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Nanostructuring of Nanorobots for use in Nanomedicine

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ABSTRACT

Submarine nanorobots are being developed for use in branchy therapy, spinal surgery, cancer therapy, etc. Nanoparticles have been developed for use in drug delivery systems and for cure in eye disorders and for use in early diagnosis. Research in nanomedicine is under way in development of diagnostics for rapid monitoring, targeted cancer therapies, localized drug delivery, and improved cell material interactions, scaffolds for tissue engineering and gene delivery systems. Novel therapeutic formulations have been developed using PLGA based nanoparticles. Nanorobots can be used in targeted therapy and in repair work of DNA. Drexler and Smalley debated whether 'molecular assemblers' that are devices capable of positioning atoms and molecules for precisely defined reactions in any environment is possible or not. Feynman's vision of miniaturization is being realized. Smalley sought agreement that precision picking and placing of individual atoms through the use of 'Smalley-fingers' is an impossibility. Fullerenes, C_{60}, are the third allotropic form of carbon. Soccer ball structured, C_{60}, with a surface filled with hexagons and pentagons satisfy the Euler's law. Fullerenes can be prepared by different methods such as: (i) first and second generation combustion synthesis; (ii) chemical route by synthesis of corannulene from naphthalene. Rings are fused and the sheet that is formed is rolled into hemisphere and stitched together; (iii) electric arc method. Different nanostructuring methods are discussed. These include: (1) sputtering of molecular ions;(2) gas evaporation; (3) process to make ultrafine magnetic magnetic powder; (4) triangulation and formation of nanoprisms by light irradiation ; (5) nanorod production using condensed phase synthesis method; subtractive methods such as; (6) lithography; (7) etching; (8) galvanic fabrication; (9) lift-off process for IC circuit fabrication; (10) nanotips and nanorods formation by CMOS process; (11) patterning Iridium Oxide nanostructures; (12) dip pen lithography; (13) SAM, self assembled monolayers; (14) hot embossing; (15) nanoimprint lithography; (16) electron beam lithography; (17) dry etching; (18) reactive ion etching; (19) quantum dots and thin films generation by; (20) sol gel; (21) solid state precipitation; (22) molecular beam epitaxy; (23) chemical vapor deposition; (24) CVD; (25) lithography; (26) nucleation and growth; (27) thin film formation from surface instabilities; (28) thin film formation by spin coating;(29) cryogenic milling for preparation of 100-300 nm sized titanium; (30) atomic lithography methods to generated structures less than 50 nm; (31) electrode position method to prepare nanocomposite; (32) plasma compaction methods; (33) direct write lithography; (34) nanofluids by dispersion. Thermodynamic miscibility of nanocomposites can be calculated from the free energy of mixing. The four thermodynamically stable forms of Carbon are diamond, graphite, C_{60}, Buckminster Fullerene and Carbon Nanotube. 5 different methods of preparation of CNTs, carbon nanotubes were discussed. Thermodynamically stable dispersion of nanoparticles into a polymeric liquid is enhanced for systems where the radius of gyration of the linear polymer is greater than the radius of the nanoparticle. Tiny magnetically-driven spinning screws were developed. Molecular machines are molecules that can with an appropriate stimulus be temporarily lifted out of equilibrium and can return to equilibrium in the observable macroscopic properties of the system. Molecular shuttle, molecular switches, molecular muscle, molecular rotors, molecular nanovalves are discussed. Supramolecular materials offers alternative to top-down miniaturization and bottom-up fabrication. Self-organization principles hold the key. Gene expression studies can be carried out in biochips. CNRs are a new generation of self-organizing collectives of intelligent nanorobots. This new technology includes procedures for interactions between objects with their environment resulting in solutions of critical problems at the nanoscopic level. Biomimetic materials are designed to mimic a natural biological material. Characterization methods of nanostructures include SAXS, small angle X-ray scattering, TEM, transmission electron microscopy, SEM, scanning electron microscopy, SPM, scanning probe microscope, Raman microscope, AFM atomic force miscroscopy, HeIM helium ion microscopy.

Keywords: *nanostructuring, nanorobots, fullerenes*

1. INTRODUCTION

In the movie, *fantastic voyage*, that came out in 1966 a group of doctors, are shrunk to microscopic size and enter the body of a patient in a submarine like capsule to set him right from the inside. In f*antastic voyage*, a secret agent is recruited by a top-secret organization to join the crew of a submarine called *Proteus*. The crew and submarine are reduced to microscopic size and injected into the bloodstream of scientist Jan Benes, who defects to the

West and goes into a coma after suffering a surgically inaccessible blood clot. They must reach the brain with a laser to melt the clot within an hour or the miniaturization effect will wear off. However, the voyage is undermined by one of the crew who is a saboteur and is prepared to risk everything to stop the mission. This is vision of nanomedicine. Feynman in his after dinner talk [1] alluded to nanomedicines being effective solutions to cardiovascular disease. Nanoscopic devices can be swallowed by the patient. These devices can me made to act as "mechanical surgeons". Through the blood vessels the device is allowed to travel to the heart and performs a "search" of faulty valves, or clogged artery etc. It can be programmed to slice out the faulty valve and repair it or clear up the clogged artery.

2. CURRENT AND FUTURE DEVELOPMENT

Dr. N. Schwalb and O. Solomon [2] at the department of mechanical engineering at Technion-Israel Institute of Technology have designed such a tiny submarine robot. The device is made capable of crawling through tubes with the diameter of human veins and arteries. It is capable of moving with or against the blood stream as needed. It can be used in *branchytherapy*. Prostate and certain other cancers of head and neck can be treated by branchytherapy. The product is in the development stage. Tiny robots can be programmed for an unlimited amount of time using an external magnetic field. The device is about 1 mm in diameter. Another similar device of 1 cm device is developed at Kyoto university [2]. Shaham has develoepd a robot for the Mazor company that is used in many hospitals world over for performing spinal surgery. Haifa/Ariel robot has a centralized structure with tiny winy arms that are used to grab onto the inside of the tubes. Movement of the device results in its advancement. Hair like structure allows for travel through miniature sized tubes. *Nanorobotics* is an emerging area. The words nanorobots, nanoids, nanomachines, nanites, nanomites etc are also used in place of nanorobots. Nanomachines are expected to be used in medical technology to destroy cancer cells.

In Figure 1.0 is shown a `nanocar' designed at Rice University [3]. The molecule consists of `H' shaped `chassis'. Fullerenes are attached at the four corners and can be viewed as `wheels'. These can be attached to a gold surface. Heating of the surface to 200 ^{0} C leads to motion of the molecules back and forth. Fullerene molecules begin to roll. The `axle' is formed from an alkyne group through a carbon-carbon sigma bond. Rotation is unhindered. These were observed using a STM, scanning tunneling microscope.

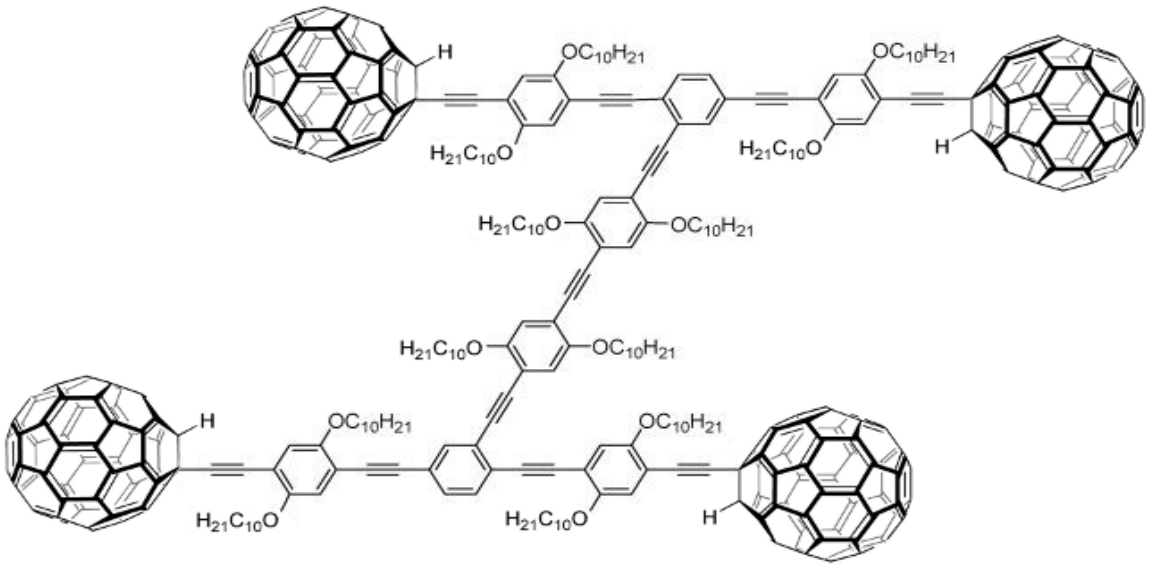

Figure 1. `Nanocar' with Fullerenes as `wheels'

According to some experts [4] nanomedicine is a medical modality where nanoparticles are used for diagnosis of diseases and subsequent treatment. Nanoparticles can be used as therapeutic agents for treatment of eye disorders. One such eye disorder is age related macular degeneration. Nanoparticles offer a number of advantages when used as drug. Greater capacity to detect diseases and early diagnois can be achieved using nanoparticles. Breast tumors and prostate cancer can be cured should they be detected early. Bone cancer can be cured using nanotherapeutic products. NMR, nuclear magnetic resonance machines can be used to effect breakthroughs in pharmaceutical development. Techniques used in nanomedicine can be used for treatment of diseases in a manner with minimization of damage to the human anatomy. This is because the disease germs are isolated in the anatomy and treatment is effected in a specific manner. Other pharmaceuticals cause damage to other parts of the human anatomy. There are ethical issues in use of genetic modification in nanomedicine that needs to be addressed in a modern society. Implantable devices 100,000 times smaller than the head of a pin can be used in disease diagnosis without surgical invasion. The diseased cells are eradicated by `pumping' medicine to the malignant site. Research in nanomedicine is under way in

development of diagnostics for rapid monitoring, targeted cancer therapies, localized drug delivery, improved cell material interactions, scaffolds for tissue engineering and gene delivery systems.

