Like eavesdropping at a party

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Cells rely on calcium as a universal means of communication. For example, a sudden rush of calcium can trigger nerve cells to convey thoughts in the brain or cause a heart cell to beat. A longstanding mystery has been how cells and molecules manage to appropriately sense and respond to the variety of calcium fluctuations within cells.

Reporting in the June 27 issue of *Cell,* a team of biomedical engineers at the Johns Hopkins School of Medicine has discovered how the calcium sensor protein calmodulin can gauge both the local flow of calcium, in through the closest channel, as well as the global calcium flow entering the many channels across the entire cell.

"It's like being at a cocktail party where the easiest person to listen to is the one closest to you, but we all have the ability to keep an ear out for other interesting conversations going on throughout the room," says David Yue, M.D., Ph.D., a professor of biomedical engineering at Hopkins. "It turns out that calmodulin is doing a similar thing, sensing the calcium coming through the closest channel through one ear while the other ear 'listens' to the calcium coming through distant channels across the cell."

Normally, calmodulin is positioned right near each calcium channel. Several years ago, scientists discovered that calmodulin somehow can switch its sensory focus between local calcium and global calcium entering the cell through channels at a distance.

The calmodulin protein, explains Yue, is made of two ball-like lobes,

and it's these two lobes that act as the different calcium-sensing "ears." The C lobe listens locally and the N lobe listens globally, across the whole cell. To figure out how calmodulin's two lobes can sense different sources of calcium, the team took a two-pronged approach.

First, they used computers to perform mathematical simulations that tested different potential calcium detection mechanisms of the calmodulin lobes. Others have shown that the C lobe of calmodulin hangs onto calcium for a long time, whereas the N lobe lets go rapidly. Their simulations suggested that these slight differences in calcium holding time might play a role in calmodulin's ability to sense both local and global calcium levels. "Once a local calcium ion sticks to the C lobe, it seldom lets go, and so the local calcium dominates," says Yue.

By contrast, the N lobe would rapidly let go of calcium and then be empty and available to bind calcium entering the cell from distant calcium channels, allowing reception of global calcium. Similar to the cocktail party, it's easiest to catch other conversations during the pauses in your own conversation.

The research team then verified their mathematical predictions by testing real calmodulin proteins attached to calcium channels. Using a new approach, they precisely controlled calcium pulses through single calcium channels and watched how calmodulin responded. They were able to confirm the mathematical models.

Understanding the language of calcium is critical for understanding how cells communicate, says Yue, and also important for understanding neural diseases. For instance, early antipsychotic drugs may work by blocking calmodulin action. "Now that we are learning how these drugs actually work," Yue says, "we can contribute our new understanding of calmodulin to the design of next-generation drugs with greater potency and fewer side effects."

Source: Johns Hopkins Medical Institutions