Dissecting the logic of PCP signaling: complex patterns from simple rules

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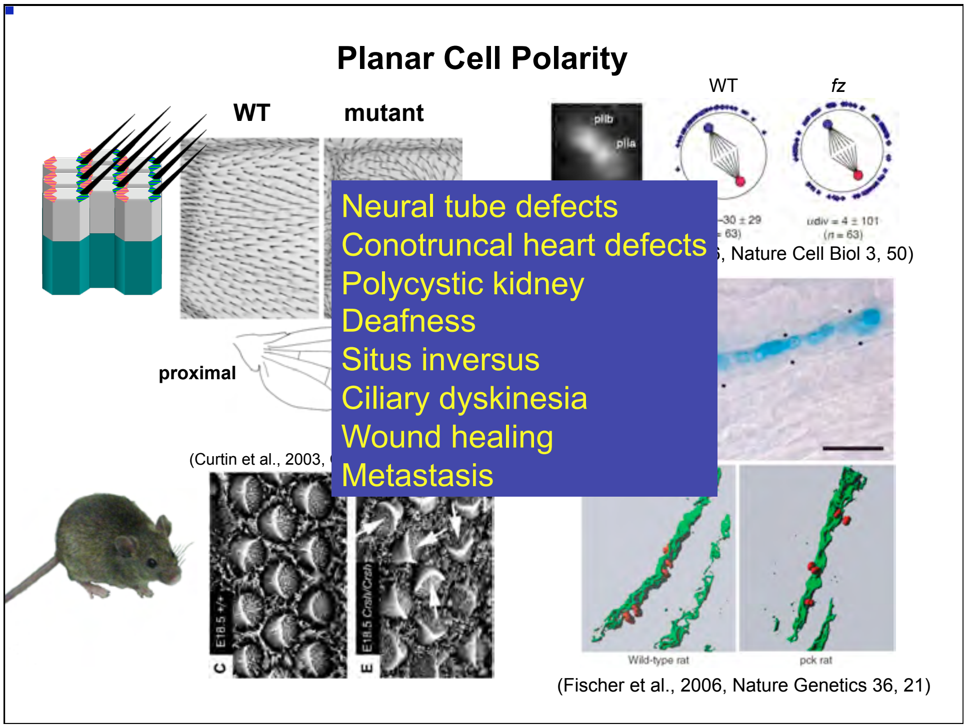
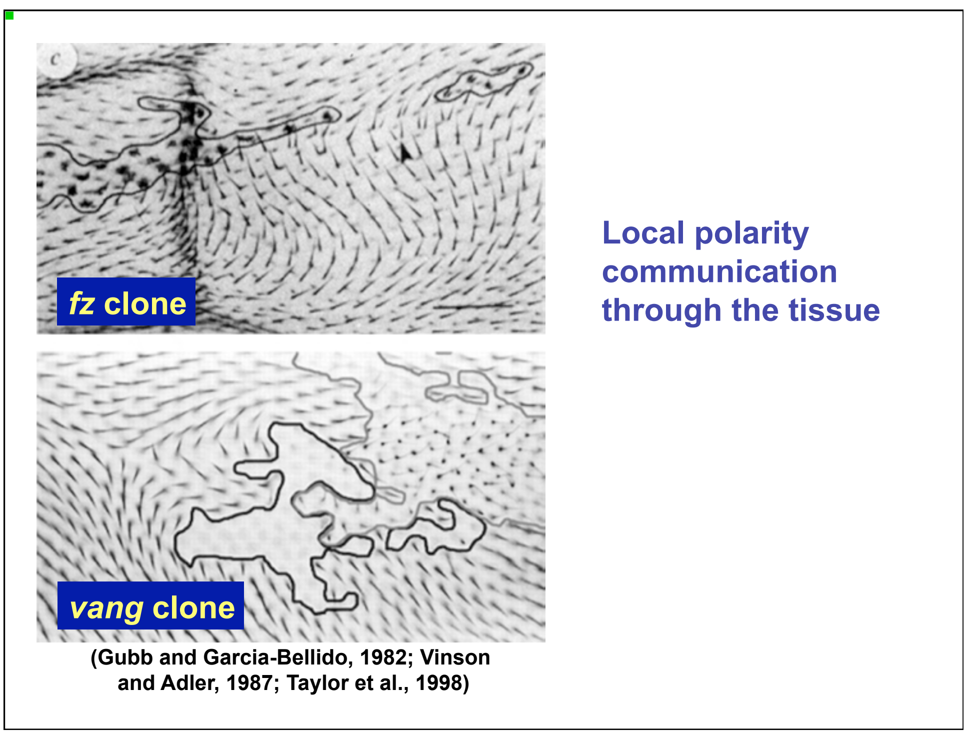
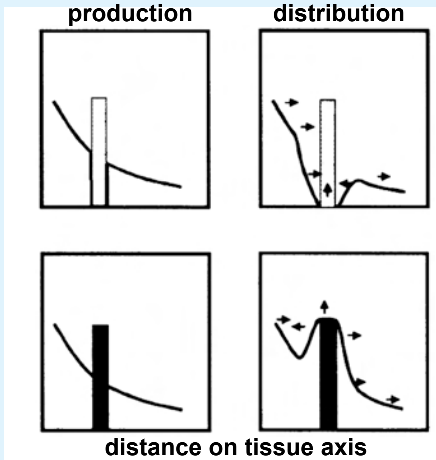
Nutrition Facts


PEPSI
Nutrition Facts


Planar Cell Polarity
WT
mutant
proximal
(Curtin et al., 2003,
WT
fz
, Nature Cell Biol 3, 50)
Neural tube defects
Conotruncal heart defects
Polycystic kidney
Deafness
Situs inversus
Ciliary dyskinesia
Wound healing
Metastasis
Wild-type rat
pck rat
(Fischer et al., 2006, Nature Genetics 36, 21)

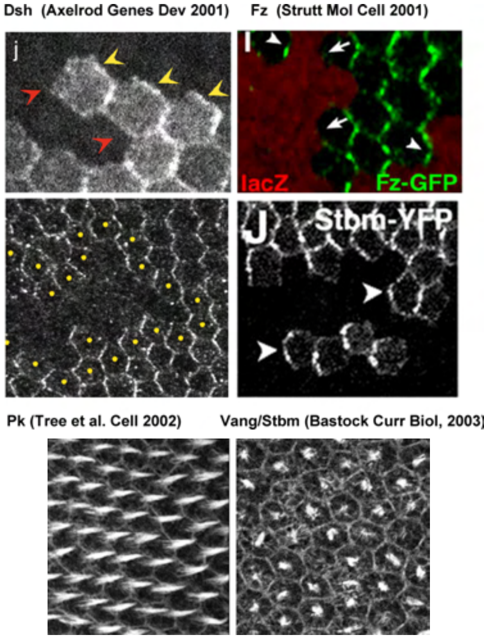

fz clone
vang clone
(Gubb and Garcia-Bellido, 1982; Vinson
and Adler, 1987; Taylor et al., 1998)
Local polarity
communication
through the tissue

