Polymers in Nanotechnology
NanoSonic’s Metal Rubber™ is a highly electrically conductive and highly flexible elastomer. It can be mechanically strained to greater than 1000 percent of its original dimensions while remaining electrically conductive. As Metal Rubber can carry data and electrical power and is environmentally rugged, it opens up a new world of applications requiring robust, flexible and stretchable electrical conductors in the aerospace/defense, electronics and bioengineering markets.

http://videos.howstuffworks.com/sciencentral/2938-metal-rubber-video.htm

“Today in class you mentioned "metal rubber" briefly and the graphic showed the process of dipping a polymer sheet into solutions of positive and negative ions to build up layers on the polymer. This got me thinking, can you build epitaxial layers on top of malleable polymers? and more so, can you do this by atomic layer deposition? I assume nastier deposition methods (like plasma assisted vapor deposition) would most likely destroy or heavily alter the polymer base, but the idea of vapor deposition of say hexagonal boron nitride would be neat though I'm not sure how useful. Just something my mind latched on to during lecture.”

Layer-by-layer (LBL) process takes a long time for molecule by molecule. Atom by atom will take even longer, but automation can be easily done.
Two-dimensional (2D) Materials

The atomicwise chemical approaches and reactions suitable for 2D structures. These approaches work as a “lancet” which can add, remove, and replace the desired atoms in 2D materials at will, with the rest of the atoms well preserved (Figure 1). In this way, the physical and chemical properties can be finely tuned, and various new properties can emerge. The rise in precision chemistry for 2D materials will enable a boom in relevant fields in materials science, physics, and engineering.

Figure 1. Scheme of some 2D structures enabled by precision chemistry.

Figure 2. (a) Two-step plasma-assisted chemical vapor deposition method. (b) 3D atomic structure illustration of the MoS$_2$ monolayer, Janus H–Mo–S monolayer, and Janus Se–Mo–S monolayer.

Figure 4. (a) Schematic illustration of the KCl-catalyzed growth of the 2D MoS$_2$ nanosheet. (b) Schematic illustration of the vapor-liquid-adatom-solid (VLAS) mechanism. An adatom is an atom that lies on a crystal surface.

Yang 2121, Precision chemistry in two-dimensional materials
Figure 1. (a) Chemical structures of chitosan (CH) and pectin (PT). (b) Schematic of the edible polyelectrolyte complex dip-coating process.

Figure 3. (a) Comparison of CH/PT-coated and uncoated banana ripening as a function of time. Bananas were aged under ambient conditions. (b) Comparison of CH/PT-coated and uncoated apple browning as a function of time under ambient conditions.

Cheng 2021, Edible polyelectrolyte complex nanocoating for protection of perishable produce
History of Nanotechnology
The Big Picture on Nanotechnology

The Beginning

Gerd Binnig & Heinrich Rohrer
Inventors of the Scanning tunneling microscope (STM)
Nanotechnology: Introduction

It is debatable when nanotechnology, as we now know it, began. Perhaps, we can trace the beginnings to the invention of the scanning tunneling microscope in 1980, as it and the subsequently developed atomic force microscope enabled manipulation of individual atoms and molecules.

The nanotechnology fever began when the United States launched the National Nanotechnology Initiative (https://www.nano.gov/), the world's first program of its kind, in 2000. Since then, we have been bombarded by the dazzling images and cartoons of nanotechnology, such as nanorobots killing cancer cells resembling the plot of Fantastic Voyage. Tens of thousands of articles have been published on nanotechnology, and the press feed the public a steady diet of potential advances due to nanotechnology.

Park 2913, Facing the truth about nanotechnology in drug delivery
In 1965, Gordon Moore made a prediction that would set the pace for our modern digital revolution. From careful observation of an emerging trend, Moore extrapolated that computing would dramatically increase in power, and decrease in relative cost, at an exponential pace. The insight, known as Moore’s Law (the number of transistors in a dense integrated circuit (IC) doubles about every two years), became the golden rule for the electronics industry, and a springboard for innovation. As a co-founder, Gordon paved the path for Intel to make the ever faster, smaller, more affordable transistors that drive our modern tools and toys. Even over 50 years later, the lasting impact and benefits are felt in many ways.

The Accelerating Pace of Change & Growth

The accelerating pace of change...

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agricultural Revolution</td>
<td>8,000 years</td>
</tr>
<tr>
<td>Industrial Revolution</td>
<td>120 years</td>
</tr>
<tr>
<td>Light-bulb</td>
<td>90 years</td>
</tr>
<tr>
<td>Moon landing</td>
<td>22 years</td>
</tr>
<tr>
<td>World Wide Web</td>
<td>9 years</td>
</tr>
<tr>
<td>Human genome sequenced</td>
<td></td>
</tr>
</tbody>
</table>

...and exponential growth in computing power...

Computer technology, shown here climbing dramatically by powers of 10, is now progressing more each hour than it did in its entire first 90 years.

**COMPUTER RANKINGS**

- **Analytical engine**: Never fully built, Charles Babbage's invention was designed to solve computational and logical problems.
- **Colossus**: The electronic computer, with 1,500 vacuum tubes, helped the British crack German codes during WW II.
- **UNIVAC I**: The first commercially marketed computer, used to tabulate the U.S. Census, occupied 943 cu. ft.

**Power Mac G4**: The first personal computer to deliver more than 1 billion floating-point operations per second.

...will lead to the Singularity

- **Apple II**: At a price of $1,298, the compact machine was one of the first massively popular personal computers.
- **Supersnail power of mouse in 2015**: Surpasses brainpower of human in 2023.

https://external-preview.redd.it/IHdaR-B3P5Ul0n520AVuKE_qQhBuljB44JA7GZRM.png?auto=webp&s=9ce56f8924ba75ace566c1de53d41793831c0b
https://ourworldindata.org/technological-progress
Definitions of Nanotechnology
A very good place to learn the basic of nanotechnology is the National Nanotechnology Initiative (NNI) (https://www.nano.gov/).

Nanomedicine: What are the Fundamental Concepts?

Nanotechnology has been considered as an enabling technology. If nanotechnology is such an enabling technology, however, why have nanoformulations been used only for targeted delivery to tumors? Why has none of the nanotechnology been used to treat other important diseases? Even for tumor targeting, no nanoformulations have been effective. The main problem is that nanoparticles have been simply assumed to have a targeting property. It was just an assumption based on in vitro cell culture studies.

NIH Nanomedicine website (https://commonfund.nih.gov/nanomedicine/overview) does not provide any scientific reasons or evidence why nanomedicine will be better in treating various diseases. The National Nanotechnology Initiative does not provide any scientific evidence either.

Under the section of “Fundamental concepts in nanoscience and nanotechnology”, the National Nanotechnology Initiative says, “Although modern nanoscience and nanotechnology are quite new, nanoscale materials were used for centuries. Alternate-sized gold and silver particles created colors in the stained glass windows of medieval churches hundreds of years ago. The artists back then just didn’t know that the process they used to create these beautiful works of art actually led to changes in the composition of the materials they were working with”.

It is well known that Michael Faraday was fascinated by the ruby color of colloidal gold (https://link.springer.com/content/pdf/10.1007/BF03215598.pdf). The size of colloidal gold particles ranges from a few nanometers to micrometers. Does this mean that the current nanotechnology is simply a rehash of the hundreds-year old technology? Then, what does nanotechnology really mean? The National Nanotechnology Initiative further describes, “Nanotechnology is not simply working at ever smaller dimensions; rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale” (https://www.nano.gov/nanotech-101/special). It continues, “Nanoscale materials have far larger surface areas than similar masses of larger-scale materials. As surface area per mass of a material increases, a greater amount of the material can come into contact with surrounding materials, thus affecting reactivity”. The larger surface area of nanoscale materials has a few advantages in drug delivery, but it still does not explain how nanotechnology, or nanomedicine, brings new properties that traditional drug delivery systems do not have, and thus improved treatment.
Definitions of Nanotechnology and Nanomedicine

The term “nanotechnology” was defined as “science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers” (https://www.nano.gov/nanotech-101/what-definition).

The term “nanomedicine” refers to “highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve”. It is further explained that “It is at this size scale - about 100 nanometers or less - that biological molecules and structures operate in living cells” (https://commonfund.nih.gov/nanomedicine/overview).

These definitions sound magnificent and futuristic, but closer examination of the definitions to acquire better understanding makes it confusing. First, if the matter we are dealing with is larger than 100 nm, is it not qualified to be called nanotechnology? What are the scientific criteria that set the boundary at 100 nm? Would it make a sense, if the size is limited to 200 nm, 300 nm, or larger?

Second, the description of nanomedicine is so generic that the term “nanomedicine” can be easily named by others, e.g., “molecular medicine”. After all, if medical interventions are made at the molecular level, isn’t it better to call it “molecular medicine”? If engineering occurs at the molecular level, isn’t it what we call chemistry, biochemistry, and molecular biology? The prefix “nano” has dominated the science throughout the world with no particular rationale; just like the prefix “i” dominated the market since the successful introduction of iPod. It is this arbitrary, generic definitions of nanotechnology and nanomedicine that set the stage of a decades-long stray from the otherwise more productive, useful, and practical path. Even nowadays, many scientists, engineers, and clinicians who are not familiar with the drug delivery field think that nanotechnology or nanomedicine, will solve their research problems regardless of the nature of the problems.

In drug delivery systems, there are not many systems that are truly less than 100 nm in size. The drug delivery systems exist to deliver a drug, and the system less than 100 nm does not have enough reservoir space for effective drug delivery. Most polymer micelles, which are one of the main representatives of nanomedicine, are much larger than 100 nm, especially after a drug is loaded. The drug delivery systems are usually larger than 100 nm by necessity, but they are not really nanosystems according to the definition provided by the National Nanotechnology Initiative [14]. What nonsense! More correctly, what nano-nonsense!

For the drug delivery field the definition of nanomedicine described by the FDA may be more relevant. According to the FDA Guidance for Industry regarding nanotechnology products, nanomaterials are defined as materials that have at least one dimension in the size range of approximately 1 nm to 100 nm (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology). This follows the definition by the National Nanotechnology Initiative. The FDA, however, chose to include a much broader meaning of nanomaterials by asking “Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)”. This definition is very forgiving in the size limitation, and indeed many products can fall into the definition of the nanotechnology product. This is why when drug products containing nanomaterials in the U.S. were analyzed, more than 350 products were shown to contain nanomaterials (https://www.nature.com/articles/nnano.2017.67). This number, however, is misleading, because the number is based on mostly traditional formulations, such as liposome, emulsion, and drug crystals which were introduced several decades ago.

Look at the Data, Nothing Else

To understand why and how we ended up where we are now, we need an “independent” examination. The term “independent” here means an impartial approach between “confirmation bias” and “negativity bias”. A mind with a confirmation bias seeks out data that support the preconceived idea, while a mind with a negativity bias does the same with the opposite goal.

Talking about the truth and criticizing something that most believe is difficult. Quite often, those who criticize the mainstream idea are labeled as pessimistic or politically motivated, as if science has to rely on the majority opinion or blind optimism. Accurate data interpretation has nothing to do with one’s feeling. If the data point to a different direction from the expected, a new direction should be explored. This is of course assuming that the data are not fake. In his book “Only the Paranoid Survive”, Andy Grove pointed out that an industry going through a strategic inflection point follows a sequence of denial, anger, bargaining, depression, and ultimately, acceptance (Only the Paranoid Survive). Going through an unknown future requires an accurate grasp of the reality, identification of the source of the problems, and preparation for the future. Only those with an independent mindset can go through such due diligent work, because they are not biased and not influenced by internal and external factors.
Think, Think, and Think

Then, You Will Become Better than the Most.
Scientists are supposed to have a clear, open mind just following the data, and should not fall into the populism and the fashion. At the height of the nanofashion, many started adding the prefix 'nano' to almost all words in the dictionary.

