# Chapter 6

# Global Health and Environmental Implications of Mimicking Biological Ion Channels Using Nanotubes

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This chapter discusses both positive and negative impacts of synthetic nanotube devices designed to be selective to water molecules, cations (positively charged ions), or anions (negatively charged ions) for applications in medicine and the environment.

## 6.1 Introduction

Biological ion channels exist in all living cells, for example, plants, bacteria, and humans. Their function is to regulate the movement of charged particles, such as sodium, chloride, and potassium ions, across the cell membrane by providing a water-filled pore through

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which ions can pass. Ion channels regulate all electrical activities in the nervous system by allowing specific ions to move across the cell membrane (Hille, 2001). By disrupting the balance between ions in the extracellular (outside) and intracellular (inside) compartments of a cell, it is possible to damage the cellular equilibrium and even cause cell death.

Engineered channels, such as nanotubes, are far less complex than biological systems; yet, they have the ability to perform some of the functions biological ion channels carry out. Single-walled nanotubes may be manufactured from various materials, for example, carbon, boron nitride, and silicon carbide. They are ideal candidates to mimic biological ion channels because of the following reasons:

i. Their nanoscale diameter, which resembles that of biological ion channels. Ion channels have diameters of approximately 1 nm ($10^{-9}$ m). The nanotube diameter can vary depending on the fabrication method used. For example, carbon nanotubes fabricated using electric arc discharge produce diameters ranging from 1.1 nm to 1.5 nm (Farhat, de La Chapelle, Loiseau et al., 2001) and using gas-phase catalytic growth can be 0.7 nm in diameter (Nikolaev, Bronikowski, Bradley et al., 1999).
ii. The ability to precisely control their length (Wang, Liang, Wang, Zhang, and Rahman, 2007) to target cells with a specific membrane thickness. For example, gram-negative bacteria have thinner cell membranes than human cells, allowing these bacteria cells to be targeted without affecting normal cells.
iii. The fact that they can embed in the cell membrane and form an open channel spanning the entire membrane (Lopez, Nielsen, Moore, and Klein, 2004; Hilder, Gordon, and Chung, 2010).
iv. Their drastically enhanced flow of water and ions compared to biological ion channels, which will be highlighted in Section 6.2.
v. The ability to modify their surface chemistry to target specific cells, such as specific bacteria or cancer cells. For example, folate receptors are often expressed in large numbers on cancer cells compared to healthy cells. Nanoparticles with

folate receptor targeting have been successfully delivered to folate receptor–expressing cells (Hilgenbrink and Low, 2005).

In Section 6.2, we highlight recent work that illustrates the ability of various nanotubes to mimic the function of biological ion channels and thus their enormous potential in the development of novel nanoscale devices and products. Our computational work has shown that it is possible to design a nanotube with the ability to either reject all charged particles or selectively reject positive or negative ions.

In mimicking the function of biological ion channels, we may be able to fabricate nanoscale devices for various applications, including desalination, water purification, and ultrasensitive detection. Water shortage and water contamination are important global challenges. Over a third of the world's population lives in a region where water is scarce (Elimelech and Phillip, 2011), and about one-sixth of the population doesn't have access to safe drinking water (Botes and Cloete, 2010). Nanotube-based applications may provide significant benefits to both industry and local communities, such as through more efficient desalination membranes and improved access to safe drinking water. Nanotube-based devices may also enable the detection of very small concentrations of contaminants in water, such as heavy metals and bacteria. In addition, we may be able to design new pharmaceutical products for the treatment of bacterial infections, cancer, cystic fibrosis, and many other diseases. Section 6.3.1 examines the positive potential impacts of nanotube-based devices for a secure and sustainable future.

Unfortunately, since nanotubes can affect cells, they could also have negative health and environmental risks, and issues such as safe handling and disposal will need to be carefully considered. To facilitate the development of these nanotube-based devices, it is vital that we have an in-depth understanding of their impact on global health and the environment. Section 6.3.2 examines the negative implications of developing a nanotube-based device that mimics biological ion channels. The dissemination of their impact will enable policy makers and the public to make informed decisions and have a better understanding of the technology that may result from such research.

