



Polypeptides Based Molecular Electronics

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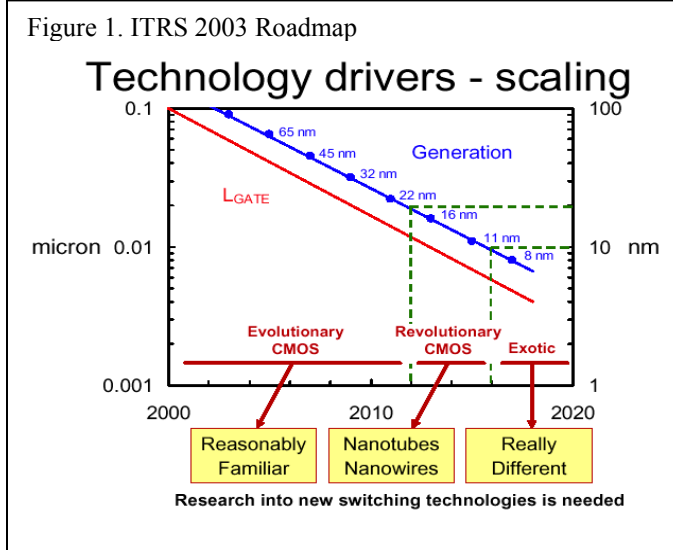
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14. ABSTRACT This report discusses use of polypeptide supramolecules that will self assemble from solution and will form molecular wires that exploit quantum mechanical transport mechanisms thus enabling the formation of molecular devices such as transistors, diodes, and sensors. We have designed the peptides, arranged them on substrates using self-assembly, Dip-PEN nanolithography, and also e-beam assisted lithography. The peptides are characterized using AFM and the electrical properties of the self-assembled interconnects are characterized as well. These peptides can be nanoengineer/nanoassemble individual building blocks at the molecular level, atom by atom, to form conducting channel towards realization of molecular MOSFETs/CMOS device technology.					
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CHAPTER 1

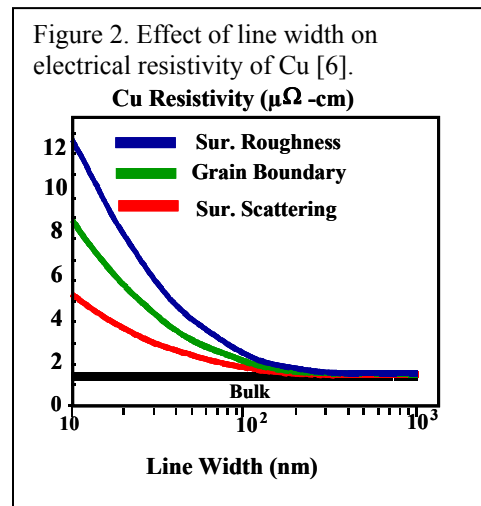
Background and Motivation

The International Technology Roadmap for Semiconductors (<http://public.itrs.net>), 2003 (figure 1) predicts that extensions of today's computer chip and system architectures are expected to achieve marginal performance gains at or below the 50nm device node, even with the introduction of new generations of metals with higher conductivity and insulators with lower dielectric constant [1]. The most severe limitations to the realization of giga-scale and tera-scale integration schemes will be imposed by the basic laws of physics [2-5].



The continual decrease in the feature size of integrated circuits (ICs) has three major issues [6]: (1) Electrical resistivity in sub-50nm conductor lines rises prohibitively due to quantum mechanical phenomena and microstructural limitations (shown in Figure 2).

(2) Surface scattering, i.e., scattering of electron wave from boundaries of ultra-narrow conductors inhibits electronic conduction & stands as serious roadblock to Moore's Law at the most fundamental level. (3) As line width approaches the mean free path λ_0 , surface scattering inhibits conductivity in conventional electrical wires.



Single molecule based molecular electronics approaches have been long explored and are still limited to scanning tunneling microscopy enabled applications. Self assembled monolayer and multilayer based approaches have been suggested for molecular electronics. In these approaches, the tail group is covalently attached to a substrate and the head group provides the semiconductor functionality. The alkyl chain provides the dielectric function. Devices based on this approach are promising and bring us closer towards accomplishing molecular electronic devices. Polypeptides may also be tailored with head and tail group functionalities and the peptide chains are known to provide excellent dielectric functionalities.

In this project, we propose the use of polypeptide supramolecules that will self assemble from solution and will form molecular wires that exploit quantum mechanical transport mechanisms thus enabling the formation of molecular devices such as transistors, diodes, and sensors. We have designed the peptides, arranged them on substrates using self assembly, Dip-PEN nanolithography, and also e-beam assisted lithography. The peptides are characterized using AFM and the electrical properties of the self-assembled interconnects are characterized as well. These peptides can be nanoengineer/nanoassemble individual building blocks at the molecular level, atom by atom, to form conducting channel towards realization of molecular MOSFETs/CMOS device technology.

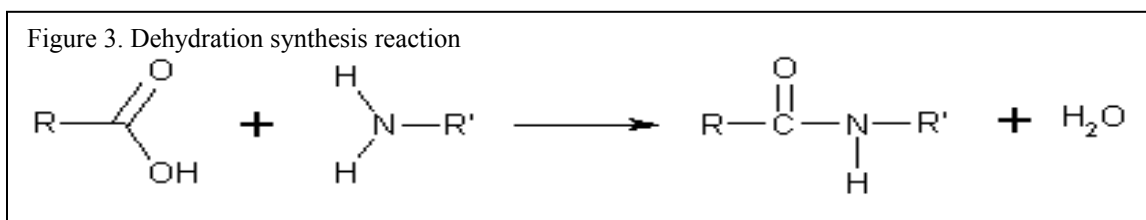
CHAPTER 2

Review of Literature

2.1 Peptides

2.1.1 Introduction to peptides

Peptides are biomolecules formed from the 20 naturally occurring amino acids. *Figure 3* shows dehydration synthesis reaction (known as condensation reaction) occurs between the COOH group of one amino acid with the NH₂ of the other amino acid, forming a CO-