Does anybody know what 'nanoage' means? Or 'nanoworld'? Isn't nanocomponent called atom or molecule?

When iPod was first introduced and became hugely popular, almost all product names in Walmart began with 'i', such as iFlower, iChair, etc.

Simply changing the name to more fancy names, like including "i' or 'nano', does make things better.

How about “iNano”? iNanoBME
Trust Scientists? Earn the Trust

America and many countries around the world have systematically downplayed the importance of science for the special interest groups who increase their political power through dismissing science and promoting their agendas. Even then, the trust in scientists is as high as that in the military. It is not surprising that the trusts in business leaders and politicians are very low. Scientists need to work hard to tell the truth and improve the public's trust to close to 100%. Telling the truth based on accurate data is the best weapon scientists have.

---

**Americans’ trust in military, scientists relatively high; trust in media, business leaders, elected officials low**

% of U.S. adults who say they have ___ of confidence in each of the following groups to act in the best interests of the public

<table>
<thead>
<tr>
<th>Group</th>
<th>A great deal</th>
<th>A fair amount</th>
<th>Not too much</th>
<th>No confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The military</td>
<td>33%</td>
<td>46%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Scientists</td>
<td>21%</td>
<td>55%</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>K-12 principals and superintendents</td>
<td>13%</td>
<td>63%</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>Religious leaders</td>
<td>13%</td>
<td>39%</td>
<td>32%</td>
<td>14%</td>
</tr>
<tr>
<td>The news media</td>
<td>5%</td>
<td>33%</td>
<td>40%</td>
<td>21%</td>
</tr>
<tr>
<td>Business leaders</td>
<td>4%</td>
<td>37%</td>
<td>44%</td>
<td>14%</td>
</tr>
<tr>
<td>Elected officials</td>
<td>3%</td>
<td>24%</td>
<td>54%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Note: Those who gave other responses or who did not give an answer are not shown

PEW RESEARCH CENTER

Why We Must Rebuild Trust in Science

A scientific endeavor that is not trusted by the public cannot adequately contribute to society (February 9, 2021, By Sudip Parikh)

Despite failures in our public health response to the pandemic, the biomedical research enterprise has never worked more quickly than during its quest to understand and address COVID-19. While basic researchers work around-the-clock to answer fundamental questions about the coronavirus’ structure, transmission, and impacts, clinicians and physician scientists are testing therapeutics and vaccines.

One element is absolutely critical to the success of our mission to improve the human condition: trust. It’s a foundational element of any relationship, but for the mutual benefit of the scientific enterprise and the people who support it, trust is essential. Simply put, a scientific endeavor that is not trusted by the public cannot adequately contribute to society and will be diminished as a result. The COVID-19 pandemic presents us with just such an example. Late last year two of the vaccine candidates in clinical trials demonstrated safety and effectiveness in preventing infection of the virus that causes COVID-19. Although this was a remarkable accomplishment on its own, manufacturing and delivering these vaccines to the world’s population will be an enormous challenge. To further complicate this situation, a public that is generally trusting of scientists and health professionals is receiving vastly different information, guidance, and recommendations based on its news consumption, political leaders, and geography. A September 2020 Pew Research Center survey found that Americans were evenly divided as to whether they would get a vaccine to prevent COVID-19 if one were available now.

Importantly, it is not enough to say the public should trust scientists because we know better or because we know more. Trust must be earned. Unfortunately, science and scientists have not consistently earned and nurtured this trust. In some respects, this is the result of the advancement of the scientific enterprise. Science in the 21st century is much more removed from daily life because of the necessity of speaking with precision by using technical terms and jargon.

The COVID-19 pandemic will not be the last time that science will be essential to society’s triumph over existential threats.

The practice of science is messy. Hypotheses are put forward and tested. Understanding evolves and comes in fits and starts. The trial and error in research methodology and the repetitive testing in laboratories are often hidden behind the end products of scientific research - a new treatment, a new piece of technology, a new or revised piece of public health guidance - without the public seeing the puts and takes that are required along the way. When that process is then seen in real time, as we’re all experiencing during the COVID-19 pandemic, the public has little context for updates in public health guidance, such as the change to recommending wearing face masks to limit and prevent infection.

More disturbingly, science has sometimes lost the trust of the public through researchers’ own painful missteps and blatant violations of that trust. Science, engineering, and medicine are not immune to the discrimination, subjugation, and silencing of marginalized people and voices. We have too often been unwitting perpetuators of the status quo, and the reasons are deeply ingrained in the systems that govern our society.

At the same time, increased political polarization and an outspoken faction of Americans who distrust experts, including scientists who develop evidence-based findings that may challenge closely held opinions, have also widened the gap between Americans’ trust in science and scientists. Science is not just for the few. It is for everyone and can be used by anyone.

Why are Americans so slow to get booster shots?

The New York Times (February 7, 2022, By David Leonhardt)

The enemy of the good
The United States has a vaccination problem. And it is not just about the relatively large share of Americans who have refused to get a shot. The U.S. also trails many other countries in the share of vaccinated people who have received a booster shot.

In Canada, Australia and much of Europe, the recent administering of Covid-19 booster shots has been rapid. In the U.S., it has been much slower. The booster shortfall is one reason the U.S. has suffered more deaths over the past two months than many other countries.

Two explanations
What explains the American booster shortfall? I think there are two main answers, both related to problems with the American health system.

First, medical care in the U.S. is notoriously fragmented. There is neither a centralized record system, as in Taiwan, nor a universal insurance system, as in Canada and Scandinavia, to remind people to get another shot. Many Americans also do not have a regular contact point for their health care.

The second problem is one that has also bedeviled other aspects of U.S. Covid response: Government health officials, as well as some experts, struggle to communicate effectively with the hundreds of millions of us who are not experts. They speak in the language of academia, without recognizing how it confuses people. Rather than clearly explaining the big picture, they emphasize small amounts of uncertainty that are important to scientific research but can be counterproductive during a global emergency. They are cautious to the point of hampering public health. As an analogy, imagine if a group of engineers surrounded firefighters outside a burning building and started questioning whether they were using the most powerful hoses on the market. The questions might be reasonable in another setting — and pointless if not damaging during a blaze. A version of this happened early in the pandemic, when experts, including the C.D.C. and the World Health Organization, discouraged widespread mask wearing. They based that stance partly on the absence of research specifically showing that masks reduced the spread of Covid. But obviously there had not been much research on a brand-new virus. Multiple sources of scientific information did suggest that masks would probably reduce Covid’s spread, much as they reduced the spread of other viruses. Health officials cast aside this evidence.

Tests, vaccines, boosters
Similar problems have occurred since then, especially in the U.S.: (1) slow to give formal approval to the Covid vaccines, (2) slow to approve rapid tests, and (3) slow to tell people who had received the Johnson & Johnson vaccine to get a follow-up shot.

In the U.S., some officials and experts continue to raise questions about whether the evidence is strong enough to encourage boosters for younger adults. Two top F.D.A. officials quit partly over the Biden administration’s recommendation of universal boosters. The skeptics say they want to wait for more evidence.

I don’t fully understand why statistical precision seems to be a particularly American obsession.
Self-Assembly

Life began with self-assembly.
Natural Systems

Efficacy and Simplicity at the Molecular Level (Bottom-up)

↓

Survival

↓

Biological Needs

In nature, bottom-up approaches are achieved through self-assembly of molecules. No matter how small or large a structure is, it must have a building block. If building blocks are assembled by themselves, it can be called self-assembly. But if the building blocks have to be assembled by external forces, it cannot be called self-assembly.

Bottoms-up Approach: Building brick by brick the Great Wall (>20,000 km long) or the Great Pyramid (230 m x 230 m x 147 m).

Synthetic Systems

Efficiency and Selectivity at the Macro Level (Top-down)

↓

Miniaturization

↓

Clinical Efficacy
TABLE 1. Synthetic and Biological Building Blocks Used in Supramolecular Self-Assembly for Obtaining Diverse Complex Structures and Their Potential Biomedical Applications.

<table>
<thead>
<tr>
<th>Building Blocks</th>
<th>Supramolecular Assemblies</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synthetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear (e.g., block-co-polymers)</td>
<td>[Diagram of various polymers]</td>
<td>Nanoreactors; artificial organs (e.g., nanohydrogels)</td>
</tr>
<tr>
<td>Branched (e.g., dendrimers)</td>
<td>[Diagram of various dendrimers]</td>
<td>Nanocarriers for drug and gene delivery</td>
</tr>
<tr>
<td><strong>Surfactants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anionic</td>
<td></td>
<td>Drug and gene delivery systems; antimicrobial and antifungal activity</td>
</tr>
<tr>
<td>Neutral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cationic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptides</td>
<td></td>
<td>Drug delivery; hydrogel formation</td>
</tr>
</tbody>
</table>

| **Biological**  |                           |              |
| Viruses         |                           | Biomaterials; cell culture substrates |
| Nucleic acids   |                           | Therapeutics (vehicles for drug delivery; diagnostics (biosensing)) |
| Lipids          |                           | Membranes; liposomes |
| Saccarides      |                           | Drug delivery; biosensors |
| Peptides        |                           | Hydrogel biomaterials; drug delivery; tissue engineering; 3D cell culture |


FIGURE 4. Length scales of the forces involved in self-assembly (first panel) and the hierarchical complex structures generated by peptide self-assembly (second panel). Spectroscopy and microscopy techniques used for structural characterization of peptide molecules and assemblies from the nanometer to centimeter length scales (third panel). NMR, nuclear magnetic resonance; X-ray, X-ray diffraction; CD, circular dichroism; AFM, atomic force microscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy.
Self-Assembly

**Self-assembly is the process by which individual components arrange themselves into an ordered structure.** While sufficiently broad to include crystallization of atomic solids, the term is generally reserved for building blocks not linked together via covalent bonds but ordered through weak forces (e.g., van der Waals, hydrogen bonding) or hard-particle (e.g., excluded volume) interactions. Following this classification, examples of self-assembled structures include DNA, proteins, lipid vesicles, block copolymer melts, opals, and nanocrystal superlattices. Self-assembly can also make use of external forces such as electric/magnetic fields or fluid flows, but the term does not extend to serial manipulation of building blocks (e.g., dragging individual particles into position).

---

**Figure 2.** Nanocrystal self-assembly is a process that involves control over several length scales. The nanocrystal core (typically 1–100 nm across) is surrounded by a layer of surface ligands (with length typically between 1 nm and up to tens of nanometers). The assembly environment can be used to control interparticle interactions and impart geometric constraints with characteristic length scale exceeding nanocrystal size. The resulting superstructures are typically produced with domain size falling between 1 μm and several millimeters. Details about the nanocrystal composition, assembly conditions, and references for the systems shown in this figure are given in Table 1.

10.3 PRINCIPLES OF SELF-ASSEMBLY

Self-assembly is the reversible and cooperative assembly of predefined parts into an ordered structure, which assembles with no external influences after the initial trigger. Currently, self-assembly has been broken down into two categories: static and dynamic. **Static self-assembly** refers to systems at equilibrium which do not dissipate energy. The formation of the nanostructure may require energy, but the structure is stable once it has been formed. **Dynamic self-assembly** refers to the formation or patterning of structures when the system does, in fact, dissipate energy.

