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Carbon nanotubes as electrode material for electrochemical sensing of neurotransmitters

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Abstract in English:

Dopamine, serotonin and epinephrine are electrochemically active neurotransmitters. Dopamine's role is in neuronal reward, decision-making and motor control. Abnormal functioning of dopamine is linked to diseases such as Parkinson's disease, attention deficit hyperactivity, schizophrenia, depression and addiction. Serotonin's role is in regulation of mood, sleep, sexuality and appetite. Abnormal function of serotonin is linked to depression, anxiety and migraines. Epinephrine controls 'fight or flight' response and is involved in physical and mental stress, blood pressure, heart rate, immune system and glycogen metabolism. Abnormal function of epinephrine has also been linked to Parkinson's disease.

The monitoring of these neurotransmitters has difficulties. The quantities are low (5-500 nM for dopamine) and the changes in concentration are fast. Electrochemical sensing is studied for continuous monitoring of neurotransmitters, but new electrode materials are needed for improving the sensitivity, selectivity and fouling resistance of the electrodes. One studied material is carbon nanotubes.

Carbon nanotubes have great electrical properties and are inert in a biological environment. Both multi wall and single wall carbon nanotubes have been studied to improve electrodes. This thesis reviews academic papers that have carbon nanotubes used as electrodes or carbon nanotubes added on existing electrodes, such as glassy carbon electrodes or carbon fiber electrodes. Incorporating carbon nanotubes seem to increase the selectivity, sensitivity and resistance to fouling of the working electrode in cyclic voltammetry setting. Even though lower quantities of neurotransmitters can be detected with carbon nanotube electrodes, the sensitivity isn't quite enough for continues monitoring of neurotransmitter quantities in the brain.

Abstract in Finnish:

Dopamiini, serotoniini ja epinephriini ovat elektrokemiallisesti aktiivisia välittäjäaineita. Dopamiinin rooli liittyy aivojen palkitsemisjärjestelmään, päätöksentekoon ja motoriikkaan. Poikkeavuudet dopamiinijärjestelmässä on linkitetty sairauksiin kuten Parkinsonin tauti, tarkkaavaisuushäiriö, skitsofrenia, masennus ja riippuvuus. Serotoniini säätelee mielialaa, unta, seksuaalisuutta sekä ruokahalua. Poikkeavuudet serotoniinjärjestelmässä on linkitetty mm. masennukseen, ahdistukseen ja migreeniin. Epinephriini kontrolloi 'taistele ja pakene' – reaktiota, sekä liittyy fyysiseen ja psyykkiseen stressiin, verenpaineeseen, sykkeeseen, immuunijärjestelmään sekä glykogeenin aineenvaihduntaan. Poikkeavuudet epinephriinijärjestelmässä on myös linkitetty Parkinsonin tautiin.

Näiden välittäjäaineiden mittaaminen on haastavaa. Välittäjäaineiden määrät ovat pieniä (dopamiinin normaalimäärät ovat 5-500 nM) sekä pitoisuuksien vaihtelu on nopeaa. Välittäjäaineiden elektrokemiallista mittausta tutkitaan jatkuvan mittauksen menetelmänä, mutta uusia elektrodimateriaaleja tarvitaan parantamaan herkkyyttä, valikoivuutta sekä parantamaan käyttöikää estämällä likaantumista. Yksi tällainen tutkittu materiaali on hiilinanoputket.
Hiilinanoputkilla on erinomainen sähkönjohtavuus sekä ovat inerttejä biologisessa ympäristössä. Sekä yksiseinäisiä, että moniseinäisiä hiilinanoputkia on tutkittu elektrodimateriaalina. Tässä diplomityössä käydään läpi tutkimuksia sekä akateemisia julkaisuja, joissa tutkitaan hiilinanoputkista tehtyjä

elektrodeja sekä hiilinanoputkilla paranneltuja jo olemassa olevia elektrodeja, kuten lasihiilielektrodeja ja hiilikuituelektrodeja. Hiilinanoputkien käyttö näyttäisi parantavan elektrodin herkkyyttä, valikoivuutta sekä vähentävän likaantumisherkkyyttä, kun menetelmänä on käytetty syklistä voltammetriaa. Vaikka hiilinanoputkielektrodit parantavat mittauksen herkkyyttä, ei tutkitut elektrodit näyttäisi pystyvän vielä tarpeeksi tarkkoihin mittauksiin, jotta aivojen välittäjäainepitoisuuksien jatkuva mittaus olisi vielä mahdollista.

Key words: Carbon nanotube, CNT, MWCNT, SWCNT, electrochemistry, cyclic voltammetry, neurotransmitter, dopamine, serotonin.

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1 Introduction

Nanomaterials are researched for several fields including medicine, energy and electronics. In medicine, nanomaterials are studied for a number of applications, including drug delivery and diagnostics. This thesis focuses on literature and academic study made in the field of electrochemical sensing of neurotransmitters using electrodes modified with carbon nanotubes. More specifically, in the direct sensing of dopamine, serotonin and epinephrine.

Electrochemical study, i.e. voltammetry, is used as a faster way of detecting biomolecules without the need for bulky equipment. It is hoped to be an answer for quantifying neurotransmitters, which then would help fight neurotransmitter related diseases such as Parkinson's and ADHD. For now, neurotransmitter quantifying is difficult because they are situated in the brain, the levels of these molecules are small and there are biomolecules that interfere with the analysis because of their similar electrochemical properties. Carbon nanotube modified electrodes have shown an increase in the selectivity and sensitivity of when studying neurotransmitters while achieving a size that could be used in implants.

This thesis goes through the properties of carbon nanotubes, the basics of electrochemical analysis and reviews study articles where carbon nanotubes are used as a modification for the analysis of neurotransmitters. The review is divided into electrodes with single wall carbon nanotubes, multiwall carbon nanotubes and then macro-sized carbon nanotube structures, such as carbon nanotube yarn.

2 Carbon Nanotubes

CNTs have great physical properties. They are stronger than steel, they have high melting point, and they are lighter when compared to metals. CNTs are also chemically inert. CNTs are electrically either metallic or semiconducting and great conductors of heat. CNTs have large surface area with sp^2 hybridized bonds that gives them the ability to accept and donate electrons easily, which is the basis of electrochemical sensing. Studies have shown that incorporating CNTs with electrodes can improve sensitivity and selectivity. CNTs are also viewed as biocompatible with human tissues. These properties make an interesting material for producing next generation biosensors [1].

2.1 Structure

Carbon nanotubes (CNTs) are either single walled (SWCNT) or multi walled (MWCNT). SWCNTs consist of a single layer of tubularly formed sheet of graphite, which is called graphene, and in MWCNTs there are several of these layers nested in each other. Graphene, and therefore a layer of CNT, is one atom thick and consist of hexagonal honeycomb structure that can be seen in Figure 1 [2].

The honeycomb structure of graphene consists of carbon atoms that form a σ-bond with three of the closest carbon atoms and one π-bond. The σ-bonds are formed in the direction of the plane and the π-bond is formed out of the plane, in z-axis of the carbon atoms. The π-bonds are hybridized together to form a π and π*-bands, which are formed on both sides of the honeycomb structure. The σ-bond and π-bonds are visible in Figure 1. The π-band is the one where electrons normally are, which is a lower energy state and π*-band is normally available for electron deposition, allowing electrons in the π- and π*-bands can move freely. These π-bonds give graphene and therefore CNTs their unique electron conducting properties [3].

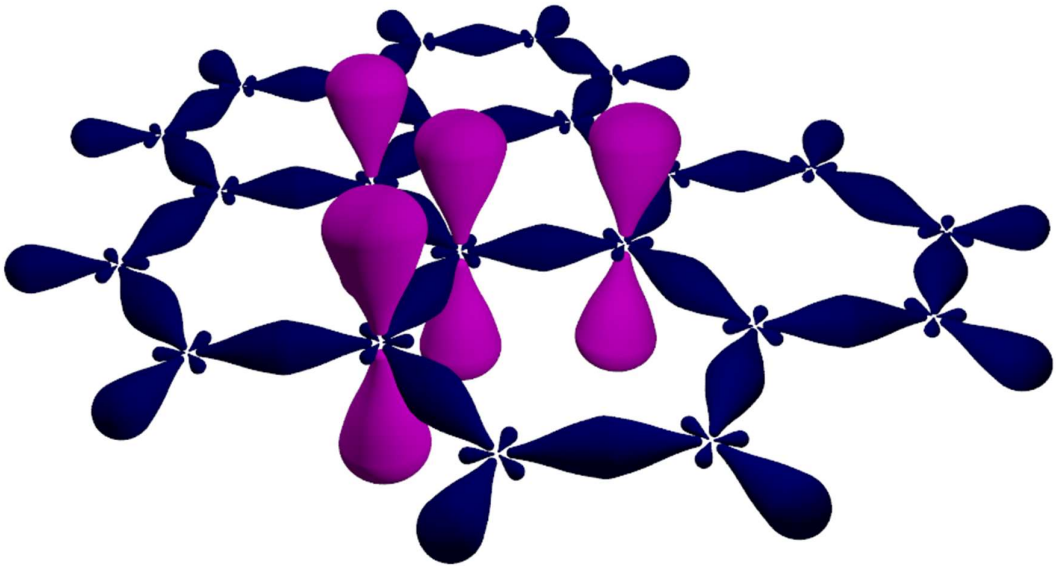

Figure 1. Pi and sigma bonds of graphene. Username Ponor on en.wikipedia, CC BY-SA 4.0 <http://creativecommons.org/licenses/by-sa/4.0/>, via Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Graphene_-_sigma_and_pi_bonds.svg.

2.2 Properties

As mentioned CNTs have great properties that makes them a very potential material. Thermal conductivity for SWCNTs is 6600 $W \cdot m^{-1} \cdot K^{-1}$ and for MWCNTs 3000 $W \cdot m^{-1} \cdot K^{-1}$. Electric conductivity for SWCNTs can be up to 10 000 S/cm^{-1} and 1850 S/cm^{-1} for MWCNTs. Young's modulus for SWCNTs and MWCNTs is 270–950 GPa and Tensile strength ranges from 11 to 63 GPa for both SWCNTs and MWCNTs [4].

