Oligonucleotide synthesis as a tool in drug discovery research

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Facile methods for oligonucleotide synthesis have been responsible for the development of several enabling technologies, thereby creating new opportunities in pharmaceutical R&D. It has therefore become necessary for successful drug discovery enterprises to be well versed in the rapid synthesis and distribution of oligonucleotides. To achieve this goal, automated DNA synthesizers have been coupled with downstream automated workstations and a relational database to keep track of all aspects of the oligonucleotide production process. The use of the workstation approach allows for the rapid synthesis, purification, analysis and distribution of oligonucleotides and their analogs.

The development of efficient chemistry and automated instrumentation have brought the once highly specialized and laborious process of DNA synthesis to an unprecedented level of accessibility[1]. For example, in 1977, two reports were published detailing studies of the *lac* operator using a synthetic 21-nucleotide DNA duplex[2,3]. The synthesis of this fragment required the equivalent of four man years of highly skilled, intense effort[4]. Today, the equivalent task could be accomplished in approximately 4 h, mostly unattended, and would include purification to greater than 92% and characterization by MS. This ready access to synthetic oligonucleotides has revolutionized the fields of molecular biology and biochemistry, facilitating the development of PCR[5], terminator DNA sequencing[6], recombinant DNA technology, gene construction, chromosome mapping, site-directed mutagenesis and numerous other powerful techniques. As a result, synthetic oligonucleotides have helped drive the development of biotechnology, nucleic acid therapeutics and genomics sequencing efforts, facilitated target identification for traditional pharmaceutical development and improved the sensitivity and scope of diagnostics.

A centralized facility for oligonucleotide synthesis is a valuable asset to companies that are conducting drug discovery projects using any of the above technologies. The localization of core competencies in emerging and established nucleic acid technologies can have a positive impact on research and development at several levels. Oligonucleotides have clear utility for complementary DNA (cDNA) library construction and DNA sequencing. In addition, the ability to produce high-quality materials rapidly allows for a higher probability of success in the more critical tasks of full-length cloning and sequencing. Thereafter, the ability to produce large oligomers and synthetic genes allows for optimization of protein expression levels. For genes of unknown function, the use of antisense technologies and the construction of knockout and transgenic animals can be important in defining the biochemical role of the protein product. The successful implementation of these technologies is again rooted in the construction of high-quality oligonucleotides and their analogs. Whether in the quest for protein therapeutics or biochemical targets, nucleic acid synthesis can play an important role in drug discovery.

The core technology that drives the most widely used automated oligonucleotide synthesis devices is the phosphoramidite method of DNA synthesis, as developed in the laboratory of M.H. Caruthers[7,8]. The method relies on an

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initial support-bound nucleoside upon which the desired oligomer is assembled (Figure 1). Attachment of the product to an insoluble support allows for multiple chemical manipulations without the need for intermediate purification. Monomeric nucleoside phosphoramidites are added to extend the DNA chain during a mildly acidic coupling reaction. Treatment with acetic anhydride 'caps' any unreacted support-bound hydroxyl groups, thereby eliminating potential sequence mixing. Exposure to iodine and water oxidizes the newly formed phosphite triester to the phosphate triester. Acid treatment then liberates the protected hydroxyl group of the recently added nucleoside, allowing the cycle to be repeated. Iteration of the four-step solid-phase synthesis cycle with any of the four nucleoside inputs results in polynucleotides of any desired sequence. The method can be used reliably to produce oligonucleotides of 100 or more bases. Automated syntheses of such large molecules is possible because of the high coupling efficiency per nucleoside addition (> 99%), very fast reaction times (<30 s) and stability of the monomers in the absence of acid. An extensive review of the phosphoramidite approach can be found in an excellent article by Beaucage and Iyer[9]. Alternative methods, including the phosphate triester[10–14] and the H-phosphonate[15,16] approaches, have also been successfully applied to DNA synthesis. However, the phosphoramidite approach remains the method of choice because of overall higher product yield and quality, and speed of synthesis.

