

Multidrop Combi Reagent Dispenser Workflow Solutions

A new workflow solution to increase throughput, reproducibility, and speed

Diane F. Baraket

Rosalinda M. Savoy, PhD.

Improving high throughput workflows

The cost of high-throughput sample processing is an expense that most labs cannot afford. Automated Liquid Handlers (ALHs) are becoming bigger and better, but with an expensive price tag. Scientists at Thermo Fisher Scientific have recently developed a new workflow for automating their samples, incorporating the smaller footprint of a Thermo Scientific™ Multidrop™ Combi Reagent Dispenser, instead of an ALH. This workflow is designed to save costs and improve the number of samples processed per week. This workflow can also be applied to multiple workflow applications as a way for labs to implement high throughput testing at reduced costs.

The Applied Biosystems™ GeneTitan™ Multi-Channel (MC) Instrument was developed to improve sample processing and increase automation in the microarray workflow. The GeneTitan instrument combines a hybridization oven, fluidics station, and imaging device under a single instrument with less than 30 minutes of hands-on time. However, the sample preparation and target preparation steps still require a long intensive process. The current workflow uses ALHs to increase automation and decrease sample prep time. When utilizing the Multidrop Combi Reagent Dispenser, they have significantly increased throughput from 768 samples (8/96-well plates) per week to over 2,800 samples (29/96-well plates) per week per system, a factor of ~3.6 more.



Figure 1. The High Throughput MCRD Workflow

In the revised workflow, the Multidrop Combi Dispenser replaces the aspiration and dispense step. Instead of using a pipette for a mixing step, this is replaced by sealing the microplate, shaking for ~30 seconds, and spinning for ~30 seconds. With the dispensing speed of the Multidrop Combi Dispenser and the 4 plate positions of the Compact Digital Microplate Shaker, labs can process 4 plates per reagent faster than it would take using an ALH.

The high throughput Multidrop Combi Reagent Dispenser (MCRD) workflow increases throughput in labs by dedicating one Multidrop Combi Dispenser to one specific reagent. By assigning each reagent in the protocol to its own Multidrop Combi Dispenser and cassette, this allows for faster filling of plates. Once plates are filled with a reagent, rather than using the conventional method and a pipette to mix the sample, the plates are sealed with a microplate heat sealer. Next, the sealed plate is shaken for 30 seconds and then spun for an additional 30 seconds (Figure 1). Once this step is completed, the sealing film is removed, and the plate would be placed in the next Multidrop Combi Dispenser with the next reagent and the process is repeated.

Reduce time

To highlight the speed of the high throughput MCRD workflow, we compared the workflow using several different dispense volumes, with the same workflow on the Thermo Scientific™ Versette™ Automated Liquid Handler, and an alternative ALH. The Multidrop Combi Dispenser time was the total time needed to dispense the appropriate amount of volume for 4 plates, heat seal each plate, shake and spin plates for 30 seconds. The Versette ALH and the alternative ALH times were the total time needed to load tips, dispense the volume, mix the indicated volume 3 times, and unload tips. The high throughput MCRD workflow timings are significantly less in comparison to using either of the tested ALHs.

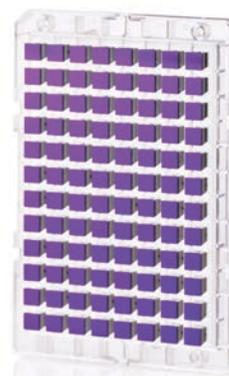


Figure 2. Array plate for GeneTitan

Furthermore, if more than 3 mixes are needed, this would increase the time for both ALHs thus further increasing the difference in the amount of time the ALHs require in comparison to the Multidrop Combi Dispenser workflow. It is also important to note that for higher dispense volumes, i.e., 660 µL, most ALHs don't have tips large enough for this volume. Therefore, multiple aspirations and dispenses are required. An additional benefit of using multiple Multidrop Combi Dispensers is the time saved during equipment downtime. ALHs need frequent maintenance and, whether for maintenance or repairs, can be unavailable for use for days at a time. With multiple Multidrop Combi Dispensers on hand, if one requires maintenance or repair, another may be substituted in its place providing continuous workflow.

Decreased processing time with the high throughput MCRD workflow

Dispense volume (µL)	Mix volume (µL)	Multidrop Combi (seconds)	Versette (seconds)	Alternative ALH (seconds)
20	10	80	268	129.28
35	10	83.6	272	131.44
60	15	90	280	132.8
80	20	95.2	288	138.4
105	20	102	296	141.4
130	40	108	316	147.56
150	50	113.6	328	151.88
220	100	130.6	376	169.76
230	100	134	380	203.6
660	100	242.4	808	246.12

Table 1. Multidrop Combi Dispenser method includes dispensing time for 4 plates, sealing time for 4 plates (2 seconds per plate), 30-second shake, and a 30-second spin. Other ALH methods include time to load tips, move into position above liquid, aspirate sample, move into position over microplate, dispense sample, perform 3 mix cycles, and move into position to unload tips for 4 plates.



