Reliable cell cycle commitment in budding yeast is ensured by signal integration

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Cell fate decisions are critical for life, yet little is known about how their reliability is achieved when signals are noisy and fluctuating with time. Here we show that in budding yeast, the decision of cell cycle commitment is determined by the time integration of its triggering signal Cln3. We further identify Whi5 as the integrator. The instantaneous activity of Cln3-Cdk1 is recorded over time on the phosphorylated Whi5. Our work shows that the strategy of signal integration, which was also found in decision-making behaviors of animals, is adopted at the cellular level to reduce noise and minimize uncertainty.

Keywords **—Decision making, Signal integration, Start transition.**

I. Introduction

EXTENSIVE studies have shown the importance of precise cell fate decisions in many life activities[1-3]. However, little is known about how cells utilize the information of the input signal to make robust and reliable decisions especially in the case of noisy and time-varying signals. We address this issue using a well-studied system, the budding yeast Start checkpoint, an irreversible commitment [4], as a model. Under various environmental conditions, yeast cells have to decide whether and when to commit to cell division. While a fast division cycle is in general advantageous, it would be detrimental if the cell finds itself short of resources in the middle of the process. The circuitry making the commitment is well known. The sensor of the external and internal conditions is Cln3 [5], a G1 cyclin. The actuator is a biochemical switch made of a positive feedback loop, which is triggered by Cln3. However, the important question of what information of the sensor Cln3 is being used in the decision-making has not been addressed. It was accepted (as in a typical "intuitive" and qualitative picture of signaling) that when the signal Cln3 reaches a high enough concentration (over a threshold) the switch would be turned on.

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II. Summary of Results

Using a quantitative single cell assay with a controllable and quantifiable Cln3 signal, we discovered that it is not the instantaneous value of the Cln3 concentration, but rather the integration of the concentration over time, that triggers the Start transition. Compelling evidences of this point are listed.

A. Inverse correlation between G1 length and Cln3 signal

By using an *IPTG* inducible *CLN3* as the signal to trigger Start in a *CLN3* Δ *BCK2* Δ strain, we observed that G1 length is inversely proportional to the average Cln3 concentration in G1: $T_{G1} - T_0 = \frac{A}{<Cln3>-Cln3_c}$. This inverse correlation can be rewritten into an integral form: $\int_{T_0}^{T_{G1}} (Cln3(t) - Cln3_c)dt = A$. Both mathematical and experimental methods were combined to confirm this result. We have further identified Whi5 as the underlying integrator (i.e. A in the above formulas).

B. "Model Selection" with G1 Distribution data

We compared G1 distribution data generated by two hypothetical models (the Instantaneous Model and the Integration Model) with experimental G1 distribution results. Parameters in both models were derived from published papers. Although both models generate the same G1 average with experiments, the Instantaneous Model leads to an approximately twofold larger variability than experimental data. Meanwhile, the Integration Model generates the same variability with experimental data.

III. Conclusion

The time integration of Cln3-Cdk1 activity on Whi5 phosphorylation filters out noise and ensures reliable cell cycle commitment.

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