Supplementary Information File

The linear interplay of intrinsic and extrinsic noises ensures a high accuracy of cell fate selection in budding yeast

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Table of Contents

Supplementary Text:

The consistence between the simulation results of mathematical models and the experimental observations under wild type. In Fig.S1,*A*, the points marked by star are taken from the published experimental data[1] and the solid line is the simulation result of our ODE model. When the pheromone is added into WT cell at different time, as shown in Fig.S1, the different addition time may lead to a specific cell fate. If the addition time is long enough, as observed in Fig. S1 *B*, the proteins Cln1/2 and Whi5P related to cell-cycle are expressed at high levels, which mean a different fate, i.e., cell-cycle commitment. However, if the addition is quick, as shown in Fig.S1 C, the proteins $Ste5_{mem}$ and Far1 corresponding to the mating pathway are produced at high levels, indicating the mating arrest. In addition, according to the definition of the *Start* point described in METHODS, the relationship between the activation of Whi5P (i.e. the proportion of Whi5 that has been exported from the nuclear at 30 min) and the addition time of pheromone is showed in Fig.S1, *D*. Through the calculation, in the *Start* point, the critical ratio of Whi5P for WT is about 52.92%.This result is quite close to the experimental phenomenon that *Start* is the point where the WT cells arrest, which occurs when approximately half the Whi5-GFP (52% ± 3%) has been exported[1].

The ODE model used in the study. The deterministic model used in the study is described as follows:

$$\frac{d[Ste5]}{dt} = -\alpha(t)[Ste5] + k_1[Ste5]_{mem}[\mathrm{Cln1/2}] + k_4[Ste5]_{mem} - d_1[Ste5] \quad (1)$$

$$\frac{d[Ste5]_{mem}}{dt} = \alpha(t)[Ste5] - k_1[Ste5]_{mem}[\mathrm{Cln1/2}] - k_4[Ste5]_{mem} \quad (2)$$

$$\frac{d[Far1]_{inact}}{dt} = -k_2[Ste5]_{mem}[Far1]_{inact} + k_5[Ste5]_{mem} + k_3[Far1]_{act} - d_2[Far1]_{inact} \quad (3)$$

$$\frac{d[Far1]_{act}}{dt} = k_2[Ste5]_{mem}[Far1]_{inact} - k_6[Far1]_{act}[\mathrm{Cln1/2}] - k_3[Far1]_{act} - d_2[Far1]_{act} \quad (4)$$

$$\frac{d[\mathrm{Cln1/2}]}{dt} = -k_7[Far1]_{act}[\mathrm{Cln1/2}] + a_1 + \frac{k_8[\mathrm{Cln1/2}]^2}{k_9 + [\mathrm{Cln1/2}]^2} - k_{10}[\mathrm{Cln1/2}] - k_{14}[Whi5] \quad (5)$$

$$\frac{d[Whi5]}{dt} = -\frac{k_{11}[Whi5][\mathrm{Cln1/2}]^2}{k_{12} + [\mathrm{Cln1/2}]^2} + k_{13}[Whi5P] \quad (6)$$

$$\frac{d[Whi5P]}{dt} = \frac{k_{11}[Whi5][\mathrm{Cln1/2}]^2}{k_{12} + [\mathrm{Cln1/2}]^2} - k_{13}[Whi5P] \quad (7)$$

Here [•] denotes the activation of each component.

The comparisons between the simplified and original models. It should be pointed out that the original model is used to study the mechanisms of Start transition, and the units of outputs in the original model are nanomole. However, in this study, the activation is in the unit of A.U.. Therefore, we transform the outputs (Cln1/2 and Whi5, specifically) of both models into the same unit by dividing the corresponding maximum of activations. Here the pheromone is added at 0 min and the sample interval is set to [1, 30] with time step 0.1. We calculated the relative error $\frac{\left|\mathrm{out}_{\mathrm{simp}} - \mathrm{out}_{\mathrm{ori}}\right|}{\mathrm{out}_{\mathrm{ori}}}$ between the outputs of the simplified model $\mathrm{out}_{\mathrm{simp}}$ and the original model $\mathrm{out}_{\mathrm{ori}}$ .The simulation results show that the average relative errors of two outputs Cln1/2 and Whi5 are 0.4949 and 0.2059, respectively. Moreover, in this study, we mainly use this simplified model to fit the critical transition value for Start and the histograms in the previous experiment in Doncic A. et al.[1]. Therefore, we also calculated the relative error of the critical transition value, which is 0.0219. These results indicate that the simplified model is reasonable

Supplementary Figures:

Summary of all Supplementary figures.

Fig.S1 shows the consistence between the simulation results of mathematical models and the experimental observations under wild type.

Fig.S2 simulates the relationship between the duration time of Cln1/2 signal pulse and the maximum Whi5P value about 10 min after the end of the pulse. From this result we find that the critical point has a critical Whi5P amount of 65.42%, which is consistent well with the experimental observation.

Fig.S3 indicates the number distribution of cells selecting different fates in WT yeast cell (the number of cells vs. the fraction of exported Whi5). Furthermore, for different stochastic conditions, simulation histograms are provided in Figs.S4 –S21, respectively. The details can be found in main text.

Fig.S22 presents the roles of single intrinsic noises in each reaction channel. It is found that all the reaction channels are classified into two categories.

Finally, the correlations between entropy-decreasing and cell fate for CLE model with some other tuples of $(\log_{10}(1/\sqrt{V}), \log_{10}(\sigma))$ characterized by the two linear models in Fig.8 are showed in Fig.S23.

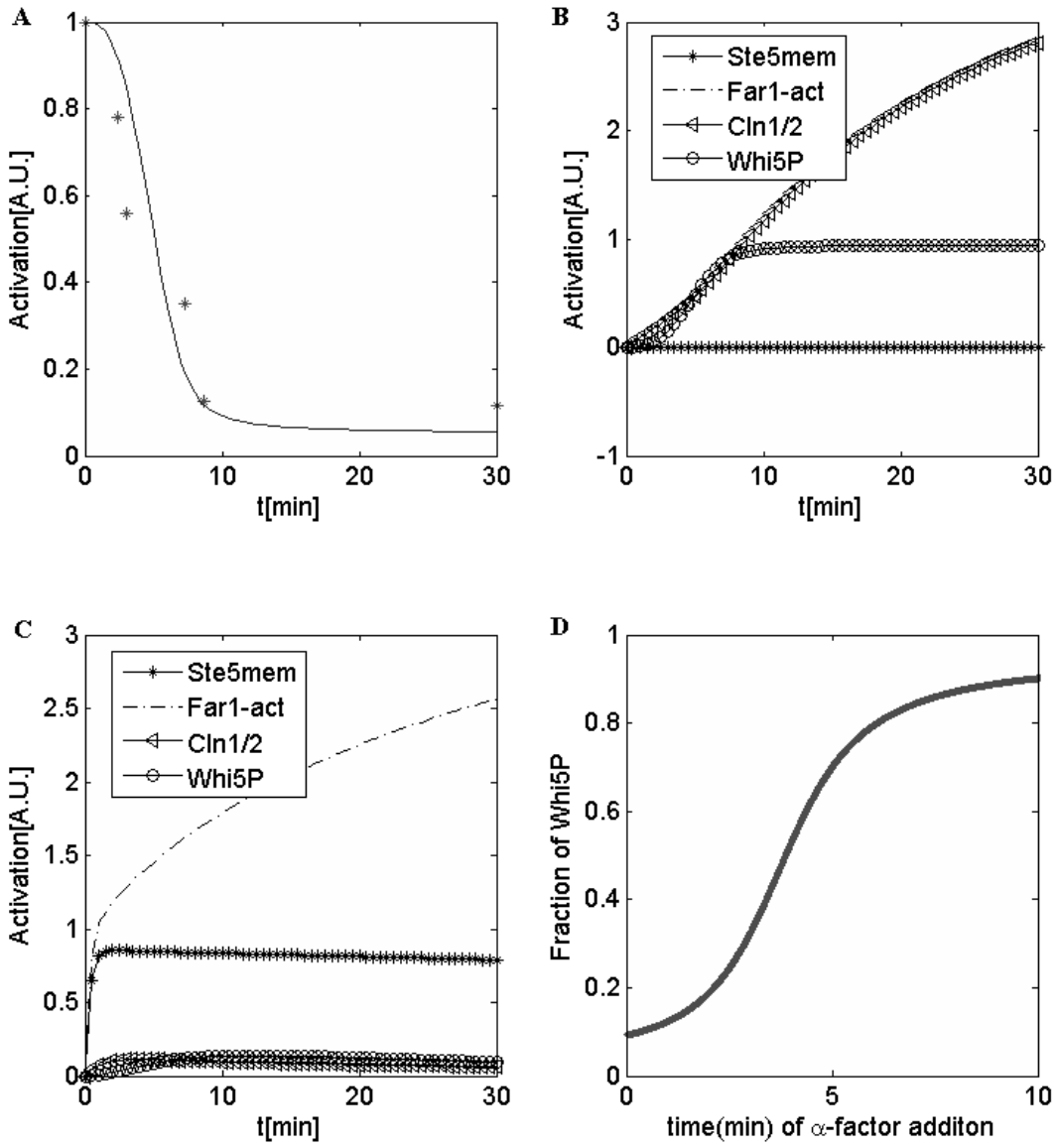


Fig. S1 | (A) Time course of Whi5P in our ODE model, the experimental data is marked with a star. (B) The time course of a WT yeast cell when no pheromone is added. (C)The time course of a WT yeast cell when pheromone is added at 0 min. (D) Relationship between the addition time of pheromone and the activation of Whi5P.

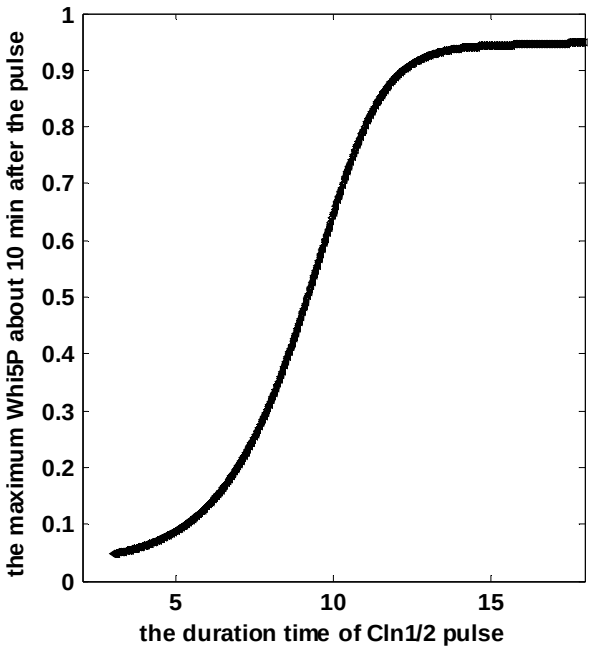


Fig.S2|Relationship between the duration time of Cln1/2 signal pulse and the maximum Whi5P value about 10 min after the end of the pulse.

