjusting the extent and content of internalization process, it essentially controls the lipid and protein compositions of the plasma membrane and plays a master regulatory role in diverse cellular processes including growth, proliferation, migration, polarity and cell-cell communication. The mechanism underlying the modulation of endocytic activity is very poorly defined. Better understandings of the membrane morphological pathways and the molecular determinants of the switches between pathways are required to delineate the complex reaction. Not surprisingly, defects in endocytosis are linked to serious medical consequences, such as cancer, heart diseases, diabetes and neurological disorders [5].

Figure 2: Endocytic intermediates captured by cell-free assay. (a) Plasma membrane labeled GFP (PM-GFP) shows a punctate appearance due to membrane invagination. Scale bar: 5 μm. (b) Coupling of clathrin and dynamin with FBP17-coated tubule revealed by two-color 3D-STORM imaging. (c) EM image of tubular intermediate capped with clathrin-coated pit.

Figure 3: Morphological model of clathrin-mediated endocytosis and clathrin-dependent tubular endocytosis.

Outlook
Endocytosis is indispensable for many housekeeping functions that are general and fundamental in all eukaryotic cells, such as nutrient uptake, receptor and membrane turnover. By adjusting the extent and content of internalization process, it essentially controls the lipid and protein compositions of the plasma membrane and plays a master regulatory role in diverse cellular processes including growth, proliferation, migration, polarity and cell-cell communication. The mechanism underlying the modulation of endocytic activity is very poorly defined. Better understandings of the membrane morphological pathways and the molecular determinants of the switches between pathways are required to delineate the complex reaction. Not surprisingly, defects in endocytosis are linked to serious medical consequences, such as cancer, heart diseases, diabetes and neurological disorders [5].

References
Designer Small Molecules

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Introduction

Life as we know it functions as a result of a complex interplay of processes that is controlled by organic molecules. At the fundamental level, these molecules are responsible for the regulation and survival of organisms. Although organic molecules can be large complex structures, surprisingly small molecules play important roles in matters of life and death. Small molecules are defined as organic substances of low molecular weights with an upper limit of 800 Daltons. Small molecules can have a variety of biological functions, from cell signaling to chemical defense. It is thus not surprising that scientists have been fascinated with the idea of using small molecules to advance the quality of life and to understand how nature functions. These small molecules can either be derived from nature (natural products) or are man-made (synthetic).

Drug discovery and medicinal chemistry

One of our targeted areas of interest is in the area of drug discovery and medicinal chemistry where ‘lead’ compounds are designed and synthesized to function as potent small molecules that could halt or slow down specific diseases. An example of one such research that shows much promise is in the development of cancer chemotherapeutics. Cancer is a complex multifactorial disease – one of the hallmarks of cancer cells is their ability to gain survival advantage over normal cells. Despite the advances in chemotherapeutic drugs, cancers cells are hard to kill because of their enhanced resistance to apoptosis signaling. The Bcl-2-family of proteins constitutes the molecular gateway to the execution step of cell death (apoptosis) signaling. Pro-survival and pro-death proteins regulate the sensitivity of individual cells to apoptosis signaling and in cancers, certain pro-survival Bcl-2 proteins are over-expressed, thus tipping the balance towards survival of cancer cells. The therapeutic modulation of the Bcl-2 pathway by novel classes of cancer chemotherapeutics represents new treatment options in cancer treatment. The approach taken in our research is to inhibit the pro-survival Bcl-2 family of proteins so as to promote the death of cancer cells through programmed cell death or apoptosis[1, 2].

In recent decades, epigenetics has been...
implicated in the cause of certain diseases including cancer. Epigenetics refer to changes in the gene expression that is not related to changes in the DNA, i.e. our genetic makeup does not always control the outcome. For example, in the latter, there are proteins that are activated in response to triggers that in turn suppresses the tumour suppressor genes, leading to the onset of cancer. One such protein is known as the histone methyl transferase (HMT) and our research is targeted at making small molecules that can modulate the activity of the HMTs so as to control the proliferation of cancer cells [3].

In addition to the development of cancer chemotherapeutics, we are also interested in the design and development of small molecules as chemotherapeutics for the treatment of re-emerging tropical infectious diseases such as malaria and chikungunya. Both of these diseases are mosquito-borne and while there are treatments for malaria, the problems with resistance to these treatments have necessitated the search for alternative anti-malarials. Chikungunya virus causes Chikungunya fever (CHKIF) for which there is no specific or effective treatment. CHIKF is an acute illness with abrupt fever, skin rash, arthralgia, and occasional involvement of the nervous system, heart and liver. In recent years, CHIKF has emerged as an important viral disease in Asia and the Pacific region.

