INORGANIC BIONANOBOTS TO TARGET CANCER CELLS

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ABSTRACT

Inorganic nanobots are functional machines that exist and operate at the nanometer to micrometer scale. Being able to operate at this scale allows nanobots to interact with other incredibly small things, like animal cells, bacteria, viruses, etc. Because diseases are often caused by living animal cells (cancer), bacteria, and viruses, we want to selectively kill these cells. However, to interact with these pathogens, we must first create and control these nanobots. This paper introduces a few viable methods of fabricating inorganic nanobots, making them biocompatible, powering them, enabling endocytosis, sensing their environment, killing the pathogens, and detailing the near and far future work that can be discovered from these nanobots.

Index Terms— nanobot, nanorobot, nanite, cancer

1. INTRODUCTION

Nanobots are incredibly small (on the nanometer scale) programmable or functionally designed devices. They can perceive their environment and act accordingly. They can potentially be used to cure diseases like cancers and infections. Up until recently, nanobots have been organic or hybrid organic. There are many known and unknown diseases in the world, each with their own imperfect treatment. One of the biggest goals of humanity today is to prevent and cure each of these diseases. Sufficiently advanced nanobots can achieve this goal.

The nanobots discussed here are intelligent and are just small integrated circuits (IC). ICs are integral to society today – they are in computers, ovens, cars, and much, much more. ICs use millions or billions of transistors to serve their processing needs. ICs are typically fabricated on silicon wafers, but there are other fabrication techniques to achieve different goals.

Thin film transistors (TFT) are transistors that are fabricated on a nonreactive surface (substrate) [1]. TFT are most frequently used in scenarios where they are also on a transparent surface.

Next, we need to understand different diseases and their causes.

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. This occurs when the body's normal control mechanisms malfunction or stop working, and instead of dying, mutated cells can survive and form a mass of tissue called a tumor. Not all tumors are cancerous; benign tumors typically do not spread to other parts of the body and are not usually life-threatening. However, malignant tumors can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body, a process called metastasis. The exact cause of cancer is not completely understood, but it's believed to result from a combination of genetic factors and environmental exposures. Cancer can affect individuals at any age, and the risk increases with age. Treatments vary but can include surgery, radiation, chemotherapy, immunotherapy, and targeted therapies [2].

Bacteria are single-celled microorganisms that are among the earliest forms of life on Earth and can be found in virtually every environment. They have a simple cellular structure, usually without a defined nucleus (prokaryotic), and their genetic material, DNA, is freely floating within the cell. Bacteria come in a variety of shapes and sizes, including spheres (cocci), rods (bacilli), and spirals (spirilla). They reproduce rapidly through a process called binary fission, where one cell divides into two. While many bacteria are beneficial, aiding in processes such as decomposition, nitrogen fixation, and human digestion, others can cause diseases, including strep throat, tuberculosis, and many forms of food poisoning [3]. Bacteria can also be harnessed in numerous biotechnological applications, from fermentation in food production to the creation of biofuels and medicines.

Viruses are tiny, infectious particles that exist on the boundary between living and non-living entities. They consist of genetic material, either DNA or RNA, encapsulated within a protein coat known as a capsid, and sometimes a lipid envelope. Viruses are obligate intracellular parasites, which means they lack the capability to replicate or carry out metabolic processes outside of a host organism's cells. Upon infecting a host, they hijack the host cell's machinery to replicate, producing numerous copies of themselves. This process often results in the destruction of the host cell. Viruses can infect a wide variety of organisms, from bacteria and plants to animals and humans, and they are responsible for a range of diseases, including the common cold, influenza, HIV/AIDS, and COVID-19 [4].

Next, we'll review many of the recent advances that we

can build off of for our nanobots.

Quantum dots are nanoparticles that interact with light and electric fields that have been studied in recent years and these nanobots can incorporate these findings as well. Nanobots can also provide improvements over quantum dots because nanobots are smarter and more configurable [5].