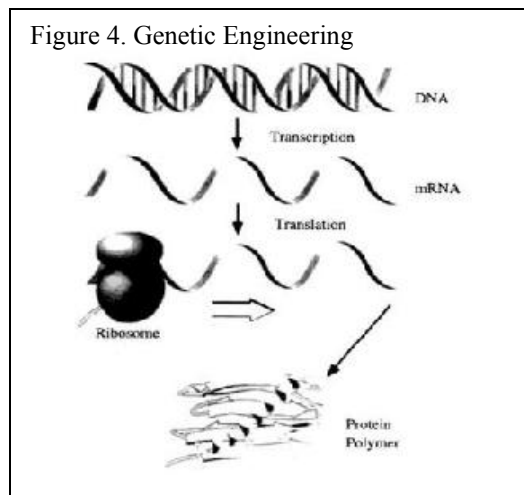


NH bond which is known as the amide bond or peptide bond. One end of the peptide has a free amino group and is known as the amino terminal or N-terminal. The other end of the peptide has a free carboxyl group and is known as the carboxyl terminal or C-terminal. Peptides are made of amino-acids linking into a linear chain with overall length up to 100 amino-acids. Scientists nowadays usually describe peptide of 50 amino-acids and more as polypeptides. Peptides have many advantages over conventional polymers since they are able to self assemble hierarchically into stable ordered conformations [21]. Peptides have defined molecular weight, monodispersity, stereoregularity, sequence and composition controlled at monomer level allowing formation of ordered conformations.

2.1.2 Synthesis of Peptides: Genetic Expression

Peptide can be either formed biologically or chemically. Peptides have been formed biologically in animals and plants and are essential to all living things. Scientists have been trying to make improvement in the peptides by genetically engineering the peptides and also chemically synthesizing the peptides. Extraction of useful peptides from animal or plants has been done with great cost since the peptides are in small quantities. Genetically engineered peptides have hence been studied to increase the supply of useful

peptides. Peptides are genetically engineered by substituting the different amino-acids from the naturally occurring sequence. This sequence can be changed by producing a synthetic DNA that encodes this new sequence of the peptide as shown in *Figure 4* [22]. The advantage of genetically expressed peptides is that long peptide chains up to 1200 amino-acids can be produced efficiently in large scale by this method; it may be impossible to produce long peptides using chemical



synthesis method. Even though the construction of the DNA takes several months, it only has to be done once. After the introducing the DNA into a genetically engineered production organism, the peptide can be produced with great precision and indefinitely. However, the limitation of genetically engineered peptide is that only small changes can be made before the bioactivity of the peptide is completely lost [22].

2.1.3 Synthesis of Peptides: Chemical Synthesis

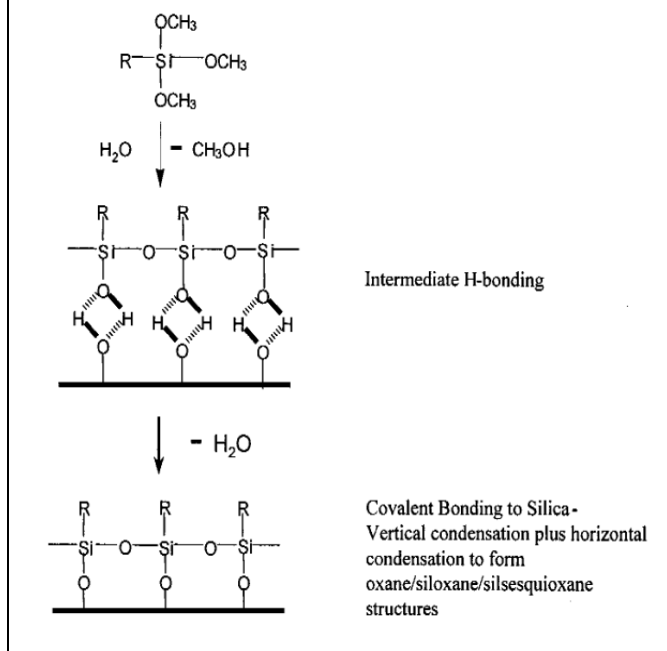
Chemical synthesis of peptides on the other hand is cost effective and a rapid method when synthesizing short peptides. Chemical synthesis of peptides is classified into two main categories, solution phase synthesis and solid phase synthesis. Synthesis of peptides in solution phase involves the condensation of short peptide sequence via a step growth into a longer peptide sequence. Solution phase synthesis is the most useful way to produce short peptides of 3-6 residues. The advantages are that pure intermediate products are formed after every synthesis step and it is flexible since the peptides can be deprotected and recombined forming peptides of longer chains. However, the limitation of solution phase synthesis is that it is costly and the difficulty in preparation for cyclization reaction. New strategies in solution phase have been developed by using functional groups for side reaction [23] and using of new coupling reagents [24]. Synthesis of peptides in solid phase involves the stepwise addition of N-protected amino-acids to a peptide chain that is anchored to matrix [25]. Solid phase synthesis has the

drawback that the purification of peptides is done only after cleavage from the matrix. However, there are advantages of solid phase synthesis over solution phase. The reaction can now be automated and solubility of peptides is no longer a problem since it remains on the solid matrix. An additional advantage is that the peptides synthesized by solid phase synthesis is that after cleaving from the matrix can be cyclized to form small peptides of alternating stereoisomer. This alternating stereoisomer allows the rings to form hydrogen bond with adjacent rings like beta sheets, causing self assembly. In this report, both biologically and also chemically synthesized peptides are used.

2.2 Self Assembly of Silane onto Silicon substrate

Silane is a silicon-based chemical that consist of organic and inorganic reactive group in the same molecule. The typical structure of silane is $(\text{RO})_3\text{SiCH}_2\text{CH}_2\text{X}$, where RO is a hydrolyzable group such as methoxy, ethoxy, or acetoxy and X is an organofunctional group such as amino, methacryloxy, epoxy or mercapto. Silane is used as a linker to bond an organic material such as polymer to an inorganic substrate such as silicon, glass or metal. It is useful in this report as a linker to

Figure 5. Condensation reaction of Silane onto Silicon Wafer



bind peptide (organic component) to silicon substrate (inorganic component). *Figure 5* shows the condensation reaction of silanes onto silicon substrate [26]. The silanes are reversibly physisorbed onto the hydrated silicon substrate through hydrogen bonding, bringing the silanes near to the water layer on the silicon substrate. Covalent bonding occurs and water is produce as a side product. During the initial stage, only few molecules are chemisorbed onto the silicon substrate, forming a disordered layer.