Typically, a combination of approaches is employed for the identification of promising compounds for drug development. Where a particular protein is targeted e.g. a pro-survival Bcl-2 protein, computer-aided drug design methods can be used. This utilizes knowledge of the interactions of small molecules with the protein active site to design-in chemical functionalities that would promote binding. Another approach is to consider the use of natural products as natural-products and natural-products derived and inspired compounds have traditionally been a source of new drugs. Natural products are generally complex chemical structures that can be derived from a variety of sources, e.g. plants, marine, microbial, etc. They are not easily developed as drugs as natural products are usually produced in small quantities in nature (limited in resource). In addition, the structural complexities often mean that chemical synthesis is a daunting and uneconomic task. Strategies using natural products in my group focus on identifying the minimal structural unit required for biological activity. The scaffold is then elaborated to enhance binding and impart drug-like properties to facilitate absorption and delivery. Compounds derived from this approach are known as ‘natural-product inspired’. Other approaches for hit and lead compound identification include mining the literature for biologically active scaffolds and decorating these scaffolds with functionalities to enhance their desired properties.

Small molecule anti-foulant additives

The principles of small bioactive molecule design and synthesis extend far beyond applications to drug discovery and development. We have applied similar strategies in the development of small molecule anti-foulant additives. Imodium™, a drug used for the treatment of diarrhea was shown to be effective in the prevention of barnacle settlement [4]. In collaboration with the Tropical Marine Science Institute, NUS, we chemically ‘de-engineered’ the structure to understand the structural features that give rise to the anti-settlement effects [5, 6]. These features were retained and additional groups were added to improve biodegradability. The creation should be a compound or compounds that are anti-foulant in nature, while minimizing toxicity as well as being able to degrade quickly in the waters by bacteria to yield benign byproducts. From these studies, a family of compounds possessing precisely the properties that were desired was created!
References


Estimation Stability Cross Validation

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Department of Statistics and Applied Probability

Introduction

There is an ever increasing amount of data in all fields of science and engineering. Often, this data comes in high dimensions relative to the sample size, posing a new challenge to scientists, engineers, and decision makers. These problems, plagued by the curse of dimensionality, suffer from overfitting when classical methods are applied.

Regularization methods are used to tackle this problem of overfitting head on, usually by imposing a penalty on the complexity of the solution or through early stopping. For example, in fitting the usual linear regression model, the Lasso [1] and ridge regression [2] adds a L1 and L2 penalty on the coefficient estimates respectively to the usual least squares fit objective function. Regularization methods can also take the form of early stopping iterative algorithms like classical forward selection or L2-Boosting [3].

Common to these methods is that they provide a family of possible estimators instead of just one estimator, with the unregularized solution at one end of the spectrum. This family is indexed by a regularization parameter and is commonly referred to as the solution path. For the Lasso and ridge regression, the parameter determines the extent of the respective penalties.

Regularization methods have been shown to be L2-consistent [3] and model selection consistent [7, 8, 9, 10] in the high dimensional setting when respective conditions are met. These results guarantee the existence of the λ needed, but offer little guidance on how to find the desired λ in practice.

One can rely on traditional model selection criteria like Akaike's information criterion (AIC) [11] and Bayesian information criterion (BIC) [12]. They are easy to compute but their validity rely on model assumptions. Furthermore, they are derived from asymptotic results, so even when model assumptions are satisfied, they may not work well in the finite sample case.

More commonly used today are model-free approaches like cross-validation (CV) and bootstrap methods. They have become computationally feasible for increasingly large data sets with the rapid advancements in computing power. These methods rely on data resampling to assess prediction error of candidate solutions and can be found in various statistics and machine learning literature [13, 14]. In particular, it can be used within regularization methods to select (and the corresponding estimate). Doing so often leads to estimators with good predictive performance. However, there are other performance metrics that are also of interest in statistics, among them parameter estimation losses and variable selection consistency, with important practical connections. Unsurprisingly, optimizing predictive performance does not necessarily translate to having success with respect to these other performance metrics.

Estimation Stability

Statistical estimation is random by definition: the estimate depends on the sample taken. We should hope that
our estimate does not change too much if we take a different (identically distributed) sample.

It is clear that estimation stability is a necessary property for a reasonable estimation procedure: the solution is not meaningful if it varies considerably from sample to sample. This begs the question of whether the converse is true. Are estimates that vary least most meaningful? Are statistically stable solutions automatically good? This certainly cannot be true in general: an arbitrary constant estimate will not vary but is certainly meaningless. We need an extra model fit check to validate the stable solution.

Our “Estimation Stability Cross Validation (ESCV)” criterion for selecting λ is based on estimation stability but adds a cross validation check to filter out erroneously stable solutions. We line up solution paths based on resampled data and find λ corresponding to where the different paths are most similar. We then check to make sure this selection lies before the cross validation’s choice as it is known that cross validation overselects [15].

We show that ESCV provides a viable alternative to CV and BIC. In particular, we compare the three approaches with respect to various performance metrics when applied to the Lasso on both simulated and real data sets. We find that our criterion compares favorably with CV and BIC where they are known to excel, and outperforms them in other scenarios over different performance criteria. In particular, we get excellent model selection results, both in simulations and our real data sets, where the results are validated by subject knowledge.

Related Work

Previous works based on stability of solutions have shown positive results in terms of model selection [13, 16, 17]. ESCV differs from them in two substantial ways. Firstly, we restrict our attention to selecting the regularization parameter. Even though we evaluate our choice by the performance of the corresponding solution, our focus remains on determining the right amount of regularization. Secondly, we do not introduce any further tuning parameters. Our aim is to prescribe a method for tuning regularization methods.

References

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