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Intelligent mechanisms in *E. coli* in processing carbon sources

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Abstract

E. coli is "wise" enough to take suitable responding time, and suitable responding behaviors, when facing different kinds and intensities of stimulations. In a network of glycogen metabolism, a shorter time stimuli result in *the post translation level* reactions for quicker response, and a longer time stimuli will activate more time consuming *the central dogma level* reactions. In addition, different intensities of signals caused by different actions was illustrated by using gene products expression system based on ppGpp concentration.

Keywords: chemotaxis, PTS, ATP, ppGpp, the central dogma, post translation

1. Introduction

A human's body will initiatively or positively take reactions via reflex arc system or deep tendon reflexes system, facing to different kinds and intensities of stimulations. *E. coli*, a bacterium, is it "wise" enough to take suitable reactions towards the variety signals? Here the word "suitable" includes suitable responding time, and suitable responding behaviors. Our answer is "Yes". In *E. coli*, different kinds, time length or intensities of signals can drive suitable functioning units (e.g. proteins) on suitable levels to make suitable reactions.

According to the time cost of a respond to a signal, we divide the intracellular processes into 2 levels: *central dogma level* and *post translation level* (**Fig 1**). *The central dogma level* includes the whole process of a gene transcribed to an mRNA then translated to a protein. *The post translation level* includes other intracellular process of non direct relation with genetic DNA or mRNA, for example protein-protein interaction, protein-metabolite interaction, protein localization, protein motion, etc. The time consuming for an action in *the central dogma level* is longer than that in *the post translation level*.

For *E. coli*, the average length of coding sequences is 1068 bp [1], and the maximal transcription speed is about 40-80 bp/sec [2, 3], the maximal translation speed is about 20 aa/sec [3, 4], then the average time cost for a gene expression in an optimal condition is about 40 second. But in reality, a g ene's expression may costs

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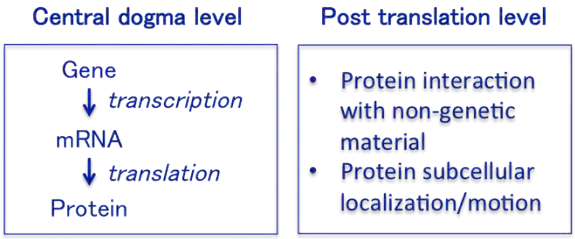

Fig. 1 According to the time cost of intracellular action, we divide the intracellular processes into two levels: *the central dogma level* and *the post translation level*

from several minutes to several days. And the time consuming in post translation level is commonly much shorter then that of central dogma level. For example, the for a chemotaxis reaction in *E. coli*, only need few seconds, or even in a sub-second time scale [5], which includes at least 6 steps actions of *the post translation level* from a signal to a chemoreceptor, …, at last to a flagella.

In this context, examples (a) uses a systematical model of PTS-Chemotaxis-glycogen to describe different levels' responds resulted from a same kind of stimuli coming with different time lengths.

According to intensity of a signal, the respond should be classified into *low*, *mid* and *high* intensity cases, which is illustrated by the example (b): Using a ppGpp-RNAP model to explain different kinds of actions are caused by different intensities of the stimuli.

2. Example (a): the same kind of stimuli coming with different time lengths result in different levels' responds

In studies on *E. coli*, PTS, glycogen, and flagellum are common objects, but always studied separately. PTS is the transport system for an *E. coli* intaking cultural glucose [6]. Glycogen is a polymer functioning as a carbohydrate intracellular storage [7]. Flagellum together with FilM and CheY forms the *E. coli* motion driver, which gives in time response to the five kinds of chemoreceptors [8].

Intra these 3 systems, EI, HPr, $EIIA^{Glc}$ and ATP are key mediators. Un-phosphorylated EI (EI) inhibits the auto-phosphorylation of CheA (P~CheA), which in turn stops the transferring of phosphate group from P~CheA to the flagella motor CheY; this will causes flagella rotating in clock-wise (CW) direction and *E. coli* will tumbling

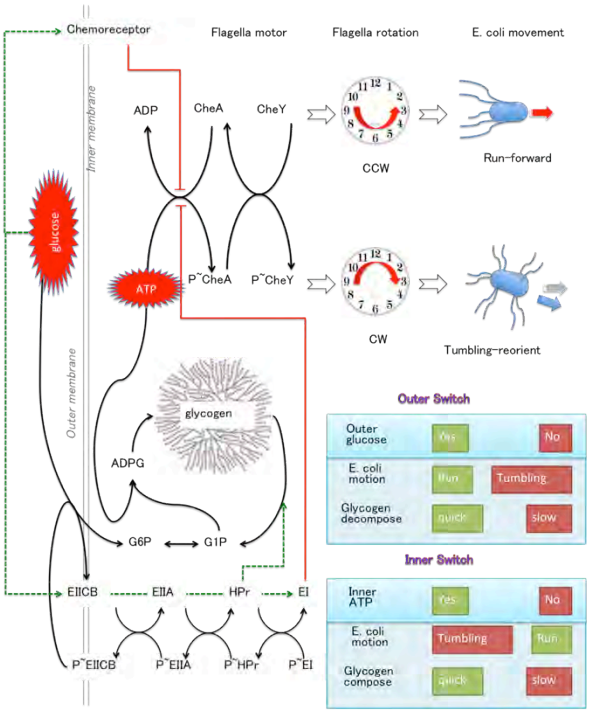

Fig. 2 Shorter time stimulation causes responses on *the post translation level*, which is realized by the network of PTS, glycogen and chemotaxis system.

