

A new approach to recording cellular activities

In living cells, a vast number of transient events occur simultaneously, each of them important for a given cell in carrying out its function. The faithful recording of these transient activities is a prerequisite for a molecular understanding of life, yet obtaining such recordings is extremely challenging. Scientists at the Max Planck Institute for Medical Research in Heidelberg and their collaboration partners have created a novel technology that allows cellular events to be recorded through chemical labeling with fluorescent dyes for later analysis, opening up completely new ways to study cellular physiology. This new method has now been published in *Science*.

The recording of transient cellular events plays a decisive role in examining and understanding biological processes, yet it presents significant technical challenges. An ideal recording method would observe large populations of cells simultaneously, would work in the test tube and in living animals, and would allow the recorded observations to be retrieved and analyzed at a later time. So far, methods that meet these criteria have been largely lacking; a gap that the new technology could now bridge.

Recorder proteins can be irreversibly marked

“Our technology is based on a recorder protein which becomes irreversibly labeled with a fluorescent dye when an event of interest occurs in its vicinity”, explains Magnus-Carsten Huppertz, postdoctoral researcher in the Department of Chemical Biology at the MPI for Medical Research. “This enables scientists to study very large numbers of cells in parallel *in vivo* or *in vitro*.”

Distinguishable substrates record successive periods of activity

The team, led by Kai Johnsson and Julien Hiblot, designed proteins that become labeled when a specific cellular activity and a fluorescent substrate are simultaneously present. The washing-in and the washing-out of the substrate defines the recording period, while the cellular activity determines the degree of the labeling. Moreover, by using distinguishable substrates, different phases within a period of activity can be recorded.

In their studies, constructed recorders for three different processes of central interest: receptor activation, protein-protein interactions and changes in calcium ion (Ca^{2+}) concentration. The latter was employed to study the heterogeneity of Ca^{2+} changes in cellular networks derived from glioblastoma, an aggressive brain tumor. In close collaboration with the groups of Lisa Fenk and Herwig Baier at the Max Planck Institute for Biological Intelligence in Martinsried, the authors successfully recorded patterns of neuronal activity in flies and zebrafish.

“In the end, we have developed such a versatile recording platform for the parallel analysis of numerous simultaneous transient cellular events *in vitro* and *in vivo*”, concludes Jonas Wilhelm, postdoctoral researcher at in the same department. The scientists present their approach and their findings in the latest issue of *Science*.

Tested in complex experimental settings

The main challenge the scientists faced during their work was to refine the newly developed recorder platform to ensure its robustness and efficient performance across a range of biological model systems. To explore the use of this new technology under various conditions, they established a variety of composite experimental arrangements.

Potential for accelerating research

“We are excited to provide new molecular tools with the potential to enable new types of experiments and accelerate research across different fields such as neurobiology and oncology”, say Magnus-Carsten Huppertz and Jonas Wilhelm. “We were lucky

to be able to collaborate with scientists from different disciplines to make this new technology possible." In addition to the Max Planck Institute for Biological Intelligence, scientists at the German Cancer Research Center (DKFZ), the National Center for Tumor Diseases (NCT), Heidelberg University, Janelia Research Campus, Virginia, USA, and École Polytechnique Fédérale de Lausanne (EPFL), Switzerland contributed to the work.

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