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Synthesis and Biomedical Applications of Graphene: Present and Future Trends

Ajay Kumar and Chee Huei Lee

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1. Introduction

In 1959 great physicist Richard P. Feynman through his statement: “There is a plenty of room at the bottom”, predicted a new era of technology known as nanotechnology, where manipulation of the properties of a device is possible at atomic, molecular and macromolecular scales [1, 2]. Nanotechnology is basically a technology based on structures of sizes varying between 1 nm to 100 nm. Figure 1 illustrates the scale of nanomaterials with comparison with some biological systems. At nanoscale, materials properties are changed drastically due to quantum mechanical phenomena, which come into play at these sizes [3-5]. Nanomaterials exhibit higher surface to volume ratios which is inversely proportional to the size of the nanomaterials. There are also numerous properties which obey the same scaling law, e.g. melting and other phase transition temperatures. Atoms in these structures lie near to the surface, which are also known as higher energy sites. The behaviour of atoms at these higher energy sites has a significant influence on the properties of the material. Edge and corner atoms in the nanomaterials have lower coordination and bind foreign atoms and molecules more tightly [6].

Among other nanomaterials, graphene has become a rising star in condensed matter physics and material research. Graphene is defined as an atomic thick planar sheet of sp^2 -hybridized carbon atoms that pack into a two-dimensional (2D) honeycomb lattice made out of hexagons, as presented in Figure 2a. Because of its novel and unique properties, tremendous fundamental and technological studies have been stimulated. Graphene has a unique band structure in which the conduction band and valence band just touch each other, forming an exactly zero-band gap semiconductor (also known as semi-metal). The charge carriers behave as Dirac fermions, which has a zero effective mass at the K and K' point (named as Dirac points) at the corners of its Brillouin zone [8]. This gives rise to many extraordinary phenomenon, for examples ultrahigh carrier mobility (theoretical prediction up to $200,000\text{cm}^2\text{V}^{-1}\text{s}^{-1}$) [9-11], half-

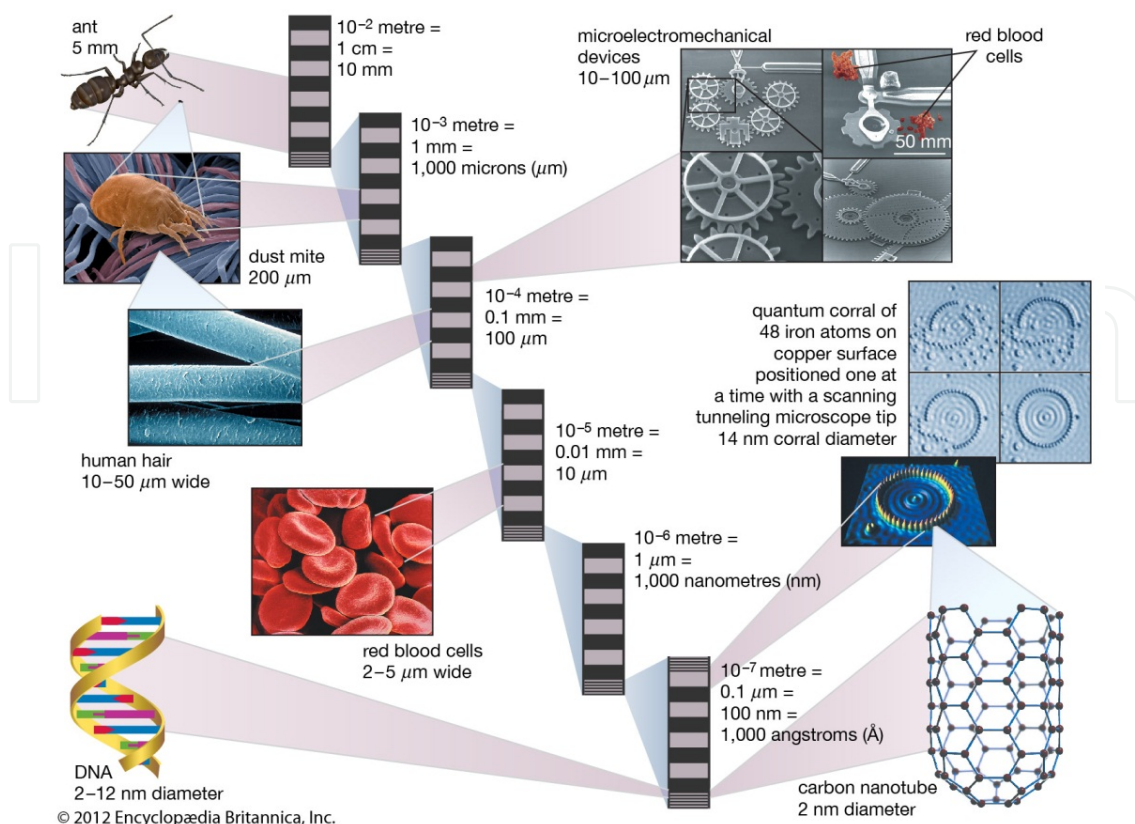


Figure 1. Scale of nanomaterials [7].

integer quantum Hall effect [12, 13], absorption of 2.3% of visible light [14], a high thermal conductivity [15], the correspondent Young's modulus and intrinsic strength of 1.0 TPa and 130 GPa respectively (the breaking strength is about 200 times larger than that of steel) [16]. Furthermore, graphene can be seen on a "magic substrate" ($\sim 300\text{nm SiO}_2/\text{Si}$) with a standard optical microscope [17]. These interesting properties have been shown to have huge potential applications in many areas, such as graphene electronic transistors [18, 19], integrated circuits [20], transparent and flexible electronics [21, 22] as well as supercapacitors [23]. In a recent study, detection of the adsorption of a single gas molecule was done using graphene sensor, as graphene is highly sensitive to any change in the electrical resistance attributed to the local changes in carrier concentration. The importance of these structures is not only due to their future technological applications, but also because they may define a stage in the formation of other nanostructures, such as nanotubes [24]. Some of the very promising biomedical applications of these materials can be such as joint replacement prostheses, vascular grafts, and intraocular lenses/other ophthalmological devices.

