Faculty of Science

RESEARCH

Newsletter

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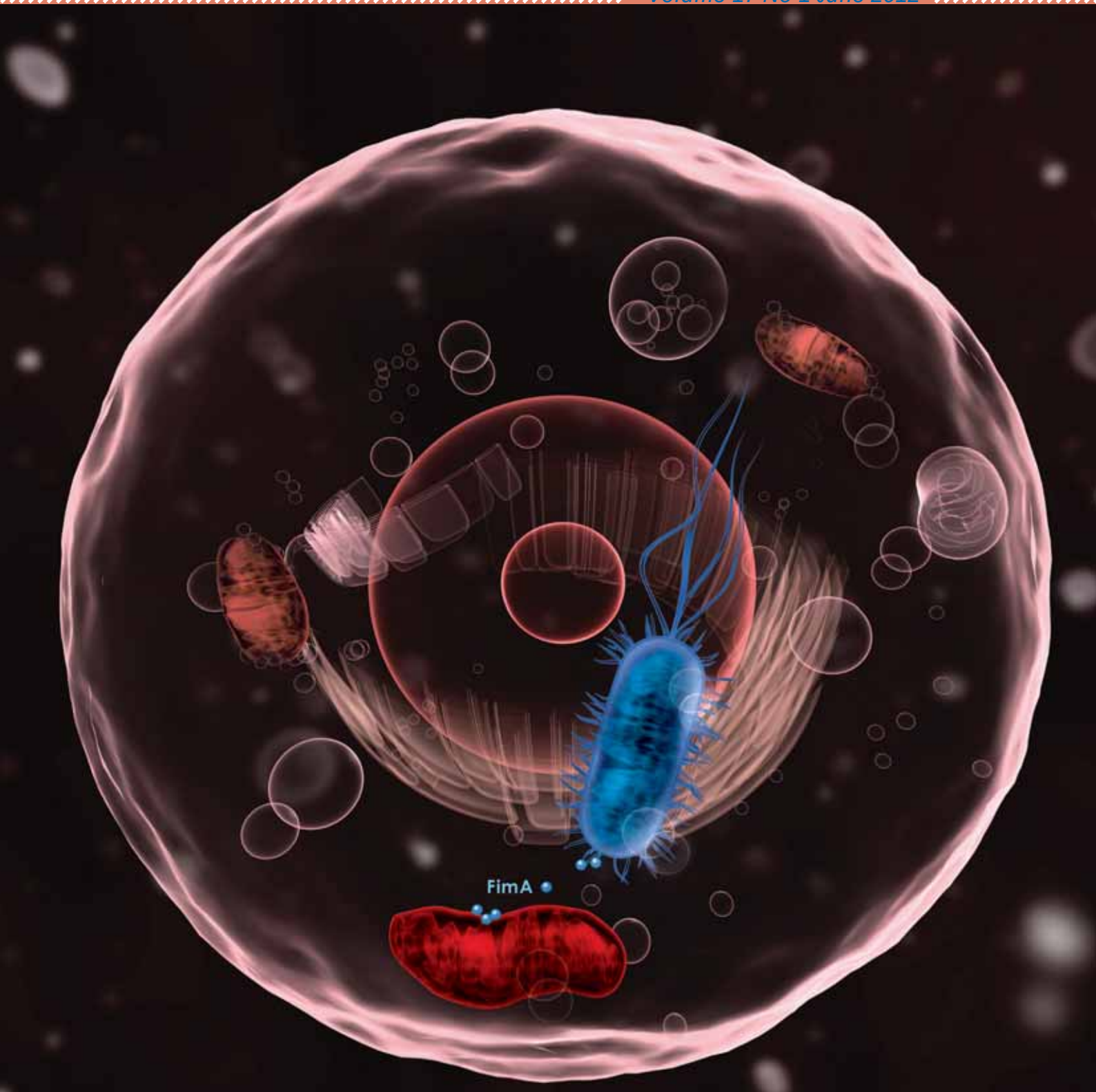

Turning off the "self-destruction" mechanism of a cell

Content

For more information on the publications, please contact Prof Loh Kian Ping (email: scilohkp@nus.edu.sg) or Mr Soh Kok Hoe (email: scisohkh@nus.edu.sg) at the Dean's Office, Faculty of Science, National University of Singapore.

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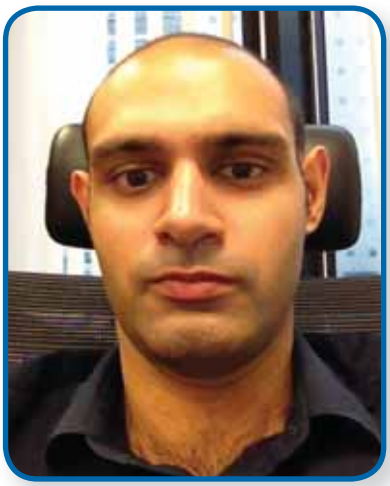
Sequential Monte Carlo Methods in High Dimensions

Assoc Prof Ajay Jasra
Department of Statistics and Applied Probability



Assoc Prof Ajay Jasra

Academic Profile:

A/P Jasra joined the Department of Statistics and Applied Probability in December 2011 as an Associate Professor. He graduated from University of Exeter (BSc, 2001), then from University of Oxford (2002, MSc) and Imperial College London (Ph.D, 2005) under the supervision of Prof. Chris Holmes and Prof. Dave Stephens. He has held a variety of post-doc positions including University of Cambridge (2006) with Prof. Arnaud Doucet, the Chapman Fellowship in Mathematics at Imperial College (2006-2008) and Institute of Statistical Mathematics Japan (2008). He joined National University of Singapore from Imperial College London where he was a tenured assistant professor in Mathematics (2008-2011).

Research Interests:

- Monte Carlo Methods
- Bayesian Statistics
- Markov Chain Theory
- Computational Finance

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Introduction

The amount of data in our world has been increasing at a rapid rate in a wide variety of applied disciplines such as in finance (the advent of high-frequency algorithmic trading) and genetics (recent experimental advances have led to vast amounts of new data-sets). As a result, analyzing large data sets is becoming a key basis of competition, supporting new waves of productivity growth and technological innovations. The primary role of many statisticians has evolved to develop advanced and often highly complex stochastic models to determine the underlying physical phenomenon in the datasets. In many of these statistical models, it is important to estimate a variety of parameters which can accurately describe the data. For example, in the financial industry, fund managers are concerned with the "price volatility" of the financial assets as it helps them allocate their investments to balance the risk level. In such scenarios, this information is obtained by evaluating an integral, or a "theoretical average", in very high-dimensional space. If a financial data set consists of only a time-series of prices, the integration task has to be carried out in as much as over 1000 dimensions to arrive at a correct estimate of the price volatility In practice to calculate this integral, the analytical value is not known due to the high-dimensional nature of the integral (i.e. one cannot simply perform mathematical calculations on a computer/by hand and obtain the answer). As a result, this has lead to a substantial literature on numerical approximation of integrals, which can be roughly divided into two main groups - stochastic methods and deterministic methods.

Methods to Handle Complex Probability Distributions

It is widely believed that stochastic numerical integration methods out-perform deterministic methods for dimensions greater than three. In general, statisticians and probabilists focus upon stochastic ideas, in particular Monte Carlo approaches. Monte Carlo methods are based on the use of random numbers and probability statistics to investigate problems, and are believed (wrongly) to always break the curse of dimensionality and accurately estimate integrals in very high-dimensions. This is true in some scenarios, but there are instances whereby the methodology has very poor performance and yields inaccurate outcomes. That is, if the dimension of the problem is d, then it is thought that the method can work well if, for some "good" behavior the cost is polynomial function of d, and work poorly if the cost is an exponential function of d. Roughly, the idea of Monte Carlo is to re-write an integral as a theoretical average of a function with respect to a probability model (this is automatic in most statistical applications as the probability model is often given by the problem of interest). Then one seeks to simulate samples from this probability distribution and approximate the integral by an average of the function, evaluated at the simulated samples. It is a standard result in probability that as the sample size increases, the approximation will converge in a probabilistic sense to the integral. Although this method provides a reasonably accurate result, a major difficulty lies in obtaining the samples. This has lead to substantial efforts from physicists, statisticians and probabilists to develop methods to sample from complex probability distributions. This includes the well-known "Markov Chain Monte Carlo" (MCMC) method [1] and the "Sequential Monte Carlo" (SMC) method [2]. The cost and accuracy of these methods in high-dimensions is one of the major research areas in the theoretical statistics and applied probability community.