However, at a longer time, the surface coverage would reach a well ordered and compact layer. The functional group at the other end of the silanes can subsequently react with the functional groups of peptide, forming strong covalent bonds.

2.3 Nanopatterning

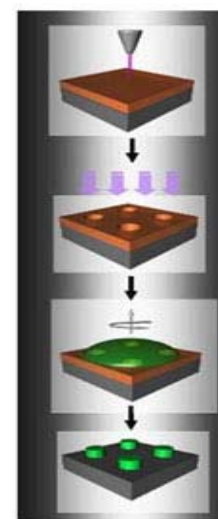
Nanopatterning is developing over the years due to increasing needs for smaller features down to sub 100 nm. There are two classes of patterning, the top-down and bottom-up techniques. Top-down technique involves the use of lithography to decrease the feature sizes of devices and bottom-up technique involves the building of features from molecular level. In this report, we are using top-down which is soft electron beam lithography and bottom-up which is dip pen lithography to pattern the peptides.

2.3.1 Nanopatterning of Peptides with Soft Electron Beam Lithography

Soft electron beam lithography (eBL) is a specialized top-down technique for creating the extremely fine patterns required by electronics industry for integrated circuits. This is made possible due to small spot size of the electrons, unlike optical lithography where the resolution is limited by the wavelength of light used for exposure. The electron beam has wavelength so small that diffraction no longer defines the lithographic resolution. eBL involved exposing a photoresist to scanning beam of electron in patterned manner, removing either the exposed area or unexposed area depending on the type of resist. Positive resists develop away after exposal, whereas the negative resist remain after exposal after development. A layer

of co-polymer is first spin onto the wafer, followed by another layer of PMMA. *Figure 6* shows both the co-polymer and PMMA are positive resist that will be broken down by the electron beam after exposal, creating a pattern when it is developed. After the pattern is created, we can attach the molecules that we need into this patterns.

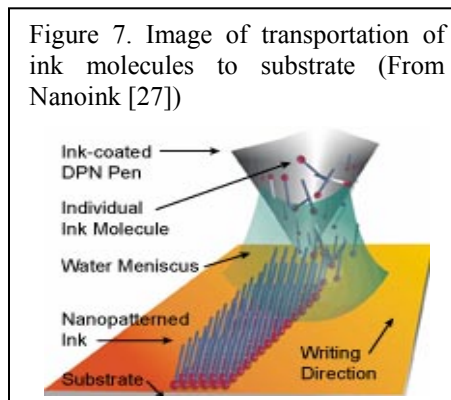
Figure 6. Soft eBL



2.3.1 Nanopatterning of Peptides with Dip-Pen Lithography

Dip-Pen Lithography (DPN) is a bottom-up technique that involves dipping an atomic force microscopy tip into a specially formulated ink and writing this ink onto the substrate. It works just like a pen writing ink onto paper. *Figure 7* shows that the water meniscus forms naturally in air between the tip and substrate and this meniscus aids the transport of ink molecules onto the substrate.

There are several variables when considering DPN as a nanolithography method: dwell time, humidity, diffusion coefficient of ink and temperature. The time the tip spends on the substrate is called the dwell time and this is



directly related to the size of the pattern created. For example, a 5 second dwell time may create a 10 μm dot while a 10 second dwell time may create a 30 μm dot. Humidity on the other hand would play a part in the size of the water meniscus, allowing more or less ink to flow from the tip to the substrate, hence affecting the amount of ink absorbed onto the substrate. Diffusion coefficient of the ink plays an important role in deciding the rate of writing. Diffusion coefficient is unique for every ink. For example, an ink with high diffusion coefficient may produce a 30 μm line width whereas an ink with a lower diffusion coefficient may produce a 10 μm line width even though they are both written at the same rate. Hence, every ink should be calibrated first before writing in order to produce the line width required. Temperature of the environment will determine how quickly the ink will dry on the tip, thereby limiting the amount of time on hand for patterning the ink onto the substrate. Hence, when writing the peptide molecules using DPN, we have to take into consideration of these conditions.

CHAPTER 3

Objectives of R&D work

The objectives of the research work carried out in Singapore (NTU), United States (NU) and also India (IMT) during the project period are:

1. Design and synthesize of polypeptide with functionalized groups for attachment to substrates.
2. Immobilize the peptides onto the silicon substrate and characterize the self-assembled morphology of these peptides using Bioscope II and Digital Instrument Atomic Force Microscopy.
3. To develop two-terminal device fabrication concepts using different peptides for transistor application.
4. Test the electrical properties of the immobilized peptides on the two-terminal devices.
5. To nanopattern the peptides between the electrodes using Soft Electron Beam Lithography (Soft eBL) and Dip-Pen Lithography (DPN) for future electrical testing of peptides.

CHAPTER 4

Research Outcome and Achievements

4.1 Synthesis, Characterization and Electrical Testing of $\text{His}_6\text{-}\{(AlaGly)_3GlyLys(AlaGly)_3GlyTyr(AlaGly)_3GlyGlu(AlaGly)_3GlyTyr\}_{256}\text{-His}_6$

