The coming invasion of the medical nanorobots

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An interventional radiologist looks at a computer display showing images of a tumour in the body of a patient lying inside a clinical magnetic resonance imaging (MRI) system. After a careful examination using MRI and other imaging modalities, he and his team observe that the tumour did not spread yet (i.e. no sign of metastases). They know then that the best treatment relies on a new approach based on medical nanorobotics where small devices acting like smart bombs can navigate under computer control through the blood vessels to reach a specific target to be destroyed. But they have to act fast, otherwise the tumour will spread and other techniques such as chemotherapy with the well known disadvantages of such therapies would have to be considered.

Yes, this may look like a remake of the 1966 science fiction movie “Fantastic Voyage”. In fact it is, but as a new reality show. MRI has replaced the small radar devices surrounding the patient as the imaging modality and the process of shrinking a submarine with its onboard crew to a size small enough to be propelled inside the blood vessels have been replaced by agglomerations of crewless devices made of magnetic nanoparticles, biodegradable polymer, and various biomolecules, where each device carries a load of the therapeutic compound to be delivered.

Here, engineers used to applying the laws of physics at the macroscale have discovered a new set of tools at the nanometre scale, where new forces and new rules dominate. They continue the tradition by exploiting the laws of physics to develop solutions to modern problems. The tradition continues but the vocabulary used by these new engineers extends beyond traditional physics, material sciences, and engineering as we know them today, to name but only a few examples, to include nanotechnology and nanomedicine[1] along with biology, biochemistry and many other fields. As for space exploration, tiny robotic vehicles or satellites are now considered as instruments to conquer new frontiers—deep inside the human body. But since in robotics the level of difficulty seems often inversely proportional to the size of the object being controlled, engineers and scientists have no choice but to continually learn and maintain an open-minded approach with a highly inter-disciplinary vision and work environment in

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[1] Freitas Jr, R.A., “Current status of nanomedicine and medical nanorobotics [invited survey],” *J. Comp. Theor. Nanosci.* **2**, pp. 1–25, 2005.

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attempting to solve, using nanoscale components and phenomena, our modern medical issues by developing instrumentation platforms based on new hardware and software—welcome to the world of medical nanorobotics.

At first, people were excited with the vision of nanorobots circulating in the human blood vessels. Many drawings of nanorobots made by artists contributed to such excitement. On the other hand, they could also contribute to lower the credibility of nanorobotics in the scientific community, because they often show designs based on a purely mechanical approach. This is somewhat human nature, considering that what will first attract the attention of people are the movements of a robot—its mechanical motion. Just look at the robots used to build cars. People are generally more interested to look at the fast and precise motions of many synchronized robotic arms than the background computer software and algorithms responsible for such coordinated movements. Thus, for instance, nanorobots in the blood vessels are often represented with having tiny mechanical tweezers, which from an engineering point of view is certainly not the best approach, at least for the short and medium terms. It is true that the mechanical field still plays a critical role in the conception of such nanorobots, but considering the level of complexity involved in building these tweezers at such a scale, and considering the fabrication and assembly techniques now available, and the need to integrate sufficient control to accurately perform grasping tasks, this approach just does not make sense at present. On the other hand, engineers can use many available nanoscale "bio-components" to accomplish the same task. For instance, such nanorobots can be coated with phages (approximately 90 nanometres (nm) in size) or antibodies (a few tenths of a nanometre) that will bind to or "grasp" predefined entities, or other biomolecules that will bind to specific types of cells, including cancer cells, to act like intelligent nano-anchors for our tiny submarines. Here, the computational power that would be required by these nanorobots to control grasping or anchoring tasks together with input from the required sensors, and 'intelligence' to make decisions based on the sensory information as is typically done for robots operating at the macro- or human-scale level, are replaced by deftly integrated solutions provided by biochemistry.

