

Lab Automation Protocols and Virtual Workcells

Flexible Screening System Can Be Created with The VaryScreen Using SoftLinx Software

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Laboratory automation typically involves integrating key instrumentation with liquid- and microplate-handling robots creating workcells that are often designed for a single protocol. The scheduling software for such a system is used simply to reproduce the required steps with some step modifications to study samples of varying nature. This approach, however, can lead to the purchase of underutilized liquid- and plate-handling robots along with lack of automation of instrumentation that does not take part in frequently used procedures.

Scheduling software has become more versatile over the years, making it easy for different pieces of equipment to share the same automation robots. One can then design a series of virtual workstations, employing overlapping components of a workcell in various sequences, even at the same time.

With the recent proliferation of multimode microplate readers, it is now possible to support a wide variety of screening protocols typically used in exploratory drug discovery. By building an automated workcell around such a device and employing advanced scheduling

software technology, it is possible to create a highly flexible, general screening system that can run a FRET assay one day and an ELISA assay the next, simply by loading the appropriate file into the system. This tutorial will demonstrate an approach to this system developed at the Hudson Control Group (www.hudsoncontrol.com).

Biological Assay Screening System

The VaryScreen™ system (Figure 1) was designed to carry out many of the screens that are accessible using the detection technologies supported by most multimode readers such as fluorescence adsorption, fluorescence polarization, luminescence, and UV/Visible adsorption.

The system includes a multichannel dispenser, automatic pipettor, and a microplate washer to support most liquid-handling needs. An automatic incubator and a microplate shaker nest control reaction conditions. Plates are stored and transported by a stacking system connected to the liquid handlers by a moving track. A robotic arm in the center of the system moves plates from this unit to the remaining instruments.

Samples can be prepared and read by combining the appropriate sequence of

steps, as prescribed by the individual protocols. Then by applying the appropriate detection method one can carry out all sorts of assays such as FRET, TR-FRET, HTRF, LANCE, AlphaScreen™, ELISA, FP, and reporter assays including Luciferase and beta-galactosidase.

Software Integration

Hudson Control Group has developed a workcell scheduler software called SoftLinx For Systems™ to design virtual workcells. Software interfaces for each of the previous-

ly mentioned pieces of equipment were written and loaded into SoftLinx. The location of the various nests denoted in Figure 1 are stored, and the types of plates and pipette tips being used by the system are defined. The system is then ready for protocol design.

Protocols are then sketched in a method editor by building process flowcharts. Icons for each instrument are dragged into position, and experimental conditions are detailed (such as buffer volumes or incubation times and temperatures).

For example, to perform a BCA UV protein assay, one would dispense a mixture of the BCA reagents in a BPA buffer. The test protein sample is added, warmed

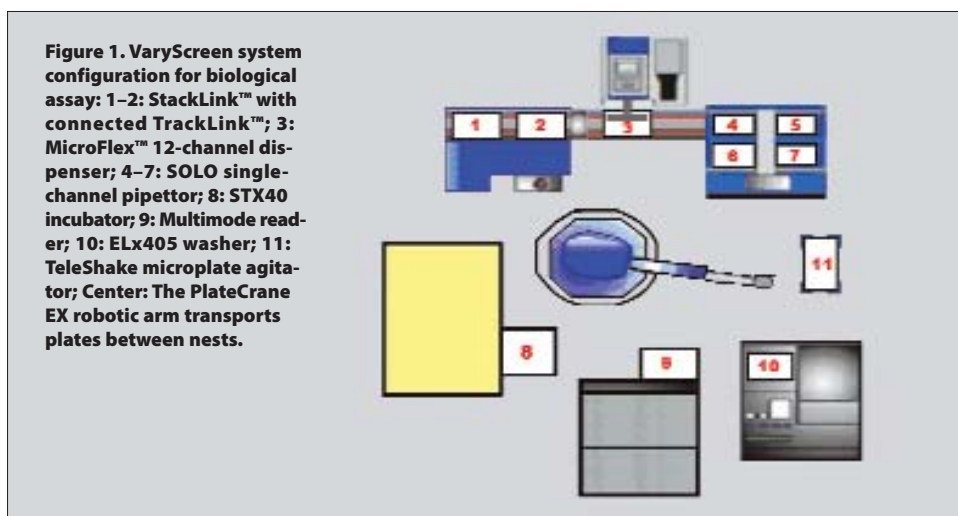


Figure 1. VaryScreen system configuration for biological assay: 1-2: StackLink™ with connected TrackLink™; 3: MicroFlex™ 12-channel dispenser; 4-7: SOLO single-channel pipettor; 8: STX40 incubator; 9: Multimode reader; 10: ELx405 washer; 11: TeleShake microplate agitator; Center: The PlateCrane EX robotic arm transports plates between nests.

