Chapter 6. Diamondoid Nanorobotics

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Abstract

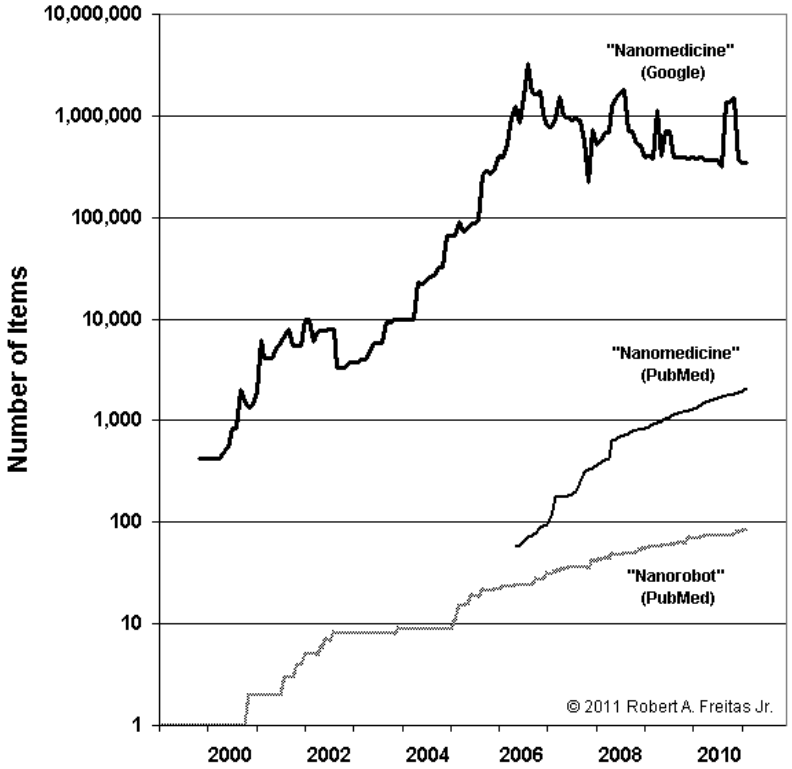
Activity in the field of nanorobotics, as measured by published literature, has been growing at +30%/yr for the last decade. A wide variety of simple nanorobotic mechanisms have already been fabricated, but much of the interest in nanorobotics is focused on the future of medicine. Diamondoid nanorobots potentially offer the most powerful medical applications. Technologies required for the atomically precise fabrication of diamondoid nanorobots in macroscale quantities at low cost requires the development of a new nanoscale manufacturing technology called positional diamondoid molecular manufacturing, enabling diamondoid nanofactories that can build nanorobots. Achieving this new technology will require the significant further development of four closely related technical capabilities: (1) diamond mechanosynthesis, (2) programmable positional assembly, (3) massively parallel positional assembly, and (4) nanomechanical design.

Keywords: atomically precise, chromallocyte, diamond, diamondoid, DMS, mechanosynthesis, microbivore, molecular manufacturing, Nanofactory Collaboration, nanomedicine, nanorobot, nanorobotics, positional assembly, respirocyte

1. Introduction

Nanorobotics most broadly involves the study of robotic mechanisms and devices that either possess functional features or components with nanoscale size (i.e., below 100 nm, all the way down to single-atom) in one or more dimensions, or can produce effects or influence processes that are taking place at nanoscale dimensions. A narrower definition that hints at the tremendous future importance of this discipline regards the primary object of the field of nanorobotics to be the "nanorobot", which has been defined as "a computer-controlled robotic device constructed of nanometer-scale components to molecular precision, usually microscopic in size." [1] The nanorobotics field has been quickly attracting interest and activity, as measured by the growing number of unique literature references to nanorobots or nanorobotics in the PubMed database (**Figure 1**) which during the past decade have been climbing at a +30%/yr rate (~2.4-yr doubling time).

Figure 1. Number of papers mentioning "nanorobot*" in the PubMed database, 2000-2010.



Seeman and others have published numerous nanorobotics papers describing a variety of robotic nanomechanisms fabricated via DNA nanotechnology [2-5] while others are investigating DNA-based nanotransport devices [6], DNA-based actuation of carbon nanotube based servomotors for drug delivery [7], protein-based nanoactuators [8], biological molecular motors [9] and bionanorobot prototyping methodologies [10] as alternative approaches to the field of bionanorobotics. Chemically actuated cantilever arrays that transform biochemical reactions into

nanomechanical motion may be useful for biosensing and other nanorobotic applications [11]. Mobile wireless nanorobots, e.g., with motion control and onboard power supplies, are being more widely discussed than even just a few years ago [12-16].