Self-assembly in materials relies on the fact that the fluctuations in the orientation and position of the molecules or particles due to random movements have energies in the order of thermal energy. Thermal energy has a significant impact on materials on the nanoscale as non-covalent bonds are often broken and reformed in a new manner. Due to these non-covalent interactions between molecules, structure changes can be obtained by changes in the conditions provided for the molecules. For instance, temperature and pH changes help to initiate the transition of a structure to another.

Fig. 1. Graphical rendition of static and dynamic self-assembly and how they relate to co-assembly, hierarchical assembly and directed assembly.


10.3.1 NON-COVALENT INTERACTIONS

In order for self-assembly to occur, the non-covalent forces between the molecules need to be broken and reformed. In doing so, the molecules are not changed chemically, but are structured in a different orientation. The weak intermolecular interactions that govern molecular ordering in materials include hydrogen bonds, ionic interactions, dipolar interactions, van der Waals forces, and hydrophobic interactions.

Hydrogen bonding is especially important in biological systems. Protein structures in water are held together by hydrogen bonds (Kelsall et al., 2005). Hydrogen bonds are weaker than covalent bonds (about 20 kJ/mol compared to about 500 kJ/mol for hydrogen bonds and covalent bonds, respectively) (Kelsall et al., 2005). As a result, structures can self-assemble without chemical reactions needing to occur, and the bonds are strong enough to hold the structures together once they have been formed.

Dipolar interactions follow the same principles as hydrogen bonding, except they are not limited to just hydrogen atoms. Dipolar interactions refer to the direct interactions between two magnetic dipoles. The dipoles are a result of the difference in electronegativity within molecules creating partial positive and negative charges within the molecule.

The van der Waals forces are the sum of the attractive or repulsive forces between molecules—other than those due to covalent bonds. The forces include those between a permanent dipole and a corresponding dipole, as well as the London dispersion forces.

The hydrophobic effect arises when a nonpolar solute is inserted into water. The hydrophobic effect is attributed to the ordering of water molecules around a hydrophobic molecule. The ordering leads to a reduction in entropy (Kelsall et al., 2005). The entropy loss can be offset when association of hydrophobic molecules into micelles occurs, as this results in an increase in entropy.
Self-Assembly

10.3.2 INTERMOLECULAR PACKING

At higher concentrations, the packing of block copolymer or amphiphilic molecules in solution leads to the formation of lyotropic liquid crystal phases (Kelsall et al., 2005). These crystal phases include cubic-packed spherical micelles, hexagonal-packed cylindrical micelles, lamellae, and bicontinuous cubic phases. The phase that forms is dependent on the curvature of the surfactant–water interface. To understand the lyotropic phase behavior, there exist two approaches. The first approach computes the free energy associated with curved interfaces; the curvature is analyzed using differential geometry, while not incorporating details of the organization of the molecules. The second approach uses a molecular packing parameter to describe the interfacial curvature.

Fig. 1. Schematic representation of the lyotropic liquid crystalline phases commonly found in neutral lipid/water systems. (a) Lamellar phase (b) reverse hexagonal phase (c) reversed micellar cubic of Fd3m (d) reversed bicontinuous cubic (Im3m) (e) reversed bicontinuous cubic (Pn3m) (f) reversed bicontinuous cubic (Ia3).


Fig. 2. Schematic representations of common structures and their corresponding CPP: bicontinuous cubic (Ia3).
Self-Assembly of Virus

Viruses infect cells in all kingdoms of life and, from a physicochemical perspective, can be regarded as molecular machines that have successfully evolved to spread between related organisms. They hijack their host cell's machineries in a highly efficient and minimalistic manner, in order to ensure their propagation. The molecular mechanisms behind the viral life cycle are not only complex, these processes also require a remarkably low number of essential viral components to be successful.

FIGURE 1 Assembly of empty particles through the nucleation, growth, and completion pathway. (a) Schematic representation of the free energy profile of the nucleation-and-growth/elongation pathway: first, nuclei are formed; then, the reaction proceeds downhill until the complete closure of the capsid. (Reprinted with permission from Michaels, Bellaiche, Hagan, and Knowles (2017)). (b) Self-assembly model proposed for MVM empty capsids based on the sequential addition of trimeric subunits, or CBBs (capsid building blocks). (Reprinted with permission from Medrano et al. (2016)). (c) MVM particles imaged by TEM (left): light blue, Types I + II particles (complete capsids); green, Type I (complete capsids in basal state); magenta, Type II (complete rearranged capsids); blue, Type IIIA (large incomplete capsids); red, Type IIIB (smaller incomplete capsids). Progression of the total number of particles during disassembly (left graph) and assembly (right graph) over time. (Reprinted with permission from Medrano et al. (2016)).
Self-Assembly to Generate Complex Structure

Only some selected classes of chemical compounds are capable to lead to useful self-assembled structures. Amphiphiles, simultaneously possessing polar and apolar moieties within their molecular architecture, can give a wide scenario of possible intermolecular interactions: polar–polar, polar–apolar, apolar–apolar interactions, eventual directional H-bonds, steric hindrance and so on. This peculiarity efficiently triggers the possibility of originating complex behavior, i.e., the formation of interacting structures at hierarchical length-scales characterized by emerging and specific properties and functions. However, if one places in a becher the molecules constituting a living cell, he does not observe the formation of a living cell even after vigorous and prolonged stirring and/or heating. This consideration suggests that the building up of complex structures is not only an affair of molecular structure, system composition and self-assembling processes but additional subtle features can contribute to the overall process.

Fig. 3. Different mechanisms for complexity generation. (a) the building blocks are assembled through soft interactions. The structure formation is reversible and usually temperature-dependent. The assemblies show emerging properties with respect to those possessed by their constituents. (b) the building blocks are assembled in such away to template or to drive the formation of successive structures. See for example nanoparticle synthesis through the use of microemulsions. (c) the building blocks are assembled through strong interactions. Such structures are less sensitive to temperature changes and may be needed for the preparation of building blocks for the formation of complex structures of successive level of complexity.

Fig. 4. The aggregation of amphiphiles can give supra-structures with various dimensionalities: 0D (micelles) 1D (cylinders or cylindrical micelles), 2D (lamelles). The structures can be reversed (upper panel) or direct (lower panel) depending on the polarity of the solvent. In apolar solvent reversed structures are formed, in polar solvent direct structures are the stable ones.

Calandra 2015, How self-assembly of amphiphilic molecules can generate complexity in the nanoscale.

The self-assembly events that led to the first minimal cell and genome capable of growth and division are highly debated. Fig. 1 is a proposed sequence of major events that may have occurred initially at a molecular level and then progressed to a nanocell level and finally to the bacterial cell dimensions (μm) that we know today. In this review we will examine the major self-assembly events for cells as outlined in Fig. 1. We will also discuss the possibility that nanobacteria, which are small spherical and ovoid structures discovered in rocks and minerals, may be the fossil evidence of the earliest life forms on Earth and outer space. Fig. 1 also indicates a role for extraterrestrial inputs which may have included living spores.
Miniaturization

https://defense-update.com/20101231_miniature_weapons.html
https://www.defenceiq.com/defence-technology/articles/nano-drone-tech-is-advancing
Prey- Written by Michael Crichton
Illustrated by Will Staehle, Reviewed by Matthew W. (age 10, 4th Grader))

Have you ever heard of a nano particle? Well Prey is about a company called Xmos that develops nano technology and creates nano particles. Nano particles are micro super computer robots capable of intelligent life. Jack (a father of three kids who had been working at Xmos but was fired several weeks ago) has been asked to come back to Xmos by his best friend, Ricky. Ricky says that they have a runaway swarm of nano particles. After several days at Xmos, Jack gets suspicious of his wife, Julia, who is working to solve the mystery as well. She is acting very strangely toward him and Jack wants to know what's wrong. What Jack doesn't know is that the answer could get him killed!

I highly recommend this book. The plot was fantastic and exiting. I was never bored because the book moved fast and there was always an adventure going on. Jack was very interesting. His brightness and curiosity helped solve the mystery. He knows a lot about computers and he saves many lives. The book was scary and strange. I do not recommend this book for all ages. Unless you are a good reader and your parents will let you read it you should not read this book. If you read it, I hope you like it.

I recommend this book to boys who like scary and weird books. You can find this book at your local library. I hope you like it!
Nanomaterials: From Natural To Synthetic
Nanostructures in Nature

An overview of the hierarchical nature of the gecko adhesive system. (A) A ventral view of a tokay gecko on glass, showing the toe pads. (B) Lamellae on the gecko toe pads. (C) The setae that make up the lamellae. (D) The flattened tips of branched setae (spatulae).

https://jeb.biologists.org/content/219/7/912.figures-only

Figure 7: (A) Photograph of peacock feathers showing various colors and patterns. (B) Cross-sectional SEM images of the transverse (top) and longitudinal (bottom) sectionals of green barbule cortex [196], copyright 2012, Royal Society of Chemistry.

Figure 8: The macro- and microstructure of bone and its components with nanostructured materials employed in the regeneration of bone. (a) Macroscopic bone details with a dense cortical shell and cancellous bone with pores at both ends. (b) Repeating osteon units within cortical bone. (c) Collagen fibers (100–2000 nm) comprised of collagen fibrils [254], copyright 2015, Springer Nature.

Jeevanandam 2018, Review on nanoparticles and nanostructured materials
Diatoms are single-celled algae that live in houses made of glass. They are the only organism on the planet with cell walls composed of transparent, opaline silica. Diatom cell walls are ornamented by intricate and striking patterns of silica. Diatoms turn energy from the sun into sugar. Diatoms produce 50% of the air we breathe. Diatoms remove carbon dioxide (CO2) from the atmosphere. Diatoms are food for the entire food web.
Nanostructures in Nature: Planktonic Diatoms

By definition, plankton are waterborne animals or plants that cannot swim against an ambient current. For the most part they float, although some can maneuver as long as they “go with the flow.” Phytoplankton are single-celled plants. The largest can be divided into three groups: coccolithophorids, diatoms, and dinoflagellates. The exterior of the coccolithophorid, a Syracolithus quadriperforatus, is made of calcium carbonate, the stuff of chalk. By contrast, the shell of the diatom Cyclotella pseudostelligera is silica, the material that makes up sand, glass, and quartz. Coccolithophorids and dinoflagellates are largely marine plants, meaning they live in salt water. Diatoms exist in both fresh and brackish environments. The oldest diatom fossils are about 140 million years old, leading some scientists to speculate that they evolved along with the ascent of terrestrial grasses, which released silica into the sea after separating it from minerals. | SEM scan courtesy of Markus Geisen.

Plankton are literally at the bottom of the food chain, a source of nourishment for virtually every animal in the sea. They are ancestors to terrestrial plants, which seem to have evolved from certain ocean phytoplankton hundreds of millions of years ago.

Scanning electron microscope (SEM) images show that they can be arrestingly beautiful. Coccoliths are not always round, flat plates, like hubcaps; many look like trumpets, cabbage leaves, daisies, or stars.

https://www.discovermagazine.com/environment/plankton-planet
From Nature to Fabrication

Fig. 1. The typical self-cleaning surfaces in nature and their SEM images. The droplets of water on the surfaces can roll off following a preferential direction dictated by the structural features.

