A model for the Fat pathways role in cellular polarity and growth regulation

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- Growth and form:

  "An organism is so complex a thing, and growth so complex a phenomenon, that for growth to be so uniform and constant in all the parts as to keep the whole shape unchanged would indeed be an unlikely and an unusual circumstance. Rates vary, proportions change, and the whole configuration alters accordingly." - D'Arcy Thompson

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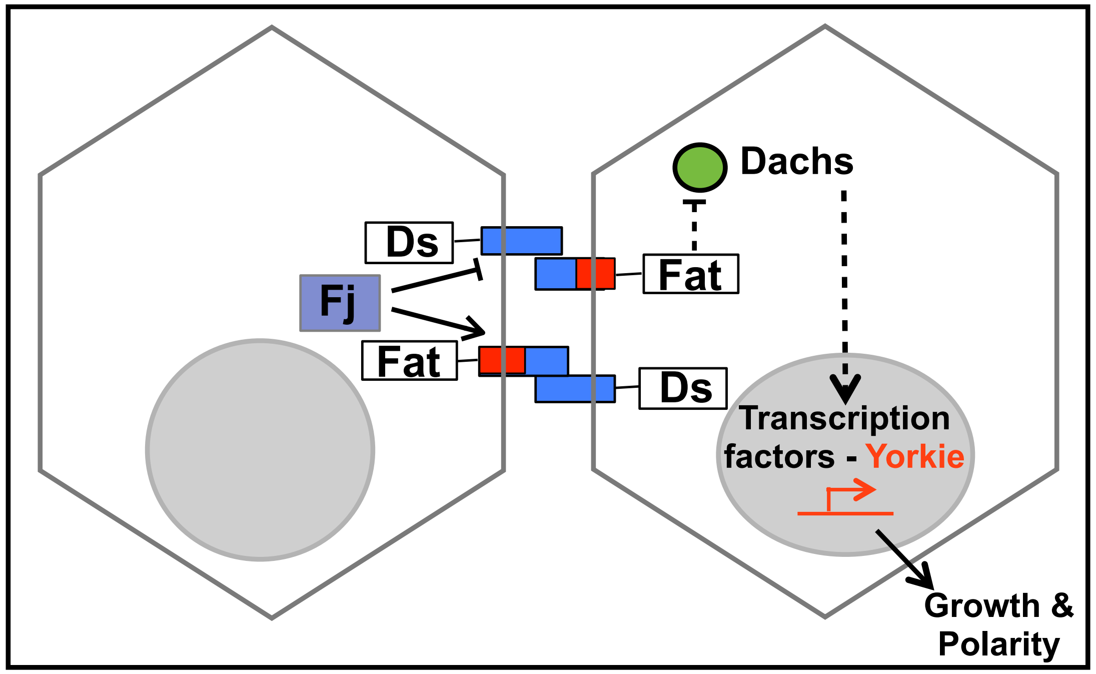
Observations - Who signals to whom? With what molecules?



Note: lacZ

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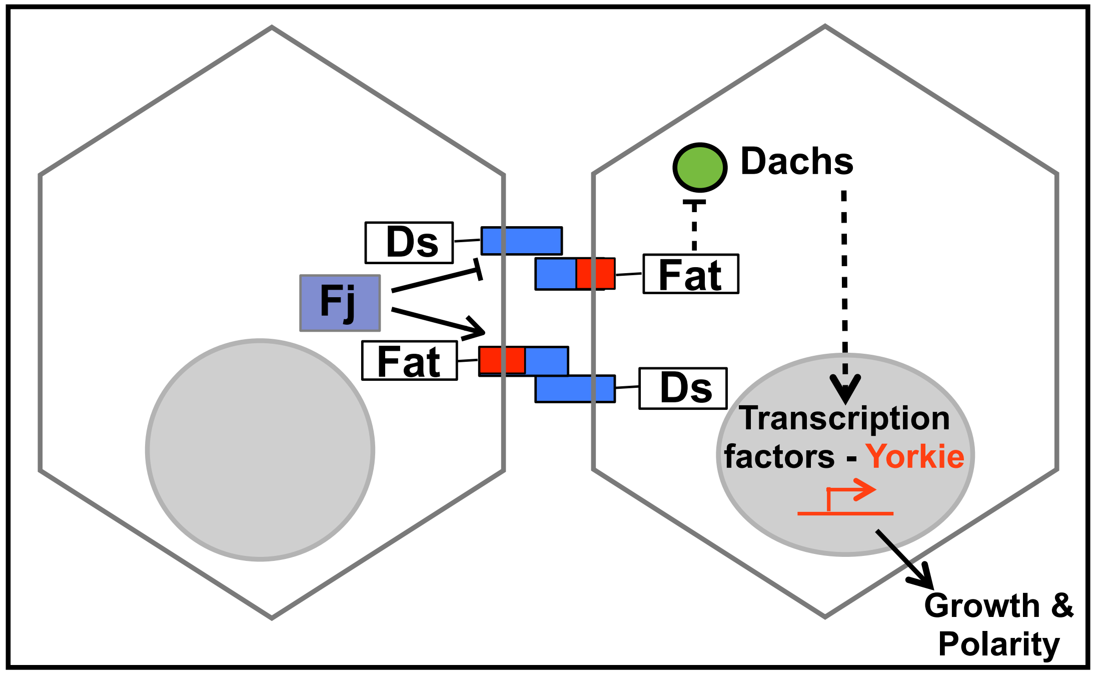
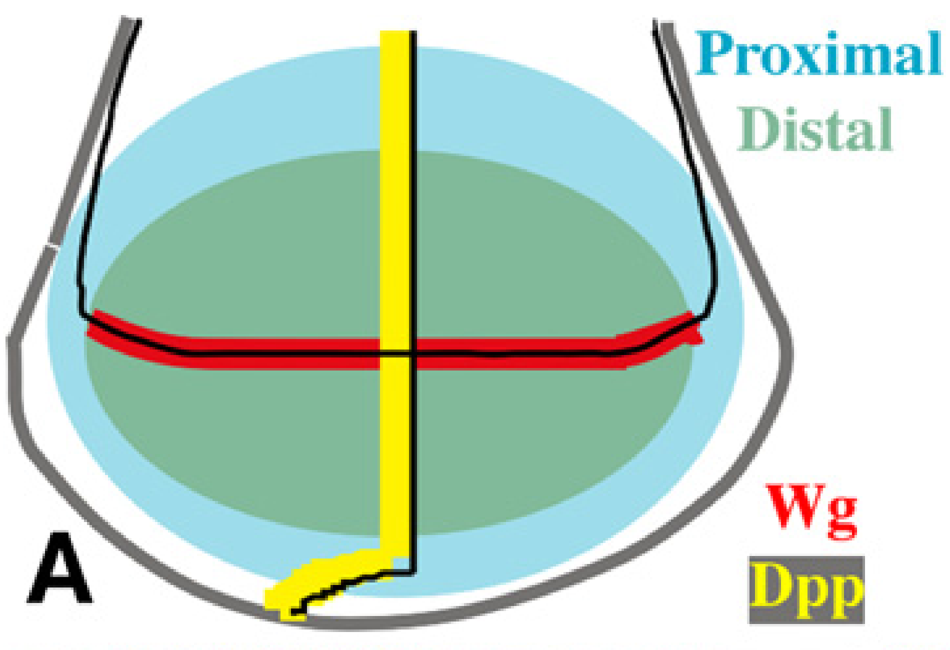
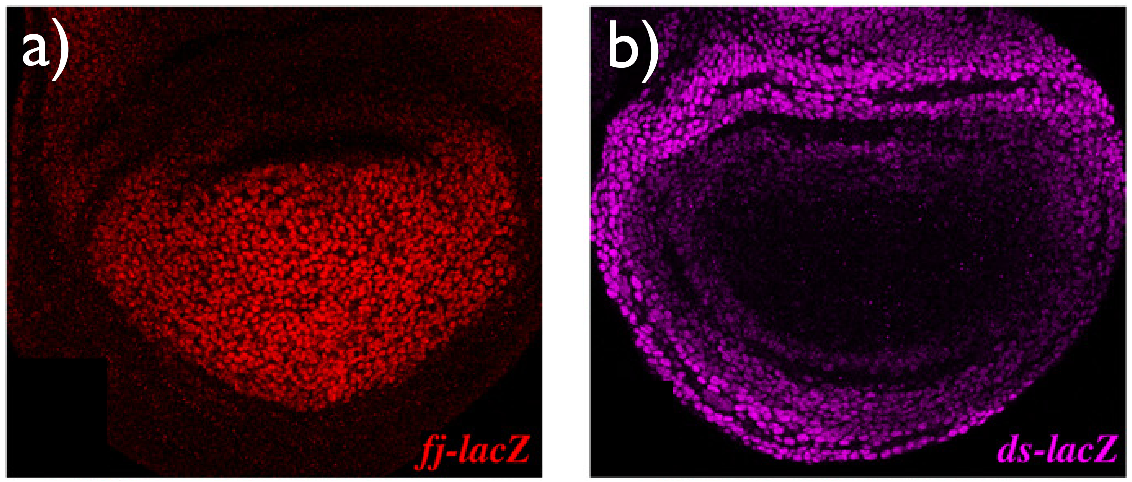


Expression of core components





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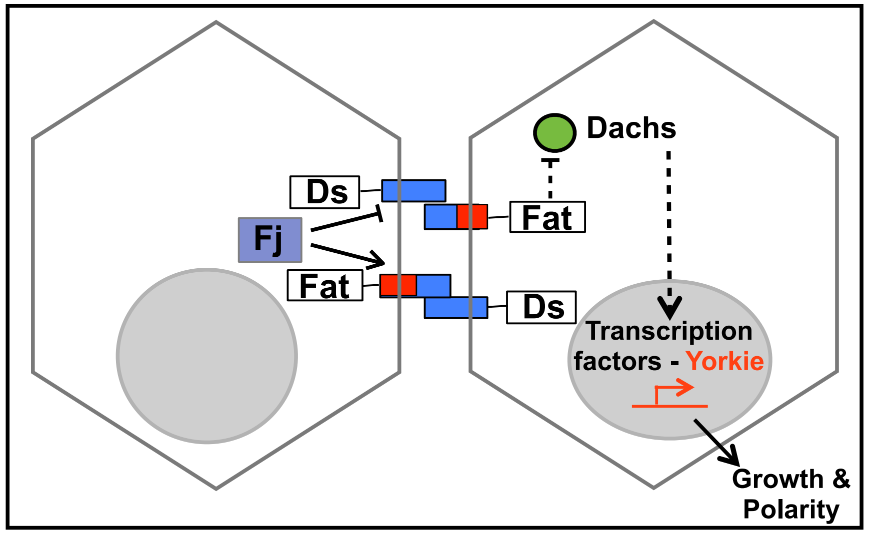

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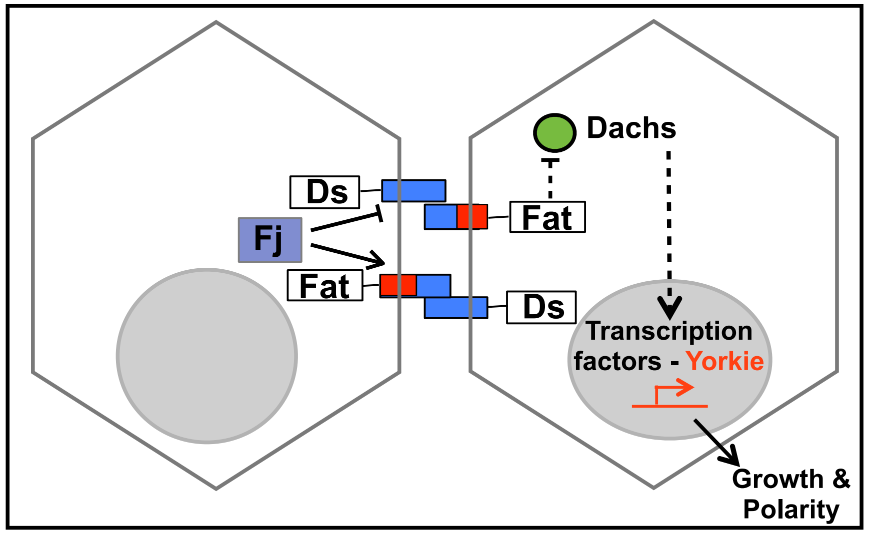

Dachs polarity and build up of nuclear Yorkie

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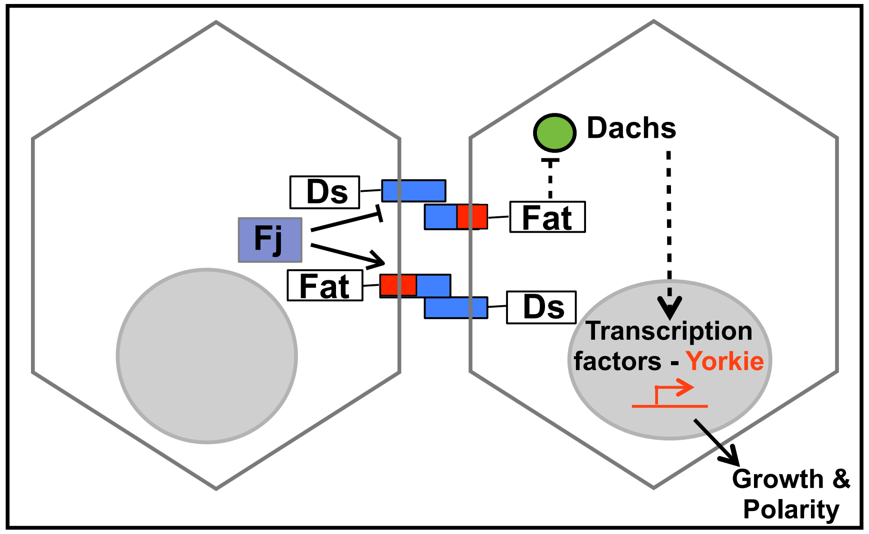

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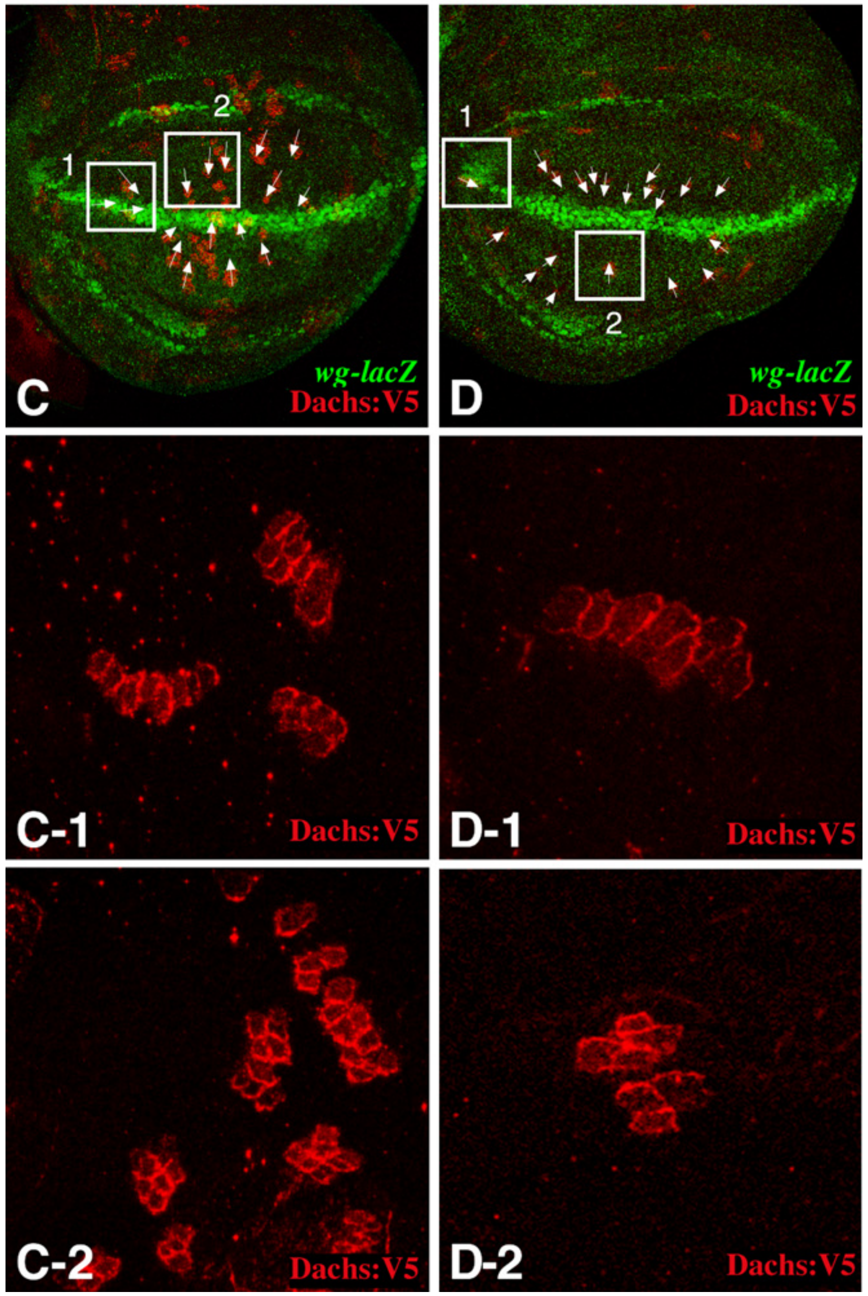

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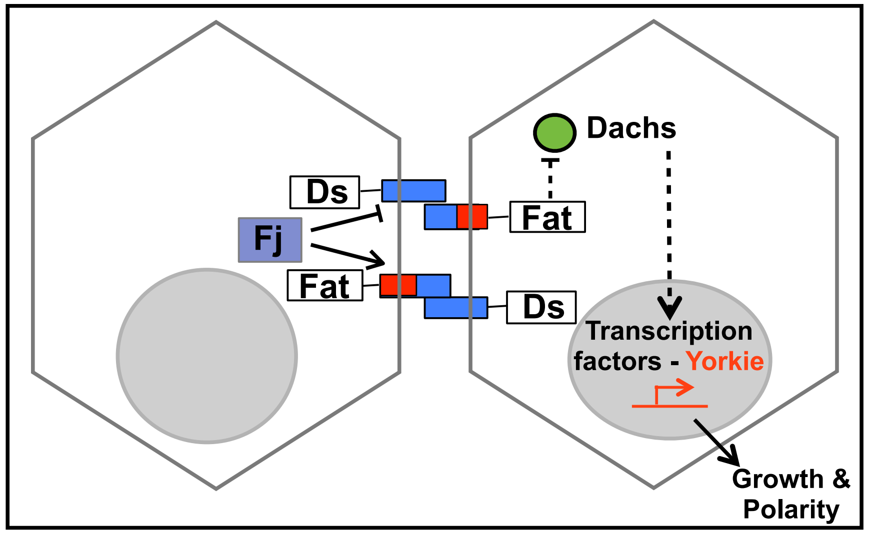

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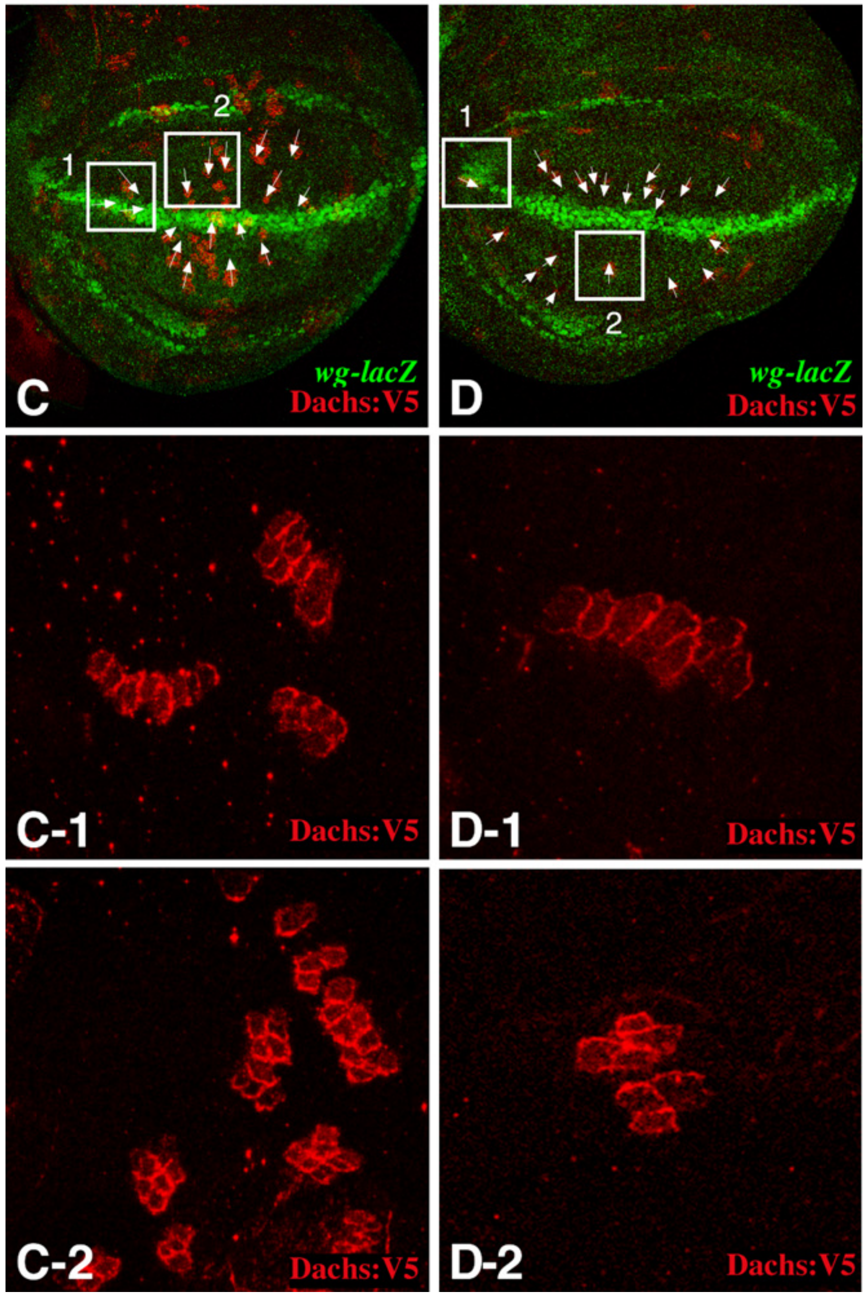
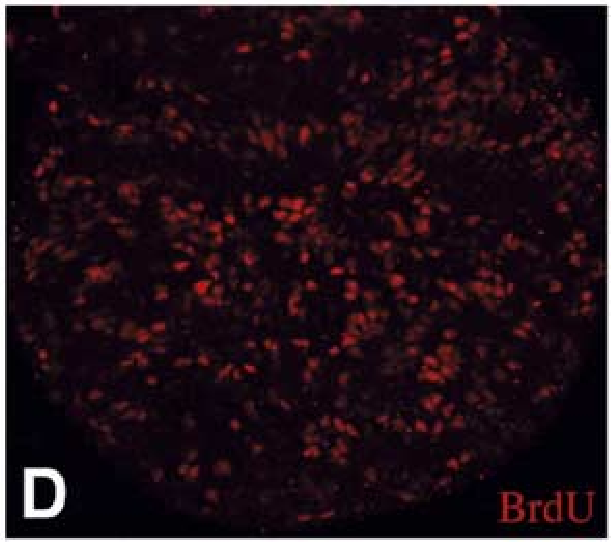
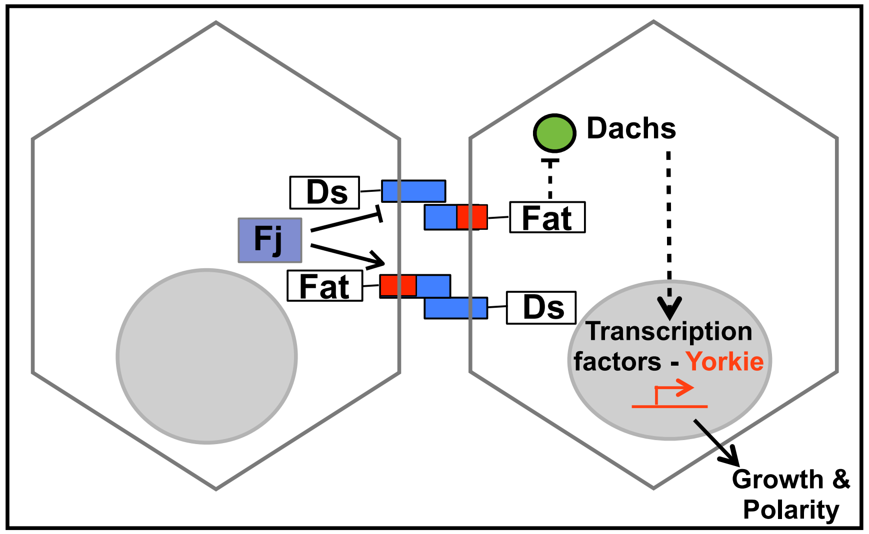
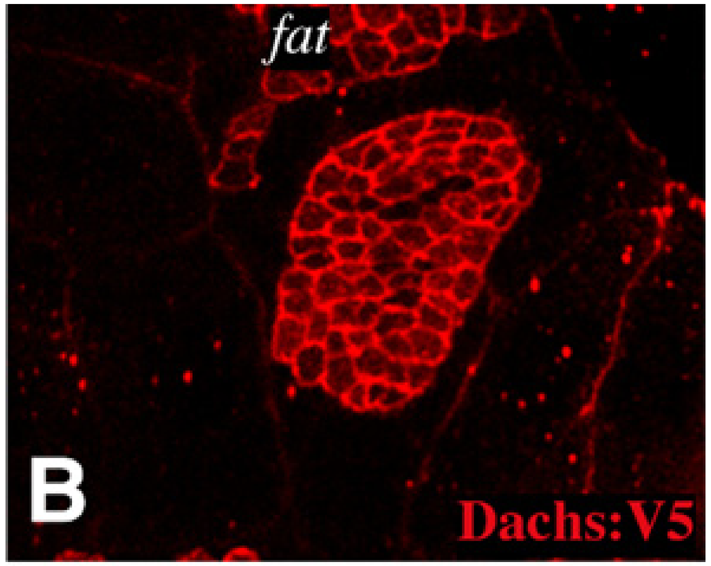
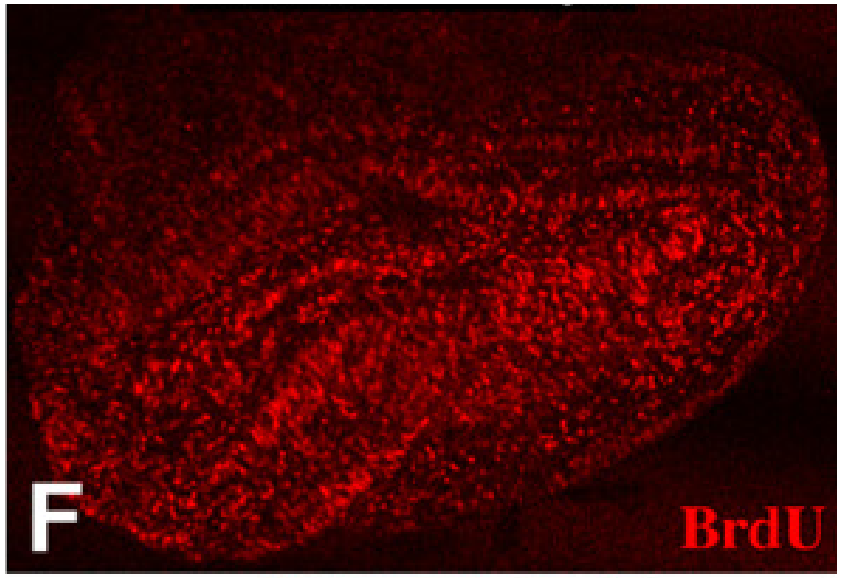




Observations - To what end?







fat mutant → Loss of polarity → overgrowth

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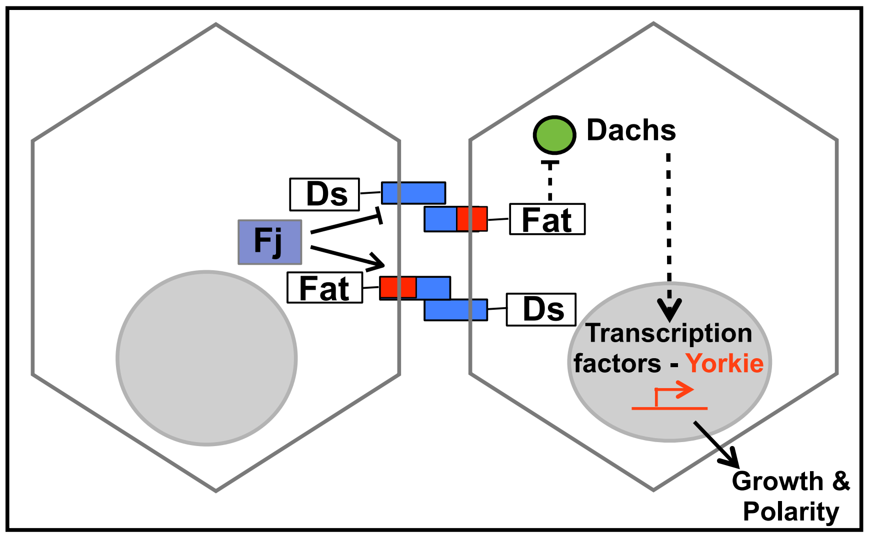
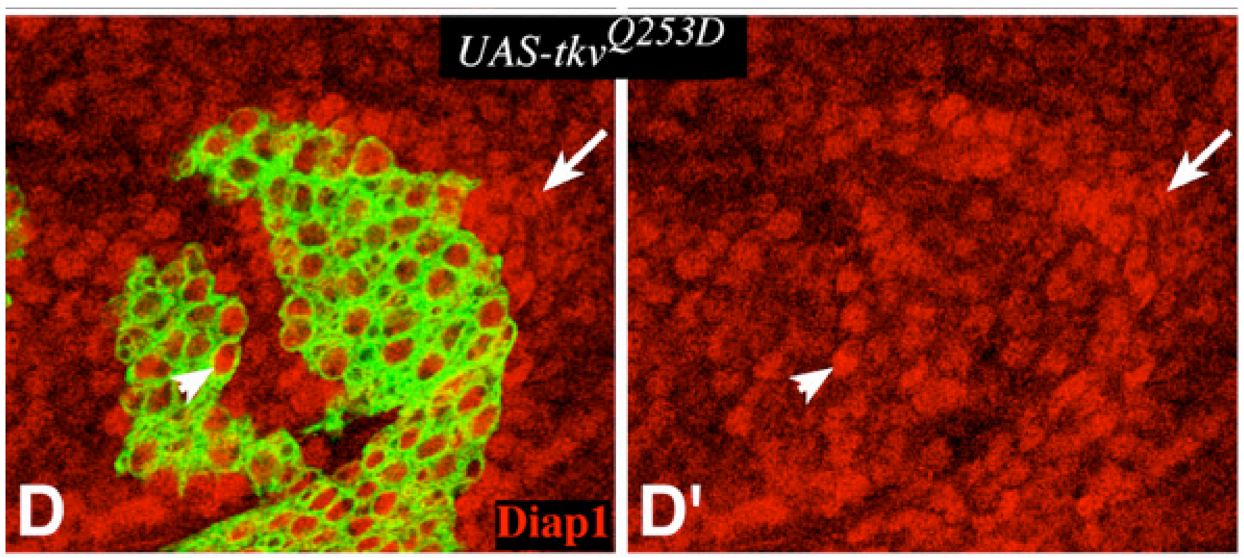


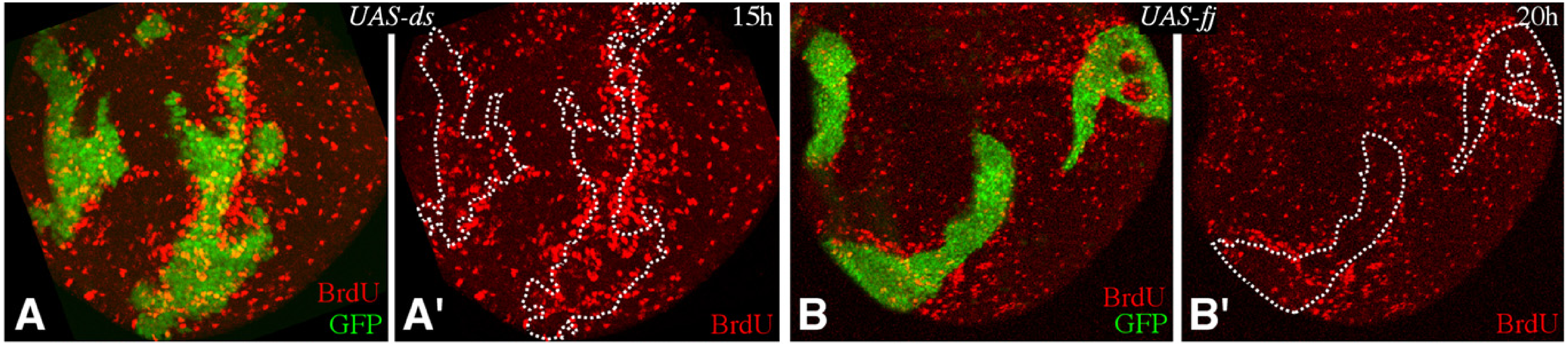
Dpp "gradients" induce growth



tkv: receptor for Dpp (ligand)

Diap1: Apoptosis inhibitor and reporter for Yorkie

"Gradients" in the Fat pathway components induce growth



Key Facts

- Fact 1) Transmembrane interaction & variations in level of core components signal
- Fact 2) Fat pathway is polarized in WT
- Fact 3) Gradients --> Growth

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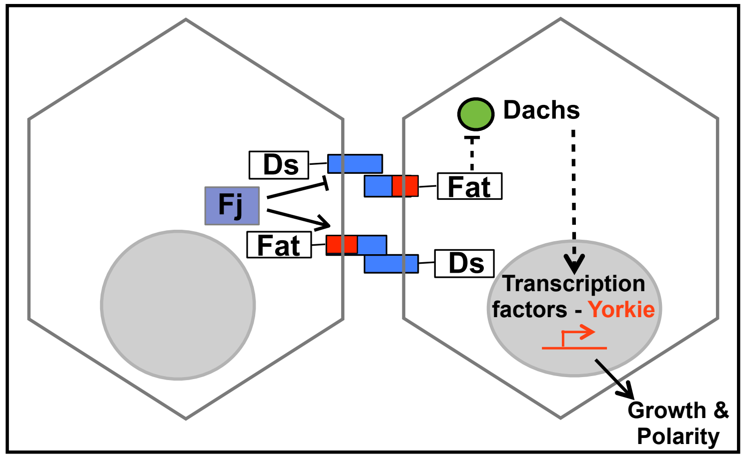
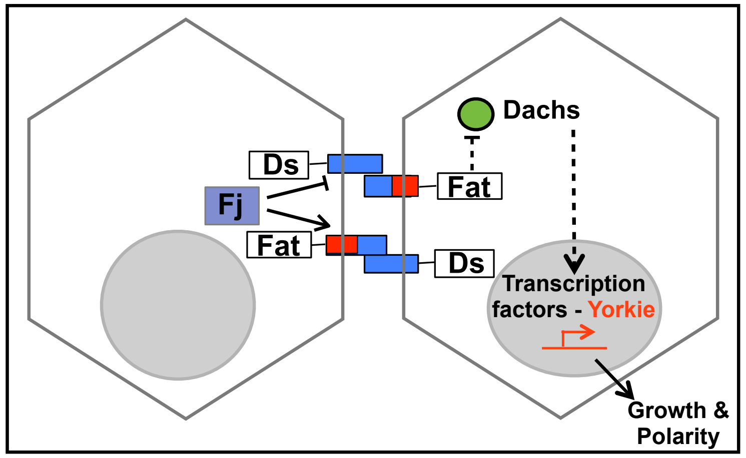
- Input 1) Polarity generating mechanism
- Input 2) Cytosolic read out of polarity