In short, the use of advanced probabilistic models is often limited by a lack of adequate computational tools (or at least the understanding of these tools) for extracting information from existing data and performing inference in complex models. For example, a major bottleneck in the application

of probabilistic models to biology is that their calibration is thought to be computationally expensive. Thus, researchers often prefer to use simple summary statistics to characterize the underlying biological process; this approach is obviously unsatisfactory and caution must be exercised when drawing conclusions from it. Our research examines the computational cost of applying advanced simulation techniques, which are designed to deal with these latter complex models.

Computational Cost Considerations

As remarked above, it is important to evaluate the cost of simulation methods for statisticians. In a landmark article, Roberts et al. [3] established not only the cost, in d, of the most used MCMC method, but also some optimality results associated to it. The article showed that, using diffusion limits, the computational cost was only a polynomial function of d, although the major result of the article went far beyond this point. It should be noted that this result is within the confines of the Monte Carlo method: if the estimation of an integral is of cost that is (in some sense) an exponential function of d for Monte Carlo, it is still the case for MCMC. It is only that the cost to obtain samples is a polynomial function of d for MCMC. This is the context of all the results that we discuss below.

In many empirical studies [4], it has been found that SMC techniques out-perform MCMC methods and as yet, no study of the computational cost has been undertaken. However a distinctly negative result of Bickel et al. (2008) [5] showed that importance sampling (the basis of SMC) has an exponential cost in d, leading to many researchers avoiding SMC. It should be noted that a study of SMC in high-dimensions is important as it applies to many problems beyond MCMC (the problems discussed in this article), such as "sequential inference" (filtering). This refers to the updating of estimates as new data becomes available and is used in many real-life applications.

In his recent work, Beskos et al. [6, 7] has shown that a particular SMC method has a cost in the dimension that is only a polynomial function of d, albeit the same order as some MCMC algorithms. These are the first positive results in this area and help to confirm that SMC is a viable option in high-dimensional problems. These mathematical results also shed some light on the phenomena observed by practitioners, although their impact is much less than Roberts et al. (1997). Unfortunately, at present, they do not extend to filtering applications, and this is perhaps the major research challenge in the field: to find an SMC algorithm for filtering applications, that has a cost determined by a polynomial function of d for a wide class of problems.

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Understanding Complex Energy Landscapes and Rare Events

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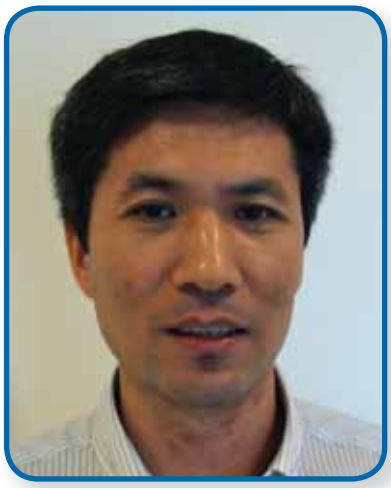

Assoc Prof Ren Weiqing

Academic Profile:

A/P Ren obtained his PhD from the Courant Institute of Mathematical Sciences at New York University in 2002. He was a member of the Institute for Advanced Study at Princeton (2002-2003) and an instructor at Princeton University (2003-2005) before joining the faculty of Courant Institute as an assistant professor in 2005. In 2011, he joined the National University of Singapore as an Associate Professor of Mathematics and the Institute of High Performance Computing as a senior scientist.

Research Interests:

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- Analysis and algorithms for multiscale problems
- Complex energy landscapes and rare events
- Multi-phase flow and moving contact lines

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Introduction

Many problems arising from applied sciences can be abstractly formulated as a system navigating over a complex energy landscape. Well-known examples include conformational changes of bio-molecules, chemical reactions, nucleation events during phase transitions, etc. The dynamics proceeds by long waiting periods around metastable states followed by sudden jumps or transitions from one state to another. These transition events happen infrequently compared with the relaxation time scale of the system. However, when they do happen, they usually happen rather quickly and have important consequences. Typically a small amount of noise is present in the system and it is this that drives these rare events. For such an event to happen, the system has to wait for a long time in metastable states until the different components of the noise work together to bring the system over some energy barrier or go through a sequence of correlated changes.

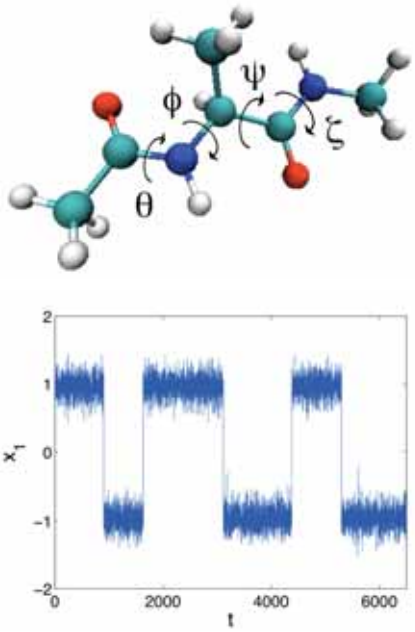

Figure 1: Alanine dipeptide (upper) and the time history of the (normalized) torsion angle (lower panel).

For illustration purposes, let us consider the dynamics of a small molecule, the alanine dipeptide, at room temperature. The molecule in vacuum has two main meta-stable configurations, which can be characterized by different values of the torsion angles along the backbone. Figure 1 shows the time history of one of the torsion angles obtained from the Langevin dynamics. It is seen that the system spends most of time in the two metastable states, with infrequent transitions (conformational changes) from one to the other.

It should be noted that the rare events that we are interested in are not really unusual. For example, conformational changes of biomolecules as in the above example usually happen on the time scale of microseconds or milliseconds. These events are rare on the time scale of molecular vibration (which is typically on the order of femtoseconds, s), but they are not rare on the time scale of our daily lives, which is often measured in minutes, hours or days. After all, all biological processes are driven by such events.

Our objective here is not to keep track of the detailed dynamics of the system but rather to capture statistically the sequence of transitions between different metastable states. This means that, effectively, the dynamics of the system is modeled by a Markov chain: the metastable states are the states of the chain and the hopping rates are transition rates between different metastable states. Therefore the main objects we need to compute are the transition pathways and the transition rates. The computation of these quantities represents one of the major challenges in computational science. The difficulty is mainly due to the disparity of time scales involved in the system, which makes conventional simulation techniques (e.g. the direct simulation of the Langevin dynamics or molecular dynamics, Monte Carlo simulations, etc.) prohibitively expensive. Indeed, one has to use a very small time step and resolve the relaxation time scale in Langevin dynamics or molecular dynamics for numerical stability, thus it takes a huge

number of time steps on average to observe a transition event in these simulations.

My work on modeling rare events (joint with Weinan E and Eric Vanden-Eijnden) has centered on developing the string method, which is now quite popular in computational chemistry and materials science, as well as the minimum action method for analyzing transition events in non-gradient systems (i.e. systems without an underlying energy landscape).