Fig. 2. Image and SEM images of lotus leaf surface. (a) A fresh lotus leaf in nature, (b) the micro-structure of lotus leaf, (c) the nano-structure of lotus leaf, (d) the micro-structure of annealed lotus leaf, (e) the nano-structure of annealed lotus leaf, (f) a droplet placed on an untreated lotus leaf, and (g) a droplet placed on an annealed lotus leaf, then tilted to an angle of 90°. (Scale bar: (b and d) 10 μm, (c and e) 3 μm).

Fig. 6. Droplet on the fabricated micro/nano roughened hierarchical surface. (a-c) Nano-scaled roughness etched by XeF2 gas that conformally covers the micro-scale array of pillars fabricated through deep reactive etching. (d-e) Droplet sitting on the double roughness with the value of the pillar spacing to width ratio at 7.5, supported by only several pillars. The contact angle at this state is 173°. (Scale bar: (a) 50 μm, (b) 10 μm, and (c) 2 μm).

Electrochromics

Innovation in electrochromics

Bioinspired Dynamic Camouflage from Colloidal Crystals-Embedded Electrochromics

Ke Chen
Synthetic biology centers on the design and modular assembly of biological parts so as to construct artificial biological systems.

Figure 1. Philosophy of synthetic biology. From the perspective of a synthetic biologist, all biology is decomposable into modular biological parts which can be synthesized, characterized, and rearranged like LEGO bricks to create functional systems. A few examples of biological parts are plasmids, chromosomes, coding sequences, transposons, protein domains, and inverted terminal repeats. Synthetic biologists also employ chassis, which are existing biological systems that incorporate edits and parts. Two canonical examples of chassis are E. coli and S. cerevisiae. The Ad represents another important chassis system.

Collins 2021, Synthetic biology approaches for engineering next-generation adenoviral gene therapies

Figure 2. Synthetic biology strategies to help mitigate the immunogenicity of Ads. (A) Structure of the Ad capsid and its external components. Three more structural proteins (not shown) can be found on the inner surface of the Ad capsid: pIIIa, pVI, and pVIII. (B) The Ad hexon includes seven highly immunogenic HVR sequences. Replacing these sequences with versions from rare Ad serotypes such as Ad4812 can mitigate immunogenicity since the human body has fewer antibodies against rare Ad serotypes. (C) Insertion of an albumin binding domain (purple) into the hexon protein has sterically shielded the Ad from neutralizing antibodies by sequestering serum albumin upon injection.38 (D) Encapsulation of the entire Ad inside of erythrocyte-derived membrane has protected the Ad from immunological assaults.39 To facilitate tissue targeting, glycoporphin proteins with an NGR tripeptide have been included in the encapsulating membrane.
Nano (Maybe Pico) Camouflage Technology
Invisibility — like time travel, teleportation, flying, and super-speed — has been a fixture in science fiction ever since science fiction has existed. The most well-known examples range from the one used by the Romulans in Star Trek, Harry Potter’s deathly hallows cloaking device, and the elven cloak Frodo and Sam used to evade Sauron’s army at the gates of Mordor.
Human Camouflage

@rody_eug1, TikTok

https://www.proapto-camouflage.com/neuropsychology-of-camouflage
Invisibility in Real World through Camouflage

Tasseled Anglerfish

Cuttlefish

Leafy Sea Dragon

Trumpetfish

Reef Stonefish

http://ocean.nationalgeographic.com/ocean/photos/undersea-camouflage/#/camouflage05-trumpetfish_13511_600x450.jpg
Invisibility in Real World

Octopus Camouflage
An amazing transformation of colors that match with the background in a matter of seconds.

http://www.youtube.com/watch?v=eS-USrwUFoA
Invisibility in Real World

**Octopus Camouflage**

It is even more amazing that octopus is color blind.

http://www.youtube.com/watch?v=eS-USrwuUfA

TikTok. @oceanwild247
My Octopus Teacher (Netflix 2020)

A filmmaker forges an unusual friendship with an octopus living in a South African kelp forest, learning as the animal shares the mystery of her world (1:05:34)
Almost Instant Changes in Color, Pattern, and Shape of the Skin

Cephalopods (Squid, Octopus, Cuttlefish) have several tricks for blending in with their undersea surroundings: they can change color, pattern and even the shape of their skin.

http://www.youtube.com/watch?v=eS-USrwuUfA

Cuttlefish-inspired smart camouflage could make for sneakier soldiers. The US Army has pondered the development of camouflage that mimics how cephalopods rapidly change their colour and patterning. They call it 'signature management'. By Stilgherrian | February 12, 2020

For some time, engineers have been experimenting with robotic tentacles modelled on the octopus. Now they're being inspired by their camouflage. Cephalopods -- cuttlefish, octopus, and squid -- are renowned for their ability to rapidly change their skin colour and patterns to match their surroundings or warn off attackers. Their skin is studded with sacs full of pigment called chromatophores, each one surrounded by 18 to 30 muscle fibres that can rapidly change how much pigment is exposed. It also seems that the skin itself is somehow "smart" and can, in some circumstances, work independently from the animal's brain.

According to Alon Gorodetsky Associate Professor of Chemical and Biomolecular Engineering at the University of California, Irvine, understanding these biological capabilities could inspire the engineering of dynamic materials for military camouflage applications. That could include reconfigurable infrared (IR) camouflage coatings and IR invisibility covering -- something that's of increasing importance as more IR sensors are deployed on the battlefield. Gorodetsky and his colleagues have already demonstrated the potential of such a "dynamic thermoregulatory material" which was inspired by squid skin. "We draw inspiration from the static infrared-reflecting space blanket and active colour-changing squid skin to design and develop a tuneable thermoregulatory material," they wrote. By varying the mechanical strain on the fabric, thereby changing its characteristics, they could regulate the body temperature of its wearer. The potential military applications of such technology were discussed at a workshop, called Bio-Inspired Signature Management for the US Army, convened by the National Academies of Sciences, Engineering, and Medicine.

While the workshop was held in September 2019, the in-brief proceedings were published last week. It's a fascinating read. Participants discussed the possibility of "smart skin" fabrics that would include light sensors that could enable "adaptive optoelectronic camouflage systems inspired by cephalopod skins". The fabric wouldn't have to be smart enough to exactly match its surroundings. Disruptive dazzle patterns could be more effective than background-matching, particularly against edge-detection algorithms, participants said. Dazzle markings make estimates of speed and trajectory difficult.

One example cited was a school of stripe-patterned fish, which utilize their speed and shifting direction to confuse predators. Predators also use disruptive camouflage. A cuttlefish might do five primary camouflage changes in the course of 20 minutes to approach prey. The challenge, participants said, is how you would actually manufacture a smart skin. Smart skins would have to include micro-structure components yet be made in metre-scale fabric. They would also have to be flexible. The possibility of commercial manufacturing techniques are "nearing short-term now", said Dr Michelle Povinelli from the University of Southern California. But not all participants agreed. "To date, the participants had not seen engineered systems actively change shape after receiving cues with an active skin," said the proceedings. "Knowledge is lacking as to the level of effort needed to understand these observed capabilities from biology and bring them to practical systems. Its associated timeline -- be it a 1-year, 10-year, 20-year, or beyond challenge -- is unknown as well."

https://www.zdnet.com/article/cuttlefish-inspired-smart-camouflage-could-make-for-sneakier-soldiers/#ftag=CAD-03-10abf5f
Nanofabrication & Microfabrication

Nanofabrication deals with smaller structural sizes than microfabrication does, but the borderline size is not well defined, and is not necessary.

Except manufacturing of evermore powerful computer chips, nanofabrication and microfabrication in most applications, especially in biomedical applications are intimately tied together.

Thus, the two terms are frequently used together and/or used interchangeably.
There is no single accepted definition of nanofabrication, nor a definition of what separates nanofabrication from microfabrication. To meet the continuing challenge of shrinking component size in microelectronics, new tools and techniques are continuously being developed. Component sizes that were in tens of micrometers became single-digit micrometers, and then hundreds of nanometers, and then went down to a few tens of nanometers where they stand today. As a result, what used to be called microfabrication was rebranded as nanofabrication, although the governing principles have remained essentially the same. The main driver of this technology has been the manufacture of integrated circuits, but there have been tremendous fallout benefits to other areas, including photonics.

Nanofabrication can be loosely divided into three major areas: thin films, lithography, and etching.
Computers today comprise different chips cobbled together. There is a chip for computing and a separate chip for data storage, and the connections between the two are limited. As applications analyze increasingly massive volumes of data, the limited rate at which data can be moved between different chips is creating a critical communication "bottleneck." And with limited real estate on the chip, there is not enough room to place them side-by-side, even as they have been miniaturized (a phenomenon known as Moore's Law).

Nanofabrication: Three-Dimensional Chip

The new prototype chip is a radical change from today's chips. It uses multiple nanotechnologies, together with a new computer architecture, to reverse both of these trends. Instead of relying on silicon-based devices, the chip uses carbon nanotubes, which are sheets of 2-D graphene formed into nanocylinders, and resistive random-access memory (RRAM) cells, a type of nonvolatile memory that operates by changing the resistance of a solid dielectric material. The researchers integrated over 1 million RRAM cells and 2 million carbon nanotube field-effect transistors, making the most complex nanoelectronic system ever made with emerging nanotechnologies. The RRAM and carbon nanotubes are built vertically over one another, making a new, dense 3-D computer architecture with interleaving layers of logic and memory. By inserting ultradense wires between these layers, this 3-D architecture promises to address the communication bottleneck.

Microfabrication: Gecko's Attachment Pads

This review paper discusses design parameters that were found to be instrumental to the adhesive properties of synthetically fabricated adhesive structures, currently available fabrication methods for producing these adhesive structures, as well as the various testing methods that have been used experimentally to characterize adhesion performance.

Fig. 2. Adhesion map for spherical tip contacts.

Pan 2019, Bioinspired Adhesives, Reference Module in Materials Science and Materials Engineering
Microfabrication: Sticky Fingers

Sticky fingers: Novel robotic grippers expand role in fulfillment

These cool gecko-inspired grippers show how the best innovations don't add complexity, but eliminate it. Greg Nichols, 2020.

Robots with gecko-inspired hands are becoming more important during the rise of on-demand-everything. That's prompting a leader in robotic end-of-arm tooling to expand its lineup of the biologically-inspired gripper pads for robots that work in various industries, including fulfillment and logistics.

The company's gripper uses millions of "micro-scaled fibrillar stalks" to stick to smooth surfaces using van der Waals forces, which is the mechanism geckos use to climb. The technology was first developed with space in mind and grew out of a Stanford research project that inspired work at the NASA Jet Propulsion Lab. NASA was exploring van der Waals forces as an effective way to capture orbiting satellites for salvage or repair. Suction cups and vacuum grippers aren't effective in space, and traditional robotic end effectors can push objects away in zero gravity.

OnRobot's Gecko no-mark adhesive gripper seemed like a grippy solution to a sticky situation, and the company's success with its grippers has reinforced the market need for this sort of product. Last year OnRobot won silver at the Edison Awards Gala, which came on the heels of the Gecko Gripper winning the Robotics Award at the Hannover Messe in Germany.

The following example describes interchangeable use of nanofabrication (nanoengineering in this article) and microfabrication, and the difficulty of separating the two.

Fig. 3. Basic micro and nanoengineering methods used in cardiac tissue engineering. Schematic representations of the method, followed by advantages and disadvantages for their use in cardiac tissue engineering.

