Matthew Levy, Jeffrey J. Tabor,
and Stephen T.C. Wong

Taking Pictures with E. coli: Signal Processing Using Synthetic Biology

On 24 November 2005, the journal *Nature* published an article [1] that disclosed how researchers at the University of California, San Francisco, and the University of Texas created photographs using the bacterium *E. coli*. This achievement was made possible by genetically manipulating the bacterium, engineering in light-sensitive genes from algae. The news (discussed widely in the media) is the latest advance in synthetic biology. We discuss the new image acquisition model proposed, its implications on digital signal processing as we know it, the development of synthetic biology, and the societal controversy stirred by this discovery in particular and synthetic biology in general.

E. coli is often selected in synthetic biology research because its genetics are extremely well known. In addition, this bacterium is also very easy to manipulate in the laboratory. As a result, previous efforts in the field have used genes and proteins within this organism to engineer a ring oscillator [2], demonstrate the spatiotemporal control of gene expression by linking a biochemical pulse generator with a cell-to-cell communication system [3], and program a bandpass filter behavior into a population grown in a petri dish [4].

In the work presented in [1], light responsivity was engineered into *E. coli* by fusing a light-sensing protein (known as phytochrome Cph1) from the photosynthetic cyanobacterium Synechocystis, to an *E. coli* protein called EnvZ. This protein is typically located within the outer membrane of *E. coli* and is part of the well-studied, two-component system EnvZ-OmpR. This system is responsible for maintaining optimal salt concentrations within the organism. The protein EnvZ naturally exists in two states: a phosphorylated (On) form and an unphosphorylated (Off) form. By splicing Cph1 and EnvZ together with a series of different linker regions, chimeric proteins were generated. (Chimeric proteins are human-engineered proteins that are encoded by a nucleotide sequence, which is obtained by a splicing together two or more genes.) These fusion proteins were then screened for variants, in which the phosphorylation state of EnvZ could be controlled by light. The change of state in the presence of light was detected by connecting the phosphorylation state of EnvZ to the expression of an enzyme. In the presence of the appropriate substrate, the enzyme produced a black pigment, which was later used to create the photographs.

To demonstrate the spatial control that can be accomplished with light-regulated gene expression, the researchers developed a light-generated

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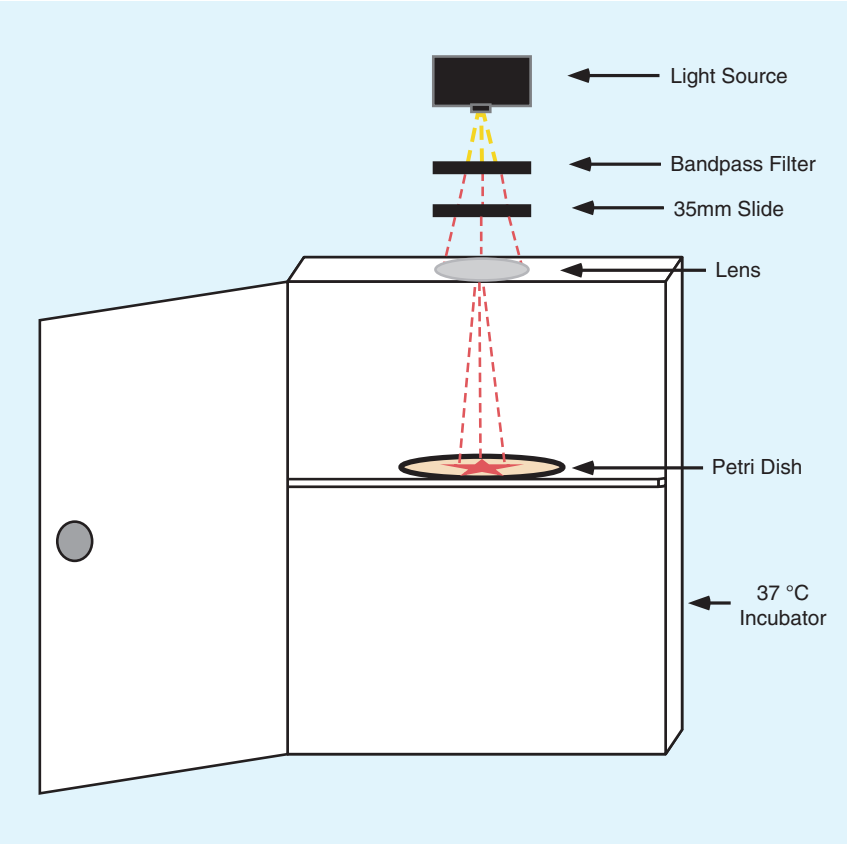

[FIG1] Block diagram of the system used for taking bacterial photographs.