## 6.2 Mimicking Biological Ion Channels

Interest in mimicking the function of biological ion channels is rapidly gaining momentum. Several attempts have been made to design (Kalra, Garde, and Hummer, 2003; Won and Aluru, 2007; Corry, 2008; Suk, Raghunathan, and Aluru, 2008; Hilder, Gordon, and Chung, 2009a) and fabricate (Fornasiero, Park, Holt et al., 2008) nanotubes that can selectively allow water molecules to pass through, while rejecting charged particles, for application in water purification. These nanotube-based water channels have shown flow rates substantially higher than both biological water channels and currently used desalination membranes.

Recently, the possibility of engineering ion-selective nanotubes has also been explored. Ion-selective nanotube-based devices, if successfully engineered, could be used as antibiotics or could be targeted to specific cells to modify their functions or render them unviable. The placement of a rim of partially charged atoms at the open-ended entrance makes it possible for ions to surmount the energy barrier at the entrance and enter the nanotube interior. This effect has been confirmed in experiments by Majumder, Chopra, and Hinds (2005), whereby the nanotube tips were functionalized with various molecules, including negatively charged dye molecules. Moreover, various computational studies have been conducted illustrating the ability of nanotubes to be selective to both positive and negative ions (Joseph, Mashl, Jakobsson, and Aluru, 2003; Park, Sinnott, and Aluru, 2006; Hilder, Gordon, and Chung, 2009b; Won and Aluru, 2009).

The following subsections highlight recent results where we have demonstrated the possibility of mimicking various biological ion channels using nanotubes, namely, biological water channels (aquaporin), and channels selective to either positively charged or negatively charged ions. To investigate the conductance of water molecules and ions through synthetic nanotube channels we use two computational tools, (i) molecular dynamics and (ii) distributional molecular dynamics. Distributional molecular dynamics was devised by our group to study the conduction of ions across nanoscale channels at longer time scales than possible using molecular dynamics (Gordon, Krishnamurthy, and Chung, 2009; Hilder, Gordon, and Chung, 2010). Employing this computational tool enables our theoretical results to be directly compared to future experimental measurements of ion conduction.

### 6.2.1 Water Channels (Aquaporin)

We show (Hilder, Gordon, and Chung, 2009a) computationally that a boron nitride nanotube with a diameter of 0.69 nm embedded in a silicon nitride membrane is able to reject salt ions at seawater concentrations while conducting water molecules. The water flow rate is as high as 10.7 water molecules per nanosecond, or 0.93 L $m^{-2}$ $hr^{-1}$. Moreover, at the same operating pressure, the water conduction is four to five times faster than currently used premium-grade seawater reverse osmosis membranes. The boron-nitride-nanotube-embedded silicon nitride membrane we designed can, in principle, achieve 100% salt rejection. Furthermore, a unique water structure forms within the nanotube, developing from a single-file chain, as shown in Fig. 6.1, to an ordered spiral and 4-gonal tube as the nanotube diameter increases.

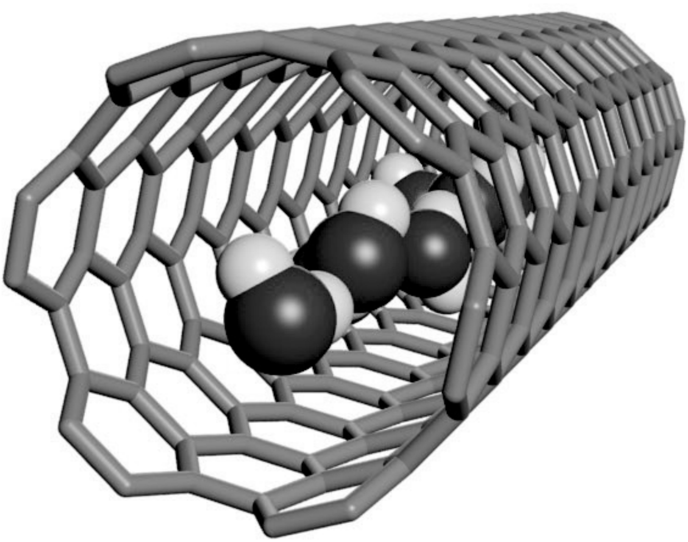

**Figure 6.1** A generic single-walled nanotube filled with a single-file chain of water molecules. Figure reprinted in part with permission from Hilder, Yang, Gordon, Rendell, and Chung (2012). Copyright 2012, American Chemical Society.

