Lab on a Chip

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Frontiers of optofluidics in synthetic biology†

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The development of optofluidic-based technology has ushered in a new era of lab-on-a-chip functionality, including miniaturization of biomedical devices, enhanced sensitivity for molecular detection, and multiplexing of optical measurements. While having great potential, optofluidic devices have only begun to be exploited in many biotechnological applications. Here, we highlight the potential of integrating optofluidic devices with synthetic biological systems, which is a field focusing on creating novel cellular systems by engineering synthetic gene and protein networks. First, we review the development of synthetic biology at different length scales, ranging from single-molecule, single-cell, to cellular population. We emphasize light-sensitive synthetic biological systems that would be relevant for the integration with optofluidic devices. Next, we propose several areas for potential applications of optofluidics in synthetic biology. The integration of optofluidics and synthetic biology would have a broad impact on point-of-care diagnostics and biotechnology.

Introduction

Synthetic biology is a multi-disciplinary field, which integrates understanding in biology with principles from engineering, physics, and chemistry for the design and creation of new biologically-relevant systems.[1–5] To create synthetic biological systems, multi-disciplinary principles have been integrated to control biological functions such as modularity, *a priori* modeling prediction, standardization, as well as noise control. For example, modularity is the control of both dynamic and functional isolation of synthetic components,[6] to enable the components to be assembled in a bottom-up manner to form devices with higher functional capabilities. The modularity of these synthetic biological systems is complemented by mathematical modeling that generates *a priori* and predictive models, which enable the simulation of system dynamics for both design and hypothesis formulation. This integrated approach provides tremendous efficiency and novel designs before new synthetic systems are constructed. Furthermore, the standardization of synthetic biological parts has streamlined the design of synthetic

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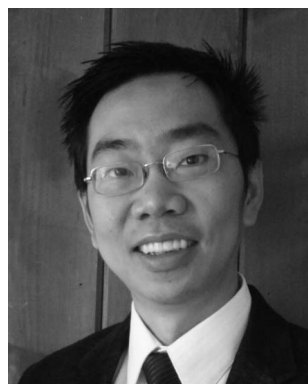
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biological systems.[7] These synthetic biology approaches underlie the discovery of novel insights into noisy dynamics of cellular pathways.[8,9]

These *trans*-disciplinary approaches in synthetic biological systems have made significant impact on the understanding of natural biological systems [9–12] and the innovation of therapeutic strategies.[13,14] However, the advancement of synthetic biology, by itself, may reach a limit for practical biomedical applications. For example, in clinical applications, synthetic biological systems need to be controlled by miniaturized hardware devices, in order to facilitate sample manipulation and the readout of diagnostic tests. Thus, one approach to circumventing these hardware requirements is by using inputs and outputs that can be manipulated within the devices (Fig. 1a). The control of inputs and outputs in biological systems will likely create tremendous advances in the future.[15] Optofluidics represent a promising area because of the ability to apply inputs or read outputs optically with minimal invasiveness. This ability of optofluidics complements recent advancement of synthetic biology in the aspects of light sensitive systems and fluorescence biosensors.

Optofluidics is directly related to microfluidics, which has been pursued for over a decade to control fluidic dynamics at the micro- and nano-meter levels. Microfluidic studies have led to the discovery of distinct fluidic dynamics that are different from large-scale dynamics.[16–19] Such distinct dynamics at the micro-meter scale have been exploited for applications in biological studies, including spatio-temporal control of developmental biology systems,[20,21] the generation of small scale microbial fuel cells,[22] polymerase chain reaction (PCR),[23] DNA sequencing,[24] the growth of synthetic bacteria,[25] the sorting of mammalian cells,[26] and single-molecular biophysics.[27] Recently, microfluidic-based devices have been integrated with optical control and readouts toward standalone lab-on-a-chip systems.[28–30]

Based on microfluidics, optofluidics have made excellent advances especially in microscale devices with the ability to change optical properties using fluids.[31] For example, mutable fluidic lenses can be generated by modulating the curvature of interfaces between two immiscible fluids with different refractive indexes;[32] light paths through the lenses can be controlled by using refractive index gradients of fluids generated by molecular diffusion.[31,33] Based on these fundamental techniques, opto-fluidic lasers[34] and optofluidic-based microscopes[35] have been constructed. Optofluidic devices have also applied electricity to modulate device dynamics. For example, an electrowetting lens[36] utilized an external voltage to change the surface tension of liquid–solid interfaces of the lens, which resulted in corresponding changes in the curvature of liquid–liquid interfaces and focal length of the fluidic lens. This fundamental technique has been extended to photo-electrowetting,[37] which was designed to move liquids on semiconductors using light. Both applied voltage and light were used to control semiconductor surface charges, which led to the movement of liquids on the surface. This technology opens doors to potential integration of semiconductors and optofluidic devices.