Hence, knowing that a robot is typically a relatively complex machine made of several components, a nanorobot made of several or even huge quantities of nanometre-scale components necessary to accomplish its task will have to become much larger than nanometric. Then comes the question: how small do these medical nanorobots need to be? Fundamentally, not only the tasks or functionalities need to be considered when designing these nanorobots, but the environment where such tasks will be performed will also influence the final design in somewhat the same way that a robot designed to operate at the surface of the planet Mars will typically have different specifications than one designed to work on our own planet. Hence, to answer this question, we need to consider the physiological environment of the nearly 100 000 km of blood vessels inside the human body that could provide the best routes for conducting new or improved medical interventions non-invasively and where nanorobotics could play a significant role. In particular, the smaller diameter blood vessels such as arterioles and capillaries that are out-of-reach for modern interventional tools such as catheters, are of special interest.

Tumours for instance grow very small blood vessels to reach other existing blood vessels in the human body, a process referred to as angiogenesis. At the same time that such complex networks of new blood vessels are formed to bring the oxygen and nutrients necessary for the tumour to grow, they open the doors for nanorobots to allow them to reach their targets. But prior to reaching such targets, the nanorobots must navigate in blood vessels with diameters that can be as small as 4 micrometres (the thickness of a human hair is approximately 80 micrometres). Studies based on hydrodynamics at such a scale and considering other aspects such as propulsion force and the quantity of therapeutic agents being loaded show that an object such as a robot with a spherical shape should when being propelled ideally have a diameter of approximately half of the inner diameter of the blood vessel being navigated. When larger than that, the robot will experience an additional drag force acting against its motion due to the effect of the blood vessel wall. On the other hand, from an engineering point of view, there is no real advantage in going smaller than approximately two micrometres in overall diameter. Larger robots can carry a larger therapeutic charge and may provide room for larger engines, which typically provide more propulsion force, a key element to the success of such interventional procedures. Hence, two micrometres (corresponding to 2000 nm, which is 20 times larger than the largest truly nanometre-scale robot—assuming 100 nm as the maximum size of a device that strictly belongs to the field of nanotechnology) seems to be a much better choice for operations in the human blood vessels.

So, does this mean that medical nanorobots are already doomed to extinction? The answer may be "no" depending upon how we define a nanorobot. Among the many existing definitions, in this particular context one may attempt to define a nanorobot by dividing the word as 'nano' referring to the nanotechnology used to construct its internal mechanism instead of referring to the overall dimension of the robot; and "robot" itself. As nanotechnology relies on nanometre-scale components to build or conceive larger entities, nanorobots may be defined as robots that depend on parts of nanometre-scale dimensions (typically less than 100 nm) to embed functionalities that otherwise could not be implemented if the parts would not be at the nanometre scale. Some more examples of such components embedded in nanorobots will follow. The same idea also applies to other nano-related fields, such as nanoelectronics where "nano" refers to the feature sizes or the sizes of components such as transistors, and not to the systems or circuits that use huge quantities of these nanocomponents to implement functionalities. As for the term "robot" in "nanorobot", although the literature mentions various definitions for the word "robot", most agree that 'intelligent' robots in particular (unlike robots pre-programmed to accomplish repetitive tasks and hence without processing sensory information, e.g. robots used to build cars) are typically moving devices or systems that can make decisions by processing incoming information and act accordingly to accomplish a specific task autonomously. Because of the many uncertainties and unpredictable perturbations encountered in the endovascular system, such a level of 'intelligence' is often a must for medical nanorobots. As such, an untethered medical nanorobot must not just have the capability to move or travel in the blood vessels, but must have or at least be linked to a system having the capability to capture and process information to determine and perform actions needed to accomplish the mission, as well as be designed as mentioned earlier to operate within specific constraints, including real-time, technological and physiological constraints.

Embedding enough computing power for such tasks within an untethered two micrometre diameter device is also still beyond the possibilities of today's technologies. As stated earlier, various nano-components can be integrated to reduce the amount of 'intelligence' or computational power required. Furthermore, even if we could shrink the most intelligent human beings with a technique similar to the one proposed in the movie “Fantastic Voyage”, they would probably get lost in the maze of the human endovascular system. Indeed, if one could travel at the same speed limit allowed for cars in highways, it would take close to 1000 hours to travel through all the locations in the blood circulatory network, conditional on not going twice to the same location. It is then obvious that to go to a specific target via the shortest path without getting lost, these nanorobots must be guided by a navigation system in a similar way that smart bombs are guided by the global positioning system (GPS). At the nanoscale, such guiding must be provided by systems such as computer tomography (CT) or magnetic resonance imaging (MRI) scanners that can locate and track the nanorobots inside the human body with sufficient resolution. These medical imaging systems are operated using one or several powerful computers, providing the option to centralize the computational intelligence and hence, simplifying the design and helping medical nanorobots to become a reality in the shorter term. But one may argue that by doing so, they will not be defined as nanorobots anymore. Then, what about the robots mentioned earlier, the ones used to build cars? They do not have any embedded intelligence but are all connected to a central network of computers that can even be located physically very far from them—and we still refer to them as robots! In fact, these nanorobots navigating under the guidance of an external computer can be regard as nanorobotic carriers being wirelessly controlled by a central intelligence.