Experts in Canada have obtained approval of PLGA based nanoparticles for suitable therapeutic formulation for clinical use in human anatomy. Degradation products of nanoparticles were lactic acid and glycolic acid and are non-toxic. At UCSF, University of California, San Francisco a function relationship was developed between bone-tooth complex and nanotechnology use.

Scientists at Rice University, Houston, TX have approached the FDA, Food and Drug Administration for clinical trials in humans of an interesting development in nanomedicine. Trials in mice have proved succesful. Nanoparticles were injected into malignant cancer cells. The cells were overheated with lasers. The nanoparticle exploded and the malignant cells were destroyed. The surrounding cells were left unharmed. These trials have lot of potential in cancer therapy. In tradiational chemotherapy both the malignant cells and normal cells get damaged. Nanorobots can be used in drug delivery and for performing repair work of DNA molecule.

Agriculture is expected to benefit from the advances made in nanomedicine. Nanoparticles can be used to enhance photosynthesis, improve seed germination, soil clean-up and nutrient supply, fertilizer production, food processing and fisheries.

Nanoscale science and engineering pertains to the synthesis, characterization and applications of matter with at least one or more dimensions less than 100 nm. Prescott introduced by Intel in Pentium IV chip has the dimensions of about 90 nm. Per the Rayleigh criterion the minimum resolution size achievable is half the wavelength of light ~ 200 nm. Nanotechnology is derived from the Greek words *nanos* which means dwarf and *technologia* which means a systematic treatment of an art or craft. Nanotechnology is rapidly emerging as a distinct discipline in its own right. Vision precedes invention. The movie fantastic voyage provided a vision where doctors where shrunk to nanoscopic size and allowed to enter the patient's anatomy in order to affect the cure. Nanoporous catalysts have been used for years now in the chemical industry. Commercial products introduced into the marketplace such as clay filled nylon nanocomposite by Toyota corp., clay intercalated polyolefin nanocomposite by General Motors, nanocomposite nylon in biomedical applications, chemical resistant coating made of nanometer sized particles suspended in epoxy, CNTs, carbon nanotubes, Li-ion battery electrode of Altair nanotechnologies offer the proof in the pudding about the concern of achieving targeted levels of miniaturization.

Richard Feynman's after dinner talk [1] in 1959 provided the vision for storage of Encyclopedia within the size of a pin head, method of writing small using ions, focus of electrons on a small photoelectric screen, etc. He called for the design and development of better electron microscopes with capability to view atoms, better f value lenses, making computer that filled several rooms to make small, elements of computer to be made submicroscopic. He alluded to a process of evaporation and formation of layered materials much like ALD methods used currently. He called for drilling holes, cutting things, soldering things, stamping things out, molding different shapes at an infinitesimal level. A pantograph can make a smaller pantograph that can make a smaller pantograph and so on and so forth. He mused whether atoms can be re-arranged at will. He offered $1000 to the first guy who can take the information on the page of a book and put in on the area 1/25,000 smaller in linear scale in such a fashion that is can be read using an electron microscope.

The chronology of events that mark the rise of nanotechnology as a discipline is shown in Table 1.0 in [5] from Feynman's talk in 1959 to the nanoethics meeting in 2005. Wide range of applications is expected in nanotechnology ranging from solar cells with increased photovoltaic efficiency, to sunscreens to GMR, Giga magnetic hardrives. The challenges in nanotechnology that need to be overcome are fundamental physical limits to miniaturization, thermodynamic stability of nanostructures and existence of a minimum size below which spheres tend to agglomerate, layer arrangement and why tubular morphology is preferred to spherical morphology in the nanoscale range. Some characterization tools needed in nanotechnology are SEM, AFM, SAXS, WAXS, etc.

Nanoparticles in the size range 10 nm – 1000 nm can be used to entrap or encapsulate drugs. *Nanodrugs* can be synthesized on nanodrugs. *Nanocapsules* contain drug in the cavity and is surrounded by polymer layer. *Nanopores* refer to the pore size in materials that are that small. Encapsulated systems can be used in constant rate drug delivery processes. Biodegradable polymeric nanoparticles can be used in drug delivery applications. Drug attachment to nanosystems can be by electrostatic interactions or covalent bonds. The *absorption* of drug can be affected by different methods. Drugs administered through the gastrointestinal tract, GI is referred to as enteral route of entry. Parenteral routes refer to all other types of drug entry. Drug administration: [6] i) beneath the tongue is by sublingual entry; ii) via the mouth is by buccal cavity; iii) through stomach by gastric entry; iv) through veins by IV therapy; v) within the muscular by intramuscular therapy; vi) beneath the epidermal and dermal skin layers via subcutaneous therapy; vii) within the dermis by intradermal therapy; viii) by topical treatment applied to the skin by percutaneous therapy; ix) through mouth, nose, pharynz, trachea, bronchi, bronchioles, alveolar sacs, alveoli by inhalation; x) is introduced into artery by intrarterial route; xi) to cerebrospinal fluid by intrathecal route; xii) within the vagina by vaginal route and; xiii) through eye, intraocular route. Systemic circulation is reached by the drugs absorbed from the buccal cavity and the lower rectum. The *splanchnic circulation* is arrived at by the drugs absorbed from the stomach, intestines, colon and upper rectum.

Nanopeapods can be grown as shown in [7]. *Nanoshells* were made out of a coating of $CoAl_2O_4$ on nanoparticles made of platinum. *Nanowires* can be made by alternating

layers of cobolt and platinum by electrodeposition. Nanoropes are affected by allowing strong van der Waals forces to take place in extended carbon structures.

Nanoshells are made by coating drugs on metal nanoparticles. The therapeutic response of these drugs depends on the thickness of the coating and capping agent used. Laser irradiation of the nanoshells causes release of the drug coat. Magnetic field can also be used to release the drug. These methods can be used in cancer therapy. Larger amounts of drugs can be treated on account of the higher surface to volume ratios associated with nanoparticles.

3. FULLERENES – DISCOVERY AND SYNTHESIS METHODS

Fullerenes, C_{60}, is the third allotropic form of carbon. The Nobel Prize for their discovery was awarded in 1996 to Curl, Smalley and Kroto. Soccer ball structured, C_{60}, with a surface filled with hexagons and pentagons satisfy the Euler's law. Euler's law states that no sheet of hexagons will close. Pentagons have to be introduced for hexagon sheets to close [4]. Stability of C_{60} requires Euler's 12 pentagon closure principle and the chemical stability conferred by pentagon non-adjacency. C_{240}, C_{540}, C_{960} and C_{1500} can be built with icosahedra symmetry.

Howard [8] patented the 1st generation combustion synthesis method for fullerene production, an advance over the carbon arc method. In the second generation combustion synthesis method optimizes the conditions for fullerene formation. A continuous high flow of hydrocarbon is burned at low pressure in a three dimensional chamber. Manufacturing plants have been constructed in Japan and USA with production capacity of fullerenes at 40 metric tons/year. Purity levels is greater than 98%. The reaction chamber consists of a primary zone where the initial phase of combustion synthesis is conducted and a secondary zone where combustion products with higher exit age distribution do not mix with those with lower exit age distribution. Flame control and flame stability is critical in achieving higher throughputs of fullerenes. Typical operating parameters include residence time in the primary zone of 2 – 500 ms, residence time in the secondary zone from 5 ms – 10 s, total equivalence ratio in the range of 1.8-4.0, pressure in the range of 10-400 torr and temperature in the range of 1500-2500 K.

A chemical route has been developed by Scott [9] to synthesize C_{60}. Corannulene is synthesized from naphthalene structure. As the rings fuse and the sheet forms then it is rolled into soccer ball structure. The challenge is how to stitch up the seams between the arms to make the ball. Oligoarenes are transformed into highly strained curved Pi surfaces. The molecule needs to bend to effect ring closure on a 'soccer ball' structure at 1000 ^{0} C. 60 carbon ring system can be built by acid catalyzed aldol trimerization of ketone. Oligoarene zips up to the soccer ball structure affected by cyclodehydrogenations.

In order to generate higher yield, supercritical ethanol [10] was used to react with naphthalene with ferric chloride as catalyst for 6 hours. The reaction products were subjected to extraction with toluene. The reactor temperature range was 31 – 500 ^{0} C, pressure range was 3.8 – 60 MPa. Smalley patented a process to make fullerenes by tapping into the solar energy [11]. The carbon is vaporized by applying focus of solar arrays and conducting the carbon vapor to a dark zone for fullerene growth and annealing. Fullerene content of soot deposits collected on the inside of the Pyrex tube was analyzed by extraction with toluene.

In the electric arc process [12] for fullerene production, carbon material is heated using an electric arc between two electrodes to form carbon vapor. Fullerene molecules are condensed later and collected as soot. Fullerenes are later purified by extraction of soot using a suitable solvent followed by evaporation of the solvent to yield the solid fullerene molecules.