Recently, we examined the conduction of water and ions through silicon carbide nanotubes 3.6 nm in length and of various diameters, ranging from 0.9 nm to 1.2 nm (Hilder, Yang, Gordon, Rendell, and Chung, 2012). All investigated nanotubes have water conduction rates an order of magnitude higher than the biological water channel aquaporin and current reverse osmosis membranes. Moreover, Khademi and Sahimi (2011) find that silicon carbide nanotubes exhibit enhanced water flow when compared to carbon nanotubes. As expected, the water conduction increases as the nanotube radius increases, as shown in Fig. 6.2, but ions are no longer rejected. In particular, we find that a silicon carbide nanotube approximately 0.9 nm in diameter rejects all ions and has an osmotic permeability of approximately $7.34 \times 10^{-13}$ $cm^3/s$. These silicon carbide nanotubes present advantages over carbon nanotubes for ion-selective membranes since chemical functionalization of their surfaces is not required to achieve selectivity.

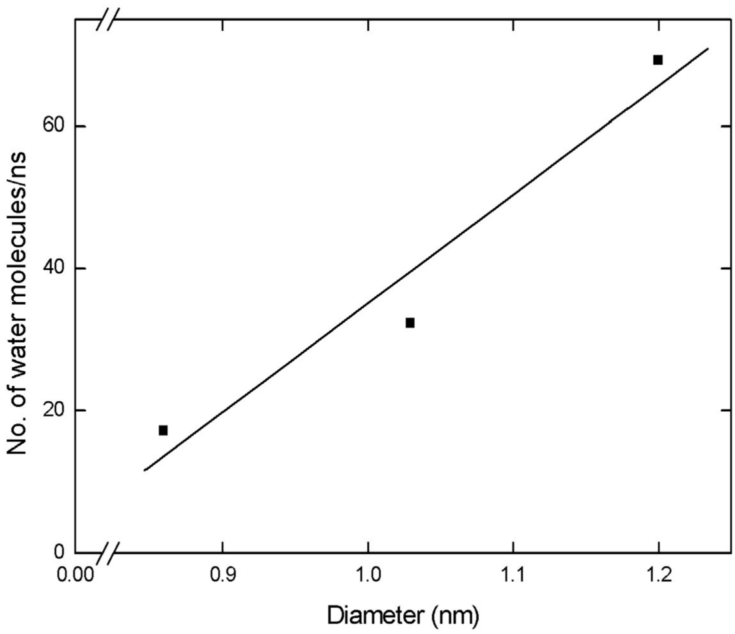


**Figure 6.2** Water conduction through silicon carbide nanotubes as a function of diameter, determined using an applied pressure of 100 MPa, 500 mM salt concentration.

### 6.2.2 Ion-Selective Channels

We have successfully designed ion-selective carbon nanotubes (Hilder, Gordon, and Chung, 2010; Hilder and Chung, 2011; Hilder, Gordon, and Chung, 2011) that are selective to either positive or negative ions, depending on their chemical functionalization and nanotube diameter. For example, terminating a carbon nanotube 0.91 nm in diameter with carbonyl (C=O) groups (Hilder, Gordon, and Chung, 2010) or a carbon nanotube 1 nm in diameter with carboxylic acid (COOH) groups (Hilder, Gordon, and Chung, 2011) makes the nanotube selective to negative or positive ions, respectively. Each nanotube is embedded in a lipid bilayer separating two reservoirs, as illustrated in Fig. 6.3 for the carboxylic acid–terminated carbon nanotube.



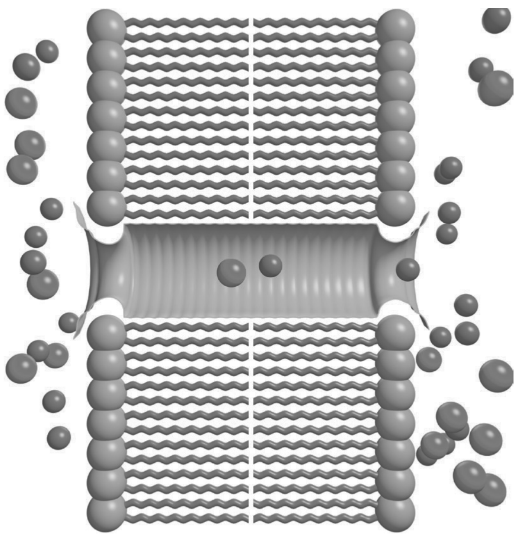

**Figure 6.3** Schematic of the computational simulation assembly for the carbon nanotube terminated with carboxylic acid embedded in a lipid bilayer separating two reservoirs containing charged particles (blue and green balls). For clarity not all ions are shown. Figure reprinted in part with permission from Hilder, Gordon, and Chung (2011). Copyright 2011, American Institute of Physics.

