ment direction weighted by the activity of neurons then accurately predicts the actual movement performed. This explains many properties of the motor cortex, but also raises several questions. How is the sensory system, with its emphasis on specificity of representation, coupled to the distributed representations of the motor system? How many motor cortex neurons need to be recorded simultaneously in order for real-time movements to be controlled (*7*)?

Taylor *et al.* (*2*) begin to shed light on some of these puzzles. They recorded neuronal activity in the motor cortex of monkeys as the animals made real and virtual arm movements in a computer-generated 3D virtual environment. The monkeys moved a cursor from a central start position to one of eight targets located at the corners of an imaginary cube (see the figure). Their hand movements were represented by two spheres: one being the stationary "target," and the other a mobile "cursor" whose motion was controlled either by the monkey's hand (hand control) or by recorded activity of cortical neurons (brain control). Taylor and colleagues investigated the effects of visual feedback on the monkey's hand movements generated by cortical signals in a closed-loop system. This system differs from the classical open-loop system where animals do not receive visual feedback (see the figure). In the closed-loop system, the monkey's hand movements depended only on the activity of the few recorded neurons, and not on the millions of other active neurons in the motor cortex. Surprisingly, the new study reveals that a few dozen neurons (a tiny fraction of those constituting the motor cortex) are sufficient to generate accurate hand movements.

Intriguingly, the notion of a widely distributed population code is the foundation on which Taylor *et al.* built their study. Yet, their results seem to suggest that effective encoding of motor actions can be accomplished with a very small number of neurons. There are several explanations for this paradox. The first is that learning is crucial. The properties of the recorded cortical neurons became adapted over the course of days, allowing more and more precise control of the cursor. Second, the monkeys relied on visual feedback to fine-tune the properties of the small group of recorded neurons, demonstrating that the visual and motor systems are tightly coupled rather than separate modules. The two new elements in the Taylor *et al.* study—namely, the closed-loop system and visual feedback—are likely to have practical consequences for the design of neuroprosthetic devices. It now seems that only a few recorded neurons, or local groups of neurons, become adapted to actually control movement.

Independently, Brecht and colleagues have shown that injecting a current into a single neuron in the rat cortex elicits a short sequence of action potentials that lead to detectable whisker movements (*8*). Thus, the cortical representations of the motor system may not be that global after all. This is reassuring given the similarities in the anatomical organization of sensory and motor cortical structures. The functional properties of different cortical areas, like their anatomical organization, may turn out to be variations on a common theme.

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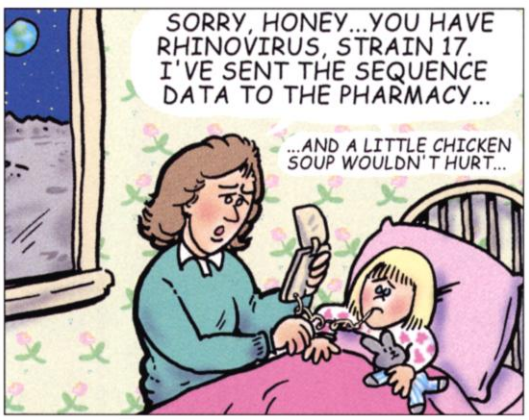
PERSPECTIVES: ANALYTIC CHEMISTRY

Everyone's a (Future) Chemist

Mark A. Burns

Miniaturized chemical analysis systems ("labs-on-chips") (*1*–*4*) have the potential to revolutionize analytical chemistry. A roomful of equipment and several trained technicians may be replaced with a few small, battery-powered devices. These portable systems could make complex chemical analysis available to the untrained, providing individuals with better tools for investigating the world around them (see the figure).

What stands in the way of further advancing this technology? An analogy with the computer industry may help to understand the challenges ahead. The computer industry was born not when the transistor was invented but when versatile and efficient integrating systems on and off the chip were invented (*5*, *6*). For microfabricated integrated chemical systems, one of the biggest challenges has been how to control fluid flow on a micrometer scale. Many individual components now exist, from pipes and fluid channels to the pumps and valves needed for full fluidic control. The difficulty lies in integrating them into the same device with other analysis components.



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Over the past 15 years, the length scale of fabrication has continued to decrease from the micrometer-scale that is widely used in the production of computer chips to the submicrometer scale (*7*). Recent advances in molecular-level engineering and assembly ("nanofabrication") and soft lithography are expanding the pool of microfabrication tools and materials (*8*, *9*). By combining these and other fabrication or manipulation techniques, simple but powerful components can be constructed.

An example of combining different techniques for component development is given by Terray *et al.* on page 1841 of this issue (*10*). The authors use latex spheres manipulated by optical traps to pump fluids. To fabricate their devices, they use standard channel-etching procedures combined with latex spheres that serve as pump vanes, and optical traps to control the spheres' motion. The beauty of their approach is that they have accounted for future integration into larger, more complex devices: Multiple pumps are controlled on the same device with the aid of a piezoelectric mirror.