Although at first such nanorobots may look similar to other particles loaded with therapeutic agents that could be injected into the systemic blood circulation until a relatively small fraction of them reach the target (as in traditional chemotherapy), these nanorobotic entities, unlike other therapeutic carriers, are designed not only with a means of propulsion and steering in mind, but also to allow them to be tracked and guided automatically by an external computer through a closed-loop control scheme. The use of such closed-loop control, where incoming information such as the positions of the nanorobots are processed by special algorithms to establish corrective actions such as propulsion and navigation commands to bring the robots back to the planned trajectory inside the blood vessels towards the target, is fundamental to interventional medical nanorobotics. Such planned and controlled trajectories improve the efficacy of the treatment through direct targeting, hence avoiding systemic circulation in the blood circulatory network. This is significant since direct targeting may translate to significantly lower dosages of toxic compounds in the systemic circulation, herefore resulting in the potential elimination or at least a significant reduction of undesired side effects for the patient.

But one major issue remains—the ‘engine’ or ‘motor’ required for propulsion of each nanorobot. Conceiving such a propulsion system capable of sufficient thrust force, considering the power source and the size of each robot, is still a challenging, indeed formidable task at the present time. Many mention developing artificial molecular machines through the assembly of a discrete number of molecular components designed to carry out a concerted specific action,[2] such as propelling a nanorobot. But for a relatively near term invasion of these nanorobots to occur, existing components and methods instead of farther future prospective components need to be considered.

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[2] Drexler, K.E., “*Nanosystems: Molecular Machinery, Manufacturing, and Computation,*” John Wiley and Sons, New York, 1992.

For instance, an immediate solution to this propulsion problem can be realized by combining physics and materials sciences. As in many other fields, one of the important design rules in nanorobotics is to keep it as simple as possible because things might get complicated anyway as the project progresses. Hence at such a small scale, the simplest motor is a motor without moving parts. Interestingly enough that such a motor can now be realized. A ferromagnetic material, for instance, when magnetically saturated by being placed in a high intensity magnetic field, can be moved by varying the intensity of the magnetic field in one direction, referred to here as a magnetic gradient. In this case, the ferromagnetic object will go in the direction of higher field intensity. But technologically speaking, how can we do that inside the human body? Well, remember the MRI system used as the tracking and navigation system for our nanorobots inside the human body; when a patient is placed inside the large magnet of a clinical MRI system, the magnetic field intensity is high enough to saturate the ferromagnetic material core acting as a motor or propulsion system embedded in the nanorobot. This is like starting the engine by turning the ignition key. But the nanorobots are still not moving until we press the accelerator or, to use a more technical term, produce a magnetic gradient. In fact, the same three orthogonal coils used in conventional MRI systems for slice selection during MR imaging can, besides being used to track the nanorobots inside a living body, also create the magnetic gradients necessary to propel and steer the nanorobots in a 3D space at a speed and direction necessary for effective navigation in the blood vessels.[3] The nanorobots are then put on autopilot where the MRI computer generates the appropriate directional magnetic gradients several times per second based on recorded MR tracking information, to navigate them directly to a target location.

Although this may still appear like science-fiction, it is not as we seem to be stepping inexorably closer to an invasion of medical nanorobots. In fact, an untethered 1.5 mm ferromagnetic bead has recently been navigated automatically, i.e. without human intervention, at an average velocity of 10 cm/s along pre-programmed trajectories inside the carotid artery of a living swine using the same type of clinical MRI systems presently used for humans.[4] More convincing is the fact that this was done inside an animal that is anatomically very close to the human. Furthermore, other experiments have also been successfully performed in laboratory settings precisely reproducing complex human blood vessel pathways, suggesting that the same technique could be successfully applied in the blood vessels of a human.

