Faculty of Science

RESEARCH

Newsletter

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Content

Cover photos - Aquatic alien species in Singapore (clockwise from top left): alien marine crabs (A, *Glabropilumnus seminudus*; B, *Platypodia tomentosa*; C, *Carupa tenuipes*; D, *Liomera monticulosa*); redclaw freshwater crayfish (*Cherax quadricarinatus*); and ocellate river stingray (*Potamotrygon motoro*) (Photographs © Tan Heok Hui and Raffles Museum of Biodiversity Research) (see Pp 1–2: Investigating Aquatic Invasive Alien Species In Singapore Waters).

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Systematics, taxonomy, and biogeography of decapods crustaceans (especially freshwater crabs)
Biological invasions
Freshwater ecology

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Investigating Aquatic Invasive Alien Species in Singapore Waters

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Alien species in Singapore—why bother?

In a recent op-ed piece in the New York Times (NYT), the qualities of a few alien (i.e. non-indigenous) species were extolled with the message that all alien species should be welcomed for the benefits that they bring—likening species introductions to immigration that adds dynamism to human societies (Raffles 2011). This elicited responses against such a "melting pot" advocacy, with different researchers highlighting many cases of invasive alien species that have caused serious consequences (http://www.nytimes.com/2011/04/10/opinion/l10species.html accessed 9 May 2011). The main issue here is that the term "alien" species, despite the negative-sounding connotation, does not necessarily imply negative impacts and merely refers to non-native species. That been said, there are some harmful alien species that cause problems and these are termed invasive species (a term that was not used at all in the NYT article). What invasion biologists actually argue therefore is not the opposite extreme (i.e. all aliens are bad and should be gotten rid of!) but rather that the precautionary principle should be exercised when dealing with alien species introductions. As one respondent wrote: "Efforts to curb non-native species focus on those that cause harm and give others a pass….drawing from the writer's comparison to human immigration, let's at least make sure they (alien species) all have a visa." (William Y. Brown, science adviser to the interior secretary during the Clinton administration).

What about Singapore? Should alien species even matter here? The simple and practical answer is YES, if they are invasive, i.e. they are abundant and/or widespread and have impacts or potential impacts on the country's interests, be it in terms of environmental harm (e.g., by threatening native biodiversity, causing modification of habitats), economic costs (e.g., through financial and human resources spent on control/management), or harm to humans (e.g., dangerous species in publicly accessible areas). The problem, however, is that the ecology and impacts of most alien species in Singapore (hence whether they are invasive or not) are not yet well-understood, if at all.

Up till now, much of the alien species investigations in Singapore have taken the shape of mere reports, descriptive accounts, or inventories (see Yeo and Chia 2010). Little else is known because research in Singapore is relatively recent, and mostly still at the "discovery phase" of finding out what alien species are present.

Alien species in Singapore freshwaters

We are now beginning to address this gap through research into the diversity and ecology of freshwater alien species in Singapore, which is a focal area of the collaborative work with various colleagues and students.

A recently completed four-year broad-based biodiversity survey of Singapore's reservoirs (which are hotspots for aquatic alien species) commissioned by the Public Utilities Board (Yeo and Chia 2010; Yeo 2010; Ng and Lim 2010; Ng and Tan 2010) has provided a much more complete picture of the diversity and distribution of freshwater alien species in Singapore. This is the first but nevertheless important step in starting a concerted research program on dealing with invasive species.

One of the more alarming findings from the study was that the South American ocellate river stingray, *Potamotrygon motoro* (see photo on front cover), was confirmed to be breeding in Singapore (Ng et al. 2010). There is a possibility that this large predator might threaten native freshwater fauna in the forest stream catchments of the reservoirs, but of additional concern is the potential hazard posed to humans as it spreads and as more reservoirs are opened to public recreational water sports (Ng et al. 2010). The stingray was introduced via the ornamental fish trade, probably through releases by bored pet owners. Interestingly, the Agri-Food and Veterinary Authority of Singapore (AVA), which regulates import and sale of exotic species, stated in 2007 that sale of stingrays by pet shops was banned because of the potential health hazard to humans (Tan 2007); they added in March 2010 that the ban did not apply to fish farms (Chua 2010). However, in August 2010, AVA reversed the policy altogether, allowing pet shops and fish farms to sell stingrays as pets, which may fetch up to $200,000 per

fish (Yang 2010). Economic factors aside, the apparent policy "U-turn" by the AVA could conceivably also be due to insufficient information regarding the species' spread and impacts, pressure by dealers and traders, and lack of understanding about invasive species, and is symptomatic of uninformed policy decisions regarding alien species. This is one area the present work can surely contribute to.

Another freshwater alien which the survey helped to shed light on was the Australian redclaw crayfish, *Cherax quadricarinatus* (see photo on front cover), known from urban ponds and reservoirs with multiple size cohorts confirming its established breeding population status (Yeo 2010; Belle et al. 2011). That they have been found in core nature areas close to areas of high biodiversity conservation value and may potentially threaten endemic crustacean and other species in pristine habitats is a major concern (Ahyong and Yeo 2007; Belle et al. 2011). Besides potential physical and ecological impacts on the environment and native species, crayfish are also known to be intermediate hosts of the flatworm *Paragonimus*, which causes lung fluke disease in humans and other vertebrates (Lane et al. 2009).

The reservoir survey contributed much to a recent review that documented 142 alien animals in Singapore, of which, freshwater fishes and reptiles comprised the majority (61%), suggesting that the ornamental and live food trade, the main pathways bringing freshwater fishes and reptiles into Singapore, are potential key drivers of aquatic invasions in Singapore (Yeo and Chia 2010). The above study also revealed some interesting trends including:

(1)   After Asia, the source region that contributed the most alien species to Singapore was Central or South America (19%), which is where many species in the ornamental trade originate;

(2)   A total of 101 species (71% of the alien animals listed) were regarded as being established in Singapore, signaling an 84% increase in just seven years since the last review (Tan and Tan 2003). This statistic is not surprising given that most alien species in Singapore occur in man-made or modified habitats such as urban areas, parks and gardens, wasteland, canals, ponds, and reservoirs, which Singapore certainly has no lack of, but is worrying because once established, an invasive alien species can be nearly impossible to eradicate; and

(3)   More than 50% of the alien animals documented (including eight species that were as yet unconfirmed as being established) have a known history of invasion elsewhere, which is a strong predictor of the invasive potential of an alien species (Williamson and Fitter 1996; Kolar and Lodge 2002; Ricciardi 2003).