Fig. 5. Schematic representations of the four most widely used techniques of 3D printing for cardiac tissue engineering (reprinted with permission). (A) Laser-assisted bioprinting (LAB) which is based on laser-induced forward transfer (LIFT). (B) Multiphoton excitation (MPE) which is also called stereolithography. (C) Inkjet printing. (D) Microextrusion ink deposition.

Nanofabrication for Functional 3D Architectures


Fig. 1. Top-down approaches for the fabrication of functional 3D nanostructures.

Fig. 2. Bottom-up approaches for the fabrication of functional 3D nanostructures.
Figure 2. Fabrication process of creating microfluidic devices. 
(a–c) Schematic illustrations of preparing PMMA stickers on PP backing using laser cutting. 
(a) Coating the PMMA film on the PP sheet. 
(b) Laser cutting of PMMA patterns and removal of the unnecessary PMMA film. 
(c) Stickers of different microfluidic structures. 
(d) Laser-cut microfluidic stickers. 
(e–h) Schematic illustrations of creating microfluidics using the stickers. 
(e) Arranging and sticking the stickers on PDMS substrate. 
(f) Casting liquid PDMS and curing. 
(g) Acetone bathing. 
(h) Completed microfluidic chip. 
(i–l) Photograph of the process shown in (e)–(g). 
(m) Photograph of linking separate stickers with styrene acrylate copolymer emulsion. 
(n) Schematic illustration of wettability-guided emulsion linking of the stickers shown in (f) when two stickers are not in contact (top) and stickers overlap (bottom). 
(o) Schematic illustration of dissolving the template and evacuating the chip. Left: dissolving the template sticker in an acetone bath. Right: evacuation of the chip.
Molecular transport in confined nanoscale geometries is the basis for many emerging biotechnologies and biological processes. Polymer translocation across a nanoscale pore has been one of the most intensively studied topics in this field. Motivated in part by the goal of DNA sequencing, a rich phenomenology of behaviour has been observed, requiring ideas from polymer physics, surface science and fluid mechanics. Nanopore sensors work by measuring the modulations in ionic current as single molecules are electrophoretically driven through the pore. Ever since the first demonstration of nucleic acid detection, intensive efforts have focused on understanding the physics governing key experimental observables such as the translocation time ($\tau$).

Fig. 1 | Translocation of dsDNA through synthetic nanopores is a non-equilibrium process. Schematic illustrating directed polymer translocation through a nanoscale aperture. The entropic forces due to thermal noise are indicated together with the driving force, for example, an electrophoretic force due to an applied potential difference.

Synthetic nanopores and nanostructured DNA molecules were used to directly measure the velocity profile of driven polymer translocation through synthetic nanopores. The results reveal a two-stage behaviour in which the translocation initially slows with time before accelerating close to the end of the process. Distinct local velocity correlations as the DNA polymer chain passes through the nanopore. Brownian dynamics simulations show that the two-stage behaviour is associated with tension propagation, with correlations arising from the random-walk conformation in which the DNA begins.

Chen 2021, Dynamics of driven polymer transport through a nanopore
A Nanopore Protein Reader

Since the 1990s, nanopores have been used for sequencing strands of DNA. A voltage is applied across the nanopore, which is embedded in a thin lipid membrane, causing a stretch of DNA to thread through the pore. A helicase enzyme then methodically pulls the molecule back through. As this happens, the nitrogenous bases that make up the DNA affect the ion current flowing through the pore, and by measuring these current changes, researchers can decode the DNA sequence. Now, biophysicist Cees Dekker of Delft University of Technology in the Netherlands and colleagues have repurposed this technology for deciphering amino acid differences among peptides (Science, 374:1509-13, 2021).

Dekker’s team starts by linking a synthetic peptide with the 5’ end of a single strand of DNA. After a zap of voltage sends the conjugated molecule through the nanopore, the Hel308 helicase walks on the DNA section, pulling both the DNA and the attached peptide back through the nanopore. As with DNA sequencing, ratcheting the peptide through the nanopore changes the ion current, and the researchers can link the changes to a specific sequence of amino acids in their designed peptide. The target peptide is read in this way multiple times, threading back through the pore as the helicase falls off and being pulled back through again by another, improving the technique’s fidelity. In a proof-of-principle study, the researchers were able to distinguish three different 26-amino-acid-long peptides that only varied by a single amino acid.

The method cannot be used to decode protein sequences without a known reference for comparison, however. That’s because not only does the amino acid at the pore’s entrance affect the ion current, but the eight surrounding amino acids do as well. “Right now, it is not yet a full de novo sequencing tool,” Dekker writes in an email to The Scientist. “Yet it is very powerful since we showed that by changing even a single amino acid within the chain, we observed dramatic differences in the current step signals.” The new method therefore could be useful for detecting amino acid mutations or identifying the presence of a specific peptide of interest within a mixture of proteins, he says.

In theory, this method is “perfect” for analyzing proteins, says Giovanni Maglia, a chemical biologist at the University of Groningen who recently published a proteasome-nanopore that can unfold proteins for sequencing. The helicase is already known to work for DNA sequencing, he notes, and it pulls the DNA through the pore in a controlled way. Maglia points out that this approach is limited to peptides that are 26 amino acids or shorter; however, this is because the helicase sits on top of the pore and can only pull the molecule by its DNA tail.

Dekker acknowledges this limitation but notes that this read length is enough to discriminate all proteins in the human proteome if they are broken into pieces. Also, the nanopore-based approach requires smaller samples than does mass spectrometry—a commonly used protein analysis approach—and would be able to detect rare variants, something mass spec can’t, Dekker says.

Researchers link a stretch of DNA to a peptide of interest and measure changes in electrical current as the molecule is pulled by a helicase through a nanopore (Sophie Fessl).
Semiconducting Polymers

Photoacoustic Imaging in The NIR-II Window Using Semiconducting Polymers

Dr. Jiayingzi Wu
Graduated in April 2020
Currently, research faculty at Shenzhen University


Thermal Reflow of Polymers

In micro- and nanofabrication, thermal reflow generally describes the concept of reshaping initial patterns into new profiles. While the initial structure can be obtained from efficient standard processes, the reshaped and new profile can most often only be obtained with reasonable efforts by reflow. In non-technical applications, reflow is like melting sugar grains into droplets or merging them into a smooth crust of caramelized sugar on a Crème brûlée. On the technical side, one prominent example is the fabrication of microlenses, i.e., lenses with curved surfaces and some tens of micrometer up to a few millimeters in diameter.

Fig. 14. SEM micrographs for PMMA microscopic structures (a-b) before and (c) after reflow: (a) cross-section of vacuum UV (VUV) created low Mw and low Tg section on top of unmodified bulk section for a microscopic step profile, (b) 3×3 lenslets after replication in PMMA, (c) VUV exposed and reflowed surface with ultra-smooth surface finish and minimal effects on the total (bulk) geometry.

Fig. 2. (a) Mechanical properties of polymers dependent on temperature, molecular weight, and crosslinking (Ref [58], modified from Ref [59]. Schematic for a polymer with a Tg around 100 °C for normal process conditions.

Kirchner 2019, Thermal reflow of polymers for innovative and smart 3D structures
Figure 3. Centrifugal multispinning of different polymers. (A) Schematic illustration of centrifugal multispinning using three different polymer solutions.

Figure 2. Production rate calculation of PS nanofibers. (A) Weight of nanofibers that were spun by centrifugal spinning and electrospinning according to spinning time. (B) Photographs of the prepared PS nanofibers spun by centrifugal multispinning with a different number of subdisks.

Figure 3. (E) Contact angle of spun nanofiber webs with different ratios of flow rates of PS and PVP solutions. Deionized water was used to measure the contact angle.

Filtration mechanisms of air filter.

Figure 4. Mask filter application of PS nanofibers. The fabricated PS nanofiber-based mask for fine dust capture and filter for measurements of capture efficiency and resistance (inset).

Kwak 2021, Large-scale centrifugal multispinning production of polymer micro- and nanofibers for mask filter application.
Figure 6. Delignification of wood toward thermal-management material. (a) Near-complete delignification reduces the thermal conductivity of wood by removing high thermal-conductivity lignin and creating more nanopores. Near-complete delignification endows the nanowood with a thermal conductivity of \( \sim 0.03 \text{W} \cdot \text{m}^{-1} \cdot \text{K}^{-1} \), which is lower than those of thermally insulating materials, such as Styrofoam, expanded polystyrene (EPS), wool, and grass. (b) Near-complete delignification and compression result in the cooling wood with a temperature lower than ambient temperature, in which the temperature reduces \( > 9 ^\circ \text{C} \) during the night and \( > 4 ^\circ \text{C} \) between 11 am and 2 pm due to the coverage of the cooling wood. (c) Near-complete delignification and hydrophobic modification via fluoroalkylsilane treatment prepare the hydrophobic wood enabling thermal-efficient distillation with a high flux of water.

Figure 7. Delignified wood–polymer composites toward light-management materials. (a) Delignification and polymer infiltration modulate the optical performance of wood via making wood transparent. The transparent wood features a transparency of 90% in the radial direction and almost 80% in the longitudinal direction, both of which are much higher than the natural wood. (b) Spatial-selective delignification and polymer infiltration enables a high transparency and aesthetic patterns of wood, thus constructing an aesthetic transparent wood. (c) Solar-assisted chemical brushing strategy for manufacture the patternable transparent wood. The most lignin of wood is reservation and just light-absorbing chromophores of lignin are removed, which endows the patternable transparent wood with high strength and flexibility, as well as reducing the consumption of energy and chemicals.

Li 2021, In situ wood delignification toward sustainable applications
**Polydimethylsiloxane Vitrimer for Ultra-thin Durable Hydrophobic Films**

**dyn-PDMS**: polydimethylsiloxane network strands and dynamic boronic ester crosslinks. Dyn-PDMS can also be utilized to fabricate superhydrophobic surfaces ($\theta_a > 150^\circ$) on textured substrates by a variety of techniques like spin-coating and dip-coating.

**Fabrication of superhydrophobic dyn-PDMS sample.**

A solution of 1.7:1 PDMS to boric acid was prepared by dissolving the boric acid in 3 mL of IPA and mixing with the 1 mL PDMS in a 20 mL vial at 60 °C. The solution was then stirred at 110 °C on a hot plate and most IPA evaporated. When the solution in the vial decreased to 2 mL, the solution was in a 1:1 ratio of PDMS to IPA. The etched aluminum substrate was washed sequentially with ethanol/water/IPA and blown dry. 150 μL of 1.7:1 dyn-PDMS solution was pipetted onto the 2 cm² substrate and spun coat following the same procedure as all above samples. The substrate was the cured in a vacuum oven at 110 °C for 17 h.

Ma 2021, Ultra-thin self-healing vitrimer coatings for durable hydrophobicity
Organogel

Soft hydrogels and organogels combined with suitable solvents are commonly employed for the cleaning of dirty surfaces, especially when the substrate is susceptible to swelling and its functionality is compromised by the solvent itself. The benefits of gels rely on their capability to entrap the solvent to minimize substrate damage and to adapt their shape to maximize the contact with the surface, necessary to achieve good cleaning efficiency. Traditionally, natural resins, such as dammar and shellac, have been widely used for the preparation of varnishes. With the passing of time, natural resins change their chemical, optical, and mechanical properties because of the oxidative actions of light, air, and the interaction with pollutants. The most common procedure for the removal of the discolored and degraded varnishes consists in applying solvents with cotton swabs. However, this approach is extremely risky for the painting because the solvent action is highly uncontrollable and leads to saponification, swelling, and leaching of the painting layer components, with decrease of the surface mechanical strength. A valid alternative is the use of gels able to exert a controlled solvent action. Consequently, chemical and physical gels have become popular for the removal of aged varnishes or coatings from artwork surfaces through a “press and peel” approach.