Optofluidics have also been applied to measure analytes with low concentrations. For instance, flow-through nano-holes were designed to increase both detection speed and sensitivity.[38] A metallic nano-hole array under an applied electric field caused an accumulation of an anionic analyte near a boundary of a charge depletion region. After concentrating the analyte at the boundary, a flow pressure was applied to shift the concentrated analyte toward a sensor region for surface plasmon based sensing. Furthermore, optofluidic devices have also been proposed for an extension to energy-relevant applications[39] (Fig. 1b) that involve both photo-bio- and photo-catalytic reactions. Fluids would be used to transport reactants, collect sunlight, and control light inputs for chemical-based reactions. These optofluidic devices could be used to produce either energy or fuel.

Here, we propose that synthetic biology and optofluidics should be on a path towards convergence, with great potential for creating novel and useful biotechnologically-relevant applications in the future. To start, we first summarize the development of synthetic biology that would be relevant for the integration with optofluidic devices. Next, we review recent research that paves the way towards integration of optofluidics

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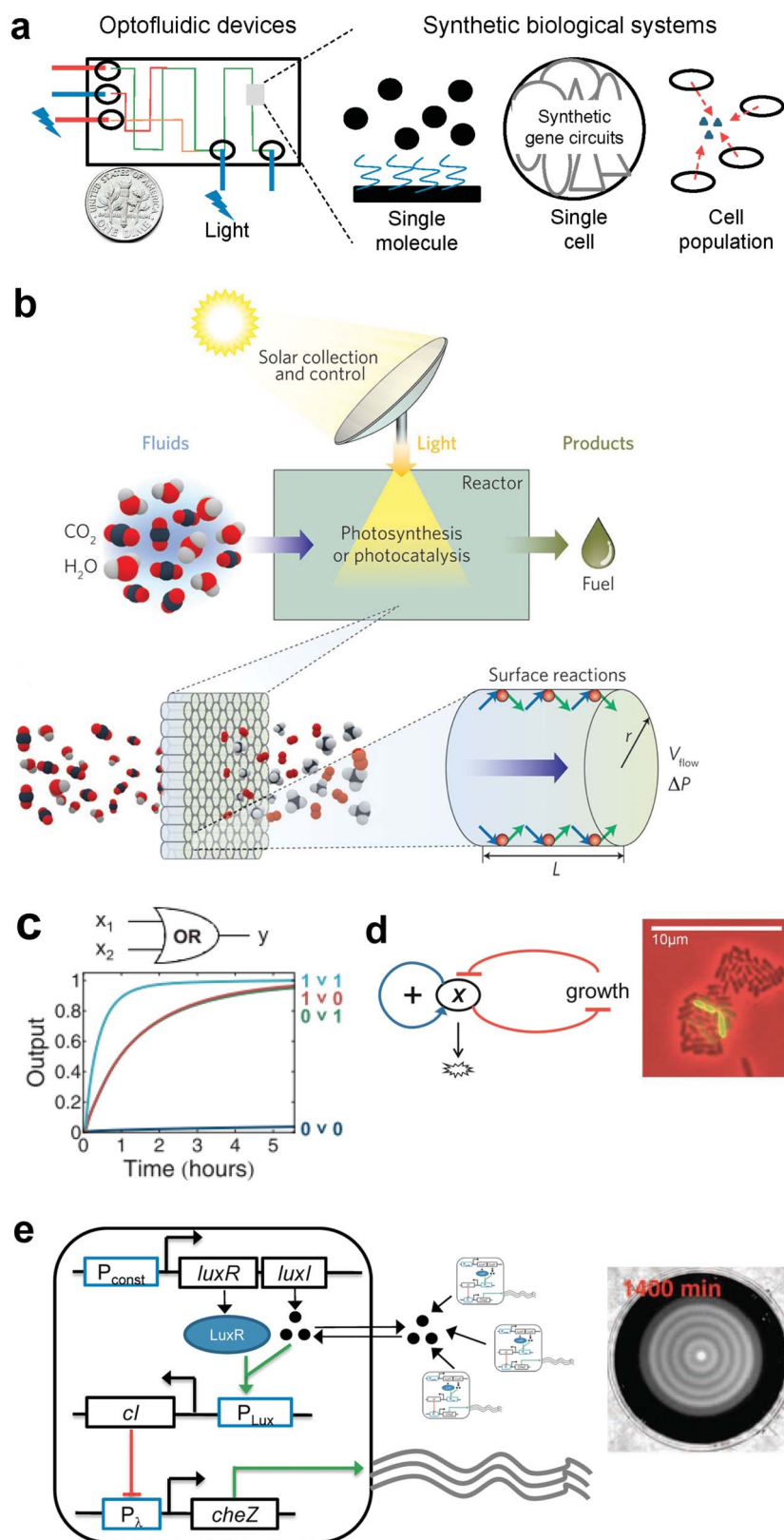
Fig. 1 The integration of synthetic biology and optofluidics. a) Synthetic biological systems of different length scales, ranging from single molecule, to single cell, and cellular population have been engineered for both biotechnology and therapeutic applications. To further extend functions of synthetic biological systems, optofluidic devices can be used to manipulate both input and output signals. Such integrated opto-bio-fluidic devices can be deployed as standalone devices that do not require additional equipment for either system maintenance or measurement. b) A schematic of an optofluidic device for an energy-relevant application. Fluids transport reactants into a reactor. Light is collected from sunlight and channeled to