Alien species in Singapore seas

We know even less about marine alien species in Singapore compared to terrestrial and freshwater environments. To date, only three alien marine species (two mollusc and one annelid species) are confirmed established in Singapore seas (Yeo et al. 2011). This apparent "lack" of marine alien species in Singapore could be due to inadequate taxonomic resolution and/or insufficient historical baseline data of marine species as well as possibly to a phenomenon whereby tropical communities with high connectivity and biodiversity and low endemicity are less susceptible to invasions (see Hutchings et al. 2002). Nevertheless, we do know from studies of crustaceans that there is a high potential for marine invasions here. As many as 55 species of alien crustaceans (barnacles, crabs, prawns, and lobsters), including several known invasives, are known from three major marine invasion pathways: shipping (specifically hull-fouling on visiting vessels) (see photo in front cover), the ornamental pet trade, and the live seafood trade in Singapore (Yeo et al. 2009; Yeo et al. 2011). Work to better comprehend marine alien species in Singapore is ongoing.

Where do we go from here?

The growing pool of baseline information puts us in a better position us to embark on ecological studies of alien species at various scales ranging from individual species level (e.g., autecological studies such as feeding and reproductive ecology) to community/ecosystem level (e.g., food web and trophic interactions with other species and ecological effects on the environment). Only when armed with the relevant fundamental ecological knowledge, can we then also tackle the more pertinent and applied invasion biology questions here: What impacts are aquatic alien species having in Singapore waters? And how do we manage and/or control aquatic invasive species?

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Nanogap DNA Biosensors

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- Synthesis of multifunctional biotags
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Introduction

Over the past decade, many important technological advances have provided us with the tools and materials needed to construct functional nanostructure-based devices. With a rich inventory of nanomaterials and nanofabrication techniques, new avenues have been opened up in the field of biosensors. Researchers around the world have been tailor-making a multitude of nanostructure-based devices and developing new protocols to harness them for ultrasensitive biosensing applications. Biological events occurring at the surface of nanostructured devices result in unique modes of signal transduction, not discernible at a bulk structure of the same material. Owing to the presence of a much larger number of atoms or molecules on the material surface, most of the atoms are capable of transducing an event occurring at the interface or in the vicinity. Therefore, a higher shift from the baseline physical properties is expected from nanomaterials and the nanostructure-based devices than from their bulk counterparts. In this report, major advance in the field of nanogap DNA biosensors with an electrical transduction mechanism is summarized. Representative examples from recent work of the author and others are provided to illustrate the operating principles of various nanogap DNA biosensors and their characteristics.

Nanogap DNA Biosensors

The application of nanostructured devices in biosensing has been studied most extensively in the past decade. The nanogap DNA biosensors are among the most studied nanostructured devices, because of their potential of being easily integrated with a complementary metal-oxide-semiconductor platform. The sensing mechanism of the nanogap DNA biosensors primarily depends on the modulation of the conductance or capacitance upon the introduction of biological species. A nanogap DNA biosensor usually consists of two electron-conducting electrodes separated by an insulating gap/layer of nanometer dimension, which would ideally forbid a current to flow between the electrodes. Nevertheless, it is almost impossible to completely dispose of the leakage current originated from quantum mechanical tunneling. Controlled fabrication of the nanogap is crucial for the device to effectively recognize biological species of interest. Some of the techniques involve expensive tools and long turnaround times, while others may compromise the reproducibility of the nanogap. In order to convey any of the techniques from laboratory to the production scale, it is essential to make a right poise between expense and excellence.

One of the early reports on the application of the nanogap DNA biosensors to highly sensitive detection of DNA came from a team at UC Berkeley.[1] They developed an elegant technique, coined "spacer lithography", which could generate 10-nm features by using standard photolithographic techniques. For the DNA detection, the nanogap was fabricated in which two electrodes were separated from each other by a 50-nm gap. Monolayers of oligonucleotide capture probes were then formed on the sidewalls of the two electrodes. Due to the lack of rigidity, the immobilized capture probes are randomly tangled, whereas a specific conformation is assumed when they hybridize with complementary DNA strands. The difference in geometric structure associated with a change in counterion concentration upon hybridization, leads to a change in the capacitance of the nanogap. It was revealed that the rate of increment in capacitance is steadier after hybridization, as the input frequency decreased gradually. In contrast, there is no significant difference in the measured capacitance before and after hybridizing to noncomplemenetary DNA strands, thus ratifying the specificity of the device.

The detection of DNA based on its native charge transport properties in nanogaps, was investigated by Shiigi et al.[2] In their report, a film of nanometer-spaced decanedithiol coated

gold nanoparticles (GNPs) was deposited between two platinum electrodes of 5-μm apart. The nanogap was defined by the decanedithiol spacer between two neighboring GNPs (Fig. 1a). Then, thiolated DNA capture probes (12-bp) were immobilized on the GNPs. It was estimated that a target DNA strand of 4 nm in length would bridge up two consecutive GNPs located about 1.3 nm apart. A real-time conductance measurement was performed while introducing complementary as well as mismatched target DNA strands to the device. Depending on the degree of mismatch, the resistance of the single-stranded DNA (ss-DNA)-GNP film dropped accordingly (Fig. 1b). The authors reported that the nanogap DNA biosensor is able to detect a single-base mismatch, but the output signal, which is <0.1% change over its baseline, definitely invites some doubts over the accuracy and reproducibility of the device.