4. SUMMARY OF NANOSTRUCTURING METHODS

Nanostructures can be several kinds: nanowires; nanorods; nanotetrapods; nanoscrystals; quantum dots; nanosheets; nanocylinders; nanocubes; nanograins; nanofilaments; nanolamella; nanopores; nanotrenches; nanotunnel; nanovoids; nanoparticles. Nanostructuring methods encompass a wide range of technologies. Nanostructures can either be generated by building up from atoms using methods classified as 'bottom-up' strategy or by diminishing of size from nanoparticles using methods grouped under 'top-down' strategy. Bottom-up strategies use self-assembly concepts, are cheap, more scalable, more flexible and leads to molecular level engineering. Top down strategy are expensive, less scalable and inflexible.

Sputtering of molecular ions under ultrahigh vacuum is used in the vacuum synthesis method of nanostructuirng [13] . Sputtering process is followed by annealing process. Crystalline silicon is made to form into isolated quantum wires. Gas evaporation [14] technique is a dry process to make ultrafine metallic magnetic powders. Metal is evaporated onto a thin film under vacuum conditions. Metal atoms are allowed to impinge on the surface of the dispersing medium. Condensation of metal atoms can also be accomplished using cooling nozzle. Nanoparticles in the size range of 50 nm – 4 μm can be prepared using this technique.

Triangular nanoprisms can be generated by exposure to light [15] at different wavelengths between 400 nm – 700 nm. Ostwald ripening concepts are used. Edge lengths range from 31-134 nm can be prepared. Nanorods may be produced using condensed phase synthesis method [16] The starting material is heated until the material vaporizes. Later the vapor is condensed. Aggregate of nanoparticles are formed. Particles are delivered by boundary layer delivery and thermophoresis assisted deposition to form the epitaxial deposit. CNTs, carbon nanotubes can also be made using this method.

Subtractive and additive fabrication methods can be used for nanostructuring operations. Lithography, etching,

galvanic fabrication processes are subtractive. A series of chemical reactions effects removal of the layer in the apertures of the mask and transfer of material into gas phase. Lift-off processes are employed in the fabrication of IC circuit. Nanotips and nanorods can be efficiently formed using conventional CMOS processes. Patterning Iridium oxide nanostructures [17] consists of the steps of; i) forming a substrate with first and second regions adjacent to each other; ii) growing IrO_x structures from a continuous oxide film overlying the first region; iii) simultaneously growing IrO_x nanostructures from a con-continuous oxide film overlying the second region; iv) selectively etching area of second region; v) lifting off overlying IrO_x structures and vi) forming a substrate with nanostructures overlying the first region. The second material can be SiO_x.

Dip Pen lithography, SAM,. Self Assembled Monolayers, hot embossing, nanoimprint lithography, electron beam lithography, dry etching, reactive ion etching are techniques that can be used to prepare nanostructures with 50 – 70 nm dimensions [18,19]. Nanomechanical techniques include processes that include local transfer of material from a tool onto a substrate when either the tool or the substrate is pre-structured.

Quantum dots [20] are structures where quantum confinement effects are significant. Reproducibility of organized arrays of quantum dots is an identified problem. Techniques such as sol gel, solid state precipitation, molecular beam epitaxy, chemical vapor deposition, CVD and lithography were developed to enhance uniformity, control morphology and determine spatial distribution of quantum dots in thick and thin films. QDs can be prepared at low temperatures by precipitation from solution by sol-gel methods. Uniformly sized QDs are affected by control of nucleation and growth of particles within a lithographically or electrochemically designed template. FCC packing of silica balls can be used as template for melt/infusion of the semiconductor InSb.

Nanostructures of metal oxides can be prepared by sol-gel processing methods. Chemical reactions are conducted in solution to produce nanosized particles called ‘sols’. The ‘sols’ are connected into a 3-dimensional network called a gel. Controlled evaporation of liquid phase leads to dense porous solids called ‘xerogel’ [21]. Surface instabilities and pattern formation in polymer thin films can lead to formation of nanostructures [22]. The control of morphology of phase separated polymer blends can be result in nanostructures. Kinetic and thermodynamic effects during phase separation can be used in preparation of nanostructures [23]. Nanostructure can be synthesized by quenching of a partially miscible polymer blend below the critical temperature of demixing. Spin coating can be used to prepare polymer film. Pattern formation from polymer solvent systems is stage wise. A stage of layered morphology, followed by destabilization of layers by capillary instability and surface instability leads to nanostructure formation.

Cryogenic milling [24] is a top-down approach to prepare nanoscale titanium of 100-300 nm size. Several mechanical deformations of large grains into ultrafine powder degassing lead to nanopowder with improved characteristics.

Atomic lithography is the method of choice to generate structures less than 50 nm dimensions. A laser beam forms a high intensity optical spot allowing formation of 2-dimensionsl pattern of atoms on the surface of the substrate [25]. Nanostructured thin film nanocomposites can be manufactured using electro deposition method [26]. Electro deposition can be used to form nanostructured films within the pores of mesoporous silica. Silica is then removed from the nanocomposite by dissolution in a suitable etching solvent such as HF, hydrogen fluoride. Plasma compaction techniques [27] can be used to form nanoparticles of semiconductor compounds resulting in improvements in the figure of merit. Nanoparticles can be expected as reaction product after the reactant mixture is subject to sufficient time, under prescribed temperature and pressure. Plasma compaction apparatus may comprise of two high strength pistons capable of compressive pressure in the range of 100-1000 MPa to a sample of nanoparticles that is disposed within a high strength cylinder. The desired level of compaction is achieved by varying the applied pressure, applied current and time duration of the process.

In direct write lithography, [28] a tip can be used to pattern a surface and prepare polymeric nanostructures. Polymerization is initiated by the tip and pattern is formed. Polymer brush nanostructures can be synthesized using ROMP, ring opening metathesis polymerization. Edge distances of less than 100 nm is possible and control over feature size, shape and inter-feature distance is achievable.

Nanofluids [29] comprises of nanoparticles dispersed in a suitable solvent. The surface to volume ration is increased by 1000 times. Nanofluids are expected to have enhanced thermal conductivity comparable that of copper [30]. Materials with pre-defined morphology can be made using self-assembly of block copolymer principle [31]. Nanospheres, nanolamellae, nanopores both cylindrical and spherical are possible using this approach. Thickness of interfacial layer if 2-30 nm. Using PLD, pulse layered deposition, pulses of laser are used to evaporate the starting material [32] and then deposited into a substrate to produce thin films with profound nanotechnological significance. Typical temperature of evaporation surface is 5000 K, average velocity of atoms in vapor flow is 2000 m/s and the expansion front moves at 6000 m/s. Laser intensity is optimized for more efficient evaporation of target.

18 different nanostructuring methods were reviewed by Sharma [33]. Three different methods of synthesis of CNTs, carbon nanotubes were compared side-side by side [34]. Metal nanopowders can be isolated using gravity methods [35,-37]. Rapid quenching of nanopowders in a sub atmospheric fluidized bed was discussed [38]. Nanopore filters can be used in dialysis [39].

The solid colloid dynamics that can be expected in nanocomposites [40,41] was discussed. The modified laws of motion were used in the study. This included long range, short range, dissipative and random forces. Smaller the particle size is made the greater the tendency for it to

agglomerate can be expected. An algorithm to determine the particle size distribution and particle shape distribution from data from SAXS [42], small angle x-ray scattering device was developed. The size of the nanoparticle is less than the wavelength of light that is 400 nm in the visible region. The higher the scattering intensity the better are the chances for the detection of the presence of nanoparticles and determination of particle size distribution. The quality of the nanoparticulatre morphology for the target topology is evaluated using the entropic difference model. Stochastic simulations [43,44] using the supercomputer were used to better understand the process of spinodal nucleation and in situ laser ablation. The Equation of State, EOS for nanocomposite may be derived. This can be used to derive the stability curves for exfoliation of elastomeric nanocomposites. These simulations can be used to predict performance properties such as ballistic impact resistance [45].

Nanocomposites can be structured to prepare materials with higher thermal conductivity compared with copper [46, 47] for use in laptop computer casings and reducing the weight of automobiles. Nanoprobes can be devices to measure: (i) cellular signal [48]; (ii) nanobolometer to measure chemical plumes [49]; (iii) fiber-optic nanobiosensor [50]; (iv) nanoscale temperature distribution [51]. Nanocomposites can be modeled and the glass transition temperature of polymer nanocomposites can be estimated [52,53].

5. THERMODYNAMIC STABILITY OF NANOSTRUCTURES

The solvation thermodynamics define the stability of a system. It can be stable, metastable or unstable. UCST and LCST define the critical consolute temperatures of two phase systems. When a supersaturated system is disturbed the particles begin to nucleate, grow and form into stable structures. The process can be arrested sufficiently early to form nanosphere. But the free energy of formation of the structure and the surface energy of the solid can be equated with each other at equilibrium. For stability the *free energy has to be negative or equal to zero*. From these criteria a minimum stable size of the solid particle formed can be calculated. This depends on the solid-liquid surface tension values and other parameters of the system. In one system for example, the engineering thermoplastic, ABS, Acrylonitrile-Butadiene-Styrene, the smallest stable butadiene particle size can be calculated as 200 nm from Gibbs free energy. When attempted to be made any smaller the rubber phase particles agglomerated with each other to a size larger than 200 nm. It was reported by a number of investigators that making the rubber particles smaller and smaller was difficult. Maybe if they were made into tubes, they can be made into nanotubes. The free energy and surface energy analysis will still hold good. The shape is different in the derivation.