Much of the interest in nanorobotics – and its brightest future – is focused on the medical and surgical applications areas [17]. There have already been early attempts to build less sophisticated stand-alone microrobots for near-term *in vivo* surgical use. For example, Ishiyama's group [18] at Tohoku University developed tiny magnetically-driven spinning screws intended to swim along veins and carry drugs to infected tissues or even to burrow into tumors and kill them with heat. Martel's group at the NanoRobotics Laboratory of Ecole Polytechnique in Montreal has used variable MRI magnetic fields to generate forces on an untethered microrobot containing ferromagnetic particles, developing sufficient propulsive power to direct the small device through the human body [19]. In 2007 they reported injecting, guiding via computer control, and propelling at 10 cm/sec a prototype untethered microdevice (a ferromagnetic 1.5- millimeter-diameter sphere) within the carotid artery of a living animal placed inside a clinical magnetic resonance imaging (MRI) system [20] – the first time such *in vivo* mobility has been demonstrated. Martel's group continues to make progress using this approach [21-22].

Nelson's team at the Swiss Federal Institute of Technology in Zurich has pursued a similar approach, in 2005 reporting [23] the fabrication of a microscopic robot small enough (~200 μm) to be injected into the body through a syringe and which they hope might someday be used to perform minimally invasive eye surgery. Nelson's simple microrobot has successfully maneuvered through a watery maze using external energy from magnetic fields, with different frequencies able to vibrate different mechanical parts on the device to maintain selective control of different functions. More recently the team has fabricated oxygen-sensing microrobots [24] and investigated artificial bacterial flagella for lab-on-a-chip applications [25], and Nelson has reviewed progress in the medical microrobotics field [26]. The Mavroidis group is also investigating MRI-based guidance of nanoparticulate and nanorobotic systems for targeted drug delivery [27].

Sitti's group at Carnegie Mellon's NanoRobotics Laboratory investigated [28] a <100-micron swimming microrobot using biomimetic flagellar motors borrowed from *S. marcescens* bacteria "having the capability to swim to inaccessible areas in the human body and perform complicated user directed tasks." Sitti believes that tiny, tetherless microrobots might be able to access small spaces inside the human body that can currently be reached only using invasive surgical methods [29]. Friend's group in the Micro/Nanophysics Research Laboratory at Monash University in Australia began designing a 250-micron microrobot [30-31] to perform minimally invasive microsurgeries in parts of the body outside the reach of existing catheter technology – such as delivering a payload of expandable glue to the site of a damaged cranial artery, a procedure typically fraught with risk because posterior human brain arteries lay behind a complicated set of bends at the base of the skull beyond the reach of all but the most flexible catheters. The completed device was to have been inserted and extracted using a syringe and driven by an artificial flagellar piezoelectric micromotor; however, there have been no updates on this project since 2008 [32].

Nanosurgery has been reported on subcellular and even nanoscale structures deep inside individual living cells without killing them. For instance, femtolaser surgery has performed: (1) microtubule dissection inside live cells [33-35], (2) severing a single microtubule without disrupting the neighboring microtubules less than 1 micron away [36], (3) altering depolymerization rate of cut microtubules by varying laser pulse duration [37], (4) dissection of

individual dendritic spines of a specific neuron in a live brain without damaging adjacent structures [38], (5) selective removal of sub-micron regions of the cytoskeleton and individual mitochondria without altering neighboring structures [39], (6) noninvasive intratissue nanodissection of plant cell walls and selective destruction of intracellular single plastids or selected parts of them [40], and even (7) the nanosurgery of individual chromosomes (selectively knocking out genomic nanometer-sized regions within the nucleus of living Chinese hamster ovary cells) without perturbing the outer cell membrane [41]. Zettl's group has demonstrated a nanoinjector consisting of an AFM-tip-attached carbon nanotube that can release injected quantum dots into cell cytosol, with which they plan to carry out organelle-specific nanoinjections [42].

Nanomedicine [1, 43] is the application of nanotechnology to medicine: the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body. Nanomedicine encompasses at least three types of molecularly precise structures [44]: nonbiological nanomaterials, biotechnology materials and engineered organisms, and nonbiological devices including diamondoid nanorobotics. In the near term, the molecular tools of nanomedicine will include biologically active nanomaterials and nanoparticles having well-defined nanoscale features. In the mid-term (5-10 years), knowledge gained from genomics and proteomics will make possible new treatments tailored to specific individuals, new drugs targeting pathogens whose genomes have been decoded, and stem cell treatments. Genetic therapies, tissue engineering, and many other offshoots of biotechnology will become more common in therapeutic medical practice. We also may see biological nanorobots derived from bacteria or other motile cells that have had their genomes re-engineered and re-programmed [45], along with artificial organic devices that incorporate biological motors or self-assembled DNA-based structures [46] for a variety of useful medical purposes.

