Evaluating microscopic robots for medical diagnosis and treatment

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Nanotechnology has the potential to revolutionize many activities, including health care. In particular, the manufacture of programmable machines comparable in size to bacteria and able to sense and modify their environments could provide significant medical benefits by operating within the body [8, 22]. Such microscopic robots ("nanobots") extend today's much larger ingested or implanted medical devices. These current medical devices include pill-sized cameras to view the digestive tract as well as implanted glucose and bone growth monitors to aid treatment of diabetes and joint replacements, respectively. Such devices gather information continually over a period of time, in contrast with the more limited monitoring possible with a series of conventional laboratory tests.

Nanorobots would be small enough to move through the tiniest blood vessels. For example, the robots could operate as passively circulating sensors to detect preprogrammed patterns of chemicals as they pass near cells. Communicating results to external detectors would allow real-time in vivo monitoring of many cells. The robots could also act on their environments, e.g., releasing drugs at locations with specific chemical patterns or mechanically manipulating objects for microsurgery.

Realizing these benefits requires fabricating the robots cheaply and in large numbers. Such fabrication is beyond current technology. Nevertheless, ongoing progress in engineering nanoscale devices could eventually enable production of such robots. One approach is engineering biological systems, e.g., bacteria executing simple programs [2]. However, biological organisms have limited material properties and computational speed. Instead we focus on machines based on plausible extensions of currently demonstrated molecular-scale electronics, sensors and motors [6, 7, 17, 11, 21, 32] as early versions of components for stronger and faster microscopic robots than is possible with biological organisms. These nonbiological robots contain nanoscale sensors and electronics, along with a power source, within a protective shell. Of particular interest are biomedical applications requiring only modest hardware capabilities, which will be easier to fabricate than more capable robots. Understanding the behaviors of such "first generation" nanobots will identify design tradeoffs among hardware capabilities, control methods and task performance.

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A major challenge for nanorobots arises from the physics of their microenvironments and the hardware limitations of the robots, which differ considerably from experience with today's larger robots. For example, the physical environment will often consist of cells in fluids dominated by viscous forces. Second, thermal noise is a significant source of sensor error and Brownian motion limits the ability to follow precisely specified paths. Third, relevant objects are often recognizable via chemical signatures rather than visual markings or shape. Fourth, the tasks involve large numbers of robots, each with limited abilities. Moreover, a task will generally only require a modest fraction of the robots to respond appropriately, not for all, or even most, robots to do so. This observation contrasts with teams of larger robots with relatively few members, such as robot soccer or surveillance: incorrect behavior by even a single robot can significantly decrease team performance.

To illustrate the potential of microscopic robots for medicine, this paper describes plausible robot capabilities from early nanotechnology based on extrapolations from current laboratory demonstrations of nanoscale devices. The physical properties of task environments are then discussed in the context of a prototypical diagnostic task of finding a small chemical source in a multicellular organism via the circulatory system. Theoretical studies suggest these robots can give significantly better performance than current medical technology, not only for diagnostics but also for interventions such as drug delivery and aiding microsurgery. Thus we can expect benefits from even relatively early developments of nanotechnology, which will in turn pave the way for more significant applications as the technology matures.

Capabilities of microscopic robots

Minimal robot capabilities needed for biomedical tasks include chemical sensing, computation and power. Additional capabilities, enabling more sophisticated applications, include abilities to stick to specific cell surfaces, communicate and move.

Sensing

Large-scale robots often use sonar or cameras to sense their environment. These sensors locate objects from a distance, and involve sophisticated interpretation algorithms. In contrast, microscopic robots for biological applications will mainly use chemical sensors, e.g., the selective binding of molecules to receptors altering the electrical characteristics of nanoscale wires.

Microscopic robots and bacteria face similar physical constraints in detecting chemicals [5]. Current molecular electronics [32] and nanoscale sensors [20, 24, 27] indicate plausible sensor capabilities. At low concentrations, sensor performance is primarily limited by the time for molecules to diffuse to the sensor.