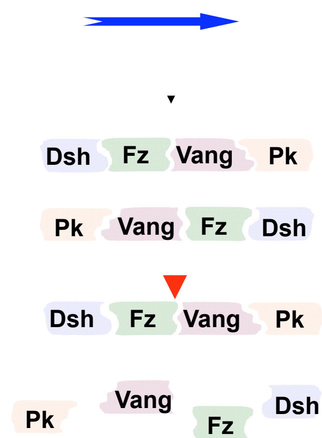
Factor X Model



(Wehrli and Tomlinson, 1998; Adler et al., 2000; Rawls et al, 2002; Adler, 2002; Strutt and Strutt, 2002; Lawrence et al. 2002; Fanto et al. 2003; Bastock et al. 2003)

Model for Fz and Pk participation in a feedback loop

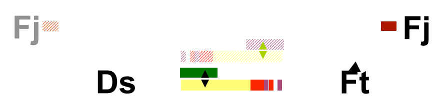




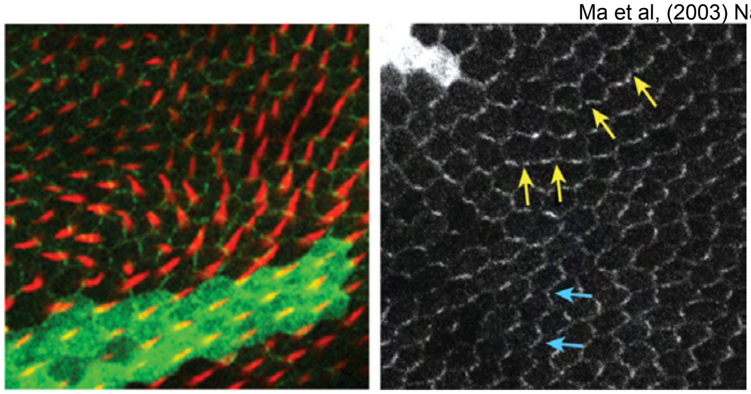
bistability
tendency to local alignment

adapted from Tree et al. (2002) Cell

Gradient conversion and amplification

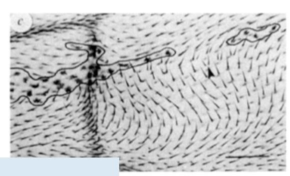


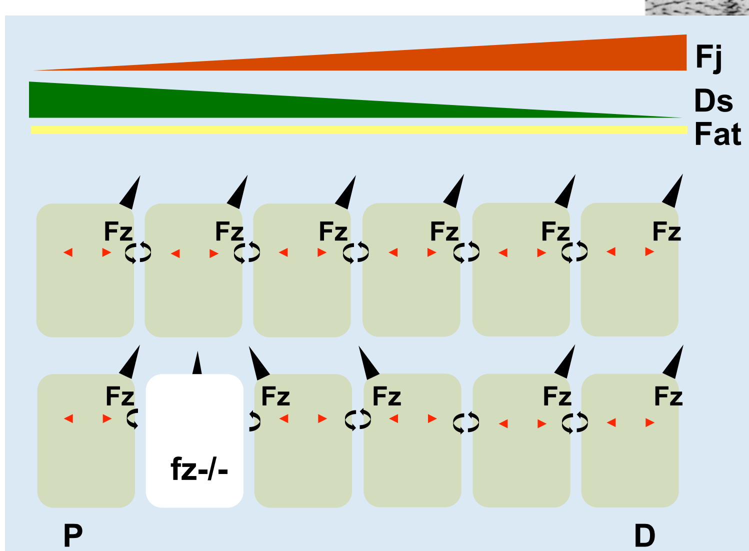
Ma et al, (2003) Nature



33hour Dsh::GFP phalloidin 30hour Dsh::GFP

A model for domineering non-autonomy





Is this a "feasible" model for PCP signaling?

emergent properties

Bottom-up model beginning with intermolecular influences

$$\mathrm{Dsh} + \mathrm{Fz} \underset{A_1 B \lambda_1}{\overset{R_1}{\rightleftarrows}} \mathrm{DshFz}$$

$$\mathrm{Fz}^{\dagger} + \mathrm{Vang} \underset{\lambda_2}{\overset{R_2}{\rightleftarrows}} \mathrm{FzVang}$$

$$\mathrm{Vang} + \mathrm{Pk} \underset{\lambda_3}{\overset{R_3}{\rightleftarrows}} \mathrm{VangPk}$$

$$\mathrm{DshFz}^{\dagger} + \mathrm{Vang} \underset{\lambda_4}{\overset{R_4}{\rightleftarrows}} \mathrm{DshFzVang}$$

$$\mathrm{Dsh}^{\dagger} + \mathrm{FzVang} \underset{A_1^{\dagger} B^{\dagger} \lambda_5}{\overset{R_5}{\rightleftarrows}} \mathrm{DshFzVang}$$

$$\mathrm{Fz}^{\dagger} + \mathrm{VangPk} \underset{\lambda_6}{\overset{R_6}{\rightleftarrows}} \mathrm{FzVangPk}$$

$$\mathrm{FzVang} + \mathrm{Pk} \underset{\lambda_7}{\overset{R_7}{\rightleftarrows}} \mathrm{FzVangPk}$$

$$\mathrm{Dsh}^{\dagger} + \mathrm{FzVangPk} \underset{A_1^{\dagger} B^{\dagger} \lambda_8}{\overset{R_8}{\rightleftarrows}} \mathrm{DshFzVangPk}$$

$$\mathrm{DshFz}^{\dagger} + \mathrm{VangPk} \underset{\lambda_9}{\overset{R_9}{\rightleftarrows}} \mathrm{DshFzVangPk}$$

$$\mathrm{DshFzVang} + \mathrm{Pk} \underset{\lambda_{10}}{\overset{R_{10}}{\rightleftarrows}} \mathrm{DshFzVangPk}$$

Reaction equations

Dsh Fz Vang Pk

Dsh Fz Vang Pk

Reaction Equations

Inhibition of DshFz:

$$B = (1 + K_b(K_{\mathrm{Pk}}[\mathrm{Pk}] + [\mathrm{VangPk}] + [\mathrm{FzVangPk}] + [\mathrm{DshFzVangPk}] + K_{\mathrm{Vang}}([\mathrm{Vang}] + [\mathrm{FzVang}] + [\mathrm{DshFzVang}]))^{Kp})$$

Asymmetry:

$$A_1 = \begin{cases} M_1, & \text{Distal region of the cell} \\ 1, & \text{Otherwise} \end{cases}$$

$$\mathrm{Dsh} + \mathrm{Fz} \underset{A_1 B \lambda_1}{\overset{R_1}{\rightleftarrows}} \mathrm{DshFz}$$

$$\mathrm{Dsh}^{\dagger} + \mathrm{FzVang} \underset{A_1^{\dagger} B^{\dagger} \lambda_5}{\overset{R_5}{\rightleftarrows}} \mathrm{DshFzVang}$$

$$\mathrm{Dsh}^{\dagger} + \mathrm{FzVangPk} \underset{A_1^{\dagger} B^{\dagger} \lambda_8}{\overset{R_8}{\rightleftarrows}} \mathrm{DshFzVangPk}$$

Pk Vang Fz Dsh

Dsh Fz Vang Pk

Reaction Equations

The net reaction production rates:

Net production rate = Forward reaction rate – Backward reaction rate

$$P_1 = R_1[\mathrm{Dsh}][\mathrm{Fz}] - A_1 B \lambda_1 [\mathrm{DshFz}]$$
$$P_2 = R_2[\mathrm{Fz}]^\dagger[\mathrm{Vang}] - \lambda_2[\mathrm{FzVang}]$$
$$P_3 = R_3[\mathrm{Vang}][\mathrm{Pk}] - \lambda_3[\mathrm{VangPk}]$$
$$P_4 = R_4[\mathrm{DshFz}]^\dagger[\mathrm{Vang}] - \lambda_4[\mathrm{DshFzVang}]$$
$$P_5 = R_5[\mathrm{Dsh}]^\dagger[\mathrm{FzVang}] - A_1^\dagger B^\dagger \lambda_5[\mathrm{DshFzVang}]$$
$$P_6 = R_6[\mathrm{Fz}]^\dagger[\mathrm{VangPk}] - \lambda_6[\mathrm{FzVangPk}]$$
$$P_7 = R_7[\mathrm{FzVang}][\mathrm{Pk}] - \lambda_7[\mathrm{FzVangPk}]$$
$$P_8 = R_8[\mathrm{Dsh}]^\dagger[\mathrm{FzVangPk}] - A_1^\dagger B^\dagger \lambda_8[\mathrm{DshFzVangPk}]$$
$$P_9 = R_9[\mathrm{DshFz}]^\dagger[\mathrm{VangPk}] - \lambda_9[\mathrm{DshFzVangPk}]$$
$$P_{10} = R_{10}[\mathrm{DshFzVang}][\mathrm{Pk}] - \lambda_{10}[\mathrm{DshFzVangPk}]$$

Reaction-Diffusion Model

Addition of diffusion terms: **Results in system of nonlinear PDEs**

Local time rate of change of protein/complex concentration = Reaction production rate + Diffusion rate

$$\frac{\partial[\mathrm{Dsh}]}{\partial t} = -P_1 - P_5^\dagger - P_8^\dagger + \mu_{\mathrm{Dsh}}\nabla^2[\mathrm{Dsh}]$$
$$\frac{\partial[\mathrm{Pk}]}{\partial t} = -P_3 - P_7 - P_{10} + \mu_{\mathrm{Pk}}\nabla^2[\mathrm{Pk}]$$
$$\frac{\partial[\mathrm{Fz}]}{\partial t} = -P_1 - P_2^\dagger - P_6^\dagger + \mu_{\mathrm{Fz}}\nabla^2[\mathrm{Fz}]_D$$
$$\frac{\partial[\mathrm{Vang}]}{\partial t} = -P_2 - P_3 - P_4 + \mu_{\mathrm{Vang}}\nabla^2[\mathrm{Vang}]$$
$$\frac{\partial[\mathrm{DshFz}]}{\partial t} = P_1 - P_4^\dagger - P_9^\dagger + \mu_{\mathrm{DshFz}}\nabla^2[\mathrm{DshFz}]_D$$
$$\frac{\partial[\mathrm{VangPk}]}{\partial t} = P_3 - P_6 - P_9 + \mu_{\mathrm{VangPk}}\nabla^2[\mathrm{VangPk}]$$
$$\frac{\partial[\mathrm{FzVang}]}{\partial t} = P_2 - P_5 - P_7 + \mu_{\mathrm{FzVang}}\nabla_s^2[\mathrm{FzVang}]_D$$
$$\frac{\partial[\mathrm{DshFzVang}]}{\partial t} = P_4 + P_5 - P_{10} + \mu_{\mathrm{DshFzVang}}\nabla_s^2[\mathrm{DshFzVang}]_D$$
$$\frac{\partial[\mathrm{FzVangPk}]}{\partial t} = P_6 + P_7 - P_8 + \mu_{\mathrm{FzVangPk}}\nabla_s^2[\mathrm{FzVangPk}]_D$$
$$\frac{\partial[\mathrm{DshFzVangPk}]}{\partial t} = P_8 + P_9 + P_{10} + \mu_{\mathrm{DshFzVangPk}}\nabla_s^2[\mathrm{DshFzVangPk}]_D$$

Solve the equations given a set of feature constraints

Table 1. Feature constraint functions representing the characteristic PCP phenotypes reproduced by the mathematical model.

Phenotype	Objective	Constraint description
Wild-type	J_{wt}	Asymmetric accumulation of Dsh and Fz on the distal cell membrane. Asymmetric accumulation of Pk and Vang on the proximal cell membrane (*28, 30, 31, 33*).
dsh	J_{dsh}	Polarity disruption inside of the mutant clone. Autonomous phenotype (*22, 23*).
fz	J_{fz}	Distal domineering non-autonomy (*9*).
Vang	J_{Vang}	Proximal domineering non-autonomy (*7*).
pk	J_{pk}	No polarity reversal. (this paper)
>>dsh	$J_{>>dsh}$	Proximal domineering non-autonomy. (our unpublished observations)
>>fz	$J_{>>fz}$	Proximal domineering non-autonomy (*30*).
>>Vang	$J_{>>Vang}$	Distal domineering non-autonomy. (our unpublished observations)
>>pk	$J_{>>pk}$	Distal domineering non-autonomy.
$fz^{autonomous}$	J_{fza}	Polarity disruption inside of the mutant clone. Autonomous phenotype (*20*).
$>>fz^{autonomous}$	$J_{>>fza}$	Proximal domineering non-autonomy (*30*).
EnGAL4, UASpk	$J_{>>pk\text{-}en}$	Overexpression of *pk* results in protein accumulation to a degree greater than or equal to that for wild-type results (*31*).

Parameter Identification

All of the model parameters are unknown

- Express PCP phenotypes as feature constraints
- Search for a feasible solution by adjusting model parameters using an optimization algorithm

Optimizer

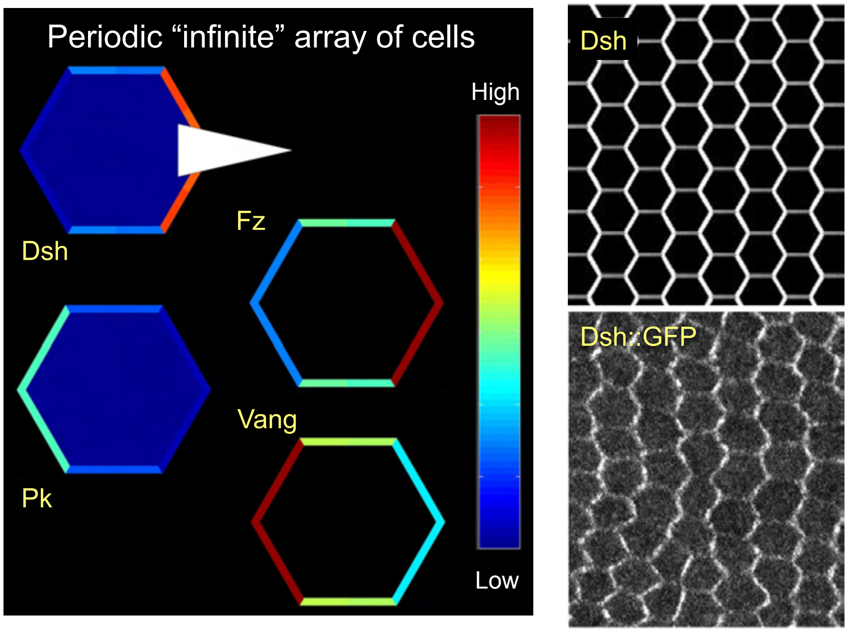
Minimize sum of quadratic penalty functions enforcing feature constraints