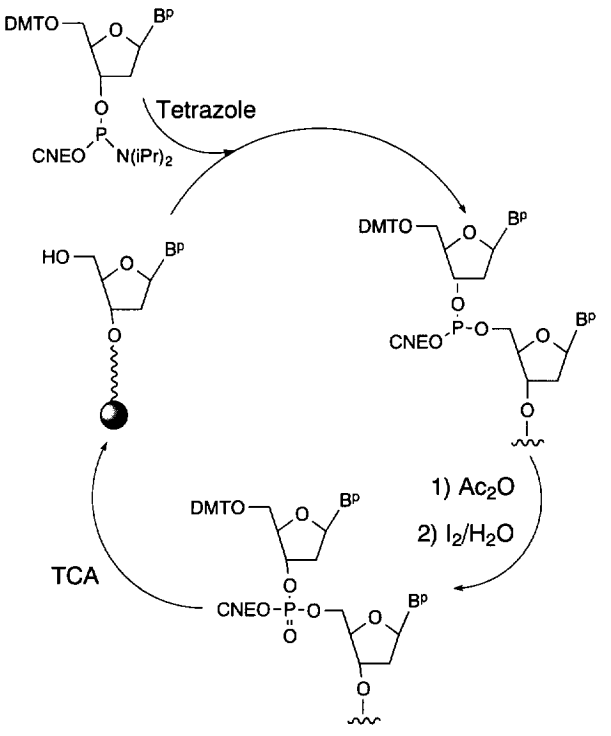

Figure 1. *Solid-phase DNA synthesis cycle using the phosphoramidite approach. DMT, dimethoxytrityl; CNE, cyanoethyl; Bp, exocyclic amino protected base; iPr, isopropyl; Ac_2O, acetic anhydride; TCA, trichloroacetic acid.*

High-throughput oligonucleotide production

To meet the demands for these useful tools, we have developed a high-throughput oligonucleotide synthesis facility that takes full advantage of nucleic acid synthesis and automation technology. The overall process flow is outlined in Figure 2. The goal of the laboratory is to produce oligonucleotides of unquestionable quality to maximize the probability of experimental success. The efforts of the synthesis team to ensure the high quality of the materials produced are integral to the overall achievement of Company research goals.

Workstation approach

The laboratory takes advantage of both commercially available automated nucleic acid synthesizers and liquid-handling workstations as well as custom automated workstations (Table 1). All syntheses are barcoded to allow for efficient tracking through the process. The workstation approach to the production process allows for extremely rapid output of synthetic materials with a sophisticated level of characterization. Although most oligonucleotides produced are short lengths (<30 nucleotides) of native nucleic acid, the laboratory is able to produce any modification or nucleic acid analog at a wide variety of synthesis scales. Most of the materials synthesized in the laboratory are purified by reverse-phase cartridge chromatography[17], analyzed by MS and aliquoted in requested quantities for distribution.

In the workstation approach, synthesis is performed on Applied Biosystems 394 DNA synthesizers. The instrument uses argon pressure to deliver reagents and solvents in an inert atmosphere to the reaction chambers. A network of delivery tubing and solenoid valves is used to deliver reagents and solvents without cross-contamination. Each instrument is capable of simultaneously synthesizing four different oligonucleotides at a rate of one synthesis cycle every 7 min. In an average workday, the laboratory is capable of synthesizing more than 300 20-base oligomers on these instruments.

Deprotection and sorting

Deprotection of oligomers is achieved in sealed vials using concentrated aqueous ammonium hydroxide at elevated temperature. This treatment cleaves the oligonucleotide from the support and removes all phosphate and base protecting groups. The first downstream automated workstation was implemented at this process step to achieve several tasks. The sorting workstation (Table 1) has a temperature-conducting aluminium deck into which a programmable circulating water bath delivers either a heated or cooled solution. The deprotection vials are prepared and placed on the instrument at any time during the day. Beginning in the early evening, the deck is heated to achieve deprotection. After the appropriate deprotection time, the circulating water bath is programmed to deliver a chilled solution to cool the vials so that the samples are ready for processing in the morning. Although deprotection can be performed rapidly at any period of the day for extremely urgent requests, overnight deprotection provides a good starting point for the overall process during working hours. The workstation scans the barcode on each synthesis and removes the cap from the vial. Using the scanned information, the syntheses are sorted into groups on moveable racks that mate with receptacles on the downstream automated workstations.