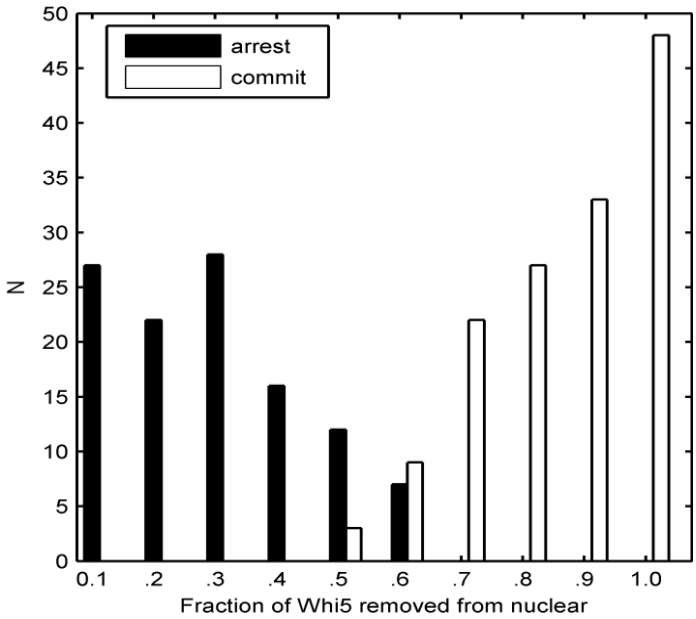


Fig.S3 | Histogram based on cell fates determined by the fraction of exported Whi5 when the pheromone is added.

The histogram is redrawn from Ref.(1).

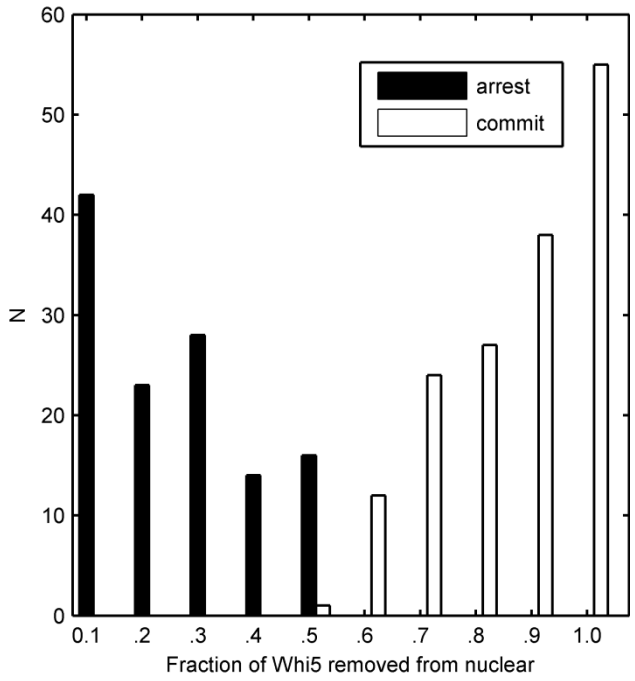


Fig.S4| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when the pheromone is added. Here the initial concentrations of Whi5P for different cells are sampled from the probability distribution of concentrations in Fig.S3. The cell fate is distinguished by the impulse of Cln1/2 in the CLE model.

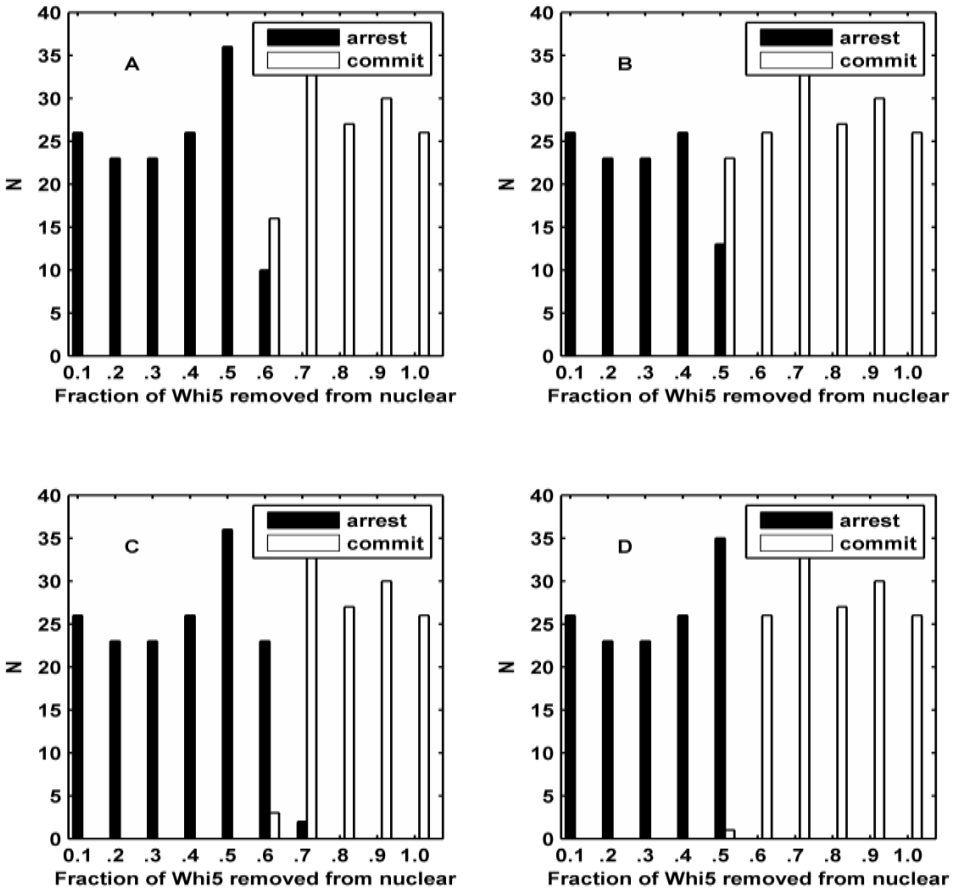


Fig.S5| Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.(A)The cell fate is distinguished by Whi5P after G1 duration in the ODE model. (B)The cell fate is distinguished by the impulse of Cln1/2 in the ODE model. (C)The cell fate is distinguished by Whi5P after G1 duration in the CLE model. (D)The cell fate is distinguished by the impulse of Cln1/2 in the CLE model. We set R=0.25 for (C) and (D).

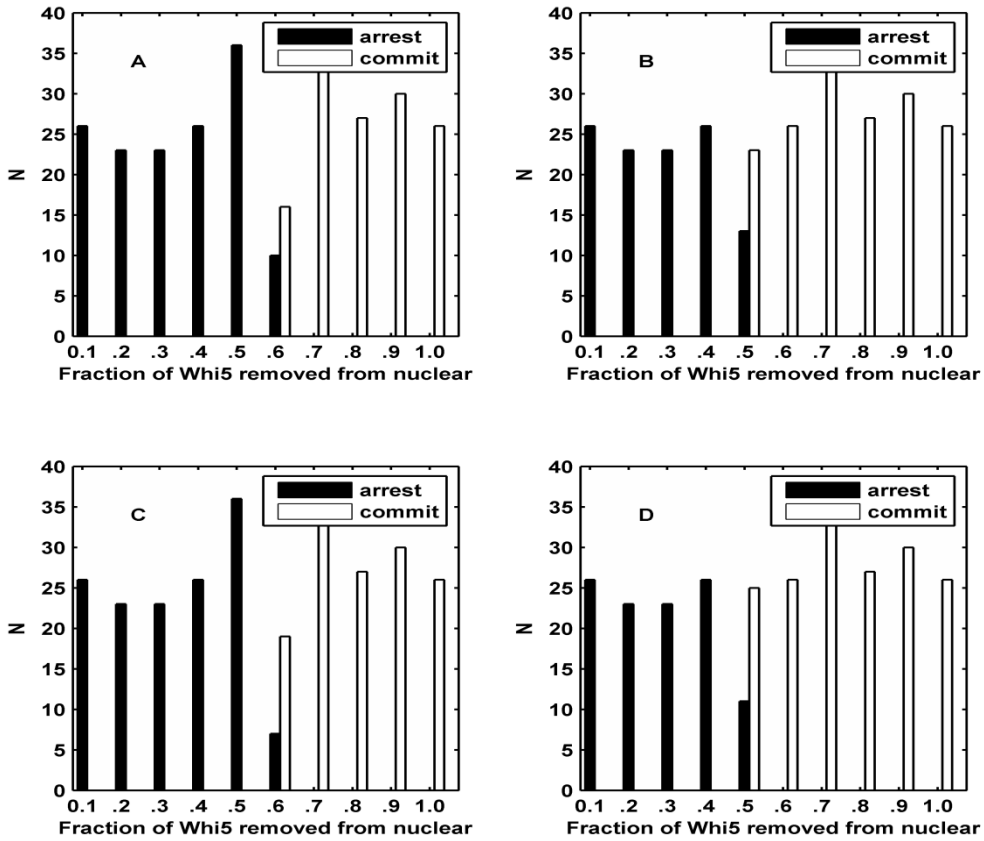


Fig.S6| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when the pheromone is added. (A)The cell fate is distinguished by Whi5P after G1 duration in the ODE model. (B)The cell fate is distinguished by the impulse of Cln1/2 in the ODE model. (C)The cell fate is distinguished by Whi5P after G1 duration in the CLE model. (D)The cell fate is distinguished by the impulse of Cln1/2 in the CLE model. We set R=0.75 for (C) and (D).

