

Alive! The race to create life from scratch

12 February 2005
NewScientist.com news service
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YOU might think Norman Packard is playing God. Or you might see him as the ultimate entrepreneur. As founder and CEO of Venice-based company ProtoLife, Packard is one of the leaders of an ambitious project that has in its sights the lofty goal of life itself. His team is attempting what no one else has done before: to create a new form of living being from non-living chemicals in the lab.

Breathing the spark of life into inanimate matter was once regarded as a divine prerogative. But now several serious and well-funded research groups are working hard on doing it themselves. If one of them succeeds, the world will have met alien life just as surely as if we had encountered it on Mars or Europa. That first alien meeting will help scientists get a better handle on what life really is, how it began, what it means to be alive and even whether there are degrees of "aliveness". "We want to demonstrate what the heck life is by constructing it," says Packard's business partner and colleague Steen Rasmussen, a physicist at Los Alamos National Laboratory in New Mexico. "If we do that, we're going to have a very big party. The first team that does it is going to get the Nobel prize."

Although the experiments are still in the earliest stages, some people, especially those with strong religious beliefs, feel uneasy at the thought of scientists taking on the role of creators. Others worry about safety - what if a synthetic life form escaped from the lab? How do we control the use of such technology?

Finding a way to address these worries will have benefits beyond helping scientists answer the basic questions of life. The practical pay-offs of creations like Rasmussen's could be enormous. Synthetic life could be used to build living technologies: bespoke creatures that produce clean fuels or help heal injured bodies. The potential of synthetic organisms far outstrips what genetic engineering can accomplish today with conventional organisms such as bacteria. "The potential returns are very, very large - comparable to just about anything since the advent of technology," says Packard. And there is no doubt that there is big money to be made too.

Only a few research groups have explicitly set themselves the goal of making a synthetic life form (see "Race for the ultimate prize" - bottom). Most are adapting bits and pieces from existing organisms. ProtoLife's plans are the most ambitious and radical of all. They focus on Rasmussen's brainchild, which he has nicknamed the Los Alamos Bug. Still but a gleam in its creator's eye, the Bug will be built up from first principles, using chemicals largely foreign to existing creatures. "You somehow have to forget everything you

know about life," says Rasmussen. "What we have is the simplest we could dream up."

To achieve this radical simplicity, Rasmussen and his colleagues had to begin with the most basic of questions: what is the least something must do to qualify as being alive? Biologists and philosophers struggled to answer that question for decades (*New Scientist*, 13 June 1998, p 38).

However, most now agree that one key difference - perhaps the only one - between life and non-life is Darwinian evolution. For something to be alive, it has to be capable of leaving behind offspring whose characteristics can be refined by natural selection. That requires some sort of molecule to carry hereditary information, as well as some sort of process - elementary metabolism - for natural selection to act upon. Some kind of container is also needed to bind these two components together long enough for selection to do its work.

Containment, heredity, metabolism; that's it in a nutshell. Put those together in the simplest way possible, and you've got the Los Alamos Bug. But every step is completely different from what we're used to (see graphic - the four stages shown are described further in "The Los Alamos Bug" - below).

Take containment, for example. Terrestrial life is always water-based, essentially a watery gel of molecules enclosed within an oily membrane. Modern cells move nutrients across this membrane with the help of an array of different proteins embedded in the membrane. The Los Alamos Bug, however, is completely different. For a start it is oil-based, little more than a droplet of fatty acids. "Instead of having a bag with all the good stuff inside, think of having a piece of chewing gum," says Rasmussen. "Then you stick the metabolic molecules and genetic molecules into the chewing gum, so they are attached on the surface or sitting inside the chewing gum."

The bare necessities

The container is the easy part. The next step - heredity - is where most efforts to create synthetic life get bogged down. The challenge is to create a molecule complex enough to carry useful genetic information, which can also replicate. In modern organisms DNA has a whole army of enzymes to help it replicate its genetic information - far too complicated a process for the Bug. Instead, Rasmussen plans to use a molecule called peptide nucleic acid, or PNA. It uses the same "letters" of genetic code as DNA, but has two forms, one soluble only in fat, the other also attracted to water. Rasmussen hopes to put PNA's dual nature to use in a rudimentary form of replication (see Graphic).