In addition to chemical sensing, robots could sense other properties of their environment. For example, nanoscale sensors for fluid motion can measure fluid flow rates at speeds relevant for biomedical tasks [13], allowing robots to examine microfluidic behavior in small vessels. Since boundaries significantly alter fluid behavior far into the vessel [28], several such sensors, extending a small distance from the robot surface in various directions, could detect changes in the vessel geometry. Such estimates of local geometry might, for example, help distinguish normal vessels from leaky new vessels formed within tumors.

Communication

Several forms of communication could be useful for nanorobots. The simplest form of communication is receiving electromagnetic or acoustic signals broadcast from outside the body. Such signals could activate robots only within certain areas of the body at, say, centimeter length scales.

Communication between nearby robots and sending information to detectors outside the body require more difficult fabrication and increase robot power use compared to just receiving broadcast signals. But such communication abilities increase the range of tasks for the robots. For instance, acoustic communication among nearby robots (e.g., within about 100 μm of each other [8]) allows coordinating their activities.

For limited communication with the attending physician, the robots could carry nanoscale structures with high response to some external signals. Such structures could respond to light of particular wavelengths when near the skin, or give enhanced imaging via MRI or ultrasound. Such visualization mechanisms combined with a selective ability to stick to vessel walls allows detecting aggregations of devices at specified locations near the surface of the body. This visualization technique could be useful even if the tissue volume of interest is too deep to image effectively at high resolution. In particular, robots could use various areas near the skin (e.g., marked with various light or ultrasound frequencies) at centimeter scales as readout regions during operation. For example, robots that have detected certain chemicals could aggregate at the corresponding readout location, which would then be visible externally. Robots could choose how long to remain at the aggregation points based on how high a concentration of the chemical pattern they detected. Robots with local communication capabilities could compare observations while in these aggregation regions, allowing further computation to influence the communicated result, e.g., by changing how long the devices remain at the readout location or whether they aggregate in other locations at a later time. This indication of whether, and (at a coarse level) what, the devices have found could help decide how long to continue circulating to improve statistics for weak chemical signatures. These aggregation points could also be used to signal to the devices, e.g., instructing them to switch to another of a few preprogrammed modes of operation.

Locomotion

Biomedical applications will typically involve robots operating in fluids. A key physical parameter for an object moving in fluid is the ratio of inertial to viscous forces, which depends on the size and speed of the object. This ratio is called the Reynolds number. Using typical values for density and viscosity (e.g., of water or blood plasma) and noting that reasonable speeds for robots with respect to the fluid [8] are comparable to the fluid flow speed in small vessels, i.e., ~ 1 mm/s, motion of a 1-micrometer robot has a Reynolds number of about 10^{-3}. Thus viscosity dominates the robot motion, with different physical behaviors than for larger organisms and robots [25, 31, 28]. For instance, robots applying a locomotive force quickly reach terminal velocity in a fluid, i.e., applied force is proportional to velocity rather than the more familiar proportionality to acceleration of Newton's law $F = ma$. By contrast, a swimming person has a Reynolds number about a billion times larger, and viscous forces are minor. Figure 1 illustrates the variation in fluid speed in small vessels.

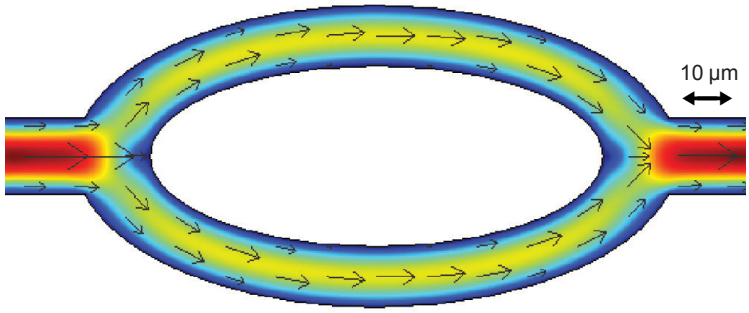

Figure 1. Example of fluid flow in small branching vessels. The vessels are about 10 μm in diameter and have average flow speed of a millimeter per second. Fluid moves fastest at the center of the vessels and is stationary along the vessel walls. Color indicates flow speed, ranging from 0 (blue) to 2 mm/s (red). For simplicity, this numerically evaluated example uses two-dimensional fluid flow and does not include any objects, e.g., blood cells, moving with the fluid.