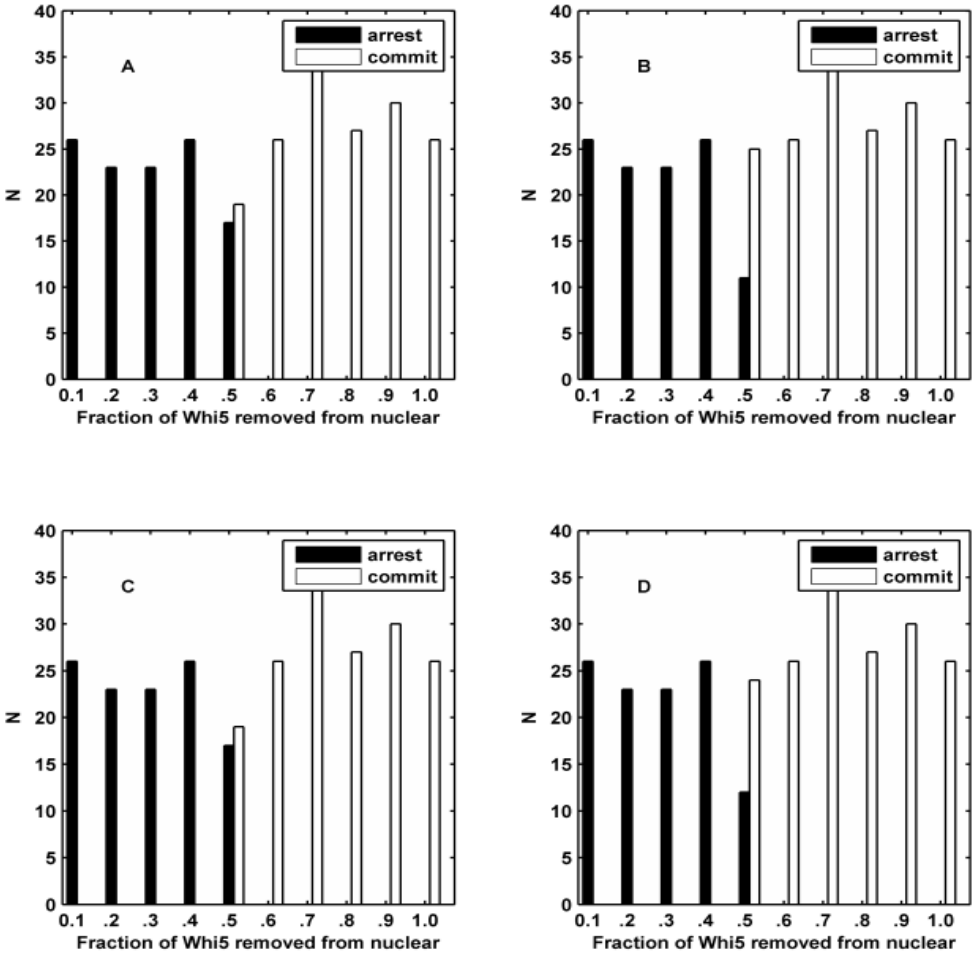


Fig.S7| **Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.1). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc}=0.1 and σ_{mating}=0.1). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal cell-cycle pathway (σ_{brc} =0.1 and σ_{cycle}=0.1). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters, the signal of mating pathway and the signal of cell-cycle pathway (σ_{brc} =0.1, σ_{mating}=0.1and σ_{cycle}=0.1). R_{ex}=1.

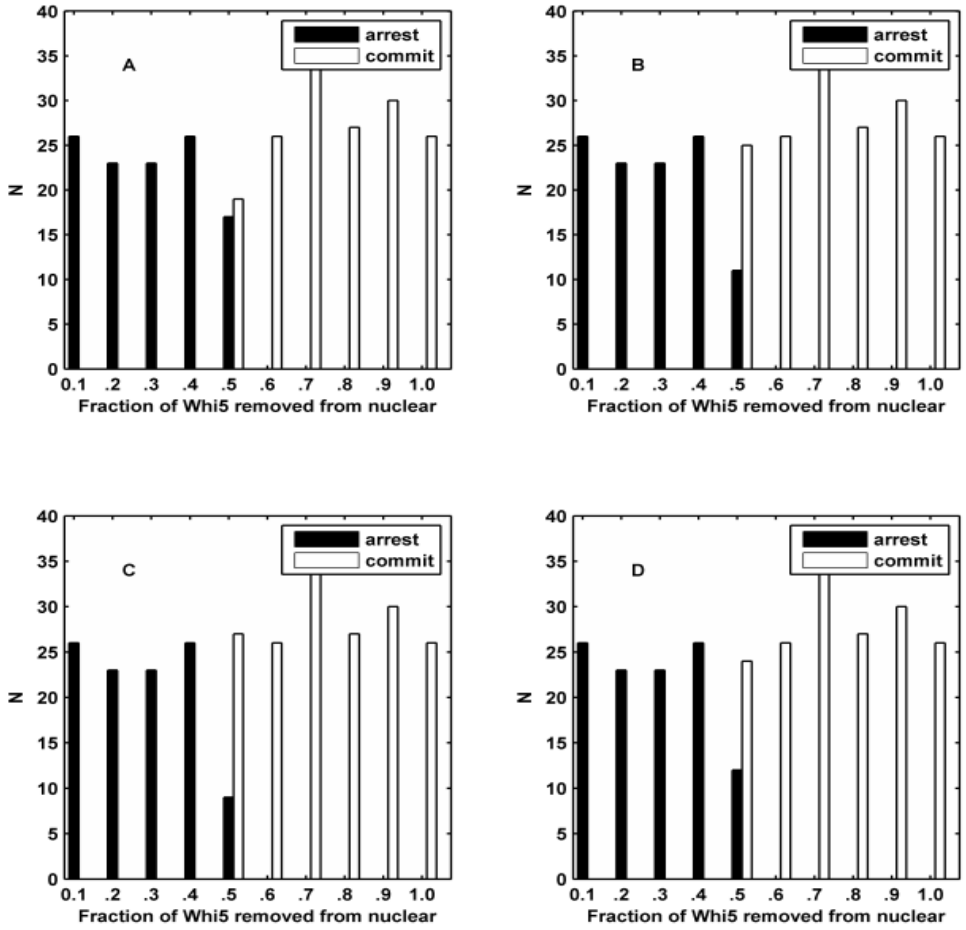


Fig.S8| **Simulation histograms based on cell fates determined by the fraction of exported Whi5 when the pheromone is added.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.2). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc}=0.2 and σ_{mating}=0.2). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal cell-cycle pathway (σ_{brc} =0.2 and σ_{cycle}=0.2). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters, the signal of the mating pathway and the signal of the cell-cycle pathway (σ_{brc} =0.2, σ_{mating}=0.2and σ_{cycle}=0.2). R_{ex}=1.

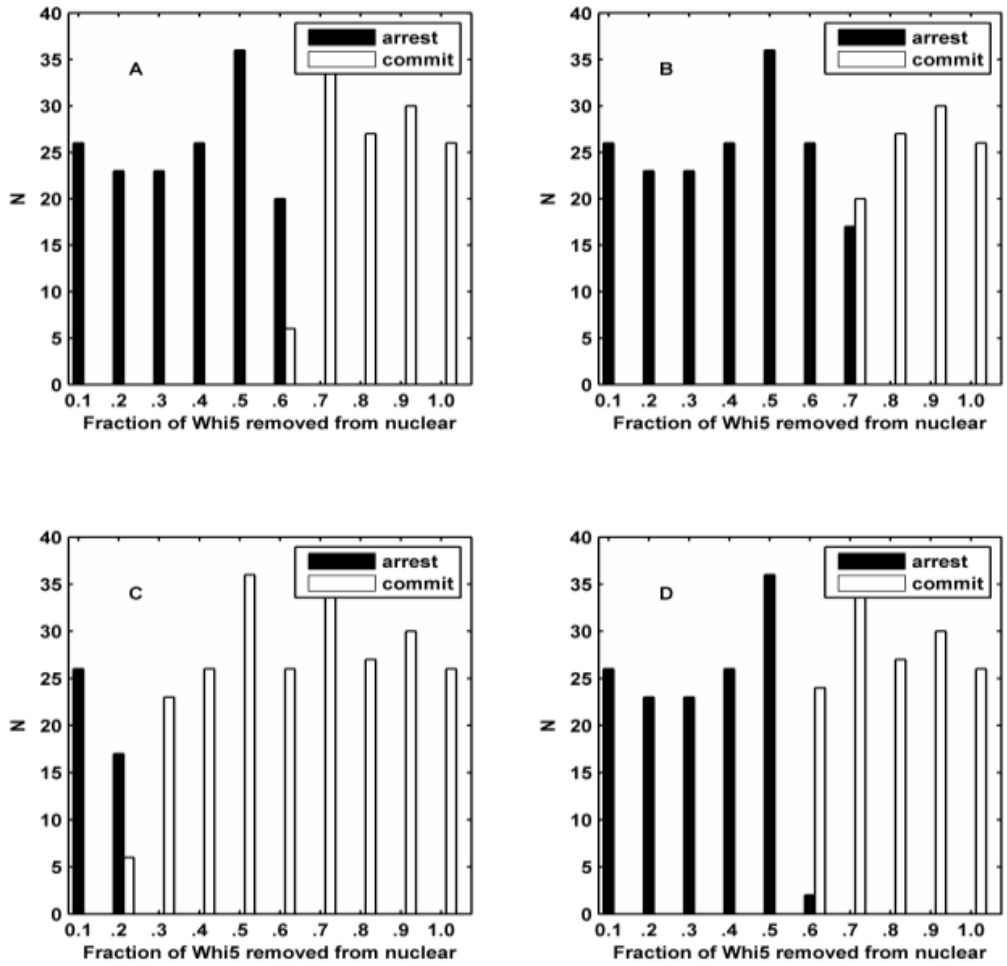


Fig.S9|**Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.5). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc}=0.5 and σ_{mating}=0.5). (C) The result of ODE model with extrinsic noise in biochemical reaction parameters and signal of the cell-cycle pathway (σ_{brc} =0.5 and σ_{cycle}=0.5). (D) The result of ODE model with extrinsic noise in biochemical reaction parameters, the signal of the mating pathway and the signal of the cell-cycle pathway (σ_{brc} =0.5, σ_{mating}=0.5and σ_{cycle}=0.5). R_{ex}=1.