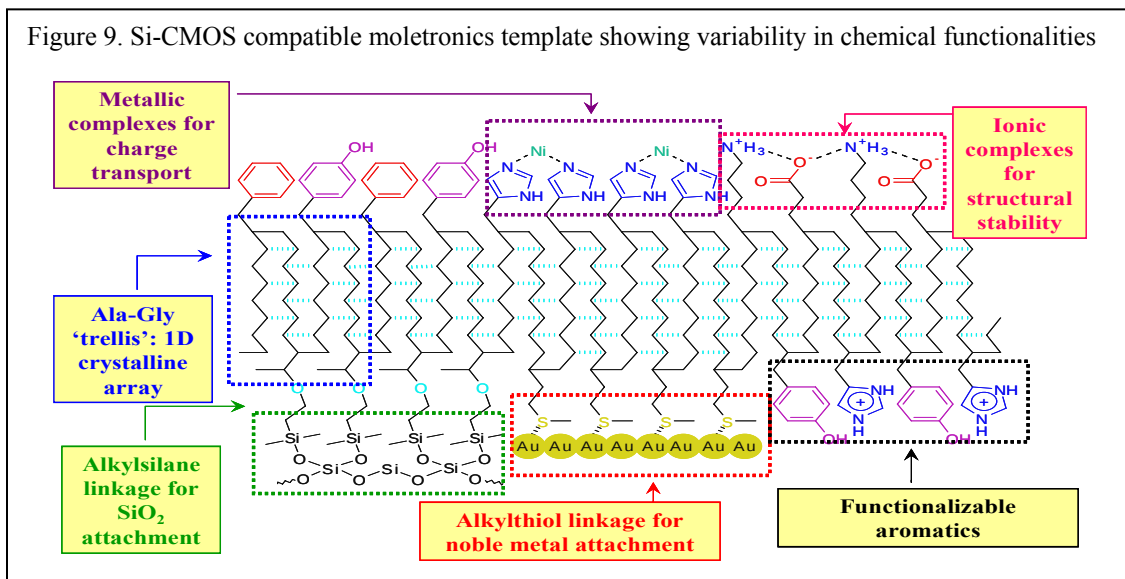
4.1.1 Methodology for Polypeptides β -sheet Engineering

Polypeptides were engineered to contain specific amino acid sequences, chain lengths, and conformation with an extremely high degree of monodispersity. The polypeptide polymers with repetitive AlaGly sequences were designed and subsequently synthesized via over expression by E.Coli. Molecular biological techniques permit peptide engineering via the replacement of naturally occurring amino acids with synthetic analogues by relaxing the specificity of the aminyl-tRNA synthetase [28-30]. Such a methodology was developed here for the monodisperse synthesis of functionalized polypeptides for surface-directed assembly.

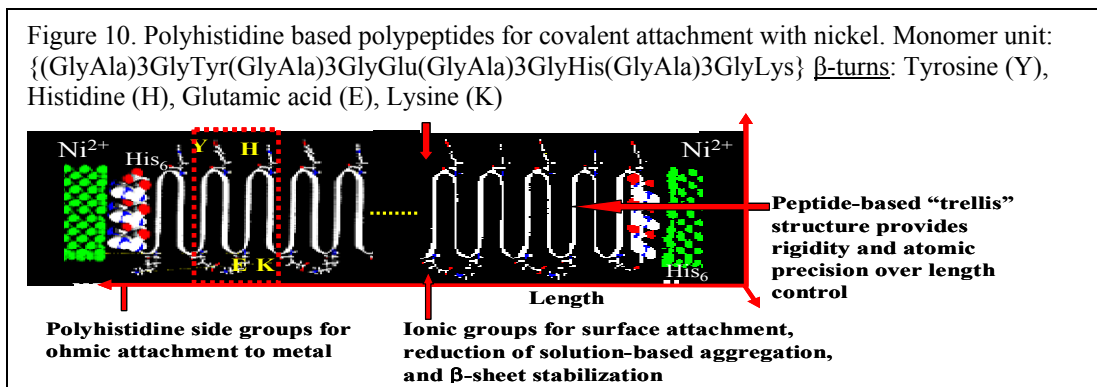
4.1.2 Candidate Peptide Design and Methodology

A polypeptide (shown in Figure 9), which is composed of amino acid chain comprised of Alanine (Ala), Glycine (Gly), Phenylalanine (Phe) and Cysteine (Cys) with the sequence

Figure 9. Si-CMOS compatible moletronics template showing variability in chemical functionalities



$\{(\text{GlyAla})_3\text{GlyCys}(\text{GlyAla})_3\text{GlyPhe}\}_n$, was developed by Dr. Shekhawat group in Northwestern and have the same conformation as those previously prepared by Parkhe *et al.* [31]. This peptide was utilized in this work. The desired polypeptide should adopt an antiparallel β -sheet conformation with more sterically demanding amino acids positioned



at the β -turn so that the system can be stabilized by antiparallel alignment of the dipoles. Here, regular turns were being created with cysteine residues at the site of one β -turn and phenylalanines at the alternate site. This molecular design will facilitate overlap of the aromatic groups to enhance the formation extended π -electron systems potentially contributing to charge transport along the axis of the β -sheet. The cysteine residues constitute the alternate β -turn that presents the histidine residues providing a mechanism for covalent attachment to Ni surfaces (e.g. as shown for cysteine esters and cysteine containing functional proteins [32-31]).

For this work, the attachment to polypeptide via polyhistidine side groups was carried out as it gives a very good ohmic contact with metals such as nickel (*shown in Figure 10 above*). Nickel was selected as the electrode surface to allow covalent attachment of the polypeptide functional end moieties.

4.1.3 Polypeptide Repeat Lengths, Characterization and Directed Self-Assembly

A series of polypeptides at different concentration was prepared. The peptides have 256 repeats which correspond to channel length of about 3-5 micron).

AFM/STM analyses.

Atomic force microscopy surface topography measurements of self-assembled polypeptide nanostructures was carried out using BioScope II to document the surface roughness, determine polypeptide domain structure and evaluate lamellae assembly.

Figure 11a shows the

surface morphology of polypeptide having a concentration of 0.05 mM.

Topographical image shows the domain structure and indicates that peptides were not fully formed at this low concentration. Figure 11b shows the cross section view of the domain structure.

