Robustness of the BMP morphogen gradient in Drosophila embryonic patterning

BMP成形素浓度梯度在果蝇胚胎发育中的鲁棒性

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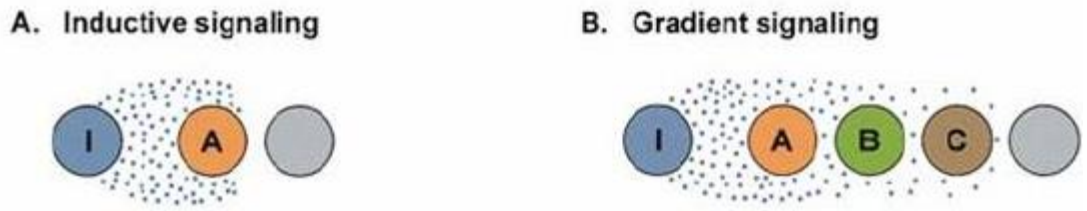
胚胎发育中的信号类型



诱导信号；
梯度信号；

C. 梯度信号：外界信号呈梯度分布，细胞具有不同的响应阈浓度，导致不同的分化命运，随着外界信号浓度高低的不同，细胞的分化结果也不同，通常把在一个

E. 细胞或一个形态发生场中，按浓度梯度决定胚胎分化形式的信号分子叫做成形素（morphogen）。在果蝇中，胚胎的前后轴和背腹轴就是通过这种梯度信号来控制的。

Morphogen：成形素

- BMP(bone morphogenetic protein,骨质成形素蛋白,转化生长因子-β亚家族成员)在果蝇中的异种同源基因是Decapentaplegic (Dpp)

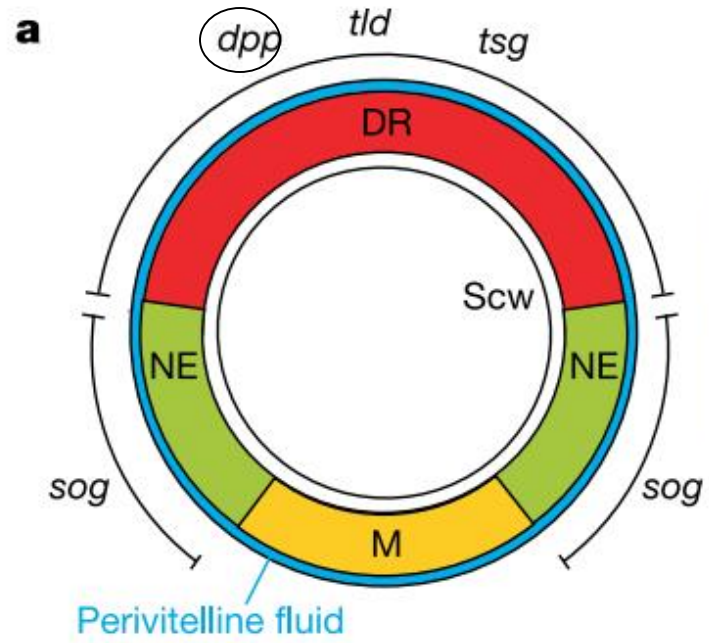
表1 一些诱导信号

信号途径	配体	受体	拮抗物
受体酪氨酸激酶	EGF	EGF受体	Argos
	FGF（branchless）	FGF受体	
	ephrins	Eph受体	
TGFβ家族	TGFβ	TGFβ受体	
	BMP（Dpp）	BMP受体	Chordin（Sog）,noggin
	Nodal		
WNT	WNT	Frizzled	Dikkopf，sFRP，Cerberus
Hedgehog	Hedgehog		
Notch	Delta	Notch	Fringe

Robustness：鲁棒性

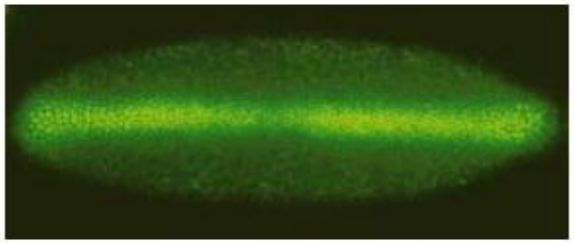
- 所谓“鲁棒性”，是指控制系统在一定（结构，大小）的参数摄动下，维持某些性能的特性。
- Developmental patterning relies on morphogen gradients, which generally involve feedback loops to buffer against perturbations caused by fluctuations in gene dosage and expression.