2.3 Chirality

The structure of the CNT dictates its electrical properties. Based on how the graphene sheet has been 'cut' i.e. how many vertical and horizontal unit cells the 2D structure has, also known as roll-up vectors, SWCNT can have armchair, zigzag or chiral 3D structure. If the roll-up vectors (n,m) are n-m=3q or 0, where q is an integer, the SWCNT is metallic and otherwise it is semiconducting. Armchair structure comes when n=m. If m=0, the structure is called zigzag. The rest are called chiral [5].

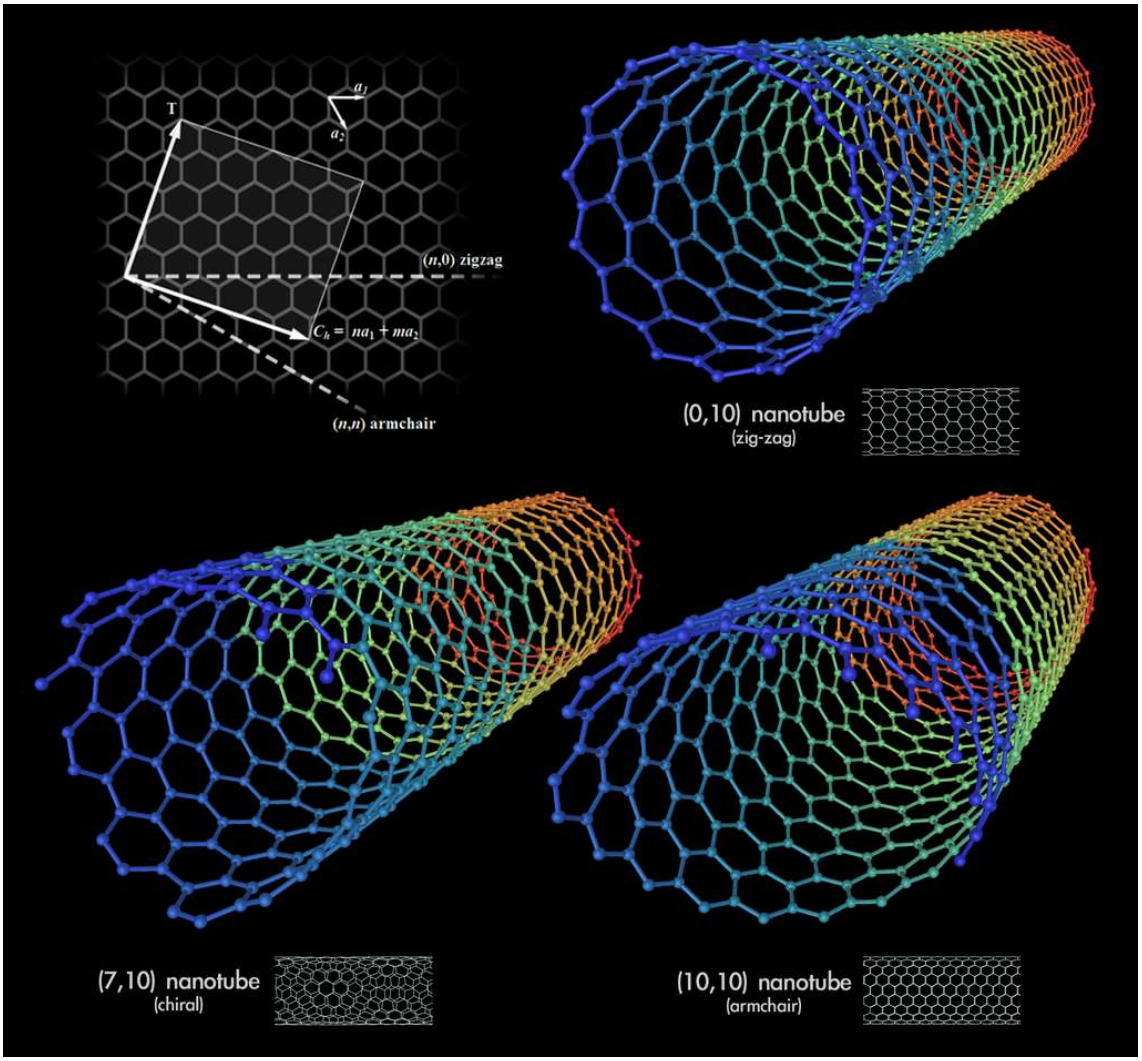

Figure 2. The honeycomb structure and different chiralities of carbon nanotubes. Michael Ströck on en.wikipedia, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons.

As stated above the electric properties of CNTs are either metallic or semiconducting based on chirality. Armchair type CNTs are always metallic as the condition for armchair is n=m, and the condition for metallic electron conductance is n-m=3q or 0. Zigzag type CNTs and chiral CNTs are mostly semiconducting but can be metallic if n-m=3q is met. In metallic conductance the electrons can move freely along the CNT structure. This happens when the π-bands in the graphene structure are dispersed linearly allowing movement of the electrons. In semiconducting CNTs the π-bands have a bandgap in electron pathways that require additional energy for allowing the flow of electrons. The conductance in metallic CNTs is ballistic, where the electrons move along the CNT without dispersion or scattering [6].

In MWCNTs individual nanotube chirality has little effect on electric properties. Almost all MWCNTs have metallic conducting properties. For MWCNT to be semiconductive, the individual nanotubes need to be semiconductive, the bandgaps need to overlap and the distance between the nanotubes needs to be relatively large. With smaller distances between the nanotubes the π-bands overlap resulting in metallic conductivity. [7]

2.4 Doping

As stated above the structure and morphology of CNTs determine its properties. To attain CNTs with suitable properties they can be doped. Doping can happen either with an atom or molecule replacing an atom in the CNT lattice or an atom or molecule adsorbing on the surface of the CNT. Adsorbed atoms either make a chemical bond or a physical bond with the atoms in CNT lattice, this is also called surface functionalization. One of the main reasons for doping is to alter the electric properties of CNTs. It can affect the conductance, resistance and electronic structure. As CNTs are highly inert, doping with changes in the lattice structure are normally done while producing the CNTs and adsorption doping can be done to pristine CNTs, which makes it viable for changing the properties of bulk produced CNTs. [8]

In studies that focus on electrochemical analysis of neurotransmitters, surface functionalization is used extensively to achieve an oxidative surface on CNT electrodes. The functionalization introduces groups containing oxygens, mostly carboxyl and hydroxyl, on the surface. One generally used method for surface functionalization is acid treatment. [9] Functionalization has also been done with basic solution while simultaneously applying potential to the electrode. [10]

Introducing other atoms than carbon in CNT structure seems to be rarer, at least in neurotransmitter detection. At least boron and nitrogen have been studied with density functional theory. This type of doping is also targeted to make the CNT electrodes attract neurotransmitters easier, to achieve higher sensitivity. [11]

2.5 Production

2.5.1 Arc discharge method

Arc discharge method is one method used to produce MWCNTs. In a low-pressure environment and in the presence of helium gas, a hot plasma discharge is created between two graphite electrodes. This evaporates graphite from the anode and the evaporated graphite is deposited on the cathode, where MWCNTs and other types of carbon structures, e.g. fullerenes, are formed. To achieve fine structure MWCNTs the material needs to be purified with carbon dioxide or oxygen in the synthesis process. Methane, CH_4, can also be used as a source for the carbon in arc discharge method. [12]

Arc discharge method is considered to achieve a large quantity of CNTs with low number of structural deficits. With arc discharge straight CNTs can be produced. On the downside the chirality of the CNTs cannot be controlled. [13]

2.5.2 Laser ablation method

In laser ablation carbon source is vaporized with a pulse laser. The vaporization is also done in a lower pressure environment with an inert gas like in arc discharge, but in laser ablation method the gas used is normally argon. The source of carbon has also catalytic metals such as cobalt or nickel. The vaporized carbon

condenses in a lower temperature environment resulting in CNTs and other carbon materials, which need to be purified with gasification to achieve high quality CNTs. Variance in achieved CNTs, e.g. diameter, is created with furnace temperature, catalytic metals and laser beam flow rate. [12]

CNTs produced with laser ablation method have low metallic impurities. Drawbacks of laser ablation method are branching of the CNTs and not being cost effective. [13]

2.5.3 Chemical vapour deposition

Chemical vapour deposition is used to produce high quantity and high quality CNTs, with relatively low cost. Figure 3 shows the process of CVD. In CVD, hydrocarbon gas is inserted in a 500-1000 ºC furnace with an inert gas. Heat and catalyst help the decomposition of the

carbon material and carbon atoms start to crystallize because of the hot metal catalyst. This results in a CNT structure. As can be seen in Figure 3 b) the CNT can form as a base growth, where the metal catalyst forms a base where CNT grows up or as in Figure 3 c) as tip growth, where the CNT structure forms under the metal catalyst making the metal a tip of as for the CNT [14].

CVD can be used to produce SWCNTs and MWCNTs. MWCNTs are normally produced from ethylene or acetylene and the furnace is heated at 550-700 ºC. SWCNTs on the other hand are normally produced using methane and the furnace is heated to higher temperatures, at 850-1000 ºC [14].