An overall diameter of 1.5 mm was adequate for the first proof-of-concept but it is still 750 times larger than the diameter required for the nanorobots to be able to navigate inside the human microvasculature. In fact, this miniaturization process has already been achieved with automatic navigation being validated in laboratory settings. But by doing so, the propulsion

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[3] Mathieu, J.-B., Martel, S., Yahia, L., Soulez, G. and Beaudoin, G., “MRI systems as a mean of propulsion for a microdevice in blood vessels,” In: *Proc. 25th Annual Intl Conf. IEEE Engng in Med. and Biol.*, Cancun, Mexico, Sept. 17–21, 2003; Mathieu, J.-B., Beaudoin, G. and Martel, S., “Method of propulsion of a ferromagnetic core in the cardiovascular system through magnetic gradients generated by an MRI system”, *IEEE Trans. Biomed. Engng* **53**, pp. 292–299, 2006.

[4] Martel, S., Mathieu, J.-B., Felfoul, O., Chanu, A., Aboussouan, É., Tamaz, S., Pouponneau, P., Beaudoin, G., Soulez, G., Yahia, L.H. and Mankiewicz, M., “Automatic navigation of an untethered device in the artery of a living animal using a conventional clinical magnetic resonance imaging system,” *Applied Physics Letters* **90**, 114105, 2007.

system or volume of magnetic material embedded in each nanorobot becomes smaller, and hence less powerful. This situation becomes even worse when considering that such propulsion systems cannot occupy the whole volume of the nanorobot since room must be available for loading the therapeutic agents.

But to appreciate the solution to this problem, one must understand the environmental conditions and the forces that interact with such small robots. Fortunately, unlike larger untethered objects such as the 1.5 mm bead mentioned earlier, these smaller untethered robots are significantly less influenced by inertia, buoyancy and gravity. Instead, the motion of these nanorobots is governed by several factors besides the magnetic force, including viscous drag, robot-blood cell interactions, thermal kinetics or Brownian motion, nanorobot-fluid interactions or perturbations to the blood flow field, and inter-nanorobot effects such as magnetic dipole interactions. Remember the modified design rules when I mentioned the planet Mars: here is a situation with far fewer effects from gravity and different environmental conditions that influence the operational characteristics of our nanorobots. As an example, magnetic dipole interactions between nanorobots can be exploited to form clusters of nanorobots with sufficient coupling to allow huge quantities of the individual engines embedded in each nanorobot to work together to achieve higher propulsion forces, while at the same time delivering a higher quantity of therapeutic agents. And along the way to the target, the environment also changes as well as the means of propulsion. Because the blood is no longer experienced as homogeneous (since our nanorobots are smaller than the red blood cells), hence unlike when operating in larger blood vessels, the blood flow itself can be used in very small capillaries as a means of propulsion for the nanorobots interposed between red cells, while magnetic gradients are used only to steer these nanorobots towards the target at blood vessel bifurcations.

But there is more. Another fundamental design rule in nanorobotics for achieving smaller and more effective devices is multifunctionality, where the same components are designed to be used for many purposes. For example, the same magnetic material used for propulsion and steering will also disturb the magnetic field, and as such it can be used as a marker for the nanorobots to allow them be tracked with MRI. But even at the micrometre scale, the MR image distortion is too large, preventing effective and accurate localization of the nanorobots when access to neighbouring anatomical information must be maintained. The solution is then to replace a single micrometre-sized magnetic core by many magnetic nanoparticles. By reducing their sizes to the nanometre scale, each of these particles becomes a single magnetic domain—entities that act like imaging contrast agents that will not disturb the immediately surrounding MR image. These same nanoparticles will also act as nanoengines, being mechanically coupled using the polymeric body of each nanorobot to together achieve propulsion forces that are equivalent to the forces achieved using a single microengine approach.