catalyze chemical reactions on reactor surfaces. After the process, fuel was obtained. This figure is adapted from ref. 39. c) In synthetic biology, a DNA logic gate can be engineered by using strand displacement. Signal DNA displaces the direct strand of a gate DNA strand. This leads to a cascade of strand displacement reactions, which eventually results in the fluorescence emission of a DNA strand that carries a fluorescent tag. The construct produced an OR logic gate. When either input signals x_1 and x_2 were present, the circuit was turned ON. Otherwise, the circuit was OFF. This figure is adapted from ref. 43. d) In synthetic biology, a positive feedback loop that interfaces with bacterial growth can give rise to bistable dynamics (right panel). Specifically, the expression of a gene X inhibited bacterial growth (red lines), hence reducing bacterial growth rates. Therefore, X enhanced its own expression by reducing dilution rates (left panel). The figure is adapted from ref. 45. e) A synthetic bacterial population was constructed to generate striped patterns on agar (right panel, adapted from ref. 62). Quorum sensing components LuxR/LuxI were interfaced with CheZ that modulated chemotaxis of bacteria (left panel).

and synthetic biology. Finally, we propose potential applications of optofluidics in opto-bio-fluidic devices.

The past and future eras of synthetic biology for integration with optofluidics

Synthetic biology has been rapidly evolving over the past decade and is now poised to be expanded into other exciting new areas such as optofluidics. Synthetic biology can be classified into three general eras: early establishment, functional enhancement, and application. The first era of synthetic biology focused on establishing basic cellular components, including synthetic signaling molecules,[40,41] logic gates[42–44] (Fig. 1c), bistable switches [10,45] (Fig. 1d), a repressilator,[46] autoregulation,[47] population control circuits,[48] and a band-pass filter.[49] These circuits were used primarily to both demonstrate the engineered control of biological systems and unravel insights into natural biological systems. Specifically, bistable switches were used to confer bistable states of a cellular population, enable inheritance of expression states, and study noise and switching rates between binary cellular decisions.[11,45,50,51] Autoregulatory circuits have been shown to reduce noise,[47] linearize dose-response of gene circuits,[52] and speed up gene expression rates.[53]

In the second era of synthetic biology, more sophisticated synthetic systems with multiple integrated components were created to perform more complicated functions.[54] For example, light sensitive sensors were integrated with quorum-sensing components to create a detector that sensed the edge of light input signals in a two dimensional domain.[55] Synthetic bacterial and yeast populations were engineered to mimic the predator-prey relationship in nature,[56–59] to create oscillatory gene expression dynamics,[60,61] and to form stripe patterns[62] (Fig. 1e). In addition, a bacterial population consisted of different engineered strains was engineered to perform Boolean logic calculation.[42]

The establishment of these basic synthetic components and modules has enabled the advance of synthetic biology into the next era of biotechnological applications.[63] Synthetic systems have been applied to improve bacterial strains for drug synthesis. Specifically, ribozyme-based circuits were created *a priori* using mathematical models to modulate metabolic fluxes of bacteria for the production of arteminisin.[64] A RNA circuit that consisted of feedforward inhibition loops was constructed to differentiate cancer and normal cells.[13] DNA nanobots were engineered to deliver specific drugs to cells.[44] Artificial cells that mimic specific properties of natural cells were created to study protein dynamics,[65–67] gene circuits,[68,69] and drug delivery.[70,71] Synthetic cells were created with either chemically synthesized DNA[72] or reduced genomes,[73] which could facilitate the bottom-up design of a synthetic genome. In order to move synthetic biology further into practical biomedical applications, it will be important to integrate synthetic biology with optofluidics. Such

integration could enable the miniaturization and fine control of synthetic biological systems using non-invasive approaches such as optofluidic control and feedback.
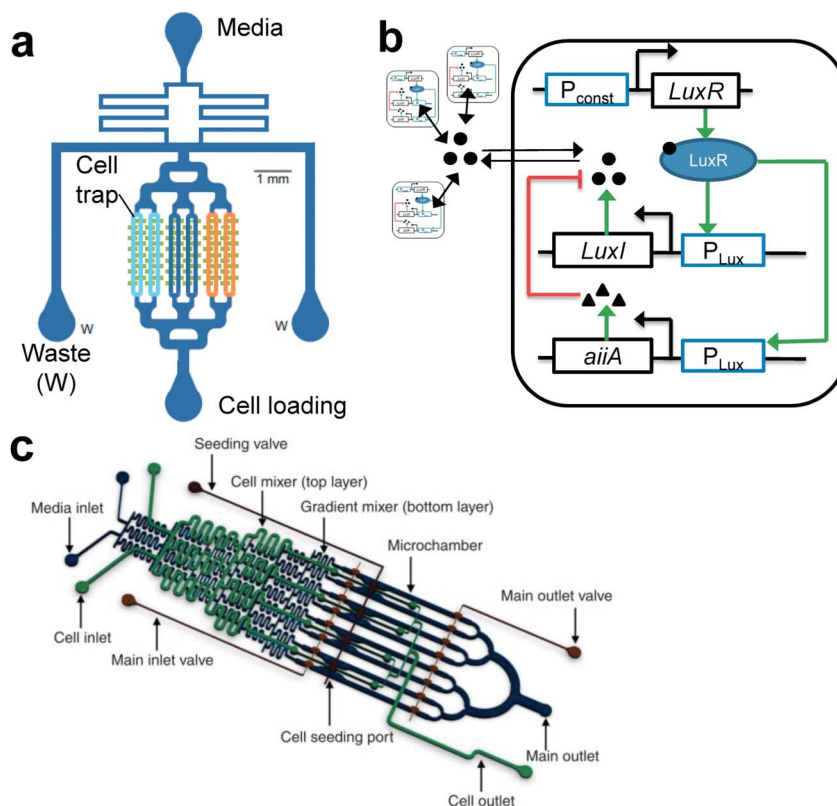
The integration of synthetic biology and microfluidics: a pathway toward optofluidics