The four thermodynamically stable forms of Carbon are diamond, graphite, C_{60}, Buckminster Fullerene and Carbon Nanotube. It would be a challenge to extend the experience gained in CNT to nanotubes made of other material other than Carbon. It would also be interesting to form stable spherical structures in the nanoscale dimensions without agglomeration. At what scale would the quantum analysis for atoms be applicable when compared with the Newtonian mechanics used to describe macro systems. Nanostructures of all the different shapes and Bravais lattices in several materials need to be established. Nanostructures that are known today and successfully used in the industry are in the form of tubular morphology, gate patterns of oxidation and packing transistors that leave some features at the nanoscale dimensions. Why is tubular morphology favored over spherical morphology during the formation of carbon nanotubes [54-57]? The layered materials of the nanoscale dimension made using Atomic Layer Deposition techniques break no known laws of thermodynamics. But one issue is the layer re-arrangement due to Marangoni instability.

Thermodynamic miscibility of nanocomposites can be calculated from the free energy of mixing.

$$\Delta G = \Delta H - T\Delta S \tag{1}$$

Where ΔG is the free energy change of mixing the dispersed and continuous systems, ΔS is the entropic change of mixing and T is the temperature of the blend. The thermodynamic basis to explain miscibility in nanocomposites is similar to the one seem in polymer blends. In polymer blends, it is an exothermic heat of mixing as entropic contributions are small for such systems. Intramolecular repulsions may be an important factor in realizing exothermic heats of mixing. This approach was independently presented by Kambour, Bendler and Bopp [58], Brinke, Karasz and MacKnight [59] and Paul and Barlow [60].

An additional condition for stability for binary mixtures is given by;

$$\frac{\partial^2 \Delta G_m}{\partial \phi_i^2} > 0 \tag{2}$$

where ϕ_i is the volume fraction of either component -any suitable measure of the concentration can be used. This model further assumes that the heat of mixing is described by a van Laar expression [60];

$$\Delta H_m = (V_A+V_B)B\phi_A\phi_B \tag{3}$$

Where, B is the binary interaction energy density. The B parameter is related to the Flory-Huggins interaction parameter, χ by;

$$\frac{B}{RT} = \frac{\chi_A}{\tilde{V}_A} = \frac{\chi_B}{\tilde{V}_B} = \tilde{\chi}_{AB} \tag{4}$$

B is preferred since its basis is always clearly a unit mixture of volume. The binary interaction model for the

heat of mixing can be extended to multicomponent mixtures as follows:

$$\frac{\Delta H_m}{V} = \sum_{i>j} B_{ij}\phi_i\phi_j \quad (5)$$

The sum in Eq. (5) excludes terms with i=j, and obviates double counting of terms with $i \neq j$. Further, $B_{ij} = B_{ji}$

The sign of combinatorial entropy, always favors mixing, its value is diminished for molecular weights of the order of those for most important polymers. Thus, in the limit of high molecular weights, the conditions of miscibility can only be satisfied by a negative interaction parameter leasing to the conclusion that exothermic mixing is a requirement for miscibility in high molecular weight polymer blends.

This is a simple model and cannot account for all the issues of mixture thermodynamics. Interaction parameters deduced from various phase behavior information are often believed to include other effects other than purely enthalpic ones. This way, the LCST (lower critical solution temperature) behavior observed in polymer blends can be explained and accounted for quantitatively. These theories refine the binary interaction parameter by removing extraneous effects. EOS effects do not favor phase stability and the B parameter must be negative to have miscibility in high molecular weight blends. Interaction parameters used in the ensuing sections are not limited to the Flory-Huggin framework and can be viewed as ones free of equation of state effects.

The role of intramolecular repulsions as a causative factor in driving blend miscibility can be seen readily by considering mixtures of copolymers with homopolymers. Reports in the literature indicate cases of miscibility involving copolymers when their corresponding homopolymers are not miscible. For instance pure Polystyrene and pure polyacrylonitrile are not miscible with poly methyl methacrylate. But the copolymer SAN is miscible with PMMA over a range of AN compositions. The same is the case with PEMA in place of PMMA. Ethylene vinyl acetate, EVA copolymers are miscible with polyvinyl chloride, PVC for a range of VA composition in the copolymer. Neither polyethylene nor polyvinyl acetate are miscible with PVC. In a similar fashion, Butadiene-Acrylonitrile copolymers are found to be miscible with PVC for a range of AN compositions. Similarly, poly-AMS, alpha methyl styrene, AN copolymers are miscible with PMMA and PEMA; poly o-chlorostryene-p-cholorostryene copolymers are miscible with PPO, poly pheylene oxide over a range of p-chlorostyrene composition. The higher the phase separation temperature, LCST, more negative is the binary interaction parameter.

The dispersion of particles in polymeric materials has proven difficult and frequently results in phase separation and agglomeration. Mackay et. al. [61] showed that thermodynamically stable dispersion of nanoparticles into a polymeric liquid is enhanced for systems where the radius of gyration of the linear polymer is greater than the radius of the nanoparticle. Dispersed nanoparticles swell the linear polymer chains, resulting in a polymer radius of gyration that grows with the nanoparticle volume fraction. It was proposed that this entropically unfavorable process is offset by an enthalpy gain due to an increase in molecular contacts at dispersed nanoparticle surfaces as compared with the surfaces of phase-separated nanoparticles. Even when the dispersed state is thermodynamically stable, it may be inaccessible unless the correct processing strategy is adopted, which is particularly important for the case of fullerene dispersion into linear polymers. More on stability is given in Kumar and Krishnamoorti [62].

6. NANOROBOTS IN NANOMEDICINE

According to Frietas [62] “Nanomedicine is the preservation and improvement of human health using molecular tools and molecular knowledge of the human body." Tiny magnetically-driven spinning screws were developed by Ishiyama et. al. [63,64]. These devices were intended to swim along veins and carry drugs to infected tissues or even to burrow into tumors and kill them with supply of heat. Untethered microrobot containing ferromagnetic particles under forces generated by MRI magnetic fields were tested for travel through the human anatomy at the NanoRobotic laboratory at Montreal, Canada [65] in 2003.

7. MOLECULAR COMPUTING

When the limits of miniaturization of transistor packing and gate width in silicon chips are reached where will further increases in microprocessor speed come from? It can come from *biochemical nanocomputers*. The area of DNA computing was flagged off when a programmable molecule computing machine composed of enzymes and DNA molecules was unveiled in 2003 at Weizmann Institute of Science in Rehovot, Israel. The computer operations were at a rate of 330 terraflops. This was 100,000 times faster than the personal computer. It was entered into the Guinness Book of World records as the ‘smallest biological computing device’ ever constructed. Molecular computing is expected to emerge when the limits of miniaturization is realized in the silicon chips as the key to further increases in computing speed. In 1994 the idea to use DNA, De-oxy-ribonucleic acid molecules to *store and process information* took shape when a scientist from California used DNA in a test tube to solve a simple mathematical problem. Designs of DNA computers were drawn up where ATP molecules where thrown in to provide a steady supply of energy and fuel. The enzymes served as the hardware and the DNA served as the software. The ways in which molecules undergo chemical reactions with each other allow simple computer operations to be performed as byproduct of the reactions. The devices are programmed by scientists by controlling the composition of DNA software. A trillion biomolecular devices can be fitted into a single drop of water. Results are analyzed by a method where the length of the DNA output molecule is seen, in place of computer monitor.

Rudimentary operations are performed by this computer. Self-organization of molecules are used in the design of molecular computation. This give rise to the field of *molecular electronics*. Processing in biological systems are used to device nanomachines. The autonomous formation of complex nanostructures are considered as one type of computation. In a cellular computer, membrane proteins are expected as I/O, input/output devices. Living cells are tapped into and the signal transduction functions are used for computations.

DNA computing was born when Aldeman [66] in 1994 proposed a molecular algorithm to solve the Hamiltonian path problem with DNA and solved an instance of a directed graph with 7 nodes. The parallelism of DNA molecules were exploited. This offered faster solution of NP complete problems. Reactions at the nanoscale are used to perform computations with less energy. Several nanofabrication techniques were developed in the area of DNA nanotechnology. Scientists are beginning to obtain a better handle on the electric charge distribution in DNA and the charge transfer observed in DNA is used in device of novel molecular electronic circuits. The automata and the computational model are implemented using hairpin formed DNA molecules. The PCR, polymerase chain reaction that is found during DNA transcription and translation is tapped into. Autonomous assembly of molecular structures are used in devising DNA computation in the solid phase. The number of DNA molecules needed for effecting automated molecular computation are calculated. Suyama and Yoshida [67] studied the application of DNA computer to biotechnology such as gene expression analysis and molecular memory. In *aqueous computing*, the write once memory is represented by double stranded circular DNA. Plasmid contains multiple regions whose terminals are flanked by restriction sites. The write operation is implemented by removing a particular region using specific restriction enzyme. Head and Yamamura [68] proposed the molecular solution with write once memory to obtain solutions of NP complete problems as Max-Clique.

8. MOLECULAR MACHINES

Molecular machines are molecules that can with an appropriate stimulus be temporarily lifted out of equilibrium and can return to equilibrium in the observable macroscopic properties of the system. There is considerable 'debate' in the literature as the exact constitution and properties of molecular machines. The controlled motions of synthetic molecular systems have been harnessed to cause observable macroscopic changes in bulk systems as a result of *stereochemical* rearrangement at the molecular level. The construction of molecular machines has been enabled by:

- Progress in Organic Synthesis – Living Free Radical Polymerizations, Asymmetric Catalysis, Metal Catalyzed Cross-Coupling Reactions, Metathesis
- Powerful Computational Techniques
- Advent of Collection of Powerful Single Molecule Analytical Tools

The design of molecular components is constructed in such a fashion as to interact favorably with each other and that they can *self-organize* and *self-assemble* into larger well defined architectures. The advances in spectroscopic techniques are also tapped into.

