SCIENTISTS STUDY COMPLEX CHEMICAL SYSTEMS

Much of our work in the Center for Sustainable Nanotechnology lies in the realm of chemistry. That is to say, our work seeks to understand phenomena at the molecular level. For example, we want to know what molecules we can add to the surface of a nanoparticle to control how stable it is and how it interacts with cells. But how exactly do we tackle problems in chemistry?

To address molecular-level questions like these, we conduct experiments using instruments that can probe the characteristics of molecules. Molecules are the smallest units of most chemicals—many being *smaller* than the nano-scale, around 1 billionth of a meter. Some instruments that we use provide direct information about molecules, like how they rotate, vibrate, absorb and emit energy. Other instruments that we use don't necessarily provide direct information about molecules, but they allow us to visualize things much closer to the scale of molecules than we otherwise can.

image source

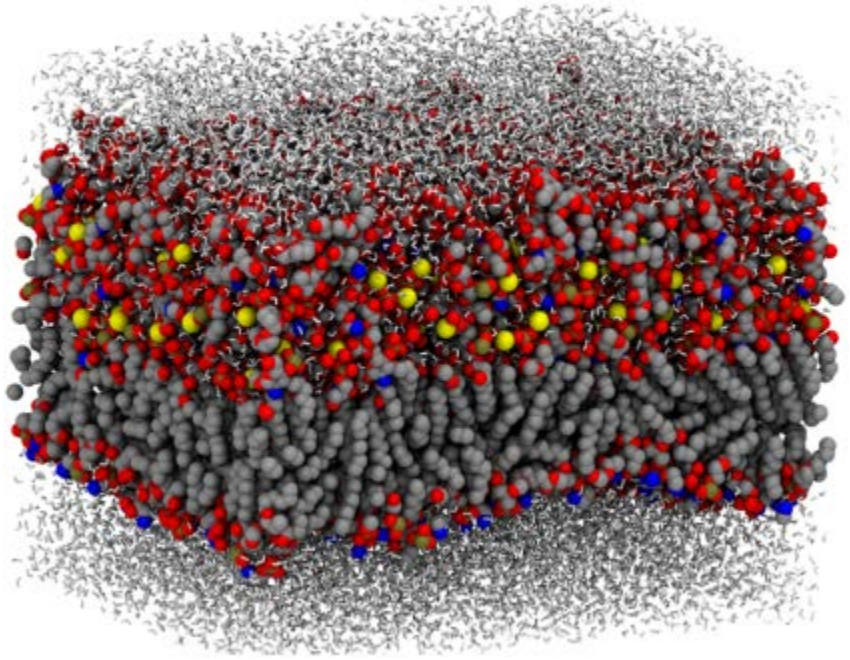
Before I give the false idea that we can probe the world of molecules with ease, let me mention some of the limitations of these techniques. We discussed in a previous post how the diffraction of visible light limits us from resolving (or distinguishing) objects less than about

200 nanometers apart. Since molecules are much smaller than 200 nanometers (e.g., protein molecules have diameters between about 1 and 10 nanometers), this means that we can't directly visualize molecules using visible light. Even when we use instruments that can characterize molecules directly (like how they rotate or vibrate), interference from nearby molecules often limits how much we can learn about a given system. Imagine that we are trying to learn which molecule (or molecules) a nanoparticle sticks to on the surface of a cell. There are many molecules present on the cell surface, each of which rotates, vibrates, etc. in a unique way. Finding the one molecule or few molecules that stick to a nanoparticle is somewhat like finding the one person or few people shouting for your attention at a rock concert—the information is available, but it is so overlapped with other information (or noise) that you can't find it (or hear it).

Given these limitations, you might be wondering, with good reason, how we will ever understand something as complex as cell-nanoparticle interactions at the molecular level. One approach that we use is something that I will call **Simplify and Isolate**. The Simplify and Isolate approach involves breaking down complicated problems into many simpler, smaller problems that can be more easily tackled. As an example of this approach, let's go back to thinking about which molecules a nanoparticle sticks to on the surface of a cell. Probing this interaction directly is difficult due to interference among the many molecules on the cell surface. To get around this problem, we could use what we know about the molecules on the cell surface to test (one at a time) how well each molecule sticks to a nanoparticle. This reduces interference by limiting the number of molecules present. Once we've measured the extent of molecule-nanoparticle interaction for all possible molecules on the cell surface, we can identify which one is most likely responsible for sticking to nanoparticles on a real cell surface. So, let's say there are 100 different kinds of molecules in the surface of a cell. In this case, we would run at least 100 different experiments to find out how each kind of molecule interacts with one kind of nanoparticle.

The Simplify and Isolate approach is fundamental to experimental science and can provide great insight into complex problems that cannot be solved with one big, complex effort. But following this approach requires performing many experiments, and this requires investment of time and financial resources. What are we to do if we can't afford to perform so many

experiments or if there are other experimental limitations standing in our way? In cases where the Simplify and Isolate approach is not feasible, the **Build-Up** approach can be used. Instead of breaking down a complex problem into smaller bits, the Build-Up approach recreates a picture of the complex problem by stacking up fundamental rules on top of each other. These rules come mostly from knowledge of physics, which makes sense, given that physics focuses on fundamentals. Once a complete picture of the problem has been recreated from many fundamental rules, we are done—by recreating the problem, we have learned (almost) everything about it. This is much like a teacher creating an exam: writing exam questions (recreating problems) requires that they know (or have learned) the answers. An alternative name for the Build-Up approach is the **Computational** approach, since computers are often used to stack up fundamental rules in order to recreate (or simulate) a problem.



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In fact, the Computational approach, while relying on information acquired through experiments, itself requires no experimentation—through this approach, scientific questions can be addressed using only computers. Given that requisite computer technology has existed for only a few decades, this approach is relatively new, but it has already provided insight into questions that cannot be easily answered using the Simplify and Isolate approach (an inherently experimentation-based approach) due to experimental limitations or constraints of

time and/or resources. The Computational approach also has limitations, the most significant being that very complex systems can be difficult to accurately build up from fundamental rules! For example, it may be possible to use the Computational approach to learn which molecules a nanoparticle sticks to on the surface of a cell or how it binds to those molecules, but it will be much more difficult to learn how the cell as a whole will respond to this interaction. In more complex cases like these, experiments are necessary, meaning that the Simplify-and-Isolate and Computational approaches work best when used together.

In the Center for Sustainable Nanotechnology, we have focused a lot on the Simplify-and-Isolate approach. However, we are beginning to address questions about nanomaterials and their interactions with cells using the Computational approach. For example, we are working on building computer models for the molecules on the surface of a cell. Using these models, we can test whether the molecules we identified as being sticky for nanoparticles in our simplified laboratory experiments are still responsible for sticking to nanomaterials in the context of the more complex cell surface. This Computational approach not only gives us greater confidence in our laboratory results, but also provides more fundamental insight into problems than is sometimes possible to obtain through experiments conducted in the lab. We are just starting to use this approach—stay tuned for exciting results!

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