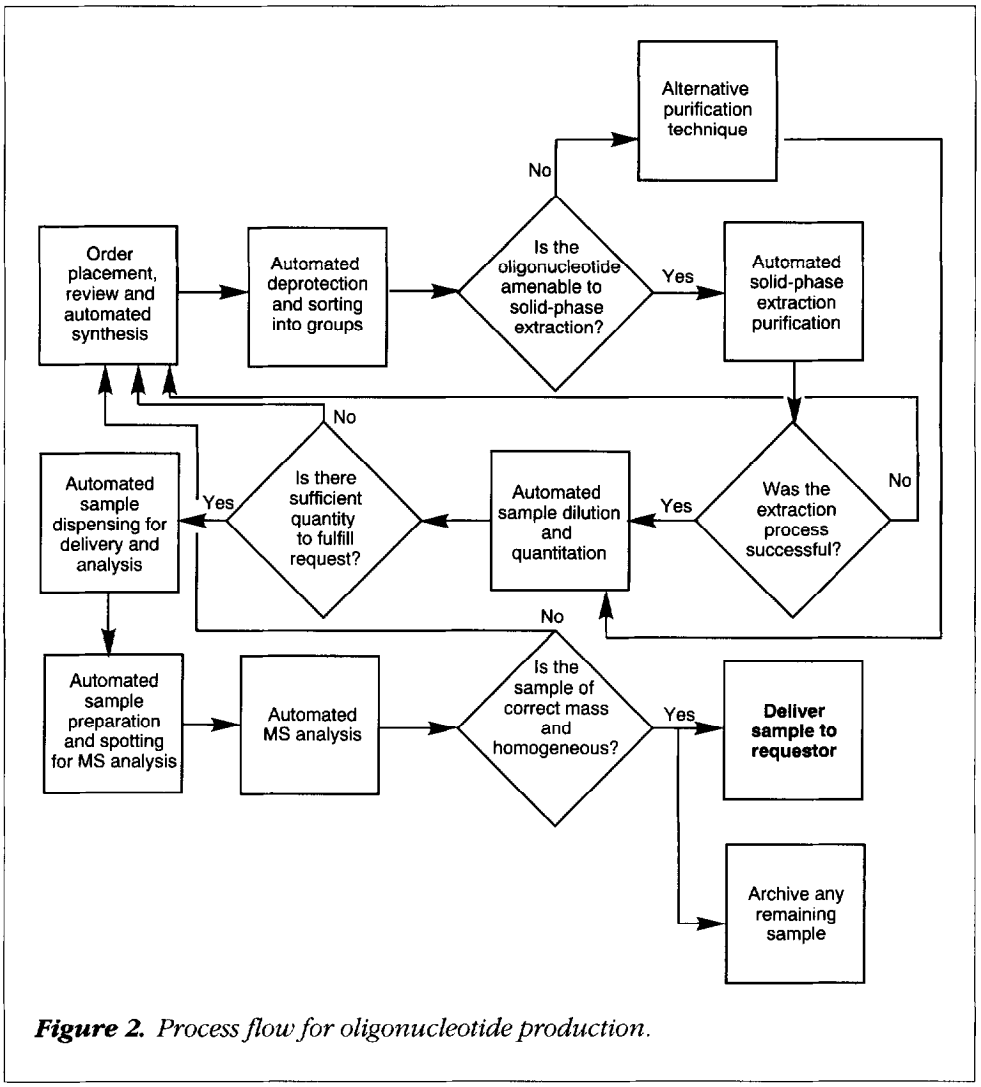

Figure 2. *Process flow for oligonucleotide production.*

Purification

All materials of less than 55 nucleotides can be routinely purified by solid-phase extraction. Longer oligomers, or those with modifications not compatible with the extraction procedure, are processed by other purification methods such as polyacrylamide gel electrophoresis (PAGE) or high-performance liquid chromatography (HPLC). For those oligonucleotides that can be purified by solid-phase extraction, synthesis is completed leaving the dimethoxytrityl protecting group from the last nucleotide addition in place. This provides a hydrophobic handle that can be used to separate the full-length oligomer from any failure sequences by reverse phase chromatography[17]. Automated solid-phase extraction workstations are used to purify the oligonucleotides (Table 1). The racks created on the sorting workstation are transferred to the deck of the purification workstation. Using a vacuum manifold system, the samples are loaded onto the reverse-phase cartridges, washed with an aqueous solution to remove failure sequences, acid deprotected and then neutralized and extracted with an organic solvent into collection tubes. The resultant materials are typically greater than 92% desired full-length DNA, as shown by capillary gel electrophoresis (Figure 3).

