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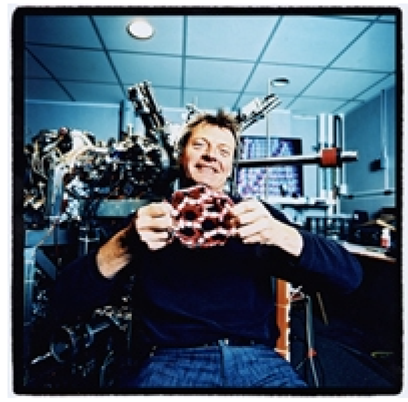
Buckyballs and Screaming Cells

The amazing miniature world of UCLA chemist Jim Gimzewski

by Margaret Wertheim



Gimzewski and his scanning tunneling microscope
(Photo by Debra DiPaolo)

Just before noon on a crisp spring day, Jim Gimzewski is looking a little rusty around the edges. Walking across the UCLA campus, he stops to cadge a cigarette from a couple of students deep in conversation. It's one thing to light up in the land of never-never, it's quite another to bum fags from strangers, and the students eye him suspiciously. Tall and reedy, dressed in black from head to toe, hair graying and spiky, Gimzewski might easily be mistaken for a refugee from an aging British rock band. Nick Lowe comes to mind. Perhaps it's that obvious sense of the foreign — the lilting charm of his Scottish brogue — or maybe just the unrepentant nature of the gesture; this is clearly not an L.A. moment. One of the students pulls a pack from his pocket. Puffing contentedly, Gimzewski muses on the chemical pleasures of life. "I do yoga, and I figure that entitles me to drink. I run, that means I can smoke. I do everything," he says, with an unsullied joie de vivre that seems to have disappeared from the American psychological spectrum. Then, after a beat, he adds slyly, "In moderation."

Few people are more acquainted with the pleasures of chemistry than James Gimzewski — it's pronounced Jim-zes-ski, though back home in Scotland his mates just called him "Get-me-whiskey." However you parse the Polish, he's a world expert on the physics and chemistry of single molecules. At IBM's legendary research laboratory in Zurich, Gimzewski headed a team that fabricated a molecular propeller, a molecule shaped like the blades of a helicopter that spins on an atomic surface like a minuscule wheel. That made the cover of *Science* magazine. His IBM team also fashioned the world's smallest abacus out of "buckyballs," soccer ball-shaped molecules of carbon that are currently the focus of so much scientific interest. A few years ago, UCLA made him an offer he couldn't refuse, including a brand-new lab, and in 2001 he moved out here to set up shop.

At the moment, however, it is not molecules that are exercising Gimzewski's attention, but cells. He has zoomed out, as it were, and in doing so has hit upon something that may usher in a powerful new field of medical diagnostics. Gimzewski has discovered that living cells generate high-pitched sounds, a cytological song whose harmonies potentially encode a hidden language of health and disease. If we can decipher this microscopic symphony, we may be able to *hear* the difference between sick and healthy cells.

Re-energized by the nicotine and almost thrumming with excitement, Gimzewski recounts the unorthodox circumstances behind his amazing discovery. Bizarrely, the trigger was 9/11. On the day when the Twin Towers fell, he had been awaiting a package from a medical researcher in Sardinia named Carlo Ventura. The two scientists had met earlier that year at a conference in Rome where Ventura had acquainted Gimzewski with his research into childhood heart abnormalities. Ventura was working with the stem-cell precursors to heart cells known as myocardiocytes, and he was trying to determine what genetic aberrations were responsible for various pulmonary disorders.

Gimzewski had never given much thought to cells, but with his training in physics he knew that any vibrating object must be emitting sound. Since heart cells beat, he figured that they must be making some kind of noise. He wondered if we listened to that sound, could we discern a difference between healthy heart cells and diseased ones. Ventura believed it was worth a try, and agreed to send a sample of his myocardial stem cells. But while his package was in transit, two jumbo jets fatefully plowed into the World Trade Center, imprinting onto the nation's consciousness an indelible image and propelling the Customs Department to declare a state of lockdown. Stem cells from Sardinia. "The customs officials took one look at that," Gimzewski says, and they hit the roof: 'Fucking hell, it's biological warfare!'" The package was confiscated, and by the time he received it, a few weeks later, all the cells had died.