The greatest power of nanomedicine [1, 43] will emerge, perhaps starting in the late 2020s, when we can design and construct complete artificial nanorobots using rigid diamondoid nanometer-scale parts like molecular gears and bearings [47]. These medical nanorobots will possess a full panoply of autonomous subsystems including onboard sensors, motors, manipulators, power supplies, and molecular computers. But getting all these nanoscale components to spontaneously self-assemble in the right sequence will prove increasingly difficult as machine structures become more intricate. Making complex nanorobotic mechanical systems requires new manufacturing techniques that can build a molecular structure by what is called positional assembly. This will involve picking and placing molecular parts one by one, and moving them along controlled trajectories much like the robot arms that manufacture cars on automobile assembly lines. The procedure will then be repeated until the final product, such as a medical nanorobot, is fully assembled, inside a desktop nanofactory [47-49].

2. Nanorobotic Treatments for Most Human Diseases

The ability to build complex diamondoid medical nanorobots [44, 50-53] to molecular precision, and then to build them cheaply enough in sufficiently large numbers to be useful therapeutically, will revolutionize the practice of medicine [17] and surgery [54].

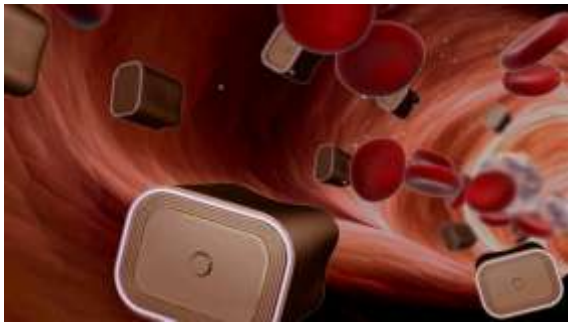
The first theoretical design study of a complete medical nanorobot ever published in a peer-reviewed journal described a hypothetical artificial mechanical red blood cell or "respirocyte" made of 18 billion precisely arranged structural atoms [50]. The respirocyte would be a bloodborne spherical 1-micron diamondoid 1000-atmosphere pressure vessel with reversible

molecule-selective surface pumps powered by endogenous serum glucose. This nanorobot would deliver 236 times more oxygen to body tissues per unit volume than natural red cells and would manage carbonic acidity, controlled by gas concentration sensors and an onboard nanocomputer. A 5 cc therapeutic dose of 50% respirocyte saline suspension containing 5 trillion nanorobots could exactly replace the gas carrying capacity of the patient's entire 5.4 liters of blood. Of course, nanorobots, no matter how capable, always have very well-defined physical limitations. In general, they are limited by mobility constraints, by the availability of energy, by mechanical and geometric constraints, by diffusion limits and biocompatibility requirements, and by numerous other constraints [1, 43]. Nanorobots cannot act instantly – they take time to effect their cure. Biocompatibility issues related to diamondoid medical nanorobots have been examined elsewhere at length [43].

Nanorobotic artificial phagocytes called "microbivores" could patrol the bloodstream, seeking out and digesting unwanted pathogens including bacteria, viruses, or fungi [44]. Microbivores would achieve complete clearance of even the most severe septicemic infections in hours or less. This is far better than the weeks or months needed for antibiotic-assisted natural phagocytic defenses. The nanorobots don't increase the risk of sepsis or septic shock because the pathogens are completely digested into harmless sugars, amino acids and the like, which are the only effluents from the nanorobot. Similar nanorobots can digest cancer cells and vascular blockages that produce heart disease and stroke.

Even more powerful applications – most importantly, involving cellular replacement or *in situ* repair of individual cells – are possible with medical nanorobotics. For example, most diseases involve a molecular malfunction at the cellular level, and cell function is significantly controlled by gene expression of proteins. As a result, many disease processes are driven either by defective chromosomes or by defective gene expression. So in many cases it may be most efficient to extract the existing chromosomes from a diseased cell and insert fresh new ones in their place. This cell repair procedure is called "chromosome replacement therapy" [53]. During this future procedure, your replacement chromosomes first would be manufactured to order, outside of your body, in a clinical benchtop production device that includes a molecular assembly line. The patient's individual genome is used as the blueprint. If the patient wants, acquired or inherited defective genes could be replaced with nondefective base-pair sequences during the chromosome manufacturing process, thus permanently eliminating any genetic disease. Nanorobots called chromallocytes [53], each carrying a single copy of the revised chromosomes, would be injected into the body and travel to the target tissue cells (**Figure 2**). Following powered cytopenetration and intracellular transit to the nucleus [1], the chromallocytes would remove the existing chromosomes and then install the properly methylated replacement chromosomes in every tissue cell of your body (requiring a total dose of several trillion nanorobots), then exit the cell and its embedding tissue, re-enter the bloodstream, and finally eliminate themselves from the body either through the kidneys or via intravenous collection ports (coincident, most likely, with the original injection mechanism).

