Bacterial second messengers achieve extraordinary signal capacity

Second messengers are intracellular signalling molecules that relay environmental changes and prompt cellular responses. Through an information-theory framework coupled with quantitative experiments, the second-messenger molecule cAMP, in the bacterium *Pseudomonas aeruginosa*, is shown to achieve information transmission rates of up to 40 bits per hour.

This is a summary of:
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The question

Bacteria face the fascinating challenge of needing to respond to countless environmental changes, and to do so through a so-called bow-tie communication system[1] – one that has many diverse inputs and outputs but only a few processes connecting them (the 'knot' of the bow-tie, Fig. 1a). Inside each bacterial cell, molecules called second messengers (such as cyclic adenosine monophosphate, cAMP) act as critical signal relays, responding to various environmental signals and triggering appropriate cellular responses. These messenger molecules somehow manage to convey enough information for bacteria to make complex decisions[2].

This raises a fundamental question: how much information can these second-messenger molecules actually transmit? Although their precise responses to various environmental changes can be observed, the communication limits of these molecular messengers are not yet understood. What determines their maximum information transmission capacity, and what factors might limit their signalling ability? Our research aims to quantitatively measure these limits and understand the factors that influence how effectively these molecular messengers transmit information within bacterial cells.

The solution

We used two optical tools to investigate cAMP signalling in the bacterium *Pseudomonas aeruginosa*: optogenetics for blue-light-controlled cAMP synthesis, and cAMP molecular probes for real-time concentration monitoring. These tools operate at distinct wavelengths, enabling decoupled manipulation and measurement.

Using a PAO1-derived knockout strain (PAO1 is a common reference strain of *P. aeruginosa*), we eliminated endogenous cAMP production by deleting genes encoding adenylate cyclases (ΔcyaA, ΔcyaB) and its downstream transcription factor Vfr (Δvfr), which normally binds cAMP to regulate target proteins. This triple knockout enabled us to engineer a single isolated cAMP channel under precise experimental control, in contrast to the bow-tie architecture (Fig. 1a). Using this controlled system, and combining it with information theory as a comprehensive quantitative framework, we were able to study cAMP frequency response capabilities through light-frequency stimulation and probe signal transmission.

Our investigation revealed that the cAMP channel functions as a low-pass filter, with signal strength attenuating at higher input frequencies. Through a 'birth–death process' analysis of cAMP synthesis and degradation, we found that the variance of the noise in the system equals the average number of cAMP molecules per cycle, independent of the input frequency. Using information theory[3], we explored the relationship between input frequency and limits on the information transmission rate (Fig. 1b). Our results pointed to an optimal input frequency, dependent on cAMP molecule numbers, that maximizes the information transmission rate at 40 bits per hour in our system, modulated by the cAMP degradation rate. Notably, at this optimal frequency, bacteria employ a binary coding strategy for cAMP-mediated information transmission.

The implications

Our quantitative analysis reveals the upper limit for the rate of information transmission through cAMP signalling: this high capacity enables the regulation of dozens of independent downstream genes within one cell cycle. The experimental strategy and theoretical framework developed in this study extend beyond cAMP signalling and can serve as a template for investigating the information-processing capabilities of other second messenger molecules.

Our study does not address the complex environmental signals that bacteria typically respond to in their natural habitat, nor does it specify which signals trigger cAMP signalling in physiological settings. Furthermore, we have not determined the extent to which downstream target proteins utilize the information carried by cAMP molecules, or how this information processing varies under different conditions.

Our next research priority is to investigate whether these frequency-encoded signals are accurately transmitted by cAMP molecules to downstream targets, and if so, to elucidate the biological significance of this frequency-dependent information transmission.

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EXPERT OPINION

"This research provides new insights into bacterial adaptation mechanisms and the potential for fine-tuned gene regulation through temporal encoding. Moreover, the result can be applied not only to cAMP signals but also potentially to any biochemical reaction, and hence I think that it is appealing to a broad range of researchers across biophysics, systems biology and bioengineering." **Shinya Kuroda, University of Tokyo, Tokyo, Japan.**

FIGURE

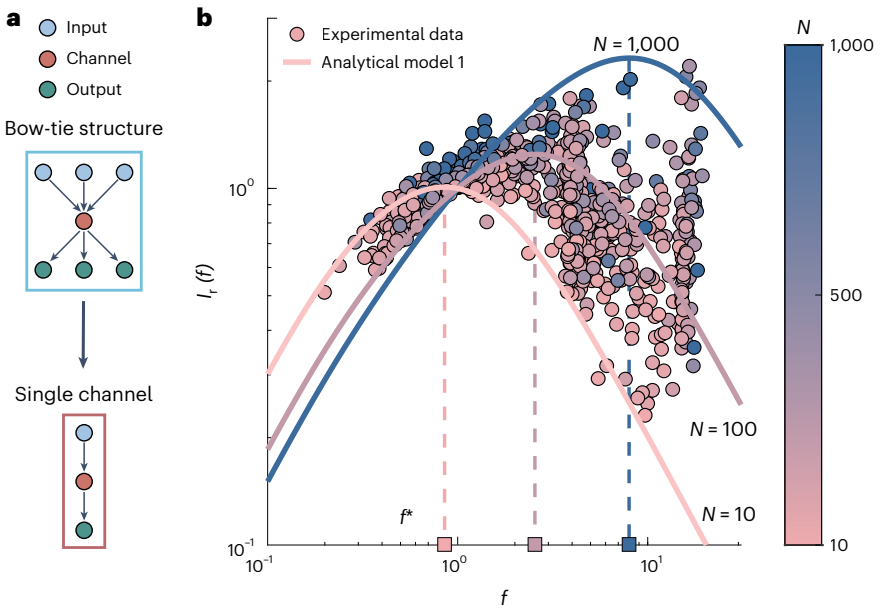

Fig. 1 | Bacterial information transmission. a, The cAMP signalling pathway has a bow-tie architecture, with upstream signals converging through cAMP synthesis and then fanning out in downstream regulation. Using gene knockouts, we created a simplified single-channel system for our quantitative study of information transmission. **b**, The relative information transmission rate (I_r), normalized as $I(f)/I(f=1)$, is plotted against the reduced frequency f (scaled by cAMP degradation rate) for individual *Pseudomonas aeruginosa* bacteria (circles). Theoretical curves are shown for increasing cAMP molecule numbers (N). The optimal reduced frequency f^* (marked on the horizontal axis) shows a positive correlation with N. The concave shape of each curve demonstrates the existence of an optimal operating frequency for information transmission.

BEHIND THE PAPER

Our research originated from a fascination with the 'bow-tie' architecture prevalent in biological systems, where diverse input signals (the input layer) converge through a limited number of messenger molecules (middle layer) to downstream target proteins (the output layer). This natural information processing system raises intriguing questions about signal transmission efficiency. We decomposed the problem into three parts: how upstream components respond to environmental signals (encoding), how effectively messenger molecules transmit information, and how downstream targets interpret these signals (decoding). Our present study focused on the middle component — the information transmission capacity of messenger molecules. The collaboration originated when our laboratory team at the Shenzhen Institutes of Advanced Technology (SIAT) discovered that colleagues from other departments within SIAT had developed a cAMP sensor, providing a crucial tool for quantifying information transmission through second messengers. **F.J.**

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FROM THE EDITOR

"The paper stood out because of its elegant combination of experiments and information theory. The experiment was designed to precisely control and quantify information transmission in a cellular signalling system, with the results then used as input for the information-theory approach." **Editorial Team, *Nature Physics*.**