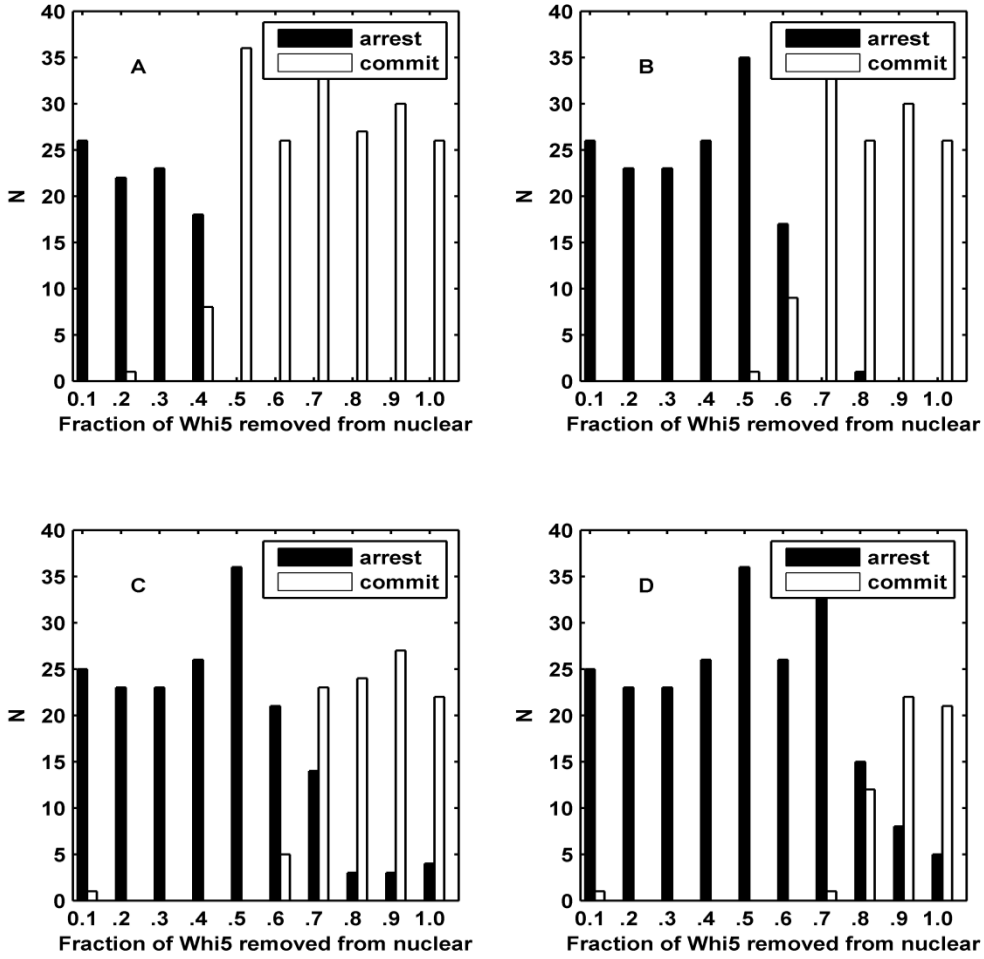


Fig.S10| **Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=1). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of the mating pathway (σ_{brc}=1 and σ_{mating}=1). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal of the cell-cycle pathway (σ_{brc} =1 and σ_{cycle}=1). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signals of the mating and cell-cycle pathways (σ_{brc} =1, σ_{mating}=1and σ_{cycle}=1). R_{ex}=0.

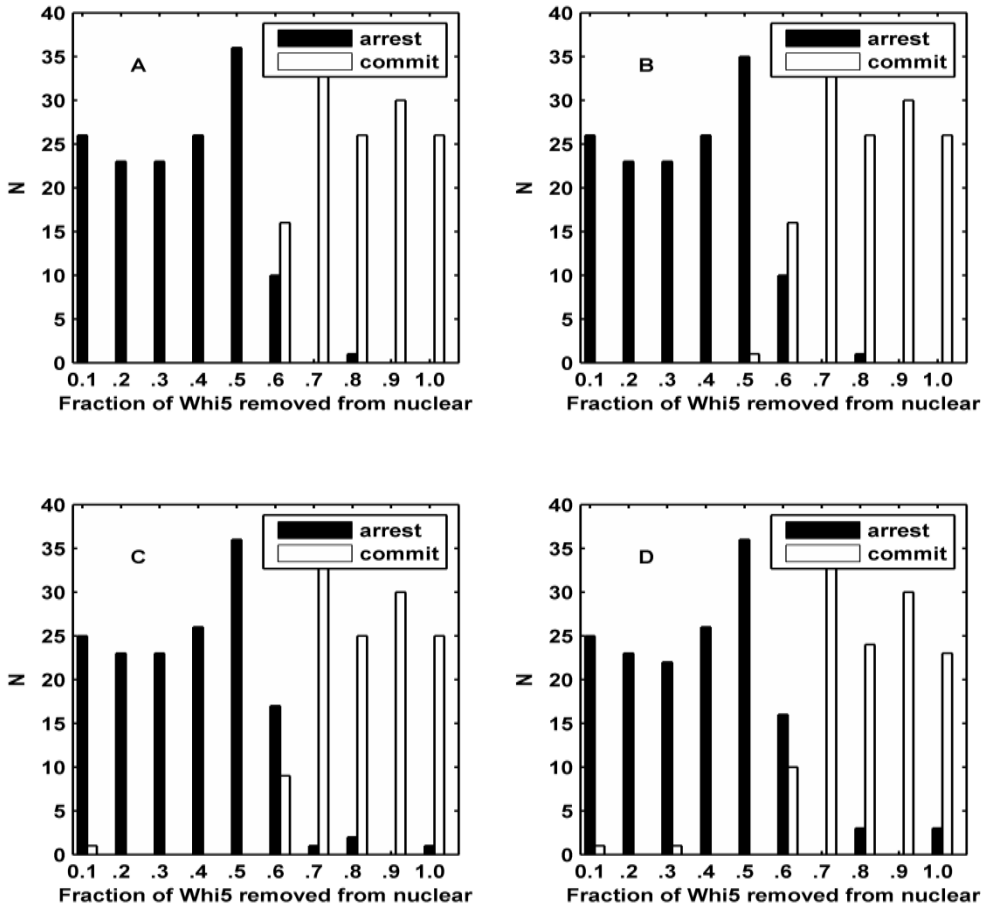


Fig.S11 | **Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2.(A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.1). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of the mating pathway (σ_{brc}=0.1 and σ_{mating}=0.1). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal of the cell-cycle pathway (σ_{brc} =0.1 and σ_{cycle}=0.1). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signals of the mating and cell-cycle pathways (σ_{brc} =0.1, σ_{mating}=0.1and σ_{cycle}=0.1). We set R_{ex}=0.

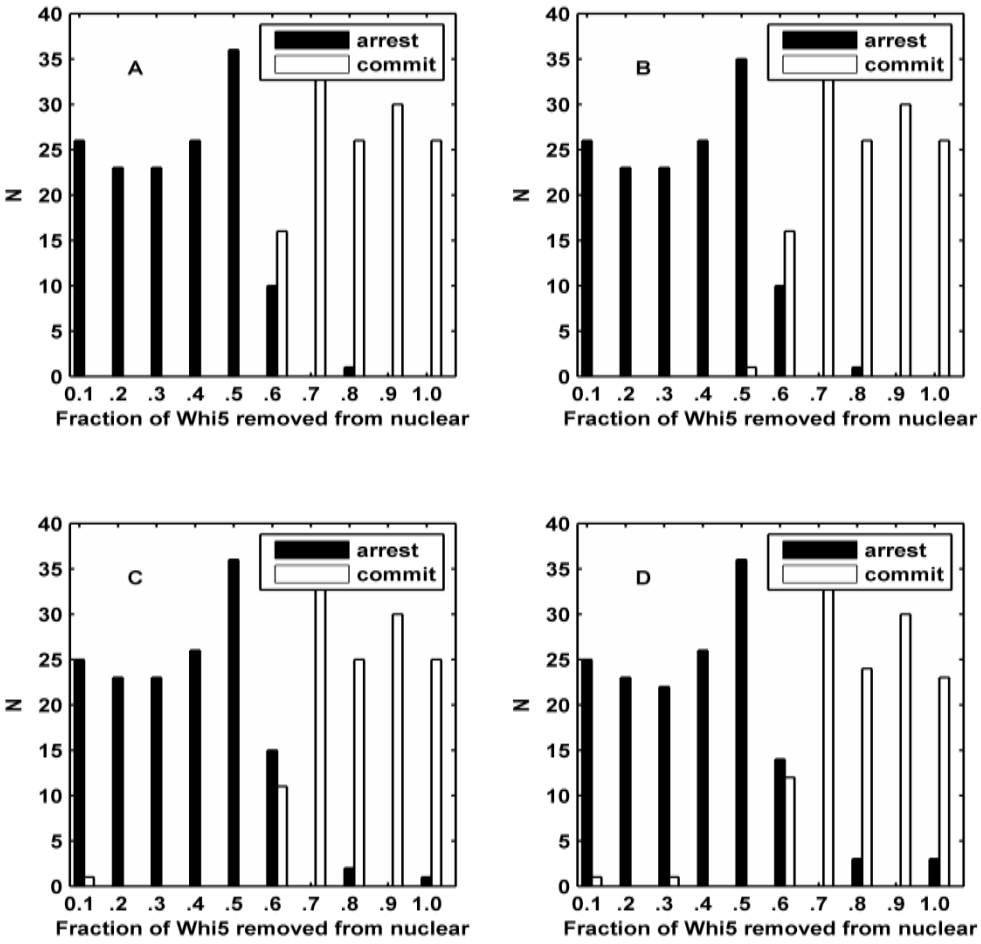


Fig.S12| **Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.2). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc}=0.2 and σ_{mating}=0.2). (C) The result of ODE model with extrinsic noise in biochemical reaction parameters and signal cell-cycle pathway (σ_{brc} =0.2 and σ_{cycle}=0.2). (D) The result of ODE model with extrinsic noise in biochemical reaction parameters, the signal of mating pathway and the signal of cell-cycle pathway (σ_{brc} =0.2, σ_{mating}=0.2and σ_{cycle}=0.2). R_{ex}=0.