We show (Hilder, Gordon, and Chung, 2010) that a carbon nanotube with an effective diameter of 0.91 nm and a length of 3.4 nm terminated with carbonyl (C=O) groups is stable in a lipid bilayer and is selective to chloride ions. Confirming the results of previous work (Lopez, Nielsen, Moore, and Klein, 2004; Nielsen, Ensing, Ortiz, Moore, and Klein, 2005), we demonstrate that the nanotube is stable in the lipid bilayer. The chloride selectivity is dependent on the carbonyl groups, which generate an energy well for chloride ions at the entrance and exit of the nanotube and a large energy barrier for sodium ions. The flow of chloride ions through this nanotube is larger than through biological chloride channels. This artificial channel shows a striking resemblance to a biological ion channel and has the potential to lead to numerous drugs designed to target ion channels, for example, for treatments for antibacterial and cystic fibrosis.

Alternatively, we show (Hilder, Gordon, and Chung, 2011) that a carbon nanotube with an effective diameter of 1 nm and a length of 3.6 nm terminated with carboxylic acid (COOH) is selective to sodium ions despite both sodium and chloride encountering an energy barrier to enter the nanotube. We find that chloride ions act as chaperones for sodium ions. Once inside the nanotube interior, resident chloride ions ferry sodium ions from the entrance to the exit. A large number of sodium ions flow through the nanotube, whereas the number of chloride ions is negligible. This artificial channel resembles the mutant glycine receptor, but the sodium conductance is seven times larger.

We also examine a carbon nanotube with an effective diameter of 0.91 nm and a length of 3.6 nm, hydrogen-terminated ends, and hydrogen attached to two short regions of the exterior surface (Hilder and Chung, 2011). This nanotube is selective to monovalent positive ions (+1), such as potassium; binds divalent positive ions (+2), such as calcium; and rejects monovalent negative ions (–1), such as chloride. The characteristics of this channel closely resemble the antibiotic gramicidin but with a potassium conductance six times larger.

## 6.3 Global Health and Environmental Implications

Using synthetic nanotubes that mimic biological ion channels to fabricate novel nanodevices may result in numerous innovative products that would positively impact global health and the environment. However, it will require significant research and development before these applications reach the market. The next section outlines applications that are likely to eventuate in the next 5 years and some others that are more idealistic and may or may not eventuate in the next 15 years. Although there are many positive impacts of these potential nanotube-based devices, the negative impacts of this technology are largely unknown due to a lack of fundamental research. Section 6.3.2 highlights some of the health and environmental issues that need to be addressed before nanotube-based devices can be realized.

### 6.3.1 Positive Impacts

Nanotube-based filtration membranes have the potential to progress toward the UN millennium development goal (MDG) to halve the number of people with access to safe drinking water by 2015. Approximately 25% of the world's population is affected by water shortage (Hilder, Gordon, and Chung, 2009a). With population growth and climate change limiting the world's freshwater stores, desalination and demineralization of seawater is fast becoming a possible solution. However, over 95% of salt ions must be removed from seawater for it to be fit for human consumption. There is an urgent and genuine need to make the process of desalination more effective and less power hungry. As discussed in Section 6.2.1, synthetic nanotubes have the ability to conduct water four to five times faster than currently available reverse osmosis membranes, while maintaining a salt rejection much greater than 95%. If nanotube-based water purification membranes can be fabricated at a reasonable cost, they could act as an alternative means of supplying safe drinking water. In recent experimental work, the feasibility of using carbon nanotubes as water purification devices was demonstrated (Fornasiero, Park, Holt et al., 2008).