2. Overview of graphene synthesis

Atomic layers of graphene were first obtained in 2004 [25]. Andre K. Geim and Konstantin S. Novoselov used a regular Scotch tape to extract thin layers of graphite from highly oriented

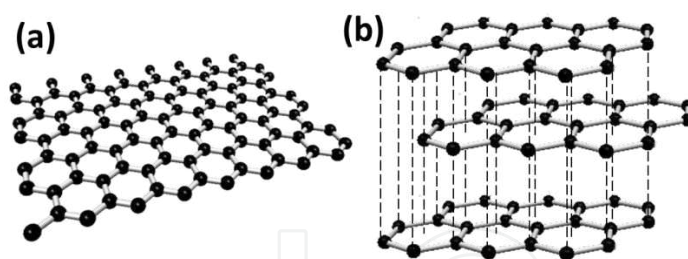


Figure 2. a) Graphene is a single layer honeycomb lattice of carbon atoms. b) Graphite viewed as a stack of graphene layers.

pyrolytic graphite (HOPG) and then transferred these layers to a silicon substrate. Since then, this technique is referred as “mechanical exfoliation”, which so far provides the best quality graphene in terms of structural integrity. Many fascinating physics have been observed based on this type of sample preparation [12, 26, 27]. Both scientists have been awarded a Nobel Prize in Physics 2010, for producing, isolating, identifying and characterizing graphene [28]. However, this technique is only limited for scientific interest, as the size, thickness and location are mainly uncontrollable, in which large scale production and applications are hindered.

Another graphene synthesis method involves solution based exfoliation of graphene oxide (GO) [29-31]. Particularly for large scale applications, such as supercapacitors, composite materials, gas sensors [32, 33] and flexible electronic materials, this solution based method becomes very promising. In general, simple graphite powders are used as a starting material. They are oxidized by chemical modification, the so-called Hummers’ method to produce water dispersible GO. GO can be easily exfoliated in water by the addition of mechanical energy (such as sonication) because of the interaction of water with the oxygen-containing (epoxide and hydroxyl) functional groups introduced during the oxidation process. GO can then be substantially reduced or restored to graphene network by thermal annealing or chemical reducing agents treatment. This “chemically derived graphene” is usually referred as reduced graphene oxide (rGO). The synthesis process can easily be scaled-up to produce gram quantities and disperse rGO in solution. However, the graphite materials undergo serious alteration during the process of oxidation and reduction. It has been recognized that solution based production of graphene contributes significant structural defects and uncompleted reduction process, leaving oxygen functional groups on graphene flakes. Nevertheless, rGO can be still useful for various applications as mentioned above.

Another relatively “straight forward” way to produce graphene is a conversion of SiC to graphene via sublimation of silicon atoms at high temperature (usually at $\sim 1300^{\circ}\text{C}$ in ultrahigh vacuum condition) [34, 35]. It has been shown that graphene via this method exhibits high mobility and remarkable 2D electron gas (2DEG) behavior. This method has the potential for large scale integration of nanoelectronic devices. However, the requirement of ultrahigh vacuum and high temperature may limit the accessibility of this method, due to a higher cost. Further review on epitaxial graphene growth using SiC substrates can be found in [36].

In the last few years, a lot of research interest has also been paid to the multilayer graphene nanoflakes films (MGNFs), also known as carbon nanowalls, nanoflakes, nanosheets or petals.

These are few nm thick graphene nanosheets, terminated with vertically aligned ultrathin graphene edges having lateral dimension in the micron range. They can be grown without the need of a catalyst. These structures exhibit a large amount of open graphitic edge planes responsible for their higher surface activity. Due to large surface area, sharp edges and vertical orientation, MGNFs hold promise as templates for various nanostructure materials e.g. magnetic, metal and oxides nanoparticles having applications as batteries, data storage media, and field emission devices. The freestanding (non-surface bound) nature and absence of catalyst made MGNFs very attractive as they also possess the combined advantages of large surface area, highly electrochemical activity and stable mechanical strength. These nanostructures have demonstrated excellent electron transfer properties, highly electrocatalytic activity and good selectivity for a number of biomolecules [37-40].

At a glance, the current graphene synthesis methods are summarized in Table 1, including the CVD method, which will be discussed in Section 3.