The control of synthetic biological systems using microfluidic-based devices has already produced novel findings in synthetic biology. For example, a microfluidic device was used to control and tune oscillatory behavior of a bacterial oscillator.[74] The synthetic gene circuit consisted of a coupled feedback loop formed by AraC and LacI. AraC activated both its own and LacI expression. In turn, LacI inhibited the expression of AraC. In addition, a microfluidic device was used to maintain a single layer of bacterial cells for single-cell measurements. Integrating the microfluidic device and the gene circuit together enabled the fine-tuning of oscillation periods since the microfluidic system controlled the spatial temporal dynamics of the chemical environments. In addition, a microfluidic device was engineered to control synthetic bacteria (Fig. 2a). Each bacterium carried a coupled feedback circuit that was constructed by using LuxI that positively fed back to itself and synthesized N-acyl homoserine lactone (AHL) [60] (Fig. 2b). LuxI also activated the expression of AiiA that degraded AHL. Since AHL diffused in the growth environment, bacteria could communicate through the signals. A microfluidic device was also used to trap bacteria within a growth chamber and to modulate the exchange of AHL between populations. This dilution period served as an entraining mechanism that synchronized the bacterial oscillator.

The integration of both microfluidics and synthetic biology has facilitated the precise modulation of mixed cell populations as well. A microfluidic device was constructed to mix and seed dispersal and colonizer cells (Fig. 2c).[75] The colonizer cells expressed bdcAE50Q upon sensing quorum sensing signals secreted by the dispersal cells. bdcAE50Q disperses biofilms by binding to cyclic diguanylate. The introduction of dispersal cells into biofilms of the colonizer cells led to the dispersal of the biofilm. Furthermore, the dispersal cells were shown to replace the colonizer cells in the growth environment. In addition, microfluidic devices could be used to control the subcellular localization of small molecules using laminar flows from multiple inlets.[76] Such devices have been used to control stimulation of both single cell and multi-cellular populations.[77,78]

Moving towards the future in integrating optofluidics with synthetic biology

Precision & sensitivity control of synthetic biological systems with light sensitive components. In the following sections, we

Fig. 2 The integration of synthetic biology with microfluidics. a) A microfluidic device was used to fine tune and modulate oscillations of a synthetic bacterial population. The device maintained homeostasis of bacterial density and controlled the exchange of signals between compartments of bacteria. The figure is adapted from ref. 60. b) A gene circuit that generated synchronized oscillations of bacteria. A constitutive promoter P_{const} synthesized LuxR. LuxR formed a positive feedback loop onto itself by up-regulating the expression of LuxI, which synthesized AHL that in turn activated LuxR. LuxR also activated the expression of AiiA that degraded AHL, hence forming a negative feedback loop. AHL diffused in the media, which helped to synchronize expression levels of the circuit. c) A microfluidic device was constructed to mix two populations of bacteria. One of the populations formed a biofilm on surfaces, while the other population dispersed the biofilm. The figure is adapted from ref. 75.

discuss the integration of optofluidics and synthetic biology to enable precise and sensitive measurements of fluorescence outputs, miniaturize synthetic biological devices, and modulate optical properties of optofluidic devices. First, to enable precise and localized control of biological systems, light sensitive components have been engineered. These components are generally classified into caged [79] and photoisomerizable molecules.[80] For example, caged adenosine triphosphates (ATP) were conjugated to photolabile protecting groups [81] and upon exposure to a light input, the photolabile groups were cleaved, which induced the release of the caged ATP as an output. Similarly, caged T7 RNAP[82] and ribonuclease [83] have been created. Light-sensitive proteins have also been developed by interlinking protein domains, which contain photoisomerizable chromophores with the proteins of interest. Upon exposure to an input excitation light, the light-sensitive domain induces conformational changes that modify protein functions as an output. The light-sensitive domain can be used to change the activated state of proteins, sub-cellular localization of proteins, and protein-protein interactions. For example, Rac was engineered to switch between a GTPase activated state and an inactivated state on light exposure.[84] Rac has also been engineered to switch between a membrane-anchored state and a free-diffusing state upon exposure to light.[85] Furthermore, this

approach has been extended to other organisms including a yeast two-hybrid system that consisted of an input activator protein and a DNA binding protein, which were designed to respond to light.[86]