Model


Dachs
Ds
Fj
Fat
Fat
Ds
Transcription factors - Yorkie
Growth & Polarity

Model



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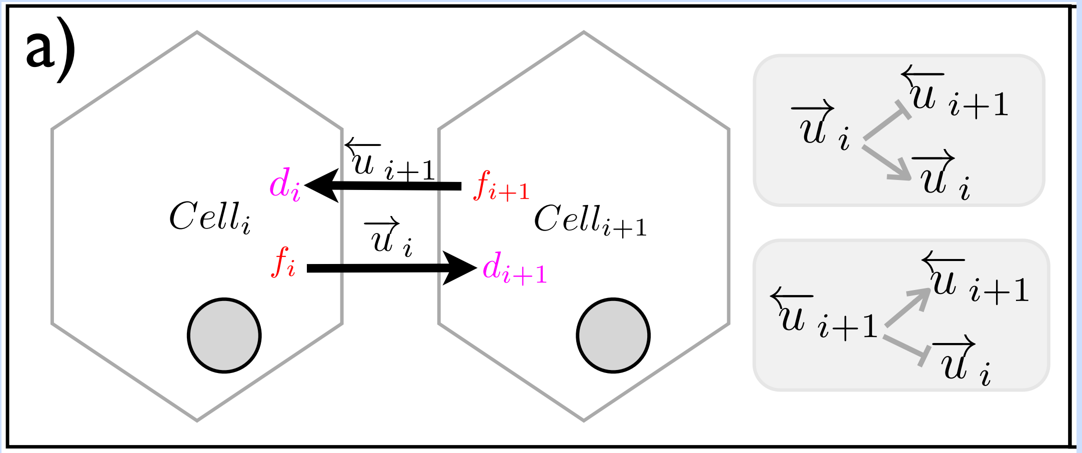

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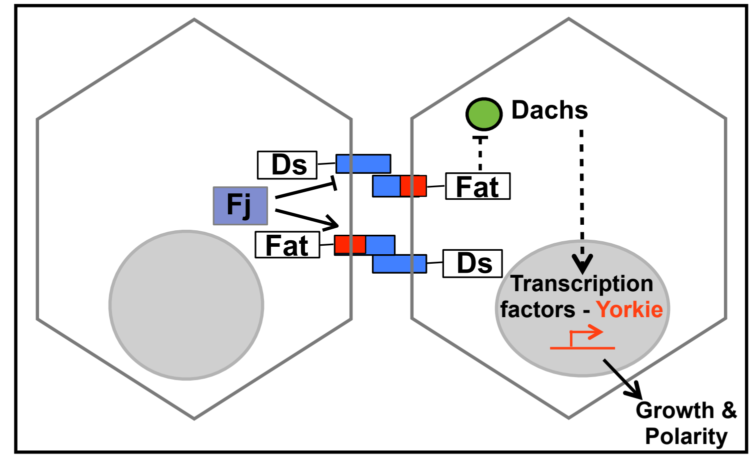

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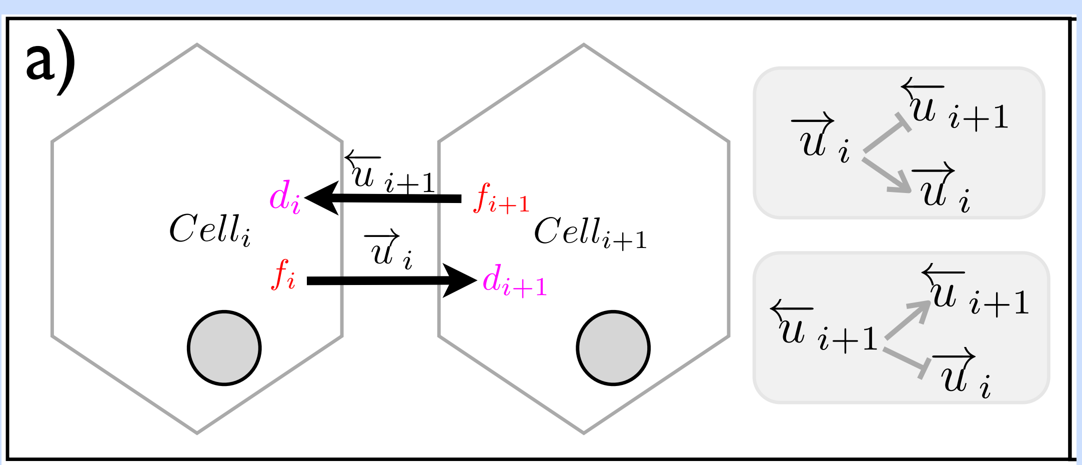

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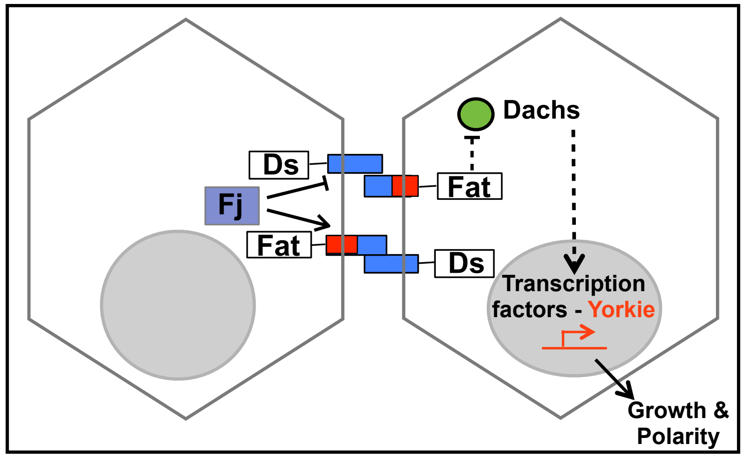

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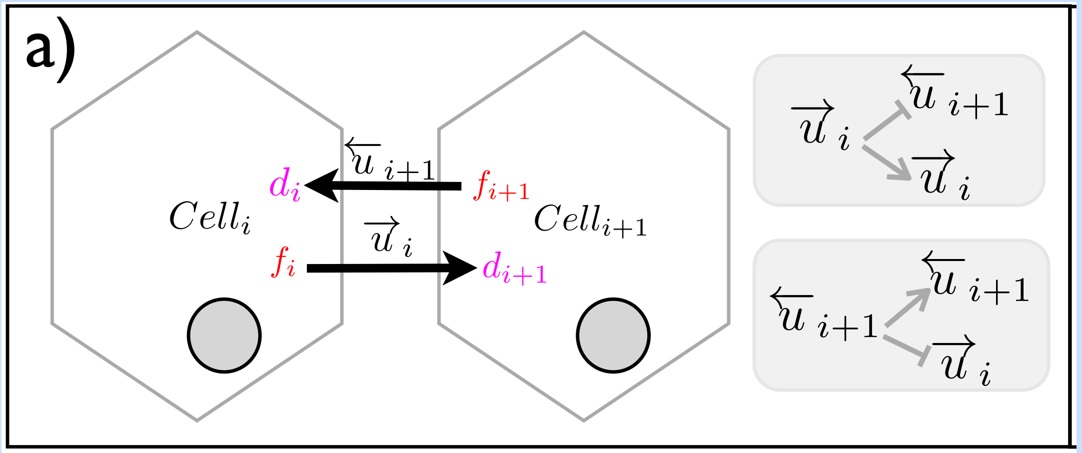

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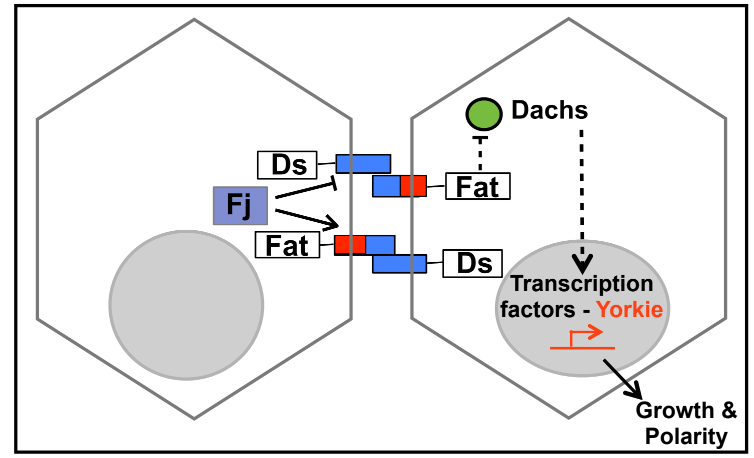

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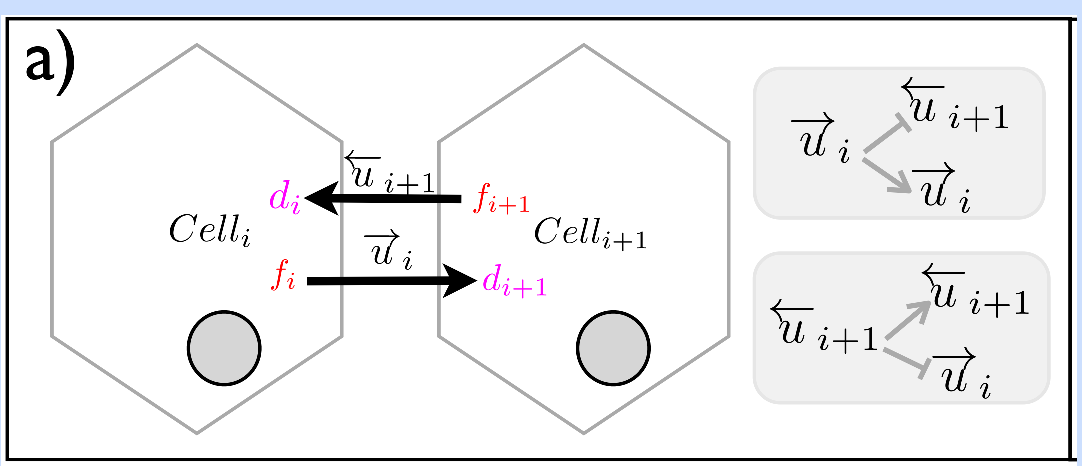

Cytosolic Intermediate

$$\frac{d\overrightarrow{c}_i}{dt} = \sigma_c - \gamma_c\overrightarrow{c}_i - \nu_c\overrightarrow{c}_i\overrightarrow{u}_i^n$$

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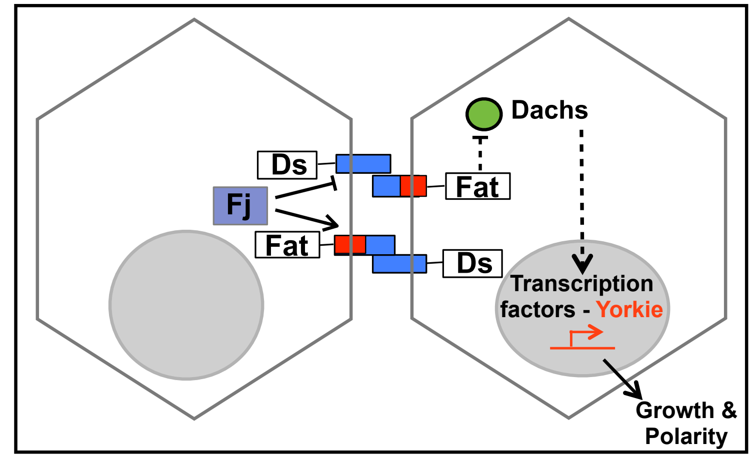

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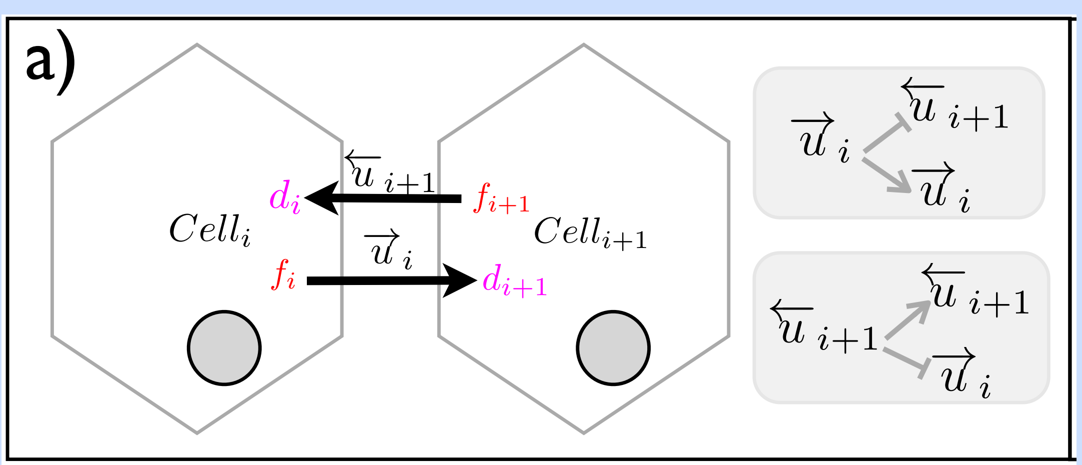

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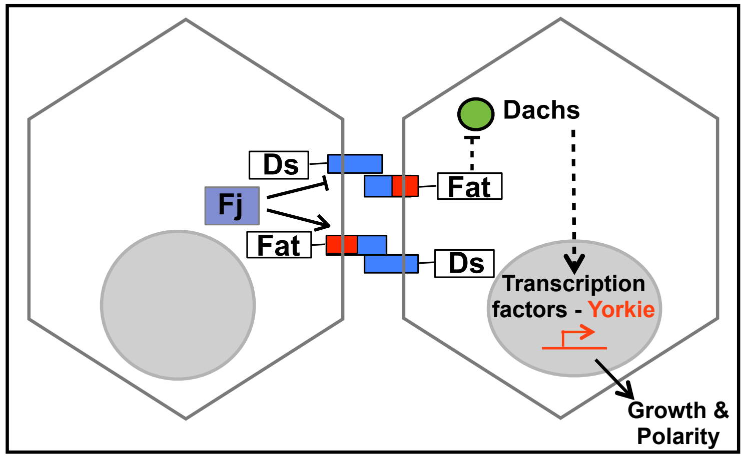
Nuclear Signal

$$\frac{dn_i}{dt} = k_n(\overrightarrow{c}_i + \overleftarrow{c}_i) - \gamma_n n_i$$

Model - Scaled & Steady State



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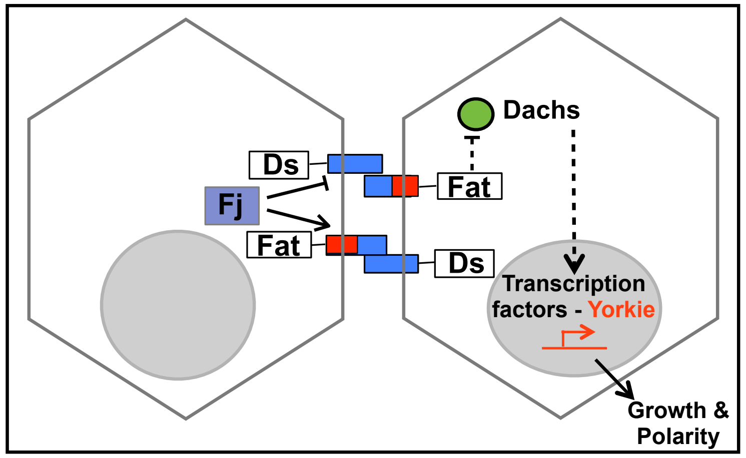

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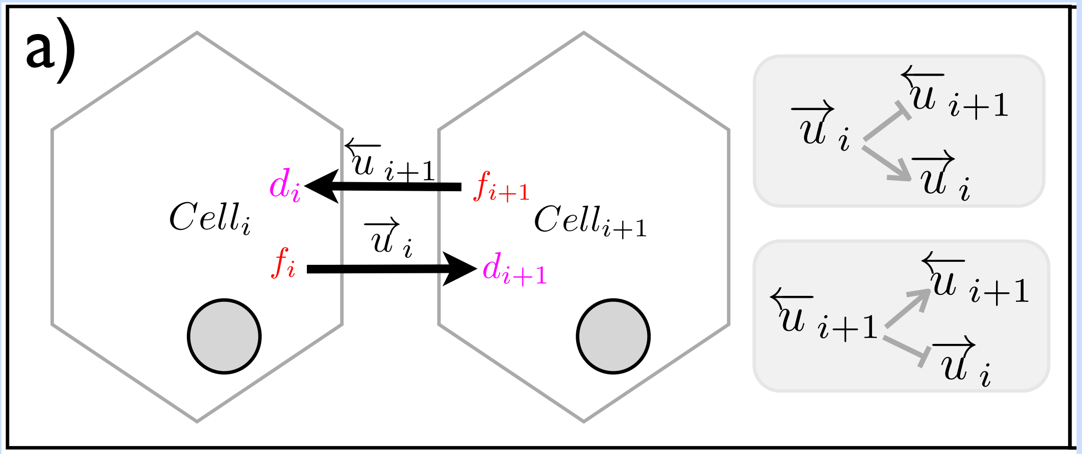

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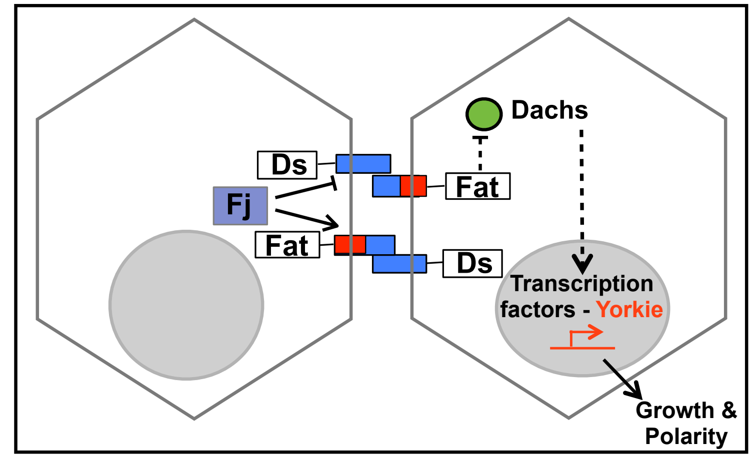

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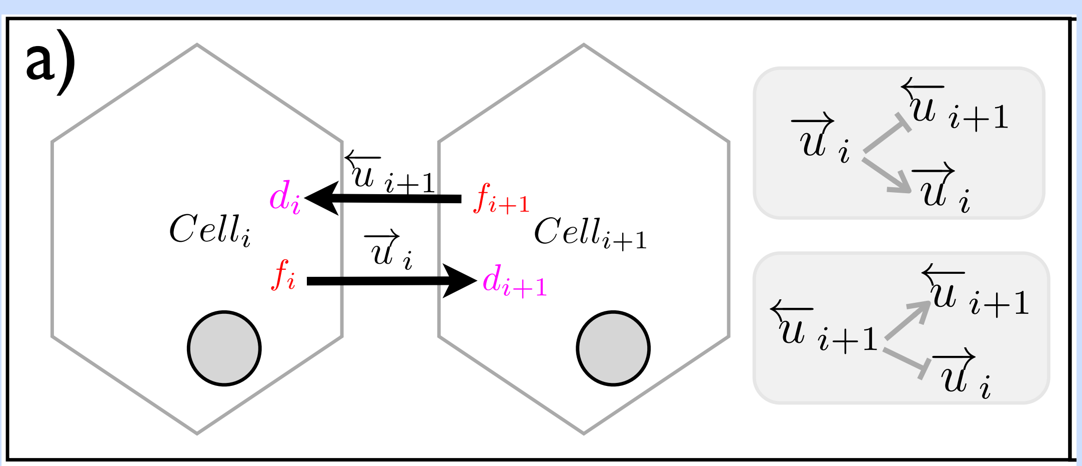

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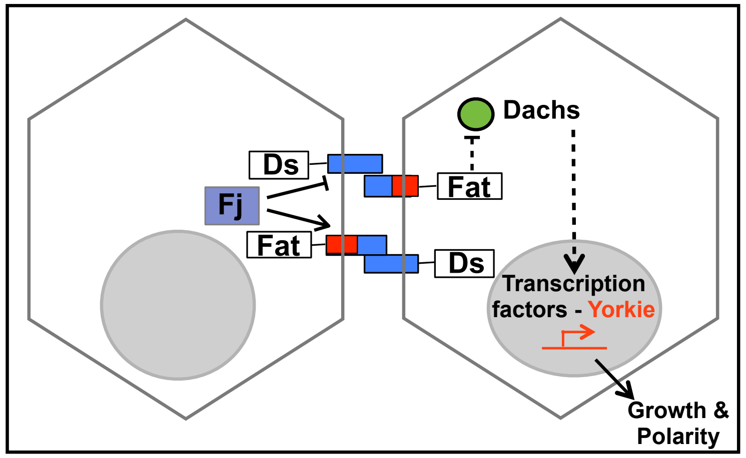

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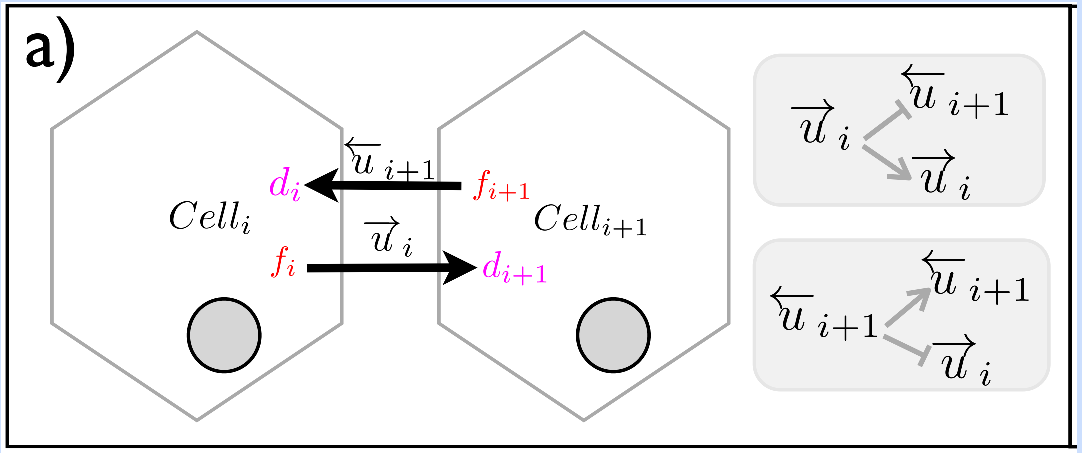

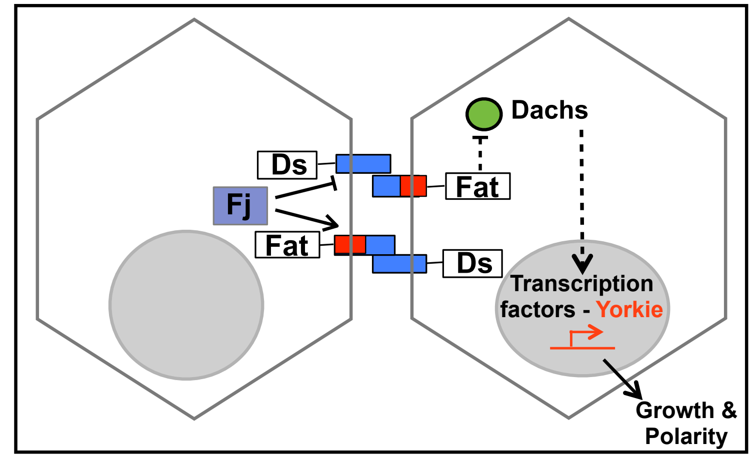

Model - Scaled & Steady State

Transmembrane Interactions

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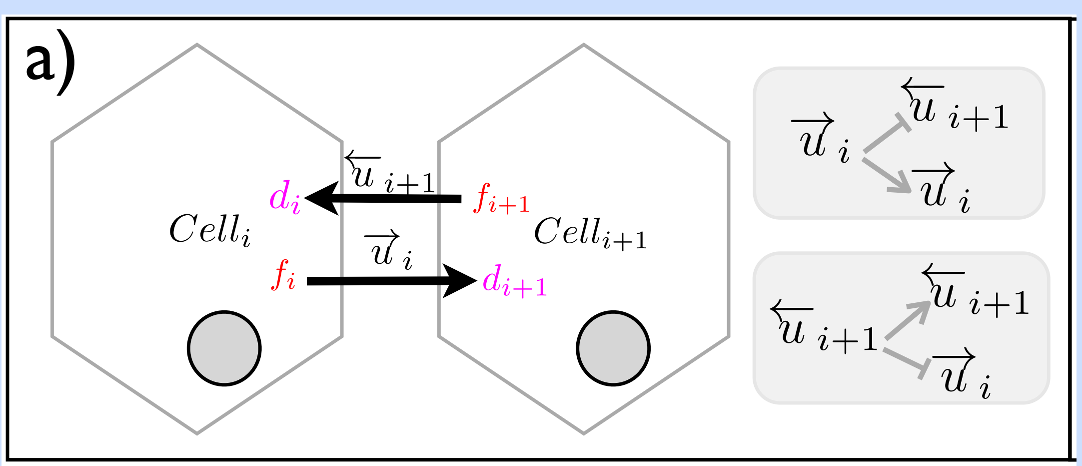

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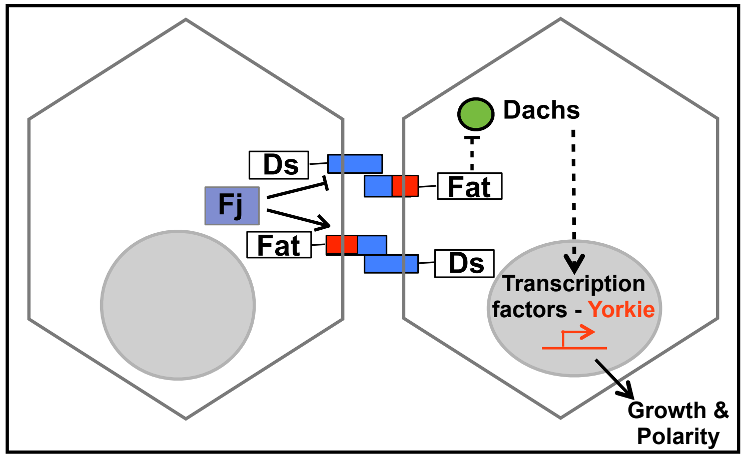

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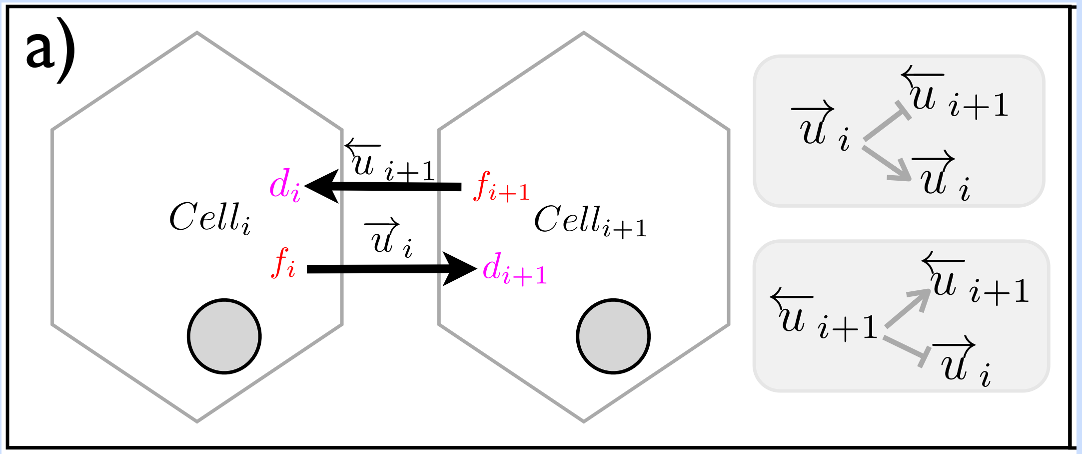

Cytosolic Intermediate

$$\overrightarrow{C}_i = \frac{1}{1+\left(\frac{\overrightarrow{U}_i}{\lambda}\right)^n}$$

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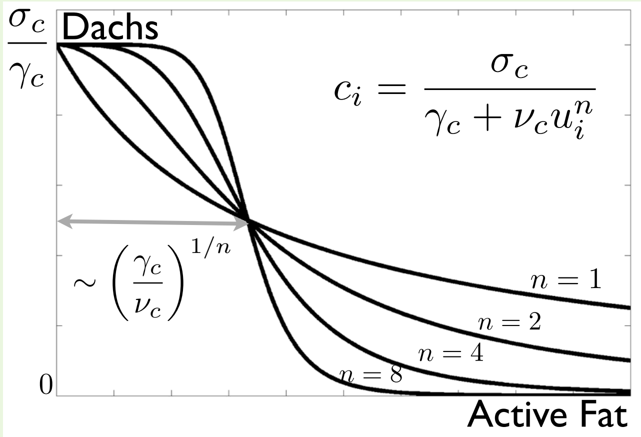
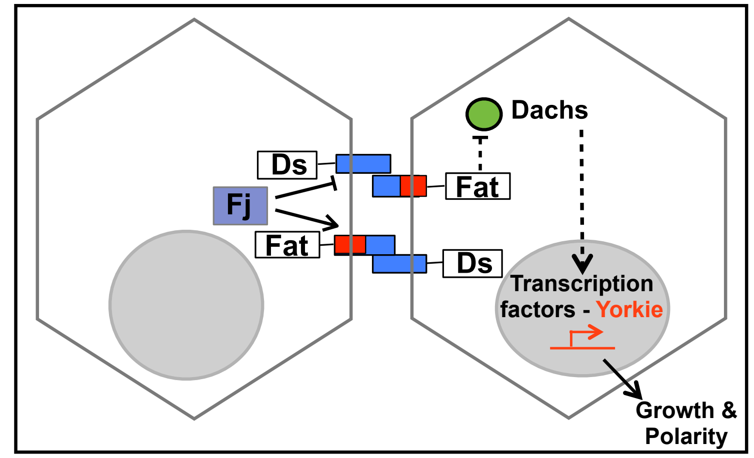


Nuclear Signal

$$N_i = (\overrightarrow{C}_i + \overleftarrow{C}_i)$$



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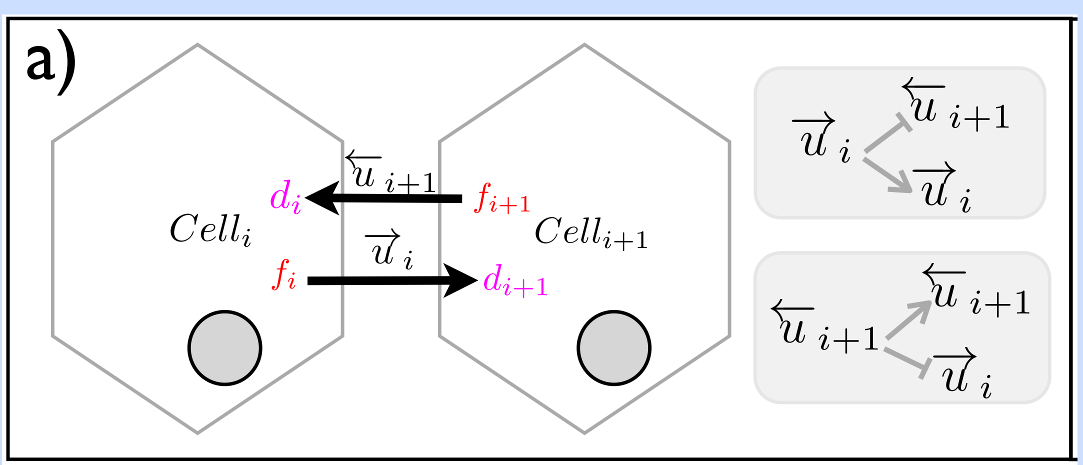

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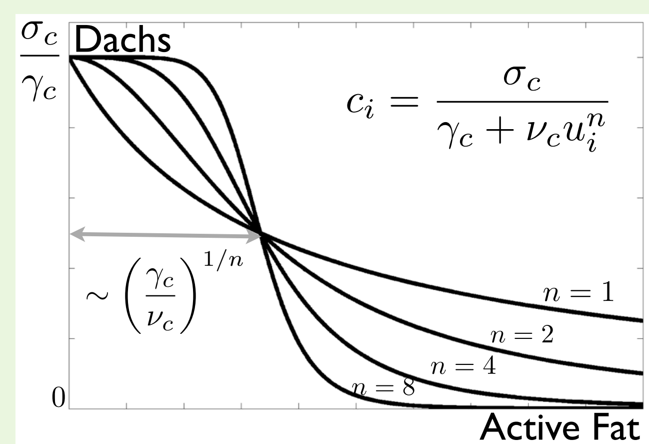

Nuclear Signal

$$N_i = (\overrightarrow{C}_i + \overleftarrow{C}_i)$$

Input: Expression levels of Fat and Dachsous

$F_i^0 \& D_i^0$

↓

Output: Polarity & Growth

$N_i \& \overleftarrow{-}, \overrightarrow{-}$

Analytic solution - Absolute level response

$$\frac{d\overrightarrow{u}_i}{dt} = k_u f_i d_{i+1}(1 + \alpha \overrightarrow{u}_i) - \gamma_u \overrightarrow{u}_i (1 + \beta \overleftarrow{u}_{i+1})$$

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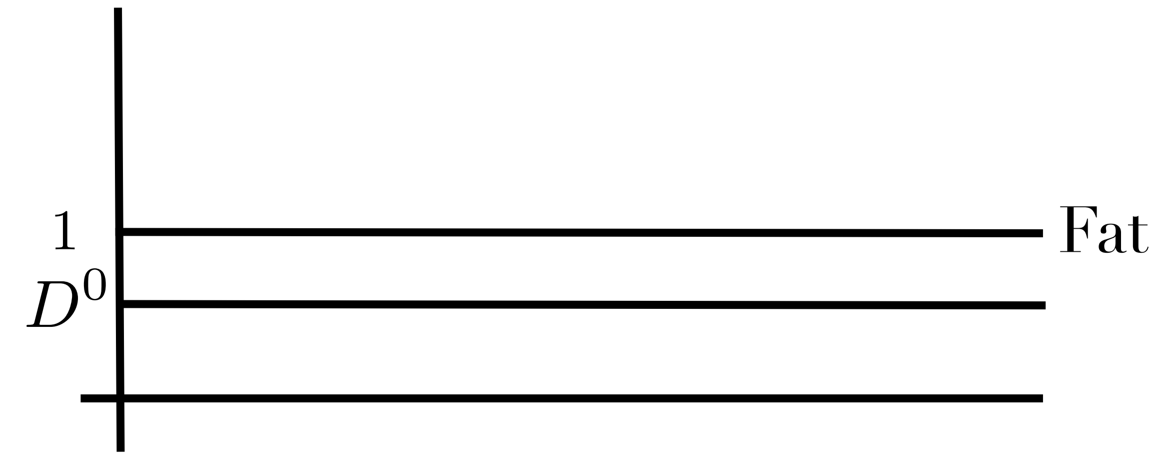
$$F_{i+1} D_i(1+\alpha\overleftarrow{U}_{i+1}) - \Gamma\overleftarrow{U}_{i+1}(1+\beta\overrightarrow{U}_i) = 0$$

$$F_i = F_i^0 - \overrightarrow{U}_i - \overleftarrow{U}_i \ \& \ D_i = D_i^0 - \overrightarrow{U}_{i-1} - \overleftarrow{U}_{i+1}$$



