Perspectives

Automation of Sample Preparation for Genomics

Guest Authors
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New technologies for genomics and proteomics, combinatorial chemistry, high-throughput screening, mass spectrometry, and bioinformatics are helping to speed the drug discovery process. Automation is important in allowing researchers to meet the high-throughput demands of today's research environment. This "Sample Prep Perspectives" column reviews the commonly used sample preparation procedures for genomic nucleic acid purification and introduces the automation choices available to drug discovery scientists who need to perform this work in a high-throughput manner.

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The modern drug discovery process emphasizes rapid data generation and analysis to identify promising new chemical entities early in the development cycle. Advances in genetics, genomics, biochemistry, and pharmacology have accelerated the changing face of drug discovery. These advances include sequencing the human genome, improvements in laboratory automation, and advances in the fields of combinatorial chemistry, high-throughput screening, mass spectrometry, and bioinformatics. The end result of all these process improvements is much faster compound synthesis and more efficient evaluation of a greater number of compounds for pharmacological and metabolic activity.

The applications for automated laboratory processes vary across the entire spectrum of drug discovery. Traditionally, the term *sample preparation* refers to the concentration of an analyte, the exchange of solvent, or the removal of interfering substances before analysis. However, automation processes in drug discovery exist for a multitude of supporting functions such as solvent delivery, sample dissolution, sample aspiration and dispensing, sample reformatting from tubes to plates, plate replication, homogenization, microplate handling, vacuum application, microplate well washing, capping and uncapping, sealing, digestion, and sample delivery to a detection system. This "Sample Prep Perspectives" column will focus on applications for sample preparation automation in the field of genomics and, more specifically, for nucleic acid purification directly preceding sequencing.

A future "Sample Prep Perspectives" column will describe sample preparation automation for the field of proteomics. Reviews and application summaries are available for automation of sample preparation processes in related areas such as pharmaceutical and clinical analysis (1), combinatorial chemistry (2,3), and solid-phase extraction for bioanalysis (4,5). Manley (6) has discussed the subject of managing overall laboratory automation for drug discovery.

Genomics: An Overview

A genome is the primary set of deoxyribonucleic acid (DNA) in an organism — a blueprint of genetic instructions required to build a functioning organism. The human genome is encoded on 23 pairs of chromosomes residing in the nucleus of nearly every cell. The number of genes encoded by roughly three billion base pairs of human DNA is estimated to be approximately 30,000. Most genes actually are segments of DNA that can act as templates for the creation of molecules of ribonucleic acid (RNA). RNA molecules then can be translated by ribosomes to make proteins. The interactions among the genes, RNA molecules, and proteins in each cell of a functioning organism are highly intricate; only with the complete set of genetic instructions can scientists truly begin to appreciate this network. Furthermore, a disruption of a certain element by disease or mutation can have a ripple effect on the health of the organism; likewise, the action of a drug molecule can reach well beyond the effect on the immediate target molecule.

One goal of genomic studies is to reveal new biological targets for drug development by identifying DNA sequences, which then enables the analysis of the genes, the resulting RNA molecules, and the proteins. To begin, this task requires the isolation and manipulation of high-quality DNA from a sample. Virtually any cell type or virus from any organism can act as a source for nucleic acids, but the process of isolating the DNA could differ based upon the physical attributes of the host organism. After isolation, the DNA must be made into a library that contains individual segments that together represent each and every nucleotide in that sample genome. Libraries often are made by inserting frag-

ments of sample genomic DNA into larger pieces of DNA from bacteria or yeasts that are highly amenable to laboratory manipulation. The manipulated DNA carrying the sample insert then can be grown in a controlled system to increase the yield. For successful genomic sequencing, the subsequent isolation and purification of the DNA constructs is critical, and it can be time-consuming.

The high throughput of the latest 96-well format DNA sequencers (for example, the ABI Prism 3700 DNA analyzer [Applied Biosystems] and the MegaBace 1000 DNA sequencing system [Amersham Pharmacia Biotech AB]) has created a need for rapid sample preparation methods that can keep pace. The objectives of this "Sample Prep Perspectives" column are to review the sample preparation procedures commonly used for genomic nucleic acid manipulation and to introduce the automation choices available to drug discovery scientists to perform this work in a high-throughput manner.

Traditional Nucleic Acid Extraction Techniques

Although nucleic acid isolation and purification techniques can vary, all must accomplish certain objectives. DNA generally is extracted by cell lysis; separated from nonnucleic cellular components such as proteins, lipids, and carbohydrates; and finally isolated using a series of precipitation and centrifugation steps (Figure 1). Most protocols also include an RNase digestion to degrade RNA.