Interactive installation based on the way a scientist manipulates a molecule and projected on a monumental scale — a collaboration between Gimzewski and Victoria Vesna, director of UCLA's Design Media Arts department, scheduled to open at LACMA this fall.

Back in Gimzewski's office, he shows me a video of heart stem cells, a petri-dish culture apparently pulsing with life. Though there is no body here, no actual organ, rhythmic waves course through the cell community. It's an eerie sight, as if the culture were straining toward organismic identity. This phenomenon has inspired Right-to-Lifers to declare that an 18-day-old fetus has a heart and is, hence, a fully charged human: I beat, therefore I am. To me, the image calls to mind the chimerical hybrid world of David Cronenberg: if this is still life, it is not as we know it.

The basic laws of acoustics tell us that any vibrating surface will generate a pressure differential in the surrounding air — that's what sound is. It is also the principle behind the speakers in your stereo system — a membrane is driven to vibrate, thereby producing noise. "You can think of the surface of a beating cell as a micro-miniature version of a speaker," Gimzewski explains, miming the effect by cupping his hands together as if clutching a ball and vibrating them rapidly. The reason we don't hear this sound is that it's so infinitesimally small. Gimzewski theorized that if he could amplify these cellular vibrations, he could boost the signal into audio awareness. Strangely, no one had ever done this before.

The problem was that with all of Ventura's myocardiocytes now dead, Gimzewski had no subjects to test. Such specialized cells are not something you can order from a catalog — they are delicate organisms that researchers must carefully coax into growth. And clearly, in the wake of 9/11, importing stem cells wasn't going to get any easier. Gimzewski could have given up then and gone back to his molecules — he still has a suite of molecular-research projects going on in his lab — but he is not a man easily deterred. He'd set up the equipment, everything was in place; damn it, he thought, let's listen to some cells. Any cell. He picked up the phone and called upstairs to his biochemical colleagues: Would they mind sending down some yeast cells? As Gimzewski tells the story, the biochemists thought he was insane — yeast cells couldn't possibly be making a noise; they are not even part of the animal kingdom. He eventually persuaded them to prepare a sample, which he ran through his setup with an atomic-force microscope (AFM). When they listened to the recordings, there was to everyone's amazement a distinct high-pitched signal. Moreover, the primary harmonic of this signal was astonishingly high, around 1,000 cycles per second — about two octaves above middle C. Gimzewski's yeast cells were miniature sopranos.

Student Andrew Pelling with the atomic-force microscope: He is going to be the first person in the world with a Ph.D. in cell sonics.
(Photo by Debra DiPaolo)

Observing subcellular scales generally requires the application of some pretty sophisticated physics. Gimzewski has spent his entire professional life in the wonderlandish realm of the very small, and, compared to most of the objects he's used to probing, cells are gargantuan. Since the early 1980s he has been one of the pioneers of scanning tunneling microscopy, a revolutionary technology that enables scientists to take pictures of atoms and molecules. A scanning tunneling microscope (STM) does not operate by any conventional imaging method — it doesn't even use light — rather, it employs a bizarre quantum mechanical process in which electrons "tunnel" through an electrical barrier and appear magically on the other side.

Ironically, STMs look like relics from the 19th century; Rube Goldberg constructions bolted together and equipped with glass-fronted viewing portholes, they are clearly homemade. In his new lab in the basement of UCLA's Department of Chemistry and Biochemistry, Gimzewski has several of these machines, all of which he had constructed in-house. In the age of the Sony Black Box there is something almost comically endearing about these devices, as if they'd been dreamed up by the art department of some B-grade Jules Verne movie. Yet, like Verne's submarines, STMs plunge us into an enchanted domain beneath the surface of mundane experience. Pinned around the walls of Gimzewski's lab are pictures of molecules his team are studying. Among them are the aforementioned buckyballs and some of their fullerene cousins, collectively named in honor of Buckminster Fuller because the soccer-shaped molecule shares the same mathematical structure as Fuller's geodesic dome. Upstairs in Gimzewski's office is a photographic triptych of his famed nano-propeller, each iteration shaded in a different Day-Glo palette. It's Andy Warhol gone atomic: a psychedelic portrait of a molecular superstar.