Higher-permeability membranes have already contributed to reducing the energy consumption of desalination and may also help reduce capital costs by reducing the membrane area needed (Elimelech and Phillip, 2011). However, to reduce energy consumption further and reduce one of the environmental impacts of desalination, it will be necessary to design fouling-resistant membranes (Elimelech and Phillip, 2011). Biofouling is the growth of microbes on the membrane surface, which results in the need to regularly clean the membrane surface to maintain its efficiency. Either nanotube-based filtration membranes could be designed such that they are coated with antibiofouling designed polymers, or the nanotubes could be directly embedded in membranes with antibiofouling and antiviral properties, such as the membranes discussed by Botes and Cloete (2010). These antibiofouling nanotube-based filtration devices would not only exhibit enhanced water flow rates and ion selectivity but also reduce the chemical cleaning requirements due to their antimicrobial surfaces.

Water contamination, such as by heavy metal ions, is one of the leading causes of water shortage (Liang, Cao, Zhang et al., 2011). One-sixth of the world's population doesn't have access to safe water (Botes and Cloete, 2010). Due to the ability to design nanotubes for specific applications, it may also be possible to ensure the removal of heavy metals or other waterborne diseases. For example, the nanotube radius could be designed to selectively remove heavy metal ions or the nanotubes could be embedded in a membrane with antiviral properties to help prevent the contamination of drinking water by waterborne viruses and bacteria. Carbon nanotube filters have already been shown to efficiently remove *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), and the polio-1 virus from water (Botes and Cloete, 2010).

The use of carbon nanotubes as single-ion detectors was recently confirmed experimentally (Lee, Choi, Han, and Strano, 2010). Therefore, in the next five years it is possible that ion-selective nanotubes will be used as ultrasensitive detection devices in much the same way that has been demonstrated with the biological ion channel gramicidin (Cornell, Braach-Maksvytis, King et al., 1997), whereby the flow of ions is prevented upon detection of a specific protein. Ion-selective nanotubes could be used to detect molecules such as trinitrotoluene (TNT) or glucose but at significantly lower concentrations than currently used detection devices. These molecules could be detected when they block the ion flow through the nanotube. As mentioned in Section 6.2.2, we have demonstrated the possibility of designing ion-selective nanotubes. In particular, we demonstrated the potential to mimic gramicidin with a potassium conductance six times larger.

A nanotube-based antibiotic that can selectively conduct either positive or negative ions across the cell membrane could be used for the purpose of killing, for example, bacteria causing meningitis and other gram-negative bacteria. It is possible to target gram-negative bacteria due to their thinner cell membranes compared to gram-positive bacteria and normal cells. The antibiotic gramicidin targets gram-negative bacteria and was one of the first antibiotics used in clinical practice. It exerts its antibacterial activity by allowing positive ions to selectively move across the thinner cell membranes of the bacteria and destroy the electric potential across the membrane, which then kills the bacterial cells (Kuyucak, Andersen, and Chung, 2001). We have demonstrated that synthetic nanotubes have the ability to be ion selective with ion conduction rates an order of magnitude larger than their biological counterparts. Moreover, synthetic nanotubes have a number of other qualities, listed in Section 6.1, that suggest they will present significant improvements as an antibacterial agent. It is unlikely that this type of nanotube-based device will be available in the next five years. However, a nanotube-based antibiotic may provide a more effective bacterial treatment in the future and, with the development of fabrication technology, will become increasingly affordable for developing countries.

Furthermore, it may one day be possible to use nanotubes to target specific cells, such as cancer cells, and destroy their membrane potential in a similar way to that described above for bacteria. Such nanotubes could have applications in the next generation of medical treatments, such as to treat cystic fibrosis, cancer, or other diseases. In addition, nanotubes that can mimic some of the functions of biological ion channels may be used in the treatment of diseases that result in ion channel mutations. For example, in cystic fibrosis, chloride channels malfunction. Thus, a nanotube such as the chloride-selective channel described in Section 6.2.2 could act as a substitute. However, these possible applications are very much futuristic ideas and much research needs to be achieved before devices such as these enter the marketplace.