Phenolic extraction of cell lysates is one of the oldest techniques for DNA preparation. Single cells in suspension are lysed with a detergent and a proteinase enzyme to degrade protein molecules. Nonnucleic acid components then are extracted into an organic (phenol–chloroform) solvent, and the process leaves nucleic acids in the aqueous layer. Analysts add isopropanol to the isolated aqueous phase to precipitate the high molecular weight nucleic acids. After precipitation, the DNA is separated from the isopropanol by spooling or centrifugation and is washed twice with ethanol. Most organic extraction procedures incorporate a DNase-free ribonuclease (RNase) incubation step to remove RNA; this step might come before or after the organic extraction. For some applications, a second organic extraction might be necessary to achieve the desired DNA purity. Organic extractions are not optimal for plasmid isolation, but they are more appropriate for whole genomic DNA isolations.

Small amounts (~1 μg from each milliliter of culture) of bacterial plasmid DNA that contain the sample insert sequence can be isolated from cell culture using a technique called *mini prep*. The individual mini prep procedure provides sufficient DNA for modern capillary and gel-based sequencers, and it is much less labor-intensive than the standard *maxi prep* technique, which uses a cesium chloride density gradient for isolating 0.5–1.0 mg amounts of plasmid DNA. Two common methods to lyse cells for mini prep plasmid isolation are the alkaline hydrolysis method, which is used by GeneMachines in its RevPrep system, and the rapid boiling procedure. Plasmid DNA can be separated from cell lysates or other reactants such as unincorporated nucleotides or linkers using magnetic particles that have both a high binding efficiency and a large capacity for plasmid DNA by instruments such as Promega's Magnesil purification system. These magnetic particle systems work by capturing sequencing extension products and purifying them in a series of successive washes that culminate in a final release step. The isolated plasmid DNA then can be used for automated DNA sequencing and additional molecular biological methods, such as polymerase chain reaction (PCR) amplification.

Gel-permeation chromatography is another common technique for efficient, rapid purification of nucleic acids. Gels are available in different porosities that exclude 10,000–200,000 Da molecules. The purification of nucleic acids from nucleotides or buffers works well when using a 25,000 Da exclusion size, because the average protein size is approximately 30,000 Da. The gels generally are supplied as a dry powder that must be hydrated and poured into columns. Disposable, economical, and centrifugeable packed gel-filtration columns are ideal for purifying small volumes (< 100 μL) of nucleic acid solutions and for separating unincorporated radioactive nucleotides from labeling reaction mixtures. The prepackaged columns, which eliminate the tedious and time-consuming steps involved in column preparation, ensure high recoveries of DNA and high retention of unincorporated nucleotides with minimal labor.

Although these various techniques have been successful for isolating DNA and sequencing certain genes, operons, and plasmids, the advent of whole-genome sequencing makes individual sample preparation somewhat obsolete. Even a medium-sized bacterial genome of 2.5 million bases would require more than 20,000 individual sample preparations to achieve eightfold coverage using a random library. Further-