Another physical effect, Brownian motion, randomly changes location and orientation of microscopic robots, thereby limiting the time over which they can reliably compare different locations or directions. This behavior contrasts with long range path planning with maps of the environment often used for larger robots.

Computation

High resolution diagnosis involves chemical sources as small as a single cell, i.e., about 10 μm. Flow in the small vessels has a range of speeds up to about a millimeter per second. Thus, robots would pass near the source, where concentration would be highest and easiest to detect, on millisecond time scales.

Recognizing a chemical species involves at least a few arithmetic operations to compare sensor counts to prespecified threshold values. An estimate of the required computational capability is about 100 elementary logic operations within a 10 ms measurement time. This gives about 10^4 logic operations per second. While modest compared to current computers, this rate is significantly faster than demonstrated for programmable bacteria [2] but well within the capabilities of molecular electronics.

Power

Robots require power. For biomedical chemical sensing tasks, computation generally uses much less power than communication or locomotion. To quantify power requirements of microscopic robots, moving through the fluid at 1 mm/s dissipates about a picowatt [4] to overcome fluid drag and the inefficiencies of locomotion. Communication could use power of a similar order of magnitude. For comparison, a typical person at rest uses about 100 watts.

For tasks of limited duration, onboard fuel created during robot fabrication could suffice. Otherwise, the robots could use energy available in their environment, such as converting externally generated vibrations to electrical energy [33] or chemical generators, e.g., a fuel cell using glucose and oxygen in the bloodstream [8].

Tasks for microscopic robots

This section describes some task scenarios enabled by the robot capabilities described above. A prototypical task is responding to chemical signals, e.g., released in the blood by tissue injury [15] or monitoring chemical behaviors within individual cells [34, 30]. The robots may detect signals and initiate response more rapidly than natural mechanisms (e.g., immune cells). They could also identify the signal's cause (e.g., a type of infecting bacteria) and, unlike cells, communicate that information to an attending physician [8], providing earlier and more accurate diagnosis. As an example, Figure 2 illustrates the environment of robots operating in small blood vessels.

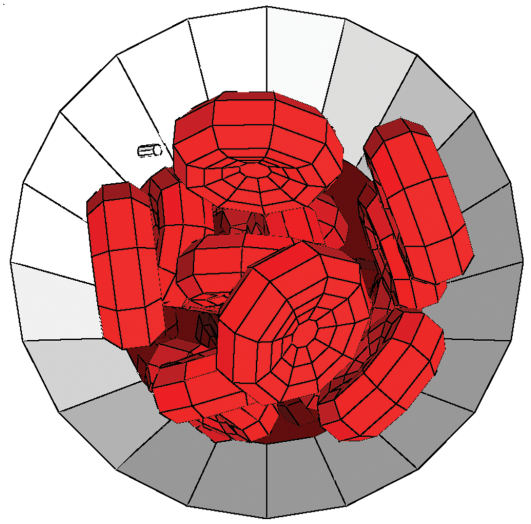

Figure 2. Schematic interior view of a small blood vessel with red blood cells (~ 7 μm diameter) and a bacterium-sized robot (small cylinder near the wall at upper left). The cells occupy about 1/5th of the vessel volume, a typical case for small blood vessels.

The number of robots involved in the task determines the time required for each vessel to have likely had at least one robot pass through it. For example, a person has several billion capillaries and circulation takes about a minute to complete a transit through the body. For high resolution diagnosis involving low concentration chemicals released into a few tiny vessels, using about a billion robots would give several opportunities for passing robots to detect the chemical during an operation time of about an hour. Using multiple detections is important for reducing false positives due to sensor errors and a low background concentration of the chemical in the bloodstream [14]. A billion robots is considerably more than used today with teams of larger robots, e.g., for robot soccer. However, such large numbers should be manufacturable as nanotechnology develops, just as today's semiconductor fabs routinely produce chips with about that many transistors. As a point of comparison, a billion of the microscopic robots discussed here would have a total mass of only a few milligrams and a total volume of a few cubic millimeters. This volume of robots is about a millionth of a person's total blood volume.