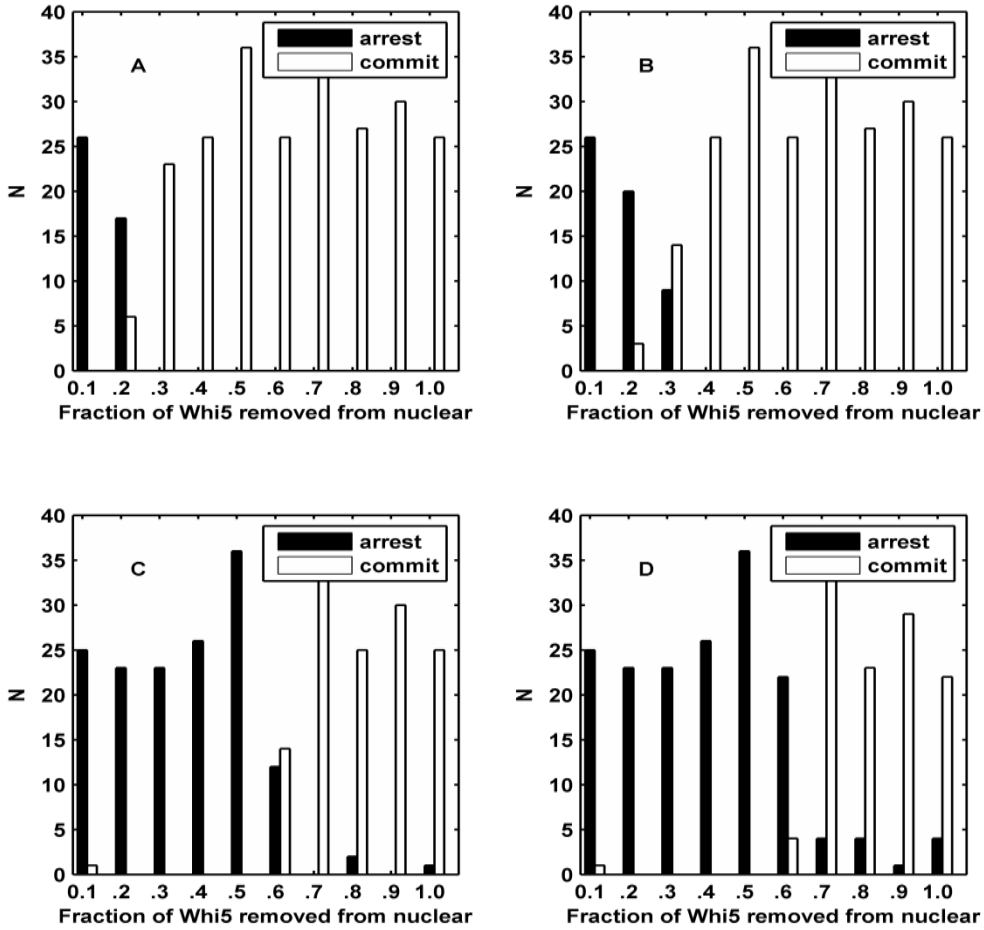


Fig.S13| **Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition.** The cell fate is distinguished by the impulse of Cln1/2. (A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.5). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc}=0.5 and σ_{mating}=0.5). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal of cell-cycle pathway (σ_{brc} =0.5 and σ_{cycle}=0.5). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signals of the mating and cell-cycle pathways (σ_{brc} =0.5, σ_{mating}=0.5and σ_{cycle}=0.5). We set R_{ex}=0.

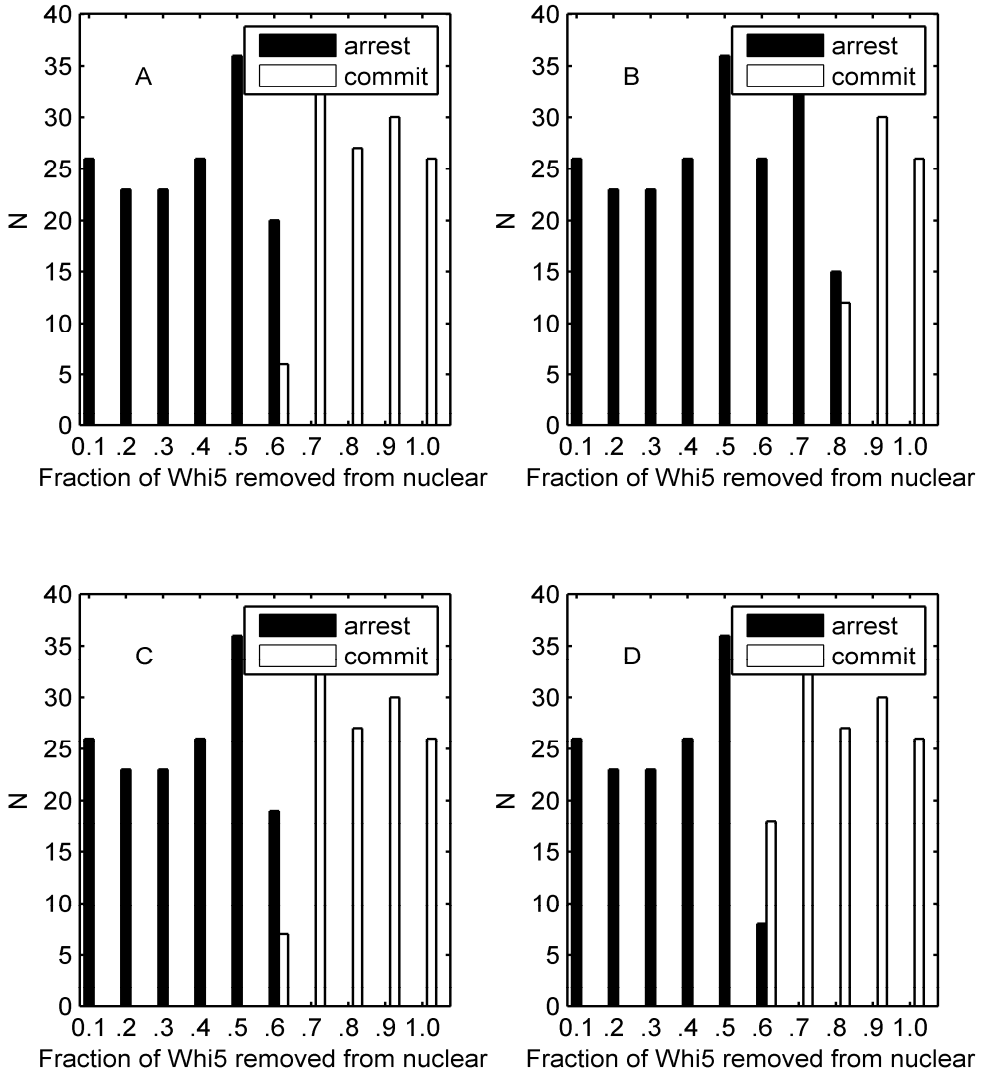
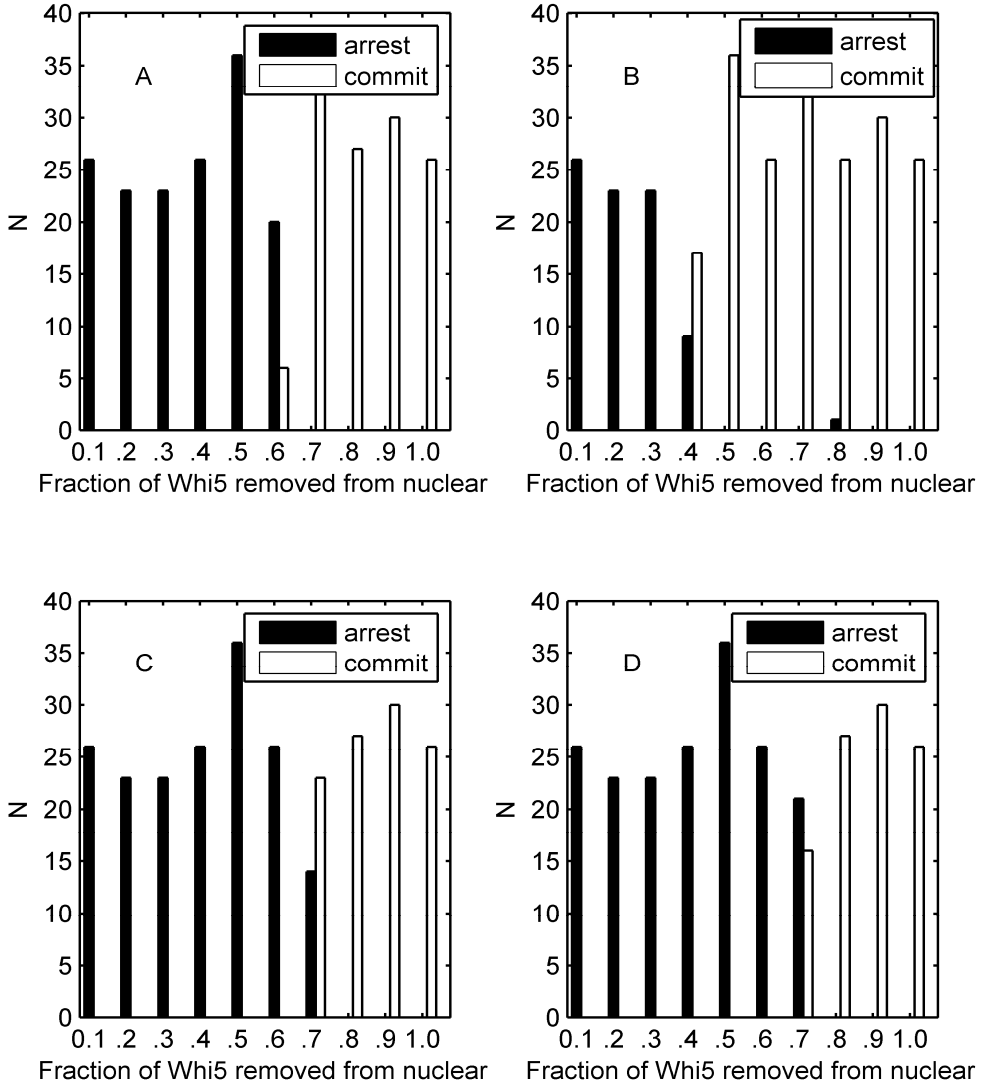


Fig.S14| Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition. The cell fate is distinguished by the impulse of Cln1/2 .(A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.5). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc} =0.5 and σ_{mating}=0.1). (C) The result of The ODE model with extrinsic noise in biochemical reaction parameters and signal cell-cycle pathway (σ_{brc}=0.5 and σ_{cycle} =0.1). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signals of the mating and cell-cycle pathways (σ_{brc}=0.5, σ_{mating}=0.1 and σ_{cycle} =0.1). We set R_{ex}=1.