The Bug's metabolism has also been pared down to the minimum. The researchers plan to "feed" it with chemicals that can be converted into fatty acids. If enough are produced, the droplet will grow and divide into two. A similar metabolic process turns PNA precursors into functional PNA.

Although most of the design is still on the drawing board or in the earliest stages of experimentation, the team has made most progress with the Bug's

metabolism. "If you look at the individual pieces, they are all sort of demonstrated in the lab. But if you put everything together, not yet," says Liaohai Chen, a biochemist at Argonne National Laboratory near Chicago, who heads Rasmussen's experimental team. If all goes according to plan, these three components - container, genome and metabolism - should fit together to provide all the essentials for Darwinian evolution.

In October 2004, Rasmussen landed a large grant from Los Alamos to begin making the Bug a reality. "I can't promise that we'll have it in three years, but I can guarantee that we'll have good progress," he says. The biggest problem may be coordinating the copying of the PNA and the metabolism of the fatty acid precursors so that replication of the genome proceeds at the same pace as the growth of the droplets. "Almost always when you put processes together there are cross-reactions, things that your theories won't tell you about."

Life support

Another fledgling research programme, known as Programmable Artificial Cell Evolution, or PACE, could provide the solution to this coordination challenge. Packard and Rasmussen are collaborating with PACE, which is focusing some of its attention on Rasmussen's design. A key idea behind PACE is to deliver precise amounts of particular chemicals to synthetic cells at specific places and times using computers to precisely control the flow of tiny amounts of chemicals. For example, a computer could use sensors to monitor the rates of PNA replication and fatty acid production in Rasmussen's experimental system, then deliver the correct amounts of each precursor. That would let researchers work out the kinks one by one in a controlled, programmable setting, providing something rather like a life-support machine that helps artificial cells through the critical steps towards becoming alive. "Once we have our hybrid unit, then we can successively withdraw the machine to approach a stand-alone cell," says John McCaskill, a chemist at Ruhr University in Bochum, Germany, who heads the PACE programme.

In this way the PACE team plans eventually to evolve its way towards a self-supporting artificial cell. To do that, though, the team will need a way to recognise the system's first tentative steps down the pathway to life. But how do you recognise something faintly lifelike, when it looks nothing like the life we know?

Look for the footprints of adaptation, says Mark Bedau, a philosopher who specialises in the boundary between life and non-life. Bedau is on leave from Reed College in Oregon to work with Packard at ProtoLife. If something is evolving then it should be generating adaptations - novel solutions to the problems of the world. And those new solutions, however subtle and incremental, become the foundation from which evolution takes its next steps. Adaptations which confer some advantage should last longer and spread faster than other variations.

Bedau is developing statistical tests which will pick up these kinds of patterns in unfamiliar life forms. But since the PACE project has not yet begun lab

experiments, he does not know whether the tests can detect the glimmerings of real life. However, he has road-tested them on a system that works in a similar way, namely human culture.

In 2002, Bedau and colleague Andre Skusa sifted through more than five years of US patent records, counting the number of times each patent has been cited as a basis for later patents. They found that a few patents - such as the one enabling a web browser to display an ad while loading the main page - were cited far more often than one would expect if the differences found in the number of citations for inventions were random. These key innovations are the equivalent of biological adaptations such as opposable thumbs. "That gives you reason to think it should be possible to do the same kind of thing in chemical systems which are not yet alive but might be on the path to being alive," says Bedau.

Using tests like these, the PACE team hopes to see its hybrid gradually become more and more lifelike. But at what point would it actually become alive? Perhaps at no particular point, says Bedau, who thinks it is quite possible that the living and the non-living are separated not by a clear, distinct line but by a wide grey area in which the Bug is partly but not totally alive. "There are shades of grey, and I imagine measuring how dark the grey is," he says. "Our conception of what life is will evolve as we learn more and acquire the ability to make things that are more and more alive."

The moment when a blob of molecules becomes a fully living, evolving being is at least several years off. "Even our optimists wouldn't put a time horizon much sooner than 10 years for that kind of achievement," says Packard. Indeed, sceptics wonder whether the Los Alamos Bug and its ilk will ever yield anything useful. "It's certainly interesting from the conceptual point of view," says Pier Luigi Luisi, a biochemist at the University of Rome 3 and an expert on synthetic life. "But nature with nucleic acids and enzymes is so much smarter, because these are products that have been optimised over billions of years of evolution. To pretend to do life with simple chemistry is a nice ambitious idea, but it's probably not going to be very efficient."