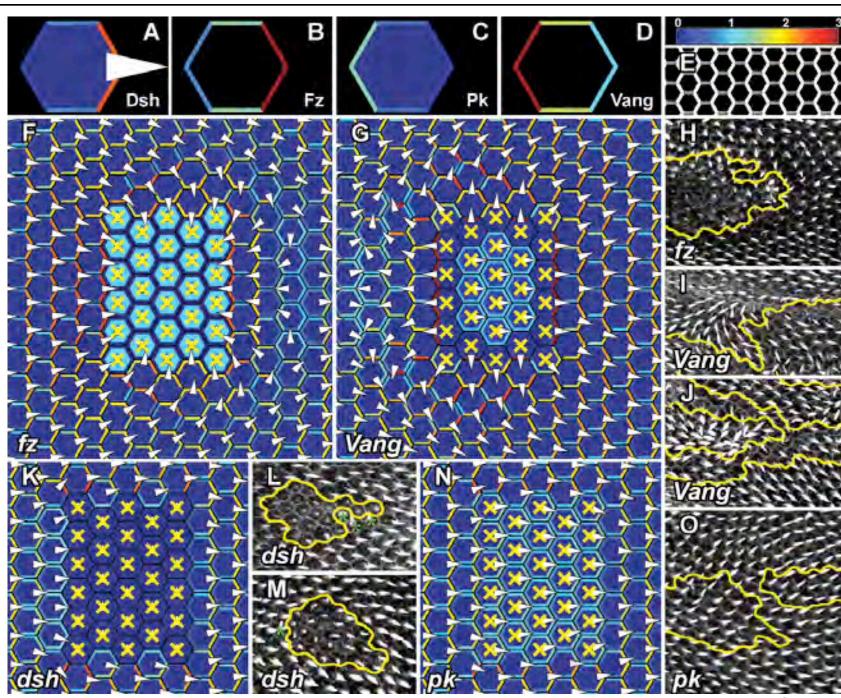
↕

Numerical Solver

Simulate wild-type and mutant clone cases

Wild type final protein distributions



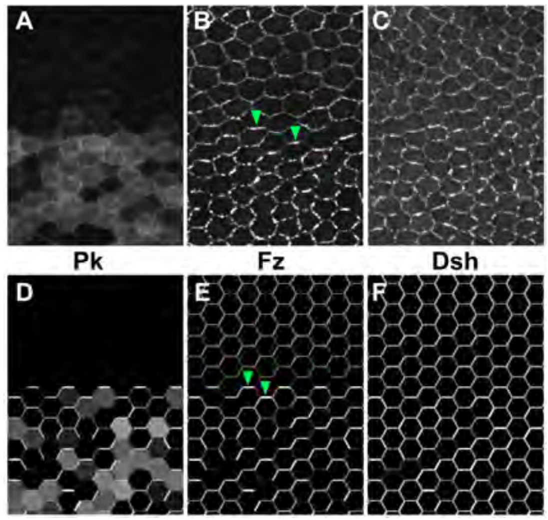


Amonlirdviman et al, (2005) Science

The model matches even counterintuitive results

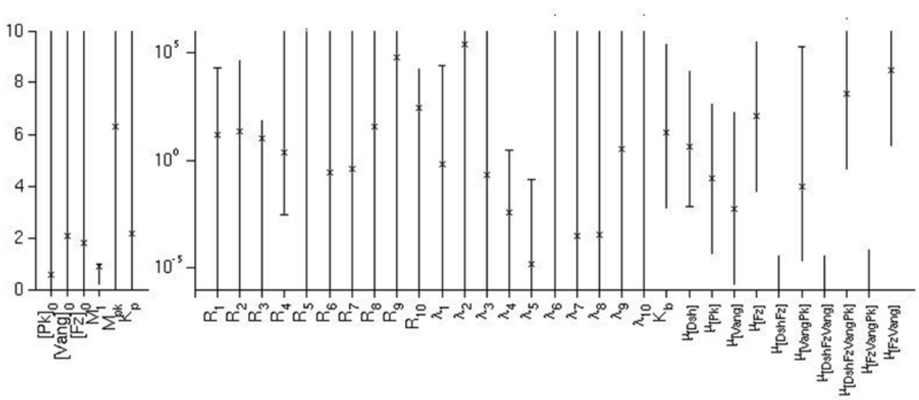
Pk Vang Fz Dsh

Dsh Fz Vang Pk



adapted from Tree et al. Cell 2002

Wild type and clonal pattern parameter sensitivity as a test of robustness



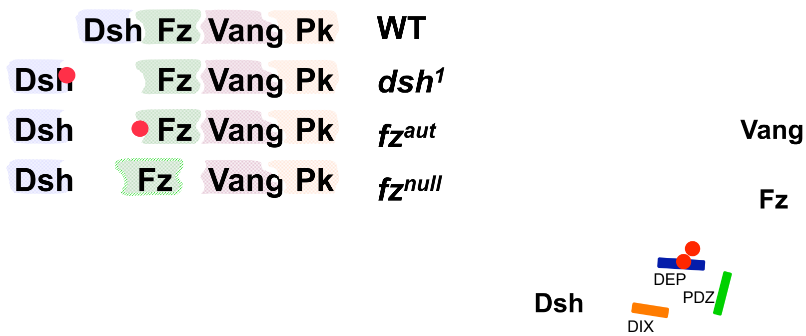
wild-type

How sensitive is the result to assumptions?

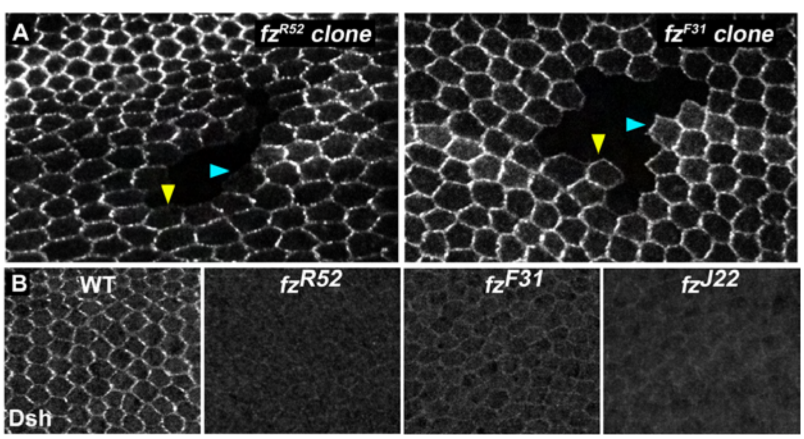
Bottom-up modeling of the proposed PCP signaling network demonstrates feasibility of the model