Analytic solution - Absolute level response

$$FD(1+\alpha\overrightarrow{U}) - \Gamma\overrightarrow{U}(1+\beta\overleftarrow{U}) = 0$$

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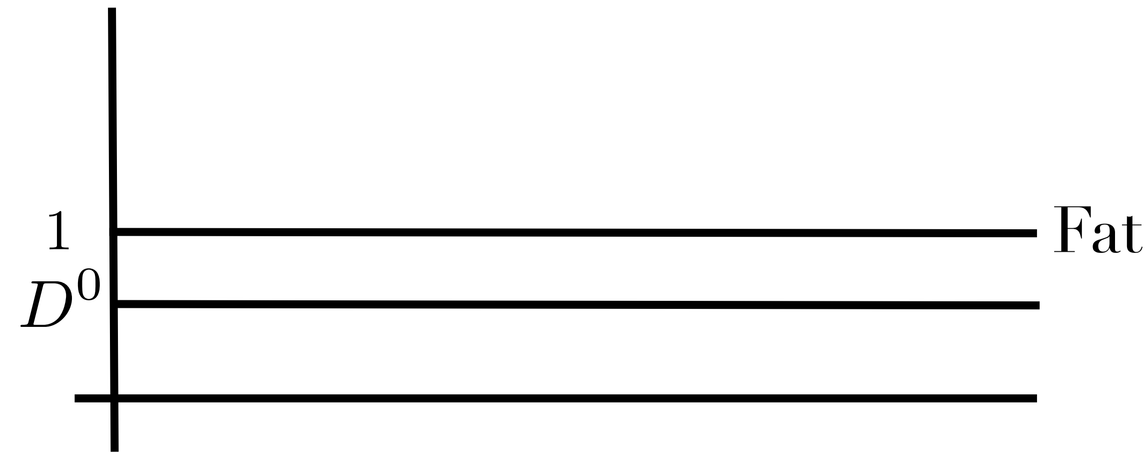
$$F = 1 - \overrightarrow{U} - \overleftarrow{U} \;\&\; D = D^0 - \overrightarrow{U} - \overleftarrow{U}$$



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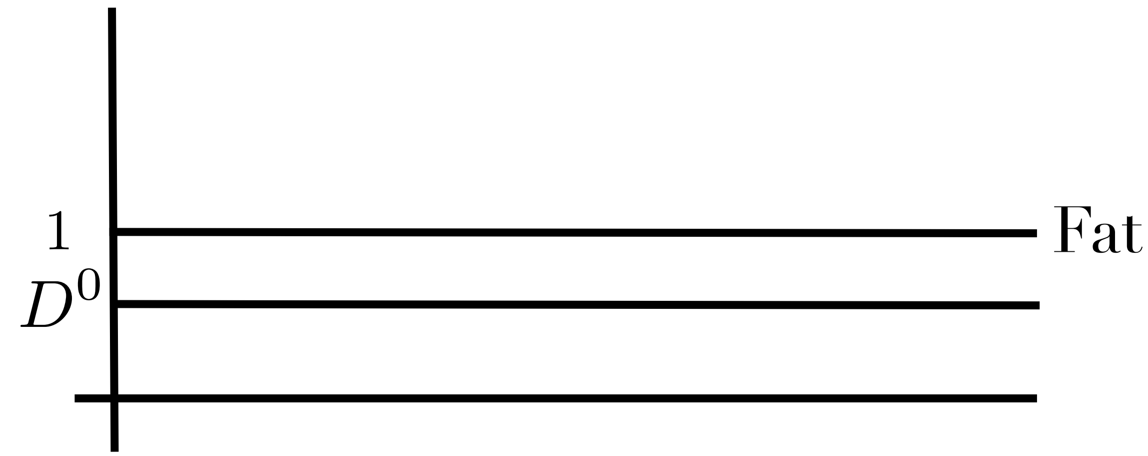
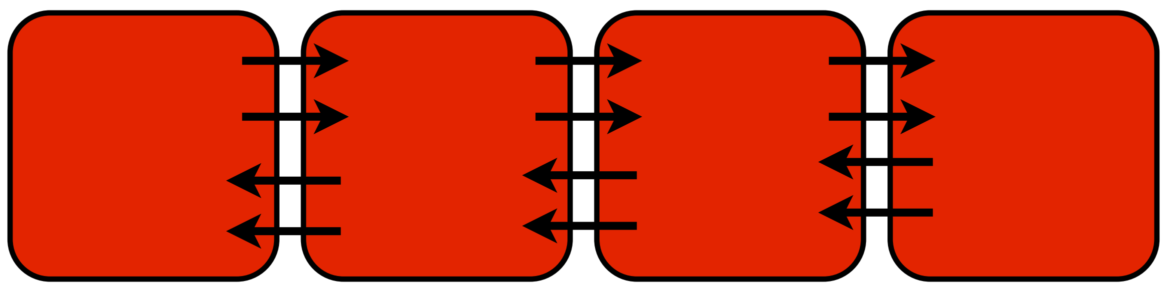
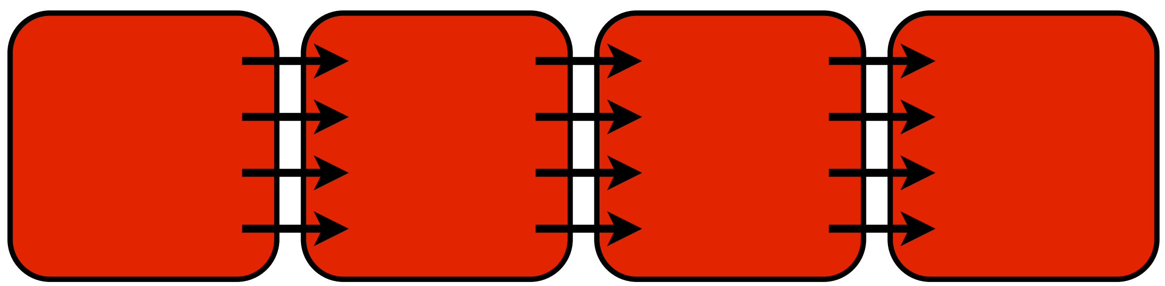




$\overrightarrow{U} \approx \overleftarrow{U}$



$\overrightarrow{U} \gg \overleftarrow{U}$

Analytic solution - Absolute level response

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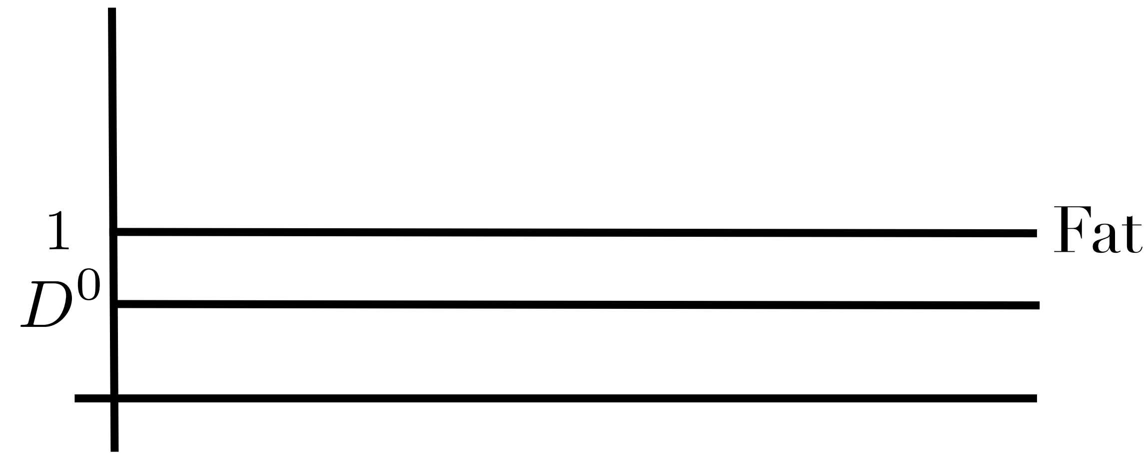

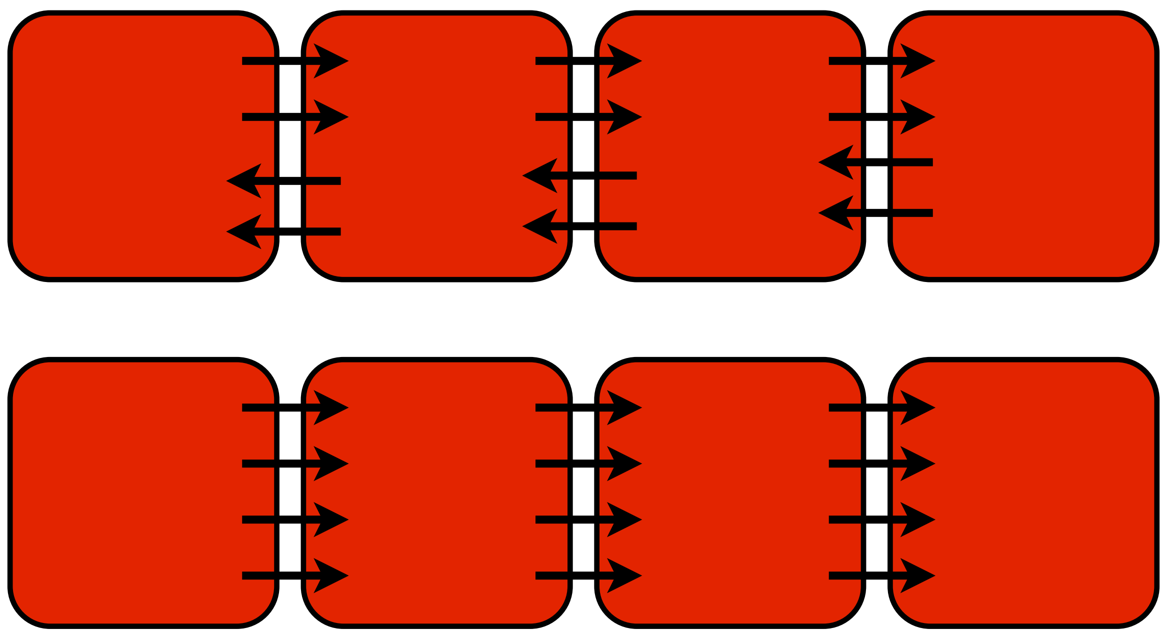

$$\overrightarrow{U} \approx \overleftarrow{U}$$

$$\overrightarrow{U} \gg \overleftarrow{U}$$

$$|\overrightarrow{U} - \overleftarrow{U}|$$

Analytic solution - Absolute level response

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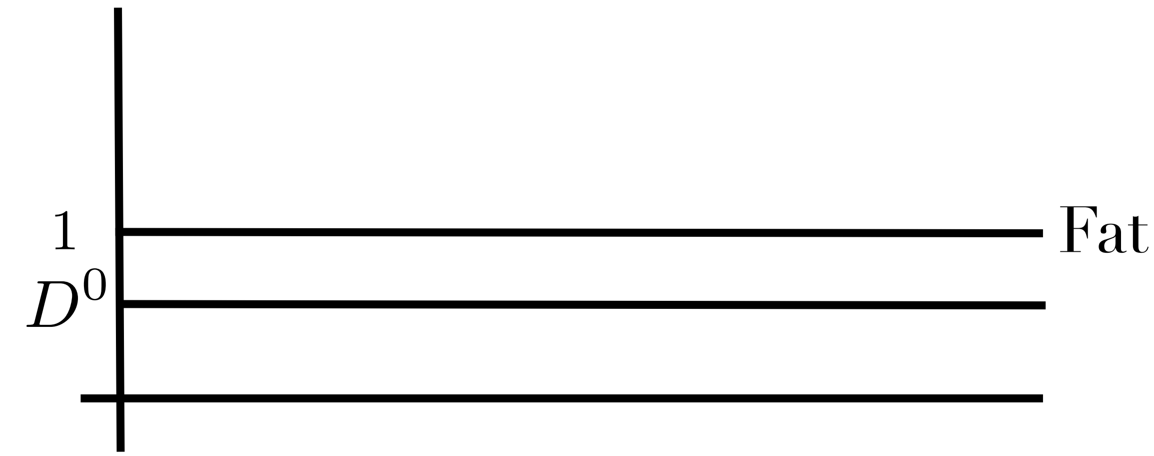

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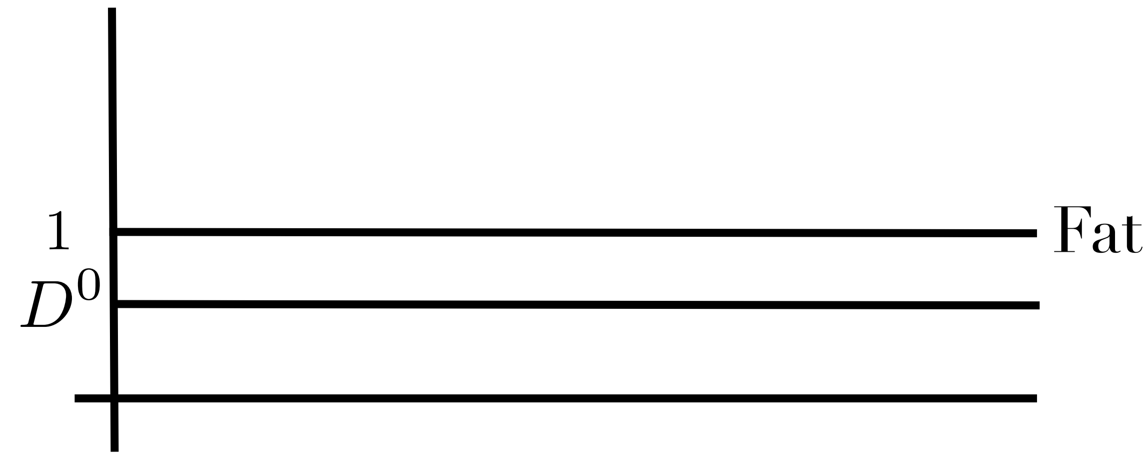

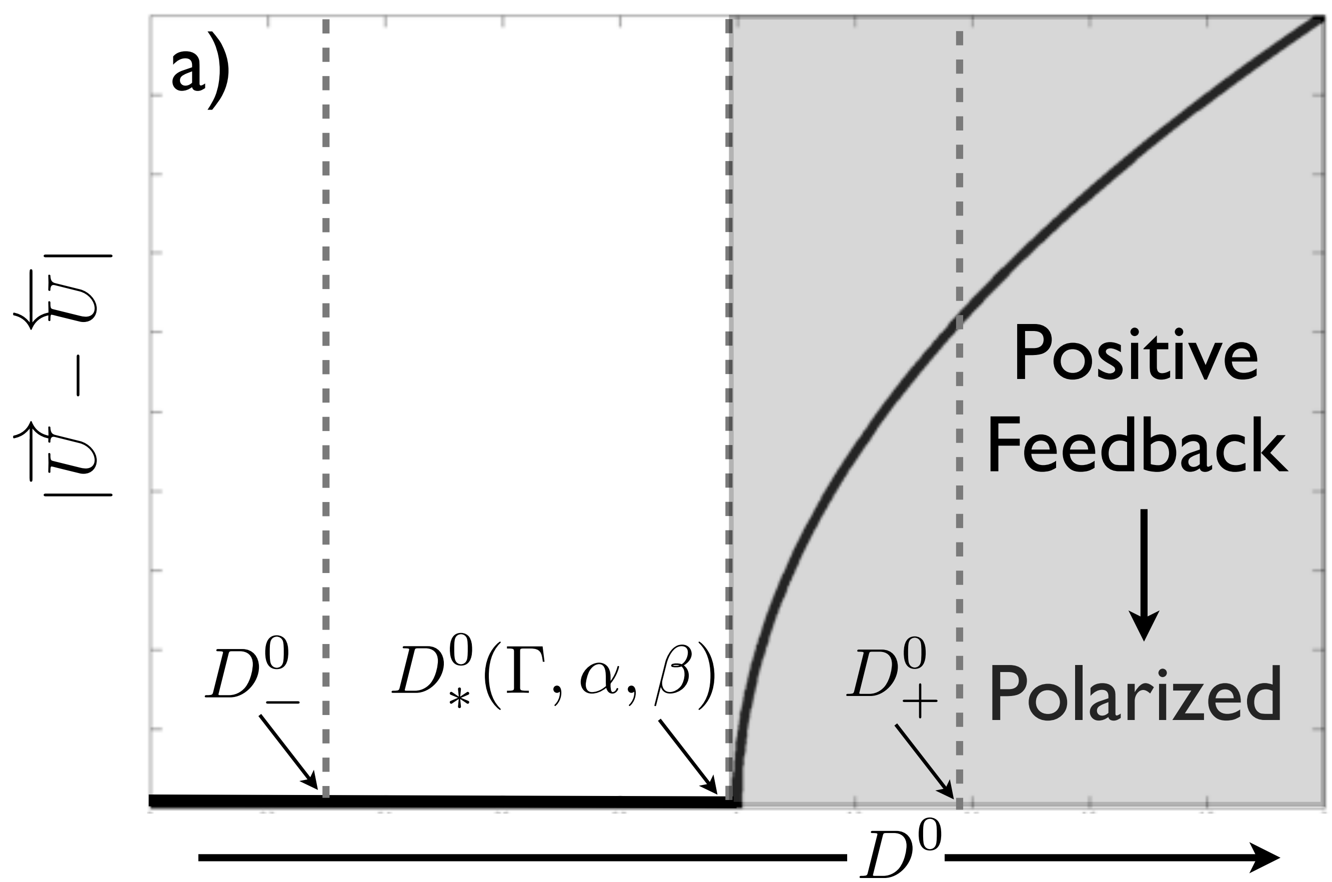

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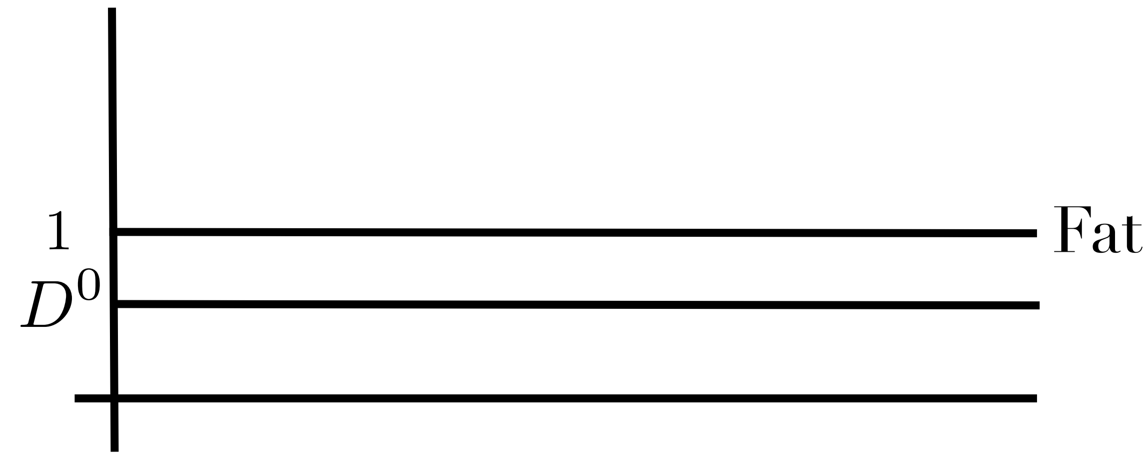

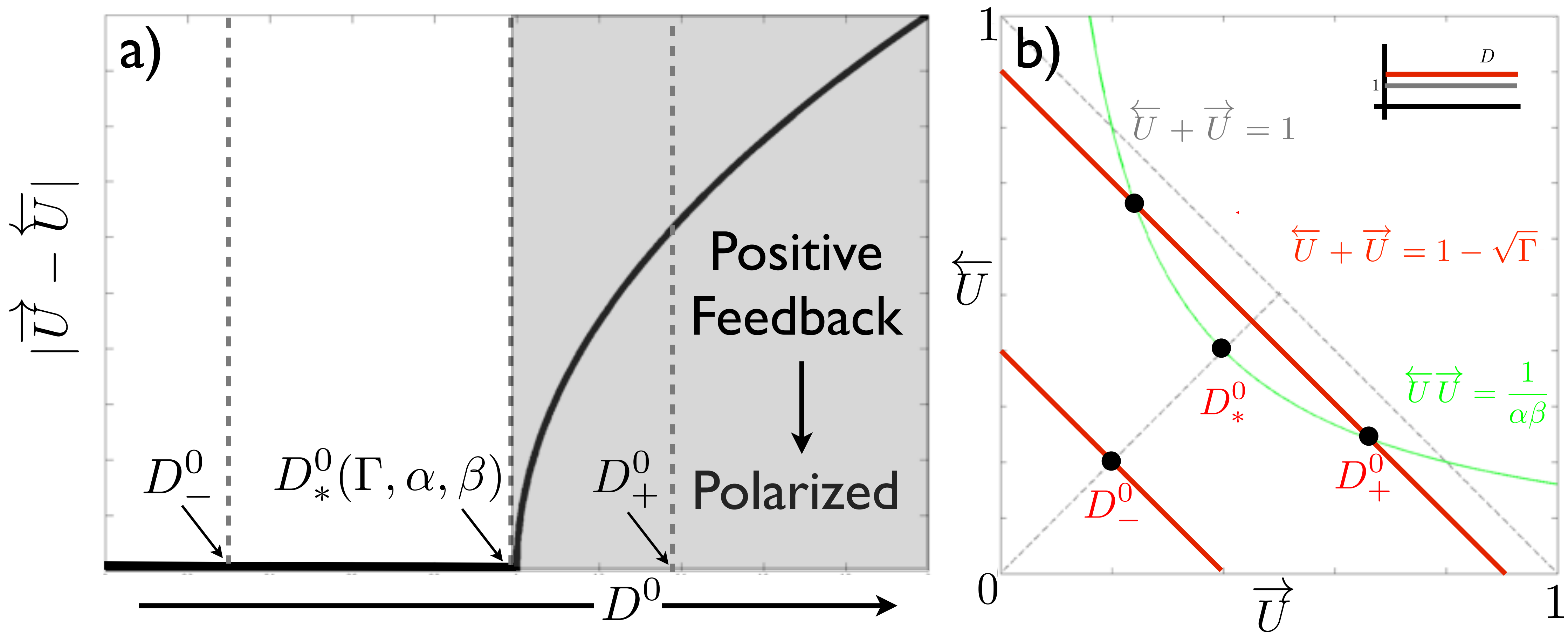

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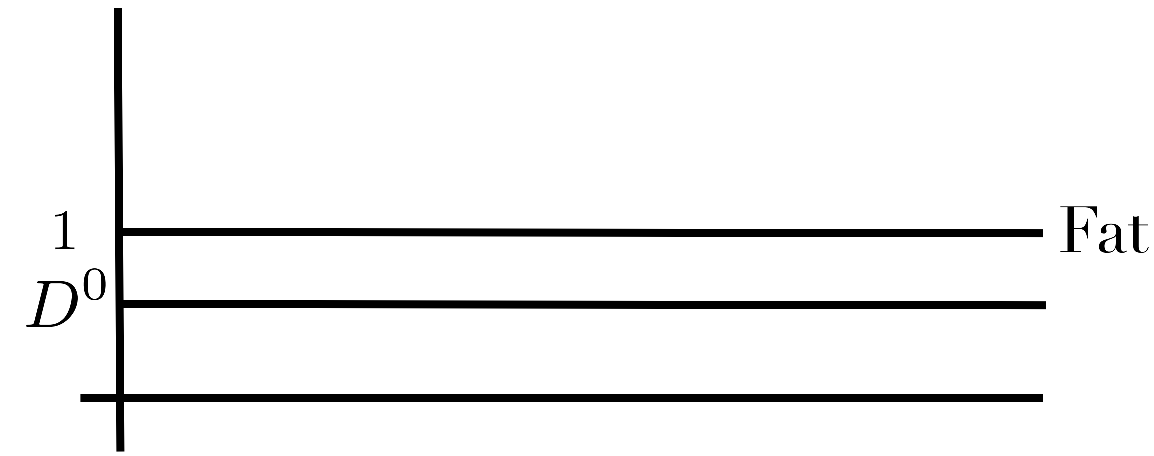

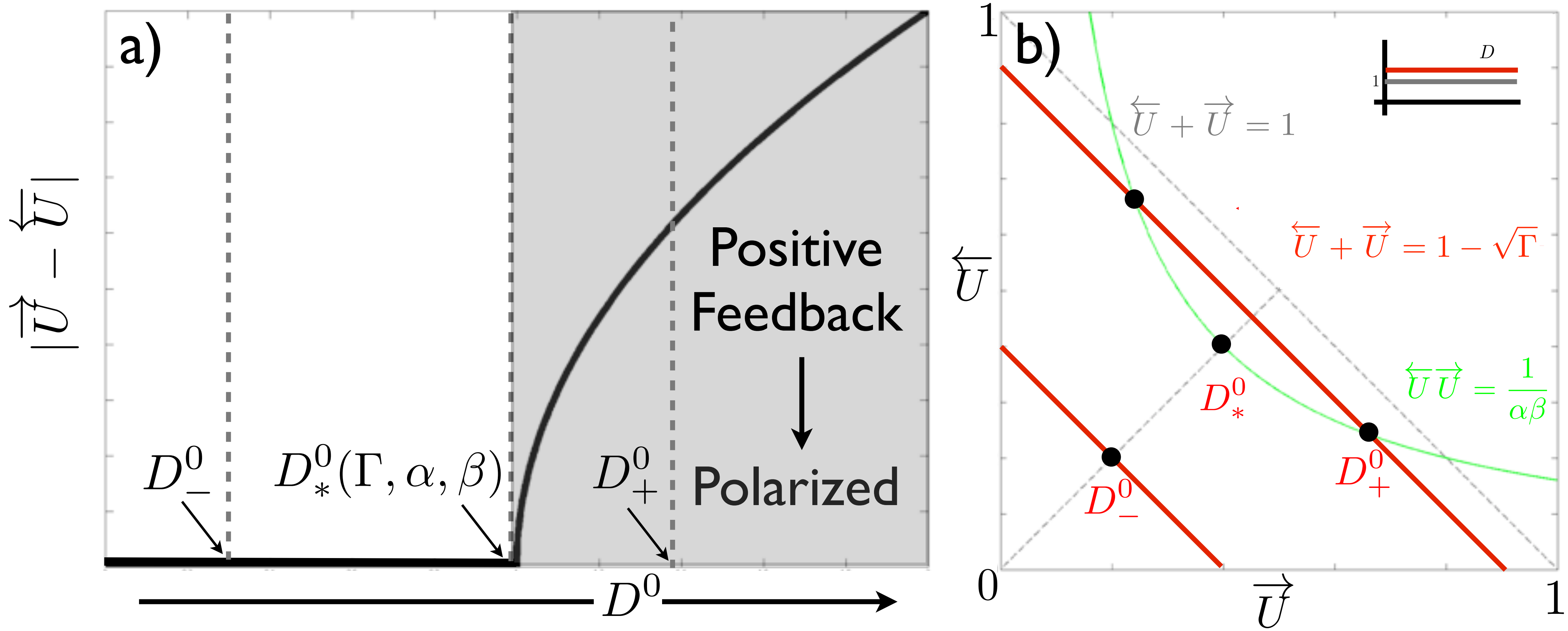

$$\alpha \& \beta \longrightarrow \text{Polarity}$$

Critical relative level of Dachsous

Analytic solution - Gradient response (main slide)

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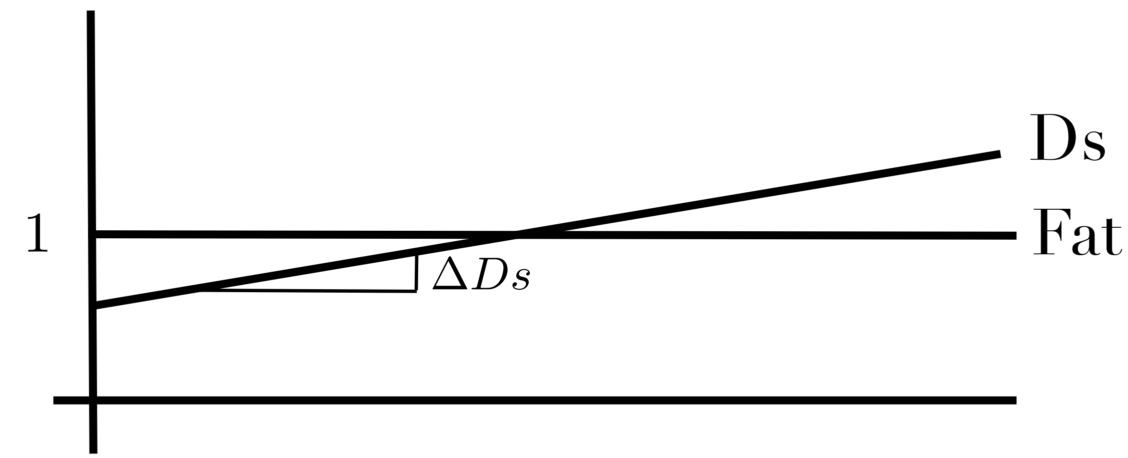

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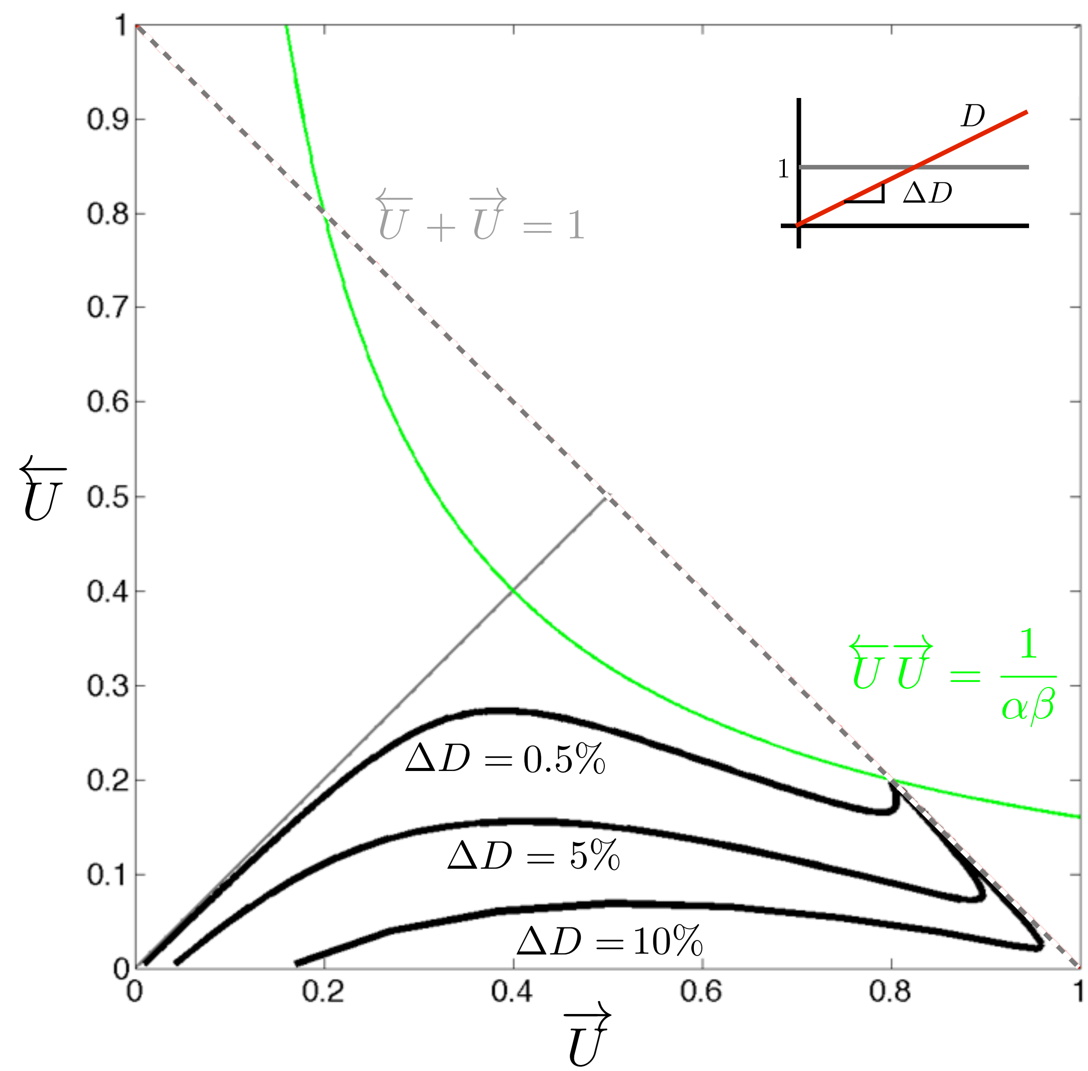

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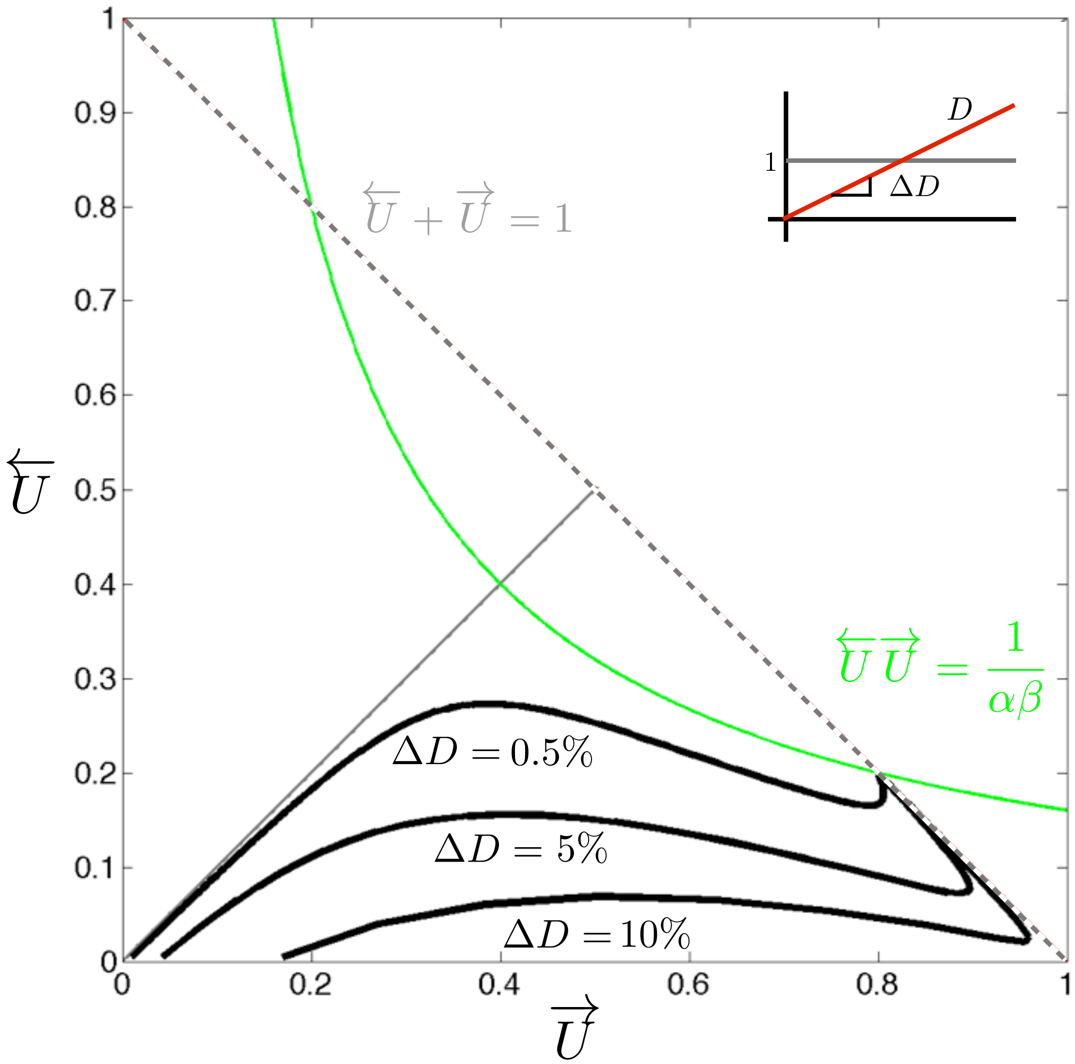

Questions about the curve:

1) Response at the critical point

2) Why does the curve settle at intersection?