The Nobel Prize in 1998 for chemistry went to Pople and Kohn for computing accurately many physical and electronic properties that have particular relevance to molecular machines and electronics. Self-Assembled Monolayers, SAMs, Langmuir-Blodgett techniques for creation of monolayer, softlithographic techniques, etching the surface, AFM, atomic force microscopy, STM, scanning tunnelling microscopy, XPS, photoelectron spectroscopy, ellipsometry and x-ray reflectometry are used in the manufacture of molecular machines.

It is difficult to create *molecular actuators*. The Feynman ratchet can be a violation of the second law of thermodynamics and may be a PMM1 or PMM2, perpetual motion machine 1. Actuation can be achieved by a 'walking mechanism' using a class of motor proteins called kinesins. The muscle contraction and expansion involves such chemical changes. ATP hydrolysis and whip like and sinusoidal movements of cilia and flagella enable them to transport cells throughput the body. Based on these observations, molecular machines, molecular shuttles, switches, muscles, nanovalves, rotors and surfaces with controlled wettability are being created. Example chemicals involved in such constructs are rotaxane molecules. Calixarenes in the cone formation has an interval cavity able to host guest molecules of complementary size. The inclusion of guests in solid state has been studies in a polar medium. The solvation phenomena is of interest. The host-guest association is governed by columbic attractions such as: i) Steric; ii) Entropic; iii) Solvation. Rotaxane synthesis involves calixarene wheels. During the synthesis of pseudorotaxanes, calixarene derivatives as host for QUATS, triphenylureidocalixarene derivative. The structure of pseudorotaxene can be studied using X-ray techniques.

Molecular shuttle consists of a ring component that is mechanically interlocked onto a dumbbell shaped component and is able to shuttle between two recognition sites as a result of thermal activation by non-covalent interactions. *Molecular switches* are compounds that can be externally stimulated to exist in either of two observably different states or conformers. *Molecular muscle* is able to expand and contract reversibly upon external stimulation. *Molecular valves* can be used to trap and release other molecules as a result of controlled molecular motions. *Molecular rotors* undergo controlled rotational motion of a rotor until relative to a stator which are controlled via an axle. The surfaces with controlled wettability can be stimulated to be hydrophobic or hydrophilic. Mechanical movements of tetracationic cyclophane CBPQT along a diaminobenzene containing

thread that is tethered to a Gold surface can be observed. A two electron reduction of the CBPQT ring erases the favorable binding interactions that exist along the ring host and diaminobenzene guest with an electron transfer rate of 80 Hz. The oxidative electron transfer rate is 1100 Hz. Reversible redox-controllable mechanical motions of the interlocked molecule on a gold surface can be detected. A contracted structure can be generated by contraction of bistable dimmer by quantitative demodulation of the cuprous ions using KCN followed by treatment with $Zn(NO_3)_2$.

Technologists are developing *molecular nanovalves*, irreversible thin film regulators, light regulated azobenzene and coumarin valves, supramolecular gatekeepers, reversible nanovalves, polymeric valves, biological nanovalves, etc. Rotation is one of the three fundamental molecular motions: a) translation; b) rotation and; c) vibration. Scientists at UCLA, university of California at Los Angeles, have demonstrated controlled unidirectional rotation of a tryptycene rotor unit relative to a helacine stator that is connected by a carbon-carbon single bond axle using phosgene as chemical fuel. The difluorophenylene rotor has been used as molecular compass and gyroscope.

9. SUPRAMOLECULAR CHEMISTRY

These are highly complex chemical systems made form components interacting through non-covalent intermolecular forces. It occurs in the interface of biology and physics [69] Strands of nucleic acids allow for huge amounts of information to be stored, retrieved and processed via weak hydrogen bonds. The principles in molecular information in chemistry were developed from these observations. Interactional algorithms were developed through molecular recognition events based on well-defined interaction patterns such as hydrogen bonding arrays, sequences of donor and acceptor groups and ion coordination sites. The goal here is to gain progressive control over complex spatio structural and temporal dynamic features of matter through self-organization. The design and investigation of pre-organized molecular receptors that are capable of binding specific substrates with high efficiency and selectivity are undertaken. The three themes are: i) Molecular Recognition; ii) Self-Organization and iii) Adaptation and Evolution.

Supramolecular materials offers alternative to top-down miniaturization and bottom-up nanofabrication. Self-fabrication is effected by controlled assembly of ordered, fully integrated and connected operational systems by hierarchical growth. The field of adaptive/evolutive chemistry emerged. Adaptive chemistry implies a selection and growth under time reversibility. The era of Darwinistic chemistry has dawned. The goal here is to merge design and selection in self-organization to perform self-design in which function driven selection among suitably instructed dynamic species generates the optimal organized and functional entity in a post Darwinian process. Chemical 'learning' systems cannot be instructed but can be trained. Time is irreversible. The passage is from closed systems to open and coupled systems that are connected spatially and temporally to their surroundings. Investigators are progressively unraveling the complexification of matter through self-organization.

Molecular computing is expected to emerge when the limits of miniaturization is realized in silicon chips as the key to further increases in computing speed. DNA molecules and enzymes and biochemical reactions can be used to realize faster operations compared even with a transistors packed silicon chip microprocessor. They can be used to store and process information. DNA computing started with the molecular algorithm to solve the Hamiltonian path problem. NP complete problems can be treated. Molecular machines can be devised using the better understanding of stereochemistry. Construction of molecular machines is driven by: i) progress in organic synthesis; ii) powerful computation techniques; iii) advent of single molecule analytical tools. Well defined architectures can be obtained by self-assembly. SAMS, Langmuir-Blodgett films, soft lithography, AFM, STM, XPS etc can be used to manufacture molecular machines. When designing molecular architectures the second law of thermodynamics should not be violated. Rotaxane molecules are used to create molecular shuttles, molecular switches, molecular nanovalves, molecular muscles, molecular rotors and surfaces with controlled wettability. Supramolecular materials offers alternative to top-down miniaturization and bottom-up fabrication. Self-organization principles holds the key.

Gene expression studies can be carried out in biochips. Target biological materials are examined using fluorescent probes in glass slides packed with thousands of genes. Disease states can be better understood using biochips and cures from better drug design can be effected. Microarray industry is expected to grow in a similar fashion to the microprocessor revolution. A microarray is an ordered array of microscopic elements in a planar substrate that allows for specific binding of gene or gene products. In order to qualify as microarray, the analytical device must be ordered, microscopic, planar and specific. Microarrays are evolving into nanoarrays with the dot size decreasing to the nanoscale. One goal of microarray analysis is to eradicate every human disease by the year 2050. Some of the interesting applications of biochips lie in the areas of gene expression, drug delivery, genetic screening and diagnostics, gene profiling, understanding mechanism of aging, the study of cancer, etc.

The confocal scanning microscope can be used in microarray detection where fluorescence scanning is used. The sample is excited by a laser beam, and fluorescence light is emitted from the probe in the sample and can be detected using the difference in wavelength of 24 nm between excitation and emitted light beams. Epi-illumination is used in the scanning process. The excitation and emitted beams pass through the objective lens to and from the sample but in opposite directions. PMT is used as a detecting element. The instrument performance measures are number of lasers and fluorescence channels, detectivity, sensitivity, crosstalk,

resolution, field size, uniformity, image geometry, throughput and superposition of signal sources. High quality surfaces are needed for the preparation of microarray samples. An ideal microarray surface has to be dimensional, flat, planar, uniform, inert, efficient and accessible.

Optimal target concentration occurs at a spacing of 1 DNA target molecule per 20 A. The probe duplex is approximately 24 A. Optimal probe concentration is the number of probe molecules per unit volume of sample that provides the strongest signal in a microarray assay. Microarrays of oligonucleotides can be prepared by using delivery or synthesis methods. The four steps in process of oligonucleotide synthesis are deprotection, coupling, capping and oxidation. The three manufacturing methods used during microarray manufacture are ink jet printing, mechanical micro spotting and photolithography. Stepwise coupling efficiency can be defined to gauge the quality of microarray synthesis. Linker molecules can be used to increase the efficiency of hybridization and DNA attachment at the surface. The time taken for ink-jet printing when jets or pins or used are compared against each other.

Statistical normalization procedures can be used to remove systematic variations in nanoarray experiments that affects the measured gene expression levels. Speed developed a normalization procedure using gene expression data from lipid metabolism in mice. He used housekeeping genes that have constant levels of expression across variety of conditions. Differentially expressed genes were identified by computing the *t statistics*. Global normalization methods, M vs A plot, paired-slide normalization, within slide normalization and multiple-slide normalization methods are discussed.

Sequence alignment [69] can be used to develop cures for autoimmune disorders, in phylogenetic tree construction, identify polypeptide microstructure, in shot gun sequencing, during drug design, in protein secondary structure determination, in protein folding, clone analysis, protein classification, etc. Optimal global alignment and local alignment can be obtained using dynamic programming. Speedups can be achieved using greedy algorithm for nearly aligned sequences. Dynamic array can be used to cut the space required form $O(n^2)$. PAM and Blossum matrices provide different penalty that are specific to the sequences aligned. Sharma discussed X-drop algorithm, banded diagonal methods, sparse tables, staircase tables, super sequence, inverse dynamic programming, and stability of alignment, suffix tree construction, generalized suffix tree procedures, and the advantages of using them. String algorithms can be used find patterns P in a text T. 19 such algorithms were discussed.