Diagnosis

The robots could detect localized high concentrations that become too low to distinguish from background concentrations when diluted in the whole blood volume as obtained with a sample for laboratory analysis. Moreover, if the detection consists of the joint expression of several chemicals, each of which also occurs from separate sources, the robot could identify the spatial locality, which would not be apparent when the chemicals are mixed throughout the blood volume. Similarly if the chemical is released in bursts, sensors nearby during a burst would encounter much higher local concentrations than the time-averaged concentration. Furthermore, by recording events over time (e.g., minutes to days), the sensors could collect information on changes (e.g., in response to an external stimulus such as the introduction of a drug) that would be impractical to obtain from repeated blood samples.

By collecting enough measurements, the robots could distinguish between a strong source and many weak sources producing the chemical at the same total rate. The strong source would give high count rates for a few robots (those passing near the source) while multiple weak sources would have some detection in a larger fraction of the robots. Thus robots could not only determine whether sources of a specified pattern of chemicals exist, but also provide information about their spatial structure.

Figure 3 illustrates the problem of distinguishing a single source from two, nearby weaker sources. In this example, fluid flows through branching vessels passing near the source(s), using the same geometry and flow shown in Figure 1. The chemical from the source(s), taken to have a diffusion coefficient of a small protein, diffuses to the nearby vessels and into the moving fluid within them. The fluid moves the chemical downstream through the vessels as it continues to diffuse in the fluid. Robots passively flowing with the fluid detect the chemical in the fluid. At low concentrations typical of chemicals released into the blood in response to initial stages of infection or minor injury [18], in this example the robots would typically encounter only a few dozen molecules of the chemical with their sensors. Statistical fluctuations in the counts are roughly the square root of the average, giving fairly large variations in the counts. Thus observations from multiple robots passing through these vessels are needed to reliably determine number and strengths of the sources. A further challenge is a lower, but not negligible, background concentration of the chemical, or other similar chemicals that could also bind to the nanoscale sensor, thereby leading to false positive detections.

Robots with other types of sensors could provide additional information about the sources. For example, fluid flow sensors would allow correlating chemical detections with properties of the flow and the vessel geometry (e.g., branching and changes in vessel size or permeability to fluids).

The information retrieved from the robots could be further analyzed in a conventional computer with far more computational resources than available to any individual microscopic robot. This computer would have access to information from many robots, allowing evaluation of aggregate properties of the population of cells that individual robots would not have access to, e.g., the number of cells presenting a specific combination of chemicals. This combined information allows estimating spatial structure and strength of the chemical sources, in analogy with reconstructing tissue structure from a series of X-rays at various angles as used with computer-aided tomography (CAT) scans.