The minimum action method [1]

The Freidlin-Wentzel theory of large deviation is a rigorous mathematical theory for analyzing rare events. It provides an estimate for the probability of the transition events between metastable states in terms of an action functional. In view of this, finding the path with maximum probability becomes a problem of finding the path with minimum action subject to the constraint that the two end points of the path are fixed at two metastable states. Based on the large deviation theory, we developed the minimum action method for analyzing transition events in dynamical systems driven by small noise. The method has been successfully applied to a variety of problems, including the finite-time switching in a Ginzburg–Landau system, the Lorenz system, the Kardar-Parisi-Zhang equation for interface growth, and transitions in the Kuramoto-Sivashinsky equation.

Smooth energy landscapes and the zero-temperature string method [2,3]

For gradient systems with a smooth energy landscape in which the metastable states are separated by a few isolated barriers, the key objects are the transition states, which are saddle points on the potential energy landscape that separate the metastable states. The relevant notion for the transition pathways is that of minimum energy paths (MEPs). MEPs are the paths in configuration space that connects the metastable states along which the potential force is parallel

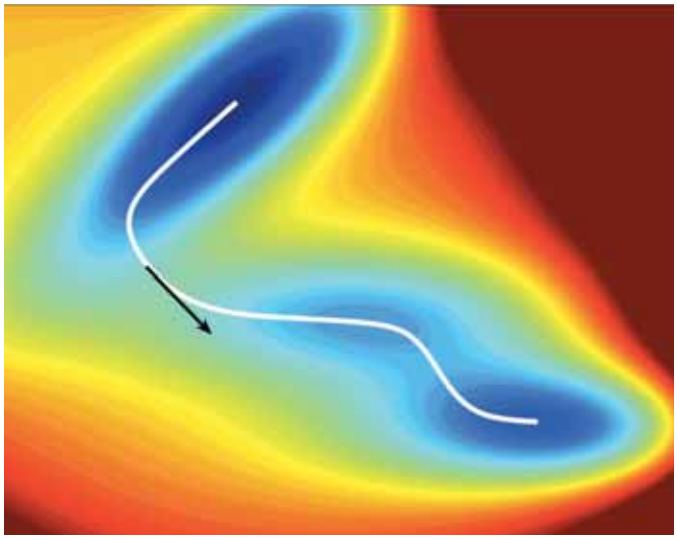

Figure 2: A smooth energy landscape and the minimum energy path.

to the tangent vector (see Figure 2). MEP allows us to identify the relevant saddle points which act as bottlenecks for a particular transition. The zero-temperature string method is designed to compute MEPs. It finds the MEP by evolving a string using the steepest descent dynamics in the path space.

As an interesting application, we used the string method to study the switching of micro-magnetic thin films [4]. Submicro-sized magnetic elements have found a wide range of applications in science and technology, particularly as storage devices. As the elements get smaller, the effect of thermal noise and the issue of data retention time become a major concern. For this reason, thermally activated switching has attracted considerable attention in the magnetics community. From the viewpoint of fundamental sciences, thermally activated switching of micro-sized magnetic elements is an example of rare events that drive a relatively complex system. Figures 3 and 4 show the critical points along two MEPs that were obtained using the string method. More details can be found in Reference 4.

Figure 3: The critical points along a minimum energy path (path a) followed by the magnetization during the switching of the element. The color code indicates the direction of the magnetization.

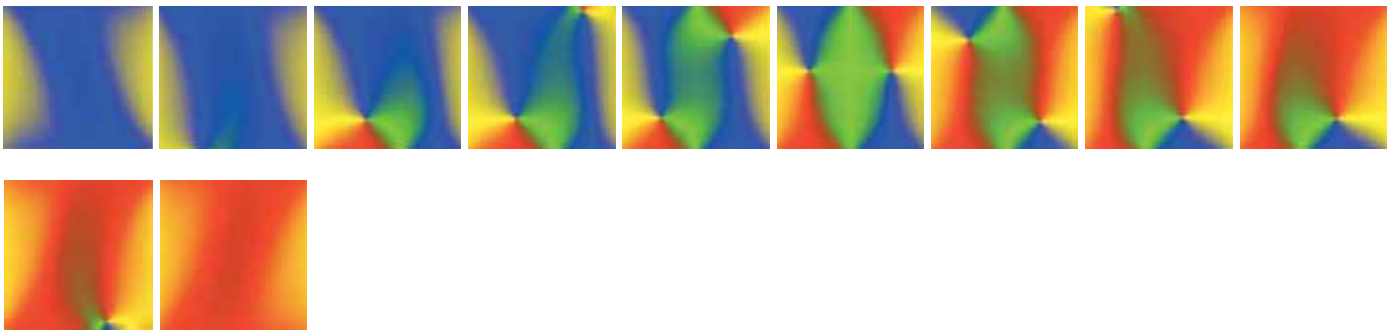

Figure 4: The critical points along a minimum energy path (path b) followed by the magnetization during the switching of the element. The color code indicates the direction of the magnetization.

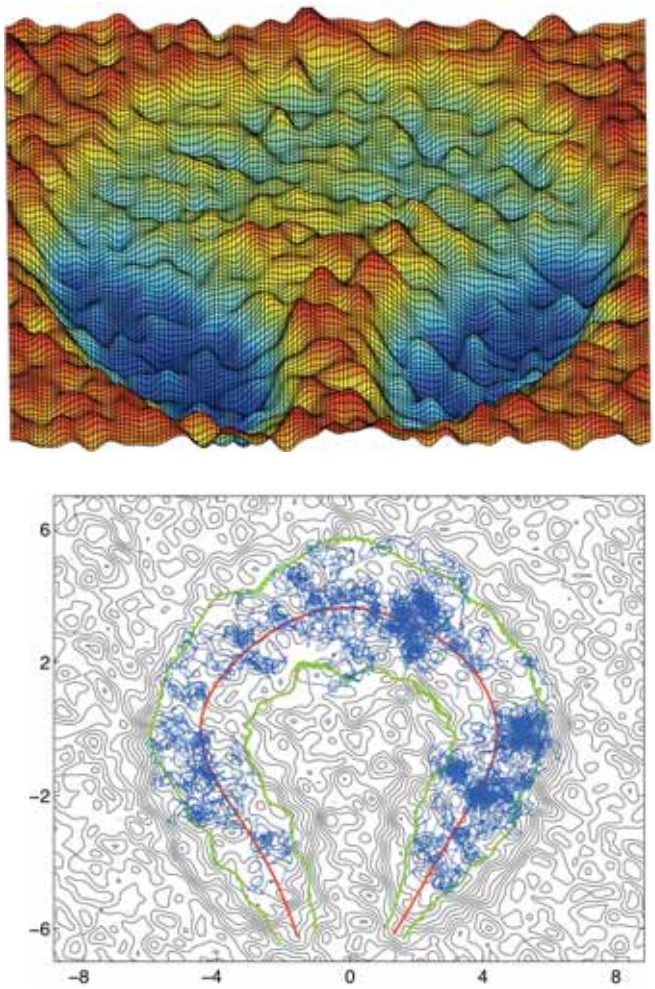

Figure 5: A rough energy landscape (upper) and the transition tube (lower panel).

Rough energy landscapes and the finite-temperature string method [5,6,7]

The situation is quite different for systems with rough energy landscapes, as is the case for typical chemical reactions of solvated systems. An example of rough energy landscape is shown in Figure 5. In this case, traditional notions of transition states have to be reconsidered since there may not exist specific microscopic configurations that identify the bottleneck of the transition. Instead the potential energy landscape typically contains numerous saddle points, most of which are separated by barriers that are less than or comparable to the noise, and therefore do not act as barriers. There is not a unique most probable path for the transition. Instead, a collection of paths is important.

In view of this, we developed the finite-temperature string method for analyzing transitions in complex systems with rough energy landscapes. The key objects in the finite-temperature string method are the transition tube and the transition state ensemble, which are defined with the help of the so-called committor function – the solution of the backward Kolmogorov equation in the configuration space with appropriate boundary conditions. Under the assumption that the transition paths are localized, we first use a variational formulation to reduce the backward Kolmogorov equation in the large dimensional configuration space to a large coupled system in one-dimensional space, then use an iterative procedure to identify the transition tube. An example of the transition tube computed using the string method is shown in Figure 5.