Synthesis Method	Brief Description/Remarks
Mechanical Exfoliation	<ul style="list-style-type: none">• Using a regular Scotch tape to peel off graphene from HOPG.• Atomic layer of graphene can be seen on ~300 nm SiO₂ substrates under an optical microscope.• Pristine graphene with highest quality of electrical properties.• The size, thickness and location are uncontrollable, with limited practical applications.
Solution based exfoliation of graphene oxide (GO)	<ul style="list-style-type: none">• Graphite powders are initially oxidized by chemical modification (Hummers' method) to be dispersed in solution.• GO are subsequently reduced to graphene by thermal annealing or chemical reducing agents.• Large scale production for bulk applications, such as supercapacitors, composite materials, etc.• Significant structural defects and leaving oxygen functional groups on the product.
Epitaxial growth using SiC substrates	<ul style="list-style-type: none">• A conversion of SiC substrate to graphene via sublimation of silicon atoms on the surface.• Done at high temperature (~1300°C) and ultrahigh vacuum condition.• Limited accessibility due to high-end equipment.
CVD growth Graphene	<ul style="list-style-type: none">• Most promising, inexpensive and feasible method for single layer or multi-layers graphene production.• Using transition metal (Ni, Cu, etc.) substrates or thin films as catalyst.• Flowing carbon source (CH₄) and reactant gases (H₂) at high temperature (~1000°C) for the nucleation of graphene.• Single layer graphene can usually be obtained on Cu.• Can be scaled up for large area graphene production for practical applications, such as transparent electrode applications.

Table 1. A Brief Summary of Graphene Synthesis Methods

3. Chemical Vapor Deposition (CVD) synthesis

Among these approaches, chemical vapor deposition (CVD) using transition metal substrates has been considered the most promising, inexpensive and feasible method to produce single layer or multi-layers graphene. Graphene grown on Ni [21], Pd [41], Ru [42], Ir [43] and Cu [44] have been demonstrated in the past few years. CVD using Cu is one of the fastest developing processes to produce single layer graphene due to the low solubility of carbon in Cu which leads to a self-limited process [44]. It has been shown that large area growth and excellent device properties can be achieved by this method [22]. Figure 3 demonstrates a schematic of an experimental setup of CVD which is commonly employed to produce single layer graphene by Cu or Ni catalysts. It basically consists of a tube furnace for high temperature heating, a quartz vacuum chamber, a vacuum and pressure control system for the growth condition adjustment, and several mass flow controllers (MFC) to provide carbon source and reactant gases with a necessary flow rate.

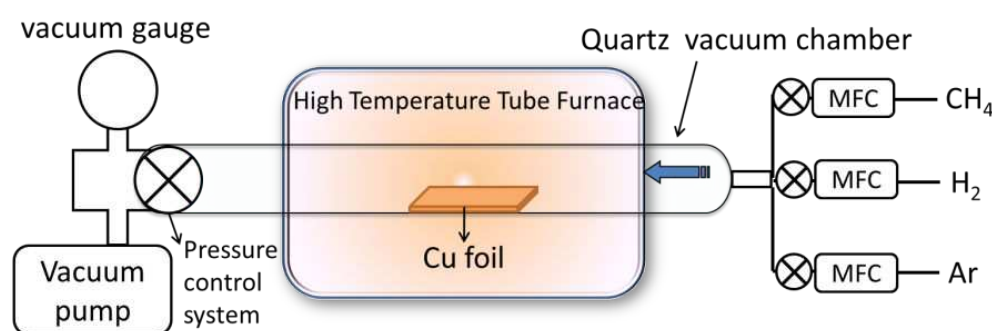


Figure 3. Schematic of a common setup for chemical vapor deposition of graphene.

3.1. Nickel as a catalyst

Learning from huge amount of studies on carbon nanotubes, different research groups have demonstrated using Ni layer as catalysts for large scale graphene synthesis [21, 45-47]. At a glance, ultrathin graphene films (1 to ~10 layers) grown on evaporated polycrystalline Ni surface have been performed in an atmospheric pressure or low pressure CVD. In brief, Ni films with 100-500 nm is first deposited by electron beam (e-beam) evaporation or sputtering on a SiO_2/Si . It was then annealed to form polycrystalline Ni grains with atomically flat surfaces and sizes of 1-20 μm . The CVD growth is carried out at 900 $^\circ\text{C}$ or 1000 $^\circ\text{C}$ under a highly diluted flow of methane (CH_4) in H_2 under ambient pressure for 5 to 10 minutes. The graphene on Ni can then be transferred to different substrates, as will be discussed in the transfer mechanism section. The geometry of graphene film can be patterned by the standard lithographic process after the transfer process. Alternatively, the Ni catalytic layer can be first pre-patterned to produce the same graphene geometry at desired locations.

It is critical to control the synthetic graphene by its parameters, for examples temperature, gas composition, gas flow rate, deposition time as well as heating and cooling rate. It has been

found that using diluted CH_4 is important to produce single and few-layer graphene. Using concentrated methane will lead to multilayers of graphene (> 5 layers) [47]. Cooling rate also significantly affects the thickness and the amount of defects of graphene on Ni. It has been reported that a fast-cooling process can suppress the amount of precipitated C, leading to single or few layers graphene. However, as more freedom participates in the deposition process, the control of deposition is of more difficulties. It is suggested that a moderate cooling rate of 10°C/s is the optimum condition for thin layer graphene growth. Generally, CVD by Ni catalysts still yields films with a wide range of graphene layer thicknesses, from one to a few tens of layers and with defects associated with fast cooling.

