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Topical Review

Lateral Flow Technology for Field-Based Applications—Basics and Advanced Developments

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In terms of their ability to provide accurate information there is a traditional continuum in diagnostics that ranges from highly accurate methods requiring infrastructure and a centralized approach to testing to less accurate technologies that can be used in a decentralized or point of care testing strategy and that require little to no supporting infrastructure. Today's lateral flow assays marry the utility of a truly field deployable, simple to use technology with the high performance of many laboratory based assay formats. Advances in recent years have allowed for the extension of performance of lateral flow assays into applications that require high accuracy and sensitivity while still maintaining the advantages of the technology from the perspective of infrastructure requirements and user friendliness. This has allowed for improved application of this technology in decentralized testing environments; veterinary, medical and otherwise. The lateral flow assay, once considered less accurate and less capable than infrastructure-heavy, laboratory based formats, is being viewed more and more as a truly versatile technology, capable of more than adequate performance at all ends of the diagnostic continuum. This article discusses the state of the art in lateral flow technology and outlines the utility of the technology in a variety of field based applications.

Introduction

There is a continuum in diagnostic technologies that range from methods that require infrastructure and a centralized approach to testing, to technologies that can be used in a decentralized testing strategy and that require little to no supporting infrastructure ("Point of contact"). Historically, those technologies employed at the point of contact have been considered to have less diagnostic accuracy than those used in centralized testing environments, so the use of field-deployed tests meant compromising performance. A major goal of advancing the design of point-of-contact technologies is to extend the reach of more accurate technologies to decentralized testing scenarios, where they can often be of most use.

Lateral flow has generally been considered to be an ideal technology for application in many point-of-contact testing environments, as it demonstrates many key attributes including the ability to apply the technology without the need for significant or complex infrastructure (Table 1). However, many of today's testing challenges require performance in point-of-contact tests that rivals that of much more costly, central laboratory methods. The performance challenges that have limited the application of lateral flow in many highly demanding applications historically have been sensitivity and reproducibility—which affects on the ability to be quantitative—and coupled with that, limitations in the ability to multiplex larger numbers of analytes. Many of the arguments that are used to dismiss the use of lateral flow in more demanding applications are based on historical design, development, and production methods, and do not reflect the reality of today's knowledge at the cutting edge of lateral flow technology.

There has been a tremendous amount of evolution in lateral flow technologies in the past decade, to the point where the lateral flow test strip sits at the heart of much more complex systems that are capable of extremely high performance. This trend has been driven by a convergence of market and technology forces, including the drive toward a digital, self-administered and consumer-based model, coupled with the ability to readily capture, transmit, interpret, archive, and utilize data in both professional and consumer environments.

Critical to successful market penetration in many of today's applications is the knowledge that the technology is not the product. This principle has been adequately demonstrated in every industry from automotive to communications in the past century; however, in diagnostics there is still a focus on technical specification rather than user-centric design. For adoption of these technologies in field-based environments, lateral flow assay systems need to be designed using user-centered principles and practices. The devices need to fit into the users' workflow, be intuitive, easy to use, and in the best technological sense, be "sticky" to the end user. This requires a shift in mindset for the designers, developers, and manufacturers of lateral flow test systems. To create products that are truly useful in point of contact, or low-resource field environments that retain high performance, it is not possible to approach the development process in the same way as it has historically been done for lateral flow. For more highly specified applications involving ease of use, quantification, high sensitivity, and multiplexing, innovation is required in each of the key components of the lateral flow system. In this article, the key components of a lateral flow system would be discussed and key advances described that facilitate higher performance in field-based applications in any market space, from veterinary infectious disease testing, to hormone and biomarker testing in animals, and equally to human diagnostic, environmental, and bio-defense applications of the technology. Some key principles of designing these devices for ease of use in field environments using user-centric design principles would also be discussed.

Key Elements of A High-Performance Lateral Flow Assay System

The key elements of a highly performing lateral flow test system (Fig 1) are as follows: Assay Format and Architecture,

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Table 1
The Advantages of Lateral Flow Assay Systems

Known and mature technology
Relative ease of manufacture—equipment and processes already developed and available
Easily scalable to high volume production
Stable—shelf lives of 12-24 months often without refrigeration
Ease of use: minimal operator-dependent steps and interpretation
Can handle small volumes of multiple sample types
Can be integrated with onboard electronics, reader systems, and information systems
Can have high sensitivity, specificity, and good stability
Relatively low cost and short timeline for development and approval
Market presence and acceptance—minimal education required for users and regulators

Biological recognition reagents, Signal generation technologies, Interpretation and signal transduction technologies, Device (cartridge) design, Sample collection and handling materials, and Manufacturing process design. Alongside the rational design and development of these system components, the design and implementation of carefully controlled manufacturing processes is critical to the ability to produce highly reproducible, quantitative, or multiplexed systems. Many of these elements need to be addressed from first principles for best performance when designing and developing any given test system.