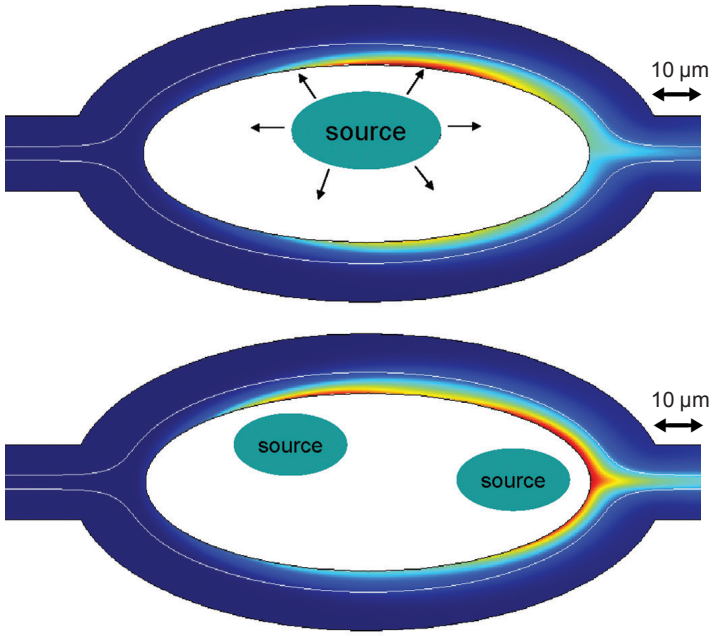

Figure 3. Example of chemical concentration in branching vessels near one or two cell-sized sources. Chemical concentration in the fluid ranges from 0 (dark blue) to 2×10^{18} molecules/m^3 (red). The white curves through the fluid show possible paths for robots passively moving with the fluid.

Modifying microenvironments

Robots able to locate chemically distinctive microenvironments in the body could modify those environments. Such active task scenarios may require more advanced robot capabilities, such as locomotion and communication, than those needed for the simplest passive sensing. With active locomotion, after detecting the chemicals of interest the robots could follow the chemical gradient to the source [14].

When robots aggregate at chemically distinctive regions, they could take actions to modify those regions. For instance, the devices could carry specific drugs to deliver only to cells matching a prespecified chemical profile [8, 10]. Robots could achieve this aggregation if they can alter their surface properties to stick to the vessel wall.

As another example, robots aggregated at chemically identified targets could perform precise microsurgery at the scale of individual cells. Since biological processes often involve activities at molecular, cell, tissue and organ levels, such microsurgery could complement conventional surgery at larger scales. For instance, a few millimeter-scale manipulators, built using micromachine (MEMS) technology, and a population of microscopic devices could act simultaneously at tissue and cellular size scales. An example involving microsurgery for nerve repair with plausible biophysical parameters indicates the potential for significant improvement in both speed and accuracy compared to larger-scale machines acting alone [29, 16].

The robots could monitor environmental changes due to their actions, thereby documenting the progress of the treatment in far greater detail than is possible today. With some

external communication, the treating physician could monitor the robots' progress and decide whether and when they should continue to the next step of the procedure. Using a series of steps, with robots continuing with the next step only when instructed by the supervising person, maintains active human control of the robots.

Evaluating robot behaviors

Because it is not yet possible to fabricate nanorobots, studies of their behavior must rely on theory and simulations. As technology develops to fabricate early versions of the robots, simple experiments with them will help validate the simulations. This section describes some of these evaluation possibilities.

Theoretical studies

A variety of theoretical approaches allows estimating the task performance of nanorobots with the capabilities described in this paper. The simplest approach relies on estimates of individual capabilities to indicate the plausible range of tasks the robots could perform [8].

More detailed studies consider the combination of robot capabilities and the physical properties of the task environment. One such theoretical approach estimates typical behavior of the robots using a statistical approximation [19]. This method has been applied successfully to teams of small numbers of large robots. Microscopic robots, with limited computational capabilities, will likely use simple controls, with minimal dependencies on events in individual robot histories, for which this statistical approximation is ideally suited. The approach can also readily incorporate spatial variations such as fluid speeds and chemical concentrations [12] relevant for nanorobot tasks.

For a more detailed look at the robot behaviors, simulations can include various levels of detail, giving a tradeoff between physical accuracy and computation required to simulate large numbers of robots over relevant time scales. Such simulations can readily include individual robot histories and correlations in behavior that are not easily treated with the statistical approximation discussed in the previous paragraph.

Theoretical studies identifying tradeoffs among control complexity and hardware capabilities can aid future fabrication. Specifically, control can compensate for limited hardware (e.g., sensor errors or power limitations), providing design freedom to simplify the hardware through additional control programs. Thus the studies can help determine minimum hardware performance capabilities needed to provide robust systems-level behavior.

One challenge for theoretical studies is the poorly characterized physical parameters of the microenvironments the robots will operate in. In a bootstrapping process, early nanorobots, with limited capabilities, could help quantify these properties, thereby leading to more accurate results and improved designs for the robots.

