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EDITORIAL

Nanotechnology, nanomedicine and nanosurgery

An exciting revolution in health care and medical technology looms large on the horizon. Yet the agents of change will be microscopically small, future products of a new discipline known as nanotechnology. Nanotechnology is the engineering of molecularly precise structures — typically 0.1 μm or smaller — and, ultimately, molecular machines.

Nanomedicine[1–4] is the application of nanotechnology to medicine. It is the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body. Present-day nanomedicine exploits carefully structured nanoparticles such as dendrimers,[5] carbon fullerenes (buckyballs)[6] and nanoshells[7] to target specific tissues and organs. These nanoparticles may serve as diagnostic and therapeutic antiviral, antitumor or anticancer agents. But as this technology matures in the years ahead, complex nanodevices and even nanorobots will be fabricated, first of biological materials but later using more durable materials such as diamond to achieve the most powerful results.

Early vision

Can it be that someday nanorobots will be able to travel through the body searching out and clearing up diseases, such as an arterial atheromatous plaque?[8] The first and most famous scientist to voice this possibility was the late Nobel physicist Richard P. Feynman. In his remarkably prescient 1959 talk ''There's Plenty of Room at the Bottom,'' Feynman proposed employing machine tools to make smaller machine tools, these are to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level, noting that this is ''a development which I think cannot be avoided.''[9]

Feynman was clearly aware of the potential medical applications of this new technology. He offered the first known proposal for a nanorobotic surgical procedure to cure heart disease: ''A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and looks around. (Of course the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. ...[Imagine] that we can manufacture an object that maneuvers at that level!... Other small machines might be permanently incorporated in the body to assist some inadequately functioning organ.''[9]

Medical microrobotics

There are ongoing attempts to build microrobots for in vivo medical use. In 2002, Ishiyama et al. 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.[10] In 2003, the ''MR-Sub'' project of Martel's group at the NanoRobotics Laboratory of Ecole Polytechnique in Montreal tested using 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.[11] Brad Nelson's team at the Swiss Federal Institute of Technology in Zurich continued this approach. In 2005, they reported the fabrication of a microscopic robot small enough (~200 μm) to be injected into the body through a syringe. They hope that this device or its descendants might someday be used to deliver drugs or perform minimally invasive eye

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surgery.[12] Nelson's simple microrobot has successfully maneuvered through a watery maze using external energy from magnetic fields, with different frequencies that are able to vibrate different mechanical parts on the device to maintain selective control of different functions. Gordon's group at the University of Manitoba has also proposed magnetically controlled ''cytobots'' and ''karyobots'' for performing wireless intracellular and intranuclear surgery.[13]

Manufacturing medical nanorobots

The greatest power of nanomedicine will emerge, perhaps in the 2020s, when we can design and construct complete artificial nanorobots using rigid diamondoid nanometer-scale parts like molecular gears (Fig. 1) and bearings.[14] These 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 complex. Making complex nanorobotic systems requires 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, 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.

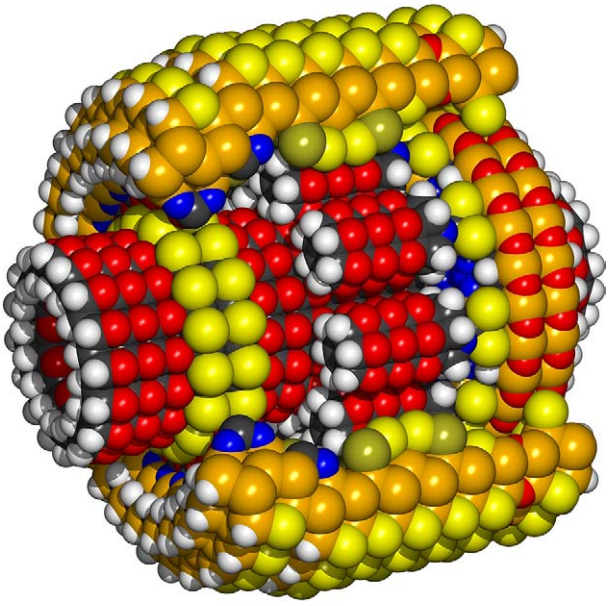

Figure 1 A molecular planetary gear is a mechanical component that might be found inside a medical nanorobot. The gear converts shaft power from one angular frequency to another. The casing is a strained silicon shell with predominantly sulfur termination, with each of the nine planet gears attached to the planet carrier by a carbon–carbon single bond. The planetary gear shown here has not been built experimentally but has been modeled computationally. Copyright 1995 Institute for Molecular Manufacturing (IMM).