Mathematical modeling reveals that non-autonomy can result from the identified network architecture, and one need not postulate Factor X

Predicted features needed to get nearly autonomous *dsh, pk and fz*^{autonomous} clones



Predictions of the autonomy model



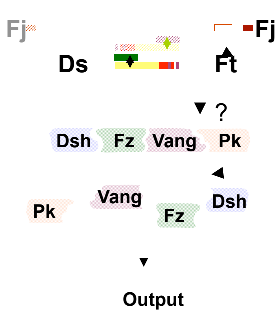
Fz^{autonomous} mutant protein retains ability to interact with Vang, but does not recruit Dsh

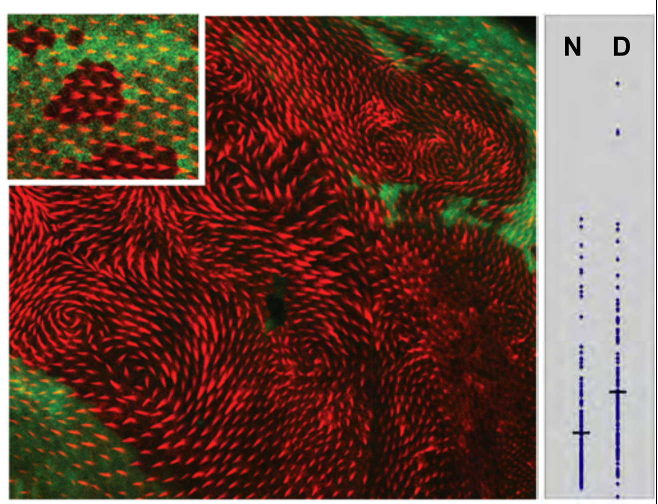
Conclusions

Mathematical modeling reveals that non-autonomy can result from the identified network architecture, and one need not postulate Factor X

Mathematical modeling predicts other testable behaviors of the system

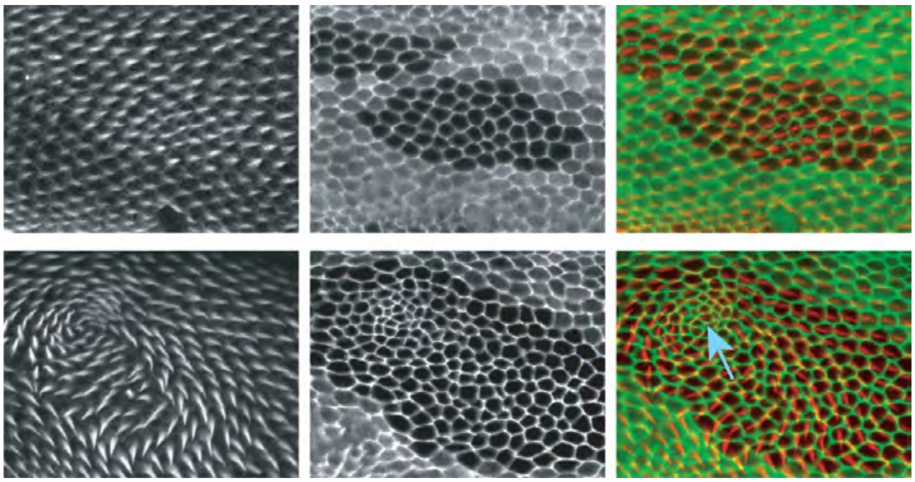
Polarity within *fat* clones results from propagation





Does cell geometry contribute to polarity?

ft clones



Actin E-cadherin merge

Does cell geometry contribute to polarity?

Experimental evidence for:

Correlation between geometry and polarity disruption

Causality between geometry and polarity defects

Is polarity disruption a natural consequence of feedback loop function in the context of irregular geometry?

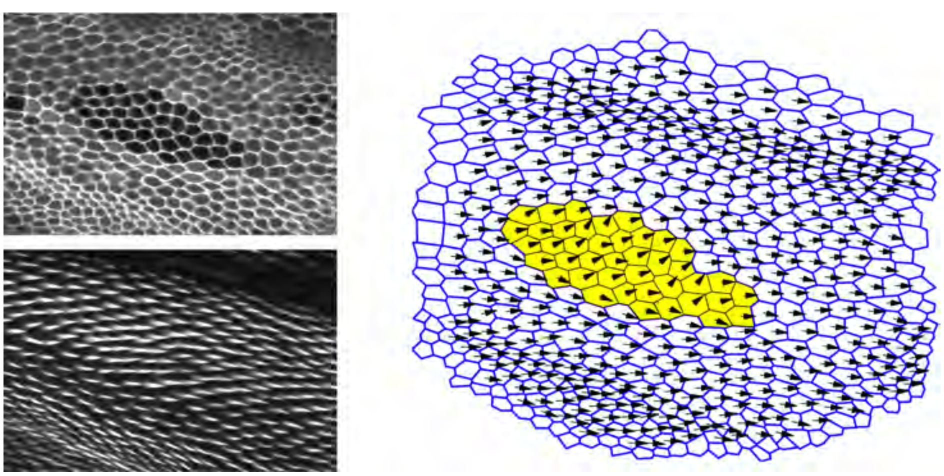
Is geometry dependence a consequence of the underlying feedback loop?

Model implementation revisions to accommodate irregular geometry

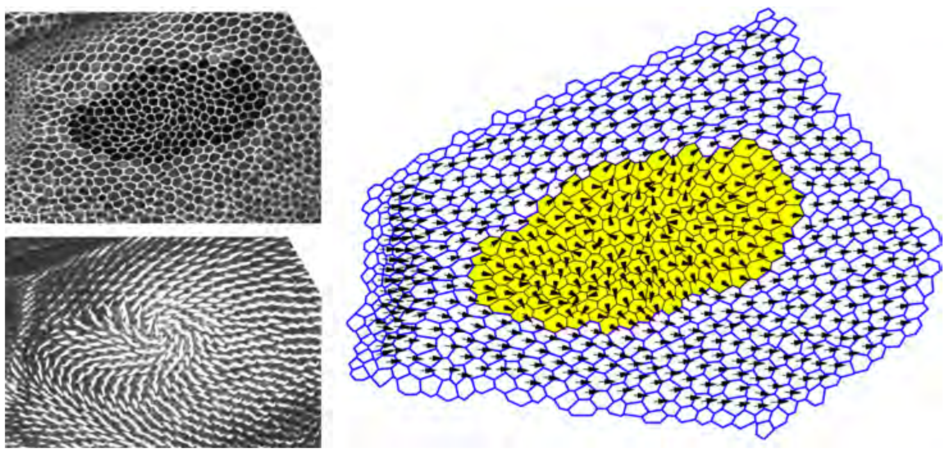
- **Replace diffusion constants with quasi-steady-state solutions**
- **Reduce PDEs to ODEs**
- **Scaling initial concentrations for apical cell area**
- **Boundary conditions**
- **Objective functions**
- **Irregular cell grid**

Can cell geometry be used to predict polarity?