The study of the DNA hybridization event using a nanogap DNA biosensor, at a single-molecule level, was reported by Roy and co-workers.[3] The nanogap was fabricated by focused ion beam technique between a pair of single-walled carbon nanotube (SWCNT) electrodes. During the formation of the nanogap on the SWCNT, the incident ion beam created a nanometer-wide trench at the substrate (Fig. 1c). A sub-pA current was observed after anchoring a ss-DNA to the SWCNT electrodes. Upon hybridization
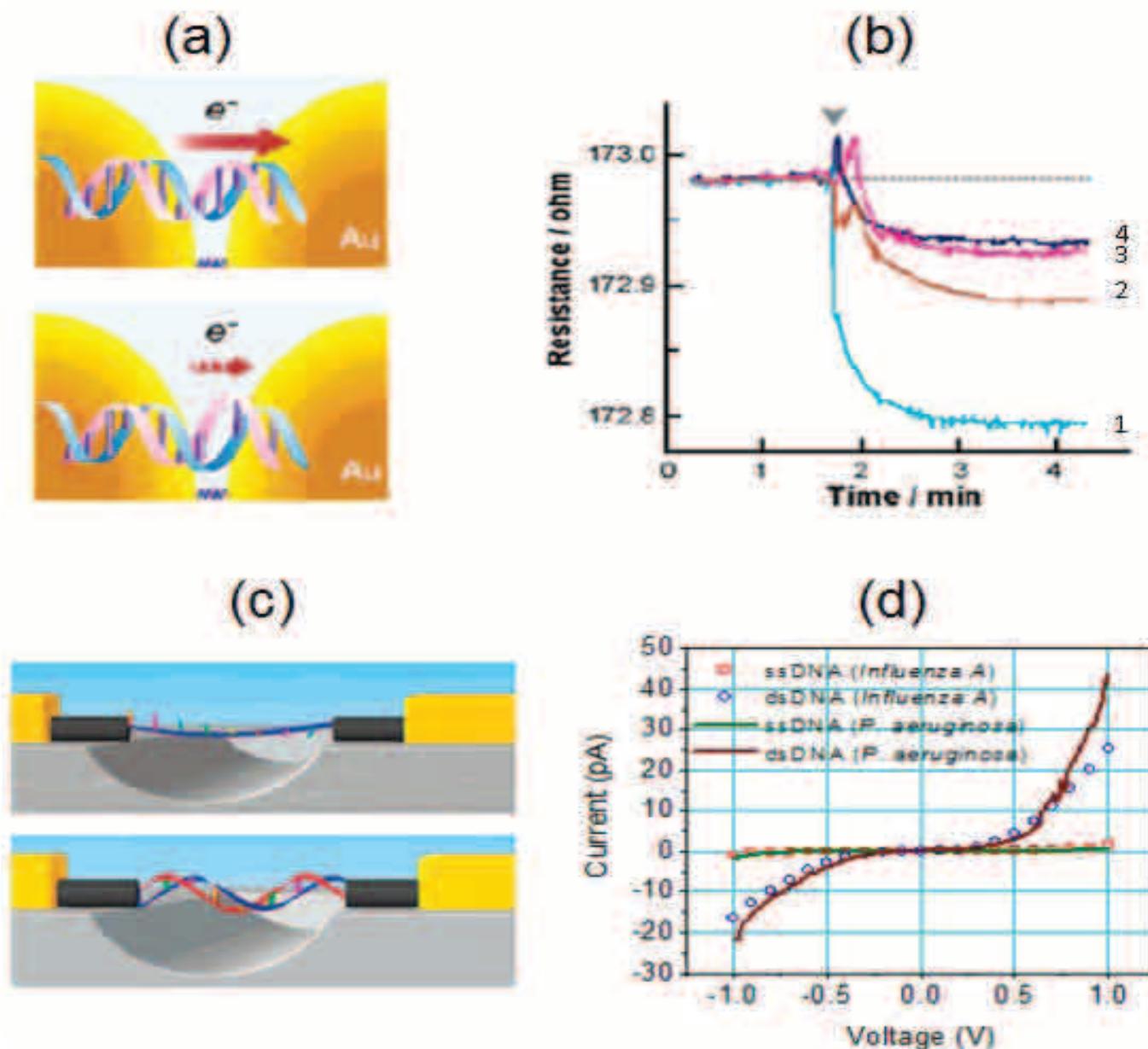
Figure 1.

(a) Schematic diagrams of charge transport through a DNA molecule attached between two GNPs, separated by a dithiol spacer. The top diagram represents a fully matched DNA duplex and the bottom one represents a single base-pair mismatch

(b) Real-time resistance changes of the GNP film; (1) - (4) represent the relative changes in resistance of different degrees of mismatch introduced; (1) fully complementary, (2) 1-bp mismatch, (3) 4-bp mismatch, and (4) 11-bp mismatch.

(c) Schematic illustrations of single DNA molecule detection. The top diagram represents an arbitrarily shaped ss-DNA, which is stretched and attached to a pair of SWCNT electrodes. The bottom one depicts the double helix. The SWCNT electrodes were separated by a 27-nm gap.

(d) The current signals for the ss-DNA and the duplex. (Reproduced with permissions from American Chemical Society)

with its complementary strand, an order of magnitude increase in current was observed at 1.0 V (Fig. 1d). This observation could be explained by the formation of the double helix in which the adjacent nucleotide bases stack up by π-conjugation, making a path for charge carriers to propagate through it.[4] Several control experiments, including those conducted after DNA denaturation or after the application of restriction enzymes, confirmed that the origin of the signal is indeed from the hybridized double helix.

The ability to affordably and efficiently fabricate highly uniformed nanostructures with a high scale-up potential is important to many technical applications, and yet it remains a technical challenge. Most of the bottom-up approaches suffer from certain limitations such as device-to-device non-uniformity, reflecting the variations in the device fabrication processes, low yield, and low scalability. On the other hand, the widely used top-down approaches for fabricating narrow nanogaps, such as electron beam lithography,[5] dip-pen lithography,[6] and transmission electron microscope-assisted nanosputtering[7] have to resolve issues such as high cost and low yield, in order to be one step closer to routine fabrications.

Recently, we successfully addressed the aforementioned issues of device uniformity and signal reliability by implementing a mass-producible fabrication technique along with a novel sensing protocol that can accurately detect nucleic acid targets at extremely low concentrations.[8-10] Design considerations of the nanogap biosensors take into account the feasibility of mass production in a cost-effective way by using standard silicon microfabrication technologies. As shown in Figure 2, instead of a reagent-free procedure for electrically bridging the nanogap by the intrinsically insulating target DNA, we appended a DNA-templated conductive nanowire formation step along the hybridized DNA strands in our detection scheme, enabling a much more sensitive electrical detection with minimal background and with enhanced mismatch discrimination.[9,10] The sensing mechanism relies on bridging the nanogap upon hybridization of the two termini of a target DNA with two different surface-bound capture probes, followed by a simple metallization step. About two orders of magnitude enhancement in conductance was obtained in the presence of as little as 1.0 fM target DNA. A linear relationship between the conductance and DNA concentration was obtained from 1.0 fM to 1.0 pM with an exceptional signal intensity of a 200-fold change per unit concentration. This change in conductivity is so large that it can unambiguously detect the concentration of DNA quantitatively and may obviate the need for target amplification used in current DNA tests. Moreover, the sensor array exhibited excellent single-base mismatch discrimination due to its unique vertically aligned nanostructure and the two-probe configuration.

Concluding Remarks

Due to its high sensitivity and wide dynamic range, the nanogap DNA biosensors may potentially find applications in molecular diagnostics. Lots of concepts have been demonstrated by the nanogap DNA biosensors in recent years, none of them has yet been uplifted to the production scale. The problem primarily stems from the device-to-device variations in their baseline electronic properties. Even more importantly, most of the tests were conducted under ideal experimental conditions, such as highly purified synthetic oligonucleotides and pure buffer solutions. The real physiological medium is far more complex and will definitely introduce a range of interfering and fouling effect. By conducting the tests only under ideal conditions, the device performance is essentially pushed down to a limit which may have only remote correlation with the real world. Therefore, the commercial viability of these biosensors still remains to be seen. Nevertheless, the eventual acceptance of the nanogap DNA biosensors will depend on how they compare with the current gold standards, i.e. quantitative polymerase chain reaction, microarray, and enzyme-linked immunosorbent assay, in terms of sensitivity, specificity, reliability, simplicity, cost, and portability.
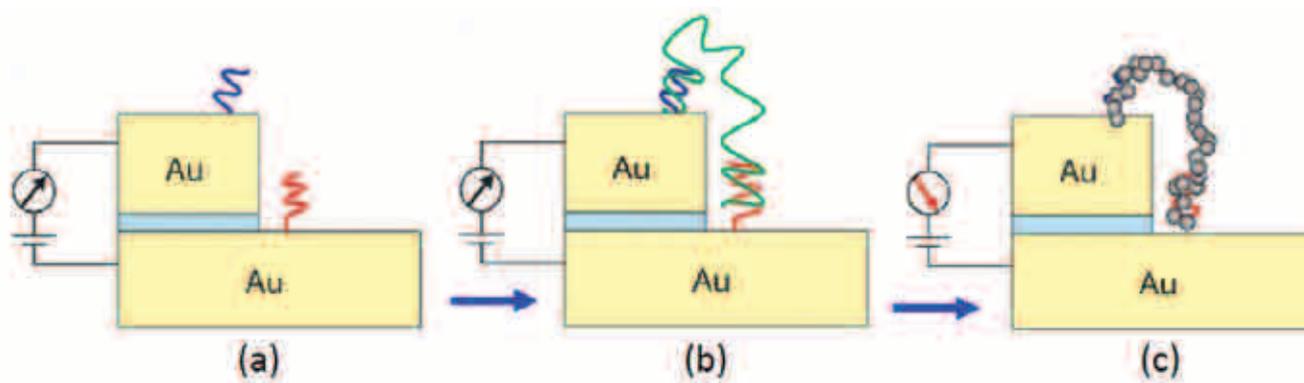
Figure 2.