The state-of-the-art/science of nanorobotics is broad. It covers topics in biology, chemistry, electronics, robotics, etc. A review in 2009 discusses using proteins for movement, using carbon nanotubes to assemble nanobots, coating nanobots with diamond, using on-chip actuation, sensing, power, data transmission, and controlling flagellated nanomotors using MRI [6]. A review in 2017 discusses nanobots smaller than 10μm, 3D printing in resin, the biocompatibility of diamond coated nanobots, the intricacies of the definitions of nanobots, using nano-tentacles, using the typical protein motor families of kinesin, dynein, and myosin, linear and rotary electrical actuators, ultrasonic sensors to prevent collisions, monitoring glucose and other nutrients using nanobots, mapping blood vessels using MRI (though we are still limited by precision capabilities), internal vs. external triggering of the nanobots, the difficulties of navigation in fluids at this scale, using chemical energy as an energy source, and discussing the problem of heat dissipation [7].

Another study on the field of nanobots defines ambitious goals and qualifications of useful bionanobots, such as automated molecule manufacturing, swarm intelligence, cooperative intelligence, self-assembly and replication, nanoinformation processing and programmability, and the nano to macroworld interface. It discusses the difficulties where nanobots adhere more to molecular and quantum physics whereas typical macrorobots adhere to newtonian physics, and even how the heisenberg uncertainty principle is more pronounced with nanobots. This review discusses combining virtual reality with nanobots, and how as of 2005 completely inorganic robots had not been realized and the focus of studying nanobots is focused on molecular nanobots [8].

Further and more recent study has discussed using nanobots for medical applications like monitoring diabetes [9], simulating nanobots in a virtual environment [10], having the nanobots behave collectively [11], propelling nanobots with ultrasound [12], and pH based movement [13]. Nanoelectronics have been fabricated using TFTs printed onto a parylene film then removed from their bulky substrate [14], grafting these nanoelectronics onto colloidal particles, using these particles powered by photodiodes to collect temporal spatial information, and bionanobots being attacked by wild-type organisms [15].

2. NANOBOT FABRICATION PROCESS

Inorganic nanobots are similar to ICs, but fundamentally different. ICs are often much bigger than 1 μm in diameter in the 2D plane, and in 3D space they are certainly much bigger than 1 μm in diameter. In the 2D plane we can easily fabricate ICs to be smaller than 1 μm in diameter, but they are printed on a silicon wafer. This silicon wafer is incredibly fragile and thick (relative to our nanometer scale). We either need to remove the excess silicon by grinding, laser cutting, or sawing. Alternatively, TFTs are incredibly thin transistors fabricated onto a substrate. We can use TFTs to fabricate nanobots by printing incredibly small ICs onto a substrate, stacking them [16], then detaching the ICs from the substrate. This concept has been used to create nanobots before, but their method involves printing nanoelectronics on parylene films, while keeping the parylene film attached [15]. While this is a step in the right direction, this parylene film is hard to manufacture thinner than 1μm, which is unacceptably large as nanobots get smaller and smaller.

To better understand this proposed nanobot fabrication process, we first need to describe the typical TFT fabrication process [1][16]:

1. Substrate preparation: the substrate is cleaned to remove any impurities
2. Deposition: a thin layer of semiconducting material, such as silicon, is deposited onto the substrate
3. Doping: the semiconductor layer is doped to control its electrical properties
4. Gate insulator formation: a thin insulating layer is deposited over the semiconducting layer
5. Gate electrode formation: a conductive material is deposited and patterned on top of the insulator to form the gate electrode
6. Source/drain formation: source and drain regions are formed in the semiconductor at the sides of the gate
7. Interlayer dielectric (ILD) deposition and contact hole formation: an insulating layer is deposited over the entire structure, then holes are etched through this layer to the source, drain, and gate areas
8. Metallization: a conductive material is deposited in the contact holes to form the interconnects
9. Passivation: the entire structure is covered with a protective layer to insulate it and protect it from damage.

To show that removing the substrate is possible and practical, this process can be described with materials already used in the TFT fabrication process: glass (typical substrate) and positive photoresist (typical photoresist used in photolithography).

By simply adding this positive photoresist after the substrate preparation step we can manufacture the nanobots using the already well-refined TFT fabrication process. With the final step of dissolving the photoresist connecting the substrate

to the TFT. This is done by exposing the photoresist through the glass substrate to UV light then using a developer solution to dissolve the photoresist. This has been done and described in the macro-scale [1]. To better illustrate this, refer to Figures 1, 2, and 3 . Figure 1 shows the current implementation of staggered bottom-gate TFT. From bottom to top layer, we have the substrate, the gate material, the insulator/dielectric, the amorphous silicon, and the source and drain. Figure 2 shows the additional removable layer between the substrate and the gate material. Figure 3 shows the final step where the removable layer has been removed and the TFT is no longer attached to the substrate.