Markov models are discussed for varying orders. Three questions in HMM, i.e., the evaluation, the decoding and the learning were reviewed. The speed up obtained using the forward algorithm, backward algorithm and viterbi algorithm were clarified. Gene finding algorithms were touched upon. Advances made in protein secondary structure prediction were traced from Chou and Fasman rules, to Qian and Sejnowski's neural networks, to the PHD server of Rost and Sander where evolutionary information was used to effect improvement in prediction accuracy. HMMs, DAG-RNNs. BRNN, can be used for protein secondary structure prediction.

Role of polymer nanoparticle in drug delivery applications were discussed. Some of the challenges in drug delivery are continuous release of agents over extended periods of time, local delivery of agents at pre-determined rates to local sites such as tumors, improved ease of administration. Polymer drug delivery systems can be nanoscopic. Self-assembled liposomes and micelles can accomplish the task. Drugs can be encapsulated in the polymer particles. Nanostructuring operations need to be compatible with the drugs. Nanoencapsulation of living cells can be effects by polymer precipitation, gelling and complexing polymer.

10. CNRs COLLECTIVES OF NANOROBOTS

Prospective medical applications of nanorobots include: (i) cardiovascular health; (ii) immune system function; (iii) cancer and diabetes; (iv) drug delivery mechanisms and diagnostics. CNRs are a new generation of self-organizing collectives of intelligent nanorobots. This new technology includes procedures for interactions between objects with their environment resulting in solutions of critical problems at the nanoscopic level. Social intelligence and self-organization are used in the development of the technology. Self-organizing entities are constructed from analogies from living species. Models on social intelligence are developed from observations of behaviors of insects. Chemical markers such as pheromones are used by individual organism to communicate a social goal. Interoperation of microbes and pathogens with the immune system of the organism leads to life/death of host. Intracellular models have been developed that can be used to show how proteins interact and how the functions governed by protein signals come about.

Biomimetic materials are designed to mimic a natural biological material. For example, the third mercaptus bone in horse's leg is used as target for design of aerospace materials. Worm micelles are prepared that resemble linear proteins found in cytoskeleton filament and collagen fibers. Copolymers with block microstructure have been found to self-assemble and organize into periodic nanophases. Molecular shape is found to be a function of fraction of hydrophilic fraction. Polymerosomes or vesicles can be formed by self-assembly of PEO-PBd in water. Lipid vesicles are formed into different morphologies such as starfish, tube, pear and string of pearl shapes. Worms with less than 10 nm diameters and membrane with 3 nm thicknesses have been observed. Stability of protein folding can be studied using self-assembly. Many biological membrane processes can be mimicked by synthetic polymer vesicles.

The equilibrium kinetics of self-assembly reactions were discussed. A cooperativity parameter is defined along with the equilibrium rate constant. Example system used to

illustrate the mathematical treatment is tropomyosin. Amino acids in position 1 and 4 are hydrophobic and in positions 2, 3, 5, 6, 7 are hydrophilic. Banding on helix structures comes about.

One property if biomaterials worthy of mimicking is capable of self-repair. Biomimetic mechanisms are stored in databases. Hydroxyapetite and collagen were used to prepare bone like nanocomposite. Howship's lacunae are cavities created by osteoclastic bone resorption. Hydroxyapetite form on Langmuir Blodgett monolayers. There is interfacial interaction between hydroxyapetite and collagen. Substitution process of composites to new bone occurs in stages similar to autogeneous bone transplantation: a) erosion of body fluid and formation of composite debris; b) phagocytosis of debris; c) resorption of composite and d) induction of osteoblast to the resorption lacunae. Reconstruction of a critical bone defect in beagles' tibia was examined for possible clinical use.

The iridescence if insects and structural colors of plants are not well understood. Optical thickness of a dielectric stack layer of alternating thickness and wave length of maximum constructive interference was quantitated. Two lycaenid butterflies were studied for development of iridescence. The mechanism of biomineralization in molluscs have been studied by investigation of 'flat pearls'. Rhombohedral calcite morphology, spherulite calcite morphology and aragonite needles are formed under different conditions. Argonite tablet growth was studied using AFM. Crystal CdS with rock salt morphology was synthesized in films made up of PEO.

Efficient film formation needs clean substrate. Polyion multilayer films are characterized by SAXR, small angle x-ray spectroscopy. Quartz crystal microbalance is used to measure mass charges in nanogram quantity materials. Mechanism of PMF film formation was studied by using AFM. Polysaccharide containing PMF biopolymers have been prepared. Adsorption kinetics depends on ionic strength. A polymer/biopolymer hybrid such as DNA and PAH were formed into a film containing alternating layers. Film containing streptavidin, glucose isomerase etc were discussed. Assembly of thin films is by sequential adsorption. 3 dimensional controls of film composition and properties are discussed.

Protein scaffold/biomimetic membrane material was discussed. Membrane material is a complex fluid made up of a mixture of a lipid, polymer amphiphile, a co-surfactant. It undergoes thermoreversible phase changes and exists as liquid below a certain threshold temperature and liquid crystalline gel above that temperature. Biomimetic nanostructures are used to examine soft tissue cellular wounds and dry sensing and development and nerve regeneration. Smart materials are developed that undergo a property change in response to environmental stimuli. These materials are used in drug delivery systems. Magnetic pigment used in magnetite memory storage devices with a maghemite phase of size ranging between 300-350 nm using biomimetic method was patented by CSIR, India [70]. Longitudinal recording requires acicular shape. Molecular identification can be prepared using biomimetic sensors. High specificity requirements lead to development of Raman spectroscope. The surface enhanced Raman scattering SERS nanostructure is shown in Figure 7.2. Nanoparticles can be photogenerated.

Development of the new generation of technology of CNRs still have to cross a few technical hurdles. These hurdles include: (i) building these nanorobots; (ii) connect nanodevices; (iii) develop power source; (iv) develop nanorobotic computation; (v) develop nanorobotic functionality; (vi) develop communication systems; (vii) develop multi-functionality; (viii) develop systems in which nanorobots work together; (ix) identify distinct nanorobotic collective behaviors; (x) activate nanorobotic functionality; (xi) activate computer programming; (xii) develop external tracking; (xiii) develop external activation; (xiii) use artificial intelligence; (xiv) reorganize nanorobot aggregates; (xv) develop sensors; (xvi) organize competing, cooperating teams of nanorobots; (xvii) emulate biological processes.

Recent developments in collective robotics have derived inspiration from complex real life phenomena. Examples of complex social behavior include flocking, herding and schooling. Ant algorithms is the state of the art in emulation of natural processes. Another system worthy of emulation is the immunological defense system of human anatomy. Evolutionary computing is a field that where emulation of biological processes of evolution is a high priority. Generic algorithms are developed from emulation of generational behavior of polpulations. Inspiration can be derived from the "bee-hive" operation. Specialist roles and coordination of tasks are examples of what came from emulation. Self-organizing models are used to aggregate, reaggregate collection of robots.

Nanorobots have characteristics lengths of 100 nm – 1 μm. A WBC, white blood cell with 100,000 molecules fits into this domain. At this size the scrutiny is mesoscopic in nature and note molecular or macroscopic. Organic material have been combined in creative ways and novel bacterial and viral organisms have been created. This is sort of artificial Darwinian system. Toxicity of an virus can be toggled off by use of recombinant DNA technology. Synthetic biology techniques can be used to engineer a new species. Biomimetic chemisty is used to synthesize organic molecules that emulate biological behavior. DNA and RNA parts and raw aminoacids are combined and novel genetic structures are created. Reverse engineering can be used in observation of natural protein behaviors emanating from specific gene sequences. Gene targeting techniques may used for this purpose. Natural proteins can be engineered from customized specific gene sequences. Small molecule ligangs can be allowed to bind to proteins resulting in change of the protein function. Protein-protein interactions are disrupted. At Harvard university, an autonomous molecular computer is arranged that performs specific cellular functions. Biomolecular computer can be used in diagnosis of disease and administration of drug on demand.

A CNR, collective nanorobots system was patented by Solomon Research [71] in 2008. Drugs are allowed to be delivered and regulated more effectively to precise targets. These methods are used in cardiovascular applications,

diabetes treatment, intracellular cancer therapies, cauterize wounds in patients with emergency trauma, in nerve cells to block pain signals, enamel repair, repair of nerve damage, hoemerage in dental applications and iun neurosurgery. The human anatomy can be mapped.

CNRs are used in insulin regulation. The pancreas produces insulin for regulation of glucose in the blood flow. Islets of Langerhans are the insulin secreting part of pancreas. Each of the million islets contain about 1000 cells that are structured in clusters. Pancreatic islets operate under a mechanism of amyloidogenesis in order to create amyloid polypeptides. 4 types of cells are created at the islets" (i) alpha cells were production and inhibition of glucagen takes place; (ii) Delta cells were somatostatin is produced; (iii) insulin and; (iv) glucagons. Polypeptides are secreted by pancreatic cells that ends up supressing the secretion and stimulating gastric secretion. Paracrine feedback system is created by activation of beta cells by insulin and inhibition of alpha cells, by activation of beta and delta cells by glucagon, inhibition of alpha and beta cells by somatostatin. Self-organizing system taps into paracrine and autocrine communication between the islets. The signals are affected by chemical messengers. Obesity and Type II diabetes can be found when too much fat and carbohuydrate are taken in the diet. CNRs can be used to regulate insulin. CNRs go beyond the paracrine and autocrine mechanims of communication. CNRs can be used to emulate proper functioning of iselts of Langerhans. A glycation process is conducted by CNRs whereby the blood sugar is treated with insulin. CNRs can be organized into an artificial implantable device that can be used in emulation of workings of a pancreas. Self-regulating pump is constructed. The pancreas-like device is exteral and can be adorned.

