Summary, “The Assembly of Protocells”
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A used wad of chewing gum is how Dr. Steen Rasmussen described the protocell that he and his colleagues at Los Alamos National Laboratory are designing. The physicist described his group of researchers as the “primitive guys trying to assemble a cell from scratch: putting together organic and inorganic materials in the lab to try and understand what it is that makes life possible.”

Team leader of the Self-Organizing Systems Program at Los Alamos, Dr. Rasmussen spoke December 1, 2005, at a lecture sponsored by the Dialogue on Science, Ethics, and Religion (DOSER), a program of the American Association for the Advancement of Science (AAAS).

Besides Los Alamos, more than 100 other laboratories around the world are trying to figure out how to assemble minimal “nanomachines” from nonliving organic and inorganic matter. The work parallels and informs other research into life such as genetic engineering, synthetic biology, and astrobiology. “It’s gone from nothing to a pretty big effort in a very short time,” said Dr. Rasmussen, noting that it was very difficult until recently to get funding for this kind of discovery science. Although nanomachines still belong to the realm of science fiction, Dr. Rasmussen urged open and public discussion about the ethical implications of protocell research.

According to Dr. Rasmussen, physicists create theoretical systems “and we try to edge our way up toward the living system.” At the same time, biologists working in the labs are edging their way down toward explanations of what they observe. The latter are way ahead of the former, Dr. Rasmussen said, in the way that French cooks can create amazing concoctions though they can’t necessarily explain the physics of how those concoctions are made. Protocell research is getting to the point where physicists and biologists have useful information to share with each other. “Sometime in the distant future the scientific community should be able to shake hands from the bottom and the top,” he said.

The physicist repeatedly used the words “awesome” and “exciting” to describe his work and the applications that may derive from living technology that can repair itself, adapt to new situations, replicate, and even evolve. Though the ultimate applications of living technology are not yet imaginable, they would certainly be broad. “Think about electricity and computers: these enabling technologies don’t impact you in just one place, they impact you all over the place.”

An operational definition of minimal life is a system that is able to take in and digest resources and turn that energy into building blocks so that the system can grow and replicate itself. Minimal life also would manifest evolution through natural selection. For researchers, the practical problems in assembling a protocell are: (1) how to create a metabolic system, (2) how to create a genetic system, and (3) how to build a container that puts the two systems in close proximity. While some labs focus on just one of these three problems, Rasmussen and his colleagues are investigating them holistically, because that could be the most effective avenue.

The protocell Rasmussen is designing “looks quite different from anything that is alive… we have to forget everything that we know about biology because this is certainly not a living system as we know it.” The cell model is about a million times smaller than a modern cell. To avoid the complexity of having to develop protein systems that can move waste and metabolized products through a cell membrane, the scientists have designed it so that all of the genes and metabolic molecules attach to the sticky exterior of the membrane. Hence the chewing gum image: “all exchanges from the environment happen from the surface.” Another important difference is that instead of DNA material, the protocell relies on PNA, peptide nucleic acid.

The research group is working on the theory that it is possible to use a charge-transfer relay, “kind of like a little electrical wire,” to serve in place of DNA, sidestepping the need to construct mechanisms for gene translation, messenger RNA, ribosomes, and protein translation. “This is certainly the simplest design [for a cell] that anybody has come up with,” Dr. Rasmussen said.

Though the actual processes underlying the designed protocell are quite complex, they rely on simple physical chemistry. “We’re basing at least the first central part of our work on making soap,” Dr. Rasmussen stated: on the fact that water and fat repel each other. That property can be used to move molecules around in the protocell. The lab group has been able to create computer simulations of these protocells through self-assembly, feeding, and resource conversion. He described the simulations as a “useful cross-grain, approximate way to anticipate what happens in the experimental situation.”