But there is even more. Their sizes also allow us to perform highly localized hyperthermia—a controlled rise of temperature at a location that can be deep inside the human body. With the use of radio frequency (RF) signals absorbed by the same magnetic nanoparticles embedded in each nanorobot, this highly localized increase in temperature may be used not only as a computer-triggered mechanism to release drugs at a specific instant or location (beside other techniques such as the use of preprogrammed time-degradable polymers or polymers reacting to pH changes in vicinity of tumours), but at the same time it contributes to an improvement of the therapeutic efficacy. Such temperature rises can also be monitored with MRI to avoid tissue damage.

Besides the therapeutic agents, bio-targeting agents can also be coated onto the surface of the nanorobots. One example is to include nanocomponents such as multifunctional micelles to provide effective cancer targeting with ultrasensitive detection by MRI.[5]

The approach described so far is part of our "MR-Sub Project", where MR-Sub stands for Magnetic Resonance Submarine; and as in a naval force where a fleet of various types of combat platforms can provide more effective strategies against the enemy, several types of medical nanorobots may prove to be more effective for fighting tumours. For instance, slightly larger "embolization nanorobots" can be used to temporarily reduce blood flow in capillaries, hence facilitating the steering of "targeting nanorobots" towards a tumour. Small diameter blood vessels are presently not visible on any medical imaging systems, thereby preventing effective path planning to reach the target. Hence "scout nanorobots" acting as navigable MRI contrast agents can also be used to gather information that will be used to plan the final attack.

But the nanomotors of these artificial nanorobots have limitations, especially in the smallest capillaries. As the total volume dedicated to the ferromagnetic nanoparticles decreases, the total induced propulsion force is also reduced significantly. Although blood flow velocities are lower in smaller diameter blood vessels compared to larger ones, additional magnetic gradient coils inside the MRI system must still be considered. But as the magnetic gradients increase to compensate for smaller volumes of ferromagnetic materials, the coils begin to overheat. Hence, to prevent a shut-down of the system, which may result in tragic consequences for the patient, the time dedicated to propulsion and steering of the nanorobots must be decreased during the tracking/propulsion cycles to allow time for the coils to cool down. The limited time dedicated to steering or propulsion may in some situations impact targeting effectiveness. Even by using for the nanomotors the best ferromagnetic materials available, such as iron-cobalt alloys, for inducing the maximum force per unit volume, this may remain an issue when navigating in the microvasculature. The limitation will be even worse when proven biocompatible materials but offering less propulsion power density (such as iron oxide[6]) are considered to preempt additional design complexities intended to prevent toxic cobalt ions coming into direct contact with the blood.

As such, a synthetic molecular motor as mentioned earlier that could run continuously while providing sufficient thrust forces would be very useful when operating in the microvasculature. But in the short term this not possible. Nonetheless, there is an alternative provided by nature—the flagellum of bacteria, which is driven by a rotary engine composed of proteins and which is powered by a transmembrane proton flux. This molecular motor measures less than 300 atoms across and has a rotor that can operate at 6000 to 17 000 revolutions per minute (rpm), but with the flagellum acting as a propeller being attached to the rotor, it usually achieves 200 to 1000 rpm.

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[5] Nasongkla, N. et al., "Multifunctional polymeric micelles as cancer-targeted, MRI-ultrasensitive drug delivery systems," *Nano Letters* **6**, pp. 2427–2430, 2006.

[6] Hütten, A. et al., "Ferromagnetic FeCo nanoparticles for biotechnology," *Journal of Magnetism and Magnetic Materials* **293**, pp. 93–101, 2005.