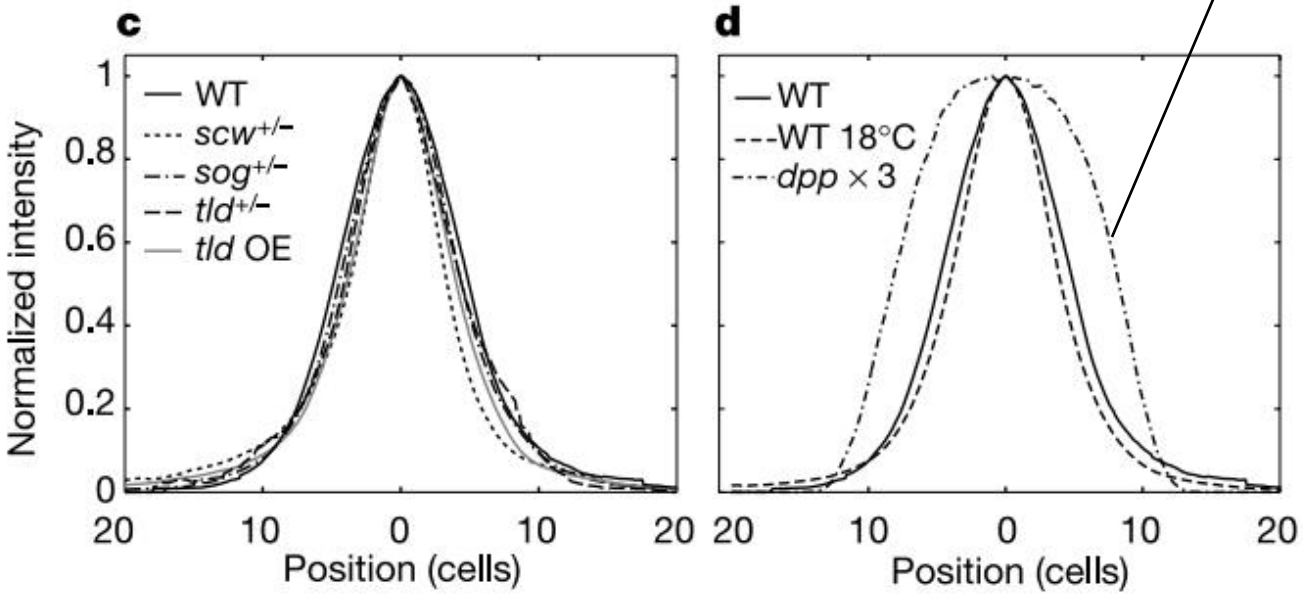
BMP信号通路



b

Dpp is exceptional among morphogens





Scw :BMP class ligand
Dpp:BMP class ligand

Sog:BMP inhibitor
Tsg: an accessory protein

Tld:protease that cleaves Sog

How to explain ?

No apparent transcriptional feedback, which might account for the robustness of dorsal patterning, has been identified so far.

Whether robustness is achieved at the initial activation gradient ?

To identify the mechanism underlying robustness, we formulated a general mathematical model of the dorsal patterning