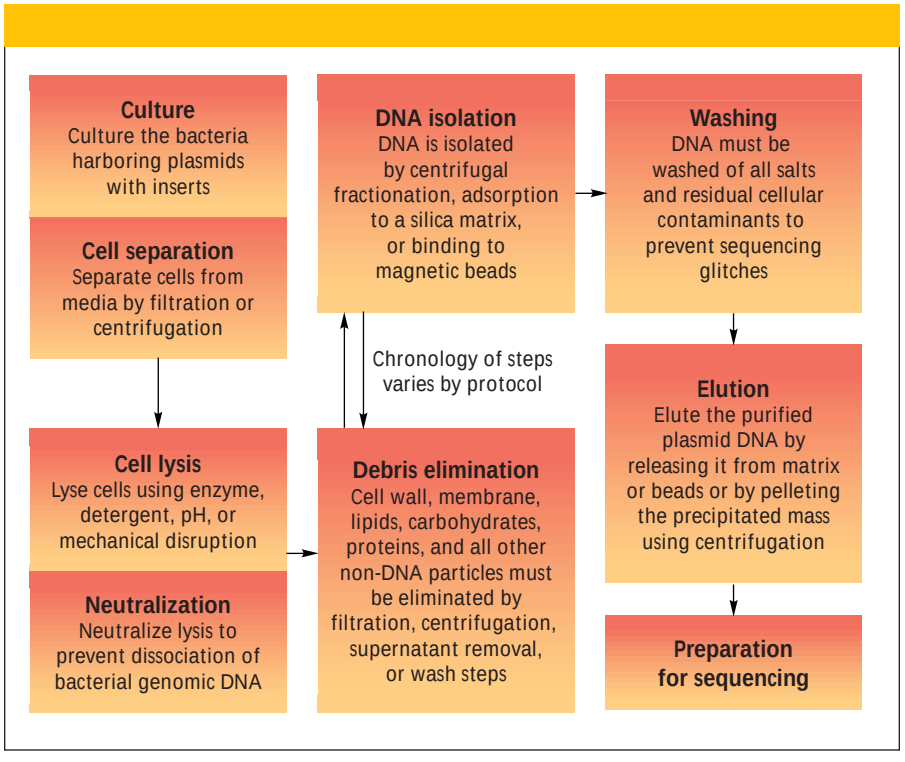

Figure 1: Diagram of a typical series of sample preparation steps required for DNA purification from bacterial cells harboring plasmids with inserts.

more, the sequencing instruments' ability to run in a 96-well plate format requires a more rapid plasmid preparation procedure to keep the sequencers running throughout the day and night. As a result, the process of plasmid purification is increasing its speed through the use of automation.

High-Throughput DNA Purification Systems

Adsorbents that provide fast, efficient DNA purification are important for making this procedure amenable to automation. The exact nature of the process varies among different manufacturers' equipment, but the basic process is uniform: After the cells are lysed using one of the aforementioned techniques, the DNA is either adsorbed onto a chemically modified silica matrix contained in 96-well flowthrough plates (Figure 2) or magnetically separated using magnetic or transient paramagnetic bead technology. RNA, proteins, and other cellular components are filtered out initially or washed free in a subsequent step. The multiple samples of purified DNA then can be eluted simultaneously in a purified form that is ready for batch sequencing. The adsorbents are available in prepackaged 96-well microplate kits from a variety of manufacturers, including BD Biosciences Clontech, Bio-Rad Laboratories, Eppendorf-5 Prime, Macherey-Nagel, Millipore, Promega, Qiagen, Sigma-Aldrich, Whatman, and Xtrana. The silica matrix and magnetic microplate kits offer much greater convenience and higher throughput than traditional phenol or gel chromatography equipment. The kits also improve upon individual mini prep methods by enabling the simultaneous generation of multiple purifications. Wolf (7) has reviewed plasmid prep kits in a recent publication.

Automating High-Throughput Systems

Automated liquid-handling workstations involve the movement of multiple probes in Cartesian axes (*x*,*y*,*z*) over a deck surface configured with labware such as microplates, tube racks, solvent reservoirs, wash bowls, and disposable tips. These instruments (Figure 3) have proven to be ideal for aspirating and dispensing solvents from a source to a destination and have revolutionized the process of nucleic acid purification with modifications such as control of vacuum manifolds, heating blocks, and shakers that use 96-well plates. Multiple-probe liquid handlers have a variable tip-spacing that allows them to expand their tip-to-tip width to aspirate from various test tube sizes and reduce the tip-spacing width when dispensing into microplate wells with 9.0-mm well-to-well spacing. As analysts needed to move microplates around on decks, manufacturers expanded their workstation model lines, and the functionality and usefulness of an integrated gripper arm became clearly evident (Figure 4). Labware movement around decks and into external devices such as microplate stackers and fluorescence readers now is possible. Brush (8) profiled automated workstations.

Table I lists typical examples of automated workstations for plasmid (and in some cases, genomic) DNA purification with examples of purification systems. These automated platforms often have two levels of demonstrated applications: manufacturers develop fully validated complete systems with business partners, and third parties develop applications on workstation platforms without manufacturer input. For information about total systems and instrument compatibility with specific sample preparation kits, readers should consult individual manufacturers. Kits for related tasks can be supported by many of these instruments as well; for example, analysts can use kits for PCR purification and sequencing reaction cleanup. Automated workstations from Beckman Coulter, Hamilton, Qiagen, and Tecan represent some typical examples of automated units; GeneMachines makes a filterless tabletop system.

AutoGen makes an automated DNA extraction robotic system, called the AutoGenprep 960, in a self-contained unit rather than in a liquid-handling workstation format. The instrument's entire process is fully automated from overnight pelleting and culturing to resuspending DNA in a 96-well format. The system uses a proprietary single-phase organic extraction chemistry comparable to the conventional phenol–chloroform method. This chemistry requires no disposable columns or magnetic beads and provides very low cost per preparation.

