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DynamicSilicon

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The Investor's Guide to Breakthrough Micro Devices

# Biology, MEMS, and Microfluidics

When I was in the military, I dreaded my annual physical. I visited a dozen test stations (hearing, vision, lab, dental, x-ray, electrocardiogram, etc.) where I was poked and prodded. My least favorite station was the lab where a technician drew five or six tubes of blood. Hey! I was using that. Why did they need so much? I didn't know, but the mortar between the clinic's bricks looked suspiciously dark. If a blood test showed something wrong, I'd get a call a week or two after the physical. Otherwise, I didn't see my results until the following year's physical, when I read my records as I waited at the various stations.

Each tube of blood went to a different test station. The clinic couldn't do all the tests. Some tubes journeyed to labs with sophisticated equipment. This process took a long time and cost a lot of money. Now, thanks to MEMS and microfluidics, that's about to change.

Semiconductor manufacturing now employs line widths comparable to those found in biological systems. Techniques from the semiconductor industry advance the state of MEMS and microfluidics. The diagnostic laboratory with test tubes, pipettes, filters, beakers, gels, reagents, burners, ovens, refrigerators, and centrifuges will give way to chips that do lab analysis better than the laboratories of today. The "lab on a chip" has so many advantages that it's hard to list them all. Tests can be run in parallel on a sample, which improves accuracy and tests for more unknowns. Samples can be tiny, which reduces the use of expensive reagents and speeds analysis. Efficiency improves because smaller samples and smaller reaction chambers heat and cool faster. Filters, pumps, reservoirs, tubing, valves, reaction chambers—all the elements of a conventional laboratory—are mass produced at low cost and are disposable. Waste products are kept on the chip, reducing the expense and difficulty of handling and disposal.

## DNA overview

You've heard the term "human genome." You've probably heard about the recent triumph in "mapping the human genome." Most people aren't sure what the human genome is or why "mapping" it would be so important.

Deoxyribonucleic acid (DNA) is a giant molecule—really a molecule of molecules—in the shape of a double helix. A double helix is a ladder-shaped structure where the sides of the ladder spiral around each other, separated by the ladder's rungs. The DNA molecule is a *database* of the information needed to construct, operate, maintain, and reproduce a living organism. Rather than electronic pulses, the ones and zeroes in this database are molecules. These molecules go by names like "base," "sugar," and "phosphate." Chemists use these terms as a shorthand for the atomic structure of these molecules. For example, the sugar is a group of carbon (C), hydrogen (H), and oxygen (O) atoms connected in a certain way. Because of the atoms present (C,