Another approach is to enhance the dynamic control of fluorescence reporters. Fluorogen activating proteins and RNAs have been created that fluoresce upon binding of specific ligands (Fig. 3a & b). In this case, a ligand is the input signal and the associated fluorescence is the output signal. In a previous study, a library of human single-chain antibodies was screened by a directed evolution approach to obtain fluorogen activating proteins (FAP) that fluoresce upon binding of either thiazole orange or malachite green.[87] The FAPs were further optimized to produce different emission spectra for multiplexed optical experiments. The FAPs can be fused to specific proteins of interests to enable inducible fluorescence for live cell imaging. A recent study has also identified RNAs that fluoresce when bound by 3,5-dimethoxy-4-hydroxybenzylidene imidazolinone (DMHBI).[88] The GFP-like RNAs have been engineered to exhibit distinct absorbance and emission spectra (Fig. 3a, right panel). Furthermore, they can be appended to mRNA species of interest for live-cell tracking of both transcription and translation dynamics, which enables many manifestations of input control with optical sensor based outputs.
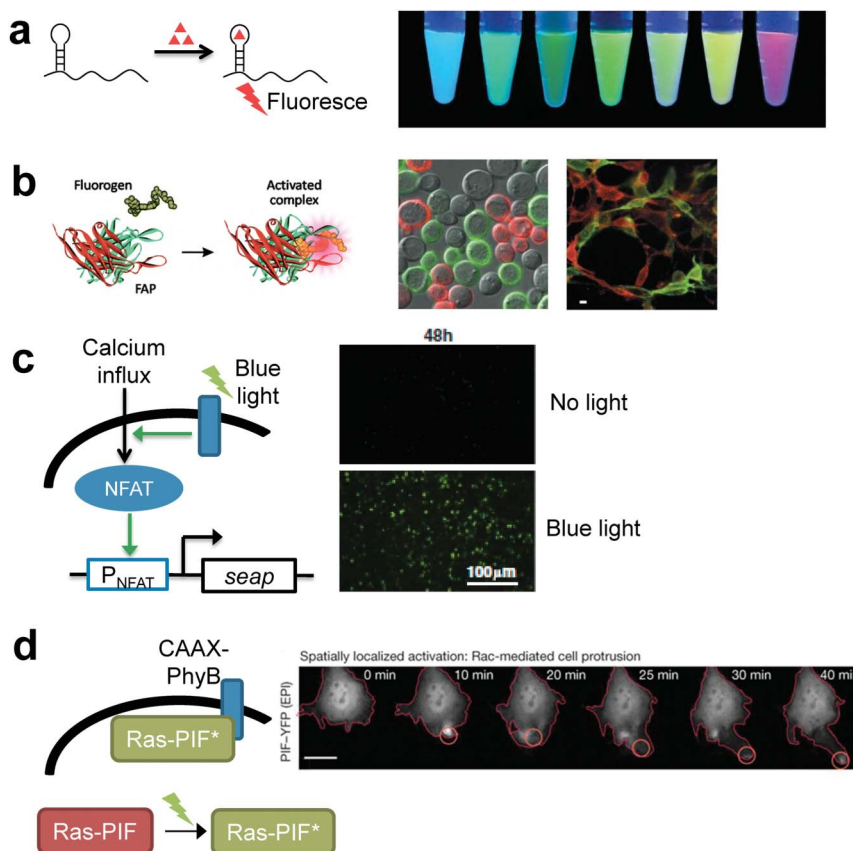
Fig. 3 Light-sensitive synthetic systems. a) A RNA mimic of a green fluorescent protein was created by using a specific aptamer that responded to DMHBI dye. The right panel shows RNA aptamers that exhibit different emission spectra. The right panel is adapted from ref. 88. b) Fluorogen-activating proteins (FAP) can fluoresce upon the binding of specific dyes. The middle panel shows yeast cells that expressed membrane bound FAPs. The right panel shows fibroblasts that present both thiazole-orange and malachite-green FAPs on membrane surfaces. The left panel is adapted from ref. 120. Both middle and right panels are adapted from ref. 87. c) Mammalian cells were engineered using a light-sensitive circuit to modulate blood-glucose levels. A blue light induced calcium influx that activated NFAT, which bound to a P_{NFAT} promoter to express SEAP (left panel). The right panel shows the image of cells that expressed luciferase upon exposure to the blue light (adapted from ref. 89). d) Cellular morphology was controlled by light-sensitive anchoring of Ras (left panel). Ras-PIF was activated by light, which then bound to membrane bound CAAX-PhyB. This way, Ras was activated locally, which subsequently activated actin filaments within the same region. The right panel shows the temporal sequence of cell protrusion controlled by a pointed light source (adapted from ref. 85).