The numerical tools we have developed have been successfully applied to many problems arising from various disciplines, including conformational changes of biomolecules, switching of micro-magnetics thin films, phase transitions of complex fluids, dislocation dynamics in crystalline solids, etc. More information on these numerical methods and their applications can be found on the website: http://www.math.nus.edu/~matrw. ■

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Molecular-Resolution Studies of Cell Division

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Research Interests:
- Chromosome segregation
- Picoplankton cell biology
- Eukaryotic ultrastructure

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Electron Cryotomography and its Application in Understanding Cell Biology

Cell division is one of the most fascinating biological processes known. Repeated rounds of cell division allow a single fertilized egg cell to transform into a human being. Before a cell divides, however, it must segregate its chromosomes so that each of the two daughter cells inherits a complete genome (see Figure 1). Hundreds of millions of cells in the human body divide every single day, so chromosomes must be segregated with exquisite precision. Unfortunately, errors do occur, and chromosome mis-segregation can lead to birth disorders and diseases such as cancer [1].

Biologists have studied chromosome segregation for more than a century and have identified most of the proteins needed to segregate chromosomes and the manner in which they function. These proteins form huge molecular machines that can detect and correct segregation errors in the human body. It is important to have a better understanding of the interactions between these protein-based molecular machines in the cell at the nanometer resolution [2].

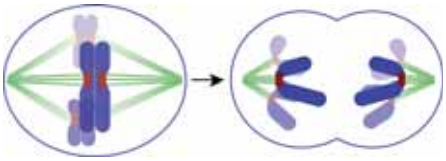

Figure 1: Illustration showing chromosome segregation. Chromosomes (purple) are segregated by straw-shaped protein complex es called microtubules (green). Microtubules work together in a machine called the spindle.

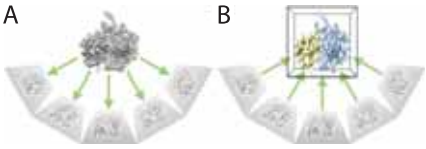

Figure 2: Principle of electron tomography. (A) A series of 2-D images are recorded from a sample (a protein-synthesis machine called the ribosome in this cartoon) while the sample is tilted around an axis. (B) The 2-D images are combined to create a 3-D image called a tomogram.

Imaging cells at nanometer resolution in 3-D is challenging and requires the most advanced microscopy techniques. One of the best ways to generate molecular images is by electron cryotomography: a series of 2-D images is taken from multiple viewpoints and then combined to generate a detailed 3-D image called a "tomogram" (See Figure 2). By using a transmission electron cryomicroscope (e.g. the Titan Krios at the NUS Centre for BioImaging Sciences), exquisite images of "frozen-hydrated" cells – cells that are cooled to liquid nitrogen temperatures so quickly that the water inside does not have enough time to reorganize into a damaging, crystalline form (like the kind used in beverages) – can be generated. Tomograms of frozen-hydrated cells can reveal how chromosome segregation machines are organized in a life-like state, without the artifacts that have clouded historical electron microscopy studies for many years [3]. By combining 3-D molecular models with decades' worth of genetic, biochemical, and biophysical knowledge, we may one day be able to simulate how a cell divides, determine the cause of chromosome segregation failure, and design a possible remedy.

High-Resolution Analysis of Picoplankton Chromosome Segregation

Picoplankton are among the smallest known cells, measuring less than 2µm across (See Figure 3). These unicellular plants can be found in all of the world's oceans and are significant contributors to the global carbon sink, yet very little is known about their life cycle. Picoplankton are nevertheless excellent models for cell biology because they have a simplified ultrastructure: each cell typically has one nucleus, one chloroplast, one mitochondrion, and one Golgi body. Remarkably, picoplankton are able to pack 20 chromosomes into their tiny nuclei [4]]!

Cells as diverse as humans, yeast, and plants use microtubules, 25-nm-wide straw-shaped protein assemblies, to grab onto chromosomes. Microtubules work together in a huge structure called the "spindle" to segregate chromosomes. Contrary to expectations, our studies using electron cryotomography showed that Ostreococcus uses a spindle which has approximately 10 microtubules to segregate its 40 chromosomes during cell division (See Figure 4 and [5]). This result was surprising because according to literature, there should be more microtubules than chromosomes for cell division to function correctly.

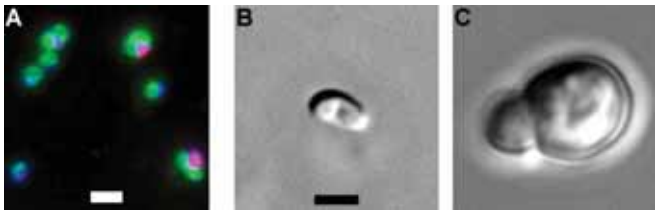

Figure 3: The picoplankton Ostreococcus is one of the smallest known cells. (A) A fluorescence image showing dividing (magenta and green) and non-diving cells (blue and green). The green bodies are chloroplasts (plant solar cells); the magenta and blue bodies are the nuclei, which contain the chromosomes. (B) Ostreococcus, which is less than 2µm wide (scale bars), is even smaller than (C) baker's yeast.

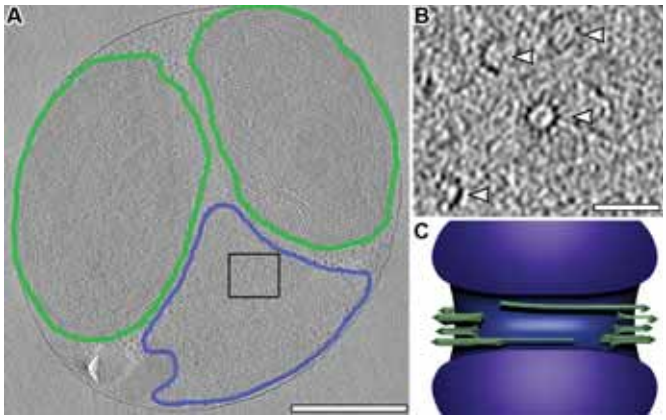

Figure 4. (A) Virtual "tomographic" slice through a frozen-hydrated dividing Ostreococcus cell. The outlines of the chloroplasts and nucleus are outlined in green and blue, respectively. The region enclosed by the black box is enlarged in (B), showing a transverse view of 4 microtubules (arrowheads). (C) Illustration of a dividing Ostreococcus cells, showing the unresolved chromosomes (blue) and spindle microtubules (green).

The team is researching on the mechanisms and processes involved when the Ostreococcus segregates its 40 chromosomes using such a small spindle. This knowledge gained can lead to a better understanding of the segregation of cancer cells with their unusually large number of chromosomes, which can be applied to develop anti-cancer agents.

Fundamental Questions in Cell Biology

When you look at the inside of a eukaryotic cell for the first time (See Figure 5) [6], you cannot help but ask questions that would not otherwise have come to mind: What are all the organelles (specialized bodies within a cell that have specific functions)? How do they divide? How does a cell make sure that each descendent inherits the right number of organelles (in this case, one)? What keeps the cell from growing too big or too small? How does the cell adapt to changes in environment?

We believe that electron cryotomography will be one of the most powerful tools to address such questions through the delineation of the molecular anatomy of cells in precisely controlled conditions.