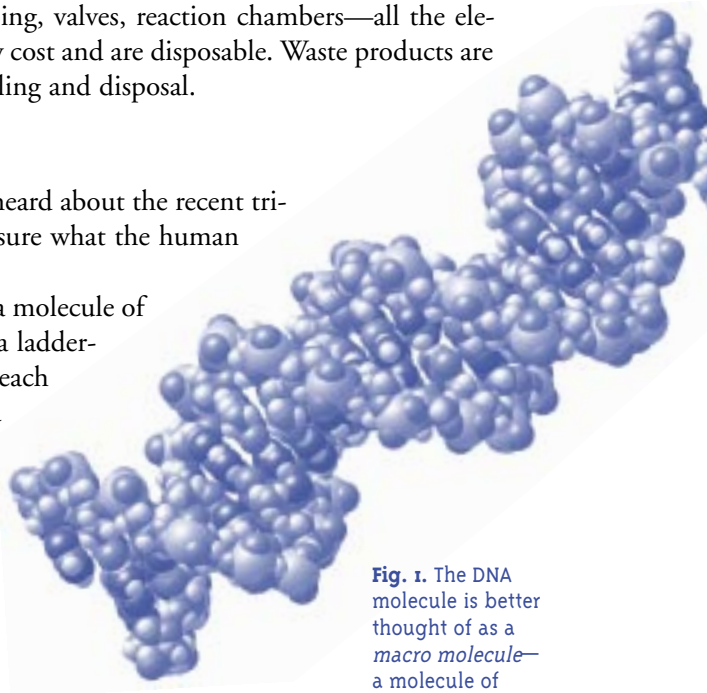

**Fig. 1.** The DNA molecule is better thought of as a *macro molecule*—a molecule of molecules.

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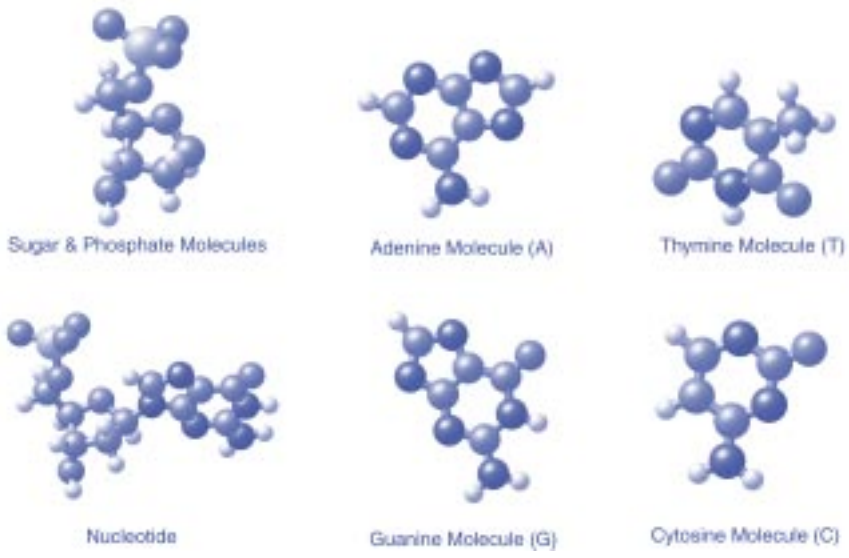


**Fig. 2.** DNA's backbone is the sugar and phosphate molecules. Links are the four base molecules A, T, C, and G. The nucleotide—the sugar and phosphate molecules together with a base molecule—is DNA's building block.

H, O) and the nature of the "bonds" among them, sugars have common properties.

The "human genome" is the DNA for a human, as opposed to the DNA for a tree or for a mouse. Before telling you why mapping this molecule is important, I'll say more about its construction.

A DNA *strand* is *half* of the double helix split down the middle of each rung of its ladder-shaped structure. A DNA strand starts with a sugar molecule ($C_5H_9O_3$). One of four bases (chemicals that react with acids to form salts), identified as A, T, C, and G, attaches to the sugar molecule's number one carbon atom. A phosphate molecule connects the sugar molecule's number five carbon atom to the number three carbon atom of the next sugar molecule and gives the strand its characteristic twist. This composition of a sugar molecule, a phosphate molecule, and a base molecule is called a nucleotide. It is the fundamental building block of a DNA strand. Think of it as a ladder with sides that rotate as they go along (rather than being straight). Each rung is a "base pair." A always pairs with T to form a rung. C always pairs with G. A DNA molecule is a long string of nucleotide pairs.

The DNA's information is in the sequence of base pairs forming the double helix. Each nucleotide in a strand contains one of four bases (A, T, C, G). Think of them as four colors of pop-beads strung together to store information. Using four colors, I can make more than a million different strings of ten pop-beads. Eleven beads makes four million strings; twelve beads makes sixteen million. A DNA strand for *E.coli* contains about 4.5 million nucleotides. A human DNA strand contains about three billion nucleotides (beads).

These are *gigantic* molecules. A single nucleotide contains about 34 atoms. A base pair is two complementary nucleotides. *E.coli*'s 4.5 million base pairs make its molecule 1.4 mm long—about 500 times the bacteria's 3-micron length. The molecule fits because it sits inside the bacteria like a tangled strand of ultra-thin spaghetti. Stretched out, our DNA, with its 3 billion base pairs, is more than *five feet* long. A five-foot-long molecule!

Each DNA molecule isn't just a unique linking of three billion base pairs; it contains code sequences of specific information called "genes." *E.coli*'s DNA contains about 4,000 genes. The human DNA molecule contains tens of thousands of genes, each composed of hundreds or thousands of base pairs. A gene contains specific instructions for such things as constructing a liver protein. To build a protein, a complex of enzymes uses the gene's nucleotide sequence (though not directly) and a collection of amino acids. An amino acid is the smallest molecule that matters in a living thing. Proteins are larger molecules made of amino acids. Each sequence of three nucleotides tells the enzyme which of twenty amino acids (for humans) to add next. Three nucleotides can represent sixty-four codes. There's a unique start code and sev-