Figure 3. Switch from an ALH to multiple Multidrop Combi Dispensers. The compact size and stack-ability helps reduce needed bench space.

Reduce cost and plastic waste

Many laboratories struggle to break into high throughput genotyping because of the high cost. To make a lab truly high throughput, some type of automation must be implemented. The obvious answer is an ALH, however, the base unit with 2 robotic arms can start at around \$300,000. Not to mention, any customization and additional tools needed, can significantly increase the price. When comparing this to the new high throughput MCRD workflow, 16 Multidrop Combi units can be purchased along with an automated microplate sealer, a digital microplate shaker, and a centrifuge and rotor for less. If using a non-automated sealer, 2 additional Multidrop Combi units could be purchased for the same price as an ALH. Switching to the high throughput MCRD

workflow can also help labs save on cost and help reduce the number of plastic consumables needed. When using an ALH, new pipette tips are needed for each reagent and after each mixing step per each plate. If a workflow has 16 different reagents, then this means using 16 tip magazines/ racks per plate. With the high throughput MCRD workflow, Multidrop Combi cassettes can be used to dispense approximately 28.8 L before needing to be replaced, or 1500 plates when dispensing a 200 μ L volume per plate. When comparing costs of one Multidrop Combi cassette to 1500 racks of tips, the cassette is significantly less expensive. Even if a lab bought 16 cassettes, one for each reagent in a workflow, the cost of the cassettes would be less than the cost of 1500 racks of tips.

Estimated savings when using the high throughput MCRD workflow

Equipment needed	Cost of ALH workflow**	Cost of the high throughput MCRD workflow**	
Base ALH unit	\$300,000		
Multidrop Combi Dispenser		\$15,000	x 16 = \$240,000
Sealer		\$39,000	
Shaker		\$2,000	
Centrifuge		\$11,000	
Microplate rotor		\$5,000	
Equipment total	\$300,000	\$72,000	\$297,000
ALH tips	\$14.1 (per rack) x 1500 = \$21,150		
Multidrop cassette		\$753	x 16 = \$12,048
Consumables total	\$21,150	\$753	\$12,048

Table 2. Cost of a base ALH unit is approximately \$300,000. For this price, a lab could purchase 16 Multidrop Combi Dispensers, the automated microplate sealer (manual microplate sealer would allow for 1-2 additional Multidrop Combi units), a 4 position microplate shaker, and a centrifuge and rotor. Additionally, because the Multidrop Combi cassettes can be cleaned daily and reused, this would further reduce costs compared to single-use ALH tips, as well as being more environmentally friendly by reducing plastic use.

**Prices based on estimated values.

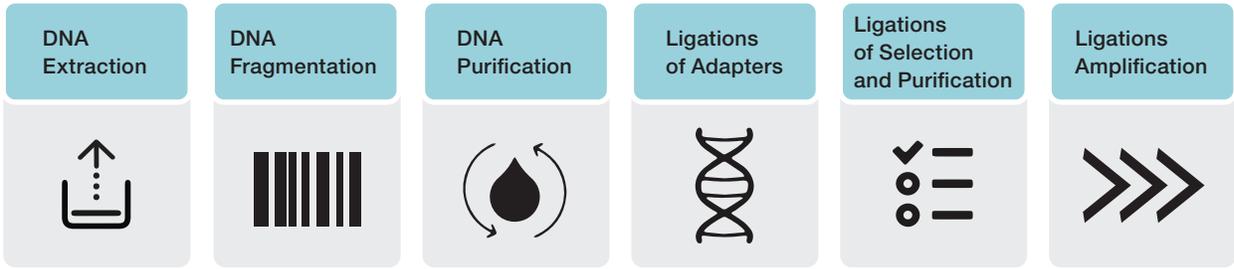


Figure 4. Next-Generation Sequencing (NGS) Sample Prep Workflow. NGS is a multistep-multiday process. This process can be sped up and improved using the high throughput MCRD workflow.

Applicable for many workflows

The high throughput MCRD workflow was originally developed for use for the microarray sample prep. However, it can be applied for use on many laboratory workflows. While the Multidrop Combi Dispenser can't be used for sample transfer, it can be used for any assay which contains reagent dispensing steps.