Based on these light sensitive components, optical regulation of cellular dynamics has been accomplished, which opens up many exciting avenues toward the area of optofluidic integration. Light sensitive control of mammalian cells has been engineered by combining a light-sensitive transmembrane protein with the NFAT pathway (Fig. 3c).[89] Specifically, a natural light sensitive membrane protein, melanopsin, can be activated by blue light to induce calcium influx. The influx of calcium activated calmodulin that activated a kinase cascade, which upregulated the expression of the transcription factor NFAT. A P_{NFAT} promoter was engineered to express a glucagon-like peptide SEAP and the SEAP synthesis was sensitive to blue light in both cell culture and mice. Another light-sensitive system has been created using phytochrome signaling pathway from Arabidopsis thaliana to control cellular morphology (Fig. 3d). In this signaling pathway, PhyB can be switched between a Pr and a Pfr state using infrared light. During the Pfr state, PIF can bind to Pfr to form a heterodimer. Based on these modular protein domains, Ras-PIF and CAAX-PhyB were engineered. CAAX-PhyB translocated to cell

membranes and anchored Ras-PIF when activated by infrared light. Since Ras is a GTPase that modulates the formation of actin cytoskeletons, the synthetic circuit allowed precise modulation of actin cytoskeleton dynamics at the micrometer length scale. This ability to interface light inputs into signaling pathways shows promise for integrating these synthetic biology approaches with optofluidics, which would enable precision control of optical input and the enhanced detection of fluorescence signals.

To enhance the precision control of synthetic biological systems, several optofluidic technologies can be exploited, including optical sorting[90] and optical trapping.[91] These technologies are widely used in microfluidic-based systems to locate particles at desired positions and control particle movement in a fluidic flow, which could be useful for positioning chemicals and cells for synthetic biology systems. Both optical methods rely on the manipulation of interaction forces between particles and optics.[92–94] Along the same line, optical tweezers have been used to place single cells in microfluidic-based channels for biomedical studies[95] (Fig. 4a) and to manipulate
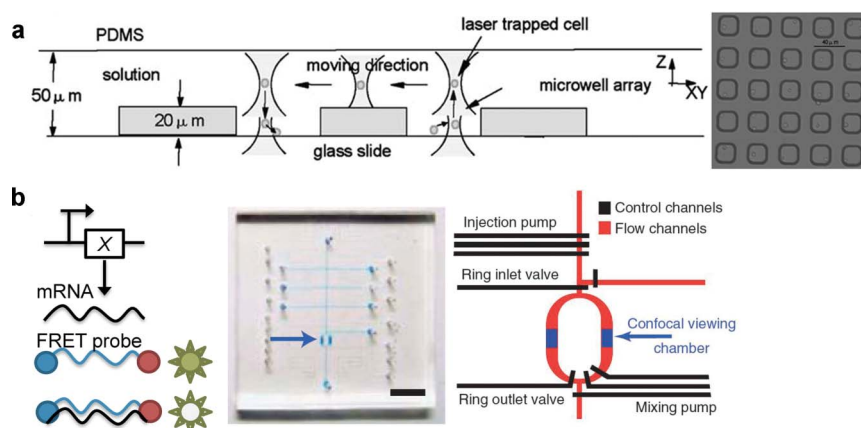
Fig. 4 Enabling precise manipulation of synthetic systems using optofluidics. a) A schematic diagram of an optical tweezer that manipulates yeast cells. Cells were trapped by a fluid flow using a designed structure. By controlling the focus of a laser beam, the cells could be moved precisely in both the z-direction and the x–y plane. The right panel shows the localization of yeast cells in 20 μm microwells (adapted from ref. 95). b) An optofluidic device was constructed for high throughput measurements of transcription activities using a FRET-based RNA probe that cannot fluoresce when bound by the target mRNA. The device consisted of mixing pumps that channeled chemicals and confocal viewing chambers for RNA measurements. The right panel is adapted from ref. 103.

live neurons into designed chambers for electrical stimulation and activity recording.[96] These optofluidic approaches could be used to position synthetic cells into specific measurement locations.

Another approach to integrate optofluidics and synthetic biology would be through enabling sensitive measurement of optical outputs using liquid-core antiresonant reflecting optical waveguides (ARROW). These have been applied in the imaging of FRET,[97] single fluorophore, liposome, virus, and chemical detection. An ARROW device typically consists of a solid-core waveguide that modulates excitation wavelength. This solid-core is then interfaced with a liquid-core waveguide that contains the samples. High sensitivity is achieved by confining light within a small volume of liquid. The liquid core can be designed to filter out the excitation wavelength and then can be interfaced with a solid core to obtain specific emission wavelengths.