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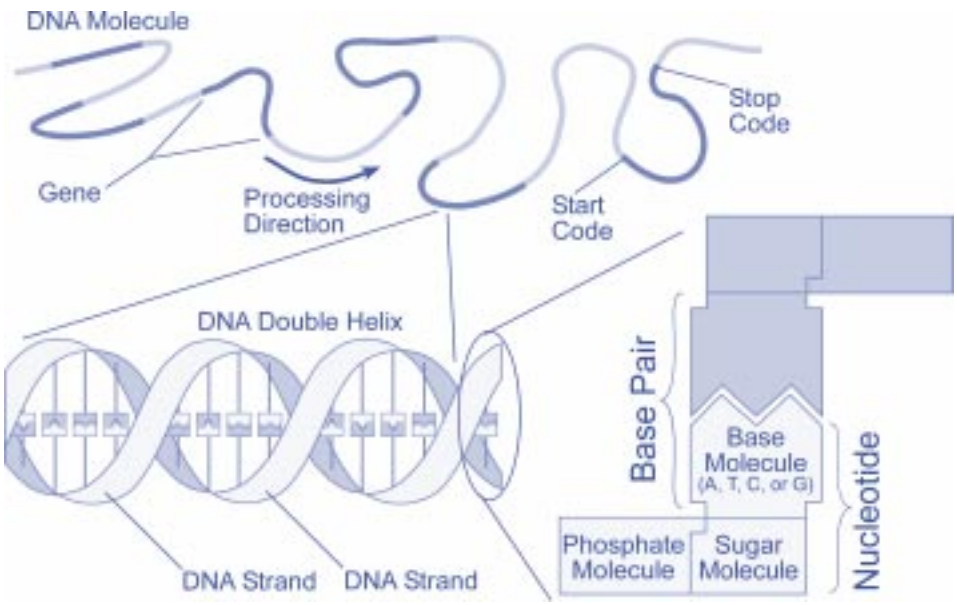


**Fig. 3.** The structure of the DNA molecule is a double helix. The double helix is comprised of two strands of nucleotides.

eral codes that tell when to stop adding amino acids. That still leaves more than twenty codes, so some amino acids have more than one code.

Mapping means locating the gene on the DNA's double helix and identifying the amino acids that are called out by the nucleotide sequence within the gene. Since the DNA contains all of the information about a particular organism, it's unique to each species. DNA analysis is a sure-fire way to identify organisms.

## Steps in DNA analysis

Suppose I'm looking for a particular strain of *E.coli* bacteria in a water sample from a local lake. I'll call this particular strain "millard." Surprisingly weak concentrations can be threatening—even less than one organism per milliliter of sample. Millard is in the sample with millions of other organic molecules and miscellaneous junk. Finding millard won't be easy; it's not like dusting for fingerprints. Millard is invisible and it's hiding in the water sample amongst substances that complicate the analysis. Analysis requires three phases: preparation, amplification, and detection.

**Sample preparation**. Here's what I have to do to prepare a sample for testing in today's laboratory. It takes hours. First, I separate and "wash" the cells. Next, a process called "cell lysing" breaks the cells down, causing them to release their constituent parts, including the DNA and RNA. Finally, I purify the sample to its constituent DNA. This sample contains the DNA from all the organisms in the original sample, including millard. But the millard concentration is so weak that it is undetectable.

**Amplification**. This is the magic. Kary B. Mullis won the Nobel Prize in chemistry in 1993 for inventing the process called polymerase chain reaction (PCR). PCR exploits DNA's ability to make copies of itself. Here's how it works. To the sample add a special polymerase enzyme, add reagents that supply nucleotides, and add a supply of "primer" molecules. Heat the sample to about 200° F. This temperature "denatures" the DNA—splitting the molecule into two complementary strands by breaking the weak bonds between the base pairs.

A primer molecule is a synthetic nucleotide strand that complements a nucleotide sequence in millard's DNA and is long enough to be unique to millard. It is a "fingerprint" for millard. For each unique primer, we must supply enough copies to complete amplification. If we want to make a million copies of millard, we supply a million primer molecules.

Lower the temperature to approximately 150° F and the denatured DNA "anneals" or recombines to form the double helix. In this case, however, with many primer molecules available, the primer anneals to the denatured version of millard. The primer's nucleotide sequence does not fit any of the other denatured DNA strands in the sample.

Raise the temperature to approximately 160° F. The polymerase enzyme catalyzes "extension" of the nucleotide strand (we supplied the reagents at the beginning of the amplification process). The primer is short compared to the original millard DNA strand. The process step extends one end of the nucleotide strand, but not the other, because the polymerase enzyme works only in one direction. This leaves the DNA molecule with completed rungs in one direction and open rungs in the other direction. This is called a singly-terminated strand.