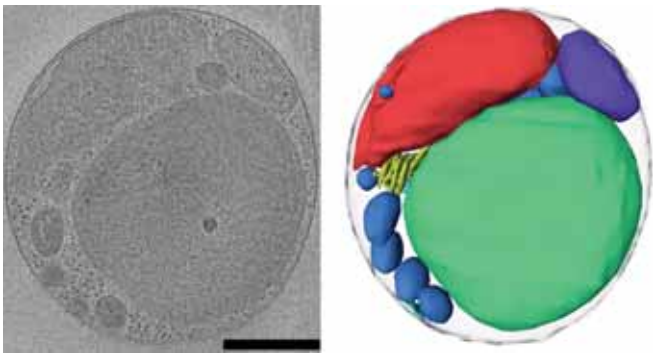

Figure 5: (Left) A tomographic slice of an Ostreococcus cell. (B) A 3-D model of the organelles (colored bodies that each have a unique function), generated from the tomographic data in (A).

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Solving the Darwin-Wallace Mystery

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Dr van Wyhe received his PhD in History from the University of Cambridge in 2001. He was a Senior Research Fellow at the University Scholars Programme at NUS 2002 - 2003. From 2003 - 2004 he was Research Assistant on the Correspondence of Alfred Russel Wallace project at the Open University. In 2004, he was visiting Associate Professor at Aarhus University. From 2005 – 2009, he was Director of the award-winning Darwin Online project at the University of Cambridge. Since 2009 he has continued Darwin Online at NUS where he is Senior Lecturer in the Departments of Biological Sciences and History and a Fellow of Tembusu College.

Research Interests:
- History of science
- History of evolutionary theories
- Charles Darwin
- Alfred Russel Wallace
- Public understanding science

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Introduction

Alfred Russel Wallace, the English naturalist who spent eight years in Singapore and South East Asia between 1854 and 1862, conceived of evolution by natural selection independently of Charles Darwin. Wallace had a dramatic eureka moment while living on the island of Ternate in the Moluccas (now Indonesia). He wrote up an essay which he sent, incredibly, to Charles Darwin who had not yet published his own very similar theory conceived many years earlier. Wallace's essay was published together with an essay by Darwin in 1858. This was the first publication of the theory of evolution by natural selection which over the ensuing twenty years resulted in one of the greatest scientific revolutions in history.

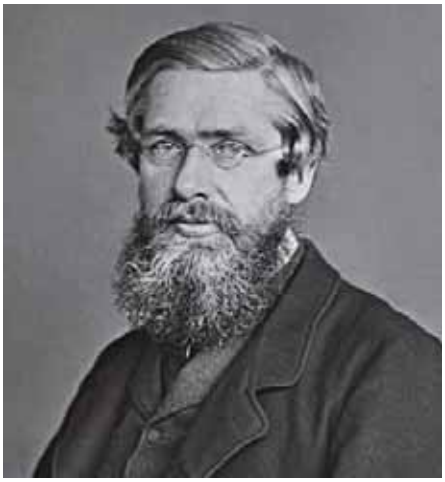

Figure 1: Alfred Russel Wallace

As is so common with history, Wallace's letter and essay no longer exist. His essay was dated "February 1858" from the island of Ternate. Darwin wrote a letter to a colleague on 18 June 1858 mentioning he had just been surprised to receive Wallace's essay "today" – with the amazing coincidence of the same theory. In later years Wallace often told the story of suddenly realizing the theory and sending his essay to Darwin "by the next post". There was then only a monthly mail ship service at Ternate. So it was assumed that the essay must have been sent to Darwin in March 1858.

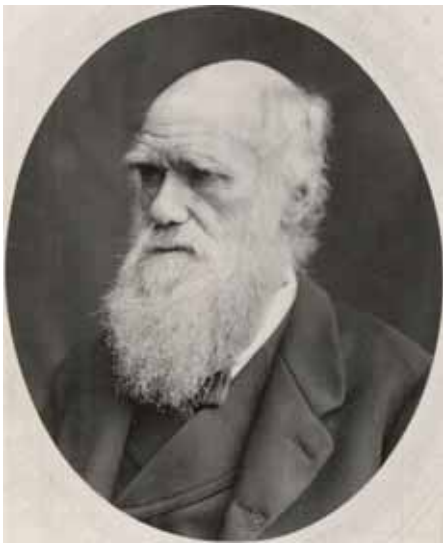

Figure 2: Charles Darwin

How the Mystery Began

In 1972 a researcher named Lewis McKinney found another letter from Wallace to a friend named Frederick Bates that was sent on that March 1858 steamer. The letter still bore postmarks from Singapore and London which showed that it arrived in London on 3 June 1858- two weeks before Darwin said he received the essay from Wallace. Thus began the mystery- how could two letters from Wallace leave Ternate on the same steamer and travel along the same mail route back to London but Darwin received his two weeks later than Bates did? This mystery has led to numerous conspiracy theories. For example several writers have claimed that Darwin stole ideas from Wallace's essay during the time he kept the letter secret. But most other evidence suggests that Darwin received the letter when he said he did.

So Did Darwin Receive The Letter When He Said He Did, or Not?

Here is what some writers have said about this mystery over the years:

> *"This is the hard-est story in science, and one day it is going to blow up"* John Langdon Brooks, 1984

> *"a problem that is…essentially unresolvable"* Barbara Beddall, 1988

"Exactly what happened next is a small nutlike riddle that science historians have never cracked. At its core is the issue of who deserves credit for one of the greatest scientific achievements in history" David Quammen, 1997

"one of the most persistent urban myths in evolutionary biology" Sandy Knapp, 2012

I was asked to write a biographical chapter on Wallace for a new Cambridge University Press encyclopaedia. In addition I am writing a book on Wallace in South East Asia. I decided to look into this mystery and see if anything could be found out. I initially assumed that it was impossible to solve since so many historians had examined it before. But it occurred to me that we really have no contemporary evidence of when Wallace sent the essay to Darwin, only his much later recollection that he sent it by the next post after writing it in February. That suggested that the essay was sent in March 1858. But this recollection from years later seemed to me not very reliable as evidence of what really happened at the time. The other evidence that Darwin received it on 18 June 1858 seemed more likely. All of his correspondence changed dramatically after that date for example. Since that side of the correspondence was all one really had to go on, it occurred to me to trace the letter from Darwin's end, rather than Wallace's.

Figure 3: Correspondence between Wallace and Darwin [Reproduced by kind permission of the Trustees of the Natural History Museum (London). With thanks to Judith Magee.]

If Darwin really received it on 18 June- how could it get there? It had come to his house in the countryside from London the day before, the 17th. I then found that a steamer arrived in England the day before, the 16th with mail from India and South East Asia. Surely this was not a coincidence! Wallace's letter was probably on that ship. I then had to trace back the remainder of the 9,240 miles of the journey from England, through the Mediterranean, across Egypt, to Sri Lanka, Penang, Singapore, Jakarta and so on. My colleague, the Senior research fellow on the Darwin Online-Wallace Online project, Dr Kees Rookmaaker, who speaks Dutch, was an invaluable help as he was able to check the ship arrival and departure times in the Dutch newspapers and sources for the Dutch East Indies as I had through the English newspapers. It was an exciting detective story, tracing the connections that mail batch took from London to South East Asia. Eventually our mail itinerary was completed all the way back to Ternate and we were astonished to find that there was an unbroken series of mail connections to Ternate- not in March as all other writers before had assumed, but in April 1858!

My further research has clarified why Wallace mailed it later than we assumed and many other parts of this famous, but misunderstood chapter in the history of science. First of all, we now know that Wallace was replying to an early letter from Darwin- and that letter from Darwin arrived in Ternate on the March steamer. We have assembled the first complete collection of all the surviving Wallace correspondence from Ternate and nearby islands. These reveal that he never replied to a letter on the same steamer which delivered it. Apparently the turn over time was too short. Therefore this is an additional reason to doubt that Wallace could have sent the famous letter to Darwin in March as so long assumed [1].

My book, tentatively entitled "Apocalypse now: Wallace, Darwin and the making of evolution" is almost finished and I believe it will completely revise the story of Wallace in South East Asia and how he really came to discover evolution here.