Figure 2. Chromallocytes. Left: Artist's conceptions of the basic chromallocyte [53] design. Devices walk along luminal wall of blood vessel using an array of cilia-like mechanical manipulator arms (not shown in the illustration) that emerge from silos embedded in the nanorobot hull. Right: Artist's conceptions of the basic chromallocyte [53] design. Schematic of nanorobot operation in which a large central manipulator (the proboscis) extends from the nanorobot core and spools existing nuclear DNA into a bolus which is then surrounded and enclosed by a telescoping funnel assembly. Images © 2006



The development pathway for diamondoid medical nanorobots will be long and arduous. First, theoretical scaling studies [44, 50-53, 55-56] are used to assess basic concept feasibility. These initial studies must then be followed by more detailed computational simulations of specific nanorobot components and assemblies, and ultimately full systems simulations, all thoroughly integrated with additional simulations of massively parallel manufacturing processes from start to finish consistent with a design-for-assembly engineering philosophy. Once nanofactories implementing molecular manufacturing capabilities become available, experimental efforts may progress from fabrication of components (using small-molecule or atomic precursors) and testing, to the assembly of components into nanomechanical devices and nanomachine systems, and finally to prototypes and mass manufacture of medical nanorobots, ultimately leading to clinical trials. By 2011 there was some limited experimental work with microscale-component microscopic microrobots (see Section 1) but progress on nanoscale-component microscopic diamondoid nanorobots today is largely at the concept feasibility and preliminary design stages and will remain so until experimentalists develop the capabilities required for diamondoid molecular manufacturing, as reviewed below.

Of all possible materials that might be used to build medical nanorobots – including borrowed biological components, dendrimers, polymers, and various linked or tethered nanoparticles – diamondoid (Section 4.1) is the best possible material for constructing rigid molecular machine systems exhibiting reliable repeatable mechanical operations because of its special properties including extraordinary strength, stiffness, and chemical stability.

3. Positional Diamondoid Molecular Manufacturing

Complex molecular machine systems, including microscale robotic mechanisms comprised of thousands or millions of nanoscale mechanical components such as gears, motors, and computer elements, probably cannot be manufactured using the conventional techniques of self-assembly. As noted in the final report [57] of the 2006 Congressionally-mandated review of the U.S. National Nanotechnology Initiative (NNI) by the National Research Council (NRC) of the National Academies and the National Materials Advisory Board (NMAB): "For the manufacture of more sophisticated materials and devices, including complex objects produced in large quantities, it is unlikely that simple self-assembly processes will yield the desired results. The reason is that the probability of an error occurring at some point in the process will increase with

the complexity of the system and the number of parts that must interoperate." Error detection and correction requires a minimum level of complexity that cannot easily be achieved via thermodynamically-driven self-assembly processes.

The opposite of self-assembly processes is positionally controlled processes, in which the positions and trajectories of all components of intermediate and final product objects are controlled at every moment during fabrication and assembly. Positional processes should allow more complex products to be built with high quality and should enable rapid prototyping during product development. Positional assembly is the norm in conventional macroscale manufacturing (e.g., cars, appliances, houses) but is only recently [49, 58] starting to be seriously investigated experimentally for nanoscale manufacturing. Of course, we already know that positional fabrication will work in the nanoscale realm. This is demonstrated in the biological world by ribosomes, which positionally assemble proteins in living cells by following a sequence of digitally encoded instructions (even though ribosomes themselves are self-assembled). Lacking this positional fabrication of proteins controlled by DNA-based software, large, complex, digitally-specified organisms would probably not be possible and biology as we know it would not exist. Guided self-assembly – a hybrid approach combining self-assembly and positional assembly – is also being investigated experimentally [59-60].

The most important materials for positional assembly may be the rigid covalent or "diamondoid" solids, since these could potentially be used to build the most reliable and complex nanoscale machinery. Preliminary theoretical studies have suggested great promise for these materials in molecular manufacturing. The NMAB/NRC Review Committee recommended [57] that experimental work aimed at establishing the technical feasibility of positional molecular manufacturing should be pursued and supported: "Experimentation leading to demonstrations supplying ground truth for abstract models is appropriate to better characterize the potential for use of bottom-up or molecular manufacturing systems that utilize processes more complex than self-assembly." Making complex nanorobotic systems requires manufacturing techniques that can build a molecular structure by positional assembly [61]. This will involve picking and placing molecular parts one by one, moving them along controlled trajectories much like the robot arms that manufacture cars on automobile assembly lines. The procedure is then repeated over and over with all the different parts until the final product, such as a medical nanorobot, is fully assembled inside a desktop nanofactory.