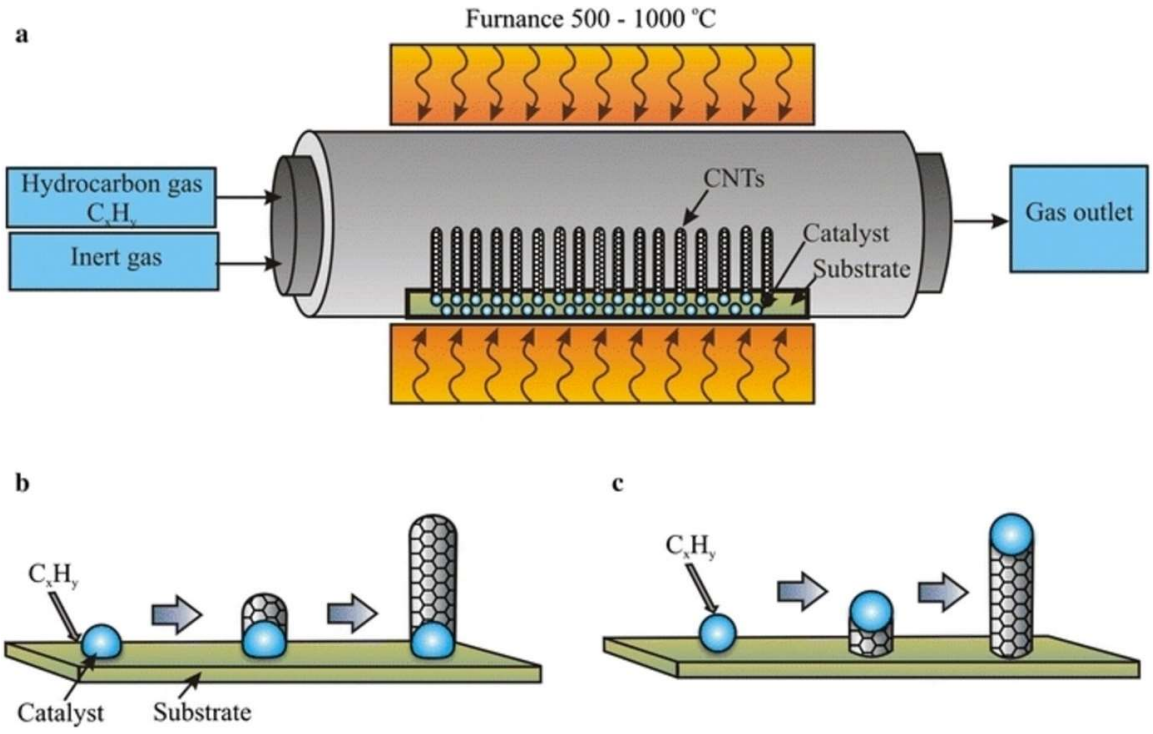

Figure 3. Chemical vapour deposition process. Image reproduced with permission from [14] Copyright 2023 Wiley-VCH GmbH.

High pressure carbon monoxide -synthesis (HiPCO) is an approach to the CVD process. SWCNTs are produced from carbon monoxide. High pressure of 30-50 Bar is used with high temperature of 900-1100 ºC. The catalyst used is $Fe(CO)_5$. SWCNTs produced with the HiPCO-process have been used as an unformal standard for SWCNT research because of their high quality, consistency and affordability. [15], [16]

Table 1 Comparison of CNT production methods

Name	Pressure (high/low)	Carbon source	CNT production method	CNT properties
Arc discharge	Low	Graphite from electrode/CH_4	Hot plasma discharge between electrodes vaporizes graphite and deposits as CNTs on cathode electrode	Straight, low number of deficits, no chirality control
Laser ablation	Low	Graphite with catalytic metals	Laser vaporizes the graphite and deposits as CNTs	Good quality, diameter control, not straight and branching
Chemical vapour deposition	High	Methane/ acetylene/ ethylene	Carbon source decomposes from heat and catalytic metals, deposits as CNTs on substrate	Bulk production, MWCNT and SWCNT production can be controlled, High number of deficits

3 Electrochemical analysis

3.1 Introduction to electrochemical analysis

Electrochemical analysis has gained popularity in biomedical and pharmaceutical monitoring because many biological reactions work on oxidation/reduction mechanisms, similar processes that are happening on electrodes surface during electrochemical analysis. Electrochemical sensors collect chemical information and convert it to electric signal that can be studied, such as the variation of potential or current. [17].

Classical electrodes such as graphite electrode, pencil graphite electrode and glassy carbon electrodes are good for analysing heavy metals and pH in a solution, but they are not selective and sensitive enough for analysing biomolecules. The study of nanomaterials such as graphene, carbon nanotubes and metal nanoparticles have made electrochemical analysis possible for biomolecules. [17].

Currently lot of biomolecule analysing is done by chromatography and spectroscopic detection and similar methods. These are reliable methods with high selectivity and sensibility but on the downside, they need bulky equipment, are expensive and need specialized people to operate them. These methods are also sample based where a sample is taken, then analysed, where fast changes in neurotransmitter concentrations can't be passively monitored. Electrochemical sensors try to tackle these downsides by being more portable, highly selective on the target molecule in complex matrices and cutting cost. Their response time is measured in minutes opposing to hours or days. [17]. With electrochemical sensors, local monitoring of biomolecule concentrations and real time data collection is researched [18].

CNTs among other carbon nanomaterials have been researched for increasing the electrodes selectivity, sensitivity and stability. The properties of CNTs that make them desired material for the job include high electric conductivity, biocompatibility, inertness and high surface to volume ratio. [17]. Studies where CNTs have improved traditional sensors are reviewed in chapter 4.

3.2 Working principles

Voltammetry, the technique of electroanalysis, is based on measuring the current through electrodes that are submerged in a solution. The solution also contains the analyte which is

studied by changing the potential step by step. The analyte is recognized from its peak potential. [17].

Figure 4 shows the voltametric setting which includes a working electrode, a reference electrode and a counter electrode. When the current is flowing, the analysed redox reactions are happening on the working electrode. The reference electrode is used as a reference point where the potential of other electrodes is compared against. The counter electrode is used to complete the electrical circuit. The current is recorded when electrons are flowing between the working electrode and counter electrode. [19] .

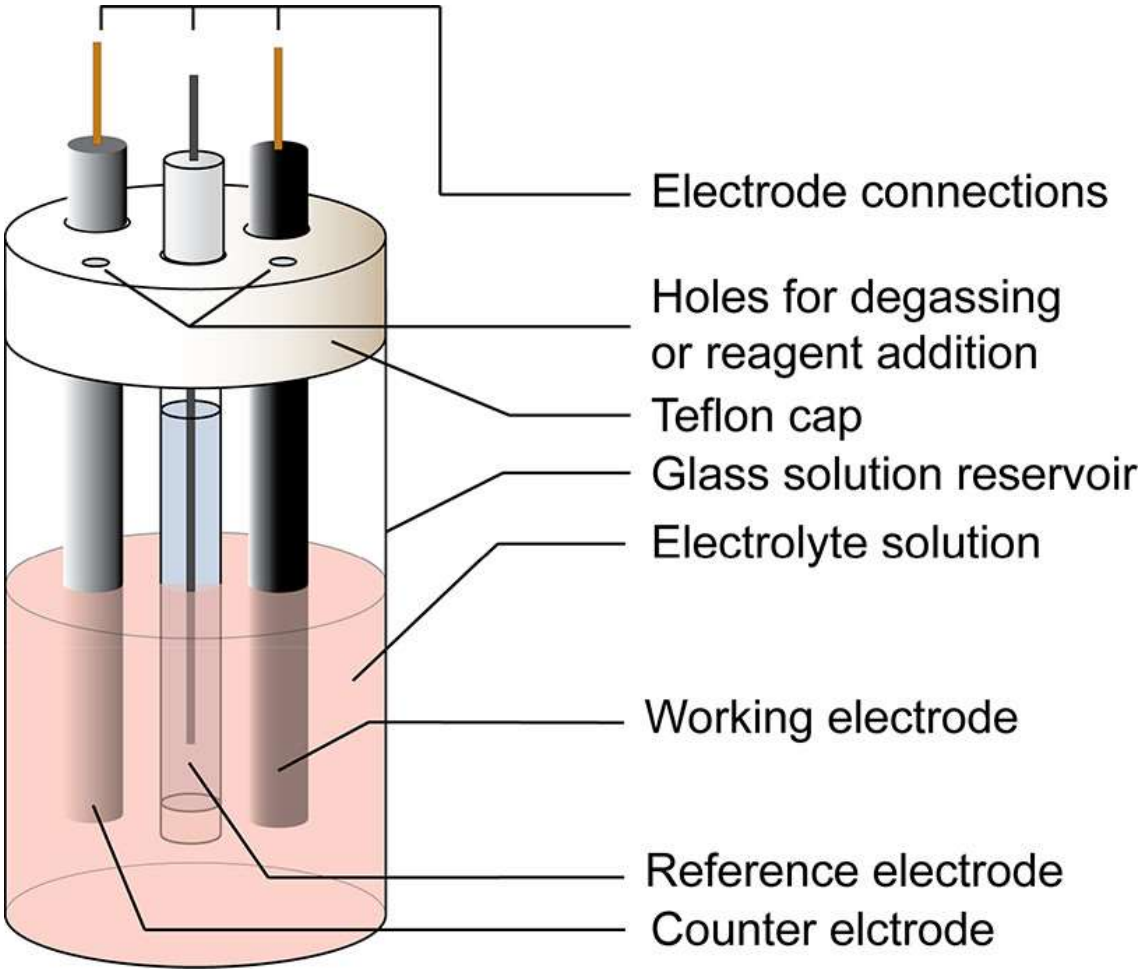

Figure 4. Electrochemical cell. Image reproduced with permission from [19]. ACS AuthorChoice Licence.

3.2.1 Cyclic voltammetry

In Figure 5, the relationship between potential and current can be seen. X-axis shows potential and Y-axis shows current. In cyclic voltammetry potential is increased linearly and a peak in the current can be seen, if the analyte is recognized. Different analytes show peak current with distinct potential, which is used to differentiate the analytes from each other. The potential is swept first positively from negative to positive potential, to show the oxidation peak over the starting line and the swept back from the positive potential to negative potential to show the reduction peak under the starting line. If the sweeping is done first from positive to negative potential, the reduction and oxidation peaks change place in the chart. [19].

