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Advancing neuroscience through real-time processing of big data: Transition from open-loop to closed-loop paradigms

The brain functions as a closed-loop system that continuously generates behavior in response to the external environment and adjusts actions based on the outcomes. Traditional research methodologies in neuroscience, especially those employed in brain imaging experiments, have mainly adopted an open-loop paradigm (Grosenick et al., 2015). Functional neural circuits are analyzed offline and subsequently tested through manipulation of neuronal activities within specific regions or with genetic markers. By establishing a closed-loop research paradigm, functional ensembles can be detected and tested in real time with temporal sequences. These functional ensembles, rather than brain regions or genetically labeled neural populations, serve as fundamental units of neural networks, offering valuable insights into the dissection of neural circuits. The closed-loop research paradigm also enables the capture of high-dimensional activities of internal brain dynamics and precise elucidation of physiological processes such as learning, decision-making, and sleep.

Recent cutting-edge research has employed activity-guided closed-loop optogenetic control in behaving animals (Grosenick et al., 2015; Zhang et al., 2018). However, the application of this technique is currently confined to small-scale optical imaging datasets. Concurrently, advancements in brain imaging technologies are pushing the boundaries toward achieving higher temporal and spatial resolutions and expanding imaging areas to better elucidate complex brain networks (Ahrens et al., 2013; Cardin et al., 2020). Furthermore, the development of Neuropixels probes has facilitated large-scale recordings across the brain for electrophysiological data (Benson et al., 2023), substantially increasing the volume of data generated. However, real-time analysis and closed-loop feedback of large-scale neuroscience datasets remain challenging.

In a recent publication in *Nature Neuroscience* (Shang et al., 2024), we developed a real-time analysis system capable of processing image streams at speeds of up to 500 MB/s. This system enables the extraction and analysis of the activities of approximately 100 000 neurons across the whole brain of larval zebrafish, with feedback signals applied within 70 ms. This advancement permits the decoding of neuronal ensemble activities across the brain to control external devices in real time.

The system utilizes an FX architecture, commonly employed in big data analyses for astronomical research (Amiri et al., 2018). The architecture incorporates custom field programmable gate array (FPGA) boards for digitization and channelization of the data ("F-Engine"), as well as a graphics processing unit (GPU) cluster for tasks such as registration, signal extraction, and clustering ("X-Engine"). The FPGA component supports a broad range of data type interfaces, while the GPU cluster offers powerful computational capabilities. This application of the FX architecture for optical imaging data analysis in neuroscience marks a significant leap forward, enhancing analysis speed by four orders of magnitude over existing methods. The "FPGA-GPU" configuration yields a system that is versatile and specialized, providing high computational power and real-time performance benefits. Furthermore, this system is applicable to different data types in various animal models, including optical imaging data of mice and flies, functional magnetic resonance imaging (fMRI) data and multi-channel electrophysiological recordings data of mice and non-human primates (Figure 1).

System performance was demonstrated across three distinct closed-loop neuroscientific research scenarios: (1) Real-time optogenetic stimulation synchronized with the activity of neuronal ensembles. This approach, triggered by the spontaneous activity of functional ensembles, effectively activated downstream brain regions compared to optogenetics trials disregarding neural activities. (2) Real-time visual stimulation in response to specific brain states. Based on real-time monitoring of locus coeruleus (LC) norepinephrinergic system activity, visual stimulation was applied during the excitatory phase of LC neurons, representing the awake state. This resulted in stronger neuronal responses across the brain, demonstrating that brain states modulate the processing of visual information. (3) Optical brain-machine interface (BMI)-driven virtual reality. The closed-loop integration of the activities of multiple neuronal ensembles with the visual environment enabled the establishment of a virtual reality system directly driven by neuronal activities in the brain. In this system, environmental changes were coupled with the activities of a group of neurons. The activity strength of the group of neurons adaptively changed in response to the change in coupling gain, suggesting intentional control of environmental changes by the activities of the group of neurons.

This system presents extensive applicability in neuroscience research, enabling online detection of neuronal functional assemblies and revolutionizing current paradigms. Traditionally, functional clusters have been defined post-experiment, limiting the exploration of their functions. Real-time identification of functional assemblies now permits the exploration of dispersed neuronal ensembles lacking shared

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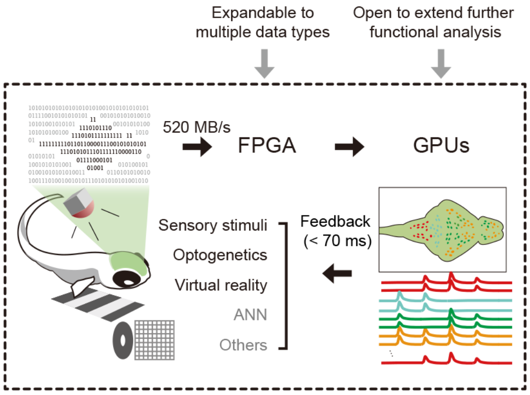

Figure 1 Real-time processing of whole-brain neuronal activities and closed-loop manipulation of brain functions using the FX design

Optical imaging data from the camera are assembled into FPGA-GPU system. Activities of neuronal ensembles are extracted and delivered to trigger external devices. ANN: Artificial neural network.

genetic markers. Combined with all-optical imaging and manipulation (Jiao et al., 2018) and photo-activable fluorescent proteins, this technology allows for the verification of neuronal function and clarification of the structural basis of functional modules. Such technological progress will advance our understanding of the neural networks underlying cognitive processes.

Furthermore, neural activity-guided real-time perturbation facilitates the study of internal brain dynamics and precise intervention at particular stages of information processing within the brain. Brain activities exhibit significant variability from moment to moment. A key challenge in neuroscience is understanding the function of spontaneously dynamic neural activity, which is difficult to replicate using traditional neural activity manipulation methods (Liu et al., 2022). Our real-time whole-brain analysis system can capture these dynamic activities and explore their functions based on real-time feedback and intervention. Consequently, this system is useful for functional studies of spontaneous activities, brain states, sleep, and wakefulness.

Finally, the system facilitates the implementation of optical BMI. Our research successfully demonstrated the utilization of motor-related neural activities within the brain to manipulate visual inputs via an optical BMI. Future studies could leverage a broader array of information to manipulate external devices. Furthermore, this technology has the potential to predict physiological functions, such as decision-making, in advance, enabling their alteration if necessary (Peixoto et al., 2021). Real-time neural activities can also be extracted and utilized as input data for machine learning networks, which subsequently generate outputs that are fed back into the brain, thereby enabling the development of hybrid computational models that integrate real brain neural networks with machine learning.

Overall, this real-time analysis system is poised to drive the transition of experimental paradigms from an open-loop to a closed-loop era, offering unprecedented opportunities to explore the dynamics and individual differences within the complex brain system.

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