.Fig.S15| Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition. The cell fate is distinguished by the impulse of Cln1/2.(A) The result of the ODE model with extrinsic noise in biochemical reaction parameters (σ_{brc}=0.5). (B) The result of the ODE model with extrinsic noise in biochemical reaction parameters and the signal of mating pathway (σ_{brc} =0.5 and σ_{mating}=1). (C) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signal cell-cycle pathway (σ_{brc}=0.5 and σ_{cycle} =1). (D) The result of the ODE model with extrinsic noise in biochemical reaction parameters and signals of the mating and cell-cycle pathways (σ_{brc}=0.5, σ_{mating}=1 and σ_{cycle} =1). We set R_{ex}=1.

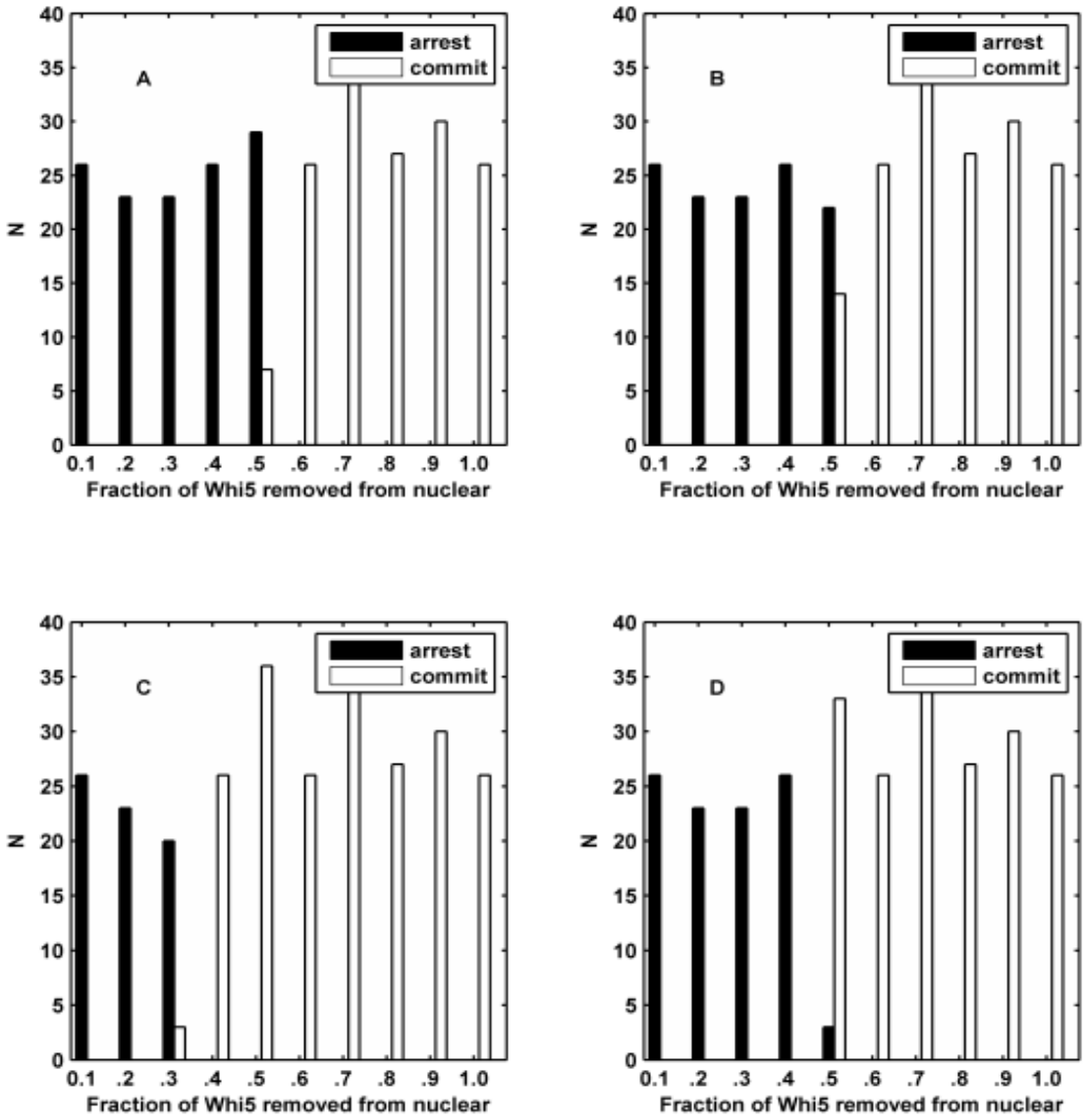


Fig.S16| Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition. The cell fate is distinguished by the impulse of Cln1/2 and extrinsic noise in the signal of mating pathway has a standard deviation σ_{cycle} =1. The extrinsic noise in the signal of the cell-cycle pathway has a standard deviation (A) σ_{mating} =0, (B) σ_{mating} =0.1, (C) σ_{mating} =0.5 and (D) σ_{mating} =1, respectively.

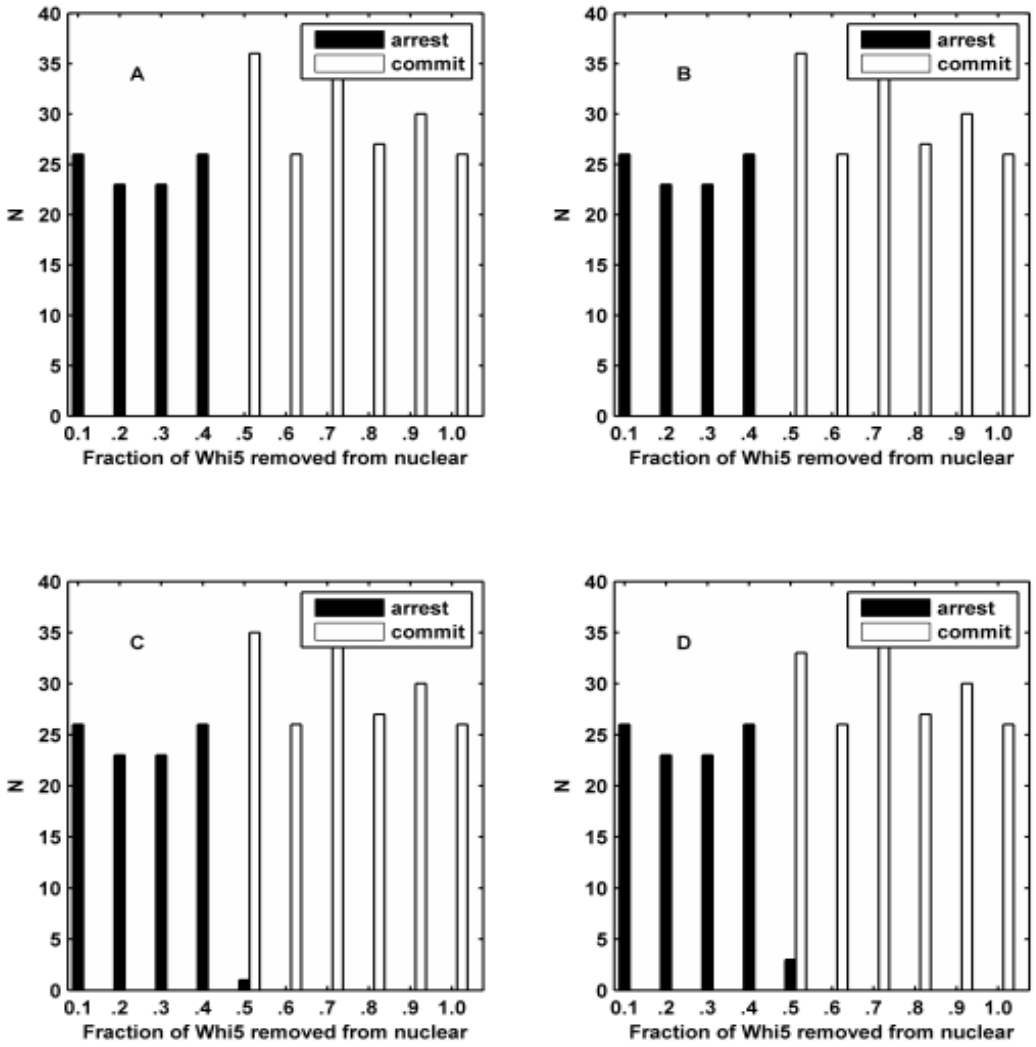


Fig.S17 | Simulation histograms based on cell fates determined by the fraction of exported Whi5 at the time of pheromone addition. The cell fate is distinguished by the impulse of Cln1/2 and extrinsic noise in the signal of mating pathway has a standard deviation σ_{mating} =1. The extrinsic noise in the signal of cell-cycle pathway has a standard deviation (A) σ_{cycle}=0, (B) σ_{cycle}=0.1, (C) σ_{cycle}=0.5 and (D) σ_{cycle}=1, respectively.