Three reaction–diffusion equations

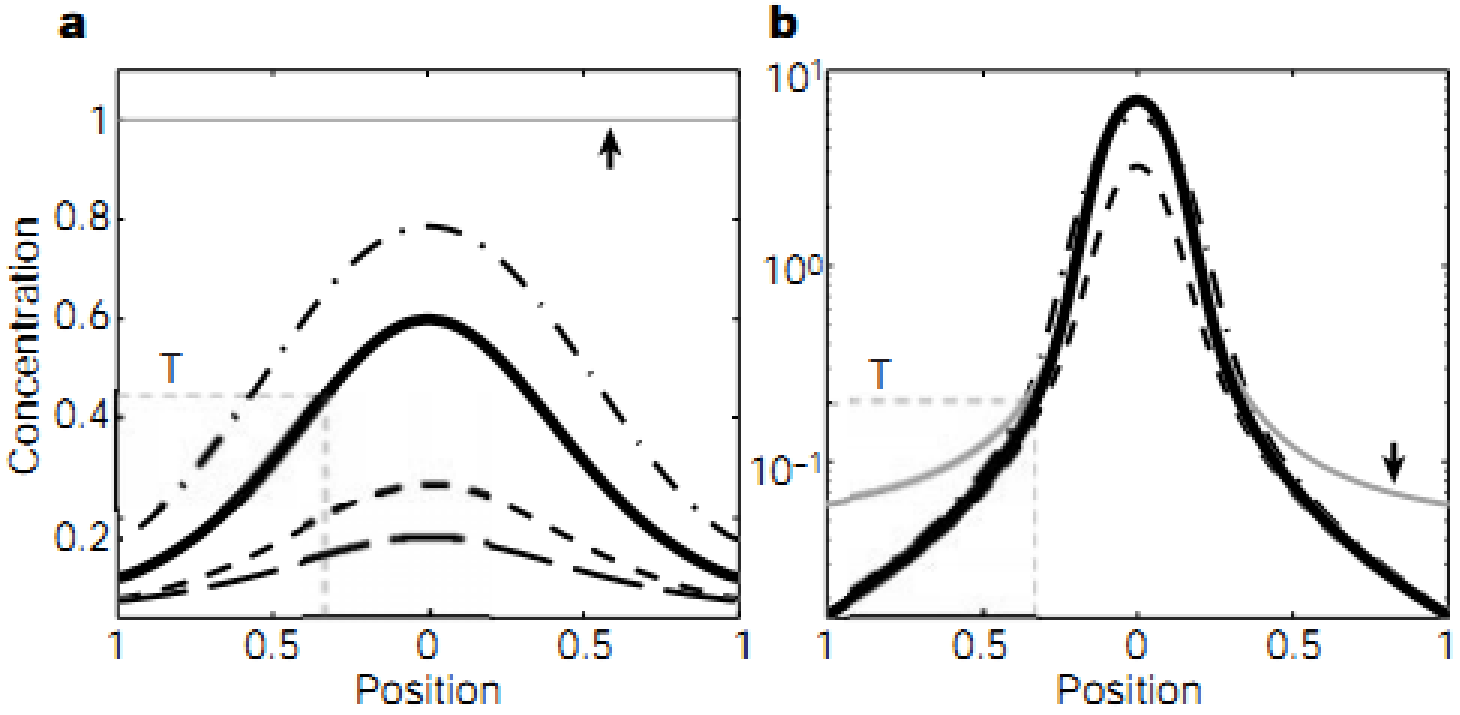
$$\frac{\partial[\mathrm{Sog}]}{\partial t} = D_S \nabla^2[\mathrm{Sog}] - k_b[\mathrm{Sog}][\mathrm{Scw}] + k_{-b}[\mathrm{Sog{-}Scw}] - \alpha[\mathrm{Tld}][\mathrm{Sog}] \quad (1)$$

$$\frac{\partial[\mathrm{Scw}]}{\partial t} = D_{\mathrm{BMP}} \nabla^2[\mathrm{Scw}] - k_b[\mathrm{Sog}][\mathrm{Scw}] + \lambda[\mathrm{Tld}][\mathrm{Sog{-}Scw}] + k_{-b}[\mathrm{Sog{-}Scw}] \quad (2)$$

$$\frac{\partial[\mathrm{Sog{-}Scw}]}{\partial t} = D_C \nabla^2[\mathrm{Sog{-}Scw}] + k_b[\mathrm{Sog}][\mathrm{Scw}] - k_{-b}[\mathrm{Sog{-}Scw}] - \lambda[\mathrm{Tld}] \times [\mathrm{Sog{-}Scw}] \quad (3)$$

