



Instrumentation Development

Challenges of developing
hematology instruments

Outsourcing for IVD Manufacturers

Sourcing clinical patient samples
for IVD development

PLUS:
Research
consortium
fights TB

The challenges of developing hematology instruments

Hematology instrumentation developers must be equipped to meet technology challenges coupled with IVD manufacturers' demands for speed-to-market and cost efficiency. **BY HENRI CHAMPSEIX AND ERIC JOLAIN**

Blood is the only fluid that flows throughout the entire human body. Blood analysis can detect a wide range of common physiological problems such as anemia, diabetes, autoimmune deficiencies, infections, and cancers. It can also expose genetic information, viruses, organ deficiencies, etc.

Hematology is the study of blood cells. Hematology analyzer instruments can take the form of a relatively simple handheld unit, a more sophisticated point-of-care diagnostic instrument, or a highly complex clinical laboratory analyzer. While all blood analyzers are designed to be accurate and reliable, the primary factors that set these three types of instrumentation apart from each other are sample throughput rate and the number of blood parameters measured.

The most common blood test is a complete blood count (CBC). This test can help to detect blood diseases and disorders such as anemia, infections, clotting problems, blood cancers, and immune system disorders. The specific blood components counted are the following:

- Red blood cells carry oxygen from the lungs throughout the human body. Abnormalities in this reading could indicate conditions such as anemia, dehydration, or bleeding.
- White blood cells are the part of the immune system that fights



infection and disease. Abnormal levels could indicate infection, blood cancer, or an immune system disorder.

- Platelets are blood cell fragments that aid in clotting. Abnormal levels could indicate a bleeding disorder, such as hemophilia, in which blood is slow to clot, or a thrombotic disorder, which exhibits too much clotting.
- Hemoglobin is an iron-rich protein in the red blood cell that carries oxygen. Abnormal levels could indicate anemia, sickle cell anemia, or other blood disorders.
- Hematocrit is a measure of how much space red blood cells take up in the blood. A high level might

indicate dehydration. A low level might indicate anemia. Abnormal readings may also be a sign of a blood or bone marrow disorder.

Other common blood tests include the following:

- Blood chemistry tests or basic metabolic panel measure different chemicals in the blood, such as glucose, calcium, and electrolytes.
- Blood enzyme tests measure enzymes such as troponin and creatine kinase, which can help to identify whether patients have had a heart attack.
- Blood tests to aid in assessing the risk of heart disease. Such tests measure cholesterol and triglycerides.

Anatomy of a Hematology Instrument

Hematology analyzers count, measure, and characterize blood cells and their components by collecting and calculating results from electrical impedance and/or light-scattering data. Comprised of pumps, motors, syringes, tubing, optics, electronics, and software, the analyzer performs an intricate and delicate task. Multidisciplinary skills in mechanics, chemistry, electronics, software, optics, and fluidics are necessary to engineer and develop such an instrument (see Figure 1).

Design and Mechanics. A hematology analyzer contains basic mechanical parts: pumps, syringes,

motors, and tubing. These mechanical parts operate in conjunction with reagents, optics, and software to deliver the appropriate test results to clinicians. In order to produce successfully such an instrument, a developer must have an intimate knowledge of the underpinnings of the system, how that system works, and what results it must deliver.

Only by having a solid knowledge in place can one develop cost-effective, innovative solutions with maximum optimization for all of the involved technologies. Engineering teams need to work with the latest CAD tools, which enable internet data exchange in many different standards including management of a database of software updates and version upgrades.

Technical specifications of the hematology analyzer are defined jointly between the customer and the developing teams. At the beginning of the project, the teams strive to find the best mechanical design solutions to improve the manufacturing process and reduce future maintenance costs. Models, prototypes, work pieces, assembling process, and tools are designed and digitized using CAD software, and then developed using either quick prototyping or machining techniques. The mounting and assembly of modules or complete instruments is performed in order to check and validate the overall design.