Schematic illustration of the sensing procedure of the nanogap DNA biosensor:
(a) two different capture probes immobilization across the nanogap,
(b) hybridization with a target DNA strand (green),
(c) formation of a silver wire along the backbone of the hybridized DNA strand that results in the formation of an electrical conducting
       pathway(s) between the electrode pair (Reproduced with permissions from American Chemical Society).

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From Coin Tosses to the Brownian Web and Net

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Introduction

An important theme in probability theory is to identify universal phenomena on large space-time scales that are independent of the microscopic details. A classic example is the Central Limit Theorem. Take for instance the coin toss example, where a fair coin is tossed N times. If we plot the frequency at which k heads are observed against k, then we find that the frequency profile roughly follows a bell curve, where the center of the bell curve is at k=N/2, and the width of the curve is roughly the square root of N. The central limit theorem tells us that, as N tends to infinity, after centering and rescaling, the frequency profile converges to an exact bell-shaped function, which is the Gaussian density function. The power of the central limit theorem lies in the fact that the Gaussian density function is ubiquitous and not just restricted to the coin toss example. In a more abstract formulation, if $X_1, X_2, \ldots$ are the outcomes of a sequence of independent and identical experiments, then after proper centering and normalizing, the partial sum of these outcomes $S_N = X_1 + \ldots + X_N$ will also asymptotically follow the Gaussian distribution. The Gaussian distribution is therefore universal in the sense that it governs, or more precisely, well-approximates the law of the fluctuation of the sum of a large collection of independent measurements, regardless of what one is actually measuring.

The central limit theorem can be extended to the functional level, which is called Donsker's invariance principle. Let us return to the coin toss example, and let $X_1, X_2, \ldots$ be the outcomes of the successive coin tosses, where $X_i=1$ if the i-th coin toss turns up head and $X_i=-1$ if it turns up tail. The partial sum $S_N = X_1 + \ldots + X_N$ then measures the difference between the number of heads and tails. Instead of only observing S_N for a large N, let us observe the whole sequence $(S_1, S_2, \ldots, S_N)$ up to time N. The central limit theorem is concerned with the distribution of the last entry S_N. The functional central limit theorem tells us that if we speed up time by a factor of N and divide S_i by the square root of N, then the sequence $(S_1, S_2, \ldots, S_N)$, regarded as a function of time, asymptotically follows the distribution of a random function defined on the time interval [0,1], known as the Brownian motion. Originally introduced by biologists and physicists on an informal level to describe the random jiggling motion of pollen and dust particles in fluids and air, Brownian motion has since been rigorously constructed mathematically, and the functional central limit theorem establishes it as the universal random process governing the large space-time scale fluctuation of the sums of a large collection of independent measurements observed over time. The universality of Brownian motion makes it an ideal candidate to model many random motions in life and nature, ranging from the motion of molecules to stock prices.

To model complex phenomena involving multiple particles, individuals, or agents, we often need to employ more than one sequence of coin tosses, whose partial sum process $S_N = X_1 + \ldots + X_N$ is also called a random walk, because we can think of a drunkard moving on the integer lattice Z, where every step he takes just equals the random coin toss X_i. The partial sum S_n records the position of the random walker at time n. A random walk can thus model the motion of an individual moving in space, and many interesting phenomena arise when there is a population of individuals interacting with each other, such as the spread of an infectious disease among a population. Various types of interactions can be introduced between the moving individuals modeled by random walks. For example, when two random walks meet, they can annihilate each other which can model the reaction of two chemical agents that become inert after reaction, or they can coalesce into a single random walk which can model the merging of two genealogical lines, or they can give birth to new random walks. Such interacting particle systems have been used to model many phenomena arising from physics, chemistry, biology etc, although their rigorous mathematical analysis is often difficult.

A special class of interacting random walks admits an analogue of the functional central limit theorem. They are the coalescing random walks on the integer lattice Z, where two walks merge into a single random walk whenever they meet. To construct the collection of coalescing random walks, for each point in the space-time lattice Z^2, we draw an arrow pointing either up-left or up-right with probability 1/2 each. In such an arrow configuration, space is plotted horizontally and time vertically. A random walk starting from a given lattice site simply follows the arrows upward in space-time, and because there is only a single arrow leading out of any site, two walks coalesce

more Brownian motions starting from every point of the continuum space-time plane R^2. This random collection of coalescing Brownian motions is called the Brownian web. The construction and analysis of the Brownian web have been carried out by Arratia [1], Toth and Werner [5], Fontes, Isopi, Newman and Ravishankar [2]. Just like the Brownian motion, the Brownian web is also a universal object and arises as the scaling limit of general coalescing systems of particles in one dimension. The Brownian web has been used to model river networks, as well as the dynamics of domain walls of a one-dimensional ferromagnet at low temperature.

either an up-left or up-right arrow as in the construction of coalescing random walks, with probability one over square root of n, we draw both the up-left and up-right arrows, which represents a branching point. A random walk encountering one of these branching points splits into two random walks, with one following each of the two arrows. It turns out that if we rescale space by the square root of n and time by n as was done for coalescing random walks, then we obtain in the limit a random collection of branching-coalescing Brownian motions. We have named the limiting object the Brownian net due to the net-like structure appearing in it. The Brownian net is also