Figure 2: Flowthrough plate containing a chemically modified silica matrix for high-throughput DNA sample preparation. (Courtesy of Qiagen.)

Figure 3: Example of a liquid-handling workstation (MBS workstation) that allows fully automated DNA purification using the microplate format. (Courtesy of Tecan.)

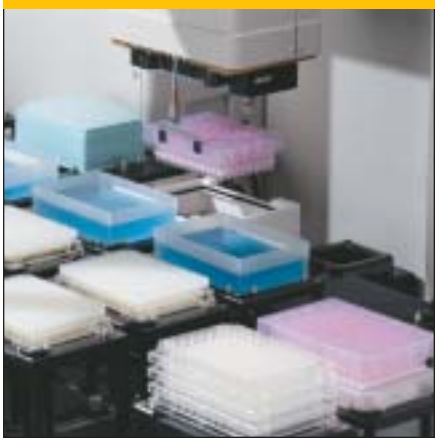

Figure 4: A gripper arm configured on a liquid handling workstation (Biomek FX) moves microplates into and around its deck and assembles and disassembles a vacuum block used for liquid processing through plates. (Courtesy of Beckman Coulter.)

Beckman Coulter provides several complete automated systems for plasmid DNA purification. The Biomek 2000 and Biomek FX instruments use preconfigured reagents (Promega's Wizard SV 96 plasmid DNA purification system) as well as magnetic bead systems and surface capture technologies (Xtrana's Xtra Amp sample preparation protocol). The Biomek FX workstation can use two liquid-handling arms, a flexible high-capacity work deck, and either 96- or 384-channel heads. This workstation also can integrate with the Sagian Core system (Beckman Coulter), which adds modules and peripherals — an Orca track robot, plate carrousel arm, or bar-code reader — to expand the system with specific functions.

GeneMachines provides an alternative approach to filter-based automated plasmid purification in its RevPrep Orbit system. This automation system begins with alkaline hydrolysis and is based on a unique array centrifugation technology (called Sutech and originally developed at Stanford University) to eliminate expensive, wasteful filtration steps and time-consuming manual transfers to a centrifuge. Each well of a 96-well array on the machine contains a separate centrifuge rotor. Each rotor functions as a sample well and a miniature centrifuge. The 96 samples are transferred from a standard sample

Table I: Typical examples of automated workstations for nucleic acid purification

Product Name	Manufacturer	Purification Systems
ABI Prism 6700	Applied Biosystems	ABI reagents and protocol
AutoGenprep 960	AutoGen	AutoGen reagents and protocols based on single-phase organic extraction
AutoPrep-12	Thermo Hybaid	Alkaline lysis chemistry with filtration and purification steps
Autopure LS	Gentra Systems	Puregene (modified salt precipitation method) for large-sample purification of genomic DNA
Biomek 2000	Beckman Coulter	DNA Direct kit (Dynal); Xtrana Xtra Amp genomic DNA extraction
Biomek FX	Beckman Coulter	Wizard SV96 and Wizard Magnesil (Promega)
BioRobot 8000	Qiagen	QIAprep 96 mini prep kit; MagAttract mini prep system
CCS Packard DNATrak	Packard BioScience	Solid-phase reversible immobilization chemistry
CCS Packard PlateTrak	Packard BioScience	Solid-phase reversible immobilization chemistry
CRS DNA purification system	CRS Robocon	All magnetic bead–based protocols such as Dynal Dynabeads DNA purification system
Cyberlab C-250 and C-400 plate-handling workstations	Gilson	MultiScreen 96 (Millipore); Montage Plasmid Miniprep-96 kit (Millipore)
DNA MiniPrep workstation	Hudson Control	Various 96-well kits
Genesis RSP	Tecan	Qiagen Ultra, Turbo, and REAL kits
GenoM-96	GenoVision	GenoPrep magnetic beads
MagnaPure LC	Roche Applied Science	Proprietary magnetic particles and specialized reagent kits
MBS workstation	Tecan	Te-MagS magnetic bead separation
Microlab MPH and automated vacuum system	Hamilton	Various 96-well kits
Microlab Star and automated vacuum system	Hamilton	Various 96-well kits
MiniPrep 24 and 48	MacConnell Research	Proprietary lysis, resolution, and electroelution procedure
MultiProbe II	Packard BioScience	Montage Plasmid Miniprep-96 kit (Millipore)
PerfectPrep-96 VAC	Eppendorf-5 Prime (with Zymark)	Alkaline lysis and filtration method
PerfectPrep-96 VAC	Zymark (with Brinkmann)	Alkaline lysis and filtration method
Plato series	Colibri Robotics	Various 96-well kits
Quadra96	Tomtec	Various 96-well kits
QuikPrep	Orochem Technologies	96-Well lysate filtration plate and DNA-binding chemistries
RevPrep	GeneMachines	Array centrifuge technology using liquid chemistries
RoboPrep 2500/4800	MWG Biotech	MWG Biotech kits
RoboSeq	MWG Biotech	Various 96-well kits
RoboSmart	MWG Biotech	Montage Plasmid Miniprep96 Kit (Millipore)
Speedy	Zinsser Analytic	Various 96-well kits
Staccato and Twister systems	Zymark (with Qiagen)	QIAprep 96 mini prep kit and other mini prep systems
T1000 automated purification system	Tepnel Life Sciences	Magnetic bead technology