Fluidics. Precise fluidics is crucial to the accurate operation of a hematology analyzer. Blood specimens travel throughout the instrument, being pushed or pulled through tubing by pumps. Specialized techniques must be used to prevent pushing or pulling too hard or too quickly, which could destroy or alter the blood components, thereby causing faulty and inaccurate results.

Electronics. Different measurement techniques are used to classify cells. Light-scattering events are translated into electrical pulses by opto-electrical devices, and thousands of measurements are performed each second (see Figure 2). Specific capa-

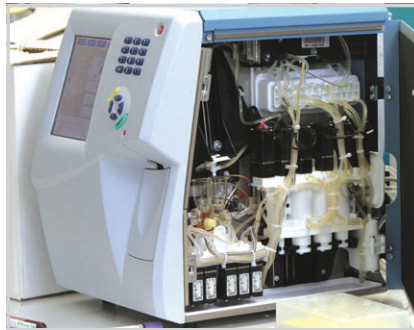


Figure 1. Comprised of pumps, motors, syringes, tubing, optics, electronics, and software, this hematology analyzer, developed and manufactured by BIT C2 Diagnostics, performs an intricate and delicate task. Multidisciplinary skills in mechanics, chemistry, electronics, software, optics, and fluidics are necessary to engineer and develop such an instrument.

bilities needed to design, prototype, and manufacture embedded system products include the following: programmable logic design, expertise in VHDL (FPGA, CPLD), 8 to 32 bits embedded processor boards for RTOS, analog and digital board design, low noise data acquisition and signal conditioning, low EMI design, motion and positioning systems, and PCB layout.

Reagents. Reagents are solutions used to either dilute the blood that is being tested or differentiate or mark various cell components in the blood sample, which enables the further electrical and optical analyses. Other reagents are used to clean the device between sample analyses to prevent cross-contamination of samples. Reagents are consumables that differ from IVD manufacturer to IVD manufacturer. Each manufacturer uses or designs its instrument to work with different reagents, and these reagents are often integrated into an instrument's unique design.

Optics. Precision optics are an integral part of a hematology analyzer. The blood cells' characterization relies on optical systems that measure scattering properties of individual cells. Sophisticated software

enables the counting and identifying of various types of blood cells. In practice, a dilute suspension of cells passes through tubing past a laser beam. Light scatter from each cell is analyzed by the software, and the resulting numerical representation is interpreted by clinicians. In this manner, cell populations are described, quantified, and classified. Fluorescent techniques may also be used to improve cell identification (see Figure 3).

Software. The software in a hematology instrument performs multiple functions. It interprets and carries out the orders of the instrument operator. It monitors and drives the operation of the instrument's working components. It collects and analyzes the resulting data. Essentially, the software pilots everything. In addition, the software works in conjunction with the graphical user interface (GUI), which is different for every customer and depends on the measurement techniques and parameters measured by the device. Menus with selections are used by the administrator of the instrument to control the underlying processes. The graphical menus serve to enrich the user experience and help to reduce operator error.

Basic functions of a common clinical analyzer might include pipetting (i.e., moving fluid from one place to another), mixing and adding reagents, and incubating the final mixture for a determined amount of time. The software coding for such basic functions controls the speed of the motor, the operation of the pumps, and the direction and precise movement of the loaders and stepper motors in order to minimize jostling of the fluids. In addition, software controls the pipetting function, higher level incubation, and the action of picking up a sample and dropping it off somewhere else inside the instrument for more processing.

For an instrument developer, the handling competencies required for full IVD automation management

include the following: design of embedded systems with real-time requirements; motor driving (continuous or step-by-step), inputs, outputs, and system control; data acquisition and signal processing; ergonomic and international GUI (languages, alphabets, unities); data transmission; modules and release downloading; software for verification and validation; and production and control tools.