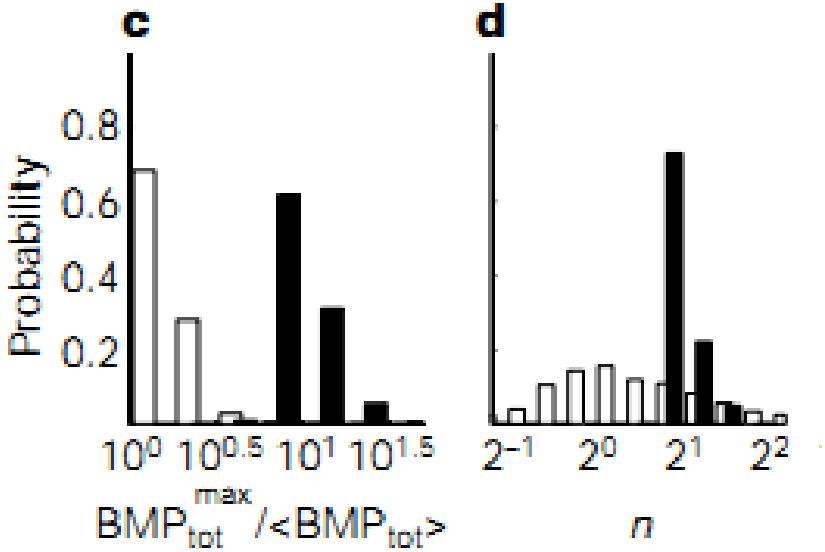
Over 66,000 simulations were carried out, with each of the nine parameters allowed to vary over four orders of magnitude.

The extent of network robustness was quantified by measuring the shift in the threshold for all three perturbed networks.



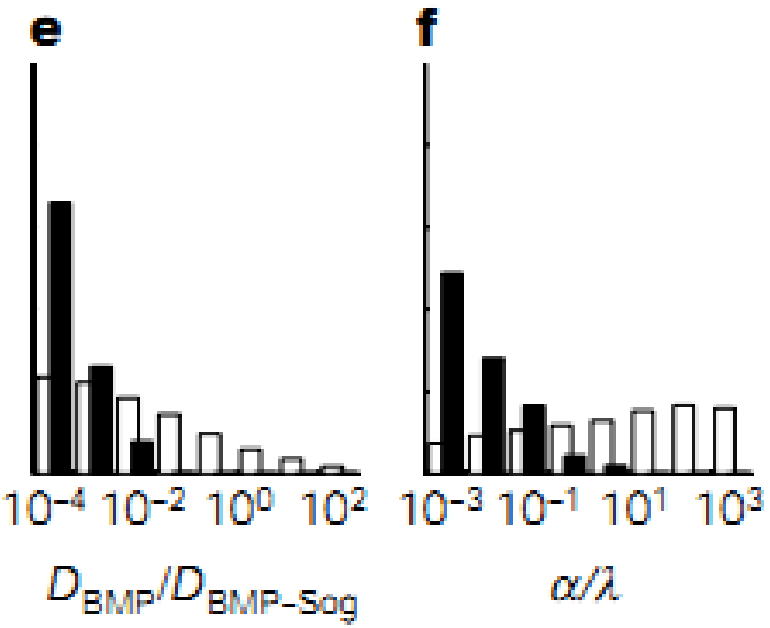
nonrobust (22,000)

robust (198)