here [6]. The binding of un-phosphorylated HPr (HPr) with GlgP (HPr::GlgP) catalyzes a quicker glycogen decomposition, $EIIA^{Glc}$ regulates expression levels of *glgBXCAP*, *ptsHIcrr* and *ptsG*, indirectly via cAMP/CRP complex [9]. ATP is a necessary member of CheA auto-phosphorylation (**Equ. 1**) and ADPG synthesis (**Equ. 2**) [10]. We can find, despite $EIIA^{Glc}$ works up to *the central dogma level*, all the other 3 mediators are mainly functioning in *the post translation level*.

$$CheA + ATP \leftrightharpoons P{\sim}CheA + ADP \qquad \textbf{(1)}$$

$$G1P + ATP \overset{GlgC}{\Longrightarrow} ADPG + PPi \qquad \textbf{(2)}$$

Shorter time stimulation causes responses on the post translation level. The analysis in this section is based on an assumption: proteins levels are sufficient to perform their functions. In **Fig. 2**, glucose and ATP are 2 stimuli of outside (in the culture) and inside (intracellular) respectively. When an *E. coli* meets glucose at the first time, it quickly activates the poles located PTS (un-phosphorylated) by passing phosphate

group to glucose. Meanwhile glucose as a chemotaxis signal has been captured by poles located chemoreceptors. Signals form both these 2 pathways

repress the CheA auto-phosphorylation, which at last result in *E. coli* run-forward by rotating flagella in counter clock-wise (CCW) direction. Simultaneously, poles located HPr::GlgP complex makes pole-located-glycogen a quick decomposition to supply more phosphate group as soon as possible, since glycogenolysis is a quicker process and needless energy driven.

If then outside glucose disappears, chemoreceptors will lose its inhibition on CheA auto-phosphorylation, so as the phosphorylated EI (P~EI). Now, *E. coli* will stop run-forward, instead, turn direction (tumbling), until catching another glucose.

If following the first step, the outside glucose is there still; the un-phosphorylated CheY will continue to drive *E. coli* run-forward. But accompany with quick glycogenolysis driven by EI, much more ATP is produced in the pathway of glycolysis and TCA cycle. Accompany with the sudden accumulation of intracellular ATP, the glycogenesis pathway is turned on, which is caused by glycogen content varies inexpertly; and the CheA auto-phosphorylation process will be returned on by the higher pressure of ATP and lower pressure of the inhibitions, which results in *E. coli* tumbling-reorient.

After the aforementioned preparation period, if there is still a glucose signal, then *E. coli* will "realize": there really has a "glucose banquet". At this time, more phosphate grout is transferred from PEP to PTS for glucose uptake, ATP is in a quite flat level. *E. coli* runs into the glucose now.

In all, for shorter time stimulation, when an *E. coli* meets glucose (outside stimulus), it quickly takes suitable types of motion and uptake simultaneously. But if the time length of this decision left for *E. coli* is limited in only a few seconds, a longer time scale would become re-oriented by Brownian motion [5]. When intracellular phosphate group (ATP) lacks (inside stimuli), the corresponding flagella motion and intracellular behavior will change.

In order to clarify the relationship with glucose, ATP, glycogen and flagella, we construct a Boolean network with Ginsim [11] (**Fig. 3a**). And from the result of its analysis (**Fig. 3b**), we can find, the system of double signals (glucose and ATP) and double responses

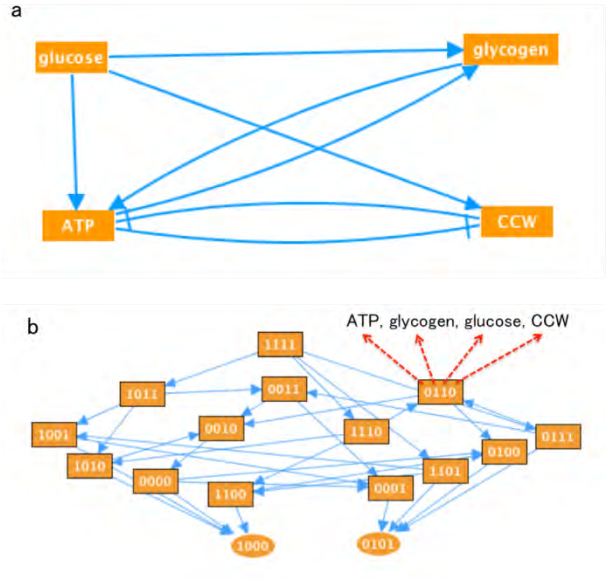

Fig. 3 Boolean network and states transition analysis result of the switch of ATP, glucose, glycogen and chemotaxis system.