From a programming perspective, IVD instruments are very complex. The more tasks an instrument performs, the more software code is required. And the more code there is, the greater the chance for software bugs to emerge. Programmers often think they can write pages of code in a day. But after debugging and making that code functional, the amount of code written is reduced to only a few lines per day. Given the time and expense needed to identify the bugs and eradicate them, it is critical to reuse clean code that has already been validated and certified. This is possible through Software Platform Technology, an innovative approach to IVD instrumentation development in which developers can utilize a layered system: building advanced features on top of a solid, tested foundation of codes dictating fundamental processes. Organizing a library of proven code sequences for reuse can effectively expedite a bug-free design of an IVD instrument (see Figure 4).

Business of Hematology Instrumentation Development

Automated blood analyzers, point-of-care instrumentation, and patient-operated handheld units have become high-tech and complex in operation yet simple to use. Research advancements have led to professional demands for more capabilities in the testing units. The business of

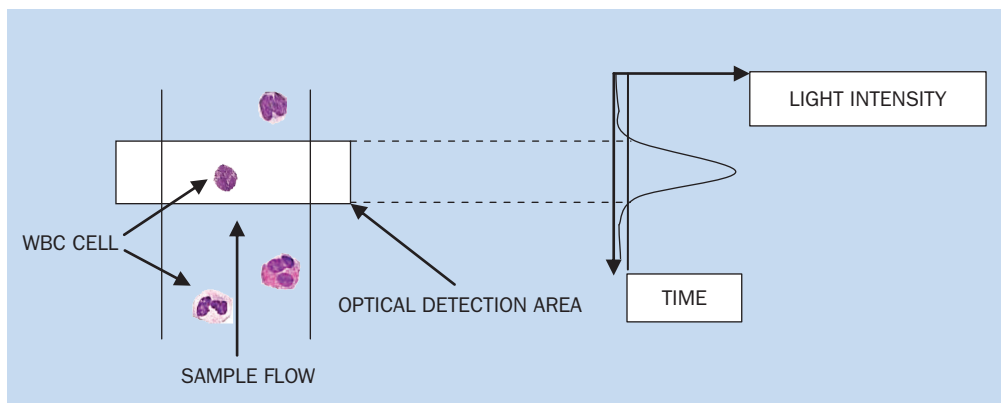


Figure 2. Electronic measurement techniques are used to classify cells. Light-scattering events are translated into electrical pulses by opto-electrical devices, and thousands of measurements are performed each second.

developing and manufacturing such precise, flexible technologies quickly and within budget has become a specialized discipline. Hematology instrumentation developers must be equipped to meet the challenges of high technology coupled with customers' demands for speed-to-market and cost efficiency. Research advancements continually drive IVD manufacturers to enhance designs, adding new features and capabilities while making the units easier to use and service.

Since speed-to-market and competitive cost structures are primary drivers when it comes to outsourcing the development of diagnostic instruments, more IVD manufacturers are considering platform technology. BIT Companies has found that by exploiting the fact that many instruments share the basic building blocks with regard to both hardware and software, a manufacturer can repurpose a foundation that is proven and validated, and spend development dollars on the proprietary technologies and features that make the instrument unique. With the availability of a virtual library of basic certified components that are scalable and updateable, platform technology has changed the way many IVD manufacturers do business.

With the development process time measured in years, and the average cost in the millions of dollars,

IVD manufacturers are eager to fast-forward their projects by repurposing fundamental, proven technology in the shape of existing, validated platform modules. Platform modules are previously designed, developed components that have been tested, proven, certified, and used in other IVD systems over time. They are composed of selections from a developer's portfolio of existing hardware, electronics, and software systems that can be scaled up or down to suit the purpose. All of the components comprising the platform module are specifically designed for operation within a complex medical diagnostic instrument, and all systems are developed on the lowest level possible to allow for the highest vertical and horizontal integration.

High-End Hematology Analyzer Market

In the high-end hematology analyzer market, there are five to six major corporate players. A high-end blood analyzer can analyze more than one hundred samples per hour and measure a multitude of parameters. Such automated instruments are very complex and usually take more than seven years to develop, validate, and release to market. IVD manufacturers nearly always choose to develop these instruments internally within their companies rather than outsource the development to an outside IVD

instrumentation development firm.