That's one PCR cycle. Run another. The singly terminated millard DNA denatures, new primer molecules anneal to the denatured original strands and to the singly terminated millard strands. This time I get two singly terminated strands and two doubly terminated strands. Run another. This leaves four singly terminated strands and eight doubly terminated strands. In each cycle, the halves of the original produce another pair of singly terminated millard strands and the number of doubly terminated strands doubles. After twenty-one cycles, each original millard DNA molecule will produce forty-two singly terminated strands and more than a million (2 to the 20th power) doubly terminated strands. These doubly terminated strands are millard's fingerprints amplified millions of times.

**Detection**. One detection method marks the DNA with a fluorescent dye and then separates molecules by size. Results differ depending on whether millard is absent or is amplified in the sample.

Another detection method attaches a fluorescent molecule to the primer. After amplification, separate unused primers from the sample. Shining a light on the sample causes the fluorescent molecule to respond with its characteristic light. If the primer binds to a DNA molecule, then the fluorescent molecule will be amplified in the final sample.

## Cepheid

Conventionally, PCR amplification uses macro-scale equipment in a laboratory. Macro-scale equipment means that samples must be brought to the laboratory. Cepheid (CPHD) is changing that. Cepheid is shrinking the lab and taking it into the field.

Microfluidics, enabled by semiconductor manufacturing techniques, helps Cepheid put PCR on a single chip. In the lab, large reaction chambers create large thermal masses that slow amplification. It can take hours to complete the necessary twenty to thirty PCR cycles. On a chip, the sample size is 25 to 100 microliters. The small reaction chamber, isolated from the surrounding silicon for efficiency, together with the small sample size has low thermal mass. Thermal cycles are quicker. Denaturing, annealing, and extension, rather than heating and cooling, dominate the processing time. Therefore, on-chip amplification can be ten times faster than laboratory PCR. In addition, because the sample spends less time at transition temperatures, fewer undesirable chemical reactions contaminate the sample—making analysis simpler.

Cepheid's PCR chip comes in a disposable cartridge that includes optics blocks that mate with laser diodes and detectors in the base system. Each cartridge contains four optical channels for real-time monitoring of fluorescence-based detection. The cartridge mates with one of up to sixteen I-Core modules in the bench-top Smart Cycler System. Each I-Core module contains microprocessor-controlled circuitry for PCR cycling and for optical detection. Up to eight Smart Cycler Systems run from a Windows PC that controls the experiments individually in each I-Core module. Experiments are not forced to run either sequentially or in parallel as they might be in a conventional laboratory. Further, the PC monitors the progress of each of the experiments, relieving the technician and adding precision.

The current cartridge shrinks and automates two of the three DNA analysis steps: amplification and detection. Cepheid's next cartridge will shrink and automate sample preparation as well. The sample, in addition to containing the nucleic acid that is the object of the analysis, will likely contain proteins and other complex chemicals that bind with the nucleic acid and interfere with the analysis. Sample preparation extracts, purifies, and concentrates nucleic acids from the collected sample. Cepheid designed a special chip to aid the process. Nucleic acids bind to glass; Cepheid exploits this property. The chip, which looks like a dense forest of telephone poles, is silicon pillars etched at just the critical spacing to collect nucleic acids. The pillars are allowed to oxidize (forming silicon dioxide, which is glass), creating a comparatively large glass surface to attract the desired molecules. This eliminates off-line sample preparation, bringing speed and portability to sample analysis.

## Nanogen

Nanogen (NGEN) builds a unique DNA analysis chip or "gene" chip. Nanogen's chip is an array of individual test sites. The current chip, housed in a transparent, $175, "NanoChip" cartridge, contains 99 test sites. Primer nucleotide sequences are bound to test sites. Test sites can have different primers. Nanogen exploits the naturally occurring positive or negative charge of most biological molecules. Addressing a particular primer test site with an electric charge attracts DNA molecules to the test site, speeding processing from hours to minutes. DNA molecules containing a complementary nucleotide sequence bind with (anneal to) the primer.