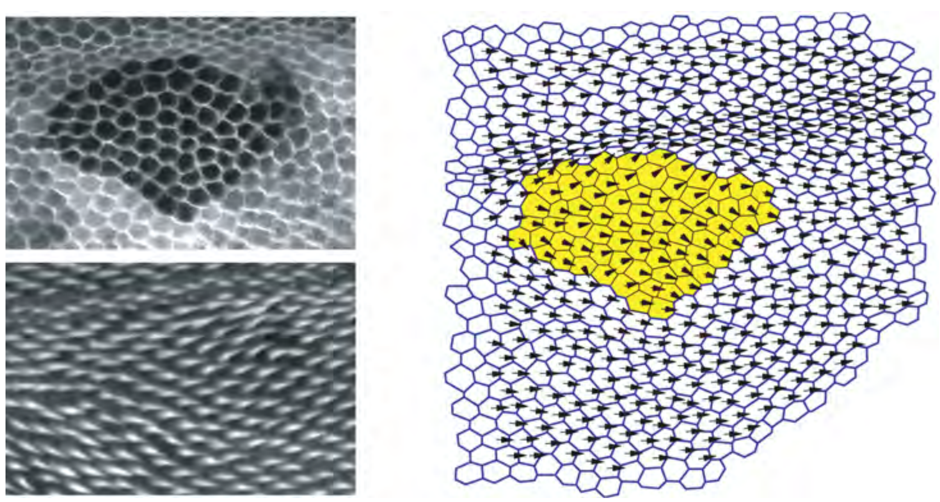
Simulation of *ft* clones with irregular geometries: training set



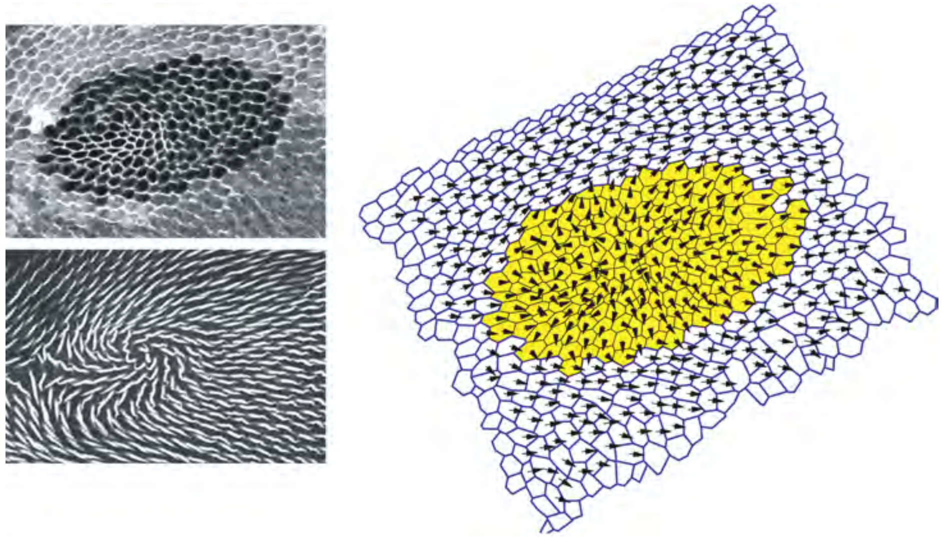
Simulation of *ft* clones with irregular geometries: training set

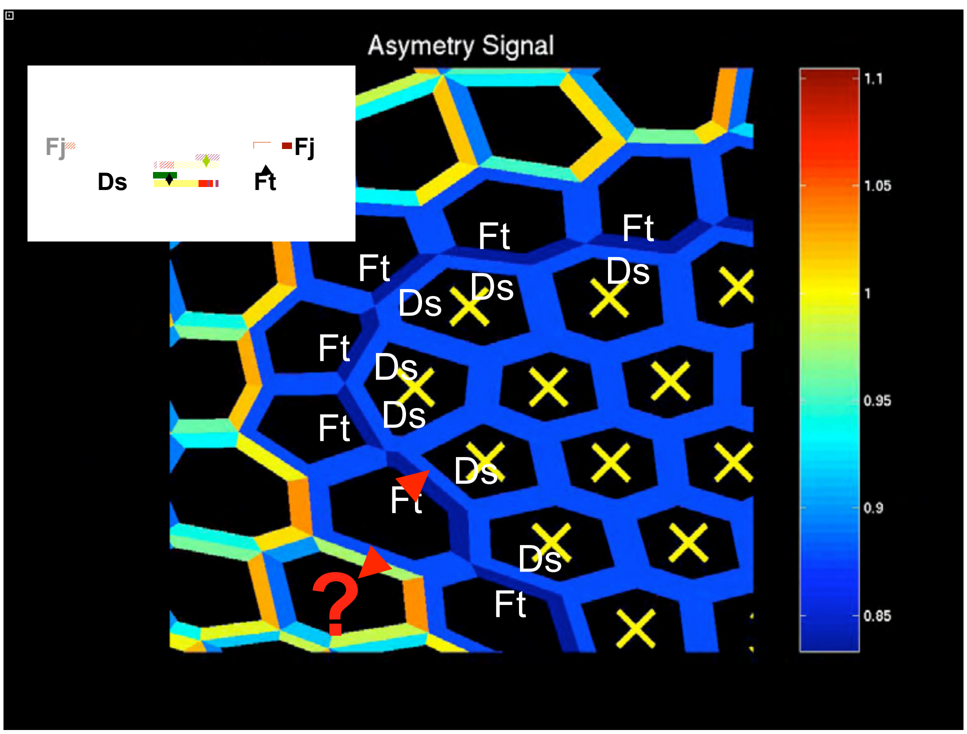


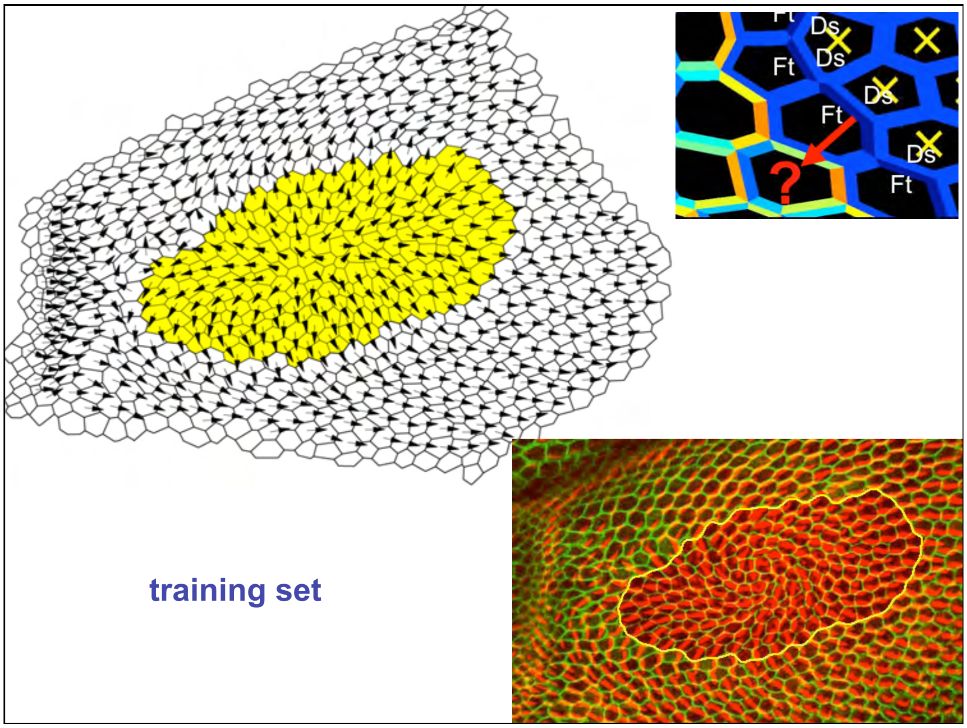
Simulation of *ft* clones with irregular geometries: test set