3.2. Copper as a catalyst

CVD graphene using Cu as a transition metal substrate for single layer graphene synthesis was first demonstrated by Rouff's group in 2009 [44]. In fact, it was a relatively new technique compared to mechanical exfoliation and the desorption of Si from single crystal SiC. Since then, there are a lot of research activities using Cu to grow single layer graphene and transfer graphene onto an insulating substrate for device fabrication and testing. In principle, graphene on Cu is grown by the decomposition of methane gas in dilute hydrogen environment over the surface at 1000°C . The thickness of the Cu substrate is usually $25\text{--}50\ \mu\text{m}$. For a typical growth process, the Cu foil is first annealed at 1000°C in dilute H_2 environment for 30 minutes. Then, a small flow rate of methane (CH_4) as the carbon source gas is introduced for about 30 minutes.

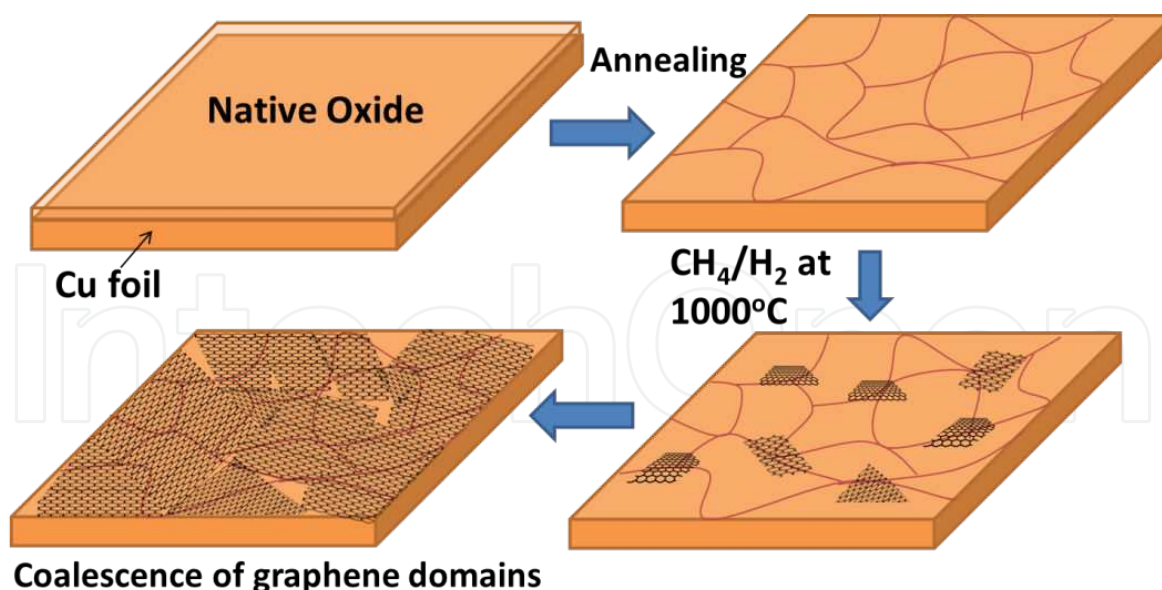


Figure 4. Schematic illustrating the proposed growth mechanism of graphene on Cu substrates by CVD: (a) copper foil with native oxide; (b) Native Cu oxide is reduced while Cu develops grains on the surface after annealing at high temperature in H_2 environment; (c) The exposure of the Cu foil to CH_4/H_2 atmosphere at 1000°C leading to the nucleation of graphene islands; (d) enlargement of the graphene flakes and coalescence of graphene domains with different lattice orientation [48].

After exposure to CH_4 , the furnace is cooled to room temperature. Because of its self-limited surface process [44], the graphene growth by Cu is robust for different growth conditions, compared to the growth by Ni. The cooling rate does not result in discernible differences in the number of layers growth.

Figure 4 illustrates the proposed growth mechanism of graphene on Cu. The annealing at high temperature in H_2 environment is to remove the native oxide layer on the Cu surface, while Cu grains will also develop. With the exposure of Cu foil in CH_4/H_2 environment, nucleation of graphene islands start taking place randomly but preferentially at the grain boundary of Cu surface. As the exposure to CH_4 continues, the graphene domains grow in size to cover the whole area of Cu substrates and eventually aggregate into a continuous graphene film.

It is noted that these initial graphene domains could have different lattice orientations depending on the crystallographic orientation of the underlying Cu grains. Therefore, it is not surprising that the large area graphene is indeed formed by multiple domains of tens of μm^2 [49]. Graphene may grow across metal steps and grain boundaries [43, 45]. This may also explain why graphene can grow laterally even on a rough Cu foil. The domains usually do not align in perfect lattice structure, therefore give rise to the inter-domain defects [50]. Despite these defects, large area graphene in industrial scale has been demonstrated for transparent and flexible electrodes to fabricate a touch screen display [22]. Many efforts have been carried out to produce CVD-graphene which has comparable quality with those produced by mechanical exfoliation. It is possible to increase the domain size by understanding the growth parameters and modifying the process control [50]. The effect of different facets of Cu has been studied extensively [51]. Generally, there is a consensus that Cu(111) facet facilitates monolayer and uniform graphene growth, due to the close lattice matching between hexagonal graphene (lattice constant of graphene, $a = 2.46\text{\AA}$) while hexagonal Cu(111)'s, $a = 2.56\text{\AA}$) [51, 52]. Furthermore, it is also important to understand the growth mechanism of graphene using metal catalysts under different growth conditions. It has been shown that Cu-graphene can be grown under atmospheric pressure [53] or low pressure [44, 54]. However, the kinetics of graphene growth is very much different under different conditions, giving rise to the uniformity issue of large area graphene.