Nanogen supplies chips with primers at the test sites or the customer can build a custom array of primers. To

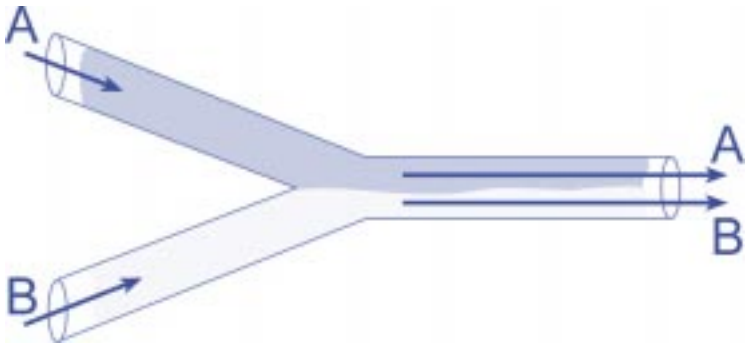


**Fig. 4.** Fluid flow is laminar in 50-micron channels. Fluids flow side by side without mixing. Particles diffuse across the flow boundary.

build a custom array, address test sites with a charge opposite to the primer's. Then, introduce the primer, which is attracted to and binds at the charged test site. Wash and repeat for other primers and other test sites.

**Single nucleotide polymorphism (SNP)**. SNP (pronounced "snip") detection is one important application of Nanogen's NanoChip. A SNP swaps the positions of a single nucleotide pair in a nucleotide strand. SNPs may be the basis for disease and for toxic reaction to a certain drug and, therefore, are important for diagnosis and treatment of disease. Among our DNA's tens of thousands of genes, there may be as many as 10,000,000 SNPs.

A drug that is effective for large numbers of people may fail regulatory approval because a few individuals experience undesirable side effects. SNPs may distinguish the groups, so the first group can benefit from the drug and the second group can be spared adverse reactions.

Caliper (CALP), Incyte (INCY), and Affymetrix (AFFX) also build chips for DNA screening. Affymetrix has about 40% of today's DNA-chip market with its GeneChip.

Identifying, cataloging, and analyzing SNPs in drug screening experiments may require millions of experiments—clearly expensive and time-consuming by conventional laboratory methods. Shrinking experiments to chip scale makes the task feasible. In chip-scale experiments, microliter raw samples become nanoliter prepared samples, shrinking sample and reagent costs and speeding analysis through automation. Caliper and Agilent (A) together develop the Agilent 2100 Bioanalyzer and system software. These systems use optical detection of fluorescent markers. Caliper claims it would be possible to perform 100,000 experiments a day on a single bench-top LabChip system. This is an astounding improvement over manual lab procedures in common use. The space in a conventional lab could easily accommodate enough of these bench-top systems to run 1,000,000 experiments a day.

## Microfluidics

**Laminar flow**. Imagine two rivers coming together down a steep slope; the water mixes rapidly. But what if the rivers, instead of being water, were two colors of hand lotion? They wouldn't mix so rapidly. How rapidly fluids mix depends on the ratio of their inertia to their viscosity. Inertia is the fluid's propensity to keep moving or to resist motion. Viscosity is the fluid's thickness or sluggishness. Water's viscosity is relatively low (at least in comparison to hand lotion) and, on a steep slope, its inertia can be high, so the water mixes. This ratio of inertia to viscosity is called the Reynolds Number. For Reynolds Numbers above 1,000, flow is turbulent; the fluid mixes. For Reynolds Numbers below 1,000, flow is "laminar," meaning the fluid follows smooth streamlines and won't mix with a neighboring flow.

**Diffusion**. Where the Missouri River enters the Mississippi, the Reynolds Number is above 1,000, so the rivers mix. Scale the flows down to sizes reasonable for laboratory manipulation and the flows still mix. If we want to do laboratory analysis on a chip, however, fluid flows will be scaled down to 50 microns (about the diameter of a human hair). At this scale, the Reynolds Number is well below one. The inertial component of fluid flow can be ignored; viscosity dominates fluid behavior, so flows are strictly laminar. Streams of red and green water entering a common 50-micron channel flow side by side. The only mixing is diffusion of particles across the boundary. Diffusion occurs naturally (no energy input is required). The amount of diffusion across the boundary depends on particle mobility (which generally decreases as particle size grows), on viscosity, and on the fluid's temperature.

Microfluidic systems exploit laminar flow and diffusion. Picture an "H"-shaped channel with the sample flowing in at $A_1$ and an electrolyte flowing in at $B_1$ (fig. 5). An electrolyte is a fluid, such as water, that contains ions. Laminar flow in the channel carries the sample out at $A_2$ and the electrolyte out $B_2$. In the horizontal channel, molecules suspended in the sample will diffuse across the laminar boundary according to their mobility. More diffusion occurs in a longer channel. This