Figure 1. Sketch describing the preparation of PA6,6/PHB−GVL and PVA/PHB−GVL sandwich-like composites (a). SEM images of PA6,6 (b,c) and PVA (e,f) fibers at different magnifications; PA6,6 (d) and PVA (g) fibers after immersion in GVL for 1 min at 110 °C and dried at RT. Representative pictures of sandwich-like composite (h,i) and PHB−GVL gel (j,k) showing the different mechanical resistance of the two types of materials under bending. (l) Single cantilever configuration for sample mounting, where the green arrow indicates the fixed clamp and the pink arrow indicates the movable clamp (a representative composite sample is mounted in the picture). (m) Force-displacement curves of PA6,6/PHB−GVL composite (blue, A), PVA/PHB−GVL composite (red, B), and PHB−GVL gel (black, C): composites resist up to 10 mm bending, whereas the gel breaks at 2 mm. Scale bar: 6 μm (b,c); 2 μm (c,d,f,g).

Materials. γ-Valerolactone (GVL), PHB, poly(vinyl alcohol) (PVA) (Mw = 85,000–124,000 g/mol, 87–89% hydrolyzed), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), absolute ethanol (EtOH), and γ-butyrolactone (BL) were purchased from Sigma-Aldrich. PA6,6 (Zytel E53 NC010) was kindly provided by DuPont.

Figure 8. Schematic representation of the mode of action of (a) sandwich-like composites and (b) PHB−GVL organogel for the cleaning of dammar varnish. (i) Solvent diffusion from the gel phase to the varnish (solvent is depicted by yellow arrows): in the sandwich-like composites GVL diffusion is limited by the presence of the fibrous layer (fibre sections are depicted as red circles). (ii) dammar swelling: dammar swells after GVL absorption from the gel phase by following either the rough surface morphology of the composites (a) or the smooth surface of the organogel (b). Higher swelling is expected in the case of organogel compared to the composites, given the higher GVL diffusion from the former. (iii) Removal of the cleaning material by peeling off: dammar layer is effectively peeled off by using composites thanks to its good mechanical adhesion with the rough surface (see SEM image), whereas residual solvent and fragments of dammar can remain on the paint when organogel is used, due to its worse adhesion with the gel (see SEM image).

Jia 2020, Organogel coupled with microstructured electrospun polymeric nonwovens for the effective cleaning of sensitive surfaces
Micro/Nanomotors

Micro/nanomotors designed for environmental applications contain functional materials that enable their swimming at the microscale and removal of pollutants from the contaminated water. The choice of the functional material depends on the target pollutants.

Pathogenic Microorganisms. The presence of pathogens in the water is a leading cause for the increase in diseases such as cholera and typhoid. Common disinfection methods use chemicals (chlorine, chloramines, and ozone) or physical processes (UV light and heat) or a combination of both due to the high resistance of some pathogens. However, the high doses of these disinfectants can be harmful or may leave toxic byproducts. Micromotors focused on the removal of pathogenic bacteria from contaminated water, integrating on their structures several bactericidal materials or molecules such as enzymes, polymers, and metals have been developed. Additionally, these micromotors can be designed for the selective isolation and destruction of bacteria by the modification of their structure with aptamers, antibodies, protein receptors, and target enzymes. Campuzano et al. described the first example of micromotors for capturing and isolating bacteria. First, Ni/Au layers were deposited by ebeam vapor deposition on the outer surface of electrosynthesized polyaniline (PANI)/Pt tubular micromotors. Afterward, the Au surface was modified using mercaptoundecanoic acid and NHS/EDC chemistry for the subsequent incorporation of the lectin receptor. Once the lectin-modified micromotors were placed in H2O2 solution, they selectively bind to the Escherichia coli (E. coli) surface by antibody–antigen interactions and capture E. coli while swimming. Later, the same research group demonstrated the first use of nanomotors for killing bacteria. The team used porous gold nanowires (p-AuNWs) propelled with an external ultrasound (US) source and functionalized their surface with lysozyme, an antibacterial peptidoglycan-hydrolase (muramidase activity) enzyme (Figure 4A) able to damage specifically the protective wall of bacteria. The p-AuNWs were fabricated using template electrosynthesis of different metal layers: (i) Ag sacrificial layer, (ii) Au layer, and (iii) Au–Ag layer being liberated after silver removal. The surface was chemically modified with cysteamine, which forms Au–S bonds and provides N-terminal groups to the AuNWs, for the subsequent use of glutaraldehyde molecule as a linker of proteins. Two kinds of bacteria, Micrococcus lysodeikticus and E. coli, were rapidly destroyed by these named “nanofighters” in comparison with static lysozyme-AuNWs and free lysozyme. This fact was attributed to the enhancement of lysozyme–bacteria interactions because of the fluid mixing generated by the nanomotors motion. After this pioneering approach, several studies have described different micromotors decorated with other antibacterial molecules, such as chitosan or silver-based materials. Spherical water propelled micromotors made of chitosan/alginate poly(lactide-co-glycolide)/alginate/gold/magnesium (Chi/Alg/PLGA/Au/Mg) have been reported for E. coli decontamination (Figure 4B). Chitosan is a hydrophilic polycationic biopolymer industrially obtained by N-deacetylation of chitin and is able to interact with negatively charged cell membranes, such as bacteria walls, leading to the leakage of proteinaceous and other intracellular constituents. These chitosan-based micromotors showed a high bactericidal effect while they were swimming in comparison with the static analogous and the nonchitosan-based micromotors. As in the previous study, the autonomous propulsion of the Chi/Alg/PLGA/Au/Mg micromotors in drinking-water provided fluid mixing and, consequently, improved the chitosan-micromotor contact with bacteria interactions and its bactericidal efficiency.

Figure 4. Removal of pathogenic microorganisms by (A) ultrasound propelled nanomotors containing lysozyme, (B and C) chitosan and silver nanoparticle-coated bubble propelled magnesium-based micromotors.

Parmar 2018, Micro- and nanomotors as active environmental microcleaners and sensors
Polymer Membranes for Water Treatment

Zhang 2018, Fit-for-purpose block polymer membranes for water treatment

Fig. 2 Scanning electron micrographs of a self-assembled block polymer membrane and b a commercial membrane made using a standard phase separation process. The highly-ordered nanostructure of the self-assembled membrane offers the potential for higher performance (i.e., higher throughput and more selective) separations relative to commercial membranes because the well-defined, narrow pore size distribution produces highly-selective filters, and generates a uniform flow distribution through each pore. The blue and red spheres represent solutes of varied size being filtered from solution. The width of the blue arrows is proportional to the volumetric flow through the associated pore. Solute selectivity and a uniform residence time for fluid flowing through the membrane pores are essential in the development of functional membranes for advanced applications.

Fig. 6 a Functional moieties can be introduced into the pore wall chemistries of membranes made from block polymer precursors through three mechanisms. (1) The functional chemistry (red block) can be incorporated into the precursor block polymer prior to membrane fabrication. With the identification of suitable SNIPS parameters, a self-assembled membrane with functional pore walls that require no further functionalization reactions is generated. (2) The block polymer chemistry facilitates formation of a self-assembled structure. Subsequently, the surface of the membrane is modified using a coating (orange dots) to which functional chemistries are attached (green brushes). (3) The pore wall-lining block (magenta) is designed as a reactive chemistry that can be converted to a variety of functional chemistries through coupling reactions that are consistent with roll-to-roll processes. b An illustration of the broad range of potential applications where membranes with functional pore wall chemistries could be utilized.
Figure 1. Water treatment membranes and their separation functions in water treatment. WW: wastewater; TDS: total dissolved solids; SS: suspended solids; BOD: biochemical oxygen demand; COD: chemical oxygen demand; REEs: rare earth elements. Microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), reverse osmosis (RO), forward osmosis (FO), and membrane distillation (MD).

Zuo 2021, Selective membranes in water and wastewater treatment- Role of advanced materials

Figure 1. Membrane preparation and morphology. (a) Schematic illustration of the electropolymerization process. (e) Surface SEM image of CMP@100-10c. (g) Cross-sectional SEM image of CMP@100-20c. The inset SEM image shows the flexibility of the composite membrane.

Zhou 2021, Precise sub-angstrom ion separation using conjugated microporous polymer membranes
The Ultimate Nanofabrication: Synthetic Bacteriophage

The ultimate nanofabrication will be the technology that can fabricate synthetic bacteriophage-type machines that can deliver a high drug load into only the targeted cells and, if necessary, reproduce itself in the cell to continuously supply the drug, e.g., insulin. The nanofabrication that scientists are talking about now is basically Lego assembly by babies. Probably 100 years from now, scientists can engineer such an artificial machine, and you will be at the forefront of these efforts. Dream Big!

See the similarity in the structures? Engineers can copy what the nature provides, as the nature has learned the good-enough form through millions of years of evolution.

https://tigerscroll.com/rare-pictures-that-will-show-you-the-unseen-side-of-things-long/22/
Nanomedicine
Current Hurdles of Nanomedicines

The field of nanomedicine has significantly influenced research areas such as drug delivery, diagnostics, theranostics, and regenerative medicine; however, the further development of this field will face significant challenges at the regulatory level if related guidance remains unclear and unconsolidated.

The major challenges associated with nanomedicine regulation.
- Lack of a unified definition or classification of nanomedicines/nanomaterials.
- Lack of agreed regulations.
- Analytical methods differ for each nanomaterial.
- PK profiles diverge from standardized constituent materials.
- Stability issues after scale-up for manufacturing.

Despite the promising advances made in preclinical animal models, the clinical translation of nanomedicines remains a slow, biased, and often failed affair. There exists a general lack of specific protocols, and the characterization of materials and biological mechanisms and the statistical analyses often employed remain inadequate. Moreover, the vast and significant heterogeneity of models adopted, a reluctance to share results, and the inaccuracy of study design have hampered the translation of nanomedicines into late clinical trial stages.

Dordević 2022, Current hurdles to the translation of nanomedicines from bench to the clinic
Nanotechnology for COVID-19

Figure 4. Nanomedicine strategies for COVID-19 therapeutics and vaccine development.

Figure 5. Nanocarrier platforms utilized for combination drug therapeutics.

Figure 6. Nanoparticle-based immune response modulation. (a) Antigen delivery by nanoparticles (size-dependent penetration and tissue or organ targeting). (b) Depot effect provides a prolonged and sustained release of stable antigen. (c) Repetitive antigen display as a result of the antigen presentation on the nanoparticle surface assists the receptor activation on APCs and B cells and (d) cross presentation of the antigen delivered by the nanoparticles (cytosolic delivery) to activate antigen specific CD8+ T cells. Antigen-presenting cell (APC); dendritic cell (DC); endoplasmic reticulum (ER); B cell receptor (BCR); T cell receptor (TCR).

Figure 7. Major delivery methods for mRNA and DNA vaccines. (I−V) Nanocarrier for mRNA delivery, (VI) nanocarriers for DNA delivery, and (VII) electroporation technology for the intradermal delivery of DNA vaccines.
Lipid Nanoparticles

Lipid nanoparticles (LNPs) play a key role in effectively protecting and transporting mRNA to cells. LNPs exhibit more complex architectures and enhanced physical stabilities than liposomes (an early version of LNPs).