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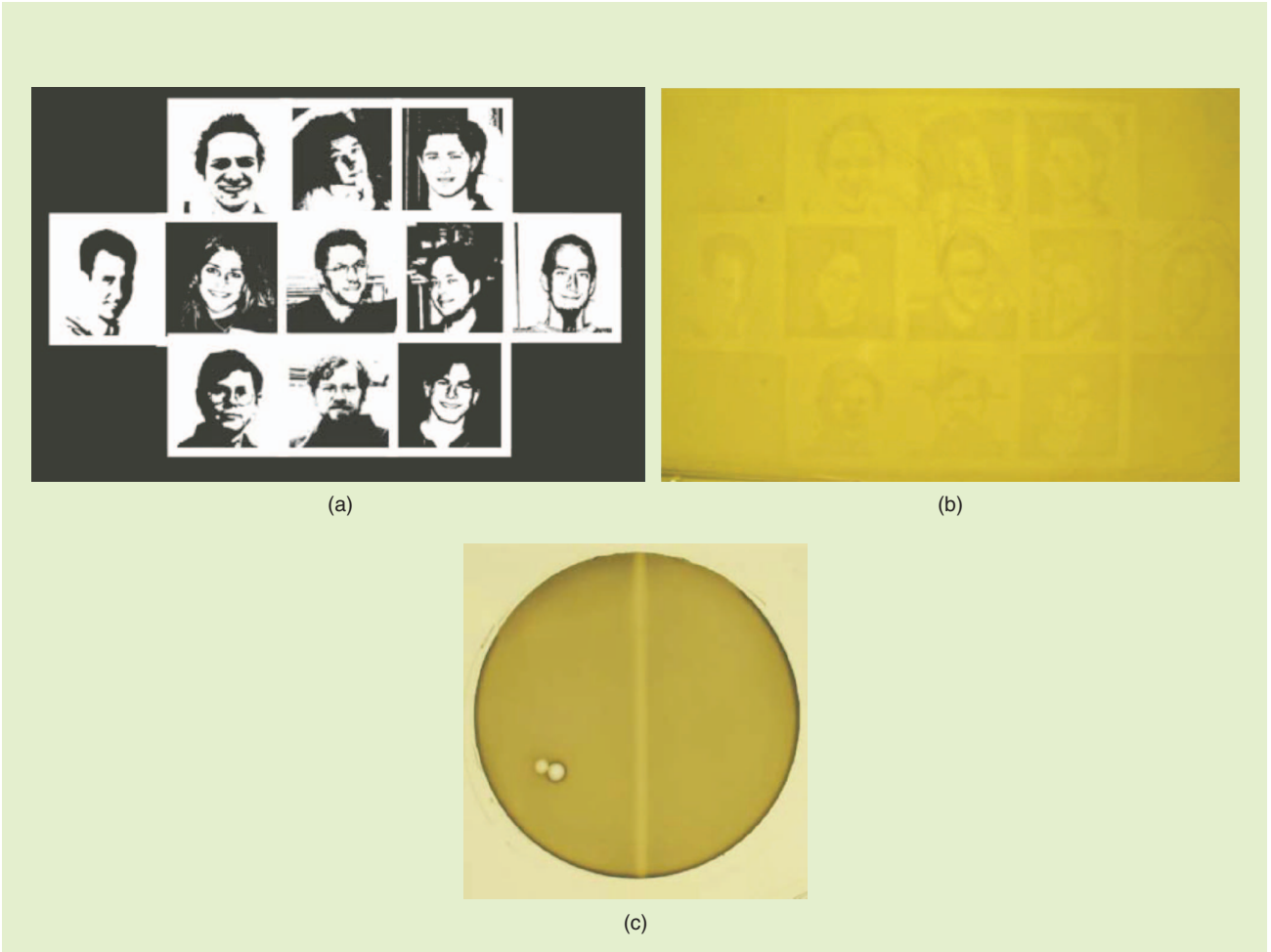
image on a two-dimensional surface. A simple projection system (illustrated in Figure 1) was constructed using a light source, a 632-nm bandpass filter, an image on a 35-mm slide [shown in Figure 2(a)], and a lens. The image was projected inside a 37 °C incubator, where bacteria expressing the fusion protein were grown in solidified media (agar). After approximately 12 hours of exposing the bacteria to light, the photograph developed in black and white, with high resolution, as illustrated in Figure 2(b). By replacing the light source with a weak red laser (630–680 nm emission), it was also possible to develop images. Using a laser has the advantage of functionality without any focusing equipment. In addition, it has potential for future applications (such as bacterial microlithography) that require the projection of extremely small-scale patterns on light-responsive cells.