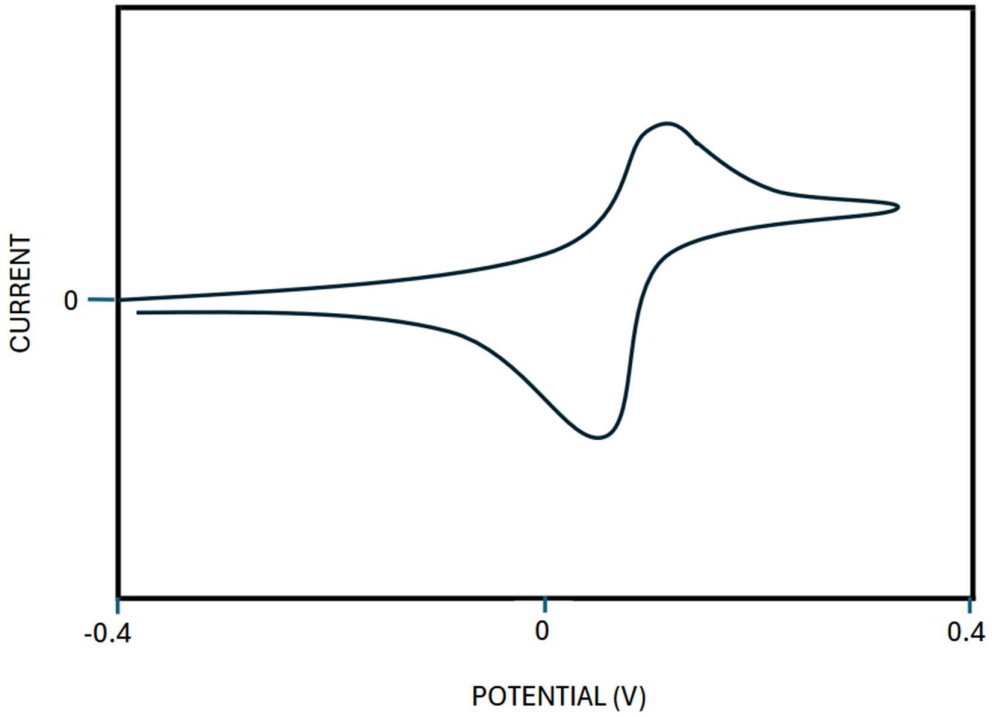

Figure 5. Simple chart of cyclic voltammetry results. Y-axis shows current and X-axis shows potential. Image modified from from [19].

4 Carbon nanotube electrodes

In this thesis electrodes that are capable of sensing electrochemically active biomolecules are focused on. Another hot field of study is electrodes that use biorecognition elements immobilized on electrode surface that attract targeted molecules. These targeted biomolecules are not normally electrochemically active. When the analyte is captured by the biorecognition element, the analyte becomes electrochemically quantifiable. These biorecognition elements that are immobilized on the electrode include at least enzymes, aptamers and antibodies. In these types of biosensors CNTs are researched extensively because of their great surface area where it is possible to immobilize large quantities of the biorecognition elements and great conductivity that enables the quantification of the small currents that are produced from the interaction of target molecules and the biorecognition element.

Even though CNTs have great electric conductivity in many cases sensitivity needs still enhancement so doping the biosensor with metal nanoparticles is common practice for improving selectivity and sensitivity. These biosensors consist of several parts, including the CNTs, metallic nanoparticles and biorecognition elements which means that the role of purely CNTs is difficult to isolate. In this thesis, studies that use CNTs as the main recognition surface are researched.

4.1 Analytes

Electrochemically active molecules can be found from neurotransmitters such as dopamine, serotonin, epinephrine and their oxidized forms. Based on the number of research articles it seems that dopamine is the most researched one. Even though dopamine and other electrochemically active neurotransmitters can be detected with more traditional electrodes, such as glassy carbon electrodes, there are problems with selectivity, sensitivity and fouling [20]. The problem with selectivity is that there are other biomolecules with similar oxidative potentials as neurotransmitters, such as ascorbic acid and uric acid and the volume of these interfering species is far greater than the volume of neurotransmitters. The problem with sensitivity is that for example the basic level of dopamine in the brain’s extracellular fluid is around 5-60nM and natural stimuli can bring it up to 500nM, which means the electrode needs to be capable of extremely sensitive quantification [21]. Fouling affects the selectivity and sensitivity of the electrode and can happen quite quickly after being taken into use,

reducing the times that a particular electrode can be used, or rendering it unusable immediately [20].

Dopamine's role is in neuronal reward, decision-making and motor control. Determining dopamine concentrations is essential for effectively studying various neurological diseases such as Parkinson's disease, attention deficit hyperactivity, Huntington's disease, schizophrenia, depression and addiction. [21]. Dopamine should be quantified from extracellular fluid in the nervous system because of the lack of dopamine in blood plasma or urine [22]. Figure 6 shows the oxidation of dopamine to dopamine o-quinone.

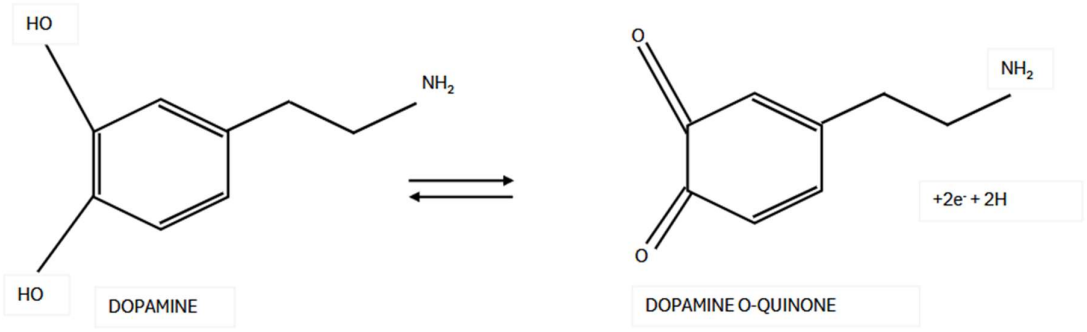

Figure 6. Dopamine oxidation to dopamine o-quinone. Modified from [23].

Serotonin's role is in regulation of mood, sleep, sexuality and appetite. Abnormal levels of serotonin are linked to depression, anxiety, migraines and extremely low levels can lead to potentially fatal serotonin syndrome [24]. Serotonin should also be quantified from extracellular fluid in the nervous system in to achieve the fastest response, but studies for the detection of serotonin in blood and urine has also been done [22]. Figure 7 shows the oxidation of serotonin to serotonin quinone.

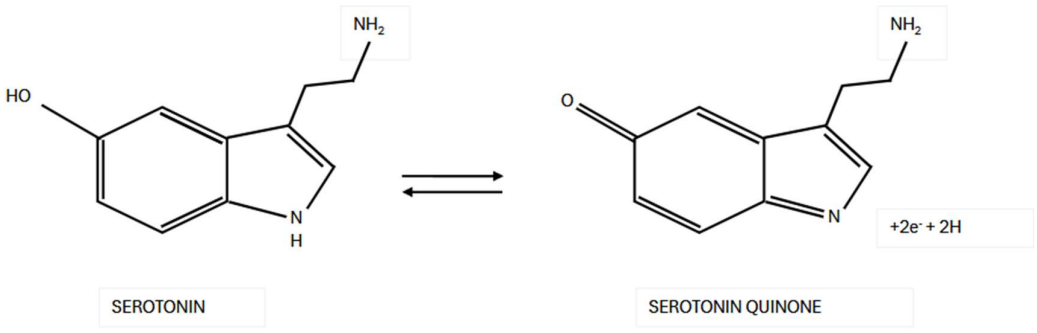

Figure 7. Serotonin oxidation to serotonin quinone. Modified from [25].

Epinephrine, also known as adrenalin, is a neurotransmitter and a hormone. It is known for its role in sympathetic nervous systems actions in 'fight or flight' response and is involved in physical and mental stress. Epinephrine affects blood pressure, heart rate, immune system, and glycogen metabolism by elevating sugar levels. Low levels of epinephrine are also linked to Parkinson's disease. Studies done on the electrochemical analysing of epinephrine seems to be limited on the quantification of epinephrine in blood and urine samples [26]. Figure 8 shows the oxidation of epinephrine to epinephrinequinone.

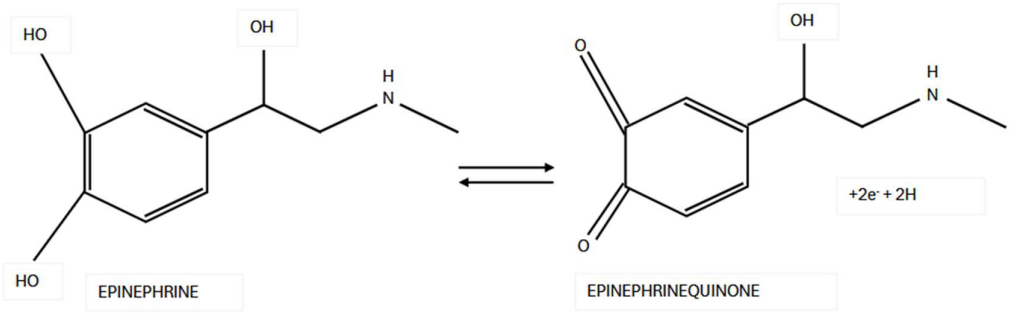

Figure 8. Epinephrine oxidation to epinephrinequinone. Modified from [27].

In table 2 can be seen the mechanisms of oxidation of various electrochemically active biomolecules[20], [26], [27], [28]. Dopamine, serotonin and epinephrine are neurotransmitters and ascorbic acid, and uric acid are biomolecules that exist in the same biological matrixes. While doing electrochemical analysis all the above biomolecules behave somewhat similar to

each other. Two of the analyte's electrons are lost to the electrode and the current flow produced is recorded [27]. The quantity of the analyte is measured from the transfer of these electrons to the electrode. The protons are lost on the surrounding matrix. With this similar oxidative behaviour, the electrode that is used needs to be highly selective and voltametric techniques needs to be known clearly for accurate and selective measurement of desired biomolecule.

Table 2 Oxidation reactions of various biomolecules

Biomolecule	**Oxidized form**	**Released protons**	**Released electrons**
Dopamine	Dopamine o-quinone	2	2
Ascorbic acid	Dehydro ascorbate	2	2
Uric acid	Uric acid 4,5 diol	2	2
Epinephrine	Epinephrinequinone	2	2
Serotonin	Serotonin quinone	2	2

CNTs are extensively researched as the answer to the problems that include selectivity, sensibility and fouling, and they have given promising results. CNTs are nanoscale structures and bioinert which means they have potential as small-scale implantable devices. It is common to research the effect of CNTs with modifying existing electrodes, such as glassy carbon electrodes, with CNTs [29] [30]. Currently it seems that the research is still focused on *in vitro* experiments where level of detection and the electrodes selectivity for targeted biomolecule in the presence of interfering species are the main research questions. CNTs are quite cheap and relatively easy to cast on glassy carbon electrodes which explains the abundance of research papers focusing on these elements of the study. For practical use, dopamine and serotonin sensors would need to be close to the cells of the nervous system i.e. implanted near brain [22]. Researching implantable electrodes needs a different type of approach as biocompatibility and miniaturization of the electrode plays a large role. It is also understandable that a sensitive, selective and reproduceable electrode is researched before *in vivo* implant tests.

