LAB-ON-A-CHIP

High-tech Petri dishes

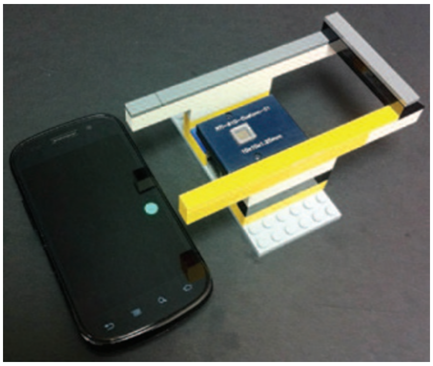
A self-imaging Petri dish monitors cell cultures as they grow in the incubator.

In a scientist's dream world, one would be able to sit quietly at the desk, browse the journals and read research highlights, even think, while still keeping an eye on the cell cultures growing in the incubator. The cell cultures would be imaged automatically and projected live on the screen of a computer, and there would be no need to shuttle the cultures back and forth from the incubator to the microscope, to monitor their growth. This would not only make things easier for the scientist, it would also help reduce contaminations and perturbations to the culture that are caused by manual movement.

Guoan Zheng, Changhuei Yang and their colleagues at the California Institute of Technology, have now made this dream a reality. In recent work, they built a Petri dish, ePetri, smart enough to autonomously image the biological sample plated on it. To build ePetri, the authors capitalized on the cheap availability of high-pixel-number so-called complementary metal–oxide semiconductor or CMOS imaging sensors that are common in cell-phone cameras. They glued a commercial CMOS sensor to the bottom of a homemade square plastic well and plated mammalian cells directly on its surface. For illumination, they used the LED screen of a cell phone supported with Lego blocks.

Whereas building ePetri could have been part of a middle-school science project, retrieving high-resolution images from it required nontrivial microscopy methods. "The current CMOS sensors have rather large pixels, so when you put the cells directly on them and strike a light, you get images that are intrinsically coarse," explains Zheng.

Zheng, Yang and colleagues devised a way to work around this by reconstructing high-resolution images from a collection of lower quality ones. They directed the illuminating light at different angles onto the cells and took sequential images in which the cells' shadow had moved by a fraction smaller than a pixel. They then combined all the low-resolution shadow images to generate one single high-resolution image of the entire culture dish using pixel super-resolution algorithms. "People have used these kinds of algorithms to generate high-quality images of the moon taken from a collection of lower-resolution images," Yang says.



The ePetri dish. Image courtesy of Guoan Zheng.

Among the advantages of this lens-less microscopy approach is that the field of view is as large as the sensor, and it does not require focusing.

The authors used ePetri to culture an embryonic stem cell line and track its growth directly from the incubator. An Ethernet cable connected ePetri from the incubator to a personal computer, and it took only a couple of minutes to reconstruct the entire high-resolution image of the culture dish. The resolution of ePetri was equivalent to the type of image you would get from a conventional microscope under the 40× objective lens and was sufficient to follow changes in the cells' morphology during differentiation and reconstruct cell lineage trees.

Yang's group is working hard to produce several prototypes of ePetri to distribute to collaborators and other scientists. Additional work is needed to test whether the resolution of ePetri is not affected by different types of culture dish coatings and whether it can support growth of primary cells. Scientists can also use ePetri to generate one single snapshot of an entire tissue, culture or organism. Future developments could also integrate ePetri into other sophisticated lab-on-a-chip designs and enable additional automation of culture maintenance.

Perhaps the biggest limitation of the current version of ePetri is that it cannot be used for fluorescence imaging but Yang assures that a fluorescence-compatible version of ePetri is soon to come.

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RESEARCH PAPERS

Zheng G. *et al.* The ePetri dish, an on-chip cell imaging platform based on subpixel perspective sweeping microscopy (SPSM). *Proc. Natl. Acad. Sci. USA* **108**, 16889–16894 (2011).