Quantitation and dispensing

The purified oligomer samples are transferred to a liquid-handling workstation (with variable-span cannulae) that

Table 1. Instrumentation for the high-throughput DNA synthesis laboratory

Manufacturer and model	Number	Function
Applied Biosystems 394	20	Nucleic acid synthesis
Bohdan Automation ASW-820	1	Deprotection and sorting workstation
Bohdan Automation ASP-710	2	Sample purification workstation
Packard Multiprobe 104	1	Sample dilution and aliquoting
Molecular Devices SpectroMax 250	1	Absorbance measurement
Bohdan Automation ASP-510	1	Mass spectrometry sample preparation and spotting
PerSeptive Biosystems Voyager DE	1	Matrix assisted laser desorption time of flight mass spectrometry
Applied Biosystems 3948	1	Nucleic acid synthesis and purification
Gilson 222 XL	1	Sample re-formatting

performs several vital tasks (Table 1). The variable-span cannulae allow for transfer of multiple samples to containers of various dimension. It first dilutes an aliquot of the oligonucleotide in a 'UV invisible' 96-well microtitre plate. This plate is transferred to a microtitre plate reader that determines the absorbance of all samples at 260 nm. Absorbance measurements on 96 samples are completed in 20 s. The relational database calculates the extinction coefficient for every oligonucleotide that is requested. This physical constant is determined by summing the molar absorbtivity coefficients of the component bases that make up each sequence (A = 1.54×10^4, C = 0.75×10^4, G = 1.17×10^4, T = 0.88×10^4 M^{-1} cm^{-1}). The database uses the absorbance value and the calculated extinction coefficient for the sequence to determine the concentration of the purified sample using Beer's Law[18]. It then uses this value to calculate the volume of solution necessary to supply the amount of material originally requested and transfers this information back to the liquid handling workstation. The workstation then dispenses this volume into a microcentrifuge tube ('shipping tube') for delivery to the requesting scientist.

Shipping tubes are arrayed in racks with a microtitre plate footprint and these are transferred to a vacuum centrifuge for lyophilization. The liquid-handling workstation also transfers a small aliquot of the purified oligomer to another 'analysis' microtitre plate, which is transferred to the MS analysis automation suite. An additional aliquot of the sample is transferred to a 96-well microtitre plate containing a pH indicator dye solution (Bromocresol Green). This allows for a quick visual inspection of the approximate pH of all the oligomer solutions. This step has been incorporated to ensure that the samples are sufficiently washed and neutralized after acid detritylation during the automated solid-phase extraction process.

System approach

In addition to the workstation approach, we are evaluating an Applied Biosystems 3948 synthesizer[19]. The instrument is able to complete synthesis, deprotection and purification in one 'system' – providing a clear advantage in terms of efficient use of space. Although the system approach is quite useful for unattended operation, the scope of synthesis options is limited. It has the potential to fulfil a useful role in allowing for increased productivity through 24 h operation. When operating reliably, the instrument is capable of producing 48 purified oligomers in about 25 h.

High-throughput MS characterization

Independent of the synthesis or purification methods used to produce an oligomer, all materials up to 80 nucleotides in length are analyzed by MS. Recent developments in matrix assisted laser desorption ionization with time of flight detection (MALDI-TOF) MS have made the routine and rapid

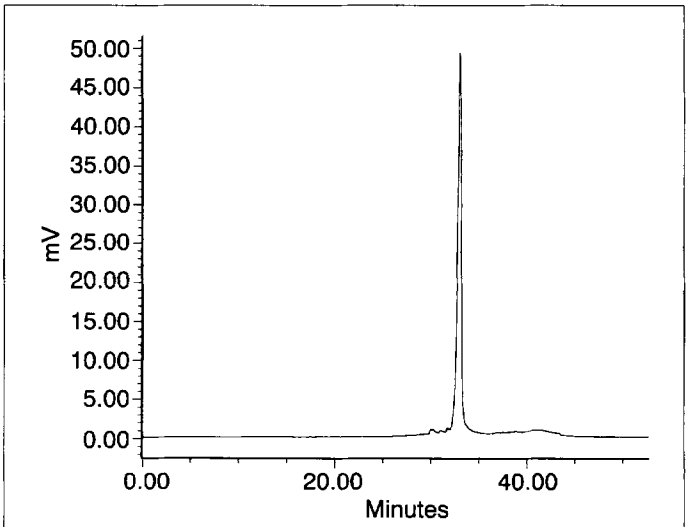

Figure 3. *Capillary electropherogram of a 25 nucleotide DNA purified by automated solid-phase extraction.*

