Supporting Information

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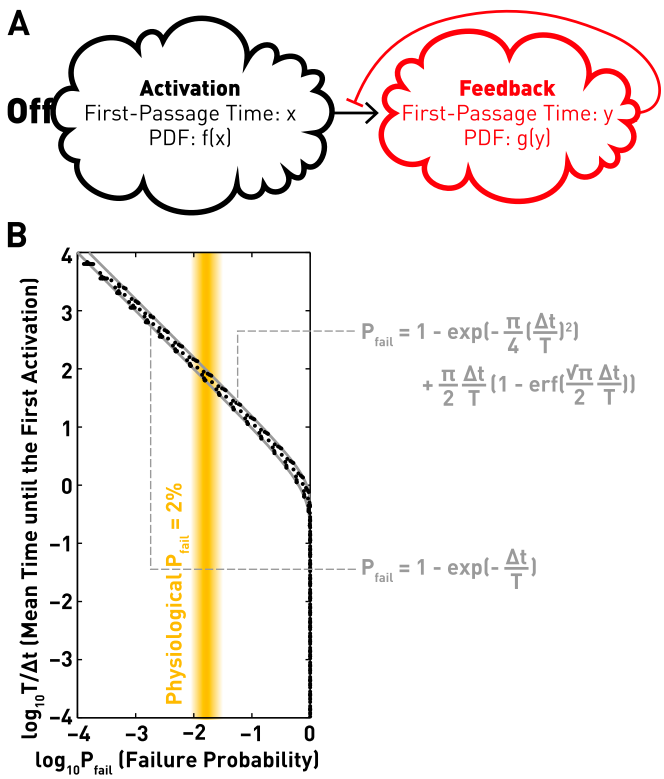

Fig. S1. Our conclusion holds for a more general model of olfactory receptor (OR) activation and feedback. (*A*) In a generalized model, the detailed kinetics of OR activation (such as H3K9me3⇄H3K9me2→on) is represented by an arbitrary stochastic process from an "off" state to an "on" state with a first-passage time *x*, whose probability density function (PDF) is $f(x)$ and cumulative distribution function (CDF) is $F(x)$. Similarly, the details of feedback (such as OR-activating *Adcy3*, which then represses *Lsd1*) are represented by another stochastic process with a first-passage time *y*: a PDF $g(y)$ and a CDF $G(y)$. The two processes are connected by an irreversible step that can be turned off after time $x+y$, which corresponds to the step of H3K9me2 demethylation by *Lsd1* in our model (Fig. 1*A*). Among all $n = 2{,}800$ alleles of ORs, the mean time of the earliest activation (namely, the smallest first-passage time of all *n* values of *x*) can be calculated according to order statistics:

$$T = \int_0^{+\infty} dx\ n\ x\ f(x)(1-F(x))^{n-1}. \tag{S1}$$

Similarly, the failure probability can be calculated given any value of the response time *y*:

$$P_{fail}|y = 1 - \int_0^{+\infty} dx\ n\ f(x)(1-F(x+y))^{n-1}. \tag{S2}$$

Eq. **S2** can be easily derived from the joint probability distribution of the earliest activation $x_{(1)}$ and the second-earliest $x_{(2)}$:

$$P_{fail}|y = 1 - P\left(x_{(2)} - x_{(1)} < y\right) = 1 - \int_0^{+\infty} dx_{(1)} \int_{x_{(1)}}^{x_{(1)}+y} dx_{(2)} n(n-1) f\left(x_{(1)}\right) f\left(x_{(2)}\right)\left(1-F\left(x_{(2)}\right)\right)^{n-2}, \tag{S3}$$

which can be simplified into Eq. **S2** by integrating out $x_{(2)}$ and rewriting $x_{(1)}$ as *x*. When *n* is sufficiently large, $(1 - F(x))^{n-1}$ decays rapidly with its argument *x*. Therefore, the above integrals are mainly determined by the behavior of $f(x)$ and $(1 - F(x))$ or $(1 - F(x + y))$ when *x* and *y* are both close to zero. First we consider two special cases where exact results can be obtained. The "survival probability" $(1 - F(x))$ must decrease with *x* and two most natural cases are exponential decay

$$1 - F(x) = \exp(-f(0)x),\ \text{corresponding to}\ f(x) = f(0)\exp(-f(0)x), \tag{S4}$$

and Gaussian decay

$$1 - F(x) = \exp\left(-f'(0)x^2/2\right),\ \text{corresponding to}\ f(x) = x\,f'(0)\exp\left(-f'(0)x^2/2\right). \tag{S5}$$