However, these same IVD manufacturers usually offer both low- and mid-range models of blood analyzers which, although using similar technologies as the high-end models, offer lower throughput rates and fewer parameters measured (see Figure 5). Mid-range models generally provide a sample throughput rate of 60-80 samples per hour and are equipped with or without an autosampler. Low-range models provide a sample throughput rate of fewer than 50-60 samples per hour.

Due to the lower throughput rates and parameter offerings (and therefore lower price and profit margin), IVD manufacturers find it more efficient and more cost-effective to outsource the low- and mid-range hematology instruments to companies that specialize in IVD instrumentation development and manufacturing. The technologies used in the low- and mid-range models offer the same reliability as the high-end models and are often based on the same underlying technologies (i.e. the same measurement techniques and reagents). However, as opposed to the high-end

model's seven-year development period, the slower, simpler models can be developed and released to market in about two years.

Due to the competitive nature among the major corporate players in the high-end hematology instrumentation segment, it is rare for a contract manufacturer to develop a line of instrumentation for more than one of the large IVD manufacturers.

Low- and Mid-Range Hematology Analyzer Market

The IVD manufacturers specializing in marketing low- and mid-range hematology analyzers include 10-15 major players. Some of these companies employ their own design teams to work in conjunction with contract manufacturers to produce the instruments, while others outsource all design, development, and manufacturing and simply market the instrument.

Since all blood analyzer instruments currently operate on the same basic principles developed more than fifty years ago, the IVD manufacturers compete on the basis of unique measurement techniques, reagents



Figure 4. The graphical user interface (GUI) provides menus with selections used by the administrator of the instrument to control the underlying processes. The graphical menus serve to enrich the user experience and help to reduce operator error.

used, and the number of parameters offered for the best price, style, and service. While the low-range instruments are easier and quicker to market, there are lower barriers to entry, and therefore there are more competitors. There is always pressure on the developer to reduce the price of development and manufacturing, and speed up the launch of the instrument to market.

Contract manufacturers must move quickly, be innovative, and have a fountain of knowledge, experience, and specialized skills. Prevalidated, proven components and software, which are modified to adapt to the needs of a specific system, can save the developer valuable time. As the impetus for hematology instruments to be smaller continues to grow, a specialty in injected plastic parts helps to reduce costs because smaller size translates directly into manufacturing cost savings. For example, ten years ago, an optical bench measured up to 50-60 centimeters long and 10 centimeters in diameter and was very expensive. Today, due to the creation of specialized injected plastic parts resulting from the drive toward miniaturization, that same optical bench measures 10-15 centimeters long and 3 centimeters in diameter.