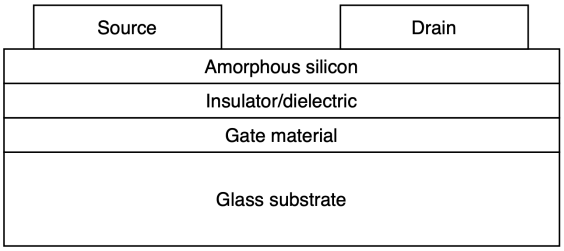

Fig. 1: Staggered Bottom-Gate TFT

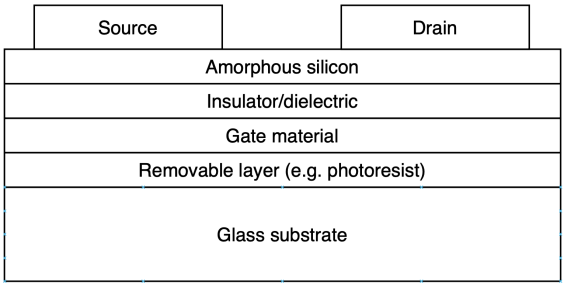

Fig. 2: Detachable Staggered Bottom-Gate TFT

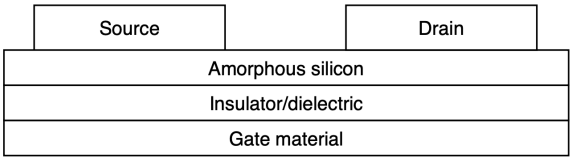

Fig. 3: Detached Staggered Bottom-Gate TFT

3. BIOCOMPATIBILITY

In order for our nanobots to be useful in the body and not immediately short circuit or get rejected by the immune system, we need a biocompatible waterproof coating for the nanobots that doesn't increase the size of the nanobots to an unacceptable extent.

There are many biocompatible materials that have been used for human implants and other biological interaction. However, few of these have been used at this scale for this purpose.

Diamond coating has been used to coat nanobots and to make them biocompatible. Section 5 discusses the process of attaching functional proteins onto the surface of the nanobots. There has been little work into this process, so another coating should be used here [6].

A well-tested and suitable coating for our purpose is polyethylene glycol (PEG). PEG is typically used at the macro-scale, so it must be used in a different method, such as layer-by-layer assembly [17].

Layer-by-layer (LbL) assembly is a nanofabrication technique used to build thin films and coatings from multiple layers of materials. The typical steps of LbL are [18]:

1. First Layer: The substrate is first immersed in a solution containing a positively or negatively charged material. The material adheres to the substrate due to Van der Waals forces, hydrophobic/hydrophilic interactions, or surface functionalization.

2. Rinse: The substrate is then rinsed to remove any excess material and non-adsorbed species.

3. Second Layer: The substrate is then immersed in a second solution containing a material of the opposite charge. This material adheres to the first layer due to electrostatic attraction.

4. Rinse and Repeat: The rinse and immersion steps are repeated alternately with the two solutions to build up multiple layers of materials.

Because PEG is a neutral polymer, it may need to be modified or used in conjunction with charged polymers to be used in LbL. One might involve functionalizing PEG with charged endgroups and using this modified PEG in an LbL assembly process. PEG can be modified to be both the first and second layer by functionalizing the PEG with oppositely charged molecules [19].

4. POWERING THE NANOBOTS

Inorganic nanobots are just small computers, so they need power. Because we cannot power the nanobots using a wire, we will have to power them wirelessly. There are a few possible ways we can do this, such as with a changing magnetic field and inducing a current [6], with light at the right frequency using antenna, using photovoltaic power with photodiodes [15], or with ultrasound [12].

The apparent easiest method of these is to use light with an antenna. Patch antennas are the best antenna for this purpose because they are the most compact antenna that can be used here. They have been used in mobile phones for many years and have been studied extensively.