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In the case of an exponential decay of the survival probability (Eq. **S4**), we can calculate the exact values of T and P_{fail} from Eqs. **S1** and **S2**:

$$T=\int_0^{+\infty} dx\ n\ x\ f(x)(1-F(x))^{n-1}=\int_0^{+\infty} dx\ n\ x\ f(0)\exp(-n\ f(0)x)=1/(n\ f(0)), \quad \text{[S6]}$$

which scales with n^{-1}, and

$$P_{fail}|y=1-\int_0^{+\infty} dx\ n\ f(x)(1-F(x+y))^{n-1}=1-\int_0^{+\infty} dx\ n\ f(0)\exp(-n\ f(0)x-(n-1)f(0)y)=1-\exp(-(n-1)f(0)y). \quad \text{[S7]}$$

If the response time is fixed at Δt (so $y = \Delta t$) and n is large [so $(n-1)/n \sim 1$], we arrive at a formula of the failure probability:

$$P_{fail}=1-\exp(-\Delta t/T) \quad \text{[S8]}$$

$$\approx \Delta t/T(\text{approximation when } \Delta t \ll T), \quad \text{[S9]}$$

which is independent of n, and completely determined by the ratio $\Delta t/T$. Similarly, in the case of a Gaussian decay (Eq. **S5**), we get

$$T=\int_0^{+\infty} dx\ n\ x\ f(x)(1-F(x))^{n-1}=\int_0^{+\infty} dx\ n\ x^2\ f'(0)\exp\left(-n\ f'(0)x^2/2\right)=\sqrt{(\pi/(2n\ f'(0)))}, \quad \text{[S10]}$$

which scales with $n^{-0.5}$, and

$$\begin{aligned}P_{fail}|y&=1-\int_0^{+\infty} dx\ n\ f(x)(1-F(x+y))^{n-1}=1-\int_0^{+\infty} dx\ n\ x\ f'(0)\exp\left(-f'(0)x^2/2-(n-1)f'(0)(x+y)^2/2\right)\right)\\&=1-\exp\left(-(n-1)f'(0)y^2/2\right)+(n-1)y\sqrt{(\pi\ f'(0)/(2n))}\left(1-\text{erf}\left((n-1)y\sqrt{(f'(0)/(2n))}\right),\end{aligned} \quad \text{[S11]}$$

where erf() is the error function. If the response time is fixed at Δt (so $y = \Delta t$) and n is large [so $(n-1)/n \sim 1$], we arrive at a formula of the failure probability:

$$P_{fail}=1-\exp\left(-\pi(\Delta t/T)^2/4\right)+(\pi/2)\Delta t/T\left(1-\text{erf}\left(\Delta t/2T\sqrt{\pi}\right)\right) \quad \text{[S12]}$$

$$\approx(\pi/2)\Delta t/T(\text{approximation when } \Delta t \ll T), \quad \text{[S13]}$$

which is again independent of n, and completely determined by the ratio $\Delta t/T$. The above calculation can be carried out not only for exponential or Gaussian survival functions, but also for any survival functions in the form of $1-F(x)=\exp(-f^{(m-1)}(0)\ x^m/(m!))$, where m is a positive integer and $f^{(m-1)}(0)$ is the $(m-1)$th derivative of the PDF at $x = 0$. In these cases, exact solutions can be obtained, and when $\Delta t << T$, we have