Figure 12a shows the surface morphology of polypeptide having

Figure 11a. Topographical image of polypeptide with low concentration and b. Cross section

Peptide Concentration of 0.05mM

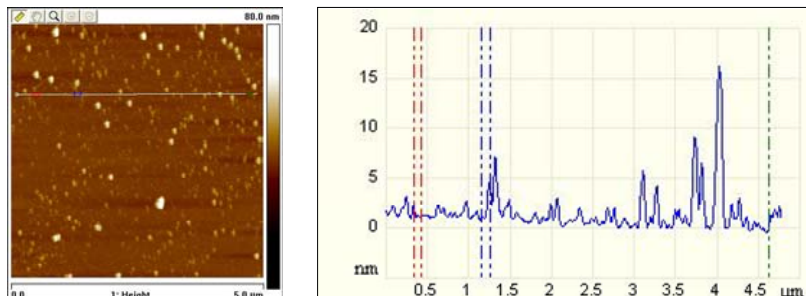


Figure 12a. Topographical image of polypeptide with low concentration and 12b. Cross section

Peptide Concentration of 0.1mM

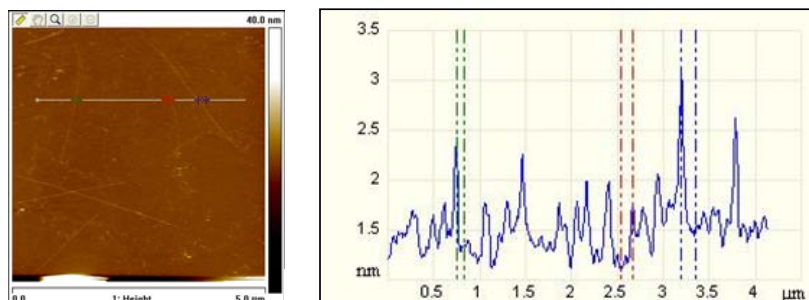
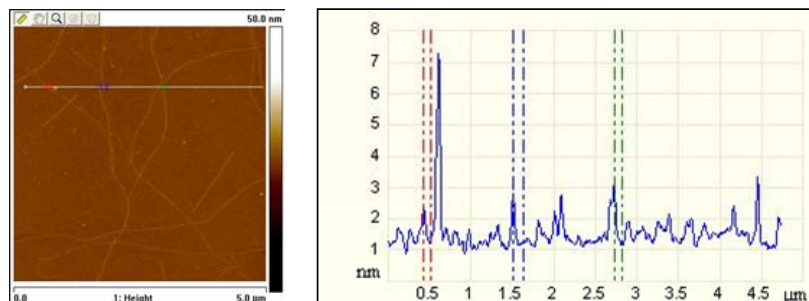


Figure 13a. Topographical image of polypeptide with low concentration and 13b. Cross section

Peptide Concentration of 0.25mM



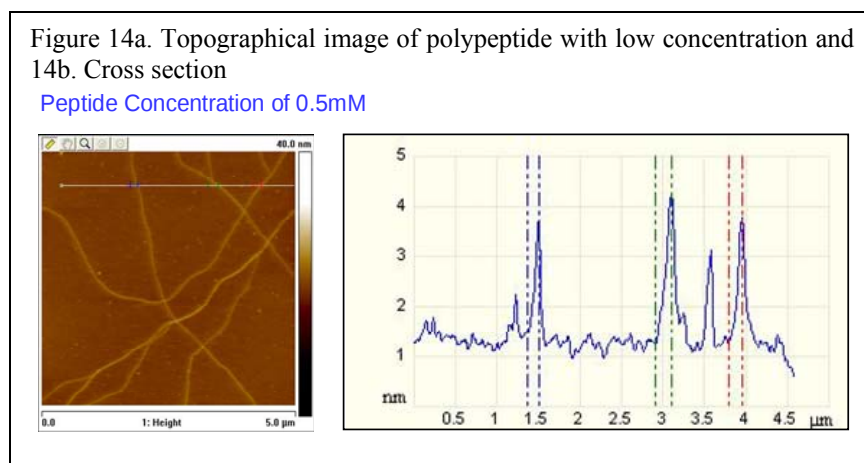
a concentration of 0.1 mM. Topographical image shows the domain structure and indicates that peptides were of short length and vastly dispersed at this low concentration.

Figure 12b shows the cross section view of the domain structure.

Figure 13a shows the surface morphology of polypeptide having a concentration of 0.25 mM. Topographical image shows the domain structure and indicates that peptides were long and well dispersed at this concentration. *Figure 13b* shows the cross section view of the domain structure and the height of the peptide has an average of 1.4nm, matching the theoretical value of 1.6nm. At 0.25mM, the peptide is at its optimum concentration.

Figure 14a shows the surface morphology of polypeptide when the concentration is increased further to 0.5 mM.

Topographical image shows the domain structure and indicates that peptides were long and well dispersed at this concentration.



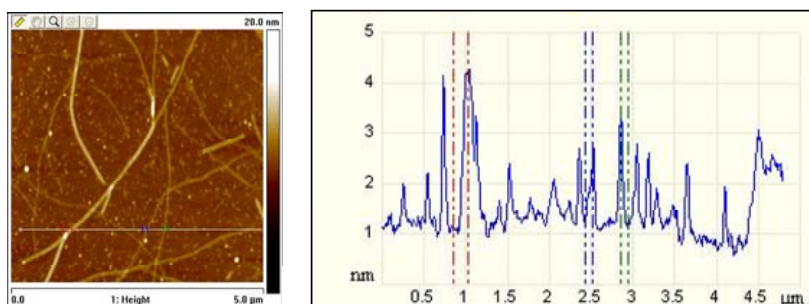
However, *Figure 14b* shows the cross section view of the domain structure and the height of the peptide has an average of 2.5nm, indicating that the peptide is aggregated.

Figure 15a shows the surface morphology of polypeptide when the concentration is 0.8 mM.

Topographical image shows the domain structure and indicates that peptides

Figure 15a. Topographical image of polypeptide with low concentration and 15b. Cross section

Peptide Concentration of 0.8mM



were long but dense at this high concentration. Figure 15b shows the cross section view of the domain structure and the height of the peptide has an average of 2.3nm, indicating that the peptide is aggregated.

From the figures above, it can be concluded that at 0.25mM, the peptide is at the optimum concentration.

4.1.4 Electrical functionality testing of Polypeptides with Scanning Tunneling Microscope on Two-terminal Device Architecture.

Electrical measurements of synthesized polypeptides were carried out using Scanning tunneling microscope. Peptides were synthesized in between two terminal electrodes made of Nickel (shown in figure 16).