Lateral Flow Assay Architecture and Formats—A Brief Introduction

A typical configuration for a standard lateral flow assay is shown in Fig 2. Traditionally designed assays are composed of a variety of materials, each serving one or more purposes, overlapping onto one another, and mounted on a backing card using a pressure-sensitive adhesive. The test device consists of several zones, typically constituted by individual segments of different materials, each of which would be briefly explained here.

When a test is run, a sample is added to the proximal end of the strip, onto a *Sample Application Pad*. Here, the sample is treated using added predetermined reagents to make it compatible with the rest of the test. Liquid-phase elements of the treated sample (which may be dissolved, suspended, emulsified, or any other liquidized formats) migrate to a next segment of the test device, the *Conjugate Pad*. Here, a detector reagent has been immobilized, typically consisting of a protein linked passively or covalently to a signal molecule or particle, typically a colloidal gold, cellulose nanobead, or a colored, fluorescent, or paramagnetic monodisperse latex particle. The signal reagent can also be another reagent, including nonparticulates (eg, soluble and directly labeled fluorophores). This label has been conjugated to one of the specific biological components of the assay, either an antigen or an antibody, depending on the assay format of the specific test device. The liquid-phase sample remobilizes the dried conjugate material causing it to incorporate into the liquid-phase sample material, and analyte in the sample interacts with the conjugate as both migrate into the next section of the test strip, the *Reaction Matrix* or "*Membrane*." The reaction matrix is typically a porous membrane with a hydrophilic, open structure for the purposes of transporting liquids to the reagent and control areas, onto which the other specific biological capture reagents have been immobilized. These are typically proteins, either antibody or antigen, which have been laid down in bands or stripes in specific areas of the membrane where they serve to capture the components of the liquid-phase sample, the analyte, and conjugate, as they migrate past, through, or over the capture lines. Excess liquid-phase materials (sample and reagents) continue to migrate across the strip, past the capture lines and are entrapped in a *Wick* or

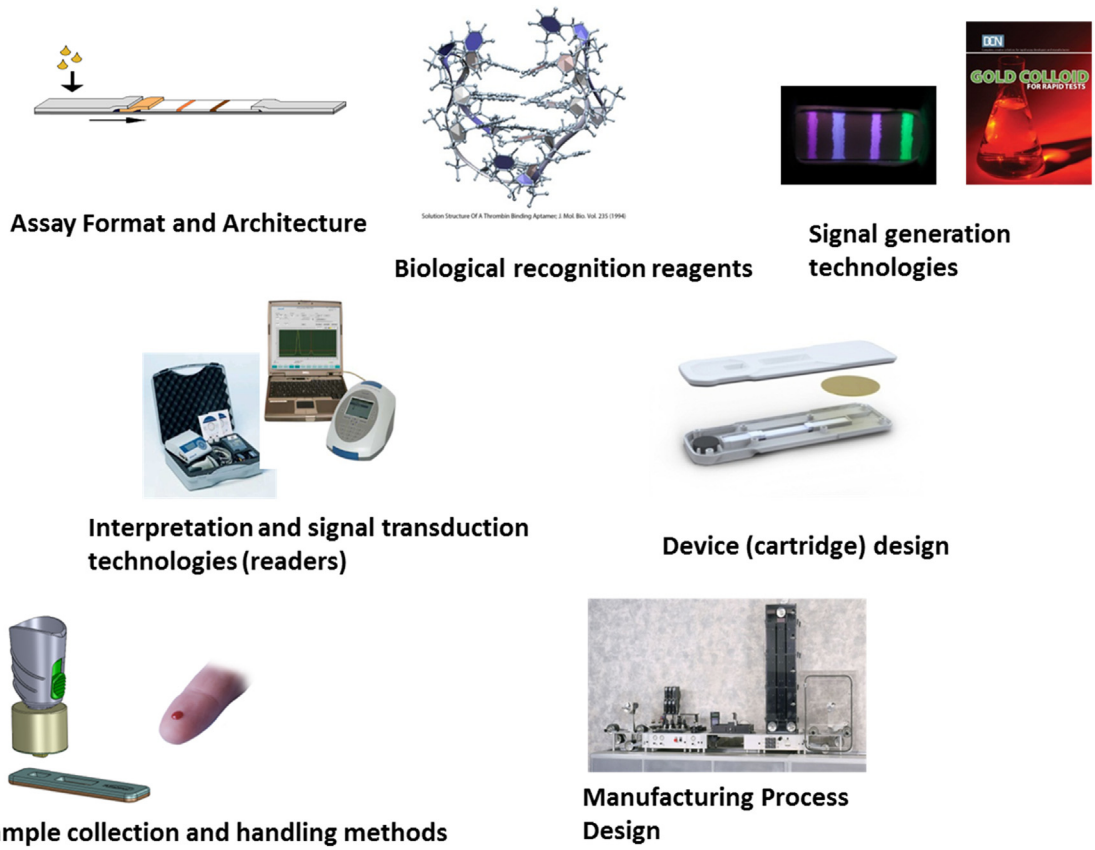

Fig. 1. The key elements of a highly performing lateral flow test system.