Adsorption of molecules on electrode surface is basic concept of electrochemical sensing. Figure 9 shows adsorption of dopamine on an unmodified SWCNT, based on a density function theory calculation made by Yeh et al. [11]. As the dopamine molecule is adsorbed to the electrode surface in cyclic voltammetry setting, it is oxidized to dopamine o-quinone, as shown in Figure 6. In oxidation, the dopamine molecule loses electrons to the electrode which results in a measurable electric current. The identity of the analyte can be determined from the potential at which the peak current occurs, while the concentration is determined from the magnitude of the peak current [31]. Figure 9 shows that dopamine has two conformers, gauche dopamine and trans dopamine. In Figure 9: (a) is gauche dopamine, (b) is trans dopamine, (c) and (e) are gauche dopamine's rotations, and (d) and (f) are trans dopamine's rotations. Dopamine can adsorb by π–π – stacking, which is a non-covalent interaction between the ring structure of dopamine and ring structure of the CNT, or dopamine can adsorb by N-H···π, from dopamine's nitrogen-hydrogen bond to CNT's ring structure. The difference in adsorption energy between the possible adsorption styles were noted to be minimal and should not affect the electrochemical analysis of dopamine. [11]

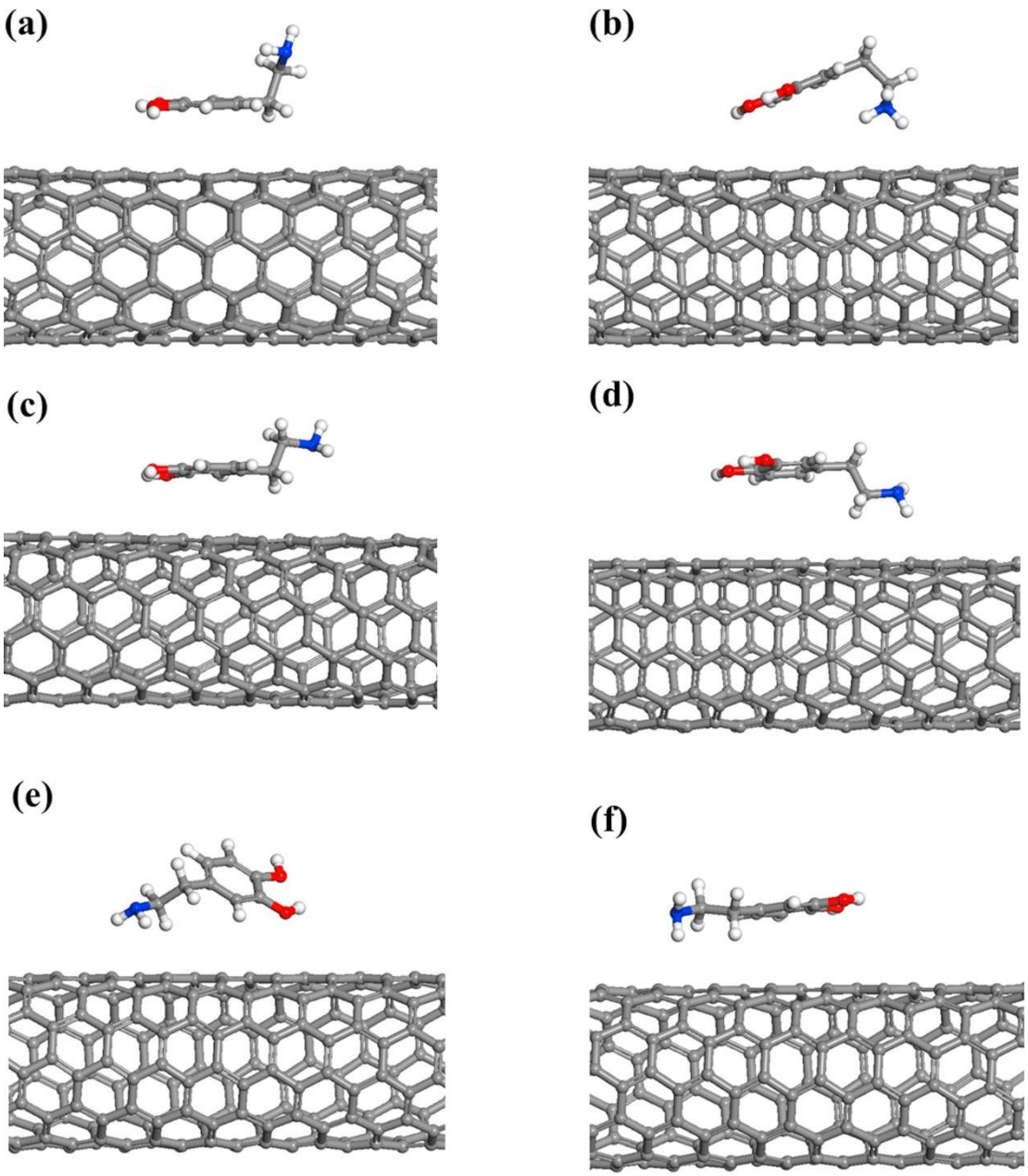

Figure 9. Dopamine on the surface of carbon nanotube. Image reproduced with permission from [11]. 0169-4332/ © 2018 Elsevier B.V. All rights reserved.

4.2 Studies of electrodes made with single walled carbon nanotubes

In the density functional theory calculation made by Yeh et al. [11] it was determined that unmodified SWCNTs were not sensitive enough for the quantification of dopamine in a voltametric setting. The research used (6,5) SWCNTs that are semiconducting. The adsorption of dopamine on the surface of the SWCNT resulted in a change in the band gap

between 0.001eV and 0.004 eV, which is minimal. The team made same calculations with SWCNTs doped with boron and nitrogen.

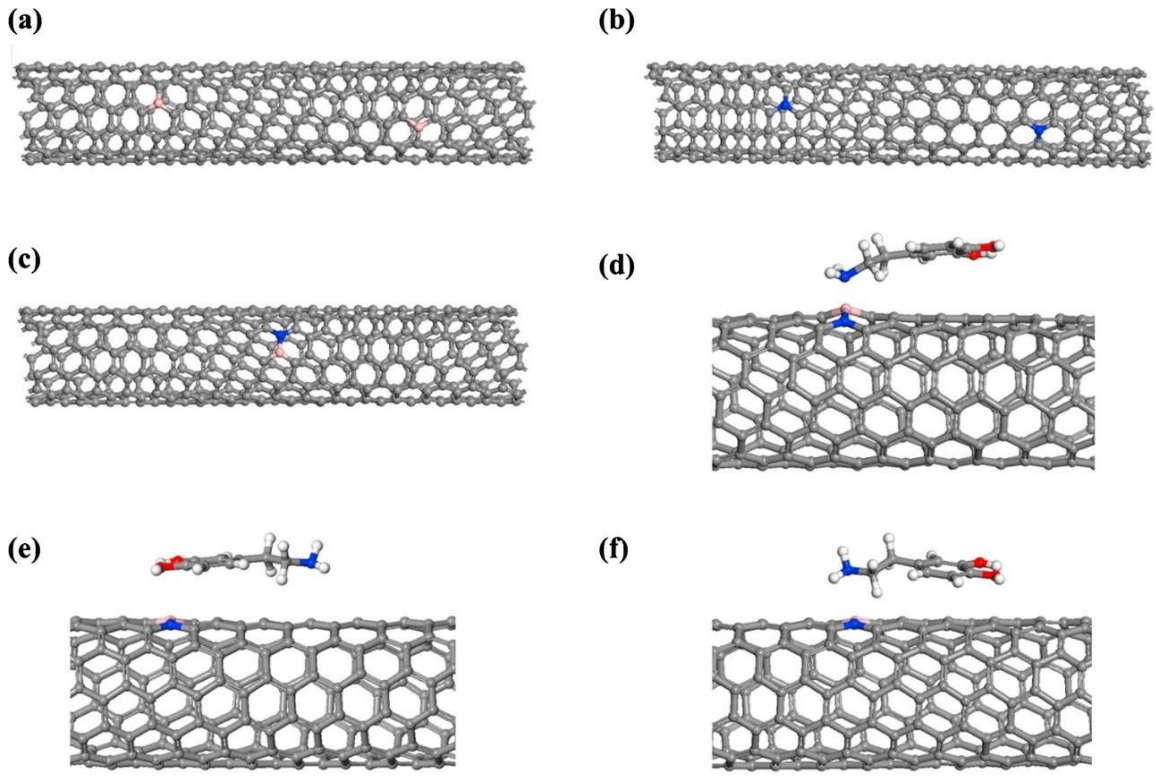

Figure 10. Dopamine on the surface of boron and nitrogen doped SWCNT. Image reproduced with permission from [11]. 0169-4332/ © 2018 Elsevier B.V. All rights reserved.

Boron and nitrogen co-doping results in a semi-conductive SWCNT. Doping with only boron or nitrogen results in semi-metallic SWCNTs. The amount of dopant was 0.55%.

In Figure 10, (a) is boron doped SWCNT, (b) is nitrogen doped SWCNT, (c) is boron and nitrogen co-doped SWCNT, and (d), (e) and (f) shows dopamine's possible ways of adsorption on boron and nitrogen co-doped SWCNT. The adsorption energy was calculated as -1.09eV, far greater than the adsorption energy on unmodified SWCNT [11].

The results in the change of adsorption energy make boron and nitrogen co-doped SWCNTs worth researching further but unfortunately the research paper did not include actual voltametric study where an electrode made of, or modified with, boron and nitrogen doped SWCNTs were used and compared it to an electrode with unmodified SWCNTs. It seems to be a standard procedure with CNTs to oxidize them with for example HNO_3 to make them

dispersible in solution [32], [33], but oxidation seems to also affect the electrochemical properties of CNTs, making them more usable in electrodes. It would also be interesting to see if oxidating the boron and nitrogen co-doped SWCNTs results in even better adsorption energy or would they possibly cancel each other somehow.