Thus much remains to be done in developing detailed theoretical evaluation of nanorobots. Nevertheless, current studies suggest robots, even with limited capabilities of early nanotechnology fabrication, should give improved diagnosis and treatment, both in speed and spatial resolution. For example, they could rapidly aggregate at cell-sized chemically distinctive locations or aid larger machines with microsurgery. The precision of localization and

the robots' programmability gives them a degree of flexibility to alter microenvironments, e.g., by releasing drugs, well beyond that possible with either large scale surgery or nonprogrammable chemically-targeted drug delivery. The full range of biomedical situations that could benefit from this flexibility, e.g., nerve repair [16], remains to be seen.

With many robots in the tissue but only a few in the proper context to perform a task, false positives are a significant issue. In some situations, these false positives may just waste resources (e.g., power). But in other cases, too many false positives could be more serious, e.g., leading to aggregation blocking blood vessels or incorrect diagnosis. Estimating the number of false positives, and suggesting control designs to minimize them, can be addressed with simulation studies [14].

Validation experiments

As technology advances to constructing early versions of microscopic robots, experimental evaluations will supplement theoretical studies.

One such experiment is embedding the devices in bacterial biofilms to monitor chemical signals exchanged among the bacteria. In this case, the robots could be fabricated on a surface and the film grown over them, greatly simplifying constructing the robots. The surface could provide power and communication during operation. This experiment would test the ability of the chemical sensors and the onboard computation to detect patterns of chemical activity, as well as the durability of the robots.

Another early validation experiment is operating the robots in manufactured microfluidic channels [28]. This would test the robots' ability for independent operation without direct connections to external devices for power or communication. Such studies would allow testing the robots' ability to infer properties of their microenvironments, such as vessel branching, based on fluid flow nanoscale sensors, and calibrating the chemical sensors with known concentrations introduced in the fluid. The robots could also demonstrate the ability to aggregate at chemically defined locations.

After such in vitro experiments, early in vivo tests could involve robots acting as passive sensors in the circulatory system. The chemical patterns found would quantify properties of microenvironments in the body. Such nanorobots will be useful not only as diagnostic tools and sophisticated extensions to drug delivery capabilities [1], but also as an aid to develop robot designs and control methods for more active tasks.

Discussion

The nanorobot capabilities and tasks described in this paper highlight key control principles for microscopic robots. By performing the task in stages, the person deploying the robots remains in the decision loop, especially for the key decision of whether to proceed with treatment (e.g., release a drug) based on diagnostic information reported by the robots. Information retrieved during treatment can also indicate how well the procedure is proceeding and provide high-resolution documentation of what was done to improve future treatments. More generally, this control approach illustrates an important technique for using microscopic robots: local, distributed control to achieve robust responsive behaviors on small scales in space

and time, combined with feedback from a slower, larger central control (e.g., a person) to verify performance and consider global constraints using information from many devices.

Safety is important for medical applications of microscopic robots. Thus, evaluating a task protocol should consider its accuracy allowing for errors, failures of individual devices or variations in environmental parameters. For the tasks discussed in this paper, statistical aggregation of many robots' measurements provides robustness against these variations, a technique recently illustrated using DNA computing to respond to patterns of chemicals [3]. Furthermore, the devices must be compatible with their biological environment [9, 23] for enough time to complete their task. Appropriately engineered surface coatings and structures should prevent unwanted inflammation or immune system reactions during robot operation [9, 26].

Despite the simplifications used to model nanorobot behavior in current studies, the estimates with plausible biophysical parameters show even relatively modest molecular hardware could provide useful in vivo sensing and manipulation capabilities [8, 16, 15]. These capabilities give far more rapid, flexible and specific performance than is possible with today's larger devices. While engineering challenges for manufacturing these robots preclude definite estimates of when they might be available, quantifying their benefits compared to existing technology can guide and motivate investment in their development. Moreover, early versions of microscopic robots will enable detailed quantitative research studies of tissue microenvironments well before the robots are ready for clinical use. The improved understanding will, in turn, indicate suitable tasks for more capable robots and appropriate tradeoffs between size and capability for hybrid systems combining coarse centralized control with the flexibility of cell-sized robots in biological microenvironments.

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