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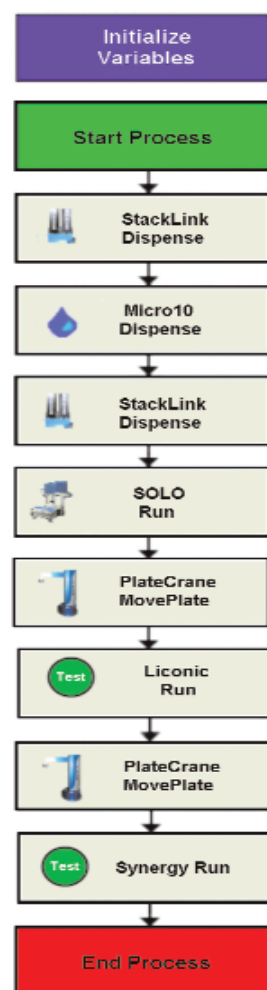


Figure 2. BCA UV protein assay

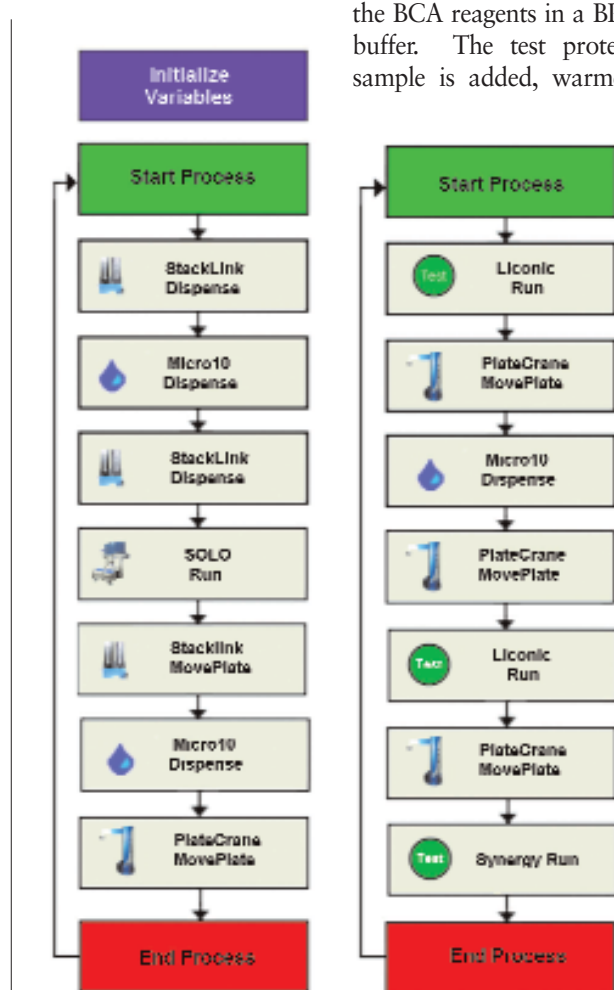


Figure 3. A typical AlphaScreen™ assay.