Lipid nanoparticles (LNPs) play a key role in effectively protecting and transporting mRNA to cells. LNPs exhibit more complex architectures and enhanced physical stabilities than liposomes (an early version of LNPs).

Note: Liposome ≠ LNP

Tenchov 2021, Lipid Nanoparticles - From liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement
Stability of Gene Therapy Products

Improving Stability for Gene Therapy Products (By Angelo DePalma, PhD, 2021)

After the genetic constructs are manufactured, doses must be stored, shipped, and stored again as they await dosing in far-flung test sites. The physical integrity of doses in these situations is paramount. The formulation, including buffers, cryoprotectants, and general storage conditions, were critical for maintaining stability. Standard storage practices involving buffer, glycerol, and -80°C storage could compromise gene delivery systems. In addition to requiring dry ice shipping such formulations also require extensive dilution before administration to reduce glycerol toxicity.

For cell therapies, storage and handling of both cells and viral vectors are quite diverse and present numerous issues for long-term cryopreservation, and to maintain viability and activity post-thaw. While we may approach a virus like AAV as nothing more than a complex protein biologic, we need to understand the impact of these factors on the virus. Viability can be measured several ways. Cells from cryopreserved thaw can be measured directly in cell counters using a combination of nuclear and live/dead stains such as DAPI, acridine orange, or propidium iodide. For activity assays, viability can be measured using the same combination of stains, as well as MTT or other functional killing assays.
Biomimetic Nanoparticles for Targeted Drug Delivery

As numerous diseases are associated with increased local inflammation, directing drugs to the inflamed sites can be a powerful therapeutic strategy. One of the common characteristics of inflamed endothelial cells is the up-regulation of vascular cell adhesion molecule–1 (VCAM-1). Here, the specific affinity between very late antigen–4 (VLA-4) and VCAM-1 is exploited to produce a biomimetic nanoparticle formulation capable of targeting inflammation. The plasma membrane from cells genetically modified to constitutively express VLA-4 is coated onto polymeric nanoparticle cores, and the resulting cell membrane–coated nanoparticles exhibit enhanced affinity to target cells that overexpress VCAM-1 in vitro. A model anti-inflammatory drug, dexamethasone, is encapsulated into the nanoformulation, enabling improved delivery of the payload to inflamed lungs and significant therapeutic efficacy in vivo. Overall, this work leverages the unique advantages of biological membrane coatings to engineer additional targeting specificities using naturally occurring target-ligand interactions.

Park, J.H. 2021, Genetically engineered cell membrane–coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs

Fig. 1. Schematic illustration of genetically engineered cell membrane–coated nanoparticles for targeted drug delivery to inflamed lungs. Wild-type cells were genetically engineered to express VLA-4, which is composed of integrins α4 and β1. Then, the plasma membrane from the genetically engineered cells was collected and coated onto dexamethasone-loaded nanoparticle cores (DEX-NP). The resulting VLA-4–expressing cell membrane–coated DEX-NP (VLA-DEX-NP) can target VCAM-1 on inflamed lung endothelial cells for enhanced drug delivery. (PLGA 50:50 (0.66 dl/g; LACTEL). For DEX-loaded PLGA cores, 500 μL of PLGA (50 mg/ml) in dichloromethane (DCM; Sigma-Aldrich) was mixed with 500 μL of DEX (10 mg/ml) in acetone.)

Fig. 4. Drug loading and in vitro activity. (A) Drug loading (DL) and encapsulation efficiency (EE) of dexamethasone (DEX) into VLA-NP (n = 3, mean + SD). (B) Drug release profile of VLA-DEX-NP (n = 3, mean ± SD). The data were fitted using the Peppas-Sahlin equation (dashed line). (C) Secretion of IL-6 by LPS-treated DC2.4 cells (n = 3, mean + SD). UD, undetectable. (D) Secretion of IL-6 by LPS-treated DC2.4 cells preincubated with DEX in free form or loaded into VLA-NP (n = 3, mean ± SD). (E) Relative inflammatory response, as measured by IL-6 secretion, of DC2.4 cells treated with LPS only, LPS and PLGA nanoparticles, LPS and VLA-NP, PLGA nanoparticles only, or VLA-NP only; all of the nanoparticles were empty without DEX loading (n = 3, mean ± SD). NS, not significant (compared to the LPS-only group), one-way analysis of variance (ANOVA).

Fig. 5. In vivo targeting, safety, and therapeutic efficacy. (A) Biodistribution of WT-NP or VLA-NP in a lung inflammation model 6 hours after intravenous administration (n = 3, mean ± SD). *P < 0.05, Student’s t test. AU, arbitrary units. (B) Creatinine levels in the plasma of mice after repeated daily administrations for 9 days with free DEX or VLA-DEX-NP (n = 3, mean ± SD). *P < 0.05, one-way ANOVA. (C) IL-6 levels in the lung tissue of mice intratracheally challenged with LPS and then treated intravenously with vehicle solution, free DEX, WT-DEX-NP, or VLA-DEX-NP (n = 3, mean ± SD). ***P < 0.001, ****P < 0.0001 (compared to VLA-DEX-NP), one-way ANOVA. (D) Representative hematoxylin and eosin–stained lung histology sections of mice intratracheally challenged with LPS and then treated intravenously with vehicle solution, free DEX, WT-DEX-NP, or VLA-DEX-NP (scale bar, 100 μm).
Biomimetic Nanobiomaterials

The design of next-generation nanobiomaterials requires precise engineering of both physical properties of the core material and chemical properties of the material’s surface to meet a biological function. A bio-inspired modular and versatile technology was developed to allow biodegradable polymeric nanoparticles to circulate through the blood for extended periods of time while also acting as a detoxification device. To mimic red blood cells, physical and chemical biomimicry are combined to enhance the biological function of nanomaterials in vitro and in vivo. The anisotropic shape and membrane coating synergize to resist cellular uptake and reduce clearance from the blood. This approach enhances the detoxification properties of nanoparticles, markedly improving survival in a mouse model of sepsis. The anisotropic membrane-coated nanoparticles have enhanced biodistribution and therapeutic efficacy. These biomimetic biodegradable nanodevices and their derivatives have promise for applications ranging from detoxification agents, to drug delivery vehicles, to biological sensors.

Fig. 1. Schematic of anisotropic nanoparticle fabrication and RBC membrane coating. (A) Spherical PLGA nanoparticles (NPs) were synthesized and cast into a thin plastic film of 10% polyvinyl alcohol (PVA) and 2% glycerol. Particles were then stretched under heat in one or two dimensions (2D) to generate prolate or oblate ellipsoidal particles, respectively. (B) RBCs underwent hypotonic lysis and were then sonicated to generate sub–200 nm vesicles. RBC-derived vesicles were then coated onto PLGA nanoparticles of all shapes under sonication.

Ben-Akiva 2020, Biomimetic anisotropic polymeric nanoparticles coated with red blood cell membranes for enhanced circulation and toxin removal

Fig. 4. In vivo clearance and biodistribution of nanoparticles. (A) Blood elimination of nanoparticles following intravenous administration as assessed by fluorescence readings of the blood sample (dots) and fit to a single exponential decay model (lines). (B) Particle bloodstream half-life was derived from the exponential fit of blood decay curves and was increased for RBC membrane-coated particles and prolate ellipsoidal particles. (C) Mice were euthanized after 24 hours, and organs were dissected out and imaged. Data are shown as means ± SEM (n = 3 mice per group).

Fig. 5. Anisotropic RBC membrane–coated nanoparticles as detoxification treatment. (A) Schematic of mechanism of RBC coated nanoparticles (NPs) as detoxification treatment. RBC NPs neutralize alpha toxin by binding toxin that would otherwise bind the body’s RBCs and cause lysis. (B) In vitro evaluation of hemolytic toxin absorption by RBC-coated nanoparticles. The anisotropic particles were able to absorb significantly more alpha toxin as evidenced by reduction in relative lysis. Data are shown as means ± SEM (n = 4 replicates). (C) Survival following intravenous alpha toxin administration followed by nanoparticle administration (n = 6 mice per group). Mice receiving prolate ellipsoidal RBC-coated nanoparticles had a significant long-term survival benefit compared to spherical coated nanoparticle, and both anisotropic particle groups had a significant survival benefit over uncoated particles.

# of NPs & Surface Area?
Molecular Imprinting

Molecular imprinting refers to the creation of specific recognition sites in polymer networks by cross-linking in the presence of a template molecule, which represents the target to be recognized. This process is performed by mixing a solution of one (or several) monomer(s) with the template, thereby forming temporary interactions between the two. Subsequent cross-linking and polymerization, followed by removal of the template, lead to the formation of a polymer structure with embedded complementary cavities for the superstructure of the imprinted molecule. These nanocavities preserve not only the shape and size but also the molecular interactions necessary for the recognition of the target. The resulting molecularly imprinted polymers (MIPs) are thus able to selectively recognize and bind the target via a “lock and key” mechanism similar to those found in biological systems (e.g., antibodies and enzymes). These biomimetic polymeric networks can be prepared by designing interactions between the building blocks of a biocompatible network and the desired specific ligand and stabilizing these interactions by a three-dimensional (3D) structure. These structures are at the same time flexible enough to allow for diffusion of solvent and ligand into and out of the network.

Fig. 2. Major steps in the process of epitope imprinting. Each one presents an array of options that must be carefully considered to optimize MIP efficacy considering the target application.

Telxera 2021, Epitope-imprinted polymers-Design principles of synthetic binding partners for natural biomacromolecules
Figure 1. Schematic illustration of the synthesis of well-defined amphiphilic brush block copolymers (BBCPs) and the preparation of multifunctional fluorescent polymeric micelles from BBCPs. Braga 2021, Near-Infrared Fluorescent Micelles from Poly(norbornene) Brush Triblock Copolymers for Nanotheranostics.

Figure 1. Schematic representation of the “one-pot” synthesis. Synthesis scheme for the ring-opening polymerization (ROP) of activated urethane of methionine in DMSO as solvent (a). Molecular model of the PEO-PMET diblock copolymer showing the partial folding of the polypeptide (b). Scheme showing the evolution from spherical micelles to cylindrical micelles to vesicles as a function of the PMET degree of polymerization with relative transmission electron micrographs (c). Scale bar = 100 nm. Duro-Castano 2021, One-Pot Synthesis of Oxidation-Sensitive Supramolecular Gels and Vesicles.
Activation of the stimulator of interferon gene (STING) pathway within the tumor microenvironment has been shown to generate a strong antitumor response. Although local administration of STING agonists has promise for cancer immunotherapy, the dosing regimen needed to achieve efficacy requires frequent intratumoral injections over months. Frequent dosing for cancer treatment is associated with poor patient adherence, with as high as 48% of patients failing to comply. Multiple intratumoral injections also disrupt the tumor microenvironment and vascular networks and therefore increase the risk of metastasis. Here, we developed microfabricated poly(lactic-co-glycolic acid) (PLGA) particles that remain at the site of injection and release encapsulated STING agonist as a programmable sequence of pulses at predetermined time points that mimic multiple injections over days to weeks. A single intratumoral injection of STING agonist–loaded microparticles triggered potent local and systemic antitumor immune responses, inhibited tumor growth, and prolonged survival as effectively as multiple soluble doses, but with reduced metastasis in several mouse tumor models.