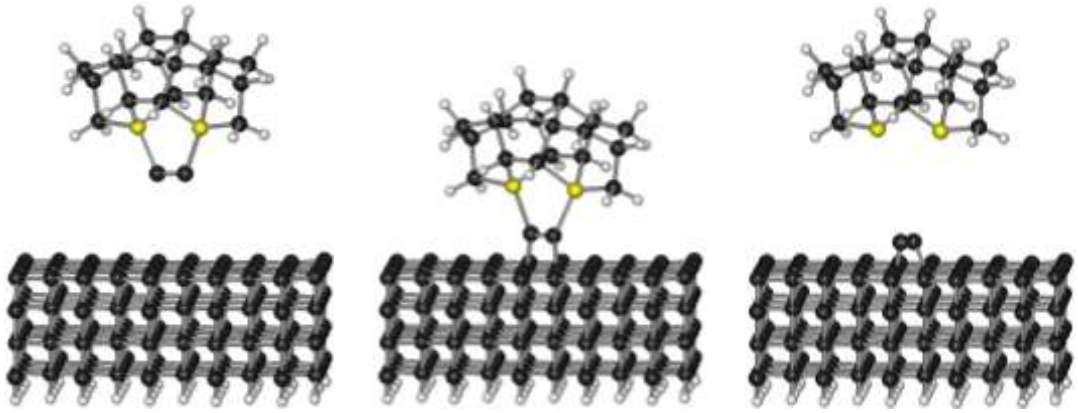
Technologies required for the atomically precise fabrication of diamondoid nanorobots in macroscale quantities at low cost requires the development of a new nanoscale manufacturing technology called positional diamondoid molecular manufacturing, enabling diamondoid nanofactories. Achieving this new technology over the next 1-3 decades will require the significant further development of four closely related technical capabilities: diamondoid mechanosynthesis (Section 4), programmable positional assembly (Section 5), massively parallel positional assembly (Section 6), and nanomechanical design (Section 7).

4. Diamondoid Mechanosynthesis (DMS)

Mechanosynthesis, or molecular positional fabrication, is the formation of covalent chemical bonds using precisely applied mechanical forces to build atomically precise structures. Mechanosynthesis will be most efficient when automated via computer control, enabling programmable molecular positional fabrication of nanostructures of significant size. Atomically precise fabrication involves holding feedstock atoms or molecules, and separately a growing

nanoscale workpiece, in the proper relative positions and orientations so that when they touch they will chemically bond in the desired manner. In this process, a mechanosynthetic tool is brought up to the surface of a workpiece. One or more transfer atoms are added to, or removed from, the workpiece by the tool. Then the tool is withdrawn and recharged (**Figure 3**). This process is repeated until the workpiece (e.g., a growing nanopart) is completely fabricated to molecular precision with each atom in exactly the right place. The transfer atoms are under positional control at all times to prevent unwanted side reactions from occurring. Side reactions are also avoided using proper reaction design so that the reaction energetics avoid undesired pathological intermediate structures and atomic rearrangements.

Figure 3. Diamondoid mechanosynthesis: DCB6Ge dimer placement tool shown depositing two carbon atoms on a diamond surface (C = black, H = white, Ge = yellow/gray) [49].



The positional assembly of diamondoid structures, some almost atom by atom, using molecular feedstock has been examined theoretically [47, 62-71] via computational models of diamondoid mechanosynthesis (DMS). DMS is the controlled addition of individual carbon atoms, carbon dimers (C_2), single methyl (CH_3) or like groups to the growth surface of a diamond crystal lattice workpiece in a vacuum manufacturing environment. Covalent chemical bonds are formed one by one as the result of positionally constrained mechanical forces applied at the tip of a scanning probe microscope (SPM) apparatus, usually resulting in the addition of one or more atoms having one or more bonds into the workpiece structure. Programmed sequences of carbon dimer placement on growing diamond surfaces *in vacuo* appear feasible in theory [67, 71].

4.1 Diamondoid Materials

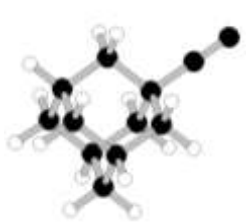
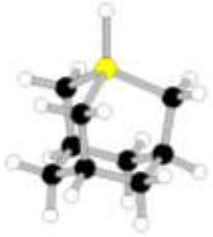
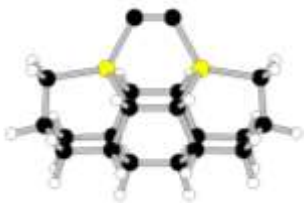
Diamondoid materials include pure diamond, the crystalline allotrope of carbon. Among other exceptional properties, diamond has extreme hardness, high thermal conductivity, low frictional coefficient, chemical inertness, a wide electronic bandgap, and is the strongest and stiffest material presently known at ordinary pressures. Diamondoid materials also may include any stiff covalent solid that is similar to diamond in strength, chemical inertness, or other important material properties, and possesses a dense three-dimensional network of bonds. Examples of such materials are carbon nanotubes and fullerenes, atomically-precise "doped" diamond, several

strong covalent ceramics such as silicon carbide, silicon nitride, and boron nitride, and a few very stiff ionic ceramics such as sapphire (monocrystalline aluminum oxide) that can be covalently bonded to pure covalent structures such as diamond. Of course, pure crystals of diamond are brittle and easily fractured. The intricate molecular structure of a diamondoid atomically precise product will more closely resemble a complex composite material, not a brittle solid crystal. Such products, and the nanofactory systems that build them, should be extremely durable in normal use.