Still, if Packard, Rasmussen and their colleagues do someday succeed in creating synthetic life forms, they will have opened the door to a world of new possibilities. "We are breaking the last barriers between us and living technology," says Rasmussen. "That's going to be a very big thing. It's going to happen, no doubt about it."

Among the most obvious payoffs could be organisms custom-designed to break down toxic compounds or produce useful chemicals such as hydrogen fuel. More conventional organisms can be genetically modified to do these tasks, but as Rasmussen points out, "the problem is these guys have evolved for billions of years. They're extremely versatile, and it's very difficult to keep them on task." An artificial organism, on the other hand, could in principle be built to do nothing but the task at hand, yet still have the evolutionary flexibility to adapt to changing conditions.

Packard hopes that this controlled adaptability could lead to even greater things. He envisions living pharmaceuticals that deliver drugs to us in an intelligent, adaptive way, or diagnostic life forms that could roam our bodies collecting information and watching for signs of a problem. The ultimate goal would be machines that repair themselves as living beings do - even computers that can handle incredibly complex calculations while coping with inevitable errors, just as our bodies tolerate errors and failures within our hundreds of billions of cells.

If life is all about the ability to evolve and adapt, then living technologies always have the potential to surprise us with unexpected new strategies that can take them beyond our control. But then again, that risk is nothing new. We already grapple with it when contemplating what would happen if robots or artificial intelligence were to get out of hand and in evaluating the safety of genetically modified fish, crossbred potatoes or even introduced rabbits. Indeed, for the foreseeable future, synthetic life probably poses much less of an escape risk, because the early versions, at least, will be so fragile and require so much life support. That means the safety of synthetic life is something to keep an eye on, not to be frightened of. "There isn't going to be some precipice we're going to fall over," says Bedau. "We'll be slowly inching our way down, and we'll have lots of opportunity to turn around."

As well as concerns about safety, synthetic life raises some profound ethical and religious issues. "Just the fact that you're making life from scratch will give some people pause. They will think that's a prerogative that humans should never take," says Bedau. If humans can create life on their own, doesn't that remove one of the last deep mysteries of existence, in effect prying God's fingers from one of his last remaining levers to affect the world?

Not necessarily, say theologians. "We are fully a part of nature, and as natural beings who are living and creating synthetic life, we are in a sense life creating more life, which is what's been going on in evolution for 4 billion years now," says John Haught, a Catholic theologian at Georgetown University in Washington DC. "And that does not in principle rule out that God would still be creating life using natural causes - namely us - which is the way in which theology understands God as always operating in the world."

One thing seems certain; synthetic life will provide philosophers with plenty to chew on right from the start. Until now, efforts to come up with a good definition of life have been hampered by the fact that we are trying to generalise from just one example, the life that arose here on Earth. Having a second form, completely independent and based on different chemistry, should give a new perspective on this age-old question. And knowing what did or did not work in the lab, may also help us understand the origin of life - the first version, that is - on Earth.

The Los Alamos Bug

Containment This relies on the fact that oil and water do not mix. The components of each individual Bug are contained by a droplet of fatty acids,

suspended in a watery solution enclosed by a test tube. Each fatty acid molecule has a negatively charged head which is attracted to water and which faces out into the watery environment, and a water-hating oily tail facing inward.

Heredity Instead of DNA the Bug has short stretches of peptide nucleic acid, or PNA. Like DNA, PNA is made of two intertwining strands containing the genetic "letters" A, T, C and G. And like DNA, the sequences of letters on these stands complement each other. A pairs up with T and C pairs with G. The strands have a peptide backbone which does not carry an electrical charge, so will dissolve in fat. This means that the molecules of PNA prefer to face the inside of the fatty acid droplet, like crumbs embedded in the surface of a piece of chewing gum.