analysis of oligonucleotides possible[20–25]. In particular, the development of effective matrices and the introduction of delayed ion extraction (DE) technology allow for the rapid and accurate analysis of such molecules. Briefly, DE MALDI-TOF-MS of oligonucleotides is accomplished using a crystalline picolinic acid matrix containing the oligonucleotide. Exposure to laser radiation ionizes the matrix, which assists in the ionization of the oligomer. Of great importance to DE is the introduction of an electrical grate above the ionization surface that is momentarily activated to retain the ionized plume, allowing for diffusion of some of the small matrix ions. An accelerating voltage is then applied to propel the ions towards a detector. The time required for the ion to reach the detector is directly proportional to the mass of the ion. The introduction of DE reduces the number of collisions between the oligonucleotide and matrix ions, thereby improving accuracy and resolution.

We have developed an automated suite that allows for rapid sample preparation, spotting and analysis[38]. The analysis microtitre plate that was created on the liquid-handling workstation is placed on the deck of a custom sample preparation and spotting workstation (Table 1). Rapid dilution of the samples with the picolinic acid matrix solution is accomplished with a six-cannula head. A dual-span, two-cannula head is then used to transfer samples from the 96-well microtitre plate (8 × 12 array) to the 100 position MS sample plate (10 × 10 array). Once spotted, the samples are allowed to air dry, thus forming circular crystalline residues. The MS plate is subsequently loaded into the DE MALDI-TOF-MS and a data file is downloaded containing all necessary information to complete fully automated data acquisition. It is possible to program the MS software to aim the instrument laser on the MS sample plate wells in a defined search pattern. The precise placement of sample drops by the automated sample preparation and spotting workstation allows for the search pattern to be intelligently programmed. This decreases the time necessary to successfully locate a sample rich region, thereby minimizing data acquisition times. Using the automation suite, sample preparation, spotting and acquisition for 100 samples can be completed in 90 min.

Quality of materials

The introduction of MS analysis into the oligonucleotide production process allows for an unquestionable level of confidence in the quality of materials produced. Masses within 0.2% of the calculated theoretical mass are typically produced. Any sample that differs in mass by more than 1% of that expected is considered to have a defect that precludes distribution to the requester. Also, if in addition to the expected oligonucleotide mass, multiple products are detected with masses indicative of synthesis failure or incomplete deprotection, the sample will be withheld from distribution. Empirically, approximately 0.9% of all samples analyzed by MALDI-TOF-MS are found to have masses that differ by more than 1.0% of the expected mass or to contain multiple products, thereby requiring re-synthesis.

This type of analytical data allows for corroboration of the presence of modifications, such as the addition of phosphate, biotin and various linkers to synthetic oligomers, that would be undetectable by any other method. MALDI-TOF-MS is also able to identify closely related impurities such as single nucleotide deletions or depurination products. Figure 4 shows an example of the ability of the MALDI-TOF-MS to identify the presence of abasic sites in a synthetic oligomer, a type of modification that would be impossible to detect directly using any other commonly utilized method. These abilities also make the instrument a valuable asset for identification of synthesizer and purification workstation malfunctions at a very early stage.

Data handling tools for large-volume sample tracking

The production of oligonucleotides can be considered a classic custom manufacturing operation, with the same necessary processes and controls. Orders must be placed and received, and the oligonucleotides must undergo the manufacturing process and pass quality control operations. Finally, the finished product must be shipped to the original requester. A small laboratory or biomolecular core facility can typically keep track of these processes with strict attention to detail and a well organized laboratory notebook. In a high-throughput environment, accurate sequence entry and sample tracking by hand is impractical.

