Spontaneous signal generation induced by reaction noise for gradient sensing in chemotaxis.

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Chemical reactions are inevitably stochastic. This stochasticity is especially pronounced in a single cell level, because the law of large number is not usually satisfied due to small copy number of each molecular species in a local area in a cell. This nature leads to a simple dogma; cellular behaviors are not deterministic but quite noisy. Since such stochastic nature may seem disadvantageous for cellular functions, one possible question arises: can cells utilize stochasticity in an active manner to persistently maintain their adaptability to the environment? To answer this question, we propose in this study a novel hypothesis on eukaryotic chemotaxis, based on non-linear dynamics and stochastic process, and examine the hypothesis through computer simulation.

In chemotaxis, a cell detects gradient of chemical substance and randomly moves with drift up toward the gradient. Even when chemical substance is uniformly distributed, cells show spontaneous movements to random directions without any drift. This would be because of spontaneous signal generation inside a cell, which drives cellular migration. Actually, in some types of cells of immune system, transient increases in PIP3 (PIP3 pulses) are spontaneously generated in a local space beneath the membrane and each PIP3 pulse induces lamellipodia extension (1). Such spontaneous signal may be used for sensing and amplifying very shallow chemical gradient information provided by the environment.

In this poster, I will show following results by theoretical analysis and simulation:

1. <u>Principle of spontaneous generation of PIP3 pulse by reaction noise</u>
   Applying phase plane analysis of non-linear dynamics to PIP3-related signal transduction, we found that the system having positive and negative feedback loop is "excitable". This signal transduction system is also "spontaneously excitable" if potential barrier for excitation is low and the system size is such small that reaction noise is strong enough against the potential barrier.

2. Principle of gradient sensing by PIP3 pulse

Analysis drawing potential landscape showed that given the shallow gradient (2%), the potential barriers decrease and increase at sides of higher and lower concentrations, respectively. According to Kramer's rate theory that describes the escape rate against potential barriers, we can see spatially biased frequency of PIP3 pulses due to the bias of barrier height. This causes efficient gradient sensing of chemotaxis.

Reference

(1) Arrieumerlou C and Meyer T. A local coupling model and compass parameter for eukaryotic chemotaxis. *Dev Cell***.** 2005 Feb; 8(2):215-27

This work was partially supported by JSPS Research Fellowship for Young Scientist, and the 21st Century COE Program, which are both from the MEXT (Ministry of Education, Culture, Sports, Science, and Technology), Japan.