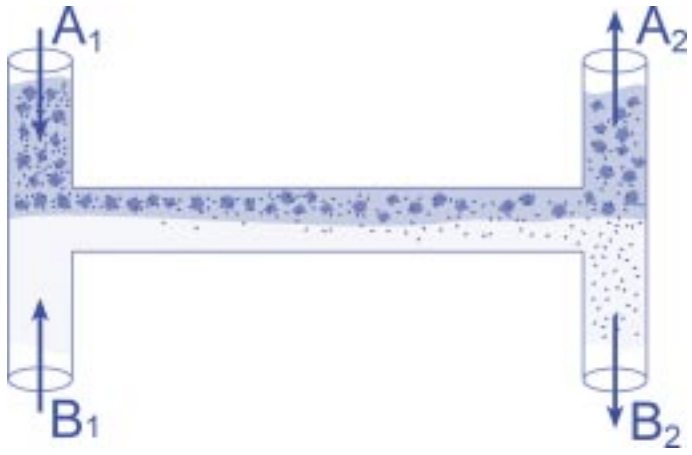


**Fig. 5.** Laminar flow and particle diffusion enable filtering with no filter element. Small particles diffuse across the fluid boundary, but the large particles do not.

offers one way to separate millard from the sample and to concentrate it in another electrolyte for detection. In a second method, small tag molecules diffuse across the laminar boundary to attach themselves to large molecules in the second stream.

This H-shaped channel is a filter. It separates particles by size and weight. It can remove large particles, such as blood cells, from a sample or it can remove small-particle contaminants. It operates continuously with no moving parts to wear out and no filter elements to clog.

At this scale, gravity is unimportant relative to viscosity, surface tension, and even the distribution of electric charges. If gravity is unimportant, we won't be pouring the contents of 50-micron beakers back and forth. We'll have to find another way to move our samples. We can use pressure or pumps—or the effect of an electric field on charges in the fluid.

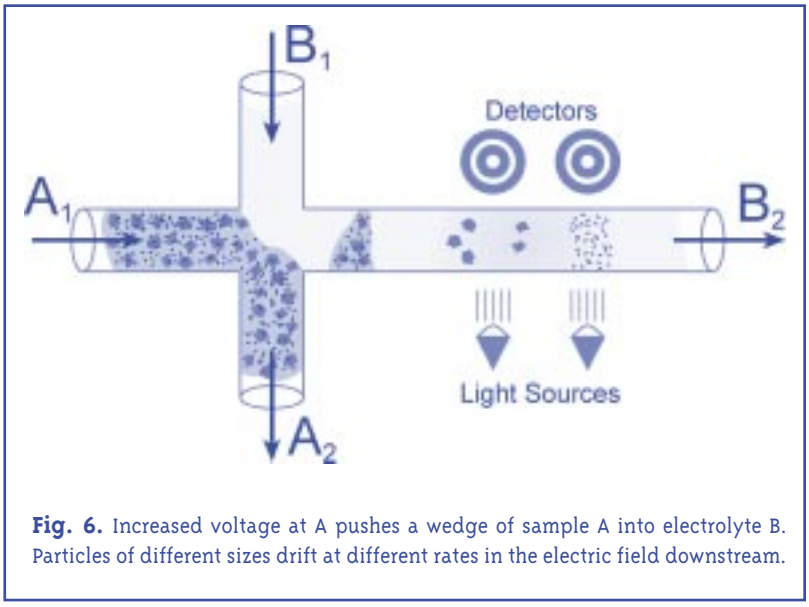


**Fig. 6.** Increased voltage at A pushes a wedge of sample A into electrolyte B. Particles of different sizes drift at different rates in the electric field downstream.

**Electroosmosis**. In an electrolyte, such as water, charges reside in a thin layer close to the channel's edges. In an electric field, the charges move, pulling along the fluid around them. Fluid flows along the channel like an electric train. This is electroosmosis.

**Electrophoresis**. For lab-on-a-chip applications, another effect, called electrophoresis, helps us distinguish among charged DNA fragments and proteins and even relatively large objects such as blood cells. In an electric field, these charged particles drift at different rates (even relative to a moving fluid) according to their characteristic mobility.

We exploit electroosmosis and electrophoresis to separate a subsample's constituents. Imagine a "+"-shaped intersection between two channels. The electric field between $A_1$ and $A_2$ causes the sample to flow from $A_1$ toward $A_2$ by electroosmosis. A similar electric field causes an electrolyte to flow from $B_1$ to $B_2$. Temporarily increasing the voltage between $A_1$ and $A_2$ forces a wedge of the sample into the electrolyte moving toward $B_2$. As the wedge moves toward $B_2$, molecules in the wedge spread out according to their (electrophoretic) mobility. Concentrations of these molecules can be detected according to their positions in the channel.