System design and implementation

Multiple variables from several laboratory instruments must be stored, retrieved and tracked, we therefore decided to pursue development of a powerful relational database. This was accomplished by designing a custom application using the 4D relational database, which is a client/server version of 4th Dimension (ACI). The choice was made because Macintosh computers are used in the laboratory to drive the DNA synthesizers. In addition, 4D was considered to be a

good choice as a database tool upon which to build the system because it could also act as the front end to an Oracle database if the need for more transactions and greater data capacity should arise. The change to Oracle would be completely transparent to the laboratory scientists.

The general approach to the table structure is a master/detail approach to order tracking and manufacturing. Without detailing the exact table structures, the concept is one of a series of lookup tables (or data dictionaries) and the master/detail relationships. The lookup tables consist of several categories of information:

- The 'laboratory constants' table contains nucleoside molar absorbtivity coefficients and molecular weights, instrumentation details, networking details and manufacturing procedural and acceptance criteria.
- The 'requester' table contains shipment, department and project information for the scientists requesting the oligonucleotides (the 'customers' table).
- The 'machine' table contains instrument-specific information including the position and types of phosphoramidites and the number of cycles that have been completed on any particular instrument.

Some examples of the names and types of information stored in the master/detail tables are as follows:

- The 'order' table is a master table and contains 'requester', date ordered, internal project tracking, notes, status and completion date.
- The 'order Line Item' table has a detail relationship to the 'order' table and contains all information specific to a particular oligonucleotide, including quantity requested, manufacturing status, date shipped, actual shipment information, base counts, length and notes.
- The 'synthesis' table is a detail table of the 'order Line Item' table in which every synthesis detail of a requested sequence is tracked. This table tracks the actual manufacturing data for a given oligonucleotide including instrument, synthesis cycle, location on instrument, location in purification rack, location within archive box, description of failure and step at which failure occurred, calculated oligonucleotide extinction coefficient and experimentally determined absorption obtained for the oligomer.

There are many additional tables required to drive the entire operation, but the overall approach is the same classic relational design.

Project management

Design and implementation of a data system for the oligonucleotide laboratory was carried out as a three-phase project. A project manager with detailed knowledge of the process and familiarity with database design was assigned to shepherd the project through completion.

Phase I was a detailed design of the data needs of the laboratory and was accomplished through a series of discussions with a focus group of scientists that were familiar with

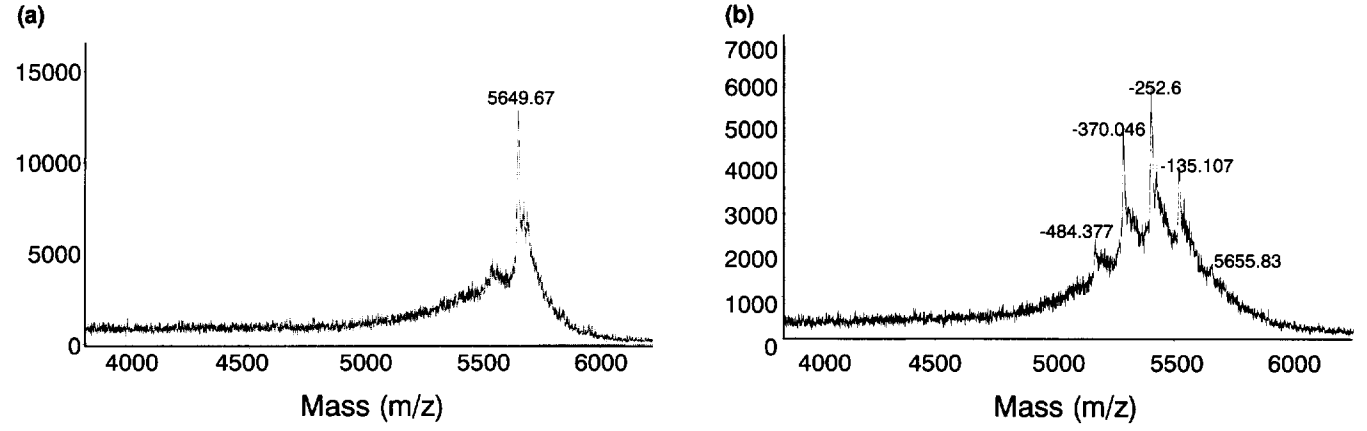

Figure 4. *Detection of abasic sites in DNA by MALDI-TOF-MS. (a) Spectrum obtained for synthetic 19 nucleotide DNA purified by automated solid-phase extraction. Theoretical mass, 5650, obtained, 5649.67. (b) Spectrum obtained for the same oligonucleotide after treatment at pH 1.75 for 18 h at room temperature.*

the process. The manufacturing process was examined in detail and broken down into modular components. Each module was designed to be as general as possible and to adhere to the 'manufacturing model'. If changes were made in any of the individual operations within the overall process, a new module could be designed, created and put in place quickly with minimum disruption to normal laboratory operations. At each step of the process, the system was designed to minimize the need for operator input to avoid data entry errors. A final design document was the 'deliverable' of this phase.