The positional assembly of diamondoid structures, some almost atom by atom, using molecular feedstock has been examined theoretically[14,15] via computational models of diamond mechanosynthesis (DMS). DMS is the controlled addition of carbon atoms to the growth surface of a diamond crystal lattice 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 apparatus, following a programmed sequence. Mechanosynthesis using silicon atoms was first achieved experimentally in 2003.[16] Carbon atoms should not be far behind.[17]

To be practical, molecular manufacturing must also be able to assemble very large numbers of medical nanorobots very quickly. 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.[18]

For example, simple mechanical ciliary arrays consisting of 10,000 independent microactuators on a 1-cm^2 chip have been made at the Cornell National Nanofabrication Laboratory for microscale parts transport applications, and similarly at IBM for mechanical data storage applications.[19] Active probe arrays of 10,000 independently actuated microscope tips have been developed by Mirkin's group at Northwestern University for dip-pen nanolithography[20] using DNA-based ''ink''. Almost any desired 2D shape can be drawn using 10 tips in concert. Another microcantilever array manufactured by Protiveris Corp. has millions of interdigitated cantilevers on a single chip. Martel's group has investigated using fleets of independently mobile wireless instrumented microrobot manipulators called NanoWalkers to collectively form a nanofactory system that might be used for positional manufacturing operations.[21] Zyvex Corp. (www.zyvex.com) of Richardson, TX has a $25 million, five-year, National Institute of Standards and Technology (NIST) contract to develop prototype microscale assemblers using microelectromechanical systems. This research may eventually lead to prototype nanoscale assemblers using nanoelectromechanical systems.

Respirocytes and microbivores

The ability to build complex diamondoid medical nanorobots to molecular precision, and then to build them cheaply enough in sufficiently large numbers to be useful therapeutically, will revolutionize the practice of medicine and surgery.[1] The first theoretical design study of a complete medical nanorobot ever published in a peer-reviewed journal (in 1998) described a hypothetical artificial mechanical red blood cell or ''respirocyte'' made of 18 billion precisely arranged structural atoms.[22] The respirocyte is a bloodborne spherical 1-μm 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 l of blood.

Nanorobotic artificial phagocytes called ''microbivores'' (Fig. 2) could patrol the bloodstream, seeking out and digesting unwanted pathogens including bacteria, viruses, or fungi.[23] 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 do not 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.

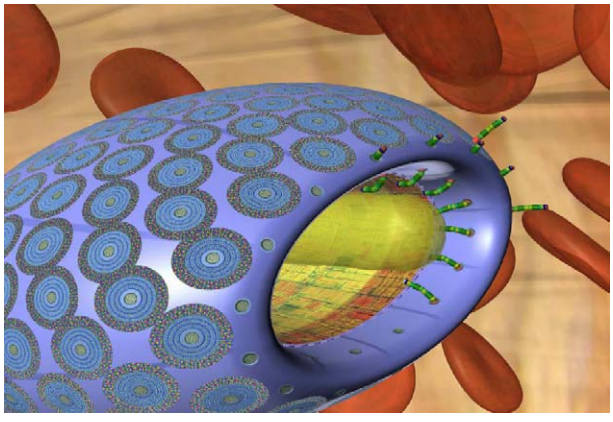

Figure 2 Nanorobotic artificial phagocytes called ''microbivores'' could patrol the bloodstream, seeking out and digesting unwanted pathogens. Copyright 2001 Zyvex Corp.; designer Robert Freitas, artist Forrest Bishop.

Surgical nanorobotics

Surgical nanorobots could be introduced into the body through the vascular system or at the ends of catheters into various vessels and other cavities in the human body. A surgical nanorobot, programmed or guided by a human surgeon, could act as a semi-autonomous on-site surgeon inside the human body. Such a device could perform various functions such as searching for pathology and then diagnosing and correcting lesions by nanomanipulation, coordinated by an onboard computer while maintaining contact with the supervising surgeon via coded ultrasound signals. The earliest forms of cellular nanosurgery are already being explored today. For example, a rapidly vibrating (100 Hz) micropipette with a $<$1-μm tip diameter has been used to completely cut dendrites from single neurons without damaging cell viability.[24] Axotomy of roundworm neurons was performed by femtosecond laser surgery, after which the axons functionally regenerated.[25] A femtolaser acts like a pair of ''nano-scissors'' by vaporizing tissue locally while leaving adjacent tissue unharmed. Femtolaser surgery has performed the following: (1) localized nanosurgical ablation of focal adhesions adjoining live mammalian epithelial cells,[26] (2) microtubule dissection inside yeast cells,[27] (3) noninvasive intratissue nanodissection of plant cell walls and selective destruction of intracellular single plastids or selected parts of them,[28] and even (4) the nanosurgery of individual chromosomes (selectively knocking out genomic nanometer-sized regions within the nucleus of living Chinese hamster ovary cells[29]). These procedures do not kill the cells upon which the nanosurgery was performed. Atomic force microscopes have also been used for bacterium cell wall dissection in situ in aqueous solution, with 26 nm thick twisted strands revealed inside the cell wall after mechanically peeling back large patches of the outer cell wall.[30]

Future nanorobots equipped with operating instruments and mobility will be able to perform precise and refined intracellular surgeries which are beyond the capabilities of direct manipulation by the human hand. We envision biocompatible[31] surgical nanorobots that can find and eliminate isolated cancerous cells, remove microvascular obstructions and recondition vascular endothelial cells, perform ''noninvasive'' tissue and organ transplants, conduct molecular repairs on traumatized extracellular and intracellular structures, and even exchange new whole chromosomes for old ones inside individual living human cells.

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