When Gimzewski first encountered this extraordinary molecule, he realized the paroxysms it would engender among the far fringes of nanotech dreamers — people like author Eric Drexler (*Engines of Creation*) who promise that any day now nanotech robots will be coursing through our bloodstreams, while nanotech factories fabricate fantastical structures on an atom-by-atom basis. Gimzewski can't abide the Drexler types, believing that their wild speculation only serves to oversell this new science before it even gets going. He knew that the "nanonuts," as he calls them, would see his work as the foundation for nanoscale motors and engines. And so, perversely, he hid the work in a drawer for a year. Then he thought: "'What the hell, let them speculate.'" The nuts duly indulged in an orgy of hype. As for what use *might* his molecular rotators have? "None whatever!" Gimzewski insists.

"If you want to understand molecules," he tells me, "then you have to understand mechanics." Gimzewski himself is something of a mechanical whiz. Though a chemist â by training, he has always felt drawn to machinery and has been building his own equipment from the start. "That's what I try to teach my students: You can't just buy this stuff, you've got to go out there and *do* it. Sometimes that means getting in there with a spanner and wrench. Sometimes it's with a nano-wrench." He is now building his seventh generation of STM, and the level of accuracy his team is achieving verges on the miraculous — their sensing tips are so stable the mechanical jitter is less than a thousandth of the diameter of a single atom. Moreover, they have developed a unique technology to control the positioning of the tip, using what is called "slipstick" motion — a microscopic version of banging on a table to cause an object to move across its surface. Their control is so fine they can move the tip by minuscule jumps or jerks measuring just 10 atoms wide: Gimzewski calls these "nanojerks." "I know a few major ones," he quips, mumbling darkly about the war.

Complex feats of engineering are not what one usually expects to see from chemists. But then, as Gimzewski points out, "You don't usually think of chemists being involved in media art either." He is referring to the fact that he's recently been invited to collaborate with UCLA's new-media doyenne, Victoria Vesna, on a forthcoming art exhibition at LACMA-Lab around the theme of nanotechnology. Gimzewski's work has always been interdisciplinary — physics, chemistry, engineering and now art, he sees it as a continuum. "I don't mind jumping outside of my box," he says.

Compared to molecules, cells are a good deal easier to observe. When listening to yeast cells, there's no need for an STM — for this essentially biological work Gimzewski can make do with an off-the-shelf atomic-force microscope. It's the AFM that relays the cellular song, channeling the cytological a cappella into the realm of human consciousness. As with an STM, an AFM works by *feeling* its way over a surface, only here the instrument measures force rather than current. At the end of a cantilevered arm is a microfine tip that hovers above an object like a highly sensitive record needle and picks up minute deviations in topography. Andrew Pelling is the young man in charge of this instrument; Gimzewski has assigned him the cell project as the basis of his doctoral thesis in physical chemistry. He is going to be the first person in the world with a Ph.D. in cell sonics. Small and nervous with dark, dancing eyes, Pelling giggles like a delighted child. And why not? At 24, he is being handed the helm of a ship heading for a new scientific continent, and in the process he may be contributing to a medical revolution.

Separated from the labyrinthine STMs, the AFM is in a room by itself where it can be carefully shielded from external interference. It's placed inside a special foil-lined enclosure to protect the apparatus from electromagnetic fields, and the whole thing is pneumatically suspended on a bed of air to insulate against sound and jitter. When Pelling is running experiments, the hood is closed, the lights are off, everyone is out of the room, and the door is closed. "It's probably overkill," he says. "But we get far better resolution than the manufacturer."