Phase II focused on the design of the data tables and the actual coding of the modules for each process. An operational database and the initiation of Phase III were the deliverable of this phase.

Phase III was the implementation and debugging of the entire system. The entire three-phase project was completed within one year. Refinements and enhancements to the system are an ongoing process.

Order entry and processing

The first step in the oligonucleotide production process is order placement. A small external module written in C++ was made available via the company intranet to individuals that use oligonucleotides in their research. The application allows not only direct electronic order placement and tracking from the researchers' personal computer, but also the ability to search the database for sequences existing in the synthesis laboratory archives. This decreases repetitive syntheses and minimizes the turnaround time necessary for the researcher to have the vital oligonucleotide in hand. The order module will soon be replaced with an identical web-based application to allow for complete platform independence.

The ordering module electronically places the requested sequences directly into an order processing module in the synthesis laboratory database. Using this module, a scientist in the synthesis laboratory can review the sequences and determine the best manufacturing method. Unique modifications and customized syntheses are flagged so that all the proper starting materials can be procured or synthesized. If any of the sequences in the order have been previously synthesized and exist in archives, a printed list of these compounds is produced for retrieval. The output of the module is transferred to a series of synthesizer queues based on the judgement of the scientist reviewing orders. The reviewing scientist will typically assign oligonucleotides to particular instruments in an effort to optimize timely reagent usage or to utilize the most appropriate type of synthesis cycle. From this point until the shipping of the orders, each oligonucleotide is handled as an individual component, separate from the order in which it was placed. The separation of order and order items is the classical manufacturing approach and lends itself to the archetypal relational data structure discussed above.

Each manufacturing queue is designed so that sequences can be sent electronically to a synthesis instrument with all of the information necessary to perform the synthesis. The synthesizer manufacturer's instrument control software is used intact, so that the manufacturer of the instrument, not the synthesis laboratory, can implement upgrades to the software and firmware of the synthesizers. A minimal input from the synthesis database of an ASCII file and a computer system event to the DNA synthesizer software is required for downloading all essential information.

Sample tracking and data transfer

Each oligonucleotide is individually barcoded prior to being placed on the DNA synthesizer so that it can be tracked throughout its lifetime in the laboratory. This allows for real-time updates to the synthesis laboratory database, which the original requester is able to access from their personal computer. The researcher is thereby updated on the progress of oligonucleotide manufacturing and expected arrival time, thus assisting in experiment planning. Individual syntheses are barcode scanned once they are removed from the synthesis instrument. As an oligonucleotide proceeds through the rest of the manufacturing process, only syntheses that fail at any step are scanned individually. Large volume sample tracking requires that individual sample handling and data entry be kept to a minimum while data capture is maximized, thus reducing the potential for error. An efficient method to optimize these disparate parameters is to track oligonucleotides in groups through common processes. As an example, the analysis module individualizes only products that do not pass analysis and considers all others acceptable, thereby maximizing data collection with minimal external input.

Interaction of the data modules with robotic systems and analytical instrumentation is handled through the exchange of data files using a network file server accessible by both

the data system and the instrumentation. The database is able to create and upload files, in any format necessary for the instrumentation, to the file server. The resultant files are downloaded to the instrument control software. Data generated by the instruments is then handled in the same manner with the opposite flow. This method allows for large volume data transfers across different platforms with simple operator input.

The utility of the modular design approach was demonstrated in the case of the analysis module. When the database was implemented, each oligonucleotide was analyzed by PAGE. The introduction of MS analysis enhanced the production process. A new analysis module was designed and constructed while the MS method was validated. Subsequently the MS data handling module was implemented in place of the PAGE analysis module with minimal disruption to laboratory operations.