3.3. Transfer mechanism

Graphene grown on transition metals must be transferred onto insulating substrates for device fabrication and electronic characterization [55-57]. Different methods have been demonstrated to transfer the as-grown graphene on metal substrates onto desired insulating substrates, such as polymeric foils (polyethylene terephthalate (PET)), glass and SiO_2/Si . Up to this date, the relatively straightforward way is to chemically etch the metal away to obtain a free standing graphene membrane. This membrane can then be scooped on a desired substrate. A general transfer technique of CVD-graphene onto a target substrate is illustrated in Figure 5. Typically, the transfer is first conducted by spin-coating a thin polymeric layer, such as poly(methylmethacrylate) (PMMA) or Polydimethylsiloxane (PDMS) on top of the as-grown graphene. This polymer provides a supportive framework for graphene before the transfer. The underneath Cu substrate is then etched away by iron chloride (FeCl_3) solution. Other etching agents that can be

employed include HCl, HNO₃, Fe(NO₃)₃, (NH₄)₂SO₈, and CuCl₂. After the Cu is completely dissolved, the floating membrane can be scooped and placed on a desired substrate. After drying, the polymeric film is dissolved with acetone or chloroform. Another successful transfer of graphene has also been performed by the roll-to-roll process using a thermal release tape as the supportive layer [22]. In brief, a thermal release tape is first attached to the graphene film grown on copper, followed by the Cu etching and rising with deionized water. This assembly together with a target substrate is inserted into a roller and exposed to mild heat to release the graphene from the tape to the target substrate. A large area touch screen is further demonstrated with the transferred graphene on a flexible PET substrate using this transfer technique [22].

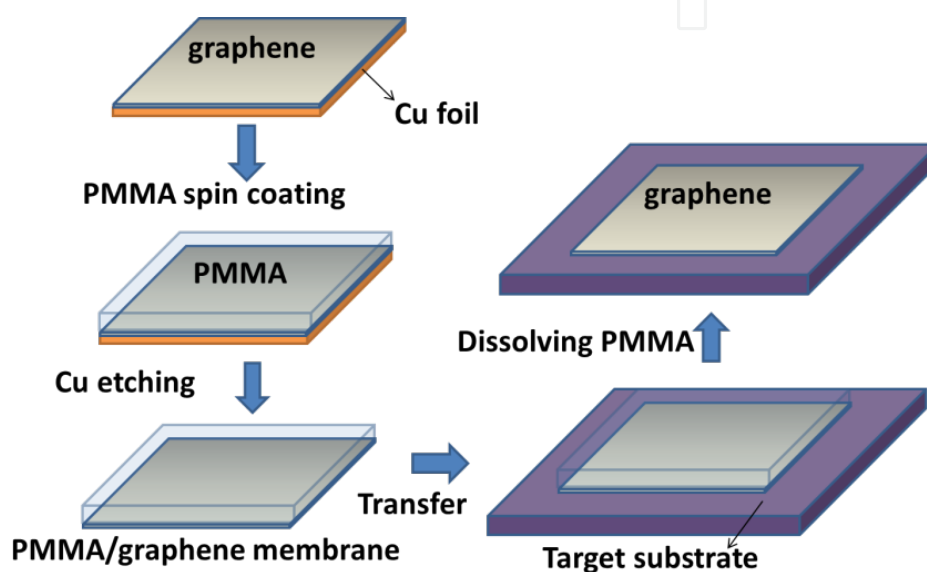


Figure 5. A cartoon showing the transfer process of graphene grown on Cu foil onto a target substrate.

Apparently, all these transfer methods of graphene from metal substrates to insulating substrates introduce certain degrees of structural defects, such as crack, wrinkles and ripples [21]. In addition, it is hard to completely remove the polymer layer, leaving certain amount of impurities on graphene. In this aspect, it is of great importance to preserve the quality of graphene during the transfer process for device performance, yield and uniformity. Additional processes such as PMMA heating, substrate treatment, high vacuum annealing, chloroform cleaning and so on, have also been introduced in order to achieve crackles and clean graphene with its intrinsic properties [58-61].

4. Biomedical applications of graphene

As mentioned in the Introduction section, graphene rises up as a promising material for many potential applications, such as graphene electronic transistors [18, 19], integrated circuits [20], transparent and flexible electronics [21, 22], composite materials [29], supercapacitors [23], as well as gas sensors [32, 33].

In addition, Dai et al was the first to study the biomedical applications of graphene by using graphene oxide as drug carrier to kill the cancer cells selectively [62]. After this study, a lot of research interest has been created to use graphene in many different applications such as the exploration of graphene-based nanomaterials for tissue engineering, molecular imaging, and drug/gene delivery applications. There are many biological interactions such as cellular uptake and cytotoxicity largely dependent on the size of nanomaterials. In addition to this, shape and surface of these nanomaterials also contribute towards their specific biomedical applications. In this section, we will discuss first the biosensing applications of graphene and in the next part graphene scaffolds will be discussed.

4.1. Biosensing

A biosensor is an analytical device that helps to gain understanding of the bio-composition, structure and function of target analytes by biological reactions. As shown in Figure 6, a biosensor mainly consists of a recognition layer, a transducer as well as electronic components. The recognition layer determines the biological response which is further converted into an electrical signal with the help of the transducer. This electrical signal is then amplified and processed by the external electronic system. Biosensors are very useful tools in many applications such as medical care, environmental field monitoring etc.