Figure 16. Optical Image of two-terminal device

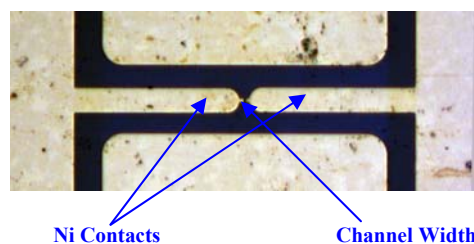


Figure 17 shows the schematic of the polypeptide based molecular quantum crystal wires as a candidate building block synthesized peptides between the two-terminal device and direction of current flow. One end of the electrode was grounded and STM conducting probe was placed on the other end of the electrode (shown in figure 18 below).

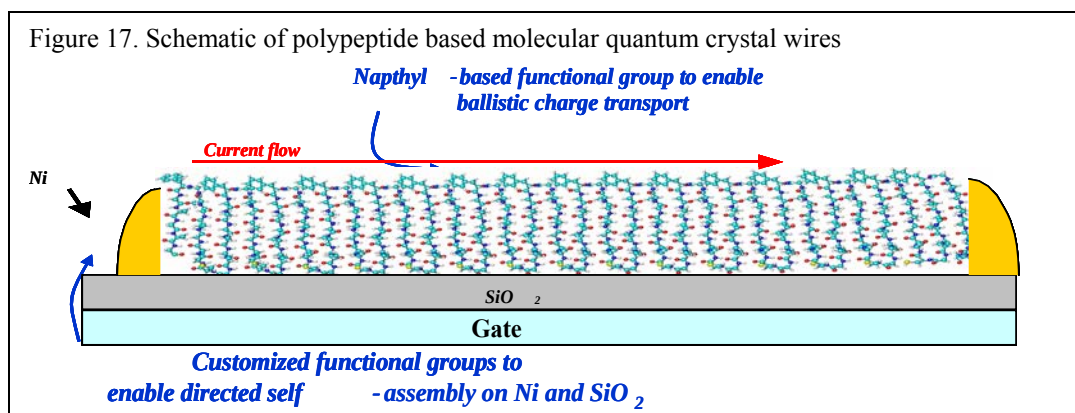
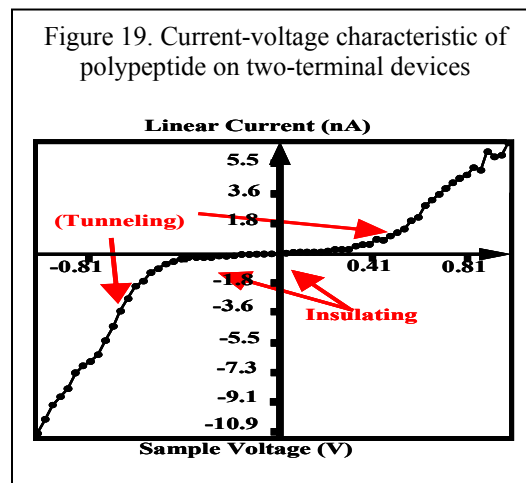
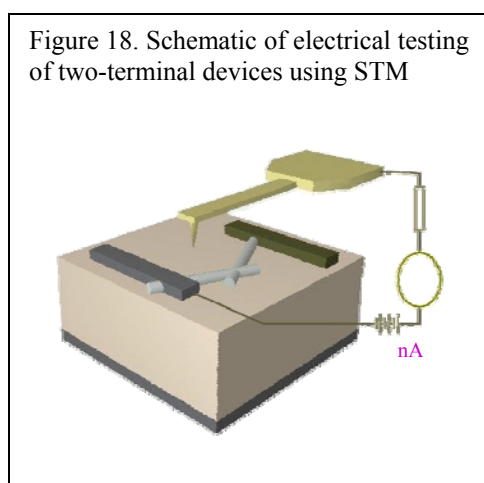


Figure 19 below shows a remarkable current-voltage characteristic of the polypeptide. It clearly indicates an electron tunnel across the phenyl rings of the polypeptides. In this case, peptides were lying flat on the ground and the characteristics show their semiconducting behavior.



4.2 Design, Development and Nanopatterning of Peptides with Soft Electron Beam Lithography(Soft eBL) and Dip-Pen Nanolithography(DPN)

4.2.1 Nanopatterning of Peptides with Soft Electron Beam Lithography

Nanopatterning of peptides was carried out as the second aspect of my research task. The motivation was to pattern the peptides in between pre-fabricated electrodes for transistor and interconnect application.

Soft eBL technique was developed at NU for patterning solgel structures. *Figure 20* shows the optical image of nanopatterns chosen and formed using soft eBL technique. The optical image shows that the trenches

formed. These nanopatterns were deposited with 3-Mercaptopropyl trimethoxysilane (MPTMS) followed by the peptides.

Figure 20. Optical Image of nanopatterns formed by eBL technique

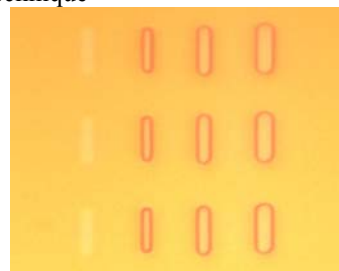
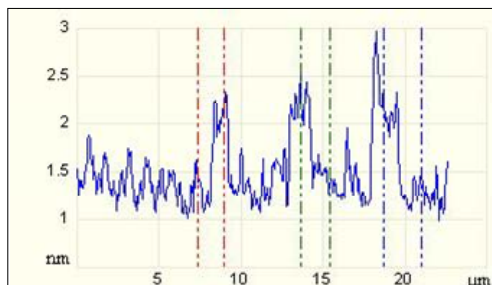
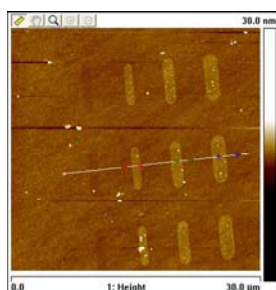


Figure 21a shows the topographical image of MPTMS layer.

Figure 21b shows the cross section view of the domain structure and the height of

Figure 21a. Topographical image of MPTMS layer and 21b. Cross section



MPTMS has an average of 0.82 nm, corresponding to the theoretical height of a MPTMS monolayer of 0.87nm. Fourier Transform Infrared Spectroscopy (FTIR) spectrum of 3-Mercaptopropyl trimethoxysilane (MPTMS) layer (*shown in Figure 22 below*) is collected and it showed the stretching of CH₂ group from MPTMS layer, further substantiating that MPTMS layer is attached onto the silicon wafer.