$$P_{fail}\approx constant\ \ \Delta t/T, \quad \text{[S14]}$$

where the constant is independent of n or the value of $f^{(m-1)}(0)$, but increases with m. When $m = 1$, constant = 1; when $m = 2$, constant = $\pi/2$. In general, a survival probability does not necessarily take the above form; however, because the integrals in Eqs. **S1** and **S2** only concern x and y very close to zero, any general distribution can be well approximated by the above forms if its PDF $f(x)$ can be Taylor expanded near $x = 0$. For example, if $f(x)$ is roughly constant around zero, namely $f(0) > 0$, it can be approximated by the first case (exponential survival function). In contrast, if $f(x)$ rises linearly around zero, namely $f(0) = 0$ but $f'(0) > 0$, it can be approximated by the second case (Gaussian survival function). Generally speaking, if $f^{(m-1)}(0)$ is the leading derivate of $f(x)$ that does not vanish at zero, it can be approximated by the exactly solvable case $1-F(x)=\exp(-f^{(m-1)}(0)\ x^m/(m!))$. (*B*) Our three-state kinetic model has $f(0) = 0$ but $f'(0) > 0$, so would in principle fall into the second case of a Gaussian survival probability ($constant = \pi/2$). However, when n = 2,800 is not large enough, the linear rise near zero can become negligible. Therefore, when $nk_{total} >> k_{bottleneck}$, the PDF is dominated by the exponential fall at longer timescales, which leads to the first case of an exponential survival probability. The two theoretical solutions (gray curves) fit well with simulations (black dots). Notice that when the feedback time y is stochastic rather than fixed, the final failure probability is the expectation value of $P_{fail} \mid y$ over all possible y:

$$P_{fail}=\int_0^{+\infty} dy\ g\ (y)\ P_{fail}|y. \quad \text{[S15]}$$

In the physiological condition, P_{fail} is very small, which means $\Delta t << T$. In this situation, Eq. **S14** shows that P_{fail} is approximately linear with respect to the value of y. Therefore, P_{fail} is determined by the mean value of y—namely, the mean response time Δt of the feedback.

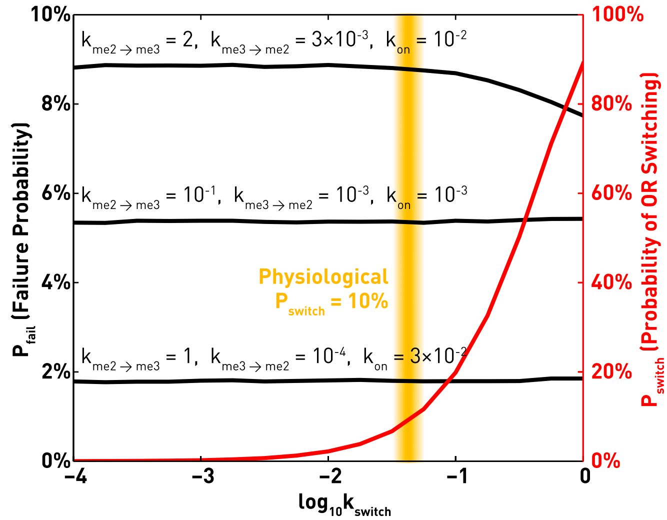

Fig. S2. Switching between ORs only marginally affects singularity under the physiological condition, even if the response time of the feedback is primarily determined by OR or *Adcy3* accumulation. In the main text (Fig. 3), we have assumed that the depletion of *Lsd1* is the primary determinant of the feedback response time Δt. Here the accumulation of either OR or *Adcy3* is instead assumed to determine Δt. In this alternative model, OR/*Adcy3* is produced at a rate proportional to the number of active OR alleles, and it decays with a rate α when no alleles are active. The steady-state concentration of OR/*Adcy3* is one when one allele is active, and it turns off *Lsd1* instantly upon reaching a concentration threshold κ. Therefore, we have the response time $\Delta t = \log(1/(1-\kappa))/\alpha$. We find that, similar to the *Lsd1*-limited model in Fig. 3*B*, OR switching at a physiological probability ~10% (yellow region) has negligible effect on the extent of singularity in this OR/*Adcy3*-limited model. In addition, changes in singularity are only apparent with a relatively large failure probability (e.g., the top black curve). The discrepancy from the *Lsd1*-limited case stems from the fact that OR/*Adcy3* production is assumed to increase when multiple alleles are active, which makes the system more likely to end up with multiple ORs and thus undermines the enhancement of singularity. Each data point is the mean of 10^6 simulations, with $\alpha = 0.1$ and $\kappa = 0.2$ (corresponding to $\Delta t \sim 2.23$).