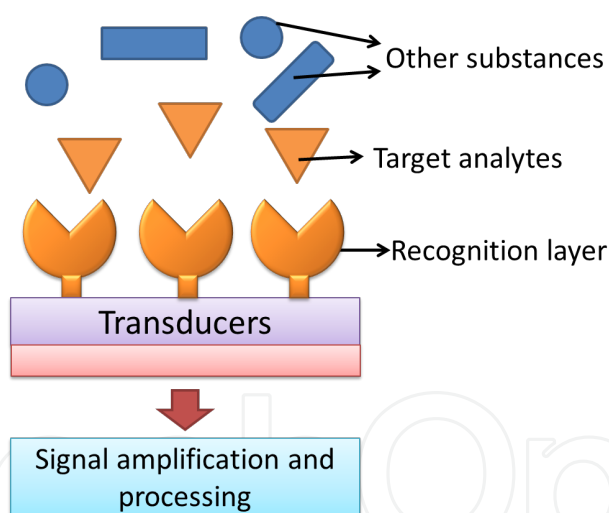


Figure 6. Schematic diagram of a biosensor

Electrochemical activity of nucleic acids was first reported by Paleček [63]. Since the discovery of electroactive behaviour of nucleic acids, a lot of research has been devoted to their quantification via electrochemistry. The aim is to use the nucleic acid recognition layers immobilized over a signal transducer (electrochemical, optical or piezoelectric), to fabricate a DNA biosensor for detecting target analytes.

Due to their interesting properties such as small size and excellent electrical conductivity, carbon based nanomaterials are very useful to manufacture the transducer electrode for electrochemi-

cal sensing applications. Britto et al. first reported the use of nanotubes for dopamine oxidation [64]. DNA electrochemical biosensing has become an attractive method due to its ease of miniaturization, low cost and direct readout of the electronic signals. Deoxyribonucleic acid (DNA) has contributed to the design of therapeutics and to many other applications via genetic engineering. Major studies on DNA have focused on the sequence-specific recognition and mutation of the single stranded DNA (ss-DNA) by various techniques [65-68]. However, DNA is rarely present in the single-stranded form in nature. The detection of double stranded DNA (ds-DNA) is important since it will allow the direct visualization of the genomic information in living cells and the development of cell based technology [69]. The electrochemical DNA biosensors can be distinguished into label free (based on intrinsic electroactivity of nucleobases) and labelled (where redox active species is used with ds-DNA) ones [70].

In case of the electrochemical label-free DNA sensors, sensing depends on the intrinsic electrochemical properties of the nucleic acid target. As guanine is the best redox active base, its oxidation signal at about +1 V (vs Ag/AgCl) is usually used to detect the hybridization process. Using this approach a detection limit below 100nM was achieved for a 19 base sequence containing 4 guanine residues [70]. Electrochemical impedance spectroscopy is another aspect where label free approaches has been used by recording any change in the faradaic impedance of a ss-DNA modified electrode to its hybridised version. Ferricyanide was used as a redox species.

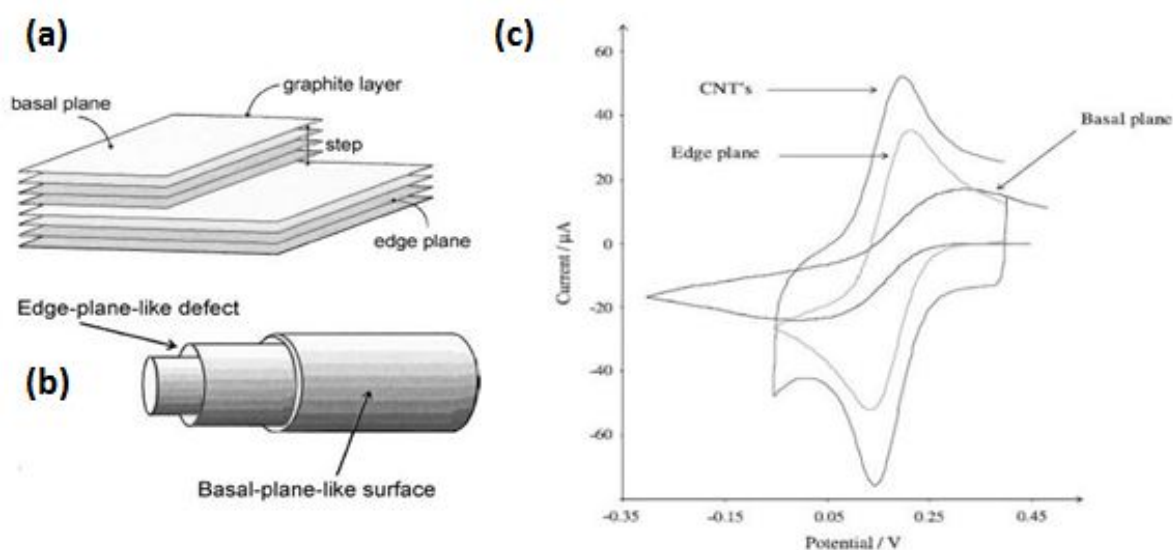


Figure 7. Schematic representation of (a) highly ordered pyrolytic graphite crystal, (b) multiwalled carbon nanotubes and (c) A comparison of electrochemical behaviour of nanotubes-modified electrode, edge- and basal plane pyrolytic graphite electrode. Reprinted with permission from Ref. [73]. Copyright 2006, John Wiley & Sons, Inc.