Simulations of cell division remain elusive. “It’s very different from contemporary biology,” he emphasized once again, since the instructions to divide are transmitted not by genetic transcription and translation but instead by the movement of an electrical charge along bases. If the movement of the charge depends on which bases are present, “then you will have a dependence of the sequence on the metabolism…. That means there is a selective advantage for protocells that have the right gene, the one that can do the metabolism. That is the hook that means that at some point we can demonstrate evolution." Theory and application are still far apart, however. "If we can get this protocell to make one replication, we will invite you all to a big party," he said.

That party will occur after the experimentalists verify the theoretical calculations of Dr. Rasmussen and colleagues. "It can get pretty complicated," he admitted. "We have written all these equations down, and the experimentalists are laughing at us because it's much easier to do this on a piece of paper than in a lab."

There is one significant finding that already has emerged from this research, however: "It doesn't matter how the metabolic machinery interacts with the container… there is only one way to have growth in a biological system, and that is exponential."

Dr. Rasmussen said that the work is unusual for him as a physicist because typically researchers in his profession use models to make predictions. "But to make predictions in these kinds of systems — forget it, it is totally out of our reach. So then what are we using this modeling for? We're using it to expose our ignorance."

While acknowledging that living technology is going to take a long time to develop, the physicist emphasized that it is "good to start the conversation now" on the ethical ramifications. As an opening question, he asked whether protocell research is a new area for ethical discussion or merely raises the same questions that might be asked in other fields of science such as genetic engineering or cloning. He also made a plea for greater balance in funding for problem-solving research (such as research into the cure for cancer) and discovery science (such as protocell assembly); currently, the former is heavily favored.

Dr. Rasmussen pointed to the 1975 Asilomar Conference on recombinant DNA and the 1987 Los Alamos workshop on artificial life, as two examples of scientists voluntarily coming together to discuss ethical concerns surrounding their research. Ethics were discussed at a workshop related to protocell research held in Venice in 2005, and it will be on the agenda for another workshop scheduled for Los Alamos this summer. "This is the first time we've had ethics in the budget at the lab in a basic science project," he noted.

Any ethics discussions will probably be dominated by the idea of utility, argued Peter Madsen, the featured respondent to Dr. Rasmussen's lecture. Dr. Madsen is the executive director of the Center for the Advancement of Applied Ethics and Political Philosophy at Carnegie Mellon University.

In economics, Dr. Madsen explained, the predominant axiom is that people make economic choices to maximize their own best interests. "Utilitarianism typifies our morés to such an extent that if we were to characterize our age, it might be best for us to call it the Utilitarian Age."

Dr. Madsen defined utilitarianism as the belief that "an action is ethically good only if it can be demonstrated that the consequences of that action created the greatest good for the greatest numbers," usually as measured by a comparison of benefits and harms. "But," he added, "it is a fair question to ask whether utilitarianism is an appropriate or workable framework for the assembly of protocells."

The utilitarian framework has been used to assess other scientific enterprises such as cloning and stem cell research. However, there are differences among utilitarians even while they use the same framework: "they tend to emphasize different benefits, while detractors will find great harms. There can be disagreements about utility calculations that can have little to do with the philosophy of utilitarianism itself. In many cases of scientific controversy, it can be said what is controversial is just this sort of disagreement, philosophical disagreements over benefits and harms."

Taking nanotechnology as an example, the benefits that are predicted include molecular systems that could be used to manufacture large complex products cleanly, efficiently, and at low-cost. Such products might include powerful computers, inexpensive energy systems, noninvasive medical devices, materials hundred times stronger and lighter than steel, and superior military devices such as "smart" bullets. Potential harms also have been envisioned. Dr. Madsen quoted from a 2000 article in WIRED Magazine, "Why the Future Doesn't Need Us" by Sun Microsystems founder Bill Joy:

> The 21st-century technologies - genetics, nanotechnology, and robotics (GNR) - are so powerful that they can spawn whole new classes of accidents and abuses. Most dangerously, for the first time, these accidents and abuses are widely within the reach of individuals or small groups. They will not require large facilities or rare raw materials. Knowledge alone will enable the use of them. Thus we have the possibility not just of weapons of mass destruction but of knowledge-enabled mass destruction (KMD), this destructiveness hugely amplified by the power of self-replication.
>
> I think it is no exaggeration to say we are on the cusp of the further perfection of extreme evil, an evil whose possibility spreads well beyond that which weapons of mass destruction bequeathed to the nation-states, on to a surprising and terrible empowerment of extreme individuals.