Figure 22. Fourier Transform Infrared Spectroscopy (FTIR) of 3-Mercaptopropyl trimethoxysilane (MPTMS) layer on Si wafer

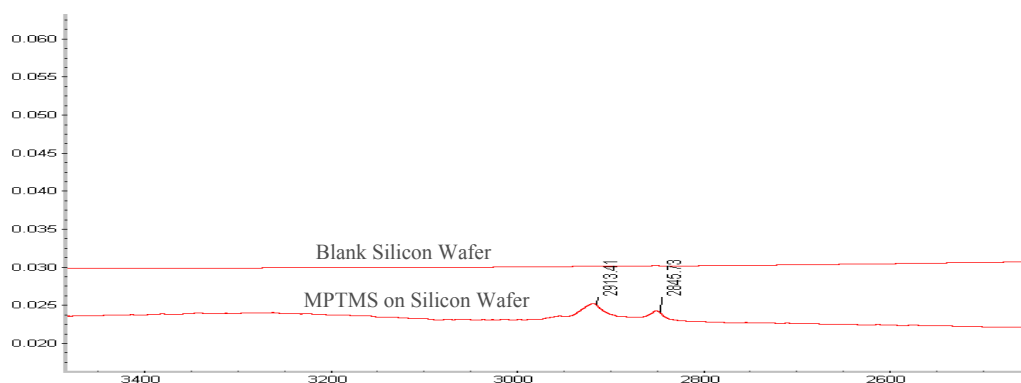
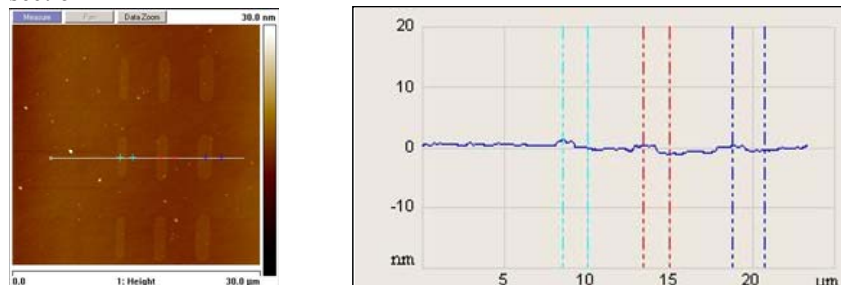


Figure 23a shows the topographical image of peptide on MPTMS layer.

Figure 23b shows the cross section view of the domain structure and the

Figure 23a. Topographical image of peptide on MPTMS layer and 23b. Cross section



height of peptide with SH end group is of an average of 1.1 nm, showing a height change due to the attachment of peptide on MPTMS layer.

Peptide with COOH end group is also carried out to show the versatility of polypeptide for electrical interconnects. Figure 24 shows the optical image of nanopatterns chosen and formed using soft eBL technique. Squares of different sizes were used to replace the former lines to show availability of choices. These nanopatterns were deposited with Aminopropyltrimethoxysilane (APTES) followed by peptide with COOH end group.

Figure 24. Optical image of fluorescence tagged peptide

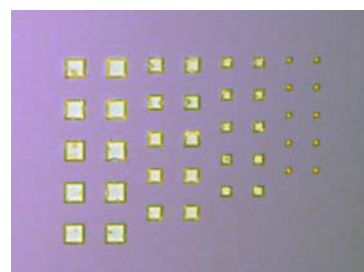


Figure 25a shows the topographical image of APTES layer. Figure 25b shows the cross section view of the domain structure and the height of APTES has an average of 11.3nm.

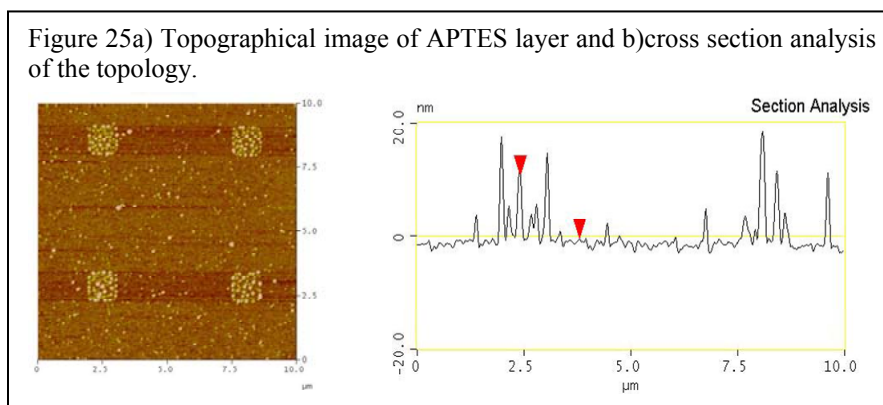
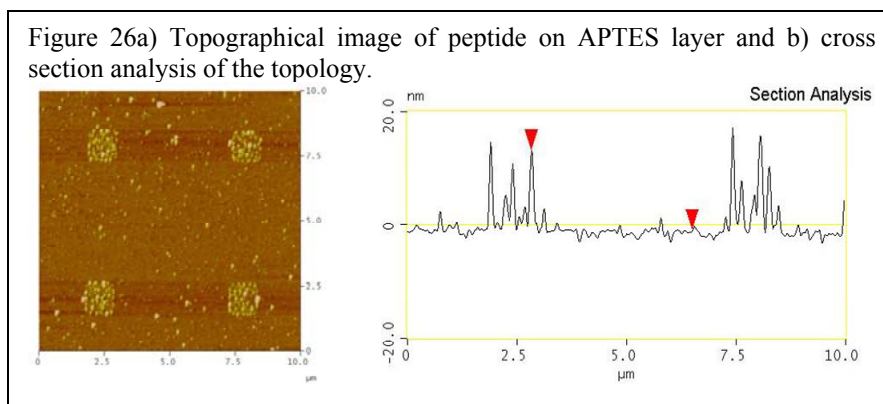


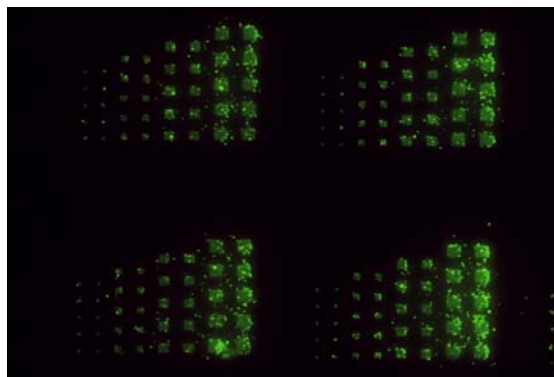
Figure 26a shows the topographical image of peptide with COOH end group on APTES layer. Figure 26b shows the cross section view of the



domain structure and the height of peptide is of an average of 2.9nm, showing a height change due to the attachment of peptide on APTES layer. However, because of the roughness in APTES layer, the height change is not a good gauge of peptide attachment. We have tagged this peptide with NHS-ester fluorophores for a stronger validation of the peptide attachment.