Coalescing Random Walks

Brownian web

$P\left(\vee \right) = \dfrac{1}{\sqrt{n}}$

Branching-Coalescing Random Walks

Brownian net
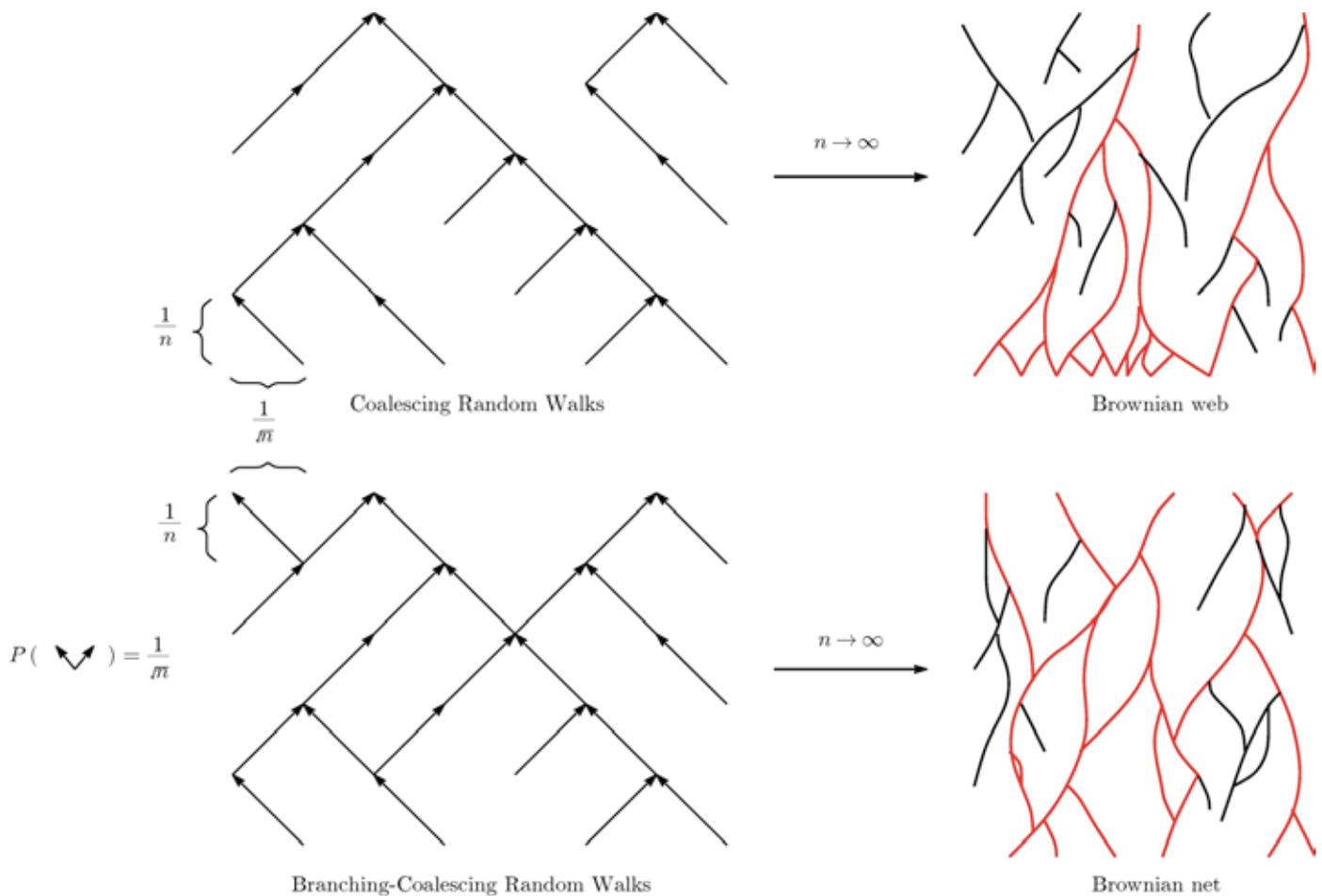
into a single walk whenever they meet. If we rescale space by a factor of square root of n and time by a factor of n, so that the lattice spacing tends to zero, then the functional limit theorem tells us that the random walk path starting from the origin will converge to a Brownian motion. However more is true. In fact the collection of all coalescing random walk paths, with one walker starting from every point of the space-time lattice Z^2, will converge to a limiting collection of coalescing Brownian motions, with one or

With coauthors Emmanuel Schertzer and Jan Swart [3, 4], we have been studying an extension of the Brownian web by allowing the extra effect of branching. Such branching effect may arise due to selection bias if the random walk paths model genealogical lines, or due to nucleation if the random walk paths model evolution of domain walls in magnets. A natural starting point is to consider branching-coalescing random walks on the space-time integer lattice Z^2. Instead of drawing

expected to arise as the universal scaling limit of general one-dimensional branching-coalescing particle systems.

The identification of universal large scale phenomena and the classification of these phenomena into different universality classes has been a central theme of modern probability theory, as well as statistical mechanics as epitomized by the renormalization group theory. The Brownian web and Brownian net are two instances

of such universal limits, which extends the classical Brownian motion by incorporating many interacting Brownian motions. The verification that a particular discrete system converges to a universal limit is often not easy due to the many interacting components. However the notion of universality is powerful and attractive.

Once a discrete system has been verified to belong to a given universality class, then it is known to share many essential properties with other models in the same universality class, and we can replace it either by the continuum limit or a different model in the same universality class which is more amenable to analysis.

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FGFR4: Identification of a new drug target through mutation analysis

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Introduction

Mutational analysis of oncogenes is critical to our understanding of cancer development and progression. Among the various families of oncogenes, tyrosine kinases stood out in significance whereby mutations and/or overexpression have frequently been implicated in several malignancies [1]. Tyrosine kinases are enzymes that bind target proteins in order to add phosphate groups to tyrosine residues. This enzymatic action can lead to post-translational modification of proteins which then triggers a cascade of intracellular events that ultimately regulates (or dysregulates) cellular activities such as growth, differentiation, apoptosis and motility. When tyrosine kinases are mutated at critical residues, their enzymatic activity can be disrupted and hence exert major consequences on cellular functions. For example, EGFR (epidermal growth factor) mutation, L858R, results in a constitutively active kinase which is found in a subset of non-small cell lung cancer population. Inhibition of this target effectively suppresses the tumor-promoting behavior of this kinase and is accountable for the development and approval of EGFR inhibitors gefitinib and erlotinib [2].

Today, tyrosine kinase inhibitors is one of the fastest growing drug class as new findings associating their signaling aberrations to cancer states continue to emerge. Yet, many other members of this large gene family (more than 90 human tyrosine kinases known today) remain largely unexplored. In our efforts to uncover new oncogenic mutations from among the tyrosine kinases, we performed a comprehensive sequencing of the coding region of each kinase gene across a few hundred cancer lines of different tissue origin. Among which, we identified a novel fibroblast growth factor receptor 4 (FGFR4) Y367C mutation in the human breast cancer cell line MDA-MB453 (Figure 1) [3].