11. DEVELOPMENTS IN NANOROBOT APPLICATIONS

A nanorobot to measure surface properties was patented [72]. This technology is 10-20 years in the future. The nanorobot unit has a manipulation unit and an end effector. The end effector can be a senor or made to move as close as possible to the surface of interest. The drive device has piezoelectric drives. The resolution of the measurement can be in the nanometer range and the actual measurement in the centimeter range. The nanorobot is made sensitive in all directions, in multiple dimensions. It can operate under vacuum. Surface roughness can be measured using nanorobots.

Geophysical formation of hydrocarbons at deeper portions of the earth's mantle can be studied using nanorobots [73]. Nanorobots of the size of less than 500 nm are inserted into the formation region. The nanorobots are allowed to propel through the formation. Fluids and conditions surrounding the nanorobots are studied using a computer in the surface of the earth. Communication between the nanorobots and the computer on the surface is via a sereis of radio frequency receivers and transmitters located at the wellbore. A 3 dimensional map of the formation is developed on the remote computer. Pockets of hydrocarbons and their territories are marked and shown clearly in the map. The untethered robots are positioned within the geophysical formation. The body of the nanorobot is made of CNT, carbon nanotubes that are capable of operations at 300 F. Kalman filters can be used to filter out the random white noise from signals from seismic exploration.

A patent was developed [74] for minimally invasive procedure by means of DPR, Dynamic Physical Rendering. Use of "intelligent", "autonomous" particles were made. An interventional aid is formed with the aid of self-organizing nanorobots. These nanorobots were made of catoms. C-arm angiography are used to monitor DPR procedures. A 3 dimensional image data record on target region is obtained. The determined form was converted to a readable and executable program code for the catoms of the nanorobots. The determined form was transferred to a storage unit. The program code was executed in order to achieve self-organization in the unstructured catoms that were introduced in the target region. The execution of the program was triggered by a timer or position sensor. The intervention aid is used as a endovascular target region.

Nanocrystal with motor properties was patented [75]. Reciprocating motor is formed by a substrate, atom reservoir, nanoparticle ram and nanolever. The nanoparticle ram is contacted by the nanolever resulting in movement of atoms between the reservoir and the ram. Substrate and nanolever are made of MWNTs, multi-walled nanotubes made of Iridium. The substrate used was a silicon chip.

Nanoscale oscillator [76] was patented by Sea Gate technology, Scots Valley, CA. A microwave output is generated by application of a DC current that is allowed to pass through layers of magnetic structure separated by nanometer dimensions. Spin Momentum Transfer, SMT is a phenomena realized to exist in 1989. It can be used in MRAM devices. Phase-locked microwave spin transfer is the next advance of the technology. The electric current produced is in the GHz spectrum. The local magnetic field source is used in the application of a magnetic field to a free layer of spin momentum transfer stack. The magnetic source can be from a horseshoe magnet with poles stationed above and below the SMT stack. The magnetic source can take on other forms such as helical coil that surrounds the SMT or pancake type coils above and below the SMT stack or an annular pole and a coil that surround the stack. A permanent magnet may be planted above the stack. SMT stack consists of a top electrode, a free layer, a non-magnetic layer a pinned magnetic structure and a bottom electrode.

Nanowhiskers can be grown by control of nucleation conditions [77]. Nanowhisker formation on substrates can be made using the VLS, vapor-liquid-solid mechanism. A particle of catalyst material is placed on a substrate is heated in the presence of gases until it melts. A pillar is allowed to form under the melt. As the melt rises up on top of the pillar and a nanowhisker is formed. Miller direction <111> may be a preferred growth direction of the whiskers. The catalytic property is present at the interface of whisker and air. InP nanowhiskers, for example, were

grown using metal-organic vapor phase epitaxy. Characterization of nanowhiskers is by electron microscopy. MOVPF is low pressure metal-orgaic vapor phase epitaxy process. 50 nm aerosol gold particles were deposited on InP substrate. This was placed on a horizontal reactor cell heated by radio frequency heated graphite suceptor. Hydrogen was used as carrier gas. Temperatuer was ramped tp 420 ^{0} C for 5 min. The molar fraction of flow rate in the cell was 0.015. Nanowhisker growth was found to commence upon addition of TMI, trimethylindium. The molar fraction of TMI was 3 millionth. Typical growth time for production of nanowhiskers was found to be 8 minutes.

12. CNTs, CARBON NANOTUBES

CNTs are rolled graphene sheets of atoms about its needle axis. They are 0.7-100 nm diameter and a few microns in length. Carbon hexagons are arranged in a concentric manner with both ends of the tube capped by pentagon containing Buckminster fullerene type structure. They possess excellent electrical, thermal and toughness properties. Young's modulus of CNT has been estimated at 1 TPa and yield strength of 120 GPa. S. Ijima verified fullerene in 1991 and observed multi-walled CNT formed from carbon arc discharge.

Five different methods of synthesis of CNTs are discusses. These are: a) Arc Discharge [78]; b) Laser Ablation [79]; c) CVD [80-81]; d) HIPCO Process [81] and e) Surface Mediated Growth of Vertically Aligned Tubes [83]. The arc discharge process was developed by NEC in 1992. Two graphite rods are connected to a power supply spaced a few mm apart. At 100 amps carbon vaporizes and forms hot plasma. Typical yield are 30 – 90%. The SWNT, MWNT are short tubes with diameters 0.6 – 1.4 nm in diameter. It can be synthesized open air. Product needs purification. CVD process was invented by Nagano, Japan. The substrate is placed in oven, heated to 600 ^{0} C and a carbon bearing gas such as methane is slowly added. As the gas decomposes it frees up the carbon atoms which recombine as a nanotube. Yield range is 20-100%. Long tubes with diameter ranging from 0.6 – 4 nm were formed. It can be easily scaled up to industrial production. The SWNT diameter is controllable. The tubes are usually multi-walled and riddled with defects. Laser vaporization process was developed by Smalley in 1996. The graphite is blasted with intense laser pulses to generate carbon gas. Prodigious amount of SWNTs are formed. Yield of up to 70% is found. Long bundles of tubes 5-20 μm with diameters in the range of 1-2 nm are formed. The product formation is primarily SWNTs. Good diameter control is possible and few defects are found in the product. Reaction product is pure. The process is expensive.

The HIPCO process was also developed by Smalley in 1998. A gaseous catalyst precursor is rapidly mixed with carbon monoxide, CO in a chamber at high pressure and temperature. Catalyst precursor decomposes and nanoscale metal particles form the decomposition product. CO reacts on the catalyst surface and form solid carbon and gaseous CO_2, carbon dioxide. The carbon atoms roll up into CNTs. 100% of the product is SWNT and the process is highly selective. Samsung patented a method for vertically aligning CNTs on a substrate. A CNT support layer is stacked on the substrate filled with pores. SAM, self-assembled monolayer is arranged on the surface of the substrate. On end of each of the CNTs are attached portions of the SAM exposed through the pores formed between the colloid particles present in the support layer. CNTS can be vertically aligned on the substrate having the SAM on it with the help of pores formed between the colloid particles.

CNTs possess interesting physical properties [84]. Thermal conductivity of CNTs are in excess of 2000 w/m/K. They have unique electronic properties. Applications include electromagnetic shielding, electron field emission displays for computers and other high –tech devices, photovoltaic, super capacitors, batteries, fuel cells, computer memory, carbon electrodes, carbon foams, actuators, material for hydrogen storage and adsorbents.

CNTs can be produced with different morphologies [85]. Examples of different morphologies include SWNT, DWNT, MWNT, nano-ribbon, nano-sheet, nano-peapod, linear and branched CNTs, conically overlapping bamboo-like tubule, branched Y shaped tubule, nano-rope, nanowires, nanofilm. Processes are developed to prepare CNTs with desired morphology. Phase separated copolymers/stabilized blends of polymers can be pyrolyzed along with sacrificial material to form the desired morphology. The sacrificial material is changed to control the morphology of the product. Self-assembly of block copolymers can lead to 20 different complex phase separated morphologies. Often times as is the precursor so is the product. Therefore even more variety of CNT morphologies can be synthesized.

13. CHARACTERIZATION OF NANOSTRUCTURES

Needs for characterization of nanostructures are on the rise. Resolution limits of optical microscopes are of the order of wavelength of light. Per the Raleigh criterion, the resolution limit of optical microscopes is of the order of 200 nm. In order to characterize nanoscale materials, x-ray and helium ion microscopes are needed. Optical microscopes, scanning electron microscope, transmission electron microscope, scanning probe microscope and helium ion microscope have increasing powers of resolution in the mentioned order.

Structural information in the scale of 2-25 nm can be characterized using SAXS [86]. Monochromatic source of x-rays are used to excite the sample and scattered x-rays are detected by 2-dimensional flat x-ray detector. Structure is deduced from patterns in the scatter. Interpretation of scattered pattern can be accomplished using Porad's law and Guiner approximation, Fourier transformation, etc. Thin films, multi-layered systems, oriented nanoparticles with different chemical compositions, colloids, proteins solutions, nanocomposites, micelles, fiber structures, etc, can be

studied using SAXS. WAXS, GISAXS, SWAXS are techniques that are variations of SAXS.