Potential harm also has been envisioned by Eric Drexler, who founded the Foresight Institute to promote the benign uses of nanotechnology. Dr. Madsen quoted from Drexler’s 1986 groundbreaking text on nanotechnology, *Engines of Creation*:

> Tough, omnivorous "bacteria" could out-compete real bacteria: they could spread like blowing pollen, replicate swiftly, and reduce the biosphere to dust in a matter of days. Dangerous replicators could easily be too tough, small, and rapidly spreading to stop - at least if we made no preparation. We have trouble enough controlling viruses and fruit flies.

Drexler referred to this as “the gray goo problem,” but it is no longer considered a significant threat because there is no motivation to build anything remotely resembling a runaway replicator, Dr. Madsen said. He added that there nonetheless remain other dangers, such as if powerful groups deliberately build cheap high-performance weapons with a billion processors in their guidance systems.

Dr. Madsen said that what Steen and his colleagues are working on is “a remarkable and radical revolution… It would seem that such work is, if not redefining life, at least adding a new category to our understanding of the ontology of entities. I’m left to conclude that ethics is left behind in advance of this special science, and that perhaps the utilitarian ethics are not sufficient to address the questions raised by this research.”

In the question-and-answer period, Dr. Rasmussen mused that he is not sure that protocell research is fundamentally different from figuring out how to fly or communicate by telephone, yet “it is clear this is something new… so the discussion is: how is what we’re doing most likely to change the fabric of society in the future, and how is that compared with how earlier scientific advances have changed the fabric of society?” He said he was curious as to whether ethicists would think there is a fundamental difference, and also as to whether the research itself is “sinning” or whether the “bad stuff” comes afterwards when the science is applied.

He admitted that in the workshops so far, it has been somewhat difficult to discuss the ethical implications because the field is so young and no one knows what direction it might take. “I wouldn’t put my money on one particular application — you have to put the wheels on the car before we decide where to go, and so far there are no wheels on.”

One questioner asked whether protocell research might result in the creation of new microbial weapons. Dr. Rasmussen responded that creating a protocell “germ warfare type weapon” is theoretically possible, but there are much simpler ways already technologically feasible to cause great destruction. “If you want to do something really terrible, make a cross between an influenza virus with a bad virus. It’s much, much easier than trying to create life first.” In fact, protocells might be safer than other life-manipulating technologies, because protocells can be kept on task ("when you design a protocell it has only one choice — it can only eat the poison") and because the protocell is so dissimilar to naturally occurring organic matter, it could not exchange genetic information. "I'm not saying that you're safe, but you don't have the same issues that you have by using genetic engineering."

Another questioner asked whether there is "such a thing as forbidden knowledge… domains in which there is moral compromise in pursuing the knowledge." Dr. Madsen noted that this question has prompted the development of such ethics tools as the "precautionary principle" and "courageous caution." But Dr. Rasmussen acknowledged that this is a question that "is brewing in my stomach from time to time… I don't know what the answer is, I've come to the conclusion that there's definitely things we shouldn't know about, many things you shouldn't do research in, some of it classified, we shouldn't even talk about it… but I think the best thing we can do is have an open dialogue." This dialogue should takes into consideration all "stakeholders," he added, including people, the environment, and the planet. "I feel a little bit odd talking about these things because it's science fiction yet; on the other hand, I think that it's maybe good to get the discussion started."