OPTICAL SYSTEMS FOR NUCLEIC ACID SEQUENCING AND METHODS THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/224,351, filed July 21, 2021, U.S. Provisional Application No. 63/334,613, filed April 25, 2022, and U.S. Provisional Application No. 63/334,609, filed April 25, 2022, each of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] In typical fluorescence-based genomic testing assays, *e.g.*, genotyping or nucleic acid sequencing (using either real time, cyclic, or stepwise reaction schemes), dye molecules that are attached to nucleic acid molecules tethered on a substrate are excited using an excitation light source, a fluorescence photon signal is generated in one or more spatially-localized positions on the substrate, and the fluorescence is subsequently imaged through an optical system onto an image sensor. An analysis process is then used to analyze the images, find the positions of labeled molecules (or clonally amplified clusters of molecules) on the substrate, and quantify the fluorescence photon signal in terms of wavelength and spatial coordinates, which may then be correlated with the degree to which a specific chemical reaction, *e.g.*, a hybridization event or base addition event, occurred in the specified locations on the substrate. Imaging-based methods provide large scale parallelism and multiplexing capabilities, which help to drive down the cost and accessibility of such technologies. However, detection errors that arise from, for example, overly dense packing of labeled molecules (or clonally-amplified clusters of molecules) within a small region of the substrate surface, or due to low contrast-to-noise ratio (CNR) in the image, may lead to errors in attributing the fluorescence signal to the correct molecules (or clonally amplified clusters of molecules).

SUMMARY

[0002a] In one aspect, provided herein is a method, comprising:

(a) providing a system comprising:

(i) a flow cell comprising a sample,

(ii) a light source,

(iii) a detector comprising a plurality of pixels, and

(iv) a pixel shifter disposed in an optical path from the flow cell to the detector;

(b) illuminating the sample using the light source, wherein the illuminating generates a signal light corresponding to an identity of a portion of the sample;

(c) shifting the signal light across the plurality of pixels using the pixel shifter; and

(d) detecting, using the plurality of pixels, the signal light from the sample to generate data related to the identity of the portion of the sample.

[0003] Aspects disclosed herein provide systems, comprising: a substrate comprising a curved surface, wherein said curved surface comprises at least one binding moiety configured to bind to an analyte; and an optical system comprising a light source, wherein said light source is configured to direct light to said curved surface and wherein said light is configured to probe a presence or absence of said analyte bound to said at least one binding moiety. In some embodiments, said analyte comprises a nucleic acid. In some embodiments, said at least one binding moiety comprises at least one nucleic acid configured to bind to said nucleic acid. In some embodiments, said curved surface is a component of a flow cell. In some embodiments, said