The first consideration when designing an antenna is the frequency of light to use. This is a complicated function of wavelength and material, along with the fact that the human body consists of many different materials [20][21][22][23]. Because of this, determining the best wavelength to use for this application is difficult. However, we will choose one to continue our analysis: 4 GHz. 4 GHz is chosen because it has a usable penetration depth and a high enough frequency to keep the antenna small enough [24]. It should be noted that very high frequencies, such as X-rays, Γ-rays, and cosmic rays have a high penetration strength through the body. However, these frequencies of light are also ionizing and could cause problems. These high frequencies might be considered in the future, but not for now.

Any low-κ dielectic can be used, but for this initial design, we will assume a dielectric of $\epsilon_r = 3.488$ as was used in this paper [25].

We have the equation for patch antennas that relates frequency, c, length of the antenna, and ϵ_r.

$$L = \frac{c}{2 * f_c * \sqrt{\epsilon_r} * 40} = \frac{2.998E8m/s}{2 * 4GHz * \sqrt{3.488} * 40} = 500\mu m \quad (1)$$

It should be noted that the additional factor of 40 is included because the mismatch loss increases as the L/wavelength factor decreases [26].

Although 500μm is larger than most human cells, a robot of this size is undoubtedly useful for studying and curing diseases within the body.

While this is bigger than desired, there are other avenues to explore to make them smaller:

1. Increased mismatch loss to have smaller antenna
2. Internal systems supply higher frequency light to the nanobots from the bloodstream or elsewhere
3. Study into the other power mechanisms listed previously

Changing magnetic fields to control nanobots has been successful for propelling flagellated nanobots [6], so powering nanobots using changing magnetic fields may induce vibrations or unwanted movements. It should be further studied but will not be considered further here.

Photodiodes and photoelectric cells cells requires relatively high frequency light [27], which tends to be absorbed quickly into the skin [23], so that will also not be considered further here.

Ultrasound has incredible penetration into the human body, but has limited study as a power source, especially for nanobots [12].

5. ENTERING AND EXITING ANIMAL CELLS

For the nanobots to more accurately target cancerous cells, the nanobots should enter the cells. The nanobots are too large for diffusion through the cell membrane, so endocytosis is the only option to enter the cell. There are three main types of endocytosis: phagocytosis, pinocytosis, and receptor-mediated endocytosis [28]. The nanobots are too large for pinocytosis so that cannot be used here. Phagocytosis is mainly used by immune cells and can be used to target those in future work. Receptor-mediated endocytosis is the process that we will mostly be discussing here as most cancer cells use this type of endocytosis.

To perform receptor-mediated endocytosis, our nanobots must have the appropriate proteins on their surface. This can be any suitable protein designed to target any suitable receptor.

Attaching the protein to the nanobots to facilitate this receptor-mediated endocytosis is called PEGylation. The process typically follows these steps[29]:

1. Coat the surface of the nanobot with polyethylene glycol.
2. Attach a functional group, such as an amine or thiol to one end of the PEG molecule
3. Have this functional group react with the suitable protein (for ideal results, the suitable protein should react at different parts when binding to the nanobot and reacting with the cell receptor)

An improvement on this design is to have the ability to selectively allow the endocytosis. Because proteins and protein receptors are based largely on localized charges and protein receptors bind with their specific receptor, a disturbance on the localized charge would prevent endocytosis. To implement this idea on the nanobots, there can be a significant charge near the protein that disrupts the binding to the protein receptor.

Exiting the cell (exocytosis) is also a valuable capability for the nanobots. Luckily, the process of exocytosis can be triggered in a similar manner as endocytosis using the protein mannose-6-phosphate. Another way to trigger exocytosis of the nanobot is to change the charges on the nanobots [30].

6. SENSING AND INTERACTING WITH THEIR ENVIRONMENT

These nanobots need to determine whether or not they should heat their surroundings. This can have many possible interpretations and implementations, such as determining that

the surroundings are too salty, the pH is too high or low, the nanobot has interacted with too many chemicals/enzymes/proteins/etc. of a specific type in a given time period, that they are in an area that needs to be targeted, or any combination of these. All of these different scenarios can be programmed into the nanobots to selectively kill the targeted cells. Any way that humans can tell whether or not a cell is cancerous can be programmed into these nanobots.

Because these nanobots are inorganic and potentially shielded from their environment with a polymer coating, they can only interact with their environment in limited ways, such as heating (discussed in Section 7), emitting light (discussed in Section 7), or physical actuation.