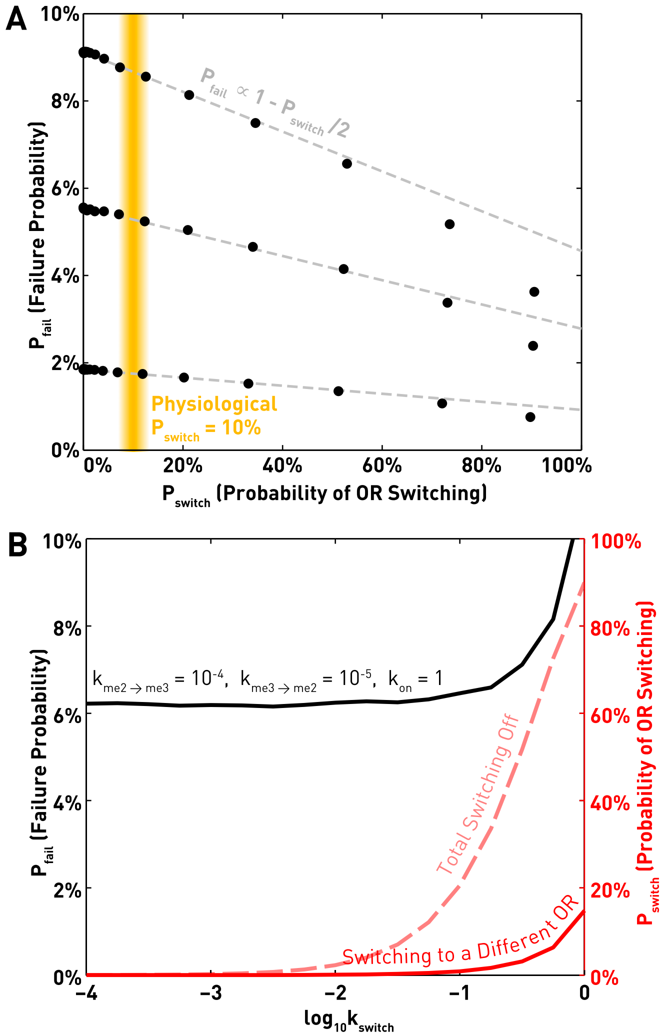

Fig. S3. Analytical calculation confirms that switching between ORs does not significantly facilitate singularity. (*A*) In most cases, when an active OR is turned off, it is unlikely to be turned on again before another OR is activated. Under this approximation, the switching probability (P_{switch}) can be calculated as the probability that the lifetime of an on state (denoted t_{on}) is shorter than the time Δt for the feedback to take effect. Therefore,

$$P_{switch} = P(t_{on} < \Delta t) = \int_0^{\Delta t} k_{switch} \exp(-k_{switch} t_{on}) dt_{on} = 1 - \exp(-k_{switch} \Delta t), \quad \textbf{[S1]}$$

which fits well with the red lines in Fig. 3*B* and in Fig. S2. The failure probability (P_{fail}) can be calculated as the probability that the two following conditions are both met: The competing allele is activated within Δt after the earlier allele, and it remains on until the feedback takes effect. Therefore, if we denote the time difference between the first and the second activations as $\Delta x = x_{(2)} - x_{(1)}$ (using the notation in Fig. S1), we have

$$\begin{aligned} P_{fail} &= P(\Delta t - t_{on} < \Delta x < \Delta t) = P(\Delta x < \Delta t) - P(\Delta x < \Delta t - t_{on} \text{ and } t_{on} < \Delta t) = P_{fail}(k_{switch} = 0)[1 - P_{switch}\ \mathrm{E}(t_{on} | t_{on} < \Delta t)/\Delta t] \\ &= P_{fail}(k_{switch} = 0)[2 - (1 - \exp(-k_{switch}\Delta t))/(k_{switch}\Delta t)]. \end{aligned} \quad \textbf{[S2]}$$

When switching is not so frequent ($k_{switch}\Delta t << 1$), the above expressions become

$$P_{switch} \approx k_{switch} \Delta t \quad \textbf{[S3]}$$

and

$$P_{fail} \approx P_{fail}(k_{switch} = 0)(1 - k_{switch}\Delta t/2). \quad \textbf{[S4]}$$

Therefore, P_{fail} is proportional to ($1 - P_{switch}/2$) under our approximations. This prediction (gray dashed lines) fits well with simulations (black dots, same data as in Fig. 3*B*). (*B*) There exists an edge case where the above approximation is not satisfied: If k_{on} is sufficiently large, an allele that is turned off can quickly revive into its on state, before the second allele is activated. This requires both $k_{on} >> k_{me2 \to me3}$ and $1/k_{on} << T$, and an example is shown above. In this case, most events of OR turning off (red dashed line) results in the revival of the same allele, whereas "true" switching between different ORs (red solid line) is relatively rare. We find that switching between ORs actually damages singularity in this case.