FGFR4 is the most recently identified member for FGFR family. The relevance of this tyrosine kinase to cancer has escalated in recent years with reports of its overexpression in various tumors such as mammary and hepatocellular carcinoma [4, 5]. Moreover, single nucleotide polymorphisms (SNPs) are rampant in this gene and at least one (G388R) has correlated with clinico-pathological outcomes of different cancer types [6-8]. In our earlier study, we found about one-third of liver cancer patients carrying this polymorphism and it is linked to an increased tumor marker, α-fetoprotein [5]. With the identification of a new somatic mutation, Y367C in MDA-MD453, we showed that this cell line exhibited the highest FGFR4 expression across all cell lines investigated and elicited constitutive tyrosine phosphorylation leading to enhanced downstream cell signaling that drives cancer phenotype. To characterize this effect further, we performed gene overexpression experiment and found the mutation to elevate cell proliferation (Figure 2) [3]. A reciprocal approach of gene silencing demonstrated a reduction of cell growth (Figure 3) [3]. This outcome strongly suggests that FGFR4 may be a driver of tumor growth, particularly when highly expressed or constitutively activated through genetic alterations.

However, one should note that the presence of a functional mutation derived from in vitro experiment alone does not translate into definite clinical relevance. Further mutational screening in patient tumor samples will be necessary to confirm these findings and to identify the tumor type and patient genetic profile where this finding is meaningful. Therefore, this finding can be the first of many steps towards characterizing a potentially new drug target. We hope that these efforts will get us closer towards a more personalized and effective cancer therapy.

Academic Profiles:

Dr Ho completed his doctorate in medicinal chemistry at the University of Washington, Seattle, in 2005, on a fellowship from the Agency of Science, Technology and Research (A*STAR) from Singapore. He worked in the area of studying the mechanistic details of various drug-induced hepatotoxicities at the lab of Prof Sid Nelson. Thereafter, he returned to Singapore as a research fellow and subsequently a project leader in the Singapore OncoGenome Programme, housed within the Institute of Medical Biology, A*STAR. This was a research stint under world renowned cancer biologist Prof Axel Ullrich. Here, he continued to focus on liver pathologies but specializing in the area of exploring new tyrosine kinase targets for the treatment of liver cancer. In July 2009, he moved on to his current post as assistant professor at the Department of Pharmacy, National University of Singapore. Currently, he is developing a research programme that amalgamates both liver toxicology and liver cancer investigations.

Research Interest:

- Drug-induced liver diseases
- Tyrosine kinases and liver cancer (and other malignancies)

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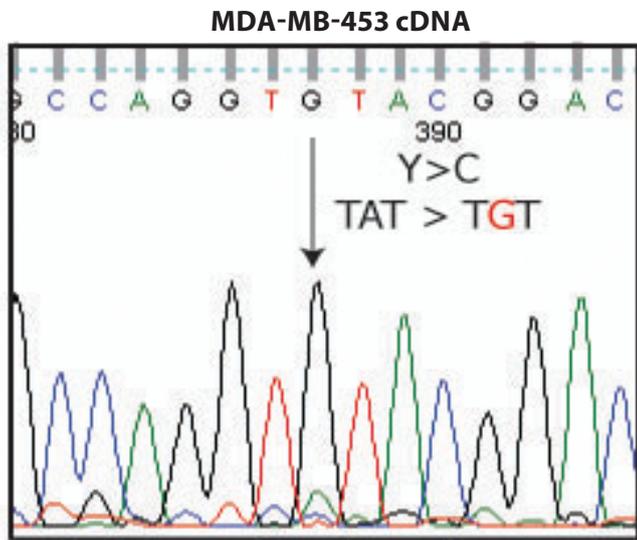
MDA-MB-453 cDNA

Figure 1:

Sequencing of FGFR4 coding region using the cDNAs derived from MDA-MB-453 cells.

A single nucleotide mutation from A to G encodes for an amino acid change from tyrosine to cysteine at position 367.
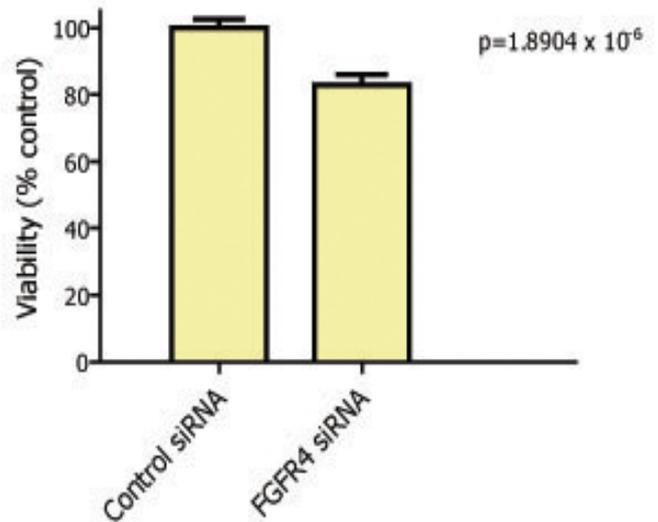
Figure 2:

Silencing of FGFR4 expression in MDA-MB-453 cells reduces its viability.

FGFR4 was silenced by siRNA approach and viability was measured by Cell Titer-Glo assay (Promega). Cell viability was reduced by 20% (P<0.05).
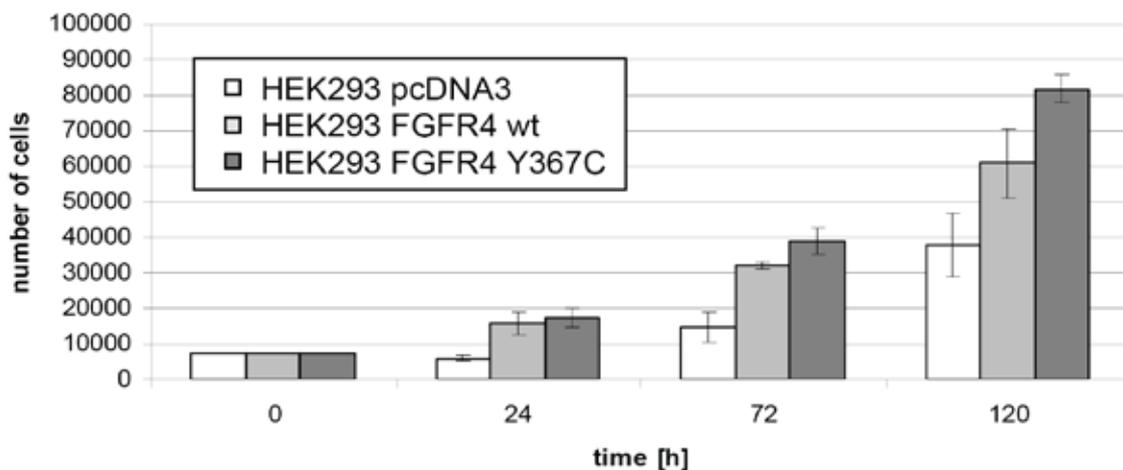
Figure 3:

Transfection of FGFR4-Y367C mutant induces cell proliferation.

Using HEK293 as FGFR4 null cell line, an empty vector (pcDNA3), wild-type FGFR4 and FGFR4 Y367C mutant were independently transfected. Cells were counted at various timepoints (0-120 h) to determine the extent of cell proliferation.