Reagents also play a key role in

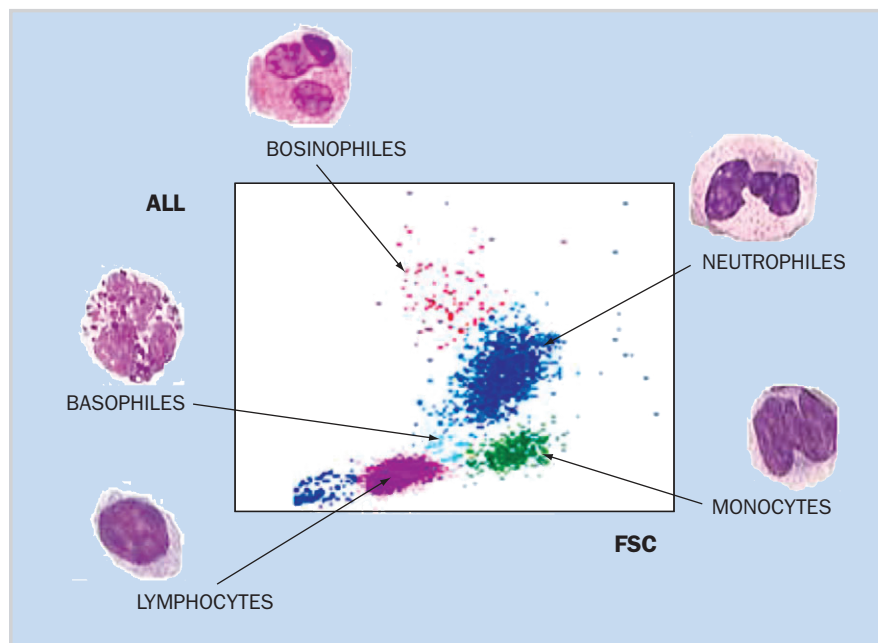


Figure 3. A blood cell's characterization relies on optical systems that measure scattering properties of individual cells. The y-axis represents axis loss light (ALL), and the x-axis represents forward side scatter (FSC).

hematology instrument development. Driven by economy of scale and a desire to recoup high-end segment instrument investment costs, IVD manufacturers often require that the same reagents used in their high-end analyzers also be used in the low- and mid-range systems. This requirement can present a challenge to developers as they simultaneously strive to respond to demands by implementing new techniques to increase reliability and reduce price. In such cases, the secret to success may lie in the process of reagent development and integration (i.e., the method by which a compound mixture is blended, the timing, the temperature, etc.). Such valuable know-how is fiercely protected. However, due to the revealing nature of the patent process, developers do not often apply for patents on this technology.

Future Demands and Advancements

The customers' unrelenting demands to reduce the size, cost, and development time of hematology instruments while increasing value



Figure 5. Low-range segment models of blood analyzers use technology similar to the high-end models' but offer lower throughput rates and fewer parameters measured.

through reliability, flexibility, ease of use, and the number of parameters tested requires developers to be innovative and highly specialized in multiple areas with systems and processes

that are streamlined and organized for efficiency.

There has recently been a movement in the IVD industry to reinvent the technology for analyzing blood samples. If successful, this significant undertaking will revolutionize the industry by increasing the ability to measure more parameters in blood with greater precision and reliability at a lower cost. With the last great technology leap occurring more than fifty years ago, such an advancement would present great changes and new opportunities in the hematology analyzer business. **IVD**



Henri Champseix is Chief Technology Officer and Director of Research and Development at BIT C2 Diagnostics, a BIT Company located in Montpellier, France. He can be reached at h.champseix@bit-c2d.com.



Eric Jolain is Chief Operating Officer of BIT C2 Diagnostics, a BIT Company, located in Montpellier, France. He can be reached at e.jolain@bit-c2d.com.

Reprinted with permission from IVD TECHNOLOGY, January/February 2012. On the web at www.devicelink.com/mtprecision.
© A UBM Canon Publication. All rights reserved. Foster Printing Service: 866-879-9144, www.marketingreprints.com.



www.BIT-Companies.com

Germany

BIT Analytical Instruments GmbH
Am Kronberger Hang 3
65824 Schwalbach :: Germany
Tel: +49 (6196) 806 100

France

BIT C2 Diagnostics
Rue de la valsière Parc
Euromédecine II
34099 Montpellier Cedex 5 :: France
Tel: +33 467 4096 00

USA

BIT Analytical Instruments Ltd.
388 Munsing Street
Ludlow, MA 01056 :: USA
Tel: +1 (413) 583 4388
Toll Free: +1 866 DEVICE1

Source Scientific, LLC
2144 Michelson Drive
Irvine, CA 92612 :: USA
Tel: +1 (949) 231 1707
Toll Free: +1 866 DEVICE1

BIT MedTech
15870 Bernardo Center Drive
San Diego, CA 92127 :: USA
Tel: +1 (858) 613 1200
Toll Free: +1 866 DEVICE1

Japan

BIT Japan Ltd.
Level 28 Shinagawa
Intercity Tower A
2-15-1 Konan Minato-ku
Tokyo 108-6028 :: JAPAN
Tel: +81 (3) 6717 2870

China

BIT Technologies
528 NanBang Road
Kunshan 215300
Jiangsu Province :: China