Fluorescence Microscopy is done to further support the above finding. The peptide is tagged with NHS-ester fluorophores. The fluorescence given out by polypeptide when it is attached is taken using fluorescence microscopy. The optical Image (shown in figure 27) further validate that peptides are attached onto APTES layer.

Figure 27. Optical image of fluorescence tagged peptide



4.2.2. Nanopatterning of Peptides with Dip-Pen Nanolithography

In addition to nanopatterning of peptides using soft eBL, DPN is also employed as an alternative method to pattern the peptides in between pre-fabricated electrodes for transistor and interconnect application. Some applications of DPN include the well-documented work with MHA or ODT on gold. MHA specifically allows for very good control with a controllable diffusion constant. This allows creating of intricate patterns with a mix of lines and dots. However, DPN gives the benefit of writing different inks and designs which allow peptides to be written onto the functionalized silicon substrate. Silicon substrate were deposited with 3-Mercaptopropyl trimethoxysilane (MPTMS) or Aminopropyltrimethoxysilane (APTES). Peptides with SH end group and COOH end group are attached onto the silane layers respectively. *Figure 23* shows peptide with SH

Figure 23. Phase image of polypeptide with SH end group on MPTMS layer

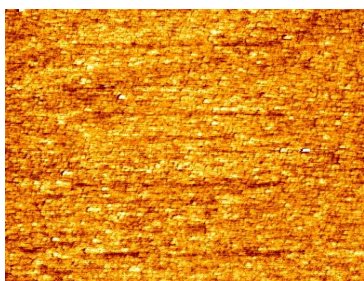
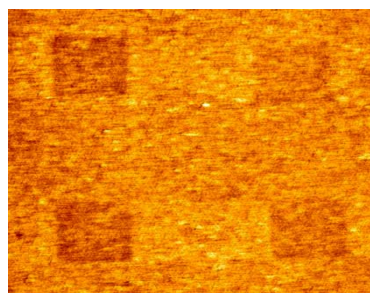


Figure 24. Phase image of polypeptide with NH₂ end group on APTES layer



end group written on top of a MPTMS covered silicon wafer, validating that DPN can be employed to pattern the peptide with SH end group. In addition, peptide with COOH end group was also tested by writing onto APTES covered silicon wafer. *Figure 24* above shows phase image of peptide with COOH end group written on top of an APTES covered silicon wafer. DPN has shown versatility with the use of different peptide ink on different functionalized surface. This versatility will give the options of patterning on different substrates targeted for different applications.

CHAPTER 5

Project Outcomes for Defence Applications

This molecular interconnects will be able form part of the building blocks for portable devices. The portable devices will have good potential for field application. Therefore, a summary of the project outcomes are:

1. Peptides can be designed to have specific affinity to the substrate.
2. Peptides can contain moieties that can be organized to serve as conducting channels.
3. Self-assembled peptides have shown to have conducting characteristics.
4. Both soft e-beam lithography and DIP-Pen method are also suitable for doing patterning for polypeptides.

CHAPTER 6

Follow-up R&D projects:

Polypeptides were engineered to contain specific functionality for binding to two different substrates. They are silicon dioxide and gold. It is shown that the scheme of using self-assembled polypeptides as the conducting channel is possible. Therefore in the future, other molecular electronic devices can be fabricated and testing methodologies for such devices can also be studied to investigate their applicability to bionano-electronics in the future. Applications in gas and biological sensing will be explored. With the use of small conducting channels, portable sensing and other electronic devices will be easily possible.

Therefore, the follow-up R&D projects that are possible are:

1. Biosensing devices making use of the sensing moieties attached to these peptides interconnects.
2. Gas sensing devices using suitable sensing moieties.
3. Nanotransistors using peptides as conducting channels.

CHAPTER 7

Recommendation and Conclusions

The concentration studies of peptide with silane end group shows that the peptide is at its optimum concentration at 0.25mM. Concentration lower than 0.25mM is not capable of forming long chain peptides and concentration higher than 0.25mM will have vertical and horizontal aggregation of peptides, increasing both the height and width of the peptide chains. Peptide with silane end group at 0.25mM is tested on STM for its electrical properties and results shows that the peptide is semi-conducting. This promising result proved that peptide can be future researched on for possibility as a new material for molecular interconnects.

Soft electron beam lithography (soft eBL) and dip-pen lithography (DPN) are used to nanopattern the peptides. Soft eBL method proved that the peptide with SH group is attached to a 3-Mercaptopropyl trimethoxysilane (MPTMS) functionalized silicon substrate by height change in atomic force microscopy images and CH₂ stretching in fourier transform infrared spectroscopy. Peptide with COOH group is proven to attach to Aminopropyltrimethoxysilane (APTES) functionalized silicon substrate by height change in atomic force microscopy images and fluorescence microscopy. DPN is used to write the peptide with SH end group as well as COOH end group and results show the possibility to write both peptides of different functional end groups onto the different functionalized silicon substrate. In industry, it is hard to synthesize peptide with silane end group; hence peptides with different functional end groups, which can be synthesized commercially, are used. This report proves that the commercially available peptides can be easily attached onto silicon substrate and can be used for future electrical testing.

Future work like electrical testing of peptides using a transistor configuration can be investigated to prove the possibility of peptide as a new material for electrical interconnects.

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