3) When does it turn around?

Analytic solution - Gradient response (main slide)

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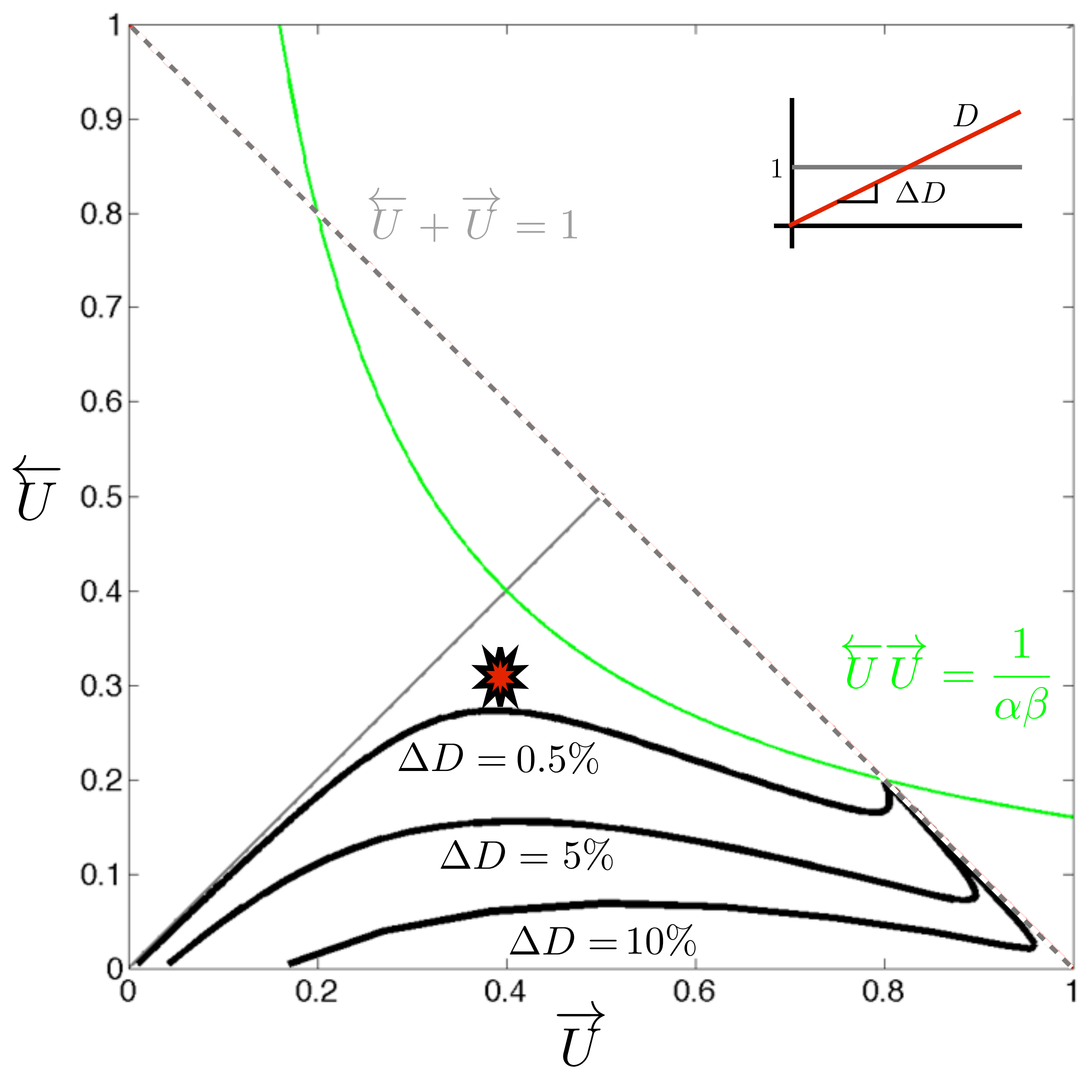

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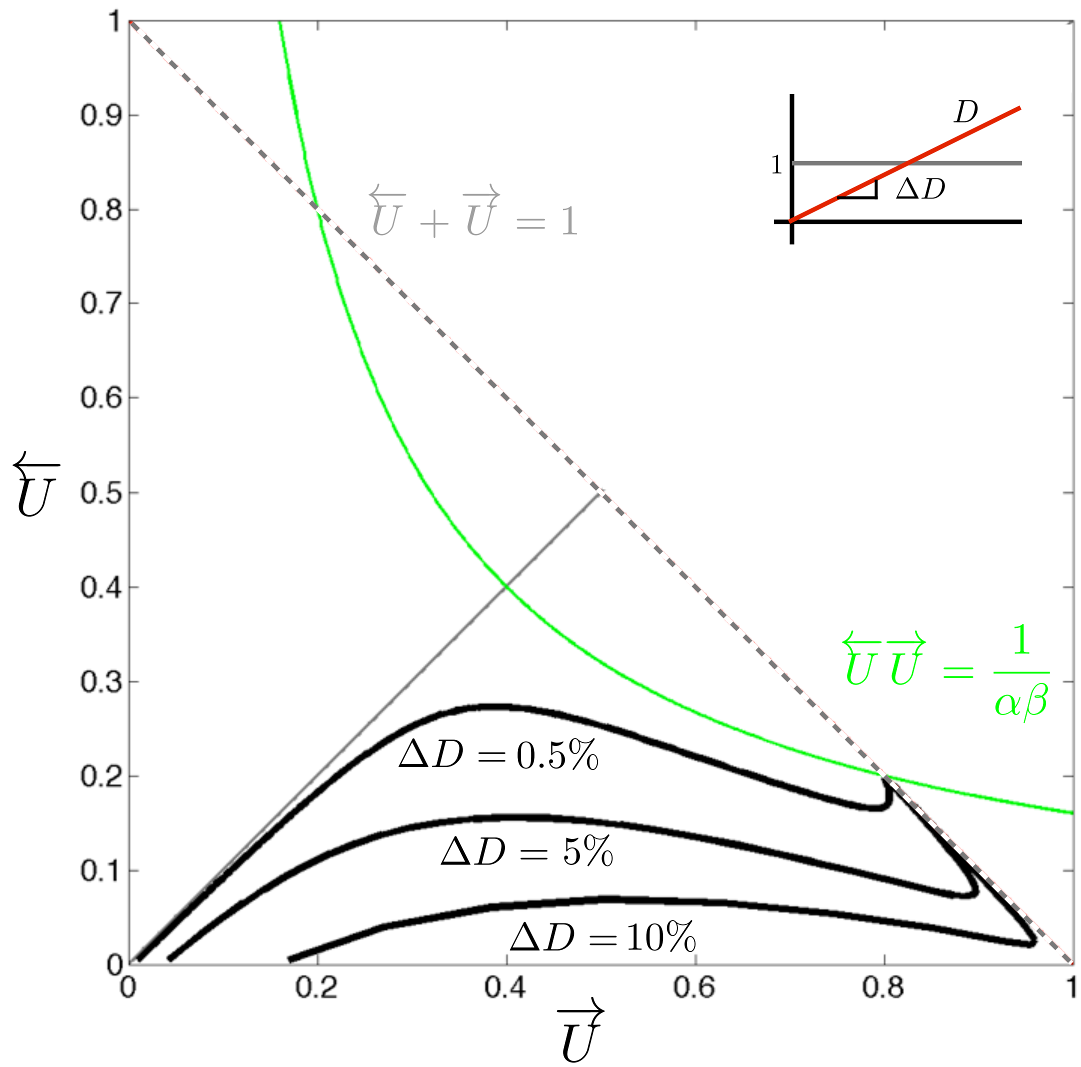

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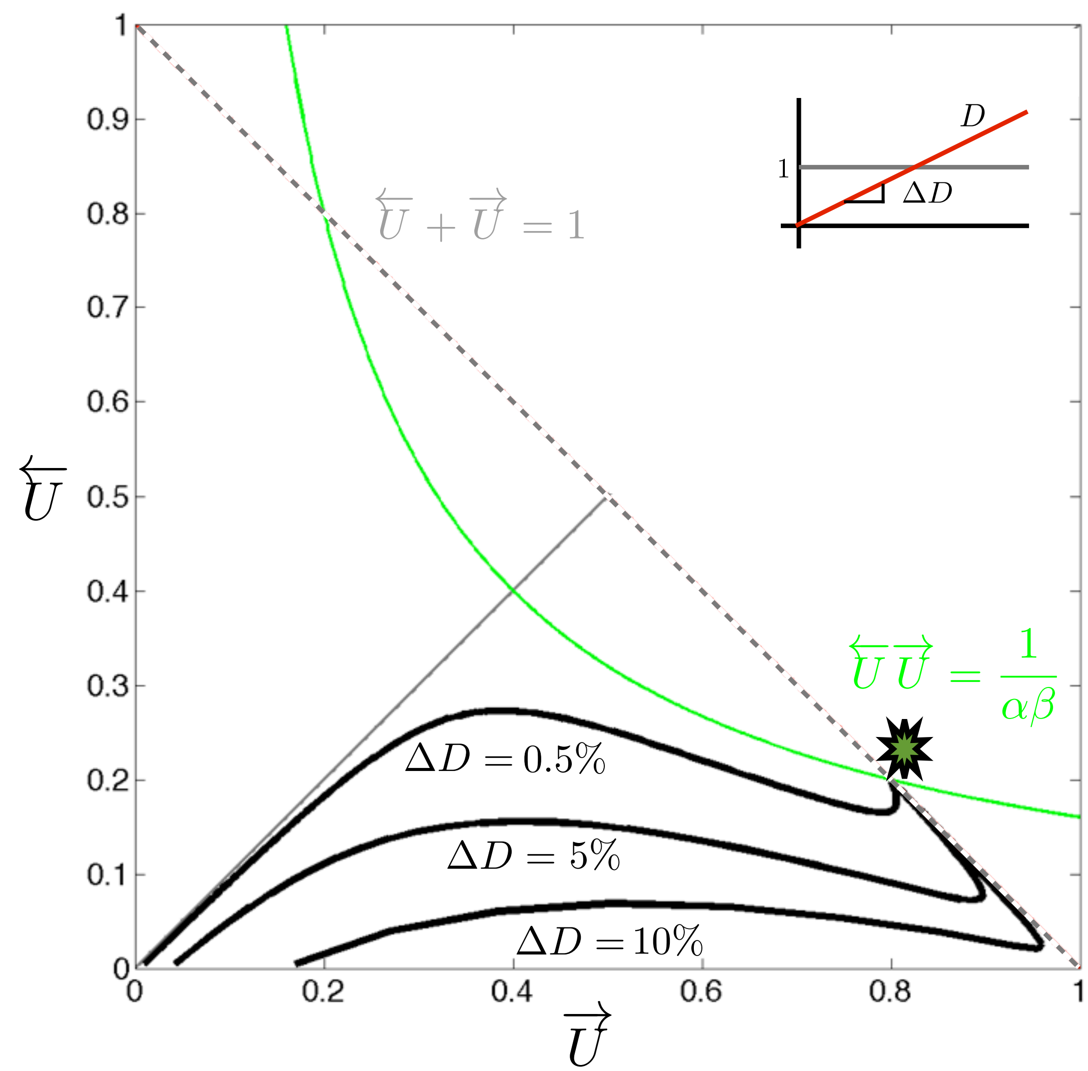

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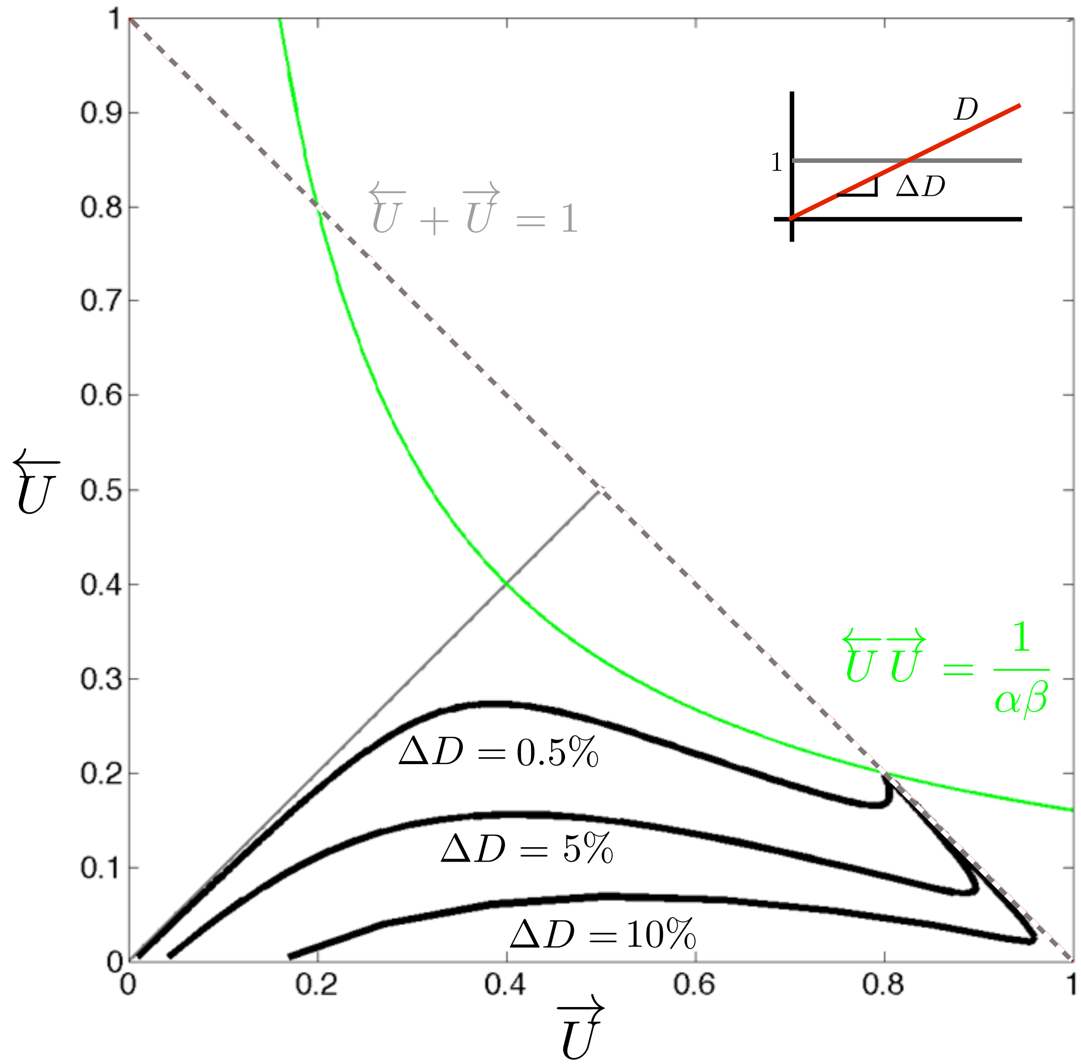

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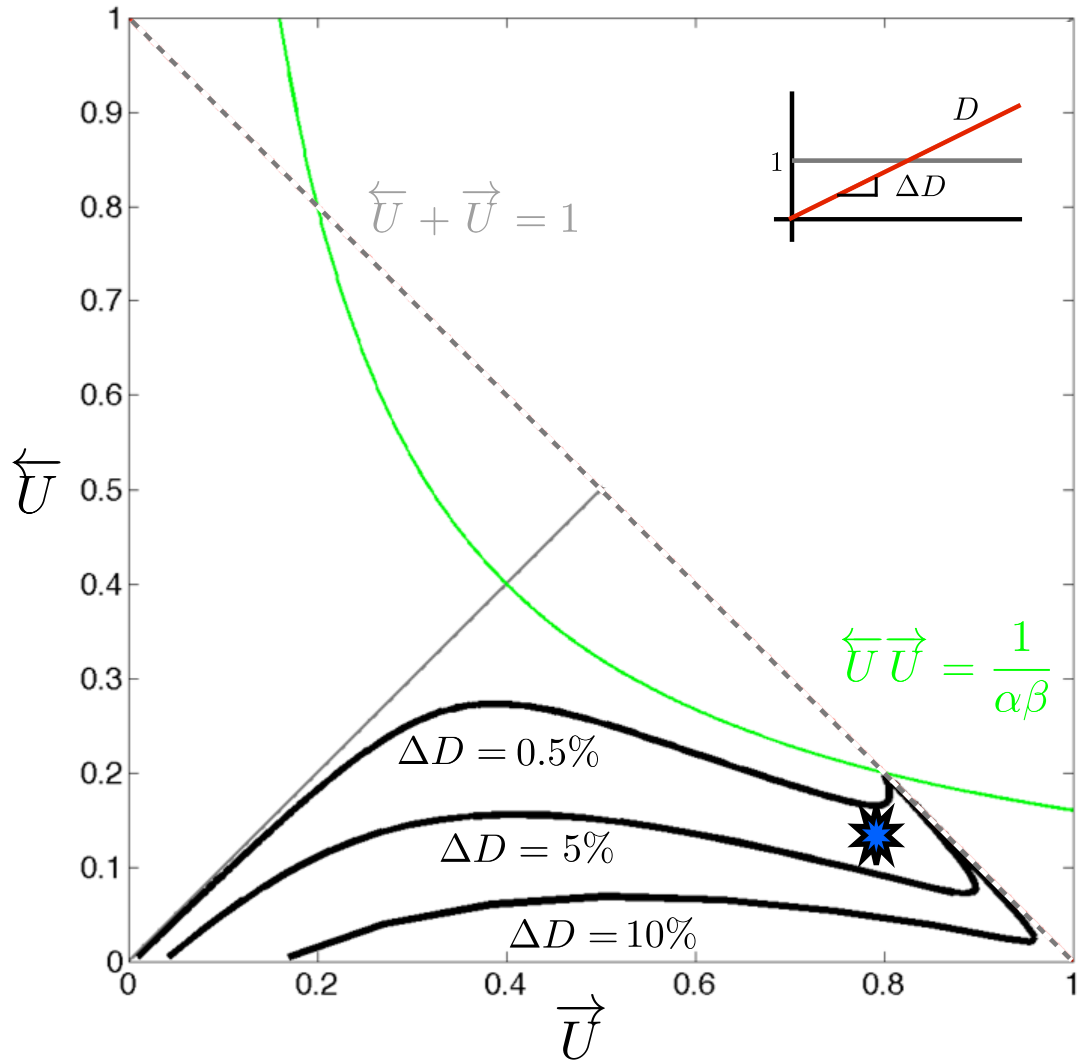

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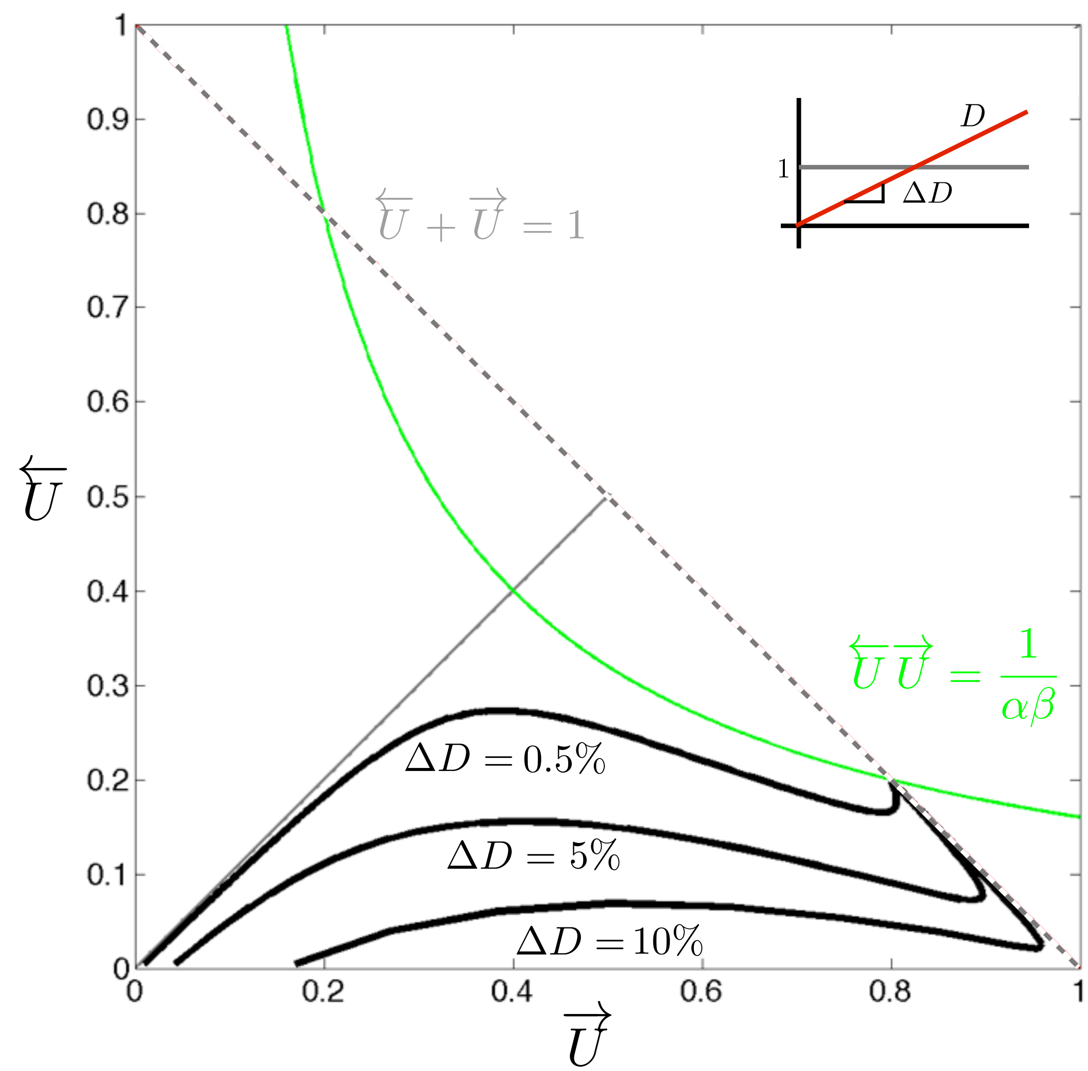

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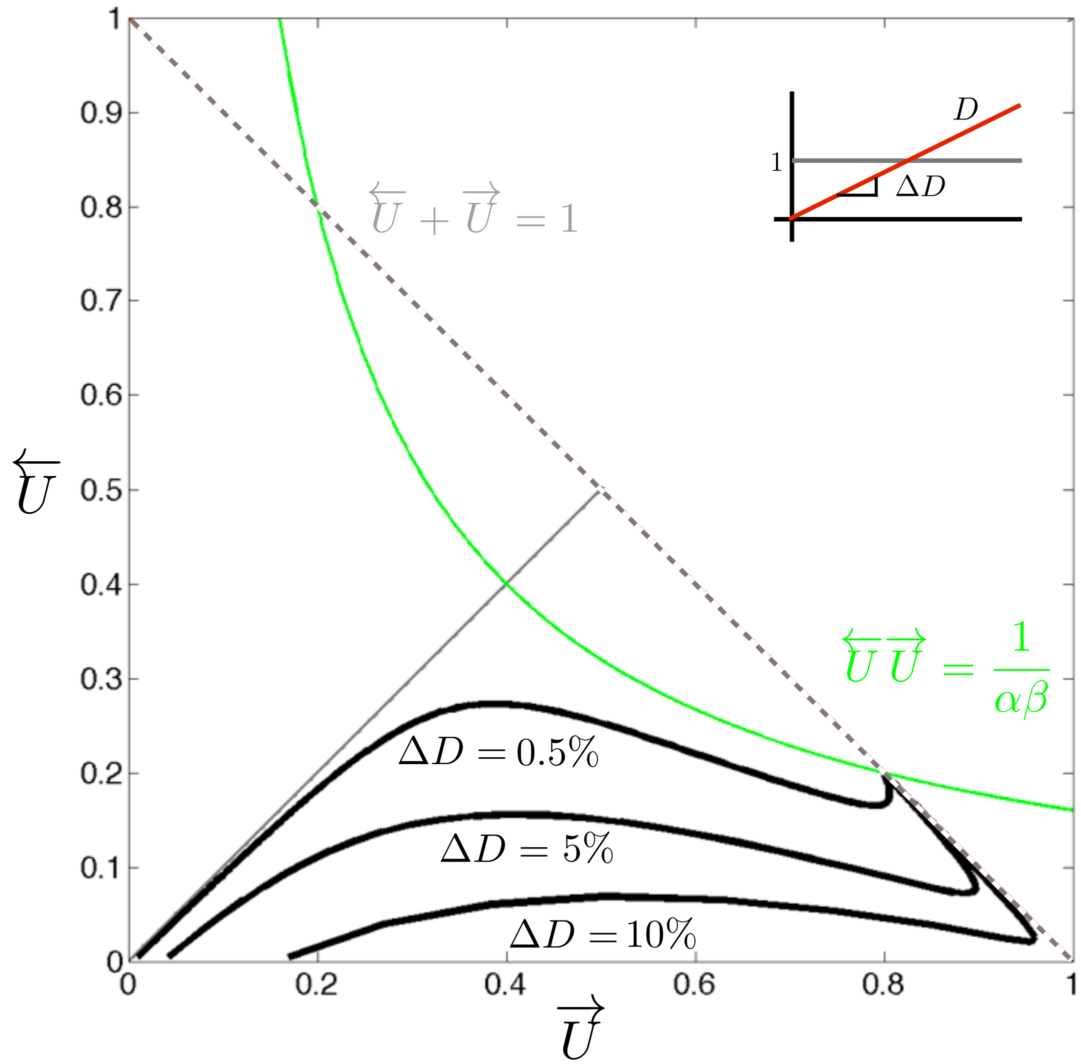

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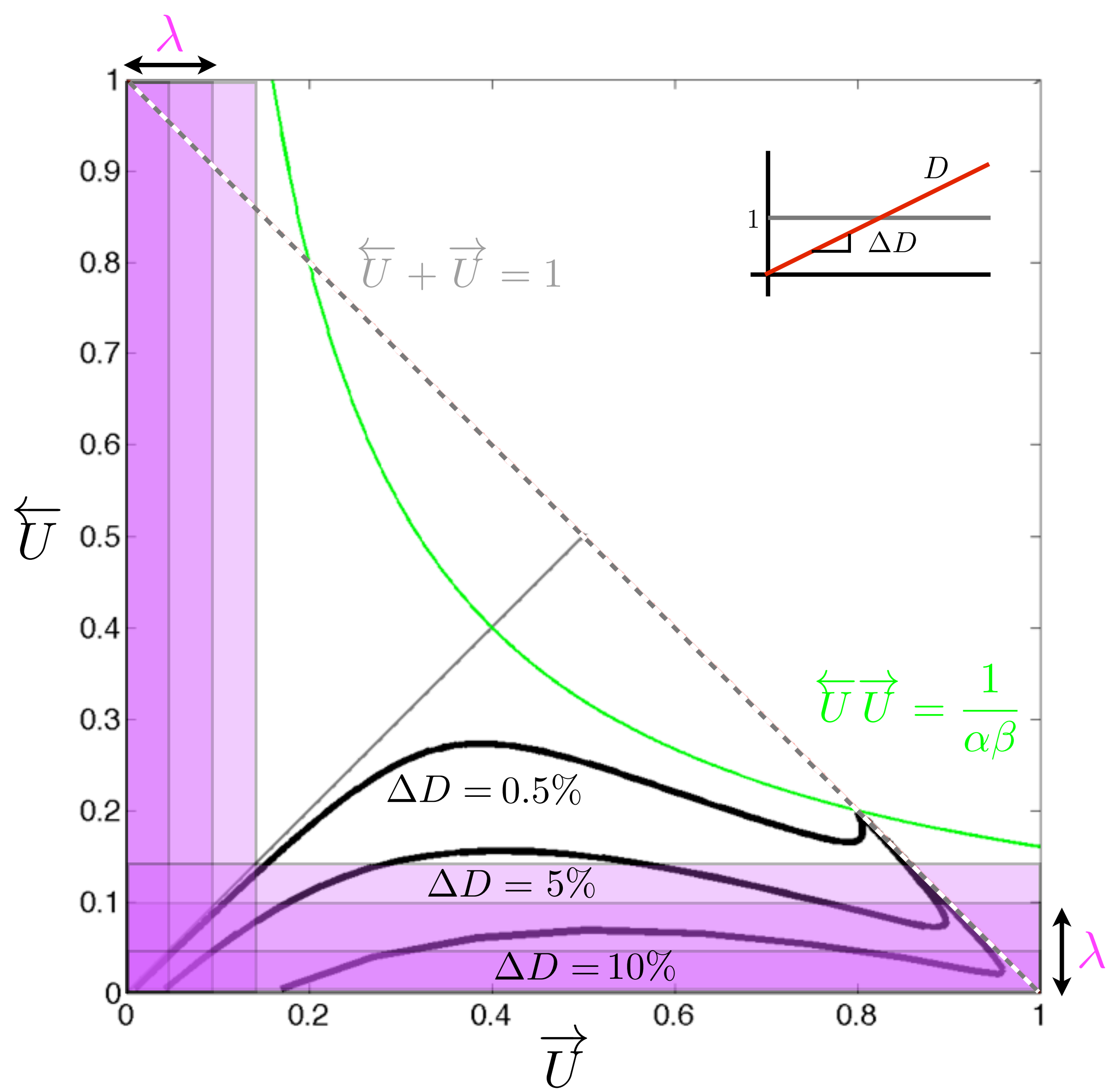

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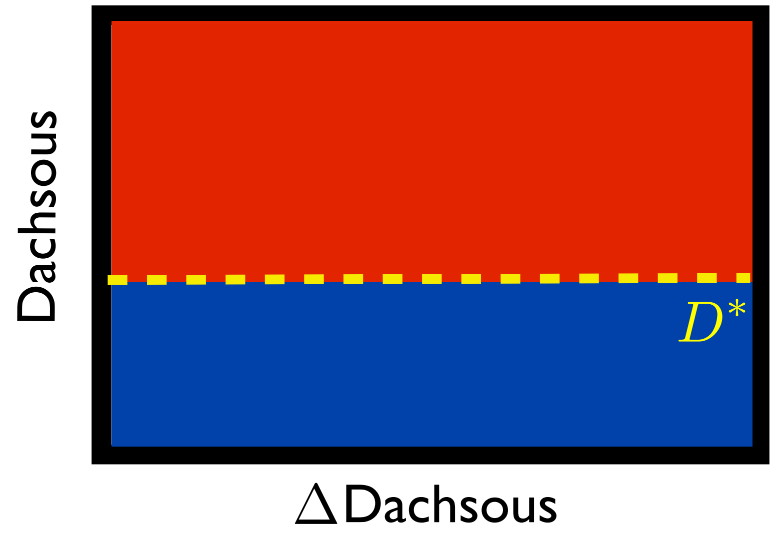
All 3 levels of model
in one figure