TEM, transmission electron microscopes have higher resolution power. Sample preparation for TEM analysis [87] is complex and the thickness of the sample has to be down to a few hundred nanometers. An electron beam is produced from a tungsten filament subjected to a high voltage. Electrons are allowed to pass through the specimen. With HRTEM, high resolution transmission electron microscope, resolutions achievable are as small as 1 A. TEM is used in life sciences, biomedical investigations, diagnostic tool in pathology, imaging of atoms, oligopeptides, nanogold, self-assembled nanotubes. It can also be used as an elemental analysis tool in addition to EDXA, energy dispersive x-ray analysis and at low temperatures as cryo-TEM.

Magnification in SEM, scanning electron microscope ranges from 25-250,000 and resolution size is down to 1 – 25 nm. Electron gun is used to generate electron beams. Spatial resolution of SEM depends on the wavelength of the electron and electro-optical system that produces the scanning beam. Resolution at an atomic scale is not possible as can be with the case of TEM and HeIM. The electrons generated are focused as a spot with nanoscale dimensions. Electrons upon impingement with the specimen undergo elastic scattering, inelastic scattering and back scattering. Raster scanning is used to image surfaces. Surface topography, composition and other properties can be obtained from raster scan.

Topographical map on atomic scale can be generated using SPM, scanning probe microscope [88,89]. Neither electrons nor light is used for formation of images. Magnification of higher than 1 billion is possible. A tiny probe with a sharp tip is brought in close proximity to within 1 nm of specimen surface and then raster scanned. Nanoscale defects, bio molecules and silicon microprocessors can be characterized using SPM. They can also be used to prepare nanostructures. Dip Pen lithography, DPN, is such a technique. Tiny probe tip is used as 'pen' to write structures consisting of a few molecules. STMs can be used to obtain conductance and current/distance measurements, AFM can be used for lateral force and adhesion measurements, NFOM can be used for laser transmission at various wave lengths and MFM can be used for temperature and other parameters.

Quantum dots contain 10-100 electrons in devices of dimensions of $(500\ nm)^2$. Photocurrent induced in quantum dots can be measured. The influence of high frequency microwave radiation [90] on single electron tunnelling through a single quantum dot was used in microwave spectroscopy. Elemental composition of test specimen can be obtained using Auger Electron Microscope. Detection limits are 0.1% of the atomic composition of the elements. Spatial resolution is about 300 nm. Depth resolution is about 10 nm and typical analysis is 30 minutes per sample.

Raman microscope [91] is designed based on the Raman effect. Molecular types can be obtained from the scattering information. Raman microscopes can be used to study gene expression and DNA sequence distribution. SERS, surface enhanced Raman spectroscopy can be used to detect single nucleotide molecules. SERS includes a laser light source that excites the molecule and a detection unit for capturing Raman emission emanating from the molecule.

STM evolved into AFM, [92] atomic force microscope. Fraction of nanometer resolution can be achieved using AFM. Specimen surface is scanned using a micro scale cantilever with a probe at its end with a sharp tip with a radius of curvature of a few nanometers. Laser source excites the sample. The laser light is reflected by the deflected cantilever. The reflected light is captured by avalanche of photodiodes. Individual atoms can be imaged using AFM.

HeIM, Helium ion microscope [93] was developed as an alternative to electron microscope. Helium ions possess shorter wavelengths compared with electrons. A space resolution of 0.24 nm was achieved by Orion HeIM. This is close to the diameter of a single atom and is three times better in resolution compared with the electron microscopes. Individual atoms can be looked at. HeIMs can be operated in RBI and secondary electron mode.

Freitas [94] went over the technologies needed for the atomically precise fabrication of diamandoid nanorobots in large scale with further cost reductions. For example the Arizona process to manufacture fullerenes was $25,000/kg [5]. This cost was reduced to $200/kg in the combustion synthesis process [8]. They say that enabling diamandoid nanofactories will require: (i) advances in mechanosynthesis of diamond; (ii) advances in programmable positional assembly; (iii) improvements in massively parallel positional assembly and; (iv) improvements in nanomechanical design. Cavalcanti et. al. [95] discuss how nanoelectronics can improve medical practices. Teleoperated techniques and nanorobots can be used for intracranial prognosis. Advances in medical nanorobotics can be achieved by interdisciplinary activities from proteomics, nanobioelectronics and electromagnetics. Nanorobots can be used for searching protein overexpression signals in order to recognize initial stages of aneurysm. Based on clinical data and nanobioelectronics the proposed model can be used to predict how a nanorobot can help with early detection of cerebreal aneurysm.

14. CONCLUSIONS

Advances have been made in development of nanorobots for medical applications. Submarine robots are used in branchy therapy, spinal surgery, cancer therapy etc. Nanocar has been designed with fullerenes as wheels, alkyne groups as axle and can be observed using a STM, scanning tunneling microscope. Nanoparticles have been developed for use in eye disorders and for early diagnosis.

Nanostructures can be nanoparticles, nanotubes, soccer ball structures, nanopores, nanopeapods, nanowhiskers, nanocapsules, nanoshells, nanowires, nanoropes, nanolayered materials, nanocomposites, nanofilm,

nanocoating, nanocrystal,nanorods, nanotetrapods, nanosheets, nanotrenches, nanotunnel, nanograins, nanocubes, nanovoids, nanolamella, nanofilament, quantum dots, etc.Fullerenes, C_{60}, is the third allotropic form of carbon. Soccer ball structured, C_{60}, with a surface filled with hexagons and pentagons satisfy the Euler's law.

The first generation combustion synthesis method for fullerene production, an advance over the carbon arc method. In the second generation combustion synthesis method optimizes the conditions for fullerene formation. Synthesis of C_{60} can be prepared using organic methods. Corannulene is synthesized from naphthalene structure. As the rings fuse and the sheet forms then it is rolled into soccer ball structure. Electric arc method can be used to prepare fullerenes. Nanostructures can either be generated by building up from atoms using methods classified as 'bottom-up' strategy or by diminishing of size from nanoparticles using methods grouped under 'top-down' strategy. Bottom-up strategies use self-assembly concepts, are cheap, more scalable, more flexible and leads to molecular level engineering. Top down strategy are expensive, less scalable and inflexible.

Different nanostructuring methods are discussed. These include: sputtering of molecular ions ; gas evaporation process to make ultrafine magnetic magnetic powder; triangulation and formation of nanoprisms by light irradiation; nanorod production using condensed phase synthesis method; subtractive methods such as lithography, etching, galvanic fabrication; lift-off process for IC circuit fabrication; nanotips and nanorods formation by CMOS process; patterning Iridium Oxide nanostructures; dip pen lithography; SAM, self assembled monolayers; hot embossing; nanoimprint lithography; electron beam lithography; dry etching; reactive ion etching; quantum dots and thin films generation by sol gel, solid state precipitation, molecular beam epitaxy, chemical vapor deposition, CVD, lithography, nucleation and growth; sol-gel processing methods; thin film formation from surface instabilities; thin film formation by spin coating; cryogenic milling for preparation of 100-300 nm sized titanium; atomic lithography methods to generated structures less than 50 nm; electro deposition method to prepare nanocomposite; plasma compaction methods; direct write lithography; nanofluids by dispersion. 34 different nanostructuring methods have been discussed. Three different methods of synthesis of CNTs, carbon nanotubes have been identified.

The solid colloid dynamics that can be expected in nanocomposites was discussed. Stochastic simulations using the supercomputer were used to better understand the process of spinodal nucleation and in situ laser ablation. Nanocomposites can be structured to prepare materials with higher thermal conductivity compared with copper for use in laptop computer casings and reducing the weight of automobiles. Thermodynamic miscibility of nanocomposites can be calculated from the free energy of mixing. The four thermodynamically stable forms of Carbon are diamond, graphite, C_{60}, Buckminster Fullerene and Carbon Nanotube. Mackay et. al. [61] showed that thermodynamically stable dispersion of nanoparticles into a polymeric liquid is enhanced for systems where the radius of gyration of the linear polymer is greater than the radius of the nanoparticle.

Tiny magnetically-driven spinning screws has been developed. *DNA computing* was born when a molecular algorithm to solve the Hamiltonian path problem was proposed and when an instance of a directed graph with 7 nodes was solved for. Molecular machines are molecules that can with an appropriate stimulus be temporarily lifted out of equilibrium and can return to equilibrium in the observable macroscopic properties of the system. Molecular shuttle, molecular switches, molecular muscle, molecular rotors, molecular nanovalves are discussed. Supramolecular materials offers alternative to top-down miniaturization and bottom-up fabrication. Self-organization principles holds the key. Gene expression studies can be carried out in biochips. Sequence alignment can be used to develop cures for autoimmune disorders, in phylogenetic tree construction, identify polypeptide microstructure, in shot gun sequencing, during drug design, in protein secondary structure determination, in protein folding, clone analysis, protein classification, etc. CNRs are a new generation of self-organizing collectives of intelligent nanorobots. This new technology includes procedures for interactions between objects with their environment resulting in solutions of critical problems at the nanoscopic level.

Biomimetic materials are designed to mimic a natural biological material. Nanorobots have characteristics lengths of 100 nm – 1 μm. Five different methods of synthesis of CNTs are discusses. These are: a) Arc Discharge; b) Laser Ablation; c) CVD; d) HIPCO Process and e) Surface Mediated Growth of Vertically Aligned Tubes. Characterization methods of nanostructures include SAXS, small angle X-ray scattering, TEM, transmission electron microscopy, SEM, scanning electron microscopy, SPM, scanning probe microscope, Raman microscope, AFM atomic force microscopy, HeIM helium ion microscopy.

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