After transferring samples to a 96 well plate, the high throughput MCRD workflow can be used in the NGS workflow during the DNA extraction steps (Figure 5). Kits like the Invitrogen™ PureLink™ gDNA Binding Plate use a 96 well SLAS format that fits seamlessly with the Multidrop Combi Dispenser. After transferring the lysate, the Multidrop Combi Dispenser can be incorporated into any reagent dispense steps to make it faster and higher throughput solution: 3 Multidrop Combi Dispensers would be used with this workflow example.

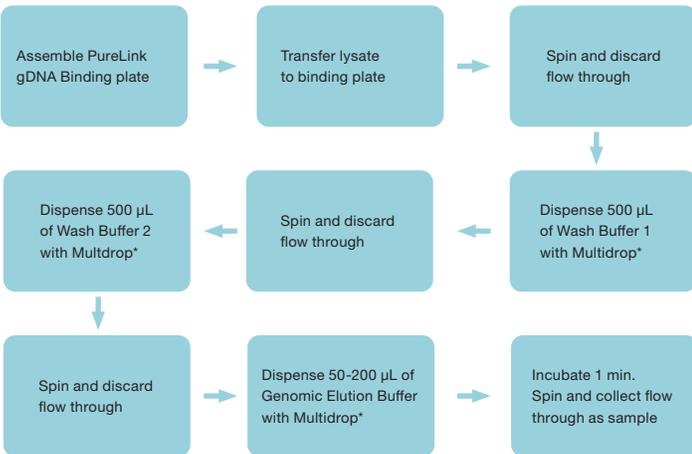


Figure 5. DNA Extraction using the high throughput MCRD workflow

Additionally, the full High Throughput MCRD Workflow can be applied in the DNA purification process (Figure 6). After the addition of the Agencourt beads with a 96-channel pipette, like the Versette Liquid Handler, the high throughput MCRD workflow can again be applied. Reagents are dispensed with the Multidrop Combi Dispenser and then the mixing step is replaced with a plate seal, shake, and spin. For the DNA purification workflow, 2 Multidrop Combi Dispensers would be used.

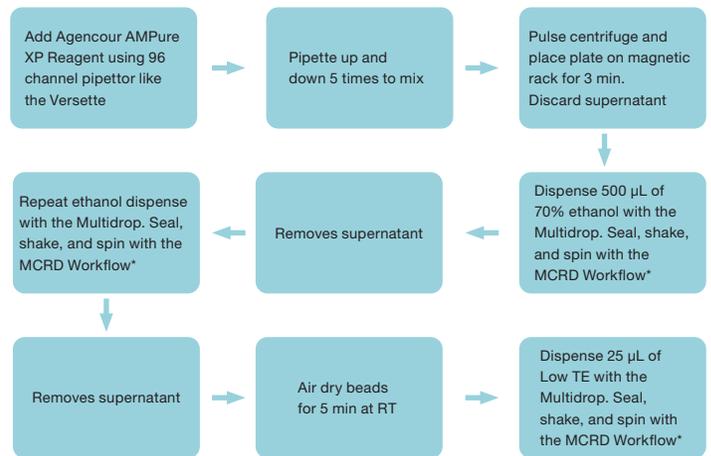


Figure 6. DNA Extraction using the high throughput MCRD workflow

Summary

Benefits of workflow solution

Feature	Benefit
Faster than an ALH or hand pipetting	More samples processed in a week
Less expensive than buying an ALH instrument	Lab costs kept at a minimum
Smaller instrument footprint	Multidrop dispensers can be stacked to save bench space
Cassettes are cleaned daily for reuse	Saves money
Fewer consumables used	Reduces environmental footprint
Reduce downtime due to machine services and maintenance	Keeps project on track and helps meet deadlines
Applicable for many workflows	Enables a variety of uses and flexibility if project changes

Conclusion

Using the high throughput MCRD workflow provides a low cost alternative to high throughput sample processing. By incorporating many Multidrop Combi Reagent Dispensers into a workflow, labs can save time and money while increasing the amount of samples processed. Furthermore, the dispenser's compact size and ability to be stacked helps reduce the footprint, freeing up valuable bench top space. Maintenance savings on PM contracts and ability to

substitute another dispenser in the place of one that may require service, provides continuous sample processing without downtime. Although this workflow was originally designed for microarray workflows, it can be used in many applications including NGS.

To learn more, visit thermofisher.com/axiom-insights

Ordering information

Product	Size or Quantity	Cat. No.
Multidrop Combi Reagent Dispenser	Each	5840300
Multidrop Combi Reagent Dispenser with SMART 2 option	Each	5840320
ALPS 5000 Automated Microplate Heat Sealer	Each	AB-5000
Compact Digital Microplate Shaker	Each	88880023
Sorvall Legend XT Centrifuge	Each	75004506
HIGHPlate™ 6000 Microplate Rotor	Each	75003606

Find out more at thermofisher.com/multidrop