Simulation of *ft* clones with irregular geometries: test set






Ft
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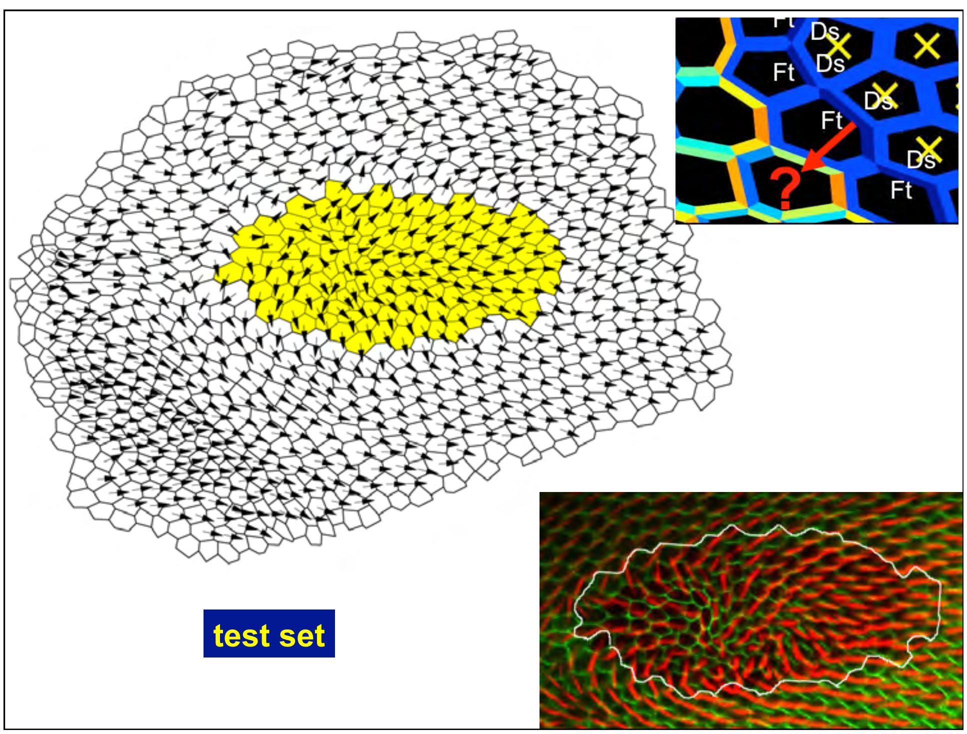
training set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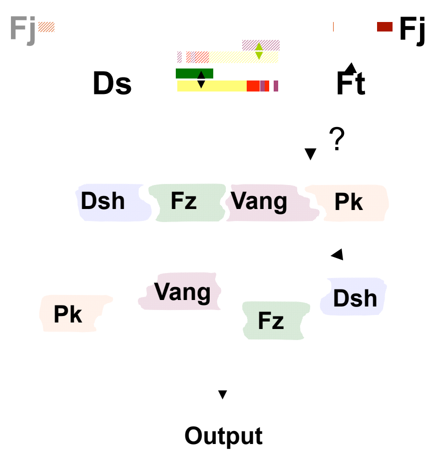


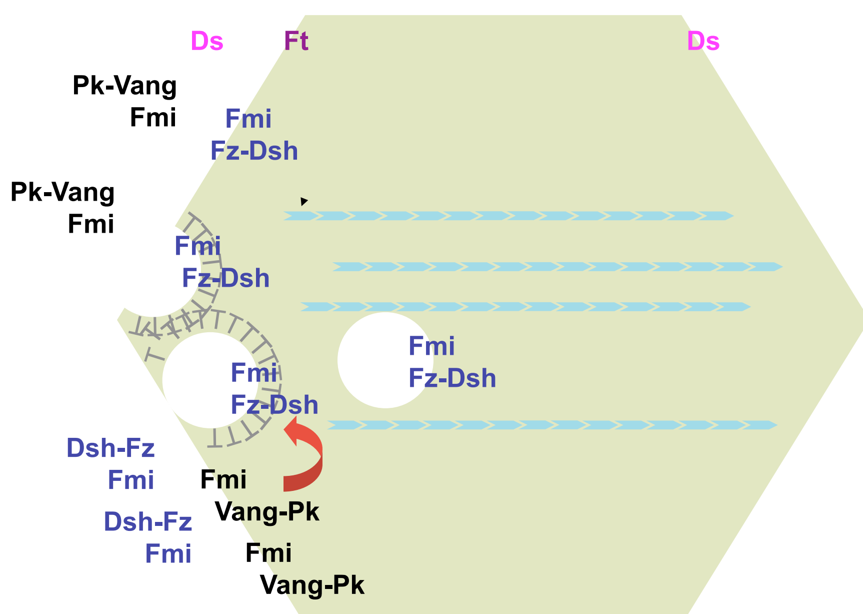
Conclusions:

Emergent properties

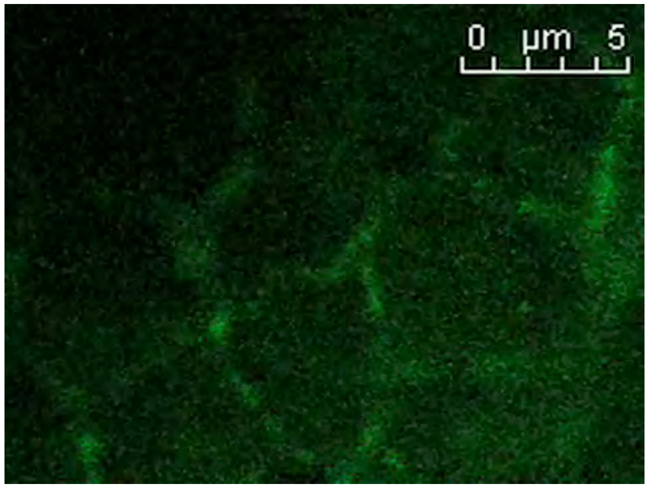
Polarity disruption in *ft* clones is a consequence of the Fz local alignment mechanism, cell geometry and Ft-Ds non-autonomy

The two tiered PCP signaling system provides robustness against aberrant cell geometries