Furthermore, optofluidics can be used both to improve sensitivity and to reduce noise of fluorescence imaging[98] in synthetic biology. Microfluidics can be used to adjust the refractive index of a fluid, hence changing the critical angle required for total-internal reflection fluorescence (TIRF).[99] When incident light is totally reflected, evanescent waves are generated at an interface. The evanescent waves exponentially decay from the interface and excite fluorescence molecules within 100 nm of the interface. In addition, measurement sensitivity can be enhanced through surface plasmon resonance (SPR) in lithographically defined nano-structures.[93,100,101] SPR occurs due to the resonance between a conductor's free charges and a light wave. The SPR can be focused using channel-type nanostructures in order to enhance localized resonance, hence enhancing signal detection limit. These optofluidic technologies could enhance the precision of bio-computers based on synthetic biological systems.[42,43,102]

Another area of opportunity is to use optofluidic devices for high throughput characterization of synthetic circuits. An optofluidic chip that consisted of a mixing ring and a confocal viewing chamber was created to measure transcription dynamics

at the single molecule level.[103] The mixing ring received solutions from three integrated push-down valves and mixed the reagents using a peristaltic pump. Furthermore, a synthetic RNA probe was designed to hybridize with specific mRNA (Fig. 4b). The RNA probes consisted of a FRET pair fused to both ends of the probe. Once the RNA probe hybridized to mRNAs, the FRET was inhibited. This approach enabled the distinction of the response as otherwise the freely diffusing probe would exhibit a high FRET signal. This optofluidic device has been used to assay multiple important contributing factors of gene transcription including six polymerase and glutamate concentrations. This example builds the foundation for potential applications of optofluidic devices in speeding up design and implementation cycles of synthetic biological systems.

Miniaturization of devices containing synthetic biological systems. As synthetic biology moves toward biotechnological applications, there is an increasing need to miniaturize devices for the control of synthetic biological systems. For example, optofluidic devices could be applied for feedback control of synthetic biological systems. In a recent study, cells were engineered with a synthetic light sensitive circuit (Fig. 5a). Specifically, a signaling protein was fused to a PIF domain that can be activated by light, which would then bind to a membrane-anchored partner with a PhyB domain.[104] Next, a specific signaling dynamic was achieved by controlling the light input to the system using a computer. As one example of how this would work, in order to achieve a constant level of cellular activity, a computer detected fluorescence signals from cell chambers and then adjusted the light input to the cells. The computer then generated a periodic input light signal, which induced a constant gene expression profile. This feedback system could benefit from optofluidic technologies, in order to establish a standalone system without external optical control.

Another synthetic system that could be miniaturized with optofluidics is an edge detector that integrates a light sensor circuit with a quorum sensing circuit (Fig. 5b).[55] Without light exposure, bacteria activated the expression of both LuxI and cI;
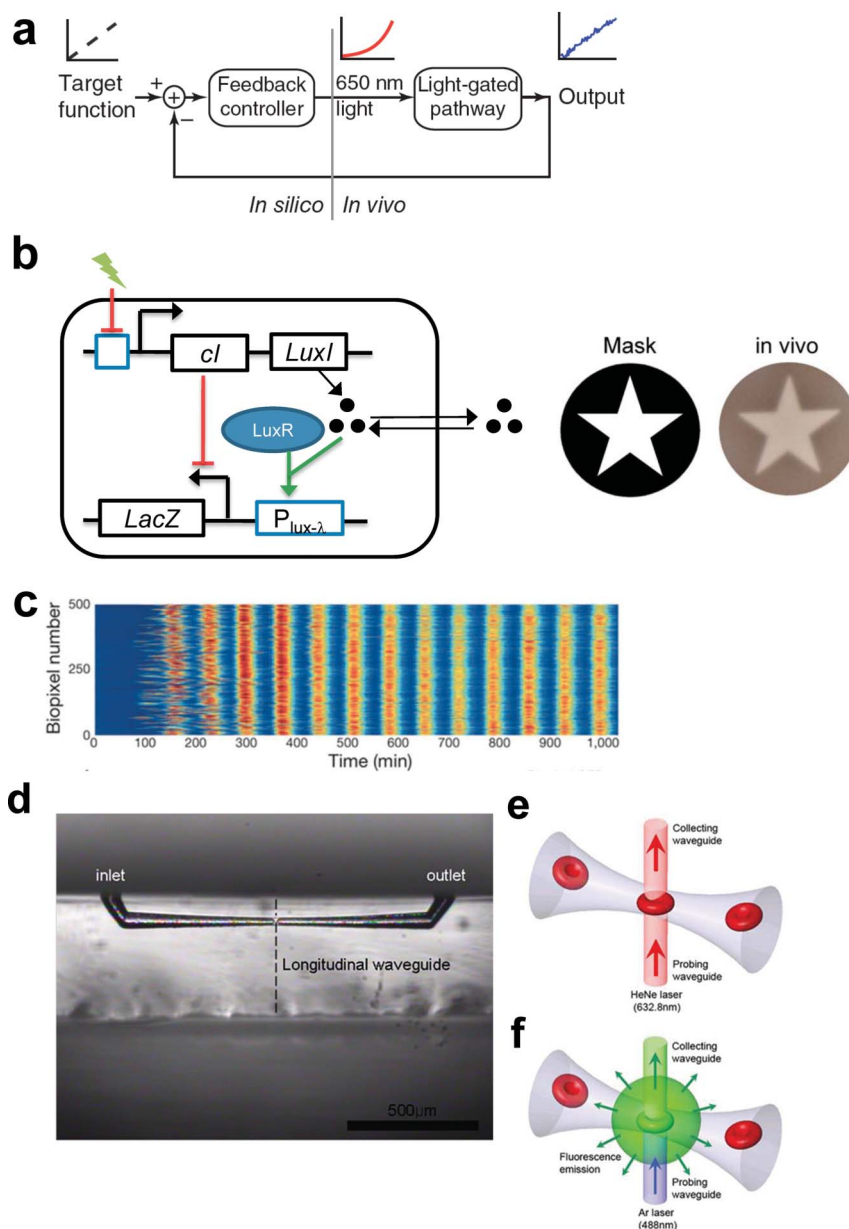
Fig. 5 Optofluidics toward miniaturization of synthetic biological systems. a) An optofluidic device was used to control dynamics of a synthetic biological system following the target dynamics. A computer could control the dynamics of light sensitive cells through an optofluidic device by modulating input light signals. The figure is adapted from ref. 104. b) Edge-detector bacteria can detect the edge between light and darkness, thereby producing fluorescence along the boundary (right panel, adapted from ref. 55). c) Biopixels responded to a stimulus by coherent fluorescence oscillations. Each biopixel consisted of a population of synthetic bacteria. The figure is adapted from ref. 61. d) The optical transmission image of a femtosecond laser fabricated microchannel. The dashed line denotes the position of a longitudinal waveguide. e) A schematic of transmission intensity changes for the detection of one cell. A He–Ne laser light was transmitted through a waveguide. A detector monitored the refractive index changes while cells were flowed through a light spot inside the micro-channel. f) A schematic of fluorescence emission for cell detection. A detector identified single cells by fluorescence signals, which were emitted by dyed red blood cells under Ar laser (488nm) excitation. (Fig. 5d–f are adapted from ref. 108)