One common detection method uses fluorescent tags on the molecules that disclose themselves in passing through the light of an LED. Another detection method, called flow cytometry, measures scattering of laser light shining through the sample. Microfluidic flow cytometry can count and classify platelets and blood cells, for example. Fig. 6 shows two wedges taken from the sample flow.

**Microfluidic components**. The figures above show some of the plumbing for a lab on a chip. In addition to these devices, microfluidics employs valves, pumps, rotary mixers, multiplexers, reservoirs, check valves, restrictors, nozzles, specialized flow channels, separators, motors, heaters, detectors, and more. Some of these devices employ standard semiconductor processing techniques to build functions with no moving parts. Others, such as the motors and check valves, are MEMS with moving parts. Materials for these microfluidic devices include silicon, plastics, glass, and even

rubber. Some manufacturers, such as Caliper, Incyte, Aclara BioSciences (ACLA), and Cepheid build microfluidic devices as a complement to system sales. Others, such as Nanostream, Micronix, Genefluidics, and Fluidigm, specialize in supplying microfluidic designs.

## Drug discovery, drug development, and toxicology

Each cell contains all of the DNA's information, but some genes are "expressed," while others lie dormant. The nerve cell, for example, "expresses" those genes necessary to build proteins and enzymes for its particular structure and function. A liver cell expresses other genes and makes different proteins. An immune cell invaded by bacteria expresses genes to build antibodies.

Normal cells and cells exposed to foreign chemicals express different genes. If the chemical causes harmful effects, we call it toxic and regulate its production or access to it; if it causes beneficial effects, we call it a therapeutic drug and sell it. Toxic chemicals and therapeutic drugs share common effects; their presence in a cell causes the "expression" of genes that produce proteins, enzymes, or antibodies. Traditional laboratory methods for detecting active genes in a cell took *three days per gene*. With tens of thousands of genes to screen for, it took years to identify which genes were "expressed" to produce antibodies in a cell exposed to foreign chemicals.

Using gene chips, MEMS, microfluidics, and modern methods, experimenters can now test for thousands of genes in a single afternoon. Today, researchers build gene-activation profiles mapping the effect of a cell's exposure to chemicals in days or in weeks. Drug discovery and drug development will accelerate tremendously. Drug screening experiments, for example, accelerate from a few a day to hundreds of thousands. Toxicology will similarly accelerate. Even drug delivery will soon benefit from technology's invasion.

These tools and techniques are changing chemical and biological analysis.

## Diagnosis and forensics

Guessing causes of illness by correlation of symptoms will give way to scientific analysis in disease diagnosis. Diagnosis will no longer be trial-and-error tests, biopsies and cell cultures, comparing samples under microscopes, and waiting weeks for results. Enabled by the combination of technology and biological information science, diagnosis will move to the field, to self-testing, and to real-time results. It will be better, faster, cheaper, and safer and it won't require twenty-five years of medical training.

Random SNPs in unused regions of the genome enable individual identification. It's no longer necessary for forensic specialists to find a fingerprint-covered lead pipe in the conservatory to track the villain—a few cells will do.

## Technology invades biology; biology invades technology

Changes are coming and there's no turning back. It may be too early to tell which companies and which new methods will dominate the market. It's not too early to predict that drug discovery, drug development, drug delivery, toxicology, diagnostics, and forensics will change dramatically in the next few years. It's happening already. Microfabrication, microfluidics, MEMS, nanotechnology, and information science are invading these areas and displacing traditional methods and equipment.

In working my way through the invasion of biology by MEMS, nanotechnology, microfluidics, and information science, I cataloged an extensive list of advantages. The only disadvantage I encountered was the newness.

Smaller samples are easier to obtain, cost less to test, conserve reagents, and reduce waste.

Lab-on-a-chip systems are portable, automate processing, analyze samples faster (increased throughput), give real-time results (reduced latency), increase precision, enable parallel testing and testing for multiple unknowns, and reduce costs through mass production. Lab-on-a-chip systems take analysis to the field—that's more efficient than taking samples to a laboratory.

Cartridge-based systems simplify sample and reagent isolation and handling (for better experimental control and better precision), improve safety, and simplify disposal.

Microfluidic systems can be self-calibrating and permit self-diagnosis because the expertise resides in the system rather than in the operator.

Information science applied to biology's base-four DNA molecule brings quantitative analysis and detailed knowledge of cause and effect.