Currently, the new image acquisition method that uses *E. coli* has obvious limitations. First, the sepia-like, ghostly hues that are present in the resulting image may not be acceptable from a visual quality standpoint in some applications. Second, the current 12-hour exposure time is clearly too long for practical purposes. These limitations suggest that the new sensor/method will not replace other image capture methods soon. However, the advantages of the *E. coli*-based image sensor are important. The images acquired have a theoretical resolution of 100-megapixels per square inch (or perhaps, more appropriately, 10^8 bacteria per square inch), which exceeds the results of other image processing acquisition techniques. The new image sensor can also be used in more complex applications, such as a light-responsive edge detector system, currently being developed at the University of Texas. Other applications that are foreseen to use the spatial and temporal controls provided by light induction include bacterial microlitography, the manufacture of biological material composites, the study of cell-to-cell communication systems, and the therapeutic delivery of drugs and toxins.



[FIG2] (a) Black and white images of the research team members printed on a 35 mm slide. The slide was projected onto an agar plate (a petri dish containing agar) inoculated with photo responsive *E. coli*; (b) Images obtained using the system in Figure 1 and the slide with the images of (a); (c) Image containing a vertical line; the line was obtained by shining a laser pointer across the surface of an agar plate inoculated with photo responsive *E. coli*. Circular white spots are air bubbles in the agar.

On a more general scale, the set of tools provided by this nascent technology allows the design of novel biological systems, as well as advances in the use of biological systems for signal processing. In this respect, perhaps the most important contribution of the work in [1] is its "proof-of-concept" of the design philosophy behind synthetic biology. Synthetic biology focuses on the design and manufacture of molecular components of biological organisms and systems for different engineering applications. However, this field goes beyond simple manipulation of single genes in the sense that the resulting systems are aimed to function as processing devices. Clearly, there are numerous challenges in developing these synthetic biology applications. These challenges stem primarily from the different behavior of biological parts as compared to other processing devices. For instance, a biological part is subject to noise in gene expression and the growth state (or physiology) of the cell, and is expected to be different in different genetic backgrounds. This makes "plugging-and-playing" with genes a significantly more challenging prospect than with transistors. Significant steps have been made in quantifying behaviors, standardizing operating conditions, and increasing the composability of biological parts [5].

Beyond the technical side, important challenges of synthetic biology in general, and of the work discussed in this commentary in particular, are related to issues that are critical to our society. From its birth, synthetic biology had to live and grow in a scientific culture that assigns tremendous weight to issues of bioethics, safety, and security. From a bioethics standpoint, there are concerns related to manipulating living organisms. From a safety standpoint, there is concern that a deadly virus with no natural foes could be engineered by biohackers and released either accidentally or maliciously. From a security standpoint, the concern is that synthetic biology results may become accessible to would-be evildoers. However, risks for each of the above have always existed in biological sciences and dire consequences can never be completely avoided. Focusing on useful applications and keeping researchers educated about the responsible and safe use of the laboratory environment reduces such risks, while allowing the field to advance.

AUTHORS

Matthew Levy and *Jeffrey J. Tabor* are with the Center for Systems and Synthetic Biology and Institute for Cell and Molecular Biology, University of Texas, Austin, Texas. *Stephen T.C. Wong* is with Harvard University, Boston.

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