This gives the molecule unusual mobility. In its usual double-stranded form, with its two peptide backbones facing outwards, a PNA molecule is completely fat-soluble, so it will sink into the oily centre of the Bug's droplet. But above some critical temperature, the two strands of the PNA double helix separate spontaneously. When this happens, the bases, which bear a slight charge, are exposed and attracted to the Bug's watery environment. So these single-stranded PNA molecules should then migrate to the edge of the droplet where the backbone can remain in the oil while the bases interact with the water outside.

This mobility provides the handle needed to control replication. The plan is to supply the Bug with short bits of single-stranded PNA precursors, just half the length of its tiny genome. If a single-stranded PNA gene on the Bug's surface encounters two of these "nutrient" PNAs with the right base sequences, it will pair with them to form a double-stranded PNA molecule. This should then sink down into the droplet, where conditions favour the joining-up of the two "nutrient" fragments into a whole strand.

Eventually, the double-stranded molecule will dissociate once again and its two strands drift back to the surface where each can pick up new partners - a rudimentary form of replication.

Metabolism The third essential part of the Bug's life - metabolism - has also been pared to its barest minimum. The researchers plan to "feed" the Bug with fatty acid precursors. These will have photosensitive molecules attached their charged "head" ends. These photosensitive caps mask the charged head, making the molecules completely fat soluble. This means they will tend to collect within the Bug's droplets.

When light strikes the photosensitive cap, it breaks off, exposing the negatively charged fatty acid head, which migrates back to the surface of the droplet. Eventually, so many new fatty acids will be produced that they will not all fit on the surface and the droplet will split in two to create a larger surface area.

The Bug will also be supplied with inactive PNA precursors bound to a photosensitive molecule. Once again, when light strikes this photosensitiser, it breaks off to release the active PNA fragment.

Effective metabolism also requires one more step to prevent the photosensitive molecule, once broken off, from re-sticking to the fatty acid or PNA and so deactivating it once again. The PNA genetic material prevents this by acting as a rudimentary wire, conducting electrons to neutralise the photosensitiser. In this way, the Bug's "genome" plays an active role in the metabolic process.

Evolution If all goes according to plan, these three components - container, genome, metabolism - should fit together to provide all the essentials for Darwinian evolution. As the Bugs grow and reproduce, corralled in a test tube, natural selection should favour PNA base sequences that pair up and split off fastest, and also conduct electrons most efficiently to the photosensitisers.

Synthetic slaves Artificial organisms could be custom-built for particular tasks:

- break down toxic compounds
- produce useful chemicals such as hydrogen fuel
- act as "living pharmaceuticals", delivering drugs in the body in an adaptive way
- be tiny diagnosticians, roaming our bodies, collecting information and checking for problems
- become part of machines that can repair themselves as living beings do

[From issue 2486 of New Scientist magazine, 12 February 2005, page 28](#)

Race for the ultimate prize

THE Los Alamos Bug has some stiff competition in the race to be the first artificial life form, especially since some of the entrants are taking much more conventional routes to that goal.

At the Institute for Biological Energy Alternatives in Rockville, Maryland, Craig Venter, leader of the private group that sequenced the human genome, and colleague Hamilton Smith are trying to create a new life form by extracting the genome from an existing bacterium and replacing it with a synthetic genome stripped down to a bare minimum of genes (*New Scientist*, 31 May 2003, p 28).

Because this approach leaves most of the cell's machinery intact, Venter's team is widely expected to be the first to succeed, perhaps within a few months or years. (Uncharacteristically, Venter is not talking to the press about this project.) However, Venter's new organism will end up looking very much like existing life.

And at the University of Rome 3, Pier Luigi Luisi is working on the "minimal cell project". Starting with a simple membrane-bound vesicle, Luisi's team plans to gradually add in off-the-shelf enzymes and other cellular components until they assemble the simplest possible working cell.

Across the Atlantic at Harvard University, Jack Szostak has been working on a synthetic life form just as simple as Rasmussen's Los Alamos Bug, but using more familiar chemistry. Szostak's design calls for a tiny membrane-bound vesicle containing little more than an RNA or RNA-like molecule with a special talent: that of catalysing its own replication.

The problem is that no one has yet developed an RNA capable of replicating more than just a small part of itself. Szostak predicts success is probably 10 or 20 years off. "I've been saying that for the last 10 or 20 years," he says, "and it's still true."