(Flagella and glycogen) reaches 2 stable states, of which: 1000 represents there is only ATP, but no glucose and glycogen, *E. coli* will tumble there to reorient; 0101 means if there is no ATP and glucose, but only glycogen remains, the *E. coli* will go straight. This mechanism can be understood as a switch of E. coli facing shorter time stimulation. In one word, E. coli now either tumbles there with ATP inside, or run forward with glycogen inside. We should not forget, afore-talked mechanism only occurs at the first few seconds.

Longer time stimulation causes responses on the central dogma level. If an *E. coli* is emerged in a glucose culture, then the stimulating time is long enough to activate the reaction of *the central dogma level*. This process includes a series of complex networks, such as PEIIAGlc&cAMP and FDP&Cra subpathways, (As show in **Fig. 4**), which were explained in the paper [9].

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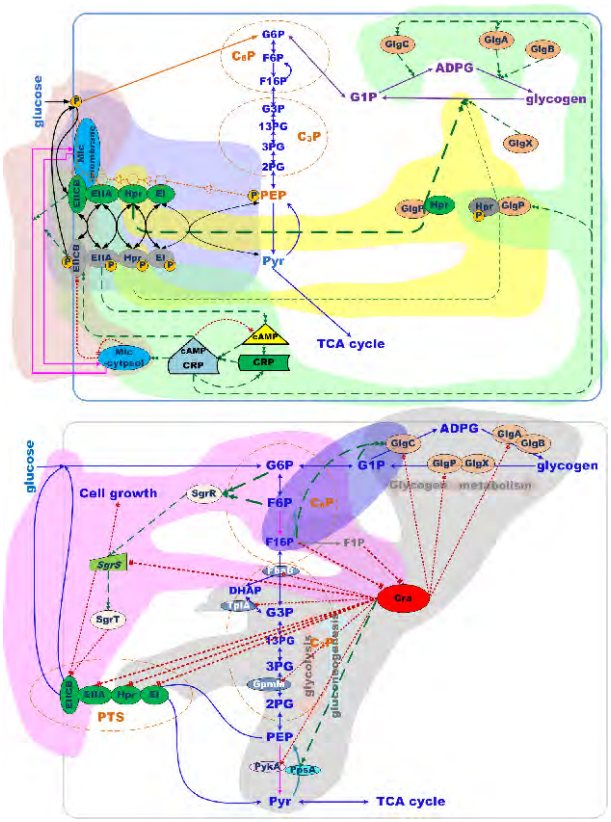

Fig. 4 Regulation mechanisms inter PTS and glycogen metabolism: PEIIAGlc&cAMP pathway, FDP&Cra pathway and HPr subcellular localization

3. Example (b): Using a ppGpp-RNAP model to explain that different kinds of actions are caused by different intensities of the stimuli

ppGpp is a stringent alarmone in *E. coli*, whose mechanism was clearly studied by Traxler et al. in their series papers [12–14]. **Fig. 5** shows that the 3 "bands" of ppGpp intensities result in 3 types of RNAP functions. If there is no starvation signal in an *E. coli* (ppGpp is null), RNAP will employ RpoD to transcribe mRNA and rRNA & stable genes in a proportion of 20% and 80%. If *E. coli* facing only amino acid starvation, a low concentration of ppGpp is produced, as a consequence, the low concentration ppGpp will bind to and drive RNAP to on ly express rRNA & stable genes. As all nutrition starvation occurs, High concentration ppGpp will be produced, which together

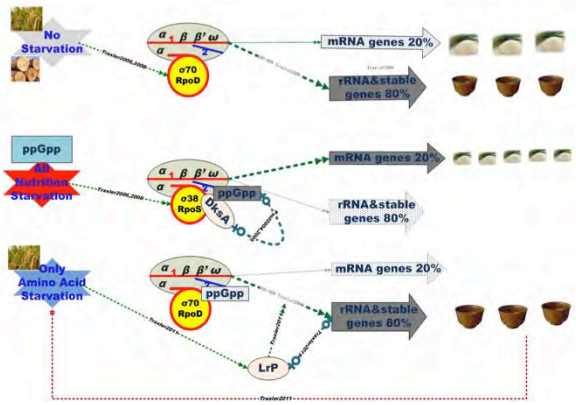

Fig. 5 Different intensities of ppGpp result in different kinds of RNAP actions.

with DksA binds to and drive RNAP employing RpoS to transcribe mRNA only.

4. Conclusion

E. coli, a bacterium, is an efficient system, when facing different circumstances. In this study, firstly, by systematically constructing a network of glucose, PTS, glycogen and chemotaxis system, we unveiled a f act that the shorter time stimuli results in *the post translation level* reactions. And further longer time stimuli will activate more time consuming *the central dogma level* reaction. Secondly, different intensities of signals result in different kinds of actions, was illustrated by ppGpp example.

The last but not the least, we would like to say, biology cannot be classified to higher or lower levels, they only evolve towards different directions.

Acknowledgement

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