4.2 Minimal Toolset for DMS

It is already possible to synthesize bulk diamond today. In a process somewhat reminiscent of spray painting, layer after layer of diamond is built up by holding a cloud of reactive hydrogen atoms and hydrocarbon molecules over a deposition surface. When these molecules bump into the surface they change it by adding, removing, or rearranging atoms. By carefully controlling the pressure, temperature, and the exact composition of the gas in this process – called chemical vapor deposition or CVD – conditions can be created that favor the growth of diamond on the surface. But randomly bombarding a surface with reactive molecules does not offer fine control over the growth process. To achieve atomically precise fabrication, the first challenge is to make sure that all chemical reactions will occur at precisely specified places on the surface. A second problem is how to make the diamond surface reactive at the particular spots where we want to add another atom or molecule. A diamond surface is normally covered with a layer of hydrogen atoms. Without this layer, the raw diamond surface would be highly reactive because it would be studded with unused (or "dangling") bonds from the topmost plane of carbon atoms. While hydrogenation prevents unwanted reactions, it also renders the entire surface inert, making it difficult to add carbon (or anything else) to it.

Figure 4. Examples of three basic mechanosynthetic tooltypes that are required to build molecularly precise diamond via positional control (C = black, H = white, Ge = yellow/gray) [71]

(A) Hydrogen Abstraction Tool	(B) Hydrogen Donation Tool	(C) Carbon Placement Tool (DCB6Ge)
		

To overcome these problems, a set of molecular-scale tools must be developed that would, in a series of well-defined steps, prepare the surface and create hydrocarbon structures on a layer of diamond, atom by atom and molecule by molecule. A mechanosynthetic tool typically will have two principal components – a chemically active tooltip and a chemically inert handle to which the

tooltip is covalently bonded. The tooltip is the part of the tool where site-specific single-molecule chemical reactions are forced to occur by the application of mechanical energy. The much larger handle structure is big enough to be grasped and positionally manipulated using an SPM or similar macroscale instrumentality. At least three types of basic mechanosynthetic tools (**Figure 4**) have already received considerable theoretical (and some related experimental) study and are likely among those required to build molecularly precise diamond via positional control:

(1) **Hydrogen Abstraction Tools**. The first step in the process of mechanosynthetic fabrication of diamond might be to remove a hydrogen atom from each of two specific adjacent spots on the diamond surface, leaving behind two reactive dangling bonds. This could be done using a hydrogen abstraction tool [68] that has a high chemical affinity for hydrogen at one end but is elsewhere inert. The tool's unreactive region serves as a handle or handle attachment point. The tool would be held by a high-precision nanoscale positioning device, initially perhaps a scanning probe microscope tip but ultimately a molecular robotic arm, and moved directly over particular hydrogen atoms on the surface. One suitable molecule for a hydrogen abstraction tooltip is the acetylene or "ethynyl" radical, comprised of two carbon atoms triple bonded together. One carbon of the two serves as the handle connection, and would bond to a nanoscale positioning device through a larger handle structure. The other carbon of the two has a dangling bond where a hydrogen atom would normally be present in a molecule of ordinary acetylene (C_2H_2), which can bond and thereby abstract a hydrogen atom from a workpiece structure. The environment around the tool would be inert (e.g., vacuum or a noble gas such as neon). The recharge sequence for this tool has been studied rather extensively [72]).

(2) **Carbon Placement Tools**. After the abstraction tool has created adjacent reactive spots by selectively removing hydrogen atoms from the diamond surface but before the surface is re-passivated with hydrogen, carbon placement tools may be used to deposit carbon atoms at the desired reactive surface sites. In this way a diamond structure can be built up on the surface, molecule by molecule, according to plan. The first complete tool ever proposed for this carbon deposition function is the "DCB6Ge" dimer placement tool [63] – in this example, a carbon (C_2) dimer having two carbon atoms connected by a triple bond with each carbon in the dimer connected to a larger unreactive handle structure via two germanium atoms. This dimer placement tool, also held by a nanoscale positioning device, is brought close to the reactive spots along a particular trajectory, causing the two dangling surface bonds to react with the ends of the carbon dimer. The dimer placement tool would then withdraw, breaking the relatively weaker bonds between it and the C_2 dimer and transferring the carbon dimer from the tool to the surface. A positionally controlled dimer could be bonded at many different sites on a growing diamondoid workpiece, in principle allowing the construction of a wide variety of useful nanopart shapes. As of 2007, the DCB6Ge dimer placement tool remains the most studied of any mechanosynthetic tooltip to date [63-64, 66-67, 69, 71], having had more than 150,000 CPU-hours of computation invested thus far in its analysis, and it remains the only tooltip motif that has been successfully simulated and theoretically validated for its intended function on a full 200-atom diamond surface [67]. Other proposed dimer (and related carbon transfer) tooltip motifs [47, 62-63, 65, 69, 71] have received less intensive study but are also expected to perform well.