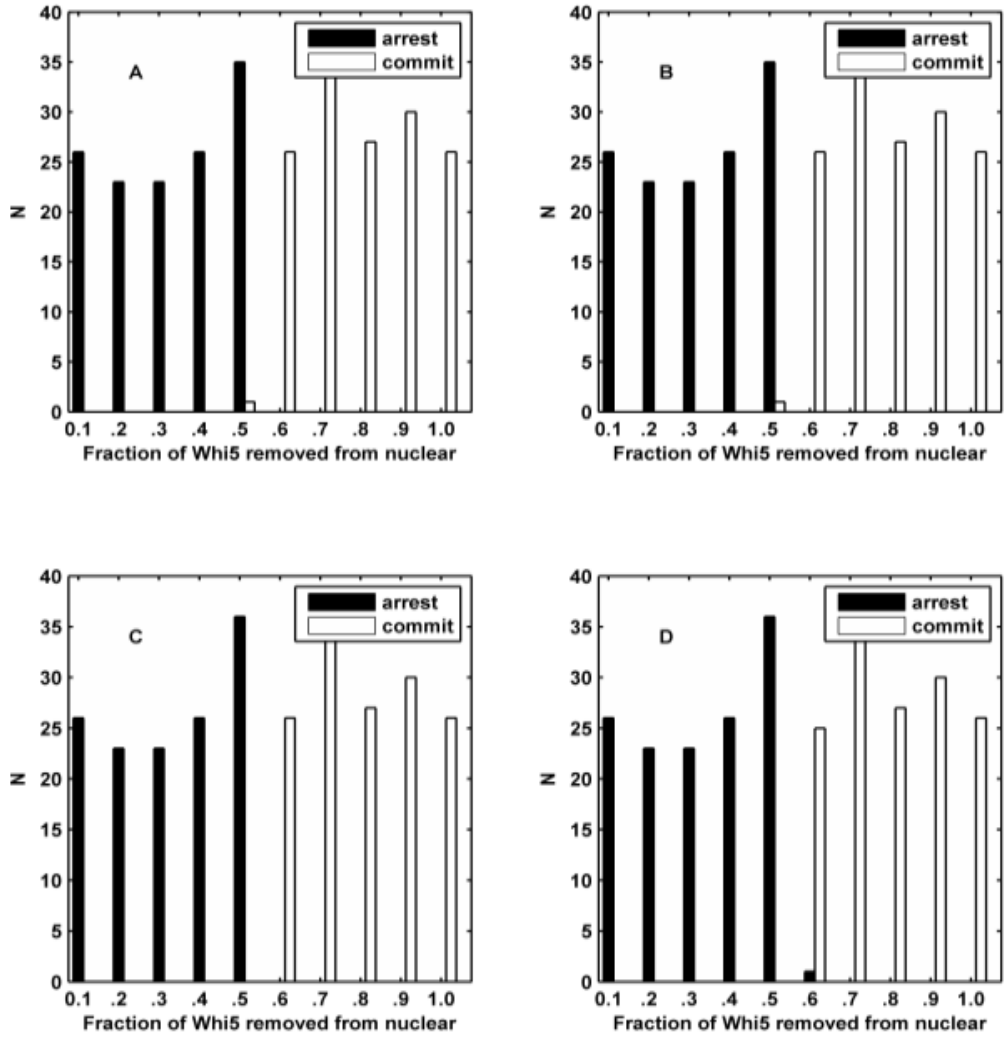


Fig.S18| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when pheromone is added. The cell fate is distinguished by the impulse of Cln1/2 and intrinsic noise has a standard deviation $1/\sqrt{V}$ ≈0.0316 (V=1000). The extrinsic noise in the signal of cell-cycle pathway has a standard deviation (A) σ_{cycle}=0.1, (B) σ_{cycle}=0.2, (C) σ_{cycle}=0.5 and (D) σ_{cycle}=1, respectively.

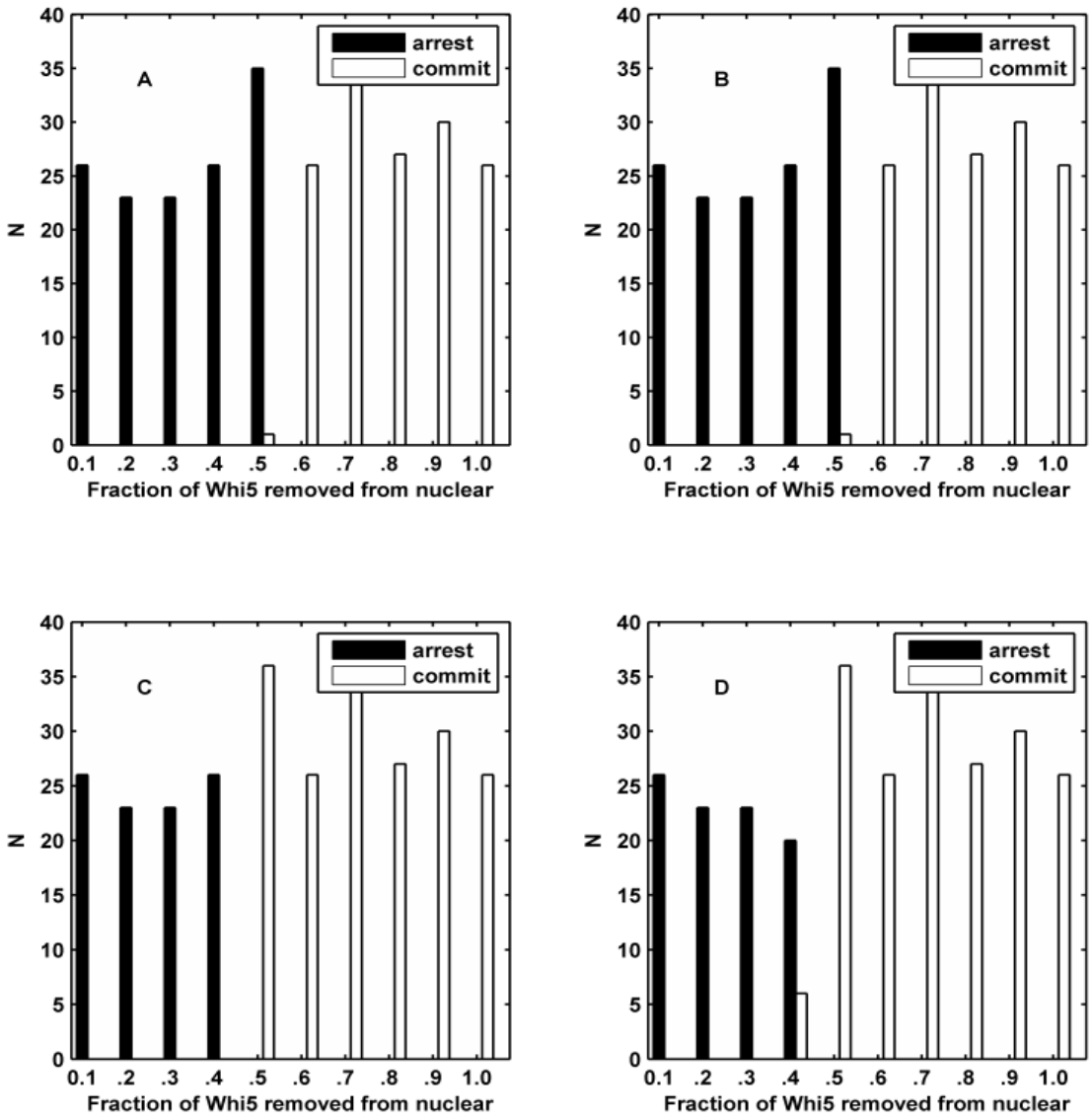


Fig.S19| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when pheromone is added. The cell fate is distinguished by the impulse of Cln1/2 and intrinsic noise has a standard deviation $1/\sqrt{V}$ ≈0.0316 (V=1000). The extrinsic noise in the signal of mating pathway has a standard deviation (A) σ_{mating}=0.1, (B) σ_{mating} =0.2, (C) σ_{mating} =0.5 and (D) σ_{mating} =1, respectively.

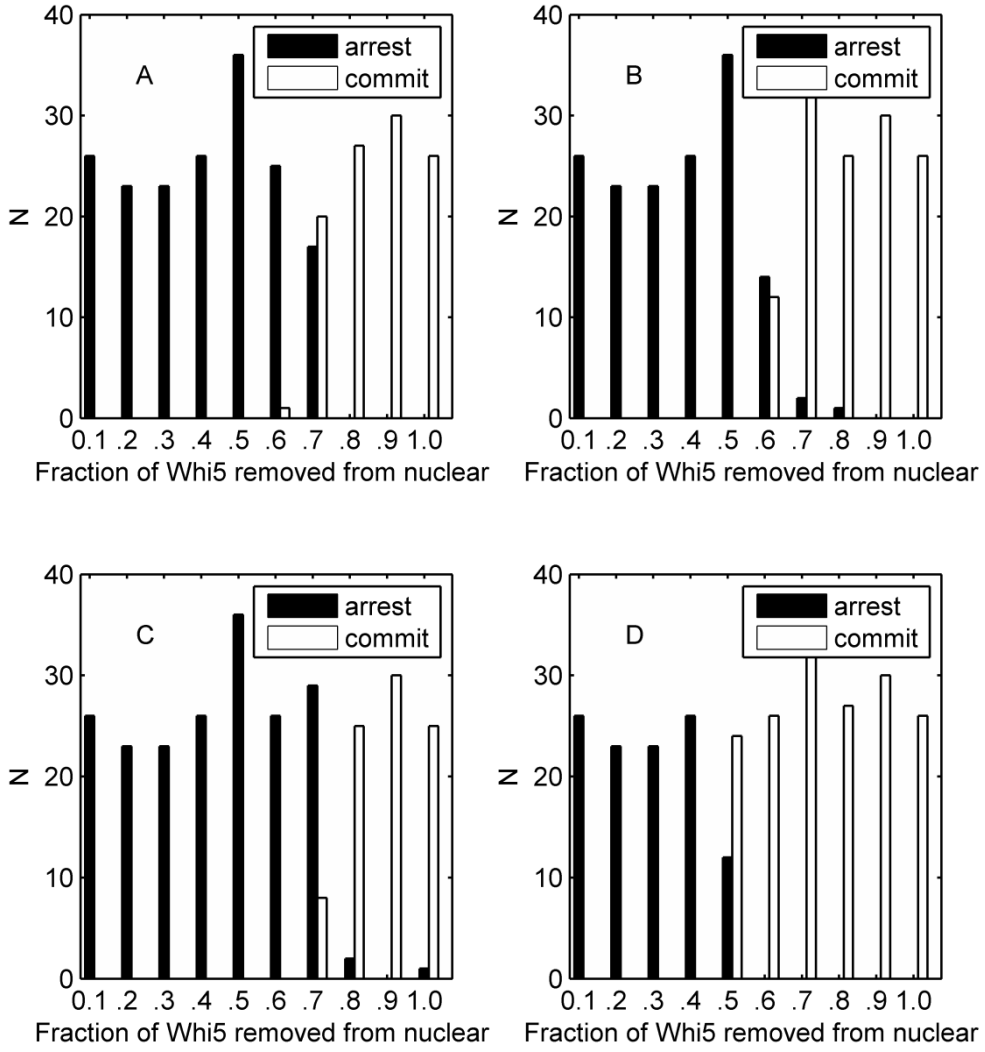


Fig.S20| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when pheromone is added. The cell fate is distinguished by the impulse of Cln1/2 and extrinsic noise has a standard deviationσ=1. The intrinsic noise has a standard deviation (A) $1/\sqrt{V}$ ≈0.01 (V=10000), (B) $1/\sqrt{V}$ ≈0.0316 (V=1000), (C) $1/\sqrt{V}$ ≈0.1 (V=100) and (D) $1/\sqrt{V}$ ≈0.3162 (V=10), respectively.