LuxR activated the expression of lacZ, but cI repressed it. Therefore, bacteria that were exposed to light and that received a high amount of AHL activated the expression of LacZ, which metabolized X-gal that induced the fluorescence signals. Thus, in a two dimensional space, bacteria fluoresced at the edges between dark and light areas. This synthetic system could potentially be adapted as a portable and light-sensitive bio-camera using optofluidic technologies that adjust the focus of light going into the system.

An optofluidic device was indeed conceptualized to manipulate and observe thousands of biopixels, each containing a population of bacteria (Fig. 5c).[61] Each bacterium carried a synthetic gene circuit (modified based on the circuit in Fig. 2b) that consisted of a P_{lux} promoter driving the expression of LuxI, AiiA, and Ndh. Through this approach, LuxI enhanced its own expression, hence forming a positive feedback loop. AiiA degraded AHL that was synthesized by LuxI, thus forming a

detection of both herpes simplex virus and avian influenza H5N1.[113] Synthetic molecules on the surface can be replaced with aptamers,[114,115] which also modify optical properties of the systems.

In addition, synthetic molecules could be used to modulate optical properties of opto-bio-fluidic devices (Fig. 6b). The molecules could change conformation upon exposure to specific excitation lights, hence modifying surface properties. Specifically, light sensitive molecules such as melanopsin (Fig. 3c) and PhyB (Fig. 3d) could be attached to surfaces through biotin-streptavidin linkages. Next, these molecules could be excited by specific excitation light to change protein conformation. Such protein conformations could potentially change light propagation or reflection on the surface, thereby altering optical properties of the system. The optical changes could also be reversed by removing the excitation light. Through this approach, an evanescent wave on the surface could be modulated in real-time to change output signals of the system.

To increase the dynamic range of the optical control, synthetic cells[116] could be used due to their large sizes and potentially large conformation changes as compared to synthetic molecules. Specifically, we propose that drastic changes of optical paths in optofluidic systems could be achieved by modulating either spatial localization of cells or whole cell morphology through synthetic cellular circuits. Through this approach and due to the micrometer length scale of these synthetic cells, we could significantly alter optical paths, hence potentially producing a larger difference in optical outputs of the altered systems. For instance, synthetic cells can be engineered using a chemo-sensing module that modulates bacteria swimming abilities through CheZ (Fig. 1d). Through this approach, bacteria could respond to specific input signals by moving in specific directions. Synthetic mammalian cells could also be engineered using a Ras-module that modulates cellular morphology through localized actin polymerization (Fig. 3d). Based on both methods, large scale changes in spatial configuration of cellular populations could be achieved, which could alter optical properties of the systems. Furthermore, synthetic cells could be engineered as complex biological computers that detect specific input signals, including light[79,84,104,117,118] and chemicals,[56,63,89,119] and then respond by migrating to change optical properties of the system. These cells could be engineered to integrate input signals using logic gates to perform cellular calculation of input conditions,[13,42] which could significantly enhance the multiplex detection of chemicals in optofluidic devices.

Conclusions

Synthetic biology has generated unique innovation in cellular engineering and controls. To further extend the functionality of synthetic biological systems, one exciting area is to integrate synthetic biology with optofluidics, which could create self-functioning systems that would minimize the use of external imaging devices and light sources toward functional chip units with engineered cellular systems. We have outlined several preliminary examples of optofluidics application in synthetic biology. Furthermore, we envisioned prototypes of next generation opto-bio-fluidic devices that can manipulate both samples and light sources. Such devices could be relevant for future applications of synthetic biology systems in point-of-care diagnostics.

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