Companies Mentioned in This Column

For more information about instrument compatibility with specific sample preparation products, contact the individual companies.

Amersham Pharmacia Biotech AB, Uppsala, Sweden
Applied Biosystems, Foster City, California
AutoGen, Framingham, Massachusetts
BD Biosciences Clontech, Palo Alto, California
Beckman Coulter, Inc., Fullerton, California
Bio-Rad Laboratories, Hercules, California
Colibri Robotics, Inc., New Castle, Delaware
CRS Robotics Corp., Burlington, Ontario, Canada
Dynal A/S, Oslo, Norway
Dynex Technologies, Inc., Chantilly, Virginia
Eppendorf-5 Prime Inc., Boulder, Colorado
GeneMachines, San Carlos, California
GenoVision AS, Oslo, Norway
Gentra Systems Inc., Minneapolis, Minnesota
Gilson Inc., Middleton, Wisconsin
Hamilton Co., Reno, Nevada
Hudson Control Group, Inc., Springfield, New Jersey
MacConnell Research Corp., San Diego, California
Macherey-Nagel GmbH & Co. KG, Düren, Germany
Millipore Corp., Bedford, Massachusetts
MWG Biotech Inc., High Point, North Carolina
Orochem Technologies Inc., Westmont, Illinois
Packard BioScience Div., PerkinElmer, Meriden, Connecticut
Promega Corp., Madison, Wisconsin
Qiagen GmbH, Hilden, Germany
Roche Applied Science, Indianapolis, Indiana
Sigma-Aldrich, St. Louis, Missouri
Stratagene, La Jolla, California
Tecan Group Ltd., Mannedorf, Switzerland
Tepnel Life Sciences PLC, Manchester, United Kingdom
Thermo Hybaid, Middlesex, United Kingdom (U.S. distributor is Thermo Labsystems)
Thermo Labsystems, Chantilly, Virginia
Tomtec, Hamden, Connecticut
Whatman Inc., Clifton, New Jersey
Xtrana, Inc., Broomfield, Colorado
Zinsser Analytic GmbH, Frankfurt, Germany
Zymark Corp., Hopkinton, Massachusetts

plate and dispensed into individual wells in their own rotors, at which time they are spun simultaneously. The rotors hold as much as 500 μL and generate forces as high as 14,000*g* per well. The total system includes two 96-channel array centrifuges, a 96-channel pipetter, an eight-reagent bulk dispenser, a wash station, a server arm, four storage cassettes for plates, and control software.

Assembly and disassembly of a vacuum manifold is necessary for a walk-away automated system. Hamilton offers a unique approach for plasmid purification with its Microlab Star pipetting workstation in combination with its Microlab automated vacuum system. The automated vacuum system optimizes throughput and minimizes manual intervention by eliminating the time-consuming steps of manifold assembly and disassembly associated with static vacuum systems. The automated vacuum system module has flexible plate adjustments and can work with either one or two vacuum manifolds placed on the deck of a Microlab Star or a Microlab MPH system. The manifold also can be loaded automatically by the Microlab Swap plate-handling robot. This plate handler performs a similar function to that of the Twister II microplate handler (Zymark), which is the most widely used universal microplate handler on the market.

The liquid-handling workstation is approaching the capabilities of full automation systems beyond sample preparation applications. MWG Biotech's RoboSmart Biosystem can perform plasmid purification, sequencing reaction setup, cycling, and nonincorporated dye terminator removal within a single platform. The complete process requires no user intervention from start to finish.

