Editorial

Time for 'digital signaling'?

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We are living in a digital age. Digital broadcasting is taking the place of analogue. Cameras, videos and TVs are going digital as well. Similarly all information circulating around the world are trials of digital zeros and ones. And what about biological information circulating in and around the cells? Will they finely go to digital as well? It was suggested that periodic Ca^{2+} signals encode information in a 'digital' manner by regulating cellular responses as diverse as enzyme activation, behavioral rhythms and gene transcription. But what is 'digital signaling' at the molecular level'? Does it exist?

In digital electronic equipment, logical switch forms the digital unit, which may have several states, but the most popular are 'zero' or 'one'. It can perform one thing in state 'one' and another if it is in state 'zero'. After receiving a signal, it may go from one state to another. Probably, in a biological system we may find many logical switches having two or even more states as well. For example, proteins can be phosphorylated or dephosphorylated, they can form monomers, dimers or tetramers, they can be bound or unbound with an activator or inhibitor.

Some biological proteins like membrane channels can even pass an electric current or stop it. Such operations resemble an electrical diode, transistor or flip-flop circuit, which are parts of electrical logical switches. But, do they really resemble them? Are channels 'biological logical switches' or part of them?

Opening or closing of membrane channel in 'analog signaling' is a result of free energy fluctuation causing its conformation changes. In 'analog signaling', channel activity depends on interactions with modulators in a concentration-dependent manner. The channel 'analog' activity possesses positive or negative feedback.

However, there are channel events those are not yet fully understood using solely the 'analog signaling'; for example, behavior of ryanodine calcium release channels during termination of Ca^{2+} release from the sarcoplasmic reticulum. Because of the positive feedback inherent in Ca^{2+}-induced Ca^{2+} release, it is not known what restrains the amplification of Ca^{2+} signaling and terminates Ca^{2+} release. What terminates calcium sparks, what is the molecular mechanism of refractoriness of Ca^{2+} release in cardiac muscle or adaptation of ryanodine channel?

We face similar problems with the behavior of inositol trisphosphate activated calcium release channel. These problems involve reversible desensitization of inositol trisphosphate-induced calcium release, slow recovery from inactivation/desensi-

tization, termination of calcium transients, generation of interspike intervals or refractory state of the channel.

Could we explain the behavior of the channels assuming they were 'biological digital switches'? In 'electrical digital signaling' the state of a logical switch depends on its history, on the previous signal, mostly electrical voltage that put it to that particular state. The switch remains in this state until a new signal puts it to a different one. In 'biological digital signaling', refractoriness of a channel depends on its history, on the previous mostly yet unknown signal that put it to the particular state. During the refractory state the channel is closed – it is in state 'zero' until a specific signal changes it to open state 'one'. Termination of calcium sparks may be a result of digital behavior of the channel going from state 'one' to state 'zero' after receiving signal, depending, for example, on an amount of Ca^{2+} in store or Ca^{2+} passing through the channel. Probably biological digital signaling may explain many other puzzles.

Digital signaling is more precise and convenient than analog. Has nature realized it? I hope it has.