A study conducted by B. Swamy and B. Venton [33] researched a carbon-fibre electrode coated with SWCNTs to detect dopamine and serotonin at the same time. The problem is that serotonin detection forms oxidation products on the electrode fouling the electrode over time and decreasing sensitivity. Serotonin and dopamine have very similar oxidation potentials so in this study the researchers used reduction potentials, which are around 200mV apart, to differentiate between the neurotransmitters. The researchers started from the premise that *in vivo* testing should be done with fast scan cyclic voltammetry rather than normal cyclic voltammetry to detect the fast changes in neurotransmitter concentration. The microelectrodes were constructed by dipping carbon-fibre disc electrodes in a solution with SWCNTs. The SWCNTs were treated with HNO_3, purifying and oxidizing them prior to the dipping.

The SWCNT coating on the microelectrode resulted in around 2.5 times oxidative current on dopamine and serotonin, compared to unmodified microelectrode. Still oxidative peaks could not be separated for dopamine and serotonin. Fouling from serotonin was found to be slower with SWCNT coating compared to bare carbon-fibre electrode. The sensitivity lost from fouling was around 10% with the SWCNT coated electrode, while bare carbon-fibre electrode had lost 40% sensitivity with the same number of cycles. It was reported that *in vivo* testing with rats resulted in detection of 250nM dopamine and 130nM for serotonin [33]. Ascorbic acid or uric acid interference was not reported, even though in later studies these interfering species are found to be extremely important in *in vivo* testing [33], [34], [35]. It can be because reduction potentials for these interfering species is not interfering with the analytes even though the oxidation potentials are.

In a study published by Oh, J. et al. [10] the researchers studied the possibility of making flexible sensor for dopamine detection in the presence of ascorbic acid and uric acid. The working electrode was made of film of PET coated with SWCNTs. It is notable that the electroactive material of the electrode is a film SWCNTs and not an electrode coated with SWCNTs. The SWCNTs were oxidized in NaOH with cyclic voltammetry 0.0V to +0.9V for 40 cycles. The SWCNTs used were metallic.

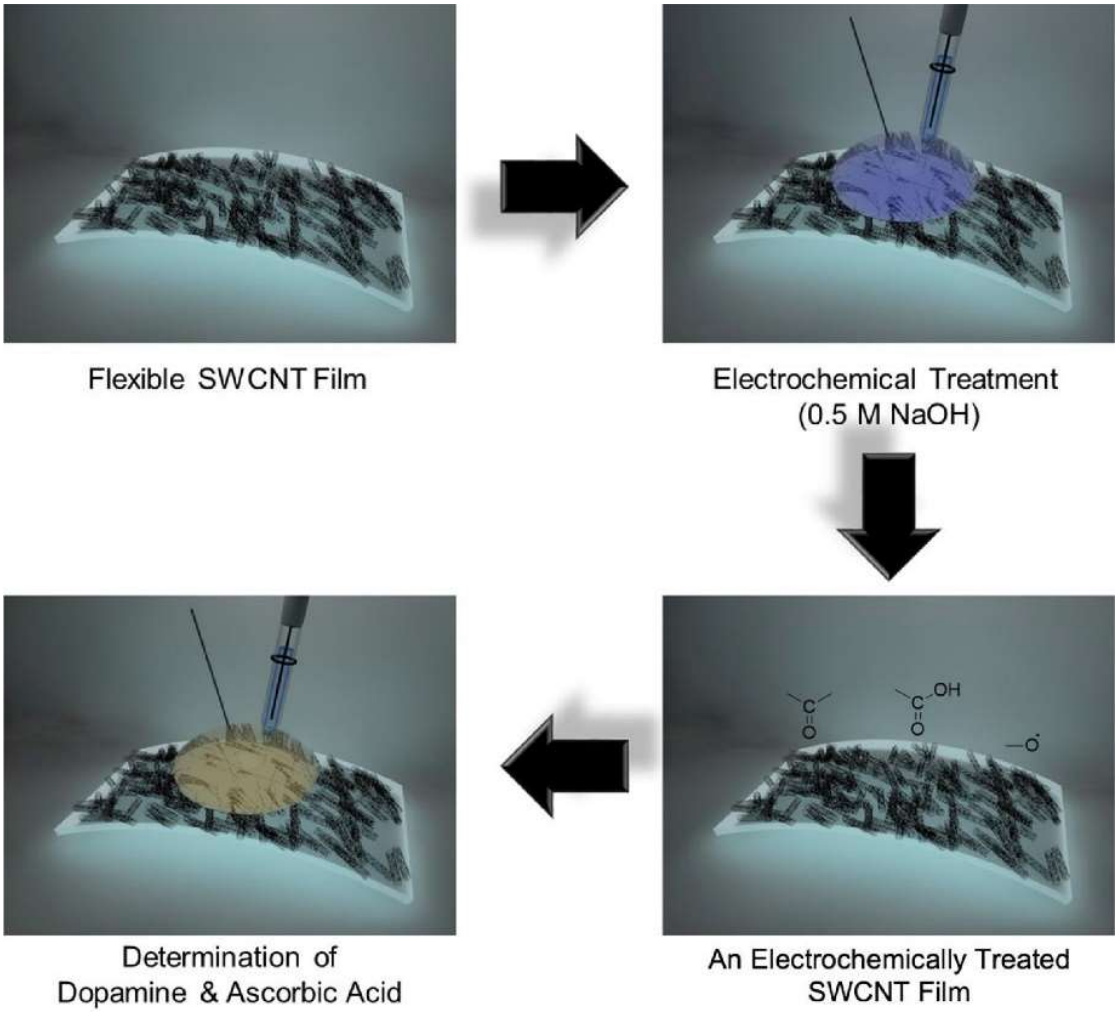

Figure 11. PET-SWCNT film electrode treatment. Image reproduced with permission from [10]. https://doi.org/10.1016/j.snb.2018.04.048 0925-4005/© 2018 Elsevier B.V. All rights reserved.

The team tested three electrodes, bare glassy carbon electrode, pristine SWCNT electrode and the oxidated SWCNT electrode, for the detection of dopamine in the presence of ascorbic acid and uric acid. Glassy carbon electrode detected only one peak. Pristine SWCNT electrode detected one peak that did not differentiate dopamine and ascorbic acid and one peak for uric acid, similar finding to the density functional theory calculation made by Yeh et al. that pristine SWCNT do not function well as electrodes. The oxidated SWCNT electrode could differentiate all three biomolecules. The limit of detection was found to be around 510nM. It was also reported that after 15 cycles the amperometric signal was 86% of the original signal [10]. The limit of detection is not quite sensitive enough for an actual dopamine sensor, since the extra cellular basal concentration of dopamine is around 10nM and in normal stimulus it can go up to around 500nM. The fouling might also be still a problem, even though after 15

cycles the decrease of amperometric signal is only around 15%, since the number of cycles for an implantable device would be a lot more and changing an implant in the brain is an unwanted procedure. It is not known from the study if the fouling of the electrode is accelerated or decelerated towards higher number of cycles. The linear range of detection was reported to be from 5µm to 60µm.

N. Xiao and B. Venton made a carbon fibre electrode with SWCNT coating that self-assembled to form a forest like structure for dopamine detection [36]. The SWCNTs were shortened in a mix of HNO_3 and H_2SO_4 and then filtered to harvest SWCNTs under 0.2µm. The self-assembly was achieved by suspending the shortened SWCNTs in dimethylformamide, dipping carbon fibre microelectrode in first nafion, then aqueous $FeCl_3$ and lastly to the SWCNT-dimethylformamide suspension.

The studies were conducted with fast scan cyclic voltammetry. The electrode achieved a limit of detection of around 17nM for dopamine with 10hz scan rate with linear range of detection from 50 nM to 25 µM. The research team reported that SWCNT forest electrode allowed the use of 90hz with a limit of detection of around 65nM achieving a high temporal resolution. This was argued to be the result of high number of functional groups that was achieved by exposing the edge planes of the SWCNTs while shortening. Figure 12 shows the scanning electron microscopy image of the SWCNT forest electrode.

Tests with ascorbic acid or uric acid interference were not made but it was reported that the SWCNT forest electrode was sensitive for norepinephrine and epinephrine, but not for serotonin.

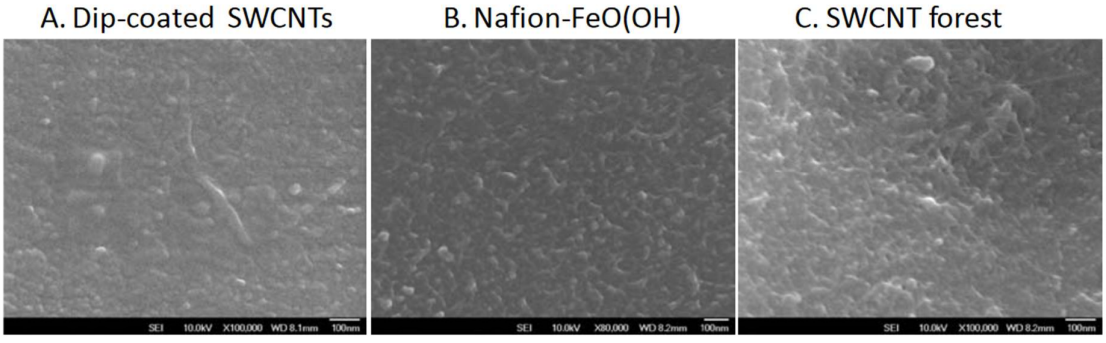

Figure 12. Images taken with scanning electron microscopy. A) Carbon fibre electrode dip coated in SWCNT solution. B) Carbon fibre electrode coated with Nafion-FeO(OH), C) Carbon fibre electrode first coated with Nafion-FeO(OH) and then dipped in SWCNT solution. Image reproduced with permission from [36]. Copyright 2012 American Chemical Society.

4.3 Studies of electrodes made with multi wall carbon nanotubes

J. Manjunatha et al. [37] conducted a study on a paste electrode consisting of MWCNTs that are surface modified with sodium dodecyl sulfate (SDS). MWCTNs were made as a paste with silicon oil and SDS was added on the electrode. The research team also tested an MWCNT paste electrode, which lacked the SDS surface modification. Dopamine was analysed in the presence of uric acid and ascorbic acid with cyclic voltammetry. The unmodified electrode could not separate between dopamine, uric acid and ascorbic acid and gave only one broad oxidation peak. It seems that like SWCNT electrodes, also MWCNT electrodes are not sensitive enough without modification. The SDS modified electrode showed three separate peaks for ascorbic acid, dopamine and uric acid, at 51 mV, 278 mV and 372 mV, respectively. The team reported a limit of detection for dopamine at 33 nM and a linear range of detection from 1 µM to 28 µM.