(3) **Hydrogen Donation Tools**. After an atomically precise structure has been fabricated by a succession of hydrogen abstractions and carbon depositions, the fabricated structure must be passivated to prevent additional unplanned reactions. While the hydrogen abstraction tool is intended to make an inert structure reactive by creating a dangling bond, the hydrogen donation tool [70] does the opposite. It makes a reactive structure inert by terminating a dangling bond by adding an H atom. Such a tool would be used to stabilize reactive surfaces and help prevent the surface atoms from rearranging in unexpected and undesired ways. The key

requirement for a hydrogen donation tool is that it include a weakly attached hydrogen atom. Many molecules fit that description, but the bond between hydrogen and germanium is sufficiently weak so that a Ge-based hydrogen donation tool should be effective.

A recently completed three-year study [71] representing 102,188 CPU hours of computing time has computationally analyzed a comprehensive set of DMS reactions and an associated minimal set of nine specific DMS tooltips that could be used to build basic diamond, graphene (e.g., carbon nanotubes), and all of the tools themselves including all necessary tool recharging reactions. The research defined 65 DMS reaction sequences incorporating 328 reaction steps, with 354 pathological side reactions analyzed and with 1,321 unique individual DFT-based (Density Functional Theory) quantum chemistry reaction energies reported. These mechanosynthetic reaction sequences range in length from 1-13 reaction steps (typically 4) with 0-10 possible pathological side reactions or rearrangements (typically 3) reported per reaction.

The first practical proposal for building a DMS tool experimentally was published in 2005 and is the subject of the first mechanosynthesis patent ever issued, in March 2010 [66]. According to this proposal, the manufacture of a complete "DCB6Ge" positional dimer placement tool would require four distinct steps: synthesizing a capped tooltip molecule, attaching it to a deposition surface, attaching a handle to it via CVD, then separating the tool from the deposition surface. An even simpler practical proposal for building DMS tools experimentally, also using only experimental methods available today, was published as part of the aforementioned minimal toolset work [71]. Processes are identified for the experimental fabrication of a hydrogen abstraction tool, a hydrogen donation tool, and two alternative carbon placement tools (other than DCB6Ge). These processes and tools are part of the second mechanosynthesis patent ever filed and provide clear developmental targets for a comprehensive near-term DMS implementation program to begin working toward a more mature set of efficient, positionally controlled mechanosynthetic tools that can reliably build atomically precise diamondoid structures – including more DMS tools.

4.3 Experimental Successes to Date

The first experimental proof that individual atoms could be manipulated was obtained by IBM scientists in 1989 when they used a scanning tunneling microscope to precisely position 35 xenon atoms on a nickel surface to spell out the corporate logo "IBM". However, this feat did not involve the formation of covalent chemical bonds. One important step toward the practical realization of DMS was achieved in 1999 [73] with the first site-repeatable site-specific covalent bonding operation of a two diatomic carbon-containing molecules (CO), one after the other, to the same atom of iron on a crystal surface, using an SPM. The first experimental demonstration of true mechanosynthesis, establishing covalent bonds using purely mechanical forces – albeit on silicon atoms, not carbon atoms – was reported [74] in 2003. In this landmark experiment, the researchers vertically manipulated single silicon atoms from the Si(111)–(7×7) surface, using a low-temperature near-contact atomic force microscope to demonstrate: (1) removal of a selected silicon atom from its equilibrium position without perturbing the (7×7) unit cell, and (2) the deposition of a single Si atom on a created vacancy, both via purely mechanical processes. The same group later repeated this feat with Ge atoms [75].

By 2008, the Custance group in Japan [76] had progressed to more complex 2D structures fabricated entirely via mechanosynthesis using more than a dozen Si/Sn or Pb/In atoms, with a 12-atom 2D pattern created in 1.5 hr (~450 sec/atom). In late 2008 Moriarty's group at the

University of Nottingham (U.K.) began a $3 million 5-year effort [77] employing a similar apparatus to produce 2D patterns using carbon atoms, to validate previous theoretical DMS proposals [71]. If successful, Moriarty's work could lead to subsequent studies extending DMS from 2D to small 3D carbon nanostructures.

5. Programmable Positional Assembly

Atomically precise nanoparts [78], once fabricated, must be transferred from the fabrication site and assembled into atomically precise complex components containing many nanoparts. Such components may include gear trains in housings, sensors, motors, manipulator arms, power generators, and computers. These components may then be assembled, for example, into a complex molecular machine system that consists of many components. A complex micron-size medical nanorobot such as a microbivore [44] constructed of such atomically precise components may possess many tens of thousands of individual components, millions of primitive parts, and many billions of atoms in its structure. The conceptual dividing line between fabrication and assembly may sometimes be blurred because in many cases it might be possible, even preferable, to fabricate nominally multipart components as a single part – allowing, for example, two meshed gears and their housing to be manufactured as a single sealed unit.