I'm eager to hear a yeast song, and Pelling produces a small test tube of urine-colored liquid with a sediment of whitish sludge congealed at the bottom. "It smells like bread," he says, opening the cap, and when I take a whiff, the aroma of a bakery fills my nostrils, reminding me that through our olfactory sense we humans still maintain a visceral connection to the chemical realm. Pelling takes a pipette and sucks out some of the sludge, then smears it onto a microscope slide.

A typical yeast cell is around 5,000 nanometers (or five microns) in diameter, 10 times smaller than the width of a human hair and well within the range of the AFM. Once the sample is dried, Pelling puts the slide under the scope and closes the hood. We go out to the main lab to watch the creation of the image on a computer monitor. Slowly a mass of cells appears on the screen, small indistinct black and white blobs. Pelling zooms in, and the screen fills with about a dozen cells. At this range they are crammed together, butting up against one another and forcing themselves into a hexagonal pattern. Some are sporting pretty circular protrusions, like microscopic ringworms. "Bud scars," Pelling explains, are the places where daughter cells have budded off from the mother cell, leaving a trace of their cellular birth. He zooms in farther to the middle of a single cell, which appears to be covered with elephant skin.

Pelling locks off the AFM's position and begins to record the up-and-down movement of the tip. This tiny motion of the cell membrane is stored as a digital file to be played back later through a speaker. Because of the extremely low amplitude of the motion, it's not possible to record sound *directly*. Nor can we hear recordings live, though Pelling is planning to connect up a mixer and some speakers so that he can pipe his minimalist symphonies to the lab at large.

In the meantime, he turns on another computer and pulls up the file of a previous recording. The background noise is especially intense and I strain to hear something coherent. For a moment, I feel like a SETI researcher desperately searching the skies for signs of intelligent life. But as I listen I become aware that amid the high-pitched buzz is a faint rhythmic clicking. The monitor displays the spectral analysis of the signal, revealing a strong, sharp spike at around 1,000 hertz. When Gimzewski and Pelling first captured this signal, they couldn't believe what they were hearing. As Gimzewski notes, "It didn't seem possible that a cell could be vibrating this fast." They had expected that if there was any movement at all, it would be *much* slower. Initially, they thought the high-pitched spike must be an artifact of their experimental setup; the proof that it's a real signal emanating from the cell is that when they listen to a dead cell, the spike disappears. Pelling plays me the file of a dead cell, and it's pure, flat, monotonous noise.

Next he juxtaposes two different varieties of yeast, one from a naturally occurring strain and another from a genetically modified mutant. Each has a slightly different sound, and the differences between them can be empirically gauged by the variations in their spectral analysis, what physicists call their Fourier transform. Even to the untrained ear, they each have their own unique call. It's weirdly unsettling, listening to the songs of these microbial creatures. Voice is something that seems such a quintessentially *intelligent* characteristic. The discovery of whale songs, for example, irrevocably altered our view of a species that had until then been largely regarded as an aqueous reservoir of rare oils, while dolphins' clicking has earned them a status in our sentimental landscape that is equaled only by the higher primates. When we hear other creatures "calling," we instinctively begin to imagine an interspecies dialogue. And that is effectively what Gimzewski and Pelling are aiming toward.

Finally, they play me a recording of a yeast cell that has been doused in isopropyl (rubbing) alcohol, and the sound it makes is distinctly higher in pitch than the previous samples, the clicking more sharply pronounced. "They're screaming!" Gimzewski declares. The pair want to record cells in a wide variety of conditions, including under the influence of various chemical substances. In particular they are interested in the effects of compounds that interfere with the underlying cytoskeletal structure of the cell, which Gimzewski theorizes may be causing these cellular vibrations.

I suggest that once sound artists get wind of these recordings, Gimzewski will be inundated with requests for tapes. Turns out there's already been one snooping around — perhaps this could be the basis of a new genre of noise music. "I'll play the drums," Gimzewski enthuses, riffing on a set of air bongos.