Framework - Map from expression levels of core components to growth/polarity response

a) Level Detector



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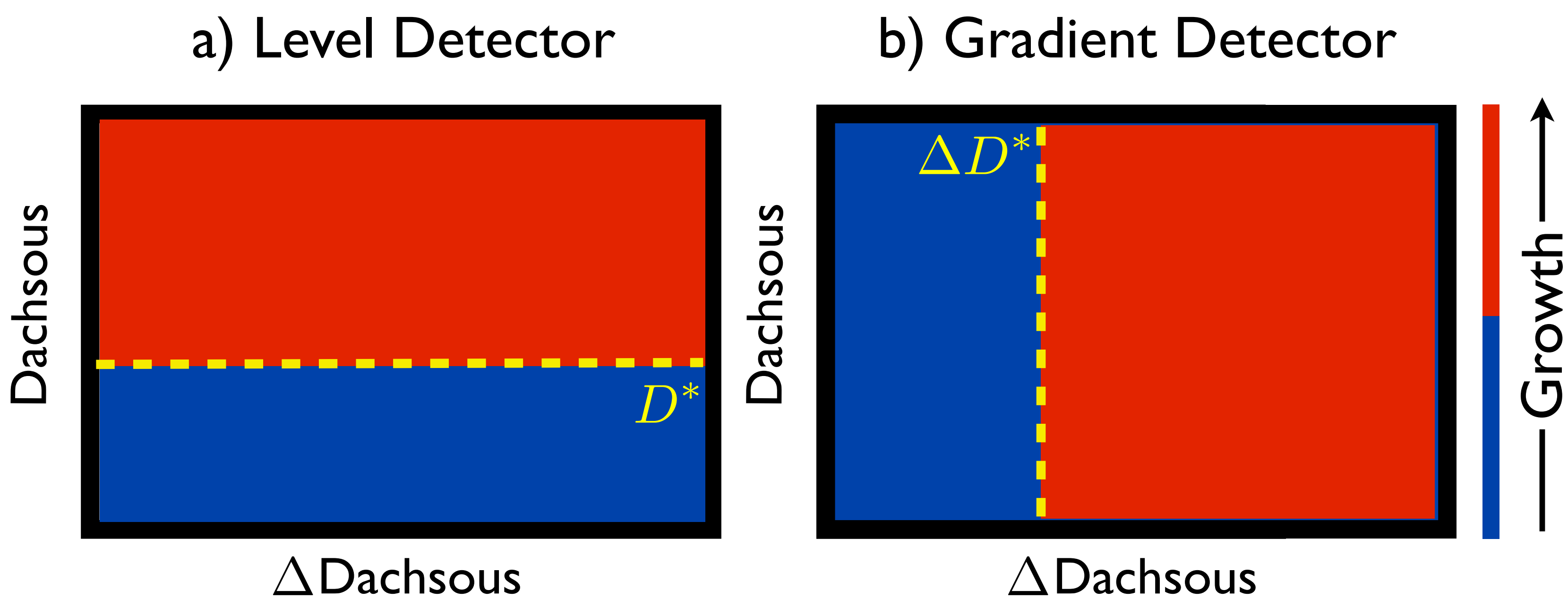
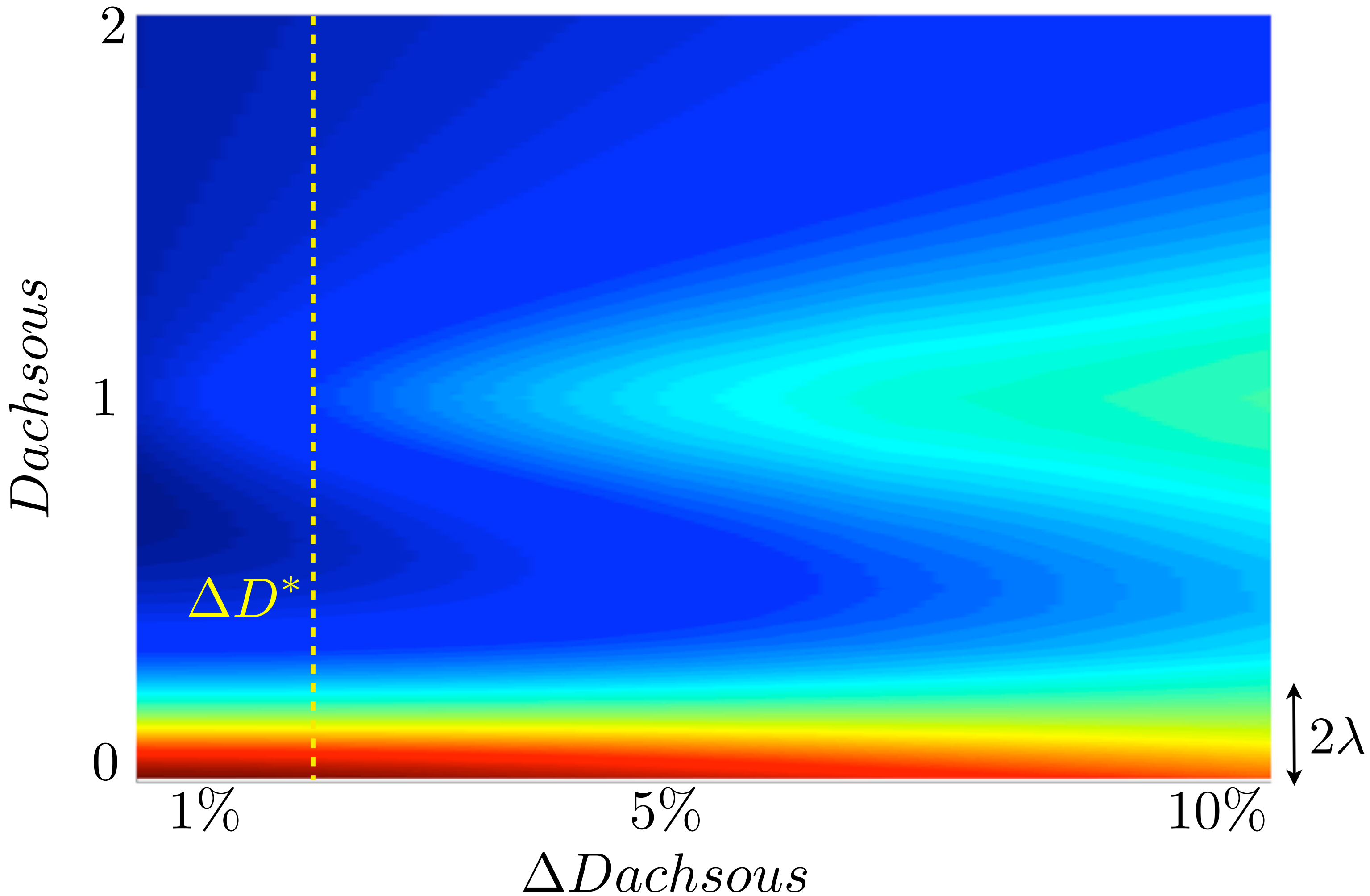


Phase diagram



Features

1) Knockout

2) Signaling peak

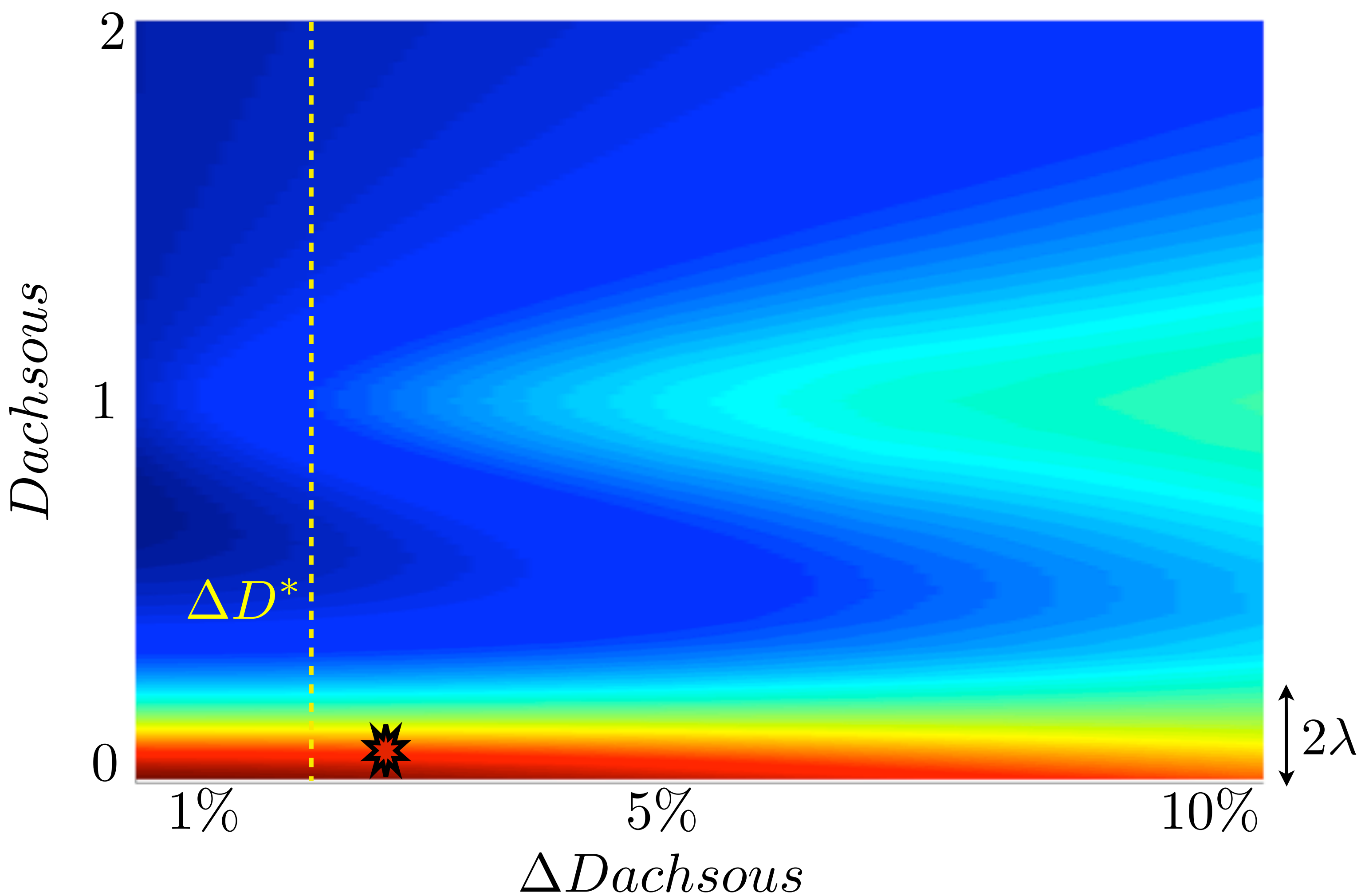
3) “Critical” gradient

4) More gradient --> More growth

5) Low (a weak knockout) levels give less growth than the signaling peak

6) Over-expression of Ds over Fat leads to no growth regardless of gradient

Phase diagram



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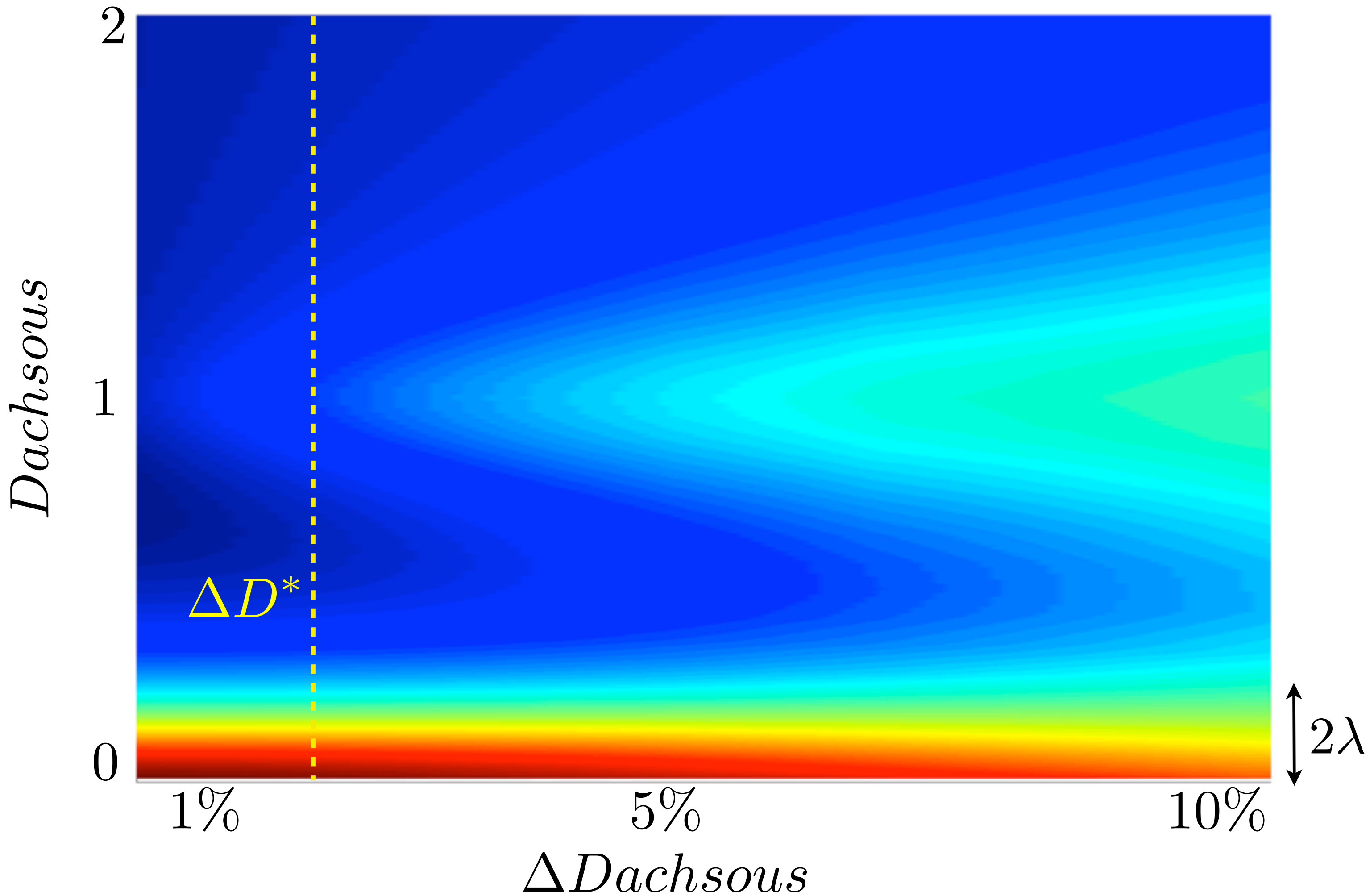

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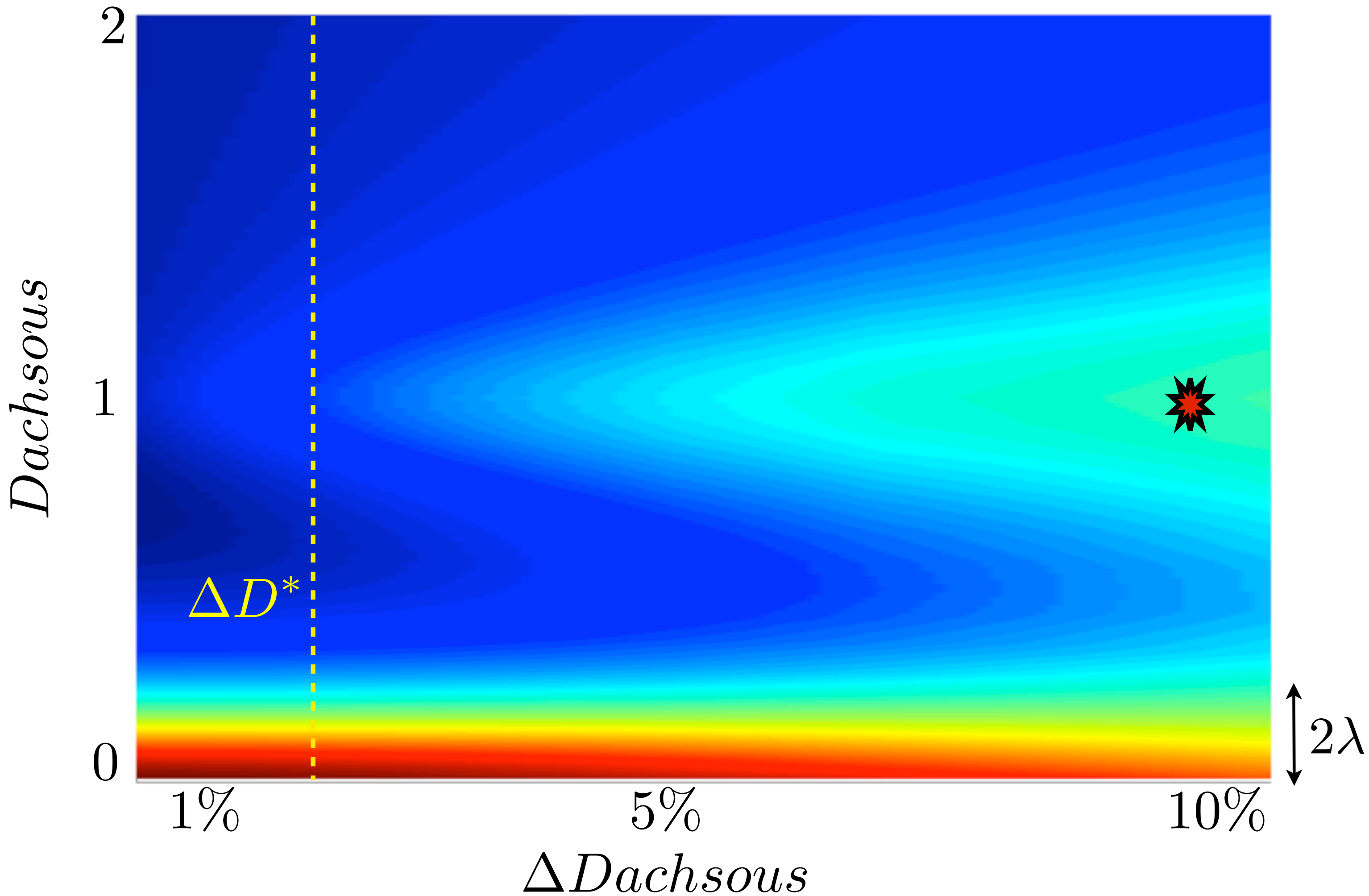

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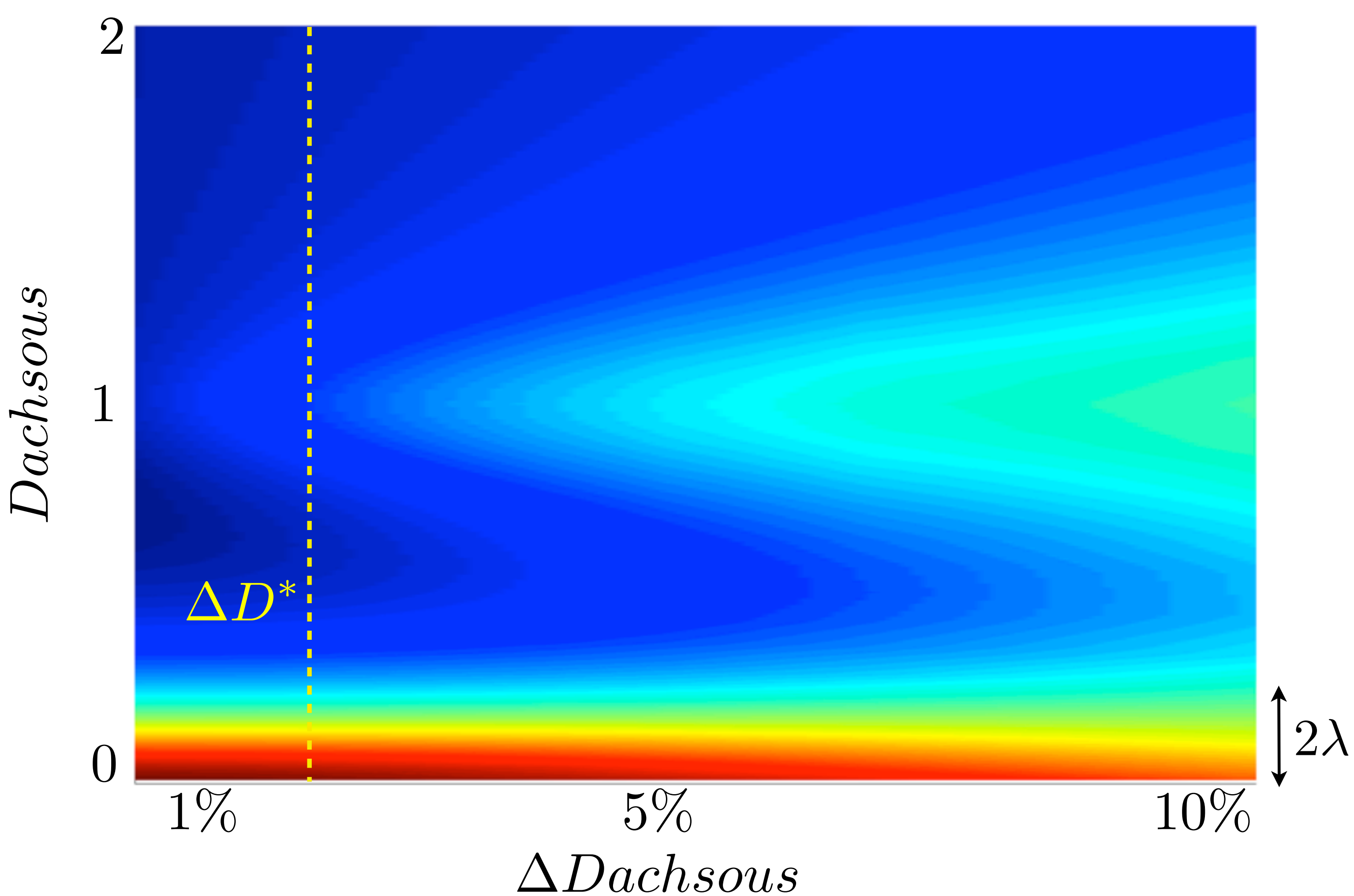

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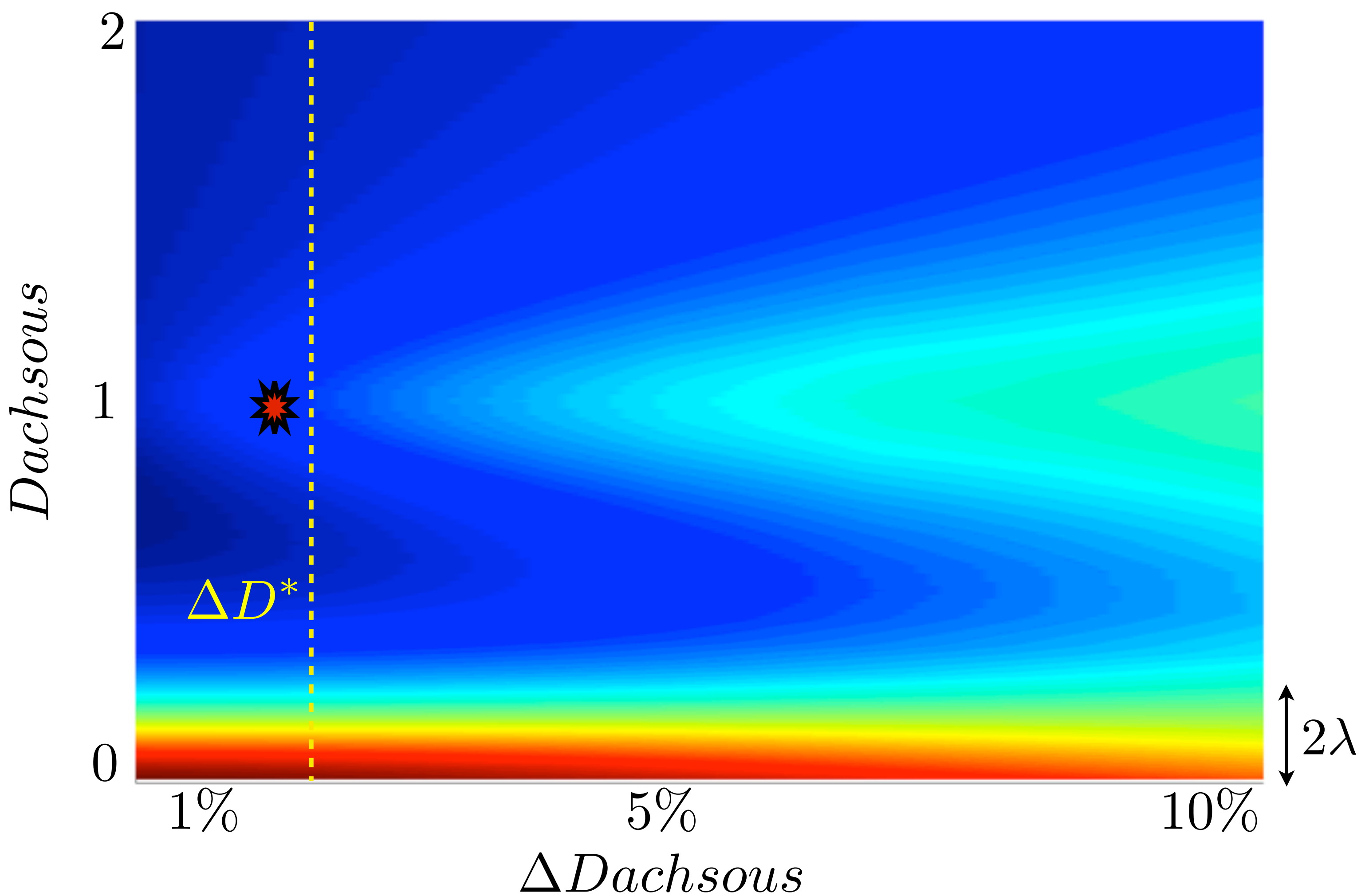

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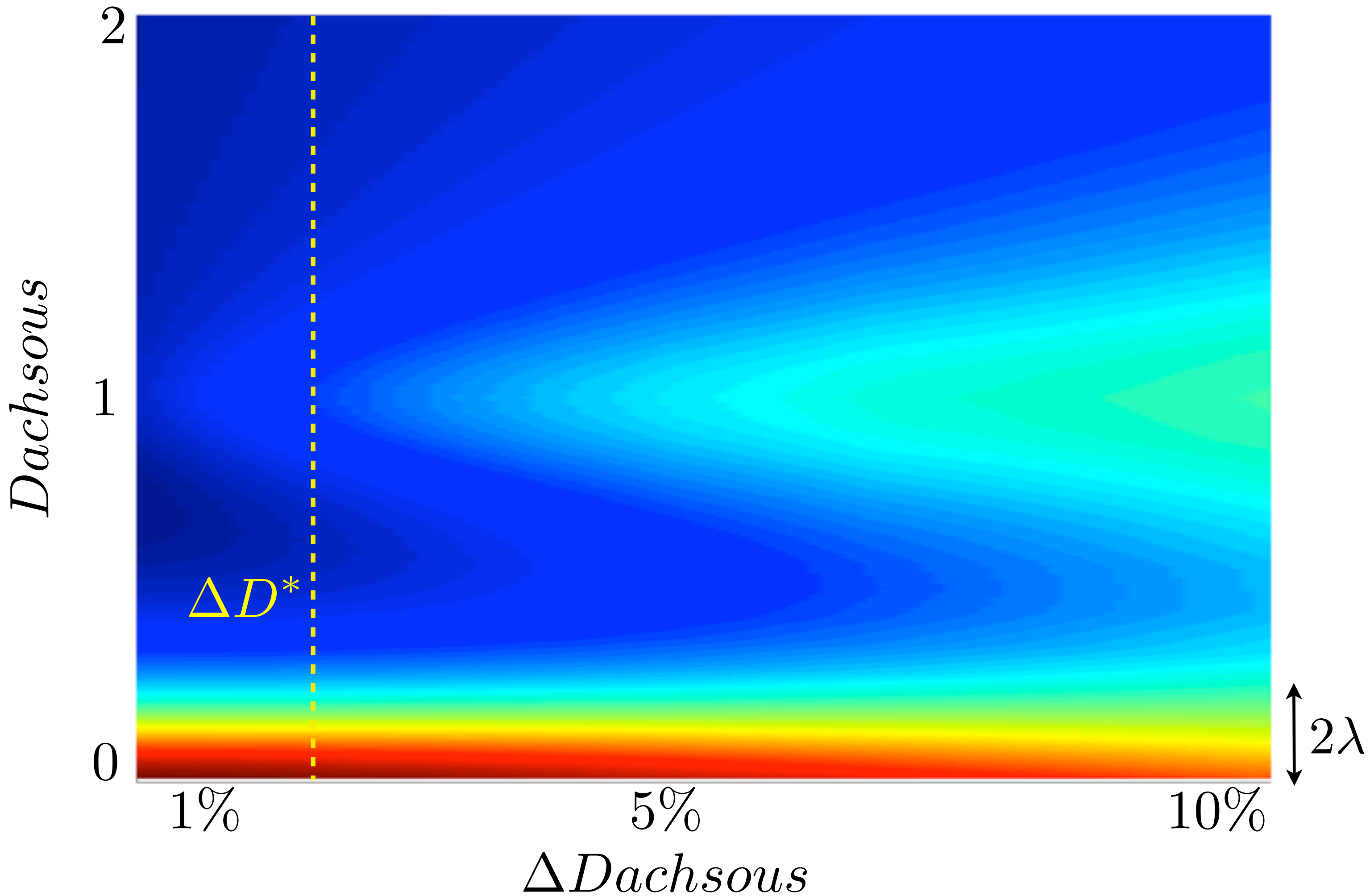

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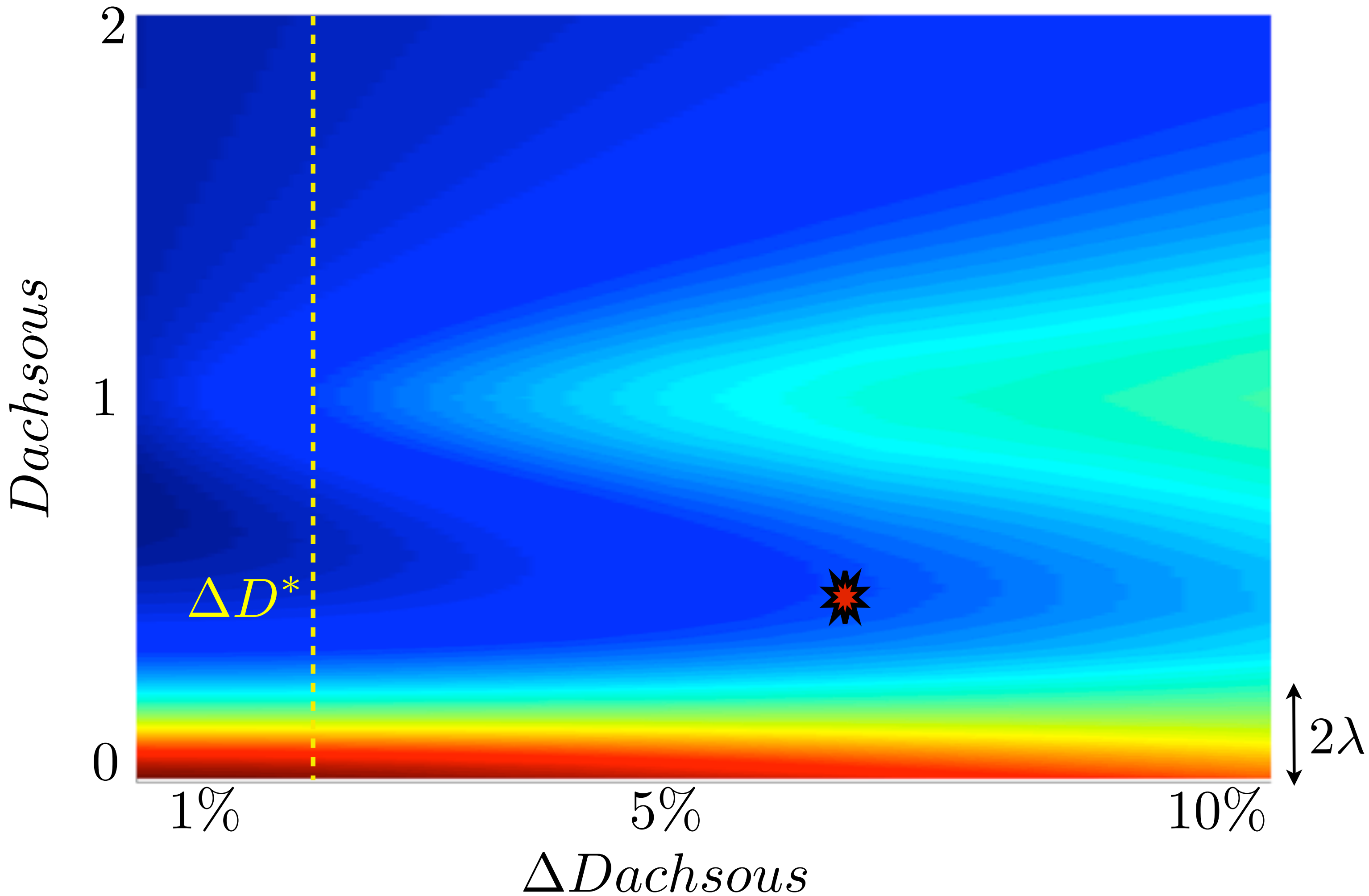

Features

1) Knockout

2) Signaling peak

3) “Critical” gradient

4) More gradient --> More growth

5) Low (a weak knockout) levels give less growth than the signaling peak

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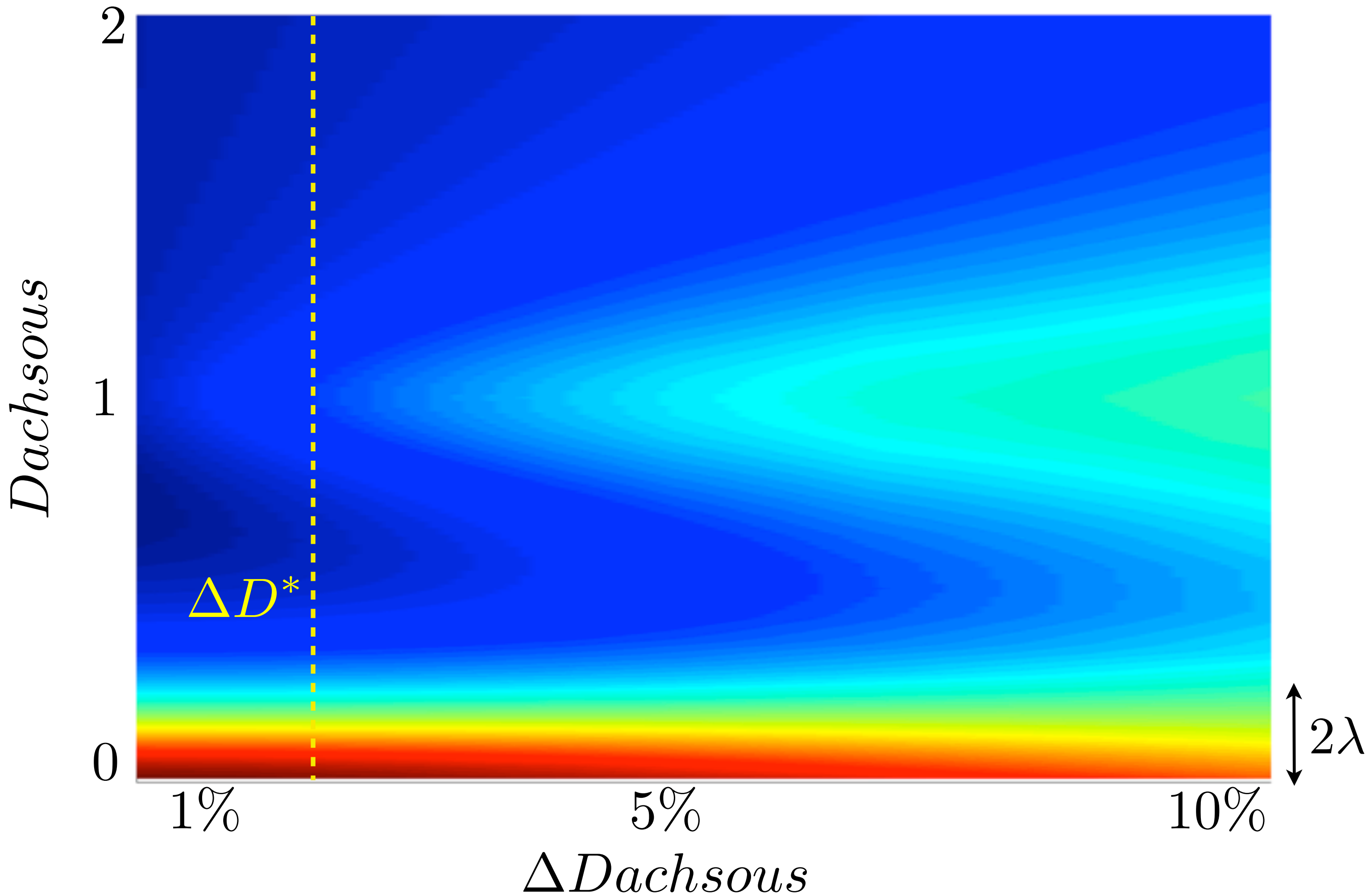