Physically actuating on the nano or micro-scale in this scenario would involve can nanoelectromechanical systems (NEMS), microelectromechanical system (MEMS), or some of the more biological/chemical based systems. NEMS and MEMS are currently under study and few of the existing NEMS or MEMS technologies are of practical use in this situation [31]. However, NEMS/MEMS may be useful in the future to do things like pierce the cell membrane, measure the width of the nucleus, move the near-protein charge discussed in Section 5, etc.

7. KILLING CELLS

The cells in our body are sensitive to heat. If we raise the temperature of a single cell high enough, the cell dies. This is true for all cells, including cancer cells and bacteria cells [32]. We can use the nanobots to selectively heat the unwanted cells. The exact numbers for how long and at what temperature the nanobot needs to heat the cell need to be studied. We know that different animal cells can survive at different elevated temperatures for different lengths of time, but that is typically when the entire cell is heated at the same time. We do not know how long it takes a cell to die when a localized area is heated within the cell. Further study into quantum dots might reveal this answer as well as further study into nanobots.

To selectively heat the nanobots, we have to change the amount of power being received by them. Both the changing magnetic field and the light with antenna methods of power can achieve this heating selectivity.

For the changing magnetic field, we can create an open circuit or similar method of resisting/impeding the flow of electricity through a wire.

For the light + antenna method of power, we can have two different frequencies of light at different power. The nanobot can operate normally at the lower power frequency of light and change its antenna shape (or otherwise get power from the higher power frequency of light) to get more power and thus heat its surroundings.

Another method for the light power is to have two antenna for two different frequencies of light and to open the circuit for the high power light selectively while the low power light is still providing power to the nanobot.

Another method of selectively heating the nanobots irrelevant to their power source is to power the nanobots in pulses. This allows them to only receive the power they need and the nanobots can choose to receive more power when they want to kill their surrounding cells. This is a little more complicated, but allows for a single antenna and a single frequency of light to power the nanobots.

Another method of killing the cells is to emit ionizing light using LEDs. However, if the frequency is not high enough then the ionizing light might not kill the intended cell.

We've been focused on killing pathogens to cure diseases, but these nanobots are much more capable than just curing diseases. For example, another capability of these nanobots is to remove excess fat cells in the body. Fat cells, like any other animal cell, die when they are heated under a process called lipolysis [33]. We can use the same process to kill cancer cells to remove excess fat from the body. This is just one example, but these nanobots have endless uses besides curing diseases.

8. COMMUNICATION

Communicating with these nanobots does not require any new technology, but finding the best technology for this situation may require experimentation. Some designs to both receive power and information with a single antenna might be:

1. RF-powered communication (also called harvest-and-communicate)

   This is used today for small devices that have similar requirements to these nanobots. This is the best avenue to explore right now.

   Both reception and transmission are possible with RF-powered communication.

2. Near field communication (NFC)

   NFC uses the device's built-in clock, but these nanobots might be too small to conveniently use a clock in this manner. Clocks are typically larger than 1μm in diameter, so the nanobots require a new way of wireless communication.

3. Additional photodiodes, phototransistors, or light sensors

   We can use the antenna for power with these additional components at any wavelength using standard communication protocols.

   These additional devices can also be used for transmission of data.

The easiest way to communicate with these nanobots would be to have one power antenna and one communication antenna, which is a standard practice that wouldn't require

any new technology. However, this brings limitations on size and ability.

9. FUTURE WORK

This paper introduces a few new ideas and a few new questions. Ideas worth exploring include:

1. Detaching nano-scale TFT ICs from their substrate in the manner proposed herein
2. Attaching proteins to the nanobots
3. Introducing a nearby charge to disable proper protein interactions to selectively disable endocytosis
4. Powering the nanobots with antenna, changing magnetic fields, and ultrasound
5. Reducing the size of the nanobots
6. Designing the nanobots to sense their environment
7. Studying the temperatures necessary to kill cancer cells
8. Communicating with these nanobots
9. Using these nanobots to explore both medical and non-medical fields with precision we've been unable to reach so far

10. CONCLUSION

This paper presents a few viable methods of fabricating inorganic nanobots, making them biocompatible, powering them, enabling endocytosis, sensing their environment, killing the pathogens, and detailing the near and far future work that can be discovered from these nanobots. Inorganic nanobots have not been seen as useful in the medical field until recently. There is much to discover and many problems that can be solved using inorganic nanobots.

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