Simultaneous detection of serotonin and dopamine with MWCNT coated glassy carbon electrode was studied by K. Wu et al. [38]. The MWCNTs were oxidized in HNO_3 and dihexadecyl hydrogen phosphate (DHP) was used as a surfactant on the MWCNTs. DHP and SDS, which was used by Manjunatha et al., both have amphiphilic nature which means it has both hydrophilic and hydrophobic parts. The electrochemical analysis was done with cyclic voltammetry. The DHP modified MWCNT electrode could detect 100 nM concentrations of dopamine and serotonin in the presence of ascorbic acid and uric acid with a linear range from 100 nM to 50 µM. The electrode was also tested in real healthy human blood sample and was able to detect 100 nM concentrations of dopamine and serotonin. Dopamine was not found on the healthy blood sample naturally, indicating it is not the right place to analyse dopamine, but serotonin was found to be around 100 nM/l. Oxidation peaks on cyclic voltammetry was found at 180 mV on dopamine and 360 mV on serotonin.

Dopamine detection on a HNO_3 functionalized MWCNT coating on a glassy carbon electrode was studied by Z. Alothman et al. [39]. The electrode was able to determine dopamine peaks in the presence of ascorbic acid and uric acid. The limit of detection for dopamine was around 800 nM and found at 127 mV and linear range of detection of 3 µM to 200 µM. The sensitivity is not in the range for real life application, but the limit of detection is similar to the SWCNT electrodes, that use only oxidization as the surface modification.

Dopamine and serotonin detection with functionalized MWCNT glassy carbon electrode was also studied by M. Bonetto et al. [28]. The difference to the study made by Alothman et al.

was that the MWCNTs were functionalized in H_2SO_4 by first applying a fixed oxidation potential and then a fixed reduction potential and continuously adding N_2 in the mixture. This creates MWCNTs that partially unzips and MWCNTs that are fused together. It was argued that unzipping results in high number of defects which are necessary for the functional groups to appear on the surface of the MWCNTs. The electrode showed selectivity towards dopamine and serotonin oxidation in the presence of ascorbic acid and uric acid, with limit of detection 235 nM for dopamine and 460 nM for serotonin. With cyclic voltammetry the peaks of oxidation were found 233 mV for dopamine and 683 mV for serotonin.

C. Yang et al. [40] grew MWCNTs on a Nb metal wire. The MWCNTs were grown with chemical vapor deposition on site. In Figure 13 are images taken with scanning electron microscopy. The MWCNTs grown on Nb substrate are oriented vertically, in a forest like composition. MWCNTs grown on Ta and carbon fibre exhibit disoriented composition, similar to CNT coated electrodes. It is argued that the edge plane structures and hybridized sp^3 carbon of the forest like structure result in large number of functional groups after oxidation when voltage is applied. In the study no treatment with, for example, HNO_3 was mentioned, and it seems that applying voltage is enough for the functional groups to appear. From Figure 13 it can be seen that the amount of MWCNTs per area on Nb is high compared to MWCNTs on Ta or carbon fibre.

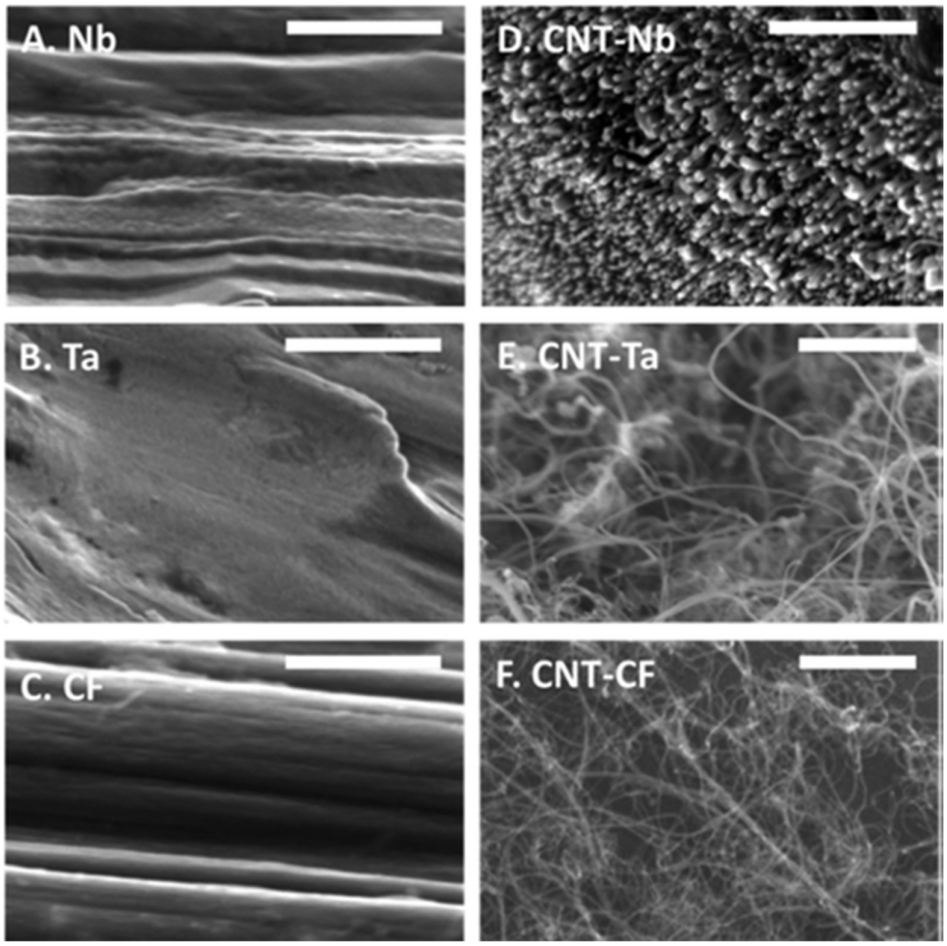

Figure 13. Images taken with SEM: A) Pure Nb, B) Bare Ta, C) Bare carbon fibre, D) MWCNTs grown on Nb, E) MWCNTs grown on Ta, F) MWCNTs grown on carbon fibre. Image reproduced with permission from [40]. Copyright 2015 American Chemical Society.

Studies with the MWCNT-Nb electrode were conducted with fast scan cyclic voltammetry. The level of detection for dopamine was around 11 nM for MWCNT-Nb electrode, around 100 nM for MWCNT-Ta electrode and interestingly around 20 nM for bare carbon fibre microelectrode but around 50 nM for MWCNT-carbon fibre electrode. Both MWCNT-Nb and carbon fibre microelectrode has limit of detection in the rage of naturally occurring dopamine. The MWCNT-Nb electrode was able to differentiate dopamine from ascorbic acid, but the bare carbon fibre electrode could not. It was also reported that various other neurotransmitters could be observed with MWCNT-Nb electrode, without further details, like serotonin, adenosine, DOPAC and histamine. The MWCNT-Nb electrode was also tested *in vivo* for the detection of dopamine in rats. The electrode showed a slightly lower sensitivity, but it was considered to be indifferent [40].

O. Fayemi et al. [41] constructed a glassy carbon electrode coated with MWCNTs doped with metal oxides for detection of serotonin in urine samples. Metal oxides used were NiO, ZnO and Fe_3O_4, all used independently on the electrode. Solution with acidified MWCNTs and metal oxides was dropped on the electrode and then dried. Electrochemical study made with cyclic voltammetry indicated that the current response with the electrodes with MWCNTs and metal oxides was higher than with only MWCNTs. Limits of detection for serotonin was reported to be 118 nM on the NiO doped electrode, 129 nM on the ZnO doped electrode and 166 nM for Fe_3O_4 doped electrode. It was reported that ascorbic acid or uric acid did not interfere with serotonin detection. With the detection limits given the research team was positive that the electrodes could be used to determine serotonin in human urine samples with relevant accuracy. Even though comparation between glassy carbon electrode and the MWCNT electrodes doped with metal oxides were made, there were no comparation between MWCNT electrode and metal oxide doped MWCNT electrode, and it would be interesting to know if metal oxides play a huge role in detection or would the results be around the same with only surface functionalized MWCNT electrode.

A highly sensitive electrode for dopamine detection was made by G. Eom et al. [21]. A silicon wafer was covered with Au and Cr by evaporation. The gold electrode was covered with MWCNT, sodium dodecyl sulfate and pyrrole by applying a voltage in the electrode in a solution, i.e. electrodepositing. Pyrrole polymerizes under electrodepositing resulting in polypyrrole. After coating the electrode, it was overoxidized in NaOH with cyclic voltammetry.

The Au-MWCNT-SDS-PPY electrode was tested with cyclic voltammetry and differential pulse voltammetry. The oxidation of dopamine was observed at 180 mV and reduction at 130 mV with cyclic voltammetry. The limit of detection was around 70 nM. With differential pulse voltammetry peak of dopamine oxidation was at 140 mV and the limit of detection was found to be low, 136 pM, which is 0.136 nM. The electrode reached optimal sensing performance after 10 seconds. The electrode was selective towards dopamine in an interference study with ascorbic acid and glucose. Interestingly ascorbic acids oxidation peaks were hardly observable, which was thought to be from the repelling of electronegative groups of the electrode towards ascorbic acid. It was reported that the results indicate that there is no electrochemical activity towards glucose, which was expected since glucose interference studies are not conducted normally, at least based on the studies referred in this thesis.

R. Goyal and S. Bishnoi studied MWCNT coated edge plane pyrolytic carbon electrode in the detection of epinephrine in blood and urine samples [42]. The electrode was made by dropping MWCNT in dimethylformamide suspension on the electrode and letting it dry. Surface functionalization was not mentioned. The research team achieved a 0.15 nM limit of detection and a linear range of detection from 0.5 nM to 1 μM for epinephrine in the presence of ascorbic acid, uric acid, dopamine and serotonin, in human blood and urine samples. The research team was confident that the electrode would be useful in real life detection of epinephrine because interfering species did not affect the detection of epinephrine, and the electrode could be regenerated with a potential of -200 mV for 60 seconds in a buffer solution.