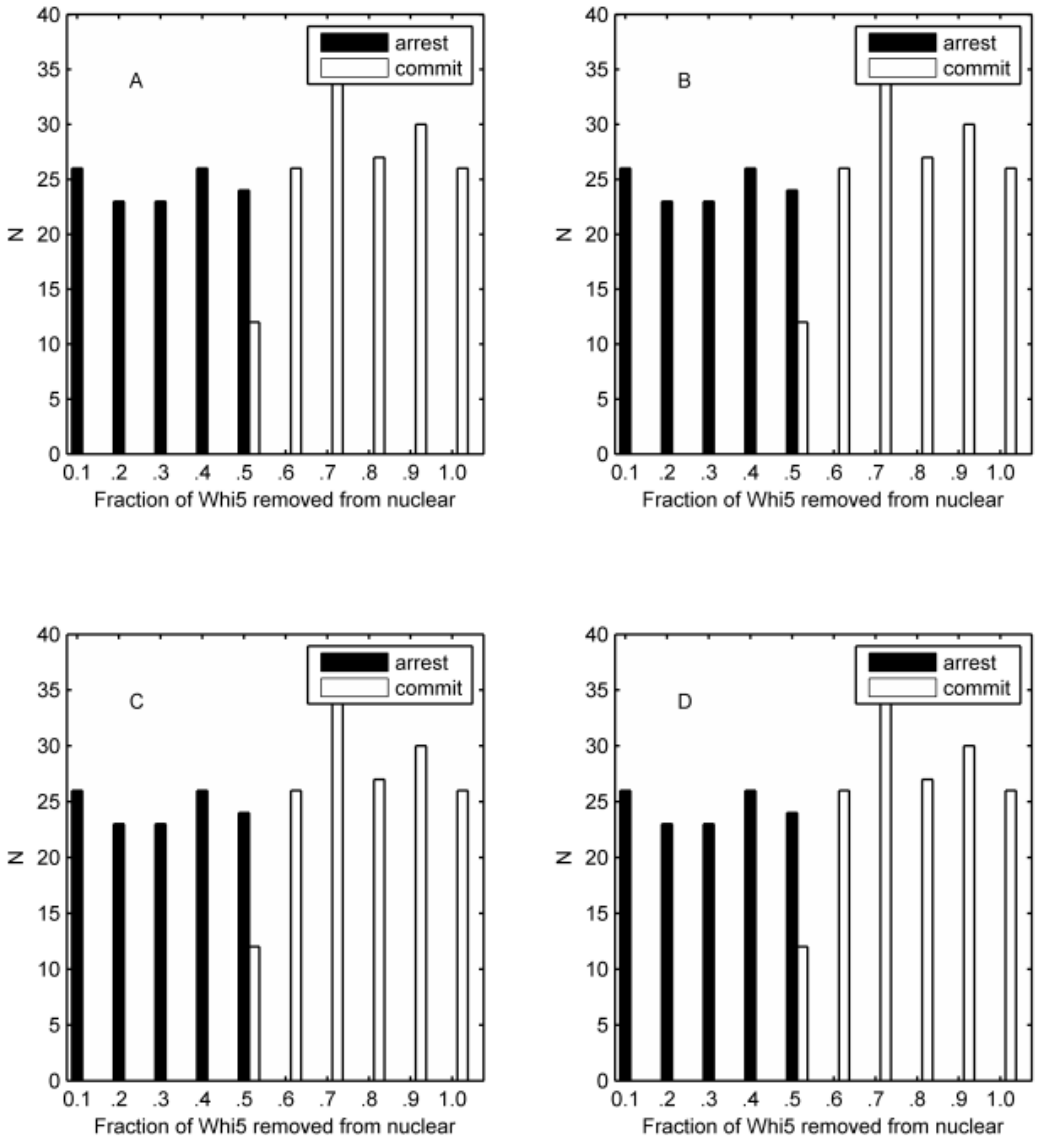


Fig.S21| Simulation histograms based on cell fates determined by the fraction of exported Whi5 when pheromone is added. The cell fate is distinguished by the impulse of Cln1/2 and only extrinsic noise in k_{10} is taken into consideration. (A) σ=0.05.(B) σ=0.1.(C) σ=0.5.(D) σ=1.

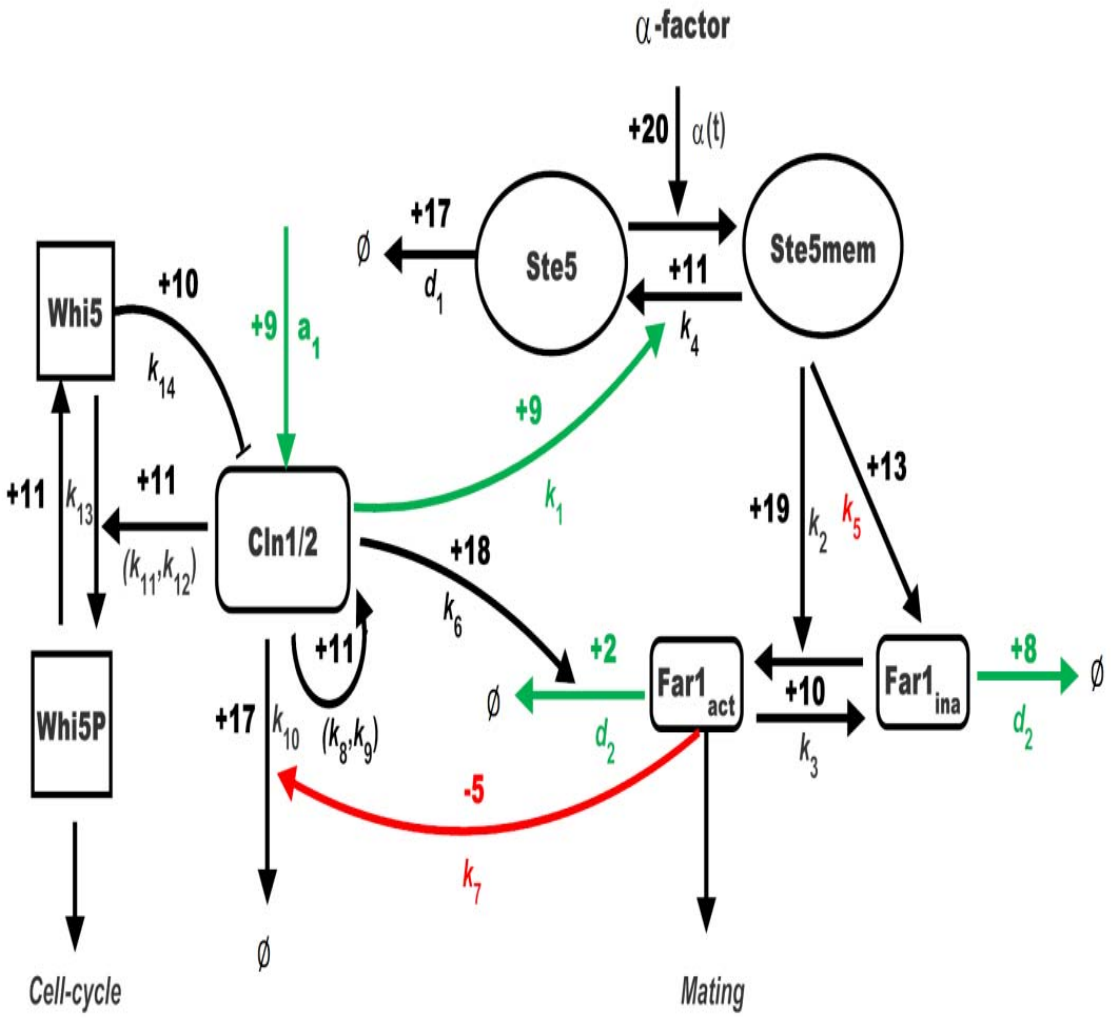


Fig.S22 | All reaction channels are divided into two species：the supporter of mating progress (black and green arrows) or cell-cycle program (red arrow). The difference between the number of mating cell calculated from the the ODE model with and without the intrinsic noise in each reaction channel.

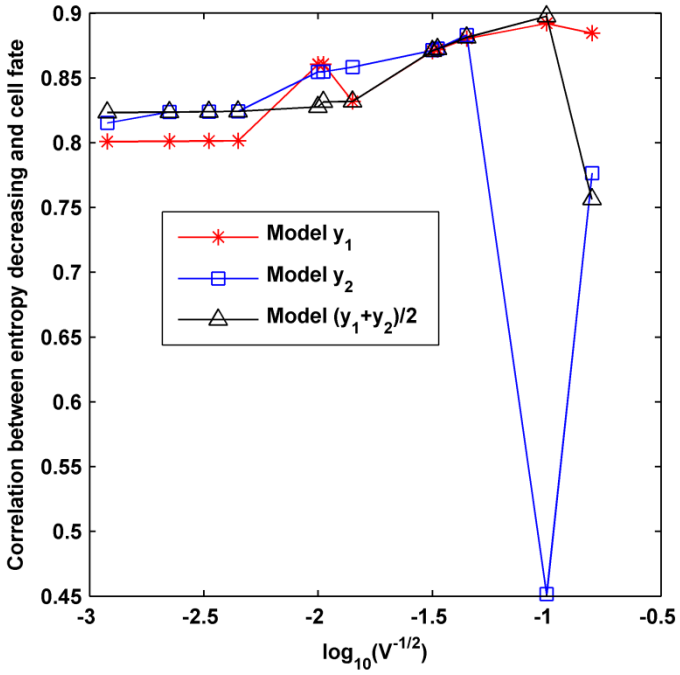


Fig.S23 | Correlations between entropy-decreasing and cell fate. The extrinsic and intrinsic noises are determined by the two linear models y_1 and y_2 in Fig.8.

1 Doncic, A., Falleur-Fettig, M. & Skotheim, J. M. Distinct Interactions Select and Maintain a Specific Cell Fate. *Mol Cell***43**, 528-539, doi:DOI 10.1016/j.molcel.2011.06.025 (2011).