c:In all of the robust cases, a high ratio (.10) was observed

d:The steady-state profile of free BMP was fit to a power-low distribution

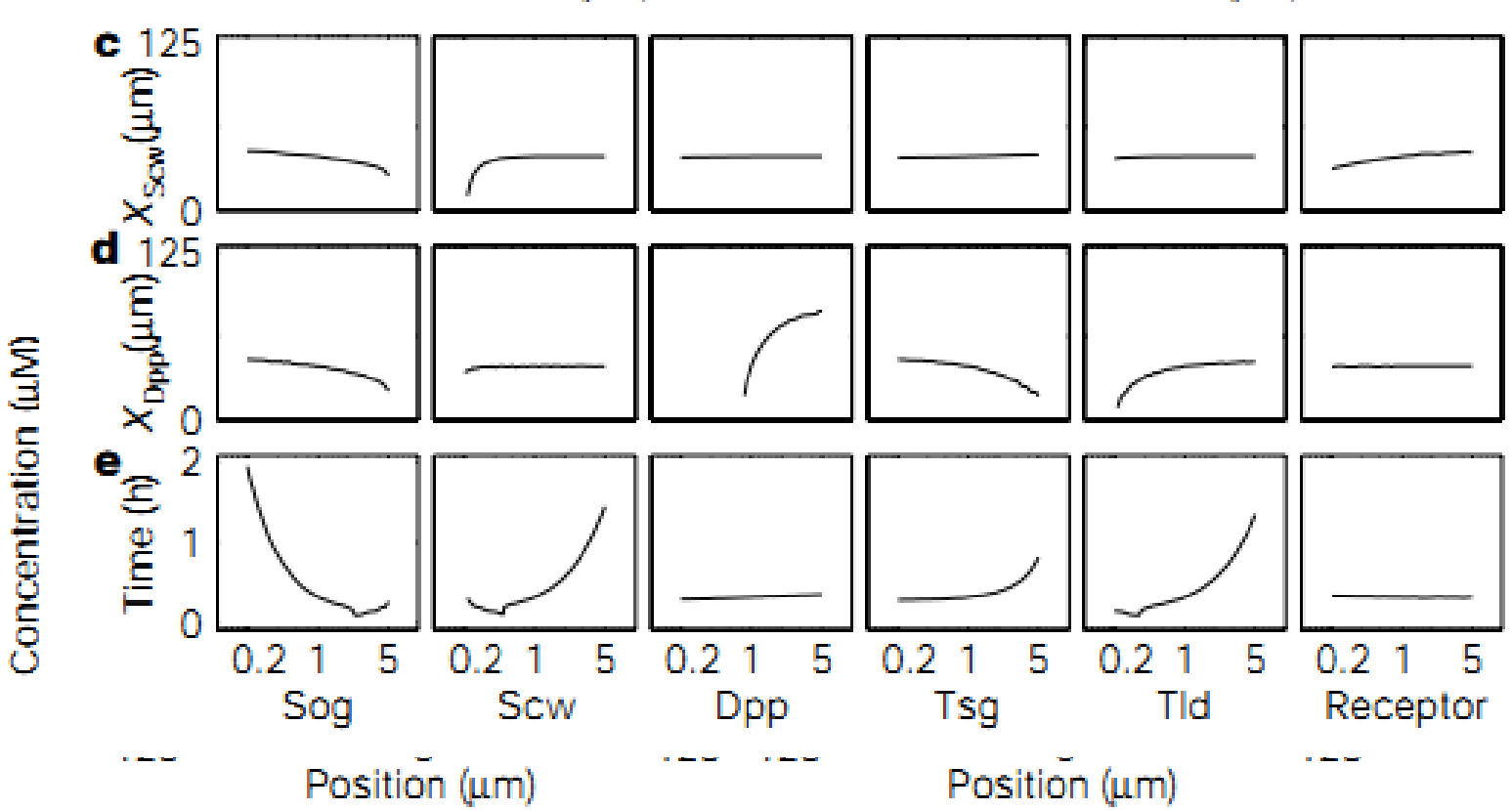


e：Ratio between the diffusion coefficient of free BMP and the complex BMP–Sog

f：Ratio of the degradation rate of free Sog (a) to that of BMP-associated Sog (l)

First, the BMP–Sog complex has a central role, by coupling the two processes that establish the activation gradient: BMP diffusion and Sog degradation.