The process of recording cells is cumbersome at the moment — every time Pelling wants to alter a cell sample, he has to take it out of the AFM enclosure. So while he can record the sound of a living cell, or one that's been killed, he cannot listen to the sound of cells dying. "That's my goal. It's a bit morbid, but that's what I'm hoping to achieve." Up till now, all the cells he has listened to have been at roughly the same stage in their life cycle. The long-term goal, however, is to record yeast cells at *every* stage of their growth cycle and to create a sonic map of a cell's life.

Gimzewski has coined a name for this fledging science, "sonocytology" — cytology being the branch of biology that deals with cells. He is hoping this technique will develop into a new form of diagnostic tool that will enable doctors to determine by listening to cells if they are healthy or sick, young or old, or potentially even cancerous. To that end Gimzewski is teaming up with Mike Teitell, head of UCLA's Department of Pediatrics and Developmental Pathology. Teitell's lab specializes in cancers of the lymphocytes, which include lymphomas and leukemias, and he is planning a series of experiments with Gimzewski that would begin to explore the potential of this technique with mammalian cells, including cancers. Teitell admits that they don't yet know if mammalian cells will exhibit a definite sonic signature, but there is every reason to be hopeful. For one thing, mammalian cells have much thinner walls than the thick-skinned yeasts; if something as gross as yeast has a distinct signal, the chances are that a mammalian signal would be even stronger.

"You never know how anything will pan out," Teitell says. "That's the nature of experimental science." But he is preparing to "ramp up" this research ASAP and is currently trying to recruit a new postdoctoral student for that task. There is what Teitell calls "the dream scenario" where "in your wildest dreams every cancer turns out to have a unique and clear signal." Then there is "the nightmare scenario" where the signal is just a jumbled mess. And then, of course, there's the "in-between scenario" (which is probably the most likely), where you see a signal but it takes time and practice to figure out what it means. Teitell compares this new field to the early days of PET scans, a technology that is now one of our primary diagnostic tools. Whether sonocytology turns out to be the next PET or

MRI, only time will tell, but when I ask Teitell when he expects to begin the mammalian work, his answer sums up the palpable excitement surrounding this research: "We want to do this yesterday."

Gimzewski is now setting his sights on even greater medical challenges. One of his research groups is currently working on a hybrid STM/AFM, which he hopes will open up further directions for cellular diagnostics. He speculates that with such a machine we might be able to watch as the pores in a cell wall open and close, and then monitor the flow of ions through the channel. Being able to observe such intricate cellular processes in situ would give doctors an enormously powerful analytical tool.

How far down might these machines take us? Until recently, most physicists believed single atoms were the smallest things we could see microscopically — any smaller and you'd have to resort to a particle accelerator. There is, however, tantalizing evidence that STMs may be able to take us *inside* the atom to see the orbits of individual electrons. According to quantum theory, electron orbits come in a wide variety of shapes, from the common spherical orbit to exotic dumbbell and doughnut shapes. Just as STMs have given us tangible images of atoms (objects long theorized but hitherto unseen), so these magical devices may finally help us to see figures of the subatomic realm.

It's exactly 20 years since Gimzewski began imaging atoms and molecules and, he says, we've come a long way. "But there is so much further we can go." As he speaks, I find myself thinking of Sergeant MacCruiskeen in Flann O'Brien's comic masterpiece about atomic science, *The Third Policeman*. MacCruiskeen has devoted himself to constructing a series of ever smaller boxes, each minuscule marvel nested inside the previous ones like a set of Russian Matryoshka dolls. After 29 boxes, MacCruiskeen is hovering at the very edge of perception, and the reader is no longer sure if he has crossed over into make-believe. The smallest of his caskets is so tiny, it is "half a size smaller than ordinary invisibility." How far can you go? O'Brien asks. Will there always be a smaller possible box? Or is there a limit to the littleness man can perceive? I put the question to Gimzewski, and his answer is worthy of MacCruiskeen himself: "When we're at the level of needing a microscope to see the microscope, then we'll know we are there."