In addition to the continuing research and publication on Darwin Online- the most widely consulted history of science website in the world, we are preparing a new website on Wallace- Wallace Online, a website which aims to be the definitive and reliable source of Wallace's work. It will contain all of Wallace's books and article, as well as a complete collection of his specimens collected from South-east Asia, and much more such as a revised itinerary of his whereabouts during these years and his notebooks edited for the first time to modern scholarly standards. The website will be launched in 2013, the centenary of the death of Wallace. ■

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Trapped Ion and Photon Quantum System

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Dr Mukherjee obtained his Ph.D. in 2004 from the University of Heidelberg & GSI, Darmstadt, Germany. He was a Lise Meitner Fellow at University of Innsbruck, Austria till 2007. He moved to the Indian Association for the Cultivation of Science in India as an Assistant Professor. In 2012, he joined the Department of Physics, and is a Principal Investigator in the Centre for Quantum Technologies.

Research Interests:
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Introduction

The laws of Physics as we know them today are fundamentally different for massive objects (which we deal with in every day life) as compared to tiny objects like atoms and molecules. The law governing the former is known as the classical mechanics while the later is known as quantum mechanics. Naively speaking, the laws should have been the same since any massive object is ultimately formed of atoms. However there is a boundary between these two worlds and the search is on to identify and manipulate this boundary. The main motivation to explore this boundary is to utilize the amazing non-intuitive behavior of the quantum world in some so-called classical objects.

Quantum Mechanics

Quantum mechanics permit two or more states of an object to co-exist at a given time. Translating it to the classical world would mean co-existence of life and death in a living object (a cat for example), which in physics is known as the Schrödinger's cat state. This peculiar behavior of a quantum object, apart from many others has been utilized to perform computation.

Theoretically speaking, a quantum computer can perform tasks that are known to be hard to compute using a classical computer. This motivates both physicists and engineers to come up with possible quantum systems which are capable of implementing quantum computation. There has been tremendous progress in the implementation of the basic building blocks for these computers and the forerunner of them all is a system consisting of a few charged atoms (ions) which can interact with light beams of different colours (energy).

Quantum mechanics can be used to describe a system consisting of a single atom and a single light particle (photon). This well-understood system has been implemented to produce light in particular quantum superposition states similar to one described earlier as CAT state [1]. Different research groups around the world has also shown that the ions can be used very efficiently to perform quantum computation with as large as 14 quantum bit (qubits) [2]. Naturally, the next logical step would be to combine ions (matter qubit) with photon (light qubit) [3]. Although, an ion-photon system works well at a preliminary level, the bulkiness of such a system limits their scalability and is a major drawback.

Research groups around the world are searching for a quantum system that can address the scalability issue without compromising simplicity and computational speed. Two different approaches have been under consideration within our group to address this issue.

One approach is to manipulate the state of a large quantum object by slowly varying the interaction of it (geometry) in such a manner that it performs the required quantum gate. The other approach uses a quantum system whereby an ion is interacting with a superconducting wire. The long-term aim of the research work is to enable the transfer of quantum states between an ion to a superconducting electronic circuit (which is also a qubit) and vice-versa.

Ion traps

At the heart of these experiments is a device called an ion trap as shown in Figure 1 that can confine a single or a few ions in ultra high vacuum (factor of 10^14 below the atmospheric pressure). The ions can be brought to almost rest by colliding them against a stream of photons (laser cooling). In this manner quantum system of trapped ions are created. This quantum system of trapped ion can exist in two internal electronic states namely, the ground state (lowest energy state) and a long-lived excited state. An ion can be transferred from its ground state to the excited state by absorption of a photon whose colour (energy) is equal

to the energy gap between the ground and the excited state. Depending on the time duration of the applied laser pulse, its intensity etc. a quantum superposition of these two states can also be created (similar to the CAT state mentioned earlier). However, these states are fragile and they disperse when the ions interact with any other system namely, other atom or molecule, light particle etc.

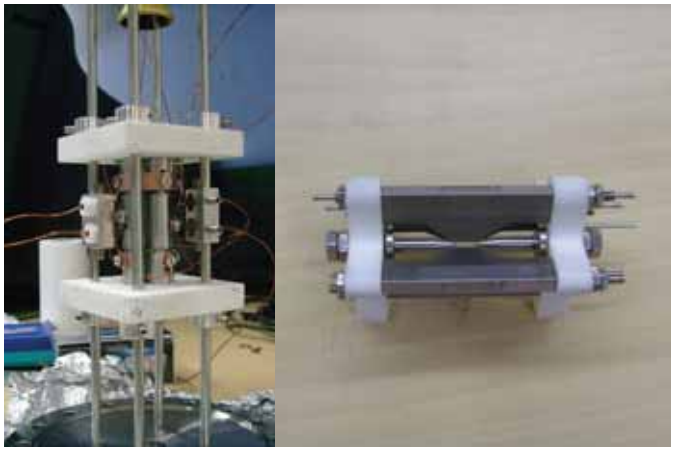

Figure 1: Two different variety of ion traps: (left) four rod structure, (right) blade structure.

The system once prepared using the ion trap can be considered in a simplistic manner as an ion subjected to a force that is always directed towards the center of the trap. The ion inside the trap oscillates like a ball attached to a spring with typical frequency of about 1 million oscillations per sec. The amplitude of the oscillations can be increased or decreased by the application of certain laser sequences. These states which are external to the ion's internal structure are called the motional states and it can be obtained by certain quantum measurement techniques.

Quantum Phases and Quantum Phase Transitions

It has been shown that under certain trapping conditions [5], this motion can exist in certain states that cannot be explained by classical mechanics. These states and their transitions are known as quantum phases and quantum phase transitions, which is similar to the phase transitions between water and ice observed in classical physics. They are responsible for certain phenomena like superconductivity and superfluidity that has rocked the quantum technology landscape for a long time. However, the basic understanding of this phenomenon is still only partially clear.

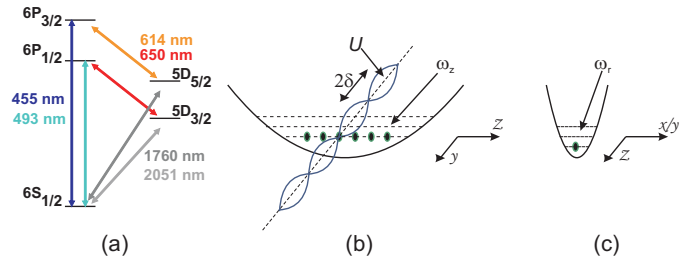

Figure 2: The internal structure of an ion (Ba+ in this case). (b and c) the motional energy levels in the three dimensions of motions. The trapping potential is considered to be harmonic.

Using the system of trapped ions, experiments can be performed in a controlled manner to understand the quantum phenomena. Complex quantum phase transitions can be mimicked to extract the exact conditions under which the phenomena will occur. This could include simple signatures such as fluctuations in the emitted light from the ions [6].

The atom species whose ion is used for our experimentation work is Barium. Its relevant internal structure is shown in figure 2(a). The two energy levels that form the qubit are known as the S1/2 and D3/2. The different colours (in terms of wavelengths) connecting the different energy levels are also shown. In addition figure 2(b) and 2(c) depicts the possible motional states of the ion when confined by the ion trapping potential.

Behaviour of Parity Violation

Trapped ion interacting with photon is a well controllable system and therefore has fundamental interest in Physics. This system under specific experimental configuration as mentioned in [7] can be used to address a peculiar behavior of nature called the parity violation. The violation of parity means that the law of nature selects one preferred orientation among different equally probable ones (a simple example is the handedness of DNA helix). Fortunately, this is not generally observed in the macroscopic world as only one (known as the "weak force") of the four fundamental forces of nature violates the spatial symmetry. In a system of trapped ions, this phenomenon which has a miniscule effect on frequency shift can be observed. By understanding the phenomena involved, we can throw light beyond the best model for describing the nature as a whole, the Standard Model of particle physics.