After the oligonucleotides have passed analysis, they are forwarded to the shipping module. From this module, each oligonucleotide is regrouped with the other components in the order and delivered to the initial requester as a unit. All outstanding orders are tracked and reported in this module. Shipping and tracking information are captured with a minimal amount of scientist input. Each order is barcode scanned as it is placed into a prescanned shipping pouch for delivery to the requester. This guarantees that all essential information is easily retrieved in the event of delivery problems.

In addition to providing sample tracking, the database provides a full complement of easily accessible reports allowing for retrieval and analysis of a wide variety of production parameters. All of the information associated with a synthesis is collected and stored in the database; this includes time stamps for completion of each operation and descriptions of where in the process and for what reason any oligonucleotide was withheld from distribution. The oligonucleotide sequence, base composition and extinction coefficient are determined and stored. Information is kept on both the crude oligonucleotide and the purified portion of the oligonucleotide because both materials are stored for later retrieval. All trends are analyzed by running a set of preprogrammed queries or by running ad hoc queries of the data tables. Trends in the performance of the instruments can be analyzed by examining the failure rate for a synthesizer or for a particular column on the synthesizer. Usage patterns from particular requesters or projects are easily tracked. Use frequency of particular sequences (e.g. universal primers) is easily obtainable so that high-use oligonucleotides are manufactured on a large scale and aliquoted as needed. Once the information is extracted from the data system, any data trending software can be used to analyze any type of trend that may be of interest (for example, mean time between failure for a given instrument or the rate of increase in usage for a particular project). Ad hoc reports can also be created to help answer any question that may come up in the production process. These functions are useful in analyzing past trends and forecasting future demands for long-range planning.

A truly relational data system that is clearly thought out prior to design can allow for a large amount of information to be collected and organized with only essential data input from users. Thus, an increase in productivity can be realized, because scientists are spending their time conducting the synthesis process rather than adding records to the data system. The system can collect large amounts of information about the oligonucleotides, allowing for analysis of trends and archive of detailed historical records.

Future demands for oligonucleotides

As the number of known nucleic acid sequences expands, it will become increasingly important to characterize fully the nature of their protein products. The current large-scale sequencing efforts have concentrated on sequencing small fragments of unknown transcripts, typically enough to uniquely define a new gene and possibly assign a potential function by homology to known proteins. Perhaps the largest and most interesting class of new genes will be those for which no homology or function is known. The important job of isolating full-length cDNAs and determining function lie ahead. Completion of these tasks will undoubtedly rely heavily on molecular biology techniques that require synthetic oligonucleotides.

In addition, several applications in the area of functional genomics will find expanded use. Oligonucleotide analogs can be used to specifically eliminate the protein product via antisense inhibition *in vitro*[26,27] and *in vivo*[28] to provide valuable information quickly on the potential therapeutic utility of the protein. With cellular uptake facilitating strategies[29] and careful control, experiments of this type can allow for rapid assignment of function. As the pressure for rapid identification of the potential utility of novel gene products grows, so will the demand for specific antisense agents and expertise in this field.

The transcriptional upregulation of genes in diseased tissues or in response to certain stimuli is extremely important in unraveling function. Quantitation of expression levels of an mRNA can be readily determined using fluorescently quenched probes in a quantitative PCR reaction[30]. With the recent introduction of commercial instrumentation, this technique will find widespread use in deciphering the role of new gene products in biochemical pathways. Also, the use of micro-arrayed nucleic acids is beginning to prove extremely useful in efforts to define the function of individual genes and gene expression networks[31–35]. The powerful method of serial analysis of gene expression is another tool allowing for the identification and quantification of transcripts derived from various cell types[36,37]. Having a strong competency in nucleic acid synthesis can facilitate the development of core expertise in all of these specialized techniques. This allows for rapid integration of new technologies into the research repertoire.

To retain a competitive advantage, the industrial nucleic acid synthesis laboratory must remain in a state of constant evolution. Emerging technologies in several fields must be constantly evaluated and implemented to facilitate the ever increasing demands for these materials. Using a modular approach to both the process and data-handling needs of the laboratory produces a malleable framework into which novel technologies can be easily instituted. Expansion of the applied technologies utilized in the nucleic acid synthesis laboratory to additional high-throughput disciplines is also of significant benefit. When properly integrated and motivated to achieve research goals, the oligonucleotide synthesis laboratory serves an integral role in the drug discovery process.

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