## 6.3.2 Negative Impacts

There is a general consensus that pristine carbon nanotubes (i.e., with no functionalization) are toxic to cells (Cui, Tian, Ozkan, Wang, and Gao, 2005), whereas boron nitride nanotubes are considered to be nontoxic (Chen, Wu, Rousseas et al., 2009). The toxicity of pristine nanotubes is largely due to their insolubility in aqueous solutions, hydrophobicity (water-repelling nature), and tendency to clump together. However, with functionalization, carbon nanotubes can be made to be soluble (Bianco, Kostarelos, and Prato, 2005; Sayes, Liang, Hudson et al., 2006), thus reducing their cellular toxicity.

An obvious problem is how to responsibly dispose of used nanotube-based devices from both medical and engineering applications or from the excretion of nanotube-based pharmaceuticals. It is not known whether these devices may pose unwanted environmental impacts. Schierz and Zänker (2009) investigated carbon nanotubes as carriers of pollutants in the case of accidental release into the environment. They found that surface treatment of the nanotubes has a pronounced influence on their behavior in aqueous suspensions and that some treatments can enhance the binding of heavy metals such as uranium to the nanotubes. This could lead to the transport of heavy metals through natural aquatic systems and even into biological systems. On the other hand, Allen, Kichambare, Gou et al. (2008) were able to biodegrade single-walled carbon nanotubes using natural, enzymatic catalysis with natural horseradish peroxidase. Such a method could be used as a means of responsibly disposing of carbon nanotubes or as a chemical spill kit to help clean up carbon nanotubes in the environment, thus mitigating carbon nanotube environmental toxicity.

As mentioned in Section 6.3.1, one possible nanotube application is as a nanotube-based antibacterial agent. Obviously the main aim here is to kill bacteria cells, but it is not known for certain what will happen to the nanotubes once their mission is complete and the bacteria cells die. However, studies (Singh, Pantarotto, Lacerda et al., 2006) have shown that water-soluble single-walled carbon nanotubes are not retained in any of the reticuloendothelial organs (liver and spleen) and are rapidly cleared from systemic blood circulation. Moreover, the use of nanotubes as a possible substitute for malfunctioning ion channels in the body could have long-term health effects. Long-term toxicity in vitro and in vivo needs to be accurately determined before such a device could be developed.

There may also be risks associated with the fabrication of such devices to the scientists producing them, through inhalation or the skin. Some studies suggest nanotubes could be as dangerous as asbestos (Poland, Duffin, Kinloch et al., 2008). A hazardous fiber is defined by toxicologists to be thinner than 3 μm, longer than ~20 μm, and biopersistent in the lungs (Poland, Duffin, Kinloch et al., 2008). Although the nanotube-based devices proposed in this chapter are typically less than 1 nm in diameter, their lengths are much shorter (nanometer versus micrometer). However, further research needs to be done and care needs to be taken when creating nanotube-based devices.

## 6.4 Conclusions and Future Work

Through our computational studies we have shown that it is possible to design nanotubes that broadly mimic biological ion channels such that they either reject all charged particles or selectively reject positive or negative ions. Using ion-selective nanotubes in applications such as detection, desalination, and antibiotics will undoubtedly benefit global health and the environment in the future.

Nanotube-based filtration membranes have the potential to improve the efficiency of desalination by increasing water flow while maintaining salt rejection, making the water suitable for human consumption. It is possible that in the future these membranes are designed such that the nanotubes are embedded in antibiofouling and antimicrobial membranes to reduce the amount of chemical cleaning currently required during desalination. This would, in turn, reduce one of the negative environmental impacts of desalination and perhaps help it become a more accepted solution to water shortages. Moreover, nanotube-based membranes and devices may also help communities decontaminate water supplies by the removal of contaminants such as lead and *E. coli* and through detection of minute quantities of the same contaminants.

Unfortunately, there are many unknown risks associated with such devices that may result in negative impacts. To gain a better understanding of both positive and negative impacts of mimicking biological ion channels and for the successful development of such devices, it is vital that future experimental work be performed. First, it is essential that we conduct experiments to confirm our theoretical studies to illustrate the real possibility of these synthetic ion channels. Once their potential as nanodevices has been confirmed through experiment subsequent testing will be required to determine the associated risks, such as cellular and environmental toxicology. Moreover, significant advances need to occur in fabrication technology to reduce costs of nanotube-based devices so that they can be made readily available to local communities. There is endless research still to come, but the potential of these nanoscale devices is well worth the effort.

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