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Graphene: more physics from the thinnest membrane

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Being a monolayer crystal of *sp²* carbon, graphene is the thinnest crystalline membrane in the universe. Yet, its properties speak of anything but flimsiness. Boasting the highest measured in-plane stiffness of any material [1], exhibiting record elasticity (strains up to 20%), sporting record-high electric current densities [2], and harbouring new quantum phenomena – like a room-temperature quantum Hall effect [3], or Klein-tunneling in transport [4] –, this thin slice of carbon hides a lot for something that has no "inside". That's correct: no inside. Graphene is the first example of a condensed matter system with no bulk, or rather, where bulk and surface are one and the same thing. This has interesting implications, both at a fundamental, and at a practical level.

Fundamentally, graphene marries the realms of *soft* and *hard* condensed matter, which generally tend not to overlap. Indeed, quantum effects and correlations between elementary constituents (e.g.: atoms, electrons) and excitations (e.g.: phonons, magnons) rule the world of hard condensed matter, and are not usually expected to influence directly (or be influenced by) the *subject* soft condensed matter, which includes the study of properties and dynamics of complex fluids, films, membranes, interfaces and surfaces. This dual nature of graphene means, for example, that one expects the nature of electronic correlations to renormalise its effective bending rigidity, thus influencing the stability against thermal fluctuations ubiquitous in membranes. Likewise, playing with structural and elastic conformations can lead to serious effects in the electronic system, as we shall shortly see.

Tailoring is key

On the more practical side, the two dimensionality is both a blessing and a curse. In most materials, the features of interest for devices – including all the ones in which our electronics industry is based – arise from their bulk properties, which do not depend on what is sitting or happening on their surfaces (surface effects tend to decay rapidly into the bulk). But in graphene it's quite obvious that, lacking a bulk, the system is fully exposed to its environment, and bound to be affected by it: the nature of substrates, the environment conditions, the fabrication steps, the existence of adsorbates or charged impurities, and any source of disorder in general, can have detrimental impact in graphene's intrinsic properties. Surprisingly enough, even the crudest samples (scotch-tape exfoliated in air, no treatments), or samples subject to a daunting number of preparation and transfer steps for a monoatomic surface, tend to give good devices, and exhibit most of the intrinsic traits we expect for graphene [5]. Such resilience arises from two key factors: carbon making the strongest covalent bonds in nature, thereby making it very difficult for lattice defects or substitutional impurities to creep in; and the massless chiral nature of the electronic excitations, which results in electrons being more difficult to scatter by conventional impurity potentials [6].

However, the planar configuration and unavoidable exposure of graphene is also a great blessing, in that it affords us innumerable opportunities and ways to deliberately interact with it, to tame its less interesting features (like the absence of a gap in the spectrum), enhance the most promising ones, and introduce new phenomenology. Indeed, the wealth of know-how, methods and techniques routinely used in surface science are a great asset here. I can list a few illustrating examples: (i) the planar structure allows expedite patterning into channels, ribbons, quantum dots and quantum point contacts [7]. (ii) one can readily create p-n junctions by playing with top and bottom gates, magnetic or non-magnetic [8]. Since gates are highly controllable in real time, one can engineer gate architectures for complex devices, whose functionalities can be changed or reprogrammed in real time, both for charge and spin transport. (iii) chemical methods can be used to functionalize, and surface science methods to "decorate" graphene with adatoms, in a *à la carte* manner to induce local gaps, electronic waveguides, quantum dots, and even tunable magnetic moments or Kondo physics [9]. (iv) judicious local straining of the crystal lattice can be used to create tunnelling barriers that control the electronic motion [10], or induce local quantum-Hall phases without any magnetic field [11].

Academic Profiles:

Vitor Pereira obtained his PhD in Theoretical Physics from the University of Porto (Portugal) and Boston University (USA) in 2006, with a thesis dedicated to studies of disorder and localization effects in correlated electronic and magnetic systems.

In 2007 he was awarded a post-doctoral fellowship and moved to Boston University, later becoming a Research Associate, in 2009, at the same University. During this period he specialized in various aspects of transport, structure and electronic properties of graphene. Since 2007 he delivered 14 invited talks at international conferences.

In September 2010 Vitor Pereira was appointed Assistant Professor in the Department of Physics, NUS. As a member of the newly created NUS Graphene Research Centre, he continues engaged in understanding graphene phenomenology, both at a fundamental level, and for its potential for new device functionalities and integration in the next generation electronics.

Research Interests

- Theoretical Condensed Matter Physics
- Graphene Physics
- Disordered and Correlated Electron Systems

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This illustrates why this system is so appealing theoretical and experimentally: not for one specific trait, but for the wide-open avenue of possibilities. It rapidly left the fundamental condensed matter laboratories where it emerged, to being now actively studied by materials scientists, chemists, or biologists. Graphene brings the concept of on-demand and real-time tunable device functionalities to fruition, and is a significant leap in the journey towards the next generation of electronics.

Stretch those magnetic fields

Allow me now to steer to the topic I have been most recently involved with, and which has gained a considerable momentum in graphene research. It has to do with yet another oddity: electrons in graphene can be fouled into feeling under the influence of a magnetic field, when there is none. In order to see how that comes about let us briefly review the low energy description of electron dynamics in graphene.

The honeycomb lattice that "holds carbons in place" in graphene is not a Bravais lattice, but rather two inter-penetrating triangular sublattices. In order to invoke translational invariance and Bloch's theorem, one needs to consider a triangular (Bravais) lattice with two carbon atoms per unit cell. Therefore, the proper quantum-mechanical wavefunction describing an electron in graphene has, in addition to the conventional quantum numbers (momentum, spin) and extra label, identifying which of the sublattices (*a* or *b*) it belongs to, and giving it a spinorial (think vectorial) nature, rather than the conventional scalar nature we are more used to in condensed matter. At the same time, the bipartite nature of the lattice and existence of one free electron per carbon atom dictates that the ground state has an exactly half-full conduction band. Since for all practical purposes the physics is determined by the behaviour of electrons in the vicinity of the Fermi level, one can work with an effective Hamiltonian on that energy scale. All this considered, the Schrödinger equation for an electron in graphene becomes [12]

$$v_F \begin{bmatrix} 0 & p_x - ip_y \\ p_x + ip_y & 0 \end{bmatrix} \begin{bmatrix} \psi_{k,\sigma}^a(\boldsymbol{r}) \\ \psi_{k,\sigma}^b(\boldsymbol{r}) \end{bmatrix} = E \begin{bmatrix} \psi_{k,\sigma}^a(\boldsymbol{r}) \\ \psi_{k,\sigma}^b(\boldsymbol{r}) \end{bmatrix}$$

or $v_F\ \sigma \cdot \boldsymbol{p}\ \psi(\boldsymbol{r}) = E\psi(\boldsymbol{r})$ in shorthand, where the Fermi velocity, $v_F = 3ta/2\hbar \approx 10^6$ m/s, $\boldsymbol{p} \to -i\hbar\nabla$, and σ_i are Pauli matrices. This wave equation has a structure completely analogous to the Dirac equation governing the motion of relativistic electrons [13], with the important difference that there is no mass! The energy dispersion reads simply $E(\boldsymbol{k}) = \hbar v_F|\boldsymbol{k}|$ and, for this reason, we say that electrons in graphene behave as massless Dirac fermions. The fact that the momentum appears non-diagonally reflects the fact that the electron moves always by hopping from one sublattice to the other. All the microscopic details are condensed in the quantum mechanical hopping amplitude *(t)* for an electron to transit between two neighbouring carbons, which is a constant in equilibrium.