The process of positional assembly, as with DMS, can be automated via computer control as has been demonstrated experimentally in the case of individual atoms in the Autonomous Atom Assembly project sponsored by NIST and ONR [79] and in the case of microscale parts in automated microelectromechanical systems (MEMS) assembly [80-81]. This allows the design of positional assembly stations which receive inputs of primitive parts and assemble them in programmed sequences of steps into finished complex components. These components can then be transported to secondary assembly lines which use them as inputs to manufacture still larger and more complex components, or completed systems, again analogous to automobile assembly lines.

6. Massively Parallel Positional Assembly

To be practical, molecular manufacturing must also be able to assemble very large numbers of medical nanorobots very quickly. It is not enough to be able to build just one molecularly precise part, component, or medical nanorobot. For nanofactories to be economically viable, we must be able to assemble complex nanostructures in vast numbers – in billions or trillions of finished units (product objects). Approaches under consideration include using replicative manufacturing systems or massively parallel fabrication, employing large arrays of scanning probe tips all building similar diamondoid product structures in unison, as in nanofactories [47-49].

This will require massively parallel manufacturing systems with millions of assembly lines operating simultaneously and in parallel, not just one or a few of them at a time as with the assembly lines in modern-day car factories. Fortunately, each nanoassembly production line in a nanofactory can in principle be very small. Many millions of them should easily fit into a very small volume. Massively parallel manufacture of DMS tools, handles, and related nanoscale fabrication and assembly equipment will also be required, perhaps involving the use of massively parallel manipulator arrays or some other type of replicative system [48].

Reliability is an important design issue. The assembly lines of massively parallel manufacturing systems might have numerous redundant smaller assembly lines feeding components into larger assembly lines, so that the failure of any one smaller line cannot cripple the larger one. Arranging parallel production lines for maximum efficiency and reliability to manufacture a wide variety of products (possibly including error detection, error correction and removal of defective parts) is a major requirement in nanofactory design.

7. Nanomechanical Design

Computational tools for molecular machine modeling, simulation and manufacturing process control must be created to enable the development of designs for diamondoid nanoscale parts, components, and nanorobotic systems. These designs can then be rigorously tested and refined in simulation before undertaking more expensive experimental efforts to build them. Basic molecular machine design and simulation software has been available for several years [82] and libraries of predesigned nanoparts are slowly being assembled. More effort must be devoted to large-scale simulations of complex nanoscale machine components, design and simulation of assembly sequences and manufacturing process control, and general nanofactory design and simulation.

8. Nanofactory Collaboration

The NMAB/NRC Review Committee, in their Congressionally-mandated review [57] of the NNI, called for proponents of "site-specific chemistry for large-scale manufacturing" to: (1) delineate desirable research directions not already being pursued by the biochemistry community; (2) define and focus on some basic experimental steps that are critical to advancing long-term goals; and (3) outline some "proof-of-principle" studies that, if successful, would provide knowledge or engineering demonstrations of key principles or components with immediate value.

In direct response to these requirements, the Nanofactory Collaboration is coordinating a combined experimental and theoretical effort to explore the feasibility of positionally controlled mechanosynthesis of diamondoid structures using simple molecular feedstock. The precursor to the Nanofactory Collaboration was informally initiated by Robert Freitas and Ralph Merkle in the Fall of 2000 during their time at Zyvex. Their continuing efforts, and those of others, have now grown into direct collaborations among 25 researchers or other participants (including 18 PhD's or PhD candidates) at 13 institutions in 4 countries (U.S., U.K., Russia, and Belgium), as of late 2011. The Collaboration website is at http://www.MolecularAssembler.com/Nanofactory.

At present, the Collaboration is a loose-knit community of scientists and others who are working together as time and resources permit in various team efforts with these teams producing numerous co-authored publications, though with disparate funding sources not necessarily tied to the Collaboration. While not all participants may currently envision a nanofactory as the end goal of their present research (or other) efforts in connection with the Collaboration, many *do* envision this, and even those who do not currently envision this end goal have nonetheless agreed to do research in collaboration with other participants that we believe will contribute important advances along the pathway to diamondoid nanofactory development, starting with the direct development of DMS. While some work has been done on each of the four primary capabilities thought necessary to design and build a functioning nanofactory, for now the greatest research

attention is being concentrated on the first key area: proving the feasibility, both theoretical and experimental, of achieving diamond mechanosynthesis.

We welcome new participants who would like to help us address the many remaining technical challenges [83] to the realization of a working diamondoid nanofactory that would permit the fabrication of medical nanorobots.

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