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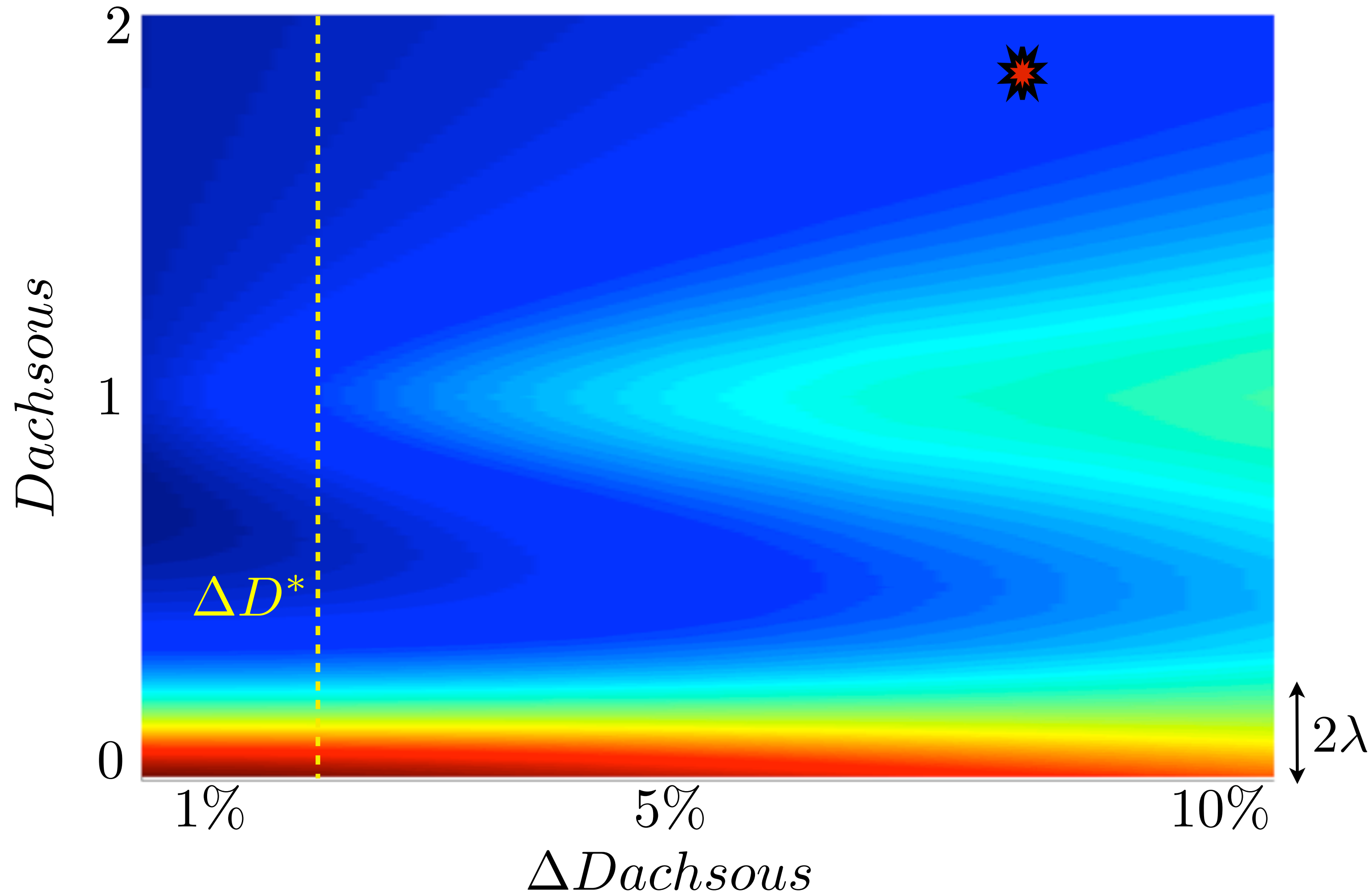

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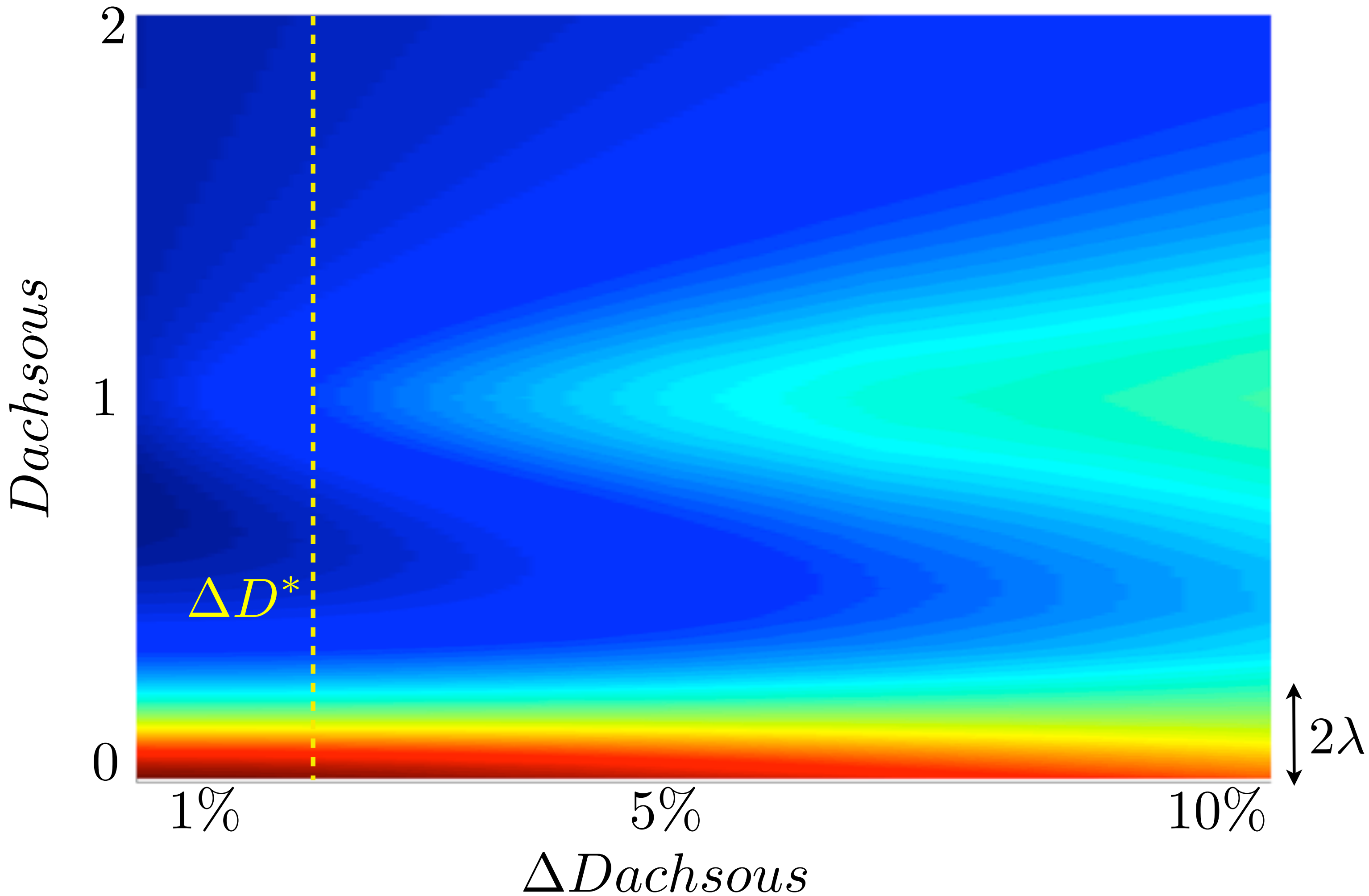

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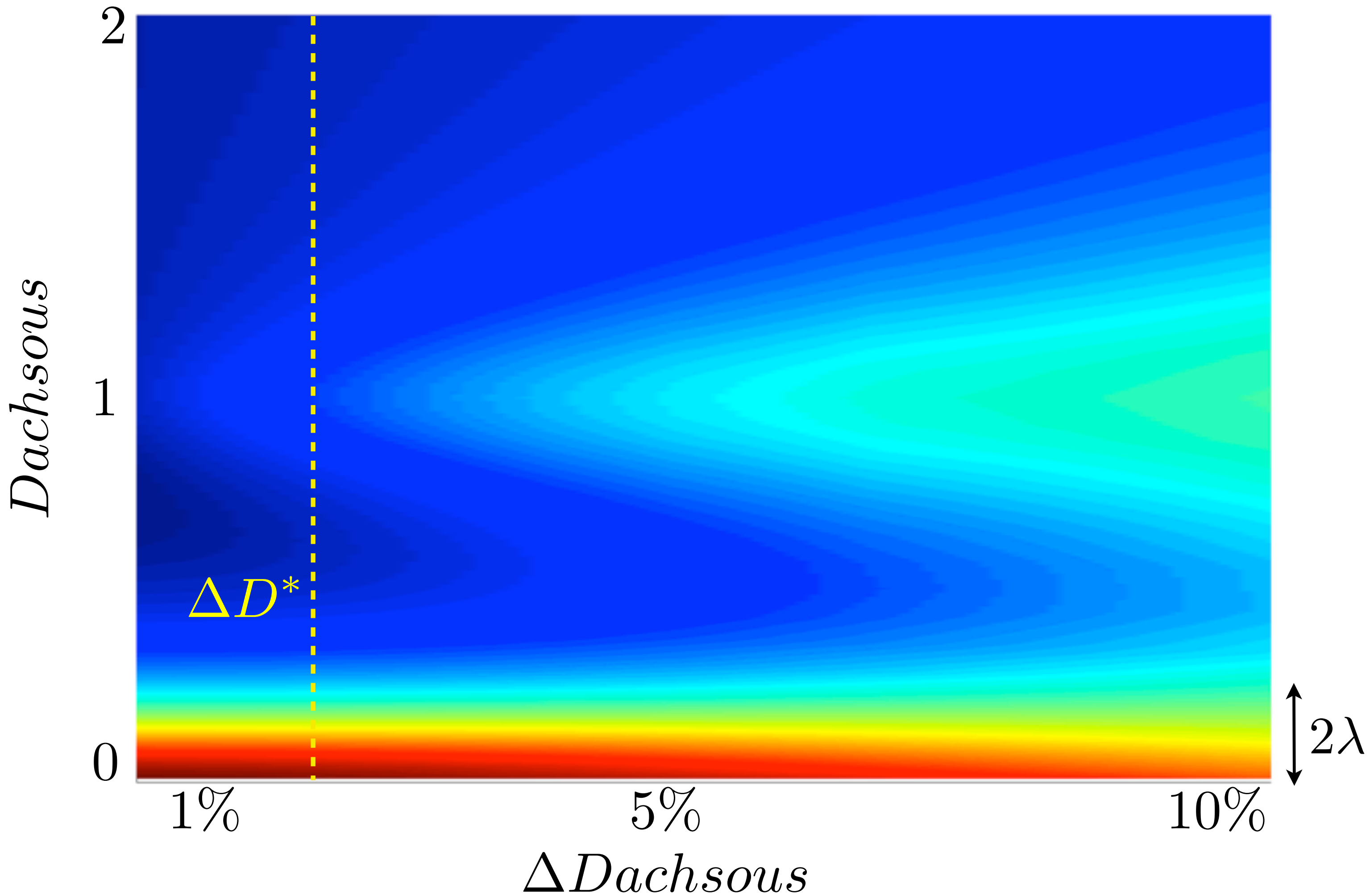

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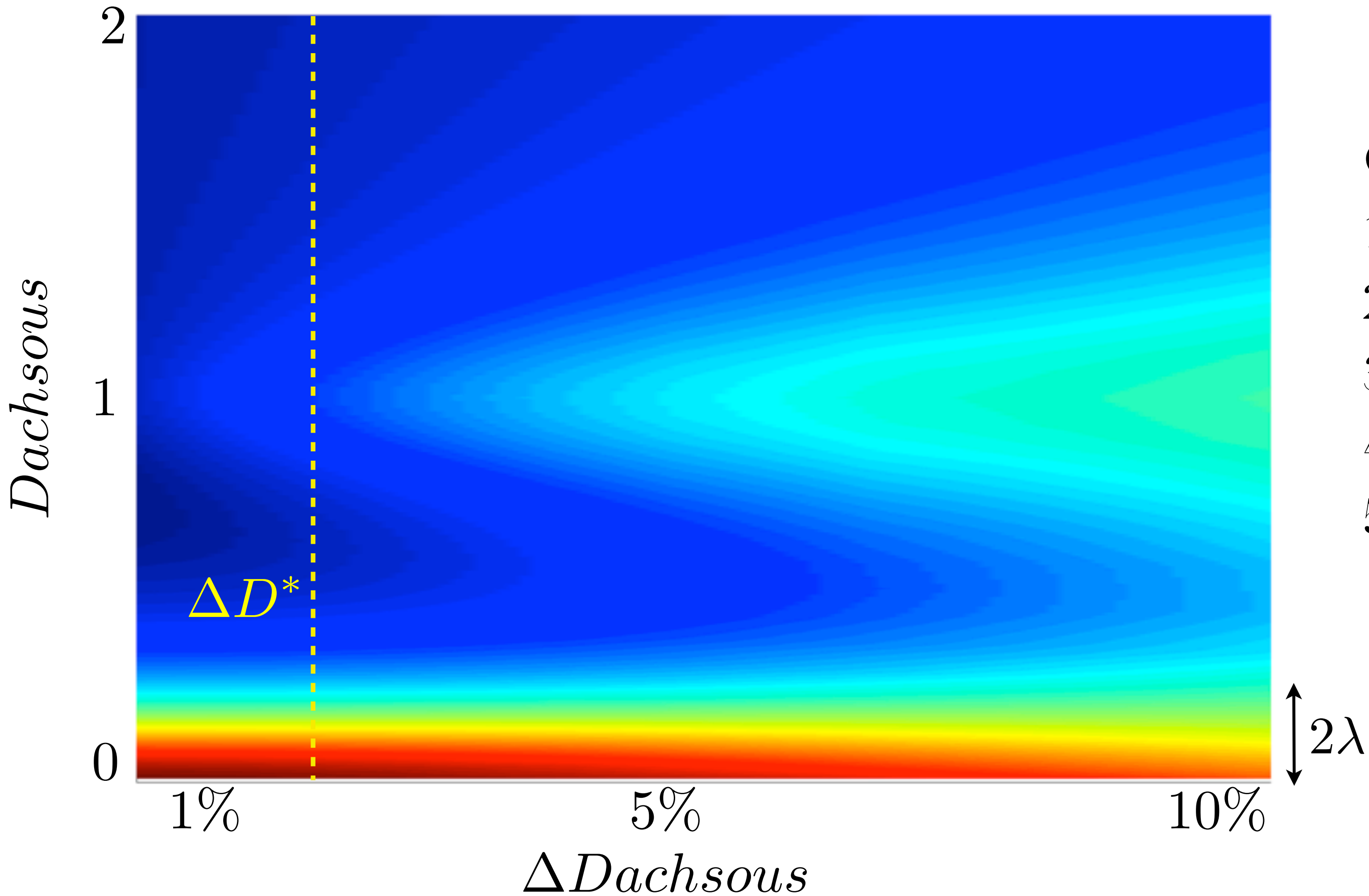
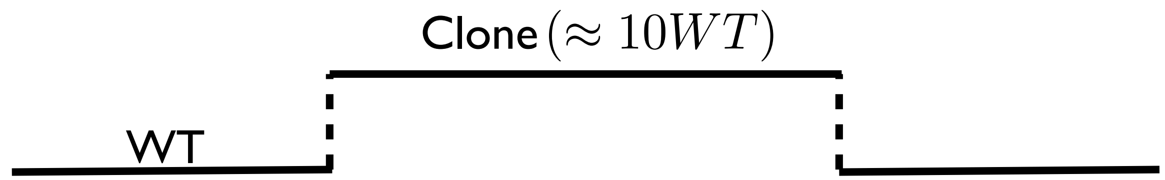


Questions

1) Signaling peak width?
2) Predictions? Quantitative vs Qualitative
3) Multiple gradients?
4) Dynamic picture?
5) Clones?

Response to over-expression (clones)



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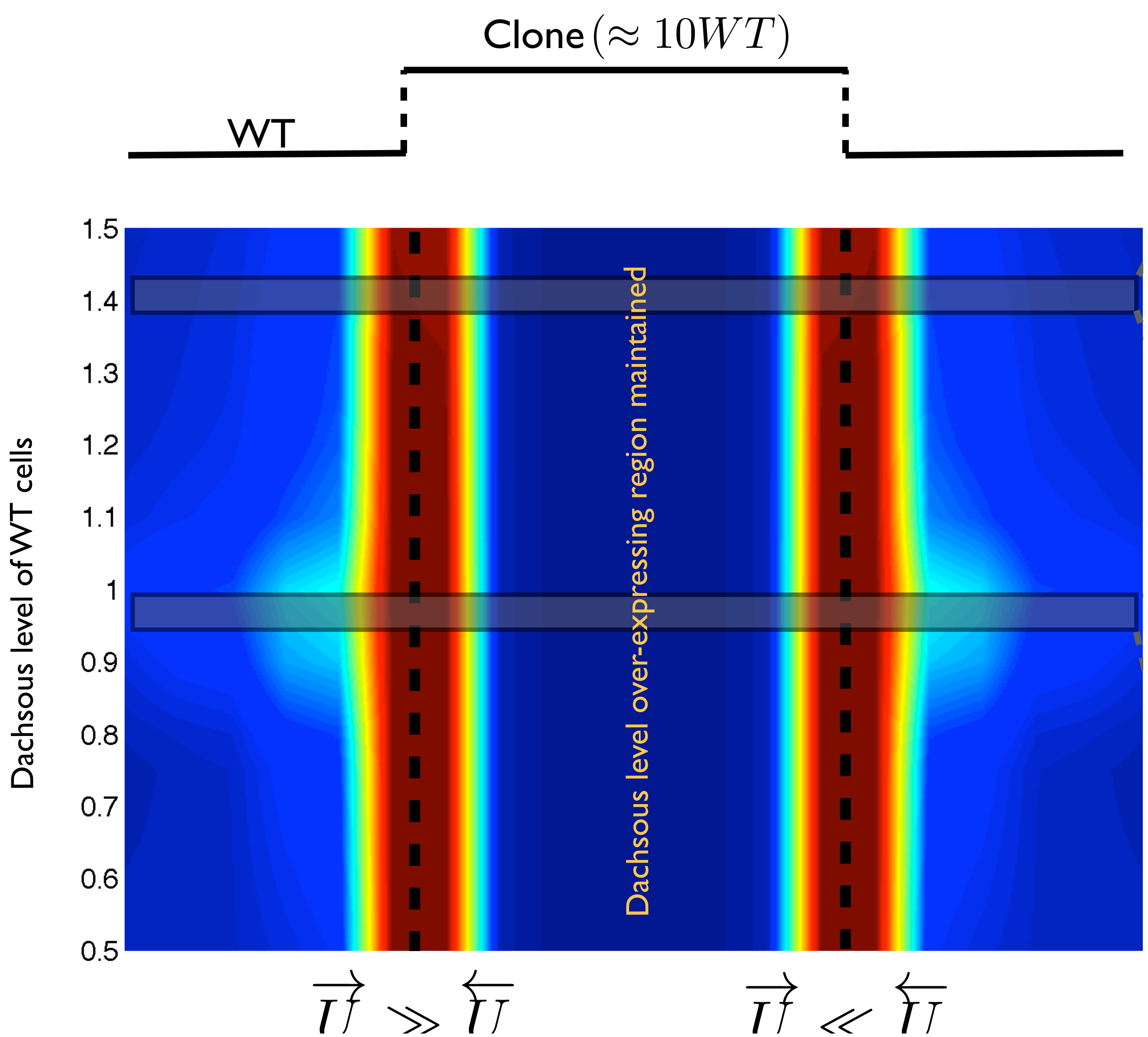

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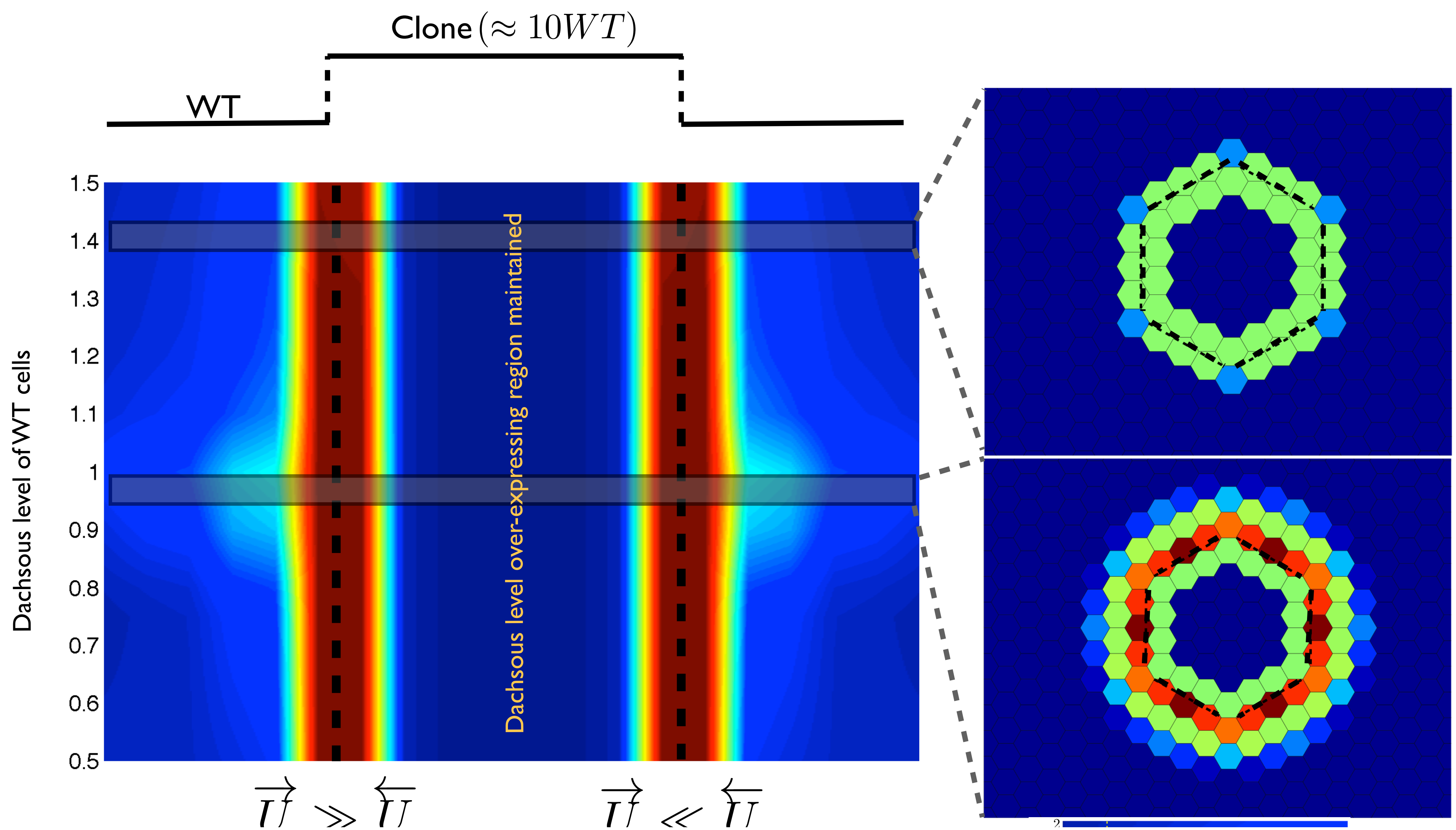

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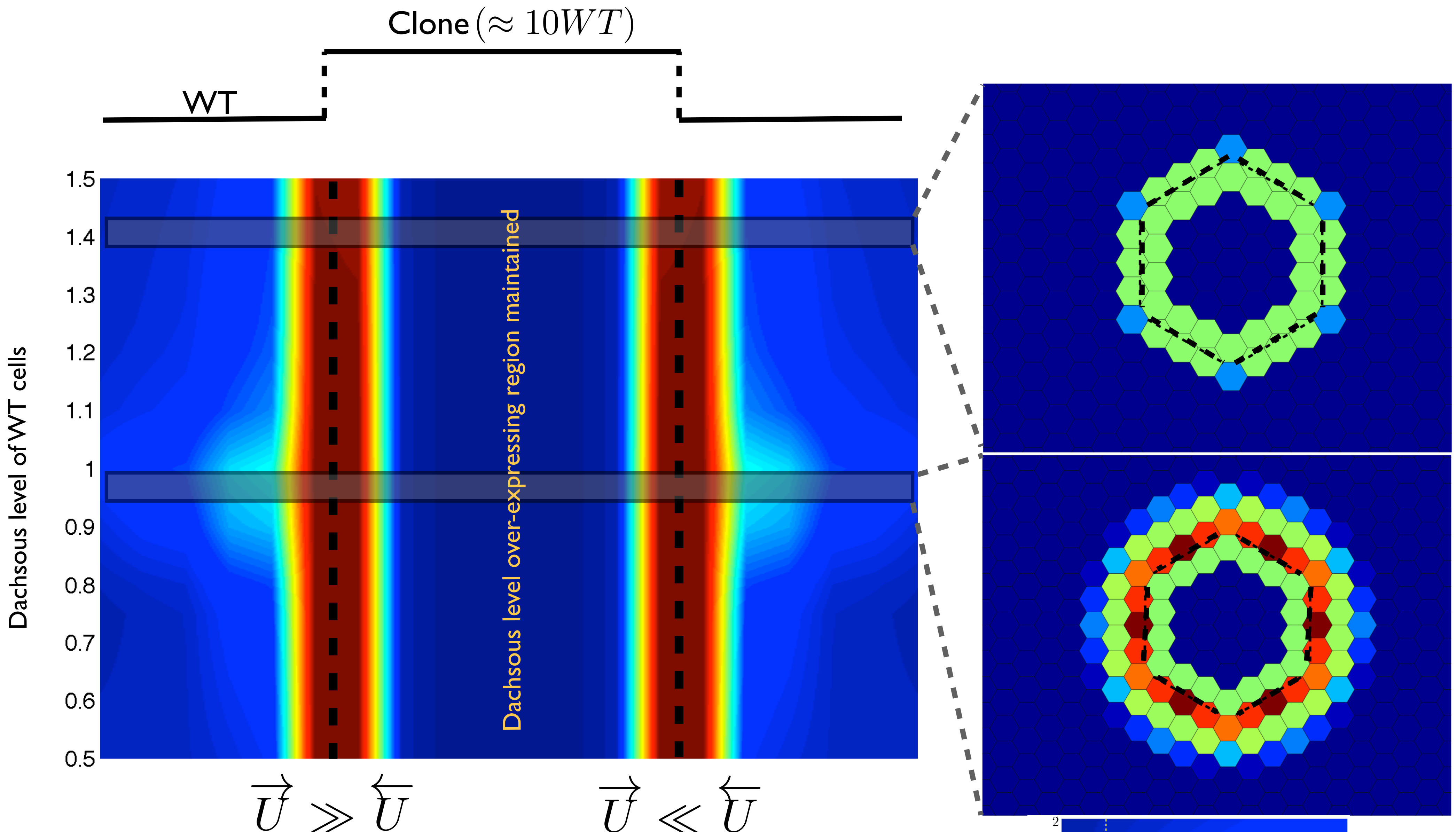
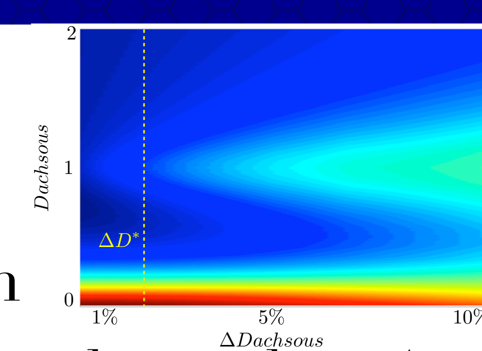




Features:

1) Edge response (with different polarity)

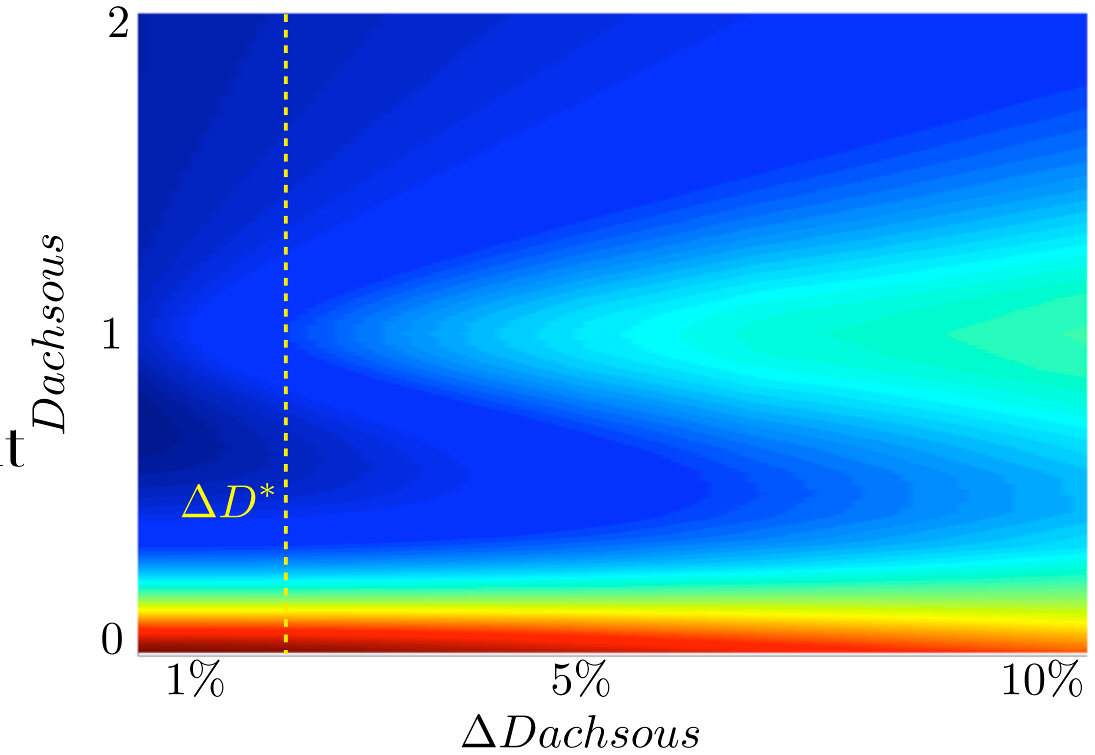
2) Low Fat-pathway activity within OE-region

3) Non-autonomous signaling that is Dachsous dependent (postional dependence of clone

4) Interpolating polarity within OE-region

Hypotheses

Qualitative hypotheses (in vivo)
1) Weak knockout --> undergrowth
2) Clones with gradient will not instigate growth
3) Position of Dachsous clone
4) Fat and Dachsous in approximately equal amount
5) Polarity in the interior of the clone ought to interpolate over a correlation length



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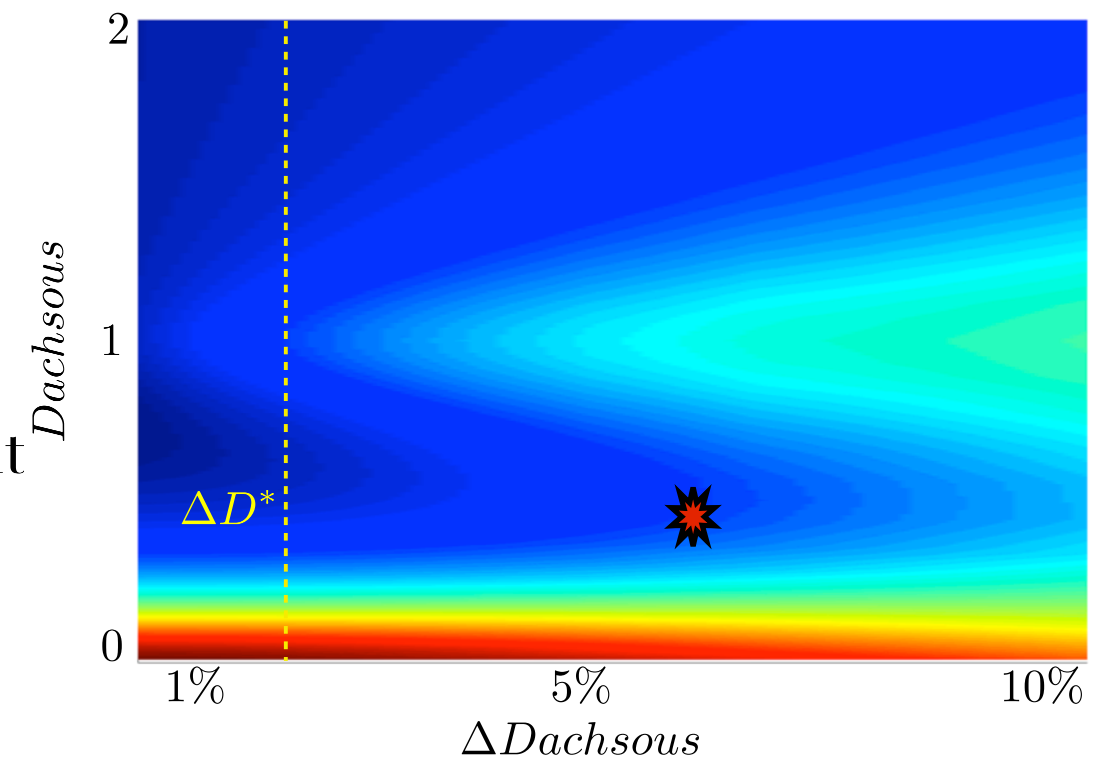

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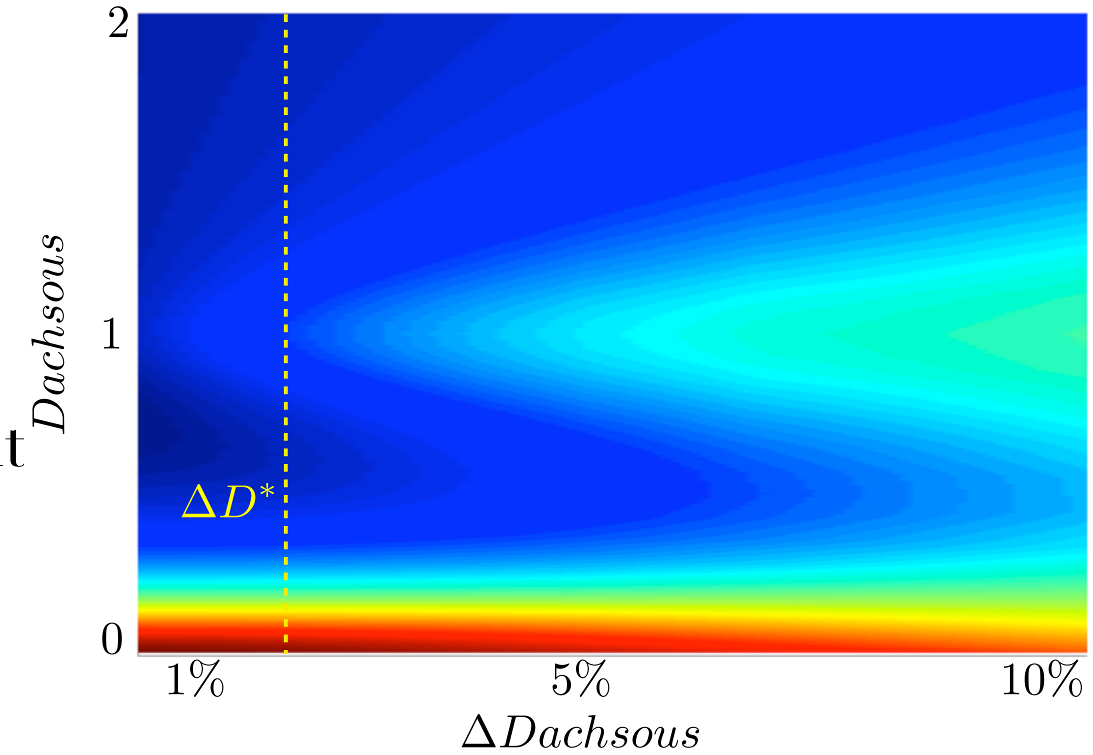