A range of other microfabricated pumps, valves, and fluid-handling systems have been reported. Some pumping systems rely on surface tension, exploiting the surface forces that dominate fluid motion at micrometer-length scales (*11*–*13*). For aqueous liquids, electroosmotic pumping provides electronic control of liquid motion. This method has been used exten-

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sively for sample loading in capillary electrophoresis systems (*14*). Relatively few of the wide range of mechanical valves that exist today (*15*) have been integrated into chemical analysis systems, not least because of noncompatible fabrication procedures. Coupling of these valves or new valving strategies into more complex systems is sorely needed. Materials that expand in response to an external stimulus (such as an electric field) also hold considerable promise for impacting this field.

Progress on the construction of fully integrated chemical systems has lagged behind component development. In a fully integrated chemical analysis system, the input to the device is a gas or liquid sample plus reagents, and the output is an electronic signal indicating the presence and/or concentration of the tested compounds. Successes include the combination of liquid metering, reaction, analysis, and detection steps necessary for DNA identification in a single device (*16*).

But not all microfabricated chemical systems require full integration. Microfabricated DNA hybridization arrays have already had a tremendous impact on genetic analysis (*17*, *18*). In these systems, the power of the analysis lies not in the movement and control of multiple liquid samples but in the multiple simultaneous hybridization events on the chip. Gas-sensing systems such as the "electronic nose" for sensing low concentrations of gas-phase compounds have a similar advantage in being able to detect many different chemical species (*19*). Nonsensing applications include chemical production, for example, of harmful chemicals from harmless precursors on site, avoiding storage of toxic material (*20*).

For chemical integrated systems to be successful, the devices need to be cheap, durable, and compact. Packaging, often overlooked in research advances, can present a significant stumbling block to the ultimate success of the device. The applications for these systems will be numerous, but two areas are particularly promising. Airborne contaminants pose a threat at home, at work, and in the battlefield. A microfabricated device for their detection should, however, be able to handle gases and liquids on the same chip, because the species of interest (for example, a biological warfare agent), though found in a gaseous or suspended state, may need to be analyzed in solution.

The second area is genetic testing and diagnosis. The technology for identifying pathogens and inborn genetic disease susceptibilities on the basis of DNA sequence information exists, but these methods are not cost effective for widespread use. Miniaturized genetic testing would provide accurate diagnosis of infectious diseases and predisposition to future ailments. This type of analysis could also be applied to other fields, including food-borne pathogens, agriculture pest isolation, and forensic identification.

The potential impact of microfabricated integrated chemical systems is substantial. The current state of chemical analysis is analogous to that of computing technology in the mid-1970s. At that time, Cray had just introduced its first supercomputer, Cray I, with a peak performance of <0.2 gigaflops (*21*). Today, one of Apple's G4 personal computers can do 15 gigaflops (*22*). The bulk of chemical analysis and testing, aside from simple test kits such as pregnancy tests and glucose measurements, is still done in large centralized laboratories. The sequencing of DNA associated with the Human Genome Project is a good example: A handful of labs produced the bulk of the current draft sequence.

If future technology developments in chemical analysis parallel those in the computer industry—and there is every indication that they will—then the power to analyze a variety of chemical information will be disseminated to the individual. Given the wide range of potential chemical and biochemical tests, the microfabricated chemical analysis device will be as ubiquitous in the future as the computer chip is today.

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PERSPECTIVES: DEVELOPMENT

Putting the Brakes on Regeneration

Lisa McKerracher and Benjamin Ellezam

Neurons communicate with each other through specialized cytoplasmic processes called axons and dendrites. During development, axons and dendrites follow separate differentiation pathways. Nerve damage in the adult caused by injury or disease usually results from loss of the long axons. Current thinking is that axons of the optic nerve, brain, and spinal cord fail to regenerate after injury because of an inhospitable environment that contains growth-inhibitory proteins. Accordingly, strategies to stimulate nerve regeneration in the central nervous system (CNS) have focused on altering the environment. An important question, however, is whether changes acquired during development also limit the ability of adult neurons to regrow their axons. On page 1860 of this issue, Goldberg *et al.* (*1*) reveal that postnatal retinal ganglion cells (RGCs) in the rat cannot grow axons as fast as embryonic RGCs, even under the most favorable test environments. With this finding, these investigators provide evidence that the poor growth of adult CNS axons is not simply a consequence of the local environment, but is a property acquired during development. Their key observation is that contact between RGCs and amacrine cells—interneurons that form part of the retinal circuitry—provides the developmental switch that drives RGCs into a dendritic growth mode, and that this switch limits the ability of older neurons to grow axons (see the figure).

Cultured neurons from embryonic animals grow axons much more rapidly than do neurons from older animals. Goldberg *et al.* (*1*) set out to discover the reasons for these differences by measuring axonal growth rates. These investigators screened

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