Speculative model of PCP signaling



Dsh-GFP vesicle movement: preliminary analysis



P

D

Dsh-GFP vesicle movement: preliminary analysis

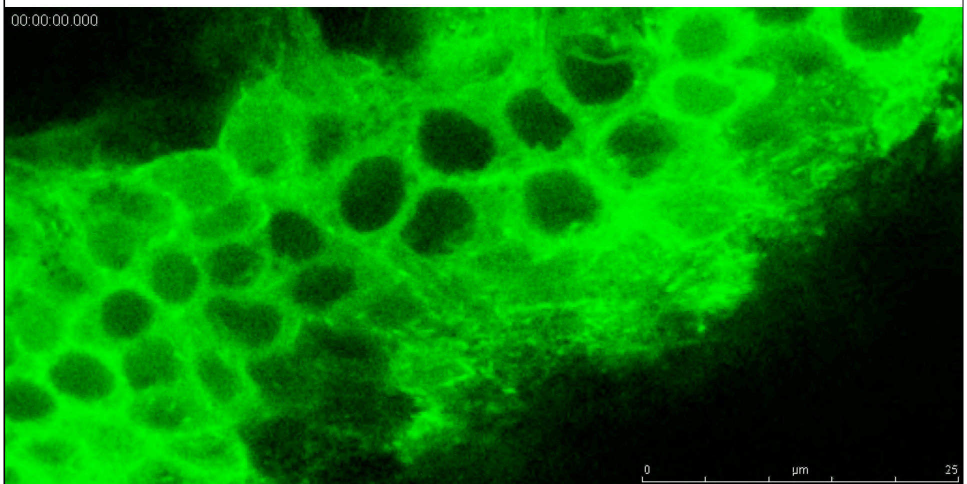
average travel time: 64 seconds
average velocity: 62.5 nm/second**

% of vesicles reaching the distal membrane: 44
% of vesicles reaching the proximal membrane: 20
% of vesicles that follow linear paths parallel to P-D axis: 96

approximate proportion of cells containing vesicles: 5%

22-26 hrs APF

Probe of MT polarity: EB1-GFP



D ‹ P

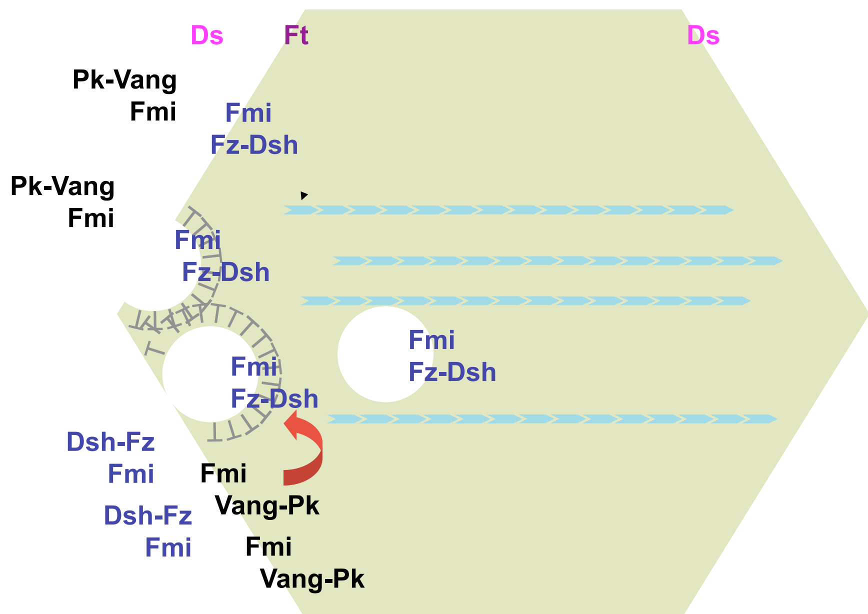
Probe of MT polarity: EB1-GFP

all EB1 particles

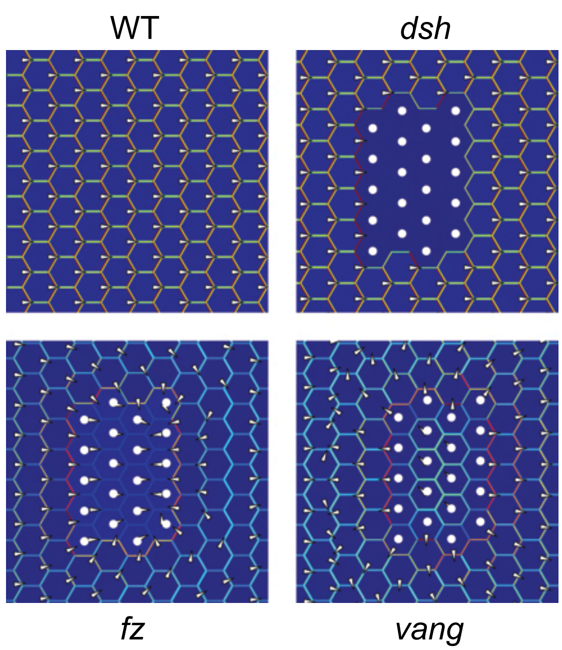
82% P-D 18% A-P

55% P->D 45% D->P

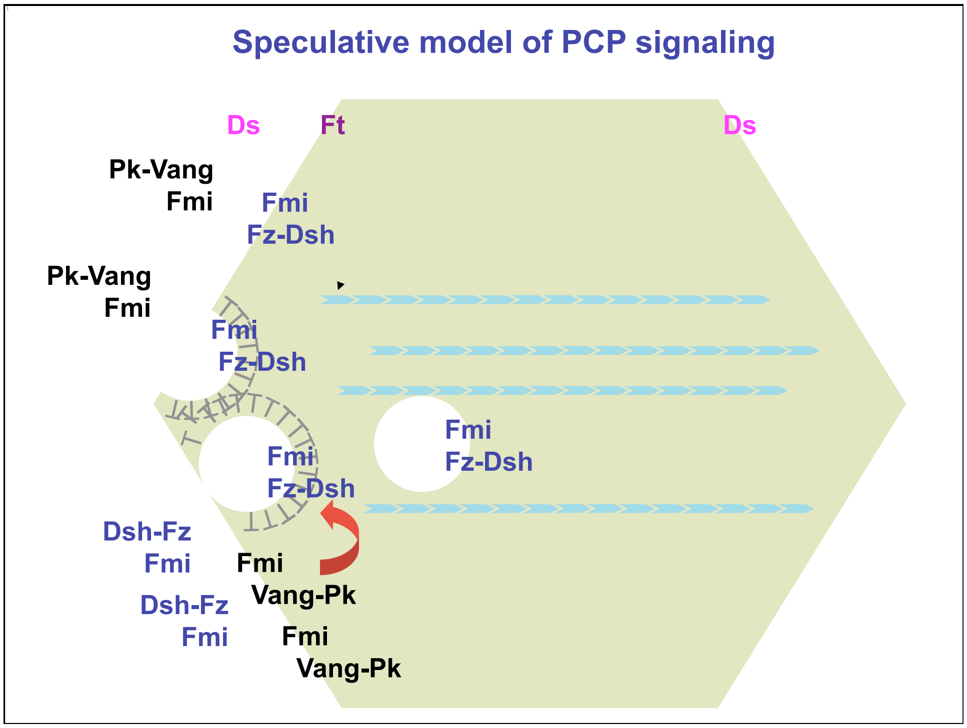
Speculative model of PCP signaling



"Convection" model of PCP signaling



Identified P->D transport bias: 53%


Speculative model of PCP signaling
Ds
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Ds
Pk-Vang
Fmi
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Fz-Dsh
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