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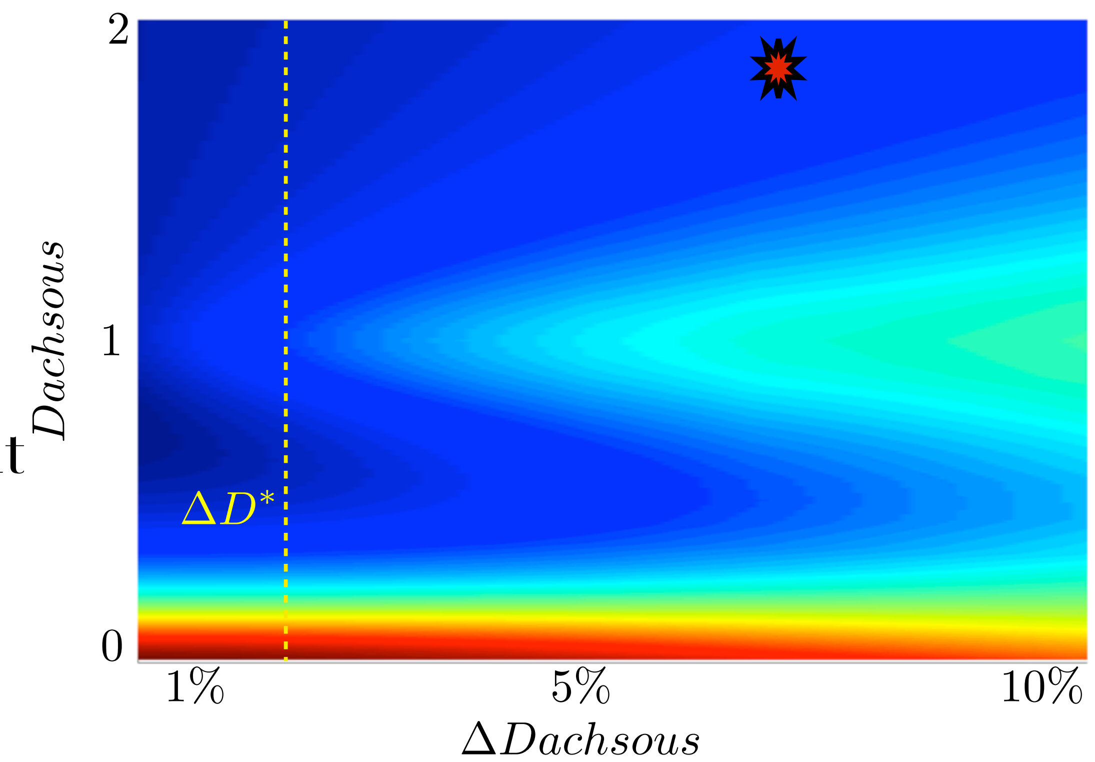

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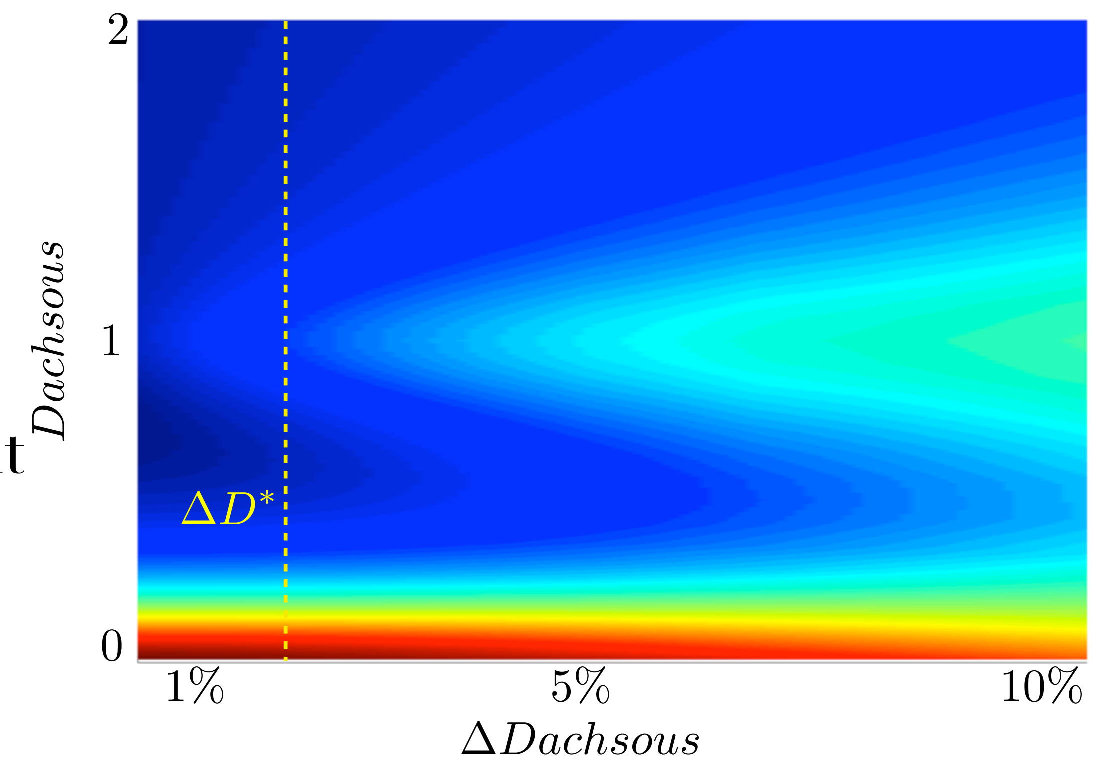

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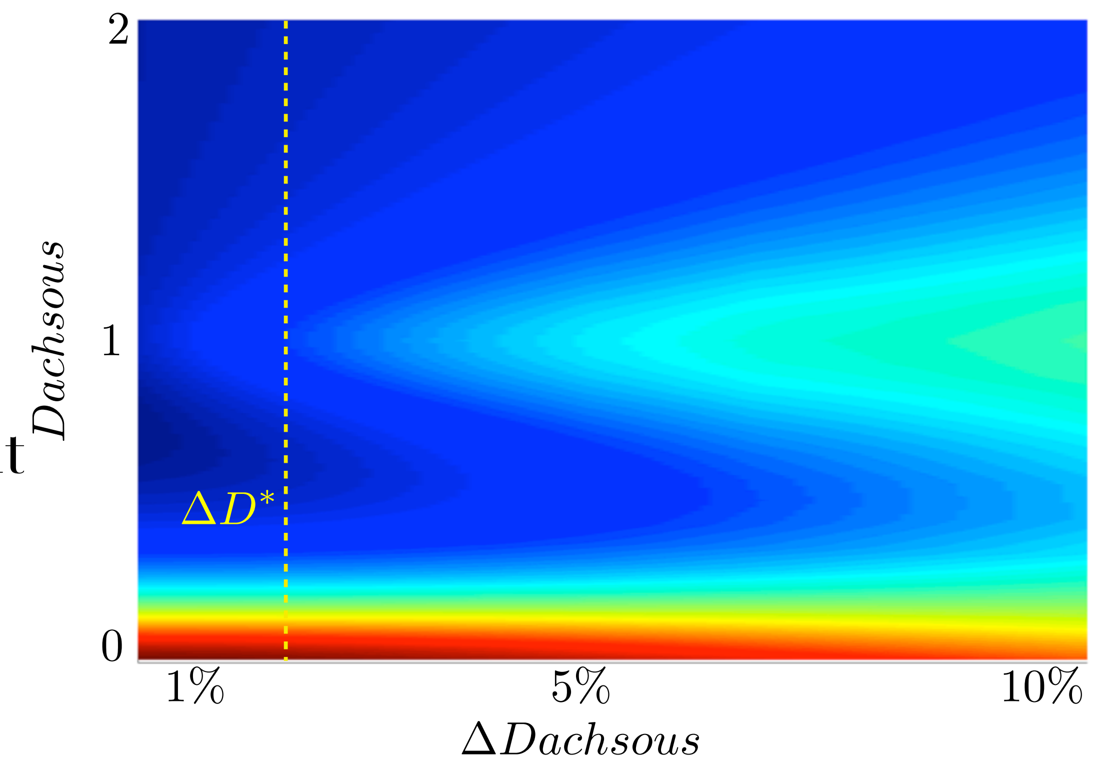

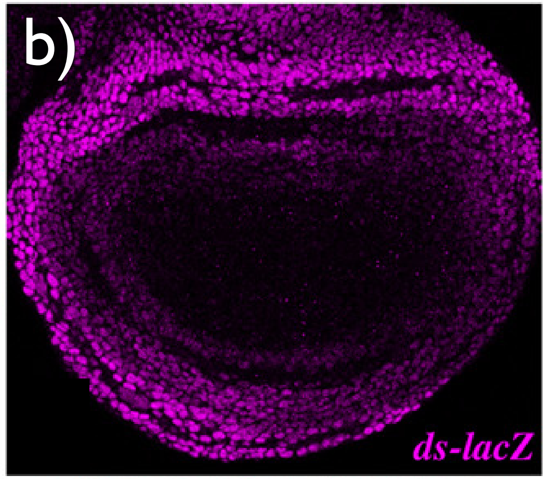

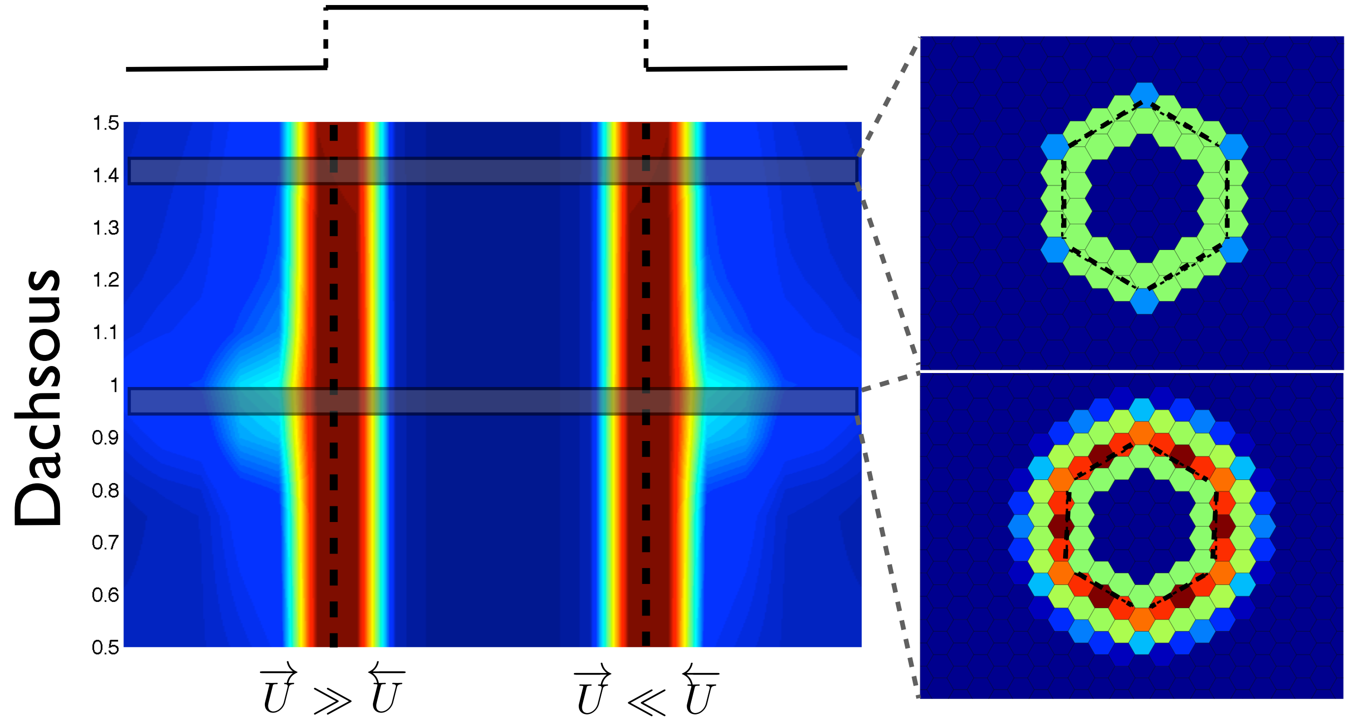

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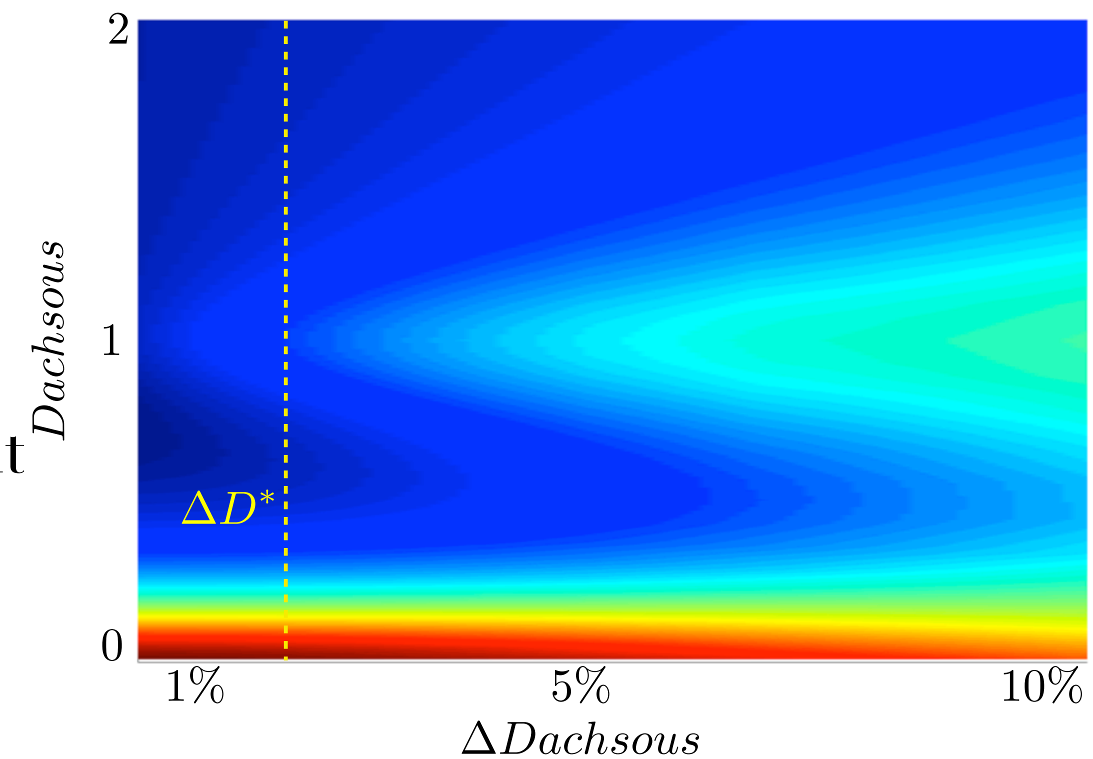

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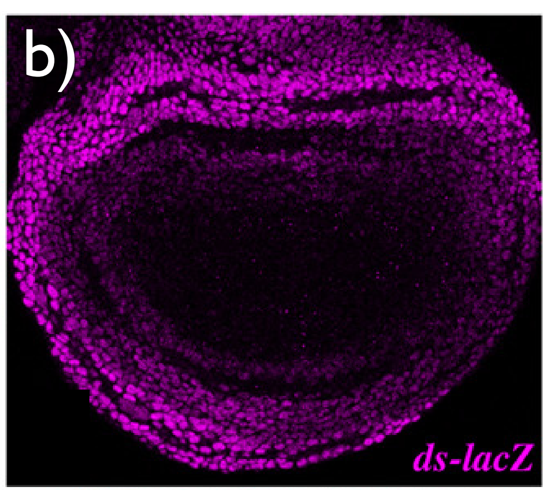

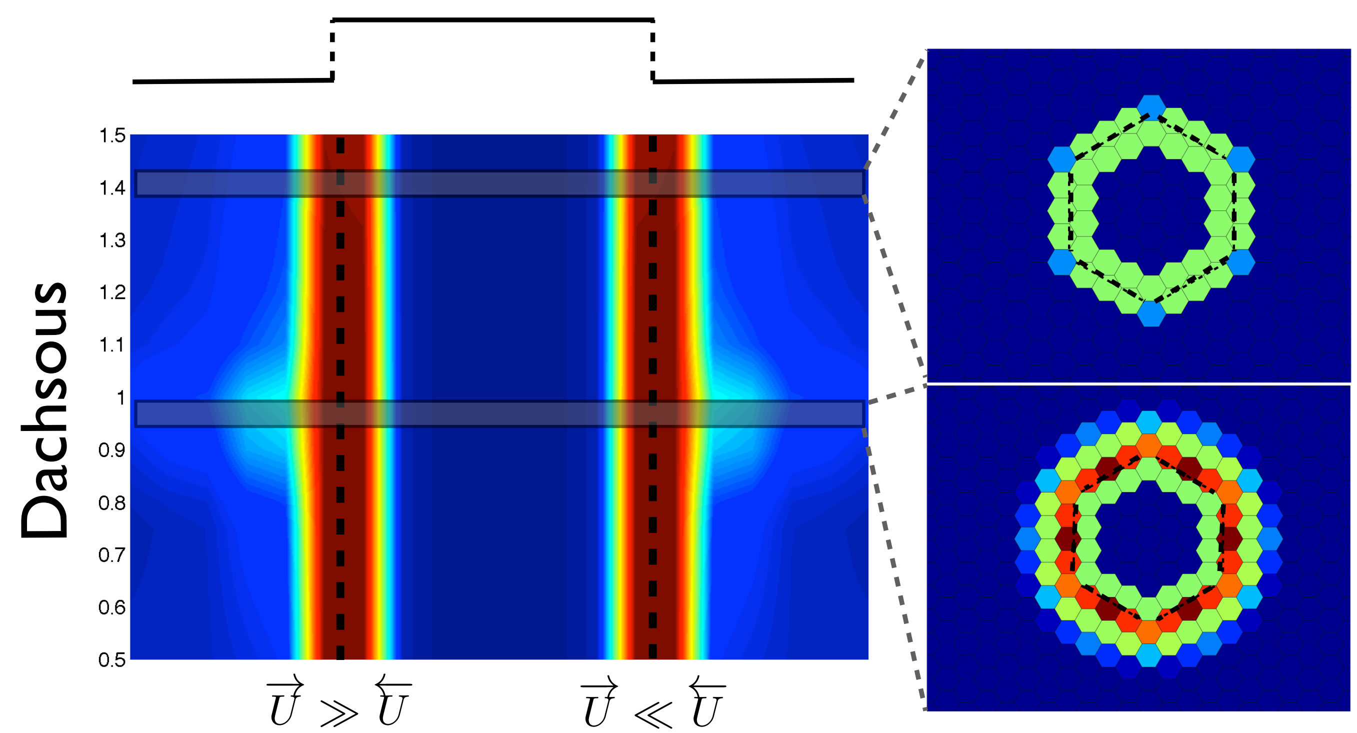

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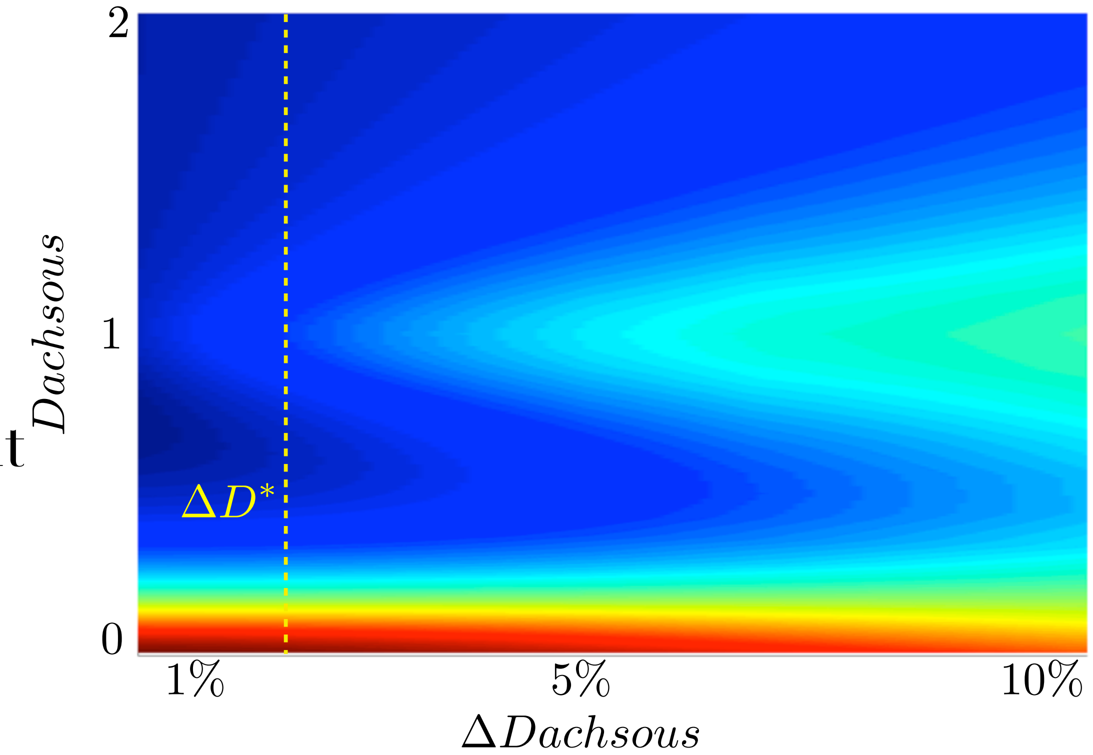

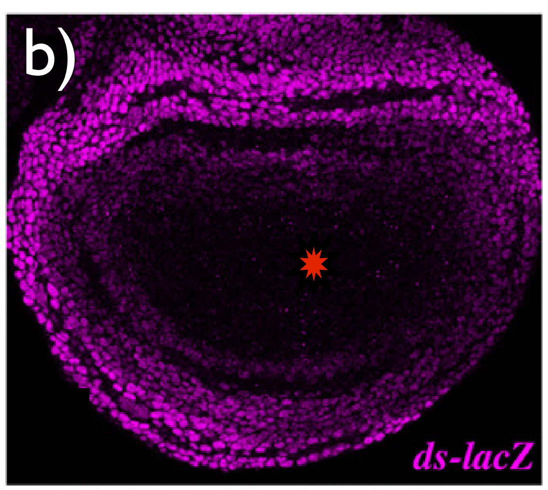

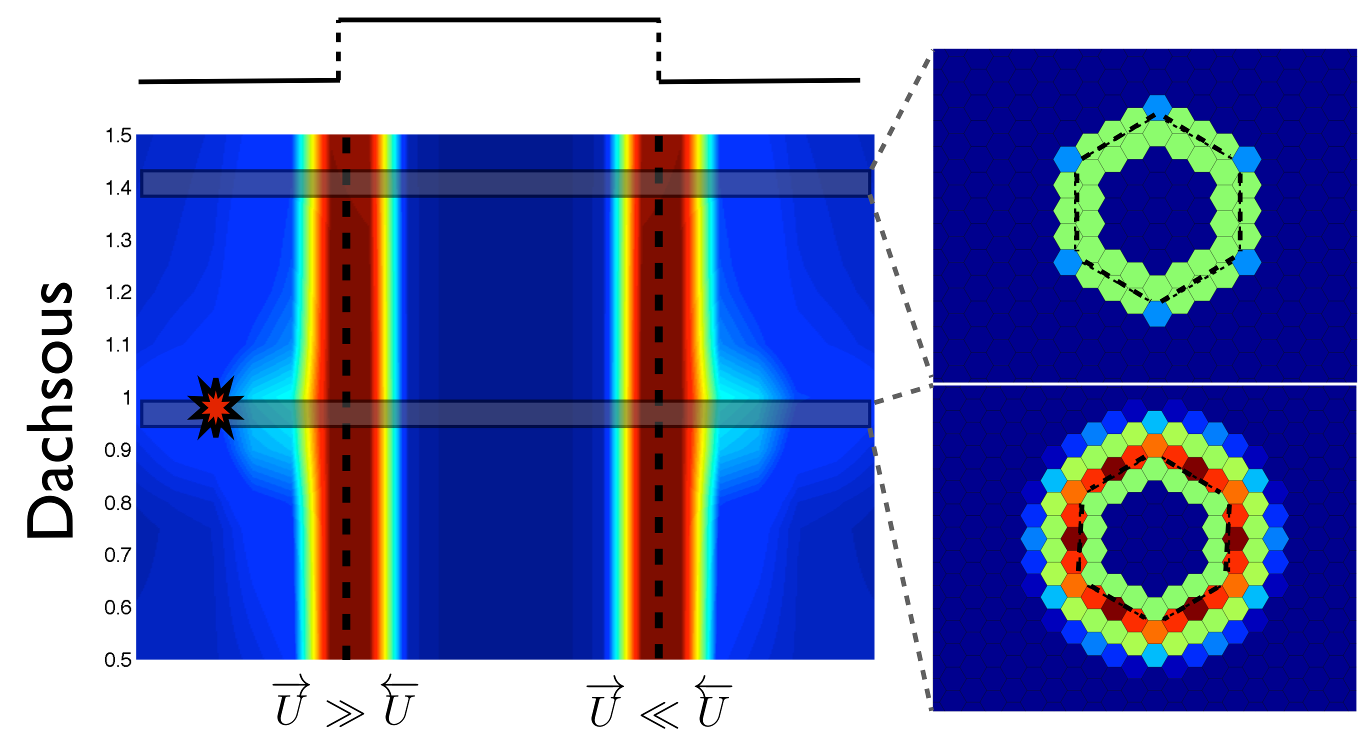

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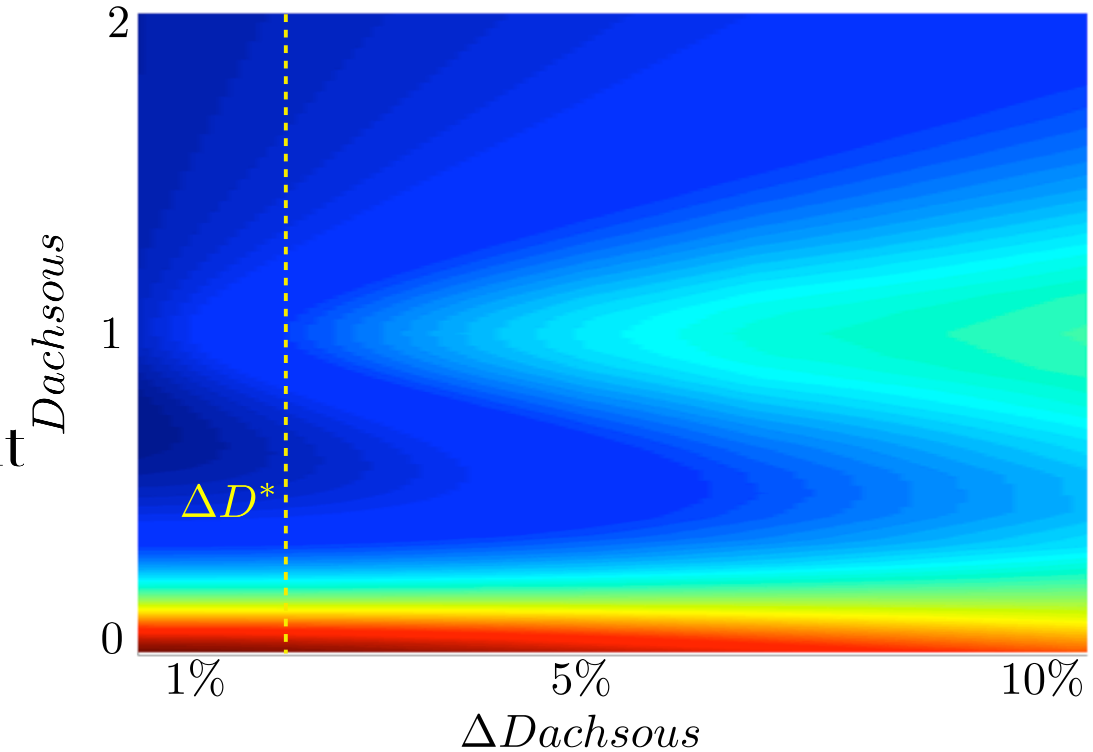

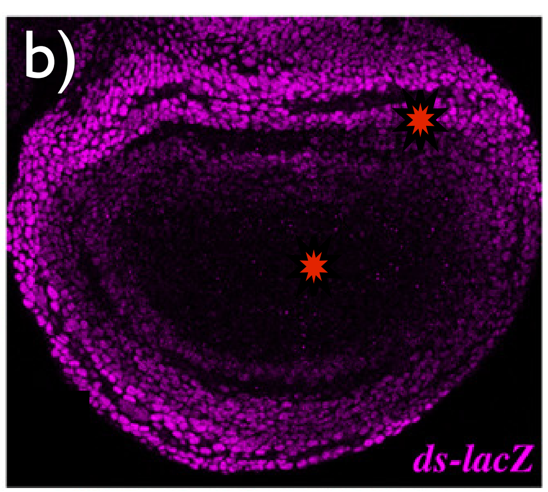

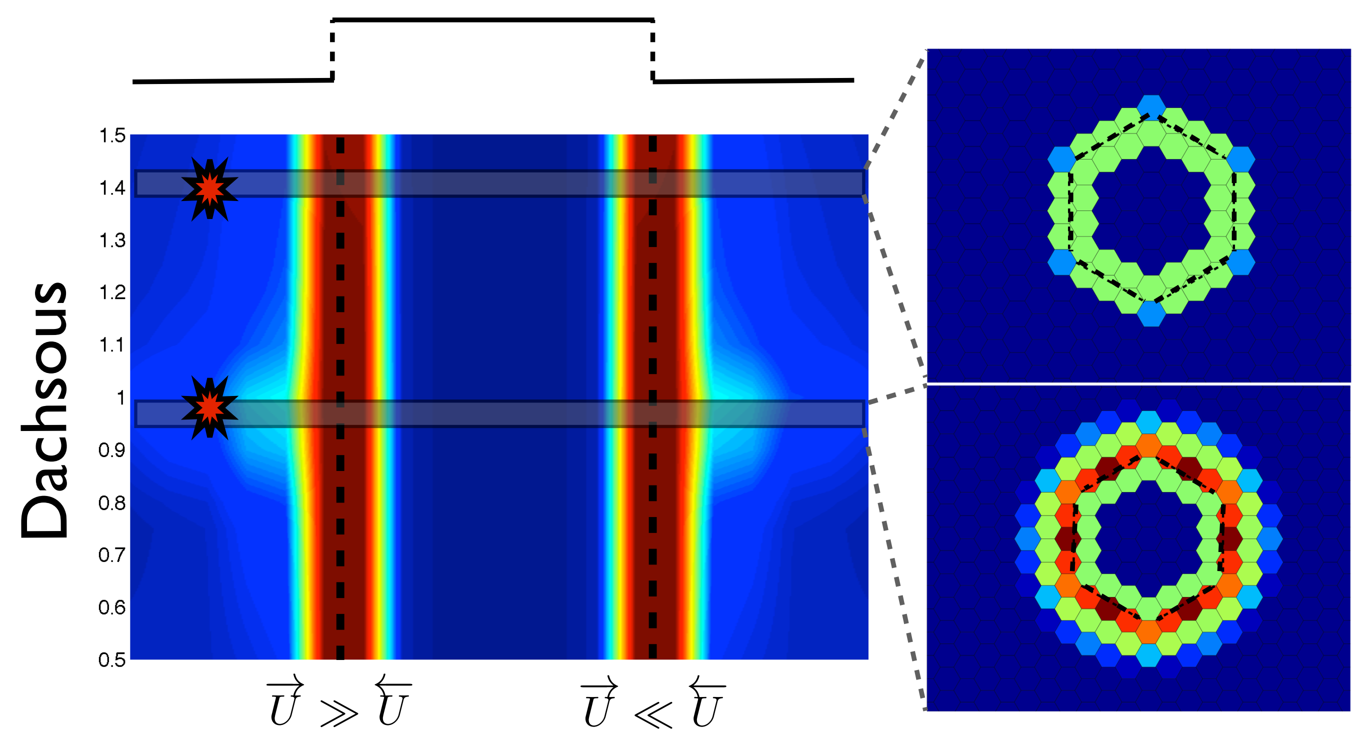

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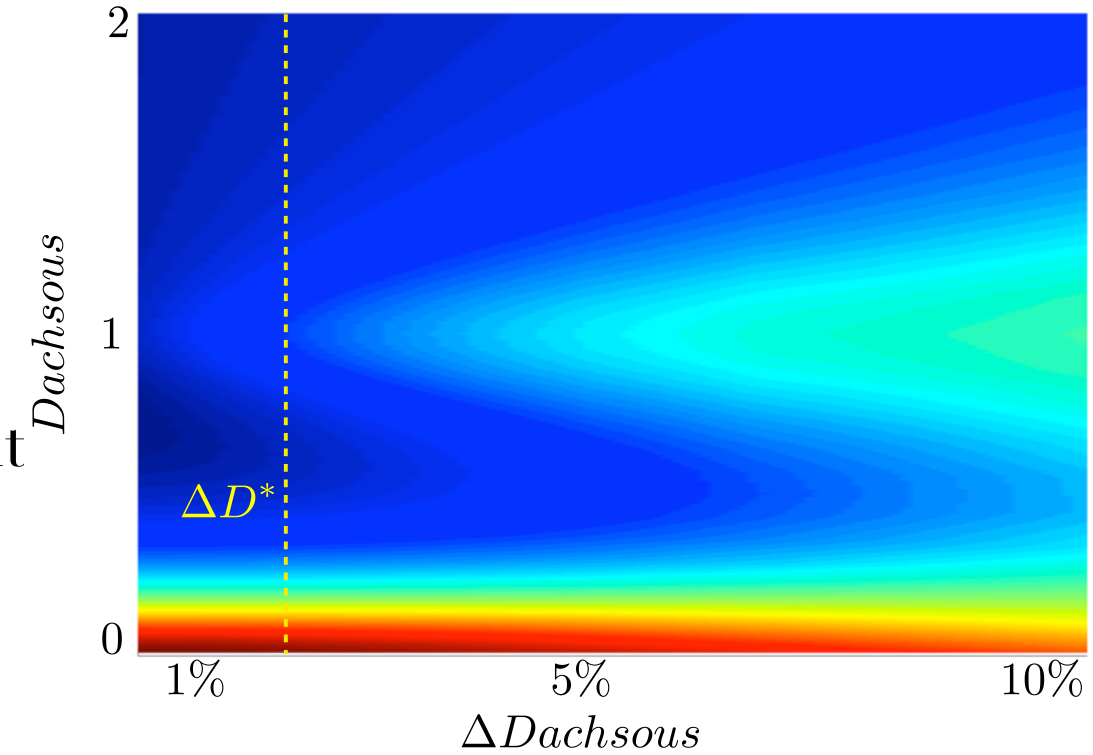