Qiagen's BioRobot 8000 is a versatile workstation for plasmid DNA purification. The workstation comprises an eight-channel pipetting system that performs liquid-handling tasks, an automated vacuum system to remove contaminants from purification modules, and a robotic handling gripper arm to move plates and manipulate module components. The workstation is available with a choice of fully automated purification technologies: either vacuum filtration or magnetic separation (the company's MagAttract 96 mini prep system). Qiagen and Zymark have partnered to combine Qiagen's BioRobot platform with Zymark's RapidPlate 96-well and 384-well pipetting systems, Twister system, and Staccato applications-focused workstation. These systems address analysts' needs for ultrahigh-throughput nucleic acid handling, separation, and purification.

Tecan provides preconfigured systems for vacuum-based nucleic acid preparation cartridges manufactured by most suppliers. Tecan also provides magnetic bead–based nucleic acid purification kits and supports kits from a variety of kit suppliers. The company's Genesis workstation can be scaled to most throughput levels by using a 96- or 384-well pipetting option or by integrating the workstation with one of the company's custom multicomponent systems served by a rail-based robotic arm. Integrating one of Tecan's fluorescence or absorbance microplate readers allows online quantitation of purified DNA and normalization of the concentrations in a fully automated process.

Although the automation systems described above are practical and affordable for high-throughput genomics laboratories, ultrahigh-throughput laboratories that process more than 5000 samples per day might need to look beyond these workstations to customized configurations. Using magnetic beads allows the elimination of buffer exchanges and the acceleration of the purification process. Two systems have filled a need for ultrahigh-throughput nucleic acid purification.

The CRS DNA purification system (CRS Robotics) is an example of a more rapid automated solution for bead-based methods. It uses magnetic particles in which a central robotic arm is the focal point for a range of instruments custom-configured around its perimeter. The system is built around a CRS A465 robot system that has six axes of motion and a CRS servo gripper with microplate fingers. According to its manufacturer, this system can process as many as 14 96-well plates/h, provides 24-h unattended operation and remote monitoring, performs error detection and recovery, and creates detailed audit records. The system is configured with the following typical components: four magnetic bead settling stations, a plate carrousel, 120-plate capacity microplate feeding stations, a CRS dispenser with a bead-dispensing module, a plate delidder with a barcode reader, a microplate shaker, a plate washer, a 96-tip pipetter with a bead settling plate, and the company's Polara software and instrument interfaces.

The PlateTrak system (Packard BioScience Div., PerkinElmer) uses another approach to ultrahigh-throughput process-

ing by using a conveyer-based paramagnetic microplate processing system to increase the speed of the automated plasmid purification process. Packard BioScience, in collaboration with the Center for Genome Research at the Whitehead Institute (Cambridge, Massachusetts), designed a pipeline of PlateTrak systems for automating the solid-phase reversible immobilization protocol (9). This system can process 200,000 DNA preparations per day (also reported as one 384-well plate/min). The solid-phase reversible immobilization procedure relies upon the binding of DNA to the surface of coated paramagnetic particles. When placed in a magnetic field, the magnetic properties of the beads are exploited to bind the DNA; these magnetic properties disappear when the magnetic field is removed. This property enables rapid, reproducible automation of traditional buffer exchanges and extensive washes necessary for DNA preparations. Although the initial system investment is quite high, the procedure reportedly is relatively rapid and economical to run and maintain and yields large quantities of high-quality DNA suitable for sequencing.

Conclusions: Automation of Biomolecule Purification

Biotechnology companies have recognized and responded to the demand for revolutionizing nucleic acid purification to accelerate the pace of genomic sequencing. The need for automated solutions to perform biomolecule purification reaches beyond plasmid purification for genomics, however. Clinical diagnostic applications benefit from automation of the PCR reaction. Some of the workstations listed in Table I can be adapted to perform high-throughput automated PCR from reagent addition to thermocycling, purification, and even on-line product concentration measurement (10).

Both high-throughput PCR and RNA isolations are important for the next step in understanding the information provided by the genome: transcriptomics. The term *transcriptomics* refers to the study of RNA transcripts detectable in cells, which can change in time and in response to environmental variables. Microarray analysis, a primary tool of transcriptomics, is moving as quickly as statistical methods and data management can keep pace. PCR frequently is used to generate as many as 30,000 probes used to spot a single microarray, and RNA-based target molecules are hybridized to the array to analyze expression patterns. Clearly, the need for high-throughput automated biomolecular machinery will escalate as the acquisition of genetic information — and our ability to understand its significance — continues to grow.

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