A paste electrode made from graphite, MWCNTs and ionic liquid, 1-methyl-3-butylimidazolium bromide, for the detection of epinephrine in human blood and urine samples was studied by T. Tavana et al. [26]. The MWCNTs were functionalized in HNO_3. Epinephrine was detected with a limit of detection 90 nM, in human urine and blood serum samples with a linear range of detection from 300 nM to 450 μM.

Epinephrine was also detected with a carbon paste electrode made of MWCNTs and graphite powder. The MWCNTs were functionalized with a mixture of H_2SO_4 and HNO_3. The electrode detected epinephrine in a buffer solution with a limit of detection of 29 nM in the presence of ascorbic acid and uric acid. The electrode showed only a slight decrease in sensitivity after six measurements, meaning that the electrode is potentially resistant to fouling.

4.4 Studies made with fibred multi wall carbon nanotubes

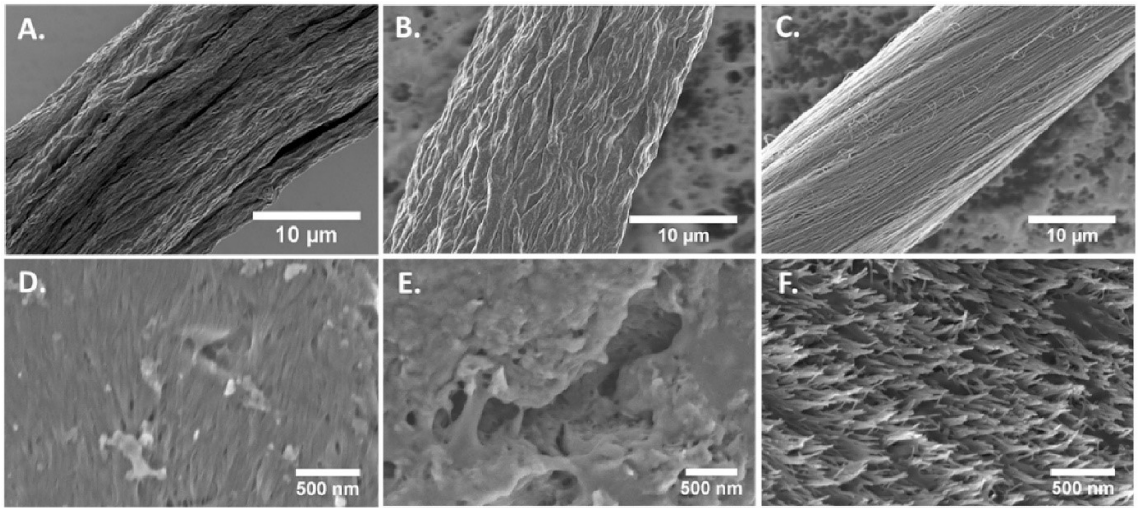

Figure 14. Sem images of A) CA/CNT sidewall, B) PEI/CNT sidewall, C) CNT yarn sidewall, D) CA/CNT tip, E) PEI/CNT tip, F) CNT yarn tip. Image reproduced with permission from[43] .Copyright 2017 Elsevier B.V. All rights reserved.

Recently, ways have been found to produce macro-structured CNTs and they have piqued interest in use as electrode materials. Handling these CNT yarns, or CNT fibres, is easier and fabricating electrodes is hoped to be more reproduceable. In Figure 14 it can be seen that these fibres can be around 20-50 µm in diameter, when a single MWCNTs diameter is around 20 nm [43].

CNT fibres or yarns can be made with a wet-spinning technique or directly spinning from a forest like CNT structure. In wet spinning first the CNTs are dispersed in a fluid and removed through a spinneret i.e. a small hole that forces the CNTs to form as a fibre and after that the dispersant is removed which makes the CNT fibre solidify. The fibres are then put in a polymer bath of poly(vinyl alcohol) (PVA) or poly(ethylene)imine (PEI). The polymers help CNTs to attach to each other, achieving width for the fibre. In wet spinning chlorosulfonic acid can be used, to achieve fibre structure without any surfactants. An alternative for the wet spinning technique, the CNTs can be harvested from a CNT forest like structure and spun as a rope. With this technique the CNTs in yarn are well-aligned and results in improved connectivity [43].

These CNT yarn and CNT fibre electrodes allow high temporal resolution. They allow 500 hz scan frequency and 2000 V/s scan rates. The improvement can be up to 50 times and allow dopamine detection in 2 ms. In a study made by A. Zestos and B. Venton [44], with fast scan cyclic voltammetry the researchers achieved around 10 nM limit of detection with CNT yarn electrode, around 5 nM limit of detection with PEI/CNT electrode and around 3 nM limit of detection with ACID-CNT electrode.

5 Discussion

Based on the studies listed in chapter 4, CNTs shows to improve the selectivity, sensitivity and electrode fouling resistance when compared to more traditional electrodes such as glassy carbon electrodes or carbon fibre electrodes. Pristine CNTs, both SWCNTs and MWCNTs seems to need modifications and/or surface functionalization to achieve these properties. The modifications needed are still quite manageable in a laboratory setting which allows testing a variety of methods with at least satisfactory results. In the studies presented in this thesis, all electrodes had added value from incorporation of CNTs on the electrode surface.

To achieve better results from the study of dopamine, it is needed to research for electrodes that are easier to produce, smaller, faster and tougher. At least at the moment, real time dopamine quantification is extremely invasive as the electrode needs to be in the brain, where the dopamine is released, and for an extensive quantification it should be measured from several parts of the brain at the same time.

There were no studies easily available that would determine the absolute range for dopamine detection, which would help to consider if an electrode is sensitive enough for real life application. This supposedly changes when the instruments become sensitive enough. But based on information of dopamine basal line (6-60 nM) and quantities on stimulus (500-1000 nM) a few possible uses can be listed. As a few electrodes had detection limit of around 10nM and we know that in natural stimulus the amount of dopamine rises to around 500nM, it could be studied that if under stimulus a normal amount of dopamine is released, when certain thresholds are crossed.

For analysing basal dopamine quantity many of the electrodes might have too low sensitivity. Only one electrode was reported to have a sub nM limit of detection. The result was obtained with differential pulse voltammetry that is more suitable for a sample-based analysis as it more sensitive method that cyclic voltammetry and fast-scan cyclic voltammetry, but on the downside, it can't achieve high enough temporal resolution. The consensus seems to be that continuous monitoring should be done with fast-scan cyclic voltammetry.

Even though resistivity to fouling is reported, it can still prevent longer monitoring times. Since replacing or cleaning a brain implant is naturally more difficult than cleaning an electrode used in urine or blood samples. Longer monitoring times could help diagnosing early stages of dopamine related diseases, for example when a person has genetic risk

developing a disease. Long monitoring times could also help determine if certain types of medicine are achieving their desired effect.

One time quantification of dopamine on a certain area is closer, electrode wise, than long time monitoring, but one time quantification might not be as wanted because of the risks involved when doing such an invasive analysis. For screening neurotransmitters such as serotonin and epinephrine from blood and urine samples the technology is promising. The electrodes modified with CNTs, or electrodes made of CNT yarn or fibres could be implemented quite fast at least based on studies.

Table 3 Comparison of electrodes reviewed in section 4

Electrode	Description of CNT	Analysed neuro-transmitter(s)	Limit of detection	Linear range of detection	Detection method	Reference
Carbon fiber disc electrode coated with SWCNTs	SWCNTs prepared by ARC method	Dopamine, serotonin	N/A	N/A	Fast-scan cyclic voltammetry	[45]
Flexible SWCNT network electrode	N/A	Dopamine	510 nM	5.0 µM to 60µM	Cyclic voltammetry	[10]
Carbon fiber electrode coated with SWCNT forest	HiPCO SWCNTs	Dopamine	17 nM	50 µM to 25 µM	Fast-scan cyclic voltammetry	[36]
MWCNT paste electrode modified with SDS	Spectroscopically pure MWCNTs, diameter 50-100 nm and length 5-10µm	Dopamine	33 nM	1 µM 28 µM	Cyclic voltammetry	[37]
MWCNT coated glassy carbon electrode	MWCNTs synthesized by cathalytic pyrolysis method	Dopamine, serotonin	100nM	100nM to 50µM	Cyclic voltammetry	[38]

Electrode	Description of CNT	Analysed neuro-transmitter(s)	Limit of detection	Linear range of detection	Detection method	Reference
MWCNT coated glassy carbon electrode	Pristine MWCNTs	Dopamine	800nM	3 µM to 200 µM	Cyclic voltammetry	[39]
Electrochemically oxidized MWCNT coated glassy carbon electrode	MWCNTS with 10nm outer diameter 4.5 nm inner diameter and 3.5 µM length	Dopamine, serotonin	235 nM for DA and 460 nM for 5-HT	5 µM to 240 µM for DA, 5 µM to 210 µM for 5-HT	Cyclic voltammetry	[28]
CNT coated Nb electrode	MWCNTs grown on-site with CVD	Dopamine	11 nM	N/A	Fast-scan cyclic voltammetry	[40]
MWCNT and Ni-Nanoparticle coated glassy carbon electrode	MWCNTs, no further explanation	Serotonin	118 nM	N/A	Cyclic voltammetry	[37]
Gold electrode coated with MWCNTs, SDS and PPY	MWCNTs, diameter 20nM, length 20-100 µM, bulk density 0.04-0.06 g/cm3	Dopamine	136pM with DPV and 70nM with CV	5 nM to 10 µM	Cyclic voltammetry	[21]
MWCNT coated edge plane pyrolytic carbon electrode	N/A	Epinephrine	0.15nM	0.5 nM to 1 µM	Cyclic voltammetry	[42]
Graphite paste electrode modified with MWCNTs and ionic liquid	N/A	Epinephrine	90 nM	0.1 µM to 450 µM	Cyclic voltammetry/ differential pulse voltammetry	[26]

Table 3 shows a comparison of electrodes reviewed in section 4. While many electrodes are reported to have a limit of detection in the nM range, it is notable that the linear range of detection is many times higher. The linear range of detection shows actual results that are observed trough the analysis. The limit of detection is a calculated value that considers a blank response i.e. the background noise and the electrodes linear response to the analyte. This means that considering the limit of detection as an indicator for the electrode's usefulness can be misleading, even though the value is largely used in academic literature and as a comparative value [46].

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