Biology will also invade technology. In "MEMS-based Storage" (*Dynamic Silicon, Vol. 1, No. 5*), I outlined how Nanomagnetics is co-opting biology's ferritin protein to push the superparamagnetic limit from today's estimate of 100-200 Gb/in$^2$ to 4,500 Gb/in$^2$. That's potentially an impressive gain, but it's nothing compared to nature's data storage density in the DNA molecule. *E.coli*'s 1.4 mm DNA molecule contains 4.5 million base pairs. Each nucleotide represents two bits of

information (since there are four bases), the base pair makes the data redundant, and the molecule's construction facilitates copying. The DNA molecule is about 2.4 nanometers ($10^{-9}$ meters) in diameter. By comparison, line widths in leading-edge semiconductors are approaching 100 nanometers. The data storage density of *E.coli*'s DNA is greater than 3,450,000 Gb/in$^2$. Today's hard disk is less than 50 Gb/in$^2$ (2001). Living organisms display an impressive range of capabilities—all performed with chemical reactions occurring at ambient temperatures. Engineers will co-opt biological mechanisms for computation, for information storage, for photosynthesis, and for a host of other applications.

Nick Tredennick and Brion Shimamoto

*P.S. This issue introduces many technical terms, so we've posted a glossary in the subscriber area of the web site.*

# Dynamic Silicon Companies

**The world will split into the tethered fibersphere (computing, access ports, data transport, and storage) and the mobile devices that collect and consume data. Dynamic logic and MEMS will emerge as important application enablers to mobile devices and to devices plugged into the power grid. We add to this list those companies whose products best position them for growth in the environment of our projections. We do not consider the financial position of the company in the market. Since dynamic logic and MEMS are just emerging, some companies on this list are startups.**

| Company (Symbol) | Technology Leadership | Reference Date | Reference Price | 8/31/01 Price | 52-Week Range | Market Cap. |
|---|---|---|---|---|---|---|
| Altera (ALTR) | General Programmable Logic Devices (PLDs) | 12/29/00 | 26.31 | 28.66 | 18.81 - 67.13 | 11.1B |
| Analog Devices (ADI) | RF Analog Devices, MEMS, DSPs | 12/29/00 | 51.19 | 47.88 | 30.50 - 103.00 | 17.3B |
| ARC Cores (ARK**) | Configurable Microprocessors | 12/29/00 | £3.34 | £0.56 | £0.48 - 4.29 | £499M |
| Calient (none*) | Photonic Switches | 3/31/01 | | | | |
| Celoxica (none*) | DKI Development Suite | 5/31/01 | | | | |
| Chartered Semiconductor (CHRT) | CMOS Semiconductor Foundry | 7/31/01 | 26.55 | 26.70 | 21.05 - 87.75 | 3.7B |
| Coventor (none*) | MEMS IP and Development Systems | 7/31/01 | | | | |
| Cypress (CY) | MEMS Foundry, Dynamic Logic | 12/29/00 | 19.69 | 21.62 | 13.72 - 49.94 | 2.7B |
| QuickSilver Technology, Inc. (none*) | Dynamic Logic for Mobile Devices | 12/29/00 | | | | |
| SiRF (none*) | Silicon for Wireless RF, GPS | 12/29/00 | | | | |
| Taiwan Semiconductor (TSM†) | CMOS Semiconductor Foundry | 5/31/01 | 19.86 | 12.89 | 11.52- 26.34 | 43.4B |
| Tensilica (none*) | Design Environment Licensing for Configurable Soft Core Processors | 5/31/01 | | | | |
| Transmeta (TMTA) | Microprocessor Instruction Sets | 12/29/00 | 23.50 | 2.54 | 2.37 - 50.88 | 341M |
| Triscend (none*) | Configurable Microcontrollers (Peripherals) | 2/28/01 | | | | |
| United Microelectronics (UMC†) | CMOS Semiconductor Foundry | 5/31/01 | 10.16 | 7.30 | 6.14 - 13.21 | 16.7B |
| Wind River Systems (WIND) | Embedded Operating Systems | 7/31/01 | 14.32 | 12.95 | 12.95 - 50.63 | 1.2B |
| Xilinx (XLNX) | General Programmable Logic Devices (PLDs) | 2/28/01 | 38.88 | 39.04 | 29.79 - 92.27 | 13.0B |

* Pre-IPO startup companies. ** ARK is currently traded on the London Stock Exchange †Also listed on the Taiwan Stock Exchange

NOTE: This list of Dynamic Silicon companies is not a model portfolio. It is a list of technologies in the Dynamic Silicon paradigm and of companies that lead in their application. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The authors and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

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