The higher charge transfer resistance was attributed to a repulsive force on ferricyanide by the DNA duplex due to its negative charge. Thus label-free DNA sensing approach is a promising way to avoid any complications for the device fabrication. It is also a cost effective and more accurate method based on intrinsic electroactivity of nucleobases [71, 72].

Labelled approached DNA sensors are based on the use of redox indicators to make a distinction between the signal and ds-DNA on the electrode [71]. Millan et al. used Co(phen)_3^{3+} as a redox indicator to probe the ssDNA hybridization with the glassy carbon electrode and observed a much better response in comparison to the ss-DNA on glassy carbon electrode. In another study, using the same indicator with carbon paste, Mycobacterium tuberculosis bacteria with detection limit as low as 3.4 nM was reported [72, 74]. Ferrocenyl-naphthalene diimide, nanoparticles and methylene blue are other indicators being used for the labelled approaches to achieve lower detection limits [75, 76]. An enzyme indicator with magnetic separator was also used to avoid the selectivity problems [77]. This approach is more complicated and costly in comparison to the labelled approach.

Current challenges to the rapid development of low-cost, label free highly sensitive ds-DNA based electrochemical sensor technology are primarily high electrochemical oxidation potentials and low electron transfer rates associated with the deep entrapment of DNA bases in the stable rigid double helix structure, preventing immediate electrical contact between the nucleic base and the electrode surface. Adenine and guanine residues of DNA can electrochemically be detected with a poor signal and a low sensitivity at various electrodes such as gold, glassy carbon (GC), carbon nanotubes (CNTs), and polymer modified graphite/GC [78-83]. From a fundamental point of view, the main problem on evaluating the use of CNTs for electrochemical applications such as sensors and energy storage devices, is the presence of metallic impurities, as the synthesis of nanotubes is usually achieved with the use of metal catalyst. First issue with these impurities is that these are electrochemically active and can dominate the electrochemistry of CNTs. The second is the toxicological hazards as they can participate in the redox activities of biomolecules. The complete removal of these metallic impurities from the nanotubes is not achievable even after purification method such as acid treatment. Acid treatment is a time consuming process which needs to be optimized first otherwise nanotubes can be completely destroyed and also CNTs after acid treatment are full of defects which deteriorate their electrical performance. This drawback can be very critical to the observed electrochemical reaction. Thus, there is a need of a material possessing similar/better electrochemical response without any metallic impurities.

Currently, due to the different electrochemical activity and assays employed, the mechanism of the electrooxidation of ds-DNA based on different electrodes is not clear and the interaction of DNA with electrodes has a non consistent behaviour. For examples, Bollo et al [80], Pedano et al. [84] and Nowicka et al. [85] found that ds-DNA exhibited weak responses at polished GC electrodes, while two other research groups reported no electrochemical response of ds-DNA at bare GC electrodes [80, 86]. Obviously, this points to the fact that the oxidation dynamics of ds-DNA on such electrodes could relate with unknown factors such as the surface roughness, surface functional species, surface area, preferential facets, grain size, electroactive media, time of exposure to air etc, many of which are difficult to be controlled by simple mechanical polishing or electrochemical activation procedures. As for electrodes modified with substances capable of catalyzing the reaction of nucleic bases, their reproducibility is highly variable, due to the difficulty in controlling the quantity, thickness and active surface area of catalytic medias by a simple method such as the drop casting or dip coating etc.

4.2. Scaffolds for bioengineered organs

Tissue engineering is a very challenging area of research and highly desirable to improve the well-being of mankind. Many three-dimensional scaffolds for bioengineered organs have been studied for their suitability for tissue growth for example carbon nanomaterials (nanotubes, nano-diamond and fullerene) [87]. Biocompatibility is a very important issue for a material to be used in biomedical applications as it initiates the cell cultivation. In the commercially used metal implants, their elastic moduli are many times higher than tissues; this causes the bone to be insufficiently loaded and eventually can hamper the growth [88, 89].

Collagen sponge honeycomb have also been reported for cell culture applications but effective cell adhesion on their surface was not good due to bigger pore sizes [90]. To overcome this issue, Multiwall CNTs were coated on these, which lead to better cell proliferation [91]. CNTs are also found to be useful for improvement of the cell adhesion and differentiation [92]. Selective bone tumor therapy was also proposed by using fullerene as a drug carrier agent by inducing the photodynamic damage on biological systems [93].