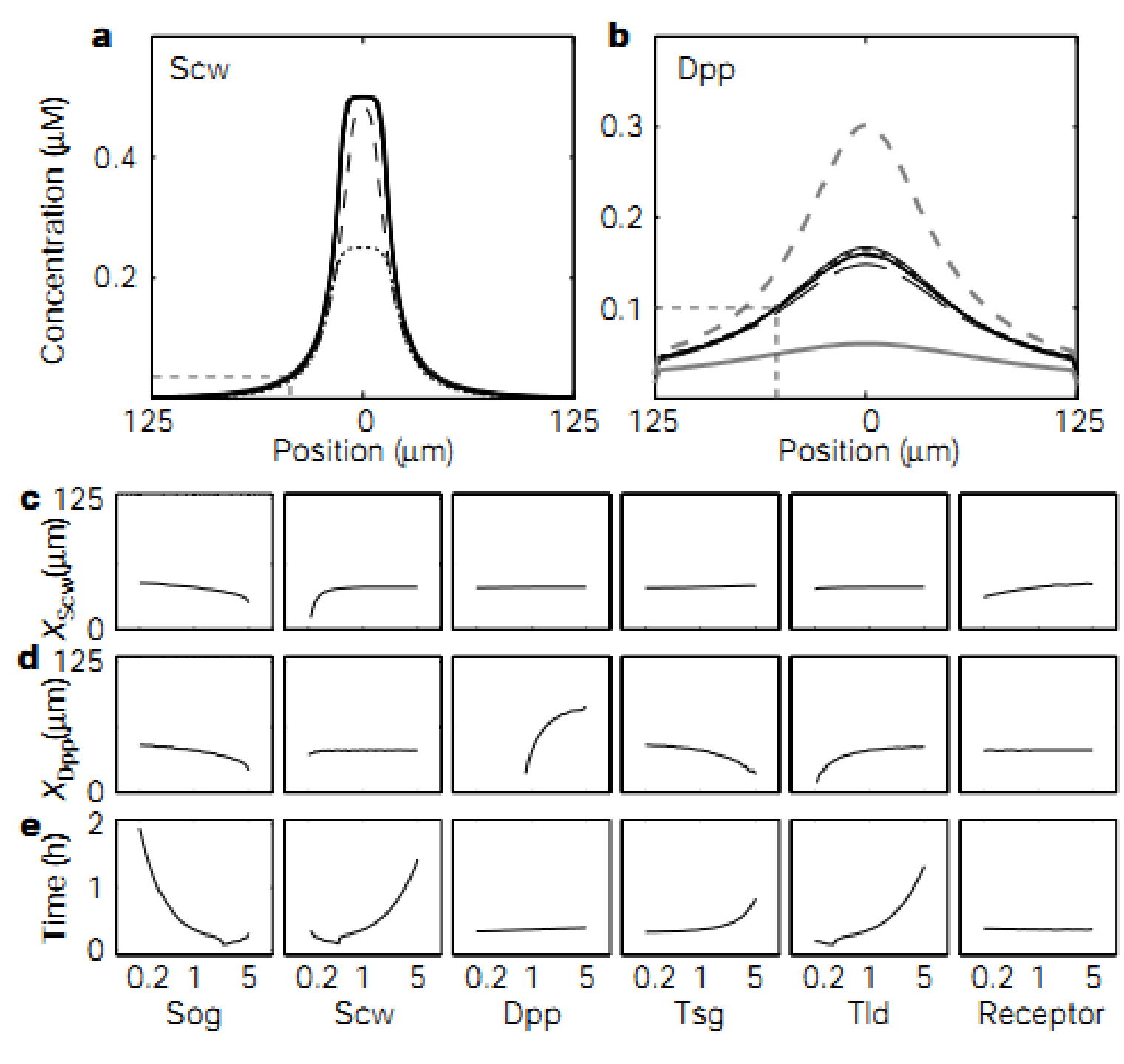
Second, restricted diffusion of free BMP enables the systemto store excess BMP in a confined spatial domain where Sog is largely absent.