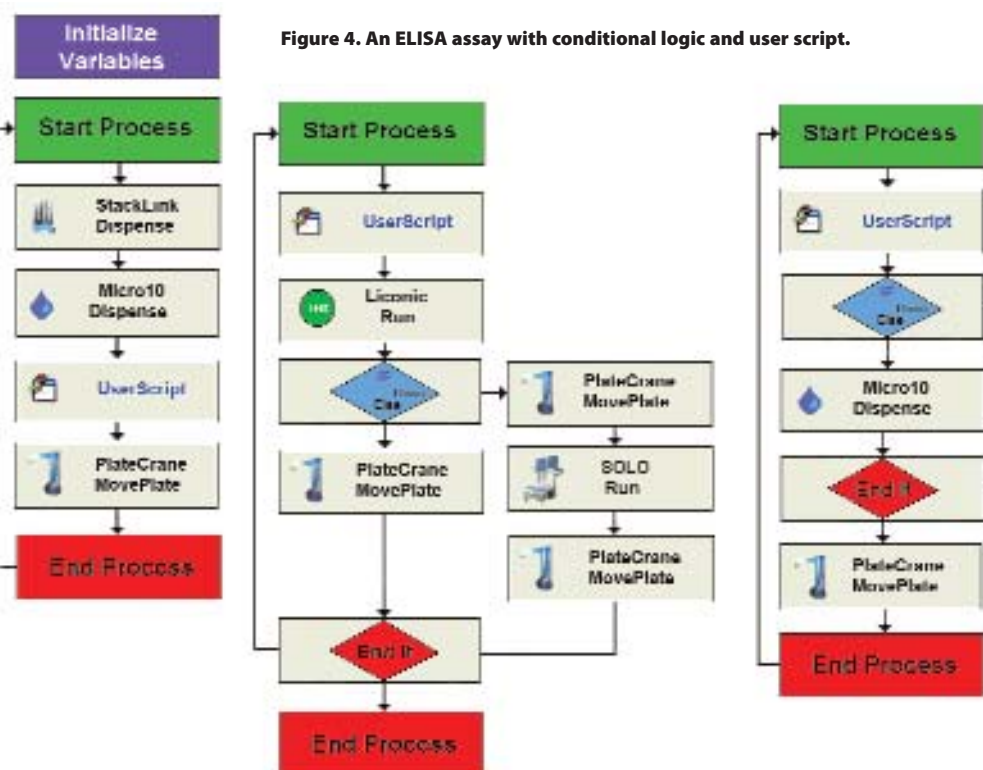


Figure 4. An ELISA assay with conditional logic and user script.

in an incubator, and then the plate is read at 563 nM. This protocol uses a subset of the instrumentation in the workcell and can easily be designed in SoftLinx. An implementation of this protocol is shown in *Figure 2*.

Parallel Processing

Most assays involve many more steps and are better represented by a series of parallel processes. For example, a typical AlphaScreen assay, shown in *Figure 3*, can easily be divided into two sequences.

In the first sequence, the various reagents, kinase, and test inhibitor are added and placed in the incubator. In the second process (which is programmed to begin when a microplate arrives at the nest of the incubator), the AlphaScreen beads are added, and after additional incubation, placed in the multimode reader for readout.

Programming Smarter Protocols

A great deal of intelligence can be included in protocol design with the inclusion of constructs found in typical programming languages. One can define global variables, conditional logic such as While loops or “If...”, “Then...”, and “Else...” statements, and can include unlimited functionality with user scripts (via access to Visual Basic for Applications in the case of SoftLinx).

These tools can be combined with parallel processes to create complex protocols that can be used to maximize the efficiency of a workcell and isolate rate-limiting sequences so that the rest of the equipment continues to be used.

For example, *Figure 4* shows a typical ELISA assay that involves multiple reagent additions, incubations, and wash cycles. Often the conditions used by each piece of

equipment will vary depending on its current position in a protocol. This would result in a long and messy process, or a large number of individual parallel processes.

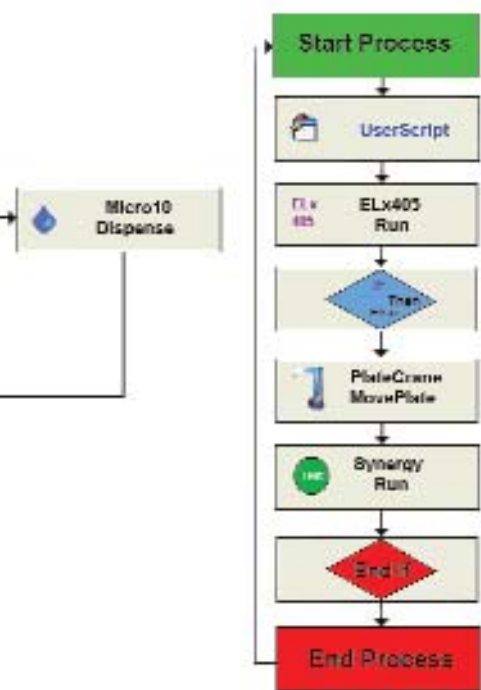
By including user scripts and global variables, however, it is possible to design efficient protocols that are easy to follow and adjust in the future when a different system is being studied. In this example, user scripts at the beginning of each process

define how the incubator, dispenser, and washer should be set through each pass. Finally, an “If...”, “Then...” construct is used to determine when it is time to transfer the plate for the final reading.

There are many additional ways in which protocols can be designed to take full advantage of all of the components of a well-designed workcell. Similar approaches can be used to divert plates containing potential

leads to an additional reader to obtain secondary assay results on-the-fly. Similar interactive-cherry-picking techniques can also be used to aid in the design of new assay protocols. One can imagine larger workcells that include additional equipment to support protein expression and purification, for example, to be used in a single system that can produce reagents, as well as support novel assay development. **GEN**

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HEK293 were transfected with: (left) empty vector, (right) TrueORF for Myc/DDK-tagged vinculin. The lysates were analyzed using anti-DDK antibody to show over-expression of vinculin. *DDK is the same as FLAG™.

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