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Apoptosis as an Ultimate Weapon to Protect Us from Getting Sick

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Academic Profile:

Born in Hong Kong, A/P Victor Chun Kong Yu obtained his B.Sc. Pharmacy (Hons) in 1982 from University of Houston and Ph.D. (Pharmaceutical Chemistry) in 1987 from University of California, San Francisco where he spent five years to investigate molecular mechanism of action of the oldest and most widely used narcotic analgesic, morphine. In his postdoctoral work, he studied nuclear hormone receptors and had identified the RXR protein as the common co-regulator for the retinoic acid (vitamin A), vitamin D and thyroid hormone receptors. The discovery had paved the way for making significant progress towards understanding of the mechanism of actions of nuclear hormones on gene regulation. He came to Singapore in 1993 to join Institute of Molecular and Cell Biology (IMCB) as a Principal Investigator. In Singapore, he has been focusing his research on elucidating the molecular circuitry of the apoptosis and other signaling networks in mitochondria that are relevant for the understanding of major human diseases such as cancer. He joined the Department of Pharmacy, NUS, in August, 2009 as tenured Associate Professor.

Research Interests:

- Molecular Mechanisms of Cell Death
- Mitochondria
- Bcl-2 family of proteins
- Diseases associated with de-regulation of cell death mechanisms in mitochondria

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Introduction

Every day, hundreds of thousands of cells in our body die by committing suicide. This is because on routine basis, many cells in our body will be infected by pathogens and others are undergoing mutations that may cause the cell to become cancerous. To contain the damage from spreading further to other cells and tissues and eventually causing diseases, these infected or mutated cells would spontaneously activate a suicide program, known as apoptosis, to permit the cells to be "self-destructed".

Interestingly, many clinically used chemotherapeutic drugs work by taking advantage of the vulnerability of rapidly dividing cancer cells to DNA damages which can be efficiently induced by these drugs. DNA damages are potent signals for apoptosis and in principle will bring death to the cancer cells [1]. Unfortunately, reduced efficiency to sense or process apoptosis signals is also a common feature associated with cancer cells. Hence, it is difficult for cancer drugs to realize their full therapeutic potentials because of the intolerable toxic side effects associated with their use at doses needed to kill the cancer cells.

Mitochondria as Arbiter for the Kill Order

Mitochondria are known to be the organelles (specialized bodies within a cell that have specific functions) that produce ATP which is the fuel for the cells. This means that mitochondria are needed to keep cells alive. Surprisingly, research in the past decade firmly established that mitochondria also play crucial role in executing the apoptosis program. It is now known that most apoptotic signals, regardless of origin, converge at mitochondria to prepare for the final irreversible execution (point of no return) step of the apoptotic process. Detailed understanding of the components constituting the molecular circuitry and the information about the control of the apoptosis signaling mechanism operating at the level of the mitochondria would therefore be vital to support the development of effective novel therapeutic strategies.

It is envisioned that small molecule compounds that target key proteins involved in regulating the execution of apoptosis signaling in mitochondria would have the potential to be used as drugs to widen the therapeutic windows of many of today's cancer drugs [2].

Cracking the "Code" of the Apoptosis Signaling Network at Mitochondria

Over the past decade, my lab has used a variety of approaches to help to identify a number of protein molecules that play an important role in regulating the apoptosis signaling network in mitochondria [3-7].

One recent approach used by my laboratory to investigate apoptosis signaling mechanism is based on a well established observation that bacterial pathogens are normally good at inhibiting ("unarming") the apoptosis mechanism in the host cells they infected. Hence, this would make them capable of surviving in the host cells long enough to cause diseases. Little is known, however, on the means by which they manage to inhibit the execution of the cell suicide program of the host cells. One interesting question is about whether bacterial pathogens are able to inhibit apoptosis program of the host cells by directly hijacking the command center of the suicide program situated at mitochondria.

A post-doctoral fellow on my team, Dr Sunil Sukumaran whom is an expert on bacterial pathogens harboring in the human gut (e.g. Salmonella) worked on this issue. It is found that once the bacterial pathogen enters the cell, a protein known as "FimA" will be released by the bacteria which cause the host cell mitochondria to turn off its cell suicide program by binding to the VDAC-hexokinase protein complex (See Figure 1) [8].

VDAC-hexokinase protein complex has long been suspected by many cancer researchers that it plays an important role in switching off the suicide program in cancer cells. This finding not only have the potential to shed light on the early events

in the pathogenesis of certain infectious diseases caused by bacterial pathogens in the gut, it could also offer new insights on the role of these pathogens in promoting cancer of the gut such as stomach and colon cancers.

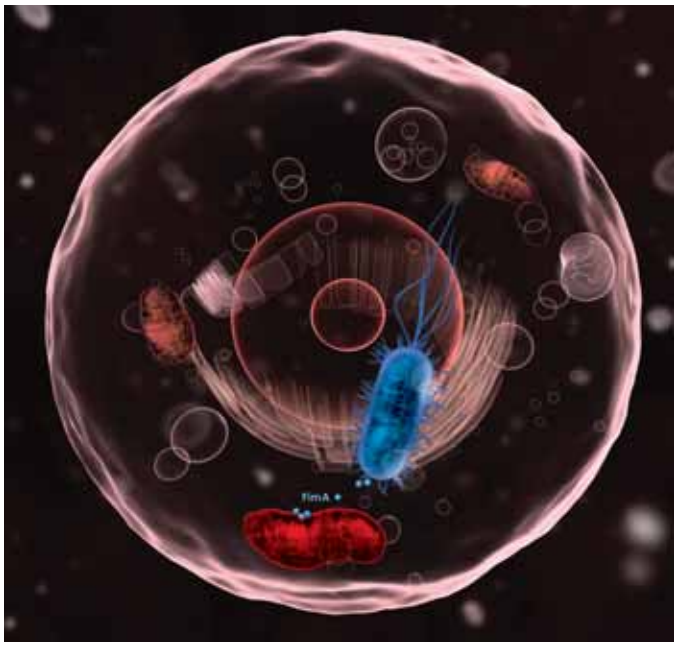

Figure 1: Bacteria pathogen releasing "FimA" to turn off the suicide program of the host cells

The Almighty Mitochondria

Mounting evidence accumulated in the past few years revealed that that other than "apoptosis", there are other forms of cell death that appears to be relevant in causing many other major human diseases [2].

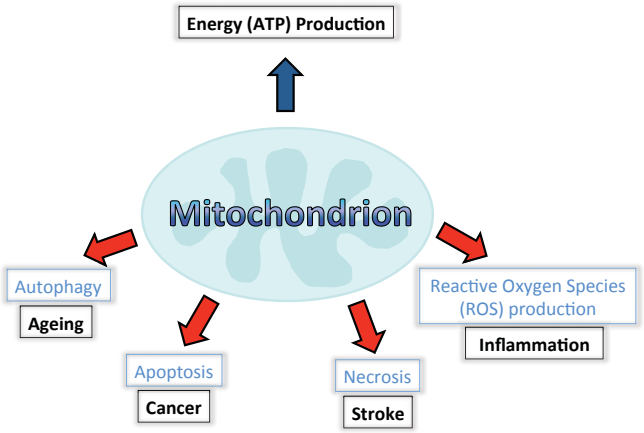

Figure 2: Expanding roles of Mitochondria

It is increasingly clear that mitochondria are also playing critical roles in regulating "necrosis" and "autophagic death", two other forms of cell death that are highly relevant for understanding certain diseases. Furthermore, example of cross-talks among cell death pathways has also begun to emerge [9]. More recently, mitochondria have been linked to other key physiological processes such as inflammation [10]. From being known as the "powerhouse" of cells, mitochondria are rapidly being recognized to be the key link to understanding a wide variety of physiological processes that are intimately linked to health and diseases [11, 12]. Our team would certainly be well-positioned to investigate the broader roles of mitochondria in regulating cell death, inflammation and ageing in future (See Figure 2).