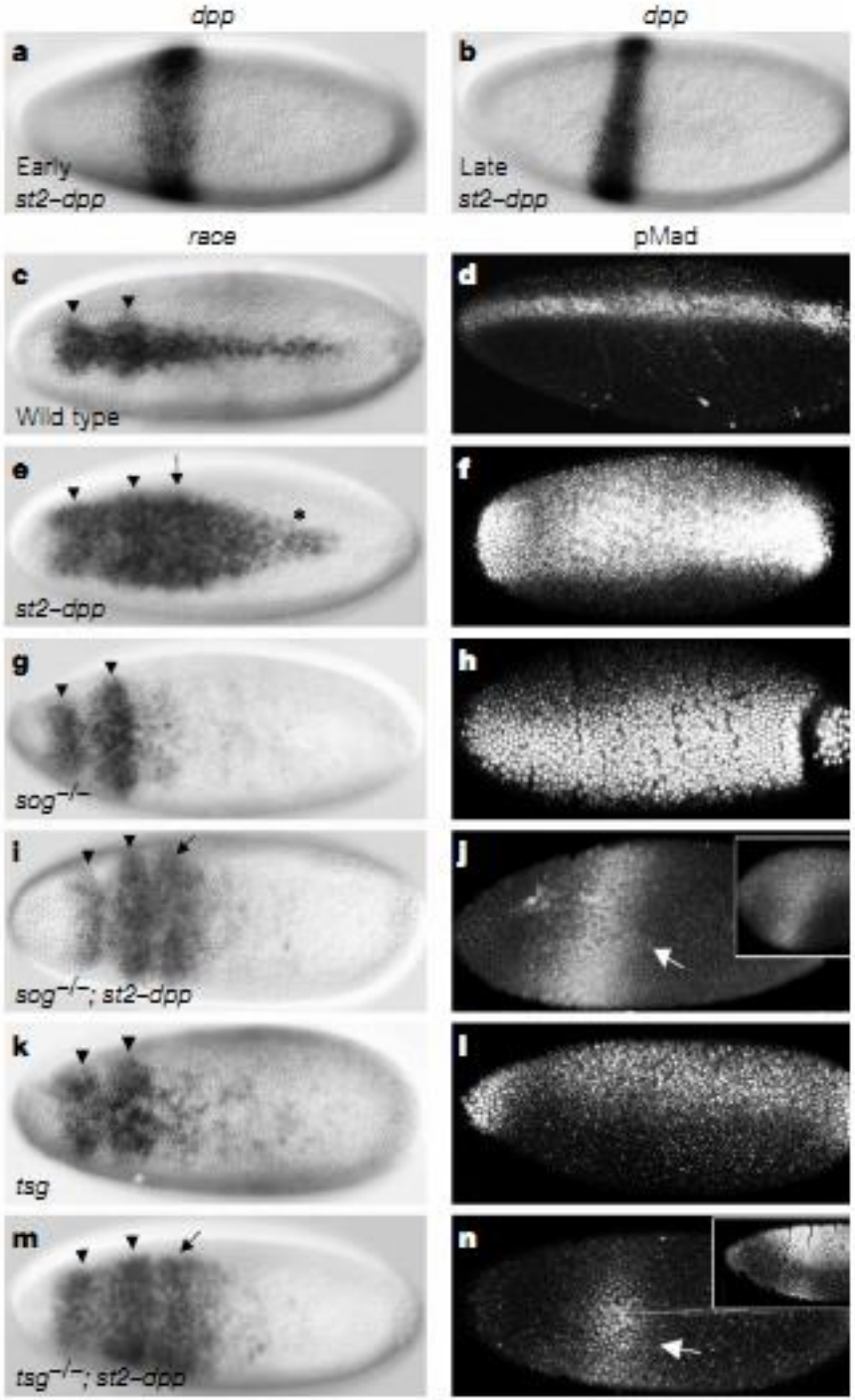


Additional molecular assumptions were required：
Dpp can bind Sog only when the latter is bound to Tsg.

Scw diffusion requires Sog
Dpp diffusion requires both Sog and Tsg.
Dpp is widely diffusible in the presence of Sog but tightly localized in its absence

谢谢！


a
Scw
Concentration (μM)
0.4
0.2
125
0
125
Position (μm)
b
Dpp
0.3
0.2
0.1
125
0
125
Position (μm)
c
125
χ_{Scw}(μm)
0
d
125
χ_{Dpp}(μm)
0
e
Time (h)
2
1
0
0.2 1 5
Sog
0.2 1 5
Scw
0.2 1 5
Dpp
0.2 1 5
Tsg
0.2 1 5
Tld
0.2 1 5
Receptor


dpp
dpp
a
Early
st2–dpp
b
Late
st2–dpp
race
pMad
c
Wild type
d
e
st2–dpp
f
g
sog−/−
h
i
sog−/−; st2–dpp
j
k
tsg
l
m
tsg−/−; st2–dpp
n