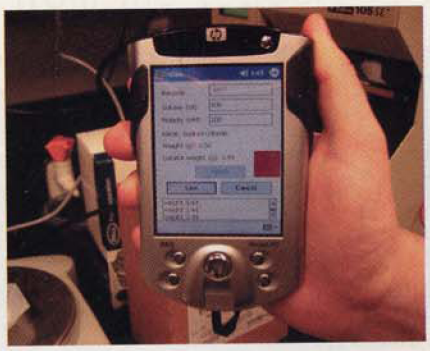
Shapiro's lab is part of the New York Structural Genomics Research Consortium, one of nine centers funded by the NIGMS. His group at Columbia recently took delivery of a new Genesis Freedom workstation, from Tecan Group Ltd., Maennedorf, Switzerland. "This robot was designed by Tecan in collaboration with Structural GenomiX [Inc., San Diego]," says Shapiro. The Tecan system is flexible, it can pipette accurately, and it can be configured in many ways, he says, plus "there is a minimal time that the protein drop is exposed to the environment."



A personal digital assistant connected to a wireless computer network in Wladek Minor's laboratory at the University of Virginia has an integrated barcode reader and details on reagents in the lab database. (Source: W. Minor)

Hanging and sitting drops

Protein crystallization typically relies on a technique known as vapor diffusion. A drop containing the protein, stabilizing buffers, precipitants, and crystallization materials is enclosed in a system with a separate reservoir of the same materials, minus the protein, at a higher concentration so that water preferentially evaporates from the drop. When the conditions are right, the concentration of the protein in the drop increases to the point where crystals can form. If the drop contains crystals of the protein, the conditions can then be optimized to give the best possible crystals before the x-ray crystallography that will reveal its proper structure.

The drop itself can be a hanging drop, which is suspended over the reservoir on the bottom of a coverslip, or a sitting drop. For a sitting drop, a shelf in the well of a microtiter plate holds the protein drop in place so that the researcher can look for crystals. Shapiro prefers the sitting drop method.

"The hanging drop is not amenable to automation," says Shapiro. "There was a first generation of robots that pipetted onto a coverslip, turned it upside down and put it onto a well. Those are gathering dust." The 96-well sitting drop system is much easier to automate, says Shapiro. "The robot can set up a 96-well sitting drop and move it right to the incubator."

The Tecan system, priced from $100,000 to $400,000, creates the initial screening stock according to a preset recipe. It then sets up as many as 1,000 different conditions in 96-well microtiter plates, by varying pH, concentration, temperature, and so forth. The solution is deposited on a shelf on the side of the well and also in the well's reservoir. A separate pipetting system then deposits the protein onto the shelf, and the plate is sealed.

"We typically set up a large screen of three 96-well plates for each protein at 4°C and 20°C," says Shapiro. "Usually we'll find some condition where there are crystals. We'll expand that by hand."

The Tecan system requires substantial programming before it can be used in most liquid handling situations, says Dave Riling, general manager of DataCentric Automation Corp., Nashville, Tenn. Riling's company is building a modular automatic crystallography system in collaboration with GlaxoSmithKline Beecham that combines liquid handling with imaging, incorporating its software to integrate the system. DataCentric chose to provide the Hamilton MicroLab Star in its system over the Tecan, because Hamilton provides class libraries for many different liquid viscosities; the Tecan system requires the generation of script to compensate for thicker solutions.

Automation as overkill?

"Our goal is not to optimize the number of trials," says Wladek Minor, PhD, professor of molecular physics at the University of Virginia, Charlottesville, Va. "Our goal is to maximize the number of structures in the Protein Data Bank." Minor is a part of another consortium in the PSI, the Midwest Center for Structural Genomics Consortium, and therefore a competitor to the other eight consortia. "People who are doing a tremendous number of trials don't have more structures," says Minor.

Minor is an outspoken critic of the trend toward expensive liquid handling tools in protein crystallography. He created a system based on a personal digital assistant (PDA) linked via wireless network to a computer that contains the recipes for the most common protein crystallization screens. A technician can then mix the stock screening solutions using only a barcode scanner, pipettes, and a scale. The PDA calculates molarity and concentration of the solution and tells the technician when to add more material. The most important aspect of this system, says Minor, is the audit trail, permitting a level of consistency and reproducibility for labs of any size. Minor loves the flexibility and low price. "Ninety-nine percent of the price is the brain power," he says.

The move toward liquid handling automation is saving time, but not helping to solve structures, says Minor. "The question is 'what would you like to automate'? Most people want to automate that which can be done by any high school student for $5 an hour."

— Chris Dickey, DrPH, *Editor in chief*

Organizations mentioned in this article:
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Midwest Center for Structural Genomics, www.mscg.anl.org
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