Imagine now that one starts deforming the lattice in some places and, as a consequence, electrons might find it easier or harder to hop around, depending on whether the carbon atoms are closer or farther from

Illustration of a device consisting of a locally strained region acting as a tunnel barrier. Upon entering the strained regions, electrons can be reflected or tunnel through depending on a combination of strain and incoming energy, and the effect can be turned on and off by a local gate.

Local strain could be achieved here by thermal expansion mismatch among substrates and graphene, substrates interating differently with graphene, or with trenches or pits in the substrate.

each other than in equilibrium. The hopping amplitude t can no longer be a constant, and will explicitly depend on the local strain in the underlying lattice. Pertubatively this can be expressed by writing $t \to t+\delta t(\boldsymbol{r})$, and recalculating the effective Hamiltonian. The result turns out quite simple: just replace $\boldsymbol{p} \to \boldsymbol{p} - A(\boldsymbol{r})/v_F$, where the vector $\boldsymbol{A(r)} = A_x(\boldsymbol{r})u_x+A_y(\boldsymbol{r})u_y$, and $A_x(\boldsymbol{r}) - iA_y(\boldsymbol{r}) = \sum n\ \delta t_n(\boldsymbol{r})\ \exp(i\boldsymbol{K}\cdot\boldsymbol{n})$, which encodes the local perturbation to the hopping amplitude from an atom at position r, to its neighbor at $\boldsymbol{r}+n$ [10,12]. This substitution $\boldsymbol{p} \to \boldsymbol{p} - A(\boldsymbol{r})$ is the familiar minimal (or Peierls) substitution that modifies the equations of motion of a charged particle under a magnetic field of magnitude $\boldsymbol{B(r)}=\nabla\times\boldsymbol{A(r)}$. Hence, even though the only thing we did was to perturb the equilibrium distance between the carbon atoms by deforming graphene, from the point of view of the electrons it is as if we had applied an external magnetic field (with an important difference though: time-reversal symmetry is preserved, and so this is actually a pseudo magnetic field). Given that the governing equations are formally the same, the behaviour is equally the same and, in the presence of appropriate strain fields, the electrons can undergo cyclotronic motion, have their spectrum quantized in Landau levels, and exhibit a pseudo quantum Hall effect.

This prediction has recently been confirmed in a spectacular way, when it was found that blisters in CVD grown graphene can appear spontaneously, and lead to enough strain inhomogeneity that local Landau level formation can be seen via STM [14]. Inspection of the Landau level spectrum reveals pseudo-magnetic fields in excess of 300T ! Now, if this does not impress you, let me give you some numbers: that corresponds to fields 6 orders of magnitude larger than earth's magnetic field; the largest magnetic fields attainable in a lab are of the order of 40T, or up to 80T in milisecond pulses, and there is no hope to increase them beyond that since no material on earth withstands the magnetic pressure of such fields without violently breaking apart [15]. One immediately can think of using such strong and steady pseudo-magnetic fields to use graphene as a test bed to explore the extreme quantum Hall limit. But, above all, this experiment shows how strongly one can affect the electronic motion by playing with strain fields in graphene, lending serious support to the idea of strain-engineering.

Strain Engineered Graphene

In 2008 we proposed the following idea [10]: create local strain profiles in graphene in such a way that electrons can become spatially confined, or so that we can channel them in strain-induced waveguides, or even so that we can pinch-off electronic current by sweeping a gate voltage. This is the essence of strain-engineering: tailoring strain fields in graphene to cater to specific device functionalities. At first, based on our experience with other materials, it might seem unusual to propose strain as a means to control electron flow. But (i), unlike conventional materials that fail structurally

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under deformations smaller than 1%, graphene happily stands very large strains in a reversible manner; (ii) being a surface, strain cannot relax into the bulk; and (iii), we just saw that deformations couple to electrons in a most peculiar way in graphene. I should underline that the " engineering" part in "strain-engineering" is not just a fashionable word play, but an actual necessity. Homogeneous strains do not lead to remarkable effects other than introducing anisotropy in the system [16], and it turns out that only certain space-dependent strain profiles and geometries turn out to be useful [11,17]. The engineering consists in, given a target functionality (a quantum dot, a channel, a tunnelling barrier, Landau levels), coming up with the strain field that leads to it, and in a way that might be implemented in real experiments or devices.

This and other related contributions stimulated the understanding of several other aspects of strained graphene, and circumstances in which strain can have unexpected effects.

One interesting situation arises from the fact that, like a sheet of paper or foil, the in-plane stiffness of graphene largely surpasses its bending rigidity, and it is very "soft" when it comes to out-of-plane deformations. One

consequence is that wrinkling should be ubiquitous, especially in suspended samples, because minimal shear and/or compression will lead to buckling and wrinkling, which is actually seen experimentally [18]. Fortunately, the geometry and mechanics of wrinkling is a topic of recent interest in the non-linear elasticity of membranes and foils, and most of the physics involved is universal. This allowed us to investigate the effects of wrinkling in the electronic transport by studying the behaviour of massless Dirac fermions in the curved background of a wrinkled graphene sheet [19]. We found that so-called conical singularities, that arise at the meeting point of any two wrinkles, act as resonant scatterers and can limit the mobility of even the cleanest suspended samples. This is also another example of soft and hard condensed matter playing along.

Finally, one last singularity of graphene: it is 98% transparent (could hardly be otherwise with the thickness of 1 atom!), while metallic, and structurally resilient [20]. Such combination makes it a perfect material for the booming field of transparent flexible electronics [21], and the role of strain can be important here as well for obvious reasons. Moreover, since the optical response of graphene is practically flat in a huge spectral range spanning the THz up to

the near UV, strain can be used to induce optical dichroism, and possibly allow optical elements (e.g.: polarizers) that can operate predictably on such large bandwidths [22].

Final thoughts

Graphene research is still a booming area of research, notwithstanding the 2010 Nobel Prize. In fact, many alleys and avenues are just now being stepped into. Tailoring and on-demand tunability of graphene's properties will certainly be a key aspect of its future in real-world applications. One such approach relies on the pseudo-magnetic fields induced in strain-engineered structures, which not only provide useful applications, but can also help us understand some fundamental aspects of quantum condensed matter. With NUS in the top three of the most active institutions researching graphene worldwide [23], much more is undoubtedly expected to come in the near future.

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