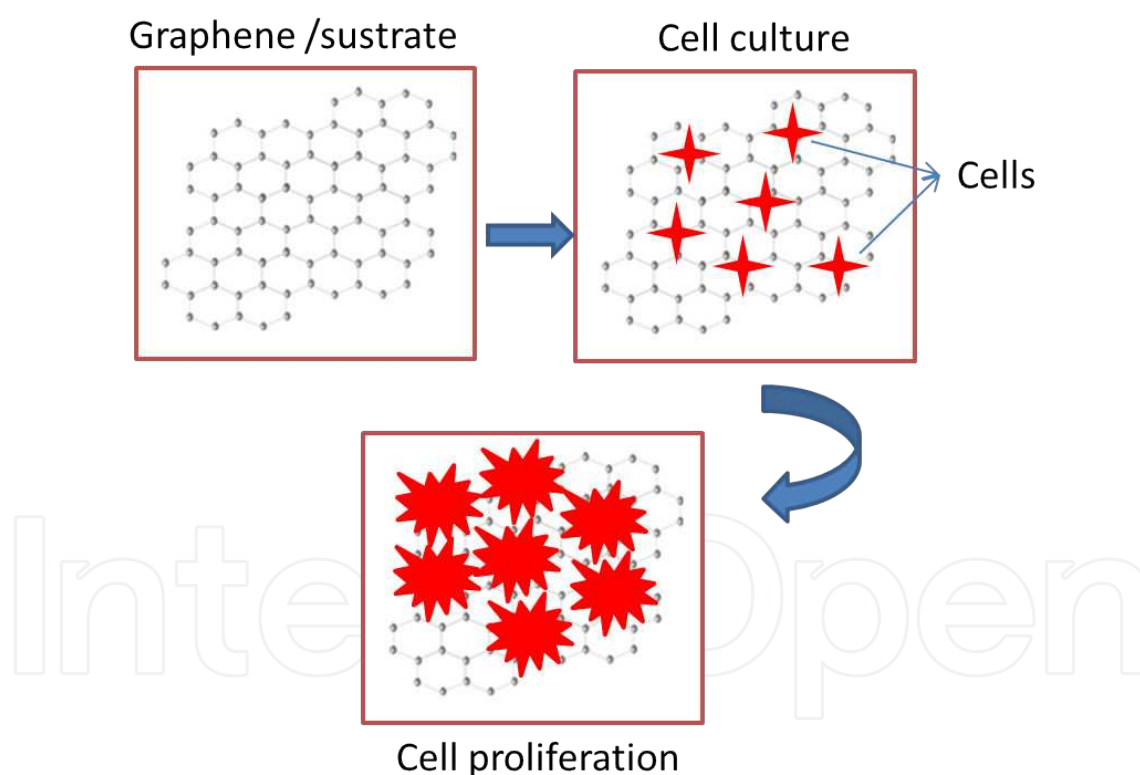


Figure 8. Schematic representation of Cell culture and proliferation on graphene platform.

Nanodiamonds are currently being used in many biomedical applications (such as drug delivery and surgical implants) due to its lack of cytotoxicity [94]. Surface area of a monolayer graphene is higher approximately by an order of magnitude in comparison to other biomaterials making it a very interesting biomaterial.

Graphene flat surface nature in addition to the many other mechanical properties can also be exploited for applications such as structural reinforcement of biocompatible films and scaffolds for bioengineered organs. Regarding their cell culture studies, an improvement of the osteogenic potential has been achieved using graphene-coated surfaces for the differentiation of human mesenchymal stem cells (hMSCs) and preosteoblasts into osteoblasts [95, 96]. Cell culture studies of graphene oxide sheets also show promise as the suitable implant material [97]. Although there have been studies on graphene for tissue engineering, there is a lack of studies for health impact issues as well as actual interaction mechanism of these materials with different cells. To address these, the studies should be more focused and different biomedical applications must be optimized.

5. Future trend and outlook

Chemical vapor deposition (CVD) using Cu as the catalyst substrate is undoubtedly a promising way to produce single layer graphene over a large area. By further understanding the growth mechanism and optimization of the growth condition, it can be foreseen that high quality of graphene can be routinely reproduced by this CVD technique. Note that this type of CVD process can be scalable easily and only limited by the size of the apparatus. Mass production is not an issue while over 30 inches diagonal size of graphene had been demonstrated. However, there are other obstacles that need to be overcome to produce as high quality as the pristine graphene from mechanical exfoliation. For examples, further improvement of the transfer process is still highly desired to minimize structural defects and impurities on graphene. On the other hand, direct deposition of graphene onto insulating substrates is still a challenge to the scientific community. There is definitely an advantage of avoiding the transfer process that can be problematic as mentioned. Besides, the transfer process can be time consuming and not an environmental friendly process.

Up to this point, direct growth of graphene with definite number of layers is of difficulties. It will be a breakthrough if one can achieve specific layers of graphene growth for particular applications. Single layer graphene has no bandgap while double layers graphene can have a small bandgap. In addition, functionalization of graphene by physical and chemical method also provide the possibilities and challenges of tailoring the electronic and sensing properties of graphene for many applications. This manipulation includes sizes, geometries, band gaps, doping levels, functionalized chemical groups and so on [98]. There are also studies implementing plasma technology for producing and manipulating graphene [99-105]. Despite of current and future challenges, graphene research provides huge potential for material and functional applications and it is still progressively active around the world.

As discussed earlier, biomedical applications of nanomaterials can be further extended to as fluorescent markers in biodetection assays, chemotherapy and transplant materials. Immobilization, electro-oxidation and quantitative analysis of a monolayer of native DNA self-assembled on the vertically aligned graphene nanoflake films have been demonstrated by Pagona's group recently [39]. Graphene nanoflakes edge planes exhibits unique electronic

structure and edge state properties. These features attribute to the exceptional electrocatalytic activity of these nanomaterials for ds-DNA detection. It can be envisioned that the use of MGNFs as nanoconnectors, which establish direct electrical communication between the graphene edge plane and the active site of DNA or other biomolecules, will create a new generation of graphene-based enabling biotechnology leading to the production of label-free DNA biodetection, biofuel cells and electrocatalytic devices. For the tissue engineering applications of graphene, a systematic optimization approach keeping in mind the environmental safety for different cells response is needed.

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Author details

Ajay Kumar^{1*} and Chee Huei Lee²

*Address all correspondence to: ajayepph@gmail.com, cheehuei80@gmail.com

1 Department of Chemical Engineering, Case Western Reserve University, Cleveland, Ohio, USA

2 Singapore University of Technology and Design, Singapore

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