But how can these nanomachines be steered with therapeutic loads towards our target? The answer[7] has been proposed and validated experimentally: with the use of special bacteria known as magnetotactic bacteria (MTB).[8] The orientation of these bacteria are controlled through magnetotaxis, in which a directional torque is induced on a chain of single-domain magnetic nanoparticles named magnetosomes, acting like a compass[9] embedded in each bacterium. Such directional torque or steering capability can be achieved using an electrical current circulating in conductors in the proximity of the navigation zone, thereby providing a communication link to allow this process to be entirely controlled by a computer. Going further, our research group now found ways to control their speeds, to stop or reverse their motions as well as controlling how they will behave when they reach an obstacle, all under computer control. The bacteria of type MC-1 have been of special interest for us for this particular application since the thrust force provided by its "twin flagellated engines" can be more than 8 times the thrust force typically provided by other types of flagellated bacteria, while reaching swimming speeds corresponding to 100 to 150 times its own body or cell length per second. (In comparison, a fast nuclear attack submarine when submerged will travel approximately one sixth of its own length per second.) Surprising enough is the fact that its body or cell is spherical with a diameter of approximately two micrometres! It almost looks as though evolution has presaged that they could be used one day to help us fighting tumours! And yes, our experiments have shown that they swim very effectively in human blood but typically for less than an hour because of the higher temperature inside the human body than that of their native environment, which is positive in a sense since it prevents them from reproducing and hence colonizing the entire blood network. And yes, as with other components for our nanorobots, these bacteria have been tested for biocompatibility to ensure appropriate responses from the immune system. Furthermore recent studies showed that they are visible under MRI (because of their magnetosomes) and therefore could be guided under computer control to swim towards a tumour. By wearing a 'jacket' made of nanoparticles loaded with therapeutic agents and attached to the outer membrane of the bacterium through the use of specific antibodies (these antibodies have been developed in our laboratory), an effective complementary means of reaching tumours for therapeutic purposes can be implemented.[10] Complementary because although very effective in small capillaries, the thrust forces of these molecular motors are insufficient to deal with the higher blood flows encountered in larger blood vessels.

This fact may suggest that some of our previous ferromagnetic carriers driven by magnetic gradients could be designed to encapsulate and transport agglomerates of these bacterial swimmers closer to the microvasculature, where they could then be released in ways similar to

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[7] Martel, S., Tremblay, C., Ngakeng, S. and Langlois, G., "Controlled manipulation and actuation of micro-objects with magnetotactic bacteria," *Applied Physics Letters* **89**, 233904, 2006; Martel, S., "Controlled bacterial micro-actuation," In: *Proc. Intl Conf. on Microtech. in Med. and Biol.*, pp. 89–92, Okinawa, Japan, May 9–12, 2006.

[8] Blackmore, R.P., "Magnetotactic bacteria," *Science* **190**, pp. 377–379, 1975.

[9] Frankel, R.B. and Blakemore, R.P., "Navigational compass in magnetic bacteria," *Journal of Magnetism and Magnetic Materials* **15–18** (Part 3), pp. 1562–1564, 1980.

[10] Martel, S., "Targeted delivery of therapeutic agents with controlled bacterial carriers in the human blood vessels," In *2nd ASM/IEEE EMBS Conference on Bio, Micro and Nanosystems*, San Francisco, USA, Jan. 15–18, 2006.

how soldiers were transported towards the beaches during the assault landings for the battle of Normandy in 1944.

Going further, if engineers consider bacteria as components to be integrated in their systems, they may, as for electronic and mechanical components, require a catalogue of various biocomponents including bacteria with various specifications to select from. This may suggest the use of genetic modifications and other techniques to enhance or adjust the characteristics of the bacteria for specific applications. The propulsion systems of flagellated bacteria for instance are only approximately 2% efficient, providing plenty of opportunities for engineers to find ways to improve such hybrid (made of biology and artificial components) systems until fully synthetic or artificial molecular motors become available.

Other designs will follow for many more applications including diagnostics and prevention. Such nanorobots may ultimately become more autonomous, especially when used for preventive tasks and early detection. Furthermore, if it ends up that some of these tiny submarines may have a crew as in the movie "Fantastic Voyage" but in the form of living bacteria, then perhaps nanometre-sized robots could also be envisioned in special cases, such as when nanorobots must traverse the blood-brain barrier.

In the meantime, with all the components and techniques now available to initiate our own fantastic voyage, we could suspect that an invasion of first generation medical nanorobots (or whatever you want to call them) may be coming in the very near future, and possibly within a period shorter than you may expect!

Besides being an engineer, professor and researcher, Sylvain Martel is also a retired military officer who acted as a commanding officer of surface ships involved in naval operations; he has also been a diver with the Canadian Navy. Initially from an electrical engineering environment, he began developing nanorobotic platforms a few years ago when he was with the Department of Mechanical Engineering at MIT.