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Understanding Outer Membrane Assembly in Gram-Negative Bacteria

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- Protein / lipid biochemistry
- Anti-microbial discovery
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The Gram-Negative Cell Envelope and Antibiotic Resistance

The cell envelope of Gram-negative bacteria consists of two lipid bilayers: an inner membrane (IM) that encloses the aqueous cytoplasm and an outer membrane (OM) that faces the extracellular milieu (See Figure 1). Between these two membranes is a second aqueous compartment known as the periplasm, which contains the peptidoglycan layer, or the cell wall, that determines the shape of the bacterial cell. This unique double-membrane envelope renders Gram-negative bacteria generally more resistant to external insults than their Gram-positive counterparts, which lacks the OM. In particular, the OM serves as a physical barrier to exclude toxic compounds such as antibiotics, detergents and dyes [1].

The OM is an asymmetric lipid bilayer in which the inner and outer leaflets are composed of phospholipids (PLs) and lipopolysaccharides (LPS), respectively [1]. In the outer leaflet, LPS [2], an anionic glycolipid that contains six fatty acyl chains, pack together in the presence of divalent cations to form an impervious polyelectrolyte with gel-like characteristics in the hydrophobic interior. The resulting LPS leaflet exhibits markedly decreased fluidity and makes the OM a very effective permeability barrier, even against small hydrophobic molecules.

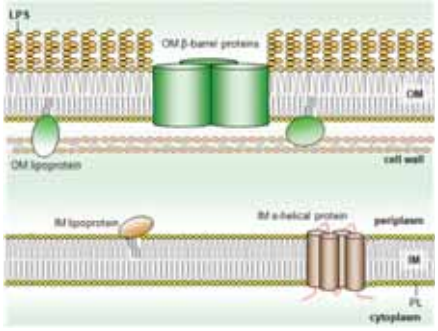

Figure 1: Schematic diagram of Gram-negative bacterial cell envelope

Consequently, Gram-negative infections are very difficult to treat; many classes of antibiotics (macrolides, glycopeptides, etc) are not effective because they cannot penetrate the OM. Furthermore, resistance to effective drug classes (β-lactams, fluoroquinolones, etc) is already on the rise [3], underscoring the need to invent new strategies to fight Gram-negative pathogens, including Pseudomonas aeruginosa. Since the OM is essential for the survival of these pathogens, and compromising the integrity of the OM enables the use of many antibiotics currently only effective against Gram-positive pathogens, the molecular machines that build the OM have great potential as new targets for antibiotic discovery. In this regard, a mechanistic understanding of how the OM is assembled would be extremely valuable. In this article, our work towards elucidating the pathway for LPS assembly is described.

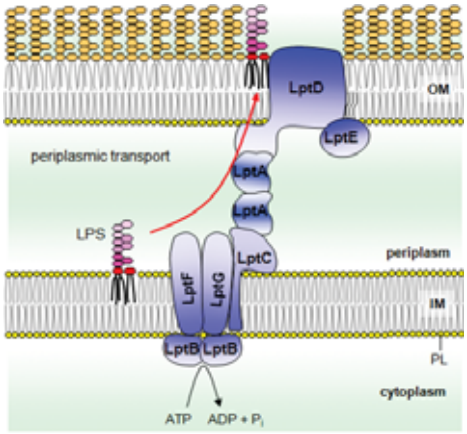

Figure 2: The Lpt proteins that mediate LPS export forms a protein complex that spans the bacterial cell envelope

LPS Export Across the Cell Envelope

LPS is synthesized at the inner leaflet of the IM via a well-characterized pathway and then translocated to the periplasmic leaflet by an ABC transporter MsbA [2]. Following that, seven essential Lpt (lipopolysaccharide transport) proteins mediate LPS transport across the periplasm and assembly into the outer leaflet of the OM (See Figure 2) [4]. We

demonstrated that the Lpt proteins form a trans-envelope complex that connects the IM and the OM; all seven Lpt proteins can be found in a cellular fraction that contains the IM and OM, and they co-purify [5]. Based on this discovery, a bridge model for LPS transport across the periplasm has emerged where the periplasmic protein LptA interacts with both IM protein LptC and OM β-barrel protein LptD to establish a physical route for LPS movement. The proteins LptBFG form an ABC transporter that uses ATP hydrolysis to release LPS from the IM, while the lipoprotein LptE form a tight complex with LptD at the OM to receive and assemble LPS into the outer leaflet of the OM (see Figure 2).

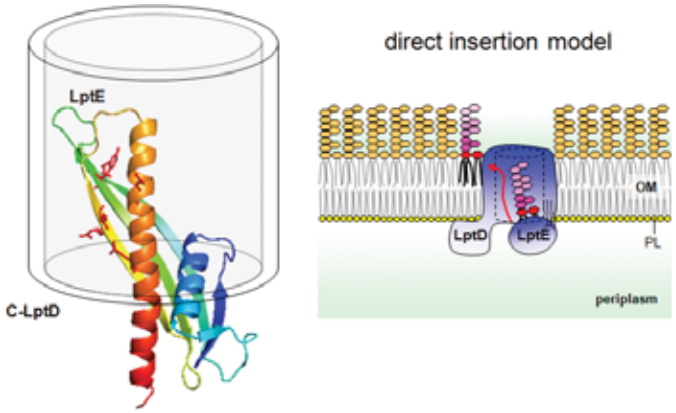

Figure 3. Plug-barrel architecture of the LptD/E complex (left) and a model for how LPS is inserted into the outer leaflet of the OM (right)

LPS Insertion into the Outer Leaflet of the OM

Once LPS reaches the OM, it is not clear how the two-protein complex LptD/E acts to place LPS exclusively in the outer leaflet of the OM. To understand each protein's role in this process, the protein complex was overexpressed (methodology to produce multiple copies of a protein) and purified as a heterodimer [6]. We showed that the C-terminal β-barrel domain of LptD interacts strongly with LptE and protects it from proteolytic degradation. Furthermore, we demonstrated that multiple faces of LptE interact with LptD [7]. These results imply that LptE sits inside the barrel of LptD and forms a plug (See Figure 3). LptE also binds LPS in a specific manner [6], suggesting that LPS may be directly inserted into the outer leaflet of the OM via the lumen (internal channel) of the LptD barrel (See Figure 3).

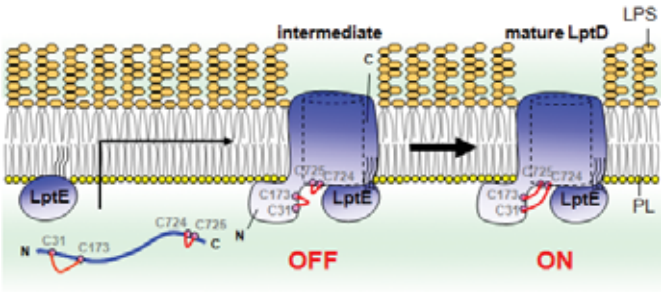

Figure 4. Disulfide bond rearrangement activates the LptD/E complex from a non-native disulfide-bonded intermediate

Activation of LPS Export via Disulfide Bond Rearrangement

LptE also plays a role in the assembly of LptD. LptD contains two disulfide bonds between non-consecutive cysteines, and the formation of both disulfide bonds is dependent on the presence of LptE [8]. Using steady state and pulse-chase measurements, we established that assembly of the native disulfide bond configuration in functional LptD proceeds via a non-functional intermediate containing non-native disulfide bonds (See Figure 4) [9]. Disulfide bond rearrangement converts the non-functional intermediate to the functional mature LptD, thereby activating the LPS transport machine. This led to the hypothesis that disulfide bond rearrangement may allow the LptD/E complex to coordinate with the rest of the Lpt machinery to assemble the trans-envelope protein bridge required for LPS export to the cell surface. ■

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