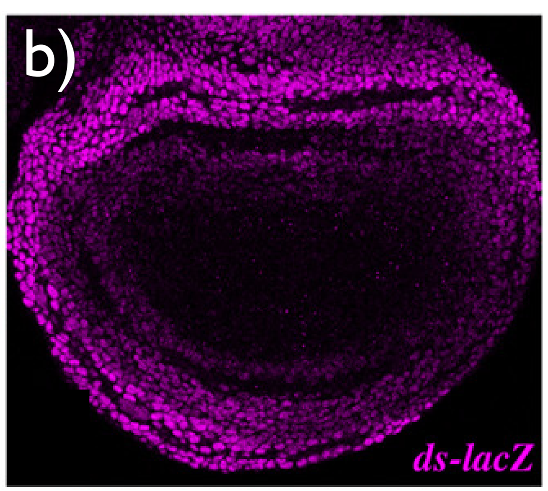

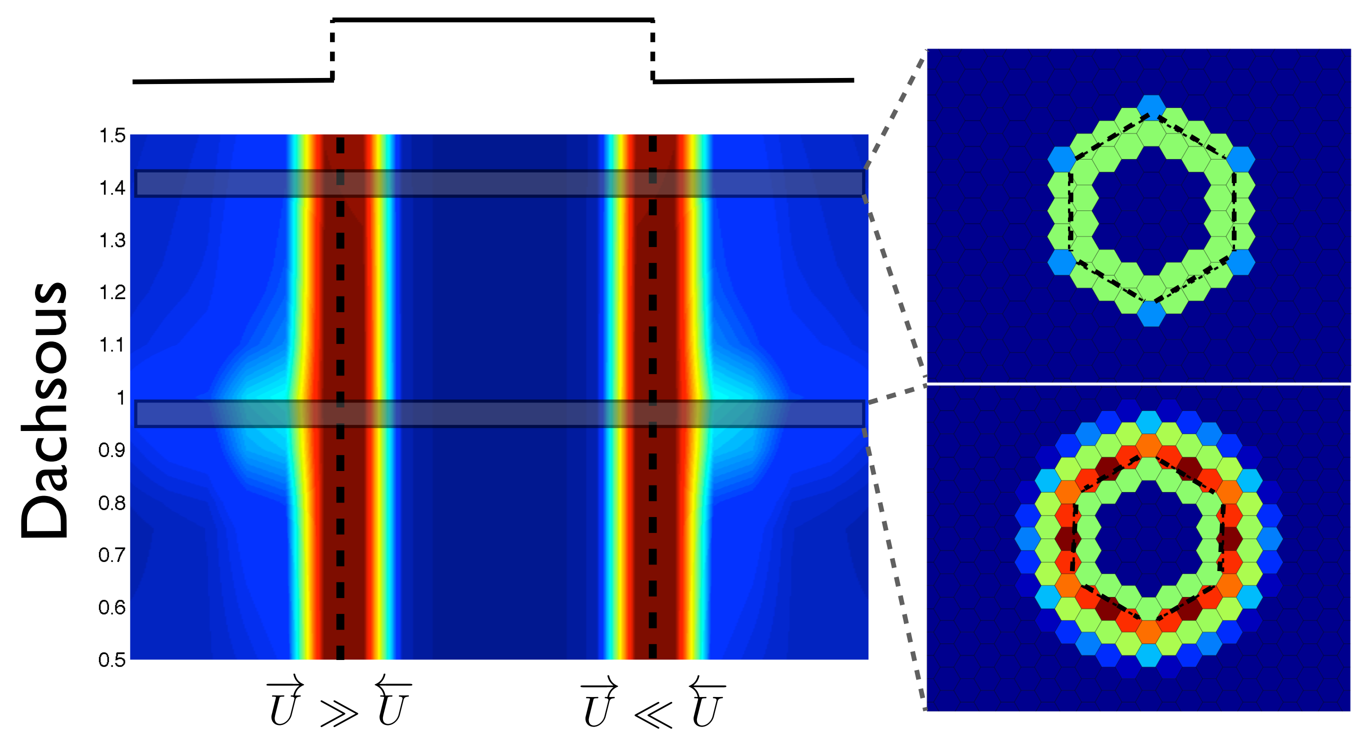

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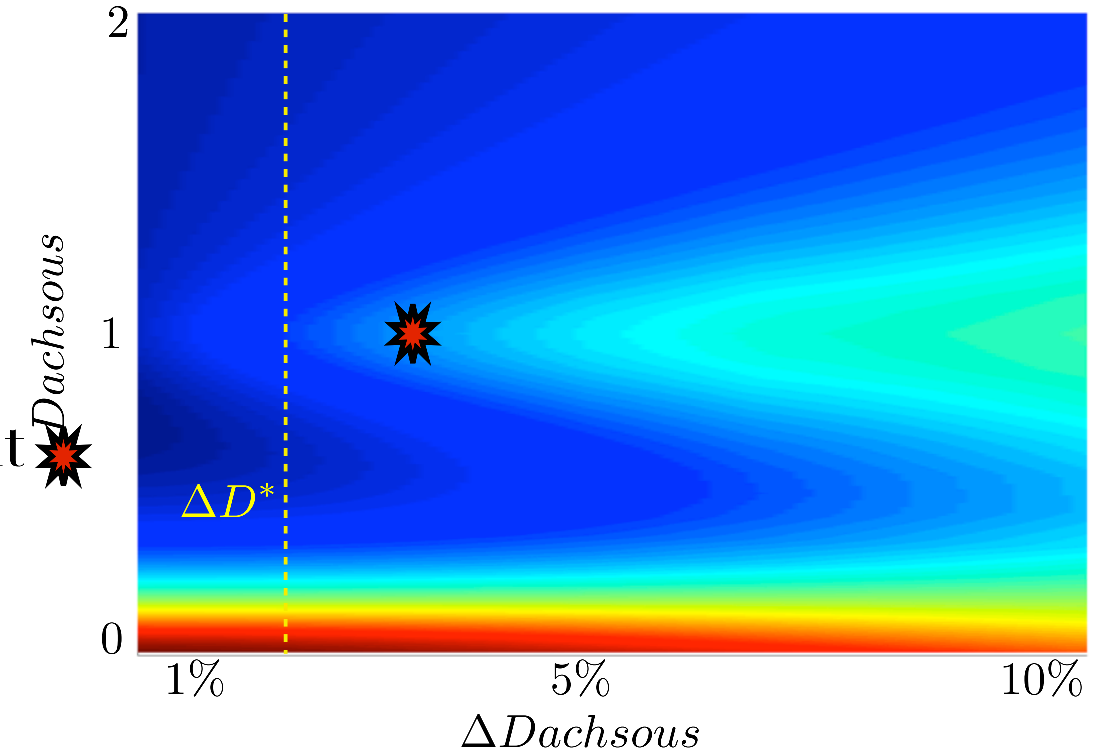

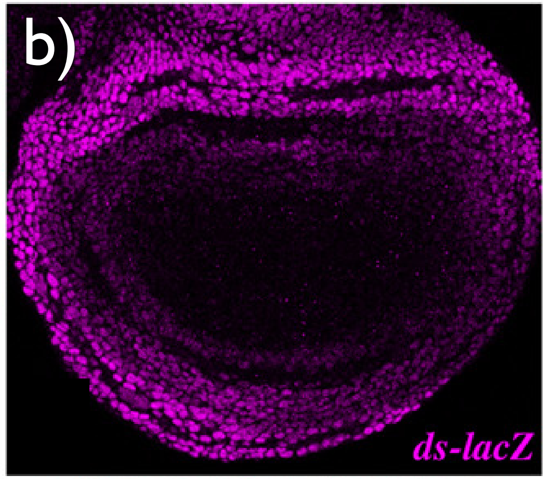

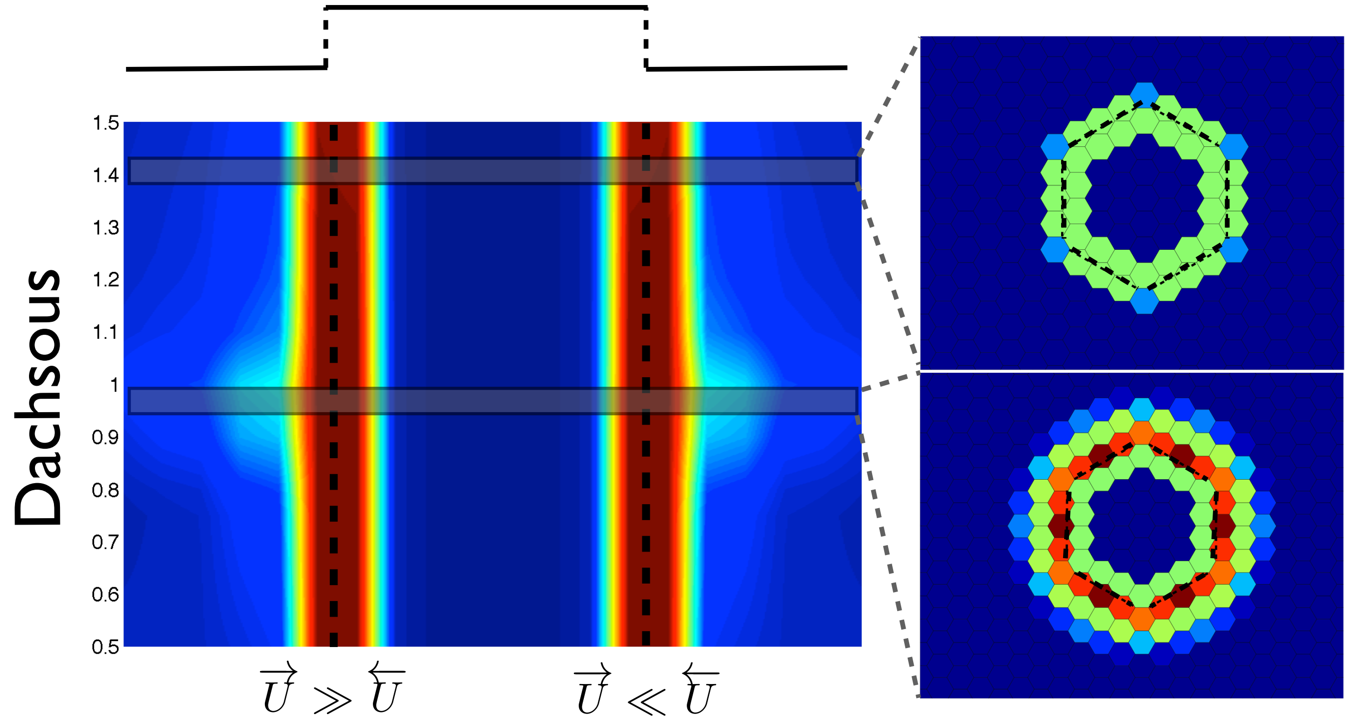

Hypotheses

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Qualitative hypotheses (synthetic - David Sprinzak)

1) Testing the existence of cooperative interactions (strength of alpha, beta etc)
2) Possibly see transition as a function of absolute level
2) Non-autonomy in a multi-cell assay

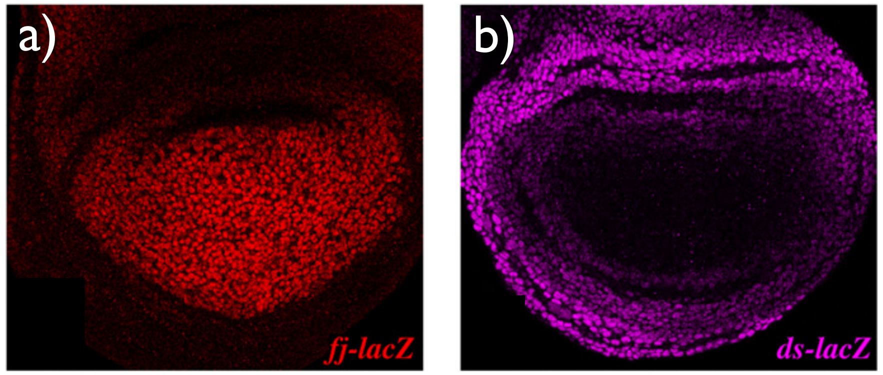
Shortcomings, Cynicism and things I don't understand

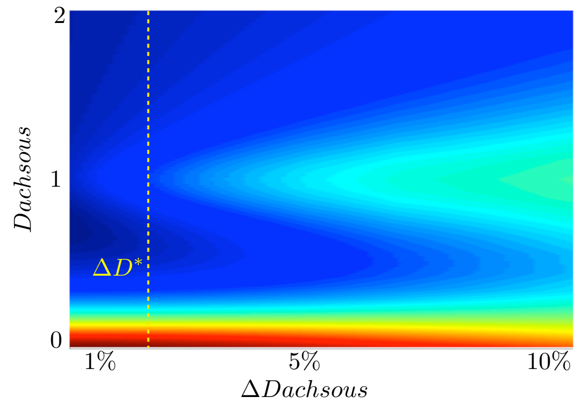
1) Why are the profiles of Fj and Ds what they are? Fail

Potentially helpful observations would be:

a) Dynamics of initiation of these profiles

b) Fat profile





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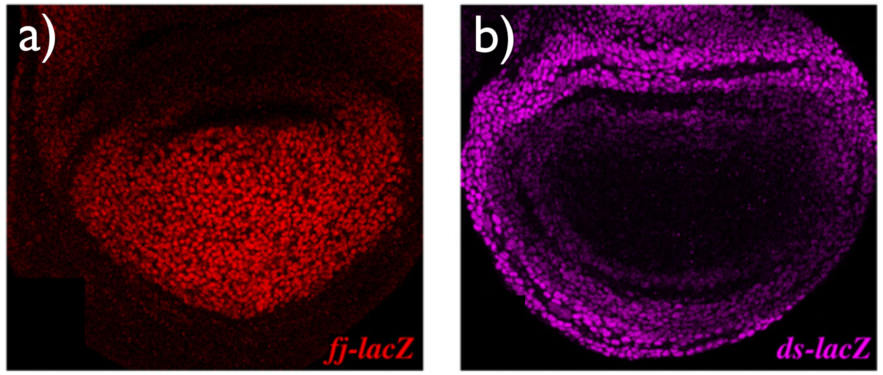
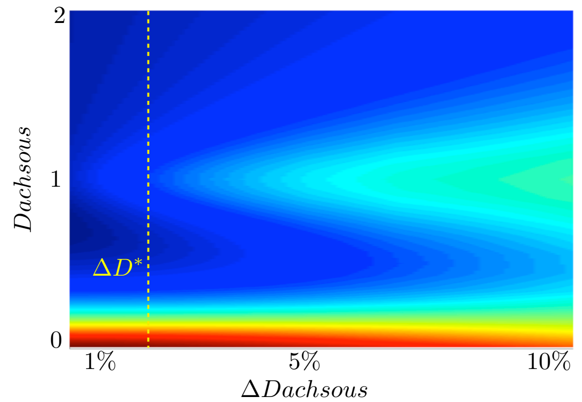


2) Four-jointed feedback: How do we include such an effect? How much of Fj is under Dpp control and how much under growth feedback?



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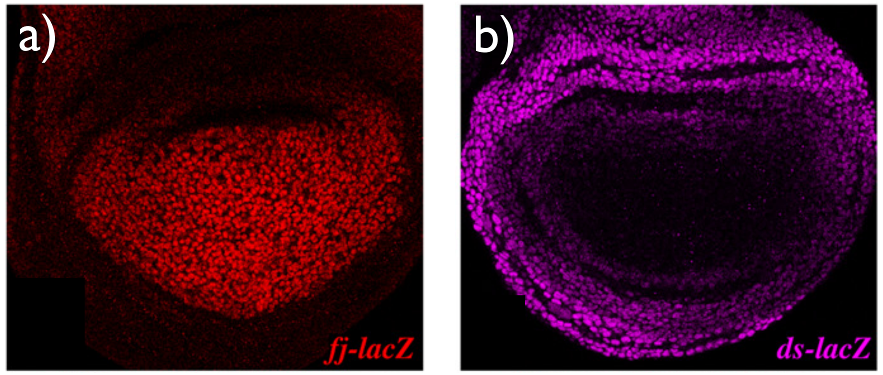

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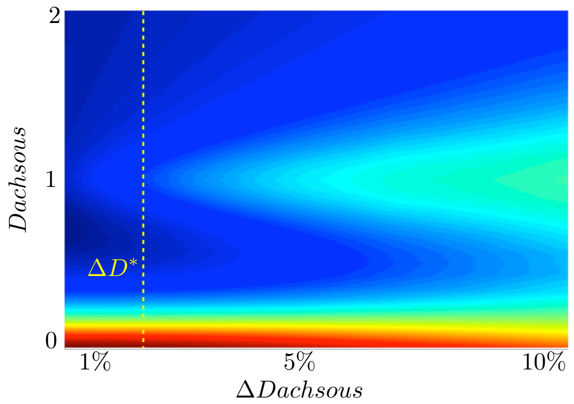

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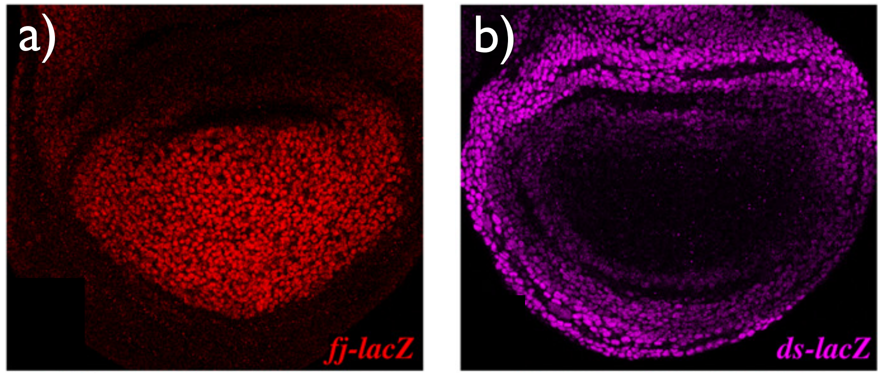

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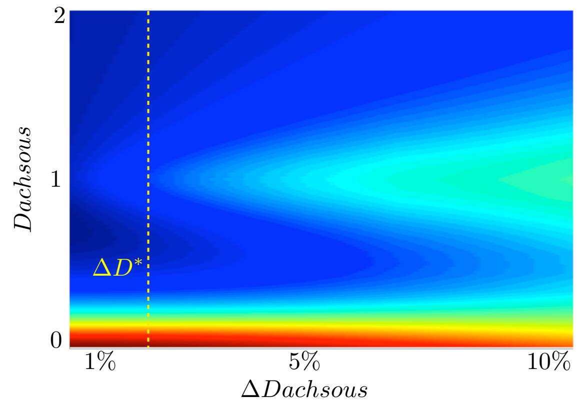

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Could the Fat pathway allow communication across the wing-disc?

A hypothesis

$$Growth$$

$$\downarrow$$

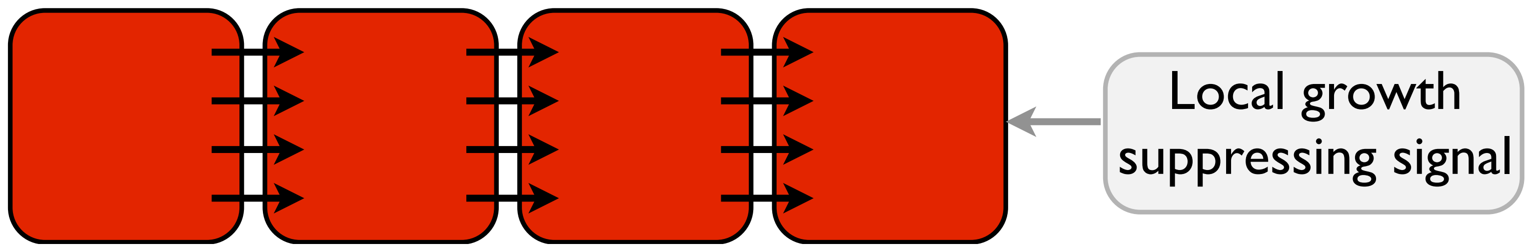
$$Four-$$

$$jointed$$

$$\downarrow$$

$$\alpha \ \& \ \beta$$

A hypothesis



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↓

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α & β

A hypothesis

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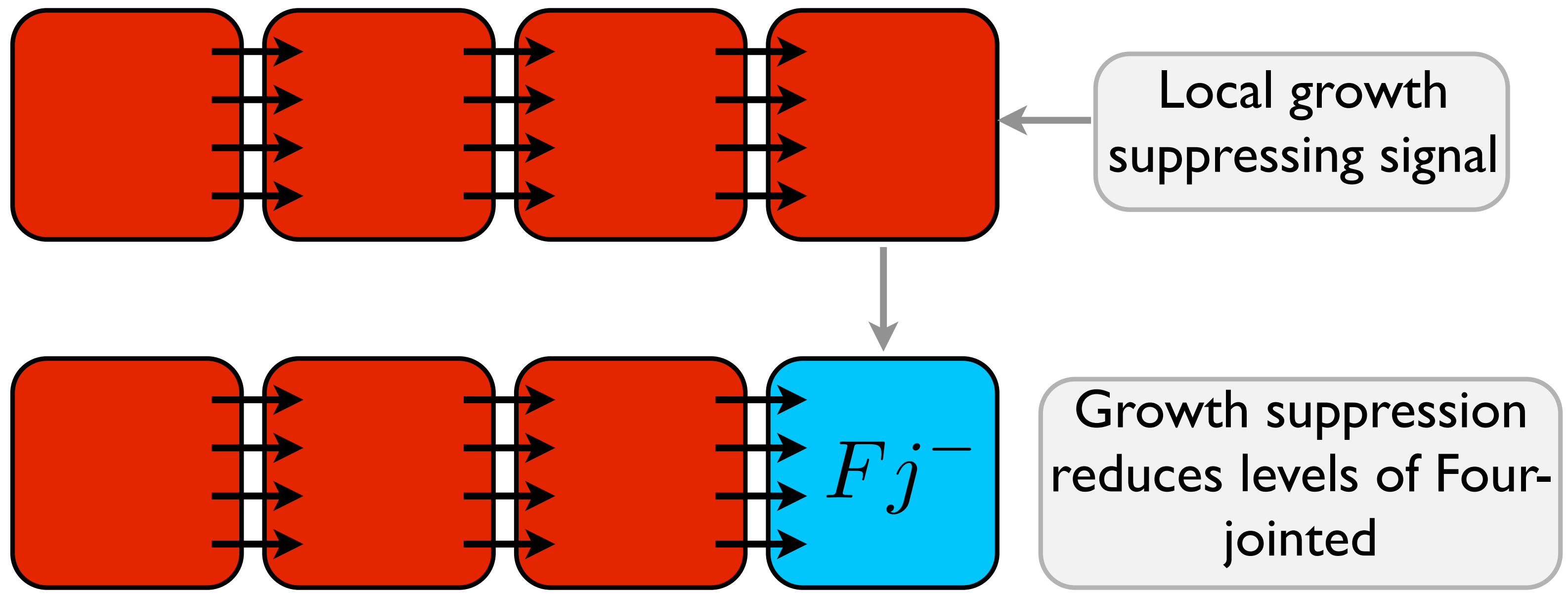

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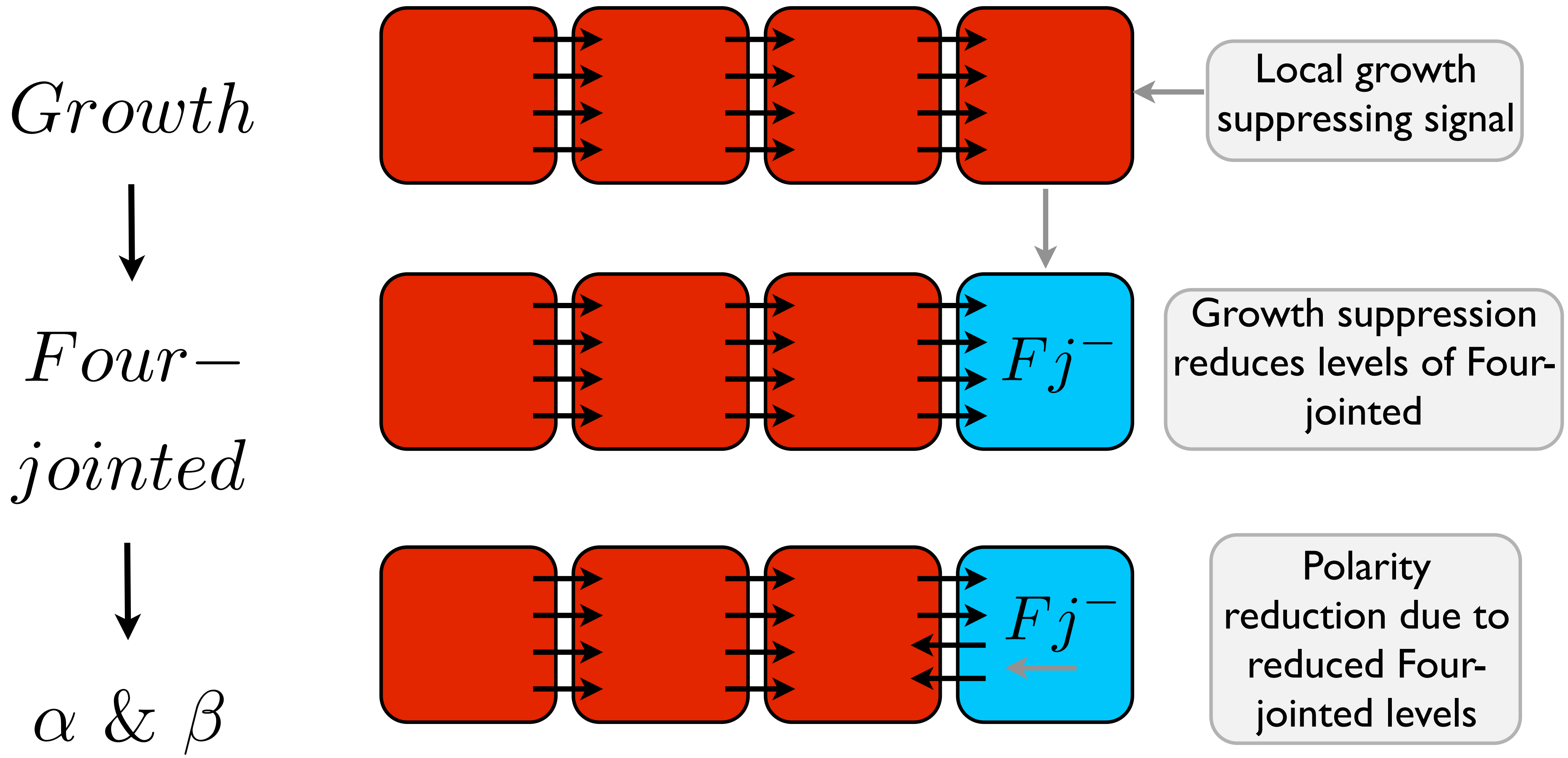

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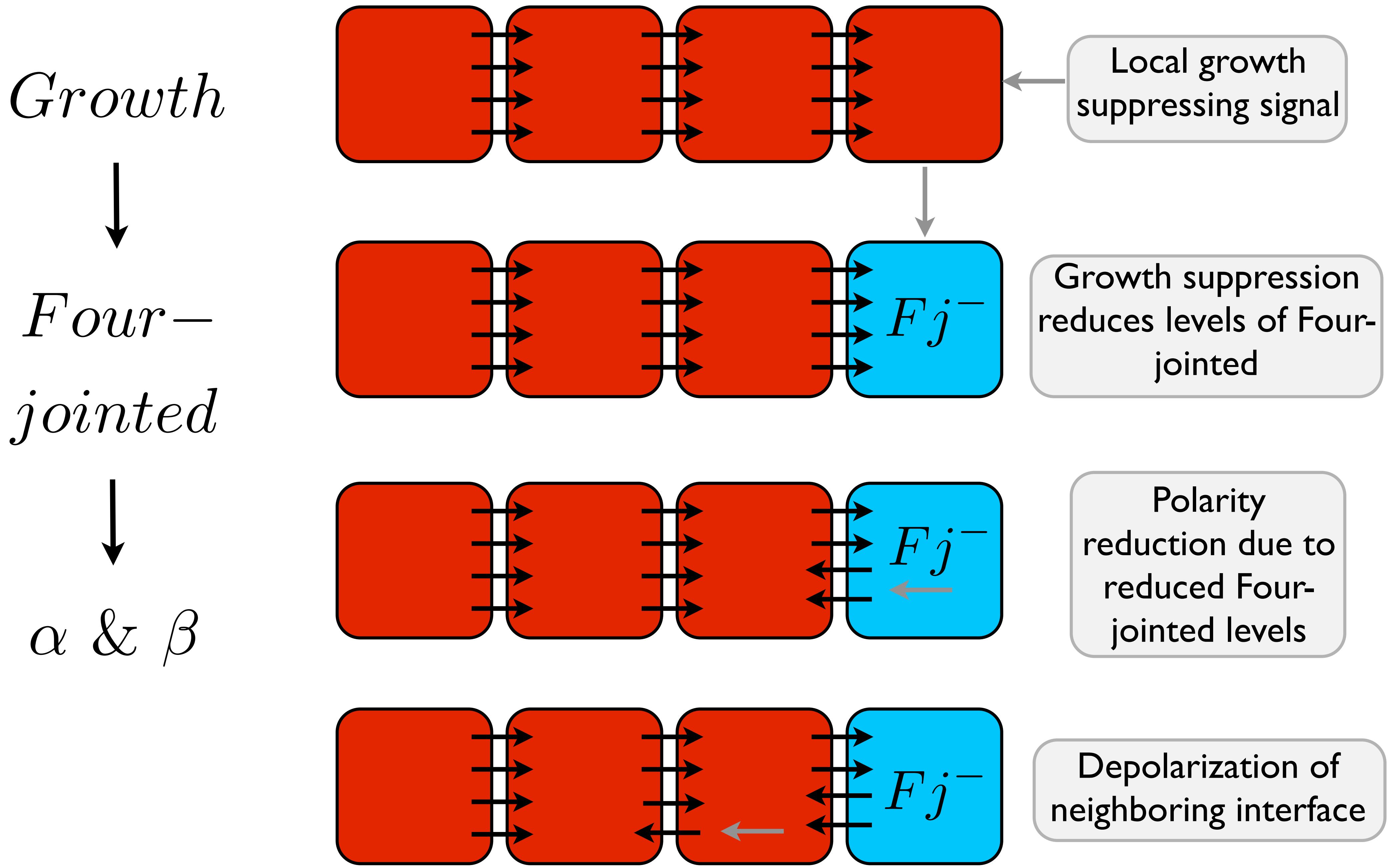

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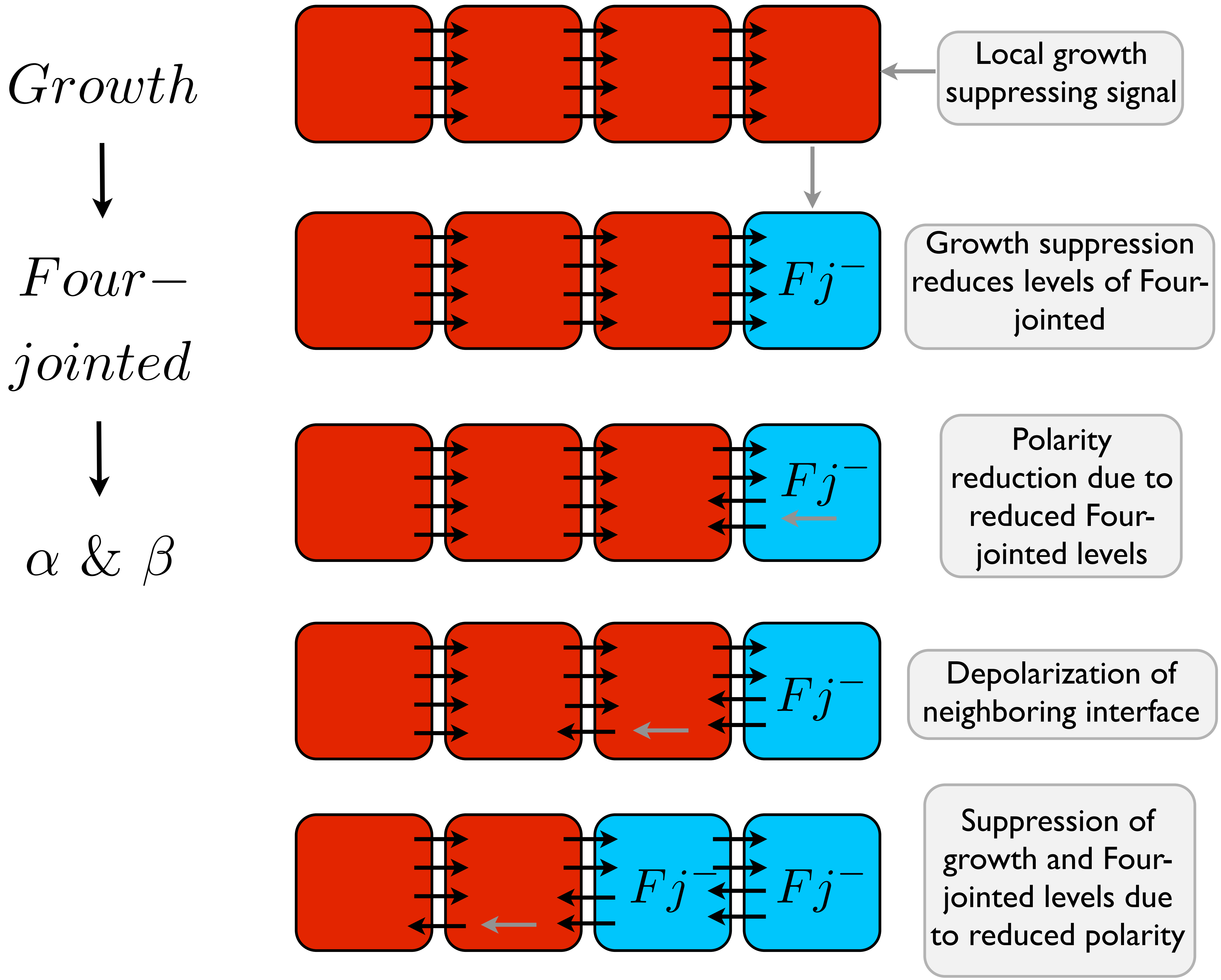

Thank you for listening

Thank you for listening

Thank you to Sid, Ken and Boris

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This fruit fly
It reveals to us
How nature designs
Amidst all the fuss

We relentlessly study
With all our might
The order and beauty
Of your bristles and stripes

When will you ever reveal
Your singular principles
Or will we forever feel
Ensconced with something mystical