Fig. 1. Design and fabrication of PLGA-MPs. (A) Schematics of single-injection drug delivery platform for cancer immunotherapy. Different PLGA microparticles reside in the tumor after a single intratumoral injection, release encapsulated STING agonist in pulses at discrete time points, and promote infiltration of TILs. (B) Schematics of the fabrication process of PLGA-MPs, which are prepared by filling cargo of interest into particle bases and then sealing the bases with corresponding particle caps by briefly applying heat. (C to E) Representative scanning electron microscopy images of EP bases (C) and sealed array of particles (D) or an individual particle (E). Scale bars, 500 μm (C and D) and 100 μm (E). (F) Representative high-resolution x-ray CT image of a sealed particle encapsulating 3′-cGAMP. Red color represents dried 3′-cGAMP. Scale bar, 100 μm. (G) Representative optical image of an array of sealed particles encapsulating Alexa Fluor 647–labeled dextran. Scale bar, 1 mm.

Fig. 3. Single injection of cGAMP-MPs inhibited tumor growth and prolonged animal survival.

Lu 2020, Engineered PLGA microparticles for long-term, pulsatile release of STING agonist for cancer immunotherapy
Figure 1. Graphical illustration of (A) virus interaction with GAGs on the cell surface and (B) on the GlycoGrip lateral flow (LF) biosensor for detecting SARS-CoV-2. The sample is deposited on the sample pad and migrates toward the conjugate. The conjugated antibodies bind the virus and migrate to the test line, where the bound target analyte is captured by the glycopolymers.

Kim 2022, GlycoGrip-Cell Surface-Inspired Universal Sensor for Betacoronaviruses

Figure 4. (A) Schematic illustration of our screening of various signaling probe candidates on heparin (HEP)-based lateral flow (LF) strip and (B) corresponding screening result with 30 and 5 min incubation. (C) Alignment of hep40mer and the N-terminal domain (NTD) Ab to the spike. (D) Computational model of NTD and the receptor binding domain (RBD, epitopes 4A8 and REGN10933, respectively) along with the angiotensin converting enzyme 2 (ACE2), binding motif. (E) Accessible surface area calculated from the RBD epitope (REGN10933), ACE2 binding motif, and NTD epitope (4A8). Dark blue bars indicate the size of the interface area as seen in Cryo-EM structures for the RBD, ACE2, and NTD binding footprints (6XDG, 6M17, and 7C2L, respectively). p values < 0.05 (*), 0.01 (**), and 0.001 (***) determined using a two-way ANOVA with Tukey’s post hoc test.
Aerosol Filtration Efficiency of Common Fabrics

Although the filtration efficiencies for various fabrics (cotton, silk, chiffon, flannel, various synthetics, and their combinations) when a single layer was used ranged from 5 to 80% and 5 to 95% for particle sizes of <300 nm and >300 nm, respectively, the efficiencies improved when multiple layers were used and when using a specific combination of different fabrics. Filtration efficiencies of the hybrids (such as cotton–silk, cotton–chiffon, cotton–flannel) was >80% (for particles <300 nm) and >90% (for particles >300 nm). The enhanced performance of the hybrids is likely due to the combined effect of mechanical and electrostatic-based filtration. Cotton, the most widely used material for cloth masks performs better at higher weave densities (i.e., thread count) and can make a significant difference in filtration efficiencies. Gaps (as caused by an improper fit of the mask) can result in over a 60% decrease in the filtration efficiency, implying the need for future cloth mask design studies to take into account issues of “fit” and leakage, while allowing the exhaled air to vent efficiently. Combinations of various commonly available fabrics used in cloth masks can potentially provide significant protection against the transmission of aerosol particles.

Figure 1. Schematic of the experimental setup. A polydisperse NaCl aerosol is introduced into the mixing chamber, where it is mixed and passed through the material being tested (“test specimen”). The test specimen is held in place using a clamp for a better seal. The aerosol is sampled before (upstream, $C_u$) and after (downstream, $C_d$) it passes through the specimen. The pressure difference is measured using a manometer, and the aerosol flow velocity is measured using a velocity meter. We use two circular holes with a diameter of 0.635 cm to simulate the effect of gaps on the filtration efficiency. The sampled aerosols are analyzed using particle analyzers (OPS and Nanoscan), and the resultant particle concentrations are used to determine filter efficiencies.

Konda 2020, Aerosol filtration efficiency of common fabrics used in respiratory cloth masks
PLGA Coating on Water Droplets

Fig. 1. Polymer packaging on water surface. (A) The mechanism for the formation of the PLGA membrane is composed of a phase of polymer solution spreading by surface tension over the free water surface while the DMC solvent diffuses, leading to the solidification of the PLGA membrane. Water packaging methods are shown in stable/static and dynamic/unstable conditions: (B) on a sessile drop on hydrophobic substrate and (C) wrapping, in real time, a drop flowing out of a needle. (D) Explanation of the 3D packaging approach over the wall of a stable liquid bridge between two plates.

Fig. 2. (A) Bright-field microscopic image of the microcapsules produced by the coaxial ultrasonic atomizer. The aqueous cores look blue due to the presence of Coomassie brilliant blue R-250. (B) CLSM cross-sectional image of the microcapsules. The cores were labelled with FITC-dextran (green), and the polymer layer with Nile Red (red). Scale bars=100 μm.

Coppola 2019, Quick liquid packaging-Encasing water silhouettes by three-dimensional polymer membranes

Yeo 2003, A new process for making reservoir-type microcapsules using ink-jet technology and interfacial phase separation

Yeo 2004, A new microencapsulation method using an ultrasonic atomizer based on interfacial solvent exchange

Yeo 2004, Solvent exchange method A novel microencapsulation technique using dual microdispensers
Among various materials, transformable and easily handled liquid metals (LMs), which have exceptional multifunctionality, might be suitable for creating the convergence concept with cutting-edge technologies, including optics, electronics, printing, robotics, and nanotechnologies. In particular, Ga- and Ga-based LM alloys are promising soft materials for various applications because of their low toxicity, excellent electrical and thermal conductivities, and fluidity at near-room temperature. More interestingly, Ga-based LM particles continue to exhibit both fluidic and metallic properties and are valuable for versatile functionalization in health monitoring devices and therapeutics.


Figure 2. Application of a LM-based healthcare device. The schematic illustration represents the potential application of an alternating magnetic field driven ingestible microdevice in digestive organs.

Figure 3. Medicinal application using the fluidity of LMs via light energy. (A) Schematic illustration of light-induced transformable EGaIn LM nanocapsules. (B) Transmission electron microscopic images of light-induced transformable EGaIn LM nanocapsules before and after laser irradiation for 1 and 3 min.
Research on Nanotechnology Formulations

Almost all papers on such nanoparticles end up with the same conclusion: nanotechnology has great potential for drug delivery. It is true. The question, then, is to ask what can be done to turn this potential into tangible outcomes, i.e., formulations that can benefit patients. It would be counterproductive only to talk about the potential for another decade. To achieve tangible outcomes, they first need to be defined. This, in turn, requires understanding the goals, which may depend on individuals.
The above billionaires are all Americans. Therefore, all Americans are billionaires.

The above drugs are all nanoparticles. Therefore, all nanoparticles are clinically effective.
Failed Clinical Trials of Nanoscale Drug Carriers

Carrying drugs

Traditional chemotherapies can be toxic but nano-sized carriers can keep them out of healthy tissue and take old drugs to new places.

Table 1: Nanoscale drug carriers in clinical trials in 2012.

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Formulation</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calando Pharmaceuticals</td>
<td>CALAA-01</td>
<td>A polymer nanocarrier containing gene-silencing RNA</td>
<td>Phase I</td>
<td>A polymer nanocarrier holds RNA that silences a gene in solid tumours needed for DNA synthesis and replication</td>
</tr>
<tr>
<td>BIND Biosciences</td>
<td>BIND-014</td>
<td>A polymer nanocarrier targeted to cancer cells carries docetaxel</td>
<td>Phase I</td>
<td>Targets solid or metastatic prostate cancer cells by binding to prostate-specific membrane antigen</td>
</tr>
<tr>
<td>Nippon Kayaku</td>
<td>NK105</td>
<td>A polymer nanocarrier containing paclitaxel</td>
<td>Phase III</td>
<td>Looking for progression-free survival in patients with metastatic or recurrent breast cancer</td>
</tr>
<tr>
<td>NanoCarrier</td>
<td>Nanoplatin (NC-6004)</td>
<td>A polymer nanocarrier containing cisplatin</td>
<td>Phase I/II</td>
<td>Evaluating Nanoplatin in combination with gemcitabine in patients with advanced or metastatic pancreatic cancer, with the aim of reducing kidney toxicity compared with cisplatin alone</td>
</tr>
<tr>
<td>Cerulean Pharma</td>
<td>CRLX101</td>
<td>A pH-sensitive polymer nanocarrier releases camptothecin in the acidic environment of cancer cells</td>
<td>Phase II</td>
<td>Separate studies testing CRLX101 in advanced non-small cell lung cancer and in ovarian cancer</td>
</tr>
</tbody>
</table>

Updated Status

- Terminated in 2013
- Terminated in 2016
- Terminated in 2016
- Terminated in 2014
- Terminated in 2016

Nanomedicine: Myths and Facts

Ligand-receptor Interaction
(“Active Targeting”)  
EPR Effect

(Tumor)

Extravasation
(“Passive Targeting”)  
Blood Circulation

Nanoparticle Targeting of Anticancer Drug Improves Therapeutic Response in Animal Model of Human Epithelial Cancer

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# Nanomedicine: Assumptions and Facts in Targeted Drug Delivery

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles deliver a drug to the target better than the solution control.</td>
<td>The improvement observed is small, usually from around 1% to 2% of the total administered dose.</td>
</tr>
<tr>
<td>PEGylation extends blood circulation time.</td>
<td>Only for a small fraction of the total nanoparticles.</td>
</tr>
<tr>
<td>Nanoparticles reach tumor by passive targeting.</td>
<td>Only 1~2% of the total dose.</td>
</tr>
<tr>
<td>Nanoparticles reach tumor by the EPR effect</td>
<td>But the EPR effect is not proven in humans.</td>
</tr>
<tr>
<td>Nanoparticles release a drug at the target tumor.</td>
<td>But only 1~2% of the total dose.</td>
</tr>
</tbody>
</table>

![Diagram](image.png)

The target tumor cells are exposed.

Lack of Translation from Mouse to Human

Size: Tumor vs. Body

Blood volume
An elephant can be described by many different ways. But which is the characteristic description of an elephant?

Different Interpretation of the Same Data

Illustration: Hans Møller, mollers.dk
Ask Questions To Make Sure!

Professor Allan Hoffman

Idea: Peter Reid. University of Edinburgh
Ask Questions To Make Sure!

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Ask Questions To Make Sure!

Professor Allan Hoffman

Idea: Peter Reid. University of Edinburgh
The Gray Bar in This Image Appears to be a Shaded Gradient.
The Gray Bar in This Image Appears to be a Shaded Gradient.

The gray bar is one color

Paul Ehrlich’s Magic Bullet

Selective targeting to a bacterium without affecting other organisms.

Selective killing

A drug that goes straight to their intended cell-structural targets to treat disease.

interacts with

The Art of War (孫子兵法)

知己知彼 百戰百勝

The Art of War against Diseases

Know the properties of the drug delivery systems in vitro and in vivo.

Know the properties (heterogeneity and dynamic states) of the body.

Nobel Prize 1908
The Dangers of Nanoparticles

Nanoparticles made of plastics (nanoplastics) are polluting the Earth. They ferry in hazardous chemicals and help them accumulate up the food chain.

We breathe, inhale, and ingest them, and we are not aware of it.